PART A: ITERATIVE ADDITION OF CARBON NUCLEOPHILES TO N,N-DIALKYL CARBOXAMIDES FOR THE SYNTHESIS OF A-TERTIARY AMINES;
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CHEN JIAHUA

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2022

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Professor Shunsuke Chiba

Authorship Attribution Statement

This thesis contains material from 2 papers published in the following peer-reviewed journals in which I am listed as an author.

Chapter 2 is published as J. Chen, J. W. Lim, D. Y. Ong, S. Chiba, *Chem. Sci.* **2022**, *13*, 99–104. DOI: 10.1039/D1SC05876B.

The contributions of the co-authors are as follows:

- Prof. S. Chiba provided overall project direction.
- The manuscript was prepared and revised by Prof. S. Chiba, Dr. D. Y. Ong, and the author.
- The author, J. W. Lim, and Dr. D. Y. Ong designed the study and performed all the experimental work at the School of Physical and Mathematical Sciences.

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The contributions of the co-authors are as follows:

- Prof. T. Hayashi provided overall project direction.
- The manuscript was prepared and revised by Prof. T. Hayashi and the author.
- The author designed the study and performed all the experimental work at the School of Physical and Mathematical Sciences.

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Date

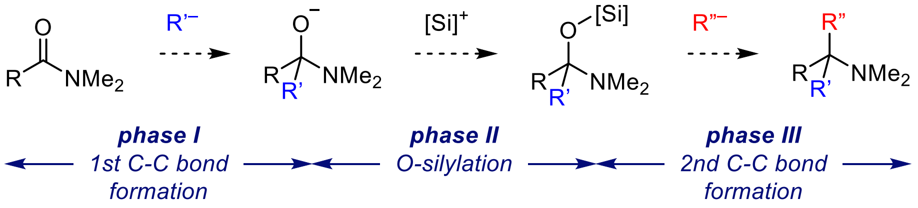
Chen Jiahua

Abstract

This thesis contains two parts. Part A (Chapters 1 and 2) describes the synthesis of α-tertiary amines by iterative addition of carbon nucleophiles to *N*,*N*-dialkyl carboxamides, and Part B (Chapters 3 and 4) describes the rhodium-catalyzed enantioselective arylative cyclization of 1,6-enynes with arylzincs for the synthesis of chiral alkylzincs.

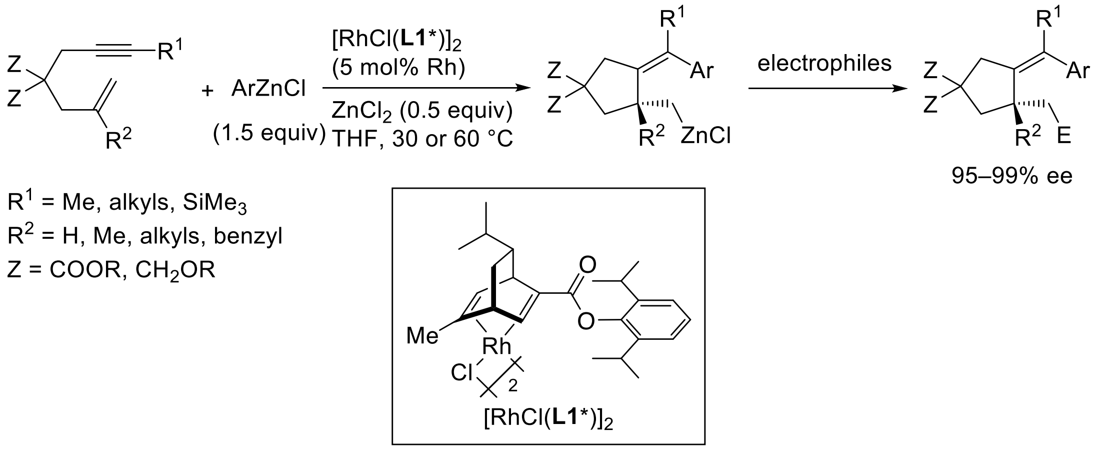
Chapter 1 provides a general overview of the synthesis of amines by nucleophilic attack of carboxamides. It covers the addition of hydride (reductive functionalization) and the addition of carbanions.

Chapter 2 describes a new protocol for the synthesis of α-tertiary amines by iterative addition of carbon nucleophiles to *N*,*N*-dialkyl carboxamides. Employment of (trimethylsilyl)methylmagnesium chloride as the second nucleophile resulting in the formation of 1,1-diarylethylenes via aza-Peterson olefination.



Chapter 3 provides an introduction to rhodium-catalyzed carborhodation of alkynes and the cascade reactions of the organorhodium intermediates.

Chapter 4 describes an asymmetric synthesis of 2-(alkylidene)cyclopentylmethylzincs with high enantioselectivities by a chiral diene/rhodium-catalyzed arylative cyclization of 1,6-enynes with arylzincs. The enantioenriched alkylzincs were readily converted in a one-pot approach into a wide variety of functionalized products.



Chapter 5 lists the experimental data for chapters 2 and 4.

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Lastly and the most important of all, I would like to thank my family for their encouragement, love, and support.

With deepest gratitude,
Jiahua

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Part B: Asymmetric synthesis of alkylzincs by rhodium-catalyzed enantioselective arylative cyclization of 1,6-enynes with arylzincs.

List of Abbreviations

α	alpha
Ar	aryl (substituted aromatic ring)
β	beta
binap	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
biphep	2,2’-bis(diphenylphosphino)-1,1’-biphenyl
brs	broad singlet
calcd.	calculated
cm^{-1}	wavenumber
cod	1,5-cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E	electrophile
EA	ethyl acetate
ee	enantiomeric excess
eq	equation
equiv	equivalent(s)
ESIHRMS	electrospray ionization high resolution mass spectrometry

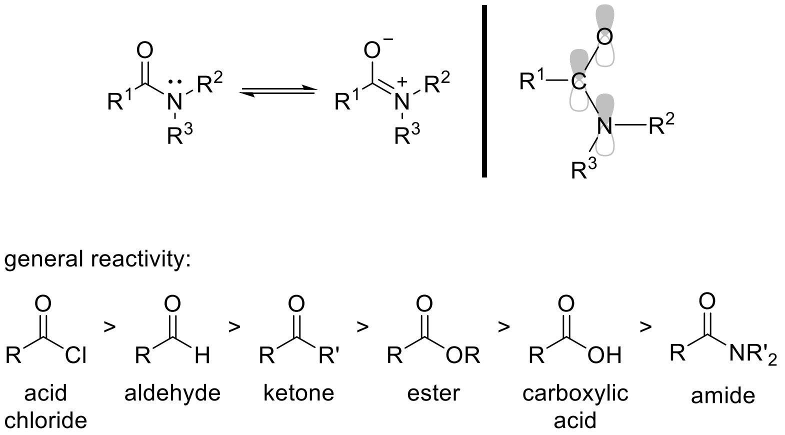
Et	ethyl
Et_2O	diethyl ether
equiv	equivalent(s)
Fc	ferrocenyl
FTIR	Fourier transform infrared spectroscopy
g	gram(s)
h	hour(s)
Hex	hexane
HEH	diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
Hz	hertz
i-Pr	isopropyl
J	coupling constant
M	concentration (N, mol/dm^{-3})
m	multiplet
Me	methyl
mg	milligram(s)
min	minutes(s)
mL	milliliter(s)
mol	mole
Nu	nucleophile
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
OMe	methoxy
Ph	phenyl

ppm	parts per million
q	quartet
γ	gama
rt	room temperature
segphos	5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
sept	septet
t	triplet
TBACN	tetrabutylammonium cyanide
t-Bu	*tert*-butyl
TMDS	1,1,3,3-tetramethyldisiloxane
THF	tetrahydrofuran
TMS	tetramethylsilane
THF	tetrahydrofuran
TLC	thin-layer chromatography
μL	microliter(s)
°C	degree Celsius
δ	chemical shift (ppm)
%	percent

Part A: Iterative addition of carbon nucleophiles to *N*,*N*-dialkyl carboxamides for the synthesis of α-tertiary amines

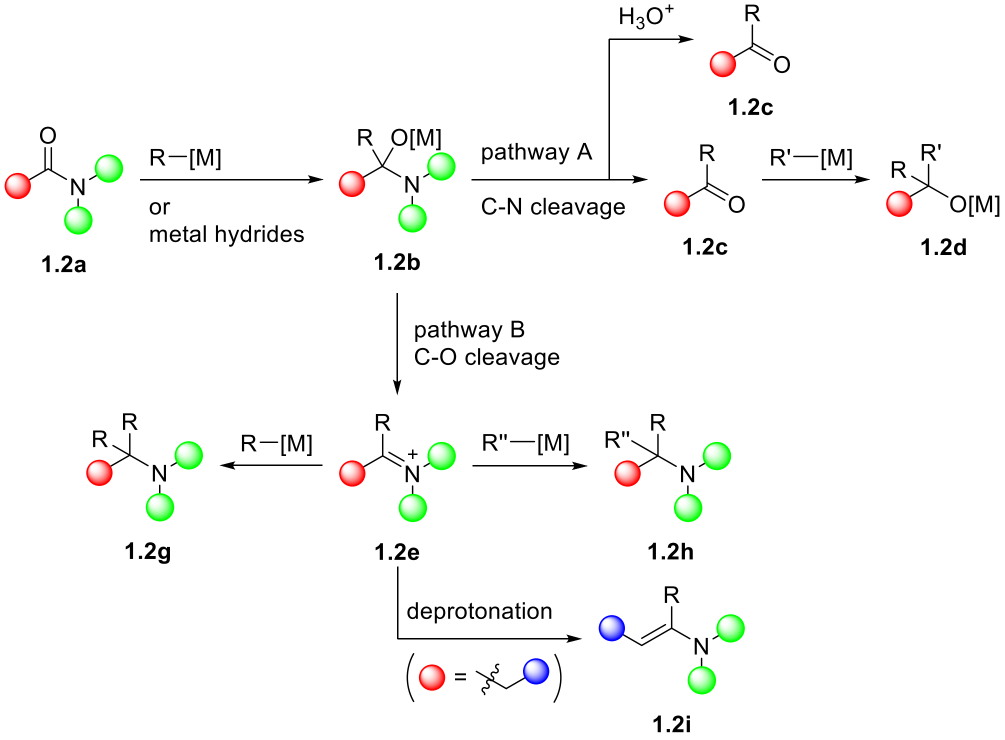
Chapter 1. General introduction

Carboxamides are an important class of compounds that widely exist and synthetic compounds[1] such as pharmaceuticals,[2] agrochemicals,[3] and polymers.[4] It has been well recognized that amides are generally more stable than other carbonyl and carboxyl derivatives due to the inherent resonance stabilization of the C-N bond (Scheme 1-1). The C-N bond possesses a partial double-bond character because of the orbital overlap between the nitrogen lone pair and the anti-bonding (π*) orbital of the carbonyl group and thus leads to the planarity of the amide moiety.[5] This electron property decreases the electrophilicity of the carbonyl carbon, making it less reactive toward nucleophilic attack.[6]



Scheme 1-1. Resonance structure and the planar conformation of amide.

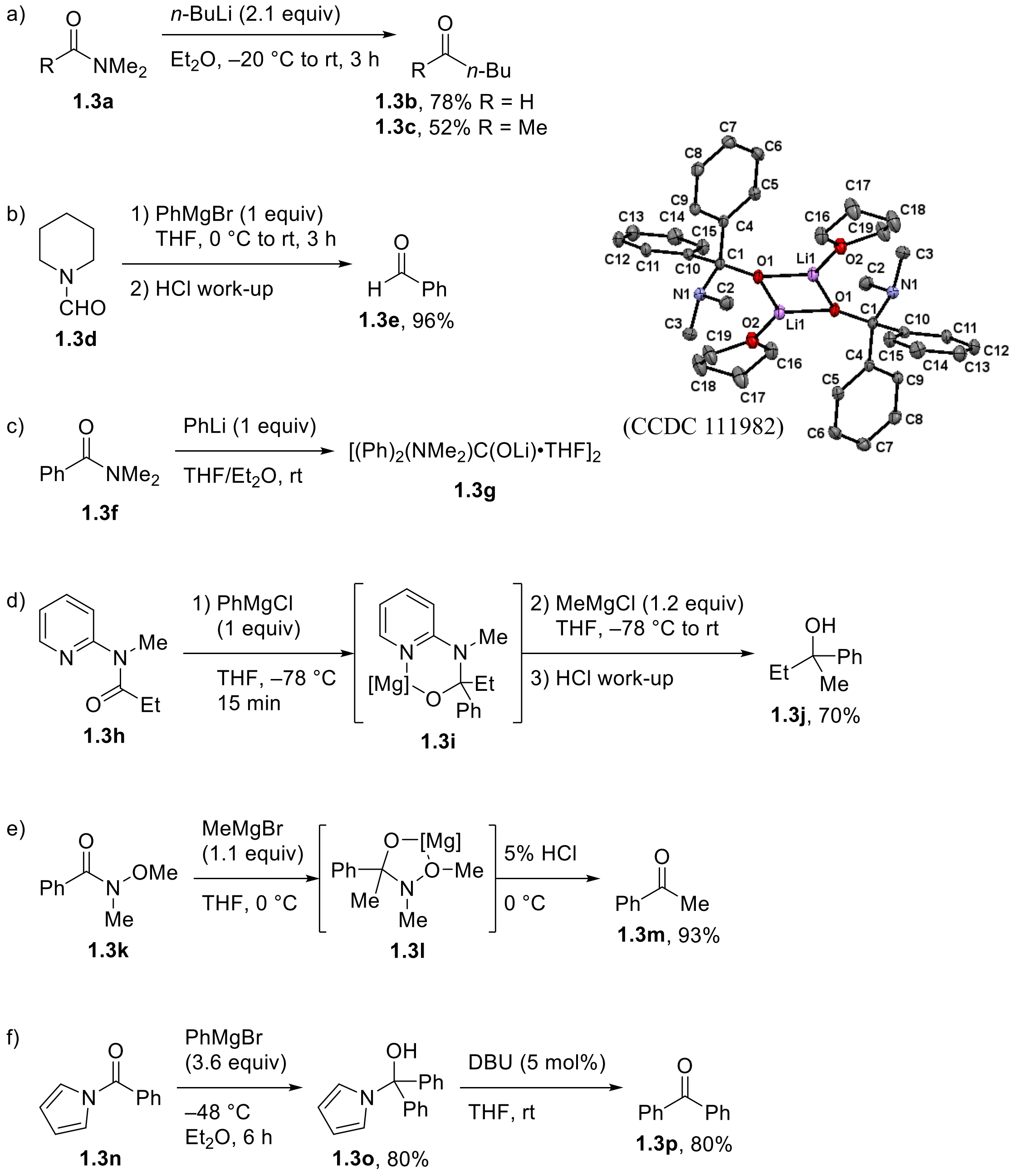
Regardless of the decreased reactivity, the nucleophilic attack on the amide carbonyl group is possible. As shown in Scheme 1-2, it has been reported that nucleophilic attack of organometallic reagents or highly reactive metal hydrides to amide is feasible, and the tetrahedral intermediate **1.2b** is generated.[7] It undergoes C-N bond cleavage to give the ketone or aldehyde **1.2c**, and the corresponding alcohol **1.2d** can be obtained in the presence of excess nucleophile (pathway A). Alternatively, the tetrahedral intermediate **1.2b** can undergo deoxygenation (C-O bond cleavage, pathway B) to generate the iminium species **1.2e**, and it is further attacked by another nucleophile to provide amine **1.2g** or **1.2h**. For iminium intermediates bearing an α-proton, deprotonation can also occur to generate the enamine **1.2i**.



Scheme 1-2. General reactivity of amides towards nucleophilic attack.

To date, pathway A has been demonstrated in numerous reports. The pioneering work from Bouveault in 1904 showed that the addition of Grignard reagents to *N*,*N*-diethylformamide led to the formation of aldehyde upon acidic workup.[8] The addition of organolithium reagents to amides was reported by Evans[9] in 1956, and Olah[10] reported the addition of Grignard reagents in 1981 (Scheme 1-3a, b). It was suggested that the tetrahedral intermediate was stable under aprotic reaction conditions, and it was later evidenced by Boche where the crystal structure of **1.3g** was obtained by the single crystal X-ray analysis (Scheme 1-3c).[11] An increased stability of the tetrahedral intermediate was observed by the chelating effect, as reported by Comins[12] and Weinreb[13], and the latter was known as the Weinreb amide

(Scheme 1-3d,e).[14] In 2002, Evans reported the nucleophilic addition of *N*-acylpyrroles[15], and the carbinols such as **1.3o** were produced. It was further treated with a base, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), to give the corresponding ketone (Scheme 1-3f). The use of distorted amides, in which the amide planarity was somewhat diminished, was also reported to facilitate the nucleophilic attack and give the ketones as the final product.[16]



Scheme 1-3. Early studies.

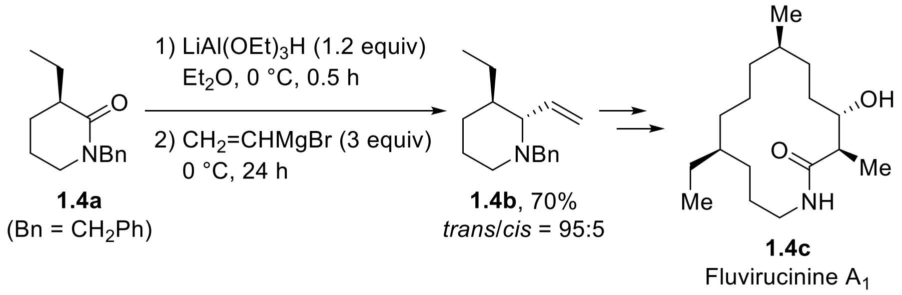
Pathway B, on the other hand, has been less explored. It should be noticed that it is one of the most straightforward methods for the synthesis of amines from readily available carboxamides. It would be even more challenging to install two different nucleophiles at the amide carbonyl carbon since the generated iminium species are generally more reactive toward nucleophilic attack, and thus, the two-fold addition of the first nucleophile would occur. The following section will discuss the synthesis of amines via controlled amide functionalization by the addition of hydrides or organometallic reagents.

1.1. Addition of hydride reagents (reductive functionalization)

The carboxamides are the least reactive toward the nucleophilic attack among the carbonyl compounds, and they are commonly reduced by reactive hydride reagents or transition metal-catalyzed hydrosilylation.

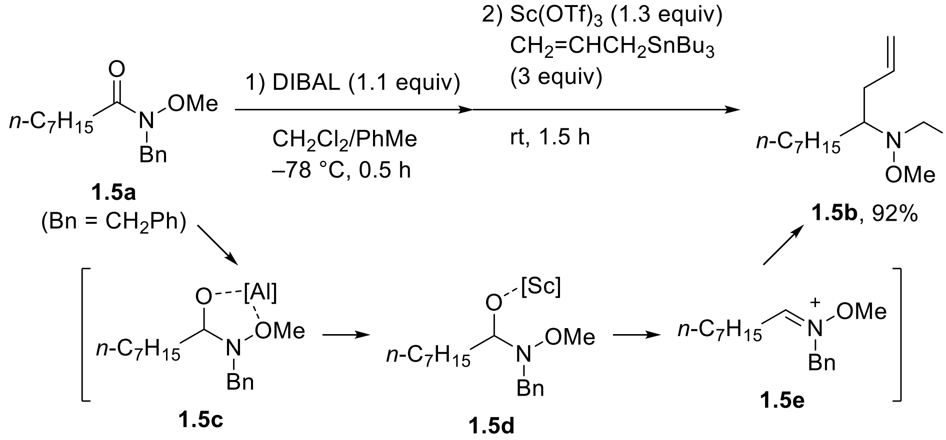
1.1.1. Metal hydrides and hydrosilanes

Aluminum hydrides have been commonly used in the reduction of carboxamides.[17] For most cases, however, two hydrides were delivered to generate the corresponding amines due to the high intrinsic reactivity of the reagent. The highly hydridic nature of aluminum hydrides also renders poor functional group tolerance. It is possible to achieve a controlled reduction of carboxamides when a stoichiometric amount of hydride reagent was used under cryogenic reaction conditions to prevent the collapse of the tetrahedral intermediate. During the studies towards the total synthesis of Fluvirucinine A_1, Suh successfully obtained the *trans*-disubstituted piperidine **1.4b** in 70% yield with good diastereoselectivity (*trans*/*cis* = 95:5) via the controlled reduction of the lactam **1.4a** with $LiAl(OEt)_3H$ (1.2 equiv) at 0 °C and subsequent treatment with vinylmagnesium bromide (Scheme 1-4).[18] Nonetheless, due to the potential over reduction, this protocol was not generally applied, except for the reduction of imides.[19]



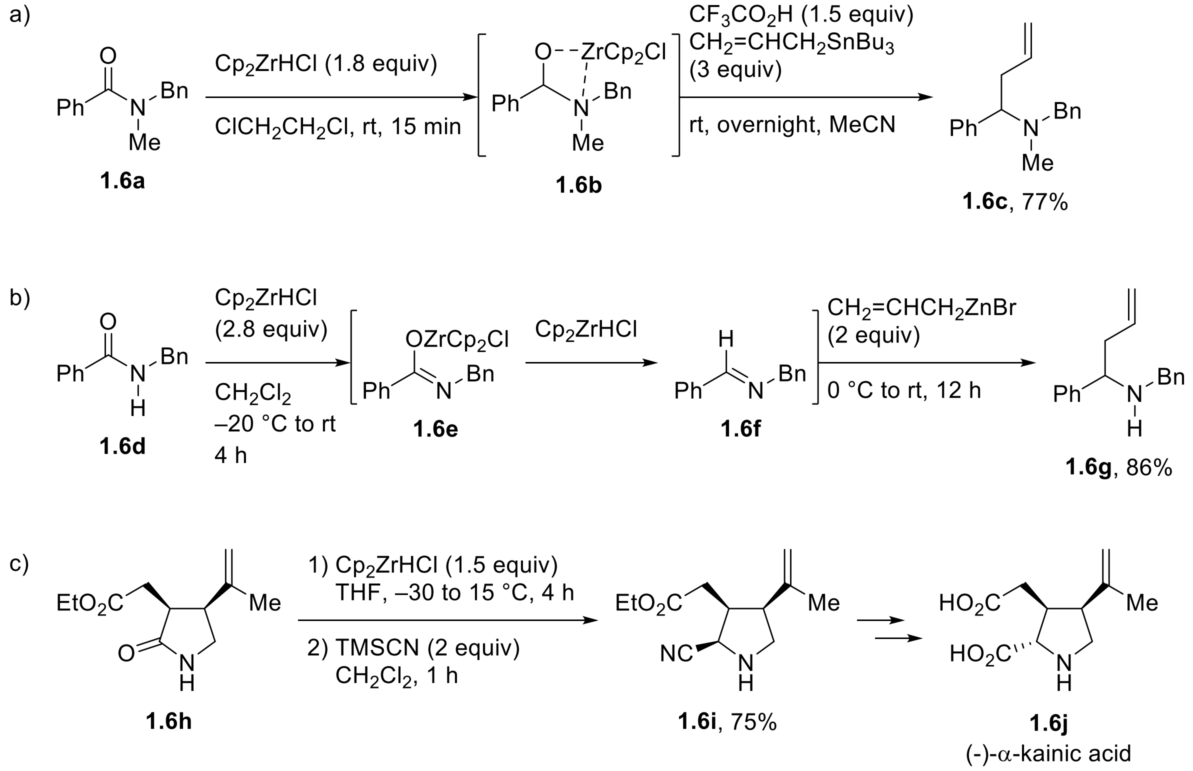
Scheme 1-4. Synthesis of Fluvirucinine A_1.

N-alkoxyamide was applied to prevent over reduction since the 5-membered chelating tetrahedral intermediate (Scheme 1-3e) generated upon the first hydride addition could be kept stable, ensuing the reaction with the second nucleophile. Chida and Sato utilized this strategy in 2010, where the Weinreb amide was reduced by diisobutylaluminium hydride (DIBAL), which is followed by the generation of iminium such as **1.5e** by the treatment with a Lewis acid. The ensuing addition of allyltrimethylsilane or trimethylsilylcyanide afforded the *N*-alkoxy amines **1.5b** (Scheme 1-5a).[20]



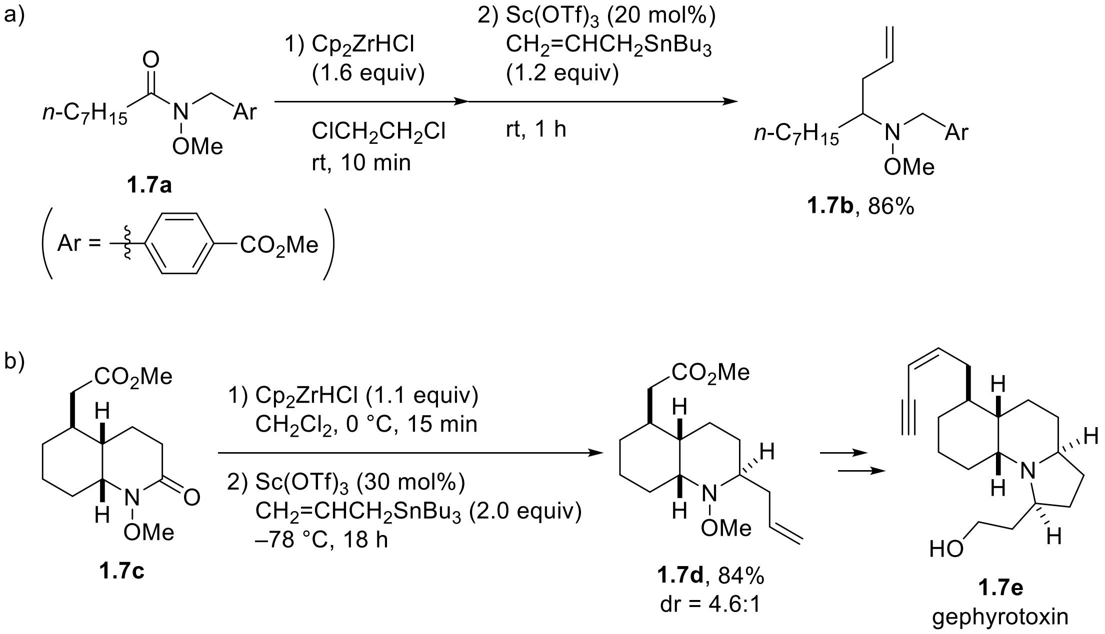
Scheme 1-5. Reductive functionalization of *N*-alkoxyamides with aluminum hydrides.

Meanwhile, the Schwartz's reagent (Cp_2ZrHCl) was identified as a versatile hydride donor to reduce various carboxamides (primary, secondary, and tertiary) to the corresponding aldehydes via a zirconacycle intermediate such as **1.6b**.[21] For tertiary carboxamides, the resulting tetrahedral intermediate can also be treated with acid to trigger the formation of the iminium intermediate, which is further attacked by an allylating agent (Scheme 1-6a).[22] Secondary carboxamides were also applicable under the same protocol, while an excessive amount of the Schwartz's reagent was required (Scheme 1-6b). For instance, Ganem reported the synthesis of α-kainic acid **1.6j** by taking the advantage of the Schwartz's reagent (Scheme 1-6c).[23] The late-stage installation of a cyanide group at the α-position to the nitrogen using Me_3SiCN was achieved in 75% yield.



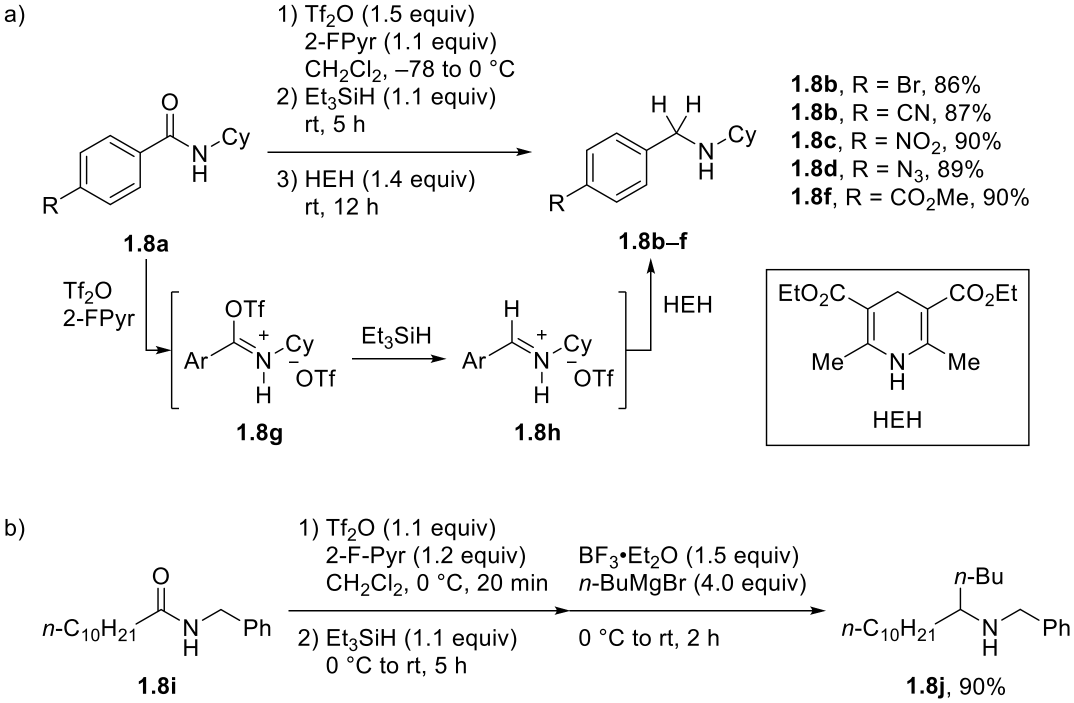
Scheme 1-6. Reductive functionalization of carboxamides with the Schwartz's reagent.

The scope of carboxamides was further extended to the Weinreb amides and their derivatives, as demonstrated by Chida and Sato in 2014 (Scheme 1-7).[24] This methodology was also employed to synthesize gephyrotoxin[24] and perhydrogephyrotxin[25] by the same group.



Scheme 1-7. Reductive functionalization of Weinreb amides and their derivatives with the Schwartz's reagent.

Charette has reported the activation of secondary carboxamides using highly electrophilic triflic anhydride (Tf_2O) and 2-fluoropyridine, which results in the generation of a highly electrophilic iminium triflate intermediate **1.8g** (Scheme 1-8a). Iminium triflate intermediate **1.8g** was first reduced by triethylsilane to give the corresponding imine intermediate **1.8h**, which is followed by the second reduction with Hantzsch ester (HEH) to provide the amines.[26] Excellent chemoselectivity and functional group tolerance were observed. Later, Huang and co-workers demonstrated the synthetic utilities of the iminium intermediates. For example, a BF_3•Et_2O promoted addition of Grignard reagents generated the α-branched amines (Scheme 1-8b).[27]

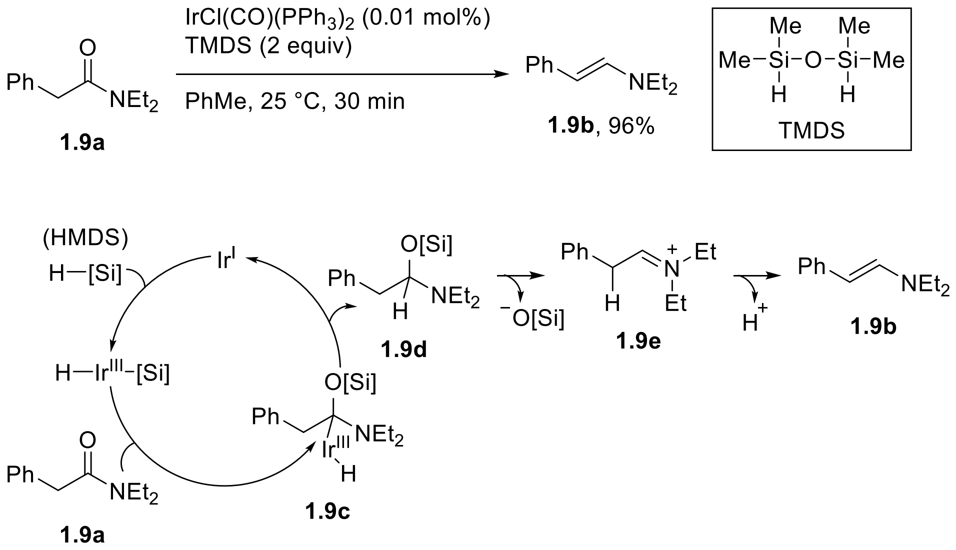


Scheme 1-8. Reductive functionalization of activated carboxamides.

1.1.2. Transition metal-catalyzed/promoted hydrosilylation

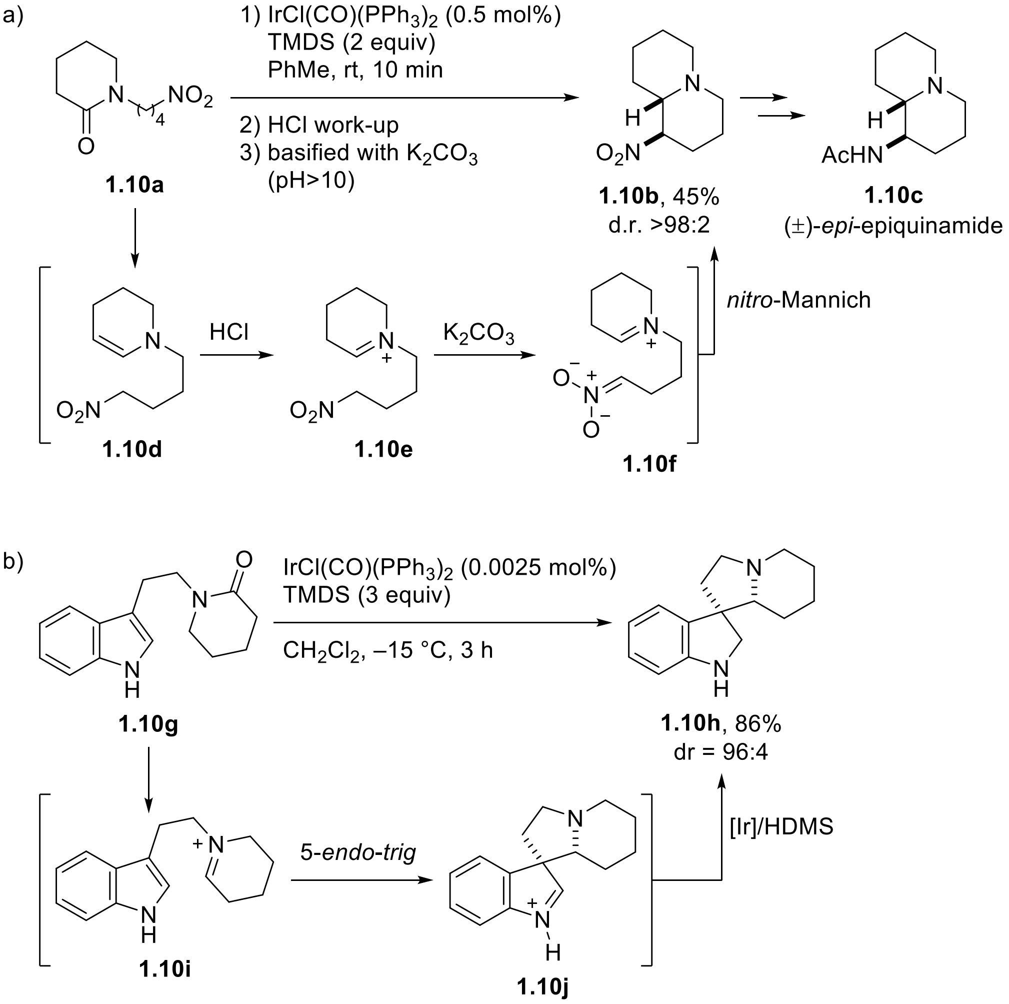
1.1.2.1. Iridium-catalyzed reactions

The pioneering work by Nagashima and co-workers in 2009 showed that carboxamides were efficiently reduced by TMDS (1,1,3,3-tetramethyldisiloxane) in the presence of a catalytic amount of the Vaska's complex [$IrCl(CO)(PPh_3)_2$] to give the corresponding enamines upon work-up (Scheme 1-9).[28] It was proposed that the Ir-catalyzed hydrosilylation took place at the amide carbonyl and the subsequent elimination of siloxane gave an iminium intermediate **1.9e**. This intermediate underwent rapid deprotonation of an α-proton to provide **1.9b**.



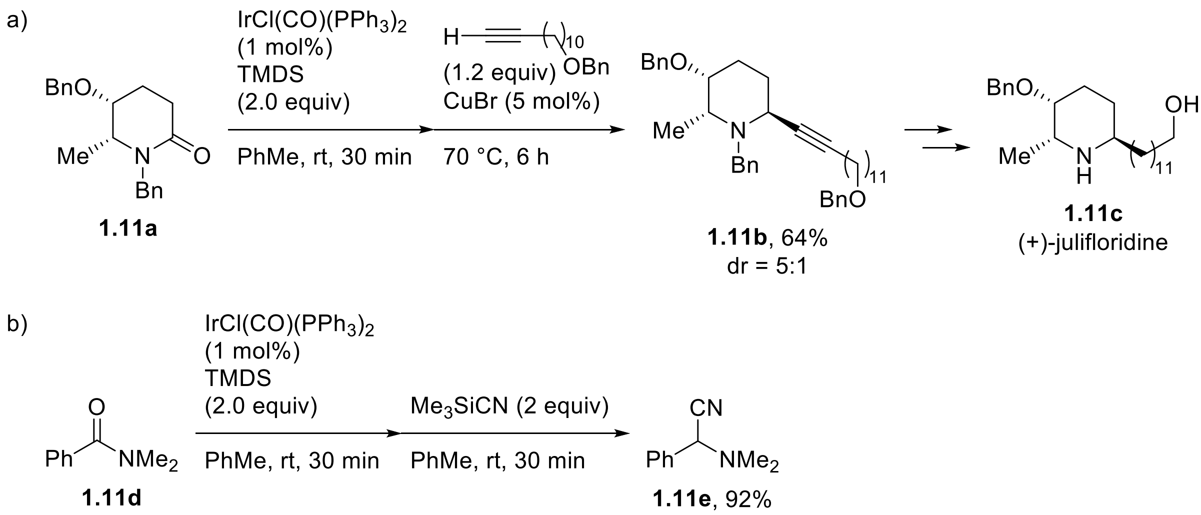
Scheme 1-9. Iridium-catalyzed conversion of tertiary amides to enamines.

Trapping of the iminium intermediate with other nucleophiles was also reported to construct complex amines.[29] In 2015, Dixon demonstrated the first reductive intramolecular aza-Henry reaction of *N*-nitroalkyl tethered lactam **1.10a** (Scheme 1-10a).[30] In the presence of the Vaska's complex and TMDS, the lactam underwent hydrosilylation and subsequent deprotonation to provide the cyclic enamine **1.10d**. The enamine was converted to the iminium ion in an acidic work-up, and the treatment of K_2CO_3 facilitated the cyclization to give the product **1.10b**. The synthesis of (±)-*epi*-epiquinamide[31] was achieved by reducing **1.10b** and concomitant acetylation with acetic anhydride. In another example, the iminium intermediate **1.10i** underwent an interrupted Pictet-Spengler reaction to give azaspirocyclic indolines **1.10h** via a 5-*endo-dig* process (Scheme 1-10b).[32] To show the practical scalability, the gram-scale synthesis of **1.10h** was achieved with a catalyst loading of 25 ppm, which did not diminish the reaction efficiency.

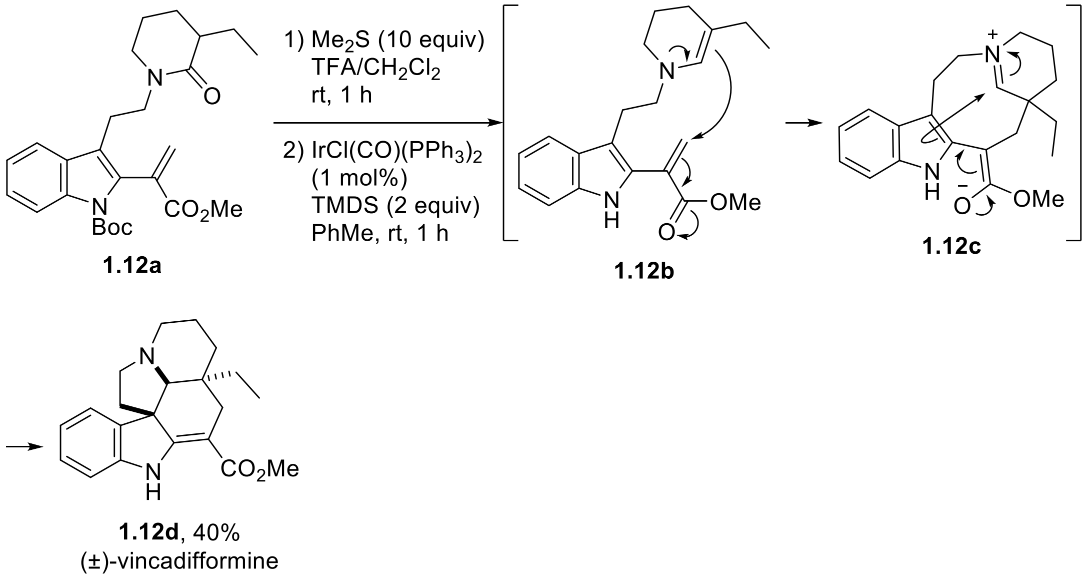


Scheme 1-10. Iridium-catalyzed reductive cyclization of carboxamides.

Intramolecular trapping of the iminium intermediates was also reported. For instance, Huang reported the synthesis of propargylic amines via the cross-coupling of alkynes and iminium intermediates in the presence of a copper catalyst,[33] and it was further applied in the total synthesis of a piperidine alkaloid (+)-juliflоridine (**1.11c**)[34] (Scheme 1-11a). Dixon illustrated the reductive functionalizations of amides and lactams with carbon nucleophiles such as Grignard reagents[35] or Me_3SiCN[36] to provide α-branched amines (Scheme 1-11b).



Scheme 1-11. Reductive intermolecular nucleophilic addition to carboxamides.



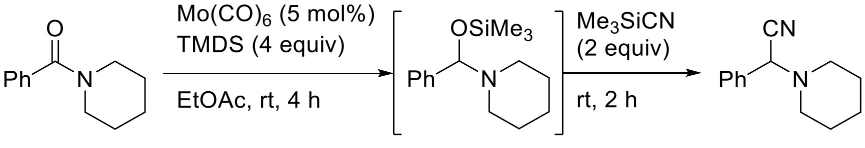
Scheme 1-12. Application of iridium-catalyzed reductive functionalization of amides.

Due to the mild reaction conditions and the excellent functional group tolerance, the iridium-catalyzed reductive functionalization of carboxamides has been applied as the key step for the synthesis of several complex natural products.[37] For example, Dixon and Seayad have shown the intramolecular cyclization of **1.12a**, which was triggered by the Ir-catalyzed reductive enamine formation.[38] Sequential transannular Mannich reaction provided (±)-

vincaminorine (Scheme 1-12).[39] This strategy was also applied to synthesize (+)-20-*epi*-ibophyllidine, an *iboga* alkaloid.[38]

1.1.2.2. Molybdenum-catalyzed reactions

Besides the iridium-based Vaska's complex, molybdenum complexes were also reported for the reductive functionalization of carboxamides. In 2013, Adolfsson has found that a catalytic amount of $Mo(CO)_6$ in the presence of TMDS is capable of reducing carboxamides into hemiaminal intermediates, which are reacted with Me_3SiCN to furnish the α-amino nitriles (Scheme 1-13).[40]

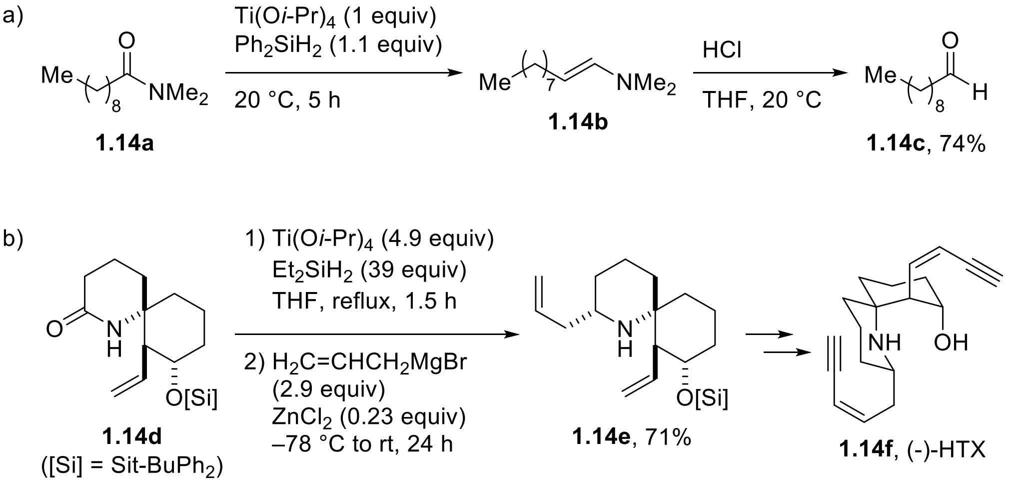


1.13a **1.13b** **1.13c**, 88%

Scheme 1-13. Mo-catalyzed reductive functionalization of carboxamides.

1.1.2.3. Titanium-promoted reactions

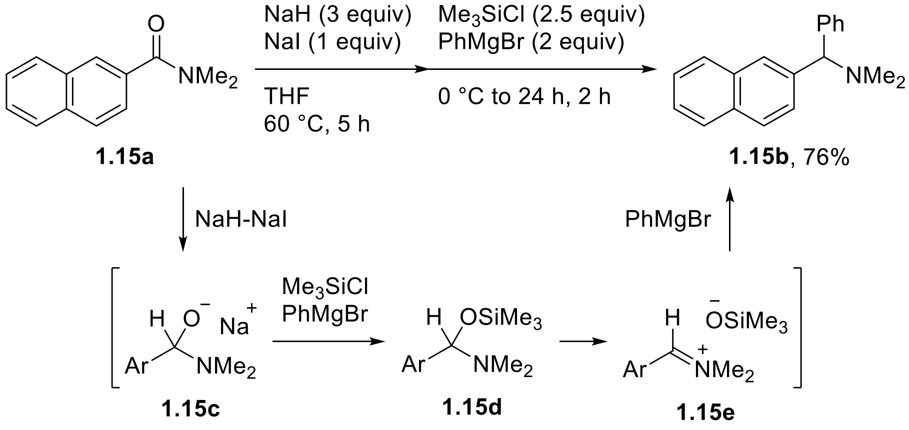
In 1996, Buchwald reported the conversion of amides to the aldehyde in the presence of a stoichiometric amount of Ti(O-*i*Pr)$_4$ and diphenylsilane (Scheme 1-14a).[42] The enamine was first generated as the key intermediate, and it was hydrolyzed under acidic workup. However, only aliphatic amides with α-hydrogen were applicable. Later, Tokuyama adopted this protocol for the total synthesis of (–)-ATX[44] via the diastereoselective reductive allylation of the spirocyclic amide **1.14d** (Scheme 1-14b).[43]



Scheme 1-14. Ti-promoted reductive functionalization of amides.

1.1.3. NaH-NaI Composite

NaH has been commonly used as a Brønsted base in organic synthesis, whereas it rarely behaves as a hydride donor.[45] However, Chiba and co-workers disclosed the unique reactivity of NaH-NaI composite,[46] and it was able to facilitate controlled hydride reduction of carboxamides,[47] hydro-decyanation of benzyl cyanides,[48] and hydrodehalogenation of haloarenes.[49] In 2020, Dixon and Chiba reported the reductive functionalization of the carboxamide with the NaH-NaI composite.[50] The reaction was initialized by the single hydride reduction of carboxamides under the NaH-NaI system to give the anionic hemiaminal intermediates (Scheme 1-15). These intermediates were stable under the reaction conditions, and thus their successive O-silylation with Me_3SiCl followed by the addition of carbon nucleophiles allowed for the production of α-functionalized amines in a one-pot fashion. Both acyclic and cyclic carboxamides were applicable for the synthesis of the corresponding α-branched amines. Moreover, the reductive Strecker type of reaction was also enabled by using tetrabutylammonium cyanide as a nucleophile, providing α-amino nitriles.



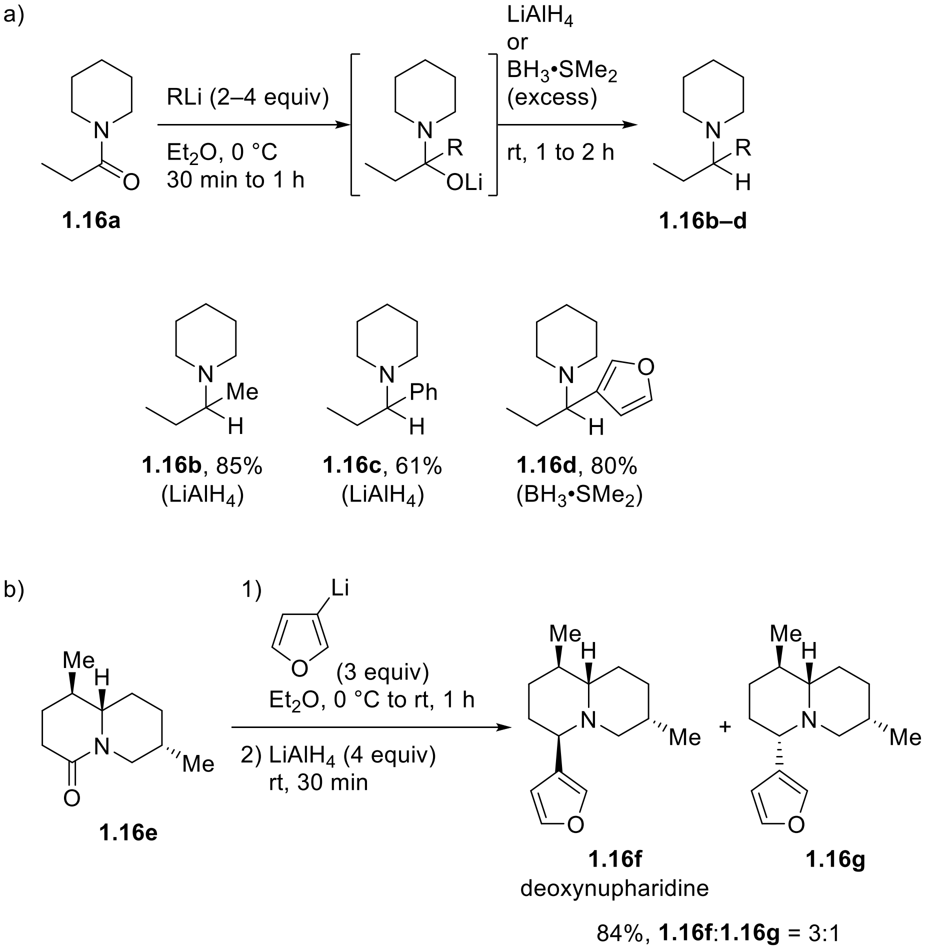
Scheme 1-15. Reductive functionalization of carboxamides using a NaH-NaI composite.

1.2. Addition of carbanions to carboxamides

Regardless of the lower reactivity of the amide carbonyl group, the nucleophilic additions of carbanions were made possible with highly reactive nucleophiles such as organolithium or the Grignard reagents. Early studies mainly focused on the formation of ketones or alcohols via the C-N bond cleavage of the resultant tetrahedral intermediate, as shown in Scheme 1-2. On the other hand, the addition of carbanions to carboxamides for the synthesis of amines has been less exploited. The geminal addition of two carbanions to the amide carbonyl group will be mainly covered in Chapter 2.

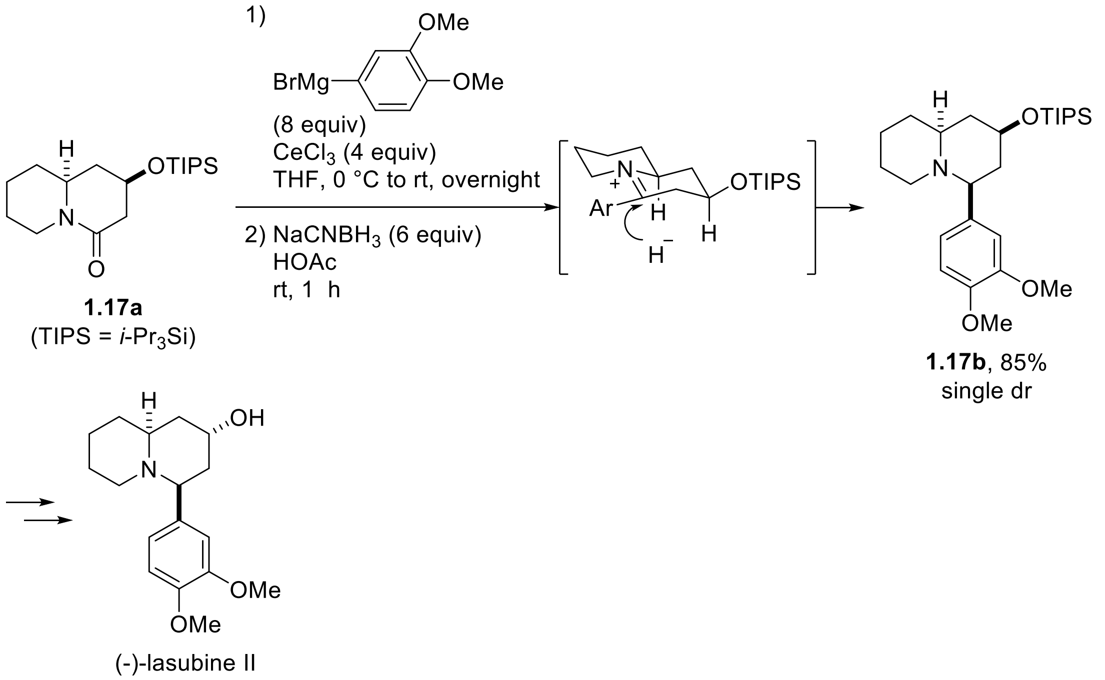
1.2.1. Unactivated carboxamides

In an early example, Flower reported the subsequent addition of organolithium reagents and hydride to cyclic amides and lactams (Scheme 1-16).[51] It was suggested that the iminium intermediates are generated upon the addition of the organometallic reagents, ensuring the subsequent hydride reduction to give the corresponding amines. This concept was first realized in the functionalization of *N*-acylpiperdine **1.16a**. A series of alkyl and aryllithiums were applied as the first nucleophile, and the reaction mixture was further treated with hydride doners to give the α-branched amines **1.16b–d** in good yields. This protocol was also applied in the synthesis of deoxynupharidine **1.16f**, where the authors found that the use of $LiAlH_4$ as the hydride donor gave a mixture of **1.16f** and **1.16g** in a 3:1 ratio.[52] This strategy was later applied in the total synthesis of several indolizine and quinolizidine alkaloids such as (–)-cermizine C[53] and (±)-porantheridine.[54] However, this protocol was mostly applied to the transformation of lactams, while the use of acyclic carboxamides was not intensively studied.



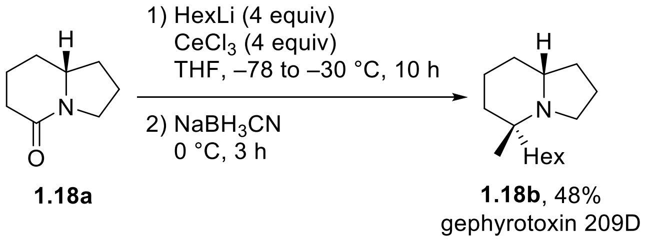
Scheme 1-16. Sequential addition of organolithiums and hydride doners to carboxamides.

In the formal synthesis of (–)-lasubine II,[55] Aubé showed that the Grignard reagent was capable to react with the lactam **1.17a**. (Scheme 1-17) It was believed the presence of $CeCl_3$ was to prevent the competing elimination of the OTIPS group. Upon the treatment of acetic acid, the iminium intermediate was generated. Subsequent diastereoselective hydride reduction of the intermediate produced **1.17b** as a single diastereoisomer in good yield.



Scheme 1-17 Addition of a Grignard reagent to lactam **1.17a**.

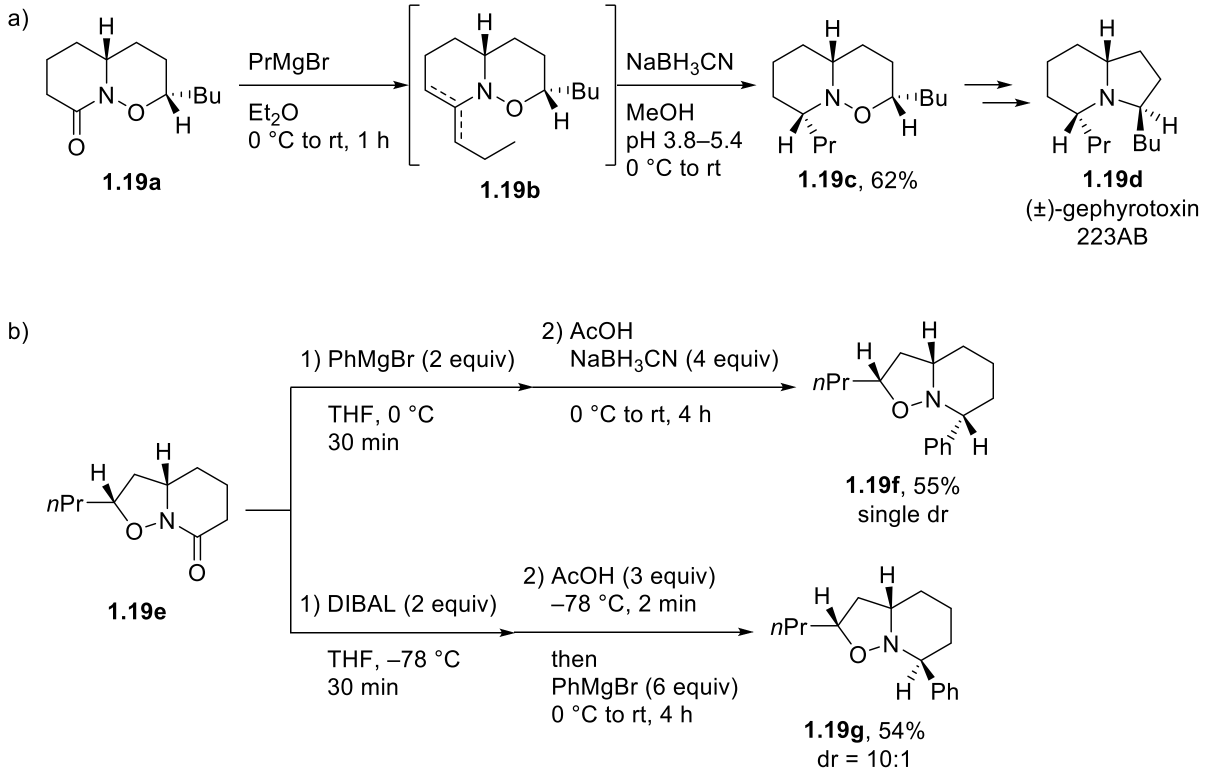
On the other hand, organocerium reagents were also reported for the nucleophilic attack of lactams. For instance, Shibasaki reported the synthesis of gephyrotoxin 209D (**1.18b**)[56] via a sequential lactam addition with *in-situ* generated alkylcerium reagent and $NaCNBH_3$ (Scheme 1-18). The advantage to use an organocerium reagent, which is considered less basic than the corresponding organolithium and Grignard reagent, was to minimize undesired enolate formation.



Scheme 1-18. Addition of an organocerium reagent to lactam **1.18a**.

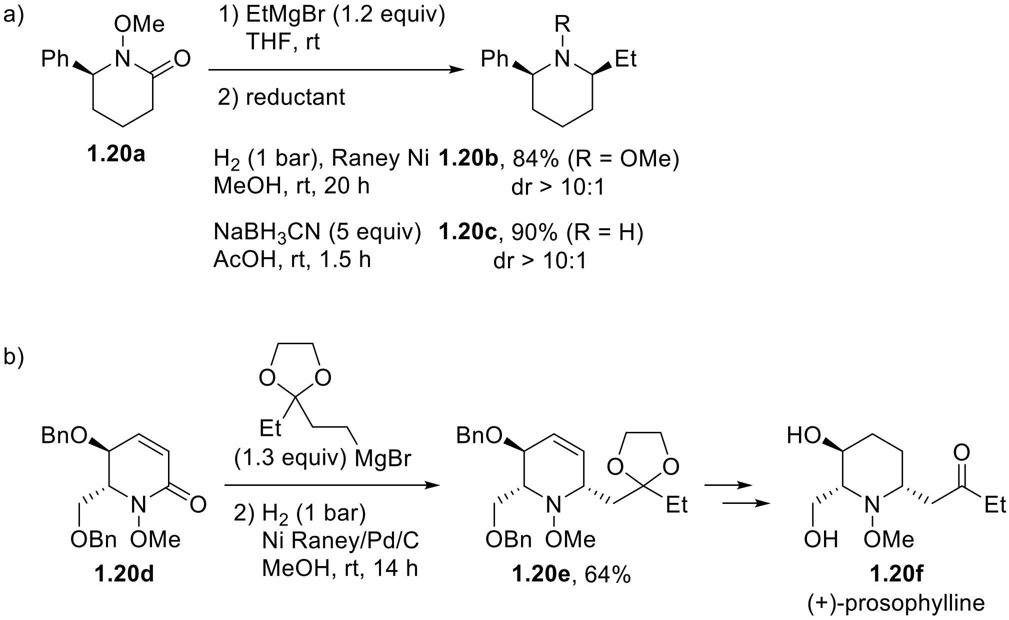
1.2.2. The Weinreb amides and their derivatives

Several research groups also reported the addition of carbanions to the Weinreb amides and their derivatives for the synthesis of amines. It was first realized by Kibayashi[57] in 1989 during their total synthesis towards (±)-gephyrotoxin 223AB (Scheme 1-19a).[58] The addition of *n*-PrMgBr to the bicyclic *N*-alkoxyaminde **1.19a** at ambient temperature led to an unstable enamine **1.19b**, which was further reduced by $NaCNBH_3$ to provide **1.19c** exclusively. Later in 2011, Vincent and Kouklovsky reported the sequential addition of organometallic reagents and $NaBH_3CN$ to *N*,*O*-bicyclic lactams (Scheme 1-19b).[59] The addition was diastereoselective, and 3a,7-*cis*-isoxazolidino[2,3-*a*]piperidines such as **1.19f** were provided in moderate yields. Interestingly, a stereodivergent synthesis was accomplished by switching the order of addition of the organometallic and hydride reagents. Thus, both diastereoisomers **1.19f** and **1.19g** were obtained by simple modification of the experimental procedures.



Scheme 1-19. Addition of carbanions to the Weinreb amides and their derivatives.

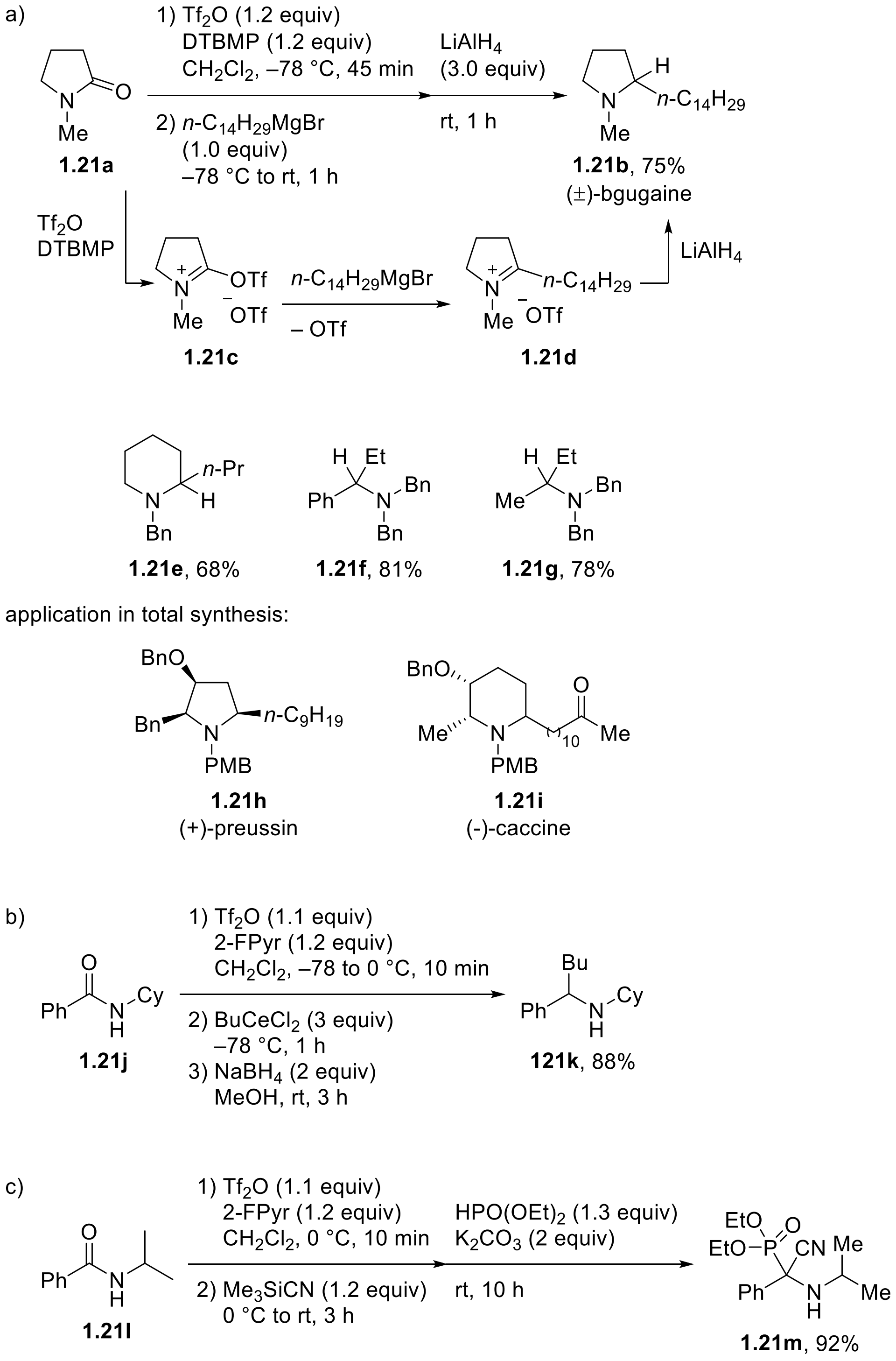
Helmchen systematically studied the addition of carbon nucleophiles to the *N*-alkoxy lactams in 2013 (Scheme 1-20).[60] A wide range of organolithium and the Grignard reagents were applicable as the first nucleophile, and the intermediate was further reduced in one pot by metal hydrides or Raney nickel in a diastereoselective manner. It should be noted that when Raney Ni was used, the *N*-alkoxyamines were further reduced to the corresponding amines as the final product. The synthetic utilities were illustrated in the total synthesis of indolizidine (–)-209D and (+)-prosophylline.



Scheme 1-20. Addition of carbanions to *N*-alkoxy lactams.

1.2.3. Via electrophilic activation of carboxamides

Huang reported that the electrophilically activated carboxamides allowed for the addition of Grignard reagents at cryogenic reaction conditions. As previously shown in Scheme 1-8a, a highly electrophilic iminium triflate intermediate **1.21c** was first generated in the presence of Tf_2O and DTBMP. The addition of Grignard reagent and the subsequent elimination of TfO^- gave **1.21d**. It was further reduced by $LiAlH_4$ to provide the α-branched amine **1.21b** (Scheme 1-21a).[61]



Scheme 1-21. Addition of carbanions to electrophilic activated amides.

This protocol was suitable for the functionalization of lactam (**1.21e**), aryl (**1.21g**), and aliphatic carboxamides (**1.21g**). Several natural products were also accomplished with this protocol (**1.21h–i**). The functionalization of more challenging secondary amides was also achieved by employing organocerium reagents (Scheme 1-21b).[62] Other than highly reactive organometallic reagents, the sequential additions of Me_3SiCN and diethylphosate to the activated amides were achieved to form α-amino-α-cyanophosphonates (Scheme 1-21c).[63]

1.3. Conclusion

Despite the lower reactivity, nucleophilic attack on the amide carbonyl group has been proven feasible, and this could be engaged as one of the most straightforward methods for the synthesis of amines from readily available and benchtop stable carboxamides. The *gem*-difunctionlization of the amide carbonyl allowed for the addition of varieties of organometallic and hydride reagents, providing α-branched or α-tertiary amines in simple operations. For non-activated carboxamides, electrophilic activation was generally required to enhance the reactivity towards nucleophilic attack, especially for the addition of carbanions. The objective of part A of this thesis is to investigate the possibility of the sequential addition of carbanions to non-activated carboxamides for the synthesis of α-tertiary amines.

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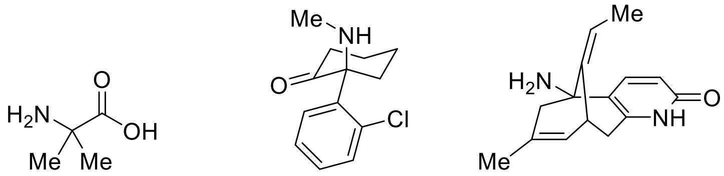
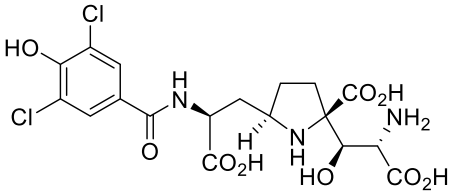
Chapter 2. Iterative addition of carbon nucleophiles to *N*,*N*-dialkyl carboxamides for the synthesis of α-tertiary amines

2.1. Introduction

α-Tertiary amines are widely existing in natural and bioactive molecules,[1] and this motif is identified as the key functional unit in medicinal chemistry program in the pharmaceutical industry.[2] For example, α-aminoisobutyric acid[3] is an unnatural amino acid that was a potent helix inducer in peptides. Ketamine,[4] an NMDA receptor antagonist, is used for anaesthesia and depression. Huperzine A,[5] a naturally occurring alkaloid in *firmoss Huperzia serrata*, is typically used to treat Alzheimer's disease. Kaitocephalin,[6] first isolated in 1997 from *Eupenicillium shearii*, exhibits potent glutamate receptor inhibitory activities (Scheme 2-1).



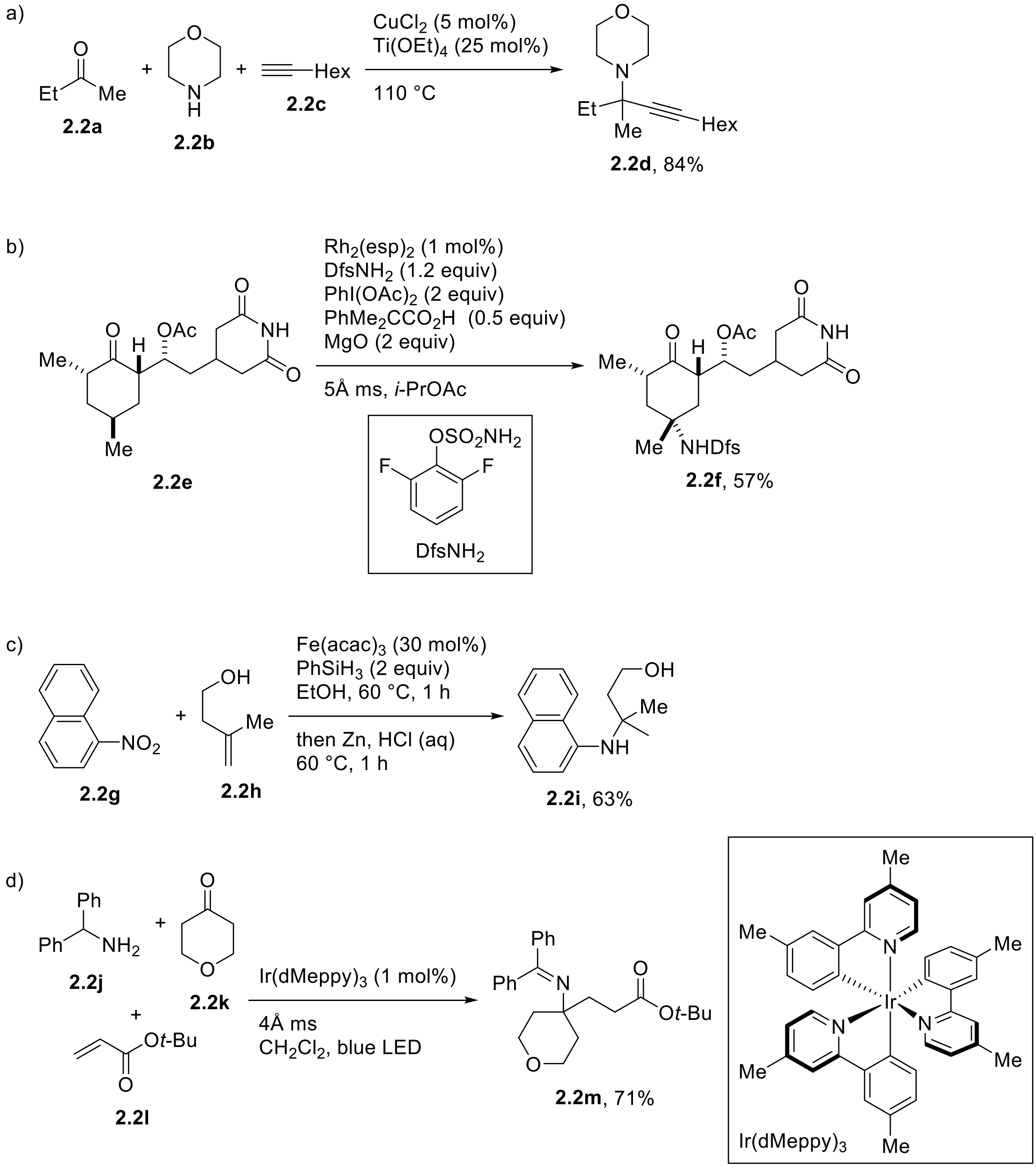
2.1a α-aminoisobutyric acid **2.1b** Ketamine **2.1c** Huperzine A



2.1d Kaitocephalin

Scheme 2-1. Natural and bioactive molecules containing an α-tertiary amine motif.

As such, the synthesis of α-tertiary amines has attracted considerable attention from the synthetic community for the past decades.[1] Although the sterically hindered nature of α-tertiary amines has rendered synthetic approaches more challenging, significant progress has recently been made.



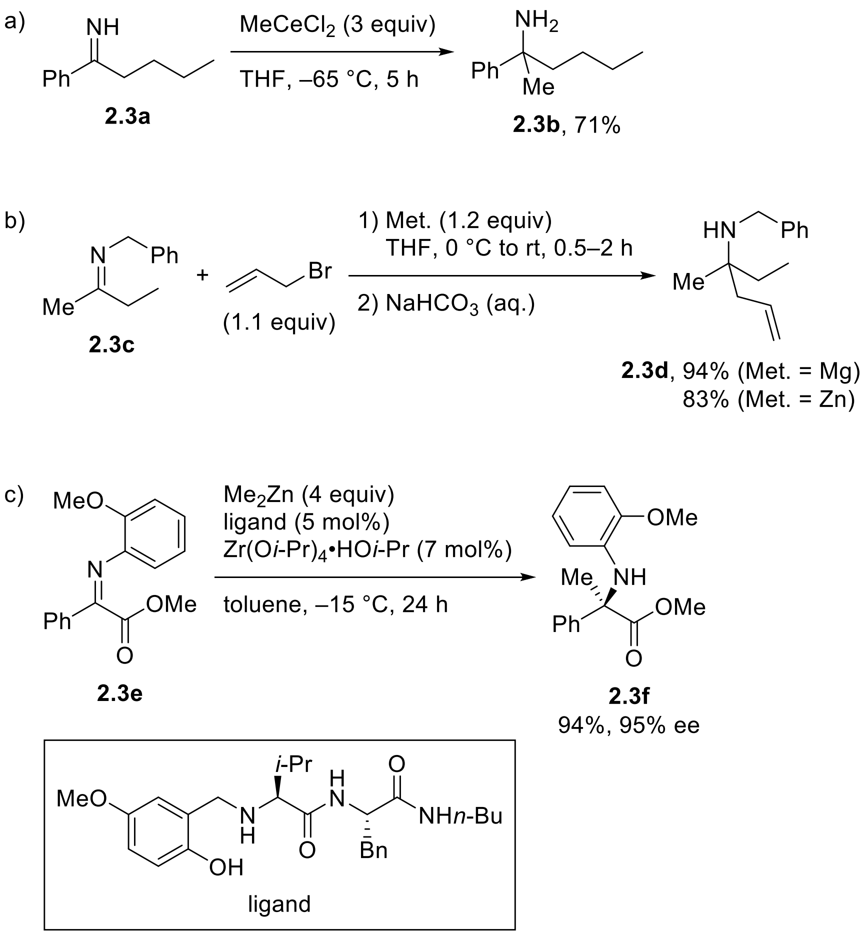
Scheme 2-2. Selected methods for the synthesis of α-tertiary amines.

For example, transition metal-catalyzed C-C bond formation to activated ketimines has been well-documented.[7] Larsen reported the copper-catalyzed multi-component coupling of amines, ketones, and alkynes (Scheme 2-2a).[8] C-H amination reactions under rhodium[9] (Scheme 2-2b) or copper[10] catalysis were also feasible. Other methods, such as hydroamination,[11] rearrangement,[12] and C-H functionalization[13] (Scheme 2-2c) were also reported. More recently, the photo-induced assemblies of α-tertiary amines have been separately reported by Gaunt[14] (Scheme 2-2d) and Cresswell.[15]

Regardless of the above strategies, leveraging of 1,2-addition of organometallic reagents to imines or iminium species offers a direct approach to the synthesis of α-tertiary amines. The following section will discuss the developments of α-tertiary amine synthesis using organometallic reagents.

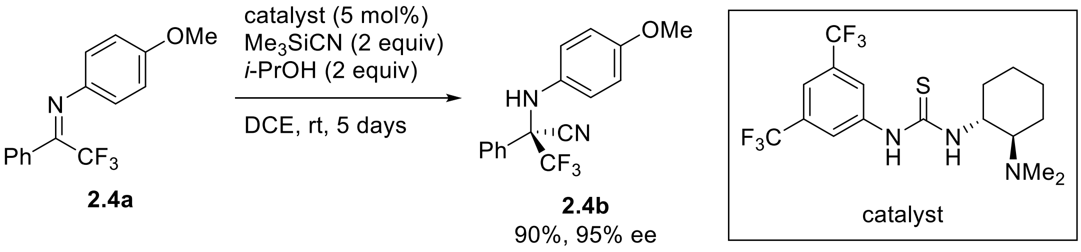
2.1.1. Synthesis of α-tertiary amines by double nucleophilic additions of carbanions

One of the most common methods to access α-tertiary amines is the addition of organometallic reagents to ketimines.[16] The challenge is the low reactivity of the imine carbons due to their poor electrophilicity, and thus, the reactions are often accomplished with undesirable side reactions, such as α-deprotonation or enolization due to the basicity of the organometallic reagent itself.[17] To overcome this problem, the use of less basic organometallic reagents such as organocopper[18] and organocerium reagents[19] were preferred. For example, Ciganek reported the addition of organocerium reagents to *N*-unsubstituted ketimine to give α-tertiary amines in good yields (Scheme 2-3a).[20] On the other hand, allylic metals, a more reactive organometallic reagent, were also used for the generation of α-tertiary amines (Scheme 2-3b).[21] Allyl organometallic reagents are considered more reactive than the non-stabilized ones as it is suggested that the resonance stabilization of the allyl anion enhanced the reactivity.[22] Another method is to utilize activated imines, either by using electron-deficient imines or adding *N*-coordinating Lewis acid to enhance the electrophilicity of the imine carbon (Scheme 2-3c).[7,23]



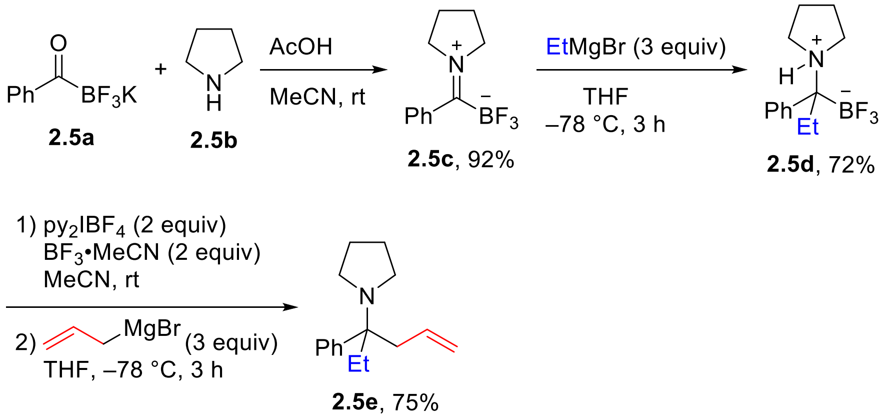
Scheme 2-3. Addition of organometallic reagents to ketimines.

Alternatively, the Strecker reaction has been well-practiced to synthesize α-amino nitriles.[24] This is a practical route to give the corresponding α-amino acids upon the hydrolysis of the cyano group. A recent example by Enders demonstrated an enantioselective Strecker reaction to generate α-trifluoromethyl-substituted α-amino nitriles in the presence of a chiral thiourea organocatalyst (Scheme 2-4).[25]



Scheme 2-4. Enantioselective Strecker reaction.

In 2008, Bode has shown the cross-coupling reaction of α-aminoalkyltrifluoroborates and Grignard reagents to form *N*,*N*-substituted α-tertiary amines (Scheme 2-5).[26] The reaction proceeds by the geminal difunctionalization on the carbonyl oxygen via i) conversion of acyltrifluoroborates to acyltrifluoroborate-iminiums such as **2.5c** by treatment with *N*,*N*-dialkylamines; ii) addition of the first Grignard reagents to form α-aminoalkyltrifluoroborates like **2.5d**; iii) oxidation with bis(pyridine)iodonium(I) tetrafluoroborate (py_2IBF_4) to iminium ions followed by addition of the second Grignard reagents.

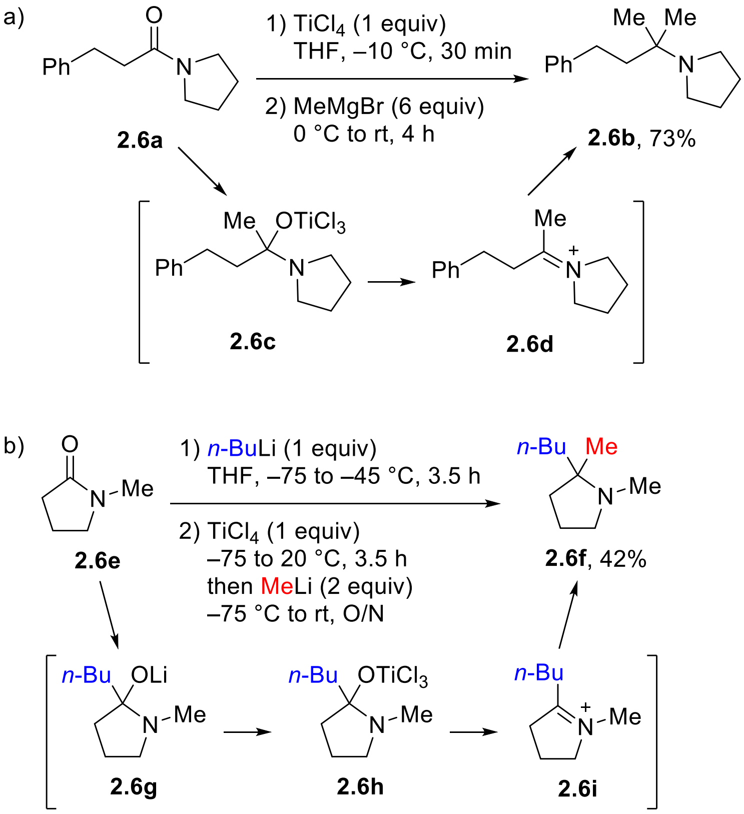


Scheme 2-5. Cross-coupling of α-aminoalkyltrifluoroborates and Grignard reagents.

While significant progress has been made, new methods that enable facile synthesis of α-tertiary amines have remained in high demand. The *gem*-difunctionalization of carboxamides or nitriles has been considered a straightforward approach.[27] One of the appealing features is the use of readily available carboxamides and nitriles, and the substitutions at the α-positions can be modified by using different organometallic reagents.

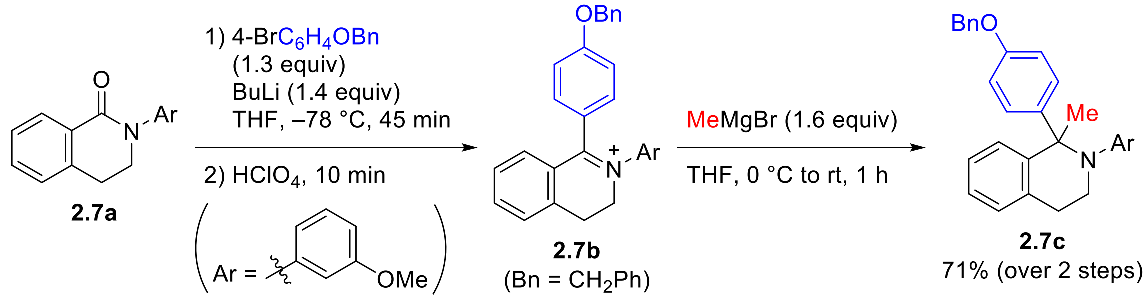
2.1.1.1. Geminal difunctionalization of non-activated amides

As an early example, Denton reported the dimethylation of carboxamides with MeMgBr in the presence of a stoichiometric amount of oxophilic Lewis acids such as $TiCl_4$ and $ZrCl_4$ (Scheme 2-6a).[28] The use of oxophilic Lewis acids is believed to promote the formation of the iminium intermediate such as **2.6d**, as observed by ^{1}H NMR studies. However, only demethylation was examined in this report. Seebach later disclosed a protocol that allows for the installation of two different nucleophiles through geminal difuncitonalization of the amide carbonyl group. The key to enable this advance is the treatment of anionic hemiaminal intermediate with $TiCl_4$ upon addition of the first organolithium reagent to carboxamides (Scheme 2-6b).[27a,c] The resulting titanium α-aminoalkoxide **2.6h** can serve as a precursor of the iminium cation, and thus addition of the second nucleophile occurs smoothly to give the amine **2.6f**.



Scheme 2-6. Double addition of organometallic reagents to amides promoted by Lewis acids.

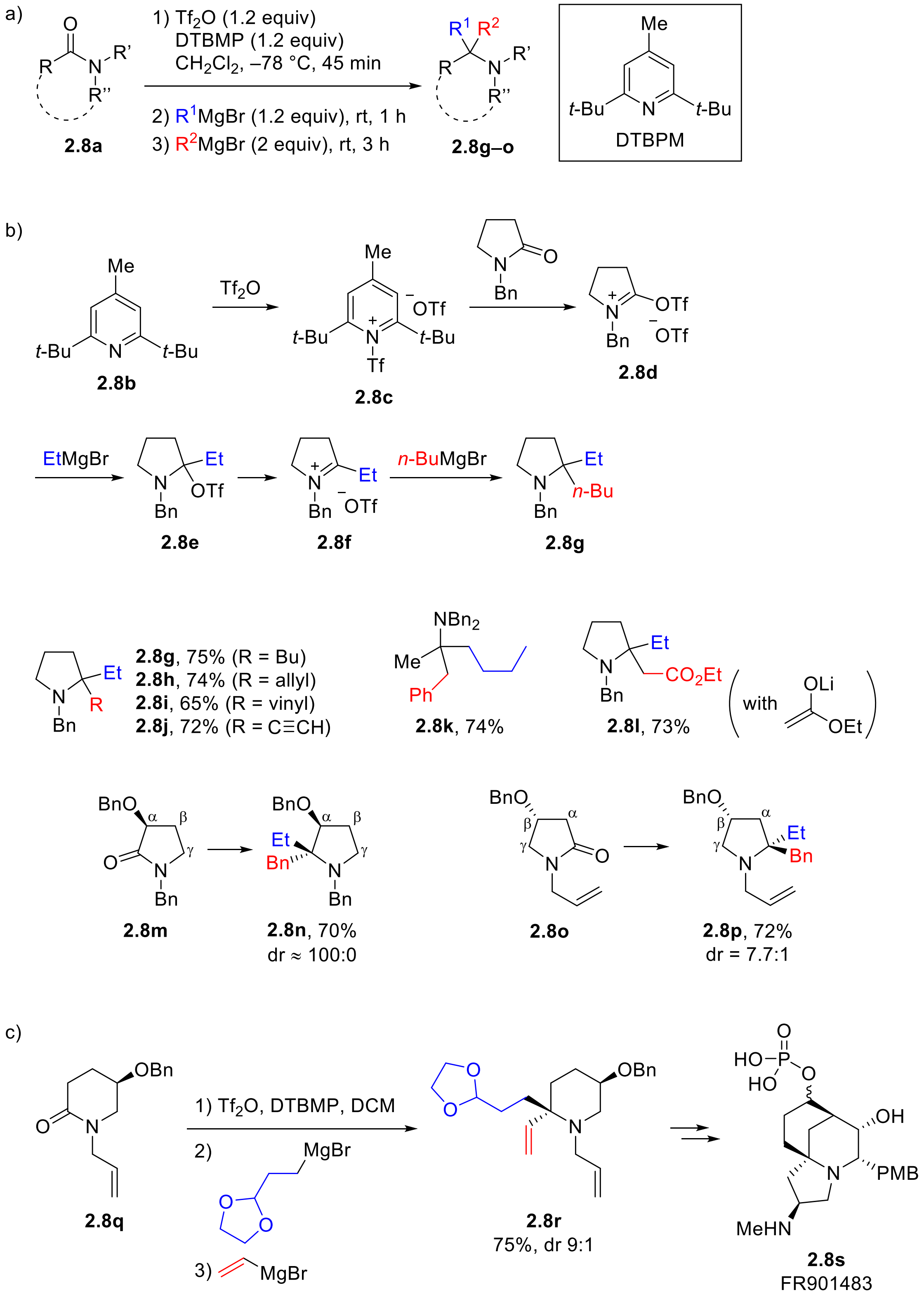
During the synthesis of estrogen receptor modulators, Renaud reported the α,α-difunctionalization of *N*-aryl lactams to provide the corresponding α-tertiary cyclic amines (Scheme 2-7). Upon the first addition of aryllithium, the mixture was treated with $HClO_4$ to generate the iminium intermediate, ensuring the second addition of MeMgBr provided the product.[29]



Scheme 2-7. Geminal difunctionalization of *N*-aryl lactams.

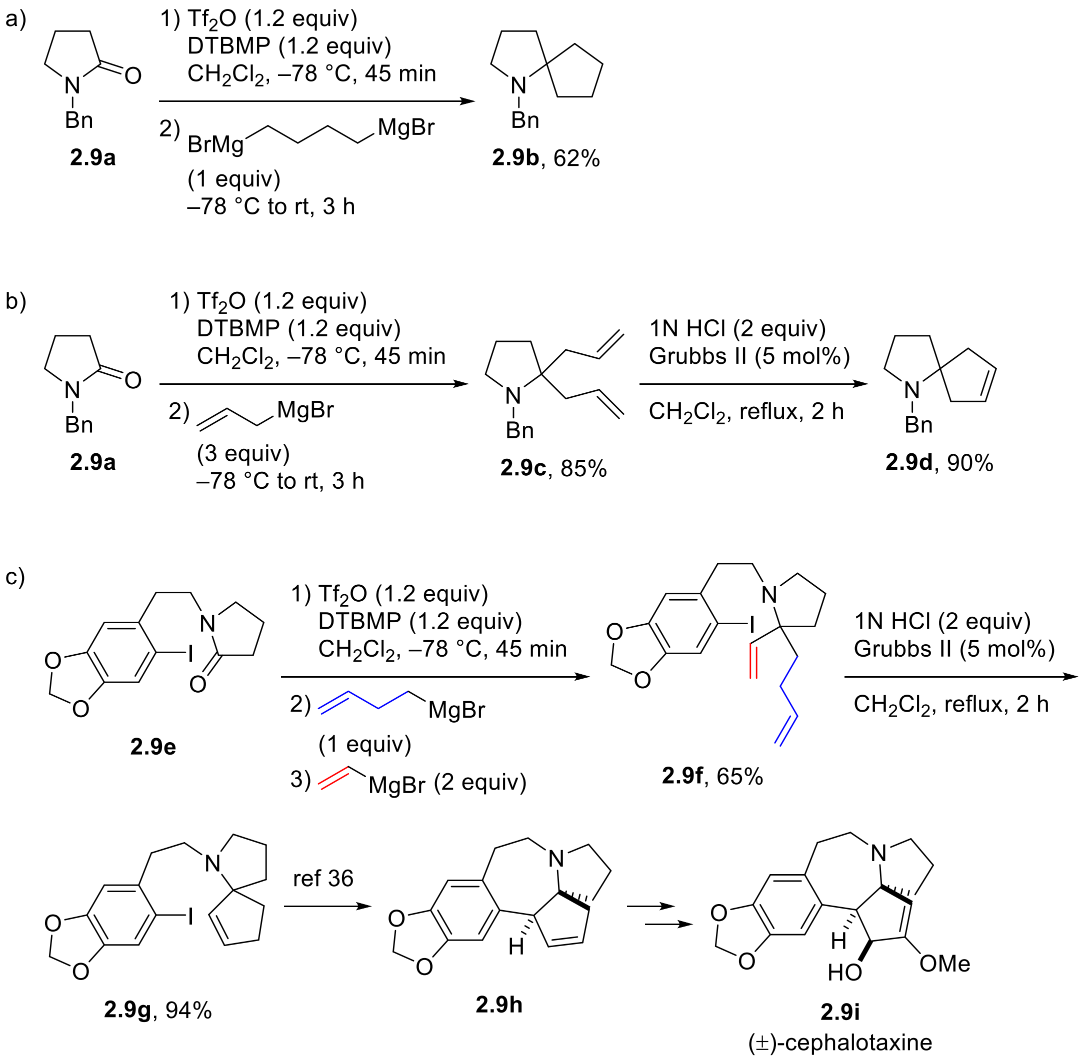
2.1.1.2. Geminal difunctionalization of carboxamides via electrophilic activation

As mentioned in Chapter 1, carboxamides can be activated with a strong electrophilic agent such as triflic anhydride in the presence of a base, ensuring the subsequent addition of organometallic reagents.[27,30] In 2010, Huang reported a *gem*-difunctionalization of carboxamides with Grignard and organolithium reagents through lactam/amide activation (Scheme 2-8a).[31] The lactam **2.8a,** for example, is first treated with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to generate a highly electrophilic iminium triflate intermediate **2.8d** (Scheme 2-8b). The intermediate reacts with the first organometallic reagent to give the *N*,*O*-acetal **2.8e**. Sequential elimination of a triflate anion generates the iminium intermediate **2.8f**, which is trapped with the second organometallic reagent to give the α-tertiary cyclic amine **2.8g**. Various organometallic reagents are applicable. The reaction is also compatible with functionalized Grignard reagents developed by Knochel[32] and lithium enolates. It should be noted that a single diastereoisomer (**2.8n**) is obtained when **2.8m** is used. The second carbanion is installed at the *trans*-position to the α-substituent, which agrees with the proposed mechanism. On the other hand, the lactams bearing a remote stereocenter, such as **2.8o** results in lower diastereoselectivity. Non-cyclic carboxamides also worked well, and the corresponding amines were obtained in high yields. The *gem*-difunctionalization was later applied to a formal enantioselective total synthesis of FR901483[33] (Scheme 2-8c) and the preparation of spirocyclic azetidines.[34]



Scheme 2-8. *Gem*-difunctionalization of carboxamides through electrophilic activation of the amide carbonyl group.

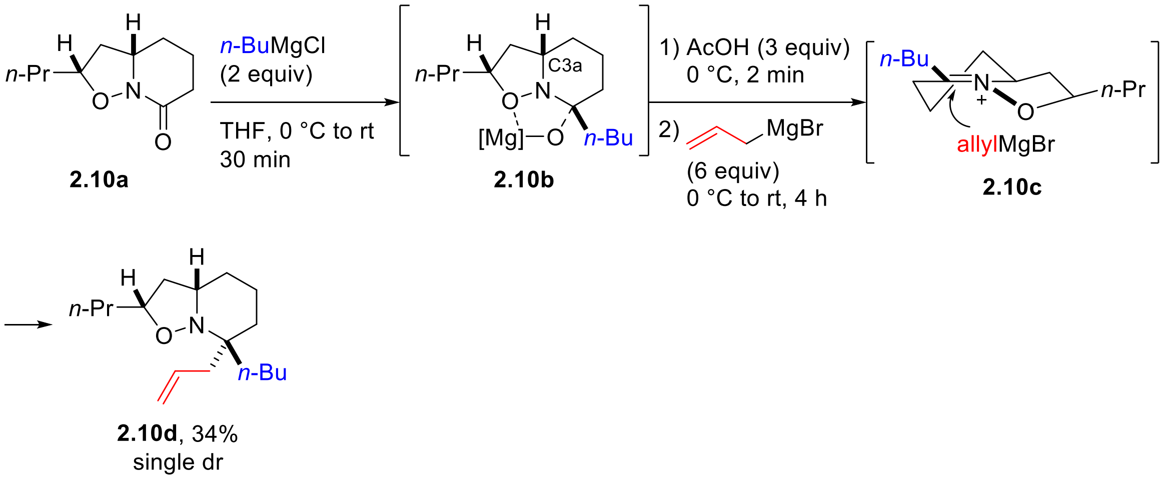
In a recent report, the same group reported the synthesis of 1-azaspirocycles with bis-Grignard reagent (Scheme 2-9a).[35] Alternatively, it can be accessed by a two-step protocol (Scheme 2-9b). Two alkyl groups with terminal alkene moiety were first installed via the *gem*-difunctionalization of lactams, and subsequent ring closure metathesis in the presence of a Grubbs II catalyst furnished the spiro compound. This strategy was applied in the synthesis of **2.9g**,[36] which is a key intermediate for the synthesis of cephalotaxine **2.9i** (Scheme 2-9c).[37]



Scheme 2-9. Synthesis of spirocyclic compounds.

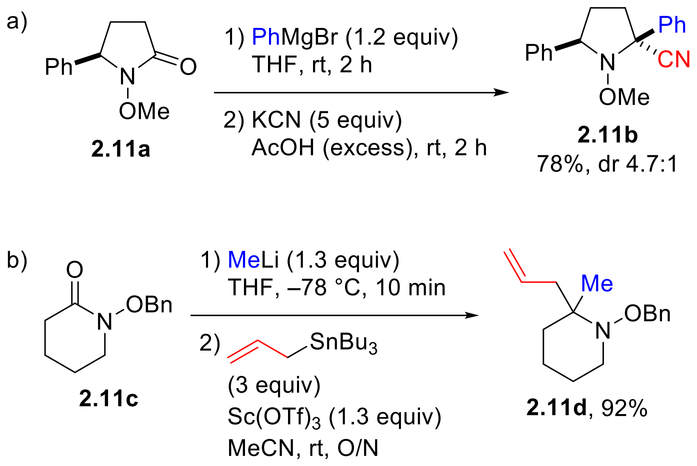
2.1.1.3. Geminal difunctionalization of the *N*-alkoxy carboxamides

In 2011, Kouklovsky reported the first example of the sequential addition of nucleophiles to *N*-alkoxybicyclolactams (Scheme 2-10).[38] The reaction was highly diastereoselective, providing a single diastereoisomer. Upon the addition of the first nucleophile (Grignard reagents or *n*-BuLi), the resultant relatively stable chelated intermediate is treated with AcOH to give the iminium intermediate, which is subsequently attacked by the second nucleophile (Grignard reagents or KCN) to give the final products. The diasterocontrol is governed by the presence of the cyclic isoxazolidine, which would force the side chain at position C3a of the alkoxypiperidinium unit in a pseudoequatorial position,[39] ensuring the nucleophilic attack of the second nucleophile[40] at the axial position.



Scheme 2-10. Kouklovsky's diastereoselective addition of nucleophiles to *N*-alkoxylactams.

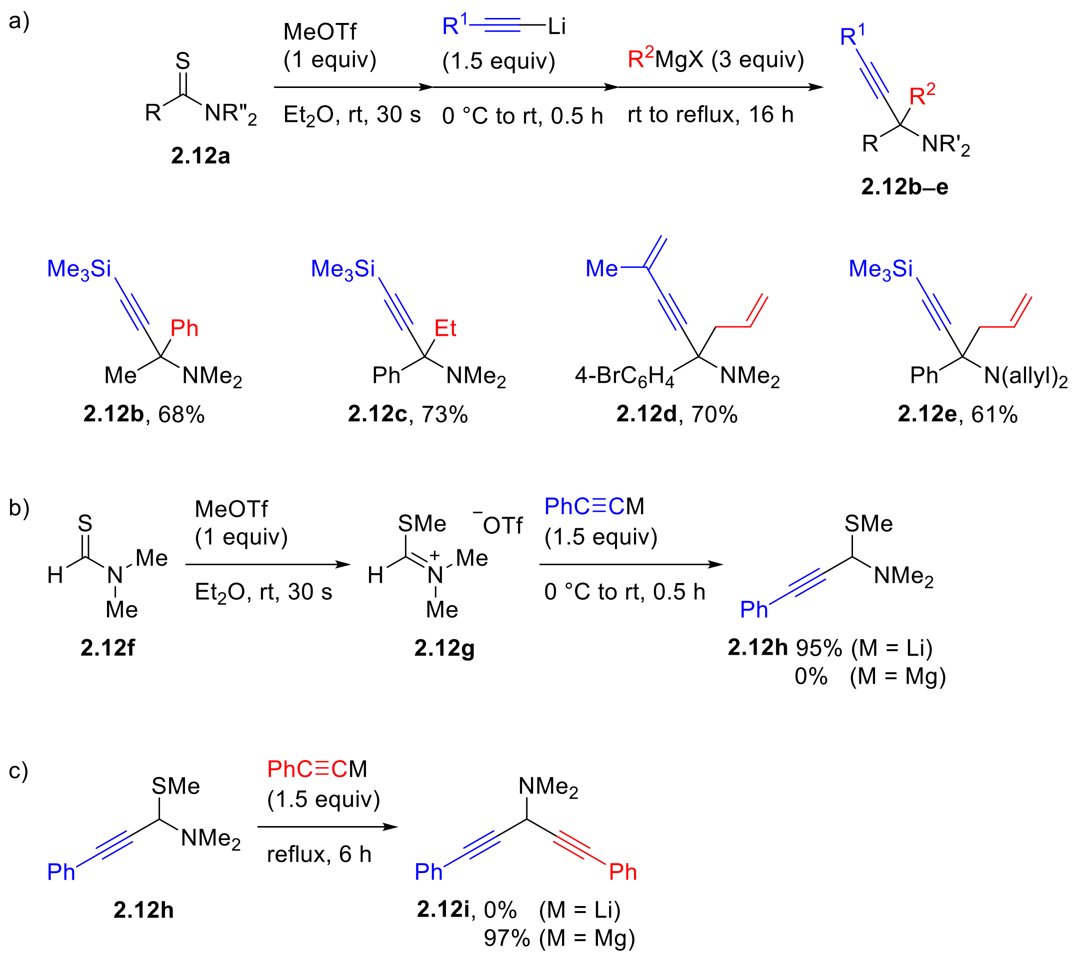
The utility of *N*-alkoxylactams was further extended to the monocyclic system, as later reported by Helmchen (Scheme 2-11a).[41] For the choice of the second nucleophile, Chida and Sato also reported allylation as the second step using allyltributylstannane (Scheme 2-11b).[42] A stoichiometric amount of $Sc(OTf)_3$ as a Lewis acid was necessary to facilitate the formation of the iminium intermediate.



Scheme 2-11. Geminal difunctionalization of *N*-alkoxylactams.

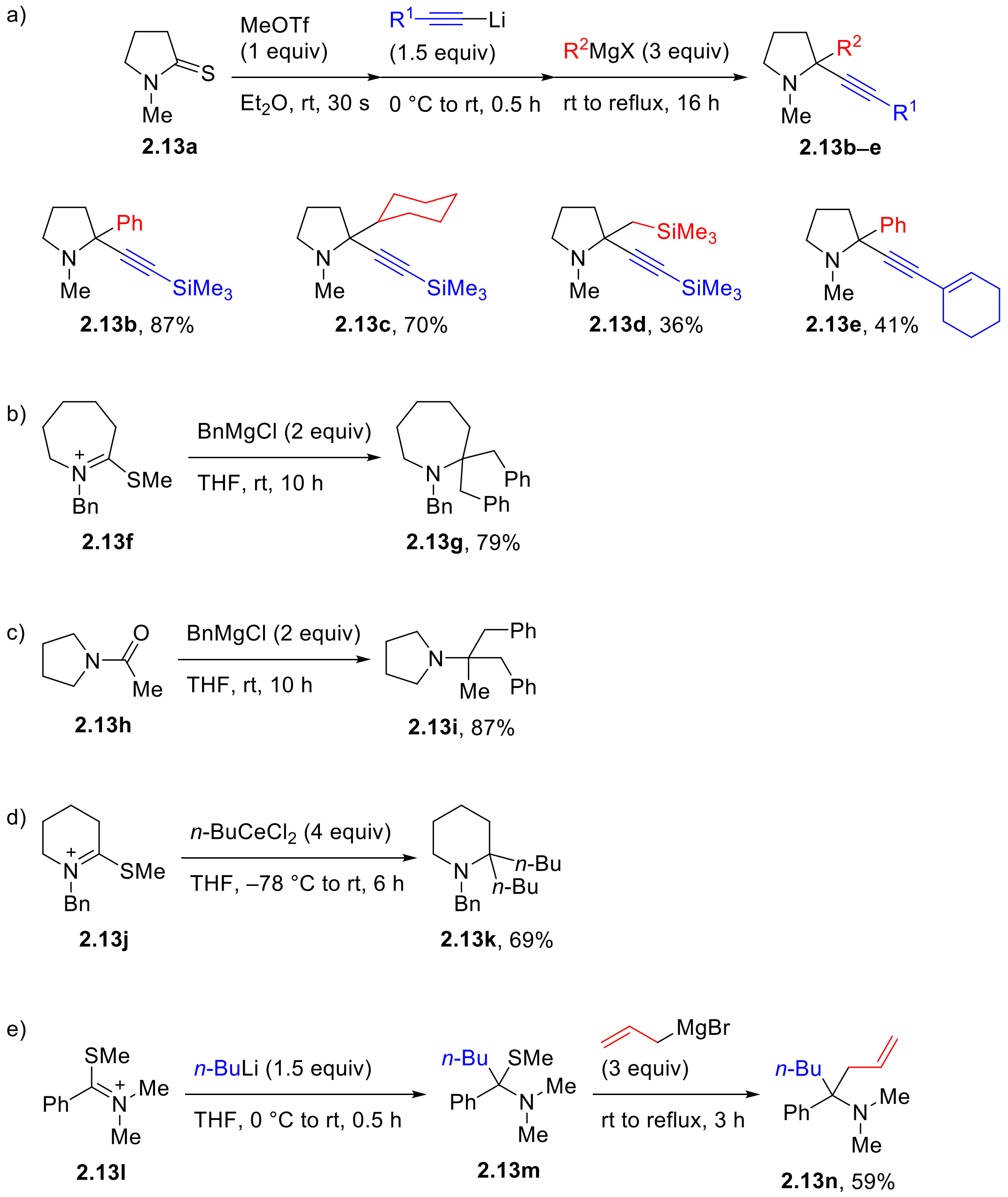
2.1.1.4. Geminal difunctionalization of thioamides

Thioamides are a class of compounds where an oxygen atom in carboxamides is replaced by a sulfur atom, and they show lower reactivity than the corresponding carboxamide.[43] Like carboxamides, thioamides can be attacked by organometallic reagents, but the pre-conversion to the activated electrophilic thioiminium salts via methylation of thioamides using methyl iodide (MeI) or methyl triflate (MeOTf) was required for most of the cases.[44] For example, Murai reported the sequential addition of lithium acetylides and Grignard reagents to in-situ generated thioiminium salts for the synthesis of tertiary propargylic amines.[45] Upon the generation of thioiminium salts via the treatment with MeOTf, an alkynyllithium is added, thus providing the *S*,*N*-ketal, which is subsequently attacked by Grignard reagents to form tertiary propargylic amines. As shown in Scheme 2-12, the thioamide only reacted with an organolithium reagent to give **2.12h**, while the reactions with Grignard reagents were unsuccessful. However, a reversed reactivity in the second step was observed. Only the use of Grignard allowed for producing the α-tertiary amines. This unique reactivity difference was used to realize a facile one-pot operation by mixing organolithium and Grignard reagents simultaneously, which afforded the crossover products **2.12b**–**e** exclusively.



Scheme 2-12. Murai's synthesis of tertiary propargylic amines from thioamides.

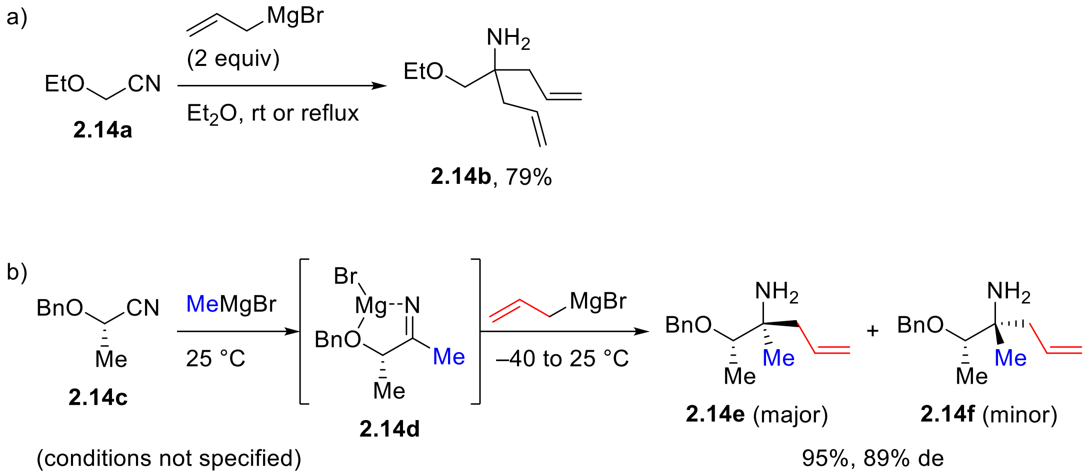
The same group later reported the conversion of thiolactams to α-tertiary cyclic amines (Scheme 2-13a).[46] Grignard and organocerium reagents could be utilized as the first nucleophile, while this protocol only allowed for the double addition of the same organometallic reagent (Scheme 2-13b–d).[47] Alternatively, the installation of two different nucleophiles was realized by a two-step reaction with organolithium reagent as the first nucleophile and Grignard reagent as the second nucleophile (Scheme 2-13e).[44]



Scheme 2-13. Geminal difunctionalization of thioamides.

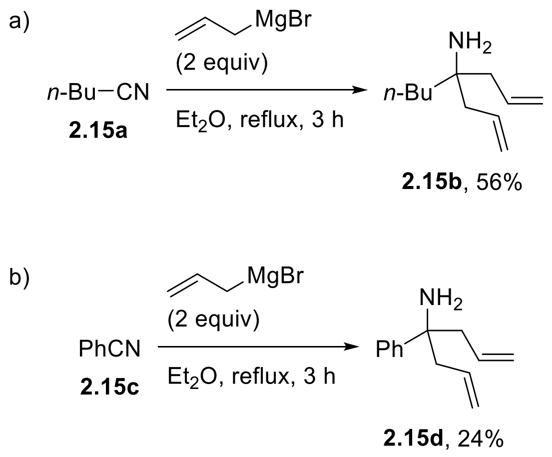
2.1.2. Geminal difunctionalization of nitriles

The geminal difunctionalization of nitriles provides an alternative method to access α-tertiary primary amines.[48] Allen and Henze first reported the synthesis of α-tertiary primary amine from nitrile in 1939, where two equivalents of allylmagnesium bromide were attacked ethoxyacetonitrile to provide **2.14b** (Scheme 2-14a).[49] This second addition was restricted to allylmagnesium bromide, since the use of other organolithium, Grignard, or even substituted allyl Grignard reagents such as methallylmagnesium bromide as the second nucleophile gave the corresponding ketone exclusively.[50] It was believed that the higher reactivity of allylmagnesium bromide facilitated the second addition.[51] The reaction was highly diastereoselective, as reported by Charette in 1998, where the successive addition of methyl and allyl Grignard reagents to a chiral cyanohydrin was demonstrated (Scheme 2-14b).[52] The authors proposed that the high selectivity was due to a chelation-controlled addition.



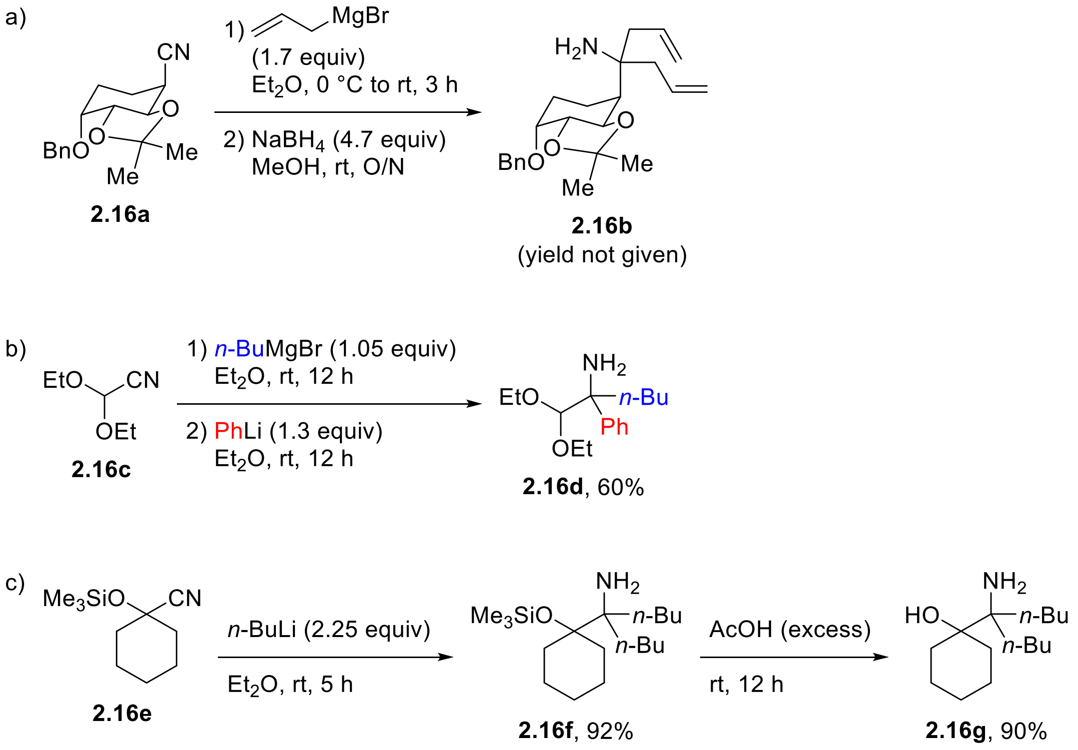
Scheme 2-14. Early examples of *gem*-difunctionalization of nitriles with the Grignard reagents.

On the other hand, the double addition to simple nitriles was also reported, although the yields are lower in general (Scheme 2-15). For instance, Allen reported the diallylation of valeronitrile (**2.15a**) to give amine **2.15b** in 56% yield.[53] It was also reported that the diallylation of benzonitrile (**2.15c**) also led to a low yield of amine **2.15d**.[54]



Scheme 2-15. Double addition of allylmagnesium bromide to nitriles.

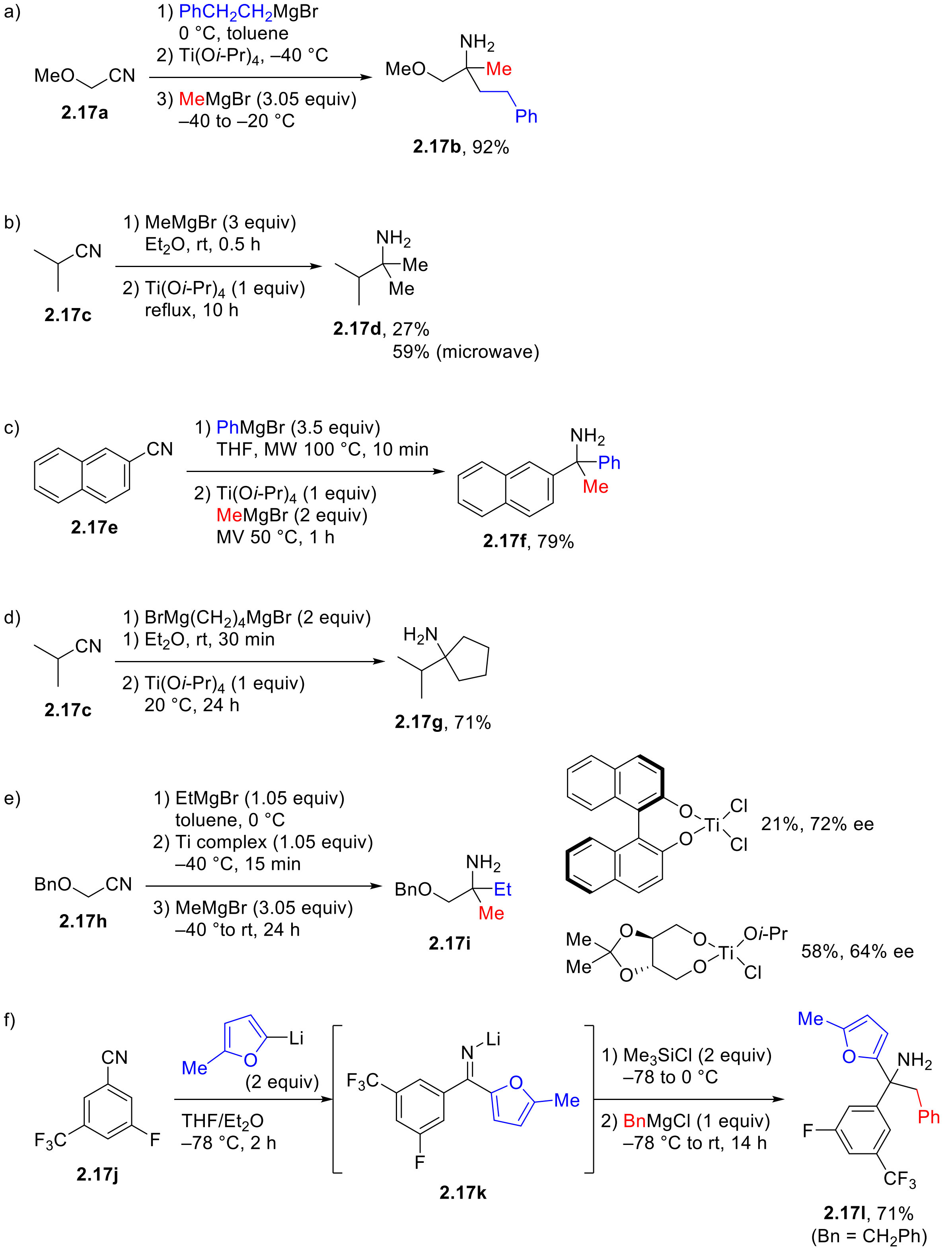
Several research groups have also reported the use of α- and β-oxygenated nitriles for the synthesis of α-tertiary amines (Scheme 2-16). For example, Withers demonstrated the diallylation of **2.16a**, derived from L-lyxose with allylmagnesium bromide (Scheme 2-16a).[55] Chastrette reported the sequential addition of two different organometallic reagents to α,α-diethoxynitrile **2.16c** providing α-aminoacetal **2.16d** in moderate yield (Scheme 2-16b).[56] Amouroux reported the facile synthesis of β-aminoalcohols via double addition of organolithium reagents to *O*-silylated cyanohydrins (Scheme 2-16c). The generated *O*-silylated β-aminoalcohols were desilylated in the presence of acetic acid to give the corresponding β-aminoalcohols.[57]



Scheme 2-16. Double addition of organometallic reagents to functionalized nitriles.

For the above examples, specialized nitriles were used, and/or the types of nucleophiles were limited. The addition of Ti(O*i*-Pr)4 was found to enhance the reactivity of the imine intermediate, ensuring the installation of a second nucleophile under milder reaction conditions (Scheme 2-17). Charette has shown that Grignard reagents other than allylmagnesium bromides, such as methyl, ethyl, or phenylmagnesium bromide, are able to act as the second nucleophile when Ti(O*i*-Pr)4 is added upon the addition of the first Grignard reagent (Scheme 2-17a).[52] Since the seminal report by Charette, the Ti-promoted reactions have been reported by several groups. For instance, the double addition of less reactive nitriles, such as isobutyronitrile was facilitated by Ti(O*i*-Pr)4. The dimethylation with excess MeMgBr was conducted at elevated temperature in the presence of 1 equivalent of Ti(O*i*-Pr)4, providing the amine in 27% yield (Scheme 2-17b). The addition of two different organometallic reagents was also applicable, although the yields were generally low. Nevertheless, an improved method by

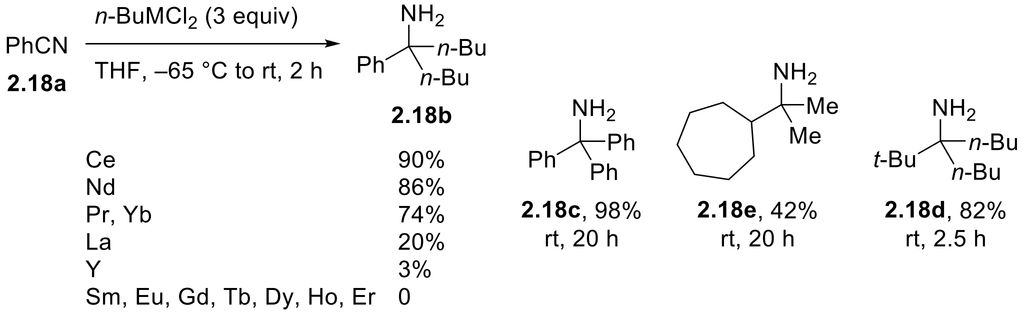
Gregg showed that microwave activated *gem*-difunctionalization gave better yields with more general substrate scope (Scheme 2-17c).[58]



Scheme 2-17. Ti-promoted addition of organometallic reagents to nitriles.

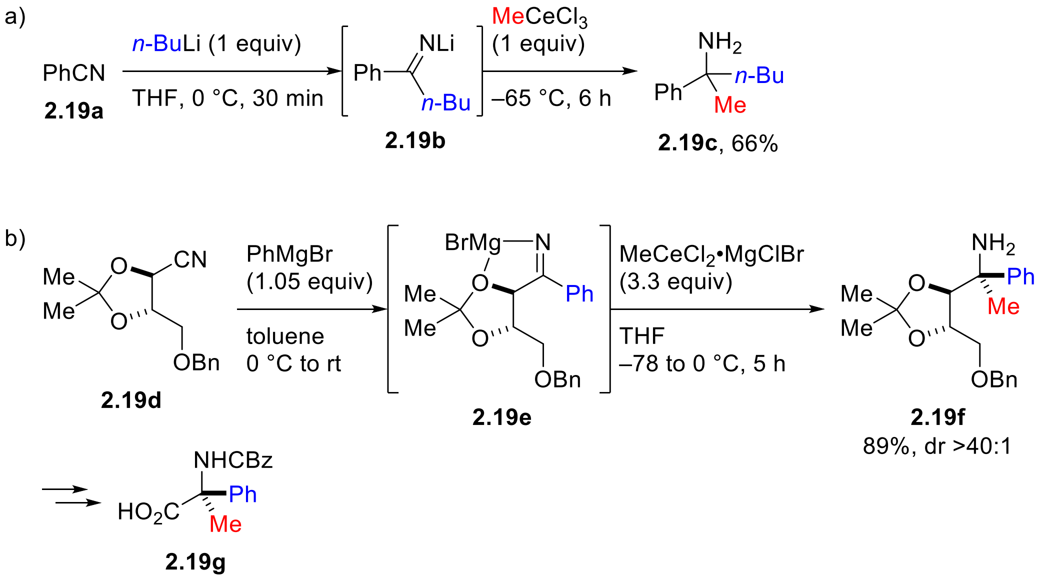
The Ti-promoted reaction was also applied to the synthesis of cyclopentylamines using di-Grignard reagents, providing the 1-substituted cyclopentylamines in good yields (Scheme 2-17d).[59] The asymmetric variant was also reported. For example, Charette reported that the employment of a chiral titanium complex, Ti-binol or Ti-TADDOL, led to the enantioselective synthesis of α-tertiary amines in moderate yield and 72% ee or 64% ee, respectively (Scheme 2-17e),[60] while a stoichiometric amount of Ti complex was required. Alternatively, the use of Me_3SiCl was also found to enhance the reactivity of the imine intermediate. For example, Kamau has shown a facile synthesis of α-tertiary amines through the in-situ generation of *N*-(trimethylsilyl)imine intermediate (Scheme 2-17f).[61] But only aromatic and heteroaromatic nitriles were applicable in this protocol.

The double addition of organocerium reagents to nitriles was also reported for the synthesis of α-tertiary amines. Organocerium reagents were nucleophilic but less basic compared to the analogous organolithium and Grignard reagents. The superior reactivity of organocerium reagents among other lanthanide organometallic reagents has been demonstrated by Ciganek, in which the use of organocerium reagent gave the best yield of amine **2.18b** in the double addition of benzonitrile (Scheme 2-18).[20] This protocol allowed the double addition of both aromatic and aliphatic nitriles, although lower yields were obtained for the latter.



Scheme 2-18. Double addition of nitriles using lanthanide organometallic reagents.

The sequential addition of *n*-BuLi and $MeCeCl_2$ to benzonitrile also gave the corresponding α-tertiary amines (Scheme 2-19a).[20] A diastereoselective double addition of tartaric acid-derived nitrile was reported by Charlette (Scheme 2-19b).[62] The diastereoselective addition of the second organocerium reagent was dominated by the chelation control. The products were readily converted to the corresponding α,α-disubstituted amino acids in high yields.[63]



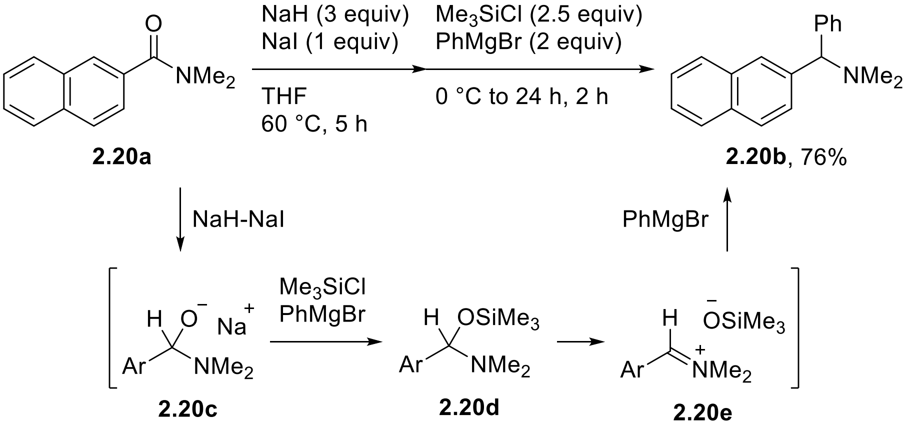
Scheme 2-19. Double addition of nitriles using organocerium reagents.

The use of other nucleophiles, such as allylsamarium,[64] allylindium,[65] and allylborane reagents[66] have also been reported, although only diallylation was demonstrated in these examples.

In summary, the double addition of organometallic reagents to carboxamides and nitriles is one of the most direct approaches to the synthesis of α-tertiary amines. As for the transformation of carboxamides, the pre-conversion of carboxamides to more reactive intermediates is generally required. The functionalization of nitriles mostly has relied on specialized substrates and organometallic reagents. Nonetheless, the synthesis of α-tertiary amines via the iterative installation of two different carbon substituents to carboxamides without pre-functionalization remains an unmet challenge.

2.2. Working hypothesis

The author's group recently reported the synthesis of α-branched tertiary amines via reductive functionalization of carboxamides and lactams (Scheme 2-20).[67] The reaction is initiated by the NaH-NaI mediated controlled reduction of carboxamides, providing a stable anionic carbinol amine intermediate, which is further treated with Me_3SiCl and nucleophiles to give α-branched tertiary amines.



Scheme 2-20. Reductive functionalization of amide with the NaH-NaI composite.

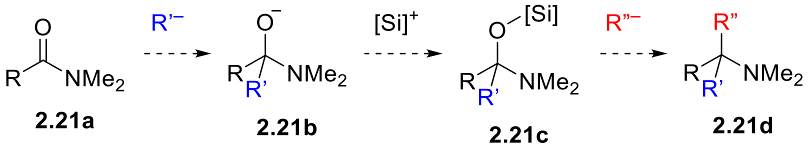
Stimulated by these results, the author became interested in the iterative addition of carbon nucleophiles of carboxamides to provide valuable α-tertiary amines (Scheme 2-21). The challenges for this proposed process are:

(1) Proper choice of the first carbon nucleophiles for the smooth formation of the anionic hemiaminal intermediates with prevention of their collapse before the engagement of the second nucleophiles.

(2) Efficient O-silylation of sterically hindered anionic hemiaminal intermediates.

(3) Proper selection of the second nucleophiles to ensure the addition of the hindered iminium intermediate.

The detailed results and discussion are described below.

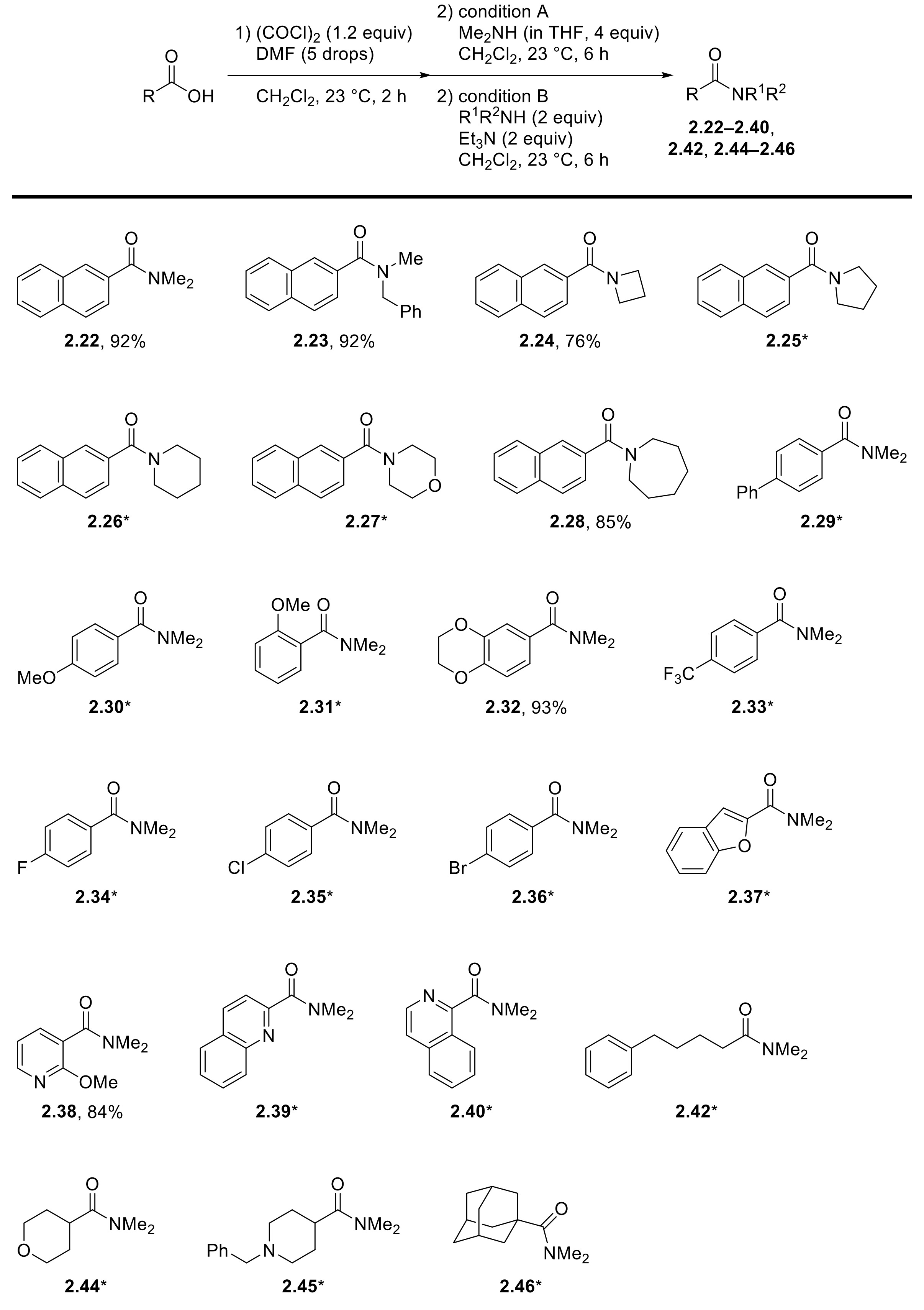


Scheme 2-21. Research proposal.

2.3. Results and discussion

2.3.1. Preparation of starting materials

Carboxamides **2.22–2.40**, **2.42,** and **2.44–2.46** were synthesized from the corresponding carboxylic acids. First, they were treated with oxalyl chloride in the presence of a catalytic amount of DMF in dichloromethane at 23 °C for 2 hours. The solvent was then evaporated, and the resultant acyl chlorides were further treated with the corresponding secondary amines in the presence of triethylamine in dichloromethane (Scheme 2-22).[67–71]



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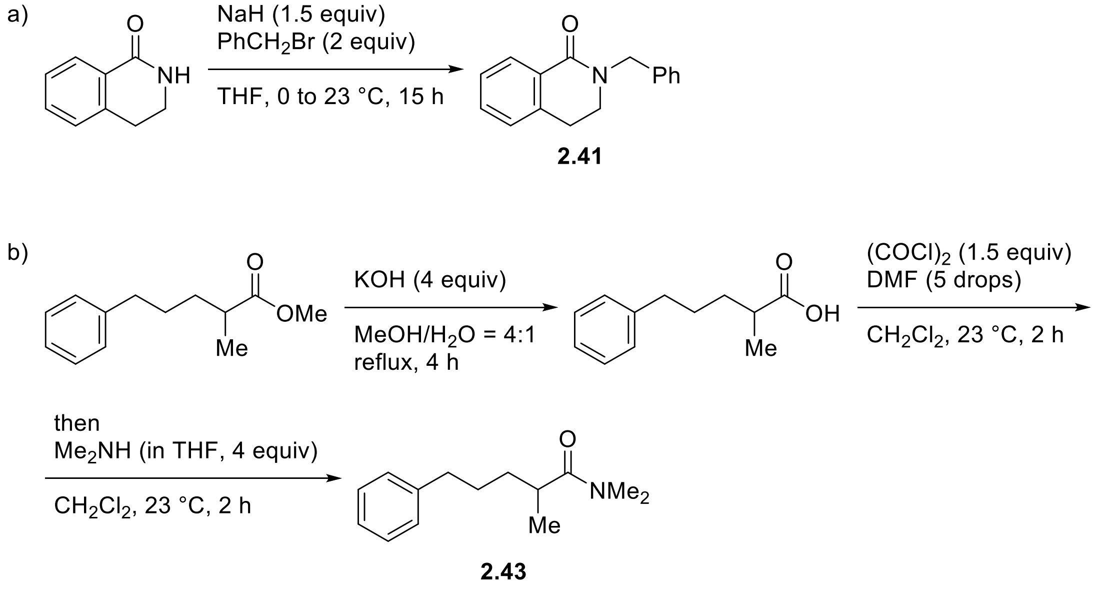
*Known carboxamides.

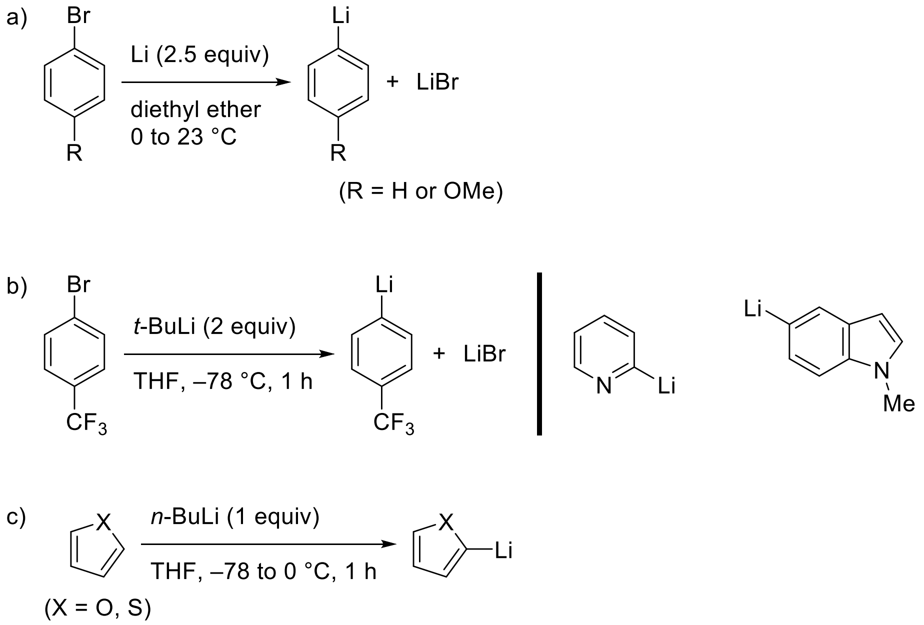
Scheme 2-22. Preparation of carboxamides **2.22–2.40**, **2.42**, and **2.44–2.46**.

Lactam **2.41** was prepared by treating 3,4-dihydroisoquinolin-1(2*H*)-one with sodium hydride and benzyl bromide in THF according to the reported procedure (Scheme 2-23a).[67] Carboxamide **2.43** was prepared from 2-methyl-5-phenylpentanoate[72] via its alkaline hydrolysis followed by amidation of the resulting carboxylic acid according to the protocol shown in Scheme 2-22 (Scheme 2-23b). The NMR spectra data are well matched with those reported.[70]



Scheme 2-23. Preparation of amides **2.41** and **2.43**.

Phenyllithium[73] and 4-methoxyphenyllithium were prepared from the corresponding aryl bromide with lithium metal in diethyl ether (Scheme 2-24a). 4-Trifluoromethylphenyllithium, 2-pyridyllithium, and (1-methyl-1*H*-indol-5-yl)lithium were prepared from the corresponding aryl bromide with *t*-BuLi in THF at –78 °C *in situ* and used directly (Scheme 2-24b).[74] 2-Thienyllithium[75] and 2-furyllithium[76] were prepared from thiophene and furan, respectively, with *n*-BuLi in THF (Scheme 2-24c). Other organolithium and Grignard reagents were commercially available and used as received. All the organolithium and Grignard reagents were titrated before use (detailed titration methods see section 5.2.4 in Chapter 5).

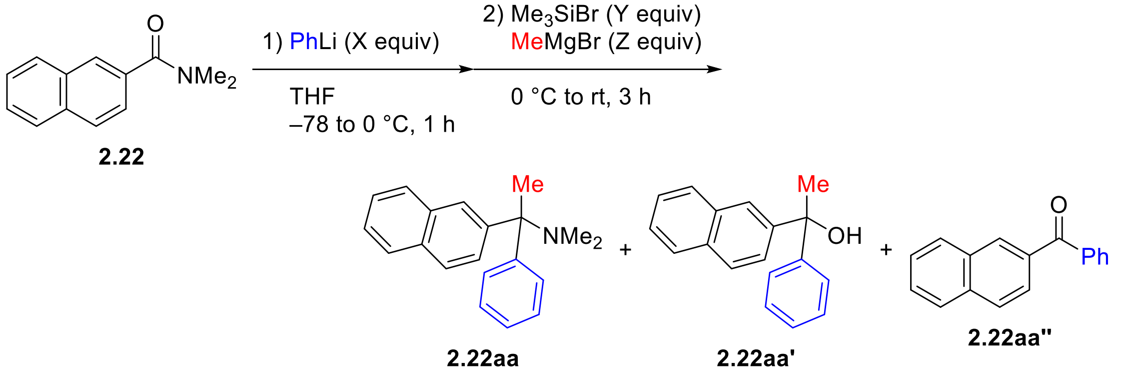


Scheme 2-24. Preparation of aryllithium reagents.

2.3.2. Optimization of the reaction conditions

Initially, the optimization of the reaction conditions was conducted using 2-naphthamide **2.22** (Table 2-1). PhLi (2.0 equiv) was added to carboxamide **2.22** at –78 °C (dry ice-acetone bath). Dry ice was taken out from the bath, and the mixture was slowly warmed up to 0 °C for 1 h (after 50 min, the cooling bath was replaced with an ice-water bath and stirred for 10 min). Subsequently, Me_3SiBr (2.5 equiv) and MeMgBr (3.0 equiv) were added at 0 °C, and the mixture was stirred at 23 °C for 3 h to provide α-tertiary amine **2.22aa** in 71% yield, along with alcohol **2.22aa’** in 12% yield and ketone **2.22aa”** in 5% yield (entry 1). The reaction in Et_2O or toluene gave ketone **2.22aa”** as the major product (79% and 67% yields, respectively) (entries 2 and 3). Heating at 60 °C for 2 h after the addition of Me_3SiBr and MeMgBr was found to afford **2.22aa** in a higher yield and minimize the formation of ketone **2.22aa”** in less than 2% yield (entry 4). The change of the initial concentration of carboxamide **2.22** (from 0.1 M to 0.2 M) did not affect the process efficiency (entry 5), whereas the addition of PhLi at 0 °C resulted in a lower yield of **2.22aa** (entry 6). Reduction of the amounts of PhLi (from 2 equiv to 1.5 equiv), Me_3SiBr (from 2.5 equiv to 2 equiv) and MeMgBr (from 3 equiv to 2.5 equiv) improved the yield of **2.22aa** to 89% (84% isolated yield) (entry 7). This protocol was found to be scalable up to a 15 mmol scale without detrimental impact on the yield of **2.22aa** (entry 8). Use of PhLi prepared *in situ* via halogen-lithium exchange using bromobenzene and *tert*-butyllithium afforded amine **2.22aa** in 70% yield (entry 9). Despite slightly diminished efficiency, this approach circumvents the pre-preparation of organolithium reagents (*vide infra*). However, the reaction with PhMgBr as the first carbanion did not afford desired amine **2.22aa** at all (entry 10). In this case, the formation of alcohol **2.22aa'** was observed in 13% yield along with ketone **2.22aa"** in 52% yield, indicating insufficient *O*-silylation of the corresponding anionic carbinol amine intermediate generated from 2-naphthamide **2.22** and PhMgBr. The use of Me_3SiCl instead of Me_3SiBr gave a lower yield (entry 11). We speculated that the lower reactivity of Me_3SiCl led to insufficient silylation. Sequential addition of MeMgBr quenched the remaining Me_3SiCl and upon heating, the tetrahedral intermediate started to collapse to give ketone **2.22aa"**, and it was attacked by MeMgBr to give alcohol **2.22aa'**. It should also be noted that the use of more reactive silylation reagents, Me_3SiI (generated *in situ* from Me_3SiCl and NaI) and $Me_3SiOSO_2CF_3$ (Me_3SiOTf), interfere in the process (entries 12 and 13). We speculated that the unselective O-silylation and N-silylation would occur in the presence of highly reactive silylating reagents. The undesired N-activation of the tetrahedral intermediate led to the production of **2.22aa"** and the sequential formation of **2.22a'**.

Table 2-1. Optimization of the reaction conditions with amide **2.22** with PhLi and MeMgBr[a]

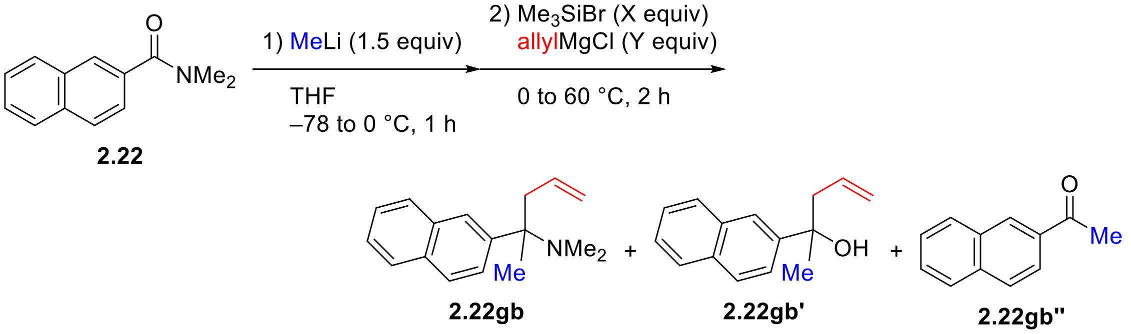


Entry	solvent	PhLi (X equiv)	Me_3SiBr (Y equiv)	MeMgBr (Z equiv)	Conditions	**2.22aa** (%)[b]	**2.22aa’** (%)[b]	**2.22aa”** (%)[b]
1	THF	2	2.5	3	0 °C to rt, 3 h	71	12	5
2	Et_2O	2	2.5	3	0 °C to rt, 3 h	9	7	79
3	PhMe	2	2.5	3	0 °C to rt, 3 h	12	23	67
4	THF	2	2.5	3	0 to 60 °C, 2 h	84	6	<2
5[d]	THF	2	2.5	3	0 to 60 °C, 2 h	84	11	<2
6[d,e]	THF	2	2.5	3	0 to 60 °C, 2 h	77	11	<2
7[d]	THF	1.5	2	2.5	0 to 60 °C, 2 h	89 (84)[c]	8	<2
8[d,f]	THF	1.5	2	2.5	0 to 60 °C, 2 h	90 (86)[c]	10	<2
9[d]	THF	1.5[g]	2	2.5	0 to 60 °C, 2 h	70	5	<2
10[d]	THF	1.5[h]	2	2.5	0 to 60 °C, 2 h	0	13	52
11[d]	THF	1.5	2i	2.5	0 to 60 °C, 2 h	68	25	<2
12[d]	THF	1.5	2[j]	2.5	0 to 60 °C, 2 h	78	20	<2
13[d]	THF	1.5	2[k]	2.5	0 to 60 °C, 2 h	45	43	11

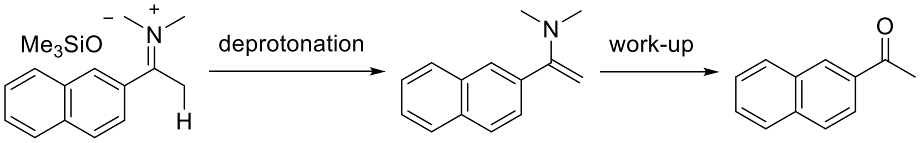
[a] The reactions were conducted by using 0.5 mmol of **2.22** in THF (5 mL, 0.1 M). [b] Crude ^{1}H NMR yield with 1,1,2,2-tetrachloroethane as internal standard. [c] Isolated yield in parenthesis. [d] Reaction with 2.5 mL THF (0.2 M). [e] Addition of PhLi was conducted at 0 °C for 1 h. [f] Reaction in a 15 mmol scale. [g] PhLi was generated *in situ* from PhBr (0.75 mmol) and *tert*-BuLi (1.5 mmol, 1.32 M in pentane) in THF and directly used for the reaction with **2.22**. [h] PhMgBr was pre-prepared from PhBr and Mg in THF and titrated before use. [I] Me_3SiCl was used instead of Me_3SiBr. [j] Me_3SiI (generated in situ using Me_3SiCl and NaI) was used instead of Me_3SiBr. [k] Me_3SiOTf was used instead of Me_3SiBr.

Employment of the optimized reaction conditions obtained in Table 2-1, entry 7 to the reactions using alkyllithium as the first nucleophile or those using aliphatic amides rendered the processes less efficient. Therefore, the modification of the reaction conditions was conducted in the reactions of carboxamide **2.22** with MeLi and allylMgCl (Table 2-2). Under the optimized reaction protocol, the reaction afforded α-tertiary amine **2.22gb** only in 42% yield along with the generation of alcohol **2.22gb'** and ketone **2.22gb"** in 15% and 43% yields, respectively (entry 1). The formation of substantial amounts of ketone **2.22gb"** was assumed presumably due to unproductive α-deprotonation of the iminium ion intermediate formed after the addition of Me_3SiBr, generating inert enamine which was converted into ketone **2.22gb"** upon aqueous work-up. It was found that quick addition of allylMgCl immediately after Me_3SiBr could suppress the formation of alcohol **2.22gb'** and ketone **2.22gb"** to some extent (the interval between addition of Me_3SiBr and allylMgCl should be less than 30 seconds) (entry 2). The addition of 3 equivalents of allylMgCl slightly improved the yield of **2.22gb** in 64% yield (60% isolated yield) (entry 3).

Table 2-2. Optimization of the reaction conditions with amide **2.22** with MeLi and allylMgCl[a]



- unproductive enamine formation via α-deprotonation of the iminium ion imtermediate

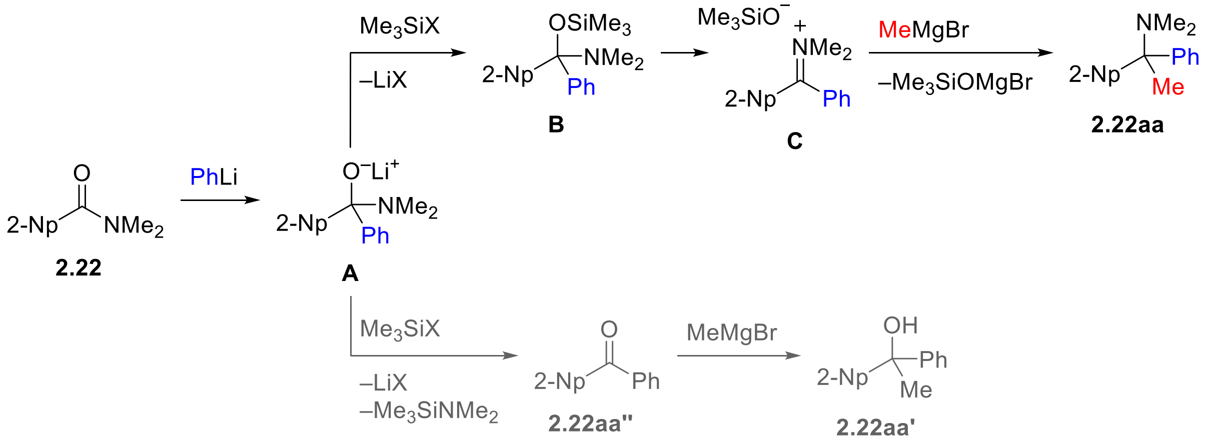


Entry	Me$_3$SiBr (X equiv)	allylMgCl (Y equiv)	**2.22gb** (%)[b]	**2.22gb'** (%)[b]	**2.22gb"** (%)[b]
1[d]	2.0	2.5	42	15	43
2[e]	2.0	2.5	59	27	14
3[e]	2.0	3.0	64 (60)[c]	11	25

[a] The reactions were conducted on a 0.5 mmol scale with 2.5 mL THF. [b] Crude ^{1}H NMR yield with 1,1,2,2-tetrachloroethane as internal standard. [c] Isolated yield in parenthesis. [d] After the addition of Me$_3$SiBr, the mixture was stirred for 5 min at 0 °C before the addition of allylMgCl. [e] Soon after the addition of Me$_3$SiBr, allylMgCl was added (less than 30 sec interval).

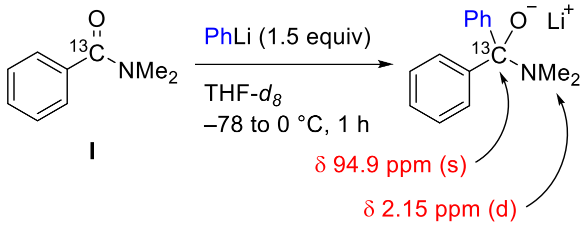
2.3.3. Mechanistic studies

The proposed mechanism of the geminal difunctionalization of 2-naphthamide **2.22** was depicted in Scheme 2-25. The addition of PhLi to the amide carbonyl group forms anionic hemiaminal intermediate **A**,[78] which could be detected as a stable form even at ambient temperature by ^{1}H and ^{13}C NMR analyses. *O*-Silylation of **A** with Me$_3$SiX resulted in the formation of silyl ether **B,** and the ensuing addition of MeMgBr resulted in the formation of amine **2.22aa** via iminium ion intermediate **C**. On the other hand, electrophilic activation of the amino group of **A** by Me_3SiX collapses **A** into ketone **2.22aa”**, which is trapped with MeMgBr to provide alcohol **2.22aa’**. It was speculated that more electrophilic Me_3SiBr renders the reaction course more selective toward the formation of iminium **C** via efficient *O*-silylation of **A** over that of ketone **D** via *N*-silylation.

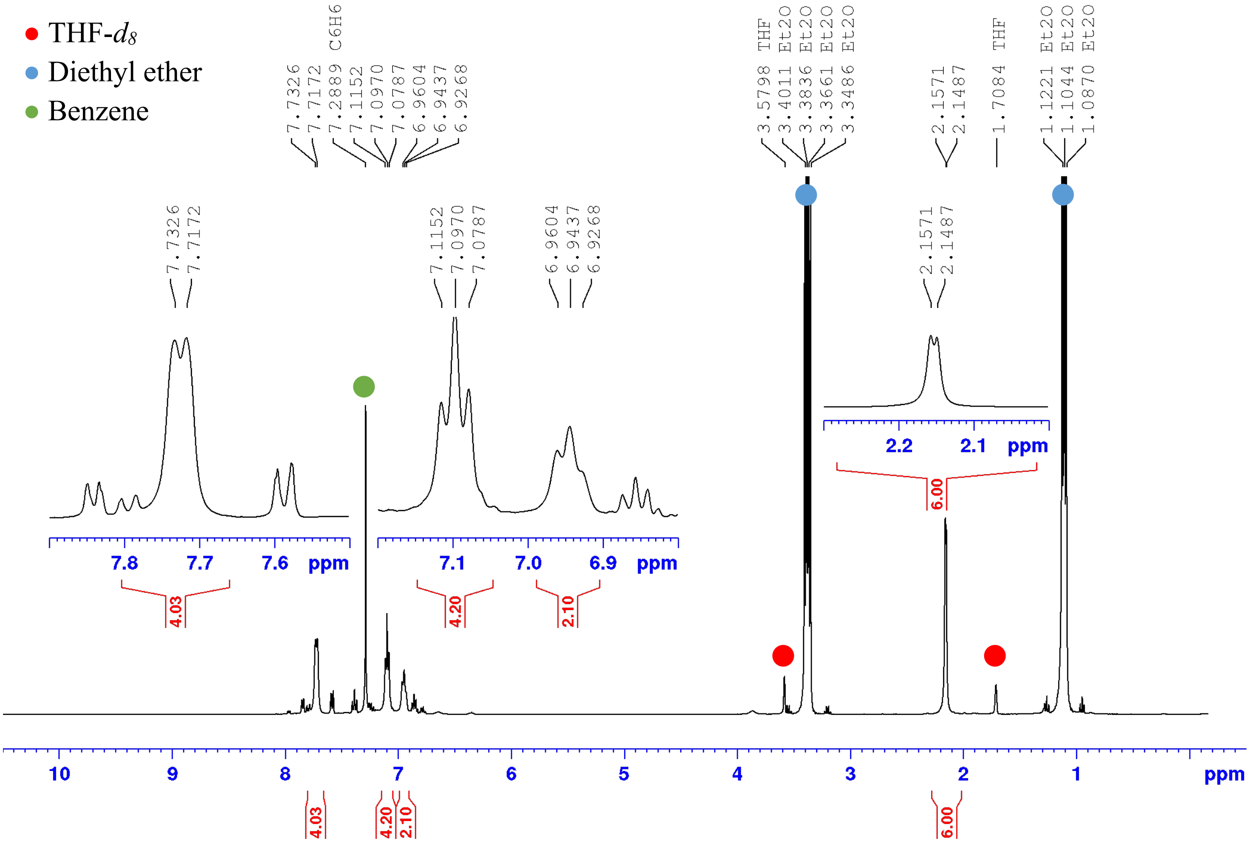


Scheme 2-25. Proposed mechanistic pathways.

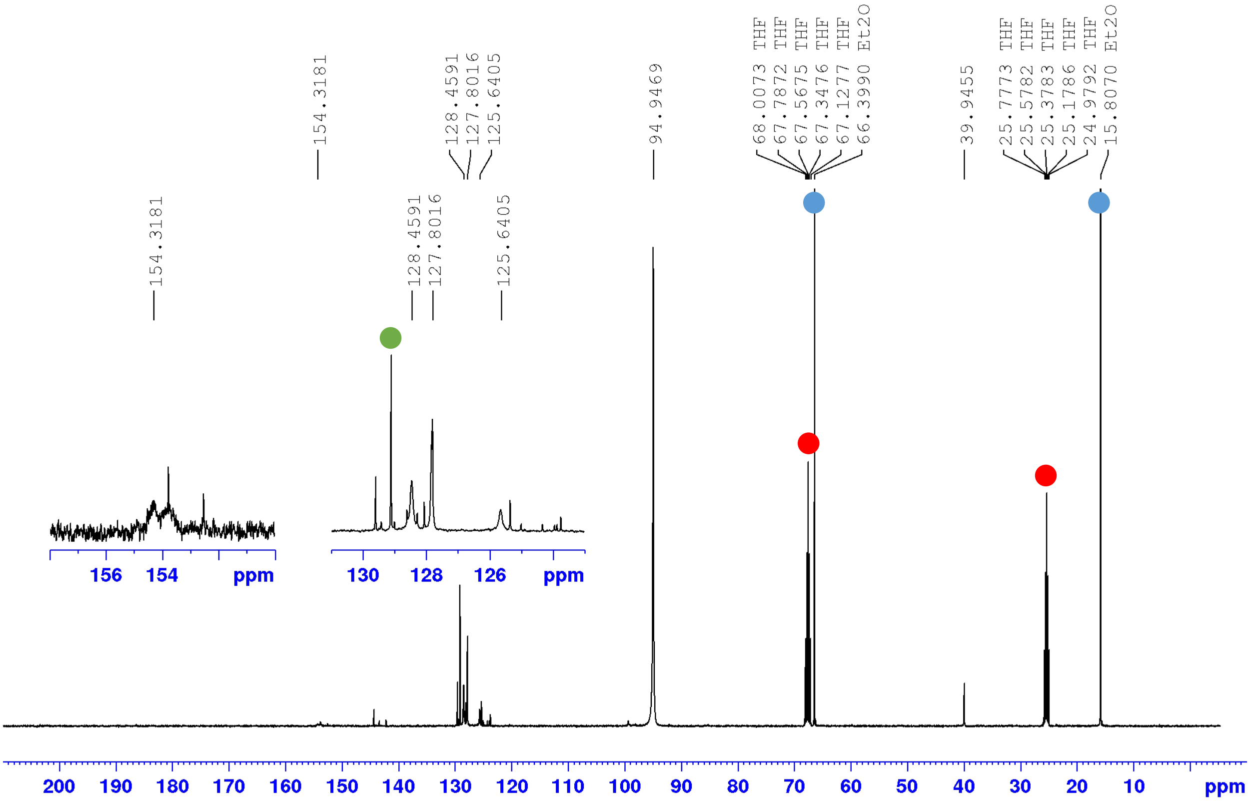
A ^{13}C-labelled benzamide **I** was used to detect and characterize the anionic hemiaminal intermediate **A** by the NMR analyses. The ^{13}C-labelled benzamide was subjected to the standard reaction conditions with PhLi as shown in Scheme 2-26, and the crude mixture was taken to argon flushed J. Young NMR tube to conduct ^1H NMR, ^{13}C NMR, and HMBC spectroscopic analyses. In the ^1H NMR spectrum (Scheme 2-27), the doublet at 2.15 ppm represents the protons of N$\underline{Me_2}$, which shows a $^3J_{^1H\text{-}^{13}C}$ coupling of 3.4 Hz with the tetrahedral carbon ($\underline{^{13}C}$) (Scheme 2-28). This correlation was further confirmed by the HMBC spectrum of the crude mixture, which showed a correlation of 2.15 ppm (N$\underline{Me_2}$) in the ^1H NMR and 94.9 ppm ($\underline{^{13}C}$) in the ^{13}C NMR (Scheme 2-29). The anionic hemiaminal intermediate was found to be stable at ambient temperature under an argon atmosphere. No significant decomposition was observed after 21 days as judged by the ^1H NMR analysis (Scheme 2-30).



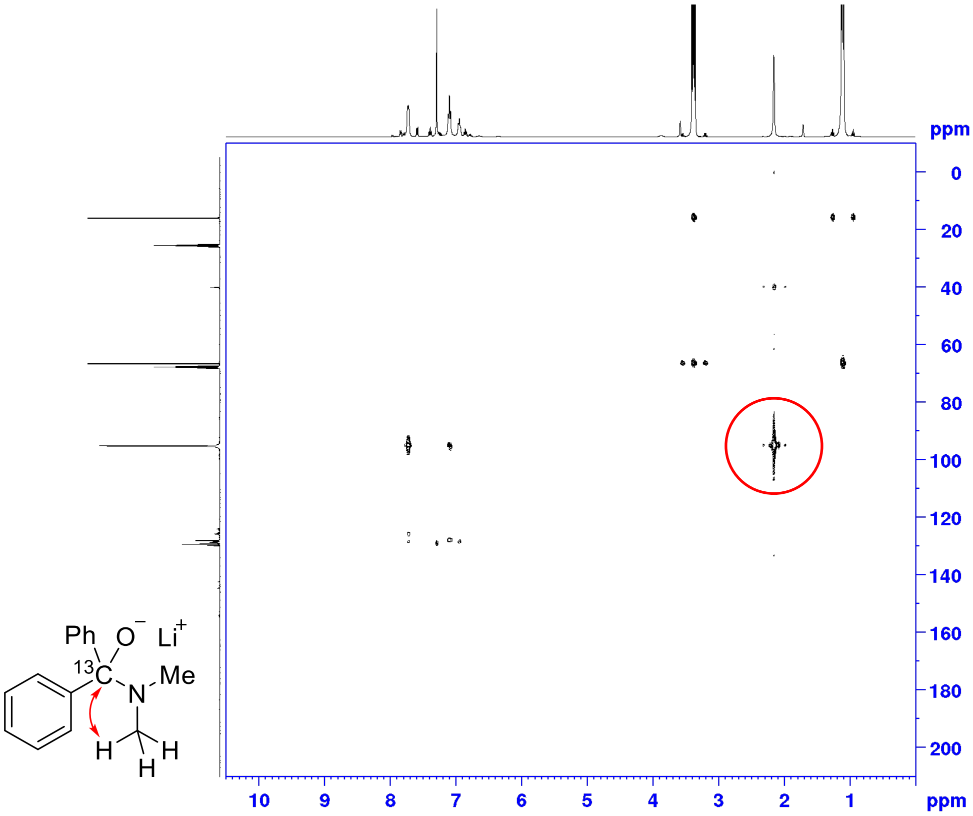
Scheme 2-26. Formation of a ^{13}C-labelled tetrahedral intermediate.



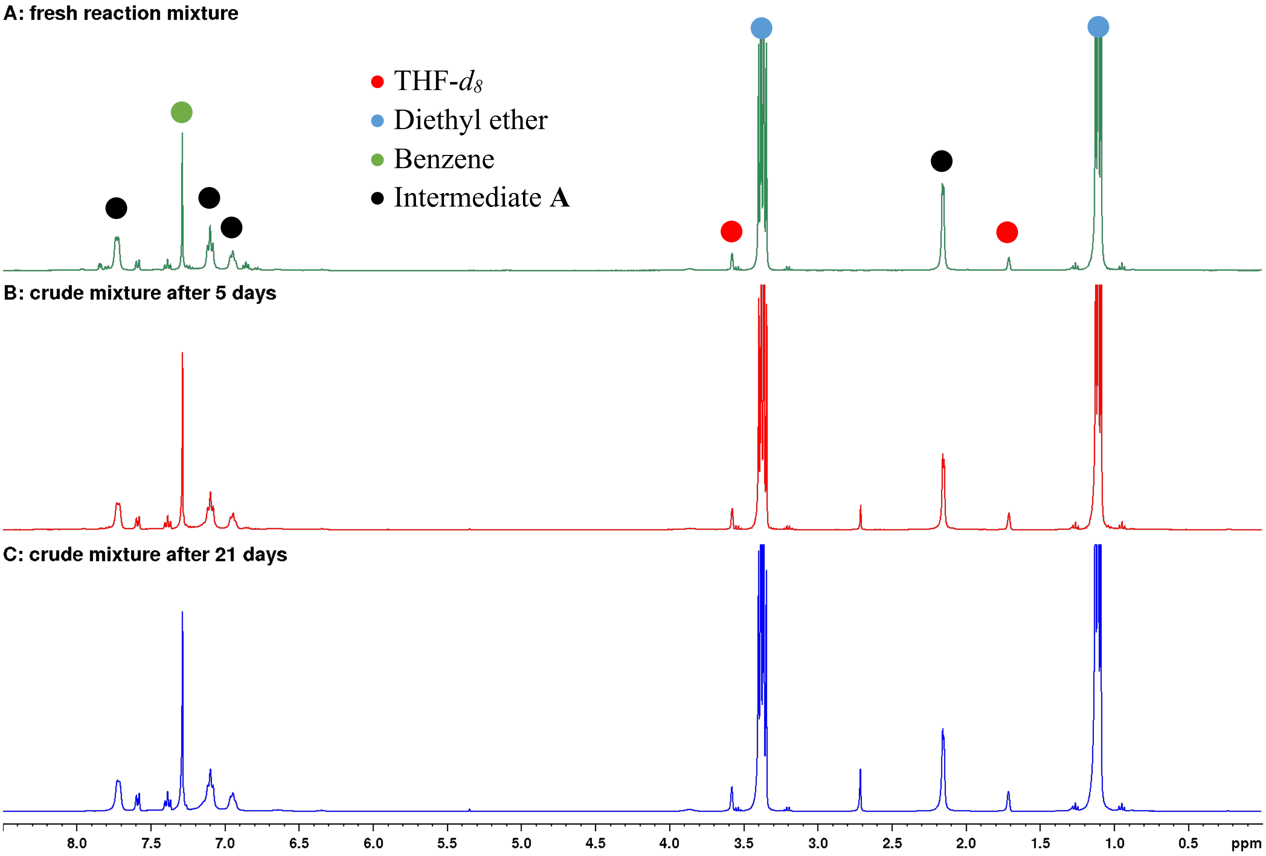
Scheme 2-27. ^{1}H NMR of the reaction of ^{13}C-labelled benzamide **I** and PhLi in THF-d_8.



Scheme 2-28. ^{13}C NMR of the reaction of **I** and PhLi in THF-*d*$_8$.



Scheme 2-29. HMBC spectrum of the reaction of **I** and PhLi in THF-*d*$_8$.

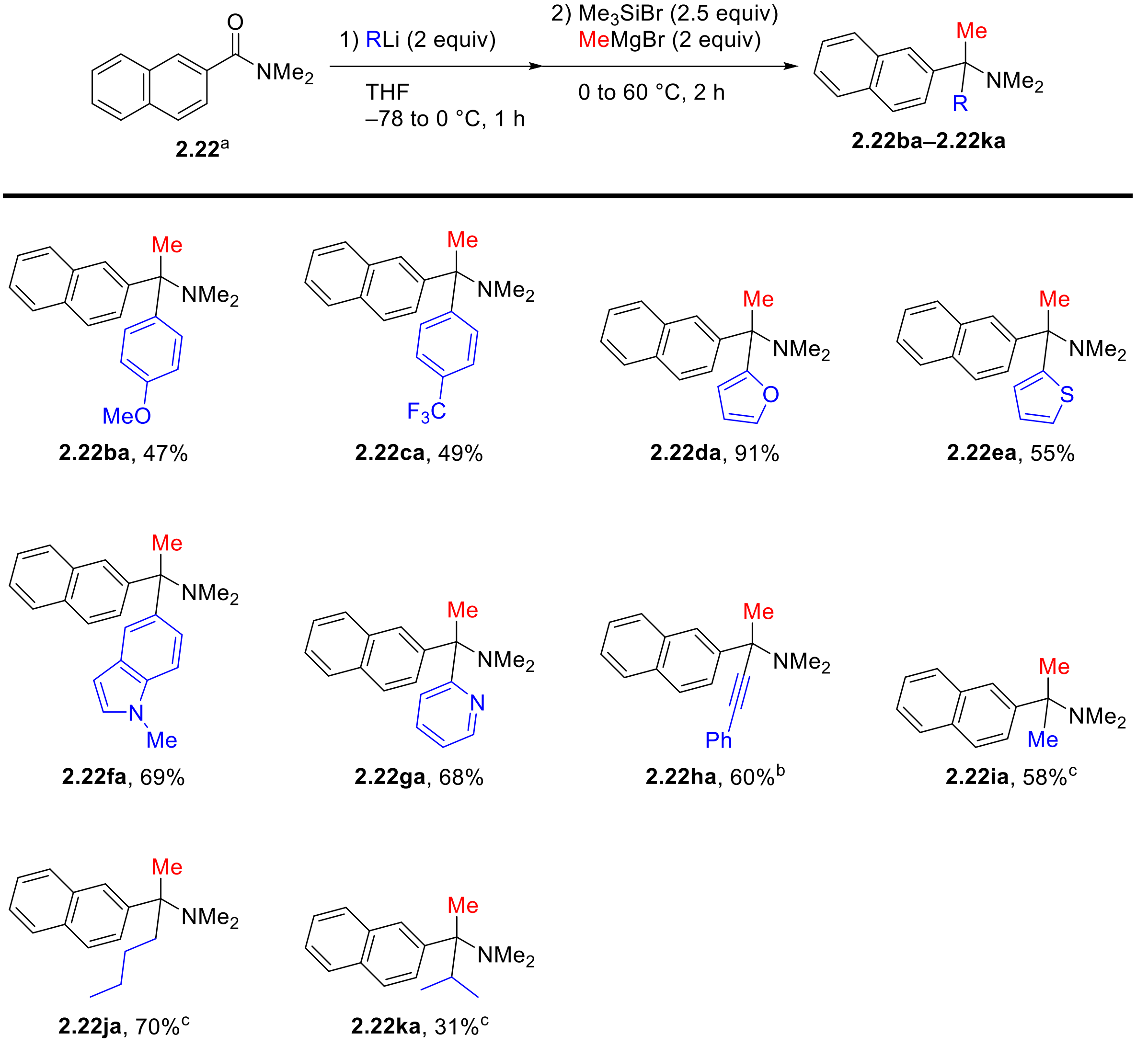


Scheme 2-30. Stability test on the anionic hemiaminal intermediate.

2.3.4. Substrate scope and limitations

With the optimized reaction conditions in hand, the scope of organolithium reagents as the first nucleophile was investigated (Scheme 2-31). This protocol allowed for the use of electron-rich (for **2.22ba**) and electron-deficient (for **2.22ca**) aryllithiums, as well as heterocyclic aryllithiums such as 2-thienyllithium (for **2.22da**), 2-furyllithium (for **2.22ea**), 5-indolyllithium (for **2.22fa**) and 2-pyridyllithium (for **2.22ga**) to give the corresponding amines in moderate to good yields. This method was also applicable to lithium phenylacetylide, providing propargylamine **2.22ha** in moderate yield, although higher temperature (60 °C) and prolonged reaction time were required for the first step. The protocol was amenable to the use of alkyllithium such as MeLi (for **2.22ia**) and *n*-BuLi (for **2.22ja**), while the reaction with *i*-

PrLi resulted in moderate efficiency for the formation of amine **2.22ka**. This may be due to the steric hindrance of the isopropyl group, which hampered the second addition of MeMgBr.



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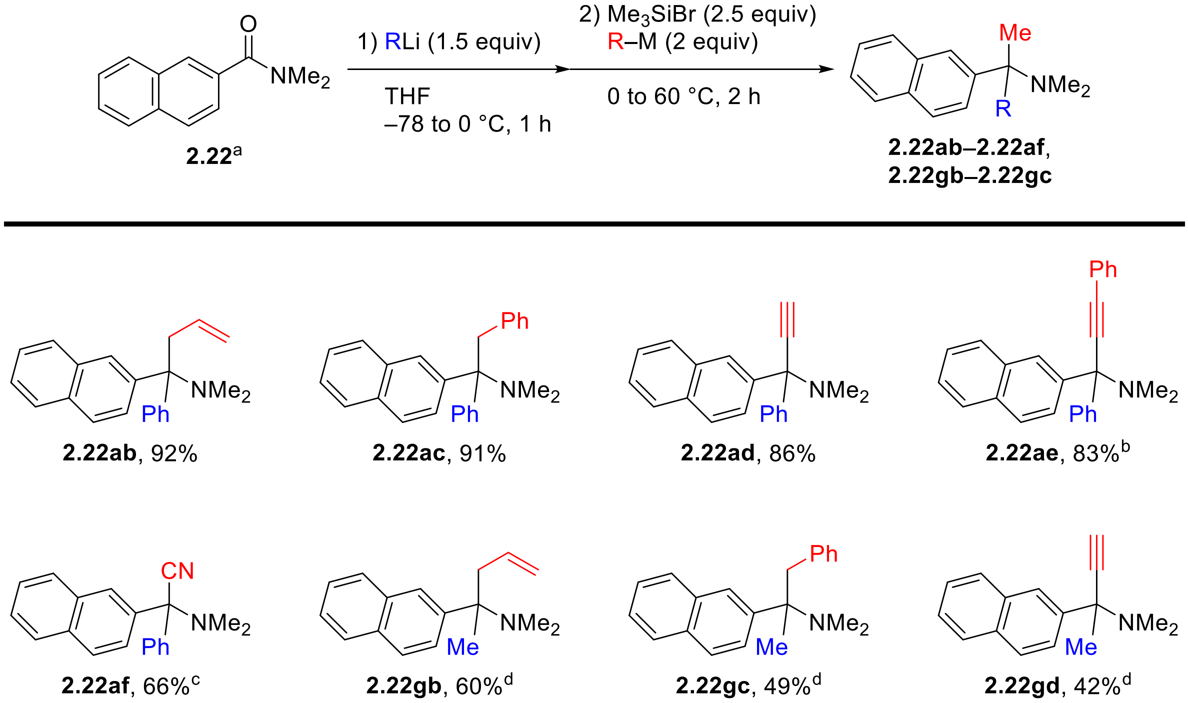
[a] The reactions conditions: 2-naphthamide **2.22** (0.5 mmol), first organolithium reagent (1.5 equiv) at –78–0 °C for 1 h, followed by Me_3SiBr (2 equiv) and MeMgBr (2.5 equiv) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b] Lithium phenylacetylide (3 equiv) at 60 °C for 2 h, followed by Me_3SiBr (2 equiv) and MeMgBr (3 equiv) at 0 °C, then stirring at 60 °C for 2 h. [c] MeMgBr (3 equiv) was used.

Scheme 2-31. Scope of the first nucleophiles.

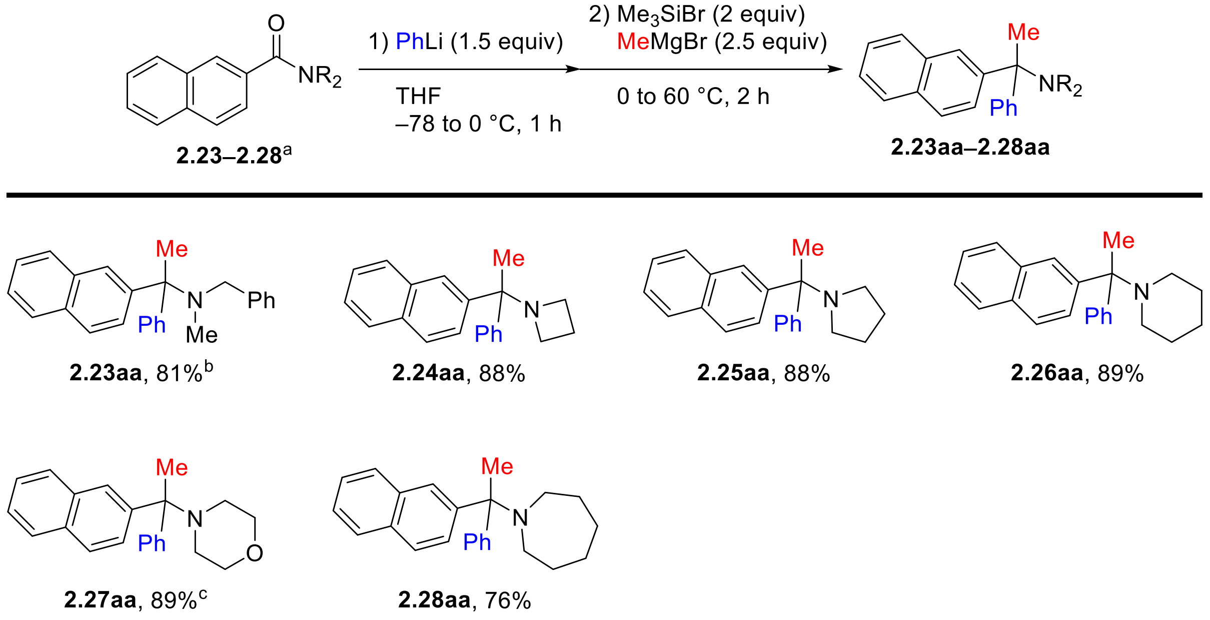
We then examined the compatibility of the second carbanion reagents using PhLi or MeLi as the first carbanion reagent (Scheme 2-32). With PhLi as the first carbanion, the method could introduce allyl (for **2.22ab**) and benzyl (for **2.22ac**) groups with good yields. Installation of acetylenic moieties (for **2.22ad** and **2.22ae**) could also be implemented with good efficiency using ethynylmagnesium bromide and lithium phenylacetylide, respectively. Instead of the Grignard reagents as a carbon nucleophile, the use of tetrabutylammonium cyanide enabled the downstream Strecker reaction to form α-cyano amine **2.22af** in good yield. With MeLi as the first nucleophile, the protocol was found to be compatible to incorporate allyl (for **2.22gb**), benzyl (for **2.22gc**), and alkynyl (for **2.22gd**) motifs in the downstream geminal difunctionalization. However, the method could not install a phenyl group using PhMgBr as the second nucleophile.



[a] The reactions conditions: carboxamide **2.22** (0.5 mmol), PhLi or MeLi (1.5 equiv) at –78–0 °C for 1 h, followed by Me_3SiBr (2 equiv) and organomagnesium reagents (2.5 equiv) as the second nucleophile (2.5 equiv) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b] Lithium phenylacetylide was used as the second nucleophile. [c] Bu_4NCN was used as the second nucleophile. [d] Grignard reagent (3 equiv) was used.

Scheme 2-32. Scope of the second nucleophiles.

Next, the substituent compatibility of the amide nitrogen was explored (Scheme 2-33). This method enabled the synthesis of *N*-benzyl-*N*-methylamine (**2.23aa**) as well as cyclic amines such as azetidine (**2.24aa**), pyrrolidine (**2.25aa**), piperidine (**2.26aa**), morpholine (**2.27aa**), and azepane (**2.28aa**) from the corresponding carboxamides.



2.23–2.28[a]

2.23aa–2.28aa

2.23aa, 81%[b]

2.24aa, 88%

2.25aa, 88%

2.26aa, 89%

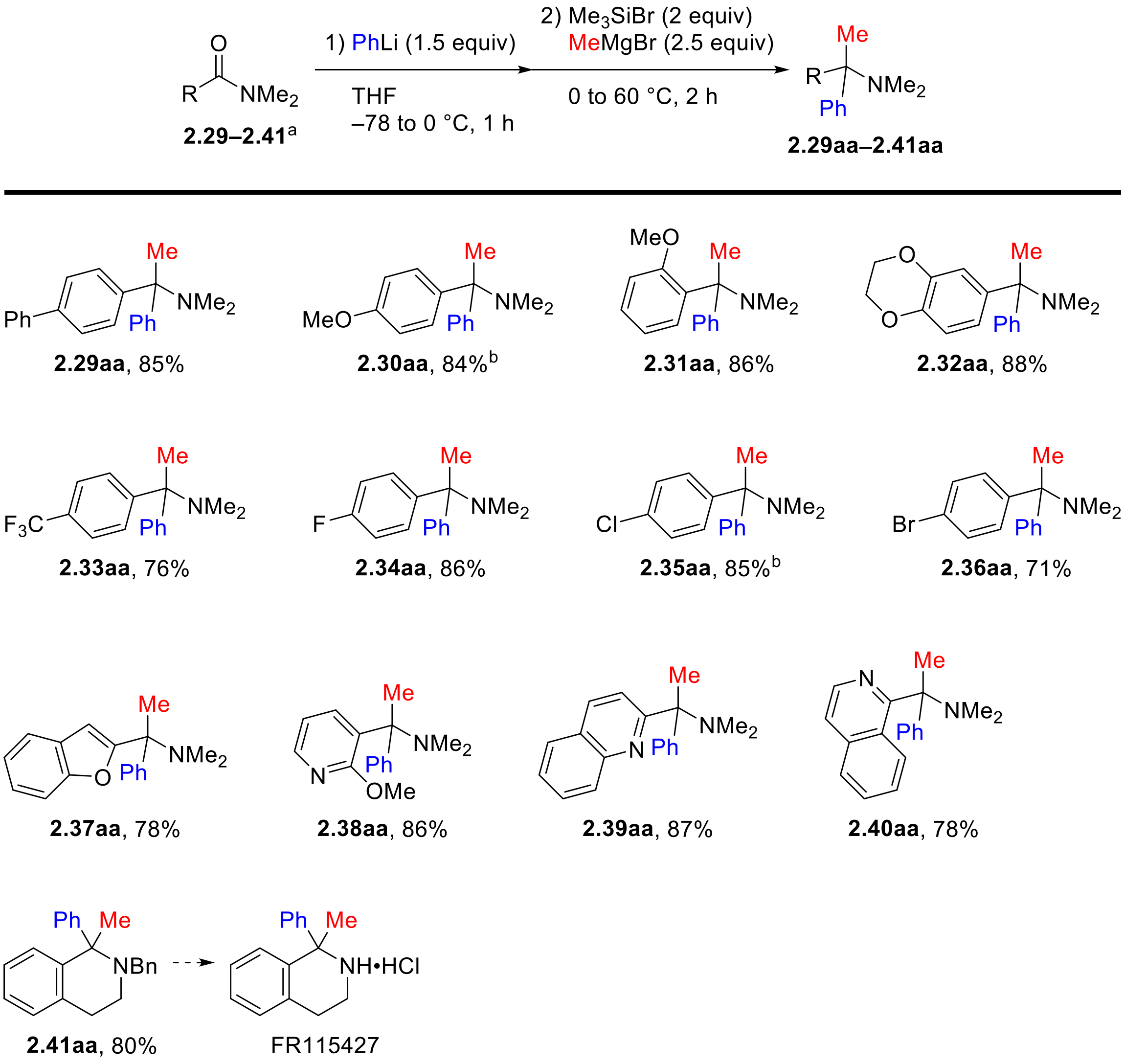
2.27aa, 89%[c]

2.28aa, 76%

[a] The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv) at –78–0 °C for 1 h, followed by Me_3SiBr (2 equiv) and MeMgBr (2.5 equiv) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b] After the addition of Me_3SiBr at 0 °C, the mixture was stirred at room temperature for 0.5 h before the mixture was treated with MeMgBr at 0 °C and heated at 60 °C for 2 h. [c] After the addition of Me_3SiBr at 0 °C, the mixture was stirred at 60 °C for 1 h before the mixture was treated with MeMgBr at 0 °C and heated at 60 °C for 2 h.

Scheme 2-33. Substituent compatibility of amide nitrogen.

The scope of various aromatic carboxamides was then examined using PhLi and MeMgBr for the geminal difunctionalization (Scheme 2-34). Both electron-withdrawing and electron-donating groups were well tolerated (for **2.29aa–2.36aa**). Heteroaromatic amides including benzofuran (for **2.37aa**), pyridine (for **2.38aa**), quinoline (for **2.39aa**), isoquinoline (for **2.40aa**) moieties were also suitable to provide the corresponding amines. The facile synthesis of 1,1-disubstituted tetrahydroisoquinoline (**2.41aa**), was also achieved using the present protocol. This is a precursor to a drug molecule FR115427, which is a non-competitive NMDA antagonist with excellent anticonvulsant activity.[77]



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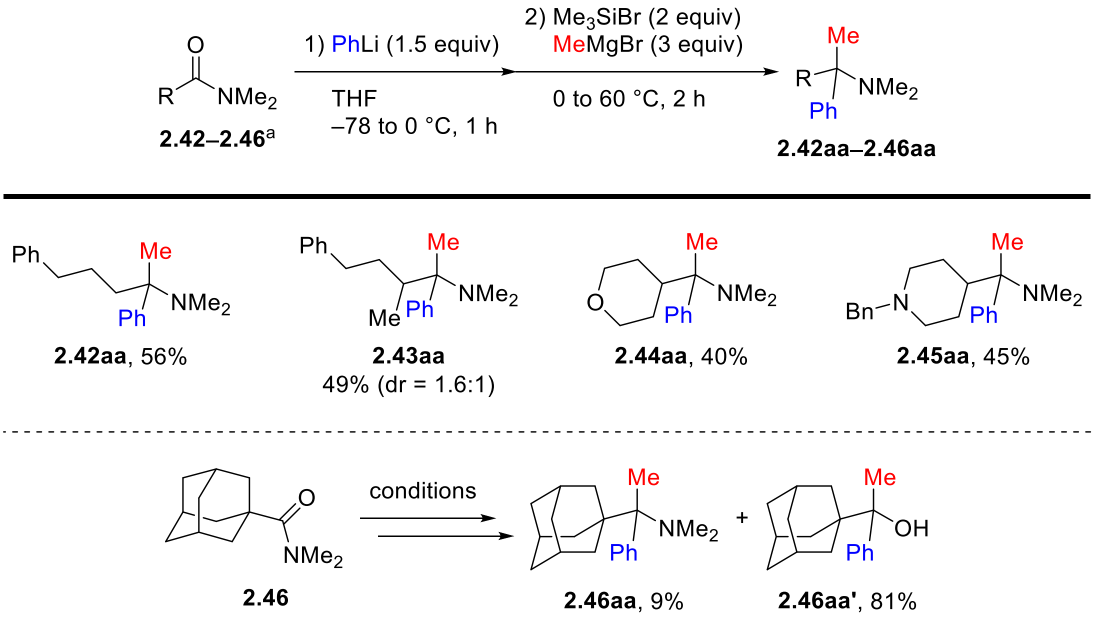
[a] The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv) at –78–0 °C for 1 h, followed by Me_3SiBr (2 equiv) and MeMgBr (2.5 equiv) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. [b] After the addition of MeMgBr (3 equiv), the reaction mixture was stirred at 60 °C for 3 h. Bn = benzyl.

Scheme 2-34. Scope of aromatic amides and lactam.

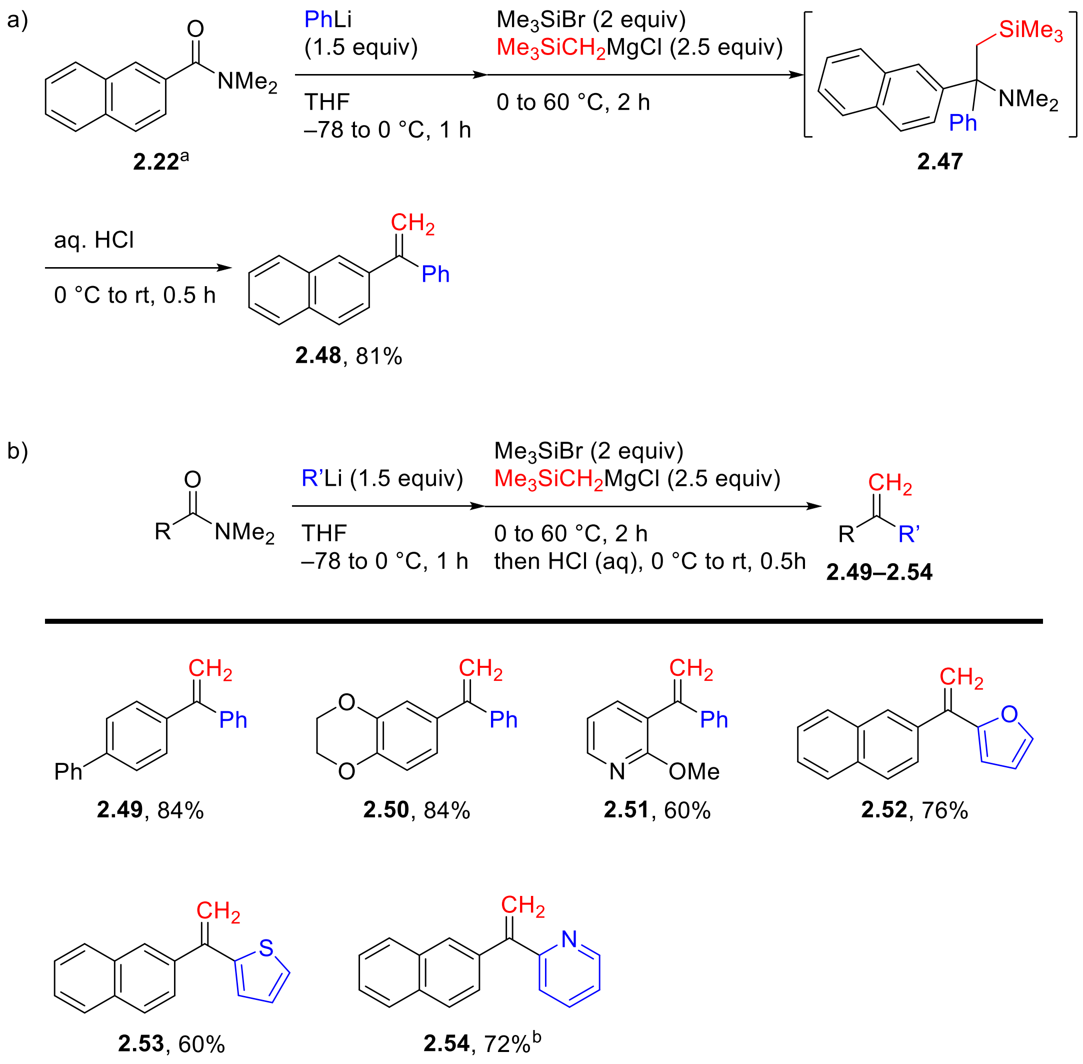
The scope of aliphatic amide was also investigated. a-Secondary and tertiary carboxamides bearing enolizable α-protons were converted to the corresponding α-tertiary amines (for **2.42aa**–**2.45aa**) with moderate to good efficiency (Scheme 2-35). However, the reaction of sterically congested 1-adamantyl carboxamide **2.46** led to the formation of alcohol **2.46aa’** as the major product in 81% yield along with amine **2.46aa** only in 9% yield.



[a] The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv) at –78–0 °C for 1 h, followed by Me_3SiBr (2 equiv) and MeMgBr (3 equiv) at 0 °C, then stirring at 60 °C for 2 h. Isolated yields were recorded. Bn = benzyl.

Scheme 2-35. Scope of aliphatic amides.

During the screening of the Grignard reagents as the second nucleophile, it was found that the use of (trimethylsilyl)methylmagnesium chloride upon treatment of 2-naphthamide **2.22** with PhLi, the resultant amine **2.47** was further converted into 1,1-diarylethylene **2.48** in 81% yield after the aqueous acid work-up via elimination of silylamine (Scheme 2-36a). This transformation could be regarded as phenylative aza-Peterson olefination[79] of 2-naphthamide **2.22.** This protocol allowed access to various unsymmetrical 1,1-diarylethylenes (**2.49–2.54**) in a facile one-pot fashion (Scheme 2-36b).



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[a] The reactions conditions: carboxamides (0.5 mmol), PhLi (1.5 equiv) at –78–0 °C for 1 h, followed by Me_3SiBr (2 equiv) and Me_3SiCH_2MgCl (2.5 equiv) at 0 °C, then stirring at 60 °C for 2 h; water (1 mL) at 0 °C, and then 3 M HCl aqueous solution (5 mL), stirring at room temperature for 0.5 h. Isolated yields were recorded. [b] After the addition of 6M HCl aqueous solution, the mixture was stirred at 60 °C for 2 h.

Scheme 2-36. Arylative aza-Peterson olefination of carboxamides.

2.4. Conclusion

In conclusion, a transition-metal-free protocol for the synthesis of α-tertiary amines from *N,N*-dialkyl carboxamides was developed. This was achieved by the iterative addition of two carbon nucleophiles to readily available and bench stable *N,N*-dialkyl carboxamides in a concise manner. Furthermore, the employment of Me_3SiCH_2MgCl as the second nucleophile led to the formation of 1,1-diarylethylenes.

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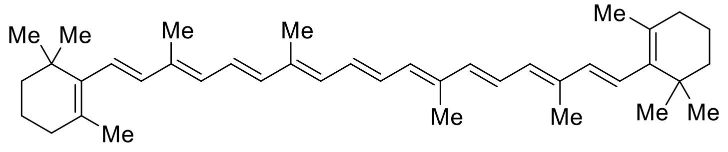
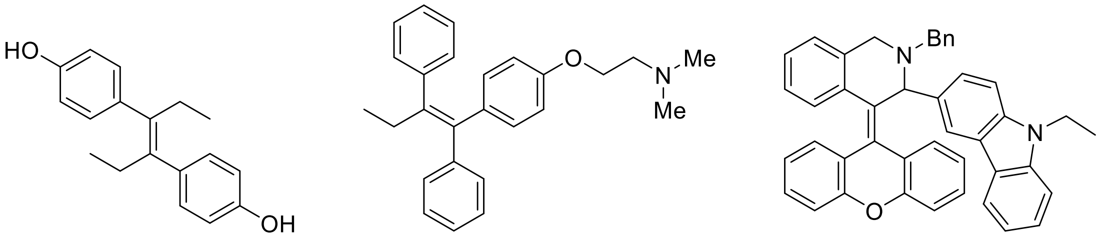
Part B: Asymmetric synthesis of alkylzincs by rhodium-catalyzed enantioselective arylative cyclization of 1,6-enynes with arylzincs.

Chapter 3. General introduction

The carbon-carbon double bond is a ubiquitous structural component in organic molecules. Due to its versatile reactivity, it is also a useful building block in organic chemistry.[1] In this context, tetra-substituted alkenes, which are widely found in natural compounds, play a crucial role among multi-substituted olefins. Examples include β-carotene[2] (**3.1a**) which is an abundant pigment in plants and Vitamin A which is essential for human growth and vision. Not limited to natural products, these double bond moieties can also be found in the pharmaceutical industry. For instance. diethylstrillbestrol[3] is prescribed for hormonal therapy, and tamoxifen[4] is a breast cancer medication that consists of triphenylethylene. Some tetra-substituted olefins have also found their applications as organic dyes due to their excellent fluorescent properties (Scheme 3-1).[5]



3.1a β-carotene



3.1b diethylstilbestrol **3.1c** tamoxifen **3.1d** fluorescence dye

Scheme 3-1. Useful compounds with a tetra-substituted alkene motif.

From a synthetic point of view, simple alkenes can be accessed by well-established methods, such as Wittig reaction,[6] Horner-Wadsworth-Emmons reaction,[7] McMurry coupling,[8] partial reduction of alkyne,[9] and Mizoroki-Heck type cross-coupling.[10] Nevertheless, the synthesis of multi-substituted alkenes is not always easy because of its congested structure. More importantly, the control of stereochemistry is rather difficult by conventional methods, especially for tetra-substituted alkenes.[1,11] Therefore, the stereoselective synthesis of multi-substituted alkenes remains a significant challenge in this field.

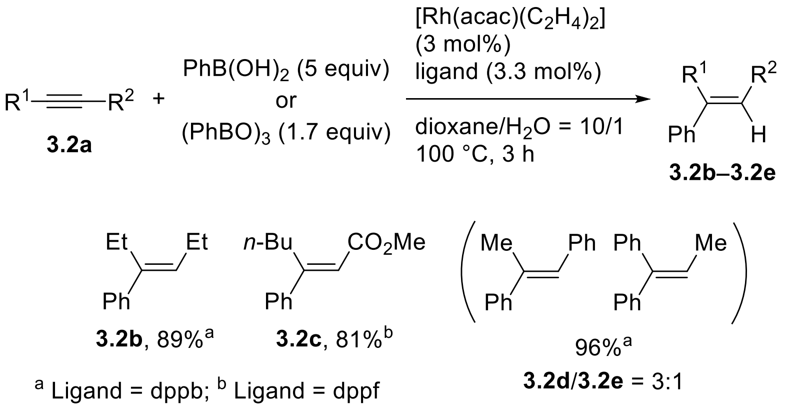
The direct addition to alkynes is a highly desirable method for this purpose but the reactivity of alkynes is generally not high, in particular unactivated alkynes.[12] Recently, metal-catalyzed hydrocarbonation and carbometalation have been realized, which is crucial for synthesizing multi-substituted alkenes.[13]

Metal-catalyzed addition reaction to alkynes provides a platform to synthesize multi-substituted alkenes.[14] The metals used for the reactions include rhodium,[15] cobalt,[16] palladium,[17] nickel,[18] and iron.[16b,19] The metal-catalyzed addition follows *syn*-addition fashion in general and, therefore, provides good selectivity. Meanwhile, boron reagents,[20] Grignard reagents,[12,21] and organozinc reagents[12,21] have also been commonly applied because of their availability and versatile reactivity.

3.1. Rhodium-catalyzed arylation of simple alkynes through carborhodation

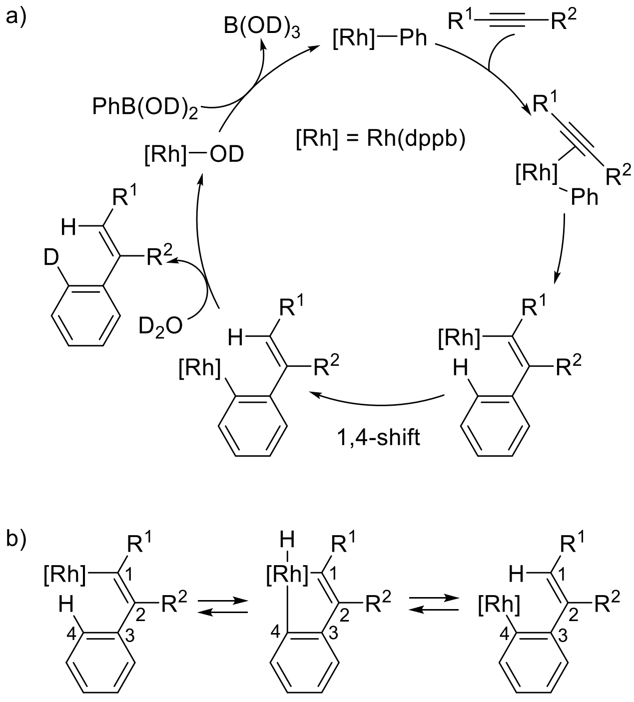
Rhodium-catalyzed carbon-carbon bond formation is one of the most established methods to access multi-substituted alkenes, and extensive studies have been investigated in this area.[15]

In 2001, Hayashi reported the first example of hydroarylation of internal alkynes with arylboronic acids (or boroxines) in the presence of a rhodium(I) catalyst (Scheme 3-2).[22] The reaction was conducted in an aqueous solvent, providing the tri-substituted olefins with good yields and high *syn*-selectivity (**3.2b**), while alkynes with an electron-withdrawing group gave excellent regioselectivity (**3.2c**). It should be noted that the reaction of unsymmetrical alkynes, such as 1-phenyl-1-propyne, gave a 3:1 mixture of regioisomers **3.2d** and **3.2e** in a combined yield of 96%.



Scheme 3-2. Rhodium-catalyzed hydroarylation of internal alkynes.

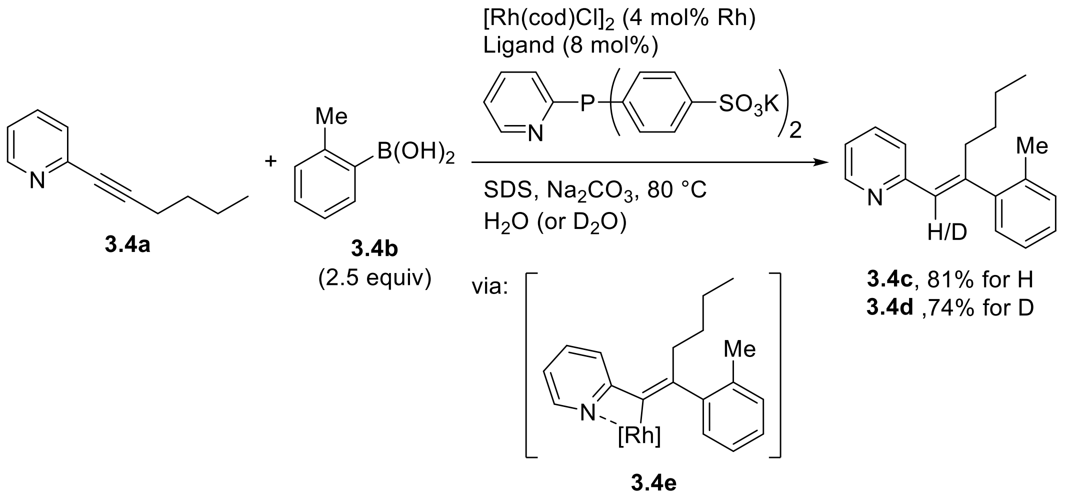
Mechanistic studies revealed that the 1,4-rhodium shift[23] from an alkenyl carbon to an aryl carbon occurred during the reaction, as indicated by the deuterium labeling study, where high deuterium incorporation was observed on the *ortho* position of the phenyl group when using D_2O instead of H_2O as the co-solvent. The proposed mechanism involves *syn*-addition of phenylrhodium to the alkyne before 1,4-rhodium shift followed by hydrolysis of the ortho-alkenylarylrhodium intermediate. (Scheme 3-3a). The mechanism for the 1,4-shift of rhodium from vinylic carbon (**3.3a**) to aromatic carbon (**3.3c**) was later rationalized by DFT calculation studies (Scheme 3-3b).[24] A 5-membered ring rhoda(III)cycle **3.3b** was formed by a C–H oxidative addition of the proximal *o*-phenyl hydrogen, and subsequent reductive elimination leads to **3.3c**. Arylrhodium **3.3c** was thermodynamically more stable, therefore favoring the formation of **3.3c**.



3.3a **3.3b** **3.3c**

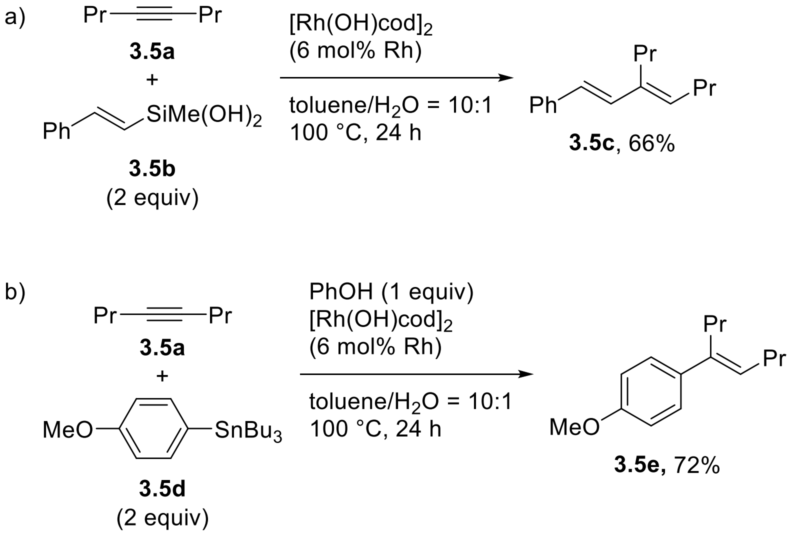
Scheme 3-3. Proposed mechanism for rhodium 1,4-shift.

Lautens demonstrated another example of hydroarylation of alkynyl heteroaromatic compounds (Scheme 3-4).[25] The reaction was highly regioselective towards β-arylation of the heteroarene. The alkynyl substitution at the 2-position of the pyridine ring was essential for this reaction since no addition products were formed when the alkyne moiety was substituted on 3- or 4-position on the pyridine ring. The authors suggested that the high regioselectivity may be caused by a strong coordinating effect of the pyridine ring on the substrate. In contrast to Hayashi's report (Scheme 3-3), deuterium labeling studies with D_2O as a solvent only provided the alkenyldeuterium product, indicating that 1,4-rhodium shift did not occur before hydrolysis due to the coordination of the pyridine nitrogen.



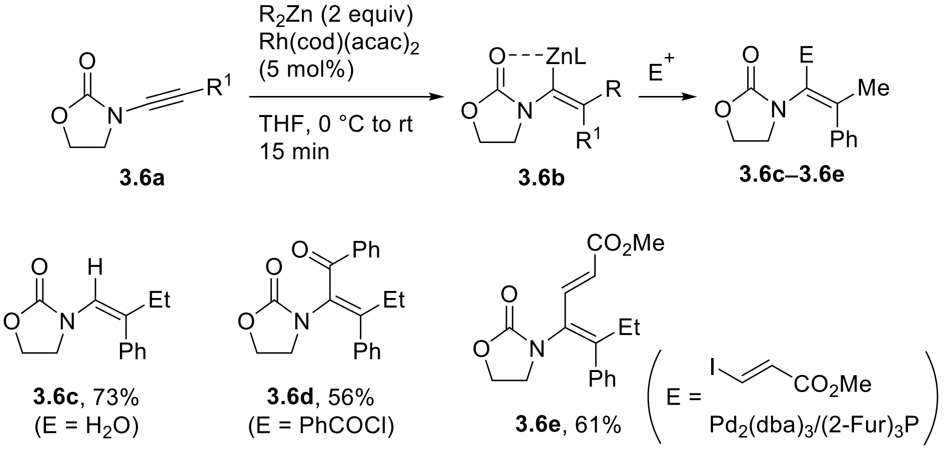
Scheme 3-4. Hydroarylation of 2-alkynyl pyridines.

Besides that, Mori showed the hydroarylation of alkynes with arylsilyldiol in the presence of $[Rh(OH)cod]_2$ in a toluene/water mixture at 100 °C.[26] Reaction of 4-octyne and vinyl silyldiol (**3.5b**) gave 1,3-diene (**3.5c**) in moderate yield (Scheme 3-5a). It was also found that, in the presence of phenol (1 equiv), the corresponding reaction of tributyl(4-methoxylphenyl)stannane (**3.5d**) and 4-octyne gave the hydroalkenylation product (**3.5e**) in 72% yield (Scheme 3-5b). The addition of phenol was essential to achieve a high yield as it is believed to promote the protoderhodation step.



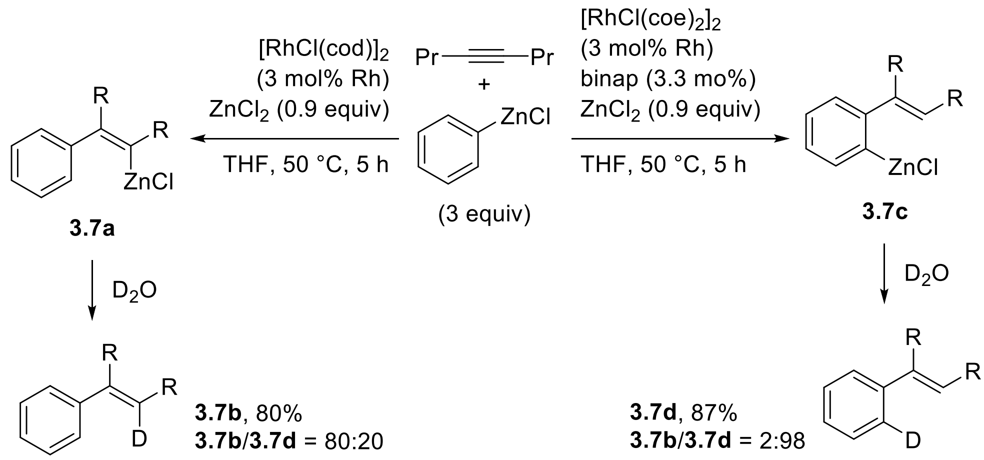
Scheme 3-5. Hydroarylation and -alkenylation of alkynes with silanediols.

A rhodium-catalyzed carbozincation of cyclic ynamide was reported by Lam in 2009, providing the enamides in good regio- and stereoselectivity (Scheme 3-6).[27] This carbozincation was applicable to dialkyl- or diarylzinc reagents. The use of noncyclic ynamide however, resulted in poor regioselectivity and low yield. Therefore, it was suggested that the high selectivity was mainly attributed to the carbonyl directing group in the carbometalation step. Mechanism studies revealed that the alkenylzinc intermediate was the actual product before protonolysis (**3.6c**). Thus, the reaction mixture was subjected to acylation with benzoyl chloride (**3.6d**) or Negishi coupling (**3.6e**) with alkenyl iodide to provide the corresponding products instead of hydrolysis.



Scheme 3-6. Rhodium-catalyzed carbozincation of ynamides.

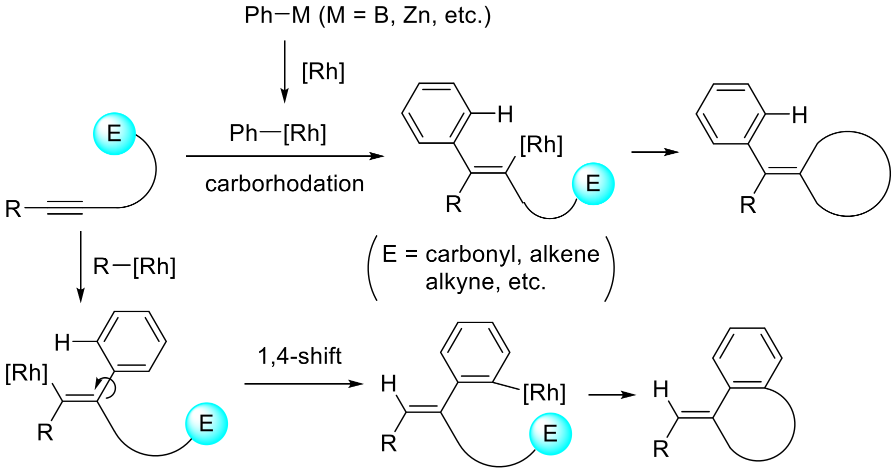
To date, only limited studies on rhodium-catalyzed addition of arylzinc reagents to unactivated alkyne are reported, and this field remains to be explored. In 2018, Hayashi reported the first example of rhodium-catalyzed arylzincation of unfunctionalized alkynes with good yields and regioselectivities (Scheme 3-7).[28] Catalytic amount of $ZnCl_2$ was found to be essential for the transformation, and the ligands are influencing product formation Alkenylzinc chloride **3.7a** was formed with cod as the ligand; while *ortho*-alkenylarylzinc species **3.7c** was generated in the presence of binap. It was suggested that the 1,4-rhodium shift is an intramolecular reaction and is not strongly affected by the ligand. On the contrary, transmetalation is an intermolecular reaction, and the use of a smaller ligand (cod in this case) accelerates this process. Fast transmetallation promoted by cod as the ligand resulted in **3.7a** as the major product while slow transmetallation with binap led to **3.7c** as the major product.



Scheme 3-7. Selective 1,4-rhodium shift control by ligands.

3.2. Cascade reactions

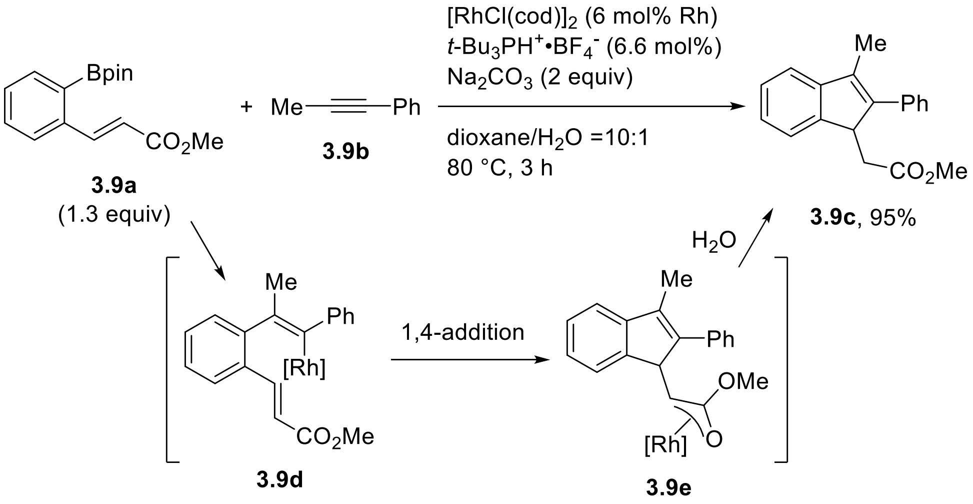
Transition metal-catalyzed cascade reactions allow multiple C-C bond formation in one pot, and it is one of the most powerful methods for constructing complex molecules.[29] The tandem reaction of the generated organorhodium was made possible by substrate development.[14,15] Like other organometallic species, the organorhodium undergoes addition to other electrophiles or unsaturated components to form cyclic or acyclic compounds. In general, the reaction proceeded by generating R-Rh species from transmetallation, and subsequent insertion to alkyne gave the corresponding alkenylrhodium intermediate. This intermediate can then react with an electrophile directly or undergo a 1,4-rhodium shift to generate a new organorhodium species before reacting with an electrophile. (Scheme 3-8).



Scheme 3-8. A general reaction scheme of rhodium-catalyzed tandem reactions.

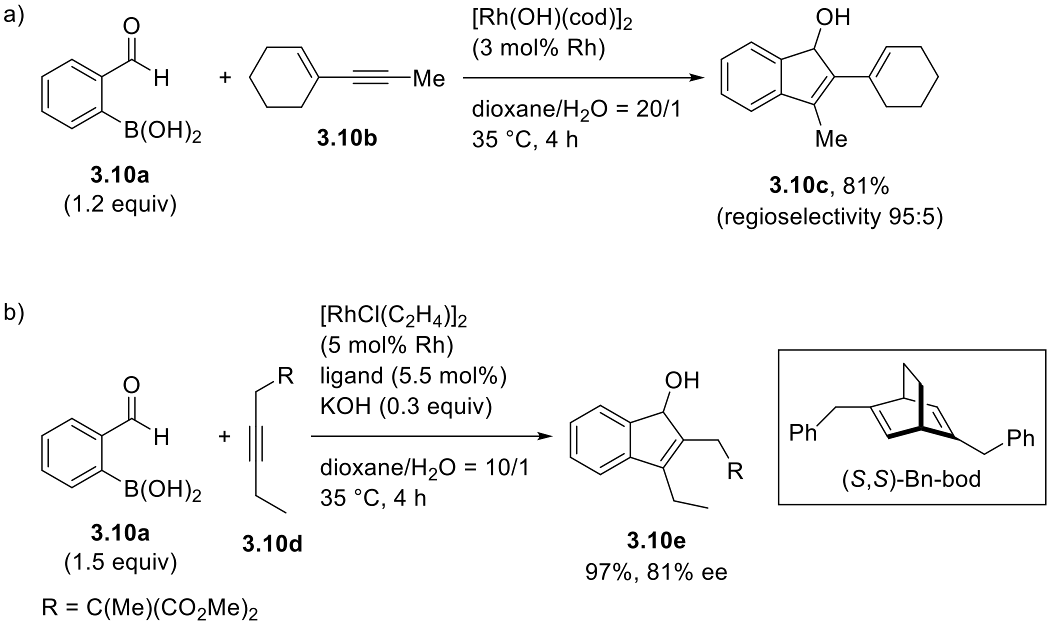
3.2.1. Use of functionalized organoboron reagents

One strategy is to utilize a bifunctional organoboron reagent bearing an unsaturated component at the *ortho*-position. This approach was realized by Lautens, as shown in Scheme 3-9.[30] In this report, the authors applied a functionalized arylboronate ester such as **3.9a**, which contains an α,β-unsaturated ester at *ortho*-position. The reaction proceeded via carborhodation of the alkyne (**3.9d**), followed by an intramolecular 1,4-addition (**3.9e**) to provide 1*H*-indene (**3.9c**) in good yield. The use of tri-*tert*-butylphosphine, which is an electron-rich and bulky ligand, stabilizes the organorhodium and inhibits protodeborylation.[31]



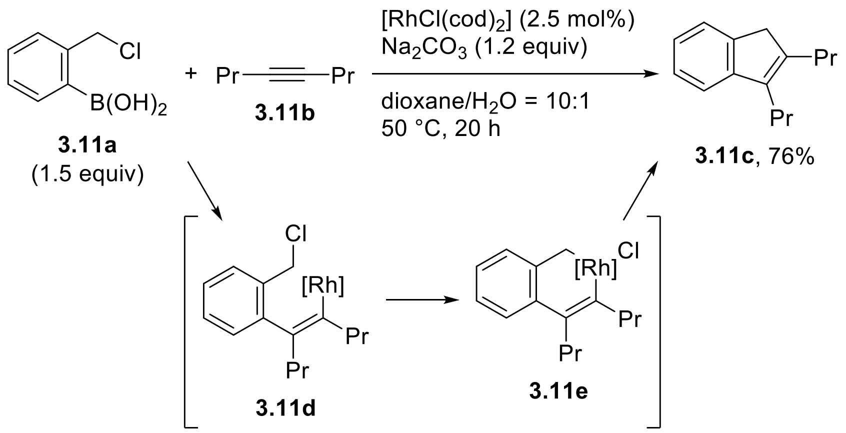
Scheme 3-9. Rhodium-catalyzed tandem alkyne addition/1,4-addition.

A rhodium-catalyzed reaction of 2-formyl substituted arylboronic acids with alkynes has been developed to give 1*H*-inden-1-ol in good yield (Scheme 3-10).[32] Unsymmetrical alkyne such as **3.10b** was also applied with high regioselectivities (**3.10c**). An enantioselective variant was also illustrated in the same report. A chiral diene ligand (*S*,*S*)-Bn-bod, developed by Hayashi, was employed to give indenol in excellent regio- and enantioselectivity (**3.10e**). The reaction of 2-acetyl phenylboronic was reported to give good yields of 1-methyl-1*H*-inden-1-ol, albeit under a higher temperature.[17]



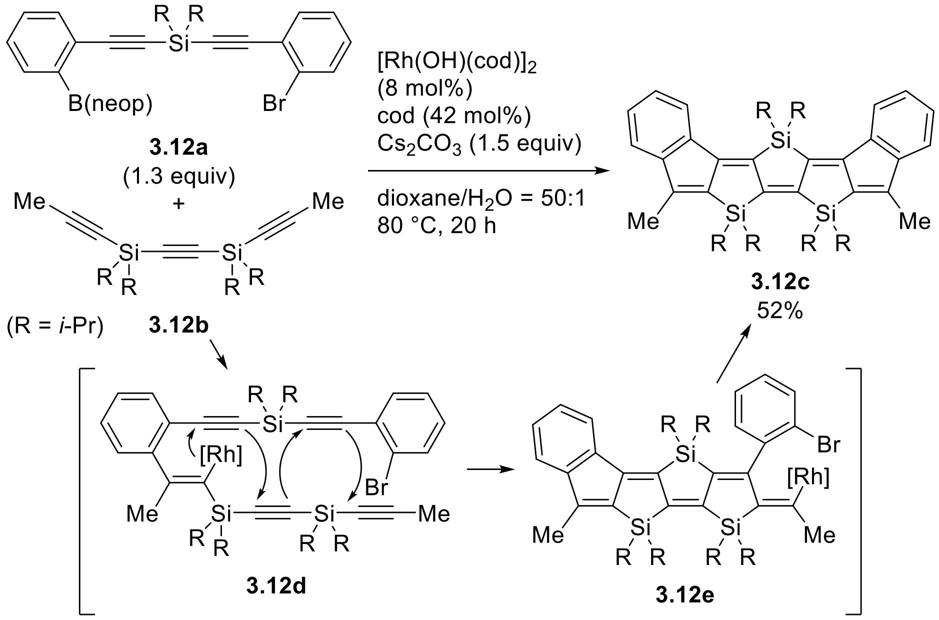
Scheme 3-10. Enantioselective formation of indenol by rhodium/chiral diene catalysis.

In 2008, Chatani reported a rhodium-catalyzed cyclization of 2-(chloromethyl)phenylboronic acids and alkynes to give indene derivatives (Scheme 3-11).[33] Upon the generation of alkenylrhodium by alkyne insertion (**3.11d**), oxidative addition to an adjacent C-Cl bond then occurred (**3.11e**). The resulting rhodium(III) intermediate underwent reductive elimination to furnish the product (**3.11c**).



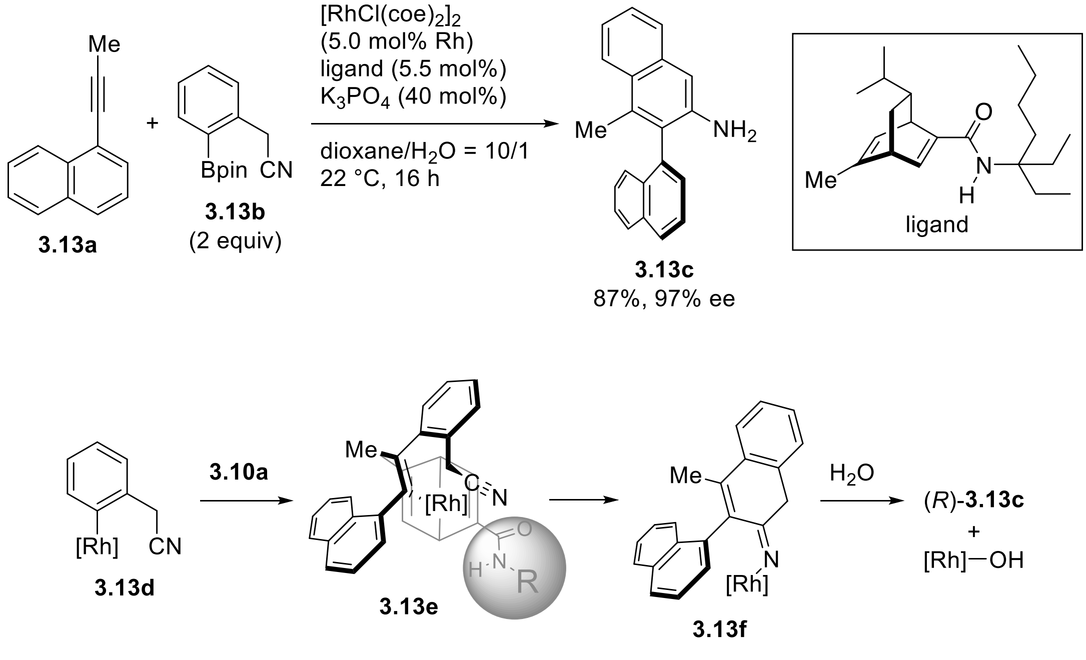
Scheme 3-11. Rh-catalyzed cyclization of 2-(chloromethyl)phenylboronic acid and alkyne.

A rhodium-catalyzed "stitching" cyclization was used to synthesize quinoidal fused oligosiloles (Scheme 3-12).[34] The reaction proceeded by the addition of initially generated arylrhodium to the alkyne to give the alkenylrhodium (**3.12d**). The addition was repeated intramolecularly until the formation of intermediate **3.12e** where a nearby C-Br bond is presented. Subsequent oxidative insertion and reductive elimination gave the final product **3.12c**.



Scheme 3-12. Synthesis of quinoidal fused oligosiloles.

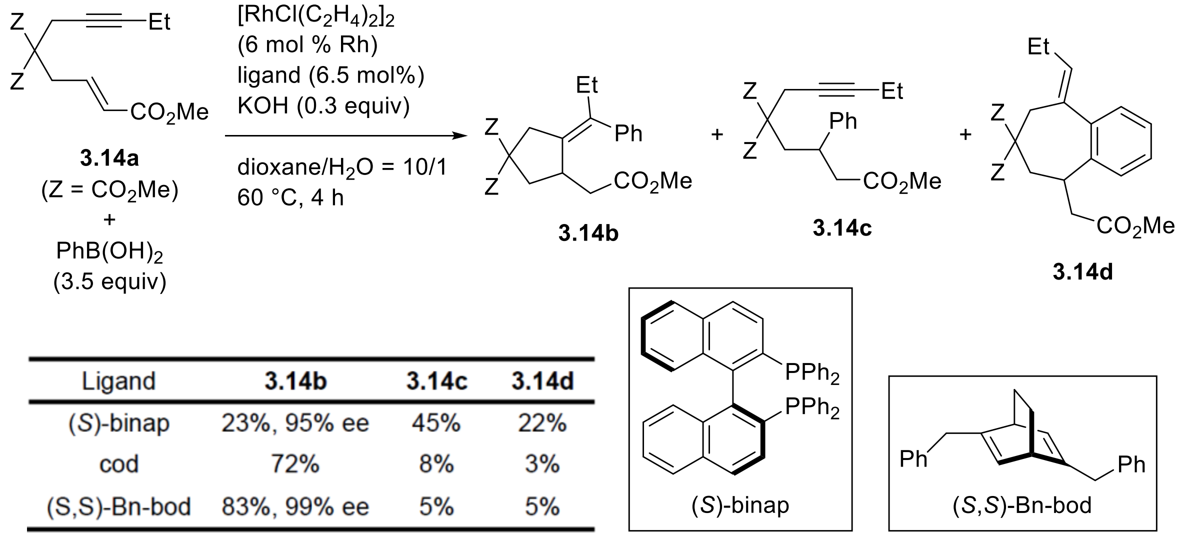
Rapid construction of axially chiral biaryls was realized with rhodium-catalyzed benzannulation of 1-arylalkynes with 2-(cyanomethyl)phenylboronates (Scheme 3-13).[35] In the presence of a chiral diene, the resulting axially chiral 2-aminobiaryl such as **3.13c** was obtained in 87% yield with 97 % ee. Carborhodation of the alkyne first occurred before the enantioselective intramolecular addition of the cyanide group, where the alkenyl-rhodium intermediate adopted the conformation like **3.13e** to avoid the steric repulsion between the naphthyl group and bulky amide moiety in the ligand. Hydrolysis of the generated imino-rhodium intermediate (**3.13f**) subsequently afforded the product.



Scheme 3-13. Rhodium-catalyzed asymmetric synthesis of axially chiral 2-aminobiaryls.

3.2.2. Michael acceptor as the second nucleophile

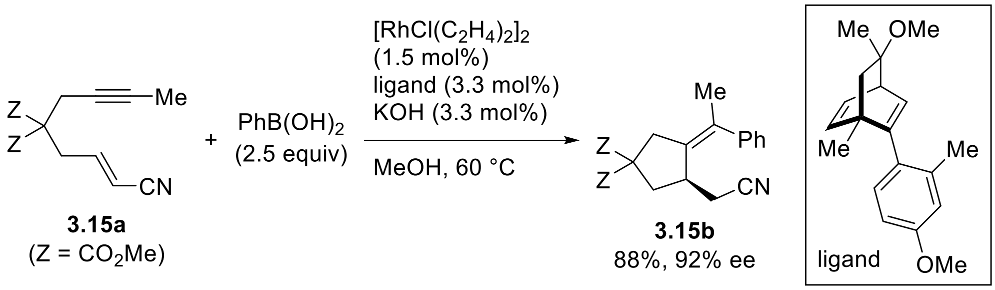
On the other hand, the cascade strategy can be accomplished by using alkyne substrates with another unsaturated functional group in an appropriate position. As shown in Scheme 3-14, an enantioselective cascade addition to 1,6-enyne was achieved in the presence of a chiral diene/rhodium catalyst.[36] An alkenylrhodium intermediate was first generated by regioselective arylrhodation. This is followed by an enantioselective addition to the pendant α,β-unsaturated ester in a 5-*exo* fashion to give compound **3.14b**. It is well known that rhodium complexes catalyzed both arylrhodation of alkyne and 1,4-addition to unsaturated esters[37] and that the choice of ligand affects the reaction sequence. Compound **3.14c** was formed by direct 1,4-addition, while **3.14d** was formed by sequential reactions constituting of 1,4-addition, 1,4-rhodium shift, and alkyne addition. The experimental results from Scheme 3-14 indicated that a Rh/binap complex favored 1,4-addition, while a Rh/diene complex had higher reactivity towards alkyne addition.



Ligand	3.14b	3.14c	3.14d
(*S*)-binap	23%, 95% ee	45%	22%
cod	72%	8%	3%
(S,S)-Bn-bod	83%, 99% ee	5%	5%

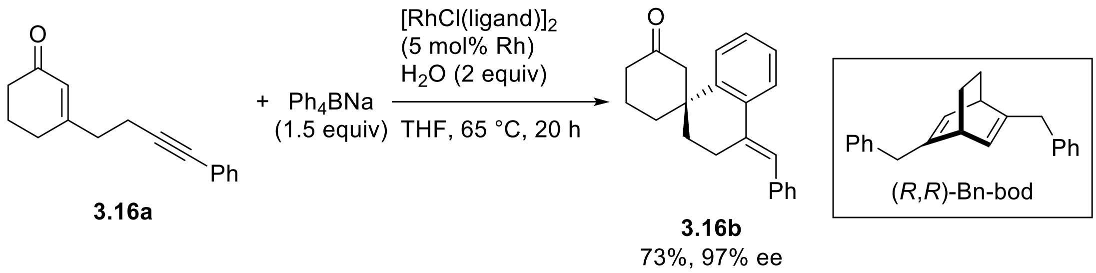
Scheme 3-14. Enantioselective cascade addition of 1,6-enyne.

While the bod type diene ligand worked well for α,β-unsaturated ester, the analogous α,β-unsaturated nitrile was generally not satisfactory.[38] Darses found the use of a chiral diene ligand allowed the intermolecular addition of conjugated nitrile (**3.15a**) whereas no product was formed when (*R*,*R*)-Ph-bod was used (Scheme 3-15). The cyano-containing 5-membered carbocycle (**3.15b**) was obtained in good yield and high enantioselectivity.[39]



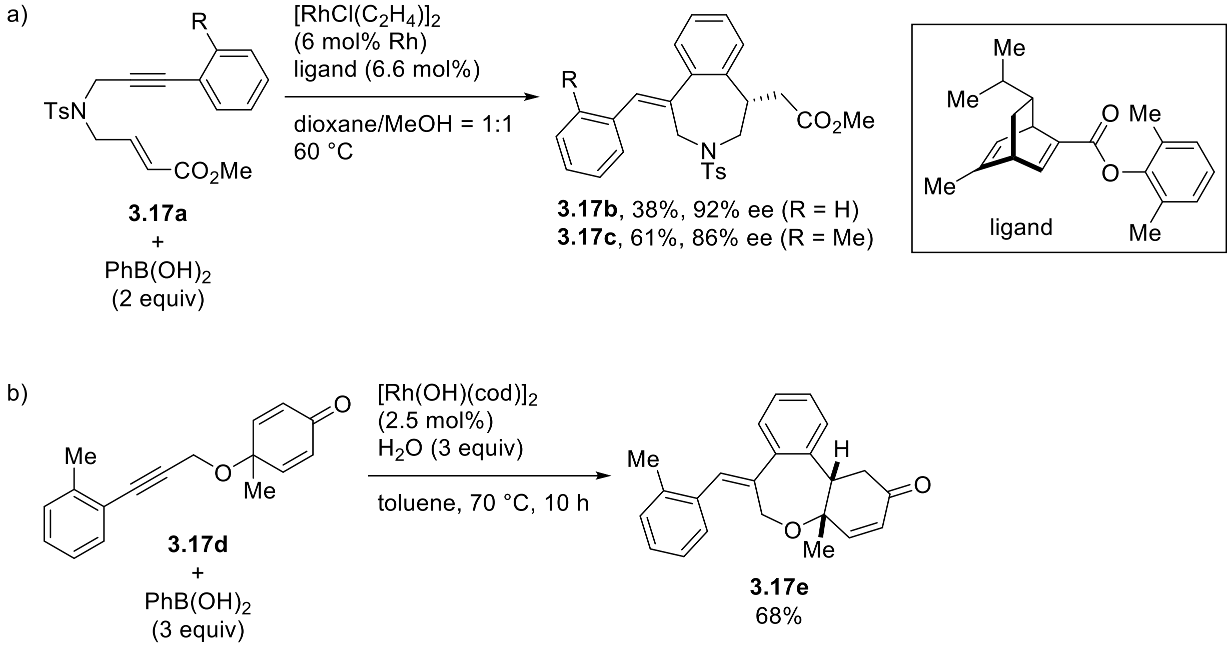
Scheme 3-15. Arylative cyclization of α,β-unsaturated nitrile-containing 1,6-enynes

Alternatively, opposite regioselectivity of the first insertion of alkynes was found with the use of aryl-substituted alkynes. For example, Hayashi reported the rhodium-catalyzed arylative cyclization of alkyne-tethered 2-cycloalken-1-ones (**3.16a**) with sodium tetraarylborates (Scheme 3-16).[40] The use of a chiral diene ligand (*R*,*R*)-Bn-bod provided the spirobicyclic ketones with a quaternary spirocarbon stereocenter **3.16b** in high yields and enantiopurities.



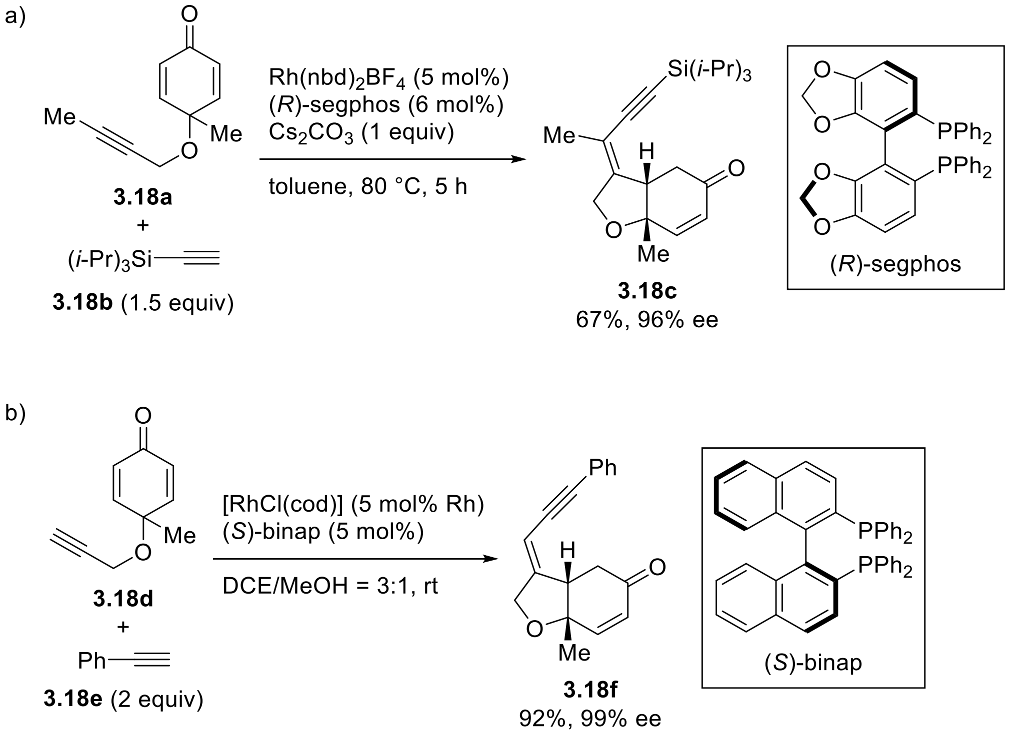
Scheme 3-16. Rhodium-catalyzed asymmetric synthesis of spirocarbocycles.

Darses reported the rapid synthesis of *N*-tosyl azepane in the presence of a rhodium/chiral diene complex. As shown in Scheme 3-17a, the use of aryl-substituted alkyne (**3.17a**) led to the favorable formation of seven-membered ring heterocycles (**3.17b–c**).[41] It was shown that the use of an *ortho*-tolyl group attached to the alkyne moiety was required to provide good regioselectivity of the alkyne arylrhodation step. In contrast, five-membered ring heterocycles were formed exclusively when alkylalkynes were used.[42] A similar strategy was also demonstrated by Zhao and co-workers, where cyclohexadienone-tethered o-tolyl-substituted alkynes such as **3.17d** were used to give hydrobenzo[*b*]oxepine **3.17e** (Scheme 3-17b).[43]



Scheme 3-17. Synthesis of seven-membered heterocycles.

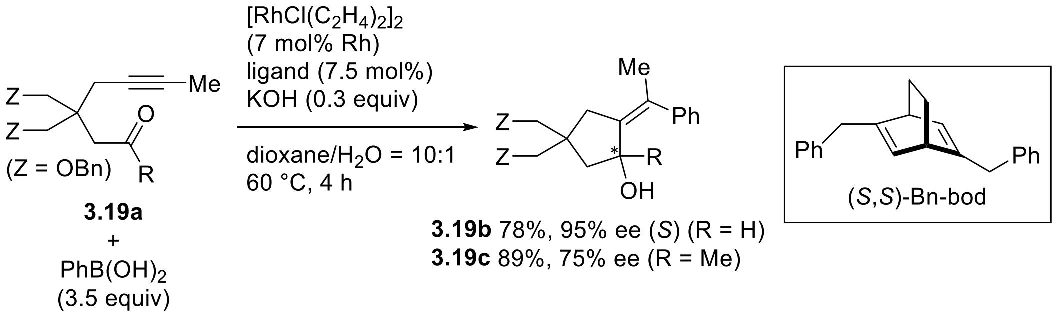
Despite the extensive use of organoboron reagents, alkynes were also reported as coupling partners in rhodium-catalyzed reactions.[44] In 2019, Lin[45] and Xu[46] independently reported the rhodium-catalyzed alkynylative cyclization of alkyne-tethered cyclohexadieonones[47] (**3.18a** and **3.18d**) to afford *cis*-hydrobenzofuran frameworks (**3.18c** and **3.18f**) in good yields and excellent enantioselectivities (Scheme 3-18).



Scheme 3-18. Rhodium-catalyzed alkynylation of alkyne-tethered cyclohexadieonones.

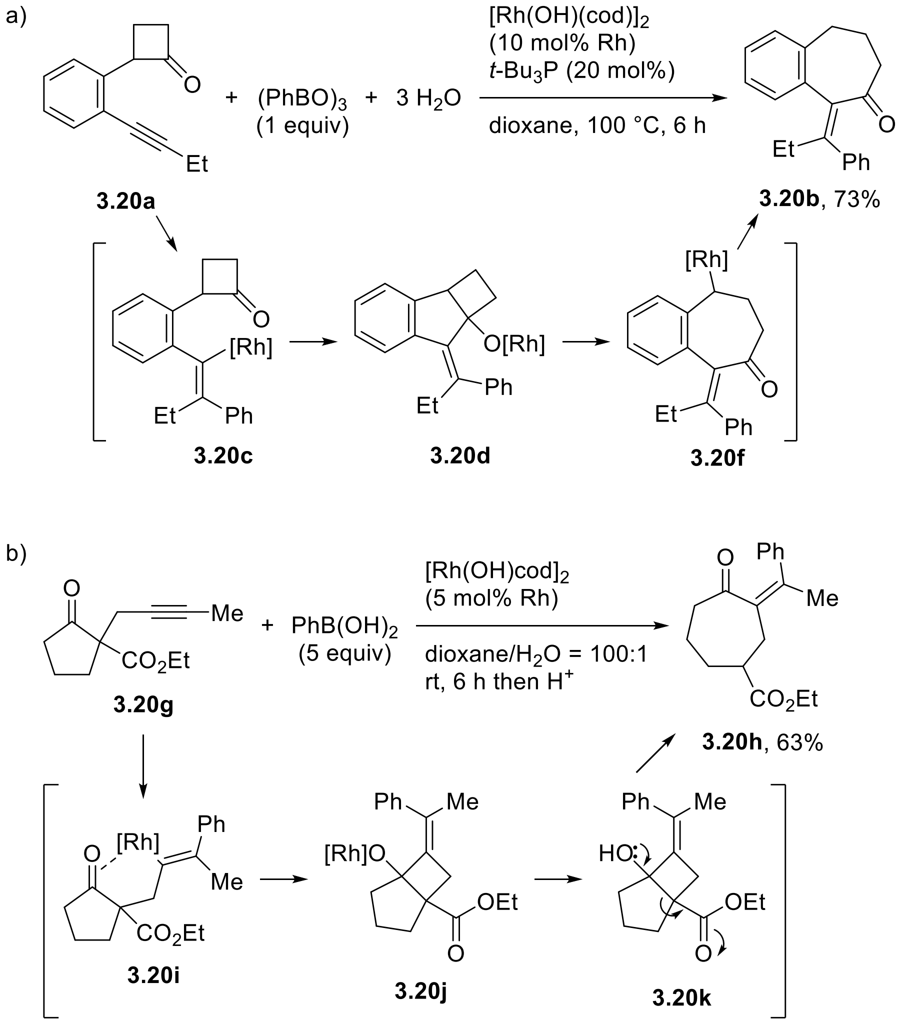
3.2.3. Carbonyl and its derivatives as the second nucleophile

In 2005, Hayashi reported the rhodium-catalyzed asymmetric arylative cyclization of alkynals (Scheme 3-19).[48] Upon the regioselective arylrhodation of the alkyne, the alkenylrhodium intermediate underwent enantioselective nucleophilic addition to the aldehyde or ketone, providing the cyclic allylic alcohols (**3.19b**–**c**). The superior reactivity of a diene ligand (*S*,*S*)-Bn-bod led to the formation of allylic alcohols in high yields and enantioselectivities, while phosphine ligands gave poor results. Murakami also reported the use of ketones as electrophiles in a later report.[49]



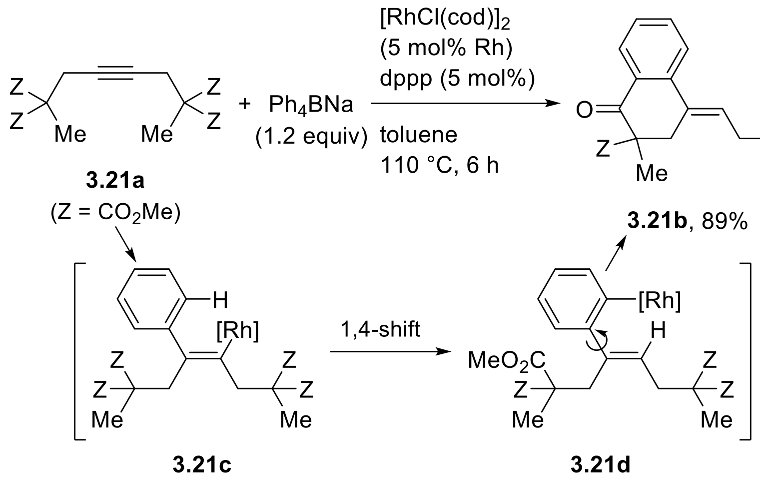
Scheme 3-19. Rhodium-catalyzed asymmetric arylative cyclization of alkynals.

In another study, Murakami disclosed an interesting ring-expansion reaction with rhodium-catalyzed acyl 1,3-migration of acetylenic β-ketoesters (Scheme 3-20a).[50] When an alkyne-substituted cyclobutanone (**3.20a**) was used, the addition of alkenylrhodium to the cyclobutanone under aprotic conditions (**3.20c**) resulted in β-carbon elimination (**3.20f**) to provide a two-carbon ring-expansion product (**3.20b**). A series of seven-membered ring ketones were obtained in moderate to high yields. In their later report, it was found that a cyclobutanol intermediate **3.20k** was obtained after chromatographic isolation (Scheme 3-20b) when the reaction was conducted in a protic solvent (dioxane/H_2O = 10:1).[51] In a one-pot protocol, where upon the generation of cyclobutanol, the ring expansion product was provided after the treatment with acid by a retro-aldol process. The reaction was extended to the formation of five- to eight-membered ring ketones in good yields.



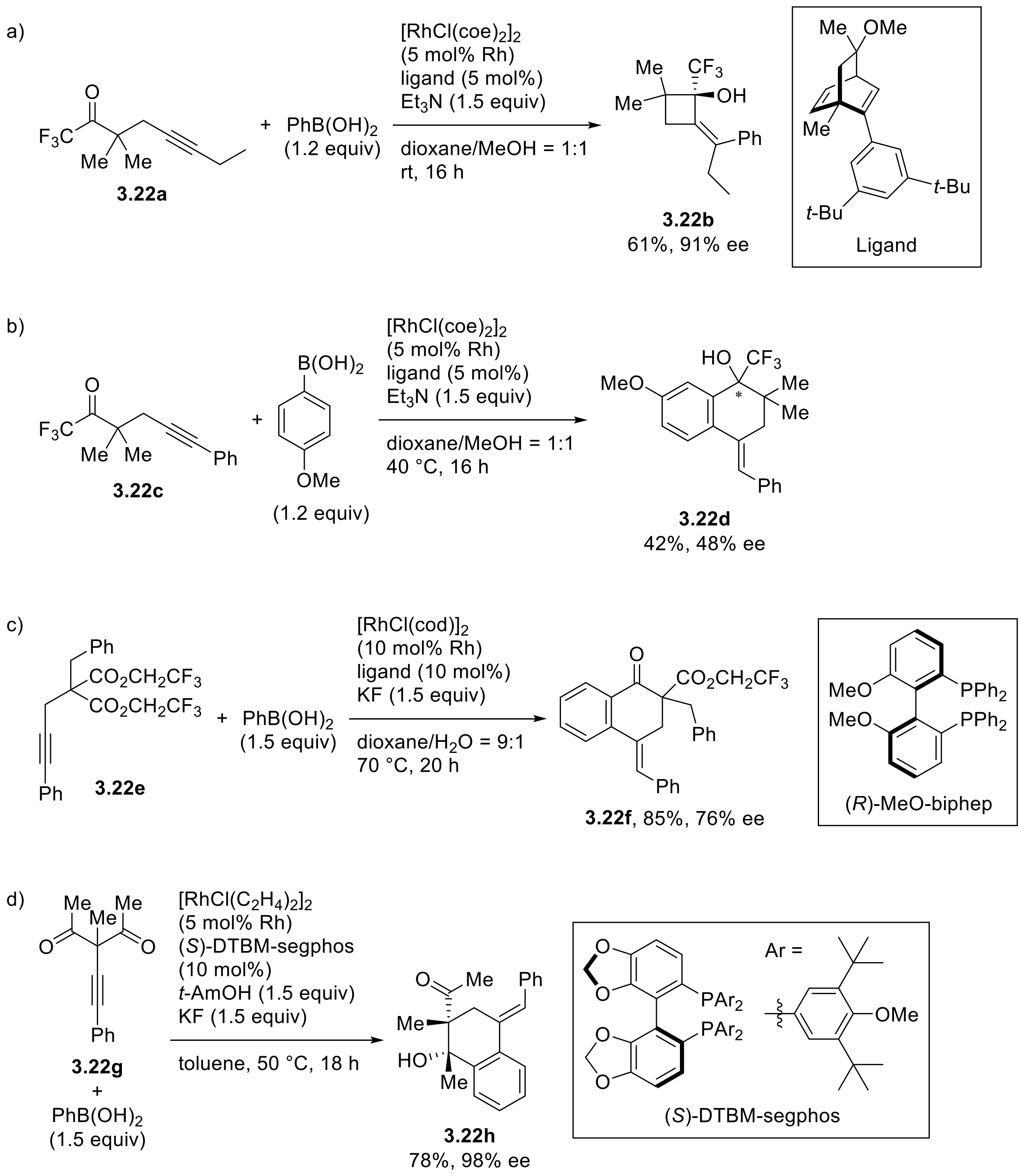
Scheme 3-20. Seven-membered ring formations by a two-carbon ring expansion.

An efficient α-teralone synthesis was achieved by Murakami in 2005 (Scheme 3-21).[52] Ph_4BNa in anhydrous condition was found to be an optimal choice for this reaction. In the report, the generated alkenylrhodium underwent 1,4-rhodium shift before acylation with the ester group, which served as a secondary electrophile to produce the product.



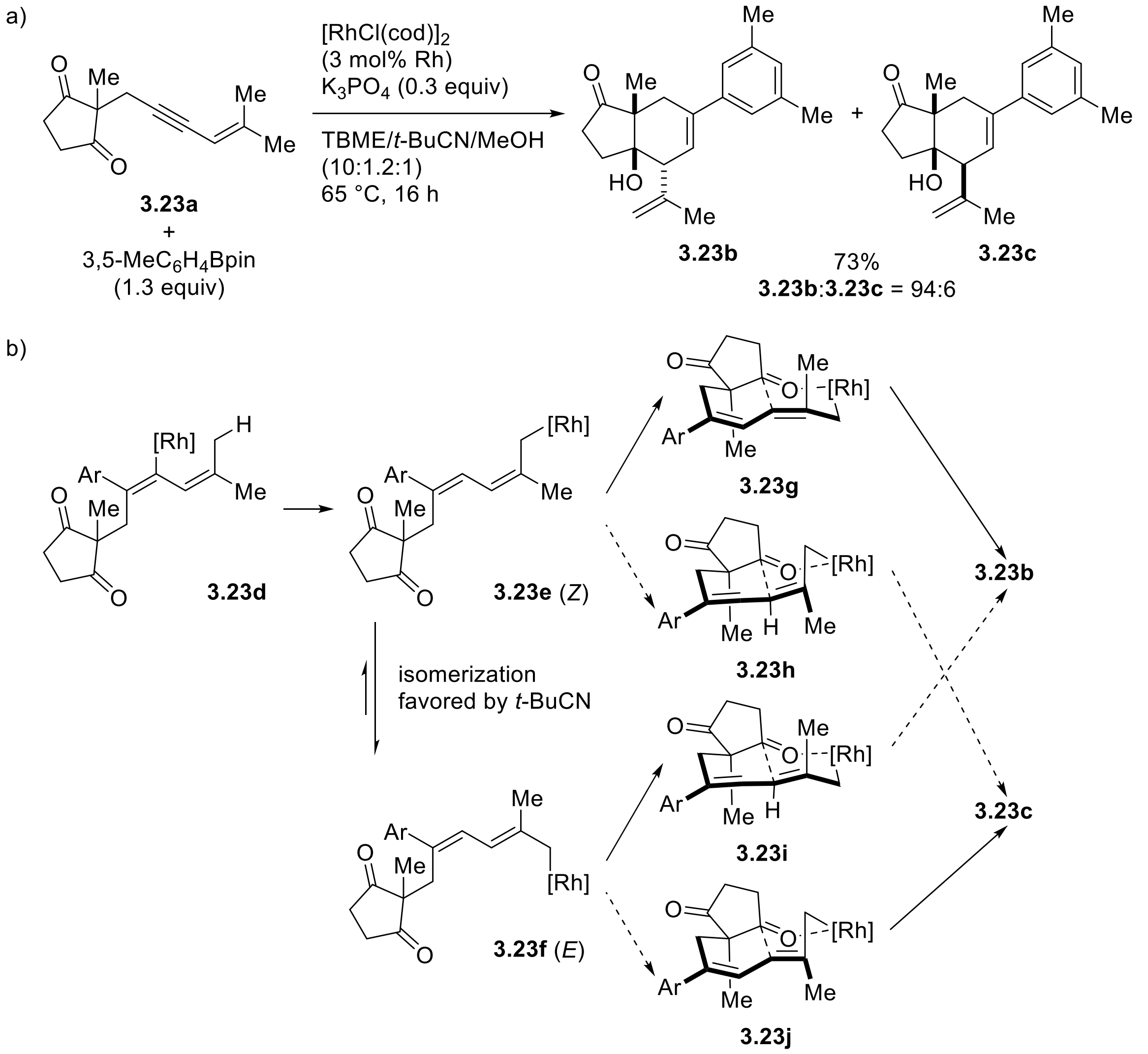
Scheme 3-21. α-Teralone synthesis promoted by a rhodium catalyst.

Rhodium catalyzed arylative cyclization with **3.22a** was also applied to synthesize enantioenriched trifluromethylated cyclobutanol.[53] Among all the diene ligands screened, the ligand illustrated in Scheme 3-22a provided the best enantioselectivity and yield. When the alkyne substituted with an aryl group (**3.22c**) was used, the opposite regioselectivity for the alkyne insertion step was observed as expected, leading to the formation of **3.22d** in a moderate yield and %ee (Scheme 3-22b). In a similar context, Lam reported a ligand-free rhodium-catalyzed arylative cyclization of alkynyl malonates to obtain 1-tetralones. In the presence of a chiral bisphosphine ligand (*R*)-MeO-biphep, the desymmetrization provided a quaternary stereocenter in moderate enantioselectivity (Scheme 3-22c).[54] Later, the same group reported the highly enantioselective cyclization of alkynyl 1,3-diketones to generate tetralol with a sterically hindered ligand (*S*)-DTBM-segphos (Scheme 3-22d).[55]



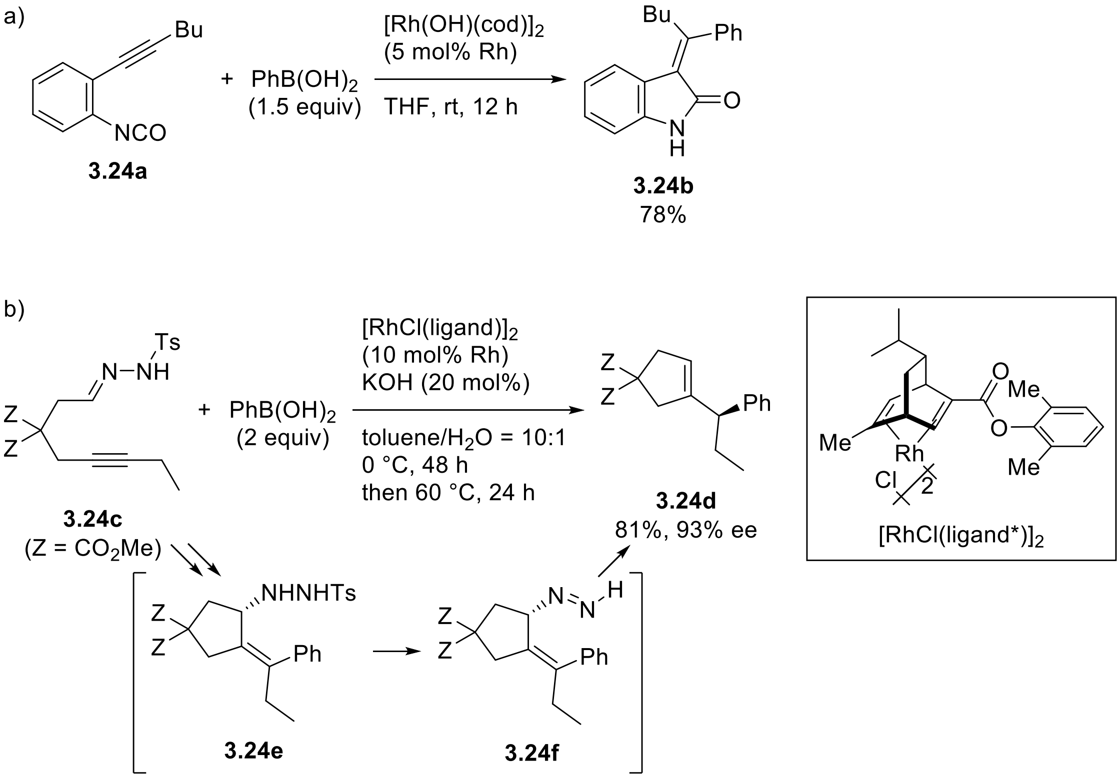
Scheme 3-22. Rhodium-catalyzed arylative cyclization of alkynyl esters and ketones.

In 2017, Lam reported a rhodium-catalyzed arylative allylation of enynones with arylboron reagents using substrates **3.23a** (Scheme 3-23).[56] The key to this transformation was the 1,4-shift from the alkenylrhodium **3.23d** to allylrhodium **3.23e**. When a 3,5-disubstituted arylboron reagent was used, in which a slower 1,4-rhodium shift was observed as reported previously,[53] the rhodium migration to the allyl position was more favorable. Succeeding allylative cyclization onto the ketone furnished the product with good diastereoselectivity. The authors also observed the reversed diastereoselectivity when using THF/MeOH as the solvent. It was proposed that (*Z*)-**3.23e** was formed upon the 1,4-rhodium shift and led to the formation of **3.23g** via a six-membered chair-like arrangement, with the boat-like arrangement **3.23h** being less favorable. On the contrary, when a coordinating solvent, such as *t*-BuCN was presented, the cyclization was slower, and the isomerization from (*Z*)-**3.23e** to (*E*)-**3.23f** occurred. Similarly, (*E*)-**3.23f** undergoes cyclization in a chair-like arrangement to give **3.23b**.



Scheme 3-23. Rhodium-catalyzed allylation of ketones with 1,3-enynes.

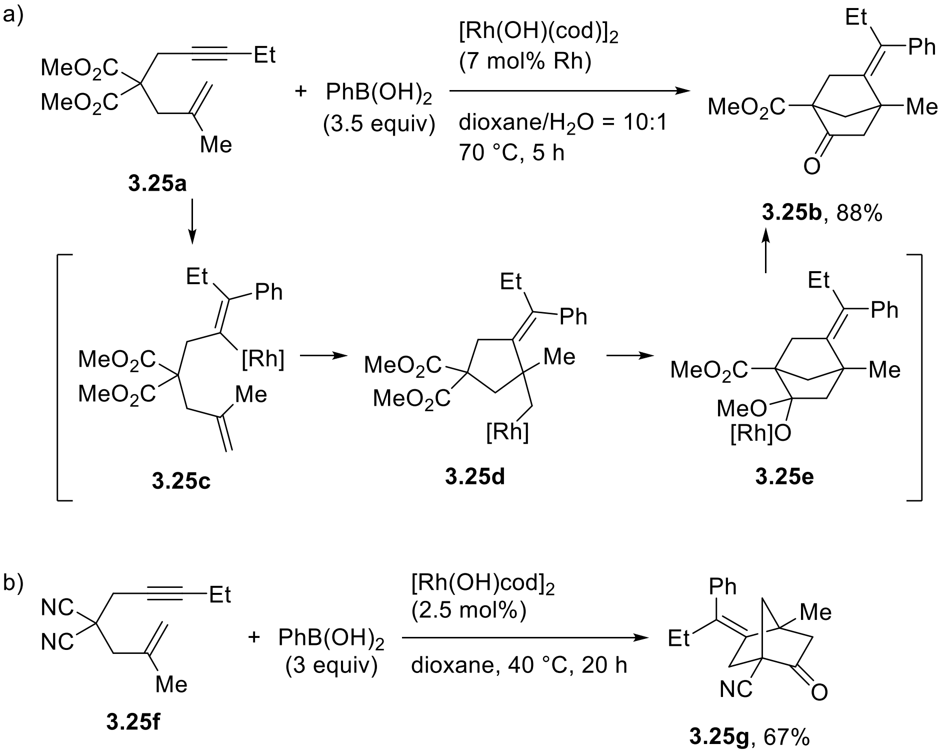
Analogs of the carbonyl group were also reported in rhodium-catalyzed cyclizations. For example, Murakami reported the use of 2-alkynylaryl isocyanates for the synthesis of 3-alkylideneoxindoles in a stereoselective manner (Scheme 3-24a).[57] In another example, Lee reported an asymmetric synthesis of enantioenriched cycloalkene with 2-alkynyl hydrazones (Scheme 3-24b).[58] The rhodium-catalyzed arylative cyclization first generated hydrazide **3.24e**, before undergoing an intramolecular retro-ene reaction to give the final product.



Scheme 3-24. Rhodium-catalyzed arylative cyclizations with functionalized alkynes.

3.2.4. Unactivated alkene as the second nucleophile

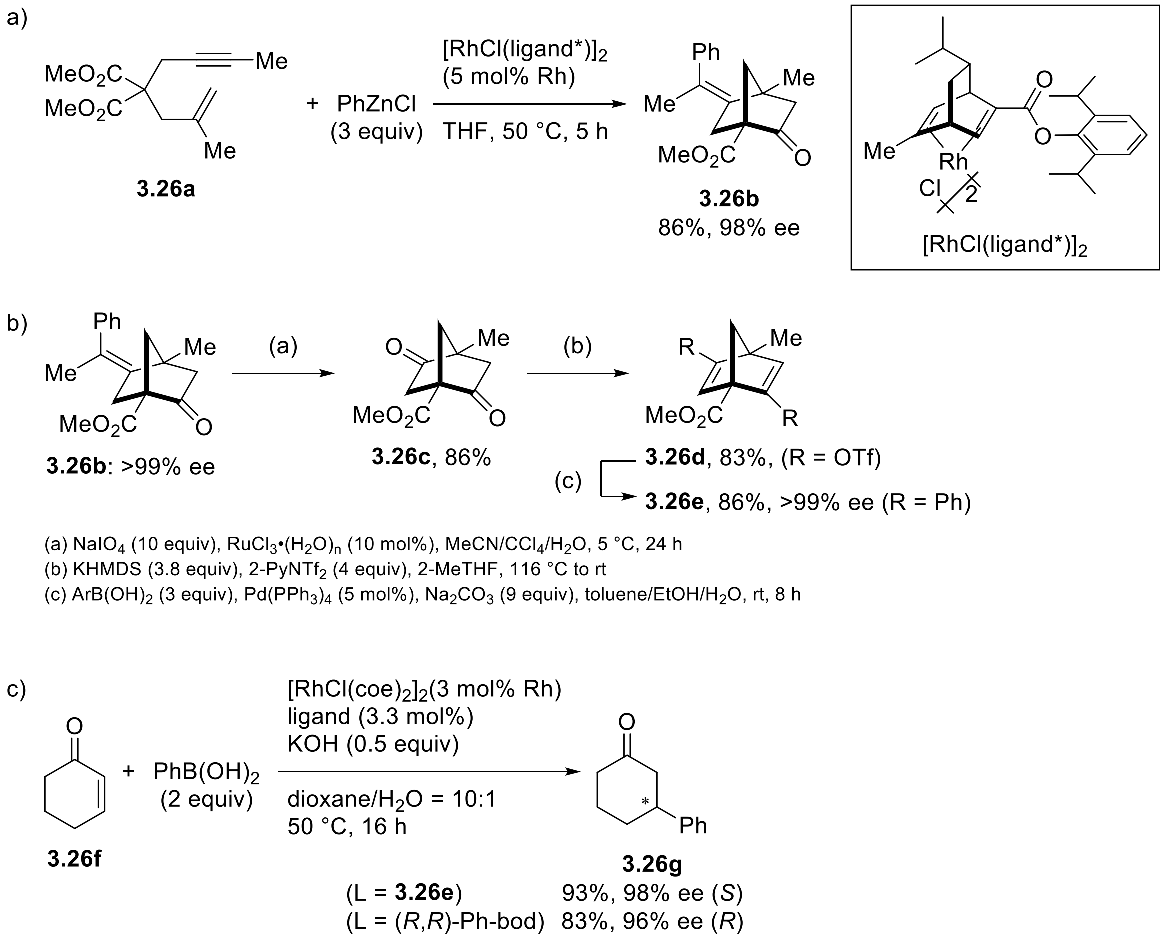
Multi-bond forming reactions can be realized by appropriate substrate design. Hayashi reported a multistep reaction in 2001, where bicyclo[2.2.1]heptan-2-one **3.25b** was formed in good yield (Scheme 3-25a).[48] Initial arylrhodation of alkyne gave an alkenylrhodium intermediate (**3.25c**) and successive 5-*exo* cyclization with an intramolecular methyl allyl moiety led to an alkylrhodium species (**3.25d**). Subsequent addition to ester carbonyl followed by β-oxygen elimination would provide the product **3.25b**. It should be noted that this is the first report where an alkylrhodium undergoes acylation with an ester to give a ketone. Similarly, when a 1,6-enyne was tethered through a malononitrile backbone **3.25f**, a bicyclic nitrile **3.25g** was obtained (Scheme 3-25b).[59]



Scheme 3-25. Bicyclo[2.2.1]heptan-2-one synthesis by a cascade reaction.

Almost at the same time, Murakami reported the enantioselective version of the reaction as shown in Scheme 3-25a, where (*R*)-binap was used as the chiral ligand, giving the product in moderate yield and 94% ee.[52] An improved synthesis was recently demonstrated by Hayashi where phenylzinc chloride was used instead of phenylboronic acid (Scheme 3-26a).[60] In the presence of a rhodium/chiral diene catalyst, the bicyclic compound **3.26b** was obtained in excellent yield as well as enantioselectivities (89% yield, 98% ee). It was readily transformed into a new type of bicyclo[2.2.1]heptadiene (nbd) ligand in three steps (Scheme 3-26b): A ruthenium-catalyzed oxidation of the tetra substituted alkene furnished the chiral diketone

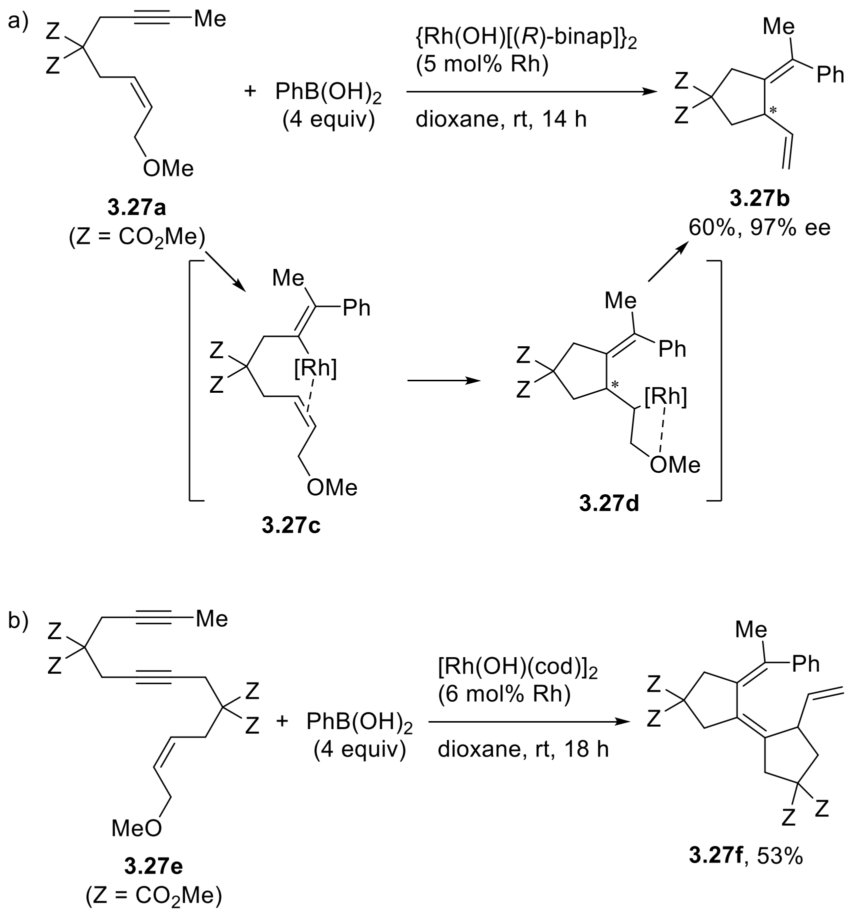
3.26c,[61] and it was converted to the corresponding ditriflate **3.26d** using KHMDS and 2-PyNTf in cryogenic condition.[62] Subsequent Suzuki coupling of **3.26d** with arylboronic acid furnished **3.26e**[63] without any loss of enantiopurity. The newly synthesized ligand **3.26e** showed improved stability compared to previously reported nbd type ligands that readily decomposed in solution or under light.[64] This ligand exhibited good catalytic activity and enantioselectivity in rhodium-catalyzed asymmetric 1,4-addition of aryl/alkenylboronic acids to α,β-unsaturated ketones or esters (Scheme 3-26c).[37]



(a) $NaIO_4$ (10 equiv), $RuCl_3{\bullet}(H_2O)_n$ (10 mol%), $MeCN/CCl_4/H_2O$, 5 °C, 24 h
(b) KHMDS (3.8 equiv), 2-$PyNTf_2$ (4 equiv), 2-MeTHF, 116 °C to rt
(c) $ArB(OH)_2$ (3 equiv), $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (9 equiv), toluene/EtOH/H_2O, rt, 8 h

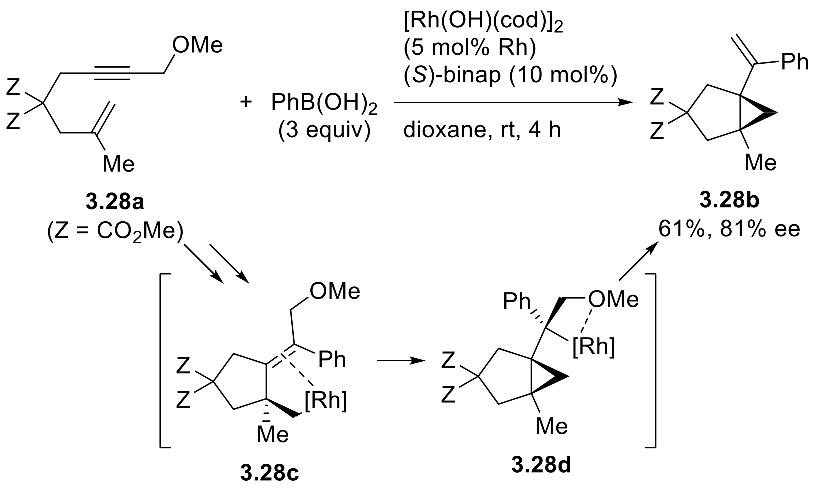
Scheme 3-26. Synthesis of a chiral nbd type ligand through rhodium-catalyzed cyclization.

In 2005, Murakami reported a cascade reaction using **3.27a**, where the 1,6-enyne was bearing a methoxy group at the allylic position, and the generated alkylrhodium intermediate **3.27d** undergoes β-oxygen elimination to give an alkene in preference to nucleophilic attack on the ester carbonyl group (Scheme 3-27).[65] A domino cyclization using enediyne **3.27e** gave a bicyclic triene derivative **3.27f** in 53% yield as a single isomer.



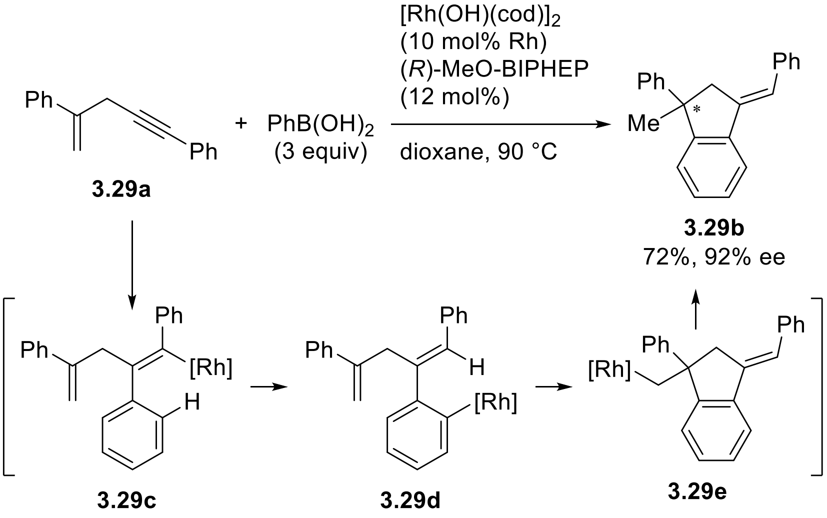
Scheme 3-27. Vinylcyclopentane derivatives formation by β-oxygen elimination.

When a methoxy group is at the propargylic position, the reaction proceeds in another pathway. As shown in Scheme 3-28, enyne **3.28a** was allowed to react with phenylboronic acid in the presence of a rhodium/(*S*)-binap complex, providing bicyclo[3.1.0]-hexane **3.28** in 61% yield and 88% ee.[66] Upon the generation of the alkylrhodium intermediate **3.28c**, the second carborhodation of alkene provided **3.28d** in a 3-*exo-trig* pathway. Eventual β-oxygen elimination afforded the desired product **3.28b**. It was proposed that the oxygen coordination to rhodium facilitated the formation of **3.28d** and the subsequent β-oxygen elimination was the driving force for the product formation.



Scheme 3-28. Vinylcyclopropane derivatives formation by β-oxygen elimination.

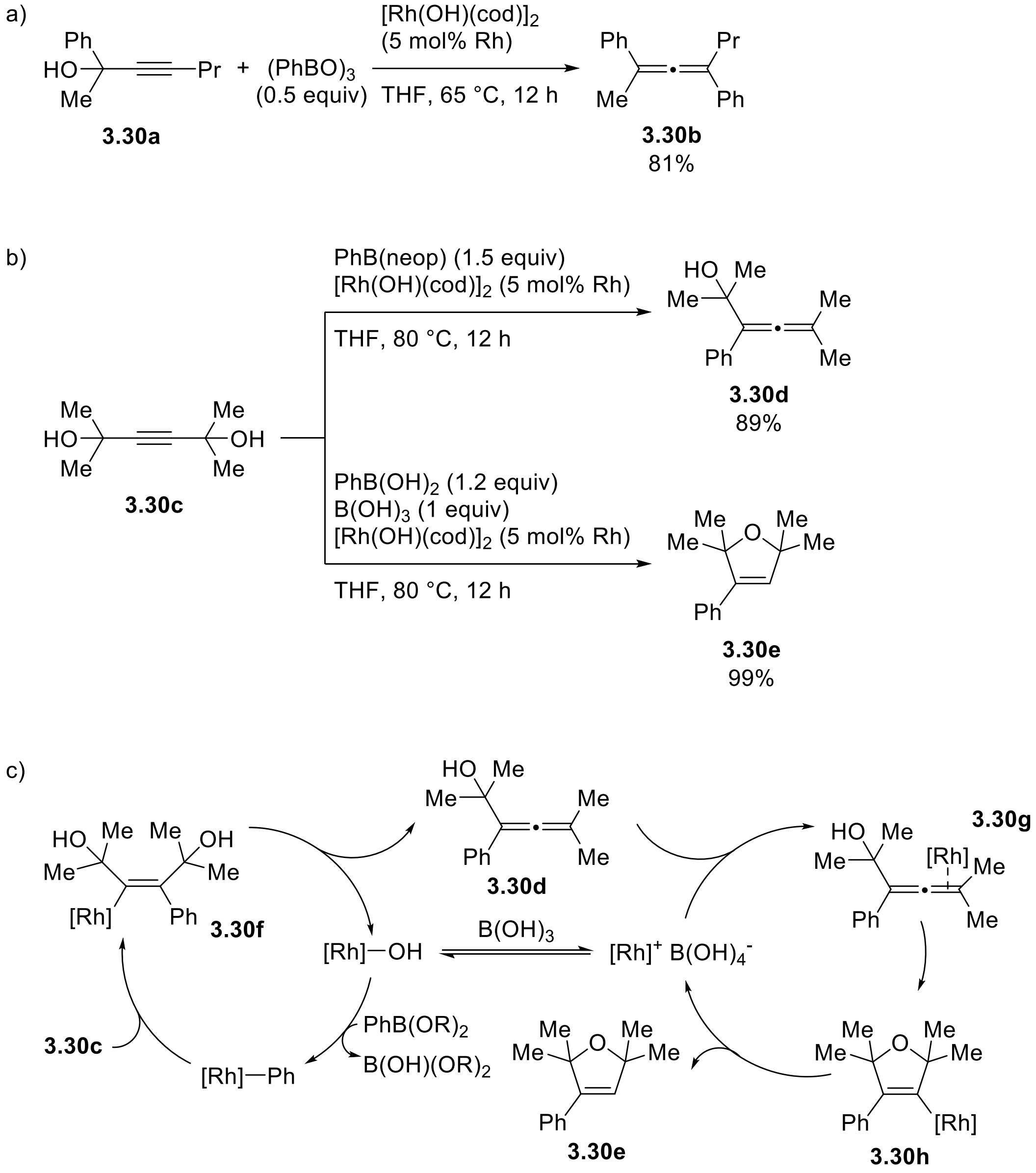
In 2015, Matsuda reported the synthesis of substituted indanes by a rhodium-catalyzed arylative cyclization of 1,4-enynes like **3.29a** with arylboronic acids (Scheme 3-29).[67] An asymmetric variant was developed with (*R*)-MeO-BIPHEP as the ligand to furnish a series of enantioenriched indanes with an all-carbon quaternary chiral center.



Scheme 3-29. Rhodium-catalyzed arylative annulation of 1,4-enynes.

3.2.5. Cascade β-elimination reactions

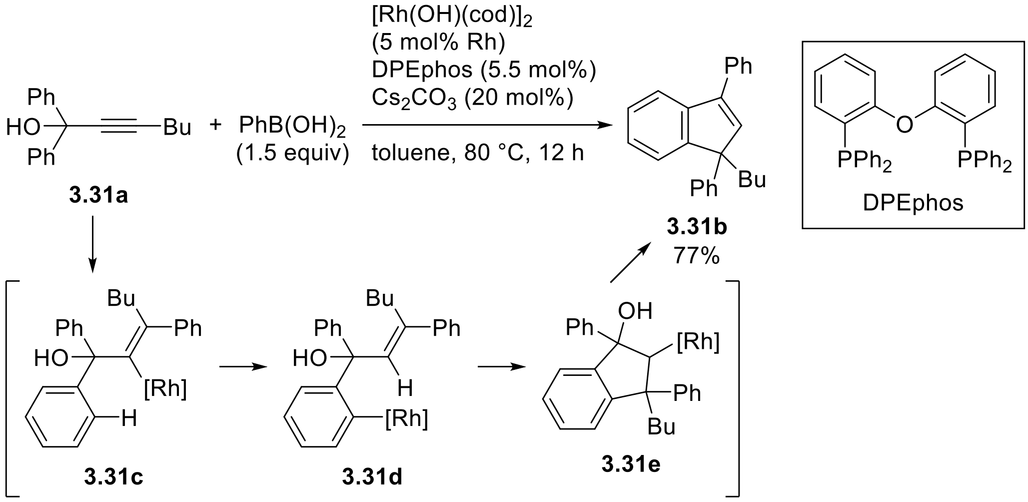
In 2017, Dow reported a rhodium-catalyzed arylation/dehydroxylation of *tert*-propargylic alcohols (**3.20a**) with arylboroxines to give tetrasubstituted allenes (Scheme 3-30a).[68] The reaction was proposed to be initialized by regioselective carborhodation of the alkyne, followed by the subsequent *syn*-β-oxygen elimination. In a later report, the same group reported a divergent synthesis of allenic alcohols and 2,5-dihydrofurans using propargylic diols by switching different organoboron reagents (Scheme 3-30b).[69]



Scheme 3-30. Rhodium-catalyzed additions to *tert*-propargylic alcohols.

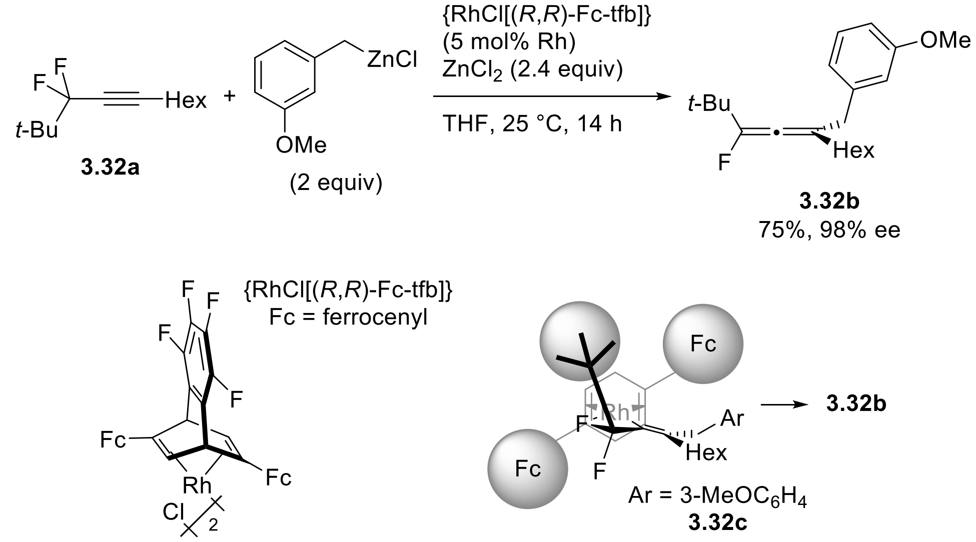
Allenic alcohol **3.30d** was produced by employing phenylboronic ester in a similar pathway illustrated in Scheme 3-30c. In contrast, the use of phenylboronic acid favored the formation of 2,5-dihydrofuran **3.30e**. It was suggested that in the presence of phenylboronic acid, **3.30d** was first generated before the ensuing formation of cationic rhodium complex **3.30g**. The complex served as a Lewis acid to trigger the cyclization to provide **3.30e** as the final product.

In 2019, Dou and Tian reported the cyclization of *tert*-propargylic alcohols with arylboronic acids to give indenes (Scheme 3-31).[70] In contrast to Dow's report (Scheme 3-30), the authors found that using a bisphosphine ligand, DPEPhos, facilitated the rhodium 1,4-shift process and suppressed β-oxygen elimination of **3.31c**. Upon cyclization, the alkylrhodium underwent β-oxygen elimination to furnish **3.31b**.



Scheme 3-31. Indene synthesis via arylative cyclization of *tert*-propargylic alcohols.

In 2021, Hayashi reported the synthesis of axially chiral fluorinated allenes by a rhodium/(*R*,*R*)-Fc-tfb complex using propargyl difluorides and alkylzincs (Scheme 3-32).[70] Alkenylrhodium **3.32c** was first generated which led to the enantioselective elimination of one of the enantiotropic fluorides at the β-position of rhodium to produce the product. The introduction of a sterically demanding tertiary alkyl group adjacent to the difluoromethyl group, such as *tert*-butyl, was essential to maintain high enantioselectivity.



Scheme 3-32. Enantioenriched fluorinated allene synthesis.

3.3. Conclusion

This chapter discussed the latest development of rhodium-catalyzed carborhodation of alkynes and the cascade reactions of the organorhodium intermediates. Since the seminal report by Hayashi, the research topic has been significantly studied. The regioselective addition of alkynes provided an alternative to synthesize multi-substituted alkenes. The use of well-designed substrates allowed cascade reactions for constructing complex molecules. High enantioselectivities were usually obtained with the employment of chiral ligands, especially chiral diene ligands. On the other hand, the 1,4-rhodium shift enabled the generation of new organorhodium species and further elaborate new reactivities. Nonetheless, in most of the examples, organoboron reagents were used to generate the organorhodium intermediates initially. The use of terminal alkynes and organozinc reagents was reported, but the studies are still limited. The objective of part B is to investigate the use of organozinc reagents in chiral diene/rhodium-catalyzed carbometallation of enynes to construct enantioenriched carbocycles by taking advantage of the rhodium-zinc transmetallation and the unique reactivity of organozinc reagents.

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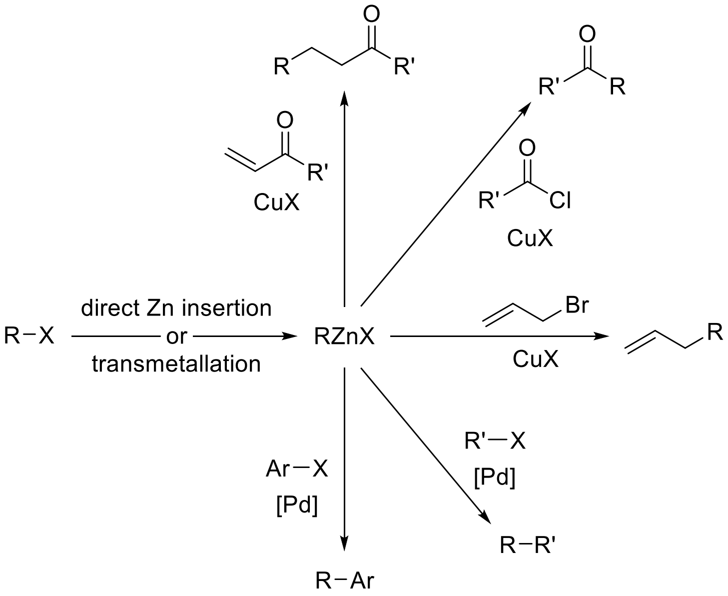
Chapter 4. Asymmetric synthesis of alkylzincs by rhodium-catalyzed enantioselective arylative cyclization of 1,6-enynes with arylzincs.

4.1. Introduction

Organozinc reagents have been widely used in organic synthesis since the first discovery of diethylzinc by Edward Frankland in 1849.[1] It has a lower reactivity than other analogous organometallic reagents, such as organomagnesium and organolithium reagents.[2] This feature allows both high functional group compatibility and relatively high reactivity towards electrophiles, and the preparation of polyfunctional organozinc reagents is made possible (Scheme 4-1).[2,3]

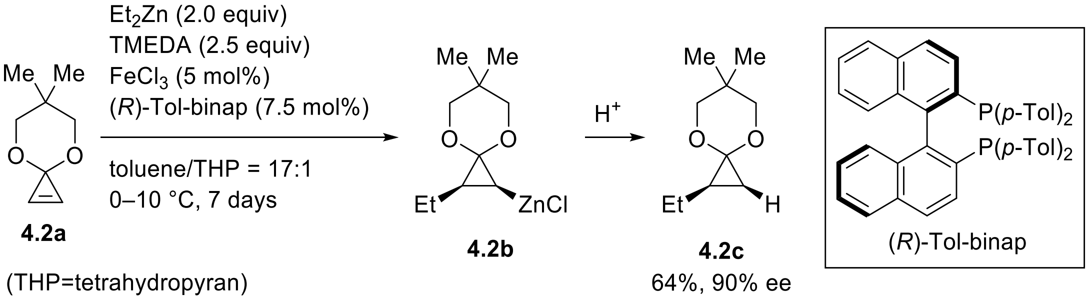


Scheme 4-1. Preparations and applications of organozinc reagents.

In general, organozinc reagents can be prepared by direct insertion reaction with organic halides and zinc metal or by the lithium-zinc or magnesium-zinc transmetallation.[2,3] Carbozincation is defined as a reaction that involves the addition of the carbon-zinc bond of an organozinc reagent across a carbon-carbon multiple bond, providing a new organozinc species.[4] In general, organozinc reagents are not reactive towards alkenes and alkynes. The reported examples were mostly limited to intramolecular reactions.[5] Harsh conditions were employed for intermolecular reactions, or a directing group was required, which somehow diminished its synthetic utility.[6] Transition metal-catalyzed carbozincation reaction provides alternative access to new organozinc reagents, and it has been reported with various metal catalysts.[4,7] One advantage of carbozincaiton is that it will generate the corresponding alkenylzinc or alkylzinc species, which can be further transformed by trapping with various electrophiles. Among them, transition metal-catalyzed asymmetric carbozincation of alkenes allows the direct functionalization of alkenes in an enantioselective manner, providing chiral alkylzincs as the product. To date, there have been only a few reports regarding this strategy.

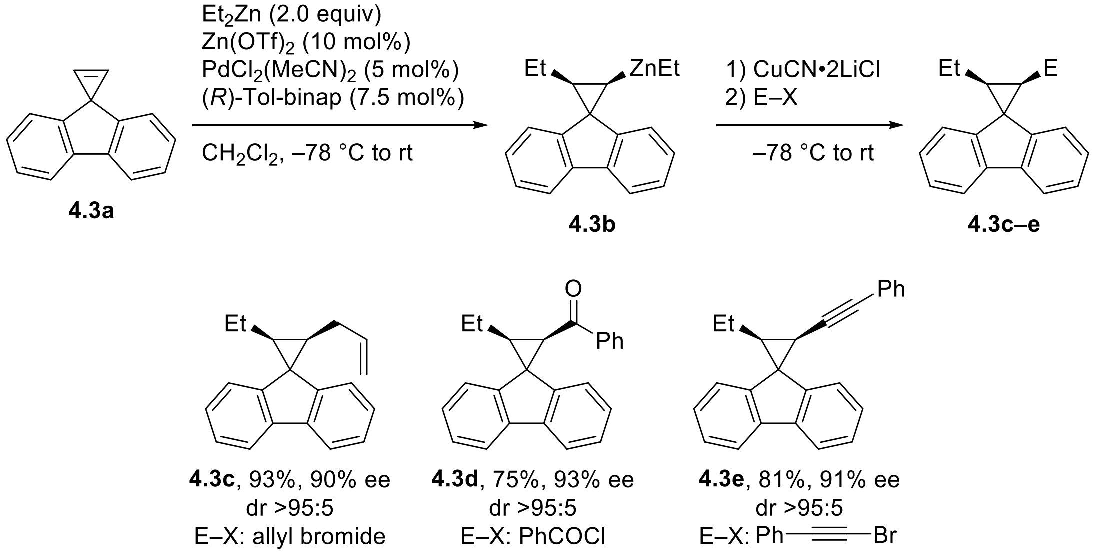
4.1.1 Transition metal-catalyzed asymmetric carbozincation

In 2000, Nakamura reported the seminal work of carbozincation of cyclopropene acetal with diethylzinc and dipropylzinc using $FeCl_3$/(*R*)-Tol-binap (Scheme 4-2).[8] The generated chiral alkylzinc was quenched with acid, providing the enantioenriched cyclopropane in 60% yield and 90% ee. It should be noted that an excess amount of diamine ligand (TMEDA) was required to obtain high enantioselectivity. In the absence of TMEDA, a racemic mixture was formed.



Scheme 4-2. Iron-catalyzed carbozincation of cyclopropene acetals.

A highly diastereo- and enantioselective palladium-catalyzed carbozincation of spiro-cyclopropenes was later reported by Lautens (Scheme 4-3).[9] The generated alkylzincs were further transmetallated with copper and subsequently trapped with various electrophiles to provide highly enantioenriched cyclopropane derivatives.



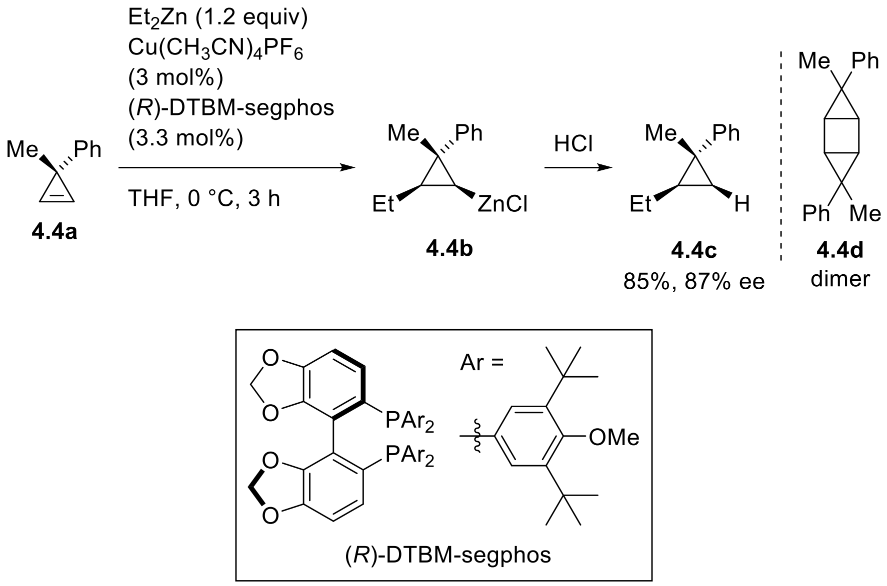
4.3c, 93%, 90% ee
dr >95:5
E–X: allyl bromide

4.3d, 75%, 93% ee
dr >95:5
E–X: PhCOCl

4.3e, 81%, 91% ee
dr >95:5
E–X: Ph—≡—Br

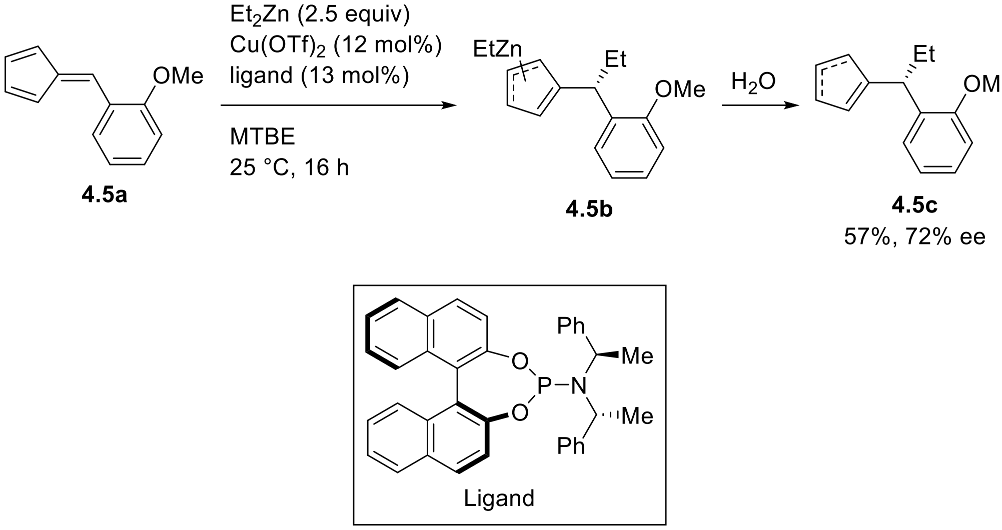
Scheme 4-3. Palladium-catalyzed enantioselective carbozincation.

The asymmetric carbozincation of cyclopropene was also made possible with copper catalysis. Following the pioneering works of Nakamura and Lautens, Marek reported the asymmetric synthesis of polysubstituted cyclopropanes (Scheme 4-4).[10] The combination of (*R*)-DTBM-segphos with Cu(CH$_3$CN)$_4$PF$_6$ or CuTC was found to give the best diastereo- and enantioselectivity, as well as to minimize dimeric side product.



Scheme 4-4. Copper-catalyzed asymmetric carbozincation.

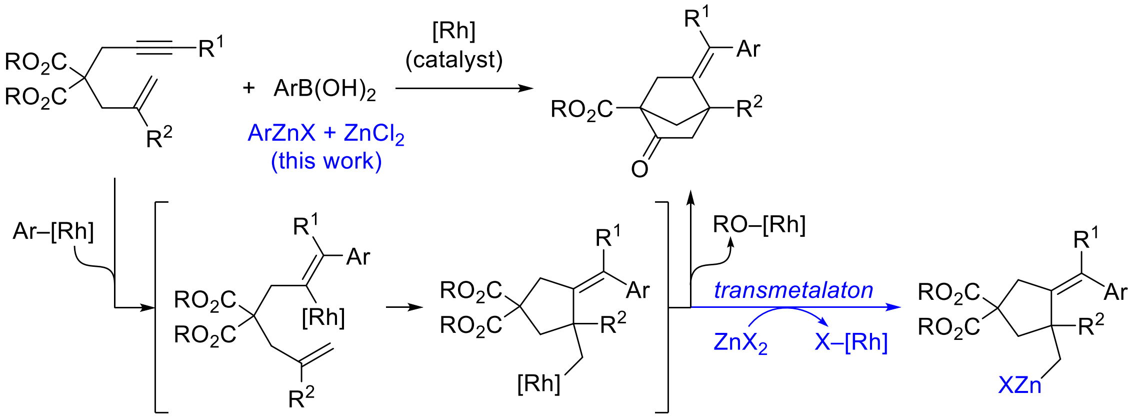
Aside from the highly reactive cyclopropane, Cini later disclosed a copper-catalyzed diethylzinc addition to pentafulvene derivatives in the presence of a chiral phosphoramidite ligand (Scheme 4-5).[11]



Scheme 4-5. Copper-catalyzed asymmetric carbonzincation of pentafulvene derivatives.

Catalytic enantioselective carbozincation of alkenes would be one of the most promising methods of synthesizing chiral alkylzincs, but, unfortunately, this type of asymmetric reaction has not been well developed except for the addition to cyclopropene derivatives[8–11] and electron-deficient alkenes.[12] Therefore, it is of great interest to develop new methods to construct highly enantioenriched alkylzincs.

On the other hand, Hayashi[13] and Murakami[14] independently reported rhodium-catalyzed arylative cyclization of a malonate-tethered 1,6-enyne with $ArB(OH)_2$ producing a bicyclo[2.2.1]heptanone derivative. The catalytic cycle involves an alkyl-Rh species which is formed by carborhodation of alkene,[15,16] and attacks ester carbonyl to result in the formation of ketone (Scheme 4-6). If the $ArB(OH)_2$ is replaced by ArZnX and the transmetalation with ZnX_2 takes place for the alkyl-Rh intermediate, the overall reaction would be a new type of catalytic carbozincation giving alkylzinc product.

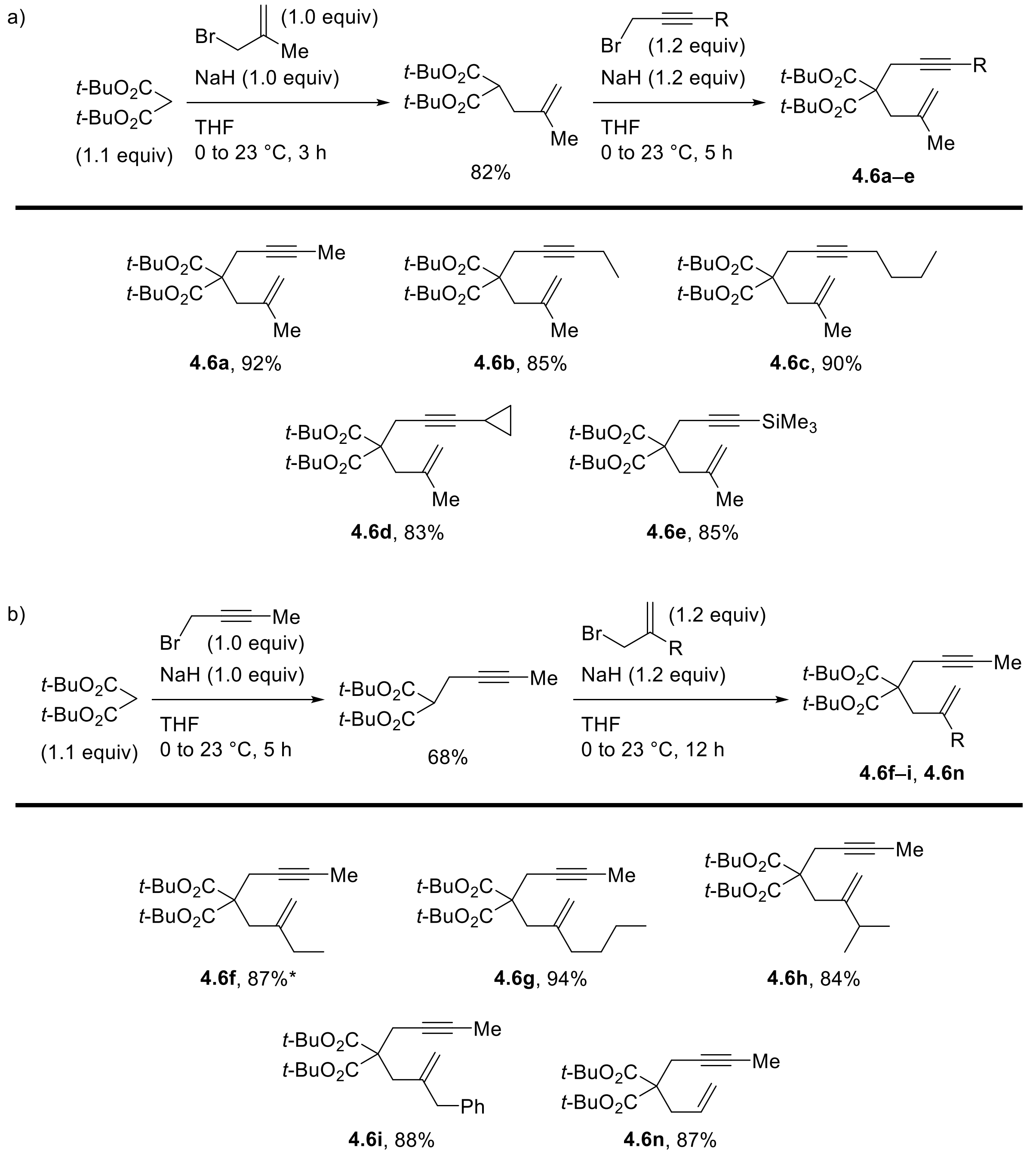


Scheme 4-6. Research proposal.

4.2. Results and discussion

4.2.1. Preparation of starting materials

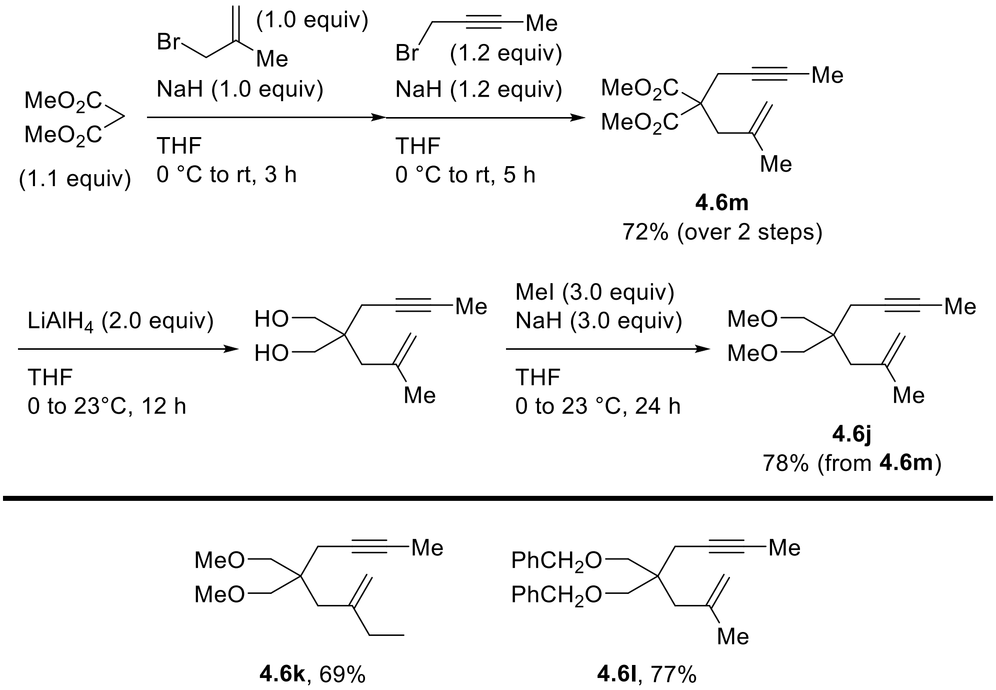
The 1,6-enynes **4.6a**–**4.6i** and **4.6n** were prepared from a two-fold alkylation of di-*tert*-butylmalonate with the corresponding allylic bromides and propargyl bromides in the presence of NaH in THF (Scheme 4-7a and Scheme 4-7b). The isolated yields are summarized in Scheme 4-7.



* Allyl tosylate (1.2 equiv) was used instead of allyl bromide.

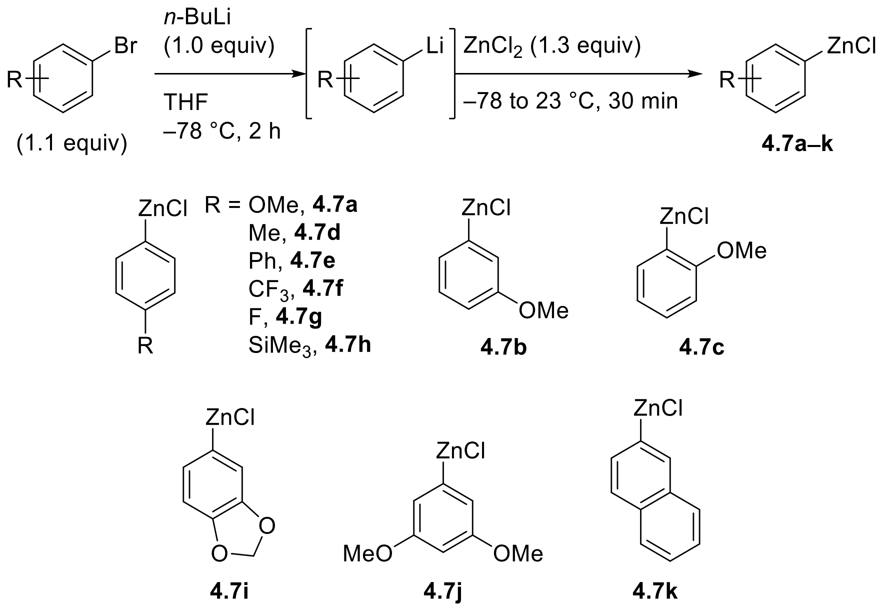
Scheme 4-7. Synthesis of substrates **4.6a**–**4.6i**, and **4.6n**.

For **4.6m**, it was prepared with dimethylmalonate using a similar protocol as for **4.6a**. The synthesis of **4.6j**–**4.6l** was conducted through a two-step synthesis from **4.6a**: 1) reduction of the methyl ester with $LiAlH_4$ in THF gave the diol without further purification; 2) dialkylation of the crude diol with methyl iodide (**4.6j**–**k**) or benzyl bromide (**4.6l**) in the presence of NaH in THF (Scheme 4-8).



Scheme 4-8. Synthesis of substrates **4.6j**–**4.6m**.

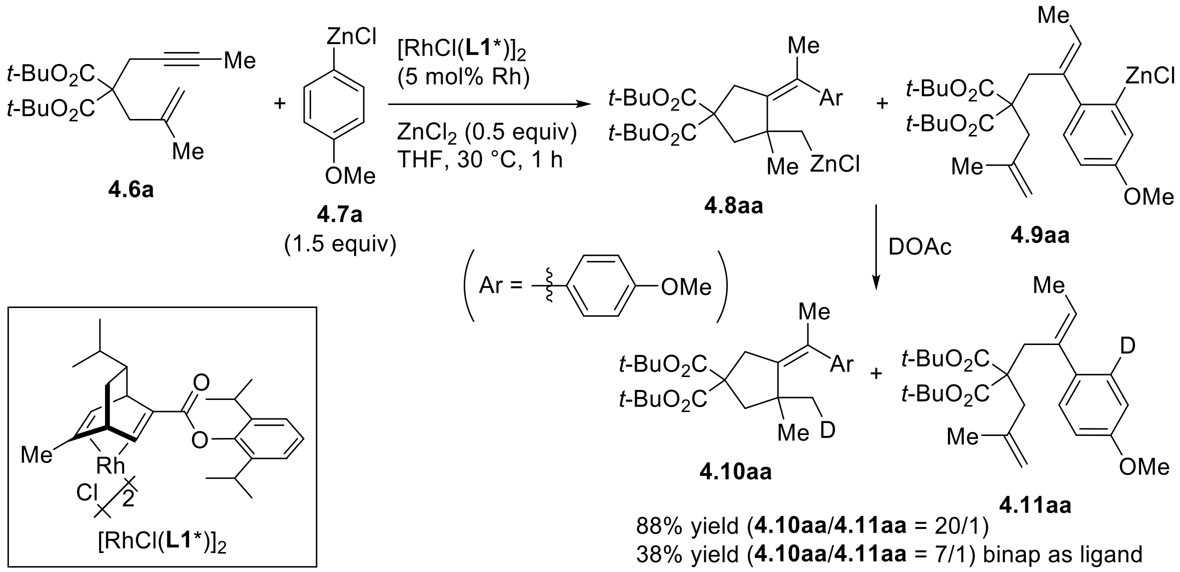
The arylzinc reagents (**4.7a**–**k**) were prepared from the corresponding aryl bromides and *n*-BuLi in THF at –78 °C, followed by transmetallation with excess $ZnCl_2$ (Scheme 4-9). The arylzinc solutions were used directly.



Scheme 4-9. Preparation of arylzinc reagents **4.7a**–**4.7k**.

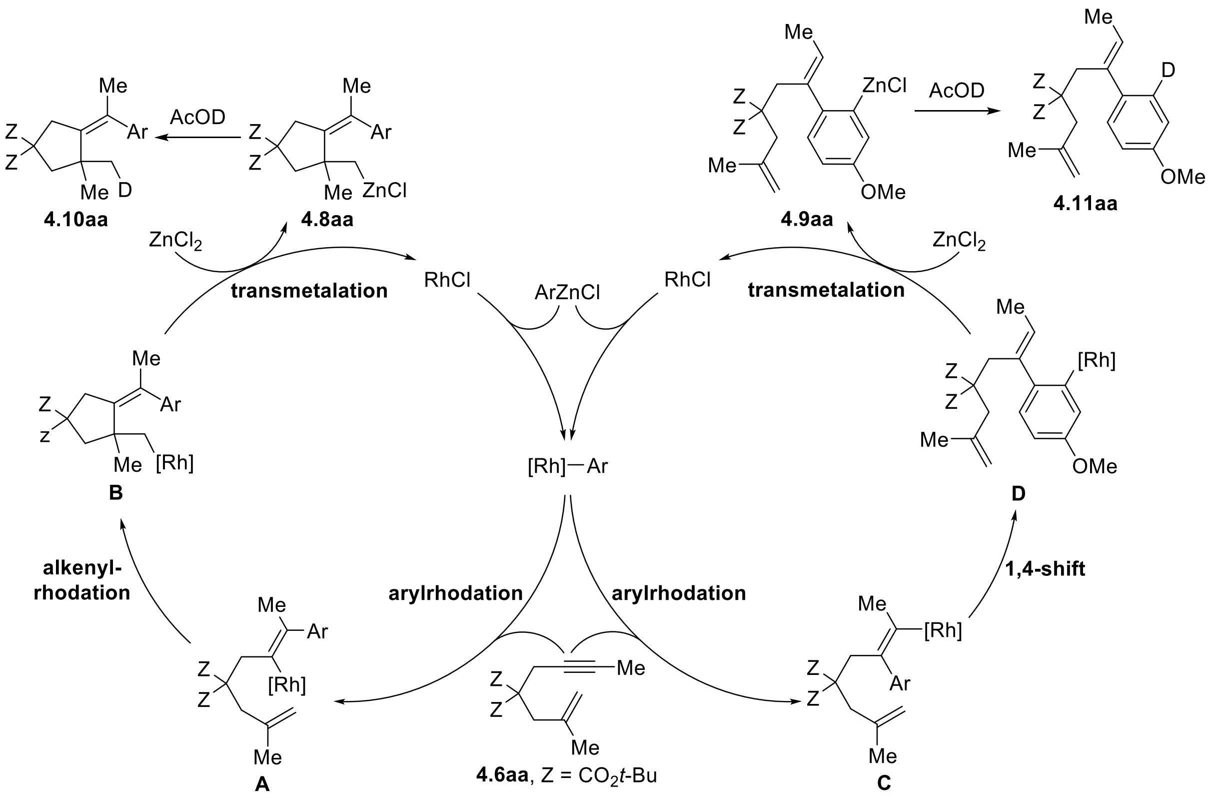
4.2.2. Optimization of reaction conditions

Initially, in the presence of 5 mol% of a chiral diene/Rh catalyst, [RhCl(**L1***)]$_2$, 1,6-enyne **4.6a** was allowed to react with 4-MeOC$_6$H$_4$ZnCl **4.7a** and ZnCl$_2$ at 30 °C for 1 h, and the reaction mixture was quenched with AcOD at 0 °C to give cyclopentane derivative **4.10aa** in 88% yield along with a minor amount of side product **4.11aa** (**4.10aa**/**4.11aa** = 20/1). The deuterium was found at one of the two methyl groups in **4.10aa** and ortho position to the alkenyl group on the phenyl ring in **4.11aa**. The use of a bisphosphine ligand, binap, led to a slower reaction, and the **4.10aa**/**4.11aa** selectivity was lower (Scheme 4-10).



Scheme 4-10. Rhodium-catalyzed asymmetric arylative cyclization producing alkylzincs.

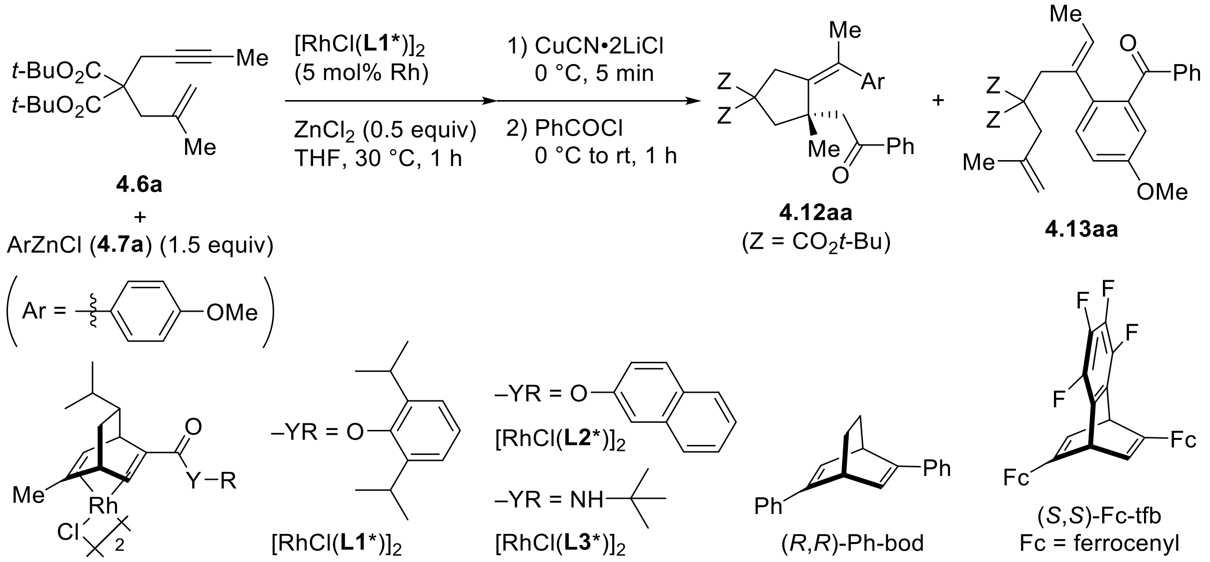
These results of the deuterium quenching studies clearly showed that alkylzinc **4.8aa** and arylzinc **4.9aa** were produced by the Rh-catalyzed arylzincation of **4.6a**. Based on the reaction pathways reported for Rh-catalyzed arylation of alkynes[13,14,17] and cyclization reactions,[16a-c] the catalytic cycle was depicted in Scheme 4-11. Firstly, the addition of an aryl–Rh intermediate to the alkyne component in **4.6a** provided alkenyl–Rh intermediate **A,** and it was followed by the addition to alkene intramolecularly to generate the alkyl–Rh intermediate **B**. Transmetalation between **B** and $ZnCl_2$[18] produced alkylzinc **4.8aa** and a Rh–Cl species, the latter underwent the reaction with ArZnCl regenerating aryl-Rh species. On the other hand, the formation of **4.11aa** was rationalized by the opposite regiochemistry at the arylrhodation of alkyne. Since the generated alkenyl–Rh intermediate **C** cannot participate in the intramolecular addition to the alkene moiety, it underwent a 1,4-Rh shift from alkenyl to the phenyl ring to give aryl–Rh species **D**, and subsequent transmetalation with $ZnCl_2$ produces arylzinc **4.9aa**.



Scheme 4-11. Proposed mechanism.

Since both enantiomers of the deuterated compound **4.10aa** were not well separated on HPLC, other electrophiles were investigated. The alkylzinc product **4.8aa** itself was found not very reactive towards electrophiles other than a proton. However, fortunately, it was found that the copper-mediated acylation developed by Knochel[1–5] proceeded well and gave the corresponding benzoylation product **4.12aa** smoothly in a high yield, which was readily analyzed for its enantiomeric purity. Therefore, the reaction mixture resulting from arylzincation of **4.6a**, which contains **4.8aa**, was treated first with CuCN followed by benzoyl chloride to give phenyl ketone **4.12aa** in 91% yield with 99% ee (reaction scheme in Table 4-1). The optimization of the reaction of 1,6-enyne **4.6a** with 4-MeOC$_6$H$_4$ZnCl **4.7a** was summarized in Table 4-1. The chiral diene ligand **L1***,[21,22] which bears a bulky ester group, was found to be the most effective in both the chemo- and enantioselectivities (entry 1). Other chiral diene ligands, such as **L2***,[23] **L3***,[24] (*R*,*R*)-Ph-bod,[25] and (*S*,*S*)-Fc-tfb,[26] were less effective, giving the product **4.12aa** in a lower yield or with lower **4.12aa**/**4.13aa** selectivity and/or enantioselectivity (entries 2–5). Rhodium complexes with binap[27] and segphos[28] also catalyzed the reaction, but the yields and/or the selectivity were lower (entries 6 and 7). The reaction did not take place with bulky DTBMsegphos[28] (entry 8). The presence of $ZnCl_2$ is essential for the reaction to proceed efficiently, which is probably because $ZnCl_2$ participates in the catalytic cycle at the transmetalation step, giving the final alkylzinc product.[18] While the high yield (91%) of **4.12aa** was obtained under standard conditions with 0.5 equiv of $ZnCl_2$ (entry 1), the reaction was slower in the absence of excess $ZnCl_2$ (entry 9), and a large excess of $ZnCl_2$ retarded the reaction (entry 11). The % ee of **4.12aa** was kept high (99% ee) irrespective of the amount of $ZnCl_2$ (entries 1 and 9–11). The use of ArZnBr/$ZnBr_2$ instead of ArZnCl/$ZnCl_2$ did not affect the enantioselectivity or **4.12aa**/**4.13aa** selectivity, although the yield was somewhat lower (entry 12). A prolonged reaction time (24 h) did not cause a significant change, demonstrating that the alkylzinc product **4.8aa** is stable under the present reaction conditions (entry 13). The 30 °C is the optimal reaction temperature. At lower temperature (0 °C) the reaction is much slower, although the **4.12aa**/**4.13aa** selectivity is slightly higher (entry 14).

Table 4-1 Catalytic asymmetric arylative cyclization of enyne **4.6a** with 4-methoxyphenylzinc chloride **4.7a.**[a]

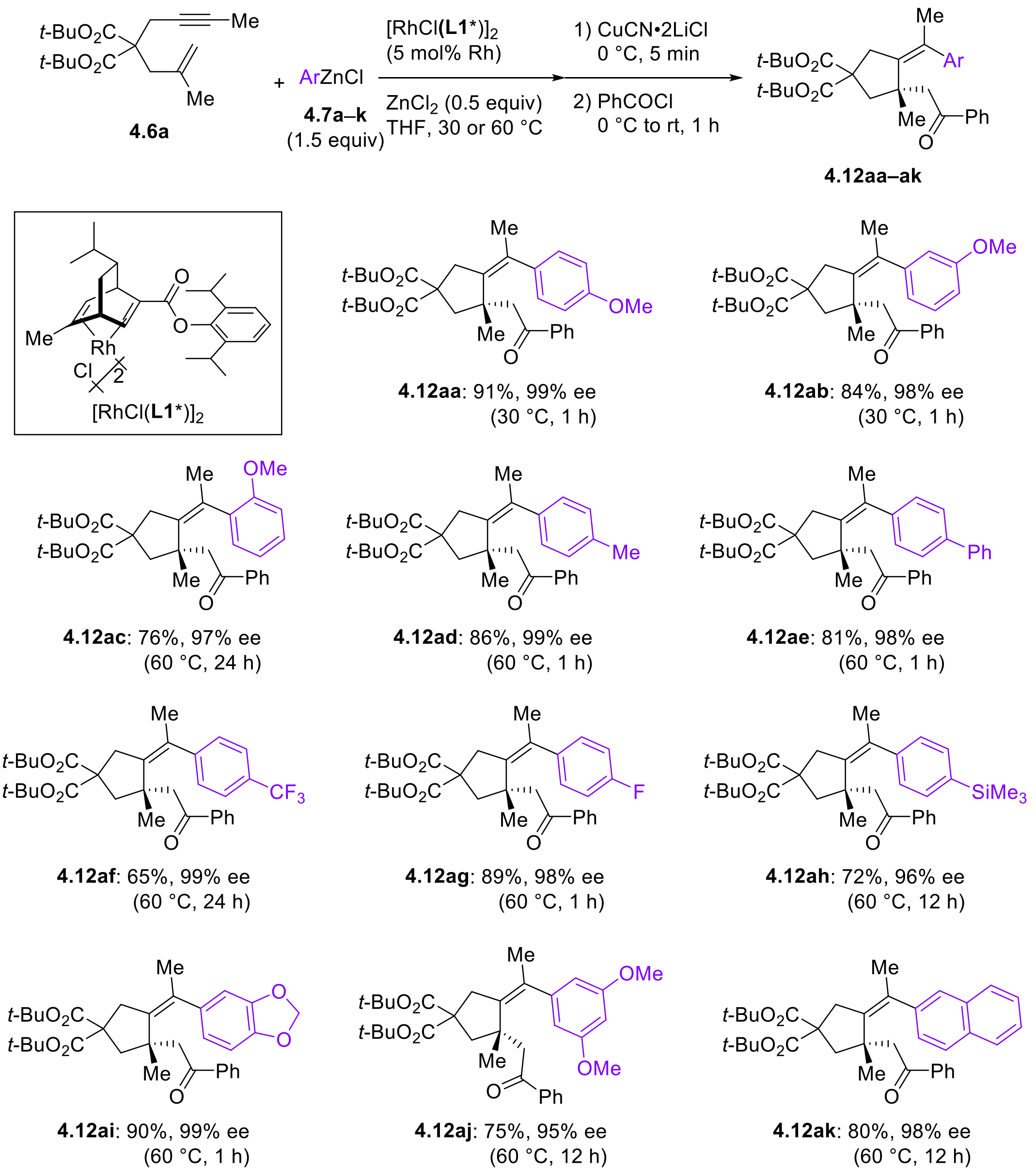


Entry	Variations from standard conditions (shown above)	Yield (%)[b] of **4.12aa**	% ee[c] of **4.12aa**	Ratio[d] of **4.12aa:4.13aa**
1	none	91	99 (*S*)	20:1
2	[RhCl(**L2***)]$_2$	70	96 (*S*)	14:1
3	[RhCl(**L3***)]$_2$	85	98 (*S*)	10:1
4	[RhCl(coe)$_2$]$_2$ + (*R,R*)-Ph-bod	12	94 (*S*)	5:1
5	[RhCl(coe)$_2$]$_2$ + (*S,S*)-Fc-tfb	62	91 (*S*)	50:1
6	[RhCl(coe)$_2$]$_2$ + (*R*)-binap	35	99 (*S*)	10:1
7	[RhCl(coe)$_2$]$_2$ + (*R*)-segphos	63	98 (*S*)	4:1
8	[RhCl(coe)$_2$]$_2$ + (*R*)-DTBMsegphos	<5	—	—
9	ZnCl$_2$ (0.0 equiv)	44	99 (*S*)	20:1
10	ZnCl$_2$ (0.1 equiv)	88	99 (*S*)	20:1
11	ZnCl$_2$ (1.0 equiv)	68	99 (*S*)	20:1
12	ArZnBr + ZnBr$_2$ (0.5 equiv)	75	99 (*S*)	20:1
13	24 h instead of 1 h	84	99 (*S*)	20:1
14	0 °C instead of 30 °C	24	99 (*S*)	22:1
15	60 °C instead of 30 °C	76	99 (*S*)	17:1

[a] Reaction conditions: Enyne **4.6a** (0.20 mmol), ArZnCl **4.7a** (0.30 mmol), ZnCl$_2$ (0.10 mmol), and Rh catalyst (5 mol% of Rh) in THF (2.0 mL) at 30 °C for 1 h. To the reaction mixture was added CuCN•2LiCl (0.36 mmol) and subsequently benzoyl chloride (0.36 mmol). [b] Isolated yield. [c] The % ee was determined by HPLC on a chiral stationary phase column. [d] The ratio of **4.12aa**/**4.13aa** was determined by the ^{1}H NMR of the crude reaction mixture.

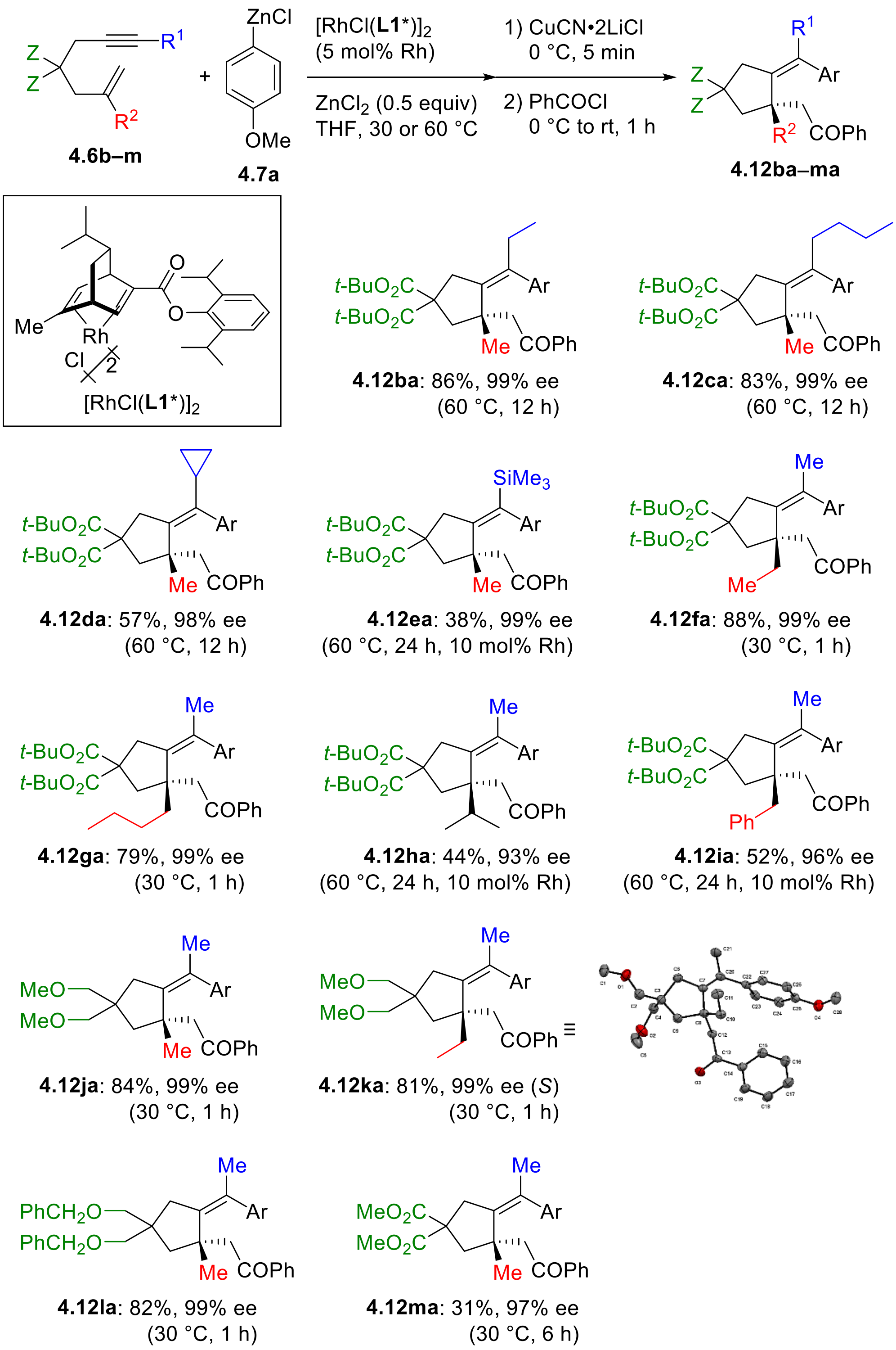
4.2.3. Substrate scope and limitations

The optimized condition for the reaction of **4.6a** with **4.7a** (entry 1 in Table 4-1) was applied to **4.6a** and various arylzincs, and the results were summarized in Scheme 4-12. The reaction of 3-$MeOC_6H_4ZnCl$ proceeded smoothly to give **4.12ab** in high yield with high enantioselectivity. The use of 2-$MeOC_6H_4ZnCl$ was also applicable, although higher temperature and prolonged reaction time were required, with a slightly diminished yield and enantioselectivity (**4.12ac**). In general, the aryl groups bearing both electron-rich and electron-poor functionalities at the para position (**4.12ad**–**4.12ah**) were all successfully introduced into the products with high enantioselectivity (96–99% ee). For those zinc reagents whose reactions were slow (**4.12ac**–**4.12ak**), the reaction temperature was increased to 60 °C and/or in prolonged reaction time. Reactions of disubstituted phenylzincs and 2-naphthylzinc proceeded well to give the corresponding products **4.12ai**–**4.12ak** of high % ee.



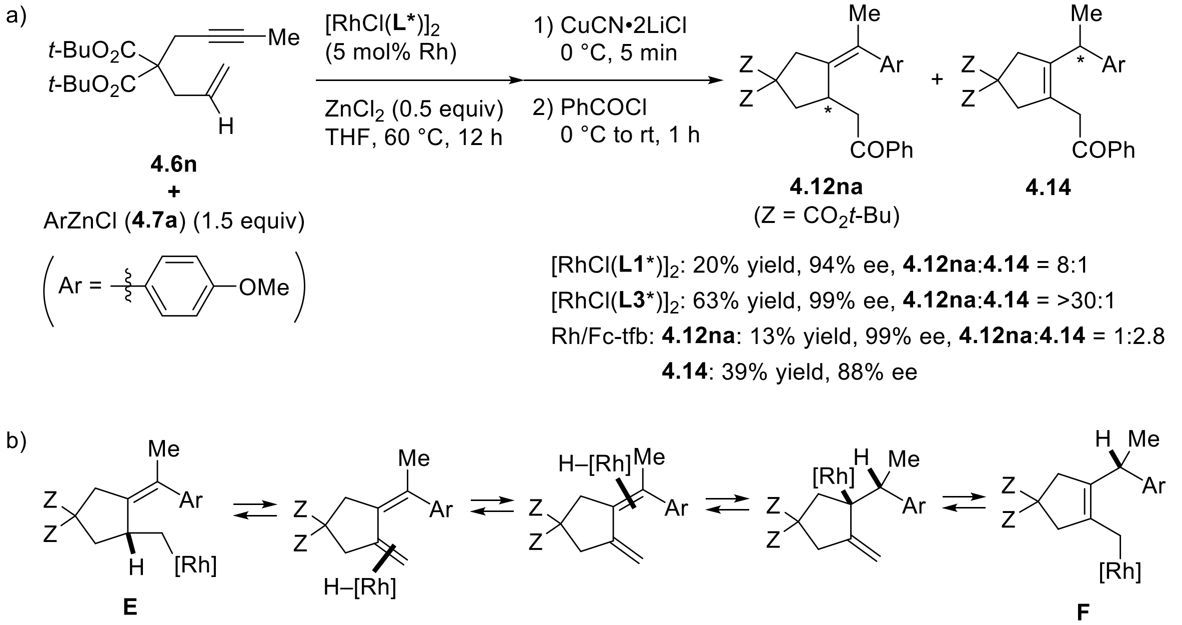
Scheme 4-12. Substrate scope for arylzincs **4.7a**–**4.7k**.

Next, the scope of various 1,6-enynes was also tested using 4-MeOC$_6$H$_4$ZnCl **4.7a** (Scheme 4-13). Substitution of a primary alkyl group (**4.6b** and **4.6c**), as well as cyclopropyl group at the alkyne terminus (**4.6d**), were tolerated, and the corresponding products **4.12ba**–**4.12da** were obtained with high % ee. Aromatic groups such as R^1 at the alkyne terminus caused the opposite regiochemistry at the arylrhodation of alkyne,[18a] and hence the target alkylzincs were not formed. The use of **4.6e** bearing a sterically demanding trimethylsilyl group as R^1 provided the target product in high % ee, although with a lower yield. For the alkene substitution, the reaction proceeded smoothly where R^2 was primary alkyls (**4.12fa** and **4.12ga**). When the R^2 groups were secondary alkyl **4.12ha** or benzyl **4.12ia**, the reactions were also tolerated, although 10 mol% of catalyst loading was required to achieve moderate yield. Dimethyl and dibenzyl ethers at the carbon connecting propargyl and allyl groups underwent the arylative cyclization well (**4.12ja–la**), the yields and selectivity being comparable to the *tert*-butyl esters. The absolute configuration and *Z*-geometry of the double bond were determined by X-ray crystal analysis of **4.12ka**. However, the yield of **4.12ma** was low in the reaction of methyl ester in place of *t*-butyl ester. This is because of the formation of a bicyclo[2.2.1]heptanone derivative as a side product, which was formed through the intramolecular addition of alkylrhodium to the ester carbonyl, followed by the β-oxygen elimination.[13,14]



Scheme 4-13. Substrate scope for 1,6-enynes **4.6b–4.6m**.

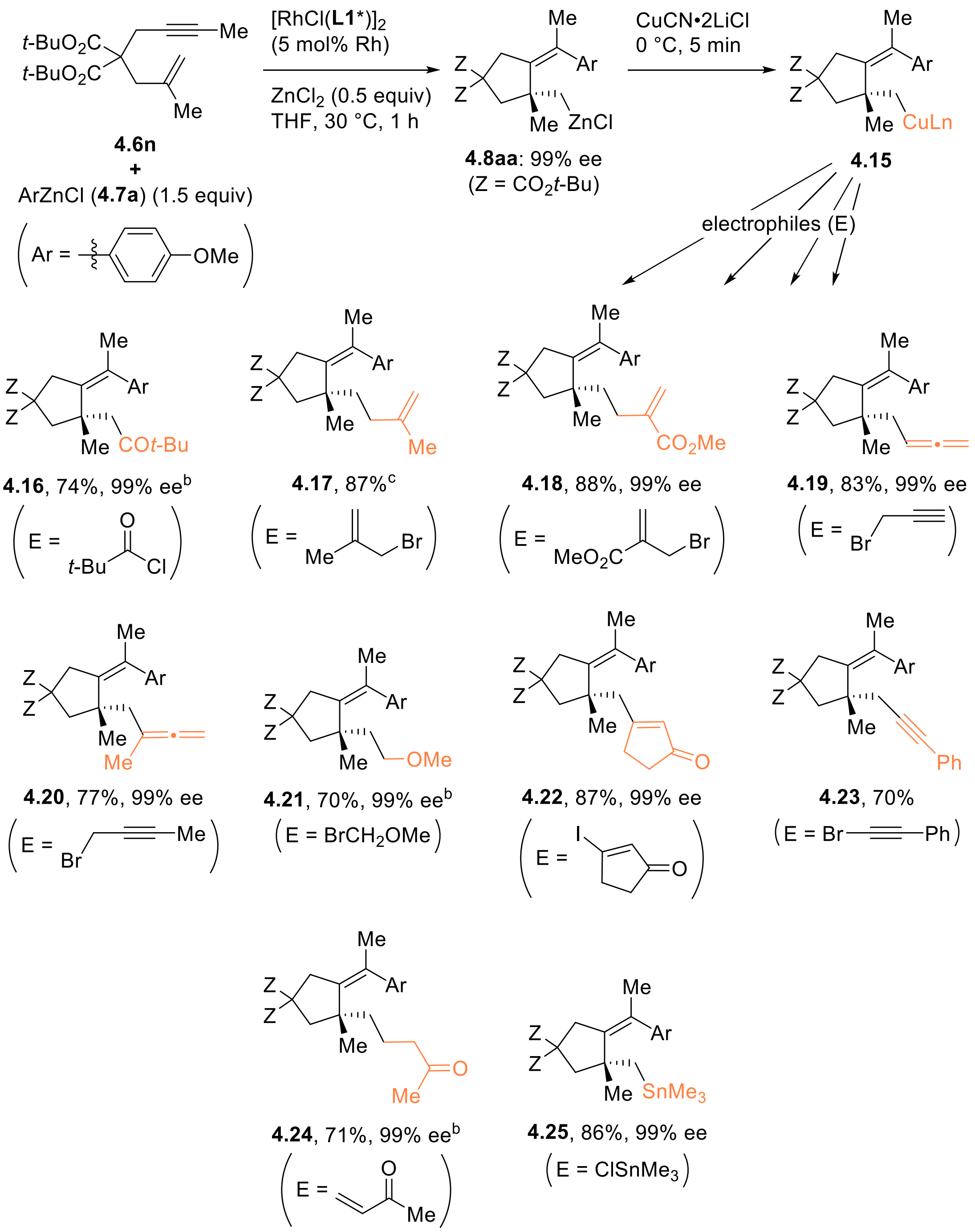
The reaction of **4.6n**, which has an unsubstituted allyl group as the alkene moiety, provided some information on the stability and reactivity of the alkylrhodium intermediate bearing a β-hydrogen (Scheme 4-14a). It was found the use of **L1***, which was used for other 1,6-enynes, the yield of the desired product **4.12na** was lower, and the olefin isomer **4.14** was formed as a minor product. It was also found that **4.12na** was formed exclusively with high enantioselectivity (99% ee) when **L3*** was used. It is remarkable that the use of (*S*,*S*)-Fc-tfb ligand gave the olefin isomer **4.14** as the main product (**4.12na**/**4.14** = 1/2.8) and that high % ee was observed in **4.14** (88% ee) as well as in **4.12na** (99% ee). The product **4.14** should be formed through isomerization of homoallylic Rh intermediate **E** to allylic intermediate **F**, before transmetalation giving the corresponding homoallylic or allylic zinc species. It is most likely that the isomerization proceeds through several steps consisting of β-hydrogen elimination, migration of hydrido-rhodium to the other double bond, hydrorhodation, and allylic 1,3-shift. The high % ee of the isomerized product **4.14** may indicate that the hydrido-rhodium does not move from one coordination site to the other during those steps for isomerization (Scheme 4-14b).[29]



$[RhCl(\mathbf{L1}^*)]_2$: 20% yield, 94% ee, **4.12na**:**4.14** = 8:1
$[RhCl(\mathbf{L3}^*)]_2$: 63% yield, 99% ee, **4.12na**:**4.14** = >30:1
Rh/Fc-tfb: **4.12na**: 13% yield, 99% ee, **4.12na**:**4.14** = 1:2.8
4.14: 39% yield, 88% ee

Scheme 4-14. Rhodium-catalyzed carbonzincation of **4.6n.**

In addition to benzoylation, the downstream functionalization of the enantioenriched alkylzinc **4.8aa** was also amenable to various types of electrophiles in a one-pot fashion (Scheme 4-15).[30]

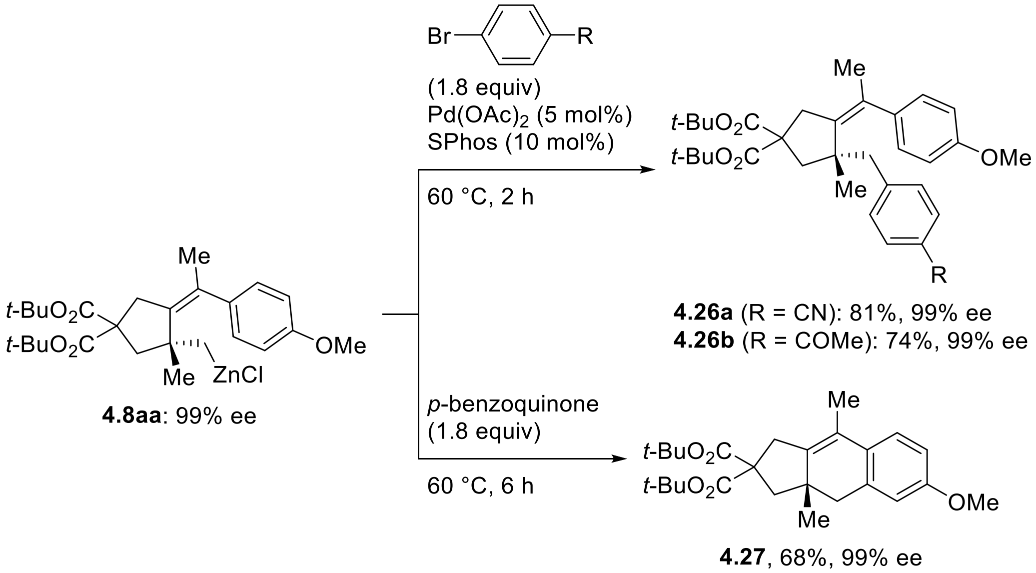


[a] Yields are based on the amount of 1,6-enynes **4.6a** used; [b] Reaction time: 12 h; [c] 20 mol% CuCN•2LiCl was used.

Scheme 4-15. Functionalization of the alkylzinc **4.8aa** (99% ee) obtained by the Rh-catalyzed asymmetric arylation/cyclization.[a]

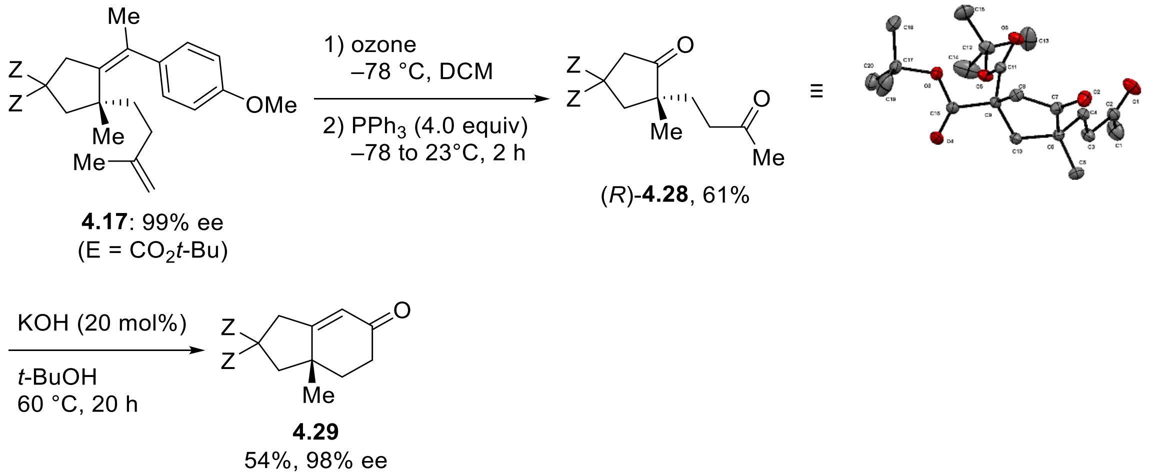
For example, the copper-mediated acylation **4.16** and allylation (**4.17** and **4.18**) proceed well. Reaction with propargylic bromides gave corresponding allenes **4.19** and **4.20** via S_N2' reaction. Coupling with alkyl, vinyl, and alkynyl halides provided **4.21–4.23** in good yields. Other reactions such as 1,4-addition **4.24** and stannylation **4.25** also worked well to furnish the products. It should be noted that, for compounds **4.17** and **4.23**, the enantiomeric excess was not determined by HPLC analysis due to poor separation of the peaks. Considering the reaction pathway, it is assumed to be the same as that of **4.12aa** (99% ee).

Negishi coupling of **4.8aa** with aryl bromides in the presence of a catalytic amount of Pd/Sphos was also applicable to give **4.26a** and **4.26b** (Scheme 4-16).[31] Treatment of **4.8aa** with *p*-benzoquinone led to the formation of tricyclic compound **4.27** by oxidative cyclization. It should be noted that all the reactions shown in Scheme 4-15 were based on 1,6-enyne **4.6a** employed. The enantiomeric purities were all kept 99% as expected.



Scheme 4-16. Cross-coupling and oxidative cyclization of the alkylzinc **4.8aa** (99% ee) obtained by the Rh-catalyzed asymmetric arylation/cyclization.

As one example of the transformation of the products obtained in Scheme 4-15, the synthesis of [4.3.0]bicyclic enone **4.29** was achieved by ozonolysis of **4.17** to give the chiral diketone **4.28**, followed by an intramolecular aldol reaction, as shown in Scheme 4-17.



Scheme 4-17. Application of product **4.17**.

4.3. Conclusion

A chiral diene–rhodium complex was found to catalyze the reaction of 1,6-enynes with ArZnCl to give high yields of 2-(alkylidene)cyclopentylmethylzincs with high enantioselectivity (95–99% ee). The enantioenriched alkylzincs were readily converted in one pot into a wide variety of functionalized products by taking advantage of the unique high reactivity. The catalytic cycle involves arylrhodation of alkyne, intramolecular alkenylrhodation of alkene, and transmetalation of the alkyl-rhodium intermediate into alkylzinc.

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Chapter 5. Experimental section

5.1. General information

5.1.1. Nuclear magnetic resonance (NMR) spectroscopy

^{1}H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 MHz NMR, QNP probe or Bruker Avance III 400 MHz NMR, BBFO probe in $CDCl_3$ [using TMS (for ^{1}H, δ = 0.00) as internal standard], THF-d_8 [using THF (δ = 3.58) as internal standard], or benzene-d_6 [using C_6H_6 (δ = 7.16) as internal standard]. ^{2}H spectra (61 MHz) were recorded on a Bruker Avance 400 MHz NMR, QNP probe or Bruker Avance III 400 MHz NMR, BBFO probe in $CHCl_3$ [using $CDCl_3$ (δ = 7.26) as internal standard]. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 MHz NMR, QNP probe or Bruker Avance III 400 MHz NMR, BBFO probe in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard], THF-d_8 [using THF (δ = 67.58) as internal standard], or acetone-d_6 [using acetone (δ = 29.92) as internal standard]. Proton decoupled ^{19}F NMR spectra [$^{19}F\{^1H\}$] (376 MHz) were recorded on a Bruker Avance III 400 MHz NMR, BBFO probe. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet.

5.1.2. Mass spectroscopy

Mass spectra (ESI) were obtained with a Thermo Finnigan LCQ Fleet mass spectrometer. High-resolution mass spectra (ESI) were obtained with a Waters Q-Tof Premier mass spectrometer.

5.1.3. Melting point

Melting points (uncorrected) were recorded on an MPA 100 OptiMelt Automated Melting Point System.

5.1.4. IR

IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer. The absorption data only for the key functional groups were recorded in the characterization of the respective substrates.

5.1.5. Single-crystal X-ray diffraction

X-ray data collection, structural refinement, and intensity data were collected on a Bruker D8 Quest diffractometer. The structures were solved by the intrinsic phasing method with SHELXTL XT (SHELXTL XT, Program for crystal structure solution, Bruker AXS Inc.) and refined for all data by full-matrix least-squares method on F^2. All non-hydrogen atoms were subjected to anisotropic refinement. The hydrogen atoms were generated geometrically and allowed to ride in their respective parent atoms; they were assigned appropriate isotropic thermal parameters and included in the structure-factor calculations.

5.1.6. Enantiomeric excesses (ee)

Enantiomeric excesses (ee) were determined by HPLC analysis on Shimadzu HPLC with Daicel chiral columns.

5.1.7. Optical rotations

Optical rotations were measured on an Anton Paar MCP 150 machine.

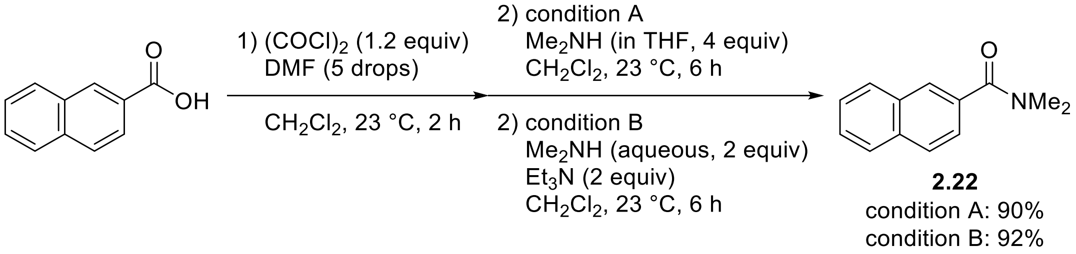
5.2. Experiment data for Chapter 2

5.2.1. Materials

All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under argon gas. All glassware was oven-dried for at least 24 h at 120 °C before use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium benzophenone ketyl and stored over 4Å molecular sieves. Dichloromethane (CH_2Cl_2) and toluene were taken from a solvent purification system (PS-400-5, innovative technology Inc.). Methylmagnesium bromide solution (MeMgBr, 3.0 M in Et_2O, Sigma-Aldrich 189898), allylmagnesium chloride solution (allylMgCl, 2.0 M in THF, Sigma-Aldrich 225908), benzylmagnesium chloride solution ($PhCH_2MgCl$, 1.0 M in THF, TCI B1933), ethynylmagnesium bromide solution (0.5 M in THF, Sigma-Aldrich 346152), (trimethylsilyl)methylmagnesium chloride solution (Me_3SiCH_2MgCl, 1.0 M in Et_2O, Sigma-Aldrich 256021), lithium phenylacetylide solution (1.0 M in THF, Sigma-Aldrich 340677), methyllithium solution (MeLi, 3.1 M in diethoxymethane, Sigma-Aldrich 514330), *n*-butyllithium solution (*n*-BuLi, 2.6 M in hexane, Kanto Chemical 04935), *i*-propyllithium solution (*i*-PrLi, 0.7 M in pentane, Sigma-Aldrich 529745), and *t*-butyllithium solution (*t*-BuLi 1.7 M in pentane, Sigma-Aldrich 186198) were purchased and they were titrated before use (see section 5.2.4 for details). Other solvents and reagents, unless otherwise noted, were commercially available and used as received. Tetrabutylammonium cyanide (Sigma-Aldrich 358665) was purchased from Sigma-Aldrich, Inc. and it is handled under an argon atmosphere in a glovebox or with Schlenk techniques under an argon atmosphere due to its moisture sensitivity. Bromotrimethylsilane (Me_3SiBr, Sigma-Aldrich 194409) was purchased from Sigma-Aldrich, Inc. and distilled before use. Due to the instability of Me_3SiBr, it should be distilled regularly and stored in dark.

5.2.2. Synthesis of starting materials 2.22–2.46

N,*N*-Dimethyl-2-naphthamide (**2.22**)[1]



Condition A *(with Me_2NH solution in THF):*

To a suspension of 2-naphthoic acid (8.61 g, 50.0 mmol, 1.0 equiv) (Sigma-Aldrich 180246) in anhydrous CH_2Cl_2 (100 mL) was added $(COCl)_2$ (5.2 mL, 60.6 mmol, 1.2 equiv) (Sigma-Aldrich O8801) and *N*,*N*-dimethylformamide (DMF, 5 drops) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h and then the volatile materials were removed *in vacuo*. The crude mixture was redissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C. A solution of Me_2NH in THF (2 M, 100 mL, 200 mmol, 4 equiv) (TCI D3948) was added dropwise, and the reaction mixture was stirred continuously at 23 °C for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 2:1→1:4) to give **2.22** as light yellow solid (9.76 g). The product was further purified by recrystallization from hexane to give **2.22** as colorless crystal (9.05 g, 45.4 mmol) in 90% yield.

Condition B *(with Me_2NH solution in water):*

To a suspension of 2-naphthoic acid (5.17 g, 30.1 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (60 mL) was added $(COCl)_2$ (3.1 mL, 36.9 mmol, 1.2 equiv) and DMF (5 drops) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h and then the volatile materials were removed *in vacuo*. The crude mixture was redissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C.

An aqueous solution of Me_2NH (40% *wt*, 7.6 mL, 60.0 mmol, 2.0 equiv) (Acros 163670025) was added dropwise. Triethylamine (8.4 mL, 60.3 mmol, 2.0 equiv) was then added dropwise to the resulting mixture at 0 °C, and the mixture was stirred continuously at 23 °C for 6 h. The same work-up and purification procedures as above were conducted to give **2.22** as colorless crystal (5.49 g, 27.6 mmol) in 92% yield after recrystallization from hexane.

M.p. 86.4 – 88.0 °C. (lit 82 – 83 °C)[2]

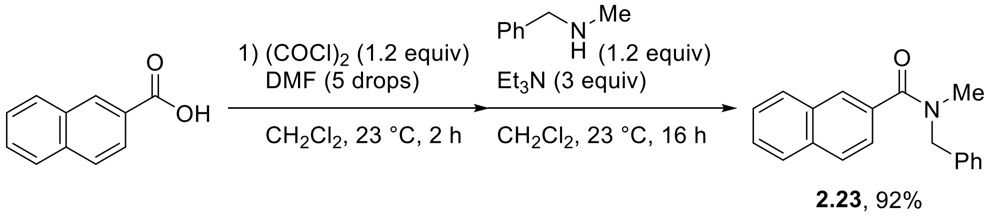
R*f* = 0.18 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.88 − 7.84 (m, 4H), 7.55 − 7.50 (m, 3H), 3.16 (brs), 3.03 (brs).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 133.6, 133.5, 132.6, 128.3, 128.1, 127.7, 126.9, 126.8, 126.5, 124.4, 39.6, 35.3.

MS (ESI) *m*/*z* 200.09 [(M+H)$^+$].

N-Benzyl-*N*-methyl-2-naphthamide (**2.23**)[3]



2.23, 92%

Prepared from 2-naphthoic acid (1.72 g, 10.0 mmol, 1.0 equiv), $(COCl)_2$ (1.0 mL, 11.7 mmol, 1.2 equiv), *N*-methylbenzylamine (1.46 g, 12.1 mmol, 1.2 equiv) (Sigma-Aldrich B25606), and triethylamine (4.2 mL, 30.1 mmol, 3.0 equiv) according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

Purification silica gel, hexane/ethyl acetate = 4:1→1:1.

Yield 92% yield (2.53 g, 9.20 mmol) as white solid.

M.p. 75.6 – 77.0 °C.

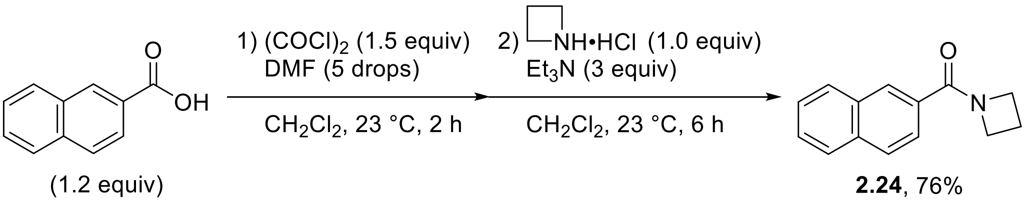
R*f* = 0.37 (eluent: hexane/ethyl acetate = 4:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) (1:1 mixture of rotamers) δ 7.95 (s, 2H), 7.85 (m, 6H), 7.55 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.52 (m, 4H), 7.38 – 7.32 (m, 8H), 7.19 (m, 2H), 4.81 (brs, 2H), 4.57 (brs, 2H), 3.08 (brs, 3H), 2.92 (brs, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) (1:1 mixture of rotamers) δ 172.2, 171.5, 137.0, 136.5, 133.5*, 133.4*, 132.6*, 128.7*, 128.3*, 128.2*, 127.7*, 127.5*, 126.9*, 126.63*, 126.56*, 124.2**, 55.2, 50.8, 37.2, 33.2 (*2C overlapped; **4C overlapped).

MS (ESI) *m*/*z* 276.23 [(M+H)$^+$].

Azetidin-1-yl(naphthalen-2-yl)methanone (**2.24**)



Prepared from 2-naphthoic acid (1.66 g, 9.66 mmol, 1.2 equiv), (COCl)$_2$ (1.0 mL, 11.7 mmol, 1.5 equiv), azetidine hydrochloride (749 mg, 8.00 mmol, 1.0 equiv) (Sigma-Aldrich 471283), and triethylamine (3.3 mL, 23.7 mmol, 3.0 equiv) according to the condition **B** described in section 5.2.2.

Purification silica gel, hexane/ethyl acetate = 2:1→1:4.

Yield 76% yield (1.28 g, 6.07 mmol) as white solid.

M.p. 115.0 – 116.1 °C.

R*f* = 0.14 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

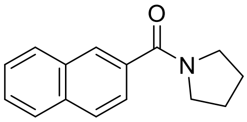
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12 (s, 1H), 7.90 – 7.84 (m, 3H), 7.72 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.57 – 7.50 (m, 2H), 4.37 (t, *J* = 7.7 Hz, 2H), 4.28 (t, *J* = 7.7 Hz, 2H), 2.36 (tt, *J* = 7.7, 7.7 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.3, 134.3, 132.5, 130.6, 128.7, 128.14, 128.08, 127.7, 127.4, 126.5, 124.5, 53.5, 49.0, 16.1.

IR (KBr, neat) ν_{max} 2970, 2881, 1633, 1614 [ν (C=O)], 1409, 839, 759 cm^{-1}.

HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}NO$ [$(M+H)^+$]: 212.1075, found: 212.1073.

Naphthalen-2-yl(pyrrolidin-1-yl)methanone (**2.25**)[1]



2.25

Prepared from 2-naphthoic acid, pyrrolidine (Sigma-Aldrich P73803), and triethylamine according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 76.4 – 77.6 °C. (lit. 76 – 77 °C)[4]

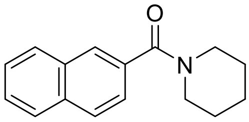
R*$_f$* = 0.18 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (s, 1H), 7.88 – 7.84 (m, 3H), 7.62 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.55 – 7.49 (m, 2H), 3.71 (t, *J* = 6.7 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.00 (tt, *J* = 6.7, 6.7 Hz, 2H), 1.88 (tt, *J* = 6.7, 6.7 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 169.6, 134.5, 133.7, 132.5, 128.4, 128.0, 127.7, 126.93, 126.87, 126.4, 124.4, 49.6, 46.2, 26.4, 24.4.

MS (ESI) *m*/*z* 226.15 [$(M+H)^+$].

Naphthalen-2-yl(piperidin-1-yl)methanone (**2.26**)[1]



2.26

Prepared from 2-naphthoic acid, piperidine (Sigma-Aldrich 104094), and triethylamine according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 101.6 – 102.6 °C. (lit. 97 – 98 °C)[4]

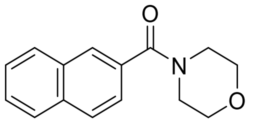
R*f* = 0.30 (eluent: hexane/ethyl acetate = 4:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 – 7.84 (m, 4H), 7.54 – 7.51 (m, 2H), 7.48 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.76 (brs, 2H), 3.40 (brs, 2H), 1.69 (brs, 4H), 1.54 (brs, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.3, 133.8, 133.5, 132.7, 128.3, 128.1, 127.7, 126.8, 126.5, 126.4, 124.2, 48.8, 43.2, 26.5, 25.6, 24.6.

MS (ESI) *m/z* 240.17 [(M+H)$^+$].

Morpholino(naphthalen-2-yl)methanone (**2.27**)[1]



2.27

Prepared from 2-naphthoic acid, morpholine (Alfa Aesar A10355), and triethylamine according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 97.1 – 98.5 °C. (lit. 101.3 − 102.2 °C)[5]

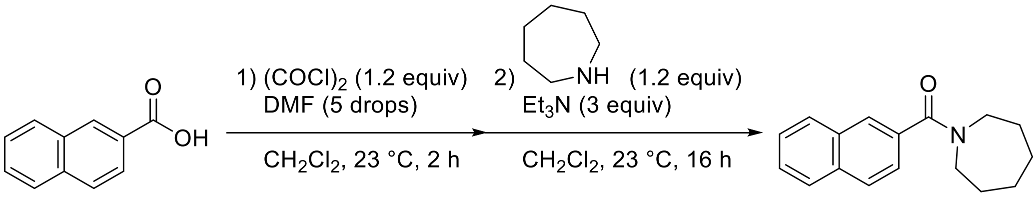
R*f* = 0.27 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.89 – 7.85 (m, 3H), 7.56 – 7.51 (m, 2H), 7.49 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.72 – 3.55(m, 8H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 133.7, 132.6, 132.5, 128.4, 128.3, 127.7, 127.1, 127.0, 126.7, 124.2, 69.9 (2C overlapped), 48.3, 42.6.

MS (ESI) *m/z* 242.16 [(M+H)$^+$].

Azepan-1-yl(naphthalen-2-yl)methanone (**2.28**)



2.28, 85%

Prepared from 2-naphthoic acid (1.72 g, 10.0 mmol, 1.0 equiv), (COCl)$_2$ (1.0 mL, 11.7 mmol, 1.2 equiv), azepane (1.4 mL, 12.4 mmol, 1.2 equiv) (Sigma-Aldrich, H10401), and triethylamine (4.2 mL, 30.1 mmol, 3.0 equiv) according to the condition **B** described in section 5.2.2.

Purification silica gel, hexane/ethyl acetate = 2:1→1:4.

Yield 85% yield (2.15 g, 8.50 mmol) as light yellow oil.

R$_f$ = 0.36 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

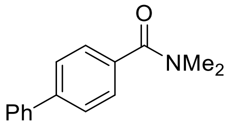
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87 – 7.84 (m, 4H), 7.54 – 7.50 (m, 2H), 7.48 (dd, J = 8.5, 1.4 Hz, 1H), 3.75 – 3.72 (m, 2H), 3.43 – 3.41 (m, 2H), 1.91 – 1.86 (m, 2H), 1.71 – 1.61 (m, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 171.5, 134.6, 133.3, 132.7, 128.2, 128.1, 127.7, 126.7, 126.5, 125.9, 124.0, 49.8, 46.3, 29.5, 27.8, 27.2, 26.4.

IR (KBr, neat) $\nu_{\max}$ 2926, 2854, 1614 [ν (C=O)] 1423, 758 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{20}NO$ [(M+H)$^+$]: 254.1545, found: 254.1547.

N,*N*-Dimethyl-[1,1'-biphenyl]-4-carboxamide (**2.29**)[6]



2.29

Prepared from biphenyl-4-carboxylic acid (Sigma-Aldrich B34729) and Me_2NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

R*f* = 0.18 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

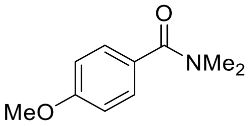
M.p. 106.4 – 107.7 °C. (lit. 104 – 105 °C)[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 3.13 (brs, 3H), 3.04 (brs, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 142.4, 140.3, 135.1, 128.8, 127.7, 127.6, 127.1, 127.0, 39.6, 35.4.

MS (ESI) *m*/*z* 226.15 [$(M+H)^+$].

4-Methoxy-*N*,*N*-dimethylbenzamide (**2.30**)[1]



2.30

Prepared from 4-methoxybenzoic acid (Sigma-Aldrich 8.05971) and Me_2NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

Colorless oil.

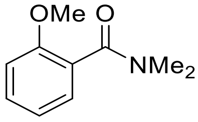
R*f* = 0.24 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.05 (brs, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 171.5, 160.5, 129.0, 128.3, 113.5, 55.3, 39.7, 35.6.

MS (ESI) *m*/*z* 180.05 [(M+H)$^+$].

2-Methoxy-*N*,*N*-dimethylbenzamide (**2.31**)[1]



2.31

Prepared from 2-methoxybenzoic acid (Sigma-Aldrich 169978) and Me$_2$NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

Colorless oil.

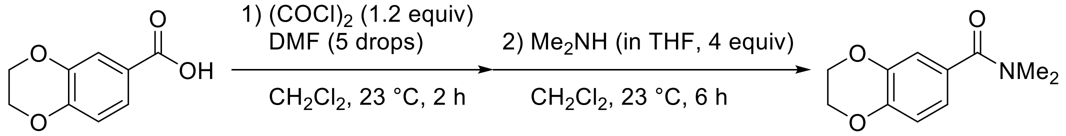
R*f* = 0.21 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.98 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 3.12 (s, 3H), 2.85 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 169.4, 155.2, 130.2, 127.8, 126.3, 120.8, 110.9, 55.5, 38.1, 34.7.

MS (ESI) *m*/*z* 180.06 [(M+H)$^+$].

N,*N*-Dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (**2.32**)



2.32, 93%

The titled compound was synthesized using 1,4-benzodioxane-6-carboxylic acid (1.80 g, 10.0 mmol, 1.0 equiv) (Sigma-Aldrich 658375), $(COCl)_2$ (1.0 mL, 11.7 mmol, 1.2 equiv), and Me_2NH in THF (2 M, 20 mL, 40 mmol, 4.0 equiv) by following the condition **A** described in section 5.2.2.

Purification silica gel, hexane/ethyl acetate = 2:1→1:4.

Yield 93% yield (1.93 g, 9.32 mmol) as light yellow solid.

M.p. 89.5 – 90.7 °C.

R*f* = 0.17 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

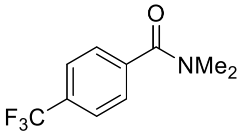
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.97 (d, J = 1.9 Hz, 1H), 6.85 (dd, J = 8.3, 1.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 4.29 – 4.25 (m, 4H), 3.04 (brs, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.9, 144.7, 143.1, 129.3, 120.7, 117.0, 116.7, 64.4, 64.2, 39.6, 35.4.

IR (KBr, neat) ν_{max} 2933, 2881, 1608 [ν (C=O)], 1575, 1489, 840 cm^{-1}.

HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}NO_3$ [$(M+H)^+$]: 208.0974, found: 208.0974.

N,*N*-Dimethyl-4-(trifluoromethyl)benzamide (**2.33**)[1]



2.33

Prepared from 4-(trifluoromethyl)benzoic acid (Sigma-Aldrich 196894) and Me_2NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 96.0 – 97.1 °C. (95 – 96 °C)[7]

R*f* = 0.37 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

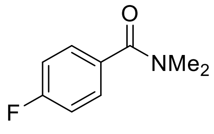
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 3.13 (brs, 3H), 2.97 (brs, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.0, 139.9, 131.4 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 127.3, 125.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 123.7 ($^1J_{C\text{-}F}$ = 270.7 Hz), 39.3, 35.2.

^{19}F NMR (376 MHz, CDCl$_3$) δ −62.9.

MS (ESI) *m*/*z* 218.06 [(M+H)$^+$].

4-Fluoro-*N*,*N*-dimethylbenzamide (**2.34**)[6]



2.34

Prepared from 4-fluorobenzoic acid (Sigma-Aldrich 128384) and Me$_2$NH (40% *wt* in H$_2$O) according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 64.1 – 65.2 °C. (lit. 65 °C)[8]

R$_f$ = 0.28 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

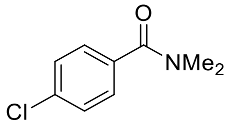
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 – 7.41 (m, 2H), 7.11 – 7.06 (m ,2H), 3.10 (brs, 3H), 2.99 (brs, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.6, 163.2 (d, $^1J_{C\text{-}F}$ = 249.3 Hz), 132.3 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 129.3 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 115.3 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 39.6, 35.4.

^{19}F NMR (376 MHz, CDCl$_3$) δ −110.7.

MS (ESI) *m*/*z* 168.01 [(M+H)$^+$].

4-Chloro-*N*,*N*-dimethylbenzamide (**2.35**)[9]



2.35

Prepared from 4-chlorobenzoic acid (Sigma-Aldrich 135585) and Me_2NH (40% *wt* in H_2O) according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 58.8 – 59.9 °C. (lit. 56 – 57 °C)[10]

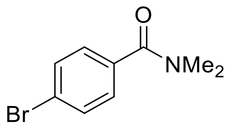
$\mathbf{R}_f$ = 0.31 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 4H), 3.10 (brs, 3H), 2.98 (brs, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 135.5, 134.6, 128.5, 39.5, 35.3.

MS (ESI) *m*/*z* 184.05 [$(M+H)^+$].

4-Bromo-*N*,*N*-dimethylbenzamide (**2.36**)[1]



2.36

Prepared from 4-bromobenzoic acid (Sigma-Aldrich 108510) and Me_2NH (40% *wt* in H_2O) according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 72.0 – 73.6 °C. (lit. 76 – 77 °C)[7]

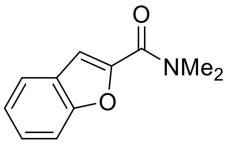
$\mathbf{R}_f$ = 0.31 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 3.10 (brs, 3H), 2.97 (brs, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 135.0, 131.5, 128.7, 123.7, 39.4, 35.3.

MS (ESI) *m*/*z* 218.06 [(M+H)$^+$].

N,*N*-Dimethylbenzofuran-2-carboxamide (**2.37**)[6]



2.37

Prepared from benzofuran-2-carboxylic acid (Sigma-Aldrich 307270), Me$_2$NH (40% *wt* in H$_2$O), and triethylamine according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 73.7 – 75.1 °C. (lit. 71 – 73 °C)[11]

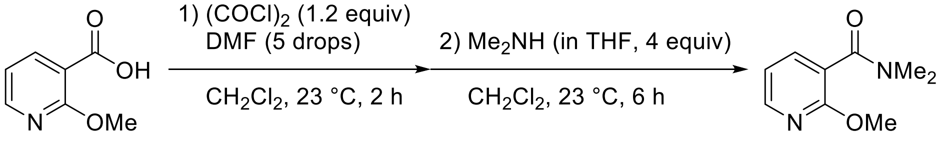
R$_f$ = 0.33 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.39 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 3.35 (brs, 2H), 3.15 (brs, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 160.9, 154.6, 149.2, 127.0, 126.3, 123.4, 122.2, 111.8, 111.6, 38.4, 36.4.

MS (ESI) *m*/*z* 190.08 [(M+H)$^+$].

2-Methoxy-*N*,*N*-dimethylnicotinamide (**2.38**)



2.38, 84%

The titled compound was synthesized using 2-methoxynicotinic acid (1.53 g, 10.0 mmol, 1.0 equiv) (TCI M2041), $(COCl)_2$ (1.0 mL, 11.7 mmol, 1.2 equiv), and Me_2NH in THF (2 M, 20 mL, 40 mmol, 4.0 equiv) by following the condition **A** described in section 5.2.2.

Purification silica gel, hexane/ethyl acetate = 2:1→1:4.

Yield 84% yield (1.51 g, 8.39 mmol) as white solid.

M.p. 95.0 – 96.8 °C.

R*f* = 0.20 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

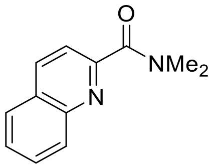
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.58 (dd, *J* = 7.2, 1.9 Hz, 1H), 6.94 (dd, *J* = 7.2, 5.0 Hz, 1H), 3.98 (s, 3H), 3.12 (s, 3H), 2.87(s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 167.7, 159.4, 147.7, 137.1, 120.4, 116.8, 53.6, 38.1, 34.9.

IR (KBr, neat) ν_{max} 2954, 2933, 1625 [ν (C=O)], 1402, 1012, 777 cm^{-1}.

HRMS (ESI) *m*/*z* calcd for $C_9H_{13}N_2O_2$ [$(M+H)^+$]: 181.0977, found: 181.0979.

N,*N*-Dimethylquinoline-2-carboxamide (**2.39**)[12]



2.39

Prepared from 2-quinolinecarboxylic acid (Sigma-Aldrich 160660) and Me_2NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

Light yellow oil.

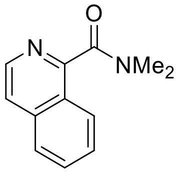
R*f* = 0.20 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.76 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.60 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 3.20 (s, 3H), 3.17 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 168.9, 154.0, 146.4, 137.0, 129.9, 129.4, 127.8, 127.5, 127.3, 120.4, 38.9, 35.6.

MS (ESI) *m*/*z* 201.08 [(M+H)$^+$].

N,*N*-Dimethylisoquinoline-1-carboxamide (**2.40**)[9]



2.40

Prepared from isoquinoline-1-carboxylic acid (TCI I0671) and Me$_2$NH (2 M in THF) according to the condition **A** described in section 2.1. The NMR spectra data are well matched with those reported.

Light yellow solid.

M.p. 135.8 – 137.8 °C. (lit. 139 – 141 °C)[13]

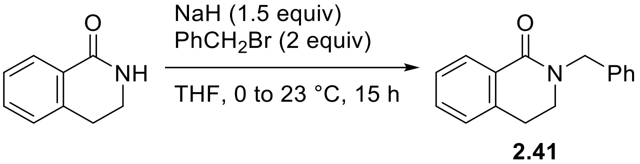
R$_f$ = 0.14 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.52 (d, *J* = 5.7 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.68 (d, *J* = 5.7 Hz, 1H), 7.62 (dd, *J* = 8.2, 7.5 Hz, 1H), 3.27 (s, 3H), 2.87 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 168.2, 155.6, 141.6, 136.4, 130.7, 128.0, 126.9, 125.9, 125.3, 121.2, 38.3, 34.8.

MS (ESI) *m*/*z* 201.08 [(M+H)$^+$].

2-Benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2.41**)[1]



2.41

Prepared by treating 3,4-dihydroisoquinolin-1(2*H*)-one (Fluorochem 076493) with sodium hydride (Sigma-Aldrich 452912) and benzyl bromide (Sigma-Aldrich B17905) in THF according to the reported procedure. The NMR spectra data are well matched with those reported.

Light yellow oil.

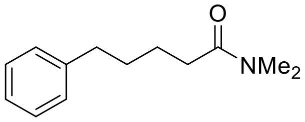
R*f* = 0.30 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.15 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.41 (ddd, *J* = 7.4, 7.4, 1.4 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.25 (m, 5H), 7.15 (d, *J* = 7.4 Hz, 1H), 4.80 (s, 2H), 3.48 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 164.5, 138.0, 137.4, 131.7, 129.4, 128.6, 128.4, 128.0, 127.4, 127.0, 126.9, 50.4, 45.3, 28.1.

MS (ESI) *m/z* 238.17 [(M+H)$^+$].

N,*N*-Dimethyl-5-phenylpentanamide (**2.42**)[9]



2.42

Prepared from 5-phenylvaleric acid (Sigma-Aldrich P37602) and Me$_2$NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

Light yellow oil.

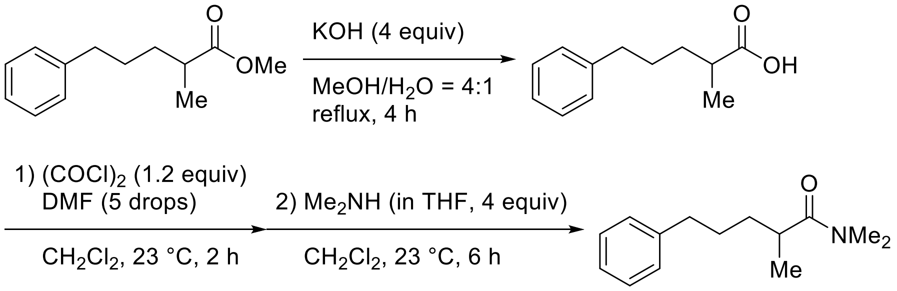
R*f* = 0.33 (eluent: hexane/ethyl acetate = 1:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 – 7.24 (m, 2H), 7.18 – 7.15 (m, 3H), 2.97 (s, 3H), 2.93 (s, 3H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.69 – 1.67 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 172.8, 142.2, 128.3, 128.1, 125.6, 37.1, 35.7, 35.2, 33.1, 31.1, 24.7.

MS (ESI) *m*/*z* 206.14 [(M+H)$^+$].

N,*N*,2-Trimethyl-5-phenylpentanamide (**2.43**)[9]



2.43

Prepared from 2-methyl-5-phenylpentanoate via its alkaline hydrolysis followed by amidation of the resulting carboxylic acid according to the reported procedure. The NMR spectra data are well matched with those reported.

Light yellow oil.

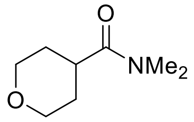
R*f* = 0.31 (eluent: hexane/ethyl acetate = 2:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 – 7.25 (m, 2H), 7.18 – 7.16 (m, 3H), 3.00 (s, 3H), 2.94 (s, 3H), 2.76 – 2.53 (m, 3H), 1.79 – 1.70 (m, 1H), 1.67 – 1.52 (m, 2H), 1.46 – 1.37 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 176.5, 142.3, 128.3, 128.2, 125.6, 37.1, 36.0, 35.55, 35.47, 33.7, 29.4, 17.4.

MS (ESI) *m*/*z* 220.16 [(M+H)$^+$].

N,*N*-Dimethyltetrahydro-2*H*-pyran-4-carboxamide **(2.44)**[1]



2.44

Prepared from tetrahydropyran-4-carboxylic acid (Fluorochem 043853) and Me_2NH (40% *wt* in H_2O) according to the condition **B** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 70.6 – 72.0 °C. (lit. 65 – 67 °C)[14]

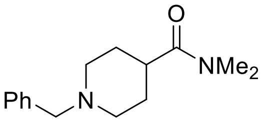
R*f* = 0.30 (eluent: hexane/ethyl acetate = 1:1, visualized by phosphomolybdic acid stain).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (ddd, *J* = 11.8, 4.1, 2.1 Hz, 2H), 3.45 (ddd, *J* = 11.8, 11.8, 2.1 Hz, 2H), 3.06 (s, 3H), 2.95 (s, 3H), 2.75 (tt, *J* = 11.3, 3.8 Hz, 1H), 1.91 (dddd, *J* = 13.5, 11.8, 11.8, 4.4 Hz, 2H), 1.61 (dddd, *J* = 13.5, 5.6, 2.1, 2.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 67.2, 37.7, 36.9, 35.6, 28.8.

MS (ESI) *m*/*z* 157.21 [$(M+H)^+$].

1-Benzyl-*N*,*N*-dimethylpiperidine-4-carboxamide (**2.45**)[1]



2.45

Prepared from 1-benzylpiperidine-4-carboxylic acid and Me_2NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

Light yellow solid.

M.p. 84.6 – 85.4 °C. (lit. 83.5 – 84.5 °C)[14]

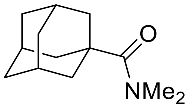
R*f* = 0.24 (eluent: ethyl acetate, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.22 (m, 5H), 3.51 (s, 2H), 3.03 (s, 3H), 2.96 – 2.93 (m, 2H), 2.93 (s, 3H), 2.47 (tt, *J* = 11.3, 3.8 Hz, 1H), 2.00 (ddd, *J* = 11.7, 11.7, 2.1 Hz, 2H), 1.87 (dddd, *J* = 12.7, 12.0, 12.0, 3.5 Hz, 1H), 1.67 – 1.64 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 175.0, 138.4, 129.0, 128.1, 126.9, 63.2, 53.1, 38.9, 36.9, 35.5, 28.5.

MS (ESI) *m*/*z* 247.16 [(M+H)$^+$].

N,*N*-Dimethyladamantane-1-carboxamide (**2.46**)[1]



2.46

Prepared from 1-adamantanecarboxylic acid (Sigma-Aldrich 106399), Me$_2$NH (2 M in THF) according to the condition **A** described in section 5.2.2. The NMR spectra data are well matched with those reported.

White solid.

M.p. 80.3 – 81.1 °C. (lit. 79 – 80 °C)[15]

R$_f$ = 0.34 (eluent: hexane/ethyl acetate = 2:1, visualized by phosphomolybdic acid stain).

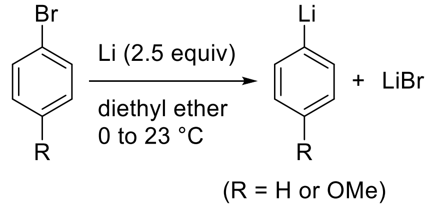
^{1}H NMR (400 MHz, CDCl$_3$) δ 3.06 (s, 6H), 2.05 – 1.99 (m, 9H), 1.76 – 1.70 (m, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 176.9, 41.6, 38.7, 38.5, 36.6, 28.5.

MS (ESI) *m*/*z* 208.15 [(M+H)$^+$].

5.2.3. Preparation of organometallic reagents

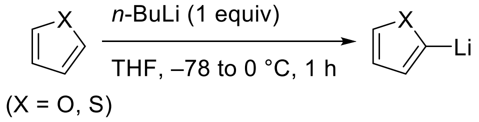
5.2.3.1. Preparation of phenyllithium[15]



In a 250 mL three-necked flask fitted with a dropping funnel, a reflux condenser, and a PTFE coated stir bar was added lithium metal granular (3.48 g, 501 mmol, 2.5 equiv) (Sigma-Aldrich, 499811) under an argon atmosphere. It was stirred vigorously for 10 min to scrape the lithium surface, and anhydrous Et_2O (20 mL) was added. A solution of bromobenzene (21 mL, 201 mmol, 1.0 equiv) (TCI B0439) in anhydrous Et_2O (80 mL) was added to the dropping funnel, and 10 mL of the solution was added to the lithium suspension at 0 °C. Vigorous reaction should take place within 5 min and a silvery surface on lithium was observed. The rest of the bromobenzene solution was then added dropwise (about 1 drop/sec) over 2 h at 0 °C and the mixture was stirred for another 30 min before warming up to 23 °C. At this moment, most of the lithium metal should have disappeared, and the mixture was heated at 40 °C for 1 h. After cooling down to 23 °C, the stirring was stopped, and the mixture was stand for 1 h to settle the precipitate. (Occasionally, crystals of PhLi might be formed upon cooling. In this case, minimum amounts of Et_2O (5 – 10 mL) was added and the mixture was stirred until the crystals were fully dissolved before transferred to the Schlenk filter.) The mixture was cannulated to a Schlenk filter, and it was filtered under an argon atmosphere to obtain a brown solution. The solid residue was washed with another 15 mL of Et_2O. The concentration was determined by the titration against *N*-benzylbenzamide. The final concentration of PhLi should be 1.00 – 1.30 M.

4-Methoxyphenyllithium was prepared by the same method using 4-bromoanisole (6.4 mL, 50.1 mmol, 1.0 equiv) (Fluorochem BR1023) and lithium metal (868 mg, 125 mmol, 2.5 equiv) in anhydrous Et_2O.

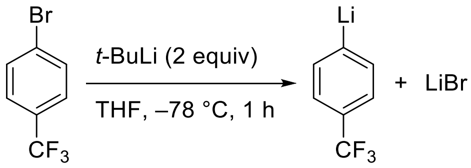
5.2.3.2. Preparation of 2-thienyllithium[17] and 2-furyllithium[18]



In a 25 mL sealed tube equipped with a PTFE coated stir bar was added distilled thiophene (1.6 mL, 20.0 mmol, 1.0 equiv) and anhydrous THF (10 mL). The mixture was cooled to –78 °C (acetone-dry ice bath). *n*-BuLi (7.8 mL, 20.0 mmol, 1.0 equiv) (2.56 M in hexane, Kanto Chemical 04935) was added dropwise over 10 min and the mixture was slowly warm up to 23 °C over 1 h. The resulting light yellow solution was titrated against 2-propanol/1,10-phenanthroline.

2-Furyllithium was prepared by the same method as above using distilled furan (1.5 mL, 20.6 mmol, 1.0 equiv) and *n*-BuLi (7.8 mL, 20.0 mmol, 1.0 equiv) in anhydrous THF (10 mL).

5.2.3.3. Preparation of aryllithium with *t*-BuLi[19]



In a 25 mL sealed tube equipped with a PTFE coated stir bar was added 4-bromobenzotrifluoride (115 µL, 0.82 mmol) and anhydrous THF (3 mL). The mixture was cooled to –78 °C (acetone-dry ice bath), and *t*-BuLi (1.2 mL, 1.58 mmol, 2.0 equiv) (1.32 M in pentane, Sigma-Aldrich 186198) was added dropwise over 5 min. The mixture was stirred at –78 °C for 1 h and used directly.

2-Pyridyllithium and (1-methyl-1*H*-indol-5-yl)lithium was prepared by the same method as above.

5.2.4. Titration of organometallic reagents

To ensure the quality of the organometallic reagents, all the organolithium reagents and Grignard reagents except for those prepared by Br-Li exchange with *t*-BuLi (section 5.2.3.3) were titrated before use. Frequently used organometallic reagents (PhLi, MeMgBr and Me_3SiCH_2MgCl) were titrated on a weekly basis. The titration methods are described below:

5.2.4.1. Titration against *N*-benzylbenzamide[20]

In a sealed tube equipped with a PTFE coated stir bar was added accurately weighted *N*-benzylbenzamide (recrystallized before use), and it was dissolved in anhydrous THF (5 mL). The solution was cooled to 0 °C, and PhLi solution in Et_2O was added dropwise *via* syringe until a light blue color persisted for 30 seconds. For example, 0.61 mL of PhLi solution was used against 145 mg (0.687 mmol) of *N*-benzylbenzamide: concentration of PhLi = 1.13 M.

MeLi (Sigma-Aldrich, 514330), *n*-BuLi (Kanto, 04935-25), *i*-PrLi (Sigma-Aldrich, 446904), and *t*-BuLi (Sigma-Aldrich, 186198) were titrated with this method (titration for *t*-BuLi was performed at –78 °C).

5.2.4.2. Titration against 2-propanol/1,10-phenanthroline[21]

The 2-propanol solution in toluene with 0.2% *wt* 1,10-phenanthroline (phen) was prepared by adding freshly distilled 2-propanol (2.5 mL, 32.7 mmol), 1,10-phenanthroline (78 mg, Sigma-Aldrich 131377) and anhydrous toluene in a 25 mL volumetric flask (1.31 M).

In a sealed tube equipped with a PTFE coated stir bar was added accurately measured MeMgBr solution in Et_2O (Sigma-Aldrich, 189898), and it was diluted with anhydrous THF (2.5 mL).

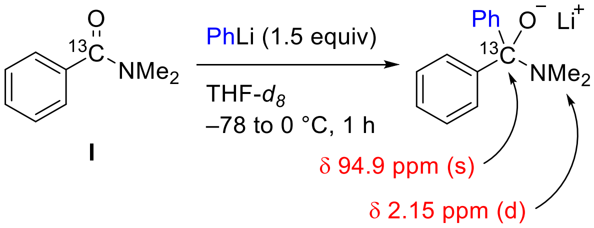
The solution was cooled to 0 °C and a stock solution of 2-propanol in toluene (1.31 M, with 0.2% *wt* phen) was added dropwise. A red/purple color appeared upon the addition of 2 to 3 drops of 2-propanol solution, and it was added until the purple color disappeared. For example, 0.56 mL of 2-propanol solution (0.734 mmol) was used for 0.25 mL of MeMgBr solution: concentration of MeMgBr = 2.93 M.

$PhCH_2MgCl$ (TCI B1933), allylMgCl (Sigma-Aldrich 225908), and ethynylmagnesium bromide (Sigma-Aldrich 346152) were titrated with this method.

5.2.4.3. Titration against a standardized HCl solution

A solution of Me_3SiCH_2MgCl in THF (Sigma-Aldrich, 256021) was carefully added to deionized water (15 mL) with vigorous stirring. Two drops of 0.1% methyl orange solution were added, and it was titrated with a standardized HCl solution (1.04 M, TCI H1202) until an orange color persisted for 30 seconds. For example, 0.47 mL of HCl solution (0.489 mmol) was used for 0.50 mL of Me_3SiCH_2MgCl solution: concentration of Me_3SiCH_2MgCl = 0.98 M. Lithium phenylacetylide (Sigma-Aldrich 340677) was titrated with this method.

5.2.5. NMR studies of anionic hemiaminal intermediate



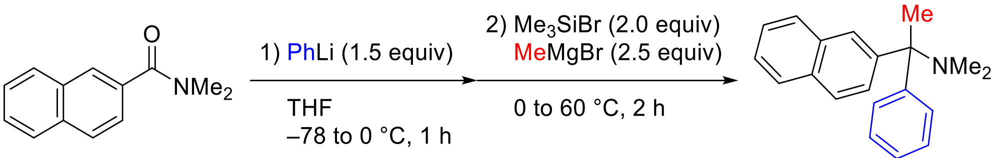
In a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of amide **I** (75.2 mg, 0.500 mmol, 1.0 equiv) in THF-d_8 (2.5 mL), and the mixture was cooled to –78 °C (dry ice-acetone bath). PhLi (0.65 mL, 0.754 mmol, 1.5 equiv) (1.16 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warm up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). After stirring at 23 °C for 15 min, an aliquot was taken to an argon flushed J. Young NMR tube to conduct ^{1}H, ^{13}C and HMBC spectroscopic analyses. NMR data for the resulting anionic hemiaminal intermediate:

^{1}H NMR (400 MHz, THF-*d$_8$*) δ 7.72 (d, *J* = 7.2 Hz, 4H), 7.10 (dd, *J* = 7.2, 6.8 Hz, 4H), 6.94 (t, *J* = 6.8 Hz, 2H), 2.15 (d, *J* = 3.4 Hz, 6H).

^{13}C NMR (100 MHz, THF-*d$_8$*) δ 154.3, 128.5, 127.8, 125.6, 94.9, 39.9.

5.2.6. General procedures for reductive functionalization of amides with Grignard reagents

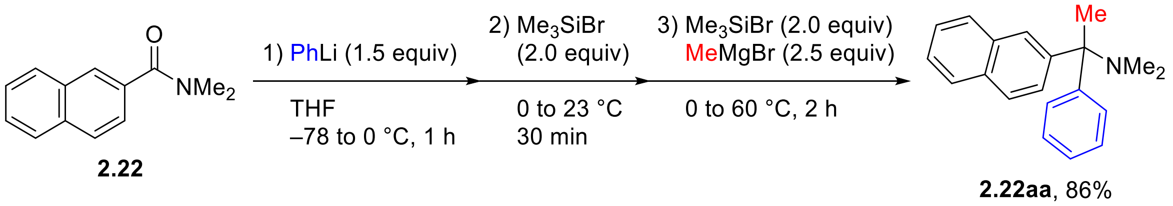
5.2.6.1. General Procedure A: in 0.5 mmol scale



2.22aa, 84%

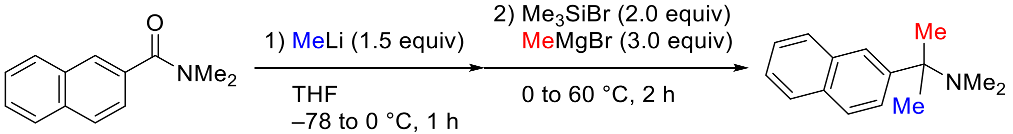
Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.22** (99.7 mg, 0.500 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (dry ice-acetone bath). PhLi (0.67 mL, 0.757 mmol, 1.5 equiv) (1.13 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was then added in one portion, and the mixture was stirred for 5 min at 0 °C. MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O) was added and the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C (ice-water bath) and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 100:4) to give a-tertiary amine **2.22aa** as light yellow solid (115 mg, 0.418 mmol) in 84% yield.

5.2.6.2. In 15 mmol scale for the synthesis of 2.22aa



Under an argon atmosphere, in a 250 mL three-necked flask fitted with a reflux condenser, a thermo sensor, and a PTFE coated stir bar was added a solution of carboxamide **2.22** (2.99 g, 15.0 mmol, 1.0 equiv) in anhydrous THF (75 mL) and it was cooled to –78 °C (dry ice-acetone bath). PhLi (16.8 mL, 22.5 mmol, 1.5 equiv) (1.34 M in Et_2O) was added dropwise over 10 minutes. After the addition of PhLi, dry ice was taken out from the bath, and the mixture was slowly warmed up to 0 °C for 1.5 h. (After 1 h, the internal temperature reached –10 °C, and the bath was replaced to an ice-water bath and stirred for 30 min). Me_3SiBr (4.0 mL, 30.3 mmol, 2.0 equiv) was added in one portion, observing that the internal temperature reached 18 °C rapidly. The ice-water bath was removed, and the mixture was stirred at 23 °C for another 30 min. The mixture was again cooled in an ice-water bath for 10 min (until the internal temperature reached 1 °C), MeMgBr (12.4 mL, 37.7 mmol, 2.5 equiv) (3.04 M in Et_2O) was added dropwise over 10 min and the mixture was then heated at 60 °C (oil bath) for 2 h (the internal temperature reached 53 °C). The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (100 mL) at 0 °C (ice-water bath) and the organic materials were extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 100:4) to give amine **2.22aa** as light yellow solid (3.54 g, 12.9 mmol) in 86% yield.

5.2.6.3. General procedure for the functionalization of carboxamides with alkyllithium reagents and functionalization of aliphatic amides (General procedure B)

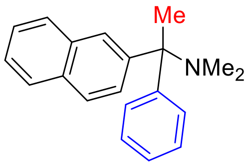


2.22

2.22ia, 58%

Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.22** (99.7 mg, 0.500 mmol) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (dry ice-acetone bath). MeLi (0.27 mL, 0.753 mmol, 1.5 equiv) (2.79 M in diethoxymethane) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me$_3$SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and then MeMgBr was **immediately** added (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et$_2$O). The mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH$_4$Cl-NH$_3$ buffer (10 mL) at 0 °C and the organic materials were extracted with CH$_2$Cl$_2$ (20 mL × 3). The combined organic layers were dried over MgSO$_4$ and filtered. The volatile materials were removed *in vacuo* and the resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate/trimethylamine = 100:5:1) to give amine **2.22ia** as colorless oil (61.9 mg, 0.290 mmol) in 58% yield.

N,*N*-Dimethyl-1-(naphthalen-2-yl)-1-phenylethan-1-amine (**2.22aa**)



2.22aa

M.p. 100.8 – 102.1 °C.

R$_f$ = 0.21 (eluent: hexane/DCM/Et$_2$O = 10:1:1, visualized by UV).

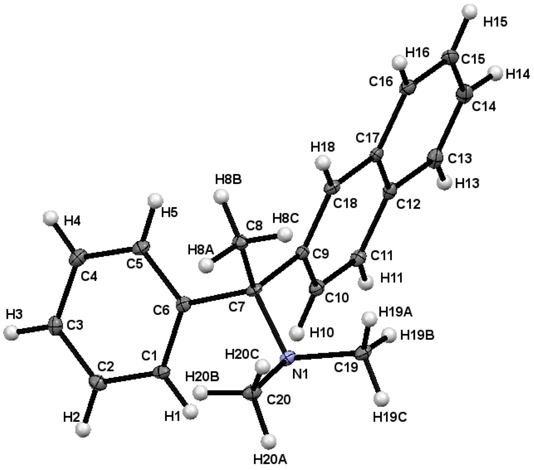
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (s, 1H), 7.82 – 7.80 (m, 1H), 7.77 – 7.75 (m, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.52 – 7.50 (m, 2H), 7.46 – 7.39 (m, 2H), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 2.20 (s, 6H), 1.85 (s, 3H).

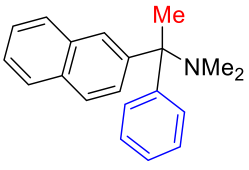
^{13}C NMR (100 MHz, CDCl$_3$) δ 145.5, 143.8, 133.1, 132.0, 128.1, 127.8, 127.7, 127.28, 127.26, 126.8, 126.1, 125.7, 125.6, 125.4, 67.0, 39.9, 19.1.

IR (KBr, neat) $\nu_{\max}$ 3055, 2983, 2821, 2779, 1597, 1490, 744, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N$ [(M+H)$^+$]: 276.1752, found: 276.1750.

Crystals of **2.22aa** suitable for X-ray crystallographic analysis were obtained by recrystallization from hexane. The ORTEP drawing of **2.22aa** is shown in Figure **5-1** (CCDC 2105303).





2.22aa

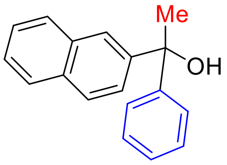
Figure 5-1 ORTEP illustration of compound **2.22aa**.

Table 5-1. Sample and crystal data for 2.22aa.		
Chemical formula	$C_{20}H_{21}N$	
Formula weight	275.38 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.160 x 0.200 x 0.220 mm	
Crystal habit	colorless block	
Crystal system	orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 23.603(2) Å	α = 90°
	b = 6.0263(7) Å Å	β = 90°
	c = 10.4104(12) Å	γ = 90°
Volume	1480.8(3) $Å^3$	
Z	4	
Density (calculated)	1.235 g/cm^3	
Absorption coefficient	0.536 mm^{-1}	
F (000)	592	

Table 5-2. Data collection and structure refinement for 2.22aa.

Theta range for data collection	5.67 to 68.21°	
Index ranges	-27<=h<=28, -6<=k<=7, -12<=l<=12	
Reflections collected	5414	
Independent reflections	2169 [R(int) = 0.0534]	
Coverage of independent reflections	98.1%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9190 and 0.8910	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	Σ w $(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2169 / 1 / 194	
Goodness-of-fit on F^2	1.043	
Final R indices	2080 data; I>2σ (I)	R1 = 0.0453, wR2 = 0.1222
	all data	R1 = 0.0465, wR2 = 0.1237
Weighting scheme	$w=1/[\sigma^2 (F_o^2)+ (0.0750P)^2+0.1116P]$ where $P= (F_o^2+2F_c^2)/3$	
Absolute structure parameter	-1.1(7)	
Extinction coefficient	0.0074(16)	
Largest diff. peak and hole	0.259 and -0.184 eÅ^{-3}	
R.M.S. deviation from mean	0.045 eÅ^{-3}	

1-(Naphthalen-2-yl)-1-phenylethan-1-ol (**2.22aa'**)[22]



2.22aa'

Light yellow oil.

Purification silica gel, hexane/ethyl acetate = 100:10.

R$_f$ = 0.29 (eluent: hexane/ethyl acetate = 20:1, visualized by UV).

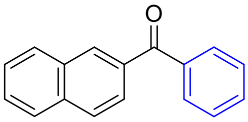
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J* = 1.4 Hz, 2H), 7.84 – 7.82 (m, 1H), 7.80 – 7.78 (m, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.43 (m, 4H), 7.40 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.31 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 2.28 (s, 1H), 2.04 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 147.7, 145.2, 133.0, 132.4, 128.22, 128.19, 127.9, 127.5, 127.0, 126.1, 125.9 (2C overlapped), 124.9, 123.7, 76.3, 30.7.

HRMS (ESI) *m/z* calcd for $C_{18}H_{17}O$ [$(M+H)^+$]: 249.1279, found: 249.1281.

IR (KBr, neat) ν_{max} 3417 [ν (O–H)], 3055, 2978, 2929, 1598, 1446, 746, 700 cm^{-1}.

Naphthalen-2-yl(phenyl)methanone (**2.22aa”**)[23]



2.22aa"

White solid.

Purification hexane/ethyl acetate = 100:1.

M.p. 71.2 − 73.0 °C. (lit. 72 – 73 °C)[24]

R$_f$ = 0.27 (eluent: hexane/ethyl acetate = 30:1, visualized by UV).

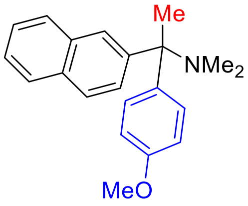
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.27 (s, 2H), 7.95 (d, *J* = 1.1 Hz, 2H), 7.93 – 7.90 (m, 2H), 7.88 – 7.85 (m, 2H), 7.64 – 7.59 (m, 2H), 7.57 – 7.50 (m, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 196.7, 137.8, 135.2, 134.8, 132.3, 132.2, 131.8, 130.0, 129.3, 128.28, 128.27, 128.24, 127.8, 126.7, 125.7.

IR (KBr, neat) ν_{max} 3057, 1651 (C=O), 1597, 1467, 1288, 750, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{13}O$ [$(M+H)^+$]: 233.0966, found: 233.0963.

1-(4-Methoxyphenyl)-*N*,*N*-dimethyl-1-(naphthalen-2-yl)ethan-1-amine (**2.22ba**)



2.22ba

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of 4-methoxyphenyllithium (0.46 mL, 0.750 mmol, 1.5 equiv) (1.63 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.41 mL, 1.25 mmol, 2.5 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/ethyl acetate = 100:4.

Yield 47% yield (71.3 mg, 0.233 mmol) as light yellow oil.

R*f* = 0.19 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

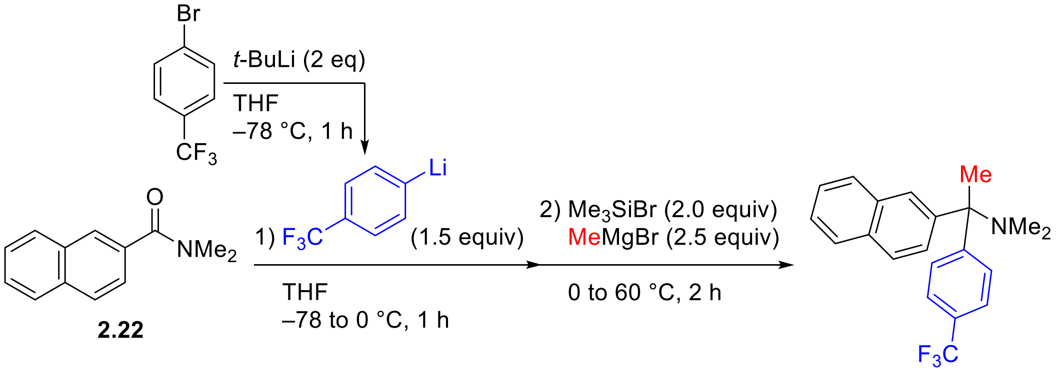
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.39 (m, 4H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 2.20 (s, 6H), 1.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 144.3, 137.5, 133.1, 132.0, 128.9, 128.1, 127.28, 127.25, 126.7, 125.7, 125.5, 125.2, 113.0, 66.5, 55.1, 39.9, 19.3.

IR (KBr, neat) ν_{max} 3055, 2821, 2779, 1606, 1502, 1180, 1249 [*v* (C–O)], 1031 [*v* (C–O)], 746 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{21}H_{24}NO$ [$(M+H)^+$]: 306.1858, found: 306.1860.

N,N-Dimethyl-1-(naphthalen-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-amine (**2.22ca**)



2.22

2.22ca, 50%

In a 25 mL sealed tube equipped with a PTFE coated stir bar was added 4-bromobenzotrifluoride (185 mg, 0.82 mmol) and anhydrous THF (3 mL). The mixture was cooled to –78 °C (dry ice- acetone bath), and *t*-BuLi (1.2 mL, 1.58 mmol, 2.0 equiv) (1.32 M in pentane, Sigma-Aldrich 186198) was added dropwise over 5 min. The mixture was stirred at –78 °C for 1 h. A solution of carboxamide **2.22** (99.6 mg, 0.500 mmol) in THF (3.0 mL) was added at –78 °C and slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C. MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/ Et_2O = 100:4) to give **2.22ca** as colorless oil (84.9 mg, 0.248 mmol) in 50% yield.

R_f = 0.38 (eluent: hexane/ethyl acetate = 50:1, visualized by UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.82 – 7.80 (m, 1H), 7.78 – 7.76 (m, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.52 (m, 3H), 7.47 – 7.41 (m, 2H), 2.20 (s, 6H), 1.87 (s, 3H).

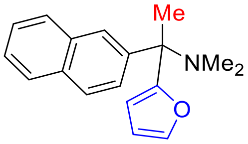
^{13}C NMR (100 MHz, CDCl$_3$) δ 150.2, 142.5, 133.1, 132.1, 128.3 (q, $^2J_{C\text{-}F}$ = 32.3 Hz), 128.2, 127.9, 127.5, 127.3, 126.5, 126.0, 125.9, 125.5, 124.8 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 270.7 Hz), 67.0, 39.8, 18.7.

^{19}F NMR (376 MHz, CDCl$_3$) δ −62.4.

IR (KBr, neat) ν_{max} 3059, 2825, 2785, 1616, 1504, 1120, 746 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NF_3$ [(M+H)$^+$]: 344.1626, found: 344.1629.

1-(Furan-2-yl)-*N*,*N*-dimethyl-1-(naphthalen-2-yl)ethan-1-amine (**2.22da**)



2.22da

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of 2-furyllithium (0.67 mL, 0.750 mmol, 1.5 equiv) (1.12 M in THF), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.41 mL, 1.25 mmol, 2.5 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:4.

Yield 91% yield (120 mg, 0.452 mmol) as colorless oil.

R$_f$ = 0.21 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

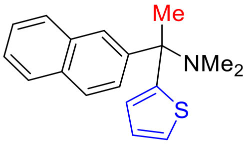
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 – 7.77 (m, 4H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.44 – 7.41 (m, 3H), 6.36 – 6.35 (m, 1H), 6.30 – 6.29 (m, 1H), 2.25 (s, 3H), 1.78 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 157.2, 143.3, 141.7, 133.2, 132.4, 128.2, 127.5, 127.3, 125.9, 125.7, 125.6, 125.4, 109.6, 108.3, 64.6, 40.0, 22.1.

IR (KBr, neat) ν_{max} 3055, 2825, 2781, 1597, 1504, 1012, 734 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NO$ [(M+H)$^+$]: 266.1545, found: 266.1542.

N,*N*-Dimethyl-1-(naphthalen-2-yl)-1-(thiophen-2-yl)ethan-1-amine (**2.22ea**)



2.22ea

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of 2-furyllithium (0.77 mL, 0.755 mmol, 1.5 equiv) (0.98 M in THF), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.41 mL, 1.25 mmol, 2.5 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:4.

Yield 55% yield (77.5 mg, 0.276 mmol) as light yellow oil.

R_f = 0.30 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

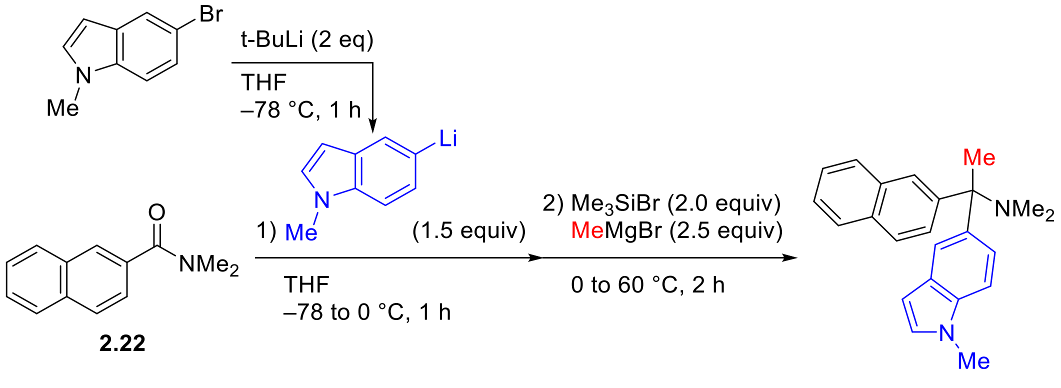
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.84 – 7.75 (m, 4H), 7.44 – 7.42 (m, 2H), 7.20 (dd, J = 2.9, 2.9 Hz, 1H), 6.92 – 6.92 (m, 2H), 2.25 (s, 6H), 1.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 144.4, 133.1, 132.3, 128.2, 127.5, 127.3, 126.0, 125.9, 125.8, 125.7, 125.2, 125.0, 124.3, 65.8, 39.9, 21.7.

IR (KBr, neat) ν_{max} 3055, 2823, 2781, 1597, 1504, 1458, 947, 746, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NS$ [$(M+H)^+$]: 282.1316, found: 282.1316.

N,*N*-Dimethyl-1-(1-methyl-1*H*-indol-5-yl)-1-(naphthalen-2-yl)ethan-1-amine (**2.22fa**)



2.22fa, 69%

In a 25 mL sealed tube equipped with a PTFE coated stir bar was added 5-bromo-1-methylindole (168 mg, 0.80 mmol) (Sigma-Aldrich 718300) and anhydrous THF (3 mL). The mixture was cooled to –78 °C (dry ice-acetone bath), and *t*-BuLi (1.2 mL, 1.61 mmol, 2.0 equiv) (1.34 M in pentane, Sigma-Aldrich 186198) was added dropwise over 5 min. The mixture was stirred at –78 °C for 1 h. A solution of carboxamide **2.22** (99.6 mg, 0.500 mmol) in THF (3.0 mL) was added at –78 °C and slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (ice-water bath). MeMgBr (0.42 mL, 1.28 mmol, 2.5 equiv) (3.04 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O/triethylamine = 100:5:1) to give **2.22fa** as yellow oil (114 mg, 0.347 mmol) in 69% yield.

R*f* = 0.33 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

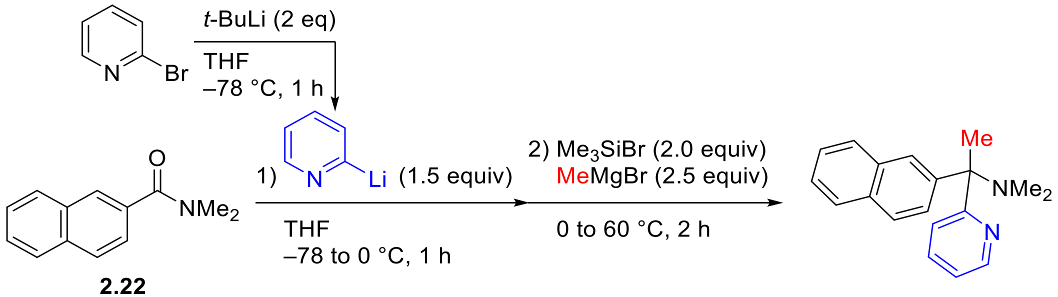
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 1.1 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.35 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 2.9 Hz, 1H), 6.43 (d, *J* = 2.9 Hz, 1H), 3.74 (s, 3H), 2.24 (s, 6H), 1.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 136.4, 135.3, 133.1, 131.9, 128.8, 128.2, 127.9, 127.2, 127.1, 127.0, 125.6, 125.4, 125.3, 122.5, 119.6, 108.4, 101.2, 67.1, 40.1, 32.8, 19.7.

IR (KBr, neat) ν_{max} 3055, 2981, 2819, 2779, 1599, 1487, 1460, 748, 723 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{23}H_{25}N_2$ [$(M+H)^+$]: 329.2018, found: 329.2018.

N,*N*-Dimethyl-1-(naphthalen-2-yl)-1-(pyridin-2-yl)ethan-1-amine (**2.22ga**)



2.22

2.22ga, 68%

In a 25 mL sealed tube equipped with a PTFE coated stir bar was added 2-bromopyridine (127 mg, 0.80 mmol) (Sigma-Aldrich B80100) and anhydrous THF (3 mL). The mixture was cooled to –78 °C (dry ice-acetone bath), and *t*-BuLi (1.2 mL, 1.61 mmol, 2.0 equiv) (1.34 M in pentane, Sigma-Aldrich 186198) was added dropwise over 5 min. The mixture was stirred at –78 °C for 1 h. A solution of carboxamide **2.22** (99.6 mg, 0.500 mmol) in THF (3.0 mL) was added at –78 °C and slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me$_3$SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (ice-water bath). MeMgBr (0.41 mL, 1.25 mmol, 2.5 equiv) (3.05 M in Et$_2$O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH$_4$Cl-NH$_3$ buffer (10 mL) at 0°C and the organic materials were extracted with CH$_2$Cl$_2$ (20 mL × 3). The combined organic layers were dried over MgSO$_4$ and filtered. The volatile materials were removed, and the resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate/triethylamine = 100:6:1) to give **2.22ga** as light brown solid (93.6 mg, 0.339 mmol) in 68% yield.

M.p. 103.4 – 105.0 °C.

R$_f$ = 0.31 (eluent: hexane/ethyl acetate = 5:1, visualized by UV).

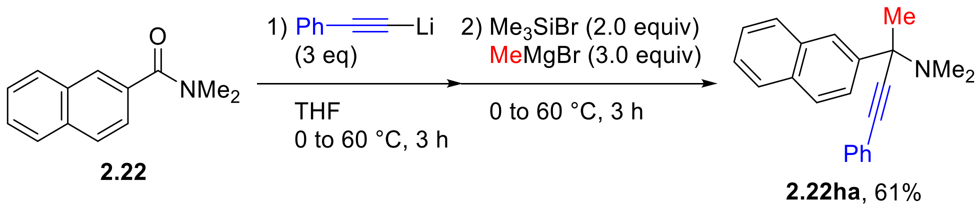
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.0 Hz, 1H), 7.98 (s, 1H), 7.81 – 7.80 (m, 1H), 7.75 – 7.68 (m, 4H), 7.58 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.04 (dd, *J* = 5.8, 5.8 Hz, 1H), 2.25 (s, 6H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 148.3, 143.4, 135.9, 133.2, 133.1, 128.2, 127.4, 127.2, 126.2, 125.7, 125.63, 125.60, 122.6, 121.1, 69.2, 39.9, 15.4.

IR (KBr, neat) ν_{max} 3055, 2823, 2783, 1585, 1504, 1460, 746 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2$ [(M+H)$^+$]: 277.1705, found: 277.1704.

N,*N*-Dimethyl-2-(naphthalen-2-yl)-4-phenylbut-3-yn-2-amine (**2.22ha**)



The titled compound was synthesized with a modified protocol from general procedure **A**: Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.22** (99.7 mg, 0.500 mmol) in anhydrous THF (2.5 mL) and it was cooled to 0 °C. Lithium phenylacetylide (1.7 mL, 1.56 mmol, 3.1 equiv) (0.915 M in THF) was added dropwise over 30 seconds, and then the mixture was heated at 60 °C (oil bath) for 2 h. After the mixture was cooled to 0 °C (ice-water bath), Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C. MeMgBr (0.50 mL, 1.53 mmol, 3.1 equiv) (3.05 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O = 50:1) to give **2.22ha** as yellow oil (91.8 mg, 0.418 mmol) in 61% yield.

R$_f$ = 0.26 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

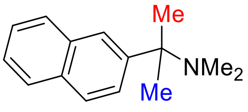
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24 (s, 2H), 7.88 – 7.82 (m, 4H), 7.61 – 7.59 (m, 2H), 7.51 – 7.43 (m, 2H), 7.40 – 7.33 (m, 3H), 2.33 (s, 6H), 1.79 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 142.6, 133.1, 132.8, 131.9, 128.4, 128.21, 128.15, 128.0, 127.5, 125.9, 125.8, 125.4, 124.5, 123.3, 88.4, 87.8, 64.4, 40.6, 31.0.

IR (KBr, neat) ν_{max} 3057, 2821, 2779, 2222 [ν(C≡C)], 1633, 1598, 754 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N$ [(M+H)$^+$]: 300.1752, found: 300.1751.

N,*N*-Dimethyl-2-(naphthalen-2-yl)propan-2-amine (**2.22ia**)



2.22ia

This compound was prepared according to general procedure **B** (section 5.2.6.3) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of MeLi (0.27 mL, 0.753 mmol, 1.5 equiv) (2.79 M in diethoxymethane), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/Et_2O/triethylamine = 100:5:1.

Yield 58% yield (61.9 mg, 0.290 mmol) as colorless oil.

R$_f$ = 0.24 (eluent: hexane/DCM/ ethyl acetate = 10:1:1, visualized by UV).

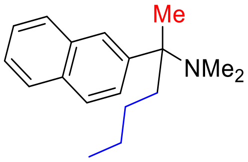
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82 – 7.79 (m, 4H), 7.75 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.47 – 7.40 (m, 2H), 2.20 (s, 6H), 1.45 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 146.6, 133.2, 132.2, 128.0, 127.5, 127.3, 125.7, 125.39, 125.37, 124.0, 59.6, 39.1, 23.1.

IR (KBr, neat) ν_{max} 3057, 1598, 1502, 744 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}N$ [(M+H)$^+$]: 214.1596, found: 214.1599.

N,*N*-Dimethyl-2-(naphthalen-2-yl)hexan-2-amine (**2.22ja**)



2.22ja

This compound was prepared according to general procedure **B** (section 5.2.6.3) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of *n*-BuLi (0.30 mL, 0.768 mmol, 1.5 equiv) (2.56 M in diethoxymethane), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.50 mL, 1.53 mmol, 3.0 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/Et_2O/triethylamine = 100:5:1.

Yield 66% yield (83.8 mg, 0.329 mmol) as light yellow oil.

R*f* = 0.36 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

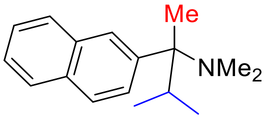
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 4H), 7.69 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.47 – 7.41 (m, 2H), 2.19 (s, 6H), 1.84 (ddd, *J* = 12.7, 12.7, 4.5 Hz, 1H), 1.70 (ddd, *J* = 12.7, 12.7, 4.5 Hz, 1H), 1.40 (s, 3H), 1.16 (tq, *J* = 7.3, 7.3 Hz, 2H), 1.04 – 0.93 (m, 1H), 0.87 – 0.79 (m, 1H), 0.75 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 133.0, 132.2, 128.0, 127.32, 127.28, 125.9, 125.6, 125.4, 125.3, 62.6, 41.5, 38.9, 27.0, 23.3, 14.0, 13.9.

IR (KBr, neat) ν_{max} 3057, 2935, 2819, 2777, 1634, 1598, 1504, 1463, 744 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{26}N$ [(M+H)$^+$]: 256.2065, found: 256.2065.

N,*N*,3-Trimethyl-2-(naphthalen-2-yl)butan-2-amine (**2.22ka**)



2.22ka

This compound was prepared according to general procedure **B** (section 5.2.6.3) from amide **1** (99.6 mg, 0.500 mmol) through addition of *i*-PrLi (1.6 mL, 0.770 mmol, 1.5 equiv) (0.481 M in pentane), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.50 mL, 1.53 mmol, 3.0 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/Et_2O/triethylamine = 100:5:1.

Yield 31% yield (37.7 mg, 0.156 mmol) as colorless oil.

R*f* = 0.36 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

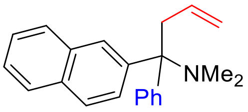
^{1}H NMR (400 MHz, C_6D_6) δ 7.84 (s, 1H), 7.78 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.76 – 7.73 (m, 1H), 7.69 – 7.65 (m, 2H), 7.31 – 7.26 (m, 2H), 2.10 (s, 6H), 1.95 (sept, *J* = 6.7 Hz, 1H), 1.26 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.65 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 132.8, 132.1, 128.1, 127.25, 127.22, 127.0, 126.1, 125.5, 125.4, 65.7, 39.0, 34.4, 18.7, 17.2, 12.8.

IR (KBr, neat) ν_{max} 3057, 2976, 2821, 2779, 1631, 1598, 1502, 1463, 744 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N$ [$(M+H)^+$]: 242.1909, found: 242.1906.

<u>*N*,*N*-Dimethyl-1-(naphthalen-2-yl)-1-phenyl-2-(trimethylsilyl)ethan-1-amine (**2.22ab**)</u>



2.22ab

This compound was prepared according to general procedure **A** (section 5.2.6.1)from amide **2.22** (99.6 mg, 0.500 mmol) through addition of PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and allylMgCl (0.68 mL, 1.26 mmol, 2.5 equiv) (1.86 M in THF).

Purification silica gel, hexane/Et_2O = 100:2.

Yield 92% yield (137 mg, 0.461 mmol) as colorless oil.

R*f* = 0.38 (eluent: hexane/ethyl acetate = 50:1, visualized by UV).

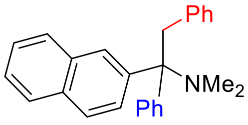
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.85 – 7.81 (m, 2H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.48 – 7.46 (m, 2H), 7.38 – 7.25 (m, 6H), 5.57 (dddd, *J* = 17.0, 10.1, 6.9, 6.9, 1H), 4.91 – 4.86 (m, 2H), 3.09 (dd, *J* = 14.3, 6.9 Hz, 1H), 3.04 (dd, *J* = 14.3, 6.9 Hz, 1H), 2.15 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 140.0, 138.7, 134.5, 132.6, 132.2, 129.6 (2C overlapped), 128.3 (2C overlapped), 128.0, 127.3, 127.1, 126.5, 126.3, 125.7, 117.0, 71.0, 43.5, 39.7.

IR (KBr, neat) ν_{max} 3055, 2937, 2823, 2781, 1637 [ν (C=C)], 1597, 1444, 912 [ν (C=C)], 746, 705 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N$ [(M+H)$^+$]: 302.1909, found: 302.1907.

N,*N*-Dimethyl-1-(naphthalen-2-yl)-1,2-diphenylethan-1-amine (**2.22ac**)



2.22ac

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and $PhCH_2MgCl$ (1.4 mL, 1.30 mmol, 2.6 equiv) (0.931 M in THF).

Purification silica gel, hexane/ethyl acetate = 100:2.

Yield 91% yield (160 mg, 0.455 mmol) as light yellow oil.

R$_f$ = 0.28 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

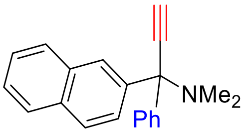
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 – 7.79 (m, 1H), 7.75 – 7.73 (m, 2H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.29 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.26 – 7.22 (m, 5H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.90 (dd, *J* = 7.4, 7.4 Hz, 2H), 6.61 (d, *J* = 7.4 Hz, 2H), 3.60 (d, *J* = 13.8 Hz, 1H), 3.58 (d, *J* = 13.8 Hz, 1H), 2.20 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 139.7, 137.9, 137.5, 132.5, 132.1, 130.5, 129.9, 128.5 (2C overlapped), 128.2, 127.2, 127.1, 126.8, 126.3, 125.8, 125.63, 125.59, 125.5, 72.7, 44.8, 40.0.

IR (KBr, neat) *ν*$_{max}$ 3055, 2937, 2823, 2781, 1597, 1494, 746, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N$ [(M+H)$^+$]: 352.2065, found: 352.2066.

N,*N*-Dimethyl-1-(naphthalen-2-yl)-1-phenylprop-2-yn-1-amine (**2.22ad**)



2.22ad

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and ethynylmagnesium bromide (2.5 mL, 1.28 mmol, 2.6 equiv) (0.51 M in THF).

Purification silica gel, hexane/Et_2O = 100:2.

Yield 86% yield (122 mg, 0.428 mmol) as light yellow solid.

M.p. 103.2 – 106.3 °C.

R*f* = 0.36 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

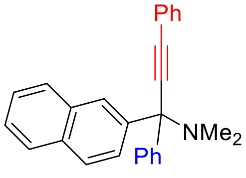
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.30 (s, 1H), 7.86 – 7.82 (m, 4H), 7.74 – 7.70 (m, 2H), 7.45 – 7.38 (m, 2H), 7.25 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 2.91 (s, 1H), 2.27 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.8, 141.5, 133.2, 132.5, 128.23, 128.20, 128.0, 127.4, 127.0, 126.9, 125.9, 125.8, 125.4, 124.9, 80.7, 77.4, 72.6, 40.9.

IR (KBr, neat) *ν*$_{max}$ 3290 [*ν* (C≡C)], 3055, 2987, 2864, 2783, 2099 [*ν* (C≡C)], 1597, 1489, 742, 700, 678 [*ν* (≡C–H)] cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N$ [(M+H)$^+$]: 286.1596, found: 286.1596.

N,*N*-Dimethyl-1-(naphthalen-2-yl)-1,3-diphenylprop-2-yn-1-amine (**2.22ae**)



2.22ae

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.7 mg, 0.500 mmol) through addition of PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and lithium phenylacetylide (1.4 mL, 1.29 mmol, 2.6 equiv) (0.92 M in THF).

Purification silica gel, hexane/Et_2O = 100:1.

Yield 83% yield (150 mg, 0.416 mmol) as light yellow solid.

M.p. 117.8 – 119.5 °C.

R*f* = 0.36 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

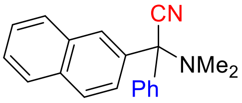
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.92 – 7.89 (m, 3H), 7.85 – 7.83 (m, 1H), 7.75 – 7.72 (m, 2H), 7.69 – 7.66 (m, 2H), 7.45 – 7.37 (m, 5H), 7.27 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 2.35 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 144.3, 142.1, 133.2, 132.5, 132.0, 128.4, 128.30, 128.27, 128.2, 128.0, 127.4, 127.03, 126.96, 125.9, 125.8, 125.5, 125.1, 123.3, 89.9, 87.0, 73.1, 41.1.

IR (KBr, neat) ν_{max} 3057, 2987, 2862, 2781, 2214 [ν (C≡C)], 1597, 1489, 750, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{27}H_{24}N$ [(M+H)$^+$]: 362.1909, found: 362.1908.

2-(Dimethylamino)-2-(naphthalen-2-yl)-2-phenylacetonitrile (**2.22af**)



2.22af

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of PhLi (0.66 mL, 0.752 mmol, 1.5 equiv) (1.14 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and tetrabutylammonium cyanide (337 mg, 1.25 mmol, 2.5 equiv) (Sigma-Aldrich 358665).

Purification neutral alumina, hexane/CH_2Cl_2 = 100:15.

Yield 66% yield (95.2 mg, 0.332 mmol) as white solid.

M.p. 108.6 – 110.5 °C.

R*f* = 0.29 (eluent: hexane/ethyl acetate = 50:1, visualized by UV).

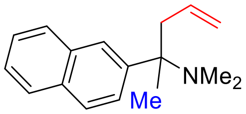
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.86 (d, *J* = 7.4 Hz, 1H), 7.79 – 7.71 (m, 5H), 7.50 – 7.44 (m, 2H), 7.32 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 2.36 (s, 6H).

^{13}C NMR (100 MHz, acetone-*d*$_6$) δ 141.3, 138.9, 134.1, 134.0, 129.94, 129.91, 129.3, 129.2, 128.5, 127.7, 127.6, 127.1, 125.9, 124.4, 117.2, 78.1, 41.7.

IR (KBr, neat) ν_{max} 3059, 2997, 2956, 2870, 2789, 2222 [ν (C≡N)], 1597, 1448, 744, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_2$ [$(M+H)^+$]: 287.1548, found: 287.1548.

N,N-Dimethyl-2-(naphthalen-2-yl)pent-4-en-2-amine (**2.22gb**)



2.22gb

This compound was prepared according to general procedure **B** (section 5.2.6.3) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of MeLi (0.27 mL, 0.753 mmol, 2.5 equiv) (2.79 M in diethoxymethane), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and allylMgCl (0.81 mL, 1.51 mmol, 3.0 equiv) (1.86 M in THF).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:5:1.

Yield 60% yield (72.4 mg, 0.302 mmol) as colorless oil.

R$_f$ = 0.22 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

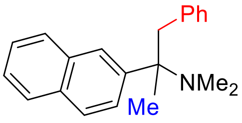
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 – 7.78 (m, 3H), 7.75 (s, 1H), 7.71 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.47 – 7.41 (m, 2H), 5.34 (dddd, *J* = 17.0, 10.0, 8.1, 6.0 Hz, 1H), 4.92 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.83 (dd, *J* = 10.0, 1.6 Hz, 1H), 2.68 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.50 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.22 (s, 6H), 1.41 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.7, 135.3, 133.0, 132.3, 128.1, 127.4, 127.3, 125.9, 125.6, 125.54, 125.47, 117.0, 62.5, 46.0, 39.0, 14.1.

IR (KBr, neat) ν_{max} 3057, 2976, 2819, 2777, 1637 [ν (C=C)], 1599, 1504, 1369, 966, 912 [ν (C=C)], 740, 690 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{22}N$ [(M+H)$^+$]: 240.1752, found: 240.1750.

N,*N*-Dimethyl-2-(naphthalen-2-yl)-1-phenylpropan-2-amine (**2.22gc**)



2.22gc

This compound was prepared according to general procedure **B** (section 5.2.6.3) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of MeLi (0.27 mL, 0.753 mmol, 1.5 equiv) (2.79 M in diethoxymethane), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and $PhCH_2MgCl$ (1.7 mL, 1.56 mmol, 3.1 equiv) (0.92 M in THF).

Purification silica gel, hexane/Et_2O/triethylamine = 100:5:1.

Yield 49% yield (71.5 mg, 0.247 mmol) as white solid.

M.p. 91.0 – 92.7 °C.

R$_f$ = 0.19 (eluent: hexane/ethyl acetate = 5:1, visualized by UV).

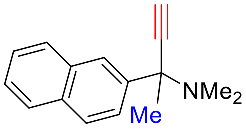
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 – 7.76 (m, 3H), 7.71 (dd, *J* = 8.7, 1.2 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.44 – 7.37 (m, 3H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.91 (dd, *J* = 7.3, 7.3 Hz, 2H), 6.54 (d, *J* = 7.3 Hz, 2H), 3.14 (d, *J* = 12.7 Hz, 1H), 3.12 (d, *J* = 12.7 Hz, 1H), 2.29 (s, 6H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.1, 138.1, 132.9, 132.3, 130.6, 128.1, 127.3, 127.2, 127.1, 126.3, 126.2, 125.7, 125.5, 125.4, 64.0, 47.9, 39.2, 12.3.

IR (KBr, neat) ν_{max} 3057, 2978, 2819, 2777, 1598, 1506, 742, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N$ [(M+H)$^+$]: 290.1909, found: 290.1909.

N,N-Dimethyl-2-(naphthalen-2-yl)but-3-yn-2-amine (**2.22gd**)



2.22gd

This compound was prepared according to general procedure **B** (section 5.2.6.3) from amide **2.22** (99.6 mg, 0.500 mmol) through addition of MeLi (0.27 mL, 0.753 mmol, 1.5 equiv) (2.79 M in diethoxymethane), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and ethynylmagnesium bromide (3.0 mL, 1.56 mmol, 3.1 equiv) (0.52 M in THF).

Purification silica gel, hexane/Et_2O = 100:5, then PTLC, hexane/acetone = 10:1.

Yield 42% yield (47.0 mg, 0.210 mmol) as light yellow solid.

M.p. 103.2 – 106.3 °C.

R*f* = 0.32 (eluent: hexane/ethyl acetate = 15:1, visualized by UV).

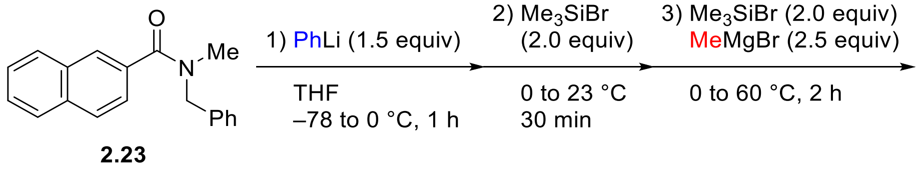
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.19 (s, 1H), 7.87 – 7.81 (m, 3H), 7.78 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.49 – 7.43 (m, 2H), 2.69 (s, 1H), 2.24 (s, 6H), 1.70 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 142.4, 133.1, 132.8, 128.2, 128.0, 127.4, 125.9, 125.8, 125.2, 124.3, 81.9, 75.6, 63.7, 40.4, 31.2.

IR (KBr, neat) ν_{max} 3296 [*ν* (C≡C)], 2086 [*ν* (C≡C)], 3059, 2987, 2860, 2783, 1595, 1558, 1508, 819, 740, 639 [*ν* (≡C–H)] cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{18}N$ [(M+H)$^+$]: 224.1439, found: 224.1441.

N-Benzyl-*N*-methyl-1-(naphthalen-2-yl)-1-phenylethan-1-amine (**2.23aa**)



2.23

2.23aa, 81%

The titled compound was synthesized with a modified protocol from the general procedure **A** (section 5.2.6.1): Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of amide **2.23** (138 mg, 0.502 mmol) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (dry ice-acetone bath). PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was warmed up to 23 °C and stirred for 30 min. The mixture was cooled to 0 °C (ice-water bath). MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O = 100:1) to give **2.23aa** as colorless oil (142 mg, 0.405 mmol) in 81% yield.

R_f = 0.38 (eluent: hexane/ethyl acetate = 50:1, visualized by UV).

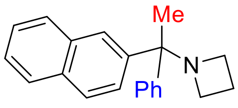
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.83 – 7.79 (m, 2H), 7.76 – 7.72 (m, 2H), 7.67 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.4 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.35 (dd, J = 7.4, 7.4 Hz, 2H), 7.30 – 7.22 (m, 3H), 7.15 (t, J = 7.4 Hz, 1H), 3.57 (d, J = 14.3 Hz, 1H), 3.55 (d, J = 14.3 Hz, 1H), 2.13 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 146.3, 144.2, 140.7, 133.2, 132.0, 128.2, 128.12, 128.08, 128.0, 127.6, 127.4, 127.3, 126.52, 126.46, 126.2, 125.8, 125.6, 125.2, 67.6, 56.2, 36.3, 18.6.

IR (KBr, neat) ν_{max} 3057, 2985, 2845, 2796, 1599, 1492, 740, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N$ [(M+H)$^+$]: 352.2065, found: 352.2063.

1-(1-(Naphthalen-2-yl)-1-phenylethyl)azetidine (**2.24aa**)



2.24aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.24** (106 mg, 0.502 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:4:1.

Yield 88% yield (126 mg, 0.439 mmol) as white solid.

M.p. 101.4 – 102.9 °C.

R$_f$ = 0.16 (eluent: hexane/ethyl acetate = 15:1, visualized by UV).

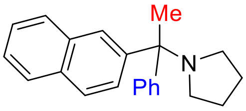
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (s, 1H), 7.86 – 7.84 (m, 1H), 7.80 – 7.77 (m, 1H) ,7.70 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.36 – 7.26 (m, 5H), 7.22 (t, *J* = 7.0 Hz, 1H), 3.22 – 3.14 (m, 4H), 1.90 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.77 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 144.3, 142.6, 133.0, 132.1, 128.2, 128.1, 127.7, 127.4, 127.2, 127.0, 126.4, 125.8, 125.62, 125.59, 65.4, 48.0, 23.2, 16.7.

IR (KBr, neat) ν_{max} 3053, 2956, 2912, 2848, 1597, 1489, 746, 702 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{21}H_{22}N$ [(M+H)$^+$]: 288.1752, found: 288.1751.

1-(1-(Naphthalen-2-yl)-1-phenylethyl)pyrrolidine (**2.25aa**)



2.25aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.25** (113 mg, 0.500 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:4:1.

Yield 88% yield (133 mg, 0.442 mmol) as light yellow oil.

R*f* = 0.26 (eluent: hexane/ethyl acetate = 100:1, visualized by UV).

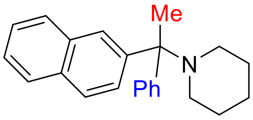
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, *J* = 0.9 Hz, 1H), 7.82 – 7.80 (m, 1H), 7.78 – 7.76 (m, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.50 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.46 – 7.39 (m, 4H), 7.28 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 2.56 – 2.47 (m, 4H), 1.89 (s, 3H), 1.73 – 1.66 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 145.5, 143.5, 133.0, 132.0, 128.2, 128.0, 127.6, 127.3, 127.2, 126.9, 126.1, 125.7, 125.6, 125.5, 65.1, 46.7, 23.5, 23.4.

IR (KBr, neat) ν_{max} 3059, 2966, 2872, 2810, 1632, 1504, 744, 703 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N$ [(M+H)$^+$]: 302.1909, found: 302.1910.

1-(1-(Naphthalen-2-yl)-1-phenylethyl)piperidine (**2.26aa**)



2.26aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.26** (120 mg, 0.502 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate = 200:1.

Yield 89% yield (140 mg, 0.444 mmol) as light yellow solid.

M.p. 112.1 – 113.9 °C.

R*f* = 0.29 (eluent: hexane/ethyl acetate = 100:1, visualized by UV).

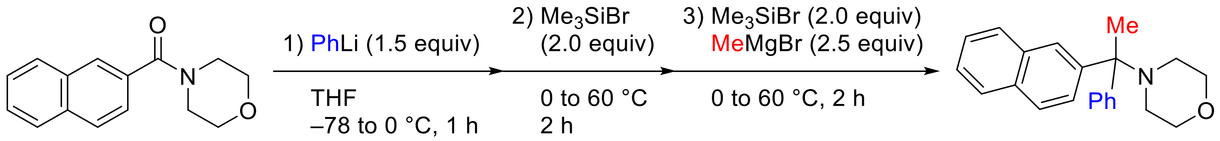
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.79 – 7.77 (m, 1H), 7.75 – 7.72 (m, 1H), 7.69 (s, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 2.41 – 2.38 (m, 4H), 1.86 (s, 3H), 1.64 – 1.58 (m ,4H), 1.48 – 1.42 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 144.5, 133.2, 131.9, 128.1, 127.8, 127.4, 127.31, 127.26, 126.5, 125.9, 125.6, 125.5, 125.0, 67.3, 48.6, 26.9, 25.2, 18.3.

IR (KBr, neat) ν_{max} 3055, 2929, 2846, 2804, 1596, 742, 702 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{23}H_{26}N$ [$(M+H)^+$]: 316.2065, found: 316.2067.

4-(1-(Naphthalen-2-yl)-1-phenylethyl)morpholine (**2.27aa**)



2.27

2.27aa, 89%

The titled compound was synthesized with a slightly modified protocol from the general procedure **A** (section 5.2.6.1): Under argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.27** (127 mg, 0.502 mmol) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (acetone-dry ice bath). PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was heated at 60 °C (oil bath) for 2 h. After the mixture was cooled to 0 °C (ice-water bath), MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O) was added and then the mixture was heated at 60 °C 2 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0°C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O = 100:5) to give **2.27aa** as colorless oil (142 mg, 0.446 mmol) in 89% yield.

M.p. 96.5 – 98.7 °C.

R*f* = 0.30 (eluent: hexane/ethyl acetate = 15:1, visualized by UV).

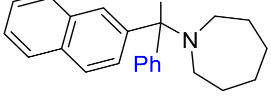
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.81 – 7.79 (m, 1H), 7.76 – 7.74 (m, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.65 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.28 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 3.77 (dd, *J* = 4.5, 4.5 Hz, 4H), 2.51 (ddd, *J* = 11.6, 4.5, 4.5 Hz, 2H), 2.46 (ddd, *J* = 11.6, 4.5, 4.5 Hz, 2H), 1.90 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 145.3, 143.2, 133.1, 132.0, 128.1, 128.0, 127.6, 127.5, 127.3, 126.4, 126.3, 125.8, 125.7, 125.4, 67.8, 66.8, 47.8, 18.6.

IR (KBr, neat) ν_{max} 3055, 2958, 2848, 1597, 1504, 1444, 1114 [ν (C=O)], 862, 744, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{22}H_{24}NO$ [(M+H)$^+$]: 318.1858, found: 318.1856.

1-(1-(Naphthalen-2-yl)-1-phenylethyl)azepane (**2.28aa**)



2.28aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.28** (127 mg, 0.502 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:1.

Yield 76% yield (125 mg, 0.380 mmol) as yellow solid.

M.p. 98.0 – 99.9 °C.

R_f = 0.31 (eluent: hexane/ethyl acetate = 100:1, visualized by UV).

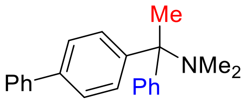
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.82 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.73 – 7.71 (m, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.36 (m, 2H), 7.24 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 2.67 – 2.57 (m, 4H), 1.91 (s, 3H), 1.75 – 1.70 (m, 4H), 1.62 – 1.56 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 146.0, 133.2, 131.9, 128.1, 127.9, 127.4, 127.3, 126.9, 126.2, 125.8, 125.6, 125.4, 124.5, 69.0, 52.7, 30.0, 26.5, 17.5.

IR (KBr, neat) ν_{max} 3055, 2980, 2920, 2850, 1597, 1504, 1444, 740, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N$ [$(M+H)^+$]: 330.2222, found: 330.2224.

1-([1,1'-Biphenyl]-4-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.29aa**)



2.29aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **2.29** (113 mg, 0.502 mmol) through addition of PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:5.

Yield 85% yield (129 mg, 0.429 mmol) as white solid.

M.p. 79.2 – 81.8 °C.

R*f* = 0.19 (eluent: hexane/ethyl acetate = 20:1, visualized by UV).

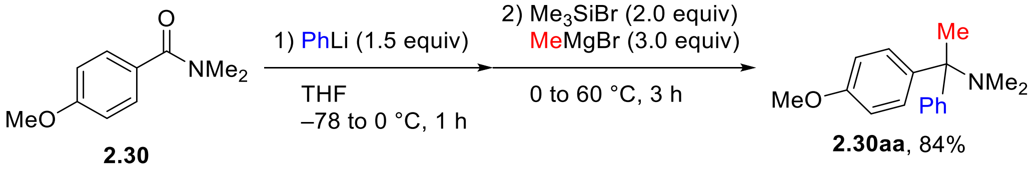
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.54 – 7.49 (m, 6H), 7.40 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.18 (t, *J* = 7.4 Hz, 1H), 2.18 (s, 6H), 1.78 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 145.7, 145.0, 140.8, 138.8, 128.7, 128.1, 127.8, 127.7, 127.0, 126.9, 126.4, 126.1, 66.8, 39.9, 19.6.

IR (KBr, neat) ν_{max} 3055, 2983, 2939, 2821, 2779, 1598, 1485, 761, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N$ [(M+H)$^+$]: 302.1909, found: 302.1908.

1-(4-Methoxyphenyl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.30aa**)



The titled compound was synthesized with a slightly modified protocol with general procedure **A** (section 5.2.6.1): Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.30** (89.6 mg, 0.500 mmol) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (dry ice-acetone bath). PhLi (0.66 mL, 0.752 mmol, 1.5 equiv) (1.14 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (ice-water bath). MeMgBr (0.50 mL, 1.53 mmol, 3.1 equiv) (3.05 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 3 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate/triethylamine = 100:5:1) to give **2.30aa** as colorless oil (107 mg, 0.420 mmol) in 84% yield.

R*f* = 0.35 (eluent: hexane/ethyl acetate = 20:1, visualized by UV).

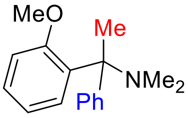
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H), 2.13 (s, 6H), 1.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 146.3, 137.8, 128.8, 127.7, 127.6, 125.9, 112.9, 66.4, 55.1, 39.8, 19.9.

IR (KBr, neat) ν_{max} 3057, 2985, 2935, 2821, 2779, 1608, 1508, 1249 [*ν* (C–O)], 1182, 1043 [*ν* (C–O)], 848, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{22}NO$ [$(M+H)^+$]: 256.1701, found: 256.1702.

1-(2-Methoxyphenyl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.31aa**)



2.31aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.31aa** (89.6 mg, 0.500 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/Et_2O/triethylamine = 100:5:1

Yield 86% yield (110 mg, 0.431 mmol) as light yellow solid.

M.p. 53.7 – 56.0 °C.

R*f* = 0.17 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

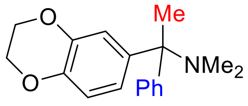
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.24 – 7.20 (m, 4H), 7.17 – 7.11 (m, 1H), 7.01 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 1H), 6.79 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.37 (s, 3H), 2.13 (s, 6H), 1.80 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 157.6, 143.6, 135.3, 129.0, 127.6, 127.3, 126.9, 125.5, 120.1, 112.8, 65.7, 55.2, 40.0, 19.2.

IR (KBr, neat) $\nu_{\max}$ 3055, 2987, 2935, 2823, 2781, 1597, 1483, 1240 [ν (C–O)], 1028 [ν (C–O)], 756, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{22}NO$ [(M+H)$^+$]: 256.1701, found: 256.1698.

1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.32aa**)



2.32aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **3.32** (104 mg, 0.502 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et$_2$O), followed by addition of Me$_3$SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et$_2$O).

Purification silica gel, hexane/ethyl acetate = 100:10.

Yield 88% yield (125 mg, 0.441 mmol) as white solid.

M.p. 86.4 – 87.4 °C.

R$_f$ = 0.25 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

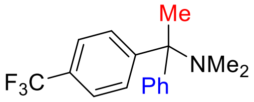
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.26 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.22 (brs, 4H), 2.14 (s, 6H), 1.69 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 146.2, 142.6, 141.7, 139.3, 127.7, 127.5, 126.0, 120.9, 116.7, 116.2, 66.3, 64.3 (2C overlapped), 39.8, 19.2.

IR (KBr, neat) ν_{max} 3057, 2981, 2870, 2820, 2781, 1587, 1502, 1286, 1066 [ν (C–O)], 880 [ν (C–O)], 746, 702 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_2$ [(M+H)$^+$]: 284.1651, found: 284.1651.

N,*N*-Dimethyl-1-phenyl-1-(4-(trifluoromethyl)phenyl)ethan-1-amine (**2.33aa**)



2.33aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.33** (109 mg, 0.502 mmol) through addition of PhLi (0.65 mL, 0.748 mmol, 1.5 equiv) (1.15 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:2.

Yield 76% yield (111 mg, 0.378 mmol) as a colorless oil.

R*f* = 0.33 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.29 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 2.14 (s, 6H), 1.76 (s, 3H).

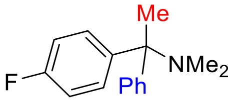
^{13}C NMR (100 MHz, CDCl$_3$) δ 150.5, 144.5, 128.3 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 127.91, 127.89, 127.6, 126.5, 124.7 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 67.0, 39.8, 19.4.

^{19}F NMR (376 MHz, CDCl$_3$) δ −62.9.

IR (KBr, neat) ν_{max} 3059, 2987, 2827, 2785, 1618, 1446, 1409, 1327, 1122, 1008, 860, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NF_3$ [(M+H)$^+$]: 294.1470, found: 294.1469.

1-(4-Fluorophenyl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.34aa**)



2.34aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **2.34** (104 mg, 0.502 mmol) through addition of PhLi (0.66 mL, 0.752 mmol, 14.5 equiv) (1.14 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.41 mL, 1.25 mmol, 2.5 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:10.

Yield 86% yield (105 mg, 0.432 mmol) as colorless oil.

R*f* = 0.22 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 4H), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.94 (dd, *J* = 8.7, 8.7 Hz, 2H), 2.13 (s, 6H), 1.73 (s, 3H).

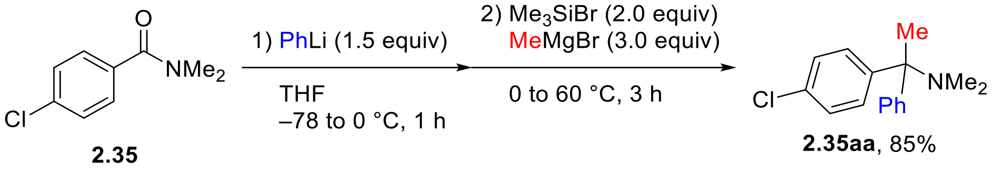
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 145.6, 141.6 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 129.2 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 127.8, 127.6, 126.2, 114.4 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 66.5, 39.8, 19.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ −117.4.

IR (KBr, neat) ν_{max} 3059, 2985, 2823, 2783, 1600, 1504, 1222 [ν (C–F)], 802, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NF$ [$(M+H)^+$]: 244.1502, found: 244.1500.

1-(4-Chlorophenyl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.35aa**)



The titled compound was synthesized with a slightly modified protocol with general procedure **A** (section 5.2.6.1): Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.35** (91.8 mg, 0.502 mmol) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (dry ice-acetone bath). PhLi (0.64 mL, 0.756 mmol, 1.5 equiv) (1.18 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (ice-water bath). MeMgBr (0.50 mL, 1.53 mmol, 3.1 equiv) (3.05 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 3 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed, and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O = 100:10) to give **2.35aa** as colorless oil (111 mg, 0.429 mmol) in 85% yield.

R*f* = 0.33 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

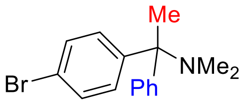
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 4H), 7.29 – 7.22 (m, 4H), 7.18 (t, J = 7.2 Hz, 1H), 2.13 (s, 6H), 1.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.6, 131.8, 129.1, 127.85, 127.83, 127.6, 126.3, 66.6, 39.8, 19.5.

IR (KBr, neat) ν_{max} 3084, 2985, 2823, 2783, 1598, 1487, 1222, 1093 [ν (C–Cl)], 1012, 759, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NCl$ [$(M+H)^+$]: 260.1206, found: 260.1208.

1-(4-Bromophenyl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.36aa**)



2.36aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.36** (114 mg, 0.500 mmol) through addition of PhLi (0.66 mL, 0.752 mmol, 14.5 equiv) (1.14 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.41 mL, 1.25 mmol, 2.5 equiv) (3.05 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:2.

Yield 71% yield (107 mg, 0.353 mmol) as light yellow oil.

$\mathbf{R}_f$ = 0.30 (eluent: hexane/ethyl acetate = 40:1, visualized by UV).

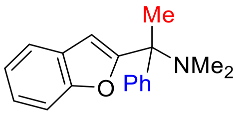
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.33 (m, 6H), 7.27 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 2.13 (s, 6H), 1.72 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 145.2, 145.0, 130.8, 129.5, 127.8, 127.6, 126.3, 120.0, 66.7, 39.8, 19.5.

IR (KBr, neat) ν_{max} 3057, 2985, 2823, 2781, 1485, 1008 [ν (C–Br)], 758, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NBr$ [$(M+H)^+$]: 304.0701, found: 304.0703.

1-(Benzofuran-2-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.37aa**)



2.37aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **2.37** (94.6 mg, 0.501 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate = 100:5.

Yield 78% yield (104 mg, 0.392 mmol) as light brown solid.

M.p. 59.5 – 60.7 °C.

R*f* = 0.22 (eluent: hexane/ethyl acetate = 20:1, visualized by UV).

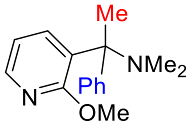
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.52 (m, 3H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.24 – 7.17 (m, 3H), 6.65 (d, *J* = 0.6 Hz, 1H), 2.28 (s, 6H), 1.80 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 160.4, 154.7, 144.8, 128.05, 128.01, 127.2, 126.8, 123.7, 122.5, 120.7, 111.3, 105.0, 64.9, 40.0, 21.9.

IR (KBr, neat) ν_{max} 3082, 2985, 2825, 2783, 1600, 1454, 1253 [ν (C–O)], 935, 750, 702 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NO$ [(M+H)$^+$]: 266.1545, found: 266.1546.

1-(2-Methoxypyridin-3-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.38aa**)



2.38aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from amide **2.38** (90.1 mg, 0.501 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et$_2$O), followed by addition of Me$_3$SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et$_2$O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:20:1.

Yield 86% yield (110 mg, 0.430 mmol) as light yellow oil.

R*f* = 0.26 (eluent: hexane/ethyl acetate = 20:1, visualized by UV).

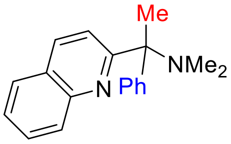
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (dd, *J* = 7.5, 1.9 Hz, 1H), 8.04 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.26 – 7.14 (m, 5H), 6.94 (dd, *J* = 7.5, 4.9 Hz, 1H), 3.63 (s, 3H), 2.11 (s, 6H), 1.79 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 161.4, 144.6, 142.5, 137.5, 129.3, 127.4, 127.2, 125.9, 116.4, 65.0, 52.6, 39.8, 17.9.

IR (KBr, neat) $\nu_{\max}$ 3055, 2985, 2825, 1783, 1577, 1454, 1398, 1242 [ν (C–O)], 1018 [ν (C–O)], 750, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{21}N_2O$ [(M+H)$^+$]: 257.1654, found: 257.1650.

N,*N*-Dimethyl-1-phenyl-1-(quinolin-2-yl)ethan-1-amine (**2.39aa**)



2.39aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **2.39** (100 mg, 0.501 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:10:1.

Yield 87% yield (121 mg, 0.438 mmol) as white solid.

M.p. 110.9 – 112.2 °C.

R$_f$ = 0.25 (eluent: hexane/ethyl acetate = 5:1, visualized by UV).

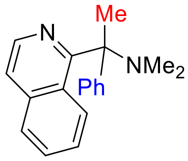
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.61 (m, 3H), 7.45 (ddd, *J* = 8.2, 6.8, 1.1 Hz, 1H), 7.26 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 2.25 (s, 6H), 1.98 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 165.1, 147.0, 146.1, 135.4, 129.6, 128.7, 128.0, 127.4, 127.1, 126.6, 126.2, 126.0, 121.0, 69.7, 39.9, 14.1.

IR (KBr, neat) $\nu_{\max}$ 3059, 2981, 2825, 2783, 1597, 1498, 958, 852, 756, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2$ [(M+H)$^+$]: 277.1705, found: 277.1706.

1-(Isoquinolin-1-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.40aa**)



2.40aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **2.40** (100 mg, 0.501 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:30:1.

Yield 78% yield (108 mg, 0.391 mmol) as yellow solid.

M.p. 124.0 – 125.4 °C.

R*f* = 0.14 (eluent: hexane/ethyl acetate = 5:1, visualized by UV).

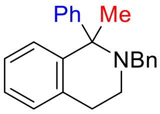
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 8.8 Hz, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.38 – 7.33 (m, 1H), 7.20 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 2.34 (s, 6H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 145.0, 140.4, 136.9, 129.0, 128.3, 127.7, 127.6, 127.2, 127.1, 126.0, 125.7, 120.5, 72.3, 40.5, 18.3.

IR (KBr, neat) ν_{max} 3053, 2985, 2829, 2787, 1556, 952, 819, 752, 705 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2$ [$(M+H)^+$]: 277.1705, found: 277.1703.

2-Benzyl-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2.41aa**)[25]



2.41aa

This compound was prepared according to general procedure **A** (section 5.2.6.1) from carboxamide **2.41** (119 mg, 0.502 mmol) through addition of PhLi (0.63 mL, 0.750 mmol, 1.5 equiv) (1.19 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.43 mL, 1.26 mmol, 2.5 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/Et_2O = 100:2.

Yield 80% yield (125 mg, 0.399 mmol) as white solid.

M.p. 105.0 – 105.9 °C. (lit. 102 – 103 °C)[25]

R*f* = 0.55 (eluent: hexane, visualized by UV).

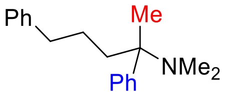
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.4 Hz, 2H), 7.30 – 7.23 (m, 6H), 7.18 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.07 – 7.02 (m, 2H), 6.96 (t, *J* = 7.1 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.56 (d, *J* = 13.8 Hz, 1H), 3.29 (d, *J* = 13.8 Hz, 1H), 3.09 (ddd, *J* = 15.9, 8.3, 8.3 Hz, 1H), 2.85 (dd, *J* = 8.3, 2.9 Hz, 2H), 2.70 (ddd, *J* = 15.9, 2.9, 2.9 Hz, 1H), 1.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 144.8, 140.7, 134.0, 129.1, 128.4, 128.3, 128.2, 128.0, 127.7, 126.6, 126.5, 125.6, 125.4, 64.1, 54.1, 42.3, 30.2, 19.7.

IR (KBr, neat) ν_{max} 3059, 2974, 2804, 1600, 1491, 752, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{23}H_{24}N$ [$(M+H)^+$]: 314.1909, found: 314.1912.

N,*N*-Dimethyl-2,6-diphenylhexan-2-amine (**2.42aa**)



2.42aa

This compound was prepared according to general procedure **B** (section 5.2.6.3) from carboxamide **2.42** (103 mg, 0.502 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:5:1.

Yield 56% yield (79.0 mg, 0.281 mmol) as colorless oil.

R$_f$ = 0.14 (eluent: hexane/ethyl acetate = 10:1, visualized by UV).

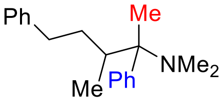
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.30 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.24 – 7.18 (m, 3H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 2H), 2.49 (ddd, *J* = 13.7, 7.6, 7.6 Hz, 1H), 2.45 (ddd, *J* = 13.7, 7.6, 7.6 Hz, 1H), 2.15 (s, 6H), 1.79 (ddd, *J* = 12.6, 12.6, 4.4 Hz, 1H), 1.65 (ddd, *J* = 12.6, 12.6, 4.4 Hz, 1H), 1.47 (tt, *J* = 7.7, 7.7 Hz, 2H), 1.29 (s, 3H), 1.14 – 1.02 (m, 1H), 1.02 – 0.91 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 146.2, 142.7, 128.2, 128.1, 127.7, 127.0, 126.0, 125.5, 62.4, 41.5, 38.8, 35.7, 32.1, 24.4, 14.5.

IR (KBr, neat) *ν*$_{max}$ 3024, 2937, 2858, 2770, 1602, 1494, 746, 698 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N$ [(M+H)$^+$]: 282.2222, found: 282.2226.

N,*N*,3-Trimethyl-2,6-diphenylhexan-2-amine (**2.43aa**)



2.43aa

This compound was prepared according to general procedure **B** (section 5.2.6.3) from carboxamide **2.43** (110 mg, 0.502 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et$_2$O), followed by addition of Me$_3$SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et$_2$O). It was isolated as a pair of an inseparable mixture of diastereomers. The dr ratio (1.6:1) was assigned by ^{1}H NMR of the reaction crude mixture using the ratio of the methyl protons on the tertiary carbon (see below).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:5:1

Yield 49% yield (72.2 mg, 0.245 mmol) as colorless oil (dr 1.6:1).

R$_f$ = 0.15 (eluent: hexane/ethyl acetate = 10:1, visualized by UV)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.37 (m, 2H, both isomers), 7.30 – 7.13 (m, 8H, both isomers), 2.65 – 2.58 (m, 1H, both isomers), 2.55 – 2.46(m, 1H, both isomers), 2.10 (s, 6H, both isomers), 1.95 – 1.83 (m, 2H, both isomers), 1.74 – 1.59 (m, 2H, both isomers), 1.52 – 1.37 (m, 1H, both isomers), 1.30 (s, 3H, minor isomer), 1.29 (s, 3H, major isomer), 0.87 – 0.68 (m, 4H, both isomers), 0.59 – 0.51 (m, 0.4H, minor isomer).

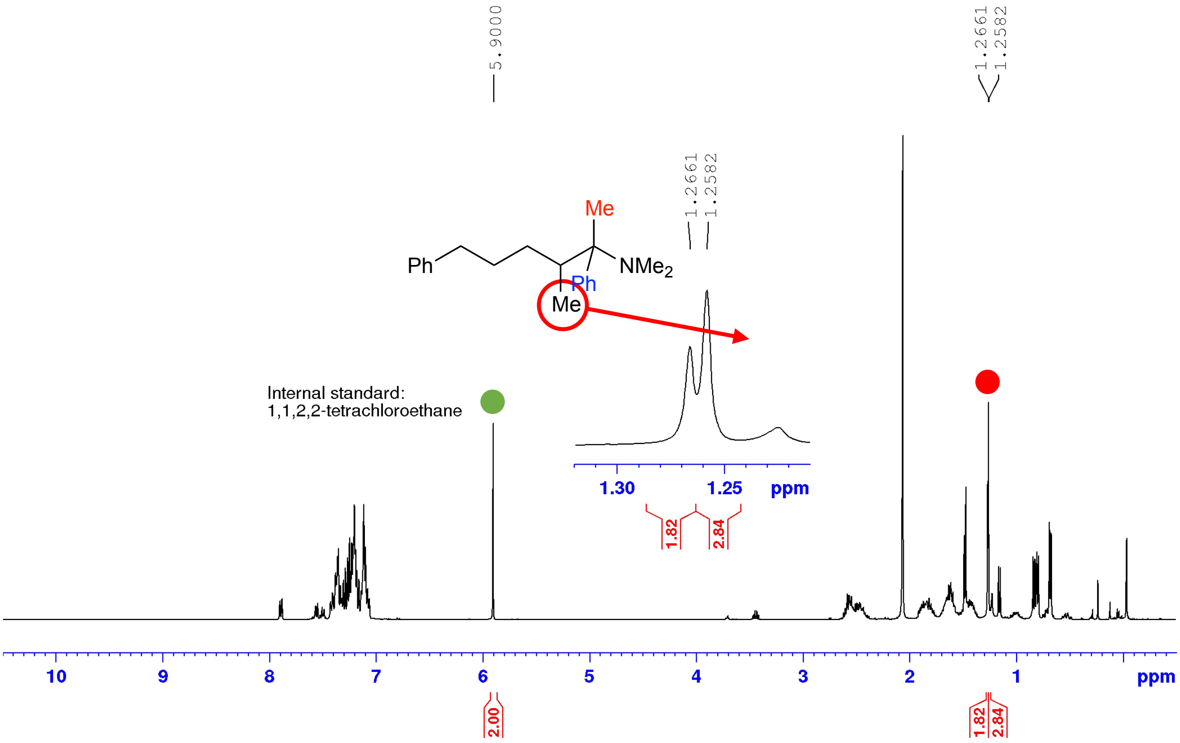
Major isomer ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.9, 142.3, 128.3, 128.21, 128.17, 127.0, 126.0, 125.51, 65.4, 39.7, 38.8, 36.5, 30.7, 30.6, 15.3, 13.1.

Minor isomer ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.8, 142.2, 128.3, 128.17 (2C overlapped), 127.0, 126.0, 125.54, 65.1, 39.3, 38.8, 36.3, 32.4, 30.5, 14.1, 13.2.

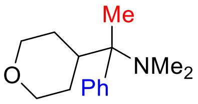
IR (KBr, neat) *ν*$_{\text{max}}$ 3059, 2970, 2935, 2858, 1602, 1494, 1446, 763, 700 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{21}H_{30}N$ [(M+H)$^+$]: 296.2378, found: 296.2376.

Determination of dr ratio in crude NMR:



N,*N*-Dimethyl-1-phenyl-1-(tetrahydro-2*H*-pyran-4-yl)ethan-1-amine (**2.44aa**)



2.44aa

This compound was prepared according to general procedure **B** (section 5.2.6.3) from carboxamide **2.44** (78.5 mg, 0.500 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/ethyl acetate/triethylamine = 100:5:1.

Yield 40% yield (46.1 mg, 0.198 mmol) as white solid.

M.p. 60.3 – 62.7 °C.

R_f = 0.17 (eluent: hexane/ethyl acetate = 5:1, visualized by UV).

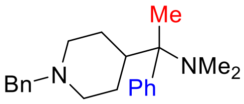
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 2H), 7.29 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 3.90 (ddd, *J* = 11.7, 11.7, 3.6 Hz, 2H), 3.35 (ddd, *J* = 11.7, 11.7, 1.8 Hz, 1H), 3.32 (ddd, *J* = 11.7, 11.7, 1.8 Hz, 1H), 2.15 (s, 6H), 1.90 (dddd, *J* = 11.8, 11.8, 3.0, 3.0 Hz, 1H), 1.74 (dddd, *J* = 13.5, 4.3, 2.2, 2.2 Hz, 1H), 1.52 (dddd, *J* = 13.5, 4.3, 2.2, 2.2 Hz, 1H), 1.31 (s, 3H), 1.24 (dddd, *J* = 13.5, 12.3, 12.3, 4.3 Hz, 1H), 0.88 (dddd, *J* = 12.3, 12.3, 12.3, 4.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 128.2, 127.2, 126.2, 68.6 (2C overlapped), 64.6, 43.1, 38.7, 29.2, 27.3, 12.2.

IR (KBr, neat) ν_{max} 3055, 2949, 2825, 2781, 1492, 1097 [ν (C–O)], 833[ν (C–O)], 771, 702 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NO$ [$(M+H)^+$]: 234.1858, found: 234.1859.

1-(1-Benzylpiperidin-4-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.45aa**)



2.45aa

This compound was prepared according to general procedure **B** (section 5.2.6.3) from carboxamide **2.44** (123 mg, 0.500 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and MeMgBr (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et_2O).

Purification silica gel, hexane/acetone = 100:10.

Yield 45% yield (73.0 mg, 0.227 mmol) as yellow oil.

R_f = 0.34 (eluent: hexane/ethyl acetate = 5:1, visualized by UV).

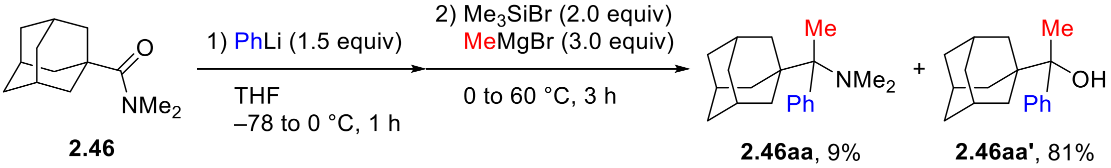
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.6 Hz, 2H), 7.28 – 7.15 (m, 8H), 3.41 (m, 2H), 2.88 – 2.57 (m, 2H), 2.12 (s, 6H), 1.93 – 1.78 (m, 3H), 1.66 – 1.60 (m, 2H), 1.30 (s, 3H), 1.16 (dddd, J =12.4, 12.4, 12.4, 2.7 Hz, 1H), 0.85 (dddd, J =12.4, 12.4, 12.4, 2.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 138.2, 129.2, 128.2, 128.0, 127.1, 126.8, 126.0, 64.6, 63.4, 54.6, 54.4, 44.1, 38.7, 28.3, 26.4, 12.6.

IR (KBr, neat) ν_{max} 3059, 2941, 2821, 2781, 1494, 771, 736, 698 cm^{-1}.

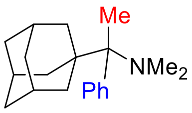
HRMS (ESI) m/z calcd for $C_{22}H_{31}N_2$ $[(M+H)^+]$: 323.2487, found: 323.2485.

The reaction of amide **2.46**:



The titled compound was synthesized with a modified protocol of general procedure **A** (section 5.2.6.1): Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.46** (104 mg, 0.502 mmol) in anhydrous THF (2.5 mL) and it was cooled to –78 °C (dry ice-acetone bath). PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h. Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (ice-water bath). MeMgBr (0.52 mL, 1.52 mmol, 3.0 equiv) (2.92 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 3 h. The mixture was carefully quenched with pH 10 NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel to give **2.46aa** (hexane/Et_2O = 100:10) as white solid (12.5 mg, 0.0442 mmol) in 9% yield and **2.46aa'** (hexane/Et_2O = 100:20) as white solid (104 mg, 0.406 mmol) in 81% yield.

1-(Adamantan-1-yl)-*N*,*N*-dimethyl-1-phenylethan-1-amine (**2.46aa**)



2.46aa

M.p. 120.8 – 123.1 °C.

$\mathbf{R_f}$ = 0.24 (eluent: hexane/ethyl acetate = 15:1, visualized by iodine in silica gel).

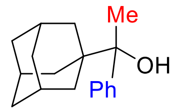
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.25 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 2.22 (s, 6H), 1.88 (m, 3H), 1.78 (m, 3H), 1.58 – 1.55 (m, 3H), 1.51 – 1.48 (m, 3H), 1.39 (m, 3H), 1.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 128.5, 126.8, 125.7, 68.2, 42.3, 39.3, 37.9, 36.9, 29.2, 9.7.

IR (KBr, neat) ν_{max} 2945, 2908, 2848, 2775, 1442, 736, 705 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{20}H_{30}N$ [$(M+H)^+$]: 284.2378, found: 284.2379.

1-(Adamantan-1-yl)-1-phenylethan-1-ol (**2.46aa'**)[26]



2.46aa'

M.p. 69.8 – 71.4 °C.

R*f* = 0.35 (eluent: hexane/ethyl acetate = 15:1, visualized by phosphomolybdic acid stain).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.30 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 1.95 (m, 3H), 1.67 – 1.60 (m, 6H), 1.55 – 1.52 (m, 9H).

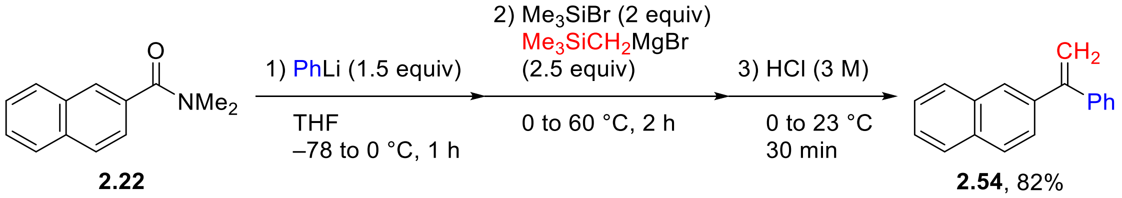
^{13}C NMR (100 MHz, CDCl$_3$) δ 145.5, 127.2, 126.9, 126.2, 78.6, 39.0, 36.9, 36.5, 28.6, 24.0.

IR (KBr, neat) ν_{max} 3460 [ν (O–H)], 2902, 2946, 1439, 746, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{25}O$ [(M+H)$^+$]: 257.1905, found: 257.1903.

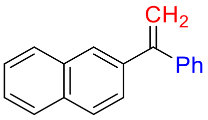
5.2.7. General procedure for the synthesis of 1,1-diarylethylenes

General Procedure C



Under an argon atmosphere, in a 25 mL sealed tube equipped with a PTFE coated stir bar was added a solution of carboxamide **2.22** (99.7 mg, 0.500 mmol) in anhydrous THF (2.5 mL) and the mixture was cooled to –78 °C (dry ice-acetone bath). PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O) was added dropwise over 30 seconds, and the mixture was slowly warmed up to 0 °C over 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (water-ice bath). Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with water (1.0 mL) at 0 °C, and 3 M aqueous HCl (5 mL) was added with vigorous stirring. The mixture was stirred at 23 °C for 30 min, and 3 M aqueous NaOH (5 mL) was added at 0 °C to neutralize the excess HCl. A solution of pH 10 NH_4Cl-NH_3 buffer (10 mL) was added, and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O = 100:1) to give **2.48** as white solid (94.3 mg, 0.410 mmol) in 82% yield.

2-(1-Phenylvinyl)naphthalene (**2.48**)[27]



2.48

This compound was prepared according to general procedure **C** (section 5.2.7) from carboxamide **1** (99.6 mg, 0.500 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O). The crude was subsequently treated with 3 M aqueous HCl (5 mL).

M.p. 55.2 – 56.7 °C. (lit. 53 – 55 °C)[28]

R_f = 0.35 (eluent: hexane, visualized by UV).

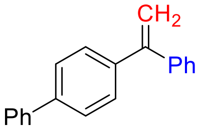
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 – 7.78 (m, 4H), 7.49 – 7.44 (m, 3H), 7.40 – 7.34 (m, 5H), 5.59 (d, *J* = 1.0 Hz, 1H), 5.54 (d, *J* = 1.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 150.0, 141.5, 138.9, 133.3, 132.9, 128.4, 128.21, 128.16, 127.8, 127.7, 127.6, 127.3, 126.4, 126.1, 126.0, 114.8.

IR (KBr, neat) ν_{max} 3053, 1610, 1504, 896, 860, 777, 750, 696 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{18}H_{15}$ [(M+H)$^+$]: 231.1174, found: 231.1172.

4-(1-Phenylvinyl)-1,1'-biphenyl (**2.49**)[29]



2.49

This compound was prepared according to general procedure **C** (section 5.2.7) from carboxamide **2.29** (113 mg, 0.502 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et$_2$O), followed by addition of Me$_3$SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and Me$_3$SiCH$_2$MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et$_2$O). The crude was subsequently treated with 3 M aqueous HCl (5 mL).

Purification silica gel, hexane/Et$_2$O = 100:2.

Yield 84% yield (108 mg, 0.422 mmol) as white solid.

M.p. 93.9 – 95.2 °C. (lit. 96 – 98 °C)[30]

R*f* = 0.57 (eluent: hexane, visualized by UV).

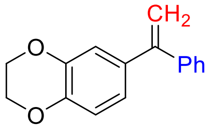
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.33 (m, 10H), 5.53 (s, 1H), 5.48 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 149.6, 141.4, 140.7, 140.5, 140.4, 128.8, 128.6, 128.3, 128.2, 127.7, 127.3, 127.0, 126.9, 114.3.

IR (KBr, neat) ν_{max} 3051, 3030, 1602, 1485, 902, 850, 770, 740, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{20}H_{17}$ [$(M+H)^+$]: 257.1330, found: 257.1329.

6-(1-Phenylvinyl)-2,3-dihydrobenzo[*b*][1,4]dioxine (**2.50**)



2.50

This compound was prepared according to general procedure **C** (section 5.2.7) from carboxamide **2.32** (104 mg, 0.502 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O). The crude was subsequently treated with 3 M aqueous HCl (5 mL).

Purification silica gel, hexane/Et_2O = 100:5.

Yield 84% yield (100 mg, 0.420 mmol) as light yellow oil.

R_f = 0.28 (eluent: hexane/ethyl acetate = 50:1, visualized by UV).

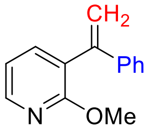
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 5H), 6.87 – 6.86 (m, 1H), 6.82 – 6.81 (m, 2H), 5.39 (d, *J* = 1.0 Hz, 1H), 5.33 (d, *J* = 1.0 Hz, 1H), 4.29 – 4.24 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 143.3, 143.1, 141.5, 135.0, 128.3, 128.1, 127.6, 121.4, 117.1, 116.8, 113.2, 64.4, 64.3.

IR (KBr, neat) ν_{max} 3078, 3053, 1612, 1577, 1504, 1066 [ν (C–O)], 885 [ν (C–O)], 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_2$ [$(M+H)^+$]: 239.1072, found: 239.1070.

2-Methoxy-3-(1-phenylvinyl)pyridine (**2.51**)



2.51

This compound was prepared according to general procedure **C** (section 5.2.7) from carboxamide **2.38** (90.0 mg, 0.500 mmol) through addition of PhLi (0.64 mL, 0.755 mmol, 1.5 equiv) (1.18 M in Et_2O), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O). The crude was subsequently treated with 3 M aqueous HCl (5 mL).

Purification silica gel, hexane/ethyl acetate = 100:10.

Yield 60% yield (63.5 mg, 0.301 mmol) as yellow oil.

R*f* = 0.26 (eluent: hexane/ethyl acetate = 50:1, visualized by UV).

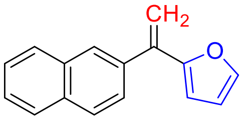
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.28 – 7.26 (m, 5H), 6.91 (dd, *J* = 7.0, 5.0 Hz, 1H), 5.74 (s, 1H), 5.39 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 146.2, 145.4, 140.3, 139.3, 128.1, 127.6, 126.5, 124.8, 116.6, 116.5, 53.4.

IR (KBr, neat) ν_{max} 3054, 3024, 2847 [*ν* (C–O)], 1575, 1465, 1255 [*ν* (C–O)], 1018, 778, 708 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{14}H_{14}NO$ [(M+H)$^+$]: 212.1075, found: 212.1073.

2-(1-(Naphthalen-2-yl)vinyl)furan (**2.52**)[31]



2.52

This compound was prepared according to general procedure **C** (section 5.2.7) from carboxamide **2.22** (99.6 mg, 0.500 mmol) through addition of 2-furyllithium (0.67 mL, 0.750 mmol, 1.5 equiv) (1.12 M in THF), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O). The crude was subsequently treated with 3 M aqueous HCl (5 mL).

Purification silica gel, hexane/Et_2O = 100:1

Yield 56% yield (60.8 mg, 0.281 mmol) as orange oil.

R*f* = 0.60 (eluent: hexane, visualized by UV).

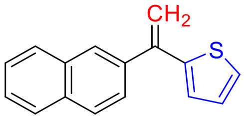
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (s, 1H), 7.87 – 7.83 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.50 – 7.47 (m, 3H), 6.41 (dd, *J* = 3.0, 2.0 Hz, 1H), 6.23 (d, *J* = 3.0 Hz, 1H), 5.83 (s, 1H), 5.35 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 154.1, 142.5, 139.3, 137.0, 133.2, 133.1, 128.1, 127.7, 127.6, 127.2, 126.5, 126.2, 126.1, 112.5, 111.3, 109.3.

IR (KBr, neat) ν_{max} 3053, 3008, 1598, 1539, 1504, 1432, 889, 749, 689 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{13}O$ [(M+H)$^+$]: 221.0966, found: 221.0968.

<u>2-(1-(Naphthalen-2-yl)vinyl)thiophene (**2.53**)</u>



2.53

This compound was prepared according to general procedure **C** (section 5.2.7) from carboxamide **2.22** (99.6 mg, 0.500 mmol) through addition of 2-thienyllithium (0.77 mL, 0.755 mmol, 1.5 equiv) (0.98 M in THF), followed by addition of Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) and Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O). The crude was subsequently treated with 3 M aqueous HCl (5 mL).

Purification silica gel, hexane/Et_2O = 100:1.

Yield 60% yield (71.3 mg, 0.302 mmol) as colorless oil.

R*f* = 0.67 (eluent: hexane, visualized by UV).

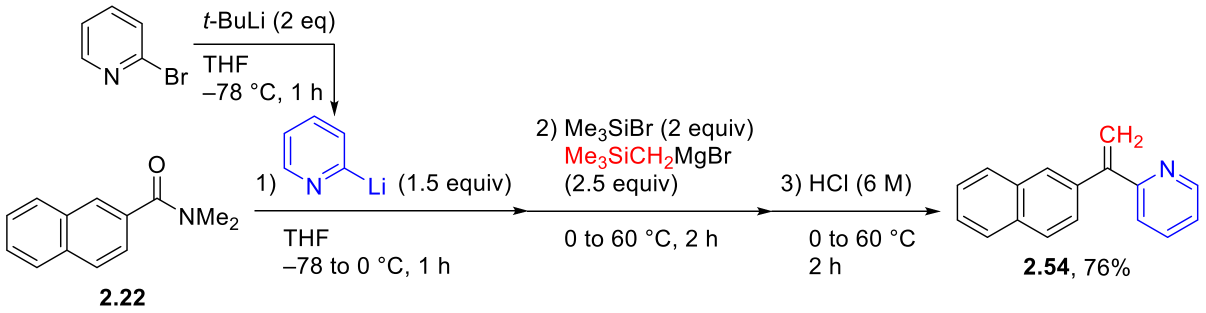
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.86 – 7.81 (m, 3H), 7.55 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.50 – 7.46 (m, 3H), 7.25 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.94 (dd, *J* = 3.6, 1.1 Hz, 1H), 5.66 (s, 1H), 5.37 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 144.8, 143.3, 138.4, 133.2, 133.1, 128.2, 127.7, 127.6, 127.3, 127.2, 126.6, 126.5, 126.2, 126.1, 125.1, 114.2.

IR (KBr, neat) *ν*$_{max}$ 3093, 3057, 1598, 1506, 1432, 890, 752, 704 cm^{-1}.

HRMS (ESI) *m/z* calcd for $C_{16}H_{13}S$ [(M+H)$^+$]: 237.0738, found: 237.0738.

<u>2-(1-(Naphthalen-2-yl)vinyl)pyridine (**2.54**)</u>[32]



The titled compound was synthesized with a modified protocol with general procedure **C** (section 5.2.7): In a 25 mL sealed tube equipped with a PTFE coated stir bar was added 2-bromopyridine (127 mg, 0.80 mmol) (Sigma-Aldrich B80100) and anhydrous THF (3 mL). The mixture was cooled to –78 °C (dry ice-acetone bath), and *t*-BuLi (1.2 mL, 1.58 mmol, 2.0 equiv to 2-bromopyridine) (1.32 M in pentane, Sigma-Aldrich 186198) was added dropwise over 5 min. The mixture was stirred at –78 °C for 1 h (after 50 min, the cooling bath was replaced to an ice-water bath and stirred for 10 min). A solution of amide **2.22** (99.6 mg, 0.500 mmol) in THF (3.0 mL) was added at –78 °C and the mixture was slowly warmed up to 0 °C over 1 h. Me_3SiBr (0.13 mL, 0.985 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred for 5 min at 0 °C (ice-water bath). Me_3SiCH_2MgCl (1.3 mL, 1.27 mmol, 2.5 equiv) (0.98 M in Et_2O) was added and then the mixture was heated at 60 °C (oil bath) for 2 h. The mixture was carefully quenched with water (1.0 mL) at 0 °C, and 6 M aqueous HCl (5 mL) was added with vigorous stirring. The mixture was stirred at 60 °C (oil bath) for 2 h, and 6 M aqueous NaOH (5 mL) was added at 0 °C (ice-water bath) to neutralize the excess HCl. A solution of pH 10 NH_4Cl-NH_3 buffer (10 mL) was added, and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. The volatile materials were removed, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 100:10) to give **2.54** as light yellow oil (87.8 mg, 0.380 mmol) in 76% yield.

R*f* = 0.28 (eluent: hexane/ethyl acetate = 20:1, visualized by UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.2 Hz, 1H), 7.85 – 7.80 (m, 4H), 7.65 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.48 – 7.46 (m, 3H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.23 – 7.22 (m, 1H), 6.08 (s, 1H), 5.73 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 149.4, 149.2, 137.8, 136.3, 133.3, 133.0, 128.1, 127.8, 127.6, 127.4, 126.5, 126.1, 126.0, 122.9, 122.5, 118.1.

IR (KBr, neat) ν_{max} 3053, 3010, 1583, 896, 748 cm^{-1}.

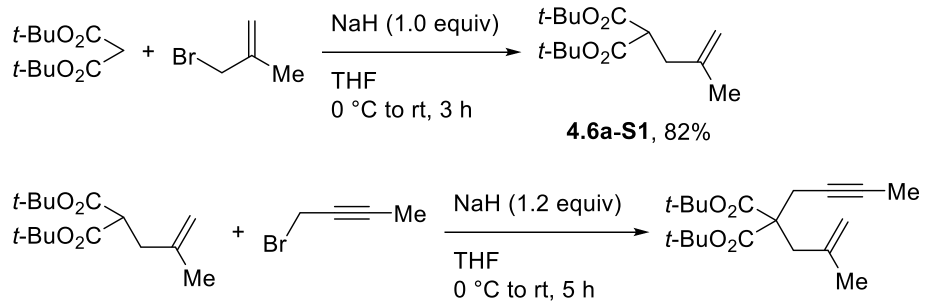
HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N$ [$(M+H)^+$]: 232.1126, found: 232.1128.

5.3. Experiment data for Chapter 4

5.3.1. Materials

Tetrahydrofuran (THF), dichloromethane (DCM), and diethyl ether were taken from a solvent purification system (PS-400-5, innovative technology Inc.). All commercially available reagents, (*R*)-binap (Kanto Chemical 04969), (*R*)-segphos (TCI S0930), (*R*)-DTBM-segphos (TCI D4501) were used as received for the reactions without further purification. $[RhCl(cod)]_2$,[33] $[RhCl(coe)_2]_2$,[34] [RhCl(**L1***)]$_2$,[35] [RhCl(**L2***)]$_2$,[36] [RhCl(**L3***)]$_2$,[37] [RhCl((*R,R*)-Ph-bod)]$_2$,[38] and [RhCl((*S,S*)-fc-tfb)]$_2$,[39] were prepared according to the reported procedures. Substrate **4.6m** was prepared according to the reported procedure.[40] CuCN•2LiCl in THF (1.0 M) was prepared according to the reported procedure.[41]

5.3.2. Synthesis of starting materials 4.6a–4.6i and 4.6n



4.6a-S1, 82%

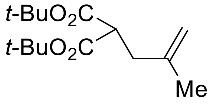
4.6a-S1

4.6a, 92%

Under nitrogen atmosphere, to a suspension of NaH (60% in mineral oil, 4.00 g, 100 mmol, 1.0 equiv) in THF (250 mL) was added a solution of di-*tert*-butyl malonate (23.7 g, 105 mmol, 1.1 equiv) in THF (50 mL) dropwise over 20 min at 0 °C, and the mixture was stirred at room temperature for 30 min. Subsequently, a solution of 3-bromo-2-methylpropene (13.4 g, 100 mmol, 1.0 equiv) in THF (20 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 30:1) to give **4.6-S1** (CAS No.: 380379-92-0) as colorless oil (22.1 g, 82% yield).

Under nitrogen atmosphere, to a suspension of NaH (60% in mineral oil, 2.40 g, 60 mmol, 1.2 equiv) in THF (100 mL) was added a solution of **4.6a-S1** (13.6 g, 50 mmol, 1.0 equiv) in THF (20 mL) dropwise over 10 min at 0 °C, and the mixture was stirred at room temperature for 30 min. Subsequently, a solution of 1-bromo-2-butyne (8.00 g, 60 mmol, 1.2 equiv) in THF (20 mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 5 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 30:1) to give **4.6a** (CAS No.: 184949-93-7) as white solid (14.9 g, 92% yield).

Compound **4.6a-S1**[42]



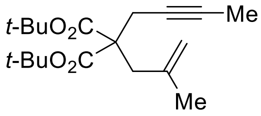
4.6a-S1

R*f* = 0.20. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 18H), 1.75 (s, 3H), 2.53 (d, *J* = 7.8 Hz, 2H), 3.37 (t, *J* = 7.8 Hz, 1H), 4.73 (m, 1H), 4.78 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 27.9, 36.5, 52.3, 81.4, 112.0, 142.1, 168.5.

Compound **4.6a**[43]



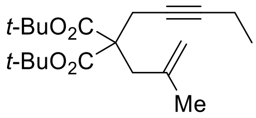
4.6a

R*f* = 0.22. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 18H), 1.71 (s, 3H), 1.75 (t, *J* = 2.4 Hz, 3H), 2.67 (q, *J* = 2.5 Hz, 2H), 2.72 (s, 2H), 4.85 (m, 1H), 4.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.4, 22.9, 23.6, 27.8, 39.2, 57.5, 74.3, 78.5, 81.5, 115.5, 140.9, 169.7.

Compound **4.6b**



4.6b

It was synthesized from **4.6a-S1** with 1-bromopent-2-yne according to the procedure for **4.6a** in 5 mmol scale.

Yield 1.43 g, 85% yield as colorless oil.

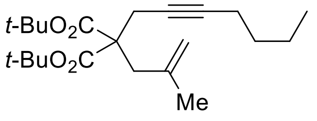
R*f* = 0.23. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, *J* = 7.5 Hz, 3H), 1.46 (s, 18H), 1.72 (s, 3H), 2.13 (qt, *J* = 7.5 Hz, 2.3 Hz, 2H), 2.68 (t, *J* = 2.2 Hz, 2H), 2.72 (s, 2H), 4.85 (m, 1H), 4.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 14.1, 22.9, 23.6, 27.8, 39.1, 57.5, 74.5, 81.4, 84.7, 115.5, 140.9, 169.7.

HRMS (ESI) calcd for $C_{20}H_{33}O_4$ $[M+H]^+$ 337.2379, found 337.2375.

Compound **4.6c**



4.6c

It was synthesized from **4.6a-S1** with 1-bromohept-2-yne according to the procedure for **4.6a** in 5 mmol scale.

Yield 1.64 g, 90% yield as colorless oil.

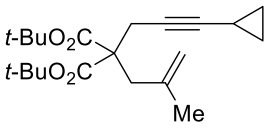
R*f* = 0.26. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.36–1.45 (m, 4H), 1.45 (s, 18H), 1.72 (s, 3H), 2.10–2.15 (m, 2H), 2.69 (t, *J* = 2.4 Hz, 2H), 2.73 (s, 2H), 4.85 (m, 1H), 4.87–4.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 18.3, 21.8, 22.9, 23.6, 27.8, 31.0, 39.1, 57.5, 75.1, 81.4, 83.4, 115.5, 140.9, 169.7.

HRMS (ESI) calcd for $C_{22}H_{37}O_4$ $[M+H]^+$ 365.2692, found 365.2697.

Compound **4.6d**



4.6d

It was synthesized from **4.6a-S1** with (3-bromo-1-propyn-1-yl)cyclopropane according to the procedure for **4.6a** in 5 mmol scale.

Yield 1.45 g, 83% yield as colorless oil.

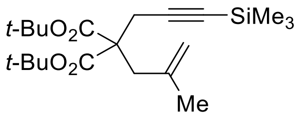
R*f* = 0.20. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.55−0.59 (m, 2H), 0.66−0.71 (m, 2H), 1.12−1.20 (m, 1H), 1.45 (s, 18H), 1.71 (s, 3H), 2.65 (d, *J* = 2.9 Hz, 2H), 2.70 (s, 2H), 4.83 (m, 1H), 4.87−4.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.5, 7.9, 22.9, 23.6, 27.8, 39.1, 57.5, 70.5, 81.4, 86.5, 115.5, 140.8, 169.6.

HRMS (ESI) calcd for $C_{21}H_{33}O_4$ $[M+H]^+$ 349.2379, found 349.2381.

<u>Compound **4.6e**</u>



4.6e

It was synthesized from **4.6a-S1** with 3- (trimethylsilyl)propargyl bromide according to the procedure for **4.6a** in 5 mmol scale.

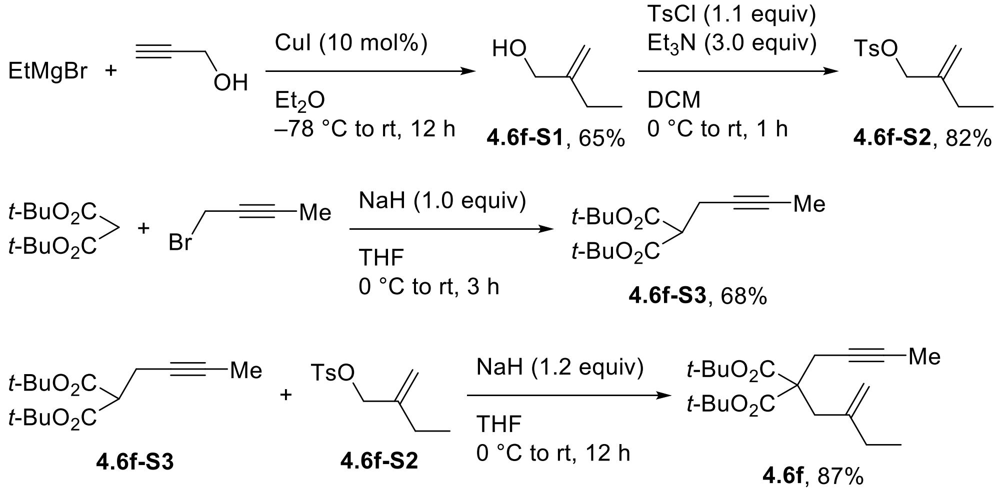
Yield 1.62 g, 85% yield as white solid.

R*f* = 0.26. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 9H), 1.43 (s, 18H), 1.69 (s, 3H), 2.71 (s, 2H), 2.72 (s, 2H), 4.84 (m, 1H), 4.86−4.87 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ –0.1, 23.5, 23.9, 27.8, 39.1, 57.2, 81.5, 87.9, 102.4, 115.7, 140.6, 169.3.

HRMS (ESI) calcd for $C_{21}H_{37}O_4Si$ $[M+H]^+$ 381.2461, found 381.2463.



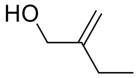
4.6f-S1 (CAS No.: 92269-61-9) was prepared according to a reported procedure with modifications:[44] To a mixture of ethylmagnesium bromide in diethyl ether (1.35 M, 72 mL, 97 mmol, 2.6 equiv) and copper iodide (726 mg, 3.8 mmol, 10 mol%) was added a solution of propargyl alcohol (2.14 g, 38 mmol, 1.0 equiv) in diethyl ether (15 mL) dropwise over 30 min at −78 °C. The mixture was stirred at room temperature for 12 h, and it was cooled to 0 °C before the addition of saturated aqueous NH_4Cl. After stirring at room temperature for 20 min, it was filtered through Celite®, and the filtrate was extracted with diethyl ether (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Diethyl ether was removed by distillation under atmospheric pressure and the residue was further distilled under vacuum to give **4.6f-S1** (CAS No.: 4435-54-5) as colorless oil (2.13 g, 65% yield).

To a solution of **4.6f-S1** (1.72 g, 20 mmol, 1.0 equiv) and triethylamine (8.4 mL, 60 mmol, 3.0 equiv) in DCM (20 mL) was added dropwise a solution of TsCl (4.20 g, 22 mmol, 1.1 equiv) in DCM (30 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was quenched with water and extracted with DCM (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 10:1) to give**4.6f-S2** as colorless oil (3.93 g, 82% yield).

Under nitrogen atmosphere, to a suspension of NaH (60% in mineral oil, 2.40 g, 60 mmol, 1.0 equiv) in THF (200 mL) was added a solution of di-*tert*-butyl malonate (14.30 g, 66 mmol, 1.1 equiv) in THF (20 mL) dropwise over 15 min at 0 °C, and the mixture was stirred at room temperature for 30 min. Subsequently, a solution of 1-bromo-2-butyne (8.00 g, 60 mmol, 1.0 equiv) in THF (10 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 30:1) to give **4.6f-S3** (CAS No.: 158044-35-0) as colorless oil (10.9 g, 68% yield).

Under nitrogen atmosphere, to a suspension of NaH (60% in mineral oil, 240 mg, 6.0 mmol, 1.2 equiv) in THF (10 mL) was added a solution of **4.6f-S3** (1.34 g, 5.0 mmol, 1.0 equiv) in THF (5 mL) dropwise over 5 min at 0 °C, and the mixture was stirred at room temperature for 30 min. Subsequently, a solution of **4.6f-S2** (1.45 g, 6 mmol, 1.2 equiv) in THF (5 mL) was added at 0 °C. The mixture was stirred at room temperature for 12 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 30:1) to give **4.6f** (CAS No.: 184949-93-7) as colorless oil (1.47 g, 87% yield).

Compound **4.6f-S1**[44]



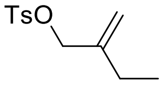
4.6f-S1

R*f* = 0.24. (eluent: hexane/ethyl acetate = 10:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, *J* = 7.5 Hz, 3H), 1.62 (br s, 1H), 2.09 (q, *J* = 7.4 Hz, 2H), 4.09 (d, *J* = 5.5 Hz, 2H), 4.88 (d, *J* = 1.2 Hz, 1H), 5.01 (d, *J* = 1.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 25.7, 66.0, 108.0, 150.7.

Compound **4.6f-S1**[44]



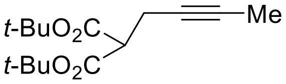
4.6f-S2

R*f* = 0.25. (eluent: hexane/diethyl ether = 10:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, *J* = 7.4 Hz, 3H), 2.02 (q, *J* = 7.4 Hz, 2H), 2.45 (s, 3H), 4.47 (m, 2H), 4.96 (m, 1H), 5.02 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.6, 21.6, 25.5, 73.0, 114.0, 127.9, 129.8, 133.2, 143.5, 144.7.

Compound **4.6f-S3**



4.6f-S3

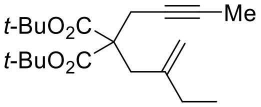
R*f* = 0.23. (eluent: hexane/diethyl ether = 40:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 18H), 1.75 (t, *J* = 2.5 Hz, 3H), 2.61 (dq, *J* = 7.8 Hz, 2.5 Hz, 2H), 3.30 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.4, 18.6, 27.8, 53.4, 75.1, 77.4, 81.6, 167.6.

HRMS (ESI) calcd for $C_{15}H_{25}O_4$ $[M+H]^+$ 269.1753, found 269.1761.

Compound **4.6f**



4.6f

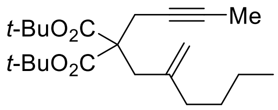
R*f* = 0.30. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.02 (t, *J* = 7.4 Hz, 3H), 1.45 (s, 18H), 1.75 (t, *J* = 2.6 Hz, 3H), 1.99 (q, *J* = 7.4 Hz, 2H), 2.67 (q, *J* = 2.5 Hz, 2H), 2.73 (s, 2H), 4.87 (m, 1H), 4.88−4.89 (m, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 3.4, 12.6, 22.9, 27.8, 29.5, 37.2, 57.6, 74.4, 78.5, 81.4, 113.0, 146.5, 169.7.

HRMS (ESI) calcd for $C_{20}H_{33}O_4$ $[M+H]^+$ 337.2379, found 337.2371.

Compound **4.6g**



4.6g

It was synthesized from **4.6f-S3** with 2-(bromomethyl)hex-1-ene according to the procedure for **4.6f** in 5 mmol scale.

Yield 1.70 g, 94% yield as colorless oil.

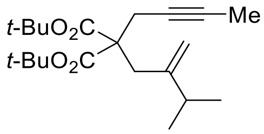
R*f* = 0.30. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.24−1.33 (m, 2H), 1.38−1.45 (m, 2H), 1.45 (s, 18H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.97 (t, *J* = 7.6 Hz, 2H), 2.67 (q, *J* = 2.4 Hz, 2H), 2.70 (s, 2H), 4.86–4.87 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 3.4, 14.0, 22.3, 22.8, 27.8, 30.2, 36.5, 36.9, 57.7, 74.4, 78.5, 81.4, 113.9, 145.0, 169.7.

HRMS (ESI) calcd for $C_{22}H_{37}O_4$ $[M+H]^+$ 365.2692, found 365.2681.

Compound **4.6h**



4.6h

It was synthesized from **4.6f-S3** with 3-methyl-2-methylenebutyl 4-methylbenzenesulfonate according to the procedure for **4.6f** in 5 mmol scale.

Yield 1.47 g, 84% yield as colorless oil.

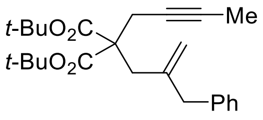
R*f* = 0.25. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (d, *J* = 6.8 Hz, 6H), 1.45 (s, 18H), 1.75 (t, *J* = 2.6 Hz, 3H), 2.13 (sept, *J* = 6.7 Hz, 1H), 2.66 (q, *J* = 2.5 Hz, 2H), 2.75 (s, 2H), 4.83 (m, 1H), 4.90 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.4, 22.0, 22.7, 27.8, 33.5, 36.1, 57.7, 74.4, 78.5, 81.4, 110.7, 151.1, 169.7.

HRMS (ESI) calcd for $C_{21}H_{35}O_4$ $[M+H]^+$ 351.2535, found 351.2539.

Compound **4.6i**



4.6i

It was synthesized from **4.6f-S3** with (2-(bromomethyl)allyl)benzene according to the procedure for **4.6f** in 5 mmol scale.

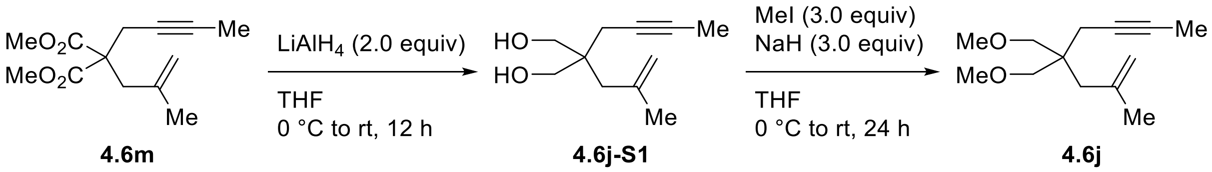
Yield 1.75 g, 88% yield as white solid.

R*f* = 0.21. (eluent: hexane/diethyl ether = 40:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 18H), 1.73 (t, *J* = 2.5 Hz, 3H), 2.71 (s, 2H), 2.75 (q, *J* = 2.5 Hz, 2H), 3.32 (s, 2H), 4.82 (m, 1H), 4.97 (m, 1H), 7.18−7.20 (m, 3H), 7.26−7.29 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.4, 23.0, 27.8, 36.3, 43.7, 57.9, 74.3, 78.8, 81.5, 116.1, 126.0, 128.2, 129.2, 139.4, 144.2, 169.6.

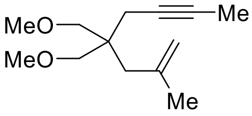
HRMS (ESI) calcd for $C_{25}H_{34}O_4$ $[M+H]^+$ 399.2535, found 399.2534.



Under nitrogen atmosphere, to a suspension of $LiAlH_4$ (610 mg, 16 mmol, 2.0 equiv) in THF (20 mL) was added dropwise a solution of **4.6m** (1.91 g, 8 mmol, 1.0 equiv) in THF (5 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h. The mixture was cooled to 0 °C and carefully quenched with water. After stirring at room temperature for 10 min, the solid was filtered off. The filtrate was dried over $MgSO_4$ and filtered. Volatiles were removed to give the crude diol **4.6j-S1** as colorless oil, which was used for the next step without further purification.

A THF (10 mL) solution of the diol **4.6j-S1** obtained above was added dropwise to a suspension of NaH (60% in mineral oil, 960 mg, 24 mmol, 3.0 equiv) in THF (50 mL) over 10 min at 0 °C. The mixture was stirred at room temperature for 30 min, and a solution of MeI (3.41 g, 24 mmol, 3.0 equiv) in THF (5 mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 24 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Volatiles were removed and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether = 30:1) to give **4.6j** as colorless oil (1.30 g, 78% yield from **4.6m**).

Compound **4.6j**



4.6j

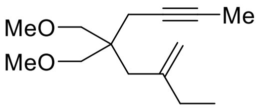
R*f* = 0.26. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (s, 3H), 1.80 (t, *J* = 2.6 Hz, 3H), 2.12 (s, 2H), 2.15 (q, *J* = 2.5 Hz, 2H), 3.22 (d, *J* = 9.0 Hz, 2H), 3.24 (d, *J* = 9.0 Hz, 2H), 3.32 (s, 6H), 4.76 (m, 1H), 4.89–4.90 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.5, 22.6, 25.0, 38.4, 42.4, 59.0, 74.3, 75.8, 77.5, 114.7, 142.1.

HRMS (ESI) calcd for $C_{13}H_{23}O_2$ $[M+H]^+$ 211.1698, found 211.1691.

Compound **4.6k**



4.6k

It was synthesized from **4.6m** according to the procedure for **4.6j** in 5 mmol scale.

Yield 1.23 g, 69% yield as colorless oil.

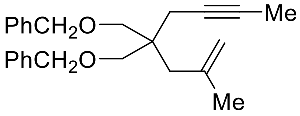
R*f* = 0.26. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (t, *J* = 7.4 Hz, 3H), 1.80 (t, *J* = 2.6 Hz, 3H), 2.03 (q, *J* = 7.3 Hz, 2H), 2.12 (s, 2H), 2.13 (q, *J* = 2.6 Hz, 2H), 3.20 (d, *J* = 8.9 Hz, 2H), 3.22 (d, *J* = 9.0 Hz, 2H), 3.31 (s, 6H), 4.80 (m, 1H), 4.90 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.5, 12.8, 22.6, 30.6, 36.7, 42.5, 59.0, 74.3, 75.9, 77.5, 112.3, 147.8.

HRMS (ESI) calcd for $C_{14}H_{25}O_2$ $[M+H]^+$ 225.1855, found 225.1851.

Compound **4.6l**



4.6l

It was synthesized from **4.6m** with benzyl bromide according to the procedure for **4.6j** in 5 mmol scale.

Yield 1.40 g, 77% yield as colorless oil.

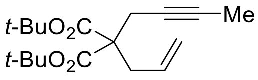
R*f* = 0.25. (eluent: hexane/diethyl ether = 50:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (t, *J* = 2.6 Hz, 3H), 1.77 (s, 3H), 2.19 (s, 2H), 2.24 (q, *J* = 2.5 Hz, 2H), 3.37 (d, *J* = 8.8 Hz, 2H), 3.39 (d, *J* = 8.8 Hz, 2H), 4.48 (s, 4H), 4.78 (m, 1H), 4.87–4.88 (m, 1H), 7.21–7.36 (m, 10H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.5, 22.8, 25.1, 38.4, 42.8, 71.9, 73.1, 76.0, 77.6, 114.8, 127.2, 127.3, 128.2, 138.8, 142.1.

HRMS (ESI) calcd for $C_{25}H_{31}O_2$ $[M+H]^+$ 363.2324, found 363.2314.

Compound **4.6n**



4.6n

It was synthesized from **4.6f-S3** with allyl bromide according to the procedure for **4.6f** in 5 mmol scale.

Yield 1.40 g, 77% yield as colorless oil.

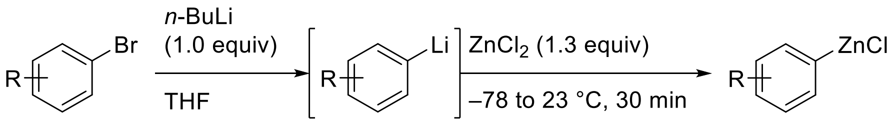
R*f* = 0.20. (eluent: hexane/diethyl ether = 50:1, visualized by $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 18H), 1.75 (t, *J* = 2.6 Hz, 3H), 2.63 (q, *J* = 2.6 Hz, 2H), 2.69 (d, *J* = 7.5 Hz, 2H), 5.10 (dd, *J* = 10.1 Hz, 2.1 Hz, 1H), 5.16 (dd, *J* = 17.0 Hz, 2.0 Hz, 1H), 5.64 (ddt, *J* = 17.0 Hz, 10.0 Hz, 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.4, 22.7, 27.8, 36.3, 57.6, 73.8, 78.3, 81.4, 119.0, 132.5, 169.3.

HRMS (ESI) calcd for $C_{18}H_{29}O_4$ $[M+H]^+$ 309.2066, found 309.2056.

5.3.3. Preparation of arylzinc reagents 4.7a–4.7k[46]

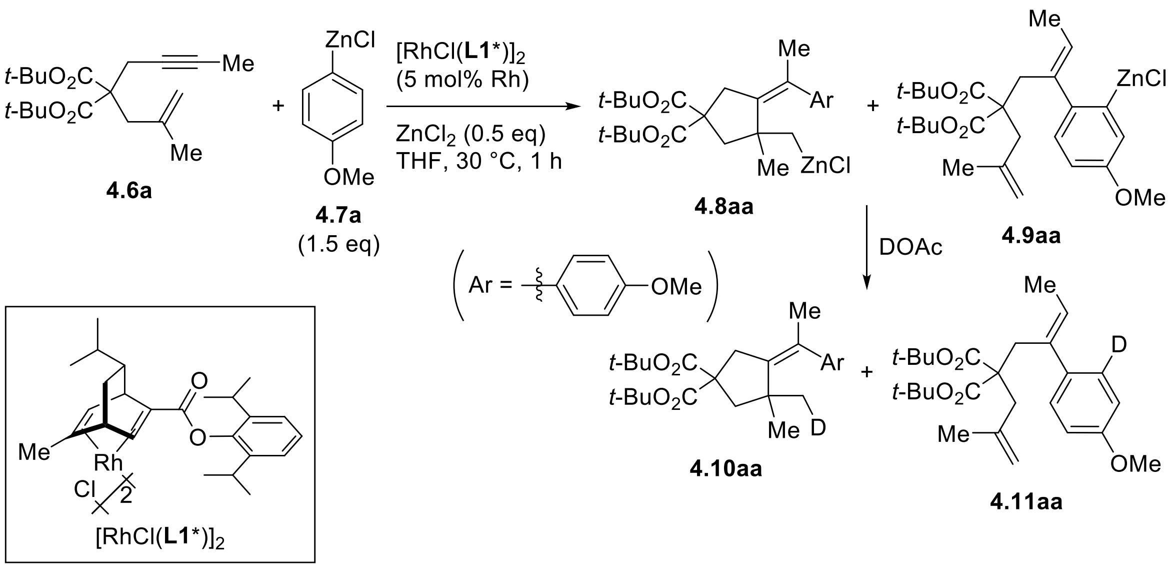


4.7a–k

A typical procedure for 4-MeOC$_6$H$_4$ZnCl (**4.7a**): Under nitrogen atmosphere, in an oven-dried Schlenk flask equipped with a stir bar were placed 4-MeOC$_6$H$_4$Br (1.65 g, 8.8 mmol, 1.1 equiv) and THF (9.0 mL). The solution was cooled down to −78 °C and a 2.7 M solution of *n*-BuLi (3.0 mL, 8.0 mmol, 1.0 equiv) in hexane was added dropwise over 10 min. The mixture was stirred at −78 °C for 2 h before a 1.5 M solution of ZnCl$_2$ in THF (6.9 mL, 10.4 mmol, 1.3 equiv) was added over 5 min. The mixture was kept stirring at –78 °C for 10 min, and it was allowed to warm to room temperature over a period of 30 min. The resulting solution, which should contain 0.40 M of 4-MeOC$_6$H$_4$ZnCl (**4.7a**) and 0.12 M of ZnCl$_2$ if the lithiation and zincation proceeded in quantitative yields, was used for the rhodium-catalyzed arylzincation of enynes **4.6a**, which is described in the next section.

Other arylzinc reagents **4.7b–4.7k** were prepared in a similar manner as 4-MeOC$_6$H$_4$ZnCl (**4.7a**) in THF.

5.3.4. Rhodium-catalyzed arylzincation of 4.6a with 4.7a followed by deuteration (Scheme 4-10)



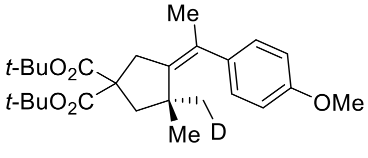
The reaction consists of two reactions, 1) rhodium-catalyzed arylzincation generating alkylzincs **4.8aa** and **4.9aa** (**Procedure A**) and 2) deuteration of the alkylzincs with acetic acid-*d₁*.

Procedure A

In an oven-dried Schlenk tube equipped with a stir bar were placed [RhCl(**L1***)]$_2$ (5.0 mg, 0.0050 mmol, 5 mol% of Rh) and **4.6a** (64.5 mg, 0.20 mmol, 1.0 equiv). The tube was evacuated and re-filled with nitrogen gas for 3 cycles, and 0.75 mL of the THF solution prepared above in Section 5.3.4, which contains 0.3 mmol (1.5 equiv) of $4\text{-MeOC}_6\text{H}_4\text{ZnCl}$ (**4.7a**) and 0.1 mmol (0.5 equiv) of ZnCl_2, was added at room temperature. The mixture was stirred at 30 °C in a pre-heated bath for 1 h.

The resulting mixture containing the alkylzincs **4.8aa** and **4.9aa** was cooled to 0 °C and acetic acid-d_1 (100 μL) was added in one portion. After stirring at room temperature for 10 min, saturated aqueous NaHCO_3 solution (1 mL) was added to neutralize the remaining acid. The mixture was extracted with diethyl ether (5 mL × 3). Volatiles were removed and the residue was subjected to NMR analysis. A flash column chromatography on silica gel with hexane/DCM/diethyl ether (*v*/*v*, 10:1:0→20:2:1) as eluent gave **4.10aa** (76.0 mg, 88% yield) as a mixture with **4.11aa** (**4.10aa**/**4.11aa** = 20:1).

Compound **4.10aa**



4.10aa

Colorless oil.

R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 40:4:1, visualized by UV)

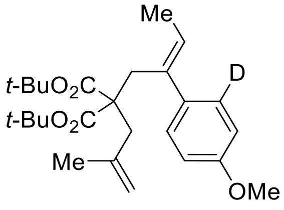
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (br s, 2H), 0.81 (br s, 3H), 1.47 (s, 18 H), 1.87 (s, 3H), 2.18 (s, 2H), 3.05 (s, 2H), 3.79 (s, 3H), 6.81 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H).

^{2}H NMR ($CHCl_3$, 61 MHz) δ 0.82 (br s).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 27.9, 29.3 (t, $J_{C\text{-}D}$ = 19.1 Hz), 29.6, 40.0, 42.4, 50.8, 55.1, 58.4, 81.1, 113.0, 128.7, 129.7, 136.8, 142.4, 157.8, 171.8.

HRMS (ESI) calcd for $C_{26}H_{38}DO_5$ $[M+H]^+$ 432.2860, found 432.2837.

Compound **4.11aa**



4.11aa

It was obtained through the reaction using [RhCl(*R*)-segphos]$_2$ (5 mol% Rh) as a catalyst, which gave the products **4.10aa** and **4.11aa** in a ratio of 4 to 1. Analytical sample was purified by preparative TLC (hexane/DCM/diethyl ether = 100:30:1) as colorless oil

R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 40:4:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 18H), 1.54 (s, 3H), 1.79 (d, J = 6.9 Hz, 3H), 2.31 (s, 2H), 3.24 (s, 2H), 3.78 (s, 3H), 4.67 (m, 1H), 4.76 (m, 1H), 5.55 (q, J = 7.0 Hz, 1H), 6.77−6.80

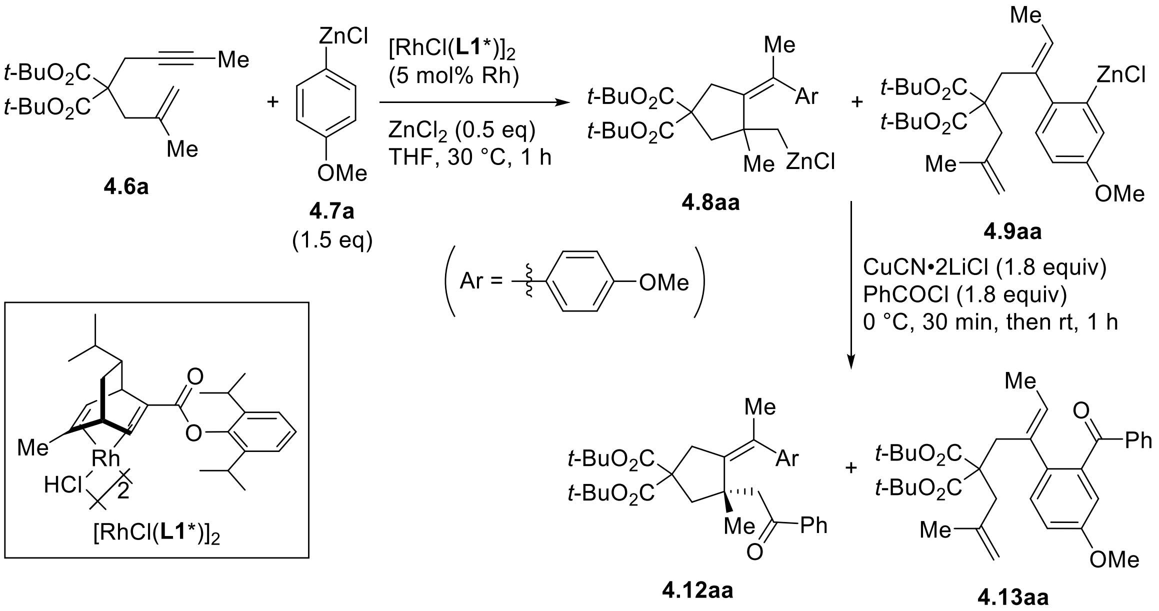
(m, 2H), 7.12−7.15 (m, 1H).

^{2}H NMR ($CHCl_3$, 61 MHz) δ 7.18 (br s).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1, 24.6, 27.7, 31.1, 40.0, 55.3, 57.8, 81.3, 112.2, 113.2, 113.3, 127.9 (t, $J_{C\text{-}D}$ = 22.4 Hz), 128.1, 128.2, 137.0, 137.1, 141.8, 158.4, 170.7.

HRMS (ESI) calcd for $C_{26}H_{38}DO_5$ $[M+H]^+$ 432.2860, found 432.2848.

5.3.5. Rhodium-catalyzed arylzincation of 4.6a with 4.7a followed by copper-mediated benzoylation (Table 4-1, entry 1)



The arylzincation generating a THF solution containing the alkylzincs **4.6a** and **4.7a** was performed according to the **Procedure A** (section 5.3.4), and the THF solution was subjected to the copper-mediated benzoylation, which is shown below as **Procedure B**.

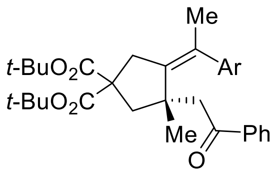
Procedure B

The THF solution obtained by the arylzincation (**Procedure A,** section 5.3.4) was cooled to 0 °C and a 1.0 M solution of CuCN•2LiCl in THF (0.36 mL, 0.36 mmol, 1.8 equiv) was added. It was stirred at 0 °C for 5 min, before benzoyl chloride (50.7 mg, 0.36 mmol, 1.8 equiv) was added. After 30 min at 0 °C, the mixture was warmed to room temperature, and it was kept stirring at room temperature for 1 h.

As a work-up after **Procedure B**, saturated aqueous NH_4Cl (1 mL) and saturated aqueous $NaHCO_3$ (2 mL) were added successively, and the mixture was stirred at room temperature for 10 min. The mixture was extracted with diethyl ether (5 mL × 3). Volatiles were removed and the residue was subjected to NMR analysis, which showed the presence of **4.12aa** and **4.13aa** in a ratio of 20 to 1. A flash column chromatography on silica gel with hexane/DCM/diethyl ether (*v*/*v*, 10:1:0→10:1:1) as eluent gave **4.12aa** (96.8 mg, 91% yield) as colorless oil.

A racemic sample of **4.12aa** for the HPLC analysis was obtained by the reaction using $[RhCl(cod)]_2$ instead of $[RhCl(\mathbf{L1}^*)]_2$.

<u>Compound **4.12aa**</u>



4.12aa

$[\alpha]^{25}_D$ −49 (*c* 0.85, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol/DCM = 88/2/10, flow 1.0 mL/min, 230 nm, t_{major} = 8.6 min, t_{minor} = 10.2 min.

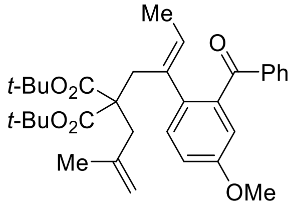
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.91 (s, 3H), 2.28 (d, *J* = 13.8 Hz, 1H), 2.67 (d, *J* = 17.6 Hz, 1H), 2.79 (d, *J* = 13.8 Hz, 1H), 2.88 (d, *J* = 17.7 Hz, 1H), 3.00 (dd, *J* = 16.9 Hz, 1.3 Hz, 1H), 3.28 (d, *J* = 16.9 Hz, 1H), 3.75 (s, 3H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 25.1, 27.9, 28.7, 39.9, 44.0, 47.1, 48.2, 55.2, 58.8, 81.1, 81.2, 113.4, 127.8, 128.2, 128.7, 129.7, 132.5, 136.6, 137.9, 142.5, 158.0, 171.5, 171.9, 198.6.

HRMS (ESI) calcd for $C_{33}H_{43}O_6$ $[M+H]^+$ 535.3060, found 535.3057.

Compound **4.13aa**



4.13aa

It was obtained through the reaction using [RhCl(*R*)-segphos]$_2$ (5 mol% Rh) as a catalyst in **Procedure A**, which gave the products **4.12aa** and **4.13aa** in a ratio of 4 to 1 (entry 7 in Table 4-1). Analytical sample was purified by preparative TLC (hexane/DCM = 1:1) as colorless oil.

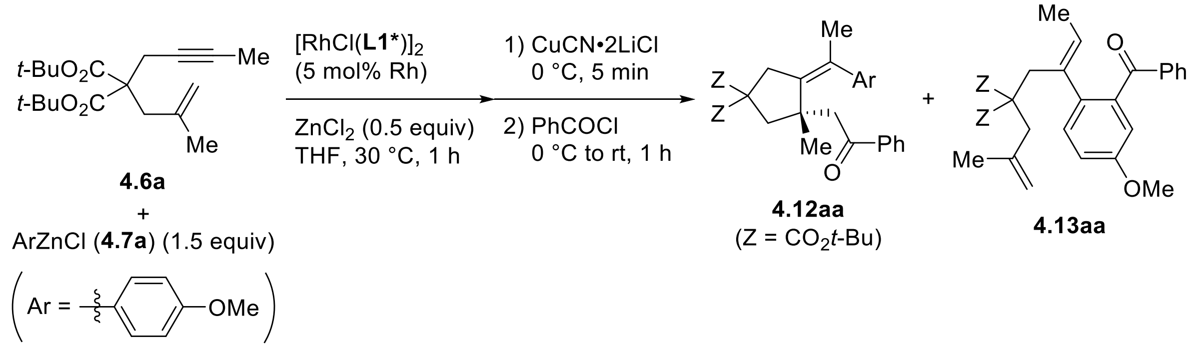
R*f* = 0.19. (eluent: hexane/DCM /diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.35 (s, 18H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.54 (s, 3H), 2.36 (s, 2H), 2.76 (s, 2H), 3.80 (s, 3H), 4.47 (m, 1H), 4.66 (m, 1H), 5.42 (q, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 2.7 Hz, 1H), 6.95 (dd, *J* = 8.5 Hz, 2.7 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.9, 24.2, 27.7, 34.7, 41.1, 55.5, 58.1, 81.3, 113.4, 113.9, 115.8, 127.9, 130.2, 131.8, 132.1, 132.6, 135.8, 136.9, 137.7, 138.8, 141.7, 158.0, 170.5, 198.2.

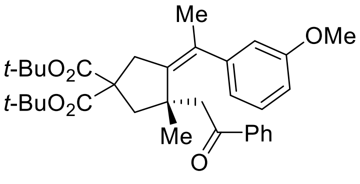
HRMS (ESI) calcd for $C_{33}H_{43}O_6$ $[M+H]^+$ 535.3060, found 535.3050.

5.3.6. Rhodium-catalyzed arylzincation of 4.6a with 4.7a followed by copper-mediated benzoylation (Scheme 4-12, Scheme 4-13, and Scheme 4-14 eq 1)



The reactions shown in Scheme 4-12, Scheme 4-13, and Scheme 4-14 eq 1 were carried out according to the **Procedure A** using several other arylzinc reagents **4.7b**–**4.7k** or enynes **4.6b**–**4.6m**, which was followed by **Procedure B** (section 5.3.5). The reaction temperature and the reaction time in **Procedure A** (section 5.3.4) were modified depending on the reactivity of the rhodium-catalyzed arylzincation.

Compound **4.12ab**



4.12ab

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 1 h with **4.6a** (64.5 mg, 0.20 mmol) and 3-methoxyphenylzinc chloride (**4.7b**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 90 mg, 84% yield as colorless oil.

[α]$^{25}_{D}$ −44 (*c* 0.88, $CHCl_3$) for 98% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 8.3 min, t_{minor} = 9.8 min.

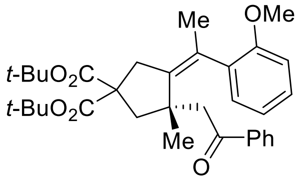
R*f* = 0.22. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.93 (s, 3H), 2.28 (d, *J* = 13.7 Hz, 1H), 2.69 (d, *J* = 17.8 Hz, 1H), 2.80 (d, *J* = 13.7 Hz, 1H), 2.89 (d, *J* = 17.8 Hz, 1H), 3.02 (d, *J* = 16.9 Hz, 1H), 3.30 (d, *J* = 17.0 Hz, 1H), 3.61 (br s, 3H), 6.58 (br s, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.73 (dd, *J* = 8.1 Hz, 2.3 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 27.8, 28.6, 39.8, 43.9, 47.1, 48.1, 54.9, 58.7, 81.1, 81.2, 112.0, 113.9, 121.1, 127.7, 128.2, 128.7, 129.0, 132.5, 137.8, 142.0, 145.8, 159.2, 171.4, 171.9, 198.4.

HRMS (ESI) calcd for $C_{33}H_{43}O_6$ $[M+H]^+$ 535.3060, found 535.3051.

Compound **4.12ac**



4.12ac

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 24 h with **4.6a** (64.4 mg, 0.20 mmol) and 2-methoxyphenylzinc chloride (**4.7c**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 82 mg, 76% yield as a 2:1 mixture of atropisomers.

[α]^{25}$_{D}$ −34.4 (*c* 1.05, $CHCl_3$) for 97% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 21.6 min, t_{minor} = 28.4 min.

R$_f$ = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

Major isomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 3H), 1.46 (s, 9H), 1.49 (s, 9H), 1.87 (s, 3H), 2.36 (d, *J* = 13.7 Hz, 1H), 2.73−2.87 (m, 3H), 3.00 (d, *J* = 16.8 Hz, 1H), 3.32 (d, *J* = 16.8 Hz, 1H), 3.58 (s, 3H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.17, 27.82, 28.28, 39.65, 43.73, 46.78, 47.14, 54.80, 58.96, 80.99, 81.06, 110.04, 119.97, 126.19, 127.68, 127.84, 128.12, 130.98, 132.30, 132.69, 137.92, 142.79, 156.19, 171.39, 171.94, 198.55.

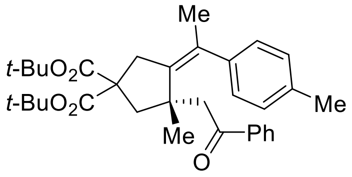
Minor isomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (s, 3H), 1.42 (s, 9H), 1.49 (s, 9H), 1.89 (s, 3H), 2.29 (d, *J* = 14.0 Hz, 1H), 2.73−2.87 (m, 2H), 3.08 (d, *J* = 17.3 Hz, 1H), 3.13 (d, *J* = 16.7 Hz, 1H), 3.20 (d, *J* = 16.6 Hz, 1H), 3.75 (s, 3H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 6.8 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.49, 25.60, 27.75, 39.74, 44.05, 46.33, 48.26, 54.86, 58.82, 80.94, 81.10, 110.63, 119.75, 126.01, 127.86, 127.96, 128.21, 130.11, 132.44, 132.82, 138.01, 142.27, 156.42, 171.58, 171.76, 198.92.

HRMS (ESI) calcd for $C_{33}H_{43}O_6$ $[M+H]^+$ 535.3060, found 535.3057.

Compound **4.12ad**



4.12ad

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 1 h with **4.6a** (64.6 mg, 0.20 mmol) and 4-methylphenylzinc chloride (**4.7d**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 89 mg, 86% yield as colorless oil.

$[\alpha]^{25}_{D}$ −48.2 (*c* 1.22, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 13.1 min, t_{minor} = 15.4 min.

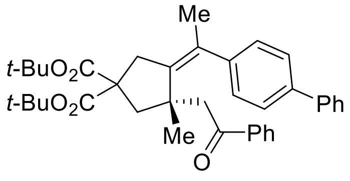
R_f = 0.21. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.93 (s, 3H), 2.31 (s, 3H), 2.31 (dd, *J* = 13.6 Hz, 0.9 Hz, 1H), 2.66 (d, *J* = 17.6 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 17.6 Hz, 1H), 3.01 (dd, *J* = 16.9 Hz, 1.4 Hz, 1H), 3.28 (d, *J* = 16.9 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.47 (tt, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.59 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 25.0, 27.8(1), 27.8(3), 28.5, 39.8, 44.0, 47.1, 48.2, 58.7, 81.0, 81.1, 127.8, 128.1, 128.5, 128.6, 129.0, 132.4, 135.7, 137.9, 141.4, 142.2, 171.5, 171.8, 198.6.

HRMS (ESI) calcd for $C_{33}H_{43}O_5$ $[M+H]^+$ 519.3110, found 519.3107.

Compound **4.12ae**



4.12ae

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 1 h with **4.6a** (64.5 mg, 0.20 mmol) and 4-phenylphenylzinc chloride (**4.7e**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 95 mg, 81% yield as colorless oil.

$[\alpha]^{25}_{D}$ −49.6 (*c* 1.15, $CHCl_3$) for 98% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IC column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 8.3 min, t_{minor} = 10.4 min.

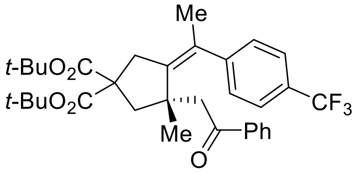
R_f = 0.21. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (s, 3H), 1.46 (s, 9H), 1.50 (s, 9H), 1.98 (s, 3H), 2.31 (d, *J* = 13.7 Hz, 1H), 2.66 (d, *J* = 17.6 Hz, 1H), 2.83 (d, *J* = 13.8 Hz, 1H), 2.93 (d, *J* = 17.6 Hz, 1H), 3.05 (dd, *J* = 17.0 Hz, 1.1 Hz, 1H), 3.32 (d, *J* = 16.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.27−7.35 (m, 3H), 7.40−7.47 (m, 5H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 27.8, 28.8, 39.9, 44.1, 47.1, 48.1, 58.7, 81.1, 81.2, 126.7, 126.9, 127.2, 127.7, 128.2, 128.5, 128.7, 129.1, 132.5, 137.8, 139.1, 140.7, 142.5, 143.4, 171.4, 171.9, 198.5.

HRMS (ESI) calcd for $C_{38}H_{45}O_5$ $[M+H]^+$ 581.3267, found 587.3264.

Compound **4.12af**



4.12af

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 24 h with **4.6a** (64.4 mg, 0.20 mmol) and 4-trifluoromethylphenylzinc chloride (**4.7f**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 74 mg, 65% yield as colorless oil.

$[\alpha]^{25}_{D}$ −36.2 (*c* 1.08, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 8.4 min, t_{minor} = 9.6 min.

R_f = 0.24. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

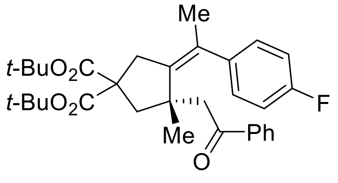
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 3H), 1.46 (s, 9H), 1.49 (s, 9H), 1.93 (s, 3H), 2.27 (d, *J* = 13.8 Hz, 1H), 2.57 (d, *J* = 17.7 Hz, 1H), 2.80 (d, *J* = 17.8 Hz, 1H), 2.84 (d, *J* = 13.9 Hz, 1H), 3.05 (dd, *J* = 17.0 Hz, 1.4 Hz, 1H), 3.32 (d, *J* = 17.1 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 27.8, 28.9, 39.9, 44.0, 47.0, 47.9, 58.6, 81.2, 81.3, 124.1 (q, $J_{C\text{-}F}$ = 272.0 Hz), 125.0 (q, $J_{C\text{-}F}$ = 3.9 Hz), 127.4, 127.5, 128.3, 128.6 (q, $J_{C\text{-}F}$ = 32.2 Hz), 129.0, 132.7, 137.6, 143.3, 148.2, 171.2, 171.8, 198.0.

^{19}F NMR ($CDCl_3$, 282 MHz) δ −58.0.

HRMS (ESI) calcd for $C_{33}H_{40}O_5F_3$ $[M+H]^+$ 573.2828, found 573.2830.

Compound **4.12ag**



4.12ag

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 1 h with **4.6a** (64.6 mg, 0.20 mmol) and 4-fluorophenylzinc chloride (**4.7g**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 91 mg, 87% yield as white solid.

$[\alpha]^{25}_{D}$ −44.3 (*c* 1.27, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IC column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 6.9 min, t_{minor} = 7.9 min.

R_f = 0.21. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

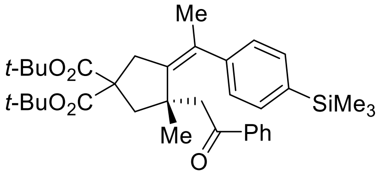
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.91 (s, 3H), 2.26 (dd, *J* = 13.7 Hz, 1.1 Hz, 1H), 2.66 (d, *J* = 17.8 Hz, 1H), 2.81 (d, *J* = 13.7 Hz, 1H), 2.84 (d, *J* = 17.8 Hz, 1H), 3.02 (dd, *J* = 17.0 Hz, 1.5 Hz, 1H), 3.30 (d, *J* = 17.0 Hz, 1H), 6.89 (t, *J* = 8.7 Hz, 2H), 6.99−7.02 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.49 (tt, *J* = 7.4 Hz, 1.3 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 27.9, 28.8, 40.0, 43.9, 47.1, 48.2, 58.7, 81.2, 81.3, 114.8 (d, $J_{C\text{-F}}$ = 20.9 Hz), 127.7, 127.9, 128.3, 130.2 (d, $J_{C\text{-F}}$ = 7.7 Hz), 132.6, 137.7, 140.1 (d, $J_{C\text{-F}}$ = 3.5 Hz), 142.9, 161.4 (d, $J_{C\text{-F}}$ = 243.9 Hz), 171.4, 171.9, 198.3.

^{19}F NMR ($CDCl_3$, 282 MHz) δ −116.5.

HRMS (ESI) calcd for $C_{32}H_{40}O_5F$ $[M+H]^+$ 323.2860, found 323.2853.

Compound **4.12ah**



4.12ah

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 12 h with **4.6a** (64.5 mg, 0.20 mmol) and 4-trimethylsilylphenylzinc chloride (**4.7h**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 81 mg, 72% yield as colorless oil.

$[\alpha]^{25}_{D}$ −43.5 (*c* 1.22, $CHCl_3$) for 95% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 9.9 min, t_{minor} = 11.8 min.

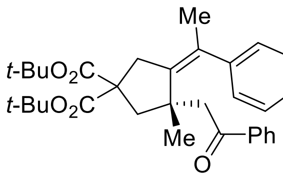
R_f = 0.24. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.23 (s, 9H), 1.09 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.93 (s, 3H), 2.31 (d, *J* = 13.8 Hz, 1H), 2.57 (d, *J* = 17.7 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.82 (d, *J* = 17.6 Hz, 1H), 3.01 (d, *J* = 17.0 Hz, 1H), 3.30 (d, *J* = 17.0 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.1, 24.8, 27.8, 28.7, 39.7, 44.0, 47.0, 48.1, 58.7, 81.1, 81.2, 127.7, 128.0, 128.1, 128.9, 132.4, 133.0, 137.9, 138.0, 142.1, 144.8, 171.5, 171.9, 198.5.

HRMS (ESI) calcd for $C_{35}H_{49}O_5Si$ $[M+H]^+$ 577.3349, found 577.3348.

Compound **4.12ai**



4.12ai

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 1 h with **4.6a** (64.5 mg, 0.20 mmol) and 3,4-methylenedioxyphenylzinc chloride (**4.7i**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→8:1:1

Yield 98 mg, 90% yield as colorless oil.

$[\alpha]^{25}_{D}$ −49 (*c* 0.99, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 10.0 min, t_{minor} = 11.5 min.

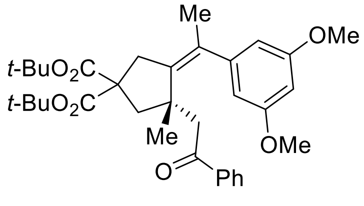
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.90 (s, 3H), 2.29 (d, *J* = 13.7 Hz, 1H), 2.74 (d, *J* = 17.7 Hz, 1H), 2.81 (d, *J* = 13.8 Hz, 1H), 2.92 (d, *J* = 17.8 Hz, 1H), 3.00 (dd, *J* = 17.1 Hz, 0.8 Hz, 1H), 3.28 (d, *J* = 17.0 Hz, 1H), 5.81 (s, 1H), 5.89 (d, *J* = 1.0 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 6.53 (s, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 27.8, 28.6, 39.8, 44.0, 47.0, 48.1, 58.6, 81.0, 81.1, 100.7, 107.8, 109.3, 121.5, 127.7, 128.2, 128.4, 132.4, 137.8, 137.9, 142.5, 145.8, 147.1, 171.4, 171.8, 198.3.

HRMS (ESI) calcd for $C_{33}H_{41}O_7$ $[M+H]^+$ 549.2852, found 549.2849.

Compound **4.12aj**



4.12aj

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 12 h with **4.6a** (64.3 mg, 0.20 mmol) and 3,5-dimethoxyphenylzinc chloride (**4.7j**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 85 mg, 75% yield as colorless oil.

$[\alpha]^{25}_{D}$ −30.0 (*c* 1.15, $CHCl_3$) for 95% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 90/10, flow 1.0 mL/min, 230 nm, t_{major} = 7.2 min, t_{minor} = 8.7 min.

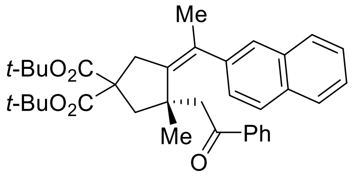
R_f = 0.21. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 3H), 1.46 (s, 9H), 1.49 (s, 9H), 1.92 (s, 3H), 2.27 (d, *J* = 13.7 Hz, 1H), 2.75 (d, *J* = 18.0 Hz, 1H), 2.84 (d, *J* = 13.7 Hz, 1H), 2.93 (d, *J* = 18.0 Hz, 1H), 3.01 (d, *J* = 17.0 Hz, 1H), 3.31 (d, *J* = 17.0 Hz, 1H), 3.58 (br s, 6H), 6.19 (br s, 2H), 6.28 (t, *J* = 2.2 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 27.8, 28.7, 39.8, 43.8, 47.0, 47.9, 55.0, 58.6, 81.0, 81.1, 98.5, 106.4, 127.7, 128.2, 128.5, 132.5, 137.7, 141.7, 146.3, 160.3, 171.3, 171.9, 198.2.

HRMS (ESI) calcd for $C_{34}H_{45}O_7$ $[M+H]^+$ 565.3165, found 565.3165.

Compound **4.12ak**



4.12ak

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 12 h with **4.6a** (64.5 mg, 0.20 mmol) and 2-naphthylzinc chloride (**4.7k**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 89 mg, 80% yield as colorless oil.

$[\alpha]^{25}_{D}$ −43.3 (*c* 1.25, $CHCl_3$) for 98% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 15.7 min, t_{minor} = 19.4 min.

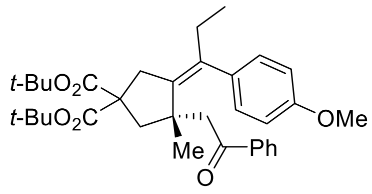
R_f = 0.24. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 3H), 1.47 (s, 9H), 1.50 (s, 9H), 2.01 (s, 3H), 2.29 (d, *J* = 13.7 Hz, 1H), 2.65 (d, *J* = 17.5 Hz, 1H), 2.84 (d, *J* = 13.7 Hz, 1H), 2.87 (d, *J* = 17.4 Hz, 1H), 3.09 (d, *J* = 17.0 Hz, 1H), 3.35 (d, *J* = 16.9 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.37−7.44 (m, 5H), 7.50 (br s, 1H), 7.58 (br s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 27.8, 28.6, 40.0, 44.0, 47.1, 48.2, 58.8, 81.0, 81.2, 125.5, 126.0, 126.8, 127.4, 127.5, 127.5(9), 127.6(1), 128.1, 128.9, 131.9, 132.4, 133.0, 137.6, 141.7, 142.7, 171.4, 171.8, 198.5.

HRMS (ESI) calcd for $C_{36}H_{43}O_5$ $[M+H]^+$ 555.3110, found 555.3112.

Compound **4.12ba**



4.12ba

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 12 h with **4.6b** (67.5 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 94 mg, 86% yield as colorless oil.

$[\alpha]^{25}_D$ −44.7 (*c* 1.16, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 16.4 min, t_{minor} = 20.5 min.

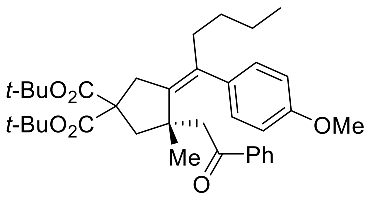
R_f = 0.22. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.06 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 2.15 (dq, *J* = 14.3 Hz, 7.5 Hz, 1H), 2.26 (d, *J* = 13.6 Hz, 1H), 2.32 (dq, *J* = 14.1 Hz, 7.6 Hz, 1H), 2.67 (d, *J* = 17.6 Hz, 1H), 2.78 (d, *J* = 13.7 Hz, 1H), 2.88 (d, *J* = 17.6 Hz, 1H), 3.04 (d, *J* = 16.6 Hz, 1H), 3.30 (d, *J* = 16.7 Hz, 1H), 3.76 (s, 3H), 6.76 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 27.8, 28.7, 31.2, 39.1, 43.9, 46.9, 48.2, 55.1, 58.8, 81.0, 81.2, 113.1, 127.8, 128.2, 130.6, 132.4, 134.7, 134.9, 137.9, 142.1, 158.0, 171.4, 171.8, 198.6.

HRMS (ESI) calcd for $C_{34}H_{45}O_6$ $[M+H]^+$ 549.3216, found 549.3215.

Compound **4.12ca**



4.12ca

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 12 h with **4.6c** (73.8 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 96 mg, 83% yield as colorless oil.

$[\alpha]^{25}_{D}$ −41 (*c* 0.97, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IC column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 8.0 min, t_{minor} = 10.0 min.

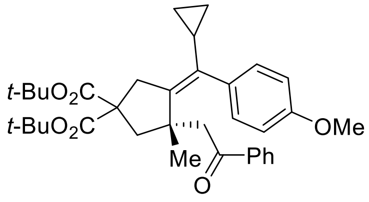
R_f = 0.22. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85−0.88 (m, 3H), 1.07 (s, 3H), 1.26−1.35 (m, 4H), 1.45 (s, 9H), 1.49 (s, 9H), 2.12−2.18 (m, 1H), 2.27 (d, *J* = 13.6 Hz, 1H), 2.25−2.33 (m, 1H), 2.66 (d, *J* = 17.6 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.88 (d, *J* = 17.6 Hz, 1H), 3.06 (d, *J* = 16.7 Hz, 1H), 3.31 (d, *J* = 16.6 Hz, 1H), 3.75 (s, 3H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.6, 27.8, 28.7, 29.5, 38.1, 39.3, 43.9, 46.9, 48.1, 55.1, 58.8, 81.0, 81.1, 113.0, 127.7, 128.1, 130.4, 132.4, 133.6, 134.9, 137.9, 142.5, 158.0, 171.4, 171.8, 198.6.

HRMS (ESI) calcd for $C_{36}H_{49}O_6$ $[M+H]^+$ 577.3529, found 577.3534.

Compound **4.12da**



4.12da

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 12 h with **4.6d** (69.3 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 64 mg, 57% yield as colorless oil.

$[\alpha]^{25}_{D}$ −46.9 (*c* 1.03, $CHCl_3$) for 98% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 18.5 min, t_{minor} = 22.4 min.

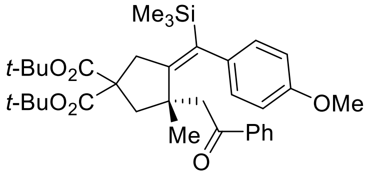
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03−0.11 (m, 2H), 0.47−0.58 (m, 2H), 1.01 (s, 3H), 1.45 (s, 9H), 1.49 (s, 9H), 1.69−1.76 (m, 1H), 2.28 (dd, *J* = 13.7 Hz, 0.9 Hz, 1H), 2.63 (d, *J* = 17.6 Hz, 1H), 2.80 (d, *J* = 13.8 Hz, 1H), 2.83 (d, *J* = 17.6 Hz, 1H), 3.17 (d, *J* = 17.0 Hz, 1H), 3.48 (dd, *J* = 16.9 Hz, 0.7 Hz, 1H), 3.74 (s, 3H), 6.68−6.93 (br m, 4H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.47 (tt, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.9, 4.0, 16.1, 27.8, 27.9, 28.4, 39.5, 44.3, 46.9, 48.2, 55.1, 58.9, 81.0, 81.1, 112.7, 127.8, 128.2, 130.1, 131.6, 132.4, 132.9, 137.9, 143.1, 158.2, 171.5, 171.9, 198.6.

HRMS (ESI) calcd for $C_{35}H_{45}O_6$ $[M+H]^+$ 561.3216, found 561.3219.

Compound **4.12ea**



4.12ea

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 24 h with **4.6e** (76.2 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution) in the presence of [RhCl(**L1***)]$_2$ (10.0 mg, 10 mol% Rh).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1 and 1% triethylamine

Yield 45 mg, 38% yield as colorless oil.

[α]^{25}$_{\mathrm{D}}$ −52 (*c* 0.81, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 9.7 min, t_{minor} = 12.5min.

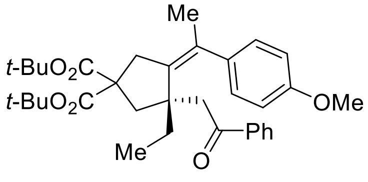
R*f* = 0.23. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H), 1.06 (s, 3H), 1.42 (s, 9H), 1.45 (s, 9H), 2.17 (d, *J* = 13.8 Hz, 1H), 2.71 (d, *J* = 13.8 Hz, 1H), 2.74 (d, *J* = 17.8 Hz, 1H), 2.95 (d, *J* = 17.7 Hz, 1H), 3.13 (d, *J* = 16.5 Hz, 1H), 3.32 (d, *J* = 16.6 Hz, 1H), 3.72 (s, 3H), 6.60 (dd, *J* = 8.4 Hz, 2.6 Hz, 1H), 6.67 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.76 (dd, *J* = 8.3 Hz, 2.6 Hz, 1H), 6.80 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0, 27.9, 28.6, 41.9, 46.3, 46.6, 48.3, 55.1, 59.6, 81.1, 81.2, 112.9, 113.0, 127.8, 128.2, 129.3, 129.9, 132.5, 135.0, 135.6, 137.9, 157.2, 158.1, 171.2, 171.5, 198.6.

HRMS (ESI) calcd for $C_{35}H_{49}O_6Si$ $[M+H]^+$ 593.3298, found 593.3297.

Compound **4.12fa**



4.12fa

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 1 h with **4.6f** (67.1 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 97 mg, 88% yield as colorless oil.

$[\alpha]^{25}_{D}$ −24.5 (*c* 1.37, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 19.5 min, t_{minor} = 39.5 min.

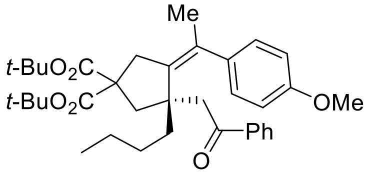
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (t, *J* = 7.3 Hz, 3H), 1.31 (dq, *J* = 14.3 Hz, 7.2 Hz, 1H), 1.43−1.50 (m, 1H), 1.45 (s, 9H), 1.48 (s, 9H), 1.93 (s, 3H), 2.37 (d, *J* = 14.1 Hz, 1H), 2.59 (d, *J* = 17.6 Hz, 1H), 2.84 (d, *J* = 14.1 Hz, 1H), 3.02 (d, *J* = 17.6 Hz, 1H), 3.04 (d, *J* = 16.5 Hz, 1H), 3.21 (d, *J* = 16.6 Hz, 1H), 3.74 (s, 3H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.3, 25.4, 27.8, 32.0, 40.7, 40.8, 45.8, 47.9, 55.1, 58.8, 81.0, 81.1, 113.3, 127.8, 128.1, 128.4, 129.4, 132.4, 136.6, 138.1, 141.4, 157.9, 171.6, 171.8, 198.7.

HRMS (ESI) calcd for $C_{34}H_{45}O_6$ $[M+H]^+$ 549.3216, found 549.3209.

Compound **4.12ga**



4.12ga

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 1 h with **4.6g** (73.0 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1, then GPC with chloroform as eluent

Yield 91 mg, 79% yield as colorless oil.

$[\alpha]^{25}_{D}$ −9.2 (*c* 1.06, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 11.7 min, t_{minor} = 22.4 min.

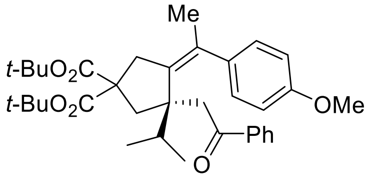
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84–0.87 (m, 3H), 1.18–1.32 (m, 6H), 1.44 (s, 9H), 1.48 (s, 9H), 1.93 (s, 3H), 2.38 (d, *J* = 14.2 Hz, 1H), 2.64 (d, *J* = 17.7 Hz, 1H), 2.86 (d, *J* = 14.2 Hz, 1H), 3.01 (d, *J* = 16.6 Hz, 1H), 3.03 (d, *J* = 17.7 Hz, 1H), 3.21 (d, *J* = 16.6 Hz, 1H), 3.74 (s, 3H), 6.72 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 23.1, 25.4, 26.9, 27.7(6), 27.8(2), 39.6, 40.7, 41.5, 46.4, 47.5, 55.1, 58.9, 80.9, 81.0, 113.3, 127.7, 128.1, 128.2, 129.4, 132.3, 136.5, 138.0, 141.7, 157.9, 171.6, 171.8, 198.7.

HRMS (ESI) calcd for $C_{36}H_{49}O_6$ $[M+H]^+$ 577.3529, found 577.3527.

Compound **4.12ha**



4.12ha

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 24 h with **4.6h** (70.0 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution) in the presence of $[RhCl(\mathbf{L1}^*)]_2$ (10.0 mg, 10 mol% Rh).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 49 mg, 44% yield as colorless oil.

$[\alpha]^{25}_{D}$ −6.9 (*c* 1.04, $CHCl_3$) for 93% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 11.5 min, t_{minor} = 16.8 min.

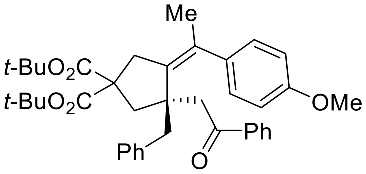
$\mathbf{R}_f$ = 0.16. (eluent: hexane/DCM/diethyl ether = 8:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.71 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 1.48 (s, 9H), 1.49 (s, 9H), 1.69 (sept, *J* = 6.8 Hz, 1H), 1.89 (s, 3H), 2.54 (d, *J* = 15.0 Hz, 1H), 2.59 (d, *J* = 15.0 Hz, 1H), 2.67 (d, *J* = 17.9 Hz, 1H), 2.85 (dd, *J* = 17.4 Hz, 1.6 Hz, 1H), 3.11 (d, *J* = 17.8 Hz, 1H), 3.59 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 3H), 6.67 (br m, 2H), 6.84 (br m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5, 18.6, 25.7, 27.9(0), 27.9(2), 36.5, 39.1, 42.1, 48.1, 51.6, 55.2, 59.4, 80.6, 81.1, 113.2, 126.9, 127.9, 128.2, 129.2, 132.3, 136.9, 137.9, 142.9, 157.8, 171.4, 172.2, 198.2.

HRMS (ESI) calcd for $C_{35}H_{47}O_6$ $[M+H]^+$ 563.3373, found 563.3376.

Compound **4.12ia**



4.12ia

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 24 h with **4.6i** (79.7 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution) in the presence of $[RhCl(\mathbf{L1}^*)]_2$ (10.0 mg, 10 mol% Rh).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 63 mg, 52% yield. As colorless oil.

$[\alpha]^{25}_{D}$ −36 (*c* 0.84, $CHCl_3$) for 96% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 18.4 min, t_{minor} = 25.2 min.

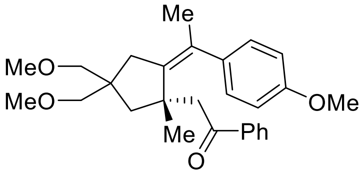
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.52 (s, 9H), 1.93 (s, 3H), 2.57 (d, *J* = 14.2 Hz, 1H), 2.60 (d, *J* = 18.6 Hz, 1H), 2.62 (d, *J* = 14.2 Hz, 1H), 2.72 (d, *J* = 18.6 Hz, 1H), 2.81 (d, *J* = 13.4 Hz, 1H), 2.85 (d, *J* = 13.5 Hz, 1H), 3.16 (d, *J* = 17.7 Hz, 1H), 3.17 (d, *J* = 17.6 Hz, 1H), 3.74 (s, 3H), 6.62−6.68 (br m, 4H), 7.08 (d, *J* = 6.4 Hz, 2H), 7.19−7.28 (m, 3H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 27.8(6), 27.9(2), 40.1, 42.1, 44.7, 46.2, 48.1, 55.2, 58.8, 81.1, 81.3, 113.3, 126.2, 127.7, 128.0, 128.2, 128.9, 129.4, 130.9, 132.5, 136.6, 137.7, 138.9, 140.9, 157.9, 171.5, 172.0, 198.1.

HRMS (ESI) calcd for $C_{39}H_{47}O_6$ $[M+H]^+$ 611.3373, found 611.3380.

Compound **4.12ja**



4.12ja

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 1 h with **4.6j** (42.2 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 71 mg, 84% yield as colorless oil.

$[\alpha]^{25}_{D}$ −24.4 (*c* 1.05, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 9.4 min, t_{minor} = 10.5 min.

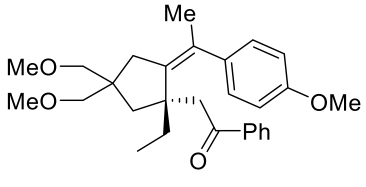
R_f = 0.20. (eluent: hexane/DCM/diethyl ether = 8:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 3H), 1.66 (d, *J* = 13.7 Hz, 1H), 1.86 (s, 3H), 1.97 (d, *J* = 13.8 Hz, 1H), 2.53 (d, *J* = 16.9 Hz, 1H), 2.64 (d, *J* = 16.9 Hz, 1H), 2.70 (d, *J* = 17.7 Hz, 1H), 2.85 (d, *J* = 17.7 Hz, 1H), 3.34 (d, *J* = 8.9 Hz, 1H), 3.34 (s, 3H), 3.37 (s, 2H), 3.38 (s, 3H), 3.41 (d, *J* = 8.9 Hz, 1H), 3.73 (s, 3H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 31.1, 39.8, 43.6, 44.5, 46.6, 49.4, 55.1, 59.2, 76.5, 77.7, 113.3, 127.7, 128.0, 128.2, 129.7, 132.4, 137.0, 138.0, 144.3, 157.8, 198.9.

HRMS (ESI) calcd for $C_{27}H_{35}O_4$ $[M+H]^+$ 423.2535, found 423.2525.

Compound **4.12ka**



4.12ka

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 1 h with **4.6k** (45.1 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 70 mg, 81% yield as white solid.

$[\alpha]^{25}_{D}$ −14 (*c* 0.82, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 0.5 mL/min, 230 nm, t_{major} = 8.9 min, t_{minor} = 10.5 min.

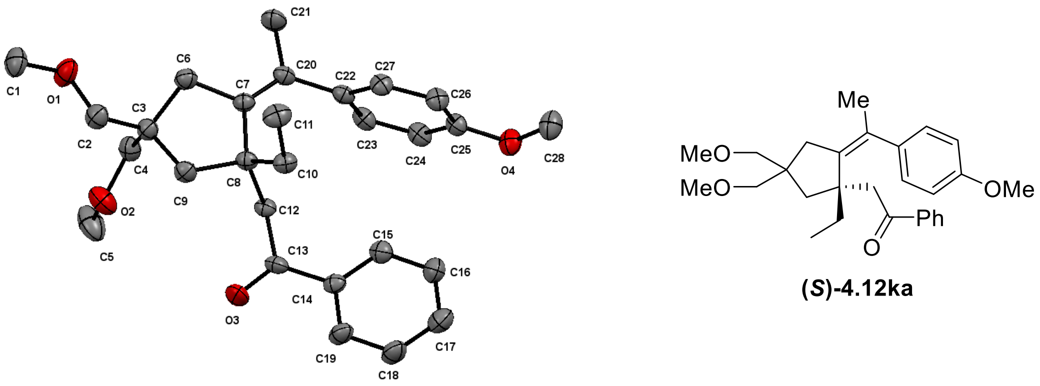
R_f = 0.20. (eluent: hexane/DCM/diethyl ether = 8:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.41 (dq, *J* = 14.5 Hz, 7.3 Hz, 1H), 1.48 (dq, *J* = 14.8 Hz, 7.4 Hz, 1H), 1.77 (d, *J* = 14.2 Hz, 1H), 1.87 (s, 3H), 1.93 (d, *J* = 14.2 Hz, 1H), 2.37 (d, *J* = 17.0 Hz, 1H), 2.61 (d, *J* = 17.4 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 3.00 (d, *J* = 17.4 Hz, 1H), 3.32 (d, *J* = 8.8 Hz, 1H), 3.36 (s, 3H), 3.35−3.39 (m, 2H), 3.38 (s, 3H), 3.42 (d, *J* = 8.7 Hz, 1H), 3.73 (s, 3H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.5, 25.6, 34.1, 40.6, 40.9, 44.4, 47.4, 47.8, 55.1, 59.2, 76.9, 77.2, 113.3, 127.8, 128.1, 128.2, 129.5, 132.4, 137.0, 138.3, 143.4, 157.8, 199.2.

HRMS (ESI) calcd for $C_{28}H_{37}O_4$ $[M+H]^+$ 437.2692, found 437.2688.

The *S* absolute configuration and the *Z* geometry of the double bond was determined by X-ray crystal structure analysis of **4.12ka**. Crystals of (*S*)-**4.12ka** (99% ee) suitable for X-ray crystallographic analysis were obtained by slow evaporation from hexane/DCM (*v*/*v*, 10:1). The absolute configuration of **4.12ka** is therefore assigned as (*S*). The ORTEP drawing of (*S*)-**4.12ka** is shown in **Figure 5-2**. (CCDC 1995060).



(*S*)-4.12ka

Figure 5-2. ORTEP illustration of compound (*S*)-**4.12ka**.

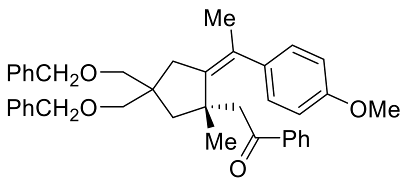
Table 5-3. Sample and crystal data for (*S*)-4.12ka.

Chemical formula	$C_{28}H_{36}O_4$	
Formula weight	436.57 g/mol	
Temperature	296 (2) K	
Wavelength	1.54178 Å	
Crystal size	0.280 x 0.300 x 0.320 mm	
Crystal habit	colorless block	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.8547 (4) Å	α = 90°
	b = 12.4012 (5) Å	β = 90°
	c = 18.8354 (8) Å	γ = 90°
Volume	2535.46 (18) Å^3	
Z	4	
Density (calculated)	1.144 g/cm^3	
Absorption coefficient	0.593 mm^{-1}	
F (000)	944	

Table 5-4. Data collection and structure refinement for (*S*)-4.12ka.

Theta range for data collection	4.27 to 68.13°	
Index ranges	-13<=h<=12, -14<=k<=14, -22<=l<=22	
Reflections collected	46505	
Independent reflections	4595 [R (int) = 0.0603]	
Coverage of independent reflections	99.4%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.8520 and 0.8330	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/5	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	Σ w $(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	4595 / 429 / 353	
Goodness-of-fit on F^2	1.067	
Δ/σ_{max}	0.001	
Final R indices	4114 data; $I>2\sigma(I)$	R1 = 0.0381, wR2 = 0.1013
	all data	R1 = 0.0451, wR2 = 0.1121
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0521P)^2+0.2850P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	-0.09 (8)	
Extinction coefficient	0.0055 (8)	
Largest diff. peak and hole	0.114 and -0.110 eÅ^{-3}	
R.M.S. deviation from mean	0.024 eÅ^{-3}	

Compound **4.12la**



4.12la

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 1 h with **4.6l** (72.4 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution).

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 94 mg, 82% yield as colorless oil.

$[\alpha]^{25}_{D}$ −15.5 (*c* 1.31, $CHCl_3$) 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 10.8 min, t_{minor} = 11.8 min.

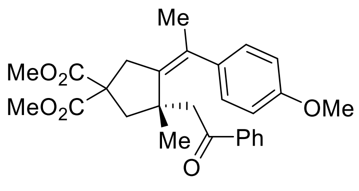
R_f = 0.23. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 3H), 1.74 (d, *J* = 13.8 Hz, 1H), 1.85 (s, 3H), 2.03 (d, *J* = 13.8 Hz, 1H), 2.58 (d, *J* = 16.8 Hz, 1H), 2.67 (d, *J* = 17.5 Hz, 1H), 2.68 (d, *J* = 16.8 Hz, 1H), 2.84 (d, *J* = 17.5 Hz, 1H), 3.47 (d, *J* = 8.8 Hz, 1H), 3.51 (s, 2H), 3.55 (d, *J* = 8.8 Hz, 1H), 3.72 (s, 3H), 4.53 (s, 2H), 4.55 (s, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 7.22−7.35 (m, 12H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 30.9, 39.7, 43.6, 44.7, 46.8, 49.4, 55.1, 73.1, 73.2, 73.9, 75.2, 113.3, 127.2, 127.3, 127.4, 127.8, 128.0, 128.1(7), 128.2(1), 129.7, 132.4, 137.0, 138.0, 138.9(5), 139.0(1), 144.5, 157.8, 199.0.

HRMS (ESI) calcd for $C_{39}H_{43}O_4$ $[M+H]^+$ 575.3161, found 575.3162.

Compound **4.12ma**



4.12ma

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 30 °C for 6 h with **4.6m** (47.5 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75

mL, 0.4 M THF solution). A chromatography on silica gel with hexane/DCM/diethyl ether (*v*/*v*, 10:1:0→3:1:1) as eluent gave the target product **4.12ma** (28 mg, 31% yield) as colorless oil together with bicyclic compound **4.12ma'** (14 mg, 22% yield) as white solid.

[α]$^{25}_{\mathrm{D}}$ −47.3 (*c* 1.13, $CHCl_3$) for 96% ee (*S*). The ee of **4.12ma** was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol/DCM = 90/10, flow 1.0 mL/min, 230 nm, t_{minor} = 20.6 min, t_{major} = 22.5 min.

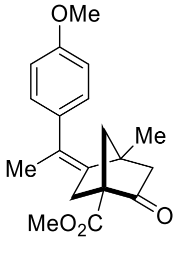
R$_f$ = 0.17. (eluent: hexane/diethyl ether = 4:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 3H), 1.91 (s, 3H), 2.42 (d, *J* = 13.6 Hz, 1H), 2.67 (d, *J* = 17.9 Hz, 1H), 2.84 (d, *J* = 13.6 Hz, 1H), 2.85 (d, *J* = 17.9 Hz, 1H), 3.19 (dd, *J* = 17.0 Hz, 1.3 Hz, 1H), 3.40 (d, *J* = 17.0 Hz, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 6.73 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 28.6, 40.2, 43.9, 47.3, 48.0, 52.7, 52.8, 55.2, 57.4, 113.4, 127.7, 128.2, 129.0, 129.5, 132.6, 136.3, 137.7, 141.5, 158.0, 172.7, 173.1, 198.4.

HRMS (ESI) calcd for $C_{27}H_{31}O_6$ $[M+H]^+$ 451.2121, found 451.2125.

Compound **4.12ma'**



4.12ma'

White solid.

[α]$^{25}_{\mathrm{D}}$ −167 (*c* 1.11, $CHCl_3$) for 99% ee (*S*,*S*). The ee was measured by HPLC (Daicel Chiralpak IB column), hexane/2-propanol = 95/1, flow 1.0 mL/min, 230 nm, t_{minor} = 8.7 min, t_{major} = 12.7 min. 14 mg, 22% yield.

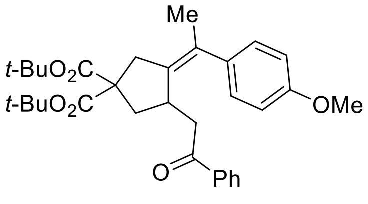
R*f* = 0.20. (eluent: hexane/diethyl ether = 4:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75 (s, 3H), 1.86 (s, 3H), 1.98 (dd, *J* = 10.1 Hz, 2.7 Hz, 1H), 2.02 (dd, *J* = 10.1 Hz, 3.9 Hz, 1H), 2.18 (d, *J* = 17.4 Hz, 1H), 2.29 (dd, *J* = 17.4 Hz, 3.9 Hz, 1H), 2.58 (dd, *J* = 16.4 Hz, 1.2 Hz, 1H), 2.91 (d, *J* = 16.4 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 23.4, 37.4, 47.6, 50.1, 51.7, 52.2, 55.2, 62.9, 113.2, 129.2, 129.3, 135.6, 135.9, 158.3, 170.3, 210.4.

HRMS (ESI) calcd for $C_{19}H_{23}O_4$ $[M+H]^+$ 315.1596, found 315.1587.

Compound **4.12na**



4.12na

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 48 h with **4.6n** (61.7 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution) in the presence of [RhCl(**L3***)]$_2$ (4.0 mg, 0.0050 mmol, 5 mol% of Rh).A chromatography on silica gel with hexane/DCM/diethyl ether (*v*/*v*, 10:1:0→10:1:1) as eluent gave the target product **4.12na** (65 mg, 62% yield) and its olefin isomer **4.14** as a minor product (**4.12na**/**4.14** = >30:1). 65 mg, 62% yield. Colorless oil.

[α]$^{25}_{\text{D}}$ +87.8 (*c* 1.14, $CHCl_3$) for 99% ee. The ee of **4.12na** was measured by HPLC (Daicel Chiralpak IA column), hexane/2-propanol = 99/1, flow 1.0 mL/min, 230 nm, t_{major} = 7.6 min, t_{minor} = 8.7 min.

R*f* = 0.23. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

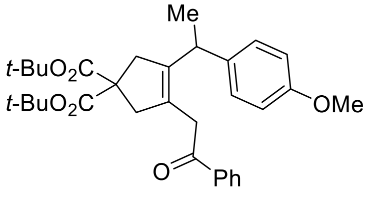
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.46 (s, 9H), 1.90 (dd, *J* = 13.6 Hz, 6.1 Hz, 1H), 1.97 (s, 3H), 2.44 (dd, *J* = 15.4 Hz, 11.4 Hz, 1H), 2.54 (dd, *J* = 13.5 Hz, 8.2 Hz, 1H), 2.86 (dd,

J = 15.3 Hz, 3.3 Hz, 1H), 2.93 (d, J = 16.4 Hz, 1H), 3.01 (d, J = 16.3 Hz, 1H), 3.35−3.37 (m, 1H), 3.79 (s, 3H), 6.87 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 7.4 Hz, 2H), 7.42 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 27.8, 37.2, 38.6, 38.7, 43.4, 55.2, 60.6, 81.0, 81.3, 114.1, 128.0, 128.3, 128.9, 129.9, 132.7, 136.2, 136.5, 138.1, 158.2, 170.9, 171.2, 199.4.

HRMS (ESI) calcd for $C_{32}H_{41}O_6$ $[M+H]^+$ 521.2903, found 521.2896.

Compound **4.14**



4.14

The rhodium-catalyzed arylzincation (**Procedure A**, section 5.3.4) was carried out at 60 °C for 48 h with **4.6n** (61.6 mg, 0.20 mmol) and 4-methoxyphenylzinc chloride (**4.7a**) (0.75 mL, 0.4 M THF solution) in the presence of [RhCl((*S*,*S*)-Fc-tfb)]$_2$ (7.5 mg, 0.0050 mmol, 5 mol% of Rh). Ratio of **4.12na** to **4.14** in the crude mixture was determined to be 1:2.8 by ^{1}H NMR. A chromatography on silica gel with hexane/DCM/diethyl ether (*v*/*v*, 10:1:0→10:1:1) as eluent followed by preparative TLC on silica gel (hexane/diethyl ether = 20/1) gave the target product **4.14** (40 mg, 39% yield) and its olefin isomer **4.12na** as a minor product (14 mg, 13% yield, 99% ee).

$[\alpha]^{25}_{D}$ +22.3 (*c* 1.07, $CHCl_3$) for 88% ee. The ee of **4.14** was measured by HPLC (Daicel Chiralpak IG column), hexane/2-propanol = 95/5, flow 1.0 mL/min, 230 nm, t_{major} = 10.7 min, t_{minor} = 14.3 min.

R_f = 0.22. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

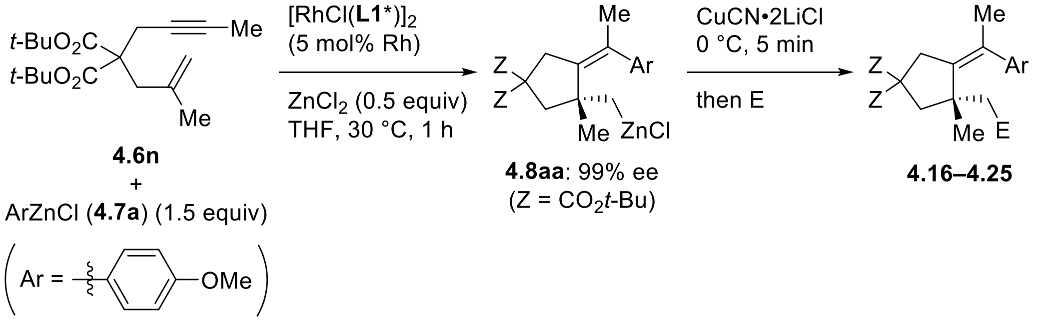
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H), 1.37 (d, J = 7.1 Hz, 3H), 1.41 (s, 9H), 2.60 (d, J = 16.6 Hz, 1H), 2.85 (d, J = 16.4 Hz, 1H), 2.96 (d, J = 16.2 Hz, 1H), 2.99 (d, J = 16.6 Hz, 1H), 3.77 (s, 3H), 3.79 (d, *J* = 14.4 Hz, 1H), 3.82 (d, *J* = 14.4 Hz, 1H), 3.86 (q, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 27.7, 27.8, 36.3, 38.5, 39.6, 43.5, 55.2, 58.9, 80.9, 81.0, 113.7, 125.8, 128.0, 128.3, 128.6, 133.1, 135.7, 136.8, 140.3, 157.8, 171.0, 171.1, 197.3.

HRMS (ESI) calcd for $C_{32}H_{41}O_6$ $[M+H]^+$ 521.2903, found 521.5899.

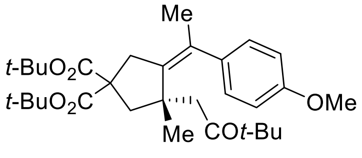
5.3.7. Rhodium-catalyzed arylzincation of 4.6a with 4.7a followed by other functionalization reactions (Scheme 4-15)

5.3.7.1. Copper-mediated reactions producing 4.16−4.25



The rhodium-catalyzed arylzincation of 1,6-enyne **4.6a** with arylzinc reagent **4.7a** was repeated according to the **Procedure A** (section 5.3.4). The reaction mixture should contain alkylzinc **4.8aa** of 99% ee in not less than 91% yield (entry 1 in Table 4-1), and it was subjected to the copper-mediated reaction with electrophiles according to the **Procedure B** (section 5.3.5). The electrophile used and the reaction time (at room temperature) after the addition of electrophile are described in each reaction shown below.

Compound **4.16**



4.16

This compound was prepared according to **Procedure B** (section 5.3.5) with pivaloyl chloride (43.9 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 12 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 76 mg, 74% yield as colorless oil. The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 7.9 min, t_{minor} = 9.0 min.

$[\alpha]^{25}_{D}$ −6.0 (*c* 0.96, $CHCl_3$) for 99% ee (S).

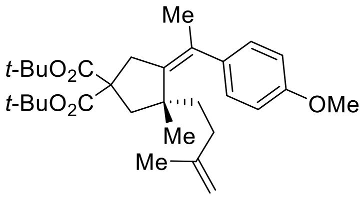
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (s, 9H), 1.00 (s, 3H), 1.45 (s, 9H), 1.47 (s, 9H), 1.89 (s, 3H), 2.19 (d, *J* = 18.5 Hz, 1H), 2.34 (d, *J* = 13.8 Hz, 1H), 2.42 (d, *J* = 18.5 Hz, 1H), 2.46 (d, *J* = 13.8 Hz, 1H), 2.83 (d, *J* = 16.9 Hz, 1H), 3.27 (d, *J* = 16.9 Hz, 1H), 3.79 (s, 3H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 26.3, 27.7, 27.8, 39.6, 43.6, 44.0, 47.2, 55.3, 58.7, 81.0, 81.1, 113.4, 128.4, 129.7, 136.8, 142.9, 158.0, 171.5, 171.8, 214.5.

HRMS (ESI) calcd for $C_{31}H_{47}O_6$ $[M+H]^+$ 515.3373, found 515.3362.

Compound **4.17**



4.17

This compound was prepared according to **Procedure B** (section 5.3.5) with 1.0 M solution of CuCN•2LiCl in THF (60 μL, 0.06 mmol, 20 mol% based on ArZnCl), 3-bromo-2-methylpropene (48.1 mg, 0.36 mmol, 1.8 equiv), and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→20:2:1

Yield 82 mg, 85% yield as colorless oil.

$[\alpha]^{25}_{D}$ −39.1 (*c* 1.12, $CHCl_3$) for 99% ee (*R*). The enantiomeric excess was not determined by HPLC analysis due to a poor separation of the peaks. Considering the reaction pathway, it is assumed to be the same as that of **4.12aa** (99% ee).

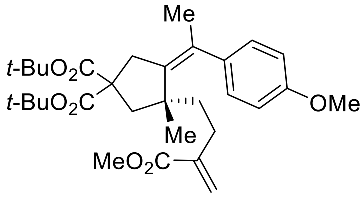
R_f = 0.22. (eluent: hexane/DCM/diethyl ether = 30:3:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 1.19−1.24 (m, 2H), 1.47 (s, 9H), 1.48 (s, 9H), 1.60 (s, 3H), 1.81−1.94 (m, 2H), 1.90 (s, 3H), 2.03 (dd, *J* = 13.6 Hz, 1.1 Hz, 1H), 2.43 (d, *J* = 13.6 Hz, 1H), 2.79 (dd, *J* = 16.8 Hz, 1.4 Hz, 1H), 3.22 (d, *J* = 16.8 Hz, 1H), 3.78 (s, 3H), 4.51 (m, 1H), 4.59 (m, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8, 25.2, 27.8(5), 27.8(6), 28.2, 32.7, 39.1, 40.6, 45.4, 46.5, 55.2, 58.5, 81.0, 81.3, 109.0, 113.0, 129.0, 129.6, 136.6, 142.0, 146.3, 157.9, 171.6, 171.7.

HRMS (ESI) calcd for $C_{30}H_{45}O_5$ $[M+H]^+$ 485.3267, found 485.3262.

Compound **4.18**



4.18

This compound was prepared according to **Procedure B** (section 5.3.5) with methyl 2-(bromomethyl)acrylate (64.6 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→10:1:1

Yield 93 mg, 88% yield as colorless oil.

$[\alpha]^{25}_{D}$ −38.0 (*c* 1.02, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol/DCM = 94/1/5, flow 1.0 mL/min, 230 nm, t_{major} = 9.8 min, t_{minor} = 10.8 min.

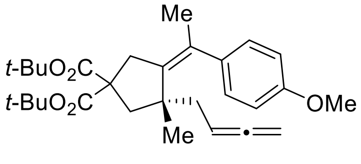
R_f = 0.16. (eluent: hexane/DCM/diethyl ether = 20:2:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (s, 3H), 1.16−1.26 (m, 2H), 1.46 (s, 9H), 1.48 (s, 9H), 1.90 (s, 3H), 2.07 (d, *J* = 13.6 Hz, 1H), 2.17 (br t, *J* = 8.3 Hz, 2H), 2.45 (d, *J* = 13.6 Hz, 1H), 2.80 (dd, *J* = 16.9 Hz, 1.3 Hz, 1H), 3.24 (d, *J* = 16.9 Hz, 1H), 3.70 (s, 3H), 3.78 (s, 3H), 5.29 (m, 1H), 6.02 (m, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 26.7, 27.8, 28.1, 39.3, 40.5, 45.4, 46.6, 51.6, 55.1, 58.5, 81.1, 81.3, 113.0, 123.7, 129.2, 129.5, 136.6, 140.9, 141.8, 157.9, 167.8, 171.5, 171.7.

HRMS (ESI) calcd for $C_{31}H_{45}O_7$ $[M+H]^+$ 529.3165, found 529.3161.

<u>Compound **4.19**</u>



4.19

This compound was prepared according to **Procedure B** (section 5.3.5) with 80% (wt. %) solution of propargyl bromide in toluene (53.7 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→20:2:1

Yield 78 mg, 83% yield as colorless oil.

$[\alpha]^{25}_{D}$ −119 (*c* 1.01, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IC column), hexane/2-propanol = 99/1, flow 1.0 mL/min, 230 nm, t_{major} = 4.2 min, t_{minor} = 4.7 min.

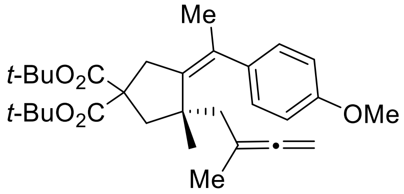
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 30:3:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (s, 3H), 1.47 (s, 9H), 1.48 (s, 9H), 1.72−1.85 (m, 2H), 1.89 (s, 3H), 2.01 (dd, *J* = 13.7 Hz, 1.2 Hz, 1H), 2.51 (d, *J* = 13.7 Hz, 2H), 2.79 (dd, *J* = 16.9 Hz, 1.5 Hz, 1H), 3.21 (d, *J* = 16.8 Hz, 1H), 3.79 (s, 3H), 4.56–4.59 (m, 2H), 4.94 (dq, *J* = 8.3 Hz, 6.8 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 27.8, 28.3, 39.8, 40.7, 45.9, 46.3, 55.1, 58.4, 73.6, 81.0, 81.2, 86.7, 113.1, 129.4(8), 129.5(2), 136.4, 141.0, 157.9, 171.5, 171.7, 209.7.

HRMS (ESI) calcd for $C_{29}H_{41}O_5$ $[M+H]^+$ 469.2954, found 469.2954.

Compound **4.20**



4.20

This compound was prepared according to **Procedure B** (section 5.3.5) with 1-bromo-2-butyne (48.4 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→20:2:1

Yield 74 mg, 77% yield as colorless oil.

$[\alpha]^{25}_{D}$ −22.7 (*c* 1.07, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IG column), hexane/2-propanol = 99/1, flow 1.0 mL/min, 230 nm, t_{major} = 4.8 min, t_{minor} = 5.4 min.

R_f = 0.20. (eluent: hexane/DCM/diethyl ether = 30:3:1, visualized by UV)

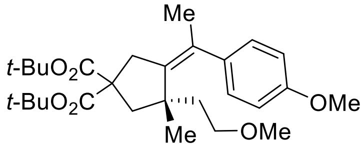
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (s, 3H), 1.46 (s, 9H), 1.48 (s, 9H), 1.49 (t, *J* = 2.8 Hz, 3H), 1.59 (dt, *J* = 16.1 Hz, 3.5 Hz, 1H), 1.67 (dt, *J* = 16.0 Hz, 3.5 Hz, 1H), 1.84 (s, 3H), 2.00 (d, *J* =

13.7 Hz, 1H), 2.71 (d, *J* = 13.6 Hz, 1H), 2.76 (dd, *J* = 16.9 Hz, 1.3 Hz, 1H), 3.22 (d, *J* = 16.9 Hz, 1H), 3.79 (s, 3H), 4.49–4.59 (m, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 24.9, 27.8, 29.5, 40.9, 43.8, 45.6, 46.5, 55.1, 58.5, 73.8, 80.9, 81.0, 95.5, 112.9, 128.7, 129.5, 136.6, 141.4, 157.8, 171.5, 172.0, 207.2.

HRMS (ESI) calcd for $C_{30}H_{43}O_5$ $[M+H]^+$ 483.3110, found 483.3109.

Compound **4.21**



4.21

This compound was prepared according to **Procedure B** (section 5.3.5) with bromomethyl methyl ether (45.4 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 12 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→8:1:1

Yield 67 mg, 70% yield as colorless oil.

$[\alpha]^{25}_{D}$ −27.2 (*c* 1.15, $CHCl_3$) for 99% ee (*S*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 99/1, flow 0.5 mL/min, 230 nm, t_{major} = 21.0 min, t_{minor} = 22.6 min.

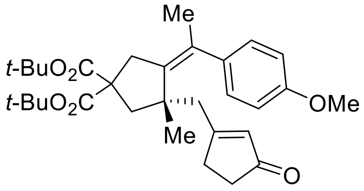
R_f = 0.17. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 1.41−1.45 (m, 2H), 1.47 (s, 9H), 1.48 (s, 9H), 1.89 (s, 3H), 2.06 (d, *J* = 13.6 Hz, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 2.83 (dd, *J* = 16.8 Hz, 1.1 Hz, 1H), 3.18 (d, *J* = 17.0 Hz, 1H), 3.23 (s, 3H), 3.28 (br t, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 27.8, 28.3, 40.0, 40.2, 44.3, 46.8, 55.1, 58.4, 58.5, 70.1, 81.1, 81.3, 113.2, 129.3, 129.5, 136.4, 141.8, 157.9, 171.5, 171.6.

HRMS (ESI) calcd for $C_{28}H_{43}O_6$ $[M+H]^+$ 475.3060, found 475.3057.

Compound **4.22**



4.22

This compound was prepared according to **Procedure B** (section 5.3.5) with 3-iodocyclopent-2-en-1-one (101.1 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 89 mg, 87% yield as colorless oil.

$[\alpha]^{25}_D$ −56.5 (*c* 1.01, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 90/10, flow 1.0 mL/min, 230 nm, t_{major} = 10.7 min, t_{minor} = 11.7 min.

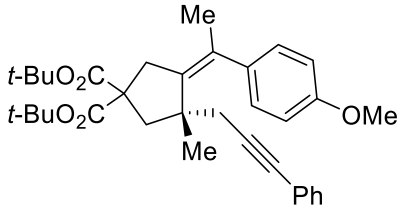
R_f = 0.15. (eluent: hexane/DCM/diethyl ether = 5:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (s, 3H), 1.46 (s, 9H), 1.48 (s, 9H), 1.89 (s, 3H), 2.05 (dd, *J* = 13.6 Hz, 1.2 Hz, 1H), 2.14 (d, *J* = 16.4 Hz, 1H), 2.19 (d, *J* = 16.3 Hz, 1H), 2.29−2.43 (m, 4H), 2.54 (d, *J* = 13.7 Hz, 1H), 2.80 (dd, *J* = 17.3 Hz, 1.6 Hz, 1H), 3.34 (d, *J* = 17.3 Hz, 1H), 3.80 (s, 3H), 5.90 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 27.8(0), 27.8(3), 29.6, 33.6, 34.9, 40.2, 44.2, 45.2, 47.0, 55.2, 58.4, 81.3, 81.6, 113.2, 129.3, 130.0, 131.2, 135.9, 140.8, 158.1, 171.2, 171.4, 180.3, 210.1.

HRMS (ESI) calcd for $C_{31}H_{43}O_6$ $[M+H]^+$ 511.3060, found 511.3059.

Compound **4.23**



4.23

This compound was prepared according to **Procedure B** (section 5.3.5) with (bromoethynyl)benzene (65.3 mg, 0.36 mmol, 1.8 equiv) and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→20:2:1

Yield 74 mg, 70% yield as colorless oil.

$[\alpha]^{25}_{D}$ −101 (*c* 0.84, $CHCl_3$) for 99% ee (*R*). The enantiomeric excess was not determined by HPLC analysis due to a poor separation of the peaks. Considering the reaction pathway, it is assumed to be the same as that of **4.12aa** (99% ee).

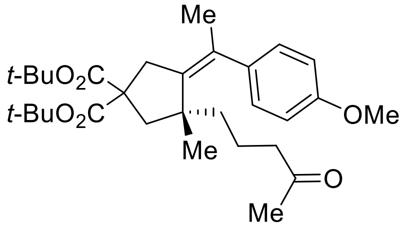
R_f = 0.19. (eluent: hexane/DCM/diethyl ether = 30:3:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (s, 3H), 1.47 (s, 9H), 1.49 (s, 9H), 1.90 (s, 3H), 2.20 (d, *J* = 16.6 Hz, 1H), 2.23 (d, *J* = 13.3 Hz, 1H), 2.24 (d, *J* = 16.8 Hz, 1H), 2.77 (d, *J* = 13.8 Hz, 1H), 3.06 (d, *J* = 16.0 Hz, 1H), 3.07 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 7.24–7.26 (m, 3H), 7.25−7.37 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 27.5, 27.8, 27.9, 31.9, 40.5, 45.7, 46.9, 55.1, 58.3, 81.2, 81.3, 81.7, 88.8, 113.3, 124.1, 127.4, 128.1, 129.6, 130.4, 131.5, 136.1, 140.6, 158.0, 171.5, 171.6.

HRMS (ESI) calcd for $C_{34}H_{43}O_5$ $[M+H]^+$ 531.3110, found 531.3101.

Compound **4.24**



4.24

This compound was prepared according to **Procedure B** (section 5.3.5) with chlorotrimethylsilane (65.2 mg, 0.60 mmol, 3.0 equiv), followed by methyl vinyl ketone (42.2 mg, 0.60 mmol, 3.0 equiv), and the reaction time of 12 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 71 mg, 71% yield as colorless oil.

$[\alpha]^{25}_{D}$ −28.7 (*c* 1.14, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 15.5 min, t_{minor} = 18.5 min.

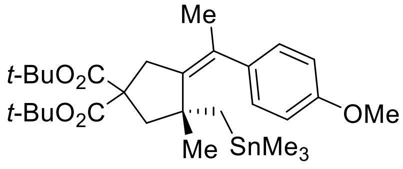
R_f = 0.23. (eluent: hexane/DCM/diethyl ether = 5:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 3H), 0.92−1.07 (m, 2H), 1.39−1.44 (m, 2H), 1.47 (s, 9H), 1.48 (s, 9H), 1.88 (s, 3H), 2.01 (d, *J* = 13.8 Hz, 1H), 2.06 (s, 2H), 2.15 (br t, *J* = 7.6 Hz, 2H), 2.41 (d, *J* = 13.6 Hz, 1H), 2.77 (dd, *J* = 17.0 Hz, 1.3 Hz, 1H), 3.23 (d, *J* = 17.0 Hz, 1H), 3.80 (s, 3H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 25.1, 27.8, 28.5, 29.8, 40.2, 40.4, 44.2, 45.6, 46.5, 55.2, 58.4, 81.1, 81.3, 113.0, 128.9, 129.5, 136.6, 141.6, 157.9, 171.6, 171.7, 209.1.

HRMS (ESI) calcd for $C_{30}H_{45}O_6$ $[M+H]^+$ 501.3216, found 501.3212.

Compound **4.25**



4.25

This compound was prepared according to **Procedure B** (section 5.3.5) with 1.0 M solution of trimethyltin chloride (0.36 mL, 0.36 mmol, 1.8 equiv) and the reaction time of 2 h.

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→20:2:1

Yield 102 mg, 86% yield as colorless oil.

[α]^{25}$_{D}$ −39.8 (*c* 1.14, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol/DCM = 96.5/0.5/3, flow 0.5 mL/min, 254 nm, t_{major} = 5.5 min, t_{minor} = 6.3 min.

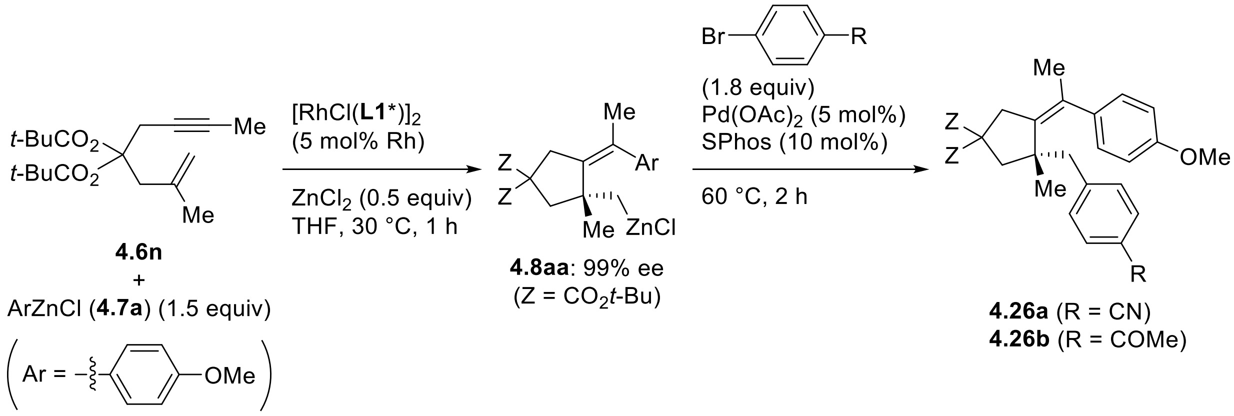
R$_f$ = 0.22. (eluent: hexane/DCM/diethyl ether = 30:3:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, $J_{H-^{119}Sn}$ = 52.0 Hz, $J_{H-^{117}Sn}$ = 49.2 Hz, 9H), 0.90 (s, $J_{H-^{119}Sn}$ = 52.7 Hz, 2H), 0.91 (s, 3H), 1.47 (s, 9H), 1.48 (s, 9H), 1.86 (s, 3H), 2.17 (d, *J* = 13.4 Hz, 1H), 2.21 (d, *J* = 13.4 Hz, 1H), 2.91 (dd, *J* = 17.2 Hz, 1.5 Hz, 1H), 3.18 (d, *J* = 17.2 Hz, 1H), 3.80 (s, 3H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ −8.3 ($J_{C-^{119}Sn}$ = 314.2 Hz, $J_{C-^{117}Sn}$ = 300.7 Hz), 25.0, 27.8(7), 27.9(1), 29.1, 31.9, 40.1, 46.2, 51.0, 55.2, 58.5, 81.1, 81.2, 113.1, 127.9, 129.7, 136.8, 144.0, 157.9, 171.6, 171.7.

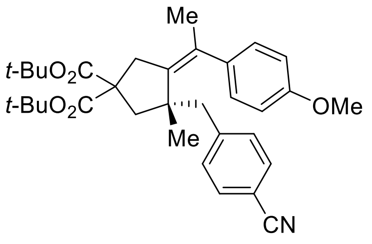
HRMS (ESI) calcd for $C_{29}H_{47}O_5Sn$ $[M+H]^+$ 595.2445, found 595.2458.

5.3.7.2. Palladium-catalyzed cross-coupling



The rhodium-catalyzed arylzincation of 1,6-enyne **4.6a** with arylzinc reagent **4.7a** was repeated according to the **Procedure A** (section 5.3.4). The reaction mixture should contain alkylzinc **4.8aa** of 99% ee in not less than 91% yield (entry 1 in Table 4-1). To the reaction mixture obtained by **Procedure A** (section 5.3.4) were added $Pd(OAc)_2$ (3.4 mg, 5 mol% based on ArZnCl), SPhos[47] (12.3 mg, 10 mol% based on ArZnCl), and 4-bromobenzonitrile (65.7 mg, 0.36 mmol) or 4'-bromoacetophenone (72.0 mg, 0.36 mmol) at room temperature, and the mixture was heated at 60 °C for 2 h. It was hydrolyzed by the addition of saturated aqueous NH_4Cl (1 mL) and saturated aqueous $NaHCO_3$ (2 mL). Extraction with diethyl ether (5 mL × 3) followed by flash column chromatography gave the cross-coupling product **4.26a** and **4.26b**.

Compound **4.26a**



4.26a

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 86 mg, 81% yield as colorless oil.

[α]^{25}D −29.1 (*c* 1.15, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IC column), hexane/2-propanol = 98/2, flow 1.0 mL/min, 230 nm, t_{major} = 17.8 min, t_{minor} = 19.5 min.

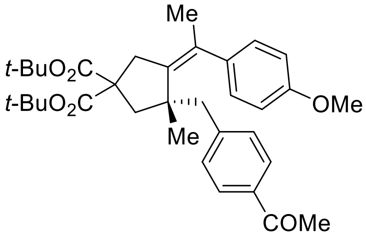
R$_f$ = 0.19. (eluent: hexane/DCM/diethyl ether = 10:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 3H), 1.44 (s, 9H), 1.48 (s, 9H), 1.76 (d, *J* = 13.8 Hz, 1H), 1.94 (s, 3H), 2.46 (d, *J* = 13.8 Hz, 1H), 2.48 (d, *J* = 13.0 Hz, 1H), 2.53 (d, *J* = 13.1 Hz, 1H), 2.87 (d, *J* = 16.9 Hz, 1H), 3.24 (d, *J* = 16.9 Hz, 1H), 3.81 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 27.7, 27.8, 27.9, 40.2, 46.2, 46.5, 46.9, 55.2, 58.4, 81.4, 81.6, 109.7, 113.3, 119.2, 129.6, 130.2, 131.2, 131.5, 136.3, 141.8, 145.2, 158.0, 171.4, 171.6.

HRMS (ESI) calcd for $C_{33}H_{42}NO_5$ $[M+H]^+$ 532.3063, found 532.3062.

Compound **4.26b**



4.26b

Purification silica gel, hexane/DCM/diethyl ether = 10:1:0→5:1:1

Yield 81 mg, 74% yield as colorless oil.

[α]^{25}D −24 (*c* 0.96, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 95/5, flow 1.0 mL/min, 230 nm, t_{minor} = 13.9 min, t_{major} = 15.4 min.

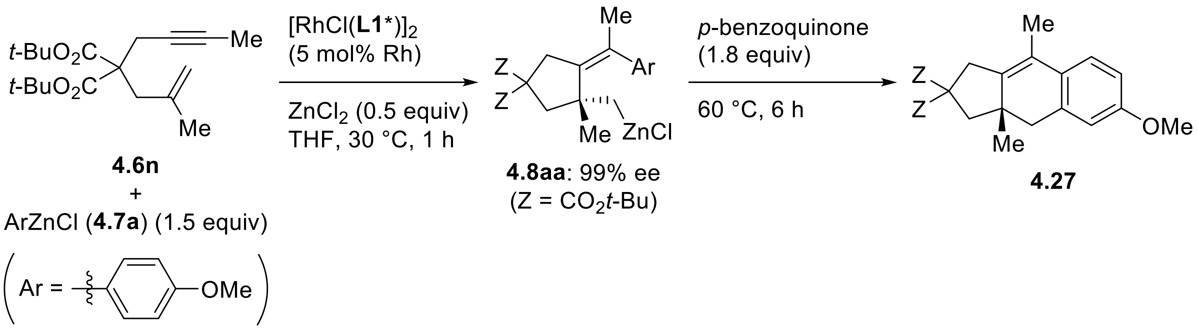
R$_f$ = 0.26. (eluent: hexane/DCM/diethyl ether = 5:1:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (s, 3H), 1.44 (s, 9H), 1.48 (s, 9H), 1.79 (d, *J* = 13.8 Hz, 1H), 1.94 (s, 3H), 2.49 (d, *J* = 13.0 Hz, 1H), 2.50 (d, *J* = 13.8 Hz, 1H), 2.54 (d, *J* = 13.0 Hz, 1H), 2.56 (s, 3H), 2.88 (dd, *J* = 16.9 Hz, 1.3 Hz, 1H), 3.23 (d, *J* = 16.9 Hz, 1H), 3.81 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 26.5, 27.7, 27.8, 27.9, 40.3, 46.3, 46.5, 46.9, 55.2, 58.4, 81.2, 81.5, 113.2, 127.8, 129.7, 129.8, 130.6, 135.0, 136.4, 142.1, 145.4, 158.0, 171.5, 171.6, 198.0.

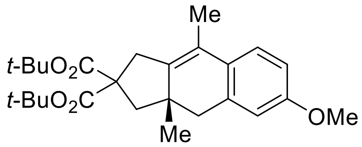
HRMS (ESI) calcd for $C_{34}H_{45}O_6$ $[M+H]^+$ 549.3216, found 549.3214.

5.3.7.3. Oxidative cyclization with *p*-benzoquinone



The rhodium-catalyzed arylzincation of 1,6-enyne **4.6a** with arylzinc reagent **4.7a** was repeated according to the **Procedure A** (section 5.3.4). The reaction mixture should contain alkylzinc **4.8aa** of 99% ee in not less than 91% yield (entry 1 in Table 4-1). To the reaction mixture obtained by **Procedure A** (section 5.3.4) was added *p*-benzoquinone (39.0 mg, 0.36 mmol, 1.8 equiv), and it was stirred at 60 °C for 6 h. It was hydrolyzed by the addition of saturated aqueous NH_4Cl (1 mL) and saturated aqueous $NaHCO_3$ (2 mL). Extraction with diethyl ether (5 mL × 3) followed by flash column chromatography on silica gel with hexane/DCM/diethyl ether (*v*/*v*, 20:2:1) as eluent gave **4.27** (58 mg, 68% yield) as colorless oil.

Compound **4.27**



4.27

[α]$^{25}_{D}$ +15 (*c* 0.81, $CHCl_3$) for 99% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/DCM = 80/20, flow 1.0 mL/min, 230 nm, t_{major} = 11.0 min, t_{minor} = 15.6 min.

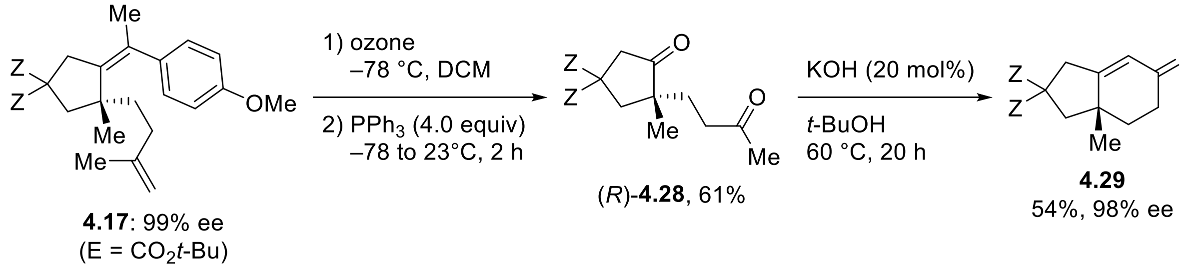
R*f* = 0.22. (eluent: hexane/DCM/diethyl ether = 30:3:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 1.45 (s, 9H), 1.47 (s, 9H), 1.94 (s, 3H), 2.31 (d, *J* = 13.5 Hz, 1H), 2.36 (d, *J* = 13.5 Hz, 1H), 2.59 (d, *J* = 14.8 Hz, 1H), 2.83 (d, *J* = 14.8 Hz, 1H), 2.97 (d, *J* = 17.5 Hz, 1H), 3.20 (dd, *J* = 17.6 Hz, 1.2 Hz, 1H), 3.79 (s, 3H), 6.66 (d, *J* = 2.2 Hz, 1H) 6.70 (dd, *J* = 8.4 Hz, 2.5 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 23.0, 27.8, 36.7, 41.7, 43.4, 47.8, 55.2, 60.8, 81.1(9), 81.2(3), 110.5, 114.6, 121.8, 123.6, 129.2, 136.6, 141.7, 157.9, 171.4, 171.6.

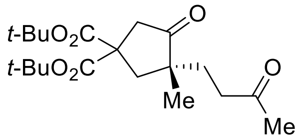
HRMS (ESI) calcd for $C_{26}H_{37}O_5$ $[M+H]^+$ 429.2641, found 429.2638.

5.3.8. Transformation of the product 4.17



A solution of **4.17** (96.8 mg, 0.20 mmol) in DCM (10 mL) was cooled to −78 °C and ozone was bubbled through the solution until the solution turned light blue. Nitrogen gas was bubbled through the solution until the blue color faded. Triphenylphosphine (210 mg, 0.80 mmol, 4.0 equiv) was added at −78 °C and the mixture was warmed up to room temperature and stirred for 2 h. Volatiles were removed and flash column chromatography on silica gel with hexane/ethyl acetate (*v*/*v*, 10:1→5:1) as eluent gave diketone **4.28** (45.0 mg, 61% yield) as white solid.

Compound **4.28**



(*R*)-**4.28**

$[\alpha]^{25}_{D}$ −26 (*c* 0.76, $CHCl_3$) for 98–99% ee (*R*). The enantiomeric excess was not determined by HPLC analysis due to a poor separation of the peaks. Considering that the cyclization product **4.29** is 98% ee (*vide infra*), **4.28** is 98–99% ee.

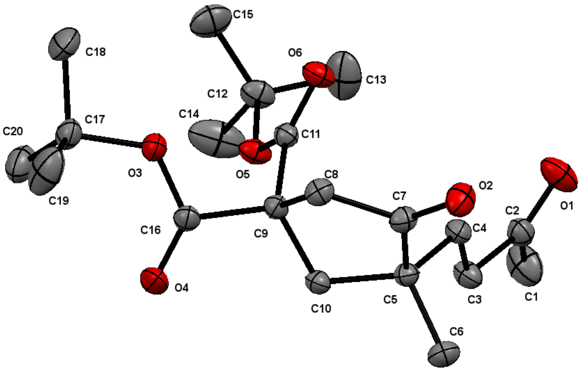
R_f = 0.24. (eluent: hexane/ethyl acetate = 5:1, visualized by $KMnO_4$)

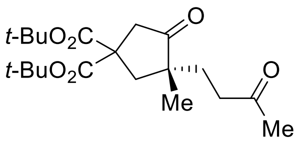
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 3H), 1.46 (s, 9H), 1.47 (s, 9H), 1.64 (ddd, *J* = 14.3 Hz, 10.5 Hz, 5.5 Hz, 1H), 1.74 (ddd, *J* = 14.4 Hz, 10.5 Hz, 5.4 Hz, 1H), 2.13 (s, 3H), 2.33 (d, *J* = 14.2 Hz, 1H), 2.38 (ddd, *J* = 17.3 Hz, 10.4 Hz, 5.5 Hz, 1H), 2.47 (d, *J* = 14.0 Hz, 1H), 2.49 (ddd, *J* = 17.3 Hz, 10.5 Hz, 5.5 Hz, 1H), 2.80 (d, *J* = 19.0 Hz, 1H), 2.95 (d, *J* = 19.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8, 27.8, 29.9, 31.4, 38.4, 42.2, 44.4, 47.7, 55.0, 82.2(6), 82.3(4), 170.4, 170.6, 207.7, 218.2.

HRMS (ESI) calcd for $C_{20}H_{33}O_6$ $[M+H]^+$ 369.2277, found 369.2265.

The *R* absolute configuration of **4.28** was determined by its X-ray crystal structure analysis. Crystals of (*R*)-**4.28** (98–99% ee) suitable for X-ray crystallographic analysis were obtained by recrystallization from hexane (100%). The absolute configuration of **4.28** is therefore assigned as (*R*). The ORTEP drawing of (*R*)-**4.28** is shown in Figure 5-3. (CCDC 1995061).





(*R*)-**4.28**

Figure 5-3 ORTEP illustration of compound (*R*)-**4.28**.

Table 5-5. Sample and crystal data for (*R*)-4.28.

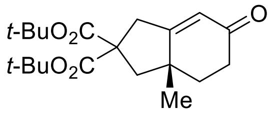
Chemical formula	$C_{20}H_{32}O_6$	
Formula weight	368.45 g/mol	
Temperature	296 (2) K	
Wavelength	1.54178 Å	
Crystal size	0.140 x 0.200 x 0.220 mm	
Crystal habit	colorless block	
Crystal system	orthorhombic	
Space group	P 21 21 2	
Unit cell dimensions	a = 17.1786 (10) Å	α = 90°
	b = 19.7291 (11) Å	β = 90°
	c = 6.4760 (4) Å	γ = 90°
Volume	2194.8 (2) Å^3	
Z	4	
Density (calculated)	1.115 g/cm^3	
Absorption coefficient	0.664 mm^{-1}	
F (000)	800	

Table 5-6. Data collection and structure refinement for (*R*)-4.28.

Theta range for data collection	3.41 to 66.74°	
Index ranges	-19<=h<=20, -23<=k<=19, -7<=l<=6	
Reflections collected	28534	
Independent reflections	3878 [R (int) = 0.0554]	
Coverage of independent reflections	99.5%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9130 and 0.8680	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/5	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	Σ w $(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3878 / 0 / 243	
Goodness-of-fit on F^2	1.030	
Final R indices	3619 data; $I > 2\sigma(I)$	R1 = 0.0425, wR2 = 0.1148
	all data	R1 = 0.0455, wR2 = 0.1184
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0714P)^2 + 0.2982P]$ where $P = (F_o^2 + 2F_c^2)/3$	
Absolute structure parameter	-0.01 (6)	
Largest diff. peak and hole	0.133 and -0.174 eÅ^{-3}	
R.M.S. deviation from mean	0.034 eÅ^{-3}	

To a solution of (*R*)-**4.28** (73.8 mg, 0.20 mmol) in *tert*-butyl alcohol (0.5 mL) was added KOH (2.7 mg, 0.04 mmol, 20 mol%), and the mixture was stirred at 60 °C for 20 h. After cooled to room temperature, water (2 mL) was added, and it was extracted with ethyl acetate (5 mL × 3). Volatiles were removed and flash column chromatography on silica gel with hexane/ethyl acetate (*v*/*v*, 10:1→5:1) as eluent gave **4.29** (38 mg, 54% yield) as colorless oil.

Compound **4.29**



4.29

[α]^{25}$_D$ −7.0 (*c* 1.05, $CHCl_3$) for 98% ee (*R*). The ee was measured by HPLC (Daicel Chiralpak IE column), hexane/2-propanol = 85/15, flow 1.0 mL/min, 230 nm, t_{major} = 9.6 min, t_{minor} = 13.0 min.

R*f* = 0.30. (eluent: hexane/ethyl acetate = 5:1, visualized by UV)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (s, 3H), 1.44 (s, 9H), 1.48 (s, 9H), 1.91−2.04 (m, 2H), 2.29 (d, *J* = 14.1 Hz, 1H), 2.32 (d, *J* = 14.1 Hz, 1H), 2.32−2.39 (m, 1H), 2.48 (ddd, *J* = 17.9 Hz, 13.8 Hz, 5.7 Hz, 1H), 2.88 (d, *J* = 18.3 Hz, 1H), 3.46 (d, *J* = 18.2 Hz, 1H), 5.78 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 27.8, 33.7, 36.1, 39.3, 42.0, 47.4, 58.8, 81.8, 82.0, 121.4, 170.6, 170.8, 173.7, 198.8.

HRMS (ESI) calcd. for $C_{20}H_{31}O_5$ $[M+H]^+$ 351.2171, found 351.2171.

5.4. References

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