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Catalytic Activation of Acetylenic Compounds by π -Acids and Halogen Bonding Catalysis

Jiaxin Tian

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Catalytic Activation of Acetylenic Compounds by
 π -Acids and Halogen Bonding Catalysis
*Activation Catalytique de Composés Acétyléniques
par des π -Acides et par Liaison Halogène*

Thèse de doctorat de l'université Paris-Saclay

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**Thèse présentée et soutenue à Paris-Saclay,
le 14 décembre 2021, par**

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List of Abbreviations and Acronyms

°C	Celsius degree
1,4-CHD	1,4-cyclohexadiene
Ar	aryl
APCI	Atmospheric Pressure Chemical Ionization
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
bp	boiling point
cat	catalyst
Cy	cyclohexyl
d	day
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	Density Functional Theory
EDG	Electron Donating Group
equiv	equivalent
ESI	Electrospray Ionization
Et	ethyl
EtOAc	ethyl acetate
EWG	Electron Withdrawing Group
h	hour
hept (NMR)	heptet
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
<i>i</i>	<i>iso</i>

IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	Infrared Spectroscopy
<i>J</i>	coupling constant
LA	Lewis acid
m (NMR)	multiplet
M	molarity, mol/L
Me	methyl
min	minute
ml	milliliter
mol	mole
MS	Mass Spectrometry
Ms	mesyl, methanesulfonyl
<i>m/z</i>	mass-to-charge ratio
nd	not determined
Nu	nucleophile
NHC	N-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
Oct	octyl
Ph	phenyl
ppm	part per million
Pr	propyl
q (NMR)	quartet
R ₃ P	trialkyl or triarylphosphine
rt	room temperature
s (NMR)	singlet
SIPr	1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene

t (NMR)	triplet
T	temperature
<i>t</i> -Bu	<i>t</i> -butyl
TBDMS	<i>tert</i> -butyldimethylsilyl
Tf	triflyl, trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
tol	toluene
TON	Turn Over Number

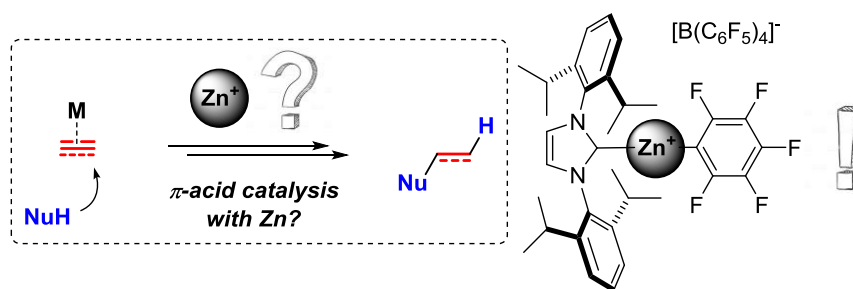
General Introduction

π -Acid catalysis, i.e. the activation of soft C-C multiple bonds towards nucleophilic attack, has become a powerful tool in organic synthesis over the last 20 years. A great number of transformations has been reported, notably in the field of platinum and gold catalysis, especially by the use of cationic gold(I) complexes of the general type LAu(I)^+ (where L is a ligand). Even though very successful, to the best of our knowledge, there is as yet no industrial applications of gold(I) catalysis. The reason could be attributed to the high cost of the catalysts, which are relatively fragile and require a high loading, its non-recyclability and the potential toxicity of its residual traces in the final products. Even if ligand design has allowed to develop robust species able to turn over at the ppm level, these specific and sophisticated complexes are not as versatile as the simple ones such as Ph_3PAu^+ .

To make π -acid catalysis more practical, our group has developed several research lines:

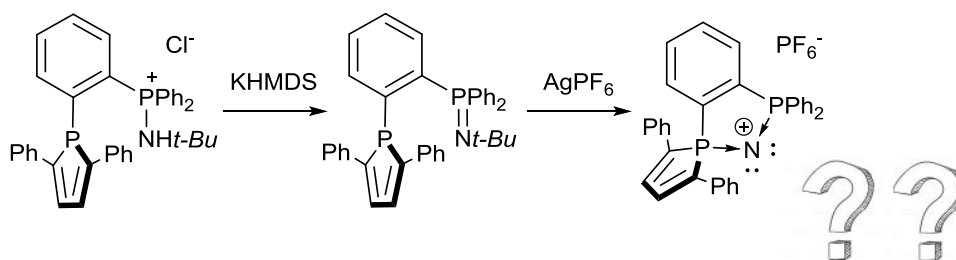
- The replacement of the expensive and fragile gold complexes by main group metal complexes (Ga, In, Ca, Li mostly)
- The development of catalytic conditions that allow to limit the decay of versatile gold catalysts such as Ph_3PAu^+ into elemental gold.

My thesis work has been focused among these lines. First, I explored the capacity of zinc catalysts to be used as soft π -acids such as LAu(I)^+ , PtCl_2 , GaCl_3 or InCl_3 (Chapter II). Compared to gallium and indium, this metal had not received attention so far from our group. Even though one could expect Zn(II) complexes to be rather hard species, we synthesized and tested some cationic zinc complexes bearing a *N*-heterocyclic carbene (NHC) as soft activators and compared them with simple ZnX_2 salts (Scheme 1).



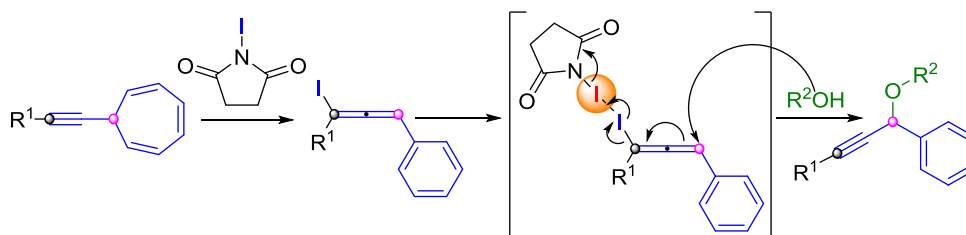
Scheme 1. Electrophilic activation of soft C-C π bonds by cationic NHC-Zn(II) complexes.

In a second project, aiming to reduce the catalyst loading in some gold-catalyzed reactions, I attempted to develop a robust gold(I) catalyst that would be stabilized by the hemilability of a modified phosphine (phosphole-iminophosphorane). While this goal was not reached, I serendipitously obtained an unusual bis-phosphane chelated N(I) compound (Scheme 2) which has been thoroughly analyzed (Chapter III).



Scheme 2. Formation of an original divalent N(I) salt.

Finally, in a third project, I opened a new research line in the group by developing a NIS-catalyzed halide abstraction of 3-iodo- and 3-bromo-1-phenylallenes by halogen bonding to promote propargylation reaction of aliphatic alcohols (Chapter IV). In my work with zinc, I used 7-alkynylcycloheptatrienes as experimental tools to reveal the π -acidity of zinc complexes. In continuation with this work on the activation of 7-alkynylcycloheptatrienes, I developed a tandem reaction consisting in an in situ iodoallene formation followed by a conjugate addition of an aliphatic alcohol to give propargylic ethers (Scheme 3).



Scheme 3. One-pot formation of propargylic ethers from 7-alkynylcycloheptatrienes.

After a bibliographical introduction, covering the concepts related to these three projects, I will expose my results in these various domains and finally make a general conclusion.

Chapter I

Bibliographical Introduction

Chapter I. Bibliographical Introduction

I-1. Activation of soft C-C multiple bonds by Lewis acids

I-1-1. Definitions of acids and bases

In 1923, two theory of acid-base reactions were proposed, the Brønsted-Lowry theory^[1] and the Lewis theory.^[2] The Brønsted-Lowry theory defines an acid AH as a substance that can lose a proton and give its conjugate base A⁻ and a base B as a substance that can accept a proton to give its conjugate acid HB⁺. Comparatively, the Lewis theory is based on the electronic structure of compounds. A Lewis acid is an electron pair acceptor whose central atom has a vacant orbital.^[3] Correspondingly, a Lewis base is an electron pair donor which has a pair of nonbonding electrons. The Lewis acid-base theory points out that acids can react with bases by sharing an electron pair and is more general than the Brønsted-Lowry acid-base theory. The number of species that can be qualified as acid or base has been largely expanded after Lewis' theory. At the same time, the number of transformations falling into the definition of acid-base reactions was also considerably enlarged.

In 1963, the concept of hard and soft acids and bases (HSAB) was introduced by Pearson.^[4] In HSAB theory, Lewis acids and bases can be generally divided into hard and soft species. Hard species are small sized, weakly polarizable, have a high oxidation state (mainly for acids) and high energy LUMOs and low energy HOMOs respectively for acids and bases. In contrast, soft species are large sized, easily and strongly polarizable, have a low oxidation state and lower energy LUMOs and higher energy HOMOs respectively for acids and bases (Figure 1).

[1] J. N. Brønsted, *Recl. Trav. Chim. Pays-Bas* **1923**, 42, 718.

[2] T. M. Lowry, *J. Chem. Technol. Biotechnol.* **1923**, 42, 43.

[3] G. N. Lewis, *Valency and Structure of Atoms and Molecules*; Wiley: New York, **1923**.

[4] R. G. Pearson, *J. Am. Chem. Soc.* **1963**, 85, 3533.

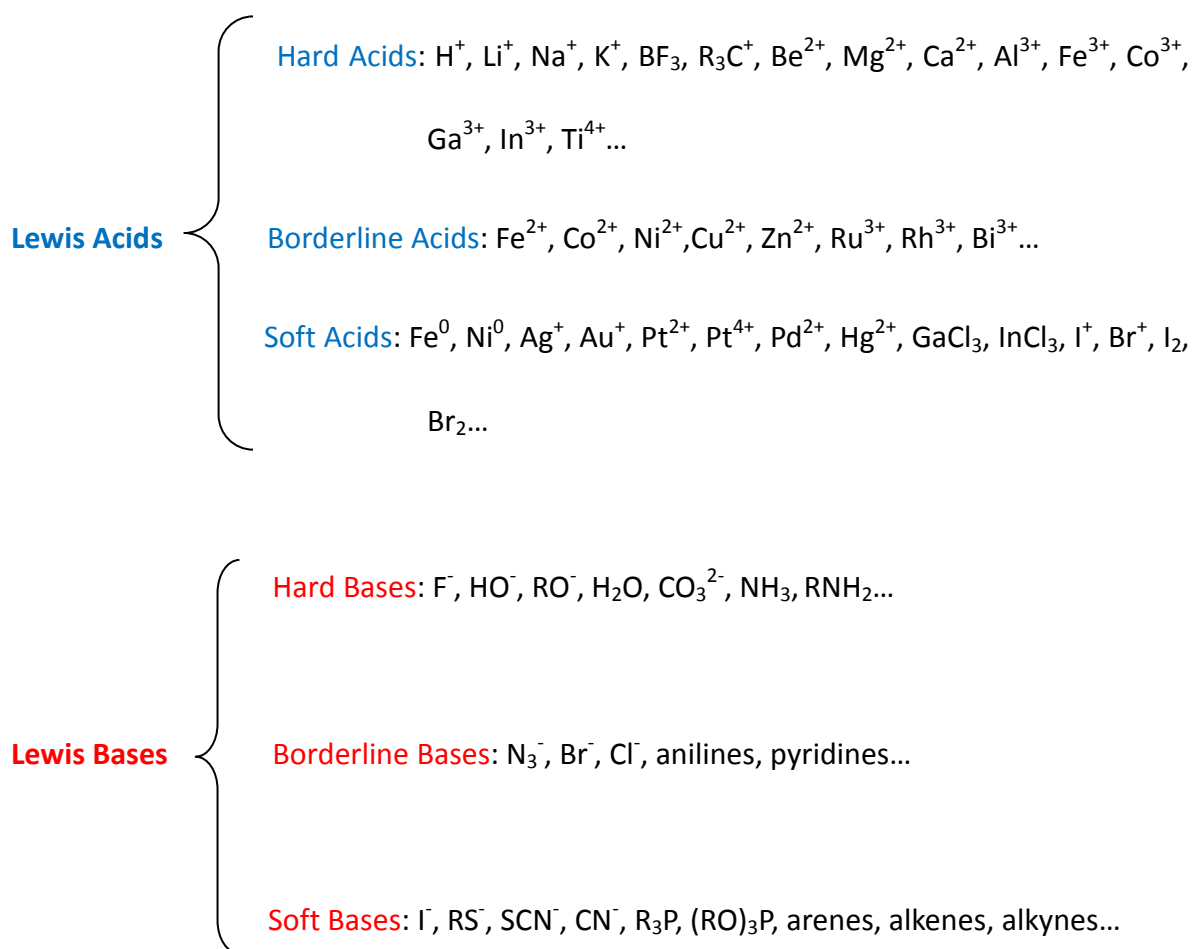


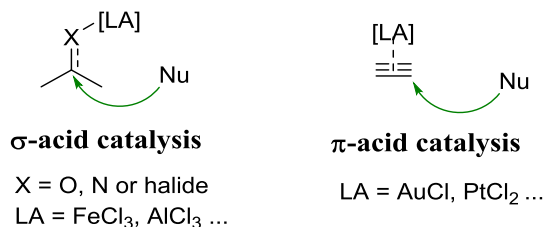
Figure 1. Some examples of Hard and Soft Acids and Bases according to Pearson's concept.^[4]

According to experimental information used to define hard and soft species, the HSAB principle states that hard acids react faster and form stronger bonds with hard bases and that soft acids react faster and form stronger bonds with soft bases. Moreover, reactions between hard species generally give rise to ionic interactions whereas reactions between soft species give rise to covalent interactions.

I-1-2. Lewis acids activation modes

In completion to Lewis acid-base theory and HSAB concept, a difference of substrate activation mode can be observed during chemical processes. Hard Lewis acids tend to accommodate an electron pair from a highly electronegative atom in the substrate, such as oxygen, nitrogen or halogen atoms (hard bases). Binding of the Lewis acid to the heteroatom can activate the substrate towards nucleophilic additions or substitutions for

example. Such activators are named σ -electrophilic Lewis acids. Soft Lewis acids preferably accept an electron pair from a delocalized π -system, i.e. from substrates containing an alkene, an alkyne, an allene or an arene motif. Such soft substrates are thus activated towards nucleophilic attack by the so-called carbophilic π -Lewis acid (Scheme 4).



Scheme 4. σ - and π -activation of substrates towards nucleophiles respectively by hard and soft Lewis acids.

Nevertheless, the border between hard and soft species, σ - and π -Lewis acids is not so well defined because the character of the Lewis acid is directly linked to that of the Lewis base as well as of the oxidation state of the central atom of the Lewis acid, the nature of its ligand(s) and counterion(s), etc.^[5]

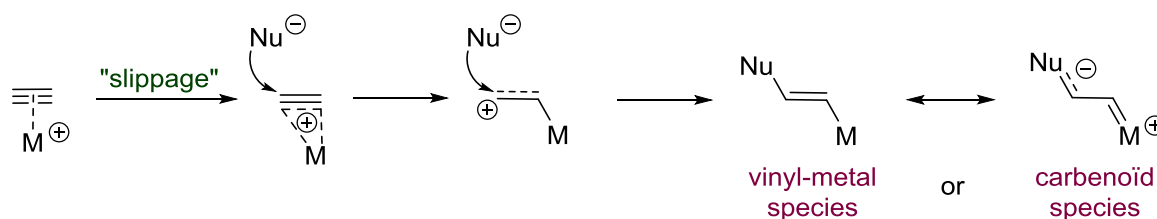
I-1-3. Catalytic activation of alkynes and allenes by soft π -Lewis acids of the late transition metal series

π -Acid catalysis has been recognized as a powerful tool to activate C-C unsaturated bonds. Gold and platinum complexes have been the most effective and efficient catalysts used so far.^[6] From a general mechanistic point of view, activation of C-C unsaturated bonds by gold and platinum towards nucleophilic attack starts with the formation of a π -complex by coordination of the metal to the triple bond for example. This coordination induces an electronic depletion that allows the nucleophilic attack. The approach of the nucleophile by the face opposite to the metal induces a slippage of the metal along the unsaturated bond and increases its electrophilicity, permitting the formation of a covalent bond

[5] F. Jaroschik, A. Simonneau, G. Lemièrre, K. Cariou, N. Agenet, H. Amouri, C. Aubert, J. -P. Goddard, D. Lesage, M. Malacria, Y. Gimbert, V. Gandon, L. Fensterbank, *ACS Catal.* **2016**, *6*, 5146-5160.

[6] (a) A. Leyva-Pérez, A. Corma, *Angew. Chem. Int. Ed.* **2012**, *51*, 614-635 ; (b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.

between the nucleophile and the complex. The intermediate product formed can be described as a vinyl-metal or as a carbenoid species (Scheme 5).



Scheme 5. Activation of an alkyne by a soft Lewis acid allowing nucleophilic addition across the C-C unsaturated bond.

As soft π -acids, Pt and Au complexes are able to promote the formation of C-O, C-N, C-C as well as C-H bond and exhibit catalytic activities for many chemical transformations of alkynes such as hydrofunctionalizations (hydration, hydroalkoxylation, hydroamination, hydroamidation, hydroacyloxylation...) or cascade cyclizations.

I-1-3-a. Hydration and hydroalkoxylation of alkynes

Hydration of alkynes into ketones is a good example of the limitation of the HSAB theory and the difficulty to define a border between σ - and π -Lewis acids since all classes of Lewis acids are able to promote this transformation.

I-1-3-a-i. Using Brønsted acids

Berthelot described the hydration of acetylene in 1863 in sulfuric acid resulting into a mixture of acetaldehyde and crotonaldehyde.^[7] Even if terminal alkynes are hydrated into ketones in water at very high temperature or under microwave irradiation,^[8] several Brønsted acids have been used to promote this reaction such as *p*-toluenesulfonic acid (*p*-TsOH) in refluxing alcohols,^[9] trifluoromethanesulfonic acid (TfOH) in hot dioxane,^[10]

[7] (a) M. Berthelot, *Ann. Chim. Phys.* **1863**, 67, 52; (b) H. Lagermarck, A. Eltekoff, *Chem. Ber.* **1877**, 10, 637.

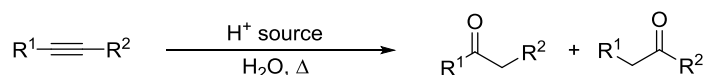
[8] (a) A. Desgrez, *Ann. Chim.* **1894**, 3, 209; (b) A. Vasudevan, M. K. Verzal, *Synlett* **2004**, 631; (c) J. M. Kremsner, C. O. Kappe, *Eur. J. Org. Chem.* **2005**, 3672.

[9] N. Olivi, E. Thomas, J.-F. Peyrat, M. Alami, J.-D. Brion, *Synlett* **2004**, 2175.

[10] T. Tsuchimoto, T. Joya, E. Shirakawa, Y. Kawakami, *Synlett* **2000**, 1777.

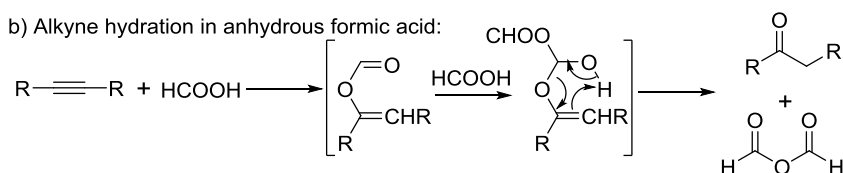
aqueous trifluoroacetic acid (TFA) a room temperature (Scheme 6a).^[11] An attractive method is the hydration of alkynes in refluxing formic acid. In this case, addition of formic acid onto the unsaturated C-C bond is followed by decarboxylation of the enol formate intermediate (Scheme 6b).^[12]

a) Alkyne hydration using Brønsted acid an water:



Acid	Acid loading	Reaction Conditions
H ₂ O	as solvent	200-350 °C, 0.5 to 3 h
H ₂ SO ₄ (aq)	as solvent	280 °C, 1 h
<i>p</i> -TsOH	20 mol%	ROH/H ₂ O, 80-170 °C, 6 to 144 h
HOTf	10-20 mol%	dioxane/H ₂ O, 100 °C, 50 h
TFA	> 100 mol%	H ₂ O, rt to 60 °C

b) Alkyne hydration in anhydrous formic acid:



Scheme 6. Pt(II) and Pt(IV)-catalyzed hydration of alkynes.

Even if strong Brønsted acids promote the hydration of alkynes, reaction conditions are harsher than those using a catalytic amount of a transition metal complex.

I-1-3-a-ii. Using platinum catalysts

In 1990, Jennings and Hiscox reported the use of Zeise's dimer as an efficient catalyst for the hydration of alkynes with a low catalytic loading to give the corresponding ketones (Scheme 7a).^[13] Even if simple Pt salts could be used (PtX₂, PtBr₂ or PtI₂),^[14] the yields of hydration of internal alkynes fall under 50%. In 1992, Blum and co-workers firstly

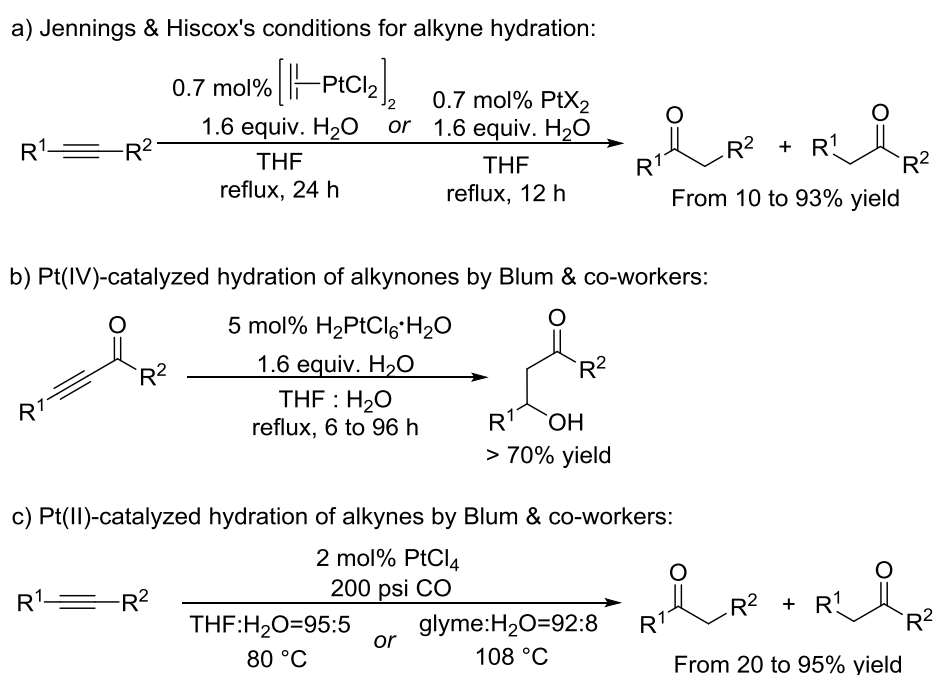
[11] (a) B. Meseguer, D. Alonso-Díaz, N. Griebenow, T. Herget, H. Waldmann, *Angew. Chem. Int. Ed.* **1999**, *38*, 2902; (b) S. Duclos, H. Stoeckli-Evans, T. R. Ward, *Helv. Chim. Acta* **2001**, *84*, 3148.

[12] (a) N. Menashe, Y. Shvo, *J. Org. Chem.* **1993**, *58*, 7434; (b) G. Xu, T. L. Hartman, H. Wargo, J. A. Turpin, R. W. Buckheit, M. Cushman, *Bioorg. Med. Chem.* **2002**, *10*, 283.

[13] W. Hiscox, P. W. Jennings, *Organometallics* **1990**, *9*, 1997-1999.

[14] J. W. Hartman, W. C. Hiscox, P. W. Jennings, *J. Org. Chem.* **1993**, *58*, 7613-7614.

demonstrated that H_2PtCl_6 promotes hydration of alkynes (Scheme 7b).^[15] Five years later, they finally reported that the PtCl_4/CO combination was a better system to catalyze the hydration of alkynes.^[16] Due to the presence of several side products such as alkenes or oligomers of methylketones during hydration of internal and terminal alkynes respectively. Blum and co-workers reinvestigated all parameters of this catalytic process to optimize their reaction conditions. Finally, in 2002, they found that the use of an aqueous glyme solution of PtCl_4 , under a CO atmosphere, allows for a reproducible hydration of alkynes at 108 °C in moderate yields (Scheme 7c).^[17]



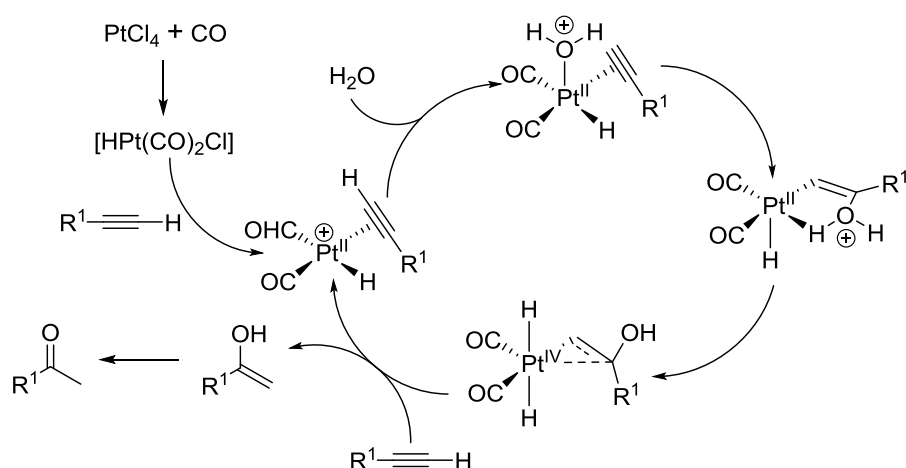
Scheme 7. Pt(II) and Pt(IV)-catalyzed hydration of alkynes.

In the latter case, from a mechanistic point of view, the active catalyst proposed for this transformation is the platinum(II) carbonyl complex $\text{HPtCl}(\text{CO})_2$, formed by hydrolysis and reductive carbonylation of PtCl_4 . Addition of water is supposed to proceed via addition onto the metallic center to form an 18e- Pt(II)-complex, facilitating the addition of water onto the triple bond and the hydride shift on Pt. Then, the reductive elimination of the Pt(IV)-complex formed gives the desired ketone (Scheme 8).

[15] Y. Badrieh, A. Kayyal, J. Blum, *J. Mol. Catal.* **1992**, *75*, 161-167.

[16] W. Baidossi, M. Lahav, J. Blum, *J. Org. Chem.* **1997**, *62*, 669-672.

[17] O. Israelsohn, K. P. C. Vollhardt, J. Blum, *J. Mol. Catal. A* **2002**, *184*, 1-10.

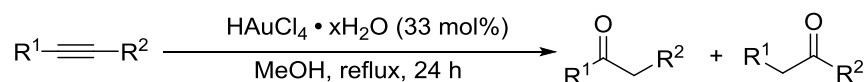


Scheme 8. Mechanism of the hydration of alkynes by the $\text{PtCl}_4\text{-CO}$ system.

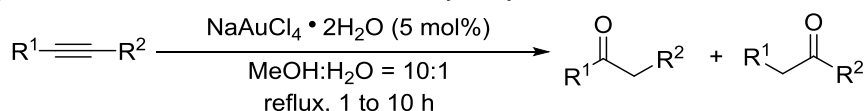
I-1-3-a-iii. Using gold catalysts

In 1976, Thomas et al. reported the HAuCl_4 -catalyzed hydration of several alkynes using water in methanol (Scheme 9a).^[18] The scope of the reaction was limited due to precipitation of reduced inactive metallic gold during the reaction. Several years later, an improvement of the performance of this catalytic process, in terms of stability of the Au(III) salt and scope, was proposed by Utimoto and Fukuda. High yields were obtained by using NaAuCl_4 instead of HAuCl_4 (Scheme 9b). Moreover, in absence of water, the solvent acts as the nucleophile partner and gives the corresponding acetals or ketals (Scheme 9c).^[19]

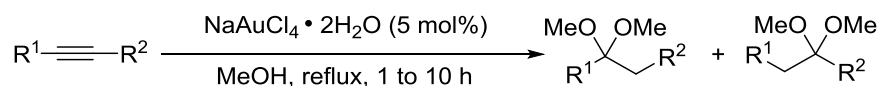
a) Thomas' conditions for alkyne hydration:



b) Utimoto and Fukuda's conditions for alkyne hydration:



c) Extension of alkyne hydration to acetals preparation by Utimoto and Fukuda:

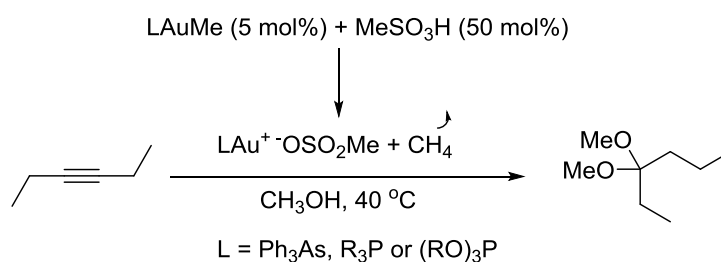


[18] R. O.C. Norman, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1976**, 18, 1983-1987.

[19] Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, 56, 3731-3734.

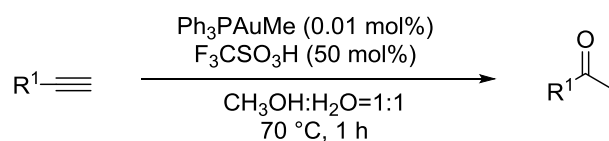
Scheme 9. Au(III)-catalyzed formation of ketones, aldehydes, acetals and ketals from alkynes.

In 1998, Teles and co-workers demonstrated that cationic Au(I) salts catalyze the addition of several alcohols to alkynes with high efficiency: total turnover numbers (TON) of up to 10^5 moles of product per mole of catalyst and a turnover frequencies (TOF) of up to 5400 h^{-1} (Scheme 10).^[20] This publication represents the first example of C-C triple bond activation by cationic Au(I) and the emergence of catalytic system to generate LAu(I)^+ *in situ*.



Scheme 10. Cationic Au(I) salts catalyzed double hydroalkoxylation.

In 2002, Hayashi and Tanaka demonstrated that the Teles' Au(I)-acid system can promote the hydration of terminal alkynes in aqueous methanol with TOF up to $14\,000 \text{ h}^{-1}$, using only 0.01 mol% of gold catalyst in presence of triflic acid, to give the Markovnikov adducts (Scheme 11).^[21]



Scheme 11. Cationic Au(I) salts catalyzed hydration of terminal alkynes in acidic media.

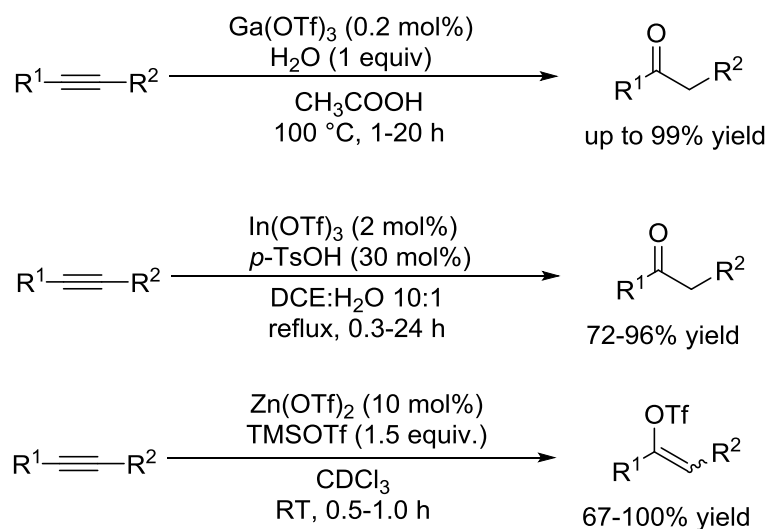
It is important to note that in the case of platinum, if water is replaced by MeOH, the hydroalkoxylation of alkynes is not observed. Moreover, Au-catalyzed hydration conditions are simpler than Pt-catalyzed ones, demonstrating a greater efficiency to give the desired ketone adducts on a wider scope of substrates.

[20] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

[21] E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed.* **2002**, *41*, 4563-4565.

I-1-3-a-iii. Using zinc, gallium and indium catalysts

The use of late transition metals or main group metals have been less extensively studied. Nevertheless, it has been recently reported that system composed of Ga(OTf)₃/AcOH^[22] or In(OTf)₃/pTSAH^[23] efficiently promoted the hydration of alkynes. Moreover, Zn(OTf)₂ in combination with TMSOTf facilitates the formation of vinyl triflates as reactive surrogates of ketones starting from alkynes (Scheme 12).^[24]



Scheme 12. Zn(II), Ga(III) and In(III) triflate salts catalyzed hydration of terminal alkynes.

I-1-3-b. Hydroamination of alkynes

Hydroamination of alkynes is an important reaction of preparation of enamines and imines but this process has a high activation energy and therefore requires a high temperature. To overcome this high barrier, several catalytic system have been studied to promote this reaction at acceptable reaction temperature especially by the design of specific ligands to avoid the deactivation of the catalyst.

I-1-3-b-i. Using platinum catalysts

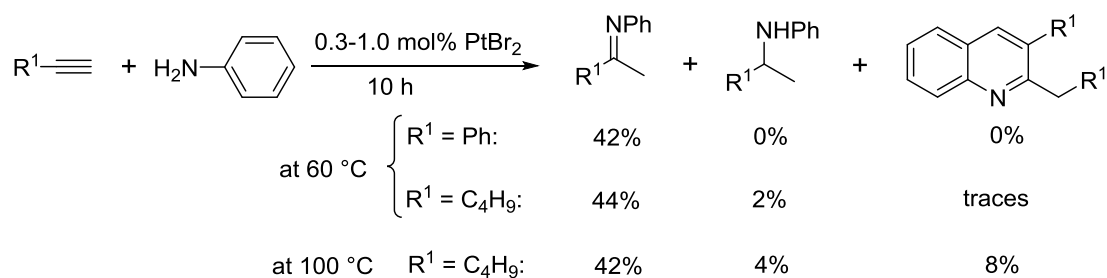
It has been demonstrated by Brunet et al. that PtBr₂ catalyzes the addition of aniline onto terminal alkyl- or arylalkynes. If in the case of phenylacetylene the hydroamination reaction gives only the Markovnikov adduct, the selectivity of the reaction is control by the

[22] S. Liang, G. B. Hammond, B. Xu, *Chem. Commun.* **2015**, 51, 903-905.

[23] Q. Gao, S. Li, Y. Pan, Y. Xu, H. Wang, *Tetrahedron* **2013**, 69, 3775-3781.

[24] M. H. Al-huniti, S. D. Lepore, *Org. Lett.* **2014**, 16, 4154-4157.

temperature using 1-hexyne as substrate. In this case, two by-products are formed in varying ratios. An *in situ* dimerization-cyclization-deamination-dehydrogenation sequence on the anti-Markovnikov formed product and the transfer hydrogenation of the Markovnikov adduct respectively lead to the quinolone derivatives and the secondary amine (Scheme 13).^[25]

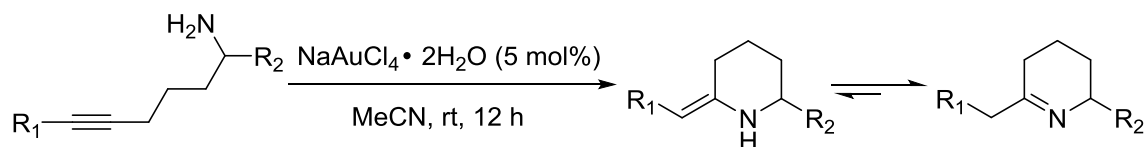


Scheme 13. PtBr₂-catalyzed hydroamination of terminal alkynes.

Nevertheless, yields are very low compared to methods using active gold complexes as well as less selective.

I-1-3-b-ii. Using gold catalysts

Intramolecular hydroamination using gold catalysts is known since 1987 when Utimoto et al. reported the cyclization of aminoalkynes using NaAuCl₄•2H₂O as catalyst. This intramolecular hydroamination proceeds via a 6-*exo-dig* cyclization, followed by isomerization of the 2-alkylidenepiperidines into the more stable imine, providing a novel access to the piperidine motif of alkaloids (Scheme 14).^[26]



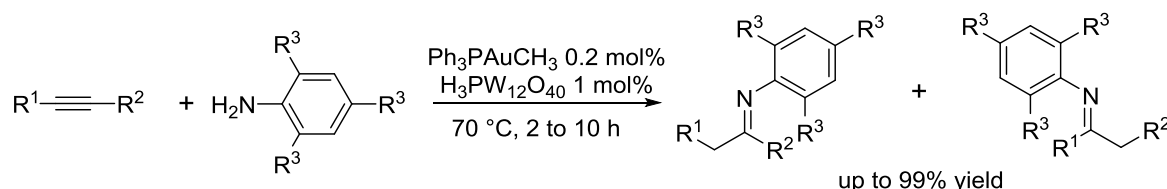
Scheme 14. Au(III)-catalyzed intramolecular addition of amines to terminal alkynes.

If intramolecular hydroamination reactions proceed smoothly at room temperature, the intermolecular version is more challenging and requires a higher temperature of reaction. In the continuation of their work on hydration of alkynes, Hayashi and Tanaka applied

[25] J.-J. Brunet, N. Châu Chu, O. Diallo, S. Vincendeau, *J. Mol. Catal. A* **2005**, *240*, 245-248.

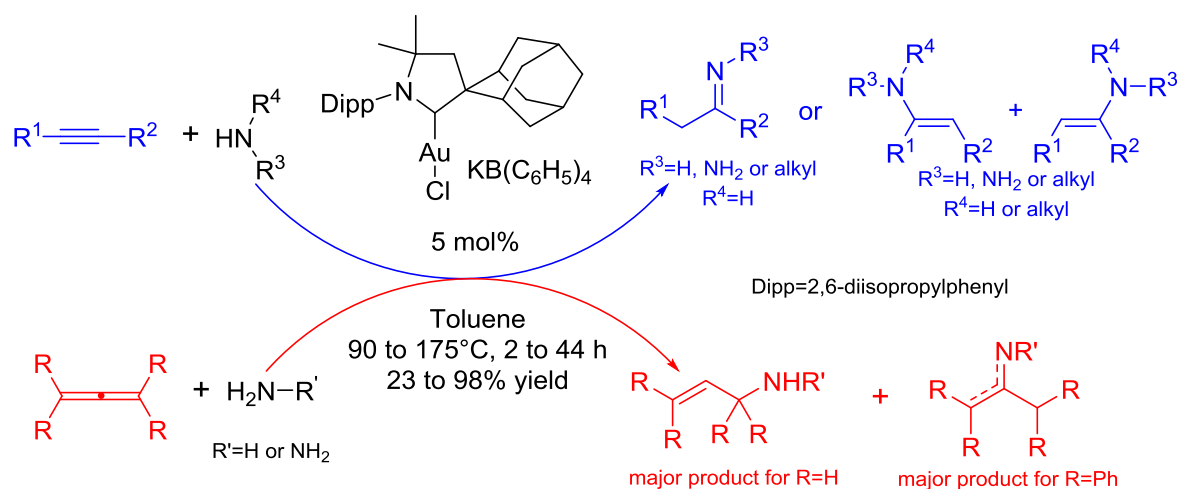
[26] Y. Fukuta, K. Utimoto, H. Nozaki, *Heterocycles* **1987**, *25*, 297-300.

these conditions of reaction to intermolecular hydroamination. By using polyoxometalate $\text{H}_3\text{PW}_{12}\text{O}_{40}$ instead of triflic acid, they demonstrated that anilines can add to terminal or internal alkynes at 70 °C, under solvent-free conditions with a low catalyst loading. In the case of terminal alkynes, the only isolated compounds are the Markovnikov adducts. (Scheme 15).^[27]



Scheme 15. Au(I)- $\text{H}_3\text{PW}_{12}\text{O}_{40}$ system for the hydroamination of terminal alkynes.

In 2008, Bertrand et al. reported for the first time that cationic Au(I)-complexes bearing a cyclic (alkyl)(amino)carbene ligand efficiently catalyze the addition of ammonia to alkynes and allenes.^[28] Those reaction conditions have been successfully extended to primary and secondary aliphatic amines,^[29] as well as hydrazines,^[30] demonstrating the robustness of such catalyst by a perfect tuning of the ligand (Scheme 16).



Scheme 16. Au(I)-catalyzed hydroamination of alkynes and allenes.

Addition of anilines to allenes can also be catalyzed by Au(III) salt at room temperature. In

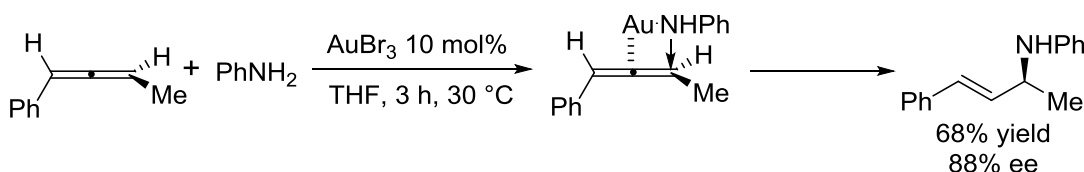
[27] E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349-3352.

[28] V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224-5228.

[29] X. Zeng, G. D. Frey, S. Kosar, G. Bertrand, *Chem. Eur. J.* **2009**, *15*, 3056-3060.

[30] R. Kinjo, B. Donnadieu, G. Bertrand *Angew. Chem. Int. Ed.* **2011**, *50*, 5560-5563.

this case, Yamamoto and Nishina reported that starting from a chiral allene, without using chiral ligand, the chirality of the starting compound is transferred to the final product, simply by using AuBr_3 salt. This observation suggests that in hydroamination reactions the amine partner coordinates to the metallic center prior to the addition to the activated alkyne bond (Scheme 17).^[31]



Scheme 17. Au(III)-catalyzed hydroamination of allenes with chirality transfer.

This axis-to-center chirality transfer can be of high importance for the synthesis of natural products and should find various applications into intramolecular process such as cycloisomerization of alkynes and allenes.

1-1-3-b-iii. Using zinc, gallium and indium catalysts

Since 2000, the use of late transition metals and main group metals has been explored to promote hydroamination reactions. For example, in 2008, Beller et al. reported that, compared to ZnCl_2 , $\text{Zn}(\text{OTf})_2$ efficiently catalyzed the hydroamination of terminal alkynes with anilines in hot toluene (Scheme 18a).^[32] In 2011, Prajapati demonstrated that $\text{In}(\text{OTf})_3$ catalyzed the sequential hydroamination/hydroalkylation of phenylacetylene derivatives with anilines to access to conjugated ketimines (Scheme 18b).^[33] In 2012, Li and co-workers described the use of GaCl_3 as a better catalyst than InCl_3 for the sequential hydroamination of terminal and internal alkynes with anilines and reduction of the intermediary imines into secondary amines (Scheme 18b).^[34] In 2014, Sakai et al. showed that InBr_3 is a better catalyst than $\text{In}(\text{OTf})_3$, $\text{Ga}(\text{OTf})_3$ or $\text{Zn}(\text{OTf})_2$ for the catalyzed hydroamination/hydrosilylation of aniline or benzylamine with terminal and internal

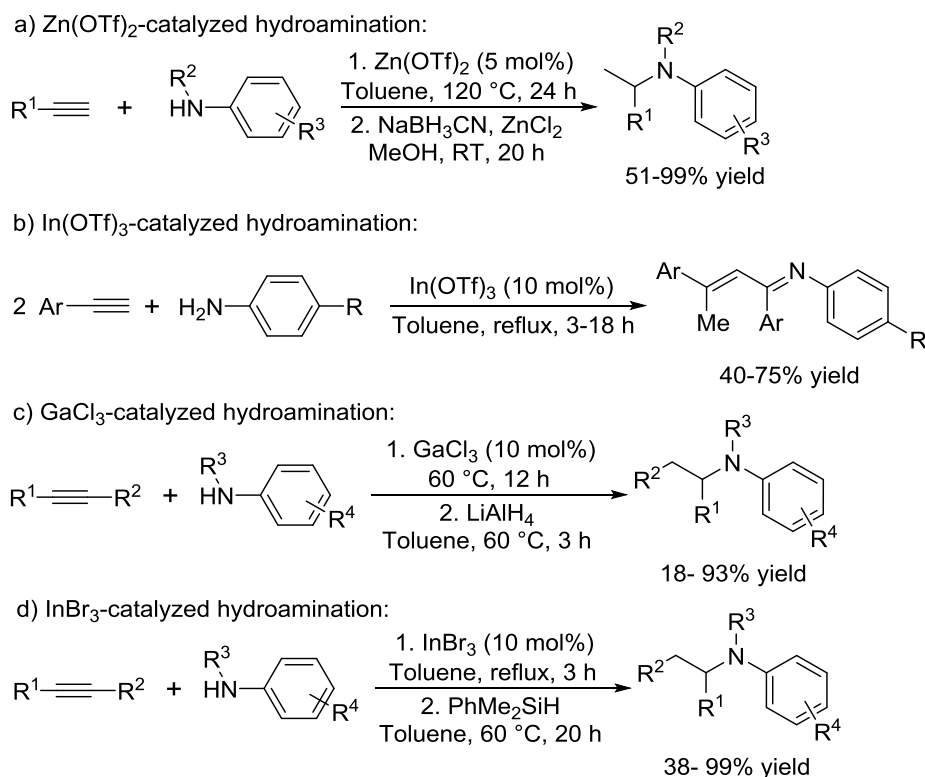
[31] N. Nishina, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 3314-3317.

[32] K. Alex, A. Tillack, N. Schwarz, M. Beller, *ChemSusChem* **2008**, *1*, 333-338.

[33] R. Sarma, D. Prajapati, *Chem. Commun.* **2011**, *47*, 9525-9527.

[34] L. Li, G. Huang, Z. Chen, W. Liu, X. Wang, Y. Chen, L. Yang, W. Li, Y. Li, *Eur. J. Org. Chem.* **2012**, 5564-5572.

alkynes when InCl_3 was inactive (Scheme 18c),^[35] demonstrating once more the versatility of the π -Lewis acid catalysis depending on the reaction conditions.



Scheme 18. Zn(II), Ga(III) and In(III)-catalyzed hydroamination of alkynes with anilines.

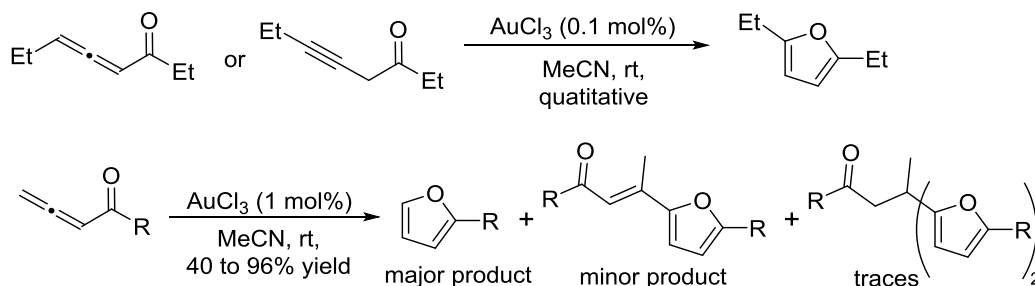
I-1-3-c. Cyclization/cycloisomerization of alkynes and allenes derivatives involving heteroatoms as nucleophiles

I-1-3-c-i. Using gold catalysts

In 2000, Hashmi reported the first examples of allene activation by Au(III) salts to provide a novel synthetic approach to furans. Interestingly, while the reaction of internal allenyl or alkynyl ketones gave only the furan derivatives, terminal allenyl ketones also gave the dimerization product after few minutes of reaction via a selective cross cycloisomerization/dimerization process (Scheme 19).^[36]

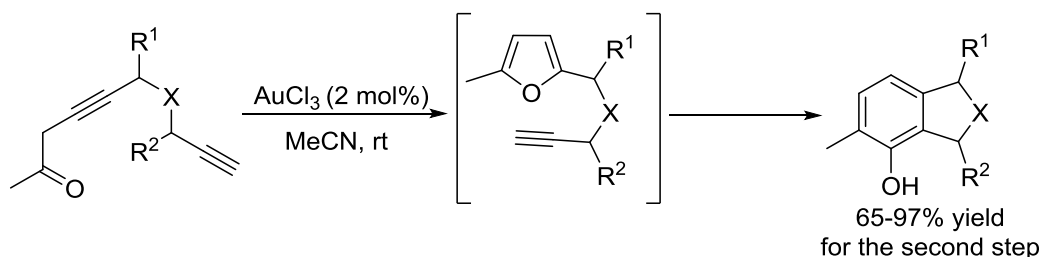
[35] N. Sakai, N. Takahashi, Y. Ogiwara, *Eur. J. Org. Chem.* **2014**, 5078-5082.

[36] (a) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288.



Scheme 19. Au(III)-catalyzed cyclisomerization, dimerization and trimerization of allenyl ketones.

Moreover, a prolonged time of reaction led to the formation of the trimer via a 1,4-conjugate addition onto the α,β -unsaturated ketone system of the dimer. They also reported that into the case of deca-4,9-diyne-2-ones, even if the ω -alkynylfurans could be obtained, a phenol can be also isolated. They proved this latter resulted from an Au(III)-catalyzed transformation of the corresponding ω -alkynylfuran (Scheme 20).^[37]



Scheme 20. Hashmi synthesis of phenols from ω -alkynylfurans.

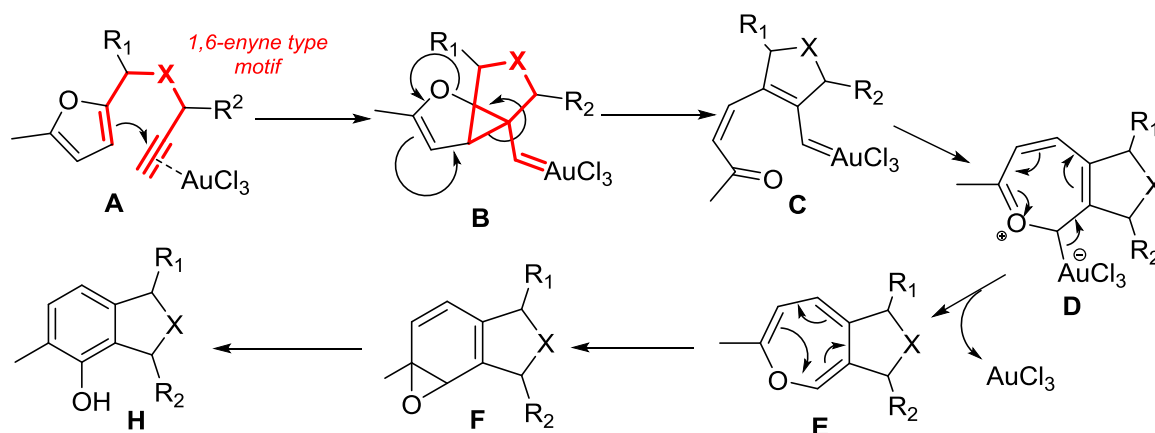
On the basis of Echavarren's Pt(II)-catalyzed phenols synthesis starting from ω -alkynylfurans^[38] and Pt(II)-catalyzed-cycloisomerization of 1,6-enynes (see section I-1-3.),^[39] Hashmi et al. proposed that the mechanism of formation of the phenol involves a 5-*exo*-dig cyclization of the furan to the complexed alkyne moiety to give the cyclopropylcarbene complex **B**, followed by cyclopropane and furan ring opening to furnish **C**. The latter condenses as to provide the 7-membered ring **D** and the oxepine **E**

[37] A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554.

[38] (a) B. Martín-Matute, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2001**, *40*, 4754-4757; (b) B. Martín-Matute, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757-5766.

[39] (a) M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520; (b) A. M. Echavarren, M. Méndez, M. P. Muñoz, C. Nevado, B. Martín-Matute, C. N. Oberhuber, D. J. Cárdenas, *Pure Appl. Chem.* **2004**, *76*, 453-463.

after catalyst recycling. After 6π electrocyclization towards epoxide **F** and aromatization, the phenol **G** is obtained (Scheme 21).^[40]



Scheme 21. Proposed mechanism for the Au(III)-catalyzed formation of phenols initiated by cycloisomerization of ω -alkynylfurans.

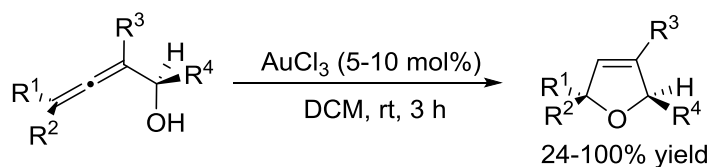
By the use of the appropriate substrate and the tuning of the ligand of Au(III) catalyst, they managed to observe the formation of **E** and **F** and their conversion to **H** by monitoring the reaction by ^1H NMR. Moreover, they trapped the intermediate **F** by a Diels-Alder reaction using 4-phenyl-1,2,4-triazoline-3,5-dione as dienophiles. This represents the first evidence of the formation of the phenol *via* the epoxide **F**.^[41]

Inspired by this work on the cycloisomerization of allenyl ketones, Krause and Hoffmann-Röder developed a gold-catalyzed cycloisomerization of α - and β -hydroxyallenes respectively into dihydrofurans and dihydropyrans. Those mild, highly efficient, stereoselective cycloisomerization methods provide the *O*-heterocycles with a complete axis to center chirality using Au(I) or Au(III) as catalysts. This method was extended by the same group to the preparation of pyrroline and tetrahydropyridine motifs respectively starting from α -aminoallenes or β -aminoallenes (Scheme 22).^[41]

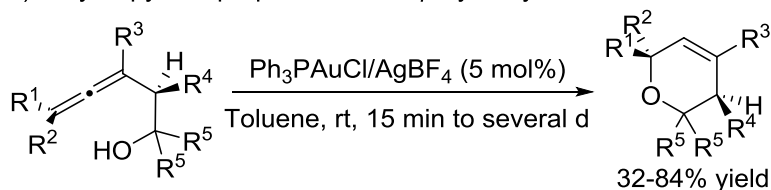
[40] A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfe, W. Frey, J. W. Bats, *Angew. Chem. Int. Ed.* **2005**, *44*, 2798-2801.

[41](a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537-2538; (b) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121-4123; (c) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485-4488.

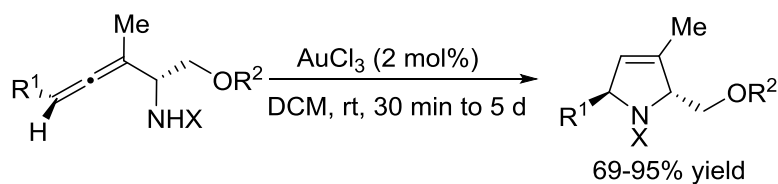
a) Dihydrofurans preparation from α -hydroxyallenes:



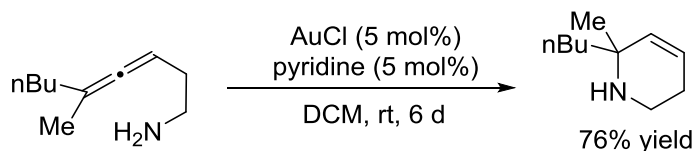
b) Dihydropyrans preparation from β -hydroxyallenes:



c) Pyrrolidines from α -aminoallenes:

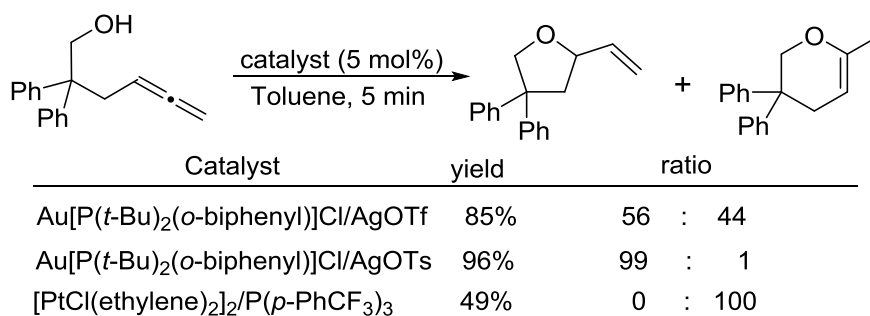


d) Dihydropyrans preparation from β -aminoallenes:



Scheme 22. Au(I)- and Au(III)-catalyzed cycloisomerization hydroxyallenes and aminoallenes.

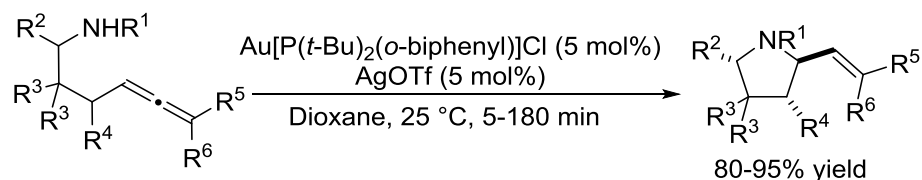
In the case of γ -hydroxyallenes, Widenhoefer reported that the rate of the reaction can be increased by the use of a more stable cationic Au(I) complex as well as the choice of the counterion. This latter is of crucial interest to favor the 5-*exo*-trig vs the 6-*exo*-dig cyclization while the use of Pt(II) complex led exclusively to the 6-*exo*-dig cyclization and therefore to the dihydropyrans instead of the tetrahydropyrans (Scheme 23).^[42]



[42] Z. Zhang, C. Liu, R. E. Kinder, X. Han, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 28, 9066-9073.

Scheme 23. Effect of the counterion of cationic Au(I)-complex on the selectivity of cyclization.

Into the case of γ -aminoallenes, the only observed product was the 2-vinyl pyrrolidine with a selectivity in favor of the E-alkene when the starting allene possessed an axial chirality (Scheme 24).^[42]

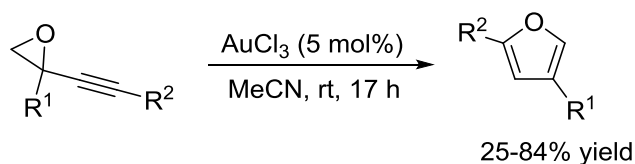


Scheme 24. Selective 5-*exo*-trig cyclization of γ -aminoallenes using cationic Au(I)-complex.

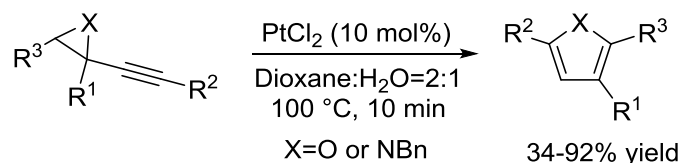
I-1-3-c-ii. Using platinum catalysts

If furans can be prepared from alkynyl ketones using gold catalysts, propargylic oxiranes can also be used as substrates. Nevertheless, the Au-catalyzed cycloisomerization reaction reported by Hashmi using this type of substrate generally gave moderate to low yields (Scheme 25a).^[43] Yoshida et al. proposed an improvement of this reaction by using PtCl_2 as catalyst. In their reaction conditions, several polysubstituted furans and pyrroles were obtained in good to high yield (Scheme 25b).^[44]

a) AuCl_3 -catalyzed cycloisomerization of propargylic oxiranes:



b) PtCl_2 -catalyzed cycloisomerization of propargylic oxiranes:

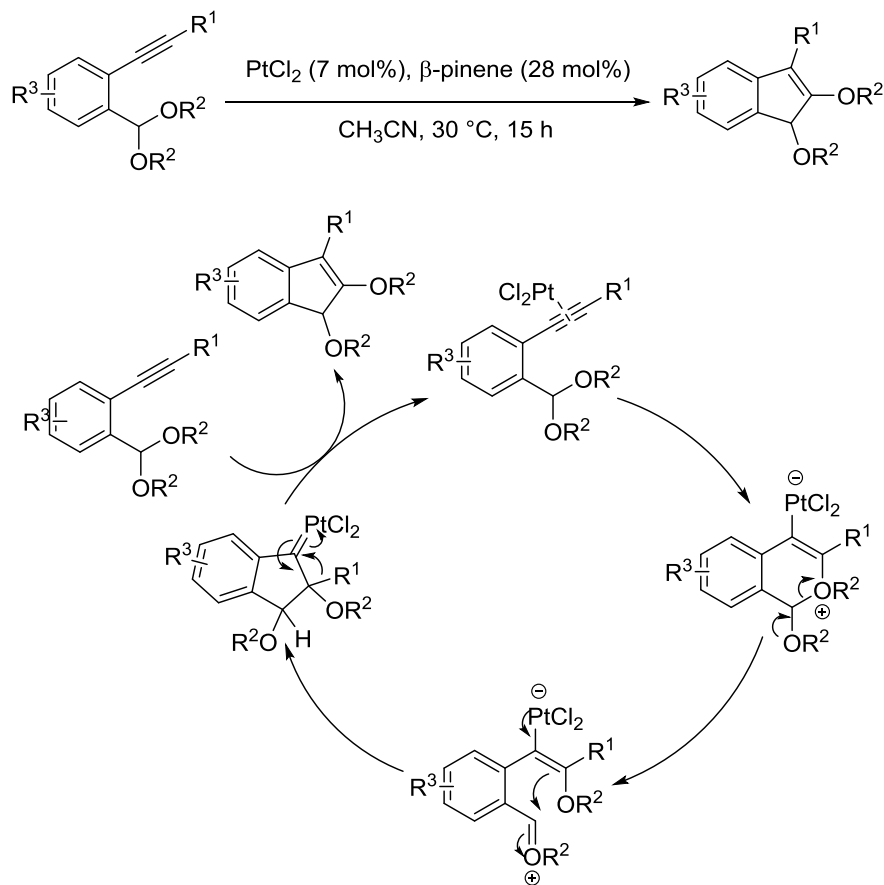


Scheme 25. AuCl_3 vs. PtCl_2 -cycloisomerization of propargylic oxiranes.

[43] A. S. K. Hashmi, P. Sinha, *Adv. Synth. Catal.* **2004**, 346, 432-438.

[44] (a) M. Yoshida, M. Al-Amin, K. Matsuda, K. Shishido, *Tetrahedron Lett.* **2008**, 49, 5021-5023; (b) M. Yoshida, M. Al-Amin, K. Shishido, *Synthesis* **2009**, 2454-2466.

In 2004, platinum catalyzed cyclization of *o*-alkynylbenzaldehyde acetals was described by Yamamoto et al (Scheme 26).^[45]



Scheme 26. Pt(II) catalyzed cyclization of *o*-alkynylbenzaldehyde acetals.

Indene derivatives were obtained via 6-*endo*-dig cyclization, C-O bond cleavage, electrophilic addition and [1,2]-alkyl shift.^[46] The role of β-pinene in this reaction was not very clear. One possible explanation could be a ligand exchange. The acetonitrile could be replaced by β-pinene in (CH₃CN)₂PtCl₂.

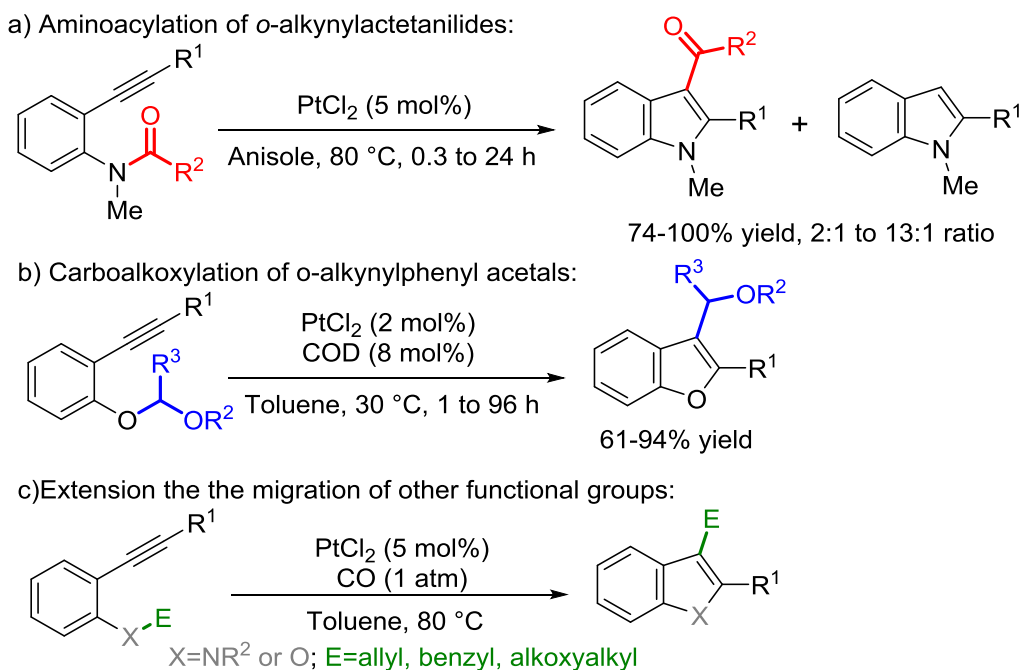
They also demonstrated that PtCl₂-catalyzed the intramolecular aminoacylation of alkynes using *o*-alkynylacetanilides, to synthesize 2,3-disubstituted indoles (Scheme 27a).^[47] They reported a PtCl₂-catalyzed cyclization of *o*-alkynylphenyl acetals in presence of

[45] I. Nakamura, G. B. Bajracharya, H. Wu, K. Oishi, Y. Mizushima, I. D. Gridnev, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15423-15430.

[46] H. Chen, Y. Li, S. Liu, Q. Xiong, R. Bai, D. Wei, Y. Lan, *Coordination Chemistry Reviews* **2021**, *437*, 213863.

[47] T. Shimada, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 10546-10547.

1,5-cyclooctadiene (COD) to prepare 2,3-disubstituted benzofurans (Scheme 27b).^[48] This strategy was concomitantly extended by the Fürstner group to the migration of several functional groups from the heteroatom to the 3-position of the corresponding 2,3-disubstituted benzofurans or indoles (Scheme 27c).^[49]



Scheme 27. PtCl₂-cycloisomerization of *o*-alkynylanilines and phenols for the preparation of 2,3-disubstituted indoles and benzofurans respectively.

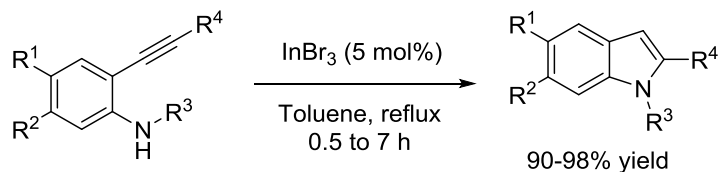
I-1-3-c-iii. Using indium, gallium and zinc catalysts

A variety of polysubstituted indoles and furans can be also prepared with good to excellent yields using indium, gallium or zinc catalysts. For example, into the case of indoles, Konakahara et al. reported in 2006 the InBr₃-catalyzed intramolecular hydroamination of 2-alkynylaniline derivatives (Scheme 27).^[50]

[48] (a) I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022-15023.

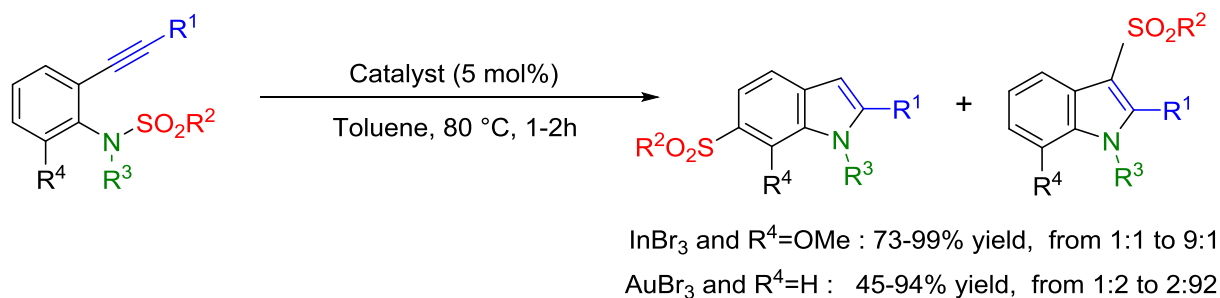
[49] (a) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024-15025. (b) A. Fürstner, E. K. Heilmann, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 4760-4763; (c) I. Nakamura, Y. Mizushima, U. Yamagishi, Y. Yamamoto, *Tetrahedron* **2007**, *63*, 8670-8676.

[50] N. Sakai, K. Annaka, T. Konakahara, *Tetrahedron Letters*. **2006**, *47*, 631-634.



Scheme 28. In(III)-catalyzed intramolecular hydroamination.

In 2008, this reaction was extended by Nakamura et al. to the preparation of 6-sulfonylindoles as major product along with the 3-sulfonylindoles. Interestingly, the removal of the methoxy group in position 7 and the use of AuBr₃ as catalyst reverse the selectivity for the 3-sulfonylindoles. This transformation started with a 5-*endo* cyclization followed by a shift of the sulfonyl group to C-3 or C-6 position of the indole motif (Scheme 29).^[51]



Scheme 29. Au(III)-catalyzed cyclization of o-alkynylsulfonylanilines.

As AuCl₃ and PtCl₂, InCl₃ catalyzes the formation of furans starting from propargylic oxiranes (Scheme 30a)^[52] or from o-alkynylphenols (Scheme 30b).^[53] Other In(III) salts, the triflate and bistriflimidate one, efficiently catalyze the cycloisomerization of α -propargyl- β -keto esters into furans as well as into pyrroles by adding a primary amine into the reaction media (Scheme 30b).^[54]

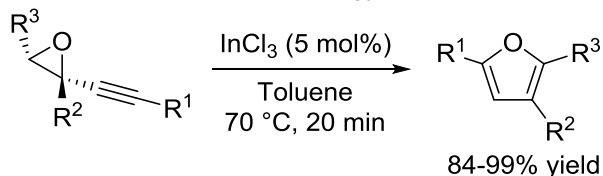
[51] I. Nakamura, U. Yamagishi, D. Song, S. Konta, Y. Yamamoto, *Chem. Asian J.* **2008**, *3*, 285-295.

[52] J. Y. Kang, B. T. Connell, *J. Org. Chem.* **2011**, *76*, 2379-2383.

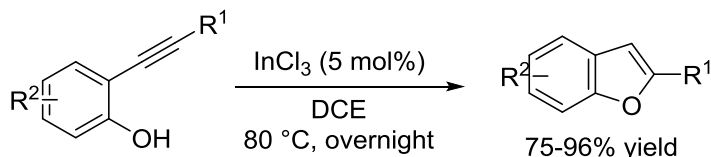
[53] L. Alonso-Marañón, M. M. Martínez, L. A. Sarandeses, E. Gómez-Bengoa, J. P. Sesteloj *J. Org. Chem.* **2018**, *83*, 7970-7980.

[54] H. Tsuji, K.-I. Yamagata, Y. Ueda, E. Nakamura, *Synlett* **2011**, 1015-1017.

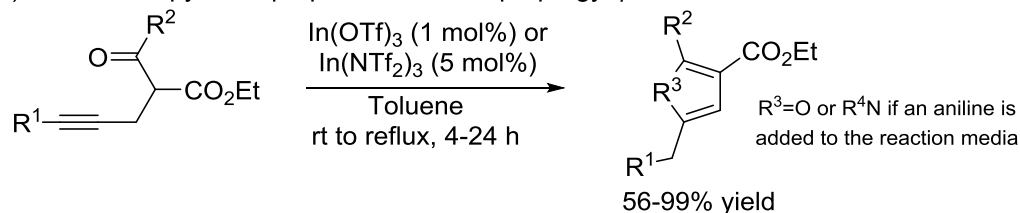
a) Furans preparation from propargylic oxiranes:



b) Benzofurans preparation from *o*-alkynylphenols:

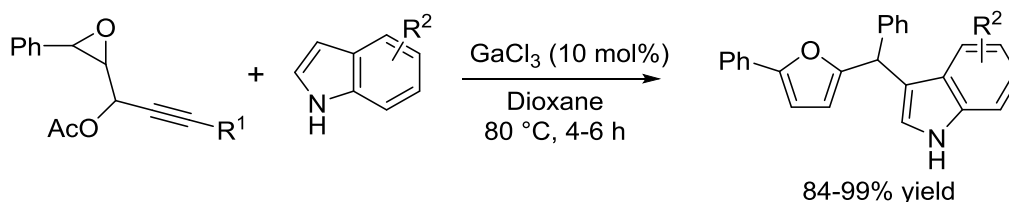


c) Furans and pyrroles preparation from α -propargyl- β -keto esters:



Scheme 30. In(III)-catalyzed formation of furans, benzofurans and pyrroles.

In 2012, Reddy and co-workers reported a $GaCl_3$ -catalyzed tandem cycloisomerization/Friedel-Crafts alkylation of indoles starting from alkynyl-epoxy acetate to access to 2,5-disubstituted furans in good yields, with a perfect regioselectivity for the C-3 position (Scheme 31).^[55]

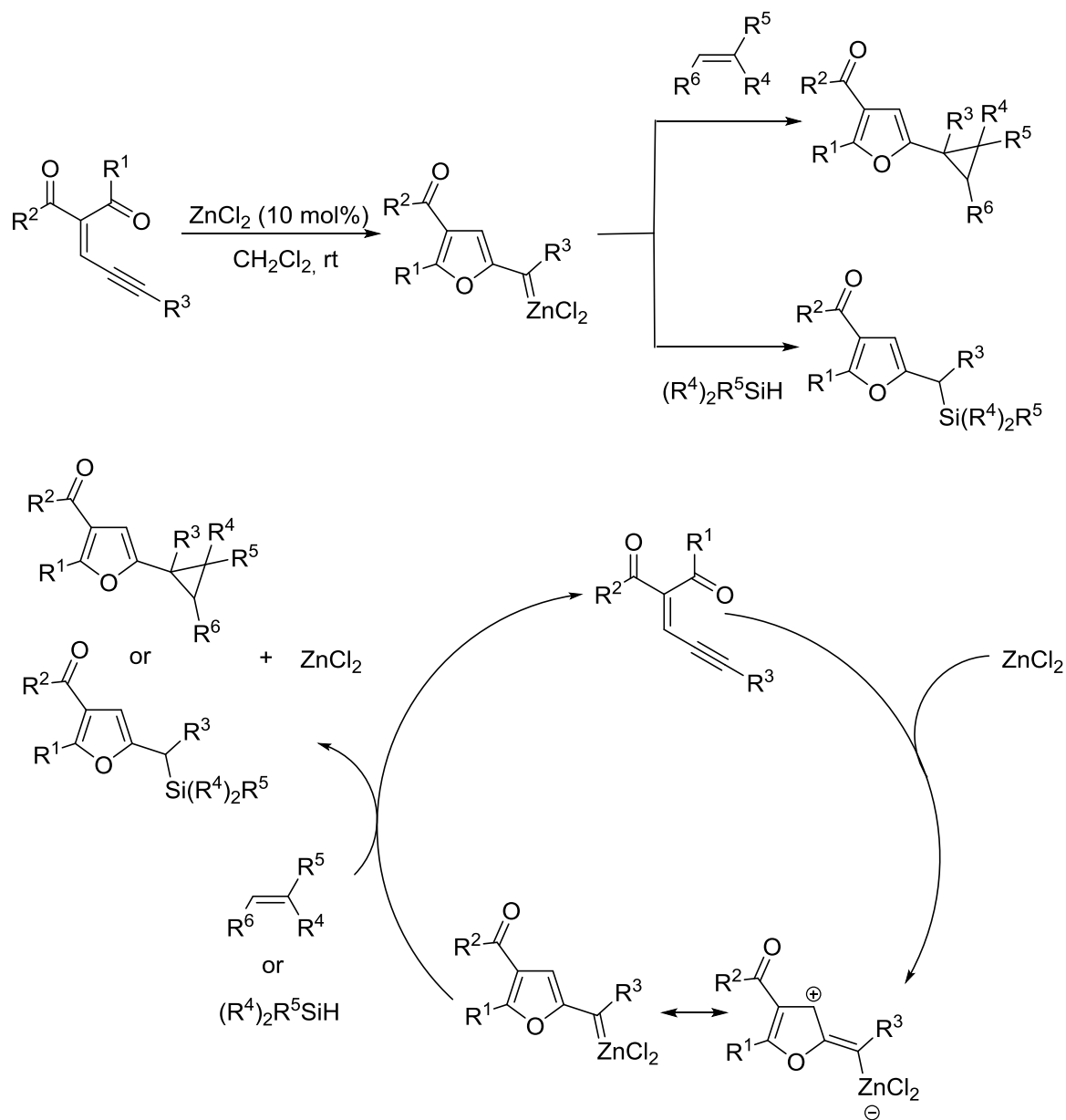


Scheme 31. Ga(III)-catalyzed tandem cycloisomerization/Friedel-Crafts alkylation of indoles.

Finally, inexpensive Zn(II) salts also catalyze cyclization of enynones and propargyl amides to furnish furans and oxazoles respectively. In 2012, López et al. reported that zinc(II) carbenes are generated *in situ* as key intermediate from enynones. These zinc carbene intermediates can be trapped by alkenes or silanes to yield cyclopropylfurans or silylated

[55] B. V. S. Reddy, B. B. Reddy, K. V. R. Rao, J. S. Yadav, *Tetrahedron lett.* **2012**, *53*, 2500-2503.

furan derivatives (Scheme 32).^[56]

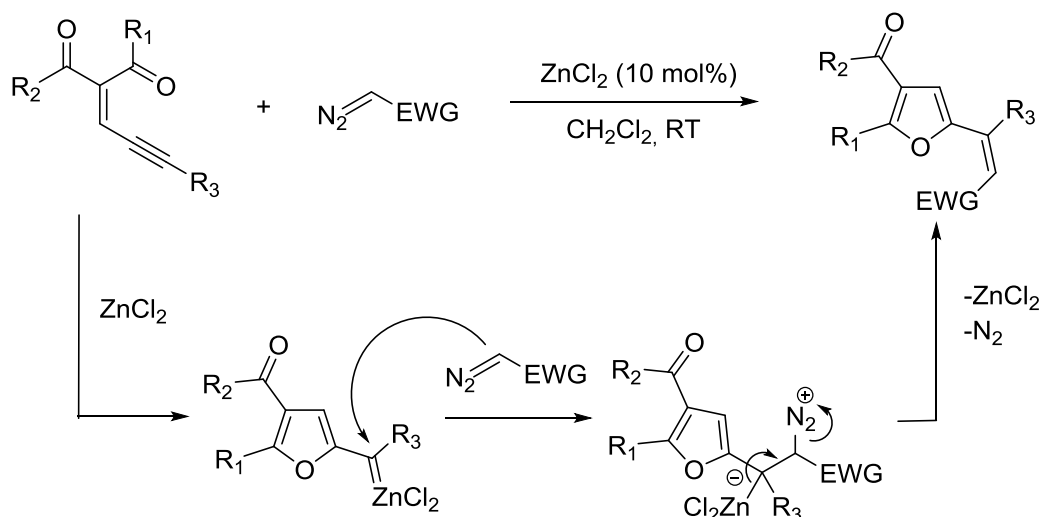


Scheme 32. Zn(II)-catalyzed cyclopropanation and Si-H bond insertion.

Two years later, the scope of zinc carbenes' reactivity was expanded by Vicente et al (Scheme 33).^[57] A suitable carbon nucleophilic reagent was disclosed. A tandem cyclization/cross-coupling reaction led to a variety of 2-alkenylfurans.

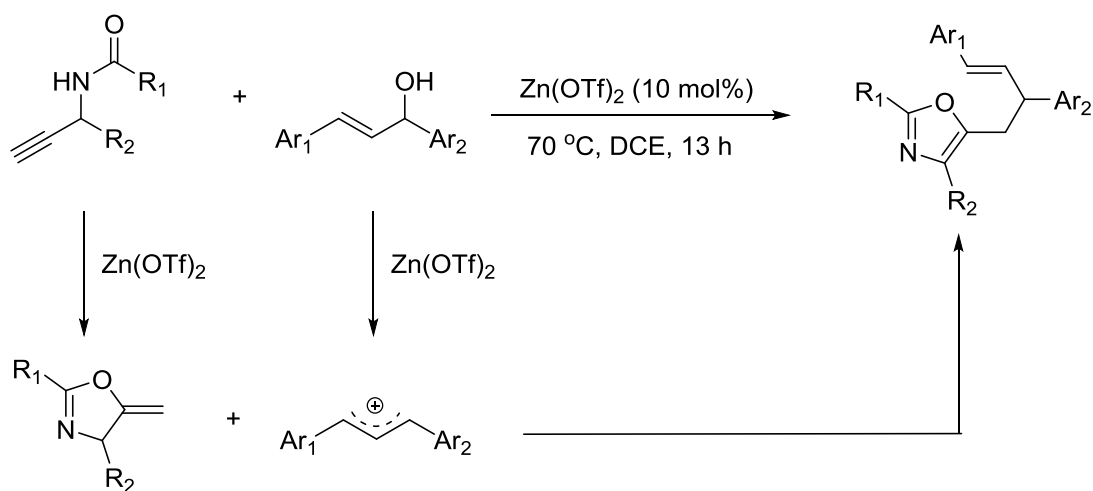
[56] R. Vicente, J. Gonzalez, L. Riesgo, J. Gonzalez, L. A. Lopez, *Angew. Chem. Int. Ed.* **2012**, *51*, 8063-8067.

[57] J. Gonzalez, L. A. Lopez, R. Vicente, *Chem. Commun.* **2014**, *50*, 8536-8538.



Scheme 33. Zn(II)-catalyzed tandem Cyclization/Cross-coupling reaction.

In 2015, Xu et al. developed a $Zn(OTf)_2$ -catalyzed cascade cyclization/allylic alkylation reaction (Scheme 34).^[58] In this study, $Zn(OTf)_2$ not only worked as a π -acid but also acted as a σ -acid to facilitate the C-O bond cleavage.

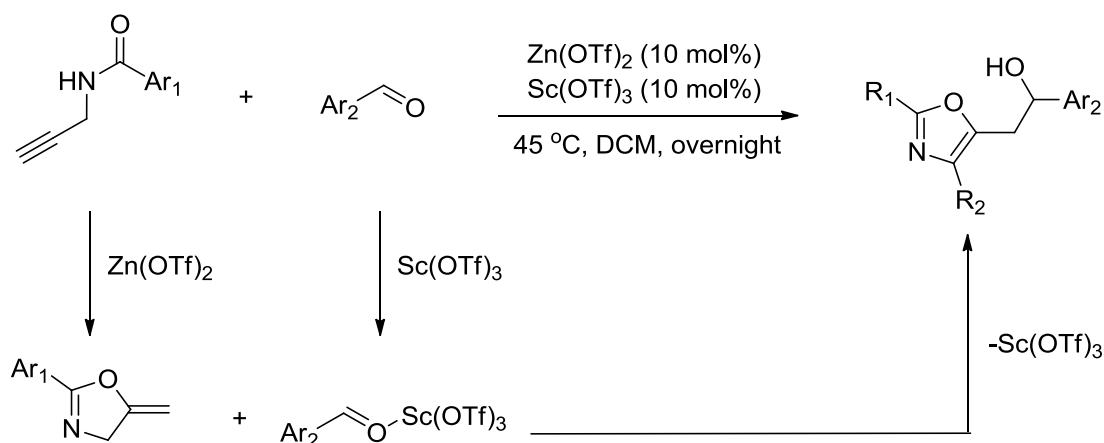


Scheme 34. Zinc(II) catalyzed cascade cyclization/allylic alkylation reaction.

One year later, a tandem $Zn(OTf)_2$ -catalyzed cyclization and $Sc(OTf)_3$ -catalyzed carbonyl-ene reaction was published by Xu et al (Scheme 35).^[59] While $Zn(OTf)_2$ was exploited as a π -acid, $Sc(OTf)_3$ served as a σ -acid to activate aromatic aldehydes.

[58] B. Wang, Y. Chen, L. Zhou, J. Wang, C-H. Tung, Z. Xu, *J. Org. Chem.* **2015**, *80*, 12718-12724.

[59] B. Wang, Y. Chen, L. Zhou, J. Wang, Z. Xu, *Org. Biomol. Chem.* **2016**, *14*, 826-829.



Scheme 35. Zinc(II)/Sc(III) bimetallic relay catalysis.

I-1-3-d. The specific case of the cycloisomerization of 1,6-enynes

Cycloisomerization reactions of 1,6-enynes are maybe the best reaction to illustrate the difference of reactivity and therefore the difference of molecular diversity offered by the use of the appropriate π -Lewis acid.^[60] Soft late metal complexes such as platinum and gold are very effective to promote the cycloisomerization of such substrates and have been widely investigated.^[61]

I-1-3-d-i. Using platinum catalysts

In 1993, Trost and Chang reported that $(\text{PPh}_3)_2\text{Pt}(\text{OAc})_2$ efficiently catalyzes the cycloisomerization of 1,6-enynes and selectively give the 1-(prop-1-en-1-yl)-cyclopent-1-ene derivative (Scheme 36a).^[62] Three years later, Murai et al. demonstrated that PtCl_2 is also a good and simple catalyst to promote the cycloisomerization of enynes. Using the 1,6-enyne bearing a terminal alkynes, they solely observed the formation of the 1,3-diene of type 1-vinylcyclopentene as described by Trost (Scheme 36b) while 1,6-enynes bearing substituted alkynes mainly lead to the formation of a skeletal isomer of the 1,3-diene (Scheme 36c).^[63]

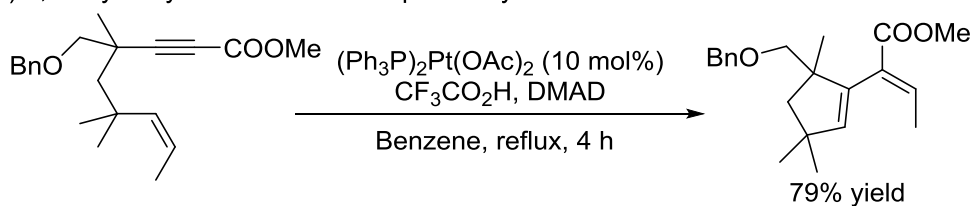
[60] (a) S. T. Diver, A. J. Giessert, *Chem. Eur. J.*, **2004**, *104*, 1317; (b) V. Michelet, P. Y. Toullec, J.- G. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.

[61] (a) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; (b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271; (c) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028.

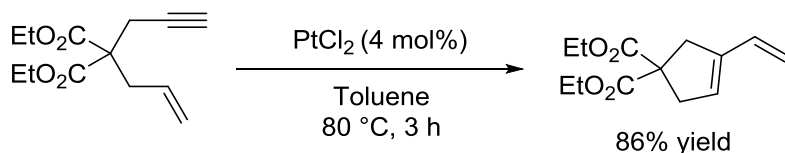
[62] B. M. Trost, V. K. Chang, *Synthesis* **1993**, 824-832.

[63] N. Chatani, T. Morimoto, T. Muto, S. Murai, *Organometallics* **1996**, *15*, 901.

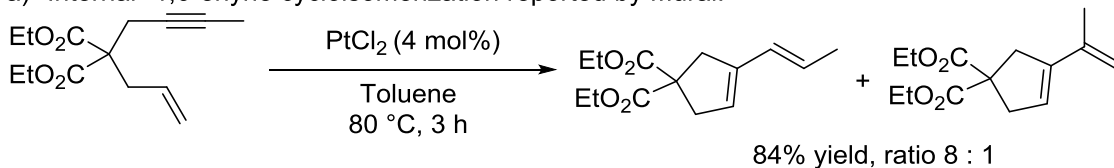
a) 1,6-enyne cycloisomerization reported by Trost:



b) Terminal 1,6-enyne cycloisomerization reported by Murai:

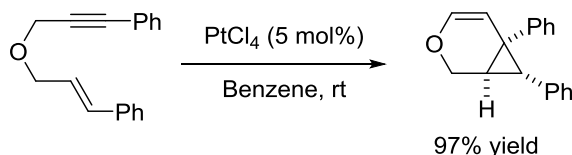


a) "Internal" 1,6-enyne cycloisomerization reported by Murai:



Scheme 36. Pt-catalyzed cycloisomerization of 1,6-enynes leading to different skeletal isomers of 1,3-diene of type 1-vinylcyclopentene.

In 1995, Blum and co-workers reported the synthesis of oxabicyclo[4.1.0]heptenes catalyzed by PtCl_4 , starting from a propargyl allyl ether, with a complete diastereoselectivity and in excellent yield (Scheme 37).^[64]



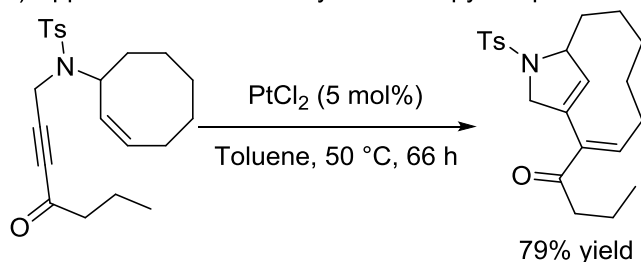
Scheme 37. PtCl_4 -catalyzed cycloisomerization of propargyl allyl ether to access oxabicyclo[4.1.0]heptane.

In 1998, Fürstner et al. accessed to the fused *m*-pyrrolophane motif via a Pt(II)-catalyzed cycloisomerization of an 1,6-enyne to construct the bicyclic system as well as the ring expansion (Scheme 38a). The scale-up of the reaction to a multigram-scale permitted them to isolate minor byproducts and therefore to propose that a nonclassical carbocation (Scheme 38b) is formed during the catalyzed process and explained the structure of isolated byproducts (Scheme 38c).^[65]

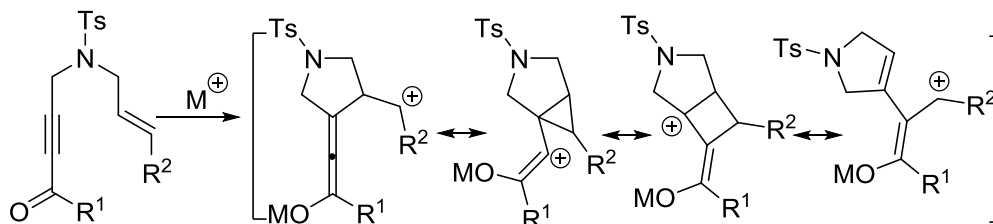
[64] J. Blum, H. Beer-Krafts, Y. Badrieh, *J. Org. Chem.* **1995**, *60*, 5567.

[65] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305-8314.

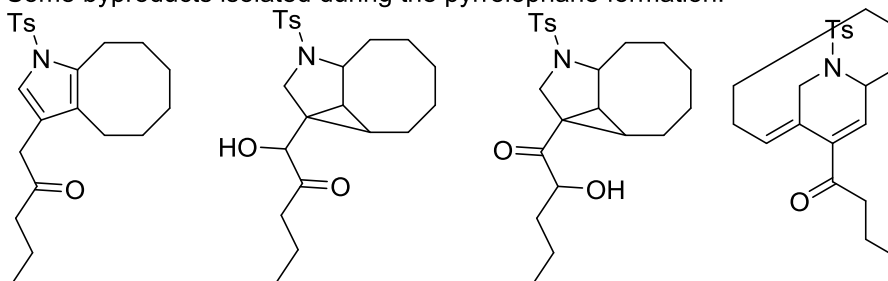
a) Application to the total synthesis of pyrrolophane derivatives:



b) nonclassical cation formed during the process:

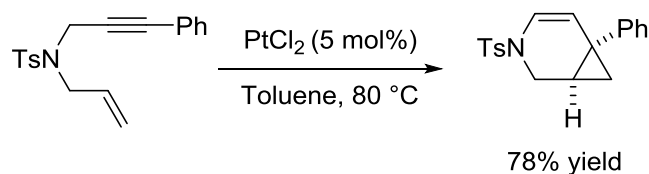


c) Some byproducts isolated during the pyrrolophane formation:



Scheme 38. PtCl₂-catalyzed cycloisomerization of 1,6-enynes for the total synthesis of pyrrolophane compounds and identification of byproducts to rationalize mechanistic pathways.

They extended this reaction to other 1,6-enynes bearing a sulfonamide and demonstrated that in the absence of the carbonyl moiety, azabicyclo[4.1.0]heptenes are obtained (Scheme 39).^[66]



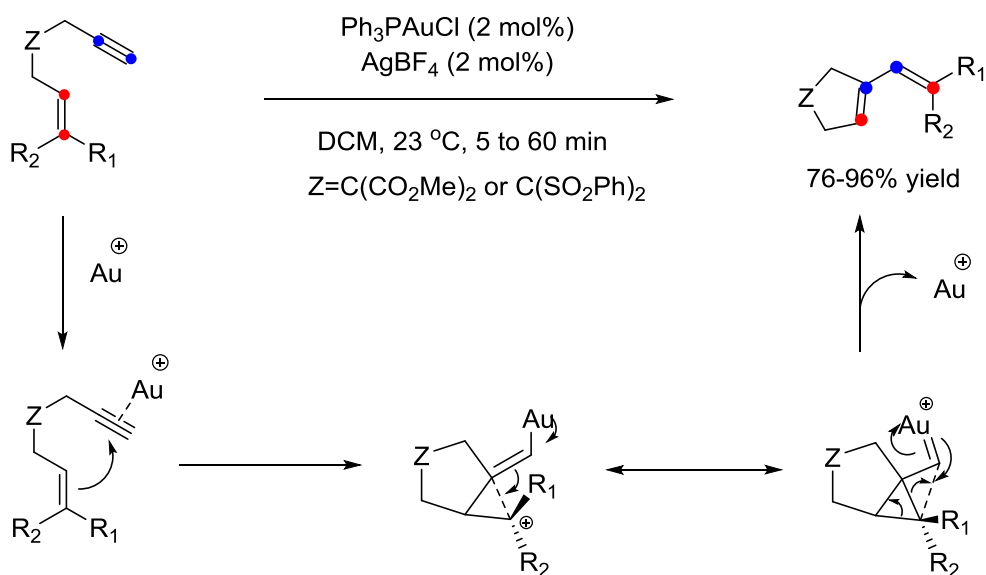
Scheme 39. PtCl₂-catalyzed the formation of azabicyclo[4.1.0]heptenes.

1-1-3-d-ii. Using gold catalysts

In 2004, Echavarren et al. reported that terminal 1,6-enynes bearing a *gem*-diester or disulfone group in the linkage undergo a cycloisomerization reaction in the presence of Ph₃PAuBF₄ generated *in situ* to form 1,3-dienes of type 1-vinylcyclopentene. The result is

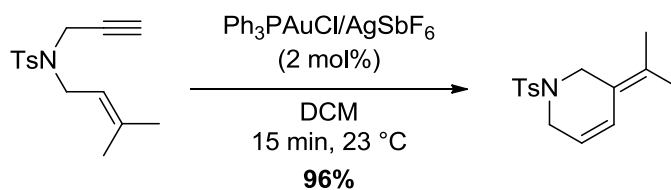
[66] A. Fürstner, H. Szillat, F. Selzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785.

the same as an enyne metathesis reaction. The activation of 1,6-enynes starts with the complexation of the alkyne, followed by nucleophilic addition of the alkene moiety to give, *via* a 5-*exo-dig* cyclisation/rearrangement sequence, a non-classical carbocation described as a cyclopropylcarbene (Scheme 40).^[67]



Scheme 40. Cycloisomerization of 1,6-enynes.

In fact, the reaction pathway is greatly influenced by the different substituents, the reaction conditions, as well as by the nature of the catalyst. For example, if an ether or a sulfonamide group is introduced into the linkage between the alkyne and the alkene, a 6-*endo-dig* cyclization is observed to furnish the 6-membered ring (Scheme 41).^[63]



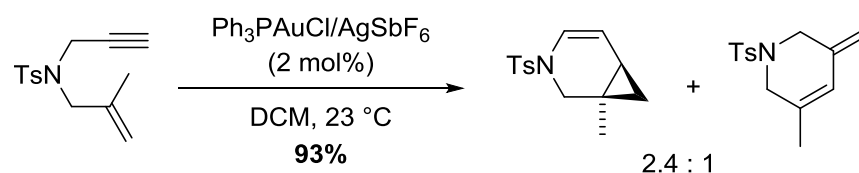
Scheme 41. 6-*endo-dig* cyclization of 1,6-enynes bearing a sulfonamide linkage.

By modifying the substrate structure, it is also possible to access to azabicyclo-[4.1.0]-heptenes along with the 6-*endo-dig* product by using the previous catalytic system (Scheme 42a), while the oxo- derivatives could be obtained using another

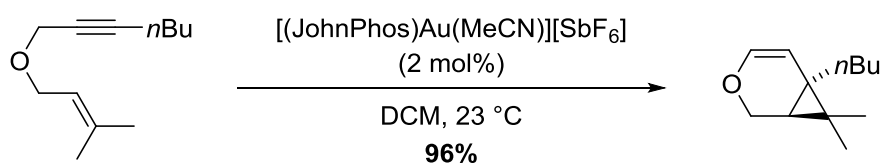
[67] C. N. Oberhuber, M. P. Muñoz, E. Bunuel, C. Nevado, D. J. Cardenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406;

cationic gold complex bearing a more electron-rich phosphine (Scheme 42b).^[68]

a) Access to azabicyclo[4.1.0]heptenes:

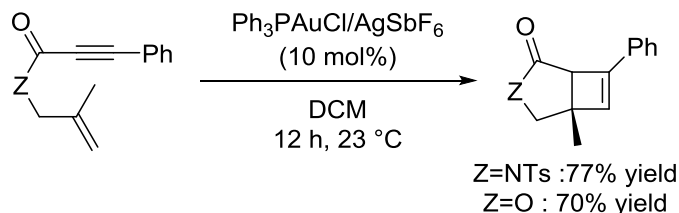


b) Access to oxobicyclo[4.1.0]heptenes:



Scheme 42. Access to aza- and oxobicyclo[4.1.0]heptenes by cycloisomerization 1,6-enynes.

Finally, in the case of 1,6-enynes bearing an ester or amide linkage and an internal alkyne motif, a 6-*endo*-dig cyclization leads to the exclusive formation of bicyclo[3.2.0]heptenes (Scheme 43).^[69]



Scheme 43. Cationic Au(I)-catalyzed formation of cyclobutenes.

In summary, upon support of experimental and DFT calculations,^[63-70] starting from the π -activated alkyne **A**, the alkene addition *via* a 5-*exo*-dig or a 6-*endo*-dig cyclization gives

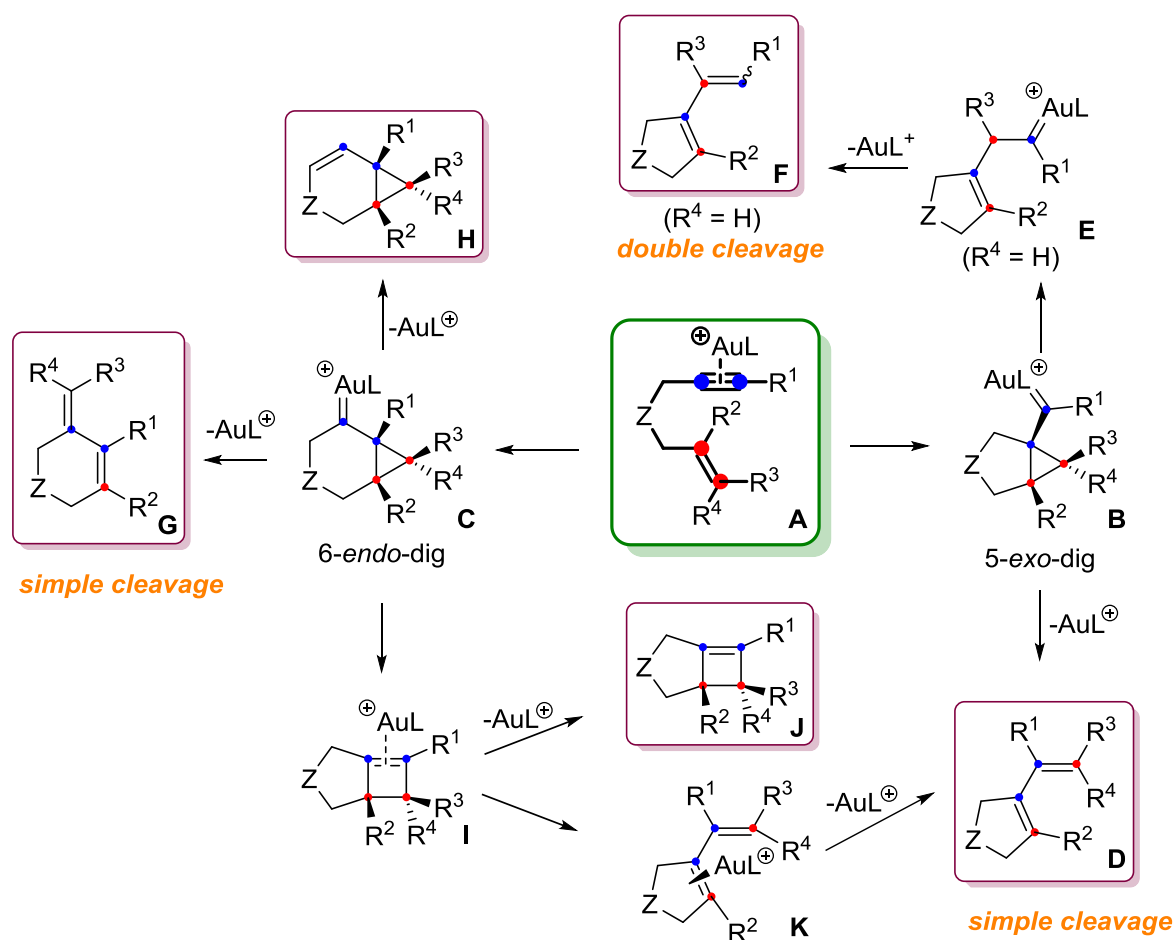
[68] C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677; Corrigendum: *Chem. Eur. J.* **2008**, *14*, 5096.

[69] Y. T. Lee, Y. K. Kang, Y. K. Chung, *J. Org. Chem.* **2009**, *74*, 7922.

[70] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305 ; (b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863 ; (c) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215 ; (d) L. Añorbe, G. Domínguez, J. Pérez-Castells, *Chem. Eur. J.* **2004**, *10*, 4938 ; (e) C. Bruneau, *Angew. Chem. Int. Ed.* **2005**, *44*, 2328 ; (f) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.

the cyclopropylcarbenes **B** and **C**, respectively (Scheme 44). In the absence of an additional nucleophile, different skeletal rearrangement of **C** and **D** can be observed:

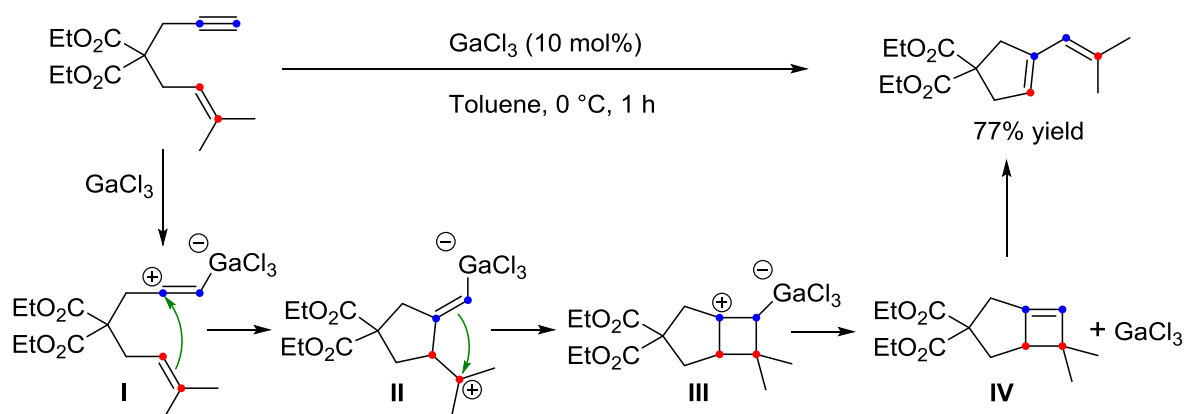
- Starting from **B**, compound **D** can be obtained via a ring opening/[1,3]-alkyl shift of the terminal carbon atom of the alkene to the internal carbon atom of the alkyne
- Compound **E** comes from the double cleavage of the alkene and alkyne and furnish **F**
- compound **G** can be obtained via a ring opening/[1,3]-alkyl shift of the terminal carbon atom of the alkene to the internal carbon atom of the alkyne
- Compound **H** directly comes from **C** via an elimination/protodeauration sequence
- A ring contraction of **C** allows for the formation of the cyclobutene compound **I** and therefore of **J**
- Compound **K** should come from a retro [2+2]-cycloaddition of **I** and lead to the formation of **D**



Scheme 44. General mechanism of the different Au(I)-catalyzed cycloisomerization pathways of 1,6-enynes.

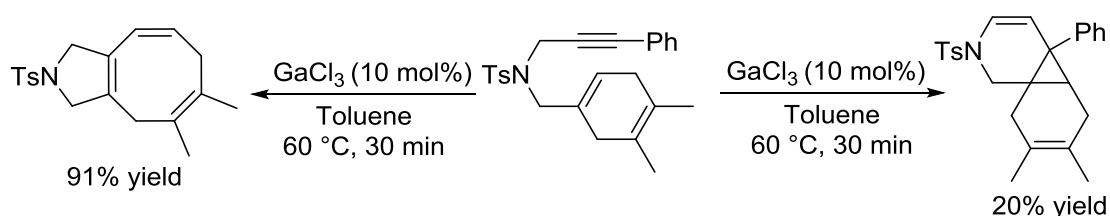
I-1-3-d-iii. Using gallium and indium catalysts

In 2002, Chatani et al. reported the GaCl_3 -catalyzed cycloisomerization of 1,6-enynes. The proposed mechanism involves the formation of a vinyl cation **I** allowing the addition of the alkene to give the cyclopentenyl derivative **II**. Addition of the vinyl gallate moiety to the tertiary carbocation leads to the cyclobutane cation **III**. Elimination of GaCl_3 and retro 4π -electrocyclization leads to the vinylcyclopentene **IV** (Scheme 45).^[71]



Scheme 45. Ga(III)-catalyzed cycloisomerization of 1,6-enynes.

In 2006, Chung et al. demonstrated that the use of 1,6-enynes bearing a sulfonamide linkage and a disubstituted alkyne gives access to original tricyclic compounds containing a cyclopropane moiety with a low yield but demonstrate that different mechanistic pathways should also be envisaged using Ga(III) as catalyst (Scheme 46).^[72]



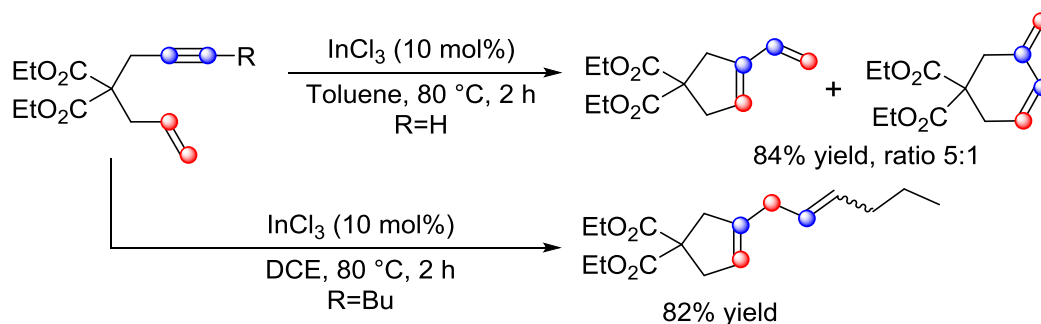
Scheme 46. Diverse skeletal rearrangement of 1,6-enynes using GaCl_3 as catalyst.

The same year, Miyanohana and Chatani reported the first example of In(III)-catalyzed

[71] N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294-12295.

[72] S.M. Kim, S. I. Lee, Y. K. Chung, *Org. Lett.* **2006**, *8*, 5425.

cycloisomerization of 1,6-enynes. When the 1,6-enyne presents a terminal alkyne, the major product obtained is the classical 1-vinylcycloalkene while those bearing a disubstituted alkyne leads to the formation of a non-conjugated diene of 1-allylcycloalkene type (Scheme 47).^[73] Relying on DFT calculations, Yu et al. suggested that this original skeletal rearrangement could be attributed to the fact that the real catalytic active species is InCl_2^+ instead of InCl_3 .^[74]



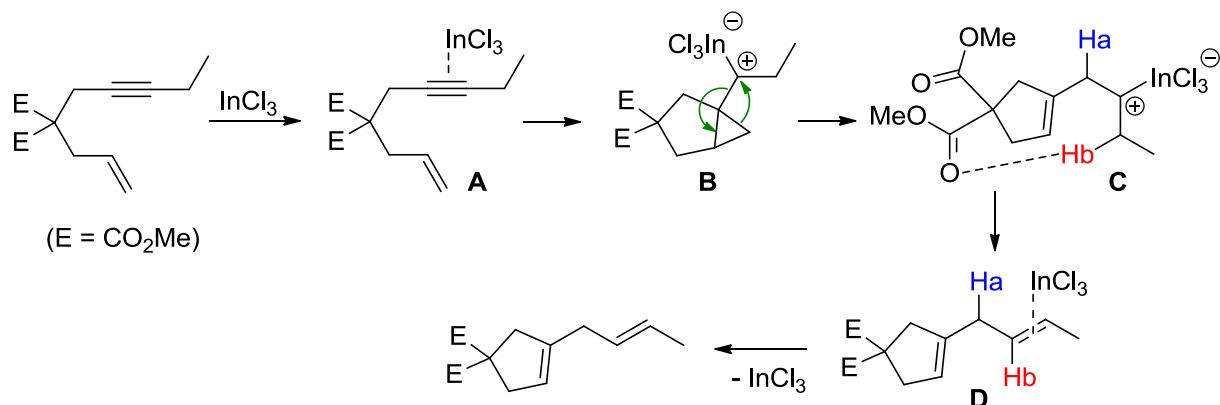
Scheme 47. InCl_3 -catalyzed cycloisomerization of 1,6-enynes.

However, to simplify the system, Yu *et al.* replaced the *gem*-diester linkage, a key structural factor of skeletal rearrangement, by a methylene group and our group demonstrated that this omission should be the cause of this suggestion. In our case, experimental results and DFT experiments allowed us to propose a mechanism involving the neutral InCl_3 as catalyst (Scheme 48).^[75] Activation of the alkyne moiety by InCl_3 promotes the 5-*endo*-dig cyclization to give the vinylcyclopropane intermediate **B** that rearranges to **C**. In this key intermediate, a selective and preferable [1,2]-hydrogen shift of H_b, mediated by an interaction of the latter with a carbonyl group, leads to **D** and therefore to the non-conjugate isolated product.

[73] Y. Miyanoana, N. Chatani, *Org. Lett.* **2006**, *8*, 2155.

[74] (a) L. -G. Zhuo, J. -J. Zhang, Z. -X. Yu, *J. Org. Chem.* **2012**, *77*, 8527 ; (b) L. -G. Zhuo, J. -J. Zhang, Z. -X. Yu, *J. Org. Chem.* **2014**, *79*, 3809.

[75] B. Michelet, G. Thiery, C. Bour, V. Gandon, *J. Org. Chem.* **2015**, *80*, 10925.



Scheme 47. Mechanism of the InCl₃-catalyzed cycloisomerization proposed by our group to give the non-conjugate 1-allylcyclopentene.

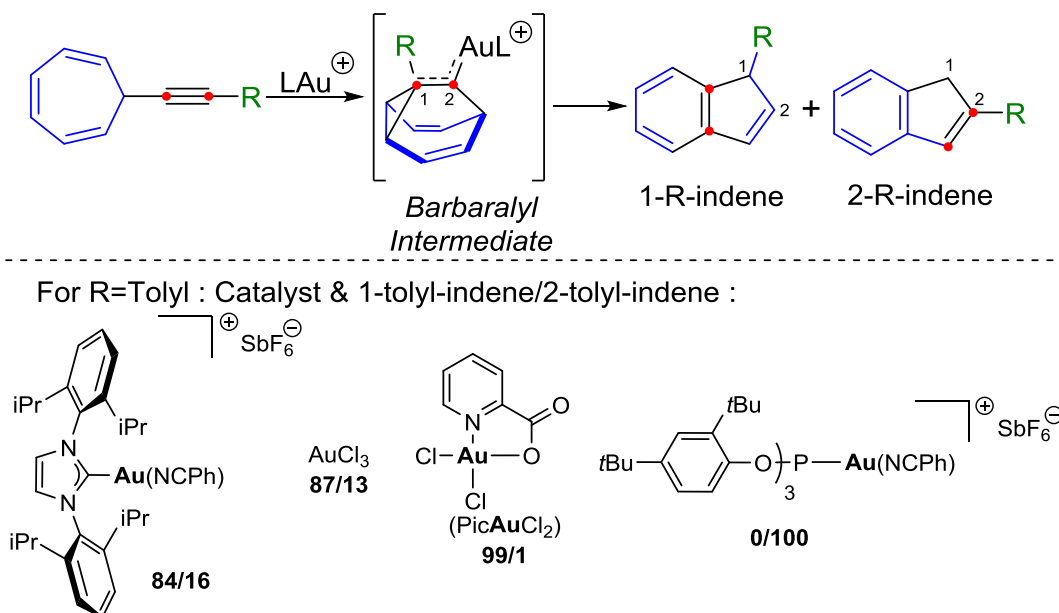
I-1-3-e. 7-alkynylcycloheptatrienes: a chemical probe to classify Lewis acid

As demonstrated by all of the above examples, there are no simple characteristics to identify the hardness or softness of a Lewis acid. To evaluate the activity of such compounds, our group designed a chemical probe allowing for the differentiation of carbene type reactivity, *i.e.* soft π -Lewis acid, or protic type reactivity, *i.e.* hard π -Lewis acid. For this purpose, we turned our attention on the 7-alkynylcycloheptatriene motif as the central reactive part of our chemical probe. Indeed, Echavarren *et al.* demonstrated that this substrate underwent cycloisomerization processes towards the formation of a nonclassical 9-barbaryl intermediates,^[76] a cation that exhibits more than 181 400 degenerated forms,^[77] to lead to two differently substituted indenenes (Scheme 48).^[78]

[76] (a) J. B. Lambert, *Tetrahedron Lett.* **1963**, 4, 1901; (b) P. Ahlberg, C. Engdahl, G. Jons-Il, *J. Am. Chem. Soc.* **1981**, 103, 1583.

[77] D. Cremer, P. Svensson, E. Kraka, P. Ahlberg, *J. Am. Chem. Soc.* **1993**, 115, 7445.

[78] P. R. McGonigal, C. de León, Y. Wang, A. Homs, C.R. Solorio-Alvarado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2012**, 51, 13093.

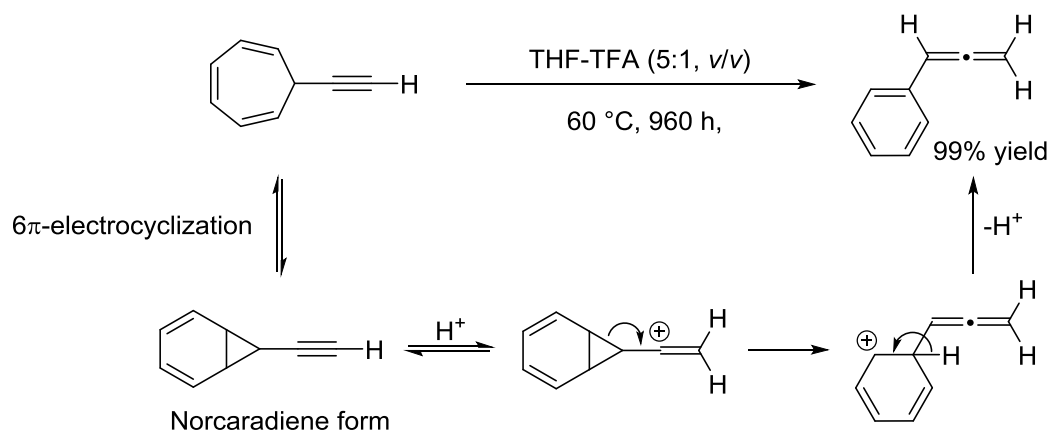


Scheme 48. Gold-catalyzed the formation of indenes from 7-alkynylcycloheptatrienes.

Evolution of the barbaralyl intermediate to the 1-substituted indene or the 2-substituted indene is highly dependent of the nature of the catalyst: when AuCl_3 or NHC-Au(I) complex give a mixture of the two substituted-indenes, the use of PicAuCl_2 only gives 1-tolyl-indene while the phosphite-Au(I) complex only gives the 2-tolyl-indene (Scheme 48). Moreover, no reaction was observed using PtCl_2 or GaCl_3 as catalyst while Kitagawa and co-workers demonstrated that TFA leads to the rearrangement of 7-alkynylcycloheptatriene into phenylallene (Scheme 49).^[79] A 6π -electrocyclization of the cycloheptatriene gives the norcaradiene motif,^[80] then the protonation^[80] of the terminal alkyne moiety leads to the rearrangement of the vinyl cation into arenium. Finally, phenylallene is obtained by rearomatization of the latter.

[79] (a) T. Kitagawa, J. Kamada, S. Minegishi, K. Takeuchi, *Org. Lett.* **2000**, 2, 3011; (b) S. Minegishi, J. Kamada, K. Takeuchi, K. Komatsu, T. Kitagawa *Eur. J. Org. Chem.* **2003**, 3497.

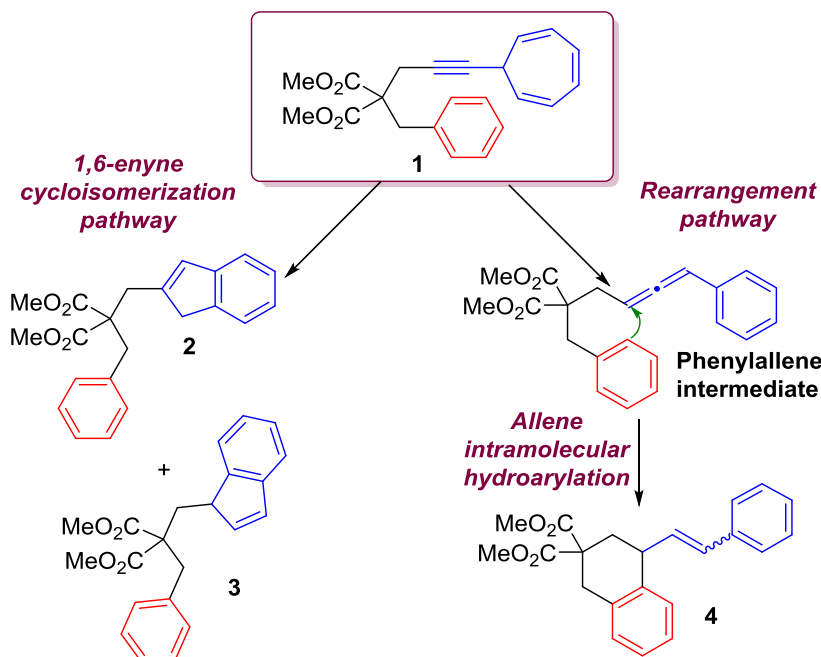
[80] K. Takeuchi, H. Fujimoto, T. Kitagawa, T. Fujii, K. Okamoto, *J. Chem. Soc. Perkin Trans. 2* **1984**, 461.



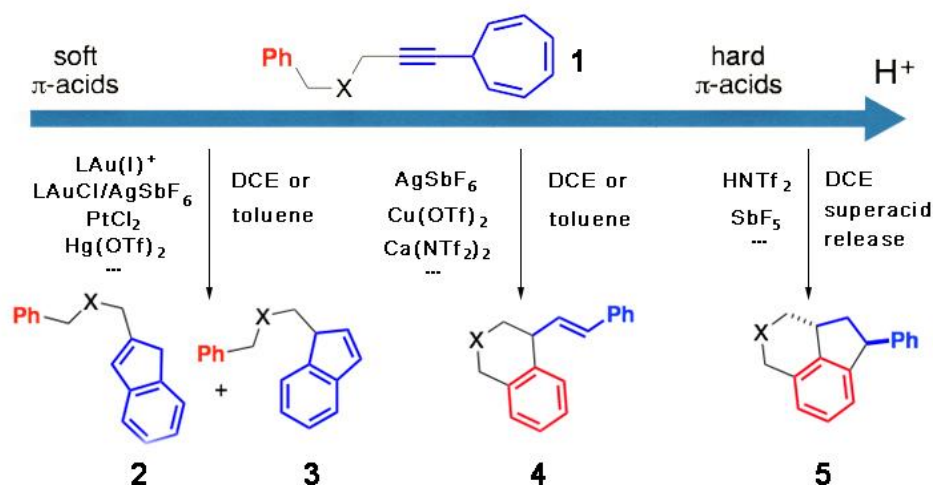
Scheme 49. Formation of phenylallene promoted by TFA.

Relying on this dual reactivity, our group prepared a 7-alkynylcycloheptatriene derivative **1** that should react with soft π -Lewis acids to give the two regioisomeric indenenes **2** and **3** or react with π -hard Lewis acids to lead to the corresponding allene that will undergo an additional hydroarylation to access to the tricyclic compound **4** (Scheme 50). As expected, our group reported that the reaction of compound **1** with soft π -Lewis acid catalysts of the gold, platinum, mercury, gallium or indium series lead to the skeletal reorganization of **1** into the regioisomeric indenenes **2** and **3** in DCE or toluene. With harder π -Lewis acids of the silver, gallium, copper, and calcium series, or even a Brønsted acid such as HOTf, the bicyclic product **4** is obtained. Moreover, the use of a solvent that can give rise to superacids such as HSbF_6 from AgSbF_6 or SbF_5 in DCE, or by using HNTf_2 , the conversion of **4** into the tricyclic compound **5** was observed. In this way, our test also informs if the catalytic conditions release protons and therefore give **5** *via* a second intramolecular hydroarylation of the alkene moiety (Scheme 51).^[81]

[81] (a) M. Vayer (2015-2018), « *Approches éco-compatibles en catalyse homogène : développement de nouvelles méthodologies de synthèse pour la formation de molécules complexes* », PhD thesis, Université Paris-Saclay; (b) M. Vayer, R. Guillot, C. Bour, V. Gandon, *Chem. Eur. J.* **2017**, *23*, 13901-13905.



Scheme 50. The 7-alkynylcycloheptatriene chemical probe prepared into our group.

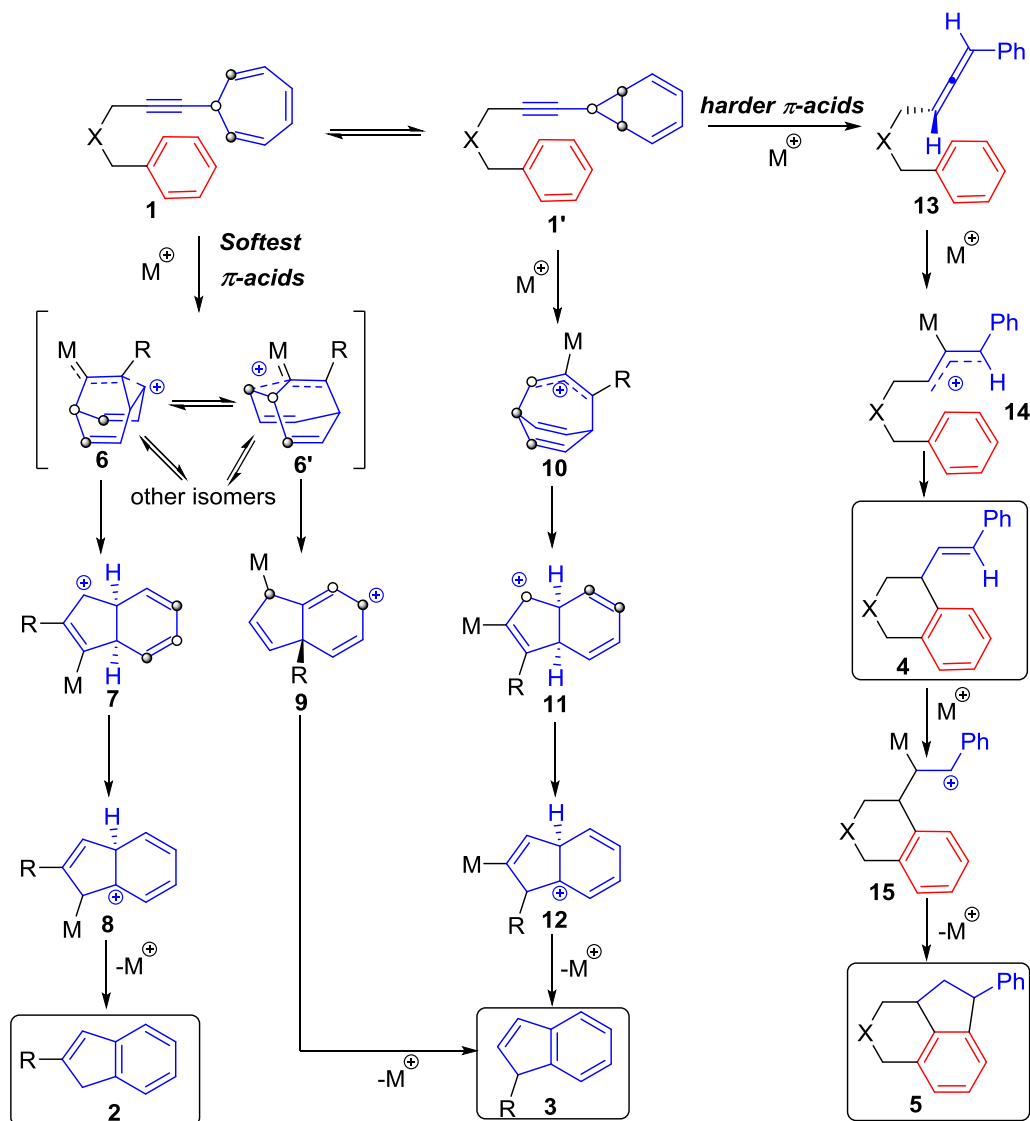


Scheme 51. The use of the 7-alkynylcycloheptatriene compound **1** ($\text{E} = \text{CO}_2\text{Me}$) as a chemical probe to evaluate the π -acidity of Lewis acids. (LA = Lewis Acid).

To summarize the mechanistic aspect of the skeletal reorganization of 7-alkynylcycloheptatriene, depending on the catalyst, **1** can give rise to either indenyl products **2** or **3**, or to the hydroarylation products **4** and **5**. Indenyl products **2** and **3** come from the fluxional nonclassical soft π -acid-stabilized 9-barbaryl cations **6**, **6'** or other isomers (Scheme 52). Their transformation could take place through the σ -complex **7**, followed by a [1,2]-H shift to give **8** and rearomatization leads to indene **2**. Alternatively, the σ -complex **9** could be formed, leading directly to indene **9** after a [1,2]-alkyl shift. Besides, 7-alkynyl

cycloheptatrienes can undergo valence tautomerism to the norcaradiene form **1'**. Computations support its transformation into the allyl cation **10**, and its isomerization into indene **3** through intermediates **11** and **12**. Since **10** is less delocalized than the barbaralyl cations, one can anticipate that this pathway will be less favorable with the softest π -acids, which is indeed corroborated by computations. Finally, under hard acidic conditions, after isomerization of **2** into phenylallene **13**, its hydroarylation leads to **4** through the allyl cation **14**, and possibly to **5** after alkene hydroarylation through the benzylic cation **15**. These steps should be favored by π -acids even harder than those leading to **4**, or even by protons. Thus, the chemoselectivity of the isomerization of **1** reveals the category to which a π -acid belongs.

Moreover, this chemical probe is a useful and efficient reactive species to identify surrogates of noble metal complexes. Our group was especially interested in broadening the scope of application of π -acid catalysis to inexpensive metals, such as zinc (this metal is often not considered to be a transition metal). Regarding zinc, only simple salts of type ZnX_2 have been used so far as catalysts. In Chapter II, are reported some representative examples that were catalyzed by simple ZnX_2 salts. The catalytic activity of cationic NHC-Zn(II) complexes in reactions that require the electrophilic activation of soft C-C π bonds are also been studied. The latter proved able to act as a soft π -Lewis acid in a variety of transformations. The benefit of the bulky IPr NHC-type ligand was demonstrated by comparison with simple ZnX_2 salts.



Scheme 52. Isomerization pathways of compound **1** ($R = \text{CH}_2\text{XCH}_2\text{Ph}$)

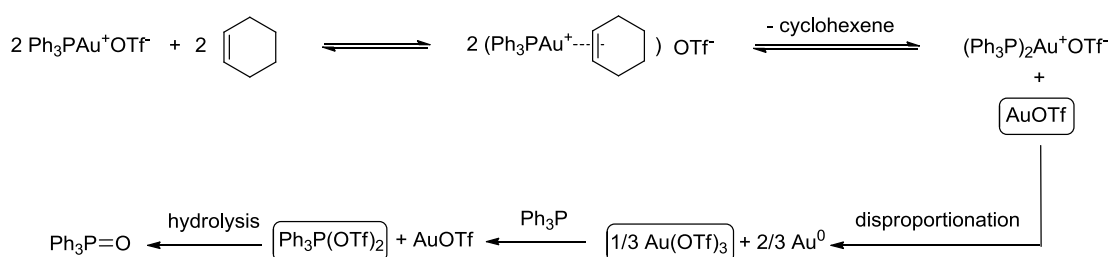
1-2. A Cyclic Divalent $N(I)$ Species Isoelectronic to Carbodiphosphoranes

In this part, I will make a brief introduction about the limitations of gold chemistry. Then, I will give some published strategies to better stabilize the active gold(I) ion. Finally, I will present our unexpected finding of a donor-acceptor bond organic compounds and discussed the related literature.

1.2.1. Limitations of gold chemistry

Gold complexes as π -acid catalysts are well-known to organic chemists. However, gold chemistry also has some limitations. In most gold-catalyzed reactions, the catalyst loading

is between 1 to 20 mol%, meaning low turnover numbers. The low TONs are attributed to the fast decay of cationic gold into its nonreactive species. In 2014, Xu *et al.* reported the experimental study of the deactivation of cationic gold catalysts.^[82] Scheme 53 presents the postulated mechanism for substrate-induced gold catalysts decay. The cationic gold complex coordinates with a substrate such as cyclohexene to form an alkene π complex. This weakens the P–Au bond, which becomes labile. This promotes the formation of $(\text{Ph}_3\text{P})_2\text{Au}^+\text{OTf}^-$ and AuOTf . The disproportionation of AuOTf yields $\text{Au}(0)$ and $\text{Au}(\text{OTf})_3$. Finally, $\text{Au}(\text{OTf})_3$ oxidizes the phosphine ligand to form the $\text{Ph}_3\text{P}(\text{OTf})_2$ and AuOTf .



Scheme 53. Alkyne/alkene/allene-induced cationic gold catalysts decay.

Since gold catalysts and silver additives are expensive and not easy to recycle, the high gold catalyst loading is unpractical in large-scale syntheses. Moreover, gold-catalyzed reactions have trouble with large-scale syntheses because of the high dilution required to avoid the decomposition of the catalysts. Thus, most gold-catalyzed reactions were reported at the mmol level.

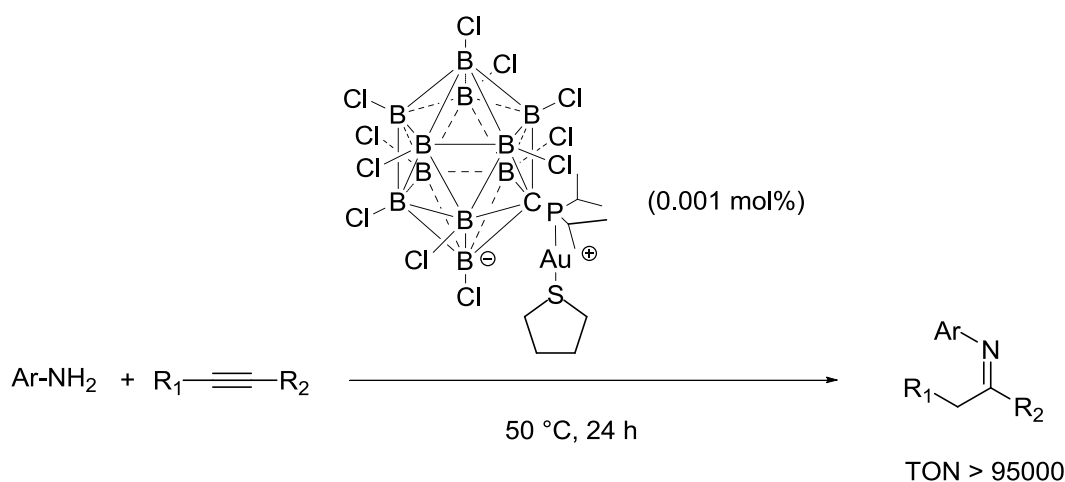
1.2.2. Attempts to achieve high TON in gold catalysis

To avoid the gold complexes decay and improve the TON, chemists have designed and synthesized some specific ligands to better stabilize the active gold(I) ion. However, most of these new gold complexes only showed high reactivity in a certain type of reaction. In 2013, Lavallo *et al.* reported that perhalogenated carba-*closo*-dodecaborate as ligands for the hydroamination of alkynes with primary amines (Scheme 54).^[83] The extraordinary

[82] M. Kumar, J. Jasinski, G. B. Hammond, B. Xu, *Chem. Eur. J.* **2014**, *20*, 3113-3119.

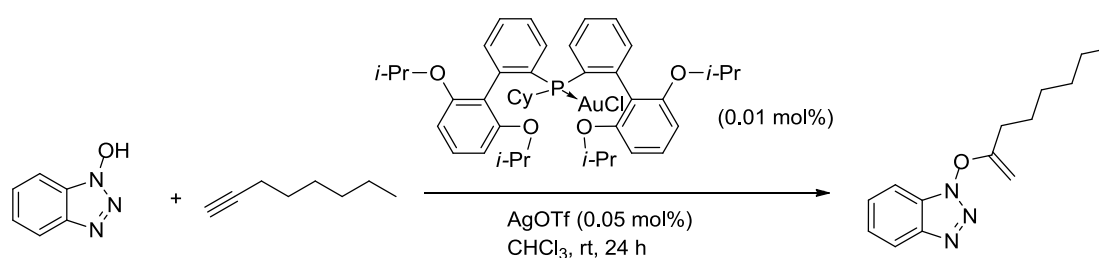
[83] V. Lavallo, J. H. Wright II, F. S. Tham, S. Quinlivan, *Angew. Chem. Int. Ed.* **2013**, *52*, 3172-3176.

catalytic efficiency of this gold complex might be due to the proximity of the anionic $\text{CB}_{11}\text{Cl}_{11}^-$ group to the Au center. This proximity may lead to the stabilization of gold(I) ion during catalysis.



Scheme 54. Perhalogenated carba-closo-dodecaborate as ligands in gold catalysis.

One year later, Xu *et al.* designed a novel ligand bearing two electron-rich *o*-biphenyl groups (Scheme 55).^[84] The presence of two electron-rich *o*-biphenyl groups may slow down the deactivation of gold(I) by a weak interaction between the gold complex and an electron-rich arene moiety. The electron-rich ligand could supply the electronic density to the gold center and help the regeneration of the cationic gold complex.



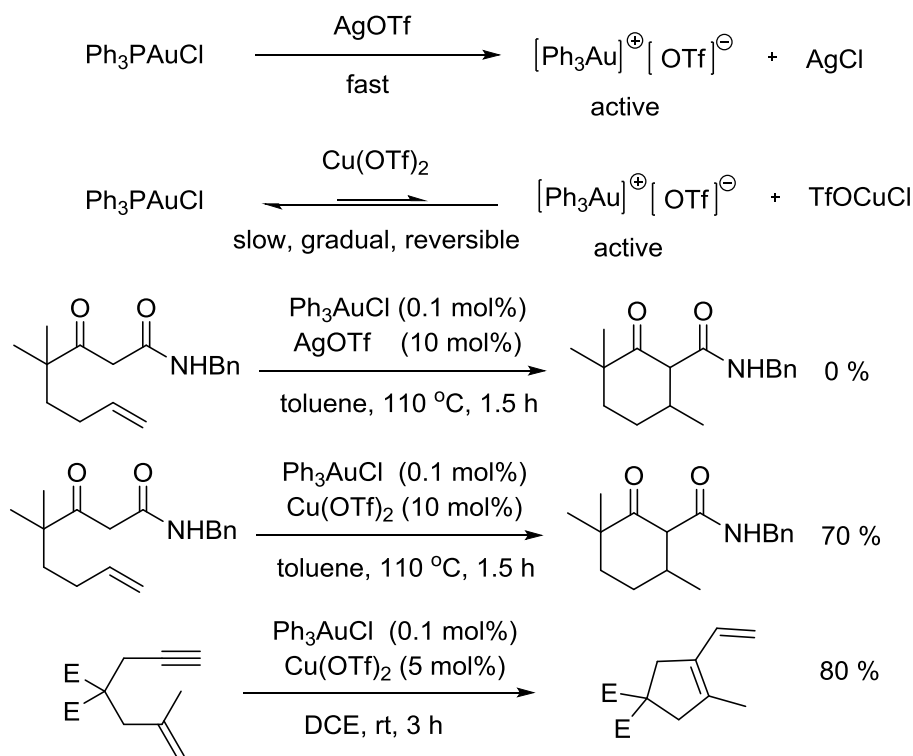
Scheme 55. BisPhePhos XD gold(I) chloride catalyzed C-O and C-C bond formations.

To avoid the fast decay of cationic gold complexes, our group also made some efforts.^[85] Instead of doing ligand design, which leads to robust but not versatile complexes in

[84] D. Malhotra, M. S. Mashuta, G. B. Hammond, B. Xu, *Angew. Chem. Int. Ed.* **2014**, *53*, 4456-4459.

[85] A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. B. Lafolie, V. Gandon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5848-5852.

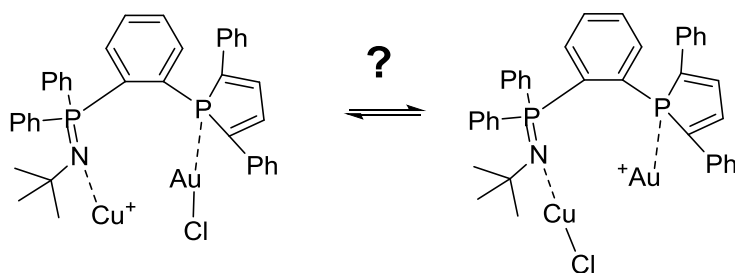
contrast to the simple and readily available gold complexes, we tried to work on slowing down the anion metathesis to release the active gold(I) ion gradually and reversibly, maintaining its concentration as low as possible. As it is well-known by chemists, the most common way to generate the active cationic gold(I) complexes is to use silver salts as additives. Due to the fast anion metathesis by Au/Ag catalytic system and its irreversible character (precipitation of the silver halide), the active gold(I) ion is formed in a rapid and irreversible way. However, the freshly generated gold(I) ion is not stable in the presence of the substrate as explained above. We proposed to slow down the anion metathesis by using an Au/Cu catalytic system so that the active cationic gold(I) complex could be delivered continuously (Scheme 56).



Scheme 56. Au/Cu catalytic system in gold(I) catalysis.

With reluctant reactions such as the Conia-ene reaction to alkenes, no product is obtained with the Au/Ag system. Only a gold mirror is formed because of the formation of inactive Au(0). Using the Au/Cu system, such reactions work fine, as well as others typical of Au(I) catalysis, such as the cycloisomerization of enynes. Based on our understanding of the substrate-induced cationic gold catalysts decay mechanism and our previous study, we

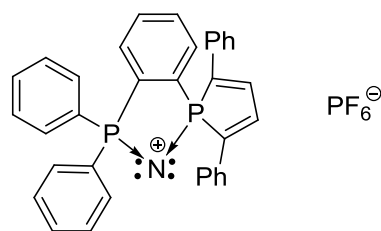
wanted to study the possibility of having the gold and the copper atom within the same complex and have a pendular system in which the halide could come and go between the two metals, i.e. leave gold to make it reactive and come back to it (or coordinate both metals) to stabilize it. For this purpose, we envisaged to use iminophosphoranes which display a hard site (N) to welcome the copper center and a soft one for gold (P) (Scheme 57). Such ligands are phosphole-iminophosphoranes, of which Dr. Audrey Auffrant is a specialist (LCM, Ecole Polytechnique).



Scheme 57. Envisaged hemilabile phosphole-iminophosphorane Au/Cu complex.

1.2.3. Some organic compounds with donor-acceptor bonds

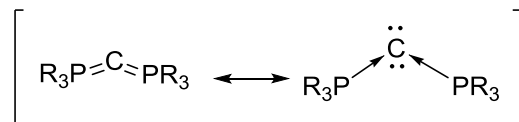
During the attempted synthesis of phosphole-iminophosphorane gold complex, we unexpectedly obtained an original bis-phosphane chelated N(I) species (Scheme 58). This N(I) complex possesses two lone pairs of electrons at its central nitrogen atom and belongs to the family of low-valent organic compounds stabilized by donor-acceptor bonds.



Scheme 58. Bis-phosphane chelated N(I) species.

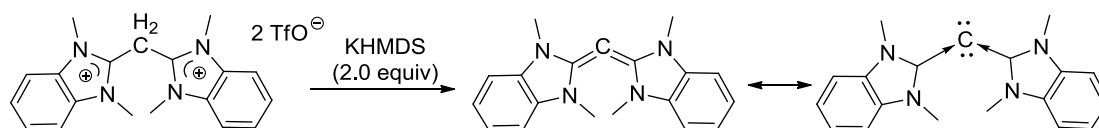
Amazed by this new species, we searched for organic compounds with similar donor-acceptor bonds in the literature. In 2006, Frenking *et al.* provided theoretical evidence that carbodiphosphoranes $(R_3P)_2C$ are better considered as carbon(0)

compounds of general formula $R_3P \rightarrow C(0) \leftarrow PR_3$ rather than allene species of type $R_3P=C(IV)=PR_3$ (Scheme 59).^[86]



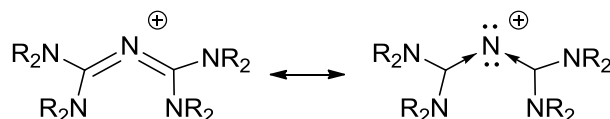
Scheme 59. Carbodiphosphorane depiction.

He also predicted that carbodicarbenes would also be carbon(0) species of type $HC \rightarrow C(0) \leftarrow NHC$, which was experimentally confirmed by Bertrand *et al.* in 2008 (Scheme 60).^[87]



Scheme 60. Synthesis of carbodicarbenes.

In 2009, Bharatam *et al.* reported that some guanidine derivatives are better regarded as $L \rightarrow N^{\oplus} \leftarrow L$ species by electronic structure analysis (Scheme 61).^[88]



Scheme 61. Guanidine-derived compounds.

We believe our compounds belongs to this category of rare species and deserved to be thoroughly analyzed, as shown in Chapter III.

l-3. Halogen bonding catalysis for the synthesis of propargyl ethers from

[86] R. Tonner, F. Öxler, B. Neumüller, W. Petz and G. Frenking, *Angew. Chem. Int. Ed.* **2006**, *45*, 8038-8042.

[87] C. A. Dyker, V. Lavallo, B. Donnadiu and G. Bertrand, *Angew. Chem. Int. Ed.*, **2008**, *47*, 3206-3209.

[88] D. S. Patel and P. V. Bharatam, *Chem. Commun*, **2009**, 1064-1066.

aliphatic alcohols

Even if the metal-based catalysis plays a crucial role to promote chemical transformation of organic compounds, especially in π -activation or cross-coupling reactions, the use of non-metallic catalysts for the acceleration of reactions, known as organocatalysis, has been tremendously developed during the last two decades and demonstrated an astounding capacity to drive multitudes of chemical reactions. Organocatalysts exhibits a high stability compared to metal-based catalysts and therefore are both environmentally friendly and cheap to produce. The popularity of the use of organic catalysts as well as its extension to asymmetric catalysis led to the awarding of the Nobel Prize in Chemistry to David W. C. MacMillan and Benjamin List in 2021.^[89] All organocatalysts developed can be classified according their activation mode: (i) by formation of covalent bonds between the catalyst and the substrate such as in iminium-based catalysts,^[90] (ii) by hydrogen bonding, allowing the assembly of well-organized intermediates *via* the hard acid hydrogen atom of the catalyst,^[91] (iii) by cation- π and anion- π interactions, which are weak and quite rare noncovalent interactions,^[92] (iv) by ion pairing, especially in phase-transfer processes or in asymmetric catalysis^[93] and finally (v) by σ -hole interaction, a complementary interaction to hydrogen bonding, using an halogen-based Lewis acid allowing the selective activation of Lewis base.^[94]

[89] www.nobelprize.org/prizes/chemistry/2021/press-release/

[90] (a) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178-2189; (b) G. J. Reyes-Rodriguez, N. M. Rezayee, A. Vidal-Albalat, K. A. Jørgensen *Chem. Rev.* **2019**, *4221-4260*.

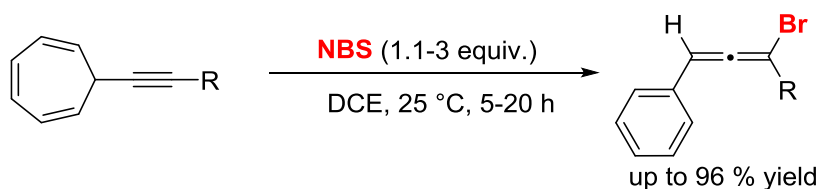
[91] (a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713-5743; (b) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *516-532*; (c) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187-1198; (d) D. Parma, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047-9153; (e) R. Maji, S. C. Mallojjala, S. E. Wheeler, *Chem. Soc. Rev.* **2018**, *47*, 1142-1158.

[92] (a) S. Yamada, J. S. Fossey, *Org. Biomol. Chem.* **2011**, *9*, 7275-7281; (b) C. R. Kennedy, S. Lin, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2016**, *55*, 12596-12624; (c) A. J. Neel, M. J. Hilton, M. S. Sigman, F. D. Toste, *Nature* **2017**, *543*, 637-646.

[93] (a) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656-5682; (b) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312-4348.

[94] (a) D. Bulfield, S. M. Huber, *Chem. Eur. J.* **2016**, *22*, 14434-14450; (b) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478-2601; (c) L. Turunen, M. Erdélyi, *Chem. Soc. Rev.* **2020**, *49*, 2688-2700; (d) M. Breugst, J. J. Koenig, *Eur. J. Org. Chem.* **2020**, 5473-5487.

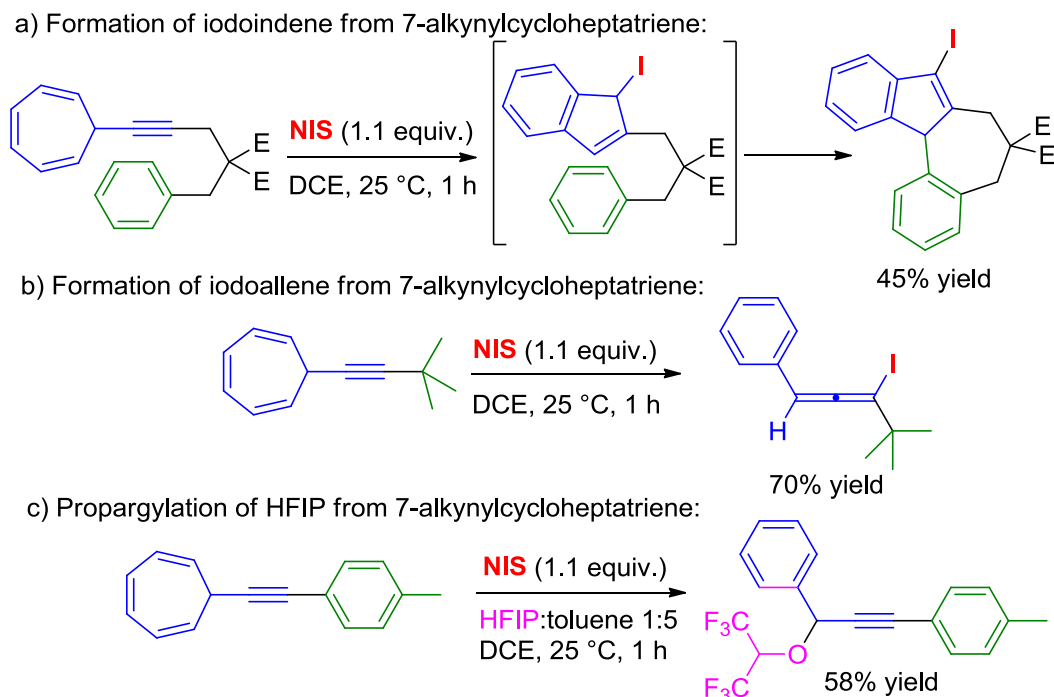
During the course of our work on the use of 7-alkynylcycloheptatrienes, our group reported that the activation of the latter by bromonium ion leads, as Brønsted acids, to the formation of 3-substituted 3-bromo-1-phenylallenes (Scheme 62).^[95]



Scheme 62. Formation of bromoallenes from 7-alkynylcycloheptatrienes using *N*-bromosuccinimide (NBS).

Switching from bromonium ion to iodonium ion, a softer π -Lewis acid, we observed a different type of reactivity depending on the substrate structure. When the 7-alkynylcycloheptatriene includes a diester linkage between the alkynylcycloheptatriene motif and the aryl group, as observed with gold catalysts, NIS leads to the formation of an iodoindene (Scheme 63a), while an iodoallene was obtained using 7-(3,3-dimethylbut-1-yn-1-yl)cycloheptatriene (Scheme 63b).^[96] This substrate was the only one allowing us to isolate the iodoallene derivative, all other 7-alkynylcycloheptatrienes led to decomposition. Finally, addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) to activate NIS and favor the formation of iodoallene surprisingly conducted to the formation of the propargylic ether of HFIP (Scheme 63c).

[95] M. Vayer, R. Guillot, C. Bour, V. Gandon, *J. Org. Chem.* **2018**, *83*, 11309-11317.



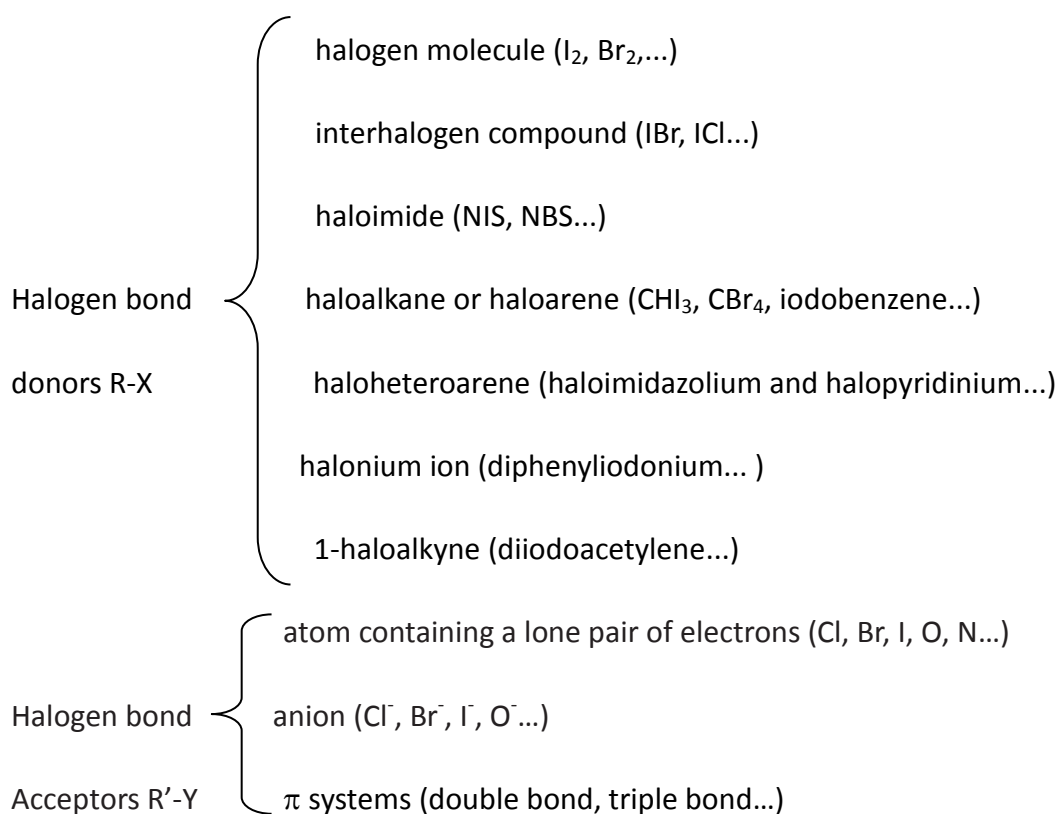
Scheme 63. Difference of reactivity of NIS depending on the substrate structure and reaction conditions.

We proposed that the last reactivity can be explained by (i) the *in situ* formation of the corresponding iodoallene followed by (ii) the NIS-catalyzed iodine atom abstraction of iodoallene by halogen bonding and nucleophilic addition of HFIP through a SN_2' . A general presentation of halogen bonding and its application in organic chemistry are introduced below, while the study of this reaction and results obtained are presented in Chapter IV.

I-3-1. Definitions of halogen bonds

A halogen bond is a directional noncovalent interaction between an electrophilic halogen atom X in one molecule and a nucleophilic site Y in a Lewis base.^[96] This kind of noncovalent interaction could be depicted by $R-X \cdots Y-R'$. R-X is the halogen bond donor and Y-R' is the halogen bond acceptor (Scheme 64).

[96] (a) O. Hassel, *Science* **1970**, *170*, 497-502; (b) G. R. Desiraju, P. Shing Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati, K. Rissanen, *Pure Appl. Chem.* **2013**, *85*, 1711–1713.



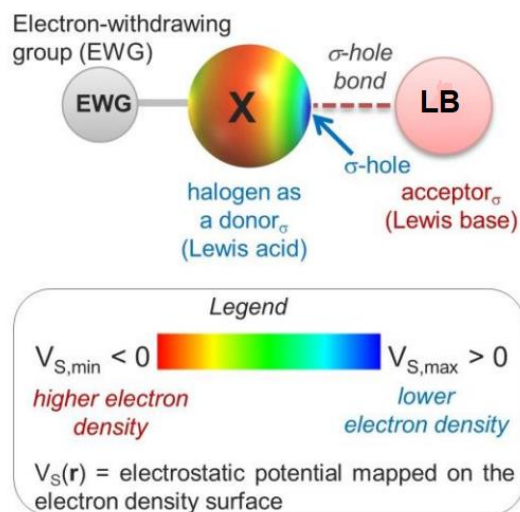
Scheme 64. Halogen bond donors and acceptors.

There are some interesting features in a halogen-bonded complex $R-X\cdots Y-R'$. More than one halogen bond could be formed ($R-X\cdots Y\cdots X-R$). The halogen bond strength increases as the electronegativity of X decreases ($F < Cl < Br < I$). Thus, the strongest interaction normally happens with iodine. The interatomic distance between X and Y is usually shorter than the sum of the van der Waals radii. The bond length in R-X mostly increases compared with unbonded R-X. The halogen bond angle in $R-X\cdots Y$ tends to be close to 180° .^[96b]

I-3-2 Electronic origin of halogen bonding

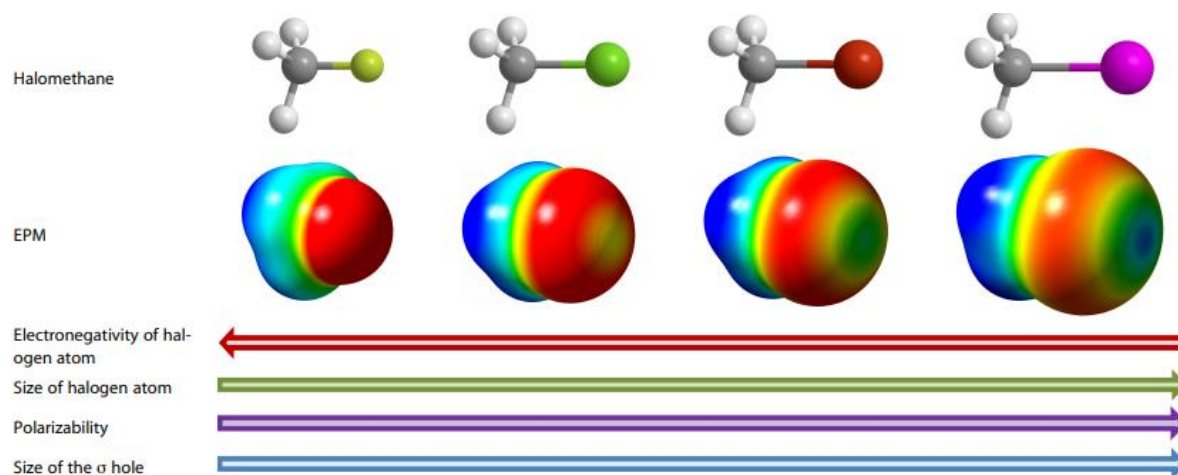
Even if halogen atoms are electronegative elements, when they are bound to electron withdrawing groups, an anisotropic distribution of charge and a region of electronic charge density depletion, called σ -hole, can be observed and represented the most accepted model for the theoretical explanation of the halogen bonding and allowed the interaction

of halogen atoms with Lewis bases (Scheme 65).^[97]



Scheme 65. Position of the σ -hole on halogen bond donors.⁹⁸

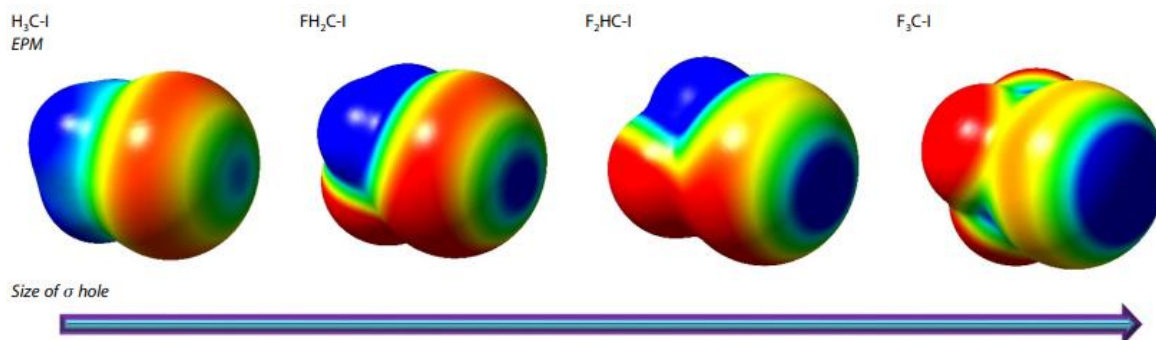
The electronic charge is redistributed toward the polarized bond, resulting in a rich electron density on the equatorial region of X as well as a depletion on its terminus. Due to this anisotropy of distribution of electrons, this electronic charge modification depends on the electronegativity of X as well as the nature of withdrawing groups (Scheme 66).^[99]



[97] (a) T. Brinck, J. S. Murray, P. Politzer, *Int. J. Quantum Chem.* **1992**, *44*, 57–64; (b) T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2007**, *13*, 291–296; (c) P. Politzer, J. S. Murray, T. Clark, *Phys. Chem. Chem. Phys.* **2010**, *12*, 7748–7757.

[98] Adapted from P. Peluso, V. Mamane, A. Dessì, R. Dallochio, E. Aubert, C. Gatti, D. Mangeling, S. Cossu, *J. Chromatogr. A* **2020**, *1616*, 460788.

[99] (a) K. Eskandari, H. Zariny, *Chem. Phys. Lett.* **2010**, *492*, 9–13; (b) K. Eskandari, M. Lesani, *Chem. Eur. J.* **2015**, *21*, 4739–4746.



Scheme 66. Effect of the nature of the halogen atom and the strength of the electronic withdrawing group on the size of the σ -hole and therefore onto the strength of the halogen bond.^[100]

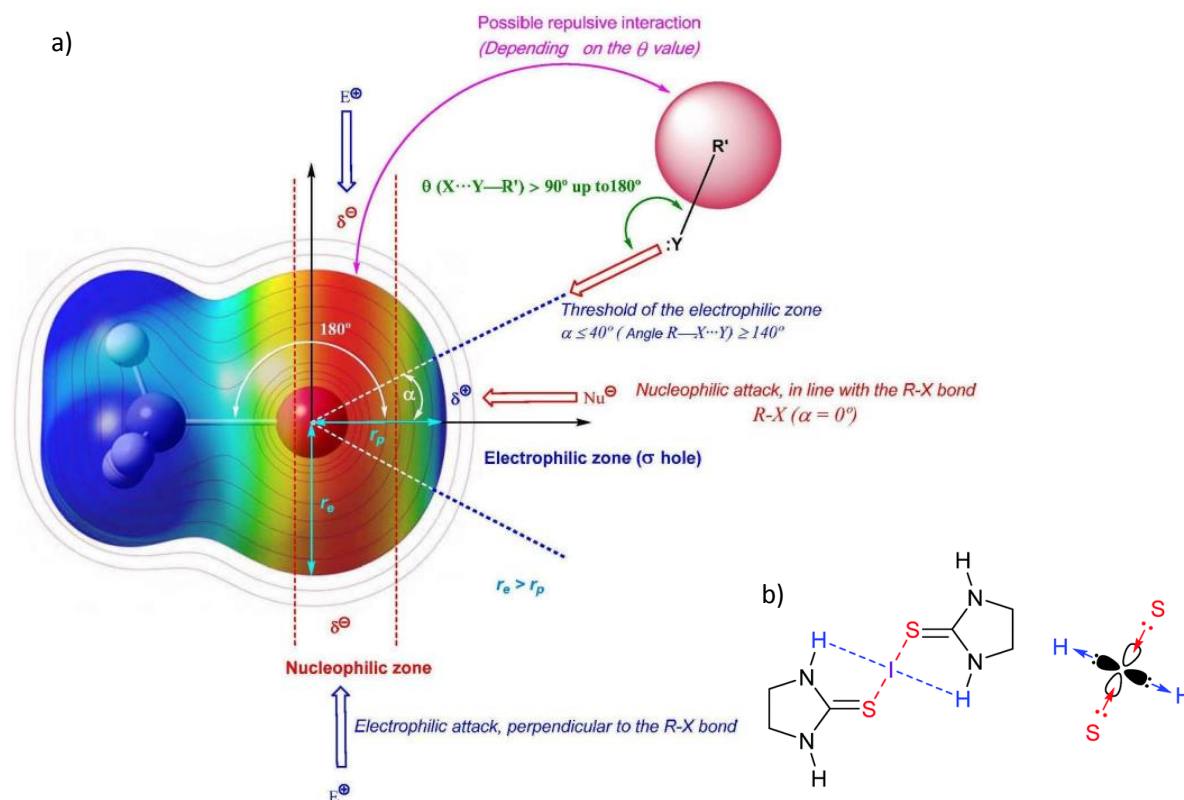
Nevertheless, even if this purely electrostatic model of halogen bonding can explain the high directionality of the interaction, it cannot explain all features. The electronic origin of such interactions is thus more complex and not addressed herein (part of charge-transfer contributions as well as dispersion).^[95,101]

I-3-3 Hydrogen bonding vs. halogen bonding

One important difference between halogen bonding and hydrogen bonding is precisely the high directionality of the interaction: the orientations and angles are dictated by the electronic charge distribution of the R-X bond while hydrogens are uniformly electropositive. Hydrogen bonds can only moderately adapt their orientations and angles within the molecule to fit with the electron lone pairs of the hydrogen bond donors. However, due to their electronegative circular crown and three lone pairs of electrons, halogen atoms are amphiphilic atoms able to form an orthogonal interaction with electrophiles in addition to the halogen bond with Lewis bases. In this way, halogen bond donors can form halogen bonding with Lewis bases as well as hydrogen bonding with hydrogen bond donors (Scheme 67).

[100] Adapted from A. M. Montaña, *ChemistrySelect* **2017**, 2, 9094-9112.

[101] L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney, P. D. Beer, *Chem. Rev.* **2015**, 115, 7118-7195.



Scheme 67. a) Representation of the σ -hole and equatorial nucleophilic zone of the iodine atom in iodomethane allowing for two orthogonal interactions and representing the amphiphilic nature of halogen atoms. b) Stable complex formed between two molecules of imidazolidinethione and iodonium ion through two halogen bonds as well as two hydrogen bonds.

Thus, the difference of the halogen bonding strength and size of the halogen atom in R-X donors can be adapted to the substrate in biological systems in a more convenient way than in hydrogen bonding interaction. Even if iodine-based donors are generally used to ensure a strong halogen bonding, it is possible to obtain a better match of orbital sizes or to modulate steric factors by switching to bromine or chlorine atom. In a similar way, modification of the electron-withdrawing effect on the backbone of R-X can conduct to a modulation of the strength of the halogen bonding in a more efficient way than in hydrogen bonding.

Finally, due to similarities between these two non-covalent interactions, several halogen bonding activators and organocatalysts bearing chemical structures based on hydrogen bonding organocatalysts, have been prepared and the scope of their synthetic application is currently evaluated.

I-3-4 Applications of halogen bonding in organic synthesis as mimics of organometallic reagents or as organocatalysts

Elemental iodine has been many times reported as a catalyst or activator in organic synthesis.^[102] Even if I₂ is a strong halogen donor, no real evidence has been established to assert that I₂ really acts *via* halogen bonding and not by giving trace amount of HI.^[103a,103] Halonium ions are also strong halogen bond donors. For example, the Barluenga's reagent could be used as organic activator for the preparation of indoles from alkynylpyrrole-2-carboxaldehydes and alkenes (Scheme 68a)^[104] or the intramolecular Friedel-Crafts acylation of arenes (Scheme 68b)^[105] while Takemoto *et al.* reported a *N*-iodosuccinimide induced desilylative semipinacol rearrangement, demonstrating the efficiency of *N*-iodosuccinimide for the C-X bond activation/halide abstraction such as silver salts (Scheme 68c).^[106]

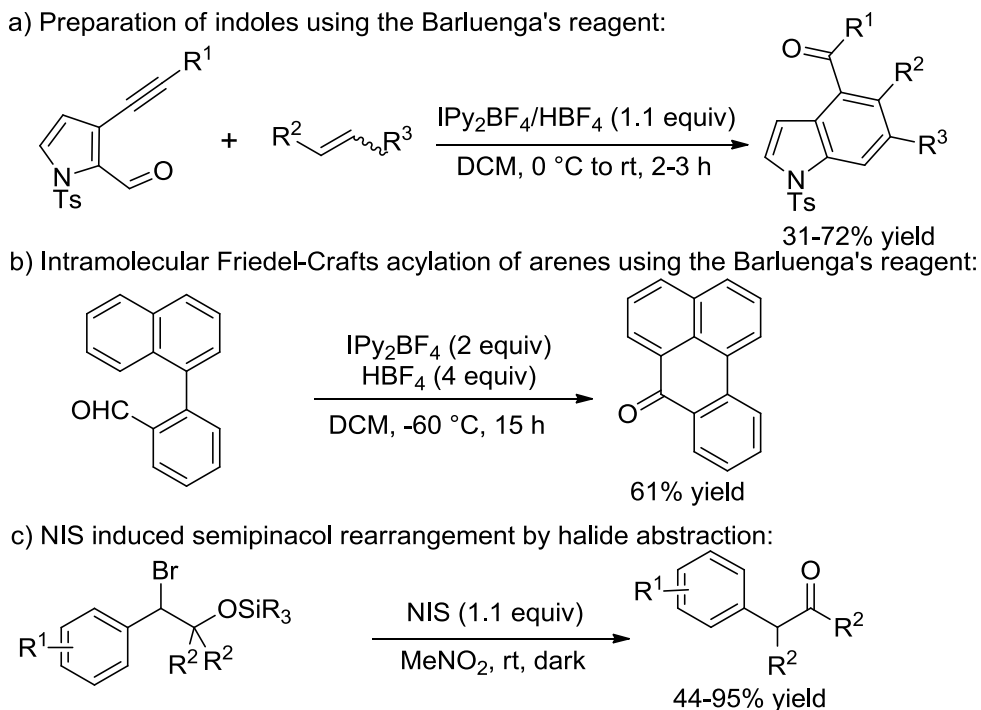
[102] (a) H. Togo, S. Iida, *Synlett* **2006**, 2159-2175; (b) M. Jereb, D. Vražič, M. Zupan, *Tetrahedron* **2011**, *67*, 1355-1387.

[103] M. Breugst, D. Von der Heiden, *Chem. Eur. J.* **2018**, *24*, 9187-9199.

[104] J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González, *Adv. Synth. Catal.* **2005**, *347*, 526-530.

[105] J. Barluenga, M. Trincado, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2006**, *45*, 3140-3143.

[106] N. Tsuji, Y. Kobayashi, Y. Takemoto, *Chem. Commun.* **2014**, *50*, 13691-13694.



Scheme 68. The use of iodonium ion as organic activator for different organic reaction.

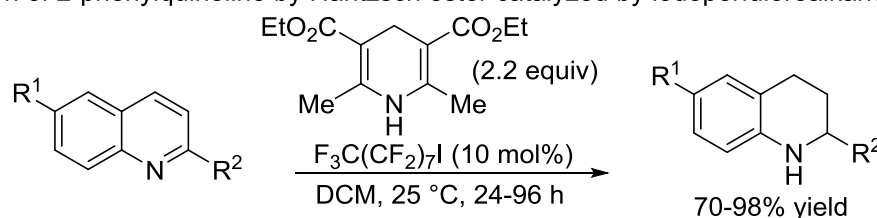
The first example of a catalytic process involving halogen bonding was reported by Bölm *et al.* in 2008. They demonstrated that iodoperfluoroalkanes catalyze the reduction of 2-phenylquinoline by Hantzsch ester (Scheme 69a).^[107] Those iodoperfluoroalkanes were also used in association with Lewis bases such as DABCO to promote the Morita-Baylis-Hillman reaction (Scheme 69b).^[108] In 2009, Bew and co-workers assumed that the fluoronium ion N-fluoropyridinium triflate acts as an organocatalyst for the preparation of aziridines from arylimines and ethyldiazoacetate (Scheme 69c).^[109]

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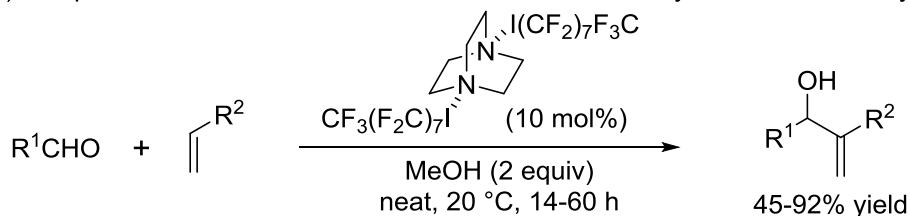
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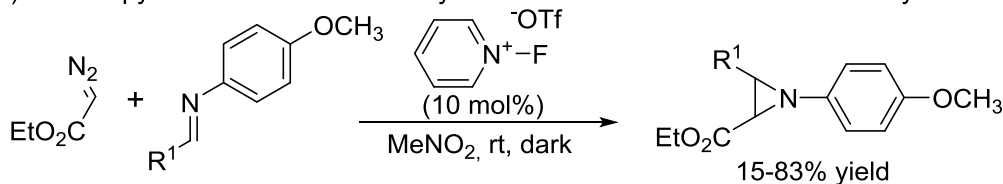
a) Reduction of 2-phenylquinoline by Hantzsch ester catalyzed by iodoperfluoroalkanes:



b) Iodoperfluoroalkanes in combination with DABCO catalyzed the Morita-Baylis-Hillman reaction:



c) N-fluoropyridinium triflate salt catalyzed the formation of aziridines from arylimines:



Scheme 69. Examples of reaction involving a catalytic amount of halogen bonding donors.

In 2011, by analogy with thioureas organocatalysts, Huber *et al.* designed a bidentate halogen bond donor. Their bis(iodoimidazolium) salts could activate the C-Br bond of benzhydryl bromide by halogen bonding to promote a Ritter-type reaction in a stoichiometric manner (Scheme 70a).^[110] Two year later, they reported that a class of neutral multidentate halogen bond donors can catalyze the reaction of 1-chloroisochroman with ketene silyl acetals (Scheme 70b).^[111] In 2014, the first catalytic application of cationic multidentate halogen bond donor was also reported by Huber *et al.* The bis(iodobenzimidazolium) salts showed high efficiency to catalyze a Diels-Alder reaction (Scheme 70c)^[112] or the Povarov reaction (Scheme 70d).^[113] To our knowledge, no reaction of halogen abstraction, using a simple and commercially available catalyst such as NIS as we did in Chapter IV has reported so far.

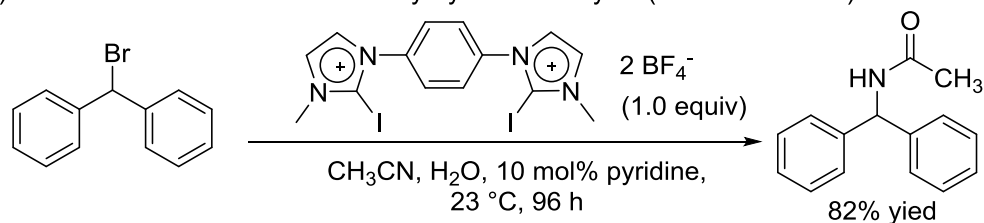
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[111] F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2013**, *52*, 7028-7032.

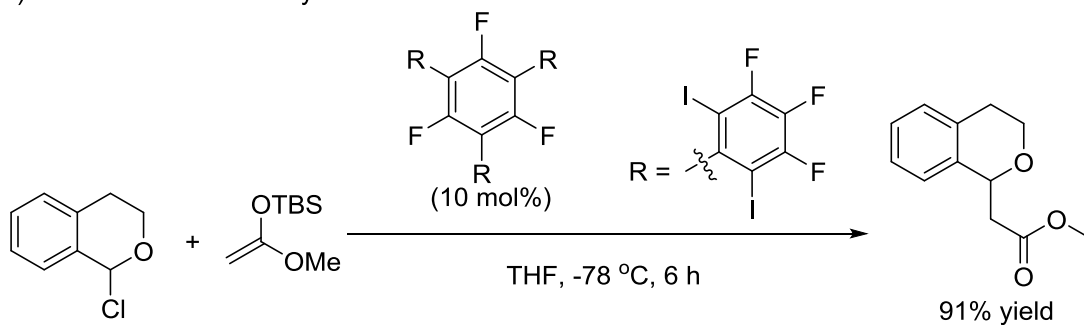
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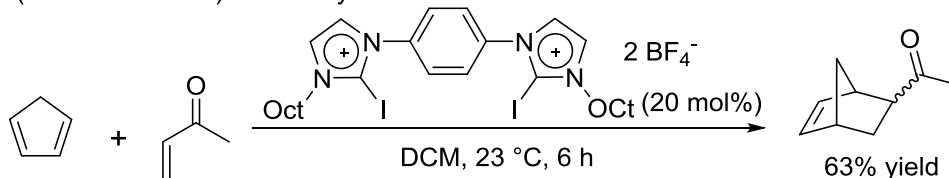
a) Stoichiometric activation of benzhydryl bromide by bis(iodoimidazolium) salt:



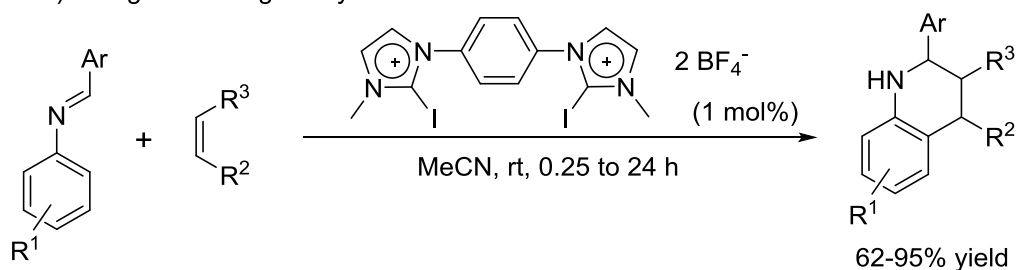
b) Neutral tridentate catalyst for the formation of C-C bond:



c) bis(iodoimidazolium) salt catalyzed the Diels-Alder reaction:



d) Halogen bonding catalyzed Povarov reaction:



Scheme 70. Examples of reaction promoted by multidentate halogen bonding organocatalysts.

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Chapter II

Exploring the Limits of π -Acid Catalysis Using Strongly Electrophilic Zinc Complexes

Chapter II. Exploring the Limits of π -Acid Catalysis Using Strongly Electrophilic Zinc Complexes

II.1. Introduction

π -Acid catalysis, that is, the electrophilic activation of C-C π bonds with a Lewis acid,^[1] is a powerful way to transform alkyne, alkene or allene derivatives into valuable building blocks. Gold and platinum complexes have been the most versatile π -acids used so far.^[2] Other elements such as gallium and indium are also well-known in this field.^[3] In fact, not all π -activators behave the same way. Whereas a simple proton can promote the addition of water to alkynes through a vinyl cation intermediate, what makes gold, platinum, gallium and indium complexes rather unique is their capacity to mediate the addition of a C-C π bond to another C-C π bond through a nonclassical carbocation.^[2, 4] The cycloisomerization of enynes is a prototypical example of such a reactivity (Scheme 1,

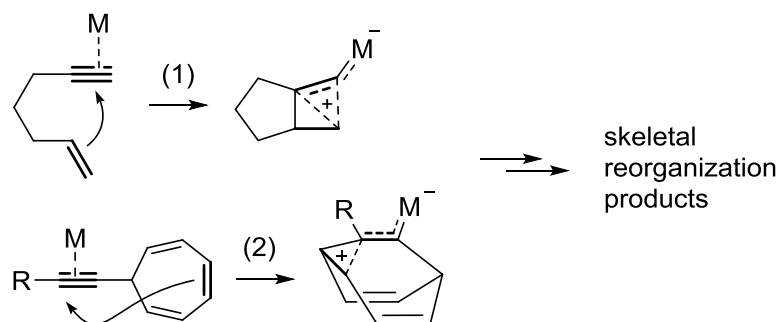
[1] (a) Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817; (b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.

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[3] (a) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294-10295; (b) Y. Miyanahana, N. Chatani, *Org. Lett.* **2006**, *8*, 2155-2158; (c) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315; (d) H.-J. Li, R. Guillot, V. Gandon, *J. Org. Chem.* **2010**, *75*, 8435-8449; (e) S. Tang, J. Monot, A. El-Hellani, B. Michelet, R. Guillot, C. Bour, V. Gandon, *Chem. Eur. J.* **2012**, *18*, 10239-10243; (f) K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2014**, *136*, 10918-10920; (g) C. Bour, V. Gandon, *Coord. Chem. Rev.* **2014**, *279*, 43-57; (h) C. Bour, V. Gandon, *Synlett* **2015**, *26*, 1427-1436; (i) B. Michelet, G. Thiery, C. Bour, V. Gandon, *J. Org. Chem.* **2015**, *80*, 10925-10938; (j) B. Michelet, S. Tang, G. Thiery, J. Monot, H. Li, R. Guillot, C. Bour, V. Gandon, *V. Org. Chem. Front.* **2016**, *3*, 1603-1613; (k) J. Pérez Sestelo, L. A. Sarandeses, M. Montserrat Martínez, L. Alonso-Marañón, *Org. Biomol. Chem.* **2018**, *16*, 5733-5747.

[4] (a) R. Dorel, A. M. Echavarren, *J. Org. Chem.* **2015**, *80*, 7321-7332; (b) Y. Wang, M. E. Muratore, A. M. Echavarren, *Chem. Eur. J.* **2015**, *21*, 7332-7339.

reaction 1).^[2a, 3c] The classification of Lewis acids between the softest ones, which will be good for mediating enyne cycloisomerizations, and harder ones, which will be more potent for C-C π bond functionalization through classical carbocations, can be easily made by using the cycloheptatriene test that we developed.^[5] As described by Echavarren *et al.*, 7-alkynylcycloheptatrienes are treated like enynes by gold(I) complexes (Scheme 1, reaction 2).^[6]



Scheme 1. Nonclassical carbocation intermediates in π -acid-catalyzed transformations of enynes.

Likewise, we reported that the reaction of compound **1** with catalysts of the gold, platinum, mercury, gallium and indium series leads to its skeletal reorganization into the regioisomeric indenenes **2** and **3** in 1,2-dichloroethane (DCE) or toluene (Scheme 2).^[5] With harder Lewis acids of the silver, gallium, copper, and calcium series, or even a Brønsted acid such as HOTf, the bicyclic product **4** is obtained. This occurs through the rearrangement of the 7-alkynylcycloheptatriene moiety into a phenylallene,^[7] which undergoes a rapid hydroarylation by the pendant phenyl group. In DCE, a solvent that can give rise to superacids, such as HSbF_6 , in the presence of AgSbF_6 or SbF_5 ,^[8, 9] or by using HNTf_2 , the conversion of **4** into the tricyclic compound **5** is observed with time, which

[5] M. Vayer, R. Guillot, C. Bour, V. Gandon, *Chem. Eur. J.* **2017**, *23*, 13901-13905.

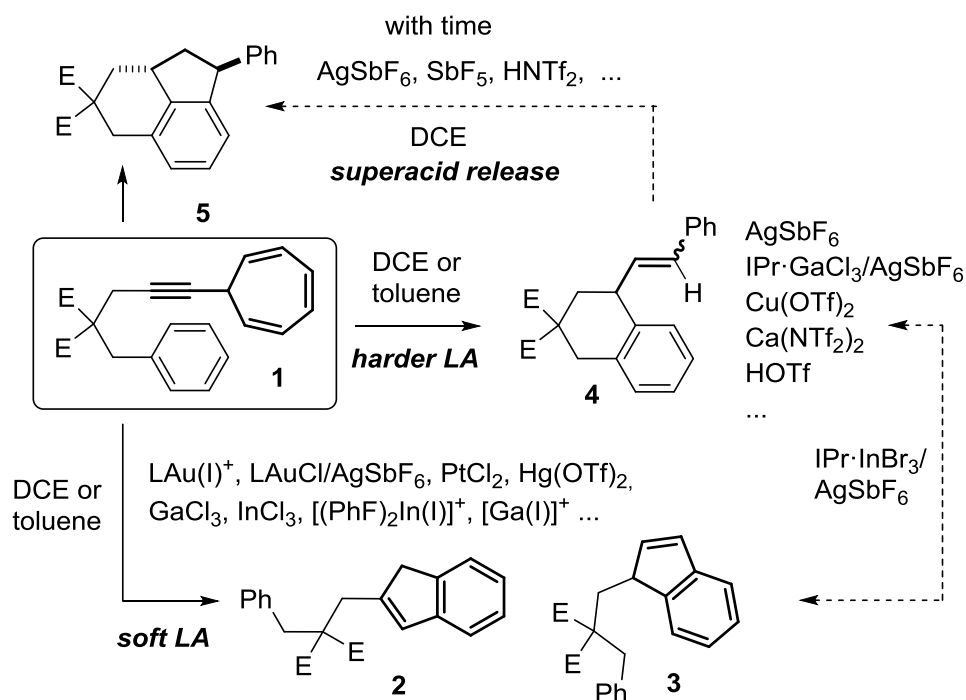
[6] (a) P. R. McGonigal, C. de León, Y. Wang, A. Homs, C. R. Solorio-Alvarado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2012**, *51*, 13093-13096; (b) S. Ferrer, A. M. Echavarren, *Organometallics* **2018**, *37*, 781-786; (c) M. Mato, C. García-Morales, A. M. Echavarren, *ChemCatChem* **2019**, *11*, 53-72.

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[8] C. Bour, R. Guillot, V. Gandon, *Chem. Eur. J.* **2015**, *21*, 6066-6069.

[9] For the formation of HOTf from AgOTf in DCE, see: T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353-9361.

corresponds to the hydroarylation of the styrene moiety through a benzylic carbocation.^[5]



Scheme 2. Isomerization pathways of the 7-alkynylcycloheptatriene compound 1 (E = CO_2Me ; LA = Lewis Acid; DCE = 1,2-dichloroethane).

One interest of this test is to identify new soft π -acids, as we did in the gallium(I) and indium(I) series.^[5, 10] Another interest is to show the efficiency of an anion exchange. Indeed, since silver salts such as AgSbF_6 , which is a widely used halide abstractor, gives a different result than the softest Lewis acids (**4** vs **2/3**), this test allows to validate the formation of the desired cationic species (such as $\text{IPr}\cdot\text{InBr}_2^+$ from $\text{IPr}\cdot\text{InBr}_3$ and AgSbF_6). Lastly, this test informs if the catalytic conditions release protons (**5**).

In this study, we have used the cycloheptatriene test and other reactions to analyze the catalytic behavior of other complexes of the main group metal series. We were especially interested in broadening the scope of application of π -acid catalysis to inexpensive metals, such as zinc. Regarding zinc, only simple salts of type ZnX_2 have been used so far as π -acids.^[11] We have studied the case of the N-heterocyclic carbene NHC-stabilized zinc(II)

[10] Z. Li, G. Thiery, M. Lichtenthaler, R. Guillot, I. Krossing, V. Gandon, C. Bour, *Adv. Synth. Catal.* **2018**, *360*, 544-549.

[11] For selected examples, see: (a) M.-Y. Lin, A. Das, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*,

species $[\text{IPr}\cdot\text{Zn}(\text{C}_6\text{F}_5)]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ (Table 1, **B**) and $\text{IPr}\cdot\text{ZnBr}_2(\text{THF})$ (Table 1, **C**). Synthesized by some of us,^[12] the aryl-zinc complex **B** has a higher fluoride ion affinity (FIA) than $\text{B}(\text{C}_6\text{F}_5)_3$ and efficiently catalyzes alkene, alkyne and CO_2 hydrosilylation. Complex **C** has thus far not been reported but the related $\text{IMes}\cdot\text{ZnCl}_2(\text{THF})$ is known,^[13] the $\text{SIPr}/\text{ZnBr}_2$ catalytic mixture has been used for the cycloaddition of CO_2 to epoxides,^[14] and $\text{IPr}\cdot\text{ZnCl}_2$ has been employed to catalyze the reductive amination of CO_2 .^[15] The new complex **C** was characterized by X-ray diffraction analyses.^[16]

II.2. Results and Discussion

As mentioned above, 7-alkynylcycloheptatrienes rearrange into indenenes under gold catalysis.^[6a] So did compound **1**^[5] when treated for instance by the cationic gold complex **A** (Table 1, 3 mol%), displaying a IPr NHC ligand, in DCE at 80°C for 20 h (entry 1). A 58 / 42 mixture of indenenes **2** and **3** has been isolated in 72% overall yield. The cationic IPr-stabilized aryl zinc complex **B** was then tested (entry 2). To our delight, under similar conditions, indene **2** was isolated as a sole product in 88% yield. The same result was obtained in toluene (entry 3). A better yield of 92% was reached when using 10 mol % of catalyst (entry 4). The IPr substituted zinc bromide complex **C** proved unreactive (entry 5). However, a catalytic mixture of **C** and AgSbF_6 (10 mol % each), provided a 93 / 7 mixture of

9340-9341; (b) R. Vicente, J. González, L. Riesgo, J. González, L. A. López, *Angew. Chem. Int. Ed.* **2012**, *51*, 8063-8067; (c) J. González, L. A. López, R. Vicente, *Chem. Commun.* **2014**, *50*, 8536-8538; (d) M. J. González, L. A. López, R. Vicente, *Tetrahedron Lett.* **2015**, *56*, 1600-1608; (e) B. Wang, Y. Chen, L. Zhou, J. Wang, C.-H. Tung, Z. Xu, *J. Org. Chem.* **2015**, *80*, 12718-12724; (f) L. Li, B. Zhou, Y.-H. Wang, C. Shu, Y.-F. Pan, X. Lu, L.-W. Ye, *Angew. Chem. Int. Ed.* **2015**, *54*, 8245-8249; (g) B. Wang, Y. Chen, L. Zhou, J. Wang, Z. Xu, *Org. Biomol. Chem.* **2016**, *14*, 826-829; (h) S. Yorimoto, A. Tsubouchi, H. Mizoguchi, H. Oikawa, Y. Tsunekawa, T. Ichino, S. Maeda, H. Oguri, *Chem. Sci.*, **2019**, *10*, 5686-5698.

[12] D. Specklin, F. Hild, C. Fliedel, C. Gourlaouen, L. F. Veiros, S. Dagorne, *Chem. Eur. J.* **2017**, *23*, 15908-15912.

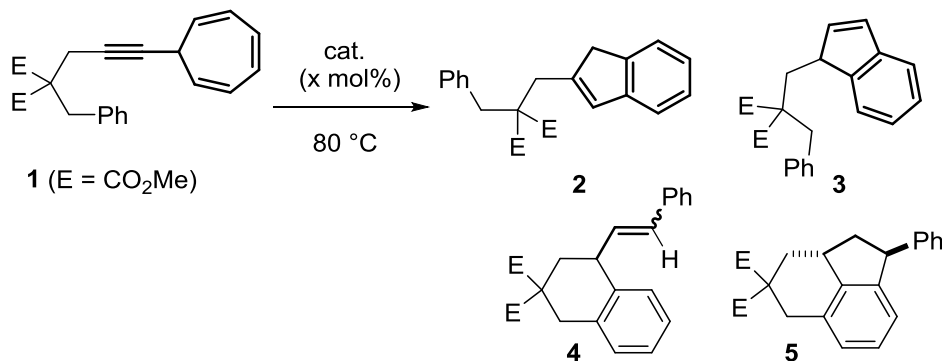
[13] Adapted from (a) D. Wang, K. Wurst, M. R. Buchmeiser, *J. Organometal. Chem.* **2004**, *689*, 2123-2130; (b) A. Rit, A.-K. Wiegand, D. Mukherjee, T. P. Spaniol, J. Okuda, *Eur. J. Inorg. Chem.* **2018**, 1114-1119.

[14] X Liu, C. Cao, Y. Li, P. Guan, L. Yang, Y. Shi, *Synlett* **2012**, *23*, 1343-1348.

[15] O. Jacquet, X. Frogneux, C. Das Neves Gomes, T. Cantat, *Chem. Sci.* **2013**, *4*, 2127.

[16] CCDC 1977549-1977550 contains the supplementary crystallographic data for this paper.

2 and **3**, isolated in 62 % yield (entry 6). This is clearly not AgSbF_6 that is responsible for this reaction since when used alone, AgSbF_6 leads to a different product type (Scheme 2, compound **4**).^[5]



Entry	cat.	x	Solvent	Time [h]	2/3/4/5	Yield [%] ^[a]
1	A	3	DCE	20	58/42/0/0	72
2	B	3	DCE	24	100/0/0/0	88
3	B	3	toluene	24	100/0/0/0	89
4	B	10	DCE	24	100/0/0/0	92
5	C	10	DCE	24	-	_[b]
6	C/AgSbF₆	10/10	DCE	24	93/7/0/0	62
7	C/AgSbF₆	10/10	toluene	24	-	_[c]
8	ZnCl_2	10	DCE	24	-	_[b]
9	ZnBr_2	10	DCE	24	86/14/0/0	33
10	ZnBr_2	10	toluene	24	-	_[c]
11	ZnI_2	10	DCE	24	83/17/0/0	34
12	ZnI_2	10	toluene	24	-	_[c]
13	$\text{Zn}(\text{OTf})_2$	10	DCE	24	-	_[d]
14	$\text{ZnBr}_2/\text{AgSbF}_6$	10/10	DCE	24	0/0/100 ^[e] /0	49

[a] Isolated. [b] No reaction. [c] Very low conversion, trace of indene product detected. [d] Phenylallene observed, 20% yield. [e] 1:1 *E/Z* mixture. Structure of corresponding catalysts:

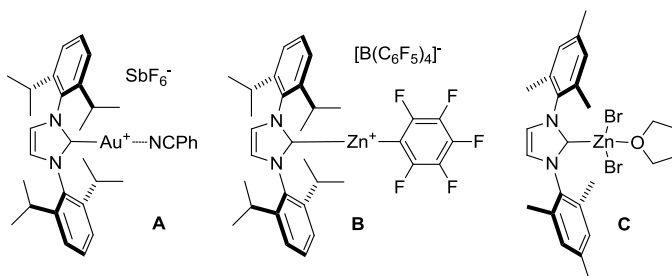
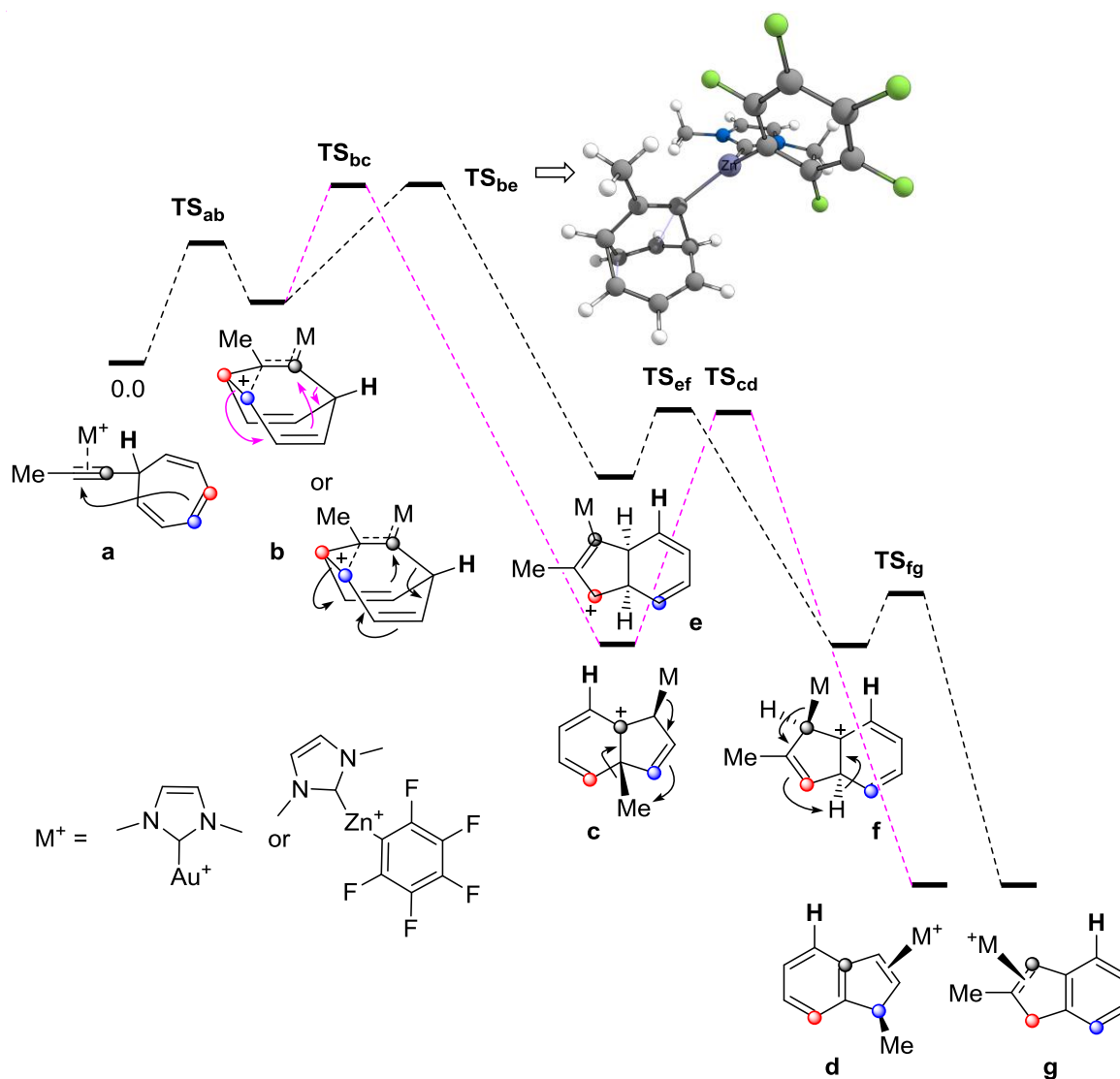


Table 1. Skeletal reorganization of **1**.

Even though it could not be isolated, this clearly supports the formation of $[\text{IPr}\cdot\text{ZnBr}]^+[\text{SbF}_6]^-$ as active species. The same transformation could not be carried out in toluene (entry 7). Nevertheless, the involvement of protons cannot be invoked in DCE since neither **4** nor **5** were detected. Importantly, these NHC-stabilized species **B** and **C** proved much more efficient than the simple zinc salts ZnCl_2 , ZnBr_2 , ZnI_2 and $\text{Zn}(\text{OTf})_2$ (entries 8–13), with which low yields and regioselectivities were at best obtained with ZnBr_2 or ZnI_2 in DCE (entries 9 and 11). It is also worthy of note that the activation of ZnBr_2 as one of these zinc salts with AgSbF_6 was not efficient, as it led to compound **4** (entry 14), that is, the same as the one obtained in our previous study with AgSbF_6 alone.^[6a]

In contrast with the other reactions studied herein, the skeletal reorganization of 7-alkynylcycloheptatrienes did not receive a detailed computational treatment. Thus, the mechanism of the indene formation promoted by the model gold and zinc NHC fragments shown in Scheme 3 was computed at the BP86/def2-QZVP(Au)-6-311+G(2d,p)(otheratoms)//BP86/LANL2DZ(Au,Zn)-6-31G(d,p)(other atoms). The 7-alkynylcycloheptatriene complex **a** was used as starting compound. Based on these calculations, the formation of the indene scaffold of complex **g**, corresponding to **2** in Table 1, can be explained as follows: the binding of the metal fragment to the triple bond triggers the nucleophilic attack of the middle double bond of the 1,3,5-triene fragment to give the cyclopropylcarbenoid **b**. The latter rearranges into the bicyclic allyl cation **e**. A 1,2-H shift transforms **e** into the Wheland-type complex **f**. A 1,2-proton shift finally gives rise to the indene complex **g**. For the formation of the other indene complex **d**, corresponding to product **3** in Table 1, the deciphered mechanism involves the rearrangement of **b** into the diallyl cation **c**, which undergoes a 1,2-methyl shift to give **d** (pink pathway).



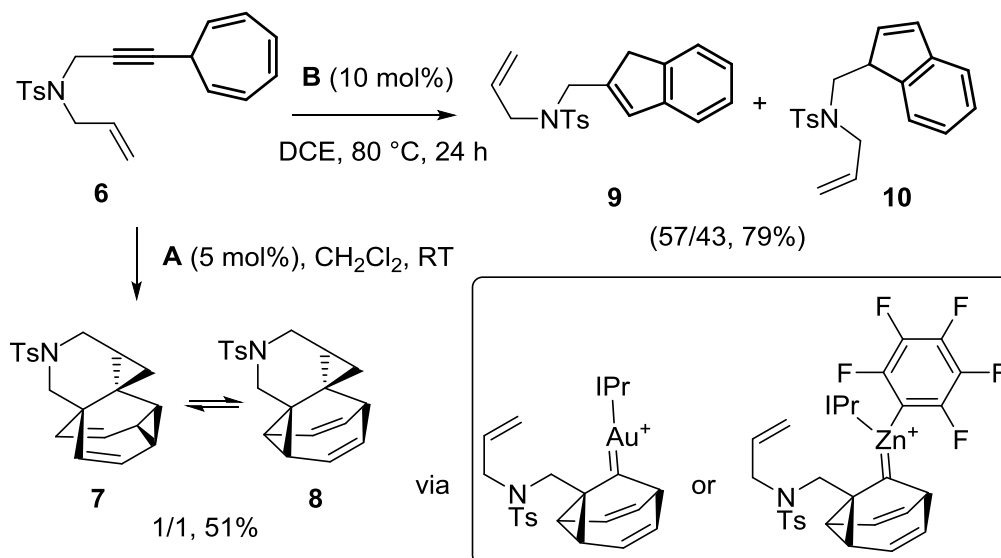
Scheme 3. Calculated intermediates and transition states for the formation of indenenes from a 7-alkynylcycloheptatriene complex.

The computed free energies corresponding to Scheme 3 are collected in Table 2. While the free energies of activation all seem reasonable, there is no kinetic preference for one indene or the other in the gold series since TS_{bc} and TS_{be} lie virtually at the same value (14.0 and 14.3 kcal mol⁻¹, respectively). Thus, a low selectivity is expected between the regioisomers, which is indeed the case between **2** and **3** when catalyst **A** is used (Table 1, entry 1). On the other hand, in the zinc series, the values are markedly different: 18.1 kcal mol⁻¹ for TS_{bc} and 14.7 kcal mol⁻¹ for TS_{be} . A high regioselectivity in favor of the indene displaying the alkyl group at the β position of the phenyl ring is therefore expected, which is corroborated by the selective formation of **2** (Table 1, entry 2).

Entry	Computed structure	Au series	Zn series
1	TS_{ab}	11.8	10.6
2	b	3.1	7.1
3	TS_{bc}	14.0	18.1
4	c	-19.6	-25.4
5	TS_{cd}	0.8	-23.6
6	d	-55.4	-60.3
7	TS_{be}	14.3	14.7
8	e	-10.3	-4.9
9	TS_{ef}	1.2	5.9
10	f	-28.8	-34.8
11	TS_{fg}	-23.1	-29.6
12	g	-59.6	-64.1

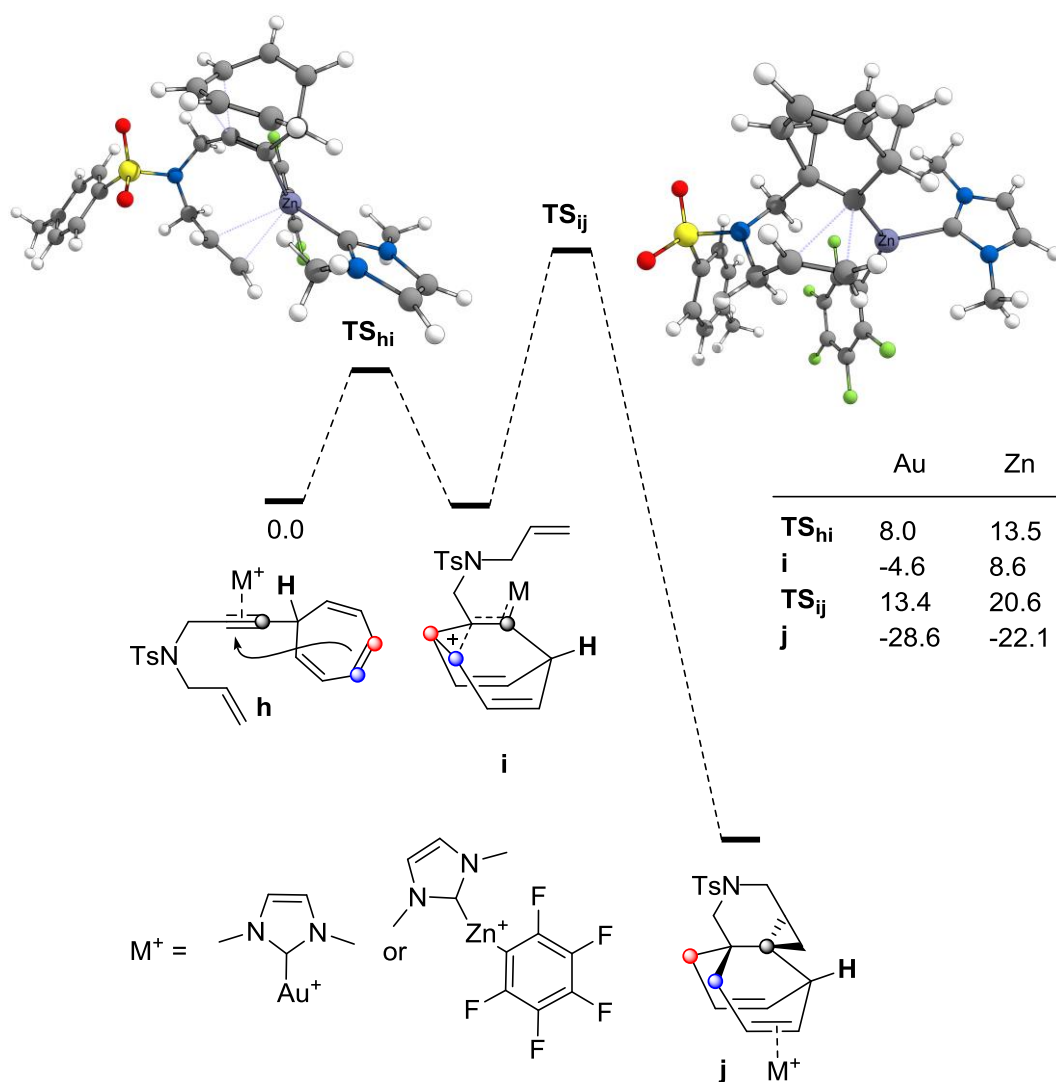
Table 2. Computed free energies (ΔG_{298} , kcal/mol) relatively to **a**.

Although the same kind of carbenoid intermediates are expected in the gold and zinc series, the zinc-derived ones seem less reactive towards double bonds. Echavarren *et al.* reported that compound **6** transforms into tautomeric barbaralanes **7** and **8** when treated with the gold catalyst **A** (Scheme 4). They interconvert rapidly through a strain-assisted Cope rearrangement.^[6a] They likely arise from the trapping of the putative barbaralyl gold carbene. Using **B**, the cyclopropanation was not observed, although the same barbaralyl carbene explains the formation of the indene isomers.



Scheme 4. Cycloisomerization of **6**.

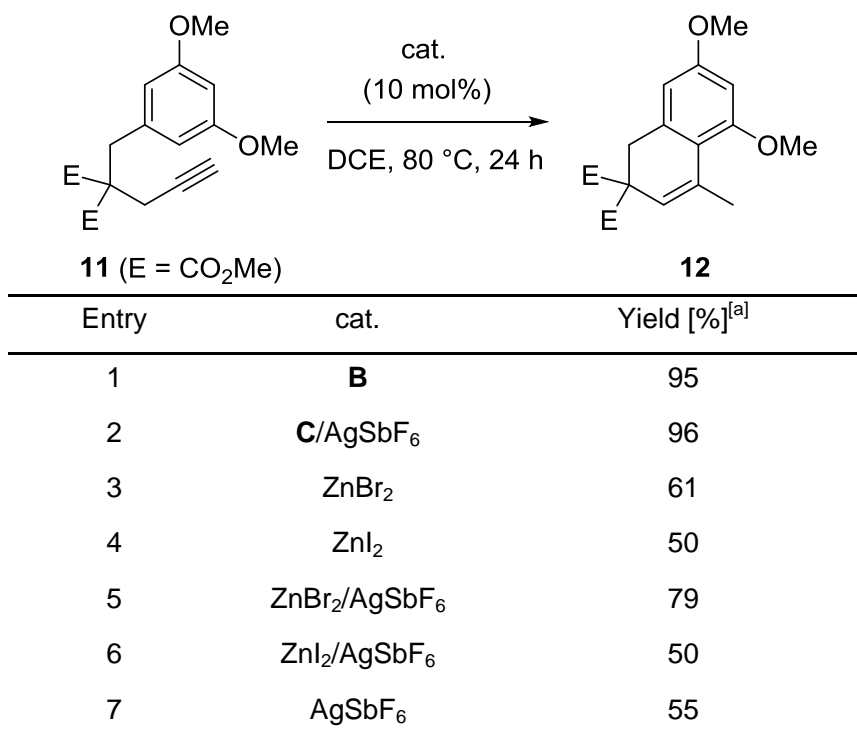
This lack of reactivity could be due to the trigonal geometry around zinc (vs. linear for gold), which brings the bulky NHC and the C_6F_5 ligands closer to the carbene center. To validate this hypothesis, DFT computations were performed by Prof. V. Gandon at the aforementioned level of theory (Scheme 5). The formation of the polycyclic scaffold of compounds **7** and **8** shown in Scheme 4 involves two main steps: formation of the cyclopropylcarbenoid **i** and the electrophilic cyclopropanation at the carbene center to give **j**. While the first step is exergonic with gold, it remains, as found before, endergonic but attainable with zinc. There is yet a major difference between gold and zinc in the cyclopropanation step, the corresponding transition states lying at $13.4 \text{ kcal mol}^{-1}$ and $20.6 \text{ kcal mol}^{-1}$, respectively.



Scheme 5. Calculated key intermediates and transition states for the cycloisomerization of compound **6** (ΔG_{298} , kcal/mol).

We attribute this difference to the higher steric crowd around the zinc carbene center due to the trigonal geometry around the metal, vs. a linear geometry with gold, which will place the bulky NHC further away from the incoming double bond.

Although the hydroarylation pathway to **4** (Scheme 2) was not observed with compound **1** under zinc catalysis (except Table 1, entry 14), such a reaction was independently tested using arenynes **11** (Table 3). This compounds was previously shown to undergo metal-catalyzed hydroarylation with PtCl_2 , $[\text{RuCl}_2(\text{CO})_n\text{L}_m]_2$, $[\text{RuCl}_2(\text{CO})_n\text{L}_m]_2/\text{AgOTf}$ and GaCl_3 .^[17] The reaction was very efficient with zinc, especially with the NHC-stabilized species (entries 1 and 2). Adding AgSbF_6 (1/1 mol% ratio) could enhance the activity of ZnBr_2 (entries 3 vs. 5), but not that of ZnI_2 (entries 4 vs. 6).



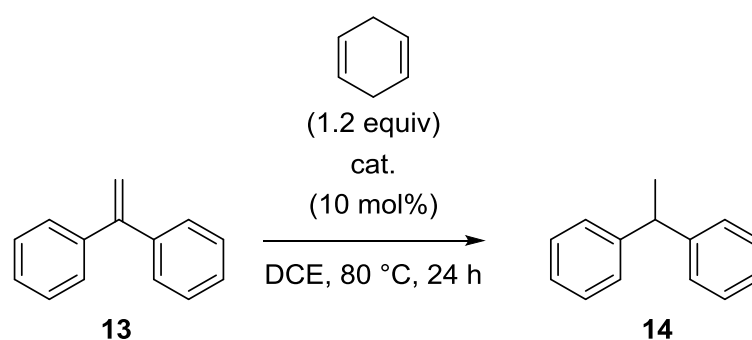
[a] Isolated.

Table 3. Hydroarylation of **11**.

The transfer hydrogenation of alkenes using 1,4-cyclohexadiene derivatives as H₂ surrogate

[17] a) N. Chatani, H. Inoue, T. Ikeda, S. Murai, *J. Org. Chem.* **2000**, *65*, 4913-4918; b) H. Inoue, N. Chatani, S. Murai, *J. Org. Chem.* **2002**, *67*, 1414-1417; c) L. V. Graux, M. Giorgi, G. Buono, H. Clavier, *Organometallics* **2015**, *34*, 1864-1871.

is a very convenient process that can be catalyzed by gallium^[18] or boron complexes.^[19] The use of zinc in this field seems to be undocumented.^[20] The reduction of compound **13** (Table 4) was previously studied with the NHC-gallium complex $[\text{IPr-GaCl}_2]^+[\text{SbF}_6]^-$, leading to the reduced product **14** in 67% yield.^[18] Here, also we observed an increased efficiency with the zinc catalyst **B**, which provided **14** in 80% yield (entry 1). Catalyst **C**, ZnBr_2 and ZnI_2 with AgSbF_6 worked, but the yields did not exceed 68% (entries 2, 5, and 6). It is striking to note that no reaction took place with ZnBr_2 or ZnI_2 alone (entries 3 and 4). The NHC-zinc complexes also proved much more potent than the corresponding gold complex (entry 7).



Entry	cat.	Yield [%] ^[a]
1	B	80
2	C / AgSbF_6	63
3	ZnBr_2	_[b,c]
4	ZnI_2	_[b,c]
5	$\text{ZnBr}_2/\text{AgSbF}_6$	64
6	$\text{ZnI}_2/\text{AgSbF}_6$	68
7	$\text{IPrAu}/\text{AgSbF}_6$	_[b,c]

[a] Isolated. [b] No reaction. [c] 20 mol% each.

Table 4. Transfer hydrogenation of **13**.

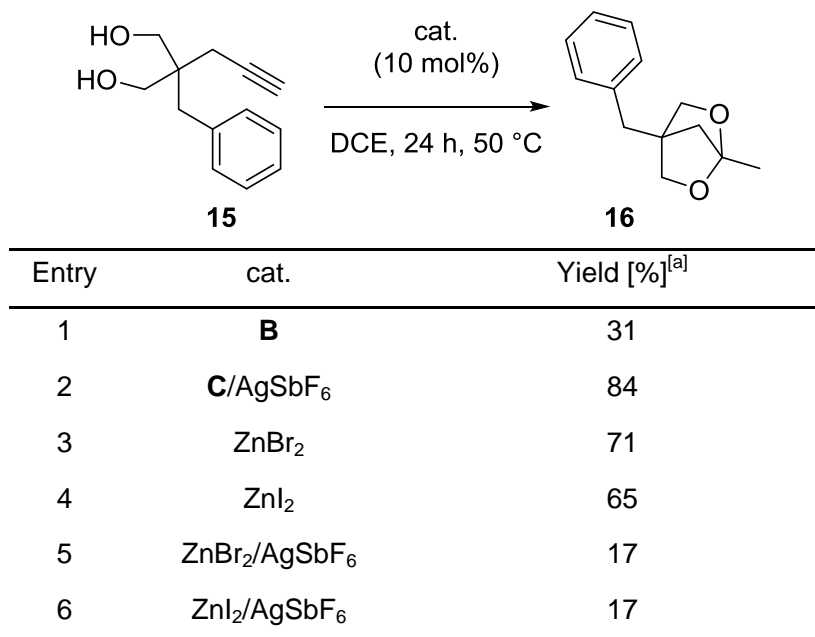
We next turned our attention to the formation of C-O bonds. Compound **15** is an interesting substrate for the evaluation of π -acids (Table 5). As shown by Michelet, Genet et al., with AuCl or AuCl_3 as catalysts, the two alcohol functionalities react with the alkyne

[18] B. Michelet, C. Bour, V. Gandon, *Chem. Eur. J.* **2014**, *20*, 14488-14492.

[19] I. Chatterjee, Z.-W. Qu, S. Grimme, M. Oestreich, *Angew. Chem. Int. Ed.* **2015**, *54*, 12158-12162.

[20] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621-6686.

moiety to furnish the bicyclic ketal **16**.^[21] A distinct behavior was reported by us when GaCl_3 was used as catalyst, as only one hydroalkoxylation took place, giving rise to a cyclic enol.^[3d] With the zinc species, similarly to gold, only product **16** was observed. It is complex **C** and AgSbF_6 that gave the best result (84% yield, entry 2). ZnBr_2 and ZnI_2 were rather deactivated this time by the presence of the silver additive (entries 3/4 vs. 5/6). These hydroalkoxylation could well be catalyzed by an unsuspected Brønsted acid, but as mentioned above, the cycloheptatriene test has not detected the release of protons. Accordingly, it is important to note that the use of 2.2 equiv of 2,6-di-*tert*-butylpyridine had no effect on the reaction outcome. It is again, for entry 2, likely that $[\text{IPr}\cdot\text{ZnBr}]^+[\text{SbF}_6]^-$ is the active species. We can also infer that the OH groups in **15** can be acidic enough to promote the cleavage of the Zn-C bond in **B**, yielding a less reactive zinc alkoxide, hence the low yield in entry 1. In that respect, the zinc species used in this study do not tolerate the presence of water and therefore do not efficiently catalyze the hydration of *p*-methyl phenylacetylene, which is a major difference with gold catalysts.^[22]



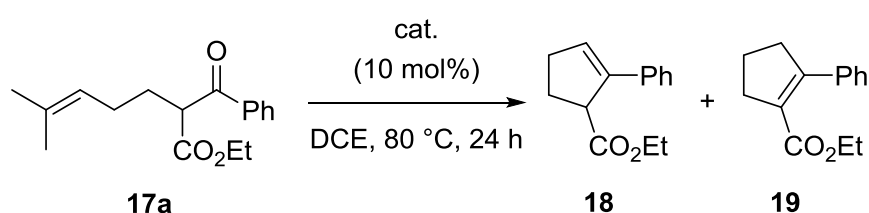
[a] Isolated.

Table 5. Hydroalkoxylation of **15**.

[21] S. Antoniotti, E. Genin, V. Michelet, J.-P. Genêt, *J. Am. Chem. Soc.* **2005**, *127*, 9976-9977.

[22] (a) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418; (b) G. A. Fernández, A. B. Chopra, G. F. Silbestri, *Catal. Sci. Technol.* **2016**, *6*, 1921-1929.

The preferred behavior of the zinc species as soft π -Lewis acids rather than hard σ -Lewis acids^[1a] was further confirmed using the β -ketoester **17a** (Table 6). It is known to undergo carbonyl-olefin metathesis by σ -Lewis acid activation of the carbonyl group.^[23] Schindler et al have shown that FeCl_3 ^[24] and GaCl_3 ^[25] are particularly efficient mediators of such transformations, including that of **17a**. However, catalysts **B**, **C**/ AgSbF_6 , ZnBr_2 and ZnI_2 proved unable to trigger the metathesis (entries 1–4). Only harder ZnX^+ ions formed by halide abstraction with AgSbF_6 provided the cyclic isomers **18** and **19** in good yields (entries 5 and 6).



Entry	cat.	18/19	Yield [%] ^[a]
1	B	-	_ ^[b]
2	C / AgSbF_6	-	_ ^[b]
3	ZnBr_2	-	_ ^[b]
4	ZnI_2	-	_ ^[b]
5	$\text{ZnBr}_2/\text{AgSbF}_6$	58/42	90
6	$\text{ZnI}_2/\text{AgSbF}_6$	82/18	84

[a] Isolated. [b] No reaction.

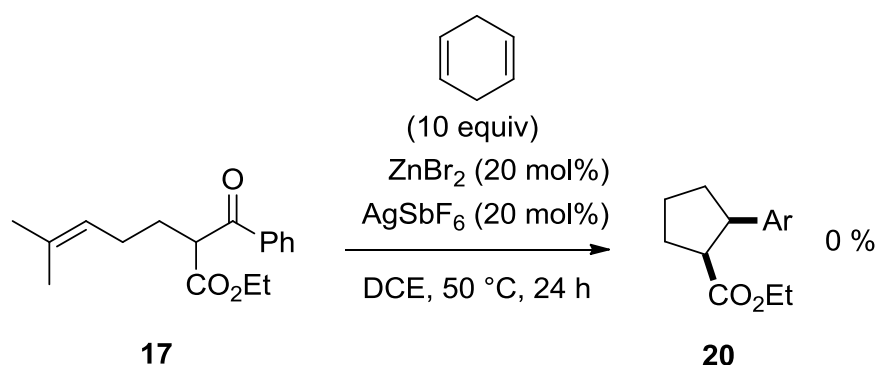
Table 6. Carbonyl-Olefin Metathesis of **17a**.

[23] L. Ravindar, R. Lekkala, K. P. Rakesh, A. M. Asiri, H. M. Marwani, H.-L. Qin, *Org. Chem. Front.* **2018**, *5*, 1381-1391.

[24] (a) J. R. Ludwig, P. M. Zimmerman, J. B. Gianino, C. S. Schindler, *Nature*, **2016**, *533*, 374-379; (b) L. Ma, W. Li, H. Xi, X. Bai, E. Ma, X. Yan, Z. Li, *Angew. Chem., Int. Ed.* **2016**, *55*, 10410-10413; (c) C. C. McAtee, P. S. Riehl, C. S. Schindler, *J. Am. Chem. Soc.* **2017**, *139*, 2960-2963; (d) J. R. Ludwig, S. Phan, C. C. McAtee, P. M. Zimmerman, J. J. Devery, C. S. Schindler, *J. Am. Chem. Soc.* **2017**, *139*, 10832-10842; (e) H. Albright, P. S. Riehl, C. C. McAtee, J. P. Reid, J. R. Ludwig, L. A. Karp, P. M. Zimmerman, M. S. Sigman, C. S. Schindler, *J. Am. Chem. Soc.* **2019**, *141*, 1690-1700.

[25] H. Albright, H. L. Vonesh, M. R. Becker, B. W. Alexander, J. R. Ludwig, R. A. Wiscons, C. S. Schindler, *Org. Lett.* **2018**, *20*, 4954-4958.

While the carbonyl-olefin metathesis discussed above is not related to π -acid catalysis, it leads to alkenes that can be activated by π -acids. The tandem carbonyl-olefin/transfer hydrogenation of **17** was thus attempted with 1,4-cyclohexadiene (1,4-CHD) as hydrogen donor (Scheme 6). This tandem process was recently reported by us using IPr-GaCl²⁺ ions as catalyst.^[26] In this reaction, **17** is first transformed into cyclopentenenes (such as **18/19**), which then undergo transfer hydrogenation to cyclopentanes **20**. Thus, σ -activation of the carbonyl is required in the first step, and then a π -activation of the C=C bond is required in the second one. While zinc remained inefficient in this tandem reaction.



Scheme 6. Hydrogenative Carbonyl-ene metathesis of **17**.

II.3. Conclusions

Starting from the cycloheptatrienyl test, we have revealed that cationic NHC-Zn^{II} complexes can be exquisite π -acids in various reactions such as skeletal rearrangements, hydroarylations, hydroalkoxylations and transfer hydrogenations. They can even compete with NHC-Au^I or NHC-Ga^{III} catalysts sometimes, although this study has delineated some of their limitations compared to gold and gallium species. This work also shows that NHC-stabilized zinc ions are more active than simple zinc halides.

II.4. Experimental Section

General Considerations. Unless otherwise stated, commercially available reagents were used as received. [(IPr)Au(NCMe)]SbF₆ (**A**) was obtained from Aldrich. Solvents were

[26] For gallium-catalyzed tandem carbonyl-olefin metathesis/transfer hydrogenation, see: A. Djurovic, M. Vayer, Z. Li, R. Guillot, J.-P. Baltaze, V. Gandon, C. Bour, *Org. Lett.* **2019**, *21*, 8132-8137.

purified by distillation under argon from the following: tetrahydrofuran (THF) and diethyl ether (Et_2O): sodium/benzophenone; toluene (tol): sodium; 1,2-dichloroethane (DCE): calcium hydride; and degassed by freeze-pump-thaw technique. Complex **B** was synthesized following a reported procedure.^[12] The following compounds were previously described: **1-5**,^[5] **6-8**,^[6a] **11-12**,^[17a] **13-14**,^[18] **15-16**,^[20] **17a-c**, **18-19** and **20a-c**.^[26] NMR spectra of the new precatalysts **C** and **D** are shown in the Supporting Information. ^1H and ^{13}C NMR spectra were recorded on Bruker 250, 300 and 360 MHz spectrometers at 20 °C. ^1H NMR chemical shifts are reported in ppm using residual solvent peak as reference (CHCl_3 : $\delta = 7.27$ ppm, CH_2Cl_2 : $\delta = 5.32$ ppm). Data for ^1H NMR are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant J (Hz) and integration; ^{13}C NMR spectra were recorded at 63, 75, 91 or 100 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference (CHCl_3 : $\delta = 77.16$ ppm, CH_2Cl_2 : $\delta = 53.84$ ppm). Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in cm^{-1} . Flash chromatography (FC) was performed with 40-63 μm silica gel with mixtures of ethyl acetate (EtOAc) and cyclohexane (Cy). Thin layer chromatography was carried out using Merck TLC Silica gel 60 F254 and visualized by short-wavelength ultraviolet light as well as by *p*-anisaldehyde stain.

Procedure for the Skeletal Rearrangement of Alkenylcycloheptatrienes **1 and **6**** (Table 1 and Scheme 4): under argon atmosphere, **1** or **6** (0.15 mmol, 1.0 equiv), the catalyst (3-20 mol%) and AgSbF_6 (0-20 mol%) were charged in a 10 mL tube equipped with a Teflon-coated magnetic stir bar. Distilled DCE or toluene (1.0 mL, 0.15 M) was added and the tube was sealed. The reaction tube was immersed and stirred in a preheated oil bath at 80 °C until completion. The reaction mixture was filtered through a pad of celite (thoroughly rinsed with Et_2O) and concentrated under reduced pressure. Purification by FC (Cy/EtOAc) afforded the corresponding product.

Procedure for the Hydroarylation of Arenyne **11** (Table 3): under argon atmosphere, arenyne **11** (0.20 mmol, 1.0 equiv), the catalyst (10 mol%) and AgSbF_6 (0 to 10 mol%) were charged in a 10 mL tube equipped with a Teflon-coated magnetic stir bar. Dry degassed 1,2-DCE (1.33 mL, 0.15 M) was added and the tube was sealed. The reaction tube was immersed and stirred in a preheated oil bath at 80 °C for 24 h. The reaction mixture was filtered through a pad of celite (thoroughly rinsed with Et_2O) and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (Cy/EtOAc).

Procedure for the Hydrogenation of Alkene **13** (Table 4): under argon atmosphere, alkene **13** (0.20 mmol, 1.0 equiv) was introduced into a 10 mL tube equipped with a Teflon-coated magnetic stir bar. The catalyst (10 mol%), AgSbF_6 (0 to 10 mol%) and then dry degassed 1,2-DCE (1.33 mL, 0.15 M) were added into the reaction vessel. The tube was capped with a rubber septum. 1,4-CHD (0.24 mmol, 23 μL , 1.2 equiv) was added through the septum with a Hamilton[®] syringe. The reaction tube was stirred for 24 h a preheated oil bath at 80 °C. The reaction mixture was filtered over a pad of celite, which was rinsed with Et_2O . Volatiles were removed by rotary evaporation under vacuum. The crude was purified by flash column chromatography on silica gel (Cy/EtOAc).

Procedure for the Hydroalkoxylation of Arenyne **15** (Table 5): under argon atmosphere, arenyne **15** (0.20 mmol, 1.0 equiv) was introduced into a 10 mL tube equipped with a Teflon-coated magnetic stir bar. The catalyst (10 mol%), AgSbF_6 (0 to 10 mol%) then dry degassed 1,2-DCE (1.33 mL, 0.15 M) were added into the reaction vessel and the tube was sealed. The reaction tube was immersed and stirred in a preheated oil bath at 50 °C for 24 h. The reaction mixture was filtered through a pad of celite (thoroughly rinsed with Et_2O) and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (Cy/EtOAc).

General Procedure for the Carbonyl-Olefin Metathesis of **17a** (Table 6): under argon atmosphere, **17a** (0.20 mmol, 1 equiv) was introduced into a 10 mL tube equipped with a Teflon-coated magnetic stir bar. The catalyst (10 mol%), AgSbF_6 (0 to 10 mol%) then dry

degassed 1,2-DCE (1.33 mL, 0.15 M) were added into the reaction vessel and the tube was sealed. The reaction tube was immersed and stirred in a preheated oil bath at 80 °C for 24 h. The reaction mixture was filtered through a pad of celite (thoroughly rinsed with Et₂O) and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (Cy/EtOAc).

General Procedure for the Hydrogenative Carbonyl-Olefin Metathesis of 17: under argon atmosphere, **17** (0.2 mmol, 1 equiv) was introduced into a 10 mL tube equipped with a Teflon-coated magnetic stir bar. The catalyst (20 mol%), AgSbF₆ (0 to 20 mol%) and then dry degassed 1,2-DCE (1 mL, 0.2 M) were added into the reaction vessel. The tube was capped with a rubber septum was added through the septum with a Hamilton® syringe. The resulting mixture was stirred for 24 h in a preheated oil bath at 50 °C, unless otherwise specified. The reaction mixture was diluted with Et₂O, filtered through a pad of celite (thoroughly rinsed with Et₂O) and concentrated under reduced pressure by rotary evaporation. Purification by FC over silica gel (Cy/EtOAc) afforded desired products **20a-c**. For **20a-c**, the *cis/trans* diastereomeric ratio was determined by ¹H NMR analysis of the crude reaction mixture.

X-Ray Analysis: X-ray diffraction data for compounds C and D were collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IuS source Cu K α radiation. Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of ± 1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97^[27] and refined against F₂ by full-matrix least-squares techniques using SHELXL-2018^[28] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map

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[28] G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, **2008**, *64*, 112-122.

and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.^[29] CCDC 1977549 (D) and 1977550 (C) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/Community/Requestastructure>.

Preparation of IPr·ZnBr₂(THF) (C): in a Schlenk flask placed in the glovebox, anhydrous ZnBr₂ (225.8 mg, 1.0 mmol) was dissolved in 15 mL of dry degassed THF. A solution of 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene (303.4 mg, 1.0 mmol) in 3 mL of THF was then slowly added. The mixture was stirred at rt for 12 h. The resulting solution was then concentrated to 5 mL. After the addition of 20 mL of pentane, a white solid precipitated, which was filtered off and washed three times with pentane and dried in vacuo for 2 h. Yield: 514 mg, 0.85 mmol (85%). Crystals suitable for X-ray diffraction analysis were obtained by recrystallization in CH₂Cl₂/hexane at -20 °C. ¹H NMR (300 MHz, CD₂Cl₂): δ 7.13 (s, 2H), 6.99 (s, 4H), 3.72-3.62 (m, 4H), 2.35 (s, 6H), 2.10 (s, 12H), 1.84-1.76 (m, 4H). ¹³C NMR (91 MHz, CD₂Cl₂): δ 140.2, 135.9, 134.4, 129.5, 123.9, 69.0, 25.6, 21.3, 18.1. FT-IR (neat, cm⁻¹): 3119, 2920, 1609, 1544, 1488. This complex appears in NMR as a 95:5 mixture of IPr·ZnBr₂(THF) and the corresponding dimer [IPr·ZnBr₂]₂.^[13b]

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Chapter III

A Cyclic Divalent N(I) Species Isoelectronic to Carbodiphosphoranes

Chapter III. A Cyclic Divalent N(I) Species Isoelectronic to Carbodiphosphoranes

III.1. Introduction

Rethinking organic compounds with donor-acceptor bonds instead of electron-sharing ones has allowed the identification of hitherto unrecognized low oxidation states of main group elements and the development of molecules with new properties.^[1] In 2006, Frenking et al reported theoretical evidence suggesting that carbodiphosphoranes $(R_3P)_2C$ are better described as divalent carbon(0) compounds of type $R_3P \rightarrow C(0) \leftarrow PR_3$ (Scheme 1, I), rather than C(IV) $R_3P=C=PR_3$ allene species (II).^[2,3] This rendition accounts for the bent structure of such molecules, known since 1961,^[4] and explains their ability to undergo double protonation or metalation at the central carbon, which actually carries two lone pairs of electrons. Shortly after, the carbodicarbenes $(NHC) \rightarrow C(0) \leftarrow (NHC)$ (III) were computationally predicted by Frenking et al^[5,6] and eventually synthesized by Bertrand and coworkers.^[7] This new paradigm has continuously stimulated developments in carbon(0) chemistry directed towards catalysis, coordination

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[5] R. Tonner and G. Frenking, *Angew. Chem. Int. Ed.*, 2007, **46**, 8695.

[6] (a) S. Klein, R. Tonner and G. Frenking, *Chem. Eur. J.*, 2010, **16**, 10160; (b) D. Martin, M. Melaimi, M. Soleilhavoup and G. Bertrand, *Organometallics*, 2011, **30**, 5304; (c) T.-H. Wang, W.-C. Chen and T.-G. Ong, *J. Chin. Chem. Soc.*, 2017, **64**, 124.

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chemistry, optoelectronics and material applications, etc.^[8] The $L \rightarrow E \leftarrow L$ donor-acceptor way of thinking molecules also led to the successful stabilization of other low oxidation main group elements such as Si(0), Ge(0), Sn(0), B(I), P(I) and N(I).^[9]

The story of divalent N(I) compounds with two lone pairs on nitrogen is similar to that of C(0) derivatives but in the other direction. In 2009, Patel and Bharatam provided computational evidence that guanidine-derived compounds are actually best described as $L \rightarrow N^{\oplus} \leftarrow L$ species (IV) that are isoelectronic to carbodicarbenes.^[10] Tamm pointed out that salts containing such cations were already described in 1968.^[11] A few more carbene-stabilized N(I) were synthesized^[12] and

[8] For selected recent examples: (a) W. Su, S. Pan, X. Sun, S. Wang, L. Zhao, G. Frenking and C. Zhu, *Nat. Comm.*, 2018, **9**, 4997; (b) M. Klein, X. Xie, O. Burghaus and J. Sundermeyer, *Organometallics*, 2019, **38**, 3768; (c) J. J. Cabrera-Trujillo and I. Fernández, *Inorg. Chem.*, 2019, **58**, 7828; (d) J. E. Walley, A. D. Obi, G. Breiner, G. Wang, D. A. Dickie, A. Molino, J. L. Dutton, D. J. D. Wilson and R. J. Gilliard Jr, *Inorg. Chem.*, 2019, **58**, 16, 11118; (e) J. S. Marcum, T. N. Cervarich, R. S. Manan, C. C. Roberts, S. J. Meek, *ACS Catal.*, 2019, **9**, 5881; (f) C. Pranckevicius, L. Liu, G. Bertrand and D. W. Stephan, *Angew. Chem. Int. Ed.*, 2016, **55**, 5536; (g) A. El-Hellani, J. Monot, S. Tang, R. Guillot, C. Bour and V. Gandon, *Inorg. Chem.*, 2013, **52**, 11493.

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[10] D. S. Patel and P. V. Bharatam, *Chem. Commun.*, 2009, 1064.

[11] (a) A. Doddi, M. Peters and M. Tamm, *Chem. Rev.*, 2019, **119**, 6994; (b) H. Quast and S. Hünig, *Liebigs Ann. Chem.*, 1968, **711**, 157.

[12] (a) R. A. Kunetskiy, I. Cisarova, D. Saman and I. M. Lyapkalo, *Chem. Eur. J.*, 2009, **15**, 9477; (b) H. Bruns, M. Patil, J. Carreras, A. Vázquez, W. Thiel, R. Goddard and M. Alcarazo, *Angew. Chem. Int. Ed.*, 2010, **49**, 3680; (c) Á. Kozma, G. Gopakumar, C. Farès, W. Thiel and M. Alcarazo, *Chem. Eur. J.*, 2013, **19**, 3542.

computationally linked^[13] to older species such as $N^+(N_2)_2$ ^[14] and $N^+(CO)_2$ ^[15] cations, as well as previously reported drugs.^[16] Reconceptualizing all these compounds as carbene-stabilized divalent N(I) species eventually raised the question of the existence of phosphane-stabilized NL_2^+ systems. Computations showed that $R_3P \rightarrow N(I)^+ \leftarrow PR_3$ compounds (R = Me, Ph) display bent geometries and have two lone pairs of electrons at the central nitrogen atoms (V).^[10,13] The corresponding salts have been found in the literature, such as $[X][N(PPh_3)_2]$ ^[17] (published in 1961 with X = Br, the same year as $C(PPh_3)_2$ ^[4]), $[X][N(P(NMe_2)_3)_2]$,^[18] and others that were characterized in the solid state.^[19]

[13] (a) D. S. Patel and P. V. Bharatam, *J. Phys. Chem. A*, 2011, **115**, 7645; (b) M. A. Celik, R. Sure, S. Klein, R. Kinjo, G. Bertrand and G. Frenking, *Chem. Eur. J.*, 2012, **18**, 5676.

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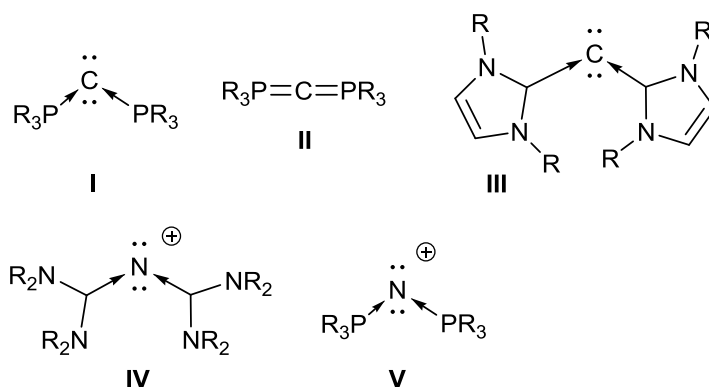
[15] I. Bernhardt, T. Drews and K. Seppelt, *Angew. Chem. Int. Ed.*, 1999, **38**, 2232.

[16] (a) D. Kathuria, M. Arfeen, A. A. Bankar and P. V. Bharatam, *J. Chem. Sci.*, 2016, **128**, 1607; (b) S. Bhatia, Y. J. Malkhede and P. V. Bharatam, *J. Comput. Chem.*, 2013, **34**, 1577; (c) P. V. Bharatam, M. Arfeen, N. Patel, P. Jain, S. Bhatia, A. K. Chakraborti, S. Khullar, V. Gupta and S. K. Mandal, *Chem. Eur. J.*, 2016, **22**, 1088.

[17] (a) R. Appel and A. Hauss, *Z. Anorg. Allgem. Chem.* 1961, **311**, 290; (b) J. K. Ruff and W. J. Schlientz, *Inorg. Synth.*, 1974, **15**, 84.

[18] (a) R. Link and R. Schwesinger, *Angew. Chem. Int. Ed.*, 1992, **31**, 850; (b) R. Schwesinger, R. Link., G. Thiele, H. Rotter, D. Honert, H.-H. Limbach and F. Mannle, *Angew. Chem. Int. Ed.*, 1991, **30**, 1372; (c) R. Schwesinger, R. Link, P. Wenzl, S. Kossek and M. Keller, *Chem. Eur. J.* 2006, **12**, 429; (d) R. Schwesinger, R. Link, P. Wenzl and S. Kossek, *Chem. Eur. J.*, 2006, **12**, 438.

[19] (a) D. W. H. Rankin, M. D. Walkinshaw and H. Schmidbaur, *J. Chem. Soc. Dalton Trans.*, 1982, 2317; (b) K. V. Katti, A. A. Pinkerton and R. G. Cavell, *Inorg. Chem.*, 1991, **30**, 2631; (c) A. Winkler, F. W. Heinemann, M. Moll and J. Ellermann, *Inorg. Chim. Acta*, 1999, **284**, 288; (d) J. Grebe, S. Schlecht, F. Weller, K. Harms, G. Geiseler and K. Dehnicke, *Z. Anorg. Allg. Chem.*, 1999, **625**, 633; (e) R. Bartsch, M. Freytag, S. Goller, R. G. Jones and R. Schmutzler, *Z. Naturforsch.*, 2001, **56b**, 1319; (f) M. Ganesan, P. E. Fanwick and R. A. Walton, *Inorg. Chim. Acta*, 2003, **346**, 181; (g) A. Hagenbach, S. Athenstädt, H. E. Daróczy, U. Abram and R. Alberto, *Z. Anorg. Allg. Chem.*, 2004, **630**, 2709; (h) J. F. Kögel, B. Oelkers, B. Kovačević and J. Sundermeyer, *J. Am. Chem. Soc.*, 2013, **135**, 17768; (i) J. F. Kögel, N.-J. Kneusels and J. Sundermeyer, *Chem. Commun.*, 2014, **50**, 4319.



Scheme 1. Representative structures of carbodiphosphoranes (**I**, **II**), carbodicarbenes (**III**) and divalent N(I) cations (**IV**, **V**).

The main difference between isoelectronic $L \rightarrow C \leftarrow L$ and $L \rightarrow N^{\oplus} \leftarrow L$ species is the much lower nucleophilicity of the latter due to the formal positive charge.^[12b] Their low nucleophilicity and also their base resistance explain the applicability of such cations, not in coordination chemistry in contrast to C(0) species,^[20] but in medicinal chemistry^[16] and as phase transfer organocatalysts for the carbodicarbenes analogues,^[21] and as spectator cations for the carbodiphosphorane analogues.^[12b]

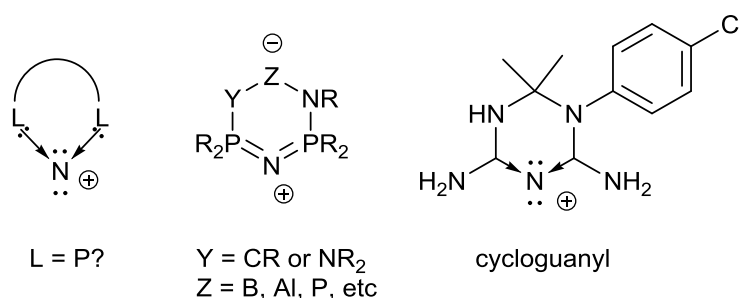
A few cyclic $[R_3P=N^{\oplus}=PR_3]$ systems have also been described, but as P(V)-N(III) species. They virtually all belong the 6-membered cyclophosphazene type (Scheme 2) and thus cannot be related to a bis-phosphane chelated N(I) species.^[22]

[20] M. Alcarazo, C. W. Lehmann, A. Anoop, W. Thiel and A. Fürstner, *Nat. Chem.*, 2009, **1**, 295.

[21] N. Patel, R. Sood and P. V. Bharatam, *Chem. Rev.* 2018, **118**, 8770.

[22] (a) D. P. Gates, R. Ziembinski, A. L. Rheingold, B. S. Haggerty and I. Manners, *Angew. Chem. Int. Ed.*, 1994, **33**, 2277; (b) D. P. Gates, L. M. Liable-Sands, G. Yap, A. L. Rheingold and I. Manners, *J. Am. Chem. Soc.*, 1997, **119**, 1125; (c) D. P. Gates, A. R. McWilliams, R. Ziembinski, L. M. Liable-Sands, I. A. Guzei, G. P. A. Yap, A. L. Rheingold and I. Manners, *Chem. Eur. J.*, 1998, **4**, 1489; (d) A. R. McWilliams, E. Rivard, A. J. Lough and Ian Manners, *Chem. Commun.*, 2002, 1102; (e) M. Fang, N. D. Jones, M. J. Ferguson, Robert McDonald and Ronald G. Cavell, *Angew. Chem. Int. Ed.*, 2005, **44**, 2005; (f) E. Rivard, P. J. Ragona, A. R. McWilliams, A. J. Lough and I. Manners, *Inorg. Chem.*, 2005, **44**, 6789; (g) M. Delferro, D. Cauzzi, R. Pattacini, M. Tegoni, C. Graiff and A. Tiripicchio, *Eur. J. Inorg. Chem.* 2008, 2302; (h) J. Ledger, R. Boomishankar and A. Steiner, *Inorg. Chem.*, 2010, **49**, 3896; (i) B. M. Barry, D. A. Dickie, L. J. Murphy, J. A. C. Clyburne and R. A. Kemp, *Inorg. Chem.*, 2013, **52**, 8312; (j) X.-N. Yao, M.-W. Yang, J. Xiong, J.-J. Liu, C. Gao, Y.-S. Meng, S.-D. Jiang, B.-W. Wang and S. Gao, *Inorg. Chem.*

Expanding the family of phosphane-stabilized divalent N(I) compounds appears useful for several reasons: i) phosphane ligands are readily available, even chiral cations. Since enantioselective phase transfer catalysis has been proven possible with chiral NHC-stabilized N(I) compounds,^[23] the much easier access to chiral phosphane ligands could lead to new developments. ii) Bis-phosphanes are much more common than bis-carbenes. In fact, to the best of our knowledge, only the cycloquanyl cation has been recognized so far as a cyclic divalent N(I) species (Scheme 2).^[16] Chelate ligands will automatically lead to more acute bending angles and possibly affect the electronic properties of the N(I) center. Thus, a cyclic platform offers a unique opportunity to study the behavior of these cations towards electrophiles.



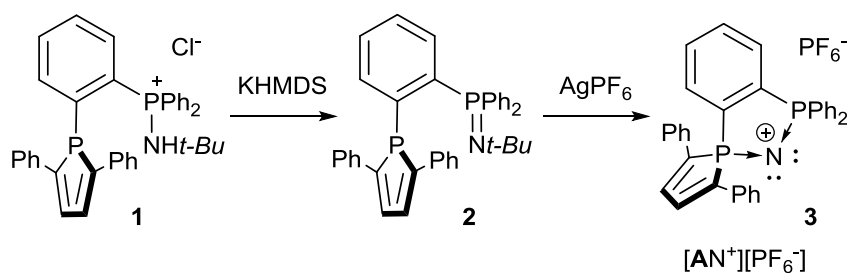
Scheme 2. Cyclic divalent N(I) species

III.2. Results and discussion

Our method to obtain a cyclic divalent N(I) cation has been to oxidize the in situ generated iminophosphorane-phosphole **2** with $AgPF_6$ (Scheme 3).

Front., 2017, **4**, 701. (k) B. Prashanth, M. Bhandari, S. Ravi, K. R. Shamasundar and S. Singh, *Chem. Eur. J.*, 2018, **24**, 4794.

[23] Y. Yang, F. Moinodeen, W. Chin, T. Ma, Z. Jiang and C.-H. Tan, *Org. Lett.*, 2012, **14**, 4762.



Scheme 3. Generation of the product.

Crystals of **3** were collected and subjected to an X-ray diffraction analysis (Figure 1).

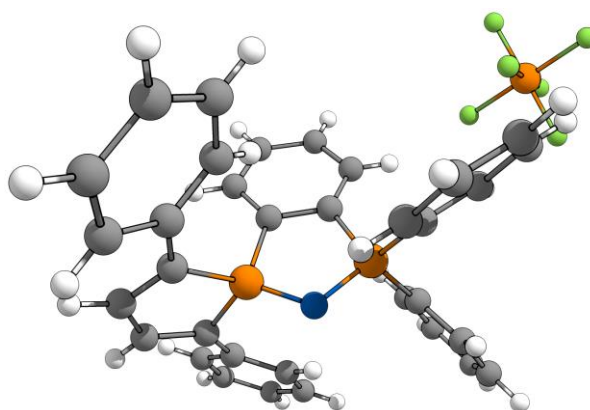


Figure 1. Molecular structure of the cyclic divalent N(I) cation **3**.

In order to gain insight into the electronic properties of the title compound, DFT calculations were performed by Prof. V. Gandon at the M062X/6-311G(d,p) level of theory. The cationic part of **3** (noted AN^+) has been computed, as well as its unknown C(0) analogue **AC**. We also used the following parent compounds: $(\text{Ph}_3\text{P})_2\text{N}^+$, $(\text{Me}_3\text{P})_2\text{N}^+$, $(\text{Ph}_3\text{P})_2\text{C}$ and $(\text{Me}_3\text{P})_2\text{C}$, which were already computed,^[10,13] but not at the same level of theory. Analysis of the frontier orbitals revealed the presence of two lone pairs of electrons at the central atoms. The HOMOs of $(\text{Me}_3\text{P})_2\text{N}^+$, $(\text{Ph}_3\text{P})_2\text{C}$ and **AC** have π -type symmetry, with the largest coefficients at the central nitrogen and carbon atom respectively. The HOMO-1 orbitals have π -type symmetry mainly localized at the central atoms. For AN^+ and $(\text{Ph}_3\text{P})_2\text{N}^+$, the HOMOs are concentrated on the aromatic rings. Similar π - and σ -orbitals located at the central atom can yet be found in HOMO-9/HOMO-12 and HOMO-12/HOMO-13 respectively (Figure 2).

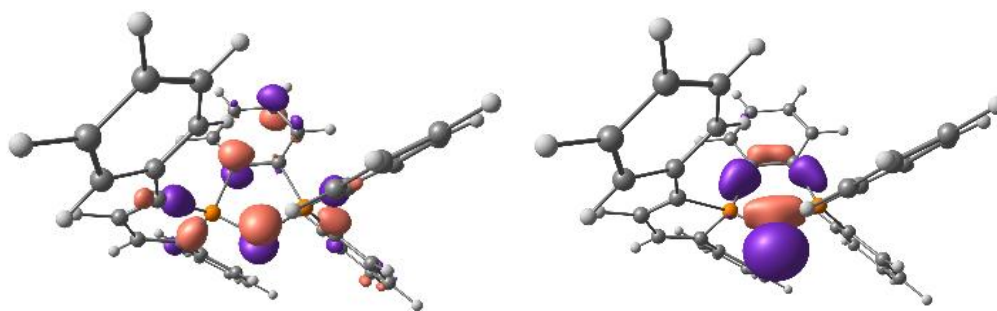


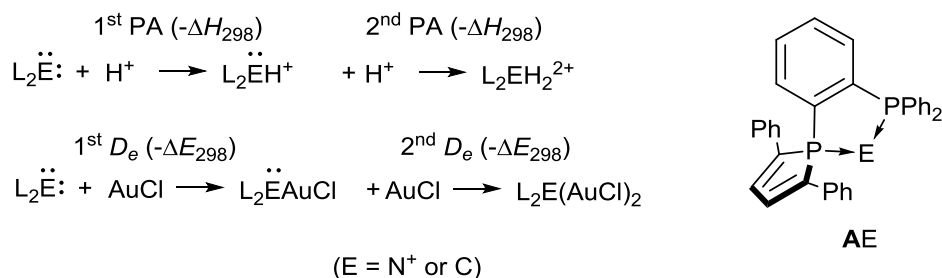
Figure 2. HOMO-9 (left) and HOMO-12 (right) of the AN^+ species (cationic part of **3**).

The two lone pairs can give rise to donor-acceptor adducts with electrophiles such as H^+ or AuCl (Table 1). The first and second proton affinities (PA)^[24] are much higher for AN^+ and $(\text{Ph}_3\text{P})_2\text{N}^+$ than for $(\text{Me}_3\text{P})_2\text{N}^+$. They are yet much lower than those computed for carbodiphosphanes, especially the second PA .^[13b] Although the level of the π - and σ -orbitals is not the only factor which determines the donor strength,^[13b] this correlation is basically respected. It is noticeable that PPh_3 and **A** strongly strengthen the N-H bonds compared to PMe_3 (~ 167 vs 137 kcal/mol for the 1st PA and $54/64$ vs 1.5 kcal/mol for the 2nd PA). This effect is not obvious on the 1st PA of the carbodiphosphanes,^[25] which remains in a narrow range (288 - 282 kcal/mol), and a bit more significant on the 2nd PA ($179/187$ vs 158 kcal/mol). N(I) compounds also form weaker donor-acceptor adducts with one or two AuCl units compared to carbodiphosphanes. Nevertheless, the BDE of the monogold complexes is significantly higher with the cyclic AN^+ species than with $(\text{Ph}_3\text{P})_2\text{N}^+$ or $(\text{Me}_3\text{P})_2\text{N}^+$ (~ 40 vs ~ 28 kcal/mol). On the other hand, the second BDE is similar between AN^+ and $(\text{Ph}_3\text{P})_2\text{N}^+$ (~ 27 kcal/mol), but higher than that of $(\text{Me}_3\text{P})_2\text{N}^+$ (~ 22 kcal/mol). Going back to the (HOMO-x) eigenvalues, one can infer that the cyclic nature of AN^+ renders the central nitrogen a better π -donor, which in first approximation makes it better suited to react with transition metals. At the same time, the π and the σ orbitals are low-lying compared to carbodiphosphanes,

[24] R. Tonner, G. Heydenrych and G. Frenking, *ChemPhysChem*, 2008, **9**, 1474.

[25] (a) C. Esterhuysen and G. Frenking, *Chem. Eur. J.*, 2011, **17**, 9944; (b) J. Vicente, A. R. Singhal and P. G. Jones, *Organometallics*, 2002, **21**, 5887; (c) A. El-Hellani, C. Bour and V. Gandon, *Adv. Synth. Catal.*, 2011, **353**, 1865.

which might considerably reduce their nucleophilicity. In that respect, attempts to react **3** with AuCl(THT), GaCl₃, BF₃·OEt₂ and HBF₄·OEt₂ all failed.



L ₂ E	PNP (°)	ε (HOMO-x) (eV)	PA (kcal/mol)		D _e (AuCl) (kcal/mol)	
			1 st	2 nd	1 st	2 nd
AN ⁺	113.6	-12.01 (x=9) -12.73 (x=12)	167.2	54.1	39.5	26.7
(Ph ₃ P) ₂ N ⁺	135.2	-12.11 (x=12) -12.24 (x=13)	167.3 ^a	64.6	28.1 ^c	27.6
(Me ₃ P) ₂ N ⁺	147.3	-12.54 (x=0) -12.65 (x=1)	137.4 ^b	1.5	28.4	21.8
AC	105.3	-6.15 (x=0) -6.78 (x=1)	288.2	178.8	76.0	55.4
(Ph ₃ P) ₂ C	124.9	-6.01 (x=0) -6.41 (x=1)	283.5	187.3	70.0 ^d	60.8
(Me ₃ P) ₂ C	134.0	-5.73 (x=0) -5.97 (x=1)	281.9	157.5	75.4	62.9

^a 167.4 kcal/mol in ref 13b. ^b 139.5 kcal/mol in ref 10. ^c 25.9 kcal/mol in ref 13b. ^d 63.1 kcal/mol in ref 13b.

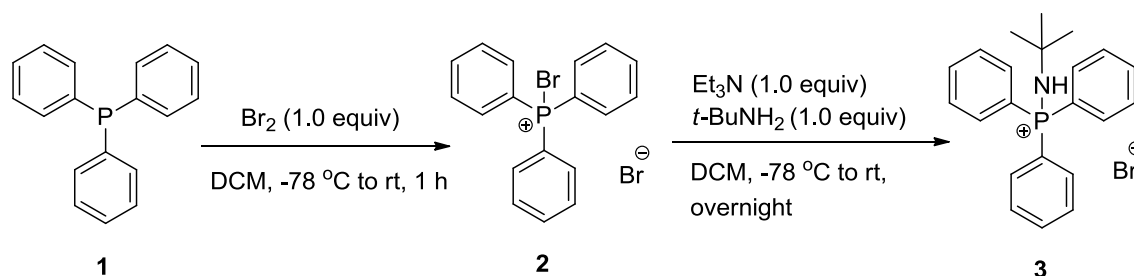
Table 1. Calculated PNP angles, eigenvalues of selected orbitals, proton affinities (PA) and bond dissociation energies.

III.3. Conclusion

In conclusion, we have synthesized the first bis-phosphane chelated N(I) compound. It is clearly distinct from a nitrenium ion and is best described as a divalent low oxidation species holding two lone pairs at the nitrogen atom. It is isoelectronic to carbodiphosphoranes but much less nucleophilic.

III.4. Experiment Section

Procedure for the synthesis of (*t*-butylamino)triphenylphosphonium bromide **3**

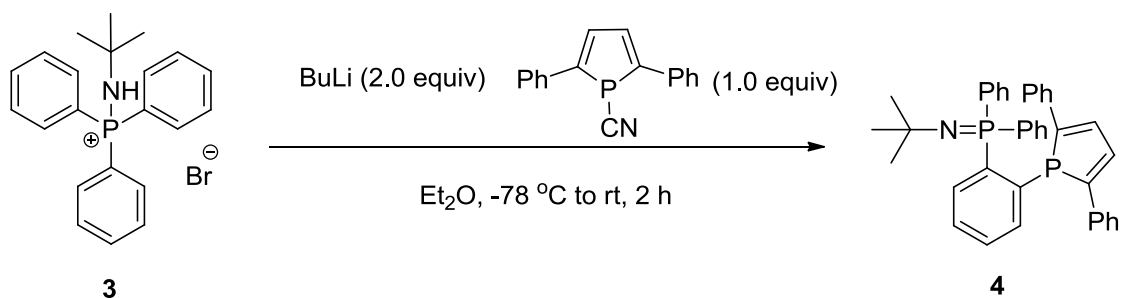


Bromine (1.95 ml, 38.1 mmol, 1.0 equiv) was added dropwise into a solution of triphenylphosphine (10.0 g, 38.1 mmol, 1.0 equiv) in DCM (80 ml) at -78°C (dry ice/acetone). The reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was cooled to -78°C again. Triethylamine (5.30 mL, 38.1 mmol, 1.0 equiv) and *t*-butylamine (4.00 mL, 38.1 mmol, 1.0 equiv) were added into the reaction mixture. After stirring overnight at room temperature, the reaction was quenched with water (50 mL). The organic layer was collected. The aqueous layer was extracted with DCM three times (3x20 mL). The combined organic extracts were dried over anhydrous MgSO_4 , filtered and concentrated to around 40 mL under reduced pressure. 50 mL THF were added into the combined organic extracts. The THF-DCM layer was concentrated again to around 40 mL under reduced pressure. The product was precipitated and filtrated. The precipitate was washed with THF (3x15 mL) and then dried under vacuum. The product **3** was obtained as a white solid (13.0 g, 31.3 mmol, 82%).

^1H NMR (300 MHz, CDCl_3) δ 8.01 – 7.90 (m, 6H), 7.76 – 7.68 (m, 3H), 7.66 – 7.58 (m, 6H), 7.48 (s, 1H), 1.34 (s, 9H). ^{31}P NMR (121 MHz, CDCl_3) δ 30.8 (s). The spectral data for **3** match those previously reported in the literature.^[26]

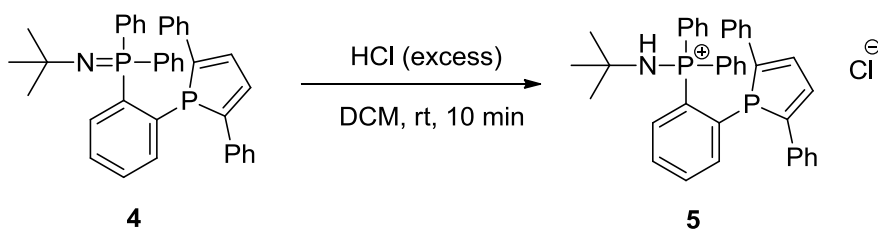
Procedure for the synthesis of N-((2-(2,5-diphenyl-1H-phosphol-1-yl)phenyl)diphenylphosphoranylidene)-2-methylpropan-2-amine **4**

[26] E. Martinez-Arripe, F. Jean-Baptiste-Dit-Dominique, A. Auffrant, X.-F. L. Goff, J. Thuilliez and F. Nief, *Organometallics*, 2012, **31**, 4854.



BuLi (4.56 mL, 1.6 M in hexane, 7.30 mmol, 2.0 equiv) was added dropwise to a solution of **3** (1.5113 g, 3.65 mmol, 1.0 equiv) in Et₂O (80 mL) at -78 °C (dry ice/acetone). After 1 hour of stirring at room temperature, the reaction mixture was cooled to -78 °C again. The solution of the phosphole (0.9530 g, 3.65 mmol, 1.0 equiv) in 30 ml THF was added to the reaction mixture. The reaction mixture was stirred at room temperature for 1 h again. The reaction mixture was filtered under a N₂ atmosphere. The organic layer was collected and the organic solvent Et₂O and THF were removed under vacuum. The crude product **4** was obtained as a yellow solid and directly engaged in the next step without further purification.

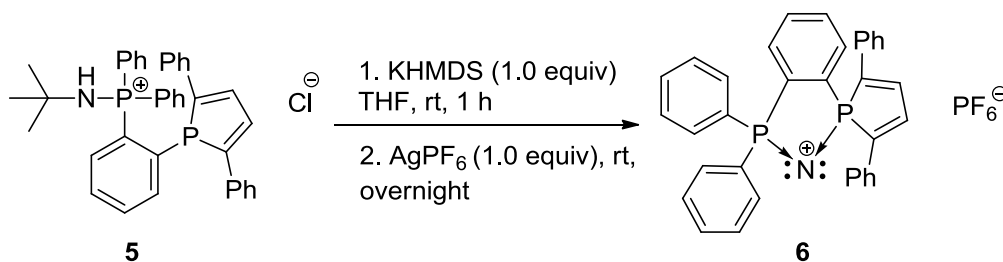
Procedure for the synthesis of (t-butylamino)(2-(2,5-diphenyl-1H-phosphol-1-yl)phenyl)diphenylphosphonium chloride **5**



Hydrochloric acid solution (1 mL concentrated HCl in 100 mL distilled water) were added to a solution **4** (567.7 mg, 1.0 mmol) in DCM (20 mL). The reaction mixture was stirred at room temperature for 10 min. The organic layer was collected. The aqueous layer was extracted with DCM three times (3x20 mL). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated under vacuum. The crude product **5** was washed with Et₂O (3x15 mL) to remove impurities. The product **5** was obtained as a yellow solid after dried under vacuum (584.4mg, 0.97 mmol, 97%, isolated yield over two steps).

^{31}P NMR (121 MHz, CD_2Cl_2) δ 35.37 (d, $J = 10.9$ Hz), -7.19 (d, $J = 10.9$ Hz). ^1H NMR (300 MHz, CD_2Cl_2) δ 8.20 (d, $J = 8.1$ Hz, 1H), 8.04 (d, $J = 7.4$ Hz, 4H), 7.90 – 7.51 (m, 8H), 7.46 – 7.05 (m, 9H), 6.87 – 6.78 (m, 3H), 6.11 (s, 1H), 5.36 (dd, $J = 2.9, 1.8$ Hz, 1H), 1.14 (s, 9H).

Procedure for the synthesis of **6**



KHMDS (62.0 mg, 0.31 mmol, 1.0 equiv) was added into a solution of **5** (187.8 mg, 0.31 mmol, 1.0 equiv) in THF (3.0 mL) inside the glovebox. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was transferred into a centrifuge tube. The precipitate (KCl) and supernatant were separated by the centrifugal machine. The supernatant was transferred into a new Schlenk flask. AgPF_6 (78.6 mg, 0.31 mmol, 1.0 equiv) was added into the Schlenk flask. The reaction was stirred at room temperature overnight. The reaction mixture was transferred into a centrifuge tube. The precipitate (Product **6** and silver salts) and supernatant were separated by the centrifugal machine again. The supernatant was removed. The precipitate was washed with THF (3x5 mL) to remove the impurities. The precipitate was dissolved with DCM (5.0 mL). The DCM solution was transferred into a new centrifuge tube. The precipitate (silver salts) and supernatant were separated by the centrifugal machine. The supernatant was concentrated under reduced pressure and dried under vacuum to afford the product **6** (Yellow solid).

Tips. The product **6** has good solubility in DCM and poor solubility in THF. The side product (impurities) has better solubility than the product **6** in THF. This is the basic rule to purify the product **6**.

^1H NMR (300 MHz, CD_2Cl_2) δ 8.35 (t, $J = 7.6$ Hz, 1H), 8.17 – 7.96 (m, 3H), 7.89 – 7.52 (m, 11H), 7.31 (m, 2H), 7.10 (m, 7H), 5.36 (s, 2H). ^{31}P NMR (121 MHz, CD_2Cl_2) δ 58.61 (d, $J = 7.0$

Hz), 55.81 (d, $J = 7.0$ Hz), -15.06 (hept, $J = 953.7$ Hz). HRMS-ESI: m/z calculated for $C_{34}H_{26}NP_2$ $[M]^+$: 510.1540, found: 510.1513.

III.5. References

- [1] L. Zhao, M. Hermann, N. Holzmann and G. Frenking, *Coord. Chem. Rev.*, 2017, **344**, 163.
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Chapter IV

NIS-Catalyzed Dehalogenation of Iodo- and Bromoallenes: Mild Reaction Conditions for the Propargylation of Aliphatic Alcohols using 7-Alkynylcycloheptatrienes

Chapter IV. NIS-Catalyzed Dehalogenation of Iodo- and Bromoallenes: Mild Reaction Conditions for the Propargylation of Aliphatic Alcohols using 7-Alkynylcycloheptatrienes

V.1. Introduction

Halogen derivatives of alkanes, alkenes, alkynes, arenes and allenes constitute one of the most important class of useful organic compounds. Even if haloalkanes and haloarenes are good solvents for relatively non-polar compounds, halogen derivatives are mostly used in the field of organic synthesis as reagents and key intermediates for the construction of complex molecules. Indeed, halogen derivatives can act as partners in numerous synthetic transformations, in particular in metal-catalyzed coupling reactions.^[1] Generally, noble and late transition metals are used to promote those cross-coupling reactions.^[2] Due to the increasing price of those metals, the toxicity and the environmental damage associated to heavy metals extraction, the development of less expensive and more sustainable alternatives is needed. The emergence of organocatalysis has allowed performing many transformations under mild reactions conditions compared to metal-based catalysis.^[3] Since few years, among the different activation mode developed so far in organocatalysis, halogen bonding^[4] as emerged as an orthogonal, complementary and promising approach

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to the well-established hydrogen bonding strategy for the design and tuning of highly efficient organocatalysts.^[5]

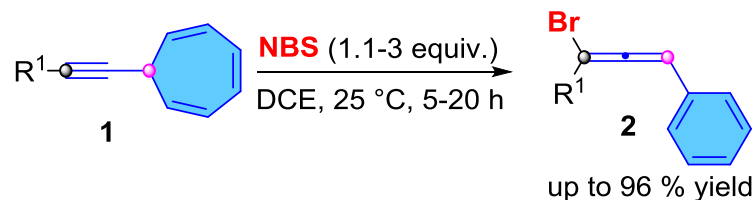
Halogen atom in R-X compounds (X = Cl, Br, I, rarely F) can give rise to attractive noncovalent interactions with halogen-bond acceptors (halogen atoms, O, N, S and aromatic rings). Although the first evidence of this type of interaction is known since 1950,^[6] halogen bonding was firstly used as a tool for the rational design of crystals,^[7] the development of new materials with electronic, semi-, supra-conductive or non-linear optical properties^[8] and supramolecular assemblies.^[9] More recently, due to the increasing number of resolved protein structures in interaction with halogenated ligands, halogen bonding exhibited its significance into rational drugs design^[10] and gained importance as a promising activation method in organic synthesis.^[4,5]

Recently, during the course of our work on the versatile reactivity of 7-alkynylcycloheptatrienes **1**, we developed a method of preparation of trisubstituted 3-bromo-1-phenylallenes **2** using an excess of *N*-bromosuccinimide (NBS) as halogenating

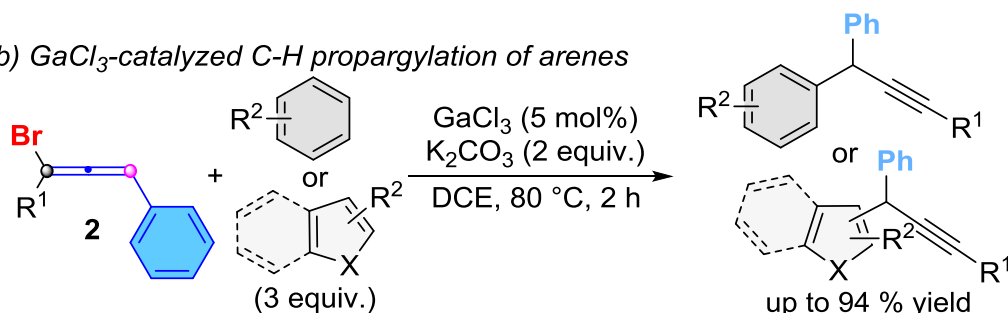
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agent (Scheme 1a).^[11] We also demonstrated that **2** were suitable partners for a Ga(III)-catalyzed C-H propargylation of arenes (Scheme 1b)^[12] and then turned our attention to the extension of this reaction to *N*- and *O*-propargylation reactions.

a) Preparation of 3-substituted 3-bromo-1-phenylallenes



b) GaCl₃-catalyzed C-H propargylation of arenes



Scheme 1. Our recent work onto the preparation and use of bromoallenes.

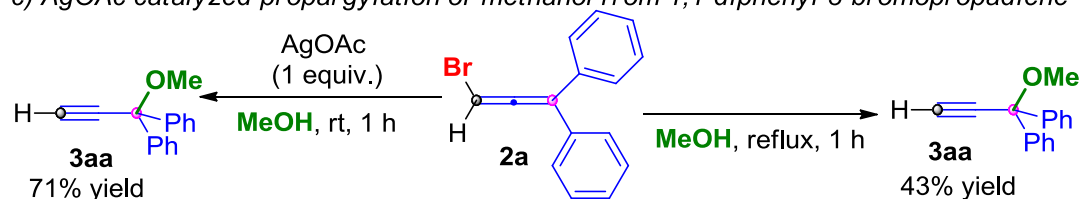
In 1968, Toda *et al.* reported that treatment of **2** by AgOAc in methanol at room temperature promoted the formation of the corresponding propargyl ether **3** while refluxing the solution for 5 hours, without metal salt, also gave **3** (Scheme 2a).^[13] Surprisingly, we observed a similar reactivity by serendipity: aiming to favor the formation of iodoallenes using *N*-iodosuccinimide, we added 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) to activate this halogenating reagent and we isolated the propargylic ether of HFIP as the major product of the reaction (Scheme 2b). A similar result was observed using isopropanol instead of HFIP, which led us to believe that an intermediary product is activated by halogen bonding and is decomposed in absence of nucleophile in the reaction media.

[11] M. Vayer, R. Guillot, C. Bour, V. Gandon, *J. Org. Chem.* **2018**, *83*, 11309-11317.

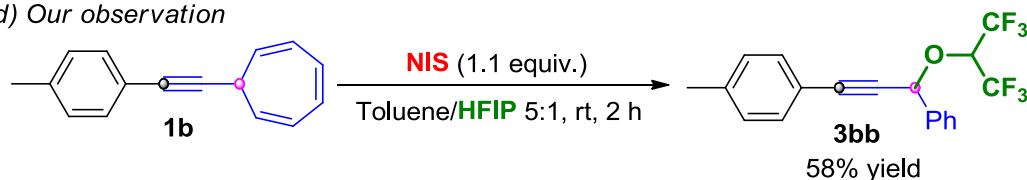
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c) AgOAc catalyzed propargylation of methanol from 1,1-diphenyl-3-bromopropadiene



d) Our observation



Scheme 2. Formation of propargyl ethers.

Since 2011, few examples of halide abstraction by organic halogen bond donors had been reported, demonstrating a comparable halophilicity of the latter compounds to silver(I) salts. 2011, Huber *et al.* demonstrated that a bis(iodoimidazolium) salt could activate the C-Br bond of benzydryl bromide by halogen bonding to promote a Ritter-type reaction (Scheme 3a).^[14] After extending this concept of activation in 2012 to bis(iodopyridinium),^[15] bis- and tri(iodotriazolium) salts,^[16] they developed from 2013 to 2015 the first halogen bonding-based organocatalysts able to promote the nucleophilic substitution of 1-chloroisochroman by ketene silyl acetal (Scheme 3b).^[17] In 2014, Takemoto *et al.* demonstrated that commercially available iodine(I) compounds, *N*-iodosuccinimide and *N*-iodosaccharin, are stoichiometric powerful C-X bond activators for the promotion of a desilylative semipinacol rearrangement of halohydrin silyl ethers (Scheme 3c).^[18] The same year, Codée *et al.* demonstrated that Huber's iodoimidazolium salts were able to activate highly reactive glycosyl halides in a Koenigs-Knorr type glycosylation reaction (Scheme 3d).^[19]

[14] S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2011**, *50*, 7187-7191.

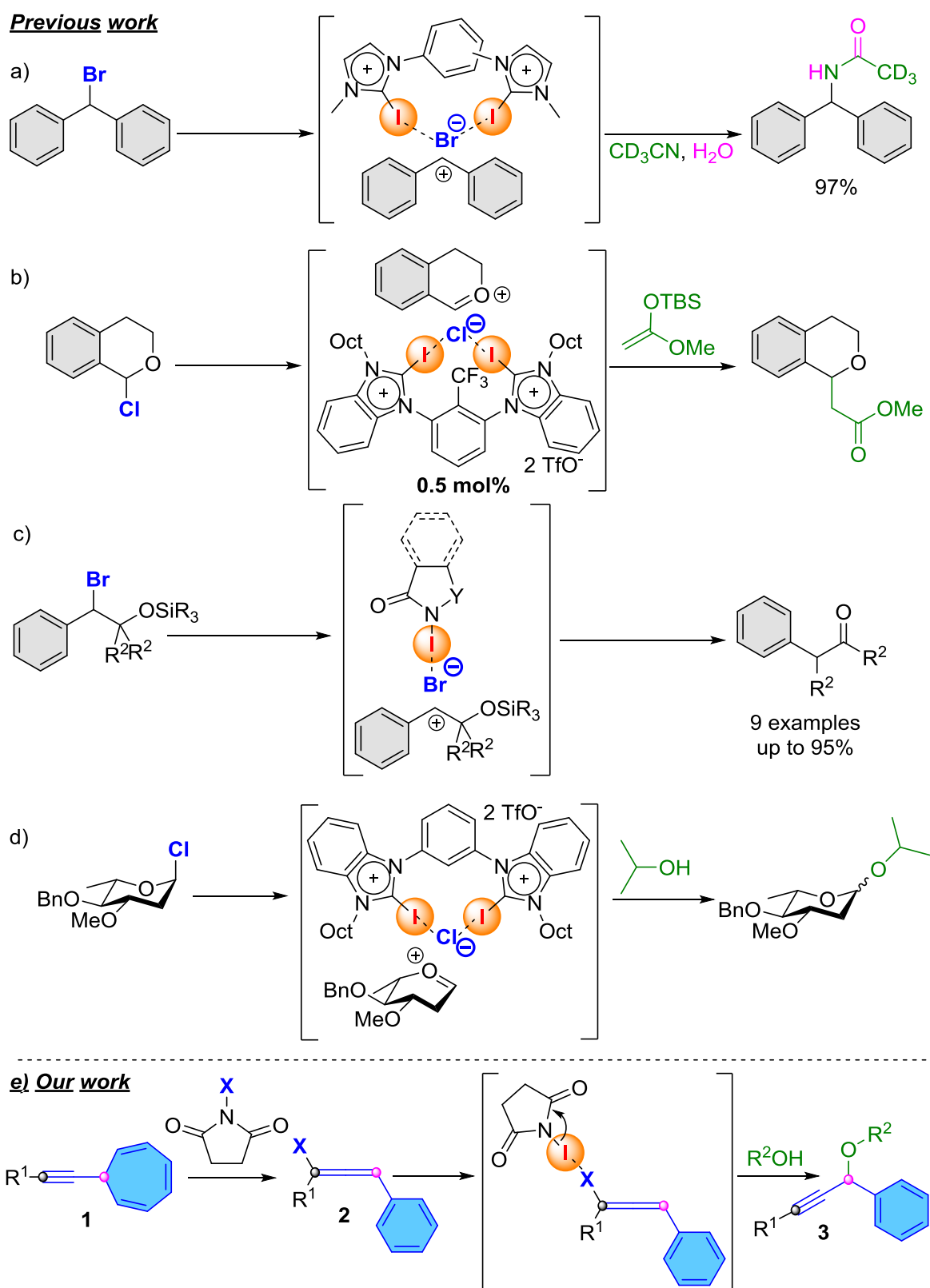
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[16] F. Kniep, L. Rout, S. M. Walter, H. K. V. Bensch, S. H. Jungbauer, E. Herdtweck, S. M. Huber, *Chem. Commun.* **2012**, *48*, 9299-9301.

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[18] N. Tsuji, Y. Kobayashi, Y. Takemoto, *Chem. Commun.* **2014**, *50*, 13691-13694.

[19] R. Castelli, S. Schindler, S. M. Walter, F. Kniep, H. S. Overkleeft, G. A. Van der Marel, S.

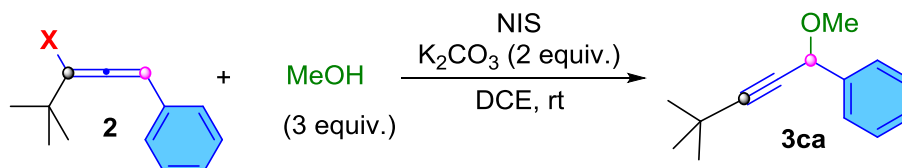


Scheme 3. Halide abstraction by halogen bonding activation and its synthetic applications.

We assumed that in our case, after the formation of the corresponding iodoallene **2** from 7-alkynylcycloheptatriene **1**, the excess of NIS acted as a halogen abstractor as silver(I) acetate by halogen bonding, allowing the nucleophilic attack of the alcohol on the benzylic carbon atom to form the propargyl ether **3** (Scheme 3f).

IV.2. Results and discussions

To validate our assumption, we examined the reaction of 3-*tert*-butyl-3-iodo-1-phenylallene **2c** with methanol in presence of NIS and K₂CO₃ in DCE at room temperature. As shown in Table 1, in few minutes, NIS efficiently promoted the propargylation of methanol using the iodoallene **2c** and bromoallene **2c'** as propargylation agent, leading to the corresponding methyl propargyl ether **3c** respectively in 78% (Table 1, entry 1) and 86% yield (Table 1, entry 2). As expected, due to the lower halogen bonding character of chlorine atom, a low conversion was observed with chloroallene **2c''** even after several hours of reaction (Table 1, entry 3).



Entry	Haloallene	NIS loading	Time of reaction	Yield ^[a]
1	2c (X=I)	1 equiv.	5 min	78%
2	2c' (X=Br)	1 equiv.	5 min	86%
3	2c'' (X=Cl)	1 equiv.	5 min	Traces (24%) ^[b]
4	2c	0.4 equiv.	10 min	94%
5	2c'	0.4 equiv.	10 min	98% (92%) ^[c]
6	2c	0.2 equiv.	10 min	36%

Table 1. Activation of haloallene by NIS allowing the formation of propargyl ether. Reaction conditions: 0.2 mmol of **2**, 0.6 mmol of MeOH, 0.4 mmol of K₂CO₃ and NIS in 0.5 mL of DCE for the indicated reaction time. [a] NMR yield determined using CH₂Br₂ as internal standard. [b] After 3 h of reaction. [c] Isolated yield.

More interestingly, to limit side reactions, we reduced the loading of promotor and

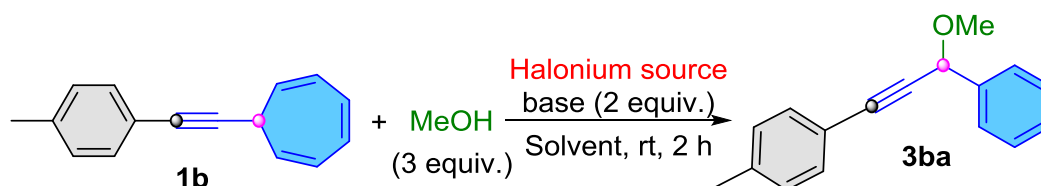
observed that 0.4 equivalent of NIS allowed for a cleaner reaction than using a stoichiometric amount and allow for a quantitative formation of **3c** (entries 4 & 5). However, even if the reaction time is prolonged to several hours, a low promotor loading led to a low conversion as well as to an important degradation of the reaction media (Table 1, entries 5 & 6).

Having demonstrated the halogen abstraction of **2c** and **2c'** by NIS, we next examined the propargylation reaction conditions of methanol through a domino iodoallene formation/nucleophilic substitution using 7-(*p*-tolylethynyl)cyclohepta-1,3,5-triene **1b** in presence of several halonium sources (Table 2). To our delight, the reaction was complete in less than 5 min and furnished the desired product **3ba** in 91% isolated yield, without observing any degradation, even after 2h of reaction (Table 2, entry 1). Results also showed that the promotion of the reaction is dramatically affected by the halonium species. The use of both NBS and *N*-chlorosuccinimide (NCS), respectively as bromonium and chloronium sources, did not promoted the reaction (Table 2, entries 2 & 3) while diiodine and iodine monochloride as iodonium sources were effective promoters of the reaction and led to **3ba** in good to moderate yield (Table 2, entries 4 & 5). A control experiment without halonium source demonstrated that the reaction was not spontaneous and the starting material was mainly recovered. If the reaction proceeded efficiently in DCM (Table 2, entry 9), other solvents such as toluene and Et₂O appeared to be incompatible with the domino reaction probably due to radical side-reactions^[20] (Table 2, entries 10 & 11) while THF and MeCN appeared to slow down the reaction rate (Table 2, entries 12 & 13). Moreover, decreasing the concentration of the reaction from 0.2 M to 0.1 M gave a reduced yield (Table 2, entry 14). We also evaluated the influence of the base on the chemical process. In absence of a base, several side-reactions were observed on TLC and lowered the yield as well as the purity of **3ba** (Table 2, entry 15). Replacing K₂CO₃ by triethylamine led to its oxidation by NIS (Table 2, entry 16) while the use of pyridine probably led to the coordination of the iodonium by pyridine to form a favored halogen-bonded iodine(I) complex^[21] in comparison with the intermediary iodoallene

[20] S. Shimizu, Y. Imamura, T. Ueki, *Org. Process. Res. Dev.* **2014**, *18*, 354-358.

[21] (a) R. W. Troff, T. Mäkelä, F. Topić, A. Valkonen, K. Raatikainen, K. Rissanen, *Eur. J. Org.*

(Table 2, entry 17).



Entry	Halonium source	Loading	Solvent	[c]	Base	Yield ^[a]
1	NIS	1.3 equiv.	DCE	0.2 M	K ₂ CO ₃	92% (91%) ^[b]
2	NBS	1.3 equiv.	DCE	0.2 M	K ₂ CO ₃	4%
3	NCS	1.3 equiv.	DCE	0.2 M	K ₂ CO ₃	n.r. ^[c,d]
4	I ₂	1.3 equiv.	DCE	0.2 M	K ₂ CO ₃	73%
5	ICl	1.3 equiv.	DCE	0.2 M	K ₂ CO ₃	47%
6	-	-	DCE	-	K ₂ CO ₃	n.r. ^[c,d]
7	NIS	1.1 equiv.	DCE	0.1 M	K ₂ CO ₃	71% ^[i]
8	NIS	1.5 equiv.	DCE	0.1 M	K ₂ CO ₃	90% ^[i]
9	NIS	1.3 equiv.	DCM	0.2 M	K ₂ CO ₃	83%
10	NIS	1.3 equiv.	Toluene	0.2 M	K ₂ CO ₃	29% ^[e]
11	NIS	1.3 equiv.	Et ₂ O	0.2 M	K ₂ CO ₃	28% ^[e]
12	NIS	1.3 equiv.	THF	0.2 M	K ₂ CO ₃	18% ^[d]
13	NIS	1.3 equiv.	MeCN	0.2 M	K ₂ CO ₃	16% ^[d]
14	NIS	1.3 equiv.	DCE	0.1 M	K ₂ CO ₃	60%
15	NIS	1.5 equiv.	DCE	0.1 M	-	57% ^[f]
16	NIS	1.3 equiv.	DCE	0.2 M	Et ₃ N	0% ^[d,g]
17	NIS	1.3 equiv.	DCE	0.2 M	Pyridine	0% ^[d,h]
18	NIS	1.3 equiv.	DCE	0.2 M	NaOAc	84%
19	NIS	1.3 equiv.	DCE	0.2 M	Cs ₂ CO ₃	86%
20	NIS	1.3 equiv.	DCE	0.2 M	K ₂ CO ₃	75% ^[i]

Table 2. Optimization of propargylation of aliphatic alcohols. Reaction conditions: 0.2 mmol of **2**, 0.6 mmol of MeOH, 0.4 mmol of base and halonium source as indicated in 0.5 mL of solvent for 2 h. [a] NMR yield determined using CH₂Br₂ as internal standard. [b]

Chem. **2013**, 1617-1637; (b) O. Makhotkina, J. lieffrig, O. Jeannin, M. Fourmigué, E. Aubert, E. Espinosa, *Cryst. Growth. Des.* **2015**, *15*, 3464-3473 ; (c) S. Guha, I. Kazi, A. Nandy, G. Sekar, *Eur. J. Org. Chem.* **2017**, 5497-5518.

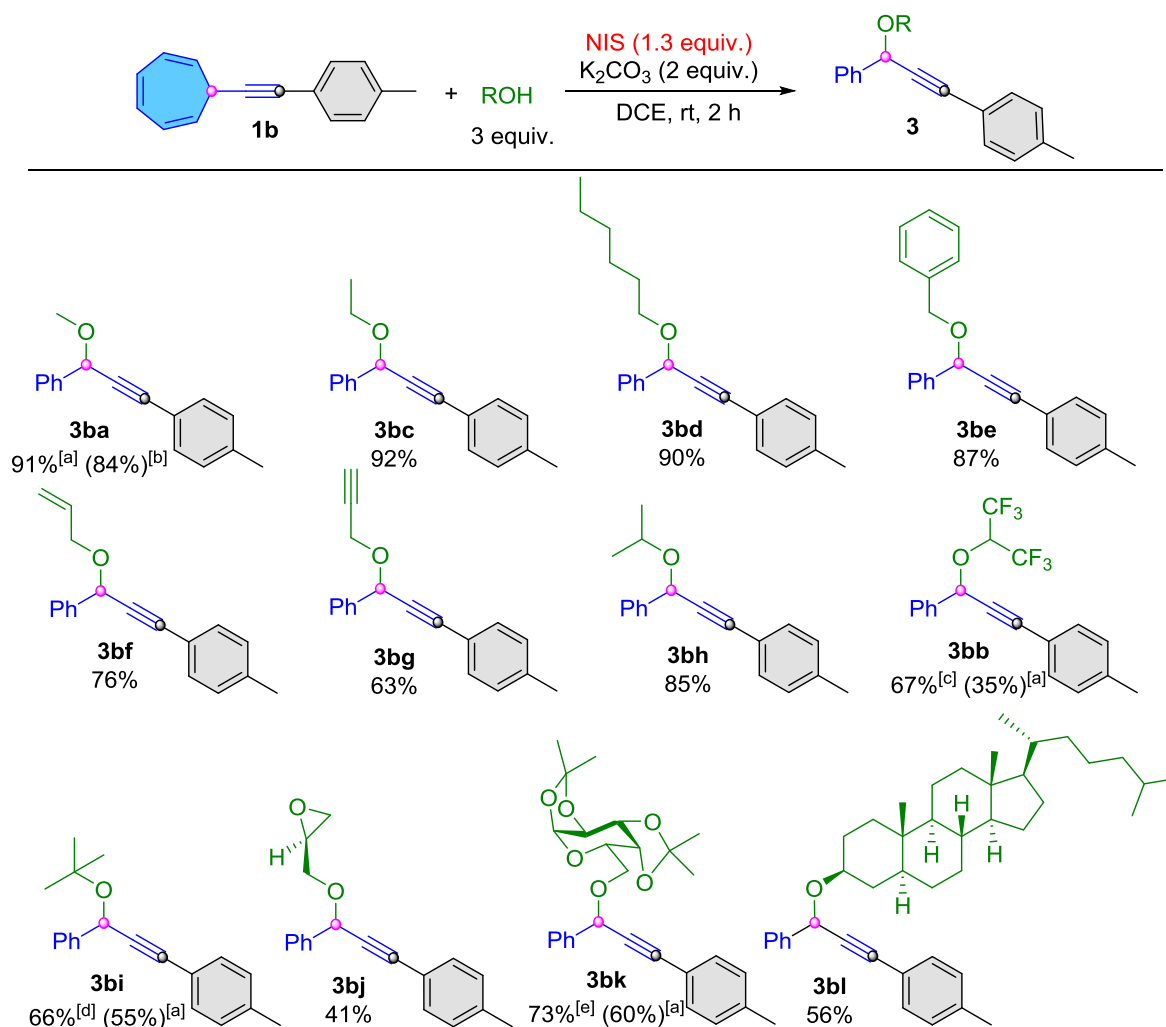
Chromatographically isolated yield. [c] n.r. stands for no reaction. [d] **1b** was mainly recovered. [e] Several unidentified products were observed on TLC. [f] Using 10 equivalents of MeOH (2 mmol). [g] NIS-oxidation of triethylamine was assumed the main reaction. [h] A stable halogen bonded NIS:pyridine complex should be formed. [i] Same reaction conditions as entry 1 except with MeOH (0.3 mmol). [j] 10 equiv MeOH.

The use of inorganic bases such as NaOAc or Cs₂CO₃ did not affect the reaction (Table 2, entries 18 & 19). Additionally, reduction of the quantity of MeOH from 3 to 1.5 equivalents slightly reduced the yield of **3ba** to 75% (Table 2, entry 20). Finally, it is important to note that no traces of iodoallene were isolated during the optimization of the reaction, demonstrating the efficiency of the deiodination process by halogen bonding. Moreover, neither the iodination of **3ba** nor the nucleophilic substitution by succinimide anion were observed, demonstrating the high chemoselectivity of the domino reaction.

Encouraged by the high reactivity of our system, we evaluated the scope of the substitution reaction to various aliphatic alcohols (Scheme 4). Using optimized reaction conditions, simple primary alcohols, such as MeOH on a gram-scale reaction (**3ba**, 84% yield), EtOH (**3bc**, 92% yield) or n-hexanol (**3bd**, 90% yield), led to the desired propargyl ethers in excellent yield. Moreover, used alcohols that are prone to iodination, such as benzyl (**3be**, 87% yield), allyl (**3bf**, 76% yield) or propargyl alcohol (**3bg**, 63% yield), could also be propargylated in good yield using these mild reaction conditions. If the secondary alcohol isopropanol also reacted well (**3bh**, 85% yield), a slight modification of reaction conditions allows for the obtaining of the propargyl ether of the poor nucleophiles HFIP (**3bb**, 67% yield) or tertiary *tert*-butanol (**3bi**, 66% yield) by increasing the amount of NIS to 2 equivalents and of the alcohol to 5 equivalents, respectively. Finally, the acidic sensitive (*R*)-glycidol (**3bj**, 41% yield) and complex alcohols, such as 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**3bk**, 73% yield) or 3 β -hydroxy-5 α -cholestane (**3bl**, 56% yield) also gave the expected propargyl ethers in moderate to good yield when engaged in our domino reaction. Our reaction system exhibits a good tolerance to various aliphatic alcohols and allows for the preparation of hindered non-terminal propargyl ethers that could be difficult to access without using transition metal catalysis.^[22] Unfortunately, aromatic alcohols such as phenol are not

[22] For review on metal-catalyzed formation of propargyl ethers from propargyl alcohols

compatible with NIS, no reaction takes place and the substrate can be fully recovered.

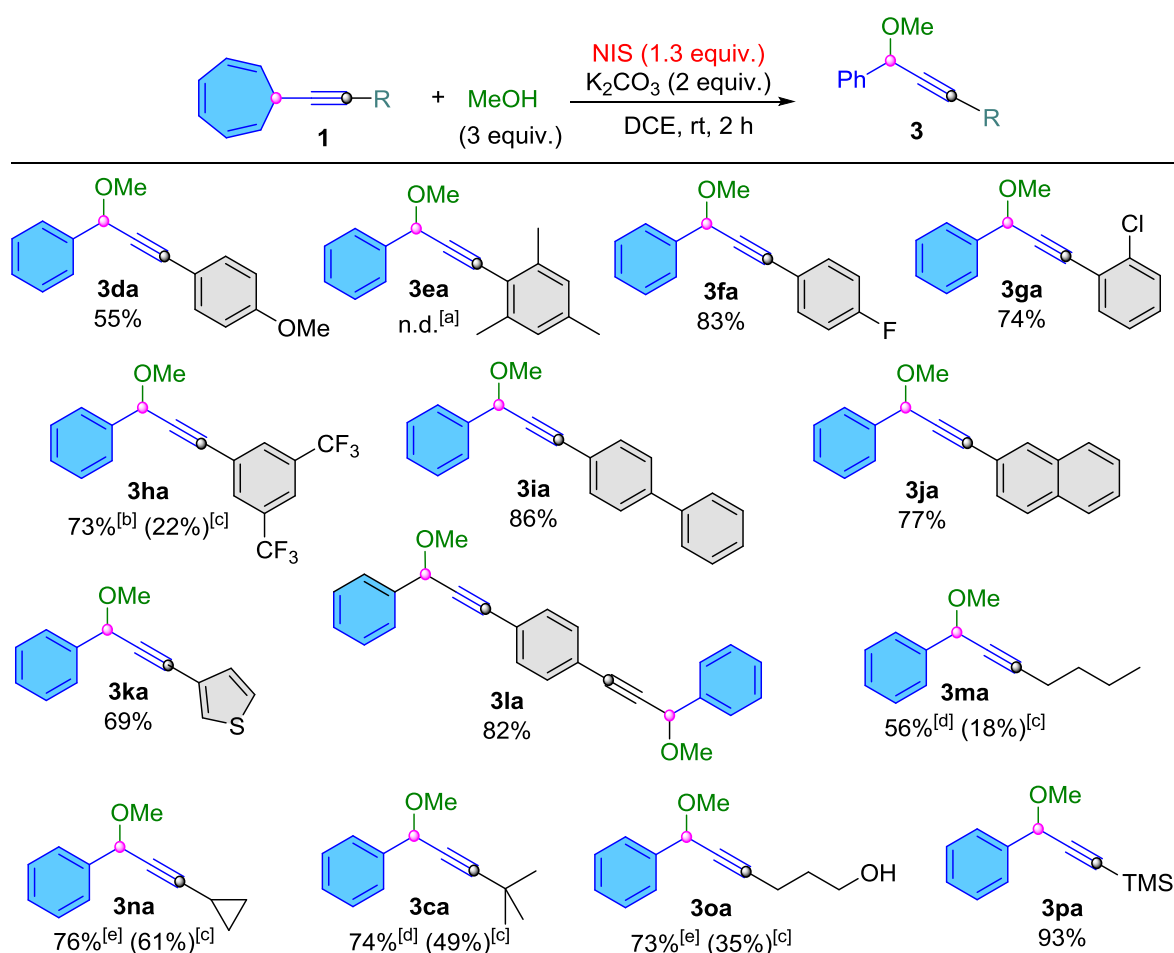


Scheme 4. Aliphatic alcohol scope of the domino reaction using 7-(*p*-tolylethynyl)cyclohepta-1,3,5-triene **1b** as propargylating agent. Standard reaction conditions: 0.2 mmol of **1b**, 0.6 mmol of alcohol, 0.4 mmol of K₂CO₃ and 0.26 mmol of NIS in 0.5 mL of DCE for 2 h. Yields refer to chromatographically isolated product. [a] Isolated yield using standard reaction conditions. [b] Isolated yield starting from 50 mmol of **1b** (1.032g). [c] Same reaction conditions as standard ones except with 0.4 mmol of NIS. [d] Same reaction conditions as standard ones except with 1.0 mmol of *t*BuOH. [e] Same reaction conditions as standard ones except with 0.3 mmol of NIS.

We also investigated the substrate scope of the iodoallene formation/iodine abstraction using different substituted 7-alkynylcyclohepta-1,3,5-trienes **1** (Scheme 5). First, various arylated derivatives were examined and the results showed that replacement of the tolyl

and derivatives, see: (a) N. Ljungdahl, N. Kann, *Angew. Chem. Int. Ed.* **2009**, *48*, 642-644; (b) R. J. Detz, H. Hiemstra, J. H. Maarseveen, *Eur. J. Org. Chem.* **2009**, 6263-6276; (c) Y. Miyake; S. Uemura, Y. Nishibayashi, *ChemCatChem* **2009**, *1*, 342-356; (d) H. Tsuji, M. Kawatsura, *Asian J. Org. Chem.* **2020**, *9*, 1924-1941.

group by a 4-methoxyphenyl one led to a reduced yield (**3da**, 55% yield) or even a complete decomposition into the case of the 2,4,6-trimethylphenyl derivative (**3ea**). This difference of reactivity could be attributed to the ability of such derivatives to undergo iodination reaction. In the opposite way, replacement of the tolyl group by aryl moiety bearing electron-withdrawing groups, such as 4-fluorophenyl (**3fa**, 83% yield) or 2-chlorophenyl (**3ga**, 74% yield), gave good yields. Into the case of the 3,5-bis(trifluoromethyl)phenyl derivative, a loss of reactivity was observed. In this case, an increase in NIS loading to 2 equivalents was required to facilitate the reaction (**3ha**, 73% yield). Moreover, replacement of the tolyl group by a 1,1'-diphenyl, naphthyl or thiophenyl moiety respectively led to **3ia**, **3ja** and **3ka** in good yield. Finally, the symmetric diether **3la** was obtained in 82% yield by using twice as much reagents.

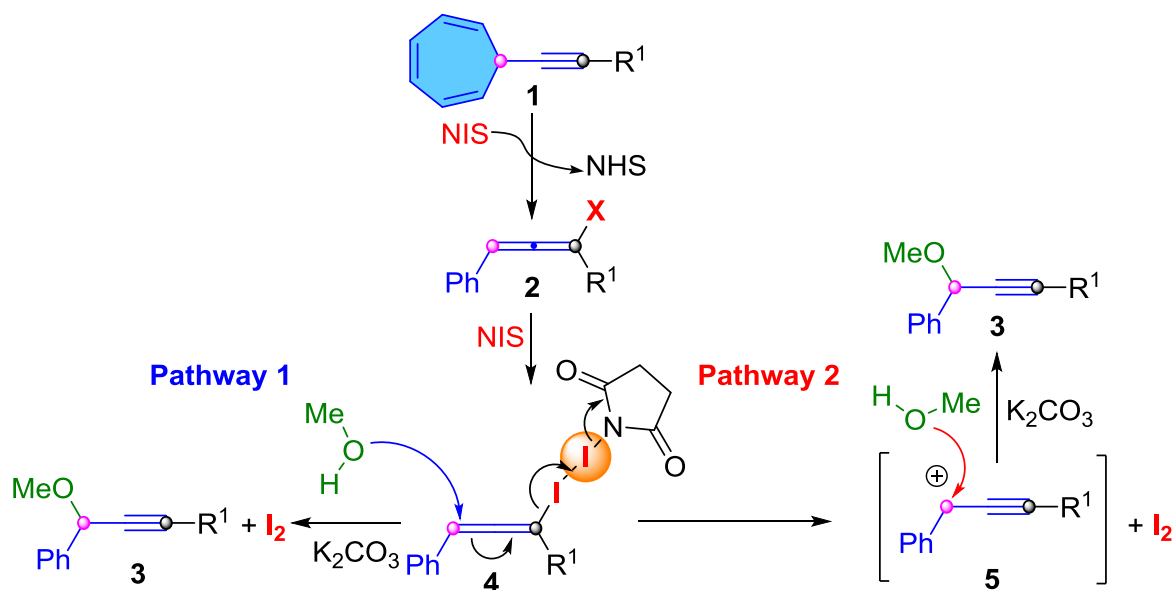


Scheme 5. 7-alkynylcyclohepta-1,3,5-trienes scope for the propargylation of methanol using NIS. Standard reaction conditions: 0.2 mmol of **1**, 0.6 mmol of MeOH, 0.4 mmol of K₂CO₃ and 0.26 mmol of NIS in 0.5 mL of DCE for 2 h. Yields refer to chromatographically isolated product. [a] n.d. stands for not detected in the crude product, complete

degradation of **1** was observed. [b] Same reaction conditions as standard ones except with 0.4 mmol of NIS. [c] Isolated yield using standard reaction conditions. [d] Same reaction conditions as standard ones except with 0.3 mmol of NIS. [e] Same reaction conditions as standard ones except with 0.3 mmol of NIS and 1.0 mmol of MeOH.

The reaction was not limited to arylated derivatives of **1**, alkylated derivatives were also tested and afforded the corresponding propargyl ethers of MeOH in moderate (**3ma**) or good yield (**3ca**, **3na**, **3oa**), even if in the latter cases slight modifications of reaction conditions were performed to improve the isolated yield. It is noteworthy that the presence of free alcohol on **1o** did not lead to intermolecular reaction in presence of 5 equivalents of MeOH and that the trimethylsilyl derivative **1p** exhibited a higher reactivity than the corresponding *tert*-butyl derivative, conducting to **3pa** in excellent yield. This observation is probably due to the σ -donor effect of the silyl group that electronically enriched the iodine atom of the corresponding iodoallene and therefore increase its ability to act as a halogen-bond acceptor.

From a mechanistic point of view, we envisaged two plausible pathways to obtain propargyl ethers **3** from 7-alkynylcyclohepta-1,3,5-trienes **1** (Scheme 6). Both are initiated by the reaction of **1** with NIS to give the corresponding iodoallene **2** followed by the catalytic activation of iodine atom of the latter by halogen bonding with the slight excess of NIS present in the reaction media. In one case, the alcohol might react with this activated intermediate **4** via a S_N2' mechanism (pathway 1). In the other case, we might envisioned formation of **3** from **4** through a S_N1' mechanism (pathway 2). The halogen bonding activation might lead to the direct iodine abstraction to form a benzyl cation intermediate **5** which might be attack by MeOH. In both cases, I_2 would be released in the reaction media, which is confirmed by the purple coloration of the reaction media during the process, and act as halogen bond donor to promote the catalytic activation of the iodoallene **2**.



Scheme 6. Putative mechanism of the domino reaction.

The NIS-triggered propargylation of MeOH to give **3ac** from iodoallene **2c** was studied computationally (by Prof. V. Gandon). DFT calculations were carried out using the Gaussian 16 software package. Geometries were optimized using the M06-2X functional, the 6-311+G(d,p) basis set for C, H, N and O, and the aug-cc-pVTZ-PP basis set for I. Thermal corrections were obtained at the optimization level. Solvation corrections for dichloroethane were obtained with the PCM method at the same level of theory. The values presented are ΔG in kcal/mol at 298.15 K. Using CO_3^{2-} as model base, this transformation is strongly exergonic by 54.9 kcal/mol (Figure 1, upper box). Optimization of **2c**, NIS and MeOH led to adduct **A** as the most stable conformer. Analysis of the maximum electron density revealed a halogen bond between the two iodine atoms, actually consistent with a weakly covalent σ interaction ($\rho_{\text{max}} = 0.016 \text{ e}/\text{\AA}^3$ in the I...I area).^[23] Cleavage of the C–I bond was achieved through transition state **TS_{AB}**, lying at 16.4 kcal/mol on the energy surface. This step is endergonic by 14.3 kcal/mol. The I–I distance of 3.0 Å and the near linear NII angle (179.6°) are consistent with the geometry of the sole X-ray structure available.^[24] The propargyl cation moiety of the resulting adduct **B** is

[23] B. P. Hay, V. S. Bryantsev, *Chem. Commun.* **2008**, 2417-2428.

[24] M. Ghassemzadeh, K. Dehnicke, H. Goesmann, D. Fenske, *Z. Naturforsch.* **1994**, 49b, 602-608.

stabilized by the inner iodine atom of the $[\text{NIS}\cdot\text{I}]^-$ anion and the oxygen atom of MeOH (both at $\rho_{\text{max}} = 0.016 \text{ e}/\text{\AA}^3$). Importantly, while the barrier of this C–I bond cleavage is easily accessible and might contribute to the racemization of the allene, the *exo* addition of MeOH to the ion pair could not be modeled. Thus, we envisaged an *endo* pathway in which MeOH lies on the same allene side than the $[\text{NIS}\cdot\text{I}]^-$ anion. The corresponding system **C** was found 1.4 kcal/mol less stable than **A**. However, the cleavage of the C–I bond proceeds at a lower free energy cost, i.e. 14.8 kcal/mol vs 16.4 kcal/mol. Interestingly, addition of MeOH to the nascent propargyl carbocation occurs spontaneously, providing the oxonium **D**, located at 4.0 kcal/mol. Its deprotonation towards **E** is highly exergonic. The 6.9 kcal/mol difference between **E** (-61.8 kcal/mol) and the free energy of the reaction (-54.9 kcal/mol) corresponds to the dissociation of I^- from $[\text{NIS}\cdot\text{I}]^-$ and therefore the recycling of the catalyst.

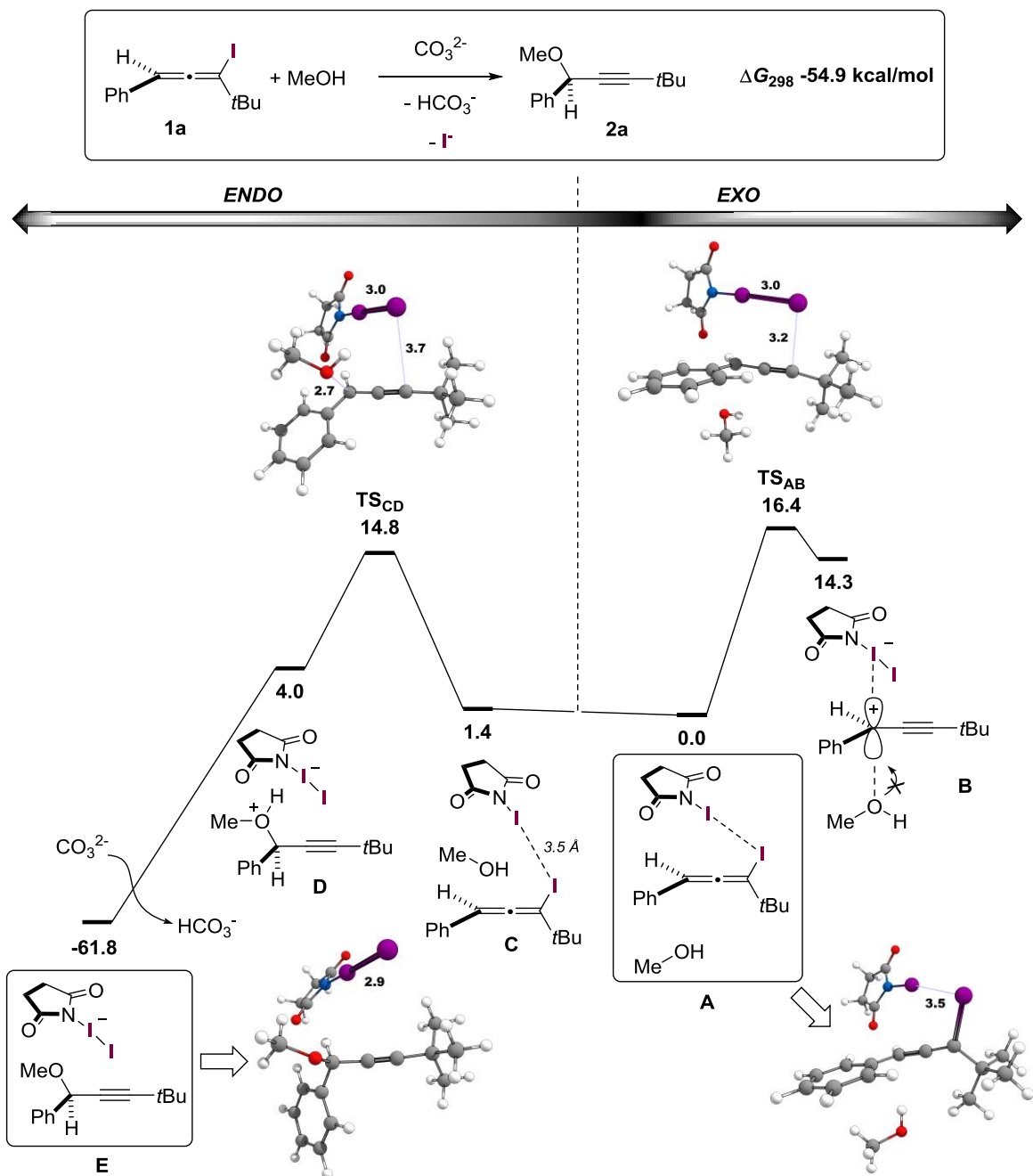


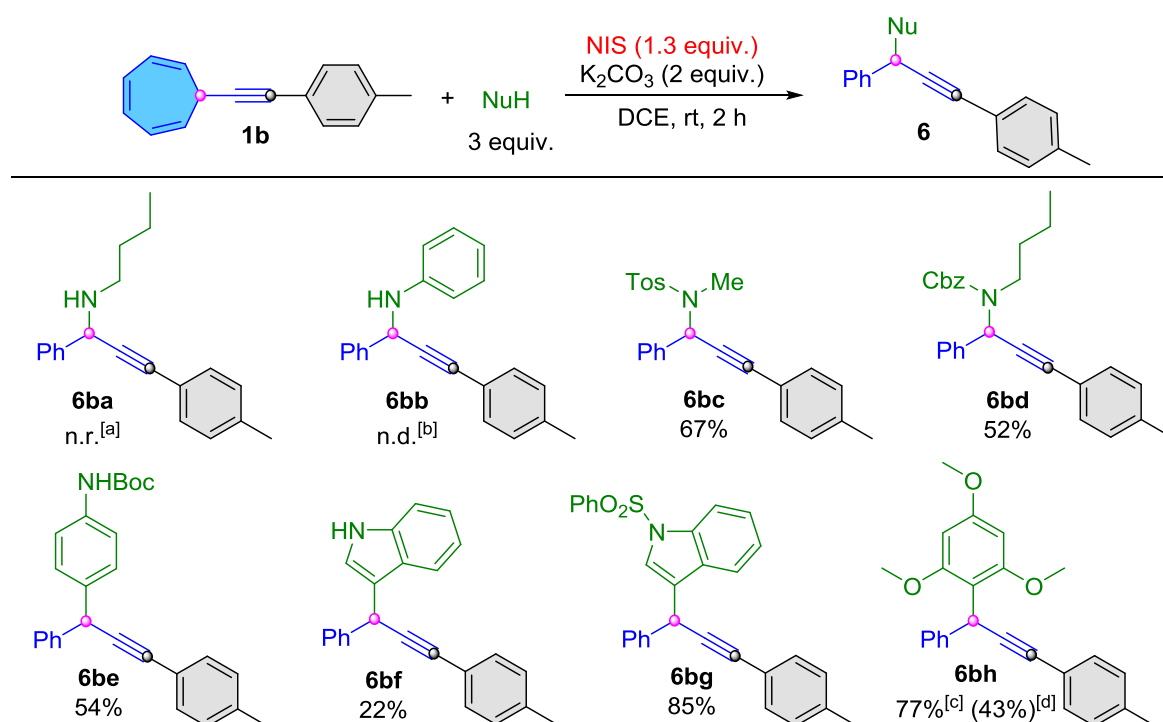
Figure 1. Free energy profile (ΔG_{298} , kcal/mol) of the NIS-triggered propargylation of methanol from iodoallene **2c**.

Overall, this DFT analysis suggest a concerted pathway in which NIS plays the role of a halogen bond donor. While a few NIS-catalyzed reactions have been described,^[25] we are

[25] (a) G.-A. Lee, W.-C. Wang, M. Shieh, T.-S. Kuo, *Chem. Commun.* **2010**, 46, 5009-5011; (b) N. George, M. Bekkaye, A. Alix, J. Zhu, G. Masson, *Chem. Eur. J.* **2014**, 20, 3621-3625; (c) A. R. Tiwari, T. Akash, B. M. Bhanage, *Org. Biomol. Chem.* **2015**, 13, 10973-10976 ; (d) M. Lamani, K. R. Prabhu, *Chem. Eur. J.* **2018**, 18, 14638-14642.

not aware of any substoichiometric use of NIS in halogen bonding catalysis.^[4,21,26]

To evaluate the robustness of this domino process, we explored the compatibility of our protocol with other nucleophiles, i.e. C- and N-nucleophiles (Scheme 7). As it should be expected, the use of Lewis bases as nucleophile, such as *N*-butylamine (**6ba**) or aniline (**6bb**), are incompatible with the propargylation reaction due to their strong halogen bond acceptor character.



Scheme 7. Selected examples of N- and C-propargylation by activation of 7-(*p*-tolylethynyl)cyclohepta-1,3,5-triene **1b** with NIS. Standard reaction conditions: 0.2 mmol of **1b**, 0.6 mmol of nucleophile, 0.4 mmol of K₂CO₃ and 0.26 mmol of NIS in 0.5 mL of DCE for 2 h. Yields refer to chromatographically isolated product. [a] n.r. stands for no reaction. [b] n.d. stands for not detected into the crude product, partial degradation of **1** was observed. [c] Reaction ran at -78 °C for 4.5 h in DCM. [d] Isolated yield using standard reaction conditions.

Fortunately, the protected *N*-methyl-*p*-toluenesulfonamide and benzyl *N*-butylcarbamate afforded the desired propargylamines **6bc** and **6bd** in 67 and 52% yield, respectively. Surprisingly, the use of *N*-Boc-aniline led to the C-propargylated derivative **6be** in 54% yield instead of the expected *N*-propargylated one. The same result was observed using

[26] R. L. Sutar, S. M. Huber, *ACS Catal.* **2019**, *9*, 9622-9639.

indole as nucleophile, leading to the C₃-propargylated derivative **6bf** in low yield (22 % yield). A new time, the reaction could be improved using the 1-(phenylsulfonyl)indole to gave the expected 1,3-disubstituted indole **6bg** in good yield (85% yield). Finally, the highly nucleophilic 1,3,5-trimethoxybenzene appeared to be a compatible C-nucleophile only if the reaction temperature was decreased to -78 °C. if even those last results should be optimized depending on the nature of the nucleophile used, they demonstrate the versatility of the developed domino reaction and the ability of NIS to catalyze the iodine abstraction of 3-substituted 3-iodo-1-phenylallenes for the promotion of *O*-, *N*- and C-propargylation reaction.

IV.3. Conclusion

In summary, we have developed a novel NIS-promoted propargylation reaction using 7-alkynylcyclohepta-1,3,5-trienes as propargylation agents. This domino reaction allowed for the rapid access to a large variety of highly functionalized ethers of primary, secondary and tertiary aliphatic alcohols. Moreover, this reaction could be extended to the use of none basic *N*-nucleophiles such as sulfonamide and carbamate as well as aromatic C-nucleophile. In this process, NIS is both a reactant for the formation of the iodoallene intermediate as well as a catalyst to promote the deiodination of the latter by halogen bonding. Further investigations in the determination of the complete mechanism and its stereoselectivity, as well as into the development of an enantioselective version, are currently in progress.

IV.4. Experimental section

General Considerations. Unless otherwise stated, commercially available reagents were used as received. Solvents were purified by distillation under argon from the following: tetrahydrofuran (THF) and diethyl ether (Et₂O): sodium/benzophenone; toluene (tol): sodium; dichloromethane (DCM) and 1,2-dichloroethane (DCE): calcium hydride. The

following compounds were previously described: **3ba**,^[27] **3ca**,^[28] **3fa**,^[29] **3ma**,^[30] **3oa**,^[31] **3pa**.^[32] ¹H and ¹³C NMR spectra were recorded on Bruker 250, 300 and 360 MHz spectrometers at 20 °C. ¹H NMR chemical shifts are reported in ppm using residual solvent peak as reference (CHCl₃: δ = 7.27 ppm). Data for ¹H NMR are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz) and integration; ¹³C NMR spectra were recorded at 63, 75, 91 or 100 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference (CHCl₃: δ = 77.16 ppm, CH₂Cl₂: δ = 53.84 ppm). Flash chromatography (FC) was performed with 40-63 μ m silica gel with mixtures of ethyl acetate (EtOAc) and cyclohexane (Cy). Thin layer chromatography was carried out using Merck TLC Silica gel 60 F254 and visualized by short-wavelength ultraviolet light.

General Procedure for the Synthesis of the 7-Alkynylcycloheptatrienes. The alkyne (1.0 equiv) was added into an oven-dried 250 mL round-bottom flask under a nitrogen atmosphere. Dry THF was added, and the resulting solution was cooled to -78 °C before adding n-BuLi (1.1 equiv) and stirred for 1 h at this temperature. The freshly prepared alkynyllithium solution was added into a solution of tropylium tetrafluoroborate (1.2 equiv) in dry THF. After stirring the mixture at RT for 1 h, the reaction was quenched with a saturated aqueous solution of NH₄Cl (30 mL), and the aqueous layer was extracted with Et₂O (3×40 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude reaction mixture was

[27] I. Suzuki, M. Yasuda, A. Baba, *Chem. Commun.* **2013**, 49, 11620-11622.

[28] A. Krueger, *Science of Synthesis*. **2008**, 43, 469-554.

[29] S. A. Savarimuthu, D. G. L. Prakash, S. A. Thomas, *Tetrahedron Lett.* **2014**, 55, 3213-3217.

[30] R. Mahrwald, S. Quint, *Tetrahedron*. **2000**, 56, 7463-7468.

[31] Toste. F. Dean, *U.S. Pat. Appl. Publ.* 20040181094.

[32] H. Hopf, E. Naujoks, *Tetrahedron*. **1988**, 29, 609-610.

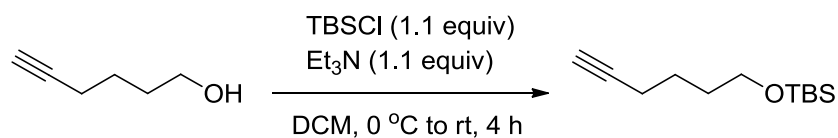
purified by chromatography on silica gel (Cy/AcOEt, 100:0 to 97:3) to afford the desired product.

Procedure for the Synthesis of haloallene **2c & **2c'**.** 7-Alkynylcycloheptatrienes (1.0 equiv), NBS or NIS (1.1 equiv) and dry DCE were added into a 100 mL round-bottom flask equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature for 6 h. Then, the reaction was quenched with a saturated aqueous solution of Na₂S₂O₃ (5 mL), and the aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Cy/EtOAc, 100:0) to afford haloallene **2c** or **2c'**.

General Procedure for activation of haloallene by NIS. NIS (1.0 equiv, 0.20 mmol) was added to a solution of 3-*tert*butyl-3-halo-1-phenylallene **2c** (1.0 equiv, 0.20 mmol), K₂CO₃ (2.0 equiv, 0.40 mmol) and nucleophile (3.0 equiv, 0.60 mmol) in dry DCE (1.0 mL). The reaction mixture was stirred at RT for 5 min. Then, the reaction was quenched with 0.1 M Na₂S₂O₃ solution (10mL), and the aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography on silica gel (Cy/AcOEt, 100:0 to 97:3) to afford the desired product.

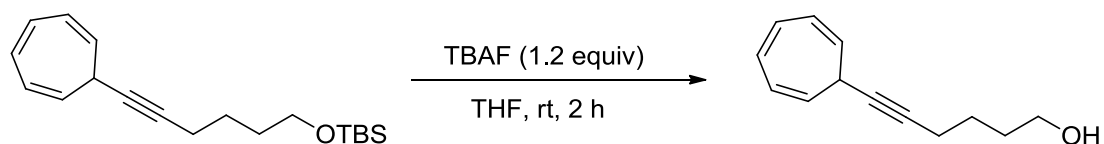
General Procedure for NIS-promoted propargylation of nucleophiles. NIS (1.3 equiv, 0.26 mmol) was added to a solution of 7-Alkynylcycloheptatrienes (1.0 equiv, 0.20 mmol), K₂CO₃ (2.0 equiv, 0.40 mmol) and nucleophile (3.0 equiv, 0.60 mmol) in dry DCE (1.0 mL). The reaction mixture was stirred at RT for 2 h. Then, the reaction was quenched with 0.1 M Na₂S₂O₃ solution (10mL), and the aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography on silica gel (Cy/AcOEt, 100:0 to 97:3) to afford the desired product.

Procedure for the synthesis of *t*-butyl(hex-5-yn-1-yloxy)dimethylsilane



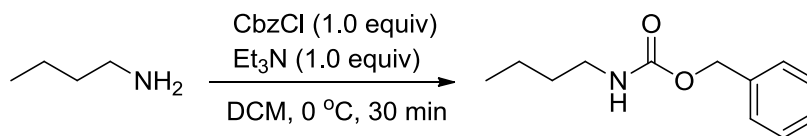
Triethylamine (1674.4 mg, 16.5 mmol, 1.1 equiv) and *t*-butyldimethylchlorosilane (2487.9 mg, 16.5 mmol, 1.1 equiv) was added to a solution of hex-5-yn-1-ol (1470.7 mg, 15.0 mmol, 1.0 equiv) in DCM (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 hours and quenched with H₂O (50 mL). The organic layer was collected. The aqueous layer was extracted with DCM (3×20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cy/EtOAc). The product was obtained as a yellow oil (2902.7 mg, 13.7 mmol, 91%).

Procedure for the synthesis of 6-(cyclohepta-2,4,6-trien-1-yl)hex-5-yn-1-ol



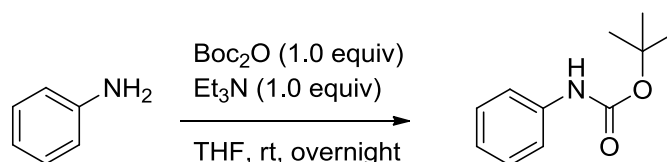
TBAF (3.3 ml, 1.0 molL⁻¹, 3.30 mmol, 1.2 equiv) was added to a solution of *t*-butyl((6-(cyclohepta-2,4,6-trien-1-yl)hex-5-yn-1-yl)oxy)dimethylsilane (839.0 mg, 2.77 mmol, 1.0 equiv) in THF (20 mL) at room temperature. The reaction was stirred for 2 hours and quenched with H₂O (50 mL). EtOAc (50 ml) was added and the organic layer was collected. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cy/EtOAc). The product was obtained as a yellow oil (494.0 mg, 2.62 mmol, 95 %).

Procedure for the synthesis of benzyl butylcarbamate



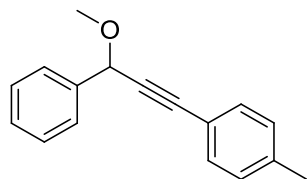
Triethylamine (1012.4 mg, 10.0 mmol, 1.0 equiv) and benzyl carbonochloridate (1706.6 mg, 10.0 mmol, 1.0 equiv) were added to a solution of butylamine (731.9 mg, 10.0 mmol, 1.0 equiv) in DCM (50 ml) at 0 °C. The reaction mixture was stirred at room temperature for 4 hour. The reaction was washed with brine (60 mL). The organic layer was collected. The aqueous layer was extracted with DCM (3x20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cy/EtOAc). The product was obtained as a colorless oil (1847.7 mg, 8.91 mmol, 89 %).

Procedure for the synthesis of *t*-butyl phenylcarbamate



Triethylamine (1015.7 mg, 10.0 mmol, 1.0 equiv) and *di-t*-butyl dicarbonate (2183.8 mg, 10.0 mmol, 1.0 equiv) were added to a solution of aniline (932.2 mg, 10.0 mmol, 1.0 equiv) in THF (40 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction was washed with brine (60 mL). The organic layer was collected. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cy/EtOAc). The product was obtained as a white solid (1621.5 mg, 8.40 mmol, 84 %).

1-(3-methoxy-3-phenylprop-1-yn-1-yl)-4-methylbenzene 3ba



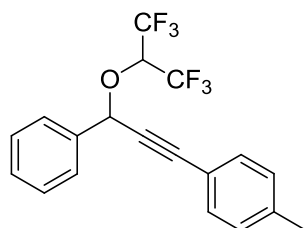
3ba

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.69 (d, $J = 7.8$ Hz, 2H), 7.57 – 7.36 (m, 5H), 7.20 (d, $J = 7.8$ Hz, 2H), 5.40 (s, 1H), 3.58 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.66 (C), 138.63 (C), 131.69 (2 CH), 129.06 (2 CH), 128.50 (2 CH), 128.41 (CH), 127.50 (2 CH), 119.48 (C), 87.91 (C), 86.01 (C), 73.52 (CH), 55.86 (CH_3), 21.45 (CH_3).

The spectral data for **3ba** match those previously reported in the literature.^[27]

1-(3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-3-phenylprop-1-yn-1-yl)-4-methylbenzene

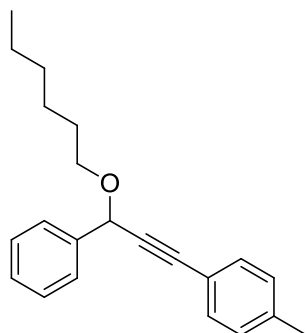
3bb



3bb

Orange oil. ^1H NMR (360 MHz, CDCl_3) δ 7.63 (d, $J = 7.9$ Hz, 2H), 7.50 – 7.38 (m, 5H), 7.19 (d, $J = 7.9$ Hz, 2H), 5.80 (s, 1H), 4.94 – 4.71 (m, 1H), 2.39 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 139.77 (C), 136.53 (C), 131.90 (2 CH), 129.56 (CH), 129.37 (2 CH), 128.89 (2 CH), 127.99 (2 CH), 118.44 (C), 91.03 (C), 82.88 (C), 75.37 (CH), 72.83 (hept, $J = 32.4$ Hz, CH), 21.66 (CH_3). ^{19}F NMR (235 MHz, CDCl_3) δ -72.70 – -72.94 (m), -73.22 – -73.44 (m). HRMS-APCI: m/z calculated for $\text{C}_{19}\text{H}_{15}\text{F}_6\text{O}$ $[\text{M}+\text{H}]^+$: 373.1022, found: 373.1035.

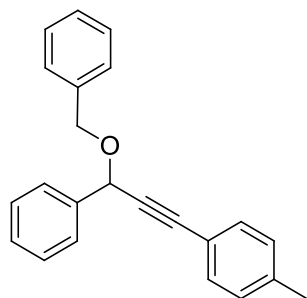
1-(3-(hexyloxy)-3-phenylprop-1-yn-1-yl)-4-methylbenzene 3bd



3bd

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.60 (d, $J = 7.4$ Hz, 2H), 7.44 – 7.30 (m, 5H), 7.13 (d, $J = 7.4$ Hz, 2H), 5.39 (s, 1H), 3.73 (m, 1H), 3.56 (m, 1H), 2.36 (s, 3H), 1.75 – 1.60 (m, 2H), 1.49 – 1.22 (m, 7H), 0.89 (t, $J = 6.3$ Hz, 3H). ^{13}C NMR (90 MHz, CDCl_3) δ 139.28 (C), 138.68 (C), 131.81 (2 CH), 129.14 (2 CH), 128.57 (2 CH), 128.34 (CH), 127.58 (2 CH), 119.76 (C), 87.53 (C), 86.76 (C), 72.13 (CH), 68.65 (CH_2), 31.79 (CH_2), 29.79 (CH_2), 26.01 (CH_2), 22.76 (CH_2), 21.62 (CH_3), 14.21 (CH_3). HRMS-ESI: m/z calculated for $\text{C}_{22}\text{H}_{26}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 329.1876, found: 329.1860.

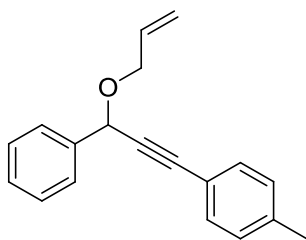
1-(3-(benzyloxy)-3-phenylprop-1-yn-1-yl)-4-methylbenzene 3be



3be

Orange oil. ^1H NMR (360 MHz, CDCl_3) δ 7.63 (m, 2H), 7.48 – 7.30 (m, 10H), 7.19 – 7.12 (m, 2H), 5.47 (s, 1H), 4.81 (d, $J = 11.8$ Hz, 1H), 4.75 (d, $J = 11.8$ Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.90 (C), 138.82 (C), 137.97 (C), 131.85 (2 CH), 129.18 (2 CH), 128.63 (2 CH), 128.55 (2 CH), 128.50 (CH), 128.30 (2 CH), 127.88 (CH), 127.73 (2 CH), 119.62 (C), 88.12 (C), 86.27 (C), 71.11 (CH), 70.11 (CH_2), 21.63 (CH_3). HRMS-ESI: m/z calculated for $\text{C}_{23}\text{H}_{20}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 335.1406, found: 335.1408.

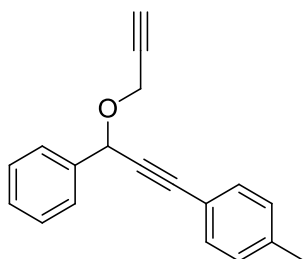
1-(3-(allyloxy)-3-phenylprop-1-yn-1-yl)-4-methylbenzene 3bf



3bf

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.74 – 7.55 (d, $J = 7.9$ Hz, 2H), 7.50 – 7.28 (m, 5H), 7.14 (d, $J = 7.9$ Hz, 2H), 6.21 – 5.87 (m, 1H), 5.46 (s, 1H), 5.38 (m, 1H), 5.26 (m, 1H), 4.32 – 4.24 (m, 1H), 4.20 (m, 1H), 2.37 (s, 1H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.92 (C), 138.78 (C), 134.47 (CH), 131.82 (2 CH), 129.15 (2 CH), 128.62 (2 CH), 128.49 (CH), 127.67 (2 CH), 119.60 (C), 117.89 (CH_2), 87.84 (C), 86.32 (C), 71.27 (CH), 69.31 (CH_2), 21.62 (CH_3).

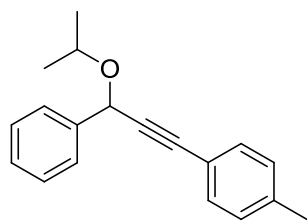
1-methyl-4-(3-phenyl-3-(prop-2-yn-1-yloxy)prop-1-yn-1-yl)benzene 3bg



3bg

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.63 (d, $J = 7.9$ Hz, 2H), 7.48 – 7.33 (m, 5H), 7.15 (d, $J = 7.9$ Hz, 2H), 5.66 (s, 1H), 4.48 (dd, $J = 15.7, 2.4$ Hz, 1H), 4.34 (dd, $J = 15.7, 2.4$ Hz, 1H), 2.52 (t, $J = 2.4$ Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.96 (C), 138.11 (C), 131.85 (2 CH), 129.18 (2 CH), 128.75 (CH), 128.68 (2 CH), 127.88 (2 CH), 119.34 (C), 88.40 (C), 85.31 (C), 79.52 (C), 75.07 (CH), 70.72 (CH), 55.56 (CH_2), 21.63 (CH_3). HRMS-APCI: m/z calculated for $\text{C}_{19}\text{H}_{17}\text{O}$ $[\text{M}+\text{H}]^+$: 261.1274, found: 261.1269.

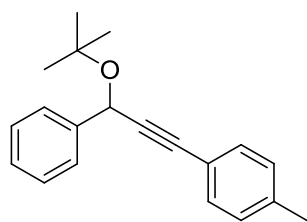
1-(3-isopropoxy-3-phenylprop-1-yn-1-yl)-4-methylbenzene 3bh



3bh

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.61 (d, $J = 7.9$ Hz, 2H), 7.45 – 7.30 (m, 5H), 7.13 (d, $J = 7.9$ Hz, 2H), 5.45 (s, 1H), 4.08 (m, $J = 6.1$ Hz, 1H), 2.36 (s, 3H), 1.31 (d, $J = 6.1$ Hz, 3H), 1.28 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 139.80 (C), 138.60 (C), 131.78 (2 CH), 129.11 (2 CH), 128.58 (2 CH), 128.26 (CH), 127.53 (2 CH), 119.82 (C), 87.42 (C), 86.88 (C), 69.83 (CH), 69.55 (CH), 23.03 (CH_3), 21.89 (CH_3), 21.60 (CH_3).

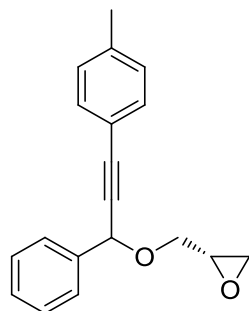
1-(3-(tert-butoxy)-3-phenylprop-1-yn-1-yl)-4-methylbenzene 3bi



3bi

Yellow solid. ^1H NMR (360 MHz, CDCl_3) δ 7.61 (d, $J = 7.9$ Hz, 2H), 7.43 – 7.28 (m, 5H), 7.12 (d, $J = 7.9$ Hz, 2H), 5.51 (s, 1H), 2.36 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (91 MHz, CDCl_3) δ 141.13 (C), 138.38 (C), 131.61 (2 CH), 129.08 (2 CH), 128.47 (2 CH), 127.80 (CH), 127.09 (2 CH), 120.19 (C), 89.90 (C), 86.03 (C), 75.74 (C), 64.75 (CH), 28.62 (3 CH_3), 21.59 (CH_3).

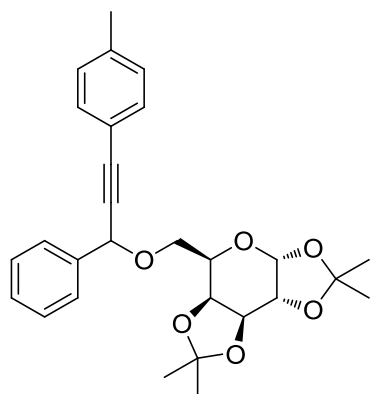
(2S)-2-(((1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)oxy)methyl)oxirane 3bj



3bj

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.61 (t, $J = 6.6$ Hz, 2H), 7.45 – 7.31 (m, 5H), 7.13 (d, $J = 7.9$ Hz, 2H), 5.51 (d, 1H), 3.95 (dd, $J = 11.3, 3.5$ Hz, 0.5H), 3.83 (dd, $J = 11.3, 3.5$ Hz, 0.5H), 3.72 (dd, $J = 11.3, 6.1$ Hz, 0.5H), 3.61 (dd, $J = 11.3, 6.1$ Hz, 0.5H), 3.29 – 3.18 (m, 1H), 2.86 – 2.79 (m, 1H), 2.66 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.92 (C), 138.51 (C), 138.46 (C), 131.83 (2 CH), 129.18 (2 CH), 128.66 (2 CH), 128.64 (CH), 127.71 (2 CH), 127.68 (2 CH), 119.42 (C), 88.31 (C), 88.26 (C), 85.84 (C), 85.78 (C), 72.50 (CH), 72.48 (CH), 69.27 (CH_2), 68.34 (CH_2), 50.93 (CH), 50.76 (CH), 44.89 (CH_2), 44.76 (CH_2), 21.63 (CH_3). HRMS-ESI: m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 301.1199, found: 301.1189.

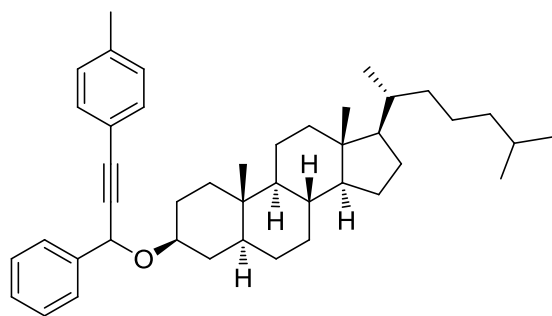
(3*aR*,5*R*,5*aS*,8*aS*,8*bR*)-2,2,7,7-tetramethyl-5-(((1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)oxy)methyl)tetrahydro-3*aH*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran 3bk



3bk

Yellow solid. ^1H NMR (360 MHz, CDCl_3) δ 7.63 (d, $J = 7.8$ Hz, 2H), 7.45 – 7.30 (m, 5H), 7.13 (d, $J = 7.8$ Hz, 2H), 5.61 – 5.50 (m, 2H), 4.62 (m, 1H), 4.39 – 4.28 (m, 2H), 4.14 – 4.04 (m, 1H), 3.98 – 3.79 (m, 2H), 2.36 (s, 3H), 1.54 (d, 3H), 1.45 (d, 3H), 1.35 (d, 6H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.83, 138.72, 138.65, 131.83, 129.10, 129.07, 128.48, 128.46, 128.39, 128.35, 127.70, 127.69, 119.70, 119.59, 109.32, 109.28, 108.67, 108.66, 96.45, 96.43, 88.08, 87.87, 86.30, 86.00, 26.20, 26.19, 26.10, 25.07, 25.03, 24.60, 24.54, 21.59. HRMS-ESI: m/z calculated for $\text{C}_{28}\text{H}_{32}\text{NaO}_6$ $[\text{M}+\text{Na}]^+$: 487.2091, found: 487.2076.

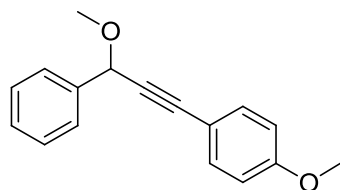
(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-(((*R*)-6-methylheptan-2-yl)-3-(((1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)oxy)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene 3bl



3bl

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.60 (d, $J = 7.8$ Hz, 2H), 7.44 – 7.29 (m, 5H), 7.13 (d, $J = 7.8$ Hz, 2H), 5.51 (d, 1H), 3.80 – 3.63 (m, 1H), 2.36 (s, 3H), 2.10 – 0.79 (m, 43H), 0.67 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 139.92, 139.85, 138.55, 131.79, 129.10, 128.57, 128.23, 127.57, 127.54, 119.88, 87.62, 87.57, 86.81, 86.77, 76.91, 69.25, 69.21, 56.63, 56.40, 54.52, 45.14, 44.99, 42.72, 40.18, 39.65, 37.28, 37.17, 36.31, 35.93, 35.88, 35.87, 35.61, 35.58, 34.66, 32.26, 32.23, 29.04, 28.99, 28.95, 28.39, 28.15, 28.11, 24.35, 23.96, 22.97, 22.71, 21.62, 21.37, 18.81, 12.43, 12.21. HRMS-APCI: m/z calculated for $\text{C}_{43}\text{H}_{61}\text{O}$ $[\text{M}+\text{H}]^+$: 593.4717, found: 593.4709.

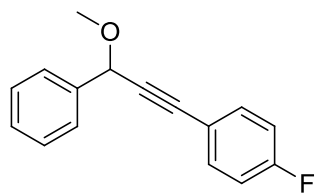
1-methoxy-4-(3-methoxy-3-phenylprop-1-yn-1-yl)benzene 3da



3da

Yellow solid. ^1H NMR (360 MHz, CDCl_3) δ 7.58 (d, $J = 8.9$ Hz, 2H), 7.47 – 7.32 (m, 5H), 6.85 (d, $J = 8.9$ Hz, 2H), 5.30 (s, 1H), 3.81 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 159.88 (C), 138.82 (C), 133.40 (2 CH), 128.64 (2 CH), 128.53 (CH), 127.64 (2 CH), 114.74 (C), 114.02 (2 CH), 87.81 (C), 85.34 (C), 73.69 (CH), 56.02 (CH_3), 55.42 (CH_3). HRMS-APCI: m/z calculated for $\text{C}_{17}\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$: 253.1223, found: 253.1210.

1-fluoro-4-(3-methoxy-3-phenylprop-1-yn-1-yl)benzene 3fa

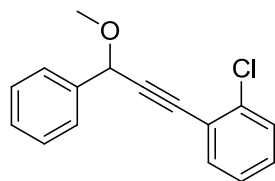


3fa

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.58 (m, 2H), 7.52 – 7.33 (m, 5H), 7.07 – 6.98 (m, 2H), 5.31 (s, 1H), 3.51 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 162.74 (d, $J = 249.7$ Hz, C), 138.54 (C), 133.83 (d, $J = 8.4$ Hz, 2 CH), 128.68 (2 CH), 128.64 (CH), 127.57 (2 CH), 118.71 (d, $J = 3.5$ Hz, C), 115.70 (d, $J = 22.1$ Hz, 2 CH), 86.72 (C), 86.53 (d, $J = 1.4$ Hz, C), 73.58 (CH), 56.11 (CH_3).

The spectral data for **3fa** match those previously reported in the literature.^[29]

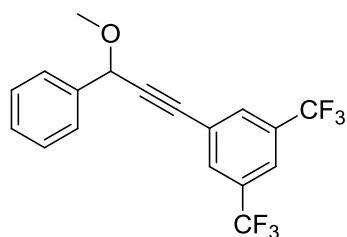
1-chloro-2-(3-methoxy-3-phenylprop-1-yn-1-yl)benzene **3ga**



3ga

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.67 – 7.61 (m, 2H), 7.53 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.46 – 7.34 (m, 4H), 7.30 – 7.20 (m, 2H), 5.41 (s, 1H), 3.55 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.25 (C), 136.26 (C), 133.59 (CH), 129.69 (CH), 129.38 (CH), 128.64 (3 CH), 127.75 (2 CH), 126.53 (CH), 122.62 (C), 91.97 (C), 84.67 (C), 73.56 (CH), 56.02 (CH_3).

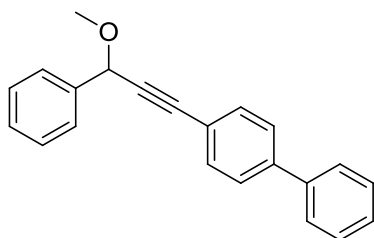
1-(3-methoxy-3-phenylprop-1-yn-1-yl)-3,5-bis(trifluoromethyl)benzene **3ha**



3ha

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 7.93 (s, 2H), 7.84 (s, 1H), 7.58 (d, $J = 7.2$ Hz, 2H), 7.42 (m, 3H), 5.33 (s, 1H), 3.53 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 137.90 (C), 132.10 (q, $J = 33.8$ Hz, 2C), 131.87 (q, $J = 3.6$ Hz, 2CH), 128.95 (CH), 128.87 (2 CH), 127.51 (2 CH), 124.98 (C), 123.03 (q, $J = 273.0$ Hz, 2CF_3), 122.11 (hept, $J = 3.7$ Hz, CH), 90.72 (C), 84.61 (C), 73.53 (CH), 56.43 (CH_3). ^{19}F NMR (235 MHz, CDCl_3) δ -63.17. HRMS-APCI: m/z calculated for $\text{C}_{18}\text{H}_{13}\text{F}_6\text{O}$ $[\text{M}+\text{H}]^+$: 359.0865, found: 359.0865.

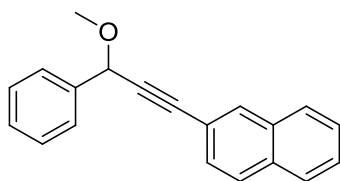
4-(3-methoxy-3-phenylprop-1-yn-1-yl)-1,1'-biphenyl 3ia



3ia

Yellow solid. ^1H NMR (360 MHz, CDCl_3) δ 7.66 – 7.57 (m, 8H), 7.50 – 7.35 (m, 6H), 5.37 (s, 1H), 3.55 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 141.39 (C), 140.37 (C), 138.62 (C), 132.34 (2 CH), 128.98 (2 CH), 128.67 (2 CH), 128.62 (CH), 127.80 (CH), 127.64 (2 CH), 127.14 (2 CH), 127.09 (2 CH), 121.52 (C), 87.73 (C), 87.42 (C), 73.67 (CH), 56.10 (CH_3).

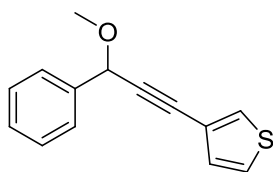
2-(3-methoxy-3-phenylprop-1-yn-1-yl)naphthalene 3ja



3ja

Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 8.06 (s, 1H), 7.83 (m, 3H), 7.69 – 7.64 (m, 2H), 7.60 – 7.36 (m, 6H), 5.41 (s, 1H), 3.58 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.63 (C), 133.00 (C), 132.97 (C), 131.88 (CH), 128.68 (2 CH), 128.62 (CH), 128.53 (CH), 128.08 (CH), 127.86 (2 CH), 127.65 (2 CH), 126.88 (CH), 126.68 (CH), 119.90 (C), 88.18 (C), 87.08 (C), 73.70 (CH), 56.13 (CH_3). HRMS-APCI: m/z calculated for $\text{C}_{20}\text{H}_{17}\text{O}$ $[\text{M}+\text{H}]^+$: 273.1274, found: 273.1291.

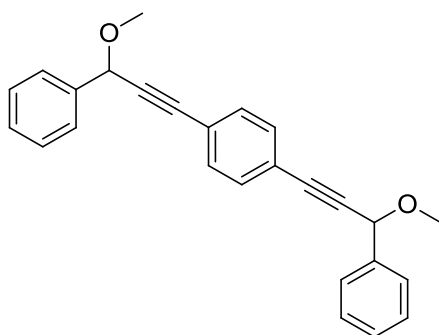
3-(3-methoxy-3-phenylprop-1-yn-1-yl)thiophene **3ka**



3ka

Brown oil. ^1H NMR (360 MHz, CDCl_3) δ 7.61 – 7.56 (m, 2H), 7.51 (dd, $J = 3.0, 1.2$ Hz, 1H), 7.44 – 7.33 (m, 3H), 7.28 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.16 (dd, $J = 5.0, 1.2$ Hz, 1H), 5.30 (s, 1H), 3.50 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.58 (C), 130.06 (CH), 129.34 (CH), 128.65 (2 CH), 128.59 (CH), 127.58 (2 CH), 125.45 (CH), 121.64 (C), 86.41 (C), 82.95 (C), 73.65 (CH), 56.11 (CH_3). HRMS-APCI: m/z calculated for $\text{C}_{14}\text{H}_{13}\text{OS}$ $[\text{M}+\text{H}]^+$: 229.0682, found: 229.0677.

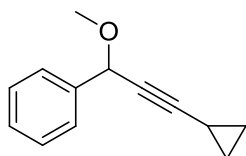
1,4-bis(3-methoxy-3-phenylprop-1-yn-1-yl)benzene **3la**



3la

Yellow solid. ^1H NMR (360 MHz, CDCl_3) δ 7.59 – 7.54 (m, 4H), 7.47 – 7.32 (m, 10H), 5.31 (s, 2H), 3.49 (s, 6H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.44 (C), 131.81 (2 CH), 128.72 (2 CH), 128.70 (CH), 127.61 (2 CH), 122.80 (C), 88.71 (C), 87.32 (C), 73.65 (CH), 56.19 (CH_3). HRMS-APCI: m/z calculated for $\text{C}_{26}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$: 367.1693, found: 367.1671.

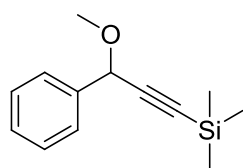
(3-cyclopropyl-1-methoxyprop-2-yn-1-yl)benzene **3na**



3na

Orange oil. ^1H NMR (360 MHz, CDCl_3) δ 7.49 (d, $J = 6.9$ Hz, 2H), 7.40 – 7.28 (m, 3H), 5.04 (d, $J = 1.2$ Hz, 1H), 3.39 (s, 3H), 1.42 – 1.22 (m, 1H), 0.87 – 0.61 (m, 4H). ^{13}C NMR (91 MHz, CDCl_3) δ 139.12 (C), 128.49 (2 CH), 128.33 (CH), 127.48 (2 CH), 91.77 (C), 73.31 (CH), 72.90 (C), 55.72 (CH_3), 8.51 (CH_2), 8.47 (CH_2), -0.31 (CH). HRMS-APCI: m/z calculated for $\text{C}_{13}\text{H}_{15}\text{O}$ $[\text{M}+\text{H}]^+$: 187.1117, found: 187.1107.

(3-methoxy-3-phenylprop-1-yn-1-yl)trimethylsilane 3pa

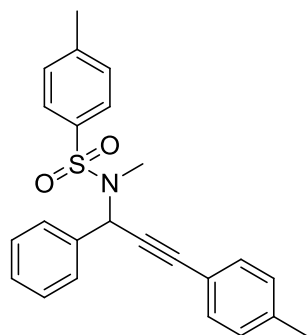


3pa

White oil. ^1H NMR (360 MHz, CDCl_3) δ 7.56 – 7.48 (m, 2H), 7.44 – 7.31 (m, 3H), 5.10 (s, 1H), 3.43 (s, 3H), 0.23 (s, 9H). ^{13}C NMR (91 MHz, CDCl_3) δ 138.29 (C), 128.57 (2 CH), 128.53 (CH), 127.65 (2 CH), 102.79 (C), 92.88 (C), 73.49 (CH), 55.84 (CH_3), 0.00 (3 CH_3).

The spectral data for **3pa** match those previously reported in the literature.^[32]

***N*,4-dimethyl-*N*-(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)benzenesulfonamide 6bc**

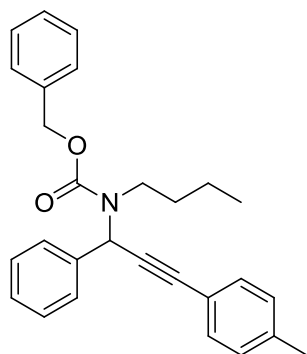


6bc

Yellow solid. ^1H NMR (360 MHz, CDCl_3) δ 7.84 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 7.9$ Hz, 2H), 7.48 – 7.27 (m, 5H), 7.08 (d, $J = 7.9$ Hz, 2H), 6.99 (d, $J = 8.1$ Hz, 2H), 6.24 (s, 1H), 2.64 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (91 MHz, CDCl_3) δ 143.57 (C), 138.86 (C), 136.22 (C), 134.80 (C), 131.53 (2 CH), 129.58 (2 CH), 128.99 (2 CH), 128.60 (2 CH), 128.42 (CH), 128.12 (2 CH), 127.99 (2 CH), 118.97 (C), 88.91 (C), 81.60 (C), 54.23 (CH), 29.98 (CH_3), 21.57 (CH_3),

21.55 (CH₃). HRMS-ESI: m/z calculated for C₂₄H₂₃NNaO₂S [M+Na]⁺: 412.1342, found: 412.1323.

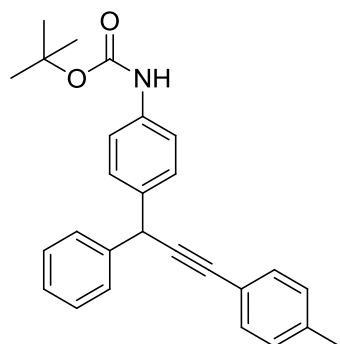
benzyl butyl(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)carbamate 6bd



6bd

Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 7.7 Hz, 2H), 7.45 – 7.27 (m, 9H), 7.16 (d, J = 7.7 Hz, 2H), 6.56 (s, 1H), 5.32 – 5.21 (m, 2H), 3.42 – 3.29 (m, 1H), 3.25 – 3.08 (m, 1H), 2.38 (s, 3H), 1.76 – 1.59 (m, 1H), 1.47 – 1.36 (m, 1H), 1.28 – 1.14 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 156.36 (C=O), 138.78 (C), 138.55 (C), 137.09 (C), 131.78 (2 CH), 129.27 (2 CH), 128.61 (4 CH), 128.08 (2 CH), 128.04 (2 CH), 127.79 (2 CH), 120.03 (C), 86.90 (C), 85.58 (C), 67.64 (CH₂), 52.49 (CH), 44.95 (CH₂), 31.51 (CH₂), 21.51 (CH₃), 20.39 (CH₂), 13.75 (CH₃). HRMS-ESI: m/z calculated for C₂₈H₂₉NNaO₂ [M+Na]⁺: 434.2091, found: 434.2070.

***tert*-butyl (4-(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)phenyl)carbamate 6be**

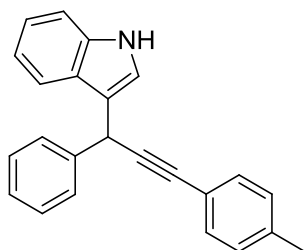


6be

White solid. ¹H NMR (360 MHz, CDCl₃) δ 7.46 (d, J = 7.9 Hz, 2H), 7.43 – 7.31 (m, 8H), 7.29 – 7.22 (m, 1H), 7.15 (d, J = 7.9 Hz, 2H), 6.51 (s, 1H), 5.19 (s, 1H), 2.38 (s, 3H), 1.54 (s, 9H). ¹³C

NMR (91 MHz, CDCl₃) δ 152.90 (C=O), 142.06 (C), 138.12 (C), 137.19 (C), 136.68 (C), 131.66 (2 CH), 129.10 (2 CH), 128.69 (2 CH), 128.60 (2 CH), 127.96 (2 CH), 126.93 (CH), 120.51 (C), 118.90 (2 CH), 89.58 (C), 85.01 (C), 80.64 (C), 43.22 (CH), 28.45 (3 CH₃), 21.58 (CH₃). HRMS-ESI: m/z calculated for C₂₇H₂₇NNaO₂ [M+Na]⁺: 420.1934, found: 420.1917.

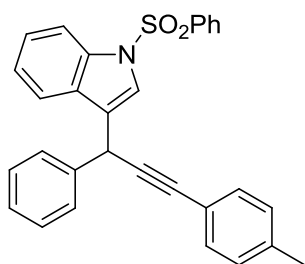
3-(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)-1*H*-indole 6bf



6bf

White solid. ¹H NMR (360 MHz, CDCl₃) δ 7.96 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.37 (dd, 5H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.16 – 7.07 (m, 4H), 5.49 (s, 1H), 2.37 (s, 3H). ¹³C NMR (91 MHz, CDCl₃) δ 141.51 (C), 137.98 (C), 136.78 (C), 131.68 (2 CH), 129.07 (2 CH), 128.59 (2 CH), 128.04 (2 CH), 126.89 (CH), 126.18 (C), 122.73 (CH), 122.28 (CH), 120.69 (C), 119.75 (CH), 119.67 (CH), 117.09 (CH), 111.34 (C), 89.86 (C), 83.48 (C), 35.60 (CH), 21.56 (CH₃). HRMS-ESI: m/z calculated for C₂₄H₂₀N [M+H]⁺: 322.1590, found: 322.1581.

3-(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)-1-(phenylsulfonyl)-1*H*-indole 6bg

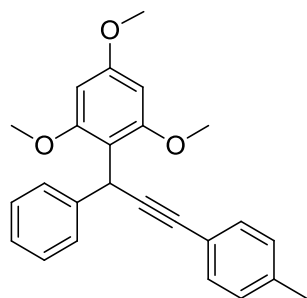


6bg

Yellow solid. ¹H NMR (250 MHz, CDCl₃) δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 7.3 Hz, 2H), 7.62 – 7.23 (m, 13H), 7.15 (m, 3H), 5.33 (s, 1H), 2.35 (s, 3H). ¹³C NMR (91 MHz, CDCl₃) δ 139.68 (C), 138.39 (C), 138.25 (C), 135.86 (C), 133.93 (CH), 131.71 (2 CH), 129.47 (C),

129.39 (2 CH), 129.14 (2 CH), 128.82 (2 CH), 127.97 (2 CH), 127.41 (CH), 126.91 (2 CH), 124.99 (CH), 124.35 (CH), 123.78 (CH), 123.40 (CH), 120.56 (CH), 120.16 (C), 113.88 (C), 88.00 (C), 84.48 (C), 35.49 (CH), 21.60 (CH₃). HRMS-ESI: m/z calculated for C₃₀H₂₃NNaO₂S [M+Na]⁺: 484.1342, found: 484.1324.

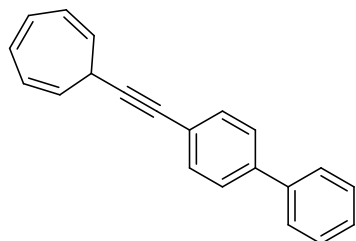
1,3,5-trimethoxy-2-(1-phenyl-3-(*p*-tolyl)prop-2-yn-1-yl)benzene 6bh



6bh

White solid. ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.27 (t, J = 7.4 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 6.17 (s, 2H), 5.87 (s, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 2.34 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 160.47 (C), 158.77 (2 C), 141.93 (C), 137.41 (C), 131.71 (2 CH), 128.98 (2 CH), 127.88 (2 CH), 127.52 (2 CH), 125.92 (CH), 121.59 (C), 111.72 (C), 91.71 (2 CH), 90.17 (C), 81.38 (C), 56.13 (2 CH₃), 55.44 (CH₃), 31.57 (CH), 21.54 (CH₃). HRMS-ESI: m/z calculated for C₂₅H₂₅O₃ [M+H]⁺: 373.1798, found: 373.1785.

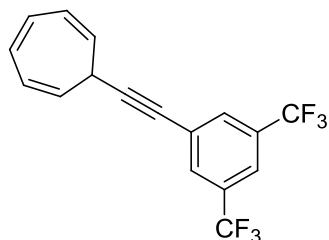
4-(cyclohepta-2,4,6-trien-1-ylethynyl)-1,1'-biphenyl



Yellow solid. ¹H NMR (360 MHz, CDCl₃) δ 7.64 – 7.53 (m, 6H), 7.50 – 7.43 (m, 2H), 7.40 – 7.34 (m, 1H), 6.74 – 6.70 (m, 2H), 6.29 – 6.20 (m, 2H), 5.47 (m, 2H), 2.76 (tt, J = 5.5, 1.2 Hz, 1H). ¹³C NMR (91 MHz, CDCl₃) δ 140.77 (C), 140.54 (C), 132.26 (2 CH), 131.18 (2 CH), 128.97 (2 CH), 127.68 (CH), 127.14 (2 CH), 127.07 (2 CH), 124.92 (2 CH), 123.31 (2 CH),

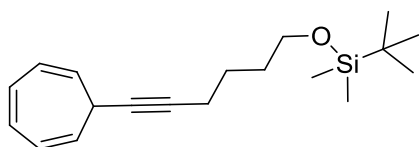
122.50 (C), 91.87 (C), 80.61 (C), 32.45 (CH). HRMS-APCI: m/z calculated for $C_{21}H_{17}$ $[M+H]^+$: 269.1325, found: 269.1309.

7-((3,5-bis(trifluoromethyl)phenyl)ethynyl)cyclohepta-1,3,5-triene



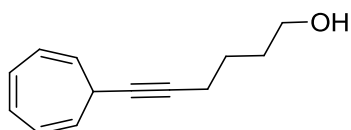
Yellow oil. 1H NMR (360 MHz, $CDCl_3$) δ 7.90 (s, 2H), 7.80 (s, 1H), 6.72 (m, 2H), 6.26 (m, 2H), 5.42 (m, 2H), 2.78 (tt, $J = 5.4, 1.1$ Hz, 1H). ^{13}C NMR (91 MHz, $CDCl_3$) δ 131.99 (q, $J = 33.3$ Hz, 2C), 131.82 (q, $J = 3.6$ Hz, 2CH), 131.30 (2 CH), 125.94 (C), 125.44 (2 CH), 123.15 (q, $J = 270.9$ Hz, $2CF_3$), 122.11 (hept, $J = 3.6$ Hz, CH), 121.94 (2 CH), 95.09 (C), 78.18 (C), 32.18 (CH). HRMS-APCI: m/z calculated for $C_{17}H_{11}F_6$ $[M+H]^+$: 329.0759, found: 329.0754.

tert-butyl((6-(cyclohepta-2,4,6-trien-1-yl)hex-5-yn-1-yl)oxy)dimethylsilane



Yellow oil. 1H NMR (360 MHz, $CDCl_3$) δ 6.64 (m, 2H), 6.15 (m, 2H), 5.39 – 5.27 (m, 2H), 3.64 (t, $J = 5.9$ Hz, 2H), 2.43 (tt, 1H), 2.25 (t, $J = 5.9$ Hz, 2H), 1.76 – 1.50 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (91 MHz, $CDCl_3$) δ 131.05 (2 CH), 124.50 (2 CH), 124.45 (2 CH), 81.80 (C), 80.48 (C), 62.88 (CH_2), 32.09 (CH_2), 31.92 (CH), 26.12 (3 CH_3), 25.50 (CH_2), 18.67 (CH_2), 18.49 (C), -5.13 (2 CH_3). HRMS-ESI: m/z calculated for $C_{19}H_{30}NaOSi$ $[M+Na]^+$: 325.1958, found: 325.1949.

6-(cyclohepta-2,4,6-trien-1-yl)hex-5-yn-1-ol



Yellow oil. ^1H NMR (360 MHz, CDCl_3) δ 6.64 (m, 2H), 6.15 (m, 2H), 5.31 (m, 2H), 3.68 (t, $J = 6.3$ Hz, 2H), 2.44 (t, $J = 7.0, 3.6, 1.6$ Hz, 1H), 2.27 (td, $J = 6.8, 1.6$ Hz, 2H), 1.78 – 1.56 (m, 4H), 1.50 (s, 1H). ^{13}C NMR (91 MHz, CDCl_3) δ 131.06 (2 CH), 124.57 (2 CH), 124.28 (2 CH), 82.04 (C), 80.24 (C), 62.61 (CH_2), 31.96 (CH_2), 31.87 (CH), 25.29 (CH_2), 18.63 (CH_2). HRMS-APCI: m/z calculated for $\text{C}_{13}\text{H}_{17}\text{O}$ $[\text{M}+\text{H}]^+$: 189.1274, found: 189.1266.

IV.5. References

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Chapter V. General conclusion and perspectives

Chapter V. General conclusion and perspectives

In this thesis, we studied the catalytic behavior of NHC-Zn(II) complexes and simple ZnX salts in a variety of transformations such as skeletal rearrangements, hydroarylations, transfer hydrogenations, hydroalkoxylations and carbonyl-olefin metatheses. NHC-Zn(II) complexes proved to be soft π -Acids and showed higher catalytic efficiency than simple ZnX salts. These findings open new perspectives in π -acid catalysis and as a perspective, enantioselective catalysis using chiral NHCs could be studied.

We have obtained a highly original cyclic divalent N(I) compound. This species had two lone pairs of electrons at the central nitrogen atom but was demonstrated to be less nucleophilic than the corresponding C(0) compounds. It would be interesting to synthesize various members of this unique family of cyclic N(I) compounds and evaluate their properties as phase transfer catalysts.

The new propargylation based on halogen bonding catalysis also deserves to be further studied as it is a very efficient transformation with a broad scope. The studies will be pursued, notably using enantioenriched substrates. If the reaction is concerted as we guess, we can anticipate to have efficient chirality transfers and grant a straightforward access to enantiopure molecules.

French Summary

La catalyse π -acide, c'est-à-dire l'activation de liaisons multiples C-C vis-à-vis d'additions nucléophiles, est devenue un outil puissant en synthèse organique au cours des 20 dernières années. De nombreuses transformations ont été rapportées dans le domaine de la catalyse au platine et à l'or, notamment par l'utilisation de complexes cationiques d'or(I) de type général LAu(I)^+ (où L est un ligand). Bien que très efficace, à notre connaissance, il n'y a pas encore d'applications industrielles de la catalyse à l'or(I). La raison pourrait être attribuée au coût élevé des catalyseurs, qui sont relativement fragiles et nécessitent une charge élevée, à sa non-recyclabilité et à la toxicité de ses traces résiduelles dans les produits finaux. Même si la conception de ligands a permis de développer des espèces robustes actives au niveau du ppm, ces complexes spécifiques et sophistiqués ne sont pas aussi polyvalents que les espèces simples telles que Ph_3PAu^+ .

Pour rendre la catalyse à l'acide π plus pratique, notre groupe a développé plusieurs axes de recherche :

- Le remplacement des complexes d'or coûteux et fragiles par des complexes métalliques du groupe principal (Ga, In, Ca majoritairement)
- Le développement de conditions catalytiques permettant de limiter la dégradation de catalyseurs polyvalents tels que Ph_3PAu^+ en or élémentaire.

Mon travail de thèse s'est concentré sur ces lignes. Dans un premier temps, j'ai exploré la capacité des catalyseurs à base de zinc à être utilisés comme acides mous tels que LAu(I)^+ , PtCl_2 , GaCl_3 ou InCl_3 (Chapitre II). Comparé au gallium et à l'indium, ce métal n'avait pas retenu l'attention jusqu'à présent de notre groupe. Même si l'on pouvait s'attendre à ce que les complexes de Zn(II) soient des espèces plutôt dures, nous avons synthétisé et testé des complexes de zinc cationiques portant un carbène N-hétérocyclique (NHC) en tant qu'activateurs mous et les avons comparés à de simples sels de ZnX_2 . Nous avons révélé

que les complexes cationiques NHC-Zn(II) peuvent être des acides très efficaces dans diverses réactions tels que des réarrangements de squelettes, des hydroarylations, des hydroalcoylations et des hydrogénations par transfert. Ils peuvent même parfois rivaliser avec les catalyseurs NHC-Au(I) ou NHC-Ga(III), bien que cette étude ait mis au jour certaines de leurs limites par rapport aux espèces d'or et de gallium. Ce travail montre également que les ions zinc stabilisés par NHC sont plus actifs que les simples halogénures de zinc.

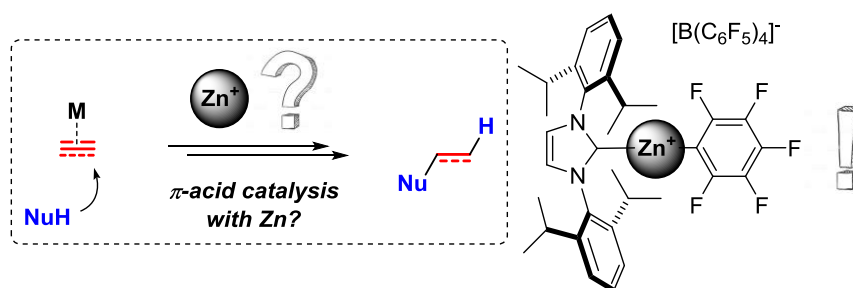


Schéma 1. Activation électrophile des liaisons multiples C-C par des complexes cationiques NHC-Zn(II).

Dans un deuxième projet, visant à réduire la charge de catalyseur dans certaines réactions catalysées à l'or, j'ai tenté de développer un catalyseur robuste à l'or (I) qui serait stabilisé par l'hémilabilité d'une phosphine modifiée (phosphole-iminophosphorane). Bien que cet objectif n'ait pas été atteint, j'ai obtenu par hasard un composé de N(I) chélaté au bis-phosphane inhabituel qui a été minutieusement analysé (chapitre III). Cette espèce a deux paires d'électrons au niveau de l'atome d'azote central, mais s'est avérée moins nucléophile que les composés C(0) correspondants.

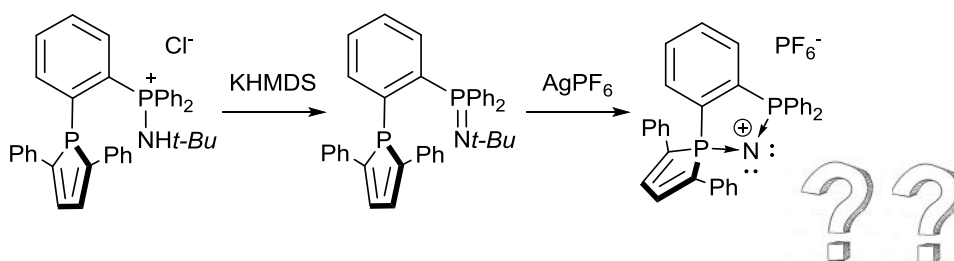


Schéma 2. Formation d'un sel de N(I) divalent original.

Enfin, dans un troisième projet, j'ai ouvert une nouvelle ligne de recherche dans le groupe en développant une abstraction d'halogénures catalysée par le NIS de 3-iodo- et 3-bromo-1-phényllallènes par liaison halogène pour favoriser la réaction de propargylation d'alcools aliphatiques (chapitre IV). Dans mon travail avec le zinc, j'ai utilisé des 7-alcynylcycloheptatriènes comme outils expérimentaux pour révéler l'acidité des complexes. Dans la continuité de ce travail sur l'activation des 7-alcynylcycloheptatriènes, j'ai développé une réaction tandem consistant en une formation in situ d'iodoallène suivie d'une addition conjuguée d'un alcool aliphatique pour donner des éthers propargyliques. Cette réaction domino a permis l'accès rapide à une grande variété d'éthers hautement fonctionnalisés à partir d'alcools aliphatiques primaires, secondaires et tertiaires. De plus, cette réaction peut être étendue à l'utilisation de N-nucléophiles non basiques tels que les sulfonamides et les carbamates, ainsi que les C-nucléophiles aromatiques. Dans ce procédé, le NIS est à la fois un réactif pour la formation de l'intermédiaire iodoallène ainsi qu'un catalyseur pour favoriser la désiodation de ce dernier par liaison halogène.

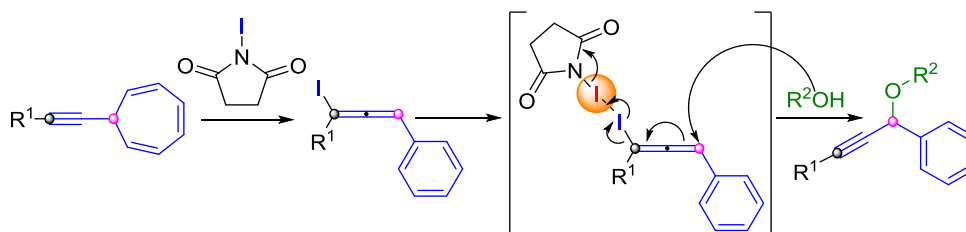


Schéma 3. Formation en un seul pot d'éthers propargyliques à partir de 7-alcynylcycloheptatriènes.

Titre : Activation Catalytique de Composés Acétyléniques par des π -Acides et par Liaison Halogène

Mots clés : catalyse π -acides, complexes NHC-Zn(II), composé de N(I) cyclique, catalyse par liaison halogène

Résumé : Ce travail de thèse a porté sur la catalyse π -acide et l'application de la catalyse par liaison halogène aux iodo- et bromoallènes. Nous avons tout d'abord synthétisé des complexes NHC-Zn(II) et étudié leur comportement catalytique dans diverses transformations, telles que la cycloisomérisation, l'hydroarylation, l'hydrogénation par transfert, l'hydroalcoxylation et la métathèse carbonyle-oléfine. Les complexes NHC-Zn(II) se sont avérés fonctionner comme des acides mous. Les complexes d'or ont été largement utilisés comme catalyseurs π -acides. Cependant, la chimie de l'or présente également certaines limites. Les charges de catalyseur sont encore très élevées dans la plupart des réactions catalysées à l'or, ce qui peut s'expliquer par la décomposition rapide des ions or.

Nous espérons stabiliser l'ion or en introduisant un site du type base de Lewis supplémentaire dans le ligand. Lors de la synthèse des ligands, nous avons obtenu de manière inattendue une nouvelle espèce à base de N(I) que nous avons étudié en détail. Notre groupe a développé une nouvelle méthode pour synthétiser les bromoallènes trisubstitués à partir de 7-alkynylcycloheptatriènes et de *N*-bromosuccinimide. Les iodoallènes pourraient a priori également être obtenus avec un procédé similaire à partir de 7-alkynylcycloheptatriènes et de *N*-iodosuccinimide. Nous avons cependant constaté qu'un excès de *N*-iodosuccinimide dans le système réactionnel pouvait activer les iodo- et bromoallènes via une catalyse par liaison halogène. Un mécanisme concerté a été proposé par nos soins après calculs DFT.

Title : Catalytic Activation of Acetylenic Compounds by π -Acids and Halogen Bonding Catalysis

Keywords : π -acid catalysis, NHC-Zn(II) complexes, a cyclic N(I) species, halogen bond catalysis

Abstract : This thesis work focused on the π -acid catalysis and the application of halogen bond catalysis into iodo- and bromoallenes. We firstly synthesized the NHC-Zn(II) complexes and studied their catalytic behavior in a variety of transformations, such as cycloisomerization, hydroarylation, transfer hydrogenation, hydroalkoxylation and carbonyl-olefin metathesis. The NHC-Zn(II) complexes were proved to work as soft π -acids.

Gold complexes have been widely used as π -acid catalysts. However, gold chemistry also has some limitations. The gold catalyst loadings are still very high in most gold-catalyzed reactions, which could be explained by the fast decay of gold ions. We hoped to stabilize the fragile gold ion by introducing

one more Lewis base site in the ligand. During the synthesis of the ligands, we unexpectedly obtained a new N(I) species.

Our group reported a new method to synthesize trisubstituted bromoallenes from 7-alkynylcycloheptatrienes and *N*-bromosuccinimide. Iodoallenes could also be obtained with a similar method from 7-alkynylcycloheptatrienes and *N*-iodosuccinimide. We further found that an excess of *N*-iodosuccinimide in the reaction system could activate the iodo- and bromoallenes via halogen bond catalysis. A concerted mechanism was proposed by us after DFT calculations.