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**Etude de la réactivité d'ynoethers et ynamines
arylogues pour des réactions d'hydroamination. Etude
visant la synthèse énantiosélective de la molécule
koumine**

Masahiro Abe

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité Chimie

Préparée au sein de l'Université de Rouen Normandie

Etude de la réactivité d'ynolethers et ynamines arylogues pour des réactions d'hydroamination. Etude visant la synthèse énantiosélective de la molécule koumine

**Présentée et soutenue par
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Thèse soutenue publiquement le 28 Mai 2019 devant le jury composé de		
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List of abbreviation

Ac	acetyl
aq.	aqueous
Ar	aryl
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
Calcd.	calculated value
CAN	ammonium hexanitratocerate(IV)
cat.	catalytic
Cbz	benzyloxycarbonyl
conc.	Concentrated
COSY	Correlation spectroscopy
CSA	10- camphorsulfonic acid
d	doublet
dd	double doublet
DMA	<i>N,N</i> -dimethylacetamide
DMAP	<i>N,N</i> -dimethyl-4-aminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereoisomeric ratio
EI	electron ionization
eq.	equivalent
Glc	Glucose
h	hour(s)
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HRMS	high resolution mass spectrometry

HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	hertz
IR	infrared spectroscopy
LRMS	low resolution mass spectrometry
m	multiplet
mCPBA	<i>meta</i> -chloroperoxybenzoic acid
mp	melting point
Ms	Mesyl
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Py	pyridine
TFA	trifluoro acetic acid
THF	tetrahydrofuran
TMS	trimethyl silyl
Tol	toluene
TsOH	<i>para</i> -toluenesulfonic acid
min	minutes
mp	melting point
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
PMP	4-methoxyphenyl
r.t.	room temperature
s	singlet
sat.	saturated
<i>t</i>	tertiary

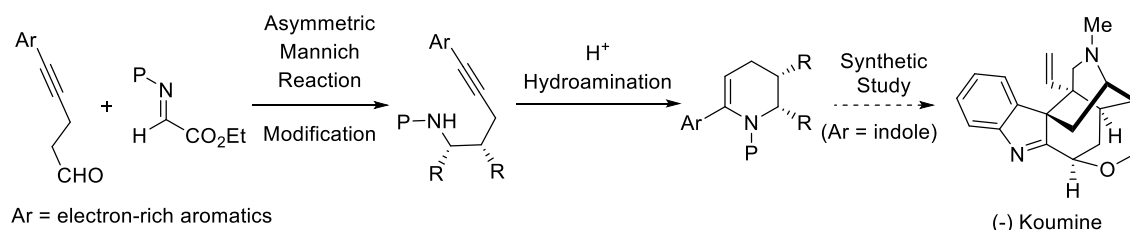
t	triplet
temp.	temperature
THF	tetrahydrofuran
Ts	<i>p</i> -toluenesulfonyl

Abstract

Piperidine ring is one of the most common heterocycles in natural products and the motif is especially well represented in pharmaceuticals. More intriguingly, enantioselective synthesis of multi-substituted piperidines has been extensively studied because most of biologically active natural products and pharmaceuticals are often functionalized with chiral carbons.

For designing highly functionalized nitrogen-containing compounds, asymmetric Mannich reactions are being established as useful tools in enantioselective organic synthesis. On the other hand, intramolecular hydroamination of alkynes is a practical strategy to construct *N*-heterocyclic products as amines don't react spontaneously with alkynes, which facilitate the construction of the acyclic products.

In this thesis, *anti*-selective enantioselective Mannich reactions are described to obtain chiral amines featuring arylogous ynolethers and ynamines. They were studied in the framework of the intramolecular hydroamination reaction promoted with Brønsted acid. It was shown that depending on the electronic density of the alkyne, these adducts were converted into 5- or 6-membered rings, highlighting the balance between H-bonding and protonation. Hence, tetrahydropyridines and piperidines were obtained with high regio-, diastereo-, and enantioselectivity. Further functionalizations were also demonstrated and, eventually, the method served as a basis for a synthetic study of *Gelsemium* alkaloid koumine.



General Introduction

~Chemistry oriented for 3D ~

In medicinal chemistry, it is considerably important to discover drug candidates with high efficiency to be approved. To this end, there are several different statistical reports (e.g. Lipinski's rule of five¹).² Notably, Lovering's report that drug candidates possessing more sp³-carbons tend to survive in clinical trials has been intriguing for pharmaceutical researchers.³ According to their report, molecule possessing more sp³-carbons provided several benefits in physical properties. For example, aqueous solubility of molecules bearing more sp³-carbons were improved than molecules bearing more aromatics. Secondly, there was a correlation between the saturation and the melting point of molecules, in which the increase of saturation afforded lower melting point. And increasing sp³ character improved the three-dimensionality and structural diversity of molecules without significantly increasing molecular weight. (e.g. Dimethyl pyridines have only 6 isomers while methyl piperidines have 30 isomers (Fig 1).

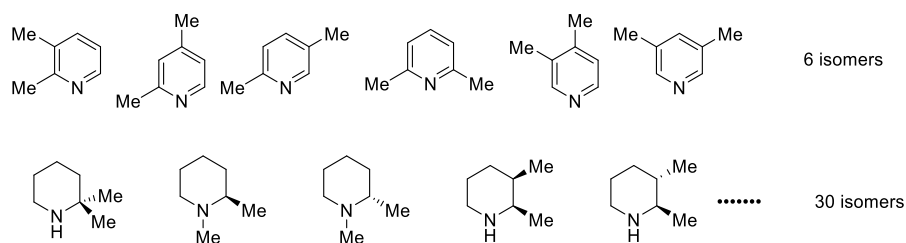


Fig 1. Isomers of dimethylpyridine and dimethylpiperidine.

Owing to those benefits, it was expected that in regards to the development of new medicines progressed (discovery, phase 1,2,3 and drugs), molecules holding higher Fsp³ would be prone to endure evaluations to the end (Fig. 2).

¹ a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug. Delivery Rev.* **1997**, *23*, 3. b) Lipinski, C. A., *Drug Discovery Today: Technologies* **2004**, *1*, 337.

² a) Nicholls, A.; McGaughey, G. B.; Sheridan, R. P.; Good, A. C.; Warren, G.; Mathieu, M.; Muchmore, S. W.; Brown, S. P.; Grant, J. A.; Haigh, J. A.; Nevins, N.; Jain, A. N.; Kelley, B., *J. Med. Chem.* **2010**, *53*, 3862. b) Ritchie, T. J.; Macdonald, S. J., *Drug Discovery Today* **2009**, *14*, 1011.

³ Lovering, F.; Bikker, J.; Humblet, C., *J. Med. Chem.* **2009**, *52*, 6752.

$$F_{sp^3} = (\text{number of } sp^3 \text{ hybridized carbon} / \text{total carbon count})$$

Therefore, there is tremendous potential in exploring ‘ sp^3 -carbon chemistry’ which should contribute in the advancement of drug discovery.

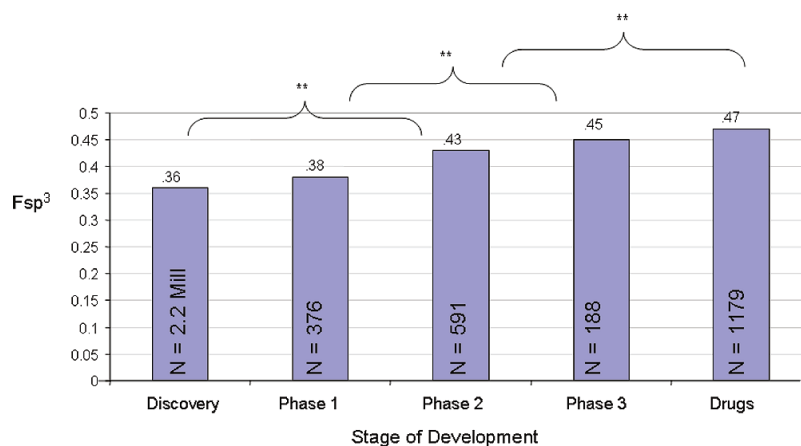


Figure 3. Mean F_{sp^3} for compounds in different stages of development. ** P value < 0.001.

Fig 2. Ratio of F_{sp^3} of molecules in each stages of development

From Lovering, F.; Bikker, J.; Humblet, C., *J. Med. Chem.* **2009**, *52*, 6752.

On the other hand, natural products frequently consist of countless sp^3 -carbons with entirely complex connections. Dobson analyzed the chemical spaces⁴ in synthetic products, natural products and pharmaceutical products.⁵ Remarkably, the chemical space of natural products is close to the chemical space of pharmaceutical products, unlike the one of synthetic products (**Fig 3**). This suggests that research on natural products or natural products-mimic compounds is likely to give clues for the development of new pharmaceuticals.

Hence, building up molecules with higher F_{sp^3} , including natural products, will contribute to the efficient exploration of drug candidates and broaden the molecular diversity.

⁴ Chemical space is defined as total descriptor space that encompasses all the small carbon-based molecules that could in principle be created. Descriptor is a molecular characteristic such as molecular mass, lipophilicity, topological features *etc.*

⁵ Dobson, C. M., *Nature* **2004**, *432*, 824.

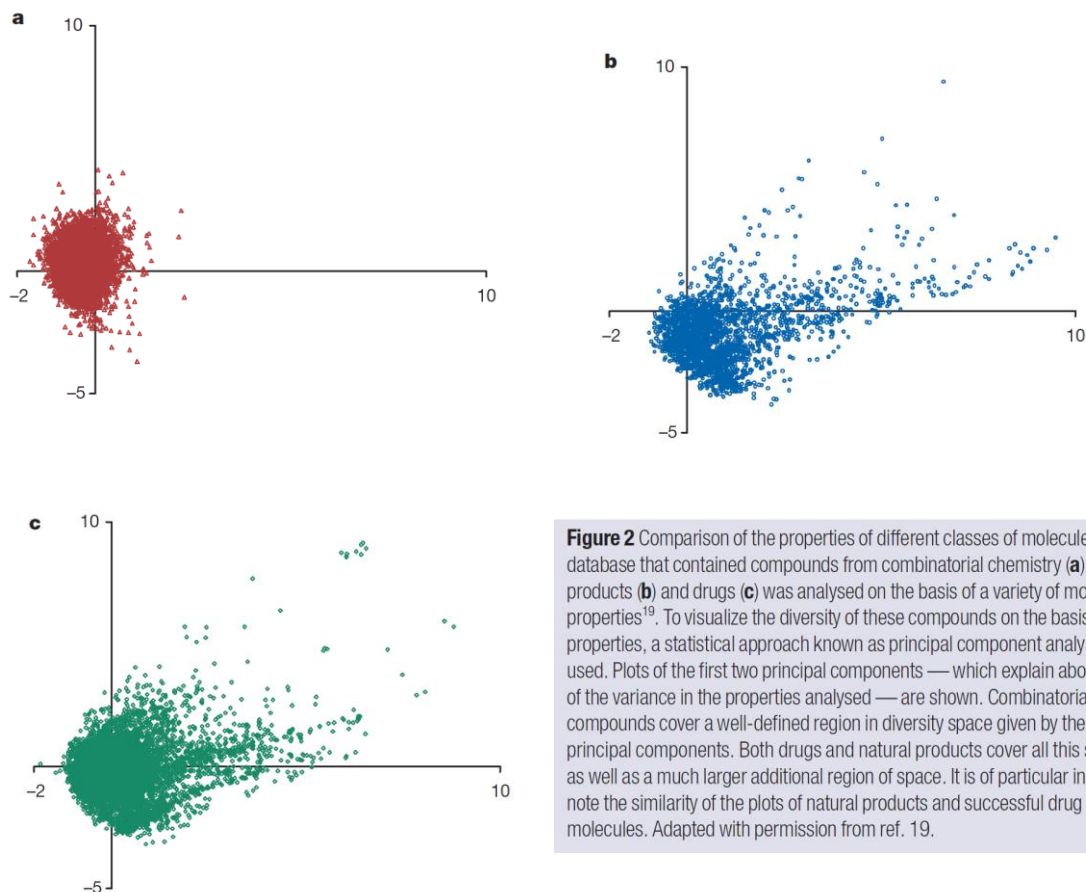


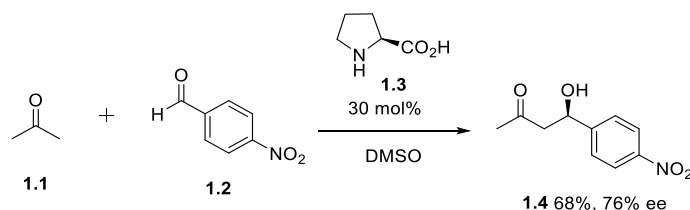
Figure 2 Comparison of the properties of different classes of molecule. A large database that contained compounds from combinatorial chemistry (a), natural products (b) and drugs (c) was analysed on the basis of a variety of molecular properties¹⁹. To visualize the diversity of these compounds on the basis of these properties, a statistical approach known as principal component analysis was used. Plots of the first two principal components — which explain about 54% of the variance in the properties analysed — are shown. Combinatorial compounds cover a well-defined region in diversity space given by these principal components. Both drugs and natural products cover all this space, as well as a much larger additional region of space. It is of particular interest to note the similarity of the plots of natural products and successful drug molecules. Adapted with permission from ref. 19.

Fig 3. Chemical space of combinatorial chemistry, natural products and drugs
 From Dobson, C. M., *Nature* **2004**, 432, 824.

1 Organocatalyzed Asymmetric Mannich Reaction

1.1 Introduction

Asymmetric organocatalysis has been developed expeditiously from the landmark discovery of the intermolecular proline-catalyzed enantioselective aldol reaction by List and Barbas *et al.* in 2000 (**Scheme 1.1**).⁶ Although almost 30 years passed since the intramolecular reaction was disclosed by Hajos-Parrish-Eder-Sauer-Wiechert in 1970s,⁷ the field of organocatalysis drew considerable attentions because most of organocatalyzed reactions are tolerant to moisture and oxygen and no metal is needed. Nowadays, asymmetric organocatalyzed reactions are being established as an important tool in enantioselective organic synthesis.



Scheme 1.1

1.2 Organocatalyzed Asymmetric Mannich Reaction

Asymmetric Mannich reaction is a useful method for designing highly functionalized nitrogen-containing compounds.⁸ β -Amino carbonyl compounds derived from the Mannich adducts are fairly profitable for building blocks in pharmaceuticals, natural products and peptidic materials. Since List first discovered that amino acid proline **1.3**, which is abundant in nature, can catalyze asymmetric Mannich reaction in excellent enantioselective fashion in 2000 (**Scheme 1.2**),⁹ a lot of researchers developed numerous asymmetric Mannich reactions with several kinds of

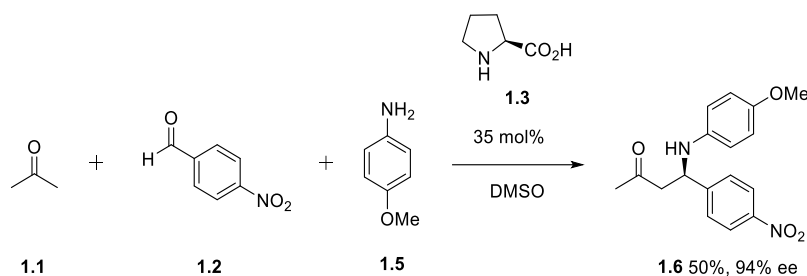
⁶ List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

⁷ (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358.

⁸ For reviews of asymmetric Mannich reactions (a) Ting A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (b) Verkade, J. M. M.; von Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (c) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.*, **2010**, *39*, 1656. (d) Karimi, B.; Enders, D.; Jafari, E. *Synthesis*, **2013**, 2769.

⁹ List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

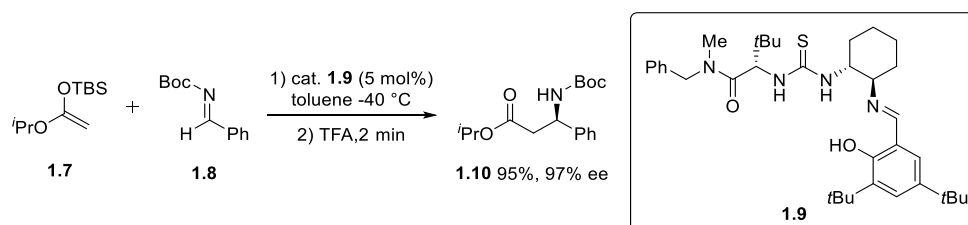
organocatalysts. Herein, I would sort these reactions into several types by catalyst's characters.



Scheme 1.2

1.2.1 Thiourea Type Catalyst

In 2002, Jacobsen *et al.* first reported the thiourea-catalyzed asymmetric Mannich reactions of ketene silyl acetals **1.7** and *N*-Boc protected aldimines **1.8** (**Scheme 1.3**)¹⁰. The mechanism was assumed that the thiourea of the catalyst **1.9** is involved in the activation of the aldimine via hydrogen bond. During the optimization of catalysts, it was found that replacement of thiourea with *O*-urea resulted in a decrease of the yield and the enantioselectivity. As limitations, *N*-allyl or *N*-benzyl benzaldimines were not suitable for this reaction.

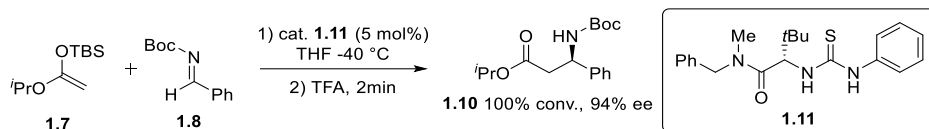


Scheme 1.3

In 2003, Jacobsen *et al.* found that the pioneer catalyst **1.9** for asymmetric Mannich reaction can be simplified into catalyst **1.11** after detail experiments on each units of catalyst **1.9** were performed to elucidate their effects (**Scheme 1.4**).¹¹ During the optimization, they uncovered that the salicylaldimine moiety of the catalyst **1.9** didn't have any responsibility for the yield and the enantioselectivity of the asymmetric Mannich reaction.

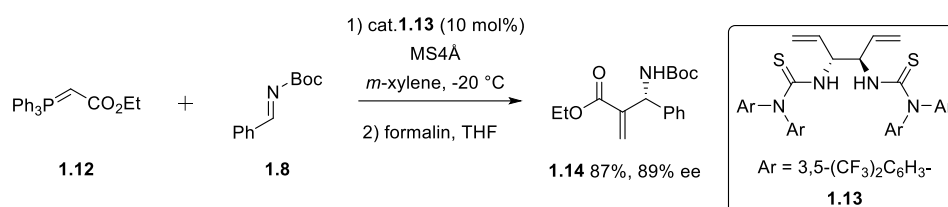
¹⁰ Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

¹¹ Wenzel, A.G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett*, **2003**, *12*, 1919.



Scheme 1.4

In 2008, Chen *et al.* reported that stabilized phosphorous ylides were good nucleophile for asymmetric Mannich reactions of *N*-Boc-protected aldimines with bistiourea catalyst **1.13** (Scheme 1.5).¹² Additionally, they discovered that subsequent addition of formalin to the Mannich adducts led to unsaturated esters in good yields in a formal aza-Baylis-Hillman reaction.



Scheme 1.5

1.2.2 Chiral Phosphoric Acid

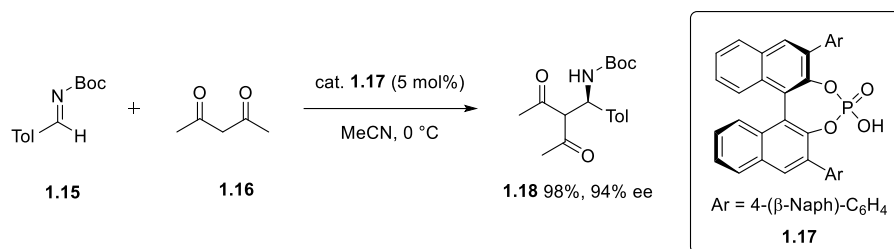
Chiral phosphoric acid is an important class of promoters in the field of organocatalysis. Chiral phosphoric acids derived from chiral BINOL and Lewis basic oxygen of the phosphoric acid of catalysts interacts with nucleophiles and the Lewis acidic oxygen interacts with electrophiles through cooperate hydrogen bonding to create chiral environment.

In 2004, Terada¹³ and Akiyama¹⁴ independently developed the asymmetric Mannich reactions with chiral phosphoric acids (**1.17** and **1.21**), in which it was identified that substituents at 3,3'-positions are extremely important to reach high enantioselectivities (Scheme 1.6 and 1.7).

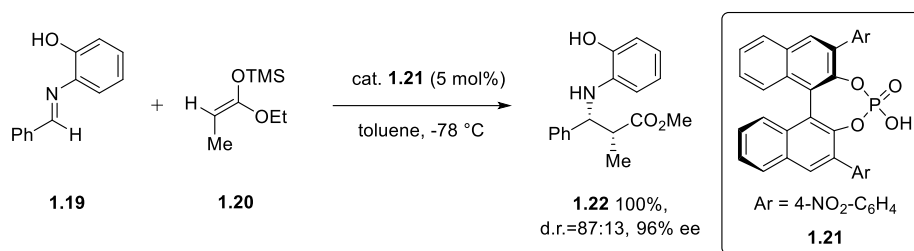
¹² Zhang, Y.; Liu, Y.-K.; Kang, T. R.; Hu, Z.-K.; Chen, Y. C. *J. Am. Chem. Soc.* **2008**, *130*, 2456.

¹³ Uraguchi, D.; M. Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

¹⁴ Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568.

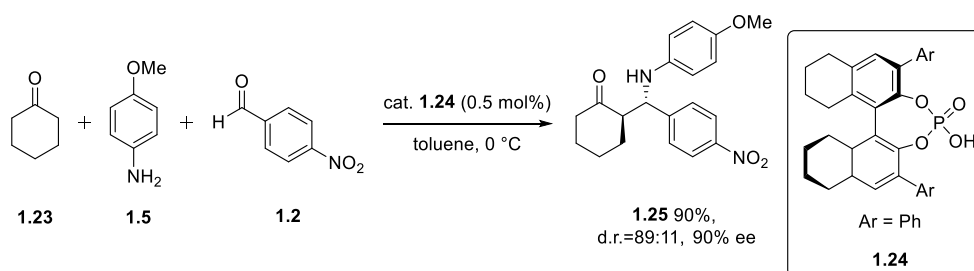


Scheme 1.6



Scheme 1.7

In 2007, Gong *et al.* reported the direct *anti*-Mannich reactions of cyclic ketones with a chiral phosphoric acid **1.24** bearing the component of octahydro-BINOL (**Scheme 1.8**).¹⁵

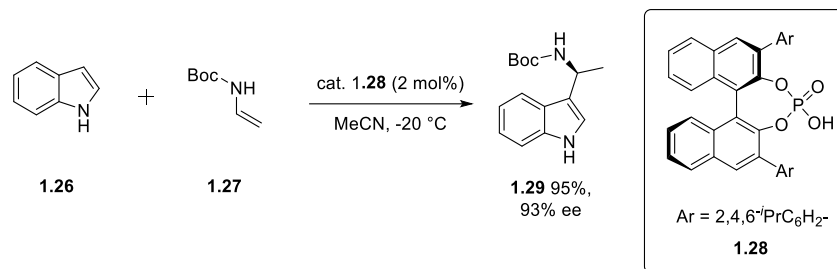


Scheme 1.8

In 2007, Terada *et al.* developed the asymmetric Mannich reactions of indoles with *N*-Boc protected aliphatic imines from ene carbamates through activation of chiral phosphoric acid **1.28** (**Scheme 1.9**).¹⁶ The indole derivatives reacted with the generated electrophilic aliphatic imines, even though dimerization between electrophilic aliphatic imines and nucleophilic ene carbamates is known. The key of the success of the reaction is that indole derivatives, in nature, are much more nucleophilic than ene carbamates. Utilization of less nucleophilic substrates than indoles resulted in the dimerization of ene carbamates.

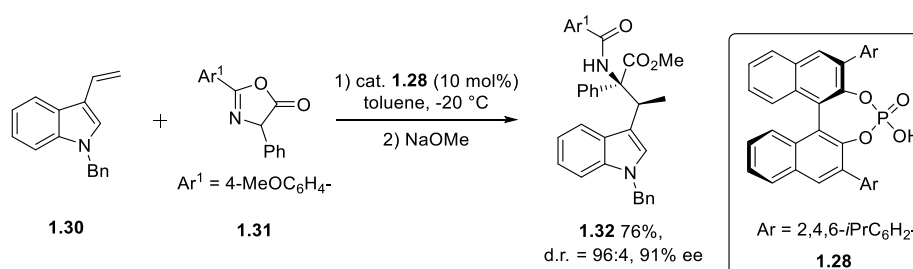
¹⁵ Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791.

¹⁶ Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.



Scheme 1.9

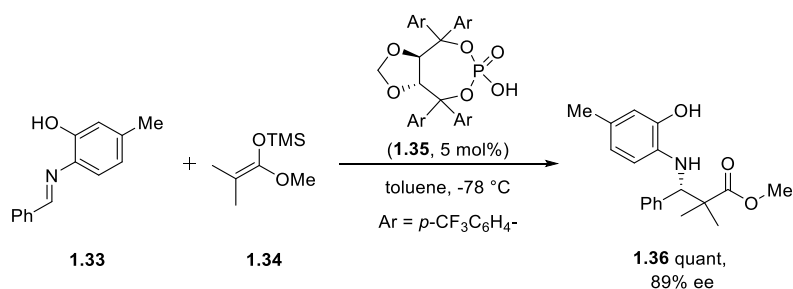
In 2011, Terada *et al.* reported that enantioselective addition of azalactones to vinyl indoles was catalyzed by chiral phosphoric acid **1.28** (Scheme 1.10).¹⁷ Their method provides a facile route to enantioenriched tryptophan derivatives bearing a quaternary carbon.



Scheme 1.10

1.2.3 Other Chiral Brønsted Acids

In 2005, Akiyama *et al.* developed the asymmetric Mannich reactions using Taddol-derived chiral phosphoric acid **1.35** which was synthesized from (+)-diethyl tartrate (Scheme 1.11).¹⁸ Considerable increase of enantioselectivity was observed by changing the imine protection to 2-hydroxy-4-methylphenyl **1.33** from 2-hydroxyphenyl **1.19** (73% ee to 89% ee).



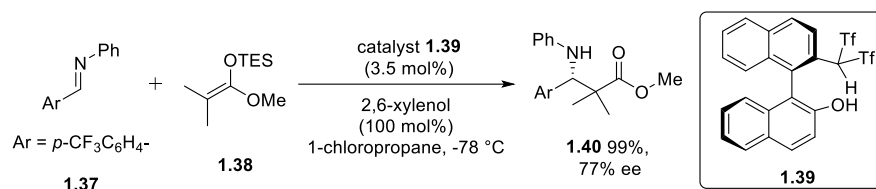
Scheme 1.11

In 2006, Yamamoto *et al.* developed chiral Brønsted acid catalyst **1.39** for the asymmetric

¹⁷ Terada, M.; Moriya, K.; Kanomata, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 12586.

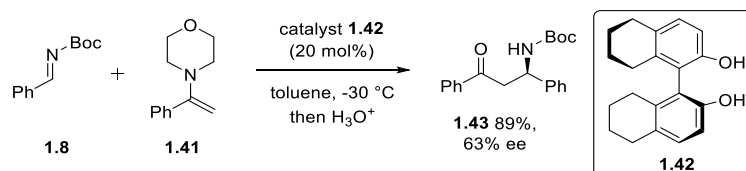
¹⁸ Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.*, **2005**, *347*, 1523.

Mannich-type reactions of ketene silyl acetals and aldimines (**Scheme 1.12**).¹⁹ Enantiomeric excess, unfortunately, is not satisfactory. We note that the addition of 2,6-xyleneol to trap silyl species improved the reactivity.



Scheme 1.12

In 2007, Dixon *et al.* reported the asymmetric Mannich reactions of acetophenone derivatives and aldimines with modified BINOL **1.42** in good yields but moderate enantiomeric excesses (63% ee) (**Scheme 1.13**).²⁰



Scheme 1.13

1.2.4 Cinchona Alkaloid Type Catalyst

Quinine has been one of the most famous natural products in cinchona alkaloids as a representative *anti*-malarial drug since over 100 years. In the field of organocatalysis, cinchona alkaloids are effective due to its bifunctionality of chiral alcohol moiety and quinuclidine moiety for forming cooperative hydrogen bond. In addition, they are commercially available. For instance, the utilization of cinchonidine **1.47** was noted in the superb total synthesis of aminocyclitol pactamycin by Johnson *et al.*²¹

In 2005, Schaus *et al.* reported the asymmetric Mannich reactions of β -ketoesters and acyl aryl imines with a cinchona alkaloid, cinchonine **1.49** (**Scheme 1.14**).²² β -Amino alcohols **1.51**

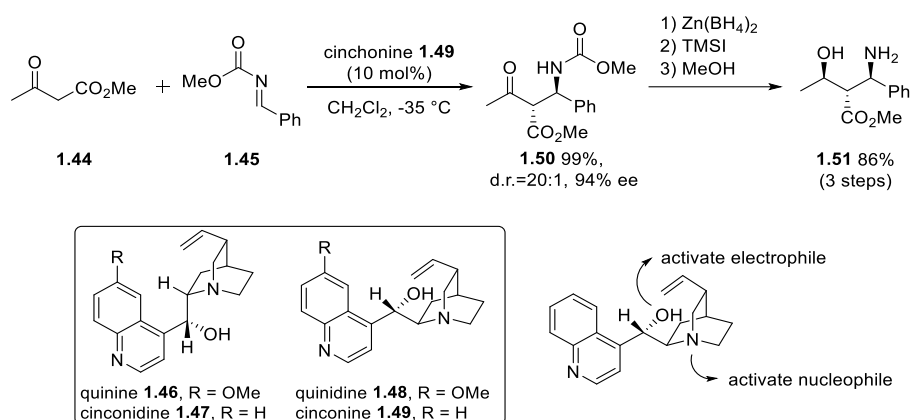
¹⁹ Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara K.; Yamamoto, H. *Org. Lett.*, **2006**, *8*, 3175.

²⁰ Tillman, A. L.; Dixon, D. J. *Org. Biomol. Chem.* **2007**, *5*, 606.

²¹ Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 47, 17990.

²² Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256.

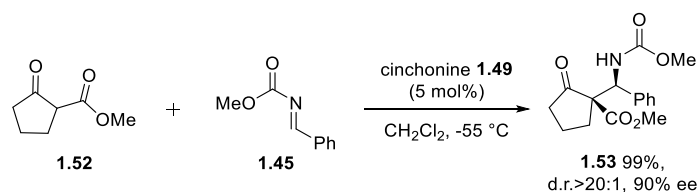
were obtained in excellent yields after the reduction/deprotection processes of the Mannich adducts **1.50**.



Scheme 1.14

A related asymmetric Mannich reaction of cyclic 1,3-dicarbonyl compounds and acyl aryl imines with cinchona alkaloid catalysts was reported by Schaus *et al* in 2006 (**Scheme 1.15**).²³

The reactions afforded β -amino esters bearing a chiral quaternary carbon in excellent yields.



Scheme 1.15

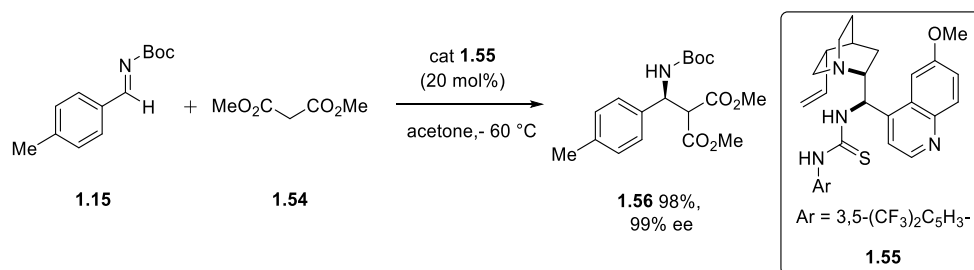
1.2.5 Bifunctional Hybrid Catalyst

Chiral thioureas and chiral phosphoric acids have been recognized as hydrogen bond donors to activate imine derivatives, while cinchona alkaloid type catalysts have shown their admirable capacity as hydrogen bond acceptors to activate nucleophiles such as acidic 1,3-dicarbonyl compounds *etc.* Hence, there has been a promising expectation that bifunctional catalysts with both features of thiourea and cinchona alkaloid catalysts would provide ideal synergy and high efficiency as asymmetric organocatalysts.

In 2006, Deng *et al.* reported the asymmetric Mannich reactions of *N*-Boc-protected aldimines and malonates in the presence of a cinchona alkaloid derivative **1.55** bearing a thiourea

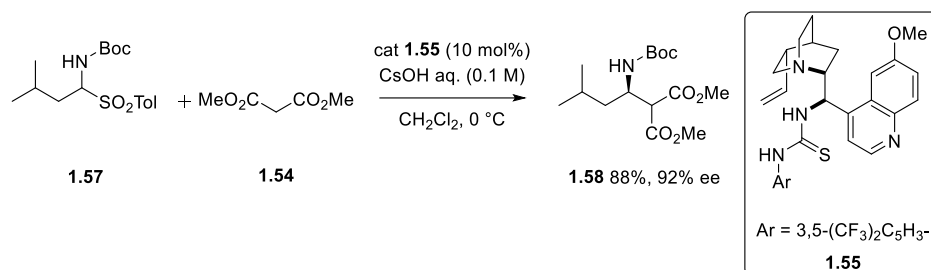
²³ Ting, A.; Lou S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003.

functionality as an effective bifunctional catalyst (**Scheme 1.16**).²⁴



Scheme 1.16

A major drawback of the employment of *N*-carbamate protected aliphatic imines is lower stability compared to *N*-carbamate protected aryl imines due to their easy tautomerization (imine/enamine). In 2007, Deng *et al.* first reported the asymmetric Mannich reactions of *in situ* generated carbamate-protected imines from bench-stable α -amidosulfones with thiourea cinchona alkaloid catalyst **1.55** (**Scheme 1.17**).²⁵ This method was also successful with aryl imines derived from the corresponding α -amidosulfones.



Scheme 1.17

In 2010, Barbas III *et al.* reported the asymmetric Mannich reactions of glycinate Schiff bases with thiourea cinchona alkaloid catalyst **1.60**, in which the Mannich adducts can be transformed into vicinal diamines by acidic hydrolysis (**Scheme 1.18**) (the product was obtained as the opposite enantiomer as shown).²⁶ However, it was shown that utilization of the *tert*-butyl ester **1.59** was unsuccessful in the context.

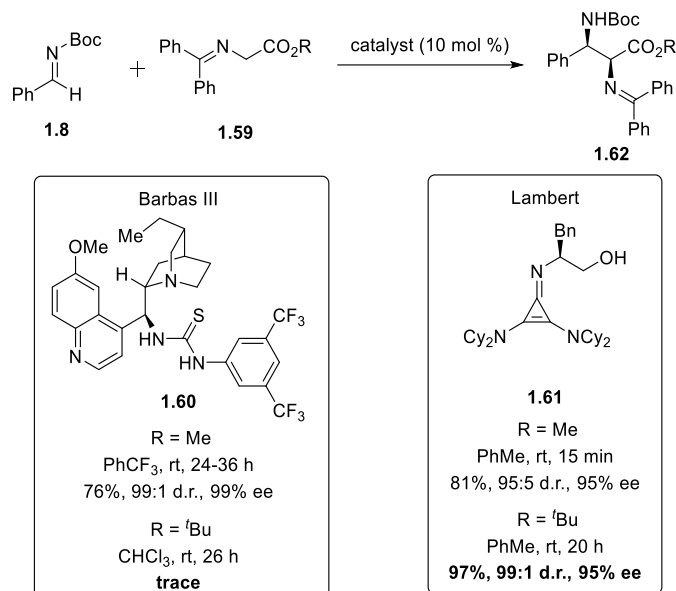
In 2013, Lambert *et al.* described the same component reactions as Barbas III group but with

²⁴ Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.

²⁵ Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603.

²⁶ Zhang, H.; Syed, S.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 708.

cyclopropenimine catalyst **1.61** (Scheme 1.18).²⁷ The reactions using cyclopropenimine catalyst **1.61** overcame the limitation encountered in Barbas III's report and afforded the desired products in excellent yields and enantioselectivities.

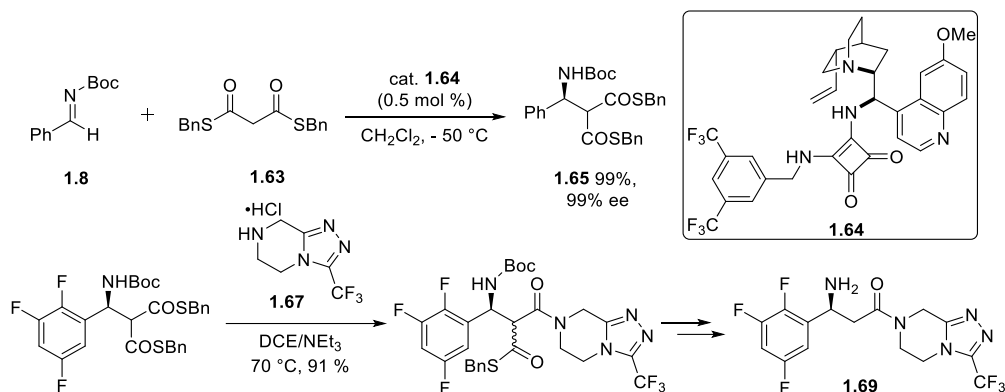


Scheme 1.18

In 2016, Song *et al.* reported the asymmetric Mannich reactions of dithiomalonates and aldimines with quite low loading of catalyst **1.64** (Scheme 1.19).²⁸ The advantage of dithiomalonates is that coupling reactions with thioesters and amines, which afford the corresponding amides, are much easier than with esters. As a demonstration, they implemented the synthesis of an antidiabetic drug, (-)-(*R*)-sitagliptine **1.69**, in which the acylation proceeded smoothly without any coupling reagents.

²⁷ Bandar, J. S.; Lambert, T. H. *J. Am. Chem.* **2013**, *135*, 11799.

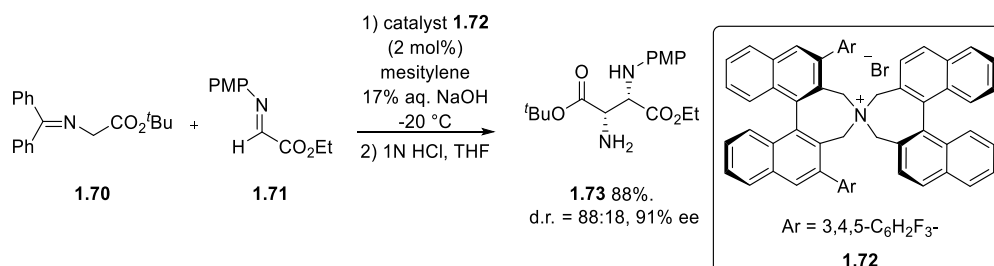
²⁸ Bae, H. Y.; Kim, M. J.; Sim, J. H.; Song, C. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 10825.



Scheme 1.19

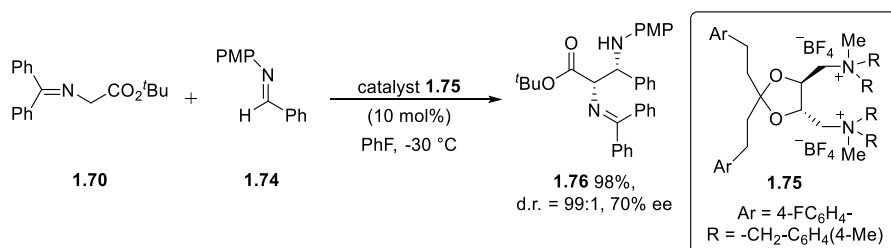
1.2.6 Phase Transfer Catalyst

In 2004, Maruoka reported the asymmetric Mannich coupling of glycinate Schiff bases with imino ester **1.71** in the presence of N-spiro C_2 -symmetric chiral ammonium bromide **1.72** as a chiral phase transfer catalyst (PTC) **1.72** (Scheme 1.20).²⁹ Their method gave α,β -diamino diesters which have a substructure of aspartic acid.



Scheme 1.20

In 2004, Shibasaki reported the asymmetric Mannich reactions of glycinate Schiff bases and aryl imine **1.74** with chiral diammonium salts **1.75** in solid-liquid phase in which counteranions were exchangeable (Scheme 1.21).³⁰

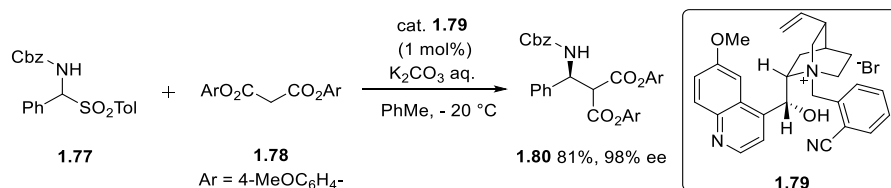


²⁹ Ooi, T.; Kameda, M.; Fujii J.-I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397.

³⁰ Okada, A.; Shibuguchi, T.; Oshima, T.; Masu, H.; Yamaguchi K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564.

Scheme 1.21

Sgarzani *et al.* reported the asymmetric Mannich reactions of *in situ* generated carbamate-protected imines from bench-stable α -amidosulfones with cinchona alkaloid type catalyst **1.79** designed as PTC (Scheme 1.22).³¹ Their method showed high yields and enantioselectivities with low loading of the catalyst **1.79** which is easily accessible from commercially available quinine **1.46**.



Scheme 1.22

1.2.7 Ion Pair Catalyst (Chiral Proton Catalyst)

The concept of chiral ion pair catalyst is based on the control of anionic species by chiral counteranions. However, it was thought to be difficult due to the fact that it is unclear interactions. From another viewpoint, ion pair catalysts are regarded as weak Brønsted acids possessing electrostatic and hydrogen-bonding interaction toward counteranions.

In 2004, Johnston *et al.* reported the asymmetric nitro-Mannich reactions of aldimines and nitroethane **1.82** with chiral ion pair catalyst **1.83** containing bis-amidine moiety (Scheme 1.23).³² The reactions afforded *syn*-secondary amines in moderate yields and good enantioselectivities

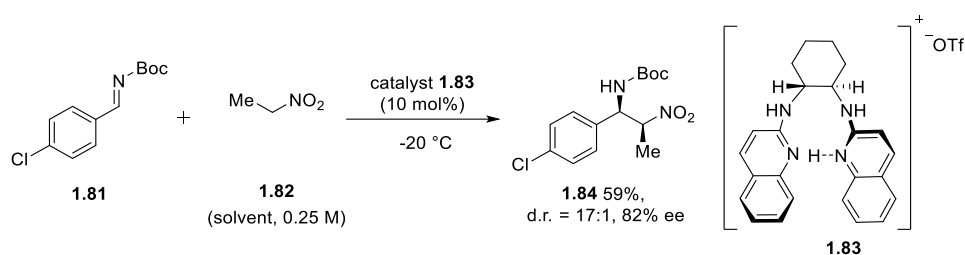
. After few years, the same group consecutively reported the more optimized catalysts (**1.86** and **1.89**) for nitro-Mannich reactions of aldimines with secondary or tertiary nitro acetates in excellent yields and enantioselectivities (Scheme 1.24a and b).³³ In the case of nitro-Mannich reactions of secondary nitro acetates (Scheme 1.24a), an *anti*-product was epimerized into the *syn*-product when the reaction was left at room temperature instead of -78 °C during the first

³¹ Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043.

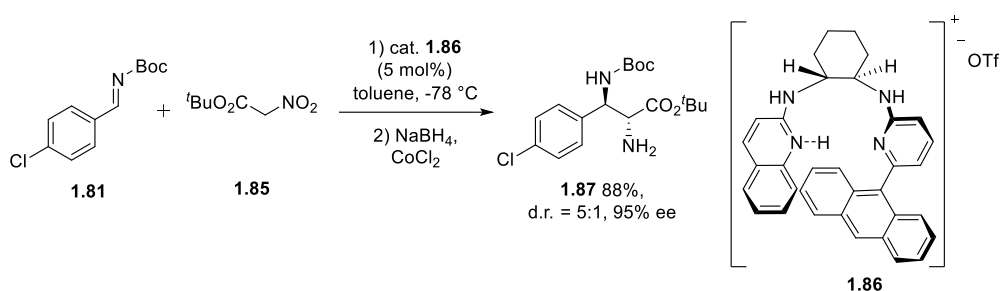
³² Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

³³ a) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466 b) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866.

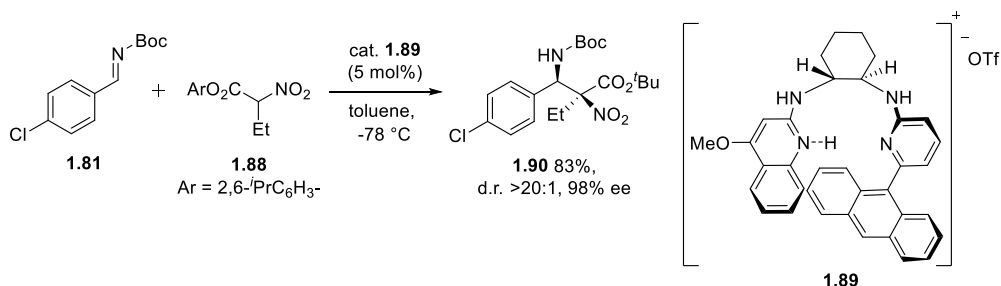
step (5:1 to 1:2 = *anti:syn*).



Scheme 1.23

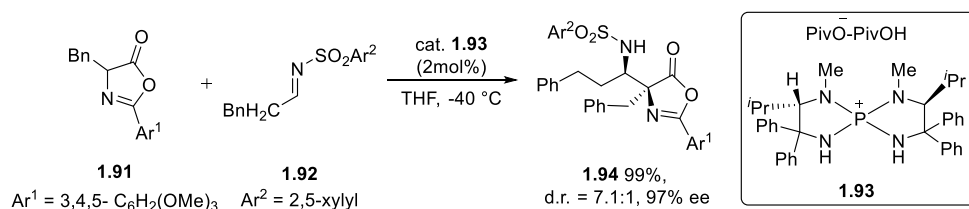


Scheme 1.24a



Scheme 1.24b

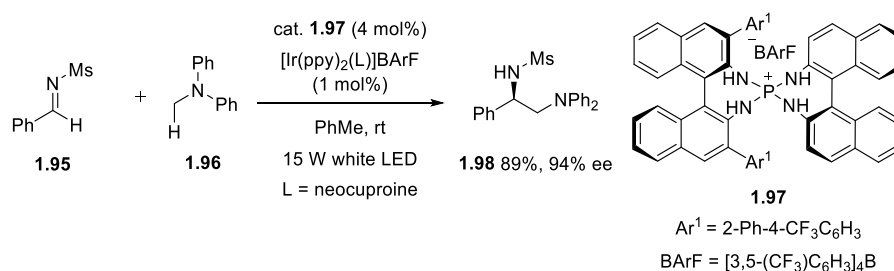
On the basis of the same concept, Ooi *et al.* reported the asymmetric Mannich-type reactions of sulfonyl imines and azalactones with *P*-spirocyclic phosphonium catalyst **1.93** (Scheme 1.25).³⁴ They demonstrated that hydrolysis of the products in aqueous H_2SO_4 afforded α,β -diamino carboxylic acids.



Scheme 1.25

³⁴ Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 5866.

In 2015, Ooi *et al.* reported the asymmetric Mannich-type reactions of *N*-sulfonyl aldimines and *N*-diarylaminometanes with *P*-spiro chiral phosphonium borate **1.97** and Ir-photocatalyst under visible light irradiation (**Scheme 1.26**).³⁵ They developed the system to form chiral ion pair between the phosphonium cation and the radical anion derived from the single electron reduction of *N*-sulfonyl aldimines by Ir(II) species. Then, the chiral radical anion was coupled with the radical *N*-diarylaminometane derived from Ir(III) single-electronic oxidation of *N*-diarylaminometanes and the subsequent deprotection by ⁻BArF (The detail mechanism is written in the paper). This method activated non-acidic methyl group by photoredox-catalyzed reaction and controlled the radical ion pairs by chiral phosphonium borate **1.97**, affording chiral amines in excellent yields and enantioselectivities.



Scheme 1.26

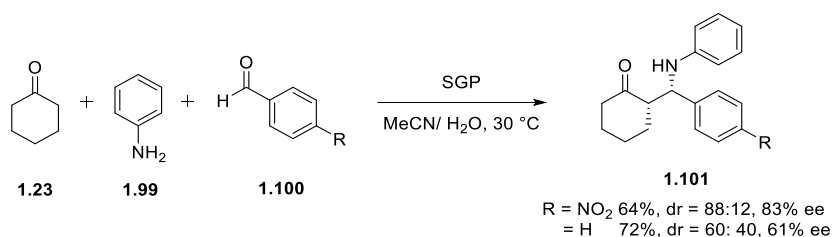
1.2.8 Enzyme Catalyst

Enzyme-catalyzed reactions attracted pervasive attentions because these processes are green and ecofriendly than general organic reactions. To identify the benefit, some asymmetric Mannich reactions with enzymes have been reported (**Scheme 1.27** and **1.28**).^{36,37} Enzyme-catalyzed reactions, unfortunately, have some drawbacks such as narrow substrate scopes and long reaction time (over days). [Protease type XIV from *Streptomyces griseus* (SGP) and Acylase I (aminoacylase) from *Aspargillus melleus* (AMA)]

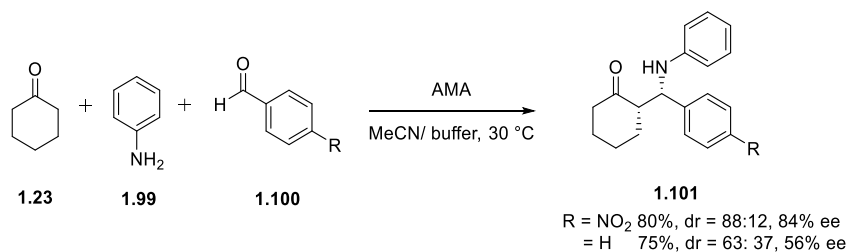
³⁵ Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768.

³⁶ Xue Y.; Li, L.-P.; He, Y.-H.; Guan, Z. *Sci. Rep.* **2012**, *2*, 761.

³⁷ Guan, Z.; Song, J.; Xue Y.; Yang, D.-C.; He, Y.-H. *J. Mol. Catal. B: Enzym.* **2015**, *111*, 16.



Scheme 1.27

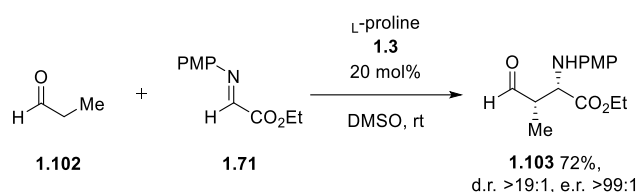


Scheme 1.28

1.3 Proline Catalyst (Enamine form type)

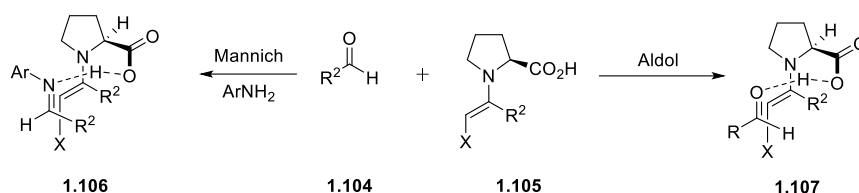
1.3.1 *syn*-Selective Mannich Reaction of PMP-Protected Imines

Barbas III first reported the *syn*-selective asymmetric Mannich reactions of aldehydes and α -iminoesters with proline **1.3** (Scheme 1.29).³⁸ The key of the reaction is the formation of the hydrogen bond between nitrogen moiety of PMP-protected imines and carboxylic acid moiety of the enamine **1.105** formed from aldehydes **1.104** and proline **1.3**, while in asymmetric aldol reaction, enamine **1.105** formed the hydrogen bond interaction with aldehydes **1.104** (Scheme 1.30).



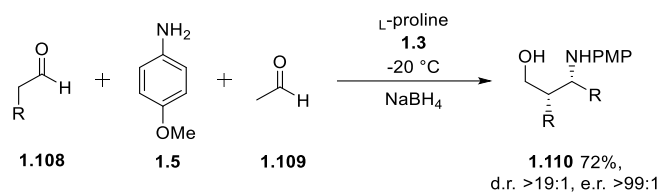
Scheme 1.29

³⁸ Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas III, C. F. *Adv. Synth. Catal.* **2004**, *346*, 1131.



Scheme 1.30

Hayashi,³⁹ Córdoba⁴⁰ and Barbas III⁴¹ reported independently direct asymmetric cross-Mannich reactions of two different aldehydes with proline (**Scheme 1.31**). The low temperature was required to suppress side reactions such as aldol condensations.



Scheme 1.31

Several kinds of catalysts were reported (**Fig. 1.1**)⁴², but in an economical point of view, proline is frequently favored because both enantiomers are commercially available.

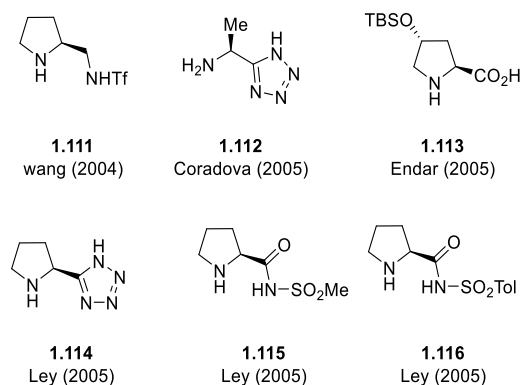


Fig. 1.1

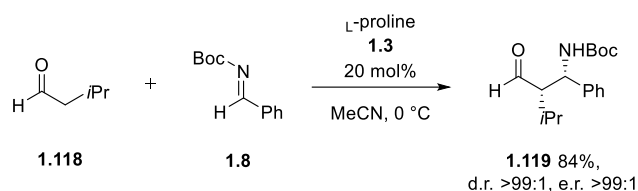
³⁹ Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677.

⁴⁰ Córdoba, A. *Chem.–Eur. J.*, **2004**, *10*, 1987.

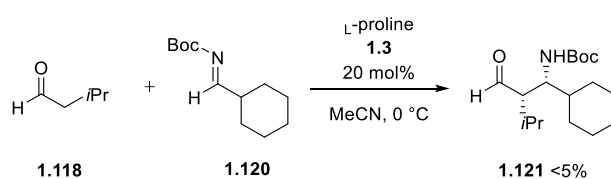
⁴¹ Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580.

⁴² a) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45* 7243. b) Ibrahem, I.; Zou, W.; Enqvist, M.; Xu, Y.; Córdoba, A. *Chem.–Eur. J.* **2005**, *11*, 7024. c) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079. d) Cobb, J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

In 2007, List reported the syn-selective asymmetric Mannich reactions of *N*-Boc-protected aldimines and aldehydes with proline **1.3** (Scheme 1.32a, b).⁴³ Regrettably, the reactions were successful only with aryl aldimines (Scheme 1.32a), while alkyl aldimines were not suitable due to their dimerization due to the enamine-imine tautomerization (Scheme 1.32b).

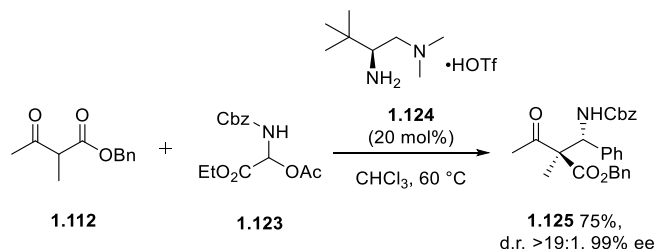


Scheme 1.32a



Scheme 1.32b

In most of enamine-formed Mannich reactions, only α -nonsubstituted aldehydes and ketones were well examined but occasionally some problems have been seen with branched aldehydes and ketones for Mannich reactions resulting in moderate diastereoselectivity. Lu *et al.* reported the asymmetric Mannich reactions of α -substituted β -ketocarboxyls and *N,O*-acetals, which are bench-stable surrogates for *N*-carbamate-protected imines, with a chiral amine **1.124**. The reactions provided β -amino dicarbonyls bearing with a quaternary carbon with excellent enantiomeric excesses (Scheme 1.33).⁴⁴



⁴³ J. W. Wang, M. Stadler and B. List, *Angew. Chem., Int. Ed.* **2007**, *46*, 609. See also: a) Enders, D.; Grondal, C.; Vrettou, M. *Synthesis* **2006**, *21*, 3597. b) Vesely, J.; Rios, R.; Ibrahim, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 421.

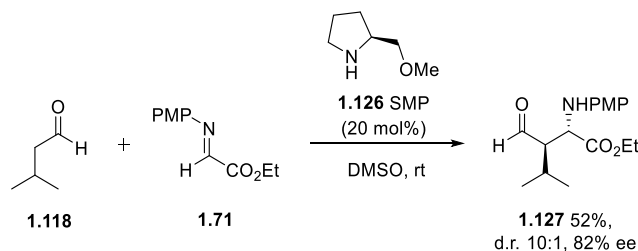
⁴⁴ You, Y. Zhang, L.; Cui, L.; Mi, X.; Luo, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 13814.

Scheme 1.33

1.3.2 *anti*-Mannich Reaction

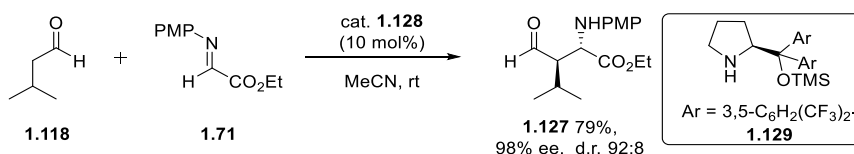
Barbas *et al.* gave an outline about *anti*-selective Mannich reactions of aldehydes and iminoester **1.71** with (*S*)-2-methoxymethylpyrrolidine **1.126** (SMP) in 2002 (Scheme 1.34).⁴⁵

The yields and enantioselectivities were far from satisfactory, but their work was touchstone for developing *anti*-selective Mannich reactions.



Scheme 1.34

Jørgensen *et al.* found that α,α -diarylprolinol silyl ether **1.129** are excellent catalysts for asymmetric *anti*-selective Mannich reactions (Scheme 1.35) as well as amination, fluorination, bromination, *etc.*⁴⁶ Silyl protection of alcohol moiety of the catalyst improved catalyst's efficiency, otherwise the enamines consisted of aldehydes and the catalyst bearing free alcohol group formed unreactive hemiaminal species which led to the decrease of yield and enantioselectivity. *anti*-Selectivity arose from the repulsion between imines and a bulky substituent of enamines consisted of aldehydes and the catalysts.



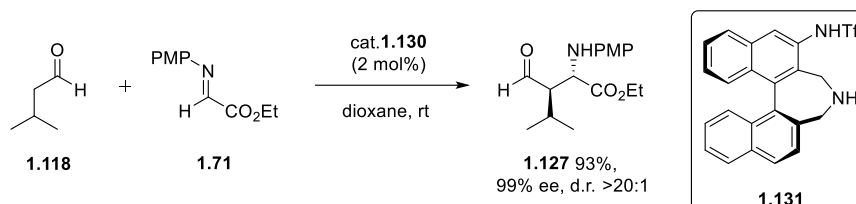
Scheme 1.35

Maruoka *et al.* reported that axial-chiral amino sulfonamide catalyst **1.131** provided *anti*-Mannich products of aldehydes and iminoester **1.71** in excellent yields and stereoselectivity

⁴⁵ Córdova, A.; Barbas III., C. F. *Tetrahedron Lett.* **2002**, 43, 7749.

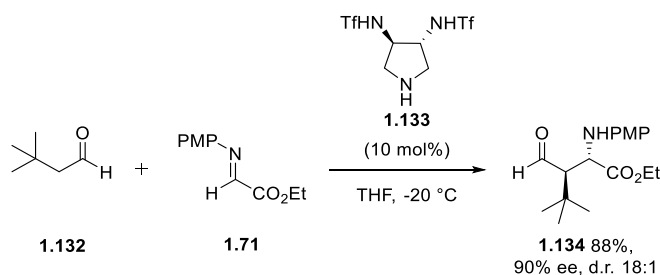
⁴⁶ Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, 127, 18296.

(Scheme 1.36).⁴⁷ Unlike Jørgensens's catalyst **1.129**, Maruoka's catalyst **1.131** handled hydrogen bond interaction between sulfonamides and the imine **1.71** for *anti*-selectivity. As limitations, however, sterically hindered aldehydes afforded the Mannich adducts in moderate yields.



Scheme 1.36

Maruoka *et al.* developed the pyrrolidine-based sulfonamide catalyst **1.133** for *anti*-selective Mannich reactions, which was synthesized in 7 steps from tartaric acid (Scheme 1.37).⁴⁸ Also, sterically hindered aldehydes were successful for the Mannich reactions in excellent stereoselectivity.



Scheme 1.37

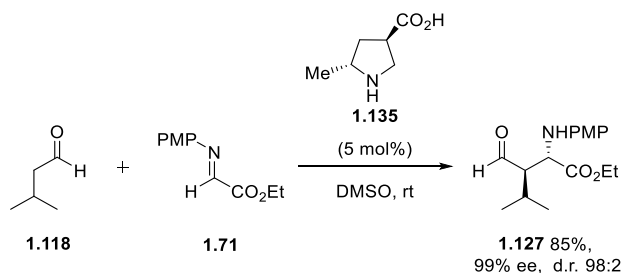
Barbas *et al.* reported that pyrrolidine-based β -amino acids (**1.135** and **1.137**) were ideal catalysts for the *anti*-selective Mannich reactions of unmodified aldehydes (Scheme 1.38)⁴⁹ and ketones (Scheme 1.39).⁵⁰ In cases of ketones, the less hindered catalyst gave much better results.

⁴⁷ a) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. b) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Chem. Eur. J.* **2009**, *15*, 6678.

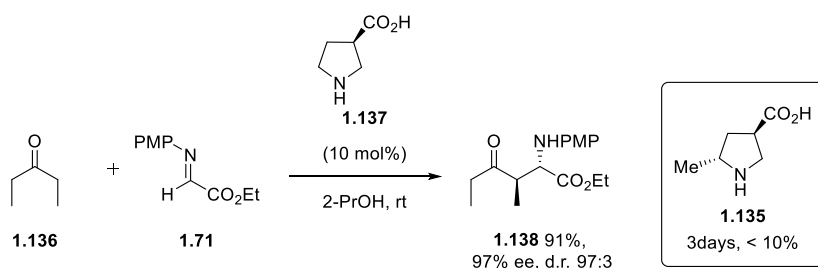
⁴⁸ Kano, T.; Hato, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 8467.

⁴⁹ Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 1040.

⁵⁰ Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 9630.

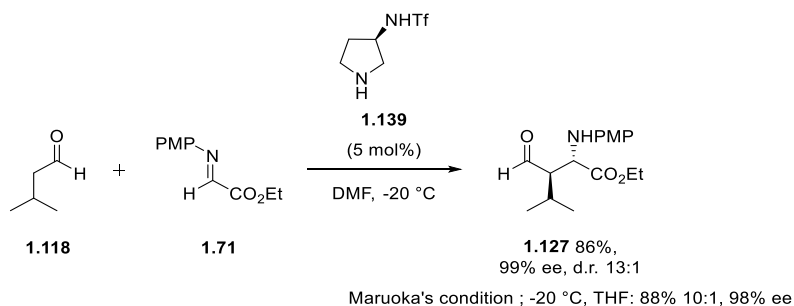


Scheme 1.38

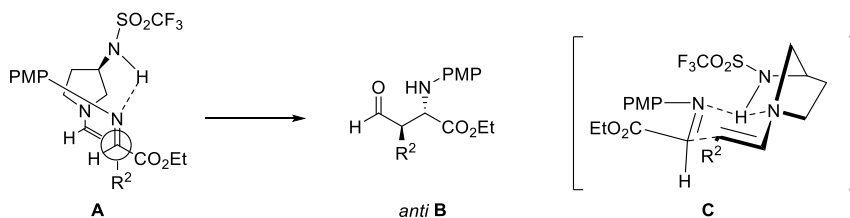


Scheme 1.39

Blanchet's group⁵¹ and Maruoka's group⁵² independently reported the *anti*-selective Mannich reactions with a pyrrolidine-based amino sulfonamide catalyst (**Scheme 1.40**). The catalyst was readily prepared from an inexpensive material (in 2 steps). The assumed reaction mechanism involving hydrogen bond interaction is shown in **Scheme 1.40a**.



Scheme 1.40

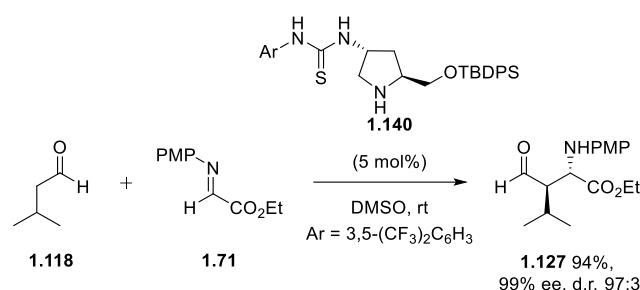


Scheme 1.40a

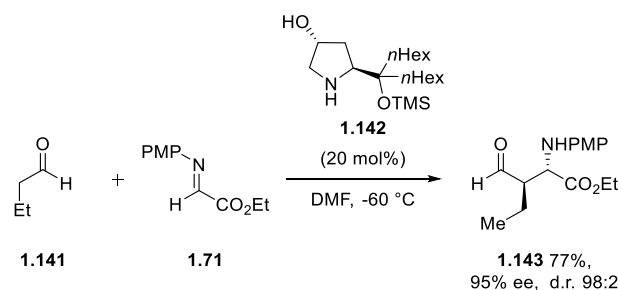
⁵¹ Pouliquen, M.; Blanchet, J.; Lasne, M.-C.; Rouden, J. *Org. Lett.* **2008**, *10*, 1029.

⁵² Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K.; *Tetrahedron* **2008**, *64*, 1197.

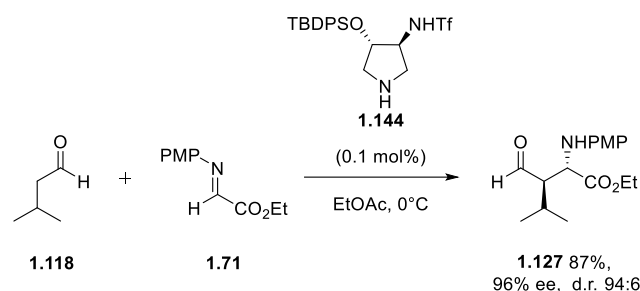
Several catalysts for *anti*-Mannich reactions were reported by Peng' group,⁵³ Palomo's group⁵⁴ and Pericàs' group⁵⁵ (Scheme 1.41, 1.42 and 1.43). Long steps, however, were needed for the preparation of the catalysts.



Scheme 1.41



Scheme 1.42



Scheme 1.43

1.3.3 *N*-Carbamate-Protected Mannich Reaction (*anti*-selective)

It has been known that *N*-carbamate-protected iminoesters are unstable, and because of it, the utilization in organic synthesis were limited.⁵⁶

Melchiorre *et al.* reported a practical method for *anti*-selective Mannich reactions of aldehydes

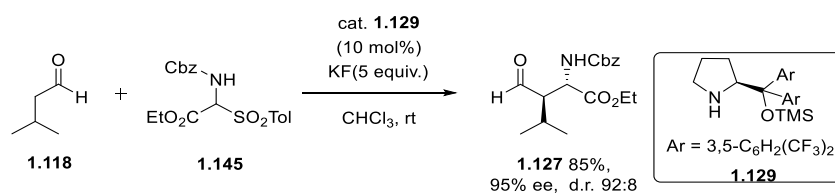
⁵³ Zhang, H.; Chuan, Y.; Li, Z.; Peng, Y. *Adv. Synth. Catal.* **2009**, *351*, 2288.

⁵⁴ Gómez-Bengoa, E.; Maestro, M.; Mielgo, A.; Otazo, I.; Palomo, C.; Velilla, I. *Chem. Eur. J.* **2010**, *16*, 5333.

⁵⁵ Rapún, R. M.; Fan, X.; Sayalero, S.; Bahramnejad, B.; Cuevas, F.; Pericàs, M. A. *Chem. Eur. J.* **2011**, *17*, 8780.

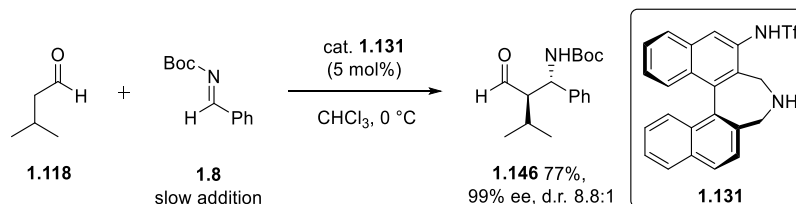
⁵⁶ Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481.

and *N*-carbamate-protected iminoesters with Jørgensen catalyst (**Scheme 1.44**).⁵⁷ *N*-carbamate-protected iminoesters were slowly generated *in situ* from α -amidosulfones and a base, and the reactions afforded the *N*-carbamate-protected Mannich adducts with excellent enantioselectivities. The Mannich adducts with *N*-carbamate protection are highly valuable for further application due to their stability in oxidative condition.



Scheme 1.44

Maruoka *et al.* reported the *anti*-selective Mannich reactions of aldehydes and *N*-carbamate-protected aldimines with axial-chiral amino sulfonamide catalyst **1.131** (**Scheme 1.45**).⁵⁸ An *N*-Boc protected aliphatic imine was applicable to their reaction when the imine was added slowly by syringe pump.



Scheme 1.45

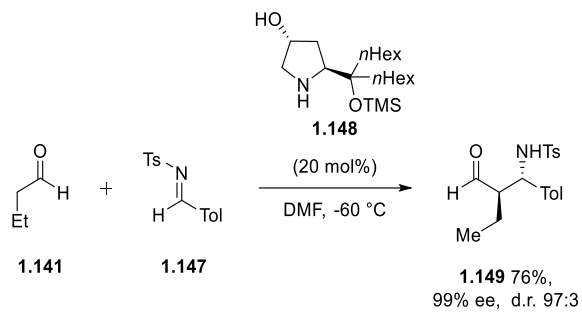
A few examples were reported about *anti*-selective Mannich reactions of aldehydes and *N*-carbamate-protected aldimines, but, in all of them, modified Jørgensen type catalysts were employed with the same concept (**Scheme 1.46** and **1.47**).^{48,59}

⁵⁷ a) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8700. b)

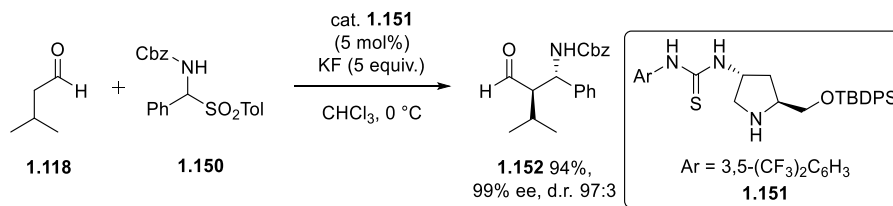
Galzerano, P.; Agostino, D.; Bencivenni, G.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2010**, *16*, 6069.

⁵⁸ a) Kano, T.; Yamaguchi, Y.; Maruoka, K.; *Angew. Chem. Int. Ed.* **2009**, *48*, 1838. b) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Chem. Eur. J.* **2009**, *15*, 6678.

⁵⁹ Gao, J.; Chuan, Y.; Li, J.; Xie, F.; Peng, Y. *Org. Biomol. Chem.* **2012**, *10*, 3730.



Scheme 1.46



Scheme 1.47

2 Piperidine

2.1 Introduction

Piperidine ring is one of the most common heterocycles in natural products and the motif is especially well represented in pharmaceuticals. (Figure 2.1). According to the analysis of Njardarson, piperidine ring is the most frequently observed structure core among U.S. FDA approved pharmaceuticals.⁶⁰ Therefore, tremendous efforts have been invested to develop new methods to efficiently access piperidine ring. More interestingly, enantioselective synthesis of multi-substituted piperidines has been extensively studied because most of biologically active natural products and pharmaceuticals are often functionalized with chiral carbons.⁶¹

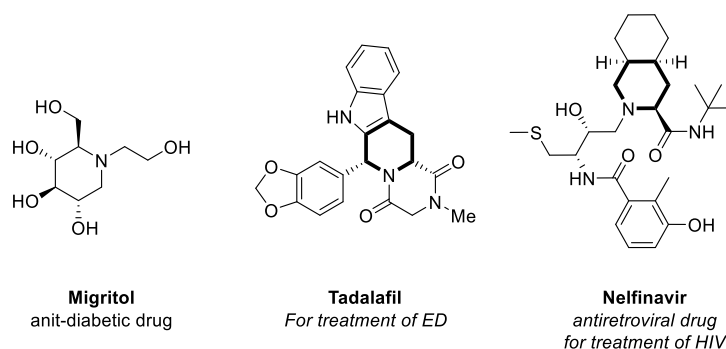


Fig 2.1

2.2 Synthesis of Piperidine

2.2.1 From Piperidone

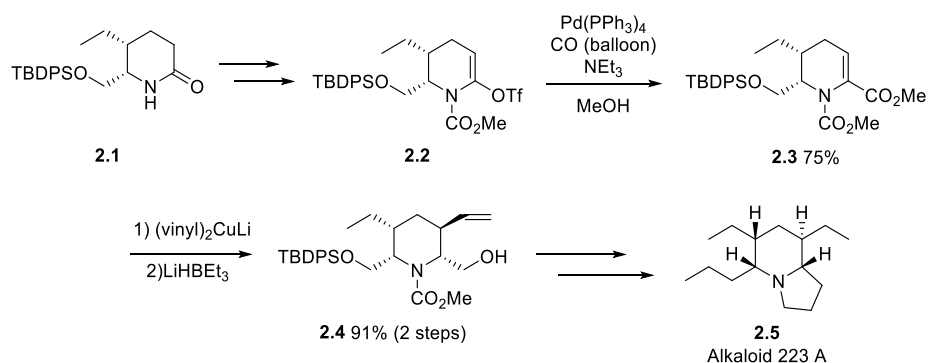
Transformation from piperidone to piperidine is a reliable method for piperidine synthesis. To that end, one major methodology involves palladium C-C coupling reaction, including Suzuki coupling and Sonogashira coupling, using vinyl triflates or phosphates easily prepared from piperidinone.

In 2002, Kaneko's group reported the synthesis and structural revision of alkaloid 223 A **2.5**,

⁶⁰ Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

⁶¹ a) Weintraub, P. M.; Sabol, J. S.; M.Kane, J.; Borcharding, D. R. *Tetrahedron* **2003**, *59*, 2953. b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

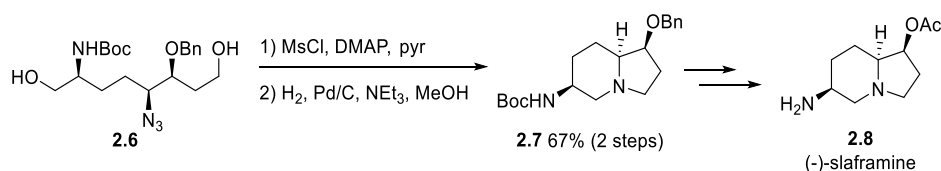
which is one amphibian alkaloid, isolated from a skin extract of the frog *Dendrobates pumilio* in Panama (**Scheme 2.1**).⁶² In their synthesis, palladium CO insertion reaction was used for building the conjugated ester **2.3** and then 1,4 addition with a cuprate reagent afforded the stereo-controlled piperidine **2.4**.



Scheme 2.1

2.2.2 Nucleophilic Substitution

The facile synthesis of (-)-slafamine **2.8** derived from azide **2.6** was achieved by intramolecular double nucleophilic substitution (**Scheme 2.2**).⁶³ The cyclization proceeded by bis-mesylation of diol **2.6** followed by hydrogenation of azide in good yield.



Scheme 2.2

2.2.3 Reductive Amination

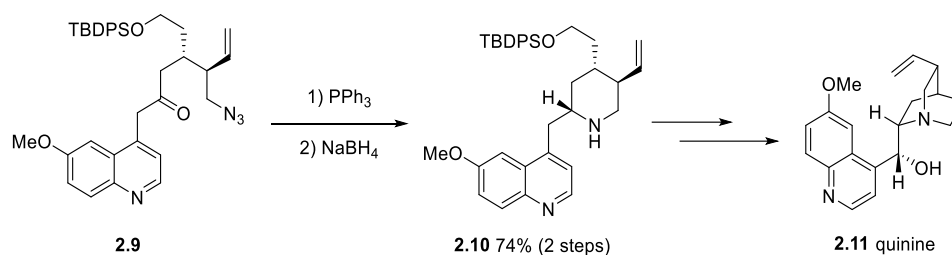
Quinine **2.11** has been considered as one of the most valuable natural products on the aspect of not only antimalarial pharmaceuticals but also recent utilization in organocatalysis. The first enantioselective synthesis of quinine **2.11** was completed by Stork's group in 2001 (**Scheme 2.3**).⁶⁴ In their excellent synthesis, the piperidine structure was synthesized by Staudinger

⁶² Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715.

⁶³ Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951.

⁶⁴ Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**,

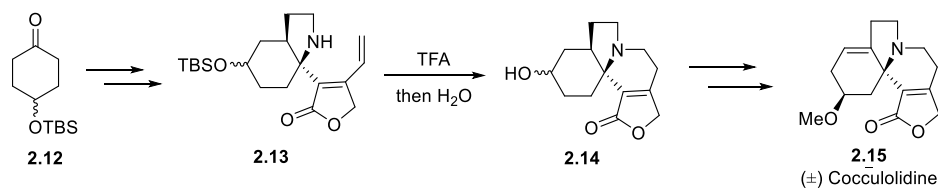
reaction and the subsequent cyclization of **2.9**, followed by the reductive amination. After several steps, they accomplished the total synthesis of quinine **2.11**.



Scheme 2.3

2.2.4 Michael Addition

In 2001, Kitahara's group reported the racemic synthesis of an erythrina alkaloid, cocculolidine **2.15** which has insecticidal activity (**Scheme 2.4**).⁶⁵ The piperidine structure was formed by the intramolecular 1,6-conjugated addition of the amine **2.13** in TFA (neat) in nearly quantitative yield.



Scheme 2.4

2.2.5 Carbonyl-Ene Reaction and Prins Reaction

Snaith's group developed a diastereoselective piperidine synthesis which is switchable to access *cis* and *trans* 3,4-substituted piperidines depending on conditions (**Scheme 2.5**).⁶⁶ Carbonyl-ene reactions with MeAlCl₂ in refluxing chloroform gave *trans* piperidines **2.17**. In contrast,

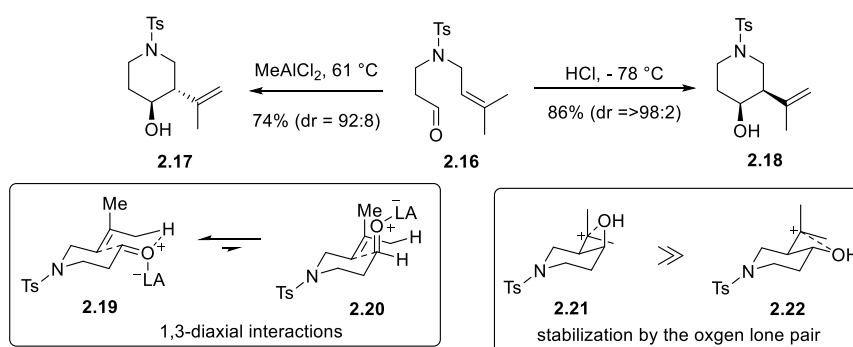
123, 3239.

⁶⁵ Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2001**, *42*, 8003.

⁶⁶ Williams, J. T.; Bahia, P. S.; Snaith, J. S. *Org. Lett.* **2002**, *4*, 3727. See also; About the mechanism; a) Williams, J. T.; Bahia, P. S.; Kariuki, B.; Spencer, N.; Philp, D.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 2460.

Cariou, C. A. M.; Snaith, J. S. *Org. Biomol. Chem.* **2006**, *4*, 51.

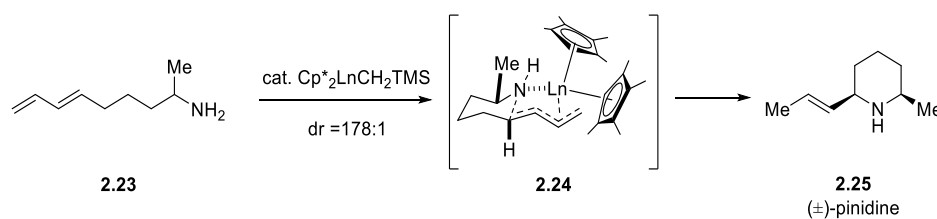
Prins reactions with HCl in dichloromethane and at low temperature provided *cis* piperidines **2.18**. The mechanism was assumed that in the Lewis acidic condition leading to *trans* piperidines **2.17**, the thermodynamic product would be assembled through chair-form transition state **2.19**. On the other hand, in the Brønsted condition leading to *cis* piperidines **2.18**, the kinetic product would be assembled through stepwise pathways **2.21** which would be protonation of aldehyde and C-C bond formation with stabilization by the overlapping between empty π -cation on the carbon and oxygen lone pair.



Scheme 2.5

2.2.6 Hydroamination

Intramolecular hydroamination of olefin is a desirable transformation for piperidine synthesis. Marks *et al.* reported the organolanthanide-catalyzed hydroamination of amine bearing a diene **2.23** with excellent diastereoselectivity (Scheme 2.6).⁶⁷ They envisaged the racemic synthesis of pinidine through chair-form like transition state. The chiral version of the reaction was up to 69% ee. As a drawback, their methodology requires to operate experiments in glove box.

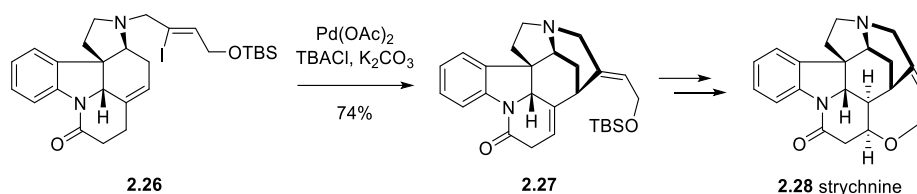


Scheme 2.6

⁶⁷ Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886.

2.2.7 Palladium Cyclization

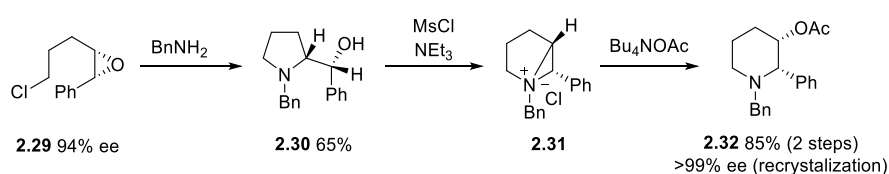
The total synthesis of strychnine **2.28** is one of the most historical studies from the first synthesis by *Woodward et al.*⁶⁸ Among a lot of approaches, *Rawal et al.* reported C-C bond formation by palladium catalyzed Heck-type reaction to forge the piperidine ring of the target (**Scheme 2.7**)⁶⁹.



Scheme 2.7

2.2.8 Ring Expansion

As a unique strategy, there is a ring expansion approach for preparing a piperidine ring from a pyrrolidine ring. *Lee et al.* reported the highly stereoselective piperidine synthesis by the ring expansion of pyrrolidine **2.30** which was prepared from intermolecular amination of a chiral epoxide **2.29** (**Scheme 2.8**).⁷⁰ It is anticipated that the bicyclic aziridinium intermediate **2.31** could be generated by mesylation of the alcohol **2.30** and then the acetate anion of TBAOAc opened the aziridinium ring. The epoxide **2.29** was easily prepared by highly enantioselective Jacobsen epoxidation.



Scheme 2.8

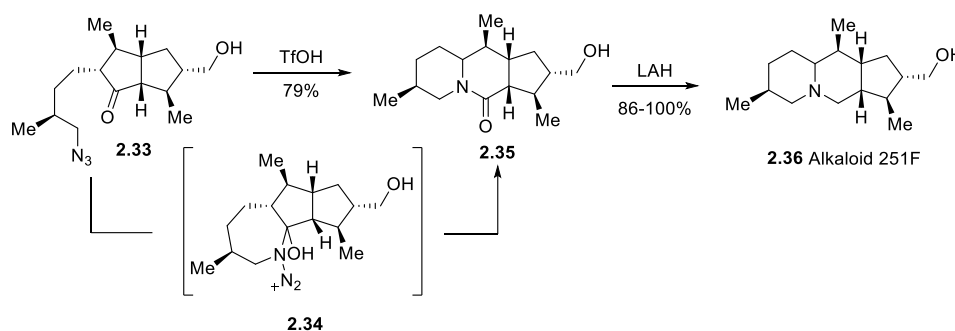
⁶⁸ Review: Cannon, J. S. Overman, L. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 4288.

⁶⁹ Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. See also: a) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamotke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324. b) Nakanishi, M.; Mori, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1934.

⁷⁰ Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223.

2.2.9 Schmidt Reaction

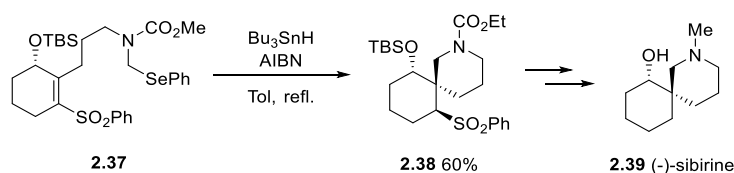
Aubé *et al.* demonstrated intramolecular Schmidt reaction for the synthesis of alkaloid 251F **2.36** which was isolated from skin exudate of a Columbian dendrobatid poison frog, *Minyobates bombetes* (Scheme 2.9).⁷¹ Treatment of **2.33** with TfOH provided the piperidine scaffold **2.35** through the azidohydrin intermediate and the subsequent reduction gave chiral alkaloid 251F **2.36**.



Scheme 2.9

2.2.10 Radical Cyclization

Koreeda *et al.* demonstrated the radical cyclization from phenyl selenide precursor **2.37** with Bu_3SnH and AIBN for the construction of spirocyclic piperidines **2.38** (Scheme 2.10).⁷² They applied their method for the asymmetric synthesis of the spirocyclic alkaloid (-)-sibirine **2.39**.



Scheme 2.10

2.2.10 Ring Closing Metathesis

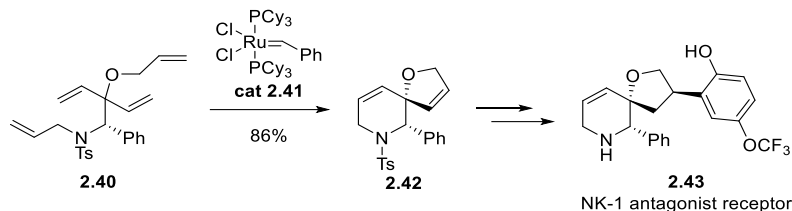
Wallace *et al.* reported double-ring closing metathesis as a key reaction for the synthesis of a NK-1 antagonist receptor **2.43** which has spirocyclic piperidine structure (Scheme 2.11).⁷³ They prepared the chiral tetraene **2.40** from a commercially available amino acid ester. The

⁷¹ Wroblewski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974.

⁷² Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett.* **2002**, *4*, 3329.

⁷³ Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H.; Reider, P. J. *Org. Lett.* **2001**, *3*, 671.

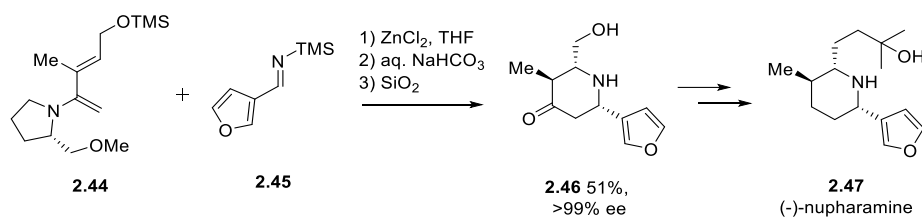
metathesis reaction was settled with the tetraene **2.40** and 1st generation Grubbs catalyst **2.41**, affording the spirocyclic intermediate **2.42**. In several transformations, the chiral NK-1 antagonist receptor **2.43** was obtained.



Scheme 2.11

2.2.11 Aza-Diels-Alder Reaction

Barluenga *et al.* described the aza Diels-Alder reaction with diene **2.44** and aldamine **2.45** for enantioselective synthesis of nuphar alkaloid (-)-nupharamine **2.47** (Scheme 2.12).⁷⁴ Treatment of diene **2.44** with aldamine **2.45** in the presence of ZnCl₂ followed by hydrolysis afforded chiral 4-piperidone **2.46**. After several transformations, the total synthesis of (-)-nupharamine **2.47** was completed.



Scheme 2.12

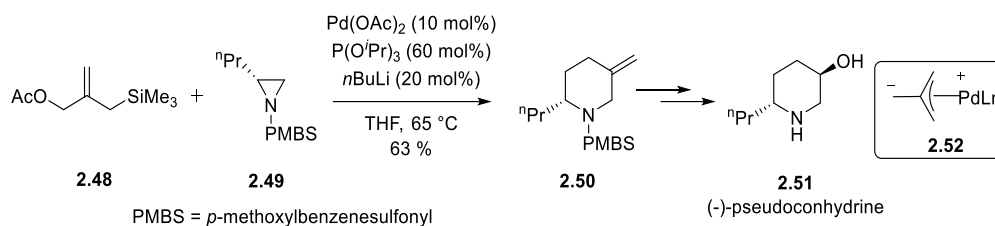
2.2.12 [3+3] Cycloaddition

Harrity *et al.* reported the [3+3] cycloaddition of aziridines with Pd-trimethenemethane complexes affording functionalized piperidines (Scheme 2.13).⁷⁵ Utilization of the enantiomerically pure aziridine **2.49** which was prepared from an appropriate amino acid provided enantiopure piperidine **2.50** under their conditions. They also demonstrated asymmetric synthesis of (-)-

⁷⁴ a) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403. b) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805. c) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736.

⁷⁵ Edwards, A. S.; Wybrow, R. A. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *J. Chem. Soc., Chem. Commun.* **2002**, 1542.

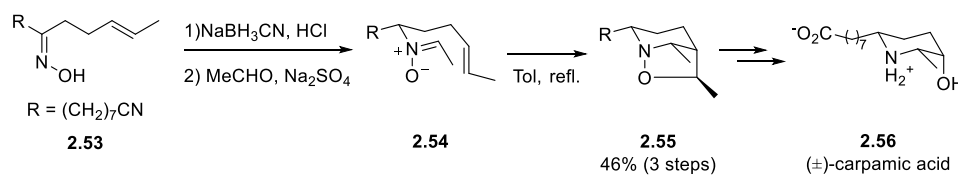
pseudoconhydrine **2.51** using chiral piperidine **2.50**.



Scheme 2.13

2.2.13 Nitronc Cycloaddition

The employment of intramolecular 1.3-dipolar cycloaddition is well-established methodology for total synthesis. Homes *et al.* reported that N-alkenylnitronc **2.54**, which was synthesized from the corresponding oxime **2.53**, was transformed to isoxazolidine **2.55** through the chair-like transition state (**Scheme 2.14**).⁷⁶ After several processes, racemic carpamic acid **2.56** was obtained.



Scheme 2.14

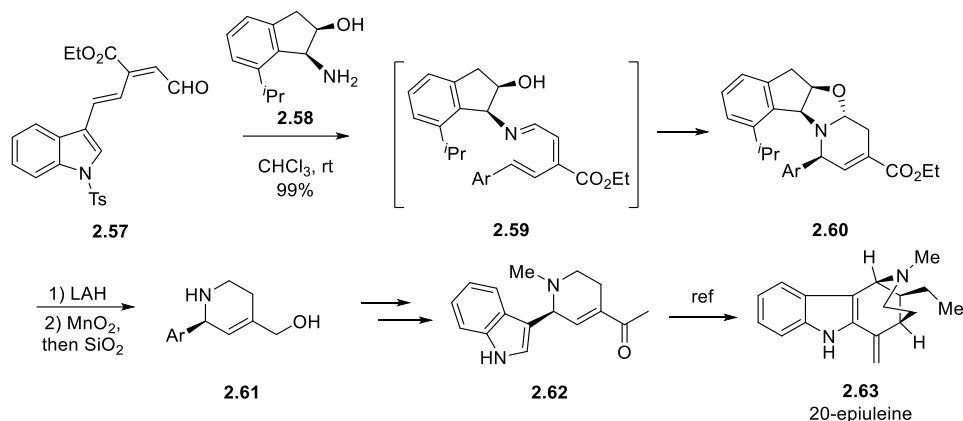
2.2.14 6π Electrocyclization

Thermal 6π-azaelectrocyclization as a pericyclic reaction is an interesting approach for diastereoselective piperidine. Katsumura *et al.* developed the asymmetric thermal 6π-azaelectrocyclization toward total synthesis of 20-epiuleine **2.63** which is one of strychnos alkaloids (**Scheme 2.15**).⁷⁷ The diastereoselectivity was controlled by alkyl substituent at 7 position on indene ring **2.58** and the enantioselectivity was managed by the enantiopure aminoalcohol moiety. They accomplished the formal total synthesis of 20-epiuleine **2.63** by building the known synthetic intermediate **2.62** through the thermal 6π-azaelectrocyclization.⁷⁸

⁷⁶ Homes, A. B.; Swithenbank, C.; Williams, S. F. *J. Chem. Soc., Chem. Commun.* **1986**, 265.

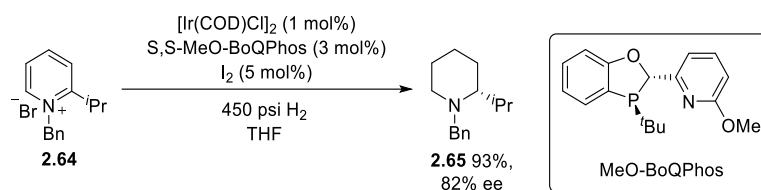
⁷⁷ Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660.

⁷⁸ ref) Harris, M.; Besselièvre, R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 331.



2.2.15 Pyridine Reduction

The exhaustive reduction of pyridine to piperidine is a simplest but powerful pathway for accessing multi-substituted piperidines. Qu *et al.* reported the Ir-catalyzed enantioselective hydrogenation of 2-alkyl pyridinium salts in which optimization of chiral ligands provided enantioenriched piperidines up to 97:3 er (**Scheme 2.16**).⁷⁹



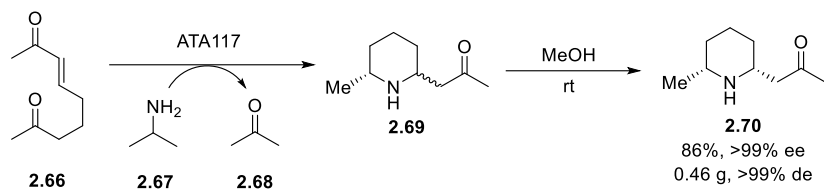
2.2.16 Biocatalyst

Biocatalysts have been emerging as powerful and economical catalysts. It was found that ω -transaminase enzymes catalyze the transamination reaction of prochiral ketone **2.66** and the subsequent enantioselective intramolecular aza-Michael addition. Epimerization in MeOH afforded enantioenriched 2,6-disubstituted piperidine **2.770** as reported by Caprio *et al.* (**Scheme 2.17**).⁸⁰ The reaction mechanism involves reversible processes and the key is that

⁷⁹ Qu, B.; Mangunuru, H. P. R.; Wei, X.; Fandrick, K. R.; Desrosiers, J.-N.; Sieber, J. D.; Kurouski, D.; Haddad, N.; Samankumara, L. P.; Lee, H.; Savoie, J.; Ma, S.; Grinberg, N.; Sarvestani, M.; Yee, N. K.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2016**, *18*, 4920.

⁸⁰ Ryan, J.; Šiaučiulis, M.; Gomm, A.; Maciá, B.; O'Reilly, E.; Caprio, V. *J. Am. Chem. Soc.* **2016**, *138*, 15798.

products are converted into the thermodynamically stable one.



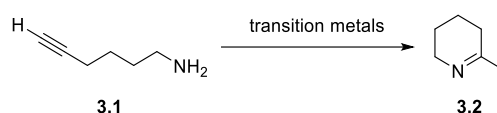
Scheme 2.17



3 Hydroamination of Alkynes

3.1 Introduction

Hydroamination of alkynes is a practical strategy to construct *N*-heterocyclic products as amines don't react spontaneously with alkynes, which facilitate the construction, enantioselective especially, of the acyclic products. It has been known that π -bonds of alkynes are activated by several transition metals (Au, Ag, Cu, Pd, Pt, Rh, Ru, Hg, Zn, In *etc.*) as well as Brønsted acids and halogens.⁸¹ For a well-classified example, Müller *et al.* evaluated the effects of late transition metals group 9-12 and Ru for hydroamination reaction of 6-aminohex-1-yne **3.1** to 2-methyl-1,2-dehydropiperidine **3.2** (Scheme 3.1).⁸² In their report, the highest activity was observed with $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$.



Scheme 3.1

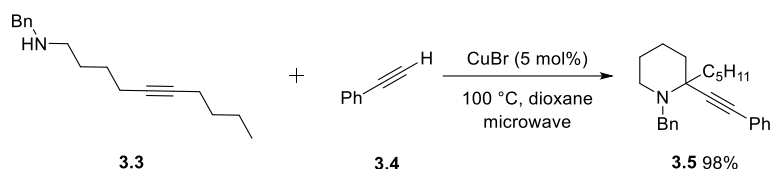
3.1.1 Copper

Hammond *et al.* reported intramolecular hydroamination of terminal alkynes in the presence of a copper catalyst under microwave irradiation (Scheme 3.2).⁸³ At the first step, CuBr promoted the cyclization of the aminoalkynes by activation of the triple bond and then the terminal alkynes attacked the cyclized iminium, affording *N*-heterocycles (5,6,7 member rings) with a quaternary carbon. Through screening of metal catalysts, CuBr was found the best metal for this reaction among various transition metals (Cu(II), Ag, Au, Pt).

⁸¹ Review: a) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. *J. Chem. Rev.* **2015**, *115*, 2596. b) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. c) Yamamoto, Y.; Gridnev, I. D.; Patil, N.T.; Jin, T. *Chem. Commun.* **2009**, 5075.

⁸² Müller, T. E.; Pleier, A.-K.; *J. Chem. Soc., Dalton Trans.* **1999**, 583.

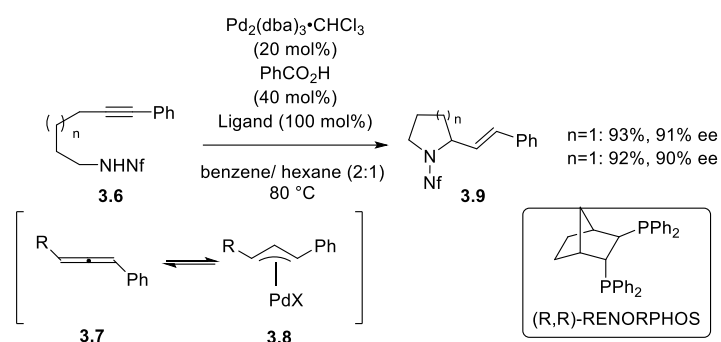
⁸³ Han, J.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 916.



Scheme 3.2

3.1.2 Palladium

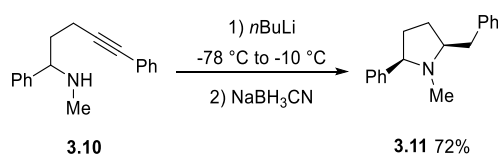
Yamamoto *et al.* reported Pd-catalyzed intramolecular hydroamination of *in situ*-formed allenes (Scheme 3.3).⁸⁴ The Nf or Tf protections of amine moiety were required for high enantioselectivity, while Bn, Ac, Boc or Ts protections gave unsatisfactory results.



Scheme 3.3

3.1.3 Anion Process

Suginome *et al.* reported base-promoted hydroamination of δ -alkynyl amines (Scheme 3.4).⁸⁵ Lithium amides, which derived from the amines and *n*BuLi, underwent 5-*exo*-dig cyclization and the unstable enamines were stereoselectively reduced with NaBH₃CN.



Scheme 3.4

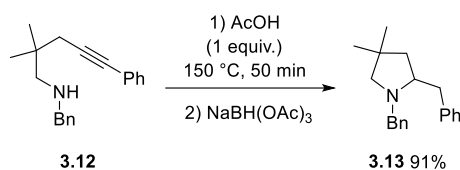
3.1.4 Brønsted acid

Cossy *et al.* reported Brønsted acid-promoted hydroamination of δ -alkynyl amines (Scheme

⁸⁴ Lutete, L. M.; Kadota, I.; Yamamoto, Y.; *J. Am. Chem. Soc.* **2004**, *126*, 1622. See also; a) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y.; *J. Org. Chem.* **1999**, *64*, 4570. b) Bajracharya, G. B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4883.

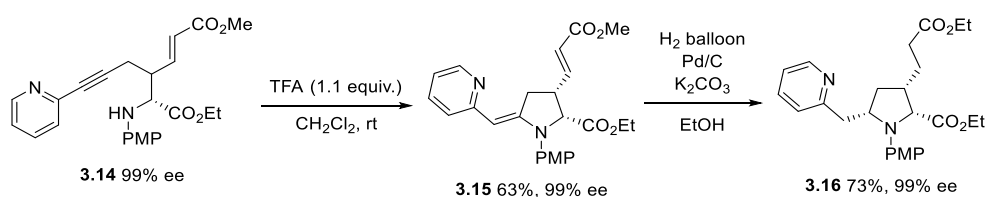
⁸⁵ Tokuda, M.; Fujita, H.; Suginome, H. *Tetrahedron Lett.* **1990**, *37*, 5353.

3.5).⁸⁶ The reactions were conducted at high temperature and they also mentioned that 5-*exo*-dig cyclized enamines were sensitive unless reduced as well as Suginome's group mentioned.



Scheme 3.5

In 2013, our group reported Brønsted acid-promoted hydroamination of chiral *N*-heteroaromatic alkynyl amines (**Scheme 3.6**).⁸⁷ The reactions were conducted with TFA at room temperature and the chiral enamines were obtained through 5-*exo*-dig cyclization without diminishing their enantiomeric excess. The key of the reactions was that protonation of basic heterocycles with Brønsted acid lowers the electronic density of the alkyne by mesomeric and/or inductive effects. Furthermore, the enamines were reduced by hydrogenation affording chiral trisubstituted pyrrolidines.



Scheme 3.6

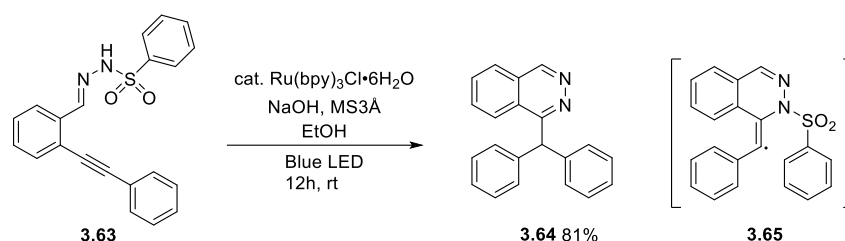
3.1.5 Radical

Belmont and Brachet *et al.* reported radical hydroamination reaction followed by a radical Smiles rearrangement under irradiation of visible light (**Scheme 3.7**).⁸⁸ The cascade reactions of alkynylsulfonhydrazones **3.64** were conducted with a Ru photocatalyst and NaOH under irradiation of blue LED. The reactions afforded phthalazine derivatives **3.65** in excellent yields.

⁸⁶ Cossy, J.; Belotti, D.; Bellosta, V.; Boggio, C.; *Tetrahedron Lett.* **1997**, *38*, 2677. See also; Cossy, J.; Belotti, D.; *Synlett* **1997**, 1249.

⁸⁷ Jean, A.; Blanchet, J.; Rouden, J.; Maddaluno, J.; De Paolis, M. *Chem. Commun.* **2013**, *49*, 1651.

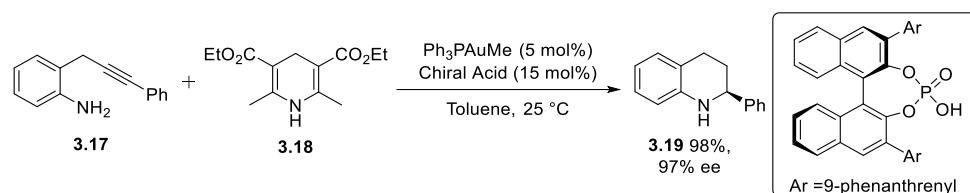
⁸⁸ Brachet, E.; Marzo, L.; Selkti, M.; König, B.; Belmont, P. *Chem. Sci.* **2016**, *7*, 5002.



Scheme 3.7

3.1.6 Gold

Gong *et al.* reported gold-catalyzed hydroamination of 2-(2-propynyl)aniline derivatives, followed by asymmetric reduction using a chiral phosphoric Brønsted acid (**Scheme 3.8**).⁸⁹ Achiral gold catalyst promoted 6-*endo* cyclization and subsequently the iminium cations generated by the chiral Brønsted acid were reduced enantioselectively by the Hantzsch ester. The relay reactions were well tolerated for the replacement of Ph group on the propynyl moiety with electron-withdrawing or electron-donating substituted aryls without losing excellent yields and enantiomeric excess.



Scheme 3.8

3.2 Selectivity of 6-*endo*-dig and 5-*exo*-dig

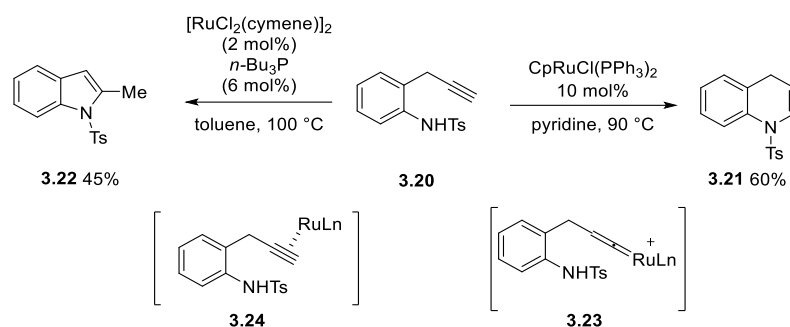
3.2.1 Ruthenium

Saá *et al.* reported 6-*endo*/5-*exo* switchable hydroamination of aniline derivatives depending on Ru complexes (**Scheme 3.9**).⁹⁰ The employment of half-sandwich complex, CpRuCl(PPh₃)₂ afforded dihydroquinolines **3.21** while the utilization of Ru catalyst with P(*n*-Bu)₃ ligand gave indoles **3.22**. They assumed the 6-*endo*-dig cyclization took place through a Ru vinylidene

⁸⁹ Han, Z.-Y.; Xiao, X.-H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182.

⁹⁰ Varela-Fernández, A.; Varela, J. A.; Saá, C. *Adv. Synth. Catal.* **2011**, *353*, 1933. See also, Varela-Fernández, A.; Varela, J. A.; Saá, C. *Synthesis*, **2012**, *44*, 3285.

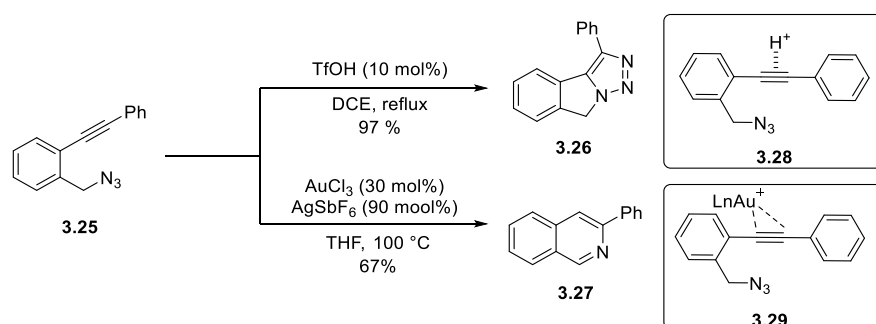
intermediate whereas π -coordination of a Ru catalyst to alkynes led to 5-*exo*-dig cyclization.



Scheme 3.9

3.2.2 Brønsted Acid vs Gold (III)

Yamamoto *et al.* reported that 2-alkynyl benzyl azide **3.25** underwent Huisgen 1,3-dipolar cycloaddition **3.26** in the presence of catalytic amount of TfOH, while ligand-free cationic Au(III) catalyst promoted 6-*endo*-dig cyclization **3.27** (Scheme 3.10).⁹¹ According to their computational study, TfOH can symmetrically activate alkynes, while Au (III) can unsymmetrically coordinate to alkynes.



Scheme 3.10

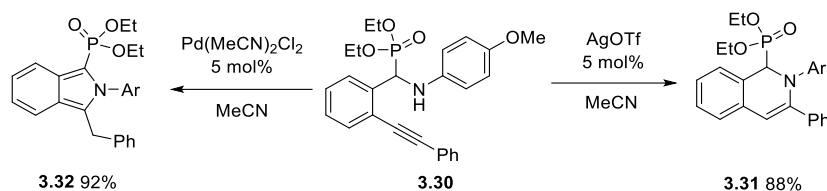
3.2.3 Pd vs Ag

Wu *et al.* reported intramolecular hydroaminations with switchable regioselectivity depending on transition metals used (Scheme 3.11).⁹² In the presence of Pd(II), the 5-*exo* products of α -amino (2-alkynylphenyl) methylphosphonates **3.32** were obtained whereas, in the presence of

⁹¹ Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651. See also; a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. b) Huo, Z. Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266. c) Computational study; Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075.

⁹² Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5439.

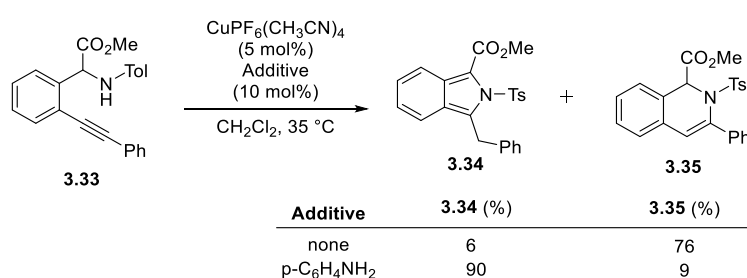
Ag(I), the 6-*endo*-products **3.32** were obtained. However, the difference of the reactivity between Pd(II) and Ag(I) is still not clear.



Scheme 3.11

3.2.4 Copper with Aniline Additive

In the similar case of Wu's work, Wang *et al.* developed the *exo/endo* selective intramolecular hydroaminations with a copper catalyst (**Scheme 3.12**).⁹³ The reactions in the presence of *p*-tolylamine **3.33** afforded isoindoles **3.34**, while the reactions without additive gave hydroisoquinolines **3.35**. They assumed steric effect of the additive, which coordinate to the copper catalyst, was responsible for this selectivity, however, it is not clear yet.



Scheme 3.12

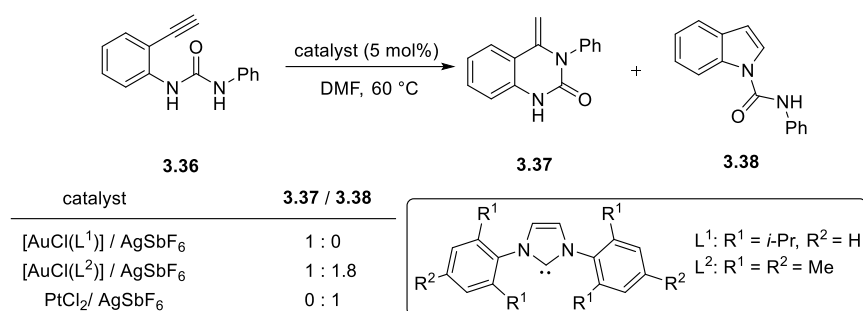
3.2.5 Gold vs Pt

Asensio *et al.* found alkyne urea **3.36** was selectively cyclized into indole **3.38** or quinazolinone **3.37** depending on the choice of transition metals or ligands (**Scheme 3.13**).⁹⁴ When using a gold catalyst with a bulky ligand and a silver salt, 6-*endo*-dig cyclization was preferred, while utilization of a ligand-free cationic catalyst based on Pt(II) and a silver salt afford indoles in the 5-*exo*-dig cyclization mode. In contrast, ureas bearing internal alkynes afforded indoles in the 5-*exo*-dig cyclization mode in spite of employing the gold catalyst with

⁹³Peng, C.; Cheng, J.; Wang, J. *Adv. Synth. Catal.* **2008**, 350, 2359.

⁹⁴ Gimeno, A.; Medio-Simón, M.; de Arellano, C. R.; Asensio, G.; Cuenca, A. B. *Org. Lett.* **2010**, 12, 1900.

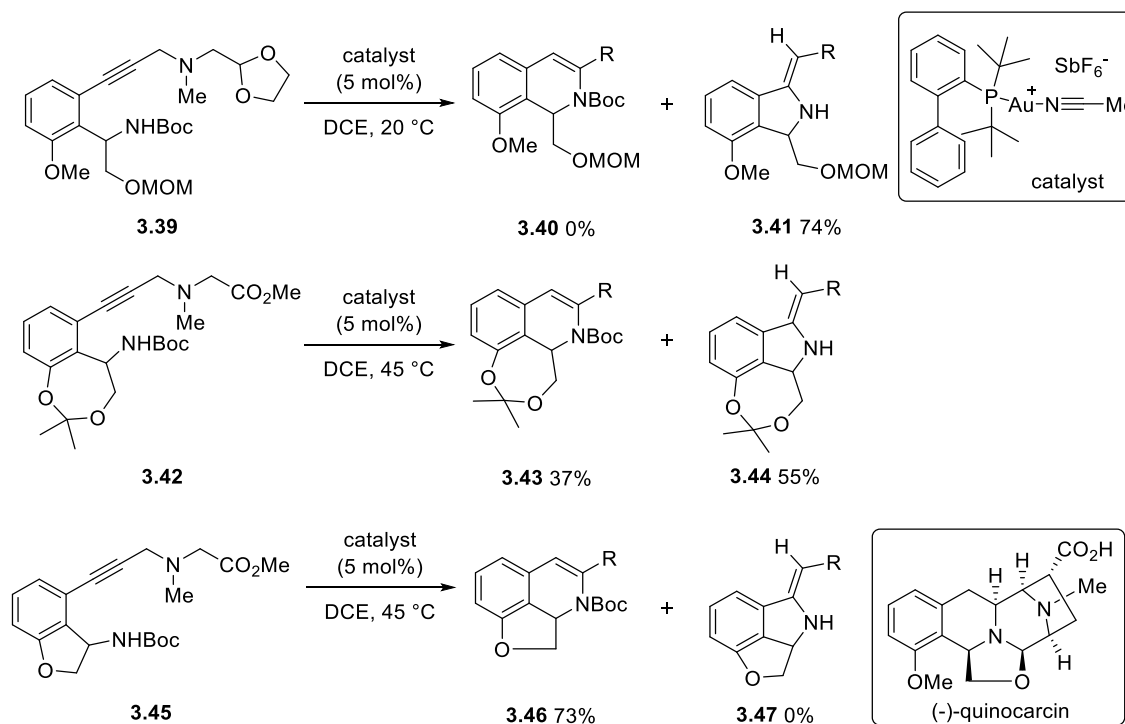
the bulky ligand.



Scheme 3.13

3.2.6 Gold with Steric Strains

Ohno *et al.* observed that the selectivity of *exo/endo* gold-catalyzed cyclizations was gradually changed depending on the steric strains of substrates (**Scheme 3.14**).⁹⁵ In substrates **3.39** and **3.42** with the open-chain ether or the large-ring acetal, 5-*exo*-dig cyclizations were preferred, while, with substrate **3.45** with 5-membered ring, 6-*endo*-dig cyclization was preferred. Thanks to the 6-*endo*-dig selective isoquinoline synthesis, the total synthesis of (-)-quinocarcin was completed.

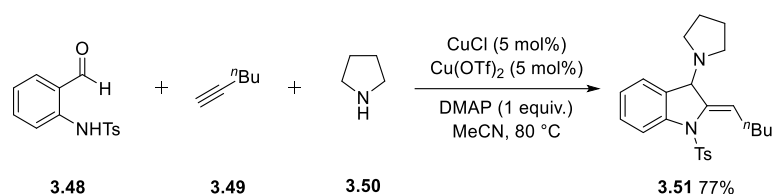


Scheme 3.14

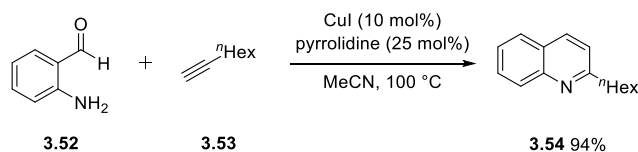
⁹⁵ Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1.

3.2.7 Copper

By comparing Gevorgyan' and Patil' works, we notice a change in the selectivity of the *exo/endo* cyclizations (**Scheme 3.15** and **3.16**). When *N*-Ts protected 2-aminobenzaldehyde **3.48**, terminal alkyne **3.49** and pyrrolidine **3.50** were employed in the presence of a copper catalyst, the propargyl amine **3.51** was obtained from the three-components reaction *in situ*. On the other hand, when 2-aminobenzaldehyde **3.52** and terminal alkyne **3.53** were employed in the presence of a copper catalyst and pyrrolidine, quinoline **3.54** was obtained. The *exo/endo* selectivity of the copper-catalyzed cyclization was dictated by the protecting group of the nitrogen atom, affording either 3-amino indolines or 2-substituted quinolines.



Scheme 3.15



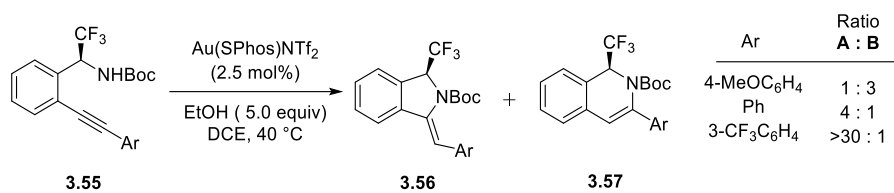
Scheme 3.16

3.2.8 Gold with Electron Populations

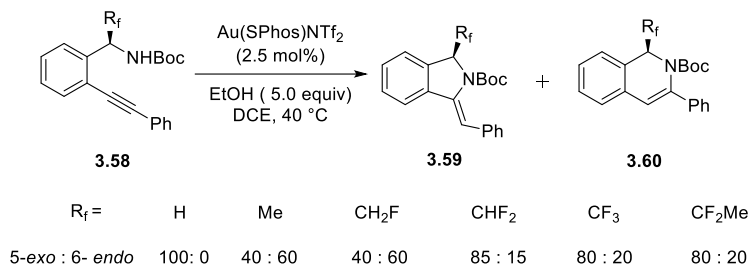
Catalán *et al.* found that gold-catalyzed *exo/endo* cyclizations of 2-alkynyl benzyl carbamates **3.55** explicitly depended on the electron density distribution of substrates (**Scheme 3.17a** and **3.17b**).⁹⁶ First, the selectivity of *exo/endo* cyclization was affected by the electronic property of Ar group (**Scheme 3.17a**), whereas installing fluoro atoms to the Ar group gradually led to 5-*exo*-cyclization (**Scheme 3.17b**). On the other hand, according to Takemoto's report, only 6-*endo* cyclizations were observed even when the alkyne was connected to an electron deficient aryl group without any substituents at the benzylic position. (**Scheme 3.18**).⁹⁷

⁹⁶ Fustero, S.; Ibáñez, I.; Barrio, P.; Maestro, M. A.; Catalán, S. *Org. Lett.* **2013**, *15*, 832.

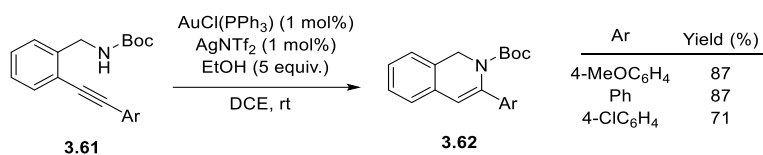
⁹⁷ Enomoto, T.; Obika, S.; Yasui, Y.; Takemoto, Y. *Synlett*, **2008**, *11*, 1647.



Scheme 3.17a



Scheme 3.17b



Scheme 3.18

In short summary, there are several reports for 5-*exo*/6-*endo* switchable hydroamination, however, in most cases, there is little clear-cut explanation for the difference of the 5-*exo*/6-*endo* selectivity due to several kinds of influences. Besides, even though Baldwin's rule is helpful to determine a pattern of cyclization, in the case of 5-*exo*/6-*endo* cyclization, the rule is not applicable as both patterns are favored.

4 Objectives

Considered from the reports above, the main factors for switchable 5-*exo*/6-*endo* cyclization can be sorted into several types;

- 1) Kind of transition metal catalysts
- 2) Bulkiness of ligand (in cases of transition metal catalysts)
- 3) Strain effect of substrates
- 4) Electron density distribution of substrates

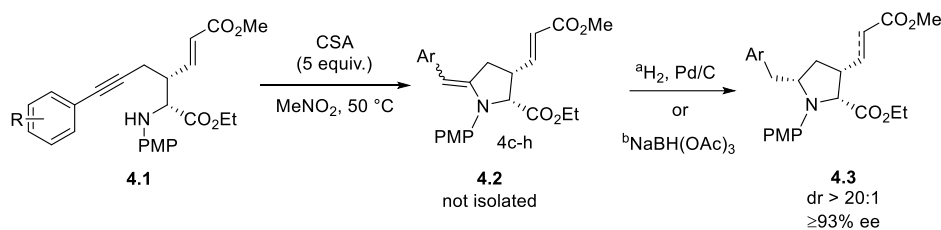
Even though Brønsted acids are less expensive and more environmentally friendly than transition metals, there are few examples, Cossy's and our reports, in which 5-*exo*-dig cyclizations were preferred in all cases (**Scheme 3.4** and **3.5**). The reason for the difficulty of hydroamination using Brønsted acid is presumably due to the protonation of a basic nitrogen atom, and the resulting ammonium salt is less nucleophile. In addition, there is no example of switchable 5-*exo*/6-*endo* cyclization in this context.

About the mechanism of the 5-*exo*-dig cyclization, there are some evidences about H⁺- π interaction between Brønsted acid and triple bond, which is an unusual and weak hydrogen bonding, in crystal phase.⁹⁸ In some examples, it was observed that a hydrogen bond was orthogonally directed toward a triple bond in crystals. These results would suggest that H⁺- π interaction between Brønsted acid and alkyne would exist not only in crystals but also in solution.

In addition, our group recently developed hydroamination reactions which would imply intermolecular H⁺- π interaction between a Brønsted acid and alkynes bearing non-basic

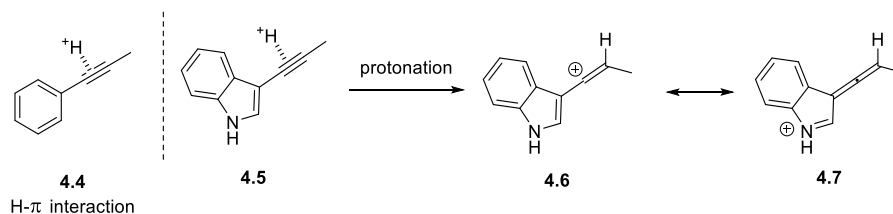
⁹⁸ a) Viswamitra, M. A.; Radhakrishnan, R.; Bandekar, J.; Desiraju, G. R. *J. Am. Chem. Soc.* **1993**, *115*, 4868. b) Pilkington, M.; Wallisand, J. D.; Larsen, S. *J. Chem Soc., Chem. Commun.* **1995**, 1499. c) Allen, F. H.; Howard, J. A. K.; Hoy, V. J.; Desiraju, G. R.; Reddy, D. S.; Wilson, C. C. *J. Am. Chem. Soc.* **1996**, *118*, 4081.

aromatics (**Scheme 4.1**). It was then demonstrated that alkynyl amines bearing non-basic aromatics **4.1** were cyclized with CSA in MeNO₂ upon heating in 5-*exo*-dig mode. The milder reaction condition than Cossy's was likely due to the fact that the anisidine moiety is less basic than the alkyl amine and the ammonium salt from the anisidine moiety was formed less preferentially in their equilibrium. (cf. Et₃N⁺H: pK_a = 10.75 and PhN⁺(Me)₂H: pK_a = 5.2 in water). As well as the cases of alkynyl amines bearing a basic heterocycle (**Scheme 3.5**), all pyrrolidine derivatives bearing non-basic aromatics **4.3** were obtained through 5-*exo*-dig cyclization. The reaction mechanism implies that H⁺-π interaction, between a Brønsted acid and arylalkynes, are involved in the process of 5-*exo*-dig cyclization since the cyclizations did not occur without acids.



Scheme 4.1

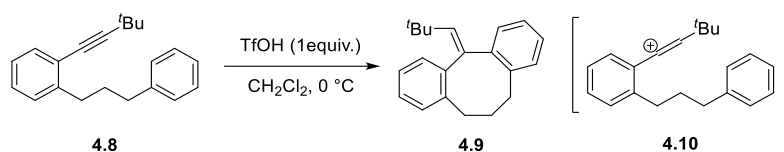
In view of these results, however, it is still unclear how would be the reactivity of alkynes connected to electron-rich aromatics such as indoles. And it remains possible that interplays of arylalkynes with H⁺ could be shifted from H⁺-π interaction to the protonation of alkyne as the electronic density of alkynes increases with such electron-rich arenes (**4.6** and **4.7**) (**Scheme 4.2**).



Scheme 4.2

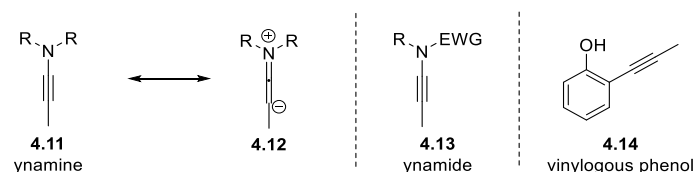
In general, protonation of alkynes has remarkably high energy barrier because of instability of their vinylic cation. Some examples were reported, but in the all cases, super acids (ex. TfOH)

were required for the protonation (e.x. **Scheme 4.3**).⁹⁹



Scheme 4.3

On the other hand, it is inferred that if alkynes are connected to electron-rich substituents, cations resulting from protonation of the alkynes could be stabilized by mesomeric effect unlike unstable vinylic cation **4.10**. For examples of similar reactivity, it is well known that ynamine **4.13**, ynamide **4.14** or arylogous phenol **4.15** have highly C-nucleophilic character. (**Scheme 4.4**).¹⁰⁰ They have strong polarization of the triple bond in which electronic bias are imposed by heteroatoms.



Scheme 4.4

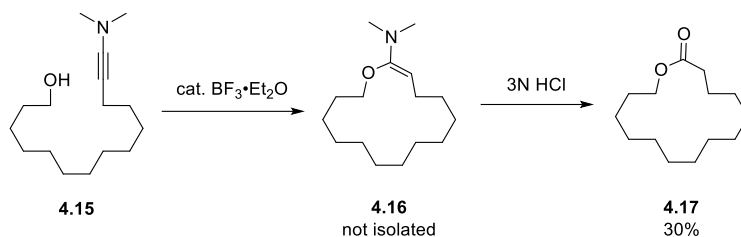
For instance, Genet *et al.* developed an intramolecular macrocyclization reaction of ynamine **4.15** catalyzed by BF₃·Et₂O (**Scheme 4.5**).¹⁰¹ Although ynamines **4.11** have unique and high reactivity, however, there has been severe limitation for synthetic application because of the difficulty of preparation and handling ynamines that are sensitive for moisture.

⁹⁹ a) Otani, T.; Ueki, K.; Cho, K.; Kanai, K.; Tateno, K.; Saito, T. *Chem. Comm.* **2015**, 51, 7895.

See also; b) Olah, G.; Mayr, H. *J. Am. Chem. Soc.* **1976**, 98, 7333. (c) Kaiser, D. Veiros, L. F.; Maulide, N. *Chem. Eur. J.* **2016**, 22, 4727. (d) Su, X.; Sun, Y.; Yao, J.; Chen H.; Chen, C. *Chem. Commun.* **2016**, 52, 4537. d) Schroeder, S.; Strauch, C.; Gaelings, N.; Niggemann, M. *Angew. Chem. Int. Ed.* **2019**, 58, 5119.

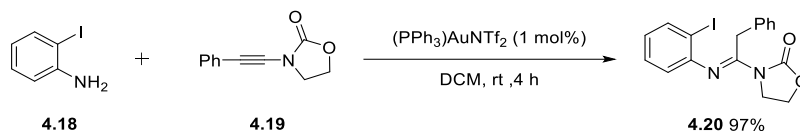
¹⁰⁰ Review: ynamine a) Zifcsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, 57, 7575. b) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, 63, 1455. Ynamide a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, 49, 2840; b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, 110, 5064. c) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, 47, 560. d) Evano, G.; Lecomte, M.; Thilmany, P.; Theunissen, C. *Synthesis*, **2017**, 49, 3183.

¹⁰¹ Genet, J. P.; Kahn, P. *Tetrahedron Lett.* **1980**, 21, 1521.



Scheme 4.5

On the other hand, ynamides **4.13** are much stable toward moisture due to the electron-withdrawing group which improves their stability, though their reactivity is attenuated. Ynamides are therefore more easily handle and are readily accessible. For an example, Skrydstrup *et al.* reported gold-catalyzed hydroamination of ynamides **4.19** and anilines **4.18**, affording amidine products **4.20** (Scheme 4.6).¹⁰²



Scheme 4.6

While the reactivity of ynamines and ynamides has been investigated extensively over the last decades as shown above,¹⁰³ little is known about their arylogous counterpart, which would increase their stability at the expense of the reactivity. It is assumed that when alkynes bearing electron-rich aromatics **4.5** undergo protonation, electrophilic allene-type intermediates **4.7**

¹⁰² Kramer, S.; Doolewerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

¹⁰³ (7) (a) Doria, F.; Percivalle, C.; Freccero, M. *J. Org. Chem.* **2012**, *77*, 3615. (b) Furusawa, M.; Arita, K.; Imahori, T.; Igawa, K.; Tomooka, K.; Irie, R. B. *Tetrahedron Lett.* **2013**, *54*, 7107. (c) Wu, X.; Xue, L.; Li, D.; Jia, S.; Ao, J.; Deng, J.; Yan, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13722. (d) Beppu, S.; Arae, S.; Furusawa, M.; Arita, K.; Fujimoto, H.; Sumimoto, M.; Imahori, T.; Igawa, K.; Tomooka, K.; Irie, R. *Eur. J. Org. Chem.* **2017**, *2017*, 6914. (e) Liu, Y.; Wu, X.; Li, S.; Xue, L.; Shan, C.; Zhao, Z.; Yan, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 6491. (f) Jia, S.; Chen, Z.; Zhang, N.; Tan, Y.; Liu, Y.; Deng, J.; Yan, H. *J. Am. Chem. Soc.* **2018**, *140*, 7056. (g) Arae, S.; Beppu, S.; Kawatsu, T.; Igawa, K.; Tomooka, K.; Irie, R. *Org. Lett.* **2018**, *20*, 4796. (h) Li, D.; Tan, Y.; Peng, L.; Li, S.; Zhang, N.; Liu, Y.; Yan, H. *Org. Lett.* **2018**, *20*, 4959. (i) Tan, Y.; Jia, S.; Yidong, F. H.; Peng, L. L.; Li, D.; Yan, H. *J. Am. Chem. Soc.* **2018**, *140*, 16893.

would be generated. Therefore, applying the concept to our Mannich adducts bearing electron-rich arenes would provide tetrahydropyridines through hydroamination reaction. (**Figure 4.1**). In addition, stereoselective functionalization of the chiral tetrahydropyridines could afford chiral tri- and tetrasubstituted piperidines which are important heterocyclic system found in natural products and molecules of pharmacological pertinence.

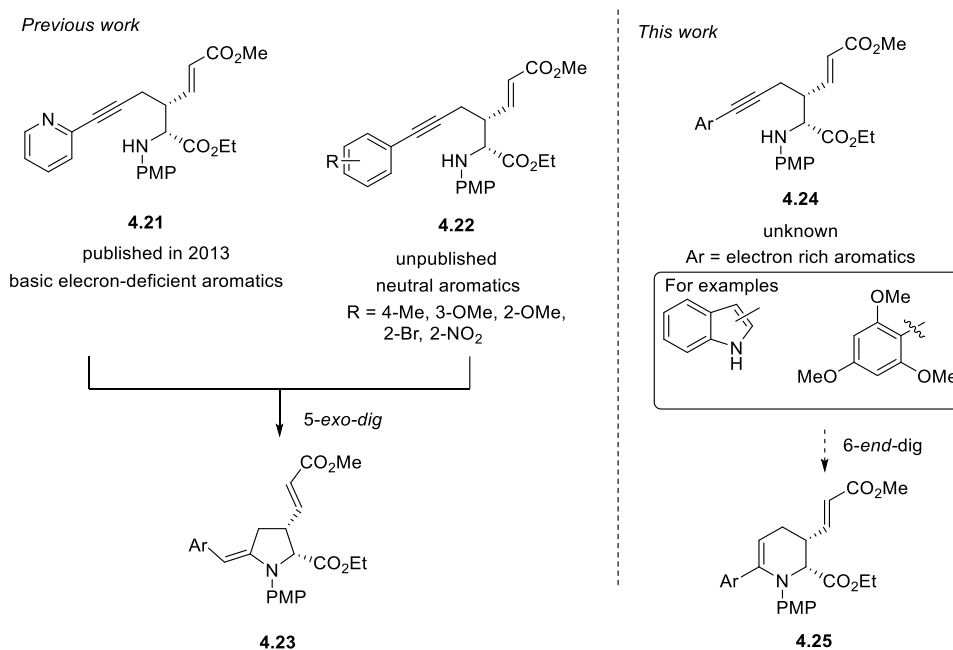
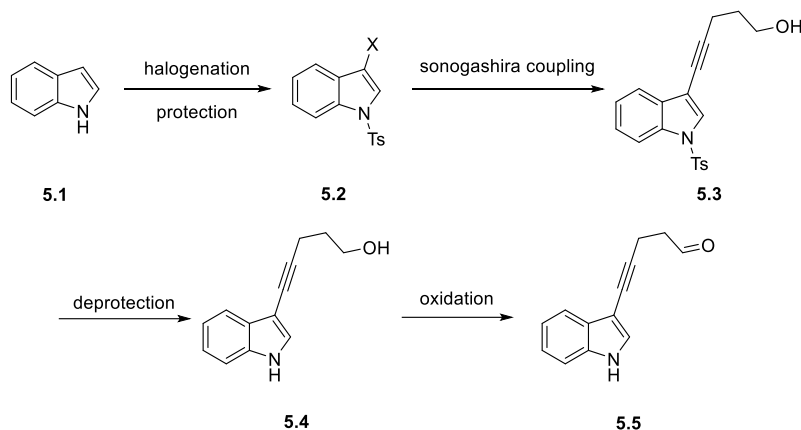


Figure 4.1

5 Results and Discussions

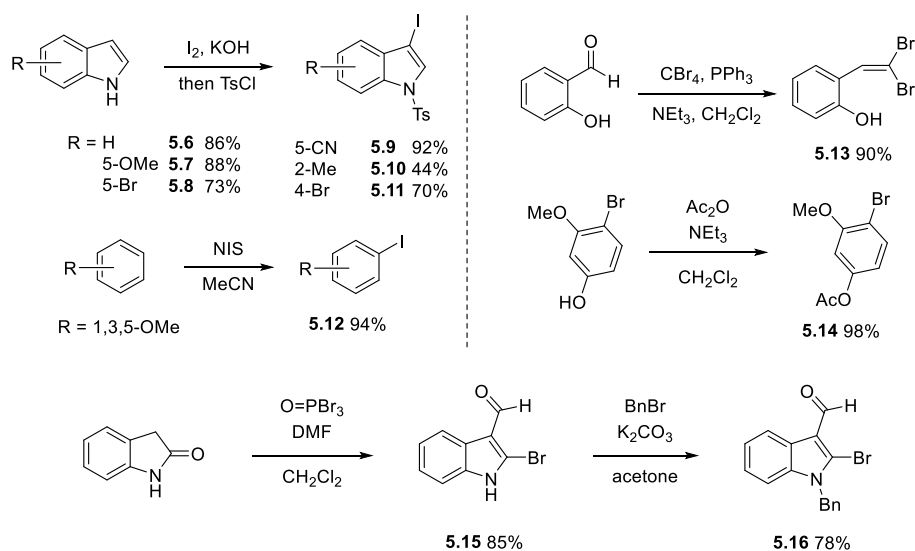
5.1 Preparation of Aldehydes

For a survey of asymmetric Mannich reactions, the synthesis of aldehydes bearing electron-rich aromatics was planned. The mainstream for the synthesis is shown below (**Scheme 5.1**).



Scheme 5.1

At first, iodinated or brominated electron-rich aromatics were obtained after some general chemical reactions (**Scheme 5.2**). 2-Bromo-1*H*-indole-3-carbaldehyde **5.15** was prepared from classical Vilsmeier-Heck bromoformylation of oxindole.¹⁰⁴

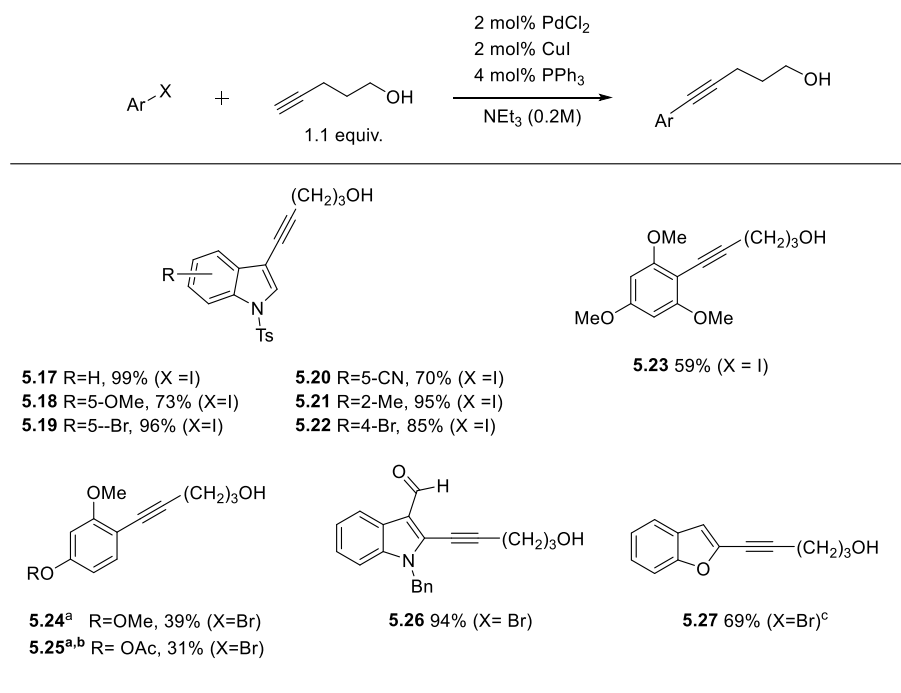


Scheme 5.2

The halo aromatic rings were submitted to a standard Sonogashira coupling condition (**Scheme**

¹⁰⁴ Tiano, M; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101.

5.3). The Sonogashira coupling of electron-rich aromatics suffered from low yields even though upon heating (**5.23**, **5.24** and **5.25**).



^a The reaction was carried out in refluxing condition.

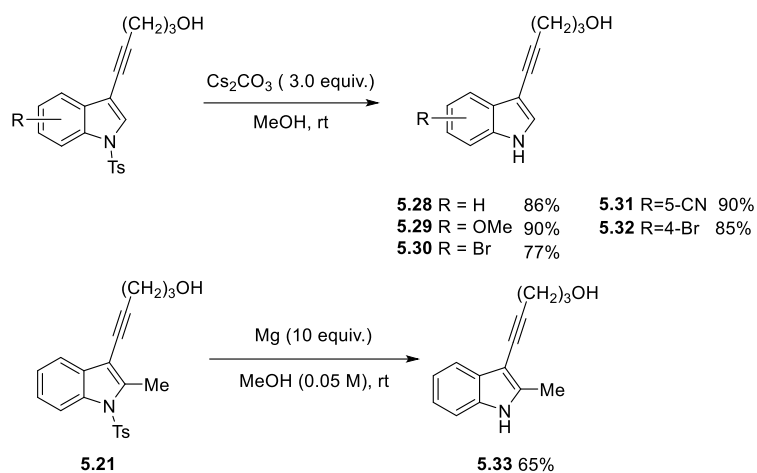
^b Pd(PPh₃)₄ was used instead of PdCl₂.

^c The reaction was carried out in 5mol% Pd/C, 5mol% CuI, 20 mol% PPh₃, alkyne (1.5 equiv,) and HNⁱPr₂ (4.0 equiv.) in Toluene/H₂O (2:1) at 100 °C.

Scheme 5.3

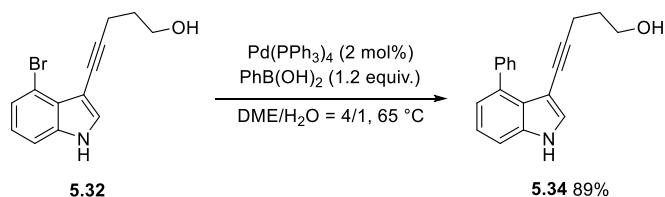
In case of indole derivatives, deprotection of the Ts group of indole rings was carried out with Cs₂CO₃ in MeOH (**Scheme 5.4**).¹⁰⁵ Exceptionally, deprotection of 2-methyl indole derivative **5.21** was carried out with Mg metal in MeOH as the starting material was recovered in the first conditions (Cs₂CO₃ in MeOH). In an interesting property of arylogous ynamines, they were more stable to protonic solvent (MeOH, H₂O) than ynamines which are known to react readily with H₂O and afford amides.

¹⁰⁵ Bajwa, J. S.; Chen, G.-P.; Prasad, K.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425.



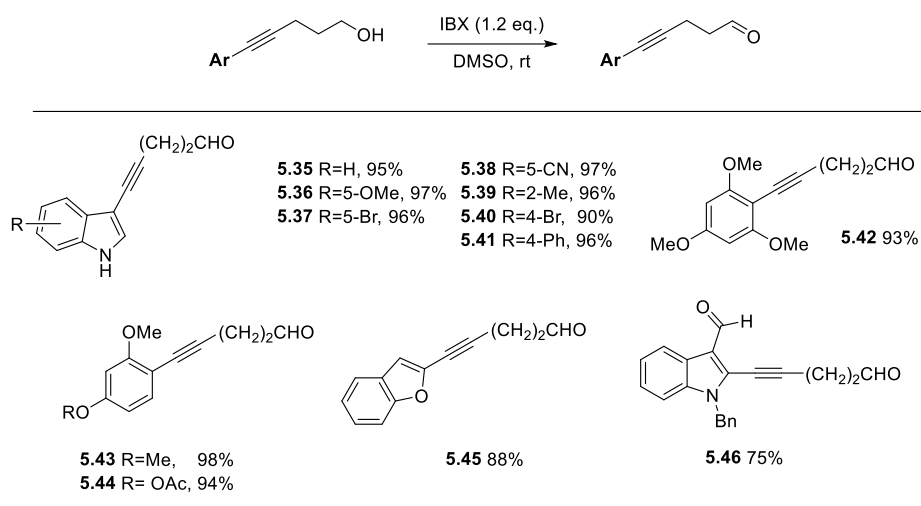
Scheme 5.4

To broaden the molecular diversity of arylogous ynamine, the coupling reaction of bromoindole **5.32** was tested. Suzuki coupling of arylogous ynamine **5.32** and phenyl boronic acid proceeded smoothly in 89% yield (**Scheme 5.5**).



Scheme 5.5

IBX oxidation of alcohols then afforded the corresponding aldehydes in excellent yields, while PDC oxidation of indole derivatives afforded complex mixtures probably because indoles were readily oxidized (**Scheme 5.6**). The twelve aldehydes were submitted to the *anti*-selective Mannich reaction subsequently since they are sensitive to air.

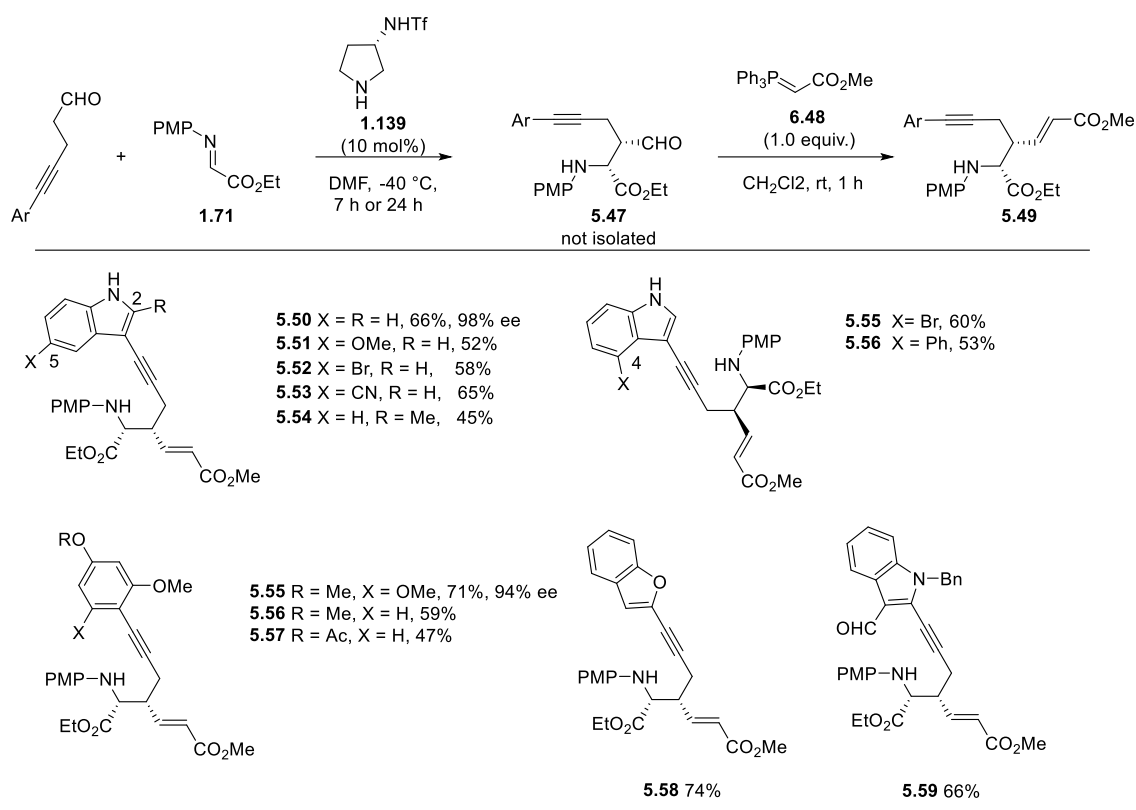


Scheme 5.6

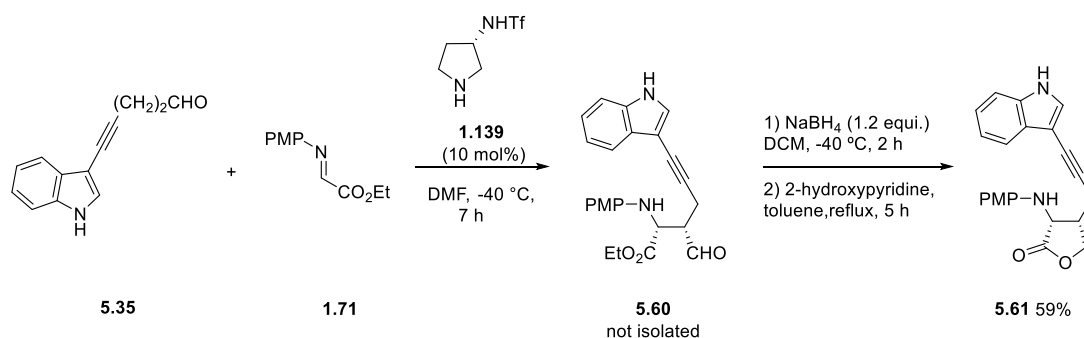
5.2 Asymmetric *anti*-Selective Mannich Reaction

Mannich reaction of aldehyde **5.35** was carried out in the presence of 10 mol% of catalyst **1.139** with a stoichiometric amount of imine **1.71** in DMF at -40°C (**Scheme 5.7**). The resulting Mannich product **5.60** was stabilized with stereoselective Wittig-Horner olefination directly due to sensitivity to air or silica gel, affording acyclic chiral amine **5.50** in 66% with excellent enantioselectivity (98% ee) over 2 steps. It was found that the chemistry has broad substrate scope in which indole derivatives bearing CN, OMe, Br or Ph and electron-rich anisole derivatives (**5.51** to **5.56**) were compatible. Alkoxy substituted arenes and benzofuran were also compatible for the Mannich reaction (**5.55** to **5.58**). In the case of 2-alkynylindole with aldehyde group at 3 position **5.46**, the Mannich and Wittig-Horner reactions proceeded well without touching aldehyde moiety on the indole ring. To extend the molecular diversity furthermore, the Mannich adduct **5.60** was reduced by NaBH_4 and subsequently intramolecular condensation were carried out in refluxing toluene with 2-hydroxypyridine, affording the lactone **5.61** in 50% yield over 3 steps (**Scheme 5.8**).

Combined with our previous results (Dr. Alexandre Jean), it was shown that *anti*-selective asymmetric Mannich reactions worked well with aldehydes bearing electron-rich or -deficient aromatics, moreover, heterocycles (indole, benzofuran, pyridine, thiazole *etc.*).



Scheme 5.7

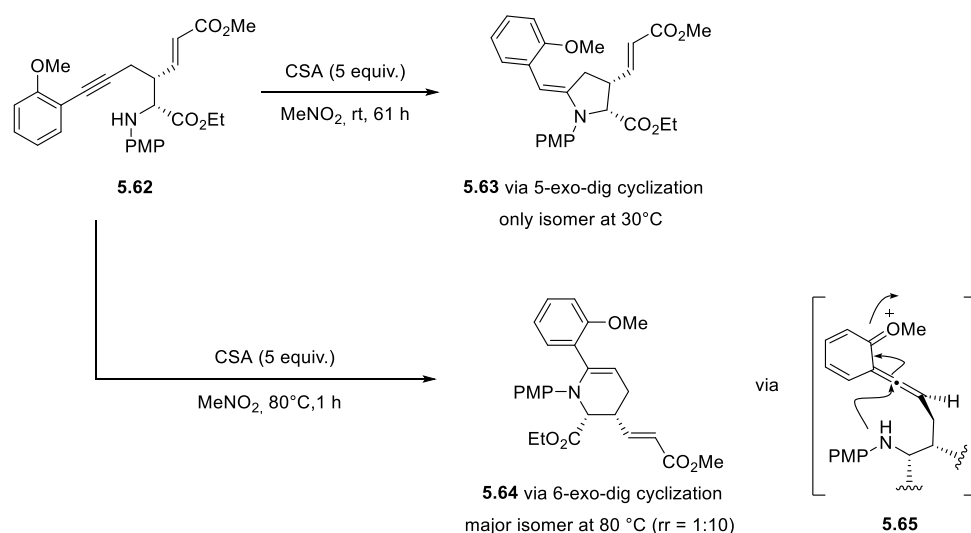


Scheme 5.8

5.3 Hydroamination of Arylogous Ynolethers

At first, as a reproductive experiment, it was confirmed that 2-methoxyphenylalkyne **5.62** which was prepared according to the procedure by a predecessor (Dr. Alexandre Jean) cyclized into pyrrolidine **5.63** under H-bonding activation at room temperature for 61 h, while tetrahydropyridine **5.64** which would be obtained through the protonation pathway was not observed at room temperature (**Scheme 5.9**). Interestingly, the protonation pathway was activated with heating. At 80°C (1 h, 10% conversion), the selectivity switched toward the

formation of the regioisomer **5.64** (rr = 1:10). Attempt to reach a full conversion revealed tetrahydropyridine **5.64** was more fragile compared to pyrrolidine **5.63** and hence, after 4 h at 80°C, the rr was decreased (1:2, 4 h, 80°C), likely hampered by the degradation of **5.64**. At any rate, the formation of tetrahydropyridine **5.64** thus illustrated a divergent reaction path triggered by the protonation of the triple bond anchimerically assisted by an arylogous ynoether in acidic condition. So far, this reactivity was documented for the carbocyclization of 2-alkynylbiaryls and, in basic conditions, vinylidene *ortho*-quinone methide were generated from the tautomerization of 2-(phenylethynyl)phenol.¹⁰⁶ In view of the importance of piperidines in drug design, this characteristic was deemed worthy to be investigated further.

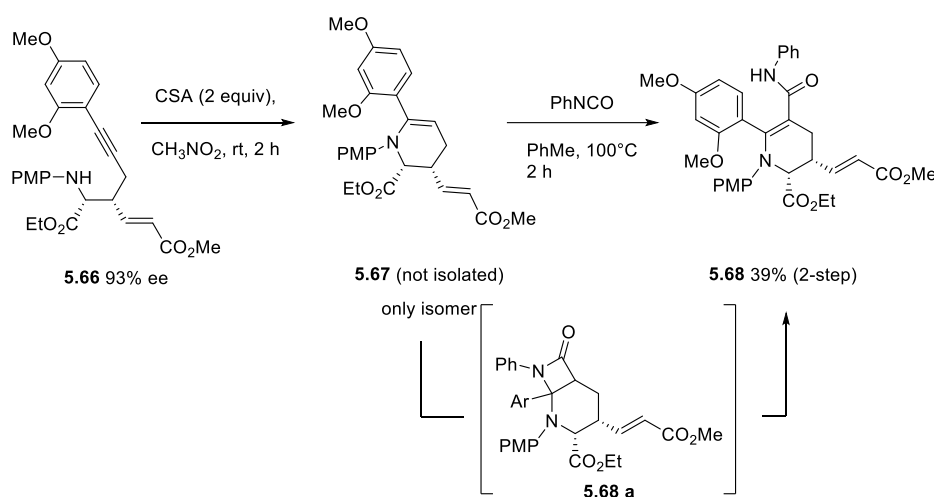


Scheme 6.9

To emphasize the phenomenon, the cases of electron-rich 1,3-dimethoxy- and 1,3,5-

¹⁰⁶ a) Doria, F.; Percivalle, C.; Freccero, M. *J. Org. Chem.* **2012**, *77*, 3615. (b) Furusawa, M.; Arita, K.; Imahori, T.; Igawa, K.; Tomooka, K.; Irie, R. *B. Tetrahedron Lett.* **2013**, *54*, 7107. (c) Wu, X.; Xue, L.; Li, D.; Jia, S.; Ao, J.; Deng, J.; Yan, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13722. (d) Beppu, S.; Arae, S.; Furusawa, M.; Arita, K.; Fujimoto, H.; Sumimoto, M.; Imahori, T.; Igawa, K.; Tomooka, K.; Irie, R. *Eur. J. Org. Chem.* **2017**, 6914. (e) Liu, Y.; Wu, X.; Li, S.; Xue, L.; Shan, C.; Zhao, Z.; Yan, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 6491. (f) Jia, S.; Chen, Z.; Zhang, N.; Tan, Y.; Liu, Y.; Deng, J.; Yan, H. *J. Am. Chem. Soc.* **2018**, *140*, 7056. (g) Arae, S.; Beppu, S.; Kawatsu, T.; Igawa, K.; Tomooka, K.; Irie, R. *Org. Lett.* **2018**, *20*, 4796. (h) Li, D.; Tan, Y.; Peng, L.; Li, S.; Zhang, N.; Liu, Y.; Yan, H. *Org. Lett.* **2018**, *20*, 4959. (i) Tan, Y.; Jia, S.; Yidong, F. H.; Peng, L. L.; Li, D.; Yan, H. *J. Am. Chem. Soc.* **2018**, *140*, 16893.

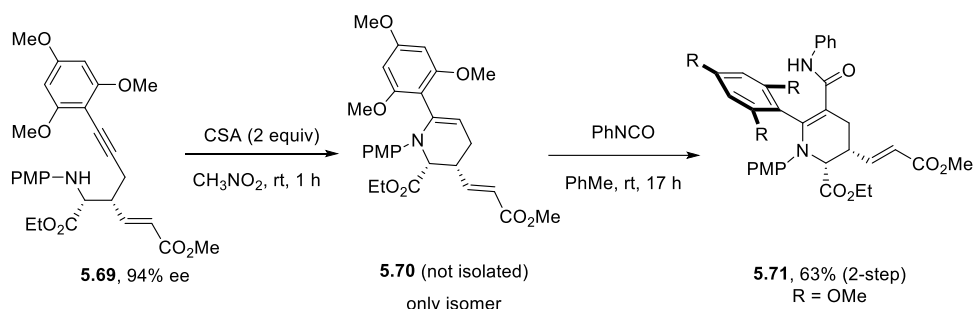
trimethoxybenzene derivatives (**5.66** and **5.69**) were studied, expecting the protonation to be more favourable than with **5.62**. Because the nucleophilic character of the arylogous ynoether was bolstered, the cyclization occurred indeed in milder conditions (rt, 2 h) upon treatment of 1,3-dimethoxybenzene alkyne **5.66** with CSA (2 equiv.), avoiding thereby the degradation of the tetrahydropyridine **5.67** in the reaction conditions (**Scheme 5.10**). Unstable to silica gel, the tetrahydropyridine **5.67** was directly exposed to phenyl isocyanate to produce the stable vinylogous urea **5.68** in 39% yield (2 steps) resulting from a process of cyclization/fragmentation of transient β -lactam **5.68a** in refluxing toluene.¹⁰⁷ Not only this derivatization improved the stability of the scaffold but additional molecular diversity was thereby introduced by grafting the aryl isocyanate.



Scheme 5.10

Furthermore, 1,3,5-trimethoxybenzene alkyne **5.69** was more reactive than 1,3-dimethoxybenzene alkyne **5.66**, as full conversion was attained after 1 h of treatment at room temperature. As previously, tetrahydropyridine **5.70** was reacted with phenyl isocyanate delivering vinylogous urea **5.71** in a better yield of 62% (2 steps) after a process occurring in milder conditions (rt, 17 h) (**Scheme 5.11**).

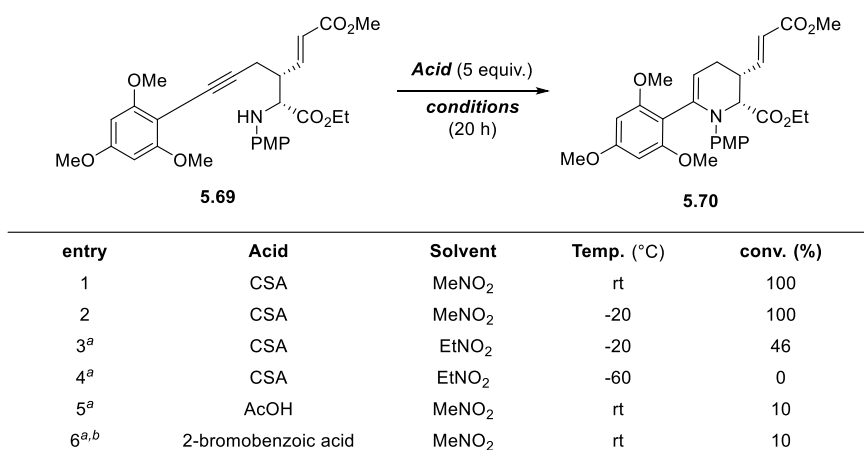
¹⁰⁷ Nisolb, C.; Uriac, P.; Huët, J.; Toupet, L. *Tetrahedron* **1992**, *48*, 1081.



Scheme 5.11

To control the selectivity of the cyclization (5 or 6-membered ring) of 1,3,5-trimethoxybenzene alkyne **5.69**, the conditions were modulated. It was found that the reaction proceeded well at -20°C with CSA, affording only the tetrahydropyridine **5.70** (Fig 5.1, entry 2). In order to promote the formation of 5-membered ring, the reaction temperature was decreased. The solvent was thus changed to EtNO₂ from MeNO₂ since the melting point of MeNO₂ is -29°C. The cyclization in EtNO₂ was found to be slower than MeNO₂ and the reaction was paused at -60°C while the 5-*exo* product by H-bonding activation was not observed at any temperature (Fig. 5.1, entry 3,4). The screening of acids with AcOH or 2-bromobenzoic acid, which are less acidic than CSA, did not work well and the 5-membered ring was not observed (Fig. 5.1, entry 5,6). (pK_a, MeSO₃H: 1.6, AcOH: 12.6, PhCO₂H: 11.1 in DMSO)

Optimization of the reaction condition



^a SM was recovered. ^b Acid was not completely soluble.

Fig 5.1

For further application, we capitalized on the nucleophilic character of enamines to construct

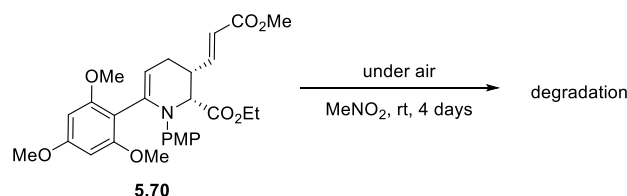
P

A

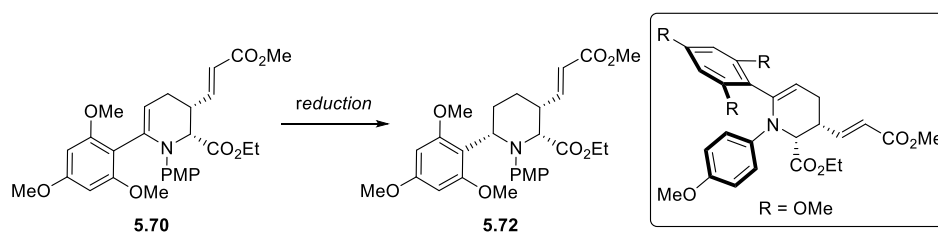
G

E

substituted piperidines in enantio- and stereoselective manner. Since tetrahydropyridine **5.70** was decomposed slowly in air (**Scheme 5.12**), several hydrogenation conditions (Pd/C, Wilkinson cat.) were attempted, which resulted in degradation or recovering of the starting material (**Fig. 5.2**, entry 1 to 5). Reductive amination conditions were also attempted, but this reaction didn't work (**Fig. 5.1**, entry 6 to 8). A possible explanation implies that since the trimethoxyaryl group was positioned next to the PMP group, the trimethoxyaryl group is twisted to avoid the steric hindrance from the PMP group. Consequently, the trimethoxyaryl group was shielding the enamine or the iminium cation, which blocked the approach of the reductants.



Scheme 5.12



entry	Redactant	Solvent	result
1	Pd/C, H ₂	THF	only unsaturated ester was reduced
2	Pd/C, H ₂	THF/AcOH (20:1)	complex mixtures
3	Wilkinson cat., H ₂	MeOH	complex mixtures
4	Wilkinson cat., H ₂	THF	no reaction
5	Wilkinson cat., H ₂	Toluene	no reaction
6	NaBH(OAc) ₃	CH ₂ Cl ₂	no reaction
7	HSiEt ₃ , (5 eq.), CSA (5 equiv.)	MeNO ₂	no reaction
8	HSiEt ₃ (5 eq.), BF ₃ •OEt ₂ (5 equiv.)	MeNO ₂	no reaction

Fig 5.2

Next, oxidation of tetrahydropyridine **5.70** was tested in view of preparing 3-oxopiperidines **5.73**, which would provide the derivative of Tadalafil after Fischer indole synthesis with **5.73** (**Fig. 5.3**). There are several reports of enamines oxidation (ene carbamates) into 3-

oxopiperidines.¹⁰⁸ However, exposure of tetrahydropyridine **5.70** to various oxidants failed to deliver 3-oxopiperidines **5.73**, which resulted in complex mixtures.

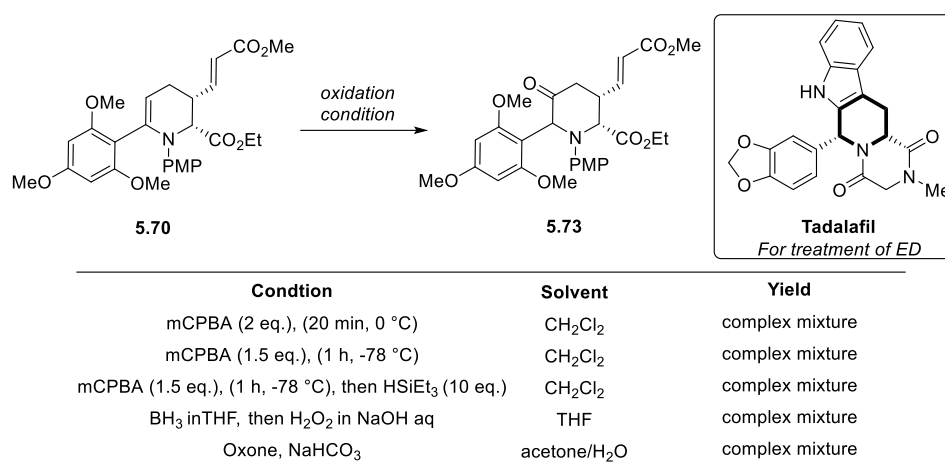
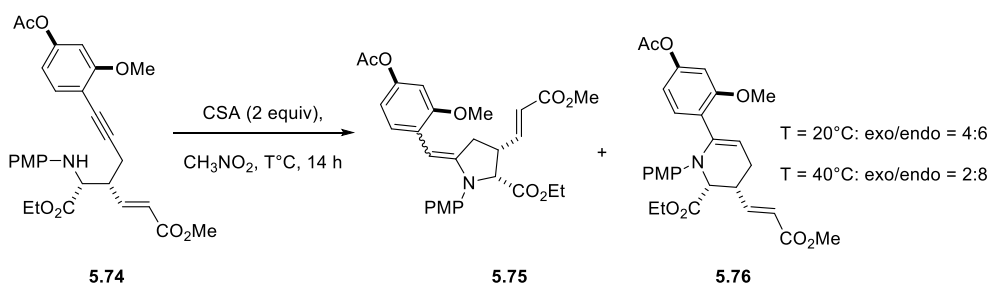


Fig 5.3

Then, the activation of the 4-acetoxy-2-methoxybenzene alkyne **5.74** was examined to evaluate the effect of the acetoxy group on the reactivity of the alkyne and steer the selectivity toward 5- or 6-membered rings (**Scheme 5.13**). But its exposure to CSA at 20°C led to a mixture of isomers **5.75/5.76** (rr = 4:6) which highlighted the preference of **5.76** for protonation, in comparison with the selective cyclization of 2-methoxybenzene alkyne **5.62** into pyrrolidine **5.63**. Raising the temperature to 40°C increased the production of tetrahydropyridine **5.74** (rr = 2:8) and confirmed the prevalent reactivity of arylogous ynoether displayed by **5.74** toward protons, despite the acetoxy group. On the other hand, when CSA (5 equiv), TFA (neat) or CF₃SO₃H (2 equiv) were employed at 0°C to selectively promote the 5-*exo*-dig pattern, the recovery or the degradation of **5.74** were instead noted.

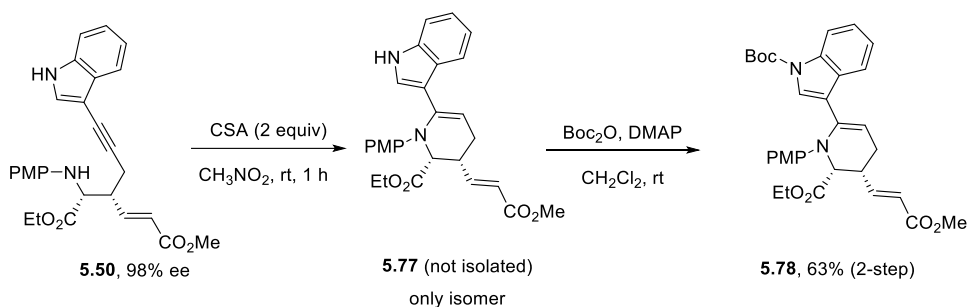
¹⁰⁸ Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894. b) Corre, L. L.; Kizirian, J.-C.; Levraud, C.; Boucher, J.-L.; Bonnet, V.; Dhimane, H. *Org. Biomol. Chem.* 2008, **6**, 3388. c) Xiong, H.; Hsung, R. P.; Shen, L.; Hahn J. M. *Tetrahedron Lett.* **2002**, *43*, 4449. d) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.



Scheme 5.13

5.4 Hydroamination of Arylogous Ynamines

In light of the reactivity of the arylogous ynoleters, the reactivity of arylogous ynamines was explored as higher reactivity could be expected. The chiral alkynylindole amine **5.50** was treated with CSA (2 equiv.) at rt and the reaction gave the enamine product **5.77** smoothly, even though indoles are known to polymerize in acidic conditions.¹⁰⁹ The isolation of enamine **5.77** was, however, unsuccessful due to instability toward air as well as **5.70**. Rather unstable over time, the molecules were stabilized by a sequence including the *N*-Boc protection of the indole (63% yield, 2-step, **Scheme 5.14**) and the subsequent stereoselective reduction of **5.77** into piperidines **5.78** (43% yield, dr > 20:1, 3-step, **Scheme 5.15**).



Scheme 5.14

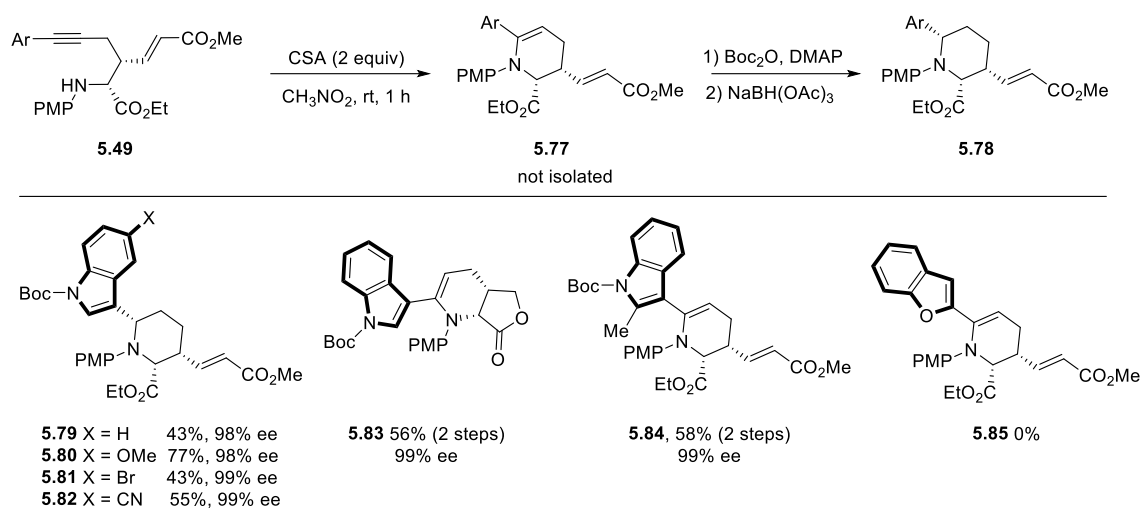
This established protocol – entailing acidic cyclization followed by subsequent *N*-Boc

¹⁰⁹ a) Noland, W. E.; Kuryla, W. C. *J. Org. Chem.* **1960**, *25*, 486. b) Noland, W. E.; Hammer, C. F. *J. Org. Chem.* **1960**, *25*, 1525. c) Ishii, H.; Murakami, K.; Sakurada, E.; Hosoya, K.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2377. d) Quartarone, G.; Ronchin, L.; Tortato, C.; Vavasori, A. *International Journal of Chemical Kinetics* **2009**, *41*, 107. e) Quartarone, G.; Charmet, A. P.; Ronchin, L.; Tortato, C.; Vavasori, A. *J. Phys. Org. Chem.* **2014**, *27*, 680.

protection and/or reduction – was then carried out with alkynylindoles **5.49** containing a lactone ring or substituted with electron-donating or –accepting groups (**Scheme 5.15**). The process was successful leading to stable tetrahydropyridines (**5.83** and **5.84**) after a simple *N*-Boc protection and to trisubstituted piperidines (**5.79** to **5.82**) after subsequent reduction in good yields, most importantly, with excellent enantioselectivities (98-99%) and diastereoselectivities (*dr* > 20:1). Of note was the compatibility of the chemistry with indoles substituted with –OMe, Br and CN groups (**5.80** to **5.82**). Probably owing to stereoelectronic effects induced by the lactone ring, compound **5.83** was stable enough to be isolated as enamine. Similarly, 2-methyl indole substituted piperidine **5.84** was isolated from the cyclization and the subsequent *N*-Boc protection of **5.54** in 58% yield (2 steps) and 99% ee. This higher stabilization could be the consequence of the low orbital overlap of the 2-methyl indole and the enamine moieties due to the collision between 2-methyl indole moiety and the PMP group.

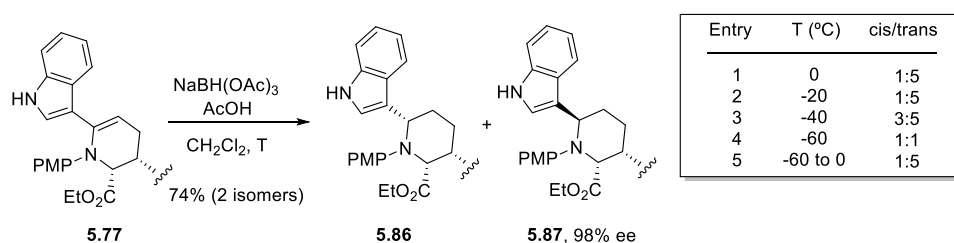
There was a limitation with benzofuran-substituted alkynylamine. The hydroamination reaction didn't proceed at room temperature and the experiment at 50°C led to a complex mixture of products without traces of the desired piperidine **5.85** probably because of the polymerization of benzofuran promoted by the acid. The same phenomenon was observed in 5-alkynyl indole-substituted amine and 2-alkynyl thiophene-substituted amine, which were fragile to acidic conditions.

In addition to the stabilization of enamine adducts, the *N*-Boc indole protection contributes to the high *cis*-stereoselectivity observed during the reduction of tetrahydropyridines (**5.79** to **5.82**).



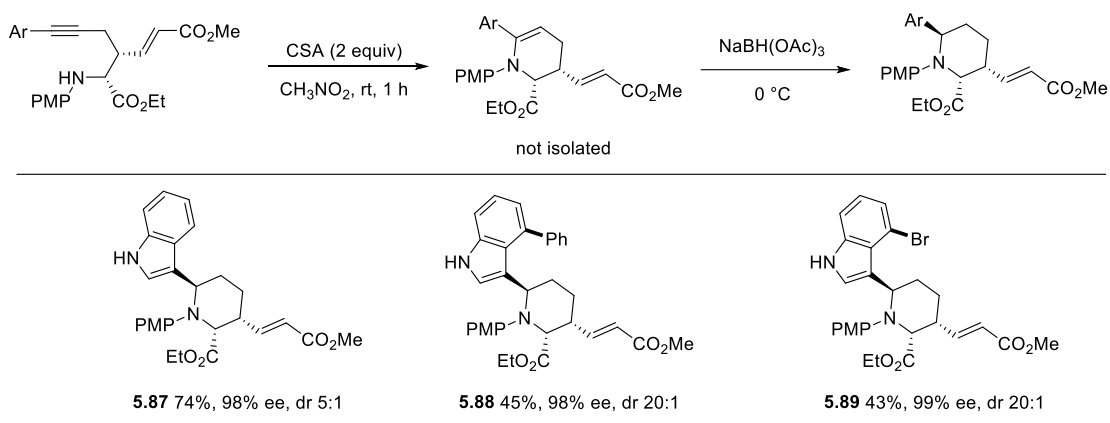
Scheme 5.15

Interestingly, reduction of tetrahydropyridine **5.77** without *N*-Boc indole protection led to the isolation of the thermodynamically more stable *trans*-isomer **5.87** as a major product (**Scheme 5.16**). To detail the mechanism, the reduction of **5.77** was investigated under several temperatures. At first, the reduction of **5.77** at 0°C gave 1:5 mixtures of *cis/trans*-isomers (**5.86/5.87**) in 74% yield with conservation of the enantiomeric excess (98% ee). Next, decreasing the temperature was attempted to improve the selectivity of the reduction. A similar selectivity was indeed noted at -20°C (Entry 2) while at -40°C the selectivity was ebbed (dr = 3:5, Entry 3). When the reduction was performed at -60°C, an equal ratio of *cis/trans*-isomers (**5.86** and **5.87**) was observed (Entry 4). As low temperatures commonly increase the selectivity in nucleophilic addition, these results indicated the reverse and rather suggested that the *cis*→*trans* epimerization was slowed by low temperatures. In fact, the epimerization was promoted when the temperature was increased from -60°C to 0°C (Entry 5) and *trans*-isomer **5.87** was then obtained predominantly (dr = 1:5).

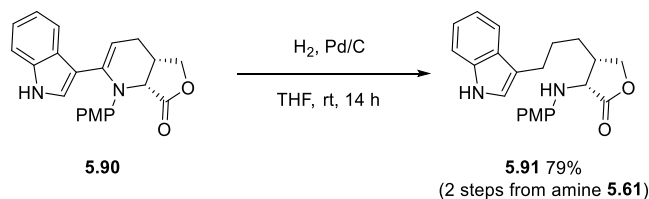


Scheme 5.16

Furthermore, as indicated in **Scheme 5.17**, the indoles **5.55**, **5.56**, with increased steric hindrance bearing 4-Ph and 4-Br substituents, were converted into piperidines (**5.88** and **5.89**) with complete *trans*-selectivity after the reduction (dr > 20:1, 43-45% yield for 2 steps). On the other hand, when the lactone **5.90** was hydrogenated (H₂, Pd/C), the over reduction was observed and **5.91** was isolated in 79% yield (**Scheme 5.18**).

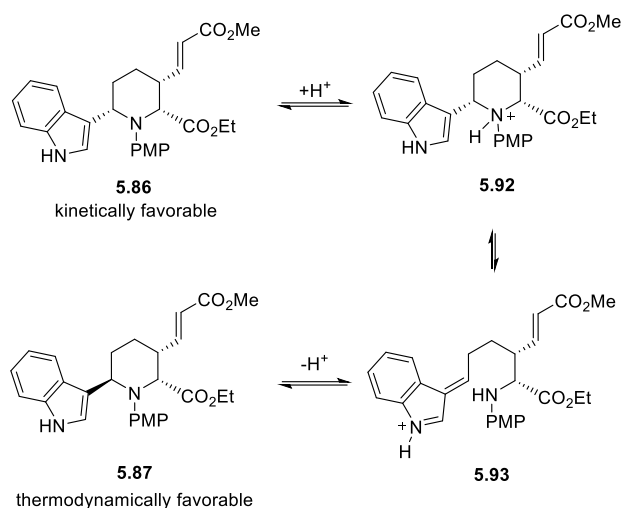


Scheme 5.17



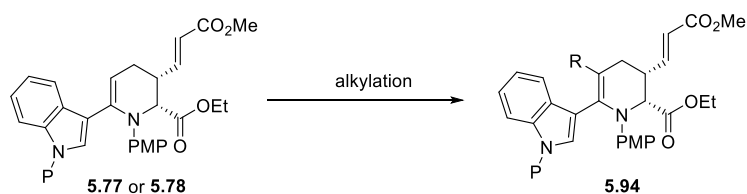
Scheme 5.18

A possible epimerization mechanism is detailed in **Scheme 5.19**. At first, the kinetic product **5.86** could be obtained by the reduction from the sterically favourable side. Then, **5.86** could be protonated, and subsequently the ring of **5.92** could be opened by the electron-pushing from the indole moiety. In the end, the intermediate **5.93** could cyclize into the thermodynamic product **5.87**.



Scheme 5.18

Next, the nucleophilic character of enamine **5.77** was explored by alkylation (**Fig 5.4**). However, any attempts of S_N2' addition (or trapping of π -allyl complex) and Michael addition were not successful. However, the Mannich type aminomethylation of *N*-Boc protected enamine **5.78** with paraformaldehyde and pyrrolidine worked well, affording a methyl aminated product which was reduced to methyl substituted piperidine by hydrogenation (H_2 , Pd/C) (**entry 10**). Probably because of the hindrance of the enamine moiety, it was not reduced upon hydrogenation. Moreover, the enamine was found unstable to air.

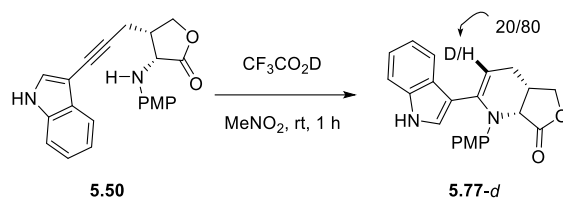


entry	P =	Reductant	Solvent	temp. (°C)	Yield
1	H	allyl acetate, Pd/C, K_2CO_3 , PPh_3	toluene	50 (19 h)	no reaction
2	H	allyl acetate, Pd/C, K_2CO_3 , PPh_3	toluene	120 (18 h)	no reaction
3	H	allyl bromide, NEt_3	CH_2Cl_2	rt (18 h)	no reaction
4	H	MVK (methyl vinyl ketone)	CH_2Cl_2	reflux (3 h)	no reaction
5	H	MVK + $Bi(OTf)_3$	MeCN	rt (18 h)	no reaction
6	H	MVK + $Bi(OTf)_3$	MeCN	reflux (18 h)	degradation
7	H	4-methoxy-3-buten-2-one	DMF	80 (2 days)	no reaction
8	H	3-(dimethylamino)acrolein+piperidine	toluene	reflux (2 h)	complex mixture
9	H	2-chloroacrylonitrile	CH_2Cl_2	rt (15 h)	no reaction
10	Boc	$(CH_2O)_n$, pyrrolidine then H_2 , Pd/C	Toluene/THF	reflux/rt	R=Me

Fig 5.4

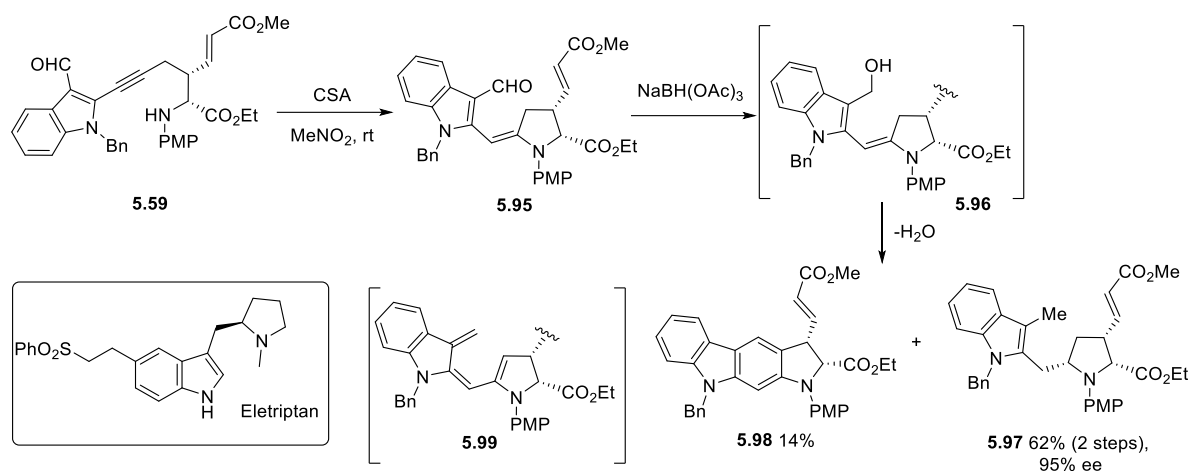
To pinpoint the role of the acid in the cyclization, the activation of alkynylindole **5.50** was

performed with $\text{CF}_3\text{CO}_2\text{D}$ to measure the level of deuterium incorporation in the cyclized product (**Scheme 5.19**). In these conditions, **5.77** was obtained with 20% deuteration. Since deuterium reduces slightly acidity and that the first step scrambles the ratio H/D by deuteration of the anisidine, this result remains consistent with the mechanism of protonation suggested at the outset of the study.



Scheme 5.19

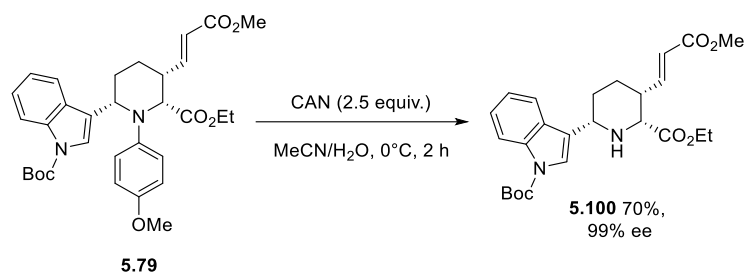
With 3-carboxaldehyde-2-alkynylindole **5.59**, the cyclization provided a divergent pathway and 5-*exo*-dig product **5.95** was observed, likely due to the protonation of the carboxaldehyde and the subsequent addition resulting from the electronic-depletion of the alkyne (**Scheme 5.20**). Direct exposure of 5-*exo*-dig product **5.95** to $\text{NaBH}(\text{OAc})_3$ induced both the reduction of the enamine moiety and the carboxaldehyde into pyrrolidine **5.97** (62% yield, dr >20:1, 95% ee). Incidentally noting that the reductive process entailed the deoxygenation of the carboxaldehyde, an intriguing pyrrolidine carbazole **5.98** was isolated (14%). Both products – **5.97** and **5.98** – are likely stemming from the same precursor; the sensitive enamine alcohol **5.96**. Upon dehydration and reduction, this intermediate would give **5.97**, while 6π electrocyclization of a plausible methylene indolenine intermediate **5.99** followed by air oxidation would explain the formation of **5.98**. Enlarging thereby the scope of this method to pyrrolidine connected to methyleneindole from electron-depleted indolylalkyne, the access is pertinent in view of the occurrence of scaffold in drugs such as eletriptan (a second generation triptan drug against migraine headaches).



Scheme 5.20

5.5 Synthetic Manipulations

To reach derivatives of pipercolic acid and extend the molecular space available from **5.79**, the removal of the PMP group was examined (**Scheme 5.21**). In the presence of indoles, it was still unclear whether oxidants employed for this purpose may be compatible. Precisely, the *N*-Boc protection of the indole allowed a successful deprotection of the piperidine ring to take place in presence of CAN, whereas the unprotected indole **5.87** was decomposed in these conditions. Gratifyingly, treatment of **5.79** with ammonium cerium (IV) nitrate salts thus delivered piperidine **5.100** in good yield (70%), preserving the enantiopurity (99% ee).

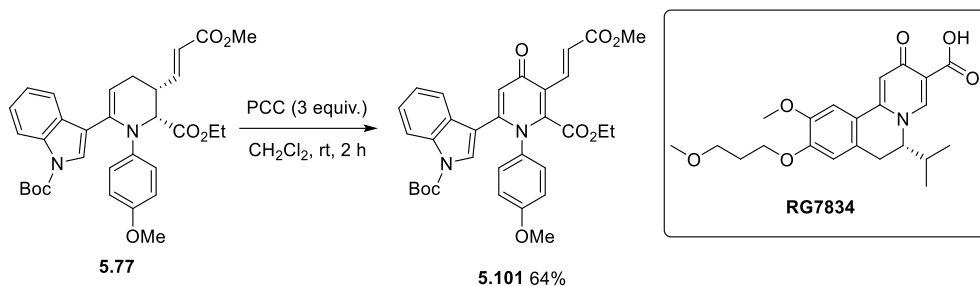


Scheme 5.21

On the other hand, the enamine **5.77** was transformed by allylic oxidation with PCC to dihydroquinolidinone **5.101** in 64% yield.¹¹⁰ The motif of dihydroquinolidinone can be seen in

¹¹⁰ a) Parish, E. J.; Chitrakorn, S.; Wei, T.-Y. *Synth. Commun.* **1986**, *16*, 1371. b) Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421.

a candidate of chronic hepatitis B virus (HBV) therapy as RG7834.¹¹¹



Scheme 5.22

In short summary, the intramolecular hydroamination of electron-rich (*N*-hetero)arylalkynes amines was demonstrated in acidic condition, which illustrated the seldom examined reactivity of arylogous ynoleters and ynamines. In one case, the 5-*exo*-dig cyclization was observed when an electron-withdrawing group was grafted to the indole **5.59** in 3-position, adding flexibility to the chemistry as demonstrated with the carboxaldehyde moiety. In terms of the preservation of to the chiral information of the Mannich adducts, we noted the production of highly functionalized piperidines in high enantio- and stereoselectivity.

¹¹¹ Han, X.; Zhou, C.; Jiang, M.; Wang, Y.; Wang, J.; Cheng, Z.; Wang, M.; Liu, Y.; Liang, C.; Wang, J.; Wang, Z.; Weikert, R.; Lv, W.; Xie, J.; Yu, X.; Zhou, X.; Luangsay, S.; Shen, H. C.; Mayweg, A. V.; Javanbakht, H.; Yang, S. *J. Med. Chem.* **2018**, *61*, 10619.

6 Synthetic study of Koumine

6.1 Gelsemium Alkaloids

Gelsemium is a genus of flowering plants in the *Gelsemiaceae* family found in Asian countries and North America. *Gelsemium* plants comprises three species, *Gelsemium elegans*, *Gelsemium rankinii* and *Gelsemium sempervirens*. *Gelsemium elegans* found in Asia are historically used in Chinese folk medicine for the treatment of spasticity, pain, skin ulcers, *etc*, even though these are highly toxic.¹¹²

Over 120 molecules of indole alkaloids were extracted from *Gelsemium* and classified into 6 types based on their chemical structures: sarpagine-type, koumine-type, humantenine-type, gelsedine-type, yohimbine-type, and gelsemine-type (**Fig. 6.1**). The alkaloids shown to possess cytotoxic, analgesic, anxiolytic, anti-inflammatory, and immunomodulating activities.¹¹³

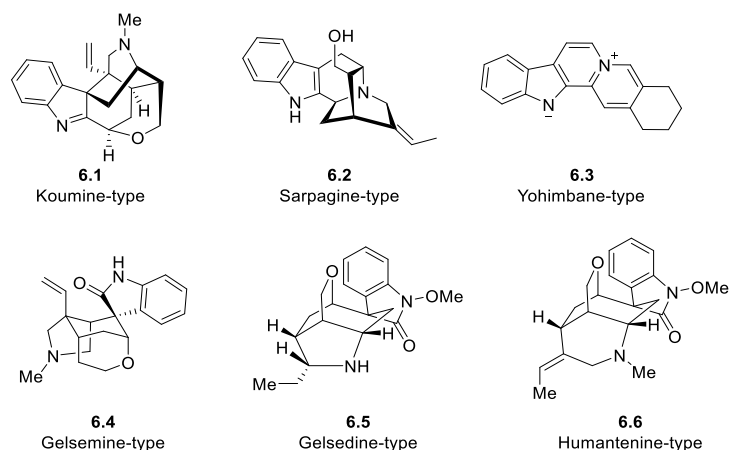


Fig 6.1

6.2 Koumine-Type Alkaloids

¹¹² Jin, G.-L.; Su, Y.-P.; Liu, M.; Xu, Y.; Yang, J.; Liao, K.-J.; Yu, C.-X. *J. Ethnopharmacol.* **2014**, *152*, 33.

¹¹³ (a) Xiong, B.-J.; Xu, Y.; Jin, G.-L.; Liu, M.; Yang, J.; Yu, C.-X. *Sci. Rep.* **2017**, *7*, 14269. (b) Xu, Y.-K.; Yang, L.; Liao, S.-G.; Cao, P.; Wu, B.; Hu, H.-B.; Guo, J.; Zhang, P. *J. Nat. Prod.* **2015**, *78*, 1511. (c) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2006**, *69*, 715.

Twelve koumine-type alkaloids have been isolated from *Gelsemium elegans* until 2017 (Fig. 6.2).^{1,114}

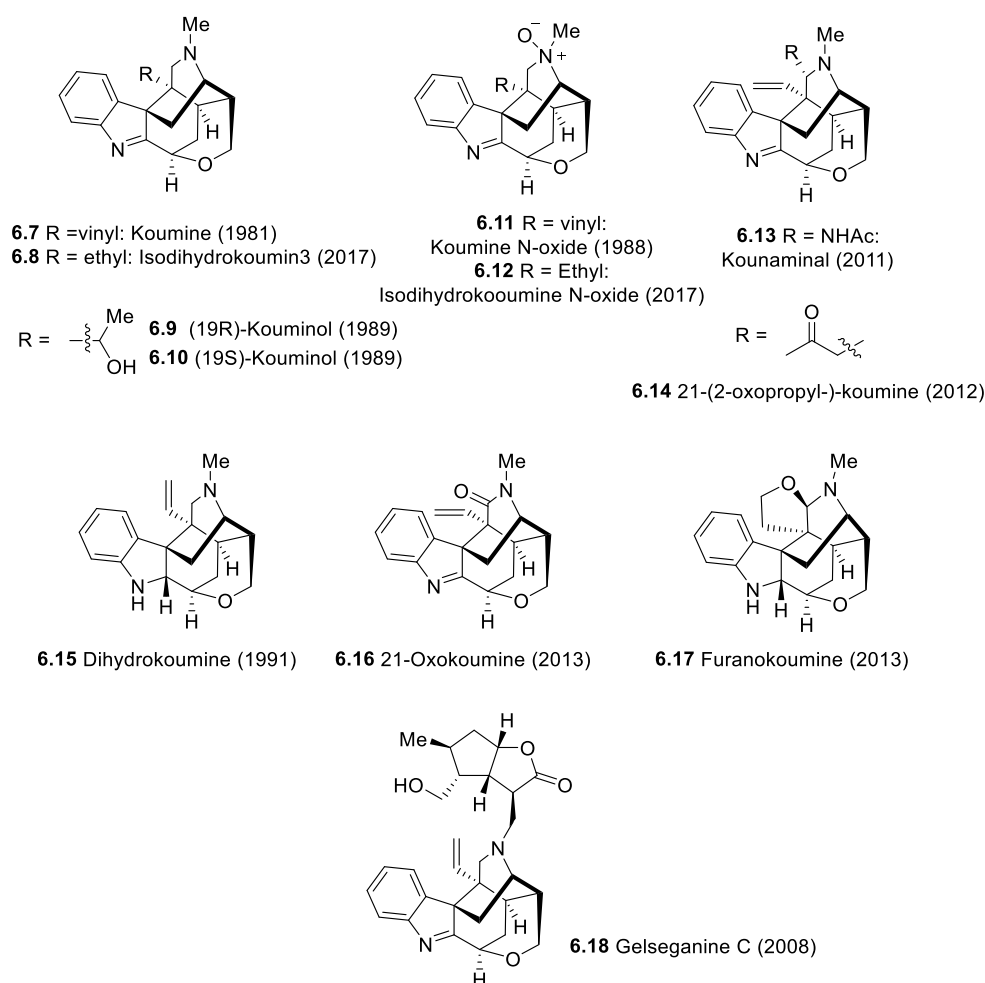


Fig. 6.2

6.3 Isolation and Identification

Koumine is one of the representative *Gelsemium* Alkaloids, which was isolated from the Chinese toxic plant Kou-wen (*Gelsemium elegans* Benth.) in 1931 by Cou.¹¹⁵ In 1981, 43 years after the isolation, its structure was finally characterized by single-crystal X-ray analysis and structural modification by chemical reactions from Liu group.¹¹⁶ At almost the same time,

¹¹⁴ Sun, M.; Hou, X.; Gao, H.; Guo, J.; Xiao, K. *Molecules* **2013**, *18*, 1819.

¹¹⁵ Chou, T.Q. *J. Physiology* **1931**, *5*, 345.

¹¹⁶ Liu C.; Wang Q.; Qang C. *J. Am. Chem. Soc.* **1981**, *103*, 4634.

Riche group also elucidated the structure by single-crystal X-ray study.¹¹⁷

6.4 Total Synthesis of Koumine

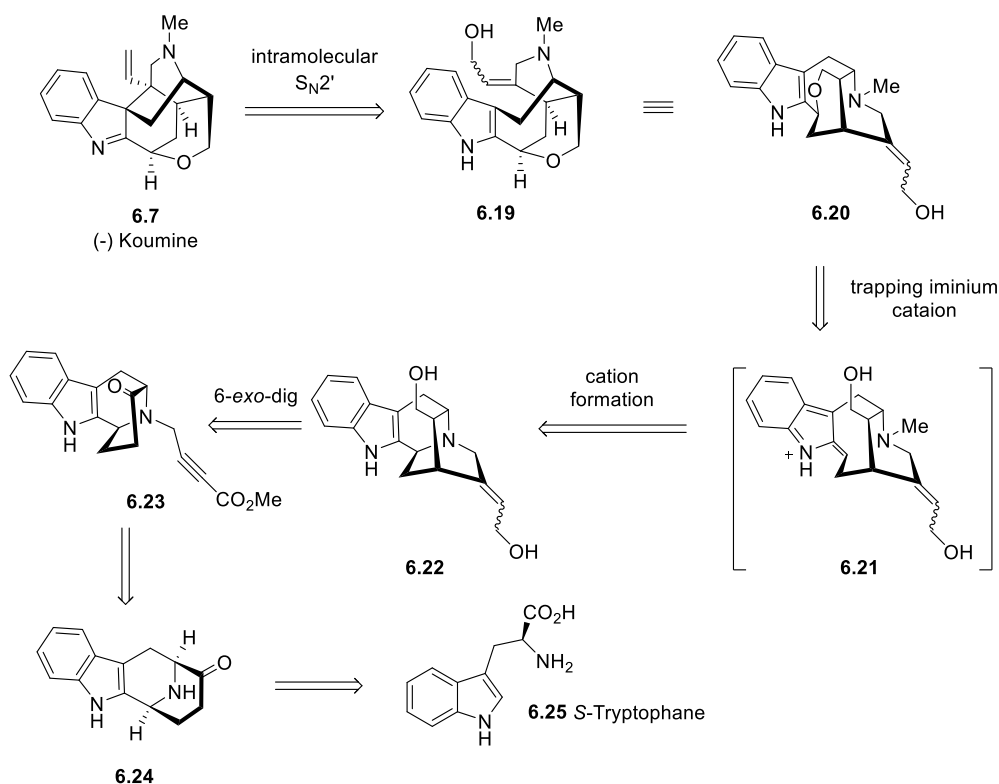
Koumine has fascinated a lot of chemists and pharmacologists due to the complex hexacyclic cage structure and the interesting biological activity. To date, three total synthesis of koumine were reported by Magnus, Takayama and Kerr respectively.

6.4.1 Magnus' Synthesis

In 1989, Magnus group reported the first asymmetric total synthesis.¹¹⁸ They envisioned an ideal route for the synthesis of koumine **6.7** derived from *S*-tryptophan **6.25** as abundant chiral pool source (**Scheme 6.1**). In their retrosynthetic analysis, koumine **6.7** was seen arising from allylic alcohol **6.19** by intramolecular S_N2' reaction which could be entropically favorable. Allylic alcohol **6.19** stemmed from a sequential stream in which the primary alcohol could capture the iminium cation **6.21**, which could be induced by exposing nucleophilic amine **6.22** to chloroformate, followed by the nucleophilic attack from the indole ring. The quinuclidine precursor **6.22** could be constructed by intramolecular conjugated addition of the ketone **6.23** to the electron-deficient alkynyl ester. And the ketoamine **6.24** derived from *S*-tryptophan **6.25** in several transformations.

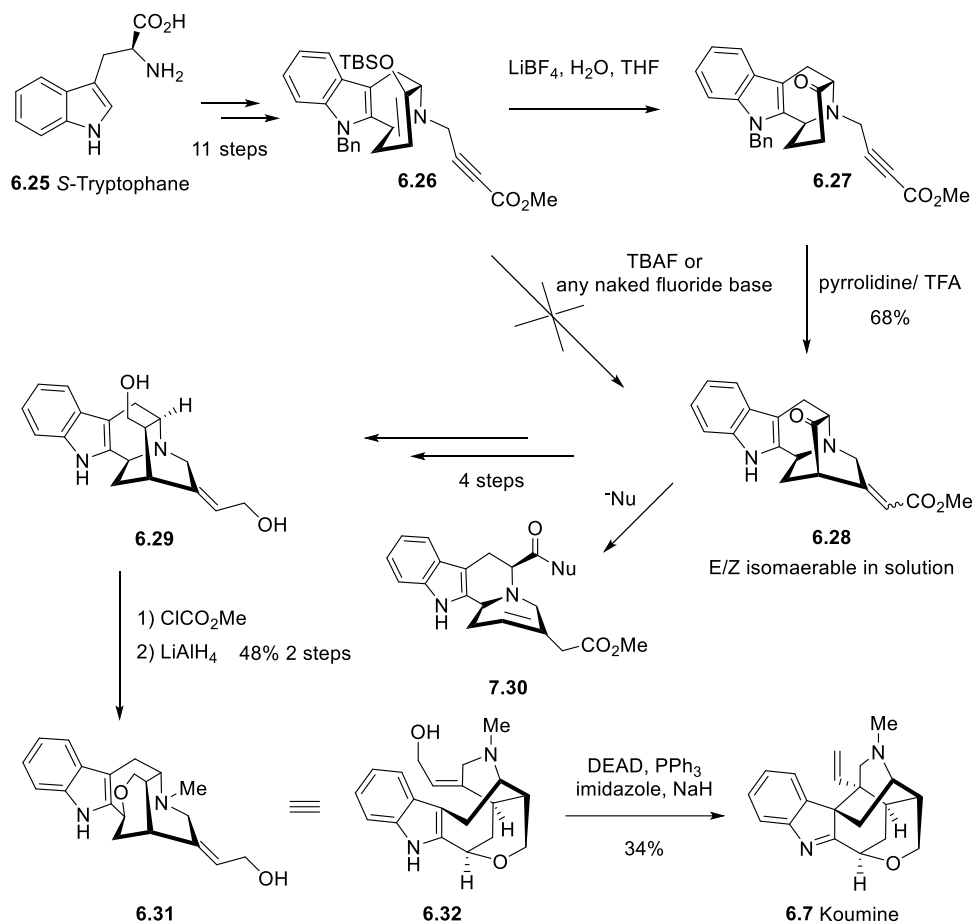
¹¹⁷ Khoung-Huu F.; Chiaroni A.; Riche C. *Tetrahedron Lett.* **1981**, 22, 733.

¹¹⁸ Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Soc. Chem.* **1989**, 111, 786.



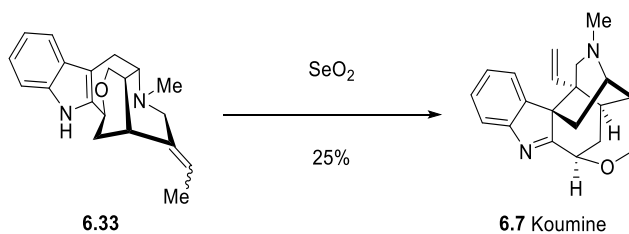
Scheme 6.1

In Magnus' synthesis of (+) koumine **6.7**, silyl enol ester **6.26** was assembled in 14 steps from commercially available *S*-tryptophan (**Scheme 6.2**). Treatment of silyl enol ester **6.26** with any naked fluoride or chloride sources for the Michael cyclization gave only complex mixtures consisting of low amount of the desilylated product and the desired product **6.28**. This uncontrollable reaction was attributed to the retro-Dieckmann fragmentation **6.30** under the basic condition releasing the enolate of **6.28**. After considerable experiments, they eventually obtained the product **6.28** in 68% yield after the stepwise route including the desilylation of silyl enol ester **6.27** with LiBF_4 in neutral condition and exposure to the mixture of pyrrolidine and TFA for Michael cyclization. The transformation to quinuclidine diol **6.29** was made in 4 steps from the product **6.28**. Intermediate **6.31** was obtained by exposing intermediate **6.29** to alkyl chloroformate following the reduction with LiAlH_4 . To conclude, (+) koumine **6.7** was formed in 40% yield from the precursor **6.32** upon treatment in the Mitsunobu conditions ($\text{DEAD}/\text{PPh}_3/\text{NaH}$ in THF at reflux).



Scheme 6.2

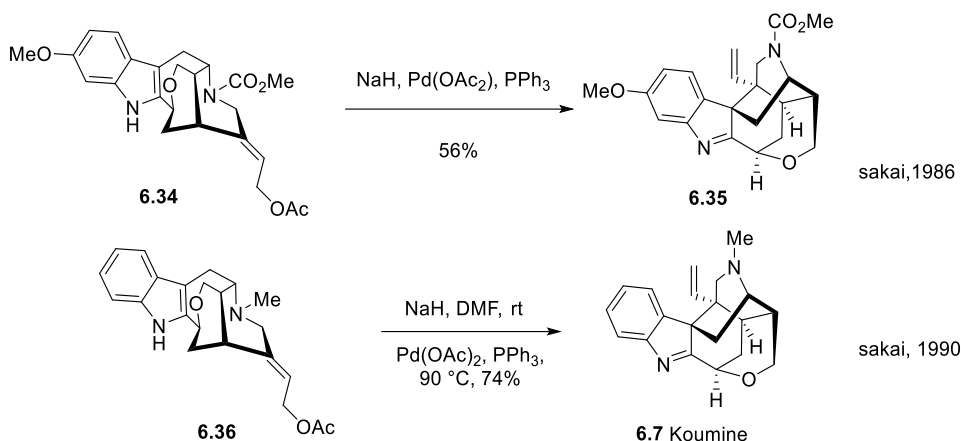
Incidentally, this kind of cyclization was reported in some papers. For example, one is about a partial synthesis of koumine **7.7** in which selective allylic C-H oxidation of **6.33** by SeO_2 was implemented in 25% yield (**Scheme 6.3**).¹¹⁹ The other one is about the synthesis of 11-methoxy koumine in which Tsuji-Trost type allylation with $\text{Pd}(0)$ was employed (**Scheme 6.4**).¹²⁰



Scheme 6.3

¹¹⁹ Zhujin, L.; Qiansheng, *vouji huaxu* **1986**, *1*, 36.

¹²⁰ Sakai, S.; Yamanaka, E.; Kitajima, M.; Yokota, M.; Aimi, N.; Wongsripatana, S.; Ponglux, D. *Tetrahedron Lett.* **1986**, *27*, 4585. Takayama, H.; Kitajima, M.; Sakai, S. *Heterocycles*, **1990**, *30*, 325.



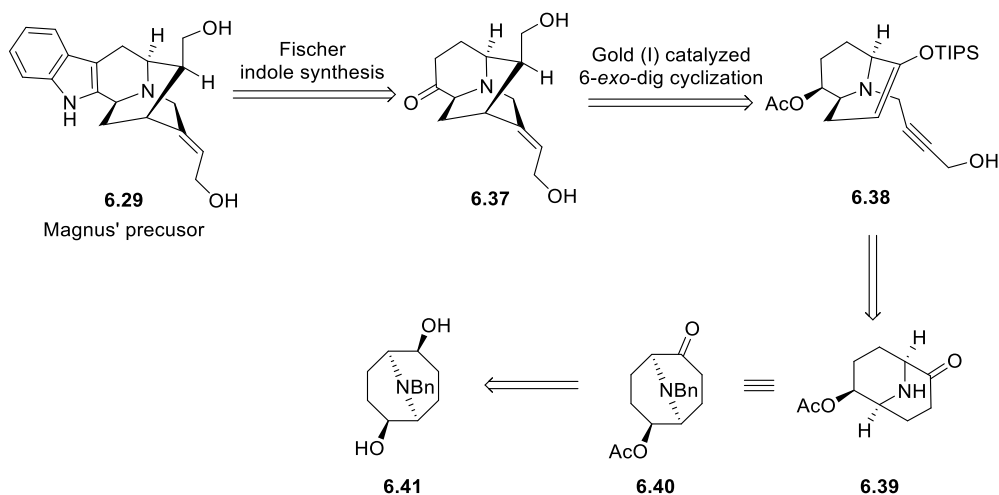
Scheme 6.4

There is one ineluctable problem in Magnus' synthesis. Their route from *S*-tryptophan cannot provide koumine belonging with reversed absolute configuration against natural one's, since *R*-tryptophan is not an essential amino acid in Nature and more expensive than *S*-tryptophan.

6.4.2 Takayama's Synthesis

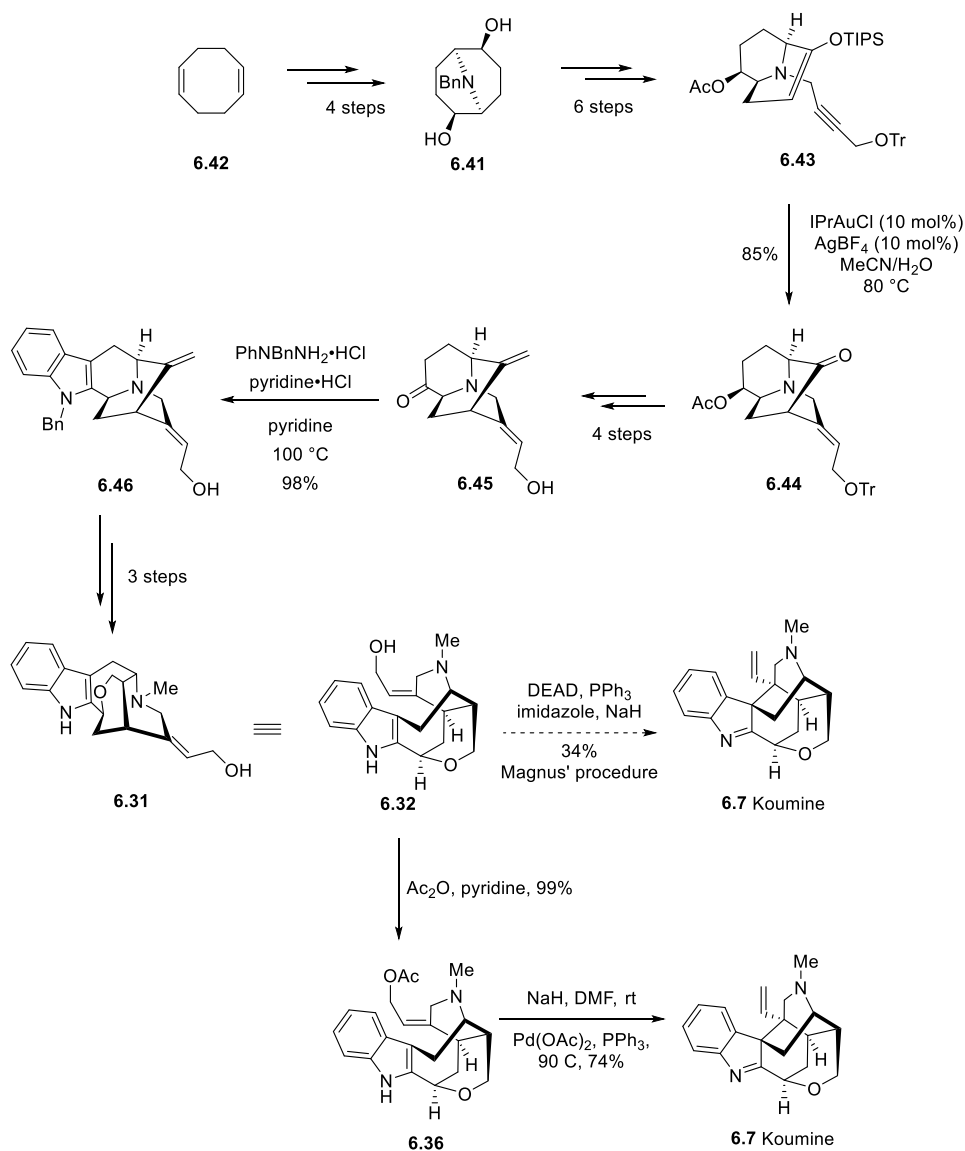
In 2006, Takayama group described the enantioselective total synthesis of koumine **7.7**.¹²¹ Takayama *et al.* envisaged the enantioselective divergent synthesis of sarpagine-type indole alkaloids and koumine **6.7** with natural absolute configuration. Focused on the synthesis of koumine **6.7**, they first settled the intermediate **6.29** from Magnus' total synthesis (**Scheme 6.5**). The intermediate **6.29** was seen arising from Fischer indole synthesis using ketone **6.37**. As their key reaction, they planned a gold (I) catalyzed 6-*exo*-dig cyclization of alkynyl silyl enol ester **6.38** which they have developed before. The silyl enol ester derived from enantiopure (+)-9-azabicyclo[3.3.1]nonane-2,6-diol derivative **6.41** was employed in several transformations.

¹²¹ Kitajima, M.; Watanabe, K.; Maeda, H; Kogure, N.; Takayama, H. *Org. Lett.* **2016**, *18*, 1912.

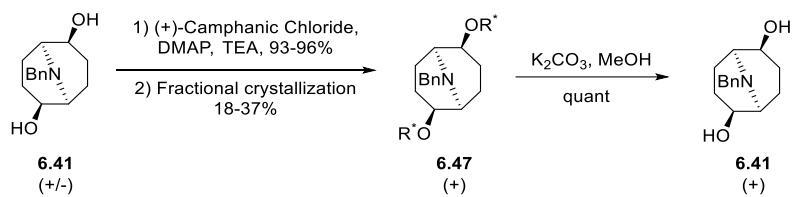


Scheme 6.5

In Takayama's synthesis (**Scheme 6.6**), they prepared the enantiopure diol **6.41** through fractional crystallization from 1,5-cyclooctadiene **6.42**. The alkynyl silyl enol ester **6.43** was built up in 6 steps in good yields. The gold (I)-catalyzed cyclization of the alkynyl silyl enol ester **6.43** was carried out with catalytic amount of IPrAuBF_4 in MeCN and H_2O . The 6-*exo*-dig cyclized product **6.44** was obtained in 85% yield accompanied with 7-*endo*-dig cyclized product in 15% yield. The cyclized product **6.44** was elaborated to the ketone **6.45** in 4 steps. The treatment of the ketone **6.45** with phenylhydrazine in Fischer indole synthesis conditions gave the indole **6.46** in excellent yield which was converted into the Magnus' intermediate **6.32** in 3 steps. The alcohol **6.32** was acetylated in one additional step and the total synthesis of (-) koumine **6.7** was accomplished under Sakai's conditions in 74% yield, in which the total yield of cyclization (Mitsunobu conditions) for (-) koumine **6.7** was better than in Magnus' conditions. On the whole, Takayama collectively synthesized five different natural products from the common intermediate **6.45**, while low yields (18-37% yield) were noted for preparing the enantiopure diol **6.41** because of the fractional crystallization (**Scheme 6.7**).



Scheme 6.6

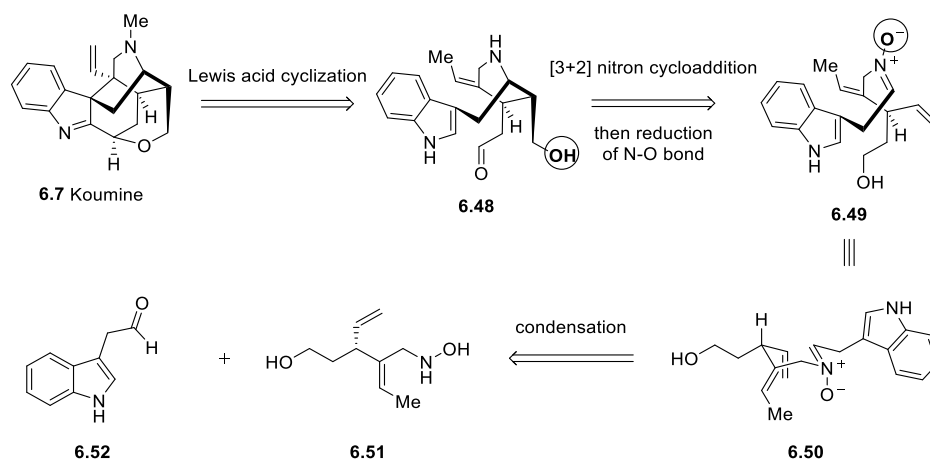


Scheme 6.7

6.4.3 Kerr's Synthesis

In 2018, Kerr *et al.* completed the racemic total synthesis of koumine **6.7** and other gelsemium alkaloids. The Kerr's approach orchestrated an intramolecular [3 + 2] nitron olefin

cycloaddition and Lewis acid mediated cyclizations of a common intermediate to quickly assemble the core structure of natural products.¹²² In their analysis (**Scheme 6.7**), koumine **7.7** was seen as the product of Lewis acid-catalyzed cyclization of indole **6.48** in a cascade reaction from a transient carboxonium ion from the indole ring according to the Friedel-Crafts pattern. The indole **6.48** was seen resulting from intramolecular [3+2] nitron olefin cycloaddition of indole **6.49** following the reduction of N-O bond in isoxazolidine. Disconnection of indole **6.50** led to indole-3-acetaldehyde **6.52** and hydroxyamine **6.51** which was seen arising from commercially available materials after several transformations.

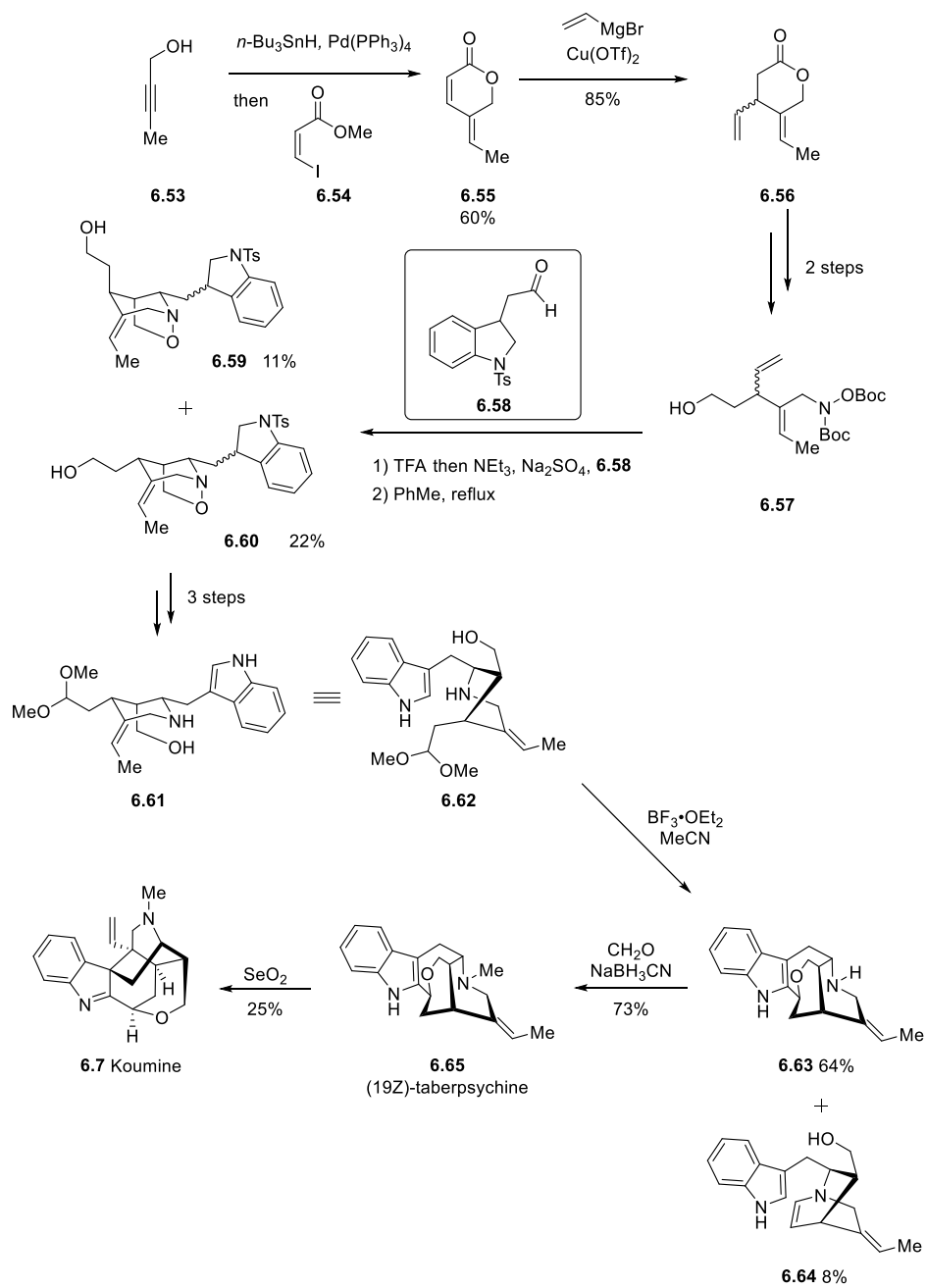


Scheme 6.8

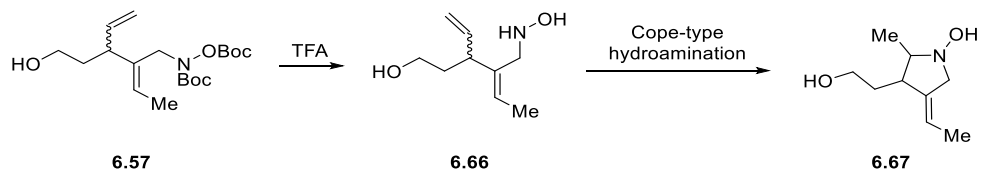
The Kerr's synthesis began with the construction of hydroxylamine **6.57** in 4 steps from commercially available reagents. They initially synthesized dihydropyranone **6.55** with the palladium-catalyzed hydrostannylation of alkyne **6.53** and the subsequent Stille coupling with iodo acrylate **6.54**. They utilized a copper catalyzed conjugate addition of vinyl magnesium bromide to dihydropyranone **6.55** with NHC ligand for the preparation of lactone **6.56**. They also attempted asymmetric reactions with chiral ligands for achieving the enantioselective total synthesis, however they never accessed the enantiopure lactone **6.56** as the enantiomer excess was always 0% ee. The racemic lactone **6.56** was converted into the bis Boc protected hydroxylamine **6.57** in 2 steps. Deprotection of hydroxylamine **6.57** for the cycloaddition was

¹²² Kerkovius, J. F.; Kerr, M. A. *J. Am. Chem. Soc.* **2018**, *140*, 8415.

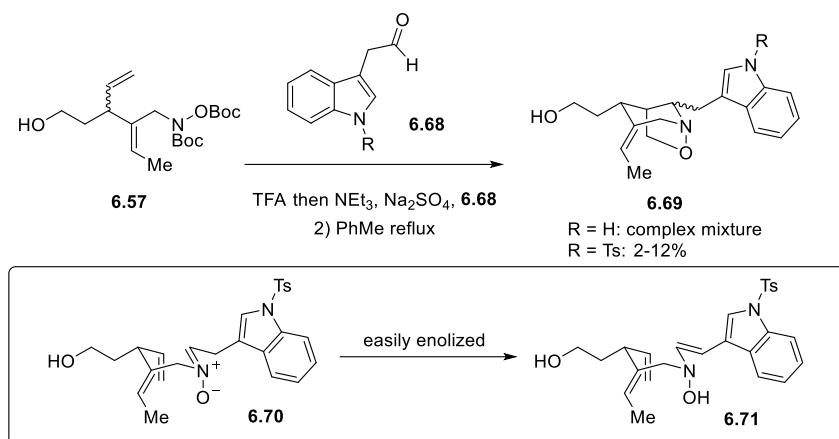
performed *in situ* since Cope-type hydroamination reaction occurred as a side reaction (**Scheme 6.10**). The nitron was generated by the condensation of hydroxylamine **6.57** with indoline aldehyde **6.58** under the basic condition and the [3+2] cycloaddition was sequentially carried out to form the isooxazoline **6.60**. After a lot of screening, indoline aldehyde **6.58** was the best among other candidate aldehydes because of the stability of the nitron which caused the polymerization or enolization (**6.70** to **6.71**) of the other candidates (**Scheme 6.11**). The isooxazoline **6.60** was transformed into amino alcohol **6.61** in 3 steps which was the central hub forward several syntheses of natural products. The treatment of amino alcohol **6.61** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in MeCN following the reductive amination gave a natural product, (19Z)-taberpsychine **6.65**. It is known in literature that (19Z)-taberpsychine **6.65** leads to koumine **6.7** upon allylic oxidation with SeO_2 and sequential cyclization (**Scheme 6.3**). Therefore, Kerr *et al.* accomplished the formal synthesis of koumine **6.7**.



Scheme 6.9



Scheme 6.10

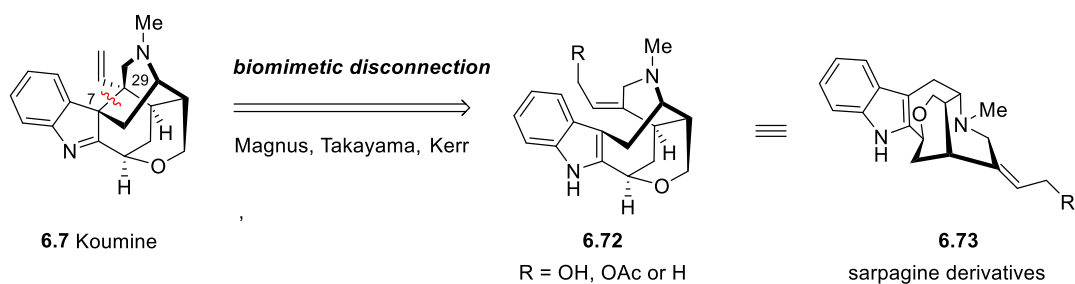


Scheme 6.11

6.5 Retrosynthesis of koumine

It is a prominent feature of three total synthesis that koumine **6.7** was synthesized through sarpagine intermediates, inspired by biogenetic synthesis which is based on Lounasmaa proposal (**Scheme 6.12**).¹²³ The main topic of those synthesis was focused on how to reach chiral sarpagine intermediates, since the routes have a merit that the intermediates could give access other *Gelsemium* alkaloids. In enantioselective synthesis of koumine **6.7**, the chirality of the molecules derived from *S*-tryptophan **6.25** (Magnus) or fractional crystallization of diastereomers (Takayama), in which there is no example using asymmetric catalysts.

Previous works



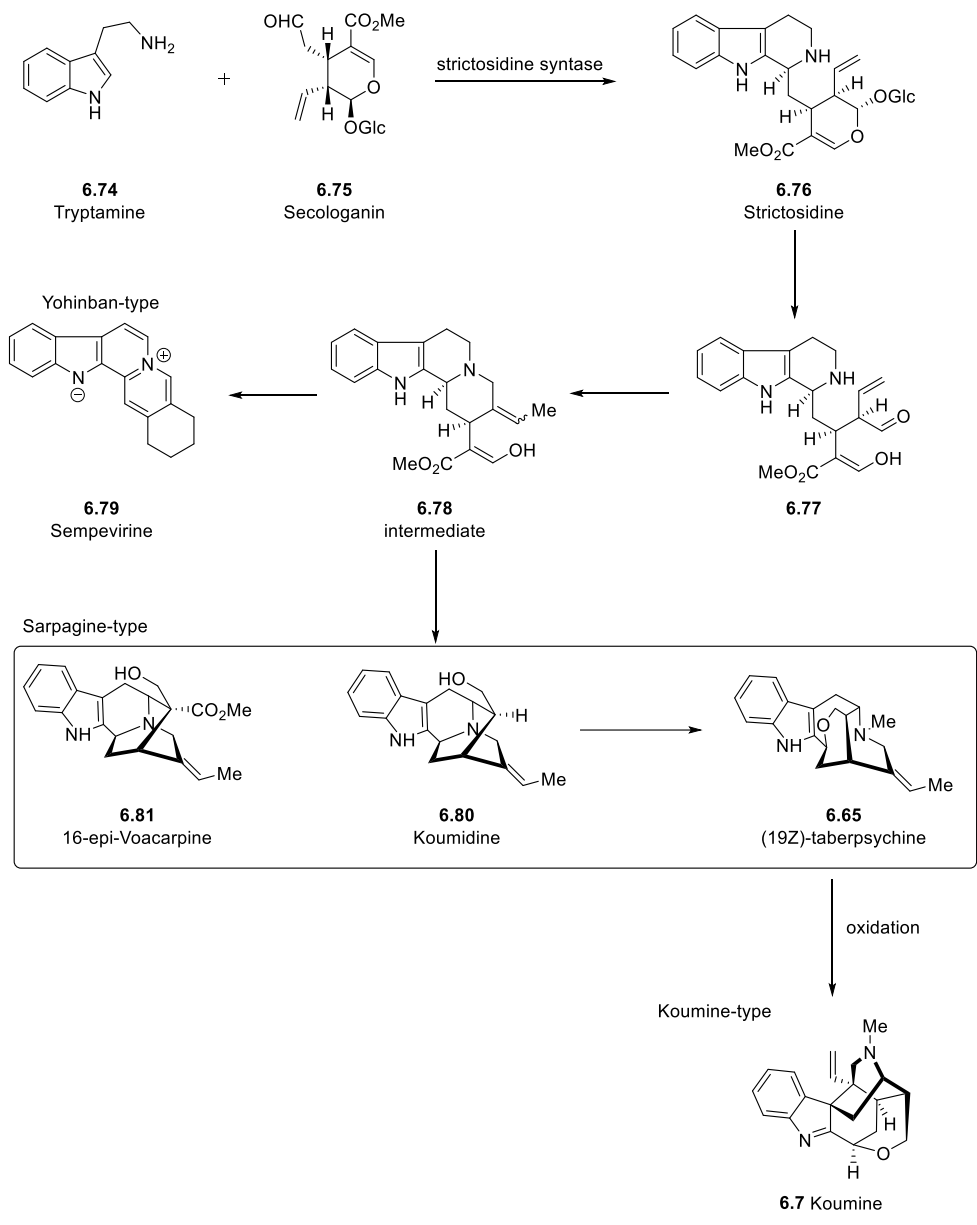
Scheme 6.12

From overweighing the biogenetic synthesis of koumine **6.7**, strictosidine **6.76**, which derived from tryptamine **6.74** and secologanine **6.75**, is the key intermediate to access monoterpene alkaloids, not only *Gelsemium* alkaloids but also other group alkaloids, for example, quinine,

¹²³ Lounasmaa, M.; Koskinen, A. *Planta Medica* **1982**, *44*, 120.

strychnine *etc.*¹²⁴ It is assumed that the hypothetical intermediate **6.78** could be constructed from strictosidine **6.76** after some steps which can access to yohinban-type alkaloids or sarpagine-type alkaloids by some transformation. Koumidine **6.80**, which is one of sarpagine-type alkaloids, leads to (19Z)-taberpsychine **6.65** by the addition of the alcohol at the benzylic position. Koumine **6.7** is then obtained by allylic oxidation and subsequent cyclization of (19Z)-taberpsychine **6.65**.

¹²⁴ a) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538. b) Ponglux, D.; Wongseripipatana, S.; Subhadhirasakul, S.; Takayama, H.; Yokota, M.; Ogata, K.; Phisalaphong, C.; Aimi N.; Sakai, S. *Tetrahedron* **1988**, *44*, 5075. c) Takayama, H.; Kitajima, M.; Wongseripipatana, S.; Sakai S., *J Chem Soc. Perkin Trans. I* **1989**, 1075. d) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc., Perkin Trans. I* **1994**, 1573. e) Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381.

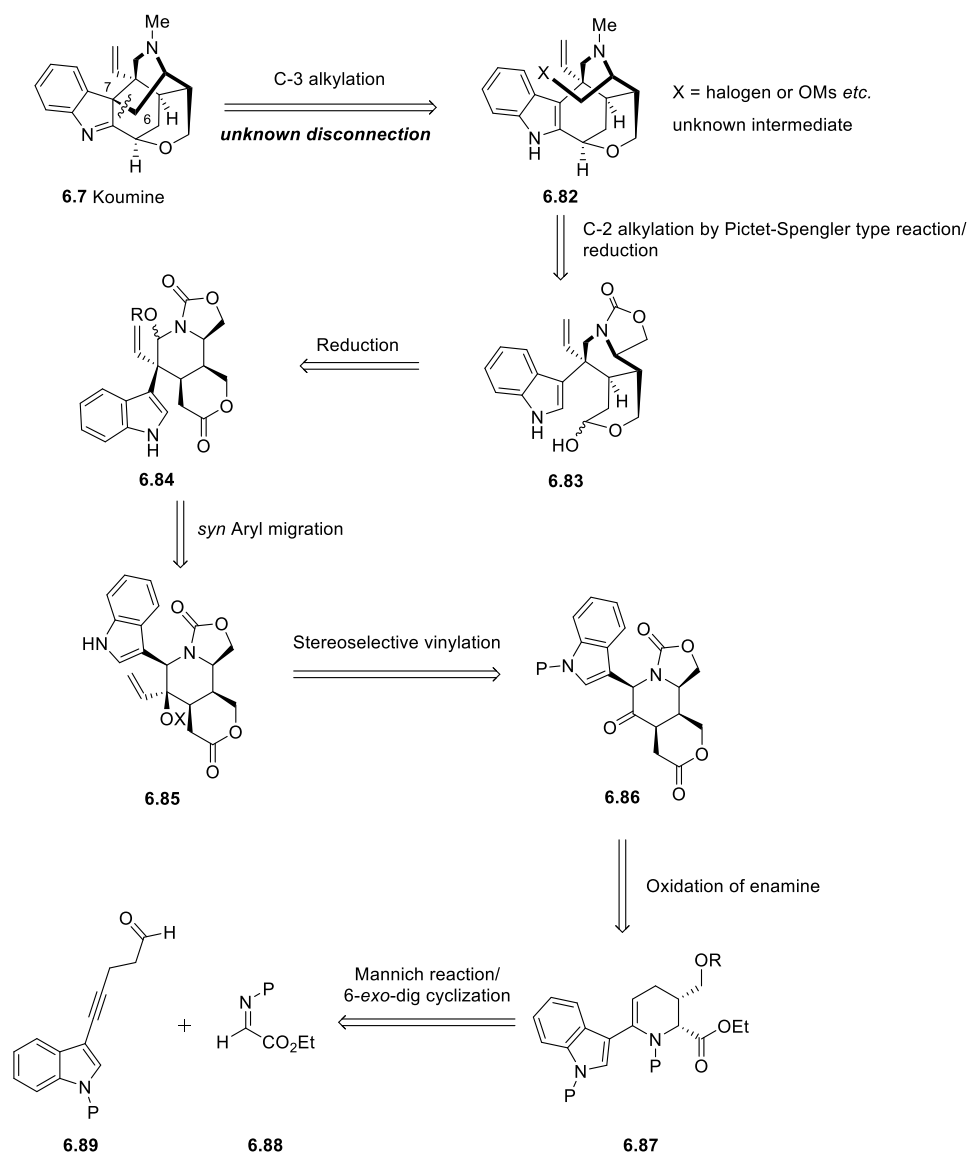


Scheme 6.13

6.6 Plan

Our retrosynthetic analysis of koumine **6.7** is shown as below (**Scheme 6.14**). The approach settled in the disconnection C-6/C-7 by nucleophilic substitution of indole, which is different from the known disconnections. Intermediate **6.82** could be obtained by Pictet-Spengler type reaction of oxonium cation which derived from lactol **6.83** in acidic conditions, followed by reduction of oxazolidinone. Intermediate **6.83** could be obtained by semi-reduction of lactone and reduction of hemiaminal ethers. Intermediate **6.84** could be obtained by *syn* 1,2-aryl migration of the indole moiety to the allylic position. A few reports about this type of migration were described.¹²⁵ The intermediate **6.85** could be obtained by stereoselective vinylation using Grignard reagents to 3-ketopiperidine **6.86**. The 3-ketopiperidine **6.86** could be the product of the oxidation of the enamine **6.87** which could derive from our 6-*exo*-dig cyclization of enantioenriched Mannich adducts.

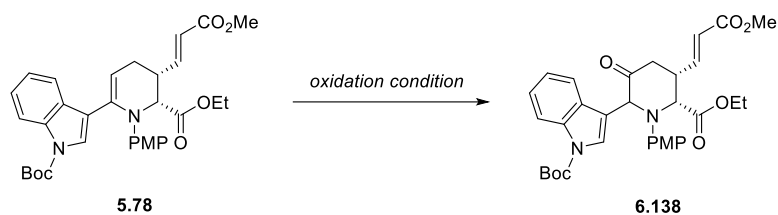
¹²⁵ a) Zhou, L.; Tay, D. W.; Chen, J.; You, G.; Leung, C.; Yeung, Y.-Y. *Chem. Commun.* **2013**, 49, 4412. b) Rowley, M.; Hallett, D. J.; Goodacre, S.; Moyes, C.; Crawforth, J.; Sparey, T. J.; Patel, S.; Marwood, R.; Patel, S.; Thomas, S.; Hitzel, L.; O'Connor, D.; Szeto, N.; Castro, J. L.; Hutson, P.H.; MacLeod, A. M. *J. Med. Chem.* **2001**, 44, 1603. c) Matsumura, Y.; Terauchi, J.; Yamamoto, T.; Konno, T.; Shono, T. *Tetrahedron* **1993**, 49, 8503.



Scheme 6.14

6.7 Toward Total Synthesis of Koumine

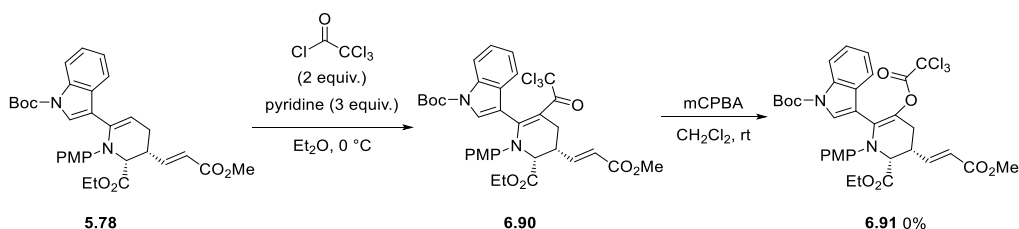
The direct oxidation of the enamine **5.78** was initially explored to attain 3-ketopiperidine **6.138**, but its exposure to various oxidants (*m*CPBA, oxone[®], PhNO, dilauroyl peroxide, *etc.*) failed to deliver 3-hydroxy or 3-keto piperidines derivatives (**Fig 6.3**). In all cases, hopeless complex mixtures were collected and it was impossible to analyse them and track the problems.



entry	Redactant	Solvent	temp.	Yield
1	mCPBA /NaHCO ₃ aq.	CHCl ₃	0 °C (30 min)	degradation
2	Oxone (in CH ₂ Cl ₂)	CH ₂ Cl ₂	0 °C (18 h)	degradation
3	Oxone (in acetone)	acetone	0 °C (4 h)	degradation
4	nitrosobenzene + TBSOTf	CH ₂ Cl ₂	0 °C (1 h)	degradation
5	Na ₂ WO ₄ 2H ₂ O	MeCN	rt (1 h)	degradation
6	Na ₂ WO ₄ 2H ₂ O + UHP	MeCN	rt (16 h)	degradation
7	Davis reagent	CHCl ₃	rt (3 h)	degradation
8	Davis reagent	MeCN	60 °C (30 min)	degradation
9	(PhCOO) ₂ , K ₂ CO ₃	CH ₂ Cl ₂	rt	degradation
10	diauroyl peroxide	CH ₂ Cl ₂	rt	degradation

Fig 6.3

An indirect approach for 3-ketopiperidine **6.138** was therefore devised. The enamine **5.78** was transformed into the vinylogous amide **6.90** with trichloroacetyl chloride. The compound **6.90** was exposed to the condition of Baeyer-Villiger oxidation but the desired product **6.91** was not obtained and instead complex mixtures were obtained (**Scheme 6.15**).



Scheme 6.15

Another route was next explored (**Scheme 6.16**). First, enamine **5.78** was brominated (NBS/DBU) delivering bromo enamine **6.92** which was followed by a reduction step to give the bromo piperidine **6.93** in 94% yield (2-step) as a single all *cis*-stereoisomer (dr > 20:1) with two new stereocenters at C2 and C3. Instead of the bromo derivative, iodo enamine **6.96** could also be obtained using iodine but the C-I bond was too fragile and was reduced by NaBH₃CN affording piperidine **5.79** (**Scheme 6.17**). Upon exposure to AgOTf (1.5 equiv) and DMF/H₂O (15 equiv) in MeNO₂, the 3-bromopiperidine **6.93** was converted into 3-hydroxypiperidine **6.95** with retention of configuration which conceivably implied, in view of precedents, the formation

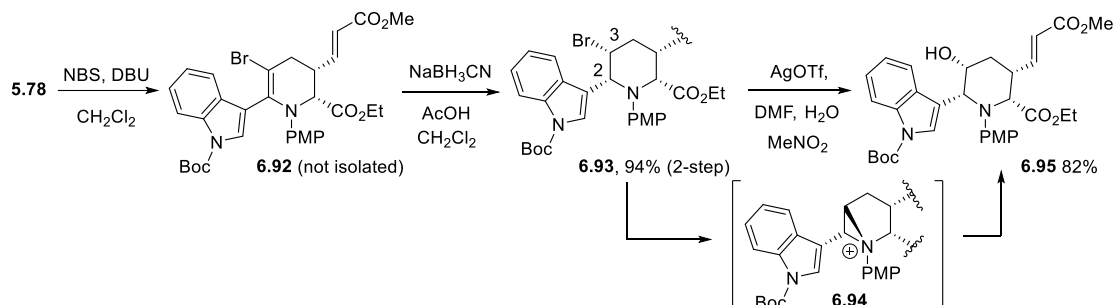
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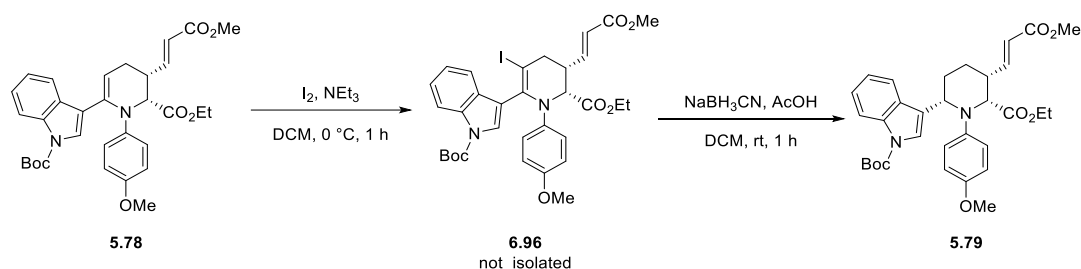
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and the ring opening of aziridinium **6.94**. The structure and relative configuration of all stereocenters were checked and determined by 2D NMR. We noted that AgOTf gave the best result among other silver salts (AgBF₄, AgTFA, AgNO₃, AgOAc).

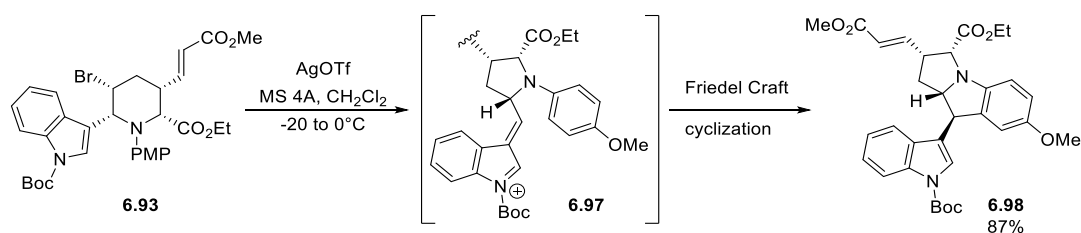


Scheme 6.16



Scheme 6.17

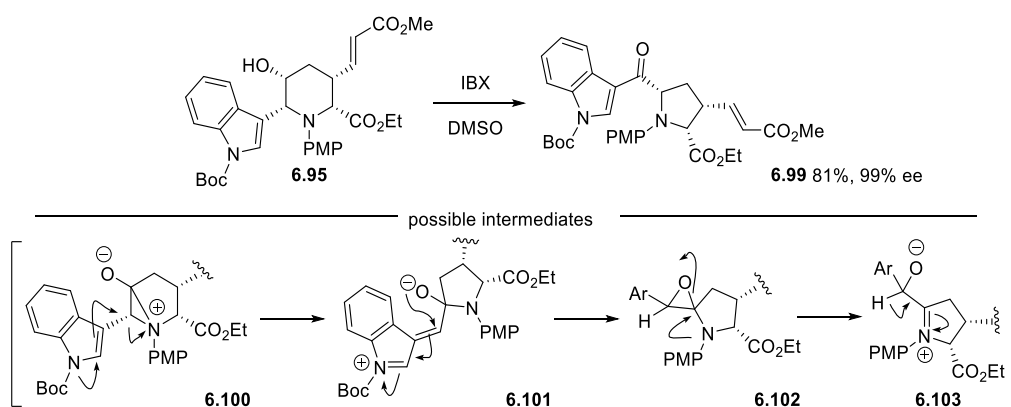
This hypothesis was given credit when the same experiment was attempted in the absence of DMF and H₂O, which was ascertained with 4 Å molecular sieves (**Scheme 6.18**). The reaction pathway was then derailed toward a ring-contracted pyrrolidine **6.98** in 87% yield as a single stereoisomer. This is consistent with a scenario in which aziridinium **6.94** would collapse into cation **6.97**, followed by C-C bond formation in a Friedel-Crafts pattern involving the PMP group. The relative configuration of each stereocenter was determined by 2D NMR.



Scheme 6.18

In the same vein, oxidation of the alcohol **6.95** triggered the ring-contraction of the piperidine

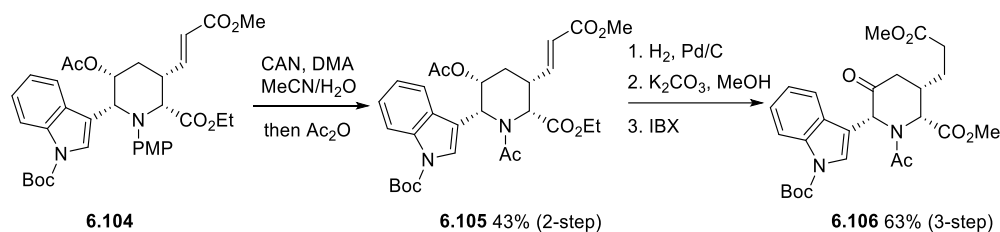
scaffold into α -keto piperidine **6.99**. IBX oxidation was the best way for obtaining α -keto piperidine **6.99** in 81% yield while preserving the enantiomeric excess (99% ee) (**Scheme 6.19**). Indeed, Parikh-Doering Oxidation ($\text{SO}_3\text{-py}$, DMSO, NEt_3) or PDC oxidation resulted in complex mixtures and TPAP oxidation led to the recovery of the starting material. When considering the mechanism, owing to the nucleophilic character of the nitrogen, the transient formation of aziridinium **6.100** is anticipated to precede its collapse into a cation **6.101** stabilized by the electronic donation of the indole moiety. Aromatization by addition of the hydroxylate into spiro epoxide **6.102** and ring opening into iminium **6.103** are possible steps toward ketone **6.99** for which the relative configuration was determined by 2D NMR. As alternative mechanism, activation of the hydroxyl by IBX could trigger the ring contraction as observed in Scheme 6.18. Then, IBX addition to **6.97** could lead to **6.99**. To distinguish these two mechanisms would be challenging as they are both intramolecular. At any rate, it is assumed that the failures encountered during the oxidation of enamine **5.78** should be attributed to the nucleophilic nitrogen of PMP group promoting the ring-contraction.



Scheme 6.19

To avoid the ring-contraction, the PMP group of nitrogen of the piperidine was therefore changed into *N*-acetyl group as electron-withdrawing group (**Scheme 6.20**). Namely, *O*-acetylated piperidine **6.104**, which was prepared from **6.95** in 87%, was exposed to CAN in the presence of H_2O and dimethylacetamide. DMA was an additive required to avoid the decomposition of the product and to improve the reproducibility. After a step of *N*-acetylation

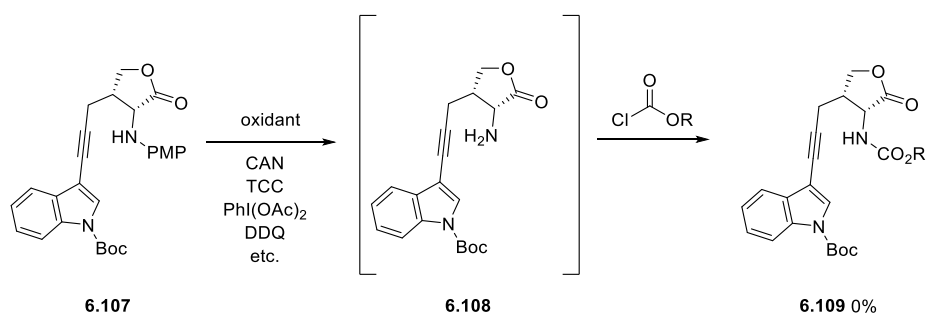
using Ac₂O, the *N*-acetyl piperidine **6.105** was thus obtained in 43% yield. The trisubstituted 3-ketopiperidine **6.106** was ultimately obtained in 63% yield after a sequence from **6.105** entailing three steps: reduction, saponification and oxidation.



Scheme 6.20

As shown above, the removal of the PMP group increases the number of steps and decreases the global yield in the planned total synthesis of koumine **6.7**. To avoid this negative impact, the synthesis of chiral amine with an electron-withdrawing group, instead of the PMP group, was explored.

At first, the PMP removal of the Mannich adduct **6.107**, which was prepared by our method from an aldehyde bearing *N*-Boc-protected indole in 33% yield, was explored (**Scheme 6.21**). Several conditions for the exchange of the protection group were tested with some oxidants (CAN, TCC, PhI(OAc)₂ *etc.*) and subsequent addition of chlorocarbamates, but all trials gave complex mixtures (**Scheme 6.21**). Therefore, it was necessary to switch protecting group earlier in the route.

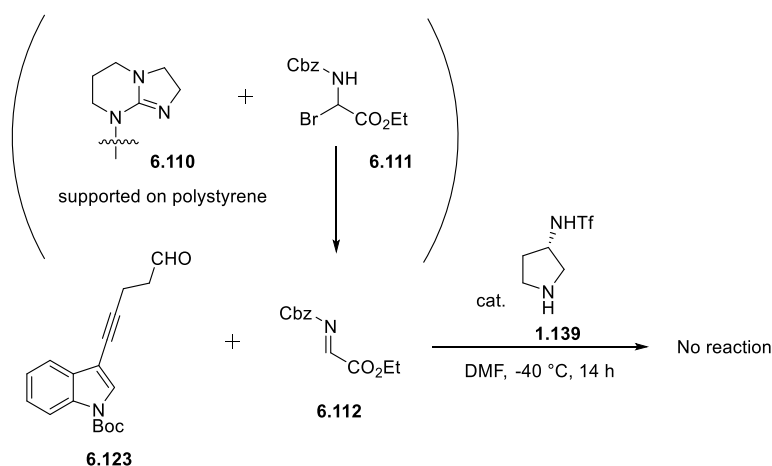


Scheme 6.21

It was anticipated that less nucleophilic amine such as carbamate would be less efficient than PMP group for the hydroamination reaction, due to the delocalization of the nitrogen lone pair in the carbonyl. Still, the stabilization provided by the carbamate to the resulting enamine was

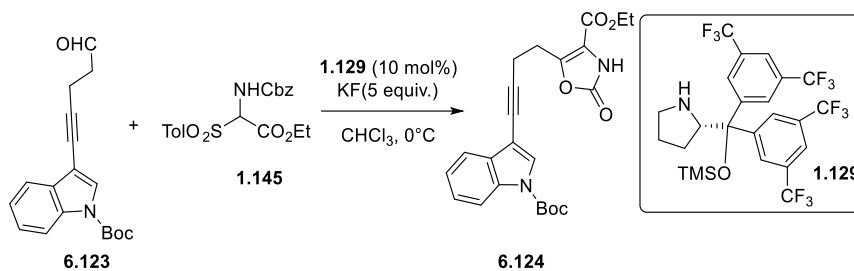
sought to shorten the route to koumine and it was valuable to examine the reactivity of arylogous ynamines toward weaker nucleophiles.

For that end, employment of carbamate-protected iminoester **6.112** in the frame of the Mannich reaction was examined (Scheme 6.22). At first, carbamate-protected iminoester **6.112** was prepared according to Kobayashi's procedure.⁵⁵ The freshly prepared iminoester **6.112** was employed in our conditions developed for the Mannich coupling, but the reaction didn't proceed at all probably because the enamine could not form the hydrogen bond with the carbamate-protected iminoester **6.112** due to the low basicity of the nitrogen moiety.



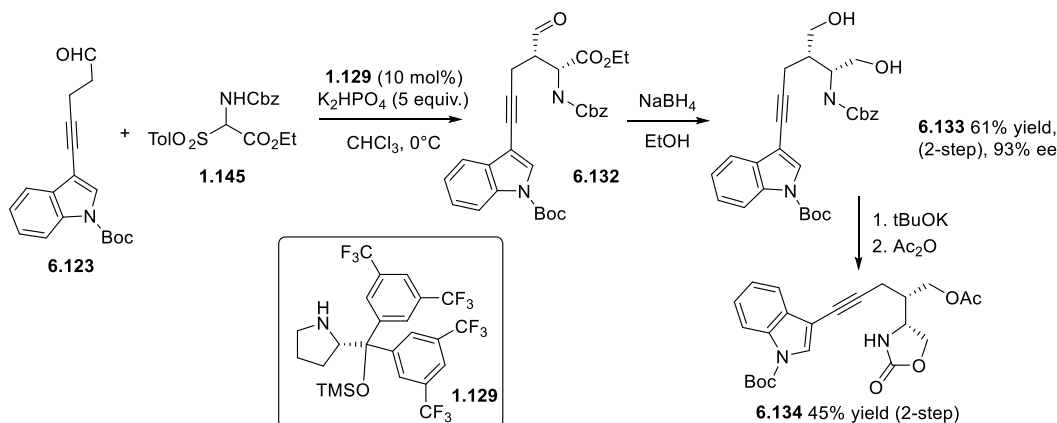
Scheme 6.22

Next, Melchiorre's procedure using *in situ* generated *N*-Cbz iminoester **6.125** from α -amid sulfone **1.145** was examined for preparation of a chiral amine with electron-withdrawing protection. The use of KF as base gave the best result in their paper. However, the Mannich reaction of aldehyde **6.123** and α -amid sulfone **1.145** using KF gave undesired oxazolone **6.124** and the trace amount of the desire product **6.132**. (Scheme 6.23). This result deserves further investigations to bring a mechanism explaining the formation of oxazolone **6.124**.



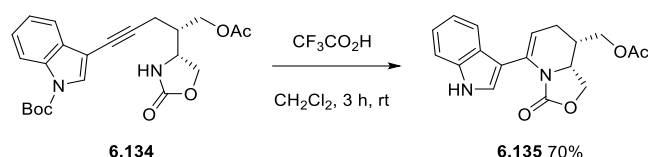
Scheme 6.23

To avoid this side reaction, several bases were explored. After screening, K₂HPO₄ was proven to be the best base among NaF, KHCO₃, KOAc, K₂CO₃. The optimized reaction provided aldehyde **6.132** which was directly reduced into diol **6.133** in 61% yield (2-step) and 93% ee (**Scheme 6.24**). To attain such enantioselectivity, the Mannich reaction was carry out at 0°C (168 h). The two hydroxyl moieties of **6.133** were discriminated by treatment with *t*BuOK (1.5 equiv) at 0°C inducing the formation of the oxazolidinone. To simplify the substrate for examination of the cyclization, for this moment, the remaining hydroxyl was then acetylated to give oxazolidinone **6.134** in 45% yield (2-step).



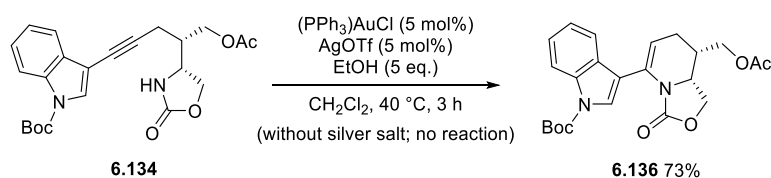
Scheme 6.24

The key cyclization was attempted with TFA (20 equiv.) at rt which, pleasingly, led to the desired tetrahydropyridine **6.135** bearing an unprotected indole in 70 % yield (**Scheme 6.25**). As anticipated, **6.135** demonstrated better stability to air and moisture. Interestingly, oxazolidinone moiety is thus an efficient nucleophile for exploiting the reactivity of arylogous ynamine in the frame of hydroamination reaction promoted by Brønsted acid.

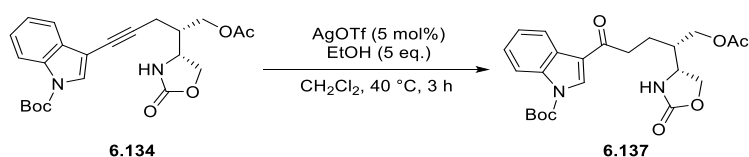


Scheme 6.25

To preserve the *N*-Boc indole protection and facilitate the oxidation of the enamine, the activation of the triple bond was envisaged without Brønsted acid but in the presence of gold catalysts. Hence, cationic gold-catalyzed cyclization of amine **6.134** was examined. It is well known that Lewis acidic gold (I) complexes activate π -bonds as in alkynes.¹²⁶ As a preliminary study, the cyclization of amine **6.134** using a catalytic amount of AuCl(PPh₃) and AgOTf in the presence of EtOH (5 equiv) afforded tetrahydropyridine **6.136** with *N*-Boc protected indole in 73% yield (**Scheme 6.26**). The reaction was successful despite the presence of *N*-Boc, oxazolidinone and acetate as potential Lewis bases and only 6-*endo*-dig cyclization was observed. The reaction didn't proceed without silver salt whereas, in the condition without gold catalyst, only hydrated product **6.137** was observed (**Scheme 6.27**).



Scheme 6.26



Scheme 6.27

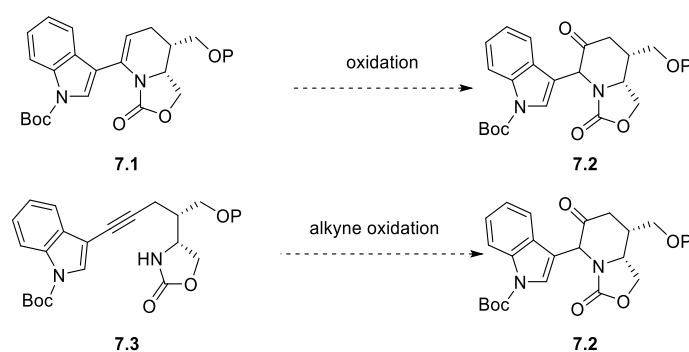
¹²⁶ Review: a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

7 Conclusion and Perspectives

In conclusion, we explored the reactivity of arylogous ynoethers and ynamines with a Brønsted acid. The reaction mechanism shifted from H-bond interaction to protonation as the electronic density of arynes increased. In addition, the cyclization proceeded while preserving the excellent enantiomeric excess of the Mannich adducts. As for synthetic manipulations, the stereoselective reduction of tetrahydropyridines and the ring-contraction reaction of piperidines were developed. In the course of the study, the epimerization of 2-indolyl piperidine in acidic condition was controlled for the production of *trans*-isomers.

The study of the reactivity of arylogous ynoethers and ynamines gave a direction for the total synthesis of koumine. The hydroamination of arylogous ynamine and carbamate protected iminoester was developed since it was discovered that the PMP group caused ring-contraction and the removal of the PMP group in the piperidine was problematic. This development provided a prospect for a shortened route to the target.

In perspectives, there are some possibilities. One is the development of enamine oxidation¹²⁷ to proceed as our synthetic plan or alkyne oxidation¹²⁸ for aiming at shorter route (**Scheme 7.1**).



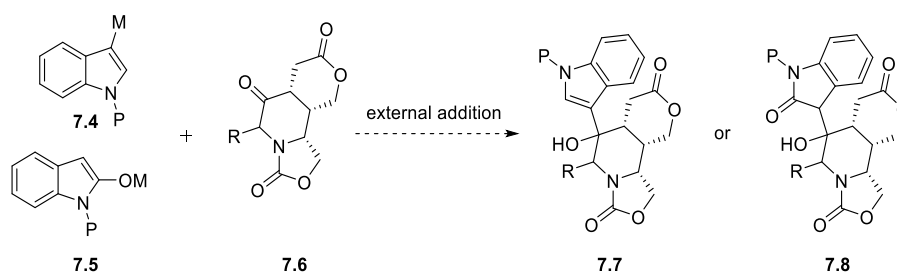
Scheme 7.1

Another plan is the development of external addition of indole moiety to the main core (**Scheme**

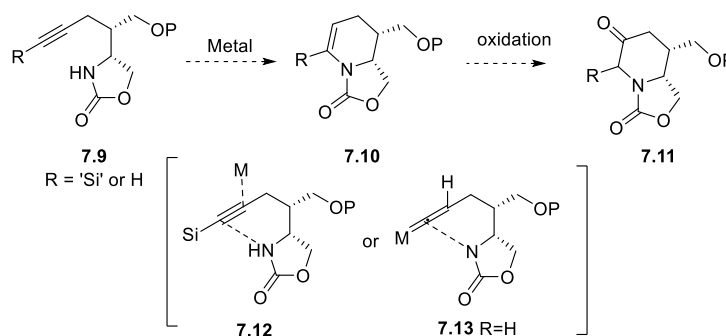
¹²⁷ Bertho, S.; Rey-Rodriguez, R.; Colas, C.; Retailleau, P.; Gillaizeau, I. *Chem. Eur. J.* **2017**, *23*, 17674.

¹²⁸ a) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, *18*, 2819. b) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chem. Soc. Rev.* **2016**, *45*, 4448.

7.2). One of the merits is that the route could be more convergent in comparison with the original plan which is more linear. The route gives a flexibility for introducing the indole part, which means it is possible to install substituted indoles. External introduction of the indole moiety could be beneficial in avoiding the oxidation of the indole during the preparation of 3-ketopiperidines, since the last steps toward koumine don't involve oxidants. For this end, we need to develop 6-*endo*-dig hydroamination of chiral amines bearing a terminal alkyne or a silyl alkyne (**Scheme 7.3**). There are some possibilities, for example, the hydroamination of allenylidene complexes derived from transition metals and terminal alkynes.¹²⁹ The chemistry is known with Ru, W, Mo, Re *etc.*, which are less expensive than gold. The strategy could provide an economically and highly divergent synthesis of koumine.



Scheme 7.2



Scheme 7.3

¹²⁹ Roh, S. W.; Choi, K.; C. Lee, C. *Chem. Rev.* **2019**, *119*, 4293.

EXPERIMENTAL SECTION

General Information:

Unless otherwise noted, reactions were carried out under an argon atmosphere.

^1H NMR and ^{13}C NMR spectra were recorded in deuterated chloroform or acetonitrile on a Bruker Avance DPX 300 spectrometer and were referenced to residual chloroform (7.26 ppm, ^1H ; 77.16 ppm, ^{13}C) or acetonitrile (1.94 ppm, ^1H ; 1.32 ppm, ^{13}C). Chemical shifts are expressed in parts per million (ppm). Data for ^1H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet), integration, coupling constant (Hz). Mass spectra and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-ToF micro instrument. IR data were obtained on a PerkinElmer Spectrum 100 FT-IR-spectrometer with only major peaks being reported in cm^{-1} . Thin layer chromatography (TLC) was performed on silica gel 60 F-254 plates (0.1 mm, Merck). Visualization was accomplished with UV (254 nm) or KMnO_4 staining solutions. Dichloromethane was dried and purified on Pure-SolvTM 400 Solvent Purification System. Triethylamine (Et_3N) was employed for Sonogashira coupling without prior purification. CuI was purchased from Alfa Aesar and were used as received. Technical grade *N,N*-dimethylformamide (DMF) was employed for this work. Catalyst **1.139** was prepared from (3*S*)-(+)-1-benzyl-3-aminopyrrolidine [114715-38-7] available from TCI.¹³⁰ α -amido sulfone **1.145**¹³¹ and IBX (2-iodoxybenzoic acid)¹³² were prepared according to known procedures. Hydrogenation was performed in normal vessel under a balloon of H_2 . Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm , Merck). Optical rotations were measured on a Perkin–Elmer 241 LC polarimeter in a 10 cm cell. $[\alpha]_{\text{D}}$ Values are

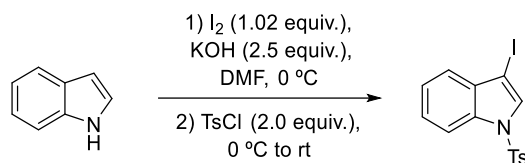
¹³⁰ Pouliquen, M. Blanchet, J. ; Lasne, M.-C. Rouden, J. *Org. Lett.* **2008**, *10*, 1029.

¹³¹ Nagano, T.; Kinoshita, H. *Bull. Chem. Soc. Jap.* **2000**, *73*, 1605.

¹³² Frigerio, M. ; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

given in units of $10^{-1} \text{ deg cm}^2 \cdot \text{g}^{-1}$. The absolute configuration of the Mannich adducts was deduced from the model presented in our previous study.² Melting points were determined on a Electrothermal digital apparatus IA9100 series and are uncorrected. Analytical high performance liquid chromatographies (HPLC) were carried out with a Waters instrument [detector M996 (200–400 nm) and pump 600] and the conditions are indicated for each compounds. Unless otherwise indicated, enantiomeric excess (ee) were determined by chiral HPLC and diastereoisomeric ratio (dr) were measured by ^1H NMR on 300 MHz. The racemic mixture of chiral products were synthesized by employing *rac*-**1.139** prepared from *rac*-1-benzyl-3-aminopyrrolidine [18471-40-4] available from TCI.

Preparation of haloaryls



General procedure: 3-iodo-1-tosyl-1H-indole (5.6) To a solution of 1H-indole (5.0 g, 42.7 mmol) in DMF (100 mL) was added KOH (6.0 g, 106.9 mmol, 2.5 equiv.). To this suspension, I₂ (11.0 g, 43.3 mmol, 1.02 equiv.) was added in 5 portions at 0°C and the reaction mixture was stirred at 0°C for 30 min. Then, KOH (6.0 g, 106.9 mmol, 2.5 equiv.) was added again, followed by TsCl (17.0 g, 89.2 mmol, 2.1 equiv.) at 0°C and the resultant mixture was allowed to stir at room temperature. After 15 h, 500 mL of water was added into the reaction mixture. The resultant precipitate was filtrated and washed with 150 mL H₂O, 50 ml cold MeOH and 100 mL pentane. The precipitate was collected and dried under reduced pressure to yield the title compound as a white solid (14.5 g, 36.5 mmol, 86 % yield over two steps).

Spectroscopic data was in agreement with the literature.¹³³

¹H NMR (300 MHz, CDCl₃) δ = 7.99 – 7.96 (m, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.71 (s, 1H), 7.46 – 7.27 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.32 (s, 3H)

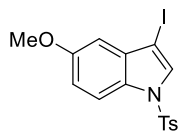
¹³C NMR (75 MHz, CDCl₃) δ = 145.5, 135.0, 134.4, 132.5, 130.1, 129.9, 127.0, 125.8, 124.0, 122.1, 113.5, 67.0, 21.7

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₅H₁₁NO₂SI: 395.9555, found: 395.9541.

R_f = 0.43 (PE/AcOEt: 10/1)

3-Iodo-5methoxy-1-tosyl-1H-indole (5.7)

¹³³ Stark, T.; Suhartono, M.; Göbel, M. W.; Lautens, M. *Synlett* **2014**, 24, 2730.



5.7 was prepared according to the general procedure, using 5-methoxy-1H-indole (2.94 g, 20.0 mmol). Yield 88% (7.49 g, 17.5 mmol) as a yellow solid.

Mp = 184-186°C from MeOH

¹H NMR (300 MHz, CDCl₃) δ = 7.85 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.65 (s, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.97 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 3.84 (s, 3H), 2.33 (s, 3H)

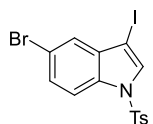
¹³C NMR (75 MHz, CDCl₃) δ = 157.2, 145.4, 135.0, 133.6, 130.5, 130.1, 129.0, 127.0, 115.3, 114.6, 104.0, 67.1, 55.9, 21.7

IR (neat): 1610, 1596, 1470, 1443, 1362, 1304, 1212, 1186, 1173, 1158, 1140, 1105, 1090, 1034, 1015, 959, 828, 816, 802, 776, 764, 702, 673, 622, 595, 564, 534, 507

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₆H₁₅NO₃SI: 427.9817, found: 427.9816

R_f = 0.33 (PE/AcOEt: 10/1)

5-Bromo-3-iodo-1-tosyl-1H-indole (**5.8**)



5.8 was prepared according to the general procedure, using 5-bromo-1H-indole (2.94 g, 15.0 mmol). Yield 73% (5.22 g, 11.0 mmol) as a white solid.

Mp = 154-156°C from MeOH

¹H NMR (300 MHz, CDCl₃) δ = 7.83 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.68 (s, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.45 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 2.35 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 145.8, 134.7, 134.3, 133.3, 131.1, 130.3, 128.8, 127.0, 125.0, 117.7, 115.0, 65.5, 21.8

IR (neat): 3123, 1595, 1439, 1373, 1283, 1248, 1142, 1170, 1112, 1091, 1027, 933, 866, 848, 814, 789, 772, 730, 702, 667, 582, 566, 539, 530, 487, 415

HRMS (TOF MS ESI-) calcd for (M-H)⁻ C₁₅H₁₀NO₂S⁷⁹BrI: 473.8660, found: 473.8659.

P

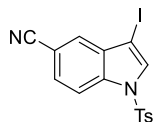
A

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Rf = 0.28 (PE/AcOEt: 10/1)

3-Iodo-1-tosyl-1H-indole-5-carbonitrile (5.9)



5.9 was prepared according to the general procedure, using 1H-indole-5-carbonitrile (2.16 g, 15.2 mmol). Yield 92% (5.92 g, 14.0 mmol) as a pale yellow solid.

Mp = 182-184°C from MeOH

¹H NMR (300 MHz, CDCl₃) δ = 8.05 (d, *J* = 8.6, Hz, 1H), 7.79 (m, 3H), 7.71 (d, *J* = 0.9 Hz, 1H), 7.61 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.37 (s, 3H)

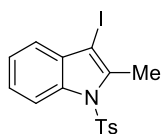
¹³C NMR (75 MHz, CDCl₃) δ = 146.3, 136.2, 134.4, 132.8, 131.9, 130.5, 128.6, 127.2, 127.1, 119.0, 114.5, 107.8, 65.7, 21.8

IR (neat): 3137, 2225, 1595, 1455, 1383, 1290, 1265, 1172, 1143, 1087, 1025, 959, 885, 817, 800, 761, 700, 670, 626, 586, 573, 553, 536, 411

HRMS (TOF MS ESI⁻) calcd for (M+Cl)⁻ C₁₆H₁₁N₂O₂SI³⁵Cl: 456.9274, found: 456.9275

Rf = 0.21 (PE/AcOEt: 10/1)

3-Iodo-2-methyl-1-tosyl-1H-indole (5.10)



5.10 was prepared according to the general procedure, using 2-methyl-1H-indole (2.00 g, 15.3 mmol). Yield 44% (2.79 g, 6.78 mmol) as a brown solid.

Mp = 158-159°C from MeOH

¹H NMR (300 MHz, CDCl₃) δ = 8.18 – 8.13 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.28 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 2.71 (s, 3H), 2.35 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 145.2, 137.5, 136.5, 136.0, 131.7, 130.1, 126.5, 125.3, 124.2, 121.5, 114.7, 73.2, 21.7, 16.6

IR (neat): 2924, 1600, 1448, 1363, 1227, 1189, 1169, 1151, 1119, 1086, 1063, 1004, 930, 811,

P

A

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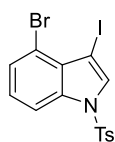
E

751, 742, 706, 693, 656, 568, 540, 486

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₆H₁₅NO₂SI: 411.9868, found: 411.9861

R_f = 0.34 (cyclohexane/AcOEt: 10/1)

4-Bromo-3-iodo-1-tosyl-1H-indole (5.11)



5.11 was prepared according to the general procedure, using 5-bromo-1H-indole (2.00 g, 10.2 mmol). Yield 70% (3.38 g, 7.1 mmol) as a white solid.

Mp = 111-112°C from MeOH

¹H NMR (300 MHz, CDCl₃) δ = 8.01 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.81 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 8.1 Hz, 1H), 2.37 (s, 3H)

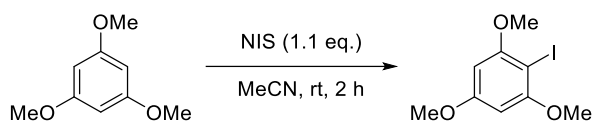
¹³C NMR (75 MHz, CDCl₃) δ = 145.8, 134.8, 134.4, 132.8, 130.1, 128.8, 127.0, 126.8, 126.0, 115.7, 113.0, 62.7, 21.6

IR (neat): 3124, 1595, 1364, 1152, 1086, 1030, 809, 771, 736, 702, 687, 658, 612, 569, 537

HRMS (TOF MS ESI-) calcd for (M-H)⁻ C₁₅H₁₀NO₂S⁷⁹BrI: 473.8660, found: 473.8667

R_f = 0.27 (cyclohexane/AcOEt: 10/1)

2-Iodo-1,3,5-trimethoxybenzene (5.12)



To a stirred solution of 1,3,5-trimethoxybenzene (10.0 g, 59.5 mmol) in acetonitrile (40 mL) was added *N*-iodosuccinamide (14.7 g, 65.4 mmol, 1.1 equiv.) in five portions at room temperature. The reaction mixture was stirred at room temperature for 2 h to obtain white solids. The precipitated solids were filtered, washed with 1N aq. NaOH, water and n-hexane, and dried to afford **5.12** as a white solid (16.5 g, 94 %) as a white solid. Spectroscopic data of **5.12** were

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in agreement with the literature.¹³⁴

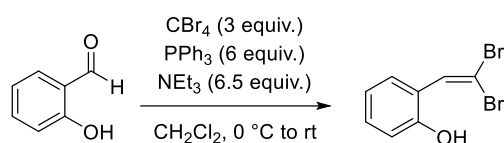
¹H NMR (300 MHz, CDCl₃) δ = 6.11 (s, 2H), 3.83 (s, 6H), 3.79 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 162.2, 159.7, 91.2, 66.6, 56.5, 55.5

MS (ESI): m/z, 294.0 (M)

R_f = 0.26 (PE/AcOEt: 10/1)

2-(2,2-Dibromovinyl)phenol (5.13)



To a solution PPh₃ (7.87 g, 30 mmol, 3.0 equiv.) in CH₂Cl₂ (25 mL) was added CBr₄ (4.97 g, 15 mmol, 6.0 equiv.) in CH₂Cl₂ (25 mL) and the mixture was stirred at 0°C for 10 min. Then Et₃N (4.5 mL, 32.3 mmol, 6.5 equiv.) and salicylaldehyde (0.53 mL, 5.0 mmol) were added to the mixture at 0°C. The mixture was stirred for 30 min and the reaction was warmed to room temperature with stirring. After 2 h, the reaction was quenched by aq. NH₄Cl and extracted with CH₂Cl₂ (x3). The organics were dried with MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 5/1) to yield **5.13** (90%, 1.25 g, 4.5 mmol) as colorless oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.61 – 7.53 (m, 2H), 7.30 – 7.20 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 5.17 (s, 1H)

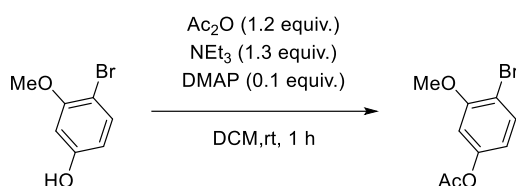
¹³C NMR (75 MHz, CDCl₃) δ = 152.5, 132.5, 130.2, 129.3, 123.0, 120.9, 115.9, 92.2

HRMS (TOF MS ES-) calcd for (M-H)⁻ C₈H₅⁷⁹Br₂: 274.8707, found: 274.8703

R_f = 0.37 (cyclohexane/AcOEt: 5/1).

¹³⁴ V. Krishna Reddy, V. K.; Rao, J.V.; Reddy, L.B.; Ram, B.; Balram, B. *Der Pharma. Chemical* **2013**, *5*, 237.

4-Bromo-3-methoxyphenyl acetate (5.14)



To a solution of 4-bromo-3-methoxyphenol (620.2 mg, 3.06 mmol) in CH₂Cl₂ (10 mL) was added NEt₃ (0.55 mL, 3.97 mmol, 1.3 equiv.), Ac₂O (0.35 mL, 3.67 mmol, 1.2 equiv.) and then DMAP (37.0 mg, 0.36 mmol, 0.1 equiv.) at room temperature. The mixture was stirred for 1 h. The reaction was quenched by H₂O and extracted with CH₂Cl₂ (x3). The organics were dried with MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 6/1 to 4/1) to yield **5.14** (98%, 733.7 mg, 2.99 mmol) as yellowish oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.46 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.56 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.77 (s, 3H), 2.21 (s, 3H)

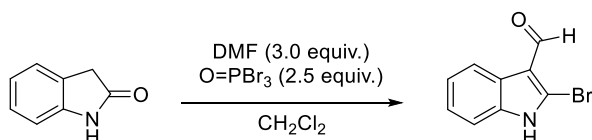
¹³C NMR (75 MHz, CDCl₃) δ = 168.7, 156.2, 150.7, 132.9, 114.6, 107.9, 106.1, 56.0, 20.7

IR (neat): 3026, 2943, 2877, 1763, 1597, 1482, 1465, 1447, 1368, 1276, 1199, 1187, 1151, 1046, 1023, 1011, 955, 891, 835, 803, 754, 684, 609, 541, 513, 454

HRMS (EI) calcd for (M)⁺ C₁₃H₁₇O₃: 243.97351, found: 243.97431

R_f = 0.21 (cyclohexane/AcOEt: 6/1)

2-Bromo-1*H*-indole-3-carbaldehyde (5.15)



To a solution of dimethylformamide (3.6 mL, 46.5 mmol, 3.0 equiv.) in CH₂Cl₂ (12 mL) was added dropwise a solution of phosphorus oxybromide (11.1 g, 38.7 mmol, 2.5 equiv.) in CH₂Cl₂ (20 mL) at 0°C. The white thick mixture was refluxed for 15 min, and then oxindole (2.05 g,

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15.4 mmol) was added portionwise. The mixture was stirred at reflux for 1 h. The reaction was quenched by addition of ice water. The mixture was stirred for 30 min, and then the two layers were separated. The aqueous layer was neutralized with solid K_2CO_3 . The pale yellow precipitate which appeared was washed with cold water, cold CH_2Cl_2 and a small amount of cold acetone. The pale yellow solid was collected and dried under vacuum to obtain **5.15** (Yield 85%, 2.94 g, 13.1 mmol). Spectroscopic data of **5.15** were in agreement with the literature.¹³⁵

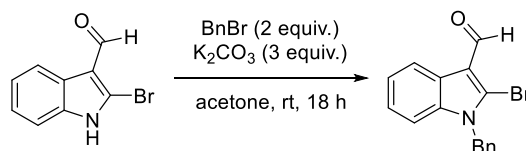
1H NMR (300 MHz, DMSO) δ = 13.05 (brs, 1H), 9.90 (s, 1H), 8.09 (d, J = 6.6 Hz, 1H), 7.43 (d, J = 6.9 Hz, 1H), 7.28 – 7.19 (m, 2H)

^{13}C NMR (75 MHz, DMSO) δ = 184.5, 136.4, 124.8, 123.7, 123.2, 122.6, 119.7, 114.3, 111.7

HRMS (TOF MS ESI+) calcd for $(M+H)^+$ $C_9H_7NO^{79}Br$: 223.9711, found: 223.9708

Rf = 0.25 (PE/AcOEt: 4/1)

1-Benzyl-2-bromo-1H-indole-3-carbaldehyde (**5.16**)



To a solution of 2-bromo-1H-indole-3-carbaldehyde **5.15** (2.24 g, 10.0 mmol) in acetone (50 mL) was added at 0°C K_2CO_3 (4.15 g, 30.0 mmol, 3.0 equiv.) and BnBr (2.4 mL, 20.0 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 18 h. The suspension was filtered washing with acetone and the filtrate was concentrated under reduced pressure to obtain the crude material. The residue was purified by flash chromatography on silica gel (PE/AcOEt: 10/1) to yield **5.16** as a pale yellow solid. Yield 78% (2.46 g, 7.8 mmol). Spectroscopic data of **5.16** were in agreement with the literature.²

1H NMR (300 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 8.42 (d, J = 7.5 Hz, 1H), 7.39 – 7.21 (m, 6H),

¹³⁵ Tiano, M.; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101.

7.19 – 7.05 (m, 2H), 5.38 (s, 2H)

¹³C NMR (75 MHz, CDCl₃) δ = 185.2, 136.9, 135.0, 128.8, 127.9, 126.3, 126.0, 125.2, 124.1, 123.3, 121.0, 115.4, 110.3, 48.4

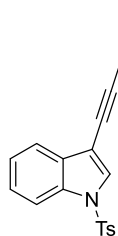
HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₆H₁₃NO⁷⁹Br: 314.0181, found: 314.0167

R_f = 0.32 (PE/AcOEt: 10/1)

Preparation of Sonogashira coupling products

General procedure for Sonogashira coupling: To a suspension of aryl halide (1 equiv.), CuI (0.02 equiv.), PdCl₂ (0.02 equiv.) and PPh₃ (0.04 equiv.) in NEt₃ (0.2 M) was added dropwise 4-pentyn-1-ol (1.1 equiv) at room temperature. The suspension was stirred for 16 h. Then, the suspension was filtered through Celite[®] washing with AcOEt and the filtrate was concentrated under reduced pressure to obtain the crude alcohol. The residue was purified by flash chromatography on silica gel to yield the corresponding alcohol.

5-(1-tosyl-1H-indol-3-yl) ent-4-yn-1-ol (5.17)



5.17 was prepared according to the general procedure for Sonogashira coupling, using 3-iodo-1-tosyl-1H-indole **5.6** (6.44 g, 16.2 mmol). Spectroscopic data of **5.17** were in agreement with the literature.¹³⁶ Purified by flash chromatography on silica gel (PE/AcOEt: 2/1 to 1/1). Yield 99%

(5.69 g, 16.1 mmol) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ = 7.96 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.66 (s, 1H), 7.64 – 7.55 (m, 1H), 7.38 – 7.30 (m, 1H), 7.29 – 7.22 (m, 1H), 7.18 (d, J = 8.4 Hz, 2H), 3.83 (t, J = 6.2 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.94 – 1.84 (m, 2H), 1.82 (brs, 1H)

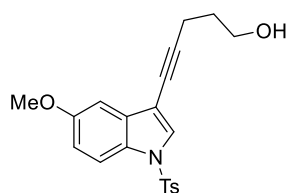
¹³C NMR (75 MHz, CDCl₃) δ = 145.3, 135.0, 134.3, 131.2, 130.0, 128.4, 127.0, 125.4, 123.7, 120.5, 113.6, 105.8, 93.9, 71.9, 61.8, 31.5, 21.6, 16.3

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₀H₂₀NO₃S: 354.1168, found: 354.1164

R_f = 0.26 (PE/AcOEt: 2/1)

5-(5-Methoxy-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol (5.18)

¹³⁶ Gericke, K.M.; Chai, D.I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002.



5.18 was prepared according to the general procedure for Sonogashira coupling, using 3-iodo-5-methoxy-1-tosyl-1H-indole **5.7** (5.13 g, 12.0 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 2/1 to 1/1). Yield 72 % (3.29 g, 8.6 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.87 – 7.80 (m, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 9.0, 2.5 Hz, 1H), 3.86 – 3.79 (m, 5H), 2.60 (t, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.93 – 1.83 (m, 2H), 1.82 (brs, 1H)

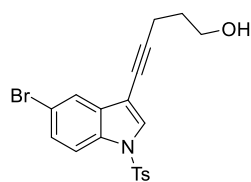
¹³C NMR (75 MHz, CDCl₃) δ = 156.9, 145.2, 134.9, 132.2, 130.0, 129.1, 128.9, 126.9, 114.7, 114.6, 105.8, 102.6, 94.0, 71.9, 61.8, 55.8, 31.5, 21.6, 16.3

IR (neat): 3344, 3131, 2957, 2835, 1612, 1596, 1475, 1436, 1369, 1293, 1248, 1212, 1169, 1125, 1098, 1085, 1029, 989, 810, 702, 676, 655, 608, 580, 537

HRMS (TOF MS ESI+) calcd for (M+NH₄)⁺ C₂₁H₂₅N₂O₄S: 401.1535, found: 401.1531

R_f = 0.26 (PE/AcOEt: 1/1)

5-(5-Bromo-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol (**5.19**)



5.19 was prepared according to the general procedure for Sonogashira coupling, using 5-bromo-3-iodo-1-tosyl-1H-indole **5.8** (5.71 g, 12.0 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 2/1). Yield 98% (5.06 g, 11.7 mmol) as a white solid.

Mp = 118–120°C from MeOH

¹H NMR (300 MHz, CDCl₃) δ = 7.82 (d, J = 8.8 Hz, 1H), 7.74-7.70 (m, 3H), 7.63 (s, 1H), 7.41 (dd, J = 8.8, 1.9 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 3.82 (t, J = 6.1 Hz, 2H), 2.59 (t, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.95 – 1.81 (m, 2H), 1.74 (brs, 1H)

¹³C NMR (75 MHz, CDCl₃) δ = 145.7, 134.7, 133.0, 132.9, 130.2, 129.3, 128.4, 127.0, 123.3, 117.4, 115.1, 105.2, 94.5, 71.1, 61.7, 31.5, 21.7, 16.2

P

A

G

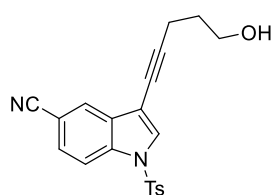
E

IR (neat): 3137, 2867, 1599, 1571, 1447, 1378, 1337, 1293, 1262, 1231, 1170, 1152, 1139, 1110, 1089, 1057, 1036, 1020, 972, 866, 803, 736, 702, 667, 620, 584, 569, 537, 491, 459, 420

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₀H₁₉NO₃S⁷⁹Br: 432.0269, found: 432.0271

R_f = 0.18 (PE/AcOEt: 2/1)

3-(5-Hydroxypent-1-yn-1-yl)-1-tosyl-1H-indole-5-carbonitrile (5.20)



5.20 was prepared according to the general procedure for Sonogashira coupling, using 3-iodo-1-tosyl-1H-indole-5-carbonitrile **5.9** (5.07 g, 12.0 mmol). Purified by flash chromatography on silica gel (PE/AcOEt:

2/1 to 1/1). Yield 70% (3.18 g, 8.4 mmol) as a white solid.

Mp = 150–151°C from PE and CH₂Cl₂

¹H NMR (300 MHz, CDCl₃) δ = 8.04 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.81 – 7.71 (m, 3H), 7.57 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.83 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 2.03 – 1.78 (m, 2H), 1.60 (brs, 1H)

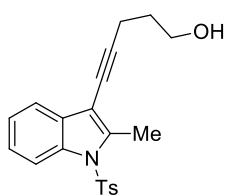
¹³C NMR (75 MHz, CDCl₃) δ = 146.2, 135.9, 134.5, 131.3, 130.4, 130.1, 128.4, 127.1, 125.7, 119.2, 114.5, 107.4, 105.7, 95.3, 70.5, 61.7, 31.4, 21.8, 16.3

IR (neat): 3504, 3133, 2926, 2234, 1609, 1596, 1459, 1439, 1378, 1302, 1233, 1189, 1169, 1154, 1133, 1094, 1057, 1001, 883, 816, 769, 703, 674, 655, 642, 594, 582, 572, 541

HRMS (TOF MS ESI+) calcd for (M+NH₄)⁺ C₂₁H₂₂N₃O₃S: 369.1382, found: 396.1370

R_f = 0.35 (PE/AcOEt: 1/1)

5-(2-Methyl-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol (5.21)



5.21 was prepared according to the general procedure for Sonogashira coupling, using 3-iodo-2-methyl-1-tosyl-1H-indole **5.10** (2.43 g, 5.9 mmol). Purified by flash chromatography on silica gel

P

A

G

E

(cyclohexane/AcOEt: 2/1 to 1/1). Yield 95 % (2.07 g, 5.6 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.19 – 8.12 (m, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.54 – 7.48 (m, 1H), 7.33 – 7.22 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 3.85 (q, *J* = 5.7 Hz, 2H), 2.68 (s, 3H), 2.62 (t, *J* = 6.9 Hz, 2H), 2.34 (s, 3H), 1.95 – 1.83 (m, 2H), 1.46 (t, *J* = 5.4 Hz, 1H)

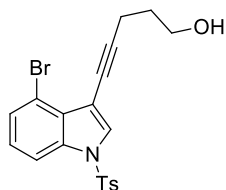
¹³C NMR (75 MHz, CDCl₃) δ = 145.0, 139.8, 135.8, 135.6, 130.0, 129.9, 126.3, 124.7, 123.8, 119.4, 114.3, 105.6, 95.8, 72.1, 61.5, 31.6, 21.4, 16.2, 14.3

IR (neat): 3335, 2927, 1597, 1353, 1435, 1380, 1361, 1299, 1242, 1188, 1171, 1152, 1118, 1089, 1021, 936, 909, 811, 760, 746, 712, 660, 638, 572, 540, 492, 429

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₁H₂₂NO₃S: 368.1320, found: 368.1317

R_f = 0.43 (cyclohexane/AcOEt: 1/1)

5-(4-Bromo-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol (5.22)



5.22 was prepared according to the general procedure for Sonogashira coupling, using 4-bromo-3-iodo-1-tosyl-1H-indole **5.11** (3.25 g, 6.8 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 2/1 to 1/1). Yield 98% (2.90 g, 6.7 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.93 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.80 – 7.70 (m, 3H), 7.39 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 3H), 7.14 (t, *J* = 8.1 Hz, 1H), 3.84 (t, *J* = 6.1 Hz, 2H), 2.58 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 1.96 – 1.83 (m, 2H), 1.47 (brs, 1H)

¹³C NMR (75 MHz, CDCl₃) δ = 145.6, 134.9, 134.2, 130.4, 129.9, 128.3, 128.1, 126.8, 125.9, 115.4, 112.7, 105.8, 95.0, 72.3, 61.5, 30.9, 21.4, 16.3

IR (neat): 3340, 3133, 2933, 2860, 2233, 1596, 1412, 1373, 1334, 1295, 1262, 1173, 1138, 1156, 1115, 1088, 1000, 905, 811, 776, 743, 706, 661, 620, 605, 570, 539

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₀H₁₇NO₃S⁷⁹Br: 430.0113, found: 430.0121

R_f = 0.42 (cyclohexane/AcOEt: 1/1)

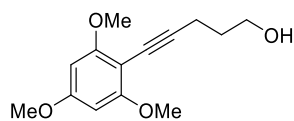
P

A

G

E

5-(2,4,6-Trimethoxyphenyl)pent-4-yn-1-ol (5.23)



5.23 was prepared according to the general procedure for Sonogashira coupling, using 2-iodo-1,3,5-trimethoxybenzene **5.12** (3.0 g, 10.2 mmol) with the modification of reaction time to 48 h. Purified by flash chromatography on silica gel (toluene/AcOEt: 2/1 to 1/1). Yield 59% (1.50 g, 6.0 mmol) as pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 6.04 (s, 2H), 3.86 – 3.78 (m, 8H), 3.76 (s, 3H), 2.82 (brs, 1H), 2.60 (t, J = 6.6 Hz, 2H), 1.90 – 1.77 (m, 2H)

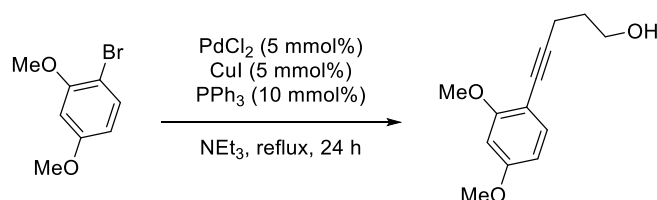
¹³C NMR (75 MHz, CDCl₃) δ = 162.1, 161.0, 96.5, 94.4, 90.4, 73.6, 62.7, 56.0, 55.4, 31.3, 17.6

IR (neat): 3378, 2941, 2840, 2247, 1602, 1577, 1498, 1456, 1414, 1226, 1204, 1156, 1122, 1059, 1032, 948, 911, 809, 729, 635, 535, 468

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₁₄H₁₉O₄: 251.1283, found: 251.1281

R_f = 0.30 (toluene/AcOEt: 1/1)

5-(2,4-Dimethoxyphenyl)pent-4-yn-1-ol (5.24)



To a suspension of 1-bromo-2,4-dimethoxybenzene (1.0 g, 4.61 mmol), CuI (43.9 mg, 0.23 mmol, 0.05 equiv.), PdCl₂ (40.8 mg, 0.23 mmol, 0.05 equiv.) and PPh₃ (120.8 mg, 0.43 mmol, 0.10 equiv.) in NEt₃ (23 mL) was added dropwise 4-pentyn-1-ol (0.47 mL, 5.07 mmol, 1.1 equiv.) at room temperature. The suspension was refluxed with stirring for 24 h. Then, the suspension was filtered through Celite[®] washing with AcOEt and the filtrate was concentrated under reduced pressure to obtain the crude alcohol. The residue was purified by flash chromatography on silica gel (PE/AcOEt: 3/1 to 1/1) to yield **5.24** (39%, 396.7 mg, 1.80 mmol)

P

A

G

E

as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.30 – 7.25 (m, 1H), 6.45 – 6.38 (m, 2H), 3.90 – 3.76 (m, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.58 (brs, 1H)

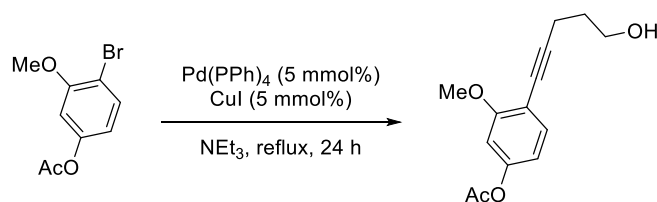
¹³C NMR (75 MHz, CDCl₃) δ = 160.9, 160.5, 133.9, 105.3, 104.6, 98.2, 92.0, 77.1, 61.8, 55.6, 55.3, 31.4, 16.5

IR (neat): 3362, 2932, 2839, 2189, 1605, 1572, 1505, 1456, 1438, 1416, 1300, 1272, 1207, 1159, 1129, 1114, 1028, 825, 799, 635, 607, 567, 541, 483, 458

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₃H₁₇O₃: 221.1178, found: 221.1189

R_f = 0.17 (cyclohexane/AcOEt: 2/1)

4-(5-Hydroxypent-1-yn-1-yl)-3-methoxyphenyl acetate (**5.25**)



To a suspension of 4-bromo-3-methoxyphenyl acetate **6.14** (630.1 mg, 2.57 mmol), CuI (24.5 mg, 0.129 mmol, 0.05 equiv.) and Pd(PPh₃)₄ (148.5 mg, 0.129 mmol, 0.05 equiv.) in NEt₃ (13 mL) was added dropwise 4-pentyn-1-ol (0.26 mL, 2.83 mmol, 1.1 equiv.) at room temperature. The suspension was refluxed with stirring for 24 h. Then, the suspension was filtered through Celite[®] washing with AcOEt and the filtrate was concentrated under reduced pressure to obtain the crude alcohol. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 3/1 to 1/1) to yield **5.25** (31%, 200.6 mg, 0.81 mmol) as yellowish oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.34 (d, *J* = 8.1 Hz, 1H), 6.67 – 6.60 (m, 2H), 3.87 – 3.81 (m, 5H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.29 (s, 3H), 1.93 – 1.82 (m, 2H)

¹³C NMR (75 MHz, CDCl₃) δ = 169.2, 160.7, 151.1, 133.6, 113.6, 110.6, 104.8, 93.8, 76.7,

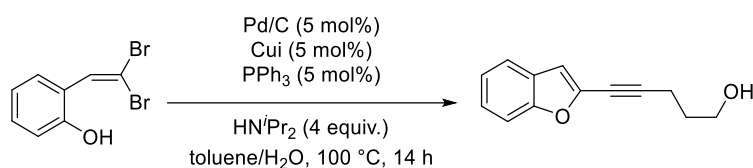
62.1, 56.0, 31.3, 21.2, 16.7

IR (neat): 3422, 2952, 2833, 1762, 1602, 1583, 1499, 1451, 1410, 1369, 1274, 1201, 1187, 1150, 1030, 1013, 956, 893, 837, 814, 730, 631, 586, 543,

HRMS (IC) calcd for (M+H)⁺ C₁₄H₁₇O₄: 249.11268, found: 249.11154

R_f = 0.23 (cyclohexane/AcOEt: 1/1)

5-(Benzofuran-2-yl)pent-4-yn-1-ol (**5.27**)



To a suspension of 2-(2,2-dibromovinyl)phenol **5.13** (1.25 g, 4.5 mmol), CuI (42.9 mg, 0.23 mmol, 0.05 equiv.), 10% Pd/C (240 mg, 0.23 mmol, 0.05 equiv.) and PPh₃ (236.1 mg, 0.9 mmol, 0.2 equiv.) in HNⁱPr₂ (2.5 mL, 18 mmol, 4.0 equiv.) and toluene (6 mL) and H₂O (3 mL) were added dropwise 4-pentyn-1-ol (0.62 mL, 6.78 mmol, 1.5 equiv.) at room temperature. The suspension was heated at 100°C with stirring for 14 h. Then, the suspension was cooled to room temperature and filtered through Celite[®] washing with AcOEt. The filtrate was extracted with AcOEt (x3) and the combined organic layers were brined, dried with MgSO₄ and concentrated under reduced pressure to give the crude alcohol. The residue was purified by flash chromatography on silica gel (PE/AcOEt: 4/1 to 2/1) to yield **5.27** (39%, 396.7 mg, 1.80 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.56 – 7.50 (m, 1H), 7.43 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.25 – 7.19 (m, 1H), 6.84 (s, 1H), 3.82 (t, *J* = 5.9 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 1.97 – 1.84 (m, 2H), 1.76 (brs, 1H).

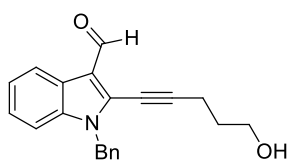
¹³C NMR (75 MHz, CDCl₃) δ = 154.6, 139.1, 127.8, 125.3, 123.2, 121.1, 111.2, 110.5, 96.1, 71.8, 61.5, 31.0, 16.2.

IR (neat): 3333, 2946, 2878, 2227, 1568, 1450, 1350, 1254, 1190, 1040, 978, 884, 807, 749, 647, 448.

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₁₃H₁₃O₂: 201.0916, found: 201.0915

R_f = 0.21 (PE/AcOEt: 2/1).

1-Benzyl-2-(5-hydroxypent-1-yn-1-yl)-1H-indole-3-carbaldehyde (**5.26**)



5.26 was prepared according to the general procedure for shonogashira coupling, using 1-benzyl-2-bromo-1H-indole-3-carbaldehyde **5.16** (1.35 g, 4.3 mmol) with the modification of using NEt₃ (5.0 equiv.) and

DMF (1M) as solvent (because of solubility of the starting material). Purified by flash chromatography on silica gel (PE/AcOEt: 2/1 to 1/1). Yield 94% (1.28 g, 4.0 mmol) as a pale yellow solid.

Mp = 86–88°C from PE and AcOEt

¹H NMR (300 MHz, CDCl₃) δ = 10.18 (s, 1H), 8.37–8.23 (m, 1H), 7.34–7.09 (m, 9H), 5.37 (s, 2H), 3.76 (t, *J* = 6.1 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.50 (brs, 1H), 1.89 (quint, *J* = 6.8 Hz, 2H)

¹³C NMR (75 MHz, CDCl₃) δ = 185.6, 136.6, 136.1, 132.9, 128.9, 128.0, 126.7, 124.9, 124.6, 123.5, 122.0, 119.7, 110.5, 103.4, 69.6, 61.1, 48.3, 31.0, 16.4

IR (neat): 3378, 2226, 1646, 1497, 1451, 1427, 1377, 1333, 1185, 1060, 913, 809, 742, 699, 615, 522

HRMS (TOF MS ESI⁺) calcd for (M+H)⁺ C₂₁H₂₀NO₂: 318.1494, found: 318.1497

R_f = 0.21 (PE/AcOEt: 1/1)

P

A

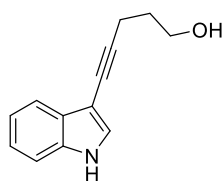
G

E

Deprotection of Ts Group

General Procedure for deprotection of Ts group: Indole (1.0 equiv.) was dissolved in MeOH (0.05 M) and Cs₂CO₃ (3.0 equiv.) was added into the reaction mixture at room temperature. The suspension was stirred at room temperature for 24 h (unless otherwise indicated). The volatiles were removed under reduced pressure and diluted with sat. aq. NH₄Cl. The resultant mixture was extracted with CH₂Cl₂ (x3). Combined organic layers were brined, dried over Na₂SO₄ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the corresponding the deprotected indole.

5-(1H-Indol-3-yl)pent-4-yn-1-ol (5.28)



5.28 was prepared according to the general procedure for deprotection of Ts group, using 5-(1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol **5.17** (3.11 g, 8.8 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 2/1 to

1/1). Yield 86% (1.50 g, 7.5 mmol) as a pale yellow solid.

Mp = 92–94°C from PE and AcOEt

¹H NMR (300 MHz, CDCl₃) δ = 8.26 (brs, 1H), 7.77 – 7.69 (m, 1H), 7.37 – 7.32 (m, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.27 – 7.15 (m, 2H), 3.89 (t, J = 6.1 Hz, 2H), 2.63 (t, J = 6.9 Hz, 2H), 1.97 – 1.85 (m, 2H), 1.84 (brs, 1H)

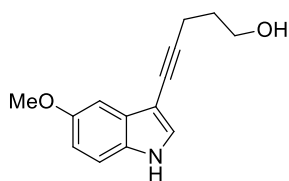
¹³C NMR (75 MHz, CDCl₃) δ = 135.3, 128.7, 127.4, 123.0, 120.6, 119.9, 111.4, 99.0, 90.6, 74.3, 62.2, 31.8, 16.5

IR (neat): 3382, 3055, 2931, 2223, 1621, 1536, 1456, 1421, 1352, 1329, 1246, 1102, 1077, 1050, 1002, 942, 811, 740, 624, 584, 528, 428

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₃H₁₄NO: 200.1075, found: 200.1077

R_f = 0.23 (PE/AcOEt: 2/1)

5-(5-Methoxy-1H-indol-3-yl)pent-4-yn-1-ol **5.29**



5.29 was prepared according to the general procedure for deprotection of Ts group, using 5-(5-methoxy-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol **5.18** (2.70 g, 7.0 mmol) with the modification of the reaction time to 48 h. Purified by flash chromatography on silica gel (PE/AcOEt: 1/1). Yield 90% (1.43 g, 6.4 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.22 (brs, 1H), 7.29 – 7.14 (m, 3H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 3.90 – 3.85 (m, 5H), 2.63 (t, J = 6.9 Hz, 2H), 2.97 – 1.86 (m, 2H), 1.84 (brs, 1H)

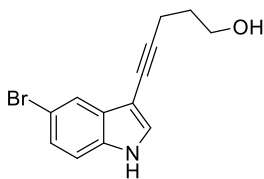
¹³C NMR (75 MHz, CDCl₃) δ = 154.9, 130.3, 129.3, 128.1, 113.5, 112.2, 101.4, 98.8, 90.7, 74.3, 62.2, 56.0, 31.8, 16.6

IR (neat): 3394, 2937, 2832, 2223, 1658, 1622, 1584, 1532, 1484, 1455, 1438, 1348, 1328, 1288, 1259, 1239, 1210, 1174, 1085, 1024, 946, 920, 837, 797, 749, 636, 556, 519, 429

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₄H₁₆NO₂: 230.1181, found: 230.1171

R_f = 0.33 (PE/AcOEt: 1/1)

5-(5-Bromo-1H-indol-3-yl)pent-4-yn-1-ol **5.30**



5.30 was prepared according to the general procedure for deprotection of Ts group, using 5-(5-bromo-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol **5.19** (2.16 g, 5.0 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 1/1). Yield 77% (1.68 g, 3.8 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.46 (brs, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.18 (d, J = 8.6 Hz, 1H), 3.86 (t, J = 6.1 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H), 1.94 (brs, 1H), 1.93 – 1.83 (m, 2H)

¹³C NMR (75 MHz, CDCl₃) δ = 133.9, 130.4, 128.5, 125.9, 122.5, 113.9, 112.9, 98.7, 91.1, 73.5, 62.1, 31.7, 16.4

P

A

G

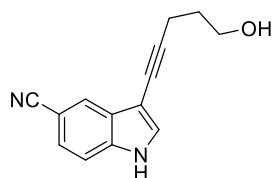
E

IR (neat): 3412, 3252, 2935, 2225, 1709, 1614, 1568, 1457, 1412, 1341, 1275, 1236, 1100, 1045, 941, 907, 884, 794, 731, 690, 582, 540, 491, 419

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₃H₁₃NO⁷⁹Br: 278.0181, found: 278.0172

R_f = 0.25 (PE/AcOEt: 1/1)

3-(5-Hydroxypent-1-yn-1-yl)-1H-indole-5-carbonitrile **5.31**



5.31 was prepared according to the general procedure for deprotection of Ts group, using 3-(5-hydroxypent-1-yn-1-yl)-1-tosyl-1H-indole-5-carbonitrile **5.20** (1.89 g, 5.0 mmol). Purified by flash chromatography

on silica gel (PE/AcOEt: 2/1 to 1/1). Yield 90% (1.01 g, 4.5 mmol) as a pale yellow solid.

Mp = 103–104°C from CH₂Cl₂

¹H NMR (300 MHz, CDCl₃) δ = 8.55 (brs, 1H), 8.07 – 8.05 (m, 1H), 7.48 – 7.40 (m, 3H), 3.91 – 3.85 (m, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 1.97 – 1.82 (m, 2H), 1.61 – 1.57 (m, 1H)

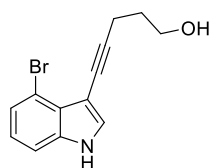
¹³C NMR (75 MHz, CDCl₃) δ = 136.8, 129.1, 128.7, 126.0, 125.8, 120.5, 112.4, 103.8, 100.6, 92.2, 72.5, 62.0, 31.7, 16.4

IR (neat): 3457, 3188, 3040, 2950, 2224, 1750, 1661, 1617, 1536, 1468, 1440, 1393, 1356, 1331, 1279, 1244, 1185, 1112, 1049, 995, 924, 908, 878, 815, 762, 736, 638, 536, 502, 417

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₄H₁₃N₂O: 225.1028, found: 225.1018

R_f = 0.23 (PE/AcOEt: 1/1)

5-(4-Bromo-1H-indol-3-yl)pent-4-yn-1-ol **5.32**



5.32 was prepared according to the general procedure for deprotection of Ts group, using 5-(4-bromo-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol **5.22** (2.90 g, 6.7 mmol). Purified by flash chromatography on silica gel

(cyclohexane/AcOEt: 2/1 to 1/1). Yield 85% (1.58 g, 5.7 mmol) as brown oil.

P

A

G

E

¹H NMR (300 MHz, CDCl₃) δ = 9.24 (brs, 1H), 7.37 (d, *J* = 2.7 Hz, 1H), 7.33 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.27 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 3.92 (t, *J* = 6.1 Hz, 2H), 3.02 (brs, 1H), 2.62 (t, *J* = 6.9 Hz, 2H), 1.94 (quint, *J* = 6.6 Hz, 2H)

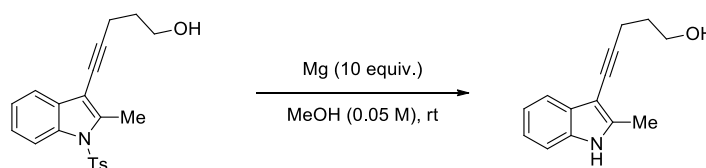
¹³C NMR (75 MHz, CDCl₃) δ = 136.1, 130.0, 125.8, 124.6, 123.4, 114.6, 111.1, 98.7, 91.3, 75.0, 61.9, 31.0, 16.4

IR (neat): 3237, 2931, 2865, 2223, 1646, 1612, 1560, 1517, 1480, 1412, 1329, 1306, 1190, 1142, 1108, 1047, 942, 910, 811, 773, 737, 596, 568, 515, 491

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₃H₁₃NO⁷⁹Br: 278.0181, found: 278.0174

Rf = 0.35 (cyclohexane/AcOEt: 1/1)

5-(2-Methyl-1H-indol-3-yl)pent-4-yn-1-ol **5.33**



To a solution of 5-(2-methyl-1-tosyl-1H-indol-3-yl)pent-4-yn-1-ol **5.21** (1.85 g, 5.0 mmol) in MeOH (100 mL) was added one portion of metal Mg (1.22 g, 50.2 mmol, 10 equiv.). After 24 h, three-quarters of the volume of solvent was evaporated in *vacuo* and sat. aq. NH₄Cl was added. The resultant mixture was extracted with CH₂Cl₂ (x4). Combined organic layers were brined, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (cyclohexane/AcOEt: 2/1 to 1/1) to yield **5.33** (65 % yield, 702.7 mg, 3.3 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.94 (brs, 1H), 7.64 – 7.56 (m, 1H), 7.28 – 7.21 (m, 1H), 7.18 – 7.10 (m, 2H), 3.90 (t, *J* = 6.1 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.47 (s, 3H), 1.98 – 1.87 (m, 2H), 1.73 (brs, 1H)

¹³C NMR (75 MHz, CDCl₃) δ = 139.1, 134.7, 129.3, 121.8, 120.1, 118.9, 110.7, 96.0, 92.1,

P

A

G

E

74.5, 61.9, 31.8, 16.5, 12.4

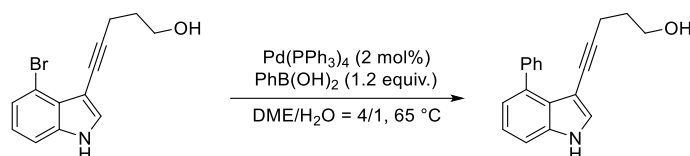
IR (neat): 3375, 3056, 2949, 2907, 2221, 1619, 1557, 1488, 1458, 1430, 1356, 1334, 1308, 1245, 1174, 1108, 1069, 1031, 1020, 925, 907, 842, 738, 674, 651, 614, 584, 534, 492, 457, 430

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₄H₁₆NO: 214.1232, found: 214.1223

R_f = 0.31 (cyclohexane/AcOEt: 1/1)

Suzuki Coupling

5-(4-phenyl-1H-indol-3-yl)pent-4-yn-1-ol **5.34**



A round Schlenk flask equipped with a stirring bar was charged with **5.32** (278.1 mg, 1.0 mmol), phenylboronic acid (146.3 mg, 1.2 mmol, 1.2 equiv.), Pd(PPh₃)₄ (23.1 mg, 0.02 mmol, 2 mol %), and K₃PO₄ (424.5 mg, 2.0 mmol, 2.0 equiv.). The Schlenk flask was evacuated and back-filled with Ar (3 times), and DME (4 mL) and H₂O (1 mL) were added. After the reaction mixture was stirred at 65 °C for 17 h, it was allowed to cool down to room temperature. The reaction mixture was diluted with AcOEt (30 mL), washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (cyclohexane/AcOEt: 2/1 to 1/1) to yield the title compound **5.34** (89% yield, 246.3 mg, 0.89 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.27 (brs, 1H), 7.52 – 7.45 (m, 2H), 7.36 – 7.22 (m, 5H), 7.20 – 7.13 (m, 1H), 6.98 (dd, J = 7.1, 1.1 Hz, 1H), 3.41 (t, J = 6.0 Hz, 2H), 2.10 (t, J = 6.8 Hz, 2H), 1.50 – 1.36 (m, 2H), 1.32 (brs, 1H)

¹³C NMR (75 MHz, CDCl₃) δ = 140.0, 136.0, 135.9, 130.4, 129.2, 127.2, 126.8, 124.8, 122.7, 122.3, 110.7, 98.5, 91.7, 75.9, 61.9, 31.1, 16.2

IR (neat): 3397, 3054, 2937, 2226, 1610, 1531, 1483, 1427, 1405, 1323, 1175, 1132, 1107, 1048, 942, 910, 822, 795, 748, 700, 598, 510

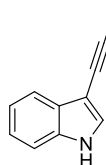
HRMS (TOF MS ESI⁺) calcd for (M+H)⁺ C₁₉H₁₈NO: 276.1388, found: 276.1376

R_f = 0.28 (cyclohexane/AcOEt: 1/1)

Oxidation of Alcohols

General Procedure for IBX oxidation: To a solution of alcohol (1 equiv.) in DMSO (0.2 M) was added in one portion IBX (1.2 equiv.). The reaction mixture was stirred at room temperature for 21 h. After that, water was added into the reaction mixture and the resultant suspension was filtered by Celite[®]. The filtrate was extracted with AcOEt (x3) and the combined organic layers were washed with water (x2), brined, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel or used without further purification.

5-(1H-Indol-3-yl)pent-4-ynal 5.35



5.35 was prepared according to the general procedure for IBX oxidation, using **6.28** (5185.2 mg, 0.93 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 3/1). Yield 95% (175.0 mg, 0.89 mmol) as a pale yellow solid.

Mp = 128–130°C from PE/AcOEt

¹H NMR (300 MHz, CDCl₃) δ = 9.89 (s, 1H), 8.22 (brs, 1H), 7.75 – 7.67 (m, 1H), 7.39 – 7.29 (m, 2H), 7.28 – 7.16 (m, 2H), 2.89– 2.75 (m, 4H)

¹³C NMR (75 MHz, CDCl₃) δ = 201.2, 135.2, 128.7, 127.6, 123.1, 120.7, 119.9, 111.4, 98.8, 89.1, 74.7, 43.1, 13.2

IR (neat): 3301, 1709, 1459, 1430, 1344, 1239, 1175, 1110, 1008, 826, 743, 654, 604, 585, 494, 431

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₃H₁₂NO: 198.0919, found: 198.0909

R_f = 0.24 (PE/AcOEt: 3/1)

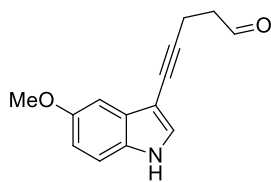
5-(5-Methoxy-1H-indol-3-yl)pent-4-ynal (5.36)

P

A

G

E



5.36 was prepared according to the general procedure for IBX oxidation, using **5.29** (536.4 mg, 2.34 mmol). The crude was used to the next reaction without further purification. Yield 97% (517.4 mg, 2.28 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.87 (s, 1H), 8.25 (brs, 1H), 7.27 (d, *J* = 2.7 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.88 (s, 3H), 2.88 – 2.74 (m, 4H)

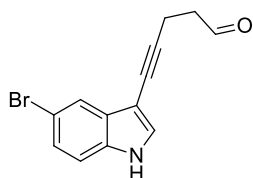
¹³C NMR (75 MHz, CDCl₃) δ = 201.2, 155.0, 130.3, 129.2, 128.2, 113.5, 112.3, 101.3, 98.4, 89.1, 74.8, 55.9, 43.1, 13.3

IR (neat): 3390, 2933, 2827, 2177, 1718, 1621, 1583, 1483, 1455, 1438, 1330, 1288, 1259, 1210, 1175, 1086, 1026, 908, 838, 798, 728, 636, 520, 430

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₄H₁₄NO₂: 228.1025, found: 228.1019

R_f = 0.35 (Pentane/AcOEt: 2/1)

5-(5-Bromo-1H-indol-3-yl)pent-4-ynal (**5.37**)



5.37 was prepared according to the general procedure for IBX oxidation, using **5.30** (556.3 mg, 2.0 mmol). The crude was used without further purification. Yield 96% (533.7 mg, 1.93 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.89 (s, 1H), 8.38 (brs, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.21 (d, *J* = 8.6 Hz, 1H), 2.81 (s, 4H)

¹³C NMR (75 MHz, CDCl₃) δ = 201.1, 133.9, 130.4, 128.6, 126.0, 122.5, 114.1, 112.9, 98.6, 89.6, 73.9, 43.1, 13.1

IR (neat): 3280, 1707, 1458, 1421, 1359, 1275, 1233, 1102, 1048, 877, 791, 670, 654, 614, 546, 418

HRMS (TOF MS ESI-) calcd for (M-H)⁻ C₁₃H₉NO⁷⁹Br: 273.9868, found: 273.9864

P

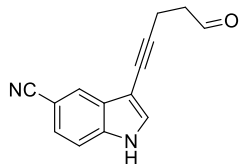
A

G

E

R_f = 0.26 (Pentane/AcOEt: 2/1)

3-(5-Oxopent-1-yn-1-yl)-1H-indole-5-carbonitrile **5.38**



5.38 was as prepared according to the general procedure for IBX oxidation, using **5.31** (445.6 mg, 1.99 mmol). The crude was used to the next reaction without further purification. Yield 97% (427.3 mg, 1.92 mmol) as yellow

oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.89 (s, 1H), 8.55 (brs, 1H), 8.04 (s, 1H), 7.49 – 7.40 (m, 3H), 2.83 (s, 4H)

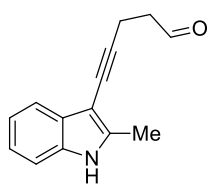
¹³C NMR (75 MHz, CDCl₃) δ = 200.9, 136.9, 129.6, 128.5, 125.9, 125.6, 120.6, 112.6, 103.6, 100.0, 90.5, 73.1, 43.0, 13.1

IR (neat): 3306, 2906, 2220, 1719, 1617, 1471, 1426, 1357, 1330, 1290, 1243, 1183, 1099, 1055, 908, 805, 729, 638, 496, 417

HRMS (TOF MS ESI-) calcd for (M-H)⁻ C₁₄H₉N₂O: 221.0715, found: 221.0717

R_f = 0.21 (Pentane/AcOEt: 2/1)

5-(2-Methyl-1H-indol-3-yl)pent-4-ynal (**5.39**)



5.39 was prepared according to the general procedure for IBX oxidation, using **5.33** (324.2 mg, 1.52 mmol). The crude was used to the next reaction without further purification. Yield 96% (309.1 mg, 1.46 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.90 (s, 2H), 8.03 (brs, 1H), 7.61– 7.54 (m, 1H), 7.26 – 7.18 (m, 2H), 7.16 – 7.08 (m, 2H), 2.90 – 2.75 (m, 4H), 2.46 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 201.6, 139.3, 134.7, 129.2, 121.8, 120.2, 118.8, 110.7, 95.8, 90.5, 75.0, 43.2, 13.3, 12.4

IR (neat): 3386, 3060, 2915, 2842, 2227, 1718, 1616, 1458, 1430, 1331, 1245, 1173, 1013, 908,

P

A

G

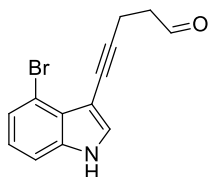
E

729, 661, 576, 541, 432

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₄H₁₄NO: 212.1075, found: 212.1069

R_f = 0.21 (Cyclohexane/AcOEt: 2/1)

5-(4-Bromo-1H-indol-3-yl)pent-4-ynal **5.40**



5.40 was prepared according to the general procedure for IBX oxidation, using **5.32** (262.0 mg, 0.94 mmol). The crude was used to the next reaction without further purification. Yield 90% (234.7 mg, 0.85 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.90 (s, 1H), 8.32 (brs, 1H), 7.37 (d, *J* = 2.7 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.07 – 6.98 (t, *J* = 7.8 Hz, 1H), 2.80 (s, 4H)

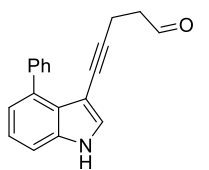
¹³C NMR (75 MHz, CDCl₃) δ = 201.9, 136.2, 129.7, 126.1, 124.9, 123.7, 114.9, 111.1, 99.1, 89.8, 75.3, 42.4, 13.3

IR (neat): 3396, 2918, 1717, 1559, 1417, 1331, 1306, 1191, 1047, 911, 812, 774, 738, 597

HRMS (TOF MS ES+) calcd for (M+H₃O)⁺ C₁₃H₁₃NO₂⁷⁹Br: 294.0130, found: 294.0128

R_f = 0.31 (Cyclohexane/AcOEt: 3/1)

5-(4-Phenyl-1H-indol-3-yl)pent-4-ynal **5.41**



5.41 was prepared according to the general procedure for IBX oxidation, using **5.34** (97.7 mg, 0.35 mmol). The crude was used for the next reaction without further purification. Yield 96% (93.4 mg, 0.34 mmol) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.59 (t, *J* = 1.3 Hz, 1H), 8.37 (brs, 1H), 7.62 – 7.51 (m, 2H), 7.46 – 7.32 (m, 5H), 7.31 – 7.22 (m, 1H), 7.08 (dd, *J* = 7.1, 1.1 Hz, 1H), 2.46 – 2.27 (m, 4H)

¹³C NMR (75 MHz, CDCl₃) δ = 201.6, 140.0, 136.1, 135.9, 130.4, 129.1, 127.2, 126.9, 124.9, 122.9, 122.4, 110.7, 98.6, 90.2, 76.0, 42.6, 13.0

IR (neat): 3355, 3060, 3034, 2968, 2935, 1706, 1598, 1509, 1455, 1403, 1329, 1213, 1176,

P

A

G

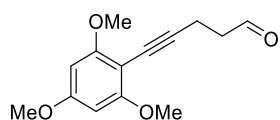
E

1050, 1027, 748, 697, 596, 520, 455

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₁₉H₁₆NO: 274.1232, found: 274.1233

R_f = 0.20 (Cyclohexane/AcOEt: 3/1)

5-(2,4,6-Trimethoxyphenyl)pent-4-ynal (5.41)



5.41 was as prepared according to the general procedure for IBX oxidation, using **5.23** (824.9 mg, 2.84 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 2/1). Yield 93% (658.0 mg, 2.65 mmol) as yellow solid.

Mp = 86-88°C (PE/AcOEt)

¹H NMR (300 MHz, CDCl₃) δ = 9.85 (t, *J* = 1.4 Hz, 1H), 6.05 (s, 2H), 3.81 (s, 6H), 3.78 (s, 3H), 2.85 – 2.71 (m, 4H)

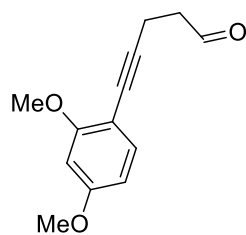
¹³C NMR (75 MHz, CDCl₃) δ = 201.4, 162.3, 161.2, 94.5, 94.4, 90.5, 73.8, 56.1, 55.4, 42.9, 13.7

IR (neat): 2933, 2842, 2720, 1721, 1464, 1600, 1579, 1416, 1337, 1229, 1208, 1158, 1120, 1061, 1026, 818, 799, 730

HRMS (EI) calcd for (M)⁺ C₁₄H₁₆O₄: 248.1049, found: 248.1054.

R_f = 0.24 (PE/AcOEt: 2/1)

5-(2,4-Dimethoxyphenyl)pent-4-ynal 5.43



5.43 was prepared according to the general procedure for IBX oxidation, using **5.24** (230.7 mg, 1.05 mmol). The crude was used without further purification. Yield 98% (224.0 mg, 1.03 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.83 – 9.80 (m, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 6.44 – 6.37 (m, 4H), 3.82 (s, 3H), 3.77 (s, 3H), 2.80 – 2.69 (m, 4H)

P

A

G

E

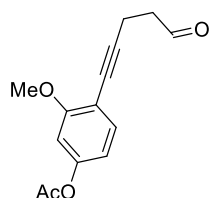
^{13}C NMR (75 MHz, CDCl_3) δ = 200.8, 161.0, 160.7, 134.1, 104.9, 104.6, 98.2, 90.1, 77.5, 55.6, 55.2, 42.6, 13.0

IR (neat): 3004, 2932, 2839, 2728, 1723, 1605, 1572, 1505, 1456, 1439, 1415, 1301, 1275, 1241, 1208, 1159, 1130, 1114, 1027, 934, 827, 800, 636, 542, 487

HRMS (EI) calcd for $(\text{M})^+$ $\text{C}_{13}\text{H}_{14}\text{O}_3$: 218.0943, found: 218.0946

R_f = 0.28 (cyclohexane/AcOEt: 3/1)

3-Methoxy-4-(5-oxopent-1-yn-1-yl)phenyl acetate (5.44)



5.44 was prepared according to the general procedure for IBX oxidation, using **5.25** (121.8 mg, 0.49 mmol). The crude was used without further purification. Yield 94% (113.7 mg, 0.46 mmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) δ = 9.81 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.64 – 6.57 (m, 2H), 3.81 (s, 3H), 2.74 (s, 4H), 2.25 (s, 3H)

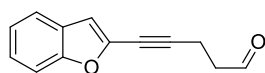
^{13}C NMR (75 MHz, CDCl_3) δ = 200.7, 169.1, 160.7, 151.3, 133.9, 113.5, 110.2, 104.9, 91.9, 77.0, 56.0, 42.6, 21.1, 13.1

IR (neat): 2973, 2905, 2833, 2734, 1762, 1723, 1602, 1583, 1499, 1466, 1451, 1409, 1369, 1275, 1201, 1186, 1150, 1117, 1030, 956, 893, 839, 815, 626, 586, 543

HRMS (IC) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{14}\text{H}_{15}\text{O}_4$: 247.09703, found: 247.09585

R_f = 0.27 (cyclohexane/AcOEt: 2/1)

5-(Benzofuran-2-yl)pent-4-ynal 5.45



5.45 was prepared according to the general procedure for IBX oxidation, using **5.27** (493.3 mg, 2.46 mmol). The crude was used without further purification. Yield 88% (430.0 mg, 2.17 mmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) δ = 9.86 (s, 1H), 7.56 – 7.50 (m, 1H), 7.42 (dd, J = 8.2, 0.7 Hz,

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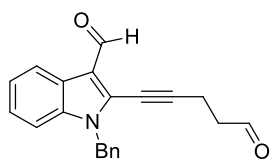
1H), 7.35 – 7.27 (m, 1H), 7.25 – 7.18 (m, 1H), 6.84 (d, $J = 0.7$ Hz, 1H), 2.86 – 2.80 (m, 4H)
 ^{13}C NMR (75 MHz, CDCl_3) $\delta = 199.6, 154.5, 138.7, 127.6, 125.4, 123.2, 121.1, 111.1, 110.8,$
94.5, 72.0, 42.0, 12.7

IR (neat): 2989, 2831, 2724, 2234, 1722, 1568, 1449, 1351, 1306, 1253, 1198, 1142, 1108,
1003, 964, 884, 809, 749, 647, 613, 446

HRMS (IC) calcd for $(\text{M})^+ \text{C}_{11}\text{H}_{11}\text{O}_2$: 199.0759, found: 199.0749

$R_f = 0.21$ (cyclohexane: $\text{CH}_2\text{Cl}_2 = 2/1$)

Benzyl-2-(5-oxopent-1-yn-1-yl)-1H-indole-3-carbaldehyde (5.46)



5.46 was as prepared according to the general procedure for IBX oxidation, using **5.26** (1.08 g, 3.18 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 2/1 to 1/1). Yield 75% (745.8

mg, 2.37 mmol) as a yellow solid.

$\text{Mp} = 88\text{--}89^\circ\text{C}$ from PE/AcOEt

^1H NMR (300 MHz, CDCl_3) $\delta = 10.07$ (s, 1H), 9.68 (s, 1H), 8.23 – 8.20 (m, 1H), 7.22 – 7.10 (m, 6H) 7.07 – 7.04 (m, 2H), 5.32 (s, 2H), 2.78 – 2.67 (m, 4H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 199.1, 185.4, 136.7, 136.1, 132.2, 129.0, 128.0, 126.8, 125.1,$
124.6, 123.6, 122.2, 120.1, 110.5, 101.3, 70.1, 48.4, 42.0, 13.0

IR (neat): 2842, 2745, 2236, 1727, 1519, 1443, 1430, 1387, 1345, 1230, 1230, 1124, 1043, 962,
743, 728, 699, 560, 457

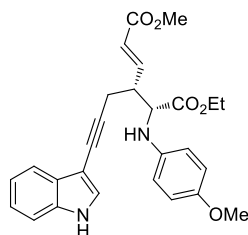
HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+ \text{C}_{22}\text{H}_{18}\text{NO}_2$: 316.1338, found: 316.1346

$R_f = 0.18$ (PE/AcOEt: 2/1)

General procedure for enantioselective Mannich reaction

Aldehyde (1.0 equiv.) and imine **1.71** (1.05 equiv.) were dissolved in DMF (0.33 M). The resultant solution was cooled to -40°C and catalyst **1.139** (0.1 equiv) was added into the reaction mixture in one portion. The reaction mixture was stirred at -40°C for 7 h. The reaction mixture was diluted with CH_2Cl_2 (0.17 M) and ylide **5.48** (1.0 equiv.) was added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred. After 1 h, water was added and the resultant mixture was extracted with AcOEt (x3). Combined organic layers were brined, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure to give a crude compound which was purified by flash column chromatography on silica gel.

(E)-6-Ethyl 1-methyl 4-(3-(1H-indol-3-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate **5.50**



5.50 was prepared according to the general procedure using aldehyde **5.35** (360.0 mg, 1.82 mmol). Purified by flash chromatography on silica gel (PE/AcOEt: 3/1). Yield 66% (552.2 mg, 1.20 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.75 (brs, 1H), 7.76 (dd, J = 6.4, 2.3 Hz, 1H), 7.35 – 7.14 (m, 4H), 7.04 (dd, J = 15.7, 8.7 Hz, 1H), 6.88 – 6.71 (m, 4H), 6.07 (d, J = 15.7 Hz, 1H), 4.53 (brs, 1H), 4.29 – 4.08 (m, 2H), 4.02 (brs, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.25 – 3.10 (m, 1H), 2.97 (dd, J = 16.7, 8.3 Hz, 1H), 2.76 (dd, J = 16.7, 5.8 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 172.9, 166.4, 153.2, 146.1, 141.3, 135.2, 128.6, 127.9, 123.8, 122.8, 120.4, 119.7, 116.4, 114.9, 111.5, 98.2, 87.5, 76.8, 61.5, 60.8, 55.6, 51.7, 45.0, 22.0, 14.2

IR (neat): 3286, 2929, 1723, 1660, 1511, 1436, 1387, 1238, 1180, 1093, 1032, 823, 745, 660, 513, 426

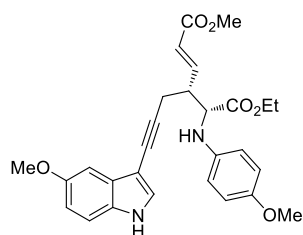
HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_5$: 461.2076, found: 461.2066

HPLC: Daicel Chiralpak[®] IA (60% n-heptane, 40% isopropanol), 20°C, 1 mL/min, 254 nm, t_1 = 6.1 min (major), t_2 = 9.1 min (minor). 98% ee;

$[\alpha]^{20}_D +2.4$ (c 1.01, CHCl₃)

$R_f = 0.32$ (PE/AcOEt: 2/1)

(E)-6-Ethyl 1-methyl 4-(3-(5-methoxy-1H-indol-3-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.51



5.51 was prepared according to the general procedure using aldehyde **5.36** (298.5 mg, 1.31 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 2/1). Yield 52% (332.1 mg, 0.68 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.43 (brs, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 15.7, 8.7 Hz, 1H), 6.88 (dd, J = 8.8, 2.4 Hz, 1H), 6.82 – 6.71 (m, 4H), 6.03 (dd, J = 15.7, 0.9 Hz, 1H), 4.48 (brs, 1H), 4.27 – 4.12 (m, 2H), 4.02 – 3.91 (m, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.22 – 4.07 (m, 1H), 2.96 (dd, J = 16.7, 8.2 Hz, 1H), 2.74 (dd, J = 16.7, 5.9 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 172.9, 166.4, 155.0, 153.3, 146.2, 141.4, 130.3, 129.3, 128.4, 123.8, 116.5, 115.0, 113.5, 112.3, 101.3, 98.3, 87.7, 76.84, 61.6, 61.0, 55.8, 55.7, 51.8, 45.1, 22.1, 14.3

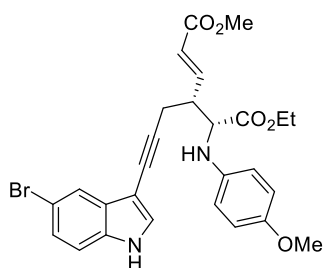
IR (neat): 3364, 2946, 1721, 1653, 1511, 1485, 1438, 1237, 1211, 1176, 1096, 1027, 911, 820, 800, 730, 520

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₈H₃₁N₂O₆: 491.2182, found: 491.2173

$[\alpha]^{20}_D -3.2$ (c 1.10, CHCl₃)

$R_f = 0.25$ (Pentane/AcOEt: 2/1)

(E)-6-Ethyl 1-methyl 4-(3-(5-bromo-1H-indol-3-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.52



5.52 was as prepared according to the general procedure using aldehyde **5.37** (414.2 mg, 1.50 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 2/1). Yield 58% (470.7 mg, 0.87 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.58 (brs, 1H), 7.85 (d, J = 1.9 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 6.98 (dd, J = 15.7, 8.7 Hz, 1H), 6.77 (s, 4H), 6.03 (dd, J = 15.7, 1.0 Hz, 1H), 4.43 (brs, 1H), 4.28 – 4.13 (m, 2H), 3.91 (brs, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.20 – 3.06 (m, 1H), 2.93 (dd, J = 16.8, 8.2 Hz, 1H), 2.71 (dd, J = 16.8, 5.8 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 173.0, 166.5, 153.4, 146.0, 141.3, 133.9, 130.4, 128.8, 126.0, 124.0, 122.5, 116.5, 115.0, 114.1, 113.0, 98.4, 88.2, 76.0, 61.7, 61.0, 55.8, 51.9, 45.1, 22.1, 14.4

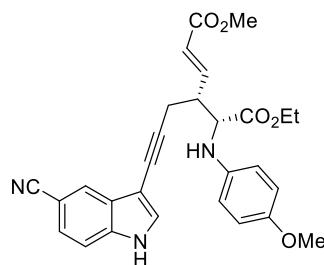
IR (neat): 3351, 2956, 2832, 1719, 1658, 1510, 1457, 1276, 1235, 1179, 1138, 1099, 1031, 886, 822, 796, 730, 611, 544, 513, 421

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_5^{79}\text{Br}$: 539.1182, found: 539.1168

$[\alpha]^{20}_{\text{D}}$ +3.3 (c 0.10, CHCl_3)

R_f = 0.17 (Pentane/AcOEt: 2/1)

(E)-6-Ethyl 1-methyl 4-(3-(5-cyano-1H-indol-3-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.53



5.53 was prepared according to the general procedure using aldehyde **5.38** (420.5 mg, 1.89 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 3/2). Yield 65% (595.5 mg, 1.23 mmol) as yellow oil.

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¹H NMR (300 MHz, CDCl₃) δ = 9.15 (brs, 1H), 8.03 (s, 1H), 7.45–7.37 (m, 3H), 6.99 (dd, *J* = 15.7, 8.7 Hz, 1H), 6.82 – 6.69 (m, 4H), 6.05 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.43 (brs, 1H), 4.29 – 4.13 (m, 2H), 3.94 (brs, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.21 – 3.06 (m, 1H), 2.93 (dd, *J* = 16.8, 7.8 Hz, 1H), 2.73 (dd, *J* = 16.8, 6.2 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 172.8, 166.5, 153.4, 145.9, 141.2, 137.0, 129.8, 128.6, 125.8, 125.5, 124.1, 120.5, 116.4, 115.0, 112.7, 103.6, 99.6, 89.1, 75.2, 61.8, 61.0, 55.8, 52.0, 44.9, 22.0, 14.4

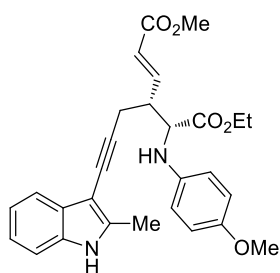
IR (neat): 3342, 2951, 2834, 2222, 1720, 1657, 1618, 1471, 1511, 1435, 1366, 1289, 1238, 1180, 1099, 1030, 983, 912, 819, 729, 639, 498, 417

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₈H₂₈N₃O₅: 486.2029, found: 486.2053

[α]_D²⁰ +3.5 (*c* 1.13, CHCl₃)

R_f = 0.23 (Pentane/AcOEt: 3/2)

(4*R*,5*R*,*E*)-6-Ethyl 1-methyl 5-((4-methoxyphenyl)amino)-4-(3-(2-methyl-1*H*-indol-3-yl)prop-2-yn-1-yl)hex-2-enedioate 5.54



5.54 was prepared according to the general procedure using aldehyde **5.39** (103.5 mg, 0.476 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1 to 5/2). Yield 45% (100.8 mg, 0.212 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.02 (s, 1H), 7.64 – 7.58 (m, 1H), 7.29 – 7.24 (m, 1H), 7.17 – 7.12 (m, 2H), 6.98 (dd, *J* = 15.7, 8.7 Hz, 1H), 6.80 – 6.74 (m, 4H), 6.02 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.49 (s, 1H), 4.26 – 4.14 (m, 2H), 3.93 (brs, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.21 – 3.07 (m, 1H), 2.96 (dd, *J* = 16.6, 8.4 Hz, 1H), 2.75 (dd, *J* = 16.6, 5.7 Hz, 1H), 2.49 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 173.0, 166.4, 153.4, 146.2, 141.5, 139.2, 134.8, 129.5, 123.9,

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122.2, 120.5, 119.2, 116.5, 115.0, 110.6, 96.4, 89.4, 76.9, 61.6, 61.0, 55.8, 51.8, 45.4, 22.3, 14.4, 12.8

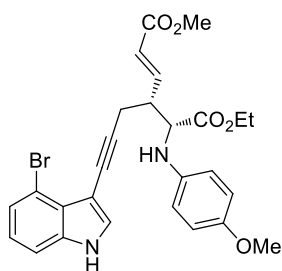
IR (neat): 3364, 2983, 2950, 2901, 2836, 2175, 1722, 1611, 1511, 1459, 1241, 1177, 1030, 823, 744, 500, 406

HRMS (TOF MS ES+) calcd for (M+H)⁺ C₂₈H₃₁N₂O₅: 475.2233, found: 475.2225

[α]²⁰_D +2.5 (c 0.20, CHCl₃)

Rf = 0.37 (cyclohexane/AcOEt: 5/2)

(4R,5R,E)-6-Ethyl 1-methyl 4-(3-(4-bromo-1H-indol-3-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.55



5.55 was prepared according to the general procedure using aldehyde **5.40** (123.1 mg, 0.446 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1 to 5/2). Yield 60% (144.4 mg, 0.268 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.48 (s, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.07 – 6.92 (m, 2H), 6.80 – 6.71 (m, 4H), 5.99 (dd, *J* = 15.8, 1.0 Hz, 1H), 4.56 (d, *J* = 4.0 Hz, 1H), 4.24 – 4.14 (m, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 3.25 – 3.12 (m, 1H), 2.97 – 2.86 (m, 1H), 2.69 (dd, *J* = 16.7, 5.4 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 173.1, 166.5, 153.3, 146.3, 141.5, 136.2, 130.1, 126.3, 125.1, 123.9, 123.9, 116.5, 115.3, 115.0, 111.0, 99.6, 88.6, 76.9, 61.7, 60.9, 55.8, 51.8, 44.7, 22.2, 14.4

IR (neat): 3350, 2949, 2906, 2830, 2181, 1721, 1658, 1611, 1510, 1436, 1368, 1305, 1239, 1190, 1030, 911, 823, 774, 737, 597, 494

HRMS (TOF MS ES+) calcd for (M+H)⁺ C₂₇H₂₈N₂O₅⁷⁹Br: 539.1182, found: 539.1174

[α]²⁰_D –4.6 (c 1.03, CHCl₃)

Rf = 0.14 (cyclohexane/AcOEt: 5/2)

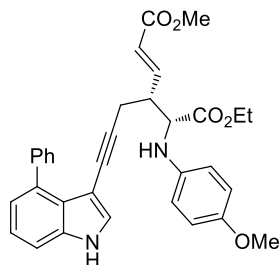
P

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(4R,5R,E)-6-ethyl 1-methyl 5-((4-methoxyphenyl)amino)-4-(3-(4-phenyl-1H-indol-3-yl)prop-2-yn-1-yl)hex-2-enedioate 5.56



5.56 was prepared according to the general procedure using aldehyde **5.41** (92.3 mg, 0.338 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1 to 5/2). Yield 53% (96.1 mg, 0.179 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.38 (brs, 1H), 7.59 – 7.51 (m, 2H), 7.43 – 7.24 (m, 6H), 7.09 (dd, J = 7.2, 1.0 Hz, 1H), 6.83 – 6.64 (m, 5H), 5.82 (dd, J = 15.7, 1.0 Hz, 1H), 4.24 – 4.09 (m, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 2.77 – 2.64 (m, 1H), 2.51 (dd, J = 16.6, 8.2 Hz, 1H), 2.24 (dd, J = 16.6, 6.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 172.8, 166.4, 153.3, 146.2, 141.5, 139.8, 136.3, 135.9, 130.39, 129.2, 127.1, 126.9, 125.0, 123.7, 123.0, 122.4, 116.5, 114.9, 110.6, 98.8, 89.1, 77.7, 61.5, 60.9, 55.9, 51.8, 44.6, 21.9, 14.4

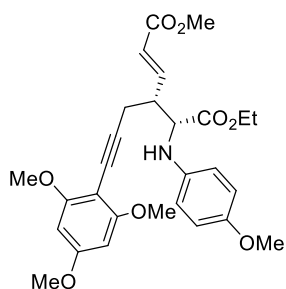
IR (neat): 3386, 2924, 2853, 1721, 1650, 1508, 1436, 1372, 1241, 1173, 1032, 983, 912, 824, 795, 749, 704, 593, 568, 482, 414

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₃₃H₃₃N₂O₅: 537.2389, found: 537.2402

$[\alpha]_D^{20}$ +8.3 (c 1.05, CHCl₃)

R_f = 0.14 (cyclohexane/AcOEt: 5/2)

(4R,5R,E)-6-Ethyl 1-methyl 5-((4-methoxyphenyl)amino)-4-(3-(2,4,6-trimethoxyphenyl)prop-2-yn-1-yl)hex-2-enedioate 5.69



5.69 was prepared according to the general procedure using **5.42** (248.3 mg, 1.0 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 4/1 to 3/1). Yield 71% (365.6 mg, 0.71 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 6.94 (dd, J = 15.7, 8.7 Hz, 1H), 6.83 – 6.70 (m, 4H), 6.11 (s, 2H), 5.96 (dd, J = 15.7, 0.9 Hz, 1H), 4.58 (d, J = 3.9 Hz, 1H), 4.24 – 4.11 (m, 2H), 3.93 (brs, 1H), 3.84 – 3.82 (m, 9H), 3.74 (s, 3H), 3.72 (s, 3H), 3.17 – 3.08 (m, 1H), 2.94 (dd, J = 16.7, 8.9 Hz, 1H), 2.69 (dd, J = 16.7, 5.3 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 173.1, 166.4, 162.5, 161.3, 153.2, 146.2, 141.7, 123.8, 116.6, 114.8, 94.6, 93.5, 90.5, 75.8, 61.5, 60.9, 56.0, 55.8, 55.5, 51.7, 45.2, 22.5, 14.4

IR (neat): 3365, 2939, 2839, 1722, 1658, 1602, 1579, 1511, 1462, 1437, 1415, 1339, 1227, 1204, 1156, 1125, 1031, 947, 814, 736, 636, 471

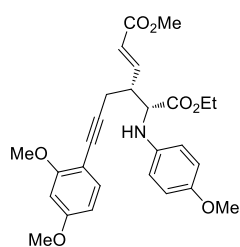
HRMS (TOF MS ES+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{28}\text{H}_{34}\text{NO}_8$: 512.2284, found: 512.2275

HPLC: Daicel Chiralpak[®] IA (50% n-heptane, 50% iPrOH), 20°C, 1 mL/min, 220 nm, t_1 = 8.8 min (major), t_2 = 13.5 min (minor). 94% ee

$[\alpha]_D^{20} +15$ (c 1.00, CHCl_3)

R_f = 0.15 (PE/AcOEt: 3/1)

(4R,5R,E)-6-Ethyl 1-methyl 4-(3-(2,4-dimethoxyphenyl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.66



5.66 was as prepared according to the general procedure, using aldehyde **5.43** (75.1 mg, 0.344 mmol). Purified by flash chromatography on silica gel (toluene/AcOEt: 20/1 to 10/1). Yield 59% (98.5 mg, 0.205 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.30 (d, J = 9.0 Hz, 1H), 6.92 (dd, J = 15.7, 8.7 Hz, 1H), 6.83

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– 6.71 (m, 4H), 6.48 – 6.40 (m, 2H), 5.96 (dd, $J = 15.7, 0.9$ Hz, 1H), 4.47 (d, $J = 3.8$ Hz, 1H), 4.25 – 4.10 (m, 2H), 3.91 (brs, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.17 – 3.04 (m, 1H), 2.89 (dd, $J = 16.7, 8.6$ Hz, 1H), 2.65 (dd, $J = 16.7, 5.6$ Hz, 1H), 1.24 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) $\delta = 173.0, 166.4, 161.5, 161.0, 153.4, 146.1, 141.6, 134.2, 123.9, 116.6, 114.9, 105.2, 104.8, 98.6, 89.2, 79.6, 61.6, 61.0, 55.8, 55.8, 55.6, 51.8, 45.1, 22.1, 14.4$

IR (neat): 3356, 2949, 2839, 1722, 1606, 1507, 1463, 1438, 1417, 1300, 1277, 1238, 1208, 1160, 1130, 1113, 1029, 984, 933, 823, 734, 637, 606, 484

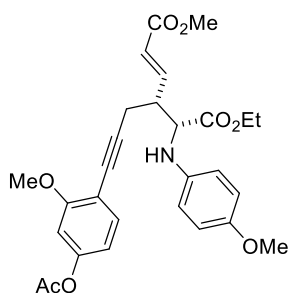
HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{27}\text{H}_{32}\text{NO}_7$: 482.2179, found: 482.2184

HPLC: Daicel Chiralpak[®] IA (70% n-heptane, 30% iPrOH), 20°C, 1 mL/min, 254 nm, $t_1 = 9.5$ min (major), $t_2 = 13.8$ min (minor). 93% ee

$[\alpha]^{20}_{\text{D}} +8.8$ (c 0.80, CHCl_3)

$R_f = 0.26$ (toluene/AcOEt: 10/1)

6-Ethyl 1-methyl (4R,5R,E)-4-(3-(4-acetoxy-2-methoxyphenyl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.74



rac-**5.74** was as prepared according to the general procedure, using aldehyde **5.44** (108.8 mg, 0.44 mmol). Purified by flash chromatography on silica gel (Toluene/AcOEt: 10/1 and Cyclohexane/AcOEt: 4/1 to 3/1). Yield 47% (105.3 mg, 0.21 mmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) $\delta = 7.39$ – 7.33 (m, 1H), 6.92 (dd, $J = 15.7, 8.7$ Hz, 1H), 6.81 – 6.71 (m, 4H), 6.69 – 6.62 (m, 2H), 5.96 (dd, $J = 15.7, 0.9$ Hz, 1H), 4.45 (d, $J = 4.2$ Hz, 1H), 4.25 – 4.11 (m, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.17 – 3.04 (m, 1H), 2.89 (dd, $J = 16.8, 8.6$ Hz, 1H), 2.65 (dd, $J = 16.8, 5.7$ Hz, 1H), 2.30 (s, 3H), 1.24 (t, $J = 7.1$ Hz, 3H)

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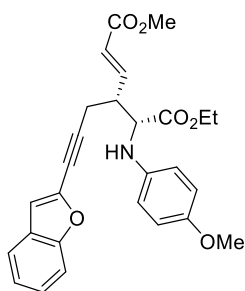
^{13}C NMR (75 MHz, CDCl_3) δ = 172.9, 169.3, 166.3, 161.1, 153.4, 151.5, 145.8, 141.4, 133.8, 124.0, 116.6, 114.9, 113.6, 110.4, 105.0, 90.9, 79.0, 61.6, 60.9, 56.0, 55.8, 51.8, 45.0, 22.0, 21.3, 14.4

IR (neat): 3372, 3954, 2910, 2844, 1728, 1602, 1512, 1369, 1276, 1203, 1153, 1031, 824

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{28}\text{H}_{32}\text{NO}_8$: 510.2128, found: 510.2122

R_f = 0.11 (cyclohexane/AcOEt: 3/1)

(4R,5R,E)-6-Ethyl 1-methyl 4-(3-(benzofuran-2-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.58



rac-**5.58** was as prepared according to the general procedure, using aldehyde **5.45** (213.7 mg, 1.08 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 6/1 to 4/1). Yield 74% (369.8 mg, 0.80 mmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) δ = 7.58 – 7.52 (m, 1H), 7.49 – 7.43 (m, 1H), 7.38 – 7.30 (m, 1H), 7.28 – 7.21 (m, 1H), 6.98 – 6.87 (m, 2H), 6.83 – 6.73 (m, 4H), 6.00 (dd, J = 15.7, 1.0 Hz, 1H), 4.37 (d, J = 4.2 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.94 (brs, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.23 – 3.10 (m, 1H), 2.97 (dd, J = 17.0, 8.0 Hz, 1H), 2.73 (dd, J = 17.0, 6.2 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ = 172.4, 166.1, 154.7, 153.5, 145.2, 141.1, 138.6, 127.6, 125.5, 124.2, 123.3, 121.2, 116.5, 114.9, 111.2, 111.1, 93.3, 74.0, 61.7, 61.0, 55.7, 51.8, 44.3, 21.8, 14.3.

IR (neat): 3363, 2951, 2834, 2227, 1722, 1511, 1449, 1237, 1189, 1142, 1033, 820, 750, 610, 450

HRMS (TOF MS ES+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{27}\text{H}_{26}\text{NO}_6$: 462.1917, found: 462.1917

R_f = 0.19 (Cyclohexane/AcOEt: 4/1)

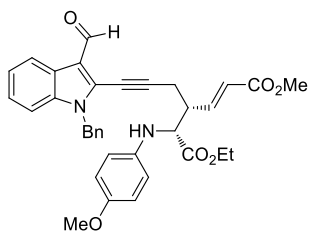
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(4R,5R,E)-6-ethyl 1-methyl 4-(3-(1-benzyl-3-formyl-1H-indol-2-yl)prop-2-yn-1-yl)-5-((4-methoxyphenyl)amino)hex-2-enedioate 5.59



5.59 was prepared according to the general procedure with the modification of the reaction time of Mannich reaction to 21 h using aldehyde **5.46** (630.7 mg, 2.00 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 5/2). Yield 66%

(765.0 mg, 1.32 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 10.22 (s, 1H), 8.37 – 8.28 (m, 1H), 7.34 – 7.10 (m, 9H), 6.91 (dd, J = 15.7, 8.7 Hz, 1H), 6.77 – 6.68 (m, 2H), 6.67 – 6.58 (m, 2H), 5.97 (dd, J = 15.7, 0.9 Hz, 1H), 5.44 (s, 2H), 4.30 – 4.09 (m, 3H), 3.89 (brs, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.20 – 3.08 (m, 1H), 3.02 (dd, J = 17.1, 7.1 Hz, 1H), 2.84 (dd, J = 17.1, 6.9 Hz, 1H), 1.25 (t, J = 7.1 Hz, 1H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 185.3, 172.1, 166.0, 153.6, 144.8, 140.8, 136.8, 136.0, 131.7, 129.1, 128.1, 126.8, 125.2, 124.7, 124.6, 123.7, 122.3, 120.5, 116.3, 115.0, 110.6, 99.8, 72.0, 61.9, 61.0, 55.8, 51.9, 48.6, 44.5, 22.3, 14.4

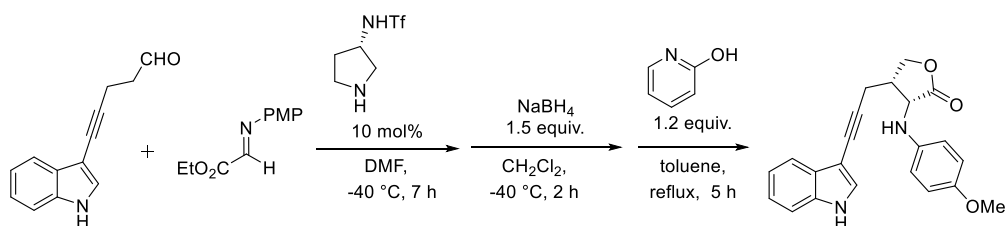
IR (neat): 3364, 2933, 2232, 1724, 1650, 1511, 1454, 1427, 1382, 1239, 1180, 1030 821, 747, 732, 700, 564, 458

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{35}\text{H}_{35}\text{N}_2\text{O}_6$: 579.2495, found: 579.2504

$[\alpha]^{20}_{\text{D}}$ –40.0 (c 0.10, CHCl_3)

R_f = 0.27 (PE/AcOEt: 5/2)

(3R,4S)-4-(3-(1H-Indol-3-yl)prop-2-yn-1-yl)-3-((4-methoxyphenyl)amino)dihydrofuran-2(3H)-one 5.61



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Aldehyde **5.35** (295.6 mg, 1.5 mmol) and imine **1.71** (326.4 mg, 1.58 mmol, 1.05 equiv) were dissolved in DMF (4.5 mL). The resultant solution was cooled to -40°C and catalyst **1.139** (32.7 mg, 0.15 mmol, 0.1 equiv.) was added into the reaction mixture in one portion. The reaction mixture was stirred at -40°C . After 7 h, the reaction mixture was diluted with CH_2Cl_2 (9.0 mL) and NaBH_4 (56.7 mg, 1.5 mmol, 1.5 equiv.) was introduced. The reaction mixture was allowed to stir at -40°C . After 2 h, water was added and the resultant mixture was extracted with AcOEt (x3). Combined organic layers were brined, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure to give a crude compound which was dissolved in toluene (30 mL) with 2-hydroxypyridine (171.2 mg, 1.8 mmol, 1.2 equiv.). The resultant solution was refluxed for 5 h. The volatiles were removed under reduced pressure to give a crude compound which was purified by flash column chromatography on silica gel (Pentane/AcOEt: 2/1 and toluene/AcOEt: 6/1) to yield the compound **5.61** (321.2 mg, 0.891 mmol, 59%) as a brown solid.

Mp = 175 - 176 $^{\circ}\text{C}$ (toluene/AcOEt)

^1H NMR (300 MHz, CDCl_3) δ = 8.17 (s, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.26 – 7.15 (m, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.66 (d, J = 8.9 Hz, 2H), 4.70 (d, J = 9.7 Hz, 1H), 4.53 (dd, J = 9.7, 5.4 Hz, 1H), 4.24 (dd, J = 7.3, 2.8 Hz, 1H), 4.17 (s, 1H), 3.77 (s, 3H), 3.23 – 3.11 (m, 1H), 2.67 (dd, J = 17.1, 4.1 Hz, 1H), 2.45 (dd, J = 17.2, 9.3 Hz, 1H)

^{13}C NMR (75 MHz, CDCl_3) δ = 175.8, 153.3, 140.8, 135.2, 129.2, 128.6, 127.9, 123.2, 120.8, 120.0, 115.3, 114.5, 111.5, 98.6, 87.2, 70.0, 56.8, 55.9, 39.9, 18.5

IR (neat): 3351, 3215, 2956, 2910, 2839, 2223, 1767, 1511, 1386, 1242, 1183, 1157, 1216, 1110, 1032, 994, 820, 764, 752, 601, 527, 424

HRMS (TOF MS ES $^+$) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_3$: 361.1552, found: 361.1551

$[\alpha]^{20}_{\text{D}}$ –191 (c 0.10, MeOH)

R_f = 0.23 (Pentane/AcOEt: 2/1)

P

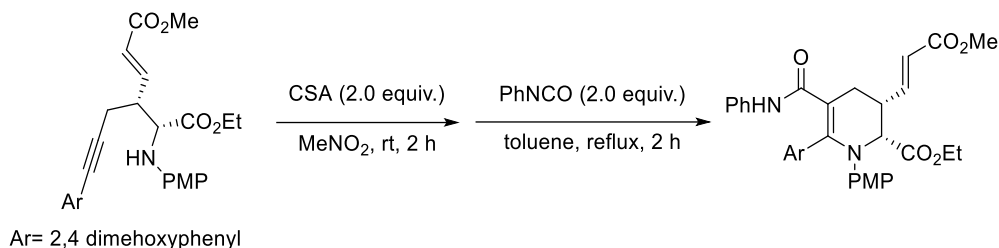
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Hydroamination of Arylogous Ynolethers

(2R,3R)-Ethyl 6-(2,4-dimethoxyphenyl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-5-(phenylcarbamoyl)-1,2,3,4-tetrahydropyridine-2-carboxylate **5.68**



In a flask containing a solution of amine **5.66** (38.7 mg, 80.4 μmol) in MeNO_2 (0.8 mL) was added CSA (37.3 mg, 0.161 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. aq. NaHCO_3 and the resultant mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude material was submitted into the next reaction without further purification.

To a solution of the crude material **5.67** in toluene (1.6 mL) was added phenyl isocyanate (17.5 μL , 0.161 mmol, 2.0 equiv.). The reaction mixture was refluxed for 2 h. The reaction mixture was cooled down to room temperature and the volatiles were removed under reduced pressure to give a crude compound which was purified by flash column chromatography on silica gel (cyclohexane/ AcOEt : 3/1) to yield the title compound **5.68** (39% 18.7 mg, 31.1 μmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.42 (d, J = 8.6 Hz, 2H), 7.25 – 7.12 (m, 5H), 7.05 – 6.89 (m, 4H), 6.38 – 6.28 (m, 2H), 6.17 – 5.98 (m, 2H), 4.65 (d, J = 9.3 Hz, 1H), 4.36 – 4.19 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 – 3.66 (m, 7H), 3.02 (dd, J = 17.4, 5.6 Hz, 1H), 2.73 (dd, J = 17.3, 3.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 170.5, 167.1, 161.3, 160.9, 159.6, 154.1, 148.3, 138.6, 134.4, 134.2, 130.4, 128.9, 123.3, 122.9, 119.6, 115.5, 105.2, 104.6, 98.4, 88.7, 80.2, 64.6, 61.7, 55.8,

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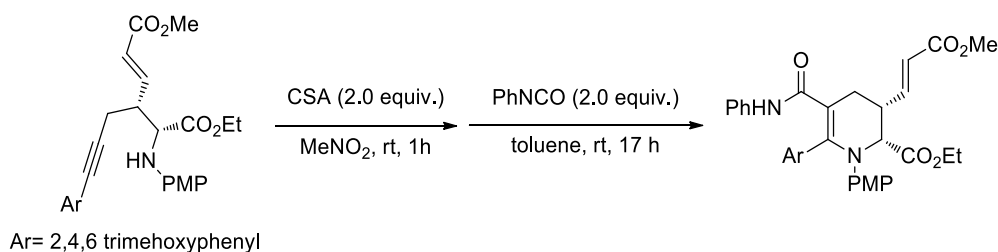
55.7, 55.5, 51.6, 42.4, 23.8, 14.4

IR (neat): 3428, 2961, 2839, 1721, 1675, 1604, 1506, 1440, 1237, 1209, 1170, 1130, 1027, 833, 753, 692, 553, 505

HRMS (TOF MS ES+) calcd for (M+Na)⁺ C₃₄H₃₆N₂O₈Na: 623.2369, found: 623.2372

R_f = 0.29 (cyclohexane/AcOEt: 2/1)

(2R,3R)-Ethyl 3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-5-(phenylcarbamoyl)-6-(2,4,6-trimethoxyphenyl)-1,2,3,4-tetrahydropyridine-2-carboxylate
5.71



In a flask containing a solution of amine **5.69** (79.4 mg, 0.155 mmol) in MeNO₂ (1.6 mL) was added CSA (72.1 mg, 0.31 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NaHCO₃ and the resultant mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude material was solubilized in toluene (1.6 mL) and phenyl isocyanate was added (34 μL, 0.31 mmol, 2 equiv.). The reaction mixture was stirred at room temperature. After 17 h, the volatiles were removed under reduced pressure to give a crude compound which was purified by flash column chromatography on silica gel (Pentane/AcOEt: 2/1 to 1/1) to yield the title compound **5.71** (62.1 mg, 98.5 μmol, 63%) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.31 (brs, 1H), 7.17 – 7.03 (m, 5H), 7.00 – 6.86 (m, 3H), 6.57 (d, *J* = 9.0 Hz, 2H), 6.02 (dd, *J* = 15.8, 1.1 Hz, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 2.1

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Hz, 1H), 4.35 (dd, $J = 4.3, 1.7$ Hz, 1H), 4.28 – 4.06 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.20 – 3.05 (m, 2H), 2.60 (td, $J = 13.0, 2.9$ Hz, 1H), 1.24 (t, $J = 7.1$ Hz, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) $\delta = 169.9, 167.4, 166.9, 162.6, 158.38, 158.34, 157.8, 148.1, 139.9, 139.2, 138.8, 128.7, 128.3, 122.6, 121.8, 119.0, 113.3, 106.3, 104.7, 90.8, 66.0, 61.1, 55.96, 55.92, 55.45, 55.38, 51.6, 37.6, 25.9, 14.3$

IR (neat): 3385, 2940, 2835, 1722, 1606, 1584, 1508, 1436, 1416, 1297, 1226, 1154, 1125, 1058, 1030, 912, 835, 755, 728, 692

HRMS (TOF MS ES+) calcd for $(\text{M}+\text{H})^+ \text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_5$: 631.2656, found: 631.2640

$[\alpha]^{20}_{\text{D}}$ +25.8 (c 0.78, CHCl_3)

$R_f = 0.30$ (PE/AcOEt: 1/1)

Representative Procedure: Hydroamination of Arylogous Ynolethers

tert-Butyl 3-((2S,5R,6R)-6-(ethoxycarbonyl)-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidin-2-yl)-1H-indole-1-carboxylate **5.79**

In a flask containing a solution of amine **5.50** (220.8 mg, 0.48 mmol) in MeNO₂ (5.0 mL, 0.1 M) was added CSA (209.3 mg, 0.96 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature for 1h. The reaction was quenched with sat. aq. NaHCO₃ and the resultant mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude material was submitted into the next reaction without further purification.

Next, the crude material **5.77** and Boc₂O (209.3 mg, 0.96 mmol, 2.0 equiv.) was dissolved in CH₂Cl₂ (5.0 mL, 0.1 M). DMAP (29.3 mg, 0.24 mmol, 0.50 equiv.) was added in one portion and the reaction mixture was stirred at room temperature. After 2 h, AcOH (0.14 mL, 2.45 mmol, 5.1 equiv.) was added into the reaction mixture. Then, the fresh prepared NaBH(OAc)₃ (5.0 equiv.) in CH₂Cl₂ (5.0 mL) was added dropwise to the reaction mixture at 0°C. The reaction mixture was warmed to room temperature and stirred for 14 h. The reaction was quenched with sat. aq. NaHCO₃ and the resultant mixture was extracted with CH₂Cl₂ (x 3). The organic layers were collected, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Pentane/AcOEt: 4/1) to yield the compound **5.79** as yellow oil (115.8 mg, 0.206 mmol, 43% over 3 steps).

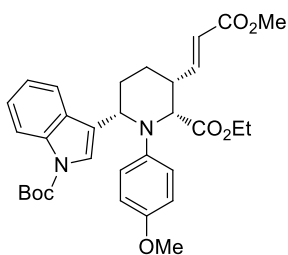
Preparation of a solution of NaBH(OAc)₃ in CH₂Cl₂: AcOH (0.82 mL, 14.4 mmol, 30 equiv.) was added dropwise over 10 min to a solution of NaBH₄ (144.1 mg, 2.4 mmol, 5 equiv.) in CH₂Cl₂ (5 mL) at rt. The mixture was allowed to stir for 30 min at room temperature. This resultant solution was used immediately for the reduction of enamine.

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¹H NMR (300 MHz, CDCl₃) δ = 8.07 – 7.92 (m, 2H), 7.84 (dd, *J* = 15.9, 8.8 Hz, 1H), 7.28 – 7.18 (m, 3H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 5.93 (dd, *J* = 15.9, 0.9 Hz, 1H), 4.16 (dd, *J* = 10.9, 3.2 Hz, 1H), 4.04 (d, *J* = 3.0 Hz, 1H), 3.87 – 3.75 (m, 5H), 3.63 (s, 3H),

3.02 – 2.92 (m, 1H), 2.47 – 2.31 (m, 1H), 2.12 – 1.97 (m, 2H), 1.83 – 1.71 (m, 1H), 1.62 (s, 9H), 0.97 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 170.9, 167.0, 156.7, 149.9, 149.2, 143.3, 135.7, 129.3, 126.9, 124.2, 123.9, 122.6, 122.4, 121.9, 121.1, 115.2, 113.5, 83.7, 70.3, 61.1, 60.5, 55.3, 51.7, 40.6, 30.4, 29.0, 28.4, 14.0

IR (neat): 2936, 1723, 1649, 1608, 1509, 1451, 1370, 1353, 1293, 1245, 1155, 1088, 1033, 983, 855, 832, 765, 747, 637, 570, 471, 424

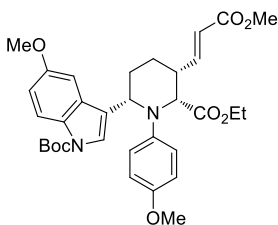
HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₃₂H₃₉N₂O₇: 563.2757, found: 563.2765

HPLC: Daicel Chiralpak[®] IC (80% n-heptane, 20% iPrOH), 20°C, 1 mL/min, 243.0 nm, *t*₁ = 9.9 min (minor), *t*₂ = 11.9 min (major). 98% ee

[α]_D²⁰ –26.6 (*c* 1.26, CHCl₃)

R_f = 0.21 (Pentane/AcOEt: 4/1)

(2R,3R,6S)-Ethyl 6-(5-methoxy-1H-indol-3-yl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidine-2-carboxylate **5.80**



5.80 was prepared according to the representative procedure, using amine **5.51** (97.0 mg, 0.198 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 4/1). Yield 77% (89.7 mg, 0.151 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.93 – 7.77 (m, 2H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.15 (s, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.86 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.55 (d, *J* = 9.0 Hz, 2H), 5.93 (dd, *J* =

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15.9, 0.9 Hz, 1H), 4.13 (dd, $J = 11.0, 3.2$ Hz, 1H), 4.03 (d, $J = 3.0$ Hz, 1H), 3.96 (s, 3H), 3.85 – 3.71 (m, 5H), 3.64 (s, 3H), 3.04 – 2.87 (m, 1H), 2.53 – 2.31 (m, 1H), 2.14 – 1.97 (m, 2H), 1.80 – 1.68 (m, 1H), 1.60 (s, 9H), 0.97 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 170.8, 166.8, 156.8, 155.5, 149.8, 149.0, 143.2, 130.4, 130.0, 127.1, 124.1, 122.4, 122.0, 115.9, 113.5$ (2C), 103.3, 83.5, 70.2, 61.3, 60.5, 55.8, 55.3, 51.6, 40.5, 30.4, 28.6, 28.3, 14.0

IR (neat): 2933, 1723, 1613, 1509, 1477, 1446, 1391, 1370, 1247, 1220, 1156, 1079, 1032, 977, 853, 831, 802, 768, 728

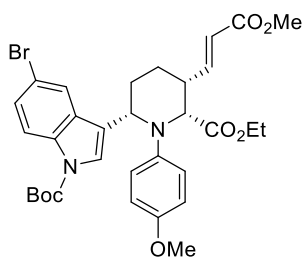
HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{33}\text{H}_{41}\text{N}_2\text{O}_8$: 593.2863, found: 593.2870

HPLC: Daicel Chiralpak[®] IA (90% n-heptane, 10% iPrOH), 20°C, 1 mL/min, 254 nm, $t_1 = 7.8$ min (major), $t_2 = 11.0$ min (minor). 98% ee

$[\alpha]^{20}_{\text{D}} -52.5$ (c 1.15, CHCl_3)

$R_f = 0.23$ (Pentane/AcOEt: 4/1)

(2R,3R,6S)-ethyl 6-(5-bromo-1H-indol-3-yl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidine-2-carboxylate (5.81)



5.81 was prepared according to the representative procedure, using amine **5.52** (78.8 mg, 0.146 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 4/1). Yield 43% (40.2 mg, 62.7 μmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) $\delta = 8.01$ (s, 1H), 7.93 – 7.72 (m, 2H), 7.33 (dd, $J = 8.8, 1.9$ Hz, 1H), 7.22 (s, 1H), 7.01 (d, $J = 9.0$ Hz, 2H), 6.57 (d, $J = 9.0$ Hz, 2H), 5.93 (dd, $J = 15.9, 0.9$ Hz, 1H), 4.12 (dd, $J = 11.1, 3.1$ Hz, 1H), 4.03 (d, $J = 3.0$ Hz, 1H), 3.89 – 3.77 (m, 5H), 3.04 – 2.89 (m, 1H), 2.46 – 2.22 (m, 1H), 2.11 – 1.96 (m, 2H), 1.82 – 1.69 (m, 1H), 1.61 (s, 9H), 1.00 (t, $J = 7.1$ Hz, 3H)

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^{13}C NMR (75 MHz, CDCl_3) δ = 170.7, 166.9, 156.7, 149.4, 148.7, 143.1, 134.4, 131.0, 127.1, 127.0, 124.8, 123.6, 122.2, 122.0, 116.7, 115.8, 113.6, 84.2, 70.1, 60.7, 60.6, 55.3, 51.8, 40.3, 30.3, 28.9, 28.3, 14.0

IR (neat): 2982, 2949, 1725, 1508, 1444, 1370, 1272, 1245, 1153, 1099, 1054, 1033, 983, 832, 803, 768, 734

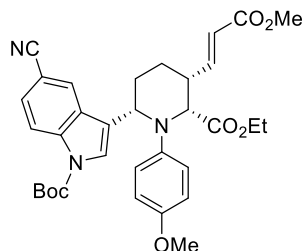
HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_7^{79}\text{Br}$: 641.1862, found: 641.1848

HPLC: Daicel Chiralpak[®] IA (90% n-heptane, 10% iPrOH), 20°C, 1 mL/min, 220 nm, t_1 = 8.9 min (major), t_2 = 13.8 min (minor). 99% ee

$[\alpha]_D^{20}$ -34.3 (c 1.18, CHCl_3)

R_f = 0.23 (Pentane/AcOEt: 4/1)

(2R,3R,6S)-Ethyl 6-(5-cyano-1H-indol-3-yl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidine-2-carboxylate (5.82)



5.82 was prepared according to the representative procedure, using amine **5.53** (81.8 mg, 0.168 mmol). Purified by flash chromatography on silica gel (Pentane/AcOEt: 3/1). Yield 55% (54.5 mg, 0.927 mmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) δ = 8.22 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.77 (dd, J = 16.0, 8.5 Hz, 1H), 7.49 (dd, J = 8.6, 1.6 Hz, 1H), 7.34 (s, 1H), 6.99 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 9.0 Hz, 2H), 5.95 (dd, J = 16.0, 0.9 Hz, 1H), 4.17 (dd, J = 11.1, 3.3 Hz, 1H), 4.04 (d, J = 3.0 Hz, 1H), 3.92 – 3.77 (m, 5H), 3.65 (s, 3H), 3.05 – 2.93 (m, 1H), 2.42 – 2.23 (m, 1H), 2.13 – 1.99 (m, 2H), 1.83 – 1.69 (m, 1H), 1.64 (s, 9H), 1.00 (t, J = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) δ = 170.6, 166.8, 157.0, 149.1, 148.3, 143.0, 137.5, 129.4, 127.4, 127.0, 125.79, 127.76, 122.6, 122.5, 120.0, 116.1, 113.7, 105.9, 85.0, 70.1, 60.7, 60.5, 55.4, 52.0, 40.2, 30.2, 29.0, 28.3, 14.0

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IR (neat): 2981, 2934, 2857, 2226, 1725, 1651, 1609, 1508, 1464, 1441, 1370, 1354, 1246, 1149, 1078, 1033, 982, 911, 813, 769, 729, 655, 556, 463, 424

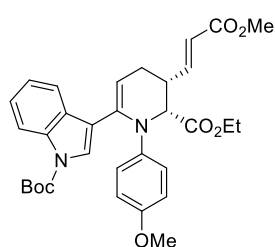
HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₃₃H₃₈N₃O₇: 588.2710, found: 588.2707

HPLC: Daicel Chiralpak[®] IA (80% n-heptane, 20% iPrOH), 20°C, 1 mL/min, 254 nm, t₁ = 7.4 min (major), t₂ = 15.0 min (minor). 99% ee

[α]²⁰_D -30.8 (c 1.03, CHCl₃)

R_f = 0.31 (Pentane/AcOEt: 3/1)

(E)-tert-Butyl 3-(6-(ethoxycarbonyl)-5-(3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridin-2-yl)-1H-indole-1-carboxylate 5.78



Representative procedure: In a flask containing a solution of amine **5.50** (142.9 mg, 0.310 mmol) in MeNO₂ (3.1 mL) was added CSA (144.2 mg, 0.621 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 1 h, the reaction was

quenched with sat. aq. NaHCO₃. The reaction mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude was submitted into the next reaction without further purification.

Next, in a flask containing a solution of the crude **5.77** and Boc₂O (135.4 mg, 0.621 mmol, 2.0 equiv.) in CH₂Cl₂ (3.1 mL) was added DMAP (19.0 mg, 0.155 mmol, 0.5 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 2 h, water was added and the resultant mixture was extracted with CH₂Cl₂ (x 3). The organic layers were collected, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Pentane/AcOEt: 4/1) to yield the compound **5.78** (109.0 mg, 0.194 mmol, 63 %) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.05 – 7.91 (m, 2H), 7.55 (s, 1H), 7.24 – 7.09 (m, 3H), 7.03 –

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6.95 (m, 2H), 6.69 – 6.60 (m, 2H), 5.86 (dd, $J = 15.8, 1.4$ Hz, 1H), 5.44 (dd, $J = 4.3, 3.0$ Hz, 1H), 4.41 (d, $J = 3.8$ Hz, 1H), 4.28 (qd, $J = 7.1, 1.1$ Hz, 2H), 3.73 (s, 3H), 3.65 (s, 3H), 3.00 – 2.83 (m, 1H), 2.67 – 2.33 (m, 2H), 1.64 (s, 9H), 1.34 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 170.6, 166.9, 155.6, 149.8$ (2C), 141.5, 135.4, 134.9, 128.8, 124.4, 124.3, 122.6, 121.4 (2C), 121.3, 120.2, 115.0, 114.2, 108.2, 83.8, 67.8, 61.3, 55.4, 51.6, 36.5, 28.3, 26.1, 14.4

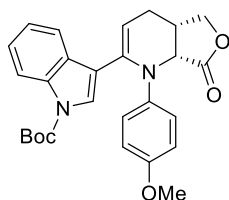
IR (neat): 2981, 1726, 1642, 1510, 1450, 1369, 1308, 1274, 1239, 1150, 1100, 1033, 914, 834, 767, 750, 732, 585, 474, 425

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{32}\text{H}_{37}\text{N}_2\text{O}_7$: 561.2601, found: 561.2597

$[\alpha]^{20}_{\text{D}} +332.5$ (c 1.03, CHCl_3)

$R_f = 0.28$ (Pentane/AcOEt: 4/1)

**tert-Butyl 3-((4a*S*,7a*R*)-1-(4-methoxyphenyl)-7-oxo-1,4,4a,5,7,7a-hexahydrofuro[3,4-
b]pyridin-2-yl)-1*H*-indole-1-carboxylate 5.83**



5.83 was prepared according to the representative procedure using amine **5.61** (128.9 mg, 0.239 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 3/1). Yield 56% (55.4 mg, 0.102 mmol) as a yellow oil.

Mp = 207-208°C (Cyclohexane:AcOEt)

^1H NMR (300 MHz, CDCl_3) $\delta = 8.05 - 7.90$ (m, 2H), 7.51 (s, 1H), 7.23 – 7.13 (m, 2H), 7.10 – 7.01 (m, 2H), 6.66 – 6.58 (m, 2H), 5.31 (t, $J = 4.0$ Hz, 1H), 4.47 (d, $J = 7.2$ Hz, 1H), 4.42 (dd, $J = 9.0, 4.5$ Hz, 1H), 4.12 (d, $J = 9.0$ Hz, 1H), 3.65 (s, 3H), 2.96 – 2.83 (m, 1H), 2.64 (ddd, $J = 18.3, 8.1, 4.3$ Hz, 1H), 2.28 (ddd, $J = 18.3, 8.2, 3.9$ Hz, 1H), 1.64 (s, 9H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 176.2, 155.7, 149.7, 141.6, 135.1, 134.70, 128.8, 124.4, 124.2, 122.8, 121.4$ (2C), 119.9, 114.7, 113.9, 106.3, 83.7, 72.2, 63.3, 55.2, 31.2, 28.2, 24.3

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IR (neat): 2979, 1728, 1507, 1368, 1239, 1150, 826, 728

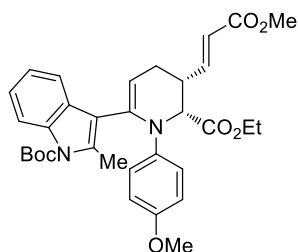
HRMS (TOF MS ES+) calcd for (M+H)⁺ C₂₇H₂₉N₂O₅: 461.2076, found: 461.2070

HPLC: Daicel Chiralpak[®] IA (90% n-heptane, 10% isopropanol), 20°C, 1 mL/min, 243.0 nm, t₁ = 11.0 min (major), t₂ = 13.7 min (minor). 99 %ee.

[α]²⁰_D +320.2 (c 1.00, CHCl₃).

Rf = 0.26 (cyclohexane/AcOEt: 3/1)

tert-Butyl 3-((5R,6R)-6-(ethoxycarbonyl)-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridin-2-yl)-2-methyl-1H-indole-1-carboxylate 5.84



5.84 was prepared according to the representative procedure using amine **5.54** (56.7 mg, 0.119 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1). Yield 58% (38.5 mg, 68.4 μmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.00 – 7.92 (m, 1H), 7.87 (s, 1H), 7.22 – 7.10 (m, 3H), 6.93 – 6.83 (m, 2H), 6.64 – 6.53 (m, 2H), 5.88 (dd, *J* = 15.8, 1.3 Hz, 1H), 5.11 (s, 1H), 4.40 – 4.21 (m, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 3.77 – 3.70 (m, 1H), 2.70 – 2.37 (m, 5H), 1.64 (s, 9H), 1.37 (t, *J* = 7.2 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 170.5, 167.0, 155.8, 150.8, 149.7, 141.5, 135.6, 134.0, 129.2, 124.7, 123.3, 122.6, 121.3, 119.8, 117.6, 115.1, 114.4, 114.1, 108.3, 83.8, 67.7, 61.3, 55.4, 51.7, 36.6, 28.4, 25.9, 14.8, 14.4

IR (neat): 2980, 2927, 2833, 1724, 1508, 1457, 1438, 1369, 1353, 1319, 1241, 1154, 1117, 1034, 911, 831, 768, 731, 666, 535, 433

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₃₃H₃₉N₂O₇: 575.2757, found: 575.2751

HPLC: Daicel Chiralpak[®] IA (90% n-heptane, 10% iPrOH), 20°C, 1 mL/min, 254 nm, t₁ = 6.9 min (major), t₂ = 11.1 min (minor). 99% ee

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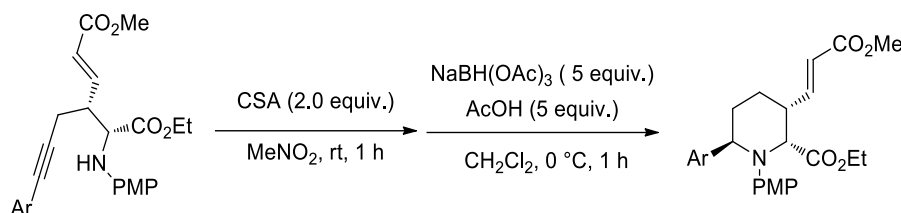
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$[\alpha]^{20}_{\text{D}} +241.6$ (c 0.99, CHCl_3)

$R_f = 0.46$ (Cyclohexane/AcOEt: 4/1)

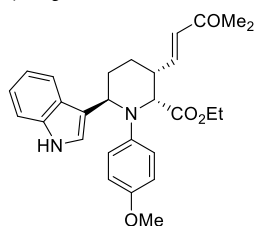
2R,3R,6S)-Ethyl 6-(1H-indol-3-yl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidine-2-carboxylate **5.87**



Representative procedure: In a flask containing a solution of amine **5.50** (46.0 mg, 0.10 mmol) in MeNO_2 (1.0 mL) was added CSA (46.5 mg, 0.20 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 1 h, the reaction was quenched with sat. aq. NaHCO_3 . The reaction mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO_4 and concentrated *in vacuo*.

Next, the crude material **5.77** was diluted in CH_2Cl_2 (1.0 mL) and AcOH (29 μL , 0.5 mmol, 5.0 equiv.) was added into the reaction mixture. Then, the freshly prepared $\text{NaBH}(\text{OAc})_3$ (5 equiv.) in CH_2Cl_2 (1.0 mL) was added dropwise to the reaction mixture at 0°C . The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with sat. aq. NaHCO_3 and extracted with CH_2Cl_2 (x 3). The organic layers were collected, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Pentane/AcOEt: 3/1) to yield the trans-isomer **5.87** and the cis-isomer **5.86** (74%, 34.1 mg, 0.737 mmol) as colourless oil.

(major diastereomer) $^1\text{H NMR}$ (300 MHz, CDCl_3) $\delta = 7.89 - 7.84$ (m, 1H), 7.81 (brs, 1H), 7.20



$- 7.14$ (m, 1H), 7.13 – 6.95 (m, 5H), 6.83 (d, $J = 2.4$ Hz, 1H), 6.52 (d, $J = 9.0$ Hz, 2H), 5.96 (dd, $J = 15.8, 1.5$ Hz, 1H), 5.37 (dd, $J = 10.8, 3.3$ Hz, 1H), 4.34 (d, $J = 5.4$ Hz, 1H), 4.06 – 3.81 (m, 2H), 3.74 (s, 3H), 3.57 (s,

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3H), 3.24 – 3.10 (m, 1H), 2.27 – 1.74 (m, 4H), 1.03 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 171.6, 167.0, 155.4, 148.7, 143.3, 136.3, 126.2, 125.8, 122.4, 121.7, 121.3, 120.1, 119.3, 119.0, 113.4, 111.1, 68.2, 59.9, 55.2, 51.7, 51.0, 42.0, 34.8, 24.4, 14.2$

IR (neat): 3398, 2935, 2857, 1721, 1652, 1507, 1455, 1436, 1318, 1266, 1233, 1179, 1142, 1124, 1033, 1010, 983, 826, 737, 703, 579, 428

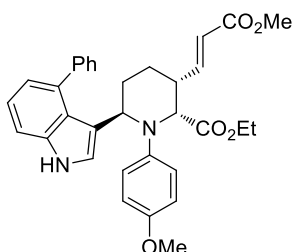
HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+ \text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_5$: 463.2237, found: 463.2233

HPLC: Daicel Chiralpak[®] IA (80% n-heptane, 20% iPrOH), 20°C, 1 mL/min, 254 nm, $t_1 = 8.1$ min (minor), $t_2 = 11.2$ min (major). 98% ee

$[\alpha]_D^{20} -94.0$ (c 1.50, CHCl_3)

$R_f = 0.22$ (Pentane/AcOEt: 3/1)

(2R,3R,6R)-Ethyl 3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-6-(4-phenyl-1H-indol-3-yl)piperidine-2-carboxylate 5.88



5.88 was prepared according to the representative procedure, using amine **5.56** (37.8 mg, 70.4 μmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 3/1). Yield 45% (17.0 mg, 31.6 μmol) as yellow oil.

^1H NMR (300 MHz, CDCl_3) $\delta = 7.94$ (brs, 1H), 7.64 – 7.43 (m, 5H), 7.29 – 7.24 (m, 1H), 7.20 – 7.13 (m, 1H), 6.97 (dd, $J = 7.1, 0.7$ Hz, 1H), 6.90 – 6.79 (m, 4H), 6.59 (d, $J = 8.9$ Hz, 2H), 5.79 (dd, $J = 15.8, 1.4$ Hz, 1H), 4.74 – 4.62 (dd, $J = 9.9, 2.8$ Hz, 1H), 4.26 (d, $J = 5.5$ Hz, 1H), 3.90 – 3.75 (m, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 2.97 – 2.79 (m, 1H), 1.99 – 1.87 (m, 1H), 1.50 – 1.32 (m, 3H), 0.93 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 170.7, 166.9, 155.0, 148.8, 143.8, 142.5, 136.2, 135.6, 129.5, 128.0, 127.3, 125.3, 124.1, 123.7, 121.5, 121.2, 121.1, 120.7, 113.6, 110.4, 68.4, 59.6, 55.4,$

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51.6, 50.3, 41.7, 36.1, 24.1, 14.3

IR (neat): 3363, 2928, 2851, 1725, 1659, 1511, 1436, 1408, 1366, 1319, 1240, 1167, 1029, 822, 797, 757, 702, 643, 584, 501

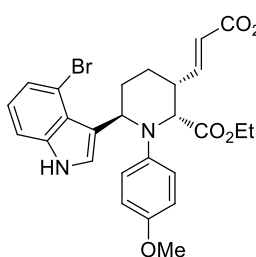
HRMS (TOF MS ES+) calcd for (M+H)⁺ C₃₃H₃₅N₂O₅: 539.2546, found: 539.2551

HPLC: Daicel Chiralpak[®] IE [90% n-heptane, 10% (EtOH/MTBE 75/25)], 20°C, 1 mL/min, 254 nm, t₁ = 9.9 min (minor), t₂ = 10.7 min (major). 98% ee

[α]²⁰_D -87.4 (c 0.17, CHCl₃)

R_f = 0.23 (Cyclohexane/AcOEt: 3/1)

(2R,3R,6R)-Ethyl 6-(4-bromo-1H-indol-3-yl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidine-2-carboxylate 5.89



5.89 was prepared according to the representative procedure, using amine **5.55** (128.9 mg, 0.239 mmol). Purified by flash chromatography on silica gel (cyclohexane/AcOEt: 3/1). Yield 43% (55.4 mg, 0.102 mmol) as a yellow solid.

Mp = 207-208°C (Cyclohexane:AcOEt)

¹H NMR (300 MHz, CDCl₃) δ = 7.91 (brs, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.06 – 6.84 (m, 5H), 6.59 (d, *J* = 8.9 Hz, 2H), 6.14 (dd, *J* = 10.8, 2.7 Hz, 1H), 5.94 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.41 (d, *J* = 5.4 Hz, 1H), 4.05 – 3.81 (m, 2H), 3.73 (s, 3H), 3.61 (s, 3H), 3.22 – 2.98 (m, 1H), 2.68 – 2.48 (m, 1H), 2.22 – 2.04 (m, 1H), 1.89– 1.70 (m, 1H), 1.68– 1.44 (m, 1H), 1.05 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 171.4, 166.9, 155.1, 148.7, 143.7, 137.0, 125.6, 124.8, 124.2 (2C), 122.4, 121.3, 121.0, 113.7 (2C), 110.5, 68.7, 60.1, 55.3, 51.7, 49.5, 42.0, 37.2, 24.3, 14.3

IR (neat): 3326, 2927, 2847, 1729, 1699, 1507, 1429, 1335, 1241, 1179, 1137, 1032, 986, 813, 766, 741, 586

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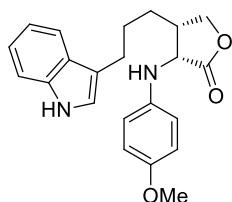
HRMS (TOF MS ES+) calcd for (M+H)⁺ C₂₇H₃₀N₂O₅⁷⁹Br: 541.1338, found: 541.1340

HPLC: Daicel Chiralpak[®] IC (80% n-heptane, 20% iPrOH), 20°C, 1 mL/min, 254 nm, t₁ = 6.2 min (major), t₂ = 9.9 min (minor). 99% ee

[α]_D²⁰ -222.0 (c 0.21, CHCl₃)

R_f = 0.24 (Cyclohexane/AcOEt: 3/1)

(3R,4S)-4-(3-(1H-indol-3-yl)propyl)-3-((4-methoxyphenyl)amino)dihydrofuran-2(3H)-one 5.91



In a flask containing a solution of amine **5.61** (195.8 mg, 0.543 mmol) in MeNO₂ (15.5 mL) was added CSA (252.3 mg, 1.09 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 1 h, the reaction was quenched with sat. aq. NaHCO₃. The reaction mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude cycloadduct **5.90** was dissolved in 30 mL of anhydrous THF and 10% Pd/C (290.6 mg, 0.273 mmol, 0.5 equiv.) was added. The mixture was stirred under hydrogen atmosphere for 14 h. Then, the suspension was filtered through Celite[®], washed with CH₂Cl₂ and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 2/1) to give the title compound **5.91** as yellow oil in 79% yield.

¹H NMR (300 MHz, CDCl₃) δ = 7.94 (brs, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.19 (td, *J* = 8.1, 1.2 Hz 1H), 7.15 – 7.06 (m, 1H), 6.88 – 6.77 (m, 3H), 6.64 – 6.54 (m, 2H), 4.33 (dd, *J* = 9.5, 4.9 Hz, 1H), 4.25 (d, *J* = 9.4 Hz, 1H), 4.12 (d, *J* = 7.2 Hz, 1H), 4.04 (brs, 1H), 3.79 (s, 3H), 2.90 – 2.57 (m, 3H), 1.89 – 1.53 (m, 3H), 1.41 – 1.19 (m, 1H)

¹³C NMR (75 MHz, CDCl₃) δ = 176.4, 153.0, 140.9, 136.4, 127.4, 122.0, 121.4, 119.2, 118.8, 115.9, 115.1, 114.4, 111.3, 70.0, 57.3, 55.9, 40.3, 27.3, 26.0, 25.1

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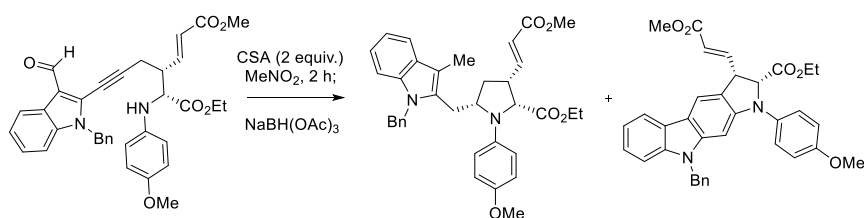
E

IR (neat): 3403, 2930, 2832, 1765, 1510, 1456, 1236, 1167, 1033, 1002, 975, 819, 740, 699, 514, 424

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₂₂H₂₅N₂O₃: 365.1865, found: 365.1865

[α]²⁰_D –118.0 (c 0.98, CHCl₃).

R_f = 0.32 (Pentane/AcOEt: 2/1).



In a flask containing a solution of amine **5.59** (115.7 mg, 0.20 mmol) in MeNO₂ (2.0 mL) was added CSA (92.9 mg, 0.40 mmol, 2.0 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 1 h, the reaction was quenched with sat. aq. NaHCO₃. The reaction mixture was extracted with AcOEt (x 3). The organic layers were collected, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude **5.95** was diluted in CH₂Cl₂ (2.0 mL) and AcOH (58 μL, 1.0 mmol, 5.0 equiv.) was added into the reaction mixture. Then, the prepared fresh NaBH(OAc)₃ (5 equiv.) in CH₂Cl₂ (2.0 mL) was added dropwise to the reaction mixture at 0°C. The reaction mixture was warmed to room temperature and stirred for 14 h. The reaction mixture was quenched with sat. aq. NaHCO₃ and extracted with CH₂Cl₂ (x 3). The organic layers were collected, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Pentane/AcOEt: 6/1) to afford **5.97** and **5.98**.

(2R,3R,5S)-ethyl 5-((1-benzyl-3-methyl-1H-indol-2-yl)methyl)-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)pyrrolidine-2-carboxylate 5.97

Yield 62% (70.2 mg, 0.124 mmol) as yellow oil

¹H NMR (300 MHz, CDCl₃) δ = 7.61 – 7.53 (m, 1H), 7.28 – 7.07 (m, 6H), 6.95 – 6.87 (m, 2H),

P

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6.85 – 6.72 (m, 3H), 6.52 (d, $J = 9.1$ Hz, 2H), 5.81 (dd, $J = 15.7, 1.2$ Hz, 1H), 5.39 (s, 2H), 4.26 – 4.03 (m, 4H), 3.74 (s, 3H), 3.73 (s, 3H), 3.37 (dd, $J = 14.8, 4.7$ Hz, 1H), 3.10 – 2.98 (m, 2H), 2.41 (s, 3H), 2.22 – 1.96 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 172.7, 166.3, 152.4, 144.9, 140.5, 138.4, 137.0, 133.9, 128.8$ (2C), 127.3, 125.9, 123.2, 121.4, 119.2, 118.4, 115.0, 114.7, 109.4, 109.1, 69.1, 61.3, 58.7, 55.9, 51.7, 46.9, 43.5, 35.6, 29.3, 14.4, 9.9

IR (neat): 2934, 1724, 1658, 1511, 1467, 1356, 1241, 1180, 1038, 815, 736, 697, 590, 452

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_5$: 567.2859, found: 567.2849

HPLC: Daicel Chiralpak[®] IA (90% n-heptane, 10% iPrOH), 20°C, 1 mL/min, 220 nm, $t_1 = 24.1$ min (minor), $t_2 = 29.0$ min (major). 95% ee

$[\alpha]_D^{20} +16.5$ (c 0.96, CHCl_3)

$R_f = 0.24$ (Pentane/AcOEt: 6/1)

(2R,3S)-Ethyl 9-benzyl-3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-1,2,3,9-tetrahydropyrrolo[2,3-b]carbazole-2-carboxylate 5.98

Yield 14% (15.3 mg, 0.0273 mmol) as yellow oil

^1H NMR (300 MHz, CDCl_3) $\delta = 7.95$ (d, $J = 7.6$ Hz, 1H), 7.69 (s, 1H), 7.65 – 7.16 (m, 9H), 7.16 – 6.99 (m, 3H), 6.93 (d, $J = 9.0$ Hz, 2H), 6.61 (s, 1H), 6.15 (dd, $J = 15.5, 0.5$ Hz, 1H), 5.36 (s, 2H), 5.00 (d, $J = 9.6$ Hz, 1H), 4.62 (t, $J = 9.6$ Hz, 1H), 4.27 – 4.05 (m, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 169.8, 166.5, 156.8, 149.0, 145.1, 142.3, 140.5, 137.2, 136.2, 128.8, 127.5, 126.7, 124.5, 123.9, 123.6, 123.3, 121.3, 119.4, 118.9, 117.1, 115.9, 114.9, 108.8, 89.1, 71.8, 61.3, 55.6, 51.7, 47.1, 46.7, 14.3$

IR (neat): 2926, 1715, 1605, 1510, 1448, 1350, 1243, 1166, 1027, 834, 728, 696, 532, 455

HRMS (TOF MS ES+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{35}\text{H}_{33}\text{N}_2\text{O}_5$: 561.2389, found: 561.2399

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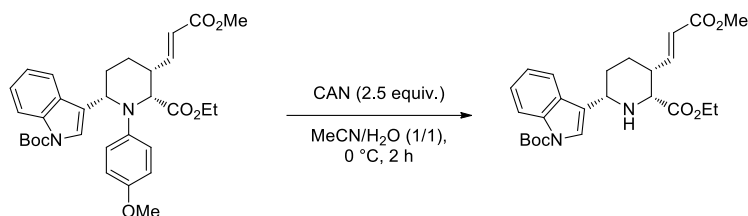
E

$[\alpha]^{20}_{\text{D}} + 9.6$ (c 1.57, CHCl_3)

$R_f = 0.26$ (cyclohexane/AcOEt: 6/1)

Deprotection of PMP Group

tert-Butyl 3-((2S,5R,6R)-6-(ethoxycarbonyl)-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)piperidin-2-yl)-1H-indole-1-carboxylate **5.100**



In a flask containing a solution of CAN (181.0 mg, 0.33 mmol, 2.5 equiv) in H₂O (1.0 mL) at 0°C was added dropwise a solution of **5.79** (74.3 mg, 0.132 mmol) in CH₃CN (1.0 mL) over 10 min. Then, the mixture was allowed to stirred at 0°C. After 2 h, the reaction was quenched by the addition of 1M aqueous solution of Na₂S₂O₃. The resultant mixture was extracted with AcOEt (x 3) and combined organics layers were brined, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (pentane/AcOEt: 6/1) on silica gel to yield amine **5.100** (42.6 mg, 0.927 mmol, 70%) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.16 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.41 – 7.18 (m, 3H), 6.00 (dd, *J* = 15.9, 1.0 Hz, 1H), 4.27 – 4.10 (m, 2H), 4.08 – 3.99 (m, 1H), 3.77 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 4.27 3.10 – 3.00 (m, 1H), 2.24 (brs, 1H), 2.03 – 1.95 (m, 2H), 1.86 – 1.76 (m, 2H), 1.68 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 171.5, 166.9, 150.0, 148.0, 135.9, 129.1, 124.6, 123.8, 122.9, 122.6, 122.4, 119.6, 115.5, 83.8, 77.6, 62.8, 61.2, 54.4, 51.6, 38.7, 31.0, 28.6, 28.4, 14.4

IR (neat): 2978, 2936, 1723, 1651, 1608. 1509, 1451, 1370, 1353, 1309, 1294, 1246, 1209, 1156, 1089, 1074, 1034, 986, 853, 832, 767, 748, 638, 590, 571, 476, 427

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₅H₃₃N₂O₆: 457.2339, found: 457.2341

HPLC: Daicel Chiralpak[®] IC (60% n-heptane, 40% iPrOH), 20°C, 1 mL/min, 254 nm, t₁ =

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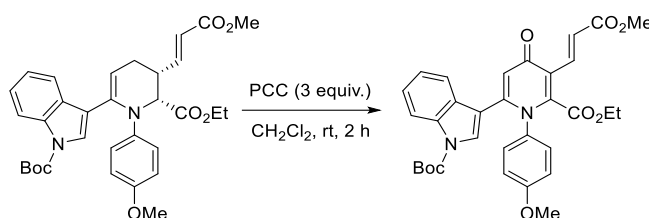
E

6.4min (major), $t_2 = 12.2$ min (minor). >99% ee

$[\alpha]^{20}_D -9.5$ (c 0.92, CHCl_3)

$R_f = 0.30$ (pentane/AcOEt: 6/1)

(E)-tert-Butyl 3-(6-(ethoxycarbonyl)-5-(3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)-4-oxo-1,4-dihydropyridin-2-yl)-1H-indole-1-carboxylate 5.101



To a solution of enamine **5.77** (56.0 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at 0°C was added Celite[®] (60 mg) and PCC (64.7 mg, 0.30 mmol, 3 equiv.). Then, the mixture was allowed to stir at room temperature. After 20 h, the suspension was filtered through Celite[®] washing with CH_2Cl_2 and the filtrate was concentrated under reduced pressure to obtain the crude **5.101**. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1) to yield the title compound **5.101** as pale yellow oil in 64 %.

^1H NMR (300 MHz, CDCl_3) $\delta = 8.28$ (d, $J = 16.1$ Hz, 1H), 8.24 – 8.16 (m, 2H), 8.11 (d, $J = 8.3$ Hz, 1H), 7.42 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 7.23 (d, $J = 8.9$ Hz, 2H), 7.08 (s, 1H), 6.90 (d, $J = 8.9$ Hz, 2H), 6.34 (d, $J = 16.0$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.85 – 3.78 (m, 6H), 1.72 (s, 9H), 1.18 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) $\delta = 180.4, 167.6, 160.3, 159.6, 149.2, 137.3, 137.0, 135.7, 133.6, 131.7, 128.7, 128.5, 127.9, 126.0, 125.2, 124.5, 122.6, 120.9, 118.8, 115.2, 114.5, 113.7, 85.9, 61.3, 55.5, 51.8, 28.3, 14.0$.

IR (neat): 2985, 2933, 2837, 1743, 1704, 1633, 1538, 1511, 1448, 1392, 1368, 1339, 1307, 1245, 1196, 1146, 1098, 1079, 1032, 991, 937, 899, 835, 804, 767, 750, 700, 609. 582, 540, 473, 425

P

A

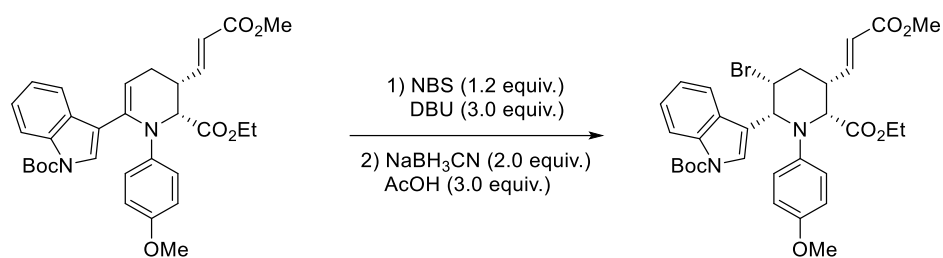
G

E

HRMS (TOF MS ES+) calcd for (M+H)⁺ C₃₂H₃₃N₂O₈: 573.2237, found: 573.2243

R_f = 0.25 (cyclohexane/AcOEt: 4/1).

tert-Butyl 3-((2S,3S,5R,6R)-3-bromo-6-(ethoxycarbonyl)-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidin-2-yl)-1H-indole-1-carboxylate 6.93



To a solution of enamine **5.78** (740.0 mg, 1.32 mmol) in dry CH_2Cl_2 (13.2 mL) was added DBU (0.59 mL, 3.96 mmol, 3 equiv.). The reaction mixture was cooled to -40°C and the solution of NBS (281.9 mg, 1.58 mmol, 1.2 equiv.) in CH_2Cl_2 (13.2 mL) was added dropwise and the reaction mixture was stirred at -40°C for 30 min. The reaction was quenched by 10 % aq. NaS_2O_3 and the resultant mixture was extracted by CH_2Cl_2 (x 3). The combined organic layers were washed with sat. aq. NaHCO_3 (x 3) (to remove succinimide), brine, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure and the crude compound was submitted into the next reaction without further purification.

The brominated crude material **6.92** was dissolved in dry CH_2Cl_2 (13.2 mL) and AcOH (0.23 mL, 3.96 mmol, 3 equiv.) was added at room temperature. NaBH_3CN (165.9 mg, 2.64 mmol, 2 equiv.) was added to the reaction mixture in one portion and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched by sat. aq. NaHCO_3 and the resultant mixture was extracted by CH_2Cl_2 (x 3). The combined organic layers were washed with sat. aq. NaHCO_3 (x 3), brine, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1) to yield the compound **6.93** as yellow oil (94%, 795.4 mg, 1.24 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.05 (d, J = 8.3 Hz, 1H), 7.82 (s, 1H), 7.26 – 7.00 (m, 6H), 6.90 (d, J = 9.1 Hz, 2H), 5.82 (dd, J = 15.9, 1.2 Hz, 1H), 5.31 (d, J = 4.8 Hz, 1H), 4.78 (dt, J = 12.0, 4.8 Hz, 1H), 4.14 (d, J = 4.8 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.49 (dq, J = 10.7, 7.2

P

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Hz, 1H), 3.33 (q, $J = 12.1$ Hz, 1H), 3.03 – 2.88 (m, 1H), 2.64 – 2.46 (m, 2H), 1.68 (s, 9H), 0.59 (t, $J = 7.2$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3) $\delta = 170.0, 166.8, 154.5, 149.8, 148.1, 144.1, 134.8, 131.1, 126.2, 124.3, 122.6, 121.6, 120.6, 120.0, 115.0, 114.9, 114.7, 84.0, 62.9, 60.5, 57.2, 55.7, 51.7, 47.2, 43.0, 34.0, 28.4, 13.3$

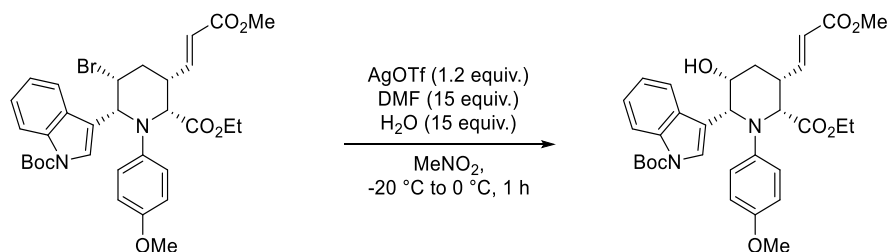
IR (neat): 2933, 1722, 1627, 1606, 1510, 1454, 1371, 1244, 1193, 1152, 1093, 1026, 913, 835, 728, 698, 643, 559, 532, 455, 425

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+ \text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_7^{79}\text{Br}$: 641.1862, found: 641.1868

$[\alpha]^{20}_{\text{D}} +139.2$ (c 1.27, CHCl_3)

$R_f = 0.31$ (cyclohexane/AcOEt: 4/1)

tert-Butyl 3-((2S,3S,5R,6R)-6-(ethoxycarbonyl)-3-hydroxy-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidin-2-yl)-1H-indole-1-carboxylate 6.95



To a solution of piperidine **6.93** (156.7 mg, 0.252 mmol) in MeNO₂ (2.5 mL) was added DMF (0.29 mL, 3.75 mmol, 15 equiv.) and H₂O (68 μL , 3.78 mmol, 15 equiv.). The reaction mixture was wrapped in aluminium foil and AgOTf (77.8 mg, 0.30 mmol, 1.2 equiv.) was added in one portion to the reaction mixture at -20°C in the dark. The resultant mixture was stirred for 10 min at -20°C and then, the reaction mixture was warmed to 0°C and stirred for 1 h in the dark. The reaction was quenched by sat. aq. NaHCO₃ and the suspension was filtered through a pad of Celite[®] washing with AcOEt. The filtered solution was extracted with AcOEt (x 3), washed with brine, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure.

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The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1) to yield the title compound **6.95** (82%, 120.0 mg, 0.207 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.22 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.40 – 7.26 (m, 2H), 6.98 – 6.90 (m, 2H), 6.84 (dd, *J* = 15.6, 7.9 Hz, 1H), 6.76 – 6.69 (m, 2H), 5.89 (dd, *J* = 15.6, 1.1 Hz, 1H), 5.60 – 5.68 (m, 1H), 4.82 (brs, 1H), 4.58 – 4.48 (m, 1H), 4.46 – 4.20 (m, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.25 – 3.14 (m, 1H), 2.58 – 2.36 (m, 1H), 1.85 – 1.72 (m, 1H), 1.68 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 175.0, 166.3, 153.2, 149.9, 144.6, 139.7, 136.1, 128.6, 124.6, 123.2 (2C), 122.7, 121.2, 119.3, 115.8, 115.32, 115.26, 83.8, 68.9, 64.4, 63.2, 62.3, 56.0, 51.8, 43.8, 28.6, 28.4, 14.3

IR (neat): 3428, 2930, 1724, 1511, 1451, 1371, 1309, 1244, 1156, 1039, 815, 768, 747, 592, 420

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₃₂H₃₉N₂O₈: 579.2706, found: 579.2720

[α]²⁰_D +38.1 (*c* 1.51, CHCl₃)

R_f = 0.21 (cyclohexane/AcOE: 4/1)

(2R,3R,9R,9aS)-Ethyl 9-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-7-methoxy-2-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole-3-carboxylate **6.98**



To a solution of piperidine **6.93** (63.7 mg, 0.103 mmol) in dry CH₂Cl₂ (1.0 mL) was added activated molecular sieves 4Å (0.1 g). The suspension was stirred for overnight at room

P

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temperature. After that, AgOTf (31.6 mg, 0.123 mmol, 1.2 equiv.) was added in one portion to the reaction mixture at -20°C in dark and the resulting mixture was stirred for 10 min. Then, the reaction mixture was warmed to 0°C and stirred for 1 h in the dark. The reaction was quenched by sat. aq. NaHCO_3 and the suspension was filtered through a pad of Celite[®] washing with AcOEt. The filtered solution was extracted by AcOEt (x 3) and washed with brine and then dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1) to yield the compound **6.98** (87%, 50.1 mg, 89.4 μmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.16 (d, J = 8.1 Hz, 1H), 7.53 (s, 1H), 7.40– 7.26 (m, 2H), 7.19 – 7.10 (m, 1H), 6.92 (dd, J = 15.7, 7.2 Hz, 1H), 6.70 – 6.50 (m, 3H), 5.98 (dd, J = 15.7, 1.4 Hz, 1H), 4.83 (d, J = 9.1 Hz, 1H), 4.52 – 4.37 (m, 2H), 4.09 – 3.88 (m, 2H), 3.74 (s, 3H), 3.64 (s, 3H), 3.60 – 3.44 (m, 1H), 2.45 – 2.22 (m, 2H), 1.67 (s, 9H), 1.08 (t, J = 7.1 Hz, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 170.9, 166.5, 155.2, 149.9, 144.7, 143.1, 138.2, 136.2, 129.6, 124.6, 123.5, 123.2, 122.6, 121.9, 120.0, 115.6, 113.5, 113.1, 111.0, 83.8, 73.0, 67.0, 60.9, 55.8, 51.8, 48.8, 48.2, 35.3, 28.4, 14.3

IR (neat): 2978, 1724, 1658, 1626, 1607, 1511, 1488, 1451, 1370, 1309, 1244, 1153, 1088, 1021, 982, 911, 857, 835, 811, 766, 730, 647, 594, 569, 533, 456, 425

HRMS (TOF MS ESI+) calcd for $(\text{M}+\text{H})^+$ $\text{C}_{32}\text{H}_{37}\text{N}_2\text{O}_7$: 561.2601, found: 561.2618

$[\alpha]^{20}_{\text{D}}$ –34.6 (c 1.00, CHCl_3)

R_f = 0.18 (cyclohexane/AcOEt: 4/1)

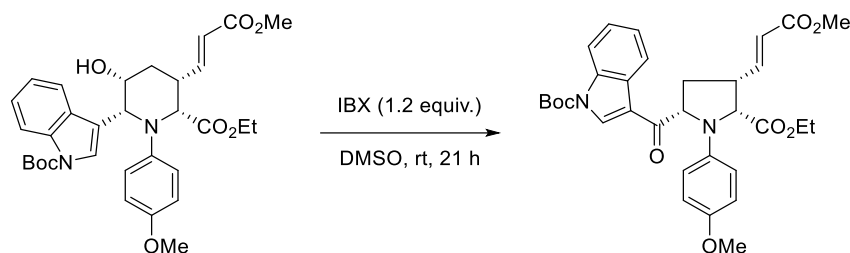
tert-Butyl 3-((2S,4R,5R)-5-(ethoxycarbonyl)-4-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)pyrrolidine-2-carbonyl)-1H-indole-1-carboxylate **6.99**

P

A

G

E



To a solution of piperidine **6.95** (67.0 mg, 0.116 mmol) in DMSO (0.58 mL) was added IBX (35.9 mg, 0.127 mmol, 1.1 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 15 h, water was added into the reaction mixture and the resultant suspension was filtered by Celite[®] washing AcOEt. The filtrate was extracted with AcOEt (x 3) and the combined organic layers were brined, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1) to yield the title compound **6.99** (81%, 54.4 mg, 94.3 μmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 9.33 (s, 1H), 8.48 – 8.42 (m, 1H), 8.16 – 8.10 (m, 1H), 7.38 – 7.31 (m, 2H), 6.88 (dd, *J* = 15.6, 7.9 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.59 – 6.52 (m, 2H), 5.95 (dd, *J* = 15.7, 1.2 Hz, 1H), 4.66 – 4.56 (m, 1H), 4.39 – 4.22 (m, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.49 – 3.33 (m, 1H), 2.62 – 2.50 (m, 2H), 1.64 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 197.0, 172.3, 166.2, 153.2, 149.3, 143.8, 141.5, 135.2, 135.1, 128.7, 125.4, 124.5, 124.0, 122.9, 115.4, 115.1, 115.0, 114.9, 85.1, 70.9, 69.1, 61.6, 55.7, 51.8, 44.0, 36.3, 28.2, 14.4

IR (neat): 3134, 2977, 2835, 1737, 1645, 1537, 1512, 1450, 1370, 1356, 1308, 1273, 1240, 1182, 1169, 1145, 1106, 1069, 1035, 1019, 985, 854, 837, 817, 769, 751, 734, 702, 586, 508, 473, 425

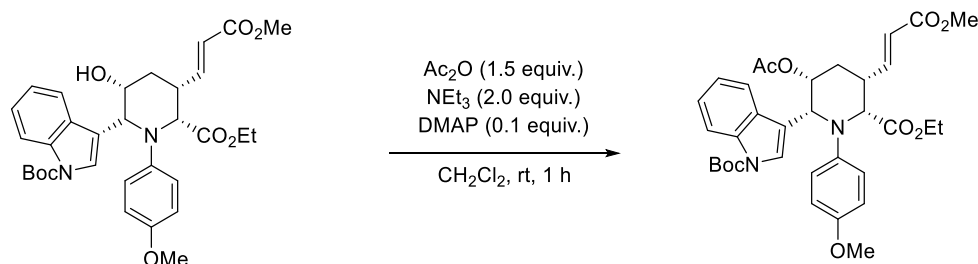
HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₃₂H₃₇N₂O₈: 577.2550, found: 577.2556

HPLC: Daicel Chiralpak[®] IA (90% n-heptane, 10% iPrOH), 20°C, 1 mL/min, 254 nm, t₁ = 13.5 min (minor), t₂ = 14.8 min (major). 99% ee

$[\alpha]^{20}_{\text{D}} +91$ (c 1.12, CHCl_3)

$R_f = 0.28$ (cyclohexane/AcOEt: 4/1)

tert-butyl 3-((2S,3S,5R,6R)-3-acetoxy-6-(ethoxycarbonyl)-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxyphenyl)piperidin-2-yl)-1H-indole-1-carboxylate (6.104)



To a solution of piperidine **6.95** (244.4 mg, 0.422 mmol) in CH_2Cl_2 (0.8 mL) was added NEt_3 (92 μL , 0.84 mmol, 2.0 equiv.) and Ac_2O (59 μL , 0.63 mmol, 1.5 equiv.) at room temperature. Then, DMAP (5.1 mg, 0.042 mol, 0.1 equiv.) was added in one portion and the reaction mixture was stirred for 1h at room temperature. The reaction was quenched with water and the resultant mixture was extracted by CH_2Cl_2 (x 3). The combined organic layers were washed with sat. aq. NaHCO_3 (x 3), brine, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 4/1) to yield the title compound **6.104** (87%, 227.0 mg, 0.366 mmol) as yellow oil.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.13 (d, J = 7.7 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.55 (s, 1H), 7.40 – 7.24 (m, 2H), 6.95 (dd, J = 15.7, 8.1 Hz, 1H), 6.84 – 6.76 (m, 2H), 6.72 – 6.64 (m, 2H), 6.62 (d, J = 2.6 Hz, 1H), 5.92 (dd, J = 15.7, 1.1 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.31 – 4.11 (m, 3H), 3.77 – 3.74 (m, 6H), 3.20 – 3.05 (m, 1H), 2.74 – 2.57 (m, 1H), 2.27 – 2.07 (m, 4H), 1.69 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 171.9, 170.2, 166.4, 153.2, 149.6, 145.4, 141.2, 135.6, 128.7, 124.8, 123.7, 123.1, 122.9, 119.9, 118.6, 116.4, 115.5, 114.7, 84.1, 69.9, 67.0, 62.9, 61.0, 55.7, 51.7, 43.5, 31.3, 28.3, 21.3, 14.4

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IR (neat): 2981, 1728, 1511, 1452, 1370, 1309, 1233, 1154, 1088, 1039, 818, 766, 748, 593

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₃₄H₄₁N₂O: 621.2812, found: 621.2813

[α]²⁰_D + 41.3 (c 0.89, CHCl₃)

R_f = 0.14 (cyclohexane/AcOEt: 4/1)

tert-butyl 3-((2S,3S,5R,6R)-3-acetoxy-1-acetyl-6-(ethoxycarbonyl)-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)piperidin-2-yl)-1H-indole-1-carboxylate (6.105):



To a solution of piperidine **6.104** (72.3 mg, 0.116 mmol) and DMA (0.10 mL, 1.12 mmol, 10 equiv.) in the component solvent of MeCN (8 mL) and H₂O (0.2 mL) at 0°C, a solution of CAN (191.6 mg, 0.35 mmol, 3.0 equiv.) in H₂O (0.8 mL) was added dropwise. The mixture was stirred at 0°C for 30 min. Then, the reaction mixture was diluted with CH₂Cl₂ (8 mL) and sat. aq. NaHCO₃ (8 mL) and subsequently Ac₂O (33 μL, 0.35 mmol, 3.0 equiv.) was added. The resultant mixture was extracted with CH₂Cl₂ (x 3) and combined organics layers were brined, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure to give a crude material which was purified by flash column chromatography on silica gel (cyclohexane/AcOEt: 2/1 to 1/1) to yield the compound **6.105** (27.6 mg, 49.6 μmol, 43%) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.08 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.50 (s, 1H), 7.36 – 7.21 (m, 2H), 7.16 (s, 1H), 6.91 (dd, *J* = 15.7, 7.7 Hz, 1H), 5.90 (d, *J* = 15.6 Hz, 1H), 4.57 – 4.43 (m, 2H), 4.34 – 4.08 (m, 2H), 3.74 (s, 3H), 3.17 – 3.00 (m, 1H), 2.53 (dd, *J* = 22.7, 12.4 Hz, 1H), 2.22 (s, 3H), 2.08 (s, 3H), 1.96 – 1.85 (m, 1H), 1.67 (s, 9H), 1.27 (t, *J* = 7.1

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Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 171.3, 170.4, 169.2, 166.2, 149.8, 144.1, 135.5, 128.5, 124.8, 123.5, 123.0, 122.2, 120.5, 119.3, 115.3, 84.1, 66.3, 64.2, 62.1, 61.5, 51.8, 43.5, 28.3 (2C), 23.2, 21.5, 14.3

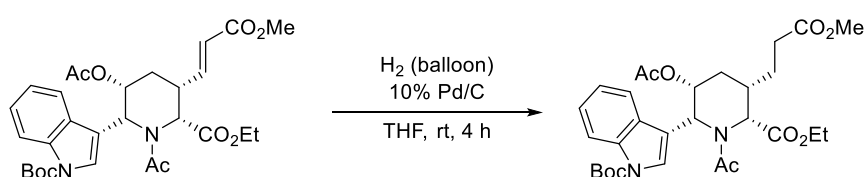
IR (neat): 2993, 1731, 1656, 1455, 1371, 1229, 1155, 1085, 1018, 763

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₉H₃₆N₂O₉: 579.2319, found: 579.2330

[α]_D²⁰ -5.6 (c 0.16, CHCl₃)

R_f = 0.26 (cyclohexane/AcOEt: 1/1)

tert-butyl 3-((2S,3S,5S,6R)-3-acetoxy-1-acetyl-6-(ethoxycarbonyl)-5-(3-methoxy-3-oxopropyl)piperidin-2-yl)-1H-indole-1-carboxylate (6.105'):



To a solution of piperidine **7.105** (69.9 mg, 0.126 mmol) in THF (2 mL) was added 10% Pd/C (13.4 mg, 0.013 mmol, 0.1 equiv.). The suspension was purged with H₂ over 10 min and was stirred with H₂ balloon for 4 h. The suspension was filtered through Celite[®], washed with AcOEt and the filtrate was concentrated to give the title compound **7.105'** (93%, 65.4 mg, 0.117 mmol.) as a yellow oil. The crude material was used for the next reaction without further purification.

¹H NMR (300 MHz, CDCl₃) δ = 8.07 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.3 Hz, 1H), 7.51 (s, 1H), 7.35 – 7.22 (m, 2H), 7.20 (s, 1H), 4.45 – 4.32 (m, 2H), 4.30 – 4.17 (m, 2H), 3.64 (s, 3H), 2.44 – 2.30 (m, 2H), 2.27 – 2.18 (m, 4H), 2.06 (s, 3H), 1.94 – 1.79 (m, 2H), 1.72 – 1.59 (m, 11H), 1.32 (t, *J* = 7.1 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 173.3, 171.3, 170.5, 170.1, 149.9, 135.5, 128.6, 124.8, 123.0, 122.2, 120.7, 119.7, 115.3, 84.0, 66.1, 64.1, 62.1, 61.3, 51.8, 41.1, 32.4, 28.7, 28.4, 25.2, 23.2,

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21.6, 14.4

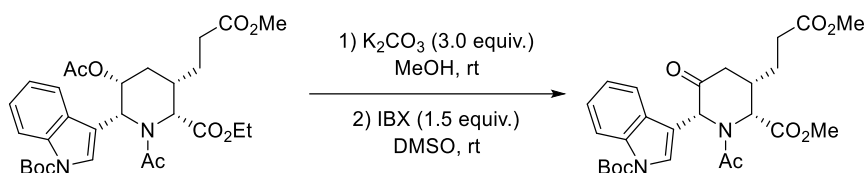
IR (neat): 2979, 1732, 1657, 1454, 1369, 1227, 1152, 1086, 1018, 749

HRMS (TOF MS ESI+) calcd for $(M+Na)^+$ $C_{29}H_{36}N_2O_9Na$: 581.2478, found: 581.2475

$[\alpha]^{20}_D$ +13.5 (*c* 0.40, $CHCl_3$)

Rf = 0.18 (cyclohexane/AcOEt: 1/1)

tert-butyl 3-((2*S*,5*S*,6*R*)-1-acetyl-5-(3-methoxy-3-oxopropyl)-6-(methoxycarbonyl)-3-oxopiperidin-2-yl)-1*H*-indole-1-carboxylate **6.106**



To a solution of piperidine **6.105'** (38.7 mg, 69.3 μ mol) in MeOH (2 mL) was added K_2CO_3 (28.7 mg, 0.208 mmol, 3 equiv.). The suspension was stirred at room temperature. After 17 h, the reaction was quenched by sat. aq. NH_4Cl and the resultant mixture was extracted by CH_2Cl_2 (x 3), brined and then dried over Na_2SO_4 and filtered. The volatiles were removed under reduced pressure and the crude compound was used for the next reaction without further purification.

To a solution of crude alcohol in DMSO (1 mL) was added IBX (29.1 mg, 0.104 mmol, 1.5 equiv.) in one portion. The reaction mixture was stirred at room temperature. After 21 h of reaction, water was added into the reaction mixture and the resultant suspension was filtered by Celite[®] washing with ethyl acetate. The filtrate was extracted with AcOEt (x 3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 1/1 to 1/4) to yield the compound **6.106** (68%, 23.6 mg, 47.1 μ mol) as yellow oil.

Rotamer ratio = 2:3

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¹H NMR (300 MHz, CDCl₃) δ = 8.53 (s, 0.4H), 8.48 – 8.40 (m, 1H), 8.37 (s, 0.6H), 8.16 – 8.04 (m, 1H), 7.45 – 7.28 (m, 2H), 5.16 (dd, *J* = 10.6, 7.1 Hz, 0.6H), 5.07 (dd, *J* = 10.4, 6.9 Hz, 0.4H), 4.82 (d, *J* = 8.1 Hz, 0.4H), 4.53 (d, *J* = 7.9 Hz, 0.6H), 3.85 (s, 1.8H), 3.78 (s, 1.2H), 3.69 (s, 1.8H), 3.68 (s, 1.2H), 2.71 – 2.36 (m, 4H), 2.26 – 1.97 (m, 3H), 1.96 – 1.79 (m, 2H), 1.78 – 1.62 (m, 11H)

¹³C NMR (75 MHz, CDCl₃) δ = 191.3, 190.8, 173.3, 173.2, 171.1, 170.8, 170.4, 169.4, 149.34, 149.25, 135.5, 135.4, 131.7, 131.5, 128.1, 127.9, 126.1, 125.7, 124.8, 124.4, 123.3, 123.1, 118.6, 117.4, 115.1, 114.9, 86.1, 85.5, 65.4, 63.9, 63.2, 62.8, 52.5, 52.1, 52.0, 51.9, 42.5, 40.0, 37.8, 34.7, 32.3, 32.2, 28.3 (2 rotamers), 24.83, 24.80, 22.3, 22.2.

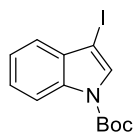
IR (neat): 2945, 1733, 1649, 1448, 1360, 1233, 1137, 749

HRMS (TOF MS ESI+) calcd for (M+H)⁺ C₂₆H₃₃N₂O₈: 501.2237, found: 501.2224

[α]_D²⁰ –30.4 (*c* 0.50, CHCl₃)

R_f = 0.17 (cyclohexane/AcOEt: 1/4)

tert-butyl 3-iodo-1H-indole-1-carboxylate (6.123a)



KOH (6.0 g, 106.9 mmol, 2.5 equiv.) was added to a solution of indole (5.0 g, 42.7 mmol, 1.0 equiv.) in anhydrous DMF (85 mL) at room temperature. The resultant mixture was cooled to 0°C. I₂ (11.4 g, 44.9 mmol, 1.05 equiv.) was added in 5 portions and the reaction mixture was stirred at 0°C for 1 h. Upon completion, ice water was added into the reaction mixture and the precipitate was collected via filtration, washed with H₂O and dried via azeotropic distillation with PhMe (twice). The resultant material was immediately used in the next step due to its instability. The resultant material was dissolved in anhydrous CH₂Cl₂ (85 mL) at room temperature. NEt₃ (17.9 mL, 128.4 mmol, 3.0 equiv.) was added and the solution was cooled to 0°C. Then, Boc₂O (18.6 g, 85.2 mmol, 2.0 equiv.) was added, followed by a catalytic amount of DMAP (0.52 g, 4.26 mmol, 0.1 equiv.). The solution was removed from ice bath and stirred at room temperature for 2 h. The volatile material was evaporated and the crude material was purified via flash column chromatography on silica gel (cyclohexane only to cyclohexane/AcOEt: 20/1) to yield the title compound **6.123a** as a yellow oil (12.3 g, 35.8 mmol, 84% over 2 steps). Spectroscopic data was in agreement with the literature.¹³⁷

¹H NMR (300 MHz, CDCl₃) δ = 8.13 (d, *J* = 7.9 Hz, 1H), 7.73 (s, 1H), 7.44 – 7.28 (m, 3H), 1.67 (s, 9H).

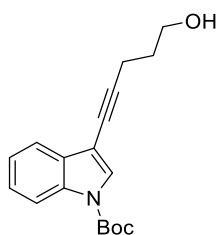
¹³C NMR (75 MHz, CDCl₃) δ = 148.6, 134.8, 132.0, 130.0, 125.3, 123.3, 121.4, 115.0, 84.1, 65.6, 28.1.

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₁₃H₁₅O₂I: 344.0148, found: 344.0144

R_f = 0.40 (cyclohexane/AcOEt: 20/1).

¹³⁷ Adam H. Trotta, *Org. Lett.* **2015**, *17*, 3358.

tert-butyl 3-(5-hydroxypent-1-yn-1-yl)-1H-indole-1-carboxylate (**6.123b**)



To a suspension of aryl halide **6.123a** (9.50 g, 27.7 mmol, 1.0 equiv.), CuI (105.4 mg, 0.55 mol, 0.02 equiv.), PdCl₂ (98.2 mg, 0.55 mmol, 0.02 equiv.) and PPh₃ (290.4 mg, 1.11 mmol, 0.04 equiv.) in Et₃N (50 mL) under argon atmosphere was added dropwise 4-pentyn-1-ol (2.80 mL, 30.3 mmol, 1.1 equiv) at room temperature. The suspension was stirred for 16 h. Then, the suspension was filtered through Celite[®] washing with AcOEt. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 5/1 to 3/1) to yield the title compound **6.123b** as a brown oil (98%, 8.11 g, 27.1 mmol).

¹H NMR (300 MHz, CDCl₃) δ = 8.12 (d, *J* = 7.9 Hz, 1H), 7.68 (s, 1H), 7.66 – 7.61 (m, 1H), 7.39 – 7.26 (m, 2H), 3.87 (t, *J* = 6.1 Hz, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 1.97 – 1.85 (m, 2H), 1.66 (s, 9H)

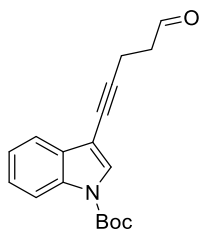
¹³C NMR (75 MHz, CDCl₃) δ = 149.1, 134.5, 130.7, 128.1, 125.0, 123.0, 119.9, 115.1, 103.9, 92.9, 84.1, 72.5, 61.5, 31.6, 28.1, 16.2

IR: 3353, 2978, 2934, 1734, 1608, 1561, 1451, 1367, 1307, 1272, 1257, 1231, 1151, 1099, 1049, 938, 907, 853, 745, 615, 580, 476, 421

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₁₈H₂₂NO₂: 300.1600, found: 300.1594

Rf = 0.24 (cyclohexane/AcOEt: 3/1).

tert-butyl 3-(5-oxopent-1-yn-1-yl)-1H-indole-1-carboxylate **6.123**



The alcohol **6.123b** (351.0 mg, 1.17 mmol, 1 equiv.) was dissolved in DMSO (6 mL) and IBX (393.9 mg, 1.41 mmol, 1.2 equiv.) was added in one portion. The reaction mixture was stirred at room temperature for 15 h. Upon completion, water was added into the reaction mixture and the resultant suspension was filtered by Celite[®]. The filtrate was extracted with AcOEt (3 x) and the

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combined organic layers were washed with water ($\times 2$), brined, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure. The residue was used in the next reaction without further purification (96%, 335.6 mg, 1.13 mmol, brown oil).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 9.89 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.66 – 7.59 (m, 1H), 7.38 – 7.25 (m, 2H), 2.82 (s, 4H), 1.66 (s, 9H)

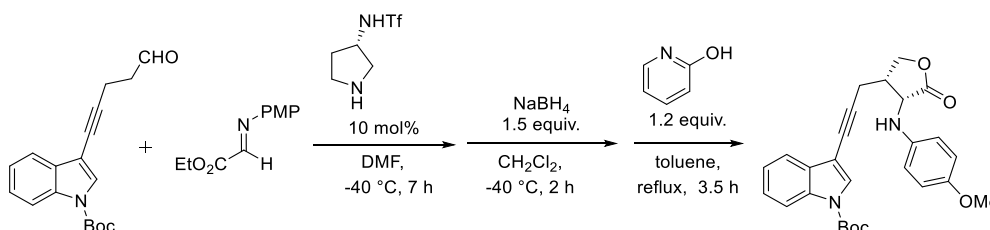
$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 200.4, 149.0, 134.5, 130.6, 128.4, 125.1, 123.1, 119.9, 115.2, 103.4, 91.3, 84.1, 73.0, 42.7, 28.1, 12.9

IR: 2978, 2927, 2727, 1733, 1604, 1452, 1368, 1307, 1233, 1152, 1099, 1050, 851, 747, 661, 578, 542, 471, 423

HRMS (TOF MS ES⁺) calcd for $(\text{M}-\text{H})^+$ $\text{C}_{18}\text{H}_{18}\text{NO}_3$: 296.1287, found: 296.1277

Rf = 0.17 (cyclohexane/AcOEt: 6/1).

tert-butyl 3-(3-((3S,4R)-4-((4-methoxyphenyl)amino)-5-oxotetrahydrofuran-3-yl)prop-1-yn-1-yl)-1H-indole-1-carboxylate (6.107)



The mixture of aldehyde **6.123b** (617.6 mg, 2.08 mmol) and imine **1.71** (452.0 mg, 2.18 mmol, 1.05 equiv) was dissolved in DMF (6.2 mL). The resultant solution was cooled to -40°C and catalyst **1.139** (45.3 mg, 0.21 mmol, 0.1 equiv.) was added into the reaction mixture in one portion. The reaction mixture was allowed to stir at -40°C . After 7 h, the reaction mixture was diluted with CH_2Cl_2 (12.4 mL) and NaBH_4 (117.9 mg, 3.12 mmol, 1.5 equiv.) was added to the reaction mixture. The reaction mixture was allowed to stir at -40°C . After 2 h, water was added and the resultant mixture was extracted with AcOEt ($\times 3$). Combined organic layers were brined, dried over MgSO_4 and filtered. The volatiles were removed under reduced pressure to give a

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crude compound. Next, the crude compound and 2-hydroxypyridine (237.0 mg, 2.49 mmol, 1.2 equiv.) was dissolved in toluene (42 mL). The resultant solution was refluxed for 3.5 h. The volatiles were removed under reduced pressure to give a crude compound which was purified by flash column chromatography on silica gel (toluene/AcOEt: 20/1) to yield the compound **6.107** (312.5 mg, 0.679 mmol, 33%) as brown oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.12 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.64 – 7.58 (m, 1H), 7.41 – 7.26 (m, 2H), 6.87 – 6.79 (m, 2H), 6.71 – 6.62 (m, 2H), 4.67 (d, *J* = 9.8 Hz, 1H), 4.53 (dd, *J* = 9.7, 5.3 Hz, 1H), 4.22 (d, *J* = 7.3 Hz, 1H), 4.16 (brs, 1H), 3.76 (s, 3H), 3.26 – 3.11 (m, 1H), 2.68 (dd, *J* = 17.2, 4.1 Hz, 1H), 2.44 (dd, *J* = 17.3, 9.6 Hz, 1H), 1.67 (s, 9H)

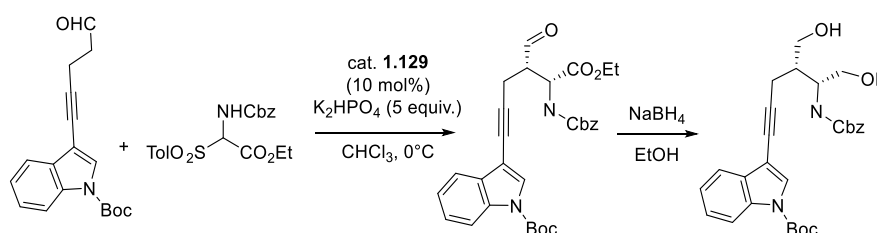
¹³C NMR (75 MHz, CDCl₃) δ = 175.6, 153.2, 149.1, 140.6, 134.6, 130.6, 128.9, 125.1, 123.2, 120.0, 115.3, 115.1, 114.3, 103.2, 89.5, 84.3, 74.7, 69.7, 56.6, 55.7, 39.7, 28.1, 18.3

IR: 2971, 1733, 1513, 1451, 1368, 1232, 1152, 747, 422

HRMS (TOF MS ES⁺) calcd for (M-H)⁺ C₂₇H₂₉N₂O₅: 461.2076, found: 461.2071

R_f = 0.28 (toluene/AcOEt: 20/1)

tert-butyl 3-((4*S*,5*R*)-5-(((benzyloxy)carbonyl)amino)-6-hydroxy-4-(hydroxymethyl)hex-1-yn-1-yl)-1*H*-indole-1-carboxylate **6.133**



To a solution of aldehyde **6.123** (672.5 mg, 2.26 mmol, 2.0 equiv.) in CHCl₃ (5.7 mL) was added catalyst **1.129** (67.5 mg, 0.11 mmol, 0.1 equiv.) at room temperature in one portion. After stirring for 5 min, the mixture was cooled to 0°C. α-Amido sulfone **1.145** (442.7 mg, 1.13 mmol, 1.0 equiv.) and K₂HPO₄ (1.01 g, 5.65 mmol, 5.0 equiv.) were added successively. The reaction mixture was stirred at 0°C for 168 h. The reaction was quenched by sat. aq. NH₄Cl and the

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suspension was filtered through Celite[®] washing with CH₂Cl₂. The filtrate was extracted by CH₂Cl₂ (x 3), brined and then dried over Na₂SO₄ and filtered. The volatiles were removed under reduced pressure. The residue was used in the next reaction without further purification.

The residue **6.122** was dissolved with EtOH (5.7 mL) and the solution was cooled to 0°C. NaBH₄ (42.8 mg, 1.13 mmol, 1.0 equiv.) was added to the solution in one portion. After stirring for 10 min, NaBH₄ (85.6 mg, 2.26 mmol, 2.0 equiv.) was added again. After stirring for 1 h at 0°C, the reaction was quenched by sat. aq. NH₄Cl and the resultant mixture was extracted by CH₂Cl₂ (x 3), brined and then dried over Na₂SO₄ and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 10/1 to 3/1 to 1/1) to yield the title compound **6.133** (61%, 339.8 mg, 0.690 mmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.12 (d, *J* = 8.1 Hz, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.39 – 7.23 (m, 7H), 5.70 (d, *J* = 8.7 Hz, 1H), 5.11 (s, 2H), 4.06 – 3.65 (m, 5H), 2.75 – 2.60 (m, 2H), 2.16 – 1.99 (m, 1H), 1.66 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) δ = 157.4, 149.2, 136.3, 134.6, 130.8, 128.6, 128.5, 128.3, 128.1, 125.2, 123.2, 120.1, 115.3, 103.6, 91.4, 84.3, 73.9, 67.2, 63.6, 61.9, 53.9, 42.0, 28.2, 20.1

IR (neat): 3366, 2976, 2937, 2894, 1733, 1514, 1452, 1370, 1232, 1153, 1099, 1049, 852, 747, 697

HRMS (TOF MS ES⁺) calcd for (M+H)⁺ C₂₈H₃₃N₂O₆: 493.2339, found: 493.2341

[α]_D²⁰ –1.6 (*c* 0.58, CHCl₃)

R_f = 0.21 (cyclohexane/AcOEt: 1/1)

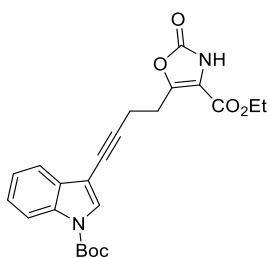
Ethyl 5-(4-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)but-3-yn-1-yl)-2-oxo-2,3-dihydrooxazole-4-carboxylate 6.124

P

A

G

E



Yellow oil

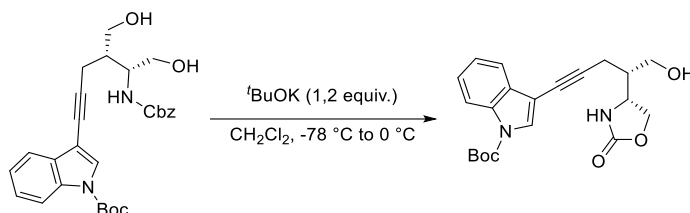
¹H NMR (300 MHz, CDCl₃) δ = 8.11 (d, *J* = 8.1 Hz, 1H), 7.67 (s, 1H), 7.61 – 7.56 (m, 1H), 7.39 – 7.24 (m, 2H), 4.75 (brs, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 1.66 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 158.8, 153.3, 149.2, 147.9, 136.3, 134.7, 130.8, 128.7, 125.2, 123.2, 120.1, 115.34, 115.27, 103.5, 90.5, 84.4, 73.9, 61.9, 28.3, 25.8, 18.2, 14.3

HRMS (TOF MS ES⁺) calcd for (M+NH₄)⁺ C₂₃H₂₈N₃O₆: 442.1978, found: 442.1973

R_f = 0.10 (cyclohexane/AcOEt: 2/1)

tert-butyl 3-((S)-5-hydroxy-4-((R)-2-oxooxazolidin-4-yl)pent-1-yn-1-yl)-1H-indole-1-carboxylate 6.134a



To a solution of diol **6.133** (108.8 mg, 0.221 mmol) in CH₂Cl₂ (2.2 mL) was added ^tBuOK (37.2 mg, 0.33 mmol, 1.5 equiv.) at -78 °C in one portion. The reaction mixture was warmed to 0 °C with stirring. After 1 h, the reaction was quenched by sat. aq. NH₄Cl and the resultant mixture was extracted by CH₂Cl₂ (x 3), brined and then dried over Na₂SO₄ and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 1/1 to 1/2) to yield the oxazolidinone **6.134a** (49%, 41.3 mg, 0.107 μmol) as yellowish oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.13 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.62 – 7.55 (m, 1H), 7.40 – 7.26 (m, 2H), 6.28 (brs, 1H), 4.62 (t, *J* = 8.6 Hz, 1H), 4.33 (dd, *J* = 8.6, 7.2 Hz, 1H), 4.19– 4.08 (m, 1H), 4.03– 3.87 (m, 2H), 2.57 (d, *J* = 6.1 Hz, 2H), 2.31 (brs, 1H), 2.12 – 1.98 (m,

P

A

G

E

1H), 1.67 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) δ = 159.8, 149.2, 134.7, 130.6, 128.9, 125.4, 123.4, 119.9, 115.5, 103.1, 89.2, 84.5, 74.9, 69.4, 63.7, 54.9, 43.9, 28.3, 18.8

IR (neat): 2971, 1733, 1513, 1451, 1368, 1232, 1152, 747, 422

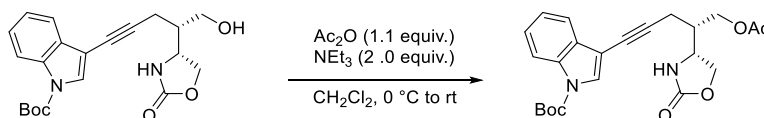
HRMS (TOF MS ES+) calcd for (M+NH₄)⁺ C₂₁H₂₈N₃O₅: 402.2029, found: 402.2034

HPLC: Daicel Chiralpak[®] IA (80% n-heptane, 20% EtOH), 20°C, 1 mL/min, 254 nm, t₁ = 14.9 min (major), t₂ = 18.3 min (major). 93% ee

[α]_D²⁰ +3.9 (c 0.36, CHCl₃)

R_f = 0.12 (cyclohexane/AcOEt: 1/2)

tert-butyl 3-((S)-5-acetoxy-4-((R)-2-oxooxazolidin-4-yl)pent-1-yn-1-yl)-1H-indole-1-carboxylate 6.134



To a solution of alcohol **6.134a** (40.5 mg, 0.105 mmol) in CH₂Cl₂ (1.0 mL) was added Et₃N (29 μL, 0.211 mmol, 2.0 equiv.) at room temperature. Ac₂O (11 μL, 0.116 mmol, 1.1 equiv.) was added at 0 °C and the mixture was stirred at room temperature. After 14 h, the reaction was quenched by sat. aq. NH₄Cl and the resultant mixture was extracted by CH₂Cl₂ (x 3), brined and then dried over Na₂SO₄ and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt: 3/1 to 1/1) to yield the title compound **6.134** (91%, 40.8 mg, 95.7 μmol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.13 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.63 – 7.56 (m, 1H), 7.39 – 7.26 (m, 2H), 6.51 (brs, 1H), 4.59 (t, *J* = 8.7 Hz, 1H), 4.43 – 4.24 (m, 3H), 4.07 (dd, *J* = 15.1, 7.6 Hz, 1H), 2.61 (d, *J* = 6.4 Hz, 2H), 2.21 – 2.11 (m, 1H), 2.10 (s, 3H), 1.66 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) δ = 171.1, 159.7, 149.1, 134.7, 130.6, 128.9, 125.3, 123.3, 119.9,

P

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115.4, 103.0, 88.7, 84.5, 75.1, 68.7, 63.6, 53.7, 42.0, 28.2, 21.0, 19.0

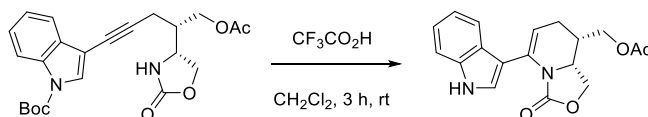
IR (neat): 3268, 2976, 2928, 1733, 1451, 1367, 1307, 1230, 1152, 1099, 1031, 934, 852. 746, 606, 463, 422

HRMS (TOF MS ES+) calcd for (M+NH₄)⁺ C₂₃H₃₀N₃O₆: 444.2135, found: 444.2124

[α]_D²⁰ -2.4 (c 1.51, CHCl₃)

R_f = 0.18 (cyclohexane/AcOEt: 1/1)

((8*S*,8*a*R)-5-(1*H*-Indol-3-yl)-3-oxo-1,7,8,8*a*-tetrahydro-3*H*-oxazolo[3,4-*a*]pyridin-8-yl)methyl acetate (6.135)



To TFA (0.13 mL, 1.7 mmol, 20 equiv.) was added dropwise a solution of **6.134** (36.2 mg, 84.9 μ mol) in CH₂Cl₂ (0.84 mL) at rt. After 3 h, the reaction mixture was cooled to 0 °C. The reaction was quenched by NEt₃ (0.8 mL) and diluted with sat. aq. NHCO₃. The resultant mixture was extracted by CH₂Cl₂ (x 3), brined and then dried over Na₂SO₄ and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (toluene/AcOEt: 2/1 to 1/1) to yield **6.135** (70%, 19.3 mg, 59.1 μ mol) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.32 (brs, 1H), 7.72 – 7.67 (m, 1H), 7.38 – 7.27 (m, 1H), 7.20 – 7.07 (m, 3H), 5.43 (dd, *J* = 4.5, 3.0 Hz, 1H), 4.61 (t, *J* = 8.9 Hz, 1H), 4.53 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.47 (dd, *J* = 11.6, 5.4 Hz, 1H), 4.31 (dt, *J* = 8.9, 3.0 Hz, 1H), 4.13 (dd, *J* = 11.6, 6.7 Hz, 1H), 2.59 (ddd, *J* = 18.8, 6.6, 3.0 Hz, 1H), 2.46 – 2.32 (m, 2H), 2.08 (s, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = 171.1, 154.7, 136.4, 130.9, 125.7, 123.7, 122.4, 120.3, 119.8, 111.7, 111.5, 108.4, 64.4, 62.6, 56.2, 34.7, 27.0, 21.1

IR (neat): 3349, 2960, 2921, 2855, 1732, 1647, 1572, 1453, 1371, 1260, 1237, 1179, 1156, 1085, 1027, 723, 697, 541

P

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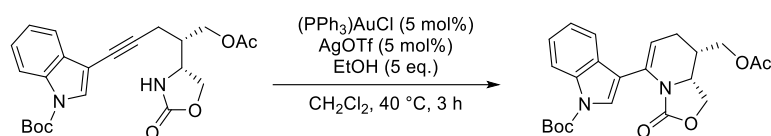
E

HRMS (TOF MS ES+) calcd for (M+NH₄)⁺ C₁₈H₂₂N₃O₄: 344.1610, found: 344.1614

[α]_D²⁰ = -29.0 (*c* 1.36, CHCl₃)

R_f = 0.25 (Toluene/AcOEt: 1/1).

tert-Butyl 3-((8*S*,8*aR*)-8-(acetoxymethyl)-3-oxo-3,7,8,8*a*-tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-5-yl)-1*H*-indole-1-carboxylate (6.136)



To a solution of **6.134** (50 μ g, 0.1714 mmol) in CH₂Cl₂ (1.7 mL) in a Schlenk flask were added EtOH (0.293 mL, 0.857 mmol, 5 equiv.) and a suspension of AuCl(PPh₃) (4.2 mg, 0.0086 mmol, 5 mol%) and AgOTf (2.2 mg, 0.0086 mmol, 5 mol%) in CH₂Cl₂ (1.7 mL) at r.t. After stirring for 4 h at 40 °C, solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (Cyclohexane/AcOEt: 2/1 to 1/1) to afford **6.136** (53.4 mg, 0.125 mmol, 73%) as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ = 8.15 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.30 (td, *J* = 7.8, 1.2 Hz, 1H), 7.22 (td, *J* = 7.8, 1.2 Hz, 1H), 5.45 (dd, *J* = 4.6, 2.8 Hz, 1H), 4.61 (t, *J* = 8.9 Hz, 1H), 4.52 (dd, *J* = 9.3, 3.2 Hz, 1H), 4.42 (dd, *J* = 11.6, 5.4 Hz, 1H), 4.31 (dt, *J* = 8.6, 3.2 Hz, 1H), 4.10 (dd, *J* = 11.6, 6.6 Hz, 1H), 2.58 (ddd, *J* = 19.2, 6.8, 2.8 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.07 (s, 3H), 1.66 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ = 171.0, 154.4, 149.7, 135.5, 129.8, 128.9, 124.7, 124.0, 123.0, 119.9, 116.4, 115.6, 110.5, 84.0, 64.5, 62.5, 55.8, 34.3, 28.3, 27.0, 21.1

HRMS (TOF MS ES+) calcd for (M+NH₄)⁺ C₂₃H₃₀N₃O₆: 444.2145, found: 444.2117

R_f = 0.35 (Cyclohexane/AcOEt: 1/1).

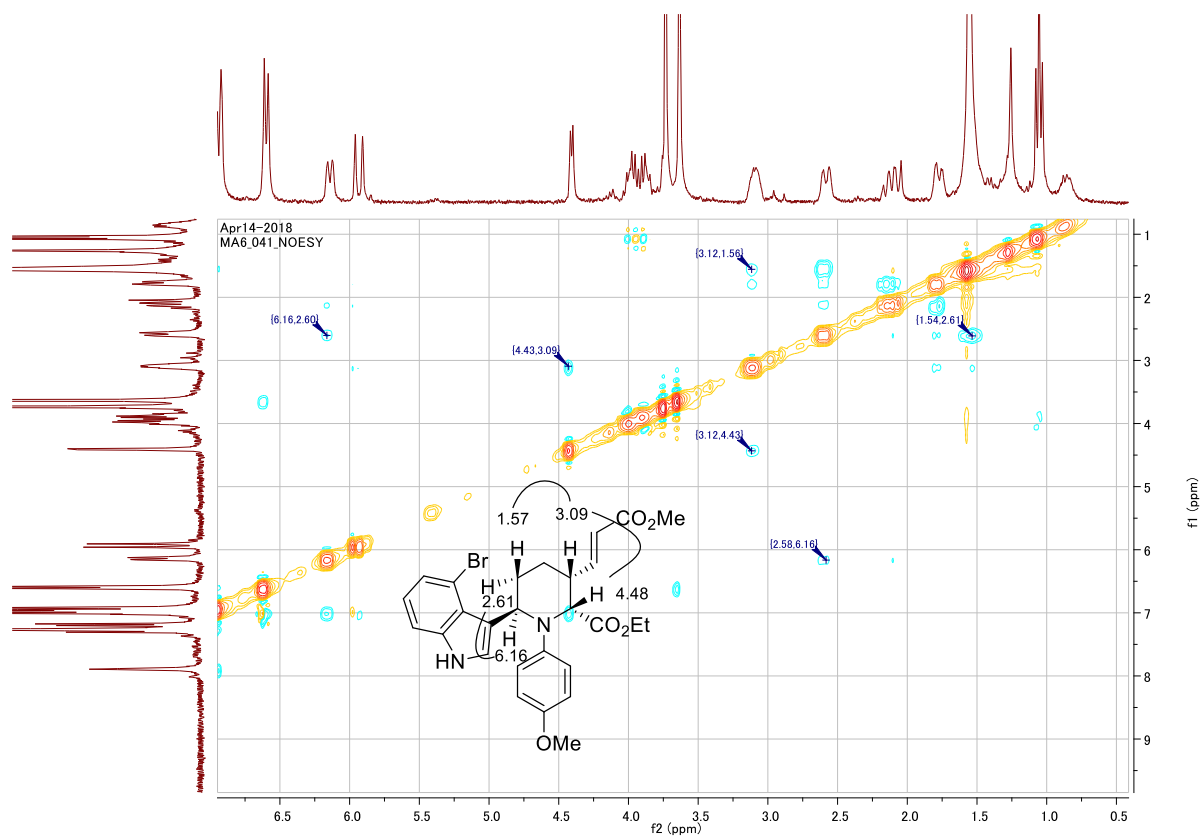
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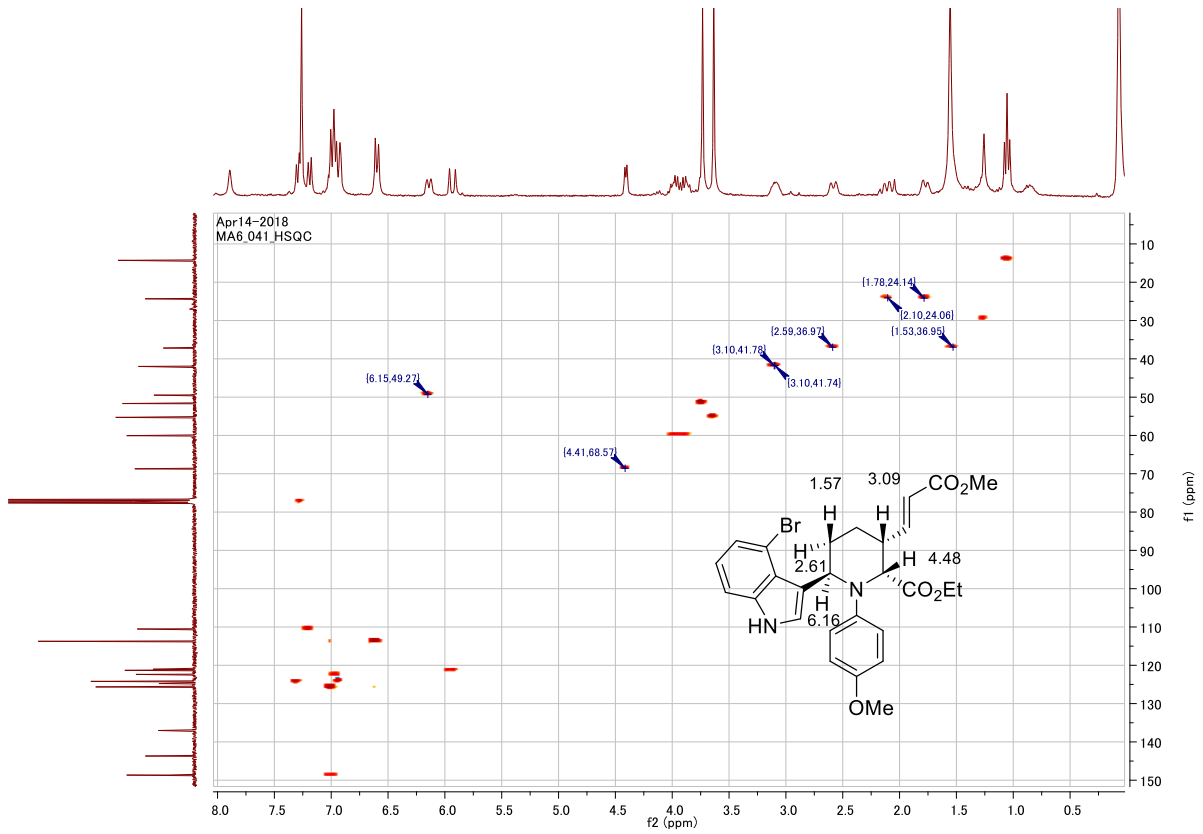
G

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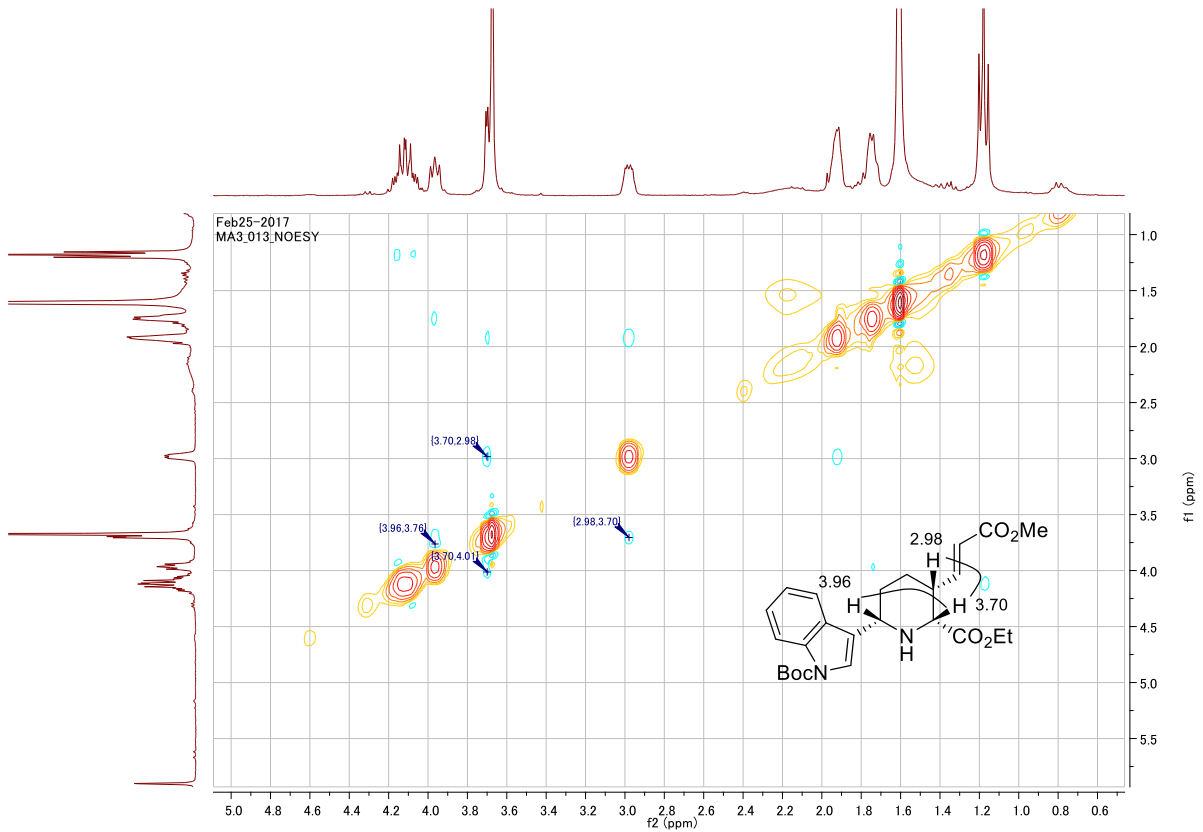
Zoom in of NOESY (300 MHz, CDCl₃)



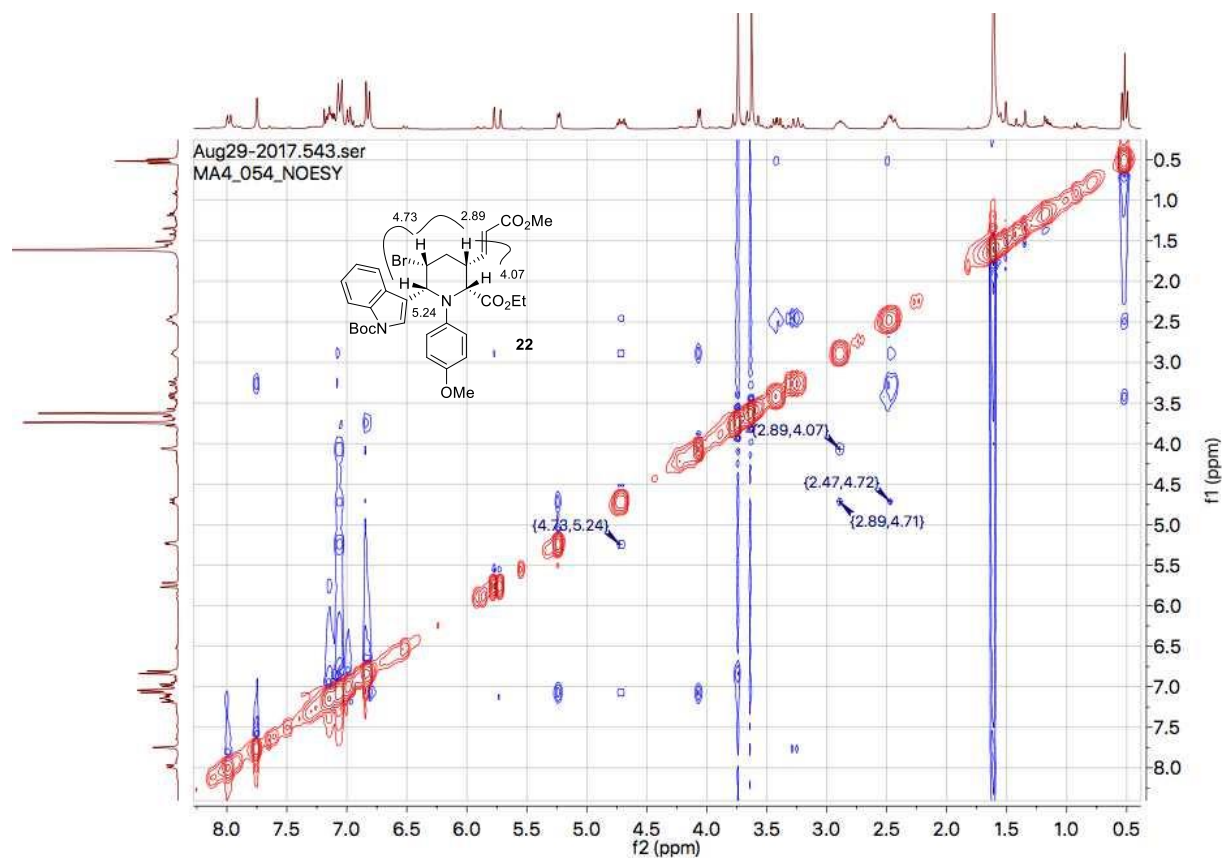
Zoom in of HSQC (300 MHz, CDCl₃)



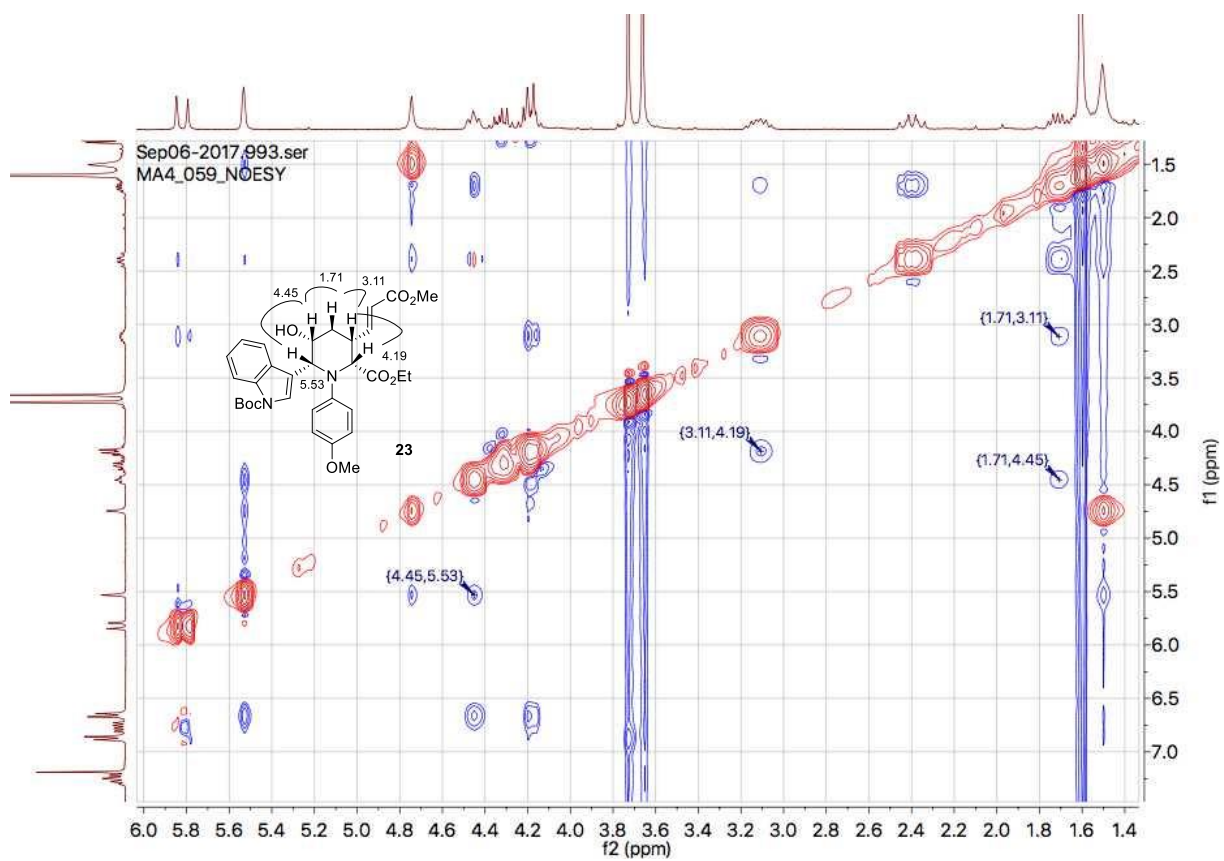
Zoom in of NOESY (300 MHz, CDCl₃)



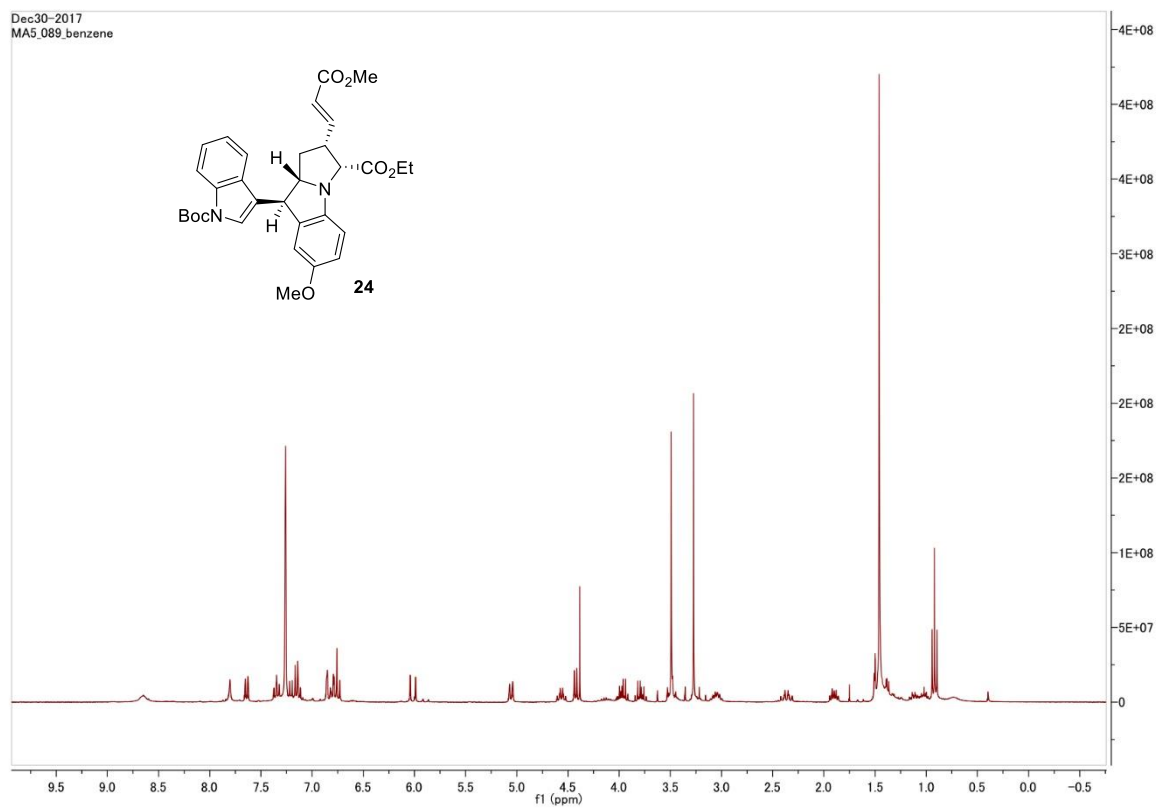
Zoom in of NOESY (300 MHz, CDCl₃)



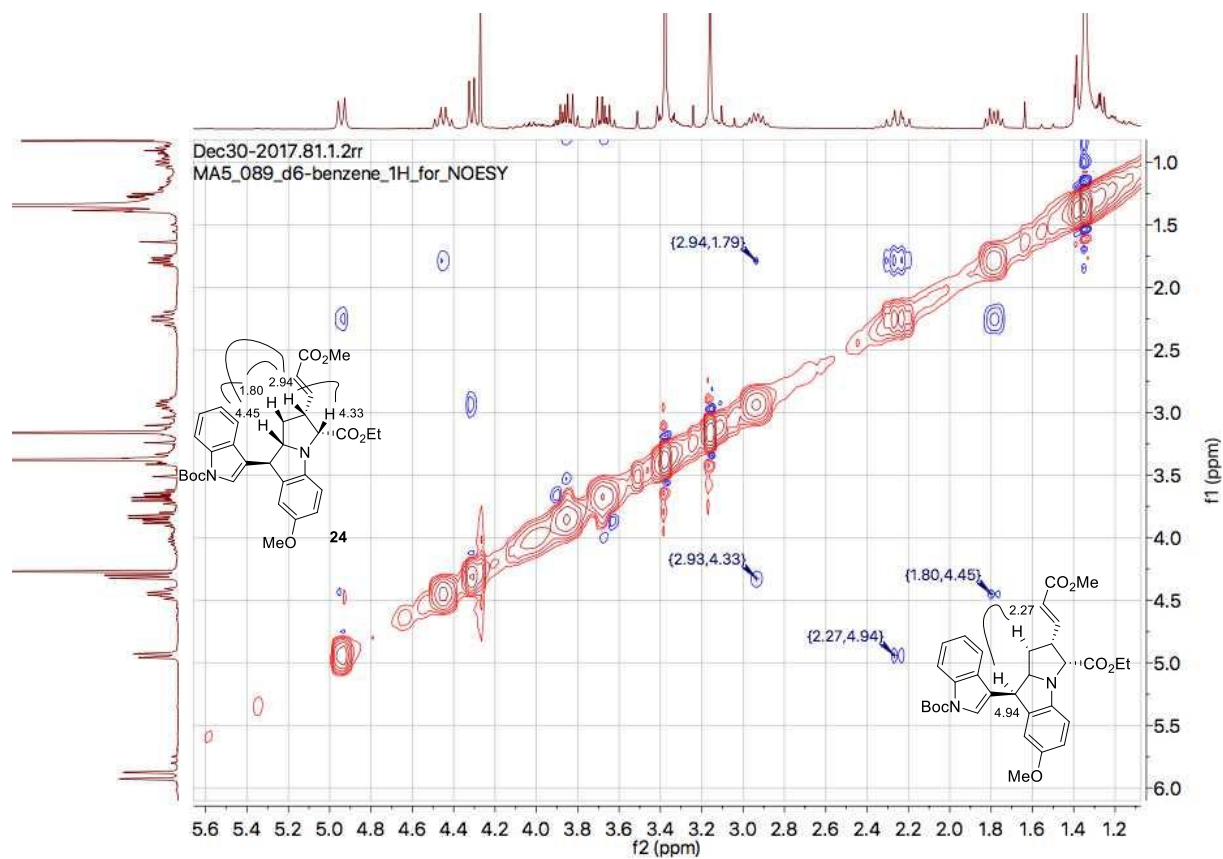
Zoom in of NOESY (300 MHz, CDCl₃)



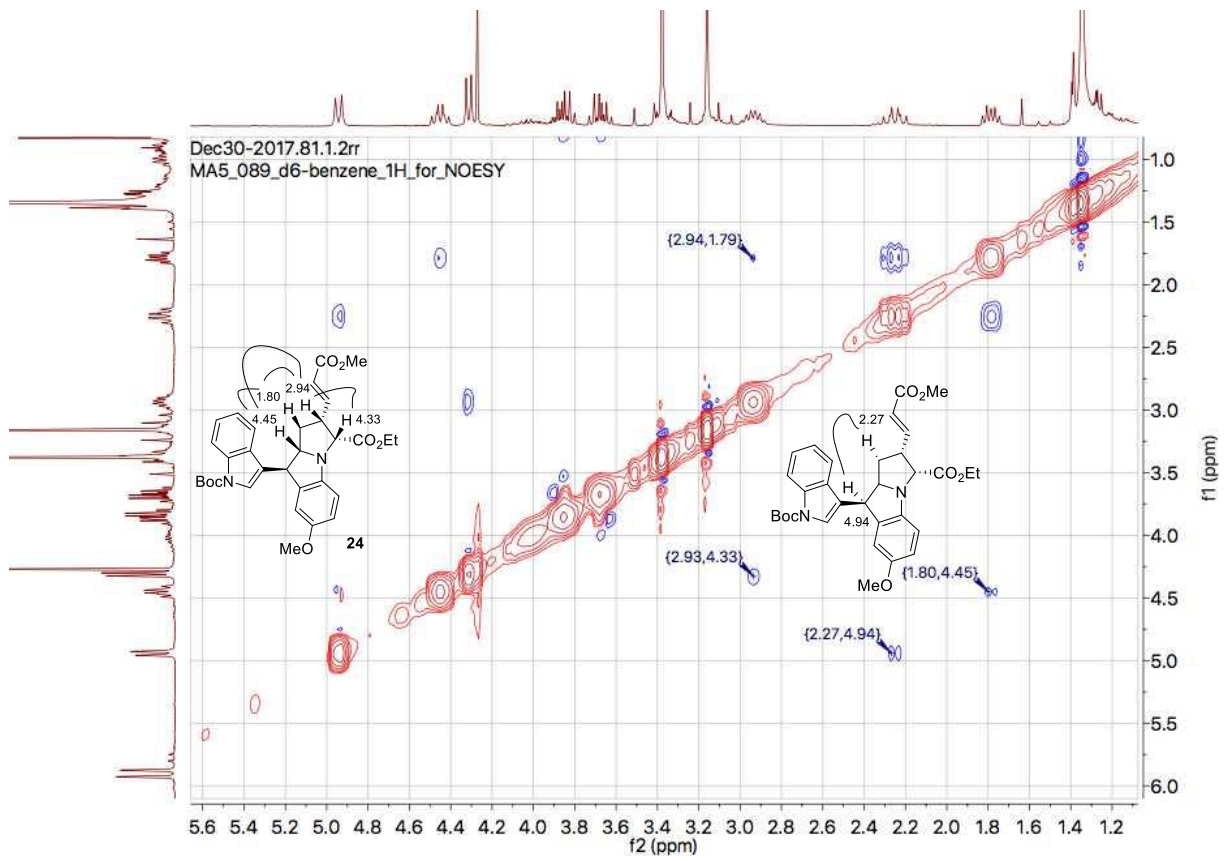
^1H NMR (300 MHz, C_6D_6) and NOESY (C_6D_6)



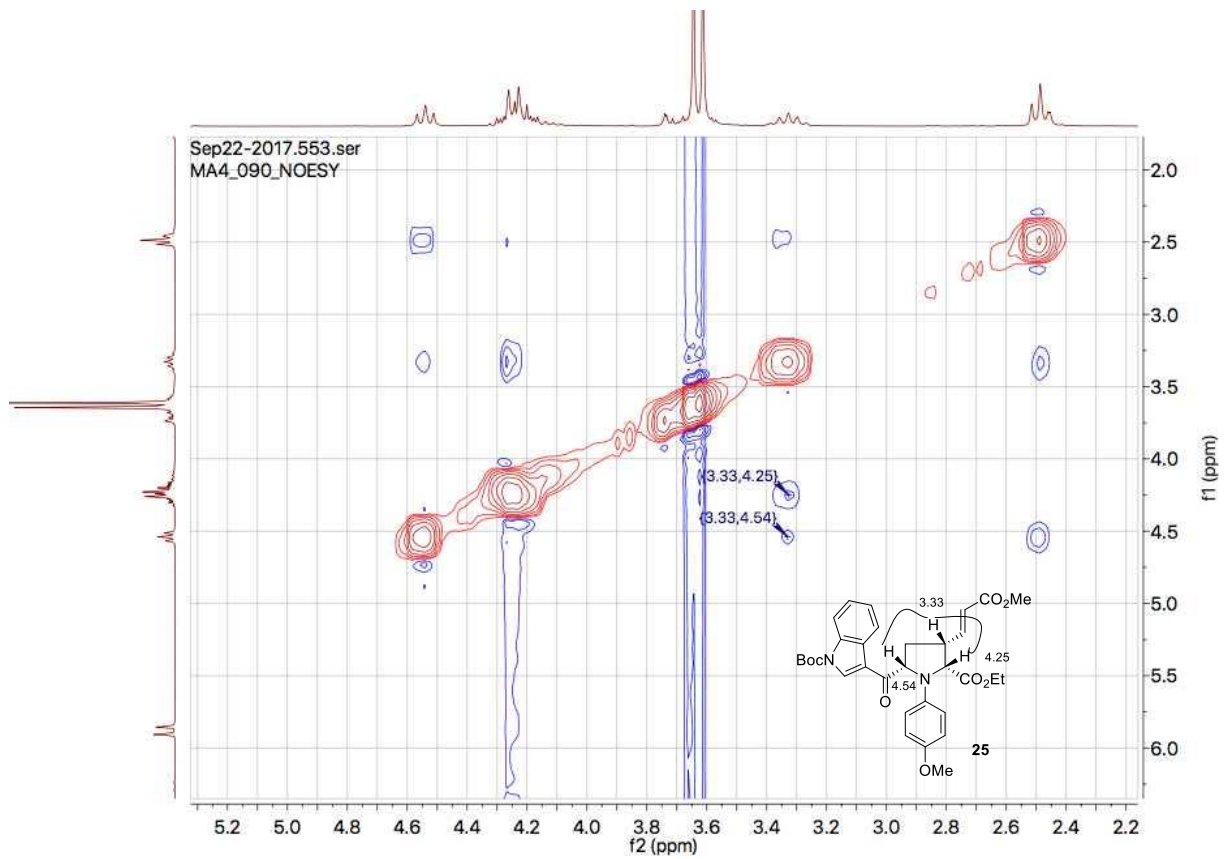
Zoom in of NOESY (300 MHz, C₆D₆)



Zoom in of NOESY (300 MHz, C₆D₆)



Zoom in of NOESY (300 MHz, C₆D₆)



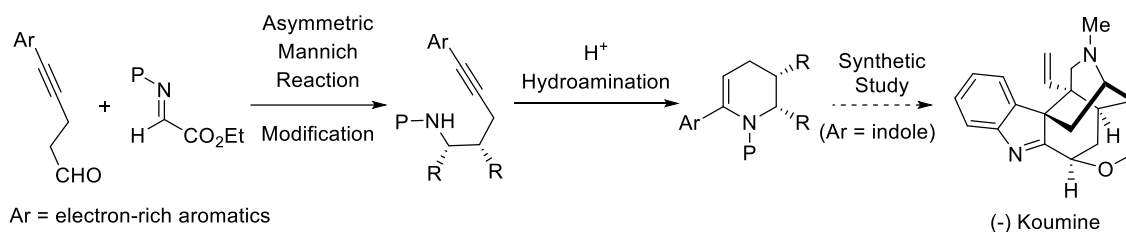
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Abstract

Piperidine ring is one of the most common heterocycles in natural products and the motif is especially well represented in pharmaceuticals. Consequently, enantioselective synthesis of multi-substituted piperidines is an important topic of investigation.

For the synthesis of nitrogen-containing compounds, asymmetric Mannich coupling is a useful strategy while intramolecular hydroamination of alkynes is a practical route to construct *N*-heterocyclic products. In this thesis, the two strategies were combined.

anti-Selective enantioselective Mannich reactions were thus employed to prepare chiral arylalkynyl amines. Connected to various aromatics, the reactivity of the triple bond was then studied in the framework of the intramolecular hydroamination reaction promoted with Brønsted acid. It was shown that depending on the electronic density of the alkyne, these adducts were converted into 5- or 6-membered rings, highlighting the balance between H-bonding and protonation. Tetrahydropyridines and piperidines were thus obtained with high regio-, diastereo-, and enantioselectivity and further functionalizations were also investigated in view of the first enantioselective total synthesis of *Gelsemium* alkaloid koumine.



Résumé

Le noyau pipéridine est un des motifs les plus courant dans les produits naturels et pharmaceutiques ce qui explique que la synthèse énantiosélective de piperidines polyfonctionnalisées soit un domaine particulièrement dynamique.

De par sa capacité à associer une fonction amine à un groupement carbonylé, la réaction de Mannich est un outil efficace pour former une liaison C-C de manière énantiosélective tandis que la réaction d'hydroamination intramoléculaire d'alcynes est pratique pour construire des hétérocycles azotés par formation de liaisons C-N. Dans cette thèse, nous avons combiné ces deux stratégies pour former de manière concise et énantiosélective des pipéridines polysubstituées.

Un couplage énantiosélectif de Mannich *anti*-sélectif fut employé pour préparer des amines chirales contenant une fonction alcyne connectée à un noyau aromatique riche en électrons. En présence d'acide de Brønsted, une réaction d'hydroamination cyclisante eut lieu démontrant une réactivité arylogue d'ynoethers et d'ynamines, la régiosélectivité de la cyclisation dépendant fortement de la densité électronique de l'alcyne. Ainsi lorsque la densité électronique est insuffisante, des pyrrolidines à cinq chaînons furent obtenus tandis que lorsque la densité électronique est élevée des piperidines furent isolées, illustrant la passage d'une activation de triple liaison par liaison hydrogène à sa protonation. A partir des tetrahydropyridines et piperidines, une étude fut lancée dans le but d'achever la première synthèse totale énantiosélective du produit naturel koumine, un alcaloïde de type *Gelsemium*.

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