Reactivity of functionalized alkynes with gold and silver : enantioselective cycloaddition and oxofluorination reactions

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Réactivité d'alcynes fonctionnalisés en présence d'or et d'argent : réactions de cycloadditions énantiosélectives et d'oxofluoration

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Abstract:

In the context of the key principles of “Green Chemistry”, the development of efficient, clean, and mild strategies to access cyclized and functionalized molecules is highly important in the field of organic chemistry. This PhD manuscript, divided into three chapters, first presents the bibliographic data on gold and silver catalysis and the reactivity of alkynes with such metals. Then, the cyclization reactions of 1,6-enynes in the presence of gold or silver complexes are discussed. Finally, the project based on the association of gold and Selectfluor is detailed.

The first chapter compiles a bibliographic overview, which introduces the general gold and silver catalysis and gives brief research data concerning a comparison of gold and silver catalysts in the carbonyl-alkynyl derivative systems. The second bibliographic chapter focuses on the cyclization reactions of 1,6-enynes. The results we obtained during the PhD project are then presented, and concern the domino enantioselective cycloaddition reactions of 1,6-enynes catalyzed by gold: after optimization, the enantiomeric excess was found to be up to 96%. Then, the project on silver-catalyzed unprecedented enantioselective intramolecular [4+2] cycloaddition reactions of amide-1,6-enynes is developed, and the best conditions implying a home-made atropisomeric ligand allowed the formation of tricyclic adducts with up to 50% *ee*. The third chapter first includes a bibliographic introduction on the interest of an incorporating fluor *via* a gold and Selectfluor partnership. The PhD project was then devoted to the synthesis of fluoroketones from aldehyde-alkynyl derivatives and alkynylaryl ketones in the presence of gold/Selectfluor partnership *via* an oxyfluorination process. The process was fully optimized and led to the fluoro compounds in good to excellent yields, up to 92%. Further efficient post-functionalization reactions afforded the corresponding 4-fluoroisoquinolines in excellent yields.

Keywords:

Gold catalysis, silver catalysis, enantioselective cycloaddition of enynes, 1,6-enynes, domino reaction, [4+2] cycloaddition reaction, Selectfluor, oxofluorination, α-fluoroketones

Réactivité d’alcynes fonctionnalisés en présence d’or et d’argent : réactions de cycloadditions énantiosélectives et d'oxofluoration

Résumé:

Dans le contexte de «chimie verte», le développement de systèmes catalytiques efficaces, propres et réalisés dans des conditions douces est fondamental en chimie organique. Ce manuscrit est divisé en trois chapitres. Le premier chapitre relate la bibliographie concernant la chimie de l’or et de l’argent lorsqu’ils sont en présence d’alcynes. Les exemples les plus significatifs et les plus proches de notre étude sont présentés. La suite du manuscrit présente les réactions de cycloaddition des enynes-1,6 catalysées par des complexes d’or et d’argent. Le troisième chapitre repose sur l’association entre l’or et le Selectfluor dans le cadre de la synthèse des composés fluorés.

Le premier chapitre propose un aperçu bibliographique, qui présente l’intérêt et l’efficacité des complexes d’or et d’argent ainsi qu’une comparaison de la réactivité de l’or vis-à-vis de l’argent dans le cas des systèmes carbonyl-alcyne. Le deuxième chapitre propose dans un premier temps les résultats bibliographiques des réactions de cyclisation des énynes-1,6. Les résultats obtenus impliquent une optimisation du système catalytique et l’accès à des dérivés fonctionnalisés *via* des réactions de cycloaddition domino énantiosélectives, la meilleure énantiosélectivité observée étant de 96%. La deuxième réaction de cycloaddition a mis en jeu des énynes-1,6 portant une fonction amide et le procédé de cycloaddition énantiosélectif [4+2] a été optimisé en présence d’argent. Le troisième chapitre propose un autre aspect de la thèse, impliquant l’association or/ Selectfluor dans le cadre de réactions de fluoration. La synthèse et l’étude de la réaction d’oxyfluoration d'aldéhyde-alcyne et d'alcynylaryl cétones en présence d'or et de Selectfluor a conduit aux dérivés fluorés fonctionnalisés avec des rendements allant jusqu'à 92%. Une transformation efficace des dérivés fluorés a consisté en la prépartion de 4-fluoroisoquinolines avec d’excellents rendements.

Mots clés:

Catalyse à l’or, argent, cycloaddition énantiosélective, énynes-1,6, réaction domino, réaction de cycloaddition [4 + 2], Selectfluor, oxofluoration, α-fluorocétones

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This thesis was performed in " Catalyse, Méthodologies de Synthèse et Chimie Fine " team at the Institut de Chimie de Nice (ICN) in Université Côte d'Azur, under the supervision of Professor Véronique Michelet and co-supervision of Doctor Sophie Poulain-Martini. I could not finish the thesis without truly helps and supports from people around me, and I would like to thank them sincerely.

First of all, I would like foremost to express my sincere gratitude to the thesis supervisor and director Prof. Véronique Michelet, for her continuous encouragement, guidance, help, patience, support, and tolerance during these three years. It is a great pleasure for me to work in the team, to learn her enthusiasm and insight for chemistry, serious scientific attitude, and wealth of knowledge. She never behaves like a "boss", even when I made some stupid mistakes, and it's like she is a big mom for the family. And I am grateful to my co-supervision of Dr. Sophie Poulain-Martini, for her useful advice in my work and her smile in daily life. She is such a friendly and patient person and gets along very well with everyone. By the way, thanks for the various festivals or travel gifts from them, like chocolates and desserts.

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creativity make me admiring. I also thank him a lot for French translation in all aspects, for discussions about chemistry, and kinds of weird knowledge. Romain Laher, he is very kind and he is good at photography, dancing, making cookies, and organizing affairs. I still remember his dancing in Marseille, and various photos of landscape, koala, kangaroo, and cat. Aurelien Dupeux, he is definitively a nice guy in the lab, warm-hearted, enthusiastic, and humorous. Thanks for the help of synthesizing substrates, asymmetric gold catalysts, preparing many documents, and Tiramisu. I am also very grateful to Sara Lachegur, Haotian Chang, Lingling Xiong, and Yue, I enjoyed chatting, listening to concerts, traveling, looking for good restaurants with them. A special acknowledgment to other PhD students: Vincent Davenel, Vincenzo Marsicano, Iryna Shcheholeva, Philippe Martinaux; Master students: Lakhwinder Kaur, Paula Ferreira, Veronika Khodureva, Marina Koleski, Marina Ayubova, and Tamba Camara, thanks for meeting them and thanks for the happy time with them.

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Do not, for one repulse, give up the purpose that you resolved to effect.

-William Shakespeare

To my motherland and my family

Table of contents

List of abbreviations

A	Å	Ångström (10^{-10} m)
	Ac	Acetyl
	Ar	Aryl
B	Bn	Benzyl
	BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
	BINOL	1,1’-Binaphthalene-2,2’-diol
	BIPHEP	2,2'-Bis(diphenylphosphino)-1,1'-biphenyl
	Boc	*tert*-Butoxycarbonyl
C	Cat.	Catalyst
	°C	Degree Celsius
	Conv.	Conversion
	Cp	Cyclopentadienyl
	Cy	Cyclohexyl
D	DCM	Dichloromethane
	DCE	Dichloroethane
	DMF	Dimethylformamide
	DMSO	Dimethyl sulfoxide
	dr	Diastereomeric ratio
	DTB	3,5-di-*tert*-butyl
	DTBM	3,5-di-*tert*-butyl-4-methoxy
E	ECD	Electronic circular dichroism
	ee	Enantiomeric excess
	equiv.	Equivalent
	Et	Ethyl
	EtOAc	Ethyl acetate
	EWG	Electron-withdrawing groups
G	g	gram
H	HPLC	High performance liquid chromatography
I	*i*-Bu	*iso*-Butyl
	IMes	*N,N’*-bis[2,4,6-(trimehyl)phenyl]imidazol-2-ylidene
	i-Pr	*iso*-Propyl
	IPr	*N,N’-bis*(2,6-di*iso*propylphenyl)imidazol-2 yidene
	IPy	Imidazo[1,5-*a*] pyridin-3-ylidene

M	M	Metal
	Me	Methyl
	MeCN	Acetonitrile
	$MeNO_2$	Nitromethane
	min	Minute
	mg	Milligram
	mL	Millilitre
	mmol	Millimole
	m.p.	Melting point
	MS	Mass spectrometry
N	NaBARF	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
	n-Bu	*n*-Butyl
	n-BuLi	*n*-Butyllithium
	NHC(s)	N-heterocyclic carbene(s)
	NMR	Nuclear magnetic resonance
P	PE	Petroleum ether
	Ph	Phenyl
	PhMe	Toluene
	ppm	Parts per million
Q	QDM	Quinodimethane
R	r.t.	Room temperature
	rac	Racemic
S	SFC	Supercritical fluid chromatography
T	T	Temperature
	t	Time
	t-Bu	*tert*-Butyl
	Tf	Trifluoromethanesulfonate
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin-layer chromotography
	TMS	Trimethylsilyl
	Ts	*p*-toluenesulfonyl
U	UV	Ultraviolet
V	v	Volume

General introduction

The key principles of "Green Chemistry"[1] were published in 1998 and have become the important philosophy to guide the practice of organic synthesis, which rethinks the design of chemical synthetic processes to reduce waste, the use of energy and resources, and the environmental impacts of chemical production. In the twelve principles, less hazardous chemical syntheses, safer solvents and auxiliaries, design for energy efficiency, and catalysis prompt us to develop new catalytic systems for useful organic molecules.

For the transition metal-catalyzed reactions, it has long been fundamental in organic chemistry and synthetic methodology research. Among the various transition metal catalysts, gold and silver, especially for homogeneous catalysis, keep exponential growths and have become one of the most powerful, innovative, fast, and direct approaches for the construction of new C-C or C-heteroatom bonds.[2]

Our PhD work was in line with gold and silver catalysis. The work presented in this PhD thesis is divided into two major parts, one focusing on cyclization reactions of 1,6-enynes *via* gold and silver catalysis, while the other one deals with oxofluorination reactions in the presence of gold and Selectfluor.

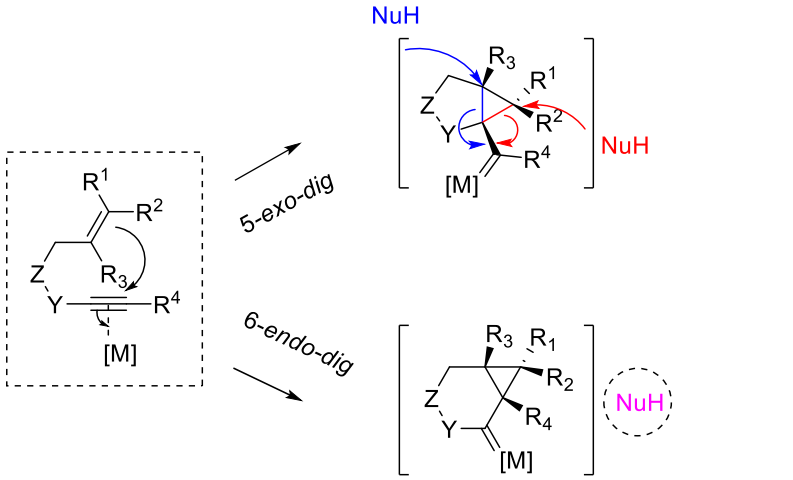
After the general introduction, **Chapter I** presents to the bibliographic study of gold and silver catalysis on alkynes.

Chapter II is dedicated to the study of cycloaddition reactions of 1,6-enynes under gold and silver catalysis. Since Trost's pioneering tandem alkylation-cycloadditions under transition-metal catalysis in 1984, the tandem cycloisomerization-nucleophile additions on various substrates to form new rings or construct new C-C and C-heteroatom bonds, have become one of the most active fields in organic synthetic methodologies. Following our team's interests, we focused on the 1,6-enyne systems in the presence of gold and silver catalysts. And in my

[1] P. T. Anastas, J. C. Warner, *Grexn chemistry: Theory and Practice*, Oxford University Press, New York, **1998**, 30.

[2] (a) M. Harmata, Silver in Organic Chemistry, John Wiley & Sons, **2010**; (b) F. D. Toste, A. S. K. Hashmi, Modern Gold Catalyzed Synthesis, John Wiley & Sons, **2012**; (c) F. D. Toste, V. Michelet, Gold Catalysis: An Homogeneous Approach, Imperial College Press, **2014**; (d) C. -J. Li, X. Bi, Silver Catalysis in Organic Synthesis, John Wiley & Sons, **2019**.

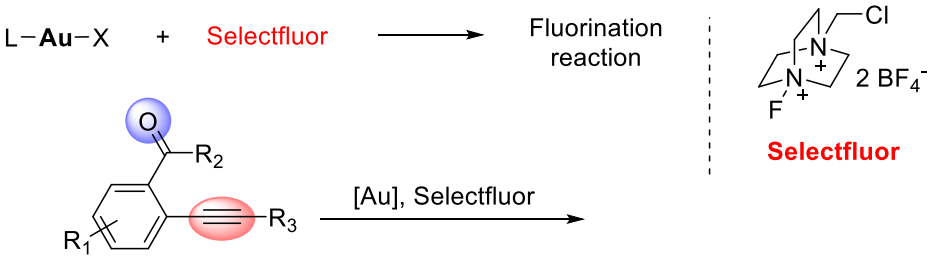
work: an enantioselective domino 1,6-enyne reaction was developed by gold-catalyzed 6-*endo-dig* pathway; the other silver-catalyzed intramolecular [4+2] cycloaddition reaction of amide-1,6-enynes, which concerned 5-*exo-dig* addition followed by a Friedel-Crafts arylation reaction, was disclosed (**Scheme 1**).



Y = CH_2, C=O, CCH_3
Z = O, N-R' (R' = alkyl, aryl, Ts), $C(CO_2Me)_2$, $C(CO_2Et)_2$, $C(SO_2Me)_2$

Scheme 1 Cycloaddition reactions of 1,6-enynes

Chapter III is centered on the fluorination with gold and Selectfluor system. The first gold-catalyzed fluorination process with electrophilic fluorine source - Selectfluor was reported by Gouverneur in 2008, and we wished like to explore the gold and Selectfluor catalytic system on aldehyde-alkynes and alkynylaryl ketones (**Scheme 2**).



Scheme 2 Gold and Selectfluor system

Finally, there is a general conclusion summarizing the results and discusions in this thesis.

Chapter I :

Bibliography

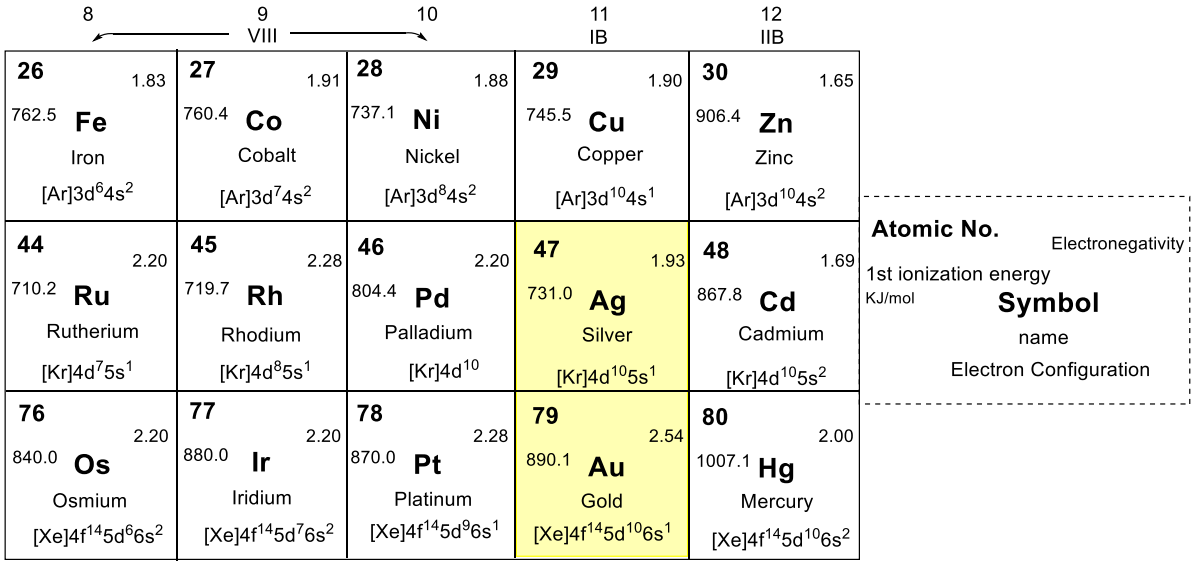
Chapter I : Bibliography

"Catalyst", is a term derived from Greek καταλύειν, and means something that could accelerate the rate of a chemical process.[3] It plays an extremely fundamental role in the modern chemical industries, and almost covers the entire field of chemical reactions. The first organic reaction utilizing a catalyst is the conversion of starch to glucose *via* acid-catalysis, and was studied in 1811 by Gottlieb Kirchhoff. In 1835, Jöns Jakob Berzelius coined the term "catalysis".[4] For the metal catalysis, the first systematic study of metal catalytic reaction that prepared "gaz hydrogène carboné huileux" (ethylene) was reported in the late eighteenth century.[5] In 1817, Humphry Davy discovered the use of platinum in catalysis and suggested to build a nonexplosive lamp in mining operations.[6] After many years, hydrogen lighter or Döbereiner's lamp, a lighter based on hydrogen and a platinum sponge was developed by Johann Wolfgang Döbereiner.[7] Since then, metal catalysis has attracted scientists' attention and has been booming ever.

Nowadays, although there are lots of researches on the use of cheap metal and metal-free organic catalysis, precious metal catalysis is still an important part of metal catalysis and has still some superiority and irreplaceability. Noble or precious metals, "Shiny, malleable, and resistant to corrosion", ruthenium, rhodium, palladium, silver, gold, and so on are some of the examples (**Scheme I-1**). Except for the use in medium of exchange or money, trade, jewelry, and arts, their catalytic potential has been discovered and led to a new era, which are key players in the chemical industry. Platinum, alone or in combination with rhodium, was the first precious metal to participate catalytically in the sulfuric and nitric acid production processes in 1831. Until now, precious metal catalysts are widely used in various fields, like industrial manufacturing, agrochemical, petrochemical, biochemistry, pharmaceutical, environment science, and so on. And in June 2020, it was reported that the global precious metal catalysts market is expected to exceed more than $ 20.50 billions by 2024 at a compound annual growth

[3] (a) M. Nič, J. Jirát, B. Košata, A. Jenkins, A. McNaught, *IUPAC, Research Triagle Park, NC*, **2009**; (b) J. Wisniak, *Educación química*, **2010**, *21*, 60.
[4] J. J. Berzelius, *Jahres-Bericht*, **1835**, *14*, 237.
[5] A. F. Fourcroy, *Ann. Chim.*, **1797**, *21*, 48.
[6] H. VIII. Davy, *Philosophical Transactions of the Royal Society of London*, **1817**, *107*, 77.
[7] (a) J. W. Döbereiner, *Journal für Chemie und Physik*., **1822**, *34*, 91; (b) J. W. Döbereiner, *Journal für Chemie und Physik*., **1823**, *38*, 321.

rate (CAGR) of 6% in the given forecast period.[8]



Scheme I-1 Partial view of periodic table of the elements

Precious metal catalysts have incompletely filled orbitals, which can provide electrons or withdraw electrons from reagents according to different chemical reaction types. Thus, each precious metal catalyst has unique characteristics and show high activity and selectivity in catalysis. Moreover, those catalysts have high thermal stability, and in the reaction system, they are stable and not easily oxidized. Among them, silver and gold, as two of the seven metals of antiquity, had an enduring role in most human history. The elemental state is used for currency, jewelry, and represents wealth and value. As catalysts, they have high catalytic activities for many chemical reactions.[2]

This Ph.D. thesis deals with three different types of reactions under gold or silver catalysis, which show similarities and differences in chemical properties and catalytic activities. Thus, the catalytic activities of gold and silver catalysts will be introduced in the next chapter.

1. Gold and silver catalysts

1.1 General introduction about gold and silver

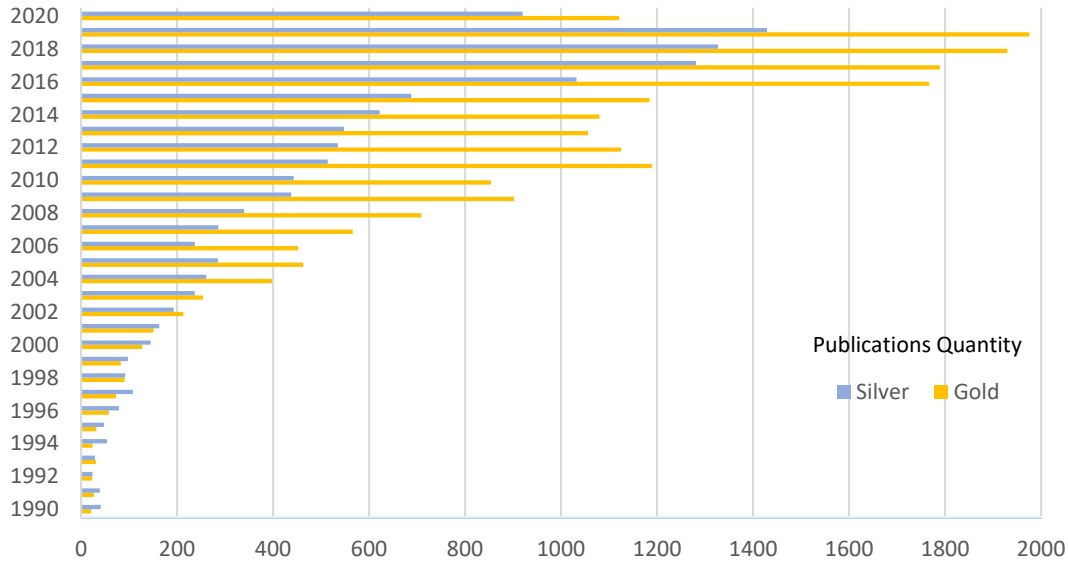
[8] Precious Metal Catalysts Market 2020, How The Industry Will Witness Substantial Growth In The Upcoming Years - Market Research Engine.

- Silver

Silver, atomic number 47, atomic weight 107.88, group 11 (IB) period 5 of the periodic table, and ground-state electronic configuration [Kr] $4d^{10}5s^{1}$, first appear around 5000 BC. It is a soft, malleable, ductile, white shiny precious metal. Its oxidation states are −2, −1, +1, +2, +3, and the most frequent oxidation state is +1.

Due to the outer orbital $5s^{1}$ electronic configuration, silver could form abundant silver(I) salts/complexes with various counterions, like oxide, sulfide, phosphide, olefin complexes, etc. And the typical d^{10} electronic configuration causes silver to coordinate with most of the π-donors, N-, O- or S- donor groups, like alkynes, alkenes, and various carbon-heteroatoms unsaturated bonds.[9] Moreover, due to the empty *f* orbitals and relativistic contraction, Ag exhibits σ- or π- Lewis acidity with preference to σ-coordination over π-coordination.[10]

The first example of a silver-catalyzed reaction, oxidizing the ethylene into ethylene oxide, was reported in 1933 after it was extended to butadiene.[11] Compared with other transition metals,



Scheme I-2 Number of publication on « gold catalysis» & «silver catalysis» from 1990 to 2020[12]

[9] (a) D. J. Gorin, F. D. Toste, *Nature*, **2007**, *446*, 395; (b) A. Furstner, P. W. Davies, *Angew. Chem. Int. Ed.*, **2007**, *46*, 3410; (c) M. Alvarez-Corral, M. Munoz-Dorado, I. Rodriguez-Garcia, *Chem. Rev.*, **2008**, *108*, 3174; (d) K. Gilmore, I. V. Alabugin, *Chem. Rev.*, **2011**, *111*, 6513; (e) N. T. Patil, Y. Yamamoto, *Chem. Rev.*, **2008**, *108*, 3395.

[10] (a) M. P. Munoz, *Chem. Soc. Rev.*, **2014**, *43*, 3164; (b) M. Naodovic, H. Yamamoto, *Chem. Rev.*, **2008**, *108*, 3132.

[11] (a) D. F. Othmer, M. S. Thakar, *J. Ind. Eng. Chem.*, **1958**, *50*, 1235; (b) P. P. McClellan, *J. Ind. Eng. Chem.*, **1950**, *42*, 2402; (c) S. Wilkinson, *Chem. Eng. News*, **1999**, *77*, 27.

[12] Data from Reaxys, “silver catalysis” and “gold catalysis” in July **2020**.

silver was considered to have lower catalytic activity and efficiency in the past. Until in the past few decades, the research on silver-based catalysts has developed rapidly both heterogeneous and homogeneous systems (**Scheme I-2**).[13]

Now, silver salts are extensively employed as Lewis acids, weak bases, halophiles, radical precursors, general oxidants, SET oxidants (SET = single electron transfer), and so on.[2,13] Furthermore, silver is more economical and cheaper than other precious metals. Its excellent catalytic selectivity, environmentally friendly activity, made silver catalyst providing unique opportunities, and becoming significant tools in organic methodology research, industrial catalysis, high-tech materials, and life sciences.

- Gold

Gold, atomic number 79, atomic weight 196.97, group 11 (IB) period 6 of the periodic table, and ground-state electronic configuration [Xe] $4f^{14}\ 5d^{10}\ 6s^{1}$, is the earliest recorded metal employed and its traces have been found in the late Paleolithic period 40,000 BC.[14] The purest form is a soft, the most malleable of all metals, ductile, slightly reddish yellow precious metal. Its oxidation states are −3, −2, −1, 0,[15] +1, +2, +3, +5, and the most frequent oxidation states are +1 and +3.

Except for halides, phosphates, or other common partners, gold could construct very strong chemical bonds with noble gas xenon ($AuXe_4^{2+}$). The electron affinity of Au is similar to iodine. Based on the "soft" Lewis acid properties, electrophilic gold species can activate unsaturated bonds by nucleophile addition such as alkynes, allenes, alkenes, and oxygen, nitrogen, or sulfur species, etc. Besides, gold has also the capacity to act as an electron donor. It implies that gold species could play the role of stabilizing carbocationic or other types of intermediates in the catalytic system. This peculiar and fascinating Lewis acid and electron donor dual behavior has rapidly attracted the interest of chemists and has been highlighted in diverse modes. The tolerance of gold to oxygen, the compatibility with different kinds of functional groups, or aqueous conditions, are also worth mentioning.

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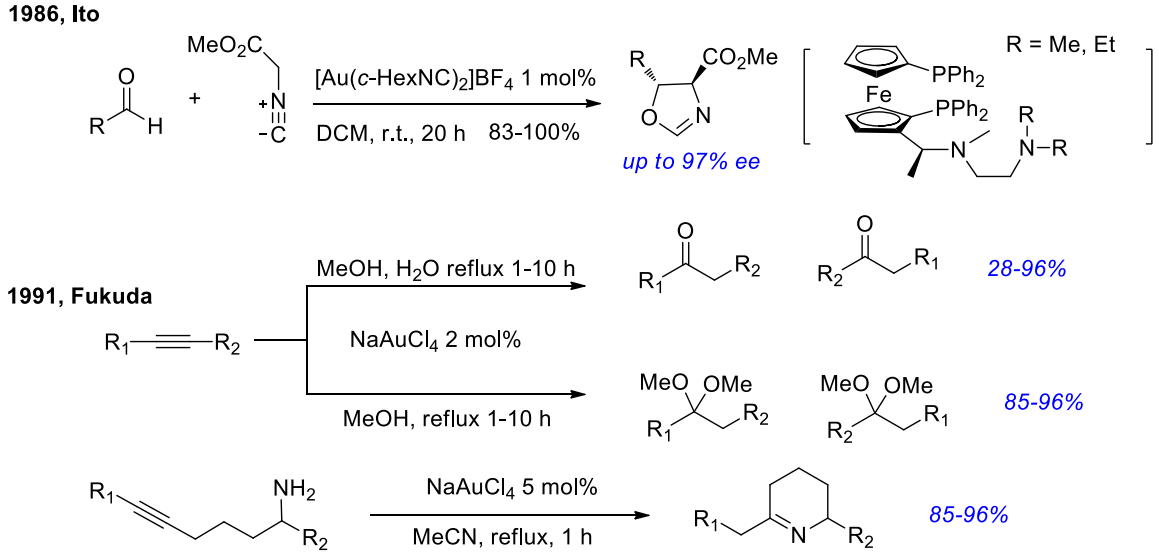
[13] (a) Q. Zheng, N. Jiao, *Chem. Soc. Rev.*, **2016**, *45*, 4590; (b) H. Pellissier, *Chem. Rev.*, **2016**, *116*, 14868; (c) G. Fang, X. Bi, *Chem. Soc. Rev.*, **2015**, *44*, 8124; (d) G. Fang, X. Cong, G. Zanoni, Q. Liu, X. Bi, *Adv. Synth. Catal.*, **2017**, *359*, 1422; (e) Y. Yamamoto, *Chem. Rev.*, **2008**, *108*, 3199; (f) H. V. R. Dias, C. J. Lovely, *Chem. Rev.*, **2008**, *108*, 3223.

[14] "History of Gold". Gold Digest. Retrieved 4 February 2007.

[15] N. Mézaille, N. Avarvari, N. Maigrot, L. Ricard, F. Mathey, P. Le Floch, L. Cataldo, T. Berclaz, M. Geoffroy, *Angew. Chem. Int. Ed.*, **1999**, *21*, 3194.

Considering gold physical and chemical properties, it's understandable that its catalytic activity was neglected up to the end of the last century in transition metals catalysis history. In 1986, Ito and collaborators reported the first notable of homogeneous gold-catalyzed reaction like a milestone in gold catalysis. The reaction shows the asymmetric addition of isocyanate and aldehyde to form oxazoline by efficiently gold catalysis that combines chiral ferrocenyl diphosphine ligands with gold.[16] In 1991, Fukuda disclosed gold(III)-catalyzed alkyne reaction to produce ketones, ketals, and cyclic imines, respectively in the presence of water, alcohols, or amines nucleophiles (**Scheme I-3**).[17] It has been recognized as a major breakthrough, and after 2001, gold catalysis was explored for its potential and has significant growth. During the last twenty years, gold catalysis has seen impressive development and became a hot topic in organic metal catalysis (**Scheme I-2**).[18] Considering the increasing number of publications and review articles, it can be evidenced that gold has come to be a powerful synthetic tool in organic synthesis.



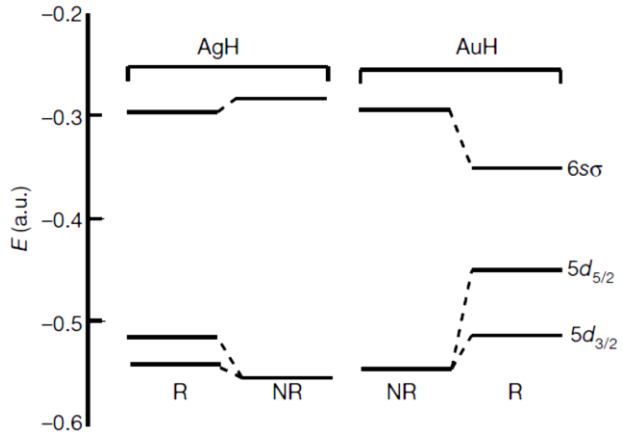
Scheme I-3 Gold-catalyzed reactions

1.2 Relativistic effects in gold and silver

In the transition metals catalysts, silver and gold have received extensive attention during the last two decades due to the excellent catalytic activity and selectivity.

[16] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.*, **1986**, *108*, 6405.
[17] (a) Y. Fukuda, K. Utimoto, *J. Org. Chem.*, **1991**, *56*, 3729; (b) Y. Fukuda, K. Utimoto, *Synthesis (Stuttgart)*, **1991**, *11*, 975; (c) Y. Fukuda, K. Utimoto, *Bull. Chem. Soc. Jpn.*, **1991**, *64*, 2013.
[18] A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6990.

Obviously, silver and gold fall into the same group of the periodic table, and it has been recognized that similar electronic arrangements are the main reason for their similar chemical properties. From non-relativistic Hartree-Fock calculations, free Ag and Au atoms or their diatomic hydrides (**Scheme I-4** NR) are strikingly similar, AgH 5σ to AuH 6σ and AgH 4*d* to AuH 5*d* bonds.[19]



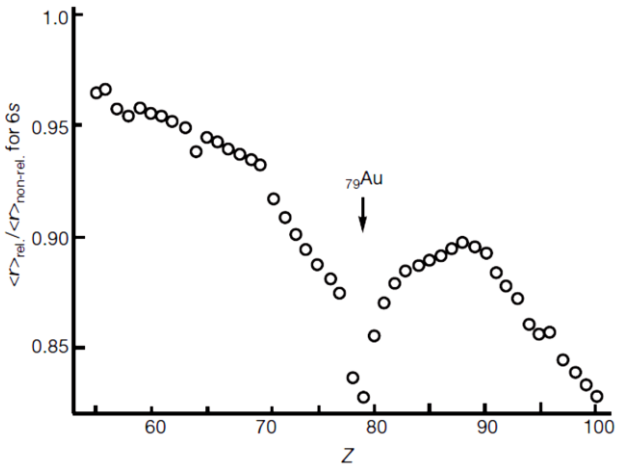
Scheme I-4 Comparison of AgH and AuH bond [AgH and AuH molecular orbital energies are shown: R - calculated (Hartree-Fock) molecular orbital energies; NR - without consideration of relativistic effects][19c]

The differences in the chemical properties of silver and gold was explained by the relativistic effect. The relativistic effect comes from the high speed of the electrons which move close to the heavy nucleus, consequently, leading to energetic stabilization and radial contraction by a mass increase.[20] From the work of Pyykkö and Desclaux,[19b] the relativistic effects push the *s* and *p* atomic orbitals (AO's) energies down, the *d* AO's up, and the effects are much smaller for silver than for gold (**Scheme I-4** R). Thus, the relativistic contraction of the 6*s* explains the shorter and stronger covalent bond with gold, as well as larger ionization potential and electron affinity. On the other hand, the 5*d* shell of gold in the relativistic effect qualitatively explains the Au^{+3} and Au $^{+5}$. In fact, the relativistic effect also explains the yellow color gold and silver's color.

Additionally, the relativistic effect of gold is larger than its neighbors and larger than any other element with Z < 100 (**Scheme I-5**). It causes a greater contraction of the 6*s* and 6*p* gold orbitals and an expansion of the 5*d* and 5*f* orbitals. In this case, gold catalysts are electrophilic and have exceptional Lewis acidity, and in the chemical reaction, the 5*d* electrons was extracted,

[19] (a) J. P. Desclaux, P. Pyykkö, *Chem. Phys. Lett.*, **1976**, *39*, 300; (b) P. Pyykkö, J. P. Desclaux, *Acc. Chem. Res.*, **1979**, *12*, 276; (c) D. J. Gorin, F. D. Toste, *Nature*, **2007**, *446*, 395.
[20] (a) S. J. Rose, I. P. Grant, N. C. Pyper, *J. Phys. B*, **1978**, *11*, 1171; (b) P. Pyykkö, *Angew. Chem. Int. Ed.*, **2004**, *43*, 4412.

used to stabilize the electron density of ligands or reaction intermediates.



Scheme I-5 The relativistic contraction of 6*s* shell in Cs (*Z* = 55) to Fm (*Z* = 100)

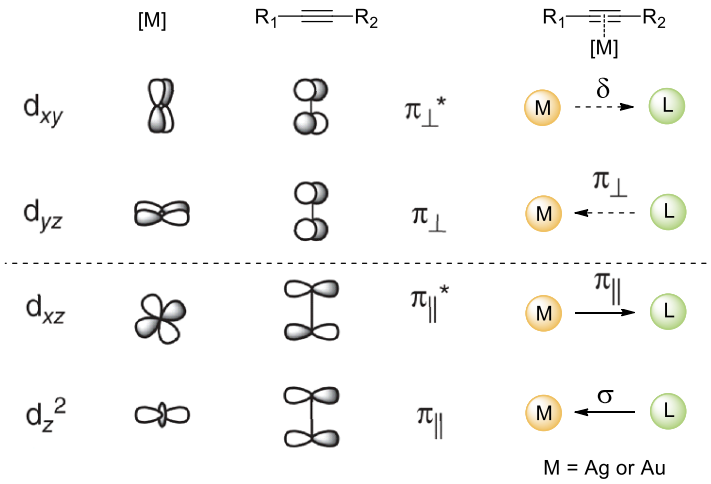
1.3 The reactivity of carbophilic species for gold and silver catalysts with alkyne

From ligand field theory (LFT) and Dewar–Chatt–Duncanson (DCD) model[21], we know that coordination chemistry makes great significance in transition metal systems, and it can consider the bond as a donor-acceptor interaction between the transition metal and π-ligands.[22] The overlap of the π-system of a suitable symmetry with empty metal orbitals could form a *σ*-bond, and the back-donation from filled *d* orbital of transition metal into an *anti*-bonding π* orbital of the ligand could cause a π-interaction.

As shown in **Scheme I-5**, there are the σ-symmetric donation and back-donation between M and L in the in-plane $\pi_{||}$ orbitals, the orthogonal out-of-plane $\pi_{\perp}$ orbitals participate to M←L π-donation, and *d* orbitals of transition metal with empty $\pi_{\perp}^{*}$ orbital of ligand give rise to M→ L back-donation.

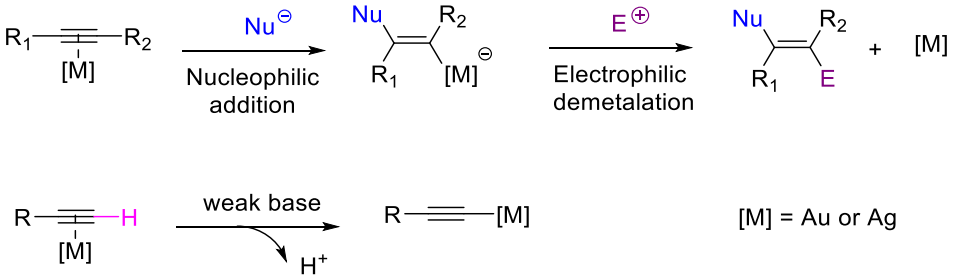
[21] (a) M. J. S. Dewar, *Bull. Soc. Chim. Fr.*, **1951**, *18*, C71; (b) J. Chatt, L. A. Duncanson, *J. Chem. Soc. (Resumed)*, **1953**, 2939.

[22] (a) D. M. P. Mingos, *Bonding of unsaturated organic molecules to transition molecules,* **1982**, 1; (b) G. Frenking, N. Frohlich, *Chem. Rev.*, **2000**, *100*, 717; (c) A. Dedieu, *Chem. Rev.*, **2000**, *100*, 543.



Scheme I-5 Orbital diagram: activation of alkyne by Au/Au catalyst

The d^{10} electronic configuration makes gold and silver catalysts able to act as a σ-Lewis acid or π-Lewis acid, and has strong carbophilic nature through favoring to interact with most of the unsaturated systems. Then, gold and silver catalysts can be considered as extremely effective alkyne activators.



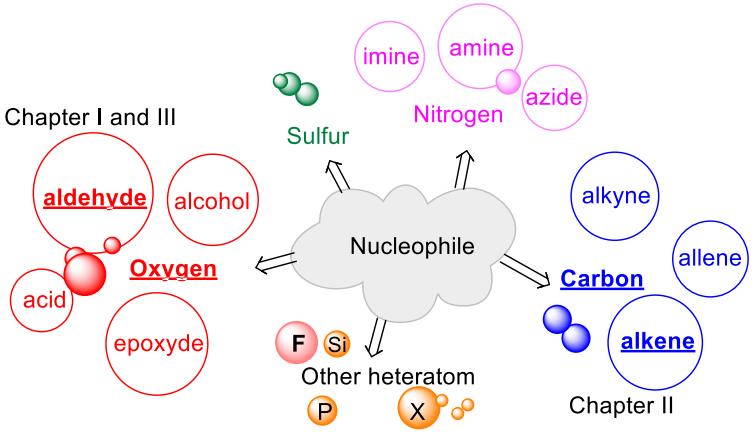
Scheme I-6 Trapping of gold/silver intermediates

Upon alkyne coordination with gold or silver (**Scheme I-6**), alkyne moiety is easily attacked by a relatively weak nucleophile. Then, the demetalation process may occur in the presence of electrophile species, the carbon-E bond sequence replaces carbon-M. If the electrophile is a simple proton, a protodemetalation delivers back the catalyst. And for the terminal alkyne, the alkynyl C-H bond is weakly acidic, and the metal coordination state increases the C-H acidity remarkably, due to silver or gold would pull electron density away from the triple bond and toward itself. In a suitable weak base case, silver acetylide and gold acetylide can be generated readily. This property is invoked in many reactions that need aqueous conditions or tolerate acid and base.[26]

2. Comparison of catalytic activity between gold and silver

Recently, gold and silver catalysis showed relevance in the field of organic synthesis and organometallic chemistry. In the case of alkynes, after recognizing the activation of alkynes, many reactions subsequently are studied with various species or functional groups as partner reagents.

The diverse modes of different nearby environments and different catalysts reactivities, which can generate molecular diversity and more complex polycyclic structures, provide opportunities to new C-C and C-heteroatoms bonds. In this part, we will introduce some selected representative examples with gold and silver activated alkynes groups.



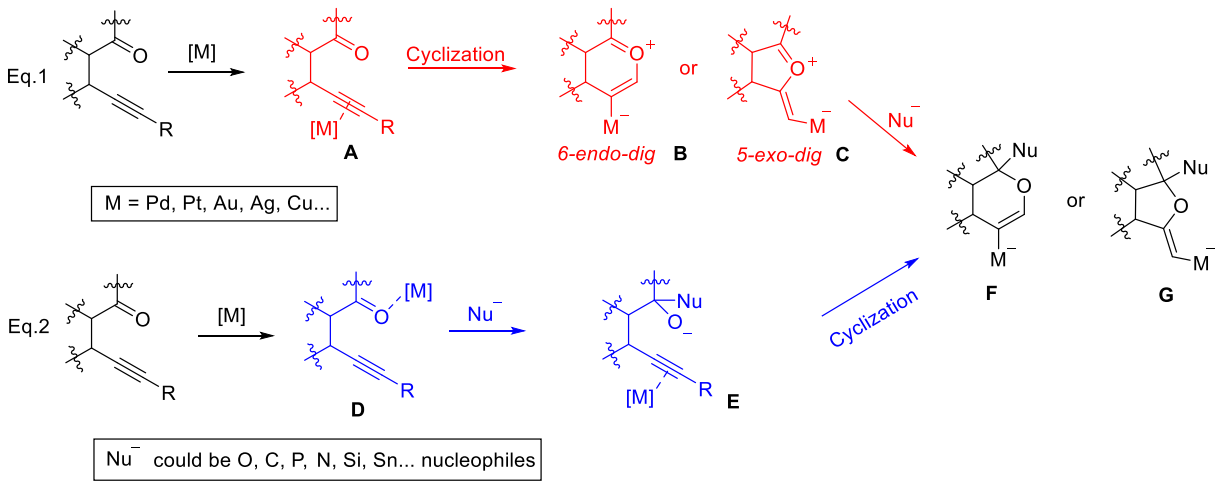
Scheme I-7 Various nucleophiles

Over the past two decades, a large number of researches have appeared in activating alkyne group with various nucleophiles, like oxygen nucleophiles, carbon nucleophiles, nitrogen nucleophiles, and so on (**Scheme I-7**).[2,9,10,13] In view of the relevance of my projects and works, alkyne with oxygen nucleophiles, cyclization reactions of carbon-carbon triple bonds with aldehyde species are presented in **chapter I** and **III**, in the presence of gold and silver catalysts. Alkene species in carbon nucleophiles, cycloisomerization reactions, and domino cyclization reactions of 1,6-enyne systems are disclosed in **chapter II**.

2.1 Cyclization reactions of carbonyl directed alkyne derivatives

The tandem reactions of nucleophilic addition/cyclization on the systems which involve a carbonyl and a carbon-carbon triple bond function *via* transition metal-catalysis, have witnessed tremendous growth, and several interesting results have been documented in the literature.

Yamamoto and co-workers reported the first example of palladium (II)-catalyzed acetalization/cycloisomerization reactions on aldehyde-alkynes, in the presence of *p*-benzoquinone and alcohol in 2002.[23(a)] Since then, the reactivity of many other transition metals or electrophiles has been very widely studied in nearly twenty years, like Pd,[24] Ru,[25] Au,[26] Ag,[27] Cu,[28] and so on.



Scheme I-8 Two pathways of cyclization of carbonyl with alkyne system

From the literature, there are two pathways that was envisaged depending on the nature of the catalyst, 5-*exo-dig* and 6-*endo-dig*, resulting in different cyclization products, as shown in **Scheme I-8**.

For the carbophilic catalyst, it favors to be coordinated by the triple bond (**A**). Then, the carbonyl group promotes a cyclization reaction followed by a 5-*exo-dig* or 6-*endo-dig* pathway,

---

[23] (a) N. Asao, T. Nogami, K. Takahashi, Y. Yamamoto, *J. Am. Chem. Soc.*, **2002**, *124*, 764; (b) Y. Yamamoto, *J. Org. Chem.*, **2007**, *72*, 7817.

[24] (a) A. Chandra, B. Singh, R. S. Khanna, R. M. Singh, *J. Org. Chem.*, **2009**, *74*, 5664; (b) N. Nardangeli, N. Topolovčan, R. Simionescu, T. Hudlický, *Eur. J. Org. Chem.*, **2020**, 227; (c) R. M. Singh, R. Kumar, K. C. Bharadwaj, T. Gupta, *Org. Chem. Front.*, **2016**, *3*, 1100; (d) A. Bacchi, M. Costa, N. D. Cà, M. Fabbricatore, A. Fazio, B. Gabriele, C. Nasi, G. Salerno, *Eur. J. Org. Chem.*, **2004**, 574.

[25] A. Saxena, F. Perez, M. J. Krische, *Angew. Chem.*, **2016**, *128*, 1515.

[26] (a) A. A. Ruch, F. Kong, V. N. Nesterov, L. M. Slaughter, *Chem. Commun.*, **2016**, *52*, 14133; (b) A. Kotera, J. Uenishi, M. Uemura, *J. Organomet. Chem.*, **2010**, *695*, 2180; (c) A. Kotera, J. Uenishi, M. Uemura, *Tetrahedron Lett.*, **2010**, *51*, 1166; (d) M. Dell'Acqua, D. Facoeti, G. Abbiati, E. Rossi, *Synthesis*, **2010**, *14*, 2367.

[27] (a) D. Garanzini, V. Pirovano, I. Menghi, G. Celentano, S. Rizzato, E. Rossi, A. Caselli, G. Abbiati, *Eur. J. Org. Chem.*, **2020**, 3660; (b) V. Pirovano, G. Hamdan, D. Garanzini, E. Brambilla, E. Rossi, A. Caselli, G. Abbiati, *Eur. J. Org. Chem.*, **2020**, 2592; (c) V. Rustagi, R. Tiwari, A. K. Verma, *Eur. J. Org. Chem.*, **2012**, 4590.

[28] (a) B. Yuan, R. He, W. Shen, C. Huang, M. Li, *J. Org. Chem.*, **2015,** *80*, 6553; (b) N. T. Patil, Y. Yamamoto, *J. Org. Chem.*, **2004**, *69*, 5139.

generating intermediates (**B**) and (**C**) respectively. Then in the presence of nucleophilic species, the addition reaction undergoes and leads to products **F** or **G** according to the cyclization mode.

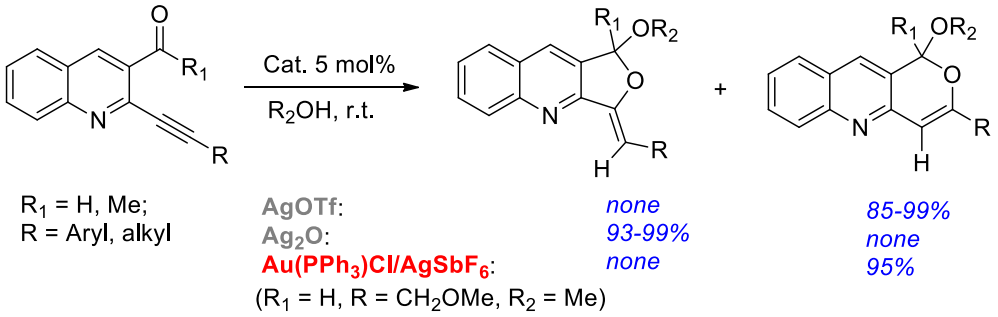
For the oxophilic catalyst, it favors to be coordinated by the carbonyl group (**D**). The nucleophiles attack to the carbon of the carbonyl group, generating unstable O^- intermediates (**E**). At last, 5-*exo*-*dig* (**G**) or 6-*endo*-*dig* (**F**) cyclization would occur to form a 6-member ring product or 5-member ring product.

It should be noted that the transition metals could act not only as carbophilic Lewis acid but also as oxophilic species. When transition metal is the catalyst in carbonyl directed alkyne derivatives system, dual-function is shown in the reaction mechanism. Next, we will mainly study the tandem nucleophilic addition/cyclization reactions of aldehyde-ynes, with various nucleophile species, *via* gold and silver catalysis, involving alcohol, acid, aromatic ring, alkyne, alkene, and diethyl phosphite as partners.

2.1.1 Aldehyde-yne with alcohol as partner

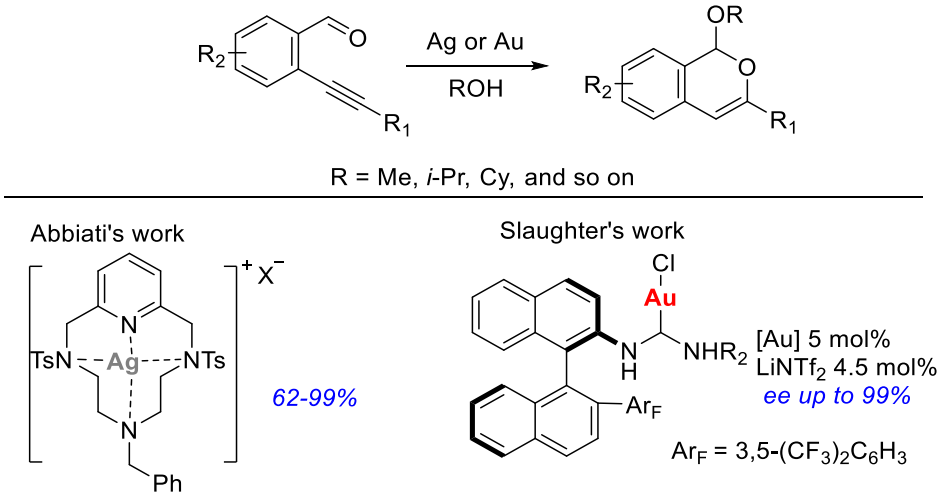
In 2007, the first example of tandem cycloisomerization reactions from 1-alkynyl-2-carbonyl substrates with different alcohols under silver catalysis, was reported by Belmont research group.[29] A series of furoquinoline and pyranoquinoline cores were obtained from 1-alkynyl-2-carbonylquinoline substrates and alcohol nucleophiles, and the selectivity toward the 5-*exo* or 6-*endo* pathway was dependent on the nature of the used silver salts' counter anion (**Scheme I-9**). From the study of the reactivity by a range of silver catalysts, three categories were defined: *p*Ka > 10 (like Ag_2CO_3, Ag_2O, AgO) favored 5-*exo* pathway; pKa < 0 (like $AgSbF_6$, $AgPF_6$, AgOTf, $AgNO_3$) favored 6-*endo* pathway; pKa in 0 ~ 10 (like $AgSO_4$, AgF, AgOCN, AgOAc) led to poor or no selectivity. When using a gold catalyst, 6-*endo* pyranoquinoline product was obtained. Then, they observed an inversion of the cycloisomerization regioselectivity, from 6-*endo*-*dig* to 5-*exo*-*dig*, with AgOTf and some amine additives, and explore the use of the silver imidazolate polymer $[Ag(Im)]_n$ as a stable catalyst for the organic reaction.[30]

[29] T. Godet, C. Vaxelaire, C. Michel, A. Milet, P. Belmont, *Chem. Eur. J.*, **2007**, *13*, 5632.
[30] E. Parker, N. Leconte, T. Godet, P. Belmont, *Chem. Commun.*, **2011**, *47*, 343.



Scheme I-9 Synthesis of furoquinolines and pyranoquinolines

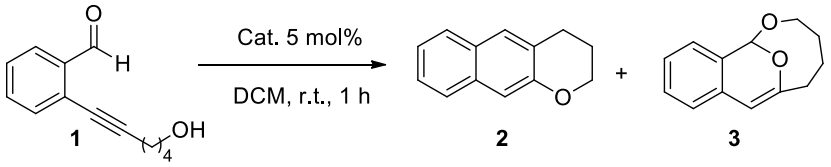
For the *ortho*-alkynylbenzaldehydes, which bear various substitution patterns on the benzaldehyde and alkynyl units, a domino hydroarylation cycloisomerization reaction process was achieved with both gold and silver catalysts. In **Scheme I-10**, the enantioselective alkynylbenzaldehyde cyclization by chiral gold catalysts was studied in the 2012 Slaughter's work,[31] and the enantiomeric excess was up to 99%. After two years, Abbiati and co-workers disclosed a mild and regiospecific method to prepare 1-alkoxy-isochromenes in the presence of [silver(I)(pyridine-containing ligand)] complexes.[32]



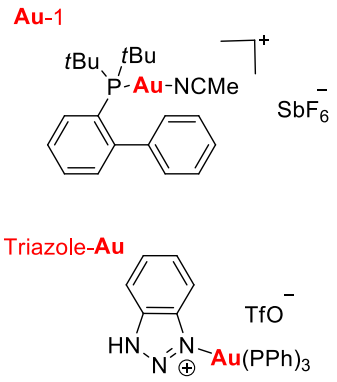
Scheme I-10 Synthesis of 1-alkoxy-isochromenes under gold and silver catalysis

The intramolecular cyclization reaction starting from aldehyde-yne bearing hydroxy group as substrate was also investigated. Liu and Hammond reported the synthesis of benzochromanes and benzobicyclo[n.3.1]acetals from 2-(ynol)arylaldehydes in 2010 (**Scheme I-11**).[33] When optimizing the conditions employing 2-(6-hydroxyhex-1-ynyl)benzaldehyde **1**, benzochromane

[31] S. Handa, L. M. Slaughter, *Angew. Chem. Int. Ed.*, **2012**, *51*, 2912–2915.
[32] M. Dell'Acqua, B. Castano, C. Cecchini, T. Pedrazzini, V. Pirovano, E. Rossi, A, Caselli, G. Abbiati, *J. Org. Chem*. **2014**, *79*, 3494.
[33] L. -P. Liu, G. B. Hammond, *Org. Lett*., **2010**, *12*, 4640.

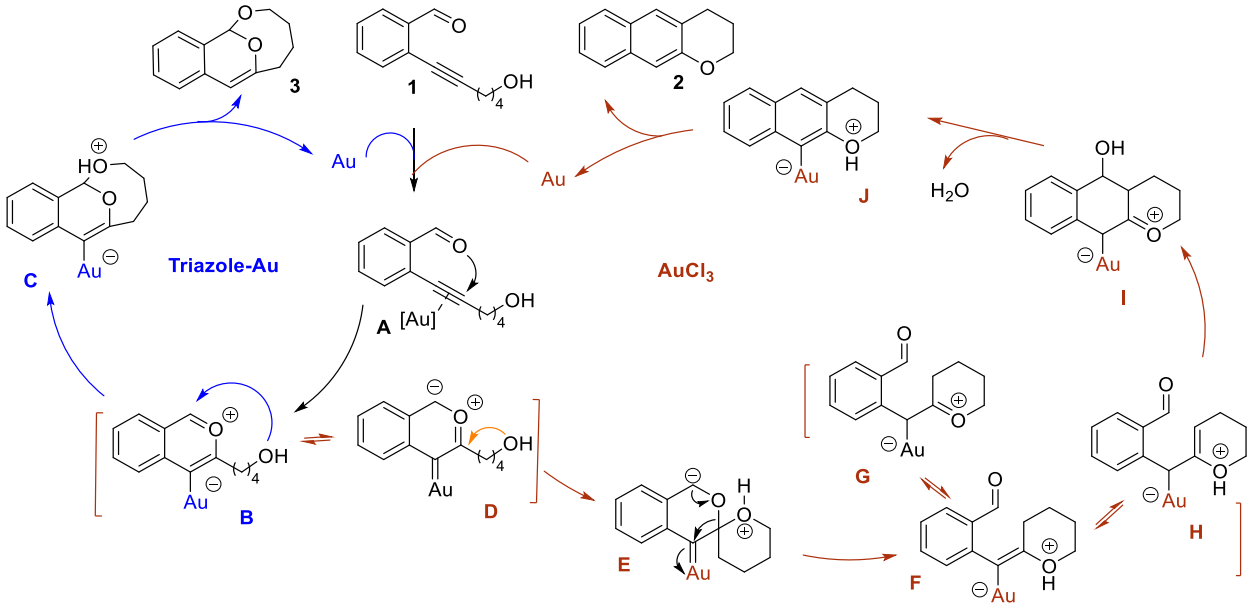


Entry	Catalyst	Yield (%) 2	Yield (%) 3
1	AgOTf	40	28
2	AuCl	79	0
3	$AuCl_3$	86	0
4	PPh_3AuCl/AgOTf	36	23
5	Au-1 (12 h)	0	58
6	Triazole-Au	0	82



Scheme I-11 Synthesis of benzochromanes and benzobicyclo[n.3.1]acetals by gold and silver

2 was only obtained with AuCl or $AuCl_3$ as the catalyst, whereas benzobicyclo[n.3.1]acetal **3** was singly produced when Au-1 or triazole-Au were employed. In the presence of AgOTf or PPh_3AuCl - AgOTf, a mixture of benzochromane and benzobicyclo[n.3.1]acetal was obtained.



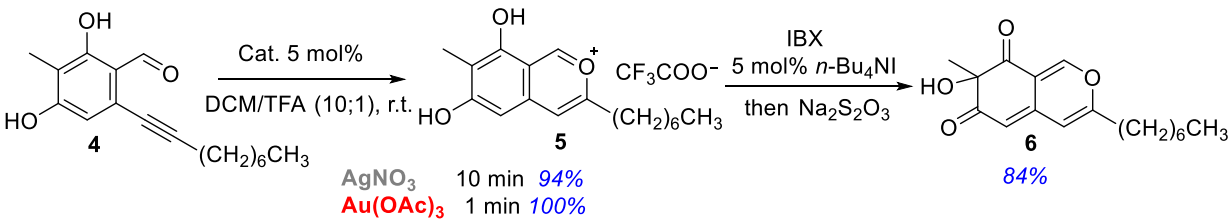
Scheme I-12 Reaction mechanism *via* triazole-Au and $AuCl_3$ catalysis

Plausible mechanisms were discussed in **Scheme I-12**. Firstly the reaction went through π-activation of alkyne **1** by coordination of the gold catalyst to carbon triple bond (**A**) and subsequent 6-*endo*-dig attack of the carbonyl moiety leading to isobenzopyrylium intermediates **B** and **D.** Then considering the triazole-Au catalytic ring, **B** cyclized to give **C**, then through protodeauration benzobicyclo[n.3.1]acetal **3** was obtained. On the other hand, when $AuCl_3$ was considered as the catalyst, intermediate **E** was formed by **D** intramolecular attack (**D** transformed from **B**). Then, after rearrangement, **F**, **G**, **H**, three intermediates in

equilibrium were formed. After a subsequent intramolecular aldol reaction, intermediate **I** was generated. After dehydration and rearrangement to form **J**, benzochromane **2** was obtained.

2.1.2 Aldehyde-yne with acid as partner

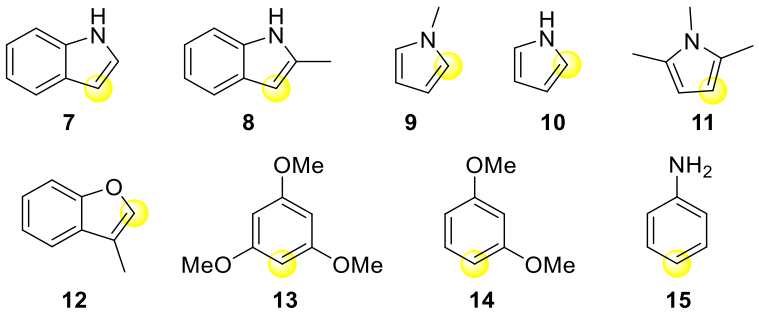
In 2004, the cycloisomerization reaction of *o*-alkynylbenzaldehydes (**4**) to 2-benzopyrylium salts (**5**) was reported by Porco team,[34] under silver or gold catalysis, in DCE/trifluoroacetic acid (TFA) 10/1 as the solvent and at room temperature (**Scheme I-14**). $Au(OAc)_3$ was the optimal catalyst, and the reaction was complete after only 1 min. $AgNO_3$ showed a satisfying conversion of 94% after 20 minutes. Subsequent *in situ* oxidation has been achieved to prepare the core structure of azaphilone natural products (**6**), such as a sphingosine kinase inhibitor and several unnatural azaphilones.



Scheme I-13 Synthesis of 2-benzopyrylium salt by $AgNO_3$ and $Au(OAc)_3$

2.1.3 Aldehyde-yne with aromatic ring as nucleophile

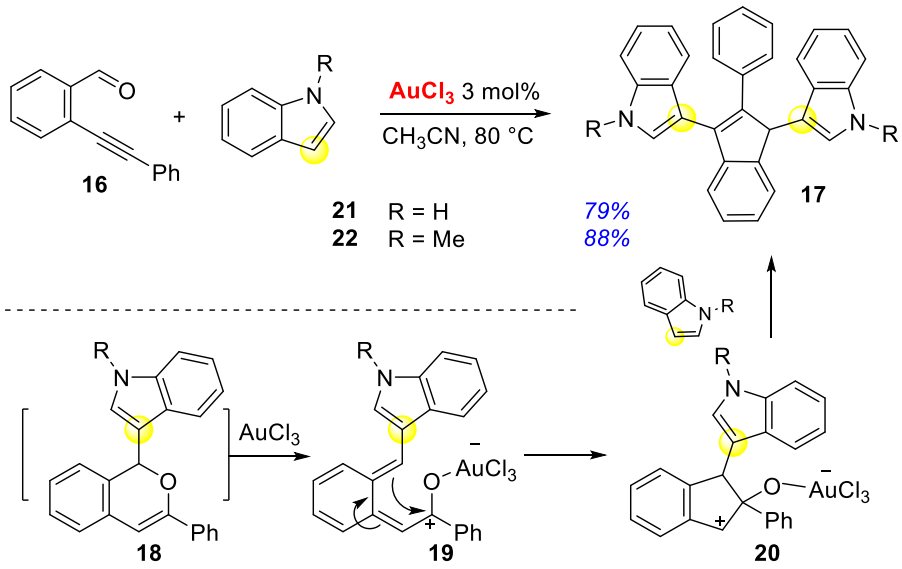
For the aromatic ring type nucleophiles, common substrates including 1*H*-indole (**7**), 2-methyl-1*H*-indole (**8**), 1-methyl-1*H*-pyrrole (**9**), 1*H*-pyrrole (**10**), heterocycles (**11**-**12**), and aryl derivatives (**13**-**15**) were tested (**Scheme I-14**).



Scheme I-14 Various aromatic rings nucleophiles

[34] J. Zhu, A. R. Germain, J. A. Porco Jr, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1239.

In 2003, Dyker[35] carried out a tandem reaction from 2-(phenylethynyl)benzaldehyde (**16**) in the presence of a gold catalyst, in acetonitrile, at 80 °C. Indene products (**17**) were obtained with indole and 1-methylindole as nucleophiles. For the proposed mechanism, the intermediate **18** was formed through isobenzopyrilium intermediate, which would later reacted with the $AuCl_3$ catalyst, and finally led to the quinonoid-type zwitterion **19**. Intermediate **20** was generated by an electrocyclization reaction, then trapped by the second equivalent of nucleophilic compound. After hydrolysis, removal of one equivalent of water subsequently, **17** would be obtained (**Scheme I-15**).

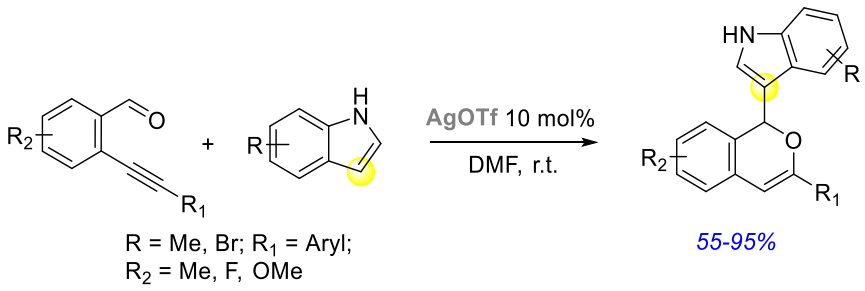


Scheme I-15 Synthesis of indene products

Moreover, aldehyde-ynes could react with various aromatic ring type nucleophiles, in moderate to good yields, under PPh_3AuNTf_2 catalysis, in DCE at 50 °C, to prepare 6-*endo* 1*H*,1-arylisochromene products (**23**), *via* a domino hydroarylation cycloisomerization reaction.[36]

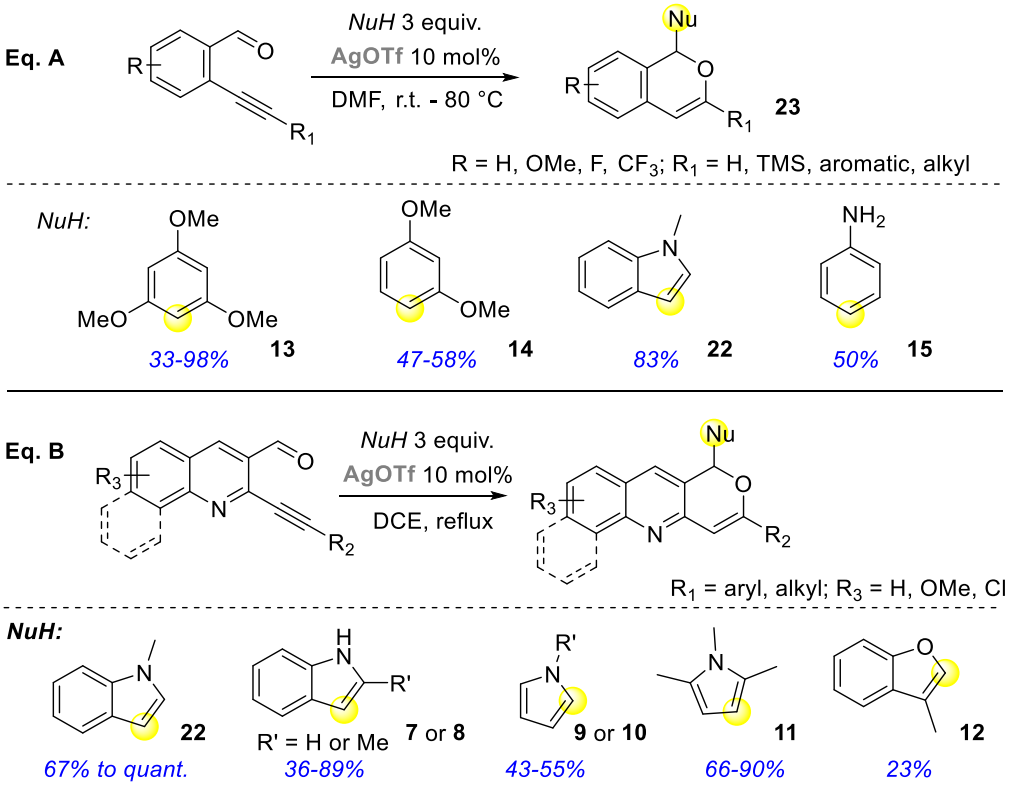
On the other hand, if interested in silver-catalyzed reactions, the first example of a tandem reaction, with carbon nucleophiles under silver catalysis, was reported by Wu in 2011.[37] During the generalization of the methodology, different aryl substituted aldehyde-ynes were reacted with indoles as a nucleophile. The corresponding products were isochromene derivatives, obtained with yields ranging from 55 to 95% (**Scheme I-16**).

[35] G. Dyker, D. Hildebrandt, J. Liu, K. Merz, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4399.
[36] Y. Tang, Catalyse asymétrique en présence de complexes d'or(I) – Un nouvel arsenal pour la construction d'architectures moléculaires, PhD from PSL University, **2019**, Oct. 25.
[37] B. Ouyang, J. Yuan, Q. Yang, Q. Ding, Y. Peng, J. Wu, *Heterocycles*, **2011**, *82*, 1239.



Scheme I-16 Synthesis of isochromene derivatives by silver catalysis (part 1)

Then, domino hydroarylation cycloisomerization reactions of aldyhyde-ynes under AgOTf-catalysis were disclosed by our group in collaboration with Belmont's team in 2014 (**Scheme I-17 Eq. A**).[38] 1,3,5-Trimethoxybenzene, 1,3-dimethoxybenzene, 1-methyl-1*H*-indole, 1*H*-pyrrole were used in this efficient method to access to 1*H*,1-arylisochromenes (**23**). According to optimized the reaction conditions, 2-alkynylquinoline-3-carbaldehydes reacted with various aromatic ring type nucleophiles, such as *N*-methylindole, 2-methylindole, 1,3,5-trimethoxybenzene, etc., to lead to the (hetero)aryl-functionalized pyranoquinoline scaffold (**Scheme I-17 Eq. B**).[39]

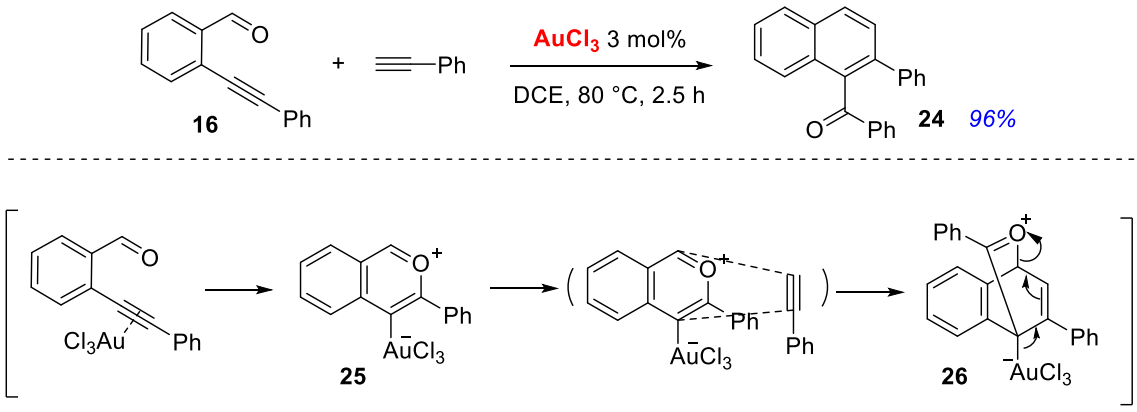


Scheme I-17 Synthesis of isochromene derivatives by silver catalysis (part 2)

[38] G. Mariaule, G. Newsome, P. Y. Toullec, P. Belmont, V. Michelet, *Org. Lett.*, **2014**, *16*, 4570.
[39] A. Bontemps, G. Mariaule, S. Debène-Finck, P. Helissey, S. Giorgi-Renault, V. Michelet, P. Belmont, *Synthesis*, **2016**, *48*, 2178.

2.1.4 Aldehyde-yne with alkyne / alkene as nucleophile

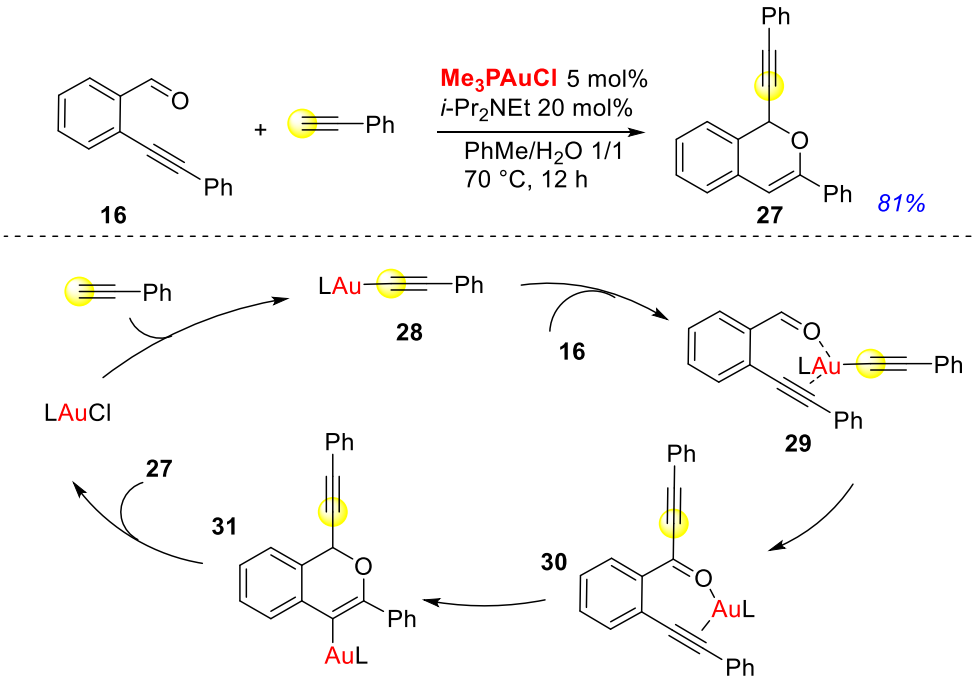
In the case of alkynes as nucleophiles, Yamamoto's group carried out a gold-catalyzed tandem reaction in the presence of a terminal alkyne with *o*-alkynylbenzaldehyde by $AuCl_3$-catalyzed reaction in 2002.[40] Only the product of a Diels-Alder reaction has been observed, resulting in a naphthalene-type derivative (**24**) (**Scheme I-18**). Mechanistically, the gold catalyst acted as a Lewis acid by coordinating at a carbon triple bond, followed by a nucleophilic attack of the oxygen from the aldehyde group on the activated alkyne, leading to isobenzopyrylium **25**. Pyrylium **25** then underwent a Diels-Alder reaction with the alkyne to form intermediate **27**. After rearrangement and regeneration of the catalyst, the naphthalene product **24** was obtained. Then the cycloaddition of *o*-alkynyl(oxo)benzenes and enynals with alkynes was also reported.[41]



Scheme I-18 Diels-Alder reaction of *o*-alkynylbenzaldehyde

In 2006, Li's group proposed a tandem reaction leading to isochromene derivatives after addition of an alkyne-type nucleophile.[42] This methodology was based on the use of a monodentate phosphine ligand with gold complex, in the presence of a catalytic amount of *N*-ethyl-*N*-isopropylpropan-2-amine and in aqueous medium solvent. The reaction occurred in PhMe/H_2O 1/1 as the solvent, with good yields. Conversely, the reaction did not take place without the presence of water.

[40] N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.*, **2002**, *124*, 12650.
[41] N. Asao, T. Nogami, S. Lee, Y. Yamamoto, *J. Am. Chem. Soc.*, **2003**, *125*, 10921.
[42] Yao, X.; Li, C.-J., *Org. Lett.*, **2006**, *8*, 1953.



Scheme I-19 Synthesis of 3-phenyl-1-(phenylethynyl)-1*H*-isochromene by Me_3PAuCl

For the proposed mechanism (**Scheme I-19**), the terminal alkyne reacted with the gold complex Me_3PAuCl, leading to acetylide **28** in the presence of a week base firstly. Then, the gold acetylide interacted with *o*-alkynylbenzaldehyde by coordinating both with the triple bond as well as with the oxygen of the aldehyde group, leading to the intermediate **29**. The acetylide was added to the activated aldehyde to give intermediate **30**, which cyclized to give intermediate **31**. After protonolysis and regeneration of the catalyst, the isochromene derivative **27** was obtained.

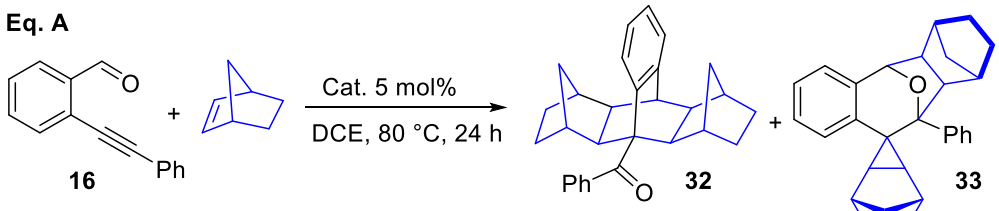
In the case of alkene as nucleophiles, enynal/enynone and alkene systems allow an efficient method for synthesizing naphthalene derivatives. Zhu and co-workers reported enynal/enynone reaction with various alkenes to contribute to new C-C bonds formation, leading to a series of different and unique polycyclic compounds.[43]

In 2013, when norbornene (NB), a naked and reactive alkene, was used with *o*-alkynylbenzaldehyde substrate,[43a] no desired product was obtained with $AgSbF_6$ or $AuCl_3$(IMes) (IMes = *N,N'*-bis[2,4,6-(trimethyl)phenyl]imidazol-2-ylidene) as the catalysts. In the presence of $AuCl_3$(IMes), Selectfluor, and (*N*-chloromethyl-*N'*-fluorotriethylenediammonium bis(tetrafluoroborate), the yields of **32** and **33** climbed to 60% and 29%, respectively (**Scheme I-20 Eq.**

[43] (a) S. Zhu, Z. Zhang, X. Huang, H. Jiang, Z. Guo, *Chem. Eur. J.*, **2013**, *19*, 4695; (b) S. Zhu, Z. Guo, Z. Huang, H. Jiang, *Chem. Eur. J.*, **2014**, *20*, 2425; (c) J. Ma, H. Jiang, S. Zhu, *Org. Lett.*, **2014**, *16*, 4472; (d) S. Zhu, L. Hu, H. Jiang, *Org. Biomol. Chem.*, **2014**, *12*, 4014.

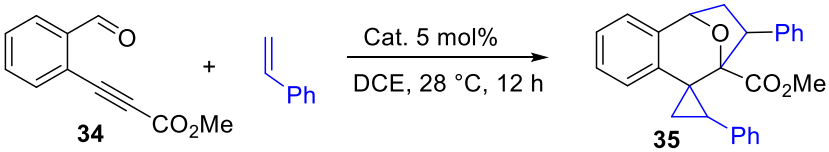
A). After one year, Zhu's group reinvestigated this reaction implying carbene intermediate when employing enynal **34** as substrate (**Scheme I-20 Eq. B**).[44] In the case of system with aldehyde-yne and an alkene, IMes-AuCl/$AgNTf_2$ or $AgNO_3$ had no catalytic activity. On the contrary, the reaction with AgOTf and $AgNTf_2$ as the catalysts afforded 44% and 82% of polycyclic products. This is the first example of 1,3-dipolar cycloaddition/cyclopropanation by using silver catalysts.

Eq. A



Entry	Cat.	Yield(%) 32	33
1	$AgSbF_6$	*0*	*0*
2	**$AuCl_3$(IMes)**/$AgSbF_6$	*0*	*0*
3	**$AuCl_3$(IMes)**/Selectfluor	*60*	*29*

Eq. B

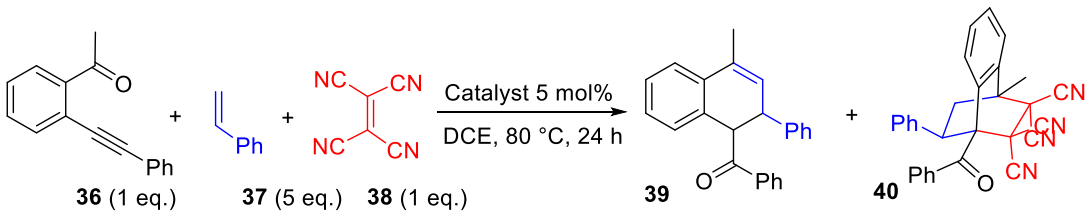


Entry	Cat.	Yield (%)
1	**IMes-AuCl**/$AgNTf_2$	*0*
2	$AgNO_3$	*0*
3	AgOTf	*44*
4	$AgNTf_2$	*82*

Scheme I-20 Synthesis of naphthalene derivatives with the system aldehyde-ynes / alkenes

Interestingly, the comparison of gold and silver catalysts was presented with a keto-yne / alkene system by Jiang's group.[45] As shown in **Scheme I-21**, the reaction starting from **36**, **37**, and **38**, led to the formation of 1,2-dihydro-naphthalene (1,2-DHN) **39**, with 69% yield, under $AgSbF_6$ catalysis, in DCE and at high temperature. On the contrary, through gold catalysts, the compound **40** was isolated, and the best reaction conditions of reaction were observed with IMes-AuCl and Selectfluor.

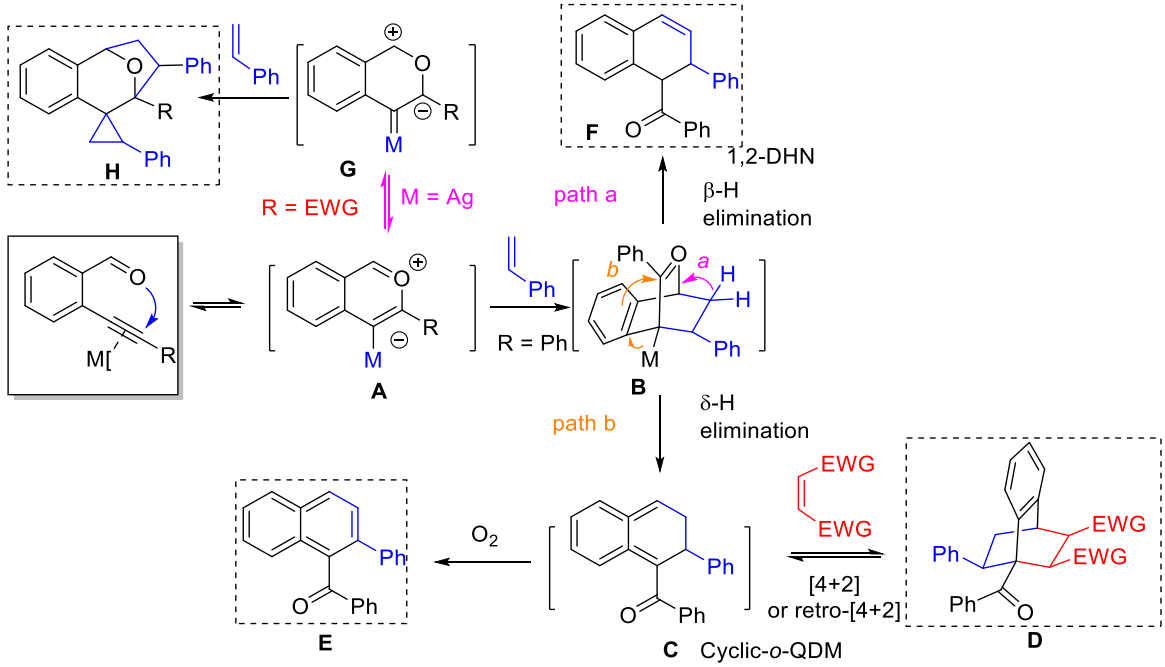
[44] R. Liang, T. Ma, S. Zhu, *Org. Lett.*, **2014**, *16*, 4412.
[45] S. Zhu, H. Huang, Z. Zhang, T. Ma, H. Jiang, *J. Org. Chem.*, **2014**, *79*, 6113.



Entry	Catalyst	Yield (%) 39	40
1	$AgSbF_6$	*69*	
2	**$KAuCl_4{\cdot}2H_2O$**		*32*
3	**IMes-AuCl**		*52*
4	**$IMes\text{-}AuCl_3$**		*57*
5	**IMes-AuCl** (+ Selectfluor 10 mol%)		*81*
6	**IMes-AuCl** (+ Selectfluor 10 mol%)[1/5/2]		***93***

Scheme I-21 The cyclization of keto-yne **36** according to Jiang's group

Considering the mechanism, there are three pathways to realize the tandem cycloaddition process under gold or silver catalysis, summarized in **Scheme I-22**.[45]



Scheme I-22 The summary of tandem cycloaddition process by gold or silver

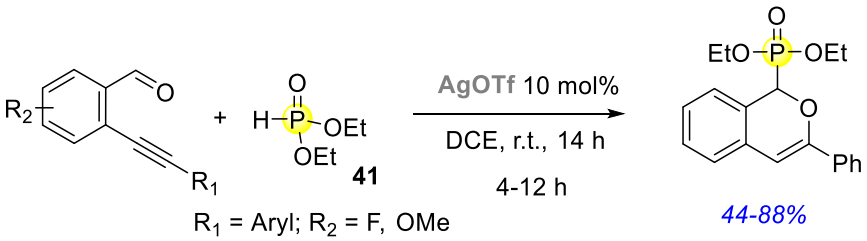
The carbonyl oxygen could attack the electron-deficient alkyne to form the intermediate pyrylium **A**.[46] After the formation of the key intermediate **B,** through a Diels–Alder reaction

[46] Representative examples of the generation and application of benzopyrilium ion: (a) N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.*, **2002**, *124*, 12650; (b) N. Asao, T. Nogami, S. Lee, Y. Yamamoto, *J. Am. Chem. Soc.*, **2003**, *125*, 10921; (c) Q. Ding, J. Wu, *Org. Lett.*, **2007**, *9*, 4959; (e) G. Dyker, D. Hildebrandt, J. Liu, K. Merz, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4399; (d) S. Bhunia, K. -C. Wang, R. -S. Liu, *Angew. Chem. Int. Ed.*, **2008**, *47*, 5063; (f) R. -Y. Tang, J. -H. Li, *Chem. Eur. J.*, **2010**, *16*, 4733; (h) D.

between **A** and styrene, there would be two different possible ways, depending on gold or silver catalysts. When silver salts were used as the catalysts, a β-H elimination was observed, leading to the formation of 1,2-DHN **F** (pathway a). Interessingly, it was demonstrated that the intermediate **G** was efficiently stabilized by introducing an electron-withdrawing group (EWG), so that product **H** was generated. When gold catalysts were employed, a δ-metal elimination was mentioned, leading to a cyclic-*o*-QDM (QDM = quinodimethane) product (pathway b). In path b, intermediate **C** could undergo a second Diels−Alder reaction to produce naphthalene **E** in the presence of O_2, or could produce polycyclic compound **D** after reaction with another alkene bearing EWG.

2.1.5 Aldehyde-yne with diethyl phosphite as nucleophile

In order to obtain organophosphorus compounds of high biological interest,[47] Wu's team developed a strategy for the synthesis of 1*H*-isochromen-1-ylphosphonates, *via* a tandem cycloaddition reaction, under silver catalysis, in 2008 (**Scheme I-23**).[48] 2-Alkynylbenzaldehydes reacted with diethyl phosphite **41** in the presence of 10 mol% AgOTf, in DCE, at room temperature, for 4-12 hours. Through this mild and efficient strategy, various phosphonate derivatives were prepared in 44-88% yields. In the proposed mechanism, the key step was described as a nucleophilic attack of the diethyl phosphite, followed by the formation of the isochromene derivative.



Scheme I-23 Synthesis of 1*H*-isochromen-1-ylphosphonates

Yue, N. D. Ca, R. C. Larock, *J. Org. Chem.*, **2006**, *71*, 3381; (g) H. Kusama, H. Funami, M. Shido, Y. Hara, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.*, **2005**, *127*, 2709; (i) H. Kusama, H. Funami, J. Takaya, N. Iwasawa, *Org. Lett*., **2004**, *6*, 605.

[47] (a) D. J. McCabe, E. N. Duesler, R. T. Paine, *Inorg. Chem*. **1985**, *24*, 4626; (b) O. M. Colvin, *Curr. Pharm. Des.*, **1999**, *5*, 55560; (c) S. K. Perumal, S. A. Adediran, R. F. Pratt, *Bioorg. Med. Chem.* **2008**, *16*, 6987.

[48] X. Yu, Q. Ding, W. Wang, J. Wu, *Tetrahedron Lett.*, **2008**, *49*, 4390.

Chapter II :

Cyclization reactions of 1,6-enynes

Chapter II Cyclization reactions of 1,6-enynes

1. Bibliography

1.1 Cyclization reactions of 1,6-enynes under silver or gold catalysis

Cyclization is a type of reaction in which cyclic isomerization of the substrate is concomitant with a loss of unsaturation, without atom wasted, and with new ring(s) formation. Designing different cyclization reactions is a powerful, effective, remarkable, and economic organic synthesis method that fully complies with modern green chemistry.[1] Since the initial work of Trost's group in 1984,[49] extensive studies on various transition metal catalysts associated with different substrates, allowed to develop new carbo- and heterocyclic arrays of cycloisomerization and tandem cycloisomerization-addition reactions. It has become one of the most active fields of prototypical research in synthetic methodologies.[50,51]

On the other hand, alkenes and alkynes represent the most significant classes of unsaturated organic compounds. Thanks to their easy availability and rich reactivity, they have been important types of substrates to construct functionalized and useful molecular scaffolds in natural products, polymer materials, and pharmaceutical molecules. Cycloisomerization of 1,n-enyne system, makes it possible to rapidly increase the structural complexity from relatively simple acyclic subunits containing fragments of alkenes and alkynes, depending on the different functional groups and reaction conditions. Moreover, there are many advantages in cyclization reactions of 1,n-enynes, such as simple and convenient reaction conditions.[52]

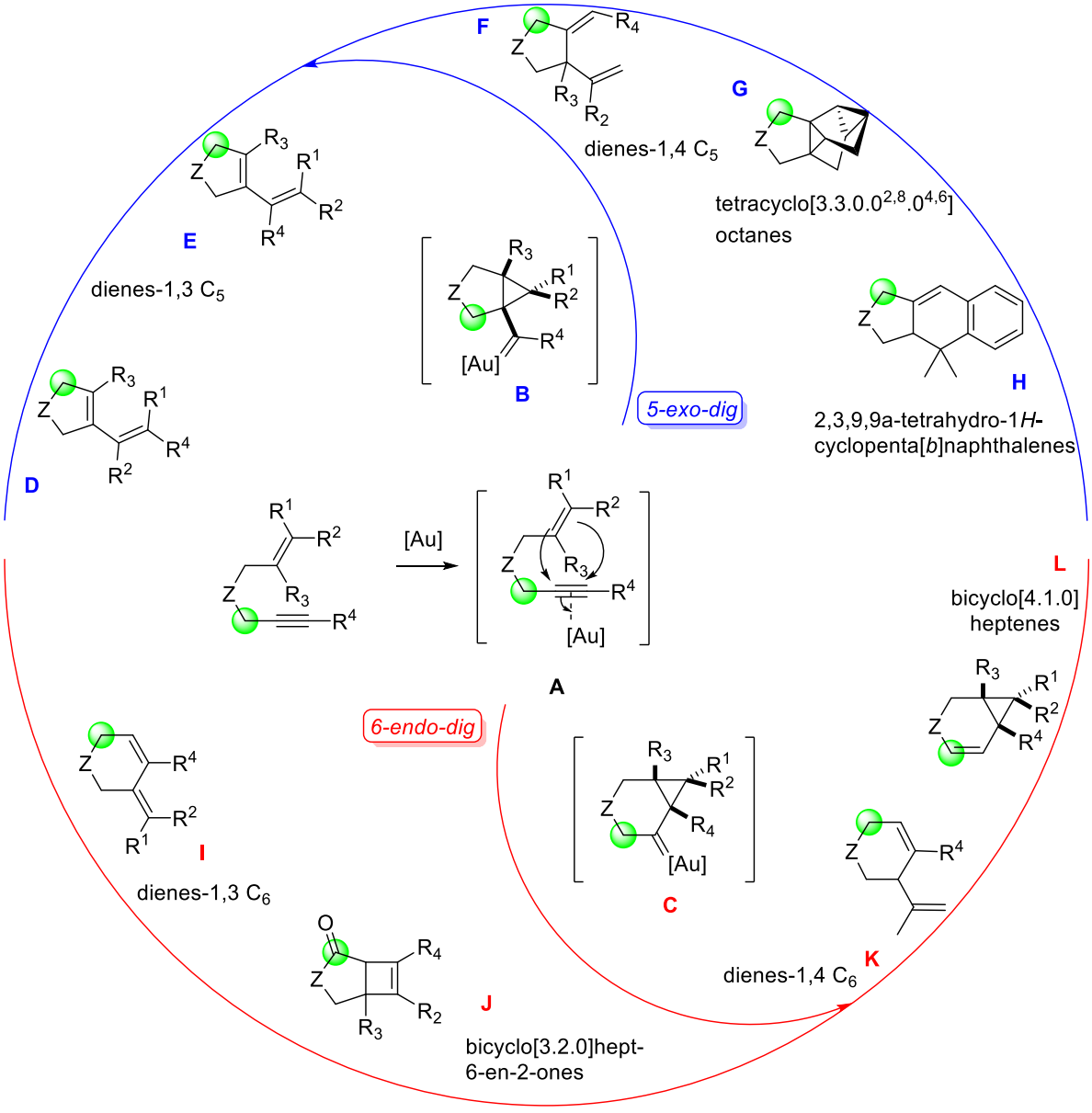
In this chapter, we will focus on cycloisomerizations and tandem cycloisomerization-nucleophile addition transformations of 1,6-enynes systems under gold and silver catalysis.

1.1.1 Cycloisomerization of 1,6-enynes

Over the past several years, numerous elegant examples have successfully allowed the

[49] B. M. Trost, M. Lautens, M. H. Hung, C. S. Carmichael, *J. Am. Chem. Soc*., **1984**, *106*, 7641
[50] E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.*, **2008**, *108*, 3326.
[51] D. V. Patil, H. S. Park, J. Koo, J. W. Han, S. Shin, *Chem. Commun*., **2014**, *50*, 12722.
[52] (a) V. Michelet, P. Y. Toullec, J. -P. Genêt, *Angew. Chem. Int. Ed*., **2008**, *47*, 4268; (b) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.,* **2002**, *102*, 813; (c) B. M. Trost, M. J. Krische, *Synlett.*, **1998**, 1; (d) S. T. Driver, A. J. Geissert, *Chem. Rev.,* **2004**, *104*, 1317; (e) J. Xuan, A. Studer, *Chem. Soc. Rev*., **2017**, *46,* 4329.

construction of various useful molecular scaffolds from 1,6-enynes. According to the studies on 1,6-enynes cycloisomerization *via* gold catalysis, the mechanism involves a catalytic electrophilic activation of the alkyne, followed by a nucleophilic addition on the 6-position of the alkene.



Scheme II-1 Synthesis of various molecules

The cycloisomerization of 1,6-enynes has been proposed to occur through two different pathways in the presence of a gold catalyst : the key step of the first path is a 5-*exo-dig* reaction whereas a 6-*endo-dig* reaction can be observed in the second path.[53] After the coordination

[53] C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. JiménzNúñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.*, **2006**, *12*, 1677.

of the gold catalyst to the triple bond of **A**, species **B** and **C** was generated through a 5-*exo* and 6-*endo* cycloisomerization. Depending on the different types of 1,6-enynes substrates, on the reaction conditions, and on the gold pre-catalysts used, a large array of cyclic molecules has been obtained by rearrangement and protodemetalation. As shown in **Scheme II-1**, dienes **D**, **E**, **F**, **I** and **K**, 2,3,9,9*a*-tetrahydro-1*H*-cyclopenta[*b*]naphthalenes **H**, bicyclo[3.2.0] **J**, bicyclo[4.1.0]heptenes **L**, or tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octanes **G** was prepared.[54,55,56,57,58]

The cycloisomerization reaction under silver catalysis presents a similar reactivity, and the details will be commented later.

Considering the large number of examples, we won't develop these examples and will only focus on domino processes.

1.1.2 Domino cycloisomerization-nucleophile addition reactions of 1,6-enynes

Considering the cycloisomerization reactions of 1,6-enynes, the cyclizations and formations of C-C bonds, may be accompanied by the formation of C-C, C-N or C-O bonds, in the presence of different nucleophiles.

In the presence of nucleophiles, 1,6-enynes can be cyclized and functionalized to form new C-C or C-heteroatom bonds. Gold or silver catalyzed domino cyclization of 1,6-enynes, follows a 6-*endo-dig* and a 5-*exo-dig* pathway. The reaction was interpreted by a nucleophile attack on the intermediate cyclopropyl carbon to give the corresponding products (**Scheme II-2**). According to the literature survey,[52-58] a large number of studies have led to various adducts depending on different nucleophiles species.

According to our project, we focused on the formation of C-C and C-O bonds, *via* domino hydroxycyclization / alkoxycyclization reactions and intramolecular [4+2] cycloadditions.

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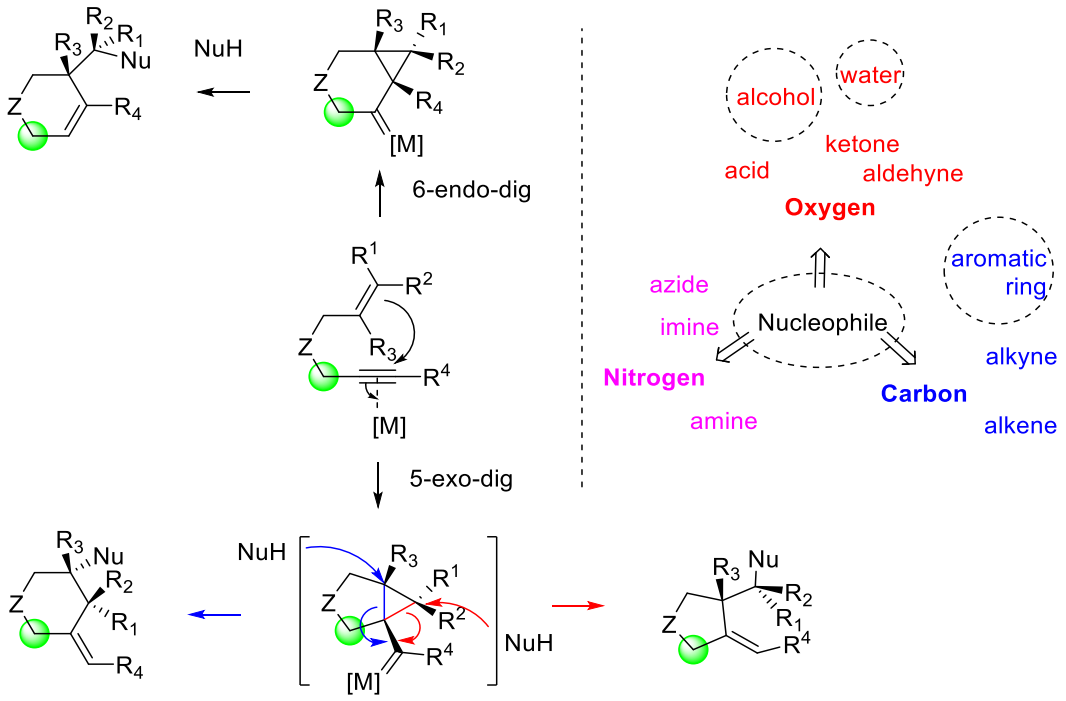
[54] C. Bruneau, *Angew. Chem., Int. Ed.*, **2005**, *44*, 2328
[55] M. Méndez, M. P. MuGoz, C. Nevado, D. J. CHrdenas, A. M. Echavarren, *J. Am. Chem. Soc.*, **2001**, *123*, 10511.
[56] C. Nieto-Oberhuber, S. López, M. P. Munoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6146.
[57] E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.*, **2008**, *108*, 3326.
[58] C. Bartolomé, Z. Ramiro, D. García-Cuadrado, P. Pérez-Galán, M. Raducan, C. Bour, A. M. Echavarren, P. Espinet, *Organometallics*, **2010**, *29*, 951.

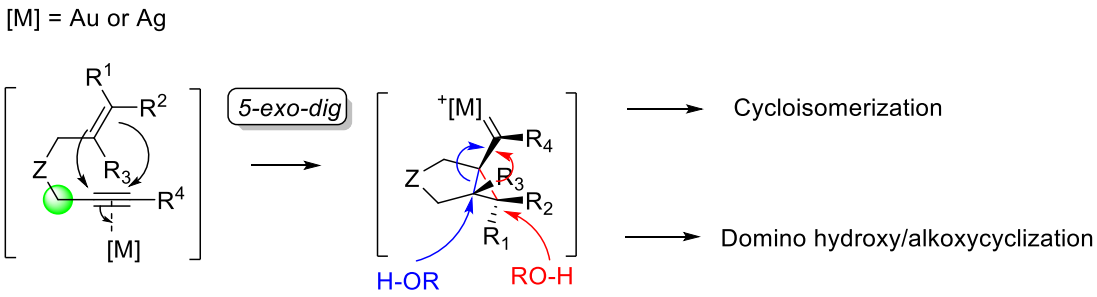


Scheme II-2 Cycloisomerization-nucleophile addition reactions

We will present selected examples implying 5-*exo-dig* on a first part and then 6-*endo-dig* process. In each part, we will present cycloisomerization examples and then domino processes. We will also focus on asymmetric processes.

1.2 5-*Exo-dig* cyclization reactions of 1,6-enynes

Concerning the 5-*exo-dig* cyclization reactions of 1,6-enynes, the introduction is divided into two parts, the first one focusing on gold-catalyzed cycloisomerization reactions and domino cyclization reactions, whereas the other one deals with silver catalysis.

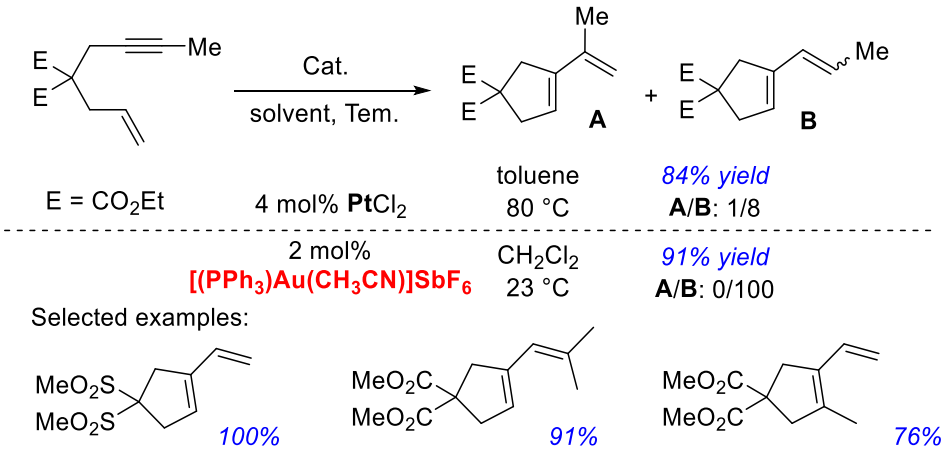


Scheme II-3 5-*Exo-dig* cyclization reactions by gold and silver

1.2.1 Gold-catalyzed cycloisomerization reactions

Synthesis of 1,3-Dienes and 1,4-dienes

The first report dealing with an enyne cycloisomerization reaction and leading to a diene product dates from 1996, where a 1-vinylcyclopentene was obtained under $PtCl_2$ catalysis by Murai's group.[59] A gold-catalyzed reaction through a 5-*exo*-*dig* pathway was described in 2004 to synthesize 1,3-dienes.[60] Echavarren's team documented many *exo*-cyclization reactions of enynes by highly lipophilic cationic Au(I) catalysts. Through precatalyst and co-catalyst $Au(PPh_3)Cl/AgX$ (X = BF_4 or SbF_6),[61,62] enynes underwent skeletal rearrangements to give the awaiting products in 47%-100% yields. The reaction proceeded readily at room temperature, in DCM, in less than 1 hour. The reaction did not proceed in solvents such as MeCN or toluene (**Scheme II-4**).



Scheme II-4 Synthesis of 1,3-dienes under gold catalysis

Two years later, the same team reported one example of the formation of 1,4-diene from 1,6-enyne bearing a terminal alkyne.[53] In the presence of a catalytic amount of a cationic gold(I) complex, in DMSO, at 50 °C, during five hours, the starting material, the dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate, was transformed to a mixture of two products, the 1,4-diene **43** and the 1,3-diene **44**, in a ratio of 2:1, with an overall yield of 67% (**Scheme II-5 Eq. A**).

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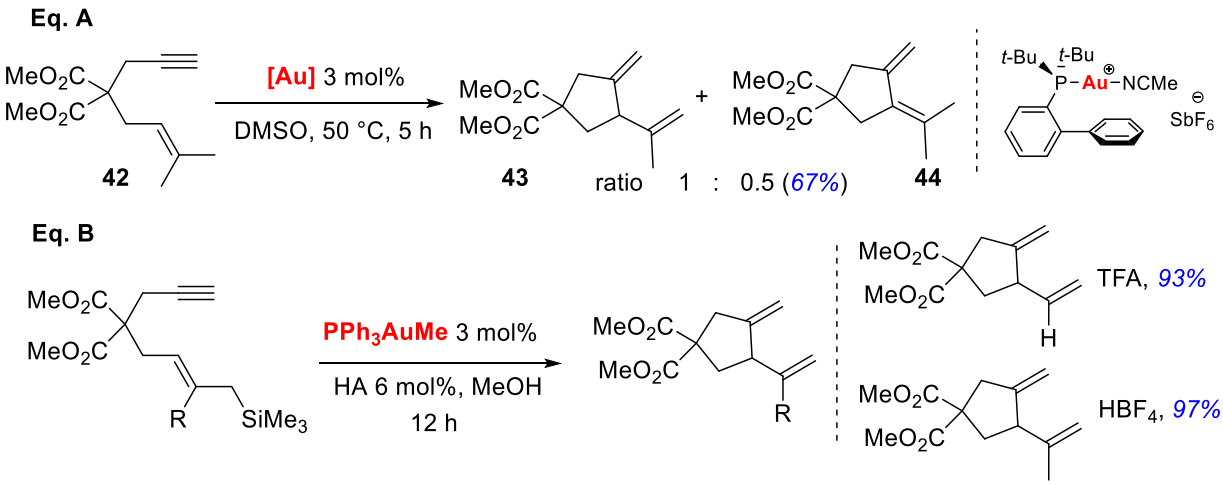
[59] N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics*, **1996**, *15*, 901.
[60] C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.*, **2004**, *43*, 2402.
[61] M. Preisenberger, A. Schier, H. Schmidbaur, *J. Chem. Soc., Dalton Trans.*, **1999**, 1645.
[62] Hydroarylation of alkynes catalyzed by $[Au(PPh_3)Cl]$ and silver salts: M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.*, **2003**, 3485.



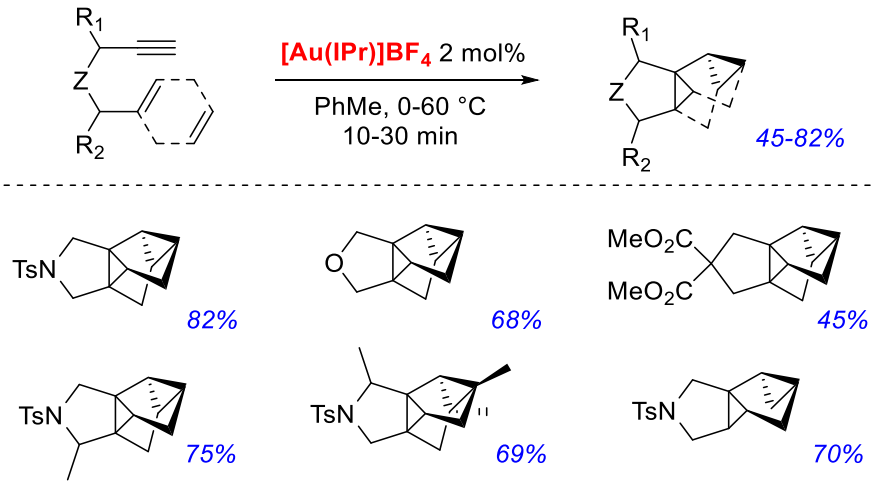
Scheme II-5 Synthesis of 1,4-dienes *via* gold catalysis

Allylsilanes reacted with 3 mol% of cationic gold(I) complex PPh_3AuMe and protic acid (HA) in MeOH as solvent at room temperature, to afford the 1,4-dienes in excellent yields, through cycloisomerization (not domino alkoxycyclization) (**Scheme II-5 Eq. B**).[53]

Tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octanes

The cycloisomerization of dienynes containing a cyclohexadiene unit was developed, in 2007, in the presence of a catalytic amount of NHC(N-heterocyclic carbenes)-gold complexes.[63] This reaction afforded the 5-*exo*-*dig* products: tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane derivatives were readily prepared from enynes bearing a cyclohexadiene group and the procedure was quite simple. This is the first report on an intramolecular double-cyclopropanation, leading to tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octanes from dienynes (**Scheme II-6**). After preliminary results, extrapolation of the reaction, changing the tether group from *N*-tosyl to oxygen and malonate group, made it possible to prepare the corresponding desired products in good yields, under the same reaction conditions (Au(IPr)BF_4 2 mol% in toluene).

[63] S. M. Kim, J. H. Park, S. Y. Choi and Y. K. Chung, *Angew. Chem., Int. Ed.*, **2007**, *46*, 6172

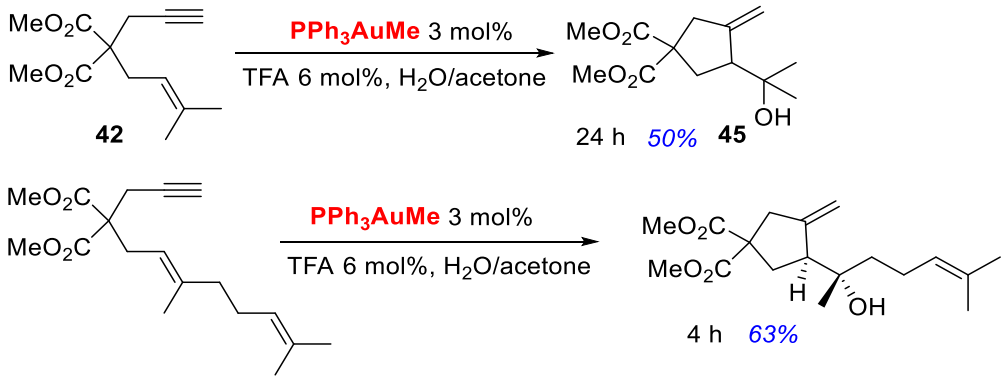


Scheme II-6 Synthesis of tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octanes

1.2.2 Gold-catalyzed domino cyclization reactions

Domino hydroxy/alkoxycyclization reactions

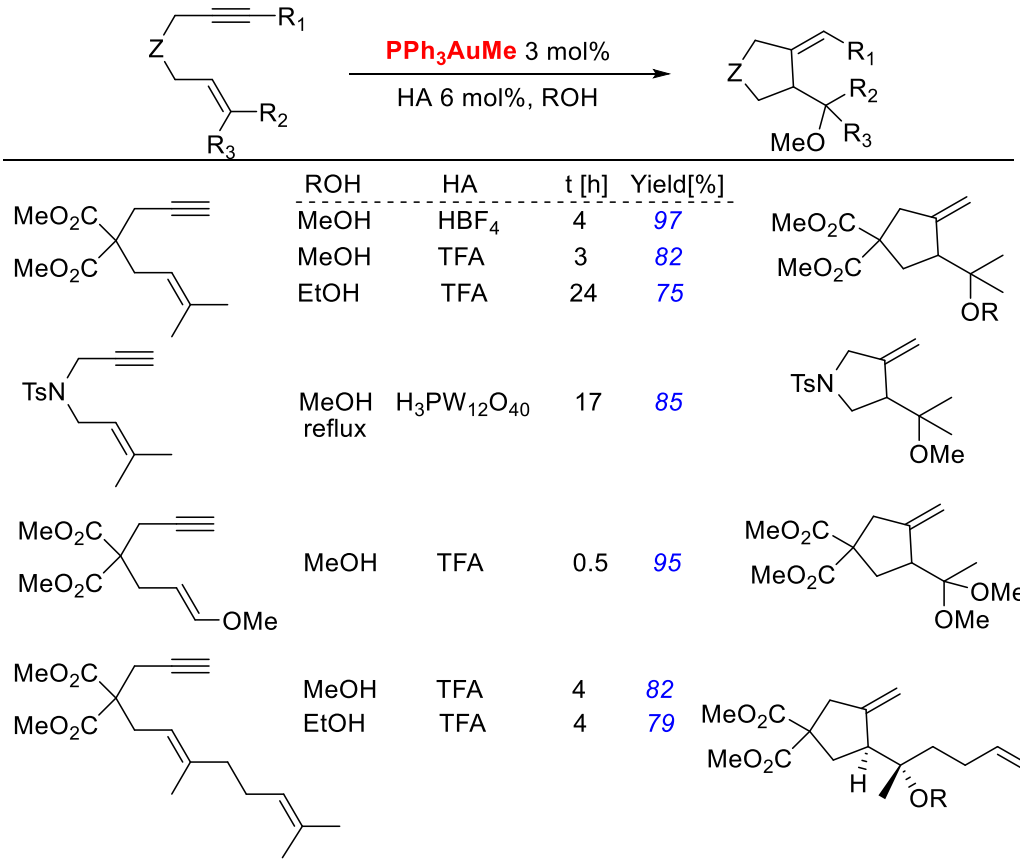
The work of Echavarren's team, published in 2006, is one of the first example of domino process *via* a 5-*exo*-*dig* pathway.[53] Starting from 1,6-enyne system of the tether groups from malonate **42**, hydroxycyclization afforded 50% of alcohol **45,** in the presence of 3 mol% of [PPh_3AuMe] and 6 mol% of trifluoroacetic acid (TFA), in aqueous acetone (H_2O/acetone). Alcohol adduct of skeletal rearrangement was given as a single diastereomer, isolated in 63% yield (**Scheme II-7**).



Scheme II-7 Domino hydroxycyclization reactions

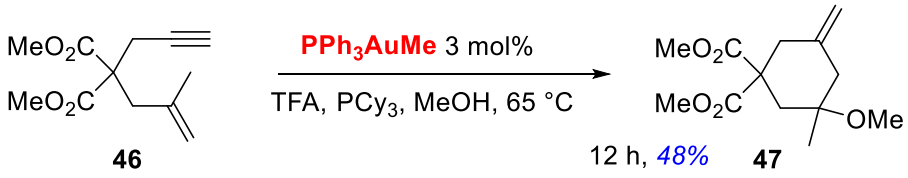
The same study mentioned also alkoxycyclization reactions of 1,6-enynes, carried out under Au(I) catalysis, in the presence of protic acids such as HBF_4, phosphotungstic acid trihydrate or trifluoroacetic acid (**Scheme II-8**). In this reaction, the complex $[Au(PPh_3)(ROH)]^+$ was

presumably generated. The desired products were isolated with good to excellent yields. Alkoxycyclization of the less reactive substrate (TsN-tether) was performed under reflux of methanol. The reaction of bissulfone, which presented a strongly electron-withdrawing effect due to the sulfone group, proceeded too slowly to afford the corresponding cyclized product.



Scheme II-8 Domino alcoxycyclization reaction with gold catalyst and protic acid (part 1)

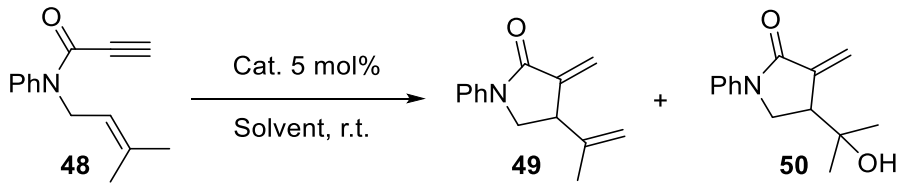
Moreover, the 1,6-enyne system **46** reacted *via* a 5-*exo-dig* pathway, to afford the hexacyclic ether **47**. The catalytic species was formed *in situ* from PPh_3AuMe 3 mol%, TFA, PCy_3, at 65 °C. The regioselectivity of the six-membered derivative was dictated by the substituent present on the alkene (**Scheme II-9**).



Scheme II-9 Domino alcoxycyclization reaction with gold catalyst and protic acid (part 2)

Other examples have been described in the presence of Au(III) and Au(I) complexes from our group.[64]

In 2013, Shin's group explored the cycloisomerization reactions of propiolamide derivatives.[65] Reaction under Au(*t*-Bu-XPhos)NTf_2 catalysis, in $CHCl_3$, at room temperature, led to a mixture of two 1,3-enones **49** and **50**, a skeletal rearrangement product and an hydroxycyclization product. Among the results obtained with different gold catalysts or Ag salts, it is interesting to note that 45% of hydroxycyclization product **50** was observed when using Au(*t*-Bu-XPhos)NTf_2 (**Scheme II-10**).



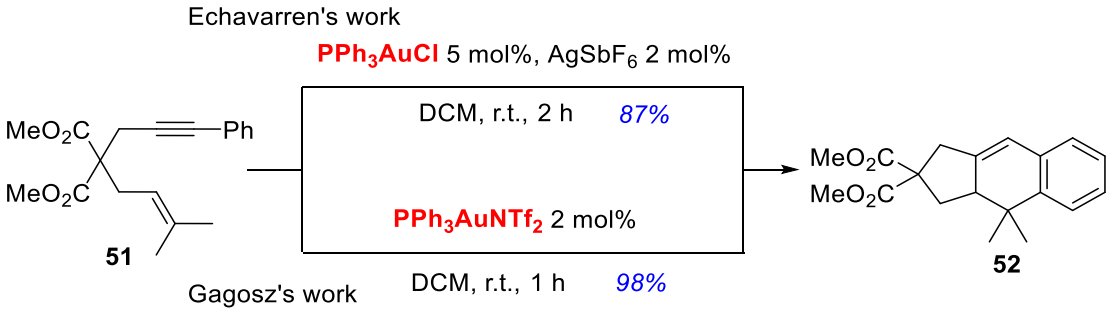
Entry	Cat.	Conditions	Yield (%)(**49**/**50**)
1	**Au(*t*-Bu-XPhos)NTf_2**	$CHCl_3$, 1 h	*28*/*45*
2	**Au(IPr)NTf_2**	DCE, 1 h	*43*/*41*
3	**$AgNTf_2$**	DCE, 1 h	*91*/*8*

Scheme II-10 Cycloisomerization reactions of propiolamide derivatives

Intramolecular [4+2] cycloadditions (5-*exo* + Friedel-Crafts reaction)

Besides, 1,6-enyne systems bearing an aryl ring on the alkyne of the malonate tether group were transformed to the 2,3,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalenes in good yields, obtained after an intramolecular [4+2]-cycloaddition of a 5-*exo*-*dig* pathway, followed by a Nazarov-type ring expansion.[66,67] The first example of gold-catalyzed this domino reaction starting from enyne **51** was reported by Echavarren in 2005,[68] Gagosz's team developed a similar work during the same year (**Scheme II-11**).[69]

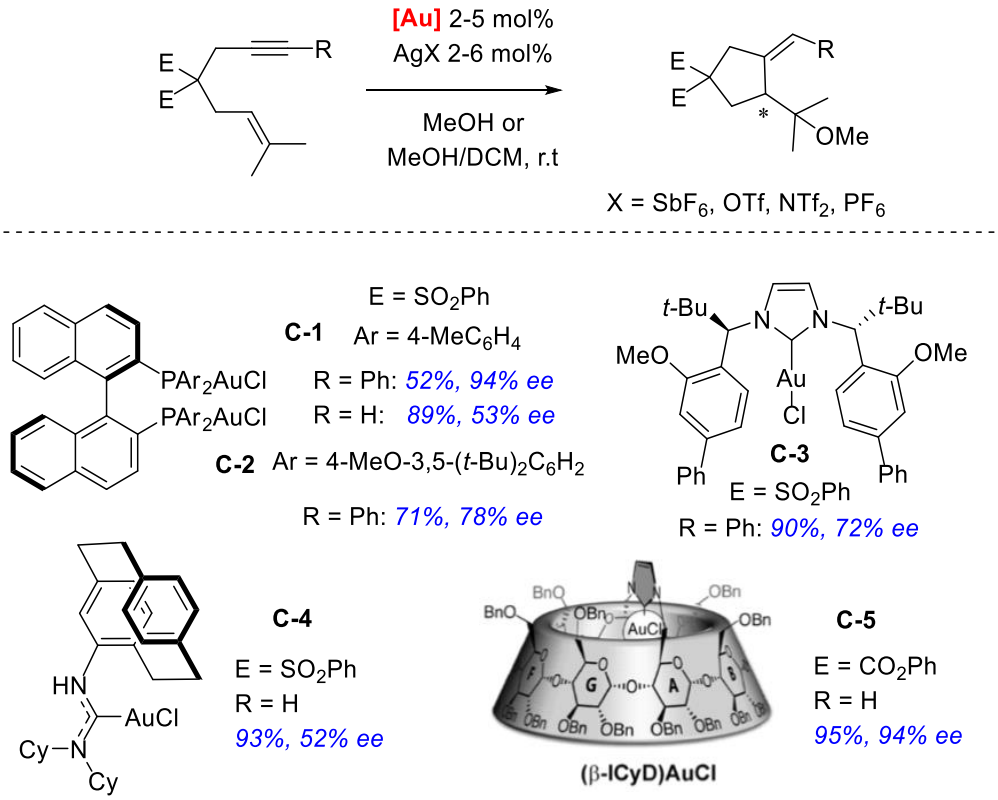
[64] (a) E. Genin, L. Leseurre, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Synlett*, **2007**, *11*, 1780; (b) C.-M. Chao, P. Y. Tollec, V. Michelet, *Tetrahedron Lett.*, **2009**, *50*, 3719.
[65] J. Koo, H. S. Park, S. Shin, *Tetrahedron Lett.*, **2013**, *54*, 834.
[66] S. I. Lee, S. M. Kim, S. Y. Kim, Y. K. Chung, *Synlett,* **2006**, *14*, 2256, corrected: *Synlett,* **2009**, *8*, 1355.
[67] W. Fang, M. Presset, A. Guérinot, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Chem. Eur. J.*, **2014**, *20*, 5439.
[68] C. Nieto-Oberhuber, S. López, A. M. Echvarren, *J. Am. Chem. Soc.*, **2005**, *127*, 6178.
[69] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett*., **2005**, *7*, 4133.



Scheme II-11 Intramolecular [4+2] cycloaddition under gold catalysis

1.2.3 Asymmetric 5-*exo* reaction under gold catalysis

In the context of on asymmetric gold-catalyzed domino hydroxy/alkoxycyclizations and intramolecular [4+2] cycloadditions of 1,6-enynes, several groups have described catalytic chiral systems.

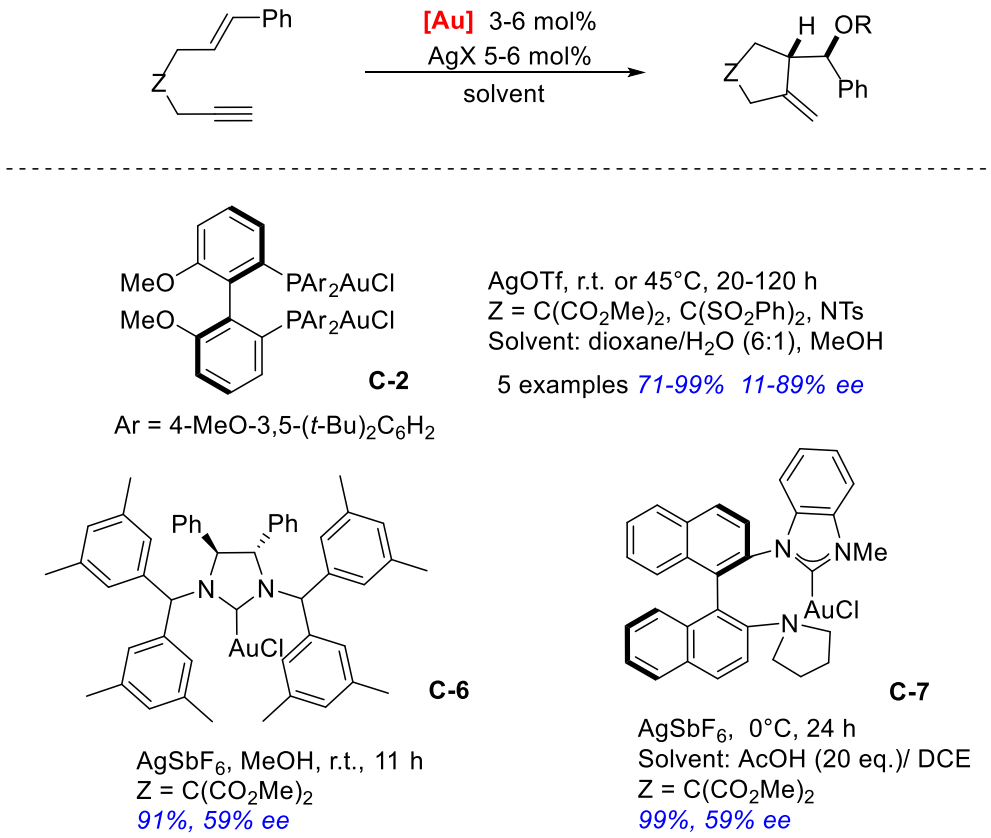


Scheme II-12 Asymmetric 5-*exo-dig* reactions under gold catalysis (part 1)

The first asymmetrical example was described in 2005 by Echavarren's team.[70] Ether product was transformed starting from corresponding substrate by 5-*exo-dig* pathway, under (*R*)-

[70] M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics,* **2005**, *24*, 1293.

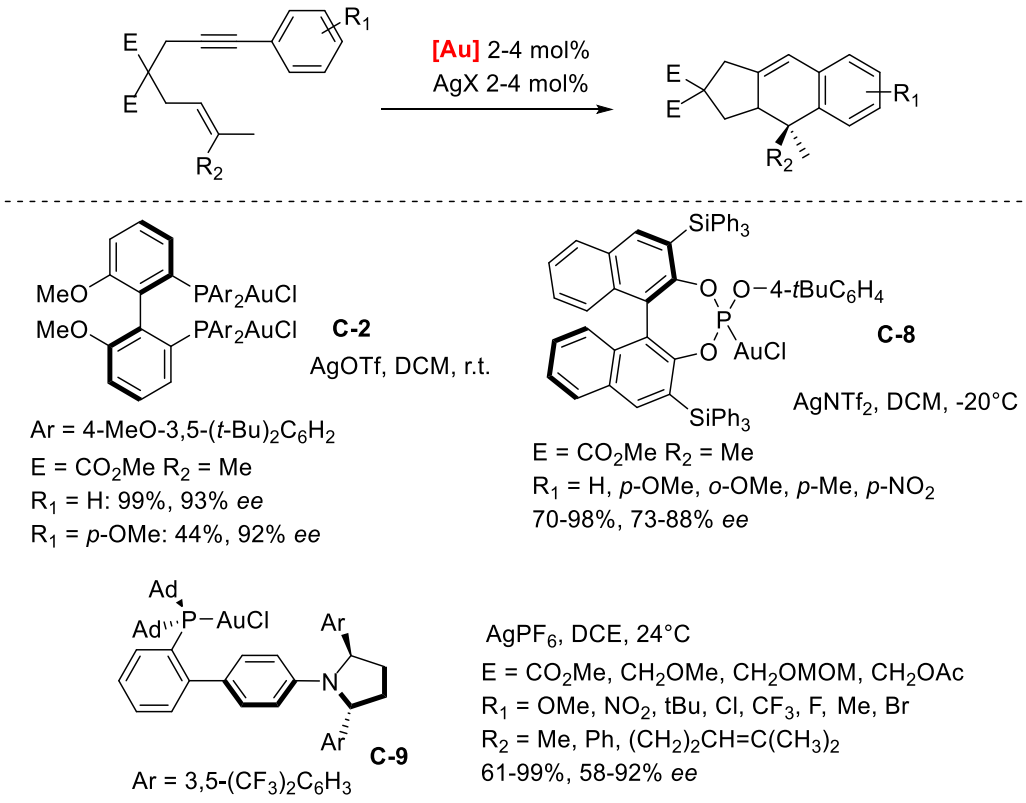
TolBINAP-$(AuCl)_2$ **C-1** catalysis, in MeOH. For R = Ph, the targeted compound was obtained in 52% yield and 94% *ee* (**Scheme II-12**). Other chiral gold complexes were tested in order to estimate the activity of BINAP ligands : (*R*)-DTBM-MeOBIPHEP$(AuCl)_2$ **C-2** led to a better yield but lower enantiomeric excess when R was a phenyl group.[71] For the *N*-heterocyclic carbene gold chloride complex **C-3** which ligands incorporating bulky alkyl groups and *o*-substituted aryl rings at the two stereogenic centers, the reaction was achieved with this complex, at room temperature, affording 90% yield and 72% of enantiomeric excess when R was a phenyl group.[72] In 2015, Hashmi and collaborators reported the use of chiral [2.2]paracyclophane (PCP)-based NAC- and NHC- gold complexes, prepared by using isonitriles and amines.[73] The complex (*Sp*)-LAuCl **C-4** gave the best performances with a 93% yield, but only 52% of *ee*. In 2020, NHC-capped β-cyclodextrin (β-ICyD) was reported as a new ligand for gold complexes, allowing alkoxycyclization reactions of enynes and affording *ee* up to 94% (**C-4**).[74]



Scheme II-13 Asymmetric 5-*exo-dig* reactions under gold catalysis (part 2)

[71] C.-M. Chao, E. Genin, P. Y. Toullec, J.-P. Genêt, V. Michelet, *J. Organomet. Chem.,* **2009**, *694*, 538.
[72] D. Banerjee, A. K. Buzas, C. Besnard, E. P. Kündig, *Organometallics,* **2012**, *31*, 8348.
[73] V. Göker, S. R. Kohl, F. Rominger, G. Meyer-Eppler, L. Volbach, G. Schnakenburg, A. Lützen, A. S. K. Hashmi, *J. Organomet. Chem.,* **2015**, *795*, 45.
[74] C. Tugny, N. Del Rio, M. Koohgard, N. Vanthuyne, D. Lesage, K. Bijouard, P. Zhang, J. M. Suárez, S. Roland, E. Derat, O. Bistri-Aslanoff, M. Sollogoub, L. Fensterbank, V. Mouriès-Mansuy, *ACS Catal*., **2020**, *10*, 5964.

The efficient Au(I) catalytic system (*R*)-DTBM-MeOBIPHEP-$(AuCl)_2$ **C-2** (**Scheme II-13**), was also described for the asymmetric domino cyclization of malonate and NTs tethered 7-phenyl-1,6-enynes. The reaction ran smoothly in the presence of oxygen nucleophiles (water and methanol), and good enantiomeric excesses up to 98% were given.[75] Then, Yamada and his collaborators tested a series of C2-symmetry chiral *N*-heterocyclic carbenes (NHCs) ligands, in a gold-catalyzed asymmetric reaction, in 2010.[76] Treatment of the gold complex (*S*, *S*)-L-AuCl (**C-6**), the ether product was isolated with 91% yield and 59% *ee*. One year later, Shi's team employed a new class of axially chiral gold complexes, NHC-Au (I) (*R*)-L-AuCl (**C-7**), and performed the asymmetric acetoxycyclization of a 1,6-enyne, at 0 °C, allowing the formation of the awaiting product in 99% yield and 59% *ee*.[77]



Scheme II-14 Asymmetric [4+2] cyclization under gold catalysis

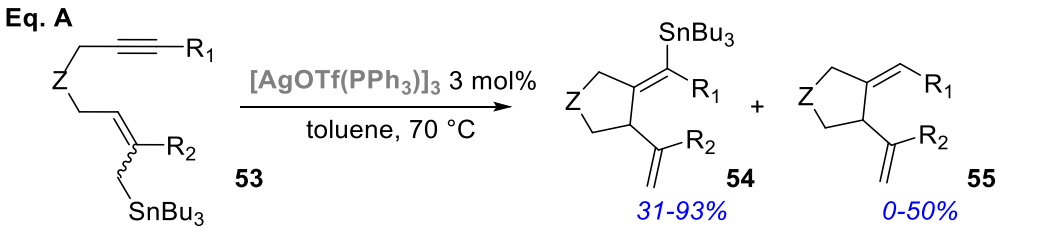
For the enantioselective [4+2] cyclization of 1,6-enynes with different types of chiral gold catalysts, the desired product was isolated with 93% *ee* in the presence of (*R*)-4-MeO-3,5-(*t*-

[75] A. Pradal, C.-M. Chao, M. R. Vitale, P. Y. Toullec, V. Michelet, *Tetrahedron*, **2011**, *67*, 4371
[76] Y. Matsumoto, K. B. Selim, H. Nakanishi, K. Yamada, Y. Yamamoto, K. Tomioka, *Tetrahedron Lett.*, **2010**, *51*, 404.
[77] W. Wang, J. Yang, F. Wang, M. Shi, *Organometallics*, **2011**, *30*, 3859.

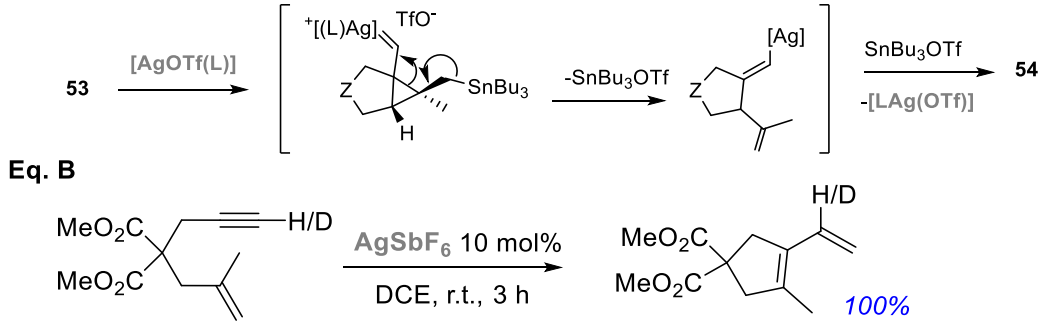
$Bu)_2$MeOBIPHEP$(AuCl)_2$ complex **C-2** (**Scheme II-14**),[78] and 73-88% *ee* with the chiral phosphite gold complex, prepared in a modular manner from BINOL **C-8**.[79] In 2019, Echavarren's group published the preparation of 17 examples of enantioselective [4+2] cycloaddition products, in the presence of the chiral mononuclear catalyst **C-9,** in 61-99% yield, with 58-92% *ee*.[80]

1.2.4 Silver-catalyzed cycloisomerization reactions

In the case of 1,6-enynes, the literature presents few examples of silver-catalyzed cyclization reactions. In 2007, Porcel and Echavarren reported the first silver-catalyzed intramolecular carbostannylation reaction of 1,6-enynes (**Scheme II-15 Eq. A**).[81] With $[AgOTf(PPh_3)]_3$ as a catalyst, a series of (*E*)-alkenylstannanes **54** was stereoselectivily isolated as a single isomer, but 1,4-diene by-products **55** was possibly observed. The reaction proceeded by *exo* attack of the allyl nucleophile on the alkyne to form carbocycles with five-membered ring.



Entry	Substrate	Time	Yield (%)(**54**/**55**)
1	(*Z*) Z = $C(SO_2Ph)_2$, R_1 = H, R_2 = Me	0.5 h	*91*/*0*
2	(*E*) Z = $C(SO_2Ph)_2$, R_1 = Ph, R_2 = Me	3 h	*50*/*50*

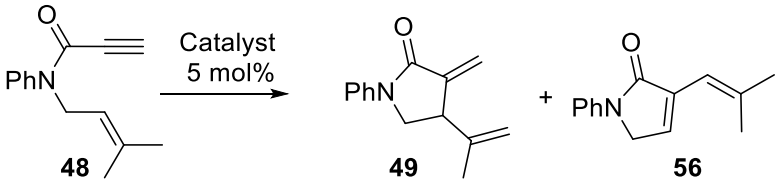


Scheme II-15 Synthesis of 1,4-dienes under silver catalysis

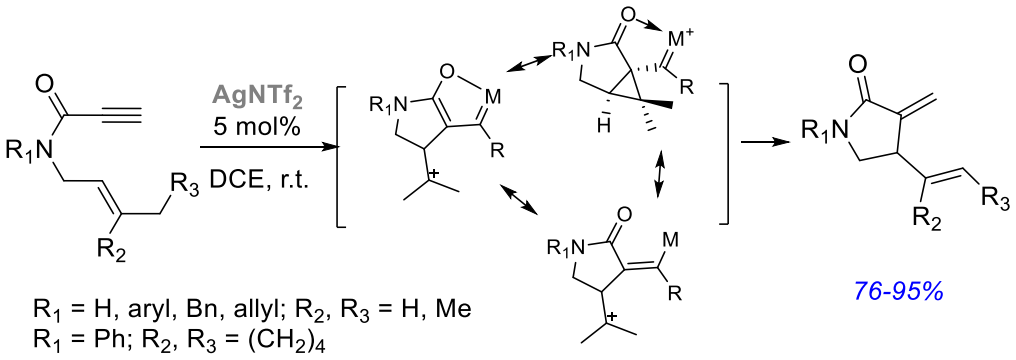
[78] C.-M. Chao, M. R. Vitale, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Chem. Eur. J.*, **2009**, *15*, 1319.
[79] N. Delpont, I. Escofet, P. Pérez-Galán, D. Spiegl, M. Raducan, C. Bour, R. Sinisi, A. M. Echavarren, *Catal. Sci. Technol.*, **2013**, *3*, 3007.
[80] G. Zuccarello, J. G. Mayans, I. Escofet, D. Scharnagel, M. S. Kirillova, A. H. Pérez-Jimeno, P. Calleja, J. R. Boothe, A. M. Echavarren, *J. Am. Chem. Soc.*, **2019**, *141*, 11858.
[81] S. Porcel, A. M. Echavarren, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2672.

In the same paper, they also reported the first example of silver-catalyzed skeletal rearrangement and intramolecular cyclopropanation reaction of 1,6-enynes. This reaction implied a silver-carbene intermediate.[82,83] It allowed the preparation of 1,3-diene products in quantitative yields (**Scheme II-15 Eq. B**).

In 2013, Shin's group reported silver-catalyzed cycloisomerization reactions of propiolamide derived 1,6-enynes, in the case of *N*-arylamides.[65] For this kind of substrate, the carbonyl was demonstrated to be a key group for the silver-catalyzed 5-*exo-dig* selective reaction. Employment of Au(IPr)NTf_2, AgOTf, and $AgNTf_2$ led to 1,4-enynes **49** but skeletal rearrangement product **56** could also be observed with AgOTf or $AgNTf_2$ (**Scheme II-16**). The reaction was examined under $AgNTf_2$ catalysis in DCE, at rt, which constitutes simple and mild reaction conditions. When the NTs-tethered 1,6-enyne which devoided the C(5)-carbonyl group was tested, it gave extensive decomposition and a low yield of the awaiting product.



Entry	Catalyst	Conditions	Yield (%)(**49**/**56**)
1	**Au(IPr)NTf_2**	r.t., DCE, 1 h	*43*/*13*
2	**AgOTf**	100 °C, $CHCl_3$, 1 h	*36*/*0*
3	**$AgNTf_2$**	100 °C, $CHCl_3$, 1 h	*76*/*0*
4	**$AgNTf_2$**	r.t. DCE, 1 h	*91*/*0*



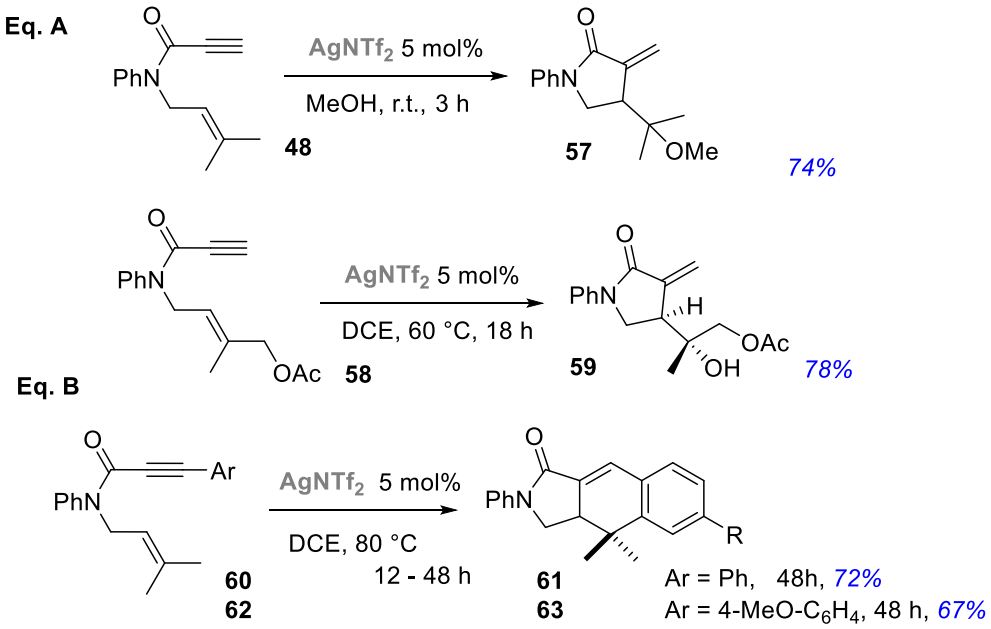
Scheme II-16 Synthesis of 1,3-diene and 1,4-dienes from *N*-arylamides

[82] For leading references on silver(I)–carbene complexes, see: (a) J. C. Garrison, W. J. Youngs, *Chem. Rev.*, **2005**, *105*, 3978; (b) P. de FrKmont, N. M. Scott, E. D. Stevens, T. Ramnial, O. C. Lightbody, C. L. B. Macdonald, J. A. C. Clyburne, C. D. Abernethy, S. P. Nolan, *Organometallics*, **2005**, *24*, 6301; (c) R. R. Julian, J. A. May, B. M. Stoltz, J. L. Beauchamp, *J. Am. Chem. Soc.*, **2003**, *125*, 4478; (d) A. J. Arduengo III, H. V. R. Dias, J. C. Calabrese, F. Davidson, *Organometallics*, **1993**, *12*, 3405.

[83] For discussions on π-back bonding in silver(I)–carbene complexes, see: (a) X. Hu, I. Castro-Rodriguez, K. Olsen, K. Meyer, *Organometallics*, **2004**, *23*, 755; (b) D. Nemcsok, K. Wichmann, G. Frenking, *Organometallics*, **2004**, *23*, 3640.

1.2.5 Silver-catalyzed domino cyclization reactions

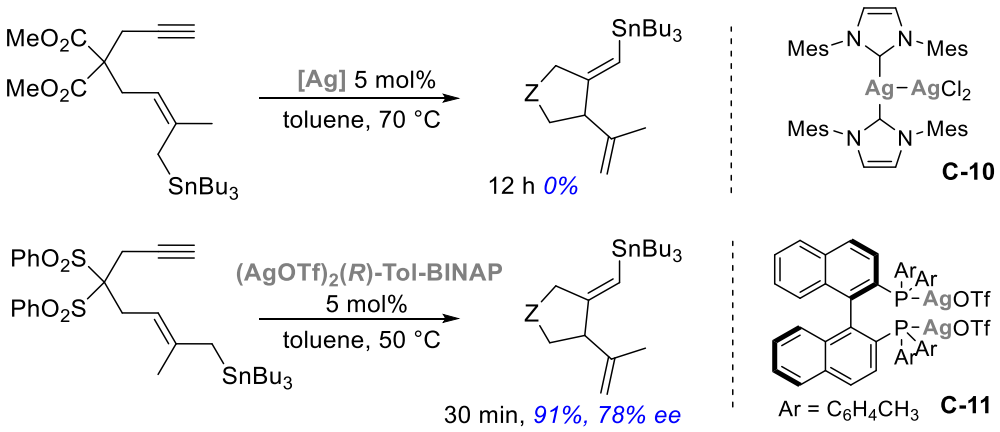
The domino 5-*exo*-*dig* cycloaddition reaction under silver catalysis, starting from of 1,6-enynes, was also reported in Shin's work.[65] The reaction of *N*-tosylpropiolamide in methanol at room temperature in the presence of $AgNTf_2$ catalyst, led to alkoxycyclization adduct **57** in 74% yield. On the other hand, the reaction of an allyl acetate slowly gave the hydroxycyclization product **59** in 78% yield, after warming at 60°C during 18 h (**Scheme II-17 Eq. A**). Friedel-Craft arylated products **61** and **63** were isolated when using **60** and **62** as starting materials, in the presence of $AgNTf_2$, in DCE, at 80 °C (**Scheme II-17 Eq. B**).



Scheme II-17 Silver-catalyzed domino cyclization reaction from *N*-arylamides

1.2.6 Asymmetric 5-*exo* reaction under silver catalysis

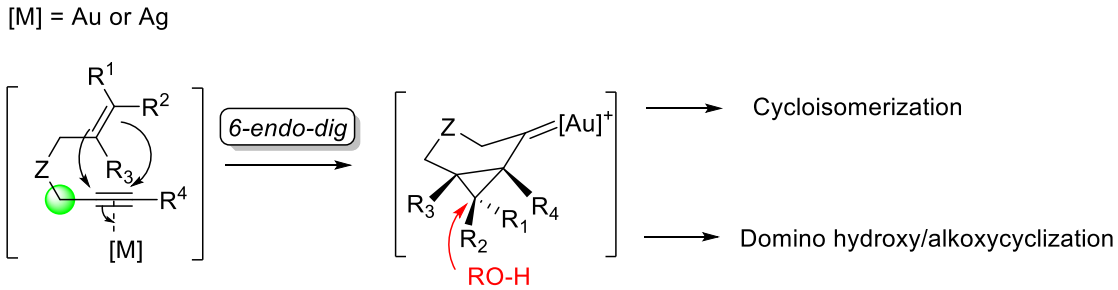
For the 1,6-enyne system, only few examples of asymmetric silver-catalyzed cyclization reactions were reported in the literature. The intramolecular carbostannylation of 1,6-enynes by asymmetric silver species was published by Echavarren group in 2007. In this study, chiral silver complex **C-10** was ineffective for (*Z*)-enyne. Remarkably, with 5 mol% of [$(AgOTf)_2$(*R*)-Tol-BINAP] **C-11** as the catalyst, in toluene, at 50 °C, a 78% *ee* of the awaiting 1,4-diene was described (**Scheme II-18**).[81]



Scheme II-18 Asymmetric 5-*exo* reaction under silver-catalysis

1.3 6-*Endo* cyclization reactions

We will present in this paragraph the 6-*endo-dig* gold-catalyzed cycloisomerization reactions and domino cyclization reactions.

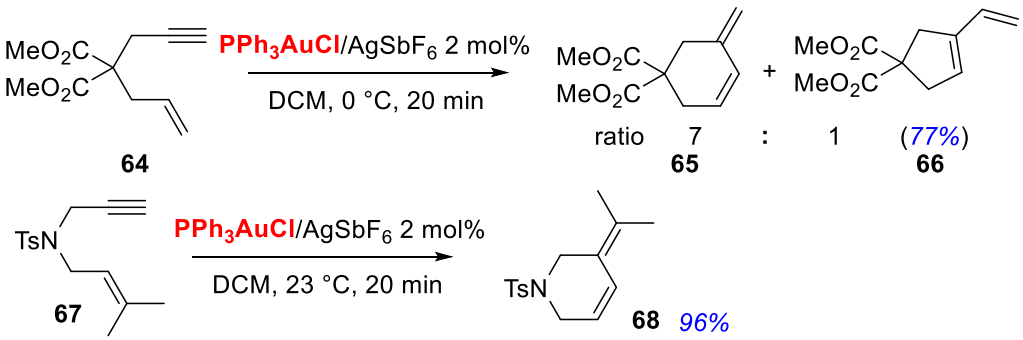


Scheme II-19 6-*Endo-dig* cyclization reactions by gold and silver

1.3.1 Gold-catalyzed cycloisomerization reactions

1,3-Dienes

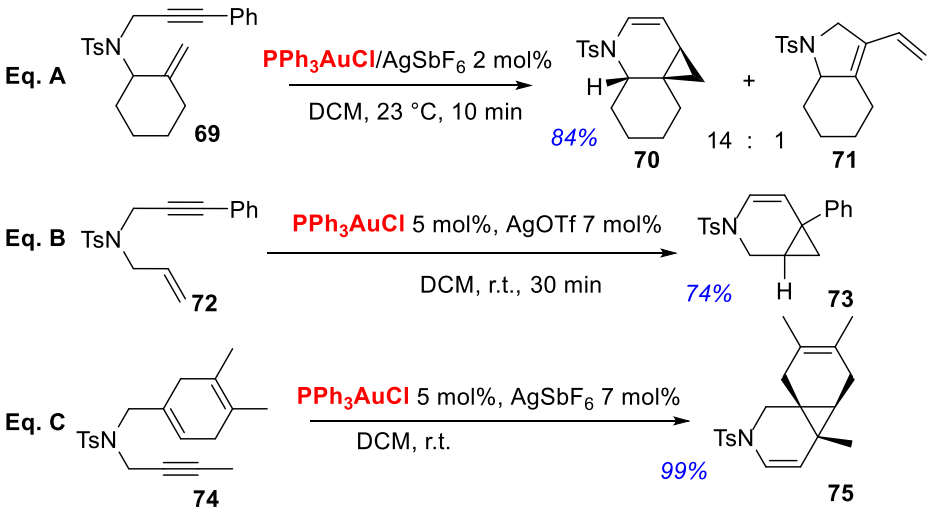
The first example of gold-catalyzed skeletal rearrangement of enynes by the endocyclic cyclization pathway was disclosed by Echavarren's team in 2004.[60] When employing the 1,6-enyne **64**, the major endocyclic intermediate evolved to give **65**, with the concomitant formation of the exocyclic rearranged derivative **66**, with a total yield of 77%. When using the TsN- substrate **67**, 96% of endocyclic rearrangement adduct **68** was reported (**Scheme II-20**).



Scheme II-20 Synthesis of 1,3-diene by gold-catalyzed *endo-dig* cyclization reactions

Bicyclo[4.1.0]heptenes

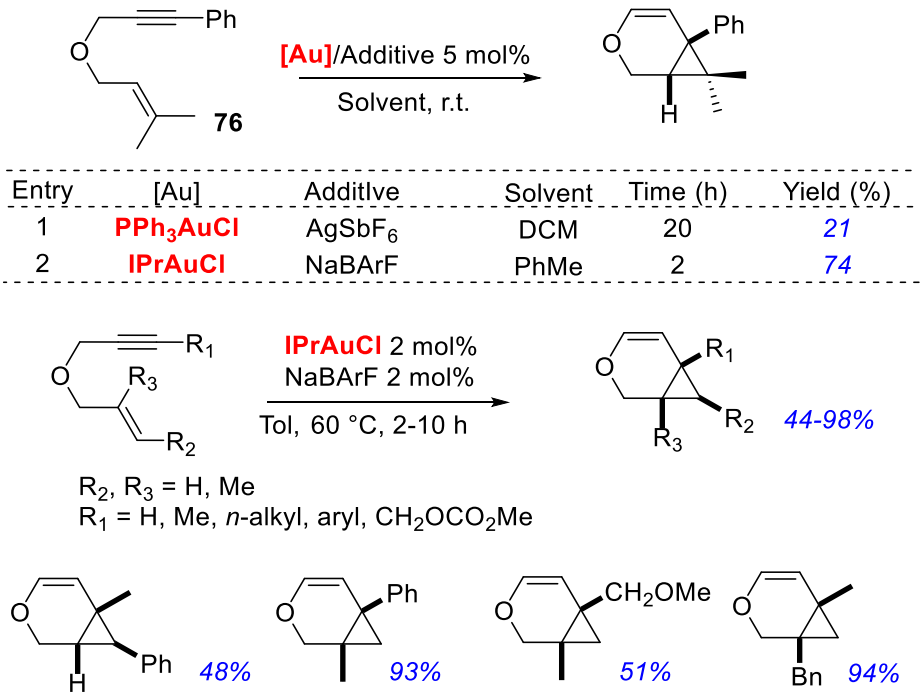
Blum reported the first method of synthesis 3-oxabicyclo[4.1.0]heptene, in the presence of platinum in 1995,[84] whereas the synthesis of bicyclo[4.1.0]heptene derivatives through gold-catalyzed cycloisomerization reaction was reported in 2004.[60] In the case of the 1,6-enyne **69**, a mixture of the major endocyclic adduct **70** and minor exocyclic rearranged derivative **71,** was obtained in 84% yield (**Scheme II-21 Eq. A**). Chung's team described a 6-*endo-dig* cyclization, allowing the preparation of the bicyclo[4.1.0]heptane **73,** starting from the 1,6-enyne **72** (**Scheme II-21 Eq. B**).[66] Gold(I)-catalyzed cyclization of enynes containing an olefinic cycle has also been reported in 2006 : replacement of the terminal alkene of the enyne, by an olefinic ring, increased the yield of the reaction up to 99% (**Scheme II-21 Eq. C**).[85]



Scheme II-21 Synthesis of bicyclo[4.1.0]heptenes under gold catalysis

[84] J. Blum, H. Beer-Kraft, Y. Badrieh, *J. Org. Chem.*, **1995**, *60*, 5567.
[85] S. I. Lee, S. M. Kim, M. R. Choi, S. Y. Kim, Y. K. Chung, W.-S. Han, S. O. Kang, *J. Org. Chem.,* **2006**, 71, 25, 9366.

For the 1,6-enyne ethers, Au(I)-catalyzed cycloisomerization was inclined to generate 1,4-bicycle[4.1.0] compounds. A lot of studies reported interesting informations to describe efficiency of different catalysts, additives, solvents or reaction temperatures. [60,86]



Scheme II-22 Synthesis of bicyclo[4.1.0]heptenes from 1,6-enyne ethers

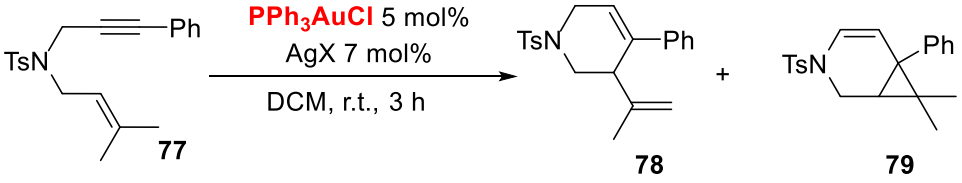
In 2020, our team reported an efficient method, with IPrAuCl and NaBArF as an additive, for the synthesis of oxa-bicyclo[4.1.0]-hept-4-enes in 44−98% isolated yields.[87] We initiated our study by investigating the reaction of the enyne **76** as the substrate, in the presence of different gold catalysts and additive combinations. Then, effective reaction conditions with the system IPrAuCl/NaBArF, in toluene, at 60 °C, were used to explore the substrates range (**Scheme II-22**).

1,4-Dienes

Chung's team described a 6-*endo-dig* cyclization to prepared 1,4-dienes in 2006, in the presence of a cationic triphenylphosphinegold(I) system.[66] The silver salts additive nature was demonstrated to affect the reaction. When the additive was $AgSbF_6$ or $AgPF_6$ (entries 1 and 4), cycloisomerized 1,4-diene product **79** was obtained in 69% and 85% yields respectively, with the concomitant formation of bicyclo[4.1.0]heptene product **78**, in 7% and 5% yields respectively. When using $AgBF_4$, $AgClO_4$ or AgOTf (entries 2, 3, and 5), the reaction led

[86] Y. T. Lee, Y. K. Kang, Y. K. Chung, *J. Org. Chem.*, **2009**, *74*, 7922.
[87] R. Laher, C. Marin, V. Michelet, *Org. Lett.*, **2020**, *22*, 4058.

selectively to the single 1,4-diene **78**. (**Scheme II-23**).

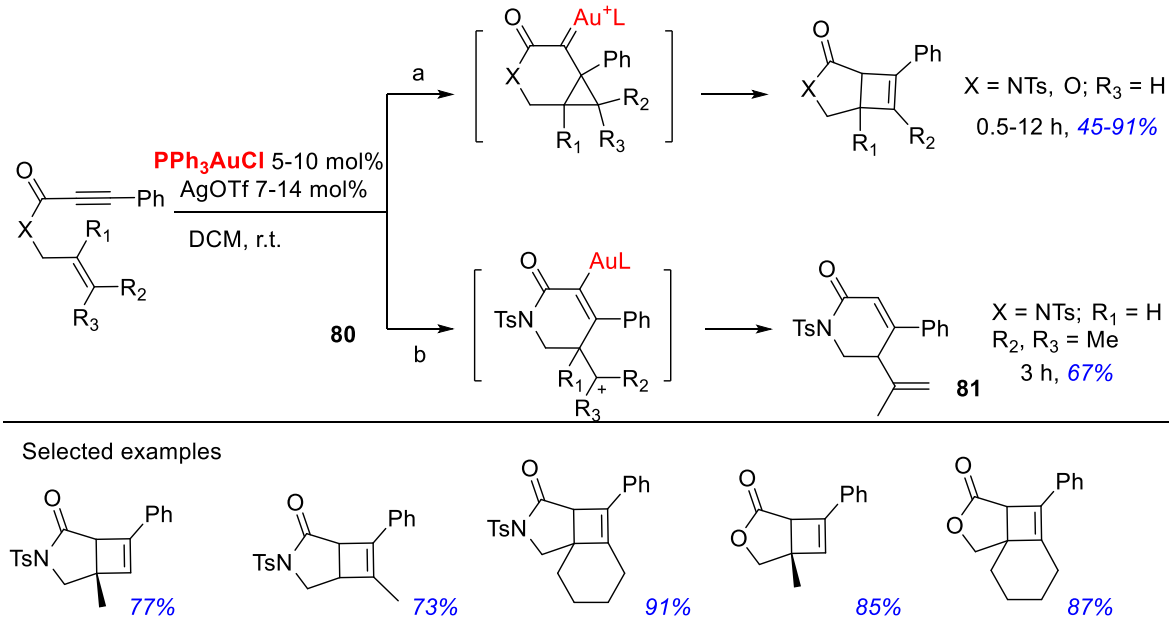


Entry	Additive	Time (h)	Yield (%)(**78**/**79**)
1	$AgSbF_6$	0.5	*69* / *7*
2	$AgBF_4$	5	*82* / *0*
3	$AgClO_4$	4	*84* / *0*
4	$AgPF_6$	3	*85* / *5*
5	AgOTf	3	*97* / *0*

Scheme II-23 Synthesis of 1,4-dienes from 1,6-enynes

Bicyclo[3.2.0]hept-6-en-2-ones and 5,6-dihydropyridin-2(1*H*)-one

In 2009, Chung and co-workers also reported the cycloisomerization reaction of amide- or ester-tethered 1,6-enynes, in the presence of cationic triphenylphosphinegold(I). In this study, a stepwise 6-*endo-dig* reaction afforded the bicyclo[3.2.0]hept-6-en-2-ones, in reasonable to high yields, between 45 to 91%.[88] By employing **80** as substrate, 5,6-dihydropyridin-2(1*H*)-one **81** was produced in 67% yield. Theoretical calculations with a density functional theory (DFT) suggested that both an aryl group at the alkyne terminal position and a carbonyl group at the C(5) position of the 1,6-enyne system could play a complementary roles (**Scheme II-24**).



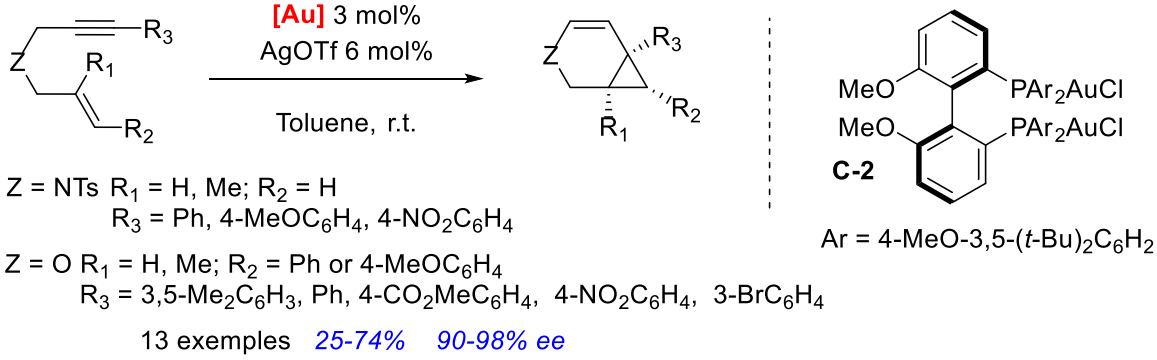
Scheme II-24 Synthesis of bicyclo[3.2.0]hept-6-en-2-ones and 5,6-dihydropyridin-2(1*H*)-ones

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

1.3.2 Asymmetric 6-*endo* reaction under gold catalysis

Asymmetric bicyclo[4.1.0]heptenes

Enantioselective asymmetric cycloisomerization reactions of heteroatom tethered 1,6-enynes were undertaken with the (*R*)-4-MeO-3,5(*t*-Bu)$_2$-MeOBIPHEP-(AuCl)$_2$/AgOTf system, in toluene, at room temperature. The reaction allowed the synthesis of functionalized bicyclo[4.1.0]heptene derivatives, in excellent enantiomeric excesses of 90-98% (**Scheme II-25**).[89,90] This is the first asymmetric system of 1,6-enynes cycloisomerization described by using a chiral gold catalyst (**C-2**). Oxygen- and TsN- tethered 1,6-enynes could be transformed into bicyclo[4.1.0]heptanes. In this asymmetric system, the best results were obtained with 74% yield and with an excellent enantiomeric excess of 98%.

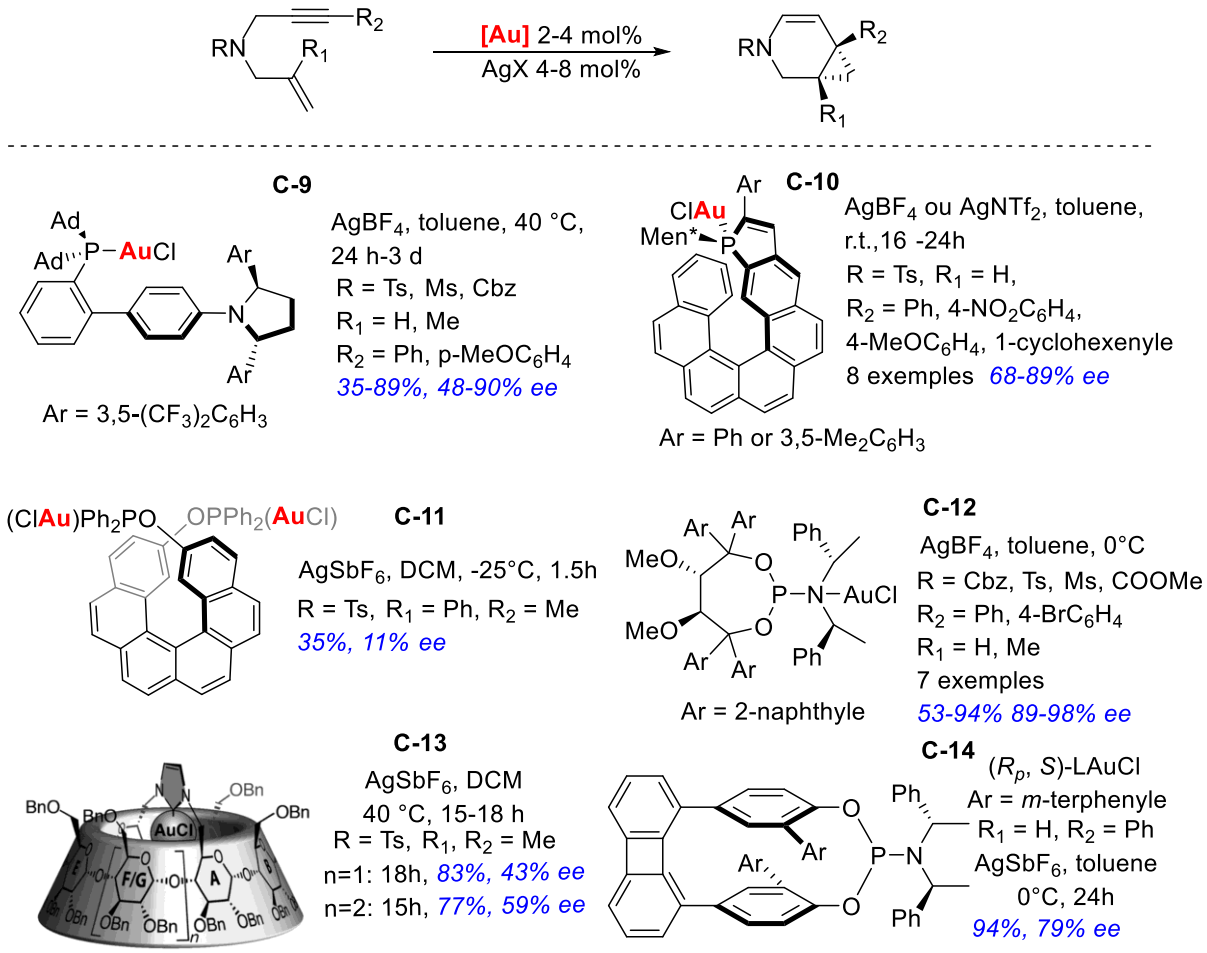


Scheme II-25 Enantioselective synthesis of bicyclo[4.1.0]heptenes (part 1)

As shown in **Scheme II-26**, the 6-*endo*-*dig* cyclization reaction of *N*-tethered 1,6-enynes allowed the synthesis of azabicyclo[4.1.0]hept-4-enes, in moderate to good yields, with 48-90% *ee*.[79] In this reaction, the chiral mononuclear catalyst **C-9** was prepared with a modified JohnPhos ligand (biaryl group replaced by a distal C$_2$-2,5-diarylpyrrolidine). According to the gold complexes with the HelPHOS helical ligands (**C-10**), developed by Marinetti, Voituriez, and Licandro in 2014,[91] enantioselectivities for the cycloisomerization of various 1,6-nitrogen enynes gave desired azabicyclo[4.1.0]heptenes derivatives with 68-89% *ee*. In 2019, Barbazanges group reported a new helical bis(phosphinite gold) complex (**C-11**) derived from

[89] C.-M. Chao, D. Beltrami, P. Y. Toullec, V. Michelet, *Chem. Commun.*, **2009**, *45*, 6988.
[90] A. Pradal, C.-M. Chao, P. Y. Toullec, V. Michelet, *Beilstein J. Org. Chem.*, **2011**, *7*, 1021.
[91] (a) K. Yavari, P. Aillard, Y. Zhang, F. Nuter, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem. Int. Ed.*, **2014**, *53*, 861; (b) P. Aillard, A. Voituriez, D. Dova, S. Cauteruccio, E. Licandro, A. Marinetti, *Chem. Eur. J.*, **2014**, *20*, 12373.

HELIXOL.[92] Cycloisomerization of enyne in the presence of chiral gold complex **C-11,** in DCM, at -25 °C, for 1.5 h, led to bicyclo[4.1.0]heptane in 11% *ee*, whereas no enantiomeric excess was observed, when the mixture was reacted at 25 °C.



Scheme II-26 Enantioselective synthesis of bicyclo[4.1.0]heptenes (part 2)

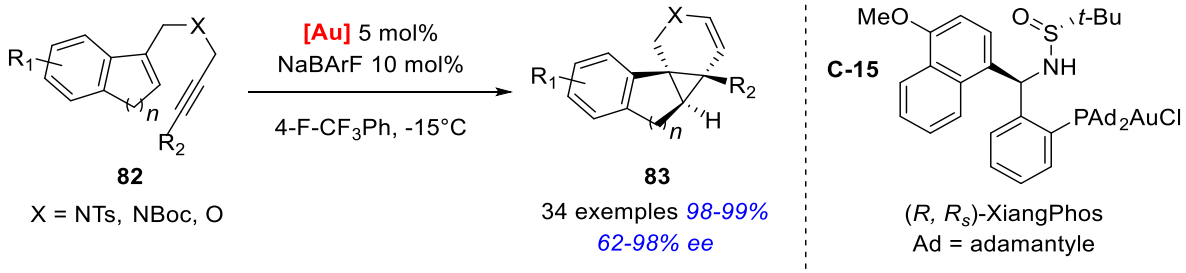
The phosphoramidite ligands of the TADDOL, developed by Fürstner group, performed excellent enantioselectivity for the cycloisomerization of 1,6-enynes.[93] When using the 2-naphthyl complex (*S, S, S, S*)-L-AuCl (**C-12**) as a catalyst and $AgBF_4$, in toluene, at 0 ° C, the azabicyclo[4.1.0]heptene was isolated with good yields (53 -94%) and excellent enantiomeric excesses (89-98%).

In 2013, Sollogoub and his collaborators synthesized a new type of NHC complex carried by a

[92] C. Medena, F. Calogero, Q. Lemoine, C. Aubert, E. Derat, L. Fensterbank, G. Gontard, O. Khaled, N. Vanthuyne, J. Moussa, C. Ollivier, M. Petit, M. Barbazanges, *Eur. J. Org. Chem.*, **2019**, *11*, 2129.
[93] H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Fürstner, *J. Am. Chem. Soc.,* **2012**, *134*, 15331.

cyclodextrin-α and -β (**C-13**). The NHC motif was attached to the top of the conical cyclodextrin as a bridge linked by two methylenes, and the metal center was encapsulated in the cavity. The induction of chirality was managed by the entire environment of cyclodextrin. Cycloisomerization of enyne provided azabicyclo[4.1.0]heptenes with medium enantioselectivity. The target molecule could be isolated with 59% *ee* in the presence of cyclodextrin-β, whereas only 43% *ee* was observed with cyclodextrin-α.[94]

In 2016, Voituriez, Betzer, and collaborators described a new catalyst **C-14** containing a planar chiral phosphoramidite with a paracyclophane scaffold, with two 1,8-biphenylene tethered aryl rings and an O-P-O bridge.[95] With (R_p, S)-L-Au-Cl (**C-14**) as a catalyst, the corresponding chiral gold-catalyzed 6-*endo* cycloisomerization led to the desired bicyclo[4.1.0]heptenes with 94% yield and 79% *ee*.



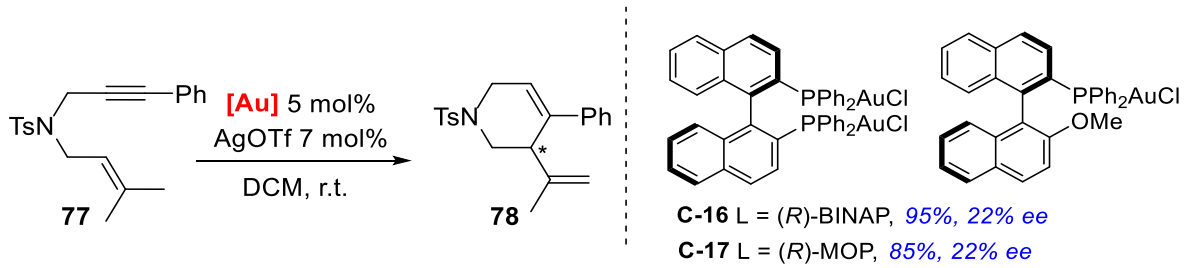
Scheme II-27 Enantioselective synthesis of [5-3-6] fused-ring compounds

In 2008, Zhang's group described the first enantioselective cyclopropanation of indenes and trisubstituted alkenes (including 1,6-enyne structures), with a new chiral phosphine ligand and a new Xiang-Phos gold complex **C-15** (**Scheme II-27**). [96] The chiral sulfinamide and monophosphine ligands form chiral gold catalyst, able to catalyze intramolecular asymmetric cyclopropanation (ACP) of indene-derived 1,6-enynes **82** to construct [5-3-6] fused-ring compounds **83**, in excellent yields up to 99% and high enantioselectivities up to 98%.

1,4-Diene

In 2006, Chung's group reported the efficiency of chiral AuCl(L) (**C-16** and **C-17**) complexes bearing ligands (*R*)-BINAP or (*R*)-MOP. The 6-*endo-dig* cyclisation of the 1,6-enyne **77** afforded the heterocycle **78** with 95% and 85% yields respectively, with 22% *ee* in each case (**Scheme II-28**).[66]

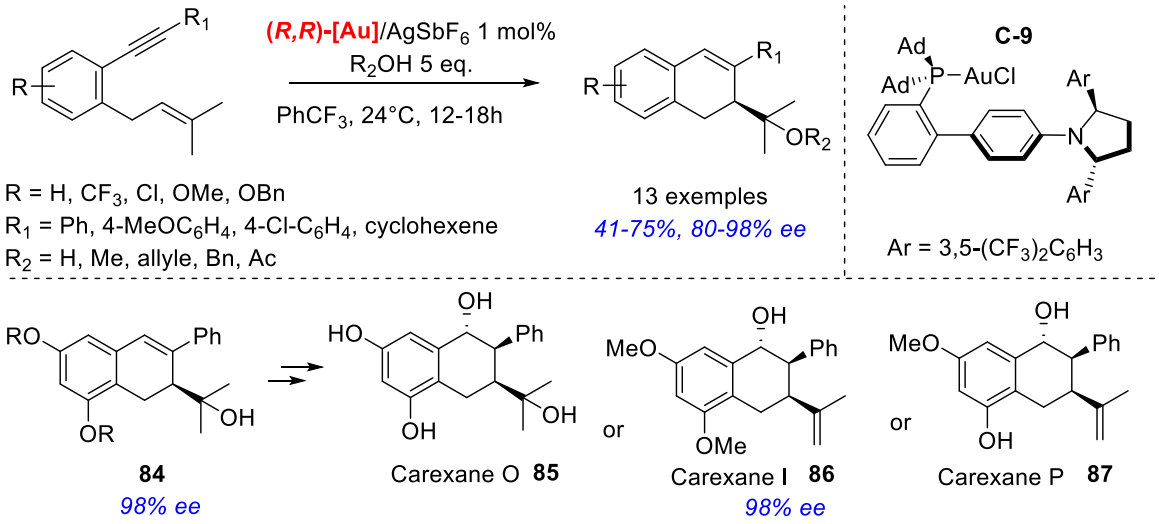
[94] M. Guitet, P. Zhang, F. Marcelo, C. Tugny, J. Jiménez-Barbero, O. Buriez, C. Amatore, V. Mouriès-Mansuy, J. -P. Goddard, L. Fensterbank, Y. Zhang, S. Roland, M. Ménand, M. Sollogoub, *Angew. Chem. Int. Ed.*, **2013**, *52*, 7213.
[95] Z. Wu, K. Isaac, P. Retailleau, J.-F. Betzer, A. Voituriez, A. Marinetti, *Chem. Eur. J.*, **2016**, *22*, 3278.
[96] P.-C. Zhang, Y. Wang, Z.-M. Zhang, J. Zhang, *Org. Lett.*, **2018**, *20*, 7049.



Scheme II-28 Enantioselective synthesis of 1,4-dienes

Asymmetric domino hydroxy/alcoxycyclization reactions

The domino hydroxy/alkoxycyclization was employed for the synthesis of 2,3-disubstituted 1,2-dihydronaphthalenes. The reaction conditions included the presence of H_2O and alcohol as a nucleophile, with a chiral gold(I) complex bearing monodentate pyrrolidiny-biphenyl phosphine ligand (**C-9**). The reaction was demonstrated to follow a 6-*endo-dig* pathway (**Scheme II-29**).[80]

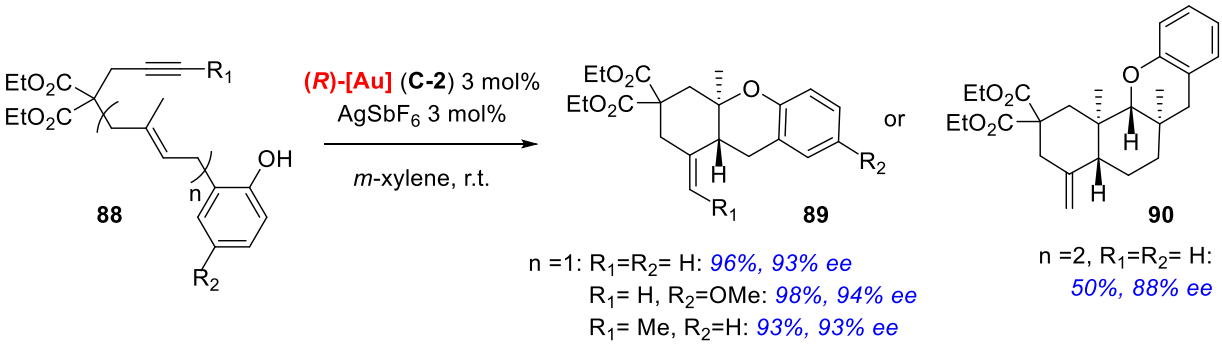


Scheme II-29 Enantioselective synthesis of 1,2-dihydronaphthalenes

After the preparation of one of the 1,2-dihydronaphthalenes **84** with 98% *ee* after recrystallization, the total synthesis of carex distachya [97] [a member of the carexane family (**85**, **86**, and **87**) in natural products] was achieved after 6-9 steps (**Scheme II-29**).

[97] (a) B. D'Abrosca, A. Fiorentino, A. Golino, P. Monaco, P. Oriano, S. Pacifico, *Tetrahedron Lett.*, **2005**, *46*, 5269; (b) A. Fiorentino, B. D'Abrosca, S. Pacifico, A. Natale, P. Monaco, *Phytochemistry*, **2006**, *67*, 971; (c) A. Fiorentino, B. D'Abrosca, S. Pacifico, R. Iacovino, A. Izzo, P. Uzzo, A. Russo, B. Di Blasio, P. Monaco, *Tetrahedron*, **2008**, *64*, 7782.

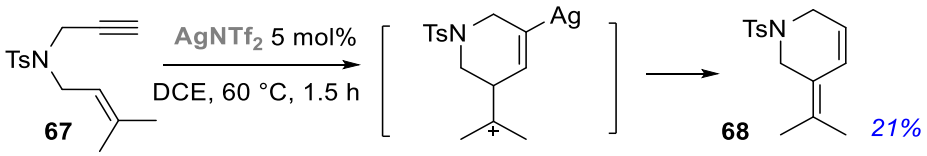
In 2010, Toste's group reported the first example of a highly enantioselective polyene domino hydroxy/alcoxycyclization reaction by the efficient (*R*)-DTBM-MeOBIPHEP-$(AuCl)_2$ **C-2** system.[98] The polycyclic compounds, whose stereochemistry is consistent with the Stork-Eschenmoser postulate, were synthesized by polyene cyclization, with *ee* up to 97%. When employing **88** as substrates, hexahydroxanthene derivatives **89** were isolated in 93-96% yields and 93-94% *ee*. When n = 2, tetracyclic ether **90** was obtained in 50% yield and 88% *ee* (**Scheme II-30**).



Scheme II-30 Enantioselective synthesis of polycyclic compounds

1.3.3 Silver-catalyzed cyclization reaction

In the literature, the only example of a 6-*endo-dig* cyclization of 1,6-enynes to the best of our knowledge was reported by Shin's group.[65] The cyclization of an NTs-tethered 1,6-enyne **67** afforded a 6-*endo-dig* Alder-ene type product **68** in low yield (21%) instead of a 5-*exo-dig* product, along with extensive decomposition of the substrate (**Scheme II-31**).



Scheme II-31 Synthesis of 1,3-diene by silver-catalyzed 6-*endo-dig* reaction

1.4 Conclusion

According to literature research, the reaction under silver catalysis is highly likely to occur *via* 5-*exo* pathway. Concerning the gold-catalysed reaction, both 5-*exo* and 6-*endo* pathways may occur, depending on the type of catalyst, substrate, and reaction conditions. Only few

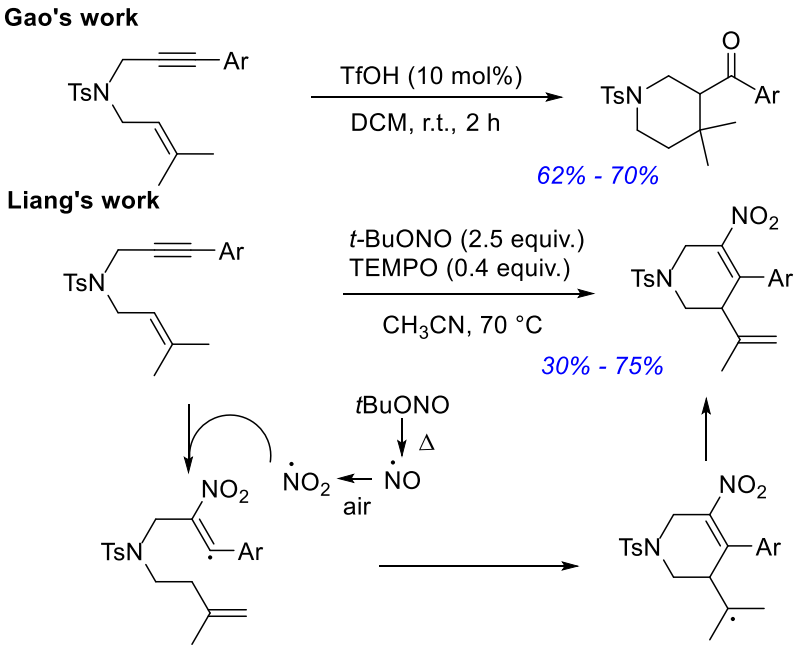
[98] S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.*, **2010**, *132*, 8276.

examples of 6-*endo* asymmetric domino reaction are described in literature.

2. Gold-catalyzed domino cycloisomerization-nucleophile additions

2.1 Objective

In view of the aforementioned examples, the literature deals with few studies focused on the synthesis of 1,4-dienes *via* the gold-catalyzed 6-*endo-dig* process. To the best of our knowledge, only one example describes the preparation of a 6-*endo* 1,4-diene under asymmetric conditions, with an enantiomeric excess of 22% (**Scheme II-28**). On the other hand, the 6-*endo* process could also be achieved by a metal-free catalyst system, like in Gao's work (a straightforward triflic acid TfOH catalysis to form hetero-hexacycle-fused ketones *via* a cation-induced cascade cyclization)[99], and Liang's work (metal-free nitro-carbocyclization with *tert*-butyl nitrite and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) by a radical pathway) [100] (**Scheme II2-1**).



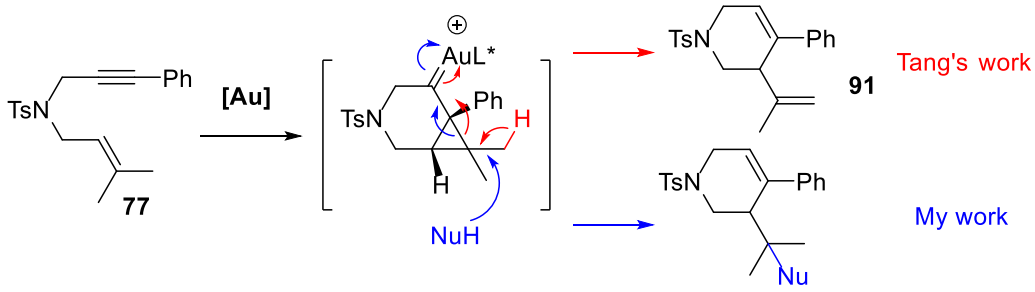
Scheme II2-1 6-*Endo-dig* reactions under metal-free conditions

In conclusion, there are still big challenges to develop 6-*endo-dig* methods and improve their enantiomeric excesses. In this context and considering our experience in gold catalysis, we

[99] X. Liu, Y. Wang, J. Zhou, Y. Yu, H. Cao, *J. Org. Chem.*, **2020**, *85*, 2406.
[100] X. -H. Hao, P. Gao, X. -R. Song, Y. -F. Qiu, D. -P. Jin, X. -Y. Liu, Y. -M. Liang, *Chem. Commun.*, **2015**, *51*, 6839.

decided to study the 6-*endo-dig* reaction from 1,6-enynes in the presence of gold catalysts. We also focused on the improvement of chiral gold catalysis to increase the asymmetric induction of this reaction

In our group, Yue Tang,[36] a previous PhD student, has developed asymmetric new conditions for the cycloisomerization reactions of 1,6-enynes, obtaining enantio induction up to 94% in the presence of (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$ (**C-18**). Following this result, we then focused on the gold-catalyzed 6-*endo* enantioselective domino cycloisomerization in the presence of nucleophile species (**Scheme II2-2**).



Scheme II2-2 Group works concerning 6-*endo* reactions under gold catalysis

2.2 Results and discussions

2.2.1 Synthesis of 1,6-enynes

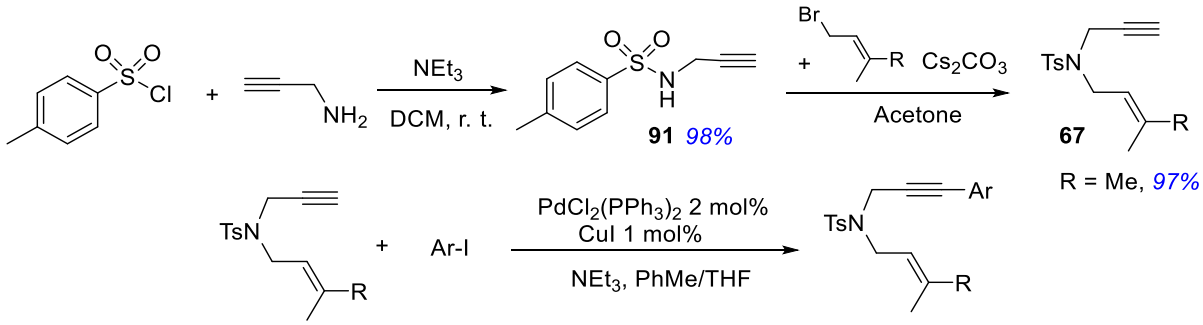
In order to evaluate the reactivity during this 6-*endo-dig* reaction, broaden the scope, and study the enantioselectivity, we prepared different types of 1,6-enynes.

We first decided to prepare various nitrogen-tethered 1,6-enynes. Following the previously described protocols,[101] a series of amide-1,6-enynes was synthesized in three steps. The procedure started with a nucleophilic substitution by propargylamine on *p*-toluenesulfonyl chloride, in the presence of triethylamine, which afforded the 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **91** in 98% yield.

The second step was an alkylation reaction carried out in the presence of 1-bromo-3-methylbut-2-ene and cesium carbonate, in acetone, at room temperature, during 3 hours.

[101] (a) T. Kataoka, M. Yoshimatsu, Y. Noda, T. Sato, H. Shimizu, M. Hori, *J. Chem. Soc. Perkin Trans. 1*, **1993**, *1*, 121; (b) A. Gansauer, M. Otte, L. Shi, *J. Am. Chem. Soc.*, **2011**, *133*, 416; (c) N. Dieltiens, K. Moonen, C. V. Stevens, *Chem. Eur. J.*, **2007**, *13*, 203.

With 4-methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfon-amide **67** in hand, we synthesized various 1,6-enynes according to the classical Sonogashira coupling reaction, which was conducted with the corresponding aryl iodides in the presence of $PdCl_2(PPh_3)_2$ and CuI in a mixture of triethylamine and toluene or THF as solvents. As shown in **Table II2-1**, enynes **77** and **93**-**100** were obtained with yields ranging from 49% to 92%, bearing both electron-donating or electron-withdrawing groups on the phenyl ring, or substituted by a thiophene group. Using (*E*)-1-bromo-3,7-dimethylocta-2,6-diene instead of 1-bromo-3-methylbut-2-ene, the enyne **101** was isolated in 73% yield.



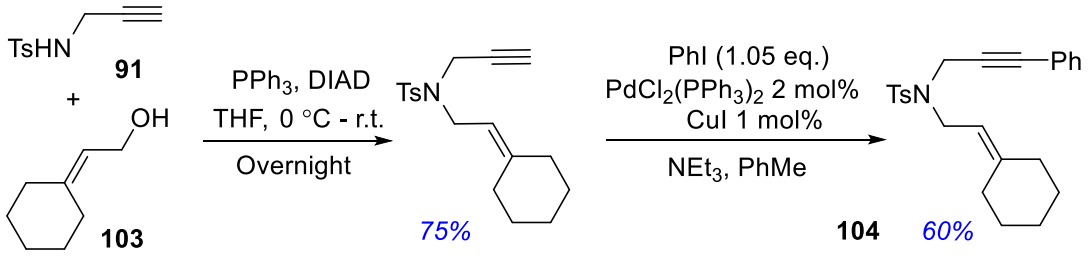
Product/yield(%)	Product/yield(%)	Product/yield(%)	Product/yield(%)
77 *71%*	**93** *63%*	**94** *60%*	**95** *68%*
96 *80%*	**97** *80%*	**98** *76%*	**99** *50%*
	100 *92%*	**101** *92%*[a]	

[a] The enyne **101** was prepared from amide **92**

Table II2-1 Synthesis of 1,6-enynes (part 1)

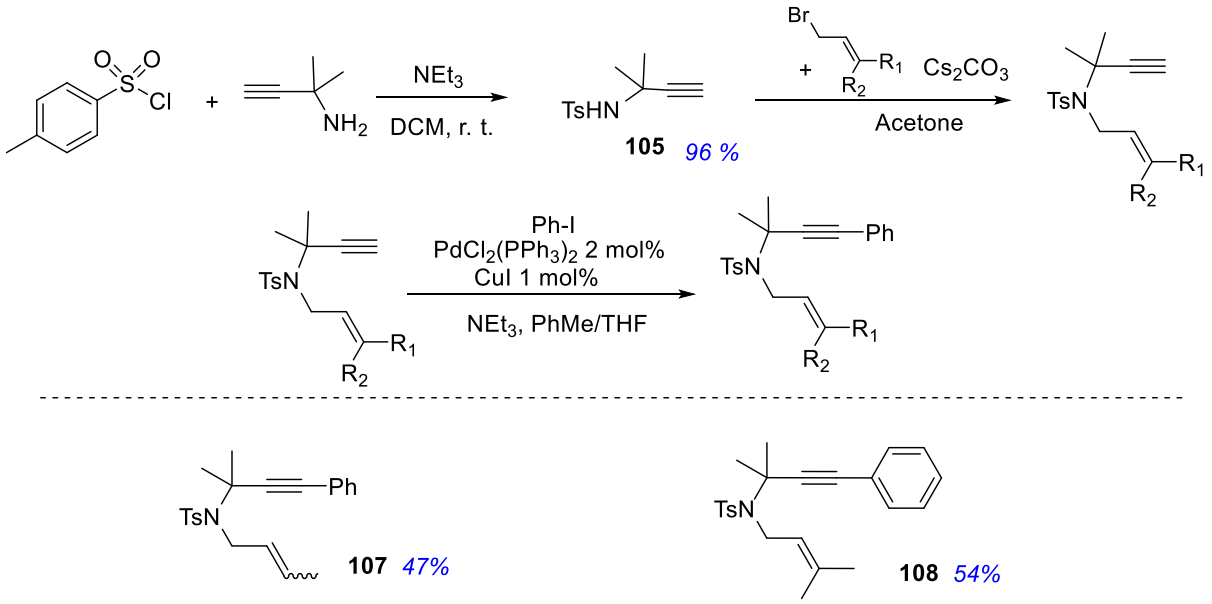
A 1,6-enyne bearing a cyclohexyl group was prepared *via* a Mitsunobu reaction starting from the alkyne **91** and 2-cyclohexylideneethan-1-ol **103**, in the presence of diisopropyl azodicarboxylate (DIAD) and triphenyl-phosphine (PPh_3), in THF, from 0 °C to room temperature. The Sonogashira coupling reaction allowed the synthesis of the 1,6-enyne **104**,

in 60% yield, in the presence of iodobenzene and Pd/Cu (**Scheme II2-3**).



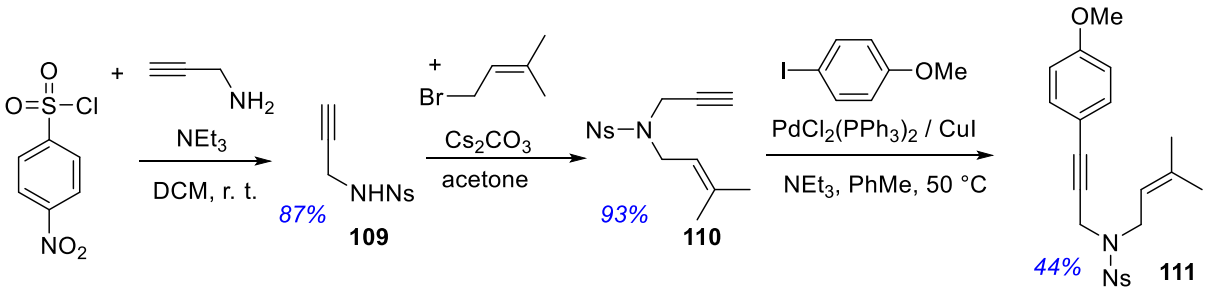
Scheme II2-3 Synthesis of 1,6-enynes (part 2)

We also envisaged to prepare *C*(5)-dimethyl-1,6-enynes as described in **Scheme II2-4**. The enynes **107** and **108** have been synthesized with moderate yields, by using the 2-methylbut-3-yn-2-amine instead of the propargylamine, following a similar three steps method.



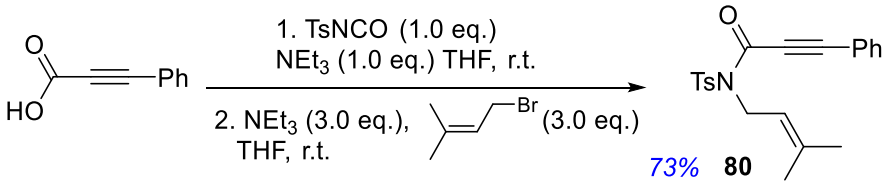
Scheme II2-4 Synthesis of *C*(5)-dimethyl-1,6-enynes

We also envisaged to introduce a different protective group than the tosyl group. We decided to introduce a nosyl group to keep the same activity and to presumably favor the deprotection reaction. Treatment of 4-nitrobenzene-1-sulfonyl with propargylamine allowed the formation of **109** in 87% yield. Then, the introduction of prenyl chain followed by a Sonogashira coupling reaction afforded the 1,6-enyne **111** (**Scheme II2-5**).



Scheme II2-5 Synthesis of NsN-1,6-enynes

According to the synthetic procedure described by Zhang,[102] *N*-tosylpropiolamide **80** was prepared based on a one-pot reaction. *p*-Toluenesulfonyl isocyanate and phenylpropiolic acid, were reacted in the presence of Et_3N, in dry THF, followed by the addition of the 1-bromo-3-methylbut-2-ene. *N*-(3-methylbut-2-en-1-yl)-3-phenyl-*N*-tosylpropiolamide **80** was thus synthesized with 73% yield (**Scheme II2-6**).



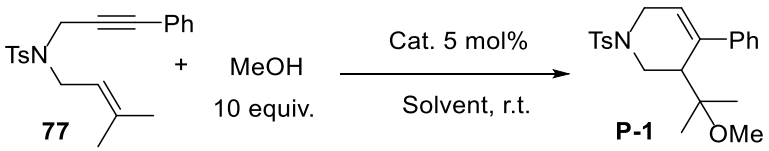
Scheme II2-6 Synthesis of *C*(5)-carbonyl 1,6-enyne

2.2.2 Gold-catalyzed domino cycloaddition reactions 1,6-enynes

2.2.2.1 Optimization of the reaction conditions

We initiated the study by establishing optimal conditions, using the model reaction of enyne **77** and MeOH (10 equiv.) as nucleophile at room temperature (**Table II2-2**). Different catalysts were screened and we found that [XPhosAu(MeCN)]SbF_6 was the most efficient and gave the desired ether in 94% yield (entry 4). PPh_3AuNTf_2 and $PPh_3AuCl/AgSbF_6$ afforded **P-1** with 47% and 65% yields respectively (entry 1 and 2). $KHAuCl_4$ exhibited very low catalytic activity in this reaction (entry 3). In an attempt to change the solvent to 1,4-dioxane, the yield was slightly reduced (entry 5). If we use MeOH as the solvent, several by-products **114** and **115** were observed as well as the desired product in 70% yield (entry 6). Therefore, we next evaluated the reactivity of the enynes, in the presence of [XPhosAu(MeCN)]SbF_6 and 10 equivalents of the nucleophilic specie, in DCM.

[102] D. Qian, J. Zhang, *Chem. Comm.*, **2011**, *47*, 11152.



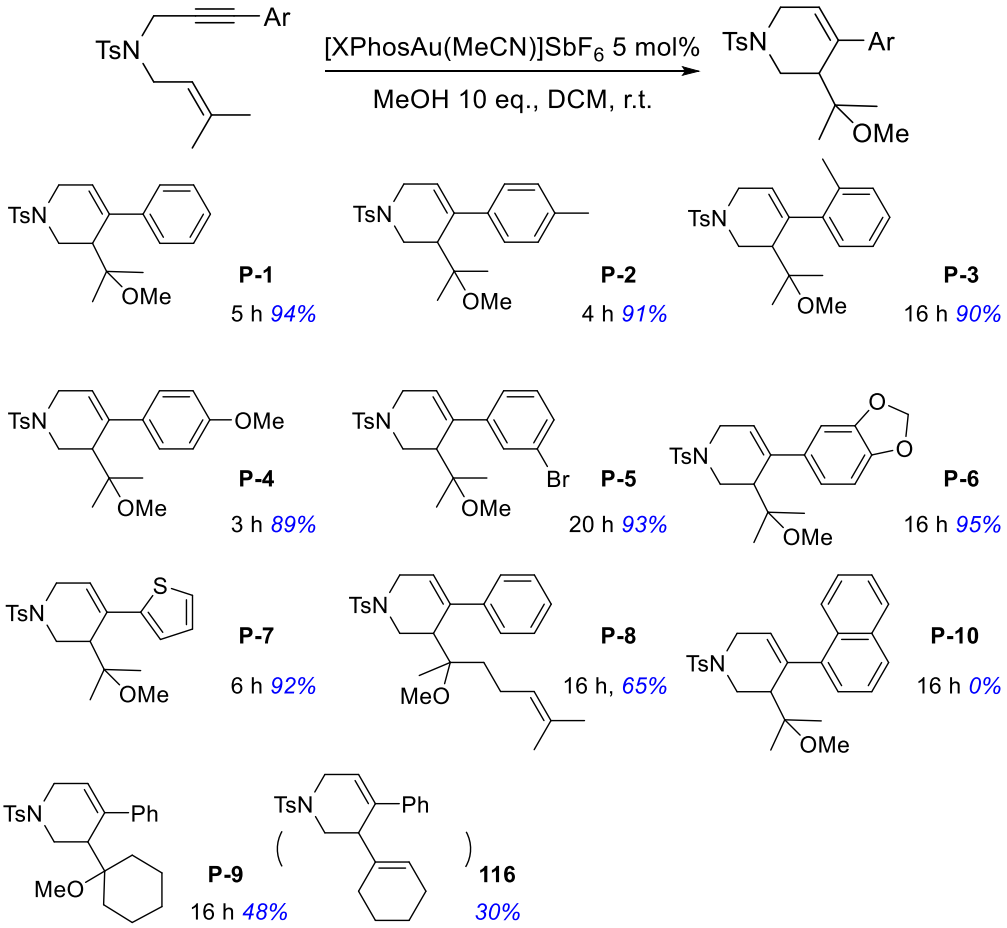
Entry	Cat.	Solvent	T (h)	Isolate Yield(%)
1	PPh_3AuNTf_2	DCM	4	47
2	$PPh_3AuCl/AgSbF_6$	DCM	4	65
3	$KHAuCl_4$	DCM	4	trace
4	$[XPhosAu(MeCN)]SbF_6$	DCM	4	94
5	$[XPhosAu(MeCN)]SbF_6$	Dioxane	7	90
6	$[XPhosAu(MeCN)]SbF_6$	MeOH	4	70

Table II2-2 Optimization of the experimental conditions

2.2.2.2 Scope and limitations

We began to examine the substrate scope of 1,6-enynes with nucleophilic alcohols.

Domino alkoxycyclization reactions

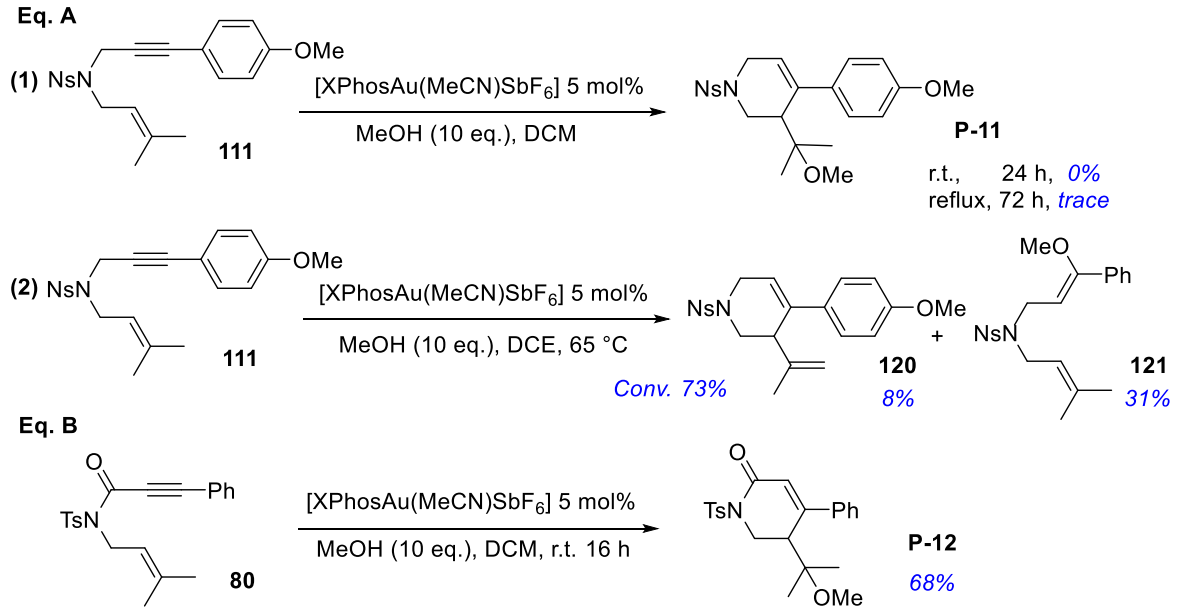


Scheme II2-7 Domino alkoxycyclization reactions with MeOH as the nucleophile (part 1)

First, the domino alkoxycyclization reaction was tested in the presence of a series of

nucleophiles. As can be seen in **Scheme II2-7**, when MeOH was used as a nucleophile, various substrates reacted smoothly with MeOH to form the desired products **P-1**-**P-7**, in excellent yields ranging from 89% to 95%. The enyne **101** was transformed and gave the corresponding adduct **P-8** in 65% yield. The reactivity of 1,6-enynes bearing a cyclohexyl group was examined : only the domino reaction product **P-9** was isolated in 48% yield, with the concomitant formation of a by-product, in 30% yield, identified as the corresponding 1,4-diene **116**. We didn't obtain the desired product **P-10** in the case of **99** even if the substrate was consumed completely.

In the case of the Nosyl-N tethered 1,6-enyne **111**, we tested the optimized conditions in the presence of MeOH, in DCM and DCE (**Scheme II2-8 Eq. A**). The enyne **111** presented a very low reactivity in DCM and we did not observe the formation of the desired product **P-11**. In the latter case, we observed the formation of **120** and **121** in 8% and 31% yields respectively.

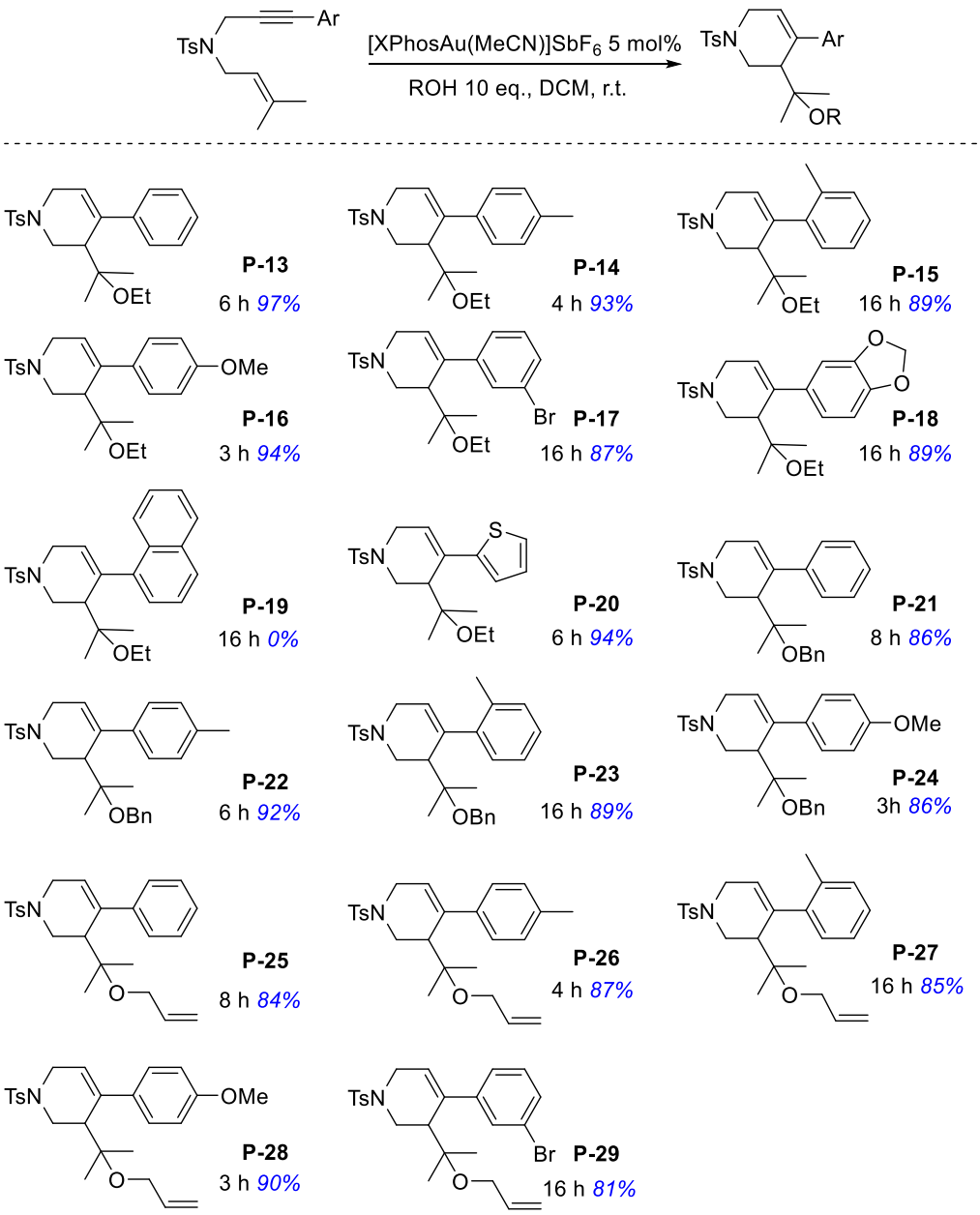


Scheme II2-8 Domino alkoxycyclization reactions with MeOH as the nucleophile (part 2)

In the presence of [XPhosAu(MeCN)]SbF_6 and MeOH, the *C*(5)-carbonyl compound **80** was converted to the ether product **P-12** in 68% yield (**Scheme II2-8 Eq. B**).

Investigations were then undertaken with ethanol, allyl alcohol and phenylmethanol to evaluate the domino 6-*endo* reaction reactivity of the enynes with different alcohols (**Scheme II2-9**). Ethanol, allyl alcohol, and phenylmethanol seemed compatible with the Au-catalyzed domino alkoxycyclization reaction with enynes (except in the case of **99**), leading to the

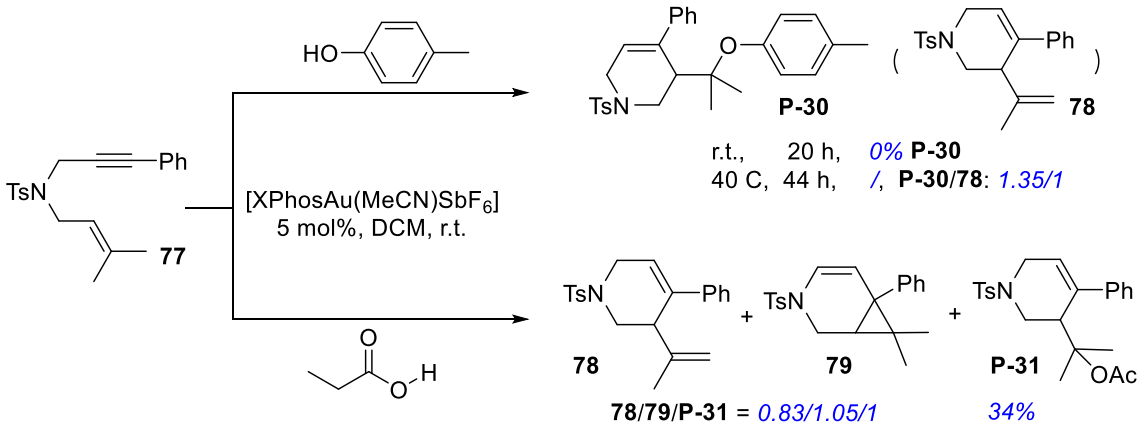
products with excellent yields, ranging from 81% to 97%.



Scheme II2-9 Domino alkoxycyclization reactions with various alcohols

The reactivity between *p*-cresol or acetic acid, and enyne **77** was also tested **(Scheme II2-9**). With regard to *p*-cresol as the nucleophile, the reaction did not occur at room temperature even after 20 hours of reaction. Further increasing of the reaction temperature to reflux of DCM resulted in a 1:1.35 ratio of the ether **P-30** and diene **78**, detected in the crude ^{1}H NMR. Despite several attempts, the desired ether could not be isolated. An explanation may be related to the nucleophilicity which is less pronounced in the case of *p*-cresol compared to alkyl alcohol. In the case of acetic acid, the cycloaddition compounds were isolated in 34%

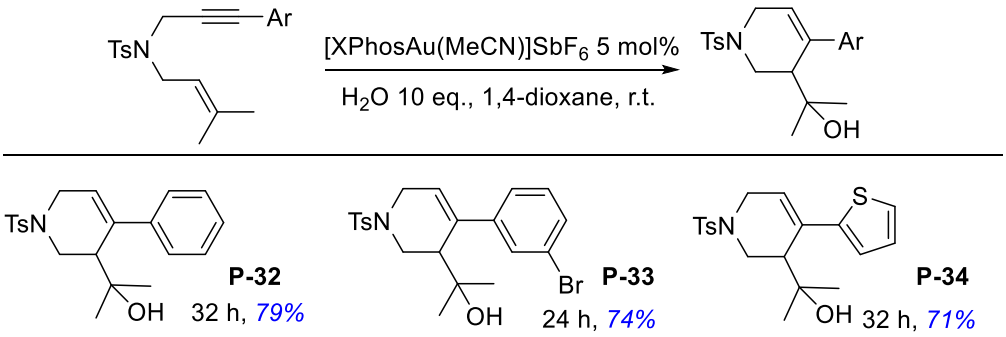
yield, with a 0.83/1.05/1 ratio between 1,4-diene **78**, bicyclo[4.1.0]hept-4-ene **79,** and ether **P-31**, detected in the crude ^{1}H NMR.



Scheme II2-10 Domino alkoxycyclization reactions with *p*-cresol and acetic acid

Domino hydroxycyclization reactions

Due to the immiscibility of H_2O and DCM, we conducted the domino hydroxycyclization reactions in 1,4-dioxane under room temperature. As described in **Scheme II2-11**, three examples of the desired products **P-32**-**P-34** were obtained in good yields (71%-79%) through hydroxycyclization reaction from 1,6-enynes (**77**, **96**, **100**).

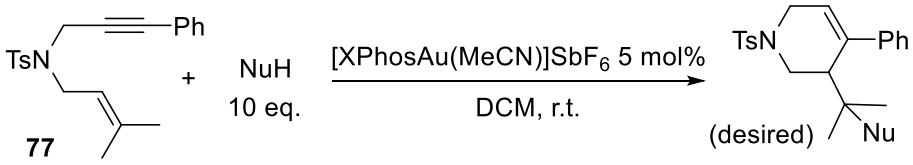


Scheme II2-11 Domino alkoxycyclization reactions in the presence of H_2O

Other nucleophilic species

Encouraged by the previous results obtained for domino hydroxy/alkoxycyclization reactions, we decided to test other types of nucleophiles as shown in **Table II2-3**.

Trimethyl(trifluoromethyl)silane, aniline, and *N*-methylethanamine seemed incompatible with the gold-catalyzed nucleophilic cycloaddition, as shown by the reactions conducted under reflux in entries 1-3/5-6 of **Table II2-3**. When 4-fluoroaniline was used as a nucleophile, the reaction did not proceed at room temperature, but afforded the product **115** in 45% yield, by warming under reflux, resulting from oxidation of **77** (entry 4). For 1-methyl-1*H*-indole, low conversion was observed at round temperature, but **P-35** was successfully obtained at higher temperature, in 64% yield after purification.



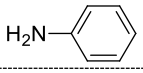
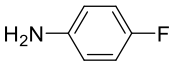
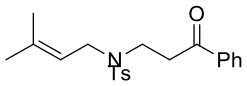
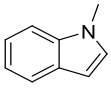
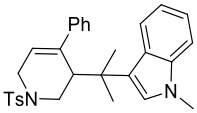
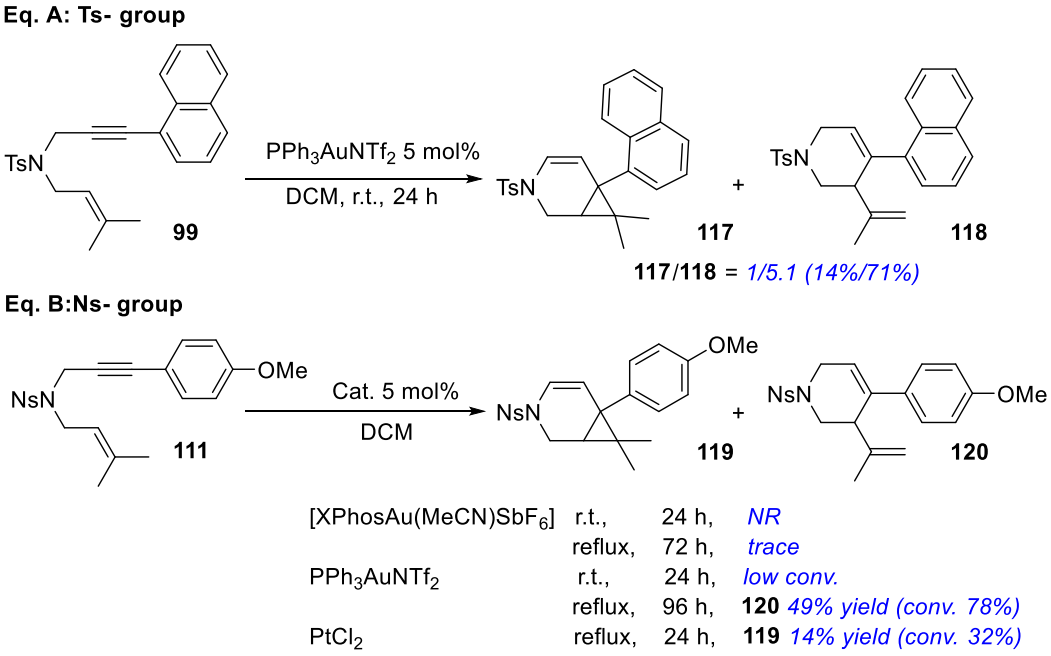
Entry	NuH	Reaction conditions	Results
1	$TMSCF_3$	r.t.	NR
2		r.t.	NR
3		r.t. 20 h	Low conv.
4		40 °C reflux, 44 h	 **115** *45% yield (conv. 48%)*
5		r.t. 20 h	NR
6		40 °C reflux, 44 h	NR
7		r.t. 20 h	*Conv. 15%*
8		40 °C reflux, 44 h	 **P-35** *64% yield*

Table II2-3 Domino cyclization reactions with various nucleophilic species

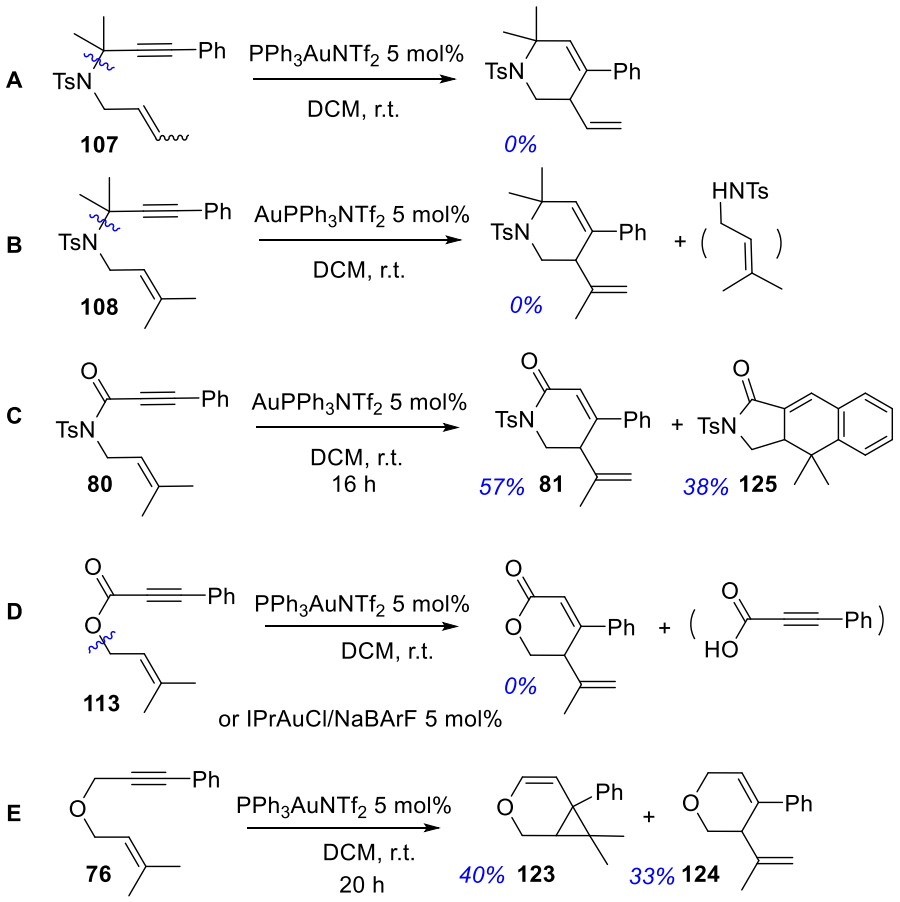
Comparison of the reactivity of 1,6-enynes without nucleophiles

It appeared to us interesting to study the cycloisomerization reaction in the absence of nucleophiles. As shown in **Scheme II2-12 Eq. A**, the use of PPh_3AuNTf_2 in DCM allowed the reaction of enyne **99** and led to a 1/5.1 ratio of bicyclo[4.1.0]hept-4-ene **117** and 1,4-diene **118**. The two products was separated and the diene resulting from the 6-*endo-dig* process was isolated in 71% yield. In the case of NsN-tethered enyne **111**, we investigated the reactivity of XPhosAu(MeCN)SbF_6, PPh_3AuNTf_2, and $PtCl_2$ as some atalysts (**Scheme II2-12 Eq. B**). At room temperature, the results were not satisfying. In the presence of 5 mol% of PPh_3AuNTf_2 as a catalyst, under reflux of DCM, during 96 h, the 1,4-diene **120** was isolated in 49% yield. When using $PtCl_2$ as a catalyst, only bicyclo[4.1.0]hept-4-ene **119** was observed.



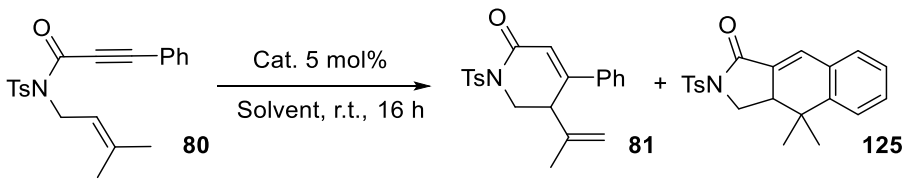
Scheme II2-12 Cycloisomerization reactions from enynes

On the other hand, for other types of 1,6-enynes bearing different functional groups that we prepared or obtained previously, we also tested the PPh_3AuNTf_2/DCM conditions. As shown in **Scheme II2-13 A** and **B**, the enynes **107** and **108**, bearing a dimethyl group on the *C*(5) position, did not react well and did not afford the corresponding 1,4-dienes. In the case of the enyne **113,** bearing carbonyl group on the *C*(5) position, a mixture of 1,4-diene **81** and 2,3,9,9*a*-tetrahydro-1*H*-cyclopenta[*b*]naphthalene **125** was obtained in 57% and 38% yields respectively (**Scheme II2-13 C**). The enyne **113**, which belongs to oxygen- tethered 1,6-enynes, afforded high conversion but invalid transformation, as we only isolated 3-phenylpropiolic acid (**Scheme II2-13 D**). Continually, we studied the reactivity of the enyne **76** with 5 mol% PPh_3AuNTf_2 in DCM, leading to 33% yield of the expected 6-*endo* product **124** and 40% yield of the bicyclo[4.1.0]hept-4-ene **123** (**Scheme II2-13 E**)[87].



Scheme II2-13 Cycloisomerization reactions tested on various 1,6-enynes **99**

In the case of cycloisomerization reactions from enyne **80**, we tried to obtain single or high-yield products through changing the reaction conditions of gold catalysts and solvents. The experiments were summarized in **Table II2-4**. In the presence of PPh_3AuNTf_2 as the catalyst (entries 1-3), compounds **81** and **125** were obtained in 77% and 18% yields in 1,4-dioxane, 60% and 20% yields in PhMe. PPh_3AuNTf_2 showed low catalytic activity in MeCN. Furthermore, [XPhosAu(MeCN)]SbF_6 gave the results summarized in entries 4-9 : no conversion in MeCN, DMSO, or DMF was observed, and the best results were observed in 1,4-dioxane (**Table II2-4** entries 4-9). Comparatively, the reaction with [IPrAu(MeCN)BF_4] and AuCl were also conducted in different solvents (**Table II2-4** entries 10-16), but the results were not good enough to hold our attention.



Entry	Cat. (5 mol%)	Solvent	Results (Yield[a])
1	PPh_3AuNTf_2	1,4-Dioxane	**81**/**125** *76%/18%*
2		PhMe	**81**/**125** *60%/20%*
3		MeCN	trace
4	[XPhosAu(MeCN)]SbF_6	DCM	**81**/**125** *11%/37%* cc
5		1,4-Dioxane	**81**/**125** *69%/27%*
6		PhMe	**81**/**125** *17%/29%* cc
7		MeCN	trace
8		DMSO	NR
9		DMF	NR
10	[IPrAu(MeCN)BF_4]	DCM	No **81**/**125,** cc
11		1,4-Dioxane	*Conv. 36%* **81** *10%* no **125**, cc
12		PhMe	**81**/**125** *56%/16%*
13		MeCN	*Conv. 20%* **81** *4%* no **125**
14	AuCl	DCM	**81** *31%* no **125** cc
15		1,4-Dioxane	**81** *16%* no **125** cc
16		MeCN	*Conv. 31%* **81** *11%* no **125**
17	$AgSbF_6$	DCM	No **81**, **125** *93%*

Table II2-4 Cyclization reactions from enyne **80** by gold and silver [[a] NMR yield; cc = complex composition]

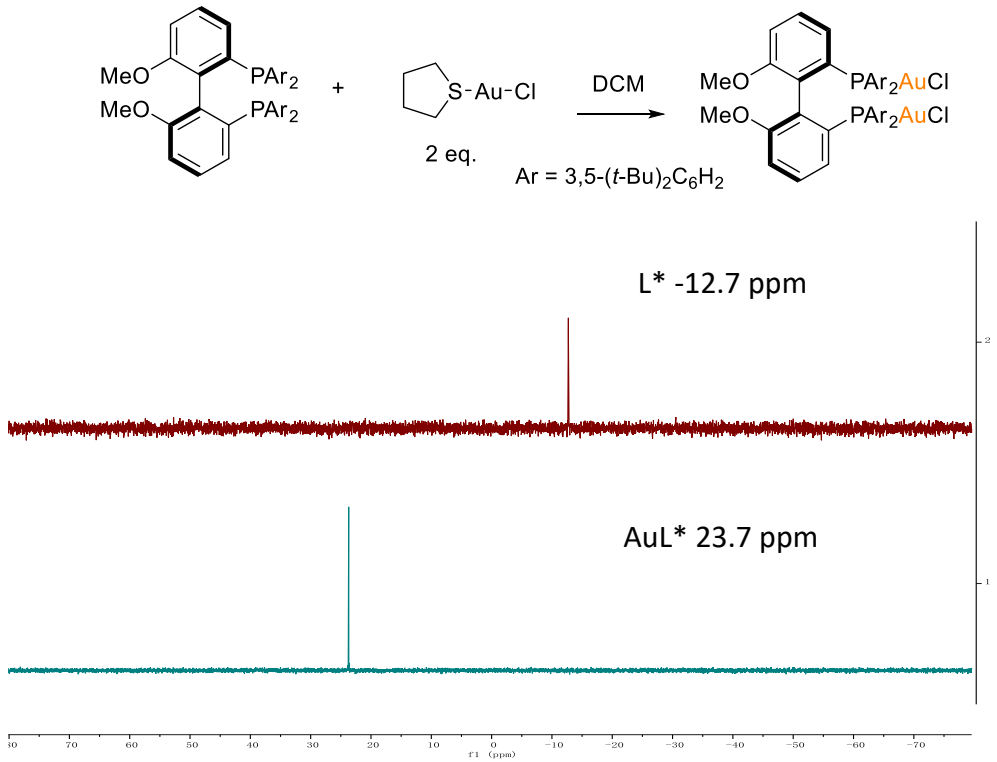
Based on the results of gold-catalyzed enyne **80**, we did not find a suitable way to afford selective and efficient 6-*endo* pathway compound. But when using $AgSbF_6$ as the catalyst, to our delight, [4+2] cyclization product was singly afforded in 93% yield (**Table II2-4** entry 17). Further studies were therefore conducted and will be presented in the paragraph dedicated to silver.

2.2.2 Enantioselective domino alkoxycyclization reactions

2.2.2.1 Asymmetric domino alkoxycyclization reaction on 1,6-enynes

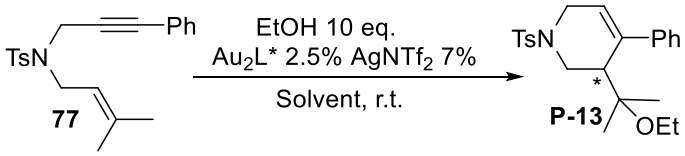
In Tang's PhD thesis, he reported an excellent 94% *ee* in the presence of (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$ **C-18** as the catalyst. Following these results, we wanted to carry out this chiral catalyst on the asymmetric enantioselective domino alkoxycyclization reaction.

The study started from preparing chiral gold catalyst (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$. Chiral diphosphine ligand (*R*)-DTB-MeOBIPHEP and (tht)AuCl [chloro(tetrahydro-thiophene)gold(I)] were employed in DCM at room temperature. Due to the strong coordination of gold-phosphine and the good volatility of tetrahydrothiophene, (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$ was obtained through full conversion by ^{31}P NMR detection in 20 min. The ^{31}P NMR δ of (*R*)-DTB-MeOBIPHEP is -12.7 ppm, and after full conversion, the chemical shift moved to 23.7 ppm (**Scheme II2-14**).



Scheme II2-14 Synthesis of chiral gold catalyst **C-18**

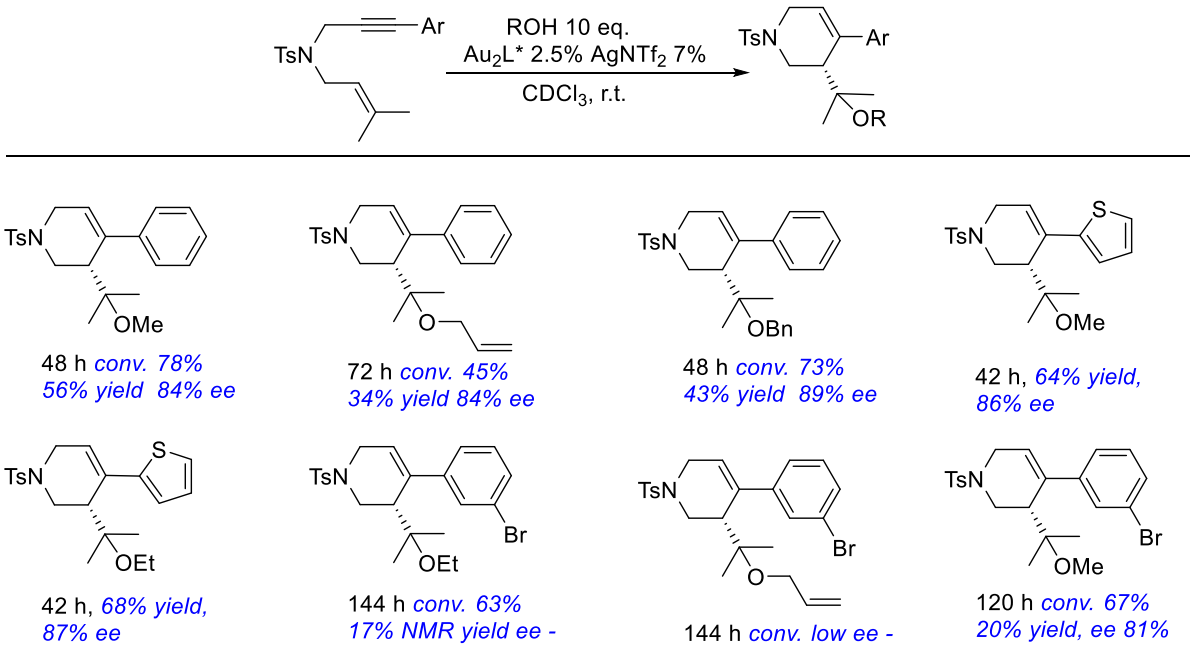
With the **C-18** in hand, we began to examine the solvent effect on the asymmetric induction, in the presence of DCM, $CHCl_3$, and $CDCl_3$. As shown in **Table II2-5**, the best enantiomeric excess value was observed in $CDCl_3$, but it needed longer reaction time and the yield was relatively low. Therefore, $CDCl_3$ as the solvent in this enantioselective domino alkoxycyclization reaction was employed.



Entry	Solvent	Time (h)	Yield (%)	*ee* (%)
1	DCM	48	94	77
2	$CHCl_3$	72	78	85
3	$CDCl_3$	72	76	90 (EtOH 5 eq., 91%)

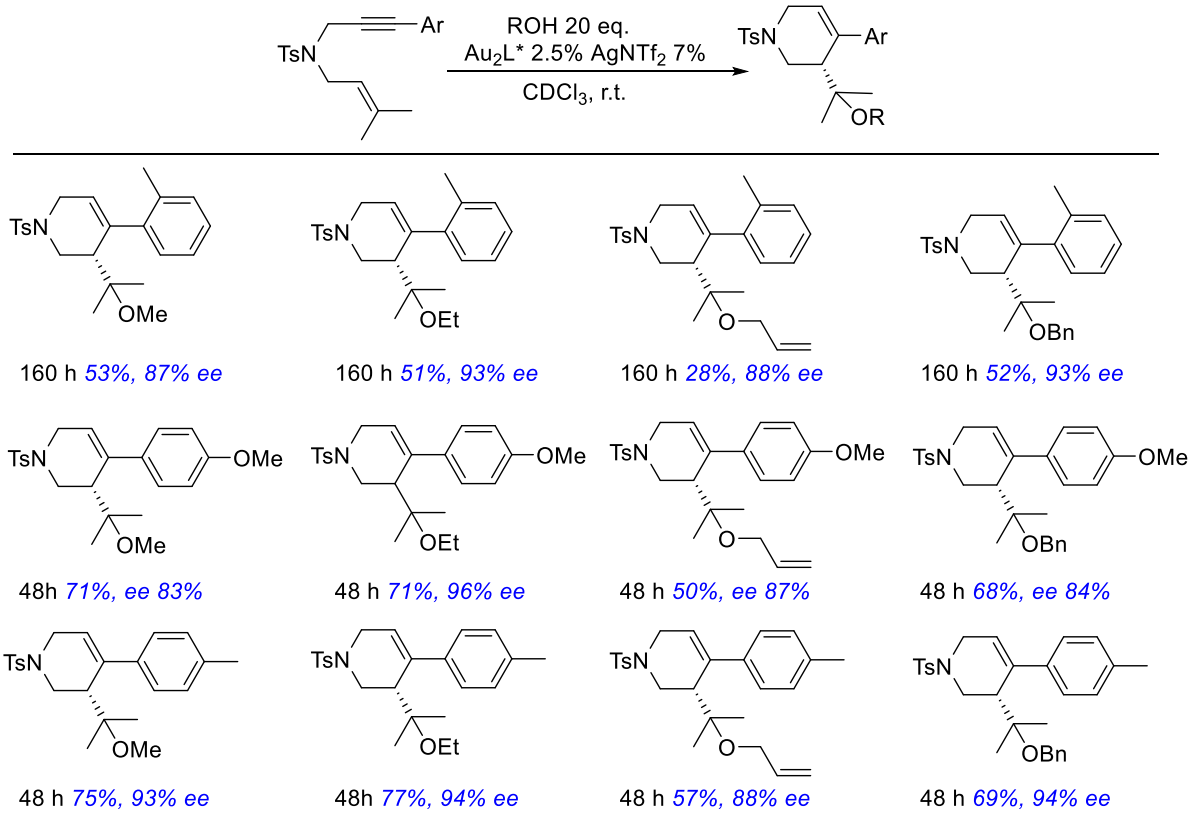
Table II2-5 Solvent effect of asymmetric induction

We examined the generality and the reactivity activity of this 6-*endo* domino alkoxycyclization reaction, with alcohol (10 equiv.), (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$ (2.5 mol%), and $AgNTf_2$ (7



Scheme II2-15 Scope for the 1,6-enynes of enantioselective domino alkoxycyclizations (part 1)

mol%) in $CDCl_3$. Enantiomeric excess values of 81% - 89% were observed, but for the enyne **96**, the corresponding desired compounds could not be observed in good conversions (**Scheme II2-15**). Next, we decided to increase the quantity of alcohol reagent to 20 equivalents.



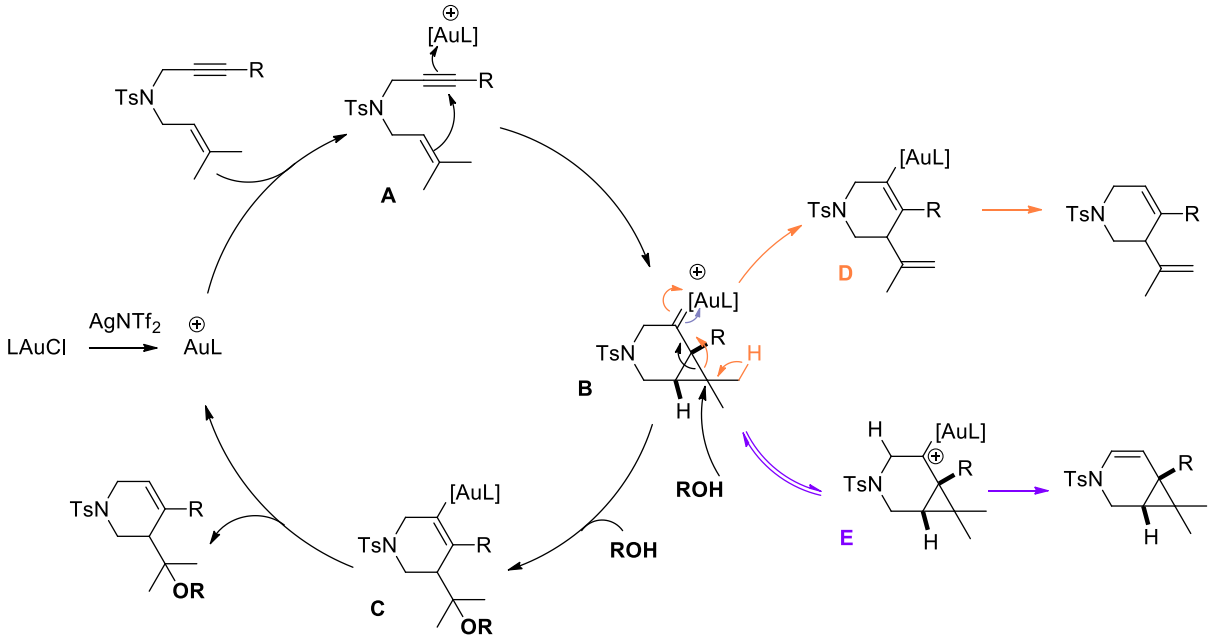
Scheme II2-16 Scope of the enantioselective domino alkoxycyclization of 1,6-enynes (part 2)

As can be seen in **Scheme II2-16**, various enynes including **93**, **94**, and **95**, reacted with a series of alcohol (methanol, ethanol, allyl alcohol, and phenylmethanol), and afforded the corresponding ether compounds in good and excellent enantiomeric excess of 84% - 96%.

2.2.2.3 Mechanism for the domino alkoxycyclization reactions of 1,6-enynes

A plausible mechanism was proposed in **Scheme II2-17**. The reaction started from the activation of the LAuCl catalyst to form the cationic complex. Then, in the presence of the gold catalyst which behaves as a carbophilic Lewis acid, the π-activation of the alkyne group by coordination of the gold to the triple bond, led to intermediate **A**. Subsequently, a 6-*endo-dig* attack of the alkene moiety would lead to bicyclo[4.1.0]heptane intermediate **B**. Next, through the nucleophilic addition of an alcohol species and a C-C bond break, ether intermediate **C** would be generated. Alkoxycyclization product would be obtained after a protodemetalation step.

In this reaction system, if the conversion into the ether adduct is not complete, some by-products may appear (like in the asymmetric transformation process). According to the rearrangement style, intermediates **D** and **E** would be advocated. By-products 1,4-diene or bicyclo[4.1.0]heptane would therefore be obtained. This proposed mechanism explains the results obtained and described previously.



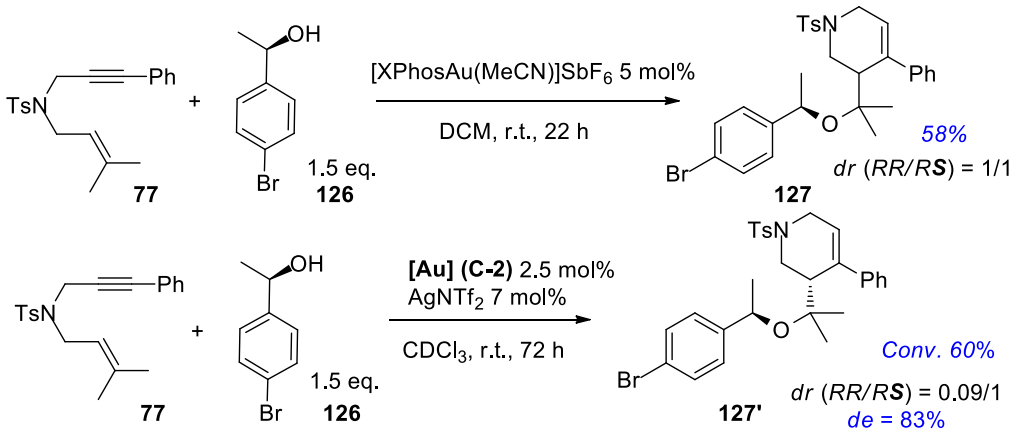
Scheme II2-17 Mechanism for the domino cycloaddition reaction

2.2.2.2 Assignement the absolute configuration of the major enantiomer

The absolute configuration of the major enantiomer was assigned *via* the experiment of 1,6-enyne **77** with a chiral alcohol reagent by the PhD student Yue Tang.[36] A screening of several chiral alcohols showed that (*R*)-1-(4-bromophenyl)ethan-1-ol (**126**), was the best choice of chiral.

Subsequently, enyne **77** reacted with (*R*)-1-(4-bromophenyl)ethan-1-ol in the presence of 5 mol% [XPhosAu(MeCN)]SbF_6 in DCM, and gave two diastereomers in total 58% yield and a 1:1 ratio (detected by ^{1}H NMR and X-ray diffraction). Next, the domino alkoxylation/cyclization reaction was carried out in the presence of our chiral gold catalyst (**C-2**), leading to the desired product with good enantioselectivities. The 83% diastereomeric excess was observed *via* ^{1}H NMR, and the preferentially *S* configuration determined after purification (**Scheme II2-18**).

Based on the result, we could thus conclude that the preferential (*S*)-ligand generated the *S* isomer by our asymmetric catalysts in this 6-*endo* domino alkoxycyclization reaction.



Scheme II2-18 Experiments to assign the absolute configuration

2.3 Conclusion

In summary, we have developed an effective route to ethers *via* a 6-*endo* domino nucleophilic addition/cyclization reaction catalyzed by gold, and the nucleophilic species include methanol, ethanol, allyl alcohol, phenylmethanol, *p*-cresol, and H_2O. Various 1,6-enynes reacted very well with nucleophiles and the yield was up to 97%. When using acetic acid as a nucleophile, 34% yield of ester product was obtained, and when 1-methyl-1*H*-indole was used as a nucleophile, enyne reacted smoothly under higher reaction temperature. On the other hand, the

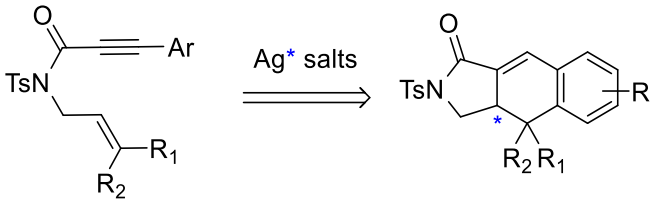
asymmetric synthesis *via* enantioselective domino alkoxycyclization reaction was studied in the presence of the (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$ catalyst in $CDCl_3$ with enantiomeric excess up to 96%. The absolute configuration of the major enantiomer has been assigned. This work will be part of a publication.[103]

3. Silver-catalyzed intramolecular [4+2] cycloaddition of *N*-tosylpropiolamide-1,6-enynes

3.1 Objective

Following the disappointing results in gold-catalyzed 6-*endo-dig* reactions of 5-carbonyl-1,6-enyne, we envisaged another strategy to favor the formation of *6-endo* products. The inspiring results we obtained in **Table II2-4** entry 17 and previous work on silver-catalyzed cyclization reactions,[38,39,104] prompted us to focus on intramolecular racemic and asymmetric [4+2] cycloaddition in the presence of achiral and chiral silver salts. Furthermore, only two examples of intramolecular [4+2] cycloisomerization on propiolamides in the presence of $AgNTf_2$ at 80 °C for 12 h - 48 h had been described in the literature.[65]

Therefore, we envisioned that silver catalysts could successfully promote intramolecular [4+2] cycloaddition reactions from amide-1,6-enynes derivatives.

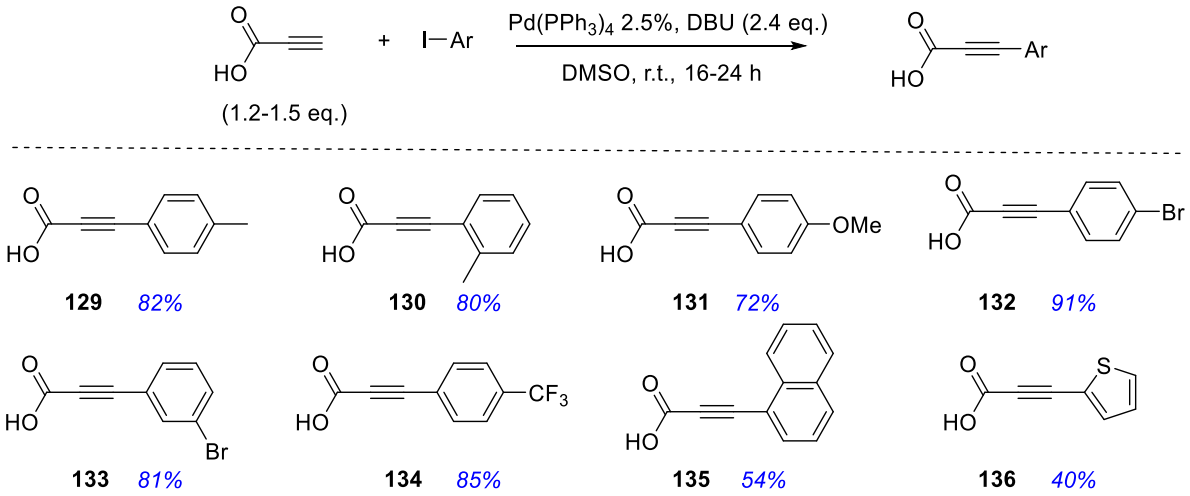


3.2 Results and discussions

3.2.1 Synthesis of *N*-tosylpropiolamide derivatives

The strategy to prepare *N*-tosylpropiolamides was realized starting from the aryl alkynyl carboxylic acid, which was obtained by Sonogashira cross-coupling from propiolic acid and aryl iodides. The next step was the condensation of commercially available 4-methylbenzenesulfonyl isocyanate, and bromo-alkene.

[103] X. Chen, Y. Tang, S. Poulain-Martini, V. Michelet, publication in preparation.
[104] A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli, V. Michelet, *Eur. J. Org. Chem.*, **2017**, 2214.

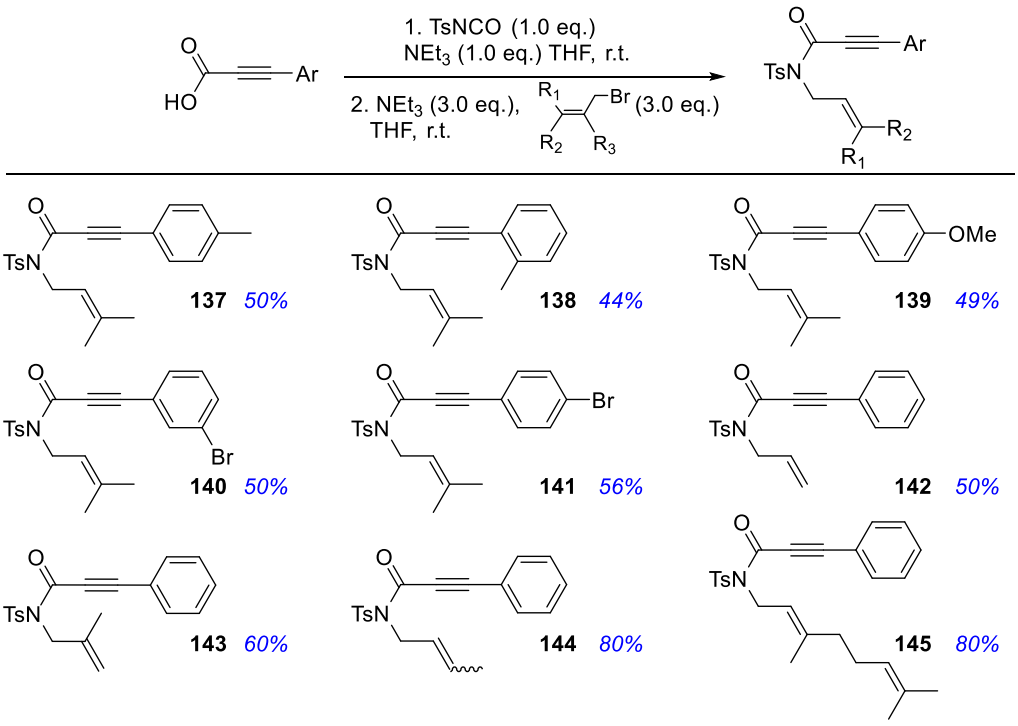


Scheme II3-1 Synthesis of aryl alkynyl carboxylic acids

Different aryl alkynyl carboxylic acids were prepared *via* copper-free Sonogashira coupling from propiolic acid and aryl halides (**Scheme II3-1**).[105] This method implied the use of 1,8-diazabicyclo[5.4.0]undec-7-ene/DBU (2.4 equivalents) and $Pd(PPh_3)_4$ (2.5 mol%) in DMSO. As shown in **Scheme II3-1**, the aryl alkynyl carboxylic acid **129** - **134** bearing electron-donating groups such as *ortho*-methyl, *para*-methyl, and *para*-methoxy, electron-withdrawing groups such as *para*-bromo, *meta*-bromo, and *para*-CF_3, on the phenyl ring, were efficiently obtained in 72% to 91% yields. The naphthyl and thiophenyl derivatives, **135** and **136** were also isolated in moderate yields.

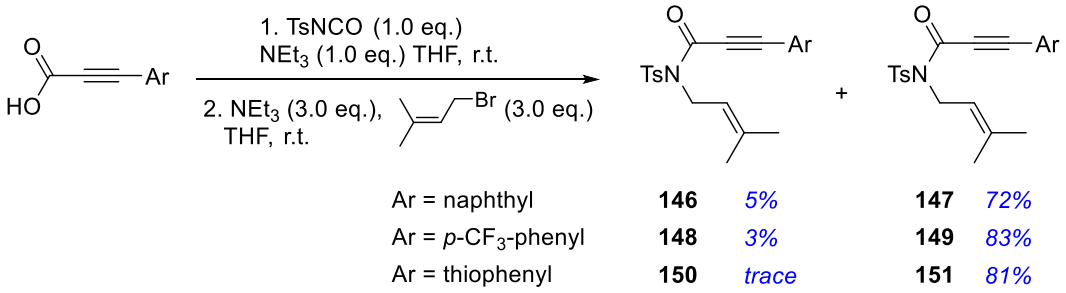
With aryl alkynyl carboxylic acids in hand, *N*-tosylpropiolamide derivatives were then obtained *via* a one-pot process from carboxylic acid, *p*-toluenesulfonyl isocyanate, and allyl bromide,[102] in the presence of Et_3N. As described in **Scheme II3-2**, several *N*-tosylpropiolamides derivative **137** - **145** were isolated in moderate to good yields. The reaction conditions were compatible with several allyl bromides such as 1-bromo-3-methylbut-2-ene, 1-bromobut-2-ene, 3-bromoprop-1-ene, 3-bromo-2-methylprop-1-ene, (*E*)-1-bromo-3,7-dimethylocta-2,6-diene, and most of the aryl propionic acids.

[105] Q. Feng, K. Yang, Q. Song, *Chem. Commun.*, **2015**, *51*, 15394.



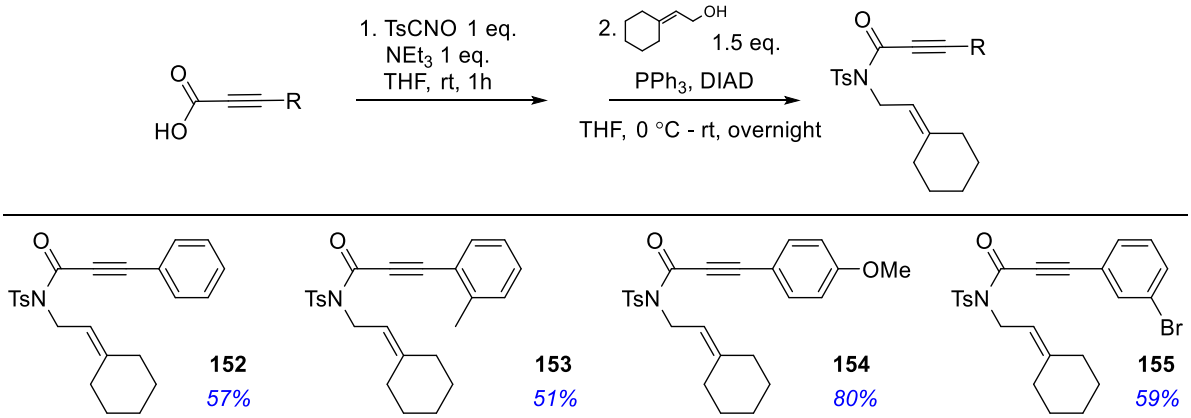
Scheme II3-2 Synthesis of *N*-tosylpropiolamides (part 1)

This method was not suitable for all substrates. In the case of *p*-CF_3-phenyl, naphthyl, and thiophenyl- substituted derivatives, the desired enynes were obtained in very low yields or as trace. The reactions led to the ester analogues **147**, **149**, **151** in 72% to 83% yields (**Scheme II3-3**).



Scheme II3-3 Synthesis of *N*-tosylpropiolamides (part 2)

We also prepared four *N*-tosylpropiolamides bearing the cyclohexyl group (**Scheme II3-4**), by the Mitsunobu reaction from 2-cyclohexylideneethan-1-ol instead of allyl bromide and Et_3N at the second one-pot step. The desired *N*-tosylpropiolamides **152** - **155** was obtained in 51% to 80% yields.



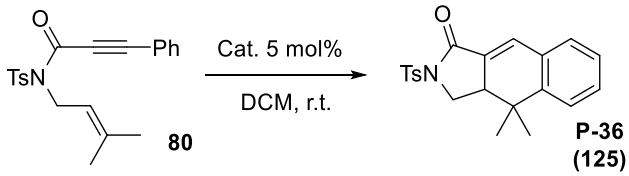
Scheme II3-4 Synthesis of *N*-tosylpropiolamides (part 3)

Having in hand several enynes, we then turned our attention to the [4+2] cycloaddition reactions.

3.2.2 Silver-catalyzed intramolecular [4+2] cycloaddition reactions

3.2.2.1 Optimization of the reaction conditions

We have chosen **80** as a model substrate and have conducted a metal screening, results are summarized in **Table II3-1**.



Entry	Cat.	Time(h)	Yield	Entry	Cat.	Time(h)	Yield
1	$PtCl_2$	16	0	12	$AgSbF_6$	6	93
2	$AgSbF_6$	6	93	13	$AgNTf_2$	10	97
3	$InCl_3$	16	0	14	AgF	16	trace
4	$Fe(OTf)_3$	16	0	15	$AgBF_4$	16	61
5	CuI	16	0	16	$AgOOCCF_3$	16	34
6	$Zn(OTf)_2$	24	0	17	AgSCN	16	trace
7	$Bi(OTf)_3$	24	0	18	$Ag[OOC(CH_2)_3C_6H_{11}]$	16	trace
8	$Sc(OTf)_3$	24	0	19	AgOTf	16	65
9	$Yb(CF_3SO_3)_3$	24	0	20	$AgNO_3$	16	0
10	$Y(CF_3SO_3)_3$	24	0				
11	$Sn(NTf_2)_4$	24	0				

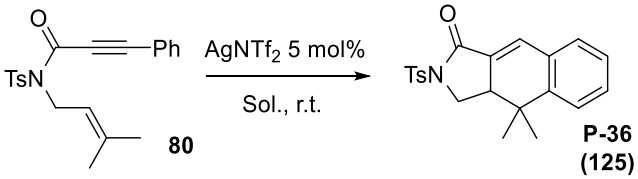
Table II3-1 Optimization of the reaction conditions (part 1)

At first, the effects of some metal salt catalysts on this [4+2] cycloaddition reaction were investigated. The reaction of **80** in DCM at room temperature was performed in the presence of different metal salts to find the most effective catalyst. The use of 5 mol% of $PtCl_2$, $AgSbF_6$, $InCl_3$, $Fe(OTf)_3$, CuI, $Zn(OTf)_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(CF_3SO_3)_3$, $Y(CF_3SO_3)_3$, and $Sn(NTf_2)_4$ was

tested, only $AgSbF_6$ salt afforded, the target product 4,4-dimethyl-2-tosyl-2,3,3*a*,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one **P-36** (**125**) in 93% yield. All the other metal catalysts exhibited no catalytic activity for this reaction (**Table II3-1**, Entries 1-11).

We then concentrated our study on various silver salts. For the Ag salts (**Table II3-1**, entries 12-20), we used various types of silver catalysts to examine the feasibility of the reaction. The use of $AgNTf_2$ afforded target product **P-36** in 97% yield, and $AgBF_4$, $AgOOCCF_3$, and AgOTf gave 61%, 34%, and 65% yields of product **P-36** were given respectively. When AgF, AgSCN, and $Ag[OOC(CH_2)_3C_6H_{11}]$ were engaged in the process (entries 14, 17, and 18), only traces of product was obtained, and no product was detected in the presence of $AgNO_3$ (entry 20).

We chose $AgNTf_2$ as the best catalyst and optimized the solvent (**Table II3-2**). Conducting the reaction in DCM and $MeNO_2$ afforded the desired product **P-36** in good yield. PhMe and 1,4-dioxane gave 6% and 11% yields determined by NMR. The use of MeCN, THF, DMF, and DMSO gave no desired product (entries 23, 25, 27, and 28).



Entry	Sol.	Time (h)	Yield[a]
1	DCM	9h	94
2	$MeNO_2$	9h	89
3	MeCN	72h	0
4	PhMe	72h	6
5	THF	72h	0
6	1,4-Dioxane	72h	11
7	DMF	72h	0
8	DMSO	72h	0

[a] NMR yield (determined by ^1H NMR analysis using 3,4,5-trichloropyridine as the internal standard).

Table II3-2 Optimization of the reaction conditions (part 2)

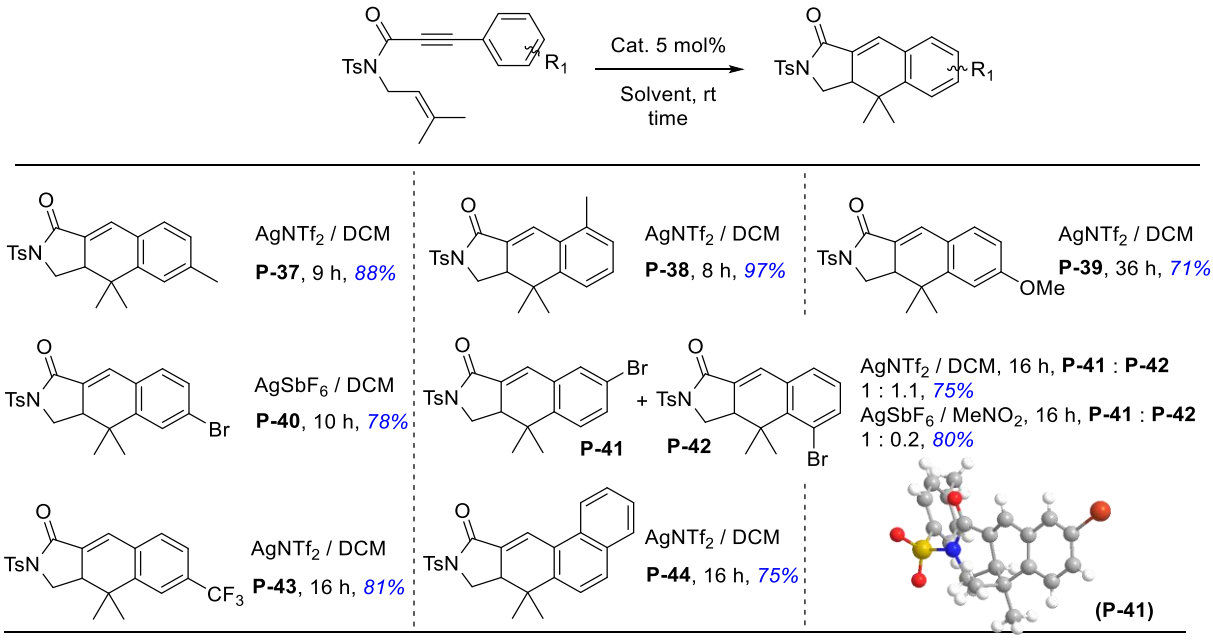
Therefore, the best reaction conditions employing $AgNTf_2$ or $AgSbF_6$ as the catalyst in DCM or $MeNO_2$ as the solvent, were chosen for further study.

3.2.2.2 Scope and limitations of silver-catalyzed [4+2] cycloadditions

With the optimized results in hand, the generality and limitations of the [4+2] process were then examined and are presented in **Scheme II3-5** and **Scheme II3-6**. The *N*-tosylpropiolamide

derivatives were engaged in the presence of 5 mol% of catalyst, $AgNTf_2$ or $AgSbF_6$ in DCM or $MeNO_2$.

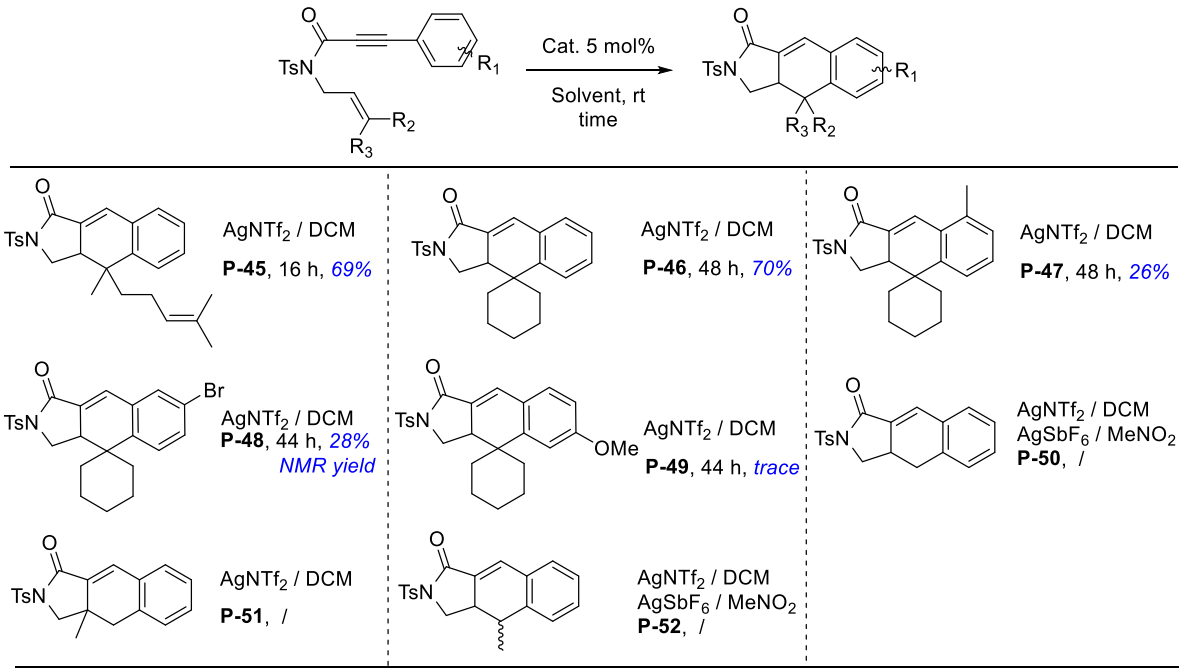
In **Scheme II3-5**, the cyclization of the substrate bearing *para*-methyl-substituted on the phenyl ring **137** afforded the desired tricycle product **P-37** 88% yield. The *ortho*-methyl-substituted compound **P-38** was obtained in excellent 97% yield. Then, *para*-methoxy **P-39** and *meta*-bromo substituted **P-40** were also obtained in good yields. Under $AgNTf_2$ catalysis, in DCM, the cyclization of 3-(3-bromophenyl)-*N*-(3-methylbut-2-en-1-yl)-*N*-tosylpropiol-amide **140**, led to a mixture of regio isomers **P-41** and **P-42**, resulting from an arylation from 2 position of the aromatic ring, in a 1:1.14 ratio (determined by ^1H NMR), in 75% global yield and. Furthermore, the structure of the tricycle **P-41** was determined by X-Ray diffraction. Under $AgSbF_6$ catalysis, in $MeNO_2$, the yield of the two isomers was slightly increased to 80%, and a ratio of **P-41**: **P-42** 1:0.2 has been determined. Meanwhile, the substrates bearing *para*-CF_3-substituted on the phenyl ring **148** and hindered naphthyl-substituted **146** could give the corresponding products **P-43** and **P-44** in 81% and 75% yields.



Scheme II3-5 Scope and limitations of [4+2] cycloaddition reactions (part 1)

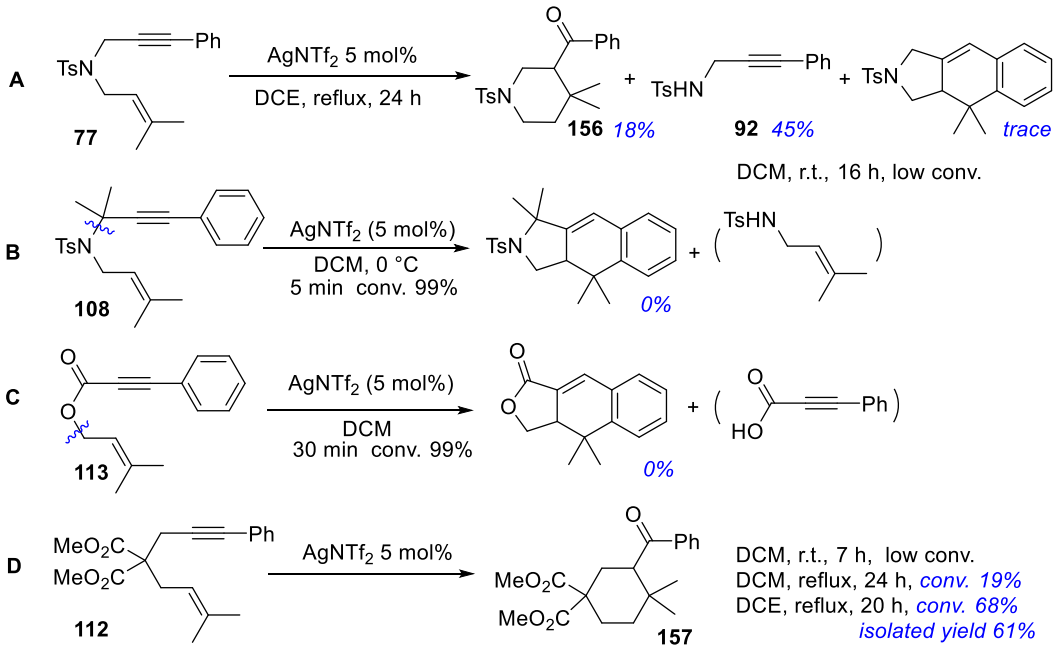
In **Scheme II3-6**, we studied the influence of R_2 and R_3. For the substrate **145**, the chemoselectivity was found to be suitable as the adduct **P-45**, with a 69% yield. Pleasingly, enyne **152** where the dimethyl group on the double bond was replaced by a hindered cyclohexyl group, reacted smoothly with silver salt, affording the corresponding desired

product **P-46** in 70% yield. But for the analogous compounds **153**-**155**, we observed **P-47** and **P-48** in low yields, and only traces of **P-49** was obtained. Steric hindrance and low flexibility may explain the results, compared to **152**. Then, some limitations were observed for the *N*-tosylpropiolamide derivatives **142**-**144**, no adducts **P-50** - **P-52** were detected.



Scheme II3-6 Scope and limitations of [4+2] cycloaddition reactions (part 2)

After these encouraging results, we then attempted to react other class of enynes in order to synthesize tricyclic products through silver-catalyzed [4+2] cycloaddition reaction. As shown in **SchemeII3-7**, tricycles could not be achieved in the presence of $AgNTf_2$ in DCM or DCE. In the case of nitrogen- tethered enyne **77**, the cyclization process led to compound **156** in 18% yield and **92** as major product, resulting from de-allylation or depropargylation reaction (Eq. **A**). In the case of **108**, no cyclization process was observed (Eq. **B**). The oxygen tethered ester reacted similarly and gave the de-allylation product (Eq. **C**). In the case of the carbon- tethered enyne **112**, it reacted at high temperature in DCE and gave the cyclic ketone derivative **157** in 61% yield (Eq. **D**).

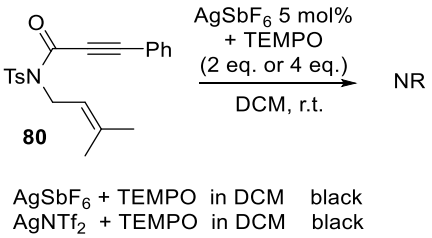


Scheme II3-7 Scope and limitations of [4+2] cycloaddition reactions (part 3)

3.2.2.3 Mechanism for the intramolecular [4+2] cycloaddition reactions

We next turn our attention to the mechanism of [4+2] cycloaddition.

Firstly, we wondered if the mechanism could imply radicals. Therefore, we carried out the reaction in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), which is a widely used as radical scavenger (**Scheme II3-8**). A black solution was observed and we also found that silver salts mixed with TEMPO also leading to the same black mixture. Thus, the radical or non-radical pathway could not be concluded.

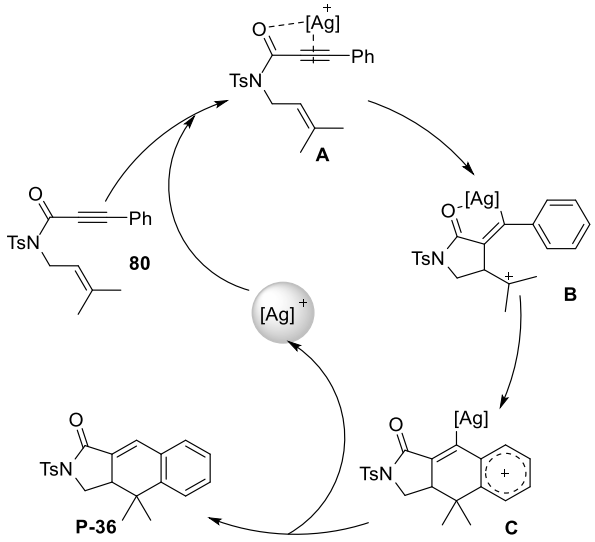


Scheme II3-8 Reaction mechanism *via* TEMPO

Based on literature,[9c, 106] a plausible mechanism for the [4+2] cycloaddition reaction was proposed in **Scheme II3-9**. It is well known that Ag(I) complex, as a common Lewis acid catalyst, could activate the alkyne group of the substrate **80** *via* π-coordination, and it also could

[106] (a) R. Sreedevi, S. Saranya, G. Anilkumar, *Adv. Synth. Catal.,* **2019**, *361*, 4625; (b) J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. H. Reisberg, M. Chen, P. Mykhailiuk, G. Beutner, M. R. Collins, A. Davies, M. Del Bel, G. M. Gallego, J. E. Spangler, J. Starr, S. Yang, D. G. Blackmond, P. S. Baran, *Nature*, **2019**, *573*, 398.

coordinate to the carbonyl group leading to **A**. Subsequently, intermediate **B** would form by a 5-*exo-dig* attack of the carbonyl moiety. Then through Friedel-Crafts arylation, intermediate **C** would give, which would evolve towards the [4+2] cycloaddition product **P-36**.

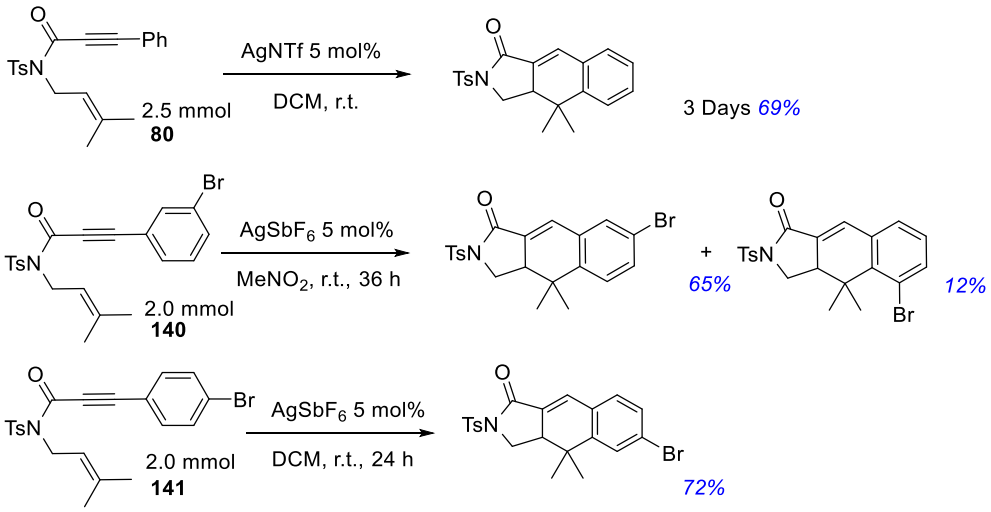


Scheme II3-9 Reaction proposed mechanism

According to the results of establishing optimal experimental conditions, the silver salts may have different catalytic activities due to the different *p*Ka (as we have discussed about Belmont's work in Chapter I 2.1.1).[29] And for the limitations in the reaction scope, regarding 1-methyl-1,6-enyne systems and *N*-allyl-3-phenyl-*N*-tosylpropiolamide (**144** and **142**), the reactions did not cleanly proceed, which was explained by the lack of stability of the reaction intermediate **C**. For substrates **153** – **155**. And steric hindrance and low flexibility caused the results obtained **P-47** - **P-49**.

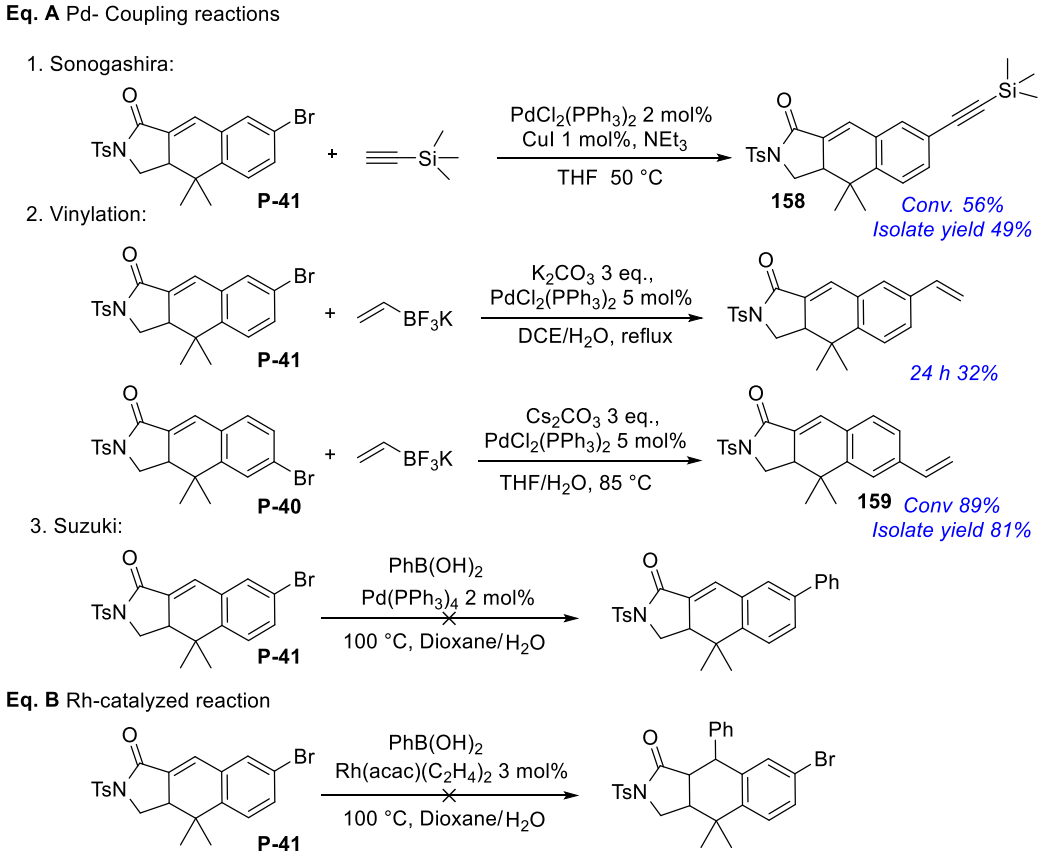
3.2.2.4 Scale-up experiments and post-functionalization reactions

The usefulness of the intramolecular [4+2] cycloaddition reaction process was also established by performing scale-up experiments and post-functionalization reactions (**Scheme II3-10**). The gram-scale transformations of substrates such as *N*-(3-methylbut-2-en-1-yl)-3-phenyl-*N*-tosylpropiol-amide **80**, 3-(3-bromophenyl)-*N*-(3-methylbut-2-en-1-yl)-*N*-tosylpro-piolamide **140**, and 4-bromophenyl **141** led to products in 69%, 65%, and 72% isolated yield.



Scheme II3-10 Gram-scale experiments

Then for the post-functionalization reactions (**Scheme II3-11**), tricyclic product **P-41** and ethynyltrimethylsilane were reacted under Sonogashira condition, gave the corresponding compound **158** in 49% isolated yield (**Eq. A** 1).

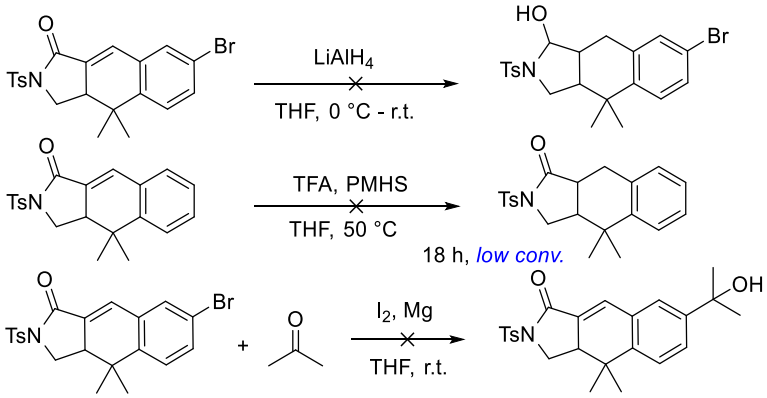


Scheme II3-11 Post-functionalization reactions (part 1)

We tried to prepare the vinylated derivative according to a Suzuki-Hiyawa cross-coupling in

the presence of potassium vinyltrifluoroborate.[107] A low yield was obtaining which prompted us to change the base and solvent. Under the conditions $PdCl_2(PPh_3)_2$ (5 mol%) and 3 equivalents cesium carbonate in THF-water 9/1,[108] the bromo tricycle **P-40** was reacted well with potassium vinyltrifluoroborate, affording 81% isolated yield of the corresponding styrene product **159** (**Eq. A** 2). Noteworthy that we tried to introduce an aromatic *via* the reaction of a boronic acid but no reaction was observed (**Eq. A** 3). The Rh-catalyzed 1,4-addition of boronic acid was attempted too without success (**Eq. B**).

We also tried other reactions such as reductions ($LiAlH_4$ and polymethylhydrosiloxane) or halogen-metal exchange and addition to ketone without success (**Scheme II3-12**).



Scheme II3-12 Post-functionalization reactions (part 2)

In parallel to this study, we envisaged to optimize an enantioselective version of this transformation.

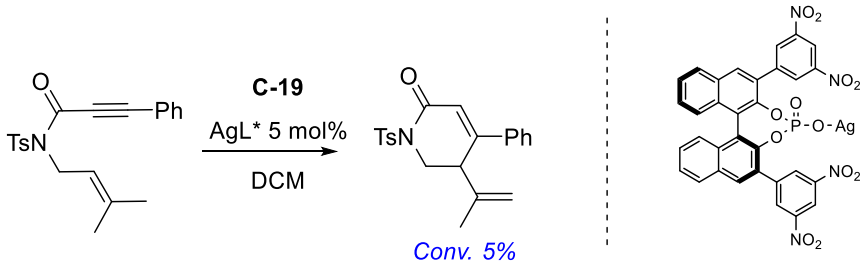
3.2.3 Enantioselective intramolecular [4+2] cycloaddition reactions

3.2.3.1 The study of chiral sliver catalyst and chiral ligands with silver salts

Following our interest in asymmetric catalysis,[71,78,89,111] we turned to the use of chiral silver complexes in the intramolecular [4+2] cycloaddition reaction of our attention in *N*-tosylpropiolamide derivatives. For the asymmetric silver-catalyzed reaction, we envisaged two ways to get the chiral environment. At first, we tested the activity of a chiral silver salt

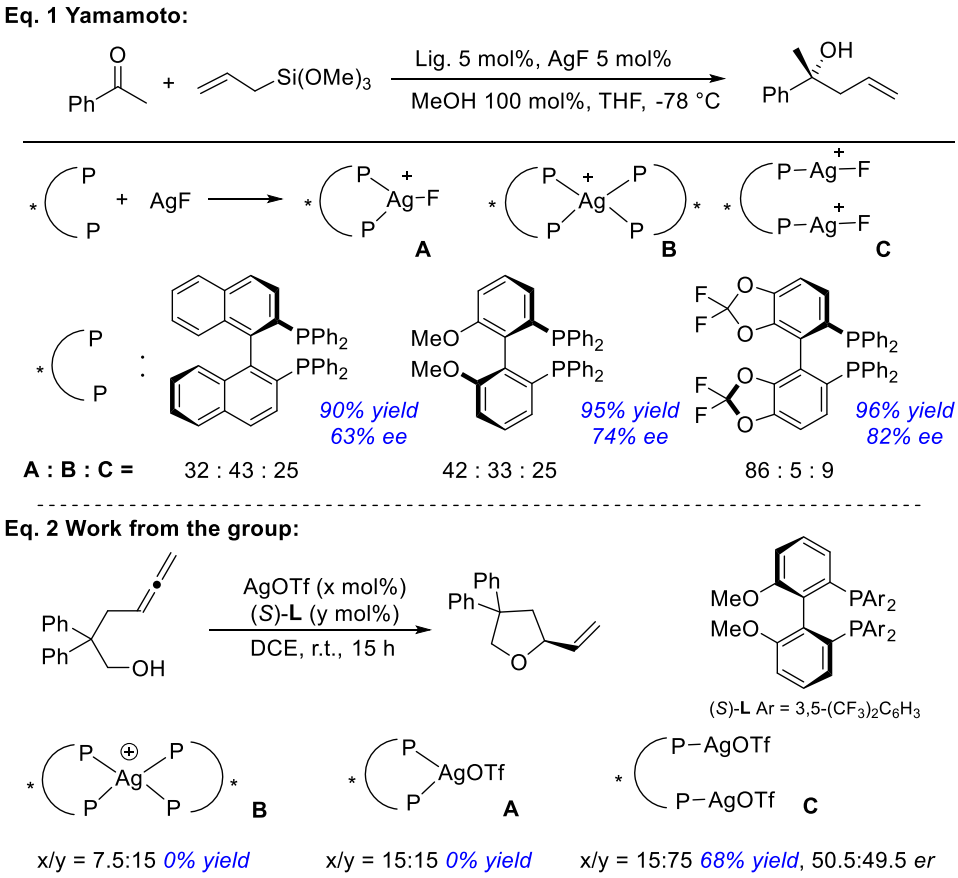
[107] (a) S. Darses, G. Michaud, J.-P. Genet, *Eur. J. Org. Chem.*, **1999**, 1875; (b) G. A. Molander, M. R. Rivero, *Org. Lett*., **2002**, *4*, 107; (c) G. A. Molander, A. R. Brown, *J. Org. Chem*., **2006**, *71*, 9681;
[108] S. E. Denmark, C. R. Butler, *Chem. Commun.*, 2009, 20.

analogous to TriP-Ag salt,[109] but the catalytic activity of the **C-19** catalyst was particularly low and the reaction conversion was only 5% (**Scheme II3-13**).



Scheme II3-13 Asymmetric reaction *via* chiral silver catalyst **C-19**

The second way to study the asymmetric silver catalysis was based on the addition of chiral ligands to silver salts.



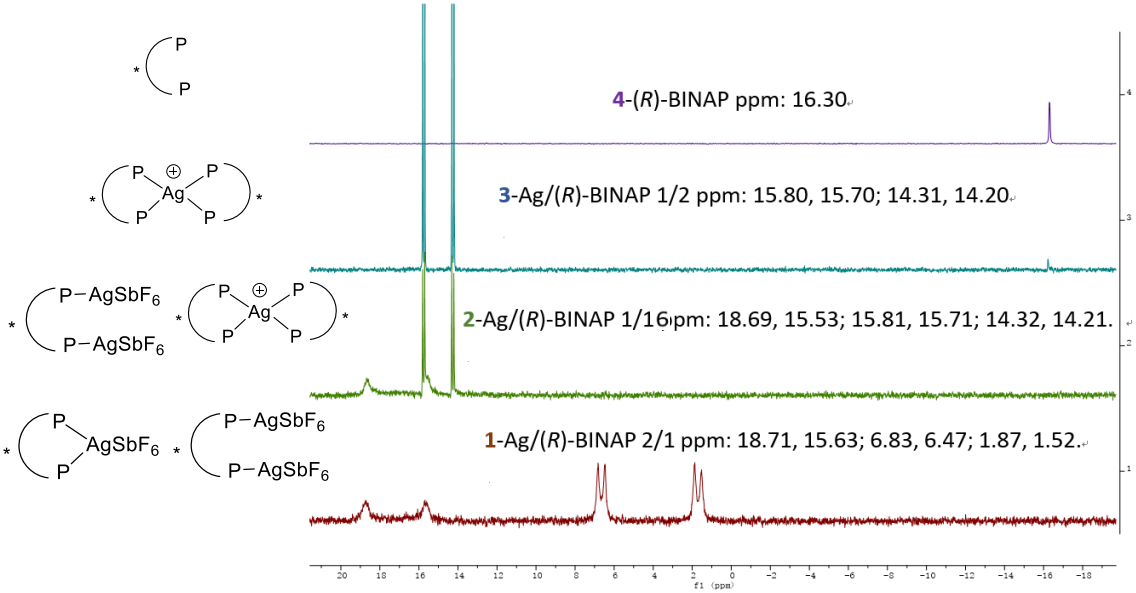
Scheme II3-14 Asymmetric reaction *via* silver and diphosphine

We therefore investigated the asymmetric intramolecular [4+2] cycloaddition reaction in the presence of Ag salts and chiral atropisomeric ligands. The catalytic enantioselective

[109] Generous gift from F. D. Toste's group and the ref. from: R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner, F. D. Toste, *Angew. Chem.,* **2010**, *122*, 608.

cycloaddition was carried based on seminal work from Wadamoto and Yamamoto[110] and our work[111] in the field. Yamamoto documented that more than three complexes between silver and diphosphine exist (**Scheme II3-14 Eq. 1**). The study of the ^{31}P NMR of 1:1 mixtures of AgF and ligands revealed that different reactivity and selectivity were shown by different complexes and silver complex **A** achieved a high stereoselective reaction. Interestingly, the use of (*S*)-L and AgOTf led to the formation of vinyltetrahydrofuran, but only a 2:1 Ag/L ratio was required to achieve the reaction (**Scheme II3-14 Eq. 2**).

In order to shed light on the possible active silver complex, we did some experiments in the presence $AgSbF_6$ and (*R*)-BINAP. We undertook a characterization of Ag-BINAP complexes by ^{31}P NMR, with different ratios of silver and ligand.

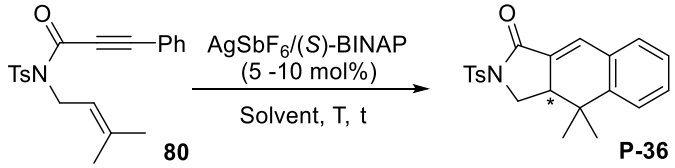


Scheme II3-15 Silver ligand complexes in DCM determined by ^{31}P NMR at room temperature

The ^{31}P NMR spectrums of (*R*)-BINAP, $AgSbF_6$/(*R*)-BINAP 1/2, $AgSbF_6$/(*R*)-BINAP 1/1, $AgSbF_6$/(*R*)-BINAP 2/1 in dry DCM, were compared in **Scheme II3-15**. When $AgSbF_6$/(*R*)-BINAP 1/2, there were two pairs of peaks, 15.80, 15.70 and 14.31, 14.20 ppm (complex **B**). When $AgSbF_6$/(*R*)-BINAP 1/1, except that, appeared one new pair, 18.69, 15.63 ppm (complexes **B** and **C**). And for the $AgSbF_6$/(*R*)-BINAP 2/1 in DCM, there were three pairs of peaks, 18.71, 15.63 and 6.83, 6.47 with 1.87, 1.52 ppm (complexes **A** and **C**).

[110] M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.*, **2005**, *127*, 14556-14557.
[111] F. L. B. d'Herouville, A. Millet, M. Scalone, V. Michelet, *Synthesis*, **2016**, *48*, 3309.

Initially, we studied the activity of different Ag salts and BINAP ratio (1:1, 2:1, 1:2). As summarized in **Table II3-3**, the desired product was not observed for a ratio of $AgNTf_2$: (*S*)-BINAP of 1:2, whereas a low yield was obtained for a 1:1 ratio. An excellent yield was obtained for a 2:1 ratio, but the enantiomeric excess dropped from 22% to 7%. Interestingly, the use of AgOTf instead of $AgNTf_2$ gave lower yields which show low catalytic activity, and $AgSbF_6$ gave high yields and similar *ee* either for a 2:1 and a 1:1 Ag: ligand ratio. Then, we attempted to perform the reaction in another solvent, such as DCM, DCE, or we added MeOH,[111] without success in increasing enantiomeric excess (entries 9-11).



Entry	Cat.	Cat/Lig.	Solvent	T., t (h)	Conv. (%)	*ee* [a](%)
1	$AgNTf_2$	2/1	DCM	rt, 115	90	+7
2	$AgNTf_2$	1/1	DCM	rt, 115	12	+22
3	$AgNTf_2$	1/2	DCM	rt, 115	0	-
4	AgOTf	2/1	DCM	rt, 140	5	-
5	AgOTf	1/1	DCM	rt, 140	3	-
6	AgOTf	1/2	DCM	rt, 115	0	-
7	$AgSbF_6$	1/1	DCM	rt, 67	73	+12
8	$AgSbF_6$	2/1	DCM	rt, 48	>99	+14
9[b]	$AgNTf_2$	2/1	DCM	reflux, 75	>99	+8
10	$AgNTf_2$	2/1	DCE	60 °C, 92	90	+13
11	$AgNTf_2$	2/1	DCM	rt, 92	39	+6
12	$AgSbF_6$	2/1	Dioxane	rt, 48	nr	-
13	$AgSbF_6$	2/1	THF	rt, 48	nr	-
14	$AgSbF_6$	2/1	MeCN	rt, 48	nr	-
15	$AgSbF_6$	2/1	$MeNO_2$	rt, 48	>99	-17
16	$AgSbF_6$	1/1	$MeNO_2$	rt, 48	75	+8

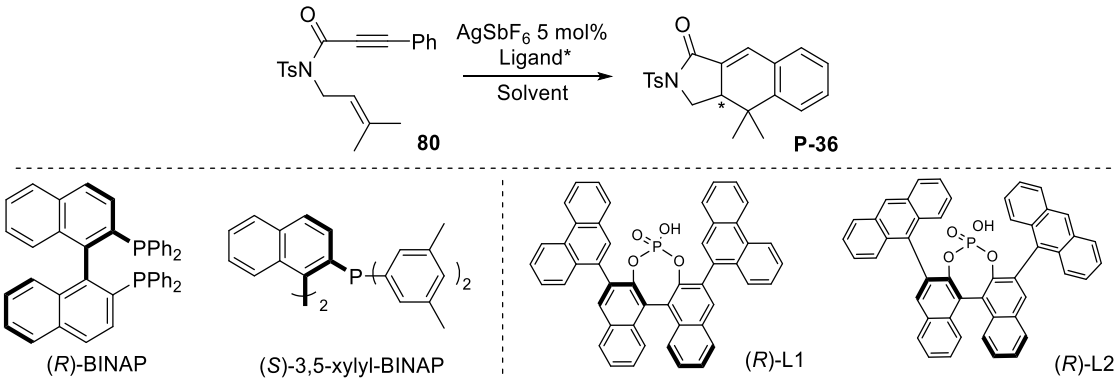
[a] (+) or (-) represents the different preferential configuration, (+) being the first peak on HPLC analysis spectra. [b] Added 2 equiv. MeOH.

Table II3-3 Enantioselective reactions of using Ag salts and (*S*)-BINAP

The effect of solvent was further investigated through $AgSbF_6$ with (*S*)-BINAP as shown in **Table II3-3** entries 12-16. In 1,4-dioxane, THF, and MeCN, the reactions did not proceed at all. In DCM and $MeNO_2$, we could get the desired product, but surprisingly, when the ratio of $AgSbF_6$ with (*S*)-BINAP was 2/1, the major opposite enantiomer were obtained. Moreover, when the ratio of $AgSbF_6$ with (*S*)-BINAP was reduced from 2/1 to 1/1, and different dominant configurations appeared. Such behavior is rare, but we can mention the work form Michon and Agbossou who observed such behavior in the case of cycloisomerization of allenamine

derivatives.[112]

In parallel, different chiral phosphine systems have been selected and tested with silver salts, to select the best one for this asymmetric reaction.



Entry	Lig.	Cat/Lig.	Solvent	T., t (h)	Conv. (%)	*ee* [a](%)
1	(*R*)-BINAP	1/1	DCM	67	70	-21
2	(*R*)-BINAP	2/1	DCM	67	77	-20
3	(*R*)-BINAP	1/1	$MeNO_2$	67	82	-16
4	(*R*)-BINAP	2/1	$MeNO_2$	67	91	+14
5	(*S*)-BINAP+(*R*)-L1 10%	2/1	DCM	7 Days rt then reflux 2days	80	+6
6	(*R*)-L1	1/2	DCM	60 h rt then reflux 24 h	>99	-6
7	(*S*)-BINAP+(*R*)-L2 10%	2/1	DCM	7 Days rt then reflux 2days	26	+7
8	(*S*)-3,5-xylyl-BINAP	1/1	DCM	16	19	+11
9	(*S*)-3,5-xylyl-BINAP	2/1	DCM	16	97(78 [b])	+2
10	(*S*)-3,5-xylyl-BINAP	1/1	$MeNO_2$	16	30	+14
11	(*S*)-3,5-xylyl-BINAP	2/1	$MeNO_2$	16	>99 (76 [b])	+4

[a] (+) or (-) represents the different preferential configuration, (+) being the first peak on HPLC analysis spectra.
[b] isolated yield.

Table II3-4 Enantioselective [4+2] Ag-catalyzed reactions (part 1)

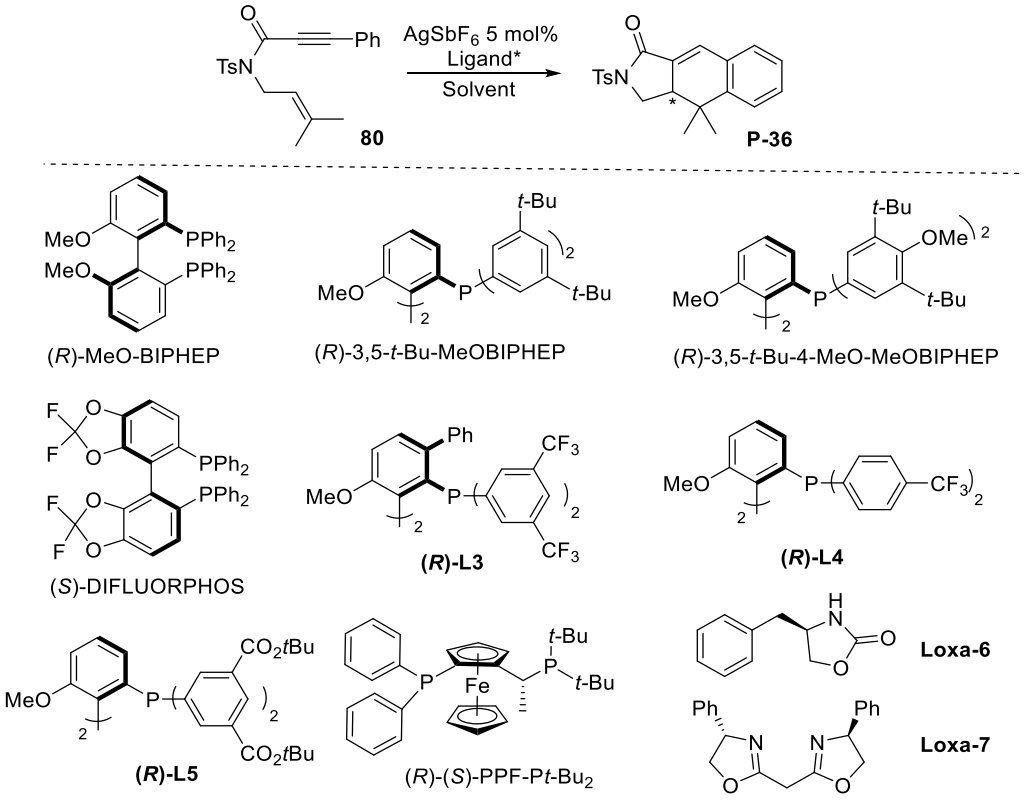
The ratio of $AgSbF_6$ with (*R*)-BINAP 2/1 and 1/1 in DCM and $MeNO_2$, results were given in **Table II3-4** entries 1-4 to have a clear comparison. Whereas opposite major enantiomers obtained in DCM and $MeNO_2$ when the ratio of $AgSbF_6$ with (*S*)-BINAP is 2/1, the use of (*S*)-3,5-xylyl-BINAP (entries 8-11) did not lead to the same phenomenon. The results in the presence of (R)-BINAP were better than the ones with (*S*)-3,5-xylyl-BINAP (entries 8-11). Finally, in order to find better experimental results, we also tested the activity of additional chiral phosphonic

[112] M. A. Abadie, X. Trivelli, F. Medina, F. Capet, P. Roussel, F. Agbossou-Niedercorn, C. Michon, *ChemCatChem*., **2014**, *6*, 2235.

acid (entries 5-7), but the results were not better.

Table II3-5 presents the activity of other ligands, analogous to BINAP. The use of (*R*)-MeO-BIPHEP, (*R*)-3,5-*t*Bu-MeOBIPHEP, (*R*)-3,5-*t*Bu-4-MeO-MeOBIPHEP led to the desired product in 10%-18% *ee* (entries 1-6). These BIPHEP ligand cases, no solvent effect (DCM or $MeNO_2$) was observed. In 2011, our group has demonstrated that atropisomeric bisphosphane was prepared under a highly efficient Pd-catalyzed reaction conditions.[113] Therefore, we tested these in-house ligands (*R*)-L3, (*R*)-L4, and (*R*)-L5 (**Table II3-5** entries 7-12). To our delight, these ligands showed higher reactivity for the formation of the expected compound comparatively to other ligands, and decent enantioselectivities were obtained (up to 36% *ee*), demonstrating that **(*R*)-L5** was the best one.

The (*S*)-DFLUORPHOS ligand[114] gave better results, as the Ag/L 1/1 and 2/1 led to 16% to 35% *ee* respectively (entries 13-16). The ferrocene ligand was also tested, affording in DCM 17% *ee* and in $MeNO_2$ 0% *ee* (entries 17-18). As previously, no solvent effect in DCM and $MeNO_2$ was observed.



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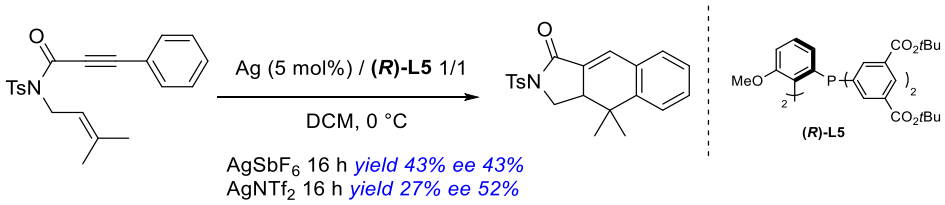
Entry	Lig.	Cat/Lig.	Solvent	T., t (h)	Conv. (%)	*ee* [a](%)
1	(*R*)-MeO-BIPHEP	2/1	DCM	60	>99	+14
2	(*R*)-MeO-BIPHEP	2/1	$MeNO_2$	60	>99	+14
3	(*R*)-3,5-*t*Bu-MeOBIPHEP	2/1	DCM	64 h rt then reflux 24 h	96	+10
4	(*R*)- 3,5-*t*Bu-MeOBIPHEP	2/1	$MeNO_2$	64 h rt then reflux 24 h	>99	+18
5	(*R*)-3,5-*t*Bu-4-MeO-MeOBIPHEP	2/1	DCM	88	95	+14
6	(*R*)-3,5-*t*Bu-4-MeO-MeOBIPHEP	2/1	$MeNO_2$	60	>99	+14
7	(*R*)-L3	1/1	DCM	24	53	-9
8	(*R*)-L3	2/1	DCM	24	78	-10
9	(*R*)-L4	1/1	DCM	24	71	-32
10	(*R*)-L4	2/1	DCM	24	90	-22
11	(*R*)-L5	1/1	DCM	24	99	-36
12	(*R*)-L5	2/1	DCM	24	99	-21
13	(*S*)-DIFLUORPHOS	1/1	DCM	16	>99	+33
14	(*S*)-DIFLUORPHOS	2/1	DCM	16	>99	+24
15	(*S*)-DIFLUORPHOS	1/1	$MeNO_2$	16	>99	+35
16	(*S*)-DIFLUORPHOS	2/1	$MeNO_2$	16	>99	+16
17	(*R*)-(*S*)-PPF-P*t*Bu_2	2/1	DCM	16	>99	+17
18	(*R*)-(*S*)-PPF-P*t*Bu_2	2/1	$MeNO_2$	16	>99	0
19	(*R*)-Loxa-6	1/1	DCM	16	>99	0
20	(*S*)-Loxa-7	1/1	DCM	65	56	1

Table II3-5 Enantioselective [4+2] Ag-catalyzed reactions (part 2)

On the other hand, the effect of chiral carbon ligands has been evaluated (**Table II3-5** entries 19-20). We were disappointed with the results of using (*R*)-4-benzyloxazolidin-2-one and bis(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane.

From these results, the enantio discrimination occured when the ratio of Ag/BINAP is 2/1 in DCM or $MeNO_2$. This abnormal solvent effect phenomenon puzzled us and encouraged us to explore the reason behind. Several attempts to isolate silver complexes or to perform ^{31}P and ^{109}Ag NMR analyses were nevertheless unsuccessful.

From these unprecedented preliminary results, the dominant combination was the use of Ag associated with home-made chiral diphosphine ligand (*R*)-L5 ligand in a 1:1 ratio in DCM at room temperature. Then, we also conducted these enantioselective reactions at 0 °C (**Scheme II3-16**). As anticipated, the reaction activity was reduced and the conversion rate was low, the enantiomeric excess increased substantially.



Scheme II3-16 Enantioselective reactions at 0 °C

3.2.3.2 The enantioselective cycloaddition reactions

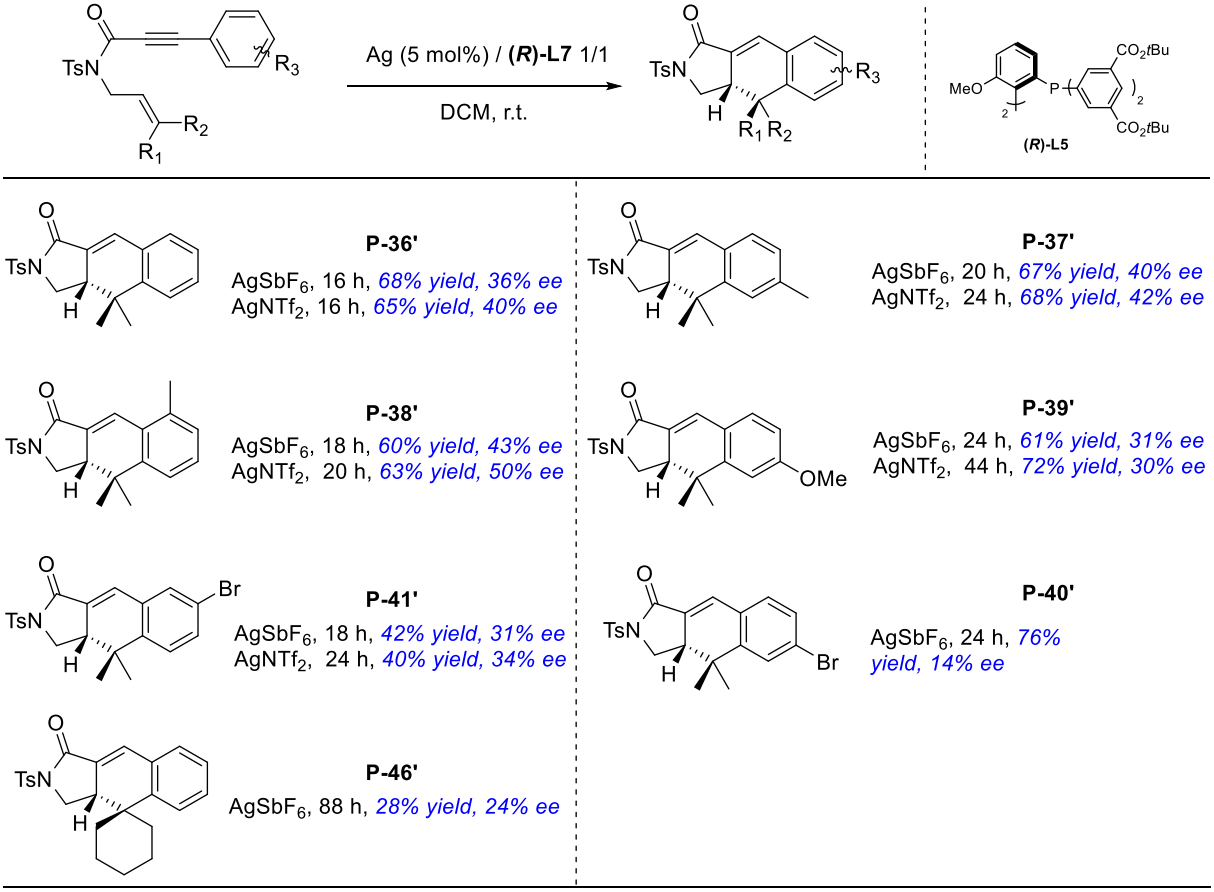


Table II3-17 The asymmetric reaction with Ag complexes and different diphosphine ligands. (The discussion of the absolute configuration of the major enantiomer is at 3.2.3.3)

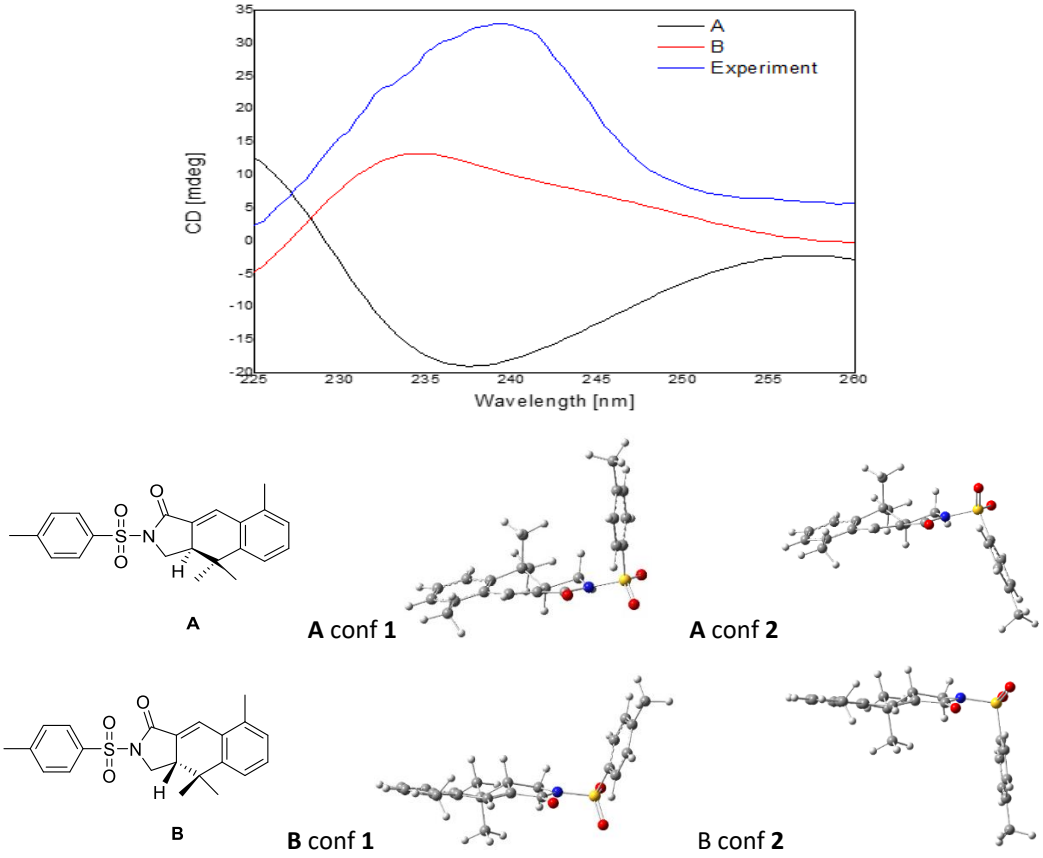
Under these reaction conditions established for Ag salts and chiral phosphine **(*R*)-L5**, enantioselective reactions have been performed in the case of other enynes to obtain tricycles products **P-36'** - **P-40'** and **P-46'**. As presented in **Table II3-17**, the reaction conditions were compatible with the enynes **80**, **137-139** while the yields were generally around 65-70% and the enantioselectivities closed to 40-50%. Following these results, 4,4,8-trimethyl-2-tosyl-

2,3,3a,4-tetrahydro-1*H*-benzo[*f*] isoindol-1-one **P-38'** was isolated with the best enantiomeric excess of 50% in the presence of $AgNTf_2$ and **(*R*)-L5**. Unexpectedly, the presence of a bromide atom such as in 6-bromo-4,4-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one or such as in **P-41'** and **P-40'**, as well as the presence of a hindered alkenyl substituent **P-46'**, had a negative effect either on the activity or on the enantioselectivity of the process.

3.2.3.3 Assignement the absolute configuration of the major enantiomer

The absolute configuration of the major enantiomer was assigned *via* a concerted use of *ab initio* time-dependent density functional theory calculations and circular dichroism on compound **P-38'** (**Scheme II3-18**).

We used the sample 4,4,8-trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*] isoindol-1-one **P-38'** having 50% enantiomeric excess, and the concentration was 100 µmol/L in $CHCl_3$. The blue line represents the experimental data from circular dichroism analysis.

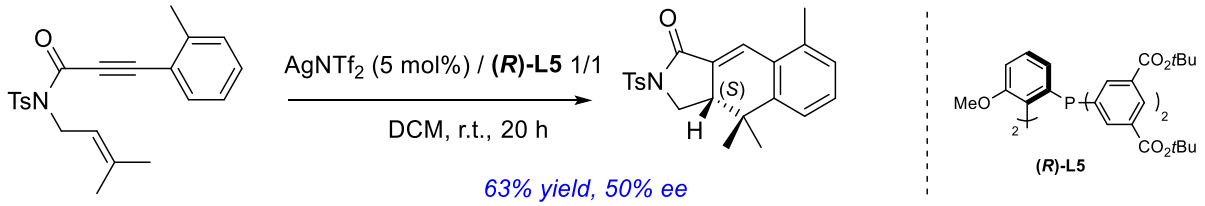


Scheme II3-18

The experimental circular dichroism spectrum was compared with the Time-Dependent

Density Functional Theory calculated ECD spectra performed with the GAUSSIAN software[115] on the most stable conformers of **A** and **B**, enantiomers of the chiral molecule. The conformational analysis provided two stable conformers for each enantiomer and the geometry optimization at the B3LYP- D3[116]/6-31+G(d,p) level of DFT theory, was combined with the PCM implicit solvation model to take into account the solvation effects of chloroform. After the structural optimization calculations, we identified a major conformer with a Boltzmann population of 60% for **A** in conformation **1**, **A** conf **2** (40%), whereas **B** has equal probability to be in conformation **1** and in conformation **2**.

The spectra were deduced from the in implementation weighting by the coefficients of each confirmation for each enantiomer. We could see the peak at around 240 nm, positive for **B** and negative for **A**. So, the comparison between the experimental spectrum with averaged calculated spectra of **A** and **B** allowed us conclude that **B** was the major enantiomer (**Scheme II3-19**).



Scheme II3-19

3.3 Conclusion

In summary, we have developed an effective and simple synthetic strategy of [4+2] cycloaddition reaction, by which various 4,4-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-

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benzo[*f*]isoindol-1-one derivatives were synthesized *via* the reaction of *N*-(3-methylbut-2-en-1-yl)-amide-1,6-enyne with silver salts under room temperature. The process was based on a 5-*exo*-*dig* addition followed by a Friedel-Crafts type arylation. The reaction conditions were optimized, then the scope and limitations, mechanism, gram scale experiments, and post-functionalization reactions were investigated one by one. This asymmetrization strategy was also investigated using a variety of Ag complexes and atropisomeric diphosphine ligands. Asymmetric reactions have been shown to lead to an enantiomeric excess up to 50%, in the presence of an in-house chiral atropisomeric ligand associated with $AgNTf_2$ catalyst.

Chapter III

Gold-catalyzed oxofluorination process: an entry to α-fluoroketones and fluorinated isoquinoline derivatives

Chapter III Gold-catalyzed oxofluorination process: an entry to α-fluoroketones and fluorinated isoquinoline derivatives

1. Bibliography

1.1 Interest of fluorine chemistry

Fluorine, atomic number 9, period 2 and group VIIA, is the 13th most abundant element in the Earth's crust. In the history of the discovery of chemical elements, the preparation of elemental fluorine was a difficult topic with long-duration and high danger. There are more than 100 years of organofluorine chemistry. Fluorine is significantly more electronegative than carbon. In the 1930s, W. Bockemuller reported that carbon-fluorine bond (~116 kcal mol^{-1}) is stronger than carbon-carbon (~83 kcal mol^{-1}) or carbon-hydrogen bond (~99 kcal mol^{-1}).[117] High electronegativity and small size caused strong polar interactions, leading unique effect on the properties of organic molecules.

Despite fluorine is abundantly distributed in nature, there are only 21 biosynthesized molecules containing fluorine known in nature. Arguably, even nature has not been able to develop a diverse set of fluorination reactions. Most fluorine-containing organic compounds are therefore man-made, and with the development of chemistry, fluoro-organic chemistry has become an essential and interconnected part of science in material application,[118] pharmaceuticals,[119] agrochemicals,[120] tracers for positron emission tomography,[121] biological study, and many other different fields. Like the structural modifications enhanced polymer photovoltaic solar cell performances by the introduction of fluorine into the polymer backbone.[122,123] Another area concerns the diagnostic tools such as positron emission tomography (PET) that employs radiotracers labeled with radioactive ^{18}F nucleus,[124] and

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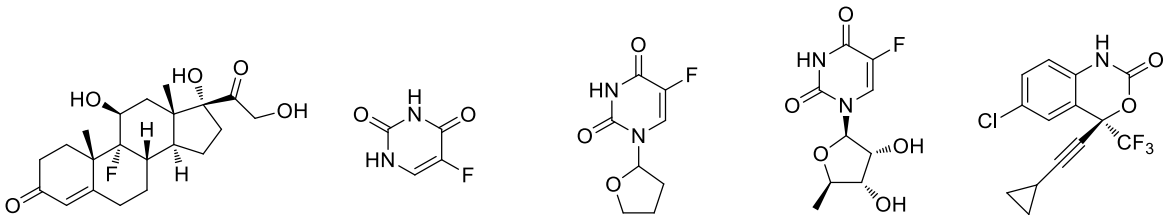
magnetic resonance imaging (MRI) which employs high sensitivity ^{19}F diagnostic technique.[125]

The introduction of fluorine into a molecule can cause dramatic changes, such as the acidity or basicity of neighboring groups, dipole moment. In pharmaceuticals, introducing fluorine is a good way to increase the interaction strength between pharmaceuticals and targeted protein, and make pharmaceuticals more bioavailable, lipophilic, and metabolically stable.[126] In pharmaceuticals, the first recognized fluorine-containing drug is fludrocortisone, which was approves in 1955 (**Scheme III-1**),[127] then the successful application of 5-fluorouracil as an anticancer drug has appeared found to be.[128,129] The studied the fluorine-substituted cortisone derivative at the 9-position was 10-20 times more active than glucocorticoids. Nowadays, nearly 150 fluorinated molecules have succeeded in reaching the market. Considering the remarkable success of the fluorine-containing drug molecules, it provided an enormous motivation for chemists to develop efficient strategies to incorporate fluorine atom into organic molecules and discover new methods for the preparation of organofluorine compound in the organic synthetic methodologies field.



Scheme III-1 Fluorine-containing drug molecules

Given that the development of new methodologies of fluorinated derivatives is challenging, and given the interest for the introduction of fluorine substituent into a certain position of organic structure, the use of fluorination reagents has appeared as highly interesting for chemists. Depending on the transfer form of fluorine, there are three general strategies for constructing C–F bonds: nucleophilic, electrophilic, and radical fluorination (**Scheme III-2**). Conceptually, fluorination can be divided into two fundamentally different classes: nucleophilic and electrophilic. Electrophilic fluorination is the combination of a carbon or

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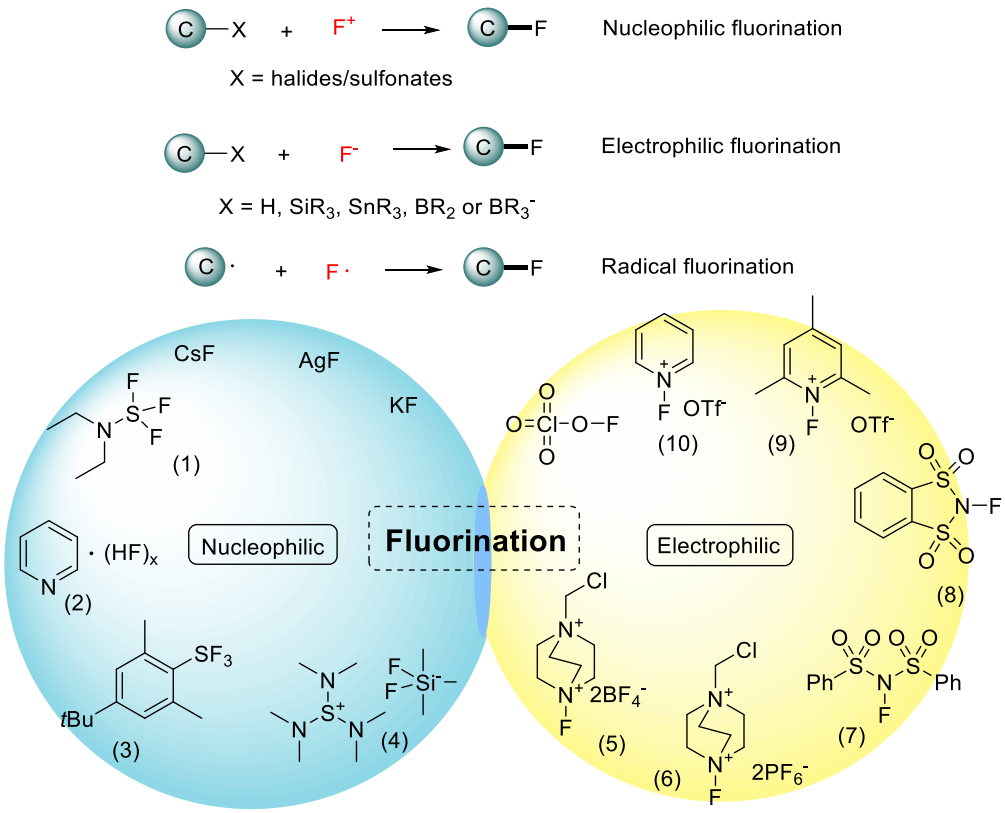
nitrogen nucleophile with an electrophilic source of fluorine to afford organofluorine compounds. Some common electrophilic fluorinating agents used for organic synthesis are *N*-fluoro-o-benzenedisulfonimide (NFOBS), *N*-fluorobenzenesulfonimide (NFSI), Selectfluor/F-TEDA-BF_4, and F-TEDA-PF_6. On the contrary, Fluolead (4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride), DAST (diethylamino)sulfur trifluoride, HF, and some fluoride compounds are the nucleophilic fluorinating agents. In the radical fluorination, C–F bonds are produced by carbon-based radicals (generated *in situ* by various methods) with "atomic fluorine" sources, such as XeF2, hypofluorite, or molecular fluorine.



(1) Diethylaminosulfur trifluoride DAST (2) Hydrogen fluoride pyridine (3) Fluolead (4) Tris(dimethylamino)sulfonium difluorotrimethylsilicate TASF (5) F-TEDA-BF_4/*N*-Chloromethyl-*N'*-fluorotriethylenediammonium bis(tetrafluoroborate)/Selectfluor (6) F-TEDA-PF_6 (7) *N*-Fluorobenzenesulfonimide/NFSI (8) *N*-fluoro-*o*-benzenedisulfonimide NFOBS (9) [Me_3pyF]OTf/ NFTPT (10) *N*-fluoropyridinium salts

Scheme III-2 Fluorination reations and fluorination reagents

1.2 Metal-catalyzed fluorination reactions

Traditional fluorination methods, such as Friedel–Crafts-type electrophilic halogenation,

Sandmeyer-type reaction,[130] commonly involve toxic reagents, multiple steps, harsh reaction conditions, low functional group tolerance, and poor regioselectivity. Among various reported methods, transition-metal-catalyzed fluorination reactions have emerged as a powerful method for the construction of these compounds due to less consumption and costs reviews.

Owing to fluorine's high electronegativity and small size, metal-fluorine bonds are significantly polarized towards fluorine, and metal–fluorine bonds are strong, and no other element makes stronger single bonds to carbon than fluorine does.[131] Therefore, most C–F bond-forming reactions are thermodynamically feasible, C–F bond formation was guided by the selection of appropriate transition metals. Besides, among the various metals developed, palladium is the most commonly employed transition-metal, followed by copper owing to its high-efficiency and cheapness.[132(a)] Meanwhile, other transition-metals, such as Au, Fe, Ni, Rh, Ag, Co, etc., have received considerable attention and are widely applied due to their respective characteristics. Notably, transition-metals are not based on one type of reaction and the same metal may be successfully applied to all three types of fluorination.

From literature (**Scheme III-3**),[131,132] application of arene fluorination was first reported in 2006 with Pd. The C_{aryl}–F bond formation has been described by using palladiumthe,[133] rhodium,[134] silver,[135] and copper[136] (including arenes, alkynes, aryl bromides, -alcohols, -triflates, and -boronic acid derivatives). For a series of allylic fluorination reactions, C-F bond formation occurred *via* fluorination of the transition-metal Pd[137], Cu[138], Ir[139]. Alkyl fluorination

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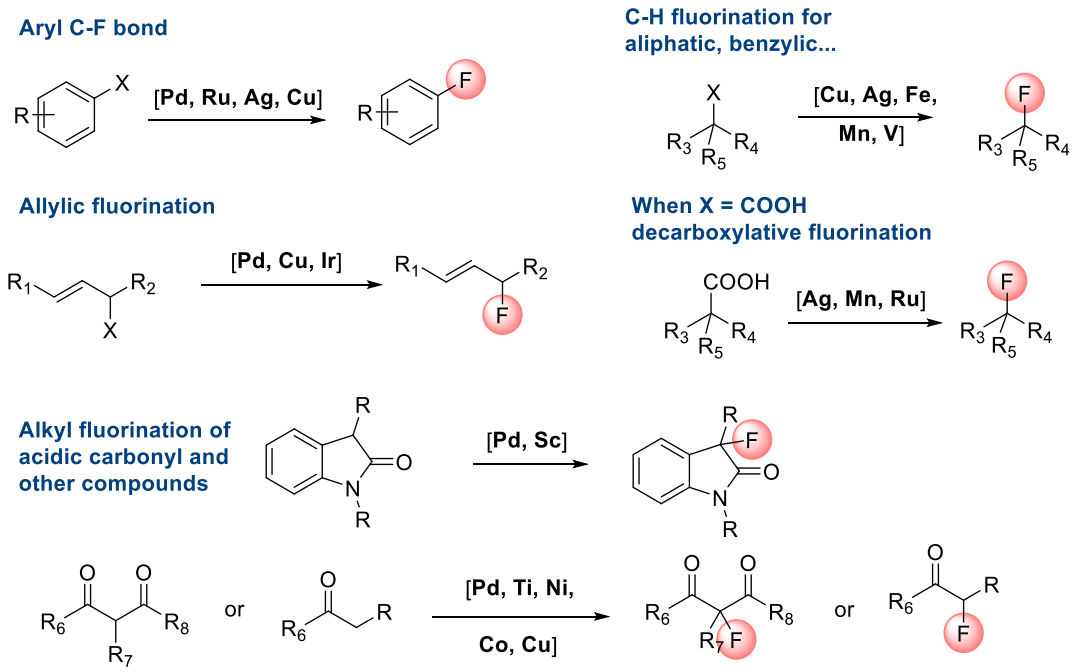
of acidic carbonyl compounds and other activated compounds (like malonate, acetylacetone, acetoacetate, and so on), in the presence of Pd,[140] Cu,[141] Sc,[142] Ti,[143] Co,[144] and Ni[145] catalysts were demonstrated to control the chemo- and regioselectivity of such fluorination reactions.



Scheme III-3 Metal-catalyzed fluorination reaction

For aliphatic, benzylic, alkyl bromides, boronates, boronic acids, or other chemicals, fluorination reactions was successfully obtained with Ag, Mn, Fe, Cu, and V catalysts.[146] More recently, decarboxylative fluorination reactions were optimized and reported with Ag, Mn,

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[144] M. Kawatsura, S. Hayashi, Y. Komatsu, S. Hayase, T. Itoh, *Chem. Lett.,* **2010,** *39,* 466.

[145] (a) S. H. Kang, D. Y. Kim, *Adv. Synth. Catal.,* **2010,** *352,* 2783; (b) Q. -H. Deng, H. Wadepohl, L. H. Gade, *Chem. Eur. J.,* **2011,** *17,* 14922.

[146] Ag: Z. Li, Z. Wang, L. Zhu, X. Tan, C. Li, *J. Am. Chem. Soc.,* **2014,** *136,* 16439; Mn: W. Liu, X. Huang, M. -J. Cheng, R. J. Nielsen, W. A. Goddard, J. T. Groves, *Science,* **2012,** *337,* 1322; Fe: S. Bloom, C. R. Pitts, R. Woltornist, A. Griswold, M. G. Holl, T. Lectka, *Org. Lett.,* **2013,** *15,* 1722; Cu: S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, *Angew. Chem. Int. Ed.,* **2012,** *51,* 10580; V: J. -B. Xia, Y. Ma, C. Chen, *Org. Chem. Front.,* **2014,** *1,* 468.

and Ru as catalysts.[147]

Considering our interest in gold and fluorination, we will present in selected examples from the next paragraph literature with gold.

1.3 Gold-catalyzed fluorination reaction on π-activation

Recently, gold catalysis has become an important and fundamental tool of carbon−carbon and carbon−heteroatom bonds generation in innovative chemical synthesis. Furthermore, special activation patterns reported by gold species associated with fluorinated building blocks or reagents have been developed and arised new methodologies attention in fluoro-organic chemistry.

In 1969, Vaughan and Sheppard reported the first contribution that incorporates gold and fluorine, synthesized gold(I) fluorophenyl isocyanides, and studied C-Au bond by ^{19}F NMR.[148] With further research on gold and fluorine, these species formed a fruitful partnership and different combinations emerged from varioustypes of reactivity.[149,150,151]

Considering that ationic gold catalysts activate π bonds, different types of fluorination, nucleophilic fluorination, and electrophilic fluorination was achieved under gold catalysis to form C-F bond.

1.3.1 Gold-catalyzed nucleophilic fluorination reactions

For gold-catalyzed nucleophilic fluorination, hydrogen fluoride (HF) is a common nucleophilic fluorinating reagent, which could form stable complexes by hydrogen bonding and selected non-basic and weakly coordinating hydrogen-bond acceptors. Au species can activate carbon−carbon multiple bonds toward nucleophilic attack by fluoride under remarkably mild reaction conditions (**Scheme III-4**). Protoderetalation would end the catalytic cycle and would regenerate the catalyst.

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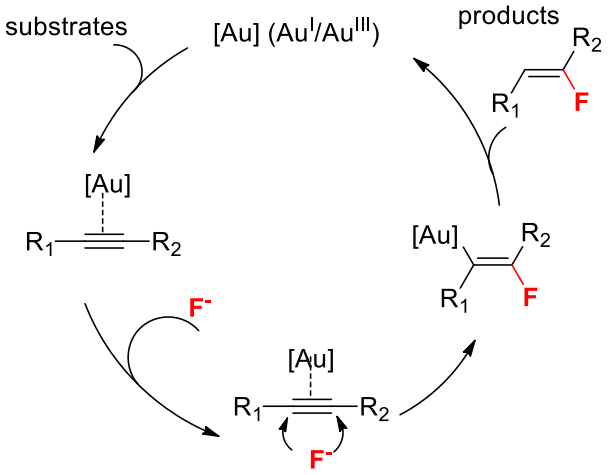
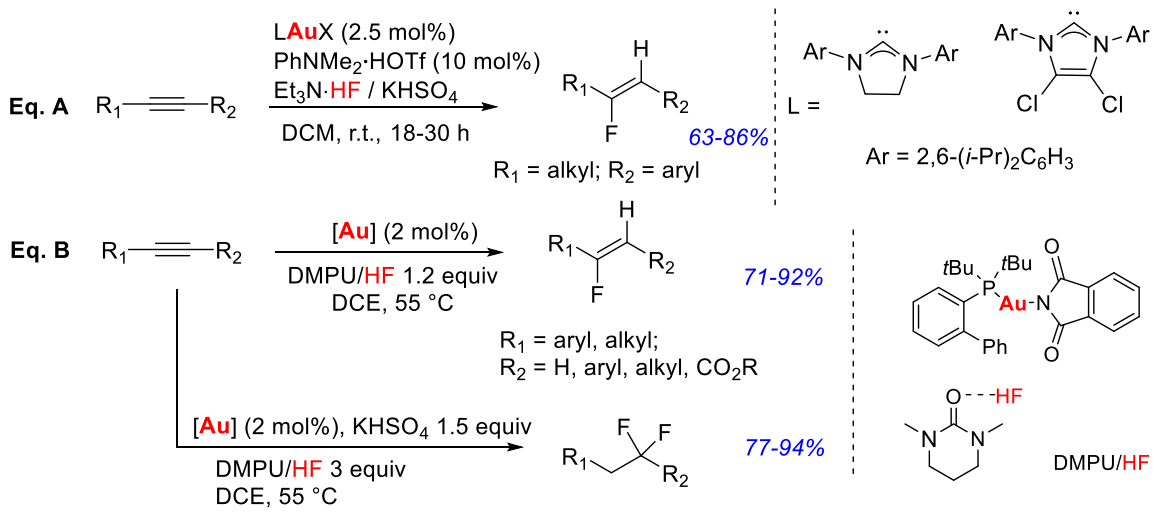
[147] Ag: F. Yin, Z. Wang, Z. Li, C. Li, C. *J. Am. Chem. Soc.,* **2012,** *134,* 10401; Mn: X. Huang, W. Liu, J. M. Hooker, J. T. Groves, *Angew. Chem. Int. Ed.*, **2015**, *54*, 5241; Ru: M. Rueda-Becerril, O. Mahe, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J. F. Paquin, *J. Am. Chem. Soc.*, **2014**, *136*, 2637.
[148] L. G. Vaughan, W. A. Sheppard, *J. Am. Chem. Soc.*, **1969**, *91*, 6151.
[149] J. Miró, C. del Pozo, *Chem. Rev.*, **2016**, *116*, 11924.
[150] K. Chen, S. Zhu, *Synlett*, **2017**, *28*, 640.
[151] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.*, **2016**, *116*, 422.



Scheme III-4 Nucleophilic fluorination reaction

The first example of Au-catalyzed hydrofluorination of alkynes with F^- was reported by Sadighi in 2007,[152] using electrophilic (NHC)gold(I) complexes, allowing the *trans*-hydrofluorination of internal alkynes with $Et_3N{\cdot}3HF$ (**Scheme III-5 Eq A**). Two years later, a new nucleophilic fluorinating reagent DMPU/HF was designed by Hammond and Xu, which has high acidity, weaker nucleophilicity, and coordination ability with metals.[153] The gold-catalyzed hydrofluorination of alkynes with DMPU/HF was performed, and mono- or dihydrofluorination led to fluoroalkenes and *gem*-difluoromethlylene compounds regioselectively (**Scheme III-5 Eq B**).



Scheme III-5 Au-catalyzed hydrofluorination of alkynes

Due to the fluorine's high electronegativity and the dual reactivity of either bases or

[152] J. A. Akana, K. X. Bhattacharyya, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.*, **2007**, *129*, 7736.
[153] B. C. Gorske, G. T. Mbofana, S. J. Miller, *Org. Lett.*, **2009**, *11*, 4318.

nucleophiles on F^-, nucleophilic fluorination is still a challenging task. Electrophilic fluorination reactions exhibited a wider profile and therefore allowed the optimization of a larger number of examples.

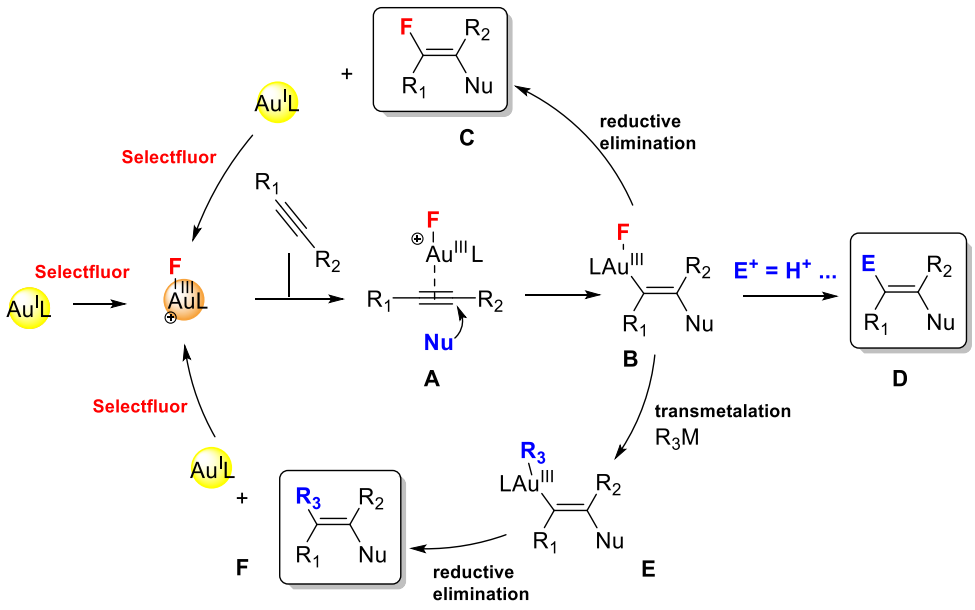
1.3.2 Gold-catalyzed electrophilic fluorination reactions

In the presence of electrophilic sources of fluorine, the fluorination event may effectively replace protodeauration and the dominance of processes relying on electrophilic fluorine sources is undeniable. Among various electrophilic fluorine sources, Selectfluor, is one of the most wised examples. The combination of Selectfluor as an external oxidant with gold catalysts has thus emerged as a powerful tool for synthesizing both fluorinated and nonfluorinated compounds, opening new departures in fluorine and gold chemistry.

Selectfluor (F-TEDA-BF_4), [154,155] is not only an exceptionally stable and strong oxidant, but also is a strong electrophilic fluorinating agent. Considering the π-acidic nature of cationic gold complexes that activate π bonds and high Au(I)/Au(III) redox potential (+1.41 V),[156] a variety of practical and new synthetic methodologies by using alkyne or alkene substrates and strong external sacrificial oxidants (like Selectfluor) have been developed.[149,157,158]

Selectfluor was demonstrated to active towards most homogeneous gold catalysts to generate gold cationic form,[159] like (PPh_3)AuCl. [Au^I] complex was oxidized to Au^{III} cation, which could catalyze the redox reactions (Selectfluor was used stoichiometrically), such as cross-coupling reaction, and redox-neutral reactions (Selectfluor was used catalytically).[150] Moreover, if the substrates included C=C and C≡C bonds, Au^{III} cationic species could act as carbophilic π acid that could activate the π bond, and favor a nucleophilic attack. Overall, this approach could deliver fluorinated and non-fluorinated building targets.[160]

[154] P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C. -H. Wong, *Angew. Chem. Int. Ed.*, **2005**, *44*, 192; S. Stavber, M. Zupan, *Acta Chim. Slov.*, **2005**, *52*, 13.
[155] K. Yang, M. Song, A. I. M. Ali, S. M. Mudassir, H. Ge, *Chem Asian J.*, **2020**, *15*, 729.
[156] Bratsh, S. G. *J. Phys. Chem. Ref. Data,* **1989**, *18*, 1.
[157] M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. Eur. J.*, **2011**, *17*, 8248.
[158] J. arlos Lima, L. Rodriguez, *Chem. Soc. Rev.*, **2011**, *40*, 5442.
[159] Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028.
[160] M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Isr. J. Chem.*, **2010**, *50*, 675.



Scheme III-6 Electrophilic fluorination reaction

In selectfluor-enabled catalytic cycle (**Scheme III-6**), cationic Au^{I} is oxidized to cationic Au^{III} by Selectfluor before the addition of nucleophiles to alkynes. Not only species **A** could favor catalyze hydration or cyclization of alkynes, but also it could lead to additional transformations. The fluoro–gold vinyl **B** may undergo reductive elimination to give a vinyl fluoride **C**, or react with an electrophile (E^{+}) to form product **D**, such as a proton, to get the product through protodeauration. The intermediate **B** could also react with an organometallic reagent R_3M (e.g. M=B, Si, Sn, etc.) *via* a transmetalatilion step, considering the weak Au-F bond[161] and the strong B-F, Si-F, and Sn-F bonds. Then, the low-valence gold(I) was further fluorinated to end the catalytic cycle and regenerate the catalyst. Finally, this general process provided access to the generation of new C−F bond and C-C bonds, and other nonfluorinated derivatives.

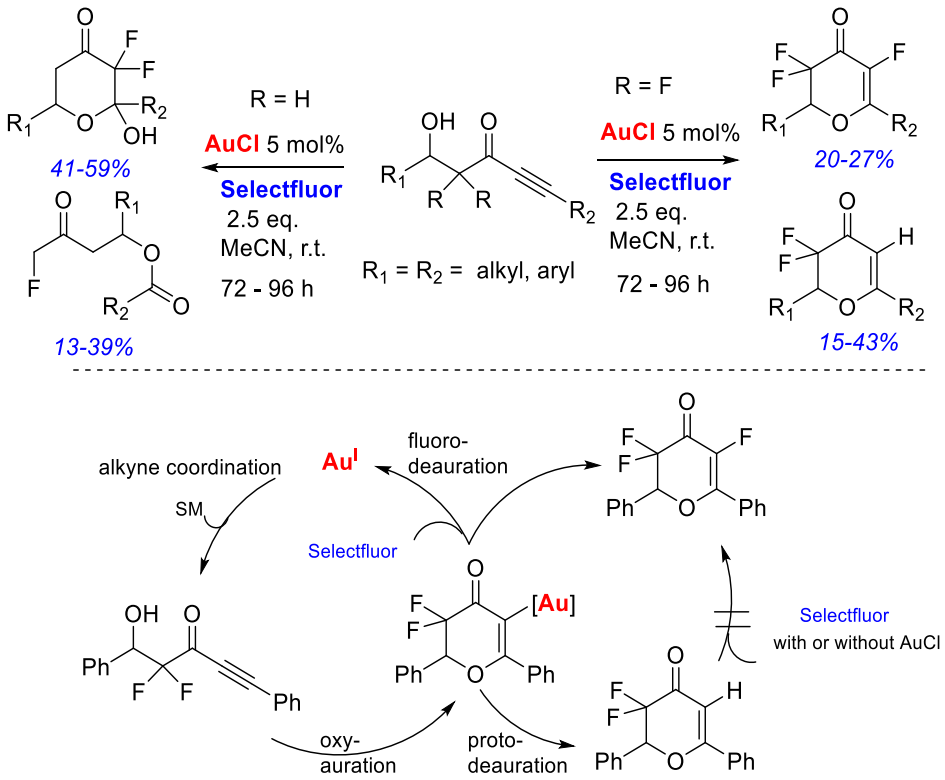
1.3.2.1 Fluorination of functionalized alkynes with oxygen as nucleophile

Alkyne with alcohol

In 2008, the first gold-catalyzed fluorination process with electrophilic fluorine source - Selectfluor was reported by the Gouverneur group.[162] This 6-*endo-dig* cyclization-fluorination process started from β-hydroxy-α,α-difluoroynones, when R = F, the cyclic tri- or bi-fluorination were obtained and the fluorinated compounds underwent intramolecular hydroalkoxylation over the triple bond in the presence of AuCl. The process generated the

[161] T. Okabayashi, Y. Nakaoka, E. Yamazaki, M. Tanimoto, *Chem. Phys. Lett.*, **2002**, *366*, 406.
[162] M. Schuler, F. Silva, C. Bobbio, A. Tessier, V. Gouverneur, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7927.

corresponding vinyl gold intermediate which evolved employing two competitive pathways. When R = H, a mixture of the difluorinated pyranones and ring-opened fluorinated ketones were obtained (**Scheme III-7**).

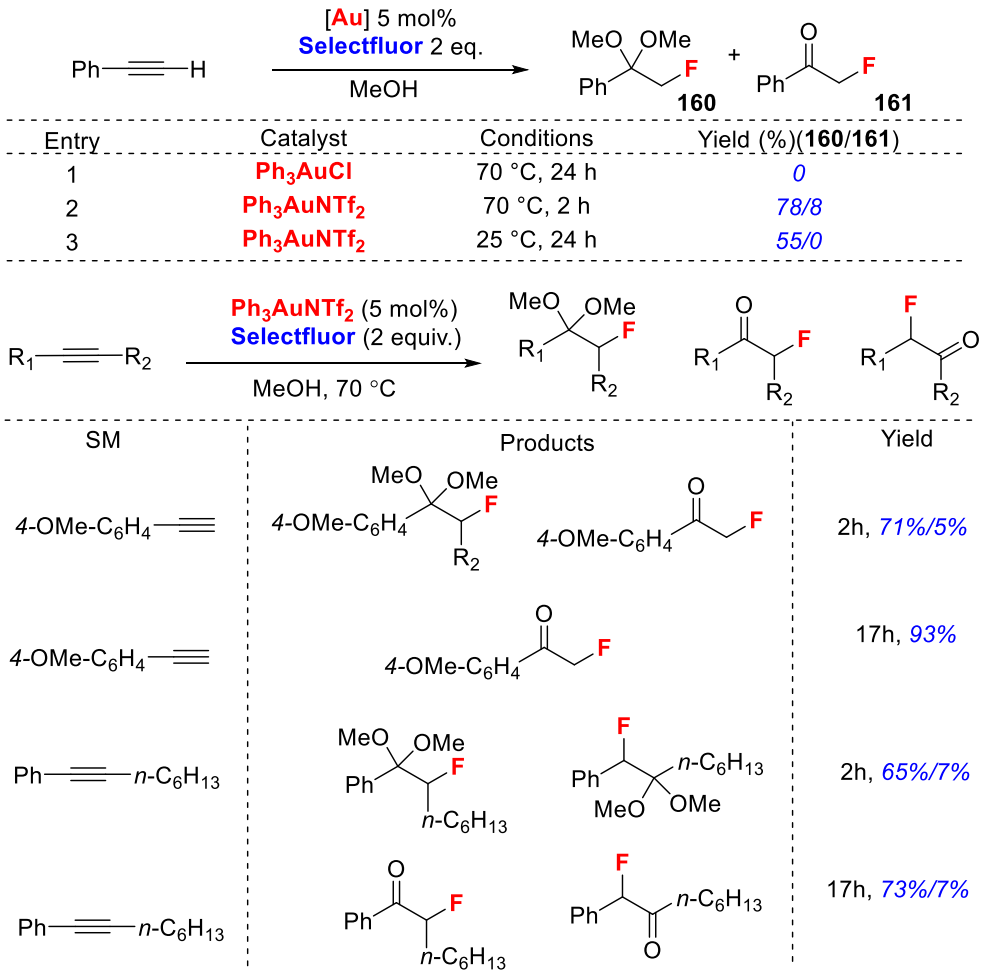


Scheme III-7 Selectfluor and gold(I)-catalyzed alkoxyfluorination of β-hydroxyynone

After Gouverneur's seminal report, several gold-catalyzed transformations involving alkynes were combined with electrophilic sources of fluorine as a mild methodology for the generation of C−F bonds, and this area has emerged as research hotspots.

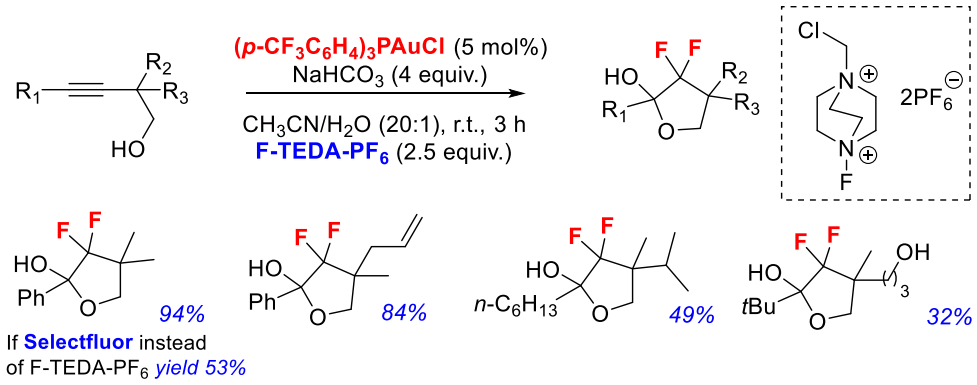
In 2010, a novel method to selectively synthesize α-fluoro acetals or α-fluoro ketones from alkynes through an alkoxylation/hydration fluorination protocol by Haro and Nevado (**Scheme III-8**).[163] In the reaction of phenylacetylene, 2 equivalents Selectfluor with Ph_3PAuCl in refluxing MeOH for 24 h afforded only starting material. Fluorodimethyl acetal **160** and ketone **161** was isolated in 78% and 8% yields in the presence of Ph_3AuNTf_2. When exploring the reaction scope with various alkynes and alcohols, the corresponding α-fluoroacetate and ketones was efficiently isolated as shown in **Scheme III-8**.

[163] T. de Haro, C. Nevado, *Adv. Synth. Catal.*, **2010**, *352*, 2767.



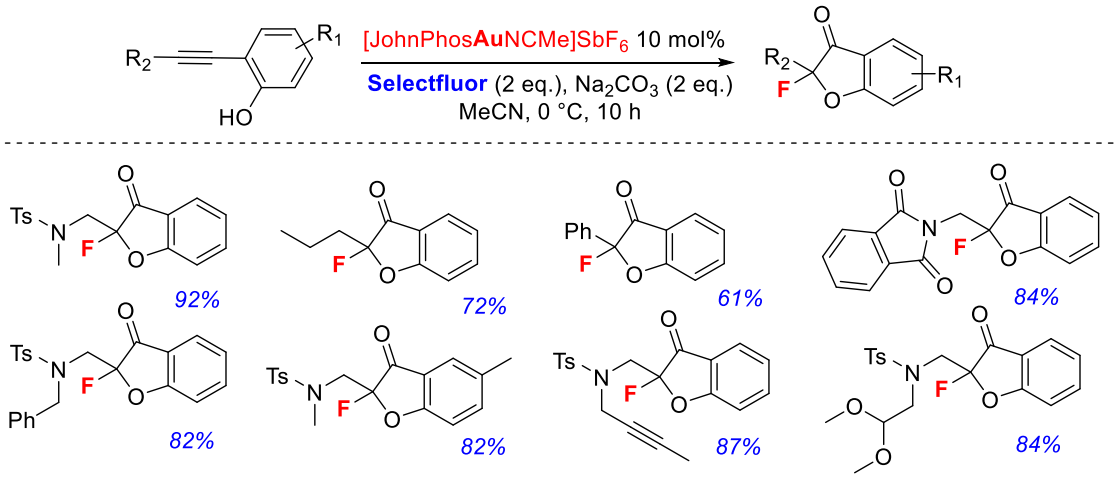
Scheme III-8 Selective synthesis of α-fluoroacetals and α-fluoroketones from alkynes

In 2014, Xu developed a gold-catalyzed hydroxyfluorination reaction of alkynyl alcohols at room temperature to form difluoro hydroxyl tetrahydrofuran compounds in moderate to good yields (**Scheme III-9**).[166] In this cycloisomerization and fluorination method, F-TEDA-PF_6 acted as an electrophilic fluorination agent, and for some substrates, the use of Selectfluor led to relatively low yield.



Scheme III-9 Synthesis of difluoro hydroxyl tetrahydrofuran compounds

Another method provided access to α-fluorobenzofuranones in 2016. Shi reported a gold-catalyzed fluorination–hydration reaction of alkylphenols in the presence of Selectfluor with the construction of C-O, C=O, and C-F bonds (**Scheme III-10**).[164] After the asymmetric variant of this reaction and other control experiments, a plausible mechanism proposed an Au^{I}/Au^{III} redox catalytic cycle.

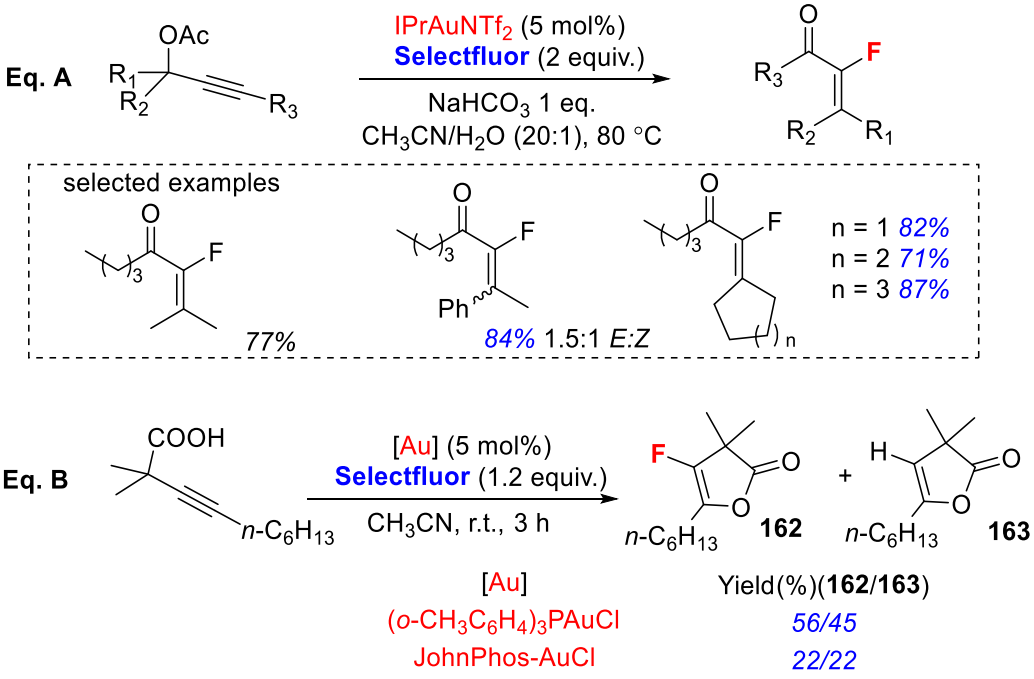


Scheme III-10 Synthesis of α-fluorobenzofuranones

Alkynes with ester or acid

Nevado and Gouverneur have shown that α-fluoroenones can be synthesized from propargylic esters with Selectfluor under gold catalysis in 2010-2011.[165] In Nevado's work, an efficient strategy for the preparation of α-fluoroenones based on a domino gold-catalyzed rearrangement and fluorination of easily available propargyl acetates, was described with the combination of $IPrAuNTf_2$ and Selectfluor with a base $NaHCO_3$ in acetonitrile and water at 80 °C (**Scheme III-11 Eq. A**). In the formation of α-fluoroenones, the reaction process involved 1,3-acyloxy rearrangement and redox Au(I)/Au(III) catalytic cycle. In the case of the substrate bearing an alkynyl carboxy acid, fluorolactonization was investigated in the presence of gold and Selectfluor, gave the fluorinated and non-fluorinated cyclized product (**Scheme III-11 Eq. B**).[166]

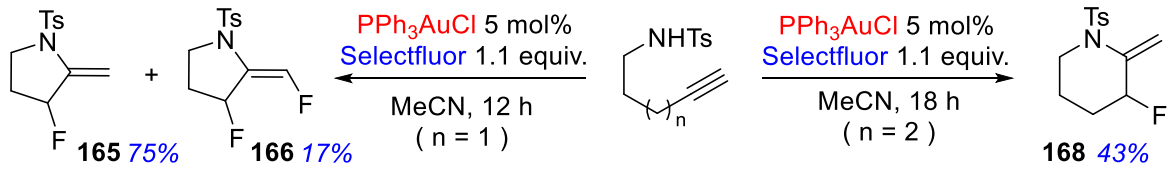
[164] Q. Wang, Y. Jiang, R. Sun, X. -Y. Tang, M. Shi, *Chem. Eur. J.*, **2016**, *22*, 14739.
[165] T. de Haro, C. Nevado, *Chem. Commun.*, **2011**, *47*, 248.
M. N. Hopkinson, G. T. Giuffredi, A. D. Gee, V. Gouverneur, *Synlett.*, **2010**, *18*, 2737.
[166] D. Malhotra, L. Liu, W. Wang, M. Durham, G. B. Hammond, B. Xu, *J. Fluor. Chem.*, **2014**, *167*, 179.



Scheme III-11 Gold and Selectfluor in the presence of alkynes bearing ester- or acid- systems

1.3.2.2 Fluorination of functionalized alkynes with nitrogen as partner

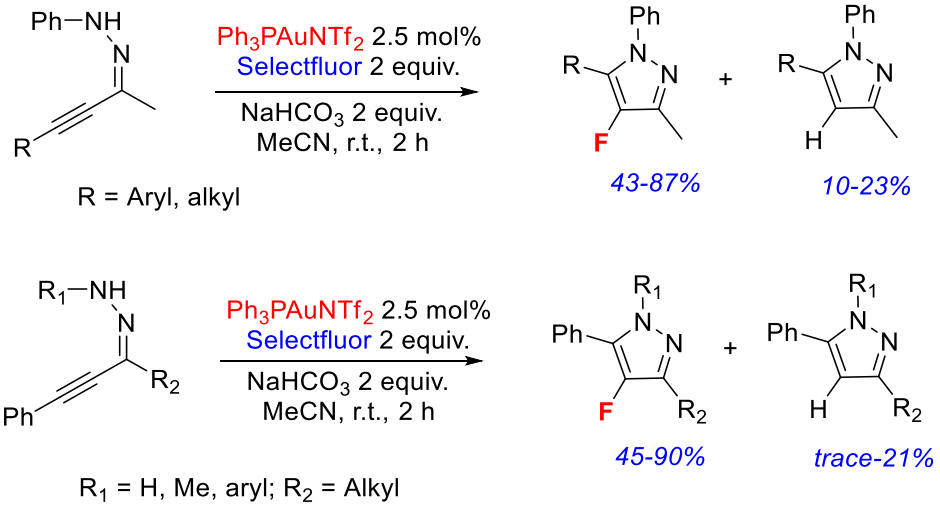
Fensterbank and co-workers reported a gold-catalyzed hydroamination reaction with Selectfluor on 1,5- and 1,6-aminoalkynes in 2010, leading to 3-fluoro-2-methylene-pyrrolidine and -piperidine scaffolds respectively. This was the first example of the cyclization-fluorination reaction of aminoalkynes.[167] When 4-methyl-*N*-(pent-4-ynyl)benzenesulfonamide **164** (n=1) was used as the substrate, a mixture of pyrrolidines **165** and **166** was isolated in 75% and 17% yields respectively. For the other substrate **167** (n=2) which is the homolog of **164**, the 6-*endo-dig* cyclization occurred and 43% yield compound **168** was isolated (**Scheme III-12**). This rapid, efficient, and mild route to substituted fluorinated adducts in position 3 of the nitrogen heterocycles was applied to the synthesis of biologically relevant substrates.[168]



Scheme III-12 Gold-catalyzed hydroamination reaction with Selectfluor

[167] A. Simonneau, P. Garcia, J. P. Goddard, V. Mouriès-Mansuy, M. Malacria, L. Fensterbank, *Beilstein J. Org. Chem.*, **2011**, *7*, 1379.
[168] C. Shu, L. Li, C. -H. Shen, P. -P. Ruan, C. -Y. Liu, L. -W. Ye, *Chem. Eur. J.*, **2016**, *22*, 2282.

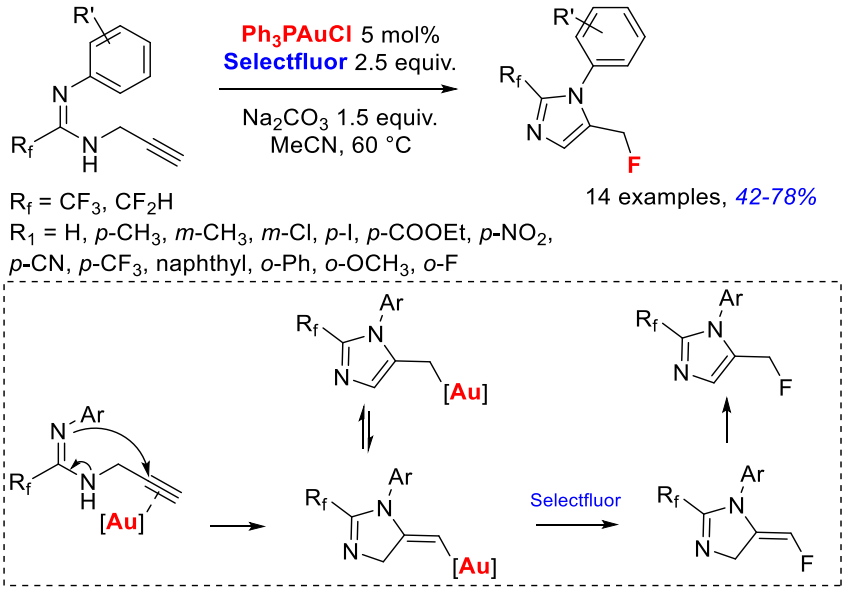
For the synthesis of fluorinated pyrazoles, a mild, efficient, and simple one-pot procedure with gold and Selectfluor was reported later by Xu in 2011 (**Scheme III-13**).[169] Under the reaction conditions with PPh_3AuNTf_2 as catalyst, Selectfluor, and a base ($NaHCO_3$) in MeCN at room temperature, this tandem aminofluorination of alkynes offered a broad substrate scope in good yields. They proposed a reaction mechanism involving a redox Au(I)/Au(III) catalytic cycle.



Scheme III-13 Synthesis of fluorinated pyrazoles

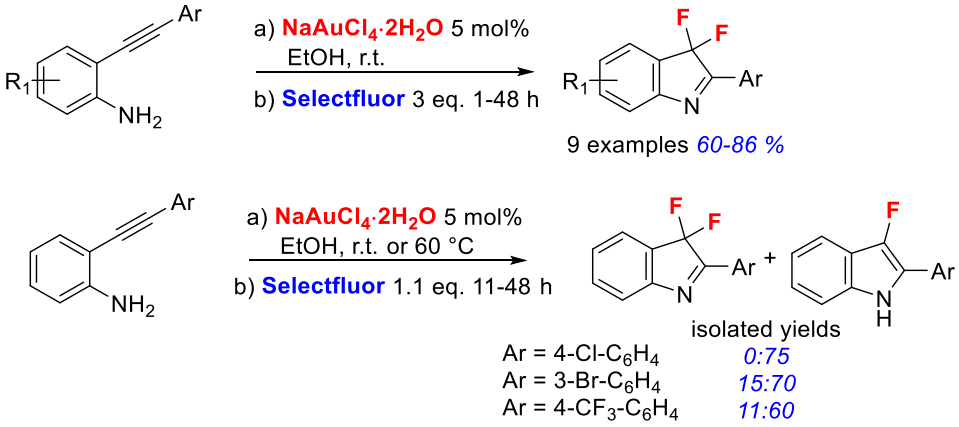
A synthetic route to prepare 2-fluoroalkyl-imidazole derivatives from fluorinated propargyl amidines was developed *via* a gold-catalyzed cyclization/fluorination cascade reaction in the presence of Selectfluor in 2013 (**Scheme III-14**).[170] Under Ph_3PAuCl catalysis, Selectfluor, and Na_2CO_3 in MeCN, substrates were converted into 5-fluoromethyl imidazoles with the construction of new C_{sp3}-F bonds in 42-78% yield. Mechanistic investigation revealed the general pathways of these transformations.

[169] J. Qian, Y. Liu, J. Zhu, B. Jiang, Z. Xu, *Org. Lett.*, **2011**, *13*, 4220.
[170] S. Li, Z. Li, Y. Yuan, Y. Li, L. Zhang, Y. Wu, *Chem. Eur. J.*, **2013**, *19*, 1496.



Scheme III-14 Synthesis of 2-fluoroalkyl-imidazole derivatives

The activation of the triple bond was followed by amination leading to vinyl gold intermediate which upon reductive elimination gives the vinyl fluoride derivative, The vinyl gold may be in equilibrium with the alkyl gold intermediate which explains the formation of imizole derivatives.



Scheme III-15 Gold-catalyzed aminocylization/fluorination

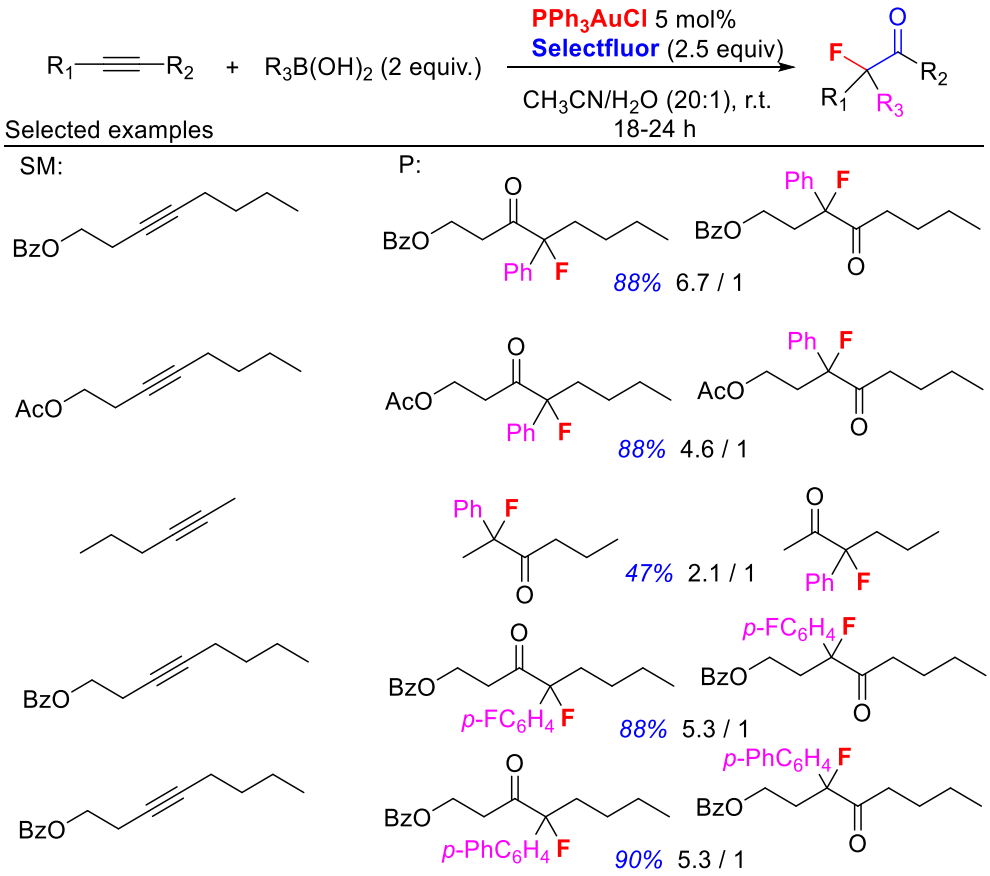
For the investigation of gold-catalyzed unprotected 2-alkynylanilines, an approach to 3,3-difluoroindole derivatives *via* gold-catalyzed aminocylization/fluorination has been developed by our team (**Scheme III-15**).[171] This one-pot, two-steps, gold(III) catalyzed cyclization /electrophilic fluorination gave 3,3-difluoro-2-substituted-3*H*-indoles in good yields using green solvent (ethanol) under mild conditions, without acid, base, and *N*-protective group.

[171] (a) A. Arcadi, E. Pietropaolo, A. Alvino, V. Michelet, *Org. Lett.,* **2013**, *15*, 2766; (b) A. Arcadi, E. Pietropaolo, A. Alvino, V. Michelet, *Beilstein J. Org. Chem.*, **2014**, 10, 449.

Further investigations using Selectfluor 1.1 equiv. in the second step, were also explored and led to different indoles.

1.3.2.3 Fluorination of functionalized alkynes with boronic acid as partner

In 2010, the group of Hammond and Xu described the hydration of alkynes to give α-substituted α-fluoroketones,[172] in a one-pot process in the presence of boronic acid, Ph_3PAuCl, and selectfluor, in CH_3CN/H_2O 20:1 at room temperature (**Scheme III-16**). In this reaction, in the presence of water acting as a nucleophile, and organoboronic acid, fluorine–gold intermediate could react with boronic acid and an electrophilic fluorine source Selectfluor to give α-aryl-α-fluoroketone.[173]

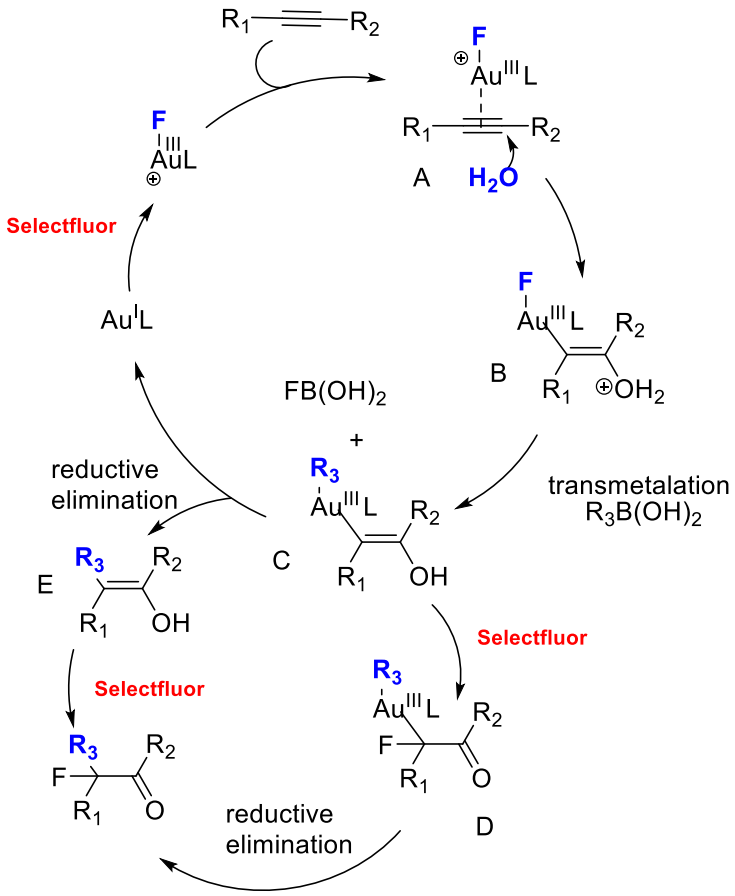


Scheme III-16 Synthesis of α-fluoroketones from alkynes and aryl boronic acids

For the proposed mechanism (**Scheme III-17**), water would add to the gold-activated alkyne **A** to form a vinyl-gold complex **B**, which would react with $PhB(OH)_2$ through a transmetalation

[172] W. B. Wang, J. Jasinski, G. B. Hammond, B. Xu, *Angew. Chem. Int. Ed.*, **2010**, *49*, 7247.
[173] B. Xu, W. Wang, G. B. Hammond, *J. Fluor. Chem.*, **2011**, *132*, 804.

process, to give intermediate **C**. Reductive elimination of **C** would give **E**. Intermediate **C** would react with Selectfluor first to give **D**, and, following reductive elimination, would allow the formation of the final product. Investigations of the reaction mechanism allowed the study of the fluorinated cationic gold^{III} species which were found to be the key intermediates by using *in situ* NMR spectroscopy and ESI-high resolution mass spectrometry.



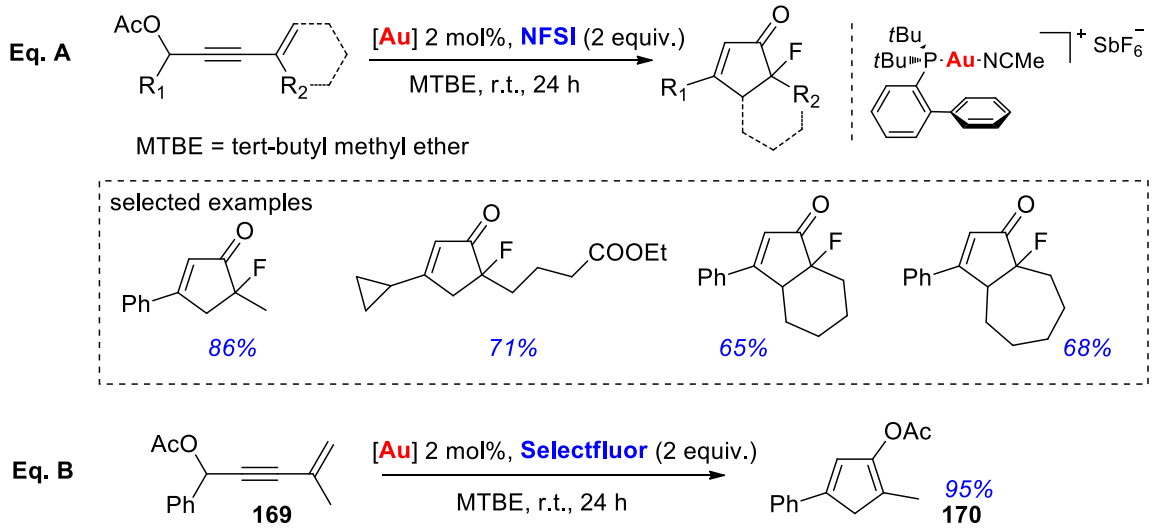
Scheme III-17 Proposed mechanism of α-fluoroketones from alkynes and aryl boronic acids

1.3.2.4 Fluorination of functionalized alkynes with an ester and an alkene as partners

In 2018, Zhang and Rao's group developed an efficient, expedient, and regioselective protocol for the synthesis of 5-fluorocyclopentenones, substituted by a carbon-fluorine stereocenter, by gold(I)-catalyzed cycloisomerization and fluorination with NFSI in *tert*-butyl methyl ether (MTBE) at room temperature (**Scheme III-18 Eq. A**).[174] When Selectfluor was used, only

[174] X. Chen, Y. Zhou, M. Hong, Y. Ling, D. Yin, S. Wang, X. Zhang, W. Rao, *Adv. Synth. Catal.*, **2018**, 360, 3700.

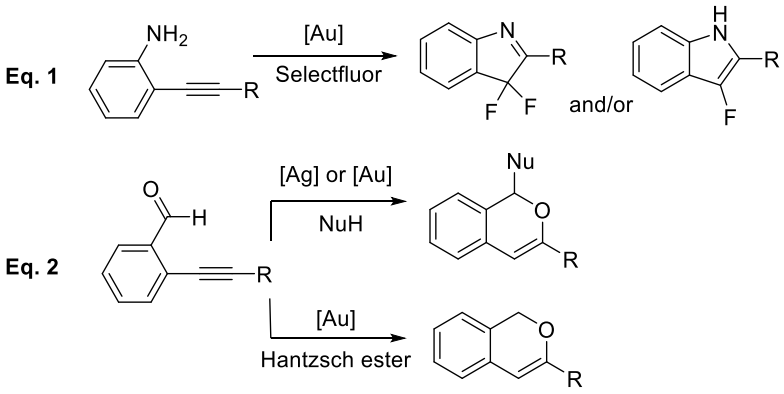
cyclopentadiene **170** instead 5-fluorocyclopentenone was obtained in 95% yield (**Scheme III-18 Eq. B**). This tandem transformation presented a broad substrate scope, high regioselectivity, and excellent functional group compatibility, providing 25 examples of 5-fluoro-cyclopentenones in good to excellent yields (62-93%) under mild reaction conditions.



Scheme III-18 Fluorination reaction of alkyne with ester and alkene

2. Objectives

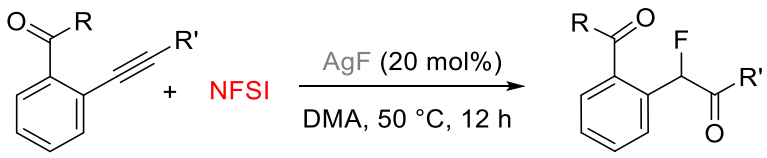
Considering the literature, the association of gold and Selectfluor could show excellent catalytic activity in many reactions, and it remained challenging to develop a regioselective strategy to incorporate fluorine atom into alkyne under mild reaction conditions. Following our interest in *ortho*-alkynylarylaldehydes cycloisomerizations,[38,171,175] we anticipated that the cycloaddition reaction and construction of fluorinated compounds was achieved *via* gold and Selectfluor partnership with *ortho*-alkynylarylaldehydes.



Scheme III2-1 Previous work in our group

[175] (a) E. Tomás-Mendivil, J. Starck, J. -C. Ortuno, V. Michelet, *Org. Lett.*, **2015,** 17, 6126; (b) E. Tomás-Mendivil, C. F. Heinrich, J. -C. Ortuno, J. Starck, V. Michelet, *ACS Catal.* **2017**, 7, 380

From the literature reported in 2017, [176] α-fluoroketone was obtained as the main product *via* a silver-catalyzed regioselective fluorination, in the presence of 20 mol% AgF and 15 equivalents NFSI in DMA at 50 °C (**Scheme III2-2**).



Scheme III2-2 Silver-catalyzed fluorination reaction

We will talk about our reaction advantages at the end of next paragraph after establishing the optimal experimental conditions.

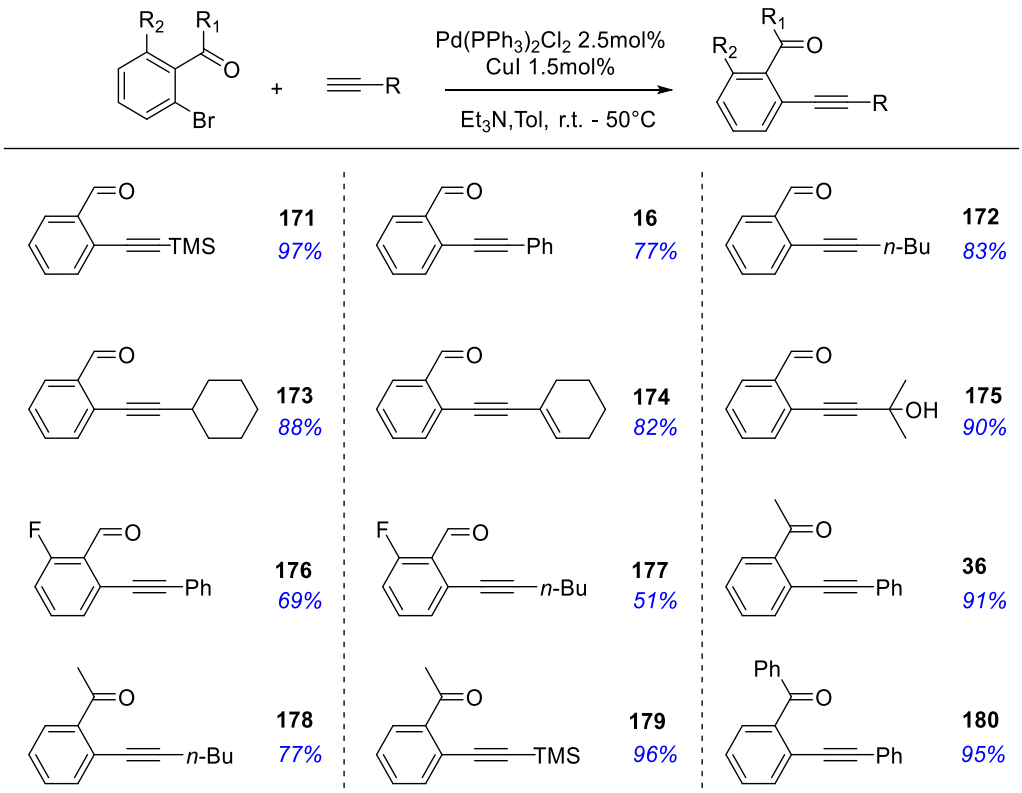
3. Results and discussions

3.1 Synthesis of the substrates

3.1.1 Synthesis of *ortho*-alkynylarylaldehydes and *ortho*-alkynyl ketones

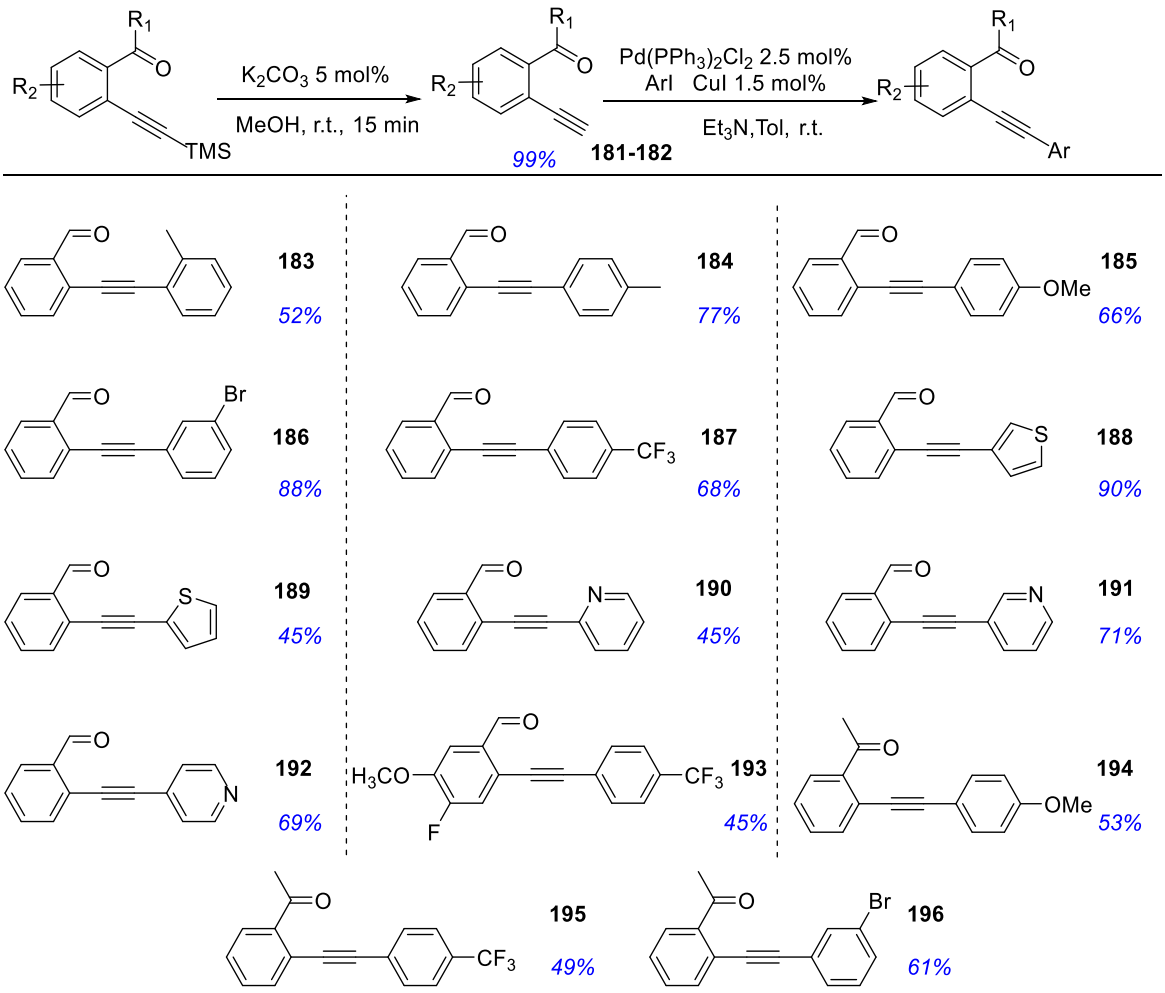
Firstly, we synthesized various *ortho*-alkynylarylaldehydes and *ortho*-alkynyl ketones by classical Sonogashira coupling reactions. As shown in **Scheme III3-1**, the 2-bromobenzaldehyde was reacted with different commercial terminal alkynes, leading to products **16**, **36**, and **171**-**180** with good yields (51-97%).

[176] F. -H. Li, Z. -J. Cai, L. Yin, J. Li, S. -Y. Wang, S. -J. Ji, *Org. Lett.,* **2017**, *19*, 1662-1665.



Scheme III3-1 Synthesis of aldehyde-ynes and alkynylaryl ketones (part 1)

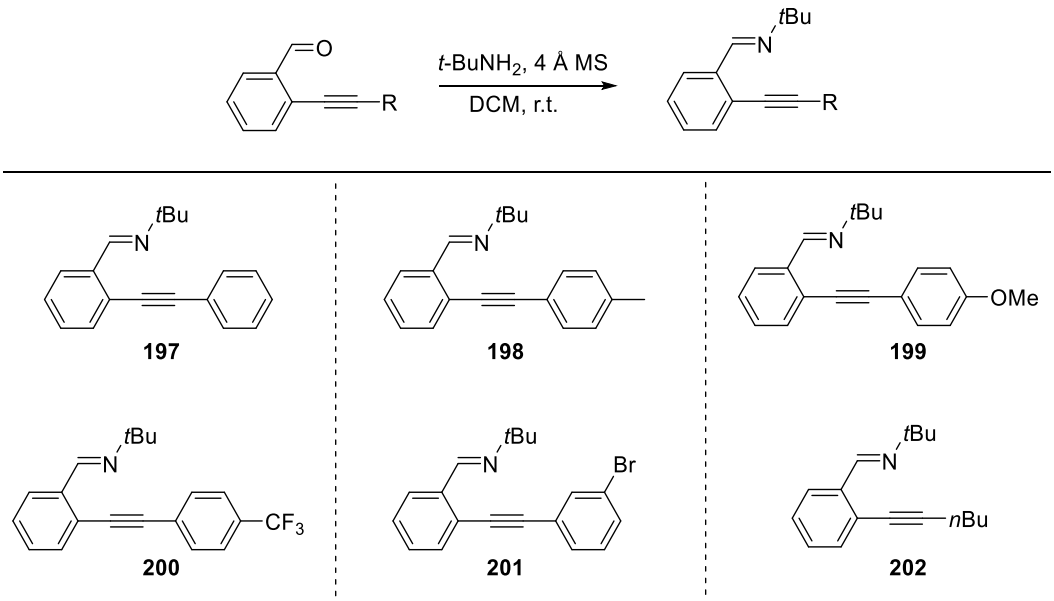
For acetylenic derivatives functionalized with other aromatic groups, 2-ethynylarylaldehydes and 2-ethynylketones were prepared first *via* deprotection of 2 - ((trimethylsilyl)ethynyl) aldehydes and ketones in the presence of K_2CO_3 5 mol% in MeOH. Then a second Sonogashira coupling was carried out in the presence of various aryl iodides, bearing *2*-methyl, *4*-methyl, *4*-methoxy, *3*-bromo, and *3*-CF_3-substituted group (**184**-**187** and **194**-**196**) (**Scheme III3-2**). We also prepared the substrates with heterocycles such as thiophenyl and pyridine-functionalized alkynes **188**-**192**. Finally, the substrate 4-fluoro-5-methoxy-2-((4-(tri-fluoromethyl)phenyl) ethynyl) benzaldehyde **193** was prepared in good overall yield.



Scheme III3-2 Synthesis of aldehyde-ynes and alkynylaryl ketones (part 2)

3.1.2 Synthesis of alkynyl imines

With a series of *ortho*-alkynylarylaldehydes in hand, alkynyl imine compounds **197**-**202** could also be prepared easily through adding *tert*-butylamine and 4 Å MS in dried DCM with almost quantitative yields, as shown in **Scheme III3-3**.



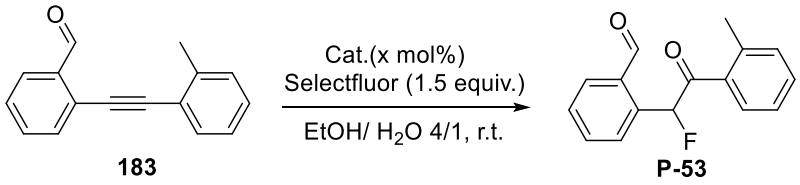
Scheme III3-3 Synthesis of alkynl-imines

3.2 Synthesis of α-fluoroketones *via* gold-catalyzed oxofluorination process

3.2.1 Optimization of the reaction conditions

We started with optimizing the experimental conditions by using the model reaction of 2-(*o*-tolylethynyl)benzaldehyde **16** with Selectfluor, as disclosed in **Table III-1**,**2**,**3**.

Initially, the effects of different metal salt catalysts were investigated (**Table III3-1** entries 1-13). When tested Ph_3PAuCl and $Ph_3PAuNTf_2$ as catalysts, they exhibited good catalytic activity for this hydration/fluorination reaction, giving oxofluorination product 2-(1-fluoro-2-oxo-2-(*o*-tolyl)ethyl) benzaldehyde **P-53** in 90% yields. Comparatively, $PicAuCl_2$, $KAuCl_4$, and AuCl displayed lower catalytic activity to form **P-53**. Conducting the reaction in the presence of $PdCl_2$, 51% yield of the desired product was obtained, and for $PtCl_2$, $InCl_3$, $CuCl_2$ and CuI as catalysts, no conversion was observed. When using AgOTf and $AgNO_3$ (10 mol%) as catalysts, 90% and 62% yields of the desired product were obtained. When decreasing the amount of Ph_3PAuCl to 2 mol% and 1 mol%, the formation of the desired derivative **P-53** was observed still in good yields (entries 14-16).

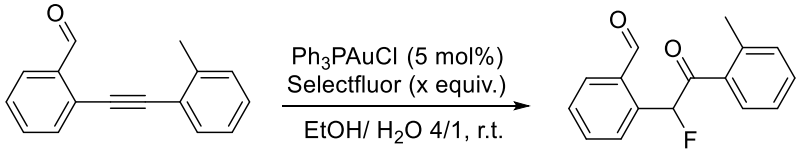


183 **P-53**

Entry	Catalyst (mol%)	Time(h)	Yield(%)
1	Ph_3PAuCl (5)	4	90
2	$Ph_3PAuNTf_2$ (5)	4	90
3	$PicAuCl_2$ (5)	4	18
4	$KAuCl_4$ (5)	4	58
5	AuCl (5)	4	trace
6	$PdCl_2$ (5)	4	51
7	$PtCl_2$ (5)	4	trace
8	$InCl_3$ (5)	4	trace
9	$CuCl_2$ (5)	4	trace
10	CuI (5)	4	trace
11	AgOTf (10)	4	90
12	$AgNO_3$ (10)	4	62
13	AgOTf (1)	12	10
14	Ph_3PAuCl (1)	12	82
15	Ph_3PAuCl (2)	6	88
16	Ph_3PAuCl (0)	6	trace

Table III3-1 Optimization of the reaction conditions (part 1)

Then, the investigation on the amount of Selectfluor from 0 to 2.0 equivalents (**Scheme III3-4**), indicated that 1.5 equivalents were the best appropriate amount of the fluorination reagent. On the other hand, we also tried to use 1.5 equivalents of NSFI in this hydration/fluorination reaction, the fluoro adduct **P-53** was observed in 79% yield, despite a much longer reaction time.



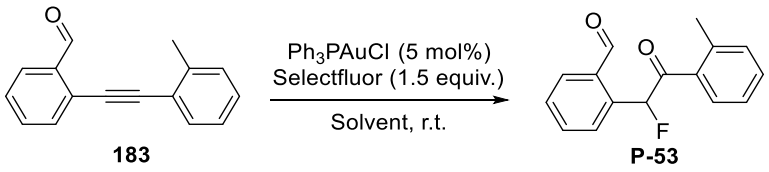
183 **P-53**

x = 0, 6 h, *0%*
1, 4 h, *85%*
2, 4 h, *81%*
0, +1.5 equiv. NFSI, 16h, *79%*

Scheme III3-4 Optimization of the reaction conditions (part 2)

Finally, the effect of the solvent on the model reaction was explored. Conducting the reaction in DCM, DMF, CH_3CN, THF, and EtOH with H_2O (**Table III3-3** entries 1-7), the best results for oxyfluorination reactions were therefore obtained in green solvents EtOH/H_2O mixture.

Interestingly, even using H_2O as the solvent, product **P-53** was obtained in 71% yield after 24 hours.



183 **P-53**

Entry	Solvent(v/v)	Time(h)	Yield(%)[b)]
1	DCM/ H_2O 4/1	5	13
2	DMF/ H_2O 4/1	5	77
3	CH_3CN/H_2O4/1	5	60
4	THF/ H_2O 4/1	5	16
5	THF/ H_2O 4/1	24	39
6	EtOH/ H_2O 1/1	4	83
7	EtOH/ H_2O 0/1	24	71

Table III3-3 Optimization of the reaction conditions (part 3)

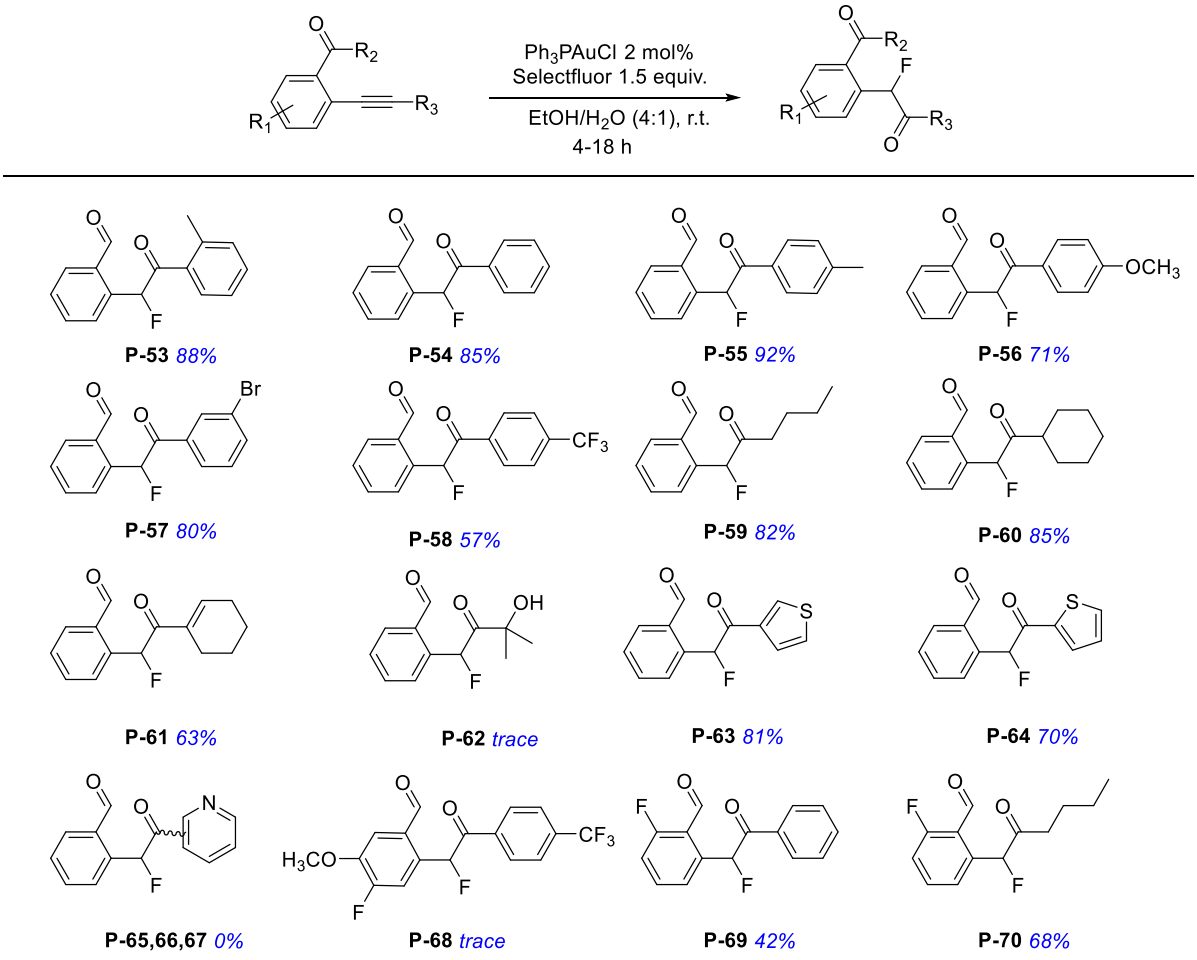
Therefore, the best yield of **P-53** was obtained by employing 2 mol% Ph_3PAuCl and 1.5 equivalents Selectfluor in 4/1 EtOH/H_2O at room temperature. Compared with Ji's work,[176] our reaction conditions were mild, e.g. room temperature versus 50 °C, preformed in green solvents (EtOH/H_2O versus DMA), with a lower catalytic amount (2 mol% gold versus 20% Ag), and shorter time (6 h versus 12 h).

3.2.2 Scope and limitations of the gold-catalyzed oxofluorination process

With a set of optimized conditions in hand, we examined the generality and the substrate scope of the gold/Selectfluor-promoted α-fluorination reaction.

As shown in **Scheme III3-5**, a variety of aldehyde-alkyne derivatives was tested. When 2-(phenylethynyl)benzaldehyde **16** was engaged as the substrate, product **P-54** was obtained in good 85% yield. As it can be seen, aldehydes bearing electron-donating groups: *ortho*-methyl-substituted (**183**), *para*-methyl-substituted (**184**), and *para*-methoxy-substituted (**185**) on the phenyl ring were efficiently transformed to the corresponding adducts **P-53**, **P-55**, **and P-56** in good to excellent yields. The substrate functionalized by *meta*-bromo (**186**) reacted smoothly with gold and Selectfluor, giving products **P-57** in 80% yield. In the case of the strong electron-withdrawing group *para*-CF_3 functionalized starting material (**187**), 57% yield of the desired adduct **P-58** was observed. When the aromatic alkyne was switched to aliphatic alkyne (**172**

and **173**), **P-59** and **P-60** were nicely isolated in good 82% and 85% yields, respectively. The cyclohexenyl derivative reacted well with gold and Selectfluor, giving **P-61** in 63% yield. Disappointingly, 2-(3-hydroxy-3-methylbut-1-yn-1-yl) benzaldehyde **175** was not compatible with the hydration/fluorination reaction. For the heterocycles, the reactivity of thiophenyl and pyridine-functionalized were explored. Sulfur-containing fluoroketones adducts **P-63** and **P-64** were prepared in 81% and 70% yields, whereas the reaction conditions were not compatible with pyridine-functionalized alkynes (**P-65** - **P-67**). On the other hand, 4-fluoro-5-methoxy-2-((4-(tri-fluoromethyl)phenyl)ethynyl) benzaldehyde gave only traces of the desired compound **P-68**, and **176**, **177** gave the corresponding products **P-69** and **P-70** in 42% and 68%, respectively.

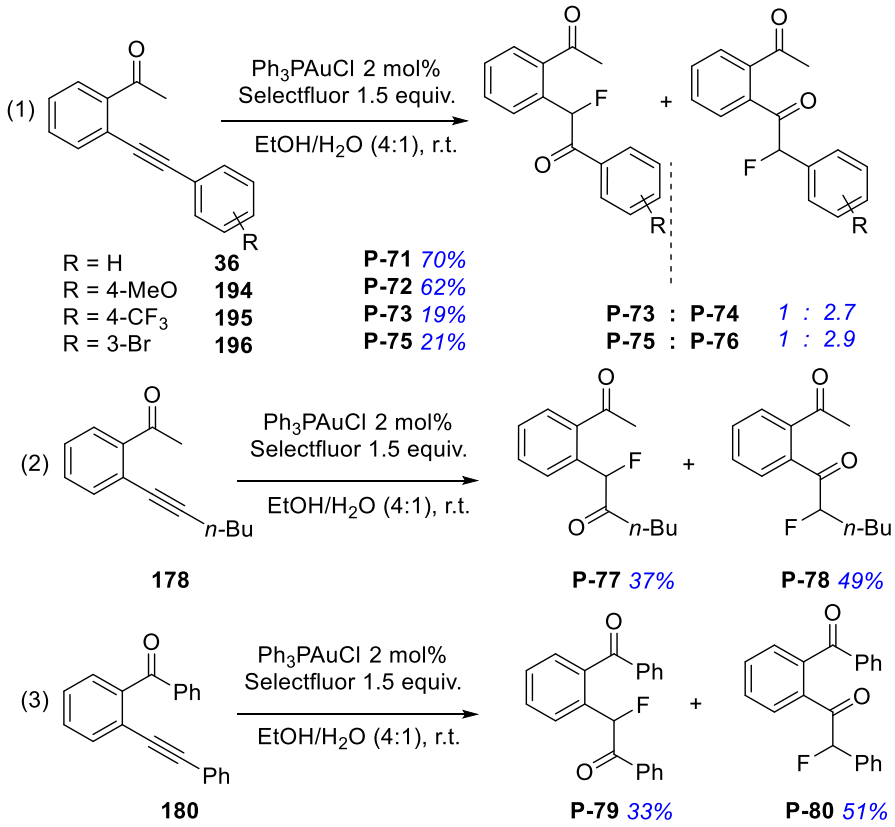


Scheme III3-5 Scope of synthesis of α-fluoroketones

The limitations were thus observed for **P-62**, **P-65** - **P-68**. For **P-62** compound, it was explained by a deactivatived complexation of alcohol with gold for **175** and excessive electronic effect for **193**. In the case of pyridine-functionalized alkynes, we proposed that it was explained by a

plausible poisoning of gold due to the Au-N complex.

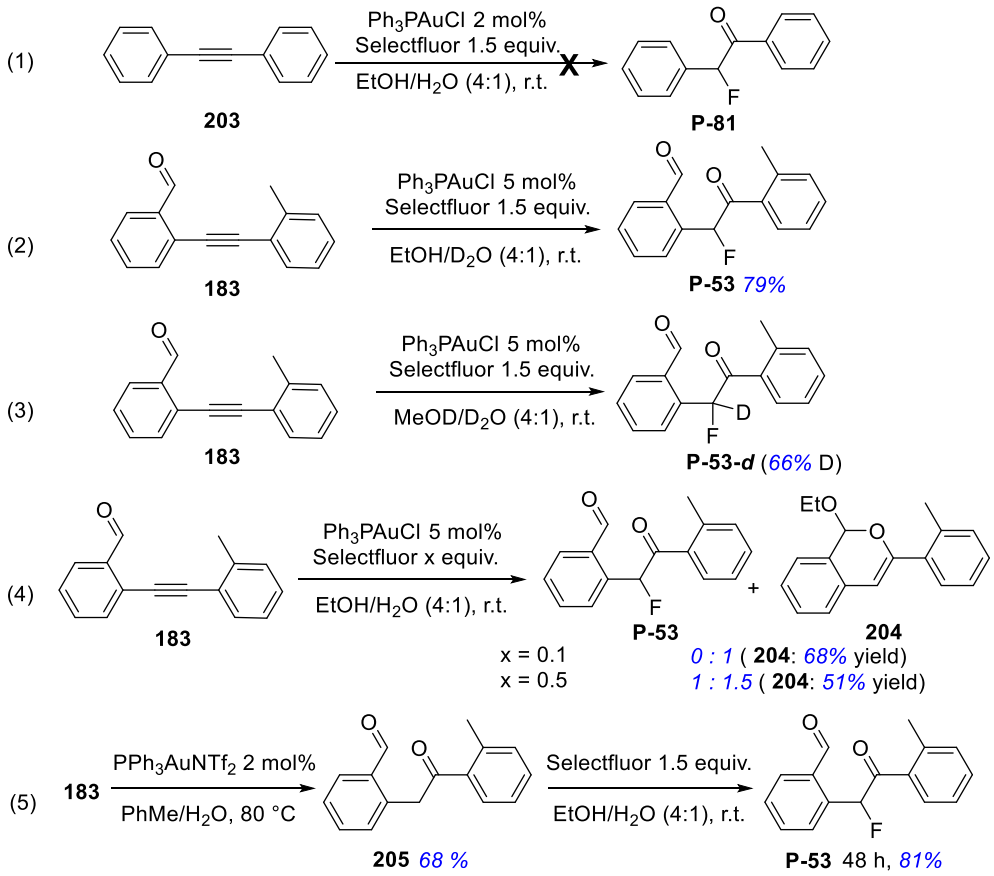
Anticipating the importance of the carbonyl aldehyde moiety and to extend the scope of the reaction, we also studied the reactivity of substituted ketones (**Scheme III3-6**). Gratifyingly, *ortho*-alkynyl ketones **36** and **194** reacted well, giving the corresponding adducts **P-71** and **P-72** in 70% and 62% yields. Compared to the reactivity of *ortho*-alkynylarylaldehydes, when substituted ketones **195** and **196** were engaged, both α- and β-fluoro regioisomers **P-73** and **P-74**, as well as **P-75** and **P-76** were identified in a 1:2.7 and 1:2.9 ratio (determined by ^{19}F NMR), and the α-fluoro products **P-73** and **P-75** were the only possible isolated isomers in 19% and 21% yields. Furthermore, when switching from an aryl to an alkyl group (substrate **178**), both isomers **P-77** and **P-78** was identified and separated, with the yields of 37% and 49%. In the case of ketone **180**, the functionalized ketones **P-79** and **P-80** were isolated in 33% and 51% yields.



Scheme III3-6 Examples of fluoroketones.

3.2.4 Mechanistic studies on gold and Selectfluor partnership

Next, we carried out five more experiments to shed light on the reaction mechanism (**Scheme III3-7**). Firstly, we performed controlled experiments in the presence of non-functionalized alkyne and in the presence of deuterated solvents. When 1,2-diphenylethyne **203** was used instead of substrate **183** with gold and Selectfluor system in EtOH/H_2O, the reaction did not proceed and no desired product 2-fluoro-1,2-diphenylethan-1-one **P-81** was obtained. It could clearly suggest that *o*-CHO moiety is a key group in this transformation and it showed that aldehyde moiety participated in the whole process by adding to the activated alkyne. (**Scheme III3-7**, Eq. 1). In the presence of deuterated solvent, such as D_2O (**Scheme III3-7**, Eq. 2), non-deuterated target **P-53** was observed, which can be correlated with the proton exchange between EtOH and D_2O. Then, we performing the reaction in a mixture of MeOD and D_2O, the deuterated fluoro derivatives **P-53-*d*** could thus be formed (**Scheme III3-7**, Eq. 3).



Scheme III3-7 Mechanistic studies

We also evaluated the importance of the partnership between PPh_3AuCl and Selectfluor (**Scheme III3-7**, Eq. 4) in order to compare with the Nevado's system.[163] When the reaction was conducted in the presence of 10 mol% of Selectfluor, the major compound was the cyclo-adduct **206** with 68% yield, resulting from classic alkoxycyclization of **183**. Increasing the

amount of Selectfluor to 50%, the formation of the fluoro derivative **P-53** was increasing, and a mixture of cyclic product **206** and fluoro derivative **P-53** in a 1.5:1 ratio was obtained.

Then, a final experiment was conducted in order to compare the fluorination step and the hydration step (**Scheme III3-7**, Eq. 5). The hydration step was evaluated and the desired adduct **205** was prepared in good 68% yield, in the presence of gold catalyst PPh_3AuNTf_2 (2 mol%) in toluene and water at high temperature. With the compound **205** in hand, the reaction of **205** with 1.5 equivalents of Selectfluor in EtOH/H_2O could indeed afford the α-fluoroketone **P-53**, but with an increasing reaction time compared to the one-pot reaction of **183** with gold and Selectfluor. Therefore, the fluorination step could occur on the ketoaldehyde without gold catalyst, but the process was kinetically slow.

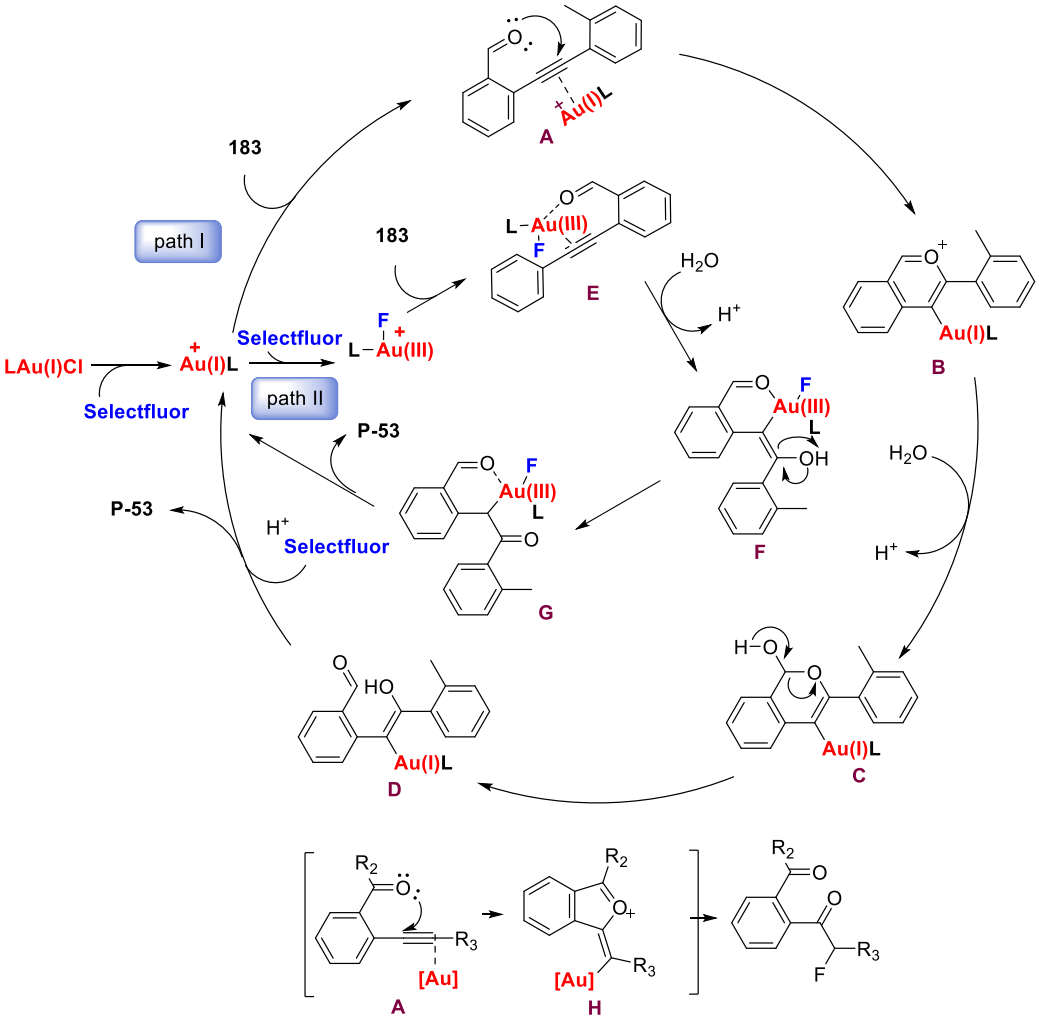
A plausible mechanism for the oxofluorination process was thus proposed accordingly as indicated in **Scheme III3-8**. We proposed there may be two gold catalytic cycles, a gold(I) pathway and a gold(III) pathway.[157] From the seminal works from Belmont,[30,38] Yamamoto, [23,28(b)] and Abbiati,[26,27,32] it is well accepted that gold catalyst easily coordinates with carbon-carbon triple, and the reaction goes *via* π-activation of alkyne **183** by coordination of the Lewis acid to form intermediate **A**. Subsequently, a 6-*endo*-*dig* attack of the carbonyl moiety leading to isobenzopyrylium intermediate **B** takes place. **B** was highly reactive towards nucleophilic addition (from H_2O) to form Au-alkenyl intermediate of **C**. Then species **C** was unstable and the six-member ring ketal easily opened to form enol **D**. Then protodemetalation and fluorination steps of metallic intermediate **D**, afforded **P-53** as shown in **Scheme III3-7**, Eq. 5.

An alternative gold(III) pathway, may be the direct Au-F interaction as proposed by Toste, Zhang, Hammond, and Xu,[172, 177] that would lead to an Au^{III} intermediate, leading to intermediate **E** through oxophilic activation of substrate **183**. Intermediate **F** was formed by hydration of **E**, which would evolve towards **G**, and then after a reductive elimination product **P-53** would end the cycle and form.

In the case of *ortho*-alkynyl ketones as substrates, the reactions were not fully regioselective and chemoselective. In the mechanism, not only 6-*endo* cycloaddition, but also 5-*exo* process was observed. The intermediate **A** could evolve toward intermediate **H**, according to a 5-*exo*-

[177] (a) G. Zhang, L. Cui, Y. Wang, L. Zhang, *J. Am. Chem. Soc.,* **2010**, *132*, 1474; (b) W. E. Brenzovich Jr., D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard III, F. D. Toste, *Angew. Chem. Int. Ed*., **2010**, *49*, 5519.

dig cyclization, which explains the formation of the other regioisomers like **P-78**, **P-80** according to the same final elementary steps (addition of water, opening of the intermediate, and fluorination). The 5-*exo*-dig cyclization was also observed in the case of the hydroamination of *ortho*-alkynyl benzylcarbamates by Catalián and co-workers.[178]

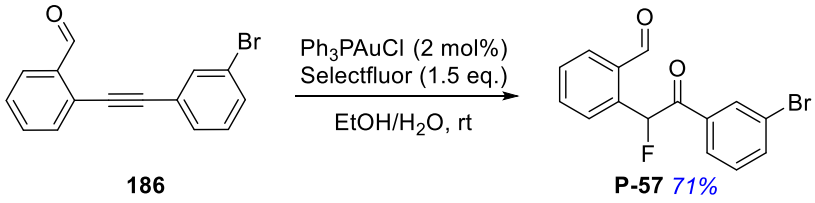


Scheme III3-8. Proposed reaction mechanism

3.2.5 Scale-up experiment and Post-functionalization reactions

The usefulness of the fluorination/hydration reaction was also established by a scale-up experiment and post-functionalization reactions. In **Scheme III3-9**, the gram-scale transformation of compound **186** led to the desired product **P-57** in 71% yield, a valuable scaffold for post-functionalization through cross-coupling reactions.

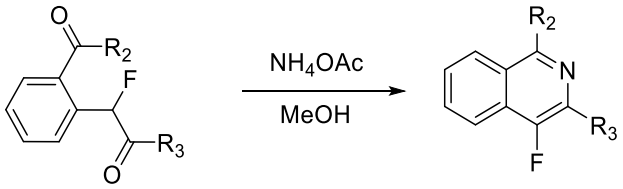
[178] Fustero, I. Ibáñez, P. Barrio, M. A. Maestro, S. Catalián, *Org. Lett.* **2013**, *15*, 4, 832.



186 P-57 *71%*

Scheme III3-9 Scale-up experiment

Then for the post-functionalization reaction in **Table III3-4**, interestingly, we demonstrated α-fluoroketones could serve as a key platform for the preparation of fluoro-isoquinoline of high pharmaceutical interest.[179] α-Fluoroketones were engaged in the presence of 3 equivalents of NH_4OAc in MeOH for 1-2 h, and gave the corresponding compounds **P-81** - **P-90** in good to excellent yields. This method was very clean, simple, and efficient to prepare 4-fluoro-isoquinoline compounds, with the yields ranged from 82% to 95%.



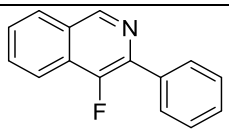
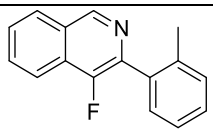
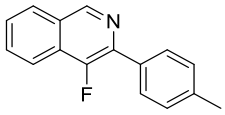
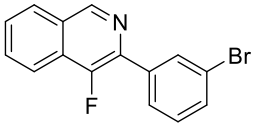
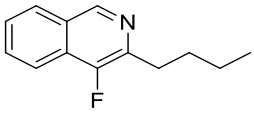
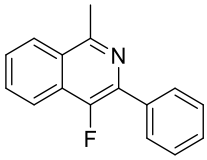
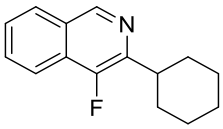
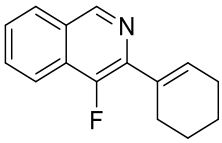
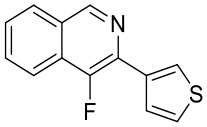
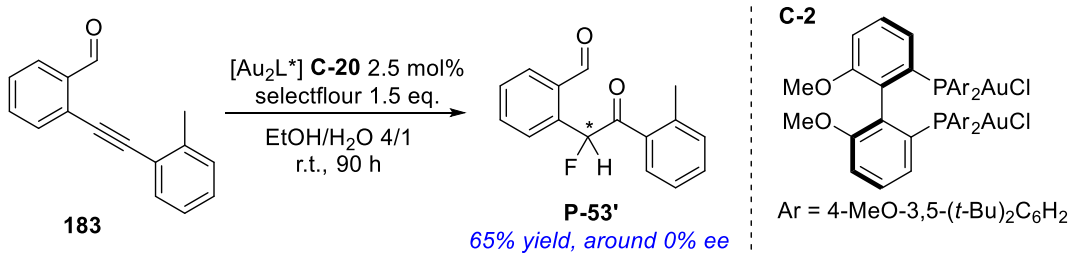
Product/yield(%)	Product/yield(%)	Product/yield(%)
 **P-82** *89%*	 **P-83** *95%*	 **P-84** *94%*
 **P-85** *93%*	 **P-86** *90%*	 **P-87** *88%*
 **P-88** *82%*	 **P-89** *83%*	 **P-90** *89%*

Table III3-4 Post-functionalization reactions

3.2.6 Asymmetric gold-catalyzed oxofluorination

[179] (a) W. Kong, J. Wei, P. Abidi, M. Lin, S. Inaba, C. Li, Y. Wang, Z. Wang, S. Si, H. Pan, S. Wang, J. Wu, Y. Wang, Z. Li, J. Liu, J. D. Jiang, *Nature Medicine,* **2004**, *10,* 1344;

For this oxofluorination process, we also wished to explore the asymmetric potential version. This study was done before emploring the mechanism of the reaction. We tested the chiral gold complex (*R*)-DTBM-MeOBIPHEP-$(AuCl)_2$ (**C-2**),[71,98] known to be efficient for several transformation, for the asymmetric gold-catalyzed reaction. The desired product was obtained in 65% yield after 90 hours, and the enantiomeric excess was less than 5 % (**Scheme III3-10**).



Scheme III3-10 Asymmetric gold-catalyzed oxofluorination

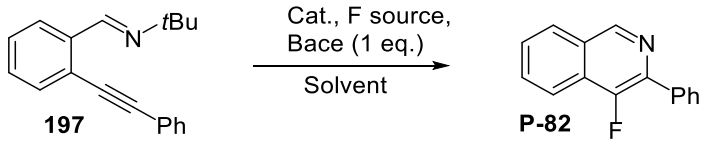
This observation was not surprising, considering the mechanism and we did not go further in this field.

3.2.7 Preliminary results in fluorination reactions of alkynyl imines

We also evaluated the catalytic efficiency of gold-catalyzed fluorination with alkynyl imines to compare with other published methods (**Table III3-5**).[180] When the reaction was conducted with 2 mol% PPh_3AuCl, 1.5 equiv. Selectfluor in $EtOH/H_2O$ (v/v 4/1) for 2 h, imine **197** was fully converted to aldehyde-yne **16** (entry 1). Similar result was observed in EtOH (entry 2). Then, according to Singh and Liu's method,[181] $AgNO_3$ was tested. The reaction conditions including solvent system, base, and fluorous sources, were investigated using the model reaction of **197** under 10 mol% $AgNO_3$ at room temperature, as summarized in entries 3-8. Whereas low yields were obtained in EtOH, CH_3CN and CH_3NO_2 (entries 3-5), 72% of **P-82** was obtained by employing 1.5 equiv. Selectfluor, 1 equiv. $NaHCO_3$, and 10 mol% $AgNO_3$ in DMA. Replacing Selectfluor by NFSI led to a clear drop of the yield (entry 7). The importance of the base was not clearly confirmed (entry 8).

[180] (a) Q. Liu, Y. Wu, P. Chen, G. Liu, *Org. Lett.*, **2013**, *15*, 6210; (b) Q. Liu, Z. Yuan, H. -Y. Wang, Y. Li, Y. Wu, T. Xu, X. Leng, P. Chen, Y. -L. Guo, Z. Lin, G. Liu, *ACS Catal.*, **2015**, *5*, 6732

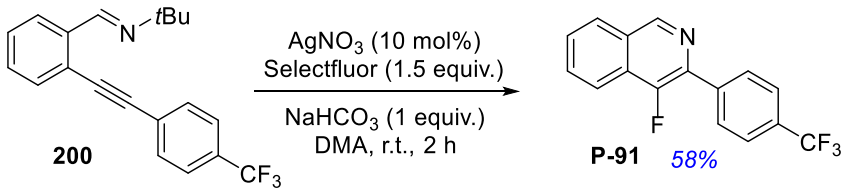
[181] (a) K. Mishra, J. B. Singh, T. Gupta, R. M. Singh, *Org. Chem. Front.*, **2017**, *4*, 1794; (b) T. Xu, G. Liu, *Org. Lett.*, **2012**, *14*, 5416.



Entry	Cat. (mol%)	Solvent	F source	Base	Time	Yield(%)
1	PPh_3AuCl (2)	$EtOH/H_2O$	Selectfluor	-	2	trace
2	PPh_3AuCl (2)	EtOH	Selectfluor	-	2	trace
3	$AgNO_3$ (10)	EtOH	Selectfluor	$NaHCO_3$	2	23
4	$AgNO_3$ (10)	CH_3CN	Selectfluor	$NaHCO_3$	16	13
5	$AgNO_3$ (10)	CH_3NO_2	Selectfluor	$NaHCO_3$	2	10
6	$AgNO_3$ (10)	DMA	Selectfluor	$NaHCO_3$	2	72
7	$AgNO_3$ (10)	DMA	NFSI	$NaHCO_3$	2	20
8	$AgNO_3$ (10)	DMA	Selectfluor	-	2	68

Table III3-5 Fluorination reactions of alkynyl imines

Under the conditions, **P-91** was prepared *via* the silver-catalyzed fluorination in 58% yield starting from **200** (**Scheme III3-10**).



Scheme III3-10 Fluorination reaction of **200**

These preliminary results were encouraging but could not be further studied because of time.

4. Conclusion

In summary, we have developed a mild, rapid, and eco-friendly straightforward access to α-fluoroketones, in the presence of a fruitful association between gold and Selectfluor starting from simple aldehyde-yne and alkynylaryl ketone derivatives as substrates. This oxofluorination green process was performed without additional acid/base or additives and reacted in environmental and friendly solvents under mild conditions ($EtOH/H_2O$, room temperature). After the reaction conditions were optimized, the scope and limitations and the influence of each part of the carbonyl-yne platform were studied, and several functionalized and synthetically relevant α-fluoroketones were isolated in good yields, up to 92%. Aldehyde-

yne derivatives as the substrate showed the fully regioselective conversion for this oxofluorination reaction (*via* 6-*endo* pathway), whereas a non-regioselective process was observed in the case of ketone-yne adducts (both 5-*exo* and 6-*endo* pathways). Then, a plausible mechanism and some light on this part for the gold-catalyzed oxofluorination reaction have been proposed, the formal hydration of the alkyne group being followed by the fluorination process. In addition, the applicability on gram scale experiment and post-functionalization reactions to prepare 4-fluoroisoquinolines were investigated. The fluoroketones were efficiently transformed into 4-fluoroisoquinolines of high pharmaceutical interest in excellent yields, up to 95% yield.

This protocol offers several advantages: i) low gold catalyst loading, ii) base or acid-free, iii) green solvent and no inert gas protection.

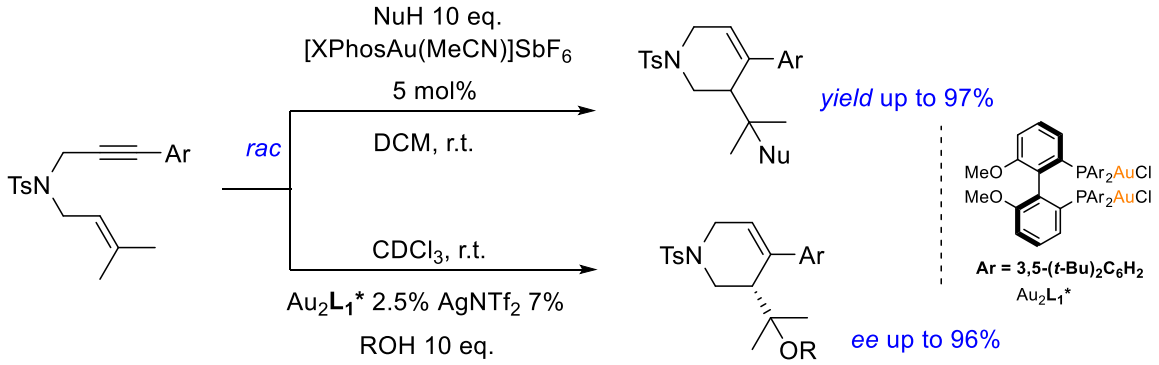
General conclusion

General conclusion

Gold and silver catalysis has been recognised to be a very powerful and an extensive synthetic tool for the chemist. Among various reactions, 1,6-enynes and *ortho*-alkynylarylaldehydes were the main focus of our work in this thesis. The first part described cyclization reactions of 1,6-enynes *via* gold and silver catalysis, while the second part was focused on fluorination/hydration on aldehyde-alkynes and alkynylaryl ketones under gold catalyst and Selectfluor.

Chapter I presented some general features on gold and silver catalysis and a comparison of gold and silver with a specific emphasis on the reactivity of aldehyde-yne derivatives.

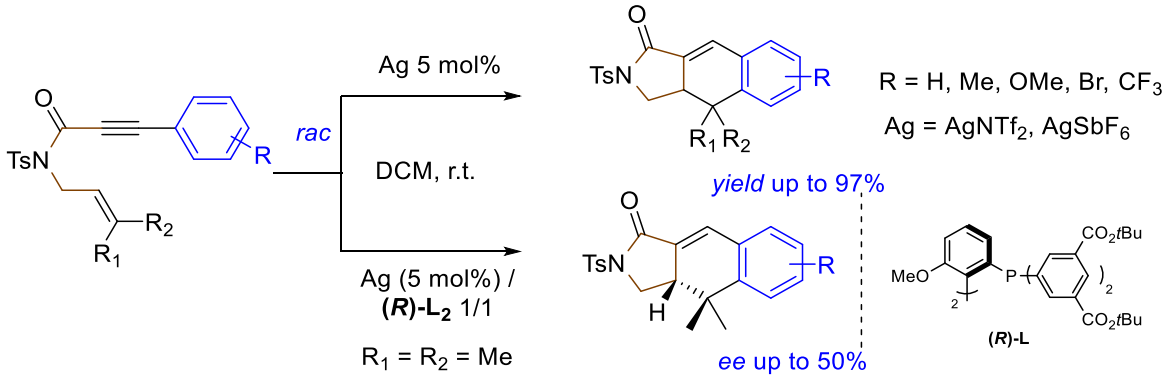
Chapter II presented the results of two projects. The work was first dedicated to the development of a domino cycloisomerization-nucleophile addition reaction of 1,6-enyne *via* a gold-promoted 6-*endo*-*dig* pathway. This transformation efficiently proceeded in the presence of [XPhosAu(MeCN)SbF_6] in DCM at room temperature, leading to a series of targeted compounds in moderate to high yields, and 31 examples were obtained with the yield up to 97%. On the other hand, the domino enantioselective alkoxycyclization reaction was studied in the presence of (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$ catalyst in $CDCl_3$ at room temperature, and the enantiomeric excess was up to 96% (**Scheme 1**).



Scheme 1 Cycloaddition reactions of 1,6-enynes *via* gold catalysis

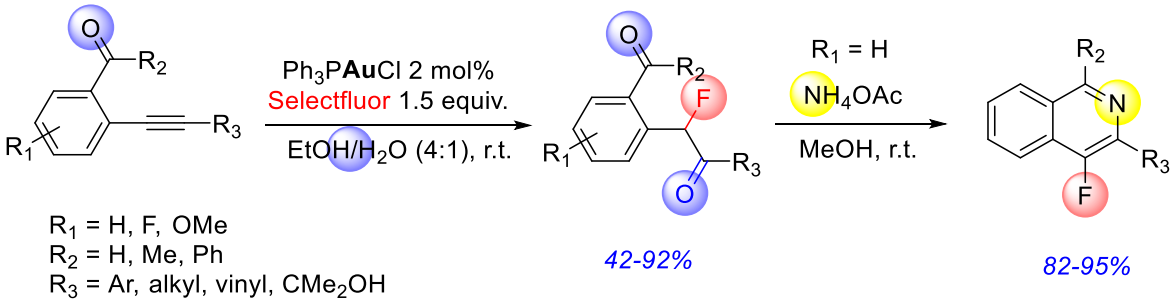
The second part of this chapter dealt with the silver-catalyzed intramolecular [4+2] cycloaddition reaction. Here, we developed an efficient, simple, and convenient route for the preparation of 4,4-dimethyl-2-tosyl-2,3,3*a*,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-ones and analogues through silver-catalyzed cycloisomerization of amide-1,6-enynes. This reaction implied a 5-*exo*-*dig* addition followed by a Friedel-Crafts arylation reaction. Consequently, asymmetric reaction conditions through Ag salts and an in-house chiral atropisomeric MeO-

BIPHEP diphosphine ligand was also investigated, affording tricycles with enantiomeric excesses up to 50% (**Scheme 2**).



Scheme 2 [4+2] Cycloaddition reactions of 1,6-enynes *via* silver catalysis

Chapter III of this thesis focused on the fluorination reaction of functionalized alkynes under gold catalysis. In this chapter, a mild and practical method for the preparation of α-fluoroketones through the oxofluorination process was developed thanks to a fruitful association between gold and Selectfluor. In the gold and Selectfluor system, the reactivity of aldehyde-alkyne, alkynylaryl ketone, and alkynyl imine derivatives was investigated. Aldehyde-yne derivatives as substrate showed the fully regioselective conversion in the gold-catalyzed oxofluorination reaction (6-*endo*), whereas both 5-*exo* and 6-*endo* pathways were observed in the case of ketone-yne derivatives. In the case of alkynyl imines did not react well under gold catalyst and Selectfluor. Finally, various α-fluoroketones were obtained with the yield up to 92%, then 4-fluoroisoquinolines of high pharmaceutical interest were transformed followed with excellent yields (**Scheme 3**).



Scheme 3 Synthesis of α-fluoroketones and 4-fluoroisoquinolines

The perspectives of this work concern the generality of the tandem cycloisomerization reactions of 1,6-enynes according to a 6-endo-process. Some other 6-*endo* processes should also be tested. The [4+2] cycloisomerization reactions need more optimization of the catalytic

chiral system, to allow the formation of the desired adduct in high enantiomeric excess. We envisage to test other chiral ligands, and to understand in more details the results optained in different solvents with the same ligand. The silver complexes will be analyzed by NMR spectroscopy. Finally, further optimization will be conducted in order to obtain a better reactivity on *ortho*-alkynylmines.

Experimental Information

1. General Information

1.1 Solvents and reagents

All the chemicals were commercially purchased from Sigma-Aldrich, Fluorochem, Alfa-Aesar, Strem, and Acros. Unless otherwise stated, commercial reagents and solvents were used without further purification. Some solvents were freshly distilled and purified, following the methods described in the literature respectively, dichloromethane (DCM), nitromethane ($MeNO_2$), acetonitrile (MeCN), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), toluene (PhMe), methanol (MeOH), ether (Et_2O), 1,4-dioxane, and so on. Reagents were either used as received from commercial sources or prepared according to the protocols provided by literature.[182]

1.2 General Analysis

Chromatography

Thin-layer chromatography (TLC) was performed on 0.20 mm pre-coated silica plates (Kieselgel 60, F254; Macherey-Nagel GmbH & Co. KG, Düren, Germany). Products were purified by column chromatography on 200-300 mesh silica gels, SiO_2. Liquid mobile phase composition was easily changed, and the common organic solvents for chromatography [petroleum ether (PE), ethyl acetate (EtOAc), toluene, and pentane (P)] were used without further purification. The spots on the TLC were detected with UV 254 nm light or revealed with the Kagi-Mosher solution (pale pink solution, composed of 5 mL *p*-anisaldehyde, 8 mL concentrated sulfuric acid, and 200 mL ethanol).

Nuclear magnetic resonance (NMR) spectroscopy

NMR spectra (^1H, ^{13}C, ^{19}F, ^{31}P, COSY, DEPT135, HSQC, HMQC) were recorded on Bruker™ Avance spectrometer at 200 MHz and 400 MHz (Bruker, Rheinstetten, Germany) at room temperature (20 ± 3 °C). All NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, and solvent residual signals were used as internal standards. The coupling constants *J* were expressed in Hertz [Hz], and the chemical shifts δ were reported in parts per million (ppm) relative to the appropriate solvent signal. The spin multiplicities of signals were indicated as s = singlet, d = doublet, dd = double doublet, t = triplet, q = quadruplet, m = multiplet.

[182] D. D. Perrin, W. L. F. Armarego, Purification of laboratory chemiicals 3rd edition, Pegamon Press, Oxford, **1988**.

Mass spectrometry (MS)

The mass spectra were recorded by GC/MS analyses, which were performed on a Shimadzu QP2010S-MS chromatograph [electronic impact (EI), 70 eV], equipped with an SLB-5ms capillary column (thickness 0.25 mm, length 30 m, and inside diameter 0.25 mm). High-resolution mass spectroscopy (HRMS) data of the new compounds were performed by Institut de Chimie de Nice using a Thermo Vanquish UHPLC-Q-Exactive Focus Mass Spectrometer equipped with heated-electrospray ionization (H-ESI) source operated in a positive mode, and Institut de Recherches Servier, using a DFS instrument (Thermo Scientific) coupled to gas chromatography as inlet method (EI-source).

Melting Point (m.p.)

Melting point values were recorded on a Köfler bench.

X-Ray Diffraction (XRD)

XRD analysis was performed at Aix-Marseille University (Dr. Michel Giorgi). A suitable crystal for compound **P-41** was measured on a Rigaku Oxford Diffraction SuperNova diffractometer at room temperature at the MoKα radiation (λ=0.71073 Å). Data collection reduction and multiscan ABSPACK correction were performed with CrysAlisPro (Rigaku Oxford Diffraction). Using Olex2 the structures were solved by intrinsic phasing methods with SHELXT and SHELXL was used for full-matrix least-squares refinement. All H-atoms were found experimentally and their coordinates and Uiso parameters were constrained to 1.5 Ueq (parent atoms) for the methyls and to 1.2 Ueq (parent atom) for the other carbons.

1.3 Analysis of chiral compounds

High Performance Liquid Chromatography (HPLC) and Supercritical Fluid Chromatography (SFC)

The enantiomeric excesses were determined by HPLC and SFC auto sampler (AS-4350) analyzes on a JASCO® instrument, a photodiode array detector (MD-4010) with a variable wavelength from 200 nm to 900 nm, a CO_2 pump (PU-4380), an HPLC pump (PU-4180), a column oven (CO-4060) equipped with chiral columns Daicel Chiralcel OD, OJ, and Chiralpak IA, AD, AD-H and IF, a control box (LC-NetII/ADC) and a back pressure regulator (BP-4340). The signal is recorded and analyzed on a computer equipped with ChromNav® software. HPLC grade hexane, isopropanol, and methanol were used.

Electronic Circular Dichroism (CD)

Electronic CD analysis was performed at University Côte d'Azur on a Jasco apparatus. Circular dichroism experiments were recorded at 20 °C on a Jasco J-810 spectropolarimeter. All the spectra were run in duplicate with 2 µM solution of the canonical and labeled model dsDNA (DFK – X opposite A, T, G, C, or Ab = abasic) in PBS pH 7.4 (50 mM sodium phosphate, 150 mM NaCl).

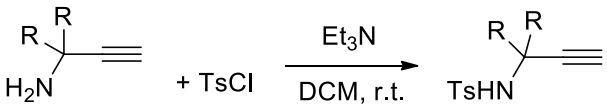
Optical Rotation

The optical rotation was measured on an Anton Paar® MCP-100 polarimeter at 589 nm (l = 0.5 dm, 20°C).

2. Experimental procedures and characterization data

2.1 Synthesis of amide-1,6-enynes substrates

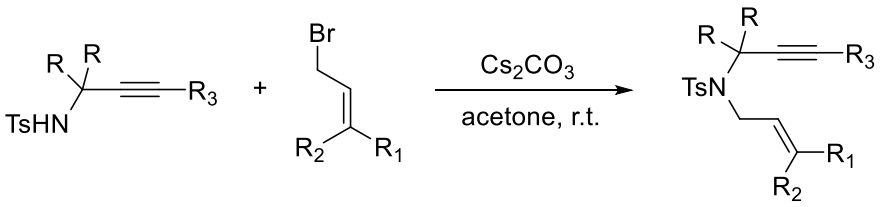
General procedure A:



R = H, Me

In a dried round-bottomed flask, TsCl (30 mmol, 1 equiv.) was dissolved in the mixture of Et_3N (75 mmol, 2.5 equiv.) and 50 mL CH_2Cl_2, amine (31.5 mmol, 1.05 equiv.) was then added drop-wise. The resulting mixture was stirred for 2 h at room temperature. After completion of the reaction by TLC monitoring, the solvents were evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography to give the corresponding sulfonamide product as a yellow solid.

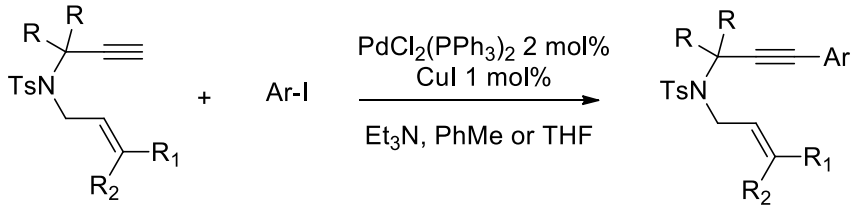
General procedure B:



Sulfonamide (1 equiv.), allylic bromide (1-1.2 equiv.), and 20 mL acetone were mixed in a flask. Cs_2CO_3 (1-1.2 equiv.) was added, and the reaction mixture was stirred at room temperature for

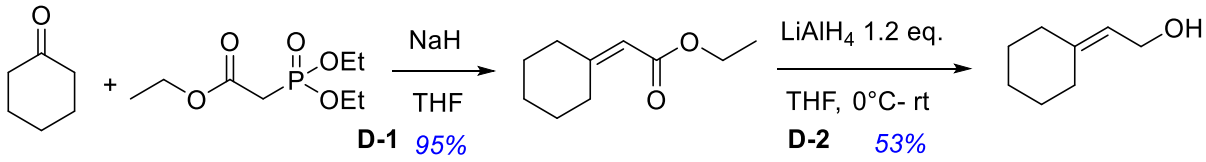
3 h. After complete consumption of the starting material, monitored by TLC, the mixture was filtered through a pad of silica gel using DCM as eluting solvent. The solvents were evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography to give the corresponding enyne.

General procedure C:



Starting from the enyne (1 equiv.) and the aryl iodide (1-1.2 equiv.) in 3/1 v/v anhydrous PhMe or THF/Et_3N, under N_2 atmosphere, [$PdCl_2(PPh_3)_2$] (2 mol%) and CuI (1 mol%) were added to the mixture. The reaction solution was stirred at room temperature until the starting material was consumed completely by TLC monitoring. The resulting solution was extracted with DCM/aqueous NH_4Cl saturated solution several times. The organic phase was dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Then the crude product was purified by silica-gel column chromatography to give the awaited product.

General procedure D:

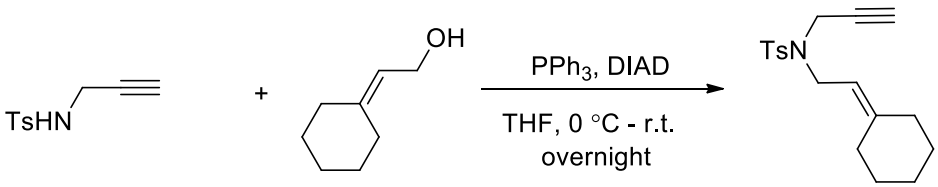


D-1 In a dried round-bottomed flask, NaH (20 mmol, 1.25 equiv.) was added wisely in dry THF (100 mL), then triethyl phosphonoacetate (20 mmol, 1.25 equiv.) was added. The bubbling solution was stirred one hour at room temperature, and cyclohexanone (16 mmol, 1 equiv.) was added to the mixture. The reaction was stirred for 16 h, and $Na_2SO_4{\cdot}10H_2O$ was added to inactivate NaH. The mixture was diluted with Et_2O and washed with a saturated aqueous $NaHCO_3$ solution, dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum. The product was isolated after a silica-gel column chromatography as a colorless liquid.

D-2 In the solution of ethyl 2-cyclohexylideneacetate (15 mmol, 1 equiv.) and 20 mL THF, the suspension of $LiAlH_4$ (18 mmol, 1.2 equiv.) in 30 mL THF was added at 0 °C. After stirring during 10 min at 0 °C, the reaction solution was stirred at room temperature for 30 min. After TLC monitoring, the reaction was quenched by $Na_2SO_4{\cdot}10H_2O$ and filtered through a short pad of

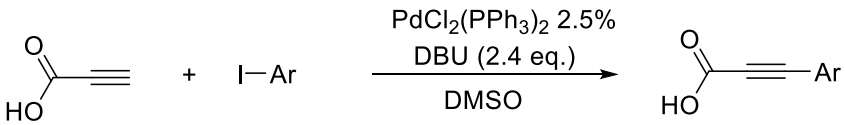
silica gel using DCM as a solvent. Afterward, the solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography, to afford the alcohol as a colorless oil.[183]

General procedure E:



In a dried round-bottomed flask, sulfonamide (5 mmol, 1 equiv.) was dissolved in dry THF (10 mL), and PPh_3 (5.5 mmol, 1.1 equiv.) and 2-cyclohexylideneethan-1-ol (7.5 mmol, 1.5 equiv.) were sequentially added. The mixture was cooled to 0 °C with an ice-water bath, and diisopropyl azodicarboxylate DIAD (5.5 mmol, 1.1 equiv.) was added drop-wise to the system. The resulting solution was stirred overnight at room temperature. The solvent was removed under reduced pressure. The crude product was extracted several times with DCM/H_2O, washed with brine, and the organic phase was dried with anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5/1) to afford the product.

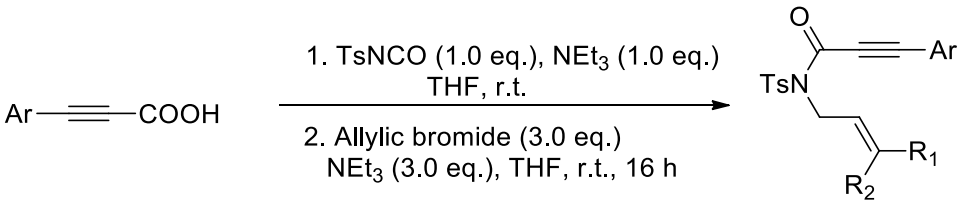
General procedure F:



A dried round-bottom flask was charged with aryl iodide (10 mmol, 1 equiv.), 2,3,4,6,7,8,9,10-Octahydropyrimidol[1,2-*a*]azepine DBU (24 mmol, 2.4 equiv.), tetrakis(triphenylphosphine)-palladium(0) $Pd(PPh_3)_4$ (2.5 mol%) and DMSO (10 mL) under N_2 atmosphere. The solution of propiolic acid (12 mmol, 1.2 equiv.) in DMSO (10 mL) was poured to the flask, and the mixture was stirred at room temperature for 16-24 h. Afterward, the reaction mixture was diluted with EtOAc (25.0 mL), and extracted with $NaHCO_3$ (sat. aq.). The aqueous layer was separated, acidified to pH=1 by adding cold HCl solution (1 N), and extracted with DCM. The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by silica gel column chromatography [ethyl acetate/hexane, 1:4 with HOAc (1 %, v/v)].[105]

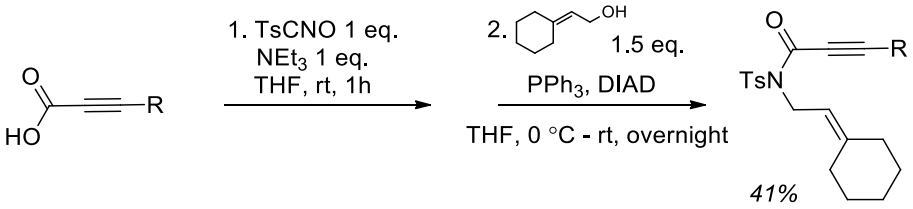
[183] R. J. Comito, F. G. Finelli, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2013**, *135*, 9358.

General procedure G:



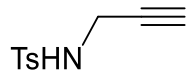
In a 100 mL dried round-bottomed flask, the carboxylic acid (10 mmol, 1 equiv.) was dissolved in dry THF (20 mL) under N_2 atmosphere at room temperature, tosyl isocyanate (10 mmol, 1 equiv.) was added, and the mixture was stirred for 10 minutes. Then NEt_3 (1 - 5 equiv.) was added drop-wise to the open flask, to allow a release of the formed CO_2. After stirring during 2 h, NEt_3 (3.0 equiv.) and allylic bromide (2 - 3 equiv.) were sequentially added in the system, and the mixture solution was stirred overnight. After complete consumption of the starting materials (monitored by TLC), the mixture was filtered through a short pad of silica gel using DCM as a solvent. After evaporation, the crude product was purified by silica-gel column chromatography (petroleum ether/ethyl acetate 5/1) to give the corresponding enynamide product.[102]

General procedure H:



3-phenylpropiolic acid (5 mmol, 1 equiv.) was dissolved in dry THF (10 mL)), under N_2 at room temperature, in a dried round-bottomed flask, then tosyl isocyanate was added (5 mmol, 1 equiv.) and the mixture was stirred for 10 minutes. Next, NEt_3 (1.0 equiv.) was added drop-wise to the open flask, to allow a release of the formed CO_2. After stirring during 2 h, PPh_3 (5.5 mmol, 1.1 equiv.) and 2-cyclohexylideneethan-1-ol (1.5 equiv.) were sequentially added. Afterward, putting the flask in an ice-water bath, diisopropyl azodicarboxylate (5.5 mmol, 1.1 equiv.) was added drop-wise. The resulting mixture was warmed to room temperature and further stirred for 16 h overnight. Then the mixture was extracted with DCM/H_2O several times, washed with brine. The organic phase was dried with anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5/1).

91 4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide



Chemical Formula: $C_{10}H_{11}NO_2S$

Molecular Weight: 209.26

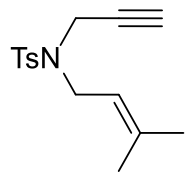
Aspect: Yellow solid

R_f = 0.22 (PE / EtOAc, 4/1)

Following the general procedure **A**, TsCl (5.72 g, 30 mmol, 1 equiv., M = 190.65 g/mol) was dissolved in the mixture of Et_3N (10.5 mL, 75 mmol, 2.5 equiv. M = 101.19 g/mol) and CH_2Cl_2 (50 mL). Then prop-2-yn-1-amine (2.02 mL, 31.5 mmol, 1.05 equiv., M = 55.08 g/mol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, and the product **91** was obtained as a yellow solid (5.96 g, 95%). The spectral data were identical to the literature.[66]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.74 (t, *J* = 5.8 Hz, 1H), 3.82 (dd, *J* = 5.8, 2.6 Hz, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.5 Hz, 1H).

67 4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide



Chemical Formula: $C_{15}H_{19}NO_2S$

Molecular Weight: 277.38

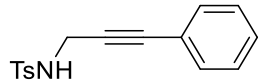
Aspect: White solid

R_f = 0.45 (PE / EtOAc, 9/1)

Following the general procedure **B**, sulfonamide **91** (5.23 g, 25 mmol, 1 equiv., M = 209.26 g/mol), 1-bromo-3-methylbut-2-ene (3.5 mL, 27.5 mmol, 1.1 equiv., M = 149.03 g/mol, d = 1.29), and Cs_2CO_3 (8.9 g, 27.5 mmol, 1.1 equiv., M = 325.82g/mol) were added to acetone (50 mL) at room temperature. The product was obtained as a white solid (6.7 g, 97% yield). The spectral data were identical to the literature.[89]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 5.10 (t, *J* = 7.1 Hz, 1H), 4.07 (s, 2H), 3.81 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.98 (s, 1H), 1.72 (s, 3H), 1.67 (s, 3H).

92 4-Methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide



Chemical Formula: $C_{16}H_{15}NO_2S$

Molecular Weight: 285.36

Aspect: White solid

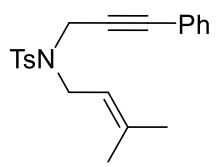
R_f = 0.32 (PE / EtOAc, 4/1)

Following the general procedure **C**, sulfonamide **91** (4.18 g, 20 mmol, 1 equiv., M = 209.26)

and iodobenzene (4.28 g, 21 mmol, 1.05 equiv., M = 204.01 g/mol) were added to Et_3N (20 mL) and PhMe (60 mL), in the presence of $[PdCl_2(PPh_3)_2]$ (280 mg, 2 mol%, M = 701.90 g/mol) and CuI (38 mg, 1 mol%, 190.45 g/mol). The product was obtained as a white solid (3.94 g, 69% yield). The spectral data were identical to the literature.[66]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.22 (m, 4H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.06 (d, *J* = 5.6 Hz, 2H), 2.33 (s, 3H).

77	**4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 353.48

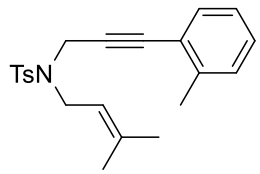
Aspect: White solid

R_f = 0.48 (PE / EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (5.55 g, 20 mmol, 1 equiv., M = 277.38 g/mol) and iodobenzene (4.28 g, 21 mmol, 1.05 equiv., M = 204.01 g/mol) were added to Et_3N (20 mL) and PhMe (60 mL). The mixture was stirred at room temperature for 18 h, in the presence of $[PdCl_2(PPh_3)_2]$ (280 mg, 2 mol%, M = 701.90 g/mol) and CuI (38 mg, 1 mol%, 190.45 g/mol). The product was obtained as a white solid (5.02 g, 71% yield). The spectral data were in accordance with literature. [66]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.08 (m, 4H), 6.94 (d, *J* = 8.3 Hz, 2H), 5.06 (d, *J* = 7.3 Hz, 1H), 4.17 (s, 2H), 3.77 (d, *J* = 7.4 Hz, 2H), 2.22 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H).

93	**4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-(*o*-tolyl)prop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_{22}H_{25}NO_2S$

Molecular Weight: 367.51

Aspect: White solid

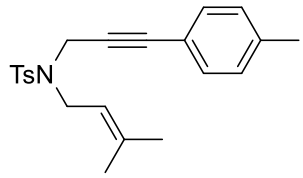
R_f = 0.46 (PE / EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 1-iodo-2-methylbenzene (2.62 g, 12 mmol, 1.2 equiv., M = 218.04 g/mol) were added to Et_3N (10 mL) and THF (30 mL). The mixture was stirred at room temperature for 18 h, in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a white solid (2.3 g, 63% yield). The spectral data were

in accordance with literature.[184]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.16 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.04 – 6.99 (m, 1H), 5.25 – 5.12 (m, 1H), 4.33 (s, 2H), 3.89 (d, *J* = 7.3 Hz, 2H), 2.27 (s, 3H), 2.16 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H).

94	**4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-(p-tolyl)prop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_{22}H_{25}NO_2S$

Molecular Weight: 367.51

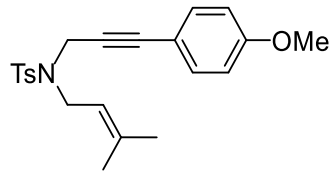
Aspect: White solid

R_f = 0.48 (PE / EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 1-iodo-4-methylbenzene (2.62 g, 12 mmol, 1.2 equiv., M = 218.04 g/mol) were added to Et_3N (10 mL) and THF (30 mL) at room temperature, in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a white solid (2.2 g, 60% yield). The spectral data were in accordance with literature.[100]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.19 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.17 (t, *J* = 7.3 Hz, 1H), 4.27 (s, 2H), 3.87 (d, *J* = 7.3 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H).

95	***N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide**



Chemical Formula: $C_{22}H_{25}NO_3S$

Molecular Weight: 383.51

Aspect: Light yellow solid

R_f = 0.30 (PE / EtOAc, 9/1)

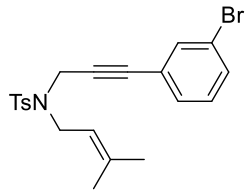
Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 4-iodoanisole (2.57 g, 11 mmol, 1.1 equiv., M = 234.04 g/mol) were added to Et_3N (10 mL) and PhMe (30 mL) at room temperature, in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a

[184] L. Zhang, Z. -Z. Zhou, Y. -T. He, L. -H. Li, J. -W. Ma, Y. -F. Qiu, P. -X. Zhou, X. -Y. Liu, P. F. Xu, Y. -M. Liang, *J. Org. Chem.*, **2016**, *81*, 66.

light yellow solid (2.6 g, 68% yield). The spectral data were in accordance with literature.[100]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.17 (tt, *J* = 7.4, 1.5 Hz, 1H), 4.26 (s, 2H), 3.86 (d, *J* = 7.4 Hz, 2H), 3.79 (s, 3H), 2.35 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H).

96	***N*-(3-(3-Bromophenyl)prop-2-yn-1-yl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzene-sulfonamide**



Chemical Formula: $C_{21}H_{22}BrNO_2S$

Molecular Weight: 432.38

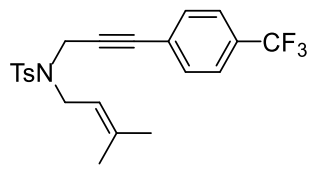
Aspect: Light yellow solid

R_f = 0.47 (PE / EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 1-bromo-3-iodobenzene (3.0 g, 10.5 mmol, 1.05 equiv., M = 282.91 g/mol) were added to Et_3N (10 mL) and PhMe (30 mL), in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a light yellow solid (3.46 g, 80% yield). The spectral data were in accordance with literature.[100]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.14 – 7.08 (m, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 5.17 (t, *J* = 7.3 Hz, 1H), 4.27 (s, 2H), 3.86 (d, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 1.75 (s, 3H), 1.68 (s, 3H).

97	**4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_{22}H_{22}F_3NO_2S$

Molecular Weight: 421.48

Aspect: Yellow solid

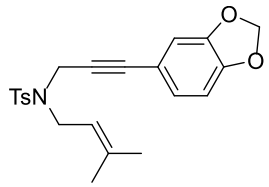
R_f = 0.48 (PE/ EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (1.39 g, 5 mmol, 1 equiv., M = 277.38 g/mol) and 4-iodobenzotrifluoride (1.63 g, 6 mmol, 1.2 equiv., M = 272.01 g/mol) were added to Et_3N (5 mL) and PhMe (15 mL), in the presence of $[PdCl_2(PPh_3)_2]$ (70 mg, 2 mol%, M = 701.90 g/mol) and CuI (10 mg, 1 mol%, 190.45 g/mol). The product was obtained as a yellow solid (1.7 g, 80% yield). The spectral data were in accordance with literature.[100]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 5.15 − 5.19 (m, 1 H), 4.29 (s, 2 H), 3.88 (d, *J* = 7.2 Hz, 2

H), 2.33 (s, 3 H), 1.75 (s, 3 H), 1.68 (s, 3 H).

98	***N*-(3-(Benzo[*d*][1,3]dioxol-5-yl)prop-2-yn-1-yl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide**



Chemical Formula: $C_{22}H_{23}NO_4S$

Molecular Weight: 397.49

Aspect: White solid

R_f = 0.30 (PE / EtOAc, 9/1)

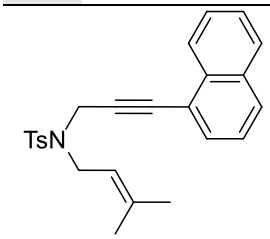
Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 5-iodo-1,3-benzodioxole (2.7 g, 11 mmol, 1.1 equiv., M = 248.02 g/mol) were added to Et_3N (10 mL) and PhMe (30 mL), in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a light yellow solid (2.9 g, 76% yield, m.p. 99-101 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.40 (d, *J* = 1.5 Hz, 1H), 5.98 – 5.87 (m, 2H), 5.15 (t, *J* = 7.3 Hz, 1H), 4.23 (s, 2H), 3.85 (d, *J* = 7.3 Hz, 2H), 2.36 (s, 3H), 1.73 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.0, 147.3, 143.4, 139.0, 136.3, 129.5, 127.9, 126.1, 118.2, 115.6, 111.5, 108.3, 101.4, 85.3, 80.6, 44.2, 36.4, 26.0, 21.5, 18.0.

HRMS (ESI) *m/z* calc. for $[C_{22}H_{23}NO_4S+H]^+$ 398.1421, found: 398.1416.

99	**4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-(naphthalen-1-yl)prop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_{25}H_{25}NO_2S$

Molecular Weight: 403.54

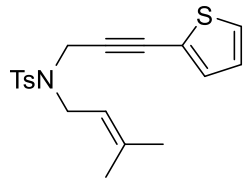
Aspect: Light yellow solid

R_f = 0.37 (PE / EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 1-iodonaphthalene (2.8 g, 11 mmol, 10 equiv., M = 254.07 g/mol) were added to Et_3N (10 mL) and PhMe (30 mL), in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a light yellow solid (2.02 g, 50% yield). The spectral data were in accordance with literature.[66]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.76 (m, 5H), 7.53 – 7.42 (m, 2H), 7.37 – 7.32 (m, 1H), 7.29 (d, *J* = 6.1 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.28 – 5.17 (m, 1H), 4.45 (s, 2H), 3.97 (d, *J* = 7.3 Hz, 2H), 2.12 (s, 3H), 1.76 (s, 3H), 1.70 (s, 3H).

100 **4-Methyl-N-(3-methylbut-2-en-1-yl)-*N*-(3-(thiophen-2-yl)prop-2-yn-1-yl)benzene-sulfonamide**



Chemical Formula: $C_{19}H_{21}NO_2S_2$

Molecular Weight: 359.50

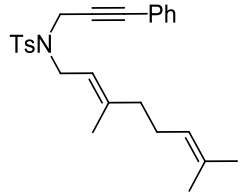
Aspect: Light yellow solid

R_f = 0.52 (PE / EtOAc, 9/1)

Following the general procedure **C**, substrate **67** (2.77 g, 10 mmol, 1 equiv., M = 277.38 g/mol) and 2-iodothiophene (2.5 g, 12 mmol, 10 equiv., M = 210.03 g/mol) were added to Et_3N (10 mL) and PhMe (30 mL), in the presence of $[PdCl_2(PPh_3)_2]$ (140 mg, 2 mol%, M = 701.90 g/mol) and CuI (19 mg, 1 mol%, 190.45 g/mol). The product was obtained as a light yellow solid (3.3 g, 92% yield). The spectral data were in accordance with literature.[100]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.19(t, *J* = 6.4 Hz, 1H), 6.90 (d, *J* = 3.2 Hz, 2H), 5.16 (t, *J* = 7.3 Hz, 1H), 4.29 (s, 2H), 3.84 (d, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.75 (s, 3H), 1.69 (s, 3H).

101 **(*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)-benzenesulfonamide**



Chemical Formula: $C_{26}H_{31}NO_2S$

Molecular Weight: 421.60

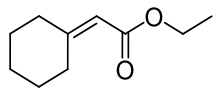
Aspect: Brown oil

R_f = 0.43 (PE / EtOAc, 9/1)

Following the general procedure **B**, substrate **92** 570 mg (2 mmol, 1 equiv., M = 285.36 g/mol), geranyl bromide 530 mg (2.2 mmol, 1.1 equiv., M = 217.15 g/mol), and Cs_2CO_3 717 mg (2.2 mmol, 1.1 equiv., M = 325.82g/mol) were added to 5 mL acetone at room temperature. The product was obtained in 92% yield (776 mg) as a brown oil. The spectral data were in accordance with literature.[99]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.17 (m, 5H), 7.07 (dd, *J* = 7.8, 1.9 Hz, 2H), 5.18 (t, *J* = 7.3 Hz, 1H), 5.07 (t, *J* = 6.0 Hz, 1H), 4.30 (s, 2H), 3.92 (d, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 2.18 – 2.01 (m, 4H), 1.71 (s, 6H), 1.62 (s, 3H).

102 **Ethyl 2-cyclohexylideneacetate**



Chemical Formula: $C_{10}H_{16}O_2$

Molecular Weight: 168.24

Aspect: Colorless liquid

R_f = 0.29 (PE / EtOAc, 4/1)

Following the general experimental procedure **D-1**, 600 mg NaH (20 mmol, 1.25 equiv., M = 24.01 g/mol) was added drop-wise to 100 mL THF, and 4.0 mL of triethyl phosphonoacetate (20 mmol, 1.25 equiv., M = 224.19 g/mol) were added to the suspension. After one hour, cyclohexanone (1.72 mL, 16 mmol, 1 equiv., M = 98.15 g/mol) was added. The product was isolated as a colorless liquid (2.55 g, 95% yield).[183]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.55 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.87 – 2.72 (m, 2H), 2.22 – 2.08 (m, 2H), 1.67 – 1.50 (m, 6H), 1.23 (t, *J* = 7.1 Hz, 3H).

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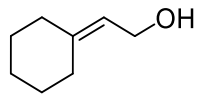
103 **2-Cyclohexylideneethan-1-ol**



Chemical Formula: $C_8H_{14}O$

Molecular Weight: 126.20

Aspect: Colorless oil

R_f = 0.40 (PE / EtOAc, 4/1)

Following the general experimental procedure **D-2**, 684 mg $LiAlH_4$ (18 mmol, 1.2 equiv., M = 37.95 g/mol) in 30 mL THF was added dropwise to a solution of ethyl 2-cyclohexylideneacetate (2.5 g, 15 mmol, M = 168.24 g/mol) in 20 mL THF at 0°C. The product was isolated as a colorless liquid (1.0 g, 53% yield).[183]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 5.33 (t, *J* = 7.1 Hz, 1H), 4.10 (d, *J* = 7.1 Hz, 2H), 2.15 (m, 2H), 2.08 (m, 2H), 1.71 (s, 1H), 1.57 – 1.44 (m, 6H).

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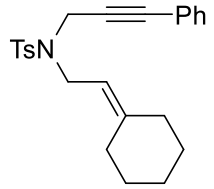
104 ***N*-(2-Cyclohexylideneethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl) benzenesulfonamide**



Chemical Formula: $C_{24}H_{27}NO_2S$

Molecular Weight: 393.55

Aspect: White solid

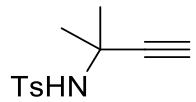
R_f = 0.48 (PE / EtOAc, 9/1)

Following the general experimental procedure **E**, substrate **91** (1.05 g, 5 mmol, M = 209.26 g/mol), PPh_3 (1.44 g, 5.5 mmol, 1.1 equiv., M = 262.29 g/mol) and 2-cyclohexylideneethan-1-ol (947 mg, 7.5 mmol, 1.5 equiv., M = 126.20 g/mol) were sequentially added. Afterwards, putting the flask in ice-water bath, DIAD (1.1 mL, 5.5 mmol, 1.1 equiv., M = 202.21 g/mol, d = 1.027) was added dropwise. The product was obtained as a white solid (1.18 g, 3.75 mmol, 75%). Then **C** (816 mg), iodobenzene (4 mmol, 1.05 equiv., M = 204.01 g/mol), 53 mg $[PdCl_2(PPh_3)_2]$ (2 mol%), and 14 mg CuI (1 mol) were added to 3.75 mL of Et_3N and 11.25 mL of PhMe at room temperature for 18 h. The product **104** was obtained as a white solid (886

mg, 60% yield). The spectral data were in accordance with literature.[185]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.19 (m, 5H), 7.04 (d, *J* = 8.0, 2H), 5.12 (t, *J* = 7.5 Hz, 1H), 4.29 (s, 2H), 3.89 (d, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.24 – 2.14 (m, 2H), 2.11 (s, 2H), 1.60 – 1.43 (m, 6H).

105 4-Methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide



Chemical Formula: $C_{12}H_{15}NO_2S$

Molecular Weight: 237.32

Aspect: Yellow solid

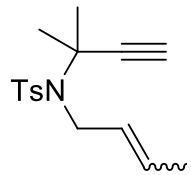
R_f = 0.40 (PE / EtOAc, 4/1)

Following the general experimental procedure **A**, 5 g of TsCl (26.3 mmol, 1 equiv., M = 190.65 g/mol) were dissolved in a mixture of 9 mL Et_3N (2.5 equiv. M = 101.19 g/mol) and 25 mL CH_2Cl_2, then 2.3 mL 2-methylbut-3-yn-2-amine (26.3 mmol, 1 equiv., M = 83.13 g/mol) was added dropwise. The resulting mixture was stirred for 2 h at room temperature, and 6.0 g of the corresponding sulfonamide product was obtained as a yellow solid (96% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.94 (s, 1H), 2.42 (s, 3H), 2.09 (s, 1H), 1.55 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.2, 138.8, 129.3, 127.6, 85.5, 71.2, 50.0, 30.7, 21.5.

106 *N*-(But-2-en-1-yl)-4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide



Chemical Formula: $C_{16}H_{21}NO_2S$

Molecular Weight: 291.41

Aspect: Light yellow solid

R_f = 0.75 (PE / EtOAc, 6/1)

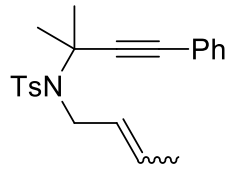
Following the general procedure **B**, 2.37 g sulfonamide **105** (10 mmol, 1 equiv., M = 237.32 g/mol), 1.33 mL crotyl bromide (11 mmol, 1.1 equiv., M = 135.00 g/mol, d = 1.31), and 3.58 g Cs_2CO_3 (11 mmol, 1.1 equiv., M = 325.82g/mol) were added to 20 mL of acetone at room temperature. The product was obtained as a light yellow solid (2.59 g, *Z*/*E* 1/4.7, 89% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 5.76 – 5.50 (m, 2H), 4.21 (*cis*) (d, *J* = 6.1 Hz, 0.35H), 4.12 – 4.07 (*trans*) (m, 1.63H), 2.40 (s, 3H), 2.33 (*cis*) (s, 0.16H), 2.32 (*trans*) (s, 0.74H), 1.71 – 1.67 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.8, 140.0, 129.3, 129.3, 128.6, 127.2, 86.4, 71.9, 56.2, 49.9, 30.6, 21.5, 17.7.

[185] M. D., L. Hou, X. Tong, *Chem. Eur. J.*, **2016**, *22*, 7734.

107	***N*-(But-2-en-1-yl)-4-methyl-*N*-(2-methyl-4-phenylbut-3-yn-2-yl)benzenesulfonamide**



Chemical Formula: $C_{22}H_{25}NO_2S$

Molecular Weight: 367.50

Aspect: Light yellow solid

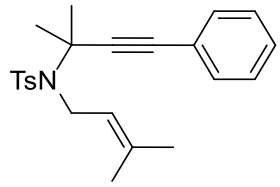
R_f = 0.24 (PE / EtOAc, 96/4)

Following the general procedure **C**, 2.59 g of substrate **106** (8.9 mmol, 1 equiv., M = 291.41 g/mol), 2.0 g iodobenzene (9.8 mmol, 1.01 equiv., M = 204.01 g/mol), 125 mg [$PdCl_2(PPh_3)_2$] (2 mol%, M = 701.90 g/mol), and 17 mg CuI (1 mol%, 190.45 g/mol) were added to 9 mL of Et_3N and 27 mL of PhMe at room temperature for 18 h. 1.3 g of product was obtained in 40% yield as a light yellow solid (*Z*/*E* 1/4.8).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.25 (m, 3H), 7.20 (dd, *J* = 7.9, 1.9 Hz, 4H), 5.76 – 5.56 (m, 2H), 4.27 (*cis*) (d, *J* = 6.0 Hz, 0.34H), 4.15 (*trans*) (d, *J* = 3.3 Hz, 1.64H), 2.34 (s, 3H), 1.78 – 1.69 (m, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.7, 139.8, 131.5, 129.6, 129.3, 128.3, 128.3, 128.2, 127.3, 122.6, 91.8, 83.6, 56.9, 50.2, 30.9, 21.4, 17.8.

108	**4-Methyl-*N*-(2-methyl-4-phenylbut-3-yn-2-yl)-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide**



Chemical Formula: $C_{23}H_{27}NO_2S$

Molecular Weight: 381.53

Aspect: Light yellow solid

R_f = 0.52 (PE / EtOAc, 8/1)

Following the general procedure **C**, 2.37 g sulfonamide **105** (10 mmol, 1 equiv., M = 237.32 g/mol), 1.34 mL iodobenzene (12 mmol, 1.2 equiv.), 140 mg [$PdCl_2(PPh_3)_2$] (2 mol%), and 19 mg CuI (1 mol%) in 40 mL PhMe/Et_3N (3:1) were stirred at room temperature for 3 h. Then 2.4 g of 4-methyl-*N*-(2-methyl-4-phenylbut-3-yn-2-yl)benzenesulfonamide was obtained in 78% yield as a brown solid (7.8 mmol). Following the procedure **B**, 2.4 g of the solid previously obtained (7.8 mmol, 1 equiv.), 1.4 mL of 1-bromo-3-methylbut-2-ene (11.7 mmol, 1.5 equiv.) and 3.8 g of Cs_2CO_3 (11.7 mmol, 1.5 equiv.) were added to 20 mL of acetone. A fter 3 h, 2.6 g of compound **108** were obtained in 89% yield as a light yellow solid (m.p. 20-25 °C).

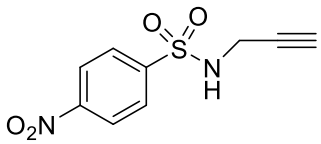
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.24 (m, 3H), 7.23 – 7.18 (m, 4H), 5.44 (td, *J* = 5.6, 5.0, 3.2 Hz, 1H), 4.21 (d, *J* = 6.1 Hz, 2H), 2.34 (s, 3H), 1.75 (s, 6H), 1.72

(s, 3H), 1.66 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.7, 139.9, 133.1, 131.5, 129.3, 128.3, 128.2, 127.3, 124.0, 122.7, 92.0, 83.5, 56.8, 46.7, 30.9, 25.8, 21.4, 18.0.

MS (EI) calculated for $[C_{23}H_{27}NO_2S]^+$ m/z = 381.

109	**4-Nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_9H_8N_2O_4S$

Molecular Weight: 240.23

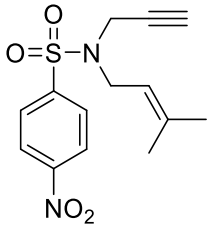
Aspect: Yellow solid

R_f = 0.19 (PE / EtOAc, 4/1)

Following the general procedure **A**, 2.22 g of 4-nitrobenzenesulfonyl chloride (10 mmol, 1 equiv., M = 221.62 g/mol) were dissolved in a mixture of 3.5 mL of Et_3N (25 mmol, 2.5 equiv. M = 101.19 g/mol) and 20 mL of CH_2Cl_2. Then, 0.67 mL of prop-2-yn-1-amine (10.5 mmol, 1.05 equiv., M = 55.08 g/mol) was added dropwise. The reaction mixture was stirred at room temperature for 16 h till completion of the reaction. Then, 2.09 g of awaited product was obtained in 87% yield as a yellow solid. The spectral data were in accordance with literature.

^{1}H NMR (200 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.15 (d, *J* = 9.0 Hz, 2H), 3.92 (d, *J* = 2.5 Hz, 2H), 2.05 (t, *J* = 2.5 Hz, 1H).

110	***N*-(3-Methylbut-2-en-1-yl)-4-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide**



Chemical Formula: $C_{14}H_{16}N_2O_4S$

Molecular Weight: 308.35

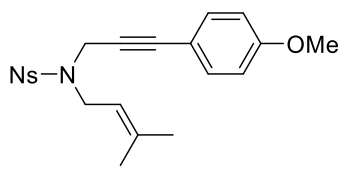
Aspect: Yellow solid

R_f = 0.57 (PE / EtOAc, 5/1)

Following the general procedure **B**, 2.09 g of sulfonamide **109** (8.7 mmol, 1 equiv., M = 240.23 g/mol), 1.5 mg of 1-bromo-3-methylbut-2-ene (9.57 mmol, 1.1 equiv., M = 149.03 g/mol) and 3.1 g of Cs_2CO_3 (9.57 mmol, 1.1 equiv., M = 325.82g/mol) were added to 20 mL of acetone at room temperature. 2.5 g of product were isolated in 93% yield. The spectral data were in accordance with literature.

^{1}H NMR (200 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 8.7 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 2H), 5.04 (t, *J* = 7.3 Hz, 1H), 4.05 (d, *J* = 2.4 Hz, 2H), 3.78 (d, *J* = 7.3 Hz, 2H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.67 (s, 3H), 1.61 (s, 3H).

111	***N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)-*N*-(3-methylbut-2-en-1-yl)-4-nitrobenzenesulfonamide**



Chemical Formula: $C_{21}H_{22}N2O5S$

Molecular Weight: 414.4760

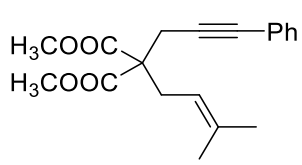
Aspect: Brown solid

R_f = 0.30 (PE / EtOAc, 5/1)

Following the general procedure **C**, 2.5 g of substrate **110** (8.1 mmol, 1 equiv., M = 308.35 g/mol), 2.09 g of 4-iodoanisole (8.9 mmol, 1.1 equiv., M = 234.04 g/mol), 114 mg of $[PdCl_2(PPh_3)_2]$ (2 mol%, M = 701.90 g/mol) and 16 mg of CuI (1 mol%, 190.45 g/mol) were added to 8 mL of Et_3N and 24 mL of PhMe, at room temperature. 1.47 g of the awaited product was obtained in 44% yield as a brown solid. The spectral data were in accordance with literature.[186]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.9 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.18 (t, *J* = 7.4 Hz, 1H), 4.30 (s, 2H), 3.91 (d, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H).

112 Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)malonate



Chemical Formula: $C_{19}H_{22}O_4$

Molecular Weight: 314.38

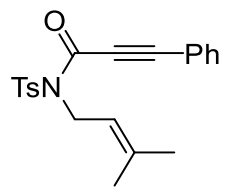
Aspect: Colorless oil

R_f = 0.89 (PE / EtOAc, 5/1)

Following the general procedure **C**, 1.19 g of the corresponding substrate (5 mmol, 1 equiv., M = 238.12 g/mol), 1.23 g of iodobenzene (21 mmol, 1.2 equiv., M = 204.01 g/mol), 70 mg of $[PdCl_2(PPh_3)_2]$ (2 mol%) and 9.5 mg of CuI (1 mol%) were added to 5 mL of Et_3N and 15 mL of PhMe, at room temperature. After 16 h of stirring, 1.07 g of product was obtained in 68% yield as a colorless oil. The spectral data were in accordance with literature.[99]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.38 – 7.35 (m, 2H), 7.29 – 7.25 (m, 3H), 4.95 (tt, *J* = 7.6, 1.3 Hz, 1H), 3.75 (s, 6H), 2.99 (s, 2H), 2.85 (d, *J* = 7.7 Hz, 2H), 1.71 (s, 3H), 1.68 (s, 3H).

80 *N*-(3-Methylbut-2-en-1-yl)-3-phenyl-*N*-tosylpropiolamide



Chemical Formula: $C_{21}H_{21}NO_3S$

Molecular Weight: 367.46

Aspect: Yellow transparent oil

R_f = 0.42 (PE / EtOAc, 4/1)

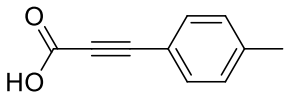
[186] F. Nuter, A. K. D. Dimé, C. Chen, L. Bounaadja, E. Mouray, I. Florent, Y. Six, O. Buriez, A. Marinetti, A. Boituriez, *Chem. Eur. J.*, **2015**, *21*, 5584.

Following the general experimental procedure **E**, substrate **91** (1.05 g, 5 mmol, M = 209.26 g/mol), PPh_3 (1.44 g, 5.5 mmol, 1.1 equiv., M = 262.29 g/mol) and 2-cyclohexylideneethan-1-ol (947 mg, 7.5 mmol, 1.5 equiv., M = 126.20 g/mol) were sequentially added. Afterwards, putting the flask in ice-water bath, DIAD (1.1 mL, 5.5 mmol, 1.1 equiv., M = 202.21 g/mol, d = 1.027) was added dropwise. The product was obtained as a white solid (1.18 g, 3.75 mmol, 75%). Then **C** (816 mg), iodobenzene (4 mmol, 1.05 equiv., M = 204.01 g/mol), 53 mg [$PdCl_2(PPh_3)_2$] (2 mol%), and 14 mg CuI (1 mol) were added to 3.75 mL of Et_3N and 11.25 mL of PhMe, at room temperature, and stirred for 18 h. The product **104** was obtained as a white solid (886 mg, 60% yield). The spectral data were in accordance with literature.[102]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.30 (t, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 2H), 2.40 (s, 3H), 1.80 (s, 3H), 1.75 (s, 3H).

MS (EI) calculated for $[C_{21}H_{21}NO_3S]^+$ m/z = 367.

129 3-(*p*-Tolyl)propiolic acid



Chemical Formula: $C_{10}H_8O_2$

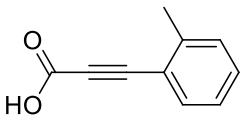
Molecular Weight: 160.17

Aspect: Light yellow solid

According to the general procedure **F**, the reaction flask was charged with 4.36 g of 1-iodo-4-methylbenzene (20 mmol, 10 equiv., M = 218.04 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a light yellow solid (2.6 g, 82% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H).

130 3-(*o*-Tolyl)propiolic acid



Chemical Formula: $C_{10}H_8O_2$

Molecular Weight: 160.17

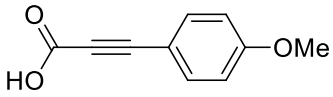
Aspect: Yellow solid

According to the general procedure **F**, the reaction flaskn was charged with 4.36 g of 1-iodo-2-methylbenzene (20 mmol, 10 equiv., M = 218.04 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a

yellow solid (2.56 g, 80% yield), and the spectral data were in accordance with literature.[187]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.61 (s, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 2.48 (s, 3H).

131 3-(4-Methoxyphenyl)propiolic acid



Chemical Formula: $C_{10}H_8O_3$

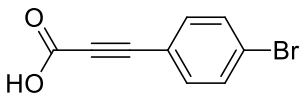
Molecular Weight: 176.17

Aspect: Brown solid

According to the general procedure **F**, the reaction flask was charged with 4.7 g of 1-iodo-4-methoxybenzene (20 mmol, 10 equiv., M = 234.04 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a brown yellow solid (2.54 g, 72% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (200 MHz, DMSO-d_6) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H).

132 3-(4-Bromophenyl)propiolic acid



Chemical Formula: $C_9H_5BrO_2$

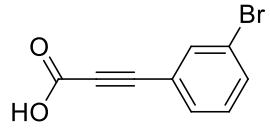
Molecular Weight: 225.04

Aspect: Yellow solid

According to the general procedure **F**, the reaction flask was charged with 5.6 g of 1-bromo-4-iodobenzene (20 mmol, 10 equiv., M = 282.91 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a yellow solid (4.1 g, 91% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H).

133 3-(3-Bromophenyl)propiolic acid



Chemical Formula: $C_9H_5BrO_2$

Molecular Weight: 225.04

Aspect: Yellow solid

According to the general procedure **F**, the reaction flask was charged with 5.6 g of 1-bromo-3-

[187] J. Moon, M. Jang, S. Lee, *J. Org. Chem*., **2009**, *74*, 1403.

iodobenzene (20 mmol, 10 equiv., M = 282.91 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a yellow solid (3.6 g, 81% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H).

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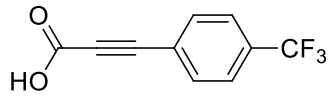
134 3-(4-(Trifluoromethyl)phenyl)propiolic acid



Chemical Formula: $C_{10}H_5F_3O_2$

Molecular Weight: 214.14

Aspect: Light yellow solid

According to the general procedure **F**, the reaction flask was charged with 5.4 g of 1-iodo-4-(trifluoromethyl)benzene (20 mmol, 10 equiv., M = 272.01 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a light yellow solid (3.6 g, 85% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (200 MHz, DMSO-d_6) δ 7.84 (s, 4H).

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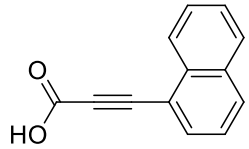
135 3-(Naphthalen-1-yl)propiolic acid



Chemical Formula: $C_{13}H_8O_2$

Molecular Weight: 196.20

Aspect: Yellow solid

According to the general procedure **F**, the reaction flask was charged with 2.54 g of 1-iodonaphthalene (10 mmol, 1.0 equiv., M = 254.07 g/mol), 3.65 g of DBU (24 mmol, 2.4 equiv., M = 152.24 g/mol), 231 mg of $Pd(PPh_3)_4$, 886 mg of propiolic acid (12 mmol, 1.2 equiv., M = 70.05 g/mol) and 15 mL of DMSO. The product was obtained as a yellow solid (1.06 g, 54% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.94 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.73 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.59 (dd, *J* = 8.2, 7.3 Hz, 1H).

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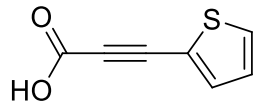
136 3-(Thiophen-2-yl)propiolic acid



Chemical Formula: $C_7H_4O_2S$

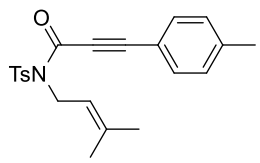
Molecular Weight: 152.17

Aspect: Yellow solid

According to the general procedure **F**, the reaction flask was charged with 4.2 g of 2-iodothiophene (20 mmol, 1.0 equiv., M = 210.03 g/mol), 7.3 g of DBU (48 mmol, 2.4 equiv., M = 152.24 g/mol), 462 mg of $Pd(PPh_3)_4$ (2 mol%, M = 1155.56 g/mol), 1.8 g of propiolic acid (24 mmol, 1.2 equiv., M = 70.05 g/mol) and 30 mL of DMSO. The product was obtained as a yellow solid (1.2 g, 40% yield), and the spectral data were in accordance with literature.[105]

^{1}H NMR (200 MHz, DMSO-*d*$_6$) δ 7.90 (d, *J* = 5.0 Hz, 1H), 7.69 (d, *J* = 3.7 Hz, 1H), 7.27 – 7.13 (m, 1H).

137 *N*-(3-Methylbut-2-en-1-yl)-3-(*p*-tolyl)-*N*-tosylpropiolamide



Chemical Formula: $C_{22}H_{23}NO_3S$

Molecular Weight: 381.49

Aspect: Yellow oil

R_f = 0.47 (PE / EtOAc, 5/1)

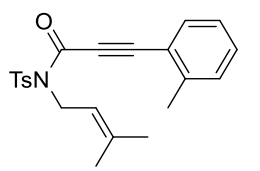
According to the general procedure **G**, the reaction flask was charged with 1.6 g of 3-(*p*-tolyl)propiolic acid **129** (10 mmol, 1 equiv. M = 160.17 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (1.9 g, 50% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.30 (t, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 2.37 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.9, 144.9, 141.7, 137.2, 136.3, 132.7, 129.5, 129.4, 128.6, 119.5, 116.4, 93.6, 81.5, 45.7, 25.7, 21.8, 21.7, 18.2.

MS (EI) calculated for $[C_{22}H_{23}NO_3S]^+$ m/z = 381.

138 *N*-(3-Methylbut-2-en-1-yl)-3-(*o*-tolyl)-*N*-tosylpropiolamide



Chemical Formula: $C_{22}H_{23}NO_3S$

Molecular Weight: 381.49

Aspect: White solid

R_f = 0.25 (PE / EtOAc, 9/1)

According to the general procedure **G**, the reaction flask was charged with 1.60 g of 3-(*o*-tolyl)propiolic acid **130** (10 mmol, 1 equiv. M = 160.17 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a white solid (1.7 g, 44% yield, m.p. 67-69 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 5.29 (t, *J* = 6.7 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.80 (s, 3H), 1.76 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.9, 144.9, 142.2, 137.3, 136.3, 133.2, 130.9, 129.9, 129.4, 128.7, 125.9, 119.5, 119.4, 92.3, 85.3, 45.8(2C), 25.7, 21.7, 20.5, 18.2.

MS (EI) calculated for $[C_{22}H_{23}NO_3S]^+$ m/z = 381.

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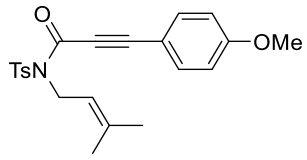
139 3-(4-Methoxyphenyl)-*N*-(3-methylbut-2-en-1-yl)-*N*-tosylpropiolamide



Chemical Formula: $C_{22}H_{23}NO_4S$
Molecular Weight: 397.49
Aspect: Yellow solid
R_f = 0.45 (PE / EtOAc, 5/1)

According to the general procedure **G**, the reaction flask was charged with 1.76 g of 3-(4-methoxyphen-yl)propiolic acid **131** (10 mmol, 1 equiv. M = 176.17 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow solid (1.9 g, 49% yield, m.p. 68-70 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.29 (t, *J* = 6.7 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 2H), 3.83 (s, 3H), 2.41 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.8, 153.0, 144.8, 137.1, 136.4, 134.7, 129.3, 128.6, 119.6, 114.4, 111.3, 94.0, 81.4, 55.5, 45.6, 25.7, 21.7, 18.2.

MS (EI) calculated for $[C_{22}H_{23}NO_4S]^+$ m/z = 397.

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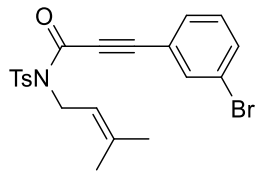
140 3-(3-Bromophenyl)-*N*-(3-methylbut-2-en-1-yl)-*N*-tosylpropiolamide



Chemical Formula: $C_{21}H_{20}BrNO_3S$

Molecular Weight: 446.36

Aspect: Yellow oil

R_f = 0.28 (PE / EtOAc, 9/1)

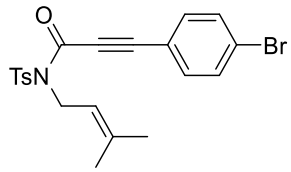
According to the general procedure **G**, the reaction flak was charged with 2.25 g of 3-(3-bromophen-yl)propiolic acid **133** (10 mmol, 1 equiv. M = 225.04 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (2.2 g, 50% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.61 (s, 1H), 7.58 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 1H), 5.27 (t, *J* = 6.7 Hz, 1H), 4.67 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.80 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.3, 145.1, 137.5, 136.2, 135.2, 134.0, 131.2, 130.2, 129.5, 128.5, 122.4, 121.6, 119.3, 90.9, 82.5, 45.6(2C), 25.8, 21.7, 18.2.

MS (EI) calculated for $[C_{21}H_{20}BrNO_3S]^+$ m/z = 445.

141 3-(4-Bromophenyl)-*N*-(3-methylbut-2-en-1-yl)-*N*-tosylpropiolamide



Chemical Formula: $C_{21}H_{20}BrNO_3S$

Molecular Weight: 446.36

Aspect: Yellow oil

R_f = 0.47 (PE / EtOAc, 5/1)

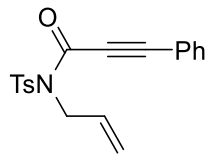
According to the general procedure **G**, the reaction flask was charged with 2.25 g of 3-(4-bromophenyl)propiolic acid **132** (10 mmol, 1 equiv. M = 225.04 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (2.5 g, 56% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.18 (t, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 2H), 2.31 (s, 3H), 1.69 (s, 3H), 1.65 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.5, 145.1, 137.4, 136.2, 134.0, 132.1, 129.5, 128.5, 125.8, 119.3, 118.5, 91.7, 82.7, 45.6(2C), 25.8, 21.7, 18.2.

MS (EI) calculated for $[C_{21}H_{20}BrNO_3S]^+$ m/z = 445.

142 *N*-Allyl-3-phenyl-*N*-tosylpropiolamide



Chemical Formula: $C_{19}H_{17}NO_3S$

Molecular Weight: 339.41

Aspect: Yellow solid

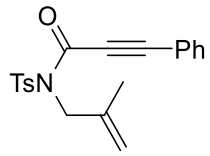
R_f = 0.31 (PE / EtOAc, 5/1)

According to the general procedure **G**, the reaction flask was charged with 1.46 g of phenylpropiolic acid (10 mmol, 1 equiv. M = 146.15 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1 h at room temperature, 2.6 mL of 3-bromoprop-1-ene (3 equiv., M = 121.0 g/mol) and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow solid (1.7 g, 50% yield, m.p. 64-66 °C), and the spectral data were identical to the literature.[86]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.48 – 7.40 (m, 1H), 7.39 – 7.31 (m, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 5.98 (ddt, *J* = 16.1, 10.6, 5.6 Hz, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 4.70 (d, *J* = 5.5 Hz, 2H), 2.38 (s, 3H).

MS (EI) calculated for $[C_{19}H_{17}NO_3S]^+$ m/z = 339.

143 *N*-(2-Methylallyl)-3-phenyl-N-tosylpropiolamide



Chemical Formula: $C_{20}H_{19}NO_3S$

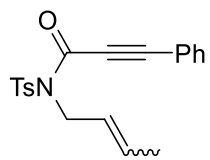
Molecular Weight: 353.44

Aspect: Yellow solid

R_f = 0.40 (PE / EtOAc, 5/1)

According to the general procedure **G**, the reaction flask was charged with 0.73 g of phenylpropiolic acid (5 mmol, 1 equiv. M = 146.15 g/mol), 0.8 mL of tosyl isocyanate, and 10 mL of dry THF. Then, 0.7 mL of Et_3N was added drop-wise to the solution. After stirring for 1 h at room temperature, 2.0 g of 3-bromo-2-methylprop-1-ene (15 mmol, 3 equiv., M = 135.0 g/mol) and 2.1 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a as a yellow solid (1.06 g, 60% yield), and the spectral data were identical to the literature.[86]

144 *N*-(But-2-en-1-yl)-3-phenyl-*N*-tosylpropiolamide



Chemical Formula: $C_{20}H_{19}NO_3S$

Molecular Weight: 353.44

Aspect: White solid

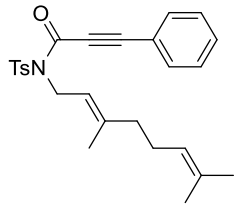
R_f = 0. 44 (PE / EtOAc, 5/1)

According to the general procedure **G**, the reaction flask was charged with 1.46 g of

phenylpropiolic acid (10 mmol, 1 equiv. M = 146.15 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 1h at room temperature, 3.6 mL of crotyl bromide (30 mmol, 3 equiv., M = 135.00 g/mol, d = 1.31) and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a white solid (2.8 g, *Z*/*E* 1/4.8, 80% yield, m.p. 79-81 °C), and the spectral data were identical to the literature.[86]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.41 – 7.35 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.87 (*trans*) (m, 0.86H), 5.73 (*cis*) (m, 0.18H), 5.67 – 5.58 (*trans*) (m, 0.83H), 5.54 (*cis*) (m, 0.17H), 4.75 (*cis*) (d, *J* = 6.6 Hz, 0.34H), 4.62 (*trans*) (d, *J* = 6.3 Hz, 1.65H), 2.41 (s, 3H), 1.81 (*cis*) (d, *J* = 6.9 Hz, 0.53H), 1.73(*trans*) (d, *J* = 6.5 Hz, 2.62H).

145 (*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-3-phenyl-*N*-tosylpropiolamide



Chemical Formula: $C_{26}H_{29}NO_3S$

Molecular Weight: 435.58

Aspect: Yellow oil

R_f = 0.42 (PE / EtOAc, 5/1)

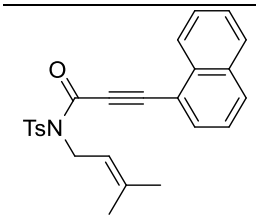
According to the general procedure **G**, the reaction flask was charged with 146 mg of phenylpropiolic acid (1 mmol, 1 equiv. M = 146.15 g/mol), 159 mg of tosyl isocyanate (1 mmol, 1 equiv., M = 197.21 g/mol), and 2 mL of dry THF. Et_3N 0.2 mL was added dropwise to the solution. After stirring for 1h at room temperature, 0.6 mL of geranyl bromide (3 mmol, 3 equiv., M = 217.15 g/mol, d = 1.094) and 0.5 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (347 mg, 80% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.54 – 7.49 (m, 2H), 7.48 – 7.43 (m, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.30 (t, *J* = 6.2 Hz, 1H), 5.08 (t, *J* = 6.0 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 2.06 (p, *J* = 8.1, 7.2 Hz, 4H), 1.81 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.7, 144.9, 140.7, 136.3, 132.7, 131.9, 130.9, 129.4, 128.7, 128.6, 123.7, 119.6, 119.2, 93.0, 81.8, 45.6, 39.5, 26.4, 25.7, 21.6, 17.7, 16.6.

MS (EI) calculated for $[C_{26}H_{29}NO_3S]^+$ m/z = 435.

146 *N*-(3-Methylbut-2-en-1-yl)-3-(naphthalen-1-yl)-*N*-tosylpropiolamide



Chemical Formula: $C_{25}H_{23}NO_3S$

Molecular Weight: 417.52

Aspect: Yellow oil

R_f = 0.45 (PE / EtOAc, 5/1)

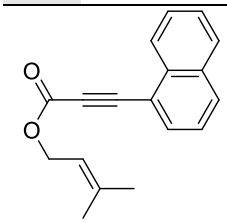
According to the general procedure **G**, the reaction flask was charged with 0.98 g of 3-(naphthalen-1-yl)propiolic acid (5 mmol, 1 equiv. M = 1.96 g/mol), 0.8 mL of tosyl isocyanate, and dry THF 10 mL. Then 2.1 mL of Et_3N were added dropwise to the solution. After stirring for 1h at room temperature, 1.92 mL of 1-bromo-3-methylbut-2-ene and 2.1 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (103 mg, 5% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.56 (pd, *J* = 6.9, 1.4 Hz, 2H), 7.48 – 7.43 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.35 (t, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 6.7 Hz, 2H), 2.39 (s, 3H), 1.81 (s, 3H), 1.77 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.8, 144.9, 137.3, 136.3, 133.6, 133.0, 132.9, 131.6, 129.4, 128.6, 128.5, 127.8, 127.0, 125.8, 125.1, 119.5, 117.2, 91.9, 86.2, 45.7, 25.7, 21.6, 18.2.

MS (EI) calculated for $[C_{25}H_{23}NO_3S]^+$ m/z = 417.

147 3-Methylbut-2-en-1-yl 3-(naphthalen-1-yl)propiolate



Chemical Formula: $C_{18}H_{16}O_2$

Molecular Weight: 264.32

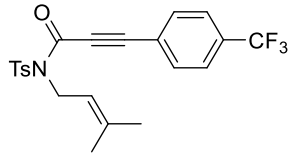
Aspect: Yellow oil

R_f = 0.78 (PE / EtOAc, 5/1)

After the above reaction, 1.04 g the product **147** was obtained as a yellow oil (79 % yield) at the same time.

^{1}H NMR (200 MHz, Chloroform-*d*) δ 8.38 – 8.25 (m, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.87 – 7.77 (m, 2H), 7.66 – 7.47 (m, 2H), 7.42 (dd, *J* = 8.2, 7.3 Hz, 1H), 5.46 (ddt, *J* = 7.4, 4.1, 1.4 Hz, 1H), 4.78 (d, *J* = 7.3 Hz, 2H), 1.79 (s, 3H), 1.76 (s, 3H).

148 *N*-(3-Methylbut-2-en-1-yl)-*N*-tosyl-3-(4-(trifluoromethyl)phenyl)propiolamide



Chemical Formula: $C_{22}H_{20}F_3NO_3S$

Molecular Weight: 435.46

Aspect: Yellow oil

R_f = 0.43 (PE / EtOAc, 5/1)

According to the general procedure **G**, the reaction flask was charged with 2.14 g of 3-(4-

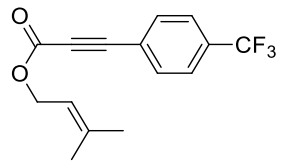
(trifluoromethyl)-phenyl)propiolic acid (10 mmol, 1 equiv. M = 214.14 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then 4.2 mL of Et_3N were added dropwise to the solution. After stirring for 2h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (85 mg, 2% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.69 – 7.59 (m, 4H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.27 (t, *J* = 6.8 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 2H), 2.43 (s, 3H), 1.80 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.2, 145.1, 137.6, 136.2, 132.4 (q, *J* = 33.0 Hz), 132.2, 129.5, 128.5, 125.7 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 272.6 Hz), 123.4, 119.2, 90.7, 83.2, 45.6, 25.7, 21.7, 18.2.

MS (EI) calculated for $[C_{22}H_{20}F_3NO_3S]^+$ m/z = 435.

149 3-Methylbut-2-en-1-yl 3-(4-(trifluoromethyl)phenyl)propiolate



Chemical Formula: $C_{15}H_{13}F_3NO_2$

Molecular Weight: 282.26

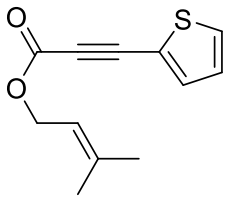
Aspect: Yellow oil

R_f = 0.79 (PE / EtOAc, 5/1)

After the above reaction, 2.5 g the product **149** was obtained as a yellow oil (88 % yield) at the same time.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 5.34 (tt, J = 7.4, 1.3 Hz, 1H), 4.67 (d, J = 7.4 Hz, 2H), 1.71 (s, 3H), 1.67 (s, 3H).

151 3-Methylbut-2-en-1-yl 3-(thiophen-2-yl)propiolate



Chemical Formula: $C_{12}H_{12}O_2S$

Molecular Weight: 220.29

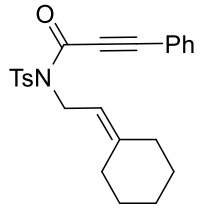
Aspect: Yellow oil

R_f = 0.78 (PE / EtOAc, 5/1)

According to the general procedure **G**, the reaction flask was charged with 1.52 g of 3-(thiophen-2-yl)propiolic acid (10 mmol, 1 equiv. M = 152.17 g/mol), 1.59 mL of tosyl isocyanate, and 20 mL of dry THF. Then, 4.2 mL of Et_3N were added dropwise to the solution. After stirring for 2h at room temperature, 3.85 mL of 1-bromo-3-methylbut-2-ene and 4.2 mL of Et_3N (3 equiv.) were sequentially added. The product was obtained as a yellow oil (2.03 g, 92% yield).

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.52 – 7.43 (m, 2H), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.41 (ddt, *J* = 7.4, 4.2, 1.4 Hz, 1H), 4.73 (d, *J* = 7.4 Hz, 2H), 1.79 (s, 3H), 1.75(s, 3H).

152 *N*-(2-Cyclohexylideneethyl)-3-phenyl-*N*-tosylpropiolamide



Chemical Formula: $C_{24}H_{25}NO_3S$

Molecular Weight: 407.53

Aspect: Colorless oil

R_f = 0.42 (PE / EtOAc, 5/1)

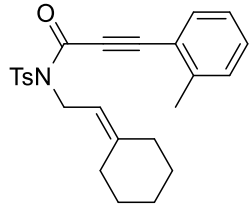
According to the general procedure **H**, the reaction flask was charged with 731 mg of phenylpropiolic acid phenylpropiolic acid (5 mmol, 1 equiv. M = 146.15 g/mol), 0.8 mL of tosyl isocyanate, and 10 mL of dry THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 2h at room temperature, 1.44 g of PPh_3 (5.5 mmol, 1.1 equiv.) and 947 mg of 2-cyclohexylideneethan-1-ol (7.5 mmol, 1.5 equiv.) were sequentially added. Afterwards, putting the flask in ice-water bath, 1.1 mL of DIAD (5.5 mmol, 1.1 equiv.) was added dropwise. The product was obtained as a colorless oil (1.2 g, 57% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.48 (m, 2H), 7.45 (m, 1H), 7.42 – 7.33 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.26 (t, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 2.32 (s, 2H), 2.12 (s, 2H), 1.58 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.8, 145.2, 144.9, 136.3, 132.7, 130.9, 129.4, 128.7, 119.6, 116.0, 93.0, 81.8, 44.9, 37.0, 29.1, 28.3, 27.5, 26.6, 26.1, 21.7.

MS (EI) calculated for $[C_{24}H_{25}NO_3S]^+$ m/z = 407.

153 *N*-(2-Cyclohexylideneethyl)-3-(*o*-tolyl)-*N*-tosylpropiolamide



Chemical Formula: $C_{25}H_{27}NO_3S$

Molecular Weight: 421.56

Aspect: Yellow oil

R_f = 0.43 (PE / EtOAc, 5/1)

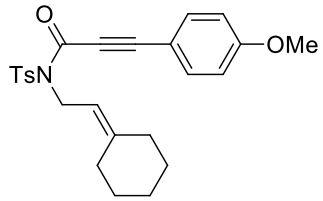
According to the general procedure **H**, reaction flask was charged with 801 mg of 3-(*o*-tolyl)propiolic acid (5 mmol, 1 equiv. M = 160.17 g/mol), 0.8 mL of tosyl isocyanate, and 10 mL of dry THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After 2h at room temperature, 1.44 g of PPh_3 (1.1 equiv.) and 947 mg of 2-cyclohexylideneethan-1-ol (1.5 equiv.) were sequentially added. Afterwards, putting the flask in ice-water bath, DIAD 1.1 mL (1.1 equiv.) was added dropwise. The product was obtained as a yellow oil (1.1 g, 51% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 5.25 (t, *J* = 6.8 Hz, 1H), 4.74 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 2.32 (s, 2H), 2.12 (s, 3H), 1.58 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.9, 145.1, 144.9, 142.2, 136.3, 133.2, 130.9, 129.9, 129.3, 128.7, 125.9, 119.4, 116.1, 92.3, 85.3, 45.0, 37.0, 29.1, 28.3, 27.5, 26.6, 21.7, 20.6.

MS (EI) calculated for $[C_{25}H_{27}NO_3S]^+$ m/z = 421.

154 *N*-(2-Cyclohexylideneethyl)-3-(4-methoxyphenyl)-*N*-tosylpropiolamide



Chemical Formula: $C_{25}H_{27}NO_4S$

Molecular Weight: 437.55

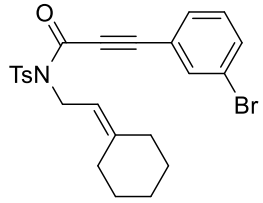
Aspect: Yellow oil

R_f = 0.42 (PE / EtOAc, 5/1)

According to the general procedure **H**, reaction flask was charged with 881 mg of 3-(4-methoxyphenyl)propiolic acid **131** (5 mmol, 1 equiv. M = 176.17 g/mol), 0.8 mL of tosyl isocyanate, and 10 mL of THF. 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 2h at room temperature, 1.44 g of PPh_3 (5.5 mmol, 1.1 equiv.) and 947 mg of 2-cyclohexylideneethan-1-ol (7.5 mmol, 1.5 equiv.) were sequentially added. Afterwards, putting the flask in ice-water bath, 1.1 mL of DIAD (5.5 mmol, 1.1 equiv.) was added dropwise. The product was obtained as a yellow oil (1.75 g, 80% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.21 (t, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 2H), 3.78 (s, 3H), 2.36 (s, 3H), 2.28 (s, 2H), 2.07 (s, 2H), 1.53 (s, 6H).

155 3-(3-Bromophenyl)-*N*-(2-cyclohexylideneethyl)-N-tosylpropiolamide



Chemical Formula: $C_{24}H_{24}BrNO_3S$

Molecular Weight: 486.42

Aspect: Yellow oil

R_f = 0.43 (PE / EtOAc, 5/1)

According to the general procedure **H**, the reaction flask was charged with 1.125 mg of 3-(3-bromophenyl)propiolic acid **133** (5 mmol, 1 equiv.), 0.8 mL of tosyl isocyanate, and 10 mL of dry THF. Then, 1.4 mL of Et_3N was added dropwise to the solution. After stirring for 2h at room temperature, 1.44 g of PPh_3 (1.1 equiv.) and 947 mg of 2-cyclohexylideneethan-1-ol (1.5 equiv.) were sequentially added. Afterwards, putting the flask in ice-water mixture to cooled 0 °C, DIAD 1.1 mL (1.1 equiv.) was added drop-wise. The product was obtained as a yellow oil (1.43g, 59% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 5.23 (tt, *J* = 6.8, 1.2 Hz, 1H), 4.69 (d,

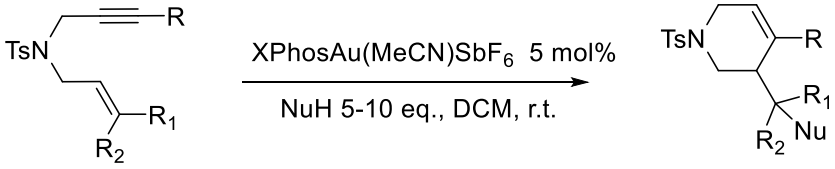
J = 6.9 Hz, 2H), 2.42 (s, 3H), 2.31 (s, 2H), 2.12 (s, 2H), 1.57 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 145.4 145.0, 136.2, 135.2 134.0, 131.2 130.2 129.5, 128.6, 122.4, 121.6, 115.9 90.9 82.5, 44.8 37.0, 29.1, 28.3, 27.5, 26.6, 21.7.

2.2 Gold-catalyzed cycloisomerization reaction

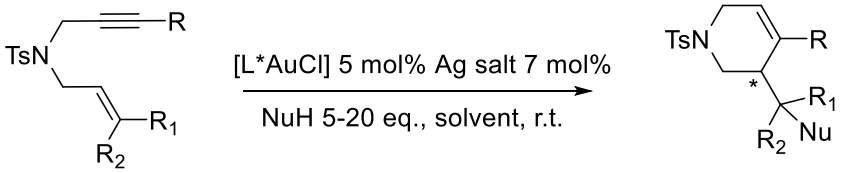
2.2.1 Domino cyclization / nucleophilic addition

General procedure I:



In a clean and dried 8 mL screw-capped vial, 1,6-enyne (0.1-0.2 mmol, 1 equiv.) and nucleophile reagent (5-10 equiv.) were dissolved in DCM. Then gold catalyst [(Acetonitrile)[2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl]gold(I)] XPhosAu(MeCN)SbF_6 (5 mol%) was added in the system. The resulting mixture was stirred at room temperature, then monitored by TLC. After completion of the reaction, the mixture was filtered through a short pad of silica with DCM and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography to give the corresponding product.

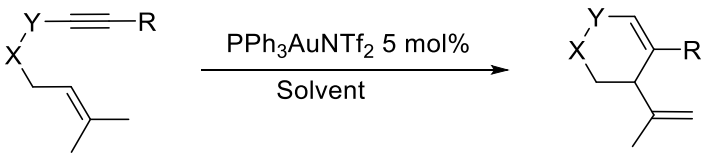
Synthetic procedure of asymmetric reaction J:



First, in a screw-capped vial, gold pre-catalyst and silver salt in the solvent were stirred under N_2 for 5 min. Then, the active catalytic species was introduced in an other vial with a mixture of 1,6-enyne (0.1-0.2 mmol, 1 equiv.), nucleophile reagent (5-10 equiv.) and solvent. The reaction was stirred at room temperature, and the mixture was monitored by TLC. The resulting mixture was filtered through a short pad of silica with DCM and the solvents were evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography to give the corresponding products.

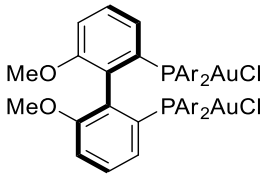
2.2.2 Cycloisomerization reaction in the absence of nucleophiles

General procedure K:



In a clean and dried 8 mL screw-capped vial, 1,6-enyne (0.1-0.2 mmol, 1 equiv.) and nucleophile reagent (5-10 equiv.) were dissolved in a solvent. Then gold catalyst $Ph_3AuPNTf_2$ (5 mol%) was added in the system. The resulting mixture was stirred and monitored by TLC. After completion of the reaction, the mixture was filtered through a short pad of silica with DCM and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography to give the corresponding product.

C-18 (*R*)-DTB-MeOBIPHEP-$(AuCl)_2$



Ar = 3,5-*t*$Bu_2C_6H_3$

Chemical Formula: $C_{70}H_{98}Au_2Cl_2O_2P_2$

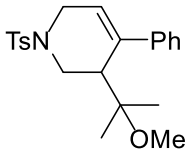
Molecular Weight: 1498.33

Aspect: white solid

515.7 mg of chiral diphosphine ligand (*R*)-DTB-MeOBIPHEP (0.5 mmol, M = 1031.49 g/mol) and 320.6 mg of (tht)AuCl (1 mmol, M = 320.59 g/mol) were stirred, in DCM, at room temperature to allow the synthesis of the chiral catalyst **C-18** (748 mg).

^{31}P NMR (121 MHz, Chloroform-*d*) δ 23.7 ppm (Ligand: ^{31}P NMR (121 MHz, Chloroform-*d*) δ -12.7 ppm).

P-1 3-(2-Mthoxypropan-2-yl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{22}H_{27}NO_3S$

Molecular Weight: 385.52

Aspect: White solid

R_f = 0.17 (PE / EtOAc, 9/1)

According to the general procedure **I**, 53 mg of 1,6-enyne **77** (0.15 mmol, 1 equiv., M = 353.48 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL DCM. 7 Mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The awaited product was obtained as a white solid (54 mg, 94% yield, m.p. 89-91 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 53 mg of **77** and 48 mg of MeOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 32 mg of **P-1'** was obtained in 56% yield and 84% *ee*.

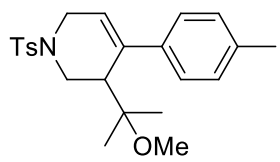
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.06 (m, 5H), 5.69 (t, *J* = 3.3 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 4.04 (dd, *J* = 17.2, 3.7 Hz, 1H), 3.21 (dt, *J* = 17.2, 3.3 Hz, 1H), 2.99 (s, 3H), 2.89 (s, 1H), 2.41 (dd, *J* = 11.5, 3.7 Hz, 1H), 2.35 (s, 3H), 1.22 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.7, 143.4, 138.7, 132.7, 129.7, 128.3, 127.9, 127.1, 126.4, 124.2, 77.9, 49.0, 45.5, 45.3, 44.2, 26.0, 22.5, 21.6.

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 2.9 and 10.7 min. **$[\alpha]_D^{20}$** : +194.7 ($CHCl_3$, c = 0.03) at 84% *ee*

HRMS (ESI) *m/z* calc. for $[C_{22}H_{27}NO_3S+H]^+$ 386.1784, found: 386.1780.

P-2 3-(2-Methoxypropan-2-yl)-4-(p-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{23}H_{29}NO_3S$

Molecular Weight: 399.55

Aspect: White solid

R_f = 0.27 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **94** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was obtained as a white solid (55 mg, 91% yield, m.p. 144-146 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **94** and 96 mg of MeOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 45 mg of **P-2'** were isolated in 75% yield and 93% *ee*.

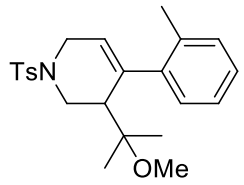
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 4H), 5.73 (t, *J* = 3.3 Hz, 1H), 4.33 (dd, *J* = 11.5, 0.9 Hz, 1H), 4.10 (dd, *J* = 17.2, 3.7 Hz, 1H), 3.28 (dt, *J* = 17.1, 2.6 Hz, 1H), 3.09 (s, 3H), 2.94 (s, 1H), 2.47 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 1.29 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.4, 138.4, 136.7, 132.7, 129.6, 128.9, 127.8, 126.2, 123.5, 77.8, 48.9, 45.3, 45.2, 44.1, 26.1, 22.3, 21.5, 21.1.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 250 nm. Retention time: 3.2 and 5.8 min. **$[\alpha]_D^{20}$** : +249.3 ($CHCl_3$, c = 0.04) at 93% *ee*

HRMS (ESI) *m/z* calc. for $[C_{23}H_{29}NO_3S+H]^+$ 400.1941, found: 400.1939.

P-3 3-(2-Methoxypropan-2-yl)-4-(*o*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{23}H_{29}NO_3S$

Molecular Weight: 399.55

Aspect: White solid

R_f = 0.20 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **93** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was isolated as a white solid (54 mg, 90% yield, m.p. 86-88 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **93** and 96 mg of MeOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 30 mg of **P-3'** were obtained in 53% yield and 87% *ee*.

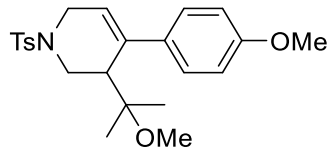
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.10 (m, 3H), 7.04 – 6.93 (m, 1H), 5.62 (t, *J* = 3.2 Hz, 1H), 4.20 (dd, *J* = 12.5 1.2 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.26 (dt, *J* = 16.9, 2.5 Hz, 1H), 2.96 (s, 3H), 2.81 (s, 1H), 2.56 (dd, *J* = 11.7, 4.2 Hz, 1H), 2.43 (s, 3H), 2.25 (s, 3H), 1.32 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.6, 143.2, 138.1, 134.4, 132.8, 130.4, 129.7, 128.4, 127.8, 126.7, 125.5, 125.2, 77.8, 48.6, 46.6, 45.0, 44.0, 25.3, 22.8, 21.6, 20.1.

SFC: Chiralcel AD, 100 bar, 15% MeOH, flow rate 3.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 3.9 and 4.9 min. **$[\alpha]_D^{20}$** : +206.5 ($CHCl_3$, c = 0.03) at 87% *ee*

HRMS (ESI) *m/z* calc. for $[C_{23}H_{29}NO_3S+H]^+$ 400.1941, found: 400.1939.

P-4	**4-(4-Methoxyphenyl)-3-(2-methoxypropan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{23}H_{29}NO_4S$

Molecular Weight: 415.55

Aspect: White solid

R_f = 0.11 (PE / EtOAc, 9/1)

According to the general procedure **I**, 58 mg of 1,6-enyne **95** (0.15 mmol, 1 equiv., M = 383.51 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was obtained as a white solid (55 mg, 89% yield, m.p. 79-81 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **95** and 96

mg of MeOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 44 mg of **P-4'** were obtained in 71% yield and 83% *ee*.

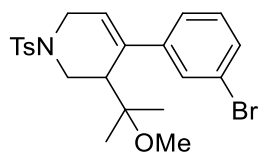
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.70 (t, *J* = 3.3 Hz, 1H), 4.32 (dd, *J* = 11.6, 1.0 Hz, 1H), 4.10 (dd, *J* = 17.1, 3.7 Hz, 1H), 3.78 (s, 3H), 3.28 (dt, *J* = 17.1, 2.6 Hz, 1H), 3.09 (s, 3H), 2.91 (s, 1H), 2.47 (dd, *J* = 11.6, 4.0 Hz, 1H), 1.29 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.7, 143.5, 138.0, 135.8, 132.7, 129.6, 127.8, 127.4, 122.9, 113.6, 77.9, 55.2, 48.9, 45.4, 45.2, 44.1, 26.0, 22.4, 21.5.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 4.1 and 14.9 min. **$[\alpha]_D^{20}$** : +185.7 ($CHCl_3$, c = 0.03) at 83% *ee*

HRMS (ESI) *m/z* calc. for $[C_{23}H_{29}NO_3S+H]^+$ 416.1890, found: 416.1889.

P-5 4-(3-Bromophenyl)-3-(2-methoxypropan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{22}H_{26}BrNO_3S$

Molecular Weight: 464.42

Aspect: White solid

R_f = 0.20 (PE / EtOAc, 9/1)

According to the general procedure **I**, 65 mg of 1,6-enyne **96** (0.15 mmol, 1 equiv., M = 432.38 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was obtained as a white solid (65 mg, 93% yield, m.p. 59-61 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **96** and 48 mg of MeOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 14 mg of **P-5'** were obtained in 20% yield and 81% *ee*.

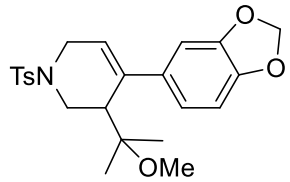
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.31 (m, 4H), 7.19 – 7.08 (m, 2H), 5.79 (t, *J* = 3.3 Hz, 1H), 4.27 (dd, *J* = 11.6, 1.0 Hz, 1H), 4.12 (dd, *J* = 17.4, 3.7 Hz, 1H), 3.28 (dt, *J* = 17.4, 2.6 Hz, 1H), 3.04 (s, 3H), 2.90 (s, 1H), 2.48 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.43 (s, 3H), 1.30 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.4, 143.7, 137.5, 132.5, 129.9, 129.7, 129.7, 129.4, 127.8, 125.1, 125.0, 122.3, 77.9, 48.8, 45.4, 45.2, 44.2, 25.7, 22.4, 21.6.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 4.5 and 16.3 min. **$[\alpha]_D^{20}$** : +154.8 ($CHCl_3$, c = 0.02) at 81% *ee*

HRMS (ESI) *m/z* calc. for $[C_{22}H_{26}BrNO_3S+H]^+$ 464.0890, found: 464.0892.

P-6	**4-(Benzo[*d*][1,3]dioxol-5-yl)-3-(2-methoxypropan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{23}H_{27}NO_5S$

Molecular Weight: 429.53

Aspect: White solid

R_f = 0.37 (PE / EtOAc, 4/1)

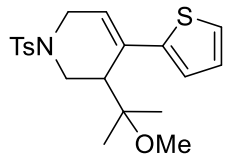
According to the general procedure **I**, 60 mg of 1,6-enyne **98** (0.15 mmol, 1 equiv., M = 397.49 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was obtained as a white solid (61 mg, 95% yield, m.p. 94-96 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.70 – 6.62 (m, 2H), 5.93 (s, 2H), 5.71 (t, *J* = 3.3 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 4.09 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.26 (dt, *J* = 17.2, 2.6 Hz, 1H), 3.11 (s, 3H), 2.85 (s, 1H), 2.47 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.43 (s, 3H), 1.29 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.6, 146.7, 143.6, 138.1, 137.6, 132.6, 129.6, 127.8, 123.4, 119.6, 108.0, 107.0, 101.1, 77.8, 48.9, 45.6, 45.1, 44.1, 26.0, 22.4, 21.5.

HRMS (ESI) *m/z* calc. for $[C_{23}H_{27}NO_5S+H]^+$ 430.1683, found: 430.1681.

P-7	**3-(2-Methoxypropan-2-yl)-4-(thiophen-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{20}H_{25}NO_3S_2$

Molecular Weight: 391.54

Aspect: Red oil

R_f = 0.22 (PE / EtOAc, 9/1)

According to the general procedure **I**, 54 mg of 1,6-enyne **100** (0.15 mmol, 1 equiv., M = 359.50 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was isolated as a red oil (54 mg, 92% yield, m.p. 117-119 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **100** and 48 mg of MeOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 37 mg of **P-7'** were obtained in 64% yield and 86% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (dd, *J* = 4.6, 1.6 Hz, 1H), 6.92 (d, *J* = 4.7 Hz, 2H), 5.95 (t, *J* = 3.5 Hz, 1H), 4.29 (dd, *J* = 11.6, 1.3 Hz, 1H),

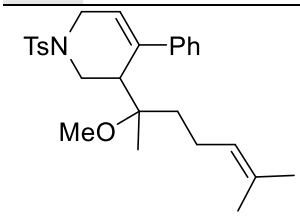
4.11 (dd, *J* = 17.7, 3.5 Hz, 1H), 3.31 (dt, *J* = 17.8, 2.6 Hz, 1H), 3.16 (s, 3H), 2.85 (s, 1H), 2.46 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.42 (s, 3H), 1.34 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.0, 143.6, 132.6, 132.2, 129.7, 127.8, 127.1, 123.8, 123.5, 123.3, 78.0, 49.0, 46.8, 44.9(*CH$_2$*), 44.0(*CH$_2$*), 25.5, 22.4, 21.5.

SFC: Chiralcel IA, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 4.4 and 7.8 min. **$[\alpha]_D^{20}$** dim light ($CHCl_3$, c = 0.01) at 86% *ee*

HRMS (ESI) *m/z* calc. for $[C_{20}H_{25}NO_3S_2+H]^+$ 392.1349, found: 392.1346.

P-8 3-(2-Methoxy-6-methylhept-5-en-2-yl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{27}H_{35}NO_3S$

Molecular Weight: 453.64

Aspect: White solid

R_f = 0.17 (PE / EtOAc, 10/1)

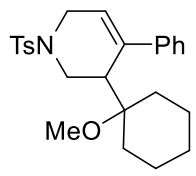
According to the general procedure **I**, 63 mg of 1,6-enyne **101** (0.15 mmol, 1 equiv., M = 421.60 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then XPhosAu(MeCN)SbF_6 (7 mg, 5 mol%, M = 950.48 g/mol) was added to the reaction mixture. The resulting mixture was stirred for 16 h, to afford the awaited product (44 mg, 65% yield, m.p. 44-46 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.19 (p, *J* = 6.9 Hz, 3H), 7.08 (d, *J* = 7.0 Hz, 2H), 5.64 (t, *J* = 3.1 Hz, 1H), 4.49 (t, *J* = 6.7 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.03 (dd, *J* = 17.2, 3.3 Hz, 1H), 3.23 (d, *J* = 17.2 Hz, 1H), 3.05 (s, 3H), 2.92 (s, 1H), 2.41 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.35 (s, 3H), 1.80 – 1.72 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H), 1.18 (s, 3H), 0.93 – 0.81 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 143.1, 138.7, 132.8, 131.0, 129.6, 128.3, 127.9, 127.1, 126.3, 124.8, 124.3, 78.8, 49.0, 45.1(*CH$_2$*), 43.9(*CH$_2$*), 42.9, 37.2(*CH$_2$*), 25.6, 21.5, 21.4(*CH$_2$*), 20.8, 17.6.

HRMS (ESI) *m/z* calc. for $[C_{27}H_{35}NO_3S+H]^+$ 454.2410, found: 454.2413.

P-9 3-(1-Methoxycyclohexyl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{25}H_{31}NO_3S$

Molecular Weight: 425.59

Aspect: White solid

R_f = 0.13 (PE / EtOAc, 92/8)

According to the general procedure **I**, 59 mg of 1,6-enyne **104** (0.15 mmol, 1 equiv., M = 393.55 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL

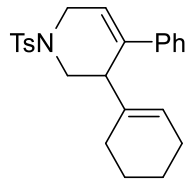
of DCM. Then 7 mg of XPhosAu(MeCN)SbF_6 (5 mol%, M = 950.48 g/mol) were added to the reaction mixture. The resulting mixture was stirred for 16 h, to afford the awaited product (31 mg, 48% yield, m.p. 138-140 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.18 (m, 4H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 2H), 5.67 (t, *J* = 3.3 Hz, 1H), 4.09 (d, *J* = 11.5 Hz, 1H), 4.00 (dd, *J* = 17.2, 3.4 Hz, 1H), 3.25 (dt, *J* = 17.2, 2.5 Hz, 1H), 2.95 (s, 4H), 2.44 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.35 (s, 3H), 1.95 (d, *J* = 12.1 Hz, 1H), 1.64 – 1.57 (m, 1H), 1.36 (ddt, *J* = 29.0, 16.9, 5.3 Hz, 6H), 0.98 – 0.85 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.6, 143.4, 138.3, 132.7, 129.6, 128.3, 127.9, 127.0, 126.1, 124.1, 78.5, 47.8, 45.1(*CH_2*), 43.9(*CH_2*), 41.6, 33.5(*CH_2*), 31.8(*CH_2*), 25.5(*CH_2*), 21.8(*CH_2*), 21.7(*CH_2*), 21.5.

HRMS (ESI) *m/z* calc. for $[C_{25}H_{31}NO_3S+H]^+$ 426.2097, found: 426.2096.

116	**3-(Cyclohex-1-en-1-yl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{24}H_{27}NO_2S$

Molecular Weight: 393.55

Aspect: White solid

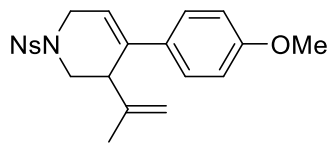
R_f = 0.20 (PE / EtOAc, 92/8)

After the above reaction, 18 mg of the product **116** were isolated in 30% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.13 (d, m, 5H), 5.95 (t, *J* = 3.3 Hz, 1H), 5.39 (s, 1H), 3.88 (dd, *J* = 17.0, 2.8 Hz, 1H), 3.47 (ddd, *J* = 12.9, 6.3, 3.2 Hz, 2H), 3.17 (s, 1H), 2.89 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.35 (s, 3H), 1.89 – 1.80 (m, 4H), 1.46 – 1.22 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.1, 137.7, 135.9, 133.8, 129.6, 128.2, 127.7, 127.2, 126.0, 125.7, 120.7, 47.5, 45.3, 45.2, 27.3, 25.3, 23.0, 22.2, 21.5.

120	**4-(4-Methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-3-(prop-1-en-2-yl)-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{21}H_{22}N_2O_5S$

Molecular Weight: 414.48

Aspect: White solid

R_f = 0.27 (PE / EtOAc, 5/1)

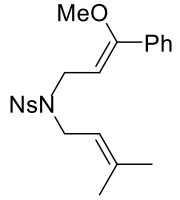
According to the general procedure **I**, 62 mg of 1,6-enyne **111** (0.15 mmol, 1 equiv., M = 414.48 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of XPhosAu(MeCN)SbF_6 (5 mol%, M = 950.48 g/mol) were added in the

reaction mixture. The resulting mixture was stirred for 16 h, to afford the awaited product (5 mg, 48% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.21 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 5.98 (t, *J* = 3.4 Hz, 1H), 4.89 (t, *J* = 1.4 Hz, 1H), 4.77 (s, 1H), 4.08 (dd, *J* = 17.0, 3.7 Hz, 1H), 3.78 – 3.75 (m, 4H), 3.57 (dt, *J* = 16.9, 2.6 Hz, 1H), 3.34 (s, 1H), 3.02 (dd, *J* = 11.8, 4.2 Hz, 1H), 1.77 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.2, 150.2, 143.1, 143.0, 137.3, 131.9, 128.8, 126.7, 124.3, 118.4, 115.4(*CH_2*), 113.8, 55.3, 47.1(*CH_2*), 45.1(*CH_2*), 44.9, 21.4.

121	**(*Z*)-*N*-(3-Methoxy-3-phenylallyl)-*N*-(3-methylbut-2-en-1-yl)-4-nitrobenzene-sulfonamide**



Chemical Formula: $C_{21}H_{24}N_2O_5S$

Molecular Weight: 416.49

Aspect: White solid

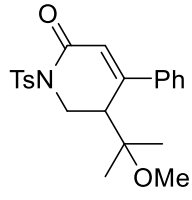
R_f = 0.24 (PE / EtOAc, 5/1)

After the above reaction, 19 mg of the awaited product were obtained in 31% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.99 (t, *J* = 7.1 Hz, 1H), 3.92 (d, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.54 (t, *J* = 7.2 Hz, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 1.65 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.4, 163.9, 149.9, 145.8, 138.3, 130.4, 129.4, 128.4, 124.3, 118.2, 113.9, 55.6, 46.9, 43.4, 38.4, 25.8, 17.9.

P-12	**5-(2-Methoxypropan-2-yl)-4-phenyl-1-tosyl-5,6-dihydropyridin-2(1*H*)-one**



Chemical Formula: $C_{22}H_{25}NO_4S$

Molecular Weight: 399.51

Aspect: White solid

R_f = 0. 54 (PE / EtOAc, 42/8)

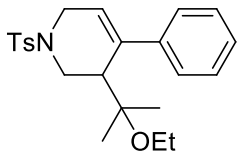
According to the general procedure **I**, 55 mg of 1,6-enyne **88** (0.15 mmol, 1 equiv., M = 367.46 g/mol) and 48 mg of MeOH (1.5 mmol, 10 equiv., M = 32.04 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, M = 950.48 g/mol) were added to the reaction mixture. The resulting mixture was stirred for 16 h, to afford the awaited product (41 mg, 68% yield, m.p. 160-162 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.39 (s, 5H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.11 (s, 1H), 5.02 (dd, *J* = 13.0, 1.1 Hz, 1H), 3.75 (dd, *J* = 13.0, 4.9 Hz, 1H), 3.18 (dd, *J* = 4.8, 1.0 Hz, 1H), 3.09 (s, 3H), 2.42 (s, 3H), 1.11 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.4, 156.2, 144.7, 139.1, 136.1, 129.8, 129.3, 128.9, 128.8, 126.7, 123.0, 76.8, 49.2, 45.6, 45.1, 25.0, 22.3, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{22}H_{25}NO_4S+H]^+$ 400.1577, found: 400.1572.

P-13 3-(2-Ethoxypropan-2-yl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{23}H_{29}NO_3S$

Molecular Weight: 399.55

Aspect: White solid

R_f = 0.28 (PE / EtOAc, 9/1)

According to the general procedure **I**, 53 mg of 1,6-enyne **77** (0.15 mmol, 1 equiv., M = 353.48 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (58 mg, 97% yield, m.p. 93-95 °C).

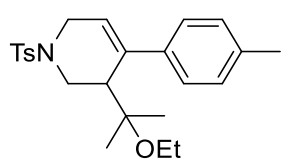
Enantioselective domino alkoxycyclization process: following procedure **J**, 53 mg of **77** and 69 mg of EtOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 46 mg of **P-13'** were isolated in 76% yield and 90% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 4H), 5.72 (t, *J* = 3.3 Hz, 1H), 4.33 (dd, *J* = 11.6, 0.9 Hz, 1H), 4.09 (dd, *J* = 17.2, 3.5 Hz, 1H), 3.37 – 3.19 (m, 3H), 2.95 (s, 1H), 2.48 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.43 (s, 3H), 2.31 (s, 3H), 1.29 (s, 3H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.6, 138.7, 136.6, 132.7, 129.6, 128.9, 127.8, 126.3, 123.2, 77.6, 56.1, 45.8, 45.2, 44.2, 26.5, 23.0, 21.5, 21.1, 15.7.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 3.0 mL / min, UV wavelength: λ = 230 nm. Retention time: 4.4 and 7.4 min.

P-14 3-(2-Ethoxypropan-2-yl)-4-(*p*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{24}H_{31}NO_3S$

Molecular Weight: 413.58

Aspect: White solid

R_f = 0.43 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **94** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (58 mg, 93% yield, m.p. 153-

155 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **94** and 138 mg of EtOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 48 mg of **P-14'** were obtained in 77% yield and 94% *ee*.

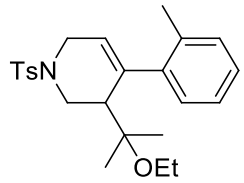
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 4H), 5.72 (t, *J* = 3.3 Hz, 1H), 4.33 (dd, *J* = 11.6, 0.9 Hz, 1H), 4.09 (dd, *J* = 17.2, 3.5 Hz, 1H), 3.37 – 3.19 (m, 3H), 2.95 (s, 1H), 2.48 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.43 (s, 3H), 2.31 (s, 3H), 1.29 (s, 3H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.6, 138.7, 136.6, 132.7, 129.6, 128.9, 127.8, 126.3, 123.2, 77.6, 56.1, 45.8, 45.2, 44.2, 26.5, 23.0, 21.5, 21.1, 15.7.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 250 nm. Retention time: 3.1 and 5.7 min. **$[\alpha]_D^{20}$**: +297.6 ($CHCl_3$, c = 0.01) at 94% *ee*

HRMS (ESI) *m/z* calc. for $[C_{24}H_{31}NO_3S+H]^+$ 414.2097, found: 414.2097.

P-15 3-(2-Ethoxypropan-2-yl)-4-(*o*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{24}H_{31}NO_3S$

Molecular Weight: 413.58

Aspect: White solid

R_f = 0.34 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **93** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture The product was obtained as a white solid (55 mg, 89% yield, m.p. 107-109 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **93** and 138 mg of EtOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 32 mg of **P-15'** were obtained in 51% yield and 93% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.12 – 7.06 (m, 3H), 7.01 (m, 1H), 5.61 (t, *J* = 3.2 Hz, 1H), 4.20 (dd, *J* = 8.0 Hz, 1H), 4.15 – 4.08 (m, 1H), 3.31 – 3.10 (m, 3H), 2.83 (s, 1H), 2.57 (dd, *J* = 11.7, 4.2 Hz, 1H), 2.44 (s, 3H), 2.24 (s, 3H), 1.32 (s, 3H), 1.01 (s, 3H), 0.80 (t, *J* = 6.9 Hz, 3H).

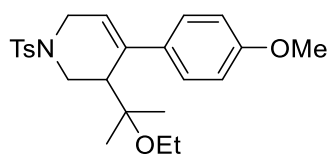
^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.6, 143.3, 138.4, 134.4, 132.8, 130.3, 129.7, 128.5, 127.8, 126.6, 125.4, 125.0, 77.5, 56.0, 46.9, 45.0, 44.2, 25.8, 23.4, 21.6, 20.1, 15.5.

SFC: Chiralcel IA, 100 bar, 10% MeOH, flow rate 3.0 mL / min, UV wavelength: λ = 220 nm.

Retention time: 6.3 and 7.2 min. **$[\alpha]_D^{20}$** : +220.9($CHCl_3$, c = 0.03) at 93% *ee*

HRMS (ESI) *m/z* calc. for $[C_{24}H_{31}NO_3S+H]^+$ 414.2097, found: 414.2096.

P-16 3-(2-Ethoxypropan-2-yl)-4-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{24}H_{31}NO_4S$

Molecular Weight: 429.58

Aspect: White solid

R_f = 0.21 (PE / EtOAc, 9/1)

According to the general procedure **I**, 58 mg of 1,6-enyne **95** (0.15 mmol, 1 equiv., M = 383.51 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (61 mg, 94% yield, m.p. 97-99 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 58 mg of **95** and 138 mg of EtOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 46 mg of **P-16'** were obtained in 71% yield and 96% *ee*.

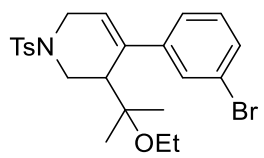
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.69 (t, *J* = 3.3 Hz, 1H), 4.32 (d, *J* = 11.6 Hz, 1H), 4.09 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.78 (s, 3H), 3.37 – 3.20 (m, 3H), 2.92 (s, 1H), 2.48 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.43 (s, 3H), 1.30 (s, 3H), 0.94 (t, *J* = 7.0 Hz, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.7, 143.5, 138.3, 136.0, 132.7, 129.6, 127.8, 127.4, 122.7, 113.5, 77.6, 56.1, 55.3, 45.9, 45.2, 44.3, 26.4, 23.0, 21.5, 15.8.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 3.9 and 8.8 min. **$[\alpha]_D^{20}$** : +211.6($CHCl_3$, c = 0.01) at 96% *ee*

HRMS (ESI) *m/z* calc. for $[C_{24}H_{31}NO_4S+H]^+$ 430.2047, found: 430.2077.

P-17 4-(3-Bromophenyl)-3-(2-ethoxypropan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{23}H_{28}BrNO_3S$

Molecular Weight: 478.45

Aspect: White solid

R_f = 0.25 (PE / EtOAc, 9/1)

According to the general procedure **I**, 65 mg of 1,6-enyne **96** (0.15 mmol, 1 equiv., M = 432.38 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (62 mg, 87% yield, m.p. 63-

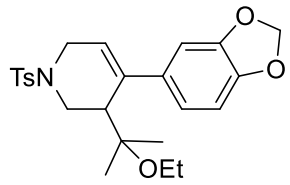
65 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.34 (m, 4H), 7.16 – 7.11 (m, 2H), 5.78 (t, *J* = 3.3 Hz, 1H), 4.24 (dd, *J* = 11.8, 1.0 Hz, 1H), 4.11 (dd, *J* = 17.3, 3.7 Hz, 1H), 3.33 – 3.16 (m, 3H), 2.90 (s, 1H), 2.50 (dd, *J* = 11.8, 4.1 Hz, 1H), 2.43 (s, 3H), 1.31 (s, 3H), 1.00 (s, 3H), 0.81 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.6, 143.7, 137.9, 132.6, 129.7, 129.7, 129.6, 129.5, 127.8, 125.1, 124.7, 122.2, 77.7, 55.9, 46.0, 45.2, 44.4, 25.6, 23.2, 21.6, 15.4.

SFC: Chiralcel ADH, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 3.8 and 9.9 min.

P-18	**4-(Benzo[*d*][1,3]dioxol-5-yl)-3-(2-ethoxypropan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{24}H_{29}NO_5S$

Molecular Weight: 443.56

Aspect: Yellow solid

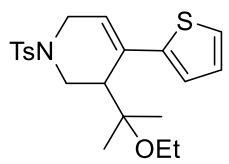
R_f = 0.48 (PE / EtOAc, 4/1)

According to the general procedure **I**, 60 mg of 1,6-enyne **98** (0.15 mmol, 1 equiv., M = 397.49 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (59 mg, 89% yield, m.p. 115-117 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.69 – 6.64 (m, 2H), 5.92 (s, 2H), 5.70 (t, *J* = 3.3 Hz, 1H), 4.30 (dd, *J* = 11.6, 1.0 Hz, 1H), 4.08 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.37 – 3.22 (m, 3H), 2.86 (s, 1H), 2.46 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.43 (s, 3H), 1.29 (s, 3H), 0.97 (t, *J* = 6.9 Hz, 2H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.5, 146.6, 143.5, 138.4, 137.7, 132.7, 129.6, 127.8, 123.1, 119.7, 108.0, 107.1, 101.0, 77.6, 56.1, 46.1, 45.1, 44.3, 26.3, 23.0, 21.5, 15.8.

P-20	**3-(2-Ethoxypropan-2-yl)-4-(thiophen-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{21}H_{27}NO_3S_2$

Molecular Weight: 405.57

Aspect: Red solid

R_f = 0.35 (PE / EtOAc, 9/1)

According to the general procedure **I**, 54 mg of 1,6-enyne **100** (0.15 mmol, 1 equiv., M = 359.50 g/mol) and 69 mg of EtOH (1.5 mmol, 10 equiv., M = 46.07 g/mol) were dissolved in 1.5 mL of

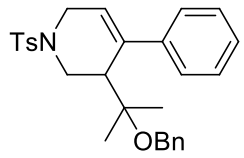
DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a red solid (57 mg, 94% yield, m.p. 95-97 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 54 mg of **100** and 69 mg of EtOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 41 mg of **P-20'** were obtained in 68% yield and 87% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.11 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.96 – 6.88 (m, 2H), 5.93 (t, *J* = 3.5 Hz, 1H), 4.30 (dd, *J* = 11.6, 1.4 Hz, 1H), 4.10 (dd, *J* = 17.7, 3.5 Hz, 1H), 3.42 – 3.25 (m, 3H), 2.86 (s, 1H), 2.47 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.42 (s, 3H), 1.34 (s, 3H), 1.07 (s, 3H), 1.03 (t, *J* = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.1, 143.6, 132.6, 132.4, 129.6, 127.8, 127.0, 123.6, 123.6, 123.1, 77.8, 56.2(*CH_2*), 47.4, 45.0(*CH_2*), 44.1(*CH_2*), 25.9, 23.0, 21.5, 15.8.

SFC: Chiralcel IA, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 4.1 and 5.5 min. **$[\alpha]_D^{20}$** dim light ($CHCl_3$, c = 0.01) at 87% *ee*
HRMS (ESI) *m/z* calc. for $[C_{21}H_{27}NO_3S_2+H]^+$ 378.1192, found: 378.1190.

P-21 3-(2-(Benzyloxy)propan-2-yl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{28}H_{31}NO_3S$
Molecular Weight: 461.62
Aspect: White solid
R_f = 0.24 (PE / EtOAc, 9/1)

According to the general procedure **I**, 53 mg of 1,6-enyne **77** (0.15 mmol, 1 equiv., M = 353.48 g/mol) and 164 mg of BnOH (1.5 mmol, 10 equiv., M =108.14 /mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added in the reaction mixture. The product was obtained as a white solid (60 mg, 86% yield, m.p. 119-121 °C).

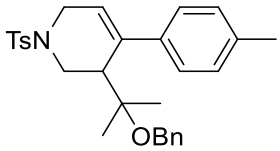
Enantioselective domino alkoxycyclization process: following procedure **J**, 53 mg of **77** and 164 mg of BnOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 30 mg of **P-21'** were obtained in 43% yield and 89% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.18 (m, 3H), 7.15 – 7.05 (m, 6H), 5.75 (t, *J* = 3.3 Hz, 1H), 4.43 (d, *J* = 10.6 Hz, 1H), 4.35 (dd, *J* = 36.4, 11.5 Hz, 2H), 4.13 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.29 (dt, *J* = 17.2, 2.5 Hz, 1H), 3.03 (s, 1H), 2.47 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 1.44 (s, 3H), 1.03 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.5, 139.4, 138.6, 136.7, 132.6, 129.6, 129.0,

128.1, 127.8, 127.5, 127.0, 126.3, 123.5, 78.6, 63.4, 46.4, 45.3, 44.4, 26.2, 22.8, 21.5, 21.1.

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 6.0 and 9.3 min. **$[\alpha]_D^{20}$** : +179.4 ($CHCl_3$, c = 0.03) at 89% *ee*

P-22 3-(2-(Benzyloxy)propan-2-yl)-4-(*p*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{29}H_{33}NO_3S$

Molecular Weight: 475.65

Aspect: White solid

R_f = 0.47 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **94** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 164 mg of BnOH (1.5 mmol, 10 equiv., M =108.14 /mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (66 mg, 92% yield, m.p. 158-160 °C).

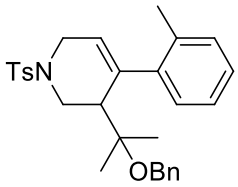
Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **94** and 328 mg of BnOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 49 mg of **P-22'** were obtained in 69% yield and 94% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.18 (m, 3H), 7.15 – 7.05 (m, 6H), 5.75 (t, *J* = 3.3 Hz, 1H), 4.43 (d, *J* = 10.6 Hz, 1H), 4.35 (dd, *J* = 36.4, 11.5 Hz, 2H), 4.13 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.29 (dt, *J* = 17.2, 2.5 Hz, 1H), 3.03 (s, 1H), 2.47 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 1.44 (s, 3H), 1.03 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.5, 139.4, 138.6, 136.7, 132.6, 129.6, 129.0, 128.1, 127.8, 127.5, 127.0, 126.3, 123.5, 78.6, 63.4, 46.4, 45.3, 44.4, 26.2, 22.8, 21.5, 21.1.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 250 nm. Retention time: 6.2 and 11.5 min. **$[\alpha]_D^{20}$** = +213.4 ($CHCl_3$, c = 0.03) at 94% *ee*

HRMS (ESI) *m/z* calc. for $[C_{29}H_{33}NO_3S+H]^+$ 476.2254, found: 476.2253.

P-23 3-(2-(Benzyloxy)propan-2-yl)-4-(*o*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{29}H_{33}NO_3S$

Molecular Weight: 475.65

Aspect: White solid

R_f = 0.36 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **93** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 164 mg of BnOH (1.5 mmol, 10 equiv., M =108.14g/mol) were dissolved in 1.5 mL

of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (63 mg, 89% yield, m.p. 120-122 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **93** and 328 mg of BnOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 37 mg of **P-23'** were obtained in 52% yield and 93% *ee*.

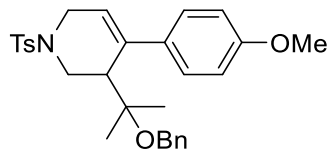
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.20 (m, 3H), 7.13 – 7.07 (m, 5H), 7.02 (d, *J* = 6.6 Hz, 1H), 5.64 (t, *J* = 3.2 Hz, 1H), 4.36 (dd, *J* = 11.7, 1.2 Hz,1H), 4.28 (s, 2H), 4.19 – 4.08 (m, 1H), 3.27 (dt, *J* = 16.9, 2.6 Hz, 1H), 2.91 (s, 1H), 2.54 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.43 (s, 3H), 2.25 (s, 3H), 1.46 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.6, 143.2, 139.4, 138.1, 134.5, 132.7, 130.6, 129.7, 128.4, 128.1, 127.8, 127.5, 127.0, 126.8, 125.6, 125.5, 78.4, 63.3, 47.8, 45.1, 44.3, 25.8, 23.2, 21.6, 20.2.

SFC: Chiralcel IA, 100 bar, 10% MeOH, flow rate 3.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 14.0 and 15.8 min. **$[\alpha]_D^{20}$** = +188.9 ($CHCl_3$, c = 0.02) at 93% *ee*

HRMS (ESI) *m/z* calc. for $[C_{29}H_{33}NO_3S+H]^+$ 476.2254, found: 476.2252.

P-24	**3-(2-(Benzyloxy)propan-2-yl)-4-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{29}H_{33}NO_4S$

Molecular Weight: 491.65

Aspect: White solid

R_f = 0.23 (PE / EtOAc, 9/1)

According to the general procedure **I**, 58 mg of 1,6-enyne **95** (0.15 mmol, 1 equiv., M = 383.51 g/mol) and 164 mg of BnOH (1.5 mmol, 10 equiv., M =108.14 /mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixtrue. The product was obtained as a white solid (63 mg, 86% yield, m.p. 150-152 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 58 mg of **95** and 328 mg of BnOH were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 50 mg of **P-24'** were obtained in 68% yield and 84% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.19 (m, 3H), 7.16 – 7.10 (m, 4H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.72 (t, *J* = 3.3 Hz, 1H), 4.43 (d, *J* = 10.6, 1H), 4.35 (dd, *J* = 35.8, 10.8 Hz, 2H), 4.13 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.78 (s, 3H), 3.29 (dt, *J* =

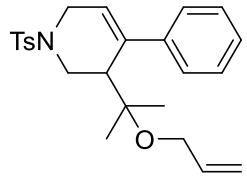
17.1, 2.6 Hz, 1H), 3.00 (s, 1H), 2.46 (dd, *J* = 11.7, 3.9 Hz, 1H), 2.42 (s, 3H), 1.44 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.8, 143.5, 139.4, 138.2, 135.9, 132.6, 129.6, 128.1, 127.8, 127.5, 127.5, 127.0, 123.0, 113.7, 78.6, 63.4, 55.2, 46.5, 45.3, 44.4, 26.1, 22.8, 21.5.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 7.7 and 17.8 min. **$[\alpha]_D^{20}$** = +199.3 ($CHCl_3$, c = 0.02) at 84% *ee*

HRMS (ESI) *m/z* calc. for $[C_{29}H_{33}NO_4S+H]^+$ 492.2203, found: 492.2202.

P-25 3-(2-(Allyloxy)propan-2-yl)-4-(phenyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{24}H_{29}NO_3S$

Molecular Weight: 411.56

Aspect: White solid

R_f = 0.26 (PE / EtOAc, 9/1)

According to the general procedure **I**, 53 mg of 1,6-enyne **77** (0.15 mmol, 1 equiv., M = 353.48 g/mol) and 88 mg of allyl alcohol (1.5 mmol, 10 equiv., M = 58.08 g/mol) were dissolved in 1.5 of mL DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (52 mg, 84% yield, m.p. 116-119°C).

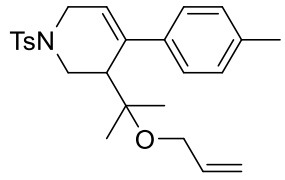
Enantioselective domino alkoxycyclization process: following procedure **J**, 53 mg of **77** and allyl alcohol 88 mg were dissolved in 1.5 mL $CDCl_3$, in the presence of **C-18** 5.6 mg (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 21 mg of **P-25'** were obtained in 34% yield and 84% *ee*.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.21 – 7.18 (m, 3H), 5.77 (t, *J* = 3.3 Hz, 1H), 5.69 – 5.51 (m, 1H), 5.08 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 4.12 (dd, *J* = 17.2, 3.7 Hz, 1H), 3.79 (qd, *J* = 12.1, 5.3 Hz, 2H), 3.29 (dt, *J* = 17.2, 2.6 Hz, 1H), 3.01 (s, 1H), 2.50 (dd, *J* = 11.7, 4.0 Hz, 1H), 2.43 (s, 3H), 1.34 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.7, 143.5, 138.9, 135.9, 132.8, 129.7, 128.3, 127.9, 127.1, 126.5, 124.1, 115.5, 78.3, 62.5, 46.2, 45.3, 44.4, 26.3, 23.1, 21.6.

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 2.9 and 5.4 min. **$[\alpha]_D^{20}$** = +114.8($CHCl_3$, c = 0.02) at 84% *ee*

P-26 3-(2-(Allyloxy)propan-2-yl)-4-(*p*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{25}H_{31}NO_3S$

Molecular Weight: 425.59

Aspect: White solid

R_f = 0.47 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **94** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 88 mg of allyl alcohol (1.5 mmol, 10 equiv., M = 58.08 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (56 mg, 87% yield, m.p. 124-126 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **94** and 176 mg of allyl alcohol were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 48 mg of **P-26'** were obtained in 75% yield and 93% *ee*.

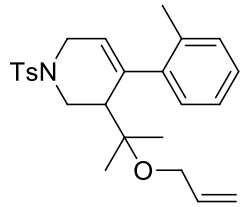
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 4H), 5.73 (t, *J* = 3.3 Hz, 1H), 5.72 – 5.59 (m, 1H), 5.13 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.7 Hz, 1H), 4.36 (dd, *J* = 12.5, 1.1 Hz, 1H), 4.10 (dd, *J* = 17.2, 3.8 Hz, 1H), 3.89 – 3.71 (m, 2H), 3.28 (dt, *J* = 17.1, 2.6 Hz, 1H), 2.98 (s, 1H), 2.48 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.43 (s, 3H), 2.31 (s, 3H), 1.33 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.5, 140.5, 138.5, 136.7, 135.9, 132.7, 129.6, 128.9, 127.8, 126.2, 123.4, 115.5, 78.2, 62.5, 46.0, 45.2, 44.2, 26.5, 22.9, 21.5, 21.1.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 250 nm. Retention time: 3.2 and 5.8 min. **$[\alpha]_D^{20}$** = +217.6 ($CHCl_3$, c = 0.01) at 93% *ee*

HRMS (ESI) *m/z* calc. for $[C_{25}H_{31}NO_3S+H]^+$ 426.2097, found: 426.2095.

P-27 3-(2-(Allyloxy)propan-2-yl)-4-(*o*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{25}H_{31}NO_3S$

Molecular Weight: 425.59

Aspect: White solid

R_f = 0.36 (PE / EtOAc, 9/1)

According to the general procedure **I**, 55 mg of 1,6-enyne **93** (0.15 mmol, 1 equiv., M = 367.51 g/mol) and 88 mg of allyl alcohol (1.5 mmol, 10 equiv., M = 58.08 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixtrue. The product was obtained as a white solid (54 mg, 85% yield, m.p. 103-105 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 55 mg of **93** and 176

mg of allyl alcohol were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 18 mg of **P-27'** were obtained in 28% yield and 88% *ee*.

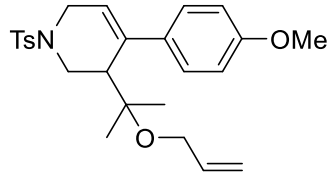
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.13 – 7.06 (m, 3H), 7.00 (m, 1H), 5.62 (t, *J* = 3.2 Hz, 1H), 5.02 (dd, *J* = 37.6, 1.5 Hz, 1H), 4.99 (dd, *J* = 30.7, 1.5 Hz, 1H), 4.24 (dd, *J* = 11.7, 1.2Hz, 1H), 4.12 (dd, *J* = 17.0, 3.6 Hz, 1H), 3.70 (qd, *J* = 12.0, 5.4 Hz, 2H), 3.27 (dt, *J* = 16.9, 2.5 Hz, 1H), 2.86 (s, 1H), 2.57 (dd, *J* = 11.8, 4.1 Hz, 1H), 2.44 (s, 3H), 2.24 (s, 3H), 1.36 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.6, 143.2, 138.2, 135.7, 134.4, 132.8, 130.4, 129.7, 128.5, 127.8, 126.7, 125.5, 125.2, 115.5, 78.1, 62.3, 47.2, 45.0, 44.2, 25.8, 23.4, 21.6, 20.1.

SFC: Chiralcel IA, 100 bar, 10% MeOH, flow rate 3.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 6.5 and 7.6 min. **$[\alpha]_D^{20}$** = +183.6 ($CHCl_3$, c = 0.02) at 88% *ee*

HRMS (ESI) *m/z* calc. for $[C_{25}H_{31}NO_3S+H]^+$ 426.2097, found: 426.2093.

P-28	**3-(2-(Allyloxy)propan-2-yl)-4-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydro-pyridine**



Chemical Formula: $C_{25}H_{31}NO_4S$

Molecular Weight: 441.59

Aspect: White solid

R_f = 0.23 (PE / EtOAc, 9/1)

According to the general procedure **I**, 58 mg of 1,6-enyne **95** (0.15 mmol, 1 equiv., M = 383.51 g/mol) and 88 mg of allyl alcohol (1.5 mmol, 10 equiv., M = 58.08 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (60 mg, 90% yield, m.p. 88-90 °C).

Enantioselective domino alkoxycyclization process: following procedure **J**, 58 mg of **95** and 176 mg of allyl alcohol were dissolved in 1.5 mL of $CDCl_3$, in the presence of 5.6 mg of **C-18** (2.5 mol%) and 4 mg of $AgNTf_2$ (7 mol%). 33 mg of **P-28'** were obtained in 50% yield and 87% *ee*.

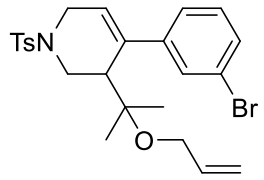
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.70 (m, 2H), 5.14 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.03 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.10 (dd, *J* = 17.1, 3.6 Hz, 1H), 3.89 – 3.73 (m, 2H), 3.78 (s, 3H), 3.28 (dt, *J* = 17.1, 2.5 Hz, 1H), 2.96 (s, 1H), 2.47 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.42 (s, 3H), 1.33 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.8, 143.5, 138.1, 135.9, 135.9, 132.7, 129.6, 127.8, 127.4, 122.9, 115.5, 113.7, 78.2, 62.4, 55.3, 46.1, 45.2, 44.3, 26.5, 22.9, 21.5.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 3.9 and 8.8 min. **$[\alpha]_D^{20}$** = +183.6 ($CHCl_3$, c = 0.02) at 87% *ee*

HRMS (ESI) *m/z* calc. for $[C_{25}H_{31}NO_4S+H]^+$ 442.2047, found: 442.2046.

P-29 3-(2-(Allyloxy)propan-2-yl)-4-(3-bromophenyl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{24}H_{28}BrNO_3S$

Molecular Weight: 490.46

Aspect: White solid

R_f = 0.27 (PE / EtOAc, 9/1)

According to the general procedure **I**, 65 mg of 1,6-enyne **96** (0.15 mmol, 1 equiv., M = 432.38 g/mol) and 88 mg of allyl alcohol (1.5 mmol, 10 equiv., M = 58.08 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (60 mg, 81% yield, m.p. 60-62 °C).

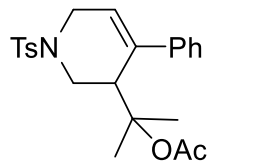
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.34 (m, 4H), 7.13 (m, 2H), 5.79 (t, *J* = 3.3 Hz, 1H), 5.57 (ddd, *J* = 22.5, 10.5, 5.3 Hz, 1H), 5.03 (dd, *J* = 28.9, 1.5 Hz, 1H), 4.99 (dd, *J* = 22.1, 1.5 Hz, 1H), 4.28 (d, *J* = 11.9 Hz, 1H), 4.12 (dd, *J* = 17.4, 3.7 Hz, 1H), 3.76 (qd, *J* = 12.0, 5.3 Hz, 2H), 3.28 (dt, *J* = 17.4, 2.5 Hz, 1H), 2.94 (s, 1H), 2.49 (dd, *J* = 11.8, 4.0 Hz, 1H), 2.43 (s, 3H), 1.34 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.5, 143.7, 137.7, 135.5, 132.5, 129.9, 129.7, 129.7, 129.5, 127.8, 125.1, 125.0, 122.3, 115.5, 78.2, 62.3, 46.2, 45.2, 44.4, 25.8, 23.1, 21.6.

SFC: Chiralcel AD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 220 nm. Retention time: 4.4 and 9.6 min.

HRMS (ESI) *m/z* calc. for $[C_{24}H_{28}BrNO_3S+H]^+$ 490.1046, found: 490.1045.

P-31 2-(4-Phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)propan-2-yl acetate



Chemical Formula: $C_{23}H_{27}NO_4S$

Molecular Weight: 413.53

Aspect: White solid

R_f = 0.33 (PE / EtOAc, 8/1)

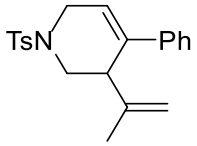
According to the general procedure **I**, 71 mg of 1,6-enyne **77** (0.2 mmol, 1 equiv., M = 353.48 g/mol) and 60 mg of acetic acid (1 mmol, 5 equiv., M = 60.05 g/mol) were dissolved in 2 mL of DCM. Then 9.5 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, M = 950.48 g/mol) were added to the reaction mixture. The resulting mixture was stirred for 16 h, to afford the awaited product (28 mg, 34% yield, m.p. 176-178 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.19 – 7.16 (m, 2H), 5.77 (dd, *J* = 3.8, 2.9 Hz, 1H), 4.14 (dd, *J* = 17.2, 3.8 Hz, 1H), 4.07 (d, *J* = 11.3 Hz, 1H), 3.84 (s, 1H), 3.26 (dt, *J* = 17.1, 2.5 Hz, 1H), 2.58 (dd, *J* = 12.2, 4.0 Hz, 1H), 2.44 (s, 3H), 1.69 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 171.0, 143.8, 142.7, 138.5, 132.5, 129.8, 128.4, 127.8, 127.0, 126.4, 124.0, 84.9, 45.3(*C*H_2), 45.0(*C*H_2), 42.7, 26.7, 25.3, 21.9, 21.6.

HRMS (ESI) *m/z* calc. for $[C_{23}H_{27}NO_4S+H]^+$ 414.1734, found: 414.1729.

78 **4-Phenyl-3-(prop-1-en-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine**



Chemical Formula: $C_{21}H_{23}NO_2S$

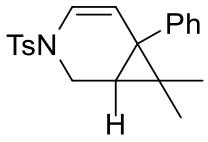
Molecular Weight: 353.48

Aspect: White solid

R_f = 0.29 (PE / EtOAc, 9/1

After the above reaction, 25 mg of the product **78** were obtained in 36% yield. The spectral data were identical to the literature.[66]

79 **7,7-Dimethyl-6-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene**



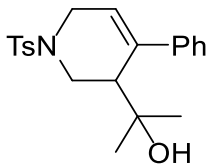
Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 353.48

R_f = 0.44 (PE / EtOAc, 9/1)

After the above reaction, 20 mg of the product **79** were obtained in 28% yield. The spectral data were identical to the literature.[66]

P-32 **2-(4-Phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)propan-2-ol**



Chemical Formula: $C_{21}H_{25}NO_3S$

Molecular Weight: 371.50

Aspect: White solid

R_f = 0.14 (PE/ EtOAc, 4/1)

According to the general procedure **I**, 53 mg of 1,6-enyne **77** (0.15 mmol, 1 equiv., M = 353.48 g/mol) and 27 mg of H_2O (1.5 mmol, 10 equiv., M = 28.02 g/mol) were dissolved in 2 mL of 1,4-dioxane. Then 9.5 mg of XPhosAu(MeCN)SbF_6 were added to the reaction mixture. The product was obtained as a white solid (44 mg, 79% yield).[188]

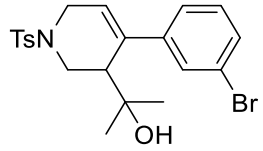
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.12 (m, 7H), 5.75 (t, *J* = 3.3 Hz, 1H), 4.22 (d, *J* = 11.9, 1H), 4.10 (dd, *J* = 17.2, 3.7 Hz, 1H), 3.25 (dt, *J* = 17.2, 2.5 Hz, 1H), 2.84

[188] D. -H. Zhang, Y. Wei, M. Shi, *Chem. Eur. J.*, **2012**, *18*, 7026.

(s, 1H), 2.46 (dd, *J* = 11.9, 3.7 Hz, 1H), 2.37 (s, 3H), 1.92 (br, 1H), 1.17 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d***)** δ 144.0, 142.6, 138.7, 132.4, 129.9, 128.7, 127.9, 127.7, 126.5, 123.6, 74.0, 47.4, 45.7, 45.5, 30.3, 28.6, 21.7.

P-33 2-(4-(3-Bromophenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)propan-2-ol



Chemical Formula: $C_{21}H_{24}BrNO_3S$

Molecular Weight: 450.39

Aspect: White solid R_f = 0.1 (PE / EtOAc, 9/1)

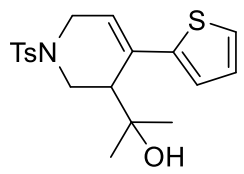
According to the general procedure **I**, 65 mg of 1,6-enyne **96** (0.15 mmol, 1 equiv., M = 432.38 g/mol) and 27 mg of H_2O (1.5 mmol, 10 equiv., M = 18.02 g/mol) were dissolved in 1.5 mL of 1,4-dioxane. Then 7 mg (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (50 mg, 74% yield, m.p. 120-122 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.32 (m, 4H), 7.17 (d, *J* = 5.1 Hz, 2H), 5.84 (t, *J* = 3.3 Hz, 1H), 4.36 – 4.26 (dd, *J* = 11.6, 1.0 Hz, 1H), 4.17 (dd, *J* = 17.4, 3.7 Hz, 1H), 3.31 (dt, *J* = 17.3, 2.4 Hz, 1H), 2.84 (s, 1H), 2.51 (dd, *J* = 11.9, 3.6 Hz, 1H), 2.44 (s, 3H), 1.86 (s, 1H), 1.23 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 144.8, 144.0, 137.5, 132.3, 130.4, 130.1, 129.8, 129.4, 127.8, 125.0, 124.8, 122.7, 73.8, 47.2, 45.6, 45.3, 30.3, 28.7, 21.6.

HRMS (ESI) *m/z* calc. for $[C_{21}H_{24}BrNO_3S+H]^+$ 450.0733, found: 450.0730.

P-34 2-(4-(Thiophen-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)propan-2-ol



Chemical Formula: $C_{19}H_{23}NO_3S_2$

Molecular Weight: 377.52

Aspect: Red oil

R_f = 0.34 (PE / EtOAc, 3/1)

According to the general procedure **I**, 54 mg of 1,6-enyne **100** (0.15 mmol, 1 equiv., M = 359.50 g/mol) and 27 mg of H_2O (1.5 mmol, 10 equiv., M = 18.02 g/mol) were dissolved in 1.5 mL of 1,4-dioxane. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a red oil (40 mg, 71% yield, m.p. 78-80 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 4.9 Hz, 1H), 7.00 – 6.90 (m, 2H), 5.97 (t, *J* = 3.4 Hz, 1H), 4.24 (d, *J* = 11.8 Hz, 1H), 4.14 (dd, *J* = 17.7, 3.5 Hz, 1H), 3.33 (d, *J* = 17.6 Hz, 1H), 2.81 (s, 1H), 2.51 (dd, *J* = 11.9, 3.3 Hz, 1H), 2.43 (s, 3H), 2.12 (s, 1H), 1.31 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.5, 144.0, 132.2, 132.2, 129.8, 127.8, 127.4, 124.4,

123.8, 122.6, 74.0, 48.3, 45.4(*CH₂*), 45.2(*CH₂*), 30.0, 28.6, 21.6.

HRMS (ESI) *m/z* calc. for $[C_{19}H_{23}NO_3S_2+H]^+$ 378.1192, found: 378.1190.

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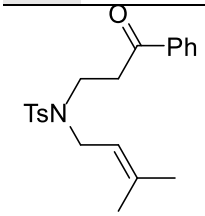
115 **4-Methyl-N-(3-methylbut-2-en-1-yl)-N-(3-oxo-3-phenylpropyl)benzenesulfonamide**



Chemical Formula: $C_{21}H_{25}NO_3S$

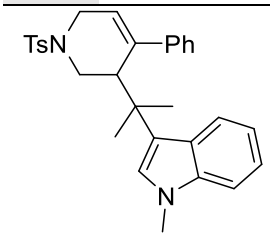
Molecular Weight: 371.49

R_f = 0.19 (PE / EtOAc, 94/6)

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 6.9 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.63 – 7.54 (m, 1H), 7.52 – 7.40 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 5.03 (d, *J* = 7.0, Hz, 1H), 3.82 (d, *J* = 7.0 Hz, 2H), 3.56 – 3.28 (m, 4H), 2.42 (s, 3H), 1.62 (dd, *J* = 3.0, 1.4 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 198.5, 143.3, 137.4, 136.6, 136.5, 133.4, 129.7, 128.7, 128.1, 127.3, 119.0, 46.9, 43.2, 39.2, 25.8, 21.5, 17.8.

P-35 **1-Methyl-3-(2-(4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)propan-2-yl)-1H-indole**



Chemical Formula: $C_{30}H_{32}N_2O_2S$

Molecular Weight: 484.66

Aspect: Brown solid

R_f = 0.22 (PE / EtOAc, 94/6)

According to the general procedure **I**, 53 mg of 1,6-enyne **77** (0.15 mmol, 1 equiv., M = 353.48 g/mol) and 197 mg of 1-methyl-1*H*-indole (1.5 mmol, 10 equiv., M = 131.18 g/mol) were dissolved in 1.5 mL of DCM. Then 7 mg of gold catalyst XPhosAu(MeCN)SbF_6 (5 mol%, 950.48 g/mol) were added to the reaction mixture. The product was obtained as a white solid (47 mg, 64% yield, , m.p. 133-135 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 3H), 7.28 – 7.20 (m, 1H), 7.16 (dd, *J* = 14.4, 4.6 Hz, 6H), 6.80 (s, 1H), 5.81 (t, *J* = 3.1 Hz, 1H), 4.18 (dd, *J* = 17.1, 3.3 Hz, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.67 (s, 3H), 3.59 (s, 1H), 3.27 (d, *J* = 17.2 Hz, 1H), 2.42 (s, 3H), 2.39 (dd, *J* = 8.0, 3.6 Hz, 1H), 1.67 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.7, 143.4, 139.5, 137.9, 132.4, 129.6, 127.9, 127.8, 127.5, 126.5, 126.0, 125.9, 123.7, 122.6, 120.8, 118.2, 109.6, 46.0(*CH₂*), 45.4(*CH₂*), 44.4, 39.7, 32.5, 29.6, 25.8, 21.5.

HRMS (ESI) *m/z* calc. for $[C_{30}H_{32}N_2O_2S+H]^+$ 485.2257, found: 485.2254.

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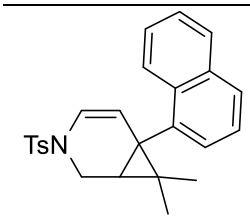
117 **7,7-Dimethyl-6-(naphthalen-1-yl)-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene**



Chemical Formula: $C_{25}H_{25}NO_2S$

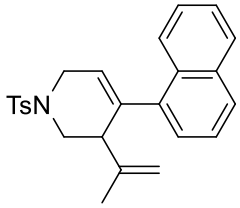
Molecular Weight: 403.54

Aspect: White solid

R_f = 0.41 (PE / EtOAc, 9/1)

According to the general procedure **K**, 61 mg of 1,6-enyne **99** (0.15 mmol, 1 equiv., M = 403.54 g/mol) was dissolved in 1.5 mL of DCM in the presence of 5.5 mg of $Ph_3AuPNTf_2$ (5 mol%, M = 739.39 g/mol). The awaited product was isolated in 14% yield. The spectral data were identical to the literature. [66]

118 4-(Naphthalen-1-yl)-3-(prop-1-en-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine



Chemical Formula: $C_{25}H_{25}NO_2S$

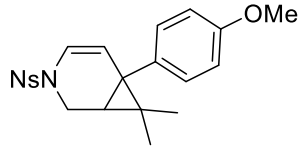
Molecular Weight: 403.54

Aspect: White solid

R_f = 0.32 (PE / EtOAc, 9/1)

After the above reaction, the awaited product **118** was obtained in 71% yield. The spectral data were identical to the literature.[66]

119 6-(4-Methoxyphenyl)-7,7-dimethyl-3-((4-nitrophenyl)sulfonyl)-3-azabicyclo[4.1.0]-hept-4-ene



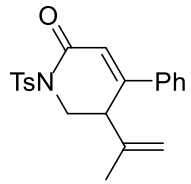
Chemical Formula: $C_{21}H_{22}N_2O_5S$

Molecular Weight: 414.48

R_f = 0.47 (PE / EtOAc, 5/1)

According to the general procedure **K**, 62 mg of the 1,6-enyne **111** (0.15 mmol, 1 equiv., M = 414.48 g/mol) were dissolved in 1.5 mL of DCM in the presence of 2 mg of $PtCl_2$ (5 mol%, M = 265.98 g/mol). The awaited product **119** was obtained in 14% yield. The spectral data were identical to the literature.[186]

81 4-Phenyl-5-(prop-1-en-2-yl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one



Chemical Formula: $C_{21}H_{21}NO_3S$

Molecular Weight: 367.46

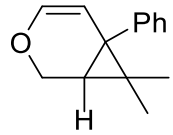
Aspect: White solid

R_f = 0.19 (PE / EtOAc 85/15)

According to the general procedure **K**, 55 mg of the 1,6-enyne **80** (0.15 mmol, 1 equiv., M = 367.46 g/mol) were dissolved in 1.5 mL of DCM in the presence of 5.5 mg of $Ph_3AuPNTf_2$ (5

mol%, M = 739.39 g/mol). The awaited product was obtained in 57% yield. The spectral data were identical to the literature. [86]

123 7,7-Dimethyl-6-phenyl-3-oxabicyclo[4.1.0]hept-4-ene



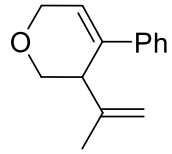
Chemical Formula: $C_{14}H_{16}O$

Molecular Weight: 200.28

R_f = 0.76 (PE / EtOAc, 10/1)

According to the general procedure **K**, 40 mg of 1,6-enyne **76** (0.2 mmol, 1 equiv., M = 200.28 g/mol) were dissolved in 2 mL of DCM in the presence of 7 mg of $Ph_3AuPNTf_2$ (5 mol%, M = 739.39 g/mol). The awaited product was isolated in 40% yield. The spectral data were identical to the literature. [87]

124 4-Phenyl-3-(prop-1-en-2-yl)-3,6-dihydro-2*H*-pyran



Chemical Formula: $C_{14}H_{16}O$

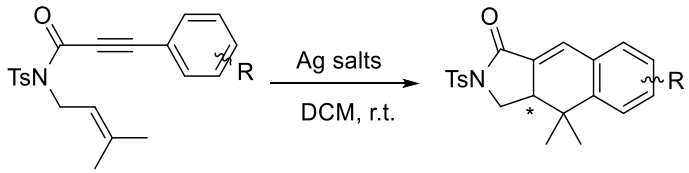
Molecular Weight: 200.28

R_f = 0.65 (PE / EtOAc, 10/1)

After the above reaction, the awaited product **124** was isolated with 33% yield and the spectral data were identical to the literature.[87]

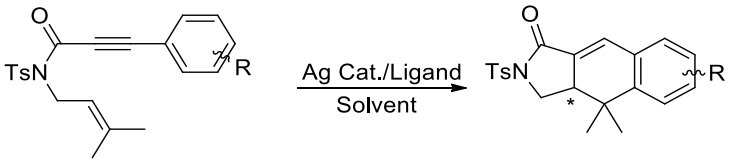
2.3 Silver-catalyzed cyclosiomerization reaction from 1,6-enyne

General procedure L:



In a clean and dried screw-capped vial, the substrate (0.2 mol, 1 equiv.) was diluted with 2 mL of dry DCM, and 5 mol% of Ag was added. The mixture was stirred at room temperature. After 8-48 hours (reaction followed by TLC), the mixture was filtered through a short pad of silica gel with DCM and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography (PE / EtOAc 5/1-4/1) to afford the corresponding product.

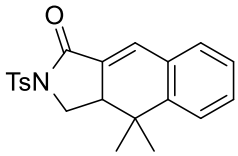
Synthetic procedure of asymmetric reaction M:



The Ag salt* (0.01 mmol, 5 mol%) and the ligand* (0.01 mmol, 5 mol%) were diluted in 2 mL of dry DCM. The mixture was stirred for 30 minutes, and the substrate (0.2 mmol, 1 equiv.) was added to the reaction mixture. The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered through a short pad of silica gel with DCM, and the crude product was purified by silica-gel column chromatography (petroleum ether/ethyl acetate 5/1) to afford the awaited product.

* Ratio Ag salt/Ligand = 1/1 as an example

P-36 4,4-Dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 367.46

Aspect: White solid

R_f = 0.27 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **80** (73.5 mg, 0.2 mol, 1 equiv., M = 367.46 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL DCM. The target molecule was obtained as a white solid (71.2 mg, 97% yield, m.p. 175-177 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.35 (m, 4H), 7.31 (d, *J* = 3.3 Hz, 1H), 7.25 – 7.17 (m, 2H), 4.18 (t, *J* = 9.8 Hz, 1H), 3.78 (dd, *J* = 9.8, 8.0 Hz, 1H), 3.09 (ddd, *J* = 9.5, 8.1, 3.4 Hz, 1H), 2.43 (s, 3H), 1.46 (s, 3H), 0.92 (s, 3H).

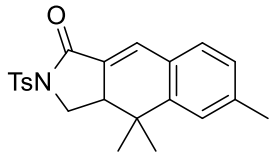
^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.2, 145.3, 145.2, 135.3, 131.8, 131.2, 130.9, 130.7, 129.9, 129.8, 128.1, 127.1, 124.0, 46.2, 41.0, 36.8, 24.8, 21.9, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{21}H_{21}NO_3S+H]^+$ 368.1315, found: 368.1311.

HPLC: Chiralcel IA, *n*-hexane / *i*-PrOH (80:20), flow rate 1.0 mL / min, UV wavelength: λ = 320 nm. Retention time: 21.3 and 23.7 min. (or Chiralcel IA, *n*-hexane / *i*-PrOH (90:10), flow rate 1.0 mL / min, UV wavelength: λ = 320 nm. Retention time: 41.8 and 46.8 min.)

$[\alpha]_D^{20}$: -32.5 ($CHCl_3$, c = 2) at 40 % *ee*.

P-37 4,4,6-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 381.49

Aspect: White solid

R_f = 0.27 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **137** (76 mg, 0.2 mol, 1 equiv., M = 381.49 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL of dry DCM. The desired compound was obtained as a white solid (67 mg, 88% yield, m.p. 191-193°C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 3.3 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 4.17 (t, *J* = 9.8 Hz, 1H), 3.77 (dd, *J* = 9.8, 8.1 Hz, 1H), 3.07 (ddd, *J* = 9.4, 8.1 3.3 Hz, 1H), 2.43 (s, 3H), 2.37 (s, 3H), 1.44 (s, 3H), 0.90 (s, 3H).

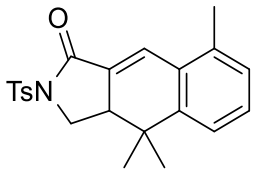
^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.4, 145.3, 145.2, 141.4, 135.4, 131.9, 129.9, 129.7, 129.5, 128.6, 128.1, 127.6, 124.9, 46.2, 41.1, 36.7, 24.8, 21.9, 21.9, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{22}H_{23}NO_3S+H]^+$ 382.1471, found: 382.1465.

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 340 nm. Retention time: 7.9 and 13.0 min.

$[\alpha]_D^{20}$: -52.1 ($CHCl_3$, c = 1.5) at 42 % *ee*.

P-38 4,4,8-Trimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 381.49

Aspect: White solid

R_f = 0.24 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **138** (76 mg, 0.2 mol, 1 equiv., M = 381.49 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL dry DCM. The desired compound was obtained as a white solid (74 mg, 97% yield, m.p. 169-171 °C).

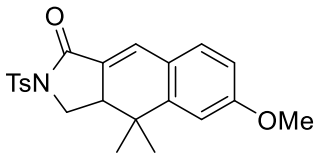
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 3.4 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.21 (m, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 4.17 (t, *J* = 9.9 Hz, 1H), 3.79 (dd, *J* = 10.1, 7.6 Hz, 1H), 3.05 (ddd, *J* = 10.4, 7.7, 3.4 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 1.43 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.4, 145.5, 145.2, 137.3, 135.4, 130.5, 130.5, 129.8, 129.7, 128.9, 128.6, 128.2, 121.7, 46.1, 40.4, 37.2, 25.1, 21.7, 21.5, 19.5.

HRMS (ESI) *m/z* calc. for $[C_{22}H_{23}NO_3S+H]^+$ 382.1471, found: 382.1464.

HPLC: Chiralcel IA, *n*-hexane / *i*-PrOH (80:20), flow rate 1.0 mL / min, UV wavelength: λ = 255 nm. Retention time: 11.9 and 15.4 min. **$[\alpha]_D^{20}$**: -32.6 ($CHCl_3$, c = 1) at 50% *ee*.

P-39 6-Methoxy-4,4-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 397.49

Aspect: White solid

R_f = 0.27 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **139** (79.5 mg, 0.2 mol, 1 equiv., M = 397.49 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL dry DCM. The desired compound was obtained as a white solid (56 mg, 71% yield, m.p. 157-159 °C).

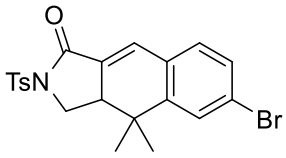
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 3.3 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.17 (t, *J* = 9.8 Hz, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 9.9, 8.1 Hz, 1H), 3.05 (ddd, *J* = 9.9, 8.0, 3.3 Hz, 1H), 2.43 (s, 3H), 1.42 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.4, 161.8, 147.6, 145.1, 135.4, 131.6, 131.5, 129.7, 128.1, 127.8, 124.4, 111.4, 110.7, 55.4, 46.1, 40.8, 37.0, 24.7, 21.8, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{22}H_{23}NO_4S+H]^+$ 398.1421, found: 398.1414.

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 340 nm. Retention time: 12.3 and 17.6 min. **$[\alpha]_D^{20}$**: -54.3 ($CHCl_3$, c = 1.5) at 31 % *ee*.

P-40 6-Bromo-4,4-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 446.36

Aspect: White solid

R_f = 0.26 (PE / EtOAc, 5/1)

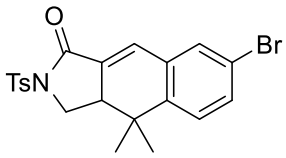
According to the general procedure **L**, a screw-capped vial was charged with the substrate **141** (89 mg, 0.2 mol, 1 equiv., M = 446.36 g/mol), $AgSbF_6$ (3.4 mg, 5 mol%, M = 343.62 g/mol) and 2 mL dry DCM. The desired compound was obtained as a white solid (69 mg, 78 % yield, m.p. 247-249 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.25 (d, *J* = 3.4 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 4.18 (t, *J* = 9.8 Hz, 1H), 3.77 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.06 (ddd, *J* = 9.5, 8.0, 3.4 Hz, 1H), 2.44 (s, 3H), 1.45 (s, 3H), 0.93 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.9, 147.2, 145.4, 135.2, 131.3, 131.0, 130.6, 130.2, 130.2, 129.8, 128.2, 127.6, 125.0, 46.0, 40.8, 37.0, 24.7, 21.8, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{21}H_{20}BrNO_3S+H]^+$ 446.0420, found: 446.0415

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 310 nm. Retention time: 13.8 and 17.9 min. **$[\alpha]_D^{20}$**: -9.2 ($CHCl_3$, c = 1) at 14 % *ee*.

P-41 7-Bromo-4,4-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$
Molecular Weight: 446.36
Aspect: White solid
R_f = 0.26 (PE / EtOAc, 5/1)

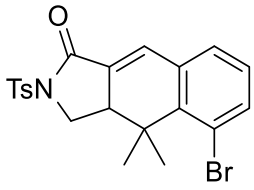
According to the general procedure **L**, a screw-capped vial was charged with the substrate **140** (89 mg, 0.2 mol, 1 equiv., M = 446.36 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL dry DCM. The desired compound was obtained as a white solid (59 mg, 67% yield, m.p. 153-155 °C). It was characterized by **X-Ray**. CDCC number: 1991079

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.35 (m, 3H), 7.24 – 7.19 (m, 2H), 4.18 (t, *J* = 9.8 Hz, 1H), 3.78 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.10 (ddd, *J* = 9.6, 7.8, 3.4 Hz, 1H), 2.44 (s, 3H), 1.44 (s, 3H), 0.91 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.7, 145.4, 144.0, 135.2, 133.4, 133.3, 132.4, 132.2, 130.2, 129.8, 128.2, 125.8, 120.8, 46.0, 40.9, 36.7, 24.7, 21.8, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{21}H_{20}BrNO_3S+H]^+$ 446.0420, found: 446.0415

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 310 nm. Retention time: 26.3 and 28.7 min. **$[\alpha]_D^{20}$**: -24.6 ($CHCl_3$, c = 1) at 34% *ee*.

P-42 5-Bromo-4,4-dimethyl-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one



Chemical Formula: $C_{21}H_{23}NO_2S$
Molecular Weight: 446.36
Aspect: White solid
R_f = 0.27 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **140** (89 mg, 0.2 mol, 1 equiv., M = 446.36 g/mol), $AgSbF_6$ (3.4 mg, 5 mol%, M = 343.62 g/mol) and

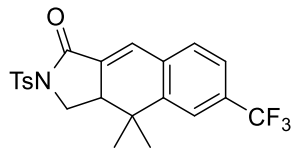
2 mL dry DCM. The desired compound was obtained as a white solid (35 mg, 40% yield, m.p. 101-103 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.52 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 3.5 Hz, 1H), 7.17 (d, *J* = 6.8 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 4.17 (t, *J* = 9.9 Hz, 1H), 3.80 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.20 (ddd, *J* = 9.5, 8.1, 3.5 Hz, 1H), 2.44 (s, 3H), 1.82 (s, 3H), 1.08 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.7, 145.4, 142.7, 138.1, 135.2, 134.7, 131.7, 130.4, 130.1, 129.8, 128.3, 128.2, 121.9, 46.5, 42.3, 40.3, 26.8, 21.7, 18.4.

HRMS (ESI) *m/z* calc. for $[C_{21}H_{20}BrNO_3S+H]^+$ 446.0420, found: 446.0414

SFC: Chiralcel AD-H, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 310 nm. Retention time: 16.8 and 19.3 min.

P-43	**4,4-Dimethyl-2-tosyl-6-(trifluoromethyl)-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one**



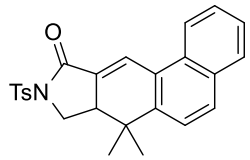
Chemical Formula: $C_{21}H_{23}NO_2S$
Molecular Weight: 435.46
Aspect: White solid
R_f = 0.29 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **148** (43.5 mg, 0.1 mol, 1 equiv., M = 435.46 g/mol), $AgNTf_2$ (2 mg, 5 mol%, M = 388.14 g/mol) and 1 mL dry DCM. The desired compound was obtained as a white solid (35 mg, 81 % yield, m.p. 173-175 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.64 (dd, *J* = 11.8, 7.6 Hz, 1H), 7.55 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 3.4 Hz, 1H), 4.21 (t, *J* = 9.8 Hz, 1H), 3.81 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.13 (ddd, *J* = 9.6, 8.0, 3.4 Hz, 1H), 2.44 (s, 3H), 1.51 (s, 3H), 0.96 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.6, 145.9, 145.5, 135.1, 134.4, 133.5, 132.2 (q, *J* = 32.3 Hz), 130.0, 129.8, 129.8, 128.2, 124.1 (q, *J* = 3.9 Hz), 123.8 (q, *J* = 272.5 Hz), 120.9 (q, *J* = 3.8 Hz), 46.0, 40.8, 37.0, 24.7, 21.9, 21.7.

HRMS (ESI) *m/z* calc. for $[C_{22}H_{20}F_3NO_3S+H]^+$ 436.1189, found: 436.1189

P-44	**7,7-Dimethyl-9-tosyl-7,7a,8,9-tetrahydro-10*H*-naphtho[1,2-*f*]isoindol-10-one**



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 417.52

Aspect: White solid

R_f = 0.30 (PE / EtOAc, 5/1)

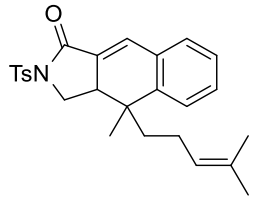
According to the general procedure **L**, a screw-capped vial was charged with the substrate **146** (42 mg, 0.1 mol, 1 equiv., M = 417.52 g/mol), $AgNTf_2$ (2 mg, 5 mol%, M = 388.14 g/mol) and 1 mL dry DCM. The desired compound was obtained as a white solid (31 mg, 75 % yield, m.p. 96-98 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 3.4 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.23 (t, *J* = 9.9 Hz, 1H), 3.86 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.19 (ddd, *J* = 10.2, 7.5, 3.4 Hz, 1H), 2.44 (s, 3H), 1.55 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.3, 145.3, 143.7, 135.4, 132.3, 131.4, 130.9, 130.8, 129.8, 128.5, 128.2, 127.4, 127.1, 126.8, 126.0, 123.0, 122.1, 46.1, 40.7, 37.8, 25.4, 21.7, 21.0.

HRMS (ESI) *m/z* calc. for $[C_{25}H_{23}NO_3S+H]^+$ 418.1471, found: 418.1470

P-45	**4-Methyl-4-(4-methylpent-3-en-1-yl)-2-tosyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]-isoind-ol-1-one**



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 435.58

Aspect: Mousse

R_f = 0.28 (PE / EtOAc, 5/1)

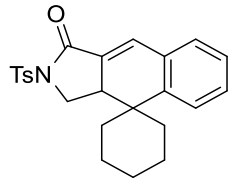
According to the general procedure **L**, a screw-capped vial was charged with the substrate **145** (43 mg, 0.1 mol, 1 equiv., M = 435.58 g/mol), $AgNTf_2$ (2 mg, 5 mol%, M = 388.14 g/mol) and 1 mL dry DCM. The desired compound was obtained as a mousse state (31 mg, 75 % yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.32 (m, 3H), 7.28 – 7.21 (m, 4H), 5.17 (t, *J* = 6.1 Hz, 1H), 4.14 (t, *J* = 9.7 Hz, 1H), 3.76 (dd, *J* = 9.9, 8.1 Hz, 1H), 3.38 (ddd, *J* = 9.3, 8.0, 3.4 Hz, 1H), 2.43 (s, 3H), 2.16 – 1.98 (m, 3H), 1.72 (s, 3H), 1.67 – 1.56 (m, 4H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.2, 145.3, 143.0, 135.3, 132.4, 132.1, 131.3, 130.9, 130.5, 130.3, 129.8, 128.2, 126.9, 124.5, 123.7, 45.9, 40.6, 36.5, 36.2, 25.7, 23.3, 22.9, 21.7, 17.9.

HRMS (ESI) *m/z* calc. for $[C_{26}H_{29}NO_3S+H]^+$ 436.1941, found: 436.1942

P-46 2-Tosyl-3,3a-dihydrospiro[benzo[*f*]isoindole-4,1'-cyclohexan]-1(2*H*)-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 407.53

Aspect: White solid

R_f = 0.35 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **152** (81.5 mg, 0.2 mol, 1 equiv., M = 407.53 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL dry DCM. The desired compound was obtained as a white solid (57 mg, 70% yield, m.p. 212-214 °C).

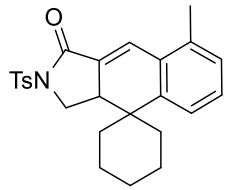
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.21 (d, *J* = 4.2 Hz, 2H), 4.11 (t, *J* = 10.0 Hz, 1H), 3.91 (dd, *J* = 10.2, 7.4 Hz, 1H), 3.06 (ddd, *J* = 10.2, 7.5, 3.3 Hz, 1H), 2.43 (s, 3H), 2.11 (d, *J* = 15.0 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.86 (d, *J* = 14.2 Hz, 1H), 1.77 (d, *J* = 12.8 Hz, 1H), 1.53 (dq, *J* = 13.1, 6.1 Hz, 2H), 1.39 (d, *J* = 13.2 Hz, 1H), 1.28 – 1.10 (m, 2H), 0.92 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.1, 145.2, 145.0, 135.4, 132.5, 132.2, 130.7, 129.8, 129.8, 129.5, 128.2, 127.1, 126.8, 46.3, 41.9, 38.9, 32.0, 28.7, 25.9, 24.1, 21.7, 21.2.

HRMS (ESI) *m/z* calc. for $[C_{24}H_{25}NO_3S+H]^+$ 408.1628, found: 408.1624.

SFC: Chiralcel OD, 150 bar, 15% MeOH, flow rate 4.0 mL / min, UV wavelength: λ = 320 nm. Retention time: 4.5 and 5.6 min. **$[\alpha]_D^{20}$**: -16.2 ($CHCl_3$, c = 0.5) at 24% ee.

P-47 8-Methyl-2-tosyl-3,3a-dihydrospiro[benzo[*f*]isoindole-4,1'-cyclohexan]-1(2*H*)-one



Chemical Formula: $C_{21}H_{23}NO_2S$

Molecular Weight: 421.56

Aspect: White solid

R_f = 0.30 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **153** (84 mg, 0.2 mol, 1 equiv., M = 421.56 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL dry DCM. The desired compound was obtained as a white solid (22 mg, 26 % yield, m.p. 243-245 °C).

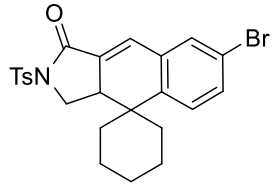
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 3.4 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.10 (t, *J* = 10.1 Hz, 1H), 3.92 (dd, *J* = 10.3, 7.0 Hz, 1H), 3.04 (ddd, *J* = 10.0, 7.0, 3.4 Hz, 2H), 2.44 (s, 3H), 2.35 (s, 3H), 2.10 – 1.95 (m, 2H), 1.89 – 1.74 (m, 2H), 1.49 – 1.35 (m, 2H), 1.22 – 1.16 (m, 2H),

0.98 – 0.86 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.3, 145.2, 137.3, 135.4, 130.9, 130.5, 129.7, 129.1, 129.1, 128.8, 128.2, 124.8, 46.3(*CH*$_2$), 41.4, 39.2, 32.1(*CH*$_2$), 28.5(*CH*$_2$), 26.0(*CH*$_2$), 24.1(*CH*$_2$), 21.7, 21.3(*CH*$_2$), 19.7.

HRMS (ESI) *m/z* calc. for [M $C_{25}H_{27}NO_3S$+H]$^+$ 422.1784, found: 422.1778

P-48 7-Bromo-2-tosyl-3,3a-dihydrospiro[benzo[f]isoindole-4,1'-cyclohexan]-1(2*H*)-one



Chemical Formula: $C_{24}H_{24}BrNO_3S$

Molecular Weight: 486.42

R_f = 0.29 (PE / EtOAc, 5/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **155** 96 mg (0.2 mol, 1 equiv., M = 486.42 g/mol), $AgNTf_2$ (3.9 mg, 5 mol%, M = 388.14 g/mol) and 2 mL dry DCM. The desired compound was observed in 25% NMR yield (determined by ^{1}H NMR).

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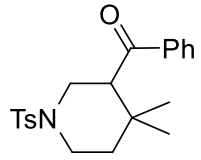
156 (4,4-Dimethyl-1-tosylpiperidin-3-yl)(phenyl)methanone



Chemical Formula: $C_{21}H_{25}NO_3S$

Molecular Weight: 371.50

R_f = 0.32 (PE / EtOAc, 6/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **77** 71 mg (0.2 mol, 1 equiv., M = 353.48 g/mol), $AgNTf_2$ 3.9 mg (5 mol%, M = 388.14 g/mol) and 2 mL dry DCE at 82 °C. The desired compound was obtained 13 mg (18 % yield). The spectral data were identical to the literature.[99]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 – 7.87 (m, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.43 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.72 – 3.62 (m, 3H), 2.77 (t, *J* = 12.5 Hz, 1H), 2.60 – 2.39 (m, 4H), 1.78 (td, *J* = 12.9, 4.4 Hz, 1H), 1.46 (dt, J = 13.5, 2.8 Hz, 1H), 0.87 (s, 3H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.4, 143.7, 138.2, 133.4, 133.2, 129.8, 128.7, 128.3, 127.7, 50.8, 44.5(*CH*$_2$), 42.4(*CH*$_2$), 40.0(*CH*$_2$), 32.5, 31.2, 21.6, 19.8.

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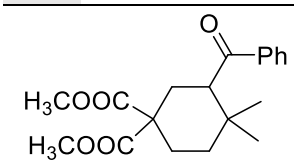
157 Dimethyl 3-benzoyl-4,4-dimethylcyclohexane-1,1-dicarboxylate



Chemical Formula: $C_{19}H_{24}O_5$

Molecular Weight: 332.40

R_f = 0.30 (PE / EtOAc, 7/1)

According to the general procedure **L**, a screw-capped vial was charged with the substrate **112**

63 mg (0.2 mol, 1 equiv., M = 314.38 g/mol), $AgNTf_2$ 3.9 mg (5 mol%, M = 388.14 g/mol) and 2 mL dry DCE at 82 °C. The desired compound was obtained 40 mg (61 % yield). The spectral data were identical to the literature.[99]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 6.7 Hz, 2H), 7.60 – 7.41 (m, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.65 (dd, *J* = 12.4, 3.6 Hz, 1H), 2.36 – 2.01 (m, 4H), 1.50 – 1.33 (m, 2H), 1.06 (s, 3H), 0.83 (s, 3H).

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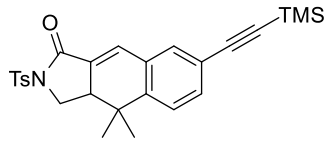
158 **4,4-Dimethyl-2-tosyl-7-((trimethylsilyl)ethynyl)-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one**



Chemical Formula: $C_{26}H_{29}NO_3SSi$

Molecular Weight: 463.67

Aspect: Brown solid

R_f = 0.21 (PE / EtOAc, 85/11)

The reaction was conducted starting from substrate **P-41** (89 mg, 0.2 mmol, 1 equiv., M = 446.36 g/mol), ethynyltrimethylsilane (39 mg, 0.4 mmol, 2 equiv., M = 98.22 g/mol), $[PdCl_2(PPh_3)_2]$ (3 mg, 2 mol%, M = 701.90 g/mol), and CuI (1 mg, 1 mol%, M = 190.45 g/mol) in Et_3N and THF at 50 °C. The desired product was obtained as a brown solid (45 mg, 49 % yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.42 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.29 – 7.24 (m, 2H), 4.18 (t, *J* = 9.8 Hz, 1H), 3.77 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.09 (ddd, *J* = 9.6, 7.8, 3.4 Hz, 1H), 2.43 (s, 3H), 1.45 (s, 3H), 0.90 (s, 3H), 0.23 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.0, 145.5, 145.4, 135.3, 134.2, 133.0, 131.6, 131.4, 131.0, 129.8, 128.3, 124.1, 122.2, 103.9, 95.2, 46.1, 40.9, 37.0, 24.8, 21.9, 21.8, 0.0.

HRMS (ESI) *m/z* calc. for $[C_{26}H_{29}NO_3SSi + H]^+$ 464.1710, found: 464.1704

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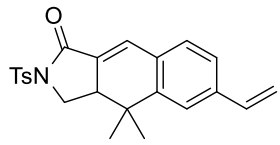
159 **4,4-Dimethyl-2-tosyl-6-vinyl-2,3,3a,4-tetrahydro-1*H*-benzo[*f*]isoindol-1-one**



Chemical Formula: $C_{23}H_{23}NO_3S$

Molecular Weight: 393.50

Aspect: Yellow solid

R_f = 0.22 (PE / EtOAc, 9/1)

The reaction was conducted starting from substrate **P-43** (89 mg, 0.2 mmol, 1 equiv., M = 446.36 g/mol), potassium vinyltrifluoroborate (54 mg, 0.4 mmol, 2 equiv., M = 133.95 g/mol), Cs_2CO_3 (195 mg, 0.6 mmol, 3 equiv., M = 325.82 g/mol), and $PdCl_2(PPh_3)_2$ (7 mg) in THF 2 mL and H_2O 0.2 mL. The desired product was obtained as a yellow solid (64 mg, 81% yield).

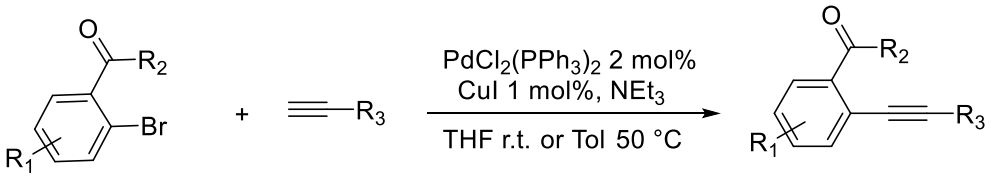
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.28 (m, 2H), 7.25 – 7.18 (m, 3H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.63 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.73 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.9 Hz, 1H), 4.11 (t, *J* = 9.8 Hz, 1H), 3.71 (*J* = 10.0, 7.9 Hz,, 1H), 3.02 (*J* = 9.5, 8.0, 3.4 Hz, 1H), 2.36 (s, 3H), 1.40 (s, 3H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.1, 144.5, 144.2, 139.0, 135.4, 134.3, 130.3, 129.8, 129.5, 129.1, 128.7, 127.1, 123.7, 120.9, 114.3(*CH_2*), 45.1(*CH_2*), 40.0, 35.8, 23.7, 20.9, 20.7.

MS (EI) calculated for $[C_{23}H_{23}NO_3S]^+$ m/z = 393.

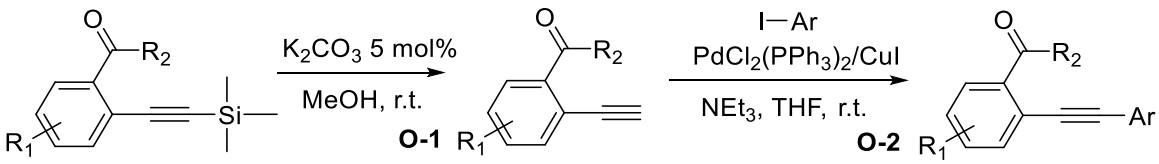
2.4 Synthesis of aldehyde-ynes, alkynylaryl ketones, and alkynyl imines

General procedure N:



In a dried round-bottomed flask, the bromoaryl derivatives (5-30 mmol, 1 equiv.), [$PdCl_2(PPh_3)_2$] (2 mol%), and CuI (1 mol%) were suspended in a 3/1 anhydrous PhMe or THF/Et_3N under N_2 at room temperature. Then the terminal alkyne (1-1.2 equiv.) was added, and the mixture was stirred at room temperature or 50 °C. The reaction mixture was stirred for 3-16 h until the 2-bromoarylaldehyde was consumed (TLC monitored). The crude product was purified by silica-gel column chromatography (PE / EtOAc 90:10 - 98:2) giving thus the desired product.

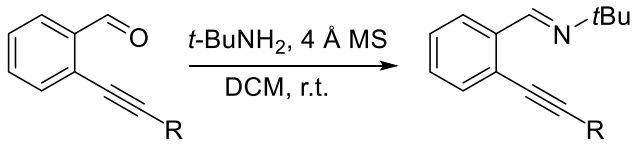
General procedure O:



O-1 In a round-bottomed flask, the substrate (10 mmol, 1 equiv.) and K_2CO_3 (5 mol%) were added in 20 mL MeOH, then stirred at room temperature around 15 minutes (TLC showed that the deprotection was accomplished). The solvent was removed under reduced pressure, and the residual mixture extracted from DCM/H_2O several times. The organic phase was washed with brine, dried the organic phase with $MgSO_4$, filtered, and evaporated.

O-2 The crude (5-10 mmol, 1 equiv.), the aryliodide (1-1.2 equiv.), [$PdCl_2(PPh_3)_2$] (2 mol%) and CuI (1 mol%) were suspended in a 3/1 anhydrous PhMe or THF/Et_3N under N_2 at room temperature, and the reaction mixture was stirred 2-16 h (TLC monitored). The crude product was purified by silica-gel column chromatography (PE / EtOAc 90:10 - 98:2) and gave the desired product.

General procedure P:



To a suspension of *tert*-butylamine (10 mmol) and 4 Å MS (0.5 g) in DCM (20 mL) in a dry flask, the *ortho*-alkynylarylaldehyde (5 mmol) was added at room temperature. The reation mixture was stirred overnight, and monitored with ^1H NMR until the signal of aldehyde proton vanished. Then the reaction mixture was filtered and the solution was concentrated, to give pure alkynyl-imine without purification in almost quantitative yield.

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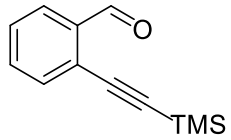
171 2-((Trimethylsilyl)ethynyl)benzaldehyde



Chemical Formula: $C_{12}H_{14}OSi$

Molecular Weight: 202.33

Aspect: Light yellow solid

R_f = 0.62 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromobenzaldehyde (5.55 g, 30 mmol, 1 equiv., M = 185.02 g/mol), ethynyltrimethylsilane (3.54 g, 36 mmol, 1.2 equiv., M = 98.2 g/mol), [$PdCl_2(PPh_3)_2$] (421 mg, 2 mol%, M = 701.90 g/mol), and CuI (57 mg, 1 mol%, M = 190.45 g/mol) were added in 30 mL Et_3N and 90 mL PhMe. The product was obtained as a light yellow solid (6.0 g, 99% yield). The spectral data were identical to the literature.[38]

^1H NMR (400 MHz, Chloroform-*d*) δ 10.55 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 0.28 (s, 9H).

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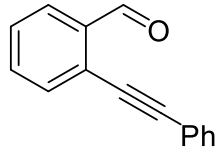
16 2-(Phenylethynyl)benzaldehyde



Chemical Formula: $C_{15}H_{10}O$

Molecular Weight: 206.24

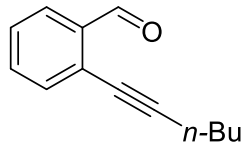
Aspect: Yellow oil

R_f = 0.50 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromobenzaldehyde (1.85 g, 10 mmol, 1 equiv., M = 185.02 g/mol), ethynylbenzene (1.23 g, 12 mmol, 1.2 equiv., M = 102.14 g/mol), [$PdCl_2(PPh_3)_2$] (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a yellow oil (1.67 g, 81% yield). The spectral data were identical to the literature.[38]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.93 – 10.44 (m, 1H), 7.99 – 7.91 (m, 1H), 7.68 – 7.62 (m, 1H), 7.63 – 7.54 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.43 – 7.36 (m, 3H).

172 2-(Hex-1-yn-1-yl)benzaldehyde



Chemical Formula: $C_{13}H_{14}O$

Molecular Weight: 186.25

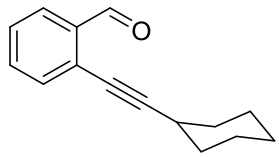
Aspect: Yellow oil

R_f = 0.70 (PE / EtOAc, 9/1)

Following the general procedure **N**, 2-bromobenzaldehyde (1.85 g, 10 mmol, 1 equiv., M = 185.02 g/mol), hex-1-yne (0.99 g, 12 mmol, 1.2 equiv., M = 82.15 g/mol), [$PdCl_2(PPh_3)_2$] (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a yellow oil (1.54 g, 83% yield). The spectral data were identical to the literature.[28(b)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.53 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 5.6 Hz, 2H), 7.40 – 7.31 (m, 1H), 2.51 – 2.44 (m, 2H), 1.62 (p, *J* = 7.0 Hz, 2H), 1.49 (p, *J* = 7.4 Hz, 2H), 0.97 – 0.91 (m, 3H).

173 2-(Cyclohexylethynyl)benzaldehyde



Chemical Formula: $C_{15}H_{16}O$

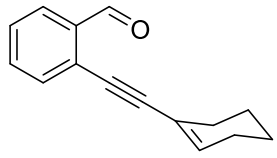
Molecular Weight: 212.29

Aspect: Colorless liquid

R_f = 0.71 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromobenzaldehyde (1.85 g, 10 mmol, 1 equiv., M = 185.02 g/mol), ethynylcyclohexane (1.30 g, 12 mmol, 1.2 equiv., M = 108.18 g/mol), [$PdCl_2(PPh_3)_2$] (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a colorless liquid (1.85 g, 87% yield), and the spectral data were identical to the literature. [46(d)]

174 2-(Cyclohex-1-en-1-ylethynyl)benzaldehyde



Chemical Formula: $C_{15}H_{14}O$

Molecular Weight: 210.28

Aspect: Colorless liquid

R_f = 0.71 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromobenzaldehyde (1.85 g, 10 mmol, 1 equiv., M = 185.02 g/mol), ethynylcyclohexane (1.27 g, 12 mmol, 1.2 equiv., M = 106.17 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product wasobtained as a colorless liquid (1.72 g, 82% yield), and the spectral data were identical to the literature.[42]

^{1}H NMR (200 MHz, Chloroform-*d*) δ 10.54 (d, *J* = 0.7 Hz, 1H), 7.97 – 7.79 (m, 1H), 7.52 (dd, *J* = 3.7, 0.9 Hz, 2H), 7.38 (dt, *J* = 8.5, 4.3 Hz, 1H), 6.30 (dq, *J* = 4.0, 1.9 Hz, 1H), 2.31 – 2.01 (m, 4H), 2.24 – 1.58 (m, 4H).

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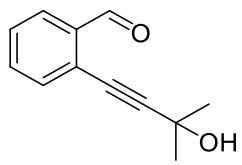
175 2-(3-Hydroxy-3-methylbut-1-yn-1-yl)benzaldehyde



Chemical Formula: $C_{12}H_{12}O_2$

Molecular Weight: 188.23

Aspect: Yellow liquid

R_f = 0.51 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromobenzaldehyde (1.85 g, 10 mmol, 1 equiv., M = 185.02 g/mol), 2-methylbut-3-yn-2-ol (1.01 g, 12 mmol, 1.2 equiv., M = 84.12 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a yellow liquid (1.69 g, 90% yield), and the spectral data were identical to the literature.[189]

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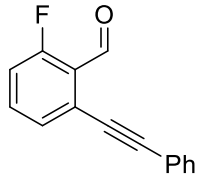
176 2-Fluoro-6-(phenylethynyl)benzaldehyde



Chemical Formula: $C_{15}H_9FO$

Molecular Weight: 224.23

Aspect: Yellow oil

R_f = 0.41 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromo-6-fluorobenzaldehyde (1.01 g, 5 mmol, 1 equiv., M = 203.01 g/mol), ethynylbenzene (6.1 g, 6 mmol, 1.2 equiv., M = 102.14 g/mol), $[PdCl_2(PPh_3)_2]$ (70 mg), and CuI (10 mg) were added in 5 mL Et_3N and 15 mL PhMe. The product was obtained as a yellow oil (0.77 g, 69% yield), and the spectral data were identical to the literature.[190]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.62 (s, 1H), 7.58 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.52 (td, *J* = 8.0, 5.4 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.38 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.15 – 7.09 (m, 1H).

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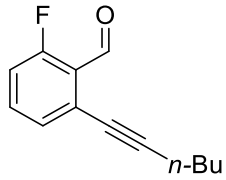
[189] K. R. Roesch, R. C. Larock, *J. Org. Chem*., **2002**, *67*,86.

[190] E. Rettenmeier, M. M. Hansmann, A. Ahrens, K.Rübenacker, T. Sabbo, J. Massholder, C. Meier, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.*, **2015**, *21*, 14401.

177 2-Fluoro-6-(hex-1-yn-1-yl)benzaldehyde



Chemical Formula: $C_{13}H_{13}FO$

Molecular Weight: 204.24

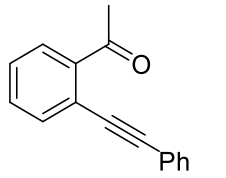
Aspect: Light yellow liquid

R_f = 0.64 (PE / EtOAc, 10/1)

Following the general procedure **N**, 2-bromo-6-fluorobenzaldehyde (1.01 g, 5 mmol, 1 equiv., M = 203.01 g/mol), hex-1-yne (0.49 g, 12 mmol, 1.2 equiv., M = 82.15 g/mol), $[PdCl_2(PPh_3)_2]$ (70 mg), and CuI (10 mg) were added in 5 mL Et_3N and 15 mL PhMe. The product was obtained as a light yellow liquid (0.52 g, 51% yield), and the spectral data were identical to the literature.[191]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.52 (s, 1H), 7.46 (q, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 9.4 Hz, 1H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.62 (p, *J* = 7.1 Hz, 2H), 1.49 (m, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 6.9 Hz, 3H).

36 1-(2-(Phenylethynyl)phenyl)ethan-1-one



Chemical Formula: $C_{16}H_{12}O$

Molecular Weight: 220.27

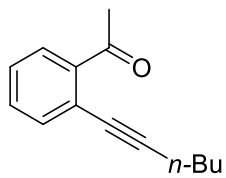
Aspect: Yellow solid

R_f = 0.46 (PE / EtOAc, 10/1)

Following the general procedure **N**, 1-(2-bromophenyl)ethan-1-one (1.0 g, 5 mmol, 1 equiv., M = 199.05 g/mol), ethynylbenzene (0.61 g, 6 mmol, 1.2 equiv., M = 102.14 g/mol), $[PdCl_2(PPh_3)_2]$ (70 mg), and CuI (10 mg) were added in 5 mL Et_3N and 15 mL PhMe. The product was obtained as a yellow solid (1.0 g, 91% yield), and the spectral data were identical to the literature.[45]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.56 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.47 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 – 7.34 (m, 4H), 2.80 (s, 3H).

178 1-(2-(Hex-1-yn-1-yl)phenyl)ethan-1-one



Chemical Formula: $C_{14}H_{16}O$

Molecular Weight: 200.28

Aspect: Yellow liquid

R_f = 0.69 (PE / EtOAc, 10/1)

Following the general procedure **N**, 1-(2-bromophenyl)ethan-1-one (1.0 g, 5 mmol, 1 equiv.,

[191] Z. Yuan, R. Chen, P. Chen, G. Liu, S. H. Liang, *Angew. Chem. Int. Ed*., **2016**, *55*, 11882.

M = 199.05 g/mol), hex-1-yne (0.49 g, 6 mmol, 1.2 equiv., M = 82.15 g/mol), [$PdCl_2(PPh_3)_2$] (70 mg), and CuI (10 mg) were added in 5 mL Et_3N and 15 mL PhMe. The product was obtained as a yellow liquid (0.77 g, 77% yield), and the spectral data were identical to the literature.[175]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 2.71 (d, *J* = 1.1 Hz, 3H), 2.45 (t, *J* = 7.0 Hz, 2H), 1.61 (p, *J* = 7.1 Hz, 2H), 1.48 (dq, *J* = 14.3, 7.1 Hz, 2H), 1.07 – 0.86 (m, 3H).

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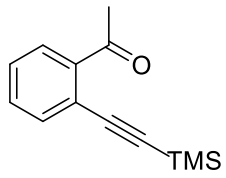
179 1-(2-((Trimethylsilyl)ethynyl)phenyl)ethan-1-one



Chemical Formula: $C_{13}H_{16}OSi$

Molecular Weight: 216.36

Aspect: Yellow solid

R_f = 0.67 (PE / EtOAc, 10/1)

Following the general procedure **N**, 1-(2-bromophenyl)ethan-1-one (3.98 g, 20 mmol, 1 equiv., M = 199.05 g/mol), ethynyltrimethylsilane (2.36 g, 24 mmol, 1.2 equiv., M = 98.2 g/mol), [$PdCl_2(PPh_3)_2$] (280 mg, 2 mol%, M = 701.90 g/mol), and CuI (38 mg, 1 mol%, M = 190.45 g/mol) were added in 20 mL Et_3N and 60 mL PhMe. The product was obtained as a yellow solid (4.28 g, 99% yield), and the spectral data were identical to the literature. [45]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.30 (m, 2H), 2.72 (s, 3H), 0.25 (s, 9H).

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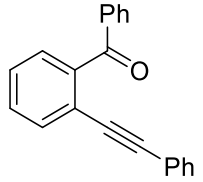
180 Phenyl(2-(phenylethynyl)phenyl)methanone



Chemical Formula: $C_{21}H_{14}O$

Molecular Weight: 282.34

Aspect: Yellow oil R_f = 0.59 (PE / EtOAc, 10/1)

Following the general procedure **N**, (2-bromophenyl)(phenyl)methanone (1.31 g, 5 mmol, 1 equiv., M = 261.12 g/mol), ethynylbenzene (0.61 g, 6 mmol, 1.2 equiv., M = 102.14 g/mol), [$PdCl_2(PPh_3)_2$] (70 mg), and CuI (10 mg) were added in 5 mL Et_3N and 15 mL PhMe. The product was obtained as a yellow oil (1.3 g, 95% yield), and the spectral data were identical to the literature.[43(a)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.87 (m, 2H), 7.62 – 7.59 (m, 1H), 7.56 (ddd, *J* = 7.4, 5.6, 1.2 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.49 – 7.40 (m, 4H), 7.24 – 7.16 (m, 3H), 7.07 – 7.00 (m, 2H).

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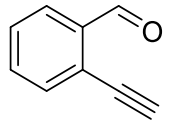
181 2-Ethynylbenzaldehyde



Chemical Formula: C_9H_6O

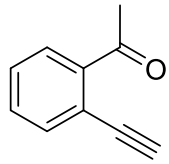
Molecular Weight: 130.15

Aspect: White solid

The substrate **171** (4.05 g, 20 mmol, 1 equiv., M = 202.33 g/mol) and K_2CO_3 (140 mg, 5 mol%, M = 138.21 g/mol) were added in 40 mL MeOH. The product was obtained as a white solid (2.56 g, 98% yield), and the spectral data were identical to the literature.[38]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.55 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 3.46 (s, 1H).

182 1-(2-Ethynylphenyl)ethan-1-one



Chemical Formula: $C_{10}H_8O$

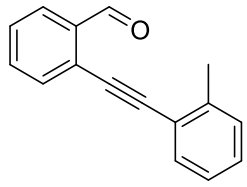
Molecular Weight: 144.17

Aspect: Light yellow solid

The substrate **179** (2.16 g, 10 mmol, 1 equiv., M = 216.36 g/mol) and K_2CO_3 (69 mg, 5 mol%, M = 138.21 g/mol) were added in 20 mL MeOH. The product was obtained as a light yellow solid (1.37 g, 95% yield), and the spectral data were identical to the literature.[45]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.1 Hz, 1H), 7.54 (d, *J* = 6.3 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.26, 3.38 (s, 1H), 2.67 – 2.64 (m, 3H).

183 2-(*o*-Tolylethynyl)benzaldehyde



Chemical Formula: $C_{16}H_{12}O$

Molecular Weight: 220.27

Aspect: Yellow solid

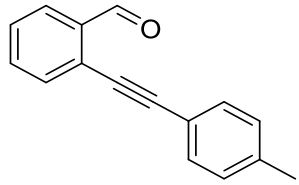
R_f = 0.35 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (1.30 g, 10 mmol, 1 equiv., M = 130.15 g/mol), 1-iodo-2-methylbenzene (2.62 g, 12 mmol, 1.2 equiv., M = 218.04 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a yellow solid (1.65 g, 75% yield), and the spectral data were identical to the literature.[192]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.68 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.28 (m, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 2.54 (s, 3H).

184 2-(*p*-Tolylethynyl)benzaldehyde

[192] Z. -L. Zhou, Y. -L. Liu, J. -L. Song, C. -L. Deng, *Synthesis*, **2016**, *48*, 2057.



Chemical Formula: $C_{16}H_{12}O$

Molecular Weight: 220.27

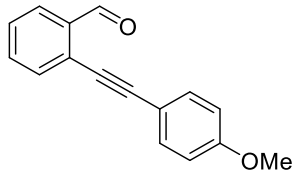
Aspect: Yellow solid

R_f = 0.36 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (1.30 g, 10 mmol, 1 equiv., M = 130.15 g/mol), 1-iodo-4-methylbenzene (2.62 g, 12 mmol, 1.2 equiv., M = 218.04 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a yellow solid (1.76 g, 80% yield), and the spectral data were identical to the literature.[38]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.66 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47-7.41 (m 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H).

185 2-((4-Methoxyphenyl)ethynyl)benzaldehyde



Chemical Formula: $C_{16}H_{12}O_2$

Molecular Weight: 236.27

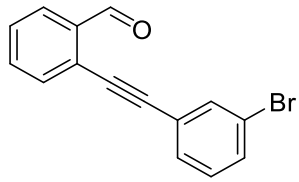
Aspect: brown oil

R_f = 0.38 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (1.30 g, 10 mmol, 1 equiv., M = 130.15 g/mol), 1-iodo-4-methoxybenzene (2.81 g, 12 mmol, 1.2 equiv., M = 234.04 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a brown oil (1.37 g, 58% yield), and the spectral data were identical to the literature.[38]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.65 (d, *J* = 0.7 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.64 – 7.60 (m, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 6.93 – 6.89 (m, 2H), 3.85 (s, 3H).

186 2-((3-Bromophenyl)ethynyl)benzaldehyde



Chemical Formula: $C_{15}H_9BrO$

Molecular Weight: 285.14

Aspect: light yellow solid

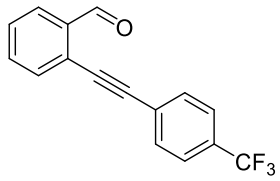
R_f = 0.59 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (1.30 g, 10 mmol, 1 equiv., M = 130.15 g/mol), 1-bromo-3-iodobenzene (3.39 g, 12 mmol, 1.2 equiv., M = 282.91 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a light yellow solid (1.48 g, 52% yield), and the spectral data were identical to the

literature.[175]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.62 (d, *J* = 0.6 Hz, 1H), 8.00 – 7.90 (m, 1H), 7.72 (t, *J* = 1.6 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.54 – 7.47 (m, 3H), 7.26 (s, 1H).

187 2-((4-(Trifluoromethyl)phenyl)ethynyl)benzaldehyde



Chemical Formula: $C_{16}H_9F_3O$

Molecular Weight: 274.24

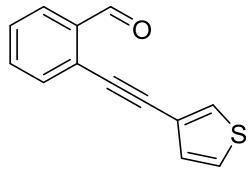
Aspect: light yellow solid

R_f = 0.38 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (1.30 g, 10 mmol, 1 equiv., M = 130.15 g/mol), 1-iodo-4-(trifluoromethyl)benzene (3.26 g, 12 mmol, 1.2 equiv., M = 272.01 g/mol), $[PdCl_2(PPh_3)_2]$ (140 mg), and CuI (19 mg) were added in 10 mL Et_3N and 30 mL PhMe. The product was obtained as a light yellow solid (1.86 g, 68% yield), and the spectral data were identical to the literature.[38]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.59 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.65 – 7.54 (m, 6H), 7.46 (t, *J* = 7.5 Hz, 1H).

188 2-(Thiophen-3-ylethynyl)benzaldehyde



Chemical Formula: $C_{13}H_8OS$

Molecular Weight: 212.27

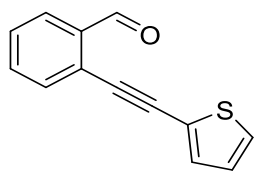
Aspect: Yellow solid

R_f = 0.41 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (390.5 mg, 3 mmol, 1 equiv., M = 130.15 g/mol), 3-iodothiophene (756 mg, 3.6 mmol, 1.2 equiv., M = 210.03 g/mol), $[PdCl_2(PPh_3)_2]$ (42 mg), and CuI (5.7 mg) were added in 3 mL Et_3N and 10 mL PhMe. The product was obtained as a yellow solid (344 mg, 54% yield), and the spectral data were identical to the literature.[176]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.60 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.21 (dd, *J* = 5.0, 1.0 Hz, 1H).

189 2-(Thiophen-2-ylethynyl)benzaldehyde



Chemical Formula: $C_{13}H_8OS$

Molecular Weight: 212.27

Aspect: Yellow solid

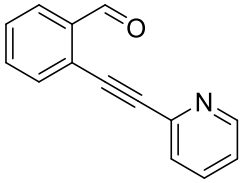
R_f = 0.47 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (390.5 mg, 3 mmol, 1 equiv., M = 130.15 g/mol), 2-iodothiophene (756 mg, 3.6 mmol, 1.2 equiv., M = 210.03 g/mol), $[PdCl_2(PPh_3)_2]$ (42

mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a yellow solid (287 mg, 45% yield), and the spectral data were identical to the literature.[176]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.56 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.05 – 6.99 (m, 1H).

190 2-(Pyridin-2-ylethynyl)benzaldehyde



Chemical Formula: $C_{14}H_9NO$

Molecular Weight: 207.23

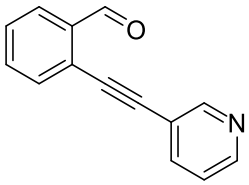
Aspect: Brown solid

R_f = 0.33 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (390.5 mg, 3 mmol, 1 equiv., M = 130.15 g/mol), 2-iodopyridine (738 mg, 3.6 mmol, 1.2 equiv., M = 205.00 g/mol), $[PdCl_2(PPh_3)_2]$ (42 mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a brown solid (280 mg, 45% yield), and the spectral data were identical to the literature.[175]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.66 (s, 1H), 8.64 (s, 1H), 7.99 – 7.83 (m, 1H), 7.75 – 7.63 (m, 2H), 7.62 – 7.53 (m, 2H), 7.53 – 7.45 (m, 1H), 7.32 – 7.24 (m, 1H).

191 2-(Pyridin-3-ylethynyl)benzaldehyde



Chemical Formula: $C_{14}H_9NO$

Molecular Weight: 207.23

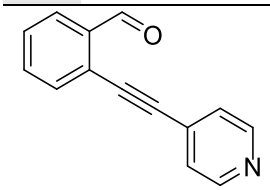
Aspect: Brown solid

R_f = 0.11 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (390.5 mg, 3 mmol, 1 equiv., M = 130.15 g/mol), 2-iodopyridine (738 mg, 3.6 mmol, 1.2 equiv., M = 205.00 g/mol), $[PdCl_2(PPh_3)_2]$ (42 mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a brown solid (441 mg, 71% yield), and the spectral data were identical to the literature.[145(a)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.62 (s, 1H), 8.86 – 8.73 (m, 1H), 8.61 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.86 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.31 (m, 1H).

192 2-(Pyridin-4-ylethynyl)benzaldehyde



Chemical Formula: $C_{14}H_9NO$

Molecular Weight: 207.23

Aspect: Brown solid R_f = 0.33 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate **181** (390.5 mg, 3 mmol, 1 equiv., M = 130.15 g/mol), 2-iodopyridine (738 mg, 3.6 mmol, 1.2 equiv., M = 205.00 g/mol), $[PdCl_2(PPh_3)_2]$ (42

mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a brown solid (429 mg, 69% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.56 (d, *J* = 2.1 Hz, 1H), 8.63 (s, 2H), 7.99 – 7.91 (m, 1H), 7.67 – 7.63 (m, 1H), 7.60 (ddd, *J* = 9.1, 5.5, 1.6 Hz, 1H), 7.50 (t, *J* = 6.8 Hz, 1H), 7.43 – 7.38 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 191.0, 149.9, 136.1, 133.9, 133.6, 130.5, 129.6, 127.8, 125.5, 125.2, 93.0, 89.3.

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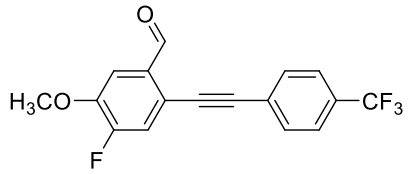
193 4-Fluoro-5-methoxy-2-((4-(trifluoromethyl)phenyl)ethynyl)benzaldehyde



Chemical Formula: $C_{17}H_{10}F_4O_2$

Molecular Weight: 322.26

Aspect: Light yellow soild

R_f = 0.32 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate 2-ethynyl-4-fluoro-5-methoxybenzaldehyde (390.5 mg, 5 mmol, 1 equiv., M = 178.16 g/mol), 1-iodo-4-(trifluoromethyl)benzene (3.26 g, 12 mmol, 1.2 equiv., M = 272.01 g/mol), $[PdCl_2(PPh_3)_2]$ (21 mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a light yellow solid (719mg, 45% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.51 (s, 1H), 7.64 (s, 4H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 10.9 Hz, 1H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.78, 155.46 (d, *J* = 258.5 Hz), 149.16 (d, *J* = 11.3 Hz), 133.30 (d, *J* = 3.1 Hz), 131.9, 130.7 (q, *J* = 32.7 Hz), 126.0, 125.5 (q, *J* = 3.8 Hz), 123.8 (d, *J* = 272.3 Hz), 120.4 (d, *J* = 20.6 Hz), 119.8 (d, *J* = 9.4 Hz), 111.0 (d, *J* = 4.0 Hz), 94.1, 85.8 (d, *J* = 2.5 Hz), 56.4.

HRMS (EI) *m/z* calc. for $[C_{17}H_{10}F_4O_2]^+$ 322.0611, found: 322.0602

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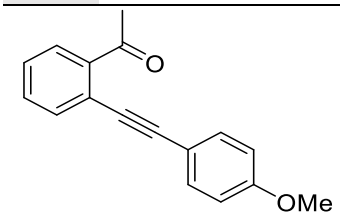
194 1-(2-((4-Methoxyphenyl)ethynyl)phenyl)ethan-1-one



Chemical Formula: $C_{17}H_{14}O_2$

Molecular Weight: 250.30

Aspect: Yellow solid

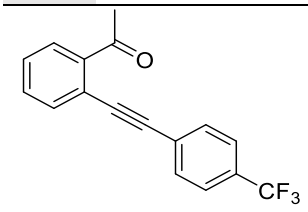
R_f = 0.43 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate 1-(2-ethynylphenyl)ethan-1-one **182** (433 mg, 3 mmol, 1 equiv., M = 144.17 g/mol), 1-iodo-4-methoxybenzene (843 mg, 3.6 mmol, 1.2 equiv.,

M = 234.04 g/mol), $[PdCl_2(PPh_3)_2]$ (42 mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a yellow solid (398 mg, 53% yield), and the spectral data were identical to the literature.[193]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.40 – 7.31 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 2.78 (s, 3H).

195 1-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)ethan-1-one



Chemical Formula: $C_{17}H_{11}F_3O$

Molecular Weight: 288.27

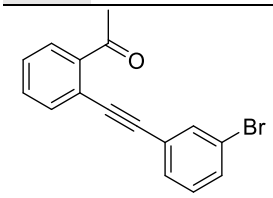
Aspect: Light yellow solid

R_f = 0.41 (PE / EtOAc, 9/1)

Following the general procedure **O-2**, substrate 1-(2-ethynylphenyl)ethan-1-one **182** (433 mg, 3 mmol, 1 equiv., M = 144.17 g/mol), 1-iodo-4-(trifluoromethyl)benzene (979 mg, 3.6 mmol, 1.2 equiv., M = 272.01 g/mol), $[PdCl_2(PPh_3)_2]$ (42 mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a light yellow solid (424 mg, 49% yield), and the spectral data were identical to the literature.[194]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.57 (m, 5H), 7.52 – 7.38 (m, 2H), 2.74 (s, 3H).

196 1-(2-((3-Bromophenyl)ethynyl)phenyl)ethan-1-one



Chemical Formula: $C_{16}H_{11}BrO$

Molecular Weight: 299.17

Aspect: Yellow solid

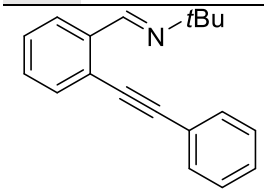
R_f = 0.40 (PE / EtOAc, 10/1)

Following the general procedure **O-2**, substrate 1-(2-ethynylphenyl)ethan-1-one **182** (433 mg, 3 mmol, 1 equiv., M = 144.17 g/mol), 1-bromo-3-iodobenzene (1.02 g, 3.6 mmol, 1.2 equiv., M = 282.91 g/mol), $[PdCl_2(PPh_3)_2]$ (42 mg), and CuI (5.7 mg) were added in 3mL Et_3N and 10 mL PhMe. The product was obtained as a yellow solid (547 mg, 61% yield), and the spectral data were identical to the literature.[194]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.69 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 2.76 (s, 3H).

[193] M. Dell'Acqua, G. Abbiati, A. Arcadi, E. Rossi, *Org. Biomol. Chem.*, **2011**, *9*, 7836.
[194] K. Saito, Y. Kajiwara, T. Akiyama, *Angew. Chem.*, **2013**, *125*, 13526.

197 (*E*)-*N*-tert-Butyl-1-(2-(phenylethynyl)phenyl)methanimine



Chemical Formula: $C_{19}H_{19}N$

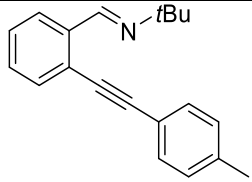
Molecular Weight: 261.3680

Aspect: Yellow solid

Following the general procedure **P**, 2-(phenylethynyl)benzaldehyde **16** (1.03 g, 5 mmol, 1 equiv., M = 206.24 g/mol), *tert*-butylamine (731 mg, 10 mmol, 2 equiv., M = 73.14 g/mol), and 0.5 g 4 Å MS were added in the system. The product was obtained as a yellow solid in a quantitative yield, and the spectral data were identical to the literature, and the spectral data were identical to the literature.[181(b)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.54 (m, 3H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.25 – 7.13 (2H, m), 1.38 (9H, s).

198 (*E*)-*N*-*tert*-Butyl-1-(2-(*p*-tolylethynyl)phenyl)methanimine



Chemical Formula: $C_{20}H_{21}N$

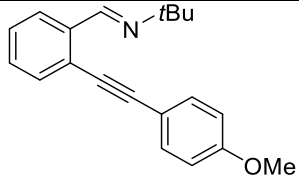
Molecular Weight: 275.40

Aspect: Yellow solid

Following the general procedure **P**, 2-(*p*-tolylethynyl)benzaldehyde **184** (1.1 g, 5 mmol, 1 equiv., M = 220.27 g/mol), *tert*-butylamine (731 mg, 10 mmol, 2 equiv., M = 73.14 g/mol), and 0.5 g 4 Å MS were added in the system. The product was obtained as a yellow solid in a quantitative yield, and the spectral data were identical to the literature.[191]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 6.9 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 7.6, 6.9 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.9, 1H), 7.15 – 7.13 (m, 1H) 2.25 (s, 3H), 1.38 (s, 9H).

199 (*E*)-*N*-*tert*-Butyl-1-(2-((4-methoxyphenyl)ethynyl)phenyl)methanimine



Chemical Formula: $C_{20}H_{21}NO$

Molecular Weight: 291.39

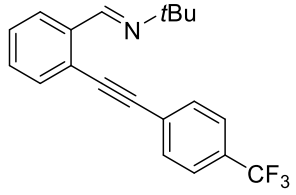
Aspect: Yellow solid

Following the general procedure **P**, 2-((4-methoxyphenyl)ethynyl)benzaldehyde **185** (1.18 g, 5 mmol, 1 equiv., M = 236.27 g/mol), *tert*-butylamine (731 mg, 10 mmol, 2 equiv., M = 73.14 g/mol), and 0.5 g 4 Å MS were added in the system. The product was obtained as a yellow

solid in a quantitative yield, and the spectral data were identical to the literature.[181(b)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 7.45 – 7.34 (m, 3H), 7.38 – 7.35 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 1.38 (s, 9H).

200 (*E*)-*N*-*tert*-butyl-1-(2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)methanimine



Chemical Formula: $C_{20}H_{18}F_3N$

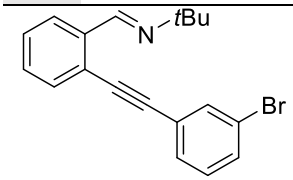
Molecular Weight: 329.37

Aspect: Yellow solid

Following the general procedure **P**, 2-((4-(trifluoromethyl)phenyl)ethynyl)benzaldehyde **187** (1.37 g, 5 mmol, 1 equiv., M = 274.24 g/mol), *tert*-butylamine (731 mg, 10 mmol, 2 equiv., M = 73.14 g/mol), and 0.5 g 4 Å MS were added in the system. The product was obtained as a yellow solid in a quantitative yield, and the spectral data were identical to the literature.[195]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.68 – 7.62 (m, 4H), 7.57 (d, *J* = 10.8 Hz, 1H), 7.42 – 7.39 (m, 2H), 1.37 (s, 9H).

201 (*E*)-1-(2-((3-Bromophenyl)ethynyl)phenyl)-*N*-(tert-butyl)methanimine



Chemical Formula: $C_{19}H_{18}N$

Molecular Weight: 340.26

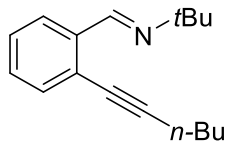
Aspect: Yellow solid

Following the general procedure **P**, 2-((3-bromophenyl)ethynyl)benzaldehyde **186** (1.43 g, 5 mmol, 1 equiv., M = 285.14 g/mol), *tert*-butylamine (731 mg, 10 mmol, 2 equiv., M = 73.14 g/mol), and 0.5 g 4 Å MS were added in the system. The product was obtained as a yellow solid in a quantitative yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 7.8, 7.5 Hz, 1 H), 7.48 – 7.44 (m, 1 H), 7.39 (dd, *J* = 8.3, 8.2 Hz, 1H), 7.32 – 7.31 (m, 3H), 1.38 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.9, 133.0, 132.4, 131.8, 130.7, 130.3, 130.1, 129.6, 128.6, 123.3, 121.6, 118.2, 91.1, 90.7, 56.9, 28.9.

202 (*E*)-*N*-*tert*-Butyl-1-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)methanimine



Chemical Formula: $C_{17}H_{23}N$

Molecular Weight: 241.38

Aspect: Yellow liquid

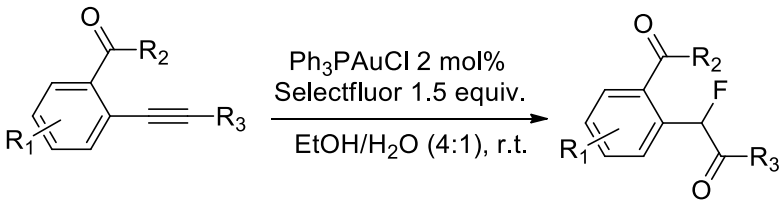
[195] M. Jeganathan, K. Pitchumani, *RSC Advances*, **2014**, *4*, 38491.

Following the general procedure **P**, 2-(hex-1-yn-1-yl)benzaldehyde **172** (931 mg, 5 mmol, 1 equiv., M = 186.25 g/mol), *tert*-butylamine (731 mg, 10 mmol, 2 equiv., M = 73.14 g/mol), and 0.5 g 4 Å MS were added in the system. The product was obtained as a yellow liquid in a quantitative yield, and the spectral data were identical to literature.[181(b)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (s, 1H), 7.65 – 7.63 (m, 1H), 7.51 – 7.42 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 2.58 – 2.32 (m, 2H), 1.75 – 1.72 (m, 2H), 1.37 (s, 9H), 1.28 – 1.25 (m, 2H), 0.88 – 0.86 (m, 3H).

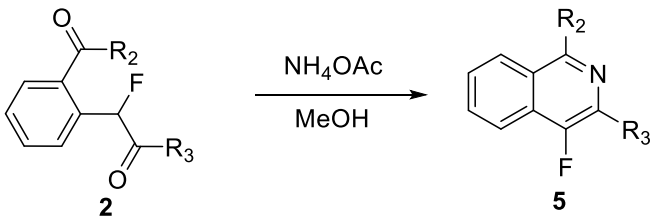
2.5 Procedure of α-fluoroketones and 4-fluoroisoquinolines compounds

General procedure Q:



In a dried screw-capped vial, the substrate (0.2-0.5 mol, 1 equiv.) and Selectfluor (1.2~1.5 equiv.) were dissolved in 3-6 mL EtOH/H_2O (v/v 4/1), then the catalyst Ph_3PAuCl (2 mol%) was added to the mixture. The reaction mixture was stirred at room temperature during around 4-16 hours (reaction monitored by TLC). The solvents were evaporated under reduced pressure, the residue was extracted from DCM/H_2O several times, washed with brine. The organic phase was dried, dried with $MgSO_4$, filtered, and evaporated. The crude product was purified by silica-gel column chromatography (PE / EtOAc 80:20-92/8) to afford the desired product.

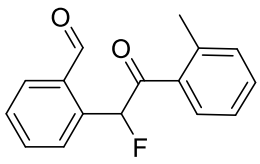
General procedure R:



In a dried 8 mL screw-capped vial, α-fluoroketones (0.2 mmol, 1.0 equiv.), and NH_4OAc (47.3-50 mg, 3 equiv.) were added to 2 mL of methanol. The reaction mixture was stirred at room temperature for 2-4 hours. After completion of the reaction monitored by TLC, the organic

solvent was removed under vacuum, and the residue was purified by silica gel column with PE / EtOAc around 8/2-9/1 to afford the desired product.

P-53 2-(1-Fluoro-2-oxo-2-(*o*-tolyl)ethyl)benzaldehyde



Chemical Formula: $C_{16}H_{13}FO_2$

Molecular Weight: 256.28

Aspect: Yellow solid

R_f = 0.35 (PE / EtOAc, 10/1)

Following the general procedure **Q**, substrate **183** (88 mg, 0.4 mmol, 1 equiv., M = 220.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (90 mg, 88% yield).

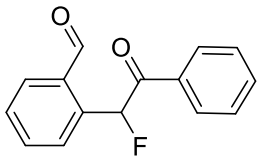
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.96 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.65 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 44 Hz, 1H), 7.42 – 7.37 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.8 (d, *J* = 21.8 Hz), 193.2, 139.5, 136.1 (d, *J* = 19.4 Hz), 135.3, 134.9, 134.3, 133.2 (d, *J* = 3.0 Hz), 132.1, 132.0, 129.2 (dd, *J* = 5.1, 2.3 Hz), 127.2, 127.1, 125.7, 90.6 (d, *J* = 180.3 Hz), 21.0.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -182.1.

HRMS (EI) *m/z*: Found: 256.0892. Calcd for $C_{16}H_{13}FO_2$: $[M]^+$ 256.0894.

P-54 2-(1-Fluoro-2-oxo-2-phenylethyl)benzaldehyde



Chemical Formula: $C_{15}H_{11}FO_2$

Molecular Weight: 242.25

Aspect: Yellow oil

R_f = 0.51 (PE / EtOAc, 10/1)

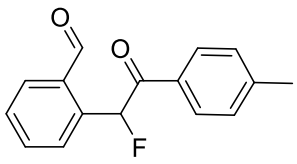
Following the general procedure **Q**, substrate **16** (82 mg, 0.4 mmol, 1 equiv., M = 206.24 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow oil (82 mg, 85% yield).

H NMR (200 MHz, Chloroform-*d*) δ 10.00 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.83 – 7.64 (m, 3H), 7.63 – 7.38 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.3, 192.4 (d, *J* = 21.4 Hz), 136.2 (d, *J* = 19.1 Hz), 135.1, 135.0 (d, *J* = 1.5 Hz), 134.4, 133.8, 133.2 (d, *J* = 3.0 Hz), 129.2 (d, *J* = 1.4 Hz), 129.2 (d, *J* = 2.1 Hz), 128.8, 127.2 (d, *J* = 13.7 Hz), 89.3 (d, *J* = 178.5 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -182.7.

P-55 2-(1-Fluoro-2-oxo-2-(*p*-tolyl)ethyl)benzaldehyde



Chemical Formula: $C_{16}H_{13}FO_2$

Molecular Weight: 256.28

Aspect: Yellow solid

R_f = 0.36 (PE / EtOAc, 9/1)

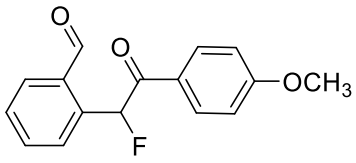
Following the general procedure **Q**, substrate **184** (88 mg, 0.4 mmol, 1 equiv., M = 220.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (94 mg, 92% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.64 – 7.57 (m, 1H), 7.54 (d, *J* = 48 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.3, 192.1 (d, *J* = 21.3 Hz), 144.8, 136.4, 136.2, 135.0, 134.3, 133.2 (d, *J* = 3.1 Hz), 132.5, 129.5, 129.3 (d, *J* = 2.1 Hz), 129.2 (d, *J* = 1.4 Hz), 127.3, 127.2, 89.2 (d, *J* = 178.5 Hz), 21.8.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -182.0.

P-56 2-(1-Fluoro-2-(4-methoxyphenyl)-2-oxoethyl)benzaldehyde



Chemical Formula: $C_{16}H_{13}FO_3$

Molecular Weight: 272.28

Aspect: Brown solid

R_f = 0.12 (PE / EtOAc, 10/1)

Following the general procedure **Q**, substrate **185** (95 mg, 0.4 mmol, 1 equiv., M = 236.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a brown solid (77 mg, 71% yield).

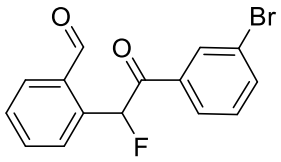
^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.62 – 7.59 (m, 1H), 7.53 (d, *J* = 47.2 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.3, 191.0 (d, *J* = 21.2 Hz), 164.1, 136.4 (d, *J* = 19.1 Hz), 134.9, 134.3, 133.2 (d, *J* = 3.1 Hz), 131.6 (d, *J* = 2.2 Hz), 129.2 (d, *J* = 1.4 Hz), 127.9 (d, *J* = 1.4 Hz), 127.3 (d, *J* = 13.3 Hz), 114.1, 89.2 (d, *J* = 178.4 Hz), 55.5.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -181.4.

HRMS (EI) *m/z*: Found: 272.0839. Calcd for $C_{16}H_{13}FO_3$: $[M]^+$ 272.0843.

P-57 2-(2-(3-Bromophenyl)-1-fluoro-2-oxoethyl)benzaldehyde



Chemical Formula: $C_{15}H_{10}BrFO_2$

Molecular Weight: 321.1454

Aspect: Yellow solid

R_f = 0.30 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **186** (114 mg, 0.4 mmol, 1 equiv., M = 285.14 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (102 mg, 80% yield).

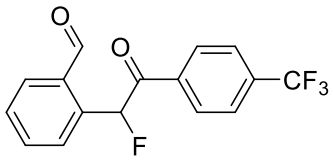
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.97 (s, 1H), 8.23 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.80 – 7.70 (m, 3H), 7.64 (td, *J* = 7.3, 1.8 Hz, 1H), 7.44 (d, *J* = 48 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.4, 190.9 (d, *J* = 21.8 Hz), 136.8 (d, *J* = 1.7 Hz), 136.6, 135.8 (d, *J* = 19.0 Hz), 135.3, 134.5 (d, *J* = 1.1 Hz), 133.1 (d, *J* = 3.1 Hz), 132.1 (d, *J* = 2.2 Hz), 130.4, 129.3 (d, *J* = 1.2 Hz), 127.7 (d, *J* = 2.3 Hz), 126.9 (d, *J* = 14.5 Hz), 123.1, 89.4 (d, *J* = 178.5 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -183.7.

HRMS (EI) *m/z*: Found: 272.0832. Calcd for $C_{15}H_{10}BrFO_2$: $[M]^+$ 319.9822.

P-58 2-(1-Fluoro-2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)benzaldehyde



Chemical Formula: $C_{16}H_{10}F_4O_2$

Molecular Weight: 310.25

Aspect: Yellow solid

R_f = 0.41 (PE / EtOAc, 9/1)

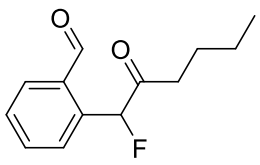
Following the general procedure **Q**, substrate **187** (110 mg, 0.4 mmol, 1 equiv., M = 274.24 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (71 mg, 57%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.96 (s, 1H), 8.22 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.80 – 7.73 (m, 4H), 7.65 (td, *J* = 7.4, 1.5 Hz, 1H), 7.48 (d, *J* = 47.1 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.5, 191.3 (d, *J* = 21.8 Hz), 137.9, 135.7 (d, *J* = 19.0 Hz), 135.4, 134.9 (d, *J* = 32.7 Hz), 134.6 (d, *J* = 1.1 Hz), 133.0 (d, *J* = 3.0 Hz), 129.5 (d, *J* = 2.2 Hz), 129.4 (d, *J* = 1.1 Hz), 126.9 (d, *J* = 14.5 Hz), 125.9 (q, *J* = 3.7 Hz), 123.6 (d, *J* = 272.8 Hz), 89.5 (d, *J* = 178.4 Hz).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -63.2, -184.3.

P-59 2-(1-Fluoro-2-oxohexyl)benzaldehyde



Chemical Formula: $C_{13}H_{15}FO_2$

Molecular Weight: 222.26

Aspect: Yellow oil

R_f = 0.52 (PE / EtOAc, 10/1)

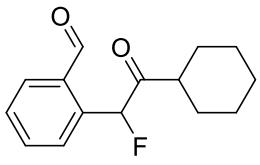
Following the general procedure **Q**, substrate **172** (75 mg, 0.4 mmol, 1 equiv., M = 186.25 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow oil (73 mg, 82%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.03 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.66 – 7.48 (m, 3H), 6.68 (d, *J* = 47.3 Hz, 1H), 2.82 – 2.49 (m, 2H), 1.56 (p, *J* = 7.4 Hz, 2H), 1.29 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 204.3 (d, *J* = 23.0 Hz), 192.7, 135.6 (d, *J* = 19.4 Hz), 134.4, 134.1, 133.3 (d, *J* = 2.9 Hz), 129.3 (d, *J* = 1.5 Hz), 127.1 (d, *J* = 11.9 Hz), 92.0 (d, *J* = 182.7 Hz), 38.5, 25.0 (d, *J* = 0.9 Hz), 22.2, 13.8.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -186.1.

P-60 2-(2-Cyclohexyl-1-fluoro-2-oxoethyl)benzaldehyde



Chemical Formula: $C_{15}H_{17}FO_2$

Molecular Weight: 248.30

Aspect: Colorless oil

R_f = 0.33 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **173** (85 mg, 0.4 mmol, 1 equiv., M = 212.29 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a colorless oil (84 mg, 85% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.04 (s, 1H), 7.87 (d, *J* = 7.3 Hz, 1H), 7.69 - 7.63 (m, 1H),

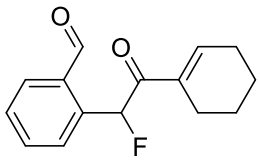
7.61 - 7.56 (m, 2H), 6.81 (d, *J* = 47.1 Hz, 1H), 2.95 - 2.87 (m, 1H), 1.91 (t, *J* = 14.4 Hz, 2H), 1.84 - 1.77 (m, 2H), 1.71 - 1.65 (m, 1H), 1.47 - 1.19 (m, 5H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.0 (d, *J* = 22.0 Hz), 192.8, 135.8 (d, *J* = 19.3 Hz), 134.5, 134.1, 133.4 (d, *J* = 2.9 Hz), 129.3 (d, *J* = 1.5 Hz), 127.4 (d, *J* = 11.9 Hz), 91.1 (d, *J* = 182.8 Hz), 46.9, 28.4, 28.0, 25.8, 25.7, 25.5.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -186.0.

HRMS (H-ESI) *m/z*: Found: 249.1282 Calcd for $C_{16}H_{12}BrFO_2$: $[M+H]^+$ 249.1285.

P-61 2-(2-(Cyclohex-1-en-1-yl)-1-fluoro-2-oxoethyl)benzaldehyde



Chemical Formula: $C_{15}H_{15}FO_2$

Molecular Weight: 246.28

Aspect: Light yellow solid

R_f = 0.28 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **174** (84 mg, 0.4 mmol, 1 equiv., M = 210.28 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a light yellow solid (62 mg, 63% yield).

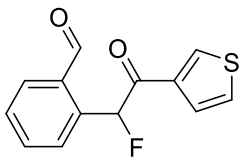
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.99 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 3.9 Hz, 2H), 7.59 (dd, *J* = 7.7, 3.8 Hz, 1H), 7.26 - 7.23 (m, 1H), 7.25 (d, *J* = 47.4 Hz, 1H), 2.31 (m, 4H), 1.70 - 1.63 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.3, 193.0 (d, *J* = 20.6 Hz), 143.1 (d, *J* = 3.2 Hz), 137.3 (d, *J* = 1.0 Hz), 137.0 (d, *J* = 19.2 Hz), 134.9, 134.2, 133.1 (d, *J* = 3.2 Hz), 128.9 (d, *J* = 1.4 Hz), 127.1 (d, *J* = 13.9 Hz), 88.3 (d, *J* = 177.6 Hz), 26.3, 23.2, 21.8, 21.5.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -180.8.

HRMS (H-ESI) *m/z*: Found: 247.1126 Calcd for $C_{16}H_{12}BrFO_2$: $[M+H]^+$ 247.1129.

P-63 2-(1-Fluoro-2-oxo-2-(thiophen-3-yl)ethyl)benzaldehyde



Chemical Formula: $C_{13}H_9FO_2S$

Molecular Weight: 248.27

Aspect: Yellow solid

R_f = 0.26 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **188** (85 mg, 0.4 mmol, 1 equiv., M = 212.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was

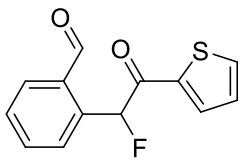
added to the mixture. The product was obtained as a yellow solid (81 mg, 81%)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.04 (s, 1H), 8.40 – 8.32 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.64 (d, *J* = 5.1 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.37 (d, *J* = 47.3 Hz, 1H), 7.33 (dd, *J* = 5.1, 2.9 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.3, 187.0 (d, *J* = 22.4 Hz), 139.3 (d, *J* = 1.8 Hz), 135.8 (d, *J* = 19.1 Hz), 134.9, 134.4 (d, *J* = 5.3 Hz), 134.3, 133.3 (d, *J* = 3.0 Hz), 129.4 (d, *J* = 1.6 Hz), 127.6 (d, *J* = 1.6 Hz), 127.4 (d, *J* = 12.5 Hz), 126.4, 90.4 (d, *J* = 180.0 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -181.1.

P-64 2-(1-Fluoro-2-oxo-2-(thiophen-2-yl)ethyl)benzaldehyde



Chemical Formula: $C_{13}H_9FO_2S$

Molecular Weight: 248.27

Aspect: Yellow solid

R_f = 0.19 (PE / EtOAc, 9/1)

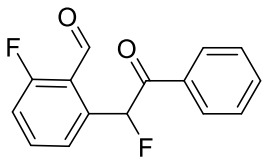
Following the general procedure **Q**, substrate **189** (85 mg, 0.4 mmol, 1 equiv., M = 212.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (70 mg, 70%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.05 (s, 1H), 8.04 (d, *J* = 3.9 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.72 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.68 (td, *J* = 7.6, 1.2 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.38 (d, *J* = 47.4 Hz, 1H), 7.18 (dd, *J* = 4.8, 4.0 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.1, 185.8 (d, *J* = 23.0 Hz), 141.3 (d, *J* = 2.2 Hz), 135.7 (d, *J* = 19.2 Hz), 135.2 (d, *J* = 1.2 Hz), 134.7, 134.3, 134.2 (d, *J* = 4.7 Hz), 133.4 (d, *J* = 3.0 Hz), 129.50 (d, *J* = 1.6 Hz), 128.5, 127.4 (d, *J* = 12.6 Hz), 90.2 (d, *J* = 181.1 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -180.3.

P-69 2-Fluoro-6-(1-fluoro-2-oxo-2-phenylethyl)benzaldehyde



Chemical Formula: $C_{15}H_{10}F_2O_2$

Molecular Weight: 260.2398

Aspect: Yellow oil

R_f = 0.47 (PE / EtOAc, 10/1)

Following the general procedure **Q**, substrate **176** (90 mg, 0.4 mmol, 1 equiv., M = 224.23 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow oil (43 mg, 42% yield).

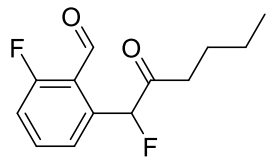
^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.39 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 2H), 7.72 (td, *J* = 8.1, 5.7 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (q, *J* = 7.7 Hz, 3H), 7.44 (d, *J* = 47.2 Hz, 1H), 7.30 – 7.23 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 191.5 (d, *J* = 21.4 Hz), 188.6 (d, *J* = 11.0 Hz), 166.1 (dd, *J* = 258.8, 1.5 Hz), 138.6 (d, *J* = 19.2 Hz), 136.4 (d, *J* = 10.3 Hz), 135.0 (d, *J* = 1.7 Hz), 133.9, 129.2 (d, *J* = 2.0 Hz), 128.8, 122.4 (dd, *J* = 16.2, 3.5 Hz), 121.3 (d, *J* = 10.6 Hz), 116.7 (d, *J* = 21.2 Hz), 89.1 (d, *J* = 178.7 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.2 (d, *J* = 5.3 Hz), -182.7 (d, *J* = 5.1 Hz).

HRMS (EI) *m/z*: Found: 260.0636. Calcd for $C_{15}H_{10}F_2O_2$: $[M]^+$ 260.0643.

P-70 2-Fluoro-6-(1-fluoro-2-oxohexyl)benzaldehyde



Chemical Formula: $C_{13}H_{14}F_2O_2$

Molecular Weight: 240.25

Aspect: Brown oil

R_f = 0.52 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **177** (82 mg, 0.4 mmol, 1 equiv., M = 204.24 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a brown oil (65 mg, 68% yield).

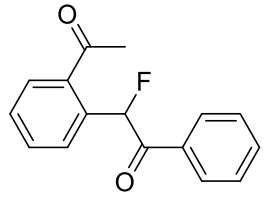
^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.35 (s, 1H), 7.58 (td, *J* = 8.1, 5.6 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.12 (m, 1H), 6.56 (d, *J* = 47.2 Hz, 1H), 2.81 – 2.60 (m, 2H), 1.55 (p, *J* = 7.4 Hz, 2H), 1.28 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.2 (d, *J* = 22.5 Hz), 188.5 (d, *J* = 11.1 Hz), 166.0 (d, *J* = 257.7 Hz), 137.7 (d, *J* = 19.4 Hz), 136.1 (d, *J* = 10.2 Hz), 122.6 (dd, *J* = 13.8, 3.6 Hz), 121.4 (d, *J* = 4.1 Hz), 116.8 (d, *J* = 21.4 Hz), 91.8 (dd, *J* = 181.6, 2.4 Hz), 39.0, 25.1, 22.2, 13.8.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.2 (d, *J* = 4.2 Hz), -186.3 (d, *J* = 4.2 Hz).

HRMS (EI) *m/z*: Found: 240.0956. Calcd for $C_{13}H_{14}F_2O_2$: $[M]^+$ 240.0956.

P-71 2-(2-Acetylphenyl)-2-fluoro-1-phenylethan-1-one



Chemical Formula: $C_{16}H_{13}FO_2$

Molecular Weight: 256.2764

Aspect: Yellow oil

R_f = 0.26 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **36** (88 mg, 0.4 mmol, 1 equiv., M = 220.27 g/mol)

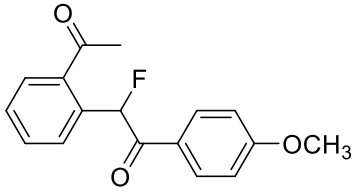
and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow oil (72 mg, 70%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 3H), 7.39 (d, *J* = 47.9 Hz, 1H), 2.58 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.3, 192.0 (d, *J* = 21.7 Hz), 136.6 (d, *J* = 18.2 Hz), 135.3, 134.6 (d, *J* = 2.7 Hz), 133.6, 133.2 (d, *J* = 1.9 Hz), 130.6, 129.1 (d, *J* = 1.6 Hz), 128.8, 128.5 (d, *J* = 1.5 Hz), 127.0 (d, *J* = 16.8 Hz), 89.7 (d, *J* = 175.7 Hz), 28.0.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -181.1.

P-72 2-(2-Acetylphenyl)-2-fluoro-1-(4-methoxyphenyl)ethan-1-one



Chemical Formula: $C_{17}H_{15}FO_3$

Molecular Weight: 286.30

Aspect: Yellow solid

R_f = 0.29 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **194** (95 mg, 0.4 mmol, 1 equiv., M = 236.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (62% yield, 70 mg).

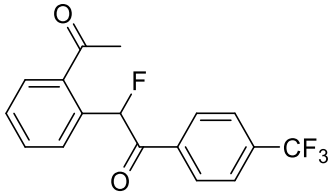
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 48.1 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.4, 190.8 (d, *J* = 21.4 Hz), 163.9, 136.7 (d, *J* = 18.3 Hz), 134.8 (d, *J* = 2.8 Hz), 133.1 (d, *J* = 1.8 Hz), 131.5 (d, *J* = 1.8 Hz), 130.4, 128.4 (d, *J* = 1.7 Hz), 128.3, 127.1 (d, *J* = 16.4 Hz), 114.0, 89.5 (d, *J* = 175.7 Hz), 55.5, 28.1.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -180.1.

HRMS (EI) *m/z*: Found: 286.1004 Calcd for $C_{17}H_{15}FO_3$: $[M]^+$ 286.1000.

P-73 2-(2-Acetylphenyl)-2-fluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one



Chemical Formula: $C_{17}H_{12}F_4O_2$

Molecular Weight: 324.27

Aspect: Yellow solid

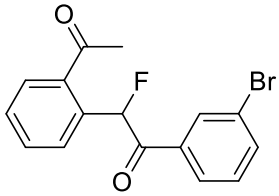
R_f = 0.42 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **193** (115 mg, 0.4 mmol, 1 equiv., M = 288.27 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (25 mg, 19% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.0 Hz, 3H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.38 (s, 1H), 2.59 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 200.3, 190.8 (d, *J* = 22.0 Hz), 138.3, 136.2 (d, *J* = 18.2 Hz), 134.8, 134.5, 134.1 (d, *J* = 2.8 Hz), 133.4, 130.9, 129.4 (d, *J* = 1.6 Hz), 128.7 (d, *J* = 1.3 Hz), 126.9 (d, *J* = 17.4 Hz), 125.9 (q, *J* = 3.8 Hz), 125.0, 122.3, 89.7 (d, *J* = 175.8 Hz), 27.8. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -63.2, -182.0.

HRMS (EI) *m/z*: Found: 324.0761 Calcd for $C_{17}H_{12}F_4O_2$: $[M]^+$ 324.0768.

P-75 2-(2-Acetylphenyl)-1-(3-bromophenyl)-2-fluoroethan-1-one



Chemical Formula: $C_{16}H_{12}BrFO_2$

Molecular Weight: 335.1724

Aspect: Yellow solid

R_f = 0.32 (PE / EtOAc, 10/1)

Following the general procedure **Q**, substrate **196** (120 mg, 0.4 mmol, 1 equiv., M = 299.17 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained as a yellow solid (28 mg, 21% yield).

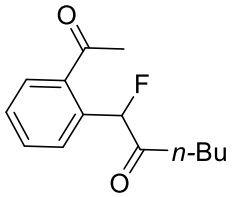
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.75 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.70 (td, *J* = 7.7, 1.1 Hz, 1H), 7.55 (td, *J* = 7.6, 1.1 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 48.0 Hz, 1H), 2.59 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.3, 190.5 (d, *J* = 22.0 Hz), 137.2 (d, *J* = 1.6 Hz), 136.4, 136.2, 134.3 (d, *J* = 2.6 Hz), 133.4 (d, *J* = 2.1 Hz), 132.0 (d, *J* = 1.6 Hz), 130.8, 130.4, 128.6 (d, *J* = 1.4 Hz), 127.6 (d, *J* = 1.7 Hz), 126.9 (d, *J* = 17.4 Hz), 123.1, 89.7 (d, *J* = 175.9 Hz), 27.9.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -181.6.

HRMS (EI) *m/z*: Found: 333.9992 Calcd for $C_{16}H_{12}BrFO_2$: $[M]^+$ 333.9999.

P-77 1-(2-Acetylphenyl)-1-fluorohexan-2-one



Chemical Formula: $C_{14}H_{17}FO_2$

Molecular Weight: 236.29

Aspect: Yellow oil

R_f = 0.45 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **178** (80 mg, 0.4 mmol, 1 equiv., M = 200.28 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. Two products were isolated as yellow oils, **P77** (35 mg, 37% yield) and **P78** (46 mg, 49% yield).

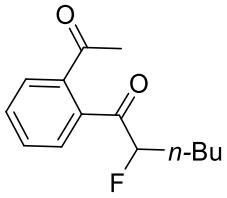
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.58 (qd, *J* = 8.0, 1.5 Hz, 2H), 7.49 – 7.42 (m, 1H), 6.50 (d, *J* = 47.7 Hz, 1H), 2.84 – 2.65 (m, 2H), 2.61 (s, 3H), 1.60 (p, *J* = 7.4 Hz, 2H), 1.33 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 204.3 (d, *J* = 22.6 Hz), 200.8, 135.7 (d, *J* = 2.8 Hz), 135.1 (d, *J* = 18.6 Hz), 132.5 (d, *J* = 0.8 Hz), 129.9, 128.6 (d, *J* = 1.5 Hz), 127.2 (d, *J* = 13.7 Hz), 92.7 (d, *J* = 180.0 Hz), 38.9, 28.5, 25.1, 22.2, 13.9.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -184.9.

HRMS (EI) *m/z*: Found: 236.1210 Calcd for $C_{14}H_{17}FO_2$: $[M]^+$ 236.1207.

P-78 1-(2-Acetylphenyl)-2-fluorohexan-1-one



Chemical Formula: $C_{14}H_{17}FO_2$

Molecular Weight: 236.29

Aspect: Yellow oil

R_f = 0.18 (PE / EtOAc, 10/1)

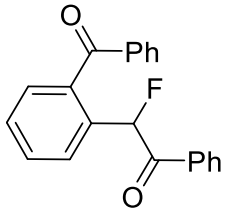
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.79 (m, 1H), 7.59 (dtd, *J* = 24.7, 7.5, 1.2 Hz, 2H), 7.33 (dd, *J* = 7.4, 1.0 Hz, 1H), 5.17 (ddd, *J* = 48.9, 9.2, 3.5 Hz, 1H), 2.62 (s, 3H), 2.09 – 1.82 (m, 2H), 1.51 – 1.33 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 205.9 (d, *J* = 27.5 Hz), 198.8, 139.2, 137.2, 132.8, 130.3, 128.7, 127.3, 95.4 (d, *J* = 184.0 Hz), 32.3 (d, *J* = 20.7 Hz), 27.1 (d, *J* = 2.4 Hz), 26.6, 22.3, 13.9.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -188.9.

HRMS (EI) ***m/z***: Found: 236.1210 Calcd for $C_{14}H_{17}FO_2$: $[M]^+$ 236.1207.

P-79 2-(2-Benzoylphenyl)-2-fluoro-1-phenylethan-1-one



Chemical Formula: $C_{21}H_{15}FO_2$

Molecular Weight: 318.35

Aspect: Yellow oil

R_f = 0.26 (PE / EtOAc, 9/1)

Following the general procedure **Q**, substrate **180** (113 mg, 0.4 mmol, 1 equiv., M = 282.34 g/mol) and Selectfluor (213 mg, 0.6 mmol, 1.5 equiv., M = 354.26 g/mol) were dissolved in 4

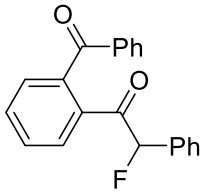
mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (4 mg, 2 mol%, M = 494.71 g/mol) was added to the mixture. Two products were isolated as yellow oils, **P79** (42 mg, 33%) and **P80** (65 mg, 51% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.59 (q, *J* = 8.4, 7.9 Hz, 2H), 7.55 – 7.50 (m, 2H), 7.45 (dt, *J* = 18.8, 7.7 Hz, 5H), 7.21 (d, *J* = 47.4 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.6, 193.5 (d, *J* = 21.1 Hz), 137.6, 137.0 (d, *J* = 3.6 Hz), 134.8 (d, *J* = 18.9 Hz), 134.5, 133.8, 133.3, 131.7, 130.7, 130.4, 129.2 (d, *J* = 2.0 Hz), 128.7, 128.5, 128.4, 128.2 (d, *J* = 9.2 Hz), 89.3 (d, *J* = 179.8 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -177.1.

P-80 1-(2-Benzoylphenyl)-2-fluoro-2-phenylethan-1-one



Chemical Formula: $C_{21}H_{15}FO_2$

Molecular Weight: 318.35

Aspect: Yellow oil

R_f = 0.24 (PE / EtOAc, 10/1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.76 (m, 2H), 7.61 – 7.51 (m, 5H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.35 (m, 5H), 6.23 (d, *J* = 47.5 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.6 (d, *J* = 26.4 Hz), 196.7, 140.0 (d, *J* = 2.4 Hz), 136.9 (d, *J* = 1.5 Hz), 136.8, 134.3 (d, *J* = 20.3 Hz), 133.1, 131.5, 130.8, 129.8, 129.7, 129.4 (d, *J* = 2.2 Hz), 129.1 (d, *J* = 2.7 Hz), 128.9, 128.5, 127.0 (d, *J* = 6.2 Hz), 94.5 (d, *J* = 187.6 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -177.7.

HRMS (EI) *m/z*: Found: 318.1051 Calcd for $C_{21}H_{15}FO_2$: $[M]^+$ 318.1051.

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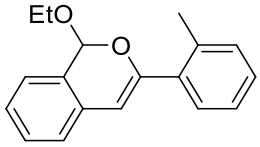
204 1-Ethoxy-3-(*o*-tolyl)-1*H*-isochromene



Chemical Formula: $C_{18}H_{18}O_2$

Molecular Weight: 266.34

R_f = 0.71 (PE / EtOAc, 10/1)

Following the general procedure **Q**, substrate **183** (88 mg, 0.4 mmol, 1 equiv., M = 220.27 g/mol) and Selectfluor (14 mg, 0.04 mmol, 0.1 equiv., M = 354.26 g/mol) were dissolved in 4 mL EtOH and 1 mL H_2O, then the catalyst Ph_3PAuCl (9 mg, 5 mol%, M = 494.71 g/mol) was added to the mixture. The product was obtained in 68% yield (72 mg).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 7.3 Hz, 1H), 7.33 (dt, *J* = 7.7, 4.3 Hz, 1H), 7.27 – 7.19 (m, 5H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.21 (s, 1H), 6.10 (s, 1H), 4.00 (dq, *J* = 9.2, 7.1 Hz, 1H),

3.80 (dq, *J* = 9.5, 7.1 Hz, 1H), 2.48 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (400 MHz, Chloroform-*d*) δ 151.8, 136.5, 135.5, 130.7, 130.3, 129.3, 129.1, 128.7, 126.7, 126.7, 125.9, 125.7, 124.3, 104.0, 98.9, 63.9, 20.6, 15.3.

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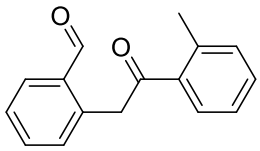
205 2-(2-Oxo-2-(*o*-tolyl)ethyl)benzaldehyde



Chemical Formula: $C_{16}H_{14}O_2$

Molecular Weight: 238.29

Aspect: Yellow oil

R_f = 0.22 (PE / EtOAc, 10/1)

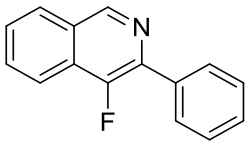
In a round-bottomed flask, to the substrate **183** (880 mg, 4 mmol) in 20 mL Tol/H_2O (v/v 9/1), was added the catalyst $Ph_3PAuNTf_2$ (50 mg, 1.7 mol%). The mixture was stirred at 80 °C, overnight (reaction followed by TLC). The solvent was removed under reduced pressure, the residual mixture was extracted from DCM/H_2O and washed with brine, the organic phase was dried with $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel column chromatography (petroleum ether/ethyl acetate: 80:20) to afford the corresponding product as yellow oil (467 mg, 68% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.04 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.31 (m, 3H), 4.66 (s, 2H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.5, 193.3, 138.5, 137.8, 136.4, 135.2, 134.5, 133.7, 132.8, 132.0, 131.4, 128.6, 127.8, 125.7, 46.5, 21.2.

HRMS (EI) *m/z*: Found: 238.0988 Calcd for $C_{16}H_{14}O_2$: $[M]^+$ 238.0988.

P-82 4-Fluoro-3-phenylisoquinoline



Chemical Formula: $C_{15}H_{10}FN$

Molecular Weight: 223.25

Aspect: Yellow oil

R_f = 0.31 (PE / EtOAc, 9/1)

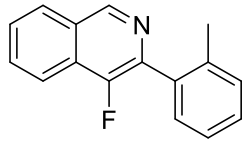
Following the general procedure **R**, in a screw-capped vial, α-fluoroketone **P-54** (48 mg, 0.2 mmol, 1 equiv., M = 242.25 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow oil (40 mg, 89%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 8.17 – 8.11 (m, 3H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.48 – 7.43 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.5 (d, *J* = 264.0 Hz), 147.7 (d, *J* = 5.8 Hz), 136.7 (d, *J* = 10.5 Hz), 135.8 (d, *J* = 5.5 Hz), 130.7 (d, *J* = 1.6 Hz), 129.5 (d, *J* = 2.8 Hz), 129.1 (d, *J* = 6.2 Hz), 128.6, 128.5, 127.9, 127.4 (d, *J* = 16.9 Hz), 127.0 (d, *J* = 1.9 Hz), 120.0 (d, *J* = 5.7 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.6.

P-83 4-Fluoro-3-(*o*-tolyl)isoquinoline



Chemical Formula: $C_{16}H_{12}FN$

Molecular Weight: 237.28

Aspect: Yellow solid

R_f = 0.29 (PE / EtOAc, 9/1)

Following the general procedure **R**, α-fluoroketone **P-53** (51 mg, 0.2 mmol, 1 equiv., M = 256.28 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow solid (45 mg, 95% yield).

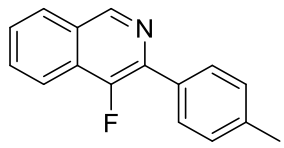
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 6.9 Hz, 1H), 7.35 (m, 3H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.8 (d, *J* = 260.2 Hz), 147.6 (d, *J* = 5.9 Hz), 138.6 (d, *J* = 15.5 Hz), 137.0, 135.3 (d, *J* = 3.5 Hz), 130.8 (d, *J* = 1.3 Hz), 130.4, 130.3 (d, *J* = 1.9 Hz), 129.6 (d, *J* = 2.7 Hz), 128.7, 128.0, 127.1 (d, *J* = 1.9 Hz), 126.9 (d, *J* = 16.8 Hz), 125.7, 120.0 (d, *J* = 4.5 Hz), 19.8 (d, *J* = 3.0 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -135.6.

HRMS (EI) *m/z* Found: 237.0943 Calcd for $C_{16}H_{12}FN$: $[M]^+$ 237.0948.

P-84 4-Fluoro-3-(*p*-tolyl)isoquinoline



Chemical Formula: $C_{16}H_{12}FN$

Molecular Weight: 237.28

Aspect: Yellow solid

R_f = 0.29 (PE / EtOAc, 9/1)

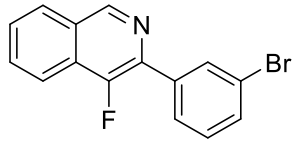
Following the general procedure **R**, α-fluoroketone **P-55** (51 mg, 0.2 mmol, 1 equiv., M = 256.28 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow solid (45 mg, 94% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 3H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.3 (d, *J* = 263.5 Hz), 147.6 (d, *J* = 5.8 Hz), 138.6, 136.8 (d, *J* = 10.5 Hz), 133.0 (d, *J* = 5.6 Hz), 130.7 (d, *J* = 1.6 Hz), 129.4 (d, *J* = 2.7 Hz), 129.3, 128.9 (d, *J* = 6.2 Hz), 127.7, 127.4 (d, *J* = 16.9 Hz), 127.0 (d, *J* = 1.9 Hz), 120.0 (d, *J* = 5.7 Hz), 21.4.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.8.

P-85 3-(3-Bromophenyl)-4-fluoroisoquinoline



Chemical Formula: $C_{15}H_9BrFN$

Molecular Weight: 302.15

Aspect: Yellow solid

R_f = 0.42 (PE / EtOAc, 9/1)

Following the general procedure **R**, α-fluoroketone **P-57** (64 mg, 0.2 mmol, 1 equiv., M = 321.15 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow solid (56 mg, 93% yield).

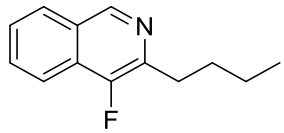
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 8.29 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.7 (d, *J* = 265.2 Hz), 147.8 (d, *J* = 5.8 Hz), 137.8 (d, *J* = 5.8 Hz), 135.0 (d, *J* = 10.1 Hz), 131.9 (d, *J* = 6.4 Hz), 131.6, 131.0 (d, *J* = 1.6 Hz), 130.0, 129.8 (d, *J* = 3.0 Hz), 128.3, 127.5 (d, *J* = 7.2 Hz), 127.3 (d, *J* = 16.9 Hz), 127.0 (d, *J* = 1.9 Hz), 122.7, 120.2 (d, *J* = 5.8 Hz).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -136.7.

HRMS (EI) *m/z*: Found: 300.9887 Calcd for $C_{15}H_9BrFN$: $[M]^+$ 300.9897.

P-86 3-Butyl-4-fluoroisoquinoline



Chemical Formula: $C_{13}H_{14}FN$

Molecular Weight: 203.26

Aspect: Yellow oil

R_f = 0.46 (PE / EtOAc, 9/1)

Following the general procedure **R**, α-fluoroketone **P-59** (44 mg, 0.2 mmol, 1 equiv., M = 222.26 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow oil (37 mg, 90%).

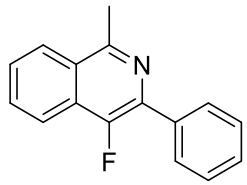
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.68 (t, *J* = 8.1 Hz, 1H), 7.54 (t, *J* = 8.1 Hz, 1H), 2.99 (td, *J* = 7.8, 3.0 Hz, 2H), 1.82 – 1.73 (m,

2H), 1.42 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.2 (d, *J* = 257.2 Hz), 146.2 (d, *J* = 6.1 Hz), 139.8 (d, *J* = 15.8 Hz), 129.3 (d, *J* = 1.4 Hz), 127.8 (d, *J* = 2.5 Hz), 125.9, 125.9 (d, *J* = 2.0 Hz), 125.5 (d, *J* = 16.6 Hz), 118.3 (d, *J* = 4.6 Hz), 30.2 (d, *J* = 1.3 Hz), 29.7 (d, *J* = 1.6 Hz), 21.5, 12.9.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -140.7.

P-87 4-Fluoro-1-methyl-3-phenylisoquinoline



Chemical Formula: $C_{16}H_{12}FN$

Molecular Weight: 237.28

Aspect: Brown oil

R_f = 0.57 (PE / EtOAc, 8/1)

Following the general procedure **R**, α-fluoroketone **P-71** (51 mg, 0.2 mmol, 1 equiv., M = 256.28 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a brown oil (42 mg, 88% yield).

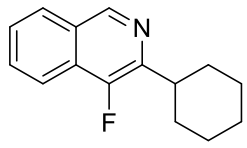
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.11 (m, 3H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.52 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 2.99 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.9 (d, *J* = 5.9 Hz), 151.4 (d, *J* = 261.6 Hz), 136.0 (d, *J* = 5.6 Hz), 134.9 (d, *J* = 10.1 Hz), 130.2 (d, *J* = 1.7 Hz), 129.0 (d, *J* = 6.1 Hz), 128.5, 128.4, 128.1 (d, *J* = 2.1 Hz), 127.7, 127.5, 125.6 (d, *J* = 1.5 Hz), 120.6 (d, *J* = 6.2 Hz), 22.3.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.1.

HRMS (EI) *m/z*: Found: 237.0939 Calcd for $C_{16}H_{12}FN$: $[M]^+$ 237.0948.

P-88 3-Cyclohexyl-4-fluoroisoquinoline



Chemical Formula: $C_{15}H_{16}FN$

Molecular Weight: 229.30

Aspect: White solid

R_f = 0.55 (PE / EtOAc, 9/1)

Following the general procedure **R**, α-fluoroketone **P-60** (50 mg, 0.2 mmol, 1 equiv., M = 248.30 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a white solid (37 mg, 82% yield).

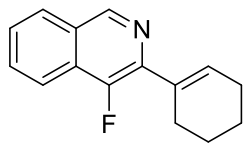
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.04 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 3.31 – 3.19 (m, 1H), 1.93 – 1.75 (m, 8H), 1.56 – 1.40 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.4 (d, *J* = 257.1 Hz), 147.3 (d, *J* = 6.0 Hz), 144.5 (d, *J* = 14.7 Hz), 130.3 (d, *J* = 1.4 Hz), 128.7 (d, *J* = 2.6 Hz), 127.0, 126.9 (d, *J* = 2.0 Hz), 126.7 (d, *J* = 16.9 Hz), 119.5 (d, *J* = 4.8 Hz), 38.7 (d, *J* = 1.4 Hz), 31.6 (d, *J* = 1.3 Hz), 26.7, 26.0.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.7.

HRMS (ESI) *m/z*: Found: 230.1335 Calcd for $C_{15}H_{16}FN$: $[M+H]^+$ 230.1340.

P-89 3-(Cyclohex-1-en-1-yl)-4-fluoroisoquinoline



Chemical Formula: $C_{15}H_{14}FN$

Molecular Weight: 227.28

Aspect: Yellow oil

R_f = 0.43 (PE / EtOAc, 9/1)

Following the general procedure **R**, α-fluoroketone **P-61** (49 mg, 0.2 mmol, 1 equiv., M = 246.28 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow oil (38 mg, 83% yield).

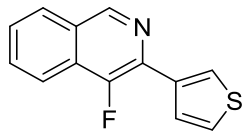
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 6.60 – 6.53 (m, 1H), 2.67 – 2.61 (m, 2H), 2.32 (dq, *J* = 5.9, 3.4 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.77 – 1.71 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.6 (d, *J* = 262.0 Hz), 146.9 (d, *J* = 5.8 Hz), 139.3 (d, *J* = 11.5 Hz), 133.5 (d, *J* = 5.4 Hz), 131.2 (d, *J* = 6.6 Hz), 130.4 (d, *J* = 1.6 Hz), 128.9 (d, *J* = 2.7 Hz), 127.4, 127.2, 126.8 (d, *J* = 1.9 Hz), 119.8 (d, *J* = 5.7 Hz), 27.4 (d, *J* = 4.0 Hz), 26.0, 23.0, 22.1.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.1.

HRMS (ESI) *m/z*: Found: 228.1178 Calcd for $C_{15}H_{14}FN$: $[M+H]^+$ 228.1183.

P-90 4-Fluoro-3-(thiophen-3-yl)isoquinoline



Chemical Formula: $C_{13}H_8FNS$

Molecular Weight: 229.27

Aspect: Yellow solid

R_f = 0.44 (PE / EtOAc, 9/1)

Following the general procedure **R**, α-fluoroketone **P-63** (50 mg, 0.2 mmol, 1 equiv., M = 248.27 g/mol) and NH_4OAc (47 mg, 0.6 mmol, 3 equiv., M = 77.08 g/mol) were added to a 2 mL methanol solution. The product was obtained as a yellow solid (41 mg, 89% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.07 (s, 1H), 8.16 – 8.10 (m, 2H), 7.99 – 7.92 (m, 2H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 5.0, 3.0 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.5 (d, *J* = 263.8 Hz), 147.6 (d, *J* = 5.5 Hz), 137.3 (d, *J* = 6.2 Hz), 133.1 (d, *J* = 11.3 Hz), 130.8 (d, *J* = 1.6 Hz), 129.2 (d, *J* = 2.9 Hz), 127.8 (d, *J* = 6.1 Hz), 127.6, 127.3 (d, *J* = 16.6 Hz), 127.0 (d, *J* = 2.0 Hz), 125.5, 125.4, 119.9 (d, *J* = 5.6 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.1.

HRMS (ESI) *m/z*: Found: 230.0430 Calcd for $C_{13}H_8FNS$: $[M+H]^+$ 230.0434.