Metal-mediated organic reactions in aqueous media

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NANYANG TECHNOLOGICAL UNIVERSITY

METAL-MEDIATED ORGANIC REACTIONS IN AQUEOUS MEDIA

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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METAL-MEDIATED ORGANIC REACTIONS IN AQUEOUS MEDIA

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School of Physical and Mathematical Sciences

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TABLE OF CONTENTS

SUMMARY

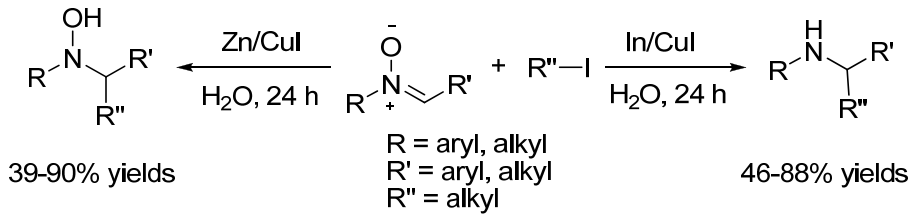
This thesis describes the indium(zinc)-copper promoted Barbier-type alkylation reactions of various nitrones with alkyl iodides in water; zinc-indium mediated pinacol coupling reaciton of aldehydes with α,β-unsaturated ketones in aqueous media; direct synthesis of alkyl indium reagents and their application in palladium-catalyzed coupling with aryl iodides; palladium catalyzed hydroboration of unactivated alkynes in water.

Chapter 1.

A brief summary of recent development of organic reactions in water is presented. The use of water has numerous advantages, including low cost, safe, synthetic efficiency, simple manipulation, environmental friendly and good selectivities. Subsequently, recent indium-mediated reactions in water or aqueous media are introduced. The reactions include: allylation reaction, alkylation reaction, reduction reaction, reductive coupling reaction, coupling reaction of aldehyde and enone, Prins-type cyclization, radical cyclization, Diels-Alder reaction *etc*..

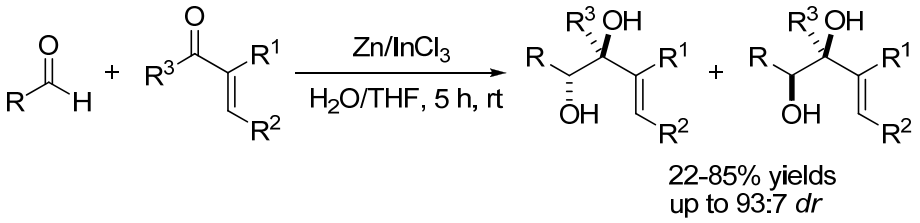
Chapter 2.

An efficient method for the Barbier-type alkylation reaction of various nitrones and alkyl halides in water is described. The amines and hydroxylamines can be obtained in good yields with high diastereoselectivities, depending on judicious choice of the metal complexes used. This findings shed light on the fact that the alkylation reaction in the presence of In/CuI or Zn/CuI could provide an easy way to synthesize chiral amines or hydroxylamines. The mild reaction conditions (can process in water), moderate to good yields with high stereoselectivities and the simplicity of the reaction procedure make this method attractive for scale-up purposes.



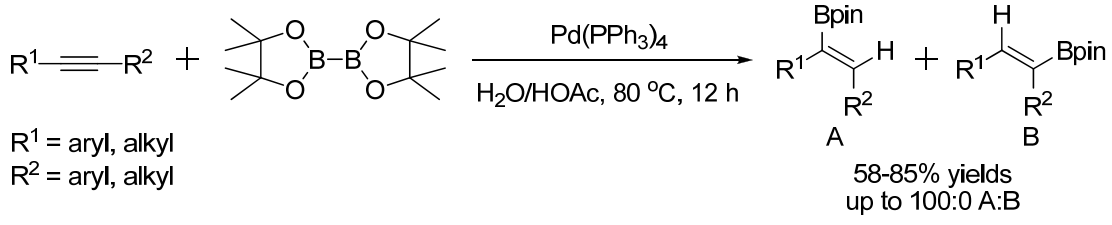
Chapter 3.

A zinc/indium chloride-mediated pinacol cross-coupling reaction between aldehyde and unsaturated ketone in aqueous media was developed. The 1,2-diols were obtained in moderate to good yields with up to 93:7 diastereoselectivity. This method provides an atom-economical and straightforward access to a wide variety of 1,2-diols.



Chapter 4.

An efficient procedure for the hydroboration reactions with various unactivated alkynes based on palladium catalyst was developed. The mild and efficient method provides a straightforward route to the synthesis of alkenyl boranes in water.



LIST OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
ABCVA	4,4'-azobis(4-cyanovaleric acid)
Ac	acetyl
Ar	aryl
t-Bu	*tert*-Butyl
br	broad singlet
Bn	benzyl
$B_2(pin)_2$	bis(pinacolato)diboron
Boc	*t*-butoxycarbonyl
calcd.	calculated
cat.	catalyst
CH_2Cl_2	dichloromethane
$CDCl_3$	deuterated chloroform
cm^{-1}	inverse centimeter
conc.	concentrate
CTAB	cetyltrimethylammonium bromide
Cy	cyclohexanyl
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublet
DFT	density functional theory
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPEphos	bis(2-diphenylphosphinophenyl)ether
EPHP	1-ethylpiperidium hypophosphite
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc or EA	ethyl acetate

FTIR	fourier transform infrared spectrometry
g	gram
h or hrs	hour(s)
H	Hydrogen
HOAc	acetic acid
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	*iso*-propyl
J	coupling constant
M	molar concentration
m	multiplet
m/z	mass per charge ratio
M^+	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
MS	mass spectrometry
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
OTf	trifluoromethane sulfonate (triflate)
p	para
Ph	phenyl
ppm	parts per million
q	quartet
R_f	retention factor
rt	room temperature
s	singlet

sat.	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
Vol	Volume
Xantphos	4,5-bis(diphenylphosphine)-9,9-dimethylxanthene

CHAPTER 1

Indium-Mediated Reactions in Water or Aqueous Media

Chapter 1. Introduction: Indium-Mediated Reactions in Water or Aqueous Media

1.1 Recent Development of Organic Reactions in Water

Most organic reactions are carried out in volatile, flammable, toxic and expensive organic solvents which usually give rise to ecological and economical concerns. The increasing environmental consciousness of the chemical community has led to the search for alternative, non-polluting media and processes for chemical and organic syntheses. Recently, green chemistry has been attracting increasingly more attention due to its continual benefits to the environment and human society.[1] In view of the natural abundance of water, as well as the inherent advantages of using water as a solvent, interests have been growing in the study of organic reactions in water.[2] Since water is clean and non-toxic, the study of water as a reaction solvent contributes to the advancement of chemistry.

The use of water as reaction solvent for organic synthesis has numerous advantages:[3]

(i) *Cost*. Water is the cheapest solvent available on earth. On Earth, the oceans contain

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[1] (a) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267; (b) Lankey, R. L.; Anastas, P. T. *Advancing Sustainability through Green Chemistry*; Oxford University Press: New York, **2002**; (c) Anastas, P. T.; Heine, L. G.; Williamson, T. C. *Green Chemical Syntheses and Processes*; ACS Symposium Series 767; American Chemical Society: Washington, DC, **2000**.

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[3] (a) Li, C. J. *Green Chemical Syntheses and Processes*, Vol. 767, Chapter 7, p. 74-86, ACS Symposium Series, **2000**. (b) Li, C. J.; Chan, T. K. *Comprehensive Organic Reactions in Aqueous Media, Second Edition*, John Wiley & Sons, Inc., Hoboken, New Jersey, **2007**.

1.4×10^{21} kg or 320,000,000 cubic miles of water. Using water as a solvent can make many chemical processes more economical.

(ii) *Safety*. Many organic solvents are flammable, potentially explosive, volatile, toxic, mutagenic, and/or carcinogenic. Water, on the other hand, belongs to none of these categories.

(iii) *Synthetic efficiency*. When organic synthesis is carried out in water, it may be possible to eliminate the need for the protection and deprotection of functional groups, such as hydroxyl groups. This would potentially increase the overall efficiency of a synthetic scheme and save many synthetic steps. Furthermore, compounds containing water molecules or biomolecules can be used directly, avoiding the troublesome purification and dehydration processes. This will be especially useful in carbohydrate and protein chemistry.

(iv) *Simple operation*. In large-scale industrial processes, isolation of organic products can be performed by simple phase-separation. In addition, it is also easier to control the reaction temperature, as water has one of the largest heat capacity of all solvents.

(v) *Environmental benefits*. The chemical industry is a major contributor to environmental pollution. Using water as reaction solvent may alleviate the problem of pollution by organic solvent since water can be recycled and purified readily and is benign when released into the environment (when no harmful residue is present).

(vi) *Good selectivities*. In some reactions, using water as reaction solvent could generate product in better selectivities. The reason can be attributed to the following properties of water: cohesive energy, hydrogen-bonding capacity, and enforced hydrophobic interactions.

(vii) *Potential for new synthetic methodologies*. Compared to reactions in organic solvents, the use of water as a reaction solvent has been much less explored in organic chemistry. There are many opportunities to develop novel synthetic methodologies that have not been discovered before.

Due to the unique properties of water, chemists have begun investigating the possibility of using water as reaction solvent in organic synthesis in recent decades. In the early 1980s, Breslow[4] and Grieco[5] studied the positive effect of water on the rates and selectivities of Diels-Alder reactions. Since then, many organic reactions that are traditionally carried out exclusively in organic solvents, such as the Barbier-Grignard-type reaction, have been successfully performed in an aqueous medium. Till now, a wide variety of organic reactions have been developed to be performed efficiently in water. For example, the Aldol reaction,[6] Prins cyclization,[7] reaction of alkynes with imines,[8] allylation of carbonyl compounds,[9] Baylis-Hillman reaction,[10] reductive coupling,[11] Diels-Alder reaction,[12] Michael addition,[13] Claisen rearrangement,[14] radical cyclization,[15] coupling reaction,[16] alkylation reactions of

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[4] (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816; (b) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901; (c) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239; (d) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *25*, 1897; (e) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137.

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[13] (a)Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879; (b) Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107; (c) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174; (d) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149; (e) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369; (f) Pietrusiewicz, K. M.; Zablocka, M. *Tetrahedron Lett.* **1988**, *29*, 937.

[14] (a) Grieco, P. A.; Brandes, E.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849; (b) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515; (c) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219.

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carbonyl compounds[17] and Reformatsky reaction[18] can all be carried out in water.

Although many advantages using water as solvent for the indium-mediated organic reactions, there also have some disadvantages in this area. For example, the difficulty of purification of waste from the aqueous layer is the major question.

1.2 Indium-Mediated Organic Reactions in Water or Aqueous Media

Compared to the other metallic elements in the vicinity of the periodic table, indium has the lowest first ionization potential. Due to this, it is relatively stable in boiling water or alkali and is not easily form oxides in air.[19] Such special properties are highly worthwhile for its development in organic reactions in water. Up till now, there are many research groups working on the development of new synthetic methods using indium as promoter in water or aqueous media.[20]

(1) Allylation Reaction

In 1991, Li and Chan reported the first indium-mediated Barbier-Grignard-type allylation reaction in water.[21] This work was designed according to the first ionization potentials of various elements.[22] Among the different elements, indium has been shown to be the best metal for such reaction (Scheme 1.1). Allylation reactions of aldehydes and ketones

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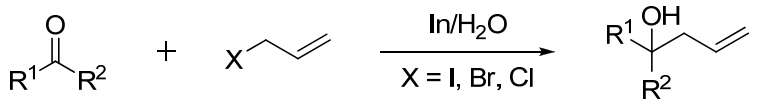
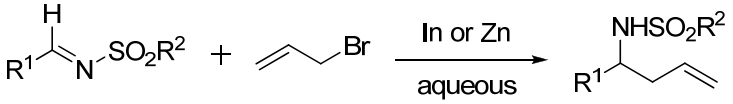
occurred smoothly with indium in aqueous media. Compared to similar reactions with zinc and tin (usually require acid catalysis, sonication or heat), the reaction with indium proceeds does not need any promoter. Furthermore, indium-mediated allylations can tolerate many functional groups due to the mild conditions.



Scheme 1.1

In 2000, Chan *et al*. investigated the indium (zinc)-mediated allylation of sulfonimines in aqueous media (Scheme 1.2).[23] They reported that sulfonimines derived from aryl and nonenolizable aliphatic aldehydes can be effectively allylated to the corresponding homoallylic sulfonamides with allylic bromides, promoted by indium or zinc. The solvent used can be water, THF, or a mixed aqueous THF solvent.

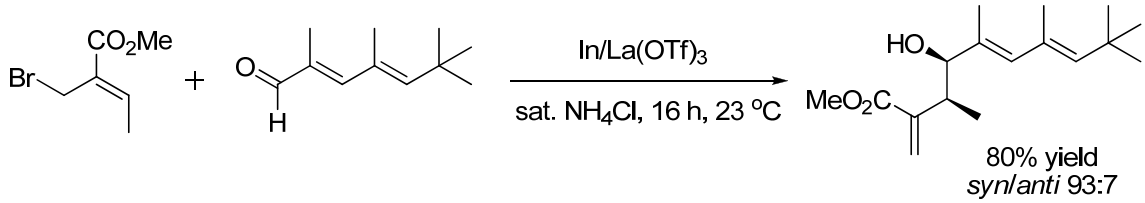


Scheme 1.2

Our group also made great contributions to the indium-mediated allylation reactions in aqueous media. The reaction was employed to the key intermediate synthesis of antillatoxin.[24] Indium-mediated allylation of *Z*-2-bromocrotyl chloride and aldehyde in saturated ammonium chloride under sonication afforded the desired intermediate in good yield in the presence of lanthanide triflate. Changing the halide compound to methyl (*Z*)-2-(bromomethyl)-2-butenoate under the same conditions yielded the desired homoallylic alcohol in 80% yield with a high 93:7 *syn*/*anti* selectivity (Scheme 1.3).[25] Our group also

[23] Lu, W. S.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589.
[24] Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453.
[25] (a) Loh T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457; (b) Loh, T. P.; Song, H. Y. *Synlett* **2002**, 2119.

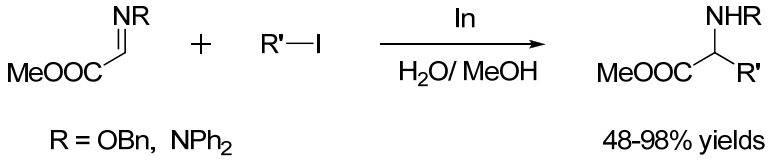
reported an easy approach to various trifluoromethyl homoallylic alcohols by the reaction of the trifluoroacetaldehyde hydrate with allylic indium in water.[26]



Scheme 1.3

(2) Alkylation Reaction

In 2002, Naito *et al.* reported that indium could efficiently mediate addition reaction of alkyl iodides to glyoxylic oxime ether and gloxylic hydrazones in aqueous media (Scheme 1.4).[27] It provided a convenient method for preparing α-amino acids. However, no reaction was observed with primary alkyl iodides (ethyl iodide) or other halides like isopropyl bromide.



Scheme 1.4

(3) Reduction Reaction

The systematic investigation of the reduction of aromatic nitro compounds mediated by indium was first reported by Moody and Pitts (Scheme 1.5).[28] The indium-mediated reduction of aromatic nitro compounds is simple and occurs under mild conditions with high yields. The reaction conditions are compatible with ester, nitrile, amide and halide substituents.

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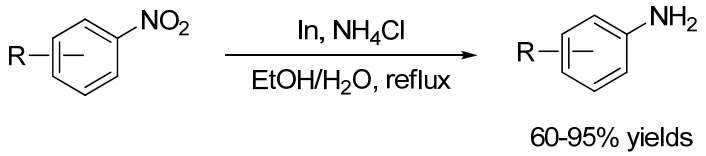
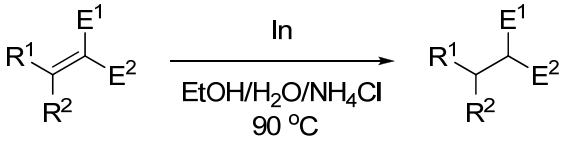


Scheme 1.5

In 2001, Ranu *et al*. investigated the reduction reaction of the C-C double bond using indium as a reducing agent (Scheme 1.6).[29] A wide range of structurally varied highly activated (electron-deficient) alkenes underwent selective reduction of the C=C bonds by this procedure to provide the corresponding alkanes. The reaction conditions are compatible with α,α-dicyanoalkene, β-aryl-substituted enone and conjugated enone ester substituents.



Scheme 1.6

(4) Cross-dehydrogenative coupling (CDC)

Li and coworkers discovered a new type of coupling termed cross-dehydrogenative coupling recently.[30] Mono- and diaryl-substituted 1,4-quinones were synthesized by the $In(OTf)_3$-catalyzed conjugate addition of aromatic *C*-nucleophiles to 1,4-quinone derivatives followed by *in situ* dehydrogenation in water (Scheme 1.7).[31] It was found that water is beneficial to the reaction. Moreover, it was observed that the reaction could proceeded "on water" without any catalyst, organic cosolvent, or additives when indoles were used as the electron-rich aromatic compounds. The "on water" conditions provided the best yields of the corresponding products and the only system to produce bis(coupling) products.[32]

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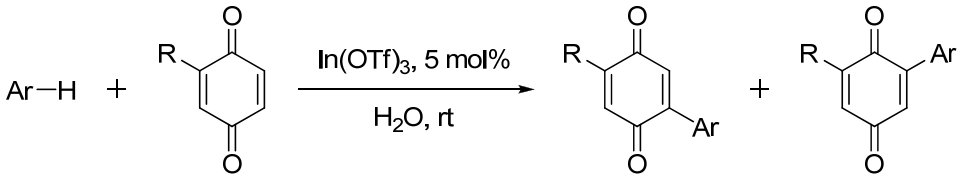
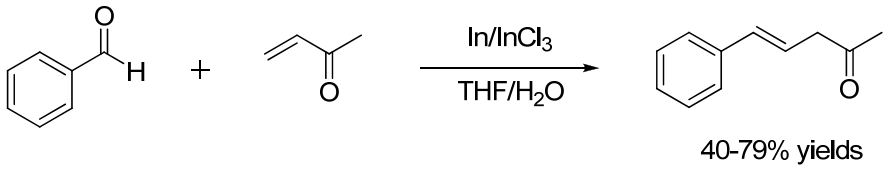
[29] Ranu B. C.; Dutta J.; Guchhait S. K. *Org. Lett.* **2001**, *3*, 2603.
[30] For selected examples, see: (a) Li, Z.; Li, C. J. *Eur. J. Org. Chem.* **2005**, 3173; (b) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 6968; (c) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 3672; (e) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 56; (f) Zhang, Y.; Li, C. J. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 1949.
[31] Zhang, H. B.; Liu, L.; Chen, Y, J,; Wang, D.; Li, C. J. *Adv, Catal, Synth.* **2006**, *348*, 229.
[32] Zhang, H. B.; Liu, L.; Chen, Y, J,; Wang, D.; Li, C. J. *Eur. J. Org. Chem.* **2006**, 869.



Scheme 1.7

(5) Coupling Reaction of Aldehyde and Enone

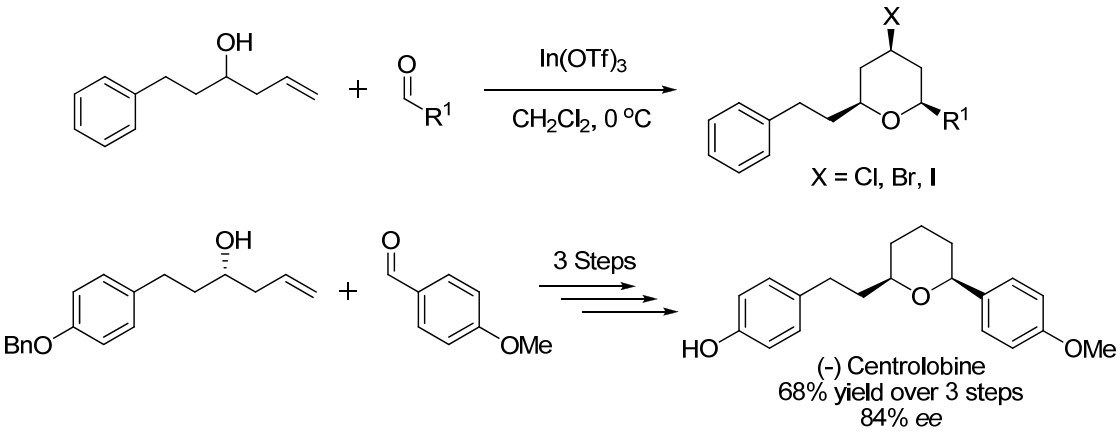
In/$InCl_3$-mediated cross-coupling reaction of methyl vinyl ketone with benzaldehyde in aqueous media has been reported (Scheme 1.8).[33] Interestingly, in this reaction, the final product was the β,γ-unsaturated ketone instead of the pinacol cross-coupling product.



Scheme 1.8

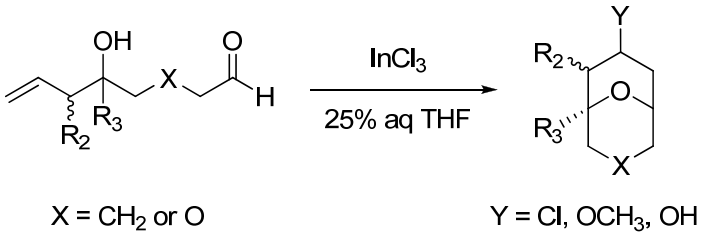
(6) Prins-Type Cyclization

Our group also make great contribution in the field of indium catalyzing Prins-type cyclization reactions. In 2005, our group reported In(OTf)$_3$ catalyzed Prins cyclization reaction in CH_2Cl_2. This method also have been applied in the total synthesis of (-)-centrolobine (Scheme 1.9).[34]



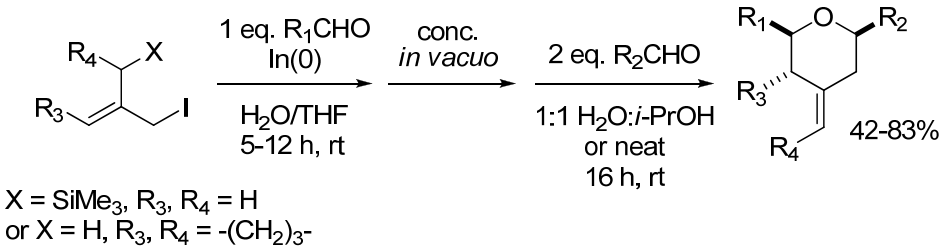
[33] Kang, S.; Jang, T.-S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *Org. Lett.* **2000**, *2*, 3615.
[34] Chan, K. P.; Loh, T. P. *Org. Lett.* **2002**, *4*, 2025.

Indium (III) trichloride could be considered as an effective Lewis acid for producing 3-substituted bicyclo[3.3.1]nonane backbones in moderate to high yields. The 3-chloro-, 3-methoxy-, or 3-hydroxy-substituted compounds could be obtained in moderate yields (Scheme 1.10).[35]



Scheme 1.10

In the presence of indium metal, 3-iodo-2-[(trimethylsilyl)-methyl]propene reacts with sequentially added aldehydes to provide *cis*-2,6-disubstituted tetrahydropyrans in good yields (Scheme 1.11).[36] It is worthy to note that evidence suggests that InI, formed upon aldehyde (R_1CHO) allylation in aqueous media, acts as a promoter for the silyl-Prins reaction with the second equivalent of added aldehyde (R_2CHO).



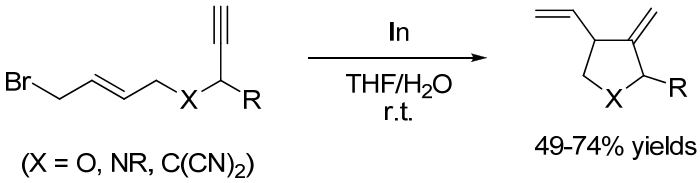
Scheme 1.11

(7) Radical Cyclization

Indium-mediated intramolecular cyclization of tethered allyl bromides with unactivated C-C triple bond could proceeded smoothly in a cosolvent of THF and water, which generated

[35] Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025.
[36] Pham, M.; Allatabakhsh, A.; Minehan, T. G. *J. Org. Chem.* **2008**, *73*, 741.

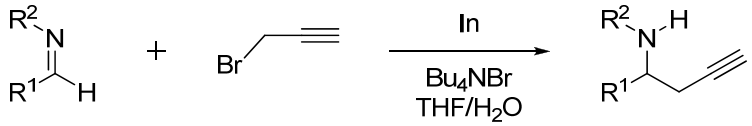
a variety of 5-membered carbocycles and heterocycles in good yields (Scheme 1.12).[37] The presence of water in the reaction medium was found to be essential for smooth and efficient cyclization.



Scheme 1.12

(8) Propargylation/Allenylation of imines

The coupling of propargyl bromide with a variety of imines and imine oxides mediated by indium afforded homopropargylamine derivatives in high yields in aqueous media (Scheme 1.13).[38] Palladium(0) complex and indium(I) iodide catalyzed propargylation of glyoxylic oxime ether in aqueous media was also studied.[39]



Scheme 1.13

(9) Diels-Alder Reaction

A catalytic amount of $InCl_3$ in a mixture of water can promote the intramolecular Diels-Alder reactions of acrolein (acrylaldehyde) and methyl acrylate with cyclopentadiene to give the corresponding cycloadducts in good yields with perfect *endo*-selectivities (Scheme 1.14).[40] $InCl_3$ can be easily recovered and reused from water after the reaction.

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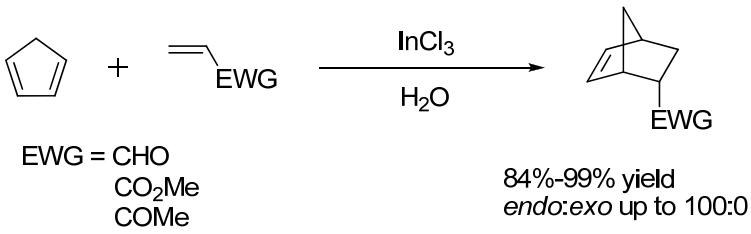
[37] Salter, M. M.; Sardo-Inffiri, S. *Synlett* **2002**, 2068.
[38] Prajapati, D.; Laskar, D. D.; Gogoi, B. J.; Devi, G. *Tetrahedron Lett.* **2003**, *44*, 6755.
[39] Miyabe, H., Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 1415.
[40] Loh, T. P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315.



Scheme 1.14

1.3 Conclusion

The advantages of using water as solvent are presented here. With the present growing concern about our environment and our future resources, the use of water in organic reactions will thus become more applicable in the future of organic chemistry. Rapid development in this field could therefore be envisioned. The synthetic advantages of indium-mediated reactions in aqueous media have been demonstrated with the numerous examples of related works published in recent years.

CHAPTER 2

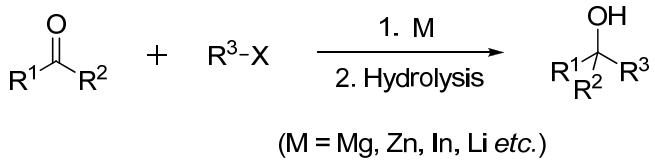
Indium (Zinc)-Copper-Mediated Barbier-Type Alkylation Reaction of Nitrones in Water

Chapter 2. Indium (Zinc)-Copper-Mediated Barbier-Type Alkylation Reaction of Nitrones in Water

2.1 Introduction

2.1.1 Conventional Methods for Barbier-Type Alkylation Reactions

In the case of unstable organometallic reagents, it is convenient to generate the reagent in the presence of the carbonyl compound, to warrant immediate reaction. The original protocol with magnesium metal was described by P. Barbier in the year of 1899.[41] More recently, other metals (e.g., Sn, In, Zn, etc.) in aqueous solvents have been used under similar conditions with good results (Scheme 2.1).

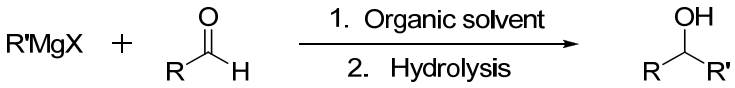


Scheme 2.1

In 1900, V. Grignard (Barbier's supervisor) reported that an alkyl halide (RX) reacted with magnesium metal (Mg) in diethyl ether can furnish a muddy solution of an organomagnesium compound (RMgX), which upon reaction with aldehydes and ketones afforded secondary and tertiary alcohols, respectively.[42] The reaction with formaldehyde leads to a primary alcohol. These organomagnesium compounds are called Grignard reagents, and their addition across carbon-heteroatom multiple bonds are called Grignard reaction.[43] Soon after its discovery, the Grignard reaction became one of the most versatile C-C bond

[41] Barbier P. *Compt. Rend.* **1899**, *128*, 110.
[42] Grignard, V. C. R. *Acad. Sci.* **1900**, *130*, 1322.
[43] For reviews, see: (a) Shirley, D. A. *Org. React.* **1954**, *8*, 28; (b) Felkin, H.; Swierczewski, G. *Tetrahedron* **1975**, *31*, 2735; (c) Erdik, E. *Tetrahedron* **1984**, *40*, 641; (d) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225; (e) Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53.

formation reactions in organic synthesis (Scheme 2.2). V. Grignard was also awarded the Noble Price in 1912 for his pioneering discovery of this reaction. The difference between Grignard reaction and Barbier reaction is that Barbier reaction is a one-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compounds.



Scheme 2.2

The success of Barbier reaction and Grignard reaction are among the milestones in the development of organometallic chemistry. More recent progresses include the use of lithium and other metals.[44]

However, these reactions must be performed in strictly anhydrous organic solvent (THF or Et_2O), and extreme measures must be taken to prevent even trace amount of water. In this regard, Barbier-Grignard-type alkylation reaction are more difficult to handle due to *β*-elimination of the pre-formed R-MgX intermediate and its corresponding Wurtz coupling with alkyl halide. Therefore, if the reaction can be developed to proceed in aqueous media, it will bring convenience to organic chemists.

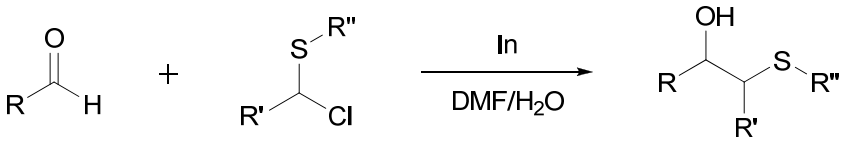
In recent years, great interest has been paid in the development of alkylation reactions in aqueous media. Several groups have investigating the alkylation reactions and have obtained significant achievements in this field.

2.1.2 Indium-Mediated Barbier-Type Alkylation Reaction in Aqueous Media

Mitzel reported the indium-mediated alkylation reaction of carbonyl compounds with *α*-chlorosulfide could run smoothly at room temperature under aqueous and mixed

[44] Dai, Z. Y.; Shao, M. R.; Hou, X. S.; Zhu, C. J.; Zhu, Y. H.; Pan, Y. *Appl. Organometal. Chem.* **2005**, *19*, 898.

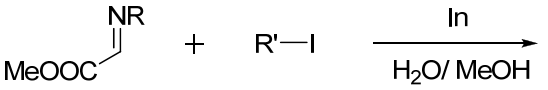
aqueous/organic conditions (Scheme 2.3).[45] The use of the halide to control *syn/anti* ratios simplifies the indium promoted coupling reaction and furnishes the corresponding products in good yields.



49-88% yields

Scheme 2.3

The first indium-mediated alkylation reaction of imine derivatives in aqueous media was reported by Naito's group (Scheme 2.4).[46] They investigated the intermolecular alkyl radical addition to imine derivatives in aqueous media by using indium as a single-electron-transfer radical initiator. The one-pot reaction based on radical addition to glyoxylic hydrazone provided a convenient method for preparing the α-amino acid.



R = OBn, R' = *i*-Pr	74% yield;
R = NPh_2, R' = *i*-Pr	98% yield;
R = NPh_2, R' = *s*-Bu	90% yield;
R = NPh_2, R' = *c*-Pentyl	79% yield;
R = NPh_2, R' = *t*-Bu	48% yield;
R = NPh_2, R' = *i*-Pr	54% yield;
R = Ts, R' = *i*-Pr	70% yield.

Scheme 2.4

Next, Naito's group performed the indium-mediated alkylation reactions for the Oppolzer camphorsultam derivative of glyoxylic oxime ether which proceeded with high diastereoselectivity in aqueous media (Scheme 2.5).[47] This method supplied a convenient way to access a variety of enantio pure α-amino acids.

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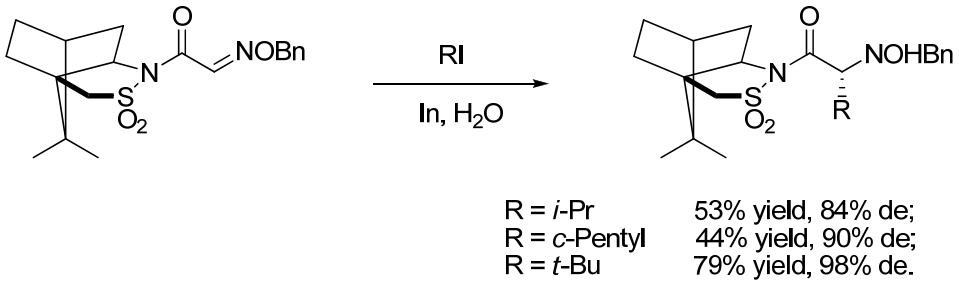
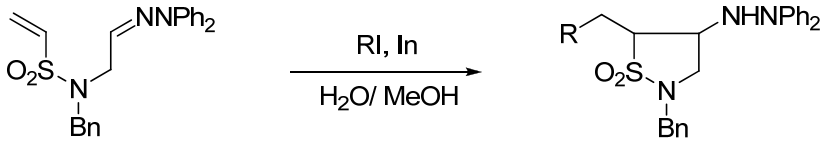
[45] Engstrom, G.; Morelli, M.; Palomo, C.; Mitzel, T. *Tetrahedron Lett.* **1999**, *40*, 5967.
[46] (a) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227.
[47] Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454.



R = *i*-Pr 53% yield, 84% de;
R = *c*-Pentyl 44% yield, 90% de;
R = *t*-Bu 79% yield, 98% de.

Scheme 2.5

According to the previous method, Naito designed a tandem C-C bond-forming reactions using indium as a single-electron-transfer radical initiator (Scheme 2.6).[48] The radical addition-cyclization-trap reaction of a substrate having a vinyl sulfonamide group and an olefin moiety proceeded smoothly to give the alkylated products in moderate to excellent yields without forming simple addition by-products in aqueous media.

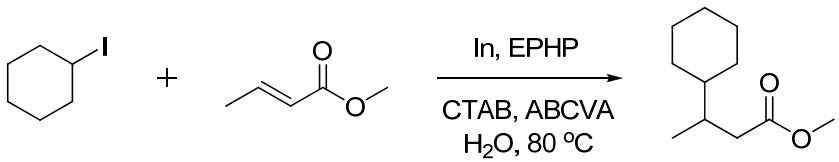


R = *i*-Pr 93% yield;
R = *c*-Pentyl 86% yield;
R = *t*-Bu 42% yield.

Scheme 2.6

Indium-mediated 1,4-addition of alkyl radical to *β*-substituted conjugated alkenes in water was reported by Cho *et al*. in 2002 (Scheme 2.7).[49] The reaction afforded 1,4-addition products to various *α*,*β*-enones regiospecifically in high isolated yields.

[48] Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835.
[49] Jang, D. J.; Cho, D. H. *Synlett* **2002**, 631.

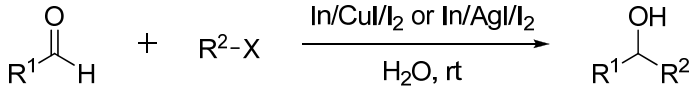


EPHP = 1-ethylpiperidium hypophosphite
CTAB = cetyltrimethylammonium bromide
ABCVA = 4,4'-azobis(4-cyanovaleric acid)

Scheme 2.7

Our group also investigated the indium-mediated Barbier-Grignard-Type alkylation reaction in water in detail recent years.

The alkylation reaction of aldehydes (including aliphatic version) with unactivated alkyl halides in water proceeded smoothly in the presence of an In/CuI/I_2 or In/AgI/I_2 system (Scheme 2.8).[50] It was found that the reactions proceeded more efficiently in water than in organic solvent. In, CuI or AgI and I_2 were all essential in these reactions.



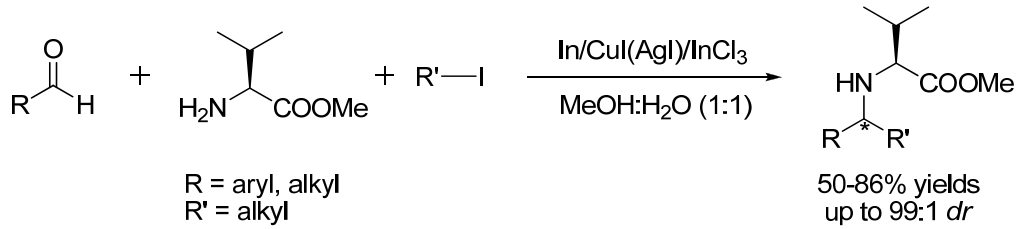
R^1 = aryl, alkyl
R^2 = alkyl

31-86% yields

Scheme 2.8

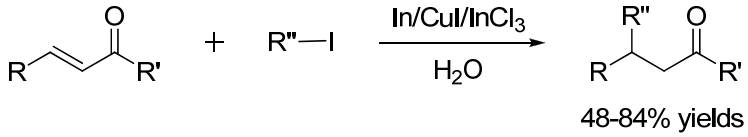
A similar system, In/CuI(AgI)/$InCl_3$, was also developed for the Barbier-Grignard-type alkylation reactions of simple imines (Scheme 2.9).[51] Various aldehydes, amines (including aliphatic and chiral version), and alkyl iodides were used as a one-pot condensation in water or aqueous media. The reactions proceeded efficiently at room temperature to give the desired products in moderate to good yields. Using *L*-valine methyl ester as substrate, it was obtained up to 99:1 *dr*.

[50] Shen, Z. L.; Yeo, Y. L.; Loh T. P. *J. Org. Chem.* **2008**, *73*, 3922.
[51] (a) Shen, Z. L.; Loh T. P. *Org. Lett.* **2007**, *9*, 5413; (b) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Chem. Eur. J.* **2008**, *14*, 1875.



Scheme 2.9

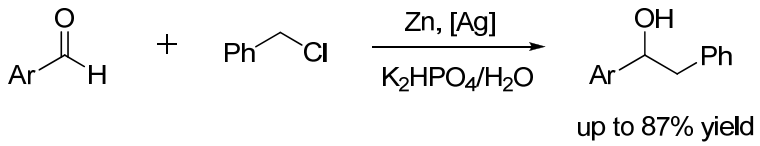
Subsequently, our group applied the In/CuI/$InCl_3$ system for the conjugate addition reaction (Scheme 2.10).[52] The unactivated alkyl iodides were conjugated to α,β-unsaturated carbonyl compounds smoothly in water.



Scheme 2.10

2.1.3 Zinc-Mediated Barbier-Type Alkylation Reaction in Aqueous Media

In 1998, Bieber *et al.* reported that benzyl chloride reacted in aqueous dibasic potassium phosphate under silver catalysis with aromatic aldehydes in the presence of zinc dust and silver catalyst to give 1,2-diaryl alcohols in moderate to good yields (Scheme 2.11).[53] Dimerization to bibenzyls and reduction of the halide are significant side reactions. The substrates include aromatic and heteroaromatic substituted aldehydes. However, aliphatic aldehydes and ketones are unreactive.

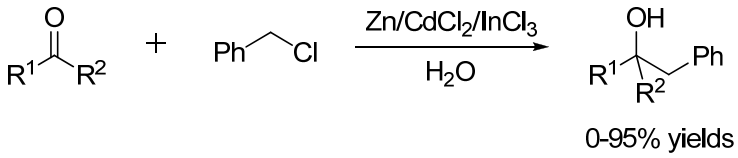


Scheme 2.11

A novel tri-metal system (Zn/$CdCl_2$/$InCl_3$) was developed by Wang *et al.* for the

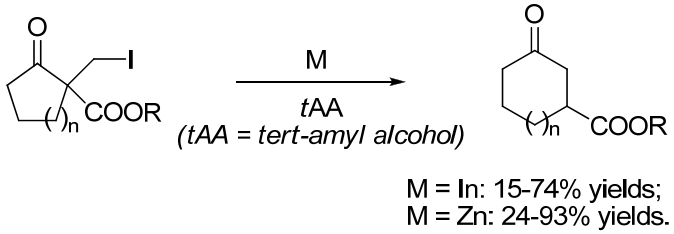
[52] Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Tetrohedron Lett.* **2009**, *50*, 1051.
[53] Bieber, L. W.; Storch, E. C.; Malvestiti, I.; Sila, M. F. *Tetrahedron Lett.* **1998**, *39*, 9393.

benzylation of various aldehydes in water, affording the corresponding alcohols in moderate to good yields (Scheme 2.12).[54] The reaction system selectively mediated the benzylation of aldehyde in the presence of ketone. The regeneration of $CdCl_2$ and $InCl_3$ was also discussed in this reaction system.



Scheme 2.12

Togo *et al.* had developed a ring-expansion reaction involving the zinc- or indium-mediated alkylation reaction of various *α*-halomethyl cyclic *β*-keto esters and *α*-halomethyl benzocyclic *β*-keto esters, as well as the chain-extension reaction of *α*-halomethyl *β*-keto esters in refluxing aqueous alcohol, to afford the ring-expansion and chain-extension products in moderate to good yields (Scheme 2.13).[55] It was found that the addition of zinc bromide as Lewis acid could increase the reaction yields, depending on different subjected substrates.

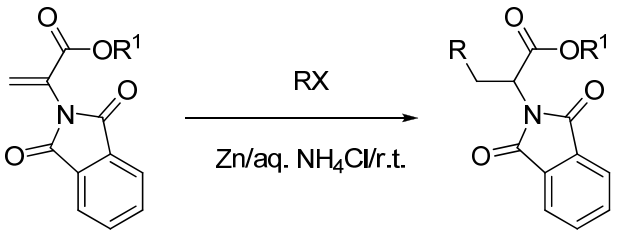


Scheme 2.13

In 2002, Li *et al.* reported zinc-mediated conjugate addition of alkyl halides to *α*-phthalimidoacrylate derivatives in aqueous NH_4Cl to generate *α*-amino acid derivatives

[54] Zhou, C. L.; Jiang, J. Y.; Zhou, Y. Q.; Xie, Z.; Miao, Q.; Wang, Z. Y. *Lett. Org. Chem.* **2005**, *2,* 61.
[55] Sugi, M.; Sakuma, D.; Togo, H. *J. Org. Chem*. **2003**, *68*, 7629

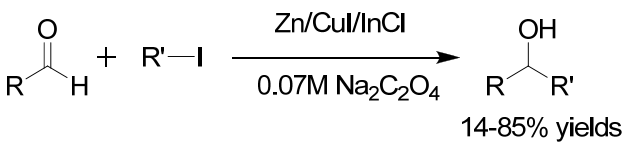
(Scheme 2.14).[56] The reaction did not occur in the absence of water. Simple methyl iodide and primary iodides also can generate the desired products in good yields.



RX	R^1	Yield
2-Iodobutane	Et	94
2-Iodo-2-methylpropane	Et	86
1-Iodocyclohexane	Et	96
1-Iodocyclopentane	Et	97
2-Iodopropane	Et	93
2-Bromopropane	Et	47
1-Iodocyclopentane	Me	85
1-Iodopentane	Me	49
1-Iodohexane	Me	51

Scheme 2.14

Soon after that, they reported an efficient Barbier-Grignard-type alkylation of aldehydes using unactivated alkyl halides in water (Scheme 2.15).[57] In the presence of Zn, CuI, and catalytic InCl, with dilute aqueous sodium oxalate, unactivated alkyl halides were found to react with aldehydes at room temperature, under an atmosphere of air, to afford the desired nucleophilic addition products in moderate to high yields. However, this method is not applicable to aliphatic aldehydes and by-products generated from the reduction or pinacol coupling of aldehydes were detected.



Scheme 2.15

[56] Huang, T.; Keh, C. C. K.; Li, C. J. *Chem. Commun.* **2002**, 2440.
[57] Keh, C. C. K.; Wei, C. M.; Li C. J. *J. Am. Chem. Soc.* **2003**, *125*, 4062.

Conclusion

Barbier-Type reactions in water have many advantages in organic synthesis: (i) It can replace the use of flammable and toxic organic solvents with water; (ii) tedious protection-deprotection processes for certain acidic-hydrogen containing functional groups can be avoided; (iii) Water-soluble compounds (such as carbohydrates) can be tolerated without the need of derivatization.

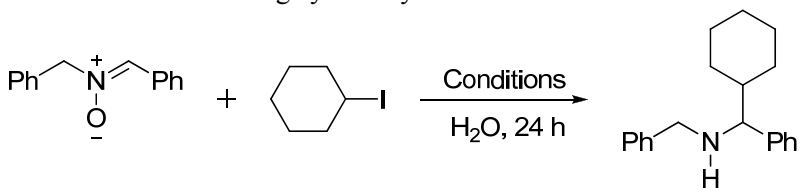
The metal-mediated alkylation reactions in aqueous media were investigated and developed over the recent decade. The reactions can be carried out in water or aqueous media efficiently and provided the desired products were obtained in moderate to high yields. However, most of the previously reported metal-mediated alkylation reactions focused on the use of activated imines, such as sulfonimines, tosyl, aryl, aryl hydrazones, and glyoxylic oxime ether, *etc*.

2.2 Results and Discussion

2.2.1 Indium-Copper Mediated Barbier Type Alkylation Reaction of Nitrones in Water

Initial studies were focused on the alkylation reaction of (*Z*)-*N*-benzylidene-1-phenylmethanamine oxide (**1a**) and cyclohexyl iodide (**2**) under different reaction conditions. The results are summarized in Table 2.1.

Table 2.1. Optimization of reaction conditions for Barbier-type alkylation reaction of nitrone **1a** using cyclohexyl iodide **2** in water[a]



1a **2** **3a**

Entry	Conditions	Solvent	Yield (%)[b]
1	Sn/CuI	H_2O	0
2	Mg/CuI	H_2O	0
3	**In/CuI**	**H_2O**	**82**
4	In	H_2O	6
5	CuI	H_2O	0
6	In/CuBr	H_2O	44
7	In/CuCl	H_2O	34
8	In/AgI	H_2O	61
9	In/AgBr	H_2O	40
10	In/AgCl	H_2O	29
11	In/CuI	CH_3CN	30
12	In/CuI	MeOH	18
13	In/CuI	CH_2Cl_2	<15
14	In/CuI	DMSO	<15
15	In/CuI	DMF	<15
16	In/CuI	THF	<15
17	In/CuI	H_2O/MeOH	60
18	In/CuI	H_2O/THF	41

[a] The reaction was carried out at room temperature for 1 day using In (2 mmol), CuI (1 mmol), **1a** (0.5 mmol), cyclohexyl iodide (2 mmol) and water (10 mL). [b] Isolated yield.

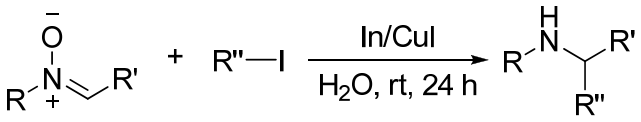
As shown in Table 2.1, among the different metals investigated, indium (good reducing metals with high potential to mediate organic transformations via single-electron transfer process) was observed to be effective for activation of the alkylation reaction of **1a** in water to afford the corresponding amine **3a** in 82% yield. It was found that without the use of CuI in In/CuI system, the reaction proceeded sluggishly to give the desired product in lower yield (Table 2.1, entry 4). In addition, using other copper(I) salts instead of CuI gave the corresponding products in relatively low yields (Table 2.1, entries 6 and 7). Moreover, the products were obtained in lower yield as compared to the reactions carried out using copper(I)

iodide when silver salts were used (Table 2.1, entries 8-10). It was also found that the use of metal such as indium is indispensable for the occurrence of this alkylation reaction (Table 2.1, entry 5). Sn and Mg were also screened for the alkylation reaction of nitrone **1a**, but did not provide any product (Table 2.1, entries 1 and 2).

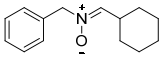
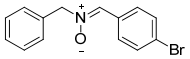
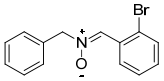
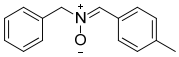
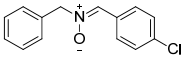
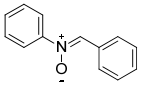
It was also found that the reaction proceeded in lower yields in organic solvents than in water. For example, only 30% and 18% yields of amine **3a** was obtained using CH_3CN and MeOH as solvents respectively (Table 2.1, entries 11 and 12), and less than 15% yield of amine was obtained using CH_2Cl_2, DMSO, DMF, THF as solvents (Table 2.1, entries 13-16). When using mixture solvents, such as H_2O/MeOH, H_2O/THF for the alkylation reaction, better yields were obtained than in the pure organic solvents (Table 2.1, entries 17 and 18).

Moreover, the reaction was carried out completely exposed to the atmosphere rather than under argon or nitrogen atmosphere. With the optimized reaction conditions, we further explored this reaction using various nitrones and alkyl iodides in water. The results were summarized in Table 2.2.

Table 2.2. Indium-copper mediated Barbier-type alkylation reactions of nitrones using various alkyl iodides in water



1a-h **3a-m**

Entry	Substrate	R''—I	Product	Yield (%)[a]
1	**1a**		**3a**	82
2	**1a**		**3b**	82
3	**1a**		**3c**	74
4	**1a**		**3d**	80[b]
5	 **1b**		**3e**	62
6	 **1c**		**3f**	88
7	 **1d**		**3g**	78
8	 **1e**		**3h**	75
9	 **1f**		**3i**	81
10	**1f**		**3j**	70
11	 **1g**		**3k**	55
12	**1g**		**3l**	46

[a] Isolated yield. [b] Diastereomeric ratio: 54:46.

As shown in Table 2.2, In/CuI efficiently mediated the alkylation reactions of various nitrones in water at ambient temperature to afford the corresponding alkylated amines in moderate to good yields. It was satisfying to find that when alkyl substituted nitrone **1b** was used as substrate, the reaction also proceeded efficiently with isopropyl iodide to furnish the desired product **3e** in good yield (Table 2.2, entry 5).

2.2.2 Indium-Copper Mediated Barbier-Type Alkylation Reaction of Chiral Nitrones in Water

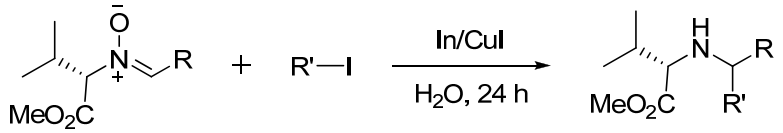
Next, we applied the alkylation reaction to various chiral nitrones. The results were summarized in Table 2.3.

As shown in Table 3, In/CuI efficiently mediated the alkylation reactions of various chiral nitrones in water at ambient temperature and provided the desired products with good yields and high diastereoselectivities. It is gratifying to find that when alkyl substituted nitrone **4d** was used, the reaction also proceeded efficiently with alkyl iodides to furnish the desired products in good yields with up to 99:1 *dr* (Table 2.3, entries 12-14). The alkylation reaction using In/CuI worked efficiently with the primary *n*-butyl iodide for the substrates **4a** and **4c** and afforded the desired products **5d** and **5k** in moderate yields (Table 2.3, entries 4 and 11).

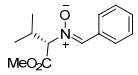
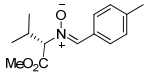
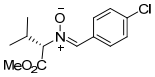
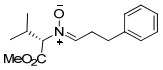
Currently, the role of the CuI is not clear. We propose that, just like the formation of zinc-copper couple which has found applications in organic synthesis (but, to date, the mechanism is not clear), in our reaction indium might also react with copper iodide to generate a more robust indium-copper couple which activates the alkyl iodide to furnish an alkyl radical. Alternatively, a more reactive indium(I) iodide might be produced via a red-ox reaction between indium and copper iodide which acts as an efficient radical initiator for our organic transformation.

It is important to note that the alkylation reaction could proceed well not only in the presence of electron-donating group (Table 2.3, entries 5-7) but also with electron-withdrawing group (Table 2.3, entries 8-10) on the chiral substrate under the same condition. For substrate **4d**, the alkylation reaction went smoothly with cyclohexyl iodide in water and furnished the desired product **5m** in 81% yield and 87:13 *dr* (Table 2.3, entry 13).

Table 2.3. Indium-copper mediated Barbier-type alkylation reactions of chiral nitrones using various alkyl iodides in water[a]



4a-d **5a-n**

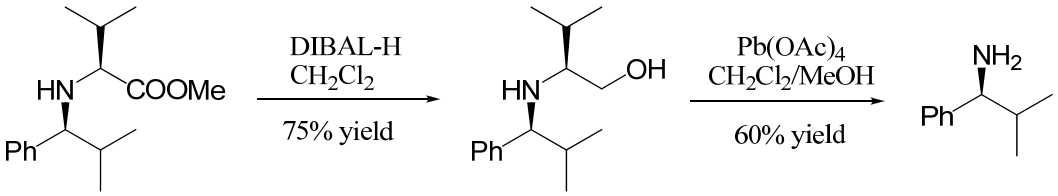
Entry	Substrate	R'-I	Product	Yield (%)[b]	*dr*
1	 **4a**		**5a**	72	92:8
2	**4a**		**5b**	67	80:20
3	**4a**		**5c**	68	92:8
4	**4a**		**5d**	32	98:2
5	 **4b**		**5e**	45	84:16
6	**4b**		**5f**	65	92:8
7	**4b**		**5g**	69	89:11
8	 **4c**		**5h**	64	72:28
9	**4c**		**5i**	52	81:19
10	**4c**		**5j**	59	64:36
11	**4c**		**5k**	31	70:30
12	 **4d**		**5l**	71	81:19
13	**4d**		**5m**	81	87:13
14	**4d**		**5n**	76	99:1

[a] The reaction was carried out at rt for 1 day, using In (2 mmol), CuI (1 mmol), **4a-d** (0.5 mmol), alkyl iodide (2 mmol), and water (10 mL). [b] Isolated yield.

The chiral auxiliary can be easily removed by reported procedures (DIBAL-H reduction followed by $Pb(OAc)_4$- or H_5IO_6-mediated oxidative cleavage of the corresponding amino alcohol) to afford the optically active amine.[58] With use of this method , the $[\alpha]_D^{23}$ we

[58] (a) Loh, T. P.; Chen, S. L. *Org. Lett.* **2002**, *4*, 3647. (b) Lee, C. L. K.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2965.

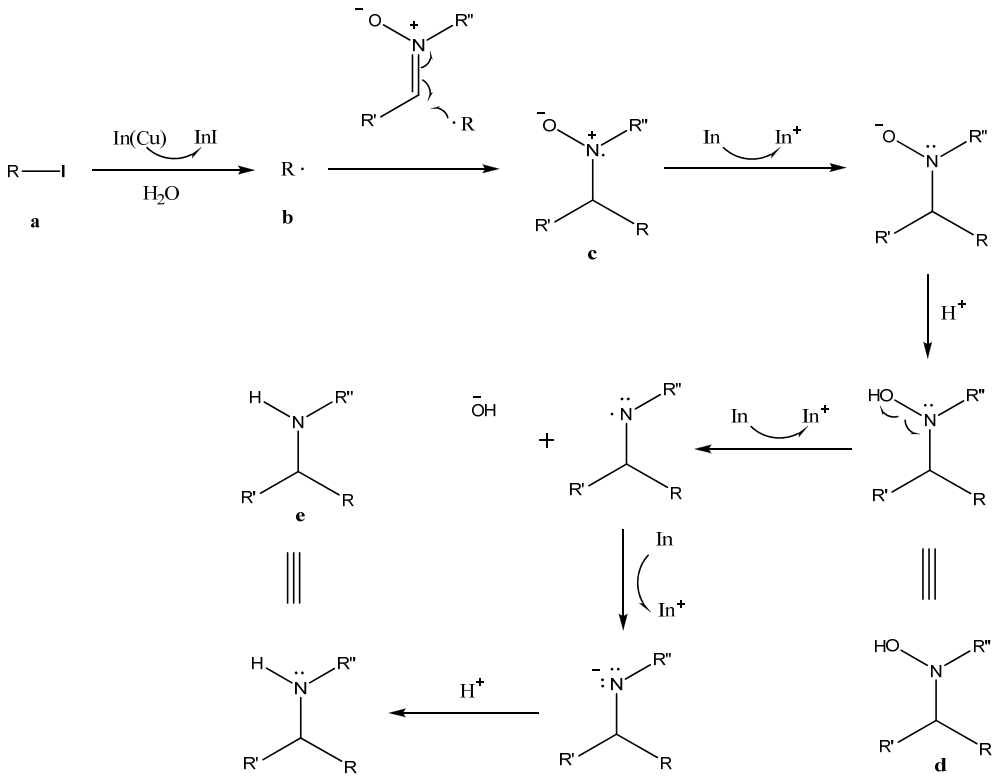
obtained for the optically active amine is -12.4 (c = 0.97, $CHCl_3$), which is compatible with the literature ($[\alpha]_D^{23}$ = -11.5 (c = 0.93, $CHCl_3$)),[59] the absolute configuration of the product was determined as shown in scheme 2.16.



Scheme 2.16

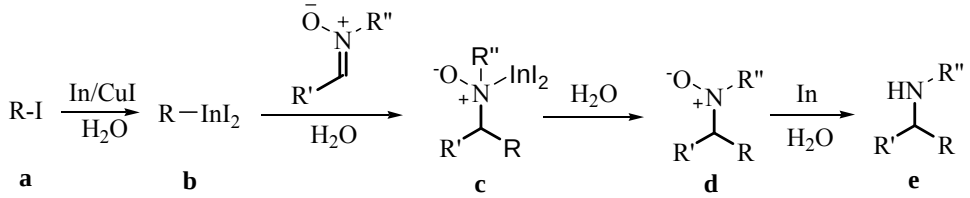
According to the previous reports, a plausible mechanism has been proposed to account for the alkylation reaction in water (Scheme 2.16). The reaction is initiated by a single-electron transfer (SET) from indium-copper to alkyl iodide **a** to generate an alkyl radical **b**. This radical **b** attacks the nitrone to generate a radical intermediate **c**. Subsequent indium-promoted reduction followed by the quenching of water afforded hydroxylamine **d**. Finally, the hydroxylamine **d** was further reduced via indium-mediated SET process to give the desired amine **e**.[60]

[59] Yang, T. K.; Chen, R. Y.; Lee, D. S.; Peng, W. S.; Jiang, Y. Z.; Mi, A. Q.; Jong, T. T. *J. Org. Chem.* **1994**, *59*, 914.
[60] Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.



Scheme 2.17

An alternative mechanism involving the production of an alkylindium species is proposed as follows (Scheme 2.18):



Scheme 2.18

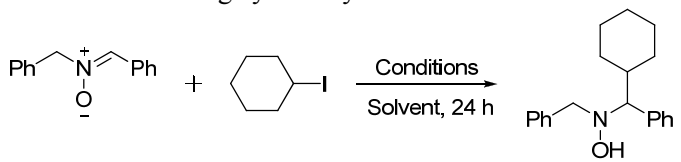
However, this mechanism is most likely impossible. Because, we have tried a lot of reaction of pre-prepared alkylindium reagent with various electrophiles such as aldehyde, imine, and alpha, beta-unsaturated ketone, either in water or in organic solvent. However, due to the poor reactivity of this alkylindium reagent, no reaction occurred. Thus, the possibility of the generation of an alkylindium reagent as reaction intermediate is precluded at present stage.

2.2.3 Zinc-Copper Mediated Barbier-Type Alkylation Reaction of Nitrones in Water

Next, we decided to investigated on the use of a cheaper metal, zinc, to substitute indium.

Initial studies were focused on the alkylation reaction of nitrone **1a** and cyclohexyl iodide **2** under different reaction conditions. The results are summarized in Table 2.4.

Table 2.4. Optimization of reaction conditions for Barbier-type alkylation reaction of nitrone **1a** using cyclohexyl iodide **2** in water[a]



1a **2** **6a**

Entry	Conditions	Solvent	Yield (%)[b]
1	Fe/CuI	H_2O	11
2	Al/CuI	H_2O	38
3	**Zn/CuI**	**H_2O**	**90**
4	Zn	H_2O	42
5	CuI	H_2O	0
6	Zn/CuBr	H_2O	72
7	Zn/CuCl	H_2O	60
8	Zn/AgI	H_2O	79
9	Zn/AgBr	H_2O	60
10	Zn/AgCl	H_2O	58
11	Zn/CuI	MeOH	28
12	Zn/CuI	CH_3CN	<20
13	Zn/CuI	CH_2Cl_2	<20
14	Zn/CuI	DMSO	<20
15	Zn/CuI	DMF	<20
16	Zn/CuI	THF	<20
17	Zn/CuI	H_2O/MeOH	64
18	Zn/CuI	H_2O/THF	48

[a] The reaction was carried out at room temperature for 1 day using Zn (2 mmol), CuI (1 mmol), **1a** (0.5 mmol), cyclohexyl iodide (2 mmol) and water (10 mL). [b] Isolated yield.

As shown in Table 2.4, Zn/CuI can efficiently mediate the alkylation of nitrone **1a** in

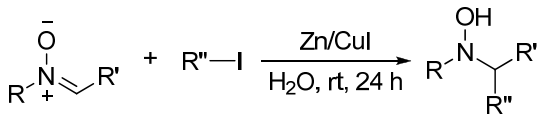
water and afforded the corresponding hydroxylamine **6a** in 90% yield (Table 2.4, entry 3). Among the several metals screened, zinc proved to be the best for this reaction, and the metal exhibited the following order for activation of the nitrone alkylation reaction: Zn >Al >Fe (Table 2.4, entries 1-3). It is interesting to note that without using CuI, the reaction could also be carried out in water and generated 42% yield (Table 2.4, entry 4). However, without using metal, the alkylation of nitrone **1a** did not occur under the same condition. When other copper salts, such as CuBr and CuCl were used instead of CuI, the reaction produced the corresponding products in relatively lower yields (Table 2.4, entries 6 and 7). In addition, when silver salts were investigated, the product was also obtained in lower yield as compared to the reactions carried out using copper iodide (Table 2.4, entries 8-10). Similar to indium-mediated alkylation, the reaction proceeded more efficiently in water than in common organic solvents such as MeOH, THF, CH_2Cl_2, DMF, DMSO *etc*. (Table 2.4, entries 11-16). It was also found that using mixed solvents such as H_2O/MeOH, H_2O/THF was not better than pure H_2O for the alkylation reaction either (Table 2.4, entries 17 and 18).

With the optimized reaction condition, we continued to apply the reaction to various nitrones and alkyl iodides to form various hydroxylamines. The results are summarized in Table 2.5.

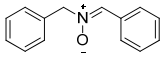
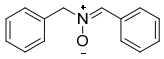
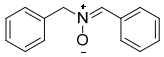
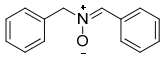
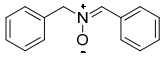
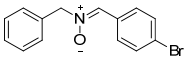
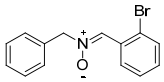
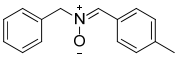
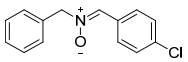
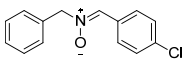
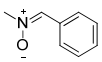
As shown in Table 2.5, Zn/CuI efficiently mediated the alkylation reaction of various nitrones in water at room temperature. The corresponding alkylated hydroxylamines were obtained in moderated to good yields. The reaction proceeded more efficiently for the substrate **1a** and cyclohexyl iodide (Table 2.5, entry 2). Interestingly, this alkylation reaction could proceed smoothly using the primary iodide, *n*-butyl iodide, to afford the corresponding hydroxylamine **6a** in moderate yield (Table 2.5, entry 1). It was also found that a moderate yield of the desired product **6k** was obtained when **1i** was used as substrate (Table 2.5, entry 11). The structures of products **6f** and **6i** (Figure 2.1) were further confirmed by a single

crystal X-ray diffraction analysis.[61]

Table 2.5. Zinc-copper mediated Barbier-type alkylation reactions of nitrones using various alkyl iodides in water[a]



1a-h **6a-k**

Entry	Substrate	R"—I	Product	Yield (%)[b]
1			**6a**	68
2			**6b**	90
3			**6c**	88
4			**6d**	83
5			**6e**	49[c]
6			**6f**	54
7			**6g**	78
8			**6h**	64
9			**6i**	80
10			**6j**	61
11			**6k**	48

[a] The reaction was carried out at rt for 1 day, using Zn (2 mmol), CuI (1 mmol), **1a-d** (0.5 mmol), alkyl iodide (2 mmol), and water (10 mL). [b] Isolated yield.

[c] Diastereomeric ratio: 55:45.

[61] Crystallographic data (including structure factors) for compounds **6f** and **6i** (CCDC 703861 and 703862) have been deposited with the Cambridge Crystallographic Data Center. See supporting information for details.

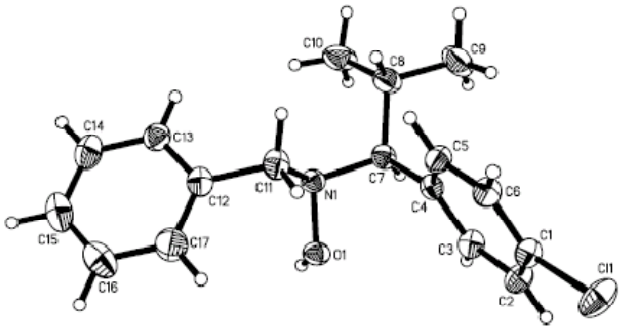


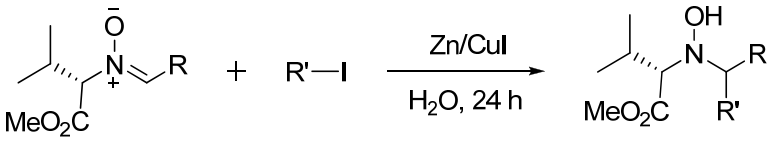
Figure 2.1. ORTEP diagram of the single-crystal X-ray structure of compound **6i**

2.2.4 Zinc-Copper Mediated Barbier-Type Alkylation Reaction of Chiral Nitrones in Water

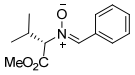
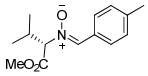
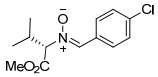
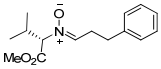
Next, we applied the alkylation reaction to various chiral nitrones in hope of developing a new method to synthesize chiral hydroxylamines. The results were summarized in Table 2.6.

As shown in Table 2.6, Zn/CuI also efficiently mediated the alkylation reactions of various chiral nitrones in water at ambient temperature. The corresponding alkylated chiral hydroxylamines were obtained in moderate to good yields. The reaction proceeded more efficiently for the substrate **4a** and cyclohexyl iodide, yielding the product **7b** in 72% yield with 98:2 *dr* (Table 2.6, entry 2). Interestingly, this alkylation reaction could proceed smoothly using the primary *n*-butyl iodide for all the substrates we have tried, affording the products in moderate yields (Table 2.6, entries 4, 8, 12, 16). It was also found that moderate yield of the desired product was obtained when alkyl substituted nitrone **4d** was used as substrate (Table 2.6, entries 13-16). This method is also compatible with both electron-donating and electron-withdrawing functional groups (Table 2.6, entries 5-12).

Table 2.6. Alkylation reactions of chiral nitrones[a]

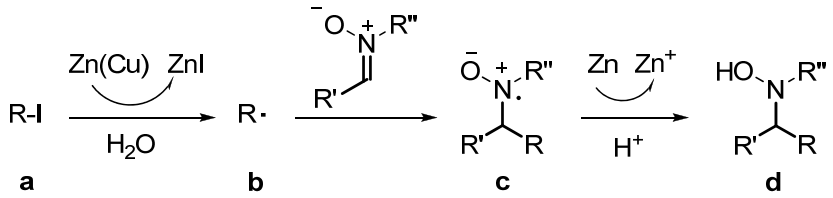


4a-d **7a-p**

entry	substrate	R'-I	product	yield (%)[b]	*Dr*
1	 **4a**		**7a**	39	88:12
2	**4a**		**7b**	72	92:8
3	**4a**		**7c**	51	96:4
4	**4a**		**7d**	30	99:1
5	 **4b**		**7e**	42	91:9
6	**4b**		**7f**	63	96:4
7	**4b**		**7g**	50	99:1
8	**4b**		**7h**	34	83:17
9	 **4c**		**7i**	41	81:19
10	**4c**		**7j**	57	85:15
11	**4c**		**7k**	35	86:14
12	**4c**		**7l**	32	88:12
13	 **4d**		**7m**	52	80:20
14	**4d**		**7n**	60	90:10
15	**4d**		**7o**	58	78:22
16	**4d**		**7p**	40	82:18

[a] The reaction was carried out at rt for 1 day, using Zn (2 mmol), CuI (1 mmol), **1a-d** (0.5 mmol), alkyl iodide (2 mmol), and water (10 mL). [b] Isolated yield.

A plausible reaction mechanism similar to the earlier one is proposed to account for the zinc-mediated alkylation reaction of nitrone (Scheme 2.19).



Scheme 2.19

The reaction is initiated by a single-electron transfer (SET) from zinc-copper to alkyl iodide **a** to generate alkyl radical **b**. This radical **b** attacks the nitrone to furnish radical intermediate **c**. Subsequent zinc-promoted reduction followed by the quenching of water afforded hydroxylamine **d**.

The difference between In and Zn mediated SET for the alkylation reaction is that indium has the lower first ionization potential (5.8 eV) which is close to alkali metals such as lithium or sodium (5 eV). While the first ionization potential of zinc is 9.4 eV, it is much higher than indium. Therefore in the last stage of the mechanism (Scheme 2.16), Indium can further reduced the resulting hydroxylamine with SET process to afford reductive product amine; while due to high first ionization of zinc, this reduced SET process cannot be activated.

2.3 Conclusion

In summary, we have developed an efficient method for the Barbier-type alkylation reaction of different nitrones (including various chiral nitrones) and alkyl halides in water. This finding sheds light on the fact that the alkylation reaction in the presence of In/CuI or Zn/CuI allows easy construction of a large library of amines or hydroxylamines. This method is attractive for scale-up purposes because of its mild reaction conditions, moderate to good yields, and the simplicity of the reaction procedure. Applying this method to the synthesis of

complex molecules as well as expanding it to the intramolecular version are in progress.

2.4 Supporting Information

2.4.1 General Methods

All nitrones were synthesized and purified before using. The chiral hydroxylamine is synthesized according to the reported method.[62] All commercially available alkyl iodides were used directly without purification.

The following commercial grade solvents and reagents were also used without further purification: indium (powder, -100 mesh, 99.99%, Aldrich chemicals), Zinc (powder, 99.9%, Aldrich chemicals), copper (I) iodide (98%, Alfa Aesar chemical), and aldehydes (Aldrich chemicals).

Deionized water was used in all reactions.

The stirrer was "Mr 3001K" type, purchased from Heidolph. It was stirred at the largest speed of 1250 rpm. The stirring bar was egg-shaped in 1.6 cm x 0.6 cm (L x Diam.).

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate or iodine.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions.

High Resolution Mass (HRMS) spectra were obtained using Waters Q-Tof Permies Mass

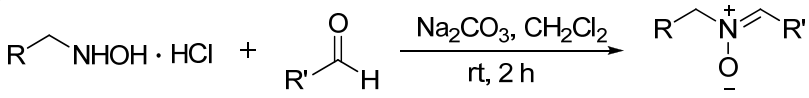
[62] Marilena, F.; Ludovico, R.; Luigino, T. *Tetrahedron* **2007**, *63* 12896

Spectrometer.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker Avance DPX 300, Bruker AMX 400 spectrophotometer and Bruker Avance DPX 500 ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra were reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.2600, singlet). Multiplicities were reported as: s (singlet); d (doublet); dd (doublets of doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants were reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.0, triplet). The proportion of diastereomers was determined from the integration of ^{1}H NMR and ^{13}C NMR spectra.

2.4.2 Representative Experimental Procedure

Preparation of nitrones



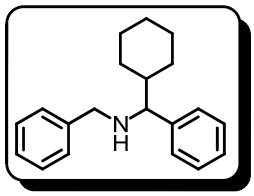
Scheme 2.20

1a-h were synthesized by the following method: In an oven dried 10 mL round-bottom flask equipped with a stirring bar, hydroxylamine hydrochloride (5 mmol), aldehyde (5 mmol) and Na_2CO_3 (5 mmol) were stirred in a solution of CH_2Cl_2 (10 mL) for 2 hours at room temperature (Scheme 2.20). After the reaction has completed, the solvent was evaporated under *vacuo* to give the residue. It was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to obtain the desired product.

General procedure for the alkylation of nitrones

To a 10 mL round-bottomed flask was added water (10 mL), nitrone (0.5 mmol), indium or zinc (2 mmol), copper iodide (1 mmol), and alkyl iodide (2.5 mmol) sequentially, then it was stirred vigorously at room temperature for 1 day. After the reaction has completed, it was extracted using diethyl ether (20 mL x 3), washed with brine, dried over anhydrous sodium sulfate, filtered. The solvent was removed under *vacuo* to give the residue. It was subjected to silica gel column chromatography using ethyl acetate and hexane as eluent to afford the desired product.

2.4.3 Spectroscopic Data of Products



***N*-Benzyl-1-cyclohexyl-1-phenylmethanamine (Table 2.2, entry 1):**

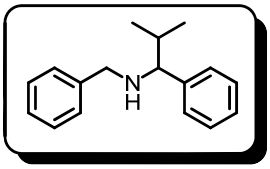
Light yellow oil; Yield: 82%; R_f = 0.21 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3431 (NH) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 0.80-1.26 (m, 5H), 1.37-1.40 (m, 1H), 1.50-1.73 (m, 5H), 1.95-1.98 (m, 1H), 3.35 (d, J = 7.24 Hz, 1H), 3.43 (d, J = 13.30 Hz, 1H), 3.56 (d, J = 13.30 Hz, 1H), 7.20-7.34 (m, 10H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 140.8, 128.2, 128.1, 128.0, 126.7, 67.9, 51.6, 44.2, 30.2, 29.8, 26.5, 26.3, 26.2 ppm;

HRMS (ESI, m/z): Calcd. for $C_{20}H_{26}N$: 280.2065, found $[M+H]^+$: 280.2060.



***N*-Benzyl-2-methyl-1-phenylpropan-1-amine (Table 2.2, entry 2):**

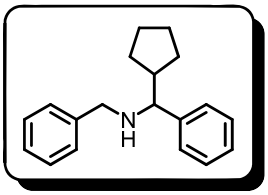
Colourless oil; Yield: 82%; R_f = 0.68 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3401 (NH) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, J = 6.78 Hz, 3H), 0.96 (d, J = 6.66 Hz, 3H), 1.64 (br, 1H), 1.80-1.91 (m, 1H), 3.32 (d, J = 6.92 Hz, 1H), 3.45 (d, J = 13.29 Hz, 1H), 3.63 (d, J = 13.29 Hz, 1H), 7.20-7.34 (m, 10H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 140.9, 128.2, 128.1 (CH x 2), 128.0, 126.7, 126.7, 68.7, 51.7, 34.4, 19.6, 19.4 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{22}N$: 240.1752, found $[M+H]^+$: 240.1746.



***N*-Benzyl-1-cyclopentyl-1-phenylmethanamine (Table 2.2, entry 3):**

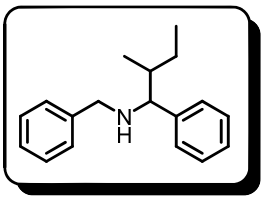
Light yellow oil; Yield: 74%; R_f = 0.29 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3418 (NH) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): δ 1.04-1.08 (m, 1H), 1.21-1.62 (m, 6H), 1.89-1.93 (m, 1H), 2.04-2.16 (m, 2H), 3.32 (d, J = 9.13 Hz, 1H), 3.43 (d, J = 13.34 Hz, 1H), 3.62 (d, J = 13.34 Hz, 1H), 7.23-7.33 (m, 10H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 140.8, 128.3, 128.1 (CH x 2), 127.8, 126.8, 126.7, 68.0, 51.4, 47.4, 30.5, 30.3, 25.3, 25.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{24}N$: 266.1909, found $[M+H]^+$: 266.1907.



***N*-Benzyl-2-methyl-1-phenylbutan-1-amine (Table 2.2, entry 4):**

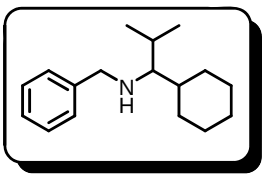
Light yellow oil; Yield: 80%, 54:46 *dr*; R_f = 0.38 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3345 (NH) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.70-0.93 (m, 6H), 0.96-1.46 (m, 2H), 1.55-1.71 (m, 2H), 3.43-3.49 (m, 2H), 3.65 (d, J = 7.30 Hz, 1H), 7.21-7.35 (m, 10H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 143.2, 142.7, 141.0, 140.9, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 126.7, 126.6, 67.0, 66.9, 51.7, 41.4, 40.8, 26.1, 26.0, 15.6, 15.3, 11.7, 11.3 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{24}N$: 254.1909, found $[M+H]^+$: 254.1902.



***N*-Benzyl-1-cyclohexyl-2-methylpropan-1-amine (Table 2.2, entry 5):**

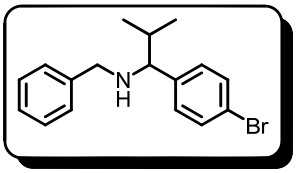
Light yellow oil; Yield: 62%; R_f = 0.55 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3418 (NH) cm^{-1};

^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (d, J = 6.75 Hz, 3H), 0.93 (d, J = 6.75 Hz, 3H), 1.13-1.86 (m, 11H), 1.81-1.86 (m, 1H), 2.03-2.05 (m, 1H), 3.78 (d, J = 12.49 Hz, 1H), 3.81 (d, J = 12.49 Hz, 1H), 7.22-7.37 (m, 5H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 141.4, 128.3 (CH x 2), 126.8, 68.2, 56.0, 41.4, 31.2, 30.1, 28.9, 26.8, 26.7, 26.6, 20.9, 17.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{28}N$: 246.2222, found $[M+H]^+$: 246.2213.



***N*-Benzyl-1-(4-bromophenyl)-2-methylpropan-1-amine (Table 2.2, entry 6):**

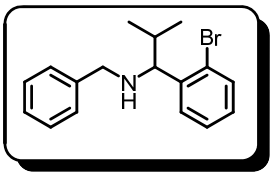
Light yellow oil; Yield: 88%; R_f = 0.67 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3420 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (d, J =6.79 Hz, 3H), 1.02 (d, J = 6.69 Hz, 3H), 2.22-2.33 (m, 1H), 3.49 (d, J = 6.69 Hz, 1H), 3.56 (d, J = 13.47 Hz, 1H), 4.12(d, J = 13.47 Hz, 1H), 7.26-7.54 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.6, 131.7, 130.5, 129.4, 128.7 128.2, 122.1, 67.2, 49.9, 33.0, 20.0, 18.7 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{21}BrN$: 318.0857, found $[M+H]^+$: 318.0849.



***N*-Benzyl-1-(2-bromophenyl)-2-methylpropan-1-amine (Table 2.2, entry 7):**

Light yellow oil; Yield: 78%; R_f = 0.67 (Ethyl acetate/Hexane 1:2);

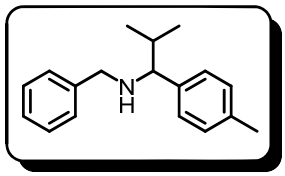
FTIR (NaCl, neat): ν 3421 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (d, J = 6.85 Hz, 3H), 0.98 (d, J = 6.70 Hz, 3H), 1.63 (br, 1H), 1.89-2.00 (m, 1H), 3.48 (d, J = 13.14 Hz 1H), 3.58 (d, J = 13.14 Hz 1H), 3.96 (d, J =

6.50 Hz, 1H) 7.06-7.12 (m, 1H), 7.19-7.34 (m, 6H), 7.47-7.55 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 140.8, 132.8, 128.9, 128.2, 128.1, 128.0, 127.3, 126.8, 125.2, 66.4, 51.7, 33.8, 19.9, 18.4 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{21}BrN$: 318.0857, found $[M+H]^+$: 318.0846.



***N*-Benzyl-2-methyl-1-*p*-tolypropan-1-amine (Table 2.2, entry 8):**

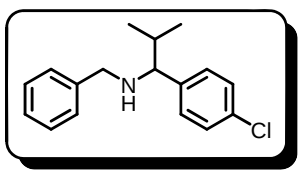
Light yellow oil; Yield: 75%; R_f = 0.63 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3424 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, J = 6.79 Hz, 3H), 0.96 (d, J = 6.67 Hz, 3H), 1.83-1.94 (m, 1H), 2.35 (s, 3H), 3.32 (d, J = 6.98 Hz, 1H), 3.46 (d, J = 13.26 Hz, 1H), 3.51 (d, J = 13.26 Hz, 1H), 7.00-7.32 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4, 139.1, 136.3, 128.7, 128.3, 128.1, 126.8, 68.3, 51.4, 34.3, 21.1, 19.7, 19.4 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{24}N$: 254.1909, found $[M+H]^+$: 254.1899.



***N*-Benzyl-1-(4-chlorophenyl)-2-methylpropan-1-amine (Table 2.2, entry 9):**

Light yellow oil; Yield: 81%; R_f = 0.62 (Ethyl acetate/Hexane 1:2);

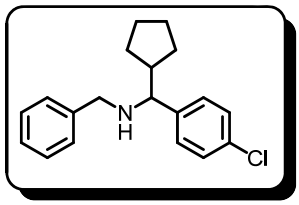
FTIR (NaCl, neat): ν 3418 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (d, J = 6.82 Hz, 3H), 0.94 (d, J = 6.70 Hz, 3H),

1.77-1.88 (m, 1H), 1.96 (s, br, 1H), 3.33 (d, J = 6.81 Hz, 1H), 3.46 (d, J = 13.38 Hz, 1H), 3.62 (d, J = 13.38 Hz, 1H), 7.21-7.32 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 140.6, 132.3, 129.5, 128.3, 128.2, 128.1, 126.8, 68.0, 51.6, 34.4, 19.5, 19.2 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{21}ClN$: 274.1363, found $[M+H]^+$: 274.1357.



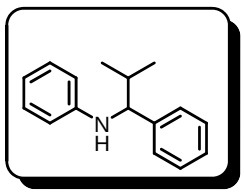
***N*-Benzyl-1-(4-chlorophenyl)-1-cyclopentylmethanamine (Table 2.2, entry 10):** Light yellow oil; Yield: 70%; R_f = 0.23 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): v 3418 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.04 (m, 1H), 1.23-1.60 (m, 6H), 1.87-1.91 (m, 1H), 2.01-2.03 (m, 1H), 2.45-2.51 (m, 1H), 3.30 (d, J = 8.95 Hz, 1H), 3.40 (d, J = 13.32 Hz, 1H), 3.60 (d, J = 13.32 Hz, 1H), 7.20-7.32 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 140.5, 132.3, 129.2, 128.3, 128.3, 128.1, 126.8, 67.3, 51.4, 47.3, 30.4, 30.2, 25.3, 25.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{23}ClN$: 300.1519, found $[M+H]^+$: 300.1515.



***N*-(2-Methyl-1-phenylpropyl)aniline (Table 2.2, entry 11):**

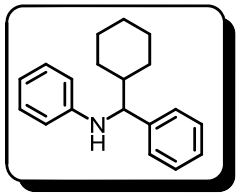
Light yellow oil; Yield: 55%; R_f = 0.20 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): v 3426 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, J = 6.84 Hz, 3H), 0.98 (d, J = 6.67 Hz, 3H), 1.43 (s, 1H), 1.95-2.09 (m, 1H), 4.12 (d, J = 5.96 Hz, 2H), 6.43-6.48 (m, 2H), 6.50-6.67 (m, 1H), 6.90-6.98 (m, 2H), 7.03-7.24 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 142.5, 129.0, 128.2, 127.1, 126.7, 117.0, 113.2, 63.7, 34.9, 19.7, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{16}H_{20}N$: 226.1596, found $[M+H]^+$: 226.1593.



***N*-[Cyclohexyl(phenyl)methyl]aniline (Table 2.2, entry 12):**

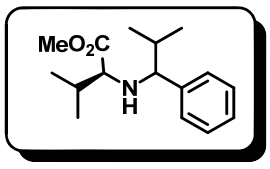
Light yellow oil; Yield: 46%; R_f = 0.75 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3418 (NH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02-1.17 (m, 5H), 1.51-1.55 (m, 1H), 1.63-1.73 (m, 4H), 1.85-1.98 (m, 1H), 4.09-4.12 (m, 2H), 6.48 (d, J = 7.71 Hz, 2H), 6.49-6.61 (m, 1H), 7.01-7.07 (m, 2H), 7.19-7.28 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 137.6, 129.1, 128.2, 127.2, 126.7, 117.0, 113.2, 63.4, 44.9, 30.3, 29.5, 26.5, 26.4, 26.4 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{24}N$: 266.1909, found $[M+H]^+$: 266.1907.



(2*S*)-Methyl 3-methyl-2-(2-methyl-1-phenylpropylamino)butanoate (Table 2.3, entry 1):

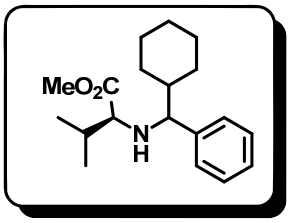
Colorless oil; Yield: 72%; R_f = 0.43 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3443 (NH), 1732 (C=O) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.73 (d, *J* = 6.84 Hz, 3H), 0.84 (d, *J* = 6.76 Hz, 3H), 0.91 (d, *J* = 6.80 Hz, 3H), 0.96 (d, *J* = 6.68 Hz, 3H), 1.76-1.94 (m, 3H), 2.72 (d, *J* = 6.40 Hz, 1H), 3.16 (d, *J* = 6.72 Hz, 1H), 3.70 (s, 3H), 7.12-7.25 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 176.4, 142.3, 128.6, 127.7, 126.9, 67.9, 64.6, 51.2, 34.7, 31.8, 19.5, 19.3, 19.3, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{16}H_{26}NO_2$: 264.1964, found $[M+H]^+$: 264.1951.



(2*S*)-methyl 2-(cyclohexyl(phenyl)methylamino)-3-methylbutanoate (Table 2.3, entry 2):

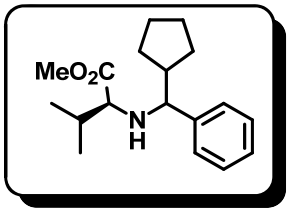
Colorless oil; Yield: 67%; R_f = 0.53 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3445 (NH), 1732 (C=O) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.83 (d, *J* = 6.76 Hz, 3H), 0.90 (d, *J* = 6.80 Hz, 3H), 0.94-1.10 (m, 3H), 1.35-1.43 (m, 2H), 1.48-1.60 (m, 2H), 1.73-1.93 (m, 5H), 2.70 (d, *J* = 6.37 Hz, 1H), 3.17 (d, *J* = 6.91 Hz, 1H), 3.70 (s, 3H), 7.19-7.27 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 176.4, 142.5, 128.6, 127.7, 126.8, 67.3, 64.6, 51.2, 44.4, 31.8, 29.9, 29.7, 26.5, 26.3, 26.2, 19.5, 18.6 ppm;

HRMS (ESI, m/z): Calcd. For $C_{19}H_{30}NO_2$: 304.2277, found $[M+H]^+$: 304.2269.



(2*S*)-methyl 2-(cyclopentyl(phenyl)methylamino)-3-methylbutanoate (Table 2.3, entry 3):

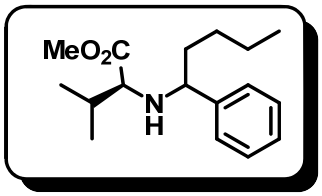
Colorless oil; Yield: 68%; R_f = 0.48 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3447 (NH), 1734 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.81 (d, *J* = 6.75 Hz, 3H), 0.88 (d, *J* = 6.75 Hz, 3H), 1.04-1.08 (m, 2H), 1.36-1.41 (m, 3H), 1.51-1.65 (m, 4H), 1.90-2.03 (m, 2H), 2.70 (d, *J* = 6.31 Hz, 1H), 3.13 (d, *J* = 8.96 Hz, 1H), 3.71 (s, 3H), 7.18-7.28 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 176.4, 143.7, 128.2, 127.9, 126.9, 67.6, 64.4, 51.2, 47.6, 31.7, 30.2, 30.2, 25.4, 25.1, 19.4, 18.5 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{28}NO_2$: 290.2120, found $[M+H]^+$: 290.2113.



(2*S*)-methyl 3-methyl-2-(1-phenylpentylamino)butanoate (Table 2.3, entry 4): Colorless oil; Yield: 32%; R_f = 0.39 (Ethyl acetate/Hexane 1:8);

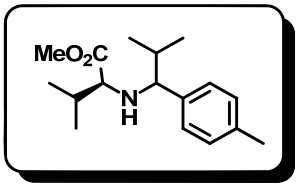
FTIR (NaCl, neat): *v* 3450 (NH), 1737 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.84 (d, *J* = 6.75 Hz, 3H), 0.84 (t, *J* = 6.74 Hz, 3H), 0.90 (d, *J* = 6.84 Hz, 3H), 1.59-1.88 (m, 7H), 2.77 (d, *J* = 6.18 Hz, 1H), 3.43 (t, *J* = 6.86 Hz, 1H), 3.71 (s, 3H), 7.21-7.33 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 176.1, 143.7, 128.2, 127.7, 127.0, 64.5, 62.1,

51.4, 38.8, 31.7, 28.3, 22.7, 19.4, 18.6, 13.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{28}NO_2$: 278.2120, found $[M+H]^+$: 278.2112.



(2*S*)-methyl 3-methyl-2-(2-methyl-1-p-tolylpropylamino)butanoate (Table 2.3, entry 5):

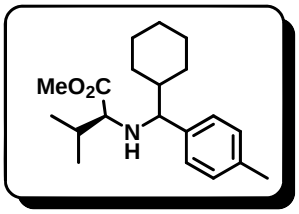
Colorless oil; Yield: 45%; R_f = 0.49 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3447 (NH), 1734 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.73 (d, J = 6.80 Hz, 3H), 0.84 (d, J = 6.80 Hz, 3H), 0.91 (d, J = 6.79 Hz, 3H), 0.95 (d, J = 6.64 Hz, 3H), 1.74-1.88 (m, 2H), 2.33 (s, 3H), 2.73 (d, J = 6.44 Hz, 1H), 3.13 (d, J = 6.69 Hz, 1H), 3.69 (s, 3H), 7.06-7.15 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 176.4, 139.2, 136.3, 128.4, 128.0, 67.6, 64.5, 51.1, 34.7, 31.8, 21.1, 19.4, 19.4, 19.2, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{28}NO_2$: 278.2120, found $[M+H]^+$: 278.2110.



(2*S*)-methyl 2-(cyclohexyl(p-tolyl)methylamino)-3-methylbutanoate (Table 2.3, entry 6):

Colorless oil; Yield: 65%; R_f = 0.40 (Ethyl acetate/Hexane 1:8);

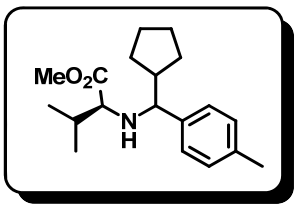
FTIR (NaCl, neat): *v* 3447 (NH), 1734 (C=O) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.82 (d, J = 6.75 Hz, 3H), 0.88 (d, J = 6.85 Hz, 3H), 1.01-1.80 (m, 8H), 1.91-1.97 (m, 1H), 2.00-2.08 (m, 1H), 2.32 (s, 3H), 2.73 (d, J = 6.25

Hz, 1H), 3.09 (d, J = 9.06 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 7.07-7.17 (m, 4H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 176.3, 140.2, 136.3, 128.6, 128.0, 67.4, 64.2, 51.2, 47.4, 31.6, 30.2, 30.0, 25.3, 25.0, 21.0, 19.2, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{20}H_{32}NO_2$: 318.2477, found $[M+H]^+$: 318.2471.



(2*S*)-methyl 2-(cyclopentyl(p-tolyl)methylamino)-3-methylbutanoate (Table 2.3, entry 7):

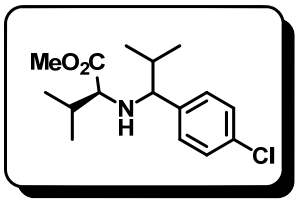
Colorless oil; Yield: 69%; R_f = 0.40 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3447 (NH), 1734 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.81 (d, J = 6.80 Hz, 3H), 0.90 (d, J = 6.76 Hz, 3H), 1.26-1.53 (m, 10H), 2.65-2.72 (m, 1H), 2.94 (d, J = 8.97 Hz, 1H), 3.32 (d, J = 10.24 Hz, 1H), 3.35 (s, 3H), 3.62 (s, 3H), 7.08-7.20 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 174.4, 173.4, 136.9, 136.9, 136.2, 134.7, 129.6, 129.0, 128.7, 128.6, 74.7, 74.3, 72.8, 70.3, 50.8, 50.7, 43.6, 42.6, 31.3, 31.3, 30.3, 29.7, 28.8, 28.6, 25.2, 25.1, 24.6, 21.1, 21.1, 20.1, 20.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{30}NO_2$: 304.2277, found $[M+H]^+$: 304.2271.



(2*S*)-methyl 2-(1-(4-chlorophenyl)-2-methylpropylamino)-3-methylbutanoate (Table 2.3,

entry 8):

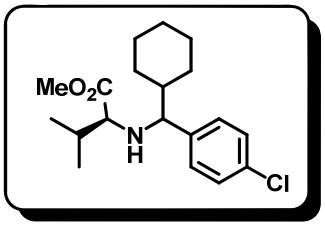
Colorless oil; Yield: 64%; R_f = 0.43 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3449 (NH), 1736 (C=O) cm^{-1};

^1H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.72 (d, J = 6.86 Hz, 3H), 0.84 (d, J = 6.80 Hz, 3H), 0.91 (d, J = 6.86 Hz, 3H), 0.94 (d, J = 6.50 Hz, 3H), 1.04-1.08 (m, 1H), 1.76-1.83 (m, 2Hz, 1H), 2.67 (d, J = 6.45 Hz, 1H), 3.15 (d, J = 6.66 Hz, 1H), 3.70 (s, 3H), 7.20-7.27 (m, 4H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (two isomers) δ 176.1, 175.6, 141.3, 140.8, 132.4, 132.3, 129.8, 129.3, 128.9, 127.9, 68.8, 67.3, 65.7, 64.6, 51.3, 51.2, 34.6, 33.6, 31.9, 31.7, 20.1, 19.5, 19.3, 19.0, 19.0, 18.9, 18.7, 18.5, 18.4 ppm;

HRMS (ESI, m/z): Calcd. For $C_{16}H_{25}ClNO_2$: 298.1574, found $[M+H]^+$: 298.1566.



(2*S*)-methyl 2-((4-chlorophenyl)(cyclohexyl)methylamino)-3-methylbutanoate (Table 2.3, entry 9):

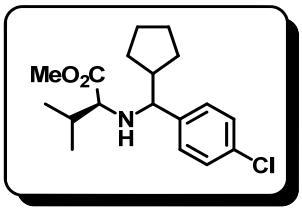
Colorless oil; Yield: 52%; R_f = 0.50 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3447 (NH), 1732 (C=O) cm^{-1};

^1H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.83 (d, J = 6.75 Hz, 3H), 0.89 (d, J = 6.80 Hz, 3H), 1.07-2.08 (m, 13H), 2.66 (d, J = 6.35 Hz, 1H), 3.15 (d, J = 6.90 Hz, 1H), 3.70 (s, 3H), 7.16-7.27 (m, 4H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 176.2, 141.0, 129.8, 129.3, 127.9, 66.7, 64.6, 51.3, 44.3, 31.7, 30.1, 29.7, 29.5, 26.4, 26.1, 19.4, 18.5 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{29}ClNO_2$: 338.1887, found $[M+H]^+$: 338.1881.



(2*S*)-methyl 2-((4-chlorophenyl)(cyclopentyl)methylamino)-3-methylbutanoate (Table 2.3, entry 10):

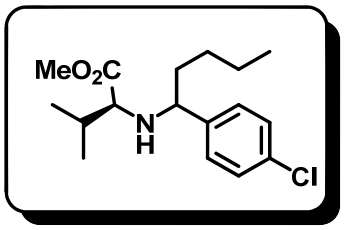
Colorless oil; Yield: 59%; R_f = 0.49 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3451 (NH), 1732 (C=O) cm^{-1};

^1H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.82 (d, J = 6.74 Hz, 3H), 0.87 (d, J = 6.76 Hz, 3H), 1.10-1.99 (m, 11H), 2.65 (d, J = 6.35 Hz, 1H), 3.11 (d, J = 8.75 Hz, 1H), 3.71 (s, 3H), 7.21-7.27 (m, 4H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 176.1, 142.2, 132.4, 129.4, 128.1, 67.0, 64.4, 51.3, 47.5, 31.6, 30.1, 29.9, 25.3, 25.0, 19.4, 18.5 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{27}ClNO_2$: 324.1730, found $[M+H]^+$: 324.1727.



(2*S*)-methyl 2-(1-(4-chlorophenyl)pentylamino)-3-methylbutanoate (Table 2.3, entry 11):

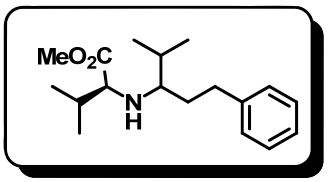
Colorless oil; Yield: 31%; R_f = 0.11 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3449 (NH), 1736 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.83 (d, J = 6.71 Hz, 3H), 0.84 (t, J = 6.56 Hz, 3H), 0.89 (d, J = 6.88 Hz, 3H), 1.52-1.89 (m, 10H), 2.68 (d, J = 6.28 Hz, 1H), 3.38 (t, J = 6.77 Hz, 1H), 3.71 (s, 3H), 7.21-7.25 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 176.2, 142.7, 132.4, 129.0, 128.3, 64.5, 61.4, 51.3, 38.9, 31.7, 28.2, 22.6, 19.4, 18.5, 13.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{27}ClNO_2$: 312.1730, found $[M+H]^+$: 312.1725.



(2*S*)-methyl 3-methyl-2-(4-methyl-1-phenylpentan-3-ylamino)butanoate (Table 2.3, entry 12):

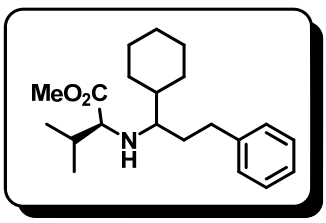
Colorless oil; Yield: 71%; R_f = 0.39 and 0.52 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): v 3449 (NH), 1736 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.83-1.00 (m, 12H), 1.56-1.84 (m, 5H), 2.21 (q, J = 5.28 Hz, 1H), 2.67 (t, J = 8.17 Hz, 2H), 3.01 (d, J = 6.52 Hz, 1H), 3.68 (s, 3H), 7.14-7.30 (m, 5H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 176.4, 143.2, 128.4, 128.3, 125.6, 65.6, 62.1, 51.3, 32.5, 32.3, 32.0, 30.1, 19.4, 18.9, 18.7, 18.1 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{30}NO_2$: 292.2277, found $[M+H]^+$: 292.2267.



(2*S*)-methyl 2-(1-cyclohexyl-3-phenylpropylamino)-3-methylbutanoate (Table 2.3, entry 13):

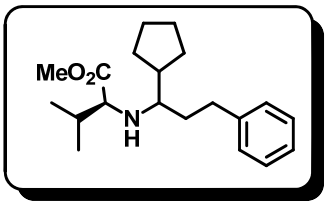
Colorless oil; Yield: 81%; R_f = 0.35 and 0.51 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3449 (NH), 1736 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.94 (d, J = 6.82 Hz, 3H), 0.98 (d, J = 6.78 Hz, 3H), 1.60-1.90 (m, 14H), 2.19-2.25 (m, 1H), 2.22 (q, J = 5.28 Hz, 1H), 2.66 (t, J = 8.10 Hz, 2H), 3.01 (d, J = 6.48 Hz, 1H), 3.68 (s, 3H), 7.14-7.29 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 176.2, 143.1, 128.3, 128.3, 125.6, 65.6, 61.5, 51.3, 40.5, 32.5, 32.1, 31.8, 29.4, 28.7, 26.6, 26.6, 26.6, 19.4, 18.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{21}H_{34}NO_2$: 332.2590, found $[M+H]^+$: 332.2581.



(2*S*)-methyl 2-(1-cyclopentyl-3-phenylpropylamino)-3-methylbutanoate (Table 2.3, entry 14):

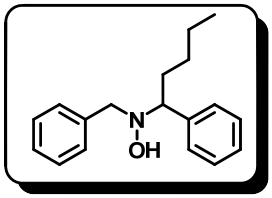
Colorless oil; Yield: 76%; R_f = 0.47 and 0.58 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3449 (NH), 1736 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.96 (d, J = 6.72 Hz, 3H), 1.00 (d, J = 6.75 Hz, 3H), 1.18-1.98 (m, 14H), 2.26-2.31 (m, 1H), 2.53-2.82 (m, 2H), 3.07 (d, J = 6.60 Hz, 1H), 3.69 (s, 3H), 7.13-7.29 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 176.2, 143.4, 128.3, 128.3, 125.5, 64.9, 60.7, 51.2, 43.1, 33.5, 32.0, 30.0, 29.6, 29.6, 25.5, 25.4, 19.5, 19.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{20}H_{32}NO_2$: 318.2433, found $[M+H]^+$: 318.2422.



***N*-Benzyl-*N*-(1-phenylpentyl)hydroxylamine (Table 2.5, entry 1):**

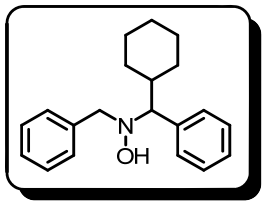
White powder; MP: 133-135 ^{o}C; Yield: 68%; R_f = 0.19 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 7.00 Hz, 3H), 1.02-1.30 (m, 4H), 1.71-1.84 (m, 1H), 2.08-2.19 (m, 1H), 3.50-3.69 (m, 3H), 5.24 (s, 1H), 7.27-7.35 (m, 10H) ppm;

^{13}C NMR (300 MHz, $CDCl_3$): δ 140.6, 138.4, 129.3, 128.9, 128.3, 128.2, 127.4, 127.1, 72.2, 61.5, 33.2, 28.5, 22.8, 14.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{24}NO$: 270.1858, found $[M+H]^{+}$: 270.1862.



***N*-Benzyl-*N*-[cyclohexyl(phenyl)methyl]hydroxylamine (Table 2.5, entry 2):**

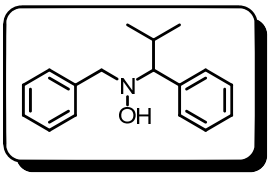
White powder; MP: 137-139 ^{o}C; Yield: 90%; R_f = 0.37 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3441 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72-1.32 (m, 6H), 1.42-1.77 (m, 3H), 2.03-2.20 (m, 2H), 3.44 (d, J = 7.99 Hz, 1H), 3.60 (dd, J = 30.39, 13.58 Hz, 2H), 4.47 (s, 1H), 7.23-7.34 (m, 10H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 138.0, 129.9, 129.0, 128.2, 127.8, 127.2, 127.0, 76.5, 61.6, 39.4, 31.2, 29.4, 26.7, 26.4, 26.2 ppm;

HRMS (ESI, m/z): Calcd. for $C_{20}H_{26}NO$: 296.2014, found $[M+H]^+$: 296.2013.



***N*-Benzyl-*N*-(2-methyl-1-phenylpropyl)hydroxylamine (Table 2.5, entry 3):**

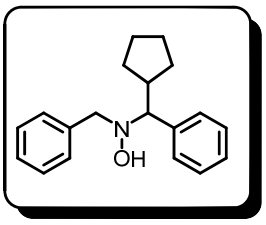
White powder; MP: 109-110 ^oC; Yield: 88%; R_f = 0.36 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 0.77 (d, J = 6.76 Hz, 3H), 1.01 (d, J = 6.64 Hz, 3H), 2.44-2.52 (m, 1H), 3.39 (d, J = 7.80 Hz, 1H), 3.61 (dd, J = 44.64, 13.57 Hz, 2H), 4.50 (s, 1H), 7.28-7.34 (m, 10H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 137.9, 129.8, 129.1, 128.2, 127.8, 127.2, 127.0, 77.4, 61.8, 29.4, 20.7, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{22}NO$: 256.1701, found $[M+H]^+$: 256.1695.



***N*-Benzyl-*N*-[cyclophentyl(phenyl)methyl]hydroxylamine (Table 2.5, entry 4):**

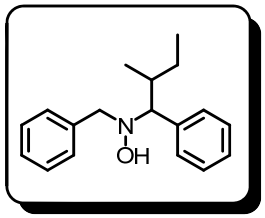
White powder; MP: 129-131 ^oC; Yield: 83%; R_f = 0.44 (Ethyl acetate/Hexane 1:4);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): δ 0.85-1.04 (m, 1H), 1.39-1.60 (m, 6H), 1.94-2.03 (m, 1H), 2.60-2.71 (m, 1H), 3.43 (d, J = 10.08 Hz, 1H), 3.59 (dd, J = 35.06, 13.40 Hz, 2H), 4.70 (s, 1H), 7.24-7.35 (m, 10H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.4, 130.0, 129.1, 128.2, 127.8, 127.3, 127.0, 75.9, 61.2, 42.2, 31.2, 30.5, 25.3, 25.1 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{24}NO$: 282.1858, found $[M+H]^+$: 282.1856.



***N*-Benzyl-*N*-(2-methyl-1-phenylbutyl)hydroxylamine (Table 2.5, entry 5):**

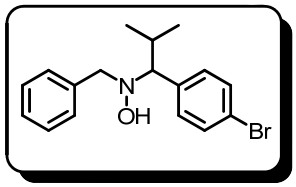
Light yellow powder; MP: 112-113 ^{o}C; Yield: 49%, 55:45 *dr*; R_f = 0.53 (Ethyl acetate/Hexane 1:4);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.75-1.04 (m, 6H), 1.44-1.71 (m, 2H), 2.19-2.32 (m, 1H), 3.43 (d, J = 8.25 Hz, 1H), 3.51-3.68 (m, 2H), 4.49 (s, 1H), 7.20-7.36 (m, 10H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 138.8, 138.1, 138.0, 129.8, 129.7, 129.1, 129.0, 128.5, 128.4, 128.2, 127.8, 127.2, 127.2, 127.0, 76.5, 75.7, 61.9, 61.8, 36.2, 35.8, 26.8, 25.1, 16.8, 14.9, 11.4 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{24}NO$: 270.1858, found $[M+H]^+$: 270.1854.



***N*-Benzyl-*N*-[1-(4-bromophenyl)-2-methylpropyl]hydroxylamine (Table 2.5, entry 6):**

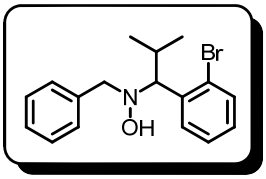
White powder; MP: 124-126 ^{o}C; Yield: 54%; R_f = 0.34 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, J = 6.75 Hz, 3H), 1.01 (d, J = 6.67 Hz, 3H), 2.38-2.49 (m, 1H), 3.33 (d, J = 7.97 Hz, 1H), 3.58 (dd, J = 26.29, 13.51 Hz, 2H), 4.53 (s, 1H), 7.19-7.31 (m, 7H), 7.46-7.48 (m, 2H) ppm;

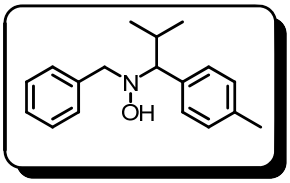
^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 137.0, 131.5, 130.9, 129.0, 128.3, 127.1, 121.2, 76.7, 61.7, 29.5, 20.6, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{21}BrNO$: 334.0807, found $[M+H]^+$: 334.0800.



***N*-Benzyl-*N*-[1-(2-bromophenyl)-2-methylpropyl]hydroxylamine (Table 2.5, entry 7):**

Light yellow powder; MP: 122-124 ^oC; Yield: 78%; R_f= 0.39 (Ethyl acetate/Hexane 1:8); FTIR (NaCl, neat): ν 3442 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (d, J = 6.78 Hz, 3H), 1.17 (d, J = 6.58 Hz, 3H), 2.36-2.48 (m, 1H), 3.42 (d, J = 13.75 Hz, 1H), 3.83 (d, J = 13.74 Hz, 1H), 4.17 (d, J = 9.03 Hz, 1H), 4.39 (s, 1H), 7.09-7.70 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 138.2, 132.7, 131.0, 129.1, 128.6, 128.2, 127.2, 127.1, 126.7, 74.5, 61.6, 31.0, 20.7, 19.2 ppm; HRMS (ESI, m/z): Calcd. for $C_{17}H_{21}BrNO$: 334.0807, found $[M+H]^+$: 334.0803.



***N*-Benzyl-*N*-(2-methyl-1-*p*-tolypropyl)hydroxylamine (Table 2.5, entry 8):**

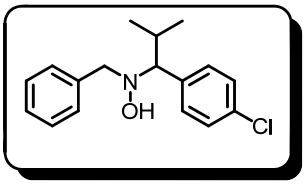
White powder; MP: 110-112 ^{o}C; Yield: 64%; R_f = 0.65 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3444 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (d, J = 6.75 Hz, 3H), 1.01 (d, J = 6.67 Hz, 3H), 2.36 (s, 3H), 2.40-2.52 (m, 1H), 3.36 (d, J = 7.81 Hz, 1H), 3.62 (dd, J = 41.38, 13.62 Hz, 2H), 4.41 (s, 1H), 7.13-7.31 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 136.7, 134.6, 129.7, 129.0, 128.5, 128.2, 126.9, 77.1, 61.7, 29.4, 21.1, 20.7, 18.7 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{24}NO$: 270.1858, found $[M+H]^+$: 270.1851.



_N_-Benzyl-_N_-[1-(4-chlorophenyl)-2-methylpropyl]hydroxylamine (Table 2.5, entry 9):

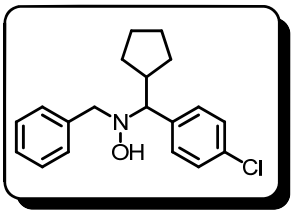
White crystal; Yield: 80%; MP: 140-142 ^{o}C; R_f = 0.66 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (d, J = 6.76 Hz, 3H), 1.02 (d, J = 6.64 Hz, 3H), 2.39-2.51 (m, 1H), 3.36 (d, J = 7.97 Hz, 1H), 3.60 (dd, J = 30.80, 13.53 Hz, 2H), 4.48 (s, 1H), 7.23-7.33 (m, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 136.5, 133.0, 131.1, 129.0, 128.3, 128.0, 127.1, 76.6, 61.8, 29.5, 20.6, 18.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{21}ClNO$: 290.1312, found $[M+H]^+$: 290.1299.



***N*-Benzyl-*N*-[(4-chlorophenyl)(cyclopentyl)methyl]hydroxylamine (Table 2.5, entry 10):**

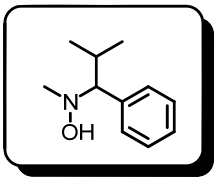
White powder; Yield: 61%; R_f = 0.36 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3448 (OH) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): δ 0.87-0.99 (m, 1H), 1.23-1.65 (m, 6H), 1.92-2.00 (m, 1H), 2.54-2.63 (m, 1H), 3.38 (d, J = 10.18 Hz, 1H), 3.56 (dd, J = 33.52, 13.35 Hz, 2H), 4.80 (s, 1H), 7.16-7.34 (m, 9H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 137.0, 133.0, 131.2, 129.1, 128.2, 128.0, 127.1, 75.1, 61.1, 42.2, 31.1, 30.0, 25.3, 25.1 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{23}ClNO$: 316.1468, found $[M+H]^+$: 316.1453.



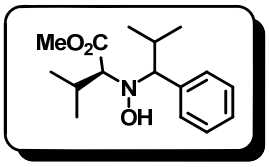
***N*-Methyl-*N*-(2-methyl-1-phenylpropyl)hydroxylamine (Table 2.5, entry 11):**

Light yellow oil; Yield: 48%; R_f = 0.14 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3442 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.78 (d, J = 6.75 Hz, 3H), 0.93 (d, J = 6.65 Hz, 3H), 2.38-2.46 (m, 1H), 2.51 (s, 3H), 3.31 (d, J = 6.48 Hz, 1H), 7.24-7.32 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3, 129.7, 127.7, 127.2, 79.5, 45.9, 29.2, 20.7, 18.2 ppm;

HRMS (ESI, m/z): Calcd. for $C_{11}H_{18}NO$: 180.1388, found $[M+H]^+$: 180.1380.



(2*S*)-Methyl 2-[hydroxy(2-methyl-1-phenylpropyl)amino]-3-methylbutanoate (Table 2.6, entry 1):

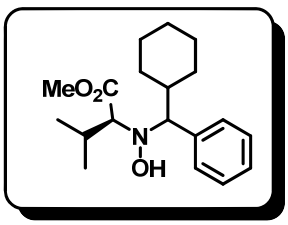
Colorless oil; Yield: 39%; R_f = 0.26 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3447 (OH), 1734 (C=O) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.69 (d, J = 7.01 Hz, 3H), 0.80 (d, J = 6.76 Hz, 3H), 0.89 (d, J = 6.80 Hz, 3H), 1.10 (d, J = 6.61 Hz, 3H), 2.30-2.36 (m, 1H), 2.60-2.65 (m, 1H), 2.94 (d, J = 9.64 Hz, 1H), 3.52 (d, J = 4.52 Hz, 1H), 3.67 (s, 3H), 5.63 (s, 1H), 7.15-7.30 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 174.7 (C), 137.4 (C), 129.4 (CH), 127.6 (CH), 127.4 (CH), 75.8 (CH), 70.6 (CH), 50.8 (CH_3), 29.3 (CH), 28.8 (CH), 20.0 (CH_3 x 2), 19.4 (CH_3), 15.9 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{16}H_{26}NO_3$: 279.1912, found $[M+H]^+$: 279.1910.



(2*S*)-methyl 2-((cyclohexyl(phenyl)methyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 2):

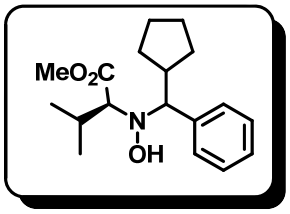
Colorless oil; Yield: 72%; R_f = 0.35 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3448 (OH), 1732 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.80 (d, J = 6.80 Hz, 3H), 0.86-0.96 (m, 2H), 1.08 (d, J = 6.61 Hz, 3H), 1.22-1.29 (m, 3H), 1.57-1.70 (m, 4H), 1.97-2.00 (m, 1H), 2.24-2.36 (m, 2H), 2.92 (d, J = 9.48 Hz, 1H), 3.52 (d, J = 4.52 Hz, 1H), 3.65 (s, 3H), 5.65 (s, 1H), 7.14-7.30 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 174.4, 138.0, 129.2, 127.5, 127.3, 75.7, 70.6, 50.7, 39.8, 30.8, 28.7, 26.7, 26.6, 26.6, 26.3, 19.9, 19.3 ppm;

HRMS (ESI, m/z): Calcd. For $C_{19}H_{30}NO_3$: 320.2226, found $[M+H]^+$: 320.2220.



(2*S*)-methyl 2-((cyclopentyl(phenyl)methyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 3):

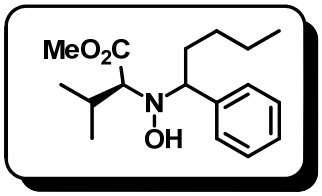
Colorless oil; Yield: 51%; R_f = 0.36 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3449 (OH), 1735 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.81 (d, J = 6.84 Hz, 3H), 1.03 (d, J = 6.68 Hz, 3H), 1.25-1.33 (m, 2H), 1.38-1.53 (m, 5H), 1.92-1.99 (m, 1H), 2.25-2.34 (m, 1H), 2.50-2.56 (m, 1H), 2.92 (d, J = 8.95 Hz, 1H), 3.61 (d, J = 7.01, 1H), 3.62 (s, 3H), 5.72 (s, 1H), 7.20-7.31 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 174.4, 139.3, 129.1, 127.9, 127.4, 75.0, 70.2, 50.8, 43.6, 31.3, 29.7, 28.7, 25.0, 24.6, 20.0, 19.1 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{28}NO_3$: 306.2069, found $[M+H]^+$: 306.2071.



(2*S*)-methyl 2-(hydroxy(1-phenylpentyl)amino)-3-methylbutanoate (Table 2.6, entry 4):

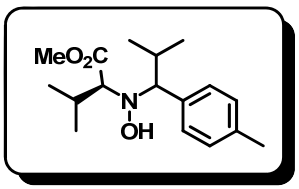
Colorless oil; Yield: 30%; R_f = 0.30 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3452 (OH), 1736 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.78 (d, *J* = 6.82 Hz, 3H), 0.79 (t, *J* = 7.33 Hz, 3H), 0.88-0.95 (m, 1H), 1.02 (d, *J* = 6.59 Hz, 3H), 1.17-1.29 (m, 3H), 1.64-1.76 (m, 1H), 2.25-2.32 (m, 2H), 2.82 (d, *J* = 9.45 Hz, 1H), 3.55-3.59 (m, 1H), 3.70 (s, 3H), 5.81 (s, 1H), 7.19-7.33 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 174.5, 141.0, 128.3, 128.2, 127.5, 71.9, 70.4, 50.9, 34.5, 28.6, 28.0, 22.7, 20.0, 19.4, 13.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{28}NO_3$: 294.2069, found $[M+H]^+$: 294.2057.



(2*S*)-methyl 2-(hydroxy(2-methyl-1-p-tolylpropyl)amino)-3-methylbutanoate (Table 2.6, entry 5):

Colorless oil; Yield: 42%; R_f = 0.25 (Ethyl acetate/Hexane 1:8);

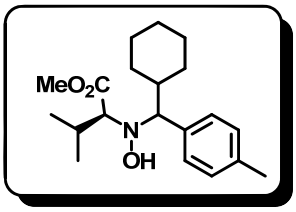
FTIR (NaCl, neat): *v* 3457 (OH), 1736 (C=O) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.68 (d, *J* = 6.94 Hz, 3H), 0.80 (d, *J* = 6.71 Hz, 3H), 0.88 (d, *J* = 6.76 Hz, 3H), 1.09 (d, *J* = 6.66 Hz, 3H), 2.29-2.34 (m, 1H), 2.34 (s, 3H), 2.56-2.62 (m, 1H), 2.95 (d, *J* = 9.66 Hz, 1H), 3.48 (d, *J* = 3.96 Hz, 1H), 3.67 (s, 3H), 5.60 (s,

1H), 7.03-7.15 (m, 4H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 174.7, 136.9, 134.3, 129.3, 128.4, 75.6, 70.6, 50.8, 29.2, 28.8, 21.1, 20.0, 20.0, 19.4, 15.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{28}NO_3$: 294.2069, found $[M+H]^+$: 294.2068.



(2*S*)-methyl 2-((cyclohexyl(p-tolyl)methyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 6):

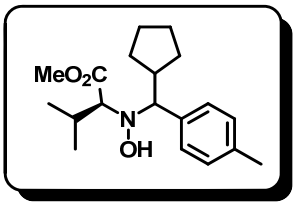
Colorless oil; Yield: 63%; R_f = 0.27 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3452 (OH), 1735 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.80 (d, J = 6.77 Hz, 3H), 0.86-0.96 (m, 2H), 1.07 (d, J = 6.60 Hz, 3H), 1.21-1.28 (m, 3H), 1.55-1.70 (m, 4H), 1.96-1.99 (m, 1H), 2.19-2.33 (m, 2H), 2.34 (s, 3H), 2.94 (d, J = 9.52 Hz, 1H), 3.48 (d, J = 4.56 Hz, 1H), 3.66 (s, 3H), 5.60 (s, 1H), 7.02-7.15 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 174.5, 136.8, 134.9, 129.1, 128.3, 75.4, 70.5, 50.7, 39.8, 30.8, 28.7, 26.7, 26.6, 26.6, 26.3, 21.1, 19.9, 19.3 ppm;

HRMS (ESI, m/z): Calcd. for $C_{20}H_{32}NO_3$: 334.2382, found $[M+H]^+$: 334.2384.



(2*S*)-methyl 2-((cyclopentyl(p-tolyl)methyl)(hydroxy)amino)-3-methylbutanoate (Table

2.6, entry 7):

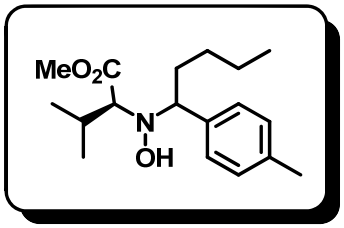
Colorless oil; Yield: 50%; R_f = 0.24 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3452 (OH), 1735 (C=O) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.81 (d, J = 6.80 Hz, 3H), 1.03 (d, J = 6.65 Hz, 3H), 1.26-1.51 (m, 7H), 1.90-1.96 (m, 1H), 2.25-2.30 (m, 1H), 2.33 (s, 3H), 2.49-2.58 (m, 1H), 2..93 (d, J = 9.01 Hz, 1H), 3.57 (d, J = 7.75 Hz, 1H), 3.62 (s, 3H), 5.66 (s, 1H), 7.05-7.10 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomers) δ 174.4, 136.9, 136.2, 129.0, 128.6, 74.7, 70.2, 50.8, 43.5, 31.3, 29.7, 28.7, 25.1, 24.6, 21.1, 20.0, 19.1 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{30}NO_3$: 320.2226, found $[M+H]^+$: 320.2219.



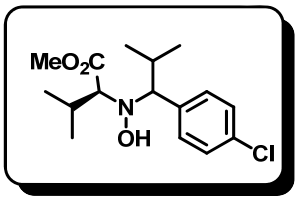
(2*S*)-methyl 2-(hydroxy(1-p-tolylpentyl)amino)-3-methylbutanoate (Table 2.6, entry 8):

Colorless oil; Yield: 34%; R_f = 0.33 (Ethyl acetate/Hexane 1:8); FTIR (NaCl, neat): ν 3459 (OH), 1736 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.80 (d, J = 7.17 Hz, 3H), 0.81 (t, J = 7.49 Hz, 3H), 1.03 (d, J = 6.61 Hz, 3H), 1.17-1.31 (m, 6H), 1.67-1.73 (m, 1H), 2.36 (s, 3H), 2.85 (d, J = 9.43 Hz, 1H), 3.52-3.57 (m, 1H), 3.72 (s, 3H), 5.82 (s, 1H), 7.08-7.28 (m, 4H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 174.6, 137.9, 137.1, 129.0, 128.0, 71.6, 70.3, 50.8, 34.5, 28.6, 28.0, 22.7, 21.1, 20.0, 19.4, 13.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{30}NO_3$: 308.2226, found $[M+H]^+$: 308.2236.



(2*S*)-methyl

2-((1-(4-chlorophenyl)-2-methylpropyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 9):

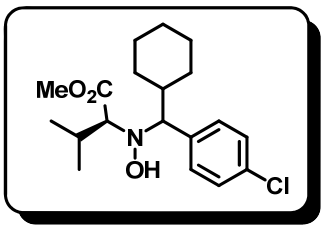
Colorless oil; Yield: 41%; R_f = 0.17 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3456 (OH), 1736 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.68 (d, J = 6.96 Hz, 3H), 0.81 (d, J = 6.76 Hz, 3H), 0.86 (d, J = 6.80 Hz, 3H), 1.08 (d, J = 6.60 Hz, 3H), 2.28-2.38 (m, 1H), 2.57-2.67 (m, 1H), 2.87 (d, J = 9.60 Hz, 1H), 3.50 (d, J = 4.48 Hz, 1H), 3.68 (s, 3H), 5.64 (s, 1H), 7.10-7.28 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 174.4, 136.0, 133.2, 130.6, 128.0, 75.1, 70.7, 51.0, 29.2, 28.8, 20.0, 19.9, 19.4, 15.8 ppm;

HRMS (ESI, m/z): Calcd. For $C_{16}H_{25}ClNO_3$: 314.1523, found $[M+H]^+$: 314.1538.



(2*S*)-methyl

2-(((4-chlorophenyl)(cyclohexyl)methyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 10):

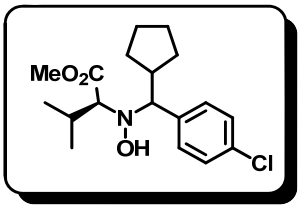
Colorless oil; Yield: 57%; R_f = 0.24(Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3447 (OH), 1736 (C=O) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.81 (d, J = 6.76 Hz, 3H), 0.86-0.96 (m, 2H), 1.06 (d, J = 6.60 Hz, 3H), 1.21-1.28 (m, 3H), 1.57-1.67 (m, 4H), 1.93-1.96 (m, 1H), 2.23-2.35 (m, 2H), 2.86 (d, J = 9.48 Hz, 1H), 3.49 (d, J = 4.56 Hz, 1H), 3.67 (s, 3H), 5.62 (s, 1H), 7.08-7.27 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 174.3, 136.7, 133.0, 130.5, 127.9, 75.0, 70.7, 50.9, 39.7, 30.8, 28.7, 26.7, 26.7, 26.6, 26.2, 19.9, 19.3 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{29}ClNO_3$: 354.1836, found $[M+H]^+$: 354.1822.



(2*S*)-methyl

2-(((4-chlorophenyl)(cyclopentyl)methyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 11):

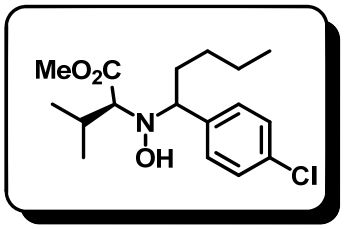
Colorless oil; Yield: 35%; R_f = 0.21 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3452 (OH), 1734 (C=O) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.82 (d, J = 6.78 Hz, 3H), 1.01 (d, J = 6.70 Hz, 3H), 1.24-1.52 (m, 7H), 1.89-1.97 (m, 1H), 2.23-2.35 (m, 1H), 2.45-2.59 (m, 1H), 2.87 (d, J = 8.85 Hz, 1H), 3.58 (d, J = 7.72 Hz, 1H), 3.64 (s, 3H), 5.67 (s, 1H), 7.14-7.28 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 174, 138.0, 133.1, 130.4, 128.1, 74.2, 70.4, 50.9, 43.5, 31.2, 29.6, 28.7, 25.0, 24.6, 20.0, 19.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{27}ClNO_3$: 340.1679, found $[M+H]^+$: 340.1670.



(2*S*)-methyl 2-((1-(4-chlorophenyl)pentyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 12):

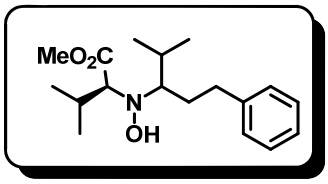
Colorless oil; Yield: 32%; R_f = 0.32 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): *v* 3459 (OH), 1736 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.79 (d, *J* = 6.73 Hz, 3H), 0.79 (t, *J* = 7.06 Hz, 3H), 0.87-0.96 (m, 2H), 1.01 (d, *J* = 6.61 Hz, 3H), 1.16-1.33 (m, 4H), 1.60-1.71 (m, 1H), 2.77 (d, *J* = 9.46 Hz, 1H), 3.53-3.57 (m, 1H), 3.71 (s, 3H), 5.78 (s, 1H), 7.10-7.32 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 174.2, 139.6, 133.1, 129.5, 128.6, 71.0, 70.5, 50.9, 34.4, 28.6, 27.9, 22.7, 19.9, 19.3, 13.9 ppm;

HRMS (ESI, m/z): Calcd. for $C_{17}H_{27}ClNO_3$: 328.1679, found $[M+H]^+$: 328.1672.



(2*S*)-methyl 2-(hydroxy(4-methyl-1-phenylpentan-3-yl)amino)-3-methylbutanoate (Table 2.6, entry 13):

Colorless oil; Yield: 52%; R_f = 0.28 (Ethyl acetate/Hexane 1:8);

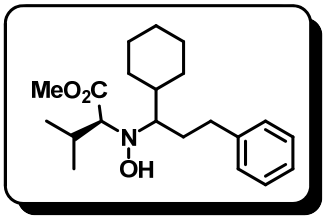
FTIR (NaCl, neat): *v* 3458 (OH), 1735 (C=O) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.89 (d, *J* = 6.97, 3H), 0.95 (d, *J* = 6.78, 3H), 0.96 (d, *J* = 6.80, 3H), 1.05 (d, *J* = 6.78, 3H), 1.18 (t, *J* = 2.63, 1H), 1.67-1.79 (m, 2H),

2.15-2.24 (m, 2H), 2.48-2.63 (m, 2H), 3.41 (d, J = 7.30, 1H), 3.73 (s, 3H), 5.10 (s, 1H), 7.18-7.31 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 173.4, 142.6, 128.2, 125.8, 125.6, 71.5, 67.7, 51.0, 34.0, 28.7, 28.5, 28.0, 20.4, 20.1, 18.2, 18.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{18}H_{30}NO_3$: 308.2226, found $[M+H]^+$: 308.2241.



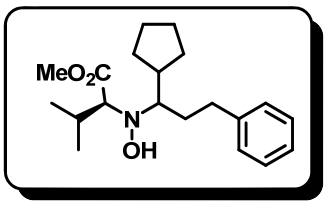
(2*S*)-methyl 2-((1-cyclohexyl-3-phenylpropyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 14):

Colorless oil; Yield: 60%; R_f = 0.31 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3458 (OH), 1736 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.95 (d, J = 6.57 Hz, 3H), 1.04 (d, J = 6.61 Hz, 3H), 1.09-1.29 (m, 6H), 1.51-1.90 (m, 8H), 2.16-2.24 (m, 1H), 2.52-2.62 (m, 1H), 2.76-2.81 (m, 1H), 3.43 (d, J = 6.75 Hz, 1H), 3.71 (s, 3H), 5.10 (s, 1H), 7.18-7.30 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 172.9, 142.3, 127.9, 127.9, 125.2, 71.4, 67.2, 50.8, 38.4, 33.7, 30.8, 29.1, 28.8, 28.1, 26.6, 26.3, 26.2, 19.8, 17.6 ppm;

HRMS (ESI, m/z): Calcd. for $C_{21}H_{34}NO_3$: 348.2539, found $[M+H]^+$: 348.2546.



(2*S*)-methyl 2-((1-cyclopentyl-3-phenylpropyl)(hydroxy)amino)-3-methylbutanoate (Table 2.6, entry 15):

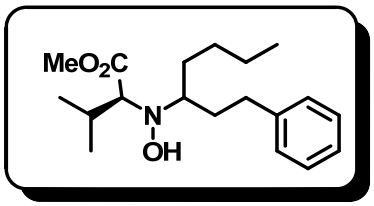
Colorless oil; Yield: 58%; R_f = 0.31 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3452 (OH), 1734 (C=O) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.95 (d, J = 6.75 Hz, 3H), 1.04 (d, J = 6.78 Hz, 3H), 1.26-1.36 (m, 2H), 1.50-1.61 (m, 4H), 1.72-1.77 (m, 3H), 1.88-2.00 (m, 1H), 2.15-2.24 (m, 2H), 2.61-2.75 (m, 2H), 2.80-2.87 (m, 1H), 3.45 (d, J = 6.72 Hz, 1H), 3.71 (s, 3H), 5.05 (s, 1H), 7.17-7.30 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 173.2, 142.7, 128.2, 128.1, 125.5, 71.8, 65.8, 51.0, 40.4, 33.3, 31.2, 30.3, 29.2, 28.3, 25.5, 24.7, 20.0, 17.7 ppm;

HRMS (ESI, m/z): Calcd. for $C_{20}H_{32}NO_3$: 334.2382, found $[M+H]^+$: 334.2387.



(2*S*)-methyl 2-(hydroxy(1-phenylheptan-3-yl)amino)-3-methylbutanoate (Table 2.6, entry 16):

Colorless oil; Yield: 40%; R_f = 0.22 (Ethyl acetate/Hexane 1:8);

FTIR (NaCl, neat): ν 3455 (OH), 1735 (C=O) cm^{-1};

^1H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.88-0.94 (m, 6H), 1.05 (d, J = 6.76 Hz, 3H), 1.25-1.35 (m, 4H), 1.51-1.95 (m, 4H), 2.14-2.23 (m, 1H), 2.57-2.69 (m, 2H), 2.72-2.82 (m, 1H), 3.34 (d, J = 7.57 Hz, 1H), 3.70 (s, 3H), 5.12 (s, 1H), 7.18-7.30 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 173.4, 142.5, 128.2, 128.2, 125.6, 71.4, 62.9, 51.1, 32.3, 31.8, 28.4, 28.4, 28.0, 22.9, 20.1, 18.2, 14.0 ppm;

HRMS (ESI, m/z): Calcd. for $C_{19}H_{32}NO_3$: 322.2382, found $[M+H]^+$: 322.2374.

2.4.4. Crystal Data and Structure Refinement

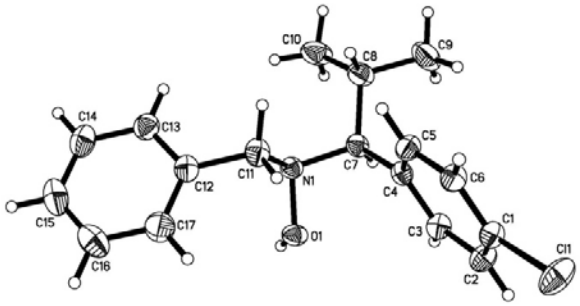


Figure I. ORTEP diagram of the single-crystal X-ray structure of compound **6i**

Table I. Crystal data and structure refinement for **6i**.

Empirical formula	$C_{17}H_{20}ClNO$	
Formula weight	289.79	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	*R*-3	
Unit cell dimensions	a = 29.6684(3) Å	α = 90°
	b = 29.6684(3) Å	β = 90°
	c = 9.2429(3) Å	γ = 120°

Volume	7045.7(2) Å^3
Z	18
Density (calculated)	1.229 Mg/m^3
Absorption coefficient	0.240 mm^{-1}
F(000)	2772
Crystal size	0.30 x 0.28 x 0.26 mm^3
Theta range for data collection	2.75 to 31.21°
Index ranges	$-43 \leq h \leq 43$, $-43 \leq k \leq 43$, $-13 \leq l \leq 13$
Reflections collected	45211
Independent reflections	5073 [R(int) = 0.0421]
Completeness to theta = 31.21°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9403 and 0.9316
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5073 / 0 / 184
Goodness-of-fit on F^2	1.077
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0415, wR_2 = 0.1074
R indices (all data)	R_1 = 0.0599, wR_2 = 0.1191
Largest diff. peak and hole	0.348 and –0.377 e.Å^{-3}

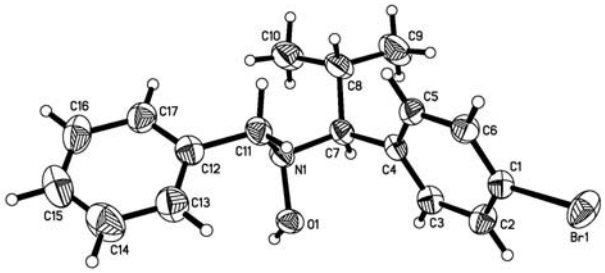


Figure II. ORTEP diagram of the single-crystal X-ray structure of compound **6f**

Table II. Crystal data and structure refinement for **6f**.

Empirical formula	$C_{17}H_{20}BrNO$	
Formula weight	334.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	*R*-3	
Unit cell dimensions	a = 29.9907(3) Å	α = 90°
	b = 29.9907(3) Å	β = 90°
	c = 9.3564(2) Å	γ = 120°
Volume	7288.07(19) Å^3	
Z	18	
Density (calculated)	1.371 Mg/m^3	
Absorption coefficient	2.534 mm^{-1}	
F(000)	3096	
Crystal size	0.30 x 0.30 x 0.22 mm^3	
Theta range for data collection	2.31 to 24.98°	
Index ranges	$-35 \le h \le 35, -35 \le k \le 35, -11 \le l \le 11$	

Reflections collected	42187
Independent reflections	2845 [R(int) = 0.0578]
Completeness to theta = 24.98	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6056 and 0.5169
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2845 / 0 / 184
Goodness-of-fit on F^2	1.184
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0589, wR_2 = 0.1666
R indices (all data)	R_1 = 0.0747, wR_2 = 0.1732
Largest diff. peak and hole	2.235 and –0.660 e.Å^{-3}

CHAPTER 3

Zn/$InCl_3$-Mediated Pinacol Cross-Coupling Reactions of Aldehydes with α,β-Unsaturated Ketones in Aqueous Media

Chapter 3. $Zn/InCl_3$-Mediated Pinacol Cross-Coupling Reactions of Aldehydes with *α,β*-Unsaturated Ketones in Aqueous Media

3.1 Introduction

The Pinacol coupling reaction,[63] although discovered in 1859,[64] still finds many applications in the diastereoselective synthesis of vicinal diols, which can be used as intermediates for the construction of biologically important natural product skeletons.[65]

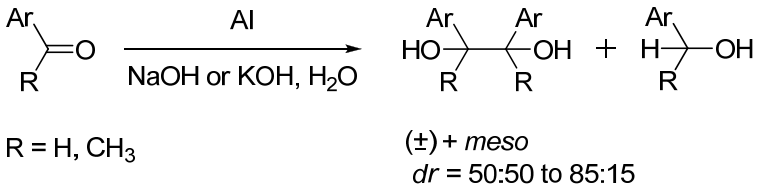
3.1.1 Recent Pinacol Homo-Coupling of Carbonyl Compounds in Aqueous Media

Pinacol coupling of carbonyl compounds is an important reaction for the formation of 1,2-diols and has received considerable attention. The metal used can be Li, Na, Ca, In, Zn, Sm and Al among others.[66] The reaction media for the metal-mediated reductions can be either aprotic or protic organic solvents. Chemically, this is quite understandable. The reactive metals such as Li and Na are far too dangerous when contacted with water, whereas less reactive metals such as Mg, Ca, and Al often form water-insoluble oxides. The recent

[63] For the reviews, see: (a) Khan, B. E.; Rieke, R. D. *Chem. Rev.* **1988**, *88*, 733; (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.
[64] Fittig, R. *Justus Leibigs Ann. Chem.* **1859**, *110*, 23.
[65] (a) Robertson, G. M. in *Comprehensive Organic Synthesis*, ed. Trost, B. M. and Fleming, I., Pergamon, New York, 1991, vol. *3*, p. 563; (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61; (c) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 159.
[66] (a) Zhang, W. C.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 3230; *J. Chem. Soc., Perkin Trans. 1* **1998**, 3131 and references in both; (b) Rieke, R. D.; Kim, S. H. *J. Org. Chem.* **1998**, *63*, 5235 and references therein; (c) Li, C. J.; Meng, Y.; Yi, X. H.; Ma, J.; Chan, T. H. *J. Org. Chem.* **1997**, *62*, 8632 and reference therein; (d) Wang, L.; Sun, X.; Zhang, Y. *J. Chem. Res. Synop.* **1998**, 336 and reference therein.

interest in green chemistry[67] has posed new challenges for organic synthesis to source for new reaction conditions which will reduce the emission of volatile organic solvents and avoid the use of hazardous toxic chemicals. With regards to that, organic reactions in aqueous media have attracted considerable recent interest because water is considered to be a safe and environmentally benign solvent. Most of the reported pinacol coupling reactions focused on homo-coupling, and in particular, several groups have investigated the pinacol homo-coupling of carbonyl compounds in aqueous media.

In 1999, Bhar and Toma reported the Al-mediated pinacol homo-coupling of aromatic aldehydes and ketones leading to 1,2-diols in water (Scheme 3.1).[68] This reaction could proceed under environmentally friendly conditions with high yield and good diastereoselectivity in the presence of aqueous sodium or potassium hydroxide. Diaryl ketones have been found to be unreactive under the present conditions. Moreover, the aluminum recovered after the reaction could be re-used after washing and drying.



Scheme 3.1

In 2000, Chan. *et al.* demonstrated that metal fluoride salts could activate aluminum in water to react with carbonyl compounds to give the pinacol homo-coupling products accompanied by reduced alcohols (Scheme 3.2).[69] The metal ion of the fluoride salt was found to play an important role in controlling the chemoselectivity and stereoselectivity of the reaction.

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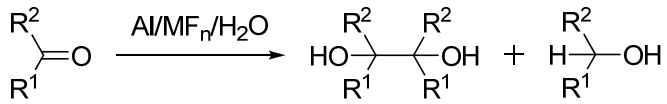
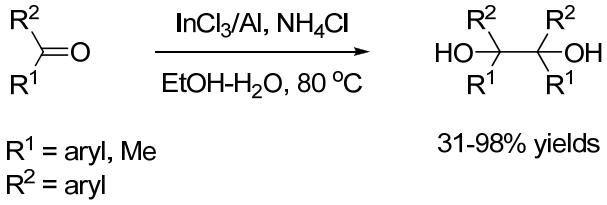
[67] See, for example: Anastas, P.; Williamson, T., Eds. *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Oxford University Press: New York, **1998**.
[68] (a) Bhar, S.; Panja, C. *Green Chem.* **1999**, 253; (b) Mecarova, M.; Toma, S. *Green Chem.* **1999**, 257.
[69] Li, L. H.; Chan, T. H. *Org. Lett.* **2000**, *2*, 1129.



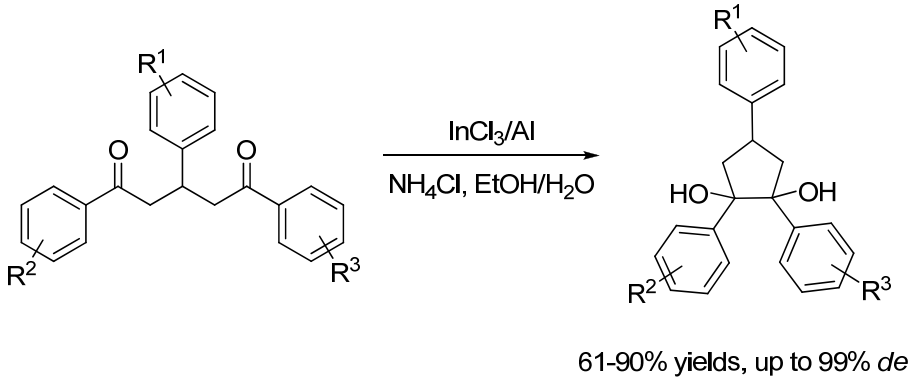
Scheme 3.2

$InCl_3$/Al reagent was employed for the pinacol homo-coupling reactions of benzophenones, benzaldehydes, and acetophenones in aqueous media successfully, in which various 1,2-diols were obtained in moderate to good yields (Scheme 3.3).[70] However, the pinacol coupling of aliphatic ketone was not amenable to this reaction.



Scheme 3.3

This $InCl_3$/Al system was also applicable for the intramolecular pinacol coupling of aromatic 1,5-diketones (Scheme 3.4).[71]

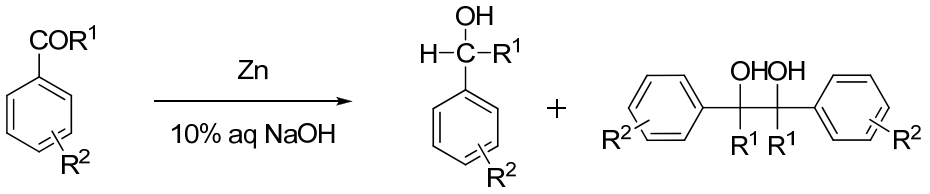


Scheme 3.4

Zinc was also a popular reagent for the pinacol coupling in aqueous media. The first pinacol homo-coupling in aqueous media using $Zn/ZnCl_2$ was reported by Toda *et al*. in the

[70] Wang, C. Y.; Pan, Y. J.; Wu, A. X. *Tetrahedron* **2007**, *63*, 429.
[71] Chen, Y. H.; Wan, J. P.; Wang, C. Y.; Sun, C. R. *Molecules*, **2008**, *13*, 2652.

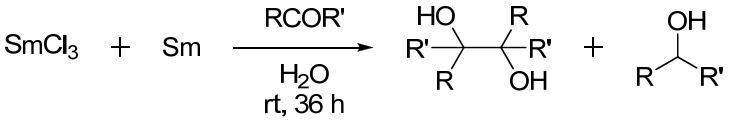
year 1990.[72] Later Tsukinoki reported that treatment of aromatic carbonyl compounds with Zn powder in 10% aq NaOH solution without using any organic solvents afforded the corresponding 1,2-diols in good yields under mild reaction conditions (Scheme 3.5).[73]



	yield	*dl*/*meso*		yield	*dl*/*meso*
1, R^1 = H, R^2 = H	82%	53:47	6, R^1 = H, R^2 = 3-OCH_3	81%	52:48
2, R^1 = H, R^2 = 2-CH_3	68%	59:41	7, R^1 = H, R^2 = 4-OCH_3	78%	75:25
3, R^1 = H, R^2 = 3-CH_3	81%	50:50	8, R^1 = H, R^2 = 4-F	81%	50:50
4, R^1 = H, R^2 = 4-CH_3	82%	50:50	9, R^1 = CH_3, R^2 = H	77%	58:42
5, R^1 = H, R^2 =2-OCH_3	67%	49:51			

Scheme 3.5

$SmCl_3$/Sm was also investigated for the pinacol coupling reaction in water to form various 1,2 diols. Various aldehydes and ketones were screened for this reaction (Scheme 3.6).[74]



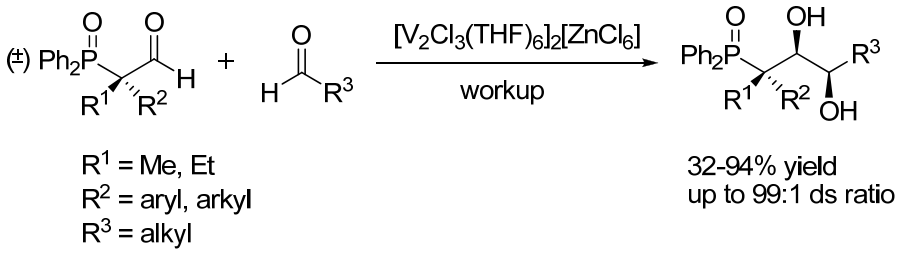
1, R = Ph,	R' = H	81% yield 52:48 (*dl*/*meso*)
2, R = 4-$MeOC_6H_4$,	R' = H	75% yield 52:48 (*dl*/*meso*)
3, R = 4-$CF_3C_6H_4$,	R' = H	83% yield 56:44 (*dl*/*meso*)
4, R = 4-ClC_6H_4,	R' = H	71% yield 56:44 (*dl*/*meso*)
5, R = Ph,	R' = CH_3	75% yield 54:46 (*dl*/*meso*)

Scheme 3.6

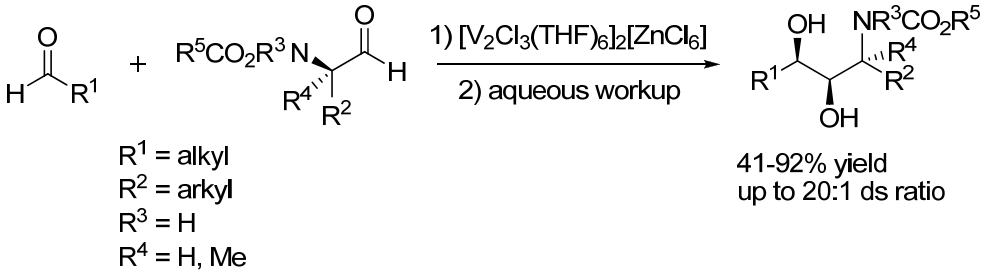
[72] Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1990**, *55*, 2981.
[73] Tsukinoki, T.; Kawaji, T.; Hashimoto, I.; Mataka, S.; Tashiro, M.; *Chem. Lett.* **1997**, 235.
[74] Matsukawa, S.; Hinakubo, Y. *Org. Lett.* **2003**, *5*, 1221.

3.1.2 Recent Pinacol Cross-Coupling of Aldehydes and Carbonyl Compounds

In 1990, Pedersen *et al.* reported the first efficient and stereoselective method for coupling two different, yet electronically similar aldehydes, employing the easily prepared vanadium(II) reagent followed by an aqueous workup (Scheme 3.7).[75] Subsequently, they reported a new route to 3-amino-1,2-diols employing such aldehydes and applied the method to the synthesis of two amino sugars.[76] According to their previous work, they applied the vanadium(II) reagent for 2-[*N*-(alkoxycarbonyl)amino] aldehydes cross-coupling with aliphatic aldehydes (Scheme 3.8).[77] In most instances, the reaction gives a good yield of one cross-coupling product, the *syn,syn* diastereomer.



Scheme 3.7

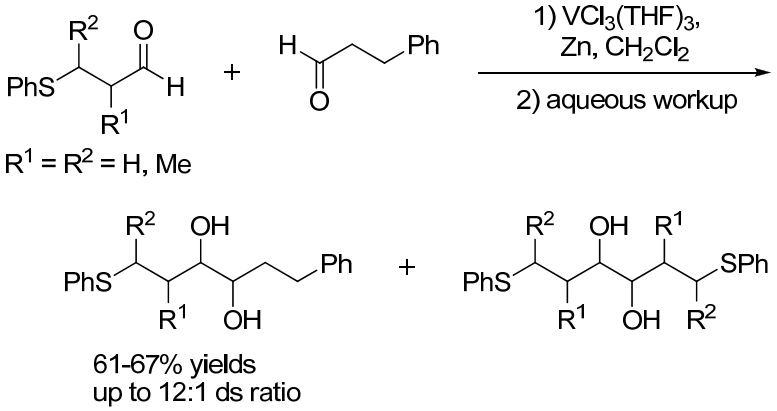


Scheme 3.8

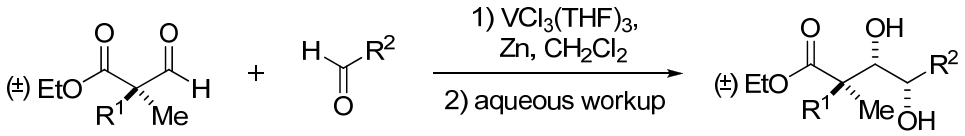
They also described the pinacol coupling reactions of aldehydes bearing sulfide and

[75] Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 5924.
[76] Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 4506.
[77] Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.

sulfone groups (Scheme 3.9). [78] The pinacol cross-coupling of ethyl 2-alkyl-2-formylpropionates with non-chelating aldehydes could be carried out smoothly in CH_2Cl_2 and afforded the corresponding products in moderate yields after aqueous workup (Scheme 3.10).[79]

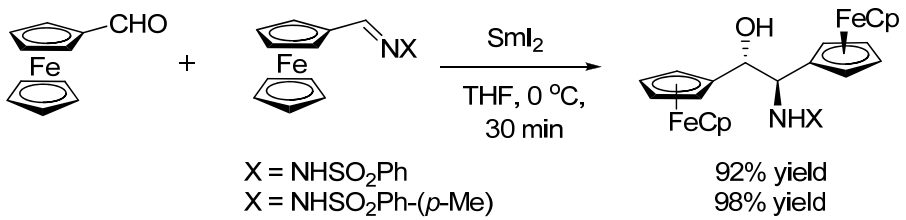


Scheme 3.9



Scheme 3.10

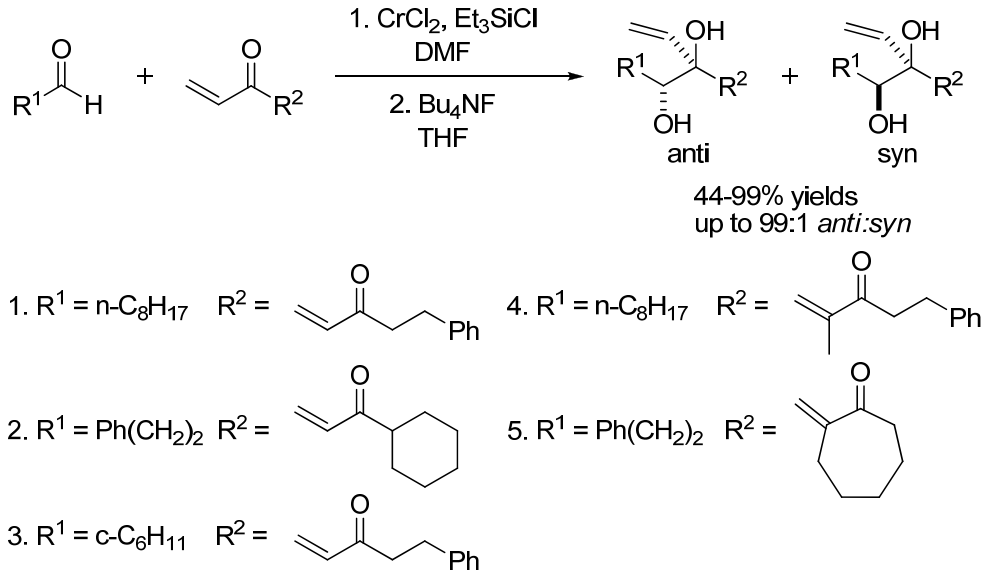
In 2000, Uemura and his coworkers reported the enantioselective synthesis of *β*-amino alcohols by samarium iodide-mediated cross-coupling of planar chiral *N*-sulfonyl ferrocenylideneamine with carboxaldehydes (Scheme 3.11). [80] It was found that an electron-withdrawing *N*-phenylsulfonyl ferrocenylideneamine was critical for the effective cross-coupling with aldehyde among various *N*-substituents studied.



[78] Kraynack E. A.; Pedersen S. F. *J. Org. Chem.* **1993**, *58*, 6114.
[79] Kang, M.; Park, J.; Pedersen, S. F. *Synlett*, **1997**, 41
[80] Taniguchi, N.; Uemura, M. *J. Am. Chem. Soc.* **2000**, *122*, 8310.

Scheme 3.11

Takai *et al.* reported the pinacol cross-coupling reaction between *α,β*-unsaturated ketones and aldehydes to form various 1,2-diols by chromium(II) and Et_3SiCl (Scheme 3.12).[81] The reaction was promoted by a one-electron transfer from chromium(II) proceed with *α,β*-unsaturated ketones and aldehydes. Substituents on the C-C double bond of the enones slow down the reaction. Furthermore, it was found that the *anti/syn* ratio was influenced by the reaction temperature dramatically.



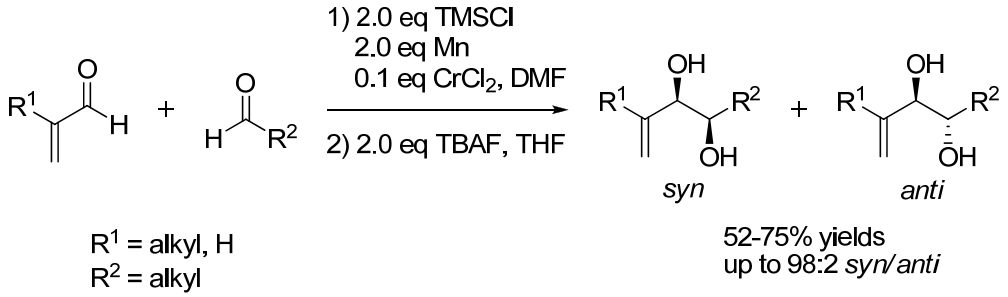
Scheme 3.12

Chromium(II) was also employed by Groth's group for the pinacol cross-coupling reaction from 2002. The reaction could be carried out using 10 mol% of $CrCl_2$ as catalyst, where acroleins and *α,β*-unsaturated ketones were coupled with aliphatic aldehydes to afford substituted 1,2-diols using manganese powder as reducing agent and TMSCl as scavenger (Scheme 3.13).[82] Later, they also applied this system to the intramolecular pinacol

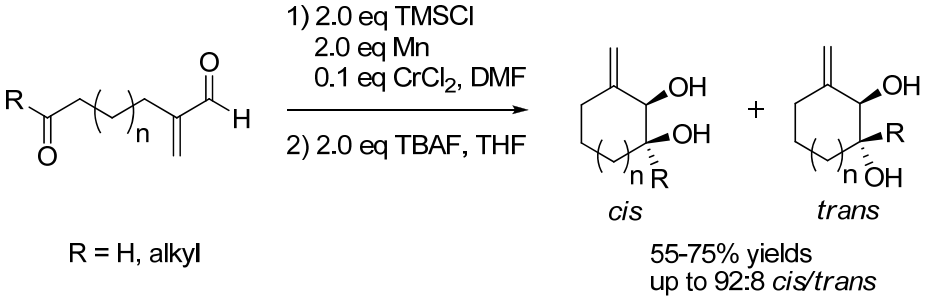
[81] (a) Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 1116. (b) Takai, K.; Morita, R.; Matsushita, H.; Toratsu, C. *Chirality*, **2003**, *15*, 17.

[82] (a) Jung, M.; Groth, U. *Synlett* **2002**, 2015. (b) Groth, U.; Jung, M.; Vogel, T. *Chem. Eur. J.* **2005**, *11*, 3127. (c) Fischer, S.; Groth, U.; Jung, M.; Lindenmaier, M.; Vogel, T. *Tetrahedron Lett.* **2005**, *46*, 6679.

cross-coupling reactions (Scheme 3.14).[83]



Scheme 3.13



Scheme 3.14

The previous reports on pinacol cross-coupling of aldehydes and α,β-unsaturated ketones were mainly carried out in organic solvents. Most of the methods using toxic and expensive $CrCl_2$ is mainly limited to aliphatic aldehydes and the reactions have to carried out under strictly anhydrous conditions. If the reaction can be developed to proceed in water with the elimination of the above limitations, its applicability will be greatly enhanced.

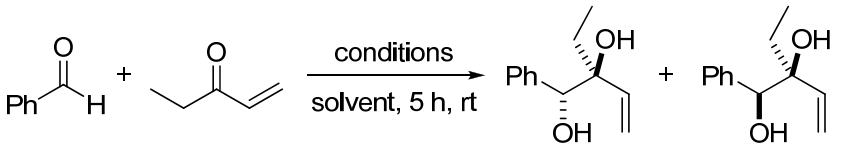
In conjunction with our efforts to develop organic transformations in aqueous media, we think if the pinacol cross-coupling can be proceed in aqueous media using less toxic metal, zinc, as the promoter, its applicability will be largely extended.

3.2 Results and Discussion

[83] Groth, U.; Jung M.; Vogel T. *Synlett* **2004**, 1054.

Initially, we examined the effect of different metallic coreductants and solvents on the pinacol cross-coupling of benzaldehyde (**8**) and ethyl vinyl ketone (**9**) at room temperature. The results are summarized in Table 3.1.

Table 3.1. Optimization of reaction conditions using benzaldehyde **8** and ethyl vinyl ketone **9**[a]



8 **9** **10**

entry	conditions	solvent	yield (%)[b] *anti*:*syn*[c]
1	$In/InCl_3$	H_2O/THF	<10[d]
2	$Al/InCl_3$	H_2O/THF	Trace
3	$Mg/InCl_3$	H_2O/THF	0
4	$Fe/InCl_3$	H_2O/THF	0
5	$Sn/InCl_3$	H_2O/THF	0
6	**$Zn/InCl_3$**	**H_2O/THF**	**80 (49:51)**
7	$Zn/ZnCl_2$	H_2O/THF	72 (48:52)
8	$Zn/In(OTf)_3$	H_2O/THF	37 (46:54)
9	$Zn/AuCl(PPh_3)$	H_2O/THF	42 (46:54)
10	Zn	H_2O/THF	21 (50:50)
11	$InCl_3$	H_2O/THF	0
12	$Zn/InCl_3$	H_2O	55 (49:51)
13	$Zn/InCl_3$	THF	18 (49:51)
14	$Zn/InCl_3$	CH_3CN	Trace
15	$Zn/InCl_3$	Hexane	Trace

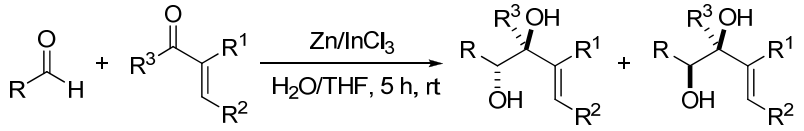
[a] The reaction was carried out at rt for 5 h using Zn (1 mmol), $InCl_3$ (0.05 mmol), **8** (0.5 mmol), **9** (1 mmol), H_2O (5 mL) and THF (5 mL). [b] Isolated yield. [c] Diastereoselectivity was determined by isolation and/or ^1H NMR analysis. [d] β,γ-Unsaturated ketone was obtained as the major product as reported previously.[84]

[84] (a) Kang, S.; Jang, T. S.; Keum, G.; Kang, S. B.; Han, S. Y.; Kim, Y. *Org. Lett.* **2000**, *2*, 3615–3617. (b) Ohe, T.; Ohse, T.; Mori, K.; Ohtaka, S.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1823–1827.

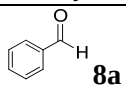
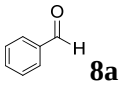
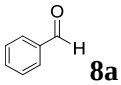
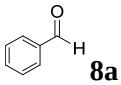
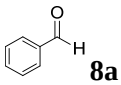
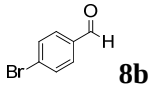
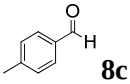
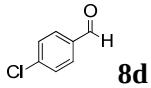
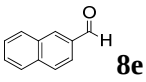
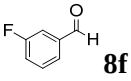
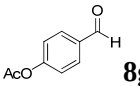
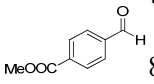
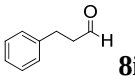
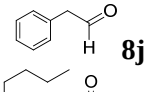
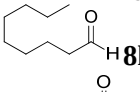
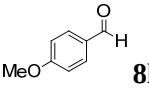
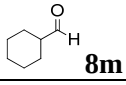
As shown in Table 3.1, among the different metals investigated, Zn/$InCl_3$ was observed to be an effective system for the pinacol coupling reaction of **8** and **9** in aqueous medium. The reaction proceeded efficiently to furnish the corresponding 2-ethyl-1-phenylbut-3-ene-1,2-diol (**10**) in 80% yield (Table 3.1, entry 6). When other metals such as In, Al, Mg, Fe, and Sn were used, poor yields or no cross-coupled 1,2-diol product was observed (Table 3.1, entries 1-5). It is important to note that the use of metal (*i.e.*, zinc) is indispensable for the pinacol coupling reaction; without it, no desired product was obtained (Table 3.1, entry 11). It is also worth noting that without the use of $InCl_3$, the reaction using Zn proceeded sluggishly to give the desired product in lower yield (Table 3.1, entry 10). Other salts were also screened for this reaction, such as $ZnCl_2$, $In(OTf)_3$, and $AuCl(PPh_3)$. However, lower yields were generated compared to $InCl_3$ (Table 3.1, entries 7-9). It was also gratifying to find that a better yield could be obtained when H_2O/THF (1:1) was used as cosolvent compared to pure H_2O, THF, or other organic solvents (Table 3.1, entries 12-15).

With the optimized conditions in hand, the generality of the pinacol cross-coupling reaction using a wide variety of α,β-unsaturated ketones and aldehydes were next examined. The results are summarized in Table 3.2.

Table 3.2. Pinacol cross-coupling reaction using various aldehydes and *α,β*-unsaturated ketones[a]



8a-m **9a-e** **10a-q**

entry	aldehyde	ketone	product	yield (%)[b]	*anti:syn*[c]
1	 **8a**	 **9a**	**10a**	55	61:39
2	 **8a**	 **9b**	**10b**	62	44:56
3	 **8a**	 **9c**	**10c**	76	42:58
4	 **8a**	 **9d**	**10d**	30	57:43
5	 **8a**	 **9e**	**10e**	80	49:51
6	 **8b**	**9e**	**10f**	70	36:64
7	 **8c**	**9e**	**10g**	76	47:53
8	 **8d**	**9e**	**10h**	82	30:70
9	 **8e**	**9e**	**10i**	59	16:84
10	 **8f**	**9e**	**10j**	75	39:61
11	 **8g**	**9e**	**10k**	85	40:60
12	 **8h**	**9e**	**10l**	63	20:80
13	 **8i**	**9e**	**10m**	51 (56)[d]	90:10[e]
14	 **8j**	**9e**	**10n**	48 (52)[d]	83:17
15	 **8k**	**9e**	**10o**	31 (41)[d]	93:7
16	 **8l**	**9e**	**10p**	30	58:42
17	 **8m**	**9e**	**10q**	22	85:15

[a] The reaction was carried out at rt for 5 h using Zn (1 mmol), $InCl_3$ (0.05 mmol),

aldehyde (0.5 mmol), α,β–unsaturated ketone (1 mmol), H_2O (5 mL) and THF (5 mL).[b] Isolated yield. [c] Diastereoselectivity was determined by isolation and/or ^1H NMR analysis. [d] Using $InBr_3$ instead of $InCl_3$ with the similar diastereoselectivity. [e] The *anti*:*syn* ratio is 65:35 when the temperature is 75 °C.

As shown in Table 3.2, $Zn/InCl_3$ efficiently mediated the pinacol cross-coupling reactions of various aldehydes and α,β-unsaturated ketones in H_2O/THF at room temperature to afford the corresponding 1,2-diols in moderate to good yields. It is gratifying to find that when aliphatic aldehyde **8i** was used as substrate, the reaction also proceeded efficiently with **9e** to furnish the desired product **10m** in moderate yield with high diastereoselectivity (Table 3.2, entry 13). However, when using long chain substitute aldehyde, nonanal, the reaction proceeded sluggishly to furnish the desired product **10o** in 31% yield (Table 3.2, entry 15). It was also found that the yields for the aliphatic aldehydes could be enhanced by using $InBr_3$ instead of $InCl_3$ (Table 3.2, entries 13-15). When the carbonyl compound was replaced with 1-cyclopentenylethanone, the coupling reaction also proceeded efficiently to afford the corresponding 1,2-diol **10b** in 62% yield (Table 3.2, entry 2). It was also found that the reaction was applicable to the benzaldehyde and acrolein despite in low yield (Table 3.2, entry 4). Similar to Takai's report, the *syn:anti* selectivity was affected by the reaction temperature (Table 3.2, entry 13). 2-Naphthaldehyde was also found to be suitable for this reaction (Table 3.2, entry 9).

The structure of compound **10e** (*syn* structure) was further confirmed by a single-crystal X-ray diffraction analysis (Figure 3.1).[85]

[85] Crystallographic data (including structure factors) for compound **10e** (CCDC 716671) have been deposited with the Cambridge Crystallographic Data Centre. See the Supporting Information for details.

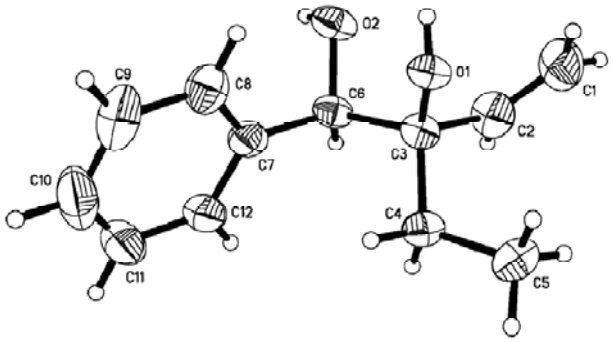
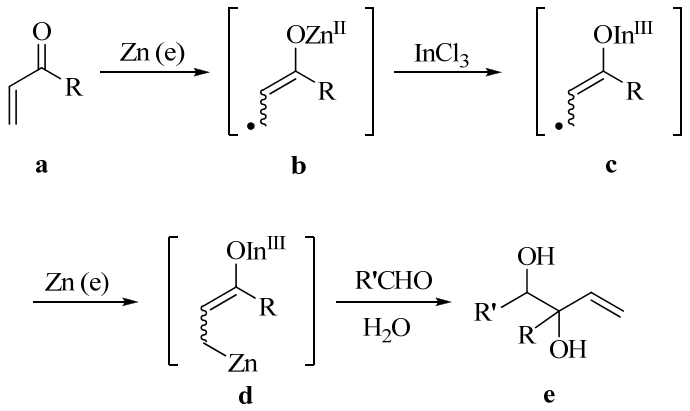


Figure 3.1. ORTEP diagram of the single-crystal X-ray structure of compound **10e** (*syn* structure)

With the confirmed *syn* crystal structure product **10e**, we get the pure NMR data. The ratio of aromatic substitute *syn* and *anti* products were determined by isolation and/or ^{1}H NMR-spectroscopy. For aliphatic substitute products (for example **10n**), we further use it to react with 3-methyl benzene boronic acid to obtain product **10np**. Determination of the *syn*/*anti* isomer mixture is carried out by Noesy NMR analysis of **10np**. (see supporting information).

A possible mechanism is proposed as shown in Scheme 3.15. The reaction is initiated by a single-electron transfer from zinc to the *α,β*-unsaturated ketone to form a radical enolate anion **b**. Fast trapping of the oxygen-metal bond in the radical enolate anion **b** by $InCl_3$ furnishes the *γ*-In(III)-substituted allylic radical **c**. The radical **c** is further reduced by zinc to obtain the corresponding allylic zinc species **d**. Finally, coupling of the *γ*-In(III)-substituted allylic zinc species **d** with an aldehyde followed by quenching of the resulting 1,2-diolate with water generates the desired product **e**.

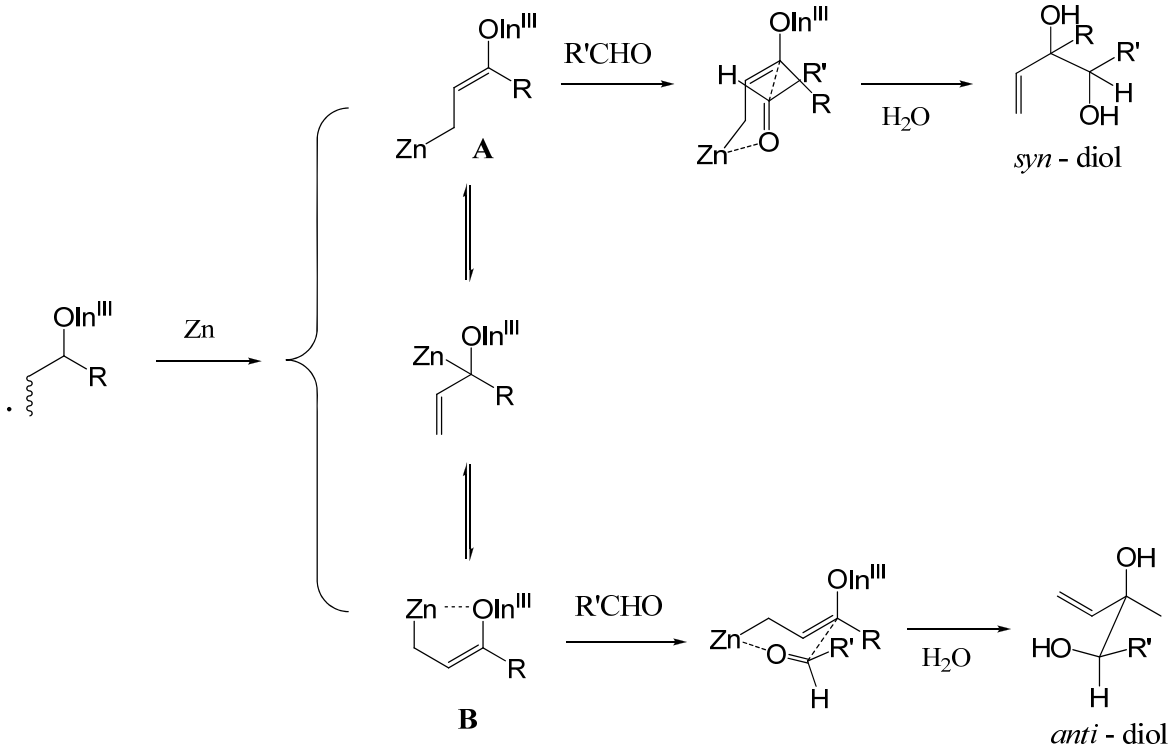


Scheme 3.15

A visual diagrammatic was also proposed for the reaction to explain the *syn*/*anti* selectivity for the two series of compounds. The addition of allylic zinc reagents to carbonyl compounds usually proceeds via a six-membered transition state with a chair form, and the diastereoselectivity reflects the configuration of the allylic zinc species (Scheme 3.16). In the case of allylic zinc species with a *γ*-indium group, the equilibrium between intermediate **A** and **B** is more quickly established than *γ*,*γ*-dialkyl-substituted allylic species.[86] There are two possible reasons that account for the temperature dependence. One is a shift in the equilibrium from **A** and **B** by increasing the temperature. The other is that the addition rate of **A** to aldehydes could be increased more by temperature than that of **B**.[87] The mechanism also suggests that the equilibrium between **A** and **B** shifts to the *trans* isomer **A** when R' becomes bulkier. For example, the proportion of *syn*-diol was increased in the case of 2-naphthaldehyde (Table 3.2, entry 9) as expected.

[86] (a) Jubert, C.; Nowotny, S.; Kornemann, D.; Antes, I.; Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 6384-6386; (b) Nowotny, S.; Tucker, C. E.; Jubert, C.; Knochel, P. *J. Org. Chem.* **1995**, *60*, 2762-2772.

[87] For the temperature dependence of reaction rates, see: (a) Otera, J.; Sato, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201-3204; (b) Sakai, T.; Kawabata, I.; Kishimoto, T.; Ema, T.; Utaka, M. *J. Org. Chem.* **1997**, *62*, 4906-4907.



Scheme 3.16

3.3 Conclusion

In summary, an efficient pinacol cross-coupling reaction of aldehydes with *α,β*-unsaturated ketones promoted by Zn/$InCl_3$ in aqueous media was developed. The mild reaction condition provides an atom-economical and straightforward access to a wide variety of 1,2-diols. Synthetic applications of the reaction to an intramolecular-type pinacol cross-coupling reaction, as well as insight into its detailed mechanism, are currently in progress.

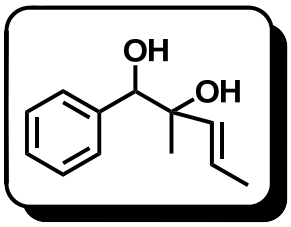
3.4 Supporting Information

3.4.1 Experimental Procedure

General procedure for the pinacol cross-coupling reaction

To a 10 mL round-bottomed flask was added water (5 mL), tetrahydrofuran (5 mL), aldehyde (0.5 mmol), *α,β*–unsaturated ketone (1 mmol), zinc (1 mmol) and indium trichloride (0.05 mmol) sequentially, then it was stirred vigorously at room temperature for 5 hours. After the reaction was completed, 2 mL HCl (1 M) was added, and then it was extracted using diethyl ether (20 mL x 3), washed with brine, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under *vacuo* to give the residue. It was subjected to silica gel column chromatography using ethyl acetate and hexane as eluent to afford the desired product.

3.4.2 Spectroscopic Data of Products



(*E*)-2-Methyl-1-phenylpent-3-ene-1,2-diol (Table 3.2, entry 1):

White solid; Yield: 55%; MP: 55-57 ^{o}C; R_f = 0.25 and 0.29 (Ethyl acetate/Hexane 1:2);

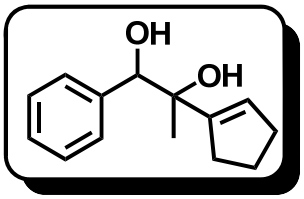
FTIR (NaCl, neat): *v* 3422 (OH) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (two isomers) *δ* 1.22, (s, 3H), 1.26 (s), 1.68 (d, *J* = 6.32 Hz, 3H), 1.71 (d, *J* = 6.40 Hz), 2.65 (br, 2H), 4.50, (s, 1H), 4.53 (s), 5.48 (d, *J* = 15.70 Hz, 1H),

5.58-5.66 (m, 1H), 5.69-5.75 (m), 7.25-7.35 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 139.8, 139.5 (C), 135.1, (CH), 132.9 (CH), 127.8, 127.7 (CH), 127.7, 127.6 (CH), 125.8, 125.3 (CH), 80.7, 79.9(CH), 75.3, 75.3 (C), 22.8, 22.7 (CH_3), 17.8, 17.4 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{12}H_{17}O_2$: 193.1229, found $[M+H]^+$: 193.1227.



2-Cyclopentenyl-1-phenylpropane-1,2-diol (Table 3.2, entry 2):

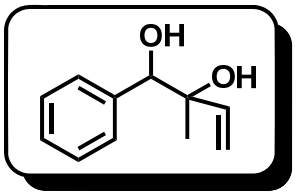
White solid; MP: 72-74 ^oC; Yield: 62%; R_f = 0.29 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3433 (OH) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (two isomers) δ 1.36 (s, 3H), 1.11 (s), 1.74-2.39 (m, 6H), 2.63 (br, 2H), 4.61 (s, 1H), 4.65 (s), 5.48 (t, J = 2.04 Hz, 1H), 5.69 (t, J = 1.96 Hz), 7.25-7.35 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 148.1, 147.1 (C), 139.8, 139.4 (C), 127.8, 127.8 (CH), 127.7, 127.7 (CH), 127.6, 127.4, (CH), 127.0, 126.9 (CH), 79.1, 78.0 (CH), 75.9, 75.9 (C), 32.7, 32.4 (CH_2), 32.4, 32.4 (CH_3), 24.1, 23.7 (CH_2), 23.6, 22.7 (CH_2) ppm;

HRMS (ESI, m/z): Calcd. for $C_{14}H_{19}O_2$: 219.1385, found $[M+H]^+$: 219.1373.



2-Methyl-1-phenylbut-3-ene-1,2-diol (Table 3.2, entry 3):

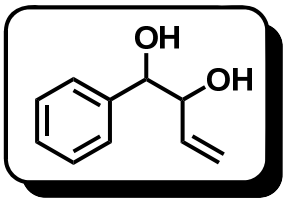
White solid; MP: 50-52 ^{o}C; Yield: 76%; R_f = 0.21 and 0.28 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3449 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (two isomers) δ 1.13 (s), 1.25 (s, 3H), 2.65 (s, 2H), 4.52 (s), 4.56 (s, 1H), 5.12-5.20 (m, 2H), 5.25-5.35 (m), 5.79-5.87 (m, 1H), 5.89-5.97 (m), 7.29-7.34 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 142.3 (CH), 140.0 (CH), 139.6, 139.3 (C), 127.8, 127.8 (CH), 127.7, 127.6 (CH), 114.5, 114.1 (CH_2), 80.5, 79.6 (CH), 75.8, 75.7 (C), 24.2, 22.7 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{11}H_{15}O_2$: 179.1072, found $[M+H]^+$: 179.1070.



1-Phenylbut-3-ene-1,2-diol (Table 3.2, entry 4):

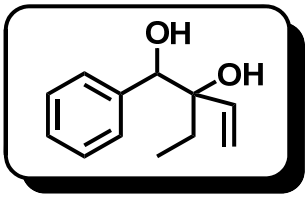
White solid; MP: 46-47 ^{o}C; Yield: 30%; R_f = 0.23 and 0.19 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3449 (OH) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): (two isomers) δ 1.64 (br, 1H), 2.64 (br, 1H), 4.24 (t, J = 6.24 Hz, 1H), 4.32 (t, J = 6.10 Hz), 4.52 (d, J = 6.89 Hz, 1H), 4.76 (d, J = 6.78 Hz), 5.16 (d, J = 10.64 Hz, 1H), 5.25 (d, J = 10.60 Hz), 5.27 (d, J = 17.23 Hz, 1H), 5.30 (d, J = 16.93 Hz, 1H), 5.70-5.78 (m, 1H), 7.25-7.36 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 140.1, 139.7 (C), 136.3, 135.8 (CH), 128.4, 128.3 (CH), 128.2, 128.2 (CH), 128.1, 127.9 (CH), 117.9, 117.1 (CH_2), 77.6, 77.6 (CH), 76.9, 76.7 (CH) ppm;

HRMS (ESI, m/z): Calcd. for $C_{10}H_{13}O_2$: 165.0916, found $[M+H]^+$: 165.0912.



2-Ethyl-1-phenylbut-3-ene-1,2-diol (Table 3.2, entry 5):

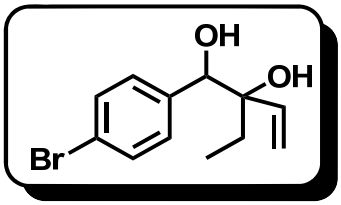
White solid; MP: 61-62 ^{o}C; Yield: 80%; R_f = 0.44 and 0.38 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3440 (OH) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): (two isomers) δ 0.80 (t, J = 7.45 Hz, 3H), 0.82 (t, J = 7.47 Hz) 1.35-1.52 (m, 2H), 1.36- 1.56 (m), 2.05 (br, 1H), 2.55 (br, 1H), 4.56 (s, 1H), 4.59 (s), 5.30-5.39 (m, 2H), 5.32-5.88 (m), 5.79-5.85 (m, 1H), 5.81-5.88 (m), 7.28-7.38 (m, 5H), 7.32-7.40 (m) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (two isomers) δ 140.7, 140.6 (CH), 139.3, 139.2 (C), 127.9, 127.9 (CH), 127.9, 127.8 (CH), 115.5, 115.4 (CH_2), 79.5, 79.5 (CH), 78.3, 78.1 (C), 28.0, 27.9 (CH_2), 7.2, 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{12}H_{17}O_2$: 193.1229, found $[M+H]^+$: 193.1223.



1-(4-Bromophenyl)-2-ethylbut-3-ene-1,2-diol (Table 3.2, entry 6):

White solid; MP: 84-85 ^{o}C; Yield: 70%; R_f = 0.30 and 0.36 (Ethyl acetate/Hexane 1:2);

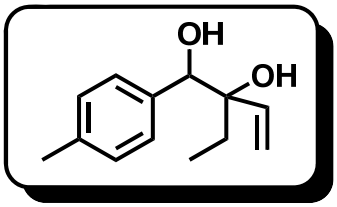
FTIR (NaCl, neat): ν 3433 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (two isomers) δ 0.78 (t, J = 7.45 Hz, 3H), 0.86 (t, J = 7.46 Hz), 1.30-1.52 (m, 2H), 1.46-1.72 (m), 2.07 (br, 1H), 2.70 (br, 1H), 4.52 (s, 1H), 5.20 (s), 5.20-5.33(m), 5.27-5.38 (m, 2H), 5.54-5.63 (m), 5.77-5.86 (m, 1H), 7.11-7.15 (m, 2H),

7.18-7.22 (m), 7.24-7.26 (m, 2H), 7.42-7.47 (m) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 140.4, 138.7 (CH), 138.3, 138.1 (C), 131.0, 130.9 (CH), 129.6, 129.4 (CH), 121.8, 121.7 (C), 115.8, 115.8 (CH_2), 79.0, 78.9 (CH), 78.2, 78.2 (C), 29.4, 27.7 (CH_2), 7.2, 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{12}H_{16}BrO_2$: 271.0334, found $[M+H]^+$: 271.0330.



2-Ethyl-1-p-tolylbut-3-ene-1,2-diol (Table 3.2, entry 7):

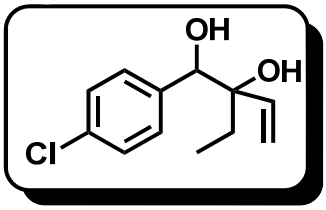
White solid; MP: 86-88 ^{o}C; Yield: 76%; R_f = 0.28 and 0.33 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3426 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (two isomers) δ 0.79 (t, J = 7.45 Hz, 3H), 0.85 (t, J = 7.46 Hz) 1.34-1.52 (m, 2H), 1.40-1.53 (m), 1.59-1.71 (m), 2.06 (br, 1H), 2.34 (s, 3H), 2.55 (br, 1H), 4.50 (s, 1H), 4.57 (s), 5.20-5.29 (m), 5.29-5.38 (m, 2H), 5.61-5.70 (m), 5.72-5.82 (m, 1H), 7.11-7.26 (m), 7.22-7.26 (m, 2H), 7.43-7.46 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 140.8, 138.6 (CH), 137.6, 137.5 (C), 136.7, 136.3 (C), 128.6, 128.5 (CH), 127.8, 127.4 (CH), 115.4, 115.3 (CH_2), 79.6, 79.3 (CH), 78.3, 78.3 (C), 29.4, 28.0 (CH_2), 21.1, 21.1 (CH_3), 7.2, 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{13}H_{19}O_2$: 207.1385, found $[M+H]^+$: 207.1415.



1-(4-Chlorophenyl)-2-ethylbut-3-ene-1,2-diol (Table 3.2, entry 8):

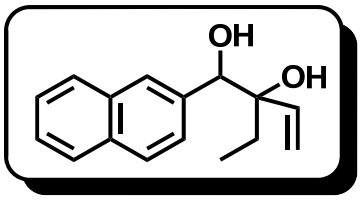
White solid; MP: 93-94 ^{o}C; Yield: 82%; R_f = 0.24 and 0.29 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3441 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (two isomers) δ 0.79 (t, J = 7.42 Hz, 3H), 0.87 (t, J = 7.45 Hz), 1.29-1.51 (m, 2H), 1.44-1.69 (m), 2.10 (br, 1H), 2.21 (s), 2.72 (d, J = 4.26 Hz), 2.76 (d, J = 2.88 Hz, 1H), 4.51 (d, J = 2.61 Hz, 1H), 4.58 (d, J = 4.20 Hz), 5.21-5.27 (m), 5.28-5.37 (m, 2H), 5.55-5.64 (m), 5.72-5.81 (m, 1H), 7.23-7.31 (m), 7.24-7.29 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 140.4, 138.9 (CH), 137.8, 137.2 (C), 133.6, 133.4 (C), 129.4, 129.2 (CH), 128.0, 128.0 (CH), 115.8, 115.7 (CH_2), 79.0, 78.8 (CH), 78.2, 78.2 (C), 28.1, 27.7 (CH_2), 7.2, 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{12}H_{16}O_2Cl$: 227.0839, found $[M+H]^+$: 227.0838.



2-Ethyl-1-(naphthalen-2-yl)but-3-ene-1,2-diol (Table 3.2, entry 9):

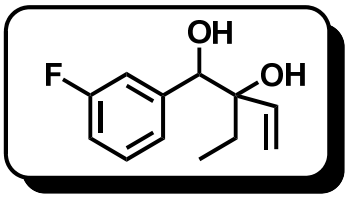
White solid; MP: 124-125 ^{o}C; Yield: 59%; R_f = 0.36 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3433 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.75 (t, J = 7.47 Hz, 3H), 1.47-1.55 (m, 2H), 2.10 (br, 1H), 2.68 (br, 1H), 5.23-5.39 (m, 2H), 5.51 (s, 1H), 5.75-5.84 (m, 1H), 7.45-7.50 (m, 3H), 7.73-7.86 (m, 3H), 8.07-8.12 (m, 1H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 140.8 (CH), 135.7 (C), 133.5 (C), 131.7 (C), 128.8 (CH), 128.4 (CH), 125.9 (CH), 125.8 (CH), 125.3 (CH), 125.2 (CH), 123.8 (CH), 115.2 (CH_2), 79.2 (C), 73.9 (CH), 28.1 (CH_2), 7.1 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{16}H_{19}O_2$: 243.1385, found $[M+H]^+$: 243.1388.



2-Ethyl-1-(3-fluorophenyl)but-3-ene-1,2-diol (Table 3.2, entry 10):

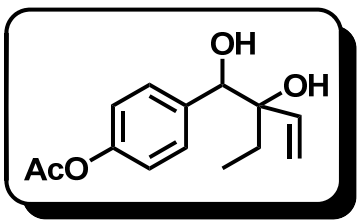
White solid; MP: 78-79 ^oC; Yield: 75%; R_f = 0.27 and 0.32 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3418 (OH) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): (two isomers) δ 0.80 (t, J = 7.44 Hz, 3H), 0.86 (t, J = 7.45 Hz), 1.39-1.48 (m, 1H), 1.41-1.66 (m), 1.55-1.64 (m, 1H), 1.67-1.75 (m), 2.17 (br, 1H), 2.71 (d, J = 4.00 Hz, 1H), 4.52 (d, J = 3.27 Hz, 1H), 4.58 (d, J = 4.20 Hz), 5.15-5.20 (m, 2H), 5.22-5.28 (m), 5.40-5.47 (m), 5.51-5.58 (m, 1H), 5.72-5.81 (m), 6.88-6.92 (m, 1H), 6.97-7.06 (m, 2H), 7.00-7.09 (m), 7.17-7.23 (m, 1H), 7.20-7.26 (m) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 164.0 (d, J = 4.7 Hz), 162.4 (d, J = 4.7 Hz, C), 142.4 (d, J = 7.0 Hz), 142.0 (d, J = 6.8 Hz, C), 140.4, 138.2 (CH), 129.3 (d, J = 8.0 Hz, CH), 129.2 (d, J = 8.2 Hz), 123.6 (d, J = 2.8 Hz), 123.3 (d, J = 2.9 Hz, CH), 115.8 (CH_2), 115.7, 114.8 (d, J = 6.2 Hz), 114.8 (d, J = 6.1 Hz, CH), 114.6 (d, J = 6.8 Hz, CH), 114.5 (d, J = 6.6 Hz), 79.1 (d, J = 2.2 Hz, CH), 79.0 (d, J = 2.1 Hz), 78.3, 78.2 (C), 29.5, 29.4 (CH_2), 7.2, 7.1 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{12}H_{16}O_2F$: 211.1134, found $[M+H]^+$: 211.1073.



4-(2-Ethyl-1,2-dihydroxybut-3-enyl)phenyl acetate (Table 3.2, entry 11):

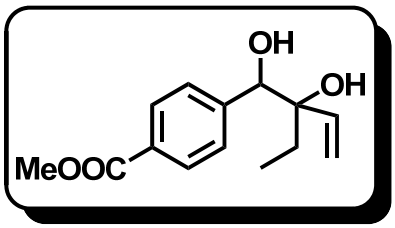
White solid; MP: 85-87 ^{o}C; Yield: 85%; R_f = 0.18 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3426 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (two isomers) δ 0.80 (t, J = 7.44 Hz, 3H), 0.86 (t, J = 7.44 Hz), 1.34-1.54 (m, 2H), 1.50-1.68 (m), 2.29 (s, 3H), 2.29 (s), 4.55 (s, 1H), 4.58 (s), 5.20-5.24 (m), 5.31-5.39 (m, 2H), 5.58-5.67 (m), 5.76-5.85 (m, 1H), 7.02-7.39 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (two isomers) δ 169.5, 169.5 (C), 150.2, 150.1 (C), 140.5 (CH), 137.4, 137.0 (C), 129.0, 128.7 (CH), 121.0, 120.9 (CH), 115.6, 115.6 (CH_2), 79.2, 79.0 (CH), 78.3, 78.2 (C), 27.8, 27.6 (CH_2), 21.1, 21.1 (CH_3), 7.2, 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{14}H_{19}O_4$: 251.1283, found $[M+H]^+$: 251.1280.



Methyl 4-(2-ethyl-1,2-dihydroxybut-3-enyl)benzoate (Table 3.2, entry 12):

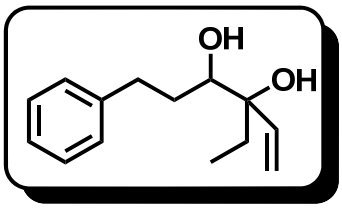
White solid; MP: 83-84 ^{o}C; Yield: 63%; R_f = 0.25 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3503 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.80 (t, J = 7.48 Hz, 3H), 1.32-1.55 (m, 2H), 2.13 (br, 1H), 2.79 (br, 1H), 3.91 (s, 3H), 4.62 (s, 1H), 5.26-5.40 (m, 2H), 5.75-5.84 (m, 1H), 7.38-8.03 (m, 4H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 166.9 (C), 144.5 (C), 140.4 (CH), 129.8 (CH), 129.6 (C), 127.9 (CH), 115.8 (CH_2), 79.2 (CH), 78.3 (C), 52.1 (CH_3), 27.8 (CH_2), 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{14}H_{19}O_4$: 251.1283, found $[M+H]^+$: 251.1279.



3-Ethyl-6-phenylhex-1-ene-3,4-diol (Table 3.2, entry 13):

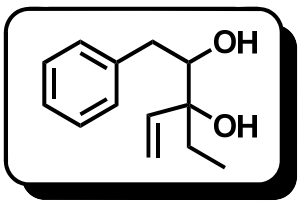
White solid; MP: 60-62 ^{o}C; Yield: 51%; R_f = 0.35 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3410 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.84 (t, J = 7.47 Hz, 3H), 1.51-1.62 (m, 3H), 1.80-1.92 (m, 2H), 2.27 (br, 1H), 2.59-2.73 (m, 1H), 2.87-2.96 (m, 1H), 3.44-3.47 (m, 1H), 5.24-5.35 (m, 2H), 5.69-5.79 (m, 1H), 7.16-7.30 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 141.9 (C), 139.1 (CH), 128.4 (CH), 128.4 (CH), 125.8 (CH), 115.5 (CH_2), 78.0 (C), 76.1 (CH), 33.7 (CH_2), 32.7 (CH_2), 29.7 (CH_2), 7.2 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{14}H_{21}O_2$: 221.1542, found $[M+H]^+$: 221.1545.



3-Ethyl-1-phenylpent-4-ene-2,3-diol (3m, Table 2, entry 14):

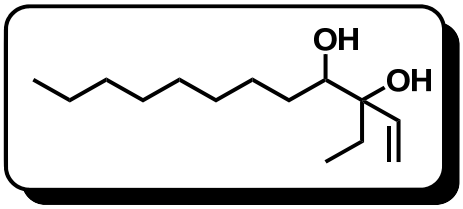
White solid; MP: 58-59 ^{o}C; Yield: 48%; R_f = 0.33 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3379 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.92 (t, J = 7.47 Hz, 3H), 1.60-1.80 (m, 2H), 2.27 (br, 1H), 2.53-2.61 (m, 2H), 2.90-2.96 (m, 1H), 3.69-3.72 (m, 1H), 5.29-5.43 (m, 2H), 5.81-5.91 (m, 1H), 7.21-7.34 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 139.1 (CH), 138.9 (C), 129.3 (CH), 128.6 (CH), 126.5 (CH), 115.4 (CH_2), 77.6 (C), 77.4 (CH), 38.3 (CH_2), 30.0 (CH_2), 7.4 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{13}H_{19}O_2$: 207.1385, found $[M+H]^+$: 207.1401.



3-Ethyldodec-1-ene-3,4-diol (Table 3.2, entry 15):

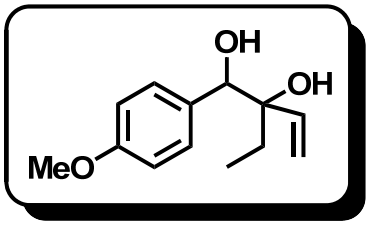
White solid; MP: 89-91 ^oC; Yield: 31%; R_f = 0.57 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3441 (OH) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 0.85-0.89 (m, 6H), 1.26-1.35 (m, 14H), 1.56-1.61 (m, 3H), 3.42-3.44 (m, 1H), 5.24-5.34 (m, 2H), 5.73-5.78 (m, 1H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 139.3 (CH), 115.4 (CH_2), 78.0 (CH), 77.1 (C), 31.9 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 7.3 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{14}H_{28}O_2$: 229.2168, found $[M+H]^+$: 229.2162.



2-Ethyl-1-(4-methoxyphenyl)but-3-ene-1,2-diol (Table 3.2, entry 16):

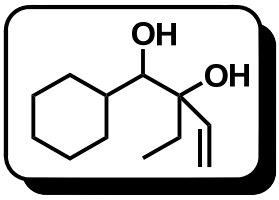
White solid; MP: 62-64 ^oC; Yield: 30%; R_f = 0.19 and 0.22 (Ethyl acetate/Hexane 1:2);

FTIR (NaCl, neat): ν 3433 (OH) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): (two isomers) δ 0.80 (t, J = 7.45 Hz, 3H), 0.86 (t, J = 7.45 Hz), 1.34-1.50 (m, 2H), 1.62-1.66 (m), 2.01 (br, 1H), 2.29 (s), 2.41 (d, J = 2.65 Hz, 1H), 2.56 (d, J = 4.04 Hz), 3.80 (s), 3.81 (s, 3H), 4.53 (d, J = 2.15 Hz, 1H), 4.56 (d, J = 3.29 Hz), 5.22-5.28 (m), 5.30-5.38 (m, 2H), 5.63-5.69 (m), 5.80-5.86 (m, 1H), 6.86-6.89 (m, 2H), 6.85-6.88 (m), 7.23-7.26 (m), 7.26-7.31 (m, 2H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (two isomers) δ 159.3, 159.2 (C), 140.9, 140.9 (CH), 131.8, 131.4 (C), 129.0, 129.0 (CH), 115.4, 115.4 (CH_2), 113.4, 113.2 (CH), 79.4, 79.4 (CH), 78.4, 78.4 (C), 55.2, 55.2 (CH_3), 29.4, 28.1 (CH_2), 7.3, 7.3 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{13}H_{19}O_3$: 223.1335, found $[M+H]^+$: 223.1338.



1-Cyclohexyl-2-ethylbut-3-ene-1,2-diol (Table 3.2, entry 17):

White solid; MP: 42-44 ^{o}C; Yield: 22%; R_f = 0.51 (Ethyl acetate/Hexane 1:2);

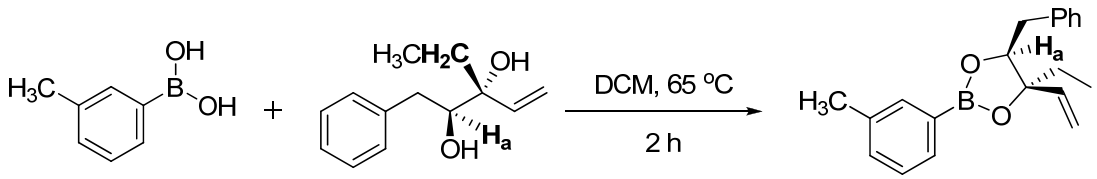
FTIR (NaCl, neat): ν 3433 (OH) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.86 (t, J = 7.47 Hz, 3H), 1.05-1.27 (m, 4H), 1.47-1.77 (m, 10H), 1.90－1.94 (m, 1H), 3.26-3.28 (m, 1H), 5.21-5.36 (m, 2H), 5.74-5.83 (m, 1H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 139.6 (CH), 114.4 (CH_2), 80.1 (CH), 78.6 (C), 39.6 (CH), 32.3 (CH_2), 31.0 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 7.5 (CH_3) ppm;

HRMS (ESI, m/z): Calcd. for $C_{12}H_{23}O_2$: 199.1699, found $[M+H]^+$: 199.1696.

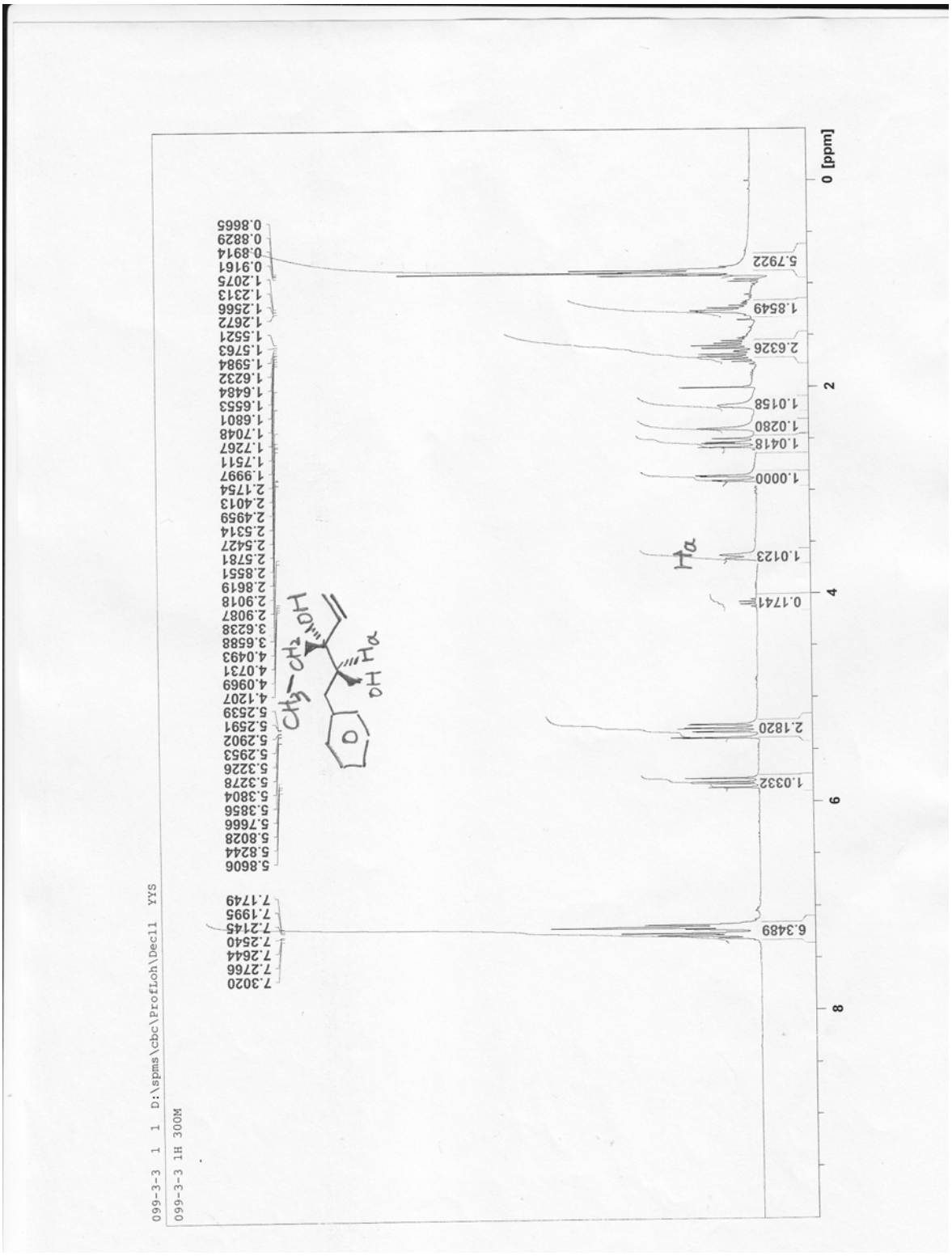
Compound **10n** was further react with 3-methyl benzene boronic acid to confirm the ratio of *anti*:*syn*.



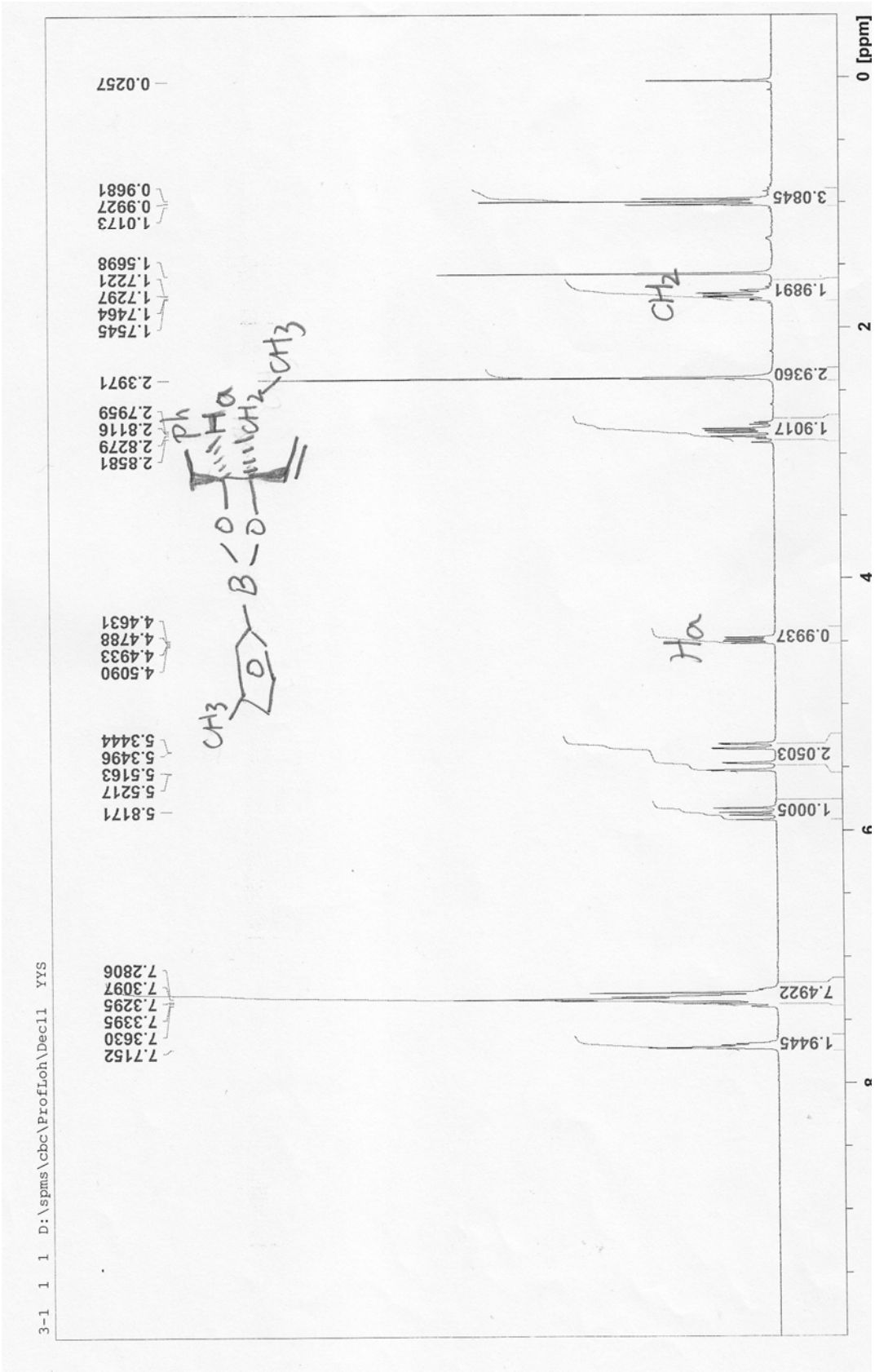
10n **10np**

The major isomer of **10n** was further react with 3-methyl benzene boronic acid and furnish **10np** as product. 2D NOESY NMR of **10np** was performed. It was found that H_a has strong correlation relationship with CH_2 of the ethyl group, but no relationship with vinyl group. It is illustrate that the major isomer of **10n** is *anti*-structure.

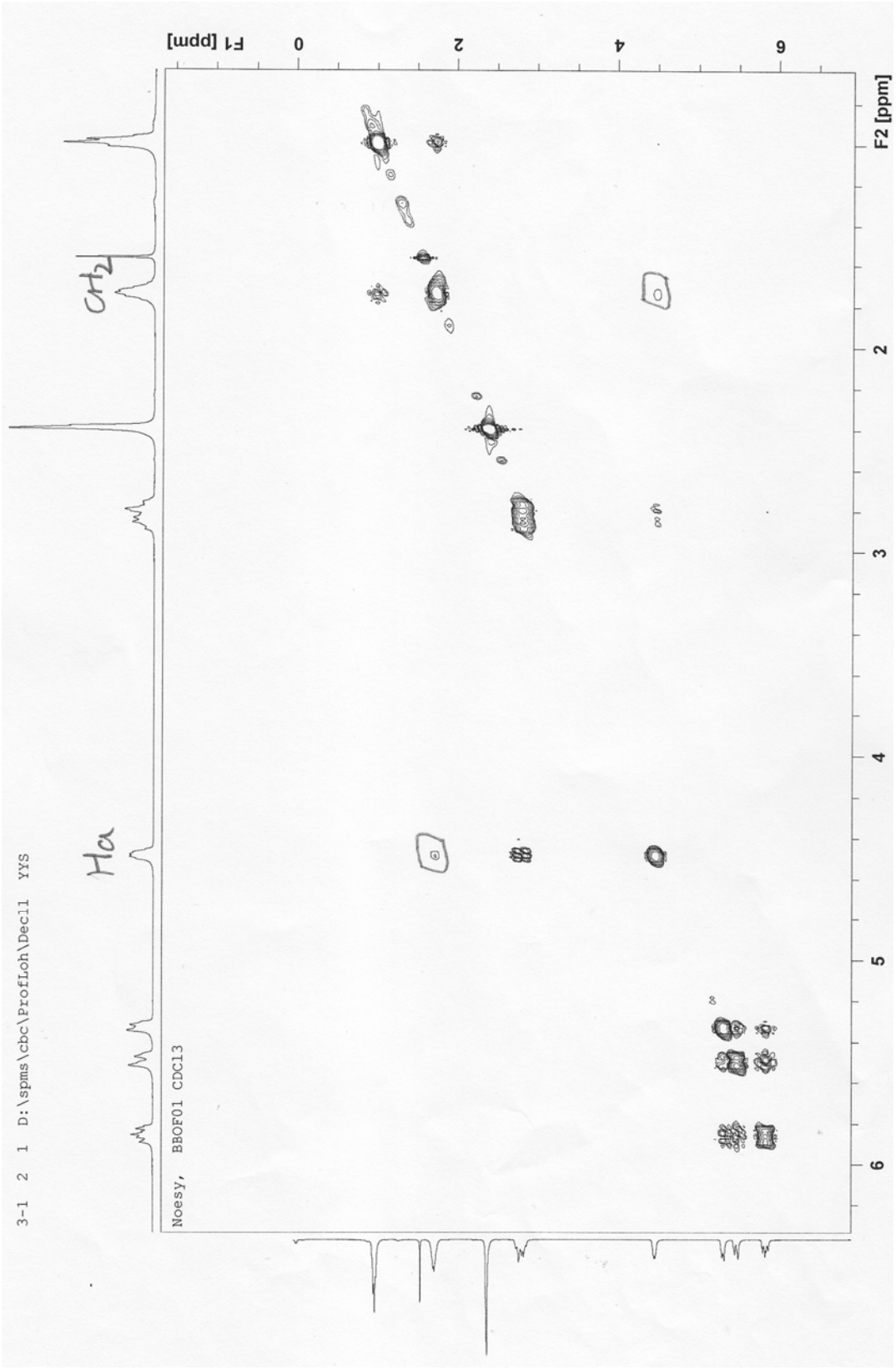
H NMR of *anti*-structure of **10n**



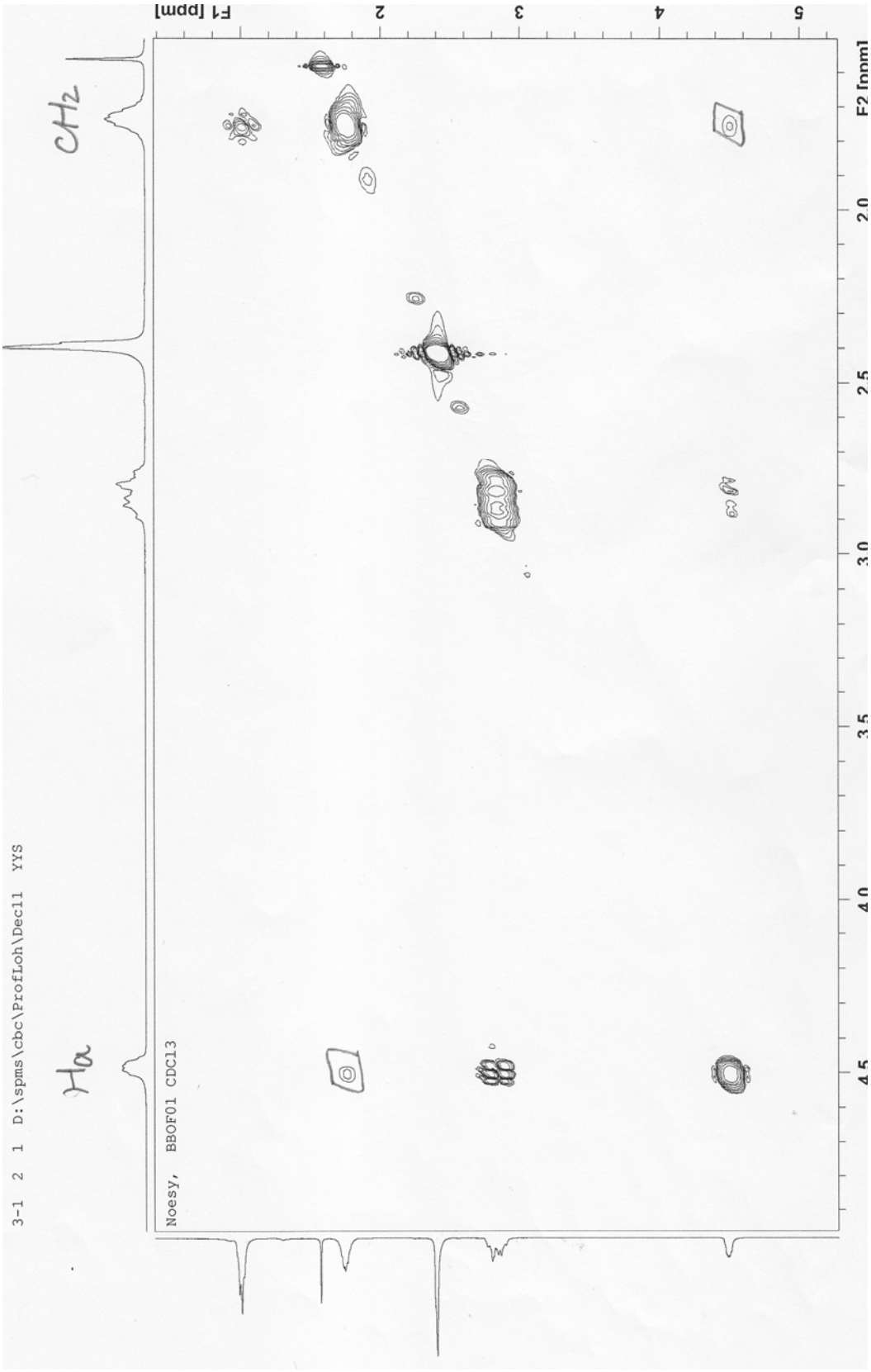
[1]H NMR of *anti*-structure of **10np**



Noesy NMR of **10np**



Noesy NMR of **10np**



3.4.3 Crystal data and structure refinement

Crystal data and structure refinement of 10e.

Empirical formula	$C_{12}H_{16}O_2$	
Formula weight	192.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 9.9349(4) Å	α = 69.982(2)°
	b = 10.4509(5) Å	β = 81.438(2)°
	c = 11.9511(5) Å	γ = 88.119(2)°
Volume	1152.69(9) $Å^3$	
Z	4	
Density (calculated)	1.108 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	416	
Crystal size	0.28 x 0.24 x 0.20 mm^3	
Theta range for data collection	1.83 to 28.35°	
Index ranges	$-13 \leq h \leq 13, -13 \leq k \leq 13, -15 \leq l \leq 15$	
Reflections collected	34871	
Independent reflections	5716 [R(int) = 0.0318]	
Completeness to theta = 24.98	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9854 and 0.9796	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	5716 / 0 / 259
Goodness-of-fit on F^2	1.065
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0533$, $wR_2 = 0.1505$
R indices (all data)	$R_1 = 0.0797$, $wR_2 = 0.1727$
Largest diff. peak and hole	0.290 and –0.232 e.Å^{-3}

CHAPTER 4

Palladium Catalyzed Hydroboration of Unactivated Alkynes with Bis(pinacolato)diboron in Water

Chapter 4. Palladium Catalyzed Hydroboration of Unactivated Alkynes with Bis(pinacolato)diboron in Water

4.1 Introduction

During the last decade, significant attention was focused on organoboron compounds because of their various biological activities and versatility as synthetic intermediates in organic synthesis.[88] In particular, vinylboronates, which are versatile organic synthetic intermediates are now gaining increasingly more attention and have been widely used in various carbon-carbon bond formation reactions.[89] Hydroboration of alkenes and alkynes is a useful and concise method for the preparation of the corresponding boranes, which are versatile organic building blocks in subsequent couplings.[90] While the addition of diboronates such as bis(pinacolato)diboron and bis(catecholato)diboron to alkenes and alkynes has been extensively studied with Pd,[91] Pt[92], Rh[93] and Cu[94] catalysts, few examples

[88] For recent reviews concerning organoboron compounds, see: (a) *Boronic Acids-Preparation and Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, **2005**; (b) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320; (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435; (d) Irvine, G. J.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R.; Robins, E. G.; Roper, W. R.; Whittell, G. R.; Wright, L. J. *Chem. Rev.* **1998**, *98*, 2685; (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (f) *Contemporary Boron chemistry*; Davidson, M.; Hughes, A. K.; Marder, T. B.; Wade, K., Eds.; RSC, Cambrigde, **2000**. For recent select examples concerning organoboron compounds, see: (f) Irving, A. M.; Vogels, C. M.; Nikolcheva, L. G.; Edwards, J. P.; He, X. F.; Hamilton, M. G.; Baerlocher, M. O.; Baerlocher, F. J.; Decken, A.; Westcott, S. A. *New J. Chem.* **2003**, *27*, 1419; (g) Ito, H.; Kawakami, C.; Sawamura, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 16034.

[89] For reviews, see: (a) Suzuki, A. in *Organoboranes in syntheses*, ACS symposium series 783, Eds: Ramachandran, P. V.; Brown, H. C., American Chemical Society, Washington, **2001**, ch. 6, p. 80; (b) Miyaura, N. in *Organoboranes in syntheses*, ACS symposium series 783, Eds: Ramachandran P. V.; Brown, H. C., American Chemical Society, Washington, **2001**, ch. 7, p. 94 (c) Tusiji, J. *Palladium reagents and catalysts*, John Wiley & Sons, Chichester, England, **2004**, p. 218.

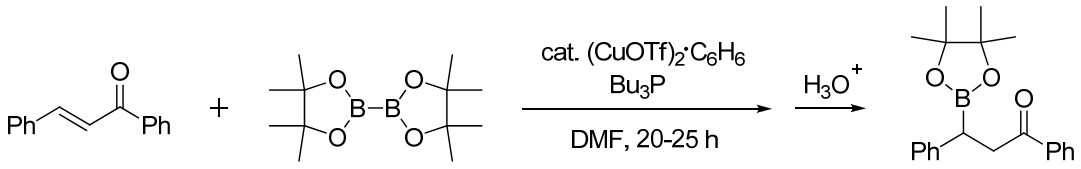
[90] Luithle, J. E. A.; Pietruszka, J.; Witt, A. *Chem. Commun.* **1998**, 2651; (b) He, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 1696; (c) Iwadate, N.; Suginome, M. *Org. Lett.* **2009**, *11*, 1899; (d) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

[91] Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, 126, 16328.

employing other metals (Au, Ag) have been reported.[95]

4.1.1 Recent Hydroboration Reactions of Alkenes

In 2000, Hosomi *et al.* first reported a copper-catalyzed conjugate addition reaction of bis(pinacolato)diboron to *α,β*-enones (Scheme 4.1).[96] It was found that the combination of a Cu(I) salt and tributylphosphine is an effective catalytic system for the addition reaction. However the individual use of Cu(I) salt and tributylphosphine is inactive for the reaction.



Scheme 4.1

Recently, Yun and coworkers have made great contributions to this area using copper as the catalyst. In 2006, they reported a highly efficient protocol for the conjugate addition of bis(pinacolato)diboron to various *α,β*-unsaturated carbonyl compounds using a combination of catalytic amounts of CuCl, NaO*t*-Bu, and DPEphos in the presence of methanol as additives to furnish the corresponding *β*-boryl carbonyl compounds in high yields (Scheme 4.2).[97] An alcohol additive was used to protonate the resulting C-Cu bond to generate a catalytically active Cu-alkoxide, thus enhancing reaction efficiency.

---

[92] (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018; (b) Iverson, C. N.; Smith, M. R., III *Organometallics* **1997**, *16*, 2757; (c) Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155.

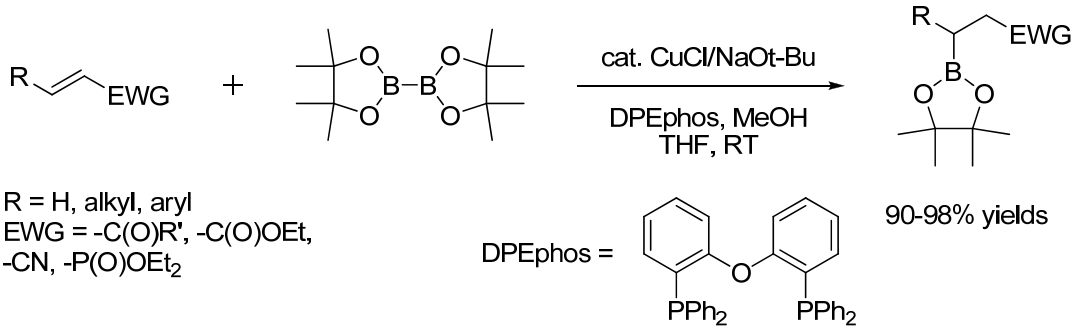
[93] (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702; (b) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77. (c) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983.

[94] Lillo, V.; Fructos, M. R.; Ramirez, J.; Braga, A. A. C.; Maseras, F.; Diaz-Requejo, M. M.; Perez, P. J.; Fernandez, E. *Chem. Eur. J.* **2007**, *13*, 2614.

[95] (a) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336; (b) Ramirez, J.; Corberan, R.; Sanau, M.; Peris, E.; Fernandez, E. *Chem. Commun.* **2005**, 3056.

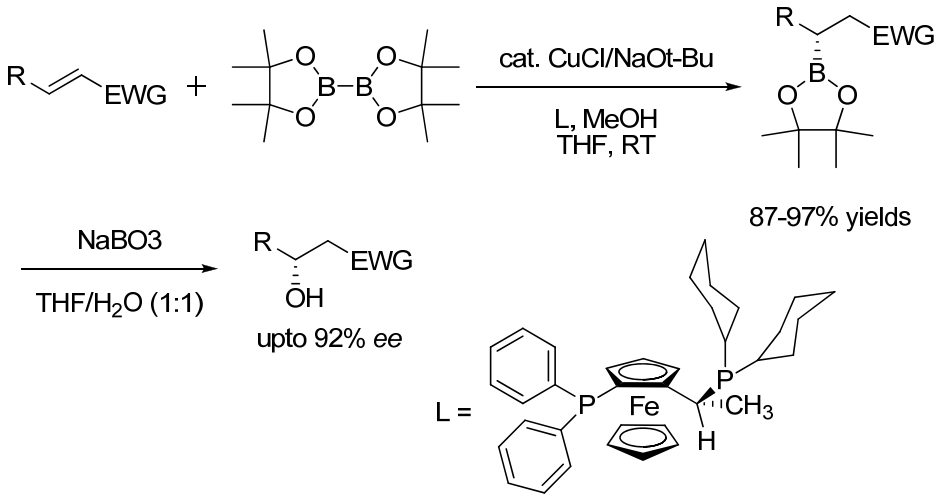
[96] Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821.

[97] Mun. S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.



Scheme 4.2

Subsequently, they described the enatioselective *β*-boration of acyclic *α,β*-unsaturated esters and nitriles catalyzed by a nonracemic copper phosphine complex that provides ready access to functionalized chiral organoboron compounds under mild reaction conditions with excellent yields and high enantioselectivities (Scheme 4.3).[98]



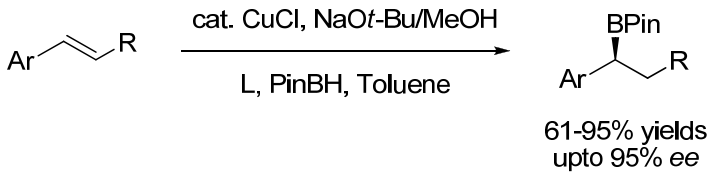
Scheme 4.3

Next, they developed an enantioselective hydroboration reaction of styrene derivatives under the catalysis of chiral copper(I)-bisphosphine complexes with pinacolborane as the hydroborating reagent (Scheme 4.4).[99] This method shows that a stereoselective transmetalation of a benzylic carbon-copper bond is possible with pinacolborane.

---

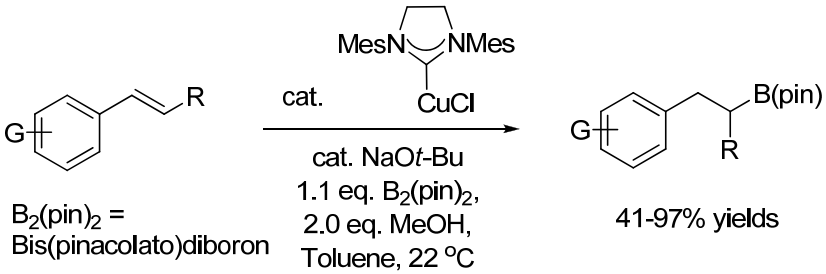
[98] (a) Lee, J. E.; Yun, J. *Angew. Chem. Int. Ed.*, **2008**, *47*, 145. (b) Chea, H.; Sim, H. S.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855; (c) Sim, H. S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939.

[99] Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062.



Scheme 4.4

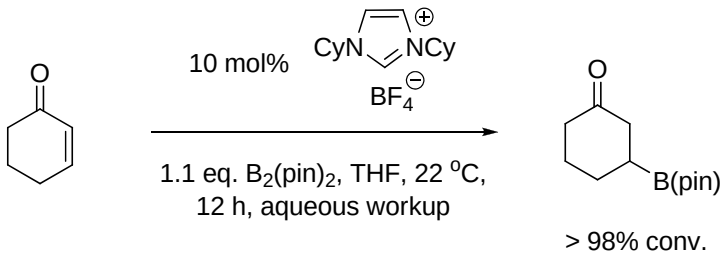
Hoveyda *et al.* also investigated the hydroboration reactions with NHC-Cu catalyst in recent years. In 2009, they disclosed a protocol for the catalytic boron-copper addition to acyclic and cyclic aryl olefins. Reactions were promoted by 0.5-5 mol% of a readily available NHC-Cu complex and proceeded with >98:2 site selectivity. With NHC complexes, Cu-catalyzed hydroborations proceeded with high enantioselectivity (Scheme 5.5).[100]



Scheme 4.5

Next, they introduced a method for efficient C-B bond formation through transformations that are catalyzed by the readily available *N*-heterocyclic carbene (NHC) present at 2.5-10 mol%. Cyclic and acyclic *α,β*-unsaturated ketones and esters served as substrates; *β*-boryl carbonyls with tertiary or quaternary *β*-substituted carbons are obtained in >98% yield (Scheme 4.6).[101]

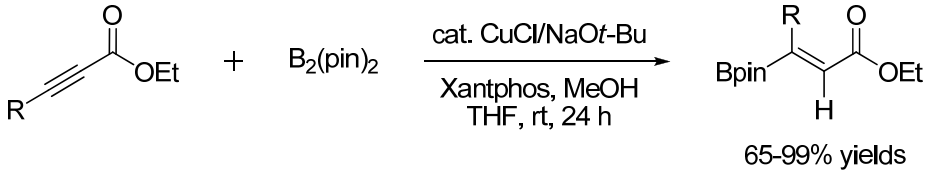
[100] Lee, Y.; Hoveyda, A. H. *J. Am. Soc. Chem.* **2009**, *131*, 3160.
[101] Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Soc. Chem.* **2009**, *131*, 7253.



Scheme 5.6

4.1.2 Recent Hydroboration Reactions of Alkynes

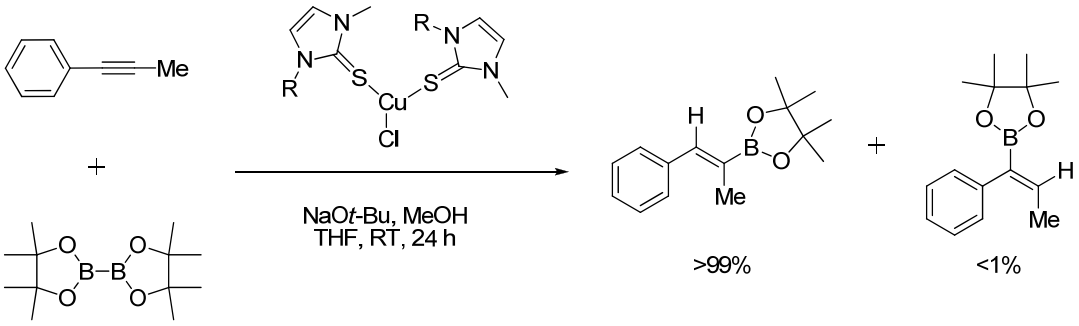
In 2008, Yun *et al.* reported an efficient procedure for the conjugate addition of bis(pinacolato)diboron to *α,β*-acetylenic esters based on a copper-phosphine catalyst, which provided a route to the stereoselective synthesis of *β*-borylated-*α,β*-ethylenic esters (Scheme 4.7).[102]



Scheme 4.7

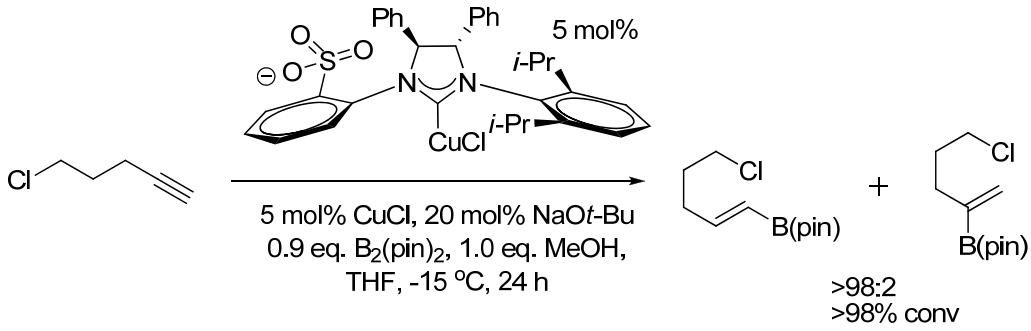
In 2010, Yun reported a copper catalyst system bearing the imidazoline-2-thione for highly regioselective boron addition to internal alkynes that produces hydroborylated alkenyl compounds (Scheme 4.8).[103] The reaction efficiency is quite sensitive to the steric effects of the alkyl groups and electronic effects of the aryl groups. The activity of the catalytic system was further improved by introduction of long alkyl chains on the imidazoline-2-thione due to enhanced solubility.

[102] Lee, J. E.; Kwon, J.; Yun J. *Chem. Commun.* **2008**, 733.
[103] Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Comm.* **2010**, *46*, 758.



Scheme 4.8

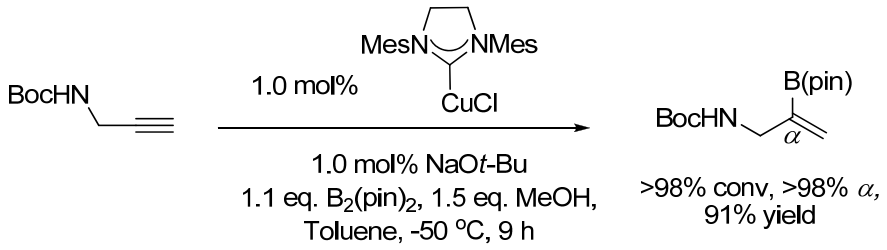
Since vinylboronates may be prepared by alkyne hydroboration, Hoveyda *et al.* further envisioned a single-vessel Cu-catalyzed process for the conversion of terminal alkynes to diboronates with high enantiomeric purity (Scheme 4.9).[104] A wide range of terminal alkynes were converted to vicinal diboronates with >98% site selectivity in 60-93% yield and up to 97:3 enantiomeric ratio (er).



Scheme 4.9

With the NHC-Cu catalyst, a site-selective hydroboration of terminal alkynes, generating α-vinylboronate predominantly (up to >98%) was disclosed in 2011 (Scheme 5.10).[105] Propargyl alcohol, amine, and the derived benzyl, *tert*-butyl, or silyl ethers as well as various amides are particularly effective substrates. Mechanistic studies indicate that α selectivity arises from the structural and electronic attributes of the NHC ligands and the alkyne substrates.

[104] Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Soc. Chem.* **2009**, *131*, 18234.
[105] Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Soc. Chem.* **2011**, *133*, 7859.



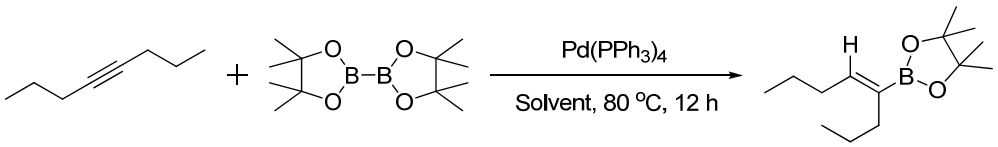
Scheme 4.10

Although, great progresses have been made and many different methods for the hydroboration of alkynes have been published, most of the reported literatures deal with activated alkynes and organic solvents such as methanol or THF are indispensable for the reaction to proceed. In continuation of our efforts to develop organic advantages over reactions in aqueous media, herein, we report a palladium catalyzed hydroboration of unactivated alkynes in water.

4.2 Results and Discussion

In our initial experiments, we investigated the hydroboration of 4-octynes by employing a catalytic amount $Pd(PPh_3)_4$ in the presence of 2 equivalents of bis(pinacolato)diboron at 80 ^oC with various solvents and cosolvents. The results are summarized in Table 4.1.

Table 4.1. Optimization of reaction conditions using 4-octyne (**14a**) and bis(pinacolato)-diboron[a]

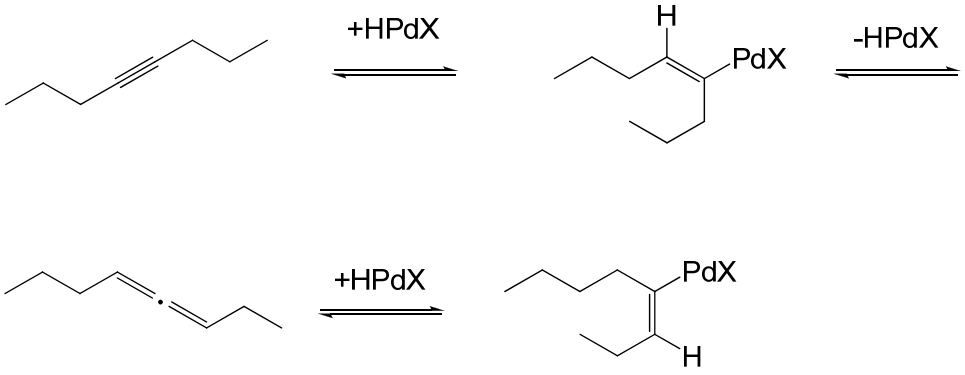


14a **15a**

Entry	Catalysts	Solvents	Temprature	Yield (%)[b]
1	$Pd(PPh_3)_4$	THF/HOAc	80 °C	45
2	**$Pd(PPh_3)_4$**	**H_2O/HOAc**	**80 °C**	**58**
3	$Pd(PPh_3)_4$	MeOH/HOAc	80 °C	52
4	$Pd(PPh_3)_4$	EA/HOAc	80 °C	50
5	$Pd(PPh_3)_4$	H_2O/CF_3CO_2H	80 °C	12
6	$Pd(PPh_3)_4$	H_2O/PTSA·H_2O	80 °C	5
7	$Pd(PPh_3)_4$	$H_2O/EtCO_2H$	80 °C	39
8	$Pd(PPh_3)_4$	DMF/HOAc	80 °C	48
9	$Pd(PPh_3)_4$	HOAc	80 °C	23
10	$Pd(PPh_3)_4$	H_2O	80 °C	12
11	$Pd(OAc)_2$	H_2O/HOAc	80 °C	trace
12	$Pd_2(dba)_3$	H_2O/HOAc	80 °C	trace
13	—	H_2O/HOAc	80 °C	0
14	$Pd(PPh_3)_4$	H_2O/HOAc	60 °C	37
15	$Pd(PPh_3)_4$	H_2O/HOAc	70 °C	51
16	$Pd(PPh_3)_4$	H_2O/HOAc	90 °C	57

[a] The reaction was carried out at rt for 12 h using Pd catalyst (5%), solvent (1.5 mL), **1** (1 eq), B_2pin_2 (2 eq), HOAc (4 eq). [b] Isolated yield.

As shown in Table 4.1, when using THF as the solvent, moderate overall yield of a mixture of regioisomers was obtained, which is confirmed by NMR and GC-MS (Table 4.1, entry 1). The formation of different isomers using THF as solvent may be due to the reversible insertion and elimination of palladium hydride to the triple bond or the allene intermediate (Scheme 4.11).

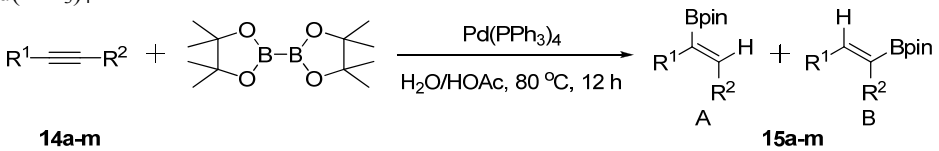


Scheme 4.11

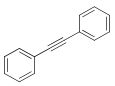
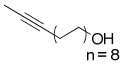
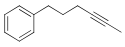
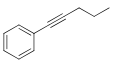
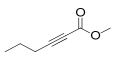
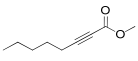
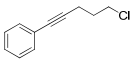
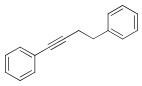
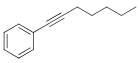
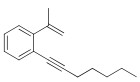
Fortunately, the isomerization problem was successfully avoided when the solvent was simply changed into H_2O/HOAc, which afford the product in moderate yield and with only one isomer (Table 4.1, entry 2). Other acids, such as CF_3COOH, PTSA·H_2O and $EtCO_2H$ were not as effective as HOAc (Table 4.1, entries 5-7). Among the different solvents investigated, H_2O/HOAc was the best solvent for the hydroboration reaction of 4-octynes. It is important to note that the employment of Pd(0) is indispensable for the hydroboration reaction; without it, no desired product was obtained (Table 4.1, entry 13). It is also noteworthy that the reaction using $Pd(PPh_3)_4$ as catalyst proceeded sluggishly to afford the desired product in lower yields when either H_2O or HOAc was used singly as solvent (Table 4.1, entries 9 and 10).

With the optimization reaction conditions, various unactivated alkynes were examined, with the results summarized in Table 4.2.

Table 4.2. Screening the reactivity of virious alkynes in the boron addition catalyzed by $Pd(PPh_3)_4$[a]



14a-m 15a-m

Entry	Alkyne	Product	Yield(%)[b]	A:B
1	 **14a**	**15a**	58	-
2	 **14b**	**15b**	70	-
3	 **14c**	**15c**	68	52:48
4	 **14d**	**15d**	75	60:40
5	 **14e**	**15e**	85	75:25
6	 **14f**	**15f**	70	84:16
7	 **14g**	**15g**	68	90:10
8	 **14h**	**15h**	60	84:16
9	 **14i**	**15i**	62	86:14
10	 **14j**	**15j**	74	75:25
11	 **14k**	**15k**	60	75:25
12	 **14l**	**15l**	61	100:0
13	 **14m**	**15m**	62	53:47

[a] Reaction conditions: 5 mol% $Pd(PPh_3)_4$, 1 equiv. Alkyne, 2 equiv. $B_2(pin)_2$, 4 equiv. HOAc in 1.5 mL H_2O at 80 °C for 12 hrs. [b] Isolated yield.

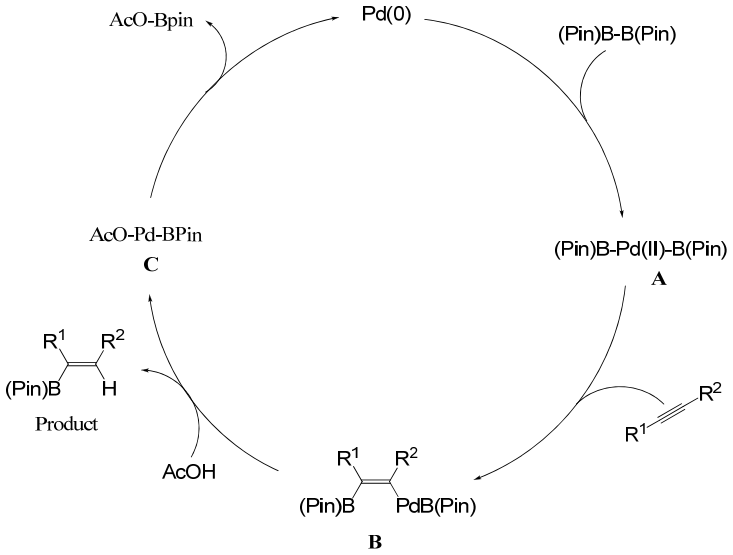
As shown in Table 4.2, $Pd(PPh_3)_4$ efficiently catalyzed the hydroboration reactions of

various alkynes and $B_2(pin)_2$ in H_2O at 80 ^oC. This generated the corresponding *syn*-adduct alkenyl boron compounds in moderate to good yields. Both aryl and alkyl substituted alkynes reacted smoothly within the reaction time to provide the desired products in good to high yield (Table 4.2, entries 1 and 2). For the activated substrates (Table 4.2, entries 7 and 8), the reaction proceeded smoothly with moderate yield. It is gratifying to find that when using substrate **14l**, the reaction delivered only one regioisomer **15l**, which may be due to the complexation effect of the *ortho* olefin substituent with the palladium catalyst (Table 4.2, entry 12). Furthermore, functional groups such as hydroxyl, ester and halide were well tolerated in this reaction, which further confirmed the high compatibility of such transformation (Table 4.2, entries 3 and 7-9). The site selectivity is quite sensitive to the electronic effects of the aryl groups.

Scheme 4.12

The *J* coupling value of H(I) (Scheme 4.12) of compound **B** is less smaller than compound **A**, the exact ratio was determined by the ^1H NMR spectrum and/or isolated yield.

On the basis of our experiments, we proposed the mechanism which is shown in Scheme 4.13.



Scheme 4.13

The palladium(0) initially insert into born-born bond to form the intermediate **A**, intermediate **A** react with alkynes after migratory transformation can afford intermediate **B**, which subsequently react with acetate acid after reductive elimination would generate the desired product and regenerate the palladium(0) to complete the catalytic cycle.

4.3 Conclusion

In conclusion, we developed a new palladium catalyst system for good regioselective boron addition to internal alkynes that produced hydroborylated alkenyl compounds in water. The reaction reactivity was quite sensitive to the electronic effects of the aryl groups. This mild condition reaction provides an efficient route to the synthesis of α–borylated-α,β-alkenes in water. Studies are underway to extend the application of the boron derivatives to organic synthesis.

4.4 Supporting Information

4.4.1 General Methods

The alkynes, $B_2(pin)_2$ and acetic acid were purchased from Aldrich and used directly without purification, while the others were synthesized according to the reported method.[106]

The following commercial grade solvents and reagents were also used without further purification: $Pd(PPh_3)_4$ (powder, 99.9%, Aldrich chemical), HOAc (Aldrich chemical).

Deionized water was used in all reactions.

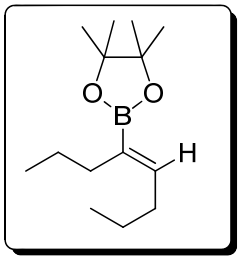
4.4.2 Experimental Procedure

General procedure for the hydroboration reaction

To a 8 mL sample vial was added tetrakis(triphenylphosphine)palladium(0) (0.01 mmol), alkyne (0.2 mmol), $B_2(pin)_2$ (0.4 mmol), water (1.5 mL) and acetic acid (0.8 mmol) sequentially, then it was stirred vigorously at 80 ^oC for 12 hours. After reaction, 2 mL H_2O was added, and then it was extracted using diethyl ether (5 mL x 4), washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated solvent under *vacuo* to give the residue. It was then purified by silica gel column chromatography using ethyl acetate and hexane as eluent to afford the desired product.

[106] Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236.

4.4.3 Spectroscopic Data of Products



(*Z*)-4,4,5,5-tetramethyl-2-(oct-4-en-4-yl)-1,3,2-dioxaborolane (Table 5.2, entry 1):

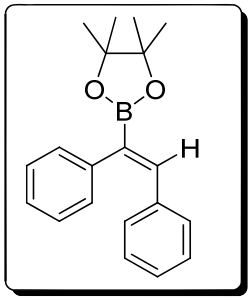
Colorless oil; Yield: 58%; R_f = 0.55 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1628 cm^{-1} (C=C);

^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.33 Hz, 3H), 0.92 (t, J = 7.36 Hz, 3H), 1.25 (s, 12H), 1.33-1.44 (m, 4H), 2.08-2.14 (m, 4H), 6.30 (t, J = 7.08 Hz, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 82.9, 30.6, 30.6, 24.7, 23.3, 22.4, 14.1, 14.0 ppm;

HRMS (ESI, m/z): Calcd. For $C_{14}H_{28}BO_2$: 239.2182, found $[M+H]^+$: 239.2189.



(*Z*)-2-(1,2-diphenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 5.2, entry 2):

White solid; Yield: 70%; R_f = 0.55 (Ethyl acetate/Hexane 1:10);

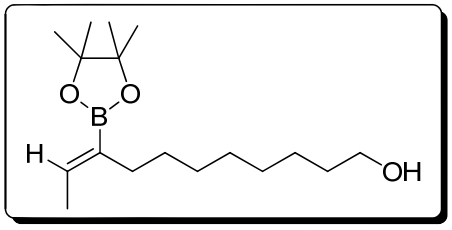
FTIR (KBr, neat): ν 1636 cm^{-1} (C=C);

^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 12H), 7.03-7.29 (m, 10H), 7.36 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 140.4, 137.0, 129.9, 128.8, 128.2, 127.8, 127.5, 126.2,

83.8, 24.8 ppm;

HRMS (ESI, m/z): Calcd. For $C_{20}H_{24}BO_2$: 307.1869, found $[M+H]^+$: 307.1869.



(*Z*)-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undec-9-en-1-ol (Table 5.2, entry 3):

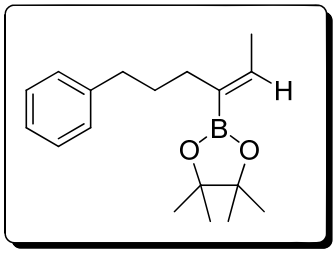
Light yellow oil; Yield: 68%; R_f = 0.43 (Ethyl acetate/Hexane 1:2);

FTIR (KBr, neat): ν 1632 cm^{-1} (C=C);

^1H NMR (500 MHz, $CDCl_3$): two isomers: δ 1.26 (s, 12H), 1.27-1.39 (m, 11H), 1.53-1.59 (m, 2H), 1.67-1.71 (m, 3H), 2.09-2.13 (m, 2H), 3.63 (t, J = 6.60 Hz, 2H), 6.30-6.42 (m, 1H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (two isomers) δ 146.6, 140.1, 83.0, 82.9, 63.1, 63.0, 32.8, 32.8, 29.8, 29.5, 29.4, 29.4, 29.4, 29.3, 28.8, 28.6, 28.0, 25.7, 25.7, 24.8, 24.7, 14.2, 13.8 ppm;

HRMS (ESI, m/z): Calcd. For $C_{17}H_{34}BO_3$: 297.2601, found $[M+H]^+$: 297.2608.



(*Z*)-4,4,5,5-tetramethyl-2-(6-phenylhex-2-en-3-yl)-1,3,2-dioxaborolane (Table 2, entry 4):

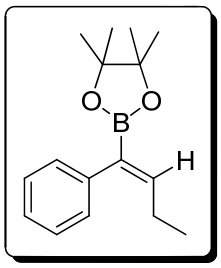
Light yellow oil; Yield: 75%; R_f = 0.56 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1632 cm^{-1} (C=C);

^{1}H NMR (400 MHz, $CDCl_3$): (two isomers) δ 1.27 (s, 12H), 1.67-1.78 (m, 5H), 2.15-2.23 (m, 2H), 2.59-2.65 (m, 2H), 6.33-6.46 (m, 1H), 7.17-7.28 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 146.0, 143.0, 142.4, 140.6, 128.4, 128.4, 128.2, 128.2, 125.6, 125.5, 83.1, 83.0, 35.7, 35.6, 31.5, 30.4, 28.2, 27.9, 24.8, 24.7, 14.2, 13.9 ppm;

HRMS (ESI, m/z): Calcd. For $C_{18}H_{28}BO_2$: 287.2182, found $[M+H]^+$: 287.2185.



(*Z*)-4,4,5,5-tetramethyl-2-(1-phenylbut-1-enyl)-1,3,2-dioxaborolane (Table 2, entry 5):

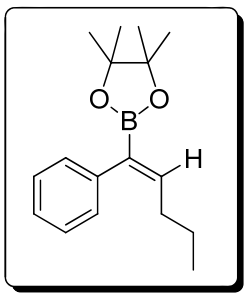
Light yellow oil; Yield: 85%; R_f = 0.59 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1620 cm^{-1} (C=C);

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 1.00 (t, J = 7.53 Hz, 3H), 1.27 (s, 12H), 2.12-2.20 (m, 2H), 6.57 (t, J = 7.29 Hz, 1H), 7.13-7.33 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 149.8, 140.2, 128.9, 127.7, 125.8, 83.4, 24.7, 23.2, 13.8 ppm;

HRMS (ESI, m/z): Calcd. For $C_{16}H_{24}BO_2$: 259.1869, found $[M+H]^+$: 259.1865.



(*Z*)-4,4,5,5-tetramethyl-2-(1-phenylpent-1-enyl)-1,3,2-dioxaborolane (Table 2, entry 6):

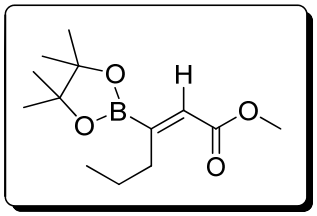
Light yellow oil; Yield: 70%; R_f = 0.31 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1616 cm^{-1} (C=C);

^1H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.87 (t, J = 7.39 Hz, 3H), 1.27 (s, 12H), 1.36-1.49 (m, 2H), 2.12 (q, J = 7.50 Hz, 2H), 6.58 (t, J = 7.26 Hz, 1H), 7.12-7.33 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major ismore) δ 148.3, 140.3, 129.0, 127.7, 125.8, 83.4, 32.0, 24.8, 22.6, 14.0 ppm;

HRMS (ESI, m/z): Calcd. For $C_{17}H_{26}BO_2$: 273.2026, found $[M+H]^+$: 273.2026.



(*Z*)-methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-enoate (Table 2, entry 7):

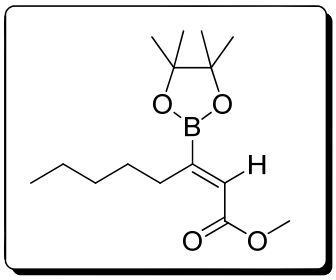
Light yellow oil; Yield: 68%; R_f = 0.64 (Ethyl acetate/Hexane 1:2);

FTIR (KBr, neat): ν 1636 cm^{-1} (C=C), 1715 cm^{-1} (C=O);

^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 0.93 (t, J = 7.40 Hz, 3H), 1.27 (s, 12H), 1.39-1.52 (m, 2H), 2.65 (t, J = 7.65 Hz, 2H), 3.71 (s, 3H), 6.42 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (major isomer) δ 166.4, 129.4, 84.0, 51.1, 31.9, 24.7, 22.8, 14.1 ppm;

HRMS (ESI, m/z): Calcd. For $C_{13}H_{24}BO_4$: 255.1768, found $[M+H]^+$: 255.1772.



(*Z*)-methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-2-enoate (Table 2, entry 8):

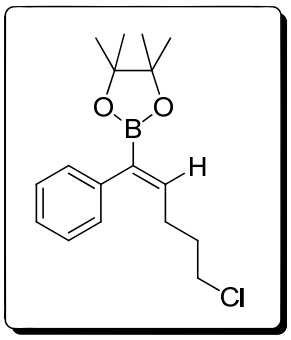
Light yellow oil; Yield: 60%; R_f = 0.22 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1633 cm^{-1} (C=C), 1720 cm^{-1} (C=O);

^1H NMR (300 MHz, $CDCl_3$): (major isomer) δ 0.88 (t, J = 6.70 Hz, 3H), 1.27 (s, 12H), 1.30-1.35 (m, 4H), 1.38-1.48 (m, 2H), 2.66 (t, J = 7.50 Hz, 2H), 3.71 (s, 3H), 6.40 (s, 1H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): (major isomer) δ 166.4, 129.2, 84.0, 51.0, 31.9, 30.0, 29.2, 24.7, 22.5, 14.0 ppm;

HRMS (ESI, m/z): Calcd. For $C_{15}H_{28}BO_4$: 283.2081, found $[M+H]^+$: 283.2084.



(Z)-2-(5-chloro-2-methyl-1-phenylpent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 9):

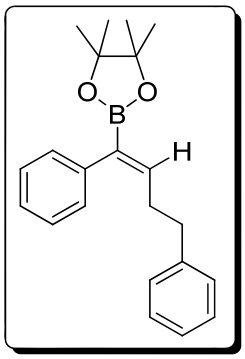
White solid; Yield: 62%; R_f = 0.24 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1622 cm^{-1} (C=C);

^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 1.27 (s, 12H), 1.84-1.90 (m, 2H), 2.27-2.32 (m, 2H), 3.47 (t, J = 6.80 Hz, 2H), 6.53 (t, J = 7.19 Hz, 1H), 7.12-7.38 (m, 5H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 139.8, 128.8, 127.8, 126.1, 83.6, 44.5, 32.2, 27.2, 24.7 ppm;

HRMS (ESI, m/z): Calcd. For $C_{17}H_{25}BO_2Cl$: 307.1636, found $[M+H]^+$: 307.1644.



(*Z*)-2-(1,4-diphenylbut-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2, entry 10):

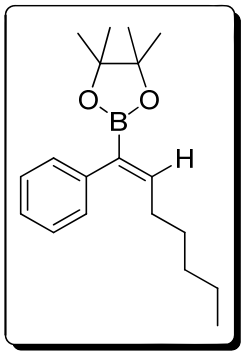
White solid; Yield: 74%; R_f = 0.21 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1616 cm^{-1} (C=C);

^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 1.27 (s, 12H), 2.43-2.48 (m, 2H), 2.70-2.73 (m, 2H), 6.64 (t, J = 7.20 Hz, 1H), 7.07-7.32 (m, 10H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 147.0, 141.8, 139.9, 128.8, 128.3, 128.3, 127.8, 125.9, 125.8, 83.5, 35.6, 31.9, 24.7 ppm;

HRMS (ESI, m/z): Calcd. For $C_{22}H_{28}BO_2$: 335.2182, found $[M+H]^+$: 335.2193.



(*Z*)-4,4,5,5-tetramethyl-2-(1-phenylhept-1-enyl)-1,3,2-dioxaborolane (Table 2, entry 11):

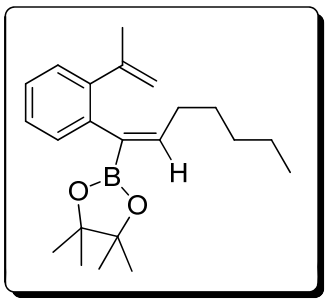
light yellow solid; Yield: 60%; R_f = 0.37 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1616 cm^{-1} (C=C);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, J = 6.84 Hz, 3H), 1.22-1.25 (m, 4H), 1.27 (s, 12H), 1.37-1.43 (m, 2H), 2.13 (q, J = 7.65 Hz, 2H), 6.58 (t, J = 7.25 Hz, 1H), 7.13-7.33 (m, 5H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): (major isomer) δ 148.5, 140.3, 128.9, 127.7, 125.8, 83.4, 31.6, 29.9, 29.0, 24.7, 22.5, 14.0 ppm;

HRMS (ESI, m/z): Calcd. For $C_{19}H_{30}BO_2$: 301.2339, found $[M+H]^+$: 301.2350.



(*Z*)-4,4,5,5-tetramethyl-2-(1-(2-(prop-1-en-2-yl)phenyl)hept-1-enyl)-1,3,2-dioxaborolane (Table 2, entry 12):

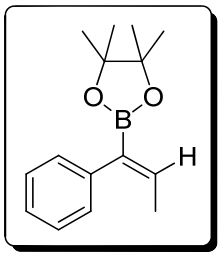
White solid; Yield: 61%; R_f = 0.40 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1618 cm^{-1} (C=C);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, J = 6.90 Hz, 3H), 1.22 (s, 12H), 1.22-1.32 (m, 4H), 1.35-1.41 (m, 2H), 1.99-2.07 (m, 5H), 4.86-4.87 (m, 1H), 5.09-5.10 (m, 1H), 6.49 (t, J = 7.15 Hz, 1H), 6.99-7.01 (m, 1H), 7.18-7.23 (m, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 145.2, 142.2, 138.3, 129.8, 127.3, 126.3, 126.0, 116.1, 83.2, 31.7, 30.2, 28.7, 24.7, 24.1, 22.5, 14.0 ppm;

HRMS (ESI, m/z): Calcd. For $C_{22}H_{34}BO_2$: 341.2652, found $[M+H]^+$: 341.2661.



(*Z*)-4,4,5,5-tetramethyl-2-(1-phenylprop-1-enyl)-1,3,2-dioxaborolane (Table 2, entry 13):

Colorless oil; Yield: 62%; R_f = 0.44 (Ethyl acetate/Hexane 1:10);

FTIR (KBr, neat): ν 1622 cm^{-1} (C=C);

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ 1.31 (s, 12H), 1.99 (d, J = 1.56 Hz, 3H), 7.30-7.39 (m, 6H) ppm;

^{1}H NMR (400 MHz, $CDCl_3$): (minor isomer) δ 1.27 (s, 12H), 1.76 (d, J = 6.96 Hz, 3H), 7.15-7.25 (m, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): (two isomers) δ 142.7, 142.3, 139.7, 137.9, 129.4, 129.1, 128.0, 127.7, 127.1, 125.8, 83.5, 83.4, 24.8, 24.7, 16.0, 15.9 ppm;

HRMS (ESI, m/z): Calcd. For $C_{15}H_{22}BO_2$: 245.1713, found $[M+H]^+$: 245.1716.

Appendix

LIST OF PUBLICATIONS

[1] Zhi-Liang Shen, Kelvin Goh, **Yong-Sheng Yang**, Yin-Chang Lai, Colin Hong An Wong, Hao-Lun Cheong, and Teck-Peng Loh, Direct synthesis of water-tolerant alkyl indium reagents and their application in palladium-catalyzed couplings with aryl halides, ***Angewante Chemie International Edition,*** **2011**, *50*, 511-514

[2] Zhi-Liang Shen, Kelvin Goh, Colin Wong, **Yong-Sheng Yang**, Yin-Chang Lai, Hao-Lun Cheong, Teck-Peng Loh, Direct synthesis of ester-containing indium homoenolate and its application in palladium-catalyzed cross-coupling with aryl halide, ***Chemical Communications,*** **2011**, *47*, 4778.

[3] Zhi-Liang Shen, Yin-Chang Lai, Colin Wong, Kelvin Goh, **Yong-Sheng Yang**, Hao-Lun Cheong, and Teck-Peng Loh, Palladium-catalyzed cross-coupling of indium homoenolate with aryl halide with wide functional group compatibility, ***Organic Letters,*** **2011**, *13*, 422-425

[4] Zhi-Liang Shen, Kelvin Goh, Hao-Lun Cheong, Colin Wong, Yin-Chang Lai, **Yong-Sheng Yang**, and Teck-Peng Loh, Synthesis of water-tolerant indium homoenolate in aqueous media and its application in the synthesis of 1,4-dicarbonyl compounds via palladium-catalyzed coupling with acid chloride, ***Journal of the American Chemical Society,*** **2010**, *132*, 15852-15855

[5] **Yong-Sheng Yang**, Zhi-Liang Shen, Teck-Peng Loh, Indium (Zinc)-copper-mediated barbier-type alkylation reaction of nitrones in water: synthesis of amines and hydroxylamines, ***Organic Letters,*** **2009**, *11*, 2213-2215

[6] **Yong-Sheng Yang**, Zhi-Liang Shen, Teck-Peng Loh, Cross-coupling reactions of aldehydes with α, β–unsaturated ketones in aqueous media, ***Organic Letters,*** **2009**, *11*, 1209-1212

[7] **Yong-Sheng Yang**, Chao Feng, Teck-Peng Loh, Palladium catalyzed hydroboration reaction of unactivated alkynes with bis(pinacolato)diboron in water, **2011**, Manuscript in preparation.

CONFERENCE PAPERS

[1] **Yong-Sheng Yang**, Zhi-Liang Shen, Teck-Peng Loh ***the ACS National Meeting & Exposition***, **2011**, Anaheim, CA. USA.

[2] **Yong-Sheng Yang**, Zhi-Liang Shen, Teck-Peng Loh ***6th Asian-European Symposium***, **2010**, P. 45, Singapore

[3] **Yong-Sheng Yang**, Chao Feng, Teck-Peng Loh ***6th Asian-European Symposium***, **2010**, P. 46, Singapore

[4] Zhi-Liang Shen, Kelvin Goh, Hao-Lun Cheong, Colin Wong, Yin-Chang Lai, **Yong-Sheng Yang**, and Teck-Peng Loh ***6th Asian-European Symposium***, **2010**, P. 43, Singapore