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Développement de nouvelles stratégies en chimie des ions N-acyliminiums catalysées par l'or

Malina Michalska

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ÉCOLE DOCTORALE NORMANDE DE CHIMIE

UNIVERSITÉ DU HAVRE
U.F.R DES SCIENCES & TECHNIQUES

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THÈSE

Pour obtenir le grade de

DOCTEUR DE L'UNIVERSITE DU HAVRE
Spécialité : Chimie Organique Fine

Présentée par

Malina MICHALSKA

Le 16 Décembre 2013

Development of new gold-catalyzed strategies in *N*-acyliminium ion chemistry

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I would also like to thank my parents and all my family for supporting me to achieve my dreams.

LIST OF ABBREVIATIONS

Ac : acetyl	EWG : electron-withdrawing group
AcOH : acetic alcohol	eq. : equivalent
Ad : adamantyl	Et : ethyl
al. (coll.) : alumni (employees)	EDG : electron-donating group
aq : aqueous	Et₃N : triethylamine
Ar : aryl	GP (PG) : protecting group
ar : aromatic	h : hour(s)
BA : Brønsted acid	HNTf₂ : bis(trifluoromethanesulfonyl)imide
BARF :tetrakis[3,5-bis(trifluoromethyl)phenyl] borate	HRMS : High Resolution Mass Spectrometry
Bn : benzyl	Hz : hertz
Boc : <i>tert</i> -butoxycarbonyl	<i>i</i>-Pr : isopropyl
Bu : butyl	IPr : 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
<i>t</i>-Bu : <i>tert</i> -butyl	IR : infrared
Bz : benzoyl	JohnPhos : (2-biphenyl)di- <i>tert</i> -butyl-phosphine
cat. : catalyst	LA : Lewis acid
CBz : benzyl chloroformate	M : molar
Cq : quaternary carbon	MAD : Methylaluminum bis(2,6-di- <i>t</i> -butyl-4-methylphenoxide)
Cy : cyclohexane	<i>m</i>CPBA : <i>m</i> -chloroperbenzoic acid
DBU : 1,8-diazabicyclo[5.4.0]undec-7-ene	Me : methyl
DCE : dichloroethane	MeOH : methanol
DCM : dichloromethane	min : minute(s)
dia(s) : diastereoisomer(s)	MS (TM) : molecular sieves
DMAP : 4- <i>N,N</i> -dimethylaminopyridine	NBS : <i>N</i> -bromosuccinimide
DMF : dimethylformamide	NHC : N-heterocyclic carbene
DMSO : dimethyl sulfoxide	NMR : Nuclear Magnetic Resonance
2,4-DNPH : 2,4-dinitrophenylhydrazine	NR : no reaction
dppf : 1,1'-bis (diphenylphosphino)ferrocene	Ns : 4-nitrobenzenesulfonyle
dppm : 1,1-bis(diphenylphosphino)methane	Nu : nucleophile
ee : enantiomeric excess	Ph : phenyl
	Phth : phthalimide

PMB : *p*-methoxybenzyl

PPTS : pyridinium *p*-toluenesulfonate

Pr : propyl

R_f : front report

rt : room temperature

RX : X-Ray

Sc(OTf)₃: Scandium(III)

trifluoromethanesulfonate

T : temperature

Tf : triflate (trifluoromethanesulfonyl)

THF : tetrahydrofuran

TIPSOTf : triisopropylsilyl

trifluoromethanesulfonate

TLC: Thin Layer Chromatography

TfOH : trifluoromethanesulfonic acid

TMS : trimethylsilyl

TMSOTf : trimethylsilyl

trifluoromethanesulfonate

Ts : tosyl

UV : ultraviolet

XPhos : 2-dicyclohexylphosphino-2',4',6'-

triisopropylbiphenyle

vs : versus

Y: yield

Numbering of molecules

Throughout the manuscript, the molecules in the literature are noted **X.n.** (X=chapter number, n = 1, 2, 3) and complexes containing gold are denoted An (n = 1, 2, 3). For molecules synthesized, as well as substrates, a common numbering is used.

References

The references cited in the general introduction will be repeated in the following chapters. Generally, the cited reference will be called within a chapter and repeated in another chapter.

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GENERAL INTRODUCTION

General introduction

Gold catalysis has become a particularly active area of research within only a few years. The reasons for such a recent interest are intimately linked with the singular reactivity of electrophilic gold species, their high Lewis acidity, and the possibility to selectively and efficiently perform a plethora of transformations.

With a few exceptions, homogeneous gold chemistry relies on the capacity of gold complexes to act as carbophilic Lewis acids activating carbon-carbon multiple bonds toward nucleophilic attack. Most of the gold-catalyzed nucleophilic additions to unsaturated C-C bonds follow the same pathway depicted on **Scheme 1**. The pre-catalyst is transformed into the catalytically active species LAuX which then coordinates to the multiple bond of the substrate activating it towards subsequent nucleophilic attack which generally proceeds in an *anti* fashion.¹ Depending on the nature of the nucleophile employed (nitrogenated, oxygenated, sulfur containing, unsaturated, aromatic compounds), new carbon-carbon or carbon-heteroatom bonds can be formed.

The following step is highly dependent on the nature of the intermediate gold species thus formed. One possible evolution of vinyl gold intermediates is the formation of the gold-cations or gold-carbenes following gold retro-donation. This last property of gold and its high π -acidity are direct consequences of the relativistic effects.² So, depending on the reaction partners different outcomes could arise such as protodeauration, addition of an electrophile, hydride ion migration, rearrangement, cyclization, a second nucleophilic attack etc, thus explaining the great variety of transformations involving gold compounds.

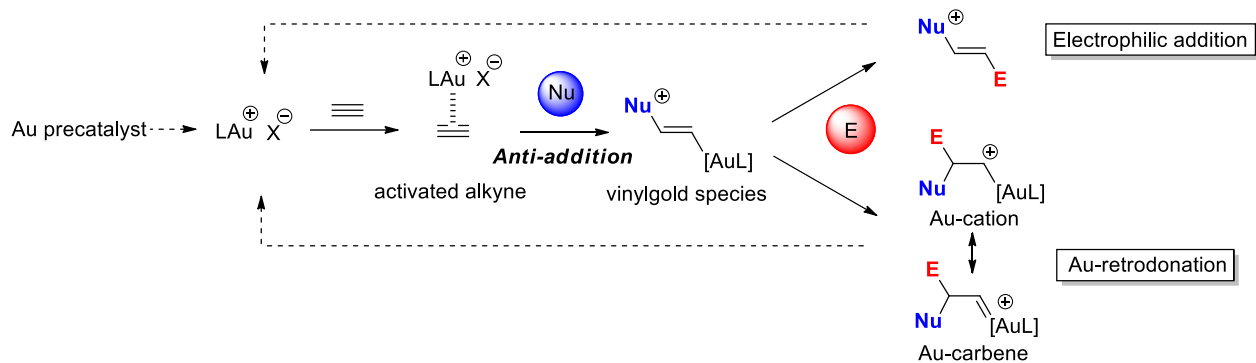
Last, the active gold species is regenerated: unlike most transition metal-catalyzed transformations, gold species do not undergo β -eliminations and carbon-gold bonds are rather labile toward protodeauration.

Noteworthy, unlike many Lewis acids, gold catalysts are exceptionally alkynophilic and in comparison less oxophilic. Thus oxygen, water, and alcohols are often well tolerated, in sharp contrast to most air- and moisture-sensitive Lewis acid or transition metal-catalyzed reactions.

¹ Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

² Gorin, D. J.; Toste, F. D. *Nature*, **2007**, *446*, 395.

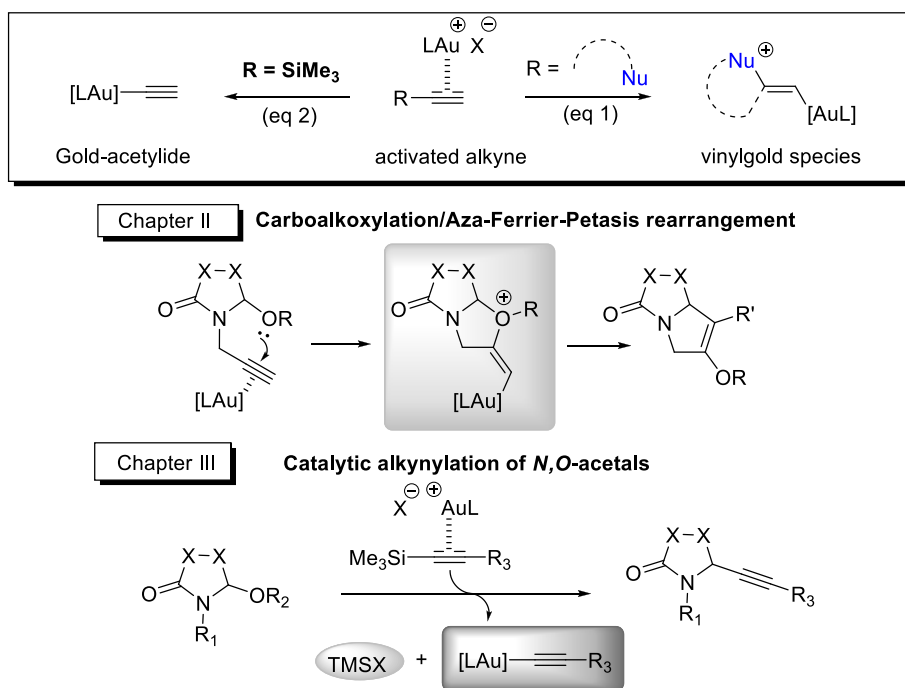
General introduction



Scheme 1. General reactivities of electrophilic gold complexes

As a part of our ongoing studies on *N*-acyliminium ion chemistry, we have been interested in using gold catalysis to promote heretofore unprecedented transformations of *N,O*-acetals, reminiscent to the (eq 1) and (eq 2) depicted in Scheme 2. This manuscript will thus begin with a bibliographic description of the state of the art concerning the catalytic methods using *N*-acyliminiums as key cationic intermediates (Chapter I).

Following the recent developments in the field of gold-catalyzed synthesis of heterocycles by nucleophilic additions onto alkynes, we surmised that a suitably designed alkynyl *N,O*-acetal could undergo a gold(I)-catalyzed intramolecular carboalkoxylation/aza-Ferrier-Petasis rearrangement sequence reminiscent to (eq 1) in the following Scheme, thus giving a rapid access to cyclic enol ethers (Chapter II).

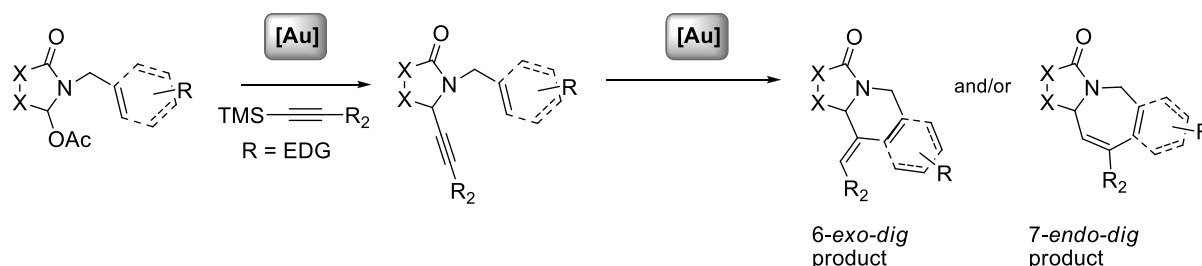


Scheme 2.

General introduction

As ordinary alkynes, silylated alkynes are nucleophilic towards electrophiles of different nature. However, the presence of the silicon atom has an important influence on the reaction, the net result being the electrophilic substitution of the trialkylsilyl group. This specific feature of TMS-alkynes was exploited in the presence of cationic gold complexes for the catalytic generation of gold-acetylide and a silyl super Lewis acid TMSX. The development of the first catalytic alkynylation reaction of *N,O*-acetals based on this innovative concept of synergistic catalysis will be presented in Chapter III (**Scheme 2.**, reminiscent to (eq 2)). Our results will be preceded by the state of the art of the alkynylation of *N,O*-acetals, and this literature survey will be completed by the catalytic alkynylation of diverse electrophiles like iminiums, imines, aldehydes, and π -activated alcohols directly from terminal alkynes (C_{sp} -H activation), with a particular emphasis on the reactions catalyzed by gold salts. This bibliography will end with a description on the interest of using TMSalkynes as surrogates of terminal alkynes in diverse applications such as deprotection, nucleophilic additions or generation of organometallic alkynes (C_{sp} -SiMe₃ activation).

To demonstrate the synthetic potential of the resulting alkynylated products, a one-pot two-steps alkynylation/hydroarylation sequence was also briefly investigated (**Scheme 3.**), and the description of our preliminary efforts in this direction will close the Chapter III.



The last Chapter (Chapter IV) will describe our efforts aimed at gaining insights into the reaction mechanism of our synergistic silyl/gold alkynylation reaction, and in particular we will try to confirm our mechanism postulate, by means of control experiments and NMR studies. Prior to discussion our, and in connection with our mechanistic results, we will comment some recent and very important advances which have contributed to considerably improve our knowledge on the discrete species that result from the initial and rapid interaction of the gold(I) salt (pre-)catalysts with terminal alkynes, and which precede the evolution of a specific reaction.

CHAPTER I:
BIBLIOGRAPHY :
CATALYTIC N-ACYLIMINIUM ION
CHEMISTRY

I. 1. GÉNÉRALITÉS SUR LES IONS N-ACYLIMINIUMS.

I.1.1. Présentation générale des ions N-acyliminiums.

Les ions iminiums constituent des intermédiaires très importants pour la construction de neuf liaisons carbone-carbone et carbone-hétéroatomes, grâce à leur caractère cationique et donc électrophile.³ Par comparaison avec les iminiums, les ions N-acyliminiums possèdent un groupe électroattracteur (GEA) conjugué à l'atome d'azote ce qui renforce son caractère électrophile et améliore ainsi leur réactivité. (**Figure I.1.**)

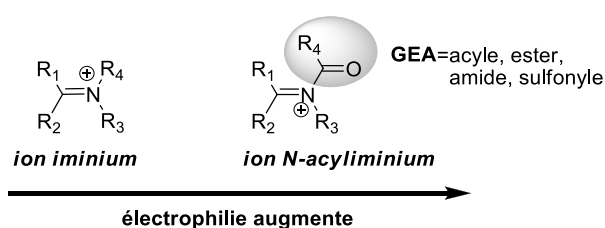


Figure I.1. Structures générales des ions iminiums et N-acyliminiums.

Les ions N-acyliminiums se caractérisent par une grande variabilité structurale. Selon la nature des substituants R₁₋₄, deux grandes familles d'ions N-acyliminiums se distinguent: les ions acycliques (**I**) et cycliques (**II-III**). Ces derniers peuvent être eux mêmes endocycliques (**II**) ou exocycliques (**III**). Aussi, les ions N-acyliminiums présentent-ils un intérêt particulier en synthèse organique (**Figure I.2.**).

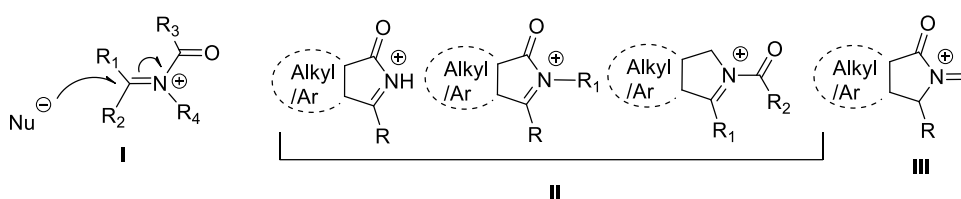


Figure I.2. Différentes structures d'ions N-acyliminiums

Ainsi, depuis plusieurs décennies les ions N-acyliminiums ont été utilisés comme intermédiaires de choix dans la construction de systèmes polyhétérocycliques et plus particulièrement dans la synthèse d'alcaloïdes.

³ (a) Speckamp, W. N. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 345; (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367; (c) Hiemstra, H.; Speckamp, W. N. *In the Alkaloids*, Ed. Bossi, A. Academic Press: New York, **1988**, *32*, 271; (d) Hiemstra, H.; Speckamp, W. N. *In comprehensive organic synthesis*, Eds. Trost, B. M.; Fleming, I. Pergamon press: Oxford, **1991**, *2*, 1047; (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

La publication récente de plusieurs revues exhaustives,⁴ complémentaires à celles plus anciennes de Hiemstra et Speckamp,³ témoigne de l'importance de ce domaine en synthèse organique contemporaine moderne.

De multiples précurseurs d'ions *N*-acyliminiums cycliques existent. En général, ces ions sont, pour la plupart, formés *in situ* en solution par traitement acide, à partir de *N,O*-acétals cycliques tels que les α -hydroxy-, α -alcoxy- ou acyloxy lactames,³ soit à partir d' α -benzènesulfonyl lactames,⁵ de *N,N*-acétals dérivés de benzotriazole,^{6c-d} ou encore à partir de lactames *N,O*-bicycliques.⁷ Une autre méthode utilise des séquences de décarboxylation radicalaire/oxydation d' α -amino-acides par voies électrochimique⁸ et chimiques.⁹

I. 1.2. Réactivité des ions *N*-acyliminiums et applications en synthèse

Les réactions faisant intervenir un ion *N*-acyliminium et un nucléophile sont appelés communément α -amidoalkylations, variantes de la réaction de Mannich. A partir du précurseur d'ion *N*-acyliminium, la réaction comprend deux étapes (**Schéma I.1**): une étape de formation de l'ion *N*-acyliminium suivie d'une étape d'alkylation avec addition du nucléophile, selon un processus de type S_N1.

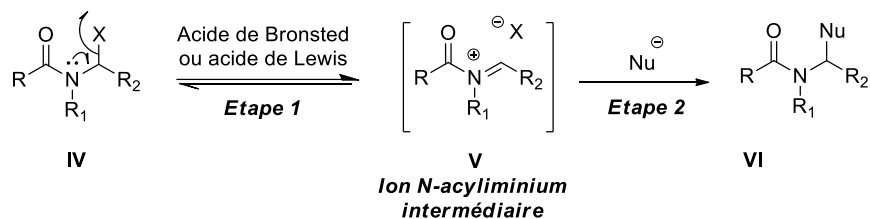


Schéma I.1. Equation générale de la réaction d' α -amidoalkylation *via* un ion *N*-acyliminium.

D'un point de vue cinétique, l'étape limitante est la formation de l'intermédiaire cationique haut en énergie **V**. Aussi, plus ce dernier sera stabilisé, plus l'équilibre sera déplacé dans le

⁴ (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

⁵ Brown, D. C.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron*, **1991**, *47*, 1311.

⁶ *N,N*-aminals dérivés du benzotriazole acycliques: (a) Katritzky, A. R.; Pernak, J.; Fan, W.-Q.; Saczewski, F.; *J. Org. Chem.* **1991**, *56*, 4439. (b) Katritzky, A. R.; Fang, Y.; Silina, A. *J. Org. Chem.* **1999**, *64*, 7622.

Analogues cycliques : (c) Katritzky, A. R.; Mehta, S.; He, H.-Y. Cui, X. *J. Org. Chem.* **2000**, *65*, 4364. (d) Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148.

⁷ Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.

⁸ (a) Padwa, A. *J. Chem. Soc., Chem. Comm.* **1998**, 1417-1424. (b) Brodney, M. A.; Padwa, A. *J. Org. Chem.* **1990**, *54*, 556.

⁹ (a) Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *65*, 4930. (b) Boto, A.; Hernández, R.; de Leon, Y.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 7796.

sens de sa formation, accélérant du même coup la cinétique de formation du produit α -amidoalkylé VI.

En considérant la structure générale de ces espèces cationiques, correspondant à la forme mésomère stabilisée d'un carbocation adjacent à l'atome d'azote d'une fonction amide, la présence du carbonyle porté par cette dernière rend l'ion *N*-acyliminium très électrophile et donc très réactif par rapport à une large gamme de partenaires réactionnels nucléophiles. Cette caractéristique a notamment permis de réaliser de multiples réactions d' α -amidoalkylations intra- ou intermoléculaires, essentiellement à l'aide de nucléophiles doux carbonés.

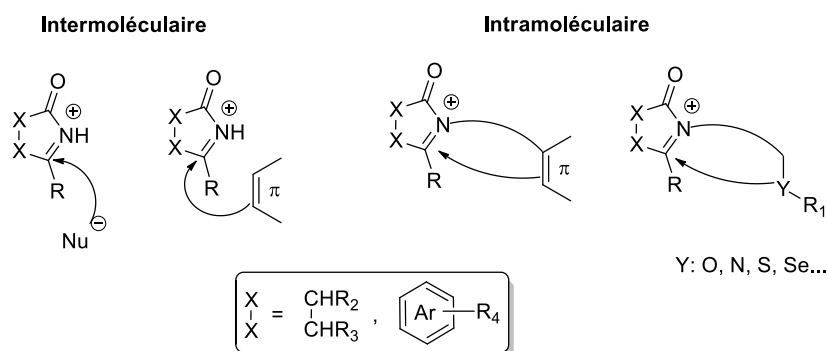


Schéma I. 2.

Parmi les principaux nucléophiles carbonés neutres couramment utilisés dans ces réactions d' α -amidoalkylations, se situent des nucléophiles π [aromatiques ou hétéroaromatiques, tels que des indoles,¹⁰ des oléfines, allènes ou alcynes (liaisons C-C doubles ou triples)]¹¹ ou des nucléophiles silylés,¹² ou des composés portant un méthylène activé (cétosters ou malonates,¹³ méthylène en α de groupement nitro¹⁴).

La littérature recense un nombre considérable d'applications de ces réactions d'amidoalkylation inter- et intramoléculaires à la synthèse de produits naturels et d'analogues. Compte tenu de cette richesse, il est difficile de dégager certaines contributions. Citons, de façon arbitraire, quelques exemples représentatifs:

¹⁰ Allin, S. M.; Thomas, C. I.; Allard, J. E.; Duncton, M.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2003**, *44*, 2335.

¹¹ Alcènes et alcynes: (a) Hanessian, S.; Tremblay, M. *Org. Lett.* **2004**, *6*, 4683. Alcynes et allènes: (b) Beyersbergen van Henegouwen, W. G.; Hiemstra, H. *J. Org. Chem.* **1997**, *62*, 8862.

¹² (a) Voir références 3(e) et références citées. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

¹³ S. Danishefsky, B. T. O'Neill, J. P. Springer, *Tetrahedron Lett.* **1984**, *25*, 4203.

¹⁴ Kraus, G. A.; Neuenschwander, K. *Tetrahedron Lett.* **1980**, *21*, 3841.

- des cyclisations intramoléculaires d'aromatiques permettant d'accéder à des alcaloïdes tels que la crispine,^{15a} et des squelettes d'alcaloïdes de type erythrina.^{15b}
- des cyclisations intramoléculaires d'alcènes conduisant à des indolizidines trihydroxylées,^{16a} et à un antithrombothique naturel d'origine marine: l'Oscillarin,^{16b} des cyclisations intramoléculaires d'allènes conduisant à la Gelsedine,^{16c} et des cyclisations intramoléculaires d'alcyne permettant de contribuer à la préparation d'antibiotiques de type carbacephem.^{16c}
- des cyclisations intramoléculaires de composés silylés tels que les vinylsilanes conduisant à la préparation d'alcaloïdes indolizidiniques (comme les elaeokanines A et B),^{17a} les allylsilanes aboutissant à la formation de l'isoretronecanol,^{17b} ou encore les propargylsilanes pour former l'alcaloïde Peduncularine.^{17c}
- des cyclisations intramoléculaires utilisant des éthers d'énol silylés comme étape clé pour la synthèse d'alcaloïdes complexes tels que la Gelsémine,^{18a} la Biotine,^{18b} la (-)-Quinocarin.^{18c}
- l'association de réactions d'allylation intermoléculaires avec une cyclisation par métathèse cyclisante d'oléfines conduisant à la synthèse d'alcaloïdes bicycliques tels que des dérivés α -lactamiques 4-6, 4-7 et 4-8,^{19a} de la coniceine,^{19b} et de la lentiginosine.^{19c}
- les amidoalkylations intermoléculaires d'éthers d'énol silylés fonctionnalisés pour permettre une réaction d'azacyclisation ultérieure conduisant à la synthèse d'alcaloïdes bicycliques tels que des indolizidines polyhydroxylées analogues de la castanospermine,^{20a} la (-)-croomine,^{20b} la stemospiroline,²¹ la stémonine,²² le stémoamide,²³ le stémonamide,²⁴ et la sténine.²⁵

¹⁵ (a) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D.; Elsegood, M. R. *J. Chem. Soc. Perkin Trans.* **2001**, 3029. (b) Zhang, F.; Simpkins, N. S.; Blake, A. J. *Org. Biomol. Chem.* **2009**, *7*, 1963.

¹⁶ (a) Wijnberg, J. B. P. A.; Speckamp, N. W.; Oostveen, A. R. C. *Tetrahedron* **1982**, *38*, 209. (b) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064. (c) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210. (d) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T. Hiemstra, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2214.

¹⁷ (a) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. (b) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (c) Klaver, W. J.; Hiemstra, H. Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588.

¹⁸ (a) Newcombe, N. J.; Fang, Y.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc. Chem. Commun.* **1994**, 767. (b) Moolenaar, M. J.; Speckamp, N. W.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem. Int. Ed.* **1995**, *34*, 2391. (c) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148.

¹⁹ (a) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893. (b) Groaning, M. D.; Meyers, A. I. *Chem. Commun.* **2000**, 1027. (c) Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605.

²⁰ (a) Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. *Eur. J. Org. Chem.* **1999**, 1395. (b) Martin, S. K.; Barr, K. J. Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

²¹ Isolation et caractérisation : (a) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Mukakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457.

I. 1.3. Relation structure-réactivité des ions N-acyliminiums

Dans leurs travaux théoriques récents, Pilli *et coll.* ont établi un ordre de réactivité électrophile des ions N-acyliminiums endocycliques selon leur spécificité structurale, en présence d'allyltriméthylsilane comme nucléophile (**Figure I.3.**).²⁶ Les expériences ont été réalisées en phase gazeuse afin de s'affranchir de l'effet de solvant ainsi que de celui du contre ion.

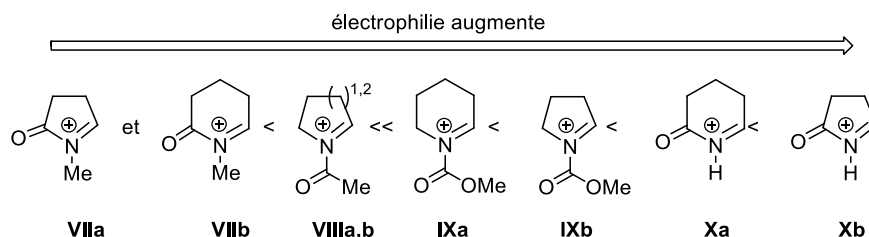


Figure I.4. Ordre de réactivité croissant des ions N-acyliminiums.

Dans ces conditions, comme indiqué dans la **Figure I.4.**, les N-méthyliminiums **VIIa**, **VIIb** se sont avérés inertes à l'addition nucléophile à cause de la diminution de la charge en C-2. Cela résulte d'une forte délocalisation de la paire libre de l'azote adjacent. Les N-acyliminiums **Xa**, **Xb** sont les plus réactifs de la série grâce à leur conformation planaire *s-trans*, qui favorise la conjugaison avec le carbonyle et rend ainsi la paire d'électrons d'azote moins disponible pour la stabilisation du cation. Leurs dérivés carbamates N-CO₂Me substitués²⁷ **IXa**, **IXb** sont plus sensibles à une addition nucléophile que les analogues où l'azote est substitué par un groupement acyle. Finalement, les ions N-acyliminiums cycliques à cinq chaînons (**IXb**, **Xb**) sont plus réactifs que leurs analogues à six chaînons (**IXa**, **IXb**).

²² Isolation et caractérisation : (a) Suzuki, K. *J. Pharm. Soc. Jpn.* **1929**, 49, 457. (b) Suzuki, K. *J. Pharm. Soc. Jpn.* **1931**, 51, 419. (c) Koyama, H.; Oda, K. *J. Chem. Soc. B.* **1970**, 1330.

²³ Isolation et caractérisation : (a) Koyama, H.; Oda, K. *J. Chem. Soc. B.* **1970**, 1330; (b) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, 122, 4295.

²⁴ Isolation et caractérisation : (a) Jizuka, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc. Chem. Commun.* **1973**, 125. (b) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, 57, 665. Synthèse totale : (c) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *J. Org. Lett.* **2001**, 3, 2505. (d) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *J. Tetrahedron* **2002**, 58, 61.

²⁵ Isolation et caractérisation : (a) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull.* **1967**, 15, 768. (b) Uyeo, S.; Irie, H.; Masaki, N.; Osaki, K.; Harada, H. *J. Chem. Soc. Chem. Commun.* **1967**, 460. Synthèse totale (c) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993**, 58, 3840. (d) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, 117, 11106. (e) Morimoto, Y.; Iwabashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed.* **1996**, 35, 904. (f) Ginn, J. D.; Padwa, A. *Org. Lett.* **2001**, 4, 1515.

²⁶ (a) D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, 66, 3854-3864; (b) Tomazela, D. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2002**, 67, 4652.

²⁷ Des résultats expérimentaux obtenus au laboratoire à partir de réactions d' α -amidoalkylation catalytiques vérifient nettement cette prédiction : Ben Othman, R.; Affani, R.; Tranchant, M. J.; Antonioti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, 49, 776.

I.2. APPLICATION DES IONS N-ACYLIMINIUMS EN CATALYSE

I.2.1. Exemples bibliographiques pour l'amélioration des réactions d' α -amidoalkylations

La chimie des ions *N*-acyliminiums endocycliques a été initiée par Speckamp et ses collaborateurs dans les années soixante-dix.²⁸ Il a été démontré qu'une réduction régiosélective de l'un des carbonyles d'un imide cyclique par le borohydrure de sodium (NaBH₄) était possible, puis que l'hydroxylactame ainsi obtenu, sous sa forme libre ou protégée (essentiellement sous les formes éthers méthylique et éthylique ou acétate) pouvait être transformé en un ion *N*-acyliminium sous l'action d'un traitement acide. Les ions *N*-acyliminiums ainsi obtenus sont alors facilement piégés par divers nucléophiles, obligatoirement présents dans le milieu réactionnel du fait de la forte instabilité présumée de ces cations iminiums.

Selon la nature des multiples nucléophiles pouvant être utilisés et du mode intra- ou intermoléculaire de la réaction d' α -amidoalkylation effectuée, une très large gamme de lactames mono- ou polycycliques diversement fonctionnalisés est accessible (**Schéma I.3**).²⁹

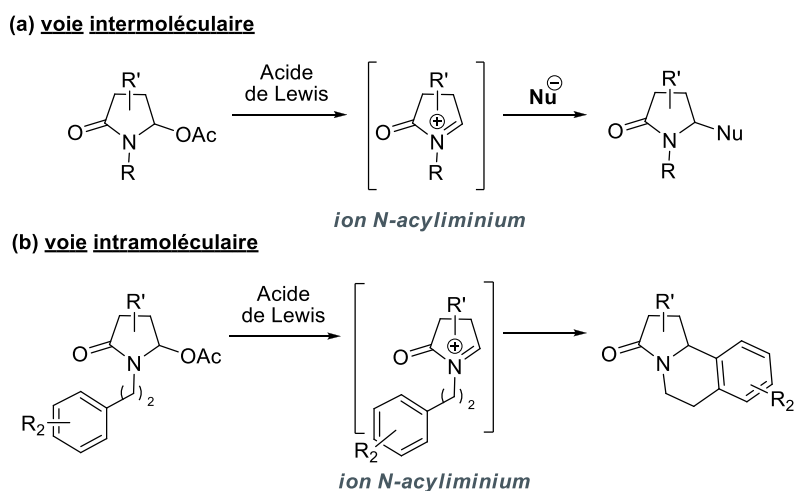


Schéma I.3. Différents types d' α -amidoalkylation.

La voie électrochimique propose une alternative intéressante avec des matières premières parfois plus facilement accessibles que celle utilisées pour la voie chimique classique et permet par ailleurs d'éviter l'étape potentiellement contraignante de la réduction

²⁸ Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

²⁹ (a) Speckamp, W.N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

d'imides. Deux approches ont été utilisées par la communauté scientifique : l'électrolyse de Kolbe (**Schéma I.4. éq. 1**)³⁰ qui consiste en la décarboxylation oxydante d' α -amino-acides et l'électro-oxydation d'amides et carbamates initiée dans les années 80 par Shono³¹ (**Schéma I.4. éq. 2**).

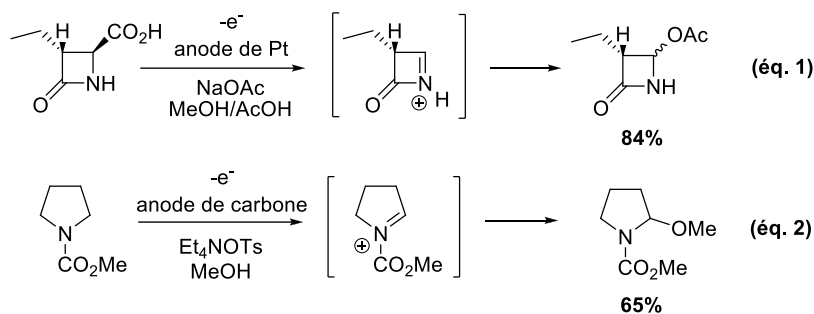


Schéma I.4. Génération des ions N-acyliminiums par voie électrochimique.

Les ions N-acyliminiums préparés *via* ces deux méthodes sont généralement piégés au cours de leur formation par un acétate ou un alcool déjà présent dans le milieu. Les substrats ainsi obtenus sont susceptibles de subir une hétérolyse ultérieure dans les conditions chimiques plus conventionnelles (acide de Brønsted ou de Lewis) précédemment discutées.

Une amélioration récente de ces méthodes permet de combiner la génération des ions N-acyliminiums par voie électrochimique avec leur piégeage direct par des nucléophiles carbonés selon la méthode dite du «pool cationique», ce qui constitue une avancée indéniable dans ce domaine.³²

Cependant, la méthode la plus usuelle pour générer les ions N-acyliminiums reste la voie chimique acide, en mettant en jeu, dans la plupart des cas, des acides de Lewis classiques tels que $\text{BF}_3 \cdot \text{OEt}_2$, FeCl_3 , TiCl_4 , TMSOTf (Triméthylsilyl trifluorométhanesulfonate), SnCl_4 .³³ Par ailleurs, la quantité d'acide de Lewis utilisée est dans la plupart des cas stœchiométrique, voire

³⁰ (a) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Tetrahedron* **1991**, *47*, 531; (b) Punniyamurthy, T. Miyafuji, A.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 8295.

³¹ (a) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264; (b) Shono, T. *Top. Curr. Chem.* **1988**, *148*, 131.

³² (a) Yoshida, J. I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735.

³³ **Utilisation de $\text{BF}_3 \cdot \text{OEt}_2$** : (a) Chen, B.-F.; Tasi, M. R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron* **2004**, *60*, 10223. (b) Breman, A. C.; Dijing, J.; Van Maarseveen, J. H.; Kinderman, S. S.; Hiemstra, H. *J. Org. Chem.* **2009**, *74*, 6327. **Utilisation de FeCl_3** : (c) Li C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036. **Utilisation de TiCl_4 et TMSOTf**: (d) Ukaji, Y.; Tsukamoto, K.; Nasada, Y.; Shimizu, M.; Fujisawa, T. *Chemistry Letters* **1993**, 221. (e) Dhiman, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhomme, G. *Eur. J. Org. Chem.* **1998**, 1955. **Utilisation de SnCl_4** : (f) Ollero, L.; Mentink, G.; Rutjes, R. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 1331.

nettement excédentaire. En effet, le rapport molaire entre le précurseur de l'ion *N*-acyliminium et l'acide de Lewis varie généralement entre 1 et 4 et les nucléophiles, composés « silylés » pour la plupart, sont également utilisés en excès. A titre d'exemple, Pilli et ses collaborateurs³⁴ ont utilisé trois équivalents de nucléophile et quatre équivalents d'acide de Lewis usuels ($\text{BF}_3 \cdot \text{OEt}_2$, TiCl_4 etc.) pour avoir un rendement satisfaisant de 83%, au cours de la réaction d'allylation à partir d'un *N,O*-acétal diacétate dérivé de l'acide malique (**Schéma I.5**).

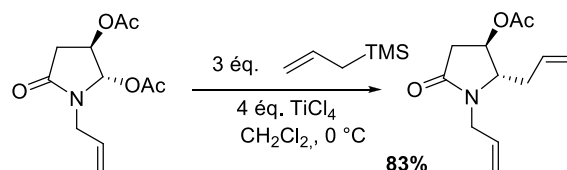


Schéma I.5. La réaction d'allylation à partir d'un *N,O*-acétal catalysée par le TiCl_4 .

Un exemple de cyclisation intramoléculaire à partir de *N,O*-acétals cycliques a été récemment développé par l'équipe de Takahashi, permettant de mettre au point une nouvelle méthode stéréosélective de synthèse de *N,N* acétals, *via* la formation d'un ion *N*-acyliminium, en présence de 1.1 équivalents de TMSOTf (**Schéma I.6**).³⁵

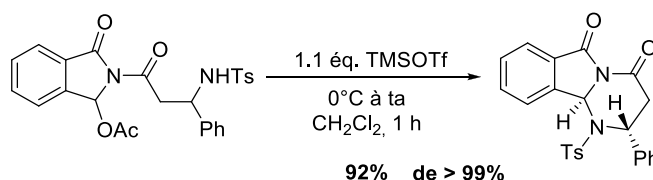


Schéma I.6. Synthèse stéréosélective de *N,N* acétals *via* la formation d'un ion *N*-acyliminium en présence de 1.1 équivalents de TMSOTf.

En raison du potentiel que peut offrir la réaction d' α -amidoalkylation en synthèse organique, plusieurs équipes de recherche se sont consacrées à l'amélioration de ce type de réaction en jouant sur la nature de l'acide de Lewis et en diminuant la quantité utilisée, dans le but de développer une version catalytique de ces réactions.

Une des réactions à laquelle notre groupe de recherche s'est le plus intéressé durant les dernières années est l' α -amidoalkylation de nucléophiles silylés, et en particulier d'énoxysilanes. Une revue exhaustive sur la chimie des ions *N*-acyliminiums, présentée par

³⁴ Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, 42, 5605.

³⁵ Yamada, S.; Takahashi, Y. *Tetrahedron Lett.* **2009**, 50, 5395.

Speckamp et Moolenaar,³⁶ énonce que l'utilisation de l'acide de Lewis TMSOTf est la plus adaptée pour la mise en œuvre de ce type de réactions (**Schéma I.7.**)³⁷

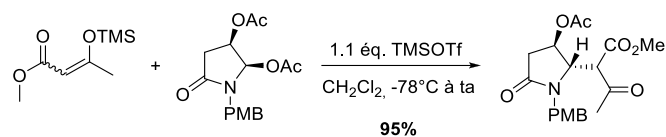


Schéma I.7. α -amidoalkylation de nucléophiles silylés, avec une quantité stoechiométrique de TMSOTf comme acide de Lewis.

Le mécanisme proposé pour cette réaction d' α -amidoalkylation du nucléophile silylé, est initié par une interaction entre l'acétoxy lactame et le TMSOTf, qui conduirait à une dissociation de ce dernier pour générer l'ion *N*-acyliminium **A** (**Schéma I.8.**). L'addition du nucléophile silylé sur l'ion iminium forme l'adduit cationique **B** porteur d'un motif silylé très appauvri en électron. A ce stade, cette entité «Me₃Si⁺» s'associerait à l'ion triflate pour régénérer l'espèce active, ce qui implique que l'utilisation d'une quantité catalytique d'un réactif trialkylsilyl triflate pour promouvoir ces réactions est envisageable.

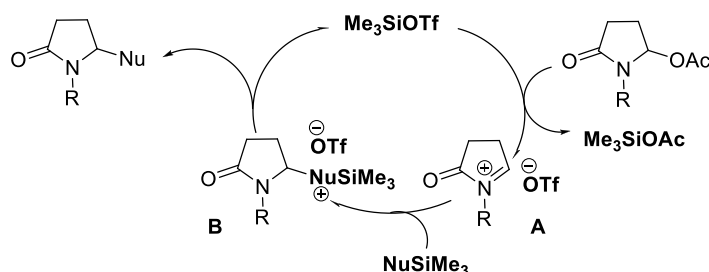


Schéma I.8. Mécanisme proposé pour l' α -amidoalkylation de nucléophiles silylés.

³⁶ Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

³⁷ Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603.

I.2.2. Application des ions *N*-acyliminiums dans des processus d' α -amidoalkylation catalytiques a partir de *N,O*-acétals.

Dans ce manuscrit nous décrivons les exemples d'amidoalkylations catalytiques développées à partir de *N,O*-acétals comme précurseurs d'ions *N*-acyliminiums. Bien que l'activation électrophile des énammides³⁸ et des ène-carbamates³⁹ cycliques aboutisse également à la formation transitoire d'ions *N*-acyliminium, nous ne détaillerons pas ces travaux puisqu'ils s'écartent légèrement de notre domaine d'intérêt. Nous ne développerons ici que les aspects de catalyse en version racémique sans discuter des approches énantiosélectives de réactions d' α -amidoalkylation ou des applications des ions *N*-acyliminiums en catalyse asymétrique.

Depuis le premier exemple décrit par l'équipe de Barrett⁴⁰ en 1981 à l'aide du TMSOTf (Schéma I.9.), les versions catalytiques des réactions d' α -amidoalkylation ont curieusement rarement été mises à profit. Cet acide de Lewis a longtemps été le catalyseur de choix pour la version catalytique des réactions d' α -amidoalkylation de type Mannich impliquant des nucléophiles silylés.⁴¹

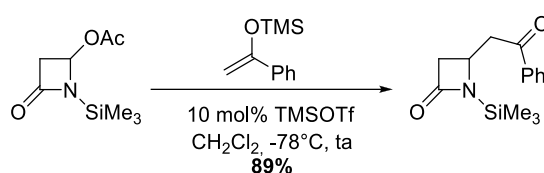


Schéma I.9. Premier exemple d' α -amidoalkylation catalytique.

Différents travaux de Pilli et son équipe illustrent l'utilisation catalytique de ce triflate dans l'étude de réactions de Mannich vinylogues, avec pour étape clé, l'addition de silyloxyfuranes

³⁸ (a) Kozak, J. A.; Patrick, B. O.; Dake, J. R. *J. Org. Chem.* **2010**, *75*, 8585; (b) Vicente-García, E.; Catti, F.; Ramón, R.; Lavilla, R. *Org. Lett.* **2010**, *12*, 860.

³⁹ (a) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023; (b) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833; (c) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367; (d) Kozak, J. A.; Dake, G. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 4221; (e) Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791; (f) Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929.

⁴⁰ Barrett, A. G. M.; Quayle, P. *J. Chem. Soc. Chem. Commun.* **1981**, 1076.

⁴¹ (a) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949; (b) Arndt, H. D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879; (c) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477.

sur des *N,O*-acétals cycliques, précurseurs d'ion *N*-acyliminium à 5, 6 ou 7 chaînons, dont la taille du cycle semble influencer la stéréosélectivité de la réaction (**Schéma I.10.**)⁴²

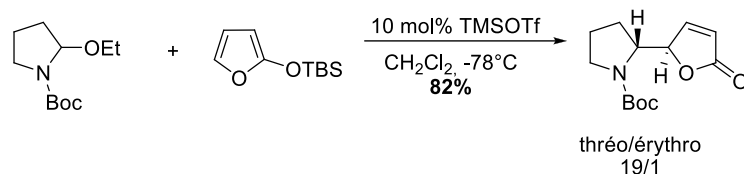


Schéma I.10. Réaction de Mannich vinylogue catalysée par TMSOTf.

Dans les réactions d'additions de 1,3-dicétones ou d'oléfinés activées (tels que les éthers d'énols silylés EES ou les vinyles éthers) sur des *N,O*-acétals cycliques, Pilli⁴³ utilise soit 3 % mol de HCl en milieu aqueux comme catalyseur ou alors 10 mol% du chlorure d'indium (III) (InCl₃). Dans la variante aqueuse catalysée par HCl, des limites liées principalement à l'hydrolyse compétitive lors de l'utilisation de nucléophiles silylés ont été rencontrées.

Ces études ont été suivies par les travaux Kobayashi et *coll.* qui ont engagé le triflate de scandium Sc(OTf)₃ comme catalyseur dans des réactions d'alkylation entre des nucléophiles silylés et divers 2-méthoxy- et 2-acétoxy- pipéridines *N*-acyloxy-carbonylées (**Schéma I.11.**)⁴⁴

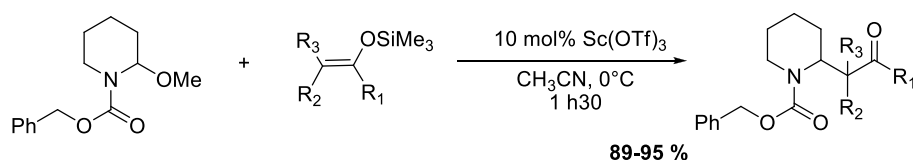


Schéma I.11. Utilisation de l'acide de Lewis Sc(OTf)₃ dans des réactions d' α -amidoalkylation.

Les travaux pionniers de Heaney avec l'utilisation de Cu(OTf)₂, bien que passés relativement inaperçus dans la littérature, constituent les premiers exemples d' α -amidoalkylations intramoléculaires catalysées par des triflates métalliques (**Schéma I.12.(a).**)⁴⁵ En 2005, Hiemstra et *coll.* ont décrit d'autres types d' α -amidoalkylations

⁴² (a) D' Oca, M. G. H.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709; (b) De Oliveira, M. C. F.; Santos, S. L.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995. Application à la synthèse totale (c) Santos, S. L.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999.

⁴³ (a) Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2004**, *45*, 2821; (b) De Godoy, L. A. F.; Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2006**, *47*, 7853.

⁴⁴ (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.

⁴⁵ (a) El Gihani, M. T.; Heaney, H.; Shuhaidar, K. F. *Synlett* **1996**, 871. (b) Heaney, H.; Simcox, M. T.; Slawin,

intramoléculaires de type Friedel-Crafts mettant en jeu des *N,O*-acétals *N*-sulfonylés acycliques, catalysées par 2 mol% de $\text{Sn}(\text{OTf})_2$ (**Schéma I.12.(b)**).⁴⁶

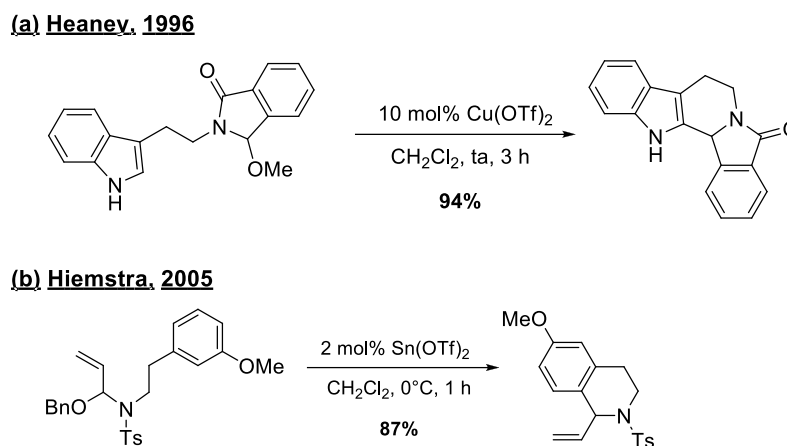


Schéma I.12. Réactions d' α -amidoalkylation catalysées par des triflates métalliques

Dans le but de développer des réactions de cycloadditions intramoléculaires entre un noyau furane et une chaîne allylique latérale, Daïch et *coll.* ont développé des réactions d' α -amidoalkylation catalytiques en utilisant 1 mol% de triflate de bismuth $\text{Bi}(\text{OTf})_3$ comme catalyseur (**Schéma I.13. (a)**).⁴⁷ Ce catalyseur a également permis une série de cyclisations intramoléculaires catalytiques (1 mol%) de substrats acétoxy lactames (**Schéma I.13. (b)**).

Une exemple de la réaction intramoléculaires est la cycloaddition entre un noyau furane et une chaîne allylique latérale présenté par Daïch et *coll.* Cette équipe a développé des réactions d' α -amidoalkylation catalytiques en présence de 1 % mol de triflate de bismuth $\text{Bi}(\text{OTf})_3$. Ce triflate est aussi utilisé dans la série de cyclisations intramoléculaires catalytiques de substrats acétoxy lactames.³⁵

A. M. Z.; Giles, R. G. *Synlett* **1998**, 641.

⁴⁶ Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519.

⁴⁷ (a) Pin, F.; Comesse, S.; Garrigues, B.; Marchalin, S.; Daich, A. *J. Org. Chem.* **2007**, *72*, 1181. (b) Pin, F.; Comesse, S.; Daich, A. *Synlett* **2009**, 3214.

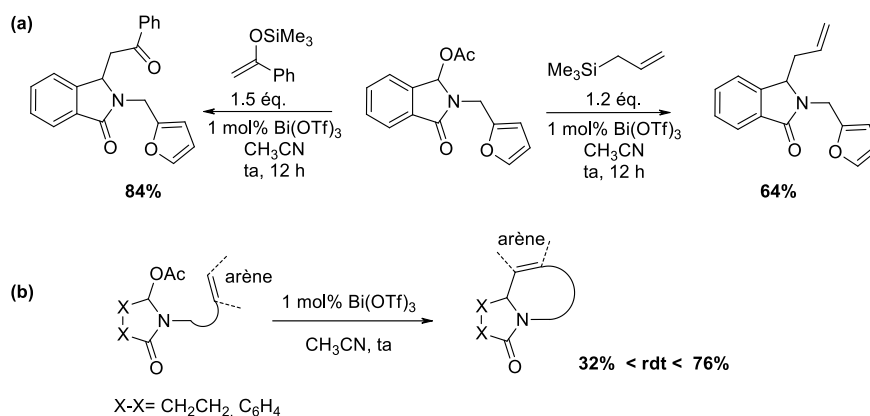


Schéma I.13. Réactions d'α-amidoalkylation catalysées par Bi(OTf)₃

Depuis 2002 notre équipe à l'URCOM (Unité de Recherche en Chimie Organique et Macromoléculaire de l'université du Havre)⁴⁸ s'est engagée dans un programme visant à améliorer les conditions d'obtention des ions *N*-acyliminiums, puis à appliquer les méthodologies développées à la synthèse rapide de molécules fonctionnalisées. Pour cela, notre groupe s'est intéressé à des catalyseurs, à la fois plus stables que TMSOTf⁴⁰⁻⁴² - car malgré sa forte efficacité catalytique dans des réactions d'α-amidoalkylations, ce dernier est difficile à manipuler et peu stable (facilement hydrolysable au contact de l'humidité de l'air) – et/ou à des catalyseurs pouvant offrir des vitesses de réaction supérieures à celle de Sc(OTf)₃.⁴⁴ Notre choix s'est d'abord porté sur l'utilisation de TIPSOTf^{48a,c} puis sur celui de TMSNTf₂.^{48b,c}

Nous avons dans un premier temps montré que le TIPSOTf,⁴⁹ un substitut beaucoup plus stable, et donc plus pratique d'emploi que TMSOTf, était à même de catalyser une large gamme de réactions d'α-amidoalkylations (Schéma I.14).^{48a,c} Notons que le TIPSOTf, grâce à sa stabilité, peut être employé avec la même efficacité sans dévaluation des résultats sur une période de temps étendue à plusieurs mois, ce que ne permettait pas l'utilisation du TMSOTf. Nos travaux complètent ainsi une brève contribution de Martin et coll. ayant trait à l'utilisation du TIPSOTf avec un succès modéré dans une réaction d'amidoalkylation vinylogue catalytique entre un dérivé 2-OTIPS d'un furane stériquement encombré et l'ester méthylique de la 2-méthoxy *N*-*tert*-butoxycarbonyl proline.⁴⁹

⁴⁸ (a) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825. (b) Othman, R. B.; Bousquet, T.; Othman, M.; Dalla V. *Org. Lett.* **2005**, *7*, 5335. (c) Tranchant M.-J.; Moine, C.; Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Tetrahedron Lett.* **2006**, *47*, 4477.

⁴⁹ (a) Martin, S. K.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299. (b) Martin, S. K.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

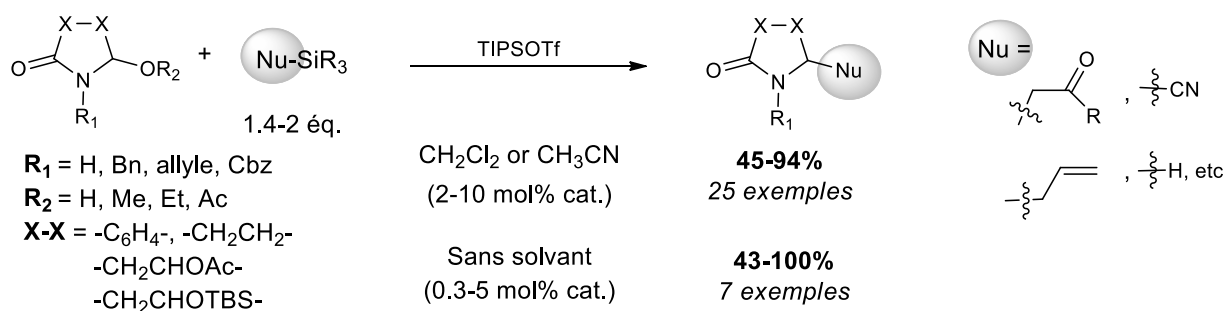


Schéma I.14. Réactions d' α -amidoalkylations catalysées par le TIPSOTf.

Plus récemment, sur la base de précédents bibliographiques associés à la réactivité unique du superacide triflimidique HNTf_2 [bis(trifluorométhanesulfonyl)imide] et de ses dérivés silylés R_3SiNTf_2 ,⁵⁰ nous avons pu démontrer que HNTf_2 était un pré-catalyseur d'une remarquable efficacité dans les réactions d' α -amidoalkylation.

En effet, les travaux du laboratoire ont mis en évidence la capacité de l'acide triflimidique HNTf_2 à catalyser les réactions d' α -amidoalkylations entre des nucléophiles silylés et des *N,O*-acétals cycliques.^{48b} Il est important de souligner que cette nouvelle méthode catalytique en chimie des ions *N*-acyliminiums présente de nombreux avantages, tels que la nette accélération des vitesses de réactions des éthers d'énol silylés par rapport aux réactions catalysées par les agents trialkylsilyl triflates usuels (**Schéma I.15.**),⁴⁸ ainsi que la possibilité d'effectuer ces réactions sans solvant, rendant ainsi possible l'utilisation d'une très faible charge de catalyseur (seulement 0.3 mol% de HNTf_2 dans certains cas).^{48c} Ces réactions constituent les exemples les plus performants jamais décrits dans la littérature pour ce type de transformations.

⁵⁰ Les réactions catalysées par Tf_2NH : (a) Foropoulos, J. J.; Desmarteau, D. D.; *Inorg. Chem.* **1984**, *23*, 3720. Revue exhaustive sur les triflimidates métalliques: (b) Antoniotti, S.; Dalla, V.; Dunach, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7860. Références sélectionnées pour des transformations catalysées par HNTf_2 avec des nucléophiles silylés (génération *in situ* de l'espèce catalytique silylée R_3SiNTf_2): (c) Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497. (d) Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215. (e) Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561. (f) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851. (g) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219. (h) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45. (i) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668. (j) Boxer, M. B.; Yamamoto, H.; *J. Am. Chem. Soc.* **2006**, *128*, 48. (k) Takasa, K.; Nagao, S.; Ihara, M. *Adv. Synth. Catal.* **2006**, *348*, 2376. (l) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 375.

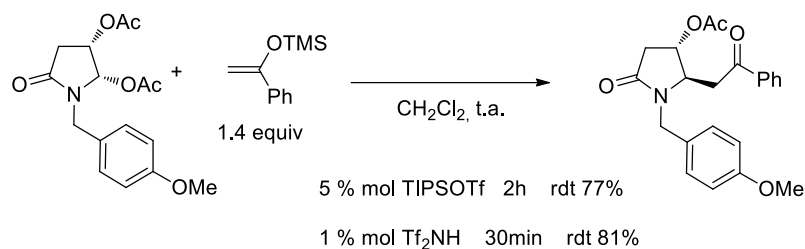


Schéma I.15. Comparaison de l'activité catalytique de Tf₂NH et TIPSOTf.

L'efficacité catalytique du système Tf₂NH/nucléophiles silylés (et aussi Tf₂NH/NuH) est telle qu'elle permet des réactions d' α -amidoalkylation de substrats *N,O*-acétaliques pourtant à priori désactivés stériquement et électroniquement par la présence de deux groupements électroattracteurs (*gem* diesters, *gem* ester/nitrile ou *gem* ester/cétone) adjacents au centre réactionnel (Schéma I. 16).⁵¹ Le succès de ces réactions serait en partie dû à la capacité du bras ester à venir délivrer de façon pseudo-intramoléculaire le catalyseur sur le motif *N,O*-acétalique et/ou à la propension de l'ester à venir stabiliser l'ion *N*-acyliminium en formation par participation anchimérique. Ce postulat est appuyé par l'excellent diastéréocontrôle obtenu à partir des substrats cyano esters, notamment dans les réactions intermoléculaires.

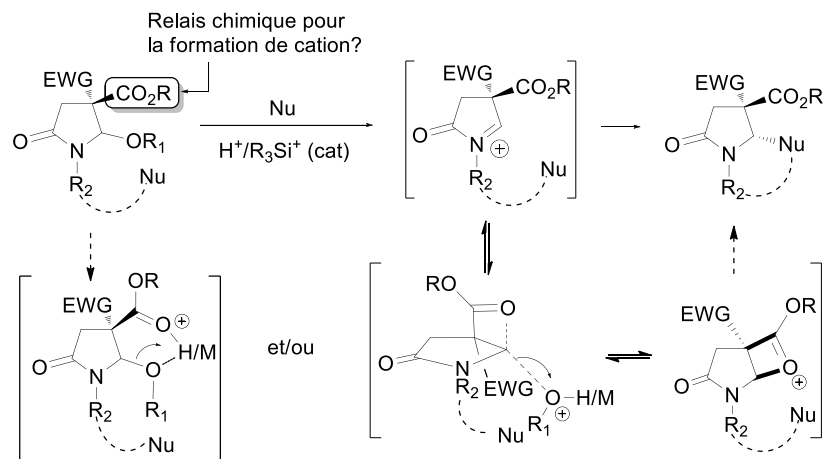
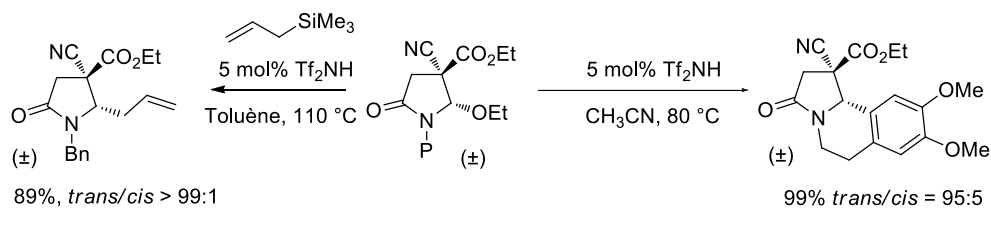


Schéma I.16. des réactions d' α -amidoalkylation catalysées par Tf₂NH.

Les divers processus discutés jusqu' alors ont été développés à partir des alcoxy et des acétoxy lactames. Bien que ces dérivés soient plus réactifs que les hydroxy parents dans les

⁵¹ Saber, M.; Comesse, S.; Daïch, A.; Dalla, V.; Netchitaïlo, P. *Synlett* **2011**, 2425.

réactions catalytiques, ils doivent d'une part être préparés, et d'autre part ils contribuent au rejet de sous produits plus lourds, nuisant ainsi aux critères d'économie d'étapes et d'atomes très prisés en synthèse organique moderne. Ainsi, le développement de processus catalytiques efficaces d' α -amidoalkylation à partir d'hydroxylactames constituerait une amélioration notable de cet axe de recherche.

Dans ce contexte, nous avons exploité la superacidité de Lewis des triflimidates métalliques, en particulier le triflimidate d'étain (IV) $\text{Sn}(\text{NTf}_2)_4$, pour développer des réactions d'amidoalkylation de substrats hémi *N,O*-acétaliques (*N*,*OH*). Ces travaux s'effectuent en collaboration avec nos collègues E. Duñach et S. Antoniotti de l'Université de Nice, qui ont développé des méthodes de synthèse efficaces de ces sels et ont démontré leur immense potentiel en catalyse électrophile.⁵²

Ainsi, l' α -amidoalkylation catalytique de plusieurs hydroxylactames a été réalisée avec une gamme assez large de nucléophiles (nucléophiles silylés, méthylène actifs (**Schéma I.17a.**), aromatiques enrichis et même cétones).⁵³ Le résultat le plus spectaculaire concerne l'alkylation directe jusqu'alors inédite des cétones; ce processus est très bénéfique, car il permet de s'affranchir de l'utilisation des éthers d'énol silylés qui étaient jusqu'alors les nucléophiles incontournables dans ce type de réactions acido-catalysées (**Schéma I.17b.**). La réaction s'effectuant directement à partir d'hydroxylactames, l'unique sous-produit libéré dans le milieu réactionnel est une simple molécule d'eau, faisant de cette transformation un processus extrêmement attractif.

⁵² (a) Favier, I.; Duñach, E. *Tetrahedron Lett.* **2003**, *44*, 2031; (b) Antoniotti, S.; Duñach, E. *Chem. Commun.* **2008**, 993; (c) Grau, F.; Heumann, A.; Duñach, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 7285; (d) Lemechko, P.; Grau, F.; Antoniotti, S.; Duñach, E. *Tetrahedron Lett.* **2007**, *48*, 5731; (e) Antoniotti, S.; Duñach, E. *Tetrahedron Lett.* **2009**, *50*, 2536; (f) Legrave, N.; Couhert, A.; Oliveira, S.; Desmurs, J.-R.; Duñach, E. *Eur. J. Org. Chem.* **2012**, 901.

⁵³ Othman, R. B.; Affani, R.; Tranchant, M. J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776.

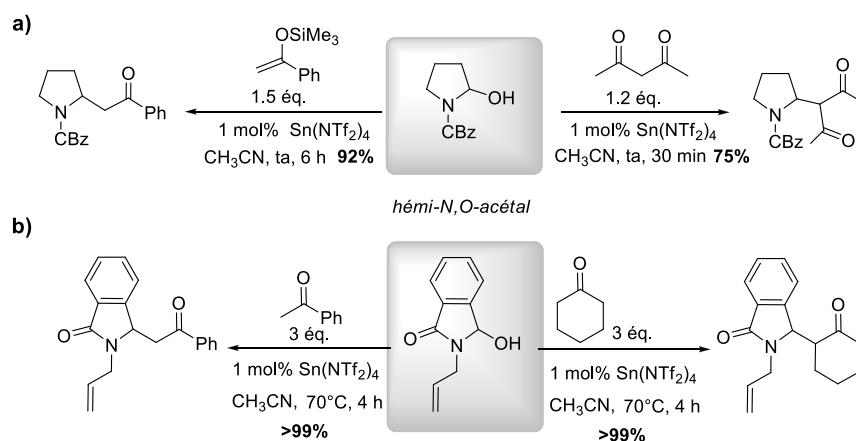


Schéma I.17. a) Réactions d' α -amidoalkylations catalysées par le $\text{Sn}(\text{NTf}_2)_4$ b) Réactions catalytiques d' α -amidoalkylation directe de cétones à l'aide de $\text{Sn}(\text{NTf}_2)_4$.

Il a par ailleurs été montré que l'acidité de type σ -Lewis de sels cationiques d'or (I) et (III) pouvait également être exploitée et permettre la génération d'ions *N*-acyliminiums en régime catalytique. Une méthode catalytique, générale et performante a été développée au cours de la thèse du docteur Liliana Boiaryna permettant de réaliser efficacement la substitution nucléophile de divers alcoxy- et acétoxy-lactames, précurseurs d'ions *N*-acyliminiums. La réaction s'est avérée compatible avec une large gamme de nucléophiles, incluant notamment l'allyltriméthylsilane, les éthers d'énols silylés, les arènes et les dérivés de méthylènes actifs. Celle-ci repose sur l'utilisation des triflates de l'or (I) et (III), formés *in situ* mais il a été montré que, dans certains cas, l'activation du sel d'or AuCl_3 par un groupement triflate n'est pas nécessaire pour générer les ions *N*-acyliminiums intermédiaires (Schéma I.18.).

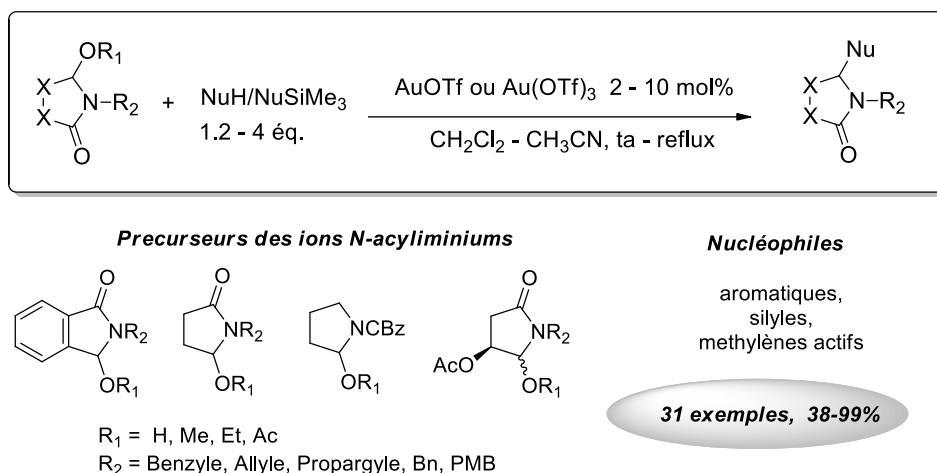


Schéma I.18. Réactions d' α -amidoalkylation catalysée par des sels d'or (I) et (III).

La possibilité d'effectuer une hydroarylation des substrats lactamiques équipé d'un bras propargyle sur l'azote par un nucléophile interne a également été étudiée. Les deux caractères carbophile et oxophile des catalyseurs à l'or ont été combinés dans un processus cascade α -amidoalkylation/hydroarylation intramoléculaires. Une seconde approche multicatalytique (acide de Brønsted – acide de Lewis) a ensuite été développée comme alternative pour pallier à certaines limites du système « tout or ». Ces séquences réactionnelles one-pot ont permis d'accéder de façon rapide et efficace à un large panel de composés polycycliques fusionnés à partir de substrats triviaux. (**Schéma I.19.**)

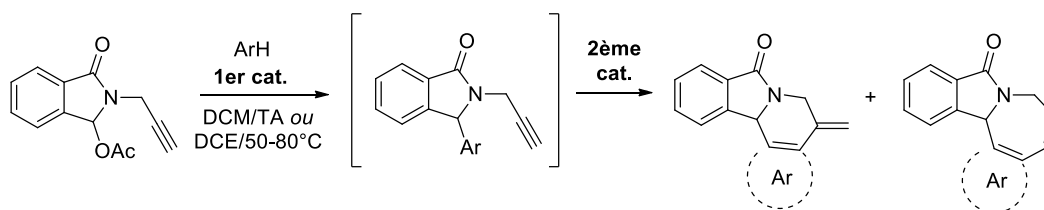


Schéma I.19. Nn processus cascade α -amidoalkylation/hydroarylation intramoléculaires.

Enfin, il est à noter que notre équipe a développé une *réaction d'amidoalkylation séquencée bicatalysée BB/AB (base de Brønsted/acide de Brønsted) inédite*, au cours de laquelle l'activation de l'hydroxy lactame, sous forme d'un groupement trichloroacétimide intermédiaire a été réalisée dans le même pot que l'étape d'alkylation acido-catalysée subséquente (**Schéma I. 20.**). Le docteur Alice Devineau⁵⁴ a montré que la quantité optimale de 1 mol% de DBU (base de Brønsted BB), nécessaire à l'étape de trichloroacétamidation, était compatible avec les 3 mol% d'acide de Brønsted (HA) requis pour l'étape suivante d'alkylation. L'originalité de ce processus bicatalytique repose essentiellement sur la particularité du groupement trichloroacétimide, qui possède une basicité intrinsèque lui permettant d'être activé en présence de catalyseurs doux tels que les acides phosphoriques $(RO)_2P(O)OH$ et dithiophosphoriques $(RO)_2P(S)SH$, ce qui pourrait être particulièrement déterminant en vue du développement d'une version énantiosélective de ces réactions à l'aide de ces acides chiraux.

⁵⁴ Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, J.; Rouden, J.; Dalla, V. *Adv. Synth. Catal.* **2010**, 352, 2881.

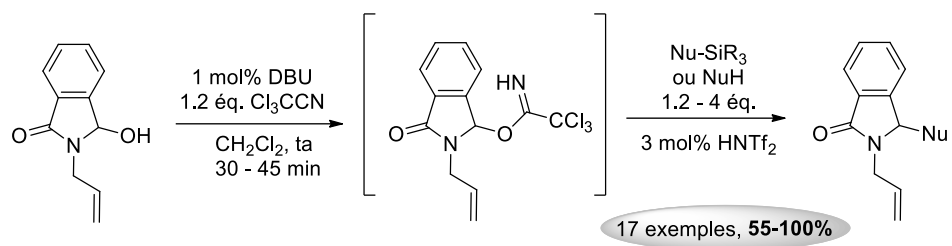


Schéma I.20. Réactions d' α -amidoalkylations séquencée bicatalysée BB/AB

CHAPTER II:
THE CYCLIZATION-FRAGMENTATION
REACTION

In the first part of the project, we envisioned exploiting the carbophilic Lewis acidity of gold(I) complexes for the development of a two-step cascade sequence in the context of *N*-acyliminium chemistry. Starting from readily available *N*-propargyl alkoxy lactams, we proposed to investigate a gold-catalyzed intramolecular carboalkoxylation/aza-Ferrier-Petasis⁵⁵ rearrangement sequence which would give direct access to cyclic enol ether of type **II**.

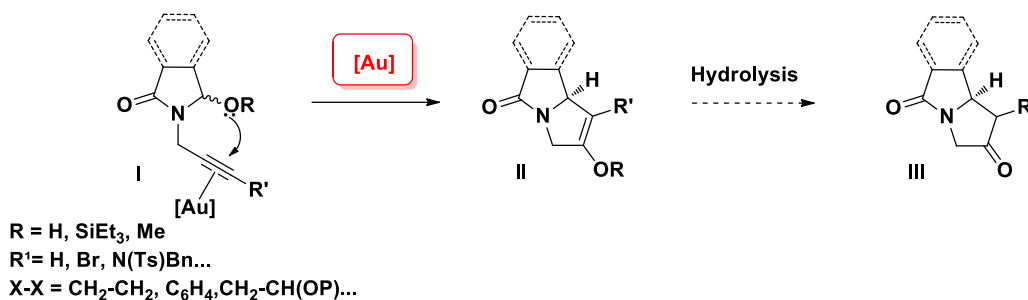


Fig. II.1.

In addition to an obvious methodological interest, the rapid synthesis of such heterocyclic compounds would be of great interest since they are often key synthetic intermediates of many natural products. (**Fig II.1.**)⁵⁶ For example, the components shown below play important role such as in antitumor therapy (**Fig II.2.**).

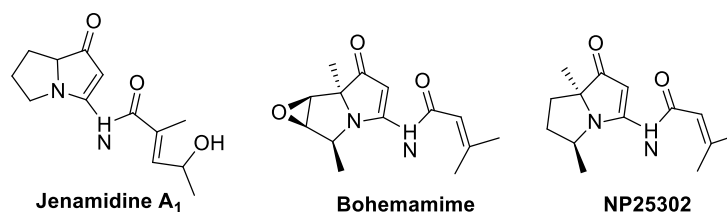


Fig II.2.

As illustrative examples, Jenamidine A₁ isolated from *Streptomyces sp.* and potent inhibitor of chronic myeloid leukemia cell line K-562 (GI₅₀ of 1.9 μL/mL), Bohemamime and NP 25302 are bioactive molecules within ‘striking distance’ of compound **II**.⁵⁷

⁵⁵ (a) Tayama, E.; Otoyama, S.; Isaka, W. *Chem. Commun.* **2008**, 4216. (b) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354.

⁵⁶(a) Michael, P. *Nat. Prod. Rep.* **2007**, *24*, 191. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773.

⁵⁷(a) Bugni, T. S.; Woolery, M.; Kauffman, Ch. A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2006**, *69*, 1626. (b) Snider, B. B.; Gao, W. *Org. Lett.*, **2005**, *20*, 4419. (c) Duvall, J. R.; Wu, F.; Snider, B. B. *J. Org. Chem.* **2006**, *71*, 8579. (d) Doyle, T. W.; Nettleton, D. E.; Balitz, D. M.; Moseley, J. E.; Grulich, R. E. *J. Org. Chem.* **1980**, *45*, 1324.

II. 1. GOLD-CATALYZED CYCLIZATION-FRAGMENTATION REACTIONS

Over the past few years, transition metal-catalyzed reactions have gained great importance as synthetic methods in organic chemistry. In this context, metal-catalyzed electrophilic activations of unsaturated carbon-carbon bonds have been recognized as particularly useful processes to access cyclic architectures. Among the transition metals that are commonly employed in these transformations (i.e. Cu, Ag, Pd, Pt and Au), platinum has been used most extensively but gold has proven to be particularly suitable given the strong π Lewis acidic property of cationic gold species and their ability to activate alkynes, allenes or alkenes towards the attack of many nucleophiles in mild conditions. Consequently, a plethora of gold-catalyzed C-X (X=C, N, O, S) bond formations has been well documented in recent years.⁵⁸

Besides, domino processes where multiple events are combined in a single transformation have been considered an excellent way to introduce molecular complexity into organic structures with high chemical efficiency. More specifically, metal-catalyzed domino reactions initiated by the intramolecular addition of a heteronucleophile to alkynes offer the unique possibility of installing various substitution patterns in cyclic compounds. The use of such transformations has effectively provided access to a number of heterocycles such as benzofurans,⁵⁹ indoles,⁶⁰ benzothiophenes,⁶¹ furans,⁶² pyrans,⁶³ pyrrolidine,⁶⁴ and isoxazoles.⁶⁵

⁵⁸ (a) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885 (b) Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem., Int. Ed.* **2006**, *45*, 7896; (d) Fürstner, A.; Davies, P. W. *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem., Int. Ed.* **2007**, *46*, 3410; (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180;

⁵⁹ (a) Manarin, F.; Roehr, J. A.; Gay, R. M.; Brandao, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153. (b) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024.

⁶⁰ (a) Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4906. (b) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346. (c) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284. (d) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881. (e) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546.

⁶¹ (a) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649. (b) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

⁶² (a) Cheong, J. Y.; Im, D.; Lee, M.; Lim, W.; Rhee, Y. H. *J. Org. Chem.* **2011**, *76*, 324. (b) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2009**, *351*, 1089. (c) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905. (d) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863.

⁶³ (a) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972. (b) Komeyama, K.; Takahashi, K.; Takai, K. *Org. Lett.* **2008**, *10*, 5119.

⁶⁴ Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.

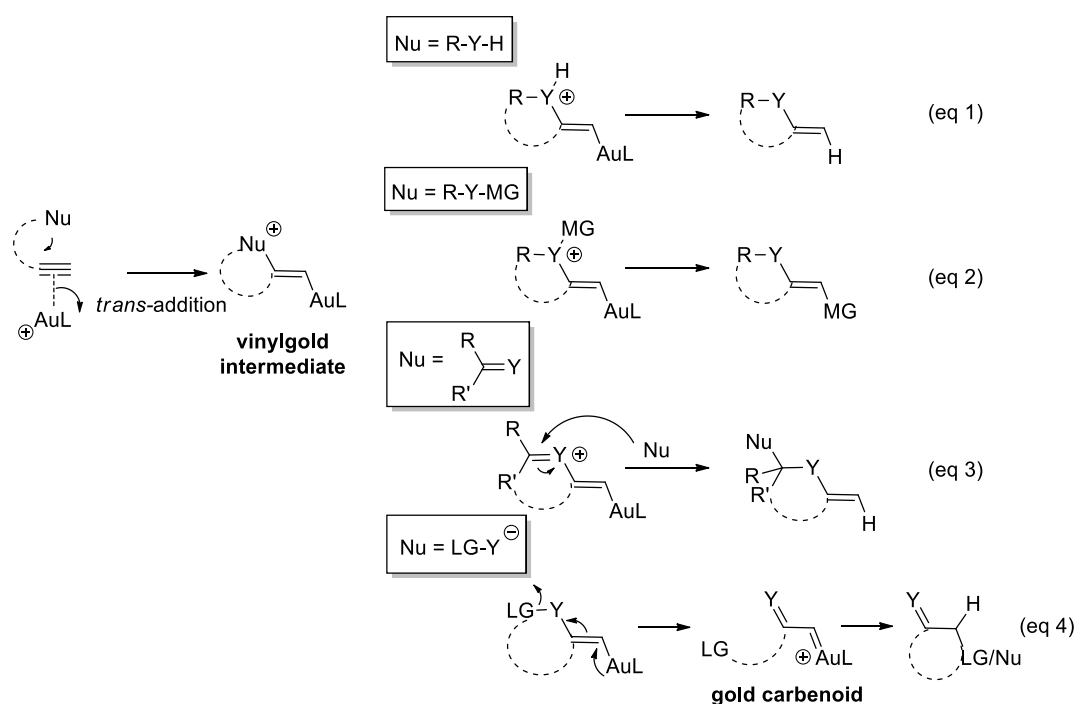
⁶⁵ Nakamura, I.; Okamoto, M.; Terada, M. *Org. Lett.* **2010**, *12*, 2453.

CHAPTER II: The cyclization-fragmentation reaction

In the specific case of gold catalysis, a large number of these reactions imply a catalytic cycle ending by trapping of a vinyl-gold intermediate with a proton, so-called protodemetalation (**Scheme II.1.**, eq 1). Typically an intramolecular C-Y bond formation followed by protodeauration leads to an Y-containing heterocycle. One alternative approach consists of replacing the proton on the heteroatom (Y) responsible for the cyclization process by another electrophilic group (MG = E). The addition of this aprotic nucleophile on a gold-coordinated alkyne leads to an increase in positive charge on the nucleophile. Fragmentation of the Y-MG single bond generates a reactive electrophile (MG⁺) which can be trapped by the vinylgold moiety (eq 2.). Then the reaction globally proceeds through a [1,3] shift of the migrating group and when realizing the intramolecular addition of an alkoxy group (MG = R), a carbon transfer during the catalytic heterocyclization occurs.

When Y is sp² hybridized, upon the addition to gold-activated alkynes, the resulting Y cation (as an electrophile) then triggers the addition of another internal or external nucleophile (eq 3.).

The use of dipolar nucleophiles to gold-coordinated alkynes must be considered separately since it results in a singular reactivity. Indeed, it is well-known that gold can act as both a π -acid and as an electron-donor. Indeed the addition of reacting ylide-like nucleophiles lead to the formation of vinyl gold intermediates that subsequently evolve to electrophilic gold-carbenoids being often trapped intramolecularly (eq 4).



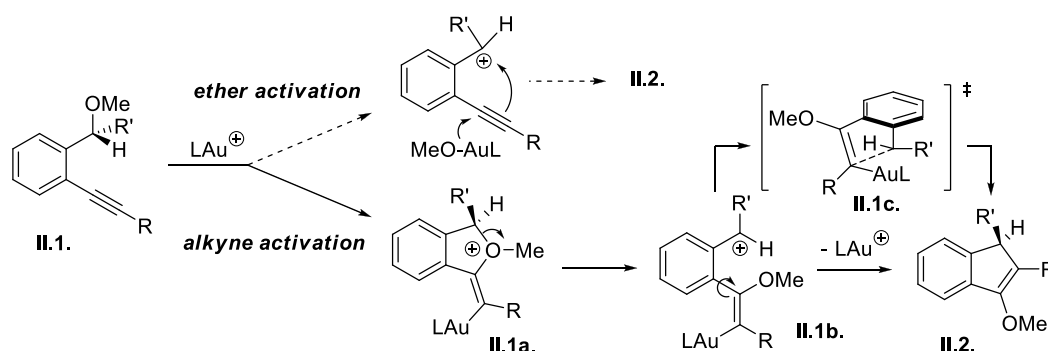
Scheme II.1. Electrophilic transfers in heterocyclization

We are aware that these types of cyclization-fragmentation sequences were exploited in many occasions with a wide scope of nucleophiles but, given our objectives, only cascade reactions involving an initial nucleophilic addition of oxygenated functionalities will be considered in this chapter.

II.1.1. Addition of alkoxygroups

As shown on the general scheme above, the carboalkoxylation (addition of ethers) to gold-activated alkynes, followed by carbodemetalation would allow a carbon-transfer during the catalytic heterocyclization. Toste and Dubé first investigated this type of strategy for the synthesis of indenyl ketals, indenyl ethers and cycloalkene ethers *via* a gold(I)-catalyzed intramolecular carboalkoxylation of alkynes (**Scheme II.2.**)⁶⁶ The mechanistic rationale, which was supported by a double label crossover experiment, involves an alkyne activation followed by C-O bond cleavage, instead of ionization of the benzylic ether (ether activation). Trapping of the resulting carbocation **1b** by the vinylgold intermediate finally lead to the indene formation.

Interestingly, this pathway allows for the central chirality of the substrate to be retained in the axial chirality of the carbocation intermediate (memory effect). The intramolecular addition of the vinylgold(I) moiety to the carbocation, *via* transition state **1c**, next transfers the axial chirality to the C-C bond central chirality of the product indene with overall inversion of the stereocenter.



Scheme II.2. A gold(I)-catalyzed intramolecular carboalkoxylation of alkynes.

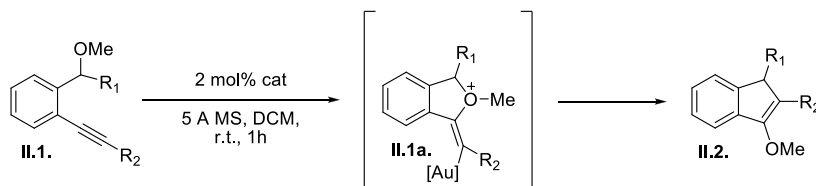
A set of representative results was presented in **Table II.1**. It was found that a more electrophilic catalyst such as $(p\text{-CF}_3\text{Ph})_3\text{PAuBF}_4$ was more efficient than Ph_3PAuCl or $\text{Ph}_3\text{PAuBF}_4$ (Entries 3 *versus* 1-2). The reaction was also found to proceed in high yields with

⁶⁶ Toste, F. D.; Dube, P. *J. Am. Chem. Soc.* **2006**, *128*, 12062.

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different substituents on the alkyne moiety ($R_2 =$ alkyl, phenyl, and esters, entries 4-8). Moreover, as predicted by the mechanism, the presence of electron-withdrawing groups on the phenyl rings of R_1 , decreased the reaction rates while electron-donating substituents improved the conversion rates and yields (entries 6 vs 7). In addition, allylic ethers were shown to accommodate this gold(I)-catalyzed cyclization (entry 8).

Table II.1. Scope of the Gold(I)-Catalyzed Carboalkoxylation.



Entry	Cat	R ₁	R ₂	Yield [%]	Entry	Cat	R ₁	R ₂	Yield [%]
1.	Ph ₃ PAuBF ₄	Ph	Me	32	5.	(p-CF ₃ Ph) ₃ PAuBF ₄	Ph	Ph	95
2.	Ph ₃ PAuCl	Ph	Me	NR	6.	(p-CF ₃ Ph) ₃ PAuBF ₄	3-CF ₃ Ph	CO ₂ Me	41 ^{a)}
3.	(p-CF ₃ Ph) ₃ PAuBF ₄	Ph	Me	81	7.	(p-CF ₃ Ph) ₃ PAuBF ₄	4-MeOPh	CO ₂ Me	99
4.	(p-CF ₃ Ph) ₃ PAuBF ₄	Ph	nBu	96	8.	(p-CF ₃ Ph) ₃ PAuBF ₄	allyl	Ph	92

a) Reaction time = 24h.

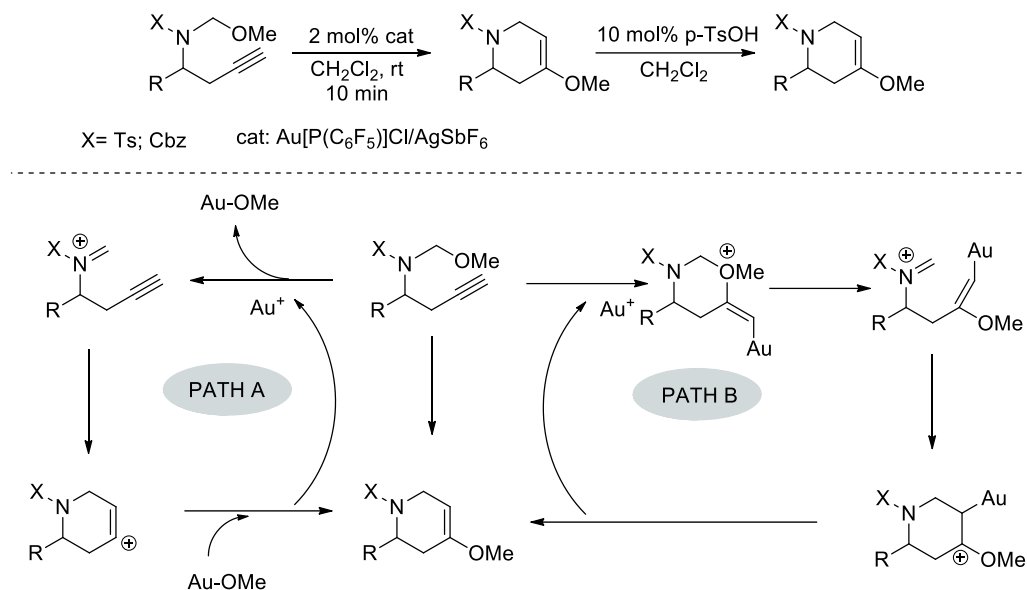
Further theoretical investigations were recently run by de Lera and co-workers, who not only characterized the proposed mechanism but also described in detail the memory of chirality that makes the process enantioselective.⁶⁷ It is worth mentioning here that this mechanism is a good example of a commonly found phenomenon in gold-catalyzed transformations: the low barriers found for the chemical steps in these reactions (consistent with mild reaction conditions) result in an uncommon importance of the barriers corresponding to conformational changes (single bond rotations, etc...) on the intermediates. The changes of conformation can then become rate-limiting steps, thus preventing the conformational scrambling that would be expected in more conventional mechanisms.

Since Toste's seminal report, several groups implemented gold-catalyzed intramolecular carboalkoxylation-carbodemetalation sequences involving ethers as oxygenated nucleophiles. An example of particular significance to us was reported recently by Rhee and co-workers

⁶⁷ Faza, O.N. ; Lopez, C.S. ; de Lera, A.R. *J. Org. Chem.* **2011**, 76, 3791.

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displaying a method for the synthesis of six-membered cyclic enol ethers from propargylamine-derived *N,O*-acetals.⁶⁸



Scheme II.3. Cycloisomerization of *N,O*-acetals generated from homopropargylic amines

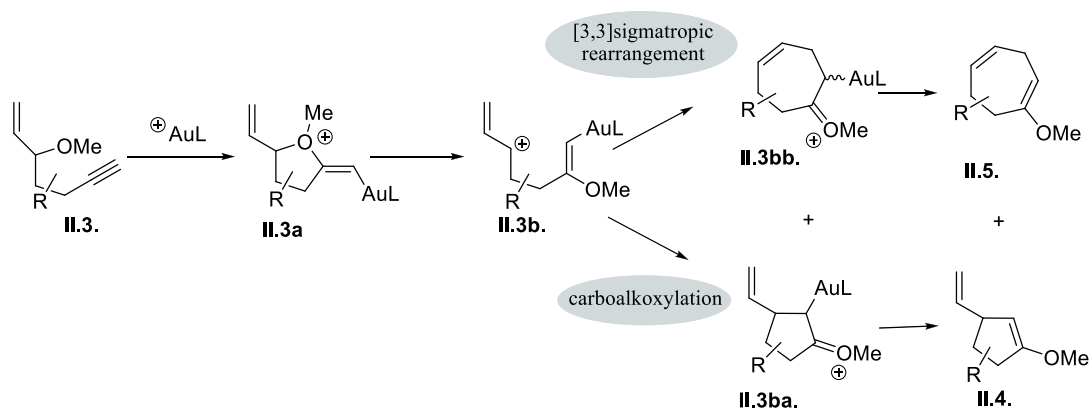
During the course of their investigation, Rhee and co-workers have demonstrated the positive influence of using highly electrophilic phosphines in the cycloisomerization of mixed acetals which are generated from *N*-tosyl or *N*-Cbz-homopropargylic amines. Only 2 mol% of a strong electrophilic (C₆F₅)₃PAuSbF₆ is needed to form the corresponding cycloadducts in good yields. Notably, no epimerization was noted for substrates bearing alkyl groups at the propargylic position. Those results proved that the reaction *via* Pathway B is faster than the competing formation of *N*-acyliminium ion (Path A). (**Scheme II.3.**) This work is of particular importance since it shows new opportunities of gold complexes and remarkable chemoselectivity for the cycloisomerization reaction which allows the catalyst to synthesize bioactive piperidine frameworks.⁶⁸ The scope of this reaction was further extended to analogous *N,S*-mixed acetals.⁶⁹

While the transition-metal-catalyzed cycloisomerization of 1,6-enynes is often proposed to occur *via* addition of internal olefins to the metal-activated alkynes, Rhee and co-workers have demonstrated that 3-alkoxy-1,6-enynes could offer an alternative mode of reaction as depicted on scheme II.4.⁷⁰

⁶⁸ Kim, Ch.; Bae, H.J.; Lee, J.H.; Jeong, W.; Kim, H.; Sampath, V.; Rhee, Y.H. *J. Am. Chem. Soc.* **2009**, *131*, 14660.

⁶⁹ Kim, Ch.; Lim, W.; Rhee, Y.H. *Bull. Korean. Chem. Soc.* **2010**, *31*, 1465.

⁷⁰ (a) Bae, H.J.; Baskar, B.; An, S.E.; Cheong, J.Y.; Thangadurai, D.T.; Hwang, I.-Ch.; Rhee, Y.H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2263.



Scheme II.4. Possible pathways for the gold-catalyzed cyclization reaction

Two possible pathways for the metal-catalyzed cyclization were considered. (**Scheme II.4.**) The oxygen atom can act as a nucleophile in the addition to the metal-activated alkynes and consequently cycloheptenyl cation can be generated *via* [3,3]-sigmatropic rearrangement. A competing pathway, that is a metal-catalyzed carboalkoxylation reaction, would be also possible. While this second alternative pathway would produce a mixture of cycloheptadiene **II.5.** and cyclopentene **II.4.**, the selective formation of **II.5.** in the presence of $(\text{C}_6\text{F}_5)_3\text{PAuSbF}_6$ rather supports a sigmatropic pathway. Further experiments next confirmed the concerted nature of the oxonium ion intermediate **II.3a** rearrangement.

This [3,3]-sigmatropic rearrangement could be performed under very mild conditions by using low catalyst loadings (*e.g.* 2mol% $(p\text{-CF}_3\text{-C}_6\text{H}_4)_3\text{PAuNTf}_2$ in CH_2Cl_2 at r.t. over 10 min⁷¹). Besides, since the enol ether moiety obtained at the end of the reaction can be chemoselectively transformed into a variety of different functional groups,⁷¹ many useful applications of this transformation could be conceivable. The synthetic potential of this gold-catalyzed cycloisomerization of 3-methoxy-1,6-enynes methodology was next demonstrated by the same authors with the formal total synthesis of (\pm)-clavukerin A, a member of marine trinorguaiane sesquiterpene natural products incorporating a cycloheptane ring.⁷²

Besides the intramolecular addition of alkyl ethers, the same authors have shown that similar transformations could efficiently use 3-siloxy-1,6-enynes **II.6.** as precursors of 4-cycloheptenones **II.7.** through a tandem siloxycyclization/sigmatropic rearrangement.⁷³

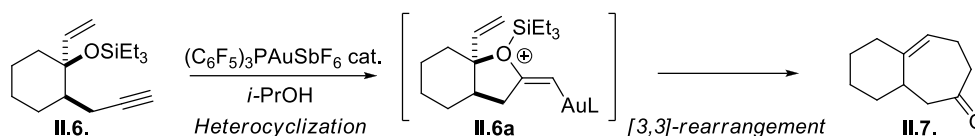
⁷¹ Florin M. Istrate and Fabien L. Gagosz, *J. Org. Chem.* **2008**, *73*, 730.

⁷² Cheong, J. Y.; Rhee, Y. H. *Beilstein J. Org. Chem.* **2011**, *7*, 740.

⁷³ Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F. *Org. Lett.* **2008**, *110*, 2605.

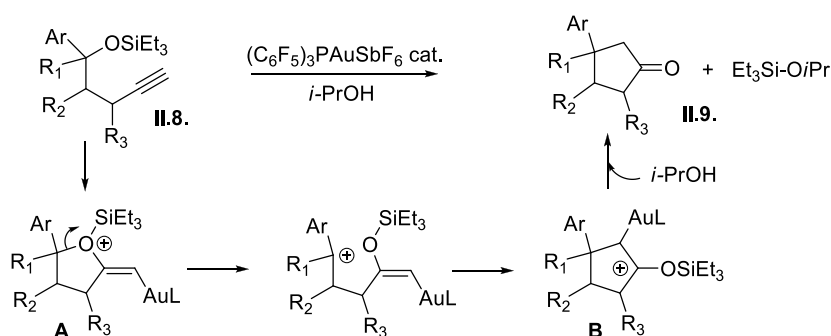
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(Scheme II.5.) A remarkable feature of this reaction is that even poorly reactive *O*-silyl ethers can add efficiently to the alkynes in the presence of cationic gold(I) complexes.



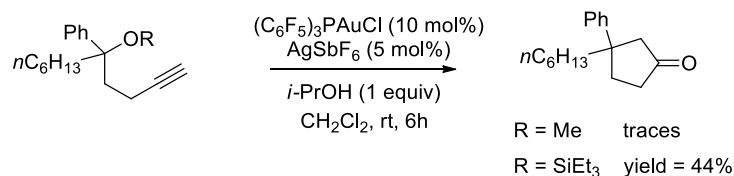
Scheme II.5. A tantem siloxycyclization/sigmatropic rearrangement catalyzed by gold (I) complex

Next, the efficiency of 5-siloxypent-3-en-1-yne gold-catalyzed cyclization-fragmentation to form substituted 2-cyclopentenones **II.9** was demonstrated.⁷⁴ (Scheme II.6.)



Scheme II.6. The gold-catalyzed cyclization-fragmentation of substrate **II.8**.

Interestingly, in the course of their investigation, the authors established the relative reactivity of a methoxypentyne and the related siloxypentyne. Contrary to their expectation, with the methoxy group being more nucleophilic than the triethylsiloxy group, a complete lack of reactivity was observed with the methoxypentyne substrate in the presence of 10 mol% of $(\text{C}_6\text{F}_5)_3\text{PAuSbF}_6$, while the silylated substrate provided the corresponding cyclopentanone in 44% yield. (Scheme II.7.) This result strongly suggests that the efficiency depends mainly upon the cyclisation of intermediate **B** rather than the initial formation of intermediate **A**.

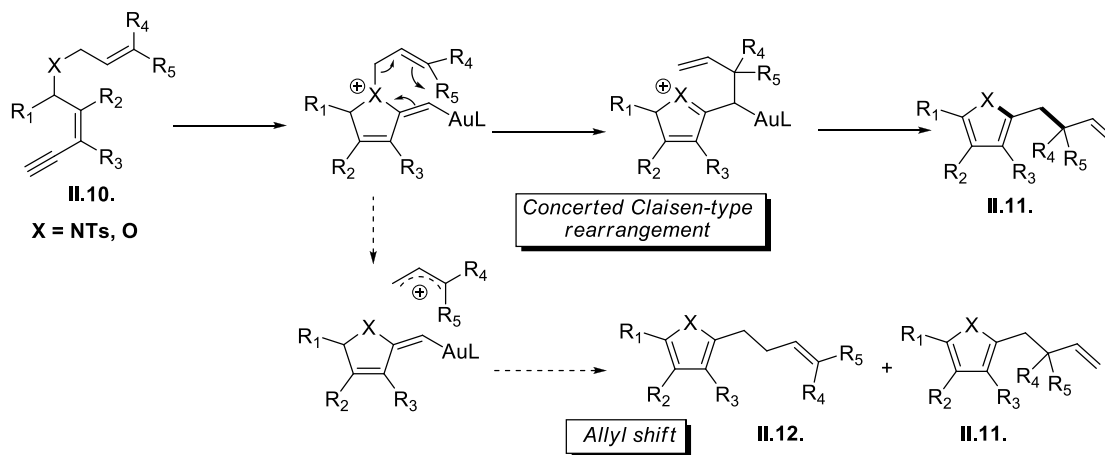


Scheme II.7. The cyclization-fragmentation reaction catalyzed by $(\text{C}_6\text{F}_5)_3\text{AuSbF}_6$.

⁷⁴ An, S. E.; Jeong, J.; Baskar, B.; Lee, J.; Seo, J.; Rhee, Y. H. *Chem. Eur. J.* **2009**, *15*, 11837.

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Reactions involving an allyl migrating group have also been studied using alkynyl allyl ethers as starting materials. In the course of their work on the development of gold-catalyzed transformations, Gagosz and co-workers recently found that a series of ynenyl allyl tosylamides (X = NTs) could be converted under mild experimental conditions into functionalized pyrroles in the presence of a gold(I) catalyst.⁷⁵ The authors next expanded their methodology to the synthesis of polysubstituted furans from ynenyl allyl ethers.⁷⁶ In contrast to Fürstner's observations for the Pt-catalyzed rearrangement of allyl pent-4-ynyl ethers,⁷⁷ the results obtained strongly suggested that no allyl cation was formed during the reaction. Indeed, the substitution pattern of the products obtained point toward the involvement of a more concerted (aza)-Claisen-type rearrangement and tend to exclude the possibility of a simple X to C allyl shift (**Scheme II.8**).



Scheme II.8. Gold-catalyzed transformation of ynenyl allyl substrates **II.10**.

As shown in the aforementioned examples, the use of a highly electrophilic gold complex was required for good efficiency. Using 2 mol% of (*p*-CF₃-C₆H₄)₃PAuNTf₂ allowed the fast formation of a number of polysubstituted furans under mild conditions (10 min, CH₂Cl₂, rt).

Similarly, the Au(I)-catalyzed reactions of 5-allyloxy-1-ynes **II.13** gave various γ -hydroxyketones **II.16** via a hydration-terminated domino sequence involving sigmatropic allyl migration as the key event.⁷⁸

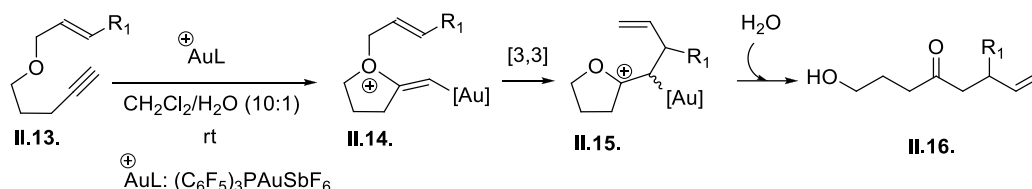
⁷⁵ Istrate, F.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.

⁷⁶ Istrate, F.; Gagosz, F. *Beilstein J. Org. Chem.* **2011**, *7*, 878.

⁷⁷ (a) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863; (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785.

⁷⁸ Cheong, J.Y.; Im, D.; Lee, M.; Lim, W.; Rhee, Y.H. *J. Org. Chem.* **2011**, *76*, 324.

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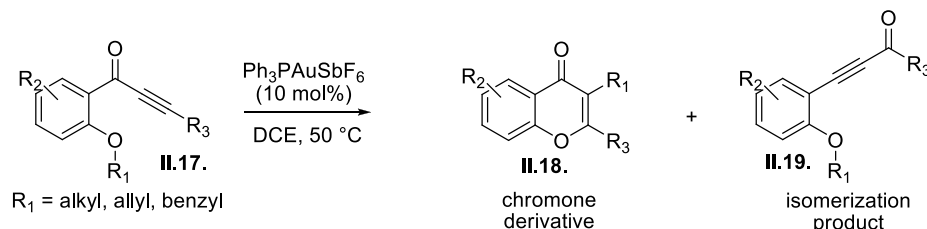


Scheme II.9. Mechanistic consideration for the gold(I) catalyzed synthesis of γ -hydroxyketones.

The mechanistic route would imply formation of an oxonium intermediate **II.14**, which rearranged and after direct hydration of the oxocarbenium ion **II.15**, would give the cycloisomerization product **II.16**. (**Scheme II.9**.)

The direct synthesis of substituted isoxazoles through gold-catalyzed domino reaction of alkynyl oxime ethers was also found to be feasible using a similar strategy.⁷⁹

The application to the synthesis of 2-chromone derivatives was also studied by Gouault *et al.* starting from alkoxyphenylpropynones **II.17**. (**Scheme II.10**.) Depending on the nature of the alkoxy groups, especially with alkyl and allyl ethers, a competing isomerization of the starting materials was observed impairing the chromone formation. Benzylalkoxy groups were found to be the most suited to the requisite intramolecular carboalkoxylation/carbodemetalation cascade albeit with limited reactivities.⁸⁰



Scheme II.10. The gold-catalyzed synthesis of chromone derivatives.

Acetals were also found to be effective oxygenated nucleophiles that can be involved in similar cascade events. As a demonstration, Rhee and co-workers developed a gold-catalyzed synthesis of highly substituted tetrahydropyran-4-ones **II.21**, using a cycloisomerization of 4-(alkoxyalkyl)oxy-1-yne **II.20** as the key transformation.⁸¹ (**Scheme II.11**.) In this sequence, the initial alkoxy cyclization, followed by cleavage of the C-O bond generates an oxocarbenium ion intermediate being trapped intramolecularly by the resulting vinylgold intermediate, the global reaction thus being similar to a formal Petasis-Ferrier rearrangement.

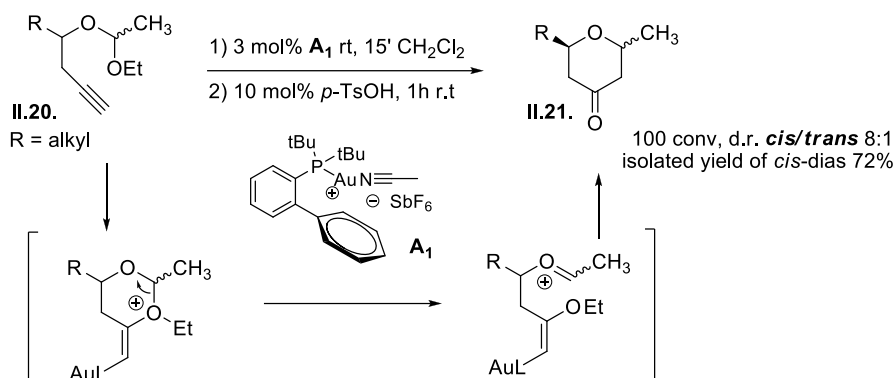
⁷⁹ Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2794.

⁸⁰ Renault, J.; Qian, Z.; Uriac, P.; Gouault, N. *Tetrahedron Lett.* **2011**, *52*, 2476.

⁸¹ Bae, H.J.; Jeong, W.; Lee, J.H.; Rhee, Y.H. *Chem. Eur. J.* **2011**, *17*, 1433.

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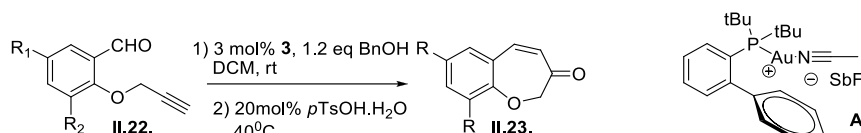
In this reaction, the commercially available catalyst **A1** bearing a bulky phosphine ligand was found to give the optimal results in terms of isolated yields and diastereoselectivity. (Scheme II.11.)



Scheme II.11. Gold(I)-catalyzed cyclization of 4-(alkoxyalkyl)oxy-1-yne

At the exact same time, Chan *et al.* exploited a comparable strategy making use of *O*-propargylated salicylaldehydes for the construction of benzo[*b*]oxepin-3(2*H*)-ones.⁸² The cationic gold catalyst **A1** was shown to effect the tandem intramolecular heterocyclization/Petasis–Ferrier rearrangement of 2-(prop-2-ynoxy)benzaldehydes **II.22**, in the presence of benzylic alcohol.

Table II.2. Intramolecular heterocyclization/Petasis-Ferrier rearrangement



Entry	R ₁	R ₂	Yield [%]
1.	I	I	93
2.	Cl	Cl	98
3.	F	F	88
4.	NO ₂	NO ₂	99

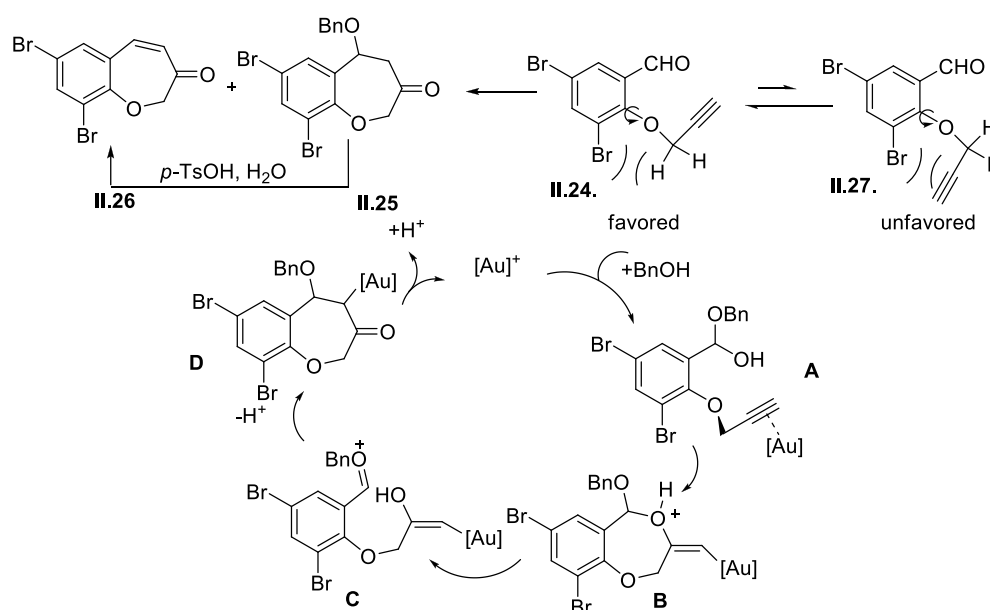
Entry	R ₁	R ₂	Yield [%]
5.	H	F	61
6.	<i>t</i> Bu	<i>t</i> Bu	66
7.	H	<i>t</i> Bu	70
8.	H	OMe	53

A study aiming at delineating the influence of a substituent at the ortho position to the ethereal moiety on the salicylaldehyde demonstrated that both the electronic and steric nature of the substrate plays a decisive role on the reactivity. Starting materials containing an electron-withdrawing group (Table II.2, Entries 1-4), require shorter reaction times and afford higher product yields than their counterparts with an electron-donating group at the same position (Table II.2, Entries 5-8). In addition, the presence and the size of a substituent

⁸² Sze, E.M.L.; Rao, W.; Koh, M. J.; Chan, P.W.H. *Chem. Eur. J.* **2011**, *17*, 1437.

(R₂) at the ortho position of the propargylic ether was found to contribute to enhance the reactivity. The author surmised this positive effect could be due to a shift of the conformational equilibrium towards the conformation of the substrate where unfavorable steric interactions between the alkyne and the bulky ortho group are being kept to a minimum.

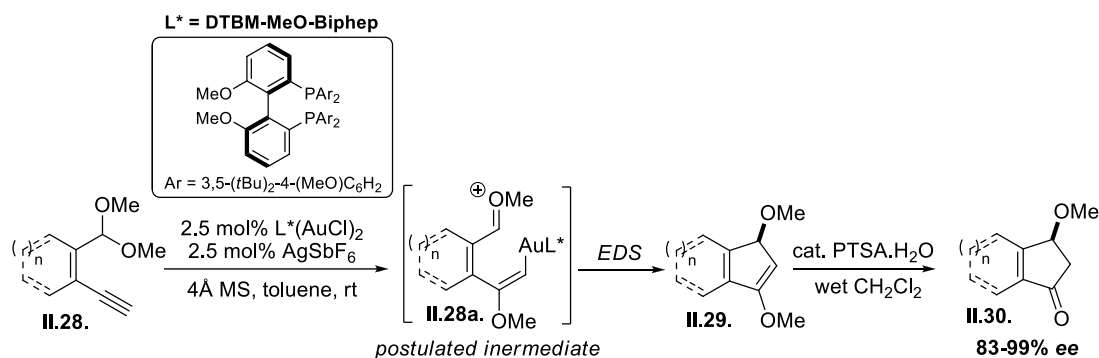
While a mechanism starting by the intramolecular addition of the carbonyl group on the activated alkyne was first envisioned, complementary experiments as well as the required use of 1 equivalent of BnOH prompted the authors to propose a revised mechanism. This would (**Scheme II.12.**) include formation of the hemiacetal **A** by addition of BnOH on the carbonyl moiety. Activation of the alkyne by the cationic gold catalyst would then trigger 7-*exo*-dig intramolecular cyclization step and formation of the benzo[*e*][1,4]dioxepine-substituted vinyl gold species **B**. Subsequent Petasis-Ferrier rearrangement involving cycloreversion to give the enolic gold adduct **C** followed by intramolecular cyclization would provide the aurated benzo[*b*]oxepin-3(2*H*)-one complex **D**. A final debenzoylative deauration or protodeauration followed by debenzoylation would then deliver the product. (**Scheme II.12.**)



Scheme II.12. Proposed mechanism for the heterocyclization/Petasis-Ferrier rearrangement

Toste very recently reported the first gold-catalyzed enantioselective carboalkoxylation of alkynyl acetals **II.28.**, including phenyl acetylene and vinyl acetylene derivatives, which allowed a variety of highly enantioenriched 3-methoxyindanones and cyclopentenones to be prepared.⁸³ (**Scheme II.13.**)

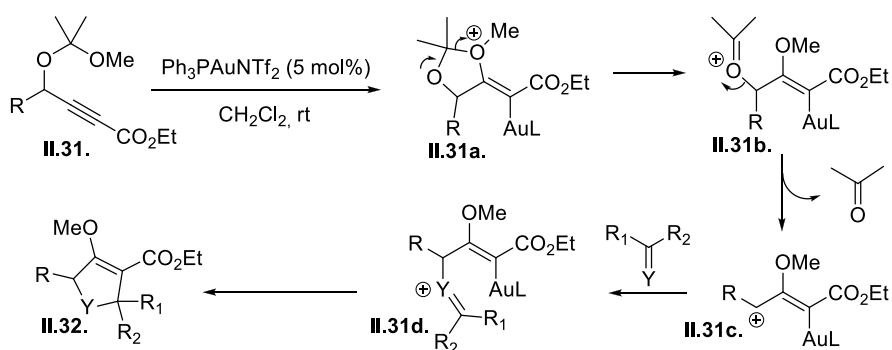
⁸³ Zi, W. ; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 12600.



Scheme II.13. The gold-catalyzed enantioselective carboalkoxylation of alkyne acetals **II.28**

Mechanistic studies suggested that a vinylgold species and a prochiral oxocarbenium ion are involved in the enantioselectivity-determining cyclization (EDS). This work thus constitutes one of the rare example of enantioselective carbon-carbon bond formation from this type of organometallic intermediate.

A distinct migration-fragmentation sequence of propargyl ketal substrates **II.31**, was described in 2008 by Zhang and co-workers in the context of gold-catalyzed cycloadditions development. Their methodology allowed the formation of Au-containing 1,3 dipoles from ketal esters. These latter were shown to undergo [3+2] cycloadditions with various enones, enals, electron-rich aromatic aldehydes leading to the rapid formation of highly functionalized 2,5-dihydrofurans and cyclopentenes with good efficiencies.⁸⁴



Scheme II.14. The gold-catalyzed migration-fragmentation sequence of substrate **II.31**.

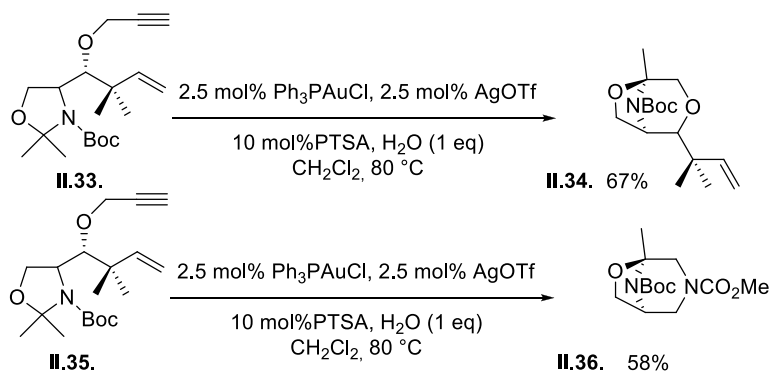
After intramolecular addition of the acetal functional group on the activated alkyne, fragmentation results in a migrated alkoxy group and acetone behaving as a good leaving group. Exchange of acetone with dipolarophiles of different types (mainly enones, enals and electron-rich aromatic aldehydes) next likely occurs via 1,3-dipole intermediate **II.31d**. Final

⁸⁴ Zhang , G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598.

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intramolecular addition of the vinylgold moiety on the electrophilic center finally yields the corresponding 2,5-dihydrofurans **II.32**. Sterics but also electronic considerations were postulated to rationalize the selective formation of the observed products. (**Scheme II.14**.)

Noteworthy, the use of mixed *N,O*-acetals was also successfully used in such transformations as shown by the methodology developed by Alcaide's research group in 2011. The synthesis of azaoxa skeletons was realized through a gold(I)-catalyzed direct bis-heterocyclization of Garner's aldehyde-derived alkynes.⁸⁵ This transformation was found to be efficiently catalyzed by a mixture of $\text{Ph}_3\text{PAuCl}/\text{AgOTf}$ 2.5 mol% in the presence of water. Interestingly, an even higher reactivity was observed when adding 10 mol % of a Brønsted acid (PTSA) which presumably facilitates the demetalation step (**Scheme II.15**).



Scheme II.15. Gold(I)-catalyzed reaction of alkyloxazolidines

Interestingly, this reaction was shown to display a broad substrate scope. In addition, when coupled with one-pot intramolecular alkylation reactions, this chemistry also provides a rapid access to quinolizidines and indolizidines.

As previously shown, in many of the previously presented examples, the *in situ* generated vinylgold intermediate is intramolecularly trapped by the migrating group or an internal electrophilic center. Hotha and co-workers postulated that the expulsion of the vinyl-Au intermediate from a pyranosyl ring could occur when treating a propargyl glucopyranoside by a gold(III) catalyst. This would result in the formation of an oxocarbenium ion which when attacked by an aglycone would yield a mixture of α,β -glucopyranosides.⁸⁶ AuCl_3 appeared the catalyst of choice to promote this type of glycosylation reactions. In addition to the alkyne

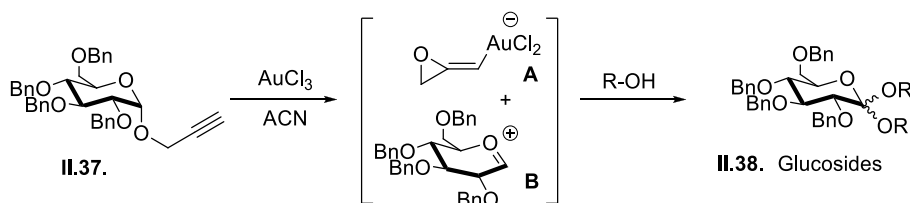
⁸⁵ Alcaide, B.; Almendros, P.; Carrascosa, R. *Chem. Eur. J.*, **2011**, *17*, 4968.

⁸⁶ (a) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620; (b) Kashyap, S.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 2021; (c) Kashyap, S.; Vidadala, S. R.; Hotha, S. *Tetrahedron Lett.* **2007**, *48*, 8960.

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activation, the gold(III) catalyst can behave as a Lewis acid to facilitate the attack of the glycosyl acceptor (**Scheme II.16.**) On this manner, various glycosides and disaccharides could be stereoselectively synthesized. The optimized conditions were applied to the glycosylation of different aglycones including aliphatic, alicyclic, steroidal and sugar alcohols.

Later on, propargyl 1,2-orthoesters were utilized for the 1,2-*trans* stereoselective synthesis of glycosides and disaccharides upon treatment with AuBr₃ in the presence of 4Å molecular sieves at room temperature.⁸⁷ Mechanistic investigation suggests that the gold(III) catalyst might again activate the propargyl moiety leading to the formation of a 1,2-dioxolenium ion and also acts as a Lewis acid to promote the aglycone attack affording 1,2-*trans* glycosides in a stereoselective fashion.



Scheme II.16. The gold-catalyzed synthesis of glucosides **II.38.**

The same research group demonstrated the efficiency of AuCl₃ to catalyse the synthesis of C-2 methylene glycosides **II.40.** from C-2 propargyloxymethyl glycols **II.39.** in a stereoselective manner.^{86c} This method was found to tolerate different functional groups in the aglycone partners, such as olefins, isopropylidenes, ethers or even azides (**Table II.3.**)

Table II.3. Gold catalyzed synthesis of glycosides.

Entry	ROH	Yield [%]	Entry	ROH	Yield [%]
1.		72	3.		61
2.		75	4.		65

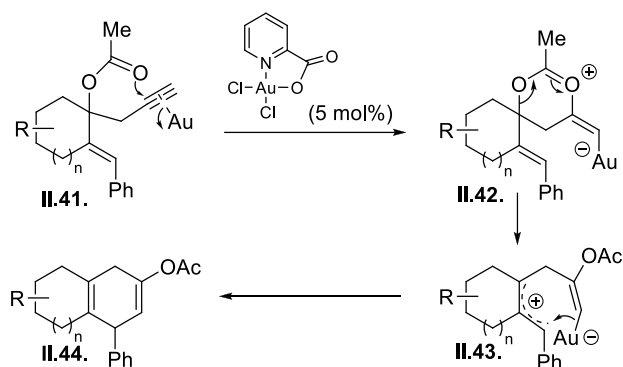
⁸⁷ (a) Sureshkumar, G.; Hotha, S. *Tetrahedron Lett.* **2007**, *48*, 6564. (b) Sureshkumar, G.; Hotha, S. *Chem. Commun.* **2008**, 4282.

Alkynophilic activation of propargyl glycosyl donors by Au (III) has been further expanded to the reaction of unprotected galactosyl, glucosyl and mannosyl donors.⁸⁸

II.1.2. Addition of carbonyl derivatives

As briefly shown in the introduction of this chapter, carbonyl derivatives constitute another class of oxygenated functionalities that could efficiently add intramolecularly onto activated alkynes (Scheme II.1. eq 3). Carboxy groups were particularly found to be convenient migrating groups in gold-catalyzed cyclization-fragmentation cascades of high interest for the organic chemist.

In this context, Zhang and co-workers reported a gold(III)-catalyzed unique cycloisomerization of 1,5 enynes **II.41.** involving migration of an acetoxy group.⁸⁹ 1-Acetoxycyclohexa-1,4-dienes and acetoxyarenes were prepared with good efficiency and with flexible substitution patterns using dichloro(pyridine-2-carboxylato)gold (5 mol%) as catalyst (Scheme II.17.).



Scheme II.17. The gold-catalyzed cycloisomerization of 1,5-enynes **II.41.**

The reaction proceeds through intramolecular addition of the carboxy group on the activated alkyne, followed by fragmentation of the oxonium intermediate resulting in the migration of the acetoxy group and formation of an allylic cation. Cyclization and demetalation finally furnish the cycloisomerization product in high yields (64-86%).

Another gold-catalyzed cyclization-fragmentation sequence involving an intramolecular addition of another carbonyl derivative that is a carboxamide function was documented a few years later by the same research group.⁹⁰ Whereas in the examples presented thus far gold catalysis was involved in the whole processes, only the initial cyclization step was gold-

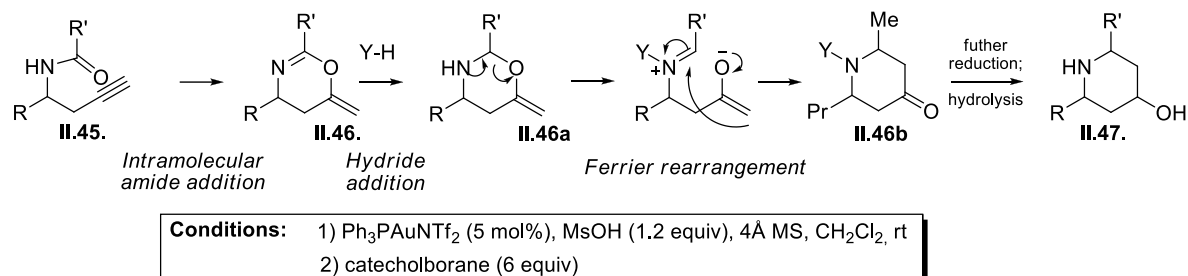
⁸⁸ Mamidyala, S.K.; Finn, M.G. *J. Org. Chem.* **2009**, 74, 8417.

⁸⁹ Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, 128, 14274.

⁹⁰ Cui, L.; Li, Ch.; Zhang, L. *Angew. Chem. Int. Ed.* **2010**, 49, 9178.

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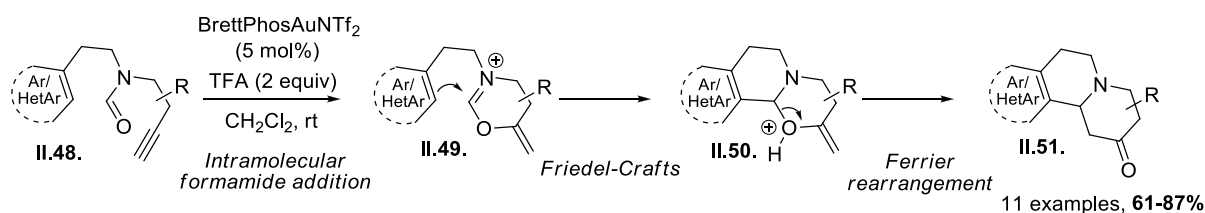
catalyzed here. The reported transformation actually combines a gold-catalyzed intramolecular addition of an amide function onto an alkyne, chemoselective reduction of the resulting intermediate and a spontaneous aza-Petasis-Ferrier rearrangement in a one-pot process for the synthesis of piperidin-4-ols **II.47**.



Scheme II.18. One-pot two-step sequence for the synthesis of *N*-unsubstituted piperidinols.

The steps involved in the transformation are presented on **Scheme II.18**. Initial gold(I)-catalyzed cyclization of propargylamide **II.45**, delivers a cyclic imidate **II.46**, which is *in situ* reduced with catecholborane (Y-H) to afford *N,O*-acetal **II.46a**. This intermediate then fragments and rearranges to furnish a piperidinone, which is further reduced *in situ* to the corresponding alcohol.

The same authors further developed an efficient synthesis of electron-rich arene-fused hexahydroquinolizinones **II.51**.⁹¹ In this cascade reaction, a gold-catalyzed amide cyclization to a tethered alkyne initiates a subsequent Friedel-Crafts-type cyclization followed by a Ferrier rearrangement. Interestingly, this methodology could be also successfully applied to the stereoselective synthesis of dihydrocorynantheol and to the formal syntheses of yohimbine and β -yohimbine. (**Scheme II.19**.)



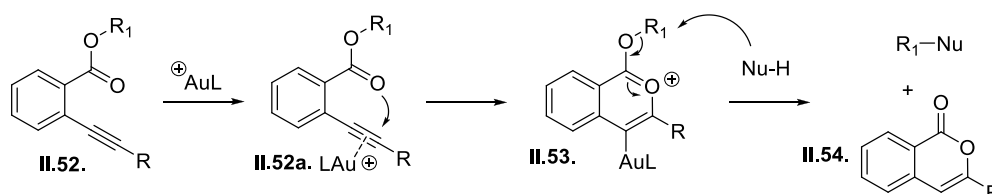
Scheme II.19. Gold-catalyzed synthesis of electron-rich arene-fused hexahydroquinolizinones.

One of the most significant applications of this category of cyclization-fragmentation cascade is exemplified by the reactions of *ortho*-alkynylbenzoic acid alkyl esters **II.52**. These compounds were used in many occasions as convenient electrophiles in gold-catalyzed

⁹¹ Liu, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 7301.

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alkylations of nucleophilic compounds of different natures. In these transformations, the intramolecular nucleophilic attack of the carbonyl oxygen to the gold-coordinated alkyne generates a cyclic zwitterionic intermediate as shown on **Scheme II.20**. Due to the strong electrophilicity of this intermediate, the attack of an internal or external nucleophile occurs on the R₁ group producing the corresponding alkylated product and isocoumarin. This latter then plays the role of a leaving group in the transformation.



Scheme II.20. The cyclization-fragmentation of *ortho*-alkynylbenzoic acid alkyl esters **II.52**.

The reaction was initially developed by Asao *et al.* in 2007 who demonstrated that the reaction of *ortho*-alkynylbenzoic acid alkyl esters with alcohols or aromatic compounds occurs in the presence of catalytic amounts of Ph₃PAuCl and AgOTf under mild conditions to produce corresponding ethers or Friedel–Crafts alkylation products in good to high yields (50-92%).⁹²

Similar strategies were next successfully applied to the alkylation of various heteronucleophiles, such as sulfonamides,^{92b} silyl enol ethers⁹³ or alkylthiols and thiophenols.⁹⁴ While some alkyl groups could be introduced in some cases, most of the examples correspond to benzylation reactions.

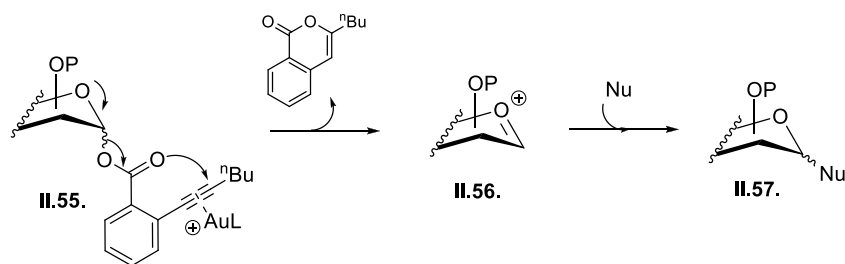
Very interestingly, this methodology found many useful applications for the synthesis of glycosides which are very often key intermediates for the preparation of various biologically important components. Yu's research group developed an efficient glycosylation protocol with glycosyl *ortho*-alkynylbenzoates **II.55** as donors and a gold(I) complex as catalyst. It implies the *in situ* generation of glycosyl oxocarbeniums **II.56** which then react with nucleophilic acceptors to provide the corresponding glycosides.⁹⁵ (**Scheme II.21**.)

⁹² (a) Asao, H.; Aikawa, S.; Tago, K.; Umetsu, K. *Org. Lett.* **2007**, *9*, 4299. (b) Aikawa, H.; Tago, S.; Umetsu, K.; Haginiwa, N.; Asao, N. *Tetrahedron* **2009**, *65* 1774.

⁹³ Aikawa, H.; Kaneko, T.; Asao, N.; Yamamoto, Y. *Beilstein J. Org. Chem.* **2011**, *7*, 648.

⁹⁴ Jean, M.; Renault, J.; van de Weghe, P.; Asao, N. *Tetrahedron Lett.* **2010**, *51* 378.

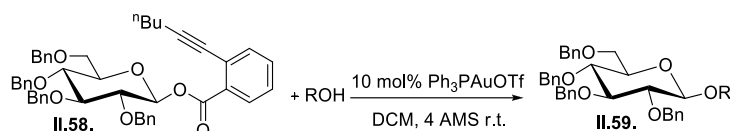
⁹⁵ (a) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871; (b) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604.



Scheme II.21. Glycosylation with II.55.

Several *O*-glycosylation reactions employing nucleophilic acceptors such as carboxylic acids,⁹⁶ alcohols,^{95b} oximes⁹⁷ or sugars⁹⁸ were thus successfully developed. In **Table II.4.** are presented some representative results obtained for the glycosylation of different classes of alcohols.

Table II.4. Ph₃PAuOTf-catalyzed glycosylation of alcohols



Entry	ROH	Yield [%]	β:α
1.		98	β only
2.		97	β only
3.		98	β only

Later on, the synthetic potential of this methodology was demonstrated by the synthesis of several biologically active targets.⁹⁹ In most cases, reactions were catalyzed by either Ph₃PAuOTf or the Gagosz catalyst Ph₃PAuNTf₂ and could be run under mild and neutral conditions.

This methodology was also shown to be amenable to *N*-glycosylation reactions. In particular, Yu and co-workers reported that the gold(I)-catalyzed glycosylation using glycosyl ortho-alkynylbenzoates as glycosyl donors was highly efficient for the *N*-glycosylation of nucleobases.¹⁰⁰ Especially, complete regioselectivity was achieved for the glycosylation of

⁹⁶ Yang, Y.; Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2010**, *51*, 1504.

⁹⁷ Yu, J.; Sun, J.; Yu, B. *Org. Lett.* **2012**, *14*, 4022.

⁹⁸ Y. Yang, Y. Li, B. Yu *J. Am. Chem. Soc.* **2009**, *131*, 12076.

⁹⁹ For some recent examples, see: (a) Yang, W.; Sun, J.; Lu, W.; Li, Y.; Shan, L.; Han, W.; Zhang, W.-D.; Yu, B. *J. Org. Chem.* **2010**, *75*, 6879; (b) Li, Y.; Sun, J.; Yu, B. *Org. Lett.* **2011**, *13*, 5508; (c) Ma, Y.; Li, Z.; Shi, F.; Zhang, J.; Yu, B. *J. Org. Chem.* **2011**, *76*, 9748.

¹⁰⁰ (a) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 4933; (b) Yang, F.; Zhu, Y.; Yu, B. *Chem. Commun.* **2012**, *48*, 7097.

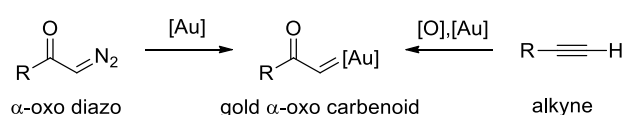
purines, contributing to the mild reaction conditions that allow purines bearing acid-labile protecting groups (*e.g.*, the *N*-Boc protecting group) to be used as the coupling partners.

Last, it is worth mentioning that an extension of the glycosylation reaction to the cationic ring-opening polymerization of THF was recently described.¹⁰¹ Interestingly, this Ph₃PAuNTf₂-catalyzed reaction could be followed by co-polymerization with different monomers, such as glycidol.

II.1.3. Addition of O-atom-donor groups

As previously discussed, gold catalysts are powerful soft Lewis acids for activating alkynes toward nucleophilic attack. A remarkable feature of such systems is that the vinylgold intermediate can further react as an α -deprotonated gold carbenoid and be nucleophilic. Consequently, one can consider the Au alkyne complex can also be considered as an α -carbene gold carbenoid.

In this context, when an oxygen-delivering oxidant is reacted with the Au alkyne complex or its equivalent α -carbene gold carbenoid *via* an addition-elimination process, an oxygen atom is transferred leading to the oxidative formation of a versatile α -oxo gold carbenoid. The global transformation is of high significance since it offers a convenient and benign alternative to generate a reactive metal carbenoid which is traditionally formed *in situ* from transition metal-catalyzed decomposition of α -diazocarbonyl compounds.



Scheme II.22. Synthetic equivalents

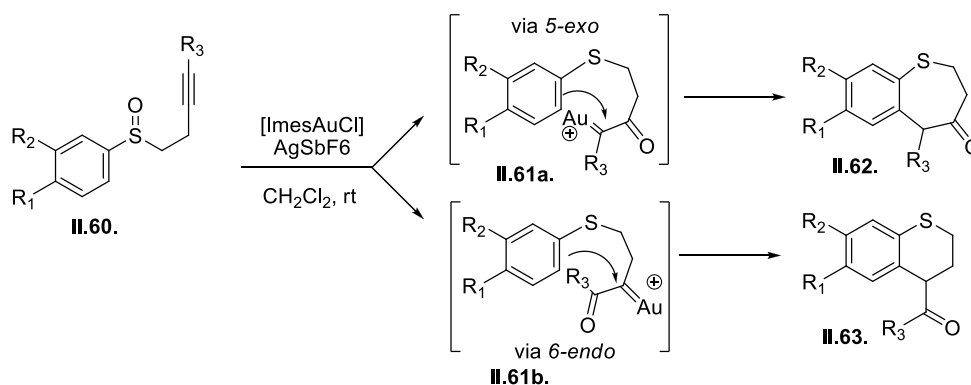
Due to the number of contributions dedicated to the generation and reactivity of these gold α -oxo carbenoids,¹⁰² only a brief overview illustrating some of the more common reactive partners and catalyst systems at play for the synthesis of cyclic architectures will be presented next.

¹⁰¹ Li, Y.; Yu, B. *Chem. Commun.* **2010**, 6060.

¹⁰² For a review, see: Xiao, J.; Li, X. *Angew. Chem. Int. Ed.* **2011**, 50, 7226.

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In 2007, Zhang and co-workers¹⁰³ and Toste and co-workers¹⁰⁴ independently documented this concept starting from alkynes equipped with a tethered sulfoxide. These gold(I)-catalyzed rearrangement of alkynyl sulfoxides take advantage of the nucleophilicity of sulfoxide oxygen and the latent sulfonium generated *in situ* as a leaving group. As a representative example, [(IMes)AuCl]/AgSbF₆ (5 mol%) was shown to smoothly catalyze the cyclization of substrates **II.60.** to give benzothiepinones **II.62.** and benzothiepine **II.63.**. Internal alkyne substrate favors the 6-endo-dig cyclization, whereas 5-exo-dig cyclization is preferred for terminal alkynes. The resulting carbenoid intermediates in both cases undergo a C-H insertion with the phenyl moiety to yield bicyclic structures **II.62.** and **II.63.**, respectively.



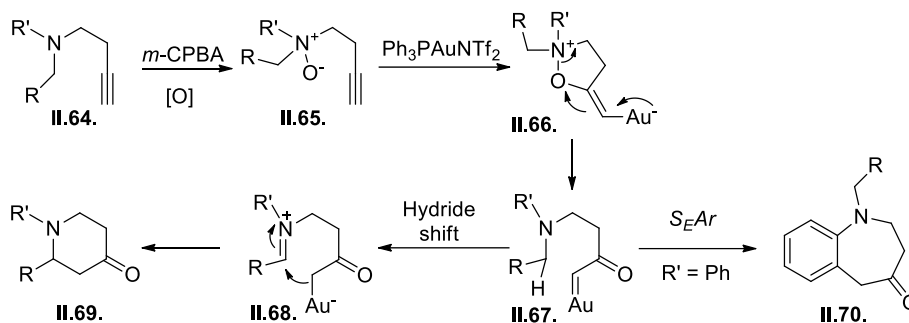
Scheme II.23. The gold catalyzed rearrangement of alkynyl sulfoxides **II.60.**

The gold-catalyzed oxidation of alkynes by means of amine- and pyridine-*N*-oxides was extensively studied since 2009. Zhang and co-workers reported the first example of redox cyclization of amine *N*-oxides (**Scheme II.24.**), synthesized by *m*-CPBA oxidation of propargylamines **II.64.**¹⁰⁵ One-pot cyclization was achieved upon treatment with a catalytic amount of Ph₃PAuNTf₂ to give piperidin-4-ones **II.69.** When two methylene groups are present on the nitrogen, the less-substituted one tends to be involved in the ring formation and when one methylene group is replaced by an aryl group, the sequence rather ends by an electrophilic substitution providing the benz[*b*]azepin-4-ones **II.70.**

¹⁰³ Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156.

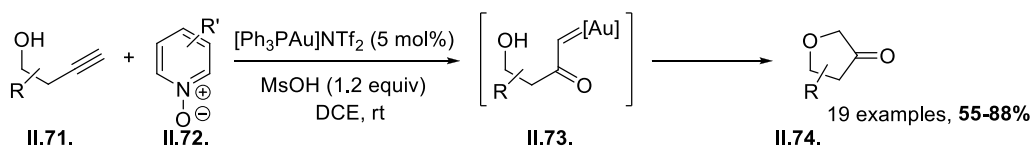
¹⁰⁴ Shapiro, N. D.; Toste, D. F. *J. Am. Chem. Soc.* **2007**, *129*, 4160.

¹⁰⁵ (a) Peng, L.C.Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (b) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225.



Scheme II.24. Redox cyclization of alkyne amine *N*-oxides

The intermolecular version of these oxygen-atom transfer reactions was subsequently developed by using pyridine *N*-oxides and several examples involving intra- or intermolecular trapping of the metal carbenoid or gold carbocation were disclosed.¹⁰⁶ Notably, this intermolecular strategy displays an improved synthetic flexibility in comparison with the intramolecular version. Its synthetic potential was demonstrated by the $\text{Ph}_3\text{PAuNTf}_2$ -catalyzed expedient preparation of dihydrofuran-3-ones **II.74** from simple homopropargyl alcohols **II.71**. (Scheme II.25.) Addition of the Bønsted acid MsOH to buffer the reaction mixture was found to be important for high reactivity. The same strategy was further expanded to the oxidative cyclization of diversely substituted alkynes to provide a wide range of products, such as strained oxetan-3-ones and azetidin-3-ones, 2,5-disubstituted oxazoles, 3-carbonyl-*1H*-indenes, indanones and cyclopentenone derivatives.¹⁰⁷



Scheme II.25. The gold(I)-catalyzed synthesis of dihydrofuran-3-ones from homopropargyl alcohols.

Inspired by these previous contributions, Yang and Tang very recently described a gold-catalyzed rearrangement of allylic oxonium ylides allowing a rapid access to highly functionalized dihydrofuran-2-ones.¹⁰⁸

Nitrones and nitro groups also proved to be efficient nucleophilic oxygen-atom-donor groups that can be involved in similar cascade sequences *via* the in situ formation of gold α -

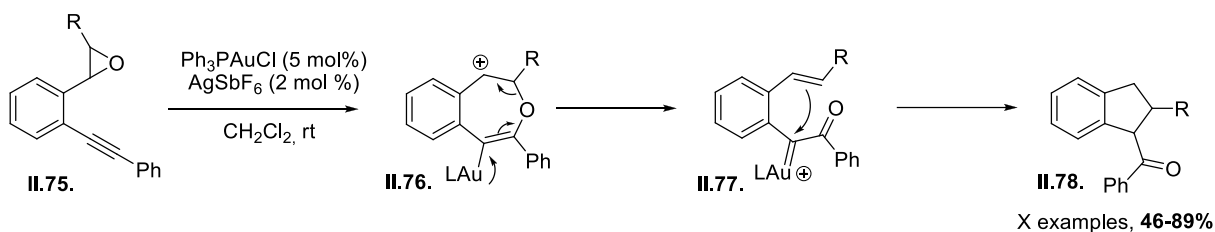
¹⁰⁶ Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258.

¹⁰⁷(a) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550; (b) Ye, L. He, W.; Zhang, L. *Angew. Chem., Int. Ed. Engl.* **2011**, *50*, 3236; (c) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482; (d) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem., Int. Ed. Engl.* **2011**, *50*, 6911; (e) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed. Engl.* **2012**, *51*, 2939;

¹⁰⁸ Fu, J.; Shang, H.; Wang, Z.; Chang, L.; Shao, W.; Yang, Z.; Tang, Y. *Angew. Chem., Int. Ed. Engl.* **2013**, *52*, 4198.

oxo carbenoid intermediates. Most of the examples developed thus far involved nitron- and nitro-tethered alkynes producing complex azacyclic compounds in a single step.¹⁰⁹

Despite the less polar character of C-O bonds in epoxides, oxygen-atom transfer from epoxydes to alkynes was successfully achieved by Liu and Hashmi research groups.¹¹⁰ The oxidative cyclization of alkynyl epoxides was performed under mild conditions with Ph₃PAuCl/AgSbF₆ as catalytic system. The proposed mechanism involves the oxygen attack at the alkyne in a 7-*endo* fashion, which gives a stabilized benzylic carbocation. **II.76**. Intramolecular elimination followed by nucleophilic attack of the alkene on the resulting a-oxo carbenoid intermediate affords **II.77**. Subsequent 1,2-H shift finally leads to the final 3-carbonyl-1*H*-indene product **II.78**.



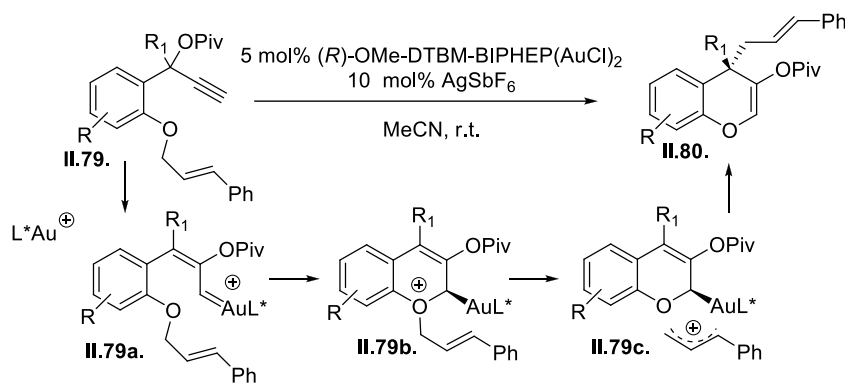
Scheme II.26. The oxidative cyclization of alkynyl epoxides.

Although esters are not oxygen-atom donors, propargyl esters can undergo analogous oxygen attack at an alkyne to give a vinyl species, which can further undergo formal 1,2-transfer of the ester group to form a gold vinyl carbenoid species. This type of strategy was elegantly documented recently by Toste and co-workers who developed the first gold-catalyzed enantioselective carboxylation reaction of propargyl esters.¹¹¹ The (*R*)-MeO-DTBM-BIPHEP(AuCl)₂-catalyzed reactions allow for the construction of benzopyrans containing quaternary stereocenters with excellent enantioselectivity (**Scheme II.27**).

¹⁰⁹ For some representative examples involving nitrones, see : (a) Cui, L.; Li, Ch.; Zhang, L. *Angew. Chem. Int. Ed.* **2010**, 49, 9178. (b) Kang, Y.K.; Kim, S.M.; Kim, D.Y. *J. Am. Chem. Soc.* **2010**, 132, 11847. (c) Xiao, J.; Li, X. *Angew. Chem. Int. Ed.* **2011**, 50, 7226. (d) Yeom, H.-S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J.-E.; Lee, S.S.; Shin, *Angew. Chem. Int. Ed.* **2010**, 49, 1611. For some representative examples involving nitro groups, see : (a) Xiao, J.; Li, X. *Angew. Chem. Int. Ed.* **2011**, 50, 7226. (b) Jadhav, A.M.; Bhunia, S.; Liao, H.Y.; Liu, R.S. *J. Am. Chem. Soc.* **2011**, 133, 1769.

¹¹⁰(a) Lin, G. Y.; Li, C. W. ; Lin, H.-H. ; Hung, S. H.; Liu, R. S. *Org. Lett.* **2008**, 10, 5059; (b) Hashmi, A. S. K.; Bürhle, M.; Salathé, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, 350, 2059.

¹¹¹ Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, 131, 3464.

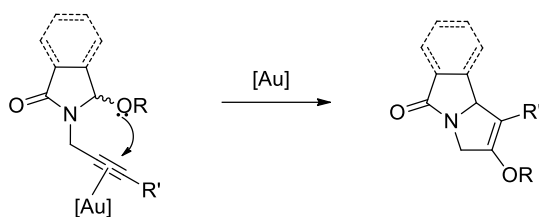


Scheme II. 27. Gold(I)-Catalyzed enantioselective carboalkoxylation of propargylic esters

Experimental evidences support a mechanism proceeding *via* the generation of a stabilized carbocation from an allylic oxonium intermediate and subsequent trapping by a chiral allylgold(I) species.

II. 2. RESULTS: THE CYCLIZATION-FRAGMENTATION REACTION

The first part of the research project presented in this manuscript is thus devoted to the evaluation of a gold-catalyzed *5-exo-dig* intramolecular carboalkoxylation/aza-Ferrier-Petasis¹¹² rearrangement sequence. This approach would give an atom economic short access to the framework of some hydroxypyrrolizidines, an interesting class of compounds which exhibits many interesting pharmacological properties (Scheme II.28.).¹¹³



Scheme II.28.

As a reminder, the synthesis of six-membered cyclic enol ethers using a similar gold-catalyzed cyclization-fragmentation sequence was recently reported by Rhee and co-workers starting from propargylamine-derived *N,O*-acetals.⁶⁸ This specific work thus strongly supports our working hypothesis and the feasibility of such a sequence.

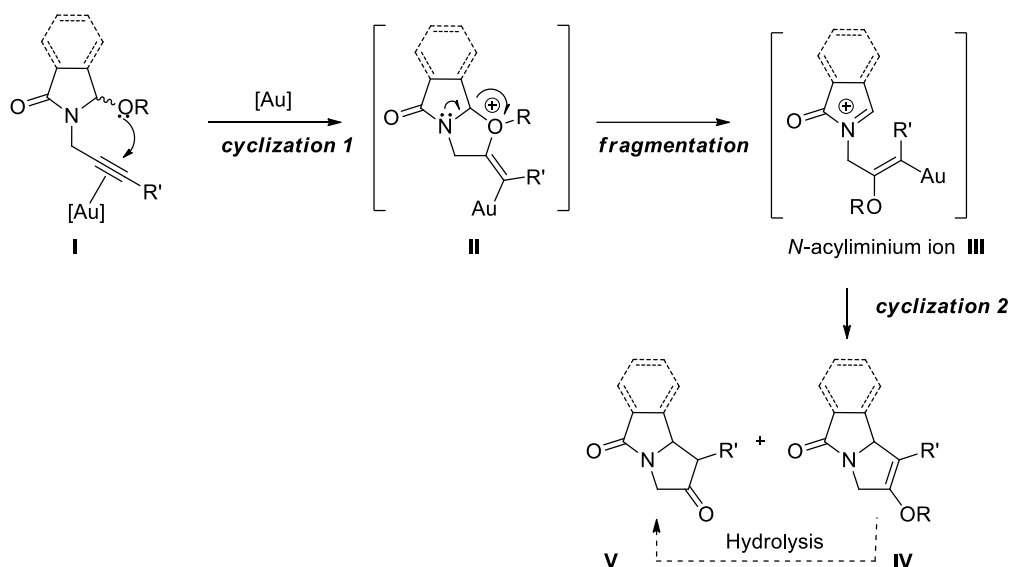
In line with Toste's and Rhee's reports,⁶⁶ the pathway depicted on Scheme II.2. was proposed for the transformation. It would first involve the intramolecular addition of the

¹¹² For two recent elegant papers on catalytic aza-Ferrier-Petasis rearrangement: (a) Tayama, E.; Otoyama, S.; Isaka, W. *Chem. Commun.* **2008**, 4216. (b) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354.

¹¹³ Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773.

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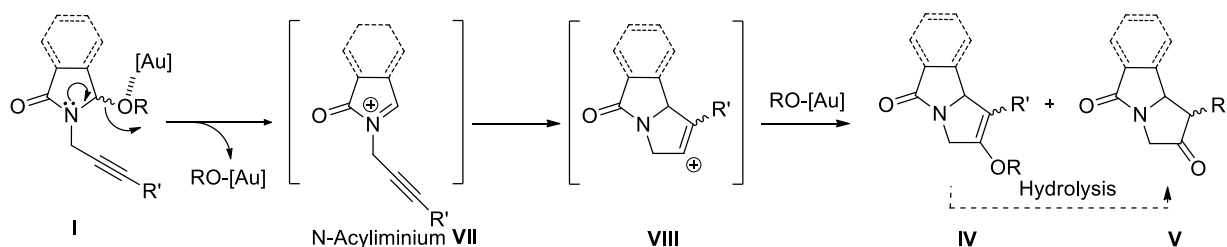
alkoxy group on the gold-activated alkyne. The resulting highly instable oxonium intermediate **II** would then evolve into a less energetic *N*-acyliminium ion **III** through a gold-catalyzed cyclization-induced fragmentation sequence, and the latter intermediate should be trapped intramolecularly by the vinyl gold moiety. Protodeauration should then deliver the expected cyclic enol ether **IV** which could also be possibly hydrolyzed under the reaction conditions to give the corresponding ketone **V** (Scheme II.29).



Scheme II.29. Proposition of the mechanism.

In this sequence, we do hope that the ring strain associated with the five-membered oxacycles combined with the high stabilization of the resulting α -*N*-acylated carbenium (*i.e.* the *N*-acyliminium ion **III**) will be the driving forces for this process (Scheme II.29.).

The direct activation of the ether function which would lead to the formation of the exact same products should also be considered, in particular with oxophilic gold complexes (Scheme II.30.).



Scheme II.30. Alternative pathway

Indeed, the OR group being a potential leaving group, an *N*-acyliminium ion could be directly formed in the first step. This latter would then cyclize to give the cationic

intermediate **VIII**, which would be trapped *in situ* by the gold-alkoxide furnishing the targeted products (**Scheme II.30.**).

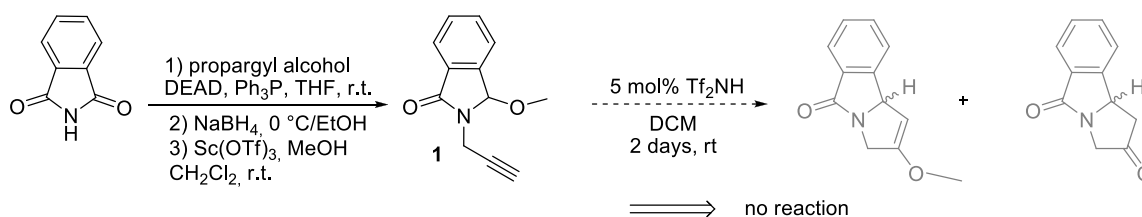
II.3.1. PRELIMINARY STUDY

• INITIAL CATALYST SCREENING

For initial screening experiments, 3-methoxy-2-(prop-2-ynyl)isoindolin-1-one **1** was selected as a model starting material.

The latter was prepared in three steps starting from the Mitsunobu reaction of phthalimide, selective reduction of one of the carbonyl with NaBH₄, followed by methoxylation of the resulting hydroxylactam with methanol and Sc(OTf)₃ under conventional conditions. (**Scheme II.31.**) Alternatively, the methoxylactam can be effectively prepared in a one-pot sequence of reduction/methoxylation operating at low temperature in dichloromethane, followed by quenching with a solution of H₂SO₄ in methanol.

First, to evaluate the methoxy leaving ability, we have chosen to test a reaction in the presence of trifluoromethanesulfonimide as a catalyst. Indeed, as previously discussed (*cf.* Chapter I), this super Brønsted acid is a powerful promoter for *N*-acyliminium ions formation. Methoxy compound **1** was then subjected to Tf₂NH (5 mol%) in dichloromethane at room temperature (**Scheme II.31.**).

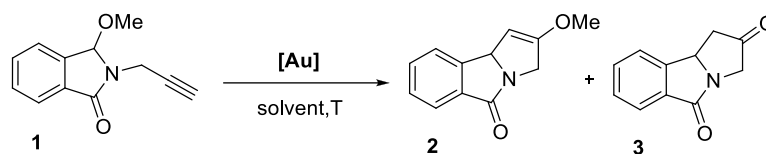


Scheme II.31. Test reaction in the presence of Tf₂NH.

After 2 days of reaction at room temperature, the starting methoxylactam **1** was fully recovered (confirmed by ¹H NMR analysis). So, if a reaction could be performed from **1** under gold catalysis, activation of the ether and initial shift of the alkoxy group could be ruled out and the transformation should rather proceed through a cyclization-fragmentation as depicted on **Scheme II.29**. However, this absence of reactivity in the presence of Tf₂NH is also indicative of the difficulty to cleave the C-O acetalic bond which is required at point of the mechanism.

CHAPTER II: The cyclization-fragmentation reaction

We started our investigations by testing influences of the nature of cationic gold (I) catalysts on the reactivity. (**Scheme II.32.**)



Scheme II.32.

It is well-known that the acidity of the gold catalysts could be modulated by changing the nature of the counterion and of the gold ligand. An ether being intrinsically poorly nucleophilic, the expected carboalkoxylation initiating the sequence may require a cationic species close to [LAu⁺]. In order to get a more active catalyst, the introduction of weakly coordinating counterions, such as ⁻NTf₂ or ⁻SbF₆, in the gold complexes was thus supposed to be highly desirable.

To access cationic complexes with different counterions and phosphines, a two-step sequence was used. At first, Ar₃PAuCl gold complexes were prepared by addition of triarylphosphines to the commercially available gold chloride complex [(Me₂S)AuCl] in dichloromethane. After isolation, an anion metathesis reaction was performed by reaction with a silver salt AgX (X = OTf, NTf₂, SbF₆, ...) which lead to the formation of the corresponding LAuX complex and precipitation of AgCl, which was not separated from the reaction mixture (**Scheme II.33.**)¹¹⁴



Scheme II.33. Catalysts generated *in situ*.

A set of gold catalysts which were found to be effective at promoting intramolecular carboalkoxylation-fragmentation cascades (as presented in the first part of this Chapter) was selected. Our first attempt used the air stable Gagosz catalyst (Ph₃PAuNTf₂) at a catalyst loading of 5 mol%. Unfortunately, no reaction took place neither at room temperature nor at 45 °C (**Table II.5.** Entry 1.). With the idea of increasing the electrophilicity of the gold-coordinated alkyne, the use of more electrophilic gold complexes was tested (**Table II.5.** Entry 2-3.) When catalysts incorporating a *tris*(*p*-CF₃-phenyl)phosphine or a *tris*(hexafluorophenyl)phosphine were used, a complete conversion of the substrate was

¹¹⁴ Kennedy-Smith, J. J.; Staben, S. T.; Toste, D. F. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

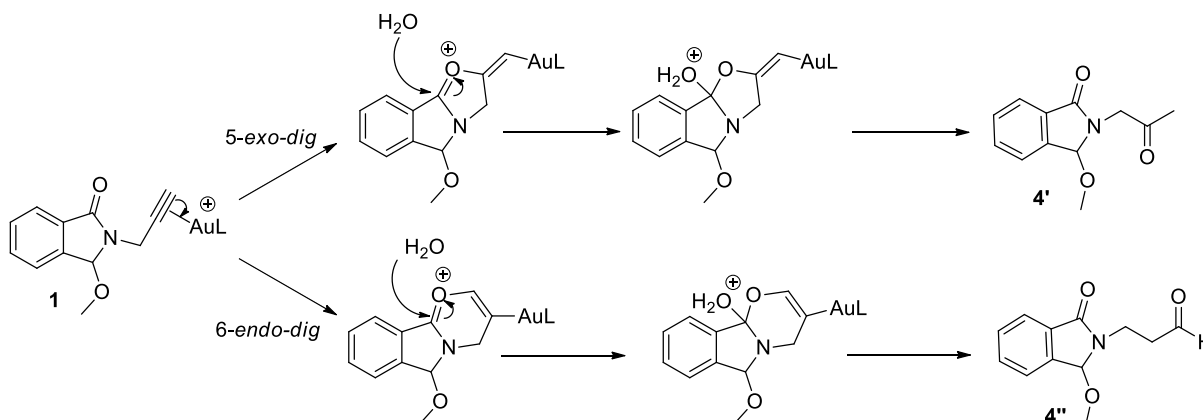
CHAPTER II: The cyclization-fragmentation reaction

observed albeit after prolonged reaction times. After purification, three new products **4-4''** were obtained (Entries 2-3).

Table II.5. Gold-catalyzed cyclization-fragmentation sequence of phthalimide derivative 1

Entry	Cat	Time	T [°C]	Result
1.	Ph ₃ PAuNTf ₂	1 d 1 d	rt 45	No reaction
2.	(p-CF ₃ -C ₆ H ₄)PAuNTf ₂	2 d 2 d	rt 45	
3.	(C ₆ F ₅) ₃ PAuSbF ₆	4 d 1 d	rt 45	

The methylketone **4'** and aldehyde **4''**, isolated as an inseparable mixture 88:12 respectively, may directly come from gold-catalyzed hydration of the alkyne moiety which is a well-known reaction in gold chemistry.¹¹⁵ While a direct addition of a molecule of water onto the activated alkyne could be proposed, participation of the carbonyl group in the hydration mechanism was also considered as depicted on Scheme II.34.¹¹⁶



Scheme II.34. Gold-catalyzed hydration of the alkyne moiety

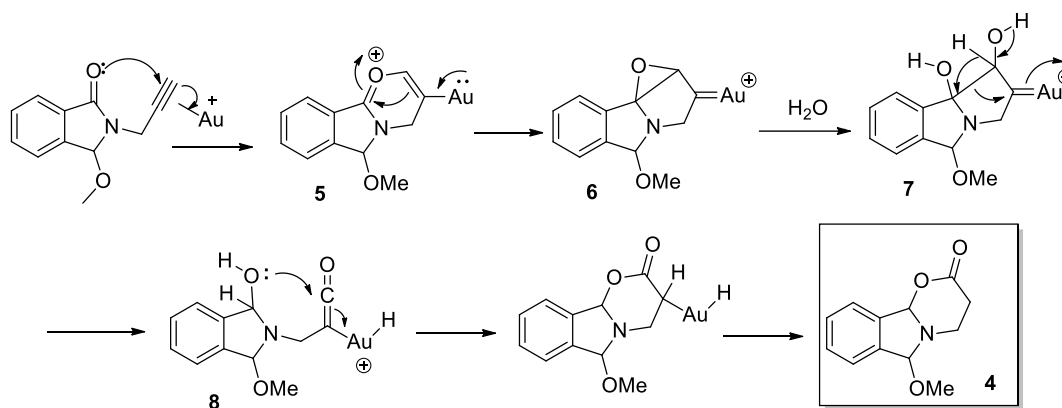
¹¹⁵ (a) Jung, H.H.; Floreancig, P. E. *J. Org. Chem.*, **2007**, *72*, 7359. (b) Saito, S.; Yamamoto, H. *Chem. Commun.*, **1997**, 1585; (c) For a review on the hydration of alkyne, see: Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121.

¹¹⁶ Wang, W.; Xu, B.; Hammond, G. B. *J. Org. Chem.*, **2009**, *74*, 1640.

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Depending on the cyclization mode for the initial intramolecular addition of the carbonyl group on the activated alkyne, the addition of water on the resulting oxacarbenium intermediates would lead to the formation of either ketone **4'** or aldehyde **4''**.

As for the formation of the oxazinone **4**, it was proposed to result from the nucleophilic addition of the carbonyl group onto the Au-activated alkyne. To explain the formation of this compound, the mechanism presented below was postulated. (**Scheme II.35**.)



Scheme II.35. Proposed mechanism for the formation of product **4**.

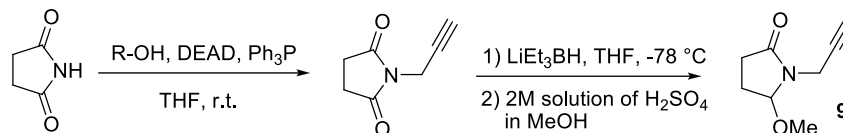
The first step of our proposed mechanism would imply coordination of the triple bond to the gold catalyst, enhancing its electrophilicity. Subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne would then form the gold oxonium intermediate **5**. Gold also being potentially an electron-donor, rearrangement of **5** could generate a gold carbene **6**. Addition of H₂O would then open the epoxide moiety affording intermediate **7**. Successive hydride transfer and ring opening would then lead to the cationic gold complex **8**. Finally, after cyclization and reductive elimination, the oxazinone **4** would be formed.

The fact that these side-reactions prevailed strongly suggests that the oxygen of the methoxy group may not be nucleophilic enough to add on the triple bond. It is also worth considering that the cleavage of the acetalic C-O bond which should result in the formation of the *N*-acyliminium **III** may be not as favored as expected (*cf.* **Scheme II.29**).

Previous studies from our research group dealing with catalytic α -amidoalkylations of *N,O*-cyclic acetals established that succinimide-derived substrates were usually found to be much more reactive than phthalimide derivatives. And indeed, even methoxylactams of this

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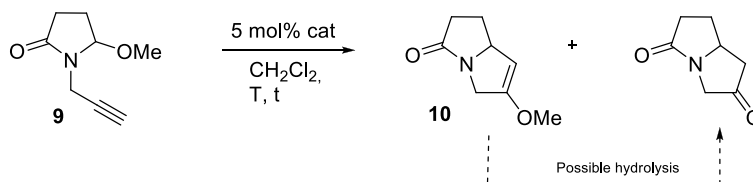
series were found to be suitable *N*-acyliminium precursors under acid catalysis (contrary to their phthalimide analog as shown previously)¹¹⁷. So, given the poor reactivity observed thus far with substrate **1**, we decided to test the *N*-propargyl derivative **9**. This substrate was easily prepared in three steps using well-established procedures as shown on **Scheme II.36**.



Scheme II.36. Synthesis of component **9**.

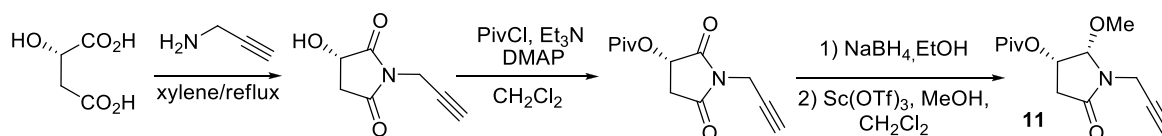
As presented in **Table II.6.**, the cyclization-fragmentation sequence catalyzed by 5 mol% of the Gagosz catalyst gave disappointing results. A complete lack of reactivity was observed even after a prolonged reaction time and the starting *N,O*-acetal was fully recovered (Entry 1). Conversely, the reaction carried out with the stronger electrophilic catalyst (*p*-CF₃-C₆H₄)PAuNTf₂ gave a complex mixture with no expected products being formed.

Table II.6. Gold-catalyzed cyclization fragmentation sequence of succinimide derivative **9**



Entry	Cat	Time	T [°C]	Result
1.	Ph ₃ PAuNTf ₂	1 d	rt	NR
		1 d	45	
2.	<i>(p</i> -CF ₃ -C ₆ H ₄)PAuNTf ₂	4 d	rt	Complex mixture
		1 d	45	

Pursuing our effort, we next tested the reaction with a (*S*)-malic acid derivative **11**. The optically pure *cis*-methoxy lactam possessing a pivaloyl protecting group on the adjacent hydroxy group was prepared from (*S*)-malic acid. (**Scheme II.37.**)

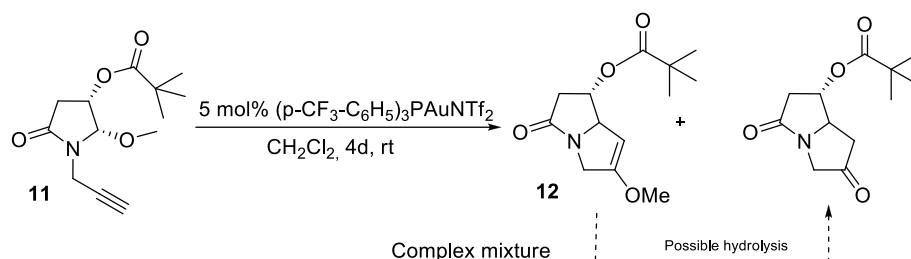


Scheme II.37. General synthesis of substrate **11**.

¹¹⁷ As previously discussed in Chapter I.

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Based on previous results, the cyclization of **11** was only tested in the presence of 5 mol% of $(p\text{-CF}_3\text{-C}_6\text{H}_4)\text{PAuNTf}_2$. However, as shown on **Scheme II.38.**, only a slow conversion of the substrate and its decomposition were observed.



Scheme II.38. Gold-catalyzed cyclization-fragmentation reaction of substrate **11**.

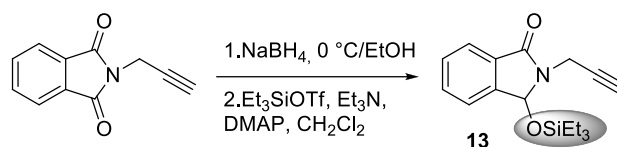
This preliminary set of results presented above strongly suggest that the oxygen of the methoxy group may not be nucleophilic enough to add on the triple bond. Conversely, despite complexation by a gold catalyst, the alkyne moiety may not be electrophilic enough thus preventing the expected cascade sequence from occurring.

*Complexation of the gold catalyst on both the triple bond and the carbonyl group could also explain the lack of reactivity observed. Indeed, this kind of complexation would completely prevent the expected cyclization step since the triple bond would be “kept away” from the methoxy group. Last, it is also reasonable to think that the targeted 5-*exo*-cyclization mode forming a 5-membered ring may be impossible for geometric reasons.*

• MODIFICATION OF THE STARTING MATERIAL

Based on primary results, modification of the structure of the starting material was next considered. The influence of different parameters was explored, such as the nucleophilic character and size of the OR group, length of the chain tethering the triple bond and the *N,O*-acetal moiety, nature and electronic character of the metal catalyst and of the triple bond.

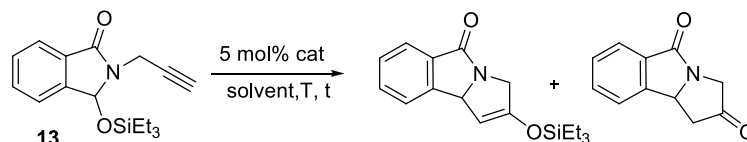
Inspired by a result reported by Rhee and co-workers showing that 5-silyloxy-pent-3-en-1-ynes could undergo gold-catalyzed cyclization-fragmentation even more efficiently than the methoxypentyne analogs (**Scheme II.5.**),⁷⁴ the silyloxy lactam **13** was prepared for testing (two steps from *N*-propargyl phthalimide, **Scheme II.39.**).



Scheme II.39. General method of synthesis of **13**.

The cyclization of this substrate was then attempted using $(\text{C}_6\text{F}_5)_3\text{PAuSbF}_6$ as the catalyst (Table II.7. Entry 1.). While this gold(I) catalyst displayed an interesting reactivity in the case of Rhee's reaction, only a very slow conversion of **13** was observed at room temperature or at reflux and only cleavage of the trialkylsilyloxy group occurred. A similar reactivity was observed when the reaction was set up with 10 mol% of $(\text{C}_6\text{F}_5)_3\text{PAuCl}$ and 5 mol% of AgSbF_6 with only the deprotected hydroxylactam being recovered (Entry 2.).

Table II.7. Gold-catalysed cyclization fragmentation sequence of phthalimide derivatives **13**.



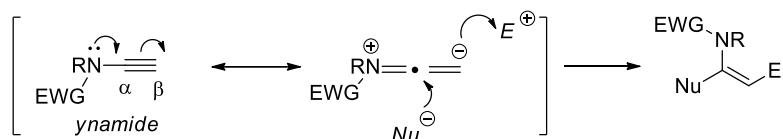
Entry	Cat/solvent	Time	T [°C]	Result
1.	$(\text{C}_6\text{F}_5)_3\text{PAuSbF}_6 / \text{CH}_2\text{Cl}_2$	5 d	rt	Deprotection of OSiEt ₃
		5 h	40	
2.	$(\text{C}_6\text{F}_5)_3\text{PAuCl}$ (10 mol%) AgSbF_6 (5 mol%) / CH_2Cl_2	5 d	rt	Deprotection of OSiEt ₃
		5 h	40	

As previously discussed, conformational constraints could potentially prevent a 5-*exo-dig* cyclization from occurring. Consequently, a substrate having a homopropargyl protecting group on nitrogen was prepared. Additionally, to favor the initial cyclization, the use of ynamide-containing substrates was envisioned. Ynamides, as electron-deficient ynamines, feature a strong polarization of the triple bond due to the electron-donating ability of the nitrogen which is however diminished by the electron-withdrawing group present for stability concern. Interestingly, the unique nature of ynamides usually allows for the regioselective addition of electrophiles or nucleophiles onto the ynamide (Scheme II.40).¹¹⁸ Several examples of transition-metal catalyzed transformation allowing for the addition of heteronucleophiles at the α -position of ynamides were developed recently, thus supporting

¹¹⁸ (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840; (b) Kyle A. DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

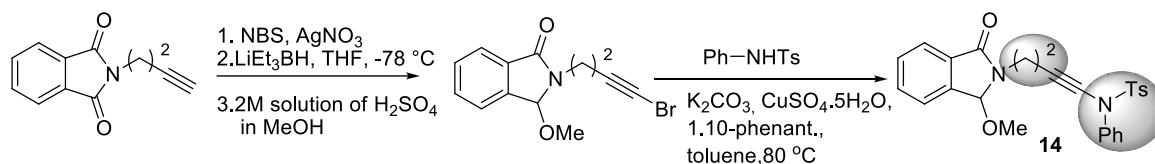
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our idea that a gold-catalyzed cyclization-fragmentation sequence starting from ynamides is worth considering.



Scheme II.40. Reactivity of ynamides.

The preparation of substrate **14** was thus realized in four steps starting from *N*-butenylphthalimide: After bromination of the terminal alkyne, a reduction-methoxylation two-step sequence was performed. Last, the ynamide was formed using a copper-mediated coupling between the bromoalkyne and the *N*-benzylsulfonamide HNTsBn. (Scheme II.41.)



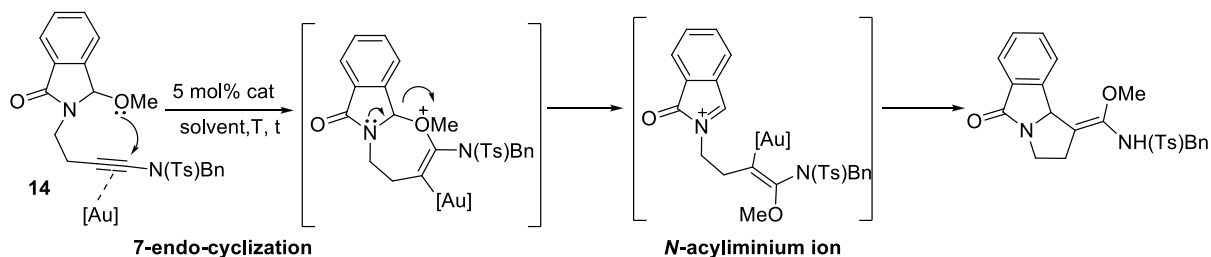
Scheme 41. The preparation of the substrate **14**.

The cyclisation-fragmentation of the ynamide **14** was then attempted. It should be noted that products resulting from an initial 7-endo-cyclization mode is expected here. In the reactions with the Gagosz catalyst ($\text{Ph}_3\text{PAuNTf}_2$) or with the more electrophilic $(\text{C}_6\text{F}_5)_3\text{PAuSbF}_6$, all the starting material **14** was consumed event at room temperature but only complex mixtures were formed. (Table II.8. Entries 1 and 2).

Our next attempts used simple catalysts such as AuCl , AuCl_3 and PtCl_2 which are well soluble in most organic solvents and also known to promote related cyclization reactions.¹¹⁹ Unfortunately, under the tested conditions, only complex mixtures with no formation of the expected product was obtained possibly due to the competitive coordination of the catalyst with the tosyl protecting group. (Table II.8. Entries 3-5)

¹¹⁹ For the use of AuCl and AuCl_3 : (a) Shi, Z.; He, Ch. *J. Am. Chem. Soc.*, **2004**, *126*, 5964; (b) Hoffmann-Roder, A.; Krause, N.; *Org. Lett.*, **2001**, *3*, 2537-2538; For the use of PtCl_2 : (a) Barluenga, J.; Dieguez, A.; Rodriguez, F.; Fananas, F.J. *Ang. Chem. Int. Ed.* **2006**, *45*, 2091; (b) Mendez, M.; Munoz, M.P.; Nevado, C.; Cardenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.*, **2001**, *123*, 10511.

Table II.8. Gold-catalysed cyclization fragmentation sequence of phtalimide derivatives 14.



Entry	Cat/solvent	Time	T [°C]	Result
1.	7 mol% Ph ₃ PAuNTf ₂ /DCE	4d	rt	Complex mixture
2.	(C ₆ F ₅) ₃ PAuSbF ₆ /DCE	21h	rt	
3.	AuCl /DCE	50h	rt	
		8h	40	
4.	AuCl ₃ /DCE	16h	80	
		4d	rt	
5.	PtCl ₂ /toluene	5h	40	
		16h	80	
		2h	rt	
		17h	50	
		30h	80	

Despite structural modification of key parts on the starting material, formation of the targeted cyclized product could never be observed under the tested conditions. Simultaneous complexation of the metal catalyst on both the triple bond and the carbonyl group was thus strongly suspected to explain the lack of reactivity observed. Indeed, this kind of complexation would completely prevent the expected cyclization step since the triple bond would be “kept away” from the alkoxy group preventing any reaction from occurring. (Fig II.1.)

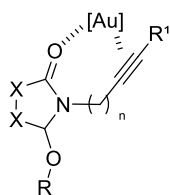


Fig II.1.

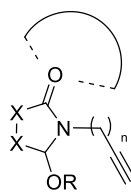


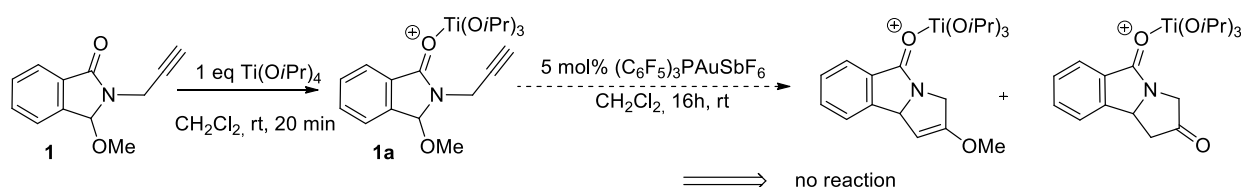
Fig II.2.

Based on those results, we next envisioned masking the carbonyl group from gold catalyst by complexation with Lewis acids. Two Lewis acids known for their oxophilicity were selected: Titanium (IV) isopropoxide Ti(OiPr)₄ and methylaluminum bis(2,6-di-*t*Bu-4-methylphenoxide), MAD.¹²⁰

¹²⁰ Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.

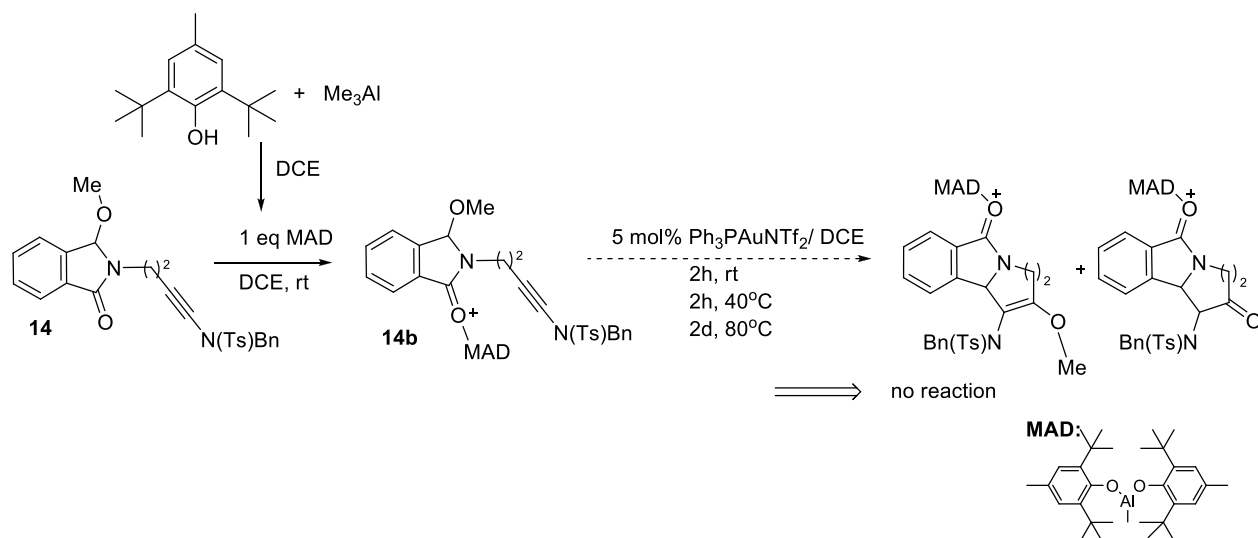
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First, to a solution of 3-methoxy-2-(prop-2-ynyl)isoindolin-1-one **1**, the Lewis acid $\text{Ti}(\text{OiPr})_4$ was added followed by addition of the catalyst formed *in situ* by premixing $(\text{C}_6\text{F}_5)_3\text{PAuCl}$ and AgSbF_6 . (**Scheme II.42.**) Unfortunately, a complete inhibition of the catalyst system was obtained and no conversion (not even hydration side reaction) was observed. To explain this complete lack of reactivity, a competitive coordination of the titanium reagent on the triple bond was suspected.



Scheme II.42. The cyclization-fragmentation of substrate **1** in the presence of $\text{Ti}(\text{OiPr})_4$.

Our next attempt used MAD as a complex agent which is expected to coordinate strongly with various oxygen-containing substrates. (**Scheme II.43.**)¹²⁰ Indeed, a carbonyl group with a relatively unhindered environment (such as in **14**) binds to this type of bulky aluminum reagents rather tightly, the Lewis Acid thus serving the role of a latent carbonyl protecting group. With the idea of making the cyclization step easier, the substrate **14** was chosen.

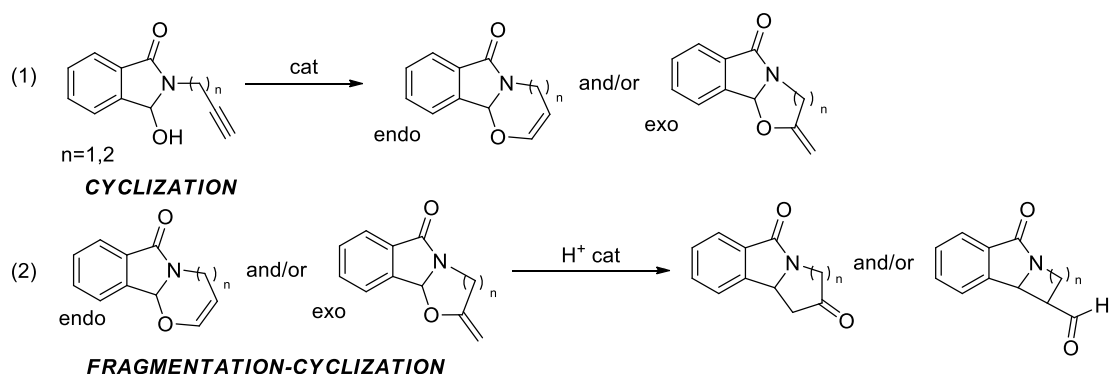


Scheme II.43. Gold-catalyzed cyclization-fragmentation of substrate **14** in the presence of MAD.

Unfortunately, no trace of the expected products was obtained even at elevated temperature. We assumed that MAD could be competitively coordinated to the oxygen atom of the *p*-toluenesulfonyl group thus blocking the whole process.

II.3.2. STEPWISE SEQUENCE

Since a cascade reaction appeared to be problematic, we thus envisioned testing the feasibility of the cyclization-fragmentation reaction in a step-wise manner. This would first involve the heterocyclization of a hydroxylactam which should be more favorable (**Scheme II.44.** eq 1), followed by a subsequent fragmentation-recyclization (**Scheme II.44.** eq 2) under acidic or gold catalysis. Depending on the cyclization mode (*exo* or *endo*), different regioisomers could be potentially formed at the end of the process as shown on **Scheme II.44.**



Scheme II.44. Stepwise strategy.

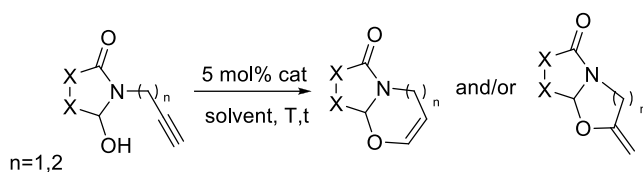
First, the cyclization of the *N*-propargyl hydroxylactam **15** was tested in the presence of some catalysts such as AuCl, AuCl₃ as well as silver salts (ex. Ag₂CO₃) which found many applications in intramolecular hydroalkoxylation reactions with excellent results.¹²¹ Unfortunately, substrate **15** appeared to be unreactive under any of the conditions tested (**Table II.9.** Entries 1-3). Even starting from substrate **16** with a longer homopropargyl chain on nitrogen did not give better results. When Ph₃PAuOTf or Ph₃PAuNTf₂ were used as catalysts, only complex mixtures were formed with no traces of expected products being observed (**Table II.9.** Entries 4-5).

The cyclization of the succinimide-derived hydroxylactam **17** which should give less strained intermediates was also tested. In the presence of 5 mol% of Au(I) catalysts, whether it be with the simplest AuCl or with gold(I) stabilized by a phosphine ligand (Ph₃PAuCl), no conversion was observed and the starting hydroxylactam was only recovered (Entries 6-7). A similar lack of reactivity was also observed when the Au(III) catalyst (AuCl₃) was used (Entry 8).

¹²¹ For some recent examples, see: (a) Reddy, M.S.; Kumar, Y.K.; Thirupath, N. *Org. Lett.*, **2012**, *14*, 824. (b) Corma, A.; Leyva-Perez, A.; Sabater, M.J. *Chem. Rev.* **2011**, *111*, 1657. (c) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174.

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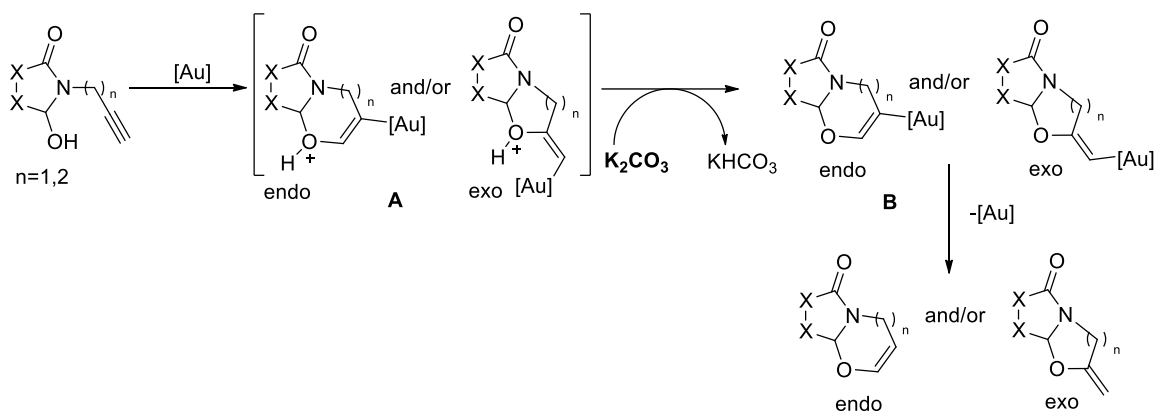
Table II.9. A stepwise sequence- heterocyclization step



Entry	substrate	Cat/solvent	Time	T [°C]	Result
1.	<p>15</p>	AuCl ₃ /DCM	2 d then 4 h	rt 45	NR
2.		AuCl/ CH ₃ CN +5 mol% K ₂ CO ₃	1 d	rt	
3.		Ag ₂ CO ₃ / CH ₃ CN	2h then 20h	rt 45	
4.	<p>16</p>	7 mol% Ph ₃ PAuNTf ₂ / DCM	4 h	rt	Complete conversion of s.m.; complex mixture formed
5.		Ph ₃ PAuOTf/ DCM	4d	rt	s.m. recovered partially
6.	<p>17</p>	Ph ₃ PAuCl/ DCM	2h then 12h	rt 45	NR
7.		AuCl/ CH ₃ CN +5 mol% K ₂ CO ₃	1.5 h then 20h	rt	NR
8.		AuCl ₃ /CH ₃ CN +5 mol% K ₂ CO ₃	1.5 h then 20h	rt 95	NR s.m. recovered partially; Complex mixture

Inspired by a result reported by Pale and co-workers¹²² showing the gold-catalyzed cyclization of acetylenic alcohols, the addition of potassium carbonate was also tested.

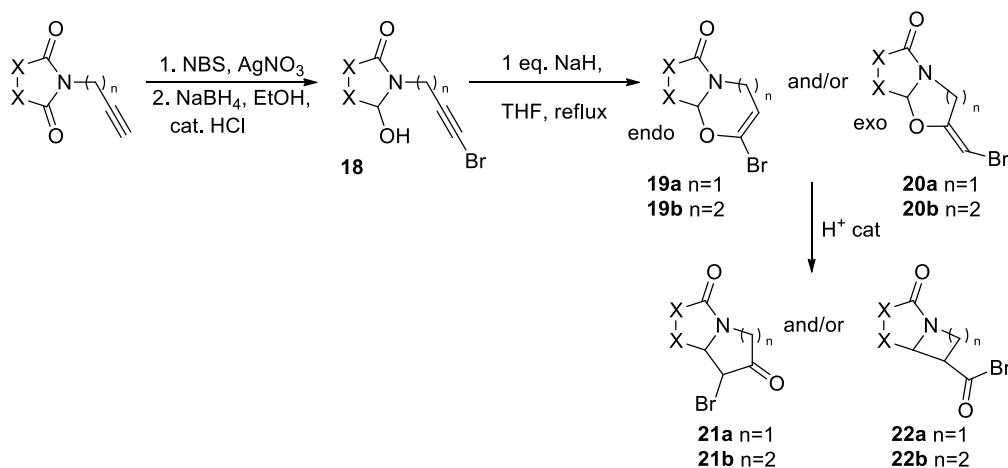
¹²² Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2007**, 48, 1439.



Scheme II.45. Proposed mechanism for the gold-catalyzed cyclization of hydroxylactam in the presence of $K_2CO_3/Au(I)$ complex.

Deprotonation of the oxonium intermediate of type **A** by potassium carbonate was indeed expected to help directing the reaction towards the formation of the expected cyclic enol ethers. Unfortunately, substrates **15** and **17** appeared to be unreactive under the tested conditions (**Table II.9**, Entries 2, 7-8).

As previously mentioned, we suspected that the initial cyclization could be prevented for geometric or electronic reasons. To enhance the electrophilicity of the triple bond, an electron-withdrawing group was next introduced at the terminal position of the alkyne. A series of hydroxylactams possessing a bromoalkyne motif was thus prepared in two steps from the corresponding *N*-propargyl or *N*-homopropargyl imides (silver-promoted bromination followed by $NaBH_4$ reduction). (**Scheme II.46**.)



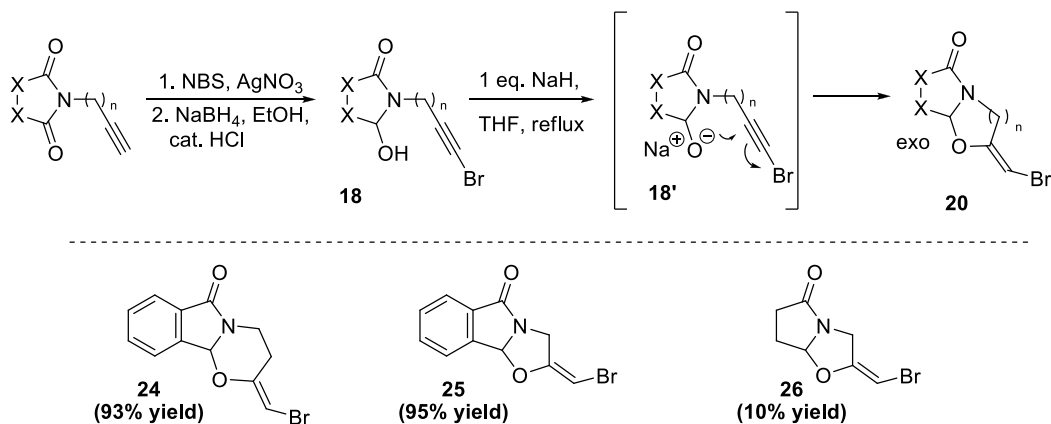
Scheme II.46. The synthesis of substrate **18** and examination of it in the tested reaction.

Since no cyclization of our substrates was observed thus far under the guidance of gold-catalysis, we wanted to check whether the selected type of substrates could actually cyclized

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or not under classical basic conditions. The intramolecular addition of hydroxy group on electro deficient alkynes is known to be feasible in the presence of sodium hydride.¹²³

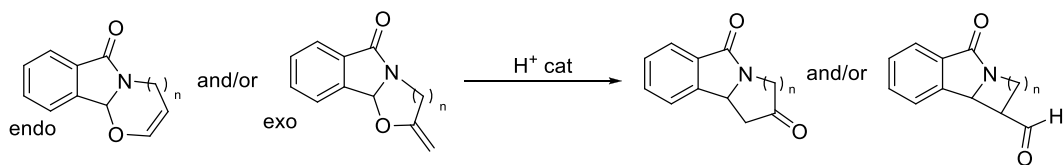
Interestingly, the cycloproducts type **20** could be formed when a stoichiometric amount of NaH was used, though in principle such type of reaction could have been done catalytically.¹²³ This result demonstrates that formation of the intermediate enol ether we expected to obtain in our initial plan, while being difficult, should be possible (**Scheme II.47.**).



Scheme II.47. Preparation of the cycloproducts **24-26**.

With the cyclized products **24** and **25** in hands, the subsequent fragmentation-recyclization step was attempted using cationic gold catalysts (**Table II.10.** Entries 1-3; 8) as well as Lewis or Brønsted acids (**Table II.10.** Entries 4; 6; 9/ 5; 7). Based on the expertise of our laboratory, reagents such as triflimidic acid and tin triflimidate were selected for their high reactivity in catalytic α -amidoalkylations. Unfortunately, the expected products could never be obtained under the different tested conditions. The degradation of the substrates under Lewis and Brønsted acid catalysis was particularly disappointing since these promoters are often recognized to efficiently promote the rearrangement of cyclic enol ethers.¹²⁴

Table II.10. Gold- or acid-catalyzed fragmentation-recyclization step

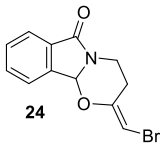
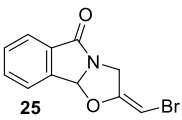
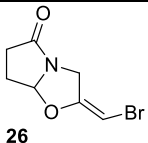


Entry	Starting material	Catalyst/solvent	Time	T [°C]	Result
1.		7 mol% Ph ₃ PAuNTf ₂ /CH ₂ Cl ₂	2h 2d	45 r.t.	NR; s.m. recovered

¹²³ Grandjean, D. ; Pale, P. ; Chucho, J. *Tetrahedron Lett.*, **1992**, 8, 4905.

¹²⁴ For more detail please see the paragraph I.2.2. in Chapter I.

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2.	 <p style="text-align: center;">24</p>	5 mol% Echavarren cat /CH ₂ Cl ₂	1h 2h 2d	r.t. 45 r.t.	
3.		5 mol% (C ₆ F ₅) ₃ PAuSbF ₆ /toluene	1.5h 16h	r.t. 110	Complex mixture
4.		5 mol% Sn(NTf ₂) ₄ /DCE	5 d 1d	r.t. 90	Degradation
5.		5 mol% Tf ₂ NH/DCE	30 min	r.t.	
6.	 <p style="text-align: center;">25</p>	2 mol % Sn(NTf ₂) ₄ /DCE	1.5h 1h	r.t. 90	Complex mixture
7.		5 mol% Tf ₂ NH/DCE	1.5h 19.5h	r.t. 90	NR
8.		7 mol% Ph ₃ PAuNTf ₂ /toluene	17.5h 3h	r.t. 80	Complex mixture
9.	 <p style="text-align: center;">26</p>	2 mol % Sn(NTf ₂) ₄ /DCE	17h	rt	Complex mixture

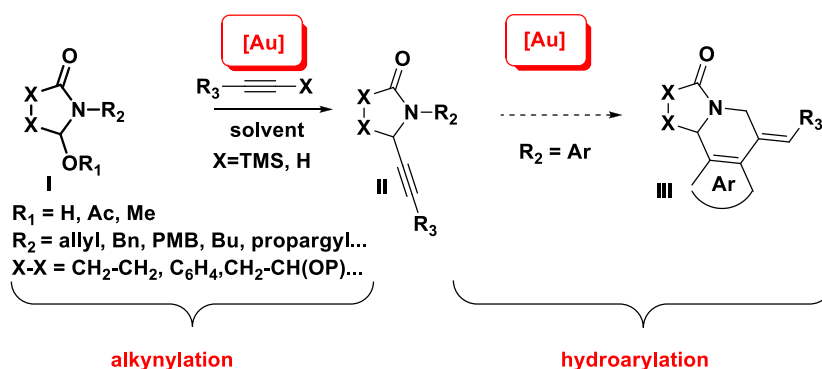
Those results again suggest that the studied systems are not appropriate and, in particular, that the presence of the carbonyl group on the starting *N,O*-acetal may have a detrimental effect on the expected reactivity. As previously mentioned, competitive complexation of the gold species is postulated to explain the lack of reactivity observed in most cases.

Given the encountered difficulties, the feasibility of the cyclization-fragmentation cascade we initially planned appeared to be questionable and we decided to close this part of the project at this point.

***CHAPTER III:
THE GOLD-CATALYZED ALKYNYLATION
REACTION OF N,O-ACETALS***

III. 1. ALKYNYLATION REACTION OF *N,O*-ACETALS

This part of the project is devoted to the development of the first catalytic alkyynylation of cyclic *N*-acyliminium ions using the parent *N,O*-acetals as substrates. (**Scheme III.1.**) This type of reaction is potentially an important transformation, giving rise to propargylic amine derivatives amenable to further interesting synthetic manipulations en route to nitrogen-containing natural products and some analogs. However, in marked contrast to the α -amidoalkylation of the other traditional nucleophiles (allyl- and propargyl trimethylsilanes, silyl enol ethers and ketene silyl acetals, (hetero)aromatics, active methylene compounds...), there are comparably few reports dealing with an alkyynylation process¹²⁵ which will be discussed in this chapter.



Scheme III.1.

Considering our objectives, we will first focus on the bibliographic description of a selection of alkyynylation reactions, that use either terminal alkynes or which are based on the activation of silyl-alkynes, to illustrate the most efficient metallic catalysts commonly used to achieve such transformations, with a special interest given to gold-catalyzed processes.

Then the optimization studies and subsequent exemplification of our own contribution will be discussed, and these will be followed by the generalization of the method to the use of different substrates *N,O*-acetals and various nucleophiles.

A final section will be devoted to the sequential catalysis, also termed as multicatalysis,¹²⁶ which designs the promotion of catalytic multistep processes, whereby one or more mutually

¹²⁵ Recent reviews : (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem Rev.* **2004**, *104*, 1431. (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

¹²⁶ For some recent reviews on multicatalysis, see: (a) Ajamian, A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Chapman, C. J.; Frost, C.-G. *Synthesis*, **2007**, 1. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (f) Palomo, C.; Mielgo, A. *Chem. Asian. J.* **2008**, *3*, 922.

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compatible catalysts work in a cooperative manner. In this way, two fundamentally distinct chemical transformations will be catalytically promoted in a single flask. This research area allows the rapid and efficient reach of complex molecular frameworks with improved yields and resource efficiency. Therefore, this is an exciting theme in modern organic synthesis that has recently stimulated the report of numerous excellent contributions.

In this context, the ultimate goal of this part of the project is to combine the gold-catalyzed alkynylation with a subsequent carbocyclization in a cascade sequence. This would be made possible by the alkynophilic properties of the metal and use of substrates equipped with a participating function at nitrogen such as electron-rich arylmethyl moieties. Thus, upon installation of properly chosen substituents on both the alkyne nucleophile and the nitrogen atom of our *N,O*-acetals, various types of cycloisomerization will occur (see substituents R_2 and R_3 in **Scheme III.1**).¹²⁶ This kind of catalytic cascade amidoalkylation-carbocyclization is unprecedented in *N*-acyliminium ion chemistry and would undoubtedly offer a very simple and straightforward access to complex alkaloid frameworks starting from trivial materials.

III.1.1. Alkynylation reaction of *N,O*-acetals

N-acyliminium ions play very important role in organic synthesis since they are intermediates in the synthesis of many compounds with important biological properties.^{125,127} Then the nucleophilic addition onto *N*-acyliminium ions, often obtained from *N,O*-acetals, is an important method to provide α -functionalized amino compounds and, in consequence, to form alkaloids or other biologically active nitrogen heterocycles.^{126d,128}

As previously mentioned, α -amidoalkylations starting from *N,O*-acetals derivatives are well documented for a wide range of nucleophiles such as allylsilanes,¹²⁹ allyl-,¹³⁰ or enol derivatives,¹³¹ while only few reports describe the reactions with alkenyl-, alkynyl- and arylmetal derivatives. After the seminal contributions of Batey's and Pyne's groups on the development of stereoselective addition reactions of alkenyl- and arylboronates to activated *N*-acyliminium ion precursor under Lewis acid catalysis,¹³² Vieira *et al.* reported the first stereoselective addition reactions of aryl- and alkynyltrifluoroborates to tartaric acid-derived endocyclic *N*-acyliminium ion intermediates (**Table III.1**).^{126d}

¹²⁷ For reviews on *N*-acyliminium ion chemistry, see: Chapter I of this manuscript; (a) de Koning, H.; Speckamp, W. N. In Houben-Weyl, Stereoselective Synthesis; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; 1995; Vol. E21, p 1953; (b) Vieira, A. S.; Ferreira, F. P.; Fiorante, P. F.; Guadagnin, R. C.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 3306.

¹²⁸ (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717; (b) Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187; (c) El-Nezhawy, A. O. H.; El-Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137; (d) Chen, B.-F.; Tasi, M.-R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron* **2004**, *60*, 10223; (e) Huang, P.-Q. *Synlett* **2006**, 1133; (f) The Alkaloids: Chemistry and Biology; Cordell, G. A., Ed.; Academic: San Diego, CA, 1998; Vol. 50.

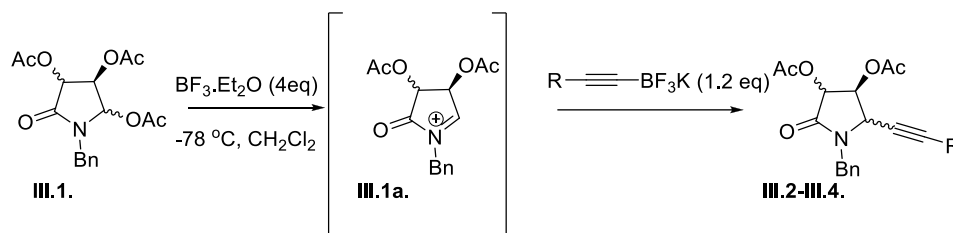
¹²⁹ (a) Russowsky, D.; Petersen, R. Z.; Godoi, M. N.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 9939; (b) Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605; (c) Andrade, C. K. Z.; Rocha, R. O.; Russowsky, D.; Godoi, M. N. *J. Braz. Chem. Soc.* **2005**, *16*, 535; (d) Ben Othman, R.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825; (e) Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335;

¹³⁰ (c) Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* **1994**, *35*, 1561; (d) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604.

¹³¹ (e) Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron* **2002**, *58*, 9359; (f) Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron* **2004**, *60*, 8089; (g) Oba, M.; Mita, A.; Kondo, Y.; Nishiyama, K. *Synth. Commun.* **2005**, *35*, 2966.

¹³² (a) Batey, R. A.; Mackay, B. D.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075; (b) Morgan, I. R.; Yazici, A.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 1409.

Table III.1. Potassium organotrifluoroborates addition to *N*-acyliminiums



Entry	Nucleophile	Product	Synt/anti ratio	Yield [%]
1.	$C_6H_5BF_3K$	 III.2.	90:10	84
2.	$Ph\equiv BF_3K$	 III.3.	90:10	73
3.	$nC_4H_9\equiv BF_3K$	 III.4.	70:30	83
4.	 $MeO\text{-}CH_2\text{-}C\equiv\text{CH}\text{-}BF_3K$	 III.5.	80:20	78
5.	$6\text{ CH}_3\text{O-C}_{10}\text{H}_6\text{-}\equiv\text{BF}_3K$	 III.6.	70:30	71
6.	$3,5(\text{CF}_3)_2\text{C}_6\text{H}_3\text{-BF}_3K$	 III.7.	70:30	65

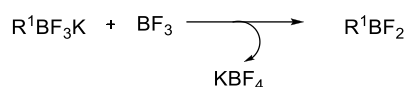
After development of an optimal set of reaction conditions for the arylation of pyrrolidinone derivative **III.1.**, it was found that presence of 4.0 equivalents of the Lewis acid $BF_3\cdot OEt_2$ was absolutely necessary to reach high level of reactivity and selectivity. The scope of the reaction was next evaluated with different potassium aryl- and alkynyltrifluoroborates and, as demonstrated in **Table III.1.**, the alkyne reaction turned out to proceed in good yields and good levels of diastereoselection in favor of the *cis*-adduct, irrespective of the substitution pattern on the triple bond.

Concerning the mechanism of the reaction, the requirement for Lewis acidic activation strongly supports the intermediacy of *N*-acyliminium ions in the reaction. Based on results described by Kaufmann *et al*¹³³, it is known that $BF_3\cdot OEt_2$ can also react with potassium organotrifluoroborate to provide organoboron difluoride which is also a Lewis acid able to

¹³³ Bir, G.; Schacht, W.; Kaufmann, D. *J. Organomet. Chem.* **1988**, 340, 267.

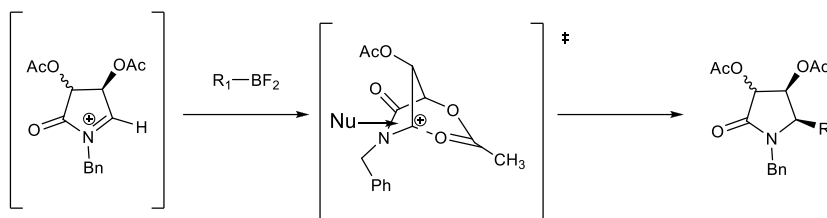
CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

activate the hemiaminal and generate an iminium and a nucleophilic species. (**Scheme III.2.**) Thus, the active nucleophile could also potentially be the corresponding R^1BF_2 species, that is to say the alkynylboron difluoride in this specific reaction.



Scheme III.2. Generation of R^1BF_2 species.

The diastereoselection in favor of the *cis*-adduct is unexpected since neighbouring group participation of the 4-O-Acetyl group in the stereocontrol does not seem to be affective. Nevertheless, it is possible that the 3-O-Acetyl group provides anchimeric assistance, which leads to preferential formation of the *syn*-isomer (**Scheme III.3.**).



Scheme III.3. Stereoselective addition of the R_1BF_2 to the *N*-acyliminium ion intermediate.

Based on the literature report on the preferential *cis* addition of nucleophiles to *N*-acyliminium ions writers hypothesized that the stereochemical outcome is not ruled by steric effects. The observed *syn* preference indicates favourable orbital interaction¹³⁴ over steric interaction experienced during *syn* approach of the boron nucleophile to the resident -OAc group of *N*-acyliminium intermediate in the presence of the Lewis acid. Danishefsky et al.¹³⁵ suggested that in the $BF_3 \cdot Et_2O$ -mediated process the stabilisation of the emerging s^* orbital interaction with the adjacent σ bonds becomes critical factors for the *syn* additions.

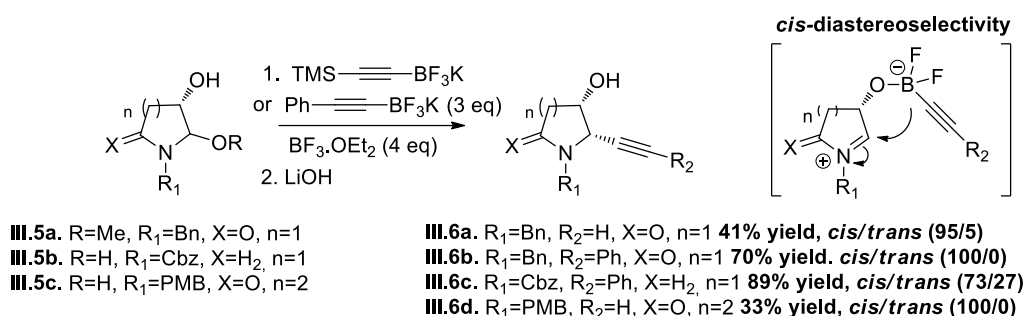
Under similar conditions, the *cis*-hydroxyalkynes **III.6a-b.** were prepared by reactions between the hemiaminal **III.5a** derived from (*s*)-malic acid and the required potassium alkynyltrifluoroborates in good yields and with high *cis*-diastereoselectivity (**Scheme III.4.**)¹³⁶ It is worth pointing out that the reaction with the more reactive *N*-Cbz-4,5-dihydropyrrolidine **III.5b.** still provided the corresponding product **II.6c.** in high yield (89%) but as a 73:27 mixture of *cis/trans* diastereomers. Extension of the scope to six-

¹³⁴ Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509.

¹³⁵ (a) Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387; (b) Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.

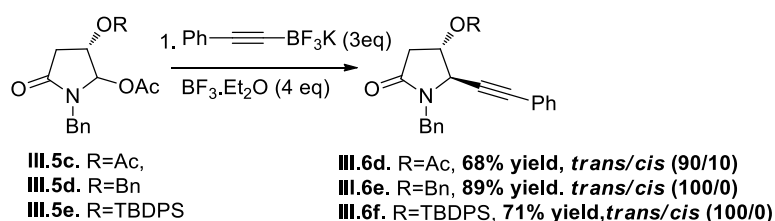
¹³⁶ Jury, J. C.; Swamy, N. K.; Yazici, A.; Willis, A. C.; Pyne, S. G. *J. Org. Chem.* **2009**, *74*, 5523.

membered analogs appeared to be more challenging due to the competitive formation of a by-product resulting from a competitive Ritter reaction. For instance, the alkynylation of hemiaminal **III.5c**. gave the expected 5,6-*cis*-adduct **III.6d**. in 33% isolated yield only. A high diastereoselectivity was however maintained. The stereochemical outcome of the reactions was proposed to arise from the formation of a boronate intermediate involving the free hydroxyl group of the substrates.



Scheme III.4. Synthesis of *cis*- β -hydroxy alkynes **III.6a-d**.

Accordingly, as depicted on **Scheme III.5**., when the reactions were conducted with the 4-*O*- and 5-*O*-protected analogous heminals **III.5c-e**. (malic acid derivatives), good yields and high *trans*-diastereoselectivities were obtained.



Scheme III.5. Synthesis of *trans*- β -hydroxy alkynes **III.6d-f**.

While the alkynylated compounds thus obtained were shown by the same authors to give access to furo[3,2-*b*]pyrrole and furo[3,2-*b*]pyridine nucleus which are interesting classes of compounds for biological applications,¹³⁷ a comparable BF₃·OEt₂-promoted alkynylation of an *N,O*-acetal derivative was successfully employed in the total synthesis of (\pm)-stemoamide.¹³⁸ This time, the key reaction involved the nucleophilic addition of an acetylenic tributylstannane onto a pyrrolidinone substrate (92% yield).

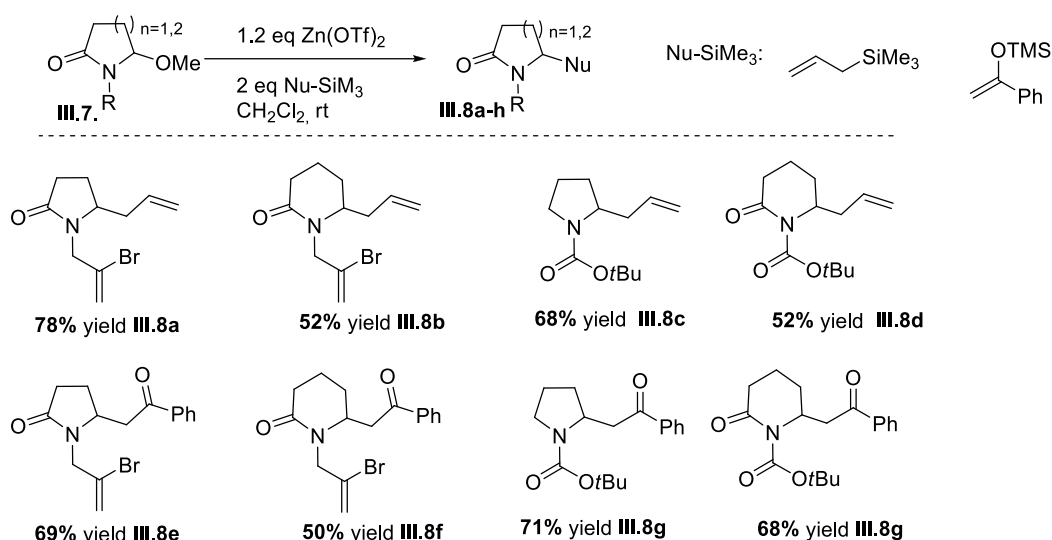
¹³⁷ (a) Bashyal, B. P.; Faeth, S. H.; Gunatilaka, A. A. L. *Nat. Prod. Commun.* **2007**, 2, 547; (b) Kakeya, H.; Kageyama, S.-I.; Nie, L.; Onose, R.; Okada, G.; Beppu, T.; Norbury, C. J.; Osada, H. *J. Antibiot.* **2001**, 54, 850.

¹³⁸ Jacobi, P.; Lee, K. *J. Am. Chem. Soc.* **1997**, 119, 3409.

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The alkynylation reaction of *N,O*-acetals was also evaluated using organozinc derivatives which constitute a class of organometallic reagents well-known for their compatibility towards a broad range of functional groups.¹³⁹

Pilli and co-workers¹⁴⁰ have tested the ability of zinc triflate to promote the formation of *N*-acyliminium ions and then their *in situ* trapping by various nucleophiles. (Scheme III.6.)



Scheme III.6. Zinc triflate mediates addition of silyl-nucleophiles to cyclic *N*-acyliminium ions derived.

During the course of the investigation it was found that the use of 1.2 eq of zinc triflate as a Lewis acid in the nucleophilic addition of the allyltrimethylsilane or the silyl enol ether to a cyclic *N*-acyliminium ions intermediates affords the corresponding products **III.8a-h** in moderate to good yields. Nevertheless, better results were observed with five-membered precursors, compared to six-membered analogues. This observation was rationalized by a difference in the intrinsic electrophilic character of the five- ad six-membered *N*-acyliminium ions¹⁴¹ or/and in their relative rates of formation.

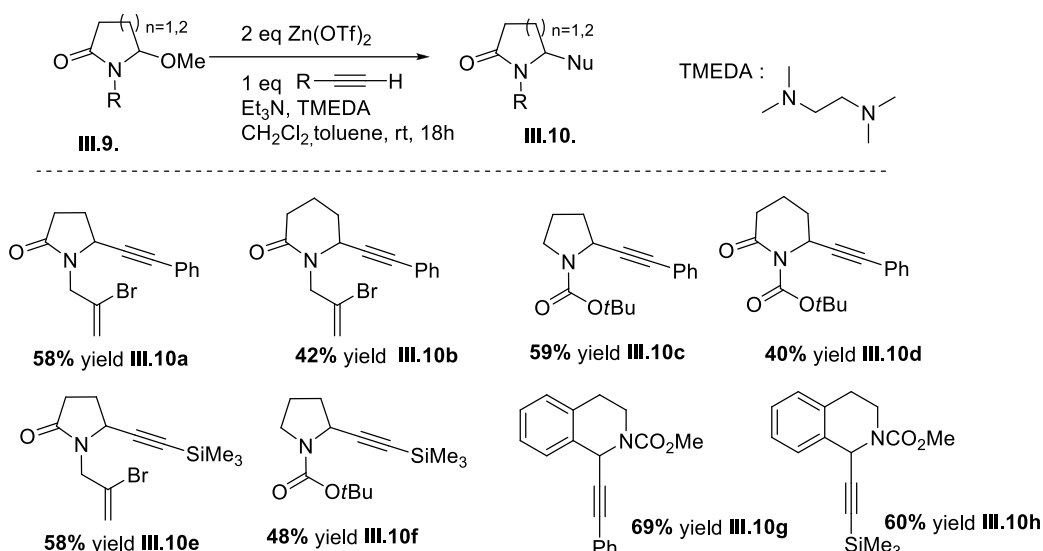
The authors have also tested the ability of zinc triflate to promote formation of propargylic adducts. (Scheme III.7.) It was demonstrated that treatment of a mixture of *N,O*-acetals, acetylene and Zn(OTf)₂ in toluene-CH₂Cl₂ solution with Et₃N and TMEDA provided the corresponding products **III.10a-h** in moderate yields. (Scheme III.7.)

¹³⁹ Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.

¹⁴⁰ Pilli, R.A.; Robello, L.G. *Synlett*, **2005**, *15*, 2297.

¹⁴¹ D'Oca, M. G. M.; Moraes, L.A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854.

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Scheme III.7. Zinc triflate-mediated addition reaction of acetylenes to cyclic *N*-acyliminium ions driven.

Du Bois *et al.* have tested a class of oxathiazinane *N,O*-acetals that function with exceptional performance as latent *N*-sulfonyliminium ions (**Table III.2**).¹⁴² Access to such substrates was realized through a Rh-catalyzed sulfamate ester C-H insertion, a method previously developed by the same research team.

Table III.2. Alkynylzinc addition reactions with *N,O*-acetals

Entry	R	Major isomer	<i>cis/trans</i>	yield
1.	Et		100:0	92%
2.	Et		20:1	85%
3.	Et		20:1	82%
4.	Me		12:1	71%

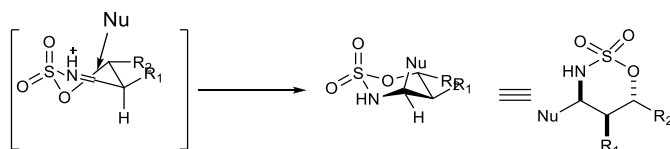
The authors demonstrated the high electrophilic reactivity of this class of *N,O*-acetals in $\text{BF}_3 \cdot \text{OEt}_2$ -promoted reactions with a range of preformed alkynylzinc reagents used in situ. A selected set of examples are presented on **Table III.2**. The addition of metal acetylides (prepared by transmetalation of the Li-acetylides with ZnCl_2) to such starting materials

¹⁴² Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, 125, 2028.

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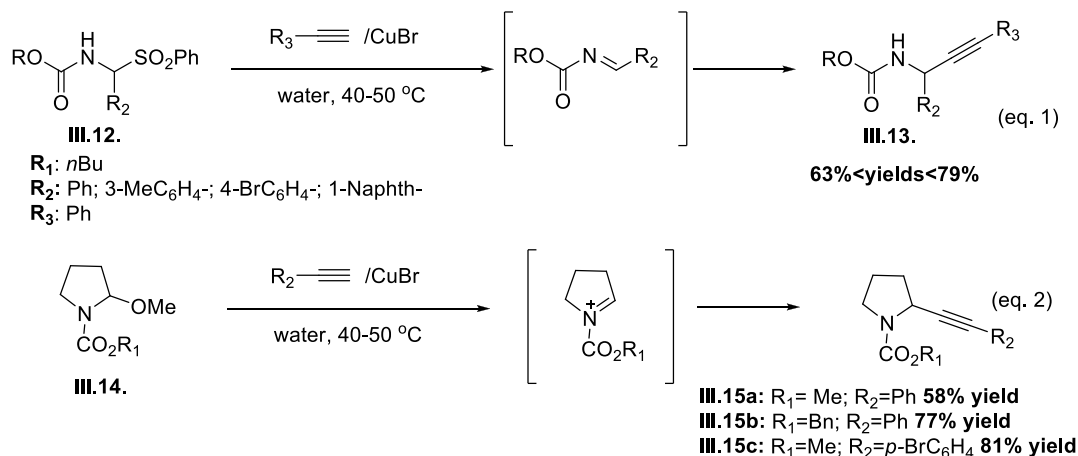
afforded the corresponding alkyne products in high yields and diastereoselectivity (in favor to the *cis* diastereomer) that could easily be used for other subsequent chemical manipulations.¹⁴³

Observation of the *cis*-diastereoselectivity was rationalized by an axial attack of the alkynyl anion on the twist-chair form of the iminium intermediate which could thus give the *cis*-C4,C5 stereochemistry (**Scheme II.8**).



Scheme III.8. Nucleophilic attack on the iminium intermediate.

Copper (I) salts, such as CuBr, were also described to efficiently promote alkyne reactions of *N,O*-acetals and even less reactive *N*-acylimine precursors. Li and co-workers¹⁴⁴ have thus developed conditions for the efficient coupling of terminal alkynes with *N*-carbamate pyrrolidine derivatives or α -sulfonyl *N*-acylamine acyclic substrates requiring the presence of 2 – 3 equivalents of CuBr in water to promote the formation of the corresponding electrophilic intermediates (**Scheme III.9**).



Scheme III.9. Terminal alkynes addition to *N*-acylimines and *N*-acyliminium ions

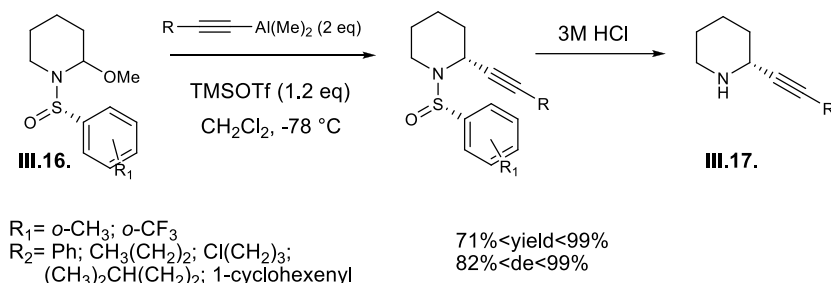
In most cases, the resulting propargylamine derivatives were obtained in satisfactory yields, greater than 58%.

The alkyne reaction of piperidine-derived *N,O*-acetals is often reported to be more problematic than pyrrolidine derivatives and thus elicited the interest of many research

¹⁴³ For the addition of zinc acetylides to a variety of electrophiles, see: Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.

¹⁴⁴ Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731.

groups.¹⁴⁵ One interesting work was reported recently by Royer and co-workers¹⁴⁶ who developed a method for the stereoselective alkyne reaction of α -methoxy *N*-sulfinylpiperidine derivatives relying on the use of an organoaluminium nucleophile. (**Scheme III.10.**)



Scheme III.10. The alkyne reaction of piperidine derivatives.

The *N*-sulfinyliminium species was *in situ* formed by addition of a stoichiometric amount of a strong Lewis acid, TMSOTf, to the methoxy compound **III.16**, followed by addition of the dimethylalkynylaluminium reagent. The method enables formation of the product in good yields and very high diastereoselectivity depending on the substitution pattern of the aromatic group on the sulfinyl auxiliary. After deprotection of the amine function under acidic conditions, the corresponding propargylamines could be obtained with yields up to 99%.

As another classical precursors of highly reactive cationic electrophilic intermediates, we also considered the alkyne reaction of acetals. This class of substrates is indeed known to undergo S_N1 -type reactions, likewise *N,O*-acetals, *via* the formation of oxocarbenium ion intermediates under Lewis- or Brønsted acid conditions. In the context of *C*-glucosides synthesis, Lubin-Germain *et al.*¹⁴⁷ tested the addition, under Barbier conditions, of *in situ* formed alkyneindium reagents on acetylated carbohydrates. (**Scheme III.11.**)

While applying this indium-mediated alkyne reaction method to 2-deoxy acetylated pyranosyl or furanosyl carbohydrates afforded the corresponding *C*-alkynylated glucosides in good yields and variable diastereoselectivities, extension of this methodology to carbohydrates bearing an oxygen atom on position 2 required nonparticipating protecting groups such as acetonide or benzyl groups for success. Presumably the anchimeric participation of a

¹⁴⁵ (a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (c) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.

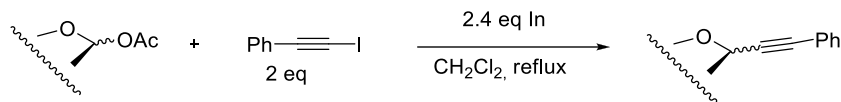
¹⁴⁶ Turcaud, S.; Sierecki, E.; Martens, T.; Royer, J. *J. Org. Chem.* **2007**, *72*, 4882.

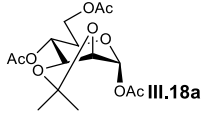
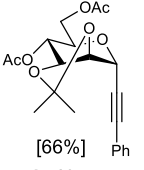
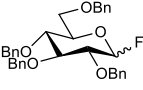
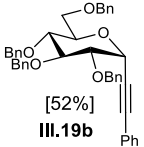
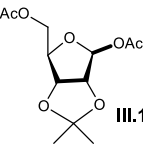
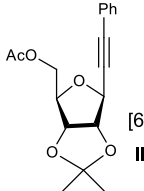
¹⁴⁷ Lubin-Germain, N.; Baltaze, J.P.; Coste, A.; Hallonet, A.; Laureano, J.; Legrave, G.; Uziel, J.; Auge, J. *Org. Lett.*, **2008**, *10*, 725.

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neighboring group stabilizes the oxocarbenium ion to such an extent that the addition of the weakly nucleophilic alkynyl partner is no longer permitted.

Table III.3. Indium-mediated alkylation of carbohydrate derivatives.



Entry	Starting material	Anomeric mixture	Time	Product [yield%]	C-1 configuration
1.	 III.18a	$\alpha/\beta > 98/2$	24h	 [66%] III.19a	$\alpha/\beta > 98/2$
2.	 III.18b	$\alpha/\beta = 10/90$	16h	 [52%] III.19b	$\alpha/\beta = 80/20$
3.	 III.18c	$\alpha/\beta = 14/86$	24h	 [60%] III.19c	$\alpha/\beta = 3/97$

III.1.2. ALKYNYLATION REACTIONS WITH TERMINAL ALKYNES

Over the past years, the importance of the chemistry of $-C\equiv C-$ has been well recognized since this functional group has been shown to be one of the main building blocks of organic and material chemistry.¹⁴⁸ Many bioactive molecules, as for example SIB-1508Y (known as altinicline), tazarotene, etc..., indeed contain an alkyne moiety in their structures.

As illustrated in the previous section, several metals were proven to insert efficiently in the $C_{sp}-H$ terminal bond of alkyne derivatives in the context of stoichiometric alkylation methodologies. Among all the methods available in the area of $C_{sp}-H$ activation, the most appealing strategies are obviously the one whereby the nucleophilic metal acetylide is generated catalytically and used directly for addition on an electrophilic species. Many examples implementing this feature were reported lately. However, considering our

¹⁴⁸ (a) Patai, S. *Chemistry of Triple-Bonded Functional Groups*, Wiley, New York, NY, **1994**, pp. 689–737; (b) Stang, P. J.; Diederich, F. *Modern Acetylene Chemistry*, VCH, Weinheim, Germany, **1995**.

objectives, the following state of the art presentation will focus on a few selected reactions to illustrate the most efficient metallic catalysts commonly used to achieve such transformations, with a special interest given to gold-catalyzed processes. Besides, many catalytic alkynylation reactions were developed with a wide variety of electrophiles in the past two decades. In this context, the palladium-catalyzed Sonogashira reaction appeared to be one of the most attractive and efficient method for the coupling of terminal alkynes and halides (C–X).¹⁴⁹ But, priority will be given in this chapter to S_N1-type reactions involving cationic intermediates generated *in situ* (i.e. *N*-acyliminiums, iminiums, and carbocations).

- Alkynylation of imines / iminiums

Due to their importance as structural building blocks in organic synthesis,¹⁵⁰ the preparation of propargylamines using alkynylation reactions was widely investigated. Traditionally, methods to prepare propargylamides include the Ritter reaction of olefins with nitriles,¹⁵¹ or the nucleophilic addition of pre-formed acetylides to imines¹⁵² followed by acylation. Because these classical methods sometimes require drastic conditions, present a lack of functional group compatibility and a limited scope, many research groups study alternative metal-catalyzed reactions based on the nucleophilic addition of *in situ* generated metal acetylides to imines.¹⁵³

Copper catalysis thanks its environmental and economic character,¹⁵⁴ has a promising potential in this area and elegant contributions involving copper salts catalysts have appeared in the recent literature.

One of the first examples of direct addition of acetylenic compounds to imines made *in situ* was reported by Li *et al.* (**Scheme II.17.**). Their A³ (aldehyde, amine, alkyne) method combined Cu–Ru catalysis for efficient addition of acetylenes to imines via C–H activation in

¹⁴⁹ Chinchilla, R.; Najera, C. *Chem. Soc. Rev.*, 2011, **40**, 5084.

¹⁵⁰ (a) Arcadi, A.; Cachi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.*, **2001**, *3*, 2501. (b) Kayaki, Y.; Yamamoto, M.; Suzuki, T.; Ikariya, T. *Green Chem.* **2006**, *8*, 1019.

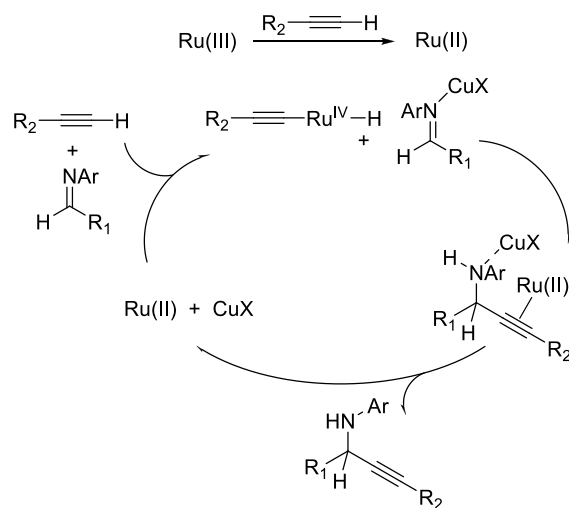
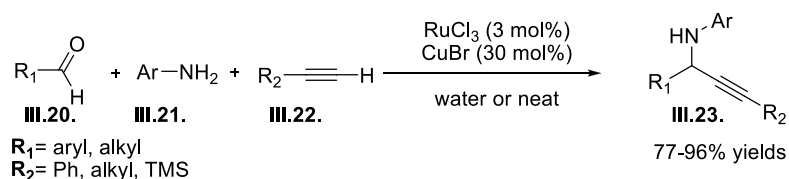
¹⁵¹ Ritter, J.J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.

¹⁵² Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

¹⁵³ (a) Wei, C.; Li, C-J.; *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Li, C-J.; Wei, C. *Chem. Comm.* **2002**, 268. (c) Koradin C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2535.

¹⁵⁴ For some reviews on copper-catalyzed reactions, see: (a) Ley, S.V.; Thomas, A.W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (b) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359. (c) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874.

water or under solvent-free conditions. The process was simple and generated a diverse range of propargylic amines in excellent yields. Aliphatic alkynes, such as hexyne and trimethylsilylacetylene, were also found to be effective for the reaction.¹⁵⁵



Scheme III.17. Cu-Ru-catalyzed direct addition of alkynes to imines.

A tentative mechanism was proposed which involves the simultaneous activation of the C–H bond of alkyne by a Ru(II) species (possibly generated *in situ* from reduction of Ru(III) by the alkyne) and the imine by the copper complex. The ruthenium intermediate thus generated then underwent Grignard-type addition to the activated imine to give the desired nucleophilic addition product and regenerated the ruthenium and copper catalysts for further reactions. It is worth pointing out that Carreira and co-worker independently, reported a very similar coupling by using an iridium catalyst in toluene or under neat conditions.¹⁵⁶

As previously mentioned, Li and collaborators also described the CuBr-promoted addition of terminal alkynes to *in situ* generated imines and iminiums (Scheme III.9).¹⁴⁴ Since these preliminary contribution which implied use of 2-3 equivalents of CuBr, developments of catalytic variants employing copper salts such as CuBr, or Cu(OTf)₂ were achieved by different groups.¹⁵⁷ Although very efficient, most of the initial examples however displayed a limited reaction scope involving mainly aromatic alkynes and/or imines resulting from

¹⁵⁵ Li, C. J. Wei, C. M. *Chem. Commun.* **2002**, 268.

¹⁵⁶ Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, 3, 4319.

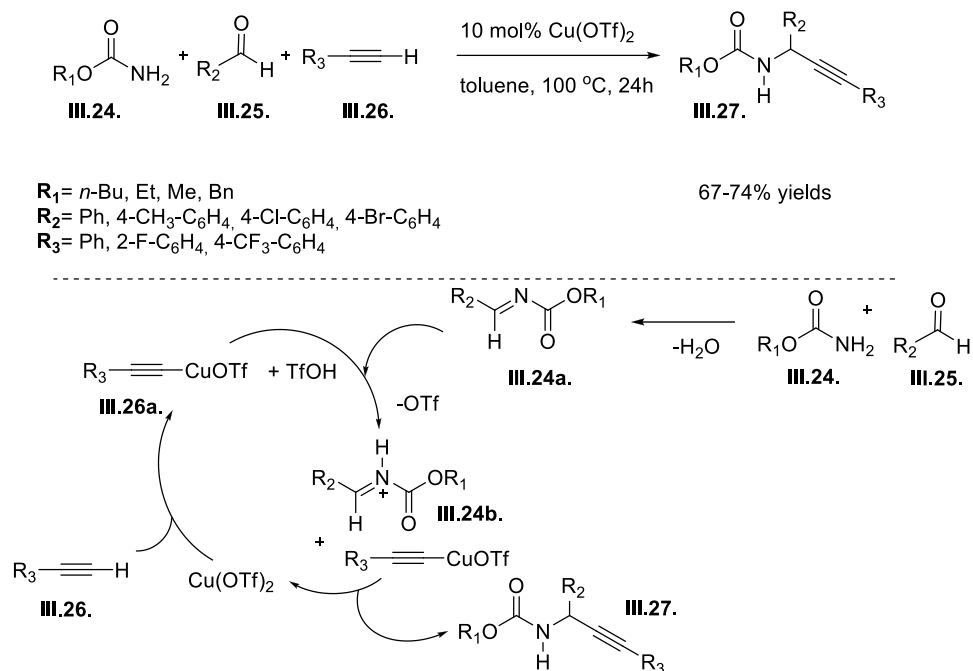
¹⁵⁷(a) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.*, **2007**, 9, 2997. (b) Feng, Y.-S.; Xu, Z.-O; Mao, L., Zhang, F.-F.; Xu, H.-J. *Org. Lett.*, 2013, 15, 1472.

condensation of amines and aldehydes both being aromatic. As shown next, a number of recent research efforts were thus focused either on the extension of the reaction scope to challenging substrates or on the use of Cu-catalyzed alkynylation in cascade sequences to demonstrate their synthetic potential. These latter transformations then yield propargylamines as intermediates being transformed *in situ*.

Due to atom-economy consideration and stability issues, imine substrates are often formed *in situ* using a multi-component reaction involving aldehydes, alkynes and amines (A³-coupling) and resulting in the formation of water as the only by-product. While a great deal of progress has been made with secondary and aromatic amines, other aliphatic primary amines and amide derivatives have long been challenging starting materials. To push the limits of this kind of transformation, Li and co-workers¹⁵⁸ have for example developed the copper-catalyzed A³-coupling reaction for the direct synthesis of propargylcarbamates, a methodology which relies on *N*-acyliminium ion chemistry. (**Scheme III.18.**) After optimization study, it was demonstrated that reaction with 1.0 eq of aldehyde **III.25.**, 1.2 eq of carbamate **III.24.** and 1.5 eq of alkyne **III.26.** in the presence of 10 mol% of Cu(OTf)₂ provided the expected products in moderate to high yields with no need of co-catalyst or ligand. The writers postulated a mechanism where copper-acetylide **III.26a.** would be formed. Meanwhile, reaction of carbamate **III.24.** with aldehyde **III.25.** would generate an imino carbamate intermediate **III.24a.** which would be next protonated by TfOH generated *in situ* to form the acyclic protio *N*-acyliminium intermediate **III.24b.** Finally, after nucleophilic addition of the copper acetylide **III.26a.**, the propargylic carbamate product would be formed. (**Scheme III.18.**)

¹⁵⁸ Dou, X.-Y.; Shuai, Q.; He, L.-N.; Li, Ch.-J. *Adv. Synth. Catal.* **2010**, 352, 2437.

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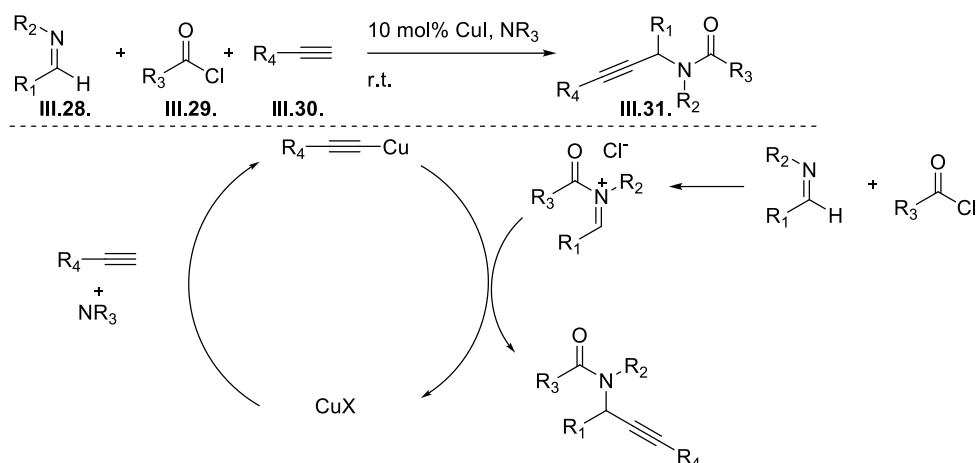


Scheme III.18. Copper catalyzed AAA-coupling reaction.

The terminal alkynes could also easily accommodate the coupling reactions with imines and acid chlorides, another sub-class of reaction based on *N*-acyliminiums. To promote such reactions, Carreira¹⁵⁹ reported the successful use of zinc triflate whereas Arndsten and Black¹⁶⁰ rather used copper salts to catalyze the formation of the corresponding tertiary propargylamides. (**Scheme III.19.**) The presented results demonstrated that in the presence of 10 mol% of CuI under basic conditions the expected products could be smoothly obtained in good yields.^{160a} The proposed mechanism of the reaction is shown on **Scheme III.19.**: a copper-acetylide is expected to be generated first, followed by its attack on an *in situ* generated *N*-acyliminium salt resulting from the attack of the starting imine to the acid chloride.

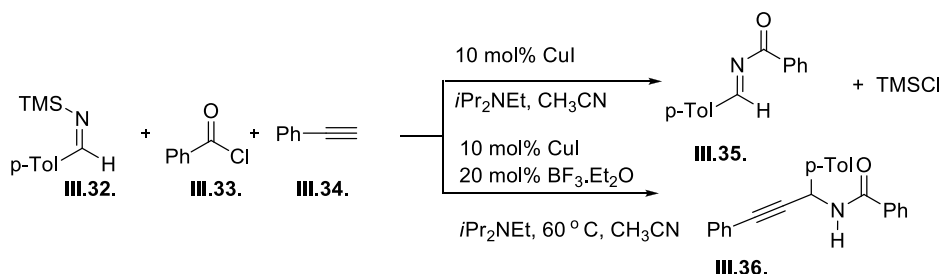
¹⁵⁹ Fisher, Ch.; Carreira, E.M. *Org. Lett.* **2004**, *6*, 1497.

¹⁶⁰ (a) Black, D.A.; Arndsten, B.A. *Org. Lett.* **2004**, *6*, 1107 (b) Black, D.A.; Arndsten, B.A *Tetrahedron*, **2005**, *61*, 11317.(c) Black, D.A.; Beveridge, R.E.; Arndsten, B.A. *J. Org. Chem.* **2008**, *73*, 1906.



Scheme III.19. Cu-catalyzed coupling reaction of imines, acid chlorides and alkynes.^{160a}

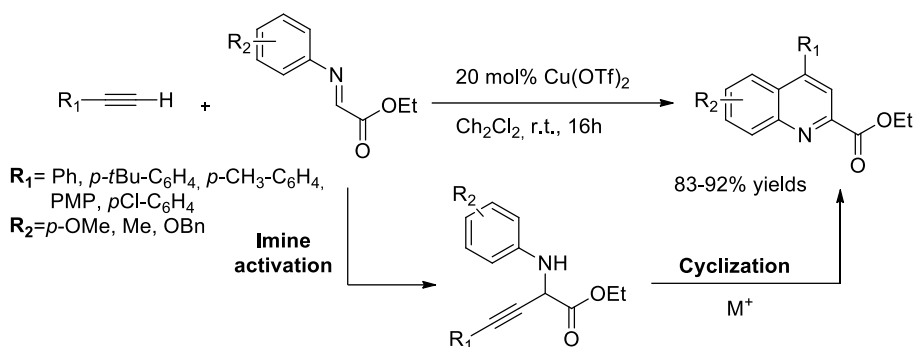
Further investigation of the same research group extended the method to the synthesis of secondary propargylamides, starting this time from trimethylsilyl-substituted imines **III.32.**, alkynes and acid chlorides in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as co-catalyst.^{160b} (Scheme III.20.) The strategy employed trimethylsilyl substituted imines **III.32.** as N-H imine surrogates. When copper(I) catalysis was tested alone, only elimination of TMSCl and formation of *N*-acyl imines **III.35.** were observed. In order to facilitate addition of the alkynyl group, use of a Lewis acid co-catalyst was tested in combination with copper salts to circumvent the low electrophilic character of *N*-acylimines (relatively to *N*-acyliminium salts). Using this multicatalytic system, the propargylamide **III.36.** could be isolated in good yield (72%).



Scheme III.20. Coupling reaction of trimethylsilyl-substituted imines, acid chlorides and alkynes.^{160b}

A nice application was reported in 2009 by Liu *et al.*¹⁶¹ who described a straightforward copper-catalyzed method for the synthesis of quinoline-2-carboxylate derivatives through sequential intermolecular addition of terminal alkynes onto imines and subsequent intramolecular ring closure by Friedel-Crafts-type arylation. (Scheme III.21.)

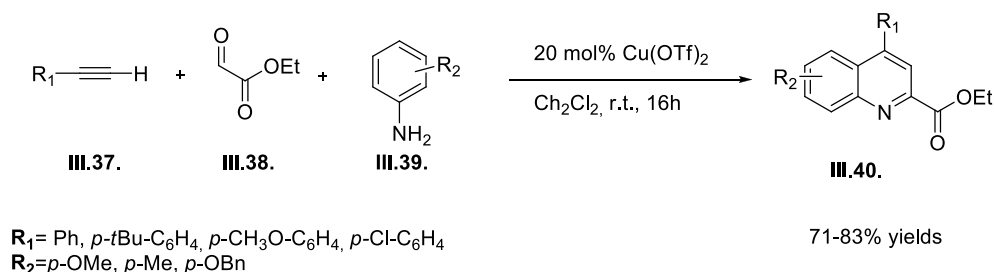
¹⁶¹ Huang, H.; Jiang, H.; Chen, K.; Liu, H. *J. Org. Chem.* **2009**, *74*, 5476.



Scheme III.21. Cu-catalyzed synthesis of quinoline-2-carboxylates.

They started their investigation with phenylacetylene and *N*-PMP α -iminoethyl glyoxylate (PMP= *p*-methoxyphenyl) as a model reaction partners and demonstrated that use of 20 mol% of $Cu(OTf)_2$ in dichloromethane proved to be the most efficient conditions. The scope of the reaction was expanded to a variety of both aromatic alkynes and α -iminoethyl glyoxylates, and moderate to excellent yields were generally obtained under the optimized conditions at room temperature. However, the catalytic process was unsatisfactory with aliphatic alkynes and a higher temperature (50 °C) was necessary for achieving sufficient conversion. Reactions of imines incorporating electron-donating or electron-neutral substituents such as methoxy, benzyloxy, or methyl groups at the 4-position on the phenyl ring were found to proceed equally well.

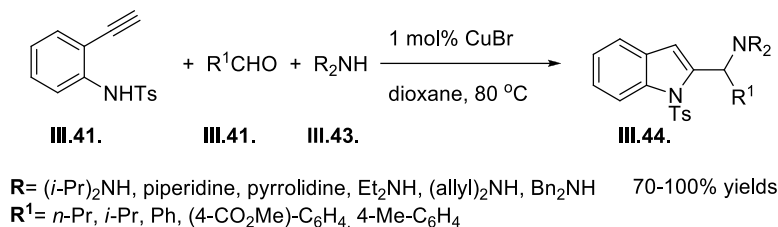
It is also important to note that this protocol could also be used in a one-pot three-component reaction. As outlined on **Scheme III.22.**, ethyl glyoxylate **III.38.** and aniline **III.39.** reacted with alkynes **III.37.** in the presence of $Cu(OTf)_2$ catalyst to afford quinoline 2-carboxylates **III.40.** under mild conditions (rt, 24h). Good yields could be obtained for reactions where representative aromatic alkynes and anilines were used as starting materials. (**Scheme III.22.**) Consistent with the previous results, the electron-neutral or electron-rich aromatic alkynes were found to be more efficient.



Scheme III.22. Cu-catalyzed three-component reaction.

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Ohno and co-workers¹⁶² have also tested the use of copper catalysts in analogous three-component coupling reactions. (**Scheme III.23.**) They developed a direct and highly efficient method using the copper(I) salt CuBr (1 mol%) for the synthesis of 2-(aminomethyl)indoles which is direct and does not produce any salts as by-products. This thus appears to be a great alternative to known methods of preparation of this type of molecules.¹⁶³



Scheme III.23. Cu-catalyzed formation of indole derivatives.

In comparison with other transition metals, silver has been relatively less exploited as a catalyst for coupling purposes. In most reactions, the silver species rather served as either a co-catalyst or a Lewis acid. Indeed, silver catalysts are commonly considered to have low efficiency and not to be as good as other late transition metals to promote the C_{sp}-H activation of terminal alkynes. In the meantime, the development of environmentally friendly synthetic methods has become an increasingly important consideration for many chemists and silver catalysts have become worthy of interest again.

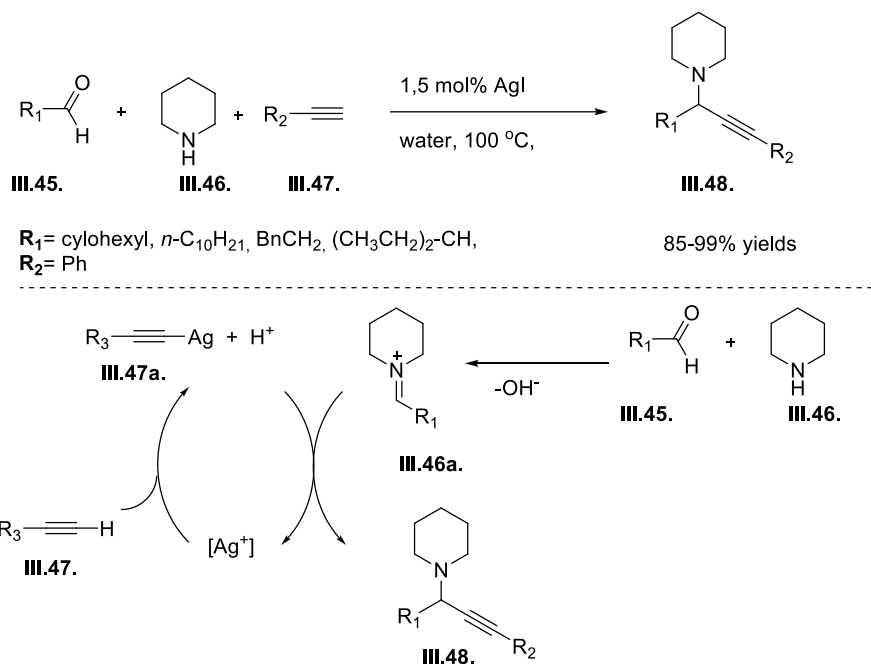
Aliphatic aldehydes are particularly effective for the silver-catalyzed reaction, which provides an effective complement to gold- and copper catalyzed A³ couplings. Li *et al.* have indeed developed a highly effective three component coupling of aliphatic aldehyde, alkyne, and amine with silver iodide as the catalyst. This process is simple and provides a diverse range of propargylamines in high yields.¹⁶⁴ (**Scheme III.24.**) It is also worthy of note that the developed conditions proceeded well not only in water but also in organic solvents such as toluene and DMF. The scope of the reaction was next examined with various aldehydes, alkynes, and dialkylamines and it appeared that aromatic as well as aliphatic aldehydes were able to undergo addition affording the corresponding propargylic amines. Nevertheless, aryl aldehydes displayed a lower reactivity, requiring longer reaction times while giving lower

¹⁶² Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 7052.

¹⁶³ For indole synthesis with dihaloarenes, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (b) Kaspar, L.T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311. For indole synthesis via Sonogashira reaction, see: (c) Cacchi, S.; Fabrizi, G.; Parisi, L.M. *Org. Lett.* **2003**, *5*, 3843. (d) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307.

¹⁶⁴ Wie, Ch.; Li, Z.; Li, Ch.-J. *Org. Lett.* **2003**, *5*, 4473.

yields. This increased reactivity of aliphatic aldehydes thus make this Ag-catalyzed variant as an effective complement of gold- and copper catalyzed A^3 coupling.

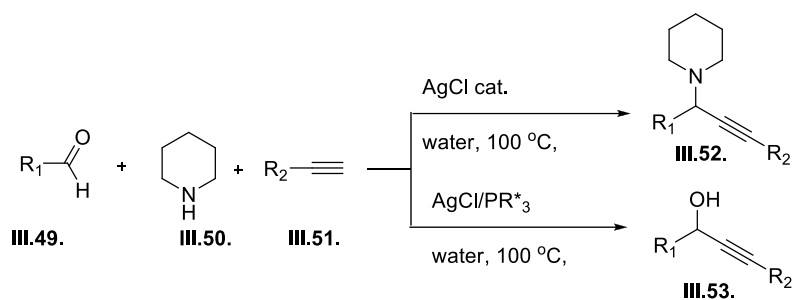


Scheme III.24. Ag-catalyzed coupling of aldehydes, amines and terminal alkynes.

From a mechanistic point of view, the authors proposed, by analogy with the previously discussed Cu-catalyzed reactions, formation of a silver acetylide intermediate **III.47a.** which could next react with the iminium ion **III.46a.**, generated *in situ* by condensation of the aldehyde and the amine, to give the corresponding propargylamine **III.48.** and regenerate the Ag(I) catalyst for further catalytic cycles.

The same research group next found that the reactivity could be modified by using phosphine ligands.¹⁶⁵ It appeared that in the reaction with silver catalyst and no other additive, only the coupling of alkynes, amines and aldehydes could be observed whereas in the presence of a phosphine ligand the exclusive aldehyde-alkyne coupling yielding the corresponding propargyl alcohol was obtained. (Scheme III.25.)

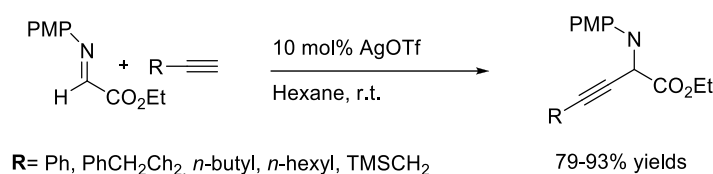
¹⁶⁵ Yao, X.; Li, Ch.-J. *Org. Lett.* **2005**, 7, 4395.



Scheme III.25. Ligand controlled alkyynylation reaction of imine and carbonyl.

To rationalize this intriguing switch in the reactivity, the authors postulated that the phosphine ligand could activate the silver-carbon bond of the silver acetylide. Alkynylsilver reagents used before are usually too stable to participate in nucleophilic additions to carbonyls.¹⁶⁶ The authors proposed that the electron-donating P-ligand on the other hand, increases the electron density on silver, thus weakening the silver-carbon bond. Our opinion is that it is also conceivable that use of an extra phosphine ligand breaks the aggregation state in which the silver acetylide component rests, then rendering it more nucleophilic. After screening of different phosphine silver catalysts for this synthesis of propargylic alcohols, the best results were obtained using a mixture of Cy_3PAuCl with 0.2 eq of *i*- Pr_2NEt .

Another silver salt, AgOTf , also demonstrated a high catalytic efficiency for the synthesis of β,γ -alkynyl α -amino acid derivatives. Chan *et al.*¹⁶⁷ have described the first example of a catalytic version of this reaction which allowed access to useful building blocks for the formation of biologically active compounds.¹⁶⁸ (**Scheme III.26.**)



Scheme III.26. Silver catalyzed addition of terminal alkynes to amino esters.

A very nice enantioselective variant of this reaction was developed in 2007 by Rueping *et al.*¹⁶⁹ using a combined silver/chiral Brønsted acid binary co-catalytic system (**Scheme III.27.**)

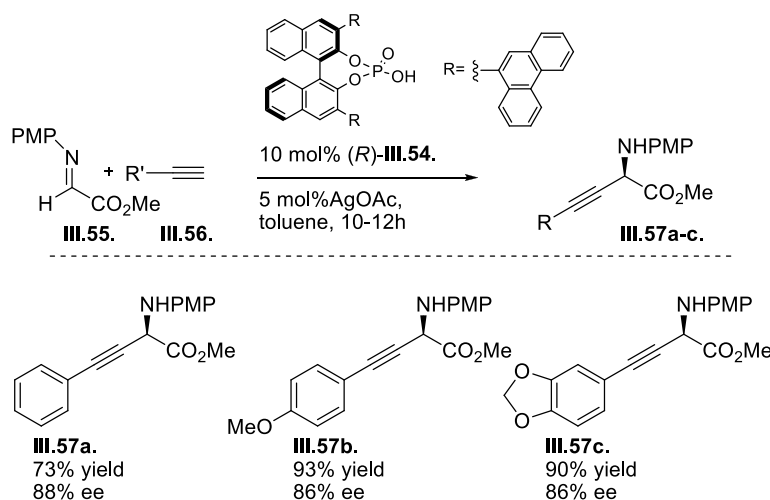
¹⁶⁶ Weibel, J.M.; Blanc, A.; Pale, P. *Chem. Rev.*, **2008**, *108*, 3149.

¹⁶⁷ Ji, J.-X.; Au-Yeung, T.T-L.; Wu, J. Yip, Ch. W.; Chan, A.S.C. *Adv. Synth. Catal.* **2004**, *346*, 42.

¹⁶⁸ Applications of β,γ -alkynyl α -amino acid derivatives in drug area, see: (a) Abdulganeeva, S. A.; Erzhanov, K. B. *Russ. Chem. Rev.* **1991**, *60*, 676; (b) Angst, C. *Pure and Appl. Chem.* **1987**, *59*, 373.

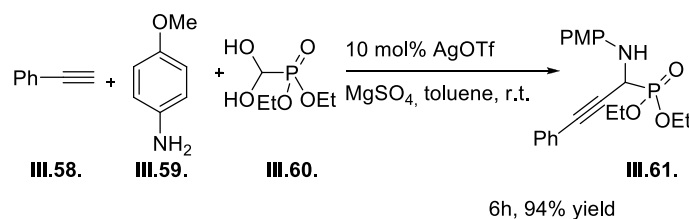
¹⁶⁹ Rueping, M.; Antonchink, A. P. Brinkmann, C. *Angew. Chem., Int. Ed.*, **2007**, *46*, 6903.

Thus, the asymmetric alkynylation of α -imino esters was performed *via* two parallel catalytic cycles; a chiral Brønsted acid activating the electrophile (the α -imino esters) and the metal salt activating the nucleophile, both proceeding simultaneously. Thus, they evaluated different parameters, such as different phosphoric acids, solvents and protecting groups at the imine, and a variety of metallic salts. The best results were obtained with the catalyst (*R*)-**III.54**, AgOAc, 30 °C, and PMP as the protecting group at the imine. The scope outlined in **Scheme III.27**. is related to the use of aromatic substituted alkynes. Although two combined cycles were proposed, an exchange of the metal counterion, which reacted and formed a chiral silver complex, could not be disregarded.



Scheme III.27. The alkynylation of imines catalyzed by (*R*)- **III.54**. and AgOAc.

Another interesting silver catalyzed alkynylation reaction was developed for the synthesis of *N*-PMP protected α -aminopropargylphosphonates using terminal alkynes, *p*-anisidine and diethyl formylphosphonate hydrate as reaction partners. Zhao and Dodda¹⁷⁰ have indeed developed the silver(I) triflate-catalyzed coupling reaction between phenylacetylene **III.58**., diethyl [(4-methoxyphenyl)imino]-methylphosphate **III.60**. and *p*-methoxyaniline **III.59**. under silver (I) triflate catalysis. (**Scheme III.28**.) Addition of MgSO₄ to trap water generated during the course of the reaction was proven to be essential for a high efficiency.

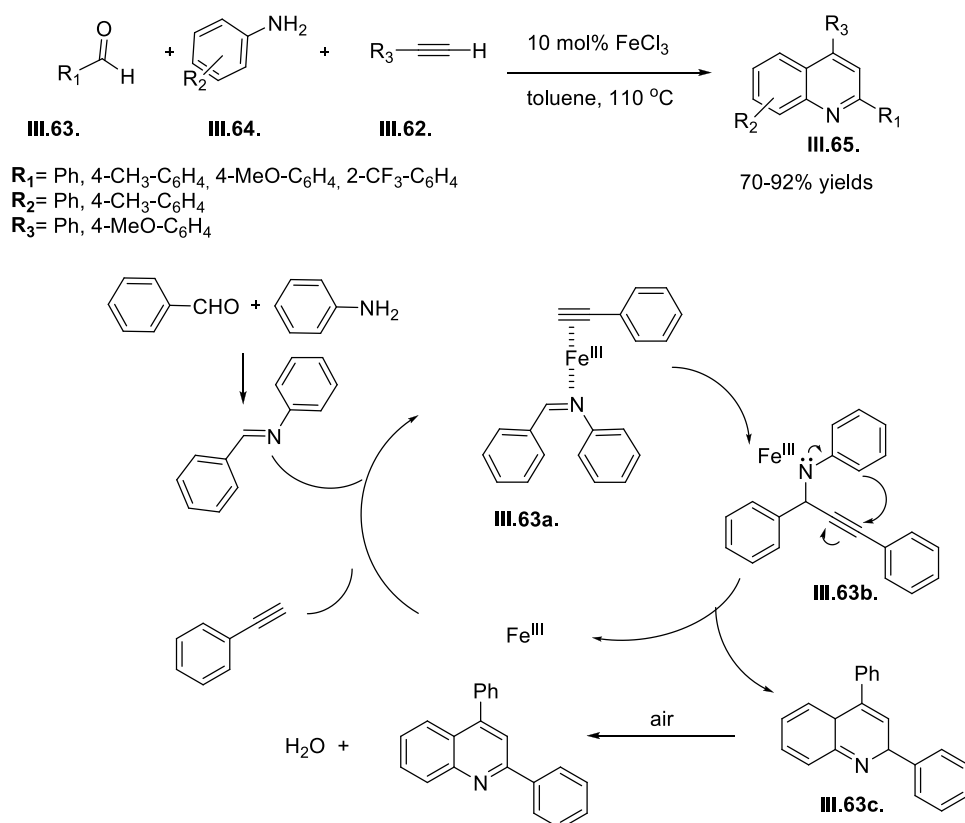


Scheme III.28. Silver catalyzed synthesis of *N*-PMP protected α -aminopropargylphosphonate.

¹⁷⁰ Dodda, R.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 165.

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Recently, due to its low price, non-toxicity and environmentally friendly character,¹⁷¹ iron has elicited the interest of many research groups as catalyst for coupling reactions. For example, Fan and co-workers¹⁷² developed the synthesis of quinolines based on a FeCl₃-catalyzed coupling of aldehydes **III.63.**, amines **III.64.** and alkynes **III.62.** (Scheme III.29.) which is quite similar to the Cu (II)-catalyzed process developed by Liu on glyoxylate imines.¹⁶¹ (Scheme III.21.) Phenylacetylene, benzaldehyde and aniline were used as model reaction partners and it was found that in the presence of 10 mol% of FeCl₃, the desired quinoline could be formed in 70% yield in refluxing toluene under an air atmosphere. A tentative mechanism assumes formation of the intermediate **III.63a** by coordination of *in situ* formed imine and alkyne to Fe^{III}, and then addition of alkyne to imine gives the propargylamine **III.63b** which undergoes an intramolecular hydroarylation of alkynes to dihydroquinoline **III.63c**. The oxygen from air was postulated to be necessary for the oxidation of intermediate **III.63c**. to the final aromatized product. The scope of the reaction could be next extended and the optimized method was well tolerated by different types of aromatic substrates.



Scheme III.29. Synthesis of quinolines.

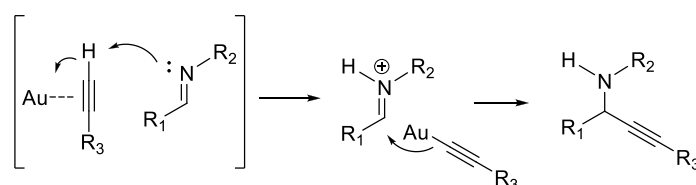
¹⁷¹ (a) Diaz, D.D.; Miranda, P.O.; Padron, J.I.; Martin, V.S. *Org. Chem.* **2006**, *10*, 457. (b) Corea, A.; Mancheno, O.G. Blom, C. *Chem. Rev* **2008**, *37*, 1108.

¹⁷² Cao, K.; Zhang, F.-M.; Tu, Y.-Q.; Zhuo, X.-T.; Fan, Ch.-A. *Chem. Eur. J.* **2009**, *15*, 6332.

Wang and co-workers¹⁷³ have also tested the same iron catalyst in a similar coupling reaction. During their optimization study it was found that the reaction of phenylacetylene, isobutyraldehyde and dibenzylamine could be completed within 24h using 10 mol% of FeCl₃ in the presence of 4Å molecular sieves without any ligand. The corresponding products were obtained in good to excellent yields. The developed method displayed a wide range of applicability allowing coupling of aromatic and aliphatic aldehydes, alkynes and aliphatic secondary amines.

As a continuing interest for the development of efficient synthesis of propargylamines *via* activation of alkynes, a great deal of interest has been devoted more recently to gold catalysis.

Gold(I) and gold(III) complexes have recently been utilized to catalyze a wide variety of transformations. In the context of alkyne activation, the interest for gold-catalyzed processes is obviously also growing.¹⁷⁴ Gold catalysts form stable complexes with alkynes through establishment of a strong coordination. These gold/alkyne π -complexes result in an electrophilic activation of the two C_{sp} alkynyl atoms, which then become highly susceptible towards nucleophilic attacks by exogenous or pending nucleophiles, thus leading to an efficient and versatile methodology to create functionalized alkenes.¹⁷⁴ In the specific case of terminal alkynes, the alkynyl C-H bond is weakly acidic but the acidity substantially increases upon coordination with a carbophilic Lewis acid. Hence, the gold/alkyne π -complexes derived from terminal alkynes are also susceptible to undergo deprotonation in the presence of a weak base, affording a readily access to gold acetylides, which can then express a Grignard type reactivity.¹⁷⁵ In the specific case of imine alkynylations, *in situ* catalytic generation of the gold acetylide is thus facilitated by the basicity of the imine itself which furthermore leads to the subsequent formation a more reactive iminium ion intermediate. (**Scheme III.30**)



Scheme III.30. The general activation of alkyne in a presence of imines.

¹⁷³ Li, P.; Zhang, Y.; Wang, L. *Chem. Eur. J.* **2009**, *15*, 2045.

¹⁷⁴ (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.*, **2006**, *45*, 7896; (b) Fürstner, A.; Davies, P. W.; *Angew. Chem., Int. Ed.*, **2007**, *46*, 3410; (c) Gorin, D. J.; Sherry, B. D.; Toste, D. F. *Chem. Rev.*, **2008**, *108*, 3351; (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.*, **2008**, *108*, 3326; (e) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.*, **2011**, *111*, 1657.

¹⁷⁵ (a) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581; (b) De Haro, T.; Nevado, C. *Synthesis* **2011**, *16*, 2530.

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Several synthetically useful applications for these gold species have been devised in nucleophilic addition and nucleophilic substitution reactions.¹⁷⁵ In 2003, Li *et al.*^{175a,176} have developed the use of gold acetylides for the synthesis of propargylamines *via* multicomponent reactions between aldehydes, terminal alkynes and secondary amines. The proposed mechanism is related to the picture shown in **Scheme III.30.**, and also relates to the imine propargylations catalyzed by the other metal salts (Cu, Fe...) as previously discussed. The authors suggested formation of a gold acetylide intermediate which reacts with an iminium ion previously generated from the condensation of the aldehyde with the secondary amine. In this case, deprotonation of the π -activated alkyne can be realized either by the amine component and/or the hydroxide anion which is released during formation of the iminium cation. Apart being one of the first examples of a gold-catalyzed C-H activation of terminal alkynes, the most remarkable feature of this work by Li, is that the reaction is carried out in water, thereby showing the compatibility of gold acetylides in an aqueous, green, environment, which markedly contrasts with most of the other metal acetylides.¹⁷⁷

Liu and Yan¹⁷⁸ have documented the gold-catalyzed one-pot synthetic route to form 1,3-disubstituted indolizines **III.68.** under solvent-free conditions or water starting from pyridine carboxaldehyde. (**Table III.4.**)

In their optimal protocol only 1 mol% of NaAuCl₄·2H₂O was used as a single-pot catalyst for the promotion of two consecutive reactions, *i. e.* imine propargylation and subsequent intramolecular hydroamination in the same flask without isolation of the propargylic pyridine intermediates. It is also worth to point out that the coupling of optically pure α -amino acid derivatives with aldehydes and alkynes produces the corresponding products without loss of enantiomeric purity. As illustrated in the **Table III.4.** this process is amenable to a large range of components and gives the bicyclic compounds in good to excellent yields. For example, pyrrolidine **III.66b.** and morpholine **III.66c.** led to 1,3-distubstituted indolizines **III.68c** in 68% and **III.68d.** in 96%. (Entries 3-4).

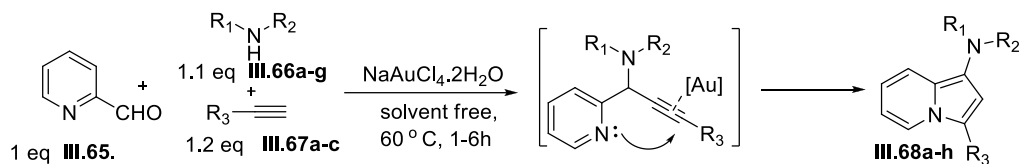
¹⁷⁶ Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

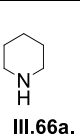
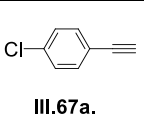
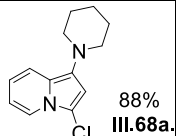
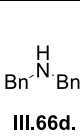
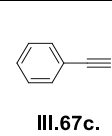
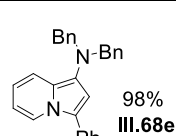
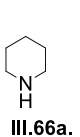
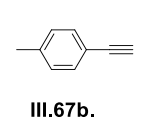
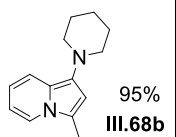
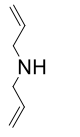
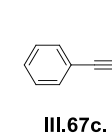
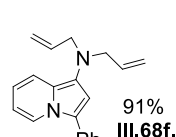
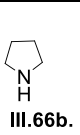
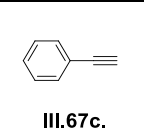
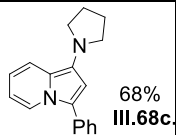
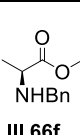
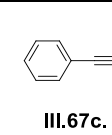
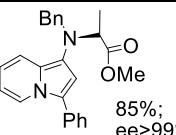
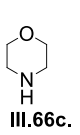
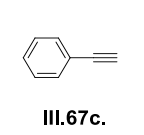
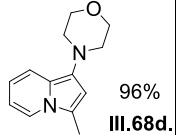
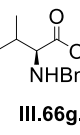
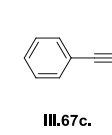
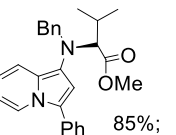
¹⁷⁷ For related contributions by the same group and others a) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. b) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953. c) Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadiou, B.; Bertrand, G. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 13569. d) Huang, B.; Yao, X.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1528. e) Liu, X. Y.; Ding, P.; Huang, J. S.; Che, C. M. *Org. Lett.* **2007**, *9*, 2645. f) Lo, V. K.-Y.; Kung, K. K.-Y.; Wong, M. K.; Che, C. M. *J. Organomet. Chem.* **2009**, *694*, 583. g) Cheng, M.; Zhang, Q.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.; Chan, A. S. C. *Adv. Synth. Catal.* **2011**, *353*, 1274. h) Campbell, M. J.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1369. i) Capretto, D. A.; Brouwer, C.; Poor, C. B.; He, C. *Org. Lett.* **2011**, *13*, 5842. j) Naoe, S.; Suzuki, Y.; Hirano, K.; Inaba, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2012**, *77*, 4907.

¹⁷⁸ Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323.

CHAPTER III: The gold-catalyzed alkylation reaction of *N,O*-acetals

Table III.4. Gold-catalyzed formation of aminoindolizines.



Entry	amine	alkyne	Product [yield %]	Entry	amine	alkyne	Product [yield %]
1.	 III.66a.	 III.67a.	 88% III.68a.	5.	 III.66d.	 III.67c.	 98% III.68e.
2.	 III.66a.	 III.67b.	 95% III.68b	6.	 III.66e.	 III.67c.	 91% III.68f.
3.	 III.66b.	 III.67c.	 68% III.68c.	7.	 III.66f.	 III.67c.	 85%; ee>99% III.68g.
4.	 III.66c.	 III.67c.	 96% III.68d.	8.	 III.66g.	 III.67c.	 85%; ee>99% III.68h.

The authors have also paid much attention to developing optically pure aminoindolizines from α -amino acid derivatives. In all cases presented the products were found to be isolated in > 99% enantiomeric excess.

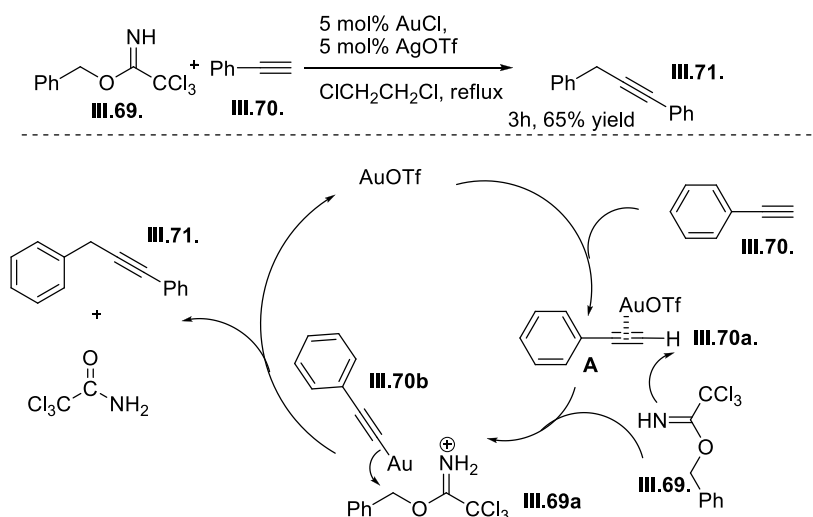
Recent efforts aimed at developing direct and atom-economical S_N1 type alkylation reactions using π -activated alcohols as an electrophilic partner have been investigated, and these will be developed in the next section. A unique alkylation strategy in this direction, but that has mechanistic similarities with the propargylamines syntheses described above, has been recently reported and is discussed here.

Wang and Li's¹⁷⁹ have developed the gold catalyzed-alkylation of alcohol derivatives *via* their trichloroacetimidate intermediates. (**Scheme III.31.**) A low catalyst loading of *in situ* prepared AuOTf (5 mol %), was found to be optimal in refluxing 1,2-dichloroethane (DCE) for the efficient addition of phenylacetylene **III.70** with benzyl 2,2,2-trichloroacetimidate **III.69**. The product **III.71** could be smoothly obtained in good yield (65%). A mechanistic

¹⁷⁹ C. Li, W. Li, J. Wang, *Tetrahedron Lett.* **2009**, *50*, 2533

proposal for this reaction is shown in **Scheme III.31**. After coordination of the gold species with alkynes **III.70** the nitrogen in the benzyl trichloroacetimidate could act as a base in a way similar as the imine nitrogen in the propargylamine synthesis, and deprotonate the Au-activated alkyne **III.70a**. Next, the gold-acetylide **III.70b** could attack the activated benzylic position of **III.69a**. to form the final product with concomitant release of neutral trichloroacetamide which does not interfere with the activity of gold catalyst.

In this alkynylation strategy, the inherent basicity of the trichloroacetimidate protecting group was judiciously exploited to serve a dual function: first, the nitrogen atom can act as a base to generate gold-acetylide through deprotonation of gold-activated terminal alkyne and then the protonated trichloroacetimidoxyl group becomes a very good leaving group, which facilitates benzyl transfer to the gold-acetylide.



Scheme III.31. A plausible mechanism for the gold-catalyzed arylmethylation reaction of phenylacetylene.

Using the optimal protocol, the authors could achieve the preparation of a wide range of arylmethylation products in moderate to good yields. (**Table III.5**)

Table III.5. The gold-catalyzed arylmethylation of terminal alkynes.

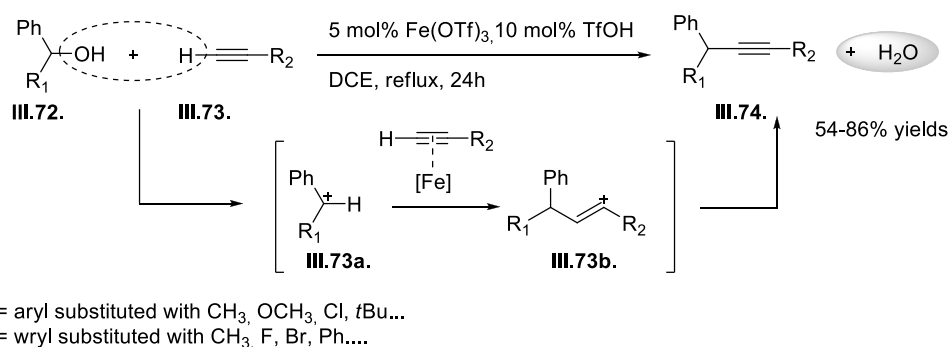
Entry	Ar, R ₁	R ₂	T[h]	Yield [%]
1.	C ₆ H ₅ , H	C ₆ H ₅	3	65
2.	<i>o</i> -BrC ₆ H ₄ , H	C ₆ H ₅	4	62
3.	<i>m</i> -ClC ₆ H ₄ , H	C ₆ H ₅	10	79
4.	<i>m</i> -BrC ₆ H ₄ , H	C ₆ H ₅	10	85

5.	<i>m</i> -Me- <i>p</i> -BrC ₆ H ₃ , H	C ₆ H ₅	3	84
6.	C ₆ H ₅ , H	<i>p</i> -BrC ₆ H ₄	4	57
7.	C ₆ H ₅ , H	<i>n</i> -C ₄ H ₉	4	30

• **Catalytic alkynylation using alcohol substrates**

In the last decade, progress has been made in the development of so-called dehydrative coupling methodologies. This direct reaction of, for example alcohols and terminal alkynes, is an ideal process to construct a new carbon-carbon bond because it only generates water as a by-product. It is an atom-economical and environmentally friendly alternative approach to the classic coupling which often involves moisture sensitive and toxic organometallic reagents (C–M; M = Mg, Zn, Sn etc.)¹⁸⁰

As for the α -amidoalkylation of *N,O*-acetals, while the catalytic S_N1-type alkylation of alcohols and their derivatives with the classical assortment of good neutral carbonucleophiles (allyltrimethylsilanes, enoxysilanes, active methylene compounds and electron-rich π -(hetero)aromatics...) has considerably developed and matured,^{180a} the related process using alkynes and their derivatives as the nucleophilic partner is still under-developed.^{180b} In 2009, Jiao *et al.*¹⁸¹ described a catalytic method for the coupling of benzylic alcohols **III.73.** and terminal alkynes **III.74.** (Scheme III.32.). As model reaction partners, benzhydrol and phenylacetylene were chosen, and use of a combination of Fe(OTf)₃ (5 mol%) and TfOH (10 mol%) in refluxing dichloroethane were found to give the best results for the coupling products.



Scheme III.32. Iron-catalyzed dehydrative coupling of alcohols and terminal alkynes.

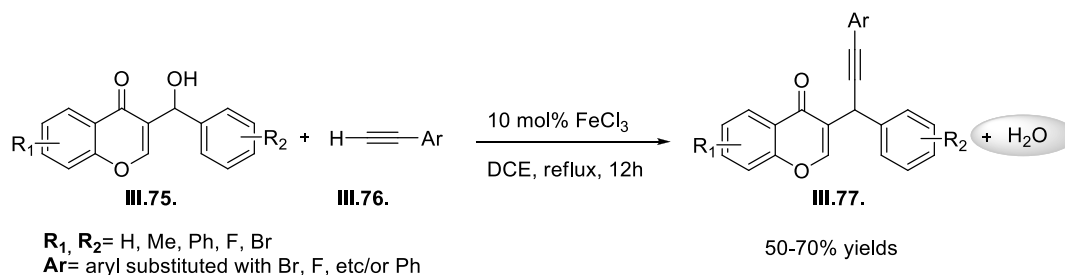
¹⁸⁰ (a) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruziello, D.; De Viscentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647. (b) Kumar, R.; van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, 42, 1121.

¹⁸¹ Xiang, S. K.; Zhang, L. H.; Jiao, N. *Chem. Commun.* **2009**, 6487.

CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

Noteworthy, nature of the solvent was shown to be critical and a polar solvent such as DMF or CH_3NO_2 proved to be ineffective. Furthermore, even if the reaction could be realized in the absence of any additive using $\text{Fe}(\text{OTf})_3$ as the only catalyst, addition of TfOH (10 mol%) improved the yield from 61% to 77%. The authors postulated that the reaction may proceed in a Friedel-Crafts type mode of nucleophilic addition, and not *via* a Grignard type mode through an hypothetical iron acetylide pathway, *via* π -addition of the activated alkynes to the carbocationic intermediate **III.73a**. (formed by activation of the alcohol with $\text{Fe}(\text{OTf})_3/\text{TfOH}$). This provides a cationic intermediate **III.73b.**, which after deprotonation leads to the expected product **III.74**. Hence the iron catalyst may serve an unusual role of protecting group for alkyne, preventing its decomposition under the rather harsh reaction conditions employed.

Interestingly, Li *et al.*¹⁸² studied the alkynylation of chromone-derived Morita-Baylis-Hillman (MBH) alcohols which are key heterocyclic motifs present in the structure of many natural or synthetic compounds with interesting biological activities. The authors indeed demonstrated that this class of compounds could also be successfully employed as substrates in a similar Fe-catalyzed coupling reaction as the one described above (see **Scheme III.32.**) with alkynes. FeCl_3 was shown to be the catalyst of choice for this transformation affording the alkynylated adducts in moderate to good yields (**Scheme III.33.**).



Scheme III.33. FeCl_3 -catalyzed dehydrative coupling of MBH alcohols with alkynes.

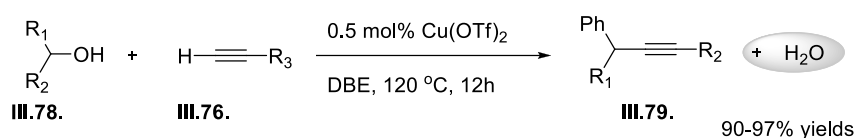
This type of dehydrative coupling was revisited in 2011 by Zhang and co-workers¹⁸³ who proved the superiority of $\text{Cu}(\text{OTf})_2$ over $\text{Fe}(\text{III})$ salts to catalyze this transformation, albeit at the expense of the energy profile of the reaction, which in this case is carried out at reflux of a solvent with higher boiling point, 1,2-dibromoethane (DBE). For example, using the mixture $\text{Fe}(\text{OTf})_3/\text{TfOH}$ (2.0 mol%/4.0 mol%)¹⁸¹ gave a lower yield (75%) than $\text{Cu}(\text{OTf})_2$ alone (0.5

¹⁸² Chen, W.; Hao, Z.; Zhe, L.; Li, L.; Dong, W.; Yongjun, C. *Chin. J. Chem.* **2011**, *29*, 2732.

¹⁸³ Ren, K.; Li, P.; Wang, L.; Zhang, X. *Tetrahedron* **2011**, *67*, 2753.

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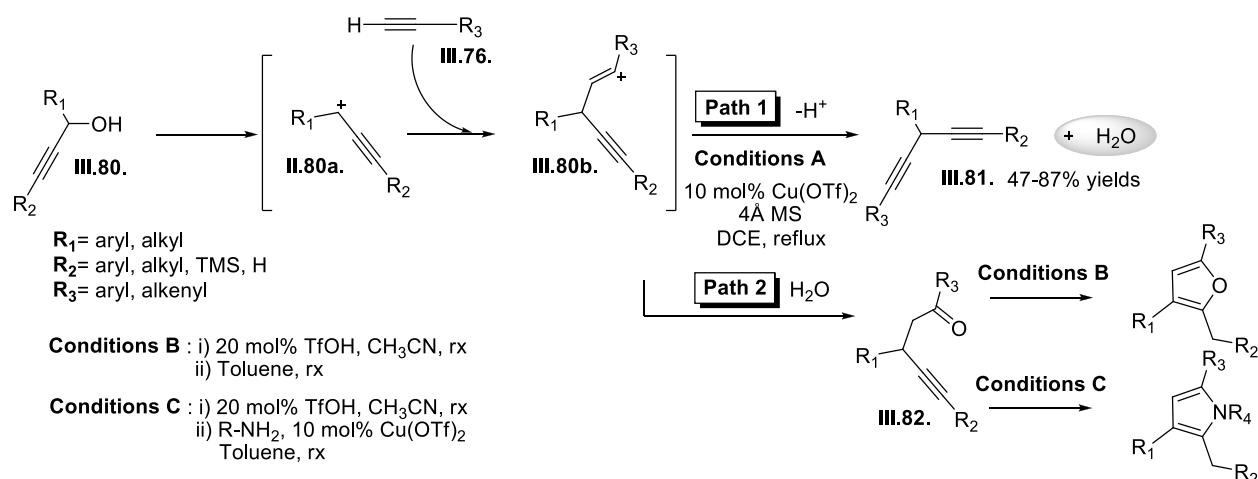
mol%, 91% yield). A very low catalyst loading of only 0.5 mol% was found to be optimal in refluxing DBE for the efficient coupling of aromatic alkynes with either diphenyl methanols possessing EWGs as well as EDGs or allylic alcohols. The products could be smoothly obtained in excellent yields (90-97%). (**Scheme III.34.**) As previously proposed for the Fe-catalyzed dehydrative coupling,¹⁸¹ the mechanism would involve the initial activation of the alcohol by $\text{Cu}(\text{OTf})_2$ resulting in the formation of a carbocation intermediate. π -Addition of the electron-rich aromatic alkyne would then afford a vinyl cation which, after deprotonation, would form the corresponding alkynylated adduct. Since $\text{Cu}(\text{OTf})_2$ is also known for its alkynophilic Lewis acidity, it is also reasonable to propose a concomitant activation of the acetylenic partner,¹⁸⁴ which in this case would react as organometallic nucleophile.



R_1, R_2 = aryl substituted with Cl, F, Br or Ph...
 R_3 = aryl substituted with CH_3 , F, Cl, Br or Ph....

Scheme III.34. $\text{Cu}(\text{OTf})_2$ -catalyzed dehydrative coupling reaction

The same research group¹⁸⁵ has recently expanded their dehydrative strategy to the synthesis of a series of 1,4-diynes by coupling the corresponding propargyl alcohols with terminal alkynes, still using $\text{Cu}(\text{OTf})_2$ as the catalyst. (**Scheme III.35.**)



Scheme III.35. Cu-catalyzed direct dehydrative synthesis of 1,4-diynes.

¹⁸⁴ Huang, H.; Jiang, H. L.; Chen, K. X.; Liu, H. *J. Org. Chem.* **2009**, *74*, 5476.

¹⁸⁵ Wang, T.; Chen, X.-L.; Chen, L.; Zhan, Z.-P. *Org. Lett.* **2011**, *13*, 3324.

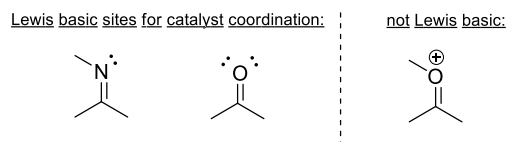
CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

This is an important alternative method for the generation of specific 1,4-diyne which is complementary to traditional, non atom-economical methods often involving the nucleophilic substitution of propargyl halides or sulfonates with metal acetylides.

Mechanistic study showed that the hydration of the alkenyl cation **III.80b**. could compete with the expected deprotonation pathway (**Path 1**), and then afford γ -alkynyl ketones **III.82**. (**Path 2**). In order to provide the 1,4-diyne selectively, 10 mol% of $\text{Cu}(\text{OTf})_2$ were used in the presence of molecular sieves (MS) to trap the water generated along the reaction. The authors also explored the possibility of exploiting γ -alkynyl ketones **III.82**. as precursors for the synthesis of polysubstituted furans and pyrroles. So, they developed specific set of conditions for the selective preparation of each class of compounds (see details on **Scheme III.35**).

- Catalytic enantioselective alkynylations

In the field of asymmetric catalysis, methods for the enantioselective addition of carbon nucleophiles to electrophiles such as aldehydes, ketones or imines often rely on the Lewis or Brønsted basicity of the electrophilic substrates. This property allows binding of the electrophile to a chiral catalyst, thereby generating a chiral electrophile *in situ*.¹⁰ Oxocarbenium or iminium ions which lack a Lewis basic site for coordination to a chiral Lewis acidic catalyst thus require alternative methods for controlling facial selectivity (**Scheme III.36**). Therefore, stereocontrol in transformations involving this type of cationic intermediates necessarily imply catalytic generation of either a chiral electrophile (left side),^{186a} using chiral Lewis acids or chiral organocatalysts, or a chiral nucleophile (right side).^{186b}



Scheme III.36. Electrophiles for asymmetric catalysis.¹⁸⁷

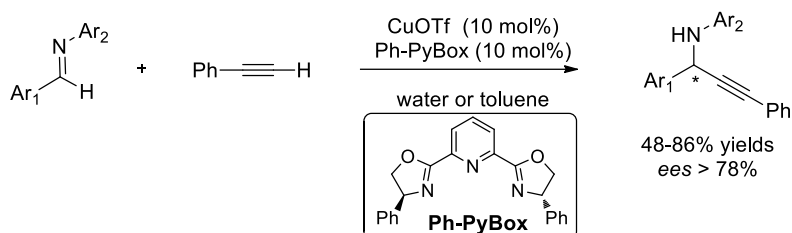
Based on these considerations, whereas no enantioselective method was developed thus far for the direct asymmetric alkynylation of *N,O*-acetals, several research groups developed methods involving the *in situ* catalytic generation of a chiral copper-acetylide which add

¹⁸⁶ (a) Braun, M.; Kotter, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 514. (b) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7096.

¹⁸⁷ Watson, M.; Maity, P. *Synlett* **2012** 1705.

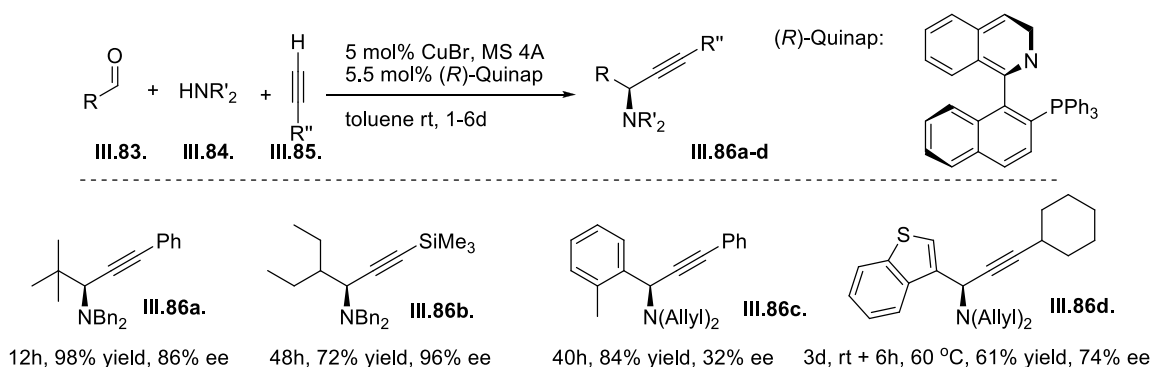
CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

enantioselectively to the cationic intermediate. As part of their work on the development of copper-promoted direct additions of terminal alkynes onto imines, Li *et al.* reported the first copper(I)-catalyzed enantioselective alkynylation reaction in 2002.¹⁸⁸ The use of chiral copper(I) triflate complexes formed by mixing CuOTf and tridentate bis(oxazolanyl)pyridines (pybox) afforded the best results yielding the corresponding products with both high reactivity and enantioselectivity in water or toluene (**Scheme III.37.**).



Scheme III.37. Copper-catalyzed addition of terminal alkynes onto imines.

Knochel *et al.*¹⁸⁹ shortly after described a one-pot three-component coupling between an alkyne, an aldehyde and a secondary amine using a combination of CuBr and (*R*)-Quinap as the chiral catalyst system. Using their protocol in the presence of 4Å MS, the authors could achieve the preparation of a wide range of chiral propargylamines in good yields and high enantioselectivities (**Scheme III.38.**). Remarkably, the Cu-catalyzed reaction was also shown to be highly diastereoselective when a chiral amine or aldehyde was used. A similar strategy using Pinap as the chiral ligand for copper was described a few years later by Carreira and co-workers.



Scheme III.38. Copper-catalyzed preparation of propargylamines.

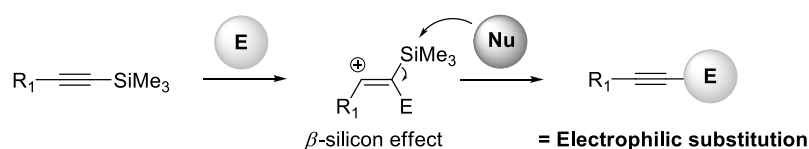
¹⁸⁸ Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.

¹⁸⁹ Gommernann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

III.1.3. ADDITION OF TMS-ALKYNES

As previously mentioned, the chemistry of alkyne motifs has been well recognized and the discovery of novel reactivity in the development of bond-forming reactions is of continuing interest. Alkynyl silanes have been widely employed as convenient partners in common organic reactions due to ready availability and high tolerance to functional group. Therefore, trialkylsilyl groups have often been employed as protecting groups in order to avoid undesired reactions that might possibly occur under specific reaction conditions if terminal alkynes are used.¹⁹⁰ Some other important applications involving alkynylsilanes are Hiyama-type couplings¹⁹¹ or metathesis reactions that give in both cases access to substituted alkynes.¹⁹²

As ordinary alkynes, silylated alkynes are nucleophilic towards electrophiles of different nature. The presence of the silicon however has a dramatic effect on the regioselectivity of these electrophilic additions, the attack only occurring at the carbon directly bonded to silicon. This directly comes from a specific feature of organosilicon compounds named the beta-effect enabling stabilization of a positive charge on a β -carbon by σ -donation (hyperconjugation). Stabilization of the cation thus results in delocalization of the electron density weakening the C-Si bond and attack of a nucleophile then removes the SiR₃ group, the net result being the electrophilic substitution of the trialkylsilyl group. In such reactions, alkynyl silanes can thus be considered as surrogates of terminal alkynes (**Scheme III.39**).



Scheme III.39. General reactivity profile for the electrophilic desilylative functionalization of TMS-alkynes.

Depending on the nature of the electrophilic partner, a number of useful transformations can be successfully realized from trialkylsilylalkynes. Given our objectives, we will mainly consider reactions involving proton donors and electrophilic metallic complexes, which

¹⁹⁰ Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed; John Wiley & Sons: New York, **1999**, 654.

¹⁹¹ (a) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 279. (b) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.

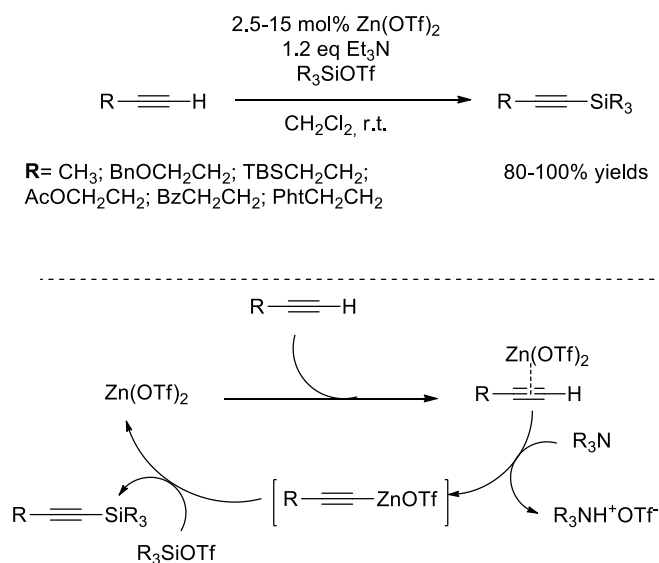
¹⁹² (a) Wang, J.; Gurevich, Y.; Botoshansky, M.; Eisen, M.S. *J. Am. Chem. Soc.* **2006**, *128*, 9350. (b) Kim, M.; Park, S.; Maifeld, S.V.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 10242.

correspond to protodesilylation and metallodesilylation reactions and respectively yield the terminal alkynes or metal acetylides.

- Preparation of alkynyl silanes

The silyl group is conventionally introduced onto terminal alkynes by deprotonation of the C-H bond of a terminal alkyne using strong bases like *n*-butyllithium or Grignard reagents, followed by treatment of the *in situ* formed acetylide with chlorotrialkylsilanes or trialkylsilyltriflates. Nevertheless, the high nucleophilicity of lithium and magnesium acetylides limits the functional group compatibility of this reaction.

Recently, many research groups have started to test if the reaction could be transposable to less nucleophilic metal acetylides generated catalytically *in situ*. Shaw *et al.*¹⁹³ were the first to develop a rapid and high yielding silylation of terminal alkynes employing zinc triflate as catalyst. These conditions worked well for a variety of substrates including esters, a functional group usually reactive with other metal acetylides. (**Scheme III.40.**)



Scheme III.40. Zinc catalyzed silylation reaction.

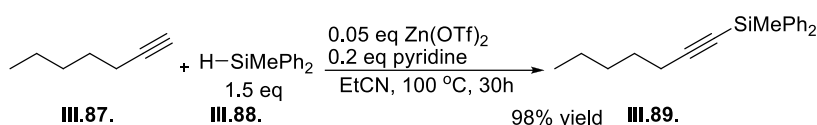
It was found that use of 2.5 to 15 mol% of Zn(OTf)_2 in dichloromethane provided the corresponding alkynylsilanes in good to excellent yields. Compared to previous methods,¹⁹⁴ the optimized conditions avoid the use of stoichiometric quantities of strong bases and metal mediators. The method was shown to tolerate a wide range of substrates but a dramatic effect

¹⁹³ Rahim, R.J.; Shaw, J. T. *J. Org. Chem.* **2008**, *73*, 2912.

¹⁹⁴ (a) Andreev, A.A; Koshin, V.V.; Komarov, N.V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett.*, **2004**, *6*, 421. (b) Jiang, H.; Zhu, *Tetrahedron Lett.* **2005**, *46*, 517.

of the silyl group on the reactivity was observed. Because of steric constraints, the bulky TBS (*tert*-butyldimethylsilyl) or TIPS (triisopropylsilyl) silyl triflates either afforded the corresponding product in low yield or an absence of reactivity was observed.

Another interesting method for Si-C≡CR bond formation was presented by Tsuchimoto and co-workers.¹⁹⁵ They developed the first dehydrogenative silylation reaction of terminal alkynes under Lewis acid catalysis. (**Scheme III.41.**) As model reaction partners, 1-octyne **III.87.** and methyldiphenylsilane **III.88.** were chosen and it was found that use of 5 mol% of Zn(OTf)₂ in combination with 20 mol% of pyridine in propionitrile proved to be the most efficient.



Scheme III.41. Zinc-pyridine catalyzed dehydrogenative silylation reaction of **III.87.**

This method also tolerated a wide range of starting materials thus displaying a high functional group tolerance. This thus appears to be one of the most promising strategy for the synthesis of complex alkynylsilanes.

- Catalytic desilylation reactions

In many applications, the terminal silyl group is used as a temporary protecting group and its removal is required at one point for any further functionalization of the alkyne moiety.¹⁹⁶ The desilylation has been traditionally carried out by treatment with a large excess of a fluoride ion donor, such as KF·2H₂O in DMF¹⁹⁷ or tetrabutylammonium fluoride (TBAF) in THF solution.¹⁹⁸ However, these methods appeared to be not selective and in the presence of other silyl-protecting groups undesired side reactions often occur. Therefore, the choice of selective desilylation conditions is critical for the synthesis of complex compounds. Carpita and Rossi¹⁹⁹ have reported the silver-catalyzed protodesilylation of TMS-alkynes. (**Scheme III.42.**) As a model silyl-compound 1-(trimethylsilyl)ethynylbenzene **III.90.** was selected and

¹⁹⁵ Tsuchimoto, T.; Fujii, M.; Iketani, Y.; Sekine, M. *Adv. Synth. Catal.* **2012**, 354, 2959.

¹⁹⁶ Yamamoto, Y. *Chem. Rev.* **2008**, 108, 3199.

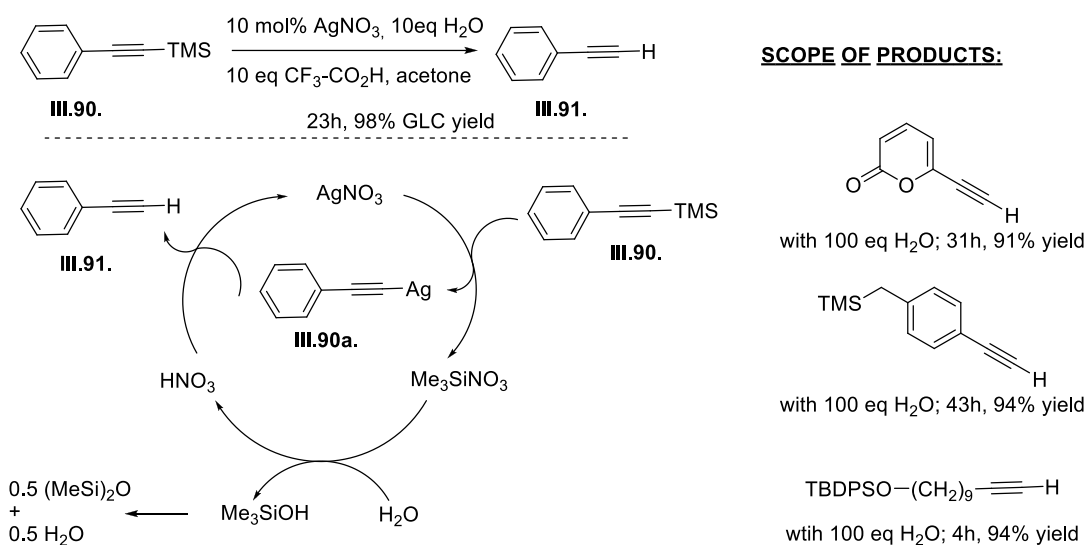
¹⁹⁷ Fiandanese, V.; Marchese, G.; Punzi, A.; Ruggieri, G. *Tetrahedron Lett.* **1996**, 37, 845.

¹⁹⁸(a) Kraus, G. A.; Bae, J. *Tetrahedron Lett.* **2003**, 44, 5505–5506; (b) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, 68, 1376.

¹⁹⁹ Carpita, A.; Mannocci, L.; Rossi, R. *Eur. J. Org. Chem.* **2005**, 1859.

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it was found that the reaction was efficiently performed in acetone containing 10 mol% of AgNO_3 , 10 eq of water and 10 eq of trifluoroacetic acid (or in dry methanol containing 10 mol% of AgNO_3). The scope of the reaction could be further successfully extended to other TMSalkynes. After slight modification of the conditions (using 100 eq of the water instead of 10 eq) the expected products were isolated in high yields and selective cleavage of the TMS- C_{sp} bond was observed even in the case of substrates possessing other silyl protecting groups. (see **Scheme III.42. Scope of products**)



Scheme III.42. Silver-catalyzed desilylation reaction of TMS-alkyne.

The proposed mechanism is depicted on **Scheme III.42.:** after treatment of compound **III.90.** with silver nitrate, the corresponding silver acetylides **III.90a.** and trimethylsilyl nitrate would be formed. Then, hydrolysis of Me_3SiNO_3 would afford trimethylsilanol and HNO_3 . Finally reaction of HNO_3 with **III.90a.** would give the terminal alkyne **III.91.** and regenerate the silver-catalyst.

Another interesting contribution was presented by Pale *et al.*²⁰⁰ where silver triflate and silver nitrate were found as species able to efficiently and selectively catalyze the deprotection of silyl alkynes. (**Table III.6.**) Considering the mechanism, it was assumed that triflate or nitrate counterions are nucleophilic enough to attack the silicon atom upon silver activation. Then after the cleavage of the C-Si bond, the *in situ* formation of an alkynyl silver and silyl-X species should take places. In protic solvents the intermediate would be hydrolyzed to a proton source strong enough to hydrolyze the alkynyl silver species. Since silver salts and

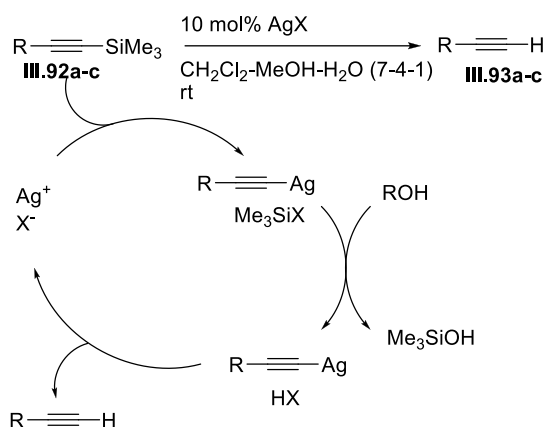
²⁰⁰ Orsini, A.; Viterisi, A.; Bodlener, A.; Weibel, J.M.; Pale, P. *Tetrahedron Lett.* **2005**, 46, 2259.

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silver acetylides are not well soluble in alcohol or water, a mixture of dichloromethane, methanol and water (ratio 7:4:1) was chosen in which various type of terminal alkynes were obtained in good to excellent yields. (**Table III.6.**)

It is important to point out that in each case reactions proved to be more rapid when catalyzed by silver triflate rather than by silver nitrate. Also, the method turned out to be selective toward other silyl protecting groups (**Table III.6.** Entries 3, 4, 7) where substrates were cleanly deprotected at the acetylenic end. Interestingly, a chemoselectivity was also observed in a diyne protected with two different silyl groups. (entries 8-9) Indeed, the TIPS protecting group remained untouched after the reaction.

Table III.6. Deprotection of trimethylsilyl acetylenes catalyzed by silver salts.

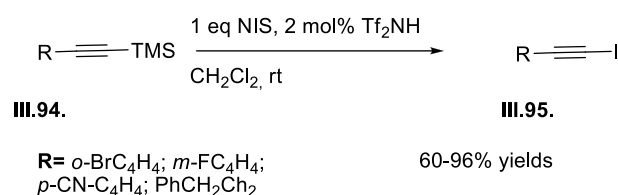


Entry	TMS-alkyne	catalyst	Time [h]	Product	Yield [%]
1.	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\begin{matrix} \text{OH} \\ \\ \text{Ph} \end{matrix}$	AgNO_3	16	$\text{H}-\text{C}\equiv\text{C}-\begin{matrix} \text{OH} \\ \\ \text{Ph} \end{matrix}$	79
2.	III.92a.	AgOTf	2.5	III.93a.	86
3.	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\begin{matrix} \text{OSitBuMe}_2 \\ \\ \text{Ph} \end{matrix}$	AgNO_3	7.5	$\text{H}-\text{C}\equiv\text{C}-\begin{matrix} \text{OSitBuMe}_2 \\ \\ \text{Ph} \end{matrix}$	88
4.	III.92b.	AgOTf	4	III.93b.	97
5.	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{OCOtBu}$ III.92c.	AgNO_3	22	$\text{H}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{OCOtBu}$ III.93c.	92
6.		AgOTf	8		95
7.	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\begin{matrix} \text{OSitBuPh}_2 \\ \\ \text{Ph} \end{matrix}$	AgNO_3	2.5	$\text{H}-\text{C}\equiv\text{C}-\begin{matrix} \text{OSitBuPh}_2 \\ \\ \text{Ph} \end{matrix}$	91
	III.92d.			III.93d.	
8.	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-\text{Si}i\text{Pr}_3$	AgNO_3	23	$\text{H}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-\text{Si}i\text{Pr}_3$	93*
9.	III.92e.	AgOTf	7	III.93e.	95

*Yield relative to conversion, some starting material being recovered.

- Catalytic transformation using TMS-alkynes as nucleophiles

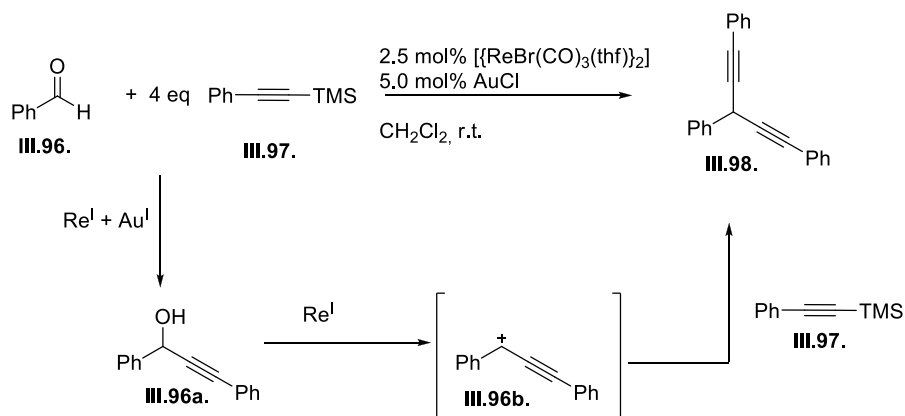
As previously discussed, silylalkynes can also be used as nucleophiles in useful synthetic transformations where they are used as terminal alkyne surrogates. Such reactivity was exploited by Sheppard *et al.*²⁰¹ who have recently reported the halogenation of TMS-alkynes. (**Scheme III.43.**) The authors reported that Tf₂NH-catalysed halogenation using NIS as a provider of electrophilic iodine could be applied to the synthesis of haloalkynes with good efficiency.



Scheme III.43. Tf₂NH catalyzed halogenations of TMS-protected alkynes.

Given their ability to undergo metallodesilylation reactions with electrophilic metal complexes, the reactivity of TMS-alkynes was evaluated in a number of metal-catalyzed reactions. Again, only some selected reactions involving cationic intermediates were chosen for discussion in this chapter.

An elegant application of this specific reactivity of alkynylsilanes was reported by Takai and Kuninobu (**Scheme III.44.**)²⁰² In this reaction catalyzed by two metal complexes, a coupling reaction between aldehydes and alkynylsilanes took place providing diethynylmethane adducts.



Scheme III.44. Metal-catalyzed coupling of aldehydes and TMS alkynes.

²⁰¹ Starkov, P.; Rota, F.; D'Oyley, J.M.; Sheppard, T.D. *Adv. Synth. Catal.* **2012**, 354, 3217.

²⁰² Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, 46, 3296.

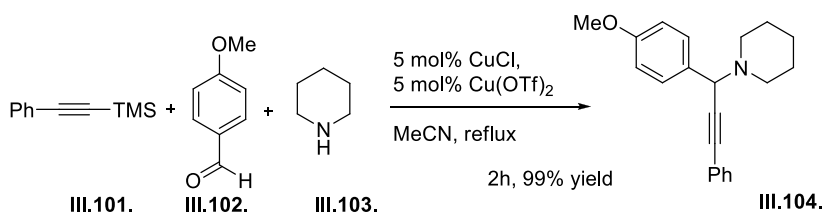
The optimization and mechanistic studies showed that the concomitant use of rhenium and gold complexes were necessary to promote the initial formation of propargyl alcohol **III.96a**. Then, a rhenium-S_N1 type substitution of the hydroxy group would occur with a second molecule of TMS-alkyne **III.97** affording the coupled product **III.98**.

The substitution of alcohols with alkynylsilanes could also be catalyzed by BiCl₃.²⁰³ De and Gibbs have successfully employed the inexpensive and relatively nontoxic bismuth (III) halide salts and the expected products could be smoothly obtained in good yields (**Scheme III.45**).



Scheme III.45. BiCl₃-catalyzed alkyne substitution of substituted alcohols.

As shown by Ito and Hosomi²⁰⁴, alkynylsilanes were also shown to be precursors of copper acetylides. These authors have indeed reported that the silyl group of TMS-alkyne could be cleaved by CuCl generating a copper acetylide which after reaction with an acid chloride could generate α -alkynones. More interestingly regarding our interest for catalytic alkyne reaction of iminium intermediates, Sakai *et al.*²⁰⁵ reported that alkynylsilanes were also found to be suitable partners (instead of terminal alkynes) in catalytic three-component coupling reactions yielding propargylamines (**Scheme III.46**).



Scheme III.46. Cu-catalyzed A³ coupling involving TMS-alkynes.

A number of catalysts such as AlCl₃, Zn(OTf)₂ and Hf(OTf)₄ were screened but the use of a mixture of Cu(OTf)₂ and CuCl in acetonitrile solution was found to shorten the reaction time while providing an increased yield (up to 99%). The role of each of these copper catalysts is not clearly established yet. The writers assumed that CuCl would be responsible

²⁰³ De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* **2005**, *46*, 8345.

²⁰⁴ Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, H. *Tetrahedron Lett.*, **1997**, *38*, 3977.

²⁰⁵ Sakai, N.; Uchida, N.; Konakahara, T. *Synlett*, **2008**, *10*, 1515.

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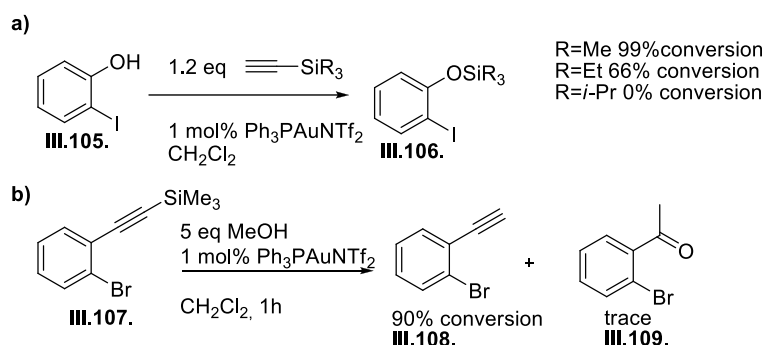
for the generation of a copper acetylide whereas $\text{Cu}(\text{OTf})_2$ would act as a Lewis acid enabling generation of the iminium intermediate which would be formed by condensation of the aldehyde and the amine. The scope of the reaction was extended to different aldehydes and amines. Although the reaction accommodated a variety of aldehydes, only cyclic and aliphatic amines like morpholine, *N*-methylpiperazine, diethylamine gave good to excellent yields.

The influence of different silyl groups were also examined and it was found that the steric demand on the silicon atom was determining, the copper catalyst cleaving selectively the smallest TMS group.

III.1.4. ACTIVATION OF SILYL ALKYNES BY GOLD COMPLEXES

As previously mentioned, silyl-alkyne motifs has been often used as convenient partners in common organic reactions due to ready availability and high functional group compatibility. Some important applications involve interaction of alkynylsilanes with gold catalysts and thus it is important to understand the reactivity of the proposed gold(I) acetylides as nucleophiles.

On the **Scheme III.42.** and **Table III.6.** it was presented that the desilylation can be catalytically carried out by treatment with AgNO_3 or AgOTf . Sheppard and co-workers²⁰¹ have observed that trimethylsilylalkynes undergoes protodesilylation also in a presence of catalytic amount of $\text{Ph}_3\text{PAuNTf}_2$. In order to investigate this gold-catalyzed cleavage of carbon-silicon bond they have explored the reaction of three silylacetylenes in a presence of 2-iodophenol **III.105** as a silyl trap (**Scheme III.47.**)

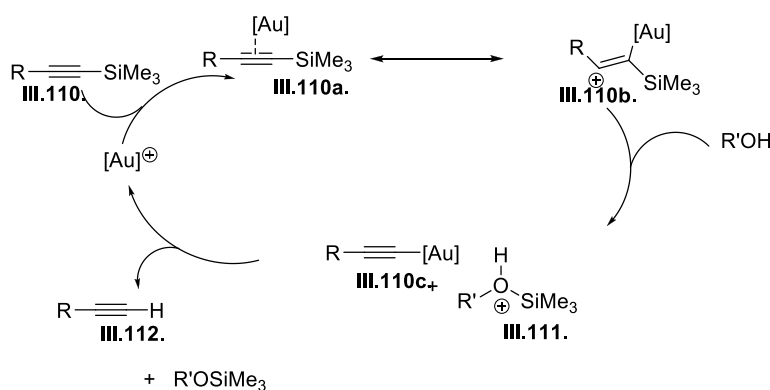


Scheme III.47. Gold-catalyzed silyl transfer from alkynes.

As it is presented on the **Scheme III.47a.**, a decrease in the reaction rate was observed as the bulkiness of the trialkylsilyl motif increased. Complete silyl transfer to the phenol was observed in a case of trimethylsilylacetylene, whereas triisopropylsilylacetylene was

completely inert under the reaction conditions. The authors have also deprotected trimethylsilyl arylalkynes such as **III.107** in the presence of methanol (**Scheme III.46.b**), and in this case the 2-bromoacetophenone **III.108**. was smoothly formed after only 1h.

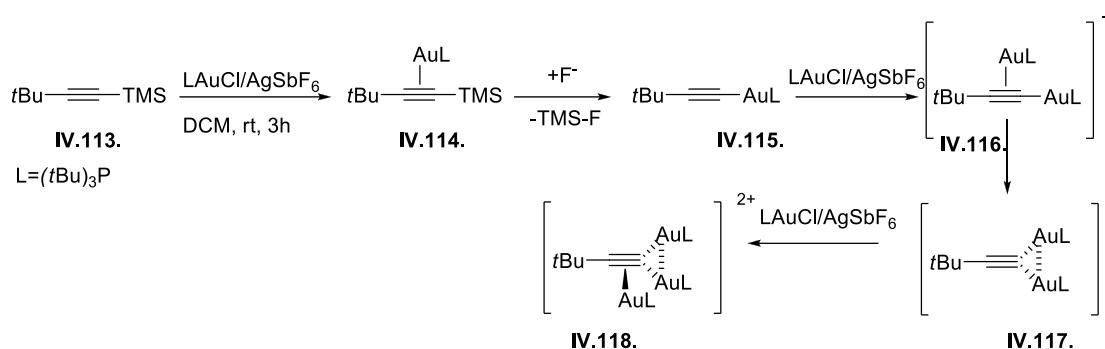
The mechanistic study suggests that after coordination of gold to the silyl alkyne generation of cation **III.110a**. with a resonance form **III.110b**. can occur where the gold-carbon bond and/or the silyl-carbon bond stabilizes the carbocation. Then nucleophilic attack of the alcohol on the silicon atom results in alkynylgold (I) species **III.110c** together with the protonated silyl ether **III.111**. The Brønsted superacid siloxonium ion **III.111**. could next easily protonate the gold acetylide to give the terminal alkyne **III.112**. (**Scheme III.48**.)



Scheme III.48. Proposition of the mechanism for the gold-catalyzed silyl transfer reaction.

The topic concerning the generation of gold-acetylides from silyl alkynes has been studied analytically by Russell's research group.²⁰⁶ $\text{Me}_3\text{Si-C}\equiv\text{CBu}^t$ as a model alkyne was selected and tested with the cationic gold (I) complex equipped with a non nucleophilic counterion ($^t\text{Bu}_3\text{P}$) AuSbF_6 . (**Scheme III.49**.) After 3h at room temperature, a 73% yield of the air-stable gold (I) π -alkyne complex **IV.114**. was isolated. When the reaction was pursued, a dicationic complex **IV.118**. was formed in 80% yield. The mechanistic study pointed out that the unusual complex **IV.118**. has its origin in a nucleophilic attack of a F^- anion delivered by SbF_6^- on the silicon center of **IV.114**. (which carries a partial positive charge) giving the gold acetylide **IV.115**. The resulting intermediate **IV.115**. could next be captured by coordination of a $\text{Bu}_3^t\text{PAu}^+$ cation onto the π -system of the acetylide.

²⁰⁶ Hooper, T. N.; Green, M.; Russell, C. R. *Chem. Commun.* **2010**, 2313.



Scheme III.49. Synthesis of cationic Au(I)-alkynes complexes.

What is important to point out, is that the presented process is continuous and is only interrupted after formation of dication **IV.118**.

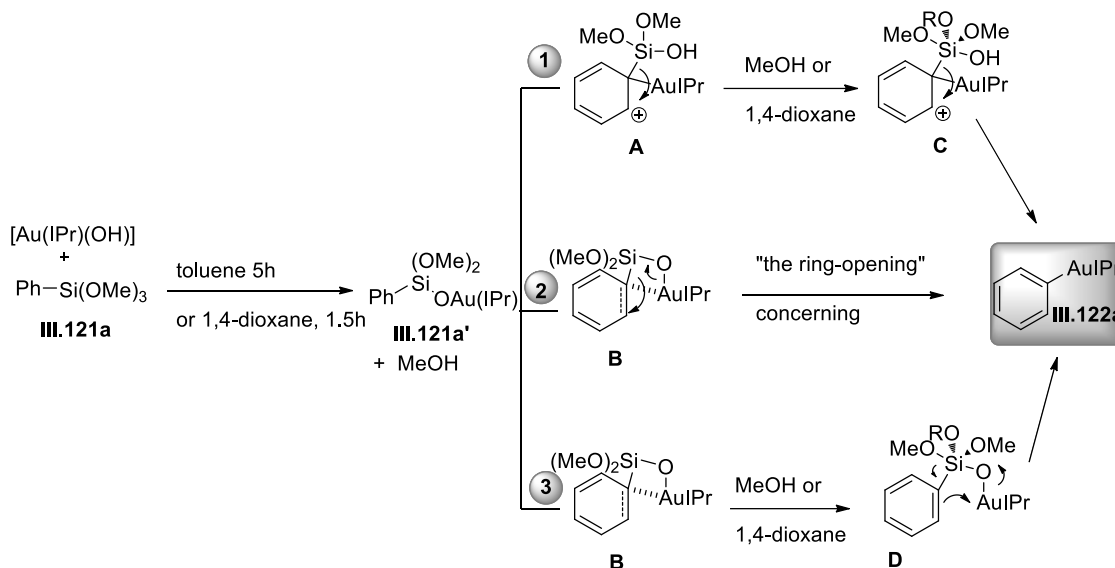
Recently, Nolan and co-workers²⁰⁷ reported a new route to access NHC-gold(I) acetylides in high yield under moderate conditions using the air stable IPrAu-OH and terminal or trimethylsilyl-protected alkynes. The reaction proceeds at 60 °C in a 1/1 mixture of MeOH/EtOH to form the gold-acetylide with concomitant formation of trimethylsilanol or water respectively. (**Table III.7**.)

It is important to point out that no significant difference was observed in the yield using either TMS or hydrogen acetylides. However, the reaction times for the displacement of TMS were longer. The NMR study shown that following use of an excess of RC≡CPh (R=H or TMS) at room temperature in a CD₂Cl₂ solution, the reaction with the terminal acetylene derivative reached complete conversion to the gold-complex within 2 h while the TMS derivatives requires 9h to complete. The author rationalized that the increased bulk of the trimethylsilyl is responsible for the retardation of the autodesilylation.

The authors have also made theoretical calculations which suggest slightly different mechanisms for the reaction of terminal and trimethylsilyl alkynes with gold (I) complex. In the reaction with HC≡CR, where the acetylide hydrogen is the most acidic proton, the mechanism is proposed to initially proceed through a proton transfer from alkyne to [Au(OH)IPr] along with Au-OH₂ bond cleavage to yield the expected products and water with a free energy charge with respect to the starting material of -8.3 kcal.mol⁻¹. In a case of Me₃SiC≡CR, the reaction proceeds through somewhat similar pathway but because of the increased bulk of the TMS group and the rigidity of the alkyne triple bond the reaction is predicted to go through intermediates surrounding the key transformation corresponding to

²⁰⁷ Fortman, G. C.; Poater, A.; Levell, J. W. Gaillard, S.; Slawin, A. M. Z.; Samuel, I. D. W.; Cavallo, L.; Nolan, S. P. *Dalton. Trans.* **2010**, 39, 10382.

As it is presented on the **Scheme III.51.**, the transmetalation of arylsilanes was clean and the arylgold compounds were obtained in good to excellent yields. Interestingly, the reaction could be transposed to vinyl- and allylsilanes, affording the vinyl- and allylgold complexes albeit in lower yields.



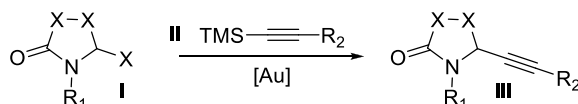
Scheme III.51. Proposition of the mechanism.

After monitoring the reaction by ^1H NMR spectroscopy, the authors could propose a mechanism where the rather unanticipated formation of the intermediate **III.121a'** is a key in the transmetalation of the organic moiety to gold (**Scheme III.51.**). Then three pathways were considered for this reaction. **III.121a'**, which was formed together with a molecule of methanol, could evolve *via* two paths, from either intermediate **A** or **B** with a β -silyl effect. In a presence of methanol, a pentavalent silicon species could be formed by nucleophilic attack on the silicon atom in **A** to lead **C**. After inversion to a more stable Si^{IV} , the intermediate would evolve into the phenylgold compound **III.122a**. For the four-membered cyclic intermediate **B**, a similar mechanism with the nucleophilic attack of methanol onto silicon would lead first to **D** and then, after rearrangement to give stable product **III.122a**.

Alternatively, heating the intermediate **III.121a'** in 1,4-dioxane directly could give rise to either **A** or **B**. From **A** the coordinating oxygen atoms of dioxane would permit to follow the two pathways previously described. Ring-opening of **B** could also provide the desired product. Unfortunately, the authors have not been able to isolate any of the presented intermediates and silicate sides products yet.

III.2. RESULTS : THE ALKYNYLATION REACTION OF *N,O*-ACETALS

A second part of the research project presented in this manuscript is then centred on the development of a catalytic alkynylation reaction of cyclic *N*-acyliminium ions using *N,O*-acetals as precursors. Key feature was the use of TMS-alkynes in conjunction with gold complexes. (Scheme III.52.)



Scheme III.52. The aim of the second part of the project

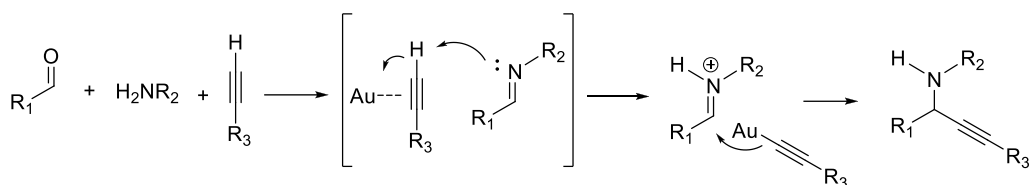
This catalytic alkynylation which we proposed to develop has never been described and is highly desirable. Indeed, even if the α -amidoalkylation of alkoxy lactams with traditional nucleophiles has been widely documented,²⁰⁹ only a few reports describing the alkynylation of *N,O*-acetals has been published to date.²¹⁰ As shown previously by the different methods reported so far, various sources of preformed metal-alkynyl nucleophiles were usually used but drastic conditions were systematically employed with respect to the *N,O*-acetal activation, with at best use of stoichiometric amount of typical Lewis acid promoters.

The C-H activation of terminal alkynes under gold catalysis in mild conditions, *i.e.* the *in situ* catalytic generation of Au-alkynylides from H-C \equiv CR, is still a challenging task. However, this can be achieved at room temperature in the presence of a stoichiometric amount of an extra base, which is needed to remove the acetylenic proton from the terminal alkyne. For a long time this drawback rendered the chemistry of gold acetylide rather limited. So far, the Au-catalyzed activation of Csp-H bond has mainly been applied to the Aldehyde-Amine-Alkyne (A³) coupling for the efficient production of propargyl amines, where the *in situ* generated imines served the dual role of bases to generate gold acetylides then resulting in the formation of iminium electrophiles. (see paragraph III.1.2., Scheme III.53)²¹¹

²⁰⁹For authoritative reviews on *N*-acyliminium ion chemistry: (a) Speckamp, W.N.; Moolenaar, M.J. *Tetrahedron* **2000**, *56*, 3817. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

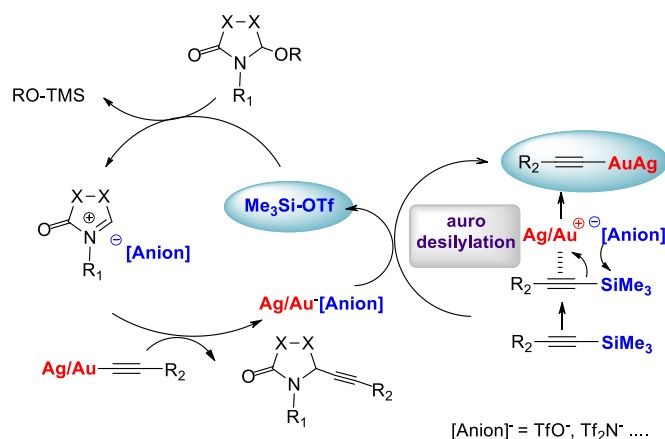
²¹⁰(a) Lundkvist, J.-R. M.; Wistrand,.; Hacksella, U. *Tetrahedron Lett.* **1990**, *31*, 719. (b) Turcaud, S.; Sierecki, E.; Martens, T.; Royer, J. *J. Org. Chem.* **2007**, *72*, 4882.

²¹¹(a) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (b) Nevado, C.; de Haro, T. *Synthesis* **2011**, 2530.



Scheme III.53. Role of the imine intermediate in gold-catalyzed A³-type couplings

In our proposition of the reaction system, such a basic entity is lacking (the *N,O*-acetals being much less basic than imines), and the required use of an extra base such an amine for acetylide formation would probably sponge the liberated proton providing an ammonium salt of insufficient strength for the *N*-acyliminium generation. The possibility to access silver acetylides from silyl acetylenes without the need of using a base was presented earlier in the manuscript.²¹² The silicon residue in silver- π -alkyne complexes are obviously electrophilic enough to be trapped by the counterion of the metal. On the other hand, a few examples involving trialkylsilyl alkynes in the context of gold catalysis (see section III.1.4. earlier in this chapter) support the idea of a possible gold-acetylide formation. Based on these considerations, we postulated that exposure of a mixture of *N,O*-acetal and TMS-alkyne to catalytic amounts of a gold catalyst of type [L-Au⁺]⁻X⁻ could generate an L-Au acetylide with concomitant release of a silyl Lewis acid, *i.e.* Me₃SiX. Such a highly Lewis acidic silicon derivative should then be able to activate the *N,O*-acetal substrate thus generating an *N*-acyliminium ion, which should be rapidly trapped by the metal acetylide (Scheme III.54.).



Scheme III.54. Proposition of the mechanism

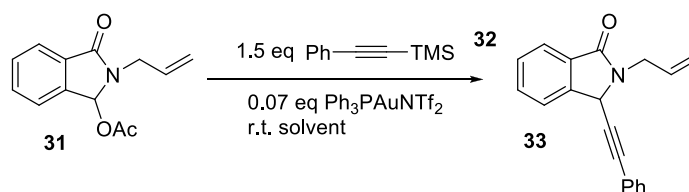
²¹² Orsini, A. ; Vitèrisi, A. ; Bodlener, A. ; Weibel, J. M. ; Pale, P. *Tetrahedron Lett.* **2005**, 46, 2259. (b) Carpita, A. ; Mannocci, L. ; Rossi, R. *Eur. J. Org. Chem.* **2005**, 1859. (c) Vitèrisi, A. ; Orsini, A. ; Weibel, J. M. ; Pale, P. *Tetrahedron Lett.* **2006**, 47, 2779.

III.2.1. OPTIMIZATION STUDY

For initial screening experiments, 2-allyl-3-oxoisindolin-1-yl acetate **31** and trimethyl(phenylethynyl)silane **32** were selected as model reaction partners and the Gagosz catalyst $\text{Ph}_3\text{PAuNTf}_2$ (7 mol%) with different solvents was tested (**Table III.8.**). The electrophile was prepared from phthalimide in few steps starting by benzylation of phthalimide under basic conditions, selective reduction of one carbonyl group of the imide moiety with NaBH_4 followed by acetylation of the resulting hydroxylactame with acetic anhydride Ac_2O under conventional conditions. The acetoxy lactam can be also very effectively prepared in a sequence of one-pot reduction / acetylation operating at low temperature in dichloromethane solution, with the couple *super* Hydride $\text{LiEt}_3\text{BH} / \text{Ac}_2\text{O}$.²¹³

The Gagosz catalyst was chosen given our knowledge that silyl triflimidate, the silylated Lewis acid $\text{Tf}_2\text{NSiMe}_3$ expected to be *in situ* formed concomitant to the generation of the gold acetylide, is an outstanding catalyst for the activation of *N,O*-acetals into *N*-acyliminiums.²¹⁴

Table III.8. Gold catalyzed alkynylation reaction of *N,O*-acetals: Influence of the solvent



Entry	solvent	Time	Conv.[%]	Entry	solvent	Time	Conv.[%]
1.	DCE	49h	100	4.	CHCl_3	72h	95 ^{a)}
2.	DCM	41h	96	5.	toluene	1.5h	100
3.	Ether	23h	93	6.	xylene	4h	100

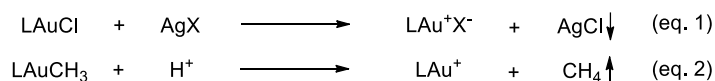
²¹³ Szemes, F.; Fousse, A.; Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Synthesis*, **2006**, 875-878.

²¹⁴ (a) Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, 7, 5335. (b) Tranchant, M. J.; Moine, C.; Ben Othman, R.; Bousquet, T.; Othman, T. M.; Dalla, V. *Tetrahedron Lett.* **2006**, 47, 4477. (c) Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, G.; Rouden, J.; Dalla, V. *Adv. Synth. Catal.* **2010**, 352, 2881. *More details can be found in Chapter I*

a) Catalyst generated *in situ*.

While high conversions were obtained in all the solvents screened using 7 mol% of the catalyst, variable reaction rates were however observed. This set of experiments revealed that the reaction with the lowest nucleophilic toluene gave the product with a significant shortest reaction time. Based on this result we decided to employ toluene in our next set of reactions.

As anticipated from our mechanistic hypothesis, we next decided to investigate the influence of the nature of the catalyst counterion on the reactivity. (**Table III.9.**) Indeed, it is well-known that generally the Lewis acidity of metallic salts, and in particular of gold catalysts, could be adjusted by varying the nature of the counterion and the gold ligand.²¹⁵ To obtain a more active catalyst, it is important to introduce a weakly coordinating group, in order to get a more cationic species close to [LAu⁺]. To access these cationic complexes, two approaches can be considered, the *in situ* generation of the cationic species or the use of a stable cationic catalyst. To realize an *in situ* anion metathesis, it is necessary to add a silver salt AgX (X = OTf, NTf₂, SbF₆, BF₄) to the gold catalyst of LAuCl type. It leads to the formation of LAuX and precipitation of AgCl (**Scheme III.55**, eq. 1).²¹⁶ A second method, developed by Teles,²¹⁷ relies on the *in situ* generation of the active species [LAu⁺] by addition of a strong acid such as HBF₄, CH₃SO₃H, H₂SO₄ (*i.e.* having conjugated species weakly coordinating) resulting in the generation of methane as a by-product (eq. 2).



Scheme III.55. Catalysts generated *in situ*.

These methods both present the disadvantage of adding either silver salts or a strong acid to the transformation; the nature of the actual active species thus being uncertain. A recent study reported by Shi and coll.²¹⁸ demonstrated that the silver salt could indeed have an influence on the nature of the intermediates in gold-catalyzed transformations. It is then systematically required to check the contribution of the additive (AgX or Brønsted acid) to every reaction catalyzed by a catalyst generated *in situ* by one of these ways. Use of stable

²¹⁵ Reviews on the role of ligands in gold complexes catalysis: (a) Gorin, D. J.; Sherry, B. D.; Toste, D. F. *Chem. Rev.* **2008**, *108*, 3351; (b) Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2012**, *134*, 5697.

²¹⁶ Kennedy-Smith, J. J.; Staben, S. T.; Toste, D. F. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

²¹⁷ Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.

²¹⁸ Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L. Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.

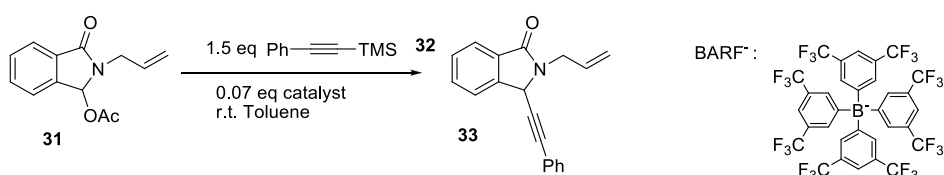
CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

catalysts of LAuNTf₂ type, developed by Gagosz and Corma,²¹⁹ could then appear to be an appealing alternative.

Comparison of Ph₃PAuNTf₂ either commercial or formed *in situ* by premixing Ph₃PAuCl and AgNTf₂ was then done first. A faster rate (1.5h compared to 4h) was observed using the commercial catalyst lacking silver salt but in both cases a full conversion of the substrate was obtained (**Table III.9.**, entries 1-2).

Catalysts with other counterions than triflimidate were next tested. Except Ph₃PAuCl which is commercially available, the cationic gold salts were generated *in situ* from Ph₃PAuCl and the corresponding silver salt AgX. While a complete lack of reactivity was observed with non nucleophilic BARF, BF₄⁻ and, to a lesser extent, SbF₆⁻, Cl⁻, I⁻ counterions (Entries 5-8, 3), the reaction with a catalyst incorporating a more nucleophilic triflate counteranion displayed complete conversion and formation of the product within only 45 min. (**Table III.9.** Entry 4) This strong effect encouraged us to use a gold catalyst with a tosylate counterion which displays a higher nucleophilic character than triflate. However, no trace of the expected product was obtained even after a prolonged reaction time and the starting *N,O*-acetal was fully recovered. According to our long-standing knowledge on the Bronsted and Lewis acid catalysts that can be used to mediate our α -amidoalkylation reactions, we assumed that even if a quick generation of the trimethylsilyltosylate occurred, this latter might be an insufficient Lewis acid to promote the formation of the *N*-acyliminium intermediate thus inhibiting the catalytic cycle (**Table 9.** Entry 9).

Table III.9. Gold catalyzed alkynylation reaction of *N,O*-acetals: Influence of a counteranion



Entry	Counteranion	Conversion[%](Time)
1.	Ph ₃ PAuNTf ₂ ^{a)}	100 (1.5 h)
2.	Ph ₃ PAuNTf ₂ ^{b)}	100 (4 h)
3.	Ph ₃ PAuSbF ₆	73 (4 h)
4.	Ph₃PAuOTf	100 (45 min)
5.	Ph ₃ PAuBARF	NR (21 h)
6.	Ph ₃ PAuBF ₄	NR (21 h)

²¹⁹ (a) Ricard, L.; Gagosz, F., *Organometallics* **2007**, 26, 4704; (b) Mezailles, N.; Ricard, L.; Gagosz, F., *Org. Lett.* **2005**, 7, 4133.

7.	Ph ₃ PAuCl	NR (24h)
8.	Ph ₃ PAuI	NR (25h)
9.	Ph ₃ PAuOTs	NR (24h)

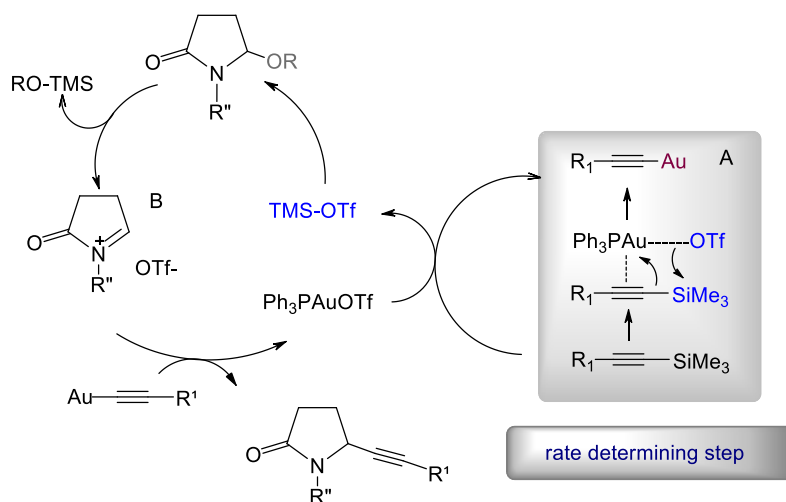
a) Commercially available catalyst; b) Formed *in situ* by premixing Ph₃PAuCl and AgNTf₂ and used as such.

These set of results are in agreement with a mechanistic study realized by Kovács and coll.²²⁰ who calculated Au-PPh₃ dissociation energies for different Ph₃PAuX complexes. This study indeed predicts that anions such as TsO⁻, NO₃⁻, CH₃COO⁻, Cl⁻ present a strong interaction with the metallic center, their respective dissociation energy being high. It is then also even possible that Ph₃PAuOTs is not electrophilic enough to form a productive π -complex with **32** that will enable the desired aurodesilylation.

Table III.10. Metal-Ligand (Ph₃PAuX) dissociation energies in DCE.

X	Ph ₃ PAuX \longrightarrow PAu ⁺ + X ⁻					
	OTf ⁻	NO ₃ ⁻	Cl ⁻	TsO ⁻	CF ₃ COO ⁻	BF ₄ ⁻
<i>E</i> , kcal/mol	24.6	201.7	307.5	155.0	324.7	- 56.6

By analogy to many S_N1-type reactions involving *N*-acyliminiums, we initially anticipated that the formation of the cationic species would be the rate determining step. However, the results presented above strongly suggest that the rate determining step in our mechanistic proposal is formation of the gold acetylide **A** rather than generation of iminium ion **B**. (Scheme III.56.) Nucleophilic attack to the activated SiMe₃ group within the alkyne-Au π -complex is facilitated with the most nucleophilic trifluoromethanesulfonate (TfO⁻) counterion (relative to Tf₂N⁻, BF₄⁻....), whereas the neutral triphenylphosphine group likely contributes to form a weak ion-pair within the catalyst structure which is easier to dissociate.

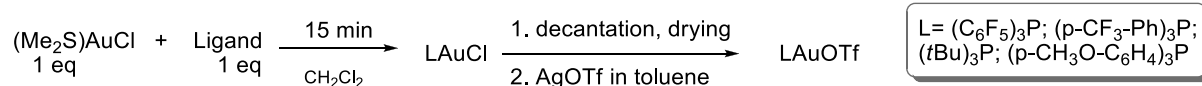


Scheme III.56. Mechanistic proposal

²²⁰ Kovács, G.; Ujaque, G.; Lledos, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.

Our next goal was to examine different types of phosphine ligands (**Table III.11**). Although a cationic gold (I) catalyst equipped with a strong electrophilic triaryl phosphine group is well known and often used in the literature,²²¹ in our case such phosphines gave disappointing results. (**Table III.11**, Entries 1-2) We have also tested the Echavarren catalyst with an acetonitrile ligand, which could easily be exchanged with an alkyne due to its low coordinating character. Unfortunately it proved to be inefficient in our model reaction which remained incomplete after a long period of time. (**Table III.11**, Entry 3.) The low conversions that were observed when more electrophilic gold catalysts such as (C₆F₅)₃PAuOTf and (*p*-CF₃-C₆H₄)₃PAuOTf (entries 1-2) were employed, strongly support our dual synergistic gold / silyl catalysis concept rather than an oxophilic gold-catalyzed *N,O*-acetal activation pathway. This view is further reinforced if one consider that the tighter ion-pair resulting from the use of gold salts with electron-poor triarylphosphines probably reduces silaphilicity of the triflate anion and then retards generation of the gold-acetylide intermediate and the overall reaction rate.

From these results it may be anticipated that use of even more nucleophilic ligands such as electron-rich alkyl- or methoxyarylphosphines, alkylphosphines or certain carbenes might accelerate the reaction further by facilitating gold-acetylide formation. As a result, following the methods developed by Gagosz, a variety of LAuOTf catalysts were easily prepared through the metathesis of either commercially available or synthesized ligated-AuCl species with AgNTf₂ (**Scheme III.57**).



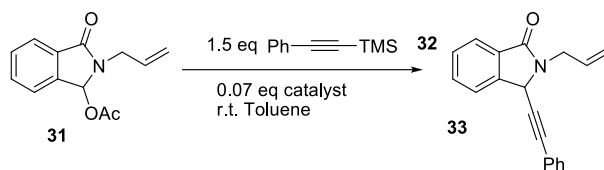
Scheme III.57. Synthesis of LAuOTf catalysts.²⁰⁴

Thus, gold triflate with an alkyl (*t*Bu)₃P group was next tested and to our surprise it appeared to be much less efficient (**Table III.11**, Entry 4). On the contrary, introduction of an electron-rich phosphine *p*-MeO-(C₆H₄)₃ as well as IPr and IMes carbenes were found to be highly efficient (Entries 5-7). Even using reduced loading of these catalysts (3 mol%) was found to surpass Ph₃PAuOTf allowing complete conversion of the starting material and smooth formation of the product after shorter reaction times (Entries 8 vs 9-10).

²²¹ Kim, Ch.; Bae, H.J.; Lee, J.H.; Jeong, W.; Kim H.; Sampath, V.; Y.H. Rhee. *J. Am. Chem. Soc.* **2009**, *131*, 14660.

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Table III.11. Gold-catalyzed alkyne reaction of *N,O*-acetals: Influence of the ligand

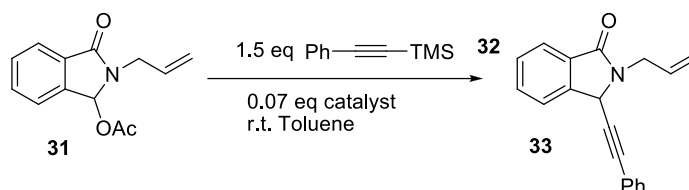


Entry	Phosphine	Time	Conversion[%]
1.	(C ₆ F ₅) ₃ PAuOTf	30' then 22h at 50 °C then 4h at 70 °C	40 ^{a)} 69 ^{a)}
2.	(<i>p</i> -CF ₃ -Ph) ₃ PAuOTf	30' 3h 19h	2 ^{a)} 5 ^{a)} Degradation
3.	Echavarren catalyst: 	30h	43
4.	(<i>t</i> Bu) ₃ PAuOTf	5.5h	48
5.	(<i>p</i> -CH ₃ O-C ₆ H ₄) ₃ PAuOTf	45'	100
6.	IPrAuOTf: 	45'	100
7.		45'	100
8.	Ph ₃ PAuOTf [3 mol%]	30'	44
9.	(<i>p</i> -CH ₃ O-C ₆ H ₄) ₃ PAuOTf [3 mol%]	30'	100
10.	IPrAuOTf: 	30'	100

a) Ratios **31/33** measured from ¹H NMR of aliquots

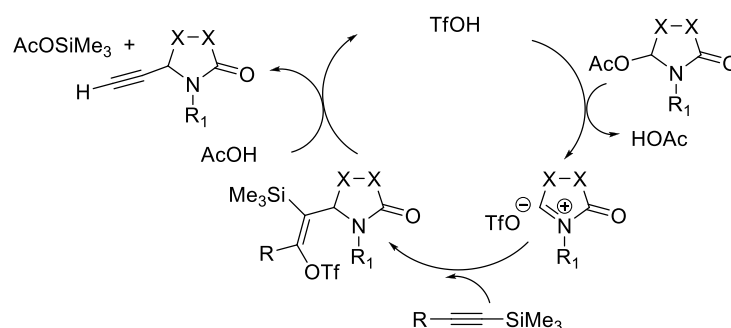
In order to simplify the catalytic system, we decided to check whether a phosphine group is necessary in the catalytic system. To this aim we examined AuOTf and Au(OTf)₃ as catalysts (**Table III.12.**). The results obtained herein proved that a ligand is essential for the reactivity and somewhat supports the idea that electron-enrichments of the metallic center facilitates the reaction.

Table III.12. Gold catalyzed alkylation reaction of *N,O*-acetals: Ligand-free catalyzed reaction



Entry	Catalyst	Time	Conversion[%]
1.	AuOTf	3h r.t.	NR
		20h 50 °C	32
		4h 70 °C	34
		2h reflux	degradation
2.	Au(OTf) ₃	2 days	Complex mixture

A brief investigation of the scope of other types of catalysts was next explored. Although we have discussed the ability of silver salts to promote a number of reactions starting from alkynylsilanes (see **Scheme III.42.** and **Table III.6.**), poor reactivity was observed using either silver triflate or silver triflimidate. These results proved that under the standard conditions used for the gold process, generation of a silver-acetylide intermediate does not take place or, if ever generated, this species is not nucleophilic enough to attack *N*-acyliminium ion. (**Table III.13.**) Importantly, Tf₂NH as well as TfOH which are highly efficient pre-catalysts for S_N1-type reactions of ketene silyl acetals, silyl enol ethers and allyltrimethylsilane with *N,O*-acetals, performed poorly in this alkylation reaction. These results are highly supportive of our mechanism manifold, which very likely surpass the possible alternative mechanism involving σ -type Au-catalyzed *N,O*-acetal activation followed by π -addition of the silylalkyne onto the *N*-acyliminium ion.²²² (**Scheme III.58.**)

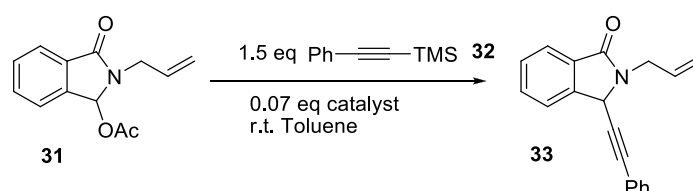


Scheme III.58. An alternative mechanism for the alkylation reaction of *N,O*-acetals.

²²² Aikawa, K.; Hioki, Y.; Mikami, K., *Org. Lett.* **2010**, *12*, 5716.

Molecular iodine was also considered as a potential catalyst. Its mild Lewis acidity and its high tolerance to air and moisture have for instance led to the development of a direct and metal-free nucleophilic substitution of "highly π -activated" aryl propargyl alcohols with alkynylsilanes with good results.²²³ So we have tested whether I_2 could promote not only the nucleophilic addition of the TMS-alkyne but also the *N*-acyliminium *in situ* formation. However, the reaction using I_2 as catalyst completely failed to provide the corresponding alkynylated product even after a long reaction time and the starting *N,O*-acetal was fully recovered. (**Table III.13.** Entry 5) This result in the presence of a weak acidic (pre-)catalyst like I_2 attests to the poor ionizing potential of these acetoxy lactams relative to the biased alcohol substrates used by the group of Yadav,²²³ and therefore emphasizes the challenge associated with, and the relevance of our synergistic gold/silyl-catalyzed alkynylation.

Table III.13. Silver and Brønsted acid catalyzed reaction



Entry	Silver catalyst	Time	Conversion[%]
1.	AgNTf ₂	3h r.t.	NR
		18h at 70 °C	16
		3h reflux	36
2.	AgOTf	3h r.t.	NR
		2.5h 60 °C	
		16h reflux	85
3.	Tf ₂ NH	51h	69
4.	TfOH	6.5h	17
5.	I ₂	25h	NR

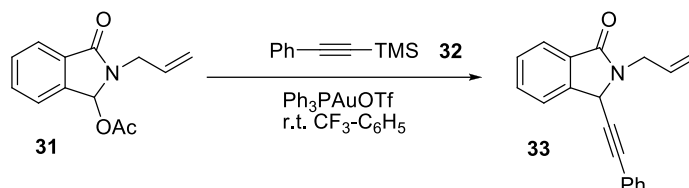
The catalysts screening thus highlights the superior efficiencies of cationic gold (I) complexes with electron-rich ligands such as *p*-CH₃O-(C₆H₄)₃P, NHC and Ph₃P. However at this stage of our study, owing to atom-economy and cost considerations, use of the simplest Ph₃PAuOTf was considered to be the most convenient and will be kept for continuation of this work.

²²³ Yadav, Y. S.; Subba Reddy, B. V.; Thrimurtulu, N.; Mallikarjuna Reddy, N.; Prasad, A. R. *Tetrahedron Lett.* **2008**, 49, 2031.

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Next, in order to further increase the reaction rate, we decided to test the reaction in α,α,α -trifluorotoluene. Its CF_3 group indeed lends to this solvent a lower nucleophilic character than toluene and based on results presented in **Table III.8.**, a positive effect on reactivity was expected. Indeed, we were delighted to observe that full conversion of the starting material was observed after only 15 min instead of 45 min as seen when toluene was used (**Table III.9.** Entry 4. versus **Table III.14.** Entry 1.).

Table III.14. Gold-catalyzed alkylation in α,α,α -trifluorotoluene

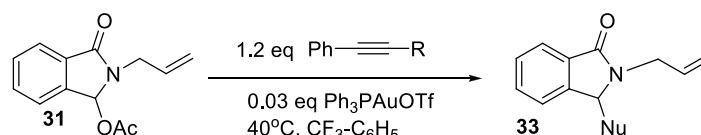


Entry	mol% catalyst	eq Nu	Time	T[°C]	Conversion[%]
1.	7	1.5	15'	r.t.	100
2.	3	1.2	overnight	r.t.	100
3.	3	1.2	15'	40	100

Using this solvent, reduction of the catalyst loading and of the nucleophile stoichiometry could be realized. Full conversion could be even obtained when the reaction was conducted at room temperature with only 3 mol % of Ph_3PAuOTf and 1.2 equivalent of TMS-alkyne **32** (**Table III.14.** Entry 2.). Warming the reaction mixture at 40 °C under the same conditions next allowed to restore a high reaction rate since the expected product could be obtained after only 15 min (Entry 3.) instead of 16 hours at room temperature.

Last, we have evaluated the impact of the silyl group on the reactivity. In full agreement with our expectation associated with the proposed mechanism, a net decrease in the reaction rate was observed as the bulkiness of the trialkylsilyl motif increased. (**Table III.15.**) While a complete absence of reactivity and no consumption of the silylated alkynes was observed with the triethylsilyl group, a very slow and low conversion was only obtained with the *t*-butyldimethylsilyl group. Presumably the activation of the R_3Si -alkynes failed, even a competitive desilylation reaction of the nucleophile in both cases did not take a place.

Table III.15. The alkylation reaction with other silylated alkynes



Reaction	nucleophile	Time	Conversion[%]
1.	$\text{Ph}-\text{C}\equiv\text{C}-\text{SiEt}_3$ 34	3d	NR
2.	$\text{Ph}-\text{C}\equiv\text{C}-\text{TBDMS}$ 35	5h40min	16

To summarize, from this preliminary set of experiments, highly efficient conditions for the alkynylation of the model acetoxylactam **31** were developed: Use of 1.2 equivalents of trimethylsilyl alkyne **32** in the presence of 3 mol% of the cationic gold(I) catalyst (Ph_3PAuOTf) in trifluorotoluene at 40 °C were indeed shown to provide the alkynylated compound **33** in a short reaction time (15 min) and high isolated yield (90% after isolation by flash chromatography). The success of the reaction is believed to be due to the efficient formation of a bicatalytic system *in situ*: concomitant generation of a gold acetylide and trimethylsilyl trifluoromethanesulfonate Lewis acid (TMSOTf) would be generated catalytically by addition of the Ph_3PAuOTf pre-catalyst on the TMS-alkyne.

Beside its doubtless synthetic utility as a novel alkynylative methodology, this mechanism-guided designed strategy also manifests a conceptual interest since it can be regarded as an unprecedented approach where the incorporation of a single pre-catalyst (LAuX) mediates the initiation and *in situ* generation of two key catalytic species, namely a σ -gold acetylide and a ‘super’ silyl transfer reagent (TMSX), which when synergistically combined with the electrophilic reaction partner promote the efficient formation of high-value entities based on **33**. When compared to ‘traditional’ synergistic catalysis, which systematically promotes reactions with the aid of *two separate* catalysts (Fig. 1A),²²⁴ our *in situ* approach to synergistic catalysis (Fig. 1B) is arguably of significant synthetic value from an academic, economic, time and atom-efficiency point of view. In addition, our approach has particular value if the catalytic species and/or catalyst(s) to be generated are not trivial to prepare and handle; as is the case here with σ -gold acetylides and the extremely water sensitive and highly reactive Lewis acids TMSOTf and TMSNTf₂.

²²⁴ Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.*, 2012, **3**, 633.

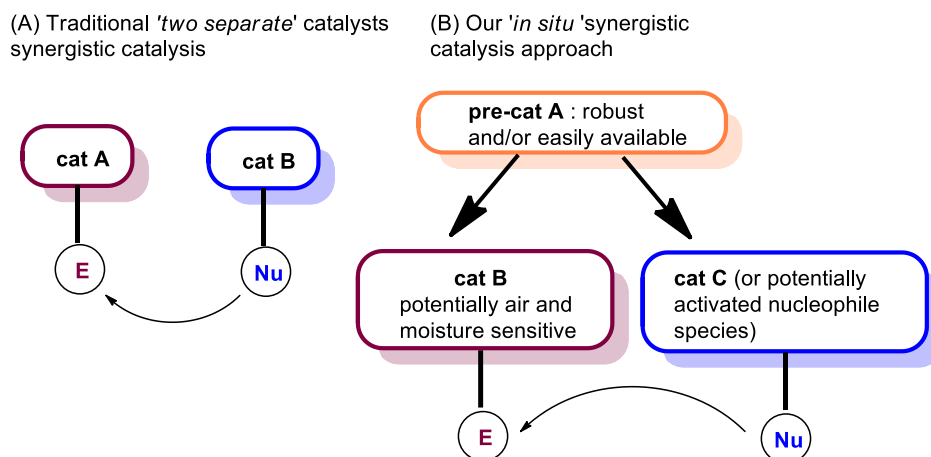


Fig. III.1. Traditional 'two separate catalysts' versus our 'in situ' synergistic catalysis.

III.2.2. SUBSTRATE SCOPE IN THE ISOINDOLONE SERIES: VARIATION OF THE PROTECTIVE GROUP AT NITROGEN

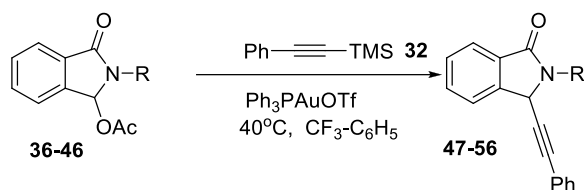
With optimal conditions in hands, we next sought to delineate the reaction scope. At first, a series of isoindolic acetoxy lactams possessing different protecting groups on the nitrogen was synthesized (using well-established procedures).

As was presented before, corresponding electrophiles were prepared from phthalimide in few steps starting by alkylation of phthalimide under basic conditions, selective reduction of one carbonyl group of the imide moiety with NaBH_4 followed by acetylation of the resulting hydroxylactame with acetic anhydride under conventional conditions. The acetoxy lactam could be also effectively prepared in a sequence of one-pot reduction / acetylation operating at low temperature in dichloromethane solution, with the couple *super* Hydride LiEt_3BH /anhydride acetic Ac_2O .

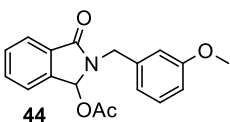
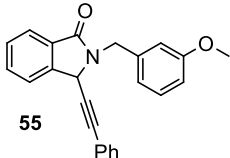
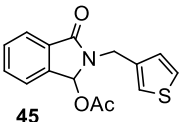
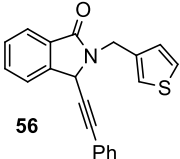
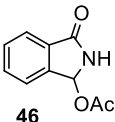
These compounds were then tested in the alkyne reaction with TMS-alkyne **32** under the optimized conditions and the obtained results are presented in **Table III.16**.

CHAPTER III: The gold-catalyzed alkylation reaction of *N,O*-acetals

Table III.16. Investigation of the scope using various *N*-substituted isoindolic acetoxy lactams



Entry	Starting material	mol% cat/ eq Nu/Time	Product	Yield [%]
1.		3/1.2/45 min		99
2.		3/1.2/45 min		95
3.		3/1.2/45 min		91
4.		3/1.5/1h		74
5.		3/1.5/3h		76 (86% conv)
6.		3/1.5/2h		53(60% conv)
7.		3/1.2/45 min		96
8.		3/1.2/45 min		69 Partial transformation of the product into an inseparable unidentified

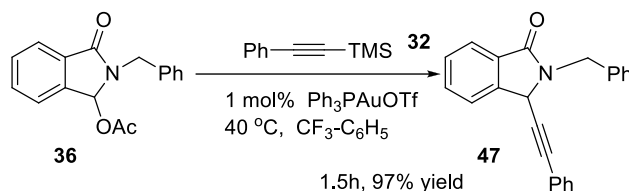
				product
9.		3/1.2/45 min		98
11.		3/1.2/15h		82
12.		15/1.2/3h	Complex mixture	

The results obtained herein proved that the method could be applied to different types of substrates possessing benzylic, allylic, propargylic, aliphatic and homologated analogous protecting groups on nitrogen. In most cases the expected products could be formed in good yields (60-98 %) within short reaction times (**Table III.16.**, Entries 1.-11.). Even presence of an heteroaromatic group such a thiophene was found to be compatible with the alkynylation conditions albeit a longer reaction time (15h) was required to get the expected adduct in 82% yield (Entry 11.). A non-protected substrate was also tested but failed to give the expected adduct showing that protection of the nitrogen is crucial (Entry 12.). It is also worth mentioning that our reaction protocol was compatible with substrates incorporating a terminal alkyne moiety, such as **40** and **41**. However, in these specific cases, a slower reaction rate was observed and use of 1.5 equivalents of TMS-alkyne only gave partial conversions (Entries 5, 6.). This strongly suggests a competitive coordination of the electrophilic gold catalyst with the triple bond of the substrates. Formation of phenyl acetylene (by proto-desilylation) was indeed observed during the reaction preventing the reaction from being complete. In order to reach full conversions of the corresponding acetoxy lactams, a portion-wise addition mode of 2.5 equiv of nucleophile was optimized. (**Table III.17.**) Thus, after consumption of the silyl-alkyne reagent (determined by ¹H NMR spectroscopy) an addition portion of the nucleophile was added to the reaction mixture and let it to complete.

Table III.17. The alkylation reaction of acetoxy lactams having a terminal alkyne moiety

Entry	R	eq Nu/Time	Product	Yield [%]
1.		1.5/3h then 1/19h		76
2.		1.5/2h then 1/25h		96

In order to further demonstrate the synthetic value of the reaction, we also checked if our catalytic optimized procedure could be amenable when scaled up. Satisfactorily, when 500 mg (1.77 mmol) of the parent acetoxy lactam **36** was reacted *using only 1 mol% of the pre-catalyst Ph₃PAuOTf*, 550 mg (1.72 mmol, 97%) of product **47** could be isolated (**Scheme III.58.**).



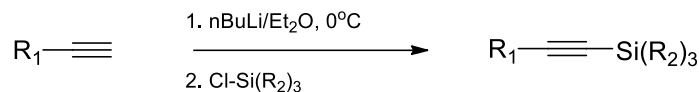
Scheme III.58. The alkylation reaction of **36** using 1 mol% of the catalyst.

III.2.3. GENERALIZATION OF THE PROCESS: DIVERSIFYING THE TMS-ALKYNE NUCLEOPHILE

To further expand the scope of the reaction, a series of TMS-alkynes equipped with various substituents was evaluated in alkylation reactions of phthalimide-derived *N,O*-acetals. At first, terminal alkynes substituted by aromatic groups or a butyl chain were silylated under standard conditions: Deprotonation at -78 °C with *n*-BuLi (1.1 equiv.), followed by addition of chlorotrimethylsilane (1.1 equiv.) yielded the corresponding TMS-alkynes in yields between 73 and 93%. (**Scheme III.59.**) Besides, trimethylsilylacetylene and

CHAPTER III: The gold-catalyzed alkylation reaction of *N,O*-acetals

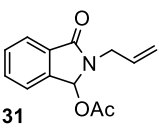
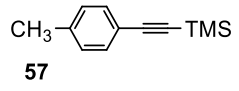
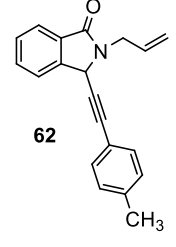
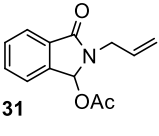
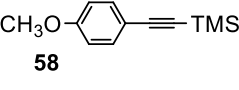
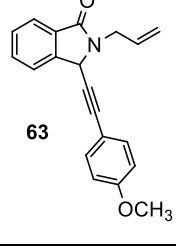
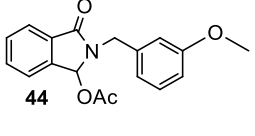
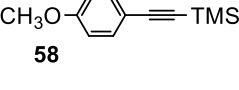
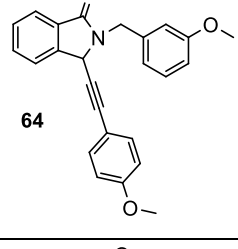
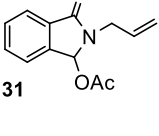
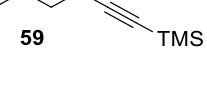
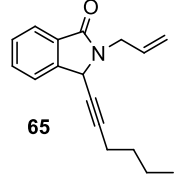
1,2-bis(trimethylsilyl)ethyne which were also considered in this set of experiments were commercially available.



Scheme III.59. General procedure for the silylation reaction of terminal alkynes.

The results obtained under the optimized alkylation conditions (3 mol% Ph_3PAuOTf , at 40 °C in $\text{CF}_3\text{-C}_6\text{H}_5$) are presented in **Table III.18.**

Table III.18. Scope of TMS-alkynes

Entry	substrate	Nu	Time	Product	Yield[%]
1.			5h		100
2.			23h		72
3.			4h		78
4.			45'		92

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5.			5h		69
6.		2 equiv. H—C≡C—TMS 60 with 7 mol% cat	2h15'		69
7.		2 equiv. TMS—C≡C—TMS 61 with 5 mol% cat	3h		73

^a The crude reaction mixture directly after the alkynylation reaction was desilylated by using at first 2M HCl and then TBAF in THF solution.

^b The reaction was set up with 4 mol % of the catalyst

At first, TMS-alkynes with electron-rich aromatic substituents were tested. When trimethyl(*p*-tolylethynyl)silane **57** or ((4-methoxyphenyl)ethynyl)trimethylsilane **58** were used, the alkynylation reactions of acetoxy lactam **31** produced the corresponding alkynylated products in good yields (100% and 72% respectively, entries 1-2). However, it is worth pointing out that increased reaction times were necessary to get full conversion of the *N,O*-acetal substrate compared to our model reaction using TMS-alkyne **32**. It was also shown that *N,O*-acetal **44** could be efficiently alkynylated using TMS-alkyne **57** affording the coupled product **64** in 78 % yield, after 4 hours of reaction that is almost 6 times faster than the reaction with its *N*-allyl analog (Entry 13. *versus* 16.). These results are indicative that the nucleophilicity of the triple bond is not the parameter of higher importance on the gold-acetylide formation but the strength of the Csp-Si bond that determines the rate of the aurodesilylation step.

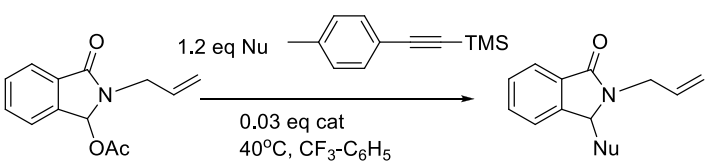
The trimethyl(1-hexynyl)silane **59** was next tested in the alkynylation of *N,O*-acetals substrates **31** and **42**. In the first case, a fast reaction was observed giving product **65** in 92% yield after only 45 minutes. In contrast, the formation of the alkynylated product **66** required a longer reaction time (5h); a difference of reactivity which was not observed in the corresponding reactions with silylated phenylacetylene **32** (table III.10.). It would be interesting here to repeat the reactions to check if this difference in reaction rates is really depending on the substrates.

To test the selectivity of the reaction, 1,2-bis(trimethylsilyl)ethyne **61** and trimethyl(ethynyl)silane **60** were also evaluated. In these reactions, 2 equivalents of

nucleophiles were used for volatility issues. Interestingly, only terminal alkyne **67** was formed in the reaction employing trimethylsilylacetylene (entry 5). It points to an unusual selective C_{sp}-Si activation of TMS-acetylene²²⁵ and supports our mechanism proposal on condition that product **67** did not result from desilylation of the acetylenic terminal position. This was confirmed in the reaction using disilylated alkyne **61**. Even if this type of substrate could potentially be further transformed under the reaction conditions used, neither desilylation, nor further alkynylation were observed and the silylated product **68** was obtained in 73% yield (entry 6).

As shown previously in the optimization part, Ph₃PAuOTf presented a good reactivity profile and was chosen for the generalization of the method. In parallel, it was also found that gold(I) catalysts possessing more electron-donating ligands such as [4-(MeO)Ph]₃P or the carbene IPr could be even more active than Ph₃PAuOTf. So, in the reaction involving trimethyl(p-tolyethynyl)silane **57**, these two catalysts were tested in order to try to shorten the reaction time without altering the efficiency. (**Table III.19.**) An acceleration of the reaction by facilitating gold-acetylide formation was indeed expected to occur (as observed for the model reaction). Unfortunately, no improvement was observed. Even little decomposition of the substrate and/or product was observed leading to slightly lower isolated yields (84 and 85 % respectively).

Table III.19. Investigation of trimethyl(p-tolyethynyl)silane as a nucleophile



Entry	cat	time	Conv[%]
1.	IPrAuOTf	19h	84
2.	(CH ₃ O-C ₆ H ₅) ₃ PAuOTf	22h	100% consumption of sm, (85% isolated yield)

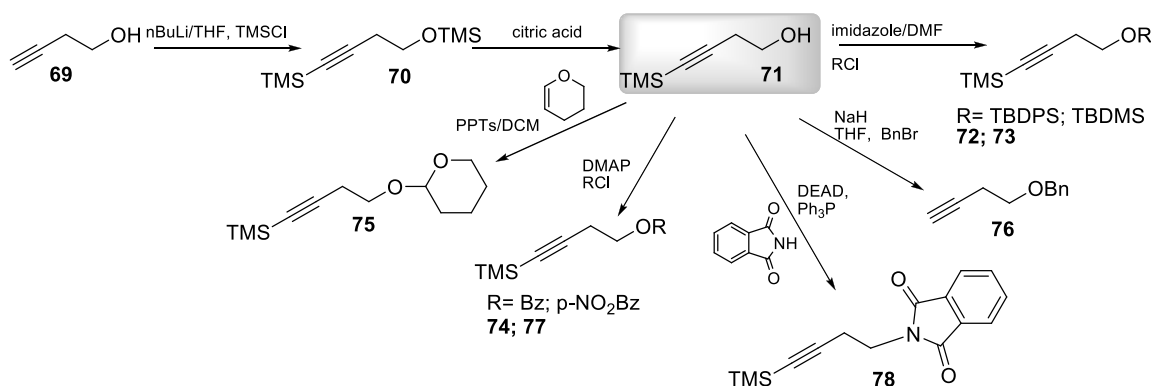
To test the tolerance of the method towards functional groups, a series of TMS-alkynes derived from 1-butyne possessing various protecting group on the oxygen was prepared. Compounds **72-77** were prepared in three steps starting from 1-butyne: Silylation under standard conditions (deprotonation at -100 °C with *n*-BuLi (2.1 equiv.), followed by addition

²²⁵ (a) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.*, **2006**, *8*, 1529. (b) Sakai, H.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Adv. Synth. Catal.*, **2008**, *350*, 2498. (c) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963 (d) Zhu, S.; Yan, W.; Mao, B.; Jiang, X.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6980.

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of chlorotrimethylsilane (2.05 equiv.)) first gave the disilylated product **70**. Selective cleavage of the silylated ether, followed by protection of the resulting hydroxyl group under classical conditions allowed formation of the corresponding TMS-alkynes in moderate to good overall yields. (Scheme III.59.)

Last, TMS-alkyne **77** was prepared by treatment of the commercially available *N*-(butynyl)phthalimide with *n*-BuLi and TMSCl. (Scheme III.59.)



Scheme III.59. General protocols for the synthesis of compounds **72-77**.

These TMS-alkynes were thus tested as nucleophiles in the alkylation reactions of *N,O*-acetal substrates **31**, **36** or **43** using our standard protocol (Table III.20). The reaction of compound **36** with TMS-alkyne **72** having a TBDMS ether gave a mixture of the expected product and its deprotected analog resulting from desilylation of the hydroxyl group (entry 1). Acidic hydrolysis (2M HCl), followed by treatment with a solution of TBAF in THF were used after full conversion of the starting *N,O*-acetal to complete the desilylation but the corresponding alcohol **79** could only be isolated in 38% yield (entry 2). However, when the reaction was done with compound **73** having a more robust TBDPS ether, the expected alkynylated product **80** was obtained in 75% yield. (entry 3 vs 1) thus demonstrating the compatibility of the method with a silyl group of this type.

Next, the alkylation of *N,O*-acetal **31** was tested with benzylated butynol derivative **76** (entry 4). Unfortunately, the expected product **81** was only isolated in 48% yield, though full conversion was observed after 3 hours. It is more likely that competitive deprotection of the hydroxyl group takes place under the reaction conditions. Changing to *N,O*-acetal **36** with a benzyl protecting group on nitrogen shortened the reaction time but the corresponding adduct was again obtained in a moderate yield of 56% despite use of 4 mol% of gold catalyst (entry 5) To limit this undesired deprotection, more robust ester groups were introduced on the TMS-alkyne partner. The reaction was thus realized with butynol derivatives **74** and **77** starting either from acetoxylactam **31** or **36**. In both cases, that is with a benzoyl group or its

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para-nitro analog, longer reaction times were required (possibly due to competitive coordination of the gold catalyst) to form the corresponding products in 40% and 54% yields respectively (entries 6-7).

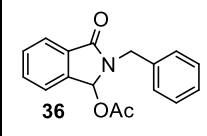
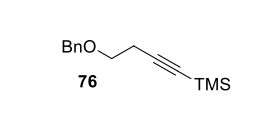
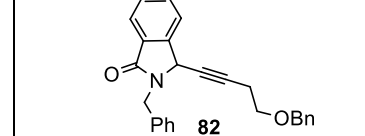
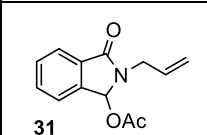
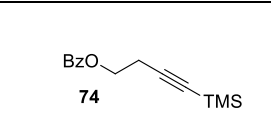
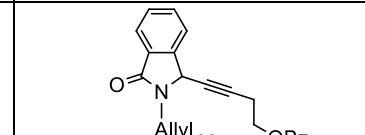
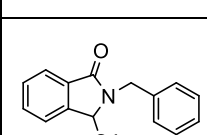
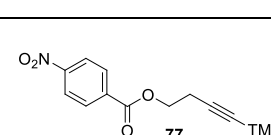
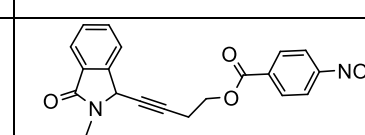
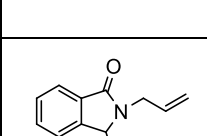
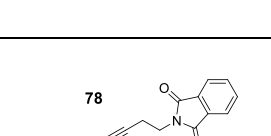
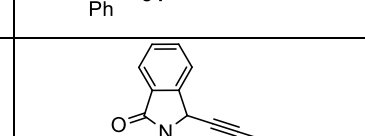
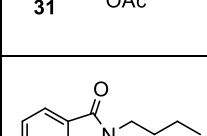
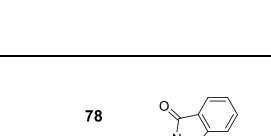
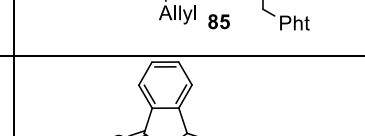
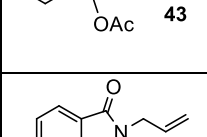
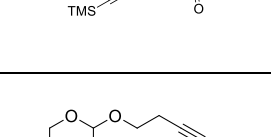
Use of the TMS-alkyne equipped with a phtalimide substituent was found to be more problematic. Indeed, only a conversion of 25% of the *N,O*-acetal substrate **31** was observed after 23h of reaction. (entry 8.) This lack of reactivity could be explained by a competitive coordination of the catalyst on the carbonyl groups of the phtalimide moiety. However, satisfactorily, the reaction with the more reactive *N*-butyl acetoxylactam **43** gave the corresponding alkyne product **86** in good yield. (74%, entry 9.)

We then envisaged testing if the reaction could tolerate the presence of an acetal group. We anticipated that this reaction would be very challenging since this functional group is highly susceptible to generate an oxonium ion intermediate in the presence of TMSOTf (presumably formed in the reaction according to our postulated mechanism) which could lead to many side-products. When the alkyne of acetoxylactam **31** was attempted under the optimized conditions with butynol derivative **75** protected with a THP group, formation of a complex mixture was only observed after a short reaction time with no trace of the expected product being formed. (entry 10.)

Table III.20. Scope of TMS-alkynes derived from 1-butynol

Entry	substrate	Nu	Time	Product	Yield[%]
1.			45'	60 Mixture of the Prod and desilylation Prod	
2. ^a			45'		38
3.			5h		75
4.			3h		48

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5. ^b			45 [°]		56
6.			2h		40
7.			6.5h		54
8.			23h		25% conv
9.			20h		74
10.			55 [°]	Full consumption	Complex mixture

^a The crude reaction mixture directly after the alkyynylation reaction was desilylated by using at first 2M HCl and then TBAF in THF solution.

^b The reaction was set up with 4 mol % of the catalyst

III.2.4. GENERALIZATION OF THE PROCESS: VARYING THE *N,O*- ACETAL FRAMEWORK

An important aspect to show the wide applicability of our method is to demonstrate that the reaction is not limited to phtalimide-derived *N,O*-acetals. We thus started the evaluation of various N-acyliminium precursors which are likely to react following this alkyynylation reaction.

The structure of the different cyclic *N,O*-acetal substrates studied is depicted on **Figure II.1.** below. Seven families of substrates were selected : *N,O*-acetals possessing pyrrolidine and piperidine skeletons or derived from maleimide, isoindolinone, oxindole and dihydroquinolinone.

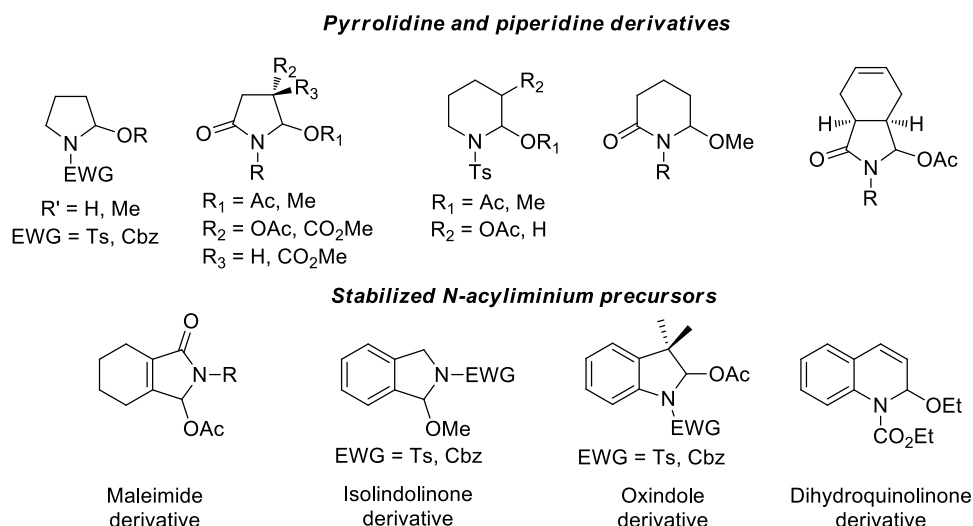


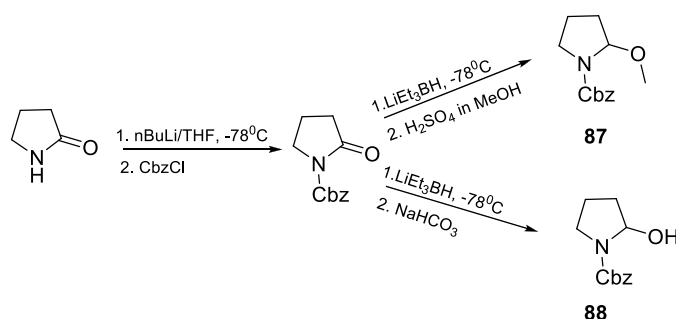
Figure III.1. Structure of the *N,O*-acetals screened

Some of these substrates are commercially available but most of them had to be prepared following usual and well-tried procedures, which are frequently used in our laboratory. The reaction sequences used for their synthesis will be presented prior to their use.

- **Alkylation of pyrrolidine and piperidine derivatives**

We thus started the generalization of our alkylation method with non-aromatic endocyclic *N*-acyliminium precursors. At first, we considered *N,O*-acetals incorporating an exocyclic electron-withdrawing group (Cbz or Ts) which are recognized for their high reactivity in catalytic amidoalkylation reactions (schemes I.X. and I.X., chapter 1).

We first synthesized *N*-Cbz and *N*-Ts acetals **87-88** from pyrrolidinone using a three step sequence depicted on **Scheme III.60**.



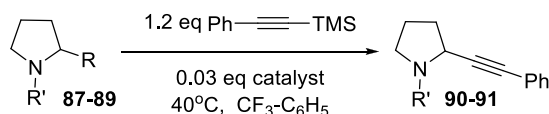
Scheme III.60. Synthesis of components 87 and 88.

This type of substrates features exceedingly high reactivity in traditional Brønsted acid-catalyzed *N,O*-acyliminium ion chemistry, and therefore excellent profile in the present

CHAPTER III: The gold-catalyzed alkylation reaction of *N,O*-acetals

alkynylation reaction was anticipated.²²⁶ However, the desired propargyl carbamate adduct **90** was only isolated in poor yield, though rapid conversions of either methoxylactam **87** or hydroxylactam **88** were observed (Table III.21, Entries 1-2). A major by-product was formed but its structure could not be fully elucidated yet. Its identification should still help to clarify the reaction course and determine the options to be investigated to overcome the current limitation. However, with this type of substrates, it is highly plausible that a competitive elimination is involved at one stage of the formation of this side-product. In order to limit the formation of any side-product, a reaction at room temperature using 7 mol% of the gold catalyst with 1.5 equivalent of TMS-alkyne was attempted, without any success (entry 3). Even if a significant decrease of the reaction rate was observed, the desired product could only be isolated in 21 % yield. We then tested pyrrolidinone derivative **89** with a tosyl protecting group on nitrogen. This group was indeed expected to display a lower reactivity than its carbamate analog. Accordingly, a longer reaction time (23 h instead of 45 min) was needed to reach full conversion but, again, the product could only be obtained in a low yield of 29%. (Table III.1421 Entry 4.)

Table III.21. The alkylation reaction of pyrrolidine derivatives.



Entry	substrate	Time	Product	Conv/Yield [%]
1.	 88 Cbz	45'	 90 Cbz	100/15
2.	 87 Cbz	45'	 90 Cbz	100/12
3 ^[a]	 87 Cbz	23 h	 90 Cbz	100/21
4.	 89 Ts	23h	 91 Ts	100/29

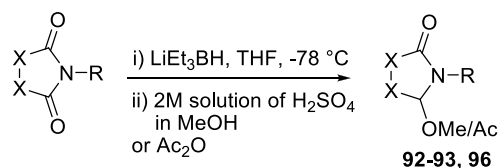
[a] The reaction was carried out in the presence of 7 mol% catalyst loading and 1.5 equiv of TMS acetylene at room temperature

We carried on the evaluation of the substrate scope of our gold-catalyzed alkylation with *N*-alkylated succinimide derivatives **92-93** and a *N*-allyl tetrahydrophthalimide derivative **96**.

²²⁶ Ben Othman, R.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.*, **2005**, *7*, 2825.

CHAPTER III: The gold-catalyzed alkyne reaction of *N,O*-acetals

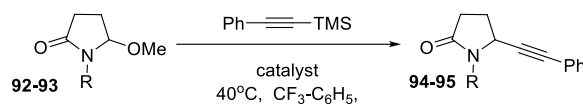
These latter were easily prepared in three steps from succinimide or *cis*-1,2,3,6-tetrahydrophtalic anhydride (**Scheme III.60.**).



Scheme III.60. General procedure for synthesis of components **92-93, 96**.

As presented on **Table III.16.**, the alkyne reaction of methoxy lactams **88** and **89** gave disappointing results. Treatment of substrate **88** under the optimized conditions, only afforded the expected alkyne **90** in 13% yield with a total consumption of the starting material. Since a reactivity slower than expected was observed, a reaction using 1 equivalent of Ph_3PAuOTf and 3 equivalents of TMS-alkyne **32** was tested. Formation of the complex mixture, possibly due to competitive coordination of the catalyst with the PMB protecting group, was obtained (entry 2). Switching to the *N*-allyl substrate **89** gave similar results with the corresponding product **91** being isolated in only 12% yield (entry 3.)

Table III.22. The alkyne reaction of succinimide-derived *N,O*-acetals.

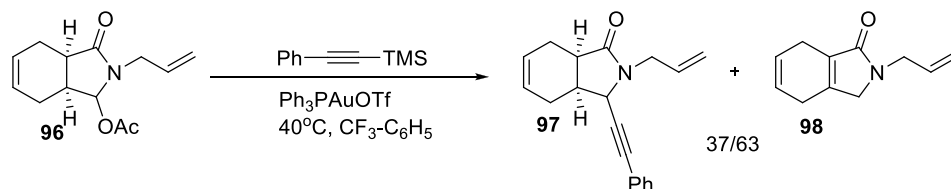


Entry	substrate	Eq Nu	Eq cat	Time	Isolated yield
1.		1.2	0.03	3 h	 94 13%
2.		3	1	45'	Complex mixture
3.		1.2	0.03	45'	 95 12%

The bicyclic acetoxy lactam **96** was then tested in the alkyne reaction (**Table III.23.**). Again, despite full conversion of the substrate under standard conditions, only 18 % of the expected alkyne product could be isolated. The formation of the α,β -unsaturated product

98 was also observed. This major by-product would obviously result from a rapid β -elimination of a proton after generation of the *N*-acyliminium intermediate. Increasing the catalyst loading to 20 mol% and the nucleophile stoichiometry to 3 equivalents was found to be detrimental reducing dramatically the yield in alkylation product.

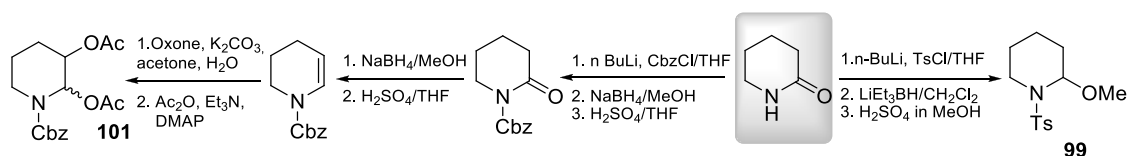
Table III.23. The alkylation reaction of bicyclic acetoxy lactam **92**



Entry	Eq Nu	Eq cat	Time	Consumption[%]	Yield[%]
1.	1.2	0.03	3 h	100	18
2.	3	0.2	45'	100	2

We next investigated the reactivity of piperidine-derived *N,O*-acetals in our alkylation reaction. It is worth pointing out here that this type of substrates are often considered as even more challenging substrates than their pyrrolidinic counterparts due to the fact that six-membered ring iminium intermediates are highly susceptible to rapid β -elimination of a proton (E1 mechanism), which can severely compete with the desired alkylation event.

Piperidine derivatives **99** and **101** were first synthesized from piperidinone following known procedures,²²⁷ as presented on **Scheme III.62**.

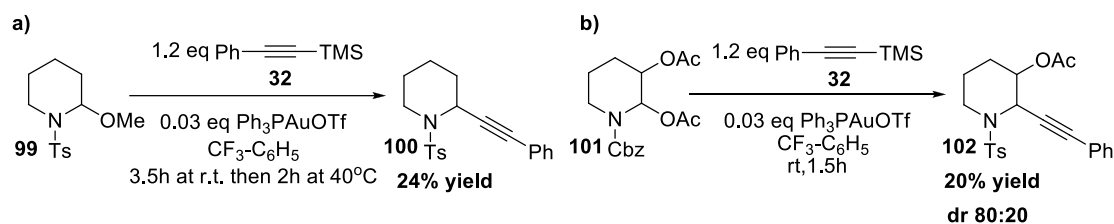


Scheme III.62. Synthesis of components **99 and **101**.**

These substrates were previously successfully used in metal triflate-catalyzed nucleophilic substitution reactions with silyl enolates.²²⁸ Hence, a good reactivity was expected for them. Under the optimized alkylation conditions (3 mol% Ph_3PAuOTf in $\text{CF}_3\text{-C}_6\text{H}_5$) with TMS-alkyne **32** (1.2 equiv), a fast conversion was observed at room temperature. However, in both cases, mainly degradation of the substrates was observed and the corresponding alkynylated products were only obtained in poor yields (24% and 20% respectively, **Scheme III.63**).

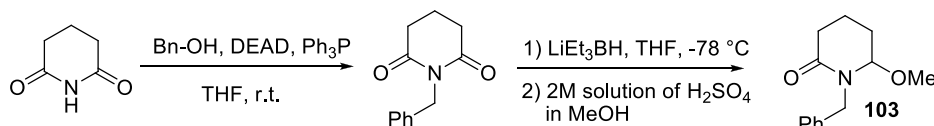
²²⁷ Respectively (a) Ahman, J.; Somfai, P. *Tetrahedron*, **1992**, 43, 9537. (b) Takeuchi, Y.; Azuma, K.; Oshige, M.; Abe, H.; Nishioka, H.; Sasaki, K.; Harayama, T. *Tetrahedron*, **2003**, 59, 1639.

²²⁸ (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.*, **2001**, 66, 809. (b) Ahman, J.; Somfai, P. *Tetrahedron*, **2009**, 48, 9537.



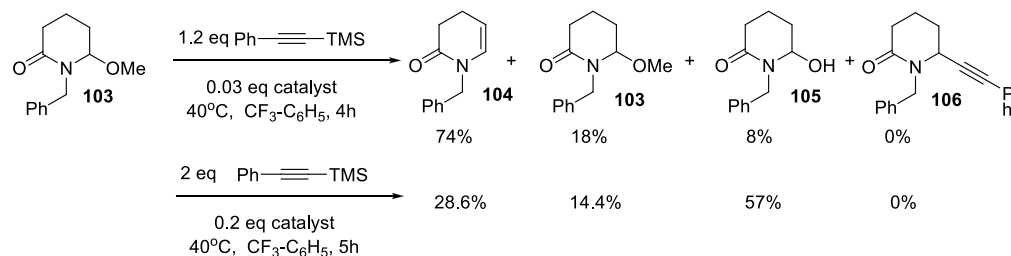
Scheme III.63. The alkylation reaction of piperidine derivatives.

Synthesis of the *N*-benzyl 6-MeO piperidinone analog **103** was next realized (**Scheme III.64.**) from piperidine.



Scheme III.64. General procedure for the synthesis of substrate **70**.

As shown on **Scheme III.65.**, the alkylation reaction using our standard protocol mainly yielded the elimination product **104** with no trace of the expected coupled product being detected. Forcing the reactions conditions by using 20 mol% of the gold catalyst and 2 equivalents of the TMS-alkyne did not improve the original result producing the hydroxyl lactam **105** as the main product.



Scheme III.65. The alkylation reaction of piperidinone derivative **103**.

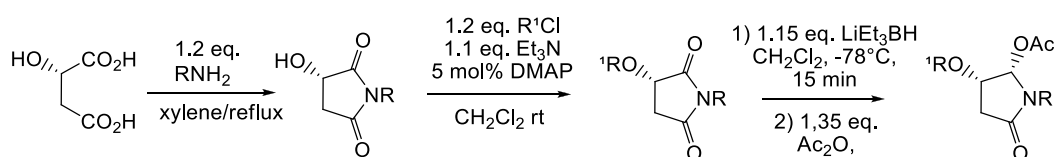
This first set of results strongly suggests that very reactive *N*-acyliminium precursors are most likely unstable under our conditions and mainly decompose before the corresponding products could be formed. This may be the result of the inherent weak nucleophilicity of the gold acetylide²²⁹ intermediate formed during the process, in line with known properties on silver acetylides²³⁰. However, at this stage of the study, the instability of the alkynylated products under the alkylation conditions cannot be excluded either. Obviously, more

²²⁹ Sun, S.; Kroll, J.; Luo, Y.; Zhang L. *Synlett* **2012**, 23, 54.

²³⁰ Halbes-Letinois, U.; Weibel, J. M.; Pale, P. *Chem. Rev.* **2007**, 36, 759.

detailed investigations of these particular catalytic alkylation would be required and should be the focus of a future effort.

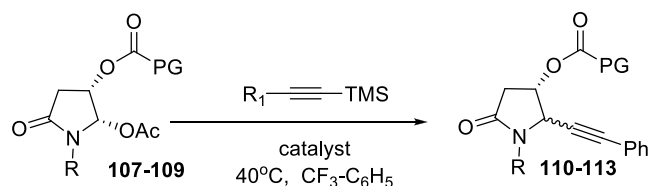
Pursuing our effort with substrates derived from bis endocyclic imides, we tested if the reaction could be extended to chiral *N,O*-acetals derived from (*S*)-malic acid. A series of optically pure *cis*-acetoxy lactams **107-109** possessing different protecting groups on the adjacent hydroxyl group was prepared from (*S*)-malic acid (**Scheme III.66.**).



Scheme III.66. General protocol for the synthesis of substrates **107-109**.

Under the optimized alkylation conditions, we were pleased to observe that the expected products were generated in good yields (77-100%) within less than 3 hours, irrespective of the protecting groups on the adjacent hydroxyl group or nitrogen. (**Table III.23.**) A poor *trans* selectivity, consistent with previous results in our group using relatively small nucleophiles such as allyltrimethylsilane and TMSCN,²³¹ (but contrasting with diastereoselectivities obtained from the reactions with more sterically demanding silyl enol ethers)²³² was observed, which may be ascribed to the linear structure of the acetylide nucleophile.

Table III.23. Investigation of the scope of other types of starting materials



²³¹ Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335.

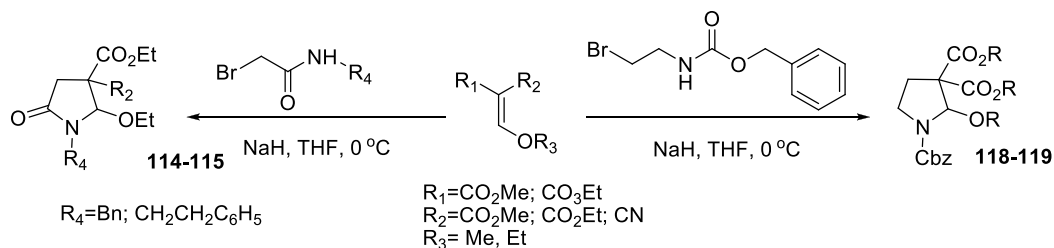
²³² See Chapter 1 for more details.

Entry	substrat	R ₁	mol% cat/eq Nu/Time	Yield [%](cis:trans)
1.		Ph	3/1.5/2h	 94 (1:1.38) ^a
2.		Ph	3/1.2/45'	 77(1:3.16) ^b
3.		Ph	3/1.2/3h then 0.3eq/45 min	 100(1:1.1) ^a
4.		CH ₂ OTBDPS	5/1.5/2h	 91 (1.23 :1) ^b

^a ratio determined on the crude ¹H NMR spectrum

^b ratio of isolated products

Another class of *N,O*-acetalic substrates developed in our laboratory was also evaluated. Their synthesis presented on **Scheme III.67**, involved an original tandem aza-Michael initiated ring closure (aza-MIRC) process between alkoxyethylene malonates or cyanoacetates and α -bromoacetamides.²³³



Scheme III.67. General protocols for the synthesis of substrates 114-115 and 118-119.

²³³ (a) Saber, M.; Comesse, S.; Dalla, V.; Daich, A.; Sansleme, M.; Netchitailo, P. *Synlett*, **2010**, 2197; (b) Saber, M.; Comesse, S.; Dalla, V.; Netchitailo, P.; Daich, A. *Synlett*, **2011**, 2425.

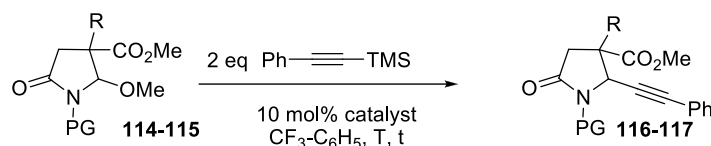
CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

These compounds were previously shown to be suitable substrates in $\text{ Tf}_2\text{NH}$ -catalyzed amidoalkylations with silylated nucleophiles despite the presence of two bulky and deactivating electron withdrawing groups adjacent to the reactive center.^{233b} As previously discussed in Chapter 1, the success of these reactions could be attributed to assistance of one ester group either for intramolecular catalyst delivery or stabilization of the *N*-acyliminium ion (anchimeric effect). In the specific case of our gold-catalyzed alkynylation, it is reasonable to fear a competitive coordination of the metal catalyst on the ester and/or cyano groups.

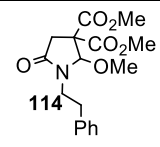
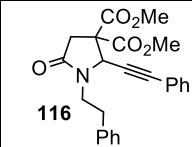
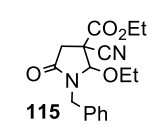
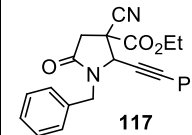
As a lower reactivity was anticipated for this type of substrates, the alkynylation of methoxy lactam **114** was attempted using 10 mol % of $\text{ Ph}_3\text{PAuOTf}$ and $\text{ Ph}_3\text{PAuNTf}_2$ as catalysts (Table III.24. Entries 1, 2). Using these conditions, we were pleased to find that the reaction performed slowly but satisfactorily with both catalysts giving the corresponding alkynylated product **116** as the major product. However, it is important to mention that in both cases the expected adduct was obtained as an inseparable mixture with one unknown product in 3:1 to 5:1 ratios (product:by-product).

The *gem*-cyano ester pyrrolidine derivative **115** could also be alkynylated by TMS-alkyne **32** using 10 mol% of the Gagosz catalyst $\text{ Ph}_3\text{PAuNTf}_2$. Due to its lower reactivity, heating the reaction mixture at reflux for 29 hours was necessary to complete the reaction. Nevertheless, the expected product could be formed as the only product and could be isolated in 69% yield (entry 3).

Table III.24. Investigation of the alkynylation of *gem*-disubstituted pyrrolidine derivatives



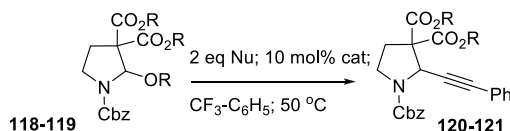
Entry	substrate	catalyst	T[°C]	Time	Product	Yield [%]
1.		$\text{ Ph}_3\text{PAuOTf}$	50	24 h		< 100 ¹

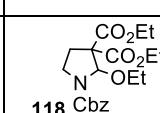
2.		$\text{Ph}_3\text{PAuNTf}_2$	50	24h		< 72 ¹
3.		$\text{Ph}_3\text{PAuNTf}_2$	reflux	29h		69

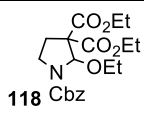
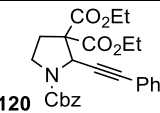
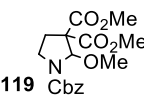
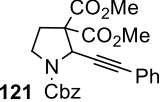
¹ inseparable mixture of the expected (major) and unidentified (minor) products

In the optimization study, it was shown that Ph_3PAuOTf displayed greater performance than $\text{Ph}_3\text{PAuNTf}_2$ in the alkyne reaction of phthalimide-derived *N,O*-acetals. In such transformations, the formation of the gold acetylide was thus proposed to be the limiting step (see **Scheme III.54.**). When a less reactive *N*-acyliminium ion precursor is involved, the situation may be reversed and the generation of the cationic intermediate may become the rate-determining step. The use of $\text{Ph}_3\text{PAuNTf}_2$ would then become preferable since a stronger Lewis acid activator TMSNTf_2 (compared to TMSOTf) would be generated in the process. This assumption was immediately rewarded when the alkyne reaction of the challenging *N,O*-acetal carbamate **105** (**Table III.25.**) equipped with two neighbouring deactivating ester groups was attempted. When substrate **118** was subjected to the standard alkyne reaction protocol in the presence of Ph_3PAuOTf (10 mol%), no reaction was observed (**Table III.25.** Entry 1.) Use of 10 mol% of $\text{Ph}_3\text{PAuNTf}_2$ instead induced a rate enhancement and the expected product **120** could be obtained in a moderate yield of 30%. To favor the reaction with this class of substrate, an analogous substrate **119** possessing less bulky ester groups as well as a better leaving group (methoxy instead of ethoxy) was tested. A full conversion of the substrate was observed after 16 hours at 50 °C, affording the corresponding alkyne product **121** in 88% isolated yield (**Table III.25.**, entry 3).

Table III.25. Investigation of the alkyne reaction of *gem*-diester *N,O*-acetal carbamates



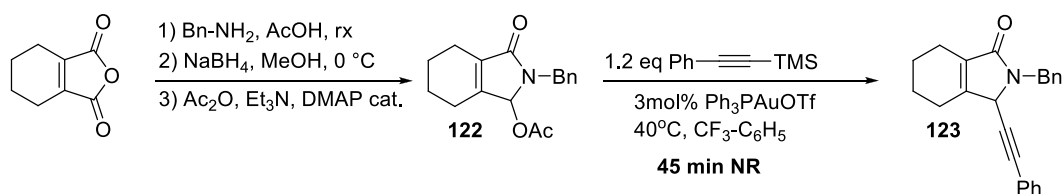
Entry	substrate	Catalyst	Time	Product	Yield [%]
1.		Ph_3PAuOTf	16h	NR	-

2.	 118 Cbz	Ph ₃ PAuNTf ₂	16h	 120 Cbz	30
3.	 119 Cbz	Ph ₃ PAuNTf ₂	16h	 121 Cbz	88

- Stabilized *N*-acyliminium precursors

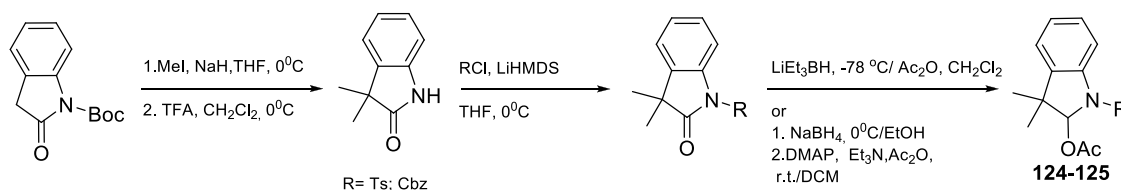
In the last part of this work dedicated to the evaluation of the *N,O*-acetalic partners, a few alkoxy- or acetoxy lactams providing stabilized *N*-acyliminium intermediates were next considered. Since our previous results demonstrated that highly reactive substrates rather favour decomposition or side-reactions than undergoing the expected alkylation reaction, we anticipated that more robust *N*-acyliminiums could give better reactivity profiles.

We started with a partially reduced phthalimide derivative **122**, which was synthesized in three steps from 3,4,5,6-tetrahydrophthalic anhydride (**Scheme III.68.**). Disappointingly, when it was reacted with TMS-alkyne **32** in the presence of 3 mol% of Ph₃PAuOTf, a complete lack of reactivity was observed (**Scheme III.68.**). This reaction was attempted only once but this would need to be tested another time to be sure that this surprising result did not arise from a catalyst of bad quality.



Scheme III.68. The alkylation reaction of *N,O*-acetal **122**.

Next, the alkylation of *N*-Ts and *N*-Cbz acetals **124** and **125** derived from oxindole was studied. To prevent any elimination from occurring, the carbon adjacent to the reactive center of these substrates was dialkylated. The preparation of these compounds from oxindole is presented on **Scheme III.69**.

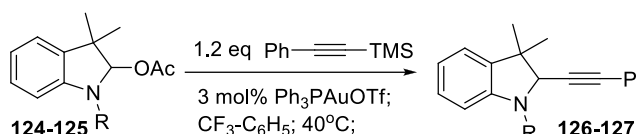


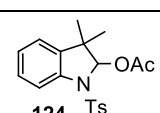
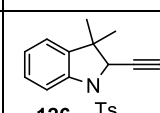
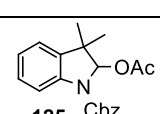
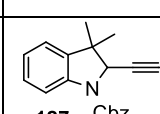
CHAPTER III: The gold-catalyzed alkylation reaction of *N,O*-acetals

Scheme III.X69. Synthesis of the substrates 124-125.

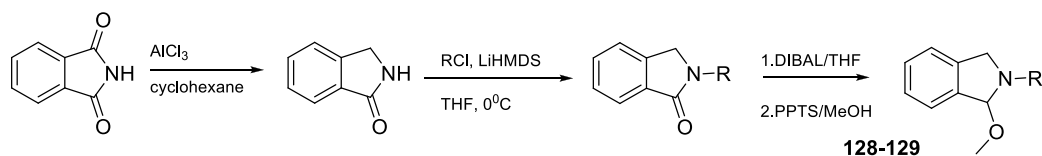
These substrates turned out to be reasonably reactive under our classical alkylation conditions (3 mol % Ph_3PAuOTf , 1.2 equiv **32**, $\text{CF}_3\text{-C}_6\text{H}_5$, 40 °C) in spite of the steric hindrance nearby the reactive *N,O*-acetalic center. Both products were obtained in less than 3 hours in 99% and 77 % isolated yields respectively (Table III.26.).

Table III.26. The alkylation of oxindole derivatives.



Entry	substrate	Time	Product	Yield [%]
1.	 124 Ts	2h then +0.5 eq Nu and 2.3h	 126 Ts	99
2.	 125 Cbz	2h45'	 127 Cbz	77

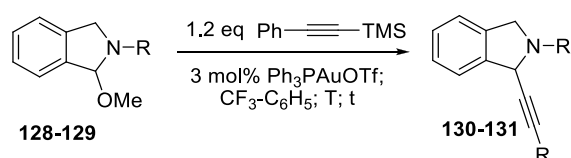
Isoindolone derivatives **128-129** equipped with an exocyclic electron-withdrawing group (Cbz or Ts) were next prepared from phthalimide (Scheme III.70.) and evaluated in the coupling with TMS-alkyne **32**.

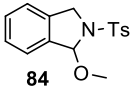
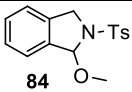
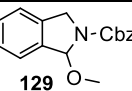


Scheme III.70. Synthesis of 128-129.

Based on the results obtained previously with their pyrrolidinic counterparts (Table III.24.), we expected the presence of the aromatic ring would bring enough stabilization to the *N*-acyliminium intermediate to limit degradation and/or side-reactions. However, a complex mixture was rapidly obtained at any temperature (from 0 °C to 40 °C) and none of the alkynylated products could be isolated (Table III.27.).

Table III.27. The alkylation of isoindolone derivatives.

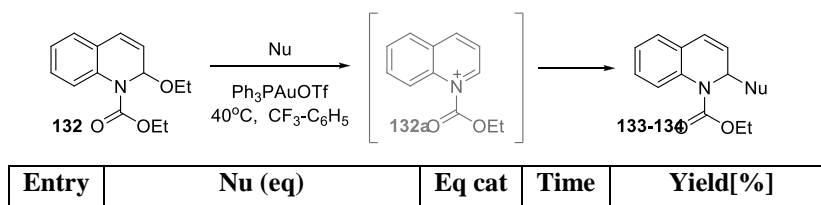


Entry	substrate	T[°C]	Time	Conversion[%]
1.	 84	40	45'	Complex mixture
2.	 84	0 rt	3.5h then 1h	Complex mixture
3.	 129	0 to rt	45'	Complex mixture

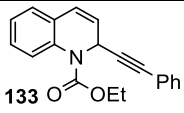
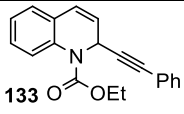
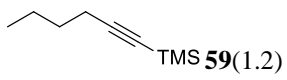
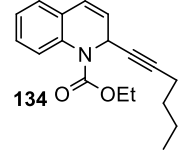
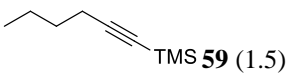
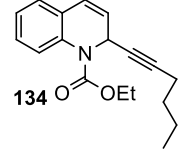
From all the experimental results we obtained thus far, we identified a last substrate which should react properly in our test reaction: the commercially available quinoline-derived *N,O*-acetal **132**.²³⁴ Additionally, during the reaction, this type of *N,O*-acetal should result in the formation of a “pseudo-aromatic” *N*-acyliminium ion intermediate which should be robust enough to react with the weakly nucleophilic gold acetylide. It is also worth mentioning that no competitive elimination could occur from this substrate. However, a competitive coordination of the electrophilic catalyst on the ester group is still possible.

When the substrate **132** was subjected to the optimized alkylation conditions with TMS-alkyne **32** as nucleophile, we were pleased to observe the formation of the alkynylated adduct with a good efficiency, albeit with a slower reaction rate (**Table III.28.**, entry 1). Whereas use of 3 mol% of Ph₃PAuOTf gave the desired product in 69% yield, increasing the catalyst loading to 5 mol % allowed its formation in up to 90% yield (entry 2). The reaction with TMS-alkyne **59** equipped with a butyl chain was also found to be successful affording the corresponding alkyne derivative **134** in 65 % yield using our standard conditions (entry 3) or in 94 % yield using slightly modified conditions (5 mol% of the catalyst with 1.5 equivalent of **59**, entry 4). This last example again demonstrates that this alkylation protocol is not limited to the introduction of aromatic alkynes.

Table III.28. The alkylation of a dihydroquinolinone derivative



²³⁴ a) Chang, Y. M.; Lee, S. H.; Nam, M. H.; Cho, M. Y.; Park, Y. S.; Yoon, C. M. *Tetrahedron Lett.* **2005**, *46*, 3053; b) Graham, T. J. A.; Shields, J. D.; Doyle, A. G. *Chem. Sci.* **2011**, *2*, 980.

1.	$\text{Ph}\equiv\text{TMS}$ 32 (1.2)	0.03	26h	 133 O=OEt Ph 69
2.	$\text{Ph}\equiv\text{TMS}$ 32 (1.2)	0.05	24h	 133 O=OEt Ph 90
3.	 59 (1.2)	0.03	46h	 134 O=OEt 65
4.	 59 (1.5)	0.05	25h	 134 O=OEt 94

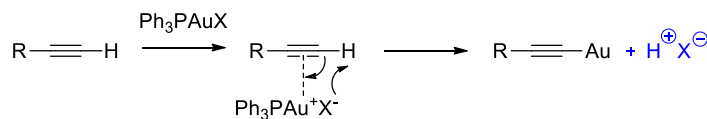
III.2.5. ATOM-ECONOMY

A transformation which would not require the preactivation of the nucleophile or the electrophile would be highly advantageous in terms of step- and atom-economy. Indeed, besides saving the preliminary step of activation, direct use of a terminal alkyne and/or an hydroxylactam as reaction partners in the alkynylation reaction would only generate a molecule of water or acetic acid as a sole by-product. So, in order to improve the efficiency and the environmental profile of our alkynylation methodology, we evaluated the reactivity of non-activated reaction partners.

- **Use of terminal alkynes**

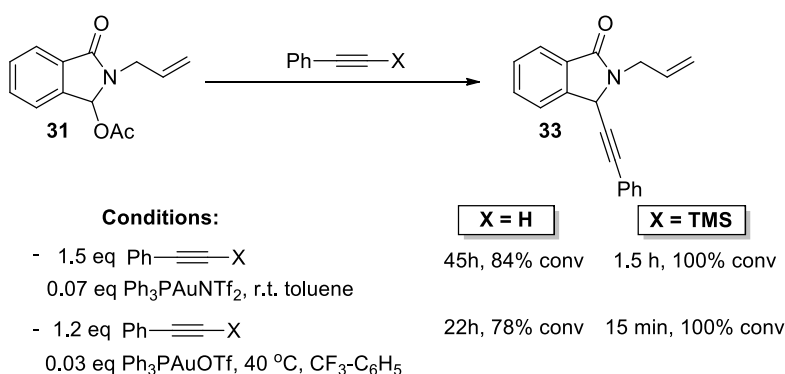
A more ideal catalytic alkynylation of *N,O*-acetals and related pro-electrophiles should use terminal alkynes for the consideration of atom-economy. While in principle a similar type of dual mechanism with a proton simply replacing SiR_3 (**Scheme III.71.**) could potentially be operative in this direct coupling, we surmised that the formation of gold acetylide might be

less favored in the presence of a Brønsted super acid which is expected to be formed when one combined a terminal alkyne and a gold(I) salt.²³⁵



Scheme III.71.

The gold-catalyzed alkyne reaction of the acetoxy lactam **31** using phenylacetylene was tested as a model reaction (**Scheme III.72**). While notable catalytic activities were observed, the reaction performances remained significantly inferior to that of the corresponding trimethylsilyl (TMS) derivative **32** with significantly slower reaction rates using either Ph₃PAuOTf or Ph₃PAuNTf₂ as catalysts. These results are in full agreement with our expected outcome associated with the proposed mechanism.

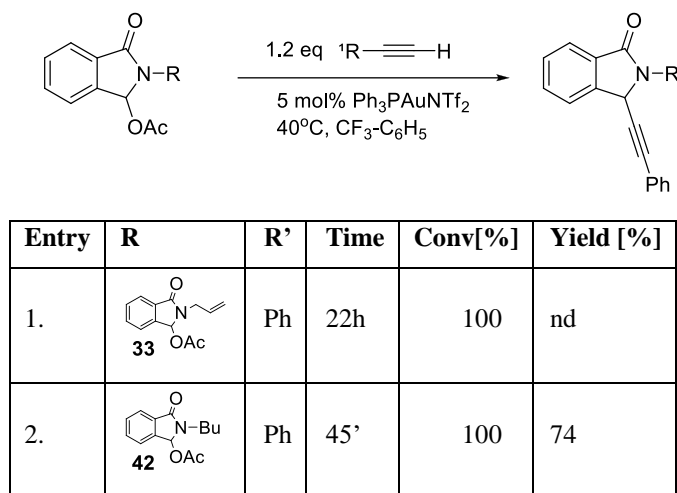


Scheme III.72. The alkyne reaction with phenylacetylene as the nucleophile.

An experiment using an increased amount of the Gagosz catalyst Ph₃PAuNTf₂ (5 mol% instead of 3 mol%) at 40 °C in trifluorotoluene was found to be the most efficient conditions enabling full conversion of the acetoxy lactam into the desired alkyne compound **33** (**Table III.29.**, entry 1). These efficient conditions were also tested with *N*-butyl acetoxy lactam **42** and the corresponding alkyne compound was smoothly obtained in 74% isolated yield (**Table III.29**, Entry 2).

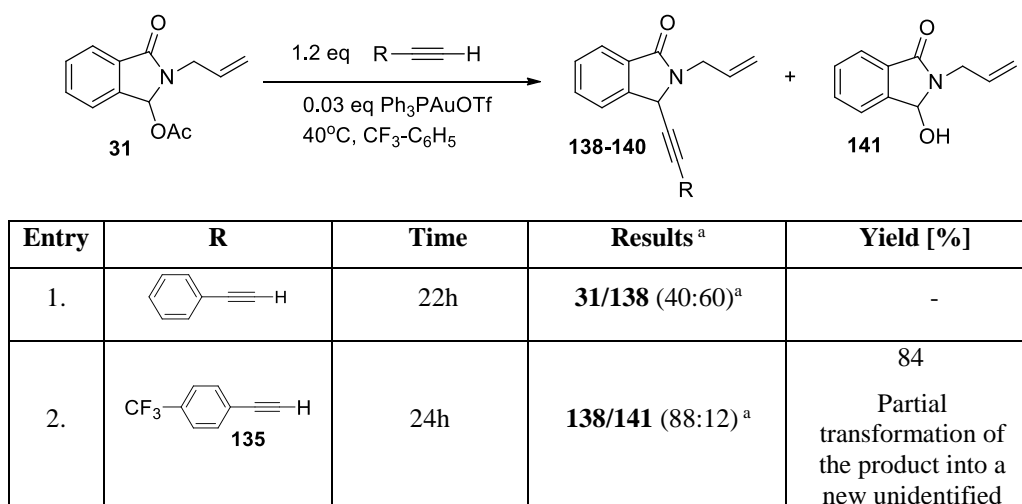
²³⁵ a) Brown, T. J.; Widenhoefer, R. A. *Organometallics*, **2011**, *30*, 6003. b) Grrirane, A.; Garcia, H.; Corma, A.; Alvarez, E. *ACS catalysis*, **2011**, *1*, 1647. c) Gómez-Suárez, A.; Dupuy, S.; Slawin, A.M.Z.; Nolan, S.P. *Angew. Chem. Int. Ed.*, **2013**, *52*, 938.

Table III.29. The alkylation reaction using terminal alkynes



To improve the conversion, we envisioned testing nucleophiles having a more acidic acetylenic proton. Results presented in **Table III.30.** proved the positive influence of an electron withdrawing *p*-trifluoromethyl group on the reactivity of arylacetylenes (entry 2 *versus* entry 1) since a significant increase of the conversion was observed with product **138** being mainly formed. However, formation of a small portion of hydroxylactam **141** was responsible for blocking the conversion to 88%. In order to push the reaction further, addition of acetic anhydride (0.5 equivalent) after 3 hours was attempted to regenerate the acetoxy lactam *in situ*. Using these conditions was found to improve the reactivity profile (entry 3). Unfortunately this appeared not to be a general trend since addition of a bromine atom on the aromatic system reduced the conversion in a significant manner while using methyl propynoate as an alternative nucleophile only afforded the undesired hydroxylactam **141**. (**Table III.30.**, entries 4-5).

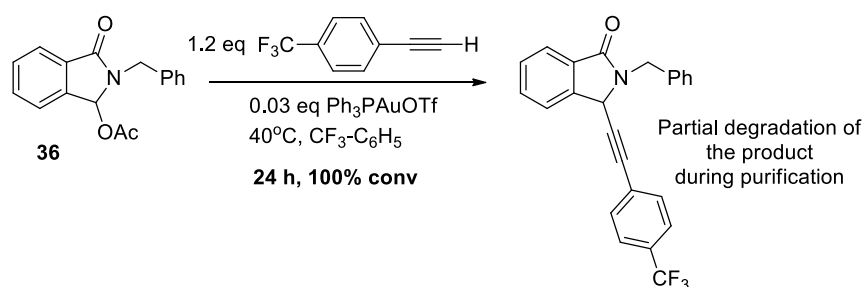
Table III.30. The alkylation reaction of starting materials with different nucleophiles.



				side-product during purification
3.		3h then +(0.5eq)Ac ₂ O 21h	138/141 (94:6) ^a	As above
4.		24h	139/141 (45/55) ^a	-
5.		23h	141 ^a	

^a Determined by ¹H NMR analysis of the crude

It is worth mentioning that the product obtained from 1-ethynyl-4-(trifluoromethyl)benzene **135** (entries 2, 3) was not stable and evolved into a new compound during purification by flash chromatography on silica gel, which could not be identified. Exchanging the allyl group on nitrogen of the substrate by a benzyl group did not improve the stability of the desired product. (**Scheme III.73.**)

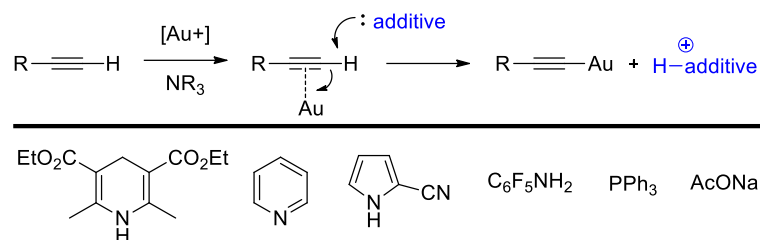


Scheme III.73. The alkyynylation reaction of modified nucleophile.

Although being sluggish, the direct alkyynylation pathway still appeared to be possible and this encouraged us to pursue our effort with the goal of improving its efficiency. As previously discussed, it is well known that terminal alkynes are easily activated when subjected to a gold complex in the presence of a common tertiary amine *e.g.* NEt₃ (see paragraph **III.1.2.**). The amine promptly deprotonates the initially formed alkyne-gold π complex, producing the gold acetylide and a weakly acidic tertiary ammonium salt. This latter is in general of insufficient strength to promote activation of an (pro)-electrophilic component, precluding implications into cooperative gold/Brønsted acid catalytic alkyynylation. We then assumed that use of additives with low nucleophilicities and significantly lower basicity than triethylamine could be capable of deprotonating an alkyne coordinated to a gold complex, thus generating a stronger acidic salt which could next mediate activation of pro-electrophiles. In particular, we surmised that this strategy might be applied to the generation of *N*-acyliminium ion, and hence could facilitate the direct catalytic alkyynylation of terminal

CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

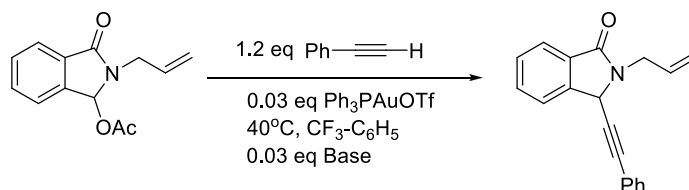
alkynes. A panel of additives expected to feature the above-mentioned requirements were then selected for evaluation (**Scheme III.74.**), and the results are presented in **Table III.31.**



Scheme III.74. Activation of terminal alkyne under basic conditions.

Unfortunately using Hantzsch ester,²³⁶ pyridine²³⁷, triphenylphosphine²³⁸ and sodium acetate resulted in no conversion (entries 2-4 and 8). These results suggest either competitive coordination of the gold catalyst on these bases or incapacity of their conjugated acid to promote the *N*-acyliminium generation. Use of 2-cyano pyrrole²³⁹ and pentafluoroaniline²⁴⁰ led to more encouraging results, however, these additives exhibited no beneficial effect on the reaction kinetic, as compared with the nearly identical conversions measured in their absence (entries 5-7 *versus* 1).

Table III.31. The alkynylation reaction of terminal alkyne



Entry	Base	Time	Conv[%]	Entry	Base	Time	Conv[%]
1.	-	1h	39	5.		45'	45
		4h	50			5h	67.5
		22h	60			6.	C ₆ F ₅ NH
2.		1h	NR	21h	70		
		18h	15.6	7.	10 mol% C ₆ F ₅ NH		
3.		45'	NR			22h	60
		4.	Ph ₃ P	22h	NR	8.	NaOAc

NR = No reaction

²³⁶ For use of Hantzsch ester as a hydrogen source, see: Ouellet, S.G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2005**, 7, 32.

²³⁷ For use of pyridinium triflate salts as Brønsted acid catalysts, see: Sniady, A.; Bedore, M. W.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, 50, 2155.

²³⁸ For the use of triphenylphosphonium triflate salt in Brønsted acid catalysis, see: Iwabashi, A. H.; Oka, T.; Abiko, A. *Chem. Lett.* **2008**, 37, 708.

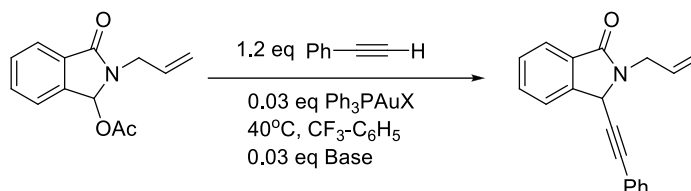
²³⁹ For the use of cyanopyrrole in enantioselective protonation, see: Hodous, B. A.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, 124, 10006.

²⁴⁰ For use of pentafluoroanilinium triflate and triflimidate salts as Brønsted acid catalysts, see: a) Iida, A.; Osada, J.; Nagase, R.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2007**, 9, 1859. b) Nagase, R.; Osada, J.; Tamagaki, H.; Tanabe, Y. *Adv. Synth. Catal.* **2010**, 352, 1128.

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We then decided to combine use of these two most efficient base additives with gold(I) salts paired with less coordinating anions than a triflate, with the expectation that only the amino additive, but not the counterion, would trigger the aurodeprotonation. As shown in **Table III.32.**, slight improvements were observed with SbF_6 and NTf_2 anions, however the catalytic performances were not beyond that of the coupling catalyzed by the Gagosz catalyst alone (entry 2). A possible explanation for the lack of improvements observed in the presence of these additives might be that, in spite of their low nucleophilicities, these substantially compete with phenylacetylene as ligands for the cationic Au(I), thereby counterbalancing the positive influence that would result from their ability to deprotonate the π -activated phenylacetylene. These opposite effective would globally maintain the reaction kinetic at its original ground.

Table III.32. Influence of the counteranion in the alkynylation reaction with a terminal alkyne.



Entry	X	Base	Time	Conversion[%]	Yield [%]
1.	SbF_6		45° 22h	30 81	73
2.	NTf_2	-	1h 22h	39 78	nd
3.	NTf_2	$\text{C}_6\text{F}_5\text{NH}$	45° 21h	34.5 83	81
4.	BARF	$\text{C}_6\text{F}_5\text{NH}$	45° 22h	NR NR	-
5.	BF_4	$\text{C}_6\text{F}_5\text{NH}$	45° 22h	18 67	nd

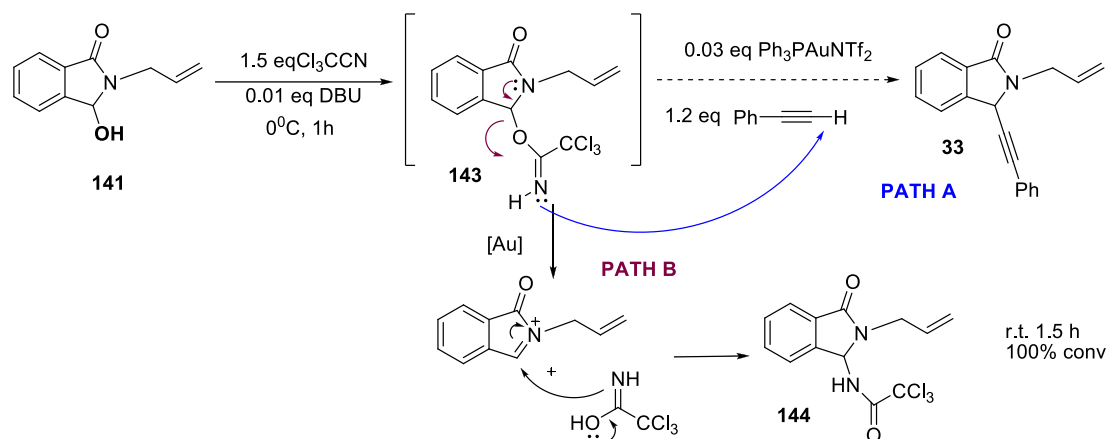
nd = not determined

Implementation of a bicatalytic one-pot Brønsted base trichloroacetimidation-gold catalyzed alkynylation sequence of hydroxy lactame was examined next.²⁴¹ In this latter option, the inherent basicity of the imidate leaving group should serve the role of the extra base in a way similar to that found in the alkynylation of imines. According to our strategy, the trichloroacetimidate group, *in situ* formed from hydroxylactam, should assist the formation of the gold acetylide and in consequence afford the final alkynylated product. **(Scheme III.75. Path A)**

²⁴¹ Inspired from a strategy recently developed in our laboratory: Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, G.; Rouden, J.; Dalla, V. *Adv. Synth. Catal.* **2010**, *352*, 2881.

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Addition of 1.5 equivalents of trichloroacetonitrile to **141** in the presence of 10 mol% of DBU led to the quantitative formation of the unstable trichloroacetimidate **143** which was directly subjected to the $\text{Ph}_3\text{PAuNTf}_2$ -catalyzed direct addition of phenylacetylene. After only 1.5 hours at room temperature, no trace of the alkyne **33** was obtained and exclusive formation of the trichloroacetamide *N,N*-acetal **144** was observed. (**Scheme III.42. Path B**). This latter would originate from a Aza-Petasis-Ferrier rearrangement (previously observed in the context of other studies in our laboratory): Gold-activation of the trichloroacetimidate would promote cleavage of the hemiaminal C-O bond thus generating a *N*-acyliminium intermediate and a molecule of trichloroacetamide. After recombination of these two partners, the aminal **144** could then be irreversibly formed.



Scheme III.75. Bicyclic hydroxylactam **141** reacts with 1.5 eq Cl_3CCN and 0.01 eq DBU at 0°C for 1 h to form trichloroacetimidate **143**. **143** then reacts with 0.03 eq $\text{Ph}_3\text{PAuNTf}_2$ and 1.2 eq $\text{Ph-C}\equiv\text{CH}$. Path A leads to alkyne **33**. Path B, catalyzed by $[\text{Au}]$, leads to *N*-acyliminium intermediate, which reacts with trichloroacetamide to form *N,N*-acetal **144**. Conditions for **144**: r.t., 1.5 h, 100% conv.

Overall, the direct alkylation of phenylacetylene remained far less efficient than its silylated variant, a point that, combined with the high yielding and reasonably low cost access to trimethylsilylalkynes, firmly exemplifies the value of our synergistic catalytic gold/silyl principle.

- **Use of hydroxylactams**

We have next examined hydroxylactams as an alternative and more atom-economical source of electrophile in comparison to acetoxy lactams.

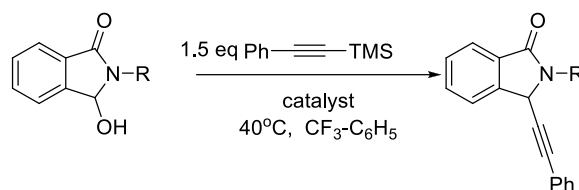
Use of the unmodified heminals instead of the more reactive acetoxy lactams, an operation that would save one step in the sequence while simply releasing TMSOH as a side-product, constitutes another direction to improve the atom economy of the coupling. Under

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the optimal reaction conditions established for the acetoxy lactame **31** (Table III.9, entry 4), neither Ph_3PAuOTf nor the Gagosz catalyst allowed the reaction of **141** to reach completion within 24 h (Table III.28.). In line with the trend observed in Table III.9., the triflate salt performed more satisfactorily than its Gagosz analog. Improving the catalyst loading to 7 mol% did not enhance the conversion substantially either, emphasizing the acknowledged poor reactivity of isoindolic hydroxy lactams in catalytic amidoalkylations,⁵⁴ as well as some deleterious effects plausibly caused by TMSOH.

Results presented below show that the alkyne reaction can be realized directly from this type of less reactive²⁴² starting materials, though a significantly diminished reactivity was observed. As observed above, the Ph_3PAuOTf catalyst turned out to be more efficient than the analogous Gagosz reagent. (Table III.28. Entry 2 vs 3; 1 vs.4)

Table III.28. The alkyne reaction of hydroxylactams.

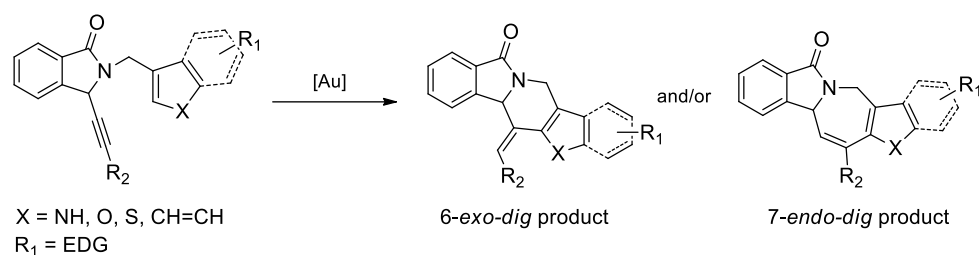


Entry	R	Catalyst [mol%]	Time[h]	Conversion[%]
1.		Ph_3PAuOTf [3]	1	76
2.		Ph_3PAuOTf [7]	1	67.5
3.		$\text{Ph}_3\text{PAuNTf}_2$ [7]	1	60
4.		$\text{Ph}_3\text{PAuNTf}_2$ [3]	1	38

²⁴² Ben Othman, R.; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dunach, E.; Dalla, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 776.

III.2.6. THE HYDROARYLATION REACTION OF ALKYNES

The introduction of an alkyne motif in the structure obviously offers many possibilities for further functionalization. After the development of an efficient gold-catalyzed alkylation method, we next envisioned realizing a subsequent catalytic transformation of the resulting products which could make use of a compatible and/or similar catalytic system. The addition of electron-neutral and electron-rich arenes to alkynes (hydroarylation of alkynes) is a well-established process promoted by late transition metal catalysts, and gold brought new perspective in the field. Consequently, we next sought to investigate the feasibility of an intramolecular gold-catalyzed hydroarylation of our alkynylated products which are equipped with electron-rich *N*-benzyl substituents. Such a transformation would allow to rapidly build new complex nitrogen-containing polyheterocyclic scaffolds, possibly via a 6-*exo-dig* and/or a 7-*endo-dig* cyclization mode (**Scheme III.76**).



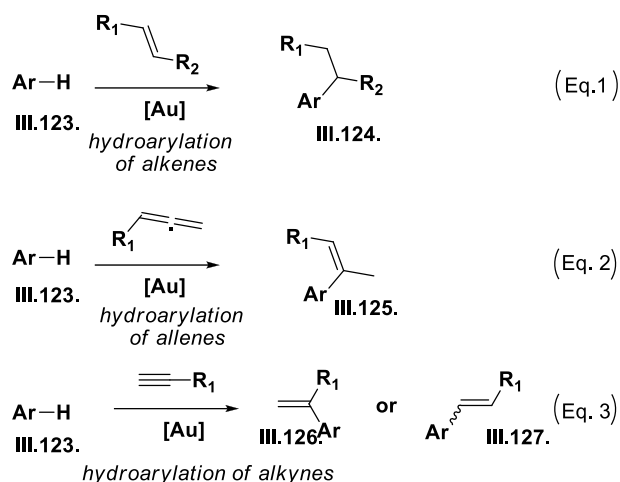
Scheme III.76.

Before the description of our efforts in this direction, a quick introduction describing selected main contributions as regards intramolecular gold-catalyzed hydroarylation of alkynes will be presented.

A. Introduction

Aromatic rings are often present in the structure of many pharmaceuticals, agrochemicals, and functional materials. In consequence, many research groups started to develop mild, selective and green methods for their synthesis. In this context, though the ability of gold complexes to interact with aromatic compounds has been known for 80 years, the direct functionalization of arenes only gained in importance recently. The development of new carbon-carbon bond forming reactions directly from C-H aromatic bonds is conceptually attractive, atom-economical and potentially harmless for the environment since it avoids pre-functionalization of the substrates by halogenation or boration. One of the pioneers in this

area is Hashmi *et al.*²⁴³ who described the hydroarylation of vinyl ketones with electron-rich furans in the presence of AuCl₃ (**Scheme III.77. Eq. 1**, R₁ = COMe) and allenyl ketones (**Eq. 2**). Since then, the number of gold-catalyzed hydroarylation of unsaturated systems increased and the essential articles dealing more specifically with gold-catalyzed addition of aromatic cores onto alkynes came out in 2003-2004 (**Eq. 3**).²⁴⁴



Scheme III.77. The gold-catalyzed hydroarylation reactions.

Concerning the hydroarylation of alkynes, which is more related to our research objectives, the intermolecular reaction developed by Reetz and Sommer^{244a} is a major contribution being at the origin of the current tendencies and new prospects for this type of transformation. For instance, the regioselectivity of the alkyne hydroarylation was demonstrated to be highly dependent on the substrate with electron-rich alkynes (**Scheme III.76. Eq 3**, R₁=Ph) providing the 1,1-disubstituted alkenes **III.126**. (Markovnikov regioselectivity), while electron-withdrawing alkynes (**Scheme III.77. Eq. 3**, R₁= COR, CO₂R) gave 1,2-disubstituted alkenes **III.127**. (anti-Markovnikov; "Michael" adducts) with *cis* or *trans* stereoselectivity. No reaction was observed with disubstituted electron poor alkynes. Furthermore, writers noticed that optimal catalysts for these two types of alkynes were not the same. If electron rich triple bonds could be efficiently converted in the presence of cationic gold (III) complexes AuCl₃/AgSbF₆, gold (I) complexes LAuCl/BF₃.Et₂O gave better *E* diastereoselectivity with electron deficient alkynes.

At the same time, Dyker *et al.*^{244b} have developed the hydroarylation reaction of benzene and azulene derivatives under similar conditions whereas He^{244c} described the intermolecular

²⁴³ Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, 39, 2285.

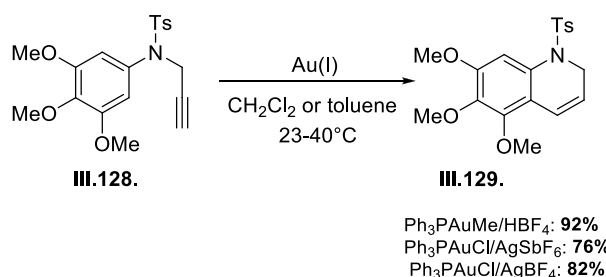
²⁴⁴ (a) Reetz, M. T.; Sommer, K.; *Eur. J. Org. Chem.* **2003**, 3485; (b) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, 345, 1247; (c) Shi, Z.; He, C. *J. Org. Chem.* **2004**, 69, 3669.

reactions with electron deficient terminal alkynes with gold (III) complexes being the catalysts of choice.

The intramolecular version of this reaction proved to be an efficient method for the construction of aromatic polycyclic architectures. A number of important heterocyclic motifs including *2H*-chromenes, coumarins, bezofurans and dihydroquinolines were rapidly formed from easily accessible starting materials using a ring-closing intramolecular gold-catalyzed hydroarylation of suitably designed alkynes. These gold-catalyzed transformations, initially limited to the formation of six-membered rings *via* selective 6-endo cyclization mode, could be further extended (nature of the substrates involved and size of the rings formed) and improved (complexity of the catalysts) over time. From now on, five-, six-, seven- and even eight-membered rings can be readily accessible in a highly regiochemical fashion.

For concision consideration and due to the actual abundance of publications reporting intramolecular alkyne hydroarylation reactions, only selected examples leading to the formation of six- and seven-membered azacycles and featuring interesting motifs for our study, that are propargyl- and homo propargylamines substrates, will be presented here. The most efficient catalysts and the regioselectivities governing this type of transformation will be presented.

An interesting gold-catalyzed 6-*endo-dig* cyclization was reported by Nevado and Echavarren²⁴⁵ for the preparation of *N*-tosyl-1,2-dihydroquinolines **III.128**. (Scheme III.78.).



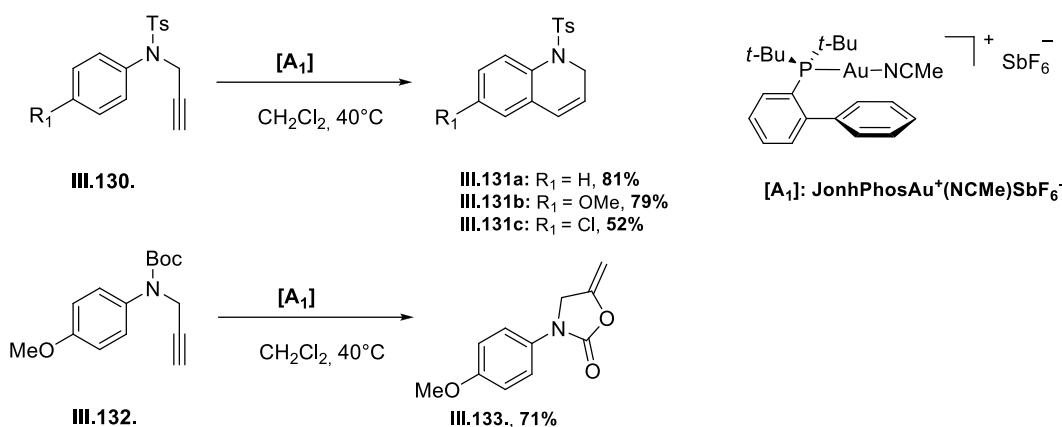
Scheme III.78. Synthesis of *N*-tosyl-1,2-dihydroquinolines.

Optimization of the reaction demonstrated that use of a cationic gold complex formed *in situ* from Ph₃PAuMe and HBF₄ in toluene gave the desired product **III.129**. in 92% yield. An excess of the acid was found to be required for gold complex activation while facilitating protodeauration of the vinyl-gold intermediates. Using Ph₃PAuCl/AgX (X = SbF₆⁻, BF₄⁻) catalysts in dichloromethane was also shown to give the product in good yields (76-82%)

²⁴⁵ Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155.

without using any additive in excess. Noteworthy, the same dihydroquinoline adduct **III.129** could also be formed by Gagosz with a comparable efficiency using $\text{Ph}_3\text{PAuNTf}_2$ as the sole catalyst.²⁴⁶

Banwell and co-workers²⁴⁷ have expanded the method to other type of starting materials with *para*-substitution on the aryl group and various protecting groups on nitrogen. (**Scheme III.79.**) The authors used the catalyst **A**₁ earlier developed by Echavarren.²⁴⁸ This catalyst possesses a ligand acetonitrile, which can easily be exchanged with an alkyne due to its low coordinating character. In most cases, the desired products were formed in good yields, except in the specific case of aromatics substituted by electron-withdrawing groups ($\text{R}_1 = \text{Cl}$, yield = 52%). Switching the tosyl by a nosyl group on nitrogen was shown to have no influence on the reactivity giving 1,2-dihydroquinoline of type **III.131** in good yield (75%, $\text{R}_1 = \text{OMe}$). Conversely, a Boc protecting group was found to interfere in the reaction mechanism and reaction with *N*-Boc aniline **III.132** exclusively provided oxazolidinone **III.133** in 71% yield. (**Scheme III.79.**)



Scheme III.79. The gold-catalyzed hydroarylation reaction of *N*-propargylanilines.

The nature of the ligands of gold complexes could also strongly influence the course of the reaction. In the cyclization of *N*-(3-iodoprop-2-ynyl)-*N*-tosylanilines **III.134.**, Gonzalez *et al.*²⁴⁹ have shown that depending on the ligand on gold, different regioisomers could be mainly obtained. When phosphite ligands $(\text{ArO})_3\text{P}$ were used, a direct 6-*endo*-cyclization took place providing compound **III.135** selectively (**Scheme III.80.**). Using σ -donor NHC ligands rather favored 1,2-migration of iodine which next led to the formation of the regioisomeric product **III.136**. Formation of this latter compound was also found to take place with aniline

²⁴⁶ Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

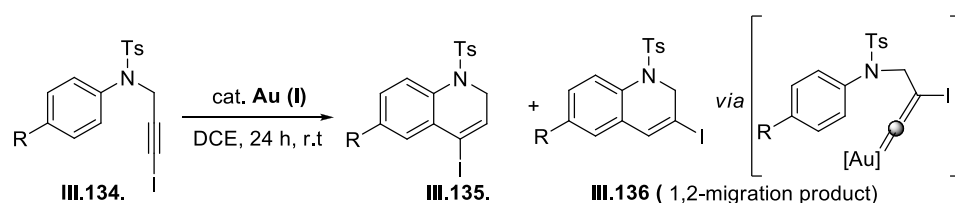
²⁴⁷ Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901.

²⁴⁸ Herrero-Gómez, E.; Nieto-Obernuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

²⁴⁹ Morán-Poladura, P.; Suárez-Pantiga, S.; Piedrafita, M.; Rubio, E.; González, J. M. *J. Organomet. Chem.* **2011**, *696*, 12.

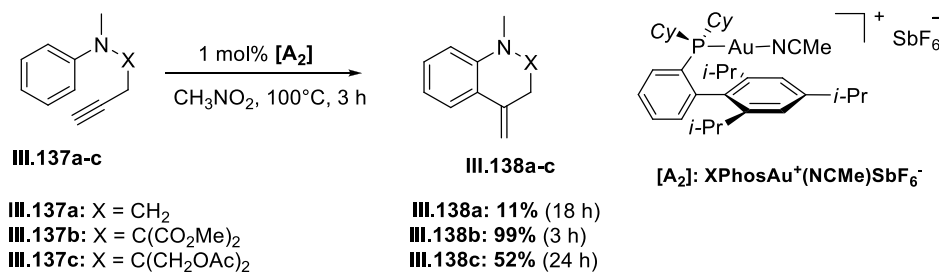
CHAPTER III: The gold-catalyzed alkyne reaction of *N,O*-acetals

derivatives having an electron-withdrawing substituent (R in the figure below), due to a slower cyclization. A few years before, Fürstner *et al.*²⁵⁰ already observed this type of influence on the regioselectivity of cyclizations yielding halophenanthrenes. In this work, it was more the nature of the metal [In (III) *versus* Au (I)] rather than the type of ligand used that controlled the position of the halogen in the final product. This was rationalized by two mechanistic propositions. The migration product would come from an η^2 -alkyne-[Au] complex which evolved to an [Au]-vinylidene intermediate with concomitant 1,2-migration of the halogen. A similar interpretation was proposed by Nolan's research group²⁵¹ to explain the formation of compound **III.136**, with the formation of [Au]-vinylidene intermediate being favored by the strong σ -donor properties of the carbene ligands.



Scheme III.80. The gold-catalyzed synthesis of 1,2-dihydroquinoline derivatives.

An additional approach relying on a gold-catalyzed 6-*exo-dig* cyclization of *N*-butynylanilines **III.137**, was developed in 2011 by Gagosz and co-workers²⁵² for the synthesis of dihydroquinoline derivatives (Scheme III.81). The authors used 1 mol% of [XPhosAu(NCMe)]SbF₆ **A**₂ as catalyst in nitromethane at 100 °C. It is important to note that substrates having a malonate tether [C(CO₂Me)] were smoothly converted into the *exo*-methylene tetrahydroquinolines. Substrates containing different tethers were found to be less productive (X = CH₂, 11% yield, X = C(CH₂OAc)₂, 52%) and required extended reaction times.



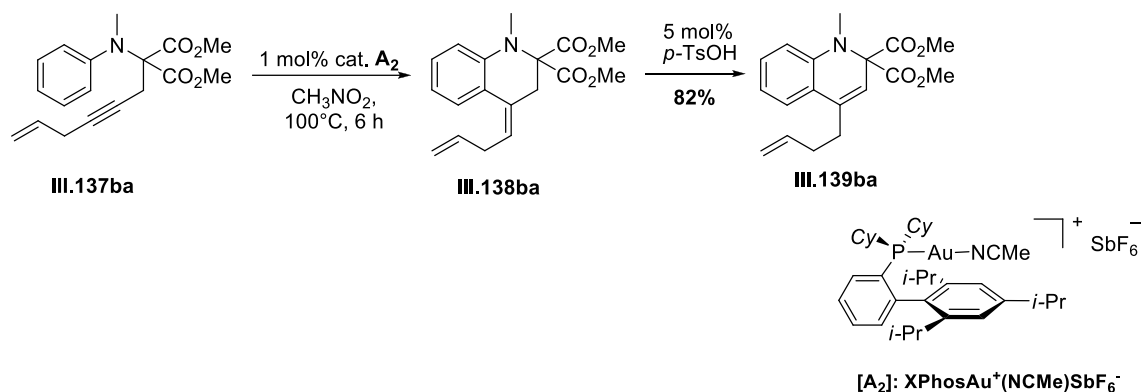
Scheme III.81. The hydroarylation of *N*-butynylanilines.

²⁵⁰ (a) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762; (b) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518.

²⁵¹ (a) Díez-González, S.; Marín, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612-3676; (b) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics*, **2005**, *24*, 2411-2418.

²⁵² Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun.* **2011**, *47*, 218.

These conditions have been applied to many other *N*-butynylanilines derivatives, equipped with various substituents or *N*-protecting groups. Different protecting groups on nitrogen such as alkyl, cycloalkyl and phenyl groups have been well tolerated. It should be noted that the efficiency and the reaction rate was only slightly influenced by the nature and position of the substituents on the aromatic ring (*ortho*-, *meta*- and *para*-substitution). Excellent selectivity was observed in the reaction with a non-terminal alkyne which provided product **III.138ba** by *anti*-addition of the arene on the gold-activated alkyne. (**Scheme III.82.**)

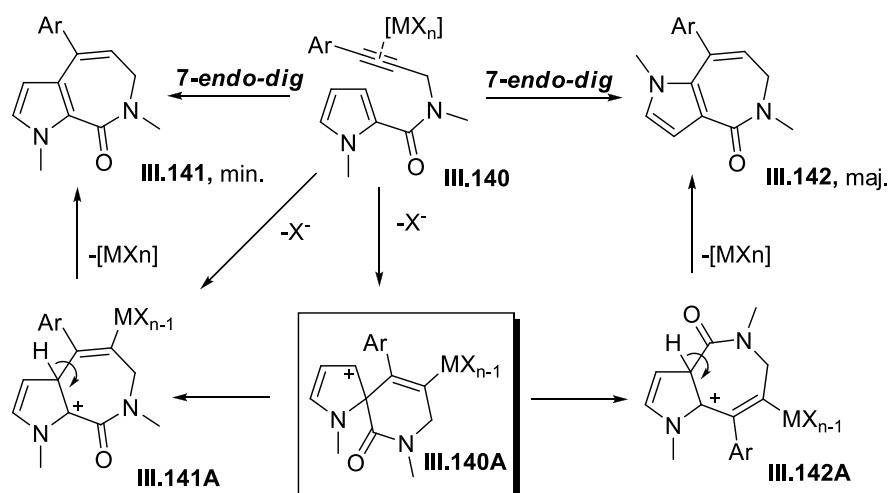


Scheme III.82. The cyclization reaction of **III.137ba**.

In all the above presented examples, the cyclization mode appeared not to be dependent (or very little) on the nature of the catalyst but would be rather controlled by the size and the stability of the ring formed. When a competition 5-*exo* versus 6-*endo* is possible, only 6-*endo* selectivities were observed, which is quite unusual in gold-catalysis and seems to be specific to these aromatic substrates. When a competition 6-*exo* versus 7-*endo* is possible, the observed selectivities strongly favored a 6-*exo* process.^{250,251}

It is however possible in some cases to direct the cyclization of acetylenic arenes towards a 7-*endo* process. A synthesis of pyrroloazepinones relying on a 7-*endo-dig* ring-closure of *N*-propargyl pyrrololecarboxamides was developed by Beller.²⁵³ Use of AuCl₃ was found to promote efficiently the formation of 7-membered products following a 7-*endo-dig* cyclization mode, with regioisomer **III.142** being the major product obtained. Whereas compound **III.141** would directly result from a direct 7-*endo-dig* process, the formation of product **III.142** would involve formation of a spirocyclic intermediate **III.140A**, followed by preferential migration of the acyl group (**Scheme III.83.**)

²⁵³ (a) Gruit, M.; Michalik, D.; Tillack, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7212; (b) Gruit, M.; Michalik, D.; Krüger, K.; Spannenberg, A.; Tillack, A.; Pews-Davtyan, A.; Beller, M. *Tetrahedron*, **2010**, *66*, 3341.



Scheme III.83.

Protection of the nitrogen as well as presence of an aromatic substituent on the alkyne were found to be highly important for the exclusive formation of *7-endo-dig* products. In all cases, the direct cyclization product **III.141** could only be obtained as traces (<5%). In a recent report, Lovely²⁵⁴ could reverse the selectivity of the reaction by using an acetylenic substrate substituted by a *N*-monoprotected imidazole (41% yield with AuCl₃ in 1,4-dioxane at 100°C). Again, a mechanism based on an *ipso*-addition/rearrangement sequence, similar to the one proposed by Beller was postulated (Scheme III.83.).

These results belong to the rare examples of *7-endo* regioselective intramolecular hydroarylations of alkynes. In particular, they contrast with results obtained by Padwa from structurally close indolic substrates which only led to *6-exo* cyclizations,²⁵⁵ thus illustrating the diversity and subtlety offered by gold catalysis.

Cascade synthetic sequences are becoming more and more important to build up complex architectural motifs, through the formation of multiple strategic bonds in a single synthetic event. In this context, gold catalysis represents a powerful tool for the promotion of one-pot syntheses of condensed heterocycles from easy to prepare starting materials. As a representative and elegant example of such a cascade sequence involving a step of gold-catalyzed hydroarylation of alkynes, one can cite the work recently reported by Wang and coworkers.²⁵⁶ The authors described a tandem cyclization reaction involving indolyl-propargylic alcohols/amines that performed under mild conditions (Ph₃PAuSbF₆ 5 mol%, CH₂Cl₂, rt) (Scheme III.84.). A range of diastereomerically pure tetracyclic indolines was

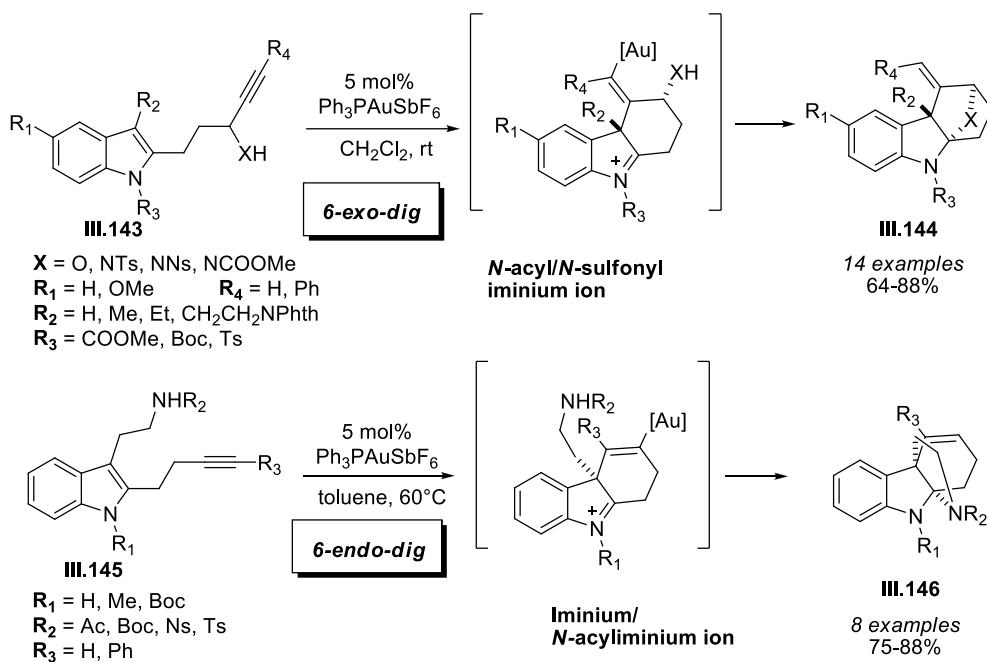
²⁵⁴ Bhandari, M. R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett.* **2011**, *12*, 1382.

²⁵⁵ England, D.B.; Padwan A. *Org. Lett.* **2008**, *10*, 3631.

²⁵⁶ Y. Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448.

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obtained by concerting the initial regioselective site-selective indole attack (C3 position) to the C–C triple bond, with the trapping of the resulting iminium ion by *O*- or *N*-based internal nucleophiles. After gold activation of the triple bond, the alkyndiindoles **III.143** and **III.145** cyclized to give exclusively the *exo*- (**III.144**) or *endo*- (**III.146**) cyclization products, in accordance to literature trends .

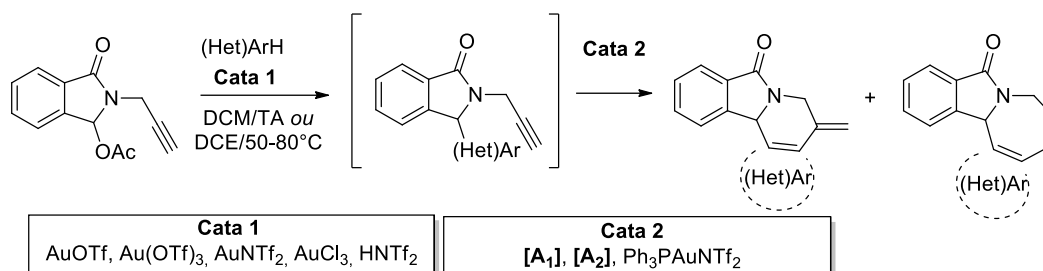


Scheme III. 84.

Since 2009, our team has been interested in the development of gold-catalyzed transformations in the context of *N*-acyliminiums chemistry. As previously presented in Chapter I, a general and efficient gold-catalyzed α -amidoalkylations of various nucleophiles with *N*-acyliminium precursors was developed. This methodology relies on the use of gold (I) and gold (III) triflates, generated in situ.²⁵⁷ Intramolecular hydroarylations of suitably designed alkyndyl substrates was next successfully undertaken and applied to cascade sequences. A clear influence of the nature of the (hetero)aryl moiety on the regioselectivity of the hydroarylation step was noted. This difference of regioselectivity could be governed by several factors, in particular by the steric and electronic nature of the internal nucleophile. For example, an exclusive *endo* selectivity was observed in the case of 1,3-dimethoxybenzene which could be controlled by the steric demand of the –OMe substituent (for kinetic reasons).²⁵⁸

²⁵⁷ Boiaryna, L., El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chem. Eur. J.* **2012**, *18*, 14192.

²⁵⁸ Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542.



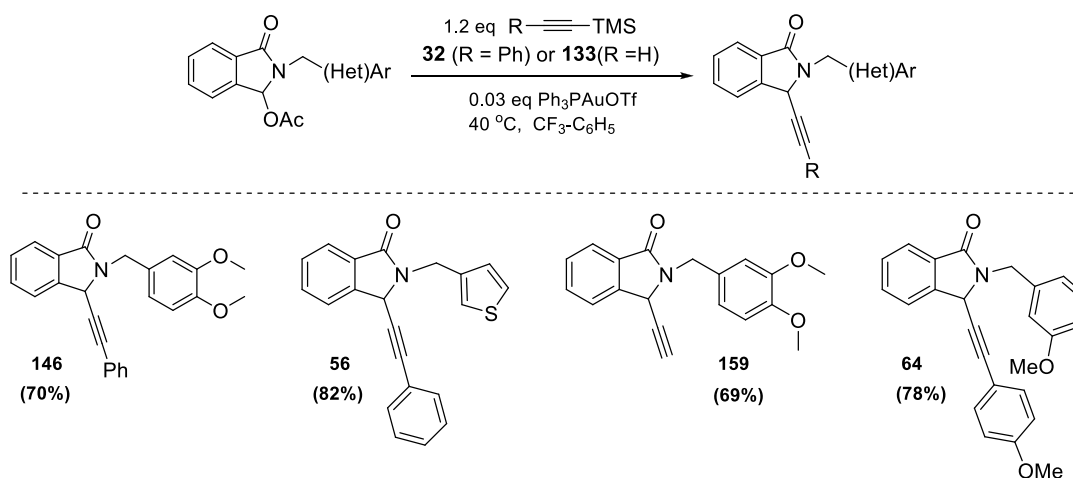
Scheme III.85. Friedel-Crafts/Hydroarylation sequence starting from *N*-propargyl acetoxy lactam

Interestingly, it was demonstrated that combination of oxophilic and carbophilic properties of gold catalysts was possible and could be successfully exploited in catalytic intermolecular Friedel-Crafts / intramolecular hydroarylation one-pot sequences. It was also shown that combining Bronsted acid and gold catalysis could efficiently promote this type of sequence. This work constitutes one of the rare example of gold-catalyzed sequence involving an *N*-acyliminium.²⁵⁹

B. Results: Hydroarylation reaction of isoindolines derivatives

- Preparation of the hydroarylation substrates

A set of alkyne compounds suitably functionalized for hydroarylation was selected: Compounds **56**, **64**, **146** and **159** possessing an alkyne motif and having electron-rich arylmethyl or heteroarylmethyl protecting groups on nitrogen were prepared using our optimized alkylation reactions (1.2 equiv TMS-alkyne **32** or TMS-acetylene **133**, 3 mol% Ph₃PAuOTf, F₃C-C₆H₅, 40 °C). For stability consideration, substrates derived from isoindolinone were preferred here.



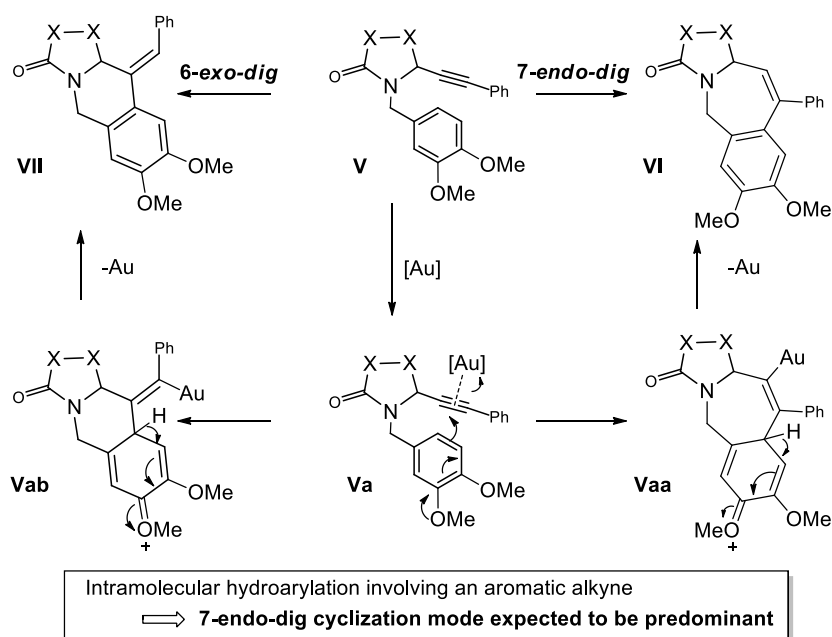
Scheme III.86.

²⁵⁹ Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070.

- Catalysts screening

We first began with the optimization of the conditions of the hydroarylation of *N*-(3,4-dimethoxybenzyl) isoindolinone substrate **146** as a model reaction. In line with previous literature results,²⁶⁰ we expected a positive impact of two electron donating groups on the aromatic ring of the *N*-benzyl group in the cyclization step.

A possible mechanistic pathways, in line with previous reports published by Echavarren,²⁶¹ Soriano²⁵⁸ or Furstner,²⁶² is presented below. (**Scheme III.87**) The electrophilic activation of the triple bond by gold offers two possibilities for nucleophilic attack: either 6-*exo-dig* or 7-*endo-dig* intramolecular addition. In both cases, Wheland intermediates of type-**Vaa** or **Vab** would be respectively formed. The loss of a proton (rearomatization) followed by protodeauration would finally led to the desired products **VI** or **VII** depending on the cyclization mode taken. So, one can possibly expect the formation of a 6-membered and/or of a 7-membered ring at the end of the reaction. However, due to the presence of a phenyl ring on the terminal position of the alkyne chain, a 7-*endo-dig* cyclization mode is rather expected for the hydroarylation of substrate **146**, in accordance to Beller's previous reports.²⁵³



Scheme III.87. Mechanistic hypothesis for the hydroarylation reaction.

²⁶⁰ (a) Ramanos, R. S.; Marion N.; Nolan, S.P. *Tetrahedron*, **2009**, *65*, 1767; (b) Alfonsi, M.; Arcadi, A.; Chiarini, M.; Marinelli, F. *Tetrahedron Lett.* **2011**, 5145; (c) Mamane, V.; Hannen, P.; Furstner, A. *Chem. Eur. J.* **2004**, *10*, 4556; (d) Echavarren, A.M. *et al. Beilstein. J. Org. Chem.*, **2011**, *7*, 1520.

²⁶¹ Nevado, C.; Echavarren, A.M. *Chem. Soc. Rev.* **2004**, *33*, 431.

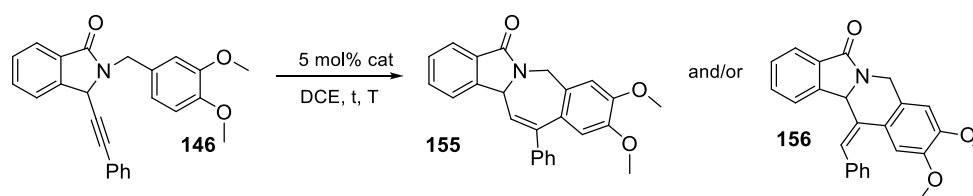
²⁶² (a) Furstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264; (b) Furstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112.

CHAPTER III: The gold-catalyzed alkynylation reaction of *N,O*-acetals

As presented in the introduction of this part, a few catalysts were found to be highly reactive at promoting regioselective intramolecular hydroarylations. The selection of catalysts we have done here was also driven by the results we obtained in our laboratory in the context of the development of alkynylation/hydroarylation cascade reactions. Different types of catalyst were examined in dichloroethane at different temperatures. (**Table III.34.**)

The catalyst [JohnPhosAu(NCMe)]SbF₆ [**A**₁] was first tested. This cationic gold (I) complex bearing a bulky phosphine ligand was indeed often shown to give very good results in intramolecular hydroarylations of alkynes.²⁶³ Moreover, it also allows to run the reaction in the absence of Ag(I) salts. When compound **146** was treated with 5 mol% of [**A**₁], a very slow conversion of the substrate was observed. Heating the reaction mixture to 80 °C only allowed partial transformation of the substrate and after 21 hours, 20 % yield of the *endo*-product **155** could be isolated. (**Table III.34.** Entry 1)

Table III.34. Influence of the catalyst in the hydroarylation reaction.



Entry	Catalyst	T[°C]	Time	Yield[%]
1.	[A ₁]	r.t. 40 80	1.5h then 40' then 21h	20% 155 , incomplete conv.
2.	[A ₂] <i>formed in situ</i>	80	6 days	100% conv; 55% 155
3.	[A ₂] (0.1 eq) <i>formed in situ</i>	80	29h	100% conv; 46% endo
4.	[A ₂] HNTf ₂	80	24h	100% conv; 18% 155
5.	(<i>p</i> -CF ₃ -Ph) ₃ PAuNTf ₂	80	24h	32% 155
6.	[A ₃]	80	29h	100% conv; 48% 155
7.	IPrAuNTf ₂	80	5 days	12% 155 15% 156

²⁶³ (a) Ferrer, C.; Amijs, C.H.M.; Echavarren, A.M. *Chem. Eur. J.* **2007**, *13*, 1358; (b) Ferrer, C.; Echavarren, A.M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.

8.	[A₂] formed <i>in situ</i> Reaction in toluene	115	4h	100% conv; 47% 155
	[A₁] : JohnPhosAu(NCMe)]⁺SbF₆⁻	[A₂] : XPhosAuNTf₂		[A₃] : RuPhosAuNTf₂

In the reaction with catalyst XPhosAuNTf₂ [A₂],²⁶⁴ which was prepared *in situ* through the metathesis of synthesized XPhos-AuCl species with AgNTf₂²⁶⁵ full consumption of the starting material was observed and the product **155** was selectively obtained in an improved yield of 55% (Table III.34. Entry 2). The reaction rate was again found to be very slow since 6 days at 80 °C were necessary to reach full conversion. Interestingly, it points out that the cyclized product **155** is stable at high temperature over time. Increasing the catalyst loading to 10 mol% was found to increase the reaction rate but only 46% yield of product **155** could be obtained (Entry 3.). In order to facilitate the protodeauration step (see mechanism Scheme III.87.), addition of a strong Brønsted acid HNTf₂ (5 mol%) was next tested. Unfortunately it caused deleterious effect and only degradation was observed. (Entry 4.)

A cationic gold (I) complex equipped with a strong electrophilic triaryl phosphine group was next tested with the idea of facilitating the activation of the triple bond by the catalyst. However, the cyclized product **155** could only be isolated in a poor yield of 32% after 24 hours of reaction. (Entry 5.)

Gold complexes possessing more electron rich ligands were next chosen. Using catalyst RuPhosAuNTf₂ [A₃] possessing a bulky electron rich phosphine ligand could promote the hydroarylation of substrate **146** but no improvement in terms of yield or reaction rate was observed. (48% yield after 29 hours, Entry 5.)

Disappointingly, when the reaction was catalyzed by a gold salt having a σ -donor NHC ligand which was often used to promote cyclization reactions,²⁶⁶ the reaction rate collapsed and a complete absence of regioselectivity was observed (Entry 7.). Indeed, after 5 days of

²⁶⁴ Nieto-Oberhuber, C.; López, S.; Echavarren, A.M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

²⁶⁵ Please see more details in the Chapter III.

²⁶⁶ For some representative publications on cyclization reactions catalyzed by carbene gold catalyst see:

(a) Brown, T.J.; Widenhoefer, R.A. *Organometallics*, **2011**, *30*, 6003; (b) Hashmi, A.S.K.; Baun, I.; Rudolph, M.; Rominger, F. *Organometallics*, **2012**, *31*, 644; (c) Cheong, P.H.-Y.; Morganelli, P.; Luzung, M.R.; Houk, K.N.; Toste., F.D. *J. Am. Chem. Soc.* **2008**, *130*, 4517.

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reaction at 80 °C, the cyclized 6-*exo-dig* product **156** and 7-*endo-dig* product **155** were obtained in 12% and 15% yield respectively.

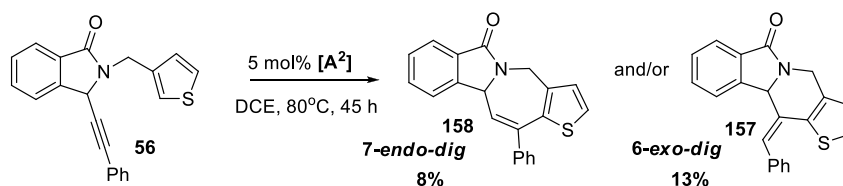
It is worth pointing out that in most cases the regioselectivity was oriented towards the formation of the 7-*endo-dig* cyclization product **155** which fits with our expectations (**Scheme III.87**).

In light of this set of results, we last tested using 5 mol % of catalyst [**A**₂] in refluxing toluene. After a reasonable time of 4 hours, the *endo*-product **155** could be selectively formed in 47% yield. (Entry 8. *versus* Entry 2.) These conditions thus appeared to be the best so far for the formation of the tetracyclic compound **155**.

- Generalization

In order to evaluate whether these hydroarylation conditions could be extended to the formation of other tetracyclic compounds, we next investigated the [**A**₂]-catalyzed cyclization of a few other alkynyl substrates equipped with electron rich (hetero)arenes.

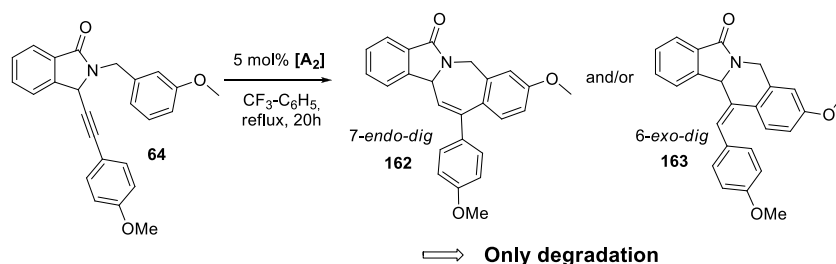
First, substrate **56** possessing a *N*-methylthiophene protecting group was reacted with 5 mol% of [**A**₂] in refluxing DCE. A slow reaction rate was again observed and poor yields of the corresponding 6-*exo-dig* and 7-*endo-dig* products were obtained (13% and 7% yields respectively) (**Scheme III.88**). The hydroarylation of **56** was thus shown to operate with a very poor regioselectivity.



Scheme III.88. Hydroarylation of thiophenyl substrate **56**

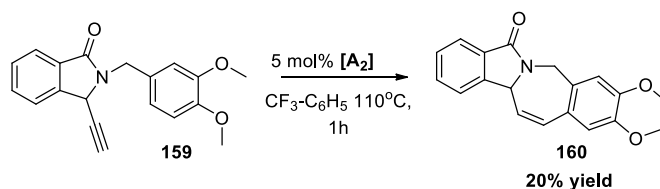
We also expected that hydroarylation of substrate **64** having an electron rich aromatic substituent on the alkyne chain would be favored for electronic reasons. The electron rich triple bond should be more easily coordinated by gold and the stabilized nature of the developing charge following complexation should facilitate the π -cyclization with any of the

aryl motifs. Unfortunately, the substrate turned out to be unstable under the reaction conditions (refluxing trifluorotoluene) and a complex mixture was only obtained. (**Scheme III.89.**)



Scheme III.89. The hydroarylation reaction with *p*-MeO-phenylacetylene isoindolinone derivative **133**.

In order to facilitate the hydroarylation, the evaluation of a substrate displaying less steric constraints was last considered. The terminal alkyne substrate **159** was then tested for comparison with the terminal alkyne substrate **146**. As presented on **Scheme III.90.**, the [A₂]-catalyzed hydroarylation of **159** afforded the corresponding tetracyclic compound **160** in 20% yield (despite full conversion of substrate **159**). Noteworthy, the reaction proceeded with a faster reaction rate and a complete *endo*-regioselectivity was again observed which contrasts with previous reports.^{250,251}



Scheme III.80. The hydroarylation reactions of substrate **159**.

Even if the hydroarylation of our alkynylated adducts appeared to be feasible, the results obtained so far were somewhat disappointing. Further investigations would obviously be needed to improve the efficiency and the scope of such a transformation.

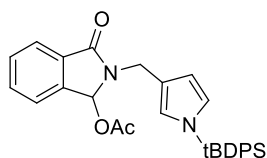
In order to facilitate the hydroarylation, the evaluation of a substrate containing a nitrogen protecting group that will tolerate well the alkynylation reaction and will favour the hydroarylation should be considered. As shown on **Scheme III.91.a**, other protecting group on nitrogen in electrophiles such as pyrrole, indole, benzo[*b*]thiophene or benzofuran derivatives may be envisioned as potential candidates in this catalytic Au-catalyzed alkynylation-hydroarylation protocol.

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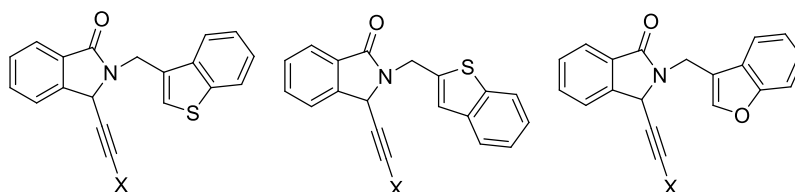
Alternatively, a very nucleophilic partner in the alkylation coupling could be provided by using silyl ynamides. This group also should give a stabilized keteniminium intermediate during the hydroarylation cyclization, thus facilitating this process. (Scheme III.91. b)

a) modification of the electrophile:

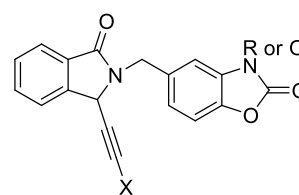
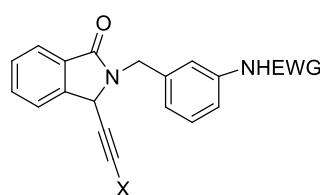
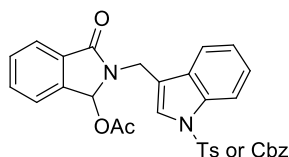
Pyrrrole derivative *N*-protecting group



Various heteroaromatics *N*-protecting group

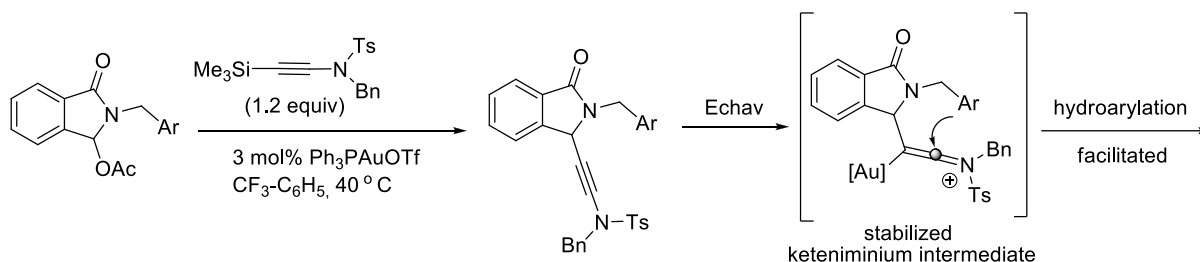


Indole derivative *N*-protecting group



EWG = Ts, Cbz, Me(CO)- Ph(CO)-

b) modification of the silyl alkyne:



Scheme III.91. Variation of substrates for the hydroarylation reaction.

- One-pot sequence alkylation-hydroarylation reaction

Among the test reactions performed, the hydroarylation of substrate **146** was found to be the most effective thus far. As the preparation of the hydroarylation substrate implied a first gold-catalyzed transformation (*i.e.* alkylation), we next envisioned testing if a one-pot tandem sequence alkylation/hydroarylation could be directly applied starting from acetoxy lactam **145** (Table III.35.).

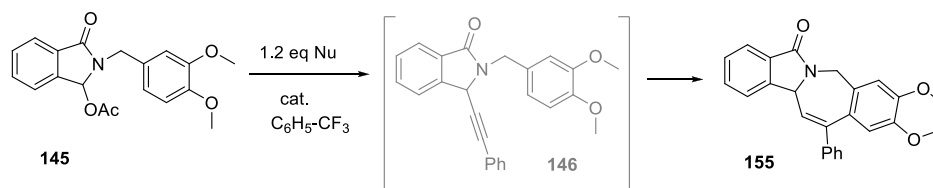
With the idea of using only one catalyst to promote both steps of the reaction sequence, we first tested the use of catalyst [A₂] (XPhosAuNTf₂) which was found to be the most effective so far for the hydroarylation of the alkynyl compound **146**. However, use of 3 mol% of [A₂] with 1.2 equivalent of TMS-alkyne in trifluorotoluene at 40 °C was found to exhibit an

unsufficient reactivity in the alkynylation step. Indeed, after a long reaction time (22 h) and despite the addition of a further equivalent of TMS-alkyne, only 37.5% of the acetoxylactam was converted to the alkynyl product **146** and no trace of the cyclised product **155** was observed. (Table III.34. Entry 1.)

We next evaluated the efficiency of Ph_3PAuOTf and $\text{Ph}_3\text{PAuNTf}_2$, two catalysts which presented significant reactivities in the alkynylation of acetoxy lactams. As expected, using 10 mol% of Ph_3PAuOTf under classical conditions led to the formation of the alkynylated intermediate **146** in only 20 minutes. Then, the reaction mixture was directly heated at reflux to assist the hydroarylation step. After only 2 hours, the intermediate **146** was fully consumed but the cyclized *endo*-product **155** could only be isolated in 34% overall yield. Despite the low yield obtained, no other product could be isolated from the crude.

Changing the catalyst was not found to be beneficial since using $\text{Ph}_3\text{PAuNTf}_2$ gave a very similar result with compound **155** being produced in only 27 % yield. (Entry 2 *versus* Entry 3.)

Table III.35. Catalyst screening for the one-pot alkynylation/hydroarylation sequence



Entry	Catalyst (mol%)	T(° C)	Time	Conversion (%) ^{a)}
1.	[A ₂] (3)	40	2h then + 1eq Nu and 20h	63% 145 37 % 146
2.	Ph_3PAuOTf (10)	40 then 110	20' 2h	34% 155
3.	$\text{Ph}_3\text{PAuNTf}_2$ (10)	40 then 110	30' 2h	27% 155

^{a)} determined by ¹H NMR

This gold-catalyzed alkynylation/hydroarylation cascade sequence enabled formation of the tetracyclic compound **155** in a single transformation step in a promising yield (34%) which rivals the global yield of the two-stage two steps sequence. Efforts towards improving the efficiency of this sequence, by screening both the reaction conditions and reaction partners in more details, need to be pursued.

CHAPTER IV:
PRELIMINARY MECHANISTIC STUDY

IV. 1. CATIONIC Au(I) ALKYNYL COMPLEXES

Over the last decade, gold complexes have become powerful tools in organic synthesis, mostly owing to their ability to activate multiple bonds such as alkynes, and to a lesser extent allenes and alkenes, towards nucleophilic additions. The still ongoing interest in gold catalysis is due to a set of peculiarities such as the ability of cationic gold species to interact with the alkynyl π clouds to form stable σ -gold(I)-alkynyl complexes (gold acetylides). Those species are highly desirable because of their very wide range of applications in different areas such as luminescence, molecular recognition, optical switches, electronics, catalysis and biological applications as therapeutic agents against different illnesses for example cancer cells or malaria.²⁶⁷ Based on their tendency to form linear geometry, gold(I)-complexes are also able to construct supramolecular components through aurophilic interactions.²⁶⁸ In spite of their organometallic nature and structural analogy with Li/Mg alkynylides, gold acetylides have surprisingly found relatively little interest from the synthetic community in comparison to the most traditional gold/alkyne chemistry where a nucleophile attacks a C-sp carbon of an electrophilic alkyne-gold π -complex.²⁶⁹ As it was presented in the Chapter III of this manuscript, most of the reports in this area deal with the implication of gold acetylides in the gold-catalyzed version of the A^3 -coupling (aldehydes, alkynes and amines leading to propargylic amines)^{270a-e} and related reactions^{270f-j} that are based on the Grignard type reactivity of a gold acetylide.²⁷¹

Surprisingly, while most of the reports published over the last years on gold chemistry involving alkynes as substrates have focused on catalysis, only little has been said about the

²⁶⁷ Lima, J. C.; Rodríguez, L. *Chem. Soc. Rev.* **2011**, *40*, 5442.

²⁶⁸ (a) Himmelsbach, A.; Finze, M.; Raub, S. *Angew. Chem.* **2011**, *123*, 2676; (b) Lu, W.; Xiang, H.F.; Zhu, N.; Che, C.M. *Organometallics*, **2002**, *21*, 2343.

²⁶⁹ For some reviews in gold catalysis with a specific emphasis on π activation, see: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.*, **2006**, *45*, 7896; (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.*, **2007**, *46*, 3410; (c) Gorin, D. J.; Sherry, B. D.; Toste, D. F. *Chem. Rev.*, **2008**, *108*, 3351; (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.*, **2008**, *108*, 3326; (e) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.*, **2011**, *111*, 1657.

²⁷⁰ (a) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581. (b) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (c) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (d) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (e) Campbell, M. J.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1369. (f) Capretto, D. A.; Brouwer, C.; Poor, C. B.; He, C. *Org. Lett.*, **2011**, *13*, 5842. (g) Naoe, S.; Suzuki, Y.; Hirano, K.; Inaba, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2012**, *77*, 4907. (h) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953. (i) Li, C.; Mo, F.; Li, W.; Wang, J. *Tetrahedron Lett.*, **2009**, *50*, 6053. (j) Li, C.; Li, W.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2533.

²⁷¹ For the halogenation of terminal alkynes catalyzed by gold(I) salts: (a) Leyva-Pérez, A.; Rubio-Marqués, P.; Al-Deyab, S. S.; Al-Resayes, S. S.; Corma, A. *CS catal.* **2011**, *1*, 601. (b) Starkov, P.; Rota, F.; D'Oyley J. M.; Sheppard, T. D. *Adv Synth. Catal.*, **2012**, *354*, 3217. For the dimerization of terminal alkynes catalyzed by gold(I) salts: (c) Sun, S.; Kroll, J.; Luo, Y.; Zhang, L. *Synlett* **2012**, *54*. (d) Odabachian, Y.; Le Goff, X.-F.; Gagosz, F. *Chem. Eur. J.* **2009**, *15*, 8966.

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discrete species emanating from the initial interaction between the gold reagent and the alkyne substrate, notably terminal alkynes. Recently, intriguing discoveries arising from mechanistic-oriented studies were published, and notably the advent of rather unexpected dinuclear gold alkynyl species has opened-up new directions in the chemistry of gold acetylides. Some of the most representative contributions involving these dinuclear gold alkynyl complexes, together with some aspects of mononuclear gold acetylides which have not been covered yet in this manuscript, will be presented in this chapter.

A final section will be devoted to define and possibly characterize entities catalytically formed in our test benchmark reaction, and subsequently to confirm the mechanism postulated and operating in Chapter III. Efforts aimed at probing the stability of the different gold species assumed to be present along our alkynylation reaction will be also discussed.

IV.1.1. OVERVIEW OF GOLD(I) ALKYNYL COMPLEXES

Gold(I) complexes have aroused as efficient homogeneous catalysts for the activation of terminal alkynes towards attack by either an external or a pending nucleophile, or, less frequently, towards evolution into a σ -gold(I) acetylide reagent. (**Fig.IV.1.**)

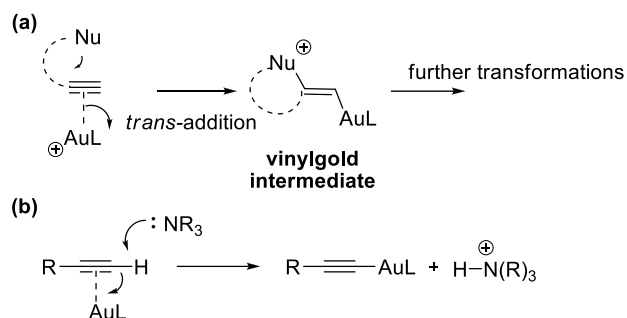


Fig IV.1.

These discoveries have led to the development of powerful new methods for synthesizing a large assortment of structurally complex molecules²⁶⁹ in order to fully operate these methodologies, it is necessary to understand the mechanisms by which these new reactions proceed, and by the way to clarify the precise structural identify of the gold intermediates involved. With these objectives in mind, the following presentation of the state of the art will focus on a careful selection of recent contributions, which provide significant insights into the mechanisms which govern the gold-catalyzed transformations affecting terminal alkynes.

In the continuity of pioneering studies by Toste, Russel, (see Chapter 3, **Scheme III.49.**) Gimbert and their respective co-workers,²⁷² Widenhoefer and Brown²⁷³ have recently, sought to synthesize and structurally identify complexes of the type $[(\text{IPr})\text{Au}(\eta^2\text{-alkyne})][\text{SbF}_6]$ **IV.1.**, which are thought to be initially involved in many gold-catalyzed transformations of terminal alkynes. (**Scheme IV.1.**) In contrast to some gold(I) π -complexes of internal alkynes which exhibit sufficient stability for isolation and characterization,²⁷⁴ this gold π -arylacetylene complex is thermally unstable so that the reaction, consisting in a mixture of (IPr)AuCl and AgSbF₆ with terminal arylacetylenes, was performed at low temperature and was monitored

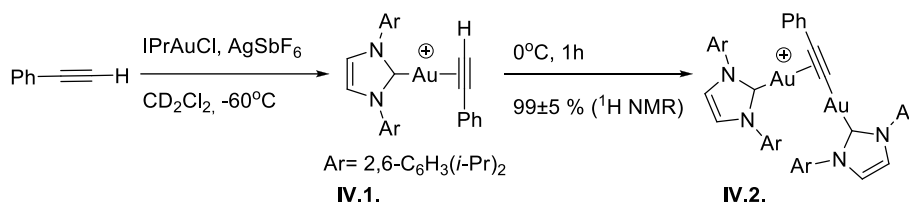
²⁷² (a) Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.*, **2008**, *130*, 4517; (b) Hooper, T. N.; Green, M.; Russell, C. R. *Chem. Commun.*, **2010**, 2313; (c) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. *Chem. Sci.* **2011**, *2*, 2417

²⁷³ Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2011**, *30*, 6003.

²⁷⁴ (a) Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. USA*, **2008**, *105*, 2779; (b) Flügge, S.; Anoop, A.; Goddard, R.; Thiel, W.; Fürstner, A. *Chem. Eur. J.* **2009**, *15*, 8558; (c) Dias, H. V. R.; Flores, J. A.; Wu, J.; Kroll, P. *J. Am. Chem. Soc.*, **2009**, *131*, 11249;

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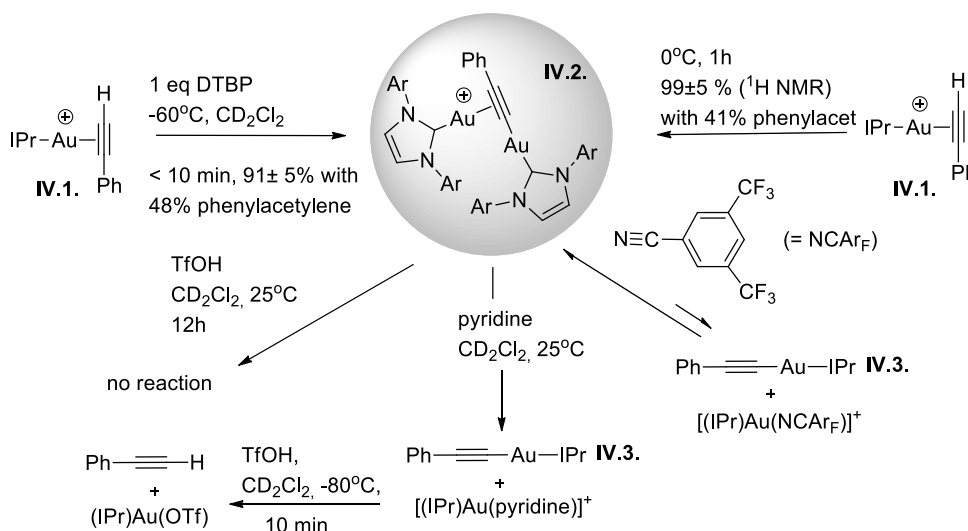
by spectroscopy at $-60\text{ }^{\circ}\text{C}$ without isolation. Coordination of phenylacetylene to gold was established by the downfield shift of the acetylenic proton of **IV.1.** (δ 4.56) relative to that of free phenylacetylene (δ 3.06) in the ^1H NMR spectrum and by the difference in the ^{13}C NMR shifts of the acetylenic carbon atoms of **IV.1.** [δ 72.7 (d), 93.5 (s)] relative to free [δ 77.3 (d), 83.7 (s)] phenylacetylene.



Scheme IV.1. Synthesis of gold π -complex of arylacetylenes and their transformation to σ,π -acetylide complex.

Interestingly, after increasing the temperature above $-20\text{ }^{\circ}\text{C}$, the complex underwent an $\text{C}_{\text{sp}}\text{-H}$ cleavage and dinuclear gold σ,π -arylacetylene complex **IV.2.** was formed.

While already suggested or demonstrated by others²⁷² this spontaneous process is rather counter-intuitive and is opposed to the empirical rule that the presence of a relatively good base is necessary to transform a gold(I)- π -terminal alkyne complex into a σ -gold(I) acetylide.²⁷⁰ This somewhat unexpected result raised the intriguing possibility that gold acetylide chemistry could be potentially developed in the absence of an exogenous base, and therefore stimulated the authors to investigate the stability of these complexes, and notably **IV.2.** (Scheme IV.2.)



Scheme IV.2. Synthesis and reactivity of the σ,π -acetylide complex (in the complexes **IV.1.** and **IV.2.**, the counter anion SbF_6^- has been omitted for clarity)

While a two electrons good donor ligand like pyridine completely and irreversibly bound to the cationic gold moiety of **IV.2.**, affording a ~ 1:1 mixture of the neutral σ -acetylide species **IV.3.** and the cationic complex $[\text{Au}(\text{IPr})(\text{Py})]^+[\text{SbF}_6]^-$ after only 10 min at room temperature, a related experiment with $\text{N}\equiv\text{C}\text{Ar}_\text{F}$ ($\text{Ar}_\text{F} = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$ (0.78 equiv. relative to **IV.2.**) in CD_2Cl_2 at -60°C led to the formation of a 4.9:1.0:1.0:3.5 equilibrium mixture of **IV.2.**, **IV.3.**, $[\text{Au}(\text{IPr})(\text{N}\equiv\text{C}\text{Ar}_\text{F})]^+[\text{SbF}_6]^-$ and $\text{N}\equiv\text{C}\text{Ar}_\text{F}$. This corresponds to an equilibrium constant for displacement of $\text{N}\equiv\text{C}\text{Ar}_\text{F}$ from $[\text{Au}(\text{IPr})(\text{N}\equiv\text{C}\text{Ar}_\text{F})]^+[\text{SbF}_6]^-$ with **IV.3.** of $K_{\text{eq}} = \frac{[\text{IV.2.}][\text{N}\equiv\text{C}\text{Ar}_\text{F}]}{[\text{IV.3.}][[\text{Au}(\text{IPr})(\text{N}\equiv\text{C}\text{Ar}_\text{F})]^+[\text{SbF}_6]^-]} = 17.2 \pm 1.2$. This observation indicates that the binding affinity of the neutral gold σ -acetylide complex **IV.3.** to the $(\text{IPr})\text{Au}^+$ fragment *exceeds the bonding affinity of free phenylacetylene ($K_{\text{eq}} = 0.21$) by a factor of ~80*. This result provides very important information in gold chemistry. Once a gold acetylide is formed in a given reaction, its ability to bind any cationic gold salt still existing in the mixture is high. This could explained why gold acetylides are not so reactive as nucleophilic reagents in organic synthesis, and also suggests that gold acetylides can act as strong ligands for cationic salts and by the way preserve these rather unstable entities against decomposition. Likewise, the evaluation of the stability of **IV.2.** towards protodeauration, showed that σ,π -arylacetylene complexes, in contrast to their mononuclear precursors, are exceedingly stable under the reaction conditions. Indeed in the presence of 1 equivalent of the Brønsted super acid TfOH, **IV.2.** remained completely untouched, while reaction of **IV.3.** led to complete conversion affording back phenylacetylene after only 10 min at low temperature.

It is worth pointing out that during formation of **IV.2.**, 1 equivalent of a strong Brønsted acid is also generated, the effect of which on the reactivity of the ensuing reactions can be significant. Corma *et al.*²⁷⁵ have widely documented these influences. (**Table IV.1.**)

They were attracted by a previous report by Echavarren and co-workers on the [2+2] cycloaddition between terminal alkynes and 1,1-disubstituted alkenes catalyzed by catalyst **[A1]** and leading to trisubstituted cyclobutenes.²⁷⁶ These authors had noticed an important decomposition of the alkene component during the reaction course, which led them to resort to 30 equivalents of it to achieve this cycloaddition in high yield. The Corma group hypothesized that this deleterious effect would probably be caused by the strong Brønsted acid which is released concomitantly to the formation of the digold $[\sigma,\pi]$ -alkyne complex, and therefore initiated a study to prove this assumption. Their most significant results obtained

²⁷⁵ Grirrane A.; Garcia, H.; Corma, A. Alvarez, E. *ACS Catal.* **2011**, *1*, 1647.

²⁷⁶ Lopez-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292.

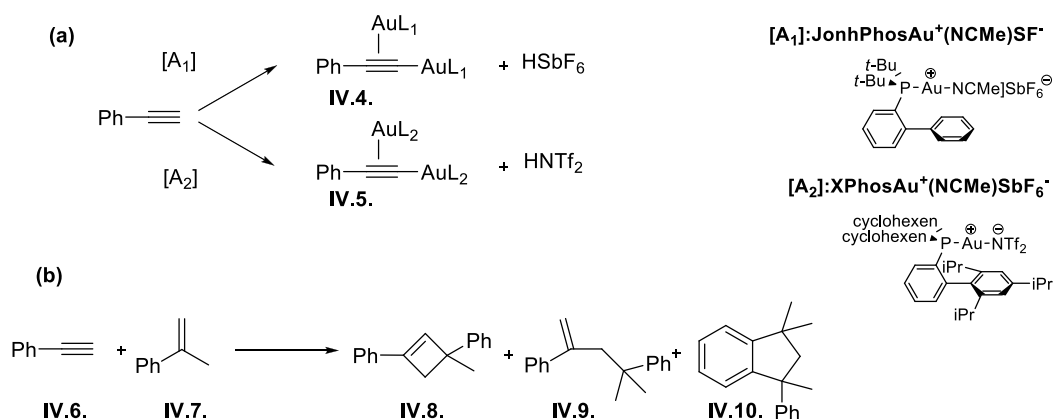
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from a set of reactions using an alkyne/alkene ratio of 1/2 are collected in **Table IV.1.** Entries 1 and 2 where reactions were carried out with ordinary well-defined catalysts [**A**₁] and [**A**₂] confirm the Echavarren's results: good conversions of the reactants, but low yields of the desired product **IV.8.** were seen.

Conversely and as anticipated by the authors, when the digold $[\sigma,\pi]$ -alkyne complexes **IV.4.** and **IV.5.** related to both [**A**₁] and [**A**₂] were isolated and used as catalysts, a much greater selectivity was achieved, with catalyst **IV.4.** exhibiting an excellent chemical efficiency relative to **IV.5.** (Entries 3-5). To provide a more conclusive evidence of the hypothesis, an experiment catalyzed by complex **IV.5.** in the presence of HSbF₆ was performed and the result almost matched that achieved starting with the parent complex [**A**₂]. (Entries 6 and 2)

It is also important to point out that complexes **IV.4.** and **IV.5.** are air-stable and their formation is favored even at high terminal alkyne/[**A**₁] ratios.

Table IV.1. Intermolecular [2+2] cyclization reaction



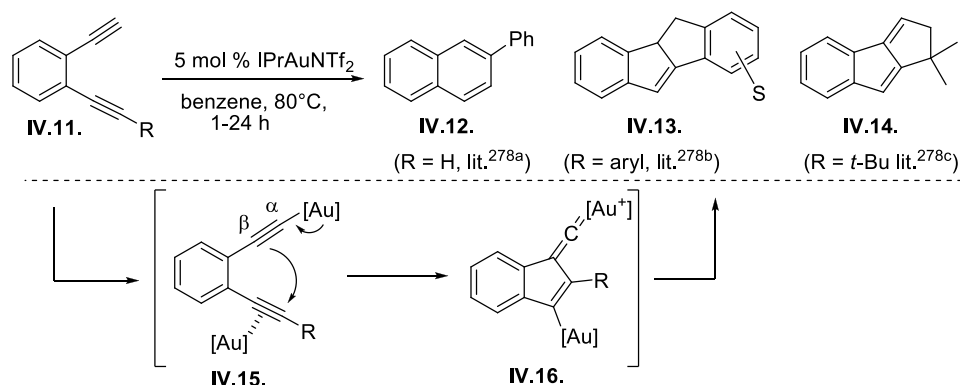
Entry	Catalyst (mol%)	Time [h]	Conv[%] IV.6.	Conv[%] ^c IV.7.	Conv[%] IV.8.	Yield[%] ^a IV.8.	Yield[%] ^a IV.9.	Yield[%] ^a IV.10.
1.	A ₁ (3)	23	82	96	52	43	33	2
2.	A ₂ (3)	24	88	94	26	23	36	
3.	IV.4. (3)	30	95	97 ^d	92	86	3	
4.	IV.4. (1.5)	26	82	58	90	75	7	
5.	IV.5. (1.4)	90	47	28	91	37	4	
6.	IV.5. (1.5) ^b +HSbF ₆ (4.3)	3	83	98	14	12	4	17

^a yields determined by using ¹H NMR spectroscopy and GC.; ^b The catalyst was a combination of Au(I) complex and HSbF₆; ^c alkyne:alkene molar ratio 1:2; ^d alkyne:alkene molar ratio 1:1

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The study by the Corma team has shown that the dinuclear gold σ,π -acetylene complexes can be applied as pre-catalysts in the most traditional type of gold-catalyzed transformations involving alkynes, *viz.* the nucleophilic attack to a π -activated alkyne to form a functionalized alkene. However, these independent contributions by Corma and Widenhoefer also suggest that some gold acetylide chemistry might be developed in the absence of an exogeneous base, an assumption which to some extent corroborates our own contribution recounted in this manuscript. This notion has been nicely proven by Hashmi and co-workers in recent studies.²⁷⁷

In a series of seminal papers these authors had investigated a fundamentally new mode of reactivity of *ortho*-dialkynylated arene substrates **IV.11**, wherein either one of the two alkyne motifs, or both, is terminal, which was catalyzed by ordinary well-defined cationic gold(I) salts.²⁷⁸ The catalysis is initiated with an intriguing dual activation mechanism without resorting to an extra base, wherein one terminal alkyne is activated under the form of a σ -gold acetylide, while the remaining alkyne (either terminal or internal) is π -activated in a traditional manner (see intermediate **IV.15**). The reaction evolves by unusual β -nucleophilic addition of the gold acetylide motif onto the π -activated alkynes. The mixed gold(I) vinylidene vinyl gold(I) system **IV.16**, that emanates from this intramolecular cyclization then evolves by different pathways depending on the substitution pattern of the substrate to give compounds **IV.12**, **IV.13**, or **IV.14**. (Scheme IV.3).



Scheme IV.3. Novel reactivity mode of aromatic *ortho*-diynes based on a dual activation mechanism catalyzed by cationic gold complex.

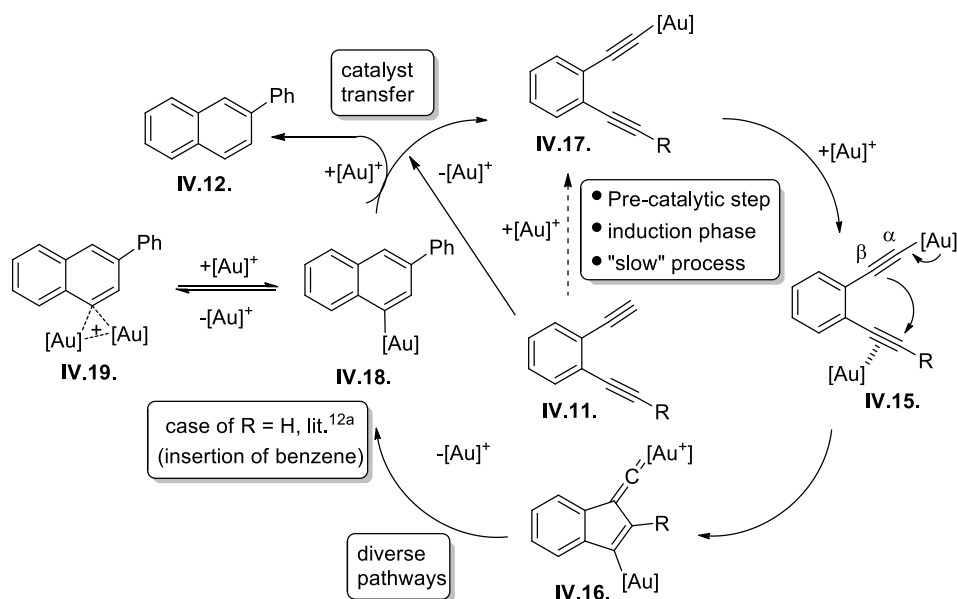
²⁷⁷ Hashmi, A. S. K.; Lauterbach, T.; Nösel, P.; Vilhelmsen, M. H.; Rudolph, M.; Rominger, F. *Chem. Eur. J.* **2013**, *19*, 1058.

²⁷⁸ (a) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644. (b) Hashmi, A. S. K.; Wietek, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555. (c) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wietek, M.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4456. (d) For a concurrent paper to the reference 9a), see: Wang, L. Ye, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31.

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During their detailed study on the mechanism of their reactions, these authors observed significant rate accelerations if an exogenous base (e.g. NEt_3) or an organogold compound (*viz.* PhAuNTf_2) were included as an additive. This led them first to question about the interesting aspect of catalyst transfer for re-initiating the catalytic cycle. In response to this, they could demonstrate that the reformation of the σ -activated substrate **IV.17.** (which precedes formation of **IV.15.** as depicted in **Scheme IV.4.**), takes place by the catalyst transfer from an organogold intermediate **IV.18.** onto a terminal alkyne of starting material **IV.11.** in a step that closes the catalytic cycle and reinitiate a dual-catalysis process. These information gained from the set of control experiments raised the important notion that a significant period of time is required before the gold acetylide **IV.17.** and free $[\text{LAu}^+\text{X}^-]$ are present in a ratio that is suitable for decent reaction rates (**Scheme IV.4.**)

In the meantime and very interestingly, the *geminal*-diaurated compounds **IV.19.**, which based on independent studies in different contexts²⁷⁹ were anticipated to be generated over the reaction course, were independently prepared from the stoichiometric reaction of a gold acetylide, for example **IV.17.**, and an activated catalyst $[\text{LAu}^+\text{X}^-]$, and evaluated as instant dual-activation catalyst.

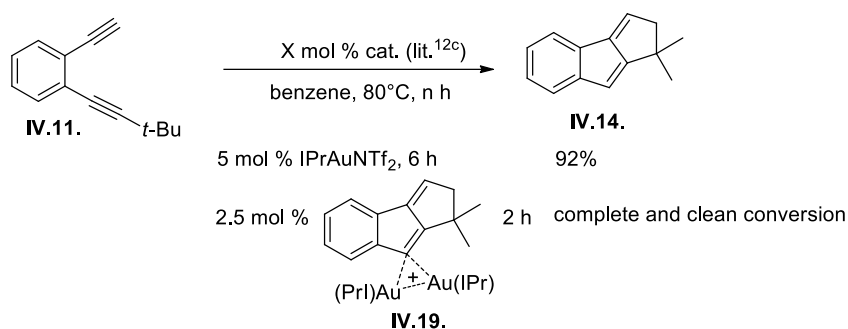


Scheme IV.4. Uniform catalytic cycle proposed for the different cyclizations of type **IV.11.** substrates

To determine whether the formation of compound **IV.19.** is only a dead end for the reaction and then exclusively responsible for catalyst consumption (catalyst resting state),

²⁷⁹ (a) Weber, D.; Tarselli, M. A.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 5733. (b) Weber, D.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 4962. (c) Seidel, G.; Lehmann, C. W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 8466. (d) Weber, D.; Jones, T. D.; Adduci, L. L.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 2452. (f) Brown, T. J.; Weber, D.; Gagné, M. R.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 9134.

catalytic amounts of *gem*-diaurated compounds **IV.19.** were added to diynes **IV.11.** wherein R = H and *t*-Bu in the absence of any additional catalyst. In all cases were these species shown to be an outstanding pre-catalyst for the two types of cyclization. By way of example, under the normal reaction conditions for the cyclization of **IV.11.** (R = *t*-Bu) a 2.5 mol % loading of **IV.19.** not only resulted in complete conversion of the starting material but the reaction was even three times faster than with the usual catalyst system (5 mol% [Au]⁺)^{278c} (**Scheme IV.5.**).



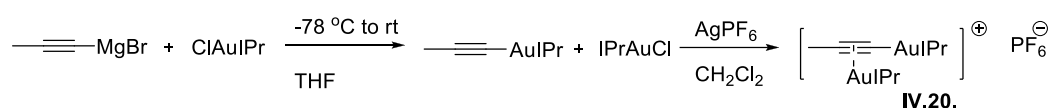
Scheme IV.5. Use of *gem*-diaurated complexes **IV.19.** as instant dual-activation pre-catalysts

This information provides significant insights into the catalytic cycle and the interesting question of catalyst transfer (**Scheme IV.4.**). Operating with the normal catalyst system [LAu⁺X⁻], the initial formation of the gold acetylide **IV.17.** from **IV.11.** is possible but slow, and only after a significant period of time are **IV.17.** and free [LAu⁺X⁻] present in a ratio that is suitable for decent reaction rates (through operating the generation of **IV.15.**). Compound **IV.19.**, on the other hand, is in direct equilibrium with two species needed for the catalyst transfer: [LAu⁺X⁻] and the vinyl monogold **IV.18.**..via [**IV.11.** + (**IV.18.** + [LAu⁺X⁻] → **IV.17.**) Providing both species in a well-defined 1:1 ratio makes complex of type **IV.19.** ideal *instant dual-activation pre-catalyst* (**Schemes IV.4.** and **IV.5.**). An underlying aspect of this analysis is that shifting the equilibrium depicted in Scheme **IV.4.** in the right side (by means of bulky ligands which impose huge steric constraints within **IV.19.**, and/or elevated temperature) is crucial not only for this type of reactions but also for other gold-catalyzed processes in which *gem*-diaurated species are involved. If this equilibrium is shifted in the left side then the catalyst rests and the reaction is slowed down, or even killed.

In the pursuit of these studies, and based on the mechanistic analysis of these reactions and the structural analogy of aromatic *gem*-diaurated complexes **IV.19.** with the Widenhoefer/Corma alkynyl counterparts **IV.4.- IV.5.**, Hashmi and his co-workers have

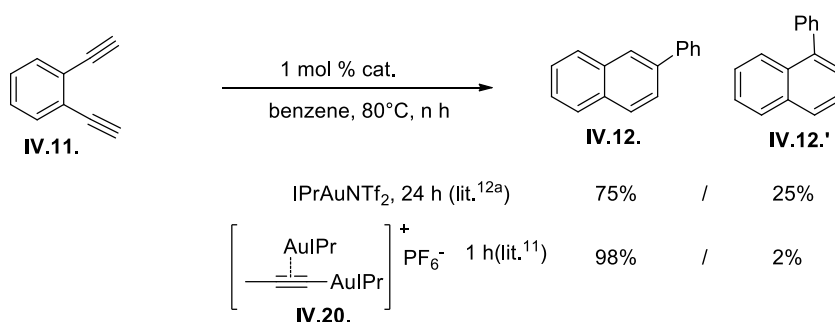
pondered that the latter could be *tailor-made dual instant pre-catalysts* for the cyclizations of substrates **IV.11.**²⁷⁷

In a first effort, they develop an alternative method for preparing the digold σ,π -acetylene complexes **IV.20.** in a fast fashion and without inconvenient by-products, by applying a very simple direct reaction of the readily available gold acetylide with commercially available IPrAuCl. After addition of the suitable silver salt, filtration over Celite and evaporation of the solvent, the compound is formed in high yield (**Scheme IV.6.**). It is also possible to first treat LAuCl with a suitable silver salt and then add the gold acetylide to this mixture. The method tolerates well different counterions, alkynyl substituents and ligands, provided the latter are sufficiently bulky (for example PPh₃ is excluded due to decomposition of the complex).



Scheme IV.6. Improved preparative method for digold σ,π -alkynyl complexes IV.20.

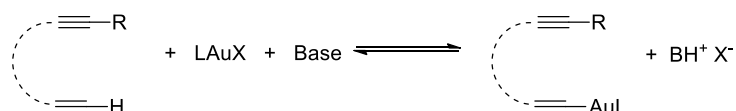
Then the catalytic ability of these dinuclear gold σ,π -acetylene complexes for the cyclization of diynes **IV.11.** was probed first with R = H. It was demonstrated that almost all of the complexes prepared can catalyze the reaction forming **IV.12.**, albeit with variable efficiencies. The PF₆⁻ salt derived from propyne (L = IPr) turned out to be a particularly efficient pre-catalyst that outperformed the well-defined gold salts for this reaction (**Scheme IV.7.**).



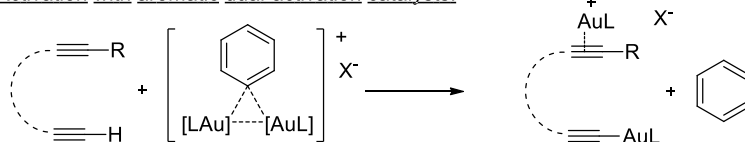
Scheme IV.7. Competency of IV.20. as traceless and instant dual-activation pre-catalyst

The superiority observed experimentally for the propyne digold derivatives over, for example, their arylacetylene counterparts, were anticipated by the authors on the fact that gaseous propyne is released, which provides an elegant traceless pre-catalytic system which, importantly, circumvents the possible equilibrium of the eq 3 in **Scheme IV.8.**

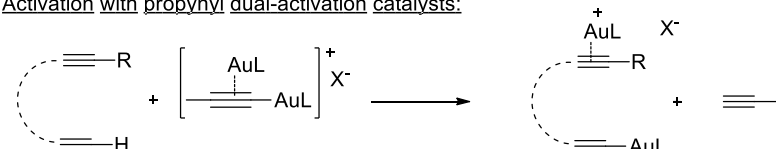
1) Activation under basic conditions:



2) Activation with aromatic dual-activation catalysts:

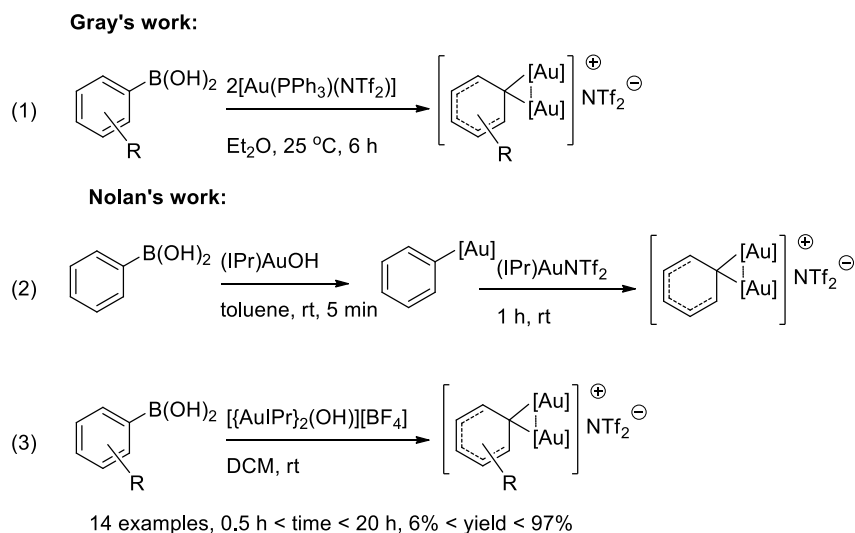


3) Activation with propynyl dual-activation catalysts:



Scheme IV.8. Overview of the different methods of activation of terminal alkynes in diyne compounds.

Recently, Nolan and co-workers²⁸⁰ have developed another straightforward methodology leading to *gem*-diaurated σ,π -acetylide species. At the outset, they notice that Gray *et al.*²⁸¹ had developed a methodology to *trans*-metalate arylboronic acids with $[\text{Au}(\text{PPh}_3)\text{Br}]$ using Cs_2CO_3 , which easily forms *gem*-diaurated gold complexes, but only few examples were described. (Scheme IV.9. eq 1). Thus, the Nolan's team decided to create an alternative methodology to synthesize a larger array of this type of species.



Scheme IV.9. Synthesis of *gem*-diaurated species by Nolan.

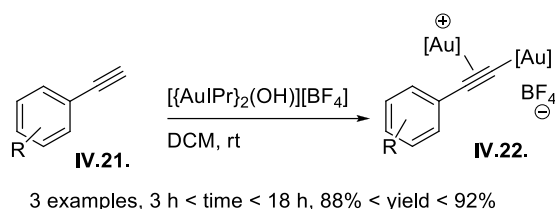
²⁸⁰ Gómez-Suárez, A.; Dupuy, S.; Slawin, A. M. Z.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 938.

²⁸¹ Partyka, D.V.; Zeller, M.; Hunter, A.D.; Gray, T.G. *Angew. Chem.* **2006**, *118*, 8368.

First, a two-steps protocol was developed *via* an extremely efficient formation of [Au(IPr)(phenyl)] catalyzed by the gold hydroxide reagent IPrAuOH previously developed in the Nolan's laboratory.²⁸² Then the addition of the complex [Au(IPr)(NTf₂)] initiates formation of *gem*-diaurated species in nearly quantitative yields after short reaction time. (**Scheme IV.9. eq 2**) Following this encouraging result, next a single-step single-catalyst approach to these *gem*-diaurated gold complexes was developed using a previously reported and very reactive digold hydroxide complex [{Au-(IPr)}₂(μ-OH)][BF₄].²⁸³ (**Scheme IV.9. eq 3**)

After the optimization study the scope of the reaction was extended to a variety of boronic acids. In most cases, the desired products were synthesized in excellent yields. Nevertheless, the reaction of phenylboronic acids with electron-withdrawing and electron-donating groups at the *para* position required longer reaction times to reach completion. Additionally, a drastic effect of the *ortho* position was observed. Substrates with EWGs at the *ortho* position were converted much faster than those with EDGs which needed a longer reaction time.²⁸⁰

In a second phase of this study the method was extended to the preparation of σ,π-activated alkyne complexes. In this variant the gold complex [{AuIPr}₂(OH)][BF₄] again appeared to be the best and also in this case the expected salts were formed in good yields. (**Scheme IV.10.**)²⁸⁰



Scheme IV.10. Application of the Nolan method to the efficient preparation of σ,π-acetylide species.

²⁸² Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2010**, 2742.

²⁸³ (a) Gaillard, S.; Bosson, J.; Ramón, R. S.; Nun, P.; Slawin, A. M. Z.; Nolan, S. P. *Chem.-Eur. J.* **2010**, *16*, 13729; (b) Ramón, R. S.; Gaillard, S.; Poater, A.; Cavallo, L.; Slawin, A. M. Z.; Nolan, S. P. *Chem.-Eur. J.* **2011**, *17*, 1238.

IV.1.2. APPLICATIONS OF CATIONIC GOLD(I)-ALKYNES INTERMEDIATES BEYOND THE A³ COUPLINGS AND ADDITIONS TO IMINES

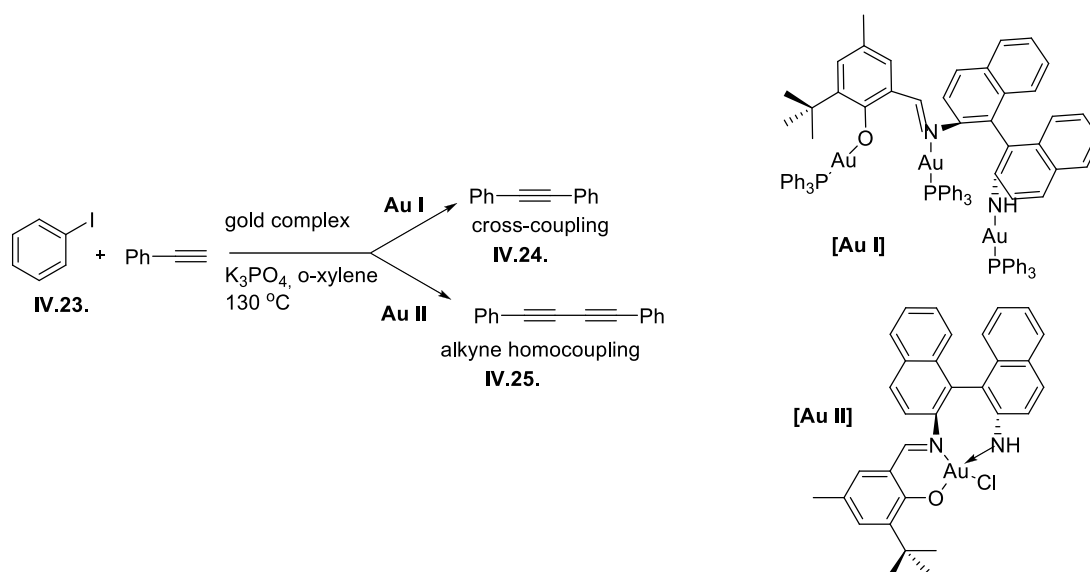
The use of gold complexes such as σ - or σ,π -acetylide in homogeneous catalysis has undergone significant progress quite recently and thus this section will be devoted to some carbon-carbon bond forming reactions which were not covered in Chapter III. One of the most studied of such reactions are with no doubt coupling type reactions, and notably the Sonogashira reaction. The most common catalytic system for the Sonogashira reaction includes $[\text{PdCl}_2(\text{PPh}_3)_2]$, $\text{PdCl}_2/\text{PPh}_3$ and $[\text{Pd}(\text{PPh}_3)_4]$ together with co-catalyst, CuI , and large excess of amines as a solvent or co-solvent.²⁸⁴

Since gold has been successful for performing the same role as palladium in new carbon-carbon bond formation in the Suzuki-Miyaura condensation²⁸⁵ and gold(I) has the same d^{10} electronic structure as Cu(I) , easy and proper interaction with the acetylenic group was expected in the Cu -free Sonogashira cross-coupling reaction.^{276,286} During the course of their investigation, Corma and co-workers have prepared new gold(I) and gold(III) catalysts derived from 1,1-binaphthyl-2,2-diamine and appended to Schiff base ligands [**Au I**] and [**Au II**]. (**Scheme IV.11.**) As the mild base K_3PO_4 , was elected to be the best. In the case of [**Au I**] moderate to excellent yields with good selectivities for the cross-coupling Sonogashira reaction were obtained while the reaction catalyzed by [**Au II**] complex afforded the desired product in lower yield. The difference in reactivity was explained by the fact that Au(I) is able to selectively catalyze the cross coupling reaction while Au(III) complexes is more specific for the alkyne homocoupling. (**Scheme IV.11.**)

²⁸⁴ Gonzalez-Arellano, C.; Corma, A.; Garcia, H.; Iglesias, M.; Sanchez, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1536.

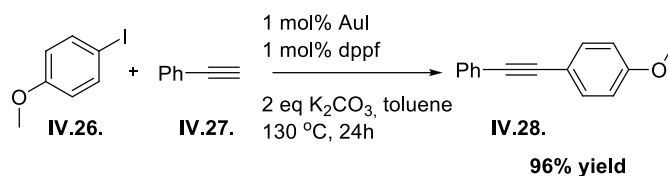
²⁸⁵ Gonzalez-Arellano, C.; Corma, A.; Iglesias, M.; Sanchez, F. *J. Catal.* **2006**, *238*, 497.

²⁸⁶ Ngassa, F. N.; Gomez, J. M.; Haines, B. E.; Ostach, M. J.; Hector, J. W.; Hoogenboom, L. J.; Page, Ch. E. *Tetrahedron* **2010**, *66*, 7919.



Scheme IV.11. Gold catalyzed Sonogashira reaction.

Wang *et al.*²⁸⁷ have also tested gold catalysts in the Sonogashira coupling reaction. (Scheme IV.12.) As model reaction partners phenylacetylene IV.27. and 1-iodo-4-methoxybenzene IV.26. were chosen and it was found that use of AuI with 1,1'-bis(diphenylphosphanyl)ferrocene (dppf) proved to be the best catalyst system, with excellent results obtained with only 1 mol % of loading. Noteworthy, the nature of the solvent appeared to be critical, with toluene being the solvent of choice and polar ones such as DMF, DMSO being ineffective.



Scheme IV.12. The Sonogashira coupling reaction catalyzed by AuI and dppf ligand.

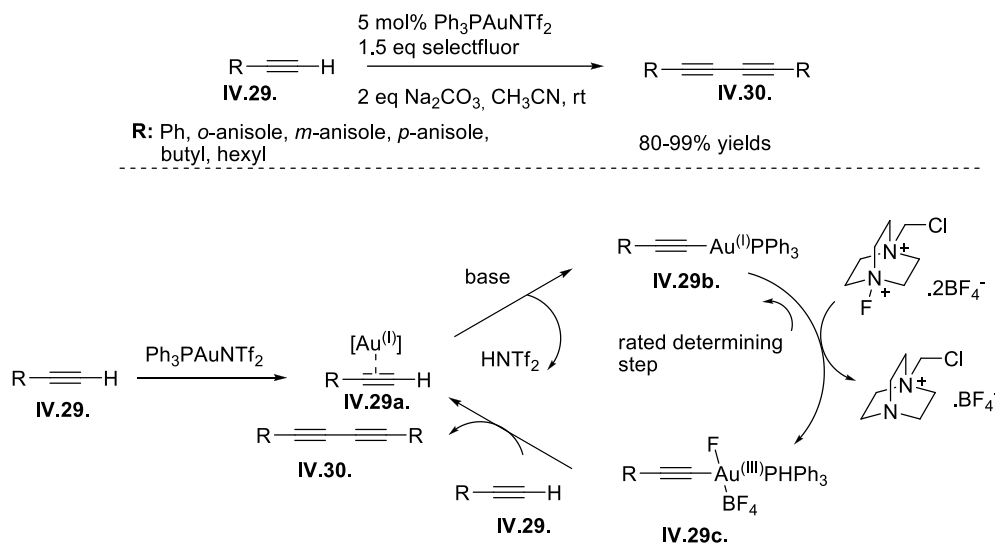
Furthermore, when the molar ratio of dppf to Au^I was less than 1:1, the reaction was not complete, while ratios equal to or greater than 1:1 gave satisfactory results. The effect of the base on the coupling reaction was also investigated and K₂CO₃ was found to be the most efficient.

The homocoupling reactions were also investigated. One of the most famous example is by Corma and co-workers²⁸⁸ where phenylacetylene was tested. During the investigation it was found that *in situ* oxidation of Au(I) to Au(III) by F⁺ in an homogeneous system could facilitate the C-C dimerization of alkynes under gold catalysis (Ph₃PAuNTf₂). Additionally, it

²⁸⁷ Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008**, 5946.

²⁸⁸ Leyva-Pérez, A.; Doménech, A.; Al-Resayes, S.I.; Corma, A. *ASC Catal* **2012**, 2, 121.

appeared that the oxidant or base is needed in a medium unless selectfluor is added in a stoichiometric amount. (**Scheme IV.13.**)

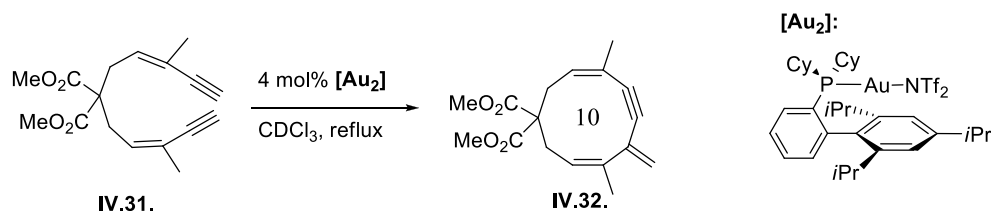


Scheme IV.13. The homocoupling reaction.

After substrate screening it was found that the rate towards product formation is higher when the reaction starts from the gold-acetylide rather than its terminal alkyne.

According to the proposed mechanism, after π -coordination of acetylene by gold(I) complex, gold(I)-acetylide **IV.29b.** is formed (by using a base) which next is oxidized by selectfluor to gold(III)-acetylide **IV.29c.** As soon as is formed, it reacts with a second molecule of gold(I)-acetylide to give the desired product. (**Scheme IV.13.**)

Gagosz and co-workers²⁸⁹ have also presented the gold-catalyzed alkyne-alkyne coupling of a series of 1,9- and 1,10-diynes and it was proved that this type of highly unsaturated compound can be efficiently cycloisomerised into medium sized cycloalkynes by using 4 mol% of catalyst **[Au₂]** in CDCl₃ solution at reflux. (**Scheme IV.14.**)

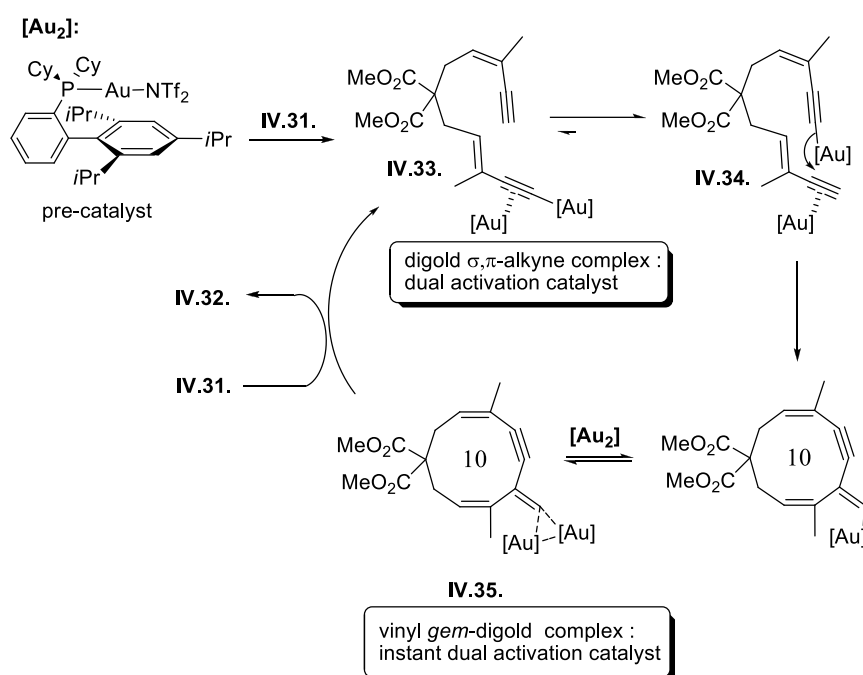


Scheme IV.14. The cycloisomerization of diynes.

The mechanistic proposal considers formation of a single gold-acetylide motif, which further attacks in a Grignard type reactivity the second alkyne, which is electrophilically π -activated by gold in a traditional fashion. This induces the formation of a vinyl-gold unit,

²⁸⁹ Odabachian, Y.; Le Goff, X.-F.; Gagosz, F. *Chem. Eur. J.* **2009**, *15*, 8966.

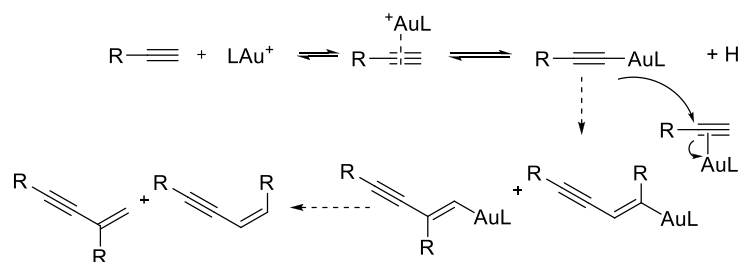
which loses one cationic gold species after protodemetalation by a protic source from the reaction medium to produce the final product and re-initiate catalytic turn-over. This work has been published in 2009, *i.e.* 3 years before the Hashmi study discussed previously (see **Schemes IV.3. to IV.8.**). In retrospect and based on the advances emphasized by Hashmi, it is likely that a more complex mechanism, based on a dual activation pathway (see species **IV.34.**) and possibly benefiting from the instant dual activation ability exerted by an *in situ* formed *gem*-diaurated complexes (see **IV.35.**), be occurring here as well. (**Schemes IV.15.**) The difference lies in the fact that in the present case the geometry of the digold intermediate **IV.34.**) is well suited for the ordinary Grignard type (versus β -carbon addition mode in the Hashmi case²⁷⁸) reactivity of the σ -gold acetylide.



Scheme IV.15. The Gagosz cycloisomerization of diynes: our mechanism proposal

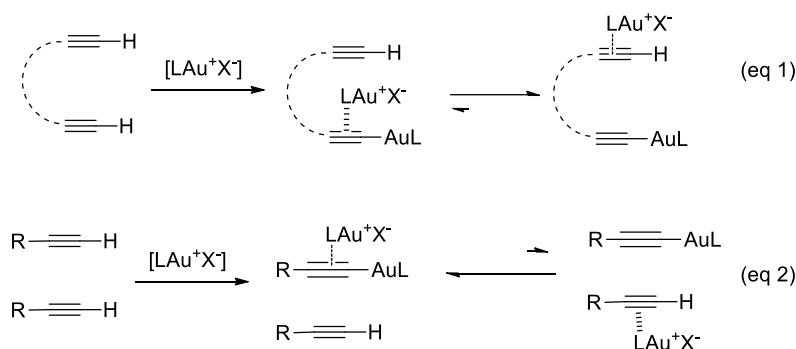
Related to the above Gagosz reaction, the gold(I)-catalyzed regioselective homodimerization of aliphatic terminal alkynes has also been reported by Zhang *et al.*²⁹⁰ who have shown that gold-alkynes formed *in situ* might act as a nucleophile to attack its precursor in a bi-molecular reaction affording enynes. (**Scheme IV.16.**)

²⁹⁰ Sun, S.; Kroll, J.; Luo, Y.; Zhang, L. *Synlett*, **2012**, 54.



Scheme IV.16. The gold catalyzed homodimerization reaction.

After optimization study it was found that bulky and less Lewis acidic *t*-BuXPhosAuNTf₂ in toluene solution at reflux provided the best catalyst system. Furthermore, addition of a base, NaOAc, avoided decomposition and thus increased the yield. The greater success of an heterogeneous base over organo-soluble amino bases here possibly contributes to prevent catalyst inhibition by nucleophilic attack of the base to the gold center, which is expected when amines are used.^{278a} It is then believed that NaOAc simply acts as a base, by deprotonating the π -gold complex or trapping any Brønsted superacid Tf₂NH released during the process (that might cause side-reactions), to form a weak organo-acid AcOH. Overall, the necessity to use an exogeneous base here points out that the ability of diaurated σ,π -alkynyl complexes to initiate gold acetylide chemistry is much more favoured in intramolecular (eq 1)^{278,289} than for intermolecular processes (eq 2), what is thermodynamically expected. (**Scheme IV.17.**)

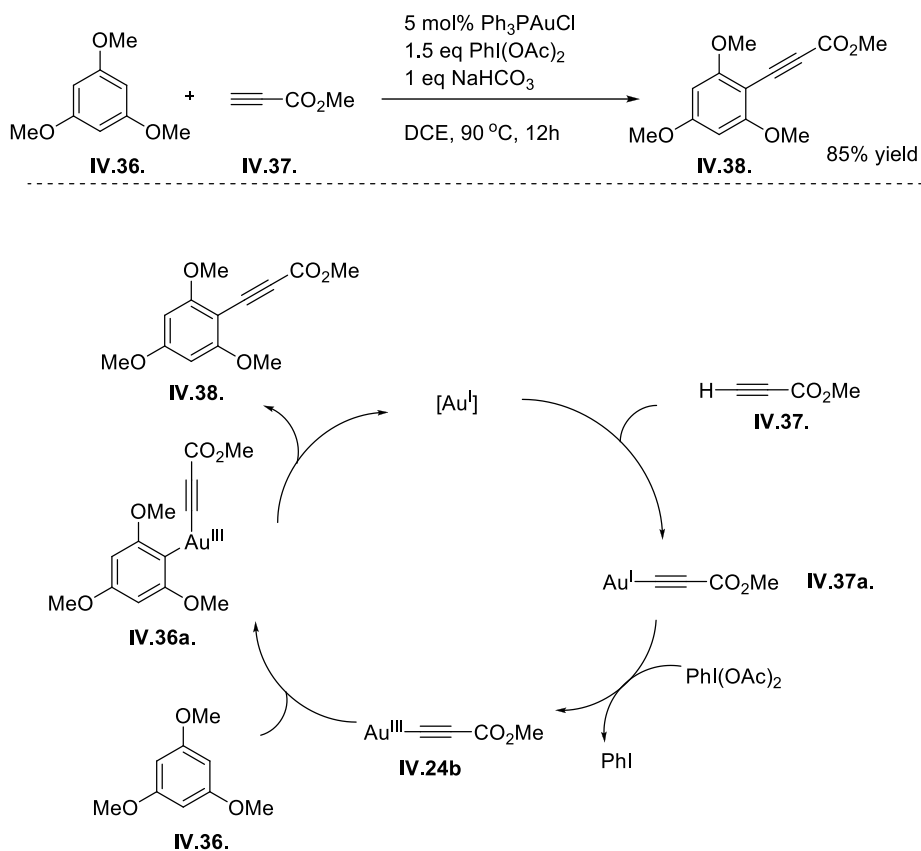


Scheme IV.17. Intramolecular *versus* intermolecular dual activation gold catalysis on alkynes.

In 2010, Nevado and de Haro²⁹¹ have reported the direct alkynylation of arenes starting from terminal alkynes. In their procedure a double C-H activation was observed which achieves the ethynylation of electron-rich arenes with electron-poor alkynes to provide aryl propiolate products in good yields. (**Scheme IV. 18.**) The proposition of the mechanism starts with C_{sp}-H activation to give gold (I)-acetylide **IV.24a**, which then oxidized in the presence of PhI(OAc)₂, to generate the gold (III)-alkynyl **IV.24b**. Finally, after the well known C_{sp2}-H

²⁹¹ De Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512.

by the gold (III)-reagent,²⁹² activation and reductive elimination, the alkynylated product was afforded. (Scheme IV.18.)



Scheme IV.18. Gold(I)-catalyzed ethynylation of IV.36.

IV.2. RESULTS: MECHANISTIC STUDY FOR THE ALKINYLIATION REACTION

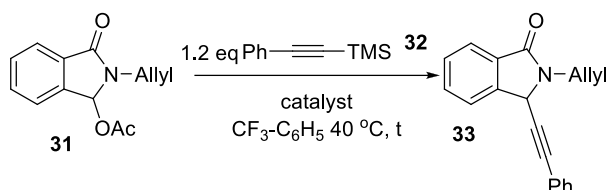
IV.2.1. INVESTIGATING THE ROLE OF THE Ph-C≡C-AuL

In order to ascertain our mechanistic postulate or to gain insights into some potential alternative mechanisms for this alkylation, we have decided to synthesize several gold acetylides of the general formula Ph-C≡C-AuL and then to evaluate their catalytic influence on the reactivity in our test benchmark reaction with 2-allyl-3-oxoisindolin-1-yl acetate **31** and trimethyl(phenylethynyl)silane **32**. (Table IV.2.)

²⁹² (a) For two reviews : (a) Skouta, R.; Li, C. J. *Tetrahedron* **2008**, *64*, 4917; (b) Hashmi, A. S. K.; Salathé, R.; Frost, T. M.; Schwarz, L.; Choi, J.-H. *Applied Catalysis A: General* **2005**, *291*, 238. (c) Shi, Z.; He, C. J. *Org. Chem.* **2004**, *69*, 3669.

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Table IV.2. Testing the influence of Ph-C≡C-AuPPh₃ on the model reaction.

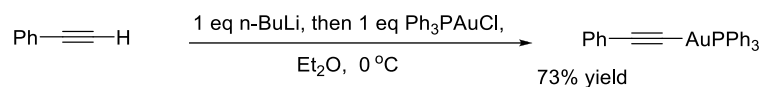


Reaction	Catalyst [mol%]	Time	Conv[%]
1.	TMSOTf[3]	5h	34
2.	TMSOTf[3] with Ph-C≡C-AuPPh ₃ [3]	15 min	100
3.	TIPSOTf[3]	2days	59
4.	TIPSOTf[3] with Ph-C≡C-AuPPh ₃ [3]	15 min	100
5.	Sc(OTf) ₃ [3]	2 days	8
6.	Sc(OTf) ₃ [3] with Ph-C≡C-AuPPh ₃ [3]	4h	100
7.	Bi(OTf) ₃ [3]	15 min	6
8.	Bi(OTf) ₃ [3] Ph-C≡C-AuPPh ₃ [3]	15 min	100
9.	TIPSOTf[3] with Ph-C≡C-AuP ^t Bu ₃ [3]	15 min	100
10.	Ph-AuPPh ₃ [3] with TMSOTf [3]	15 min	100
11.	Ph ₃ PAu OTf [3] with Ph-C≡C-AuPPh ₃ [3]	5h	100

We have started our investigation by testing Ph-C≡C-TMS as a nucleophile in the reaction catalyzed by the Lewis acid TMSOTf, which we expected to form *in situ* under standard conditions. (**Table IV.2.** Entry 1) The reaction was monitored by ¹H NMR spectroscopy and, after 5 hours only 34% of the acetoxy lactam has undergone conversion into the expected product. Compared with the optimal reaction catalyzed by 3 mol% Ph₃PAuOTf, this result tends to confirm that the silylalkyne is a weak nucleophile which does not attack the *N*-acyliminium ion intermediate in an efficient manner. Thus, we decided to recreate the conditions postulated in our working model, by subjecting a solution of *N,O*-acetal and the TMS-alkyne to a mixture of 3 mol% each TMSOTf and Ph-C≡C-AuPPh₃, which both are postulated to be generated *in situ* and in a concomitant fashion through aurodesilylation of the TMS alkyne by the gold pre-catalyst. In this aim the gold-acetylide was synthesized first, in

CHAPTER IV: Preliminary mechanistic study

an easy stoichiometric reaction between phenylacetylene and Ph_3PAuCl mediated with *n*-butyllithium (**Scheme IV.19.**) and then used in the control experiment.



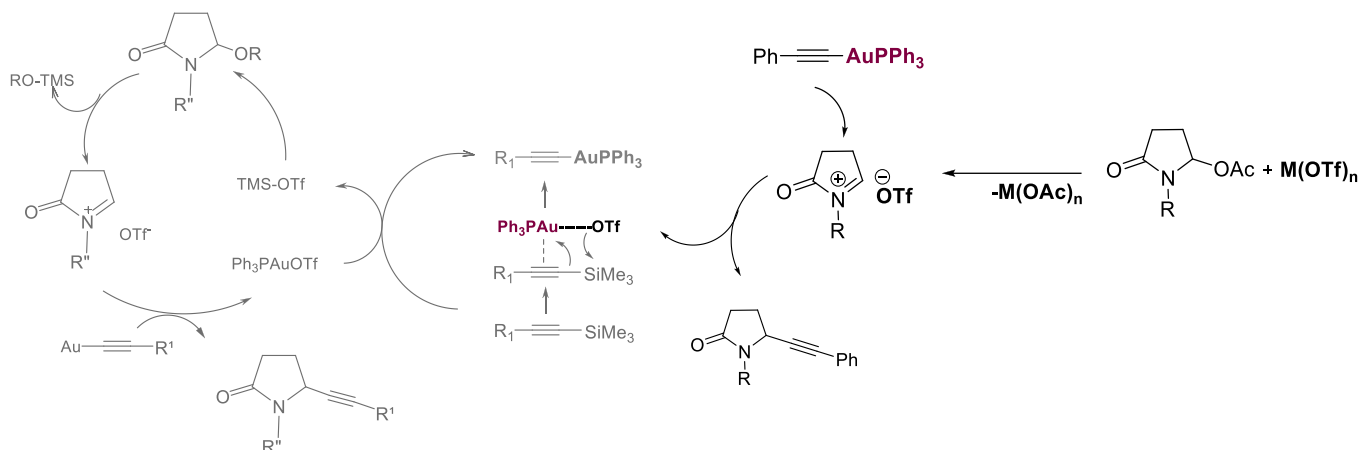
Scheme IV.19. General procedure for the formation of gold-acetylide.

As it is presented in entry 2., a huge effect of $\text{Ph}-\text{C}\equiv\text{C}-\text{AuPPh}_3$ on the reactivity was observed, which strongly supports the hypothetical mechanism. Indeed, to our delight and as anticipated, we restored the high reactivity exhibited in our optimized synergistic reaction procedure (see chapter III, **Table III.14.**). Substrate **31** was transformed in a *clean, efficient and quantitative process into alkynylated product 33 in only 15 minutes*. This result strongly corroborates our working mechanistic hypothesis that the critical formation of two synergistic gold(I) / silyl species are required for the efficient alkynylation of *N,O*-acetals.

We have also tested a more stable Lewis acid, TIPSOTf, as an alternative for the volatile and air- and moisture-sensitive TMSOTf²⁹³ and to our delight, the same effect was noted. (entry 3.) This set of results supports the notion that when the *N*-acyliminium ion intermediate is formed (by using the TMSOTf or TIPSOTf reagent) it is immediately trapped by $\text{Ph}-\text{C}\equiv\text{C}-\text{AuPPh}_3$, then releasing the product smoothly with concomitant regeneration of the gold catalyst Ph_3PAuOTf generated.

Based on these results, next we decided to test non-silylated metal triflate salts, exemplified by $\text{Sc}(\text{OTf})_3$ and $\text{Bi}(\text{OTf})_3$ in order to delineate the applicability to this synergistic Lewis acid/gold catalysis and hopefully expand its scope beyond silylium catalysis. It was observed that, in both cases, addition of the gold-acetylide favorably affects the reactivity (entry 5. *versus* entry 6. and entry 7. *versus* entry 8.). We believe that in those cases, the *N*-acyliminium ion intermediate is initially generated catalytically through ionization of the *N,O*-acetal by the metal triflate reagent and then, after nucleophilic attack of $\text{Ph}-\text{C}\equiv\text{C}-\text{AuPPh}_3$ an equimolar mixture of the final product and Ph_3PAuOTf were formed (**Scheme IV.20.**). Ph_3PAuOTf can then promote the reaction according to our hypothetical mechanism. Accordingly, both $\text{Sc}(\text{OTf})_3$ and $\text{Bi}(\text{OTf})_3$ might then simply be considered as pre-catalysts; however, it is also conceivable that these Lewis acids persist in the reaction mixture and therefore participate, in support to the *in situ* generated TMSOTf, to the ionization of the *N,O*-acetal substrates, then resulting in a very efficient catalytic system.

²⁹³ More details about these two types of catalysts have been already described in Chapter I



Scheme IV.20. Proposition of the mechanism for the alkylation reaction catalyzed by Lewis acid and gold-acetylide.

Our next goal was to check the influence of the ligand on the gold-acetylide. We selected $P(tBu)_3$ because its use as a ligand for the gold(I) triflate catalyst gave poor performance in our model reaction under the standard condition, with only 48% conversion of the starting material to the product observed after 5.5h (see Table III.12. in Chapter III.). As a tentative explanation for this rather inefficient alkylation, we suspected that the high bulkiness of the ligand makes the aurodesilylation event (*i.e.* formation of the gold-acetylide) more difficult and consequently decreases reactivity.

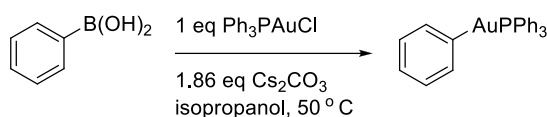
The equal success previously observed when using either $Ph_3PAuOTf$ as a single catalyst or a combination of a Lewis acid and $Ph-C\equiv C-AuPPh_3$ as a dual catalytic system (entries 2, 4, 6, 8) tends to support our mechanism design.

With these considerations in mind, a sluggish reaction was expected when using a mixture of a silyl triflate and $Ph-C\equiv C-AuP(tBu)_3$ as a dual catalyst system. Much to our surprise, the reaction with TIPSOTf and $Ph-C\equiv C-AuP(tBu)_3$, however, proceeded extremely well to give the desired product with the optimal reactivity, *i.e.* quantitative reaction within 15 min. (Entry 9.) Under the assumption that a prompt trapping of the *N*-acyliminium ion by $Ph-C\equiv C-AuP(tBu)_3$ would regenerate $(tBu)_3PAuOTf$ which is a poor catalyst, the high efficacy observed for the coupling in entry 9 clearly points to the fact that an alternative mechanism to the one originally designed might be operating in our reaction. We indeed speculated that $Ph-C\equiv C-AuP(tBu)_3$ **might act as a Lewis base co-catalyst** activating either the silylalkyne nucleophile or the Lewis acid rather than (exclusively) serving the role of a nucleophile as originally assumed. This picture suggests that, in contrast to our initial expectation, TMS-alkyne could be the active nucleophilic component, and that the gold-acetylide entity would persist all along the process. It is worth mentioning that such a mechanism proposal might be

not restricted to the specific case of Ph-C≡C-AuP(*t*Bu)₃ but could also be effective for any R-C≡C-AuL involved.

The contribution of such an original and somewhat unanticipated mechanism is reminiscent to both the relativistic effects exhibited by gold(I) salts²⁹⁴. More importantly, this mechanistic analysis suggests that co-catalytic amounts of any organogold additives might be competent in effecting the alkylation with high rate and efficiency. To test this possibility we set up the reaction using a combination of Ph-AuPPh₃ and TMSOTf. (Entry 10.)

The Aryl-gold species was first synthesized from phenylboronic acid following known procedures,²⁹⁵ as presented on **Scheme IV.21**.



Scheme IV.21. Synthesis of Ph-AuPPh₃.

As anticipated and delightfully, this dual co-catalytic system displayed an optimal catalytic activity, which is strongly supportive to the following hypothesis: a variety of organogold entities of the general formula RAuL is likely to be capable of acting as a Lewis base towards a silyl (or metal) triflate salt. This interaction causes an enhancement of the Lewis acidity of the triflate reagent through the well known hypervalent effect²⁹⁶, that results in a more efficient ionization of the *N,O*-acetal, and ultimately facilitates alkylation of the incipient *N*-acyliminium ion by the weakly nucleophilic TMS-alkyne (and/or by a proportion of free gold acetylide in solution). As mentioned above, an alternative and possibly competing mechanism could involve enhancement of the nucleophilic properties of the alkynyl silane through creation of a gold acetylide-TMS alkyne hypervalent silicate complex.

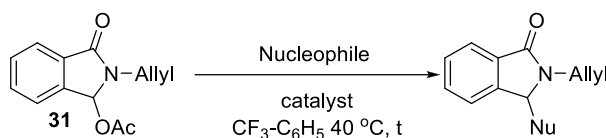
At this stage, an effort to expand the scope of this dual silyl/gold catalysis concept beyond the alkylation reaction was undertaken, by attempting related arylation and vinylation processes. Using a combination of vinyl trimethylsilane (2 equiv), PhC≡CAuPPh₃ and TMSOTf (3 mol% each) failed to produce the desired coupling product. (**Table IV.3**, entry 1.) The vinylation reaction was also unproductive under the standard protocol employing 3 mol% of Ph₃PAuOTf as precatalyst. (entry 2.) Similarly, an analogous arylation strategy using Ph-TMS (1.2 equiv) and Ph₃PAuOTf (3 mol%) also met with failure. (entry 3.)

²⁹⁴ Gorin, D.; Toste, F.D. *Nature*, **2007**, *446*, 395.

²⁹⁵ Stephen, A.; Hashmi, K.; Ramamurthi, T.D.; Rominger, F. *J. Organomet. Chem.* **2009**, *4*, 592.

²⁹⁶ (a) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391 (b) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727.

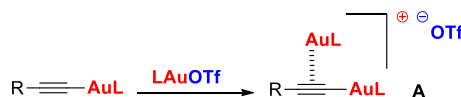
Table IV.3. The arylation and vinylation reaction of *N,O*-acetal **31** using the dual silyl/gold catalysis.



Reaction	Nucleophile [eq]	Catalyst [mol%]	Time	Conversion[%]
1.	164 [2]	TMSOTf[3] with Ph-C≡C-AuPPh ₃ [3]	6h	No reaction
2.	164 [1.2]	Ph ₃ PAuOTf [3]	3h	No reaction
3.	Ph-TMS 165 [1.2]	Ph ₃ PAuOTf [3]	3.5h	No reaction

This set of results sets the current limitation of our dual gold-silyl synergistic catalysis concept. Indeed, at least as far as *N,O*-acetals are considered as cation precursors, silicon-based reagents displaying nucleophilicities below that of trialkylsilylalkynes are seemingly not tolerated. Future work will aim at expanding the current dual catalysis concept beyond the alkylation reaction, through investigation of the arylation and vinylation of more reactive electrophilic substrates (*i.e.* some which are prone to faster ionization than *N,O*-acetals), such as for example highly π -activated alcohols.²⁹⁷

We have also tested Ph₃PAuOTf in combination with Ph-C≡C-AuPPh₃ as a dual catalytic system for our reaction. (**Table IV.2.** Entry 11.) According to the recent contributions of Hashmi,²⁷⁷ Widenhoefer,²⁷³ Corma,²⁷⁵ and Nolan²⁸⁰ previously discussed in this chapter, σ,π -digold complexes **A** are expected to be readily formed *in situ* under the conditions of entry 11 (**Scheme IV.22.**).



Scheme IV.22. Method of formation of σ,π -digold complexes **A**.²⁷⁷

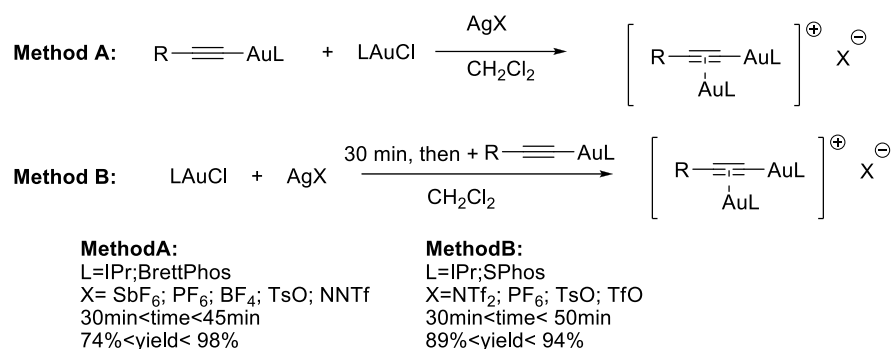
In some instances and as already commented in this chapter, such types of σ,π -digold complexes have been shown to act as an efficient pre-catalyst for certain synthetic transformations (**Table IV.1** and **Scheme IV.7.**),^{275,277} whilst in other circumstances they were not capable to mediate a synthetic transformation that had otherwise proven successful under guidance of regular gold(I) salts.²⁹⁸ On the basis of these puzzling results, we judged interesting to evaluate the ability of the catalytic combination of Ph₃PAuOTf and Ph-C≡C-

²⁹⁷ (a) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruziello, D.; De Viscentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647. (b) Jacobsen *J. Am. Chem. Soc.* **2008**, *130*, 7198. (c) Maity, P.; Srinivas, H.D.; Watson M.P. *J. Am. Chem. Soc.* **2011**, *133*, 17142.

²⁹⁸ Obradors, C.; Echavarren A.M. *Chem. Eur. J.* **2013**, *19*, 3547.

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AuPPh₃. As it has been already discussed, a series of air-stable σ,π -digold complexes were prepared and isolated as silver-free catalysts in their activated form. Two different protocols were mainly applied.²⁷⁷ (**Schemes IV.6 and IV.23.**)



Scheme IV.23. Method of preparation of σ,π -digold complexes.²⁷⁷

The most straightforward method is the direct reaction of the gold-acetylide with LAuCl compound. (**Scheme IV.23., Method A**) After addition of silver salt and filtration over Celite the desired complex can be easily isolated. This process delivers high yields of complexes for all the counterions evaluated. Alternatively, the process can be sequential; first, the pre-activation of gold chloride and silver salt takes place and then the gold acetylide is added to the reaction mixture. (**Scheme IV.23. Method B**) This way is particularly well suited for the triflimide and triflate anions²⁷⁷ and thus we decided to use it in our case.

Based on those all informations, we decided to tested Ph₃PAuOTf in combination with Ph-C≡C-AuPPh₃ as a dual catalytic system for our model reaction. (**Table IV.2.** entry 11.) 100% conversion of the starting material into the expected product was observed, however, 5h was required to reach completion, whilst the reaction took place within only 15 minutes when the combination R₃SiOTf/Ph-C≡C-AuPPh₃ was applied (**Table IV.2.** entries 2 and 4). In a general view, this experiment further reinforces the dual silyl/gold catalysis concept. It is expected from the Widenhoefer's contribution that the putative and stable σ,π -digold complex **A** forms promptly in the conditions of entry 11, thus causing sequestration of Ph₃PAuOTf due to the much stronger coordinating ability of Ph-C≡C-AuPPh₃ in comparison to TMS-alkynes (see **Scheme IV.2.** and comments thereof). This causes significant lowering of the population of the catalytically active dual combination TMSOTf/ Ph-C≡C-AuPPh₃, which explains the dramatic reduction of the kinetic observed. It would have been of interest to synthesize a σ,π -digold alkyne complex **A** and evaluate its catalytic capability in the model reaction, but this could not be done due to time limitation.

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To conclude this part of the project, Ph-C≡C-AuPPh₃ was efficiently synthesized using a well-established protocol and then tested under different conditions. Under the assumption that our standard alkynylation coupling does proceed through our speculative mechanism manifold, a set of conditions were carefully selected that were aimed at mimicking situations assumed to be occurring in the standard reaction medium, notably in terms of the identity of mixtures of catalytically active species likely to be involved. Overall, the objective of this set of mechanistic experiments was to verify whether a gold-acetylide could be generated *in situ* or not in our standard reaction protocol, and if so, to clearly define its role.

Our initial set of results proved that in its absence the model reaction is poorly efficient (entries 1 *versus* 2), thereby supporting the line that it may react as a nucleophile to trap the *N*-acyliminium ion. However, complementary investigations depicted in entries 9-10 suggested the possible involvement of an alternative mechanism for the reaction. We indeed speculated that Ph-C≡C-AuL might act as a Lewis base co-catalyst activating either the silylalkyne nucleophile or the Lewis acid, possibly through establishment of hypervalent silicate intermediates, rather than (exclusively) serving the role of a nucleophile as originally assumed. This picture suggests, in contrast to our initial expectation, that TMS-alkyne could be an active nucleophilic component, and that the gold acetylide entity would persist all along the process.

The result collected in entry 11 is also informative; it shows that the application of reaction conditions assumed to favor formation of a σ,π -digold complex leads to a net decrease of the reaction kinetic. This outcome might explain the differences of kinetics observed for certain transformations across our exemplification of this alkynylation reaction, which indeed might be correlated to the efficacy of the aurodesilylation event – in the specific case where the aurodesilylation would hardly proceed, not only the key gold acetylide/TMSOTf combination is poorly populated, but also sequestration of the residual Ph₃PAuOTf pre-catalyst by gold acetylide through generation of a σ,π -digold complex is possible, thereby provoking a net decrease of the reaction kinetic. On the basis of these grounds, additional studies aimed at gaining analytical data and characterizing the key active entities will be discussed in a next Chapter IV.2.3.

IV.2.2. TESTING THE Ph-C≡C-AuL AS A NUCLEOPHILE

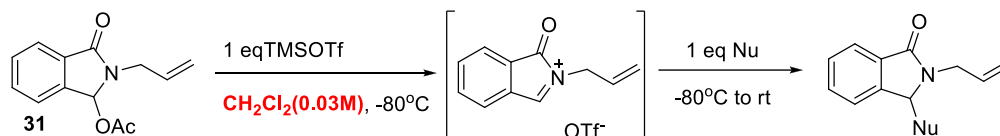
Our initial set of experiments supports the mechanistic proposal where Ph-C≡C-AuPPh₃ acts as a nucleophile to trap the *N*-acyliminium ion intermediate initially generated through ionization of the *N,O*-acetal by the Lewis acid reagent. (**Table IV.2.** entry 1 *versus* entries 2, 4, 6 and comments thereof) Nevertheless, complementary investigations presented in Entries 9, 10 outlines the possibility of an alternative mechanism where Ph-C≡C-AuL might act as a Lewis base co-catalyst which activates either the silylalkyne nucleophile or the Lewis acid and thus establishes hypervalent silicate intermediates. On the basis of these puzzling results we decided to test the nucleophilicity of the gold-acetylides.

To this aim the reaction was carried-out in a stepwise manner. The *N*-acyliminium ion intermediate was formed *in situ* in a stoichiometric reaction of the *N,O*-acetal with the super Lewis acid TMSOTf prior to the addition of the Ph-C≡C-AuL components was realized. Because the *N*-acyliminium ion intermediate is highly reactive and an unstable species, the reaction was set up at low temperature (-80 °C) and thus the solvent had to be changed from α,α,α-trifluorotoluene to a solvent exhibiting a lower melting point, *viz* dichloromethane (m.p. for CF₃C₆H₅ is -29 °C while for CH₂Cl₂ -97 °C).

We started our investigations with the silylalkyne as we wanted to check if it can react as the nucleophile under these drastic conditions and also compare its reactivity with that of the gold acetylides. (**Table IV.4.** entry 1.)

The reaction progressed very slowly and was even not completed after 3 days. The silylalkyne is apparently not nucleophilic enough to promptly attack the iminium triflate salt intermediate (or its covalently bound analog itself). The result supports the hypothesis

Table IV.4. Testing the nucleophilicity of Ph-C≡C-AuL on the model reaction



Entry	Nucleophile	Time	Conversion[%]
1.	Ph-C≡C-TMS 32	3d	95% product and 5% hydroxylactam
2.	Ph-C≡C-AuPPh ₃ 166	23h	Complex mixture
3.	Ph-C≡C-AuP ^t Bu ₃ 167	25h	Complex mixture
4.	Ph-C≡C-AuIPr 168	25h	Complex mixture
5.	-C≡C-AuPPh ₃ 169	3d	Complex mixture

that TMS-alkynes on their own are not sufficiently efficient in effecting the alkynylation coupling under the simple mediation of a trialkylsilyl triflate promoter. This indirectly supports the positive influence of a catalytic amount of gold-acetylide in the reaction mixture, either as a nucleophile to trap the *N*-acyliminium ion intermediate or as an additive to enhance the reactivity of the system.

Thus, our next choice was to test Ph–C≡C–AuPPh₃ in a similar stoichiometric reaction. (entry 2.) To our surprise, no alkynylation product was formed after a short period of time and prolonging the reaction time gave a complex mixture instead of the desired coupling product. One of the possible explanations is that the very reactive *N*-acyliminium ion intermediate reacted first with another source of nucleophile in the reaction mixture, such as for example a chloride ion through chloride abstraction from the solvent.²⁹⁹ It is also worth mentioning that in the case of a successful coupling, one equiv of Ph₃PAuOTf will be released concomitantly to the formation of the alkynylation product, and decomposition of the latter under the inevitable exposure the π -philic gold(I) salt is also plausible. In retrospect, we should have employed two equiv. of the gold acetylide, with the assumption that the second equivalent would have sequester Ph₃PAuOTf as previously mentioned (**Schemes IV.6 and IV.23**).²⁷⁷

We have also to stress that the structures of pre-synthesized gold acetylides at the solid state are oligomeric in nature and therefore might substantially differ from the one generated *in situ* in solution.³⁰⁰ Nevertheless, we have to mention that the very effective results presented in the entries 2, 4, 6, 8-11 in the Table IV.1. were all obtained using the same batches of Ph–C≡C–AuL as the one used in this stoichiometric reaction.

In order to prevent the degradation seen in the earlier experiment, we next chose to test more stable gold-acetylides (based on publication^{281,284,287,290,296} *t*Bu₃P and IPr were selected). We have also tested the analogue **169** which, as seen in the reaction development, is a less reactive species³⁰¹ and therefore possibly less susceptible to decompose under the reactions conditions. (Entries 3-5.)

Unfortunately in each case a complex mixture was formed. Similar explanations as those discussed for entry 2 can be proposed.

Whatever the exact reason of these failures, these attempts indirectly support the notion that gold acetylide is rather acting as a Lewis base co-additive rather than a *N*-acyliminium

²⁹⁹ For a recent elegant example, see: Sun, J.; Kozmin, S.A. *J. Am. Chem. Soc.* **2005**, *127*, 13512.

³⁰⁰ (a) Leyva-Perez, A.; Rubio-Marques, P.; Al-Deyab, S.S.; Al-Resayes, S.I.; Corma, A. *ACS Catal* **2011**, *1*, 601, (b) Lima, J. C., Rodríguez, L. *Chem. Soc. Rev.* **2011**, *40*, 5442. (c) Schmidbaur, H.; Schier, A. *Chem. Soc. Rev.* **2012**, *41*, 370.

³⁰¹ Please see results presented in the Chapter III.

ion trap. In retrospect, a reaction to be done in order to confirm this assessment would be to add the stoichiometric amount of TMSOTf to a mixture of the *N,O*-acetal and a gold-acetylide (2 equiv). Based on our preliminary observations and hypothesis thereof, a quick interaction between the gold-acetylide and TMSOTf is to be expected, and some, if not good, conversion into the desired coupling product should ensue. As discussed earlier, use of 2 equiv of the gold acetylide should solve the potential problem of decomposition of the alkynylation product by the gold(I) triflate salt by-product.

To conclude this part, a series of stoichiometric reactions of the *N,O*-acetal **31** and diverse gold-acetylides was realized. Unfortunately the expected products were not formed. Several potential explanations might be proposed, including for the main low nucleophilicity, and/or instability of the gold acetylides under the reaction conditions. Alternatively, the reaction might have worked, releasing simultaneously equimolar amounts of the desired alkynylation product and Ph₃PAuOTf, which are likely to interact each other, causing probable decomposition of the expected propargyl lactams.

IV.2.3. NMR STUDY

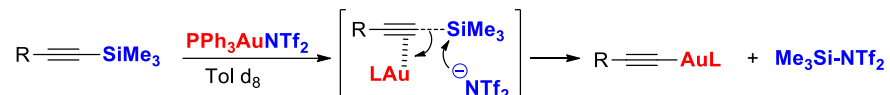
The aim of the study was to define and possibly characterize complexes formed in the reaction mixture, and subsequently to confirm the hypothetical mechanism. We also wanted to check the stability of the gold intermediates under our standard reaction conditions.

Experiments were carried out in a commercially available Toluene-d₈ solution (unless otherwise indicated) in a range of concentration 0.015-0.03 mol.dm⁻³. NMR spectra were measured at room temperature on a Bruker Avance 500 spectrometer. ¹H NMR spectra were recorded at 500 MHz. Chemical shifts (δ) are reported in ppm using residual solvent peaks as reference (Tol-d₈: δ 2.05; 7.00; 7.10). ¹³C NMR spectra were recorded at 125 MHz using broadband proton decoupling and chemicals shift are reported in ppm using residual solvent peaks as reference (Tol-d₈: δ 21.00; 125.50; 129.30; 128.50; 137.00). ³¹P NMR spectra were recorded at 202 MHz using broadband phosphorous decoupling and chemicals shifts are reported in ppm.

We have logically initiated our efforts by paying attention to the aurodesilylation step, which is the initiating step of our mechanism design. Feasibility studies on the *in situ* formation of the gold acetylide/TMSNTf₂ combination through this putative aurodesilylation

CHAPTER IV: Preliminary mechanistic study

event were examined from equimolar amounts of trimethylsilyl phenylacetylene and the Gagosz catalyst. (**Scheme IV.24.**) The latter is commercially available and was preferred over Ph_3PAuOTf for the purpose of practical simplicity (Ph_3PAuOTf is the optimal catalyst of our alkynylation reaction but has to be made *in situ*).

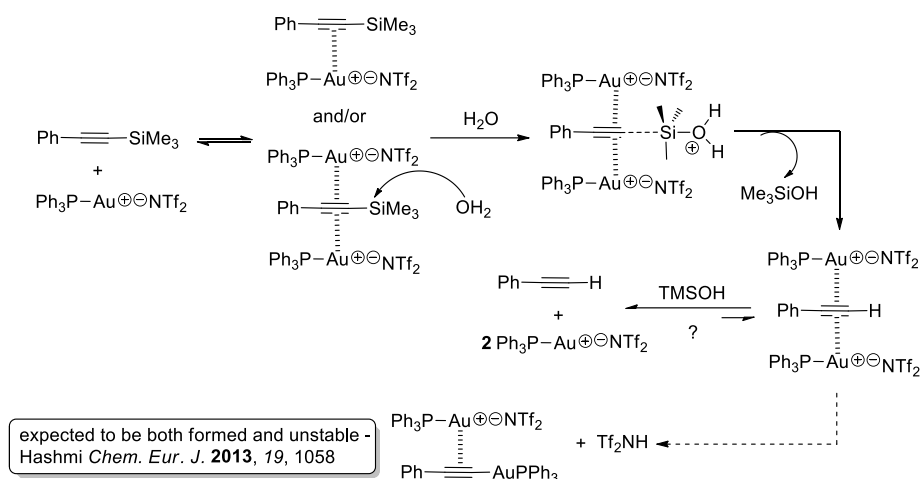


Scheme IV.24. The mixture of silylalkane and Gagosz catalyst in $\text{Tol } d_8$ solution.

Monitoring the transformation by ^1H NMR spectroscopy showed the gradual conversion of the TMS-alkyne into what seems to be phenyl acetylene as judged by the apparition of a diagnostic singlet at 2.6ppm; after 25 min on standing the mixture in the NMR tube, a 4.7/1 ratio of phenylacetylene/trimethylsilyl acetylene was observed. In addition, no peak characteristic to the gold acetylide at 42.1 ppm was found in ^{31}P NMR spectroscopy, a single peak very likely ascribable to the Gagosz catalyst itself being seen at 30.4 ppm.

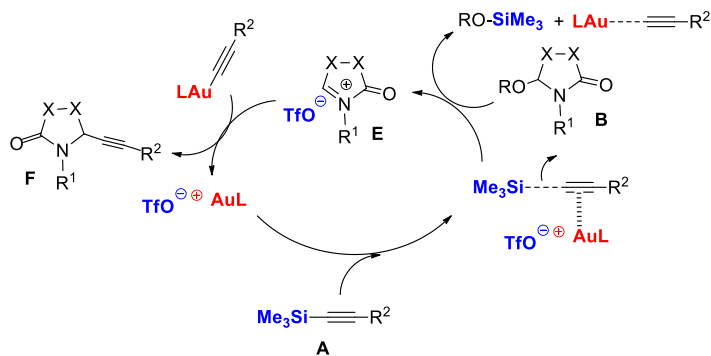
These observations are testament that a net protodeauration had taken place instead of the expected aurodesilylation. As will be seen later on, phenylacetylene might have, however, been produced from the intended mixture of gold acetylide and TMSNTf_2 (*vide infra*), so as it cannot be conclusively claimed that aurodesilylation has not proceeded.

Besides this potential gold acetylide/phenylacetylene interconversion in the presence of a super Lewis acid $\text{TMSOTf}/\text{TMSNTf}_2$, one alternative explanation for this rather unexpected result would be that the gold-(doubly)bound silylalkyne complexes would get desilylated following attack of adventitious water at the electrophilically activated silicon atom. One of the two highly acidic protons located on the resulting oxonium ion would substitute silicon at the C_{sp} center, generating mixture of TMSOH and phenylacetylene and the gold catalyst. (**Scheme IV.25.**) Based on the contributions of Widenhoefer, Corma, and Nolan who have shown that terminal alkynes are immediately consumed by gold(I) cationic salts paired with poorly coordinating counteranions (including NTf_2^-) to generate σ,π -alkynyl diaurated salts, our observation that significant amount of what seems to be a mixture of phenylacetylene and the Gagosz catalyst is formed is intriguing. If present, TMSOH might prevent formation of the diaurated σ,π -complex by, for example, facilitating dissociation of any phenylacetylene gold(I) complexes. We have also to mention that, if formed, the σ,π -alkynyl diaurated triflimidate salt is expected to be unstable as the triphenylphosphine ligand is not bulky enough to stabilize such structures, which generally require bulky phosphines^{277,278c} or bulky and σ -donor carbenes.^{273,281,284,287}



Scheme IV.25. The potential gold acetylide/phenylacetylene interconversion in the presence of a super Lewis acid.

This analysis underlines a new (previously unanticipated) and simplified mechanistic proposal which could contribute to some extent in our alkylation reaction. The gold π -activated (or possibly bis- π -activated silylalkyne complex) would enhance the silicon electrophilicity to such an extent that direct activation of the *N,O*-acetal would be possible. This would lead to the concomitant generation of the *N*-acyliminium ion and gold acetylide which would assemble to generate the alkylation product. (**Scheme IV.26.**)



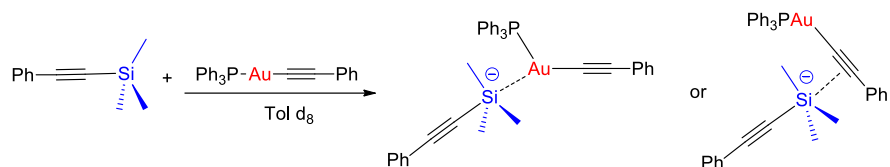
Scheme IV.26. The new and simplified mechanistic proposal.

Such a mechanistic manifold might be consistent with the observation that the reaction rate and efficiency dramatically depends on the nature of the ligand bound to gold, since the strength of the π -gold interaction as well the number of coordinations that can be established is expected to strongly vary with the sterics and electronics of the gold catalyst.

Before examining the possible interaction between gold acetylides and TMSOTf, we were eager to verify whether gold acetylide could act as a Lewis base towards trimethylsilyl acetylene to produce a pentavalent gold bound silicate phenylacetylene of enhanced

CHAPTER IV: Preliminary mechanistic study

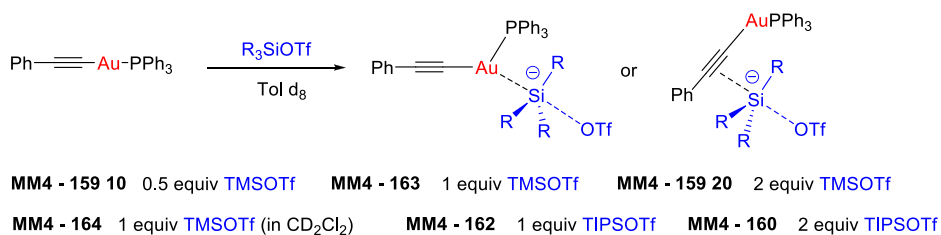
nucleophilicity, as suggested from the results depicted in the entries 9-10 of Table IV.1. While we recognize that the silicon atom of trimethylsilyl phenylacetylene is much less electrophilic than its counterpart in TMSOTf, the higher population of the former (particularly at low conversion level) led us to speculate that this interaction might indeed be feasible, and then we set up a trial to check if such a complex can form. (**Scheme IV.27.**)



Scheme IV.27. The potential interactions of trimethylsilyl phenylacetylene and gold-acetylene.

Nevertheless and as reasonably expected, no chemical shift variations in ^{31}P and ^1H NMR spectroscopies were observed for both components which were then left untouched. We can then conclude that, if formed, gold acetylides very likely do not activate trialkylsilyl alkyne components in our gold-catalyzed alkynylation.

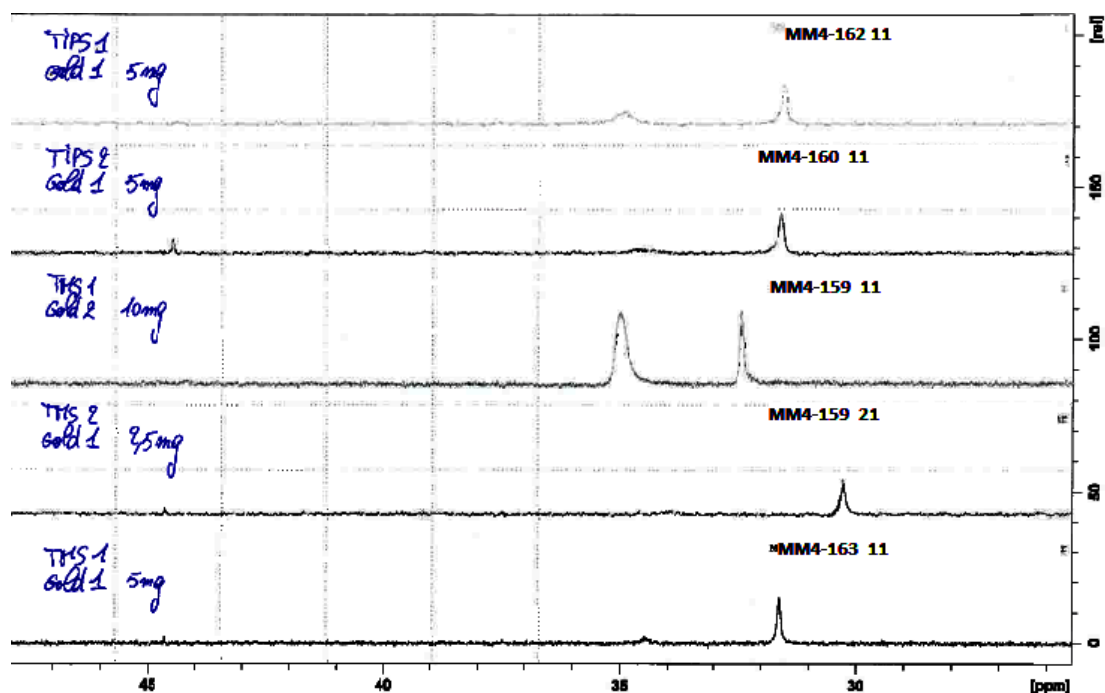
Suspecting that gold-acetylide acts as a Lewis base rather than a nucleophile (see entries 9-10 in Table IV.1. and comments thereof), and having demonstrated that trimethylsilyl phenylacetylene is not attacked by phenyl(triphenylphosphine gold)acetylide, we then sought to verify the activation of trialkylsilyl triflates by the organogold reagent. To this end, we monitored an array of experiments consisting in different ratios of phenyl (triphenylphosphine gold) acetylide and trialkylsilyl triflate (TMSOTf) or triisopropylsilyl triflate (TIPSOTf). All mixtures were dissolved in toluene d_8 , except one case where CD_2Cl_2 was used for the sake of comparison. (**Scheme IV.28.**)



Scheme IV.28. Testing the activation of trialkylsilyl triflates by the organogold reagent.

The nature of the silyl-triflate Lewis acid is seemingly not influential in the reaction outcomes, which are almost similar for both series at constant ratios of gold acetylide/silyl triflate (**Scheme IV.29.**). In every case an immediate and complete transformation took place by which all the gold acetylide was consumed. Curiously, even in the experiment using 2 equiv of the gold acetylide, the latter was completely consumed within seconds. For those

experiments carried out at an organogold/silyl triflate ratio of 1:2 (MM4 - 159 20 and MM4 - 160), it has also to be noted that most of the excess amount of the silyl triflate reagent was preserved in the solution.



Scheme IV.25. The ^{31}P NMR spectroscopy

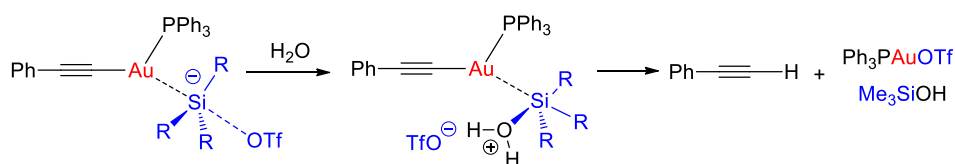
Surprisingly, in every case a significant amount of phenyl acetylene was seen in the ^1H NMR spectra (2.6 ppm, singlet), the presence of which was confirmed by ^{13}C NMR spectroscopy ($\delta_1 = 77$ ppm and $\delta_2 = 84$ ppm). No trace of trimethylsilyl phenylacetylene, which could have resulted from silylation of the gold acetylide by TMSOTf through triflate displacement, could be detected in any experiments. Note that, if formed, trimethylsilyl phenylacetylene would have probably been rapidly transformed by Ph_3PAuOTf into phenylacetylene (*vide supra*, MM4-165). Two peaks were systematically observable in ^{31}P NMR spectroscopy. For those experiments where the gold acetylide/silyl triflate ratios were 1:1 and 1:2, the major and well resolved peak reasoned in the range of 30.3-31.6 ppm, the chemical shift value slightly increasing with the concentration of the gold acetylide engaged (Scheme IV.29.). Though uncertainty remains, this peak might be consistent with Ph_3PAuOTf , which has been synthesized independently and gives a ^{31}P signal at 29.7 ppm.

A second minor, broad peak was found in the range of 34-35 ppm, the intensity of which became dominant in the case of 2 equiv of gold acetylide with respect to TMSOTf (MM4-159 - 10). Due to an overlap between the signals of toluene and the four aryl groups of the phenylacetylene and triphenylphosphine moieties, it is difficult to claim that phenylacetylene

is the only alkynylated component detectable. In this view, the 1:1 mixture of phenyl (triphenylphosphine gold) acetylide and trimethylsilyl triflate (TMSOTf) was studied in CD₂Cl₂ (**MM4-164**). It was clearly shown from the ¹H NMR spectrum that phenylacetylene is the only alkyne product detectable.

In this case, a single, broad peak at 34.8 ppm was found in the ³¹P NMR spectrum, the broadness of which might potentially be due to a superimposition of the two peaks systematically observed in toluene d₈. Again the value of the chemical shift measured might be consistent with Ph₃PAuOTf, which exhibited a signal at 32.8 ppm in this solvent – the difference of chemical shifts might originate from a difference in the concentrations applied and/or may be due to the presence of the other products. For example, formation of a π-complex between the gold catalyst and the triple bond is, at least, expected.

The origin of the production of phenylacetylene is unclear but, as for the reaction **MM4 - 165** (trimethylsilyl phenylacetylene + Gagosz catalyst), the trapping of reactive intermediates by water and subsequent formation of a protic oxonium ion may be responsible for the net protodeauration, as illustrated in the **Scheme IV.30**. below.



Scheme IV.30. A putative protodeauration of gold-acetylide by water.

To conclude, we have confirmed that gold acetylides and trialkylsilyl triflates are not mutually compatible since they react vigorously each other. This lends credence to the hypothesis that gold acetylides serve the role of a Lewis base to activate the silyl Lewis acid, that probably results in a more efficient generation of the *N*-acyliminium ions.³⁰² Unfortunately, we weren't able to gain evidence on the formation of a new gold species, due to the rapid formation of phenylacetylene as the exclusive alkynylated product even when a 2:1 ratio of phenyl (triphenylphosphine gold) acetylide /TMSOTf was applied. ³¹P NMR spectroscopy seems to testify that Ph₃PAuOTf is the main phosphorylated component produced in the process but uncertainty remains due to slight chemical shift variation with respect to the reference sample.

³⁰² For a similar discovery using organoiodines. Albert, J.; Yamamoto, H. *Angew. Chem. Int. Ed* **2010**, *49*, 2747.

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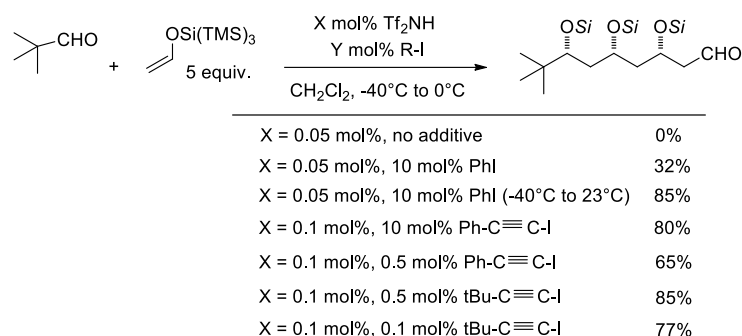
The analysis of the Lewis basic role played by gold acetylides in our catalytic alkylation reaction (Table 1, entry 9) led us to speculate that use of any organogold reagent as a co-catalyst to the metal triflate Lewis acid should result in an efficient coupling. This hypothesis was verified when the aryl gold component PhAuPPh₃ in combination with TMSOTf had performed equally well as the Ph-C≡C-Au-PPh₃/TMSOTf couple (Table 1, entries 10 and 2). We were then logically interested in studying this pair of reagents by NMR.

By analogy with the set of NMR experiments dealing with mixtures of Ph-C≡C-AuPPh₃ and silyl triflates, an immediate consumption of the aryl gold nucleophile was observed, affording benzene as the sole aromatic component detectable by ¹H NMR spectroscopy. Again in line with the above experiments, a very major peak was seen in ³¹P NMR spectroscopy. In contrast to the experiments with phenyl (triphenylphosphine gold) acetylide, its chemical shift was in this case nearly 2 ppm below the reference value ($\delta = 27.2$ ppm versus $\delta = 29.7$ ppm). This small difference of resonance again prevents us to firmly attribute this peak to Ph₃PAuOTf.

In conclusion, we have confirmed that phenyl gold reacts spontaneously with trialkylsilyl triflates. Even if the characterization of a well defined complex failed, this observation supports the ability of organogold components, beyond the specific case of gold acetylides, to express an inherent Lewis basicity that is very helpful to accelerate an intrinsically sluggish alkylation reaction, most likely by interacting with the silyl triflate catalyst and enhancing its Lewis acidity.

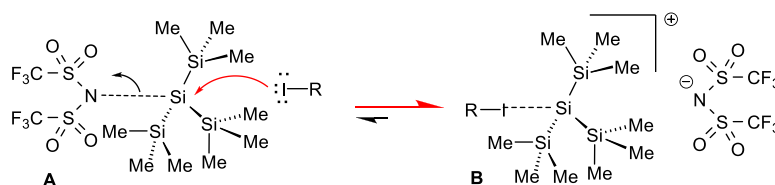
As a way to support this mechanism manifold, we have decided to use iodobenzene as an additive to TMSOTf for our model alkylation reaction. Actually, Albert and H. Yamamoto have recently demonstrated the high benefit of different iodine-containing additives in the context of a highly challenging triple-aldol cascade reaction of *tris*-(trimethylsilyl) siloxy ethylene directed to the rapid assembly of polyketides.³⁰² Of different organoiodides evaluated, *tert*-butyl alkynyl iodide (1-iodo-3,3-dimethyl-1-butyne) was by far the most efficient, but the simple and commercially available phenyl iodide displayed a significant effect (**Scheme IV.31**).

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Scheme IV.31. The triple-aldol cascade reaction of *tris*-(trimethylsilyl) siloxy ethylene directed to the rapid assembly of polyketides.

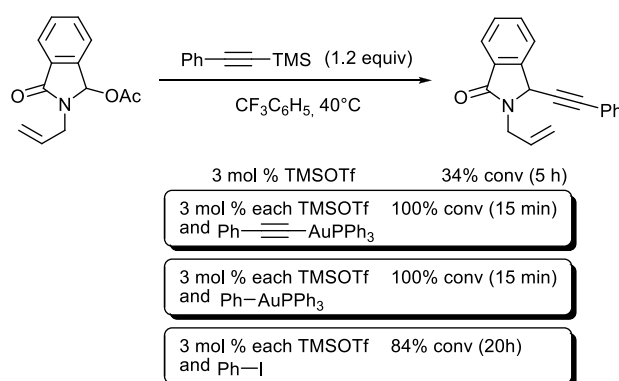
The iodinated co-catalysts were proposed to serve the role of a Lewis base activator for the *in situ* generated even Lewis super acid *tris*-(trimethylsilyl) silyl triflimidate (TTMSSNTf₂), by forming a cationic, more reactive and less sterically demanding complex (**Scheme IV.32.**).



Scheme IV.32. Formation of the cationic complex B

This mechanistic proposal resembles our proposed Lewis base assisted Lewis acid (LBLEA)³⁰³ catalysis and therefore we intended to test phenyl iodide as an activator for the TMSOTf-catalyzed alkylation reaction.

Delightfully, a significant enhancement of the reaction conversion occurred, however, phenyl iodide performed less well as PhAuPPh₃ and Ph-C≡C-Au-PPh₃ (**Scheme IV.33.**).



Scheme IV.33. Testing different activators for the TMSOTf-catalyzed alkylation reaction.

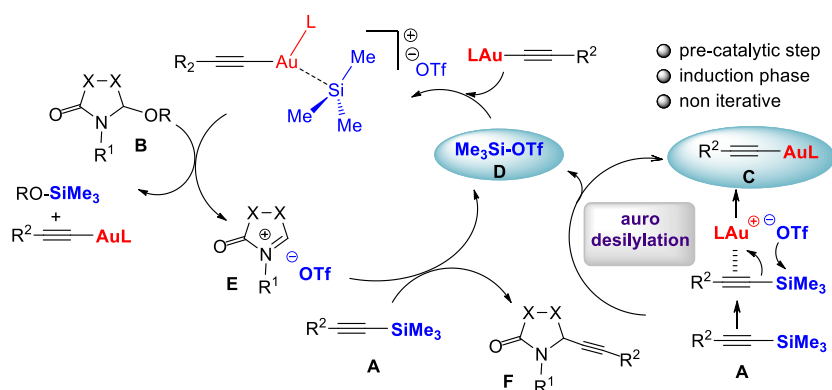
This result not only greatly supports our new mechanism scenario, which is depicted in **Scheme IV.34.**, but also given the much higher performance exhibited by the organoaurated

³⁰³ Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

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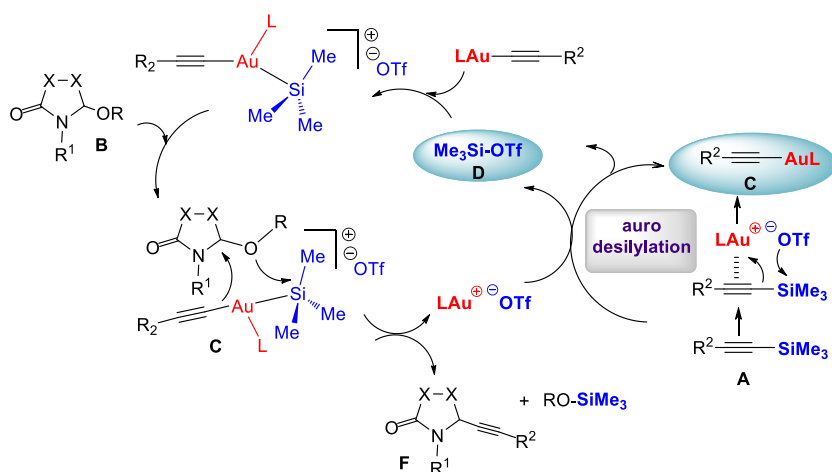
molecules relative to phenyliodide, it highlights the power of using them in this alkylation reaction.

This alternative mechanism differs from our initial design, with an aurodesilylation event which corresponds to an induction phase and proceeds non-iteratively, due to the persistence of the gold acetylide all along the process. This view is in line with the high efficiency displayed by reactions where $\text{Ph-C}\equiv\text{CAuP}(t\text{Bu})_3$ and PhAuPPh_3 were used as an additive, and is also supported by the absence of coupling products in the stoichiometric reactions (Table IV.3.).



Scheme IV.34. The alternative mechanism proposal.

It is also conceivable that for certain gold acetylides, the *N,O*-acetal activation and alkylation delivery could proceed synchronously, thus consuming the organogold and therefore rendering an hybrid mechanism between the one initially designed and the newly proposed. (**Scheme IV.35.**)



Scheme IV.35. The proposition of the mechanism where the *N,O*-acetal activation and alkylation delivery are proceeding synchronously,

For the sake of comparison and in order to fully quantify the power of organogold molecules as Lewis base additives, it will be interesting to prepare and test *tert*-butyl alkynyl iodide in our model coupling, as well as to evaluate the organogold derivatives in the

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Yamamoto's aldol cascade reaction. Irrespective of these complementary experiments, this mechanistic study seems already to open new avenues in the chemistry of organogold reagents, potentially making them promising candidates as Lewis acid activators. Such a feature might be very useful to improve the performance of synthetic transformations which are hardly catalyzed by weak, cheap and easily available Lewis acid catalysts. Important benefits such as lowering of the catalyst loadings as well as avoidance of the use of exotic and/or expensive Lewis acid catalysts are expected. It will also be necessary to expand the scope of this Lewis acid activation beyond the additions of silicon-based nucleophiles. Efforts in our laboratory will be undertaken to explore these opportunities.

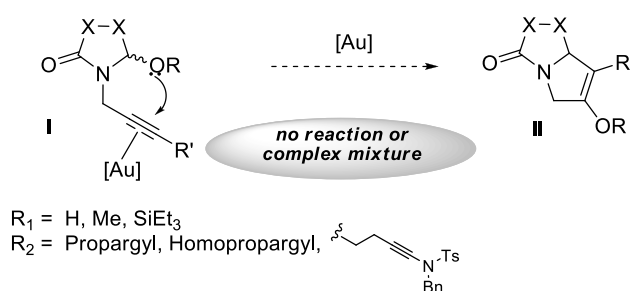
***GENERAL CONCLUSION AND
PROSPECTS***

General conclusion and prospects

This manuscript describes the results obtained in this thesis on the development of new heretofore unprecedented transformations, including tandem/cascade reactions catalyzed by gold complexes.

In the first part of the project, we envisioned exploiting the carbophilic Lewis acidity of gold(I) complexes for the development of a two-step cascade sequence in the context of *N*-acyliminium chemistry. Starting from readily available *N*-propargyl alkoxy lactames, we proposed to investigate a gold-catalyzed intramolecular carboalkoxylation/aza-Ferrier-Petasis rearrangement sequence which would give direct access to cyclic enol ether of type **II**.

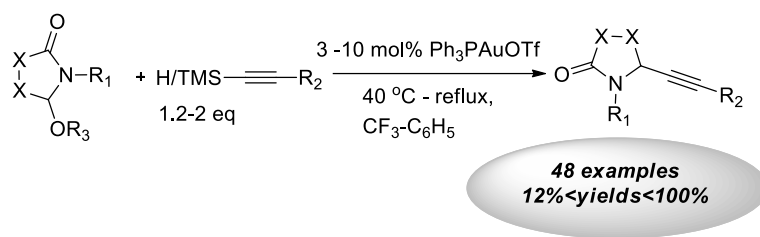
The influence of different parameters was explored, such as the nucleophilic character and size of the OR group, length of the chain tethering the triple bond and the *N,O*-acetal moiety, nature and electronic character of the metal catalyst and of the triple bond. Despite many efforts, formation of the targeted cyclized product could never be observed whatever the tested conditions. Results suggested that the studied systems were not appropriate and, in particular, that the presence of the carbonyl group on the starting *N,O*-acetal may have a detrimental effect on the expected reactivity. A competitive complexation of the gold species was postulated in most cases to explain the lack of reactivity. (**Scheme 1**.)



Scheme 1.

In a second part, a catalytic alkylation of *N,O*-acetals relying on an original synergistic silyl-gold catalysis mechanism was developed. This strategy exploits the carbophilic π -acidity of gold(I) catalysts (LAuX) to activate trimethylsilylalkynes towards desilylation, thus generating a nucleophilic gold acetylide and a silyl Lewis (super)acid TMSX catalytically. The developed methodology was found to tolerate a wide range of *N,O*-acetals and TMS-alkynes (**Scheme 2**.)

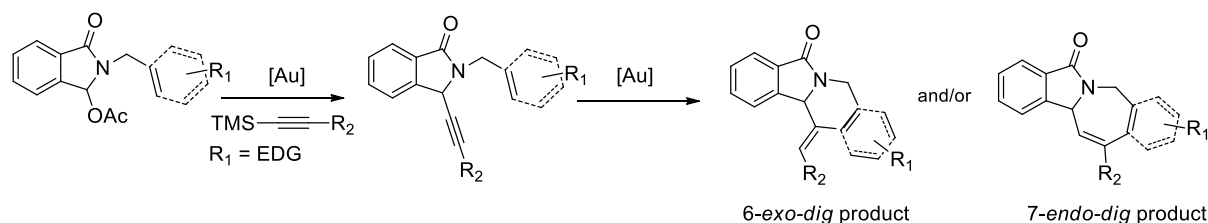
General conclusion and prospects



Scheme 2.

During the course of our investigation, a special interest was dedicated to the investigation and understanding of the mechanism involved. This allowed us to propose some modes of action for the synergistic catalytic system at play in this transformation.

To demonstrate the synthetic potential of the resulting alkynylated products, a one-pot two-step alkynylation/hydroarylation sequence was also briefly investigated starting from lactam substrates equipped with an electron rich aryl group on nitrogen. Further efforts would be required to improve the efficiency of this sequence, by optimizing the reaction conditions and screening both the reaction partners and catalysts in more details. (**Scheme 3.**)



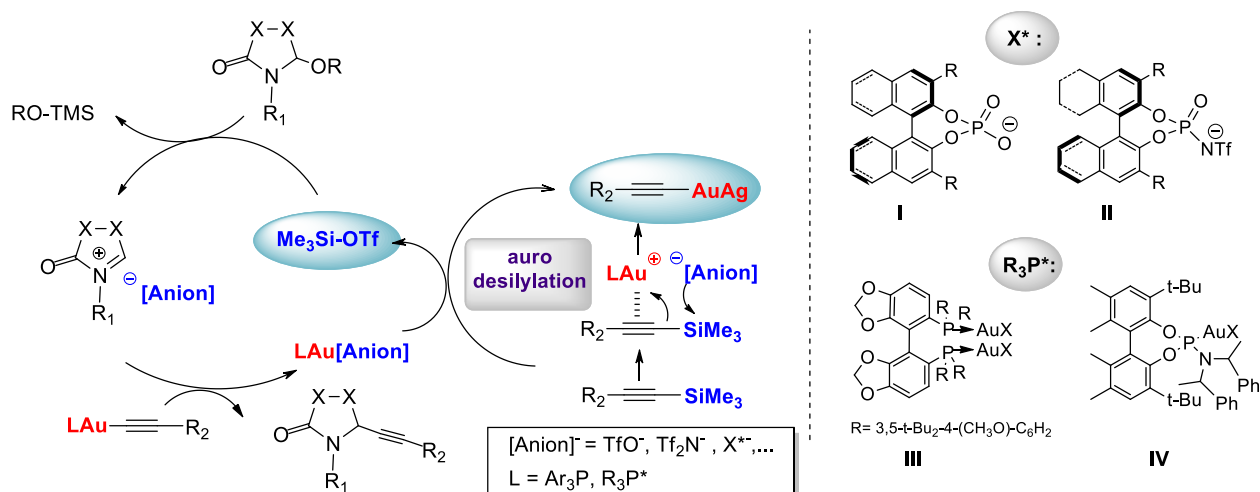
Scheme 3.

While the use of homogenous gold complexes in organic synthesis has tremendously matured in recent years, relatively few examples of enantioselective gold-catalyzed transformations have been reported thus far. While most of the reports to date utilize gold-phosphine ligand chemistry, the chiral counterion approach [employing an Au⁺ cation bound to an optically active counter-ion] is now becoming a key strategy in asymmetric metal catalysis.

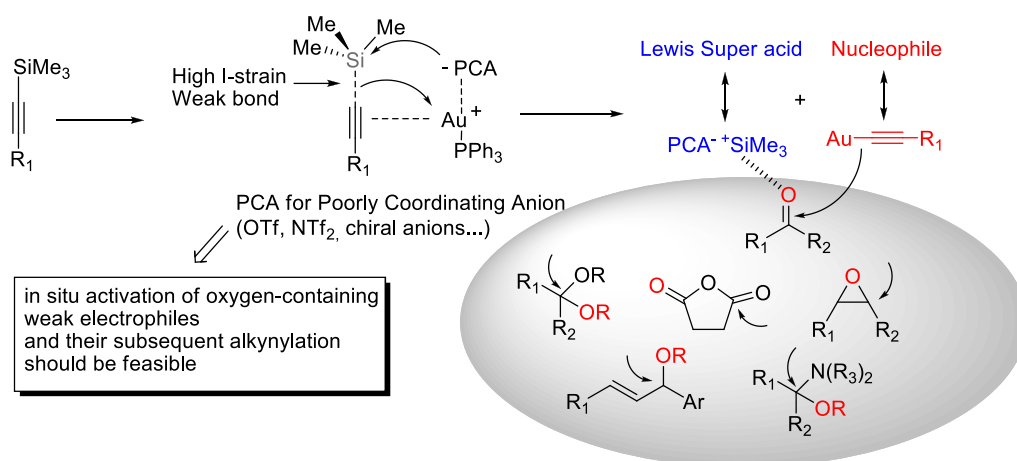
An elegant prospect of the work presented in this manuscript would thus be to apply this chiral counter-ion approach to the development of an asymmetric version of our gold-catalyzed alkynylation to give rise to optically enriched propargylic amine derivatives. Interestingly, this strategy of chiral induction should be compatible with the postulated synergistic gold-silyl mechanism: thus, exposure of a mixture of *N,O*-acetal and

General conclusion and prospects

trimethylsilylalkyne to catalytic amounts of a gold catalyst of type $[L-Au^+]\text{anion}^*$ (such as **I** or **II**, **Scheme 4**.) should generate an L-Au acetylide with concomitant release of a chiral silyl Lewis acid, *i.e.* $\text{Me}_3\text{Si}-[\text{anion}^*]$ entity. Such a highly Lewis acidic silicon derivative should be able to generate an *N*-acyliminium-chiral counterion salt, which should be rapidly trapped by the metal acetylide, hopefully in an enantioselective manner. Besides, combination of this chiral counterion strategy with the use of chiral ligands on gold (match association), such as in complexes **III** or **IV**, should also be considered.



It would be also very interesting to test the feasibility of a similar transformation on other types of electrophilic functions using the innovative catalytic gold/silyl synergistic approach we developed for the alkylation of *N,O*-acetals.



General conclusion and prospects

As shown on **Scheme 4.**, other weakly basic oxygen-containing electrophiles such as π -alcohol derivatives, acetals, aldehydes, ketones, epoxides and anhydrides may be envisioned as potential candidates in this catalytic Au-catalyzed alkynylation protocol. Indeed it is reasonable to surmise that these classes of compounds could be activated with the super Lewis acid species generated *in situ* according to our mechanistic hypothesis.

EXPERIMENTAL SECTION

1. General informations

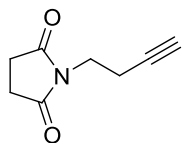
All reactions were carried out under argon atmosphere in oven-dried glassware with magnetic stirring. Commercially available compounds were used without further purification. Solvents were distilled prior to use, taking precaution to exclude moisture by refluxing over CaH₂ or over sodium (for THF, Et₂O).

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 with fluorescent indicator UV₂₅₄ TLC plates. The spots were visualized with UV light (254 nm) and staining with a solution of *p*-anisaldehyde, followed by heat. Flash column chromatography was performed using silica gel 60 (particle size 0.040-0.063 mm) typically using a cyclohexane/ethyl acetate eluent system. FT-IR spectra were recorded with a Perkin-Elmer Frontier. NMR spectra were measured at room temperature on a Bruker Avance 300 spectrometer. ¹H NMR spectra were recorded at 300 MHz. Chemical shifts (δ) are reported in ppm using residual solvent peaks as reference (CHCl₃: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, qui: quintuplet, m: multiplet), coupling constant (*J* in Hz) and integration. ¹³C NMR spectra were recorded at 75 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference (CHCl₃: δ 77.0). Carbon multiplicities were assigned by DEPT techniques. High resolution mass spectra were recorded on a 6530 Q-TOF (Agilent Technologies). The Q-TOF MS instrument was operated under the following condition: Ion source ESI⁺ Agilent Jet Stream or APCI both in positive ionization mode. Melting points were measured using open capillary tubes on a Stuart Scientific analyzer and are uncorrected.

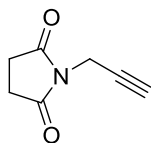
Index of characterized compounds

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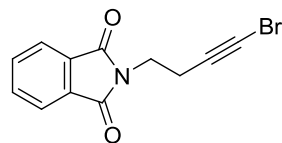
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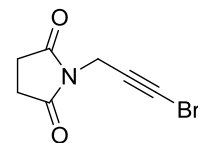
I, p. E-19



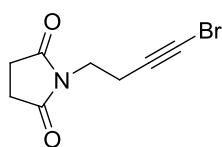
II, p. E-19



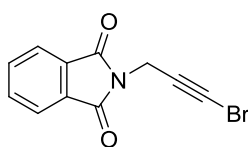
VI, p. E-21



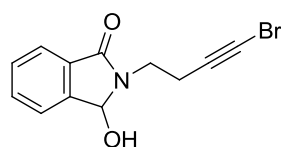
III, p. E-20



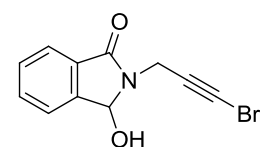
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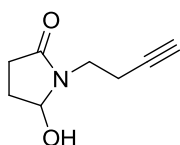
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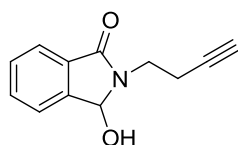
18b, p. E-23



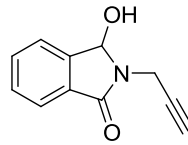
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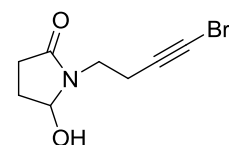
17, p. E-22



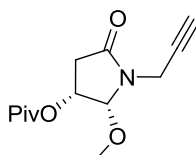
16, p. E-22



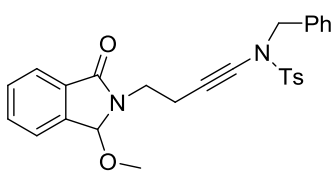
15, p. E-21



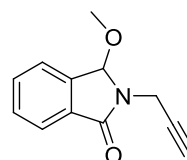
18c, p. E-24



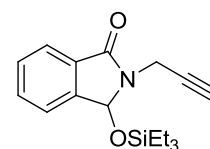
11, p. E-25



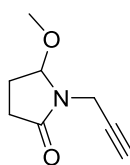
14, p. E-27



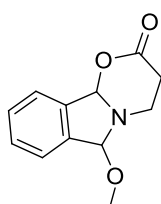
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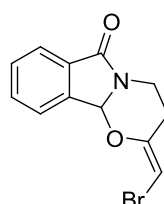
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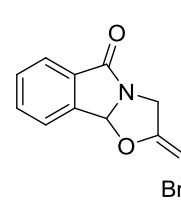
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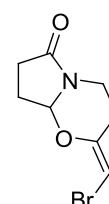
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24, p. E-28



25, p. E-29

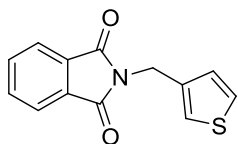


26, p. E-29

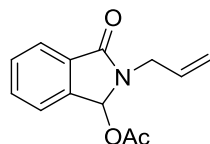
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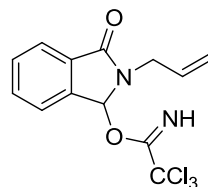
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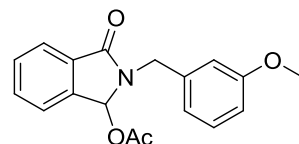
45a, p. E-30



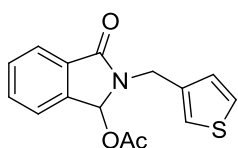
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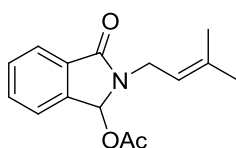
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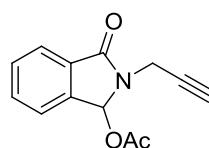
44, p. E-36



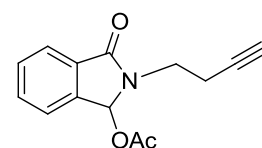
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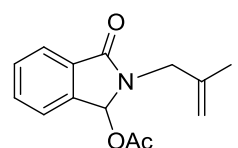
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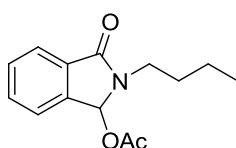
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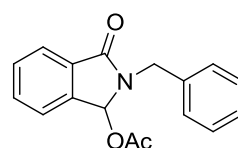
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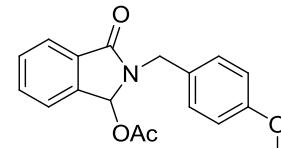
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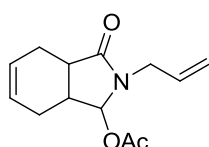
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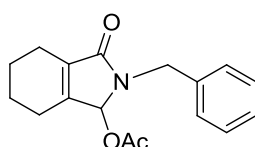
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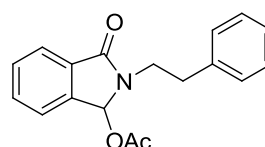
37, p. E-34



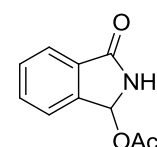
96, p. E-34



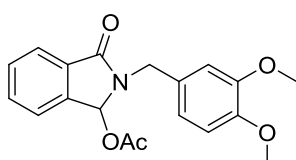
123, p. E-35



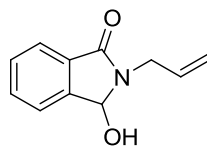
42, p. E-34



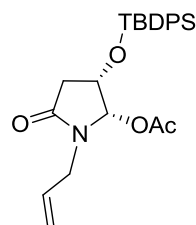
46, p. E-36



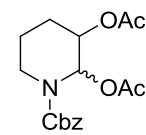
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141, p. E-30

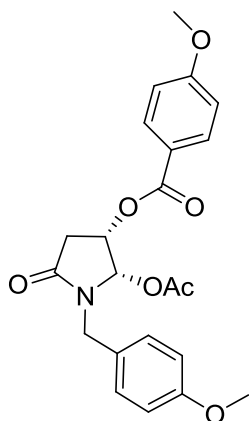


108p, E-44

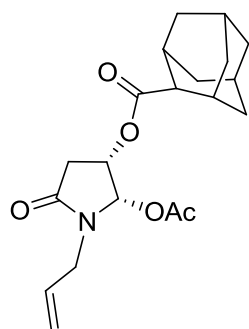


101p, E-48

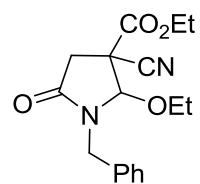
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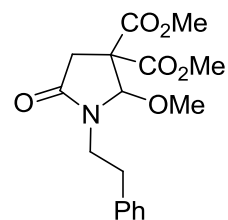
107, p. E-43



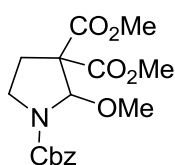
109, p. E-43



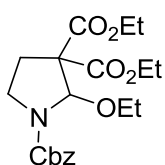
115, p. E-46



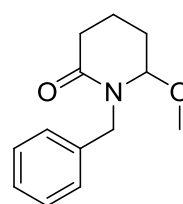
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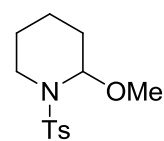
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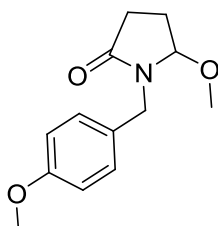
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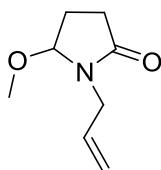
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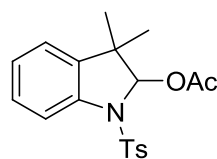
99, p. E-50



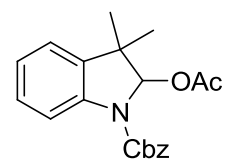
92, p. E-47



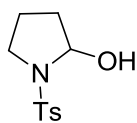
93, p. E-48



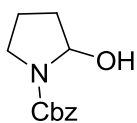
124, p. E-39



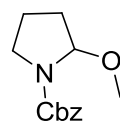
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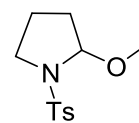
89a, p. E-51



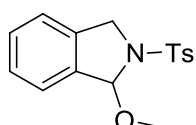
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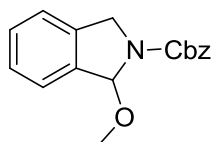
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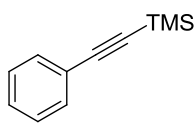
128, p. E-39



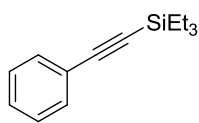
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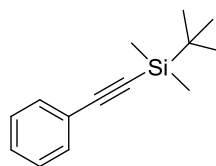
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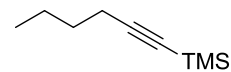
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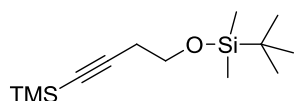
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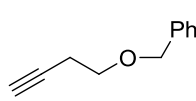
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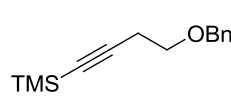
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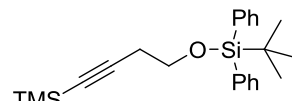
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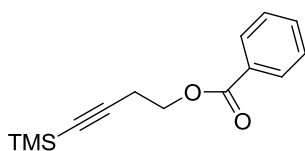
76a, p. E-57



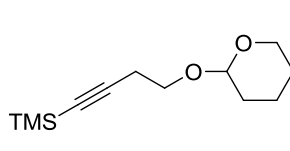
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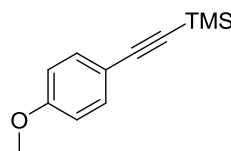
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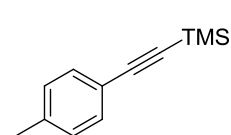
74, p. E-55



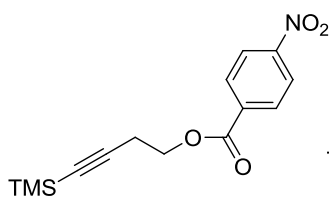
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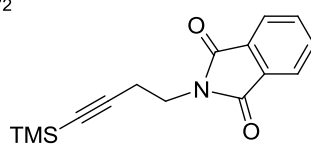
58, p. E-60



57, p. E-60



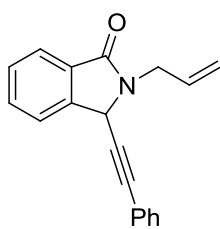
77, p. E-58



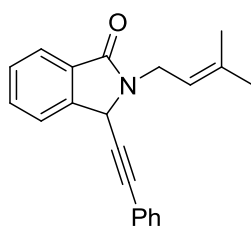
78, p. E-59

EXPERIMENTAL SECTION

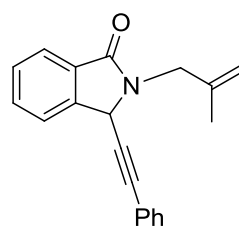
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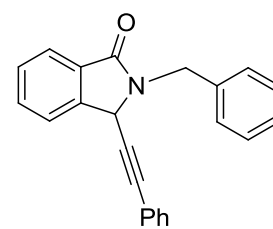
33, p. E-61



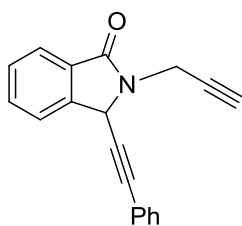
49, p. E-61



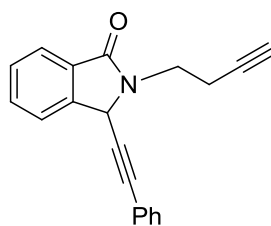
50, p. E-62



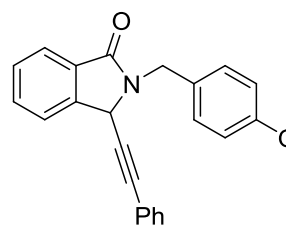
47, p. E-62



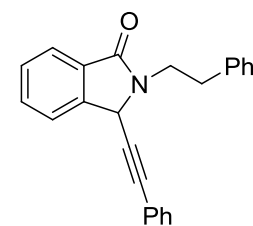
51, p. E-63



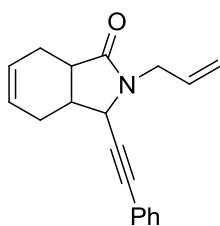
52, p. E-64



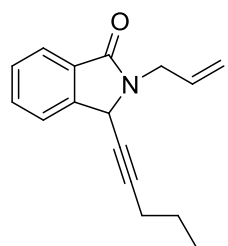
48, p. E-63



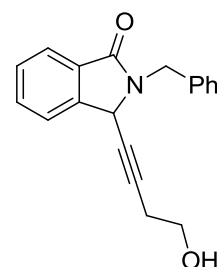
53, p. E-6



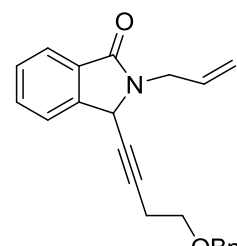
93, p. E-65



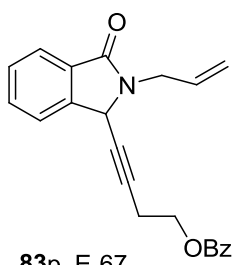
65, p. E-65



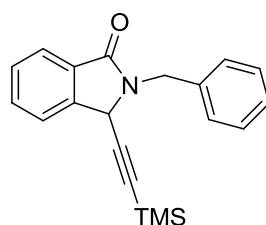
79, p. E-66



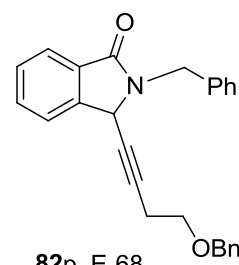
81, p. E-66



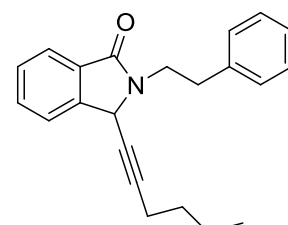
83, p. E-67



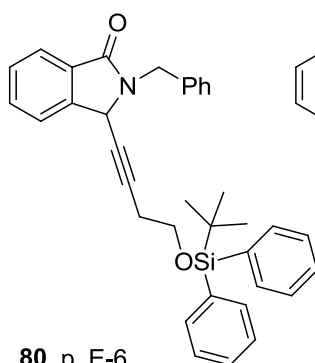
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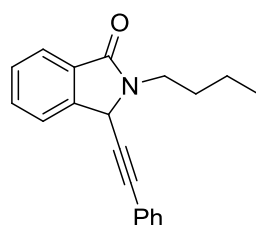
82, p. E-68



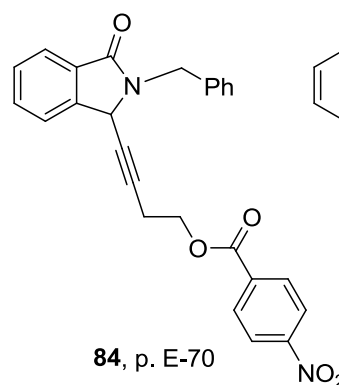
66, p. E-69



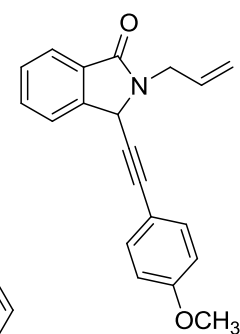
80, p. E-6



54, p. E-70

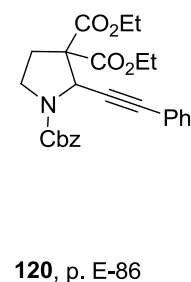
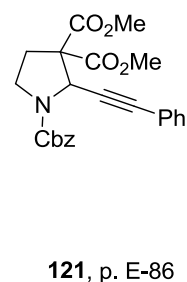
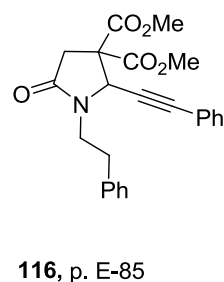
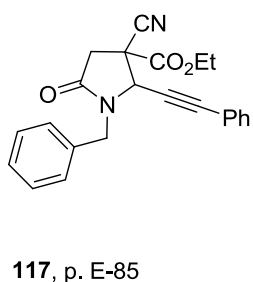
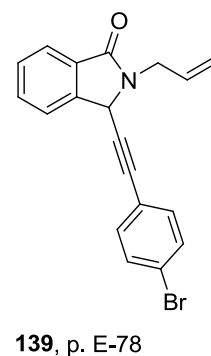
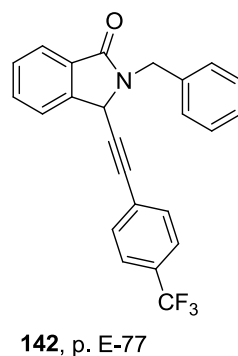
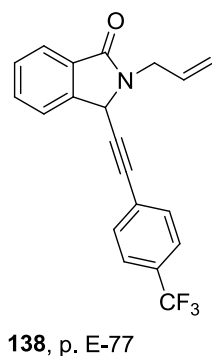
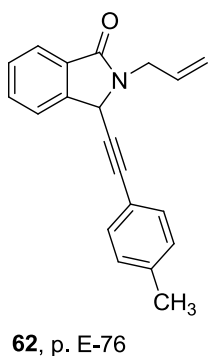
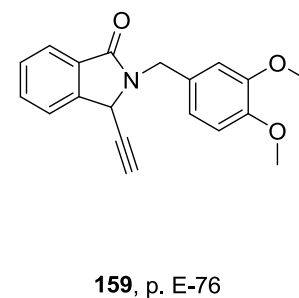
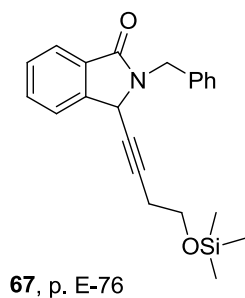
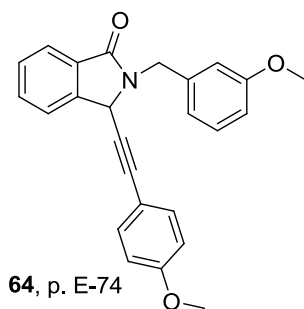
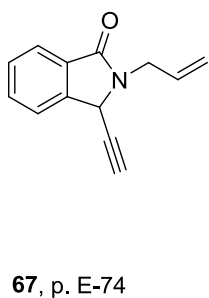
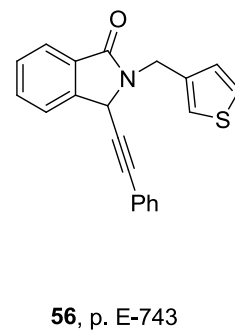
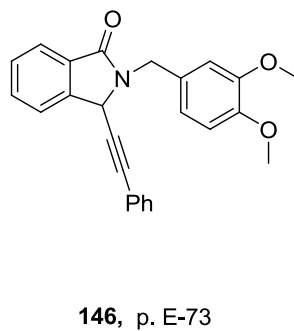
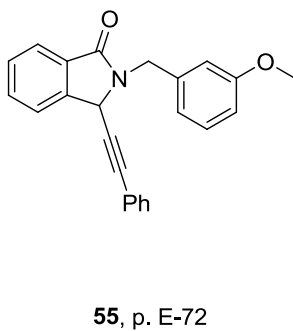
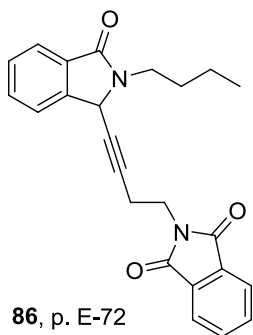


84, p. E-70

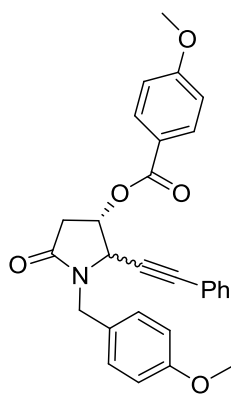


63, p. E-71

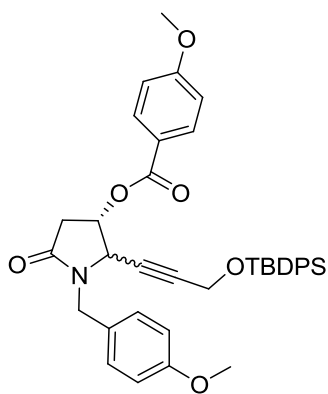
EXPERIMENTAL SECTION



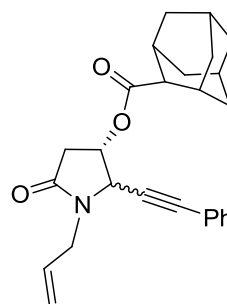
EXPERIMENTAL SECTION



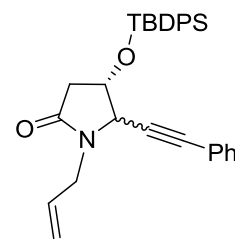
110, p. E-79



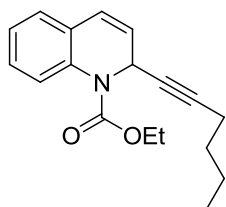
113, p. E-82



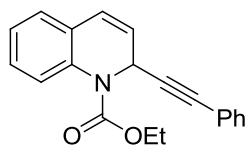
112, p. E-81



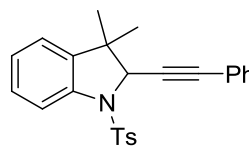
111, p. E-82



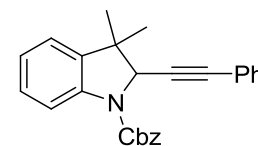
134, p. E-84



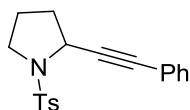
133, p. E-84



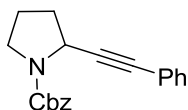
126, p. E-78



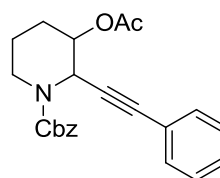
127, p. E-79



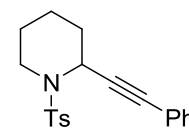
91, p. E-87



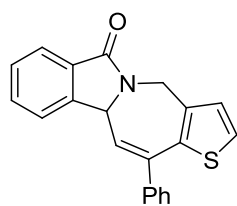
90, p. E-87



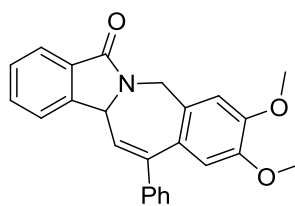
102, p. E-88



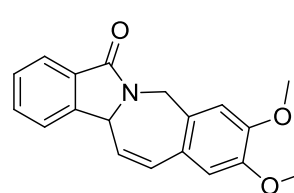
100, p. E-88



158, p. E-89



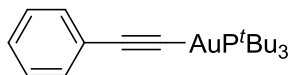
155, p. E-89



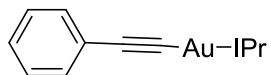
160, p. E-90

Chapter IV:

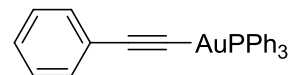
Starting materials:



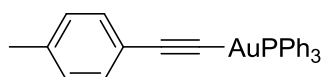
167, p. E-91



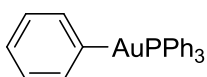
168, p. E-92



166, p.E-91



169, p. E-91

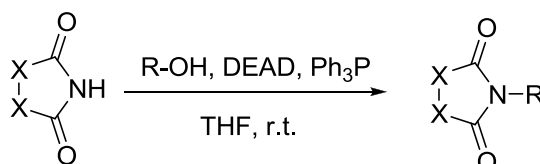


170, p. E-92

General procedures

Experimental procedures for preparation of isoindolic amidolactams

General procedure A0

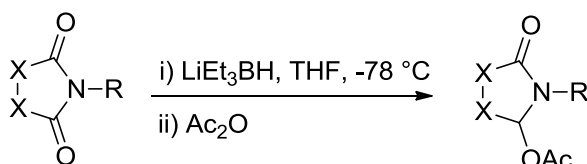


The reaction was carried out in Mitsunobu set up.

To a solution of imide (1 eq) and Ph_3P (1 eq) in THF (5.44 mL per mmol of starting material) corresponding alcohol (1 eq) was added. In a second flask DEAD (1 eq) in THF (0.44 mL per mmol of starting material) was prepared and transferred dropwise to the first flask at 0 °C. Progress of the reaction was monitored by TLC. When completed, solvent was evaporated. Next, the residue was dissolved in Et_2O (10 mL) and stirred for 15 min. In order to remove the latter, a filtration on Celite was carried out followed by evaporation of the solvent under vacuum. The resulting crude product was purified by column chromatograph to give the product as a white solid.

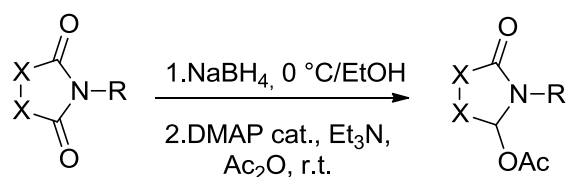
Experimental procedures for preparation of isoindolic acetoxy lactams (1A-E) :

General procedure AI



To a stirred solution of imide (1 eq) in anhydrous CH_2Cl_2 (3 mL per mmol of starting material) at -78 °C a commercially available solution of LiEt_3BH 1M in THF (1.3 eq) was added dropwise. Progress of the reaction was monitored by TLC. When completed, Ac_2O (1.5 eq) was added dropwise at -78 °C. The reaction mixture was let to warm up to room temperature. Next, charcoal was added and the mixture was stirred for 15 min. This latter was then removed by filtration on Celite and the solvent was evaporated under vacuum to afford the desired product as a solid.

General procedure AII



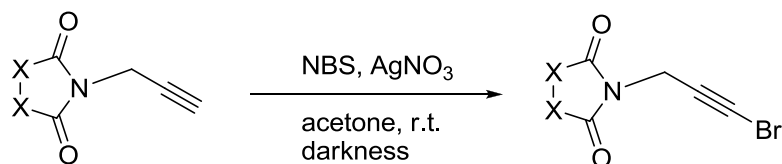
a) Imide (1 eq) was dissolved in EtOH (7.5 mL per mmol of substrate) and the solution was cooled down to 0 °C with a NaCl saturated ice bath. Then NaBH₄ (1.5 eq) was added neat in three portions, followed by addition of 10 drops of a HCl 2M ethanolic solution every 10 min (in order to adjust the pH of the reaction mixture). Progress of the reaction was monitored by TLC. When the reaction was completed the pH was adjusted to 5-6 by addition of a HCl 2M ethanolic solution and water was added. The solution was stirred at room temperature until H₂ gas emission stopped.

EtOH was evaporated and the aqueous layer was extracted three times with CH₂Cl₂. The organic layers were combined, dried over MgSO₄, filtered and concentrated under vacuum to afford the desired product as a white solid. The crude product was directly used in the next without any further purification.

b) Next, to a stirred solution of the crude hydroxylactam (1eq) and DMAP (0.05eq) in CH₂Cl₂ (4.15mL per mmol of substrate) at room temperature were successively added Et₃N (1.1 eq) followed by Ac₂O (1.3 eq) dropwise. The resulting mixture was stirred for 30 min (full conversion monitored by TLC) before evaporation of the solvent. The residue was then dissolved in EtOAc (15.5 mL per mmol of starting material) and filtered over a pad of Celite. The resulting crude product was then purified by flash column chromatography on silica gel to give the product as a solid.

Experimental procedure for bromination reaction

General procedure B



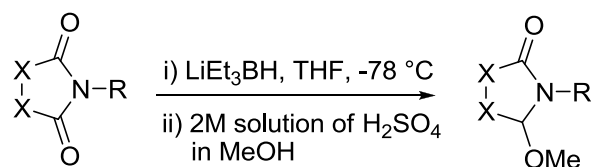
To a solution of imide (1 eq) in acetone (5 mL per mmol of substrate) *N*-bromosuccinimide (1.1 eq) and AgNO₃ (0.1 eq) were added. Progress of the reaction was monitored by TLC. When the reaction was completed Et₂O (8.8 mL) and H₂O (8.8 mL) were added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 times). The combined

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organic layers were washed with brine (30 mL), dried (MgSO_4), filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the product.

Experimental procedure for methoxylation reaction

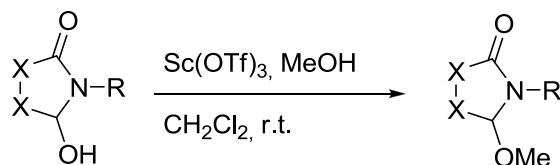
General procedure CI



To a stirred solution of imide (1 eq) in anhydrous CH_2Cl_2 (3 mL per mmol of starting material) at $-78\text{ }^\circ\text{C}$ a commercially available solution of LiEt_3BH 1M in THF (1.3 eq) was added dropwise. Progress of the reaction was monitored by TLC. When completed, the reaction mixture was quenched by addition of a 2M solution of H_2SO_4 in methanol (1.5 eq) and allowed to warm up to room temperature.

Afterwards, the reaction mixture was hydrolysed with water. The two phases were separated. The organic phase was washed with 5 mol% solution of NaHCO_3 , dried over MgSO_4 , filtered and concentrated under reduced pressure to give the expected product.

General procedure CII



To a solution of hydroxylactam (1 eq) in DCM (1 μL per 1 mmol of starting material) scandium (III) trifluoromethane sulfonate (0.05 eq) and methanol (5eq) were added at room temperature.

After complete conversion of the substrate to the expected product, the residue was washed with a saturated NaHCO_3 solution. The aqueous phase was extracted with DCM (3 times) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure.

The crude product was purified by flash chromatography [cyclohexane/ EtOAc].

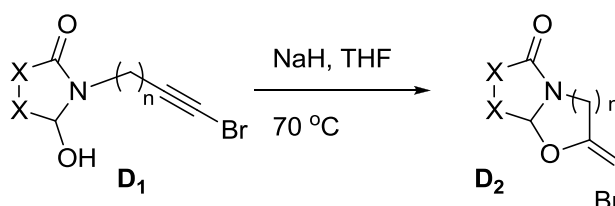
Experimental procedure for the cyclization-fragmentation reaction

General procedure D1

To a solution of the catalyst¹ LAuX (0.05eq) in a solvent ([substrate]=0.48 mol/L), were added the alkoxy lactame (1 eq). The reaction mixture was then stirred at the mentioned temperature. At the end of the reaction (¹H NMR monitoring), the reaction mixture was directly purified by flash column chromatography on silica gel to afford the corresponding alkynylated product.

Experimental procedure for the cyclization reaction

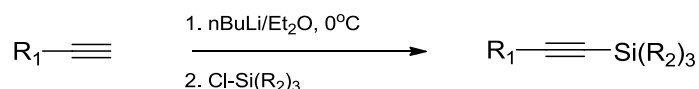
General procedure D2



To a solution of brominated compound **D₁** (1 eq) in THF (9 mL per 1 mmol of starting material), NaH (60% in oil, 1 eq) was added in two portions at 0 °C. Next, the reaction was heated to 70 °C. Progress of the reaction was monitored by TLC. When the reaction was completed, saturated solution of NH₄Cl was added and two phases were separated. The aqueous layer was washed with DCM (3 times). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and evaporated. The crude product was used directly in fragmentation-recyclization reaction without any further purification.

Experimental procedure for preparation of silylated alkynes 2B-2E:

General procedure E



To a stirred solution of the acetylenic compound (68.5 mmol, 1 eq) in anhydrous Et₂O (120 mL), a commercially available solution of *n*BuLi 2.5M in THF (30.15 mL, 75.37 mmol, 1.1 eq) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min and then the required chlorosilane (75.4 mmol, 1.1 eq) was added dropwise at 0 °C. The residue was allowed to warm to room temperature. Next, after complete formation of the expected product, 1M aqueous solution of NH₄Cl (120 mL) was added and the mixture was stirred for

¹ In the case of LAuX, the catalyst was *in situ* formed by mixing LAuCl and AgX (1/1 mixture).

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15 min. The aqueous layer was then extracted with Et₂O (three times). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated carefully under vacuum. The resulting crude product was purified by flash column chromatography on silica gel (pentane/Et₂O: 99/1) to give the desired silylated alkyne as a colorless oil.

Preparation of catalysts

- The commercially available Ph₃PAuCl, Ph₃PAuNTf₂, IPrAuCl, AgOTf, CuI, Cu(OTf)₂, I₂, Tf₂NH, TMSOTf, TIPSOTf, Sc(OTf)₃, NaBARF, AgOTs, AgSbF₆, AgBF₄ were purchased from Sigma Aldrich or Alfa Aesar.
- (C₆F₅)₃PAuCl, (*t*Bu)₃PAuCl, IPrAuCl, NHCAuCl and (4-MeO-(C₆H₄)₃)PAuCl were prepared according to the general procedure F

General procedure F

AuCl(SMe₂) (1 eq) and L₃P (1 eq) were placed under nitrogen and dissolved in dry CH₂Cl₂ (0.5 mL per 0.05 mmol of phosphine). The reaction mixture was stirred at room temperature for 15 min and the volume of the solution was reduced to 0.1 mL. Pentane was added (0.5 mL per 0.05 mmol of phosphine) resulting in the precipitation of the complex. The solvent was evaporated and the resulting white solid was dried under reduced pressure for 1h to give L₃PAuCl. The gold chloride complex was directly used as such in the alkynylation reaction.

- The gold alkynylide (Ph₃PAuC≡CPh) was prepared according to the following procedure :

To a stirred solution of phenylacetylene (1 eq) in anhydrous Et₂O (4.5 mL per 1 mmol of phenylacetylene), a commercially available solution of *n*BuLi 2.5M in THF (1 eq) was added dropwise at 0 °C. The reaction mixture was stirred for 40 min and Ph₃PAuCl (1 eq) was then added at 0 °C. The reaction mixture was then allowed to warm to room temperature. Progress of the reaction was monitored by TLC. When completed, 1M NH₄Cl aqueous solution was added and the mixture was stirred for a further 15 min. The aqueous layer was extracted with Et₂O (three times) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under vacuum. The resulting crude product was purified by

flash column chromatography (pentane/Et₂O) to give the corresponding product aminated alkyne.

- AgNTf₂ was prepared according to the following procedure:

To a solution of Ag₂CO₃ (827 mg, 3.00 mmol, 1 eq) in distilled water (10 mL) at room temperature was added HNTf₂ (72 %w/w, 1.17 mL, 5 mmol, 1.67 eq). The reaction mixture was protected from light with aluminium foil and was then heated to 65 °C for 20 min. It was next cooled down to room temperature, filtered and evaporated to give a white solid (0.82 g, 2.1 mmol, 70% yield).

The alkynylation reaction

General procedure G

To a solution of the catalyst² LAuX (0.03-0.1 eq) in a solvent ([substrate]=0.48 mol/L), were added the nucleophile (1.2-2 eq) in a solvent ([substrate]=0.8 mol/L) followed by the acetoxy- or alkoxy lactame (1 eq). The reaction mixture was then stirred at the mentioned temperature. At the end of the reaction (¹H NMR monitoring), the reaction mixture was directly purified by flash column chromatography on silica gel to afford the corresponding alkynylated product.

The sequential one pot BB/BA catalyzed alkylation of hydroxylactams.

General procedure H

To a solution of hydroxylactam (0.16 mmol) in 0.3 mL trifluorotoluene, trichloroacetonitrile (24 μL, 1.5 eq, 0.24 mmol) was added dropwise. After 10 min stirring 1 mol% DBU was introduced. As the transient trichloroacetimidate entities were found to be labile on TLC readily giving back the starting material, the completion of this step was checked by ¹H NMR spectroscopy. After formation of trichloroacetimidate intermediate, the nucleophile (1.2 eq) was added and the reaction mixture was left to warm up to room temperature. The end of the reaction was monitored by ¹H NMR spectroscopy.

The hydroarylation reaction

General procedure I

To a solution of the catalyst² LAuX (0.1 eq) in a solvent ([substrate]=0.2 mol/L), were added the alkyne (1 eq) in a solvent ([substrate]=0.5 mol/L). The reaction mixture was then stirred at

² In the case of LAuX, the catalyst was *in situ* formed by mixing LAuCl and AgX (1/1 mixture).

the mentioned temperature. At the end of the reaction (^1H NMR monitoring), the reaction mixture was directly heated to directly purified by flash column chromatography on silica gel to afford the corresponding alkynylated product

The one-pot alkynylation-hydroarylation reaction

General procedure J

To a solution of the catalyst³ LAuX (0.03-0.1 eq) in a solvent ([substrate]=0.48 mol/L), were added the nucleophile (1.2-2 eq) in a solvent ([substrate]=0.8 mol/L) followed by the acetoxy- or alkoxy lactame (1 eq). The reaction mixture was then stirred at 40 °C. After complete formation of the starting material to the alkylated intermediate, the reaction mixture was directly heated at the mentioned temperature and continuously monitored. At the end of the reaction (^1H NMR monitoring), purified by flash column chromatography on silica gel to afford the corresponding alkynylated product.

Preparation of gold – alkynylide

General procedure K

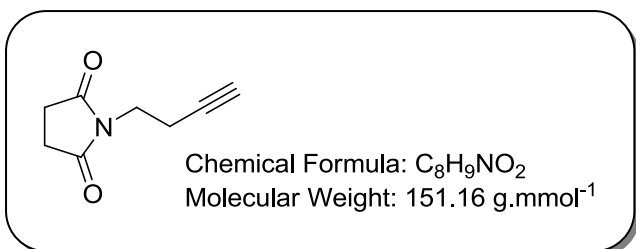
To a stirred solution of phenylacetylene (1 eq) in anhydrous Et_2O (4.5 mL per 1 mmol of phenylacetylene), a commercially available solution of $n\text{BuLi}$ 2.5M in THF (1 eq) was added dropwise at 0 °C. The reaction mixture was stirred for 40 min and Ph_3PAuCl (1 eq) was then added at 0 °C. The reaction mixture was then allowed to warm to room temperature. Progress of the reaction was monitored by TLC. When completed, 1M NH_4Cl aqueous solution was added and the mixture was stirred for a further 15 min. The aqueous layer was extracted with Et_2O (three times) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated under vacuum. The resulting crude product was purified by flash column chromatography (pentane/ Et_2O) to give the corresponding product aurated alkyne.

³ In the case of LAuX, the catalyst was *in situ* formed by mixing LAuCl and AgX (1/1 mixture).

Analyses

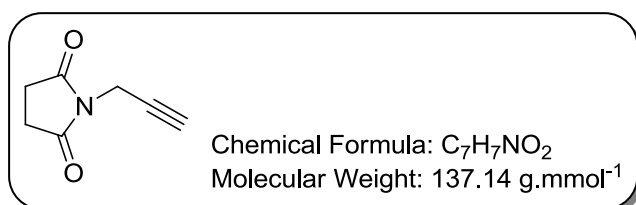
Chapter II:

Starting materials:

1-(but-3-ynyl)pyrrolidine-2,5-dione (I)

Prepared according to the general procedure **A0** from corresponding imide (99.7% yield).

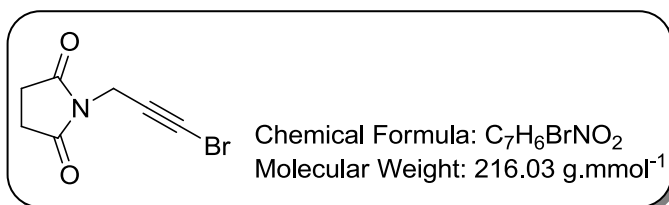
White solid. $R_f = 0.53$ [cyclohexane/EtOAc (3/7)]; **m.p.** 62 °C; **IR (neat)/v cm⁻¹**: 3289, 2945, 1670, 1464, 1422, 665 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 3.70 (t, $J = 9.0$ Hz, 2H, CH₂), 2.73 (s, 4H, 2*CH₂), 2.52 (t, $J = 6.0$ Hz, 2H, CH₂), 1.96 (s, 1H, CCH); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 176.9 (2*C_q), 80.0 (CH₂), 70.2 (CH₂), 37.1 (C_q), 28.1 (2*CH₂), 17.3 (CH);

1-(prop-2-ynyl)pyrrolidine-2,5-dione (II)

Prepared according to the general procedure **A0** from corresponding imide (87% yield).

White solid. $R_f = 0.39$ [cyclohexane/EtOAc (1/1)]; **m.p.** 56 °C; **IR (neat)/v cm⁻¹**: 1706, 1176, 666 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 2.28 (d, $J = 2.1$ Hz, 2H, CH₂), 2.77 (s, 4H, 2*CH₂), 2.19 (s, 1H, CCH); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 175.8 (2*C_q), 77.3 (C_q), 71.3 (CH), 28.2 (CH₂), 27.7 (2*CH₂); **GC-MS (EI)** requires mass m/z 137.05, found m/z 139 (23), 111 (28), 97 (100), 82 (26), 69 (10), 55 (12), 53 (15);

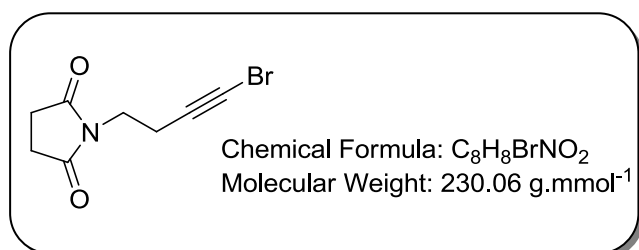
1-(3-bromoprop-2-ynyl)pyrrolidine-2,5-dione (III)



Prepared according to the general procedure **A0** from corresponding imide (89% yield).

R_f = 0.46 [cyclohexane/EtOAc (1/1)]; **m.p.** 131 °C; **IR (neat)/v cm⁻¹**: 2967, 2941, 1778, 1709, 1423, 1398, 819, 644 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 4.28 (s, 2H, CH₂N), 2.76 (s, 4H, CH₂CO); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 175.8 (2**C_q*), 72.9 (*C_q*), 43.4 (*C_q*), 29.6 (CH₂), 28.7 (2*CH₂); **GC-MS (EI)** requires mass m/z 216.0320, found m/z 217 (10), 191 (42), 190 (34), 189 (44), 188 (26), 177 (49), 176 (27), 175 (47), 174 (24), 121 (11), 119 (11), 110 (100), 109 (11), 96 (14), 82 (45), 56 (13), 55 (15), 54 (14), 53 (180), 52 (11)

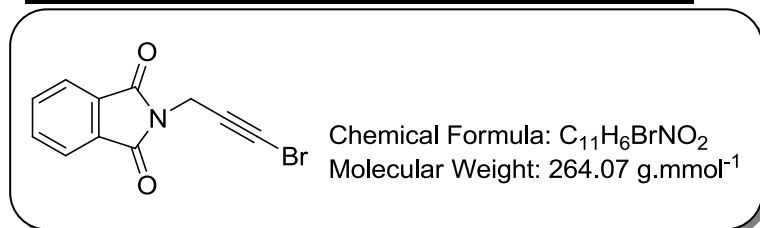
1-(4-bromobut-3-ynyl)pyrrolidine-2,5-dione (IV)



Prepared according to the general procedure **B** from corresponding imide.(99 % yield

Colorless oil. R_f = 0.6 [cyclohexane/EtOAc (3/7)]; **IR (neat)/v cm⁻¹**: 1698, 1403, 1164 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 3.71 (t, *J* = 6.9 Hz, 2H, CH₂), 2.75 (s, 4H, 2*CH₂), 2.55 (t, *J* = 6.9 Hz, 2H, CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 176.8 (2**C_q*), 76.1 (*C_q*), 40.4 (*C_q*), 36.9 (CH₂), 28.1 (2*CH₂), 14.2 (CH₂); **GC-MS (EI)** requires mass m/z 228.9738, found m/z 153 (22), 152 (100), 151 (13), 114 (13), 111 (13), 86 (37), 56 (14);

2-(bromobut-3-ynyl)isoindoline-1,3-dione (V)



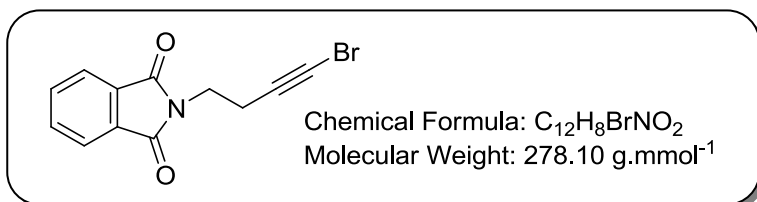
Prepared according to the general procedure **B** from corresponding imide.(98 % yield)

White solid. R_f = 0.4 [cyclohexane/EtOAc (7/3)]; **m.p.** 166 °C; **IR (neat)/v cm⁻¹**: 3472, 2960, 2222, 1770, 1717, 1469, 1425, 1354, 1328, 1188, 1126, 947, 725, 710, 640 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.90-7.88 (m, 2H, ArH), 7.76-7.73 (m, 2H, ArH), 4.47 (s, 2H,

EXPERIMENTAL SECTION

¹³CH₂); **C NMR** (75 MHz, CDCl₃, 20 °C) δ 166.9 (2*C_q), 134.3 (2*CH), 131.9 (2*C_q), 123.6 (2*CH), 73.5 (C_q), 43.6 (C_q), 28.0 (CH₂); **GC-MS (EI)** requires mass m/z 262.96, found m/z 263 (12), 185 (33), 184 (100), 183 (21), 181 (18), 156 (25), 133 (15), 132 (12), 130 (69), 129 (21), 128 (67), 117 (10), 105 (26), 104 (41), 103 (12), 102 (33), 101 (38), 77 (29), 76 (72), 75 (29), 74 (20);

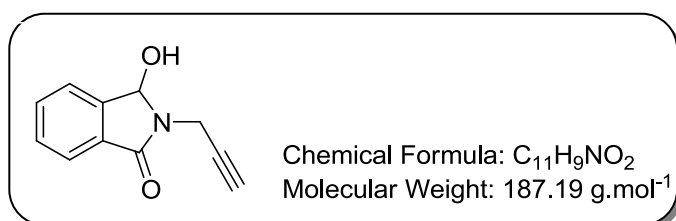
2-(4-bromobut-3-ynyl)isoindoline-1,3-dione (VI)



Prepared according to the general procedure **B** from corresponding imide.(77 % yield)

R_f= 0.58 [DCM/cyclohexane (9/1)]; **m.p.** 100 °C; **IR (neat)/v cm⁻¹**: 1772, 1709, 1441, 1396, 1366, 1189, 1115, 999, 720 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.90-7.87 (m, 2H, ArH), 7.77-7.74 (m, 2H, ArH), 3.89 (t, *J* = 6.9 Hz, 2H, CH₂N), 2.64 (t, *J* = 7.2 Hz, 2H, CH₂CCBr); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 168.0 (2*C_q), 134.1 (2*CH), 132.0 (2*C_q), 123.4 (2*CH), 76.3 (C_q), 40.5 (C_q), 36.3 (CH₂), 19.6 (CH₂); **GC-MS (EI)** requires mass m/z 276.97, found m/z 277 (17), 199 (46), 198 (100), 162 (13), 161 (100), 160 (100), 159 (66), 134 (12), 133 (99), 132 (27), 130 (52), 119 (17), 117 (18), 105 (67), 104 (99), 103 (16), 102 (23), 78 (14), 77 (99), 76 (99), 75 (40), 74 (28), 50 (20);

3-hydroxy-2-(prop-2-ynyl) isoindolin-1-one (15)

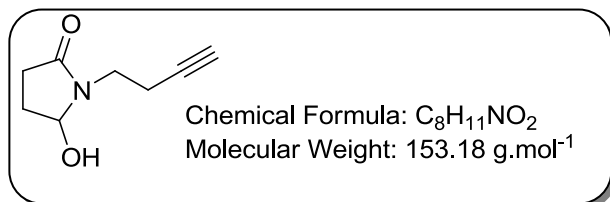


Prepared according to the general procedure **B** from corresponding imide.(87 % yield)

White solid. **R_f**= 0.28 (Cyclohexane/EtOAc, 4/6); **m.p.** 155 °C; **IR (neat)/v cm⁻¹**: 3684, 3307, 1703, 1520, 1426, 1212, 928, 749, 669. **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.78 (d, *J* = 7.4 Hz, 1H, ArH), 7.56-7.69 (m, 2H, ArH), 7.53 (t, *J* = 6.8 Hz, 1H, ArH), 6.01 (d, *J* = 11.1 Hz, 1H, CHOH), 4.61 (dd, *J* = 17.6, 2.3 Hz, 1H, CH₂), 4.07 (dd, *J* = 17.6, 2.3 Hz, 1H, CH₂), 2.59 (d, *J* = 11.1 Hz, 1H, OH), 2.25 (m, 1H, CH); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167 (C_q),

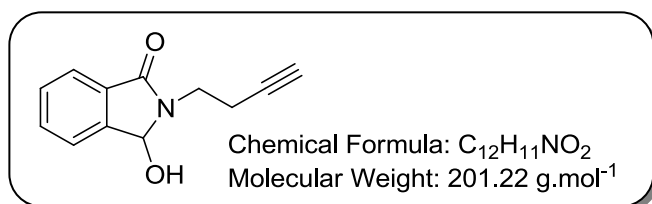
144 (*C_q*), 133.1 (*C_q*), 131.3 (*CH*), 130.3 (*CH*), 123.9 (*CH*), 81.5 (*C_q*), 78.4 (*C_q*), 72.5 (*CH*), 28.9 (*CH₂*);

1-(but-3-ynyl)-5-hydroxypyrrolidin-2-one (17)



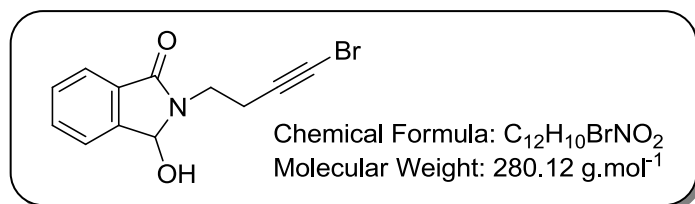
Prepared according to the general procedure **AII a** from corresponding imide. (87% yield)
White solid. *R_f* = 0.28 [cyclohexane/EtOAc (3/7)]; **m.p.** 62 °C; **IR (neat)/ν cm⁻¹**: 2945, 1670, 1465, cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 5.38 (s, 1H, *CHOH*), 3.63-3.42 (m, 2H, *NCH₂*), 2.87 (bs, 1H, *OH*), 2.69-2.53 (m, 4H, 2**CH₂*), 2.51-2.30 (m, 2H, *CH₂*), 2.09 (s, 1H, *CH*); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 175.0 (*C_q*), 100.0 (*C_q*), 83.9 (*CH*), 70.2 (*CH*), 39.52 (*CH₂*), 28.8 (*CH₂*), 28.4 (*CH₂*), 18.2 (*CH₂*);

2-(but-3-ynyl)-3-hydroxyisoindolin-1-one (16)



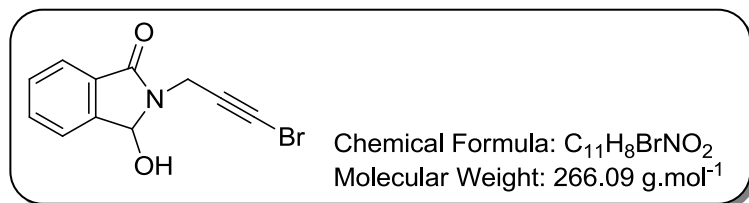
Prepared according to the general procedure **AII a** from corresponding imide. (83% yield)
White solid. *R_f* = 0.34 [cyclohexane/EtOAc (1/1)]; **m.p.** 101 °C; **IR (neat)/ν cm⁻¹**: 3289, 1682, 1472, 1439, 1421, 1322, 1109, 1057, 749, 696 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.70 (d, *J* = 6.9, 1H, *ArH*), 7.67 – 7.49 (m, 3H, *ArH*), 6.00 (s, 1H, *CHOH*), 3.89-3.67 (dm, 2H, *NCH₂*), 2.68-2.63 (m, 2H, *CH₂CCH*), 2.03 (s, 1H, alkyne *CH*); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.4 (*C_q*), 143.8 (*C_q*), 132.4 (*CH*), 131.3 (*C_q*), 129.9 (*CH*), 123.4 (*CH*), 122.8 (*CH*), 82.3 (*CH*), 77.2 (*CH*) 70.2 (*C_q*), 38.3 (*CH₂*), 17.9 (*CH₂*); **HRMS (+ESI)** calculated for C₁₂H₁₂NO₂ (*M+H*)⁺: 202.0868, found: 203.5685;

2-(4-bromobut-3-ynyl)-3-hydroxyisolidolin-1-one (18b)



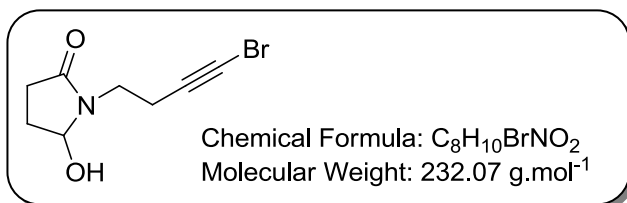
Prepared according to the general procedure **AII a** from corresponding imide. (84% yield)
White solid. $R_f = 0.5$ [cyclohexane/EtOAc (1/1)]; **m.p.** 174°C ; **IR (neat)/v cm^{-1} :** 3269, 2925, 2848, 1678, 1472, 1421, 1363, 1322, 1128, 1057, 745, 697 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20°C) δ 7.77(d, $J = 6.0 \text{ Hz}$, 1H, ArH), 7.62-7.50 (m, 3H, ArH), 5.91 (d, $J = 11.6 \text{ Hz}$, 1H, CHOH), 3.76 (m, 1H, CH_2N), 3.65 (m, 1H, CH_2N), 2.65-2.61 (m, 2H, CH_2CCBr); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20°C) δ 169.37 (C_q), 146.2 (C_q), 133.7 (CH), 132.5 (C_q), 130.8 (CH), 124.6 (CH), 123.9 (CH), 83.2 (CH), 78.2 (C_q), 41.0 (C_q), 39.3 (CH_2), 20.1 (CH_2); **GC-MS (EI)** requires mass m/z 278.9895, found m/z 279 (2), 278 (1), 201 (13), 200 (85), 199 (19), 163 (14), 162 (100), 161 (10), 78 (11);

2-(3-bromoprop-2-ynyl)-3-hydroxyisolidolin-1-one (18a)



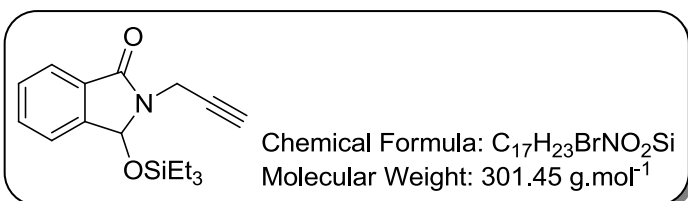
Prepared according to the general procedure **AII a** from corresponding imide. (84% yield)
White solid. $R_f = 0.5$ [cyclohexane/EtOAc (1:1)]; **m.p.** 165°C ; **IR (neat)/v cm^{-1} :** 3304, 2920, 2222, 1688, 1470, 1433, 1295, 1206, 1136, 1058, 911, 745, 706 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20°C) δ 7.80 (d, $J = 9.0 \text{ Hz}$, 1H, ArH), 7.64-7.53 (m, 3H, ArH), 5.98 (d, $J = 12.0 \text{ Hz}$, 1H, CHOH), 4.66 (d, $J = 11.0 \text{ Hz}$, 1H, NCH_2), 4.10 (d, $J = 13.0 \text{ Hz}$, 1H, NCH_2); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20°C) δ 166.7 (C_q), 143.8 (C_q), 132.8 (CH), 130.8 (C_q), 129.9 (CH), 123.6 (CH), 123.5 (CH), 81.2 (CH), 74.4 (C_q), 43.5 (C_q), 29.5 (CH_2); **GC-MS (EI)** requires mass m/z 266.9738, found m/z 267 (4), 213 (10), 211 (11), 189 (16), 188 (100), 187 (66), 186 (10), 161 (11), 160 (56), 159 (25), 147 (10), 132 (10), 131 (25), 130 (14), 104 (18);

1-(4-bromobut-3-ynyl)-5-hydroxypyrrolidin-2-one (18c)



Prepared according to the general procedure **AII a** from corresponding imide. (67% yield) colorless oil. R_f = 0.14 [cyclohexane/EtOAc (3/7)]; **IR (neat)/v cm⁻¹**: 2933, 1668, 1461 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 5.35 (t, J = 5.7 Hz, 1H, CHO), 3.61-3.44 (m, 2H, CH₂), 2.75-2.35 (m, 6H, CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 175.1 (C_q), 83.8 (CH), 82.2 (C_q), 70.1 (C_q), 39.4 (CH₂), 28.8 (CH₂), 28.3 (CH₂), 18.1 (CH₂);

2-(prop-2-ynyl)-3-(triethylsilyoxy)isoindolin-1-one (13)



To a solution of 3-hydroxy-2-(prop-2-ynyl)isoindolin-1-one (150 mg, 0.8 mmol, 1 eq) in dichloromethane (2.6 mL) triethylamine (167 μL, 1.2 mmol, 1.5 eq) and DMAP (9.78 mg, 0.08 mmol, 0.1 eq) were added and the reaction mixture was cooled down to 0 °C. Then TESOTf (181 μL, 0.8 mmol, 1 eq) was added dropwise and the residue reaction mixture was stirred at room temperature overnight.

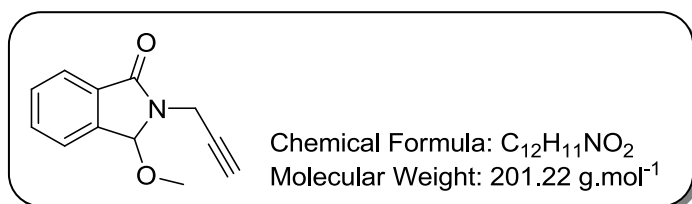
After complete formation of the expected product, the orange solution was quenched with 1.3 mL of NH₄Cl solution. The two phases were separated and aqueous layer was washed with DCM (3 times). The combined organic layer were washed with brine, dried over anhydrous MgSO₄ and evaporated. The crude product was purified by flash chromatography [cyclohexane/EtOAc (95/5) and the product was isolated as a colorless oil. (240 mg, 100% yield)

R_f = 0.34 [cyclohexane/EtOAc (8/2)]; **IR (neat)/v cm⁻¹**: 2955, 2878, 1714, 1466, 1409, 1075, 843, 747; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.81 (d, J = 7.2 Hz, 1H, ArH), 7.58 – 7.50 (m, 3H, ArH), 6.13 (s, 1H, CHOSiEt₃), 4.84 (dd, J = 17.6 and 1.9 Hz, 1H, NCH₂), 3.87 (dd, J = 17.6 and 1.7 Hz, 1H, NCH₂), 2.24 (s, 1H, alkyne CH), 1.03-0.95 (m, 9H, 3*CH₃), 0.76-0.74 (m, 6H, 3*CH₂CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 166.4 (C_q), 144.25 (C_q), 132.3

EXPERIMENTAL SECTION

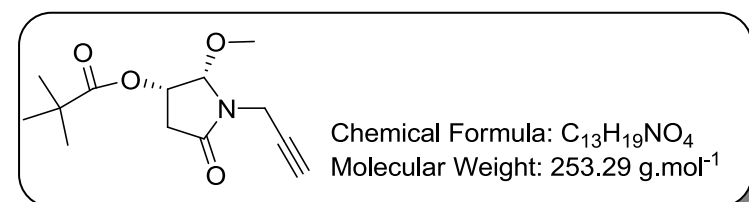
(CH), 131.4 (C_q), 129.6 (CH), 123.7 (CH), 123.1 (CH), 80.9 (C_q), 78.48 (CH), 72.1 (CH), 28.4 ($3 \times CH_2$), 6.8 ($3 \times CH_3$), 5.3 (CH_2); **GC-MS (EI)** requires mass m/z 301.1498, found m/z 301 (25), 300 (12) 286 (13), 274 (12), 273 (20), 272 (57), 259 (25), 258 (13), 246 (19), 245 (22), 244 (46), 243 (12), 235 (11), 234 (34), 233 (11), 232 (20), 231 (33), 230 (57), 229 (12), 218 (15), 217 (37), 216 (12), 207 (14), 206 (12), 119 (22), 184 (16), 172 (14), 171 (31), 170 (100), 169 (16), 160 (19), 144 (11), 143 (40), 142 (16), 141 (13), 140 (16), 133 (14), 132 (16), 130 (14), 116 (15), 115 (50), 114 (13), 104 (12), 103 (35), 102 (12), 89 (18), 88 (12), 87 (46), 76 (12), 75 (34);

3-methoxy-2-(prop-2-ynyl) isoindolin-1-one (1)



Prepared according to the general procedure **CII** from corresponding imide. (90% yield)
White solid. $R_f = 0.46$ [cyclohexane/EtOAc (1/1)]; **m.p.** 85 °C; **IR (neat)/ $\nu \text{ cm}^{-1}$** : 3307, 1707, 1470, 1405, 1138, 1076, 759, 664 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.85 (d, $J = 7.3$ Hz, 1H, ArH), 7.75 – 7.48 (m, 3H, ArH), 6.05 (s, 1H, NCH), 4.71 (dd, $J = 17.5$ and 2.3 Hz, 1H, NCH₂), 3.98 (dd, $J = 17.5$ and 2.3 Hz, 1H, NCH₂), 2.97 (s, 3H, CH₃), 2.25 (s, 1H, alkyne CH); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 166.9 (C_q), 140.47 (C_q), 132.4 (C_q), 130.1 (CH), 129.1 (CH), 123.8 (CH), 123.6 (CH), 86.0 (CH), 72.0 (C_q), 69.6 (CH), 49.9 (CH₃), 29.0 (CH_2); **GC-MS (EI)** requires mass m/z 201.2212, found m/z 201.0; 115 (20), 130 (10), 170 (100), 171 (17);

(2S, 3S)- 5-methoxy-1-(prop-2-ynyl)pyrrolidin-2-one (11)

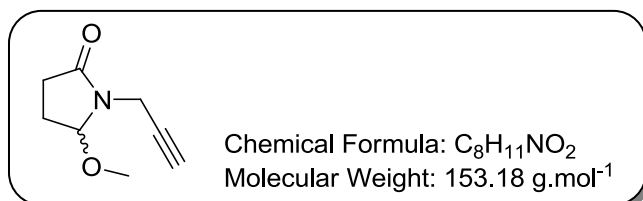


Prepared according to the general procedure **CI** from corresponding imide. (73% yield)
Colorless oil. $R_f = 0.5$ [cyclohexane/ EtOAc (7/3)]; **IR (neat)/ $\nu \text{ cm}^{-1}$** : 3308, 2935, 1720, 1443, 1371, 1280, 1235, 1151, 1086, 1039, 752, 667 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 5.1 (m, 1H, CHOPiv), 4.78 (s, 1H, CHOMe), 4.61 (dd, $J = 17.5$ and 2.3 Hz, 1H, NCH₂), 3.98

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(dd, $J = 17.5$ and 2.3 Hz, 1H, NCH_2), 3.47 (s, 3H, CH_3), 2.88 (m, 1H, $COCH_2$), 2.73 (m, 1H, $COCH_2$), 2.26 (s, 1H, *alkyne CH*), 1.22 (s, 9H, $3*CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 177.9 (C_q), 170.2 (C_q), 93.0 (CH), 93.0 (C_q), 72.4 (CH), 68.9 (CO Piv), 53.3 (O CH_3), 38.6 (C_q), 35.4 (CH_2), 32.0 (CH_2), 27.7 ($3*CH_3$); **GC-MS (EI)** requires mass m/z 253.1314, found 56 (70), 84 (11), 97 (39), 98 (35), 119 (12), 136 (14), 150 (100), 151 (39);

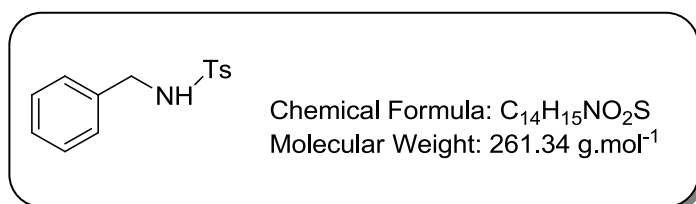
5-methoxy-1-(prop-2-ynyl)pyrrolidin-2-one (9)



Prepared according to the general procedure **CI** from corresponding imide. (71% yield)

Colorless oil. $R_f = 0.39$ [cyclohexane/ EtOAc (7/3)]; **IR (neat)/v cm^{-1}** : 3441, 3307, 3012, 2937, 2833, 1698, 1445, 1419, 1083, 666 cm^{-1} ; **1H NMR** (300 MHz, $CDCl_3$, 20 °C) δ : 5.10 (d, $J = 6.1$ Hz, 1H, $CHOMe$), 4.51 (dd, $J = 17.4$ and 2.3 Hz, 1H, NCH_2), 3.74 (dd, $J = 17.5$ and 1.3 Hz, 1H, NCH_2), 3.34 (s, 3H, CH_3), 2.55 (m, 1H, CH_2), 2.36 (m, 1H, CH_2), 2.28 – 2.09 (m, 2H, $COCH_2$), 1.99 (m, 1H, *alkyl CH*); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 174.2 (C_q), 89.1 (CH), 77.7 (C_q), 72.1 (CH), 53.7 (CH_3), 29.8 (CH_2), 29.6 (CH_2), 24.0 (CH_2); **GC-MS (EI)** m/z (rel. intensity) 137 ($[M^+]$ 3), 50 (17), 51 (46), 52 (23), 53 (88), 54 (54), 55 (25), 56 (100), 57 (11), 64 (38), 65 (71), 66 (56), 67 (39), 68 (21), 70 (11), 71 (15), 77 (11), 86 (11), 87 (15), 92 (22), 93 (13), 120 (33), 121 (83), 122 (69);

2N-benzyl-4-methylbenzenesulfonamide (VI)



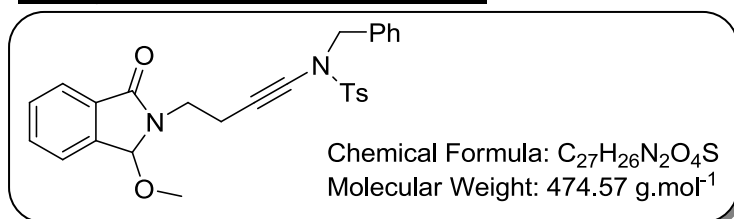
To a solution of benzylamine (0.7 mL, 6.4 mmol, 1 eq) in DCM (25 mL) were added *p*-toluene sulfonamide (1.47 g, 7.7 mmol, 1.2 eq) and triethylamine (1.78 mL, 12.8 mmol, 2 eq). After stirring for 1 h at room temperature saturated solution of NH_4Cl was added. The two phases were separated. The aqueous phase was washed with DCM, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography [cyclohexane/EtOAc (8:2)] and the product was isolated (1.51 g, 90% yield) as a white solid.

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$R_f=0.43$ [cyclohexane/EtOAc (7:3)]; **m.p.** 164-166 °C; **IR (neat)/v cm⁻¹**: 3432, 3270, 1646, 1423, 1324, 1178, 1165, 1083, 742 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.76 (d, $J = 9.0$ Hz, 2H ArH), 7.32-7.18 (m, 7H, ArH), 4.64 (bs, 1H, NH), 4.12 (d, $J = 6.0$ Hz, 2H, CH₂), 2.44 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 143.5 (C_q), 136.8 (C_q), 136.3 (C_q), 130.8 (CH), 129.8 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 47.2 (CH₃), 21.6 (CH₂); **GC-MS (EI)** requires mass m/z 261.08, found m/z 107 (19), 106 (100), 104 (11), 92 (18), 91 (59), 79 (12), 77 (11), 65 (10);

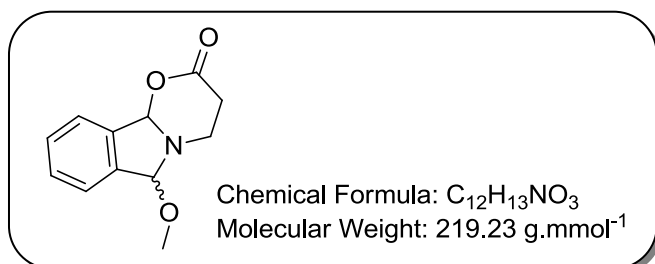
N-benzyl-N-(4-(1-methoxy-3-oxoisindolin-2-but-1-ynyl)-4

methylbenzenesulfonamide (14)



To a mixture of 2-(4-bromobut-3-ynyl)-3-methoxyisindolin-1-one (260 mg, 1 mmol, 1.1 eq), K₂CO₃ (250 mg, 1.83 mmol, 2 eq), CuSO₄·5H₂O (23 mg, 0.092 mmol, 0.1 eq) and 1,10-phenantroline (33 mg, 0.184 mmol, 0.2 eq) was added a solution of 2-(4-bromobut-3-ynyl)-3-methoxyisindolin-1-one (270 mg, 0.918 mmol, 1 eq) in toluene (2.3 mL). The reaction mixture was capped and heated in an oil bath at 80 °C for 18h. Upon completion, the reaction mixture was cooled to r.t., diluted with EtOAc and filtered through Celite. The filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography [cyclohexane/EtOAc (8/2)] and the product was isolated (319 mg, 73% yield) as a white solid. $R_f = 0.4$ [cyclohexane/EtOAc (6/4)]; **m.p.** 80-82 °C; **IR (neat)/v cm⁻¹**: 3454, 3034, 2934, 2254, 1704, 1469, 1438, 1411, 1363, 1169, 1075, 813, 747, 699, 599, 545, 557cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.82 (d, $J = 6.0$ Hz, 1H, ArH), 7.67-7.48 (m, 5H, ArH), 7.21 (s, 9H, ArH), 5.91 (s, 1H, CHOMe), 4.41 (s, 2H, CH₂Ph), 3.80 (m, 1H, NCH₂), 3.30 (m, 1H, NCH₂), 2.84 (s, 3H, OCH₃), 2.70-2.55 (m, 2H, CH₂CCN), 2.42 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.7 (C_q), 144.4 (C_q), 140.6 (C_q), 134.7 (C_q), 134.6 (C_q), 132.8 (C_q), 132.1 (CH), 129.9 (CH), 129.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 123.6 (CH), 86.7 (CH), 74.7 (C_q), 67.8 (C_q), 55.4 (CH₂), 49.4 (CH₃), 38.6 (CH₂), 21.6 (CH₃), 18.2 (CH₂); **GC-MS (EI)** requires mass m/z 474.16, found m/z 371 (17), 295 (21), 294 (100), 278 (12), 250 (14);

6-Methoxy-3,4,6,10b-tetrahydro-2H-[1,3]oxazino[2,3-a]isoindol-2-one (4)

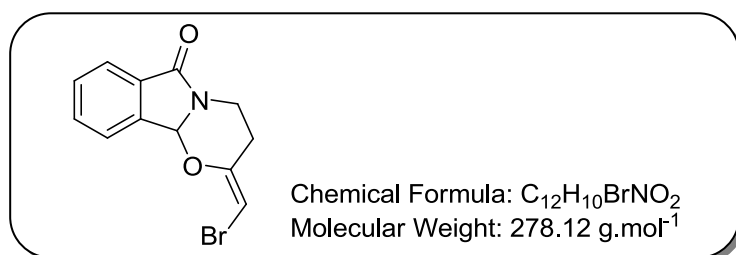


Prepared from acetoxylactam **1** following general procedure **D1** using 5 mol% of (C₆F₅)₃PAuSbF₆. (4 days at rt, 1 day at 45 °C; 38% yield).

Orange solid. *R_f* = 0.25 [cyclohexane/EtOAc (8/2)]; **m.p.** 141 °C; **IR (neat)/v cm⁻¹**: 3016, 2940, 1697, 1460, 1429, 1343, 1290, 731, 668 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (d, *J* = 6.8 Hz, 1H, ArH), 7.75–7.48 (m, 3H, ArH), 5.94 (s, 1H, CHOCO), 4.99 (s, 1H, CHOMe), 4.29 (d, *J* = 13.1 Hz, 1H, CH₂CO), 3.63 (s, 3H, CH₃), 3.53 (d, *J* = 12.9 Hz, 1H, CH₂N), 2.07-1.69 (d, *J* = 13.0 Hz, 2H, CH₂CO); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 166.2(C_q), 141.7 (C_q), 132.8 (C_q), 131.8 (CH), 129.9 (CH), 123.8 (CH), 122.9 (CH), 98.8 (CH), 77.5 (CH), 55.6 (CH₃), 33.4 (CH₂), 29.0 (CH₂); **GC-MS (EI)** requires mass *m/z* 219.0895, found *m/z* 219 (35), 158 (13), 159 (100), 160 (31);

(Z)-2-(bromomethylene)-3,4-dihydro-2H-[1,3]oxazino[2,3-a]isoindol-6-(10bH)-ne

(24)

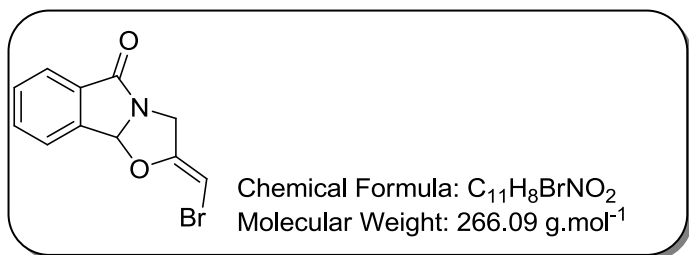


Prepared according to the general procedure **D2**. (93% yield)

Orange solid. *R_f* = 0.55 [DCM/MeOH (98:2)]; **m.p.** degradation at 170 °C; **IR (neat)/v cm⁻¹**: 1672, 1044, 697 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (d, *J* = 9.0 Hz, 1H, ArH), 7.73 (d, *J* = 6.0 Hz, 1H, ArH), 7.66-7.55 (m, 2H, ArH), 5.96 (s, 1H, CHO), 5.47 (s, 1H, C=CHBr), 4.25 (m, 1H, NCH₂), 3.46 (m, 1H, NCH₂), 2.62 (m, 1H, CH₂), 2.31 (m, 1H, CH₂);

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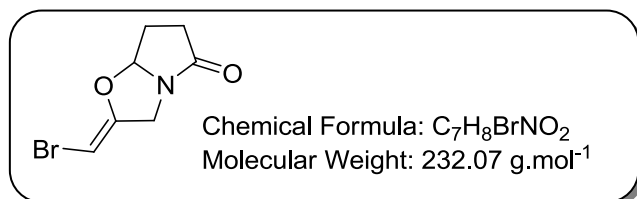
(Z)-2-(bromomethylene)-2,3-dihydrooxazolo[2,3-a]isoindol-5(9bH)-one (25)



Prepared according to the general procedure **D2**. (95% yield)

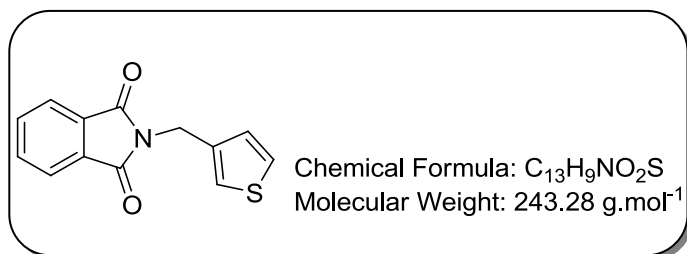
Orange solid. $R_f = 0.95$ [DCM/MeOH (98:2)]; **M.p.** 138 °C; **IR (neat)/v cm⁻¹**: 1705, 1385, 744, 719, 695 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (d, $J = 6.0$ Hz, 1H, ArH), 7.77-7.60 (m, 3H, ArH), 6.36 (s, 1H, CHBr), 5.11 (s, 1H, CHO), 4.75 (d, $J = 15.0$ Hz, 1H, NCH₂), 4.03 (d, $J = 15.0$ Hz, 1H, NCH₂); **¹³C NMR** (75 Hz, CDCl₃, 20 °C) δ 154.7 (C_q), 141.1 (C_q), 133.5 (CH), 131.5 (CH), 124.9 (CH), 123.3 (CH), 93.4 (CH), 73.9 (CH), 53.4 (C_q), 45.4 (CH₂), 29.5 (C_q);

(Z)-2-(bromomethylene)tetrahydropyrrolo[2,1-b]oxazol-5(6H)-one (26)



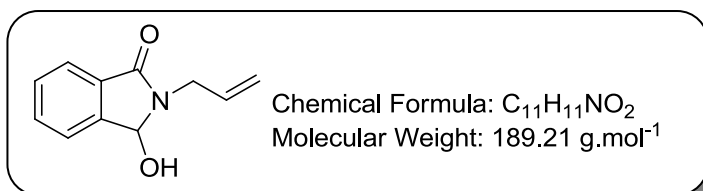
Prepared according to the general procedure **D**. (10% yield)

Orange oil. $R_f = 0.6$ [cyclohexane/EtOAc 2/8] **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 5.06 (s, 1H, C=CHBr), 5.59 (d, $J = 15.0$ Hz, 1H, CHO), 2.73-2.49 (m, 6H, 3*CH₂);

Chapter III**Starting materials from isoindolic amide-lactams series:****2-(thiopen-2-ylmethyl)isoindoline-1,3-dione (45 a)**

Prepared according to the general procedure **A0** from phthalimide (71% yield).

White solid. $R_f = 0.5$ (cyclohexane/EtOAc 7/3). **m.p.** 130 °C **IR (neat)/v cm⁻¹**: 1706, 1389, 946, 709 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.88-7.85 (m, 2H, ArH), 7.74-7.71 (m, 2H, ArH), 7.35 (bs, 1H, ThiophenH), 7.27 (m, 1H, ThiophenH), 7.17 (m, 1H, ThiophenH), 4.87 (s, 2H, NCH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.9 (2*C_q), 136.7 (2*C_q), 134.0 (2*CH), 132.1 (C_q), 128.1 (2*CH), 126.2 (CH), 124.2 (CH), 123.4 (CH), 36.2 (CH₂); **HRMS (+ESI)** calculated for C₁₃H₁₀NO₂S (M+H)⁺: 244.0422, found 244.0427;

Starting materials from isoindolic hydroxylactams series**2-Allyl-3-hydroxyisoindolin-1-one (141)**

Prepared according to the general procedure **AIIa** from corresponding imide (82% yield).

Product was used without further purification.

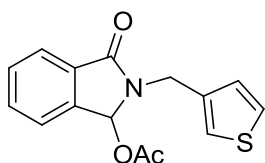
White solid. $R_f = 0.23$ (cyclohexane/ethyl acetate 7/3), **mp** 102 °C; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.60 (m, 3H, ArH), 7.47 (t, $J = 7.2$ Hz, 1H, ArH), 5.95 – 5.72 (m, 1H, CH=CH₂), 5.74 (s, 1H, CHOH), 5.28 (m, 1H, CH=CH₂), 5.22 (d, $J = 10.7$ Hz, 1H, CH=CH₂), 4.21 (dd, $J = 15.4$ and 4.4 Hz, 1H, NCH₂), 3.80 (dd, $J = 15.4, 7.2$ Hz, 1H, NCH₂), 3.33 (s, 1H, OH).

Data analyses are in accordance with previously reported results.⁴

⁴ Pin, F.; Comesse, S.; Garrigues, B.; Marchalin, S.; Daïch, A. *J. Org. Chem.* **2007**, 72, 1181.

Starting materials from isoindolic acetoxylactams series

3-oxo-2-(thiophen-3-ylmethyl)isoindolin-1-yl acetate (45)

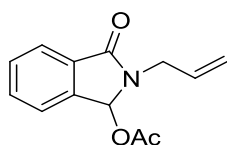


Chemical Formula: C₁₅H₁₃NO₃S
Molecular Weight: 287.33g.mol⁻¹

Prepared according to the general procedure **AI** from imide **45a** (62% yield).

White solid. $R_f = 0.43$ (cyclohexane/EtOAc 7/3). **m.p.** 117 °C; **IR (neat)/v cm⁻¹**: 1696, 1202, 749, 718 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (m, 1H, ArH), 7.57-7.50 (m, 3H, ArH), 7.27 (bs, 1H, ThiophenH), 7.23 (m, 1H, ThiophenH), 7.07 (d, $J = 3.0$ Hz, 1H, ThiophenH), 6.96 (s, 1H, CHOAc), 4.92 (dd, $J = 15.0$ Hz, 1H, NCH₂), 4.53 (d, $J = 15.0$ Hz, 1H, NCH₂), 2.04 (s, 3H, OCH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 171.0 (C_q), 167.6 (C_q), 141.0 (C_q), 137.3 (C_q), 132.5 (CH), 131.8 (C_q), 130.3 (CH), 127.8 (2*CH), 126.3 (CH), 123.8 (CH), 123.3 (CH), 80.8 (CH), 39.3 (CH₂), 20.8 (CH₃);

2-allyl-3-oxoisoindolin-1-yl acetate (31)



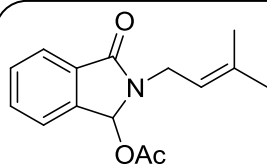
Chemical Formula: C₁₃H₁₃NO₃
Molecular Weight: 231.25 g.mol⁻¹

Prepared according to the general procedure **AI** from the corresponding imide (91% yield).

White solid. $R_f = 0.43$ [cyclohexane/EtOAc (7/3)]; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.83 (d, $J = 6.0$ Hz, 1H, ArH), 7.60-7.53 (m, 3H, ArH), 7.00 (s, 1H, CHOAc), 5.84 (m, 1H, CH=CH₂), 5.22-5.19 (m, 2H, C=CH₂), 4.37 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH₂), 3.91 (dd, $J = 15.0$ and 12.0 Hz, 1H, NCH₂), 2.14 (s, 3H, COCH₃);

Data in accordance with previously reported results.⁵

2-(3-methylbut-2-enyl)-3-oxoisoindolin-1-yl acetate (38)



Chemical Formula: C₁₅H₁₇NO₃
Molecular Weight: 259.3 g.mol⁻¹

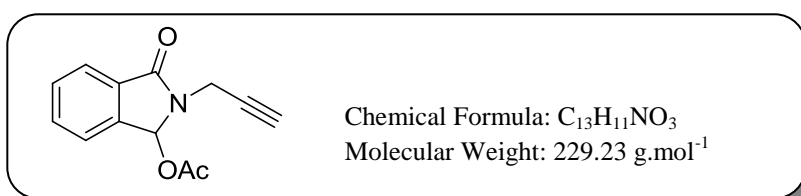
⁵ Szemes, F.; Fousse, A.; Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Synthesis*, **2006**, 5, 875.

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Previously prepared according to the general procedure **AI** from the corresponding imide (89% yield).

White solid. $R_f = 0.38$ (cyclohexane/EtOAc 7/3); **mp** 78 °C; **IR (neat)/v cm⁻¹**: 1749, 1704, 1224, 1198, 754; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.80 (d, $J = 6.0$ Hz, 1H, ArH), 7.53-7.52 (m, 3H, ArH), 6.96 (s, 1H, CH-N), 5.20 (t, $J = 6.0$ Hz, 1H, CH=C), 4.39 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH₂), 3.88 (dd, $J = 15.0$ and 9.0 Hz, 1H, NCH₂), 2.14 (s, 3H, CH₃), 1.73 (s, 6H, 2*CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 171.0 (C_q), 167.4 (C_q), 141.0 (C_q), 137.4 (C_q), 132.3 (CH), 132.1 (C_q), 130.2 (CH), 123.9 (CH), 123.5 (CH), 118.6 (CH), 80.9 (CH), 37.7 (CH₂), 25.8 (CH₃), 21.0 (CH₃), 17.7 (CH₃);

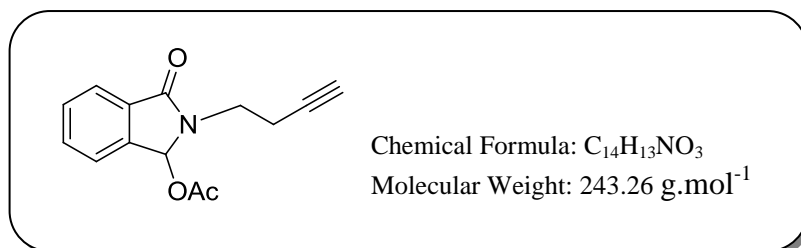
3-oxo-2-(prop-2-ynyl)isoindolin-1-yl acetate (40)



Prepared according to the general procedure **AI** from the corresponding imide (91% yield).

White solid. $R_f = 0.35$ [cyclohexane/EtOAc (7:3)]; **IR (neat)/v cm⁻¹**: 3685, 3307, 3019, 2400, 1716, 1520, 1429, 1215, 1151, 1016, 929, 749, 669 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.83 (d, $J = 6.9$ Hz, 1H, ArH), 7.63-7.48 (m, 3H, ArH), 7.15 (s, 1H, HCOAc), 4.63 (dd, $J = 17.6$ and 2.3 Hz, 1H, NCH₂), 4.09 (dd, $J = 17.6$ Hz and 2.3 Hz, 1H, NCH₂), 2.25 (s, 1H, CCH), 2.18 (s, 3H CH₃); **¹³C NMR** (75 MHz, CDCl₃) (δ ppm) 170.9 (C_q), 167.0 (C_q), 140.9 (C_q), 132.7 (C_q), 131.2 (CH), 130.3 (CH), 124.0 (CH), 123.7 (CH), 80.7 (CH), 77.5 (C_q), 72.2 (CH), 29.7 (CH₂), 20.5 (CH₃);

2-(but-3-ynyl)-3-oxoisoindolin-1-yl acetate (41)

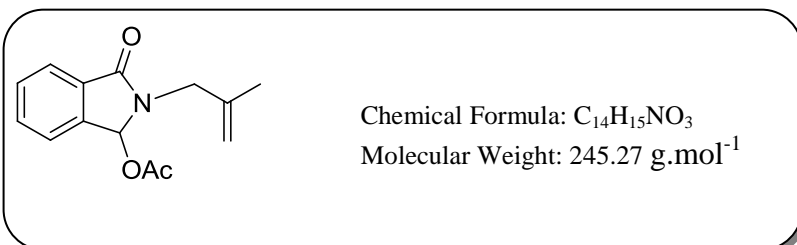


Prepared according to the general procedure **AI** from corresponding imide (90% yield).

White solid. $R_f = 0.4$ (cyclohexane/EtOAc 8/2); **mp** 67 °C. **IR (neat)/v cm⁻¹**: 3685, 3307, 3019, 2400, 1740, 1710, 1519, 1471, 1415, 1371, 1211, 1144, 1010, 929, 755, 698, 669 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.82 (d, $J = 6.2$ Hz, 1H, ArH), 7.48-7.60 (m, 3H, ArH), 7.15 (s, 1H, CHOAc), 3.95 (qd, $J = 13.7$ Hz and 6.9 Hz, 1H, NCH₂), 3.45 (td, $J = 14.0$ Hz, 6.7

Hz, 1H NCH₂), 2.51-2.66 (m, 2H, CH₂), 2.18 (s, 3H, CH₃), 1.97 (m, 1H, CH); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 171.1 (C_q), 167.8 (C_q), 141.0 (C_q), 132.5 (C_q), 1301.6 (2*CH), 130.3 (CH), 123.9 (CH), 123.6 (CH), 81.0 (C_q), 70.2 (CH), 39.1 (CH₂), 21.1 (CH₃), 18.4 (CH₂); **HRMS (+ESI)** calculated for C₁₄H₁₄NO₃ (M+H)⁺: 244.0973, found 242.5561;

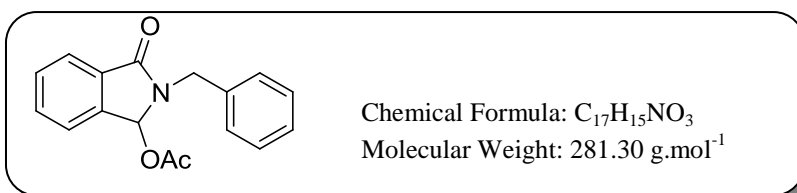
2-(methylallyl)-3-oxoisindolin-1-yl acetate (39)



Previously prepared according to the general procedure **AI** from the corresponding imide (87% yield)

White solid; **R_f** = 0.42 [cyclohexane/DCM/EtOAc (7/1/2)]; **mp** 40 °C; **IR (neat)/v cm⁻¹**: 1742, 1710, 1226, 1204; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.84 (d, *J* = 6.0 Hz, 1H, ArH), 7.59-7.53 (m, 3H, ArH), 6.96 (s, 1H, CHOAc), 4.90 (s, 1H, CH=CH₂), 4.82 (s, 1H, CH=CH₂), 4.27 (d, *J* = 15.0 Hz, 1H, NCH₂), 3.91 (d, *J* = 15.0 Hz, 1H, NCH₂), 2.12 (s, 3H, COCH₃), 1.73 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 171.0 (C_q), 167.9 (C_q), 141.0 (C_q), 140.5 (C_q), 132.5 (CH), 131.7 (C_q), 130.3 (2*CH), 123.8 (CH), 112.9 (CH₂), 81.1 (CH), 46.4 (CH₂), 20.9 (CH₃), 20.0 (CH₃);

2-benzyl-3-oxoisindolin-1-yl acetate (36)



Prepared according to the general procedure **AI** from the corresponding imide (90% yield).

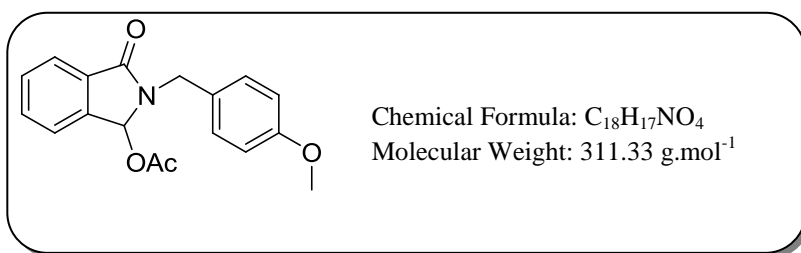
White solid. **R_f** = 0.27 [cyclohexane:DCM:EtOAc (7/2/1)].

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.88 (m, 1H, ArH), 7.63-7.49 (m, 3H, ArH), 7.32 (s, 5H, ArH), 6.95 (s, 1H, CHOAc), 4.94 (d, *J* = 15.0 Hz, 1H, NCH₂), 4.56 (d, *J* = 15.0 Hz, 1H, NCH₂), 1.97 (s, 3H, COCH₃);

Data in accordance with previously reported results.⁶

⁶ (a) Pin, F.; Comesse, S.; Garrigues, B.; Marchalin, S.; Daich, A. *J. Org. Chem.*, **2007**, *72*, 1181; Winn, M.; (b) Zaugg, H.E. *J. Org. Chem.*, **1968**, *33*, 3779.

2-(4-methoxybenzyl)-3-oxoisindolin-1-yl acetate (37)



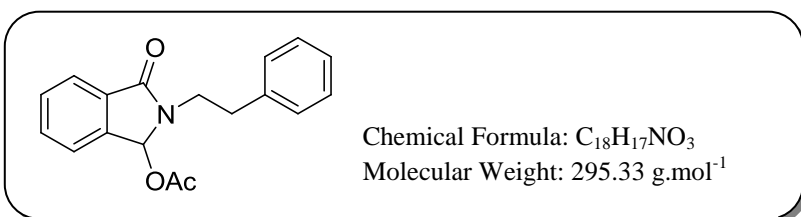
Prepared according to the general procedure **AI** from the corresponding imide (93% yield).

White solid. R_f = 0.35 [cyclohexane/EtOAc (8/2)];

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.87 (m, 1H, ArH), 7.63-7.45 (m, 3 H, ArH), 7.26 (d, J = 8.7 Hz, 2H, ArH), 6.92 (s, 1H, CHOAc), 6.85 (d, J = 8.7 Hz, 2H, ArH), 4.93 (d, J = 15.0 Hz 1H, NCH₂), 4.42 (d, J = 15.0 Hz, 1H, NCH₂), 3.80 (s, 1H, OCH₃), 2.03 (s, 3H, COCH₃);

Data in accordance with previously reported results.⁶

3-oxo-2-phenethylisindolin-1-yl acetate (42)



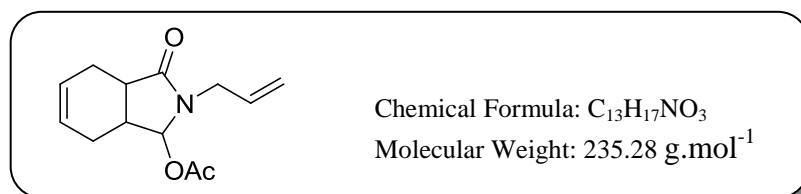
Prepared according to the general procedure **AII** from the corresponding imide (86% yield).

White solid. R_f = 0.51 [cyclohexane/EtOAc (7/3)]

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.84 (d, J = 6.0 Hz, 1H, ArH), 7.57-7.51 (m, 3 H, ArH), 7.34-7.24 (m, 5H, ArH), 6.91 (s, 1H, CHN), 4.05 (m, 1H, NCH₂), 3.49 (m, 1H, NCH₂), 3.08-2.94 (m, 2H, CC-CH₂), 2.15 (s, 3H, CH₃);

Data in accordance with previously reported results.⁷

2-allyl-3-oxo-2,3,3a,4,7,7a-hexahydro-1H-sioindol-1-yl acetate (96)



Prepared according to the general procedure **AII** from the corresponding imide 80% yield:

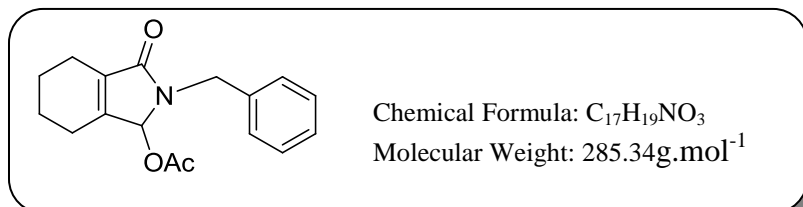
Colorless oil; R_f = 0.5 [cyclohexane/EtOAc (7/3)]; IR (neat)/ν cm⁻¹: 1738, 1708, 1235, 943 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 5.69-5.56 (m, 4H, CH=CH₂ with CH=CH and CHOAc), 5.16-5.09 (m, 2H, C=CH₂), 4.09 (dd, J = 15.0 and 6.0 Hz, 1H, NCH₂), 3.57 (dd, J =

⁷ Gormen, M.; Le Goff, R.; Lawson, A. M.; Daich, A. ; Comesse, S. *Tetrahedron Lett.* **2013**, 54, 2174.

EXPERIMENTAL SECTION

15.0 and 6.0 Hz, 1H, NCH₂), 2.89 (t, *J* = 9.0 Hz, 1H, CH-CHOAc), 2.44-2.34 (m, 2H, CH₂), 2.24-2.14 (m, 3H, CH₂ with CHCO), 1.99 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 176.2 (C_q), 169.7 (C_q), 131.0 (CH), 125.9 (CH), 123.6 (CH), 117.4 (CH₂), 87.4 (CH), 42.7 (CH₂), 36.0 (CH), 35.3 (CH), 23.0 (CH₂), 21.7 (CH₂), 20.7 (CH), 20.1 (CH₃);

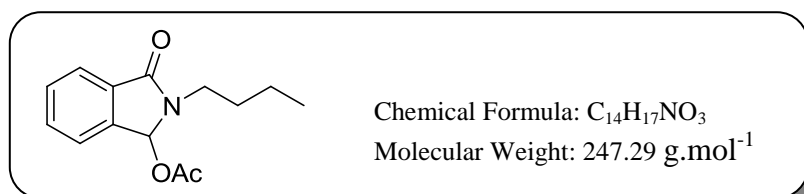
2-benzyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indol-1-yl acetate (123)



Prepared according to the general procedure **AI** from corresponding imide (63% yield).

White solid. *R_f* = 0.39 [cyclohexane/EtOAc (8/2)]; **mp** 96 °C; **IR (neat)/ν cm⁻¹**: 1743, 1702, 1225, 1213; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.24-7.14 (s, 5H, ArH), 6.30 (s, 1H, CHOAc), 4.53 (d, *J* = 15.0 Hz, 1H, NCH₂), 4.39 (d, *J* = 15.0 and 6.0 Hz, 1H, NCH₂), 2.18 (bs 2H, CH₂), 2.06-2.04 (m, 2H, CH₂), 1.79 (s, 3H, CH₃), 1.65-1.57 (m, 4H, 2*CH₂); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 170.8 (C_q), 170.7 (C_q), 149.9 (C_q), 137.4 (C_q), 134.4 (C_q), 128.5 (2*CH), 128.1 (CH), 127.4 (2*CH), 82.1 (CH), 44.2 (CH₂), 22.4 (CH₂), 21.8 (CH₂), 21.5 (CH₂), 20.6 (CH₃), 20.1 (CH₂);

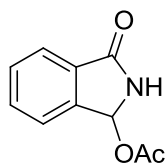
2-butyl-3-oxoisindolin-1-yl acetate (43)



Prepared according to the general procedure **AI** from corresponding imide (90% yield).

Colorless oil. *R_f* = 0.41 [cyclohexane:EtOAc (8/2)]; **IR (neat)/ν cm⁻¹**: cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.81 (d, *J*=6.0 Hz, 1H, ArH), 7.54 (s, 3H, ArH), 7.01 (s, 1H, CHN), 3.77 (m, 1H, NCH₂), 3.24 (m, 1H, NCH₂), 2.17 (s, 3H, OAc), 1.69-1.59 (m, 2H, NCH₂CH₂), 1.40-1.33 (m, 2H, CH₂CH₃), 0.94 (t, *J* = 9.0 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 171.1 (C_q), 167.8 (C_q), 140.9 (C_q), 132.2 (CH), 132.1 (C_q), 130.2 (CH), 123.7 (CH), 123.5 (CH), 81.1 (CH), 39.9 (CH₂), 30.3 (CH₂), 26.9 (CH₃), 20.0 (CH₂), 13.7 (CH₃); **HRMS (ESI)** calculated for C₁₄H₁₇NNaO₃ (M+H)⁺ :270.1101; found 270.1099;

3-oxoisindolin-1-yl acetate (46)

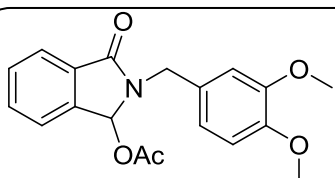


Chemical Formula: $C_{10}H_9NO_3$
Molecular Weight: $191.18\text{g}\cdot\text{mol}^{-1}$

Prepared according to the general procedure **AII** from corresponding hydroxyisindolinone (80% yield).

White solid. $R_f = 0.4$ (cyclohexane/EtOAc 1/1). **m.p.** 133 °C; **IR (neat)/ ν cm^{-1} :** 3105, 1711, 972, 739 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.85 (d, $J = 9.0$ Hz, 1H, ArH), 7.67-7.55 (m, 3H, ArH), 6.81 (bs, 1H, NH), 6.69 (s, 1H, CHOAc), 2.16 (s, 3H, CH_3); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 171.7 (C_q), 169.5 (C_q), 141.7 (C_q), 132.8 (CH), 131.4 (C_q), 130.4 (2*CH), 124.0 (CH), 78.7 (CH), 20.9 (CH_3);

2-(3,4-dimethoxybenzyl)-3-oxoisindoline-1-yl acetate (145)

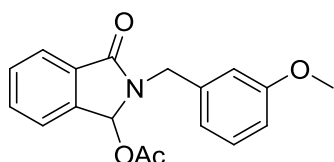


Chemical Formula: $C_{19}H_{19}NO_5$
Molecular Weight: $341.36\text{g}\cdot\text{mol}^{-1}$

Prepared according to the general procedure **A1** from corresponding imide (38% yield).

White solid. $R_f = 0.36$ [cyclohexane/EtOAc (6/4)]; **m.p.** 92 °C **IR (neat)/ ν cm^{-1} :** 1742, 1697, 1222, 1205, 751 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CD_2Cl_2 , 20 °C) δ 7.78 (m, 1H, ArH), 7.56-7.47 (m, 3H, ArH), 6.88 (s, 1H, CHN), 6.84 (s, 1H, ArH), 6.81 (m, 2H, ArH), 4.85 (d, $J = 15.0$ Hz, 1H, NCH_2), 4.33 (d, $J = 15.0$ Hz, 1H, NCH_2), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.00 (s, 3H, OAc); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 171.0 (C_q), 167.8 (C_q), 149.1 (C_q), 148.6 (C_q), 141.0 (C_q), 132.5 (CH), 131.8 (C_q), 130.3 (2*CH), 129.1 (C_q), 123.8 (2*CH), 120.7 (CH), 111.5 (CH), 111.0 (CH), 80.7 (CH_3), 55.9 (CH_3), 44.0 (CH_2), 20.9 (CH_3);

2-(3-methoxybenzyl)-3-oxoisindolin-1-yl acetate (44)



Chemical Formula: $C_{18}H_{17}NO_4$
Molecular Weight: $311.33\text{g}\cdot\text{mol}^{-1}$

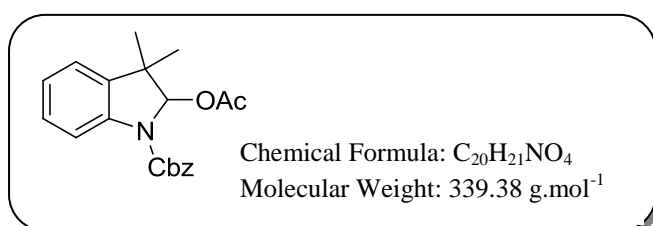
Prepared according to the general **procedure A1** from corresponding imide (92% yield).

White solid. $R_f = 0.27$ [cyclohexane/EtOAc (8/2)]; **IR (neat)/ ν cm^{-1} :** 1739, 1699, 937, 742 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.60 (m, 1H, ArH), 7.57-7.50 (m, 3 H, ArH), 7.25

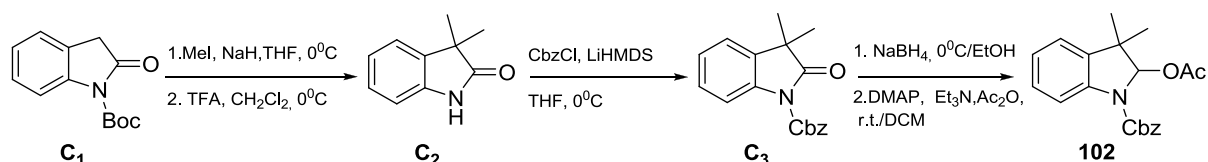
EXPERIMENTAL SECTION

(m, 1H, ArH), 6.94-6.82 (m, 4H, ArH with s, 1H, CH-OAc), 4.94 (d, $J = 15.0$ Hz 1H, NCH₂), 4.48 (d, $J = 15.0$ Hz, 1H, NCH₂), 3.80 (s, 3H, OCH₃), 2.0 (s, 3H, OCH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 170.9 (C_q), 167.8 (C_q), 159.9 (C_q), 141.0 (C_q), 138.2 (C_q), 132.5 (CH), 131.8 (C_q), 130.3 (CH), 129.7 (CH), 123.9 (CH), 123.8 (CH), 120.5 (CH), 113.7 (CH), 113.3 (CH), 80.9 (CH), 55.2 (CH₃), 44.2 (CH₂), 20.8 (CH₃); HRMS (ESI) calculated for C₁₆H₁₄NO₂ (M-OAc)⁺: 252.1019; found 252.1033;

benzyl-3,3-dimethyl-2-oxindoline-1-carboxylate (125)



Prepared in three steps from the *N*-protected oxindole derivative C1 (see scheme below):



Step 1: To a solution of *tert*-butyl-2-oxindoline-1-carboxylate C₁ (1.65 g, 7.07 mmol, 1 eq) in THF (17 mL), methyl iodide (1.32 mL, 21.21 mmol, 3 eq) was added dropwise and the mixture was cooled down to 0 °C with a NaCl saturated ice bath. Sodium hydride (60% in oil, 0.62 g, 15.55 mmol, 2.2 eq) was next added portionwise. After complete addition, the solution was stirred overnight at room temperature before water (50 mL) was added. The resulting mixture was then extracted with CH₂Cl₂ four times. The combined organic layers were washed with brine and dried over MgSO₄, filtered and concentrated under vacuum. The resulting crude product was purified by flash column chromatography on silica gel (cyclohexane/EtOAc: 95/5) to give the corresponding dimethylated product. (1.23 g, 4.71 mmol, 67% yield).

$R_f = 0.73$ [cyclohexane/EtOAc (8/2)]; ¹H NMR (300 MHz, CDCl₃) δ 7.84 (d, $J = 9.0$ Hz, 1H, ArH), 7.28-7.16 (m, 3H, ArH), 1.65 (s, 9H, C(CH₃)₃), 1.42 (s, 6H, 2*CH₃).

Data in accordance with previously reported results.⁸

⁸ Moody, Ch.J.; Slavin, A.M.; Willows, D. *Org. Biomol. Chem.* **2003**, *1*, 2716.

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Tert-butyl-3,3-dimethyl-2-oxindoline-1-carboxylate (1 g, 3.83 mmol, 1 eq) was dissolved in CH₂Cl₂ (7 mL) and cooled down to 0 °C using NaCl saturated ice bath. TFA (3.55 mL, 47.1 mmol, 12 eq) was added dropwise and the resulting mixture was stirred for 30 min. Next, the solution was evaporated in vacuo and the residue purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc (8/2) to give product **C**₂. (0.617g, 3.83 mmol, 100% yield).

*R*_f = 0.53 [cyclohexane/EtOAc (8/2)]; ¹H NMR (300 MHz, CDCl₃) δ 8.62 (bs, 1H, *NH*), 7.23 (d, *J* = 6.0 Hz, 2H, *ArH*), 7.11 (d, *J* = 6.0 Hz, 1H, *ArH*), 6.87 (d, *J* = 9.0 Hz, 1H, *ArH*), 1.43 (s, 6H, 2**CH*₃). Data in accordance with previously reported result.⁸

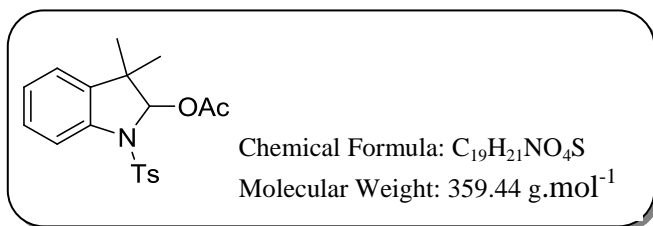
Step 2: To a solution of 3,3-dimethylindolin-2-one **C**₂ (0.36 g, 2.24 mmol, 1eq) and benzyl chloroformate (0.63 mL, 4.48 mmol, 2 eq) in THF (4 mL per 1 mmol) commercially available solution of LiHMDS 1M in THF (3.8 mL, 3.81 mmol, 1.7 eq) was added dropwise at 0 °C. Progress of the reaction was monitored by TLC (cyclohexane/EtOAc: 8/2). After 30 min, the reaction was quenched by addition of water. The product was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated under vacuum. The resulting crude product was purified by flash column chromatography on silica gel (cyclohexane/EtOAc) to give the resulting carbamate **C**₃ (0.47 g, 1.59 mmol, 71% yield).

*R*_f = 0.65 [cyclohexane/EtOAc (8/2)]; **m.p.** 75 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, *J* = 9.0 Hz, 1H, *ArH*), 7.53 (d, *J* = 9.0 Hz, 2H, *ArH*), 7.43-7.18 (m, 6H, *ArH*), 5.45 (s, 2H, *CH*₂), 1.44 (s, 6H, 2**CH*₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 180.2 (*C*_q), 151.7 (*C*_q), 138.5 (*C*_q), 135.6 (*C*_q), 135.2 (*C*_q), 129.3 (*CH*), 129.1 (*CH*), 128.8 (*CH*), 128.7 (*CH*), 125.5 (*CH*), 122.9 (*CH*), 115.9 (*CH*), 69.2 (*CH*₂), 45.3 (*C*_q), 26.0 (*CH*₃);

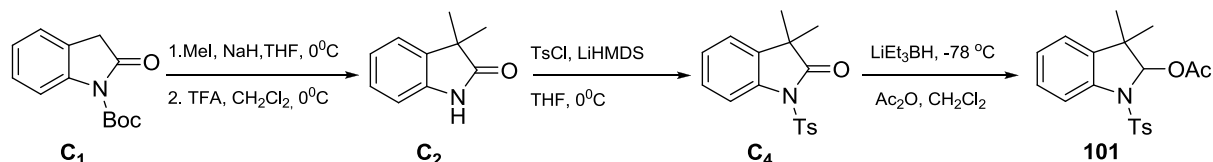
Step 3: The final acetoxy lactam **4C** was then prepared according to general procedure **AII** from compound **C**₃ (390 mg, 93% yield from **C**₃).

Colorless oil. *R*_f = 0.6 (cyclohexane/EtOAc 8/2); ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.89 (bs, 1H, *ArH*), 7.40-7.06 (m, 8H, *ArH*), 6.64 (s, 1H, *CHOAc*), 5.46 (d, *J* = 12.0 Hz, 1H, *CH*₂), 5.15 (d, *J* = 12.0 Hz, 1H, *CH*₂), 1.89 (bs, 3H, *COCH*₃), 0.90 (s, 3H, *CH*₃), 0.88 (s, 3H, *CH*₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 170.0 (*C*_q), 139.6 (*C*_q), 138.0 (*C*_q), 135.9 (*C*_q), 128.7 (*CH*), 128.4 (*CH*), 128.3 (*CH*), 128.0 (*CH*), 123.7 (*CH*), 122.0 (*CH*), 114.8 (*CH*), 90.4 (*CH*), 67.5 (*CH*₂), 44.4 (*C*_q), 28.7 (*CH*₃), 20.6 (*CH*₃), 19.6 (*CH*₃).

3,3-dimethyl-1-tosylindolin-2-yl acetate (124)



Prepared in three steps from the *N*-protected oxindole derivative C1 (see scheme below):



Step 1: Described for the benzyl-3,3-dimethyl-2-oxindoline-1-carboxylate

Step 2: Product **C4** was prepared according to the procedure described for benzyl-3,3-dimethyl-2-oxindoline-1-carboxylate (58% yield).

Data in accordance with previously reported result.⁹

$R_f = 0.48$ [cyclohexane/EtOAc (8/2)];

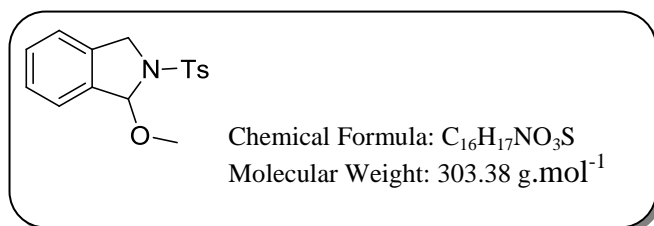
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.97-7.91 (m, 3H, ArH), 7.34-7.29 (m, 3H, ArH), 7.17 (d, *J* = 6.0 Hz, 2H, ArH), 2.41 (s, 3H, CH₃), 1.30 (s, 6H, 2*CH₃);

Step 3: Prepared according to the general procedure **AII**. (90% yield).

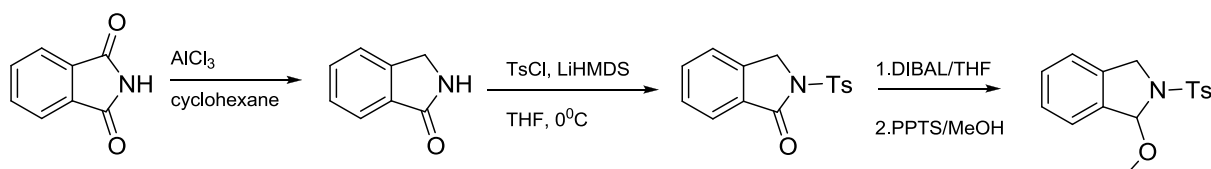
White solid. $R_f = 0.48$ (cyclohexane/EtOAc 8/2). **m.p.** 134 °C; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.78 (d, *J* = 6.0 Hz, 2H, ArH), 7.57 (d, *J* = 6.0 Hz, 1H, ArH), 7.26-7.22 (m, 3H, ArH), 7.05 (d, *J* = 6.0 Hz, 2H, ArH), 6.49 (s, 1H, CHOAc), 2.38 (s, 3H, Ar-CH₃), 2.02 (s, 3H, CO₂CH₃), 1.24 (s, 3H, CH₃), 0.91 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 169.9 (C_q), 144.4 (C_q), 139.1 (C_q), 138.2 (C_q), 136.0 (C_q), 129.8 (CH), 128.2 (CH), 127.0 (2*CH), 124.2 (2*CH), 122.5 (CH), 114.0 (CH), 91.8 (CH), 45.2 (C_q), 28.4 (CH₃), 21.6 (CH₃), 20.8 (CH₃), 19.5 (CH₃);

⁹ Jhan, Y.; Kang, T.; Hsieh, J. *Tetr. Lett.*, **2013**, 9, 1155.

1-methoxy-2-tosylisoindoline (128)



Prepared in four steps from the phthalimide (see scheme below):



Step 1: Phthalimide (1g, 6.79 mmol, 1 eq) was added to a suspension of AlCl₃ (4.5h, 33.98 mmol, 5 eq) in cyclohexane (12.6 mL). The resulting mixture was stirred at 110 °C for 23h, then cooled, poured over several grams of ice, and extracted with CHCl₃. The organic layer was dried over MgSO₄, filtered and concentrated under vacuum to afford the desired product. (0.57g, 63% yield)

Data in accordance with previously reported result¹⁰

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.88 (d, *J* = 6.0 Hz, 1H, ArH), 7.60-7.48 (m, 3H, ArH), 4.47 (s, 2H, CH₂);

Step 2: Procedure described before for *Tert*-butyl-3,3-dimethyl-2-oxoindoline-1-carboxylate (C₂) (51% yield)

Data in accordance with previously reported result.¹¹

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 8.03 (d, *J* = 6.0 Hz, 2H, ArH), 7.93-7.61 (m, 3H, ArH), 7.47 (m, 1H, ArH), 7.34 (d, *J* = 9.0 Hz, 2H, ArH), 4.91 (s, 2H, CH₂), 2.42 (s, 3H, CH₃);

Step 3: A solution of 2-tosylindolin-1-one (1 eq) in THF (6.8 mL per 1 mmol of starting material) was cooled to -78 °C and then was treated with DIBAL (3 eq) over 10 min. The reaction mixture was stirred for 1h at -78 °C followed by 1h at room temperature. The reaction was then cooled to -78 °C and quenched with MeOH (3mL per 1 mmol of the starting material), next allowed to slowly warm up to room temperature. The residue was poured onto an aqueous solution of Rochelles salts (38mL) and extracted with CH₂Cl₂ three times. The

¹⁰ Koltunov, K.Y.; Prakash, G.K.S.; Rasul, G.; Olah, G.A. *Eur. J. Org. Chem.*, **2006**, 4861.

¹¹ Ochiai, M.; Kajishima, D.; Sueda, T. *Tetrahedron Letters*, **1999**, 30, 5541.

EXPERIMENTAL SECTION

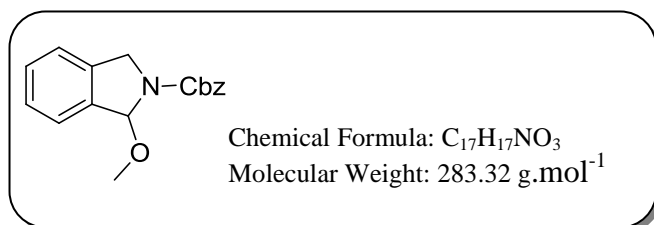
combined organic phase was next washed with brine, dried over MgSO_4 , filtered and concentrated under vacuum. The resulting crude product was purified by column chromatograph (cyclohexane/EtOAc: 7/3) to give the product. (75% yield)

White solid. $R_f = 0.33$ [cyclohexane/EtOAc (7/3)]; **m.p.** 129 °C; **IR (neat)/ ν cm^{-1} :** 3434, 1333, 1152 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.82 (d, $J = 9.0$ Hz, 2H, ArH), 7.45-7.19 (m, 6H, ArH), 6.54 (bs, 1H, CHOH), 4.70 (d, $J = 12.0$ Hz 2H, CH_2), 3.63 (d, $J = 3$ Hz, 1H, OH), 2.40 (s, 3H, Ar CH_3); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 144.0 (C_q), 137.4 (C_q), 135.9 (C_q), 135.3 (C_q), 129.9 (CH), 129.6 (CH), 128.3 (2*CH), 127.4 (CH), 126.5 (CH), 124.3 (CH), 122.6 (CH), 87.0 (CH), 51.9 (CH_2), 21.5 (CH_3);

Step 4: To a solution of hydroxylactam (1eq) in MeOH (5 mL per 1 mmol) PPTS (0.1 eq) was added at room temperature. The completion of the reaction was monitored by TLC (cyclohexane/EtOAc: 7/3). The residue precipitated product was dissolved in EtOAc and extracted with saturated solution of NaHCO_3 (three times), brine, dried over MgSO_4 , filtered and concentrated under vacuum. The resulting crude product was purified by column chromatograph (cyclohexane/EtOAc: 7/3) to give the product.(91% yield)

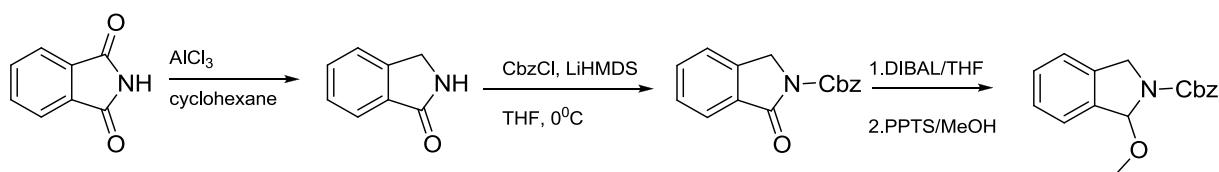
White solid. $R_f = 0.52$ [cyclohexane/EtOAc (7/3)]; **m.p.** 106 °C; **IR (neat)/ ν cm^{-1} :** 3356, 3260, 1338, 1305, 1158, 1097, 1034, 671 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.80 (d, $J=6.0$ Hz, 2H, ArH), 7.36-7.19 (m, 6H, ArH), 6.45 (s, 1H, CHOMe), 4.62 (s, 2H, CH_2), 3.06 (s, 3H, O CH_3), 2.39 (s, 3H, Ar CH_3); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 143.7 (C_q), 137.1 (C_q), 136.1 (C_q), 135.8 (C_q), 129.3 (CH), 129.6 (2*CH), 128.2 (CH), 127.3 (CH), 126.4 (CH), 124.2 (CH), 122.6 (CH), 93.1 (CH), 52.7 (CH_2), 51.6 (CH_3), 21.5 (CH_3); **HRMS (+ESI)** calculated for $\text{C}_{16}\text{H}_{17}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$: 326.0821, found 326.0821;

benzyl 1-methoxyisoindoline-2-carboxylate (129)



Prepared in four steps from the phthalimide (see scheme below):

EXPERIMENTAL SECTION



Step 1: Prepared according to the procedure described for the benzyl-3,3-dimethyl-2-oxoindoline-1-carboxylate

Step 2: Prepared according to the procedure described for *tert*-butyl-3,3-dimethyl-2-oxoindoline-1-carboxylate (**C**₂) (72% yield)

White solid. $R_f = 0.34$ [cyclohexane/EtOAc (7/3)]. **m.p.** 109 °C **IR (neat)/v cm⁻¹:** 1712, 1288, 735, 697 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.92 (d, $J = 9.0$ Hz, 1H, ArH), 7.35 (t, $J = 6.0$ Hz, 1H, ArH), 7.52-7.46 (m, 4H, ArH), 7.41-7.31 (m, 3H, ArH), 5.39 (s, 2H, CO₂CH₂), 4.83 (s, 2H, CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 166.4 (C_q), 151.7 (C_q), 140.8 (C_q), 135.4 (C_q), 133.8 (CH), 131.0 (C_q), 128.7 (3*CH), 128.4 (CH), 128.2 (2*CH), 125.2 (CH), 123.2 (CH), 68.2 (CH₂), 49.1 (CH₂); **HRMS (+ESI)** calculated for C₁₆H₁₃NNaO₃ (M+Na)⁺ : 290.0788, found 290.0799;

Step 3: Procedure described for 2-tosylindolin-1-one. (45% yield)

$R_f = 0.37$ [cyclohexane/EtOAc (7/3)]. **m.p.** 96 °C **IR (neat)/v cm⁻¹:** 3455, 1688, 1049, 756, 702 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C mixture of rotamers) δ 7.53-7.34 (m, 9H, ArH), 6.60 (bs, 0.64H, CHOH), 6.53 (bs, 0.32H, CHOH), 5.29 (bs, 0.79 H, CH₂OCOPh), 5.24 (bs, 1.30 H, CH₂OCOPh), 4.82-4.64 (m, 2H, CH₂), 4.14 (bs, 0.70 H, OH), 3.31 (bs, 0.30 H, OH); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 155.4 (C_q), 154.4 (C_q), 137.5 (C_q), 136.7 (C_q), 136.3 (C_q), 129.5 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 124.3 (CH), 122.6 (CH), 85.0 (CH), 84.3 (CH), 67.5 (CH₂), 67.2 (CH₂), 51.1 (CH₂), 50.7 (CH₂); **HRMS (+ESI)** calculated for C₁₆H₁₅NNaO₃ (M+Na)⁺ : 292.0944, found 292.0929;

Step 4: Prepared according to the procedure described for 1-methoxy-2-tosylisoindoline (78% yield)

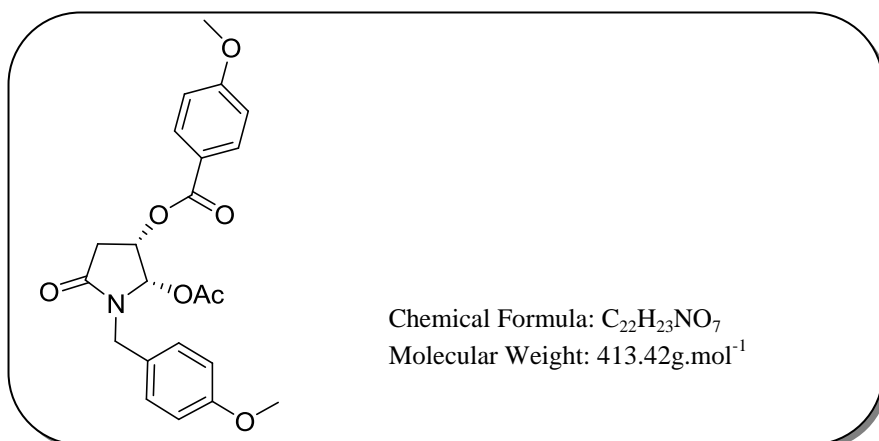
Colorless oil. $R_f = 0.39$ [cyclohexane/EtOAc (8/2)]. **IR (neat)/v cm⁻¹:** 1702, 1404, 749, 696 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C, mixture of rotamers) δ 7.41-7.26 (m, 9H, ArH), 6.44 (s, 1H, CHOMe), 5.29-5.25 (m, 2 H, CH₂OCOPh), 4.76-4.67 (m, 2H, CH₂), 3.34 (s, 1.5 H, CH₃), 3.10 (s, 1.5 H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) rotamers δ 155.4 (C_q),

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137.5 (C_q), 136.7 (C_q), 136.3 (C_q), 129.5 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 124.2 (CH), 122.6 (CH), 122.5 (CH), 91.4 (CH), 90.3 (CH), 67.3 (CH_2), 52.0 (CH_3), 51.5 (CH_2); **HRMS (+ESI)** calculated for $C_{17}H_{17}NNO_3$ ($M+Na$)⁺ : 306.1101, found 306.1097;

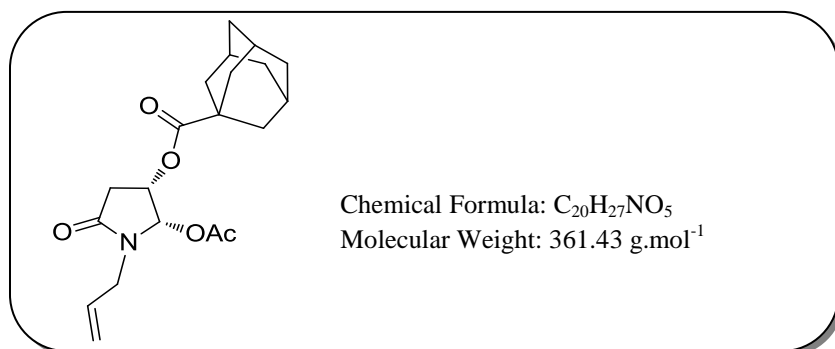
Starting materials from malic acid derivatives series:

(2S,3S)-2-acetoxy-1-(4-methoxybenzyl)-5-oxopyrrolidin-3-yl 4-methoxybenzoate (107)



Prepared according to the general procedure **AII** from the corresponding imide (48% yield);
White solid. $R_f = 0.49$ [cyclohexane/EtOAc (4/6)]; **mp** 126 °C ; $[\alpha]_D^{20} = -3.4$ (c 0.25, $CHCl_3$);
IR (neat)/v cm^{-1} : 1750.2, 1722.4, 1633.2 cm^{-1} ; **1H NMR** (200 MHz, $CDCl_3$, 20 °C) δ 7.90 (d, $J = 8.6$ Hz, 2H), 7.25 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.38 (d, $J = 5.5$ Hz, 1H), 5.41 (m, 1H), 4.71 (d, $J = 14.8$ Hz, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.93 (dd, $J = 16.8$ and 9.0 Hz, 1H), 2.81 (dd, $J = 16.8$ and 9.0, 1H), 1.88 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$, 20 °C) δ 171.5 (C_q), 170.0 (C_q), 165.1 (C_q), 163.8 (C_q), 159.3 (C_q), 131.7 (2* CH), 129.8 (2* CH), 127.9 (C_q), 121.1 (C_q), 114.1(2* CH), 113.8 (2* CH), 81.3 (CH), 66.4 (CH), 55.5 (CH_3), 55.3 (CH_3), 44.0 (CH_2), 34.3 (CH_2), 20.6 (CH_3).

(2S,3S)-2-acetoxy-1-allyl-5-oxopyrrolidin-3-yl adamantane-2-carboxylate (109)

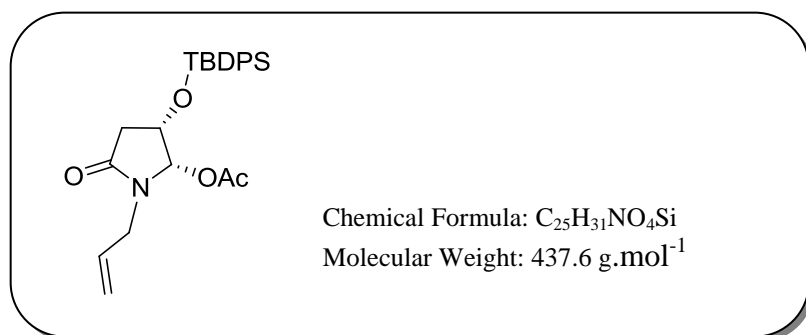


Prepared according to the general procedure **AII** from the corresponding imide (92% yield);

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White solid. $R_f = 0.59$ [cyclohexane/EtOAc (4/6)]; **mp** 124 °C ; $[\alpha]_D^{20} = -40.5^\circ$ (c 0.25, CHCl₃); **IR** (neat)/ ν cm⁻¹: 1746.2, 1716.5, 1645.1 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 6.40 (d, $J = 6.0$ Hz, 1H), 5.90-5.70 (m, 1H, CH=CH₂), 5.40-5.15 (m, 3H, CHOCOAdm with CH=CH₂), 4.15 (dd, $J = 15.0$ and 6.0 Hz, 1 H, NCH₂), 3.72 (d, $J = 15.0$ and 6.0 Hz, 1 H, NCH₂), 2.78 (dd, $J = 18.0$ and 9.0 Hz, 1H, COCH₂), 2.62 (dd, $J = 18.0$ and 9.0 Hz, 1H, COCH₂), 2.15 (s, 3H, CH₃), 2.10-1.50 (m, 15H, Adm); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 176.4 (C_q), 171.4 (C_q), 169.7 (C_q), 131.7 (CH), 118.5 (CH₂), 86.2 (CH), 65.8 (CH), 43.5 (CH₂), 40.6 (C_q), 38.7 (3*CH₂), 38.6 (3*CH₂), 38.5 (3*CH₂), 34.0(3*CH), 20.8(CH₃);

(2S,3S)-1-allyl-3-(tert-butyldiphenylsilyloxy)-5-oxopyrrolidin-2-yl acetate (108)

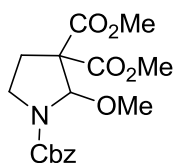


Prepared according to the general procedure **AII** from the corresponding imide (92% yield).

Colorless viscous oil. $R_f = 0.73$ [cyclohexane/EtOAc (4/6)]; $[\alpha]_D^{20} = -62.5^\circ$ (c 0.25, CHCl₃); **IR** (ν , cm⁻¹, CHCl₃) 1719.2; **¹H RMN** (300 MHz, CDCl₃, 25 °C) δ 7.68 (d, $J=6.0$ Hz, 4H, ArH), 7.30-7.53 (m, 6H, ArH), 6.19 (d, $J = 3.0$ Hz, 1H, CHOAc), 5.62-5.78 (m, 1H, CH=CH₂), 5.15-5.23 (m, 2H, CH=CH₂), 5.35-5.48 (m, 1H, CHOTBDPS), 4.04 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH₂), 2.67 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH₂), 2.45 (dd, $J = 18.0$ and 9.0 Hz, 1H, COCH₂), 2.17 (s, 3H, CH₃), 2.15 (dd, $J = 18.0$ and 9.0 Hz, 1H, COCH₂), 1.02 (s, 9H, 3*CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 172.6 (C_q), 170.4 (C_q), 135.6 (2*C_q), 132.8 (CH), 130.2 (2*CH), 130.1 (2*CH), 129.8 (2*CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 118.7 (CH), 82.7 (CH₂), 67.0 (CH), 53.4 (CH), 43.2 (CH₂), 36.2 (CH₂), 23.3 (C_q), 20.9 (3*CH₃), 18.8 (CH₃);

Starting materials from pyrrolidine derivatives series:

1-benzyl-3,3-dimethyl-2-methoxypyrrolidine-1,3,3-tricarboxylate (119)¹²



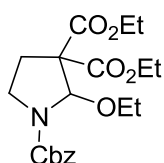
Chemical Formula: C₁₇H₂₁NO₇
Molecular Weight: 351.35 g.mol⁻¹

To a mixture of dimethyl 2-ethylidenemalonate (192 mg, 1.1 mmol, 1 eq) and benzyl 2-bromoethylcarbamate (284 mg, 1.1 mmol, 1 eq) in THF (5.5 mL), NaH (60% in oil, 53 mg, 1.32 mmol, 1.2 eq) was added in two portions at 0 °C. Next, the reaction mixture was warmed to room temperature and stirred overnight. The completion of the reaction was monitored by TLC (cyclohexane/EtOAc: 7/3). The reaction was quenched with saturated NH₄Cl solution. The aqueous layer was washed with EtOAc two times and the combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated. The product was purified by flash column chromatography on silica gel (cyclohexane/EtOAc: 7/3) to afford the desired product (274 mg, 0.78 mmol, 71% yield).

$R_f = 0.47$ [cyclohexane/EtOAc (7/3)]; ¹H NMR (300 MHz, CDCl₃, 20 °C) rotamers δ 7.47-7.28 (m, 5H, ArH), 5.61 (d, $J = 15.0$ Hz, 1H), 5.33-5.05 (m, 2H), 3.76 and 3.74 (s, 3H), 3.71 and 3.70 (s, 3H), 3.56 (dd, $J = 18.1$ and 9.1 Hz, 1H), 3.38 (m, 1H), 3.46 and 3.29 (s, 3H), 2.80 (m, 1H), 2.33 (dt, $J = 13.2$ and 6.6 Hz, 1H).

Data in accordance with previously reported results.¹³

1-benzyl 3,3-diethyl-2-ethoxypyrrolidine-1,3,3-tricarboxylate (118)



Chemical Formula: C₂₀H₂₇NO₇
Molecular Weight: 393.43 g.mol⁻¹

Prepared according to the procedure described for dimethyl 2-methoxy-5-oxo-1-phenethylpyrrolidine-3,3-dicarboxylate (114).

Colorless oil. $R_f = 0.47$ [cyclohexane/EtOAc (8/2)];

¹H NMR (300 MHz, CDCl₃, 20 °C) rotamers δ 7.36-7.30 (m, 5H, ArH), 5.72 (d, $J = 18.0$ Hz, 0.5H, CHOEt), 5.66 (d, $J = 18.0$ Hz, 0.5H, CHOEt), 5.26-5.13 (m, 2H, CH₂Ph), 4.23-4.10

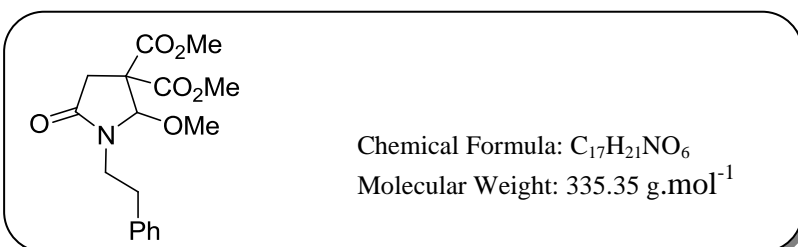
¹² Gormen, M.; Le Goff, R.; Lawson, A. M.; Daich, A. ; Comesse, S. *Tetrahedron Lett.* **2013**, 54, 2174.

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(m, 4H, 2*CH₂), 3.82 (m, 0.5H, CH₂), 3.69-3.53 (m, 2.5H, CH₂ with CH₂), 3.48-3.32 (m, 2H, CH₂), 2.82 (m, 1H, CH₂), 2.31 (m, 1H, CH₂), 1.29-1.17 (m, 5H, CH₂ with CH₃), 1.12 (m, 1.5 Hz, CH₃), 1.01 (m, 1.5 Hz, CH₃);

Data in accordance with previously reported results.¹³

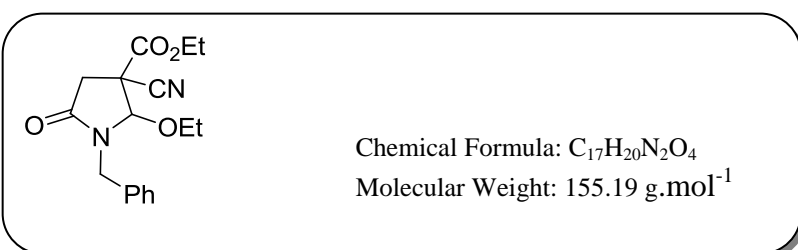
dimethyl 2-methoxy-5-oxo-1-phenethylpyrrolidine-3,3-dicarboxylate (114)



To a mixture of Michael acceptor (0.86 g, 4.96 mmol, 1.2 eq) in THF solution, α -bromoacetamide (1g, 4.14 mmol, 1 eq) was introduced and the mixture then was cooled to 0 °C. Next, to the reaction mixture sodium hydride (60% in oil, 0.2 mg, 4.96 mmol, 1.2 eq) was added in small portions, over time intervals of 5 minutes. After 3 hours of stirring for a cold, saturated ammonium chloride solution (40 mL) was added. The solid formed was next filtered, the aqueous phase extracted three times with ethyl acetate. The recombined organic phases were dried over MgSO₄ and evaporated under reduced pressure. The residue was purified by chromatography on silica gel eluting with ethyl acetate / cyclohexane.

$R_f = 0.6$ [cyclohexane/EtOAc (6/4)]; **IR (neat)/v cm⁻¹**: 2956, 1740, 1702, 908 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.34-7.23 (m, 5H, ArH), 5.31 (s, 1H, CHOCH₃), 3.85-3.76 (m, 7H, NCH₂ with 2*CO₂CH₃), 3.42-3.37 (m, 4H, CH₂ with OCH₃), 3.32 (m, 1H, NCH₂), 2.93-2.85 (m, 2H, CH₂), 2.65 (d, $J = 18.0$ Hz, 1H, NCH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 171.2 (C_q), 169.5 (C_q), 167.0 (C_q), 129.0 (2*CH), 138.9 (C_q), 128.9 (2*CH), 126.8 (CH), 93.3 (CH), 59.7 (C_q), 59.0 (CH₃), 53.6 (CH₃), 53.3 (CH₃), 42.9 (CH₂), 36.5 (CH₂), 34.3 (CH₂);

Ethyl 1-benzyl-3-cyano-2-ethoxy-5-oxopyrrolidine-3-carboxylate (115)



EXPERIMENTAL SECTION

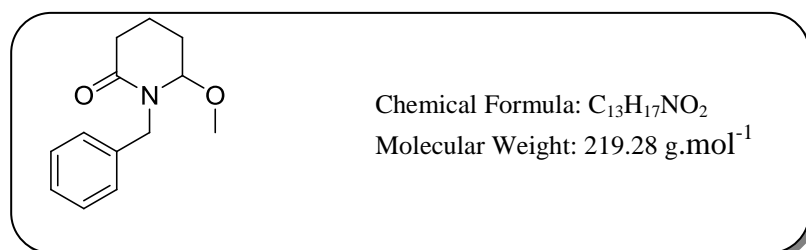
Prepared according to the procedure described for 1-benzyl-3,3-dimethyl-2-methoxy pyrrolidine-1,3,3-tricarboxylate.

Data in accordance with previously reported results.¹³

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.36-7.19 (m, 5H, ArH), 5.04 (d, *J* = 15.0 Hz, 1H, NCH₂), 4.81 (s, 1H, CHN), 4.28-4.20 (m, 2H, CO₂CH₂), 4.01 (d, *J* = 15.0 Hz, 1H, NCH₂), 3.83 (m, 1H, COCH₂), 3.57 (m, 1H, COCH₂), 3.14 (s, 2H, COCH₂), 1.30-1.21 (m, 6H, 2*CH₃);

Starting materials from piperidine derivatives series:

1-benzyl-6-methoxypiperidin-2-one (103)



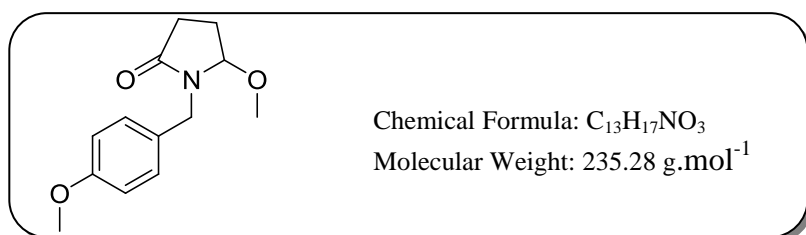
Prepared according to the general procedure **CI** from the corresponding piperidine (80% yield).

R_f = 0.41 [cyclohexane/EtOAc (6/4)];

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.34-7.24 (m, 5H, ArH), 5.38 (d, *J* = 12.0 Hz, 1H, CH₂CHOCH₃), 4.38 (s, 1H, CHOCH₃), 3.99 (dd, *J* = 15.0 Hz, 1H, CH₂CHOCH₃), 3.29 (s, 3H, CHOCH₃), 2.04-1.99 (m, 2H, CH₂), 1.7-1.61 (m, 4H, 2*CH₂);

Data in accordance with previously reported results¹⁴

5-methoxy-1-(4-methoxybenzyl)pyrrolidin-2-one (92)



Prepared according to the general procedure **CI** from the corresponding pyrrolidine (98% yield).

Colorless oil. *R_f* = 0.55 [cyclohexane/EtOAc (3/7)];

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.08-7.31 and 6.80-6.90 (m, 4H, ArH), 4.72 (dd *J* = 6.3 and 1.7 Hz, 1H, CHO), 3.95 and 4.90 (d, *J* = 14.2 Hz, 2H, CH₂N), 3.80 (s, 3H, CH₃O-C_{arom}),

¹³ Saber, M.; Comesse, S.; Dalla, V.; Daich, A.; Netchitailo, P.; Sanselme, M. *Synlett*, **2010**, *14*, 2197.

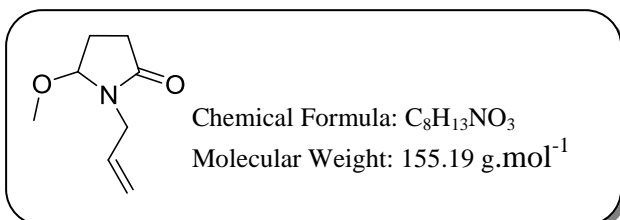
¹⁴ Takacs, J. M.; Weidner, J. J. *J. Org. Chem.*, **1994**, *59*, 6480.

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3.21 (s, 3H, CHOCH_3), 2.48-2.60 (m, 1H, HCHC=O), 2.36 (ddd, $J = 17.3$ and 9.6 and 3.7 Hz, 1H, HCHC=O), 1.92-2.13 (m, 2H, CH_2CH);

Data in accordance with previously reported results.¹⁵

1-allyl-5-methoxypyrrolidin-2-one (93)

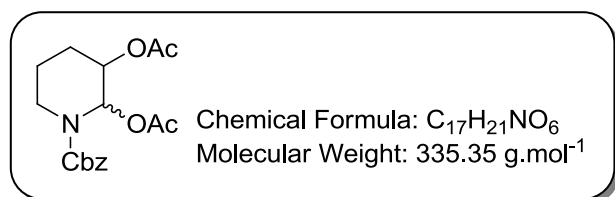


Prepared according to the general procedure **CI** from the corresponding pyrrolidine (81% yield).

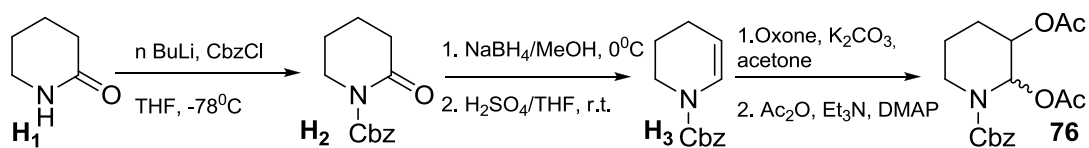
$R_f = 0.27$ [cyclohexane/EtOAc (1/1)];

$^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.08-7.31 and 6.80-6.90 (m, 4H, ArH), 4.72 (dd, $J = 6.3$ and 1.7 Hz, 1H, CHO), 3.95 and 4.90 (2xd, $J = 14.2$ Hz, 2H, CH_2N), 3.80 (s, 3H, $\text{CH}_3\text{O-C}_{\text{arom}}$), 3.21 (s, 3H, CHOCH_3), 2.48-2.60 (m, 1H, HCHC=O), 2.36 (ddd, $J = 17.3$ and 9.6 and 3.7 Hz, 1H, HCHC=O), 1.92-2.13 (m, 2H, CH_2CH);

1-(benzyloxycarbonyl)piperidine-2,3-diyl diacetate (101)



Prepared in three steps from the piperidin-2-one **H1** (see scheme below):



Step 1: To a solution of piperidin-2-one (1g, 10.09 mmol, 1 eq) in 44 mL of THF was added commercially available solution of n-BuLi 2.5 M in hexane (4.25 mL, 21.18 mmol, 1.05 eq) at -78°C over 15 min. The mixture was stirred at the same temperature for 1h and CbzCl (1.5 mL, 21.18 mmol, 1.05 eq) was added dropwise. The reaction mixture was let to warm up to -50°C over 1h and the reaction progress was monitored by TLC (cyclohexane/ ethyl acetate: 1/1). After addition of water (25 mL) the aqueous phase was extracted with diethyl ether three

¹⁵ D'hooghe, M.; Nieuwenhove, A. V.; Brabandt, W. V.; Rottiers, M.; Kimpe, N. D. *Tetrahedron*, **2008**, *64*, 1064.

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times. The combined organic layer was washed with brine and dried over anhydrous MgSO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc: 6/4) to afford the required product in 67% yield.

$R_f = 0.67$ [cyclohexane/EtOAc (1/1)];

$^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.45-7.31 (m, 5H, ArH), 5.28 (s, 2H, $\text{CH}_2\text{CO}_2\text{Ar}$), 3.76 (s, 2H, CH_2CO), 2.54 (s, 2H, CH_2), 1.85-1.82 (m, 4H, CH_2);

Data in accordance with previously reported results.¹⁶

Step 2: To a solution of benzyl 2-oxopiperidine-1-carboxylate (100 mg, 0.428 mmol, 1 eq) in MeOH (1.82 mL) NaBH_4 (16 mg, 0.428 mmol, 1 eq) was added portionwise at 0 °C. The solution was stirred at the same temperature for 20 min. The mixture was poured into ice water (5 mL) and extracted with EtOAc two times. The organic layer was washed with brine, dried under anhydrous MgSO_4 and concentrated. To a solution of the residue in THF (0.91 mL) was added H_2SO_4 (4.5 μL) and was stirred at room temperature for 1h. Then the mixture was poured into saturated aqueous KHCO_3 (3mL) and extracted with EtOAc three times. The organic layer was washed with brine, dried under anhydrous MgSO_4 and concentrated. The crude product was purified by column chromatography on silica gel to afford the product as a colorless oil. (52% yield)

$^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.36-7.32 (m, 5H, ArH), 6.89 (d, $J = 9.0$ Hz, 0.5H, $\text{CH}=\text{CH}$), 6.79 (d, $J = 9.0$ Hz, 0.5H, $\text{CH}=\text{CH}$), 5.18 (s, 2H, $\text{CH}_2\text{CO}_2\text{Ar}$), 4.97 (t, $J = 6.0$ Hz, 0.5H, $\text{CH}=\text{CH}$), 4.86 (t, $J = 6.0$ Hz, 0.5H, $\text{CH}=\text{CH}$), 3.63 (t, $J = 6.0$ Hz, 2H, CH_2), 2.04 (t, $J = 6.0$ Hz, 2H, CH_2), 1.83 (t, $J = 6.0$ Hz, 2H, CH_2);

Data in accordance with previously reported results⁹

Step 3: Solution of oxone (3.96g, 6.44 mmol, 2eq) in water (25.3 mL) was added dropwise to a solution of benzyl 3,4-dihydropyridine-1(2H)-carboxylate (0.7g, 3.22mmol, 1eq) and K_2CO_3 (0.9g, 6.44 mmol, 2 eq) in a mixture of acetone (11.5mL) and water (11.5 mL) at 0 °C for 5 min. The solution was next stirred at the room temperature for 5 h. Then it was poured into ice water (20mL) and extracted with EtOAc three times. The organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated under vacuum to afford the desired product as an oil. (95% yield)

¹⁶ Takeuchi, Y.; Azuma, K.; Oshige, M.; Abe, H.; Nishioka, H.; Sasaki, K.; Harayama, T. *Tetrahedron*, **2003**, 59, 1639.

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$^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.35 (s, 5H, ArH), 5.73 (d, $J = 3.0$ Hz, 0.5H, CHOH), 5.57 (d, $J = 3.0$ Hz, 0.5H, CHOH), 5.14 (s, 2H, $\text{CH}_2 \text{CO}_2\text{Ar}$), 3.91-3.51 (m, 5H CHOH with CH_2), 1.94-1.46 (m, 4H, 2^*CH_2);

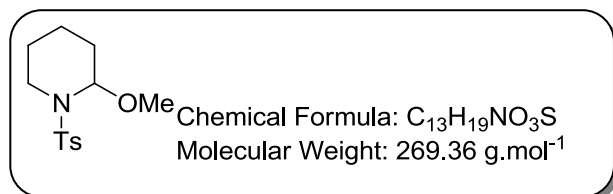
Data in accordance with previously reported result⁹

Acetic anhydride (0.84 mL, 8.91 mmol, 5.9 eq) was added dropwise to a solution of benzyl 2,3-dihydroxy-1-piperidinecarboxylate (0.38g, 1.51 mmol, 1 eq) and DMAP (18 mg, 0.151 mmol, 0.1 eq) in Et_3N (1.24 mL, 8.91 mmol, 5.9 eq). The solution was stirred at the room temperature for 1h. To the mixture was added saturated aqueous KHCO_3 solution (5 mL) and the mixture was extracted with EtOAc three times. The organic phase was then washed with brine five times, saturated solution of KHCO_3 and brine, dried over MgSO_4 , filtered and concentrated under vacuum. The resulting crude product was purified by column chromatograph to give the product as a colorless viscous oil. (0.34g, 73 % yield)

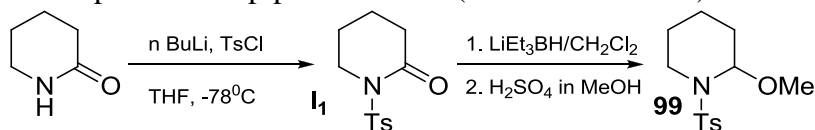
$^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.35 (s, 5H, ArH), 6.98 (d, $J = 3.0$ Hz, 0.5H, CHOAc), 6.68 (d, $J = 3.0$ Hz, 0.5H, CHOAc), 5.18 (m, 2H, CH_2), 4.89-4.84 (m, 1H CHOAc), 3.98 (m, 1H, CH_2), 3.06-2.96 (m, 1H, CH_2), 2.04-1.98 (m, 1.5H, CH_3), 1.86-1.80 (m, 1.5H, CH_3), 1.6-1.56 (m, 4H, CH_3 with CH_2);

Data in accordance with previously reported result⁹

2-methoxy-1-tosylpiperidine (99)



Prepared in three steps from the piperidin-2-one (see scheme below):



Step 1: To a solution of piperidin-2-one (1g, 10.09 mmol, 1 eq) in THF (20 mL) was added commercially available solution of n-BuLi 2.5 M in hexane (4.32 mL 10.79 mmol, 1.07 eq) at -78°C over 15 min. A solution of *p*-toluenesulfonyl chloride (2.06 g, 10.79 mmol, 1.07 eq) in THF (10 mL) was added dropwise. The mixture was warmed up to room temperature and stirred overnight. The solvent was next removed and trituration of the resulting solid with diethyl ether was next afforded followed by purification by column chromatograph to give the product as a colorless viscous oil. (30% yield)

EXPERIMENTAL SECTION

$^1\text{H NMR}$ (300 Hz, CDCl_3 , 20 °C) δ 7.90 (d, $J = 9.0$ Hz, 2H, ArH), 7.31 (d, $J = 6.0$ Hz, 2H, ArH), 3.91 (t, $J = 6.0$ Hz, 2H, CH_2), 2.42-2.39 (m, 5H, CH_2 with CH_3), 1.93-1.89 (m, 2H, CH_2), 1.80-1.76 (m, 2H, CH_2);

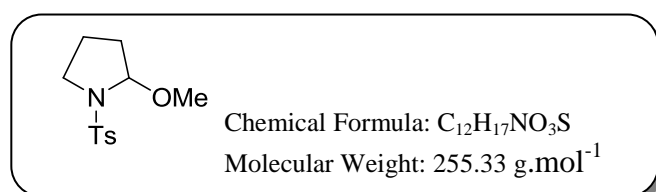
Data in accordance with previously reported result¹⁷

Step 2: Prepared according to the general procedure **CI** (44% yield)

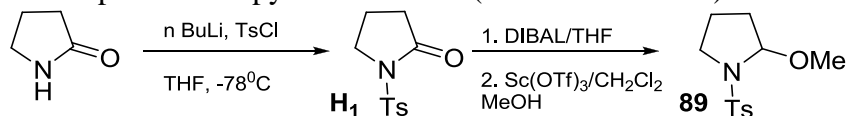
Colorless oil. $^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.72 (d, $J = 9.0$ Hz, 2H, ArH), 7.29 (d, $J = 9.0$ Hz, 2H, ArH), 5.15 (s, 1H, CHOCH_3), 3.54 (d, $J = 15.0$ Hz, 1H, CH_2), 3.39 (s, 3H, OCH_3), 3.05 (dd, $J = 12.0$ and 3.0 Hz, CH_2), 2.42 (s, 3H, CH_3), 1.89-1.22 (m, 6H, 3* CH_2);

Data in accordance with previously reported result.¹⁸

2-methoxy-1-tosylpyrrolidine (89)



Prepared in three steps from the pyrrolidin-2-one (see scheme below):



Step 1: Prepared according to procedure previously reported for the 1-tosylpiperidin-2-one as a colorless oil (82% yield)

$R_f = 0.38$ [cyclohexane/EtOAc (1/1)];

$^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.95 (d, $J = 6.0$ Hz, 2H, ArH), 7.35 (d, $J = 9.0$ Hz, 2H, ArH), 3.92 (t, $J = 6.0$ Hz, 2H, CH_2), 2.48-2.42 (m, 5H, CH_2 with CH_3), 2.14-2.07 (m, 2H, CH_2);

Data in accordance with previously reported result.¹⁹

Step 2: Prepared according to procedure synthesis of 2-tosylisindolin-1-ol as a colorless oil (93% yield).

$R_f = 0.23$ [cyclohexane/EtOAc (7/3)];

¹⁷ Dake, G.R.; Fenster, M.D.; Hurlez, P.B.; Patrick, B.O. *J. Org. Chem.* **2004**, *69*, 5668.

¹⁸ Ahman, J.; Somfai, P. *Tetrahedron*, **1992**, *43*, 9537.

¹⁹ Miao, L.; Haque, I.; Manzoni, M. R.; Tham, W. S.; Chemler, S. R. *Org. Lett.*, **2010**, *21*, 4739.

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¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.76 (d, *J* = 6.0 Hz, 2H, ArH), 7.34 (d, *J* = 6.0 Hz, 2H, ArH), 5.45 (t, *J* = 3.0 Hz, 1H, CHOH), 3.10-3.04 (m, 2H, CH₂), 2.48-2.42 (m, 4H, CH₂ with CH₃), 2.19-2.06 (m, 2H, CH₂), 1.93 (m, 1H, CH₂);

Data in accordance with previously reported result.²⁰

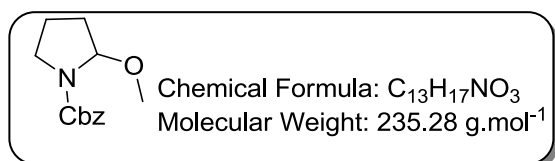
Step 3: Prepared according to the general procedure **CII**. (84% yield)

White solid. *R_f* = 0.53 [cyclohexane/EtOAc (7/3)];

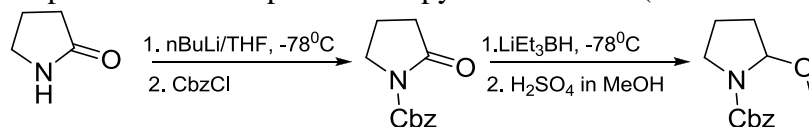
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.54 (d, *J* = 6.0 Hz, 2H, ArH), 7.33 (d, *J* = 9.0 Hz, 2H, ArH), 5.13 (d, *J* = 6.0 Hz, 1H, CHOCH₃), 3.47-3.40 (m, 4H, CH₂ with OCH₃), 3.15 (m, 1H, CH₂), 2.45 (s, 3H, CH₃), 2.08-2.03 (m, 1H, CH₂), 1.92-1.73 (m, 2H, CH₂), 1.46-1.33 (m, 1H, CH₂);

Data in accordance with previously reported result²¹

benzyl 2-methoxypyrrolidine-1-carboxylate (87)



Prepared in three steps from the pyrrolidin-2-one (see scheme below):



Step 1: Prepared according to procedure previously reported for the 1-tosylpiperidin-2-one as a colorless oil (95% yield)

R_f = 0.41 [cyclohexane/EtOAc (1/1)];

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.44-7.32 (m, 5H, ArH), 5.27 (s, 2H, CH₂), 3.81 (t, *J* = 9.0 Hz, 2H, CH₂), 2.52 (t, *J* = 6.0 Hz, 2H, CH₂), 2.03 (t, *J* = 9.0 Hz, 2H, CH₂);

Data in accordance with previously reported result.²²

Step 2: Prepared according to the general procedure **CI**. (79% yield)

R_f = 0.5 [cyclohexane/EtOAc (7/3)];

¹H NMR (300 Hz, CDCl₃, 20 °C) δ 7.76 (bs, 5H, ArH), 5.22 (bs, 2H, CH₂), 3.56-3.26 (m, 5H, OCH₃ with CH₂), 2.08-1.85 (m, 4H, 2* CH₂);

²⁰ Ahman, J.; Somfai, P. *Tetrahedron*, **1992**, 43, 9537.

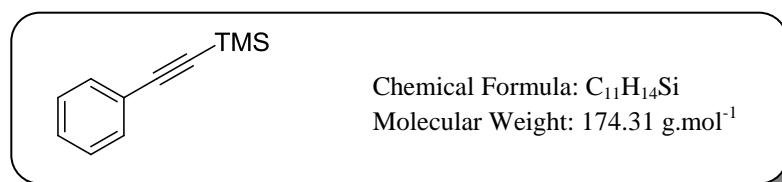
²¹ Rossiter, B.E.; Sharpless, K.B. *J. Org. Chem.* **1984**, 20, 3711.

²² Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrah. Lett.*, **2001**, 42, 4617.

Data in accordance with previously reported result.²³

Preparation of silylated alkynes :

trimethyl(phenylethynyl)silane (32)

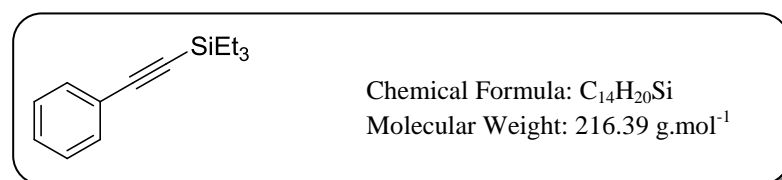


Prepared according to general procedure **E** from phenylacetylene using TMSCl as silylating agent (93% yield);

$R_f = 0.73$ (cyclohexane/EtOAc 9/1). ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.47-7.45 (m, 2H, ArH), 7.31-7.27 (m, 3H, ArH), 0.25 (s, 9H, CH₃);

Data in accordance with previously reported results.²⁴

triethyl(phenylethynyl)silane (34)

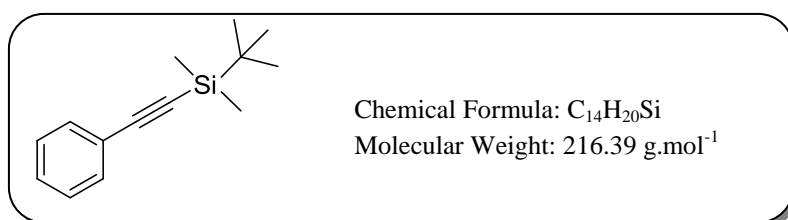


Prepared according to general procedure **E** from phenylacetylene using TESCl as silylating agent (80% yield).

$R_f = 0.79$ (cyclohexane/EtOAc 95/5). ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.51-7.48 (m, 2H, ArH), 7.33-7.28 (m, 3H, ArH), 1.07 (t, $J = 9.0$ Hz, 9H, CH₃), 0.74-0.66 (m, 6H, CH₂);

Data in accordance with previously reported results.²⁵

tert-butyl(dimethyl)(phenylethynyl)silane (35)



Prepared according to general procedure **E** from phenylacetylene using TBSCl as silylating agent (89% yield).

²³ Tajima, T.; Kurihara, H.; Fuchigami, T. *J. Am. Chem. Soc.*, **2007**, 129, 6680.

²⁴ Nishihara, Y.; Saito, D.; Tanemura, K.; Noyori, S.; Takagi, K. *Organic Letters*, **2009**, 11, 3546.

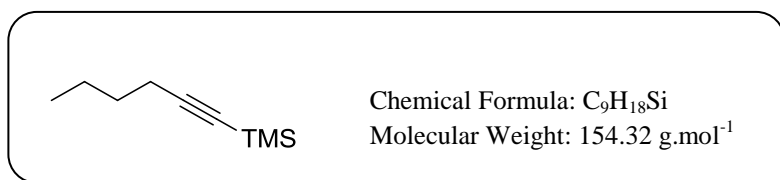
²⁵ Nadres, Enrico T.; Lazareva, Anna; Daugulis, Olafs *J. Org. Chem.*, **2011**, 76, 471.

EXPERIMENTAL SECTION

$R_f = 0.71$ (cyclohexane/EtOAc 95/5). $^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.50-7.47 (m, 2H, ArH), 7.33-7.28 (m, 2H, ArH), 1.02 (s, 9H, CH_3), 0.20 (s, 6H, CH_3);

Data in accordance with previously reported results.²⁶

hex-1-ynyltrimethylsilane (59)

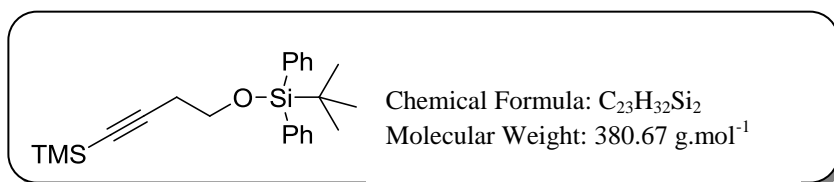


Prepared according to general procedure **E** from hexyne using TMSCl as silylating agent (73% yield).

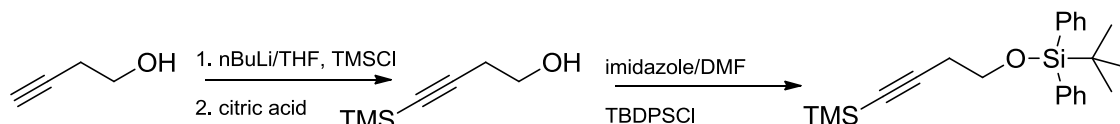
$R_f = 0.7$ (cyclohexane/EtOAc 9/1). $^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 2.22 (t, $J = 6.0$ Hz, 2H, CH_2), 1.51-1.36 (m, 4H, CH_2), 0.9 (t, $J = 6.0$ Hz, 3H, CH_3), 0.14 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

Data in accordance with previously reported results.²⁷

tert-butyl diphenyl(4-(trimethylsilyl)but-3-ynoxy)silane (73)



Prepared in two steps from homopropargylic alcohol (see scheme below):



Step 1: To a stirred solution of but-3-yn-1-ol (0.55 mL, 7.13 mmol, 1 eq) in anhydrous THF (35.6 mL), a commercially available solution of nBuLi 2.5M in THF (6 mL, 14.97 mmol, 2.1 eq) was added dropwise at -100 °C. The reaction mixture was slowly warmed up to -30 °C for 30 min and again cooled down to -100 °C. TMSCl (1.89 mL, 14.62 mmol, 2.05 eq) was then added dropwise. The reaction mixture was let to warm to room temperature. Next, after complete formation of the expected disilylated intermediate, the reaction mixture was first hydrolyzed by addition of a saturated aqueous solution of NH_4Cl (76 mL), then washed with water. The aqueous layer was extracted with Et_2O (three times) and the combined organic

²⁶ Creary, Xavier; Butchko, Mark A. *J. Org. Chem.*, **2002**, *67*, 112.

²⁷ Xu, G.; Li, X.; Sun, H. *J. Organomet.Chem.*, **2011**, *696*, 3011.

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layers were washed with brine, dried over MgSO_4 , filtered and carefully concentrated under vacuum.

Next, to a solution of the crude disilylated product in methanol (4.2 mL) at room temperature, citric acid (0.45 g, 2.35 mmol, 0.33 eq) was added and the residue was stirred for 10 min followed by addition of water. The aqueous layer was then extracted with Et_2O (three times) and the combined organic layers were then washed with brine, dried over MgSO_4 , filtered and carefully concentrated under vacuum.

The resulting crude product was purified by flash column chromatography on silica gel (pentane/ Et_2O : 8/2) to give the monosilylated product as a colorless oil (810 mg, 5.7 mmol, 80% yield).

$R_f = 0.34$ (cyclohexane/ EtOAc 8/2). $^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 3.71 (d, $J = 6.0$ Hz, 2H, CH_2), 2.50 (t, $J = 6.0$ Hz, 2H, CH_2), 0.16 (s, 9H, CH_3).

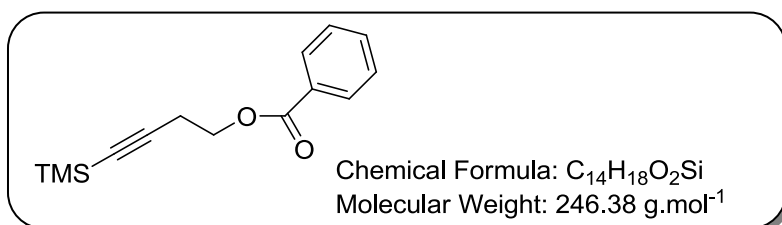
Data in accordance with previously reported results.²⁸

Step 2: TBDPSCI (615 μL , 1 eq, 2.32mmol) was added to a solution of 4-(trimethylsilyl)but-3-yn-1-ol (0.33g, 1 eq 2.3 mmol,) and imidazole (0.39g, 2.5 eq, 5.8 mmol) in DMF (2.3 mL). After stirring of the reaction mixture at room temperature for 3h, a saturated aqueous solution of NH_4Cl was added. The aqueous layer was extracted with Et_2O (three times) and the combined organic layers were washed with brine twice, dried over MgSO_4 , filtered and carefully concentrated under vacuum. Purification by flash column chromatography on silica gel then afforded product **111** as a colorless oil. (0.84 g, 2.2 mmol, 87% yield).

$R_f = 0.9$ (cyclohexane/ EtOAc 8/2). $^1\text{H NMR}$ (300 MHz, CDCl_3 , 20 °C) δ 7.69 (d, $J = 6.0$ Hz, 4H, ArH), 7.43-7.38 (m, 6H, ArH), 3.77 (t, $J = 6.0$ Hz, 2H, CH_2), 2.51 (t, $J = 6.0$ Hz, 2H, CH_2), 1.05 (s, 9H, CH_3), 0.15 (s, 9H, CH_3).

Data in accordance with previously reported results.²⁹

4-(trimethylsilyl)but-3-ynyl benzoate (74)

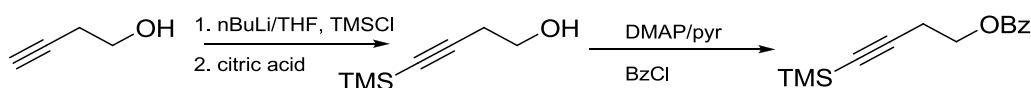


Prepared in two steps from homopropargylic alcohol (see scheme below):

²⁸ Berkessel, A.; Kramer, J.; Mummy, F.; Neudorfl J.-M.; Haag, R. *Angew. Chem.*, **2013**, 125, 767.

²⁹ Takimoto, M.; Usami, S.; Hou, Z. *J. Am. Chem. Soc.*, **2009**, 131, 18266.

EXPERIMENTAL SECTION

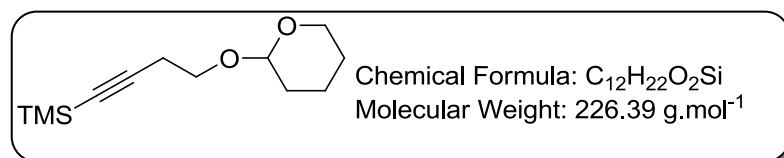


Step 1: Prepared according to the procedure described for the synthesis of tert-butyl(diphenyl(4-(trimethylsilyl)but-3-yn-1-yloxy)silane

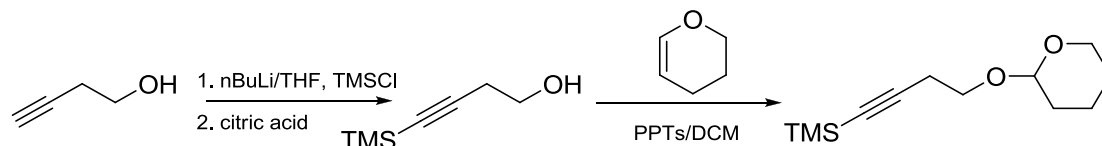
Step 2: To a stirred solution of 4-(trimethylsilyl)but-3-yn-1-ol (0.3 g, 2.1 mmol, 1 eq) and DMAP (0.025 g, 0.21 mmol, 0.1 eq) in pyridine (3 mL) benzoyl chloride (612 μ L, 5.25 mmol, 2.5 eq) was added dropwise at 0 °C. The reaction mixture was stirred for 20 min at 0 °C followed by 25 min at room temperature. The reaction rate was monitored by TLC and when it was completed, Et₂O (3 mL) was added. Organic layer was washed with saturated solution of NH₄Cl, then 5% CuSO₄, brine, dried over MgSO₄, filtered and concentrated carefully under vacuum. Purification by column chromatography afforded the product as an oil. (0.29 g, 56 % yield).

R_f = 0.73 [cyclohexane/EtOAc (7/3)]; **IR (neat)**/v cm^{-1} : 2961, 1721, 1268, 1249, 838, 708 cm^{-1} ; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 8.76 (d, J = 6.0 Hz, 2H, ArH), 7.57 (t, J = 6.0 Hz, 1H, ArH), 7.44 (t, J = 9.0 Hz, 2H, ArH), 4.41 (t, J = 9.0 Hz, 2H, CH₂OCOPh), 2.70 (t, 2H, CC-CH₂), 0.14 (s, 9H, 3*CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 166.3 (C_q), 133.1 (CH), 130.1 (C_q), 129.7(2*CH), 128.4 (2*CH), 102.3 (C_q), 86.7 (C_q), 62.6 (CH₂), 20.5 (CH₂), 0.01 (3*CH₃); **HRMS (ESI)** calculated for C₂₆H₂₁N₂O₅ (M+H)⁺: 247.1149; found 247.1146;

trimethyl(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl) silane (75)



Prepared in two steps from homopropargylic alcohol (see scheme below):



Step 1: Prepared according to the procedure described for the synthesis of tert-butyl(diphenyl(4-(trimethylsilyl)but-3-yn-1-yloxy)silane

Step 2: Dihydropyran (0.29g, 3.45 mmol, 1.33 eq) and PPTs (0.018g, 0.08 mmol, 0.03 eq) were added to a solution of 4-(trimethylsilyl)but-3-yn-1-ol (0.38g, 2.6 mmol, 1 eq) in DCM (1.8 mL). After stirring for 5 h at room temperature, the solution was washed with an NaHCO₃ soln, then water and dried over MgSO₄, filtered and concentrated under vacuum.

EXPERIMENTAL SECTION

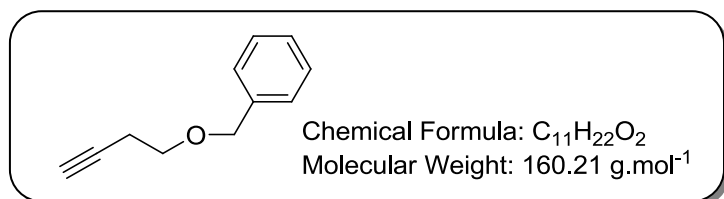
The resulting crude product was purified by column chromatograph (pentane/Et₂O: 9/1) to give the expected product.(0.41 g, 70% yield)

$R_f = 0.93$ (cyclohexane/EtOAc 8/2).

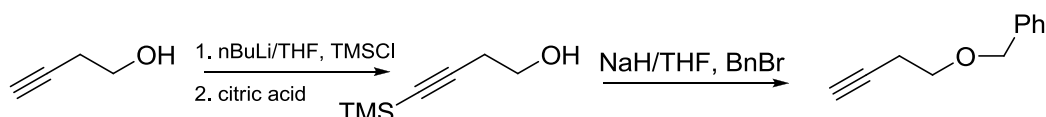
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 4.66 (bs, 1H, OCHO), 3.85 (m, 2H, CH₂), 3.54 (s, 2H, CH₂), 2.53 (t, $J = 6.0$ Hz, 2H, CH₂), 1.85-1.50 (m, 6H, 3*CH₂), 0.14 (s, 9H, 3*CH₃);

Data in accordance with previously reported results.³⁰

(4-(benzyloxy)but-1-ynyl)trimethylsilane (76a)



Prepared in two steps from homopropargylic alcohol (see scheme below):



Step 1: Prepared according to the procedure described for the synthesis of tert-butylidiphenyl(4-(trimethylsilyl)but-3-ynoxy)silane

Step 2: To a solution of but-3-yn-1-ol (0.54 mL, 7.13 mmol, 1 eq) in THF (47 mL) NaH (0.31 g, 7.8 mmol, 1.1 eq) was added portion wise at 0 °C. After stirring for 30 min a solution of BnBr (1mL, 8.55 mmol, 1.2 eq) was added and the solution was stirred at room temperature for 4 days. After adding 47 mL saturated NH₄Cl, organic layer was separated and aqueous layer was extracted with Et₂O three times. Combined organic phases were washed with water, brine, dried over MgSO₄ and finally concentrated *in vacuo*. Purification by column chromatography afforded the product. (0.97 g, 85 % yield)

$R_f = 0.75$ [cyclohexane/EtOAc (8/2)].

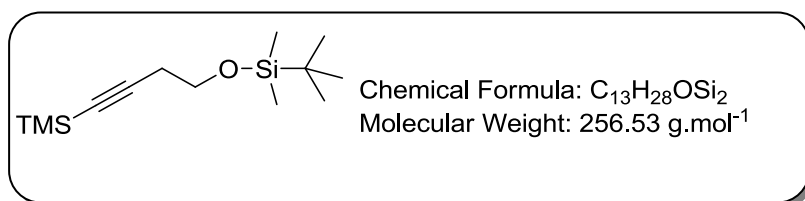
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.36-7.28 (m, 5H, ArH), 4.57 (s, 2H, CH₂), 3.61 (t, $J = 6.0$ Hz, 2H, CH₂), 2.54-2.58 (m, 2H, CH₂), 2.00 (s, 1H, CH);

Data in accordance with previously reported results.³¹

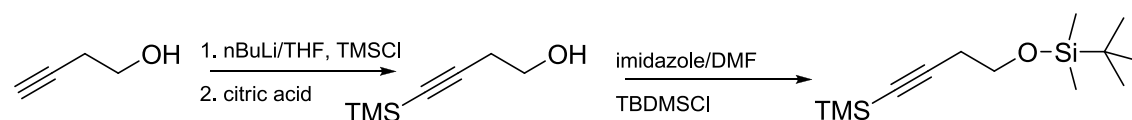
³⁰ Bestmann, H. J.; Zeibig, T.; Vostrowsky, O. *Synthesis*, **1990**, *11*, 1039.

³¹ Kollath, A.; Christoph, S.; Arseniyadis, S.; Cossy, J. *Chem. Comm.* **2012**, *48*, 10511.

tert-butyldimethyl(4-(trimethylsilyl)but-3-ynoxy)silane (72)



Prepared in two steps from homopropargylic alcohol (see scheme below):



Step 1: Prepared according to the procedure described for the synthesis of tert-butyldiphenyl(4-(trimethylsilyl)but-3-ynoxy)silane

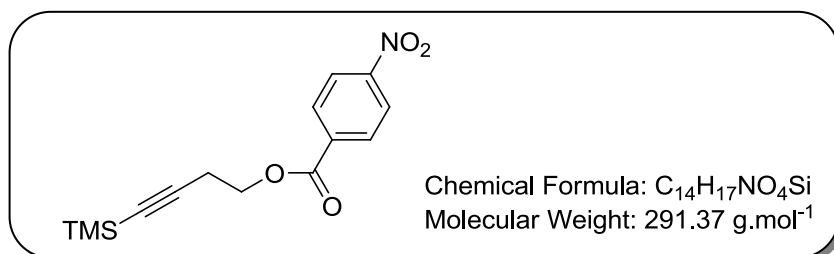
Step 2: Prepared according to procedure previously reported for the tert-butyldimethyl(4-(trimethylsilyl)but-3-ynoxy) silane (90% yield)

$R_f = 0.9$ (cyclohexane/EtOAc 8/2).

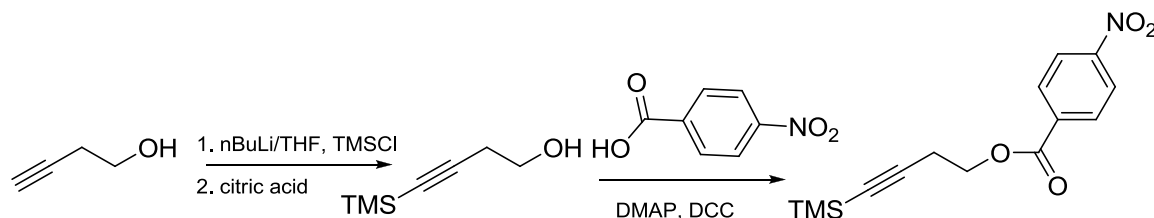
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 3.72 (t, $J = 6.0$ Hz, 2H, CH₂), 2.44 (t, $J = 6.0$ Hz, 2H, CH₂), 0.89 (s, 9H, 3*CH₃), 0.14 (s, 9H, 3*CH₃), 0.07 (s, 6H, 2*CH₂);

Data in accordance with previously reported results.³²

4-(trimethylsilyl)but-3-ynyl 4-nitrobenzoate (77)



Prepared in two steps from homopropargylic alcohol (see scheme below):



Step 1: Procedure was described for the synthesis of tert-butyldiphenyl(4-(trimethylsilyl)but-3-ynoxy)silane

³² Takimoto, M.; Usami, S.; Hou, Z. *J. Am. Chem. Soc.*, **2009**, 131, 18266.

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Step 2: Mixture of DCC (1 g, 4.8 mmol, 1.6 eq) and DMAP (0.4 g, 3.32 mmol, 1.1 eq) in 4 mL of DCM was added to a solution of 4-(trimethylsilyl)but-3-yn-1-ol (0.43 g, 3.02 mmol, 1 eq) and 4-nitrobenzoic acid (0.82 g, 4.8 mmol, 1.6 eq) in DCM (8 mL). After stirring for 3 h at room temperature. The mixture was then eluted through a plug of celite with DCM. The filtrate was washed 2 times with 1 M HCl and once with brine. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo.

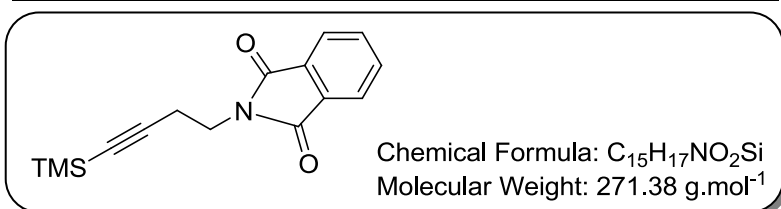
The resulting crude product was purified by column chromatograph (cyclohexane:EtOAc 9/1) to give the expected product. (0.69 g, 78% yield)

$R_f = 0.57$ [cyclohexane/EtOAc (8/2)].

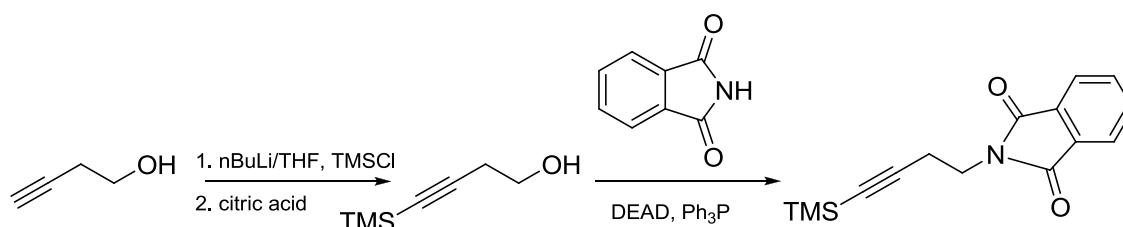
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 8.32-8.22 (m, 4H, ArH), 4.46 (t, $J = 6.0$ Hz, 2H, CH₂), 2.73 (t, $J = 6.0$ Hz, 2H, CH₂), 0.14 (s, 9H, 3*CH₃);

Data in accordance with previously reported results.³³

2-(4-(trimethylsilyl)but-3-ynyl)isoindoline-1,3-dione (78)



Prepared in two steps from homopropargylic alcohol (see scheme below):



Step 1: Procedure was described for the synthesis of tert-butyl(diphenyl(4-(trimethylsilyl)but-3-ynoxy)silane

Step 2: Prepared according to the general procedure **A0** (60% yield)

$R_f = 0.71$ [cyclohexane/EtOAc (7/3)].

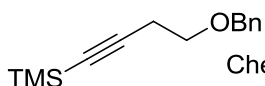
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.87-7.84 (m, 2H, ArH), 7.74-7.71 (m, 2H, ArH), 3.88 (t, $J = 6.0$ Hz, 2H, CH₂), 2.63 (t, $J = 6.0$ Hz, 2H, CH₂), 0.06 (s, 9H, CH₃);

Data in accordance with previously reported results.³⁴

³³ Rahaim, R. J.; Shaw, Jared T. *J. Org. Chem.* **2008**, 73, 2912.

³⁴ SDS Biotech K. K. Patent: EP2455371 A1, 2012.

(4-(benzyloxy)but-1-ynyl)trimethylsilane (76)



Chemical Formula: C₁₄H₂₀OSi
Molecular Weight: 232.39 g.mol⁻¹

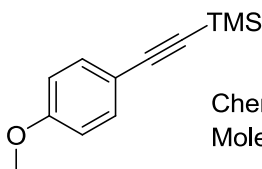
Prepared according to procedure previously reported for the 4-(trimethylsilyl)but-3-yn-1-ol (45% yield)

$R_f = 0.27$ [pentane/Et₂O (98/2)].

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.36-7.28 (m, 5H, ArH), 4.56 (s, 2H, CH₂), 3.60 (t, $J = 6.0$ Hz, 2H, CH₂), 2.55 (t, $J = 6.0$ Hz, 2H, CH₂), 0.15 (s, 9H, CH₃);

Data in accordance with previously reported results.³⁵

((4-methoxyphenyl)ethynyl)trimethylsilane (58)



Chemical Formula: C₁₂H₁₅OSi
Molecular Weight: 204.10 g.mol⁻¹

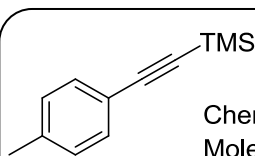
Prepared according to general procedure E from hexyne using TMSCl as silylating agent (73% yield).

$R_f = 0.69$ (cyclohexane/EtOAc 9/1).

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.42 (d, $J = 9.0$ Hz, 2H, ArH), 6.83 (d, $J = 9.0$ Hz, 2H, ArH), 3.82 (s, 3H, OCH₃), 0.26 (s, 9H, CH₃);

Data in accordance with previously reported results.³⁶

trimethyl(p-tolylethynyl)silane (57)



Chemical Formula: C₁₂H₁₆Si
Molecular Weight: 118.34 g.mol⁻¹

Prepared according to general procedure E from hexyne using TMSCl as silylating agent (93% yield)

$R_f = 0.71$ [cyclohexane/EtOAc (95/5)].

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.35 (d, $J = 9.0$ Hz, 2H, ArH), 7.09 (d, $J = 9.0$ Hz, 2H, ArH), 2.34 (s, 3H, CH₃), 0.24 (s, 9H, CH₃);

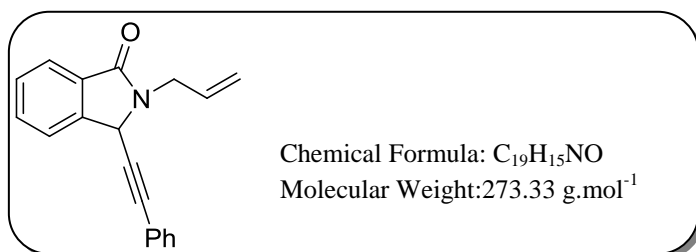
³⁵Rahaim, Ronald J.; Shaw, Jared T. *J. Org. Chem.*, **2008**, 73, 2912.

³⁶Beaulieu, Louis-Philippe B.; Delvos, Lukas B.; Charette, Andre B. *Organic Letters*, **2010**, 12, 1348.

Data in accordance with previously reported results.³⁷

Products from isoindolic acetoxylactams series:

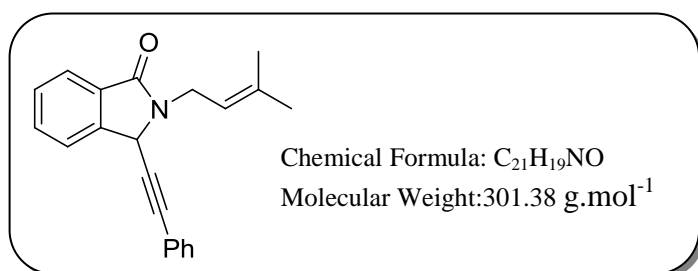
2-allyl-3-(phenylethynyl)isoindolin-1-one (33)



Prepared from acetoxylactam **31** following general procedure **G** (40 °C; 90% yield).

Yellow oil; $R_f = 0.55$ (cyclohexane/EtOAc 7/3). **IR** (neat)/ ν cm⁻¹: 2923, 1699, 1394, 759, 728, 692 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.80 (d, $J = 6.0$ Hz, 1H, ArH), 7.59-7.24 (m, 8H, ArH), 5.84 (m, 1H, CH=CH₂), 5.41 (s, 1H, CHCCPh), 5.29-5.18 (m, 2H, C=CH₂), 4.66 (dd, $J = 15.0$ and 3.0 Hz, 1H, NCH₂), 3.91 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.3 (C_q), 142.4 (C_q), 132.6 (C_q), 132.1 (CH), 131.8 (CH), 131.5 (CH), 123.8 (CH), 123.0 (CH), 118.4 (CH), 86.2 (C_q), 81.7 (C_q), 51.6 (CH), 43.1 (CH₂); **HRMS** (+ESI) calculated for C₁₉H₁₆NO [M+H]⁺: 274.1226, found 274.1227; **LRMS** (EI) m/z : 73 (93), 74 (12), 147 (98), 148 (19), 149 (11), 205 (12), 207 (47), 208 (13), 221 (100), 222 (27), 223 (16), 267 (13), 281 (43), 282 (14), 355 (36), 356 (15).

2-(3-methylbut-2-enyl)-3-(phenylethynyl)isoindolin-1-one (49)



Prepared from acetoxylactam **38** following general procedure **G** with silylated alkyne **32** (40 °C; 91% yield).

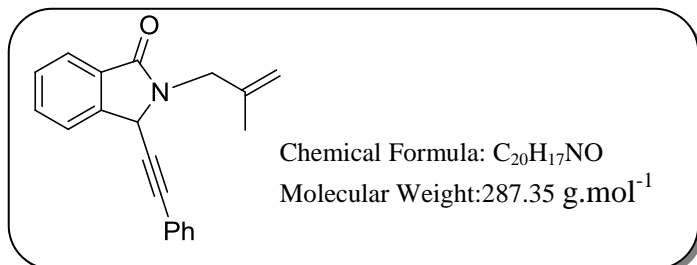
yellow oil; $R_f = 0.39$ [cyclohexane/DCM/EtOAc (7/1/2)]; **IR** (neat)/ ν cm⁻¹: 2967, 1708, 1393, 1224, 1025, 715, 692 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (d, $J = 6.0$ Hz, 1H, ArH), 7.61-7.32 (m, 8H, ArH), 5.45 (s, 1H, CH-N), 5.29 (bs, 1H, CH=CCH₃), 4.66 (dd, $J = 15.0$ and 3.0 Hz, 1H, NCH₂), 4.04 (dd, $J = 15.0$ and 9.0 Hz, 1H, NCH₂), 1.84 (s, 3H, CH₃), 1.76 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.1 (C_q), 142.4 (C_q), 137.6 (C_q),

³⁷ Atobe, S.; Sonoda, M.; Suzuki, Y.; Shinohara, H.; Yamamoto, T.; Ogawa, A. *Chem. Lett.*, **2011**, 40, 925.

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131.9 (CH), 131.8 (2*CH), 128.9 (CH), 128.4 (3*CH), 123.7 (CH), 123.0 (CH), 122.0 (C_q), 119.0 (CH), 85.9 (C_q), 83.1 (C_q), 77.3 (C_q), 51.3 (CH), 38.2 (CH₂), 25.9 (CH₃), 18.0 (CH₃); **HRMS (ESI)** calculated for C₂₁H₂₀NO (M+H)⁺: 302.1545; found 302.1544;

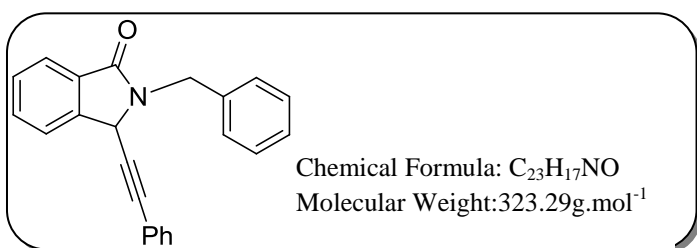
2-(2-methylallyl)-3-(phenylethynyl)isoindolin-1-one (50)



Prepared from acetoxylactam **39** following general procedure **G** with silylated alkyne **32** (40 °C; 74% yield).

yellow oil; **R_f** = 0.42 [cyclohexane/DCM/EtOAc (7/1/2)]; **IR (neat)/v cm⁻¹**: 2913, 1695, 1391, 57, 724, 689 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.88 (d, *J* = 6.0 Hz, 1H, ArH), 7.66-7.61 (m, 2H, ArH), 7.53 (t, *J* = 6.0 Hz, 1H, ArH), 7.44-7.41 (m, 2H, ArH), 7.33-7.31 (m, 3H, ArH), 5.42 (s, 1H, CH-N), 4.96 (d, *J* = 6.0 Hz, 2H, CH=CH₂), 4.66 (d, *J* = 15.0 Hz, 1H, NCH₂), 3.98 (d, 15.0 Hz, 1H, NCH₂), 1.77 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.5 (C_q), 142.5 (C_q), 140.5 (C_q), 132.2 (CH), 131.8 (CH), 131.4 (C_q), 129.0 (CH), 128.9 (2*CH), 128.4 (2*CH), 123.9 (CH), 123.1 (CH), 121.9 (C_q), 113.4 (CH₂), 86.2 (C_q), 82.7 (C_q), 51.6 (CH), 46.5 (CH₂), 20.2 (CH₃); **HRMS (ESI)** calculated for C₂₀H₁₈NO (M+H)⁺: 288.1383; found 288.1388;

2-benzyl-3-(phenylethynyl)isoindolin-1-one (47)



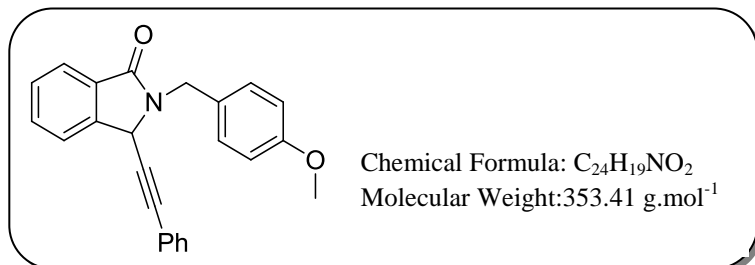
Prepared from acetoxylactam **36** following general procedure **G** with silylated alkyne **32** (40 °C; 99% yield).

Yellow solid; **R_f** = 0.38 [cyclohexane/DCM/EtOAc (7/1/2)]; **m.p.** 106 °C; **IR (neat)/v cm⁻¹**: 2919, 2850, 1698, 723, 690 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.51 (d, *J* = 4.2 Hz, 1H, ArH), 7.43-7.21 (m, 13H, ArH), 5.46 (d, *J* = 15.0 Hz, 1H, NCH₂), 5.30 (s, 1H, CH), 4.47 (d, *J* = 15.0 Hz, 1H, NCH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.4 (C_q), 142.4 (C_q), 136.8 (C_q), 132.9 (CH), 132.6 (C_q), 132.2 (C_q), 131.9 (CH), 131.4 (CH), 130.9 (CH), 130.3 (CH),

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131.9 (CH), 129.8 (CH), 131.4 (CH), 130.9 (CH), 129.8 (CH), 128.8 (CH), 123.5 (CH), 123.1 (CH), 121.8 (CH), 86.5 (C_q), 82.7 (C_q), 53.5 (CH), 44.9 (CH₂); **HRMS (EI)** calculated for C₂₃H₁₈NO [M+H]⁺: 324.1383; found 324.1381;

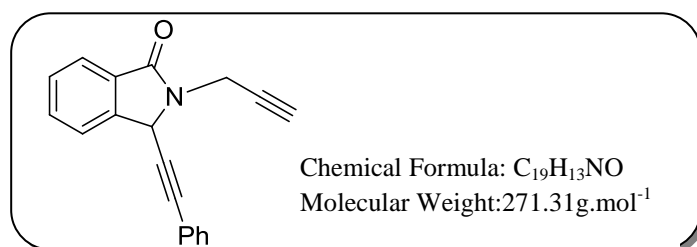
2-(4-methoxybenzyl)-3-(phenylethynyl)isoindolin-1-one (48)



Prepared from acetoxylactam **37** following general procedure **G** with silylated alkyne **32** (40 °C; 95% yield).

Yellow oil; *R_f* = 0.35 [cyclohexane/EtOAc (8/2)]; **IR (neat)/v cm⁻¹**: 1692, 1512, 1245, 757, 723, 699 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.78 (d, *J* = 6 Hz, 1H, ArH), 7.54-7.14 (m, 10 H, ArH), 6.76 (d, *J* = 8.4 Hz, 2H, ArH), 5.25 (d, *J* = 7.5 Hz 1H, NCH₂), 5.14 (s, 1H, CH-CCPh), 4.35 (d, *J* = 7.5 Hz, 1H, NCH₂), 3.66 (s, 3H, OCH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.2 (C_q), 159.2 (C_q), 142.4 (C_q), 132.9 (CH), 132.1 (C_q), 131.9 (C_q), 131.6 (CH), 131.0 (CH), 123.9 (CH), 123.5 (CH), 121.9 (C_q), 114.2 (CH), 86.4 (C_q), 82.8 (C_q), 55.3 (CH₃), 51.2 (CH), 43.8 (CH₂); **HRMS (ESI)** calculated for C₄₈H₃₉N₂O₂ (2M-2O)²⁺: 675.3001; found 675.3006;

3-(phenylethynyl)-2-(prop-2-ynyl)isoindolin-1-one (51)



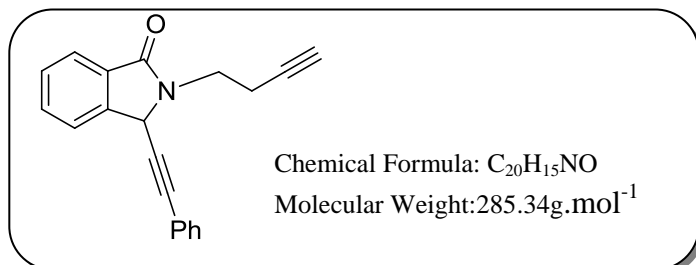
Prepared from acetoxylactam **40** following general procedure **G** with 2.5 eq of silylated alkyne **32** (40 °C; 76% yield).

Yellow oil; *R_f* = 0.44 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 1697, 1469, 1391, 1313, 1141, 723, 689 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.80 (d, *J* = 6.0 Hz, 1H, ArH), 7.62-7.20 (m, 8H, ArH), 5.61 (s, 1H, CHCCPh), 4.91 (d, *J* = 9.0 Hz, 1H, NCH₂), 4.07 (d, *J* = 9.0 Hz, 1H, NCH₂), 2.25 (d, *J* = 3.0 Hz, 1H, CCH); **¹³C NMR** (75 Hz, CDCl₃, 20 °C) δ 166.8 (C_q), 142.5 (C_q), 134.2 (CH), 132.5 (CH), 131.9 (CH), 131.6 (CH), 130.9 (C_q), 128.0

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(CH), 124.0 (CH), 123.6 (CH), 121.7 (C_q), 86.4 (C_q), 82.3 (C_q), 78.1 (CH), 72.4 (C_q), 51.2 (CH), 30.0 (CH₂); **HRMS (ESI)** calculated for C₁₉H₁₄NO [M+H]⁺: 272.1070 found 272.1065;

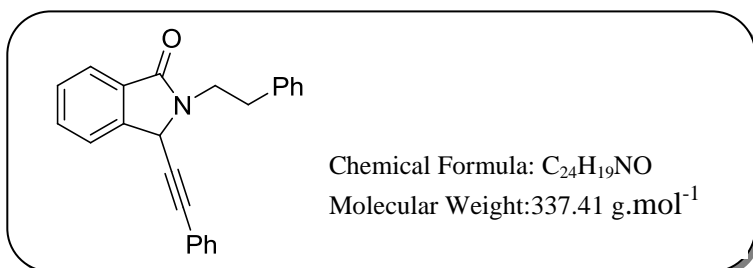
2-(but-3-ynyl)-3-(phenylethynyl)isoindolin-1-one (52)



Prepared from acetoxylactam **41** following general procedure **G** with 2.5 eq of silylated alkyne **32** (40 °C; 96% yield).

yellow oil; **R_f** = 0.38 [cyclohexane/EtOAc (8/2)]; **IR (neat)/ν cm⁻¹**: 1689, 1396, 1312, 756, 724, 688 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.87 (d, *J* = 6.0 Hz, 1H, Ar*H*), 7.66-7.26 (m, 8H, Ar*H*), 5.73 (s, 1H, CHCCPh), 4.15 (m, 1H, NCH₂), 3.72 (m, 1H, NCH₂), 2.71-2.63 (m, 2H, CH₂CCH), 2.03 (s, 1H, CCH); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.6 (C_q), 142.6 (C_q), 132.2 (CH), 131.9 (2*CH), 131.4 (C_q), 129.0 (CH), 129.0 (CH), 128.4 (2*CH), 123.8 (CH), 123.1 (CH), 121.7 (C_q), 86.3 (C_q), 82.7 (C_q), 81.5 (CH), 70.3 (C_q), 52.7 (CH), 39.7 (CH₂), 18.6 (CH₂); **HRMS (ESI)** calculated for C₂₀H₁₆NO (M+H)⁺ : 286.1232, found 286.1227.

2-phenethyl-3-(phenylethynyl)isoindolin-1-one (53)



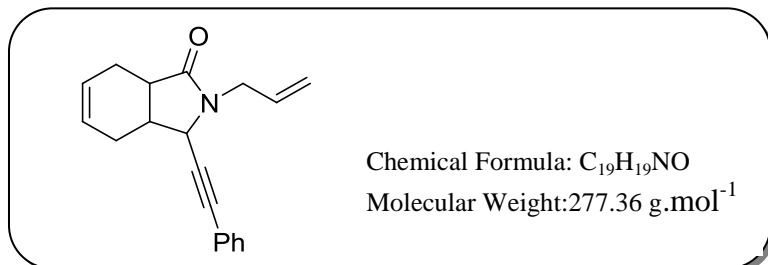
Prepared from acetoxylactam **42** following general procedure **G** with silylated alkyne **32** (40 °C; 96% yield).

yellow oil; **R_f** = 0.37 [cyclohexane:EtOAc (8/2)]; **IR (neat)/ν cm⁻¹**: 1689, 1399, 757, 724, 689 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.86 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.60-7.19 (m, 13 H, Ar*H*), 5.27 (s, 1H, CHN), 4.26 (m, 1H, NCH₂), 4.74 (m, 1H, NCH₂), 3.12-3.06 (m, 2H, CH₂Ph); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 169.5 (C_q), 142.5 (C_q), 138.8 (C_q), 132.1 (CH), 131.9 (2*CH), 131.7 (C_q), 129.0 (CH), 128.9 (CH), 128.8 (2*CH), 128.7 (2*CH), 128.5

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(2*CH), 123.7 (CH), 123.0 (CH), 121.9 (C_q), 121.9 (CH), 86.2 (C_q), 82.9 (C_q), 52.5 (CH), 42.4 (CH₂), 34.8 (CH₂); **HRMS (ESI)** calculated for C₂₄H₂₀NO (M+H)⁺: 338.1534; found 338.3418.

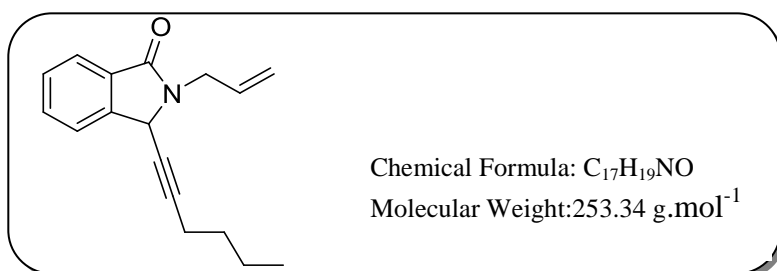
2-allyl-3-(phenylethynyl)-2,3,3a,4,7,7a-hexahydro-1H-isoindol-1-one (93)



Prepared from acetoxylactam **96** following general procedure **G** with silylated alkyne **32** (40 °C; 18% yield).

pale yellow oil; **R_f** = 0.46 [cyclohexan/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 1674, 1409, 756, 691 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.49-7.31 (m, 5H, ArH), 5.82-5.70 (m, 3H, CH=CH₂ with CH=CH), 5.30-5.21 (m, 2H, C=CH₂), 4.42 (dd, *J* = 15.0 and 6.0 Hz, 1H, NCH₂), 4.09 (d, *J* = 3.0 Hz, 1H, CHCCPh), 3.63 (dd, *J* = 15.0 and 9.0 Hz, 1H, NCH₂), 2.95 (m, 1H, CH₂), 2.67 (m, 1H, CH₂), 2.49 (m, 1H, CHCO), 2.35-2.28 (m, 2H, CH₂), 1.94 (m, 1H, CHCHCO); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 175.82 (C_q), 132.2 (CH), 131.7 (3*CH), 128.6 (CH), 128.4 (3*CH), 122.2 (C_q), 118.7 (CH₂), 85.7 (C_q), 85.3 (C_q), 54.4 (CH), 43.8 (CH₂), 38.4 (CH), 37.3 (CH), 25.4 (CH₂), 22.3 (CH₂); **HRMS (ESI)** calculated for C₁₉H₂₀NO (M+H)⁺: 278.1539; found 278.1538;

2-allyl-3-(hex-1-ynyl)isoindolin-1-one (65)



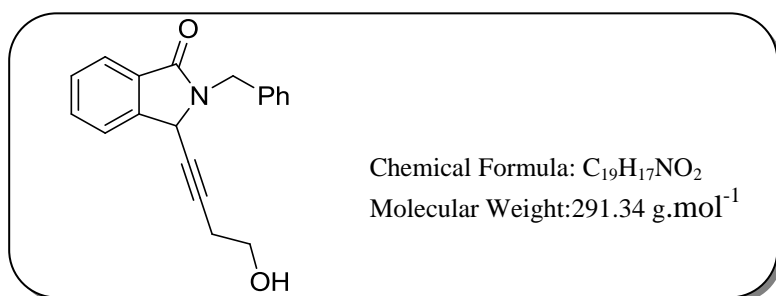
Prepared from acetoxylactam **31** following general procedure **G** with silylated alkyne **59** (40 °C; 92% yield).

yellow oil; **R_f** = 0.5 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 2959, 1694, 1391, 910, 723 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.78 (d, *J* = 6.0 Hz, 1H, ArH), 7.54-7.40 (m, 3H, ArH), 5.83 (m, 1H, CH=CH₂), 5.26 (s, 1H, CHN), 5.20-5.17 (m, 2H, C=CH₂), 4.65 (dd, *J* = 15.0 and 3.0 Hz, 1H, NCH₂), 3.91 (dd, *J* = 15.0 and 9.0 Hz, 1H, NCH₂), 2.20-2.16 (m, 2H,

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CH_2), 1.50-1.32 (m, 4H, CH_2), 0.89-0.84 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 167.2 (C_q), 143.1 (C_q), 132.7 (CH), 132.0 (CH), 131.3 (C_q), 128.7 (CH), 123.6 (CH), 122.9 (CH), 118.2 (CH_2), 87.3 (C_q), 73.6 (C_q), 51.3 (CH), 42.9 (CH_2), 30.5 (CH_2), 21.8 (CH_2), 18.3 (CH_2), 13.5 (CH_3); **HRMS (ESI)** calculated for $C_{17}H_{20}NO$ ($M+H$)⁺ :254.1545, found 254.1539.

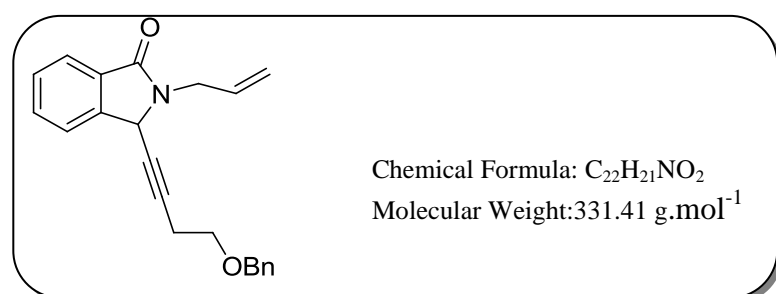
2-benzyl-3-(4-hydroxybut-1-ynyl)isoindolin-1-one (79)



Prepared from acetoxylactam **36** following general procedure **G** with silylated alkyne **72** (40 °C; 38% yield).

pale yellow solid; R_f = 0.48 [cyclohexane/ EtOAc (7/3)]; **m.p.** 82 °C; **IR (neat)/ ν cm^{-1}** : 3221, 1685, 1430, 1412, 1078, 1063, 750, 733, 697 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.86 (d, J = 6.0 Hz, 1H, *ArH*), 7.57-7.58 (m, 3H, *ArH*), 7.39-7.26 (m, 5H, *ArH*), 5.76 (s, 1H, *NCH*), 5.13 (d, J = 15.0 Hz, 1H, *NCH₂*), 4.35 (d, J = 15.0 Hz, 1H, *NCH₂*), 3.16 (m, 1H, *CCCH₂*), 3.05 (m, 1H, *CCCH₂*), 2.33-2.28 (m, 2H, *CH₂OH*), 2.00 (bs, 1H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 167.3 (C_q), 140.5 (C_q), 136.8 (C_q), 132.7 (C_q), 132.2 (CH), 130.1 (CH), 128.7 (2* CH), 128.7 (2* CH), 127.7 (CH), 123.7 (CH), 123.5 (CH), 85.4 (CH), 81.2 (C_q), 69.6 (C_q), 60.4 (CH_2), 43.4 (CH_2), 19.7 (CH_2); **HRMS (ESI)** calculated for $C_{19}H_{18}NO_2$ ($M+H$)⁺ :292.1338; found 292.1328;

2-allyl-3-(4-(benzyloxy)but-1-ynyl)isoindolin-1-one (81)

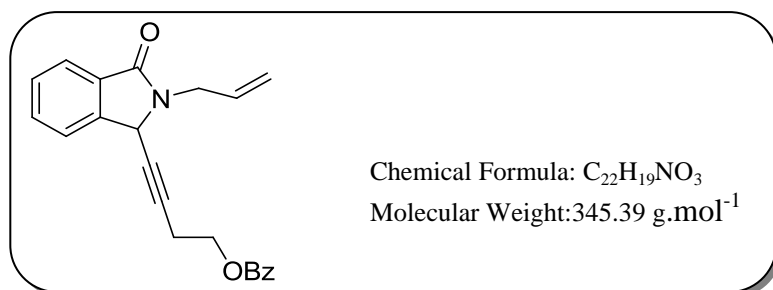


Prepared from acetoxylactam **31** following general procedure **G** with silylated alkyne **114** (40 °C; 48% yield).

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yellow oil; $R_f = 0.44$ [cyclohexane/EtOAc (7/3)]; **IR** (neat)/ ν cm^{-1} : 1696, 1095, 730, 697 cm^{-1} ; **^1H NMR** (300 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 7.83 (d, $J = 6.0$ Hz, 1H, ArH), 7.55-7.45 (m, 3H, ArH), 7.27 (bs, 5H, ArH), 5.89 (m, 1H, $\text{CH}=\text{CH}_2$), 5.28-5.19 (m, 3H, CHN with $\text{C}=\text{CH}_2$), 4.67 (dd, $J = 15.0$ and 3.0 Hz, 1H, NCH_2), 4.53 (s, 2H, CH_2Ph), 3.87 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH_2), 3.67 (t, $J = 9.0$ Hz, 2H, CH_2OBn), 2.54 (t, $J = 6.0$ Hz, 2H, CCCH_2); **^{13}C NMR** (75 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 167.2 (C_q), 142.8 (C_q), 137.9 (C_q), 132.7 (CH), 132.0 (CH), 131.5 (C_q), 128.8 (CH), 128.4 (2*CH), 127.6 (2*CH), 123.7 (CH), 123.0 (CH), 118.2 (CH_2), 84.0 (C_q), 74.9 (C_q), 73.0 (CH_2), 68.1 (CH_2), 51.2 (CH_2), 42.9 (CH_2); **HRMS (ESI)** calculated for $\text{C}_{22}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 332.1651, found 332.1652.

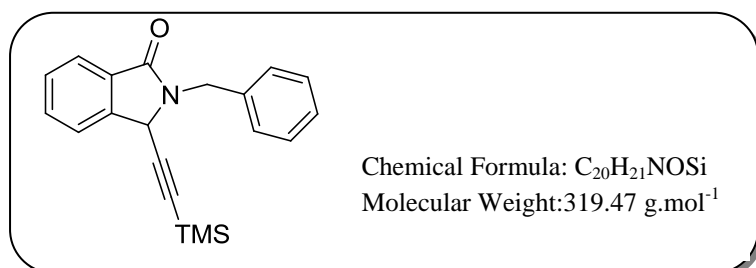
4-(2-allyl-3-oxoisindolin-1-yl)but-3-ynyl benzoate (83)



Prepared from acetoxylactam **31** following general procedure **G** with silylated alkyne **74** (40 $^\circ\text{C}$; 38% yield).

pale yellow oil; $R_f = 0.36$ [cyclohexane/EtOAc (7/3)]; **IR** (neat)/ ν cm^{-1} : 1693, 1270, 1111, 709 cm^{-1} ; **^1H NMR** (300 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.02 (d, $J = 6.0$ Hz, 2H, ArH), 7.83 (d, $J = 6.0$ Hz, 1H, ArH), 7.58-7.41 (m, 6H, ArH), 5.82 (m, 1H, $\text{CH}=\text{CH}_2$), 5.25-5.17 (m, 3H, CHN with $\text{C}=\text{CH}_2$), 4.67 (dd, $J = 15.0$ and 3.0 Hz, 1H, NCH_2), 4.42 (t, $J = 6.0$ Hz, 2H, CH_2OBz), 3.84 (dd, $J = 15.0$ and 6.0 Hz, 1H, NCH_2), 2.72 (t, $J = 6.0$ Hz, 2H, CCCH_2); **^{13}C NMR** (75 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 167.3 (C_q), 166.3 (C_q), 142.6 (C_q), 134.2 (C_q), 134.0 (CH), 133.2 (CH), 132.5 (C_q), 131.3 (CH), 129.6 (3*CH), 129.8 (CH), 128.4 (3*CH), 122.9 (CH), 118.3 (CH_2), 82.7 (C_q), 75.7 (C_q), 62.3 (CH_2), 51.1 (CH), 42.9 (CH_2), 19.4 (CH_2); **HRMS (ESI)** calculated for $\text{C}_{22}\text{H}_{20}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 346.1438, found 346.1434;

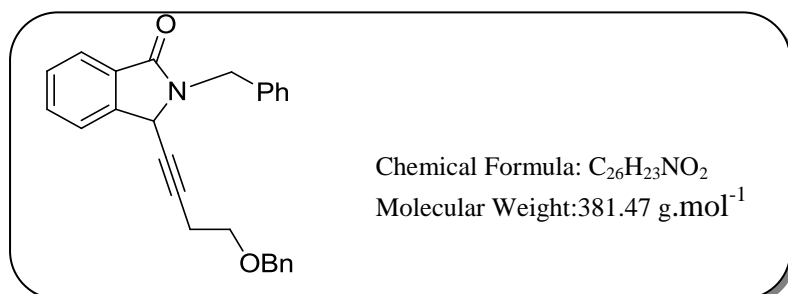
2-benzyl-3-((trimethylsilyl)ethynyl)isoindolin-1-one (68)



Prepared from acetoxy lactam **36** following general procedure **G** using 5 mol% of Ph₃PAuOTf and 2 equivalents of bis-trimethylsilylacetylene (40 °C; 73% yield).

Solid; *R_f* = 0.6 [cyclohexane/EtOAc (7/3)]; **m.p.** 90 °C; **IR (neat)/v cm⁻¹**: 1695, 841, 742, 693 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.87 (d, *J* = 9.0 Hz, 1H, ArH), 7.57-7.51 (m, 3H, ArH), 7.49-7.26 (m, 5H, ArH), 5.34 (dd, *J* = 15.0 Hz, 1H, NCH₂), 5.04 (s, 1H, CH), 4.35 (d, *J* = 15.0 Hz, 1H, NCH₂), 0.19 (s, 9H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.5 (C_q), 142.4 (C_q), 137.0 (C_q), 134.5 (CH), 134.3 (CH), 129.0 (C_q), 128.9 (CH), 128.8 (CH), 128.7 (CH), 123.5 (CH), 123.2 (CH), 120.8 (CH), 98.9 (C_q), 92.3 (C_q), 51.6 (CH), 44.4 (CH₂), 0.4 (3*CH₃); **HRMS (ESI)** calculated for C₂₀H₂₂NOSi [M+H]⁺: 320.1465; found 342.1270.

2-benzyl-3-(4-(benzyloxy)but-1-ynyl)isoindolin-1-one (82)



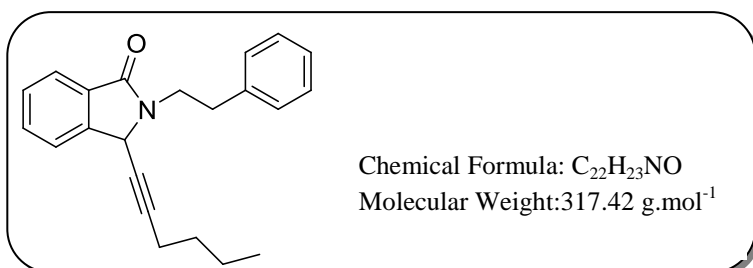
Prepared from acetoxy lactam **36** following general procedure **G** using 4 mol% of Ph₃PAuOTf (40 °C; 56% yield).

Yellow oil; *R_f* = 0.47 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 2920, 2851, 1693, 1395, 1098, 730, 697 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.87 (d, *J* = 6.0 Hz, 1H, ArH), 7.55-7.49 (m, 3H, ArH), 7.33-7.28 (m, 10H, ArH), 5.35 (d, *J* = 15.0 Hz, 1H, NCH₂), 5.03 (s, 1H, CH), 4.55 (s, 2H, CH₂), 4.35 (d, *J* = 15.0 Hz, 1H, NCH₂), 3.58 (t, *J* = 9 Hz, 2H, CH₂), 2.56 (t, *J* = 6.0 Hz, 2H, CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.3 (C_q), 142.8 (C_q), 138.0 (C_q), 137.0 (C_q), 132.0 (CH), 131.4 (C_q), 128.7 (2*CH), 128.5 (2*CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.7 (2*CH), 127.6 (CH), 123.8 (CH), 123.0 (CH), 84.3 (C_q), 74.9

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(C_q), 73.1 (CH_2), 68.1 (CH_2), 51.0 (CH), 44.1 (CH_2), 20.2 (CH_2); **HRMS (ESI)** calculated for $C_{26}H_{24}NO_2$ ($M+H$)⁺: 382.1802; found 382.1796;

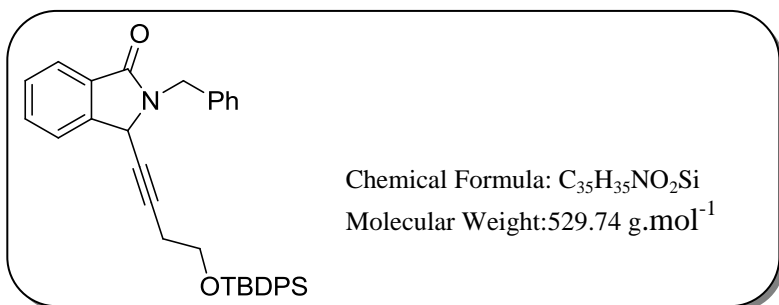
3-(hex-1-ynyl)-2-phenethylisoindolin-1-one (66)



Prepared from acetoxylactam **42** following general procedure **G** with silylated alkyne **59** (40 °C; 69% yield).

Yellow oil; R_f = 0.43 [cyclohexane/EtOAc (8/2)]; **IR (neat)/v cm^{-1}** : 2932, 1710, 1396, 1360, 721, 698 cm^{-1} ; **1H NMR** (300 MHz, $CDCl_3$ $CDCl_3$, 20 °C) δ 7.84 (d, J =6.0 Hz, 1H, ArH), 7.61-7.47 (m, 3 H, ArH), 7.30-7.28 (m, 5H, ArH), 5.04 (s, 1H, CHN), 4.18 (m, 1H, NCH_2), 3.64 (m, 1H, NCH_2), 3.06-3.00 (m, 2H, CC- CH_2), 2.20-2.00 (m, 2H, CH_2), 1.49-1.38 (m, 4H, CH_2CH_2), 0.91 (t, J =6.0 Hz, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$, 20 °C) δ 167.5 (C_q), 143.1 (C_q), 138.8 (C_q), 131.9 (CH), 131.5 (C_q), 128.7 (CH), 128.7 (CH), 128.6 (CH), 126.5 (CH), 123.5 (CH), 122.8 (CH), 87.3 (C_q), 73.8 (C_q), 52.2 (CH), 42.1 (CH_2), 34.6 (CH_2), 30.5 (CH_2), 21.9 (CH_2), 18.4 (CH_2), 13.5 (CH_3); **HRMS (ESI)** calculated for $C_{22}H_{24}NO$ [$M+H$]⁺: 318.1852; found 318.1847;

2-benzyl-3-(4-(tert-butyldiphenylsilyloxy)but-1-ynyl)isoindolin-1-one (80)



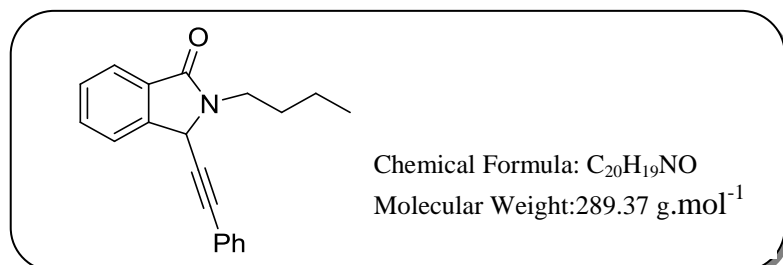
Prepared from acetoxylactam **36** following general procedure **G** with silylated alkyne **73** (40 °C; 75% yield).

yellow oil; R_f = 0.56 [cyclohexane:EtOAc (7/3)]; **IR (neat)/v cm^{-1}** : 1696, 911, 822, 728, 699 cm^{-1} ; **1H NMR** (300 MHz, $CDCl_3$, 20 °C) δ 7.86 (d, J = 6.0 Hz, 1H, ArH), 7.64 (d, J = 9.0 Hz, 4H, ArH), 7.55-7.26 (m, 14H, ArH), 5.33 (d, J = 15.0 Hz, 1H, NCH_2), 5.00 (s, 1H, CHN), 4.31 (d, J = 15.0 Hz, 1H, NCH_2), 3.74 (t, J = 6.0 Hz, 2H, CC- CH_2), 2.49 (t, J = 6.0 Hz, 2H, $CH_2OTBDPS$), 1.03 (s, 9h, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$, 20 °C) δ 167.3 (C_q), 142.9 (C_q),

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136.9 (C_q), 135.6 (CH), 133.5 (C_q), 132.0 (CH), 131.4 (C_q), 129.8 (CH), 128.8 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 123.0 (CH), 84.6 (C_q), 74.9 (C_q), 62.2 (CH_2), 51.0 (CH), 44.1 (CH_2), 26.8 ($3 \cdot CH_3$), 23.0 (CH_2), 19.2 (C_q) **HRMS (ESI)** calculated for $C_{35}H_{36}NO_2Si$ ($M+H$)⁺: 530.2510; found 530.2507;

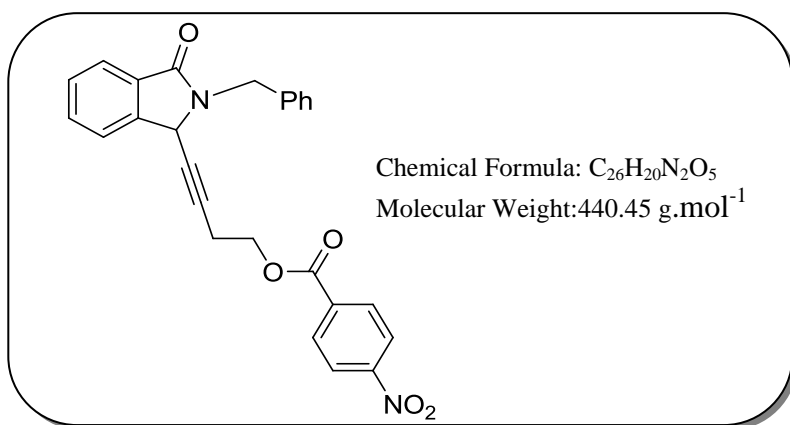
2-butyl-3-(phenylethynyl)isoindolin-1-one (54)



Prepared from acetoxylactam **43** following general procedure **G** with silylated alkyne **32** (40 °C; 69% yield).

yellow oil; R_f = 0.46 [cyclohexane/EtOAc (8/2)]; **IR (neat)/v cm^{-1}** : 1687, 907, 723, 689 cm^{-1} ; **1H NMR** (300 MHz, $CDCl_3$, 20 °C) δ 7.86 (d, J = 3.0 Hz, 1H, ArH), 7.66-7.31 (m, 8 H, ArH), 5.49 (s, 1H, CHN), 4.00 (m, 1H, NCH_2), 3.49 (m, 1H, NCH_2), 1.80-1.66 (m, 2H, NCH_2CH_2), 1.49-1.36 (m, 2H, CH_2CH_3), 0.97 (t, J = 9.0 Hz, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$, 20 °C) δ 167.5 (C_q), 142.4 (C_q), 131.9 (C_q), 131.8 (CH), 128.9 ($5 \cdot CH$), 128.4 (CH), 123.7 (CH), 122.9 (CH), 121.9 (C_q), 86.2 (C_q), 83.0 (C_q), 51.9 (CH), 40.5 (CH_2), 30.4 (CH_2), 20.2 (CH_2), 13.8 (CH_3); **HRMS (ESI)** calculated for $C_{20}H_{20}NO$ ($M+H$)⁺: 290.1539; found 290.1540;

4-(2-benzyl-3-oxoisoindolin-1-yl)but-3-ynyl 4-nitrobenzoate (84)



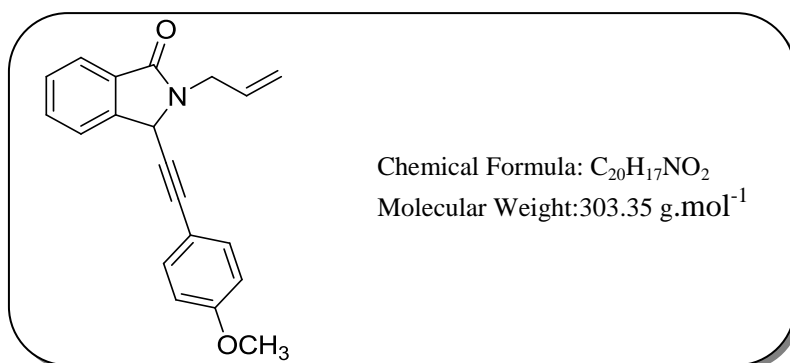
Prepared from acetoxylactam **36** following general procedure **G** using 5 mol% of $Ph_3PAuOTf$ and 1.5 eq of silylated alkyne **77**. (40 °C; 70% yield).

Yellow oil; R_f = 0.43 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm^{-1}** : 1693, 1524, , 718, 701 cm^{-1} ; **1H NMR** (300 MHz, $CDCl_3$, 20 °C) δ 8.24 (d, J = 6.0 Hz, 2H, ArH), 8.14 (d, J = 9.0 Hz, 2H, ArH), 7.84 (d, J = 9.0 Hz, 1H, ArH), 7.52-7.45 (m, 3H, ArH), 7.29-7.26 (m, 5H, ArH),

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5.31 (d, $J = 15.0$ Hz, 1H, NCH_2), 5.01 (s, 1H, CHN), 4.31 (d, $J = 18.0$ Hz, 1H, NCH_2), 4.46 (t, $J = 6.0$ Hz, 2H, CH_2), 2.75 (t, $J = 6.0$ Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 167.2 (C_q), 164.3 (C_q), 150.6 (C_q), 142.5 (C_q), 136.7 (C_q), 135.1 (C_q), 132.0 (CH), 131.3 (C_q), 130.7 (2*CH), 128.9 (CH), 128.7 (2*CH), 128.4 (2*CH), 127.7 (CH), 123.9 (CH), 123.6 (CH), 122.8 (CH), 123.0 (CH), 82.4 (C_q), 76.1 (C_q), 63.2 (CH_2), 50.8 (CH), 44.2 (CH_2), 19.4 (CH_2); **HRMS (ESI)** calculated for $C_{26}H_{21}N_2O_5$ ($M+H$)⁺: 441.1445; found 441.1441;

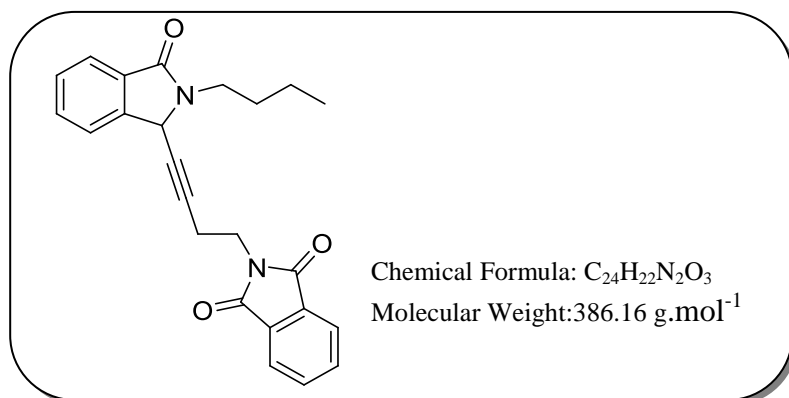
2-allyl-3-((4-methoxyphenyl)ethynyl)isoindolin-1-one (63)



Prepared from acetoxylactam **31** following general procedure **G** with silylated alkyne **58** (40 °C; 72% yield).

yellow oil; $R_f = 0.4$ (cyclohexane/EtOAc 7/3). **IR (neat)**/ ν cm^{-1} : 1694, 1509, 1247, 832, 745, 713 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.87 (d, $J = 6.0$ Hz, 1H, ArH), 7.65-7.58 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.36 (d, $J = 9.0$ Hz, 2H, ArH), 6.84 (d, $J = 9.0$ Hz, 2H, ArH), 5.91 (m, 1H, $CH=CH_2$), 5.46 (s, 1H, NCH), 5.35-5.24 (m, 2H, $C=CH_2$), 4.74 (dd, $J = 15.0$ and 3.0 Hz, 1H, NCH_2), 3.97 (dd, $J = 15.0$ and 9.0 Hz, 1H, NCH_2), 3.83 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 167.2 (C_q), 160.1 (C_q), 142.7 (C_q), 133.4 (2*CH), 132.7 (CH), 132.1 (CH), 131.5 (C_q), 128.9 (CH), 123.8 (CH), 123.1 (CH), 118.3 (CH_2), 114.0 (2*CH), 113.9 (C_q), 86.2 (C_q), 81.3 (C_q), 55.3 (CH), 51.7 (CH_3), 43.1 (CH_2); **HRMS (+ESI)** calculated for $C_{20}H_{18}NO_2$ ($M+H$)⁺: 304.1332, found 304.1332;

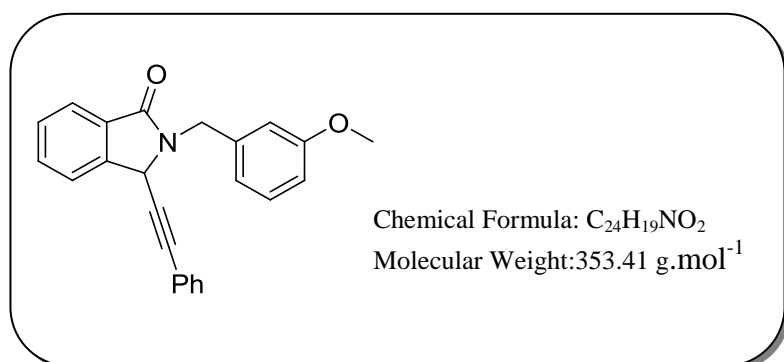
2-(4-(2-butyl-3-oxoisindolin-1-yl)but-3-ynyl)isoindoline-1,3-dione (86)



Prepared from acetoxy lactam **43** following general procedure **G** using 5 mol% of Ph₃PAuOTf and 1.5 eq of silylated alkyne **78** (40 °C; 74% yield).

Yellow oil; $R_f = 0.26$ [cyclohexane:EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 2959, 1707, 1395, 1365, 910, 716 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.82-7.80 (m, 2H, ArH), 7.75-7.69 (m, 3H, ArH), 7.48-7.41 (m, 3H, ArH), 5.14 (s, 1H, CHN), 3.87-3.83 (m, 3H, NCH₂ with CH₂), 3.25 (m, 1H, NCH₂), 2.67-2.63 (t, $J = 6.0$ Hz, 2H, CC-CH₂), 1.59-1.52 (m, 2H, NCH₂CH₂), 1.34-1.21 (m, 2H, CH₂CH₃), 0.92-0.83 (m, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.9 (2**C_q*), 167.3 (*C_q*), 142.4 (*C_q*), 134.1 (*C_q*), 131.9 (*C_q*), 131.7 (3**CH*), 131.6 (*C_q*), 128.7 (*CH*), 123.5 (*CH*), 123.3 (3**CH*), 122.8(*CH*), 82.6 (*C_q*), 76.10 (*C_q*), 51.2 (*CH*), 40.1 (*CH₂*), 36.3 (*CH₂*), 30.2 (*CH₂*), 20.1 (*CH₂*), 18.6 (*CH₂*), 13.8 (*CH₃*); **HRMS (ESI)** calculated for C₂₄H₂₃N₂O₃ (M+H)⁺: 387.1703; found 387.1701;

2-(3-methoxybenzyl)-3-(phenylethynyl)isoindolin-1-one (55)

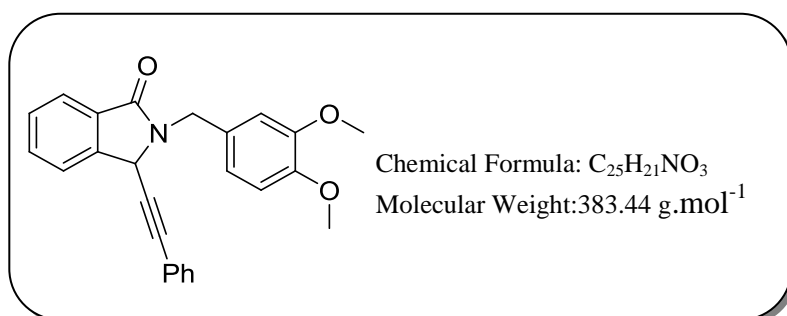


Prepared from acetoxy lactam **44** following general procedure **G** with silylated alkyne **32** (40 °C; 98% yield).

Yellow oil; $R_f = 0.3$ [cyclohexane/EtOAc (8/2)]; **IR (neat)/v cm⁻¹**: 2958, 1698, 742, 692 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.79 (d, $J = 9.0$ Hz, 1H, ArH), 7.48-7.12 (m, 9 H, ArH), 6.89-6.84 (m, 2H, ArH), 6.72 (d, $J = 6.0$ Hz, 1H, ArH), 5.29 (d, $J = 15.0$ Hz, 1H, NCH₂), 5.18

(s, 1H, *CH*-CCPh), 4.30 (d, *J* = 15.0 Hz, 1H, *NCH*₂), 3.65 (s, 3H, *OCH*₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 167.3 (*C*_q), 160.0 (*C*_q), 142.5 (*C*_q), 128.4 (*C*_q), 132.2 (CH), 131.9 (2*CH), 131.4 (*C*_q), 129.9 (2*CH), 129.0 (2*CH), 128.4 (2*CH), 124.0 (CH), 123.1 (CH), 121.9 (*C*_q), 120.9 (CH), 114.1 (CH), 113.3 (CH), 86.5 (*C*_q), 82.7 (*C*_q), 88.3 (CH₃), 51.4 (CH), 44.4 (CH₂); HRMS (ESI) calculated for C₂₄H₂₀NO₂ (M+H)⁺: 354.1489; found 354.1523;

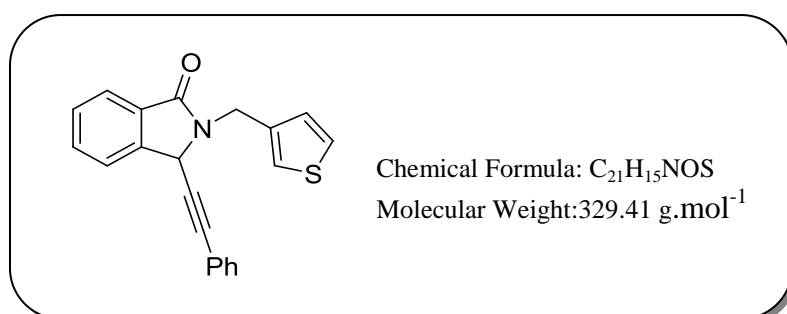
2-(3,4-dimethoxybenzyl)-3-(phenylethynyl)isoindolin-1-one (146)



Prepared from acetoxylactam **145** following general procedure **G** with silylated alkyne **32** (40 °C; 70% yield).

Yellow oil; *R*_f = 0.33 [cyclohexane/EtOAc (7/3)]; IR (neat)/v cm⁻¹: 1698, 1228, 1134, 1025, 753, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.81 (d, *J* = 6.0 Hz, 1H, *ArH*), 7.50-7.18 (m, 8 H, *ArH*), 6.90-6.86 (m, 2 H, *ArH*), 6.73 (d, *J* = 9.0 Hz, 1H, *ArH*), 5.27 (d, *J* = 15.0 Hz, 1H, *NCH*₂), 5.17 (s, 1H, *NCH*), 4.28 (d, *J* = 15.0 Hz, 1H, *NCH*₂), 3.76 (s, 3H, *OCH*₃), 3.75 (s, 3H, *OCH*₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 167.3 (*C*_q), 149.3 (*C*_q), 148.7 (*C*_q), 142.4 (*C*_q), 132.2 (CH), 131.9 (3*CH), 131.5 (*C*_q), 129.3 (*C*_q), 129.0 (2*CH), 128.4 (3*CH), 123.9 (CH), 123.1 (CH), 121.9 (*C*_q), 121.1 (CH), 111.9 (*C*_q), 111.2 (*C*_q), 55.9 (CH₃), 51.3 (CH₃), 44.3 (CH₂); HRMS (ESI) calculated for C₂₅H₂₁NNaO₃ (M+Na)⁺: 406.1414; found 406.1423;

3-(phenylethynyl)-2-(thiophen-3-ylmethyl)isoindolin-1-one (56)



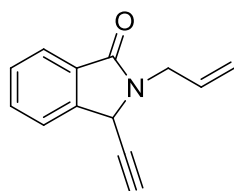
Prepared from acetoxylactam **45** following general procedure **G** with silylated alkyne **32** (82% yield)

Yellow solid; *R*_f = 0.5 (cyclohexane/EtOAc 7/3). m.p. 75 °C IR (neat)/v cm⁻¹: 1690, 908, 725, 689 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.92 (d, *J* = 6.0 Hz, 1H, *ArH*), 7.62-

EXPERIMENTAL SECTION

7.46 (m, 5H, ArH), 7.36-7.28 (m, 5H, ArH with ThiophenH), 7.15 (d, $J = 6.0$ Hz, 1H, ThiophenH), 5.39-5.33 (m, 2H, CHCCPh with NCH₂), 4.55 (d, $J = 15.0$ Hz, 1H, NCH₂); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 167.2 (C_q), 142.4 (C_q), 137.4 (C_q), 132.0 (2*CH), 131.4 (C_q), 129.0 (2*CH), 128.4 (2*CH), 128.0 (CH), 126.5 (CH), 123.9 (CH), 123.6 (CH), 125.8 (C_q), 123.1 (CH), 121.8 (CH), 86.5 (C_q), 82.7 (C_q), 51.5 (CH), 39.3 (CH₂); HRMS (+ESI) calculated for C₂₁H₁₆NOS (M+H)⁺: 330.0947, found 330.0972;

2-allyl-3-ethynylisoindolin-1-one (67)

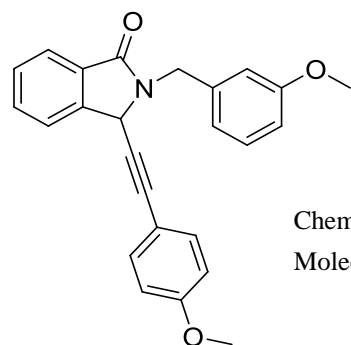


Chemical Formula: C₁₃H₁₁NO
Molecular Weight: 197.23 g.mol⁻¹

Prepared from acetoxylactam **31** following general procedure **G** using trimethylsilylacetylene (40 °C; 69% yield).

Yellow oil; $R_f = 0.48$ [cyclohexane/EtOAc (7/3)]; IR (neat)/v cm⁻¹: 1686, 1393, 738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.83 (d, $J=9.0$ Hz, 1H, ArH), 7.62-7.47 (m, 3 H, ArH), 5.84 (m, 1H, CH=CH₂), 5.31 (s, 1H, CHCC), 5.28-5.23 (m, 2H, C=CH₂), 4.73 (dd, $J = 18.0$ and 3.0 Hz, 1H, NCH₂), 3.86 (dd, $J = 9.0$ and 6.0 Hz, 1H, NCH₂), 2.50 (d, $J = 3.0$ Hz, 1H, CCH); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 167.2 (C_q), 141.9 (C_q), 132.2 (CH), 131.4 (C_q), 129.1 (CH), 123.9 (CH), 122.9 (CH), 118.7 (CH₂), 77.7 (C_q), 74.5 (CCH), 50.6 (CH), 42.9 (CH₂); HRMS (ESI) calculated for C₁₃H₁₂NO [M+H]⁺: 198.0913; found 198.0917;

2-(3-methoxybenzyl)-3-((4-methoxyphenyl)ethynyl)isoindolin-1-one (64)



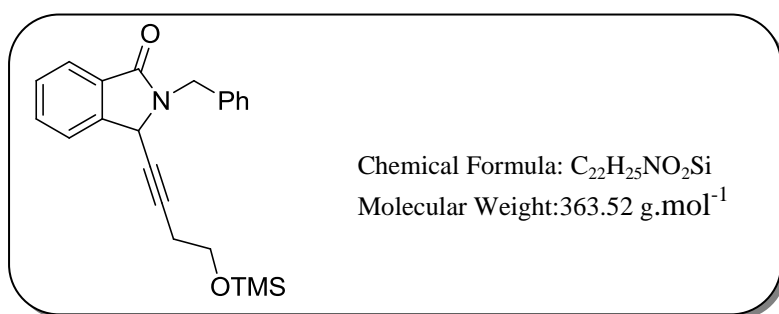
Chemical Formula: C₂₅H₂₁NO₃
Molecular Weight: 383.44 g.mol⁻¹

Prepared from acetoxylactam **44** following general procedure **G** with silylated alkyne **58** (40 °C; 78% yield).

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Yellow oil; $R_f = 0.43$ [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm^{-1}** : 1692, 1248, 1031, 729 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.82 (d, $J = 9.0$ Hz, 1H, ArH), 7.51-7.41 (m, 3 H, ArH), 7.27 (d, $J = 9.0$ Hz, 2H, ArH), 7.17 (m, 1H, ArH), 6.91-6.86 (m, 2H, ArH), 6.77-6.73 (m, 3H, ArH), 5.30 (d, $J = 15.0$ Hz, 1H, NCH_2), 5.19 (s, 1H, CH-CCPh), 4.31 (d, $J = 15.0$ Hz, 1H, NCH_2), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 167.3 (C_q), 160.1 (C_q), 159.9 (C_q), 142.7 (C_q), 138.4 (C_q), 133.4 (2*CH) 132.1 (CH), 131.4 (C_q), 129.8 (CH), 128.9 (CH), 123.9 (CH), 123.1 (CH), 120.9 (CH), 114.0 (3*CH), 113.9 (C_q), 113.2 (CH), 86.5 (C_q), 81.3 (C_q), 55.3 (CH_3), 55.2 (CH_3), 51.4 (CH), 44.3 (CH_2); **HRMS (ESI)** calculated for $\text{C}_{25}\text{H}_{22}\text{NO}_3$ ($\text{M}+\text{H}$)⁺: 384.1594; found 384.1582

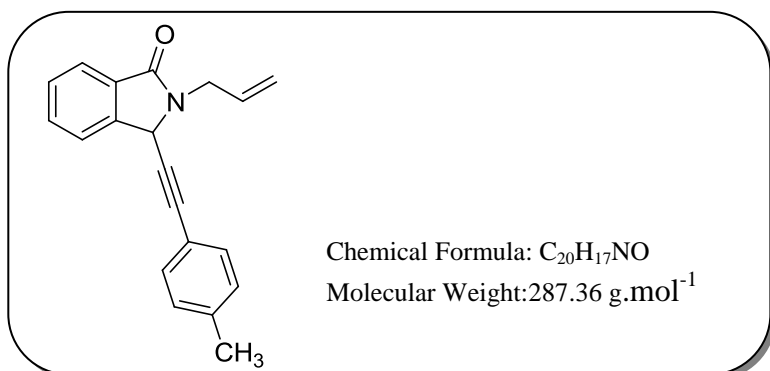
2-benzyl-3-(4-(trimethylsilyloxy)but-1-ynyl)isoindolin-1-one (75)



Prepared from acetoxylactam **36** following general procedure **G** with silylated alkyne (40 °C; 33% yield).

Yellow solid; $R_f = 0.47$ [cyclohexane/EtOAc (7/3)]; **m.p.** 71 °C; **IR (neat)/v cm^{-1}** : 1699, 1394, 1065, 839, 701 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz, CDCl_3 , 20 °C) δ 7.87 (d, $J = 9.0$ Hz, 1H, ArH), 7.58-7.51 (m, 4H, ArH), 7.45-7.30 (m, 4H, ArH), 5.73 (s, 1H, CH), 5.50 (d, $J = 15.0$ Hz, 1H, NCH_2), 4.31 (d, $J = 15.0$ Hz, 1H, NCH_2), 3.19 (m, 1H, CH_2), 3.02 (m, 1H, CH_2), 2.46-2.38 (m, 2H, CH_2), 0.17 (s, 9H, 3* CH_3); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3 , 20 °C) δ 167.3 (C_q), 140.5 (C_q), 136.7 (C_q), 132.6 (C_q), 132.6 (CH), 130.0 (CH), 128.7 (2*CH), 128.6 (CH), 127.7 (CH), 123.7 (CH), 123.5 (CH), 123.3 (CH), 103.5 (C_q), 85.9 (C_q), 85.1 (CH), 60.5 (CH_2), 43.1 (CH_2), 21.0 (CH_2), 0.01 (3* CH_3); **HRMS (EI)** calculated for $\text{C}_{22}\text{H}_{25}\text{NNaO}_2\text{Si}$ ($\text{M}+\text{Na}$)⁺: 386.1541; found 386.1556;

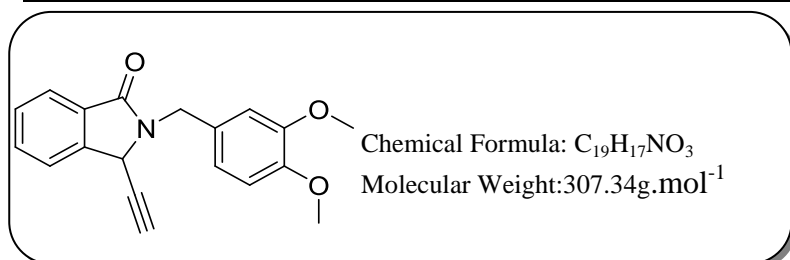
2-allyl-3-(p-tolyethynyl)isoindolin-1-one (62)



Prepared from acetoxylactam **31** following general procedure **G** with silylated alkyne **57** (40 °C; 100% yield).

Orange oil; *R_f* = 0.36 [cyclohexane/EtOAc (7/3)]. **IR (neat)/v cm⁻¹**: 2922, 1695, 1391, 816, 745 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.65-7.50 (m, 3H, Ar*H*), 7.32 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.11 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.89 (m, 1H, CH=CH₂), 5.47 (s, 1H, NCH), 5.29-5.24 (m, 2H, C=CH₂), 4.73 (dd, *J* = 15.0 and 3.0 Hz, 1H, NCH₂), 3.98 (dd, *J* = 15.0 and 9.0 Hz, 1H, NCH₂), 2.33 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 167.3 (C_q), 142.6 (C_q), 139.2 (C_q), 132.7 (CH), 132.1 (2*CH), 131.7 (CH), 131.5 (C_q), 129.1 (CH), 128.9 (CH), 123.8 (CH), 123.1 (CH), 118.8 (C_q), 118.4 (CH₂), 86.4 (C_q), 82.0 (C_q), 51.6 (CH), 43.1 (CH₂), 21.5 (CH₃); **HRMS (+ESI)** calculated for C₂₀H₁₇NNaO (M+Na)⁺: 310.1202, found 310.1210;

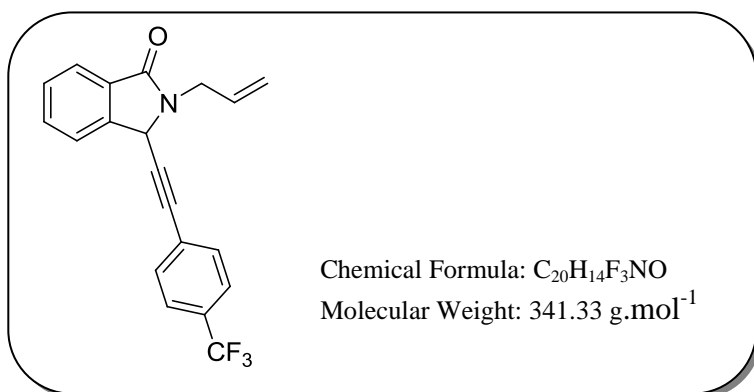
2-(3,4-dimethoxybenzyl)-3-ethynylisoindolin-1-one (159)



Prepared from acetoxylactam **145** following general procedure **G** with silylated alkyne and directly used in the hydroarylation reaction.

R_f = 0.37 [cyclohexane/EtOAc (6/4)]. **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.86 (d, *J*=6.0 Hz, 1H, Ar*H*), 7.57-7.47 (m, 3H, Ar*H*), 6.93-6.87 (m, 2H, Ar*H*), 6.81(d, *J* = 9.0 Hz, 1H, Ar*H*), 5.36 (d, *J* = 15.0 Hz, 1H, NCH₂), 5.00 (s, 1H, NCH), 4.23 (d, *J* = 15.0 Hz, 1H, NCH₂), 3.85 (s, 6H, 2*OCH₃), 2.54 (s, 1H, CCH);

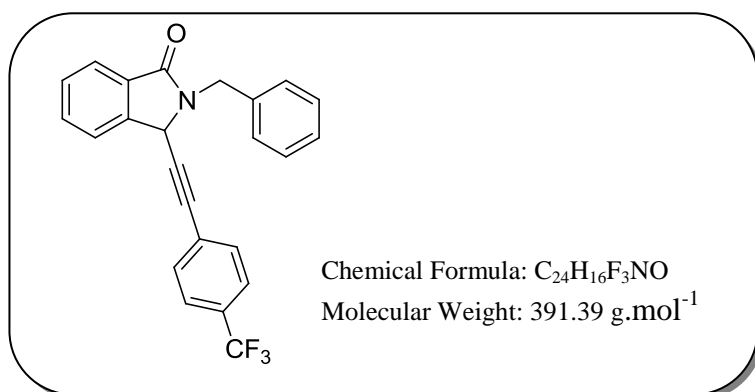
2-allyl-3-((4-(trifluoromethyl)phenyl)ethynyl)isoindolin-1-one (138)



Prepared from acetoxy lactam **31** following general procedure **G** with alkyne **135** (40 °C; 100% NMR yield).

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.93 (d, *J*=9.0 Hz, 1H, ArH), 7.76-7.41 (m, 7H, ArH), 5.93 (m, 1H, CH=CH₂), 5.53 (s, 1H, CHCCPh), 5.40-5.30 (m, 2H, C=CH₂), 4.79 (d, *J* = 15.0 Hz, 1H, NCH₂), 4.02 (dd, *J* = 15.0 and 9.0 Hz, 1H, NCH₂);

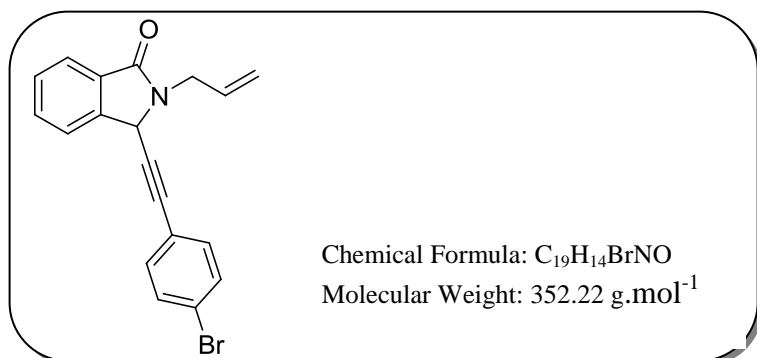
2-benzyl-3-((4-(trifluoromethyl)phenyl)ethynyl)isoindolin-1-one (142)



Prepared from acetoxy lactam **36** following general procedure **H** with alkyne **135** (40 °C; 100% NMR yield).

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.95 (d, *J* = 6.0 Hz, 1H, ArH), 7.65-7.28 (m, 12H, ArH), 5.43-5.53 (d, *J* = 15.0 Hz, 1H, NCH₂), 5.33 (s, 1H, CHCCPh), 4.50 (d, *J* = 15.0 Hz, 1H, NCH₂);

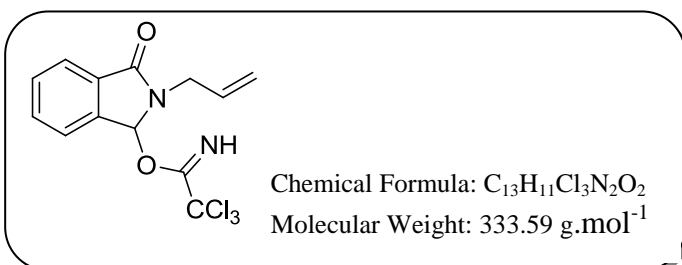
2-allyl-3-((4-bromophenyl)ethynyl)isoindolin-1-one (139)



Prepared from acetoxylactam **31** following general procedure **H** with alkyne **136** (40 °C; 45% NMR yield). The product was obtained as a mixture with the starting material.

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.95-7.25 (m, 8H, ArH), 5.94 (m, 1H, CH=CH₂), 5.53 (s, 1H, CHCCPh), 5.43-5.23 (m, 2H, C=CH₂), 4.83 (d, *J* = 15.0 Hz, 1H, NCH₂), 4.05 (d, *J* = 15.0 Hz, 1H, NCH₂);

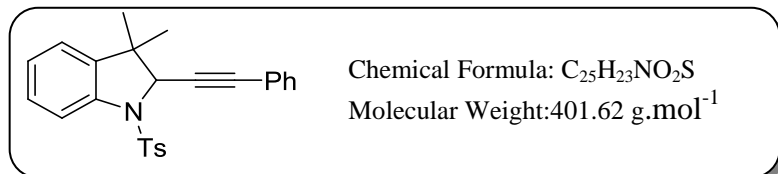
2-allyl-3-oxoisoindolin-1-yl 2,2,2-trichloroacetimidate (144)



Prepared from acetoxylactam **31** following general procedure **H**.

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 8.71 (brs, 1H, NH), 7.80 (m, 1H, ArH), 7.69 (m, 1H, ArH), 7.58-7.54 (m, 2H, ArH), 7.15 (m, 1H, CHN), 5.83 (m, 1H, CH=CH₂), 5.27-5.19 (m, 2H, C=CH₂), 4.55 (dd, *J* = 15.6 and 4.8 Hz, 1H, NCH₂), 3.90 (dd, *J* = 15.6 and 4.8 Hz, 1H, NCH₂);

3,3-dimethyl-2-(phenylethynyl)-1-tosylindoline (126)

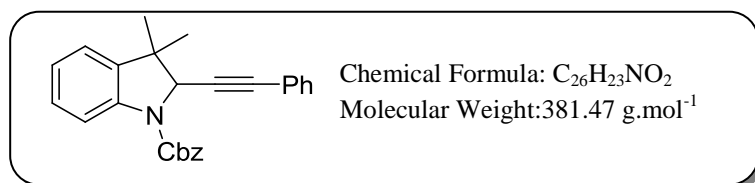


Prepared from acetoxylactam **124** following general procedure **G** with silylated alkyne **32** (40 °C; 99% yield) yellow oil; *R*_f = 0.56 [cyclohexane/EtOAc (8/2)]. IR (neat)/ν cm⁻¹: 1355, 1166, 755, 730, 661cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.86 (d, *J* = 6.0 Hz, 2H,

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ArH), 7.61 (d, $J = 6.0$ Hz, 1H, ArH), 7.29-7.18 (m, 8H, ArH), 7.09-7.04 (m, 2H, ArH), 4.89 (s, 1H, CH), 2.32 (s, 3H, Ar-CH₃), 1.49 (s, 3H, CH₃), 1.08 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 144.1 (C_q), 139.6 (C_q), 139.4 (C_q), 135.8 (C_q), 131.8 (2*CH), 129.8 (2*CH), 129.6 (2*CH), 128.2 (CH), 127.5 (2*CH), 123.9 (2*CH), 122.6 (CH), 122.4 (C_q), 144.6 (CH), 87.5 (C_q), 84.9 (C_q), 65.3 (CH), 44.9 (C_q), 29.6 (CH₃), 23.9 (CH₃), 21.5 (CH₃); HRMS (+ESI) calculated for C₂₅H₂₃NNaO₂S (M+Na)⁺: 424.1342 found 424.1339

benzyl 3,3-dimethyl-2-(phenylethynyl)indoline-1-carboxylate (127)



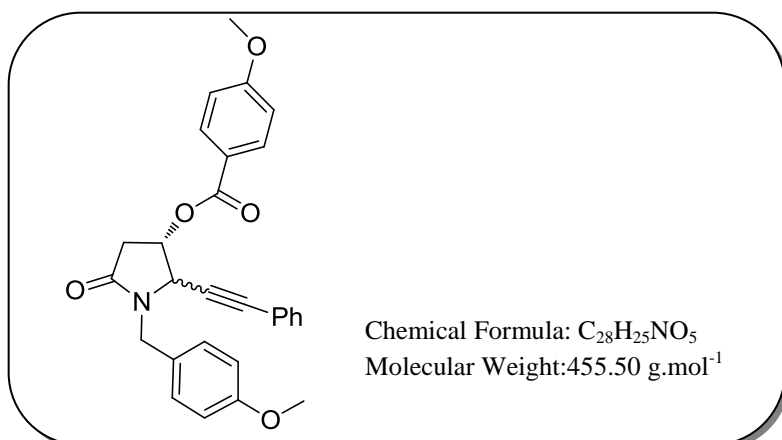
Prepared from acetoxylactame **125** following general procedure **G** with silylated alkyne **32** (40 °C; 70% yield). The desired product was isolated as an inseparable mixture with approximately 10% of an unidentified side-product.

70% yield; yellow oil; $R_f = 0.59$ [cyclohexane/EtOAc (9/1)]. IR (neat)/v cm⁻¹: 1706, 740, 696 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) rotamers δ 7.90 (bs, 2H, ArH), 7.56 7.19 (m, 10H, ArH), 7.21 (m, 1H, ArH), 7.10 (m, 1H, ArH), 5.53 (bd, $J = 12.0$ Hz, 1H, CH₂), 5.32 (bd, $J = 12.0$ Hz, 1H, CH₂), 5.09 (s, 1H, CHN), 1.66 (s, 3H, CH₃), 1.38 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) rotamers δ 153.0 (C_q), 139.9 (C_q), 139.1 (C_q), 136.3 (C_q), 131.8 (2*CH), 128.6 (2*CH), 128.4 (CH), 128.2 (2*CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 123.4 (CH), 122.7 (C_q), 122.2 (CH), 115.3 (CH), 86.0 (C_q), 85.9 (C_q), 67.4 (CH₂), 63.6 (CH), 44.1 (C_q), 30.6 (CH₃), 23.7 (CH₃); HRMS (+ESI) calculated for C₂₆H₂₃NNaO₂ [M+Na]⁺: 404.1621 found; 404.1627.

Products from malic-acid derivatives:

(S)-1-(4-methoxybenzyl)-5-oxo-2-(phenylethynyl)pyrrolidin-3-yl 4-methoxybenzoate

(110)



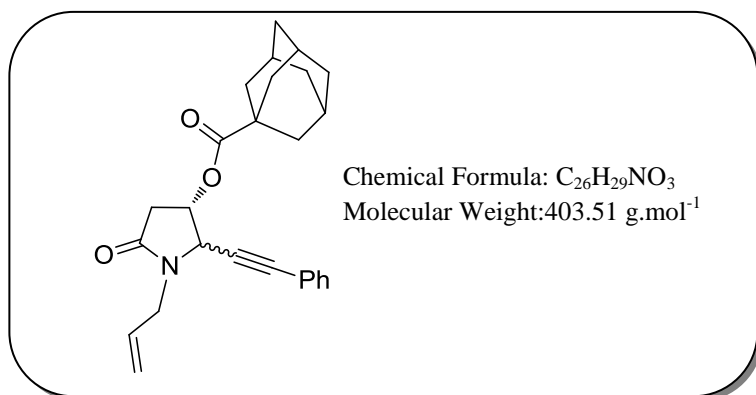
Prepared from acetoxylactame **107** following general procedure **G** with 1.5 equivalent of silylated alkyne **32** (40 °C; 94% yield). The adduct was obtained as a mixture of two diastereoisomers in a 58 : 42 ratio (*trans/cis*).

Yellow oil; R_f = 0.44 *major* and 0.38 *minor* [cyclohexane/ EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 1713, 1692, 1244, 1102, 760, 693 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 8.05 (d, J = 9.0 Hz, 2H *minor*, ArH), 7.92 (d, J = 9.0 Hz, 2H *major*, ArH), 7.46-7.19 (m, 7 H, ArH), 6.95-6.82 (m, 4H, ArH), 6.83 (d, J = 9.0 Hz, 2H *minor*, ArH), 5.65 (d, J = 6.0 Hz; 1H *major*, CH-OCOAr), 5.57 (d, J = 6.0 Hz, 1H *minor*, CH-OCOAr), 5.13 (d, J = 15.0 Hz, 1H, NCH₂), 4.76 (s, 1H, *major* CH-CCPh), 4.77 (d, J = 6.0 Hz, 1H *major*, CH-CCPh), 4.43 (s, 1H, *minor* CH-CCPh), 4.15 (dd, J = 15.0 Hz 1H *major*, NCH₂), 4.09 (d, J = 15.0 Hz, 1H *minor*, NCH₂), 3.88 (s, 3H, OCH₃), 3.82 (s, 3H, *major* OCH₃), 3.77 (s, 3H, *minor* OCH₃), 3.17 (dd, J = 16.0 and 7.5 Hz, 1H *minor*, CH₂), 2.97-2.79 (m, 2H *major*, CH₂), 2.68 (d, J = 16.0 Hz, 1H *minor*, CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 171.5 (C_q *minor*), 170.7 (C_q *major*), 165.6 (C_q *major*), 165.3 (C_q *minor*), 163.9 (C_q *minor*), 163.8 (C_q *major*), 159.3 (C_q *major*), 159.2 (C_q *minor*), 132.0 (2*CH *major*), 131.9 (2*CH *minor*), 131.8 (2*CH *minor*), 131.7 (2*CH *major*), 130.0 (2*CH *major*), 129.5 (2*CH *minor*), 129.00 (C_q *minor*), 128.7 (C_q *major*), 128.4 (2*CH *minor*), 128.2 (2*CH *major*), 127.8 (2*CH *major*), 127.6 (2*CH *minor*), 121.8 (C_q *minor*), 121.7 (C_q *major*), 121.4 (C_q *minor*), 114.8 (2*CH *major*), 114.2 (2*CH *major*), 114.1 (2*CH *minor*), 113.8 (2*CH *minor*), 113.7 (2*CH *major*), 88.7 (C_q *major*), 87.1 (C_q *minor*), 82.7 (C_q *minor*), 81.2 (C_q *major*), 72.4 (CH *minor*), 67.3 (CH *major*), 55.6 (CH *minor*), 55.5 (CH *major*), 55.5 (CH₃ *minor*), 55.3 (CH₃ *major*), 55.2 (CH₃ *minor*), 54.0 (CH₃ *major*), 44.2 (CH₂

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major), 44.0 (CH₂ minor), 37.2 (CH₂ minor), 36.7 (CH₂ major); **HRMS (ESI)** calculated for C₂₈H₂₆NO₅ [M+H]⁺: 456.1805; found 456.1805;

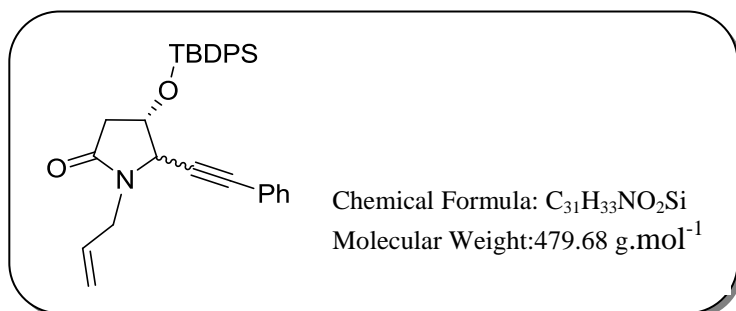
(3S)-1-allyl-5-oxo-2-(phenylethynyl)pyrrolidin-3-yl adamantane-2-carboxylate (112)



Prepared from acetoxylactame **109** following general procedure **G** with 1.5 equivalent of silylated alkyne **32** (40 °C; 100% yield). The adduct was obtained as a mixture of two diastereoisomers in a 52 : 48 ratio (*trans/cis*).

R_f = 0.68 *minor* and 0.37 *major* [cyclohexane/EtOAc (7/3)]. **IR (neat)/v cm⁻¹**: 2907, 1701, 1222, 1071, 728 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.42-7.32 (m, 10H, ArH), 5.75 (m, 2H, CH=CH₂), 5.41 (m, 1H *major*, CHO), 5.40-5.23(m, 2H + 1H *major*, CHCO₂Adm and C=CH₂), 4.90 (d, *J* = 6.4 Hz, 1H *major*, CHCCPh), 4.50 (bd, *J* = 15.0 Hz, 1H *minor* NCH₂), 4.46 (m, 1H *major* NCH₂), 4.45 (s, 1H *minor*, CHCCPh), 4.42 (s, 1H *minor*, CHCCPh), 3.72 (dd, *J* = 15.3 and 7.2 Hz, 1H, *major* NCH₂), 3.62 (dd, *J* = 15.7 and 7.3 Hz, 1H *minor*, NCH₂), 3.02 (dd, *J* = 17.7 and 6.3.0 Hz, 1H *minor*, CH₂CO), 2.83 (dd, *J* = 17.4 and 7.5 Hz, 2H, *major* CH₂CO), 2.66 (dd, *J* = 17.2 and 5.3 Hz, 2H, *major* CH₂CO), 2.48 (d, *J* = 18.0 Hz, 1H, *minor* CH₂CO), 2.04-1.62 (m, 15H, Adm-H) ; **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 176.0 (*major* C_q), 175.8 (*minor* C_q), 170.6 (*major* C_q), 169.7 (*minor* C_q), 130.8 (2*CH *major*), 130.7 (2*CH *minor*), 128.0 (CH), 127.8 (CH), 127.4 (CH), 121.0 (C_q *minor*), 120.6 (CH *major*), 117.9 (CH *minor*), 117.1 (CH *major*), 87.2 (C_q *minor*), 85.9 (C_q *major*), 81.7 (C_q *major*), 80.3 (C_q *minor*), 70.6 (CH), 65.6 (CH), 55.0 (CH), 53.1 (CH), 42.5 (CH₂), 42.0 (CH₂), 39.6 (CH₂), 37.7 (CH₂), 37.6 (CH₂), 35.9 (CH₂), 35.4 (CH₂), 35.3 (CH₂), 35.2 (CH₂), 26.8 (4*CH); **HRMS (+ESI)** calculated for C₂₆H₃₀NO₃ [M+H]⁺: 404.2220, found 404.2219.

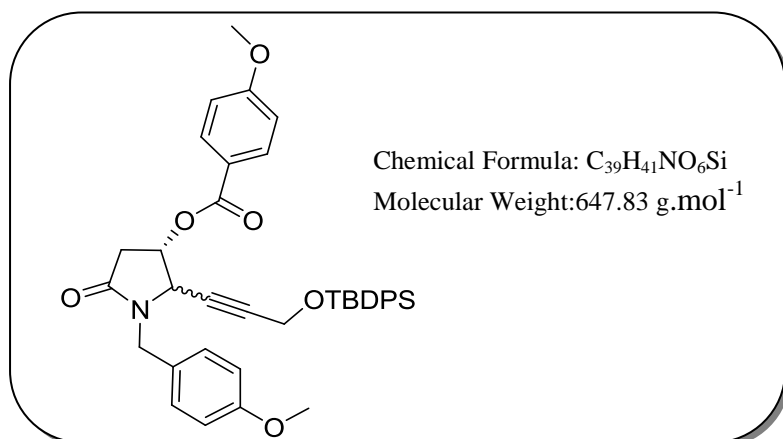
(S)-1-allyl-4-(tert-butyldiphenylsilyloxy)-5-(phenylethynyl)pyrrolidin-2-one (111)



Prepared from acetoxylactame **108** following general procedure **G** with silylated alkyne **32** (40 °C; 77% yield). The adduct was obtained as a mixture of two diastereoisomers in a 76 : 24 ratio (*trans/cis*).

R_f = 0.5 *minor*; 0.36 *major* [cyclohexan/EtOAc (8/2)]; **IR** (*neat*)/v cm⁻¹: 1701, 1105, 933, 689 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 8.08 (m, 4H, *minor* ArH), 7.69-7.63 (m, 4H, *major* ArH), 7.45-7.30 (m, 11 H, ArH), 5.79 (m, 1H, CH=CH₂), 5.34-5.22 (m, 3H, CH=CH₂ with CHOTBDPS), 4.49 (m, 1H, NCH₂), 4.40 (s, 1H, NCH), 3.58 (dd, *J* = 15.0 and 6.0 Hz, 1H, *major+minor* NCH₂), 2.62 (dd, *J* = 15.0 and 6.0 Hz, 1H, COCH₂), 2.41 (d, *J* = 12.0 and 3.0 Hz, 1H, COCH₂), 1.08 (s, 9H, ^tBu); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 171.8 (*major* C_q), 170.2 (*minor* C_q), 136.0 (*minor* 2*CH), 135.8 (*major* 2*CH), 135.7 (3*CH), 133.1 (*major* C_q), 133.0 (*minor* C_q), 131.9 (*minor* CH), 131.8 (*major* CH), 130.3 (*minor* CH), 130.2 (*minor* CH), 130.1 (*major* CH), 130.0 (*major* CH), 128.6 (2*CH), 128.3 (CH), 128.0 (CH), 127.9 (4*CH), 127.8 (2*CH), 122.6 (C_q), 118.4 (CH₂), 87.9 (C_q), 83.2 (C_q), 68.4 (*minor* CH), 67.9 (*major* CH), 55.9 (CH), 53.4 (*minor* CH₂), 43.5 (*major* CH₂), 39.4 (CH₂), 26.8 (*major* 3*CH₃), 26.7 (*minor* 3*CH₃), 19.2 (C_q). **¹HRMS** (+ESI) calculated for C₃₁H₃₄NO₂Si (M+H)⁺ 480.2353; found 480.2352 (rel. intensity);

(S)-2-(3-(tert-butyldiphenylsilyloxy)prop-1-ynyl)-1-(4-methoxybenzyl)-5-oxopyrrolidin-3-yl 4-methoxybenzoate (113)



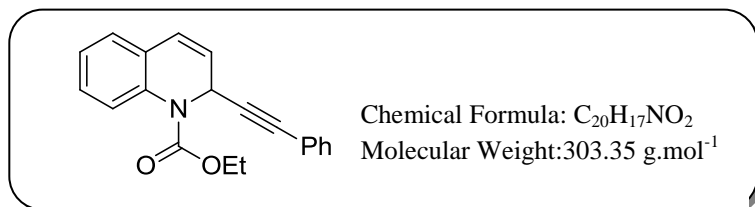
EXPERIMENTAL SECTION

Prepared from acetoxylactame **107** following general procedure **G** with 5 mol% of Ph₃PAuOTf and 1.5 equivalent of silylated alkyne **73** (40 °C; 91% yield). The adduct was obtained as a mixture of two diastereoisomers in a 55 : 45 ratio (*trans/cis*).

$R_f = 0.43$ *minor*; 0.26 *major* [cyclohexan:EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 1699, 1606, 910, 730, 701 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.93 (d, $J = 9.0$ Hz, 2H, *minor* ArH), 7.85 (d, $J = 9.0$ Hz, 2H, *major* ArH), 7.67 (d, $J = 9.0$ Hz, 4H, *major* ArH), 7.60 (d, $J = 9.0$ Hz, 4H, *minor* ArH), 7.41-7.34 (m, 6H, ArH), 7.17 (t, $J = 9.0$ Hz, 2H, ArH), 6.89 (d, $J = 9.0$ Hz; 2H, ArH), 6.84-6.76 (m, 2H, ArH), 5.50 (d, $J = 6.0$ Hz, 1H, *minor* NCH₂), 5.40 (d, $J = 6.0$ Hz, 1H, *major* NCH₂), 5.10 (d, $J = 6.0$ Hz, 1H, *major* NCH₂), 5.05 (d, $J = 6.0$ Hz, 1H, *minor* NCH₂), 4.48 (d, $J = 6.0$ Hz, 1H, *major* CH-CC), 4.18-4.11 (m, 3H, *major* CH₂OSi with *minor* CH-CC), 3.95 (d, $J = 6.0$ Hz 1H, *major* CHO), 3.88 (s, 3H, *minor* OCH₃), 3.83-3.86 (m, 10H, 2**major* OCH₃ with *minor* OCH₃ and *minor* CHO), 3.59-3.57 (m, 2H, *minor* CH₂OSi), 3.05 (dd, $J = 18.0$ and 6.0 Hz, 1H, *minor* CH₂CO), 2.99 (d, $J = 6.0$ Hz, *major* CH₂CO), 2.78 (d, $J = 9.0$ Hz, *major* CH₂CO), 2.74 (d, $J = 6.0$ Hz, *minor* CH₂CO), 2.50 (t, $J = 9.0$ Hz, 1H, *major* CH₂CO), 1.08 (s, 9H, *major* tBu), 1.03 (s, 9H, *minor* tBu); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 171.4 (C_q *major*), 170.6 (C_q *minor*), 165.5 (C_q *minor*), 165.3 (C_q *major*), 163.8 (C_q *major*), 163.6 (C_q *minor*), 159. (C_q *minor*), 159.1 (C_q *major*), 132.89 (CH), 135.6 (3*CH *major*), 135.5 (3*CH *minor*), 133.5 (C_q *major*), 133.4 (C_q *minor*), 131.8 (2*CH), 130.0 (CH), 129.8 (CH), 129.4 (CH), 127.9 (3*CH), 127.8 (3*CH), 127.7 (CH), 121.8 (C_q *minor*), 121.6 (C_q *major*), 114.1 (CH), 114.0 (CH), 113.7 (CH), 86.5 (C_q *minor*), 85.1 (C_q *major*), 75.0 (C_q *major*), 73.3 (C_q *minor*), 72.6 (CH), 67.2 (CH), 62.1 (CH₂), 55.5 (CH₃ *major*), 55.4 (CH₃ *minor*), 55.3 (CH₃ *minor*), 55.2 (CH₃ *major*), 55.1 (CH), 53.6 (CH), 43.9 (CH₂ *minor*), 43.6 (CH₂ *major*), 37.1 (CH₂ *minor*), 36.6 (CH₂ *major*), 26.8 (3*CH₃), 22.9 (CH₂ *major*), 22.8 (CH₂ *minor*), 19.3 (C_q *major*), 19.2 (C_q *minor*), **HRMS (ESI)** calculated for C₂₈H₂₅NO₅ (M+H)⁺ : 456.1766; found 456.1805;

Products from 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) derivatives:

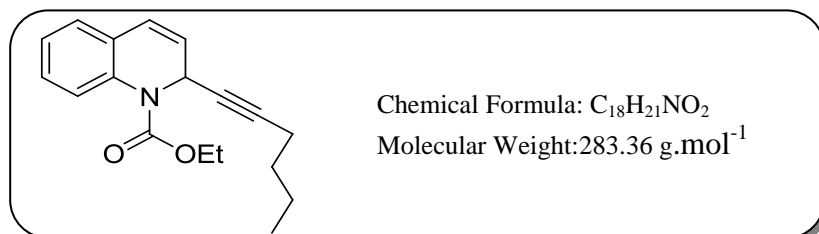
Ethyl 2-(phenylethynyl)quinoline-1(2H)-carboxylate (133)



Prepared from commercially available 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) following general procedure **G** with 5 mol% of Ph₃PAuOTf and silylated alkyne **32** (40 °C; 90% yield).

Solid; **R_f** = 0.68 [cyclohexane/EtOAc (8/2)]; **m.p.** 83 °C; **IR (neat)/v cm⁻¹**: 1698, 1257, 753, 692 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.67 (d, *J*=6.0 Hz, 1H, Ar*H*), 7.30-7.11 (m, 8H, Ar*H*), 6.56 (m, 1H, CHAr), 6.25-6.15 (m, 2H, ArCH=CH), 4.37-4.28 (m, 2H, OCH₂), 1.35 (t, *J*=6.0 Hz, 3H, CH₂CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 153.9 (C_q), 134.4 (C_q), 131.8 (CH), 128.3 (CH), 128.1 (CH), 127.9 (C_q), 126.6 (CH), 126.0 (CH), 125.2 (C_q), 124.5 (CH), 124.4 (CH), 85.7 (C_q), 83.5 (C_q), 62.6 (CO₂-CH₂), 44.7 (CH), 14.5 (CO₂CH₂-CH₃); **HRMS (ESI)** calculated for C₂₀H₁₇NNaO₂ [M+Na]⁺: 326.1151; found 326.1144;

Ethyl 2-(hex-1-ynyl)quinoline-1(2H)-carboxylate (134)



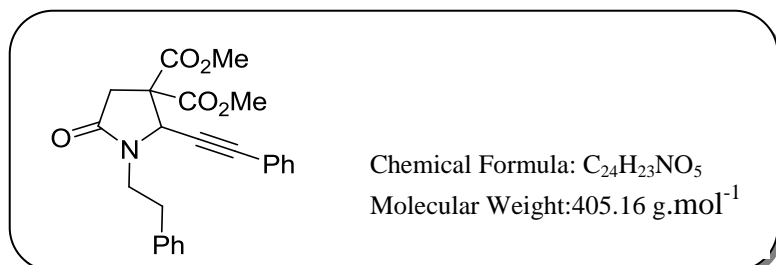
Prepared from commercially available 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) following general procedure **G** and silylated alkyne **59** (40 °C; 65% yield).

Yellow oil; **R_f** = 0.74 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 2958, 1701, 1258, , 729 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.62 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.24 (m, 1 H, Ar*H*), 7.12-7.08 (m, 2H, Ar*H*), 6.48 (d, *J* = 9 Hz, 1H, CHAr), 6.03 (m, 1H, ArCH=CH), 5.83 (bs, 1H, NCH), 4.36-4.21 (m, 2H, OCH₂CH₃), 2.06 (t, *J* = 3.0 Hz, 2H, CC-CH₂), 1.39-1.30 (m, 4H, CH₂CH₂CH₃), 1.26-1.19 (m, 3H, CH₂CH₂CH₃), 0.80 (t, *J* = 6 Hz, 3H, OCH₂CH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 153.8 (C_q), 134.5 (C_q), 127.6 (CH), 126.7 (C_q), 126.5 (2*CH), 126.1 (CH), 125.3 (CH), 124.3 (CH), 84.4 (C_q), 76.5 (C_q), 62.4 (CH₂), 44.3 (CH),

30.5 (CH₂), 21.7 (CH₂), 18.4 (CH₂), 14.5 (CH₃), 13.5 (CH₃); **HRMS (ESI)** calculated for C₁₈H₂₂NO₂ (M+H)⁺: 284.1651; found 284.1644;

Products from pyrrolidine derivatives

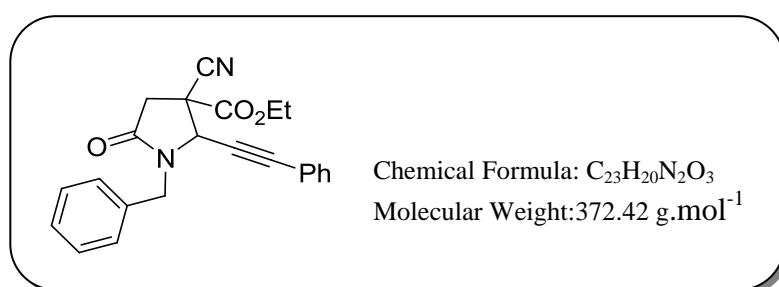
dimethyl 5-oxo-1-phenethyl-2-(phenylethynyl)pyrrolidine-3,3-dicarboxylate (116)



Prepared from methoxylactame **114** following general procedure **G** with 10 mol% of Ph₃PAuOTf and 2 equivalent of silylated alkyne **32** (540 °C; <100% yield).

The desired product was isolated as an inseparable mixture with inseparable mixture of the expected (major) and unidentified (minor) products) *R_f* = 0.31 [cyclohexane:EtOAc (7:3)]; **IR** (neat)/v cm⁻¹: 2955, 1740, 1693, 1435, 1416, 1247, 1217, 1153, 692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.48-7.21 (m, 10H, ArH), 5.33 (s, 1H, CHN), 3.95 (m, 1H, NCH₂), 3.78 (s, 6H, CH₃), 3.46 (d, *J* = 9.0 Hz, 1H, CH₂), 3.38 (m, 1H, NCH₂), 2.98-2.90 (m, 2H, CH₂Ph), 2.79 (d, *J* = 9.0 Hz, 1H, CH₂); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 169.4 (C_q), 168.1 (C_q), 166.4 (C_q), 137.3 (C_q), 130.8 (2*CH), 128.2 (CH), 127.7 (2*CH), 127.6 (2*CH), 127.4 (2*CH), 125.5 (CH), 120.3 (C_q), 92.0 (C_q), 86.7 (C_q), 57.8 (C_q), 53.1 (CH), 52.4 (CH₂), 52.3 (CH₂), 41.8 (CH₂), 35.8 (CH₂), 32.5 (CH₂); **HRMS (ESI)** calculated for C₂₄H₂₄NO₅ (M+H)⁺: 406.1649; found 406.1649

ethyl 1-benzyl-3-cyano-5-oxo-2-(phenylethynyl)pyrrolidine-3-carboxylate (117)



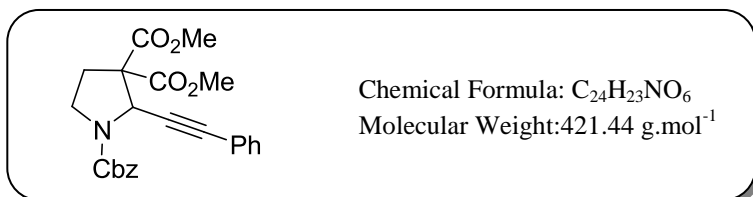
Prepared from ethoxylactame **115** following general procedure **G** with 10 mol% of Ph₃PAuNTf₂ and 2 equivalent of silylated alkyne **32** (50 °C; <68 % yield).

Yellow oil; *R_f* = 0.29 [cyclohexane/EtOAc (8/2)]; **IR** (neat)/v cm⁻¹: 1746, 1709, 1408, 1239, 1072, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.53-7.19 (m, 10H, ArH), 5.16 (d, *J* =

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6.0 Hz, 1H, NCH₂), 4.81 (s, 1H, CHN), 4.26 (d, *J* = 9.0 Hz, 2H, CO₂CH₂), 4.16 (d, *J* = 15.0 Hz, 1H, NCH₂), 3.19 (s, 2H, COCH₂), 1.30-1.21 (m, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 169.2 (C_q), 165.6 (C_q), 135.0 (C_q), 134.8 (C_q), 132.1 (CH), 129.6 (CH), 128.9 (2*CH), 128.5 (3*CH), 128.2 (2*CH), 128.1 (2*CH), 120.8 (C_q), 115.9 (C_q), 90.8 (C_q), 64.3 (CH₂), 47.8 (C_q), 45.3 (CH₂), 39.1 (CH₂), 39.1 (CH₃); HRMS (ESI) calculated for C₂₃H₂₀N₂NaO₃ (M+Na)⁺: 395.1369; found 395.1369

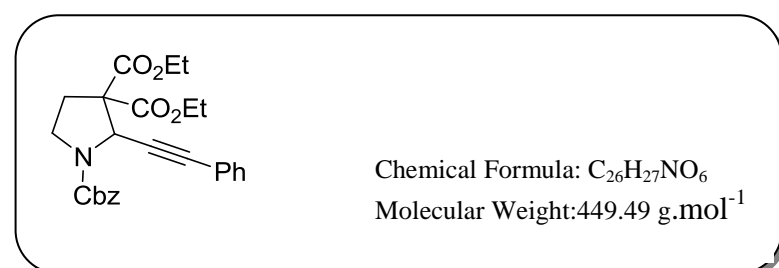
1-benzyl 3,3-dimethyl 2-(phenylethynyl)pyrrolidine-1,3,3-tricarboxylate (121)



Prepared from ethoxylactame **119** following general procedure **G** with 10 mol% of Ph₃PAuNTf₂ and 2 equivalents of silylated alkyne **32** (50 °C; 88% yield).

Yellow oil; *R_f* = 0.43 [cyclohexane/EtOAc (7/3)]; IR (neat)/ν cm⁻¹: 1738, 1705, 1407, 756, 692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.51-7.32 (m, 10H, ArH), 5.60 and 5.58 (s, 1H, NCH), 5.42-5.19 (m, 2H, CH₂Ph), 3.83 (s, 3H, CH₃), 3.82 (s, 3H, CH₃), 3.76 (m, 1H, NCH₂), 3.44 (m, 1H, NCH₂), 2.94 (d, 1H, CH₂C_q), 2.52 (d, 1H, CH₂C_q); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 169.1 (C_q), 167.4 and 167.3 (C_q), 154.1 (C_q), 136.7 and 136.5 (C_q), 131.9 and 131.7 (2*CH), 128.7 and 128.6 (CH), 128.4 (2*CH), 128.3 and 128.2 (2*CH), 128.0 (CH), 127.8 and 127.7 (CH), 127.5 (CH), 122.1 and 122.1 (C_q), 85.1 and 84.9 (C_q), 84.6 and 84.5 (C_q), 67.2 and 67.1 (CH₂), 64.8 and 63.9 (C_q), 53.6 and 53.5 (CH₃), 53.2 (CH₂), 43.9 and 43.6 (CH₂), 30.7 and 29.8 (CH₂); HRMS (ESI) calculated for C₂₄H₂₃NNaO₆ [M+Na]⁺: 444.1418; found 444.1421;

1-benzyl 3,3-diethyl 2-(phenylethynyl)pyrrolidine-1,3,3-tricarboxylate (120)



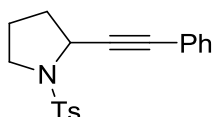
Prepared from ethoxylactame **118** following general procedure **G** with 10 mol% of Ph₃PAuNTf₂ and 2 equivalents of silylated alkyne **32** (50 °C; 30% yield).

yellow oil; *R_f* = 0.47 [cyclohexane:EtOAc (8/2)]; IR (neat)/ν cm⁻¹: 1735, 1706, 756, 692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.45-7.26 (m, 10H, ArH), 5.553-5.12 (m, 3H, CH₂Ph

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and NCH), 4.26-4.19 (m, 4H, 2*CO₂CH₂), 4.22 (m, 1H, CH₂N), 3.35 (m, 1H, CH₂N), 2.87 (m, 1H, CH₂C_q), 2.45 (m, 1H, CH₂C_q), 1.26-1.21 (m, 6H, 2*CH₃); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 168.7 (C_q), 166.7 (C_q), 136.8 (C_q), 134.0 (C_q), 131.6 (CH), 128.7 (CH), 128.6 (CH), 128.3 (2*CH), 128.2 (2*CH), 127.9 (CH), 122.2 (C_q), 85.0 (C_q), 84.8 (C_q), 67.1 (CH₂), 64.7 (CH), 63.9 (C_q), 62.4 (CH₂), 62.1 (CH₂), 53.8 (CH₂), 52.9 (CH₂), 43.8 (CH), 29.7 (CH), 14.0 (2*CH₃); **HRMS (ESI)** calculated for C₂₆H₂₈NO₆ (M+H)⁺: 450.1911; found 450.1910;

2-(phenylethynyl)-1-tosylpyrrolidine (91)

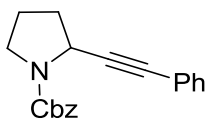


Chemical Formula: C₁₉H₁₉NO₂S
Molecular Weight: 325.42 g.mol⁻¹

Prepared from methoxylactame **89** following general procedure **G** with silylated alkyne **32** (r.t.; 29% yield).

Yellow solid; **R_f** = 0.56 [cyclohexane/EtOAc (8/2)]. **M.p.** 118 °C; **IR (neat)/v cm⁻¹**: 1156, 1087, 1008, 756, 690, 664 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.83 (d, *J* = 9.0 Hz, 2H, ArH), 7.55-7.48 (m, 2H, ArH), 7.33-7.22 (m, 5H, ArH), 4.80 (t, *J* = 3.0 Hz, 1H, CH), 3.50-3.40 (m, 2H, CH₂), 2.36 (s, 3H, CH₃), 2.13-2.06 (m, 3H, CH₂ with CH₂CH), 1.95 (m, 1H, CH₂CH); ¹³C NMR (75 MHz, CDCl₃, 20 °C) δ 143.3 (C_q), 135.7 (C_q), 131.6 (2*CH), 129.4 (2*CH), 128.3 (2*CH), 128.1 (CH), 127.7 (2*CH), 122.6 (C_q), 87.6 (C_q), 84.2 (C_q), 51.0 (CH), 47.2 (CH₂), 34.1 (CH₂), 24.4 (CH₂), 21.5 (CH₃); **HRMS (+ESI)** calculated for C₁₉H₂₀NO₂S (M+H)⁺: 326.1209 found 326.1195;

benzyl 2-(phenylethynyl)pyrrolidine-1-carboxylate (90)



Chemical Formula: C₂₀H₁₉NO₂
Molecular Weight: 305.37 g.mol⁻¹

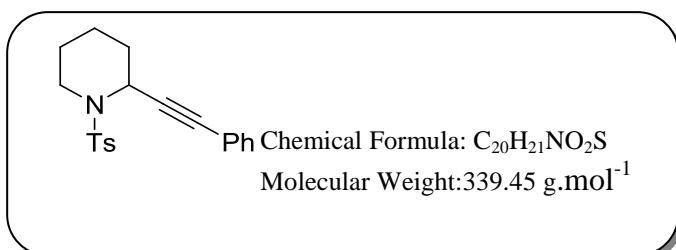
Prepared from methoxylactame **87** following general procedure **G** with silylated alkyne **32** (40 °C; 21% yield).

Yellow oil; **R_f** = 0.23 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 1699, 1407, 755, 691 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) rotamers δ 7.55-7.26 (m, 10H, ArH), 5.53 (m, 0.6H, CH₂Ph), 5.23-5.09 (m, 1.5H, CH₂Ph), 4.81 (m, 1H, CH₂), 3.59 (bs, 1H, CHCCPh), 3.44 (m, 1H, CH₂), 2.16 (m, 3H, CH₂CH₂N with CH₂CH₂), 1.96 (m, 1H, CH₂CH₂); ¹³C NMR (75 MHz, CDCl₃, 20 °C) rotamers δ 154.6 (C_q), 137.0 (C_q), 131.7 (CH), 128.4 (3*CH), 128.2 (3*CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 123 (C_q), 89.4 (C_q), 82.4 (C_q), 66.2 (CH₂), 48.7

EXPERIMENTAL SECTION

(CH), 46.2 (CH₂), 34.0 (CH₂), 23.8 (CH₂); **HRMS (+ESI)** calculated for C₁₉H₂₀NO₂S (M+H)⁺: 306.1489 found 306.1489 (rel. intensity);

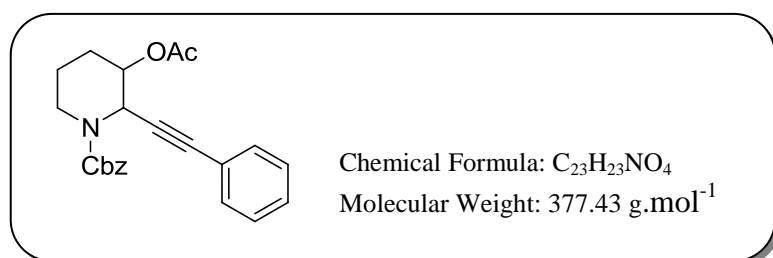
2-(phenylethynyl)-1-tosylpiperidine (100)



Prepared from methoxylactame **99** following general procedure **G** with silylated alkyne **32** (40 °C; 24% yield).

Pale yellow oil; **R_f** = 0.44 [cyclohexane/EtOAc (8/2)]; **IR (neat)/ν cm⁻¹**: 2928, 1337, 1159, 679 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C,) δ 7.75-7.64 (m, 4H, ArH), 7.34-7.20 (m, 4H, ArH), 6.99 (d, *J* = 6.0 Hz, 1H, ArH), 4.98 (m, 1H, NCH), 3.38 (t, *J* = 6.0 Hz, 2H, CH₂), 2.44 (s, 3H, CH₃), 1.93-1.91 (m, 4H, 2*CH₂), 1.76-1.65 (m, 2H, CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 143.5 (C_q), 135.1 (C_q), 131.4 (CH), 129.7 (2*CH), 129.6 (C_q), 129.3 (CH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 125.1 (CH), 108.3 (CH), 86.8 (C_q), 84.3 (C_q), 43.8 (CH₂), 42.3 (CH₂), 31.6 (CH), 21.6 (CH₃), 20.9 (CH₂), 19.4 (CH₂); **HRMS (ESI)** calculated for C₂₀H₂₁NNaO₂S (M+Na)⁺: 362.1191; found 362.1193

benzyl 3-hydroxy-2-(phenylethynyl)piperidine-1-carboxylate (102)



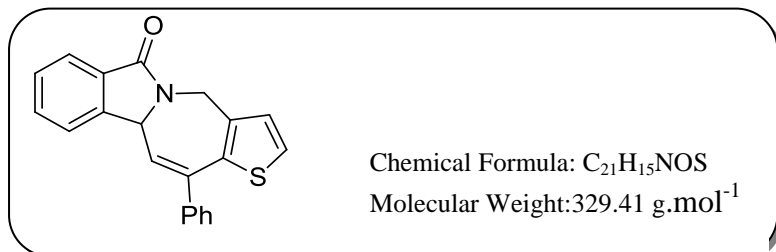
Prepared from acetoxylactame **101** following general procedure **G** with silylated alkyne **32** (rt; 18% yield).

Pale yellow oil; **R_f** = 0.53 [cyclohexane/EtOAc (7/3)]; **IR (neat)/ν cm⁻¹**: 1698, 1233, 729 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) rotamers δ 7.44-7.31 (m, 10H, ArH), 5.59 (bs, 0.2H, NCH), 5.44 (bs, 0.8H, NCH), 5.29-5.02 (m, 3H, CO₂CH₂ with CHOAc), 4.13 (m, 1H, NCH₂), 3.25 (m, 1H, NCH₂), 2.16 (s, 3H, CH₃), 1.98-1.83 (m, 4H, 2*CH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) rotamers δ 170.3 (2*C_q), 136.7 (C_q), 133.8 (CH), 131.9 (CH), 131.8 (2*CH), 128.5 (2*CH), 128.3 (2*CH), 128.0 (CH), 127.8 (CH), 122.2 (C_q), 86.5 (C_q), 83.7 (C_q), 69.7

(CH), 67.3 (CH₂), 48.2 (CH), 24.5 (2*CH₂), 21 (CH₃), 19.7 (CH₂); **HRMS (ESI)** calculated for C₂₃H₂₃NNaO₄ (M+Na)⁺: 400.1525; found 400.1530.

Products from the hydroarylation reaction:

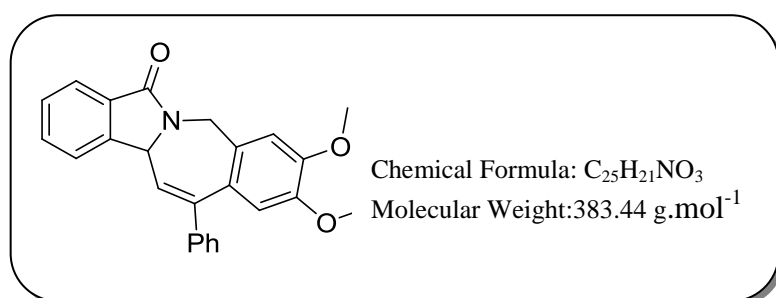
12-phenyl-4H-thieno[2',3':5,6]azepino[2,1-a]isoindol-6(10bH)-one (158)



Prepared from alkyl **56** following general procedure **I** (40 °C; 8 % yield).

R_f = 0.53 [cyclohexane/EtOAc (7/3)]; **IR (neat)/v cm⁻¹**: 1699, 1389, 696 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.85 (d, *J* = 6.0 Hz, 2H, ArH), 7.72-7.29 (m, 7H, ArH), 7.01 (s, 2H, ThiophenH), 6.14 (d, *J* = 6.0 Hz, 1H CHC=CPh), 5.14 (d, *J* = 15.0 Hz, 1H, NCH₂), 4.84 (d, *J* = 15.0 Hz, 1H, NCH₂); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 142.4 (C_q), 142.4 (C_q), 134.0 (C_q), 132.1 (C_q), 131.8 (CH), 131.5 (C_q), 129.2 (C_q), 128.6 (2*CH), 127.6 (C_q), 127.4 (2*CH), 123.2 (2*CH), 121.6 (2*CH), 118.9 (2*CH), 106.3 (CH), 42.4 (CH), 38.2 (CH₂); **HRMS (+ESI)** calculated for C₂₁H₁₅NNaOS (M+Na)⁺: 352.0767, found 352.0773

2,3-dimethoxy-13-phenyl-5H-benzo[5,6]azepino[2,1-a]isoindol-7(11bH)-one (155)



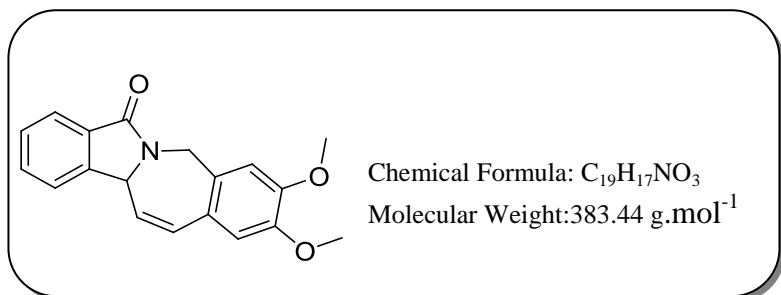
Prepared from alkyl **146** following general procedure **I** (40 °C; 47 % yield).

Yellow oil; **R_f** = 0.4 [cyclohexane/EtOAc (6/4)]; **m.p.** degradation at 140 °C; **IR (neat)/v cm⁻¹**: 1706, 1665, 1520, 1438, 1347, 1237, 1135, 1027, 967, 754, 703 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.73 (d, *J* = 9.0 Hz, 1H, ArH), 7.72 (d, *J* = 6.0 Hz, 1H, ArH), 7.47 (m, 1H, ArH), 7.38 (m, 1 H, ArH), 7.25-7.18 (m, 5H, ArH), 6.83 (s, 1H, ArH), 6.68 (s, 1H, ArH), 6.24 (d, *J* = 8.3 Hz, 1H, CH=CPh), 4.96 (d, *J* = 5.4 Hz, 2H, NCH₂ with CH-CCPh), 4.42 (d, *J* = 14.5 Hz, 1H, NCH₂), 3.79 (s, 6H, 2*OCH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 166.0 (C_q), 148.2 (C_q), 147.7(C_q), 142.7 (C_q), 146.9 (C_q), 136.3 (C_q), 136.0 (C_q), 131.7 (CH), 129.0

EXPERIMENTAL SECTION

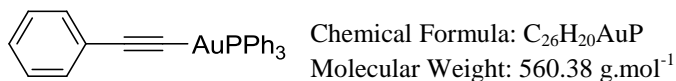
(CH), 128.6 (2*CH), 128.3 (C_q), 127.8 (2*CH), 126.8 (CH), 126.5 (C_q), 123.4 (CH), 119.1 (CH), 113.8 (CH), 113.2 (CH), 106.6 (CH), 56.1 (2*CH₃), 46.9 (CH), 42.9 (CH₂); **HRMS (ESI)** calculated for C₂₅H₂₂NO₃ (M+H)⁺ : 384.1594; found 384.1583;

2,3-dimethoxy-5H-benzo[5,6]azepino[2,1-a]isoindol-7(11bH)-one (160)



Prepared from alkyl **159** following general procedure **J** (40 °C; 15 % yield).

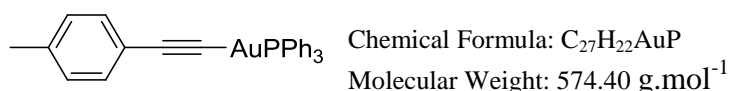
One pot reaction, 15% yield; oil; R_f = 0.27 [cyclohexane/EtOAc (6/4)]; **m.p.** degradation at 170 °C; **IR (neat)/v cm⁻¹**: 1683, 1516, 735 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃, 20 °C) δ 7.98 (m, 1H, ArH), 7.53-7.50 (m, 4H, ArH), 7.10 (m, 1H, ArH), 6.92 (s, 1H, CH), 5.93 (s, 1H, CH), 5.60 (s, 1H, CH), 5.49 (d, J = 9.2 Hz, 1H, NCH₂), 4.11 (d J = 12.0 Hz, 1H, NCH₂), 3.81 (s, 3H, OCH₃), 3.53 (s, 3H, OCH₃); **¹³C NMR** (75 MHz, CDCl₃, 20 °C) δ 168.2 (C_q), 150.3 (C_q), 149.7 (C_q), 146.6 (C_q), 132.3(CH), 131.9 (C_q), 130.6 (C_q), 128.6 (CH), 126.6 (C_q), 123.8 (CH), 123.5 (CH), 111.9 (CH), 109.0 (CH), 57.1 (CH), 56.0 (CH₃), 55.6 (CH₃), 38.5 (CH₂); **HRMS (ESI)** calculated for C₃₈H₃₃N₂O₆ (2M)⁺ : 613.2333; found 613.2329;

Chapter IV:**Gold alkynylides:****triphenylphosphine(phenylethynyl)gold(I) (166)**

Prepared from commercially available phenylacetylene following general procedure **K** (73% yield).

$R_f = 0.41$ [cyclohexane/EtOAc (8/2)]. ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.57-7.45 (m, 20H, ArH);

Data in accordance with previously reported results.³⁸

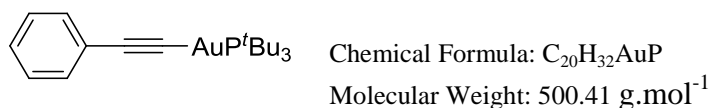
[(PPh₃)Au(4-tolylethynyl)] (169)

Prepared from commercially available 1-ethynyl-4-methylbenzene following general procedure **K** (43% yield)

$R_f = 0.46$ [cyclohexane/EtOAc (8/2)].

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.58-7.40 (m, 17H, ArH), 7.05 (d, $J = 9.0$ Hz, ArH), 2.32 (s, 3H, CH₃);

Data in accordance with previously reported results.³⁹

[(PtBu₃)Au(4-tolylethynyl)] (167)

Prepared from commercially available phenylacetylene following general procedure **K** (39% yield)

$R_f = 0.47$ [cyclohexane/EtOAc (7/3)].

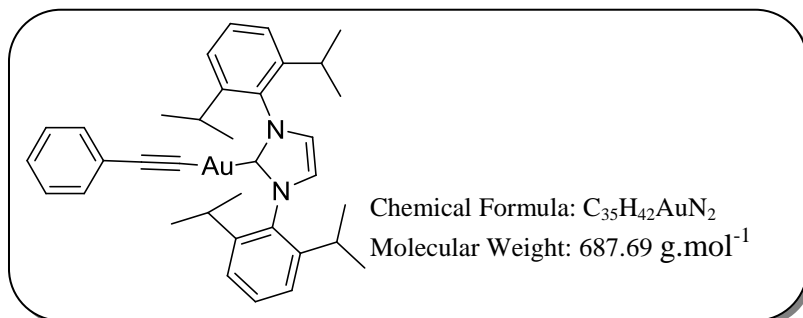
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.50 (d, $J=6.0$ Hz, ArH), 7.26-7.19 (m, 3H, ArH), 1.55 (s, 18H, 2**t*Bu), 1.51 (s, 9H, *t*Bu);

³⁸ Breen, T.L.; Stephan, D.W. *Organometallics*, **1996**, *15*, 5737.

³⁹ Partyka, D.V.; Updegraff III, J.B.; Zeller, M.; Hunter, A.D.; Gray T.G. *Organometallics*, **2007**, *26*, 183.

Data in accordance with previously reported results.⁴⁰

[(IPr)Au(4-tolylethynyl)](168)



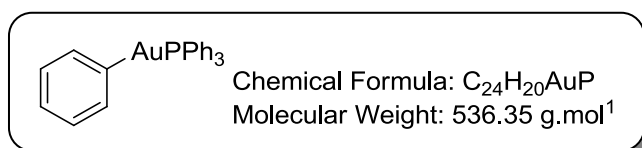
Prepared from commercially available phenylacetylene following general procedure **K** (96% yield)

$R_f = 0.46$ [cyclohexane/EtOAc (7/3)].

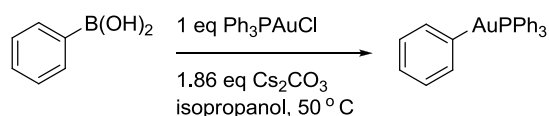
¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.48 (d, *J* = 6.0 Hz, 2H, ArH), 7.30-7.26 (m, 6H, ArH), 7.12-7.07 (m, 5H, ArH), 2.63-2.56 (m, 4H, 4*CH), 1.38 (d, *J* = 6.0 Hz, 12H, 4*CH₃), 1.21 (d, *J* = 6.0 Hz, 12H, 4*CH₃);

Data in accordance with previously reported results.⁴¹

Phenyl(triphenylphosphine)gold (170)



Prepared according to the procedure presented below:



In a dry isopropanol (5 mL) the phenyl boronic acid (35.0 mg, 0.287 mmol, 1.9 eq) was dissolved and Cs₂CO₃ (92 mg, 0.282 mmol, 1.86 eq) was added. To this suspension was added Ph₃PAuCl (74 mg, 0.15 mmol, 1 eq) and the resultant was stirred at 50 °C for 24h and taken to a dryness via rotary evaporation. The resulting crude product was then purified by flash column chromatography on silica gel to give the product as a solid. (93% yield)

Data in accordance with previously reported results.⁴²

¹H NMR (300 MHz, CDCl₃, 20 °C) δ 7.57-7.53 (m, 7H, ArH), 7.51-7.40 (m, 7H, ArH), 7.25-7.20 (m, 5H, ArH), 7.03 (t, *J* = 9.0 Hz, 1H, ArH).

⁴⁰ Layva-Perez, A.; Rubio-Marques, P.; Al-Deyab, S.S. ; Al-Resayes, S.I. ; Corma, A. *ASC Cata.*, **2011**, *1*, 601.

⁴¹ Brown, T.J.; Widenhofer, R.A. *Organometallics*, **2011**, *30*, 6003.

⁴² Hashmi, A. Stephen K.; Ramamurthi, Tanuja D.; Rominger, F. *J.Organomet. Chem.*, **2009**, *694*, 592.

RÉSUMÉ

Développement de nouvelles stratégies en chimie des ions *N*-acyliminiums catalysées par l'or

Ces dernières années, la catalyse à l'or est devenue un outil puissant en synthèse organique, principalement grâce à la capacité des sels d'or cationiques à activer des liaisons multiples, tels que les alcynes, vis-à-vis de réactions d'additions nucléophiles. Dans le contexte de la chimie des ions *N*-acyliminiums, nous nous sommes intéressés à la capacité des catalyseurs à l'or à promouvoir des transformations de *N,O*-acétals sans précédent, y compris dans des séquences réactionnelles en cascade. Dans une première partie, nous avons évalué le potentiel de la catalyse à l'or dans une séquence de carboalcoxylation intramoléculaire / réarrangement d'aza-Ferrier-Petasis qui devrait fournir un accès rapide et original à des éthers d'énols cycliques.

Dans une seconde partie, nous avons développé une procédure performante et générale pour l'alcynylation catalytique de *N,O*-acétals en s'appuyant sur un mécanisme original de catalyse synergique silyl-or. Cette stratégie exploite la π -acidité des complexes de l'or(I) (LAuX) à activer des trimethylsilylalkynes, générant ainsi, en quantité catalytique, un acétylure d'or nucléophile et un (super)acide de Lewis silylé TMSX capable de promouvoir la formation de l'espèce cationique électrophile. Cette procédure a pu être étendue avec succès à l'alcynylation de différents précurseurs d'ions *N*-acyliminiums, avec des alcynes silylés variés. Au cours de notre étude, un intérêt particulier a été porté à l'étude et à la compréhension du mécanisme impliqué. Enfin, pour démontrer le potentiel synthétique des produits d'alcynylation, une séquence en un seul pot d'alcynylation/hydroarylation a également été brièvement examinée.

Mots-clés: Catalyse à l'or, ions *N*-acyliminiums, catalyse électrophile, alcynylation, acétylure d'or, catalyse synergique, hydroarylation.

ABSTRACT

Development of new gold-catalyzed strategies in *N*-acyliminium ion chemistry

Over the last decade, gold complexes have become a powerful tool in organic synthesis, mostly owing to their ability to activate multiple bonds such as alkynes, towards nucleophilic additions. As a part of our ongoing studies on *N*-acyliminium ion chemistry, we have been interested in using gold catalysts for heretofore unprecedented transformations of *N,O*-acetals, as *N*-acyliminium ion precursors, including tandem/cascade reactions. First, a gold(I)-catalyzed intramolecular carboalkoxylation/aza-Ferrier-Petasis rearrangement sequence which was expected to give an expeditious access to cyclic enol ethers was evaluated.

In a second part, a catalytic alkynylation of *N,O*-acetals relying on an original synergistic silyl-gold catalysis mechanism was developed. This strategy exploits the carbophilic π -acidity of gold(I) catalysts (LAuX) to activate trimethylsilylalkynes towards desilylation, thus generating a nucleophilic gold acetylide and a silyl Lewis (super)acid TMSX catalytically. The developed methodology was found to tolerate a wide range of *N,O*-acetals and TMS-alkynes. During the course of our investigation, a special interest was dedicated to the investigation and understanding of the mechanism involved. Last, to demonstrate the synthetic potential of the resulting alkynylated products, a one-pot two-step alkynylation/hydroarylation sequence was also briefly investigated.

Keywords: gold catalysis, *N*-acyliminium ion, electrophilic catalysis, alkynylation, gold-acetylide, synergistic catalysis, hydroarylation.