Part I: Studies on C-C bond formation reactions :
synthesis of imino acid derivatives. Part II:
Synthetic studies towards the total synthesis of
estrone

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**NANYANG
TECHNOLOGICAL
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**PART I: STUDIES ON C-C BOND FORMATION
REACTIONS: SYNTHESIS OF IMINO ACID DERIVATIVES
PART II: SYNTHETIC STUDIES TOWARDS THE TOTAL
SYNTHESIS OF ESTRONE**

**ZHOU WEIJUAN
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2010**

PART I
STUDIES ON C-C BOND FORMATION REACTIONS:
SYNTHESIS OF IMINO ACID DERIVATIVES

PART II
SYNTHETIC STUDIES TOWARDS THE TOTAL
SYNTHESIS OF ESTRONE

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of the requirement for the degree of Doctor of Philosophy

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SUMMARY

PART I

C-C bond formation reactions are among the most important processes in organic chemistry. Furthermore, C-C bond formation through cross-coupling between two different organic components is a basic technology in organic syntheses. Compounds containing heteroatoms, such as nitrogen, are widely present in nature. The syntheses of these compounds have already attracted much attention in industrial research due to their biological and pharmaceutical properties. In this regard, we focused our efforts to explore the synthesis of imino acid derivatives through direct coupling reactions.

Alkanes as Nature's most abundant organic molecular, have attracted increasing attention on their transformations. However, functionalization of alkanes to imino acid derivatives which may serve as important structural components of biologically active compounds has not been well studied. Therefore, an efficient free radical-initiated reaction of simple cycloalkanes with iminoglyoxylates without involving metal catalysts was developed in Chapter 1, which allowed the functionalization of alkanes to useful imino acid derivatives.

Alkynes are very useful building blocks for the synthesis of diverse compounds, especially through metal-promoted reactions. In Chapter 2, a reaction of terminal alkynes with cyclic iminoglyoxylate was described, which affords either

propargylic or allylic imino acid derivatives. Meanwhile, an insight into the mechanistic pathway is also discussed.

To make this strategy more synthetically useful, a simple and efficient direct coupling reaction of terminal alkynes with cyclic iminoglyoxylate using CuCl as a catalyst, FeCl₃ as a co-catalyst and TEMPO as an oxidant was also developed.

PART 2

At the beginning of the second part, a short and efficient synthesis of (±)-dehydroestrone methyl ether **1** had been developed. The significant features of this protocol are the indium tribromide catalyzed Mukaiyama-Michael addition reaction under neat conditions which can effectively connect the ring A, B and D, and the electrophilic substitution reaction carried out under thermodynamic conditions which successfully installed the allyl group at the position of C14.

With the aim to accomplish stereoselective synthesis of estrone, further studies on the development of asymmetric Michael addition reactions by organocatalysis were subsequently demonstrated.

Reaction conditions for model conjugate addition of β -ketoester with 2-cyclopentenone was successfully optimized to give corresponding adduct with high enantioselectivity (93% *ee*, 97:3 *dr*) and satisfactory yield (68% yield). Unexpectedly, we failed to extend it to our key step reaction due to the limited reaction scope.

Next, an efficient asymmetric direct vinylogous Michael addition that employed electron deficient vinyl malononitriles as the nucleophilic species in the presence of a catalytic amount of chiral 2-azanorbornyl derivatives was demonstrated.

The reaction features a metal-free approach, high efficiency of the catalyst, mild reaction conditions, high yields, and good enantioselectivities, providing a practical method to synthesize highly enantiopure multi-functional compounds. However, the reaction of malononitrile with 2-methyl-cyclopenten-2-one was observed in low yield and low *ee*.

Redesigning a more effective asymmetric catalytic system which could be applied to the asymmetric synthesis of estrone methyl ether is still ongoing.

INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
$^{\circ}\text{C}$	degree centigrade
ABq	AB quartet
Ac	acetyl
Ar	Aryl
AcCl	acetyl chloride
AcOH	acetic acid
Al_2O_3	Aluminium oxide
aq.	aqueous
BaSO_4	Barium sulfate
Bn	benzyl
bs	broad singlet
BuLi	butyl lithium
Bz	benzoyl
C	Carbon
Calcld	calculated
Cat.	catalytic
CBS	Corey-Bakshi-Shibata
CDCl_3	deuterated chloroform
CDC	Cross-Dehydrogenative Coupling
Cp	cyclopentadienyl
CH_4	Methane
CH_2Cl_2	dichloromethane
CHCl_3	chloroform
CCl_4	Carbon tetrachloride
Cl_2	Chlorine
cm^{-1}	inverse centimeter
COD	cyclooctadiene
CuBr	copper bromide
CuH	copper hydride

d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	doublets of doublet
de	diastereomeric excess
DCE	dichloroethane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublets of triplet
<i>ee</i>	enantiomeric excess
equiv.	equivalent
EI	electron impact ionization
Et	ethyl
ether	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FG	Functional group
FTIR	Fourier transform infrared spectroscopy
g	gram
Gly	glycine
h	hour
H	hydrogen
Hex	hexane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
IBX	2-iodoxybenzoic acid

<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constants
kg	kilogram
LDA	lithium diisopropylamide
M	concentration (mol/dm ⁻³)
MAO-B	monoamide oxidase B
M ⁺	parent ion peak (mass spectrum)
m	multiplet
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
M	concentration (normality)
Na ₂ PtCl ₄	Sodium tetrachloroplatinate(II)
Na ₂ PtCl ₆	Sodium hexachloroplatinate(IV)
NaOAc	Sodium Acetate
NCS	<i>N</i> -chlorosuccinimide
<i>n</i> -Bu	<i>n</i> -butyl
nmr	nuclear magnetic resonance
N.R.	no reaction
OTf	trifluoromethanesulfonate
Pt	Platinum
Pd	Pladium
Pd / C	palladium on carbon
Ph	phenyl
PMP	<i>p</i> -methoxyphenyl
PNBA	4-nitrobenzoic acid
ppm	parts per million

Py	pyridine
q	quartet
rt.	room temperature
R _f	retention factor
s	singlet
SET	single electron transfer
t	triplet
TADDOL	(4 <i>R</i> ,5 <i>R</i>)-2,2-Dimethyl- α' , α' , α' , α' -tetraaryldioxolane-4,5-dimethanol
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethyl silyl
<i>t</i> -Bu	<i>tert</i> -butyl
<i>t</i> -BuOK	potassium <i>tert</i> -butoxide
<i>t</i> BuOOH	<i>tert</i> -butyl hydroperoxide
<i>t</i> BuOO <i>t</i> Bt	<i>di-tert</i> -butyl peroxide
td	triplets of doublet
TEBA	tetraethyl ammonium bromide
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethyl silyl
Tf ₂ N	trifluoromethanesulfonimide
Tf ₂ O	triflate anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMS	trimethyl silyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TON	turnover number
TrSbCl ₆	tritylantimonyhexachloride
VTB	vinyltriphenylphosphonium

PART I

CHAPTER 1

***Free Radical-Initiated Direct Coupling Reactions of
Alkanes with Iminoglyoxylates***

1.1 OVERVIEW OF THE BACKGROUND

Alkanes as nature's most abundant organic molecular has attracted increasing attention on their transformations.¹ Selective functionalization of alkane C-H bonds is of great challenge and has been considered as a quite demanding research topic.² The major challenge is to replace selected H substituents of alkanes by any of a variety of functional groups, X (C-H→C-X) or to transform alkanes to any other valuable compounds.

Examples of selective fuctionalizations on the targeted C-H bond are rarely reported. Recent exciting progress will be reviewed in the following part, particularly focusing on synthetically useful aspects of the reported reactions, including reactivity, regioselectivity, substrate scope and functional group tolerance.

1.1.1 TRANSITION METAL CATALYZED ALKANE C-H BOND ACTIVATION

One major challenge of transition metals in chemistry has been the selective functionalization of alkanes. Although C-H bond activation by transition metals has been known for decades, there are few reactions that selectively functionalize alkanes, particularly using catalytic amounts of transition metals. In this section, recent development on this topic will be described.

¹ For some reviews, see: (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (b) Shilov, A. E.; Shulpin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Sen, A. *Acc. Chem. Res.* **1998**, *31*, 550. (d) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047. (e) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (f) Goldberg, K. I.; Goldman, A. S.; Eds. *Activation and Functionalization of C-H Bonds*: ACS Symposium Series 885; American Chemical Society: Washington, DC, 2004. (g) Dick, R. A.; Sanford, M. S. *Tetrahedron Lett.* **2006**, *62*, 2439. (h) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, *17*, 2437. (i) Fokin, A. A.; Schreiner, P. S. *Chem. Rev.* **2002**, *102*, 1551. (j) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

² (a) Arndtsen, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970-1973. (b) Bromberg, S. E.; Yang, W.; Asplund, M. C.; Lian, T.; McNamara, B. K.; Kotz, K. T.; Yeston, J. S.; Wilkens, M.; Frei, H.; Bergman, R. G.; Harris, C. B. *Science* **1997**, *278*, 260-263.

ALKANE C-H BOND BORYLATION

Organoboron compounds are among the most versatile synthetic intermediates.³ In 1997, Waltz and Hartwig reported a photochemical reaction of $\text{Cp}^*\text{Fe}(\text{CO})_2\text{Bcat}'$ [$\text{Cp}^* = \text{C}_5(\text{CH}_3)_5$, $\text{cat}' = 1,2\text{-O}_2\text{C}_6\text{H}_2\text{-3,5-(CH}_3)_2$] **1**, $\text{Cp}^*\text{Ru}(\text{CO})_2\text{Bcat}'$ **2**, and $\text{Cp}^*\text{W}(\text{CO})_3\text{Bcat}'$ **3** with a series of alkanes to produce alkylboronate esters by functionalizing alkanes exclusively at the terminal position and high yields were obtained for tungsten complex **3** (Scheme 1).⁴ The limitation of this method is the request of stoichiometric metal complex.

Scheme 1. Selective functionalization of alkanes using tungsten complexes by Hartwig *et al*

In 1999, Chen and Hartwig reported a catalytic borylation of alkanes with Rhenium complex which could regioselectively convert alkanes into linear alkylboronate esters.⁵

Scheme 2. Rhenium-Catalyzed Borylation by Hartwig *et al*

³ (a) Suzuki, A. *J. Synth. Org. Chem. Jpn.* **2005**, 63, 312. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

⁴ (a) Waltz, K. M.; Hartwig, J. F. *Science* **1997**, 277, 211. (b) Waltz, K. M.; Muhoro, C. N.; Hartwig, J. F. *Organometallics* **1999**, 18, 3383.

⁵ Chen, H. Y.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, 38, 3391.

In 2000, Chen and Hartwig made a key advance in this area by developing Rhodium complex $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$ (Cp^* , C_5Me_5 ; Me, methyl) **17** and used it to catalyze the formation of linear alkylboranes from commercially available borane reagents.⁶ Importantly, these reactions were performed under convenient thermal conditions (Scheme 3).

Scheme 3. Thermal, catalytic and regiospecific functionalization of alkanes by Hartwig *et al*

In 2004, Lawrence and Hartwig extended their strategy to heteroatom containing moieties, such as ethers, acetals, amines, and alkyl fluorides, which were all well-tolerated (see Figure 1).⁷ The high level of regioselectivity (typically > 20:1) at the least hindered and least electron-rich methyl group was observed. Furthermore, comparable yields and selectivities were obtained when these reactions were conducted with alkane as the limiting reagent (albeit with approximately double catalyst loading, see Figure 1).

Figure 1. Scope of products obtained from borylation catalyzed by **17**

⁶ Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, 287, 1995.

⁷ Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, 126, 15334.

As shown in Scheme 4, Hartwig and co-workers⁷ also demonstrated a tandem functionalization of methyl groups directly from the crude reactions to alkyl arenes, alcohols, and alkyl trifluoroborates.

Scheme 4. One-pot functionalization of alkanes by Hartwig *et al*

ALKANE C-H BOND DEHYDROGENATION

Alkane dehydrogenation reactions to produce valuable alkenes has been represented an attractive approach (Figure 2). Many research groups such as Bergman⁸, Felkin⁹, Jensen¹⁰, Goldman¹¹, Saito¹², Crabtree¹³ *et al* were involved in this area and have already made great contributions. Rh complex and Ir complex are among the most widely metal catalysts for this reaction.

Figure 2. General alkane C-H bond dehydrogenation

⁸ Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352.

⁹ (a) Baudry, D.; Ephritilchine, M.; Felkin, H.; Holmes-Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 788. (b) Felkin, H.; Fillebeen-Khan, T.; Holmes-Smith, R.; Zakrzewski, J. *Tetrahedron Lett.* **1984**, *25*, 1279.

¹⁰ Belli, J.; Jensen, C. M. *Organometallics* **1996**, *15*, 1532.

¹¹ (a) Maguire, J. A.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1989**, *111*, 7088. (b) Maguire, J. A.; Goldman, A. S. *J. Am. Chem. Soc.* **1991**, *113*, 6706. (c) Maguire, J. A.; Petrillo, A.; Goldman, A. S. *J. Am. Chem. Soc.* **1992**, *114*, 9492.

¹² (a) Nomura, K.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 161. (b) Fujii, T.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 757. (c) Fujii, T.; Higashino, Y.; Saito, Y. *J. Chem. Soc., Dalton Trans.* **1993**, 517.

¹³ (a) Aoki, T.; Crabtree, R. H. *Organometallics* **1993**, *12*, 294. (b) Burk, M. W.; Crabtree, R. H.; McGrath, D. V. *J. Chem. Soc., Chem. Commun.* **1985**, 1829. (c) Burk, M. W.; Crabtree, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 8025.

ALKANE METHATHESIS, HALOGENATION AND OTHERS

In 2006, Brookhart and co-workers reported that *n*-hexane was converted to a mixture of C₂-C₁₅₊ alkanes catalyzed by **24** and **25** at 125 °C (Scheme 5).¹⁴ The two catalysts, one for the metathesis step and the other for the dehydrogenation and hydrogenation steps, were utilized without interfering each other. Later, Glodman and Scott demonstrated a cyclooctane methathesis using similar combination of homogeneous catalysts with the aim of synthesizing large saturated rings.¹⁵

Scheme 5. Alkane methathesis reaction by Brookhart *et al*

Halogenation is also an effective way to functionalize alkanes to valuable halides. Early studies were focused on the reaction of methane with chlorine gas. Many metal catalysts were generated for this reaction, including silica-supported Rh complexes **26**,¹⁶ Pt on Al₂O₃ **27**,¹⁷ Pd on BaSO₄ **28**,¹⁷ and aqueous mixtures of Na₂PtCl₄ and Na₂PtCl₆ **29**.¹⁸ The selectivity for monochlorinated product CH₃Cl is high, but limitations still remained, such as high reaction temperature, moderate TON, in some cases demanding superstoichiometric Pt, and furthermore inapplicable in selective halogenation of more complex hydrocarbon substrates.

¹⁴ Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, 312, 257.

¹⁵ Ahuja, R.; Kundu, S.; Goldman, A. S.; Brookhart, M.; Vicente, B. C.; Scott, S. L. *Chem. Commun.* **2008**, 253.

¹⁶ Kitajima, N.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, 106, 2220.

¹⁷ Olah, G. A.; Gupta, B.; Farina, M.; Felberg, J. D.; Ip, W. M.; Husain, A.; Karpeles, R.; Lammertsma, K.; Melhotra, A. K.; Trivedi, N. J. *J. Am. Chem. Soc.* **1985**, 107, 7097.

¹⁸ Horvath, I. T.; Cook, R. A.; Millar, J. M.; Kiss, G. *Organometallics* **1993**, 12, 8.

Figure 2. Transition metal catalyzed chlorination of methane

1.1.2 RADICAL BASED ALKANE C-H BOND ACTIVATION

Radicals are widely used as active species in alkane activation, such as halogen radicals¹⁹, oxygen-centered radicals²⁰, nitrogen-centered radicals²¹, carbon centered radicals²² and others (Figure 3). Generally speaking, simple radicals poorly discriminate primary, secondary, and tertiary positions as well as C-H and C-C bonds, while bulky radicals are more selective toward C-H bonds.

Figure 3. Representative free radicals used in alkane activation

¹⁹ Examples see: (a) Ashton, D. S.; Tedder, J. M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 965-967. (b) Ashton, D. S.; Singh, H.; Tedder, J. M.; Walton, J. C.; Watt, E. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 125-128. (c) Sedlacek, A. J.; Wight, C. A. *J. Chem. Phys.* **1988**, 88, 2847-2848. (d) Levin, M. D.; Kaszynski, P.; Michl, J. *Chem. Rev.* **2000**, 100, 169-234. (e) Eaton, P. E.; Temme, G. H., III *J. Am. Chem. Soc.* **1973**, 95, 7508-7510. (f) Christl, M. *In Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press Ltd.: London, **1995**; Vol. 4, 163-224. (g) Della, E. W.; Head, N. J.; Mallon, P.; Walton, J. C. *J. Am. Chem. Soc.* **1992**, 114, 10730.

²⁰ Examples see: (a) Burcat, A.; Dixon-Lewis, G.; Frenklach, M.; Gardiner, W. C., Jr.; Hanson, R. K.; Salimian, S.; Troe, J.; Warnatz, J.; Zellner, R. *Combustion Chemistry, 1984*; Gardiner, W. C., Jr., Ed.; Springer-Verlag: New York, **1984**. (b) Kiani, S.; Tapper, A.; Staples, R. J.; Stavropoulos, P. *J. Am. Chem. Soc.* **2000**, 122, 7503-7517. (c) Newcomb, M.; Simakov, P. A. *Tetrahedron* **1998**, 39, 965. (d) MacFaul, P. A.; Ingold, K. U.; Wayner, D. D. M.; Que, L. J. *J. Am. Chem. Soc.* **1997**, 119, 10594. (e) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F. *Tetrahedron Lett.* **1994**, 35, 3759-3762.

²¹ Examples see: (a) Ehbrecht, J.; Hack, W.; Rouveirolles, P.; Wagner, H. G. *Ber. Bun. Phys. Chem.* **1987**, 91, 700. (b) Hack, W.; Kurzke, H.; Rouveirolles, P.; Wagner, H. G. *Ber. Bun. Phys. Chem.* **1986**, 90, 1210. (c) Hennig, G.; Wagner, H. G. *Ber. Bun. Phys. Chem.* **1995**, 99, 863. (d) Krajnik, P.; Michos, D.; Crabtree, R. H. *New J. Chem.* **1993**, 17, 805.

²² Examples see: (a) Gershuni, S.; Itzhak, N.; Rabani, J. *Langmuir* **1999**, 15, 1141. (b) Huyser, E. S. *J. Am. Chem. Soc.* **1960**, 82, 391. (c) Hawari, J. A.; Davis, S.; Engel, P. S.; Gilbert, B. C.; Griller, D. *J. Am. Chem. Soc.* **1985**, 107, 4721.

Dioxiranes show remarkable reactivity toward saturated hydrocarbons. As summarized in Scheme 6, hydrocarbon oxidation proceeds smoothly under mild conditions to afford products in good yields.²³

Scheme 6. Alkane hydrocarbon oxidation with dimethyl and methyltrifluoromethyl dioxiranes

Another important type of alkane functionalization utilizes removal of an electron through single electron transfer (SET) to give a radical cation paired with the reduced oxidant.²⁴ SET alkane activation are often more selective than electrophilic

²³ (a) Teager, D. S.; Murray, R. K. *J. Org. Chem.* **1993**, 58, 5548. (b) Mello, R.; Cassidei, L.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* **1990**, 31, 3067. (c) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, 111, 6749. (d) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, 108, 2470-2472. (e) desMarteau, D. D.; Donadelli, A.; Montanari, V.; Petrov, V. A.; Resnati, G. *J. Am. Chem. Soc.* **1993**, 115, 4897. (f) Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, 120, 6611. (g) Sorochinsky, A. E.; Petrenko, A. A.; Soloshonok, V. A.; Resnati, G. *Tetrahedron* **1997**, 53, 5995. (h) Fusco, C.; Fiorentino, M.; Dinoi, A.; Curci, R. *J. Org. Chem.* **1996**, 61, 8681. (i) Dehmlow, E. V.; Heiligenstadt, N. *Tetrahedron Lett.* **1996**, 37, 5363. (j) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkotz, S.; Winde, R. *Chem. Eur. J.* **1997**, 3, 105. (k) Adam, W.; Asensio, G.; Curci, R.; Gonzalez-Nunez, M. E.; Mello, R. *J. Org. Chem.* **1992**, 57, 953.

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radical activations. Notably, oxidation of acyclic,²⁵ cyclic alkanes²⁶ and even polycyclic²⁷ hydrocarbons with 1,2,4,5-tetracyanobenzene was introduced as a preparative method for alkane functionalization (Scheme 7).

Scheme 7. SET oxidation to selective functionalize adamantane

More recently, Li and co-workers²⁸ carried out a series of reactions to functionalize alkanes to valuable compounds. Various cycloalkanes react smoothly under specific conditions to afford corresponding products in good yields, though, only in some cases can the reaction proceed with toluene, norbornane, 1,4-dioxane and *n*-octane.

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Figure 4. Alkane transformation reactions by Li *et al*

1.1.3 CONCLUSION

It is well-known that nature is far more advanced to transform alkanes to some more useful derivatives;²⁹ also she possesses the highly selective and efficient catalytic abilities which chemists currently are elucidating and mimicking. Despite the success and synthetic beauty of these transition metal catalyzed and radical initiated transformations, it is still quite demanding that the transformations are of high practical value or immediately leading to large-scale production.

²⁹ Selected examples see: (a) Loew, G. H.; Harris, D. L. *Chem. Rev.* **2000**, *100*, 407. (b) Shilov, A. E.; Shteinman, A. A. *Acc. Chem. Res.* **1999**, *32*, 763. (c) Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J. *Chem. Rev.* **2000**, *100*, 235. (d) Ridyard, C. H.; Whittaker, R. A.; Higgins, S. D.; Roberts, S. M.; Willets, A. J.; Bailey, P. D.; Rosair, G. M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1811. (e) Bailey, P. D.; Higgins, S. D.; Ridyard, C. H.; Roberts, S. M.; Rosair, G. M.; Whittaker, R. A.; Willets, A. *J. Chem. Commun.* **1996**, 1833.

1.2 FREE RADICAL INITIATED DIRECT COUPLING REACTIONS OF ALKANES WITH CYCLIC IMINOGLYOXYLATES

The works summarized in the previous part not only provided valuable insight into the whole background of alkane functionalization, but intrigued us to investigate synthetically useful methods for alkane transformations. To the best of our knowledge, functionalization of alkanes to amino acid derivatives which would serve as important structural components of biologically active compounds has not been well studied. Herein, an efficient free radical-initiated reaction³⁰ of simple cycloalkanes with iminoglyoxylates is described, which allows the functionalization of alkanes to useful amino acid derivatives (Scheme 8).

Scheme 8. Proposed alkane functionalization via radical initiated reaction

To begin our study, imine **32a** which was prepared from commercially available starting material was employed as the model substrate. The combination of 1 equiv of imine **32a** with cyclooctane (25 equiv) and 0.5 equivalent of *tert*-butyl hydroperoxide in a sealed tube at 135 °C for 15 h produced a 79 : 21 ratio of **34a** and **35a**, in a total of 16% isolated yield (entry 1, Table 1). In order to improve the chemoselectivity and yield of the product, the amount of peroxide was examined. Entries 1 to 3 illustrate that the chemoselectivity is improved by increasing the amount of peroxide. Only product **34a** was obtained when 2 equivalents of *tert*-butyl

³⁰ Selected examples on radical addition to C=N bonds: (a) Citterio, A.; Filippini, L. *Synthesis* **1986**, 473. (b) Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138. (c) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043.

hydroperoxide was used in the reaction, albeit in moderate yield (entry 3, Table 1). Next, different peroxides were screened. We found that yield of the desired product **34a** was dramatically increased to 76% yield by employing *di-tert*-butylperoxide (entry 4, Table 1), and the best yield was obtained by using 2.5 equiv of *di-tert*-butylperoxide (entry 5, Table 1). Lower temperature resulted in decrease of the product yield (entry 6, Table 1). Thus, the conditions in entry 5 were chosen as the best conditions for further study.

Table 1. Optimization of Reaction Conditions for **32a** with Cyclooctane

entry	peroxide (equiv)	temp (°C)	time (h)	yield (%) ^a
1	<i>t</i> BuOOH (0.5)	135	15	16 (34a : 35a =79:21) ^b
2	<i>t</i> BuOOH (1.0)	135	15	36 (34a : 35a =73:27) ^b
3	<i>t</i> BuOOH (2.0)	135	15	56 (34a)
4	<i>t</i> BuOO <i>t</i> Bu (2.0)	135	15	76 (34a)
5	<i>t</i> BuOO <i>t</i> Bu (2.5)	135	15	82 (34a)
6	<i>t</i> BuOO <i>t</i> Bu (2.5)	120	15	52 (34a)

^a Isolated yield. ^b The ratio was determined by ¹H NMR analysis.

Under the optimized conditions a series of readily available alkanes were examined. As summarized in Table 2, various cycloalkanes could be applied to this transformation. Cyclohexane, cycloheptane and cyclooctane reacted smoothly to afford the corresponding products in moderate to good yields (entries 1, 3 and 4, Table 2). A decrease in yield was observed when cyclopentane was used as a substrate possibly due to its low boiling point. Unfortunately, the reaction of a linear alkane, octane, gave a mixture of three regioisomers in a ratio of 1:1:1 (entry 5, Table

2).³¹ No reaction was observed when toluene, norbornane and 1,4-dioxane were subjected to the same reaction conditions.

Next, the reaction scope was extended to 5,5-dimethyl-substituted, 5-methyl-5-phenyl-substituted and 5,6-dihydro-5,6-diphenyl-substituted imine substrates **32b**, **32c** and **32d** (entries 6-14, Table 2). Imines **32d** and **32c** reacted with cycloalkanes smoothly to give the corresponding products in moderate to good yields. However, there was no desired product observed when **32d** was reacted with cyclooctane.

Table 2. The Reaction Scope of Alkanes and Imines^a

entry	substrate		product	yield (%) ^b
	32	33	34	
1			34a	82
2	32a		34b	48
3	32a		34c	65
4	32a		34d	72
5	32a		34e^c	50 ^c (1:1:1)
6			34f	76
7	32b		34g	42

³¹ The structures of three regioisomers are as follows, the ratio was determined by ¹H NMR

8	32b		33c	34h	58
9	32b		33d	34i	71
10			33a	34j	81
11	32c		33b	34k	58
12	32c		33c	34l	62
13	32c		33d	34m	74
14 ^d			33a	-	-

^a Conditions: iminoglyoxylate (0.1 mmol), **33** (2.5 mmol), di-*tert*-butyl peroxide (0.25 mmol), 135 °C, 15 hours. ^b Isolated yield. ^c Total yield of three regioisomers and the ratio was determined by ¹H NMR analysis. ^d no reaction for substrate **32d**.

As shown in Scheme 8, product **34a** could be readily transformed to amino acid derivatives **35a** via reduction using hydrogenation on Pd/C. Interestingly, when **35a** was subjected to the oxidative coupling conditions, it was reverted to **34a** in 89% yield.

Scheme 9. The Reduction of **34a** Followed by Oxidation

³² The synthesis of **32d** is as follows:

Based on these experimental observations, a possible mechanism is depicted in Scheme 10. Homolytic cleavage of the peroxide radical initiator produces alkoxy radicals, which abstract hydrogen from the cycloalkane to afford the corresponding cycloalkyl radical. Subsequently, addition of the cycloalkyl radical to imine **32a** generates an intermediate bearing a nitrogen radical, which allows the cycloalkyl radical to be regenerated. Meanwhile, **35a** is oxidized by excess peroxide to furnish the final product **34a**. In this process, 2.5 equiv of *di-tert*-butylperoxide is essential for achieving good yield. This may be due to the fact that the nitrogen radical may be easily oxidized to **34a** in the presence of excess peroxide, instead of helping to regenerate the cycloalkyl radical necessary for the catalytic cycle to propagate.

Scheme 10. Possible Mechanism for the Reaction of Cycloalkanes with Iminoglyoxylates
Mediated by Peroxide

1.3 CONCLUSION

In conclusion, we have demonstrated a highly efficient radical initiated reaction between the unactivated C-H bonds of cycloalkanes with cyclic iminoglyoxylates. With this method, cycloalkanes can be highly functionalized. The diphenylethylene group can be cleaved readily by hydrogenolysis³³ to furnish the free amino acid, which may serve as important structural components of biologically active molecules.

³³ (a) Hahn, B. T.; Frohlich, R.; Harms, K.; Glorius, F. *Angew. Chem. Int. Ed.* **2008**, 47, 9985. (b) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, 61, 2044.

1.4 EXPERIMENTAL

General information

Commercial solvents and reagents were used without further purification. *tert*-butylhydroperoxide, *tert*-butylperoxide, cycloalkanes and 2,4,4-trimethyl-2-oxazoline were purchased from Acros, Sigma-Aldrich and Alfa-Aesar and used without further purification. 5,5-dimethyl-substituted, 5,5-diphenyl-substituted, 5-methyl-5-phenyl-substituted and 5,6-dihydro-5,6-diphenyl-substituted imine substrates **32a**, **32b**, **32c** and **32d** were prepared according to relative references¹.

5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**32a**)

¹H-NMR (CDCl₃, 400 MHz): δ 7.73 (s, 1H), 4.22 (s, 2H), 1.32 (s, 6H) ppm;

¹³C-NMR (CDCl₃, 75 MHz): δ 154.0, 149.9, 73.8, 54.5, 24.1 (2C) ppm.

5,6-dihydro-5,5-diphenyl-1,4-oxazin-2-one (**32b**)

¹H-NMR (CDCl₃, 400 MHz): δ 8.08 (s, 1H), 7.52-7.28 (m, 10H), 4.86 (s, 2H) ppm;

¹³C-NMR (CDCl₃, 75 MHz): δ 153.9, 152.0, 141.3, 128.7 (2C), 128.0, 127.1 (2C), 72.3, 65.4 ppm.

¹ (a) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, 61, 2044. (b) Shafer, C. M.; Morse, D. I.; Molinski, T. F. *Tetrahedron* **1996**, 52, 14475.

5,6-dihydro-5-methyl-5-phenyl-1,4-oxazin-2-one (32c)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.99 (s, 1H), 7.43-7.31 (m, 5H), 4.86 (AB_q, J = 11.6 Hz, 2H), 1.65 (s, 3H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 154.2, 151.4, 141.1, 128.9 (2C), 128.0, 125.6 (2C), 74.2, 60.0, 25.0 ppm.

(5*S*,6*R*)-5,6-dihydro-5,6-diphenyl-1,4-oxazin-2-one

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.27 (d, J = 1.6 Hz, 1H), 7.27-7.14 (m, 6H), 6.94-6.92 (m, 2H), 6.71-6.69 (m, 2H), 5.83 (d, J = 3.8 Hz, 1H), 5.33 (dd, J_1 = 3.7 Hz, J_2 = 1.4 Hz, 1H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 155.9, 153.3, 134.1, 130.5, 128.6, 128.56 (2C), 128.51, 128.3 (2C), 128.2 (2C), 126.2 (2C), 81.0, 66.6 ppm.

General procedure for the reaction of cycloalkanes with iminoglyoxylates

A sealed tube was charged with cyclic imine (0.1 mmol, 1equiv), *di-tert*-butyl peroxide (0.25 mmol, 2.5 equiv) and cycloalkane (2.5 mmol, 25 equiv). Then the

resulting solution was stirred at 135 °C overnight. After cooling to room temperature, the mixture was directly subjected to column chromatography to afford the corresponding product.

3-Cyclooctyl-5,6-dihydro-5,5-diphenyl-1,4-oxazin-2-one (34a)

Colorless oil (29.7 mg, 82% yield); R_f = 0.55 (hexane : ethyl acetate = 3:1);

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.38-7.24 (m, 10H), 4.77 (s, 2H), 3.27-3.21 (m, 1H), 1.87-1.76 (m, 6H), 1.61-1.58 (m, 8H) ppm;

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 166.1, 155.2, 142.1 (2C), 128.6 (4C), 127.6 (2C), 127.1 (4C), 72.1, 64.3, 41.1, 29.6 (2C), 26.8 (2C), 26.3, 25.4 (2C) ppm;

FTIR (KBr, neat): ν = 3053, 2305, 1738, 1636, 1265, 895, 740 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{24}\text{H}_{28}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 362.2120, found 362.2111.

3-Cyclopentyl-5,6-dihydro-5,5-diphenyl-1,4-oxazin-2-one (34b)

Colorless oil (15.3 mg, 48% yield); R_f = 0.54 (hexane : ethyl acetate = 3:1)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.37-7.24 (m, 10H), 4.78 (s, 2H), 3.46-3.38 (m, 1H), 2.00-1.93 (m, 2H), 1.91-1.81 (m, 2H), 1.80-1.76 (m, 2H), 1.74-1.67 (m, 2H) ppm;

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 164.4, 155.5, 142.1 (2C), 128.6 (4C), 127.6 (2C), 127.1 (4C), 72.1, 64.2, 43.2, 30.4 (2C), 25.7 (2C) ppm;

FTIR (KBr, neat): ν = 3053, 2305, 1740, 1636, 1421, 1265, 895, 743 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{21}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 320.1651, found 320.1642.

3-Cyclohexyl-5,6-dihydro-5,5-diphenyl-1,4-oxazin-2-one (34c)

Colorless oil (21.7 mg, 65% yield); R_f = 0.55 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.24 (m, 10H), 4.77 (s, 2H), 3.02-2.95 (m, 1H), 1.96-1.73 (m, 5H), 1.52-1.34 (m, 5H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 165.1, 155.0, 142.1 (2C), 128.6 (4C), 127.6 (2C), 127.1 (4C), 72.2, 64.2, 41.6, 30.3 (2C), 26.0, 25.9 (2C) ppm;

FTIR (KBr, neat): ν = 3053, 2305, 1738, 1636, 1421, 1265, 895, 740 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{22}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 334.1807, found 334.1800.

3-Cycloheptyl-5,6-dihydro-5,5-diphenyl-1,4-oxazin-2-one (34d)

Colorless oil (25.0 mg, 72% yield); R_f = 0.54 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.24 (m, 10H), 4.77 (s, 2H), 3.20-3.13 (m, 1H), 1.96-1.91 (m, 2H), 1.82-1.51 (m, 10H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 165.9, 155.2, 142.1 (2C), 128.6 (4C), 127.6 (2C), 127.1 (4C), 72.1, 64.2, 42.9, 31.9 (2C), 28.3 (2C), 26.6 (2C) ppm;

FTIR (KBr, neat): ν = 3053, 2305, 1738, 1636, 1421, 1265, 895, 740 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{23}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 348.1964, found 348.1957.

3-Cyclooctyl-5,6-dihydro-5-methyl-5-phenyl-1,4-oxazin-2-one (34f)

Colorless oil (22.8 mg, 76% yield); R_f = 0.51 (hexane : ethyl acetate = 3:1)

^1H NMR (500 MHz, CDCl_3): δ 7.45-7.31 (m, 5H), 4.37 (AB_q, J = 11.5 Hz, 2H), 3.26-3.21 (m, 1H), 1.89-1.58 (m, 17H) ppm;

^{13}C NMR (125 MHz, CDCl_3): δ 165.4, 155.6, 142.3, 128.7 (2C), 127.6, 126.4 (2C), 74.8, 58.9, 41.0, 29.9, 29.8, 26.8, 26.6, 26.4, 25.5, 25.4, 25.0 ppm;

FTIR (KBr, neat): ν = 3155, 2926, 2252, 1732, 1635, 1471, 1381, 910, 732, 651 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{19}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 300.1964, found 300.1949.

3-Cyclopentyl-5,6-dihydro-5-methyl-5-phenyl-1,4-oxazin-2-one (34g)

Colorless oil (10.8 mg, 42% yield); R_f = 0.52 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 7.45-7.27 (m, 5H), 4.38 (AB_q, J = 11.4 Hz, 2H), 3.44-3.38 (m, 1H), 2.05-1.66 (m, 8H), 1.58 (s, 3H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 163.6, 155.9, 142.3, 128.7 (2C), 127.6, 125.7 (2C), 74.2, 58.9, 43.2, 30.6, 30.2, 25.6, 25.6, 25.0 ppm;

FTIR (KBr, neat): ν = 3154, 2959, 2253, 1734, 1635, 1472, 1381, 908, 733, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{16}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 258.1494, found 258.1487.

3-Cyclohexyl-5,6-dihydro-5-methyl-5-phenyl-1,4-oxazin-2-one (34h)

Colorless oil (15.7 mg, 58% yield); R_f = 0.52 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 7.45-7.29 (m, 5H), 4.37 (AB_q, J = 11.2 Hz, 2H), 3.02-2.95 (m, 1H), 1.97-1.66 (m, 6H), 1.57 (s, 3H), 1.50-1.38 (m, 4H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 164.4, 155.4, 142.3, 128.7 (2C), 127.6, 125.7 (2C), 74.2, 58.9, 41.5, 30.4, 30.2, 26.0, 26.0, 25.9, 25.0 ppm;

FTIR (KBr, neat): ν = 3155, 2932, 2252, 1732, 1636, 1466, 1381, 912, 741, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{17}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 272.1652, found 272.1645.

3-Cycloheptyl-5,6-dihydro-5-methyl-5-phenyl-1,4-oxazin-2-one (34i)

Colorless oil (20.3 mg, 71% yield); R_f = 0.51 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.29 (m, 5H), 4.37 (AB_q, J = 11.4 Hz, 2H), 3.19-3.13 (m, 1H), 1.99-1.62 (m, 12H), 1.57 (s, 3H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 165.2, 155.5, 142.3, 128.7 (2C), 127.6, 125.7 (2C), 74.2, 58.9, 42.9, 32.1, 31.8, 28.2 (2C), 26.7, 26.6, 25.0 ppm;

FTIR (KBr, neat): ν = 3155, 2928, 2253, 1732, 1636, 1472, 1381, 908, 733, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 286.1807, found 286.1810.

3-Cyclooctyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (34j)

Colorless oil (19.3 mg, 81% yield); R_f = 0.49 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 4.13 (s, 2H), 3.10-3.06 (m, 1H), 1.78-1.59 (m, 14H), 1.26 (s, 6H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 164.4, 155.8, 74.3, 54.0, 40.9, 29.9, 26.5 (2C), 26.4 (2C), 25.5 (2C), 24.8 (2C) ppm;

FTIR (KBr, neat): ν = 3156, 2926, 2253, 1732, 1633, 1468, 1381, 910, 733, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{14}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 238.1807, found 238.1807.

3-Cyclopentyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (34k)

Colorless oil (11.4 mg, 58% yield); R_f = 0.48 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 4.14 (s, 2H), 3.29-3.23 (m, 1H), 1.91-1.87 (m, 2H), 1.73-1.63 (m, 6H), 1.26 (s, 6H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 162.4, 156.0, 74.4, 54.0, 43.0, 30.3 (2C), 25.6 (2C), 24.8 (2C) ppm;

FTIR (KBr, neat): ν = 3154, 2970, 2253, 1734, 1631, 1467, 1381, 908, 733, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{11}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 196.1338, found 196.1329.

3-Cyclohexyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (34l)

Colorless oil (13.0 mg, 62% yield); R_f = 0.48 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 4.12 (s, 2H), 2.88-2.83 (m, 1H), 1.83-1.63 (m, 7H), 1.40-1.34 (m, 3H), 1.26 (s, 6H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 163.3, 155.6, 74.4, 54.1, 45.7, 41.2, 30.2 (2C), 26.0 (2C), 24.8 (2C) ppm;

FTIR (KBr, neat): ν = 3154, 2932, 2253, 1732, 1630, 1466, 1381, 910, 733, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{12}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 210.1494, found 210.1488.

3-Cycloheptyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (34m)

Colorless oil (16.6 mg, 74% yield); R_f = 0.49 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 4.13 (s, 2H), 3.0-2.96 (m, 1H), 1.84-1.73 (m, 4H), 1.55-1.49 (m, 8H), 1.26 (s, 6H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 164.1, 155.7, 74.3, 54.0, 42.9, 31.7 (2C), 28.0 (2C), 26.8 (2C), 24.8 (2C) ppm;

FTIR (KBr, neat): ν = 3154, 2253, 1732, 1645, 1466, 1381, 910, 733, 650 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 224.1651, found 224.1640.

Typical procedure for the reduction of 34a into primary amine

To a solution of **34a** (0.1 mmol, 36.1 mg, 1 equiv) in 3 mL methanol was added Pd/C (0.01 mmol, 10.5 mg, 0.1 equiv). The resulting mixture was stirred under hydrogen atmosphere for overnight. After filtration, the product **35a** was obtained by column chromatography in 90% yield as a white solid.

3-Cyclooctyl-5,5-diphenylmorpholin-2-one (35a)

White solid (32.6 mg, 90% yield); R_f = 0.50 (hexane : ethyl acetate = 3:1)

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.26 (m, 10H), 4.88 (d, J = 11.6 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 3.24 (s, 1H), 2.50-2.40 (m, 1H), 2.16-2.05 (m, 1H), 1.90-1.47 (m, 14H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 170.3, 143.7, 141.4, 129.1 (2C), 128.6 (2C), 127.9, 127.6, 127.4 (2C), 126.7 (2C), 74.7, 62.0, 60.9, 40.0, 31.3, 29.5, 26.6, 26.4, 26.3, 26.2, 26.1 ppm;

FTIR (KBr, neat): ν = 3445, 3053, 2305, 1734, 1636, 1421, 1265, 895, 740 cm^{-1} ;

HRMS (EI): m/z calculated for $\text{C}_{24}\text{H}_{30}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 364.2277, found 364.2263.

Typical procedure for the oxidation of 35a into 34a

A seal tube was charged with **35a** (0.056 mmol, 20 mg, 1 equiv), *di-tert-butyl* peroxide (0.112 mmol, 22 μL , 2.0 equiv) and cyclooctane 0.3 mL. Then the resulting solution was stirred at 135 °C for 12 hours. After cooling to room temperature, the mixture was directly subjected to column chromatography to afford the corresponding product **34a** in 89% yield (18 mg).

CHAPTER 2

*Studies on Coupling Reactions of Terminal Alkynes
with Cyclic Iminoglyoxylate*

2.1 OVERVIEW OF THE BACKGROUND

Alkynes are very useful building blocks for the synthesis of diverse compounds, especially through metal-promoted reactions, like the well-known Glaser-Hay oxidative dimerization of alkynes¹ and the Sonogashira coupling reaction². Copper-catalyzed cycloaddition of azides and acetylenes³ and the catalytic asymmetric alkynylation of aldehydes,⁴ which produces highly enantioenriched propargylic alcohols, are also milestones in the alkyne chemistry. In this section, we will be discussing the recent contributions to metal-catalyzed non-asymmetric alkynylation of C=N electrophiles and some breakthroughs in metal-catalyzed alkyne chemistry.

2.1.1 METAL-CATALYZED NON-ASYMMETRIC ALKINYLYATION OF C=N ELECTROPHILES

Propargylic amines are important building blocks for the synthesis of various nitrogen containing compounds⁵ and often used as intermediates⁶ for the preparation

¹ Siemsen, P.; Livingston, R. C.; Diederich, F.; *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

² K. Sonogashira in *Palladium-catalyzed Alkynylations, Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1 (Eds.: E.-i. Negishi, A. de Meijere), John Wiley & Sons, Inc., New York, 2002, p. 493.

³ Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

⁴ Boyall, D.; Frantz, D. E.; E. Carreira, M. *Org. Lett.* **2002**, *4*, 2605.

⁵ (a) Nilsson, B. M.; Hacksell, U. J. *J. Heterocycl. Chem.* **1989**, *26*, 269. (b) Havey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268. (c) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (d) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804.

⁶ examples see: (a) Porco, J. A.; Schoenen, J. F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) Nicolaou, K. C.; Hwang, C. -K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (c) Yoon, T.; Shair, M. D.; Danishefsky, S. J.; Schulte, G. K. *J. Org. Chem.* **1994**, *59*, 3752. (d) Formal total synthesis of (+)-conessine: Jiang, B.; Xu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2543. (e) Synthesis of (+)-saxitoxin: Fleming, J. J.; Du Bois, J. J. *J. Am. Chem. Soc.* **2006**,

of natural products. Furthermore, their derivatives were found to be biologically active⁷ such as the enzyme monoamine oxidase B (MAO-B) which could function as inhibitors.⁸

Addition of alkynes to C=N electrophiles is the most reliable and efficient method to produce propargylic amines.⁹ Classical methodologies¹⁰ for the synthesis of propargylic amines have usually employed alkynyl-metal reagents to undergo nucleophilic addition to C=N electrophiles (Scheme 1). However, the strong bases used to remove the acidic terminal acetylenic proton are incompatible with sensitive substrates. Another disadvantage is that the resulting polar alkynyl-metal reagents are too reactive to allow a stereoselective alkynylation to proceed under mild conditions.

Scheme 1. Classical alkynylation with imines

In the last several years, direct alkynylation using *in situ* generated alkynyl-metal species has undergone significant progress and will be highlighted below.

128, 3926. (f) Synthesis of β -lactams: Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, 52, 3488. Miyachi, N.; Kanda, F.; Shibasaki, M. *J. Org. Chem.* **1989**, 54, 3551. (g) Synthesis of inhibitors of the serotonin and norepinephrine transporter: Hoepping, A.; Johnson, K. M.; George, C.; Flippen-Anderson, J.; Kozikowski, A. P. *J. Med. Chem.* **2000**, 43, 2064.

⁷ Wright, J. L.; Gregory, T. F.; Kesten, S. P.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D.; Espitia, S. A.; Konkoy, C. S.; Whittemore, E. R.; Woodward, R. M. *J. Med. Chem.* **2000**, 43, 3408.

⁸ Yu, P. H.; Davis, B.; Boulton, A. A. *J. Med. Chem.* **1992**, 35, 3705.

⁹ (a) Bloch, R. *Chem. Rev.* **1998**, 98, 1407. (b) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.

¹⁰ Examples see: (a) Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett.* **2000**, 2, 1855. (b) Rosas, N.; Sharma, P.; Alvarez, C.; Gomez, E.; Gutierrez, Y.; Mendez, M.; Toscano, A.; Maldonado, L. A. *Tetrahedron Lett.* **2003**, 44, 8019. (c) Ding, C. H.; Chen, D. D.; Luo, Z. B.; Dai, L. X.; Hou, X. L. *Synlett* **2006**, 1272. (d) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, 32, 375. (e) Merino, P.; Anoro, S.; Castillo, E.; Merchan, F.; Tejero, T. *Tetrahedron: Asymmetry* **1996**, 7, 1887. (f) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051. (g) Denis, J. N.; Tchertchian, S.; Tomassini, A.; Vallee, Y. *Tetrahedron Lett.* **1997**, 38, 5503. (h) Curtois, G.; Desre, V.; Miginiac, L. *J. Organomet. Chem.* **1998**, 570, 279. (i) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J. L.; Dessinges, A. *Synlett* **1998**, 251. (j) Rae, A.; Ker, J.; Tabor, A. B.; Castro, J. L.; Parsons, S. *Tetrahedron Lett.* **1998**, 39, 6561. (k) Ahn, J. H.; Juong, M. J.; Yoon, N. M.; Oniciu, D. C.; Katritzky, A. R. *J. Org. Chem.* **1999**, 64, 488. (l) Dagoneau, C.; Denis, J. N.; Vallee, Y. *Synlett* **1999**, 602. (m) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, 64, 8970. (n) Florio, S.; Troisi, L.; Capriati, V.; Suppa, G. *Eur. J. Org. Chem.* **2000**, 3793. (o) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H. P. *J. Org. Chem.* **2000**, 65, 6423. (p) Review see: Blanchet, J.; Bonin, M.; Micouin, L. *Org. Prep. Proced. Int.* **2002**, 34, 457.

2.1.1.1 ZINC-CATALYZED ALKYNE ADDITIONS

In 1999, Carreira and co-workers reported the first zinc-catalyzed addition of alkyne to nitrones (Scheme 2).¹¹ This reaction proceeded smoothly by using of 0.1 equivalent of $\text{Zn}(\text{OTf})_2$ in combination with 0.25 equivalent of *i*- Pr_2NEt to produce *N*-hydroxy propargylamines **6** in good yields. Interestingly, nitrones derived from aliphatic aldehydes were more reactive than those derived from aromatic aldehydes.

They subsequently extended this methodology to nitronone substrates bearing mannose-derived chiral auxiliaries in order to prepare optically active *N*-hydroxy propargylamines.^{12,13} It was found that the reaction can be carried out using a variety of nitrones as well as with an equally wide range of alkynes to afford corresponding products **10** in good yields and excellent diastereoselectivities (Scheme 2). A convenient aspect of the process is the fact that removal of the auxiliary is effected upon heating $\text{MeOH} : \text{H}_2\text{O}$ (3:1) solutions of adducts **10** with 1.6 equivalent of $\text{H}_2\text{NOH} \cdot \text{HCl}$ (or $\text{N}_2\text{H}_4 \cdot 2\text{HCl}$) and 1.5 equivalent of NaOAc ,¹⁴ affording enantioenriched propargylic hydroxyl-amines in high yields.

To further extend the addition reaction, Carreira and co-workers varied the reaction conditions by using rigorously dried ZnCl_2 ¹³ and excluded ligand from the reaction. Although the yield and selectivity obtained were higher, the conditions were stoichiometric, and 1.5 equivalent of ZnCl_2 and alkynes each (mostly **3**) were necessary.

¹¹ Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

¹² Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054.

¹³ Topic, D.; Aschwanden, P.; Fassler, R.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 5329.

¹⁴ Lantos, I.; Flisak, J.; Liu, L.; Matsuoka, R.; Mendelson, W.; Stevenson, D.; Tubman, K.; Tucker, L.; Zhang, W. Y.; Adams, J.; Sorenson, M.; Garigipati, R.; Erhardt, K.; Ross, S. *J. Org. Chem.* **1997**, *62*, 5385.

Scheme 2. Zinc-mediated alkynylation of nitrones by Carreira and co-workers

In 2002, Vallee and co-workers¹⁵ reported that nitrones reacted with various terminal alkynes in the presence of 0.2 equivalent of diethylzinc in toluene to afford *N*-propargyl-hydroxylamines in excellent yields (Scheme 3). It is noteworthy that no additional base was required under these conditions. Detailed NMR studies were also conducted and discussed.

Scheme 3. Diethylzinc mediated alkynylation by Vallee *et al*

In 2003, Jiang and co-workers¹⁶ reported a diastereoselective addition of alkynes to *N*-alkylimines, catalyzed by ZnCl_2 with moderate diastereoselectivity and yield (Scheme 4). It is important to mention that TMSCl functioned as a Lewis acid to activate substrates that are less reactive than nitrones.

¹⁵ Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallee, Y. *Org. Lett.* **2002**, 4, 1463.

¹⁶ Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, 44, 6767.

Scheme 4. ZnCl_2 catalyzed alkyne-amine reaction by Jiang *et al*

In situ generated *N*-acyliminium ions are active $\text{C}=\text{N}$ electrophiles for alkyne-amine reactions. In 2004, Carreira and co-workers^{17a} reported a new addition reaction of zinc-alkynylides to *N*-acyl and *N*-phosphinoyl iminiums, allowing access to a large number of different *N*-protected propargylic amines (Scheme 5). Interestingly, cyclic substrate isoquinoline was applicable in this reaction, producing the resulting adduct in 83% yield. In 2005, Kim and co-workers further examined the cyclic substrates.^{17b}

Scheme 5. Alkyne-amine reaction using *N*-acyliminium ions

As shown in Scheme 6, protected imines were also able to participate in alkyne-amine reaction smoothly under respective conditions developed by groups of Kim¹⁸ and Bolm¹⁹. In 2006, Bolm and co-worker¹⁹ observed that Me_2Zn was more efficient than Et_2Zn for alkyne-amine reaction of imines, and 1.5 equivalent of Me_2Zn was

¹⁷ (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, 6, 1497. (b) Lee, K. Y.; Lee, M. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, 26, 665.

¹⁸ Lee, K. Y.; Lee, C. G.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2005**, 46, 69.

¹⁹ Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, 71, 1558.

required for this reaction. This differs from diethylzinc catalyzed alkynylation of nitrones reported by Vallee.¹⁵ In the course of this study, Bolm *et al* also demonstrated a one-pot method to synthesize various *N*-aryl propargylic amines directly starting from the corresponding aldehydes, amines and alkynes. However, the amount of Me_2Zn had to be increased to 3.5 equivalents.

2.1.1.2 COPPER-CATALYZED ALKYNE ADDITIONS

Copper Lewis acids possess superior abilities in catalyzing addition reactions of alkynes to $\text{C}=\text{N}$ electrophiles. In 2002, Li and co-workers²⁰ reported a highly efficient Ru/Cu catalyzed one-pot addition of acetylene to *in situ* generated imines in water or under solvent-free conditions. In this study, both metal salts were crucial for achieving high yields. Without using RuCl_3 as the catalyst, the efficiency of the reaction was reduced and no product was formed when CuBr was omitted.

²⁰ Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268.

In 2002, Knochel and co-workers²¹ reported copper catalyzed addition reactions of various alkynes to enamines, through iminium ion intermediates, to afford corresponding adducts in good to high yields. However, only enolisable aldehydes can generate the enamines, no aromatic aldehydes can be used to prepare enamine substrates; therefore, the reaction scope was limited accordingly.

Scheme 8. Alkynylation of enamines by Knochel *et al*

In situ generated iminium species acting as the electrophiles were also widely used in copper-catalyzed alkynylation reactions. In 2002, Li and co-workers²² reported a coupling reaction of alkynes with *N*-acylimines and *N*-acyliminium ions mediated by CuBr in water to generate propargyl amide derivatives (Scheme 9). Since the use of only 0.1–0.3 equivalent of CuBr resulted in low yield of the product, an excess amount of CuBr (2–3 equivalents) was required to enhance the productivity.

Scheme 9. Coupling of alkynes with *N*-acylimine and *N*-acyliminium ions in water by Li *et al*

Almost contemporary with the studies by Carreira *et al*¹⁷ on zinc-promoted alkynylation, in 2004, Arndtsen *et al*²³ employed 10 mol% of CuI as a promoter and *in situ* generated acyliminium ions as substrates, to perform the similar transformation

²¹ (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797.

²² Zhang, J. H.; Wei, C. M.; Li, C. J. *Tetrahedron Lett.* **2002**, *43*, 5731.

²³ Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

(Scheme 10). Instead of iminium ions generated from acyl chlorides, those generated from chloroformate could also participate in this reaction smoothly. Furthermore, heterocyclic substrates, even pyridine, were applicable to this method.

Scheme 10. CuI catalyzed coupling of imines, acid chlorides, and alkynes by Arndtsen *et al*

Later, Arndtsen and co-workers²⁴ extended the reaction scope to *N*-trimethylsilylimine substrates, using either copper or zinc catalyst (Scheme 11). Construction of TMS-substituted imines and *in situ* generation of *N*-acyl iminium ions were performed in the same reaction flask, followed by addition of alkynes, then the elimination of TMS-Cl to afford various propargylamides. As the cleavage of the N–Si bond was achieved in the course of reaction, secondary propargylamide products were directly obtained after reaction, which could not be accessed using the previous methodology. Secondary propargylamides are useful synthetic intermediates, as they undergo cyclization upon treatment with a strong base such as NaH to form synthetically useful 2,4,5-trisubstituted oxazoles (Scheme 11).

Scheme 11. One-pot synthesis by Arndtsen *et al*

²⁴ Black, D. A.; Arndtsen, B. A. *Tetrahedron Lett*, **2005**, 61, 11317.

In 2005, Yadav and co-workers²⁵ reported a detailed work on the addition of alkynes to iminium ions, generated *in situ* using pyridines and quinolines with ethyl chloroformate, affording the corresponding products in high yields (Scheme 12).

Scheme 12. Addition of alkynes to aza-aromatic systems by Yadav *et al*

Alper and co-workers²⁶ reported a three-component coupling reaction of aldehydes, amines and alkynes, by using readily available copper (I) catalyst in an ionic liquid to afford corresponding propargylamines with high yields. The key feature of this work is the recyclability of the catalyst.

2.1.1.3 OTHER METAL-CATALYZED ALKYNE ADDITIONS

Similar to those protocols involving zinc or copper salts described above, other metal promoters such as iridium ($[\text{Ir}(\text{COD})\text{Cl}]_2$)²⁷, gold (AuBr_3 ,^{28a} AuCl_3 ,^{28a} AuCl ,^{28a} LDH-AuCl_4 ,^{28c} Au(III) Salen ^{28b}) and silver (AgI ,^{29a} AgOTf ^{29b}) were also used in the direct addition of terminal alkynes to C=N electrophiles. Moreover, these

²⁵ Yadav, J. S.; Reddy, B. V. S.; Sreenivas, M.; Sathaiah, K. *Tetrahedron Lett.* **2005**, 46, 8905.

²⁶ Park, S. B.; Alper, H. *Chem. Commun.* **2005**, 1315.

²⁷ (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, 3, 4319. (b) Yamazaki, Y.; Fujita, K. I.; Yamaguchi, R. *Chem. Lett.* **2004**, 33, 1316.

²⁸ (a) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, 125, 9584. (b) Lo, V. K. Y.; Liu, Y.; Wong, M. K.; Che, C. M. *Org. Lett.* **2006**, 8, 1529. (c) Kantam, M. L.; Prakash, B. V.; Reddy, C. R. V.; Sreedhar, B. *Synlett* **2005**, 2329.

²⁹ (a) Wei, C. M.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, 5, 4473. (b) Ji, J. X.; Au-Yeung, T. T. L.; Wu, J.; Yip, C. W.; Chen, A. S. C. *Adv. Synth. Catal.* **2004**, 346, 42.

metal salts and complexes were highly efficient in catalyzing these alkynylation reactions.

The commonly accepted mechanism for metal-promoted direct addition of terminal alkynes to C=N electrophiles is as follows. π -Complexes form between metal salts and terminal alkynes. As a result, the C_{sp}-H bond becomes more acidic, which could subsequently react with a weak base to afford the corresponding metal acetylides. The acetylides then react with C=N electrophiles to produce corresponding adducts. Although various available efficient protocols have been discussed and reviewed, new and more efficient ways are still under investigation.

2.1.2 SOME RECENT BREAKTHROUGHS IN METAL-CATALYZED ALKYNE COUPLING REACTIONS

Ynamides have attracted increasing interests from chemists as useful synthons.³⁰ A typical method for the preparation of ynamides involves halogenation of terminal alkynes, followed by C-N cross coupling.³¹ In 2008, Stahl research group developed a copper-catalyzed aerobic oxidative coupling reaction of terminal alkynes with a variety of nitrogen nucleophiles (Scheme 13).³² Being a highly cited research work, this method not only provides an efficient access to ynamide but also provides a

³⁰ For reviews on ynamides, see: (a) Zifcsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455. For selected recent applications of ynamides, see: (d) Zhang, Y. *Tetrahedron* **2006**, *62*, 3917. (e) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586. (f) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (g) Oppillart, S.; Mousseau, G.; Zhang, L.; Jia, G.; Thuery, P.; Rousseau, B.; Cintrat J. C. *Tetrahedron* **2007**, *63*, 8094.

³¹ Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359.

³² Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

benchmark for the development of new aerobic oxidative coupling reactions. Inspired by this strategy, many other research works were reported afterwards.³³

Scheme 13. Direct amidation of alkynes by Stahl *et al*

Another copper-catalyzed reaction with alkynes was introduced as a type of CDC reaction (Cross-Dehydrogenative Coupling) by Li's research group.³⁴ As shown in Scheme 14, the sp^3 C-H bond adjacent to nitrogen in amines can be readily activated to generate iminium ions via single electron-transfer (SET) processes or by transition metals, which can react with acetylides to afford the corresponding α -substituted products.

Scheme 14. Proposed mechanism for activation of α -C-H bond adjacent to Nitrogen in Amines

A representative example was reported in 2008 (Scheme 14).³⁵ Various PMP glycine amides could be readily alkynylated at room temperature via this CDC reaction to afford the corresponding adducts in good yields. In addition, the analogous α -amino esters were unreactive under these conditions, thus setting the stage for chemoselective C-H functionalization.

³³ Examples see: (a) Chu, L. L.; Qing, F. L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (b) Chen, M.; Zheng, X. L.; Li, W. Q.; He, J.; Lei, A. W. *J. Am. Chem. Soc.* **2010**, *132*, 4101. (c) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (d) Wei, Y.; Zhao, H. Q.; Kan, J.; Su, W. P.; Hong, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (e) Rao, H. H.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Adv. Syn. Catal.* **2010**, *352*, 458.

³⁴ (a) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335. Important pioneer works: (a) Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408. (b) Murahashi, S.-I.; Komiyama, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931.

³⁵ Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075.

Scheme 15. Copper catalyzed chemoselective functionalization of terminal glycine by Li *et al*

The two reactions introduced above, have broadened the scope of metal catalyzed alkynylation. Meanwhile, other carbon-carbon bond formation reactions which use alkyne as a nucleophile source have also been under extensively developed.

2.1.3 CONCLUSION

In summary, various metal-promoted direct addition of acetylenes to C=N electrophiles as well as two recent advances in metal-catalyzed alkynylation have been discussed in this section. Recently, considerable attentions were received by these transformations and further developments are expected to be reported in the near future. Their synthetic utilities are expected to be demonstrated soon.

2.2 STUDIES ON COUPLING REACTIONS OF TERMINAL ALKYNES TO CYCLIC IMINOGLYOXYLATE

Alkynes with unique chemical reactivity have been exploited for a wide variety of organic transformations.³⁶ Recently, the interest in alkynes has expanded beyond organic chemistry to include other areas such as organometallic chemistry, chemical biology, nanoscience, and material science.

On the other hand, propargylamines are versatile building blocks and have been used in the synthesis of biologically active compounds and functionalized materials. Great efforts have been made to develop methodologies for the synthesis of propargylamines. Reported methods for alkynylation of C=N electrophiles was summarized in the previous part. To the best of our knowledge, reactions of simple terminal alkynes with cyclic iminoglyoxylates, which allow the functionalization of terminal alkynes to useful imino acid derivatives, have not been reported yet. In this part, full details of preliminary results regarding the chemoselectivity, substrate scope and mechanistic investigation will be discussed.

2.2.1 CuCl CATALYZED REACTIONS OF ALKYNES WITH CYCLIC IMINOGLYOXYLATE

³⁶ (a) *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; Part 1-2. (b) *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; VCH: Weinheim, Germany, 1995. (c) *Acetylene Chemistry*; Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; VCH: Weinheim, Germany, 2005.

Using imines as electrophiles is one of the established routes for the synthesis of chiral nitrogen-containing building blocks.³⁷ To develop an asymmetric alkynylation reaction of terminal alkynes with iminoglyoxylates, which can afford chiral propargylic imino acid derivatives, will be synthetically useful. At the beginning, we carried out the reaction of phenylacetylene with 5,5-dimethyl-substituted imine substrates **15a** in the presence of 0.2 equivalent of CuBr in toluene at 70 °C. Unexpectedly, two products **17a** and **18a** were obtained with 52% overall yield in a ratio of 40:60 (entry 4, Table 1). The two products can be easily separated by column chromatography. This interesting result intrigued us to perform further investigations into the reaction as well as its pathway.

Firstly, different reaction temperatures were examined. As shown in Table 1, decreased yields were observed when the reaction temperature were below (entries 1-3, Table 1) or above 70 °C (entries 5-8, Table 1). Therefore, we chose 70 °C as the optimal temperature for investigating other reaction parameters. Additionally, performing the reaction under nitrogen atmosphere or increasing phenylacetylene to 1.5 equivalents were all resulted in a decreased yield (entries 9-10, Table 1). Moreover, the reaction did not proceed when the ligand of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was added to the reaction system. This may be due to poisoning of the catalytic activities by the coordination of TMEDA to copper.

³⁷ (a) Kleinman, E. F. *In Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 4, p 893. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 1.

Table 1. Reaction of phenylacetylene with iminoglyoxylate **15a**^a

entry	temp (°C)	yield (%) ^e	ratio (17a : 18a) ^f
1	40	15	33 : 67
2	50	30	36 : 64
3	60	45	34 : 66
4	70	52	40 : 60
5	80	50	36 : 64
6	90	47	45 : 55
7	100	40	54 : 46
8	110	36	48 : 52
9 ^b	70	38	38 : 62
10 ^c	70	36	44 : 56
11 ^d	70	No reaction	---

^a Unless otherwise stated, the reaction was carried out with **15a** (0.15 mmol), phenylacetylene (0.45 mmol), CuBr (0.03 mmol) and 1 mL toluene in the sample vial. The reaction mixture was stirred in specified temperature for 15 hours.

^b This reaction was carried out under N₂.

^c 1.5 equiv. of phenylacetylene was used.

^d TMEDA (0.045 mmol) added as additive.

^e Isolated overall yield of **17a** and **18a**.

^f Ratio was determined by ¹H NMR analysis.

Next, different copper salts and other metal salts were tested. As summarized in Table 2, Cu (I) catalysts showed better catalytic activity than Cu (II) catalysts for this transformation. However, the ratio of the two products did not change depend on the copper catalyst, except for Cu(OTf)₂, which was in favor of the formation of product **18a** (entry 4, Table 2). Copper complexes such as [(CH₃CN)₄Cu]PF₆ and [(CH₃CN)₄Cu]BF₄ showed poor catalytic activity (entries 9-10, Table 2), and other metal catalysts such as AgI, Pd(OAc)₂, NiBr₂ and In(OTf)₃ were found to be unable to promote this reaction (entries 13-16, Table 2). Among all the catalysts tested, using 0.2 equivalent of CuCl gave the best overall yield of 67% in a ratio of 37:36 (entry 5,

Table 2). The use of 3 equiv of CuCl did not improve the yield but afforded a byproduct (entry 6, Table 2).

Table 2. Screening different Lewis acids^a

entry	Lewis acid	yield (%) ^b	ratio (17a : 18a) ^c
1	CuBr	52	40 : 60
2	CuF ₂	No reaction	---
3	CuBr ₂	13	32 : 68
4	Cu(OTf) ₂	26	15 : 85
5	CuCl	67	37 : 63
6 ^d	CuCl	63	33 : 59 : 8 ^d
7	CuCN	No reaction	---
8	CuI	No reaction	---
9	[(CH ₃ CN) ₄ Cu]PF ₆	24	31 : 69
10	[(CH ₃ CN) ₄ Cu]BF ₄	16	21 : 79
11	2CuOTf. Toluene	27	26 : 74
12	CuBr.SMe ₂	53	36 : 64
13	AgI	No reaction	---
14	Pd(OAc) ₂	No reaction	---
15	NiBr ₂	No reaction	---
16	In(OTf) ₃	No reaction	---

^a Unless otherwise, stated, the reaction was carried out with **15a** (0.15 mmol), phenylacetylene (0.45 mmol), Lewis acid (0.03 mmol) and 1 mL toluene in the sample vial. The reaction mixture was stirred in 70 °C for 15 hours.

^b isolated overall yield of **17a** and **18a**.

^c Ratio was determined by ¹H NMR analysis.

^d Three products were **17a**, **18a** and **19a** respectively.

Besides the examination of temperatures and catalysts, a variety of common solvents and additives were also investigated (Table 3). No reaction between **15a** and **16a** took place in MeCN, dioxane and ^tBuOH. Among all solvents tested, toluene was the best solvent for this reaction. Interestingly, when the reaction was carried out in DCE, a comparable yield of 57% was obtained, affording the two corresponding

products in an equal ratio of 50:50. However, additives such as triphenylphosphine as ligand, CsCO₃ and K₃PO₄ as base, as well as TBHP as oxidant, all did not facilitate the reaction. The reaction under oxygen atmosphere resulted in a lower yield of 49% (entry 12, Table 3). Ultimately, optimal conditions were found to be as follows: 0.2 equiv of CuCl as the promoter in toluene solvent at 70 °C.

Table 3. Screening different solvent^a

entry	solvent	yield (%) ^b	ratio (17a : 18a) ^c
1	MeCN	---	---
2	THF	22	75 : 25
3	Dioxane	---	---
4	<i>t</i> BuOMe	32	34 : 66
5	DCE	57	50 : 50
6	<i>t</i> BuOH	---	---
7	Toluene	67	37 : 63
8 ^d	Toluene	---	---
9 ^e	Toluene	---	---
10 ^f	Toluene	48	38 : 63
11 ^g	Toluene	---	---
12 ^h	Toluene	49	34 : 66

^a Unless otherwise, stated, the reaction was carried out with **15a** (0.15 mmol), phenylacetylene (0.45 mmol), CuCl (0.03 mmol) and 1 mL solvent in the sample vial. The reaction mixture was stirred in 70 °C for 15 hours.

^b isolated overall yield of **17a** and **18a**.

^c Ratio was determined by ¹H NMR analysis.

^d 0.4 equiv of PPh₃ added as legand.

^e 1 equiv of CsCO₃ added as base.

^f 1 equiv of K₃PO₄ added as base.

^g 1 equiv of TBHP added as oxidant.

^h The reaction was performed under oxygen atmosphere.

With the establishment of optimized reaction conditions, the scope of terminal alkynes was examined. Aromatic alkynes bearing electron donating groups, such as **16b** and **16c**, reacted with **15a** to give the corresponding products in good overall

yields (entries 1-3, Table 4). However, the reaction of **15a** with 1-ethynyl-4-nitrobenzene **16d**, which bear an electron withdrawing group, gave a low yield of 30% (entry 4, Table 4). This strategy can be extended to aliphatic alkynes to afford the corresponding aliphatic propargyliminoglyoxylates, albeit in poor to moderate yields. Interestingly, reactions of **15a** with alkynes **16e**, **16f** or **16g** preferred the formation of **17e**, **17f** or **17g** as the major products (entries 5-7, Table 4). Meanwhile, reactions of **15a** with alkynes **16h** and **16i** selectively gave products **17h** and **17i** respectively, albeit in low yields (entries 8-9, Table 4). To our disappointment, alkyne **16j** failed to participate in the reaction.

Table 4. Reaction of **15a** with various terminal alkynes^a

entry	alkyne		yield (%) ^b	product	ratio (17:18) ^c
1		16a	67	17a : 18a	37 : 63
2		16b	70	17b : 18b	49 : 51
3		16c	63	17c : 18c	54 : 46
4		16d	30	17d : 18d	31 : 69
5		16e	36	17e : 18e	83 : 17
6		16f	29	17f : 18f	69 : 31
7		16g	36	17g : 18g	83 : 17
8		16h	17	17h : 18h	0 : 100
9		16i	44	17i : 18i	0 : 100

^a Unless otherwise specified, the reaction was carried out with **15a** (0.15 mmol), alkyne (0.45 mmol), CuCl (0.03 mmol) and 1 mL toluene in the sample vial at 70 °C for 15 hours.

^b Isolated overall yield.

^c Ratio was determined by ¹H NMR analysis.

To improve the efficiency and the selectivity of the reaction, we need a working hypothesis for the formation of each of the products. Based on the commonly accepted mechanism of metal-promoted direct alkynylation of C=N electrophiles, we suspected that a Cu (III) species was involved in the catalytic cycle. Thus, we postulated that product **17a** was produced by the addition of *in situ*-formed copper (III) acetylide to iminoglyoxylate **15a** followed by elimination to afford **17a** as well as CuH and HCl, and then CuH could further reduce **17a** to give the product **18a**.³⁸ However, as shown in equation 1, product **18b** was not observed after heating the mixture of **15a**, **16a** and 15 mg of **17b** in toluene at 70 °C for 15 hours, while **17b** was fully recovered after the reaction. This experimental result suggested that product **18** formed through other reaction pathway rather than copper hydride reduction of **17**.

Equation 1.

When the reaction of **15a** with **16a** was carried out by adding 2 equivalents of NCS, a new product alkenyl chloride **19a** was observed (see Equation 2). Hence, we suspected that the formation of **18a** was possibly via radical type addition reaction. Thus, we postulated that single electron transfer occurred when substrate 5,5-

³⁸ The possible mechanism as follows:

dimethyl-substituted iminoglyoxylate **15a** was treated with CuCl to generate a corresponding radical cation.³⁹ This radical cation would undergo radical addition reaction with phenylacetylene **25a** to generate a new radical. And this newly generated radical can be trapped by the proton source from toluene to give the corresponding product **18a**. However, when we performed the reaction of **15a** with **16a** catalyzed by CuCl by employing fully deuterated toluene as solvent, no deuterated product **18a** was observed after reaction.

Equation 2.⁴⁰

In conclusion, an attractive addition reaction of terminal alkynes to cyclic iminoglyoxylate has been demonstrated. This process is simple and provides various propargylic and allylic imino acid derivatives, which are not observed previously, albeit affording products in moderate yields with modest selectivity. Investigations into the full alkyne scope, the mechanism and efforts to improve the chemoselectivity are still ongoing.

2.2.2 CuCl, FeCl₃ AND TEMPO AIDED DIRECT COUPLING REACTIONS OF ALKYNES TO CYCLIC IMINOGLYOXYLATE

³⁹ This possible mechanism as follows:

⁴⁰ The stereo and regiochemistry of **19a** can not be confirmed.

Carbon-carbon bond formation is the most fundamental part in organic synthesis as it allows the formation of complex organic compounds by connecting simple molecules together. The direct cross-coupling between terminal alkynes and the C=N double bond in imines and their derivatives is an significant process as the resulting derivatives can undergo further reactions, making them as flexible synthetic building blocks.

In the previous part, we disclosed that the reaction of phenylacetylene with 5,5-dimethyl-substituted imine substrates **15a** gives a mixture of three products **17a**, **18a** and **19a**. To make this reaction more synthetically useful, the key issue is to improve the chemoselectivity. Herein, we report that a highly chemoselective coupling reaction of terminal alkynes with cyclic iminoglyoxylate catalyzed by CuCl, with FeCl₃ as a cocatalyst and TEMPO as an oxidant.

The three products of **17a**, **18a** and **19a** were first observed by using 3 equivalents of CuCl as the promoter (entry 1, Table 5), albeit in moderate selectivity. In our lab, it was observed that the combining of two different Lewis acids could facilitate similar coupling reactions.⁴¹ Therefore, co-catalysts such as FeCl₃, NiCl₂·6H₂O and InCl₃ were examined. We found that product **17a** was favored when using FeCl₃ as co-catalyst, while product **18a** was favored when using either NiCl₂·6H₂O or InCl₃ as co-catalyst, albeit low overall yields obtained for all cases (entries 2-4, Table 5).

Prior studies have shown that the use of dichloroethane as the solvent results in an equal ratio of **17a** and **18a**. Thus, the reaction of **15a** and **16a** using CuCl and FeCl₃ as catalysts was carried out in dichloroethane as solvent (entry 5, Table 5).

⁴¹ Unpublished results of our group. And selected recent examples see: (a) Wang, H. G.; Wang, Y.; Peng, C. L.; Zhang, J. C.; Zhu, Q. A. *J. Am. Chem. Soc.* **2010**, *132*, 13217. (b) Guo, D. L.; Huang, H.; Zhou, Y.; Xu, J. Y.; Jiang, H.; Chen, K. X.; Liu, H. *Green Chem.* **2010**, *12*, 276. (c) Mao, J. C.; Xie, G. L.; Wu, M. Y.; Guo, J.; Ji, S. J. *Adv. Synth. Catal.* **2008**, *350*, 2477.

However, the chemoselectivity was not enhanced. Surprisingly, when 2.5 equivalents of oxidant *di-tert*-butylperoxide was employed, the selectivity was improved significantly (entries 6-7, Table 5), and better yield was obtained in dichloroethane compared to toluene. These observations suggested that the oxidant was essential to enhance the chemoselectivity. After a series of investigations, TEMPO was found to be ideal for this direct coupling reaction. When 1 equivalent of TEMPO was added, the chemoselectivity was dramatically increased (entries 8-9, Table 5). The highest ratio of 93: 0: 7 was obtained by using dichloroethane as the solvent (entry 9, Table 5). Thus, FeCl₃ and TEMPO played important roles in improving the chemoselectivity, and dichloroethane is the optimal solvent for this direct coupling reaction.

Table 5. Optimization of reaction conditions^a

entry	catalyst	solvent	yield (%) ^b	ratio (17:18:19) ^c
1 ^d	CuCl	Toluene	63	33 : 59 : 8
2	CuCl FeCl ₃	Toluene	43	57 : 43 : 0
3	CuCl NiCl ₂ ·6H ₂ O	Toluene	41	20 : 80 : 0
4	CuCl InCl ₃	Toluene	29	23 : 77 : 0
5	CuCl FeCl ₃	DCE	42	50 : 29 : 21
6 ^e	CuCl FeCl ₃ <i>t</i> BuOO <i>t</i> Bu	DCE	60	70 : 20 : 10
7 ^e	CuCl FeCl ₃ <i>t</i> BuOO <i>t</i> Bu	Toluene	44	63 : 37 : 0
8 ^f	CuCl FeCl ₃ TEMPO	Toluene	62	84 : 9 : 7
9 ^f	CuCl FeCl₃ TEMPO	DCE	53	93 : 0 : 7

^a Unless otherwise specified, the reaction was carried out with **15a** (0.15 mmol), **16a** (0.45 mmol), catalysts (0.03 mmol) in 1 mL solvent for 15 hours.

^b Isolated overall yield.

^c Ratio was determined by ¹H NMR analysis.

^d 0.45 mmol CuCl was used.

^e 2.5 eq. of *t*BuOO*t*Bu was added.

^f 1.0 eq. of TEMPO was added.

Following those preliminary investigations, the amounts of FeCl₃ and TEMPO were further examined. No significant improvement of the yield was observed by increasing the loading of FeCl₃ to 0.4 equivalent (entry 2, Table 6). Although higher selectivity could be achieved by increasing the amount of TEMPO from 1 to 2 equivalents, the yield was decreased from 53% to 43% (entry 3, Table 6). In addition, no reaction was observed (entry 4, Table 6). In the absence of FeCl₃, yield was decreased significantly (entry 5, Table 6). Therefore, optimal conditions were found to be as follows: 0.2 equivalent of CuCl, 0.2 equivalent of FeCl₃ as the co-catalyst, 1 equivalent of TEMPO in DCE at 70 °C.

Table 6. Further Optimize reaction conditions^a

entry	FeCl ₃ (equiv)	TEMPO (equiv)	yield (%) ^b	ratio (17:18:19) ^c
1	0.2	1.0	53	93 : 0 : 7
2	0.4	1.0	54	93 : 0 : 7
3	0.2	1.5	43	> 99 : 1
4 ^d	0.2	---	---	---
5	---	1.0	16	> 99 : 1

^a Unless otherwise specified, the reaction was carried out with **17a** (0.15 mmol), alkyne (0.45 mmol), CuCl (0.03 mmol), FeCl₃ (0.03 mmol), TEMPO (0.15 mmol) and 1 mL dichloroethane in the sample vial at 70 °C for 15 hours.

^b isolated overall yield of product **17a**, **18a** and **19a**.

^c Ratio was determined by ¹H NMR analysis.

^d No CuCl was employed.

With this optimal conditions in hand, a series of alkynes were subjected to this direct coupling reaction. Aromatic alkynes bearing electron withdrawing groups, such as **16d** and **16k**, reacted with **15a** to selectively give propargylic imino acid derivatives **17d** and **17k** in yield of 45% and 45% respectively (entries 3-4, Table 7). However, 1-ethynyl-4-methoxybenzene **16b** was found to be unreactive for this

coupling reaction, affording the corresponding product in less than 5% yield (entry 2, Table 7). Aliphatic alkynes **16e**, **16f**, **16g** and **16h** afforded the corresponding products chemoselectively in moderate yields (entries 5-8, Table 7). Notably, the reaction of **15a** with 1-octyne **16f**, employing InCl_3 as a co-catalyst achieve a higher yield (39% yield) as compared to using FeCl_3 as the co-catalyst (29% yield). Surprisingly, no coupling reaction was observed for alkynes **16i** and **16j** (entries 9-10, Table 7).

Table 7. Reaction of **15a** with various terminal alkynes^a

entry	alkyne		yield (%) ^b	product	ratio (17:18) ^c
1		16a	53	17a : 18a : 19a^e	93 : 0 : 7 ^e
2		16c	<5	17b : 18b	> 99 : 1
3		16d	45	17d : 18d	> 99 : 1
4		16k	48	17k : 18k	> 99 : 1
5		16e	50	17e : 18e	100 : 0
6 ^d		16f	39	17f : 18f	100 : 0
7		16g	37	17g : 18g	100 : 0
8		16h	34	17h : 18h	100 : 0
9		16i	No reaction	---	---
10		16j	No reaction	---	---

^a Unless otherwise specified, the reaction was carried out with **15a** (0.15 mmol), alkyne (0.45 mmol), CuCl (0.03 mmol), FeCl_3 (0.03 mmol), TEMPO (0.15 mmol) and 1 mL dichloroethane in the sample vial at 70 °C for 15 hours.

^b Isolated yield.

^c Ratio was determined by ¹H NMR analysis.

^d InCl₃ (0.03 mmol) employed instead of FeCl₃.

^e This result is from table 5 and table 6.

In conclusion, we have demonstrated a simple direct coupling reaction of terminal alkynes with cyclic iminoglyoxylate using CuCl as the catalyst, FeCl₃ as the co-catalyst and TEMPO as the oxidant. This process provides a chemoselective way to synthesis propargylic imino acid derivatives **17**.

2.2.3 CONCLUSION AND FUTURE WORKS

To summarize this chapter, prior results have already demonstrated the particular utility of this transformation. The reaction of terminal alkynes with cyclic iminoglyoxylate afforded either propargylic or allylic imino acid derivatives, which would be versatile synthetic intermediates in organic synthesis. Furthermore, halo-substituted allylic imino acid derivatives could possibly undergo coupling reactions to make further functionalization. However, a working hypothesis has not been established, and valuable insights for designing more selective and robust version remain urgent. Optimized conditions for synthesizing a series of halo-substituted allylic imino acid derivatives are still under investigation. More efforts will be required to expand the scope of this research.

2.3 EXPERIMENTAL

General procedure for the reaction of various terminal alkynes with iminoglyoxylate 15a catalyzed by CuCl

A reaction vial was charged with cyclic imine (0.15 mmol, 1 equiv), terminal alkyne (0.45 mmol, 3 equiv), CuCl (0.03 mmol, 0.2 equiv) and 1 mL toluene. Then the resulting solution was stirred at 70 °C for 15 hours. After cooling to room temperature, the mixture was directly subjected to column chromatography to afford the corresponding products.

5,6-dihydro-5,5-dimethyl-3-(2-phenylethynyl)-1,4-oxazin-2-one

Yellowish solid mp. 94-96 °C; R_f = 0.2 (hexane : ethyl acetate = 3:1);

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.62-7.60 (m, 2H), 7.43-7.34 (m, 3H), 4.27 (s, 2H), 1.38 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 153.3, 144.2, 132.5, 130.0 (2C), 128.4 (2C), 120.6, 94.2, 84.1, 74.3, 55.7, 24.6 (2C) ppm;

FTIR (neat): ν = 3019, 2229, 1639, 1215, 783 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{14}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 228.1025, found 228.1022.

5,6-dihydro-5,5-dimethyl-3-styryl-1,4-oxazin-2-one

Yellowish solid mp. 50-52 °C; R_f = 0.3 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.70 (d, J = 16.3 Hz, 1H), 7.56-7.55 (m, 2H), 7.38-7.33 (m, 3H), 7.13 (d, J = 16.3 Hz, 1H), 4.22 (s, 2H), 1.37 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 155.6, 153.8, 138.6, 135.5, 129.3, 128.6 (2C), 127.6 (2C), 121.9, 74.1, 54.6, 24.7 (2C) ppm;

FTIR (neat): ν = 3019, 1736, 1522, 1215, 771 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{16}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 230.1181, found 230.1182.

5,6-dihydro-5,5-dimethyl-3-(2-p-tolyethynyl)-1,4-oxazin-2-one

Yellowish solid mp. 92-94 °C; R_f = 0.5 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.50 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 4.26 (s, 2H), 2.37 (s, 3H), 1.38 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 153.4, 144.4, 140.7, 132.6 (2C), 129.2 (2C), 117.7, 94.9, 83.8, 74.4, 55.7, 24.7 (2C), 21.7 ppm;

FTIR (neat): ν = 3019, 2208, 1746, 1520, 1215, 781 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{15}\text{H}_{16}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 242.1181, found 242.1184.

3-(4-methylstyryl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one

Yellowish solid mp. 100-102 °C; $R_f = 0.25$ (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.68 (d, $J = 16.3$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 7.9$ Hz, 2H), 7.09 (d, $J = 16.3$ Hz, 1H), 4.22 (s, 2H), 2.36 (s, 3H), 1.36 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 155.9, 154.0, 139.8, 138.8, 133.0, 129.5 (2C), 127.7 (2C), 121.0, 74.4, 54.7, 24.9 (2C), 21.4 ppm;

FTIR (neat): $\nu = 3019, 1736, 1520, 1215, 781 \text{ cm}^{-1}$;

HRMS (ESI): m/z calc. for $\text{C}_{15}\text{H}_{18}\text{NO}_2^+ [\text{M}+\text{H}]^+$ 244.1338, found 244.1337.

5,6-dihydro-3-(2-(4-methoxyphenyl)ethynyl)-5,5-dimethyl-1,4-oxazin-2-one

Yellowish oil; $R_f = 0.15$ (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.57-7.54 (m, 2H), 6.89-6.85 (m, 2H), 4.26 (s, 2H), 3.83 (s, 3H), 1.37 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 161.1, 153.5, 144.4, 134.5 (2C), 114.2 (2C), 112.7, 95.1, 83.7, 74.4, 55.6, 55.3, 24.8 (2C) ppm;

FTIR (neat): $\nu = 3019, 2207, 1744, 1510, 1213, 783 \text{ cm}^{-1}$;

HRMS (ESI): m/z calc. for $\text{C}_{15}\text{H}_{16}\text{NO}_3^+ [\text{M}+\text{H}]^+$ 258.1130, found 258.1125.

3-(4-methoxystyryl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one

Yellowish oil; $R_f = 0.25$ (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.65 (d, $J = 16.2$ Hz, 1H), 7.51-7.48 (m, 2H), 7.0 (d, $J = 16.2$ Hz, 1H), 6.91-6.88 (m, 2H), 4.21 (s, 2H), 3.83 (s, 3H), 1.35 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 160.8, 156.0, 154.0, 138.4, 129.3 (2C), 128.5, 119.9, 114.2 (2C), 74.4, 55.3, 54.6, 24.9 (2C) ppm;

FTIR (neat): $\nu = 3019, 1746, 1512, 1215, 779 \text{ cm}^{-1}$;

HRMS (ESI): m/z calc. for $\text{C}_{15}\text{H}_{18}\text{NO}_3^+ [\text{M}+\text{H}]^+$ 260.1287, found 260.1294.

5,6-dihydro-5,5-dimethyl-3-(2-(4-nitrophenyl)ethynyl)-1,4-oxazin-2-one

Yellowish solid mp. 189-190 °C; $R_f = 0.2$ (hexane : ethyl acetate = 3:1)

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.26-8.23 (m, 2H), 7.78-7.75 (m, 2H), 4.30 (s, 2H), 1.41 (s, 6H) ppm;

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 153.0, 148.2, 144.1, 133.4 (2C), 127.4, 123.7 (2C), 90.9, 87.7, 74.4, 56.2, 24.7 (2C) ppm;

FTIR (neat): $\nu = 3053, 2986, 2220, 1748, 1595, 1524, 1346, 1265, 739 \text{ cm}^{-1}$;

HRMS (EI): m/z calculated for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4 [\text{M}+\text{H}]^+$: 273.0875, found 273.0882.

3-(4-nitrostyryl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one

Yellowish solid mp. 179-181 °C; R_f = 0.23 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.22 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 16.3 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 16.3 Hz, 1H), 4.24 (s, 2H), 1.38 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 155.4, 153.4, 147.9, 141.9, 136.0, 128.2 (2C), 126.0, 124.1 (2C), 74.3, 55.1, 24.8 (2C) ppm;

FTIR (neat): ν = 3066, 1638, 1522, 1346, 1215, 771 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 275.1032, found 275.1021.

5,6-dihydro-5,5-dimethyl-3-(4-phenylbut-1-ynyl)-1,4-oxazin-2-one

Yellowish solid mp. 45-47 °C; R_f = 0.25 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.32-7.20 (m, 5H), 4.22 (s, 1H), 2.94 (t, J = 7.7 Hz, 2H), 2.72 (t, J = 7.7 Hz, 2H), 1.33 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 153.5, 144.0, 140.0, 128.5 (2C), 128.4 (2C), 126.5, 96.1, 74.3, 55.5, 34.2, 24.7 (2C), 21.7 ppm;

FTIR (neat): ν = 3019, 2229, 1746, 1520, 1215, 779 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{16}\text{H}_{18}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 256.1338, found 256.1331.

5,6-dihydro-5,5-dimethyl-3-((E)-4-phenylbut-1-enyl)-1,4-oxazin-2-one

Yellowish solid mp. 41-42 °C; R_f = 0.35 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 7.32-7.27 (m, 2H), 7.21-7.18 (m, 3H), 6.96 (dt, J_1 = 16.2 Hz, J_2 = 6.8 Hz, 1H), 6.47 (dt, J_1 = 15.9 Hz, J_2 = 1.5 Hz, 1H), 4.17 (s, 2H), 2.82-2.77 (m, 2H), 2.58-2.50 (m, 2H), 1.31 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 155.6, 153.9, 142.3, 141.3, 128.4 (2C), 128.3 (2C), 126.1, 125.2, 74.3, 54.6, 34.9, 34.7, 24.8 (2C) ppm;

FTIR (neat): ν = 3054, 2986, 1645, 1422, 1265, 737 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{16}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 258.1494, found 258.1502.

5,6-dihydro-5,5-dimethyl-3-(oct-1-ynyl)-1,4-oxazin-2-one

Yellowish oil; R_f = 0.35 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 4.21 (s, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.63-1.58 (m, 2H), 1.43-1.27 (m, 6H), 1.33 (s, 6H), 0.88 (t, J = 6.6 Hz, 3H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 162.3, 153.6, 144.2, 97.5, 74.4, 55.4, 31.3, 28.6, 27.8, 24.7 (2C), 22.5, 19.5, 14.0 ppm;

FTIR (neat): ν = 3019, 2230, 1746, 1522, 1215, 777 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{22}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 236.1651, found 236.1645.

5,6-dihydro-5,5-dimethyl-3-((*E*)-oct-1-enyl)-1,4-oxazin-2-one

Yellowish oil; $R_f = 0.43$ (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 6.90 (dt, $J_1 = 15.8$ Hz, $J_2 = 7.0$ Hz, 1H), 6.41 (dt, $J_1 = 15.8$ Hz, $J_2 = 1.5$ Hz, 1H), 4.16 (s, 2H), 2.25-2.17 (m, 2H), 1.52-1.33 (m, 3H), 1.31 (s, 6H), 1.29-1.21 (m, 5H), 0.90-0.86 (m, 3H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 155.7, 154.0, 143.7, 124.6, 74.3, 54.4, 33.2, 31.6, 28.9, 28.4, 24.8 (2C), 22.6, 14.1 ppm;

FTIR (neat): $\nu = 3053, 2986, 1645, 1421, 1265, 737$ cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{24}\text{NO}_2^+ [\text{M}+\text{H}]^+$ 238.1807, found 238.1813.

3-(4-(tert-butyldimethylsilyloxy)but-1-ynyl)-5,5-dimethyl-5,6-dihydro-2H-1,4-oxazin-2-one

Yellowish oil; $R_f = 0.3$ (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 6.51 (d, $J = 15.7$ Hz, 1H), 6.41 (dd, $J_1 = 15.7$ Hz, $J_2 = 9.5$ Hz, 1H), 4.15 (s, 2H), 1.60-1.55 (m, 1H), 1.29 (s, 6H), 0.93-0.88 (m, 2H), 0.65-0.61 (m, 2H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 153.4, 144.0, 93.7, 77.1, 74.3, 61.0, 55.5, 25.8 (3C), 24.6 (2C), 23.8, 18.3, -5.4 (2C) ppm;

FTIR (neat): $\nu = 3019, 2230, 1746, 1639, 1215, 771$ cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{16}\text{H}_{28}\text{NO}_3\text{Si}^+ [\text{M}+\text{H}]^+$ 310.1838, found 310.1836.

3-(2-cyclopropylethynyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one

Yellowish solid mp. 77-79 °C; R_f = 0.25 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 4.20 (s, 2H), 1.51-1.45 (m, 1H), 1.31 (s, 6H), 0.94-0.92 (m, 4H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 153.5, 144.0, 100.9, 74.4, 71.8, 55.3, 24.7 (2C), 9.3 (2C), 0.24 ppm;

FTIR (neat): ν = 3019, 2222, 1745, 1521, 1215, 781 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{11}\text{H}_{14}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 192.1025, found 192.1028.

3-((E)-2-cyclopropylvinyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one

Yellowish oil; R_f = 0.31 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 6.51 (d, J = 15.7 Hz, 1H), 6.41 (dd, J_1 = 15.7 Hz, J_2 = 9.5 Hz, 1H), 4.15 (s, 2H), 1.60-1.55 (m, 1H), 1.29 (s, 6H), 0.93-0.88 (m, 2H), 0.65-0.61 (m, 2H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 155.9, 153.5, 147.8, 122.0, 74.3, 54.3, 24.8 (2C), 15.3, 8.4 (2C) ppm;

FTIR (neat): ν = 3019, 1639, 1215, 779 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{11}\text{H}_{16}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 194.1181, found 194.1186.

(2E)-ethyl 3-(5,6-dihydro-5,5-dimethyl-2-oxo-2H-1,4-oxazin-3-yl)acrylate

Yellowish oil; R_f = 0.28 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.49 (d, J = 16.0 Hz, 1H), 6.93 (d, J = 16.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.21 (s, 2H), 1.34 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 165.7, 154.5, 153.1, 136.7, 128.6, 74.1, 61.0, 55.6, 24.6 (2C), 14.2 ppm;

FTIR (neat): ν = 3019, 1738, 1639, 1213, 765 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{11}\text{H}_{16}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 226.1079, found 226.1080.

General procedure for the reaction of various terminal alkynes with iminoglyoxylate 15a catalyzed by CuCl, FeCl₃ and TEMPO

A vial was charged with cyclic imine (0.15 mmol, 1 equiv), terminal alkyne (0.45 mmol, 3 equiv), CuCl (0.03 mmol, 0.2 equiv), FeCl₃ (0.03 mmol, 0.2 equiv), TEMPO (0.15 mmol, 1 equiv) and 1 mL DCE. Then the resulting solution was stirred at 70 °C for 15 hours. After cooling to room temperature, the mixture was directly subjected to column chromatography to afford the corresponding products.

3-(2-(4-bromophenyl)ethynyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one

White solid mp. 106-107 °C; R_f = 0.2 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 7.52-7.45 (m, 4H), 4.27 (s, 2H), 1.38 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 153.2, 144.3, 134.0 (2C), 131.8 (2C), 124.8, 119.7, 93.0, 85.0, 74.4, 55.9, 24.7 (2C) ppm;

FTIR (neat): ν = 3053, 2986, 2220, 1748, 1577, 1265, 741 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{13}\text{NO}_2\text{Br}^+$ $[\text{M}+\text{H}]^+$ 306.0130, found 306.0137.

3-((Z)-2-chloro-2-phenylvinyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one¹

Yellowish solid; R_f = 0.31 (hexane : ethyl acetate = 3:1)

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.71-7.69 (m, 2H), 7.41-7.19 (m, 3H), 6.90 (s, 1H), 4.29 (s, 2H), 1.41 (s, 6H) ppm;

$^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 155.2, 153.4, 140.7, 137.6, 130.0, 128.5 (2C), 127.1 (2C), 110.7, 74.4, 55.6, 24.7 (2C) ppm;

FTIR (neat): ν = 3053, 2986, 1734, 1639, 1265, 740 cm^{-1} ;

HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{15}\text{NO}_2\text{Cl}^+$ $[\text{M}+\text{H}]^+$ 264.0791, found 264.0784.

¹ The stereo and regiochemistry of **19a** can not be confirmed.

PART II

CHAPTER 1

Background of the Total Synthesis of Estrone

1.1 GENERAL INTRODUCTION OF ESTRONE

Estrone is an estrogenic hormone secreted by the ovary as well as the adipose tissues. As an important member of the steroidal compounds, total synthesis of estrone has been widely studied during the 20th century because of its well defined tetracyclic structure which plays a vital role as the target molecule in the development of new synthetic strategies (Figure 1).

Figure 1. Estrone: key feature is the 4 core ring structure

1.2 REPORTED TOTAL SYNTHESIS OF ESTRONE

The first successful total synthesis of a steroid was reported in 1939 by Bachmann, Cole and Wilds.¹ Since then, many elegant syntheses in this area have been developed.² Selected examples will be discussed in the following part, which are classified according to the strategies used in the construction of estrone.

TORGOV SYNTHESSES

In 1963, Torgov and co-workers³ disclosed a short synthesis of ($\pm$)-estrone which marked an important development in steroid total synthesis. As shown in

¹ Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 974.

² For reviews of total synthesis of steroids, see: (a) Akhrem, A. A.; Titov, Y. A. *Total Steroid Synthesis*; Plenum: New York, NY, **1970**. (b) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. *Total Synthesis of Steroids*; Academic: New York, NY, **1974**. (c) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465. (d) Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607. (e) Saraber, F. C. E.; de Groot, A. *Tetrahedron* **2006**, *62*, 5363.

³ Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *4*, 1553.

Scheme 1, the reactive alcohol **2** was condensed with 2-methylcyclopentane-1,3-dione **3** to form the intermediate **4**, which could undergo cyclisation to afford steroid skeleton **5**. The compound **5** was reduced to alkene **6**, and then further reduced to the all *trans* estrone methyl ether **7**.

Scheme 1. Torgov synthesis in 1963

This method has been proved to be highly versatile and has already been extensively used and modified,⁴ but one limitation is that standard Torgov reaction only leads to racemic steroidal compounds.

In 2007, Corey and co-workers⁵ applied a novel CBS reduction strategy to convert the Torgov's synthesis of estrone into a highly enantioselective and efficient process. The pathway of synthesis of the natural estrone methyl ether was started from the Torgov diketone **4** (Scheme 2). Its chirality was established by the enantioselective CBS reduction. Notably, this key enantioselective reduction proceeded in a different way from the previously reported CBS reduction, the *N,N*-

⁴ For examples see: (a) Barlaam, B.; Boivin, J.; Zard, S. Z. *Bull. Soc. Chim. Fr.* **1993**, 130, 481. (b) Garland, R. B.; Palmer, J. R.; Pappo, R. *J. Org. Chem.* **1976**, 41, 531. (c) Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1968**, 33, 3126. (d) Makk, N.; Toth, G.; Tomorkeny, E. *Steroids* **1975**, 25, 611.

⁵ Yeung, Y. Y.; Chein, R. J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, 129, 10346.

diethylaniline played an important role to establish the high enantioselectivity in this process. Particularly noteworthy is that a simple recrystallization could afford **9** with 99% *ee*, which was quite straightforwardly transformed into the final chiral estrone methyl ether **11**.

Scheme 2. Enantioselective Torgov's synthesis reported by Corey *et al*

Another recent development was reported by Knochel *et al* in 2007.⁶ The chirality at position 13 (steroid numbering) was successfully introduced by a copper (I)-mediated *anti*- $\text{S}_{\text{N}}2'$ -allylic substitution reaction of dialkylzinc **13** with the chiral cyclopentene diol derivative **14**.

⁶ Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, 9, 1021.

Scheme 3. Enantioselective synthesis of natural estrone reported by Knochel *et al***RING C CLOSURE BY DIELS-ALDER OR [4+2] CYCLOADDITION REACTIONS**

Intramolecular Diels-Alder cyclisations was limited in this area⁷ compared with intermolecular version.⁸ Applying Diels-Alder cyclisation strategies for the total synthesis of steroids, first investigated as early as 1939,⁹ has a long and convoluted history, but for the most part had been disappointing until the more modern studies of Quinkert's group.¹⁰ Quinkert and co-workers successfully applied a titanium complex to the chirogenic Diels-Alder cyclisation, allowing the enantioselective formation of the desired adduct occur. After that, efficient total synthesis of estrone and norgestrel had been accomplished.

More recently, Corey and co-workers reported a new and simple enantioselective synthesis of estrone which was started from Dane's diene (Scheme 4), this route overcame some limitations of the Quinkert synthesis.¹¹ First, the dienophile component **17** is more easily available. Second, the reaction of Dane's diene **16** with aldehyde **17** was catalyzed with only 20% mmol catalyst loading of **18** to afford the desired adduct **19** in high yield with high enantioselectivity in a short reaction time, while Quinkert synthesis^{10a} needed a large quantities of Ti (IV)-TADDOL catalyst (2 equivalents of titanium Lewis acid, 2.2 equivalents of chiral ligand) and long reaction times (several days, mostly 7 days).

⁷ Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, 25, 2121.

⁸ For examples see: (a) Das, j.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, 57, 3308. (b) Quinkert, G.; del Grosso, M.; Bucher, A.; Bats, J. W.; Durner, G. *Tetrahedron Lett.* **1991**, 32, 3357. (c) Narasimhan, N. S.; Bapat, C. P. *J. Chem. Soc. Perkin Trans. I* **1984**, 1435. (d) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, 33, 1909. (e) Tanaka, K.; Nakashima, H.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, 2, 1915. (f) Couturier, M.; Deslongchamps, P. *Synlett* **1996**, 1140. (g) Ouellet, L.; Langlois, P.; Deslongchamps, P. *Synlett* **1997**, 689.

⁹ (a) Dane, E.; Eder, K. *Liebigs Ann. Chem.* **1939**, 539, 207. (b) Dane, E.; Schmitt, J. *Liebigs Ann. Chem.* **1938**, 536, 196. (c) Dane, E.; Schmitt, J. *Liebigs Ann. Chem.* **1939**, 537, 246.

¹⁰ (a) Quinkert, G.; del Grosso, M.; Bucher, A.; Bauch, M.; Doring, W.; Bats, J. W.; Durner, G. *Tetrahedron Lett.* **1992**, 33, 3617. (b) Quinkert, G.; Grosso, M. D.; Doring, A.; Doring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Durner, G. *Helv. Chim. Acta* **1995**, 78, 1345.

¹¹ Hu, Q. Y.; Rege, R. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, 126, 5984.

Scheme 4. Simple & catalytic enantioselective synthesis of estrone by Corey *et al* in 2004.

In 2008, Corey and co-workers¹² reported a more straightforward route leading to (+)-estrone. The [4+2] cycloaddition reaction was efficiently catalyzed by complex **22**, leading to the enantiomeric estrone skeleton **23** in one single step.

Scheme 5. [4+2] cycloaddition reaction to synthesize estrone by Corey *et al* in 2008

RING A, B AND D CONNECTION BY MICHAEL ADDITION REACTIONS

Michael-type additions were also involved in the total synthesis of steroidal compounds.¹³ In 1981, Posner and co-workers reported a one-pot total synthesis of

¹² Canales, E.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3217.

(±)-9,11-dehydroestrone by the tandem Michael-Michael-Ring closure reaction.¹⁴ The reaction of tetralone enolate **25** with 2-methyl-2-cyclopentenone **26** generated the regiospecifically enolate intermediate **27**, which can be further reacted with vinyltriphenylphosphonium bromide (VTB) in a one-pot manner to afford the desired steroidal skeleton **28** in 8.4% overall yield.

Scheme 6. One-pot syntheses by Posner *et al* in 1981

Based on previous work, Posner and co-workers developed a total synthesis of natural estrone in extremely high enantiomeric purity by an asymmetric Michael addition reaction in 1986 (Scheme 6).¹⁵ The key step of this route is that lithium enolate **31** reacted with an enantiomerically pure sulfoxide **32** to give the corresponding Michael adduct **33** with the desired natural absolute stereochemistry at C14. Then the compound **33** was equilibrated under basic conditions to generate the correct configuration at C8 with 95% of diastereomeric purity. Methylation of β -keto sulfone **34** followed by Me_2CuLi -induced reductive cleavage of the sulfonyl group and then subsequently C_{13} -dimethallylation afforded the key intermediate **35**. After that ozonolysis and McMurry coupling, the target molecular **11** was obtained.

¹³ For examples see: (a) Saucy, G.; Borer, R. *Helv. Chim. Acta* **1971**, *54*, 2121. (b) Saucy, G.; Borer, R. *Helv. Chim. Acta* **1971**, *54*, 2517. (c) Rosenberger, M.; Borer, R.; Saucy, G. *J. Org. Chem.* **1978**, *43*, 1550. (d) Scott, J. W.; Saucy, G. *J. Org. Chem.* **1972**, *37*, 1652.

¹⁴ Posner, G. H.; Mallamo, J. P.; Black, A. Y.; *Tetrahedron* **1981**, *37*, 3921.

¹⁵ Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239.

Scheme 7. Total synthesis of natural estrone via asymmetric Michael addition by Posner *et al*

Mukaiyama Michael additions were also extensively employed in the syntheses of steroids.¹⁶ A recent representative example was published by Professor Aede de Groot *et al* in 2003 (Scheme 8).¹⁷ The Mukaiyama reaction with transfer of the silyl group from the starting silyl enol ether **37** to the enol of the adduct **39** was followed by addition of vinyl magnesium bromide to the unprotected carbonyl group to afford the key intermediate **40**. This intermediate **40** can be converted easily into a carbocation, which then undergo intramolecular reaction with the silyl enol ether to form the C12-C13 bond to complete the synthesis.

¹⁶ For examples see: (a) Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6886. (b) Grieco, P. A.; May, S. A.; Kaufman, M. D. *Tetrahedron Lett.* **1998**, *39*, 7047. (c) Saraber, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1717. (d) Saraber, F. C. E.; Baraanovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; de Groot, A. *Tetrahedron* **2006**, *62*, 1726. (e) Goborets, E.; Urbanczyk-Lipowska, Z.; Stepanenko, V.; Wicha, J. *Tetrahedron Lett.* **2001**, *42*, 1135. (f) Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479. (g) Pogrebnoi, S.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1743.

¹⁷ Dratch, S.; Charnikhova, T.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287.

Scheme 8. Synthesis of C,D-cis coupled steroid by de Groot *et al*

TANDEM COPE-CLAISEN AND TANDEM CLAISEN-ENE STRATEGIES

In 1982, Ziegler and co-workers explored¹⁸ the tandem Cope-Claisen rearrangement, and applied to the synthesis of ($\pm$)-estrone methyl ether (Scheme 9).¹⁹

Scheme 9. Tandem Cope-Claisen rearrangement strategy by Ziegler *et al*

¹⁸ (a) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611. (b) Ziegler, F. E.; Piwinski, J. J. *Ibid.* **1980**, *102*, 880. (c) Ziegler, F. E.; Piwinski, J. J. *Ibid.* **1980**, *102*, 6576. (d) Raucher, S.; Burks, J. E. J.; Hwang, K. J.; Svedberg, D. P. *Ibid.* **1981**, *103*, 1853.
¹⁹ Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, *47*, 5230.

Although Ziegler's approach led to the racemic estrone, it inspired further studies in this particular area. The "tandem reaction sequence"²⁰, at that time, had been an efficient strategy for the stereocontrolled synthesis of complex molecules. In 1990, Mikami and co-workers reported a conceptually new and efficient asymmetric Claisen-Ene reaction sequence for the total synthesis of (+)-9(11)-dehydroestrone methyl ether in a tandem and highly stereocontrolled fashion.²¹ The allylic alcohol **54** proceeded an asymmetric tandem Claisen-Ene reaction sequence with compound **55** for the double carbocyclization of D and C rings, was quite successful, leading to **56** with 13,14-configuration exclusively *trans* and 8,14-configuration 90% *syn*. The target skeleton could be accomplished by following the literature reported procedures.¹⁷ After Ozonolysis, epimerization and McMurry coupling, (+)-9(11)-dehydroestrone methyl ether **52** was obtained in 17% overall yield.

Scheme 10. Asymmetric Tandem Claisen-Ene Strategy reported by Mikami *et al* in 1990

²⁰ For the terminology of "tandem" and examples see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, 88, 1423. (b) Nakai, T.; Mikami, K. *Ibid*, **1986**, 86, 885.

²¹ Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, 112, 4035.

In 1994, as a continuation of this work, Mikami *et al* reported stereochemical outcome studies on this tandem Claisen-Ene sequence which was used in the total synthesis of steroid (Figure 2).²²

Figure 2. The tandem Claisen-Ene reaction sequence

STRATEGY OF ASSEMBLING THE KEY D RING TEMPLATE

In 1985, Thomas Money and co-workers²³ reported the use of natural camphor as chiral starting material in the enantioselective total synthesis of estrone. The 9,10-dibromocamphor **54** which was derived from camphor underwent facile and efficient ring cleavage to afford hydroxyl-acid **56** which has the *trans* configuration on C13 and C14. The hydroxyl-acid **56** was transformed to compound **59**, which was then treated with *m*-methoxybenzylmagnesium chloride to give the tricyclic cross conjugated ketone **60**. Subsequent reduction followed by ozonolysis and acid promoted cyclhydration, afforded a mixture of **63a** and **63b**. Finally hydrogenation under palladium catalysis and demethylation by BBr₃ provided the (+)-estrone (from (-)-camphor) or (-)-estrone (from (+)-camphor).

²² Mikami, K.; Takahashi, K.; Nakai, T.; Uchimar, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948.

²³ Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, *26*, 1819.

Scheme 11. An enantiospecific synthesis of estrone by Money *et al.*

In 1988, Daniewski and co-workers utilized diisobutylaluminum hydride reduction²⁴ reaction of compound **65** with all *trans* stereo outcome in the synthesis of estrogens.²⁵ This route is short, albeit not enantioselective. Compound **66** was obtained by condensation of *m*-methoxyphenylacetaldehyde with the enolate form of **65**, and then further transformations lead to the racemic estrone **11**.

²⁴ Daniewski, A. R.; Kiegiel, J. *Syn. Commun.* **1988**, 18, 115.

²⁵ Daniewski, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, 53, 5535.

Scheme 12. Synthesis of estrone by Daniewski *et al.*

A very recent example was reported by Linclau and co-workers²⁶ in 2010. Notably, the key conjugate addition-allylation sequence was successfully accomplished either in diastereoselective or in enantioselective control, which makes this synthesis quite attractive.

²⁶ Foucher, V.; Guizzardi, B.; Groen, M. B.; Light, M.; Linclau, B. *Org. Lett.* **2010**, *12*, 680.

Scheme 13. Versatile D→BCD steroid construction strategy by Linclau *et al.*

Besides these strategies, other reactions such as Johnson's biomimetic polyolefin cyclization,²⁷ Friedel-Crafts cyclisations²⁸ and others² were also vividly involved in this area.

1.3 CONCLUSION AND FUTURE WORKS

Reported examples of total synthesis of estrone have been introduced in this part. They not only gave us an overall view of the whole history of estrone synthesis, but also gave some relevant inspiration to the synthesis of other steroidal compounds. Recently, many interesting steroids were isolated, for example, cortistatins family,²⁹ and have already been stimulated chemists to work on them. Therefore, exploration of efficient routes, which also should be short, chiral and versatile, can, however, be improved, is extremely requirable and makes the research in this area still ongoing.

²⁷ For examples see: Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, 95, 7501.

²⁸ For examples see: (a) Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, 44, 3661. (b) Lentz, C. M.; Posner, G. H. *Tetrahedron Lett.* **1978**, 3769. (c) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1544.

²⁹ Nising, C. F.; Brase, S. *Angew. Chem. Int. Ed.* **2008**, 47, 2.

CHAPTER 2

*Synthetic Studies Towards the Total Synthesis of
Estrone and Efforts on the Development of
Asymmetric Michael Addition Reaction*

2.1 GENERAL INTRODUCTION

Steroidal compounds are attractive synthetic targets, although a number of elegant steroid total syntheses had been developed since the first report in 1939 by Bachmann, Cole and Wilds,¹ many ingenious total syntheses are continued to be reported. This is not only because steroid total synthesis is a topic of interest for synthetic chemists and the pharmaceutical industry, but also because efficient routes are often desired for adequately functionalized steroid skeletons and newly isolated novel steroidal compounds. Thus the research in area is still ongoing.

In our group, four general strategies to synthesize steroidal compounds are being developed: (1) Biomimetic polyene cyclization (2) Chiral indium complex catalyzed Diels-Alder reaction (3) Chiral indium complex or organocatalyst catalyzed enantioselective Michael addition reaction and (4) Cascade reactions. Some pioneering works have already been reported in recent years.²

In this part, the synthetic studies towards ($\pm$)-9(11)-dehydroestrone methyl ether **1** (see Figure 1) which encompasses indium (III) bromide mediated Mukaiyama-Michael addition under neat conditions and thermodynamic control of enolate alkylation will be introduced. Furthermore, efforts towards the development of asymmetric Michael addition reaction to accomplish the stereoselective synthesis of estrone will also be the discussed.

¹ Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 974.

² (a) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2539. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 10024. (c) Zhao, Y. J.; Loh, T. P. *Chem. Commun.* **2008**, 1434. (d) Zhao, Y. J.; Tan, L. J. S.; Li, B.; Loh, T. P. *Chem. Commun.* **2009**, 3738.

Figure 1. The structure of (±)-9(11)-dehydroestrone methyl ether

2.2 RETROSYNTHETIC ANALYSIS OF ESTRONE

Ring C closure which relies on Michael-type additions that had already been developed in the last century. Enantioselective total synthesis of estrone can be achieved by asymmetric Michael addition of a ketone enolate to an enantiomerically pure α,β -ethylenic sulfoxide,³ which was introduced in the previous chapter. However, catalytic Michael-type addition reactions, which are more economical, have not been developed to realize enantioselective synthesis of estrone. In addition, the use of indium in organic chemistry is of growing importance and our group is one of the leading players in this field.⁴ Extending the indium chemistry to natural product syntheses is one of our goals. Accordingly, the corresponding retrosynthetic analysis was depicted in Scheme 1. Firstly, (±)-9(11)-dehydroestrone methyl ether **1** was disconnected on ring C to give compound **2**, which can be derived from key intermediate **3**. The intermediate **3** could be further disconnected into three parts and was envisioned to be directly accessed by a one-pot process involving InX or InX₃ catalyzed conjugate Michael addition followed by a subsequent nucleophilic substitution reaction. However, this approach would only give access to a convenient synthesis of racemic estrone. In order to obtain enantiomerically pure estrone, our

³ Posner, G. H.; Switzer, C. J. *Am. Chem. Soc.* **1986**, 108, 1239.

⁴ Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739.

initial strategy was to develop an indium Lewis acid catalyzed asymmetric Michael-type addition reaction to accomplish this enantioselective total synthesis.

Scheme 1. Retrosynthetic analysis

Despite the straightforward synthetic plan, one needs to keep in mind that challenges and difficulties may still arise. The diastereochemical outcome after one-pot process remains unclear. The other issue is that the catalytic asymmetric Michael-type addition reactions between cyclopentenone and cycloenolsilane are rarely reported and represent a great challenge. In the coming parts, these key issues will be addressed and presented accordingly.

2.3 SYNTHESIS OF (±)-9(11)-DEHYDROESTRONE METHYL ETHER

The starting silyl enol ether **5** was readily prepared from 6-methoxy tetralone **4** according to the literature reported method.⁵ Then, we postulated that it could undergo Michael addition reaction with 2-methyl-2-cyclopentenone **6** to generate the corresponding enolate, using indium Lewis acid as catalyst. With the transfer of the silyl group, the newly formed silyl enol ether **7** will then undergo subsequent

⁵ Dratch, S.; Charnikhova, T.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287.

nucleophilic substitution reaction with allyl bromide to afford our desired intermediate **3** (Scheme 2).

Scheme 2. The initial one-pot strategy

Previously, TrSbCl_6 ⁵ played a successful role in conducting the Mukaiyama-Michael reaction with silyl group transfer. In our strategy, indium Lewis acids would be utilized to carry out this reaction because they had shown superior results in the various organic transformations accomplished in our group.⁴ At the beginning, the Lewis acid $\text{In}(\text{OTf})_3$ and the weaker Lewis acid InCl_3 were chosen for the reaction of silyl enol ether **5** with 2-methyl-2-cyclopentenone **6** in anhydrous dichloromethane. As shown in Table 1, when 0.05 equivalent of $\text{In}(\text{OTf})_3$ was added to the reaction at -78°C , the silyl enol ether **5** was fully decomposed to starting material **4** with no silyl group transferred product obtained (entry 1, Table 1). In order to promote the Mukaiyama Michael addition, rather than the desilylation, the reaction temperature was increased to -40°C . However, only diketone product **8** was isolated as well as 6-methoxytetralone (entry 2, Table 1). By further increase of the temperature to room temperature, diketone product was obtained in 50% yield (entry 3, Table 1). These results suggested that the strong acidity of $\text{In}(\text{OTf})_3$ would make the unstable silyl enol ether **5** to desilylate easily to 6-methoxytetralone **4** instead of reacting with 2-methyl-2-cyclopentenone **6**. Moreover, desilylation continued to be observed by addition of MS 4Å or TMSCl as additive (entries 4-5, Table 1). Being a weaker Lewis

acid than $\text{In}(\text{OTf})_3$, InCl_3 was chosen next for the reaction. However, no reaction was observed at the temperature between -78°C and RT (entry 6, Table 1).

Table 1. Mukaiyama Michael addition reaction catalyzed by Indium Lewis acid^a

entry	InX_3	temp ($^\circ\text{C}$)	time (h)	yield of 8 (%) ^b
1		-78	5	---
2		-40	3	16
3	$\text{In}(\text{OTf})_3$	r.t.	1	50
4 ^c		-78	5	---
5 ^d		-78	1	---
6 ^e	InCl_3	-78 – r.t.	17	---

^a Conditions: silyl enol ether (1 mmol), 2-methyl-2-cyclopentenone (0.75 mmol), InX_3 (0.038 mmol), anhydrous DCM 2mL, under nitrogen atmosphere.

^b Isolated yield.

^c 20mg MS 4Å was added as additive.

^d 2 mmol TMSCl was added to reaction.

^e It was started from -78°C for 5 hours then slowly warm up to r.t. to stir for further 12 hours.

Following these initial attempts, we turned our attention to a moderate Lewis acid, InBr_3 . By investigating various reaction conditions, we found that the desired silyl group transferred product **7** was initially formed and then subsequently desilylated to the diketone **8**. Although it is difficult to optimize the reaction conditions to chemoselectively form the compound **7**, the diketone **8** is also a versatile and useful intermediate. Notably, organic reactions that used water as a solvent or were carried out under solvent-free conditions have become more relevant in modern synthesis. This is because such reaction conditions are economical, simple, safe and environmentally-friendly. In our group, organic reactions such as Mukaiyama aldol-type reaction,⁶ Diels-Alder reactions,⁷ Mukaiyama Michael addition,⁸ Mannich-type

⁶ (a) Loh, T. P.; Pei, J.; Cao, G. Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819. (b) Loh, T. P.; Pei, J.; Koh, S. V.; Cao, G. Q.; Li, X. R. *Tetrahedron Lett.* **1997**, 38, 3465. (c) Loh, T. P.; Pei, J.; Koh, S. V.;

reaction⁹ and conjugate addition of amine to α,β -ethylenic substrates,¹⁰ were achieved successfully in aqueous media or in pure water or under neat conditions. Therefore, the reaction of silyl enol ether **5** with ketone **6** catalyzed by InBr_3 was further investigated by conducting it in neat or aqueous solution conditions. The results were summarized in Table 2. By using 0.01 equivalent of InBr_3 and changing the ratio of silyl enol ether **5** and 2-methyl-2-cyclopentenone to 2:1, the desired diketone **8** can be obtained with 99% yield after 4 hours under neat condition (entry 3, Table 2).

Table 2. Mukaiyama Michael addition catalyzed by Indium(III) Bromide^a

Reaction scheme: Silyl enol ether **5** (4-methoxy-2-(trimethylsilyloxy)cyclohexa-1,3-diene) reacts with 2-methyl-2-cyclopentenone **6** in the presence of InBr_3 in DCM to form the diketone product **8** (4-methoxy-2-(2-methyl-2-oxocyclopentyl)cyclohexa-1,3-diene).

entry	condition	temp (°C)	time (h)	yield of 8 (%) ^b
1	neat	r.t.	2	57
2 ^c	DCM	r.t.	2	53
3	neat	r.t.	4	99
4 ^c	neat	r.t.	2	---

^a Conditions of entries 1-2: silyl enol ether (1 mmol), 2-methyl-2-cyclopentenone (0.75 mmol), InBr_3 (0.038 mmol). Conditions of entries 3-4: silyl enol ether (2 mmol), 2-methyl-2-cyclopentenone (1 mmol), InBr_3 (0.01 mmol and 0.05 mmol respectively for entry 3 and 4). All reactions were performed under nitrogen atmosphere.

^b Isolated yield.

^c Adding two drops of water.

The obtained diketone product **8** was a mixture of two diastereomers in a ratio of 27:73 which was determined by ¹H NMR analysis, but the relative stereochemistry remained unknown. When the reaction was performed in aqueous dichloromethane,

Cao, G. Q.; Li, X. R. *Tetrahedron Lett.* **1997**, 38, 3993. (d) Loh, T. P.; Chua, G. L.; Vittal, J. J.; Wong, M. W. *J. Chem. Soc., Chem. Commun.* **1998**, 861.

⁷ Loh, T. P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2315.

⁸ Loh, T. P.; Wei, L. L. *Tetrahedron* **1998**, 54, 7615.

⁹ Loh, T. P.; Wei, L. L. *Tetrahedron Lett.* **1998**, 39, 323.

¹⁰ Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975.

the yield decreased (entry 2, Table 2). Meanwhile fast desilylation of the starting silyl enol ether **5** was observed in water (entry 4, Table 2).

With the diketone product **8** in hand, electrophilic substitution reaction with allyl bromide was subsequently investigated under the condition of thermodynamic control. By adding *in situ* prepared LDA to the solution of diketone **8** in anhydrous THF at 0 °C, the corresponding enolate was generated, then allyl bromide was added and the resulting solution was slowly warmed up to room temperature and stirred overnight to afford the corresponding product **3** in a moderate yield. From the ^1H NMR of the product, the allyl group was shown clearly in the range of 5ppm to 6 ppm, and a pair of diastereomers was also observed. Fortunately, they could be separated by preparative TLC (hexane : ethyl acetate : dichloromethane = 90:6:20). Their ^1H NMR spectrums showed that the methyl group of each diastereomer is a singlet. Thus it can be concluded the enolate was formed in C-14 under the condition of thermodynamic control. Together with the analysis of ^{13}C NMR, DEPT135 and HRMS, the structures of **3a** and **3b** were confirmed. The best yield of 49% was obtained by employing 1.5 equivalents of LDA to perform the electrophilic substitution reaction of diketone **8** with allyl bromide, albeit with 45% of diketone **8** recovered (Scheme 3).

Scheme 3. Electrophilic substitution of diketone **8** with allyl bromide

Since the diastereomeric mixtures of **3a** and **3b** could not be simply separated by column chromatography, further reactions were carried out using the two diastereomers directly. As shown in Scheme 4, further transformations leading to the

dehydroestrone methyl ether were accomplished by following Ziegler's procedure¹¹ with some minor modifications.

Scheme 4. Further transformations leading to the dehydroestrone methyl ether

Ozonolysis (O_3 , $MeOH$, $-78^\circ C$, Me_2S) of **3** afforded Ziegler's diketoaldehyde **2a** and **2b** in 95% yield. The relative diastereochemistry of the two aldehydes was confirmed by comparing with their reported characteristic data. The isomeric mixture of **2a** and **2b** was subjected to epimerization at C-8 to give an *anti* rich mixture. After epimerization, the desired isomer **2a** was obtained with an average overall yield of 75%. Finally, McMurry coupling reaction ($TiCl_4$, Zn, THF) of **2a** was performed and accomplished with ring C closed targeting product **1** in 32% yield. The overall yield of **1** was 15% in 5 steps starting from 6-methoxy-1-tetralone **4** (Scheme 4).

¹¹ Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, 47, 5230.

Scheme 5. The overall synthetic route to the (±)-9(11)-dehydroestrone methyl ether¹²

In conclusion, a short and efficient formal synthesis of (±)-dehydroestrone methyl ether **1** had been developed; the overall synthetic route was outlined in scheme 5. Estrone can be readily transformed from **1** by known methods.¹² The most significant feature of this protocol is that the indium tribromide catalyzed Mukaiyama-Michael addition reaction under neat condition can effectively connect the ring A, B and D. The further studies on the asymmetric synthesis of estrone will be discussed in the following part.

¹² Representative methods for converting **1** to racemic estrone see: (a) Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, 26, 1819. (b) Foucher, V.; Guizzardi, B.; Groen, M. B.; Light, M.; Linclau, B. *Org. Lett.* **2010**, 12, 680.

2.4 EFFORTS ON THE DEVELOPMENT OF ASYMMETRIC MICHAEL REACTION CATALYZED BY ORGANOCATALYST TO COMPLETE THE STEREOSYNTHESSES OF ESTRONE

2.4.1 INTRODUCTION

Asymmetric Michael addition of a ketone enolate to enantiomerically pure cyclopentenone sulfoxide has already been successfully applied for the enantioselective synthesis of estrone.³ However, connecting ring A, B and D as well as the establishment of the π -facial diastereoselectivity by a catalytic asymmetric Michael addition reaction is more challenging and has not been reported yet. Based on our synthetic plan, achieving the enantioselective synthesis of estrone relies on the step of Mukaiyama Michael addition reaction of silyl enol ether **5** with 2-methyl-2-cyclopentenone **6**.

To the best of our knowledge, asymmetric Michael addition reaction between cycloenolsilane and cyclopentenone is rarely reported. The reported enantioselective Lewis acids catalyzed Michael reactions which employed cyclopentenone or activated cyclopentenone as the Michael acceptor were accomplished by following catalytic systems, Chiral titanium alkoxide,¹³ heterobimetallic asymmetric catalyst AlLi-BINOL,¹⁴ titanium TADDOL complex,¹⁵ and C_2 -symmetric bis(oxazoline) copper(II) complexes.¹⁶ Our group has achieved a variety of organic transformations using chiral

¹³ Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97-100.

¹⁴ Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 104.

¹⁵ Bernardi, A.; Karamfilova, K.; Boschin, G.; Scolastico, C. *Tetrahedron Lett.* **1995**, 36, 1363.

¹⁶ Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, 122, 9134.

indium complexes including allylation reaction,¹⁷ Mukaiyama-aldol reaction,¹⁸ Diels-Alder reaction¹⁹ and Ene reaction.²⁰ As a continuation of these previous works, we envisaged to develop an enantioselective Michael addition catalyzed by chiral indium-Pybox or indium-BINOL complexes (Scheme 6). Unfortunately, the Michael addition between silyl enol ether **5** with 2-methyl-2-cyclopentenone **6**, including their modified donors and acceptors, were all found to proceed in low diastereoselectivity and low enantioselectivity. To our disappointment, we were still unable to find any solutions to improve the stereoselectivities.

Scheme 6.

Since the year of 2000, there has been an explosive growth in the area of catalysis mediated solely by small organic molecules, which is also known as organocatalysis.²¹ In 2006, Deng's group reported that the cinchona alkaloid catalyzed efficient and practical Michael addition reactions of β -ketoesters to α,β -unsaturated ketones in excellent diastereoselectivity and enantioselectivity.²² It inspired us that an enantioselective synthesis of estrone might be possible by using the method described by Deng or other methods which will give versatile products with two vicinal chiral

¹⁷ (a) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 7, 1318. (b) Teo, Y. C.; Joshua, D. G.; Loh, T. P. *Org. Lett.* **2005**, 7, 2743-2745. (c) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, 7, 159-161. (d) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 1010-1012. (e) Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Chem. Commun.* **2005**, 4217-4218. (f) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345-2347.

¹⁸ Fu, F.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2006**, 47, 4267-4269.

¹⁹ (a) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, 7, 2539-2541. (b) Fu, F.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2006**, 8, 5999-6001.

²⁰ (a) Zhao, J. F.; Tsui, H. Y.; Wu, P. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, 130, 16492-16493. (b) Zhao, J. F.; Tjan, T. B. W.; Tan, B. H.; Loh, T. P. *Org. Lett.* **2009**, 11, 5714-5716.

²¹ Selected reviews see: (a) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, 34, 487. (b) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, 37, 580. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**. (d) List, B. *Chem. Rev.* **2007**, 107, 5413.

²² Wu, F. H.; Li, H. M.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, 45, 947.

tertiary carbon centers to furnish the important Michael adduct, which can be further transformed to our key intermediate **8** or equivalent. In addition, construction of the three stereocenters of estrone achieved by organocatalysis has not been reported yet. In the coming parts, development of new asymmetric Michael addition reactions by organocatalysis and extending them to the total synthesis of estrone will be discussed and presented accordingly.

2.4.2 ORGANOCATALYTIC ASYMMETRIC MICHAEL ADDITION OF CYCLIC β -KETOESTERS

Fully substituted chiral carbon centers are often essential for the biological activities of natural products and pharmaceuticals. The synthesis of all-carbon quaternary stereocenters are of great synthetic challenge, because such complex fragments are complicated due to steric factors, and appropriate catalytic systems are difficult to develop.²³ Recently, many fascinating examples that make use of organocatalysis for exquisite enantioselective construction of quaternary stereogenic centers involving β -ketoesters have been reported.²⁴ Among them, the conjugate addition of β -ketoesters to α,β -unsaturated compounds represents a highly versatile tool for the generation of chiral quaternary stereocenters. Most importantly, a wide

²³ For references on the asymmetric construction of quaternary carbon centers, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363. (b) Christoffers, J.; Baro, A. *Angew. Chem.* **2003**, *115*, 1726. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem.* **1998**, *110*, 402. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

²⁴ Selected examples: (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3792. (b) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219. (d) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551. (e) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem. Eur. J.* **2007**, *13*, 8338. (f) Poulsen, T. B.; Bernardi, L.; Aleman, J.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441. (j) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076.

range of Michael donors and acceptors were accessible and their addition reactions afforded excellent diastereoselectivity, enantioselectivity and yield by using appropriate chiral organocatalyst.²⁵ In addition, the synthetic versatility of the β -ketoester moiety makes further synthetic elaborations promising. Therefore, we tried to apply this strategy in the asymmetric synthesis of estrone methyl ether. As shown in the retrosynthetic analysis, the key step was the asymmetric Michael addition reaction of β -ketoester **10** to 2-methyl-2-cyclopentenone **6** (Scheme 7).

Scheme 7. Retrosynthetic analysis

To begin with this project, β -ketoester **10** was chosen as the model substrate and was synthesized according to reported method.^{24f, 26} It is important to mention that careful considerations were made with regards to this choice. Because β -ketoester **10** was equipped with bulky *tert*-butyl ester group which was critical for obtaining high enantioselectivity based on the reported literature.

²⁵ (a) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 4966. (b) Aleman, J.; Richter, B.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5515. (c) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798. (d) Bernardi, L.; Lopez-Cantarero, J.; Niess, B.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772. (e) Elsner, P.; Bernardi, L.; Salla, G. D.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897. (f) Luo, J.; Xu, L. W.; Hay, R. A. S.; Lu, Y. X. *Org. Lett.* **2009**, *11*, 437.

²⁶ Carpina, L. A. *J. Am. Chem. Soc.* **1960**, 2725.

Scheme 8. Preparation of the β -ketoester **10**

Cinchona alkaloids and their salts have been reported as the efficient catalysts for the conjugate addition of β -ketoesters to α,β -unsaturated compounds.²⁴ Thus, various cinchona alkaloid phase transfer catalysts were tested for the reaction of β -ketoester **10** with 2-cyclopentenon **15a** under various conditions. The reaction proceeded smoothly but the enantioselectivity was low. Then, we turned our attention to 6'-hydroxy cinchona alkaloid **12** (see Figure 2), which acted as an effective bifunctional chiral organocatalyst for the conjugate addition reactions of β -ketoesters with a wide range of α,β -unsaturated ketones reported by Deng *et al.*²² The difference is that the relatively less reactive 6-methoxy-tetralone derivated ketoester **10** served as the Michael donor.

Figure 2. Structures of some *Cinchona* alkaloid catalysts

With the model study substrates and various catalysts in our hands, we began to investigate their reactivity and behavior in the catalytic conjugate addition reaction. First, we attempted to perform the reaction under the same conditions developed by Deng *et al*, using 20 mol% of the catalyst at room temperature in dichloromethane. To our disappointment, no reactions took place with all the catalysts employed (entries 1-3, Table 3). Next, we increased the reaction temperature from room temperature to 50 °C and chose tetrahydrofuran as the solvent, instead of dichloromethane, due to its low boiling point. To our delight, the catalyst **12** promoted the reaction of β -ketoester **10** and **15a**, to give the corresponding adduct **16a** with high enantioselectivity and

regioselectivity, albeit with only 13% of conversion (entries 4-6, Table 3). Subsequently, various common solvents were screened. Although no promising results were obtained (entries 7-11, Table 3), high enantioselectivity was obtained for all cases. Next, we considered increasing the molarity of all reagents to facilitate the reaction. Therefore, the molarity was increased from 0.5 M to 4 M. A satisfactory level of yield was finally obtained with no significant drop of enantioselectivity. The best isolated yield was observed when THF was used as the solvent, with 68 % yield of Michael adduct and 29% recovery of starting material (entry 12, Table 3). Slightly lower yields were found when dichloroethane, chloroform or toluene were used as solvent (entries 13-15, Table 3).

Table 3. Screening conditions for the Michael addition of ketoester **10** with **15a**^a

entry	catalyst	solvent	temp (°C)	time (d)	yield (%)	e.e. (%) ^c	d.r. ^c
1	12	CH ₂ Cl ₂	r.t.	4	--	--	--
2	13	CH ₂ Cl ₂	r.t.	4	--	--	--
3	14	CH ₂ Cl ₂	r.t.	4	--	--	--
4	12	THF	50	2.5	13 ^d	97	1.3:98.7
5	13	THF	50	2.5	--	--	--
6	14	THF	50	2.5	--	--	--
7	12	DCE	50	2.5	10 ^d	98	1.2:98.8
8	12	EA	50	2.5	5 ^d	96	2:98
9	12	CHCl ₃	50	2.5	9 ^d	97	1.5:98.5
10	12	Toluene	50	2.5	11 ^d	96	1.8:98.2
11	12	DMSO	50	2.5	--	--	--
12 ^b	12	THF	50	7	68 (29) ^e	93	3:97
13 ^b	12	DCE	50	7	56 (27) ^e	94	3:97
14 ^b	12	CHCl ₃	50	7	59 (20) ^e	94	3:97
15 ^b	12	Toluene	50	7	55 (26) ^e	94	3:97

^a Unless otherwise specified, the reaction was performed by treatment of **10** (0.05 mmol) with **15** (0.13 mmol) and the catalyst (0.01 mmol) in 0.1 mL solvent.

^b The reactions were performed by treatment of **10** (0.2 mmol) with **15** (0.5 mmol) and the catalyst (0.04 mmol) in 0.05 mL solvent.

^c Determined by HPLC analysis.

^d Conversion was determined by crude ¹H NMR.

^e Isolated yield, the data in parentheses is the yield of recovered starting material **10**.

With the establishment of optimized conditions, we tested the reaction between **10** and 2-methyl-2-cyclopentenone **6**, which was the key step for the asymmetric synthesis of estrone (entry 2, Table 4). Unfortunately, no reaction occurred even when the temperature was increased to 100 °C in toluene. It was probably due to steric hindrance of the methyl group of **6**, making it too difficult to approach the activated reaction center of β -ketoester **10**. To our disappointment, there were also no reactions for the Michael accepters **15c** and **15d** (entries 3-4, Table 4). In addition, the conjugate additions of β -ketoester **10** with other vinyl ketones afforded with low enantioselectivities, albeit the yields were moderate (entries 8-14, Table 4). The reaction scope for the model substrate **10** was found to be very limited, making this strategy difficult to go further.

Table 4. Michael addition of ketoester **10** with various α,β -unsaturated ketones^a

10	15			16	
15a	6	15c	15d	15e	15f
15g	15h	15i	15j	15k	
entry	vinyl ketone	temp °C	time (d)	Yield (%) ^b	ee (%) ^c
1 ^d	15a	50	7	68	93 (dr 3:97)

2 ^d	6	50	7	--	--
3 ^d	15c	50	7	--	--
4 ^d	15d	50	7	--	--
5 ^d	15e	r.t.	7	51	80
6 ^d	15e	50	7	74	72
7 ^e	15e	50	7	70	78
8	15e	50	6	86	84
9	15f	50	7	76	75
10	15g	50	7	83	30
11	15h	50	7	85	26
12	15i	50	7	84	43
13	15j	50	7	90	39
14	15k	50	7	77	27

^a Unless otherwise specified, the reactions were performed by treatment of **10** (0.2 mmol) with **15** (0.5 mmol) and the catalyst (0.04 mmol) in 0.1 mL DCE (2 M).

^b Isolated yield.

^c Determined by Chiral HPLC.

^d Entries of 1-6 were carried out in 0.05 mL THF (4 M).

^e Entry 7 was carried out in 0.1 mL THF (2 M).

In conclusion, we successfully optimized the reaction conditions for model conjugate addition of β -ketoester **10** with 2-cyclopentenon **15a** with high enantioselectivity and satisfied yield, but we failed to extend it to our key step reaction due to the unexpected limiting reaction scope. Exploring a more efficient asymmetric Michael addition to accomplish the stereoselective synthesis of estrone is still ongoing.

2.4.3 ORGANOCATALYTIC ASYMMETRIC MICHAEL ADDITION OF VINYL MALONONITRILES

Recently, it was reported that α,α -dicyanoolefin compounds can behave as acceptors or vinylogous donors selectively in Michael reactions under easily controllable conditions, which then simultaneously give multi-functional products

with two vicinal chiral tertiary carbon centers.²⁷ Among these, it was found that asymmetric direct vinylogous Michael addition reactions of electron-deficient α,α -dicyanoolefins with α,β -unsaturated carbonyl compounds catalyzed by (*S*)- α,α -diphenylprolinol, could be carried out smoothly, showing excellent regio-, chemo-, diastereo-, and enantioselectivities.^{27a} Therefore, we tried to apply this strategy in the asymmetric synthesis of estrone methyl ether. The key step was the asymmetric Michael reaction of 2-(6-methoxy-2,3-dihydronaphthalen-4(1*H*)-ylidene) malononitrile **18** to 2-methyl-cyclopent-2-enone **6** (Scheme 9). However, the use of (*S*)- α,α -diphenylprolinol as catalyst gave only the racemic product in low yield (see Scheme 9). Thus, chiral azabicyclo catalysts, which match the structural requirements for some highly efficient catalytic systems,²⁸ were synthesized and applied in this Michael addition reaction (see Figure 3). Unfortunately, similar results were obtained. However, we were pleased to find that good reactivity and enantioselectivity were observed, when the chiral azabicyclo catalysts were applied in the vinylogous Michael addition of α,α -dicyanoolefins to α,β -unsaturated aldehydes.

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²⁸ (a) Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, 54, 7897. (b) Nakano, H.; Kumagai, N.; Kabuto, C.; Matsuzaki, H.; Hongo, H. *Tetrahedron: Asymmetry* **1995**, 6, 1233. (c) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, 8, 1391. (d) Shinisha, C. B.; Sunoj, R. B. *Org. Biomol. Chem.* **2007**, 5, 1287. (e) Trifonova, A.; Kallstrom, K. E.; Andersson, P. G. *Tetrahedron* **2004**, 60, 3393.

Scheme 9. Retrosynthetic analysis

Figure 3. Chiral 2-azanorbornyl derivatives used

In this part, the application of (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane -3-exo-bis(phenyl)methanol **21** as an efficient organocatalyst for the enantioselective vinylogous Michael addition of α,α -dicyanoolefins to α,β -unsaturated aldehydes will be described. In many cases, the products were obtained in almost enantiomerically pure form (>95% ee) after a single recrystallization.

Figure 4. Structures of the starting vinyl malononitriles.

Table 5. Screening of chiral 2-azanorbornyl derivatives as catalysts for the vinylogous Michael addition reaction^a

entry	catalyst	additive	yield ^b (%)	ee ^c (%)
1	19	-	89	24
2	20	-	0	-
3	20	28	0	-
4	21	-	41	81
5	21	28	84	87 (97) ^d
6	22	28	40	60
7	23	28	42	51

^a Reactions performed with 0.1 mmol of **24a**, 0.4 mmol of **25a** and 20mol% of catalyst in 1 mL of THF at r.t. for 20 hours.

^b Isolated yield.

^c Determined by chiral HPLC analysis.

^d After single recrystallization from *i*-PrOH

Our initial studies began with reaction of vinyl malononitrile **24a** (Figure 4) and crotonaldehyde **25a** in the presence of a catalytic amount of chiral 2-azanorbornyl derivative **19**. In the presence of 20 mol % of **19** in THF at room temperature, the reaction of **24a** with **25a** gave the desired product **26aa** in good yield (89%), but the *e.e.* was quite poor (entry 1, Table 5). No reaction occurred when derivative **20** was used as the chiral catalyst, even when *para*-nitrobenzoic acid (PNBA **28**) was used as an additive (entries 2-3, Table 5). Thus, tertiary amine catalysts were completely ineffective for the vinylogous Michael addition of a vinyl malononitrile and an α,β -unsaturated aldehyde. We were delighted to find that a high enantioselectivity of 87% could be obtained using (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane-3-exo-bis(phenyl)methanol **21** as the catalyst (entry 5, Table 5). However, the product could only be obtained in low yield with moderate ee in the absence of PNBA. OH-etherified catalysts, which have been used successfully in many asymmetric reactions,

were also tested in the vinylogous Michael addition. Under these reaction conditions, moderate enantioselectivities of 60% and 51% ee were observed when catalysts **22** and **23** were used respectively.

Next, we investigated the effect of the reaction temperature, acid additives and solvents on the addition reaction using catalyst **21**. The results are summarized in Table 6.

Table 6. Investigation of the reaction temperature, acid additives, and solvents using catalyst **21**^a

entry	additive	solvent	time (h)	temp (°C)	yield ^b (%)	ee ^c (%)
1	27	THF	40	rt	64	82
2	28	THF	20	rt	84	87
3	29	THF	20	rt	76	84
4	30	THF	20	rt	74	82
5	28	DCM	20	rt	58	74
6	28	Et ₂ O	20	rt	62	76
7	28	Toluene	20	rt	67	82
8	28	MeCN	20	rt	79	83
9	28	MeOH	20	rt	0	-
10	28	THF	40	0	42	88
11	28	THF	24	-30	0	-
12 ^d	28	THF	36	rt	74	81

^a Reactions performed with 0.1 mmol of **24a**, 0.4 mmol of **25a**, 20 mol% of catalyst **21** and 20 mol% of additive in 1 mL solvent.

^b Isolated yield.

^c Determined by chiral HPLC analysis.

^d 20 μ L H₂O was added.

Figure 5. Structures of the additives

Several acid additives were tested first (Figure 5). From the results, additive **28** was superior to the other additives (entries 1–4, Table 6). Next, several solvents were screened for the reaction at room temperature. A drop in both reaction rate and enantiomeric excess was observed for solvents such as DCM, Et₂O, toluene, and CH₃CN (entries 5–8, Table 6). No reaction took place in methanol (entry 9, Table 6). In general, lowering of the temperature resulted in decrease of the reaction rate but increase of the enantioselectivity. In the presence of 20 mol % of catalyst, an 88% ee of **26aa** was obtained at 0 °C, but the yield was only 42% after a long reaction time. When the temperature was decreased to -30 °C, no product was obtained even after 24 hours (entry 11, Table 6). Addition of a small amount of water resulted in slight decrease of the yield and enantioselectivity (entry 12, Table 6). The combination of catalyst **21** (20 mol %) and PNBA **28** (20 mol %) exhibited the best catalytic activity in THF at room temperature.

Having established the optimal reaction conditions, we examined a range of α,α -disubstituted vinyl malononitriles (Figure 4) and α,β -unsaturated aldehydes next in order to explore the generality of this catalytic system. The results are summarized in Table 7.

Table 7. Asymmetric vinylogous Michael addition of dicyanoolefins **24** to α,β -unsaturated aldehydes **25**^a

entry	24	R	product	yield ^b (%)	ee ^c (%)
1	24a	Me (25a)	26aa	78	87 (97) ^d
2	24b	Me (25a)	26ba	81	91
3	24c	Me (25a)	26ca	86	90 (>99) ^d
4	24d	Me (25a)	26da	56	86 (97) ^d
5	24e	Me (25a)	26ea	41	87 (96) ^d

6	24f	Me (25a)	26fa	42/8	71/32
7	24b	Et (25b)	26bb	75	88
8	24c	Et (25b)	26cb	83	88 (>99) ^d
9	24d	Et (25b)	26db	40	81
10	24a	<i>n</i> -Pr (25c)	26ac	60	80
11	24c	<i>n</i> -Pr (25c)	26cc	74	81
12	24b	Ph (25d)	26bd	80	57

^a Reactions performed with 0.1 mmol of **24**, 0.4 mmol of **25**, 20mol% of catalyst **21** and 20mol% of PNBA in 1 mL THF.

^b Isolated yield.

^c Determined by chiral HPLC analysis on a Chiral phase, the absolute configuration of the products was assigned by comparison with optical rotation and/or retention time on chiral HPLC in Ref. 25a.

^d After recrystallization from *i*-PrOH.

Several α,α -disubstituted vinyl malononitriles were tested in the reaction with crotonaldehyde. In all cases, high enantioselectivities were obtained (entries 1–5, Table 7). However, when an electron-donating group was introduced into the vinyl malononitrile, we observed a decrease in the yields (entries 4 and 5, Table 7). High ee values could also be obtained in the reaction of other alkyl α,β -unsaturated aldehydes (entries 7–11, Table 7). Unfortunately, the reaction of an aryl α,β -unsaturated aldehyde exhibited only moderate enantioselectivity (entry 12, Table 7). In all the reactions of cyclic substrates, only the *anti*-products were formed. However, the reaction of acyclic substrate **24f**, a major product was obtained in 71% ee, while the diastereomer was formed in 8% yield with 32% ee. No reaction took place when unsaturated ketone trans-4-phenyl-3-buten-2-one was used.

In summary, it has demonstrated an efficient method for the organocatalytic and asymmetric direct vinylogous Michael addition that employs electron deficient vinyl malononitriles as the nucleophilic species in the presence of a catalytic amount of chiral 2-azanorbornyl derivatives. The reaction features a metal-free approach, high efficiency of the catalyst, mild reaction conditions, high yields, and good

enantioselectivities, providing a practical method to synthesize highly enantiopure multi-functional compounds. Many of these products can be obtained in almost optically pure form after a single crystallization from isopropanol. These results open a new avenue for the design of chiral azabicyclo[2.2.1] heptane analogues as organocatalysts. Redesigning high affinity chiral 2-azanorbornyl derivatives applicable to the asymmetric synthesis of estrone methyl ether is still ongoing.

2.5 CONCLUSION AND FUTURE WORK

In conclusion, we have demonstrated an efficient formal synthesis of ($\pm$)-dehydroestrone methyl ether. Mukaiyama-Michael addition reaction catalyzed by indium tribromide under neat conditions was the key feature of in this approach. Electrophilic substitution reaction carried out under thermodynamic control also played an important role in completing this total synthesis. In the meantime, asymmetric Michael addition reactions involving organocatalysis were investigated with the aim to utilize them in the enantioselective synthesis of natural estrone. Although asymmetric Michael addition of β -ketoesters and asymmetric direct vinylogous Michael addition of vinyl malononitriles were achieved in good enantioselectivities, to our disappointment, their addition with 2-methyl-2-cyclopentenone did not proceed smoothly to give the desired products with satisfied yield and enantioselectivity, which would serve as the key intermediate in enantioselective total synthesis of estrone. However, upon doing these preliminary studies, it gave us an insight into this research corner and would instruct us to develop more effective and applicable asymmetric catalyst system for Michael addition reaction, efforts towards this is still ongoing.

2.6 EXPERIMENTAL

The preparation of silane (5)

[(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](trimethyl)silane (5): To an oven dried round-bottom flask equipped with a magnetic stirring bar was added sodium iodide (1.88 g, 12.5 mmol, 1.25 equiv.). The solid was dried under vacuum prior to the addition of triethylamine (2.8 mL, 20.0 mmol, 2.0 equiv.) and chlorotrimethylsilane (1.92 mL, 15.0 mmol, 1.5 equiv.). The mixture was treated with a solution of 6-methoxytetralone (1.76 g, 10.0 mmol, 1 equiv.) in anhydrous acetonitrile (5 mL). The reaction mixture was allowed to stir at room temperature for overnight. The solution was quenched with hexane (15 mL) and sodium bicarbonate solution (10 mL). The aqueous layer was extracted with hexane (3 × 25 mL), and the combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the product as a yellow oil (2.45 g, 99% crude yield).

$R_f = 0.87$ (hexane : ethyl acetate = 4:1);

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.33 (d, $J = 8.34$ Hz, 1H), 6.71 (d, $J = 8.34$ Hz, 1H), 6.68 (s, 1H), 5.06 (t, $J = 4.53$ Hz, 1H), 3.80 (s, 3H), 2.73 (t, $J = 7.84$ Hz, 2H), 2.30 (td, $J = 8.26, 4.61$ Hz, 2H), 0.24 (s, 9H) ppm;

$^{13}\text{C NMR}$ (75.4 MHz, CDCl_3): δ 159.0, 148.0, 138.8, 126.5, 123.0, 113.1, 110.6, 102.6, 54.9, 28.6, 22.1, 0.1 ppm;

FTIR (neat): $\nu = 3053, 2985, 2305, 1639, 1608, 1422$ cm^{-1} ;

HRMS (EI): m/z Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Si}$ $[\text{M}]^+$: 248.1227. Found: 248.1228.

The Preparation of Diketone (7) **3,4-dihydro-6-methoxy-2-(2-methyl-3-oxocyclopentyl)naphthalen-1(2H)-**

one (7): To an oven dried round-bottom flask equipped with a magnetic stirring bar was added trimethylsilylenol ether **2** (500 mg, 2.0 mmol, 2 equiv.) and 2-methyl-2-cyclopenten-1-one (96 mg, 1 mmol, 1 equiv.). InBr₃ (3.54 mg, 0.01 mmol, 0.01 equiv.) was added under nitrogen atmosphere while stirring. The reaction was allowed to stir at room temperature for 4 hours before quenching with saturated sodium bicarbonate solution. The resulting mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the diketone product as a light yellow oil (269 mg, 99% yield), diastereomeric ratio is 27 : 73.

R_f = 0.25 (hexane : ethyl acetate = 3:1);

minor isomer:

¹H NMR (300 MHz, CDCl₃): δ 7.98 (d, *J* = 8.70 Hz, 1H), 6.82 (dd, *J* = 8.71, 2.32 Hz, 1H), 6.69-6.68 (m, 1H), 3.84 (s, 3H), 3.00 (dd, *J* = 7.24, 4.47 Hz, 2H), 2.61 (dt, *J* = 4.00, 11.85 Hz, 1H), 2.52-2.41 (m, 1H), 2.38-2.34 (m, 1H), 2.31-2.25 (m, 1H), 2.23-2.08 (m, 2H), 2.06-1.92 (m, 2H), 1.81-1.67 (m, 1H), 1.05 (d, *J* = 6.88 Hz, 3H) ppm;

¹³C NMR (75.4 MHz, CDCl₃): δ 220.1, 197.2, 163.4, 145.9, 129.7, 126.3, 113.1, 112.3, 55.3, 47.9, 46.0, 42.9, 37.0, 29.1, 23.5, 22.4, 12.4 ppm;

major isomer:

^1H NMR (300 MHz, CDCl_3): δ 7.98 (d, J = 8.70 Hz, 1H), 6.82 (dd, J = 8.71, 2.32 Hz, 1H), 6.69-6.68 (m, 1H), 3.84 (s, 3H), 3.00 (dd, J = 7.24, 4.47 Hz, 2H), 2.61 (dt, J = 4.00, 11.85 Hz, 1H), 2.52-2.41 (m, 1H), 2.38-2.34 (m, 1H), 2.31-2.25 (m, 1H), 2.23-2.08 (m, 2H), 2.06-1.92 (m, 2H), 1.81-1.67 (m, 1H), 1.03 (d, J = 6.88 Hz, 3H) ppm;

^{13}C NMR (75.4 MHz, CDCl_3): δ 220.1, 197.2, 163.4, 145.9, 129.7, 126.3, 113.1, 112.3, 55.3, 48.5, 46.9, 43.9, 37.0, 29.3, 25.9, 24.3, 13.3 ppm;

FTIR (neat): ν = 3053, 2986, 2305, 1736, 1670, 1601, 1422 cm^{-1} ;

HRMS (EI): m/z Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_3$ $[\text{M}]^+$: 272.1407. Found: 272.1401.

The Preparation of compound (3)

2-(2-allyl-2-methyl-3-oxocyclopentyl)-3,4-dihydro-6-methoxynaphthalen-

1(2H)-one (3): To an oven dried round-bottom flask equipped with a magnetic stirring bar was added diisopropylamine (0.08 mL, 0.56 mmol, 1.65 equiv.) and dry THF (1 mL). The solution was cooled to 0 °C prior to addition of *n*-BuLi (0.32 mL, 0.51 mmol, 1.5 equiv.). The mixture was allowed to stir at 0 °C for 30 minutes prior to the addition of the solution of diketone (92.6 mg, 0.34 mmol, 1.0 equiv.) in anhydrous THF (1 mL). The solution was stirred at 0 °C for another 30 minutes and was treated with allyl bromide (0.04 mL, 0.41 mmol, 1.2 equiv.). The reaction was allowed to proceed for an overnight prior to quenching with ice-water (5 mL). The aqueous layer was extracted with diethyl ether (3 $\times$ 15 mL). The combined organic extracts were washed with brine (2 $\times$ 5 mL) and dried over anhydrous sodium sulfate, filtered and

concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 49% yield. (45% of diketone **4** was recovered after the reaction).

Isomer 1:

$R_f = 0.40$ (hexane : ethyl acetate = 3:1);

^1H NMR (300 MHz, CDCl_3): δ 7.97 (d, $J = 8.76$ Hz, 1H), 6.82 (dd, $J = 8.76, 2.49$ Hz, 1H), 6.68 (d, $J = 2.40$ Hz, 1H), 5.72-5.59 (m, 1H), 5.11-5.06 (m, 2H), 3.85 (s, 3H), 3.12 (dt, $J = 17.51, 6.14$ Hz, 1H), 2.93 (dt, $J = 17.51, 6.14$ Hz, 1H), 2.69 (ddd, $J = 7.06, 7.06, 4.95$ Hz, 1H), 2.49-2.34 (m, 3H), 2.23-1.88 (m, 6H), 1.03 (s, 3H) ppm;

^{13}C NMR (75.4 MHz, CDCl_3): δ 221.7, 198.4, 163.6, 145.9, 134.1, 129.9, 126.3, 118.6, 113.3, 112.4, 55.4, 52.2, 48.7, 42.9, 42.0, 36.9, 27.8, 27.8, 23.3, 18.0 ppm;

FTIR (CH_2Cl_2): $\nu = 3053, 2986, 2305, 1601, 1422\text{ cm}^{-1}$;

HRMS (EI): m/z Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_3$ $[\text{M}]^+$: 312.1720. Found: 312.1733.

Isomer 2:

$R_f = 0.37$ (hexane : ethyl acetate = 3:1);

^1H NMR (300 MHz, CDCl_3): δ 8.00 (d, $J = 8.76$ Hz, 1H), 6.84 (dd, $J = 8.76, 2.52$ Hz, 1H), 6.68 (d, $J = 2.49$ Hz, 1H), 5.51-5.37 (m, 1H), 4.88-4.84 (m, 1H), 4.71-4.65 (m, 1H), 3.86 (s, 3H), 3.08-2.86 (m, 3H), 2.63 (ddd, $J = 6.50, 8.50, 4.00$ Hz, 1H), 2.39-2.28 (m, 2H), 2.19-1.99 (m, 2H), 1.70-1.58 (m, 2H), 1.08 (s, 3H) ppm;

^{13}C NMR (75.4 MHz, CDCl_3): δ 222.5, 198.5, 163.5, 145.6, 133.6, 130.1, 126.2, 118.7, 113.3, 112.4, 55.4, 51.6, 47.6, 40.8, 39.5, 37.0, 27.6, 26.2, 22.8, 18.0 ppm;

FTIR (CH_2Cl_2): $\nu = 3053, 2986, 2305, 1601, 1422\text{ cm}^{-1}$;

HRMS (EI): m/z Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3$ $[\text{M}]^+$: 312.1720. Found: 312.1733.

The Preparation of diketone aldehyde (2**)¹ and Epimerization of *syn*-**2b** to *anti*-**2a**²**

A solution of diketone **3** (58 mg, 0.19 mmol, 2 isomer) in 1.94 mL of CH_2Cl_2 and 3.12 mL of MeOH was cooled to $-78\text{ }^\circ\text{C}$, and then an excess of ozone was passed through the mixture and monitored by TLC, when no starting material was observed, it was treated with 0.71 mL of dimethyl sulfide. The resulting mixture was allowed to warm up slowly and stirred at room temperature under nitrogen atmosphere overnight. Removal of the solvent followed by column chromatography afforded the diketonealdehydes **2a** and **2b** in 42% and 53% yield, respectively.

To a solution of a catalytic amount of sodium methoxide (freshly prepared by sodium (0.5 mg, 0.02 mmol, 0.1 equiv.) and 3 mL dry methanol) was added a solution of the diastereomeric mixture of the two aldehydes **2a** and **2b** (62.3 mg, 0.2 mmol, 1.0 equiv.) in methanol (2 mL). The resulting mixture was stirred for 4 hours at room temperature. Then the mixture was diluted and extracted with ether, washed with saturated ammonium chloride solution and brine, dried over anhydrous sodium sulfate. Removal of the solvent followed by column chromatography gave the diketonealdehyde **2a** 8,14-*anti* as the major product.

Diketone aldehyde **2a:**

¹ Gary, H. P.; Christopher, S. *J. Am. Chem. Soc.* **1986**, *108*, 1239.

$R_f = 0.27$ (hexane : ethyl acetate = 2:1);

^1H NMR (300 MHz, CDCl_3): δ 9.35 (s, 1H), 7.92 (d, $J = 8.70$ Hz, 1H), 6.80 (dd, $J = 8.70, 2.40$ Hz, 1H), 6.66 (d, $J = 2.40$ Hz, 1H), 3.84 (s, 3H), 3.12-3.02 (m, 1H), 2.93-2.82 (m, 2H), 2.79-2.76 (m, 2H), 2.70-2.37 (m, 1H), 2.29-2.05 (m, 3H), 1.72-1.60 (m, 1H), 1.06 (s, 3H) ppm;

^{13}C NMR (75.4 MHz, CDCl_3): δ 221.3, 200.0, 199.8, 163.7, 145.6, 129.7, 125.7, 113.5, 112.5, 55.4, 50.4, 48.6, 47.0, 39.7, 35.7, 26.8, 26.2, 24.1, 17.7 ppm;

FTIR (CH_2Cl_2): $\nu = 3053, 2986, 2305, 1601, 1422\text{ cm}^{-1}$;

HRMS (EI): m/z Calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_4$ $[\text{M}]^+$: 314.1513. Found: 314.1517.

Diketone aldehyde 2b:

$R_f = 0.18$ (hexane : ethyl acetate = 2:1);

^1H NMR (300 MHz, CDCl_3): δ 9.67 (s, 1H), 7.96 (d, $J = 8.40$ Hz, 1H), 6.83 (dd, $J = 8.70, 2.10$ Hz, 1H), 6.66 (d, $J = 2.10$ Hz, 1H), 3.84 (s, 3H), 3.07-2.76 (m, 3H), 2.70-2.60 (m, 2H), 2.42-2.37 (m, 2H), 2.30-1.99 (m, 3H), 1.97-1.69 (m, 2H), 1.05 (s, 3H) ppm;

^{13}C NMR (75.4 MHz, CDCl_3): δ 220.9, 200.0, 198.0, 163.7, 145.3, 130.0, 125.9, 113.6, 112.5, 55.4, 51.7, 49.2, 48.2, 40.4, 36.1, 26.9, 26.6, 24.3, 17.8 ppm;

FTIR (CH_2Cl_2): $\nu = 3053, 2986, 2305, 1601, 1422\text{ cm}^{-1}$;

HRMS (EI): m/z Calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_4$ $[\text{M}]^+$: 314.1513. Found: 314.1517.

² Koichi, M.; Kazuhiko, T.; Takeshi, N.; Tadafumi, U. *J. Am. Chem. Soc.* **1994**, *116*, 10948.

**McMurry coupling of the diketoaldehyde to achieve (±)-9(11)-
dehydroestrone methyl ether (1)**

7,8,12,13,15,16-hexahydro-3-methoxy-13-methyl-6H-cyclopenta[*a*]phenanthren-

17(14*H*)-one (1): Activated zinc powder (208 mg, 3.2 mmol, 16.0 equiv.) was placed in a flame dried 50 mL flask, then 20 mL anhydrous THF was added and stirred vigorously, when it was cooled to 0 °C, Titanium tetrachloride (189 mg, 1.6 mmol, 8.0 equiv.) was added carefully. Then the resulting mixture was slowly warm up to room temperature and refluxed for 2 hours.

The resultant dark brown low valent Titanium solution was brought to room temperature and the diketoaldehyde (63.4 mg, 0.2 mmol, 1.0 equiv.) in 15mL dry THF was added slowly *via* a syringe and kept stirring for 30 minutes at room temperature. Then the reaction mixture was under reflux for 4 hours. Upon cooling to room temperature, the mixture was quenched by saturated sodium carbonate solution and passed through celite, washed with ether.

The resulting suspension was extracted with ether and washed with brine. The organic phase was combined and dried with sodium sulfate and concentrated under reduced pressure to afford the crude product.

Preparative TLC (12.5:1 benzene / ethyl acetate) afforded the pure product (18 mg, 32%) as a cuticolor solid.

$R_f = 0.40$ (hexane : ethyl acetate = 4:1);

¹H NMR (300 MHz, CDCl₃): δ 7.53 (d, J = 8.79 Hz, 1H), 6.73 (dd, J = 8.77, 2.64 Hz, 1H), 6.62 (d, J = 2.60 Hz, 1H), 6.14-6.13 (m, 1H), 3.79 (s, 3H), 2.97-2.83 (m, 2H), 2.54-2.48 (m, 1H), 2.35-2.15 (m, 6H), 1.70-1.64 (m, 2H), 1.46 (m, 1H), 0.94 (s, 3H) ppm;

¹³C NMR (75.4 MHz, CDCl₃): δ 221.6, 158.6, 137.4, 135.3, 127.1, 125.3, 116.7, 113.4, 112.8, 55.2, 47.8, 46.2, 38.2, 36.2, 33.9, 29.9, 27.8, 22.5, 14.5 ppm;

FTIR (CH₂Cl₂): ν = 3019, 2932, 1734, 1607, 1215, 756 cm⁻¹;

HRMS (EI): m/z Calcd. for C₁₉H₂₂O₂ [M]⁺: 282.1621. Found: 282.1614.

General procedure for the preparation of the racemic 1,4-adducts

To a solution of β -ketone ester (13.8 mg, 0.05 mmol) in Toluene (0.5 mL) was added Cesium hydroxide (10.1 mg, 0.06 mmol), tetraethylammonium bromide (2.1 mg, 0.01 mmol). Then 0.1 mmol of α,β -unsaturated ketone was added, the subsequent reaction mixture was stirred at room temperature for two days. The product was isolated by preparative TLC directly.

Typical procedure for preparation of β -ketone ester³

³ (a) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, 2725. (b) Poulsen, T. B.; Bernardi, L.; Aleman, J.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2007**, 129, 441.

A solution of 9.56 mL of *t*-butyl alcohol and 8.09 mL of pyridine in 25 mL of dry dichloromethane was cooled in an ice bath, followed by dropwise addition of 14.42 mL of ethoxalyl chloride via dropping funnel with vigorous stirring. The mixture was stirred in ice bath for 4 hours at room temperature overnight. Then the resulting suspension was diluted with dichloromethane, washed with water for three times, dried with Na_2SO_4 and concentrated under vacuum. The ethyl *t*-butyl oxalate was obtained in quantitative yield.

^1H NMR (400 MHz, CDCl_3): δ 4.28 (q, $J = 7.1$ Hz, 2H), 1.52 (s, 9H), 1.33 (t, $J = 7.1$ Hz, 3H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 158.6, 157.0, 84.7, 62.7, 27.6 (3C), 13.8 ppm;

To a solution of obtained ethyl *t*-butyl oxalate in 10 mL of dry ethanol was added in 4 portions of 7 mL pyridine. The solution was allowed to stir for 12 hours at room temperature and diluted with 60 mL of DCM and 30 mL of water. The aqueous layer was extracted three times. Combined organic layer was dried with Na_2SO_4 , filtered and evaporated. *t*-butyl oxamate was obtained in 52% yield as white solid without further purification.

^1H NMR (500 MHz, CDCl_3): δ 6.99 (bs, 1H), 6.61 (bs, 1H), 1.54 (s, 9H) ppm;

^{13}C NMR (125 MHz, CDCl_3): δ 159.7, 159.1, 84.8, 27.7 (3C) ppm;

To a solution of obtained *t*-butyl oxamate and 7.36 mL of pyridine cooled in an ice bath was added 6.88 mL of trifluoroacetic anhydride dropwise with vigorous stirring. The ice-bath was removed and the thick mixture was allowed for 10 minutes at room temperature. Then 50 mL of ether was added. The resulting suspension was extracted with ether for three times. Combined organic layer was washed with once with water and twice with 1 M sodium bicarbonate solution, dried with Na₂SO₄, then filtered and evaporated. The *t*-butyl cyanoformate was obtained as oil and used directly without further purification.

¹H NMR (500 MHz, CDCl₃): δ 1.53 (s, 9H) ppm;

¹³C NMR (125 MHz, CDCl₃): δ 144.1, 142.9, 109.9, 89.2, 27.6 (3C) ppm;

A solution of a 6-methoxytetralone (1.5 mmol) in dry THF (3 mL) was slowly added to a cooled (-78 °C), stirred solution of LDA (1.65 mmol) in dry THF (3 mL). After 30 min stirring at the same temperature, a solution of *tert*-butyl cyanoformate (1.65 mmol) in dry THF (1 mL) was added, and the resulting mixture was stirred for 1 h at -78 °C, and then allowed to warm to room temperature. The reaction was then quenched by addition of saturated NH₄Cl solution, and the product was extracted with ether for three times. The combined organic phases were then dried over Na₂SO₄, filtered and evaporated under reduced pressure. Purification of the crude mixture by column chromatography gave the corresponding β-ketoester in 70% yield.

***tert*-butyl 1,2,3,4-tetrahydro-6-methoxy-1-oxonaphthalene-2-carboxylate**

¹H NMR (300 MHz, CDCl₃) (97% of keto form): δ 8.03-8.0 (m, 1H), 6.85-6.81 (m, 1H), 6.69-6.68 (m, 1H), 3.85 (s, 3H), 3.47-3.42 (m, 1H), 3.06-2.87 (m, 2H), 2.49-2.25 (m, 2H), 1.48 (s, 9H) ppm;

¹³C NMR (75 MHz, CDCl₃) (97% of keto form): δ 192.5, 169.7, 163.8, 146.1, 130.1, 125.6, 113.4, 112.6, 81.6, 55.4, 55.1, 28.0 (3C), 27.9, 26.6 ppm;

General procedure for enones (15g-15k)

An oven-dried three-neck flask was charged with aldehyde (8.0 mmol) and anhydrous ether (25 mL) under the nitrogen atmosphere. *In situ* prepared vinylmagnesium bromide (approximately 24 mmol) was added to the aldehyde solution dropwise via a syringe at 0 °C. The resulting suspension was stirred at 0 °C for 1 hour and then allowed to warm up to room temperature, after which it was stirred for another 30 min. The reaction was quenched with slow addition of an aqueous solution of HCl (1 N, 15 mL) at 0 °C. The organic layer was collected and the aqueous layer was extracted with ether (30 mL x 2). The combined organic phases were washed with water, brine, dried over sodium sulfate and concentrated. The residue was directly used for the oxidation step.

To a solution of IBX (8.4 mmol) in 8 mL DMSO was slowly added vinyl alcohol (prepared from previous step) solution in 2 mL THF and 3 mL DMSO at room

temperature. The reaction mixture was stirred and monitor by TLC. After reaction, 20 mL water was added, the resulting suspension was extracted with ethyl acetate for three times. The combined organic layer was washed with water (10 mL x 2), brine (10 mL x 3), dried with sodium sulfate and concentrated. The residue was subjected to silica gel chromatography to afford the corresponding enones.

1-phenylprop-2-en-1-one (15g)

¹H NMR (500 MHz, CDCl₃): δ 7.95-7.93 (m, 2H), 7.58-7.54 (m, 1H), 7.49-7.45 (m, 2H), 7.15 (dd, J = 21.4, 13.2 Hz, 1H), 6.43 (d, J = 21.4 Hz, 1H), 5.92 (d, J = 13.2 Hz, 1H) ppm;

¹³C NMR (125 MHz, CDCl₃): δ 190.1, 137.2, 132.9, 132.3, 130.1, 128.6 (2C), 128.5 (2C) ppm;

1-(4-bromophenyl)prop-2-en-1-one (15h)

¹H NMR (400 MHz, CDCl₃): δ 7.80-7.78 (m, 2H), 7.63-7.59 (m, 2H), 7.09 (dd, J = 17.1, 10.6 Hz, 1H), 6.43 (d, J = 17.1 Hz, 1H), 5.92 (d, J = 10.6 Hz, 1H) ppm;

¹³C NMR (100 MHz, CDCl₃): δ 189.8, 135.9, 131.9 (2C), 131.8, 130.7, 130.1 (2C), 128.1 ppm;

1-(4-methoxyphenyl)prop-2-en-1-one (15i)

^1H NMR (400 MHz, CDCl_3): δ 7.98-7.96 (m, 2H), 7.17 (dd, $J = 17.0, 10.5$ Hz, 1H), 6.98-6.95 (m, 2H), 6.42 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.87 (dd, $J = 10.5, 2.0$ Hz, 1H), 3.87 (s, 3H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 189.1, 163.4, 132.0, 130.9, 130.1 (2C), 129.1, 113.7 (2C), 55.3 ppm;

1-(naphthalen-3-yl)prop-2-en-1-one (15j)

^1H NMR (400 MHz, CDCl_3): δ 8.49-8.48 (m, 1H), 8.11-8.08 (m, 1H), 7.98-7.85 (m, 3H), 7.61-7.54 (m, 2H), 7.32 (dd, $J = 17.1, 10.5$ Hz, 1H), 6.52 (dd, $J = 17.1, 1.6$ Hz, 1H), 5.99 (dd, $J = 10.5, 1.6$ Hz, 1H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 190.7, 135.4, 134.5, 132.4, 132.2, 130.3, 130.0, 129.4, 128.5, 128.4, 127.7, 126.7, 124.3 ppm;

1-(naphthalen-4-yl)prop-2-en-1-one (15k)

^1H NMR (400 MHz, CDCl_3): δ 8.46-8.44 (m, 1H), 8.02-7.98 (m, 1H), 7.89-7.87 (m, 1H), 7.74-7.72 (m, 1H), 7.60-7.49 (m, 3H), 6.95 (dd, $J = 17.6, 10.4$ Hz, 1H), 6.27 (dd, $J = 17.6, 1.2$ Hz, 1H), 6.05 (dd, $J = 10.4, 1.2$ Hz, 1H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 195.8, 136.8, 135.6, 133.8, 131.9, 131.4, 130.5, 128.4, 127.7, 127.5, 126.4, 125.5, 124.3 ppm;

Typical procedure for enones 15c⁴

To a stirred mixture of cyclopentenone (251 μ L, 3 mmol) and KBr (1.428 g, 12 mmol) in a mixed solvent ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 25:1$), Selectfluor (1.27 g, 3.6 mmol) was added. The resulting reaction mixture was stirred overnight. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were washed with dilute solutions of NaHCO_3 , Na_2SO_3 and brine. Then it was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which were purified by column chromatography to afford pure **15c** in 86% yield.

2-bromocyclopent-2-enone

¹H NMR (300 MHz, CDCl_3): δ 7.77 (t, $J = 2.88$ Hz, 1H), 2.70-2.67 (m, 2H), 2.52-2.49 (m, 2H) ppm;

¹³C NMR (75 MHz, CDCl_3): δ 201.6, 161.8, 126.2, 32.4, 28.0 ppm;

Typical procedure for enones 15d

⁴ Ye, C. F.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561.

To a stirred solution of cyclopentone (0.84 mL, 10 mmol) and 37% aqueous formaldehyde (2 mL) in 4 mL THF was added 4-dimethylaminopyridine (122.17 mg, 1 mmol). The resulting suspension was stirred for 6 days at room temperature. The reaction was then quenched, and the product was extracted with ether for three times. The combined organic phases were then dried over Na₂SO₄, filtered and evaporated under reduced pressure. Purification of the crude mixture by column chromatography gave the corresponding alcohol in 50 % yield.

The obtained alcohol was subjected to the DMP oxidation. To a stirred solution of alcohol (112 mg, 1 mmol) in 3 mL dichloromethane was added Dess-Martin periodinane (424 mg, 1 mmol). The resulting reaction suspension was stirred and monitor by TLC. After reaction, the mixture was filtered several times using filter paper to afford corresponding aldehyde. It can be used directly without further purification.

5-oxocyclopent-1-enecarbaldehyde

¹H NMR (400 MHz, CDCl₃): δ 9.89 (s, 1H), 8.43 (t, *J* = 2.32 Hz, 1H), 2.84-2.81 (m, 2H), 2.63-2.59 (m, 2H) ppm;

¹³C NMR (100 MHz, CDCl₃): δ 201.2, 189.8, 155.5, 147.2, 34.4, 27.5 ppm;

General procedure for enantioselective / diastereoselective Michael addition

Modified 6'-OH cinchona alkaloid catalyst **QD-Bn** (0.01 mmol) was added to the β -ketone ester (0.05 mmol) solution in dichloroethane 0.1 mL. Then α,β -unsaturated ketone (0.13 mmol) was added. The resulting reaction mixture was stirred at 50 °C for 6-7 days. The product was isolated by preparative TLC directly.

***tert*-butyl-1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(3-oxobutyl)naphthalene-2-carboxylate (16e)**

Light yellow oil in 86% yield; R_f = 0.57 (hexane : ethyl acetate = 1:1);

^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.8, 2.4 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 2.94-3.02 (m, 1H), 2.83-2.89 (m, 1H), 2.68-2.77 (m, 1H), 2.39-2.55 (m, 2H), 1.98-2.15 (m, 6H), 1.37 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 208.0, 194.6, 171.1, 163.4, 145.0, 130.0, 125.8, 113.3, 112.2, 82.0, 56.7, 55.3, 39.2, 31.9, 29.8, 27.7 (4C), 26.3 ppm;

FTIR (KBr, CHCl_3): ν = 2974, 1716, 1678, 1600, 756 cm^{-1} ;

HRMS (EI, m/z): m/z calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 369.1678, found: 369.1670;

$[\alpha]_D^{20}$ = +4.49 (c = 1.3, CHCl_3);

HPLC analysis: 84% ee Daicel CHIRALPAK AS-H column (hexane/*i*-propanol = 95:5, 1.0 mL/min): t_1 = 15.5 min (major), t_2 = 20.7 min (minor).

***tert*-butyl-1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(3-oxopentyl)naphthalene-2-carboxylate (16f)**

Light yellow oil in 76% yield. R_f = 0.55 (hexane : ethyl acetate = 1:1);

^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, J = 8.4 Hz, 1H), 6.79 (dd, J = 8.8, 2.4 Hz, 1H), 6.62 (s, 1H), 3.81 (s, 3H), 2.84-2.99 (m, 2H), 2.65-2.73 (m, 1H), 2.34-2.52 (m, 4H), 1.98-2.16 (m, 3H), 1.33 (s, 9H), 1.01 (t, J = 7.2 Hz, 3H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 210.7, 194.6, 171.1, 163.4, 145.0, 130.0, 125.8, 113.3, 112.2, 81.9, 56.8, 55.3, 37.8, 35.8, 31.9, 27.8, 27.7 (3C), 26.3, 7.8 ppm;

FTIR (KBr, CHCl_3): ν = 1714, 1674, 1598, 754 cm^{-1} ;

HRMS (EI, m/z): calcd for $\text{C}_{21}\text{H}_{28}\text{O}_5\text{Na}^+$ [$\text{M}+\text{Na}$] $^+$ 383.1834, found: 383.1832; $[\alpha]_D^{20}$ = +3.90 (c = 2.6, CHCl_3);

HPLC analysis: 75% ee Daicel CHIRALPAK AS-H column (hexane/*i*-propanol = 95:5, 1.0 mL/min): t_1 = 10.7 min (major), t_2 = 13.7 min (minor).

***tert*-butyl 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(3-oxo-3-phenylpropyl)naphthalene-2-carboxylate (16g)**

Light yellow oil in 83% yield. $R_f = 0.7$ (hexane : ethyl acetate = 1:1);

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.99-8.02 (m, 3H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.8$ Hz, 2H), 6.83 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.66 (d, $J = 2.1$ Hz, 1H), 3.85 (s, 3H), 3.27-3.35 (m, 1H), 3.0-3.12 (m, 2H), 2.89-2.96 (m, 1H), 2.51 (dt, $J = 13.5, 4.8$ Hz, 1H), 2.26-2.34 (m, 2H), 2.08-2.17 (m, 1H), 1.37 (s, 9H) ppm;

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 199.7, 194.7, 171.2, 163.4, 145.1, 136.7, 132.9, 130.1, 128.5 (2C), 128.1 (2C), 125.9, 113.3, 112.2, 82.0, 56.7, 55.3, 34.5, 32.0, 28.7, 27.8 (3C), 26.3 ppm;

FTIR (KBr, CHCl_3): $\nu = 3017, 2399, 1720, 1680, 1599, 754 \text{ cm}^{-1}$;

HRMS (EI, m/z): calcd for $\text{C}_{25}\text{H}_{28}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+ 431.1834$, found 431.1833;

$[\alpha]_D^{20} = +2.48$ ($c = 2.2$, CHCl_3);

HPLC analysis: 30% ee Daicel CHIRALPAK AS-H column (hexane/*i*-propanol = 95:5, 1.0 mL/min): $t_1 = 23.2$ min (minor), $t_2 = 26.4$ min (major).

***tert*-butyl-2-(3-(4-bromophenyl)-3-oxopropyl)-1,2,3,4-tetrahydro-6-methoxy-1-oxonaphthalene-2-carboxylate (16h)**

Light yellow solid in 85% yield; $R_f = 0.73$ (hexane : ethyl acetate = 1:1);

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.0 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 2H), 7.6 (d, $J = 8.4$ Hz, 2H), 6.84 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.67 (s, 1H), 3.86 (s, 3H), 3.24-3.32 (m, 1H), 2.99-3.07 (m, 2H), 2.92 (dt, $J = 17.3, 4.8$ Hz, 1H), 2.51 (dt, $J = 13.5, 4.8$ Hz, 1H), 2.25-2.33 (m, 2H), 2.09-2.16 (m, 1H), 1.37 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 198.8, 194.8, 171.3, 163.5, 145.1, 135.5, 131.9 (2C), 130.2, 129.7 (2C), 128.1, 126.0, 113.4, 112.4, 82.2, 57.0, 55.4, 34.6, 32.3, 28.78, 27.8 (3C), 26.5 ppm;

FTIR (KBr, CHCl_3): ν = 3018, 2399, 1720, 1680, 1598, 756 cm^{-1} ;

HRMS (EI, m/z): calcd for $\text{C}_{25}\text{H}_{27}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+$ 509.0940, found 509.0931;

$[\alpha]_{\text{D}}^{20}$ = +1.21 (c = 3.7, CHCl_3);

HPLC analysis: 26% ee Daicel CHIRALPAK AD-H column (hexane/*i*-propanol = 95:5, 1.0 mL/min): t_1 = 31.0 min (minor), t_2 = 37.9 min (major).

***tert*-butyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-(4-methoxyphenyl)-3-oxopropyl)-1-oxonaphthalene-2-carboxylate (16i)**

White solid in 84% yield; R_f = 0.57 (hexane : ethyl acetate = 1:1);

^1H NMR (400 MHz, CDCl_3): δ 8.0 (m, 3H), 6.92 (d, J = 8.8, 2H), 6.83 (dd, J = 8.8, 2.2 Hz, 1H), 6.66 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.19-3.27 (m, 1H), 2.89-3.08 (m, 3H), 2.48-2.54 (m, 1H), 2.29 (t, J = 8.0 Hz, 2H), 2.08-2.17 (m, 1H), 1.37 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 198.5, 194.8, 171.3, 163.5, 163.4, 145.2, 130.5 (2C), 130.2, 129.9, 126.0, 113.7 (2C), 113.4, 112.3, 82.1, 57.2, 55.4 (2C), 34.2, 32.0, 29.0, 27.8 (3C), 26.5 ppm;

FTIR (KBr, CHCl_3): ν = 3018, 2399, 1718, 1676, 1598, 756 cm^{-1} ;

HRMS (EI, m/z): calcd for $\text{C}_{26}\text{H}_{30}\text{O}_6\text{Na}^+ [\text{M}+\text{Na}]^+$ 461.1940, found 461.1935;

$[\alpha]_{\text{D}}^{20}$ = +2.71 (c = 2.4, CHCl_3);

HPLC analysis: 37% ee Daicel CHIRALPAK OD column (hexane/*i*-propanol = 95:5,

1.0 mL/min): $t_1 = 16.6$ min (minor), $t_2 = 27.3$ min (major).

***tert*-butyl 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(3-oxocyclopentyl)naphthalene-**

2-carboxylate (16a)

Light yellow oil in 68% yield; $R_f = 0.59$ (hexane : ethyl acetate = 1:1);

^1H NMR (500 MHz, CDCl_3): δ 7.97 (d, $J = 7.0$ Hz, 1H), 6.83 (dd, $J = 7.0, 1.9$ Hz, 1H), 6.65 (d, $J = 1.7$ Hz, 1H), 3.85 (s, 3H), 3.05-3.12 (m, 1H), 2.80-2.90 (m, 2H), 2.59-2.65 (m, 1H), 2.10-2.44 (m, 6H), 1.82-1.88 (m, 1H), 1.32 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 218.3, 194.0, 170.3, 163.4, 144.7, 130.1, 126.6, 113.4, 112.2, 82.6, 58.7, 55.4, 41.7, 40.9, 38.7, 30.4, 27.8, 26.6 (3C), 24.6 ppm;

FTIR (KBr, CHCl_3): $\nu = 3018, 2399, 1735, 1720, 1678, 1600, 756 \text{ cm}^{-1}$;

HRMS (EI, m/z): calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+ 381.1678$, found 381.1671;

$[\alpha]_D^{20} = +3.07$ ($c = 2.1$, CHCl_3);

HPLC analysis: 93% ee 97:3 d.r. Daicel CHIRALPAK AS-H column (hexane/*i*-propanol = 98:2, 1.0 mL/min): $t_1 = 41.0$ min (minor), $t_2 = 45.0$ min (major), $t_3 = 63.3$ min (minor), $t_4 = 69.9$ min (minor).

***tert*-butyl 1,2,3,4-tetrahydro-6-methoxy-2-(3-(naphthalen-1-yl)-3-oxopropyl)-1-**

oxonaphthalene-2-carboxylate (16k)

Light yellow solid in 77% yield; R_f = 0.65 (hexane : ethyl acetate = 1:1);

^1H NMR (400 MHz, CDCl_3): δ 8.59 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.85 (d, J = 7.9 Hz, 1H), 7.48-7.59 (m, 3H), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 3.84 (s, 3H), 3.38-3.45 (m, 1H), 3.01-3.20 (m, 2H), 2.90-2.97 (m, 1H), 2.51-2.60 (m, 1H), 2.35-2.44 (m, 2H), 2.11-2.18 (m, 1H), 1.37(s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 203.8, 194.7, 171.3, 163.5, 145.1, 135.8, 133.9, 132.5, 130.2, 130.1, 128.3, 127.8, 127.7, 126.3, 126.0, 125.8, 124.4, 113.4, 112.3, 82.1, 57.0, 55.4, 37.9, 32.1, 28.9, 27.8 (3C), 26.4 ppm;

FTIR (KBr, CHCl_3): ν = 3019, 2399, 1720, 1678, 1598, 756 cm^{-1} ;

HRMS (EI, m/z): calcd for $\text{C}_{29}\text{H}_{30}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+$ 481.1991, found 481.1991;

$[\alpha]_D^{20}$ = +1.8 (c = 4.1, CHCl_3);

HPLC analysis: 27% ee Daicel CHIRALPAK AS-H column (hexane/*i*-propanol = 95:5, 1.0 mL/min): t_1 = 21.0 min (minor), t_2 = 25.7 min (major).

***tert*-butyl 1,2,3,4-tetrahydro-6-methoxy-2-(3-(naphthalen-2-yl)-3-oxopropyl)-1-oxonaphthalene-2-carboxylate (16j)**

Light yellow solid in 90% yield; R_f = 0.59 (hexane : ethyl acetate = 1:1);

^1H NMR (400 MHz, CDCl_3): δ 8.53 (s, 1H), 8.03-8.07 (m, 2H), 7.98 (d, J = 8.0 Hz, 1H), 7.87 (t, J = 8.6 Hz, 2H), 7.54-7.60 (m, 2H), 6.84 (dd, J = 8.8, 2.1 Hz, 1H), 6.67 (s, 1H), 3.85 (s, 3H), 3.43 (m, 1H), 3.21 (m, 1H), 2.92-3.06 (m, 2H), 2.55 (m, 1H), 2.37 (t, J = 7.9 Hz, 2H), 2.17 (m, 1H), 1.39(s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 199.7, 194.8, 171.3, 163.5, 145.2, 135.5, 134.1, 132.5, 130.2, 129.9, 129.6, 128.3 (2C), 127.7, 126.6, 126.0, 123.9, 113.4, 112.3, 82.1, 57.1, 55.4, 34.6, 32.2, 28.8, 27.8 (3C), 26.5 ppm;

FTIR (KBr, CHCl_3): ν = 3019, 2399, 1720, 1678, 1599, 777 cm^{-1} ;

HRMS (EI, m/z): calcd for $\text{C}_{29}\text{H}_{30}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+$ 481.1991, found 481.1991;

$[\alpha]_{\text{D}}^{20}$ = +2.2 (c = 1.75, CHCl_3);

HPLC analysis: 39% ee Daicel CHIRALPAK AS-H column (hexane/*i*-propanol = 95:5, 1.0 mL/min): t_1 = 42.1 min (minor), t_2 = 55.4 min (major).

General procedures for the preparation of olefins:

Malononitrile (25 mmol) and the ketone (27.5 mmol) were dissolved in 30 mL of toluene containing ammonium acetate (500 mg) and glacial acetic acid (2 mL) in a 50 mL flask. By refluxing vigorously, the water formed in the reaction was removed by a Dean-Stark trap placed under the reflux condenser. After the completion of the reaction, the reaction mixture was diluted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was recrystallized from alcohol to give pure products.

2-(2,3-Dihydronaphthalen-4(1H)-ylidene) malononitrile

^1H NMR (300 MHz, CDCl_3): δ 8.20 (d, $J = 10.5$ Hz, 1H), 7.52-7.46 (m, 1H), 7.36-7.26 (m, 2H), 3.02 (t, $J = 8.7$ Hz, 2H), 2.89 (t, $J = 8.3$ Hz, 2H), 2.02 (t, $J = 8.6$ Hz, 2H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 172.6, 142.0, 133.7, 130.0, 129.5, 127.9, 126.9, 114.0, 113.4, 79.8, 33.1, 29.7, 22.2 ppm.

2-(6-Methoxy-2,3-dihydronaphthalen-4(1*H*)-ylidene) malononitrile

^1H NMR (300 MHz, CDCl_3): δ 8.30 (d, $J = 8.9$ Hz, 1H), 6.86 (d, $J = 8.9$ Hz, 1H), 6.76 (s, 1H), 3.88 (s, 3H), 2.99 (t, $J = 6.4$ Hz, 2H), 2.85 (t, 6.2 Hz, 2H), 1.99-1.93 (m, 2H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 171.1, 163.5, 146.9, 130.4, 129.6, 126.3, 114.2, 113.0, 112.9, 55.4, 38.9, 30.2, 23.4 ppm.

2-(7-Methoxy-2,3-dihydronaphthalen-4(1*H*)-ylidene) malononitrile

^1H NMR (300 MHz, CDCl_3): δ 7.73 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 8.5$ Hz, 1H), 7.06 (dd, $J = 8.5, 2.5$ Hz, 1H), 3.84 (s, 3H), 3.00 (t, $J = 6.5$ Hz, 2H), 2.83 (t, $J = 6.2$ Hz, 2H), 1.99-1.96 (m, 2H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 172.6, 157.9, 134.5, 130.5, 130.4, 121.9, 114.2, 113.5, 110.9, 79.6, 55.7, 33.1, 28.9, 22.5 ppm;

2-(2,3-Dihydrochromen-4-ylidene) malononitrile

¹H NMR (300 MHz, CDCl₃): δ 8.36 (dd, J = 8.2, 1.4 Hz, 1H), 7.53-7.48 (m, 1H), 7.07-7.03 (m, 1H), 6.98 (dd, J = 8.4, 0.9 Hz, 1H), 4.39 (t, J = 6.3 Hz, 2H), 3.15 (t, J = 6.3 Hz, 2H) ppm;

¹³C NMR (75 MHz, CDCl₃): δ 163.4, 157.4, 136.8, 127.3, 121.7, 118.7, 117.2, 113.8, 113.2, 64.7, 30.9 ppm.

2-(2,3-Dihydrothiochromen-4-ylidene) malononitrile

¹H NMR (300 MHz, CDCl₃): δ 7.96 (d, J = 8.0 Hz, 1H), 7.42-7.40 (m, 1H), 7.38-7.27 (m, 1H), 7.22-7.18 (m, 1H), 3.31 (t, J = 6.5 Hz, 2H), 3.16 (t, J = 6.4 Hz, 2H) ppm;

¹³C NMR (75 MHz, CDCl₃): δ 169.8, 138.9, 133.5, 129.4, 128.3, 128.0, 125.0, 113.4, 112.8, 81.9, 32.7, 25.7 ppm;

2-(1-Phenylpropylidene)malononitrile

¹H NMR (300 MHz, CDCl₃): δ 7.56-7.46 (m, 5H), 2.98 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H) ppm;

¹³C NMR (75 MHz, CDCl₃): δ 181.7, 134.6, 132.0, 129.2, 127.5, 112.8, 112.5, 84.3, 31.1, 12.8 ppm;

Typical Procedure for Direct Vinylogous Michael Addition Reaction

A mixture of **24a** (19.4 mmg, 0.1 mmol), **25a** (32 μL , 0.4 mmol), catalyst **21** (5.6 mg, 0.02 mmol) and PNBA (3.4 mmg, 0.02 mmol) in THF (1 mL) was stirred for 20 h at rt. Then the reaction was quenched by adding 0.5 mL 1M HCl. The mixture was extracted with EtOAc, dried with anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel to give the desired product **26aa** in 78% yield with 87% ee, determined by HPLC (Chiralpak AS, 20% 2-propanol/hexane, 1 mL/min): $t_{\text{minor}} = 18.756$ min, $t_{\text{major}} = 26.674$ min.

2-((*S*)-3-((*R*)-1-formylpropan-2-yl)-2,3-dihydronaphthalen-4(1*H*)-ylidene)malononitrile (**26aa**)

$[\alpha]_{\text{D}}^{22} = -324$ ($c = 0.81$, DCM), 87% ee;

$R_{\text{f}} = 0.32$ (hexane : ethyl acetate = 4 : 1);

^1H NMR (300 MHz, CDCl_3): δ 9.64 (s, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.6$ Hz, 1H), 7.28-7.26 (m, 1H), 3.04-3.02 (m, 1H), 3.00-2.96 (m, 1H), 2.91-2.84 (m, 1H), 2.45-2.41 (m, 2H), 2.38-2.19 (m, 2H), 2.12-2.04 (m, 1H), 1.05 (d, $J = 6.6$ Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 200.4, 177.4, 140.2, 133.8, 129.5, 129.2, 128.3, 127.0, 113.5, 113.3, 81.1, 48.7, 47.1, 28.8, 24.9, 24.5, 17.3 ppm;

IR (KBr): $\nu = 2226, 1762 \text{ cm}^{-1}$;

MS (EI): $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$ 264.12 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 18.756 \text{ min}$, $t_{\text{major}} = 26.674 \text{ min}$.

2-((*S*)-3-((*R*)-1-formylpropan-2-yl)-2,3-dihydrochromen-4-ylidene)malononitrile

(26ba)

$[\alpha]_{\text{D}}^{22} = -436$ ($c = 0.93$, DCM), 91% ee;

$R_f = 0.24$ (hexane : ethyl acetate = 4 : 1);

^1H NMR (300 MHz, CDCl_3): δ 9.63 (s, 1H), 8.13 (d, $J = 8.2 \text{ Hz}$, 1H), 7.53 (t, $J = 7.8 \text{ Hz}$, 1H), 7.06 (t, $J = 7.6 \text{ Hz}$, 1H), 6.96 (d, $J = 8.2 \text{ Hz}$, 1H), 4.68 (dd, $J = 1.4, 11.2 \text{ Hz}$, 1H), 4.26 (dd, $J = 2.1, 12.6 \text{ Hz}$, 1H), 2.85 (d, $J = 10.1 \text{ Hz}$, 1H), 2.53-2.33 (m, 3H), 1.19 (d, $J = 6.5 \text{ Hz}$, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 199.9, 167.9, 156.2, 136.9, 127.9, 121.9, 118.2, 115.7, 113.2, 78.5, 66.3, 48.0, 44.5, 27.8, 17.9 ppm;

IR (KBr): $\nu = 2225, 1720 \text{ cm}^{-1}$;

MS (EI): $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ 266.09 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 16.176 \text{ min}$, $t_{\text{major}} = 21.493 \text{ min}$.

2-((*S*)-3-((*R*)-1-formylpropan-2-yl)-2,3-dihydrothiochromen-4-ylidene)malononitrile (26ca)

$[\alpha]_D^{22} = -503$ ($c = 0.61$, DCM), 90% ee;

$R_f = 0.16$ (hexane : ethyl acetate = 4 : 1);

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.58 (s, 1H), 7.80 (d, $J = 7.9$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.23-7.15 (m, 2H), 3.48-3.43 (m, 1H), 3.27-3.22 (m, 2H), 2.47-2.23 (m, 3H), 1.15 (d, $J = 6.3$ Hz, 3H) ppm;

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 199.8, 173.4, 138.2, 133.8, 130.3, 127.2, 125.6, 124.9, 113.0, 112.6, 82.6, 48.1, 43.9, 28.5, 27.9, 17.5 ppm;

IR (KBr): $\nu = 2229, 1721 \text{ cm}^{-1}$;

MS (EI): $\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$ 282.09 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 21.464$ min, $t_{\text{major}} = 39.825$ min.

2-((S)-3-((R)-1-formylpropan-2-yl)-2,3-dihydro-7-methoxynaphthalen-4(1H)-ylidene)malononitrile (26da)

$[\alpha]_D^{22} = -164$ ($c = 0.88$, DCM), 86% ee;

$R_f = 0.18$ (hexane : ethyl acetate = 4 : 1);

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.62 (s, 1H), 7.78 (d, $J = 8.8$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 1H), 6.74 (s, 1H), 3.86 (s, 3H), 3.06-2.82 (m, 3H), 2.45-2.38 (m, 2H), 2.36-2.21 (m, 2H), 2.09-1.99 (m, 1H), 1.04 (d, $J = 6.6$ Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 200.6, 176.4, 163.9, 142.8, 130.6, 121.9, 114.4, 114.2, 113.9, 113.1, 77.8, 55.6, 48.6, 47.0, 28.6, 25.1, 24.5, 17.5 ppm;

IR (KBr): ν = 2224, 1725 cm^{-1} ;

MS (EI): $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$ 294.14 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), t_{minor} = 20.088 min, t_{major} = 24.691 min.

2-((*S*)-3-((*R*)-1-formylpropan-2-yl)-2,3-dihydro-6-methoxynaphthalen-4(1*H*)-ylidene)malononitrile (26ea)

$[\alpha]_{\text{D}}^{22}$ = -42 (c = 0.21, DCM), 87% ee;

R_f = 0.17 (hexane : ethyl acetate = 4 : 1);

^1H NMR (300 MHz, CDCl_3): δ 9.64 (s, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.08-7.05 (m, 1H), 3.84 (s, 3H), 3.11-3.06 (m, 1H), 2.98-2.89 (m, 1H), 2.83-2.77 (m, 1H), 2.45-2.35 (m, 1H), 2.31-2.19 (m, 2H), 2.10-2.01 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 200.5, 177.5, 157.9, 132.3, 130.6, 129.6, 121.7, 113.6, 113.3, 111.6, 80.7, 55.7, 48.7, 47.1, 28.8, 24.9, 24.1, 17.4 ppm;

IR (KBr): ν = 2221, 1724 cm^{-1} ;

MS (EI): $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$ 294.4 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), t_{minor} = 12.194 min, t_{major} = 21.800 min.

2-((2*S*,3*R*)-4-formyl-2,3-dimethyl-1-phenylbutylidene)malononitrile (26fa)

$[\alpha]_D^{24} = -18$ ($c = 0.25$, DCM), 71% ee;

$R_f = 0.29$ (hexane : ethyl acetate = 4 : 1);

^1H NMR (300 MHz, CDCl_3): δ 9.75 (s, 1H), 7.53-7.48 (m, 3H), 7.30-7.28 (m, 2H), 3.16-3.09 (m, 1H), 2.63-2.58 (m, 1H), 2.39-2.21 (m, 2H), 1.22 (d, $J = 6.9$ Hz, 3H), 1.07 (d, $J = 6.5$ Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 200.6, 183.9, 134.1, 131.0, 129.1, 127.1, 111.9, 88.4, 48.0, 47.3, 31.2, 19.3, 17.3 ppm;

IR (KBr): $\nu = 2228, 1726 \text{ cm}^{-1}$;

MS (EI): $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$ 252.14 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min) after converted to the alcohol, $t_{\text{minor}} = 10.742$ min, $t_{\text{major}} = 13.389$ min.

2-((*S*)-3-((*R*)-1-formylbutan-2-yl)-2,3-dihydrochromen-4-ylidene)malononitrile

(26bb)

$[\alpha]_D^{24} = -284$ ($c = 2.9$, DCM), 88% ee;

$R_f = 0.17$ (hexane : ethyl acetate = 4 : 1);

^1H NMR (300 MHz, CDCl_3): δ 9.58 (s, 1H), 8.11 (d, $J = 8.2$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.04 (t, $J = 8.2$ Hz, 1H), 6.98 (d, $J = 7.8$ Hz, 1H), 4.64 (dd, $J = 1.7, 12.6$ Hz,

1H), 4.24 (dd, $J = 2.2, 12.6$ Hz, 1H), 2.98 (d, $J = 8.3$ Hz, 1H), 2.60-2.53 (m, 1H), 2.38-2.23 (m, 2H), 1.75-1.68 (m, 2H), 0.93 (t, $J = 7.5$ Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 199.9, 168.1, 156.2, 136.9, 127.9, 121.8, 118.1, 115.8, 113.2, 113.1, 78.5, 66.3, 44.6, 42.1, 32.6, 23.5, 9.46 ppm;

IR (KBr): $\nu = 2226, 1719\text{ cm}^{-1}$;

MS (EI): $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$ 280.12 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 14.409$ min, $t_{\text{major}} = 19.650$ min.

2-((*S*)-3-((*R*)-1-formylbutan-2-yl)-2,3-dihydrothiochromen-4-ylidene)malononitrile (26cb)

$[\alpha]_{\text{D}}^{24} = -489$ ($c = 2.1$, DCM), 88% ee;

$R_f = 0.17$ (hexane : ethyl acetate = 4 : 1);

^1H NMR (300 MHz, CDCl_3): δ 9.54 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.23-7.16 (m, 2H), 3.40 (dd, $J = 1.8, 12.5$ Hz, 1H), 3.21 (dd, $J = 2.3, 12.6$ Hz, 1H), 2.48-2.36 (m, 2H), 2.23-2.18 (m, 1H), 1.73-1.54 (m, 3H), 0.96 (t, $J = 7.5$ Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl_3): δ 199.9, 173.3, 138.2, 133.8, 130.4, 127.1, 125.8, 124.9, 113.0, 112.6, 82.7, 44.5, 41.4, 32.7, 28.5, 23.1, 9.4 ppm;

IR (KBr): $\nu = 2223, 1725\text{ cm}^{-1}$;

MS (EI): $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OS}$ 296.12 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-

propanol/hexane, 1 mL/min), $t_{\text{minor}} = 19.394$ min, $t_{\text{major}} = 31.557$ min.

2-((*S*)-3-((*R*)-1-formylbutan-2-yl)-2,3-dihydro-7-methoxynaphthalen-4(1*H*)-ylidene)malononitrile (26db)

$[\alpha]_{\text{D}}^{24} = -192$ ($c = 2.4$, DCM), 81% ee;

$R_f = 0.18$ (hexane : ethyl acetate = 4 : 1);

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.60 (s, 1H), 7.94 (d, $J = 8.9$ Hz, 1H), 6.84 (dd, $J = 2.6, 8.9$ Hz, 1H), 6.74 (s, 1H), 3.86 (s, 3H), 3.21-3.16 (m, 1H), 2.98-2.94 (m, 1H), 2.88-2.82 (m, 1H), 2.55-2.49 (m, 1H), 2.28-2.18 (m, 3H), 2.06-2.01 (m, 1H), 1.61-1.55 (m, 1H), 1.50-1.42 (m, 1H), 0.89 (t, $J = 7.5$ Hz, 3H) ppm;

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 200.7, 176.5, 163.9, 142.7, 130.7, 122.1, 114.3, 114.2, 113.9, 113.0, 77.9, 55.6, 45.2, 44.5, 33.7, 25.3, 24.5, 23.1, 9.4 ppm;

IR (KBr) : $\nu = 2225, 1726$ cm^{-1} ;

MS (EI) : $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$ 308.13 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 19.372$ min, $t_{\text{major}} = 22.184$ min.

2-((*S*)-3-((*R*)-1-formylpentan-2-yl)-2,3-dihydronaphthalen-4(1*H*)-ylidene)malononitrile (26ac)

$[\alpha]_{\text{D}}^{22} = -158$ ($c = 0.47$, DCM), 80% ee;

$R_f = 0.35$ (hexane : ethyl acetate = 4 : 1);

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.61 (s, 1H), 7.89 (d, $J = 7.9$ Hz, 1H), 7.50 (t, $J = 7.2$ Hz, 1H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.26 (d, $J = 8.5$ Hz, 1H), 3.28-3.23 (m, 1H), 3.01-2.94 (m, 1H), 2.89-2.82 (m, 1H), 2.53-2.45 (m, 1H), 2.30-2.23 (m, 2H), 2.19-2.13 (m, 1H), 2.11-2.04 (m, 1H), 1.46-1.28 (m, 4H), 1.27-1.19 (m, 1H), 0.89 (t, $J = 7.0$ Hz, 3H) ppm;

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 200.6, 177.5, 140.2, 133.7, 129.5, 129.4, 128.4, 126.9, 113.5, 113.3, 81.0, 46.0, 45.3, 33.2, 32.9, 25.2, 24.5, 18.8, 14.3 ppm;

IR (KBr): $\nu = 2225, 1730\text{ cm}^{-1}$;

MS (EI): $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$ 292.10 $[\text{M}]^+$.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 12.303$ min, $t_{\text{major}} = 14.728$ min.

2-((*S*)-3-((*R*)-1-formylpentan-2-yl)-2,3-dihydrothiochromen-4-ylidene)malononitrile (26cc)

$[\alpha]_D^{22} = -428$ ($c = 0.52$, DCM), 81% ee;

$R_f = 0.20$ (hexane : ethyl acetate = 4 : 1);

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.54 (s, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.24-7.16 (m, 2H), 3.45-3.42 (m, 2H), 3.24-3.20 (m, 1H), 2.45-2.42 (m, 2H), 2.27-2.19 (m, 1H), 1.38-1.14 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H) ppm;

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 200.7, 174.1, 137.8, 133.6, 130.2, 127.2, 126.1, 125.1, 113.1, 112.5, 82.9, 44.5, 42.7, 34.2, 32.7, 28.8, 19.6, 13.9 ppm;

IR (KBr): $\nu = 2221, 1724\text{ cm}^{-1}$;

MS (EI): C₁₈H₁₈N₂OS 310.12 [M]⁺.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 16.096$ min, $t_{\text{major}} = 22.996$ min.

2-((*S*)-3-((*R*)-2-formyl-1-phenylethyl)-2,3-dihydrochromen-4-ylidene)malononitrile (26bd)

$[\alpha]_{\text{D}}^{22} = -142$ ($c = 1.08$, DCM), 57% ee;

$R_f = 0.14$ (hexane : ethyl acetate = 4 : 1);

¹H NMR (300 MHz, CDCl₃): δ 9.44 (s, 1H), 8.20 (d, $J = 8.1$ Hz, 1H), 7.56 (t, $J = 7.8$ Hz, 1H), 7.41-7.37 (m, 2H), 7.33-7.29 (m, 3H), 7.10 (t, $J = 7.7$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 4.12-4.02 (m, 2H), 3.45-3.38 (m, 1H), 3.28-3.18 (m, 1H), 3.12-3.05 (m, 1H), 2.65-2.59 (m, 1H) ppm;

¹³C NMR (75 MHz, CDCl₃): δ 199.2, 167.1, 156.3, 139.2, 137.3, 129.4, 128.1, 128.0, 122.0, 118.4, 115.3, 113.2, 78.7, 66.5, 46.8, 45.2, 39.5 ppm;

IR (KBr): $\nu = 2224, 1719$ cm⁻¹;

MS (EI): C₂₁H₁₆N₂O₂ 327.15 [M-H]⁺.

The enantiomeric ratio was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), $t_{\text{minor}} = 18.100$ min, $t_{\text{major}} = 20.469$ min.

List of Publication

1. Zhou, W. J.; Loh, T. P. FeCl₃, CuCl and Tempo Aided Direct Coupling of Alkanes with Cyclic Iminoglyoxylates. *Manuscript in preparation*. **2010**.
2. Zhou, W. J.; Loh, T. P. Total Synthesis of (+)-9(11)-Dehydroestrone Methyl Ether by Mukaiyama-Michael Addition and Thermodynamic Control Enolate Alkylation. *Manuscript in preparation*. **2010**.
3. Zhou, W. J.; Lu, J.; Loh, T. P. Free Radical-Initiated Direct Coupling Reactions of Alkanes with Iminoglyoxylates. *Manuscript Submitted*. **2010**.
4. Lu, J.; Liu, F.; Zhou, W. J.; Loh, T. P. Enantioselective direct vinylogous Michael addition reaction catalyzed by organic molecules. *Tetrahedron Lett.* **2008**, 49, 5389.
5. Lu, J.; Zhou, W. J.; Liu, F.; Loh, T. P. Organocatalytic and Enantioselective Direct Vinylogous Michael Addition to Maleimides. *Adv. Synth. Catal.* **2008**, 350, 1976–1800.
6. Shen, Z. L.; Zhou, W. J.; Loh, T. P. One-pot Chemoenzymatic Syntheses of Enantiomerically-enriched O-acetyl Cyanohydrins from Aldehydes in Ionic Liquid. *Green Chem.* **2008**, 10, 283–286.

Conferences

1. Zhou, W. J.; Loh, T. P. *Total Synthesis of (+)-9(11)-Dehydroestrone Methyl Ether by Mukaiyama-Michael Addition and Thermodynamic Control Enolate Alkylation*. PERCH-CIC Congress V (Centre for innovation in chemistry: postgraduate education and research program in chemistry). Pattaya, Thailand, 2007.
2. Zhou, W. J.; Loh, T. P. *Radical Initialized Reaction of Cycloalkanes with Iminoglyoxylates*. 6th Asia Euro Symposium, 2010.