New strategies for the synthesis of alpha-amino acetals and their applications in the synthesis of dihydro-methano-diarylazocines and dopamine D1 receptor ligands

Tian, JieSheng

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**NANYANG
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**NEW STRATEGIES FOR THE SYNTHESIS OF α -AMINO
ACETALS AND THEIR APPLICATIONS IN THE
SYNTHESIS OF DIHYDRO-METHANO-DIARYLAZOCINES
AND DOPAMINE D1 RECEPTOR LIGANDS**

TIAN JIESHENG

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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TIAN JIESHENG

School of Physical and Mathematical Sciences

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SUMMARY

This thesis consists of five chapters and an appendix. It is primarily about new strategies for the synthesis of α -amino acetals and their applications in the synthesis of dihydro-methano-diarylazocines and dopamine D1 receptor ligands.

In Chapter 1, we summarized (1) chemical methods for the synthesis of the α -amino acid derivatives *via* the construction of a new C–N bond, (2) direct installation of functionalities on organic molecules in the area of (i) C–H bond functionalization of tertiary amines *via* iminium ion intermediates, (ii) α -functionalization of aldehydes *via* singly occupied molecular orbital (SOMO) catalysis, (iii) β -functionalization of aldehydes *via* oxidative enamine catalysis. On the basis of these research progress about the synthesis of α -amino acid derivatives and C–H bond oxidative transformation, we proposed three pathways for the synthesis of α -amino acetals: (1) oxidative rearrangement of tertiary amines, (2) rearrangement of enamines, and (3) α -amination of aldehydes with a nucleophilic nitrogen source in the catalytic systems of copper salts or organic molecules containing iodo group together with the co-oxidant, such as, molecular oxygen or hydrogen peroxide and subsequent construction of dihydro-methano-diarylazocines and potential dopamine D1 receptor ligands from α -amino acetals *via* Friedel-Crafts double cyclization reactions.

Chapter 2 described the investigation of an unexpected rearrangement of tertiary amines in the presence of dioxygen and a copper catalyst to provide α -amino acetals directly. Mechanistic studies, including trapping, control, and isotope-labeling experiments, led to the proposal of a rearrangement mechanism involving oxidation of an aliphatic C–H bond.

Subsequently, this copper-dioxygen catalytic system ($\text{CuBr}_2/\text{TMEDA}/\text{O}_2$) was successfully applied to the efficient synthesis of α -amino acetals from enamines with readily removable protecting groups *via* oxidative rearrangement. In addition, the

mild conditions displayed good tolerance to the functional groups, such as, benzyl, allyl, and olefins.

In Chapter 3, α -amination of aldehydes for the synthesis of α -amino acetals was studied by employing secondary amines with readily removable protecting groups as a nucleophilic nitrogen source in the catalytic systems of CuI(Br)-TBHP and InI(Br)- $\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$. This reaction has the advantages of simple process, commercially available aldehydes and secondary amines as the starting materials and is also regarded as a synthetic equivalent of C–H bond amination at the α -position of aldehydes. Furthermore, the enamine with readily removable protecting groups, which is attributed to be the intermediate in this reaction, was also directly converted into α -amino acetal *via* oxidative rearrangement.

(I) For the catalytic system of CuI(Br)-TBHP, this reaction can be operated under very mild conditions, affording the desired products in moderate to good yields.

(II) A novel and highly efficient indium (I) oxidative catalytic system (InI(Br)- $\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$) was developed for this α -amination of aldehydes. In comparison with CuI(Br)-TBHP, this catalytic system displayed better catalytic activity and furnished the desired products in excellent yields. Furthermore, indium catalyst can be recycled four times without obvious loss of catalytic activity.

In Chapter 4, the transition-metal-free catalytic systems of $I_2(I)-Na_2CO_3 \cdot 1.5H_2O_2$ and $RI-Na_2CO_3 \cdot 1.5H_2O_2$ showed better catalytic activities and broad scope of substrates, especially for the aldehydes with short carbon chain or bulky groups, which afforded no or trace corresponding α -amino acetals in the catalytic systems of $CuI(Br)\text{-TBHP}$ and $InI(Br)\text{-}Na_2CO_3 \cdot 1.5H_2O_2$.

(I) In situ generated hypiodite catalyzed α -amination of aldehydes with short carbon chain or bulky groups was developed through commercially available hydrogen peroxide or sodium percarbonate as the co-oxidant. In addition, a mechanism was proposed on the basis of control experiments.

(II) A highly efficient in situ generated (organo)hypervalent iodine catalyzed α -amination of aldehydes was also investigated for the synthesis of α -amino acetals. This approach displayed the advantages of having mild and environmentally benign reaction conditions, non-toxicity, and easy handling. This catalytic system was developed for the purpose of preparing for α -amino acetals to further construction the potential dopamine D1 receptor ligands.

In Chapter 5, we developed iron (III) chloride mediated Friedel-Crafts double cyclizations for the synthesis of dihydro-methano-diarylazocines and dopamine D1 receptor ligands from α -amino acetals. These straightforward processes demonstrated the simplicity and synthetic significance.

(I) Different α -amino acetals consisting of various moieties on C-13 appendage or substituents on aromatic ring led to a wide range of dihydro-methano-diarylazocines.

(II) α -Amination of aldehydes and subsequent intramolecular double Friedel-Crafts cyclizations for the synthesis of dopamine D1 receptor ligands was presented. In addition, good yields were obtained.

In the appendix, we presented a highly efficient copper-catalyzed oxidative alkynylation of tertiary aliphatic amines in air. This process is simple, easy to operate, and the reaction conditions are mild. Furthermore, no additional oxidant and additives were required. In contrast to other reported methods, functional groups which are sensitive to oxidation such as a formyl group can tolerate this very mild reaction conditions.

INDEX OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
AB_q	AB quartet
Ac	acetyl
Ar	aryl
All	allyl
Al_2O_3	aluminium oxide
aq.	aqueous
atm	atmospheric pressure
Bn	benzyl
bs	broad singlet
BuLi	butyl lithium
Bz	benzoyl
C	carbon
CAN	cerium(IV) ammonium nitrate
Cat.	catalyst
CDCl_3	deuterated chloroform
CDC	cross-dehydrogenative coupling
CH_4	methane
CH_2Cl_2	dichloromethane
CHCl_3	chloroform
cm^{-1}	inverse centimeter
CuI	copper iodide
Cy	cyclohexyl
d	doublet
DCM	dichloromethane
dd	doublets of doublet
de	diastereomeric excess
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate

DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublets of triplet
<i>ee</i>	enantiomeric excess
eq.	equation
equiv.	equivalent
EI	electron impact ionization
Et	ethyl
ether	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FG	functional group
FR	free radical
FTIR	fourier transform infrared spectroscopy
g	gram
h	hour
H	hydrogen
Hex	hexane
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
IBX	2-iodoxybenzoic acid
^{<i>i</i>} Pr	isopropyl
<i>J</i>	coupling constants
M	concentration (mol/dm ⁻³)
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
mL	millilitres
mol%	molar percent
MS	mass spectrum
M	concentration (normality)
MSG	monosodium glutamate
N	nitrogen
NBS	<i>N</i> -bromosuccinimide
Nu	nucleophile
ⁿ Bu	<i>n</i> -butyl
NMR	nuclear magnetic resonance
N.R.	no reaction
OTf	trifluoromethanesulfonate
Pd/C	palladium on carbon
Ph	phenyl
PMP	<i>p</i> -methoxyphenyl
ppm	part per million
q	quartet
rt	room temperature
R _f	retention factor
s	singlet
SET	single electron transfer
SOMO	singly occupied molecular orbital
t	triplet
TBDPS	<i>tert</i> -butyl diphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethyl silyl
^t Bu	<i>tert</i> -butyl
<i>t</i> -BuOK	potassium <i>tert</i> -butoxide
^t BuOOH	<i>tert</i> -butyl hydroperoxide
^t BuOO ^t Bu	<i>di-tert</i> -butyl peroxide
td	triplets of doublet

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethyl silyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TS	transition state

CHAPTER 1

*Synthesis of α -Amino Acid Derivatives and
Oxidative Transformations of C–H Bonds*

CHAPTER 1 SYNTHESIS OF α -AMINO ACID DERIVATIVES AND OXIDATIVE TRANSFORMATIONS OF C–H BONDS

1.1 OVERVIEW

Proteins are an important class of macromolecules that are involved in maintaining many functions of life. As a result, α -amino acids, being the basic elements of them, had attracted considerable attention in the scientific and academic areas.¹ In addition to their broad applications in the industrial area as additives to foods and animal feeds, cosmetics, detergents, chiral building blocks, chiral catalysts, their derivatives such as β -amino alcohols, α -amino aldehydes, and α -amino acetals are also very useful intermediates for the preparation of biologically active molecules². Generally, natural α -amino acids are obtained through the classical methods (chemical and enzymatic resolutions) for the commercial production. However, the increasing demand of α -amino acid derivatives prompted synthetic organic chemists to develop new methods for the synthesis of α -amino acids, especially non-natural α -amino acids. Recently, oxidative transformations to realize direct functionalization of molecules have been used as a powerful tool in organic synthesis. Such methods provide atom- and step-economical alternatives to the traditional use of expensive metal catalysts and stoichiometric metal oxidants.³ Furthermore, it is interesting that

¹ *Chemistry of Natural Products*; Bhat, S. V.; Nagasampagi, B. A.; Sivakumar, M.; Eds.; Springer: Narosa, 2005; p 317.

² (a) Wang, L.; Shultz, P. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 34. (b) Tsantrizos, Y. S. *Acc. Chem. Res.* **2008**, *41*, 1252. (c) Davie, E. A. C.; Mennen, S. M.; Xu, Y. J.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (e) Ma, D. W.; Qian, C. *Acc. Chem. Res.* **2008**, *41*, 1450.

³ (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (d) Goj, L. A.; Gunnoe, T. B. *Curr. Org. Chem.* **2005**, *9*, 671. (e) Ritleng, V.;

organocatalysts or cheap metal catalysts such as copper or iron salts together with inexpensive oxidants such as air, molecular oxygen constitutes the catalytic systems used for C–H bond functionalization or α or β -functionalization of aldehydes with nucleophiles.

Herein we mainly summarized the latest progress, including (1) chemical methods for the α -amino acid derivatives, especially electrophilic aminations of carbonyl compounds, (2) oxidative transformations to realize direct functionalization of molecules without introducing additional functional groups, including (i) C–H bond functionalization of tertiary amines *via* iminium ion intermediates, (ii) α -functionalization of aldehydes *via* singly occupied molecular orbital (SOMO) catalysis, (iii) β -functionalization of aldehydes *via* oxidative enamine catalysis, and (iv) in situ generated hypervalent iodine catalytic oxidative transformation reactions, and (3) catalytic utility of low-oxidation-state indium (I) complexes.

1.2 SYNTHESIS OF α -AMINO ACID DERIVATIVES

The amino acid industry has been a multi-billion dollar enterprise. As early as 1908, monosodium glutamate (MSG) as a flavor enhancer was isolated from the seaweed *konbu* by Dr. Kikunae Ikeda from Tokyo Imperial University in Japan. MSG was originally produced through extraction from acid hydrolysate of plant protein. It was until fermentation technology was utilized for the commercial manufacture of

Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (f) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698. (g) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (h) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (i) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (j) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (k) Davies, H. M. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6422. (l) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (m) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

MSG in the late 1950s that modern amino acid production started. Afterward, various amino acids were gradually produced by fermentation technologies. Recently, the separation of bacterial glutamate-producers made the large-scale production of MSG from cheap sugar and ammonia a reality.

The general manufacturing processes for α -amino acids are classified as: (1) extraction from hydrolysates of animal or plant protein, (2) chemical synthesis, (3) fermentation, and (4) bioconversion using enzymes. For the production of different α -amino acids, the selection of the process depends on many factors such as the available technology, cost of raw materials, market prices and sizes, cost of fermentation versus chemical synthesis, and the environmental impact of the process itself. The industrial applications of chemically synthetic methods are restricted to the synthesis of racemic α -amino acids using the Strecker synthesis, in which a variety of α -aminonitriles were obtained through the reaction of an imine or imine equivalent (ammonia and aldehyde) with hydrogen cyanide, and subsequent nitrile hydrolysis, leading directly to α -amino acids. In combination with the biocatalysis, this method also provided the convenience for enantiomerically pure amino acids.⁴

Recently, a wide variety of methods for the laboratory preparation of α -amino acids or their derivatives had been developed. These include asymmetric hydrogenation of α -amino acid derivatives, C–C bond forming reactions by the introduction of the α -side chain or carboxy group, and C–N bond forming reactions.⁵

⁴ (a) Richard, J. B. *Chem. Rev.* **1946**, 38, 501. (b) Izumi, Y.; Chibata, I.; Itoh, T. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 176. (c) Kusumoto, I. *J. Nutr.* **2001**, 131, 2552S. (d) Breuer, M.; Dittrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, 43, 788.

⁵ (a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, 107, 4584. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, 107, 5471. (c) Halfen, J. A. *Curr. Org. Chem.* **2005**, 9, 657. (d) Müller, P.; Fruit, C. X. *Chem. Rev.* **2003**, 103, 2905. (e) Katsuki, T. In *Comprehensive Coordination Chemistry*; McCleverty, J., Ed.; Elsevier Science Ltd.: Oxford, 2003; Vol. 9, p 207. (f) Jacobsen, E. N. In

Here we mainly summarize the recent progress focusing on the C–N bond forming reactions for the preparation of α -amino acid derivatives.

The general methods for the synthesis of α -amino acid derivatives *via* C–N bond formations include (1) traditional amination of α -halo carbonyl compounds (Scheme 1, eq. 1.1),⁶ (2) electrophilic aminations through the reaction of enolates with an electrophilic nitrogen source (Scheme 1, eq. 1.2),⁷ (3) aziridinations employing carbenes or nitrenes onto imines or electrophilic alkenes (Scheme 1, eqs 1.3 and 1.4, respectively),⁸ and (4) aminohydroxylations and diaminations in the presence of reagents bearing an electrophilic nitrogen atom (Scheme 1, eq. 1.5).⁹

Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, p 607.

⁶ Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

⁷ (a) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (b) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (c) Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225. (d) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708. (e) North, M. *Contemp. Org. Synth.* **1996**, 323. (f) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1540. (g) Heimgartner, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238. (h) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989.

⁸ (a) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987. (b) Krumper, J. R.; Gerisch, M.; Suh, J. M.; Bergman, R. G.; Tilley, T. D. *J. Org. Chem.* **2003**, *68*, 9705. (c) Patwardhan, A. P.; Lu, Z.; Pulgam, R.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 2201. (d) Patwardhan, A. P.; Lu, Z.; Pulgam, R.; Zhang, Y.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 6169. (e) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675. (f) Ma, L.; Jiao, P.; Zhang, Q.; Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 3718. (g) Murugan, E.; Siva, A. *Synthesis* **2005**, 2022.

⁹ (a) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451. (c) Muñiz, K. *Chem. Soc. Rev.* **2004**, *33*, 166. (d) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708. (e) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733. (f) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169. (g) Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949. (h) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507. (i) Liu, Z.; Ma, N.; Jia, Y.; Bois-Choussy, M.; Malabarba, A.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 2847. (j) Jo, C. H.; Han, S.-H.; Yang, J. W.; Roh, E. J.; Shin, U.-S.; Song, C. Z. *Chem. Commun.* **2003**, 1312. (k) Yang, X.-W.; Liu, H. Q.; Xu, M.-H.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2004**, *15*, 1915. (l) Harding, M.; Bodkin, J. A.; Hutton, C. A.; McLeod, M. D. *Synlett* **2005**, 2829. (m) Adams, B.; Lowpetch, K.; Thorndycroft, F.; Whyte, S. M.; Young, D. W. *Org. Biomol. Chem.* **2005**, *3*, 3357. (n) Muñiz, K.; Nieger, M. *Chem. Commun.* **2005**, 2729. (o) Almodóvar, I.; Hovelmann, C. H.; Streuff, J.; Nieger, M.; Muñiz, K. *Eur. J. Org. Chem.* **2006**, 704.

Scheme 1.1 Reported methods for the synthesis of α -amino acid derivatives by C–N bond formation

Among them, electrophilic amination is one of the simplest and most direct methods for the construction of C–N bonds and this method usually involves a nucleophilic carbanion and an electrophilic nitrogen source. Based on this, the common strategy for the synthesis of α -amino acid derivatives is to choose a suitable electrophilic nitrogen source for the amination of enolates. Recently, dialkyl azodicarboxylate and nitroso compounds as the nitrogen source were reported for this reaction.

1.2.1 CHIRAL TRANSITION METAL COMPLEXES AS THE CATALYST

DIAZODICARBOXYLATE AS THE NITROGEN SOURCE

In 1997, the Evans group reported the first enantioselective α -amination of an enolate using a chiral magnesium complex as the catalyst.¹⁰ Amination of *N*-acyloxazolidinones **1** afforded enantiopure α -amino acid precursor **2** in high yield in

¹⁰ Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.

the presence of the chiral sulfonamide-magnesium complex **3** (10 mol%) and *N*-methyl-*N*-(*p*-toluene)sulfonamide (20 mol%). Kinetic analysis showed that catalyst turnover, rather than enolization, is the rate-determining step because sulfonamide can accelerate the conjugate protonation and liberate the catalyst, exhibiting a first-order dependence on the reaction rate (eq. 1.6).

The copper complex from bisoxazoline ligand (*S,S*)-**7a** (eq. 1.7) (5-10 mol%) and copper triflate (5-10 mol%) can efficiently catalyze the reaction of functionalized silyl ketene acetals of thioesters **4** and **9** with unsymmetrical azodicarboxylate **5**, furnishing the desired products **6** and **10** in high yields and enantioselectivities (eqs 1.7 and 1.9). The chiral aminosulfonamide **8** (eq. 1.8) proved to be less efficient than ligand **7a** (compare eq. 1.7 vs 1.8). Especially noteworthy is that this reaction is stereospecific because the (*Z* or *E*)-O-enol of thioester **4** furnished products **6** with the opposite configuration (eqs 1.7 and 1.8).¹¹

¹¹ Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595.

The (*S*)-Binap **11**-[Ag] complex was also employed for a similar reaction using ketene acetals derived from esters and thioester **4** with dibenzyl azodicarboxylate.¹²

The (*S*)-Ph-Box **7b**-[Cu] (10 mol %) chiral catalytic complex was also used for catalyzing the α -amination of α -substituted β -keto esters **12** using dibenzyl azodicarboxylate as the nitrogen source.¹³ The resulting α -amino ester derivatives **13** were obtained with excellent enantioselectivity (eq. 1.10).

1.2.2 CHIRAL ORGANOCATALYSTS

¹² Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, 78, 666.

¹³ Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, 42, 1367.

1.2.2.1 DIAZODICARBOXYLATE AS THE NITROGEN SOURCE

Organocatalyst was used for α -amination of carbonyl compounds with an electrophilic nitrogen source beginning with the reaction of β -keto esters **14** and β -keto lactones **17** with dibenzyl azodicarboxylate using cinchonine **16** (20 mol%) as the catalyst under the reaction conditions described in eqs. 1.11 and 1.12.¹⁴ The desired compounds **15** and **18** were furnished with 80% and 64% ee respectively. It was proposed that the formation of the hydrogen bonding between the hydroxy group and the carbonyl group of the enolizable reagent in the presence of chiral base had made it possible for enantioselective induction to occur.

Ligands (β -ICD) **21–23** were also suitable for the electrophilic amination reactions using dialkyl azodicarboxylates as a nitrogen source. When α -cyanocarboxylates **19** were used as substrates, ligands (β -ICD) **21** and **23** afforded excellent enantioselectivities of the products (*S*)-**20** at very low temperatures.¹⁵ If ligand β -ICD-**21** was used with 1,3-dicarbonyl compounds **14** and **17**, analogous results with cinchonine **16** as the catalyst were obtained.

¹⁴ Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115.

¹⁵ Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, 126, 8120.

In 2002, the first organocatalytic enantioselective and direct α -amination of aldehydes was simultaneously and independently reported by the Jørgensen group¹⁶ and the List group¹⁷. Using (*S*)-proline as the catalyst and azodicarboxylates as the nitrogen electrophile with a slight excess of aldehyde, α -hydrazino aldehydes **24** were obtained in moderate to high yields and excellent enantioselectivities (Scheme 1.2). Next, the corresponding optically enriched α -amino acid derivatives such as α -amino alcohols **26** and oxazolidinones **25** were produced after simple reduction using sodium borohydride or N–N bond cleavage (Scheme 1.2, eqs. 1.14 and 1.15).

¹⁶ Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790.

¹⁷ List, B. J. *Am. Chem. Soc.* **2002**, *124*, 5656.

Scheme 1.2 Proline-catalyzed direct asymmetric α -amination of aldehydes by Jørgensen et al. (eq. 1.14) and List (eq. 1.15).

From a mechanistic standpoint, the absolute configuration of the α -aminated products might be explained by the formation of stereospecific transition state directed by the hydrogen bonding between the azo-compound and the intermediates of the iminium salt or enamine derived from the aldehyde and proline.

The scope for the proline-catalyzed direct α -amination reaction using azodicarboxylates as an electrophilic nitrogen source were successfully extended to α,α -disubstituted aldehydes¹⁸ and even further applications to the total synthesis of biologically active compounds. For example, Barbas et al. reported the synthesis of the metabotropic glutamate receptor ligands (*S*)-APICA **27** and (*S*)-AIDA **28** via proline-catalyzed direct asymmetric α -amination of α,α -disubstituted aldehydes using List's conditions (Scheme 1.3).¹⁹

¹⁸ Vögt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, 2448.

¹⁹ Suri, J. T.; Steiner, D. D.; Barbas, C. F., III, *Org. Lett.* **2005**, 7, 3885.

Scheme 1.3 Application of proline-catalyzed direct asymmetric α -amination to the synthesis of APICA and AIDA.

For the key step of asymmetric α -amination of aldehydes for the total synthesis of the LFA-1 antagonist BIRT-377 (**31**), proline was an inappropriate catalyst as the amination product **30** was obtained with only moderate enantioselectivity (44% ee) after 5 days. Therefore, (*S*)-proline-derived tetrazole **29** was chosen and further used for this amination, affording the desired product **30** in 95% yield and 80% ee after 3 h (Scheme 1.4). Subsequently, several transformations from α -aminated aldehyde **30** led to BIRT-377 (**31**).²⁰

Scheme 1.4 Enantioselective total synthesis of LFA-1 antagonist BIRT-377 through direct asymmetric α -amination of a branched aldehyde.

The Jørgensen group further developed proline-catalyzed α -amination of ketones shortly after their first report of the α -amination of aldehyde. α -Hydrazino ketones (**32** and **33**) were obtained using similar reaction conditions to those for the

²⁰ Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, 7, 867.

aldehydes in good yields and excellent enantioselectivities (eq. 1.16). Furthermore, the more bulky α -position of ketones was regioselectively aminated (major/ minor up to 10:1). In most cases, owing to slight decrease in optical purities after silica gel column chromatographic purification, the diastereoselective reduction of the keto functionality to acquire both *syn*- and *anti*- β -amino alcohols, which can easily be converted to the corresponding oxazolidinones, was adopted using different reducing agents.²¹

Adolfsson and co-workers found that sulfonamide **34** was suitable for the direct asymmetric α -amination of aldehydes with DEAD (eq. 1.17).²² After reductive cyclization, the products were isolated as enantiopure *N*-aminooxazolidinones **25a** in moderate to good yields. The advantage of this catalyst is the low catalyst loading as only 1 mol % **34** is enough to realize the transformation.

The Jørgensen group had also developed a proline derivative, (*S*)-2-[bis(3,5-bis(trifluoromethyl)phenyl)trimethylsilanyloxymethyl]-pyrrolidine **35** (eq. 1.18), for

²¹ Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.

²² Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101.

asymmetric α -amination of aldehydes.²³ The desired products *N*-amino oxazolidinones were obtained within 15 min in the presence of 10 mol % catalyst **35** in good yields and high enantioselectivities (eq. 1.18). Furthermore, compared with the aminated products obtained using proline, catalyst **35** afforded the products **25** with the opposite configuration.

The reason that compounds **25** with the opposite configuration were obtained, using L-proline and catalyst **35** with 3,5-bistrifluoromethyl phenyl groups, could be explained based on the nature of the transition states (Scheme 258). The *re*-face attack to the electrophile azodicarboxylate was assisted by the hydrogen bonding in proline-catalyzed α -amination reactions. Whereas, catalyst **35** with two bulky 3,5-bistrifluoromethyl phenyl groups underwent the electrophilic attack from *si*-face as it was much easier than from *re*-face.

²³ Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, 127, 18296.

Scheme 1.5 Transition state model for the α -amination catalyzed by proline and diarylprolinol silyl ether (*S*)-**35**

1.2.2.2 NITROSO COMPOUNDS AS THE NITROGEN SOURCE

In comparison with azodicarboxylates, electrophilic addition of nitroso compounds had the tendency to react at the oxygen atom to generate aminoxylation products or at the nitrogen atom to form hydroxyamination products. Up to now, there are only a few groups that had reported the asymmetric α -hydroamination of aldehydes using nitroso compounds as an electrophilic nitrogen source.

Jiang and co-workers reported the first asymmetric hydroxyamination of carbonyl compounds using 10 mol% prolinamide derivative **37** as the catalyst. α -Hydroxyamination (nitroso aldol reaction) of α -branched aldehydes with nitrosobenzene **36** (eq. 1.19) and subsequent reduction with NaBH₄ afforded the corresponding alcohols **38** in moderate yield and enantioselectivity. It was especially noteworthy that no aminoxylation products were observed.²⁴

A transition state model **TS** was proposed to explain how catalyst **37** activated nitrosobenzene. In the model, the formation of double hydrogen bonding between the amide and hydroxyl groups of catalyst **37** and the oxygen atom of nitrosobenzene increased the electrophilic reactivity of the nitrogen atom of nitrosobenzene.

²⁴ Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2006**, 429.

Meanwhile, in the proline-catalyzed aminooxylation reaction, the strong acidic carboxyl group of proline promotes protonation at the more basic nitrogen atom of nitrosobenzene (Scheme 1.6).

Scheme 1.6 Difference in nitrosobenzene reactivity under general and specific acid catalysis

Maruoka and co-workers designed and synthesized a new *C*₂-symmetric binaphthyl-based secondary amine **39** containing hydroxyl groups for α -hydroxyamination of aldehydes with nitrosobenzene. A series of unbranched aldehydes were suitable for this reaction, affording the products **40** in good yield and excellent enantioselectivity (up to 99% ee) after reduction (eq. 1.20).²⁵ Considering the synthetic utility of this reaction, 4-methoxynitrosobenzene, which bears an easily cleavable group, was used for this reaction and β -amino alcohol or 1,2-diamine was synthesized *via* further manipulation in good yield with a similar level of enantioselectivity.

²⁵ Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046.

For this reaction, the hydroxyl group of catalyst **39** had great effect on both the catalytic reactivity and the enantioselectivity. Based on this, a transition state model **TS** was proposed to better understand the role of the hydroxyl group (Scheme 1.7). One of the bulky hydroxydiphenylmethyl groups covers the *re*-face of the enamine, while the other directs and activates the nitrosobenzene *via* hydrogen bonding.

Scheme 1.7 Proposed transition state model for the asymmetric α -hydroxyamination of aldehydes

1.3 C–H BOND OXIDATIVE TRANSFORMATIONS

C–H bond oxidative transformations for the direct installation of oxygen, nitrogen and carbon functionalities into organic molecules have been used as a powerful tool in organic synthesis, owing to the obvious advantages of improving atom economy and efficiency of the reaction in order to shorten the synthetic routes. Recently, great progress had been made on the direct transformation of C–H bonds into functionalized molecules in the following research areas: (1) C–H bond

functionalization of tertiary amines, (2) α -functionalization of aldehydes *via* SOMO catalysis, (3) α -functionalization of aldehydes *via* oxidative enamine catalysis.²⁶

1.3.1 C–H BOND FUNCTIONALIZATION OF TERTIARY AMINES VIA IMINIUM ION INTERMEDIATE

Transition metal-catalyzed C–H bond functionalization of tertiary amines has attracted much interest in the synthetic community due to the rich variety of nitrogen-containing structural units featured widely in many natural products and pharmaceuticals.²⁷ The sp^3 C–H bond activation and carbon-carbon bond formation at the α -position of tertiary amines had been widely studied in recent years. At the beginning, a directing group was required for chelating the metal catalyst to realize the transformation of tertiary amines.²⁸ A good example was that Murai et al. reported a catalytic process for the carbonylation at sp^3 C–H bonds adjacent to a nitrogen atom of tertiary amines catalyzed by rhodium complexes.²⁹ Later, many research results about cross-coupling of tertiary amines with nucleophiles without directing groups were reported.³⁰ For instance, Murahashi et al. described the scope and reaction

²⁶ (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. W. *Chem. Rev.* **2011**, *111*, 1780. (c) Herreras, C. I.; Yao, X. Q.; Li, Z. P.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546.

²⁷ (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Wang, D. H.; Hao, X. S.; Wu, D. F.; Yu, J. Q. *Org. Lett.* **2006**, *8*, 3387. (c) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610. (d) Yoshida, J. I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

²⁸ (a) Doye, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3351. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (c) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 5284. (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 13244.

²⁹ Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882.

³⁰ (a) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 2534. (b) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 5284. (c) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 13244. (d) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (e) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769. (f) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462. (g) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610. (h) Maruyama, T.; Suga, S.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2005**, *127*, 7324. (i) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (j) Suga, S.;

mechanism of ruthenium-catalyzed oxidative cyanation of tertiary amines with sodium cyanide in detail. In the proposed mechanism, the iminium adducts of ruthenium were suggested as the key intermediates.³¹ Meanwhile, Doyle et al. developed an oxidative Mannich reaction. In his study, tertiary amines with siloxyfurans catalyzed by dirhodium capolactamate $\text{Rh}_2(\text{cap})_4$ directly formed carbon-carbon bond in the presence of *tert*-butyl hydroperoxide.³²

Although these elegant methods had been studied widely in recent years, there are still many problems associated with the existing methods. For example, the need to use expensive and moisture sensitive metal catalysts like Ru, Rh, and Ir, or strong and dangerous oxidants, the requirement of another functionalized substrate as well as the need to use harsh reaction conditions are some of the problems that remains to be solved. Therefore, many research groups have focused on exploring the direct coupling between C–H bond of organic molecules and sp^3 C–H bond at the α -position to nitrogen atom using cheap and easy to handle oxidant and catalyst under mild reaction conditions. Copper-catalyzed cross-dehydrogenative couplings (CDC) *via* the oxidative activation of sp^3 C–H bonds adjacent to nitrogen developed by Li's group were considered to be typical examples (Scheme 1.8). In the reaction systems for the oxidative α -functionalizations of tertiary amines, *tert*-butyl hydroperoxide was used as the oxidant, and various carbon nucleophiles, such as, alkynes, indoles,

Suzuki, S.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2002**, *124*, 30. (k) Yoshida, J.-I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (l) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *Organometallics* **2004**, *23*, 5392.

³¹ (a) Murahashi, S. I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (b) Murahashi, S. I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (c) Murahashi, S. I.; Komiya, N.; Terai, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 6931.

³² Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

nitromethane, and malonates, reacted with tertiary amines to obtain the corresponding α -substituted amines.³³

Scheme 1.8 CuBr-TBHP catalytic systems for CDC reactions developed by Li's group

On the basis of the literature reports about the generation of iminium ion type intermediates by single electron-transfer (SET) reagents or transition metal complexes activation, the mechanism of CDC reactions was proposed to involve a radical (Scheme 1.9) or ionic (Scheme 1.10) process.

In the radical mechanism (Scheme 1.9), the iminium type intermediate **44** could be formed *via* two possible pathways: (1) first hydrogen abstraction to provide the intermediate of a α -carbon centered radical **43**, then a single-electron transfer

³³ (a) Li, Z. P.; Bohle, D. S.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (b) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (c) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (d) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (e) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335.

(SET) leads to the iminium ion intermediate, (2) an initial SET gives an cation radical **42**, then hydrogen abstraction forms **44**. Next, the nucleophilic attack on **44** leads to the desired CDC product **45** and completes the catalytic cycle.³⁴

Scheme 1.9 Radical mechanism for the CDC reaction of amine with nucleophile

In the ionic mechanism (Scheme 1.10), the oxidation of copper catalyst first generates hypervalent copper species **46**, which coordinates with the nitrogen atom of tertiary amine to form copper complex **47**. Subsequently, intramolecular elimination of one molecular H₂O leads to the iminium-type intermediate **44** via a five-membered transition state. At last, the reaction of the intermediate **44** and nucleophile produces compound **45** and regenerates the copper catalyst.³⁵

Scheme 1.10 Ionic mechanism for the CDC reaction of amine with nucleophile

³⁴ (a) Wang, F.; Sayre, L. M. *J. Am. Chem. Soc.* **1992**, *114*, 248. (b) Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408. (c) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

³⁵ (a) Murahashi, S. I. *Angew. Chem. Int. Ed.* **1995**, *34*, 2443. (b) Barton, D. H. R.; Beviere, S. D.; Chavasiri, W.; Csuhai, E.; Doller, D. *Tetrahedron* **1992**, *48*, 2895. (c) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.

Propargylic amines are very useful intermediates for the synthesis of various nitrogen-containing compounds, owing to these structural units featured widely in many natural products and pharmaceuticals (Scheme 1.11).³⁶

Scheme 1.11 Natural products containing the structural unit of propargylic amines

Hence it is very desirable to develop novel methods for the synthesis of propargylic amine derivatives, especially alkynylation (sp^3 - sp coupling) of tertiary amines. Different catalytic systems for the alkynylation reaction were briefly introduced as follows.

1.3.1.1 COPPER-CATALYZED OXIDATIVE ALKYNYLATION OF TERTIARY AMINES

³⁶ (a) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X.-M.; Paterson, I. A.; Yu, P. H. *Drug Dev. Res.* **1997**, 42, 150. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy J. *J. Am. Chem. Soc.* **1990**, 112, 3715. (c) Jenmalm, A.; Berts, W.; Li, Y.-L.; Luthman, K.; Csoeregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, 59, 1139. (d) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, 126, 5958.

As early as 1993, oxidative coupling of 4-substituted *N,N*-dimethylanilines with terminal alkynes catalyzed by CuCl_2 in the presence of molecular oxygen was reported although the yield was only 27-43%.³⁷ Since then, many catalytic systems were developed for the oxidative alkynylation of tertiary amines.

Cu(I)Br-TBHP CATALYTIC SYSTEM

Recently, Li and coworkers investigated the direct coupling of sp^3 C-H bond adjacent to nitrogen atom with a terminal alkyne. *N,N*-Dimethylaniline and phenylacetylene were selected as the model substrates for this reaction. The best yield (74%) was obtained in the presence of CuBr (5 mol%) as the catalyst and TBHP (1.0 equiv) as the oxidant at 100 °C for 3 h when the ratio of *N,N*-dimethylaniline to alkynes to *tert*-butyl hydroperoxide was 2:1:1. A variety of alkynes reacted with dimethylaniline derivatives to afford the desired products in 12-82% yields (eq. 1.21).^{32c}

Other tertiary amines were also suitable for this coupling reaction. For example, the reaction of benzyldimethylamine with phenylacetylene provided alkynylation of the methyl group under the standard conditions. In addition, the selective conversion of tetrahydroisoquinoline derivatives into the corresponding products was also realized in good yields (eq. 1.22).

³⁷ Murata, S.; Teramoto, K.; Miura M.; Nomura, M. *J. Chem. Res. (S)*, **1993**, 10, 434.

The reaction of 1-phenyl-piperidine with phenylacetylene generated the desired product in 12% yield together with a *tert*-butoxyl alkynylation compound (12%) (eq. 1.23).

Subsequently, the asymmetric alkynylation of tetrahydroisoquinolines to generate optically active C-1 substituted derivatives that widely exist in nature was investigated. Various copper complexes in conjunction with chiral bisoxazolines **48**-**51**, Quinap **52**, and BINAP **53** as ligands were examined for this reaction under different conditions.

The highest enantioselectivity was obtained when the complex of Cu(I)OTf/pybox **48** was used as the catalyst for this asymmetric alkynylation in THF. Under the standard conditions tetrahydroisoquinolines with different functional groups were alkynylated asymmetrically through Cu(I)OTf/**48** catalysis (eq. 1.24).³⁸

³⁸ (a) Li, Z. P.; Li, C.-J. *Org. Lett.* **2004**, 6, 4997. (b) Li, Z. P.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, 17, 590.

With the constant interest in the alkynylation of tertiary amines, Li's group realized direct α -alkynylation of natural peptides. This method can potentially provide rapid access to diverse new peptides and further applications to the synthesis of natural and non-natural α -amino acids. In the report, various glycine amides with *p*-methoxyphenyl group (PMP) were selected as the starting materials and could be directly alkynylated with phenylacetylene even at room temperature under the standard conditions (eq. 1.25).³⁹

After the hydrogenation of the alkyne and removal of PMP group, a series of α -amino acid derivatives could be synthesized (eq. 1.26).

In order to explore the site selectivity of alkynylation of polypeptides, a simple dipeptide was chosen for this coupling reaction (eq. 1.27). The alkynylation product at the glycine amide site was selectively obtained in 63% isolated yield at 70 °C in dichloroethane.

³⁹ Zhao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, 47, 7075.

Cu(I)Br-NBS CATALYTIC SYSTEM

Fu and coworkers developed the CuBr-NBS catalytic system for coupling of tertiary aliphatic amines with terminal alkynes to propargylamines. The methyl group of tertiary amines was alkynylated selectively using CuBr as the catalyst, NBS as the free radical initiator, CH₃CN as the solvent at 80 °C (eq. 1.28).⁴⁰

A possible mechanism for alkylation of tertiary aliphatic amines was proposed in Scheme 1.12. Firstly, free radicals (FR), which was formed from NBS, reacted with the tertiary aliphatic amine to provide cation radical **42a**. Subsequently, abstraction of hydrogen free radical at the α -position of **42** gives the iminium ion intermediate **44a**. Finally, nucleophilic attack of copper(I) acetylide **55** to **44a** led to the target product **56**.⁴¹

⁴⁰ Niu, M. Y.; Yin, Z. M.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *J. Org. Chem.* **2008**, 73, 3961.

⁴¹ Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. *Tetrahedron Lett.* **1997**, 38, 3977.

Scheme 1.12 Proposed mechanism for alkylation of tertiary amines in the CuI-NBS catalytic system.

Cu(I)I-DEAD CATALYTIC SYSTEM

CuI-DEAD (copper iodide/diethyl azodicarboxylate) catalytic system was also suitable for the alkylation of unactivated aliphatic tertiary methylamine (eq. 1.29). This catalytic system had the advantages of simple operation, mild reaction conditions, good to excellent yields, and insensitive to air and moisture. Hence it provided an especially convenient way for the alkylation of aliphatic tertiary methylamine.⁴²

A tentative mechanism was proposed in Scheme 1.13. After nucleophilic addition, DEAD and aliphatic tertiary methylamine **41a** formed adduct **57** in equilibrium with **58** by an intramolecular hydrogen transfer. Then the cleavage provided the iminium ion intermediate and 1H-DEAD **59**, which abstracted hydrogen from the terminal alkyne to further form copper alkynylide with copper catalyst (path **b**). Further addition of copper alkynylide to the iminium ion intermediate afforded the

⁴² Xu, X. L.; Li, X. N. *Org. Lett.* **2009**, *11*, 1027.

desired product **56** and regenerated the copper catalyst. Meanwhile, adduct product **60** was formed preferably *via* path **a** if R^2 or R^3 was a phenyl group.

Scheme 1.13 Proposed mechanism alkynylation of tertiary amines in the CuI-DEAD catalytic system

1.3.1.2 IRON-CATALYZED OXIDATIVE ALKYNYLATION OF TERTIARY AMINES

Vogel and coworkers reported the first iron-catalyzed oxidative C–C cross-coupling of tertiary amines with terminal alkynes into propargylamines using *tert*-butyl peroxide as oxidant without solvent. A variety of amines and alkynes were found to be suitable for this reaction.⁴³ Furthermore, this reaction had high chemoselectivity for the methyl group. As shown in Scheme 1.14, terminal alkyne formed after desilylation of propargyl amine further reacted with *N,N*-dimethyloctylamine under the same conditions, giving the desired product **61** in 67% yield.

⁴³ Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

Scheme 1.14 Chemoselective FeCl_2 -catalyzed oxidative couplings with two different tertiary amines

In this report, the authors used Horner's mechanism to explain this iron-catalyzed oxidative alkylation of tertiary amines. In Horner's mechanism as shown in Scheme 1.15 ($\text{X} = \text{Bz}$),⁴⁴ hydrogen transfer led to the aminoalkyl radical intermediate **43** via one step (**41** to **43**) or two steps through radical cation **42**. Then collapse of **43** with $\text{BzO}^\bullet$ and subsequent electron transfer generated iminium salt **44b** or the derivative **62**. Finally, the intermediate **44b** reacted with H_2O and other nucleophile, affording the secondary amine and the derivative **45**, respectively.

Scheme 1.15 Oxidative dealkylation of tertiary amines and quenching of iminium ion intermediates with nucleophiles (Horner's mechanism)

⁴⁴ (a) Horner, L.; Schwenk, E. *Ann. Chem. Justus Liebig* **1950**, 566, 69. (b) Horner, L.; Junkermann, H. *Ann. Chem. Justus Liebig* **1955**, 591, 53. (c) Horner, L.; Kirmse, W. *Ann. Chem. Justus Liebig* **1955**, 597, 48.

Control experiments were carried out as shown in Scheme 1.16 under the standard conditions. The results showed that **41b** with FeCl_2 as the catalyst was successfully converted into α -aminoether **62a**, which could then directly afford the alkynylation product **56a** with phenylacetylene (Scheme 1.16). It was noted that no reaction took place without FeCl_2 . This showed that FeCl_2 played a crucial role in the reaction and promoted the $\text{S}_{\text{N}}1$ cleavage of the α -aminoethers **62** into iminium ion intermediate **44b** (Scheme 1.15).⁴⁵

Scheme 1.16 Formation of *tert*-butyl aminomethyl ether and subsequent coupling with phenylacetylene

1.3.2 α -FUNCTIONALIZATION OF ALDEHYDES VIA SOMO CATALYSIS

One-electron oxidation of the enamine to the 3π -electron radical cation species was first reported by electrolysis in the late 1970s.⁴⁶ General study and utility in organic synthesis was to synthesize the organic molecule containing nitrogen atom using the enamine as starting material *via* the radical cation intermediate generated by one electron oxidant, such as, cerium(IV) ammonium nitrate (CAN).⁴⁷

⁴⁵ Deng, G.; Li, C. J. *Tetrahedron Lett.* **2008**, 49, 5601.

⁴⁶ (a) Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org. Chem.* **1979**, 44, 3519. (b) Shono, T.; Matsumura, Y.; Hamaguchi, H.; Imanishi, T.; Yoshida, K. *Bull. Chem. Soc. Jpn.* **1978**, 51, 2179. (c) Torii, S.; Yamada, T.; Tanaka, H. *J. Org. Chem.* **1978**, 43, 2882.

⁴⁷ (a) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099. (b) Narasaka, K.; Kohno, Y.; Shimada, S. *Chem. Lett.* **1993**, 125.

In 2007, MacMillan's group introduced the concept of singly occupied molecular orbital (SOMO) catalysis in the asymmetric organic synthesis. This catalytic mode involved a 3π -electron SOMO-activated species. This also provided the potential to realize direct enantioselective α -functionalization of aldehydes. Generally, secondary amine and aldehydes reacted to form the enamine intermediates, which were then oxidized to the radical cation species using single electron transfer (SET) reagents like CAN. Next, π -neutral or π -rich nucleophiles were added to the 3π -electron radical cation species to construct a variety of asymmetric molecules (Figure 1.1).⁴⁸

Figure 1.1 Singly occupied molecular orbital (SOMO) catalysis

Subsequently, based on this theory, a series of novel direct asymmetric α -functionalization of aldehydes and ketones were developed by MacMillan's group, including α -carbonyl alkylation, arylation, enolation, vinylation, carboxylation, chlorination, nitroalkylation, polyene cyclizations, and multi-component cycloadditions (Scheme 1.17).⁴⁹

⁴⁸ Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

⁴⁹ (a) Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. USA* **2010**, *107*, 20648. (b) Allen, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (c) Jang, H.; Hong, J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (d) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (e) Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.*

Scheme 1.17 Direct enantioselective α -functionalization of aldehydes via SOMO catalysis developed by MacMillan's group

This strategy was also further used for intramolecular α -arylation, allylation, and polyene cyclization of aldehydes in order to construct complex organic molecules and natural products.⁵⁰

132, 10015. (f) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5121. (g) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (h) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332. (i) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494.

⁵⁰ (a) Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 1470. (b) Um, J. M.; Gutierrez, O.; Schoenebeck, F.; Houk, K. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 6106. (c) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640. (d) Nicolaou, K. C.; Reingruber, R.; Sarlah, D.; Bräse, S. *J. Am. Chem. Soc.* **2009**, *131*, 2086.

To better understand the α -functionalization of aldehydes and ketones *via* organo-SOMO catalysis, a possible mechanism was proposed using α -allylation of aldehydes as an example (Scheme 1.18).⁵¹ In the mechanism, the reversible reaction of secondary amine catalyst and aldehyde, which might be promoted by the Lewis acid (Ce^{IV} or Ce^{III}), afforded enamine and H_2O . It was shown that radical cation **64** was formed through the rate-limiting step of the oxidation of enamine using Ce^{IV} . It was then coupled to **63** to afford the intermediate **65** that was further oxidized to the silyl cation **66** by the second equivalent of Ce^{IV} . Next, β -elimination of the silyl cation **66** under the assistance of a nucleophile in solution provided the iminium intermediate **67**.⁵² Finally, hydrolysis of the iminium intermediate **67** led to the desired product **68**. At the same time, the secondary amine catalyst was regenerated. It was noted that additional base was needed to prevent protonation of secondary amine.

⁵¹ Devery III, J. J.; Conrad, J. C.; MacMillan, D. W. C.; Flowers II, R. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 6106.

⁵² Jiao, J.; Zhang, Y.; Devery III, J. J.; Xu, L.; Deng, J.; Flowers II, R. A. *J. Org. Chem.* **2007**, *72*, 5486.

Scheme 1.18 Proposed catalytic cycle for SOMO activation.

1.3.3 β -FUNCTIONALIZATION OF ALDEHYDES VIA OXADITIVE ENAMINE CATALYSIS

Quite recently, enantioselective β -functionalization of aldehydes *via* oxidative enamine catalysis was independently developed by Wang and Li⁵³ and Hayashi⁵⁴ groups on the basis of the studies about iminium, enamine, and SOMO catalysis (Figure 1.2). This effective method for β -functionalization of aldehydes involved the below process of (1) a transformation of an aldehyde to an enamine, (2) oxidative conversion of in situ generated enamines to the corresponding α,β -unsaturated iminium ions by using a stoichiometric amount of an oxidant, (3) Michael reactions to provide the desired product (Figure 1.2).

⁵³ Zhang, S.-L.; Xie, H.-X. ; Zhu, J.; Li, H. ; Zhang, X.-S.; Li, J.; Wang, W. *Nat. Commun.* **2011**, 2, 211.

⁵⁴ Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2011**, 50, 3920.

Figure 1.2 (1.30) Enamine catalysis; (1.31) Iminium catalysis; (1.32) SOMO catalysis; (1.33) Proposed oxidative enamine catalysis.

The Wang group successfully applied the catalytic systems of a secondary amine and 2-iodoxybenzoic acid (IBX) as an oxidant for realizing rapid conversion of enamines to iminium ions. In addition, this process was in accordance with a variety of novel transformations including enantioselective β -functionalization of simple aldehydes, Michael-aldol condensation reactions, inter- and intramolecular Michael additions, and even triple and quadruple cascades for one-pot construction of complex molecular architectures (Scheme 1.19). Moreover, this process had the advantages of the operational simplicity and mild reaction conditions. The corresponding α,β -unsaturated enal could also be obtained by the hydrolysis of the iminium ion intermediate without a nucleophile.

Intermolecular Michael additions:

48-74 h, up to 68% yield
er up to 98:2

48 h, 41% yield
er = 96:4

Michael-aldol condensation reactions:

5 d, 55% yield
er = 92.5:7.5

3 d, 26% yield
er = 96:4

Intramolecular Michael additions:

24 h, 55% yield
er = 95:5

5 d, 63% yield
dr = 5:1, er = 86.5:13.5

48 h, 41% yield
er = 96:4

Scheme 1.19 Enantioselective β -functionalization of aldehydes developed by Wang's group

The SET (single electron transfer) mechanism and an ionic mechanism involving 2e transfer were proposed for these amine-catalyzed IBX oxidation reactions (Figure 1.3). As the α,β -unsaturated aldehyde was produced in the absence of a nucleophile, this implied that the SET mechanism might be unsuitable for the oxidation process. On the other hand, an ionic mechanism that involves formation of iodic ester and subsequent elimination could account for this result.⁵⁵

⁵⁵ (a) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, 36, 7945. (b) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, 61, 9272.

Figure 1.3 Proposed mechanisms for amine-catalyzed oxidation of enamines to iminium ions.

(1.34) Single electron transfer (SET) pathway; (1.35) Ionic process involving an electron pair transfer.

At the same time, the Hayashi group reported a one-pot, oxidative, and enantioselective cross-coupling reaction of aldehydes and nitromethane catalyzed by diphenylprolinol silyl ether using the same strategy of oxidative enamine to α,β -unsaturated iminium ions. Several noteworthy features were summarized as follows: (1) metal-free reaction using DDQ as oxidant, (2) β -Substituted γ -nitro aldehyde obtained with excellent enantioselectivity, (3) a synthetic equivalent of C–H activation at the β -carbon atom of an aldehyde. The reaction is thought to proceed through (1) the formation of α,β -unsaturated aldehyde *via* DDQ oxidation and (2) addition to afford the desired product. The two processes proceeded *via* the key intermediate of enamine and α,β -unsaturated iminium ion derived from the secondary amine catalyst (Scheme 1.20).

Scheme 1.20 Proposed reaction mechanism for the asymmetric oxidative reaction

1.4 PROPOSED WORK

In this chapter, we summarized the research work on (1) chemical methods for the synthesis of the α -amino acid derivatives *via* the construction of a new C–N bond, (2) direct installation of functionalities on organic molecules without introducing additional functional groups in the area of (i) C–H bond functionalization of tertiary amines *via* iminium ion intermediates, (ii) α -functionalization of aldehydes *via* singly occupied molecular orbital (SOMO) catalysis, (iii) β -functionalization of aldehydes *via* oxidative enamine catalysis.

On the basis of these research progress on the synthesis of α -amino acid derivatives and C–H bond oxidative transformation, we proposed three pathways for the synthesis of α -amino acetals: (1) oxidative rearrangement of tertiary amines, (2)

rearrangement of enamines, and (3) α -amination of aldehydes with a nucleophilic nitrogen source using the catalytic systems of copper salts or organic molecules containing iodo group and co-oxidant, such as, molecular oxygen, hydrogen peroxide and subsequent construction of dihydro-methano-diarylazocines and dopamine D1 receptor ligands from α -amino acetals (Scheme 1.21).

Scheme 1.21 Our strategy for the synthesis of α -amino acetals and further construction of dihydro-methano-diarylazocines and potential dopamine D1 receptor ligands

CHAPTER 2

Copper-Catalyzed Rearrangement of Tertiary Amines or Enamines for the Synthesis of α -Amino Acetals in Air or Molecular Oxygen

CHAPTER 2 COPPER-CATALYZED REARRANGEMENT OF TERTIARY AMINES OR ENAMINES FOR THE SYNTHESIS OF α -AMINO ACETALS IN AIR OR MOLECULAR OXYGEN

2.1 OVERVIEW

Copper enzymatic activation of dioxygen by the biological method had attracted considerable attention, owing to the existence of important copper monooxygenases.⁵⁶ Mimicking this system to study copper-dioxygen interactions⁵⁷ and further applications of dioxygen-copper systems in organic synthesis, especially in the development of aliphatic C–H bond oxidation chemistry,⁵⁸ have attracted tremendous interests. For C–H bond activation, dioxygen-copper systems⁵⁹ provide

⁵⁶ (a) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047. (b) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013. (c) Prigge, S. T.; Eipper, B. A.; Mains, R. E.; Amzel, L. M. *Science* **2004**, *304*, 864. (d) Nam, W. *Acc. Chem. Res.* **2007**, *40*, 465.

⁵⁷ (a) Aboeella, N. W.; Gherman, B. F.; Hill, L. M. R.; York, J. T.; Holm, N.; Young, V. G.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc.* **2006**, *128*, 3445. (b) Mahadevan, V.; Hou, Z. G.; Cole, A. P.; Root, D. E.; Lal, T. K.; Solomon, E. I.; Stack, T. D. P. *J. Am. Chem. Soc.* **1997**, *119*, 11996. (c) Liang, H. C.; Zhang, C. X.; Henson, M. J.; Sommer, R. D.; Hatwell, K. R.; Kaderli, S.; Zuberbühler, A. D.; Rheingold, A. L.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 4170. (d) Park, G. Y.; Lee, Y.; Lee, D. H.; Woertink, J. S.; Sarjeant, A. A. N.; Solomon, E. I.; Karlin, K. D. *Chem. Commun.* **2010**, 91. (e) Fujii, T.; Yamaguchi, S.; Hirota, S.; Masuda, H. *Dalton Trans.* **2008**, 164.

⁵⁸ (a) Würtele, C.; Sander, O.; Lutz, V.; Waitz, T.; Tuczek, F.; Schindler, S. *J. Am. Chem. Soc.* **2009**, *131*, 7544. (b) Lucas, H. R.; Li, L.; Sarjeant, A. A. N.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 3230.

⁵⁹ Copper or dioxygen has been used for some reactions, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400. (c) Tsuchimoto, T.; Ozawa, Y.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 4231. (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. Dioxygen-copper catalytic system has been used for some reactions, see: (e) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (f) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (g) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (h) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (i) Gao, Y. X.; Wang, G.; Chen, L.; Xu, P. X.; Zhao, Y. F.; Zhou, Y. B.; Han, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956–7957. (j) Chu, L. L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262–7263. (k) Wei, Y.; Zhao, H. Q.; Kan, J.; Su, W. P.; Hong, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (l) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin, D.-L.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900–8902. (m) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (n) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (o) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (p) Baslé, O.; Li, C.-J. *Chem. Commun.* **2009**, 27, 4124.

the alternative to the commonly employed methods which use expensive metal catalysts and stoichiometric metal oxidants. Herein we described the novel rearrangement of tertiary amines or enamines with readily removable *N*-protecting groups for the direct synthesis of α -amino acetals in dioxygen-copper catalytic systems.

2.2 COPPER-CATALYZED REARRANGEMENT OF TERTIARY AMINES THROUGH OXIDATION OF ALIPHATIC C–H BONDS IN AIR OR MOLECULAR OXYGEN: DIRECT SYNTHESIS OF α -AMINO ACETALS

2.2.1 INTRODUCTION

As revealed in Chapter 1, many natural products or bio-molecules contain α -amino acid or β -amino alcohol units in their structures.² While these units may be obtained from naturally occurring α -amino acids, general methods to obtain other non-natural α -amino acids are still highly sought.⁴⁻⁹ Among the many reported methods, direct synthesis of α -amino acids under air by means of biomimetic methods has been regarded as one of the most challenging tasks, in particular, the development of new methods for the synthesis of α -amino acid derivatives employing copper-dioxygen catalytic systems. Herein we report a novel rearrangement of tertiary amines *via* aliphatic C–H bond oxidation in dioxygen-copper catalytic systems for the direct synthesis of α -amino acetals. Furthermore, a mechanism to account for the product observed was proposed on the basis of trapping, control, and isotope labeling experiments.

(q) Baslé, O.; Borduas, N.; Dubois, P.; Chapuzet, J.-M.; Chan, T.-K.; Lessard, J.; Li, C.-J. *Chem. Eur. J.* **2010**, *16*, 8162.

2.2.2 RESULTS AND DISCUSSION

When we subjected *N,N*-dicyclohexyl-*n*-butylamine **69a** to copper(II) bromide and oxygen in methanol/acetonitrile (2/0.2, v/v) at 40 °C, an unexpected product of α -amino acetal **70a** was obtained in low yield (11%) (Table 2.1, entry 2). The structure of **70a** was confirmed by single crystal X-ray analysis (see Experimental Section). Surprisingly, most of the substrate **69a** was converted into *N,N*-dicyclohexylformamide⁶⁰ (62%) (Table 2.1, entry 2, footnote c). With this interesting result, we started to optimize the reaction conditions (see Experimental Section). It was important to note that the reaction did not proceed without copper catalyst (Table 2.1, entry 1). Since nitrogen donor ligands played an important role in dioxygen activation, a series of nitrogen donor ligands were tested in this reaction. It reveals that *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was the best ligand for this reaction to suppress the formation of *N,N*-dicyclohexylformamide, affording the desired α -amino acetal **70a** in 66% isolated yield when the TMEDA/copper(II) bromide ratio was 2:1 (Table 2.1, entry 3). It is noteworthy that the reaction proceeded even under air without a significant decrease in the yield (Table 2.1, entry 3 vs 4). Other primary alcohols such as ethanol were suitable for this reaction although the yields were low, while secondary alcohol like isopropanol did not yield the desired product (Table 2.1, entries 5-8). Therefore, our optimal reaction conditions for the rearrangement of tertiary amines was as follows: the reaction was carried out in oxygen atmosphere (1 atm) at 40 °C using 25 mol% of copper(II) bromide and 50 mol% of TMEDA as the catalytic system, the volume ratio of methanol to acetonitrile was 1 : 4.

⁶⁰ (a) Kirmse, W. ; Siegfried, R. *J. Am. Chem. Soc.* **1968**, 90, 6565. (b) Kaneda, K. ; Itoh, T. ; Kii, N.; Jitsukawa, K.; Teranishi, S. *J. Mol. Catal.* **1982**, 15, 349.

Table 2.1 Optimization of the reaction conditions^a

Reaction scheme: N,N -dicyclohexyl-1-butylamine (**69a**) reacts with Cu catalyst, TMEDA, ROH (solvent), and O₂ (1 atm) to form the product **70 (a-e)**, which is a 1,2-dicyclohexylethane-1,2-diol derivative.

Entry	Catalyst	R	Time (h)	Product	Yield (%) ^b
1	—	Me	48	70a	0
2 ^c	CuBr ₂	Me	48	70a	11
3	CuBr ₂	Me	5	70a	66
4 ^d	CuBr ₂	Me	6	70a	58
5	CuBr ₂	Et	24	70b	25
6	CuBr ₂	ⁿ Pr	48	70c	19
7	CuBr ₂	ⁱ Pr	48	70d	0
8	CuBr ₂	<i>n</i> -Pentyl	48	70e	12

^aReaction conditions: *N,N*-dicyclohexylbutylamine **69a** (0.5 mmol, 1.0 equiv.), copper catalyst (0.25 equiv.), TMEDA (0.5 equiv.), MeOH (0.5 mL, 25 equiv.), MeCN (2.0 mL), under O₂ atmosphere (1 atm) at 40 °C.

^bIsolated yields based on *N,N*-dicyclohexyl-*n*-butylamine **69a**.

^cThe reaction was performed without TMEDA, affording the byproduct *N,N*-dicyclohexylformamide with 62% yield.

^dThe reaction was carried out in air.

Subsequently, the scope of tertiary amines for this oxidative rearrangement was investigated. Representative examples were shown in Table 2.2. Almost all the substrates containing R¹ = R² = Cy provided the desired products in moderate yields under the standard reaction conditions (Table 2.2, entries 1-8). Tertiary amine with longer carbon chain was also suitable for this reaction (Table 2.2, entry 3) although the reaction took a longer time. The reaction tolerated a wide array of functional groups including ester group (Table 2.2, entries 4 and 8), bromo group (Table 2.2, entry 5), double bond (Table 2.2, entry 6) and imido group (Table 2.2, entry 7). It was

found that the substrates of R¹ and R² groups with more branched carbon chain (Table 2.2, entries 1 and 9) showed better reactivity for this reaction than those with linear carbon chain (Table 2.2, entry 10). *Tert*-butyl-*tert*-amyl-*n*-butylamine **69k** with more bulky group such as *tert*-butyl group than cyclohexyl group was also used for this rearrangement. Unfortunately, no desired product was obtained (Table 2.2, entry 11).

Table 2.2 The oxidative rearrangement of tertiary amines.^a

Reaction scheme: Tertiary amine **69 (a-k)** reacts with CuBr₂ (0.25 equiv.), TMEDA (0.5 equiv.), MeOH/MeCN = 1 : 4 at 40 °C, O₂ (1 atm) to form product **70 (f-o)**.

Entry	Substrate			Product	Time (h)	Yield (%) ^b
	R ¹	R ²	R ³			
1	Cy	Cy	H	70a	5	66
2	Cy	Cy	Et	70f	6	65
3	Cy	Cy	<i>n</i> -Octyl	70g	24	61
4	Cy	Cy	CO ₂ Me	70h	12	60
5	Cy	Cy	CH ₂ CH ₂ Br	70i	6	54
6	Cy	Cy	CH=CH ₂	70j	24	61
7	Cy	Cy	CH ₂ NPhth	70k	20	56
8	Cy	Cy	CH ₂ OAc	70l	20	55
9	Cy	ⁱ Pr	H	70m	24	45
10	ⁿ Bu	ⁿ Bu	H	70n	72	12
11	^t Bu	^t Am	H	70o	72	0

^aReaction conditions: Tertiary aliphatic amines **69** (0.5 mmol, 1.0 equiv.), copper(II) bromide (0.25 equiv.), TMEDA (0.5 equiv.), MeOH (0.5 mL), MeCN (2.0 mL).

^bIsolated yields based on tertiary aliphatic amines **69**.

The tertiary amine with a chiral centre was utilized for this reaction, affording the desired product in a moderate yield of 52 % with two diastereomers which can be easily separated by silica gel column chromatography (Scheme 2.1).

Scheme 2.1 A chiral tertiary amine for this oxidative rearrangement.

Of mechanistic interests are the followings: (I) In the process of carrying out the experiment (see Experimental Section), it was found that a white solid with the molecular structure $\text{Cy}_2\text{NH}_2\text{Br}$ (confirmed by X-ray analysis, see Experimental Section) was isolated from the reaction mixture by a simple filtration with about 8% yield. This implies that (i) $\text{Cy}_2\text{NH}_2\text{Br}$ probably come from the hydrolysis of iminium ion or enamine. (ii) The iminium ion and enamine are possible intermediates during the reaction. As such the same oxidative rearrangement might arise from the reaction as shown in Scheme 2.2, eqs 2.1 and 2.2. Then, the following two control experiments were carried out under optimized reaction conditions, thus supporting the existence of the reversible step **1** (Scheme 2.5) and the intermediate of enamine in the reaction system.

Scheme 2.2 Control experiments

(II) To explore how the rearrangement occurred, which carbon was involved in the reaction, and which C–H bonds of long carbon chain were activated, we carried out the isotope labeling experiments (Scheme 2.3). From the isotope labeling experiments as shown in Scheme 2.3, eqs 3-5, α - and β - carbons of the aliphatic chain were involved in the reaction. The use of ^{13}C labelled methanol in the experiment (Scheme 2.3, eq. 4) showed that primary carbon of methoxy group in the α -amino acetal comes from methanol in the reaction system. Interestingly, under the standard reaction conditions, the deuterium labeled compound **69m** was used and found the incorporation of 74% hydrogen atom at the α position observed from ^1H NMR spectrum (Scheme 2.3, eq. 3). This led to the postulation that the hydrogen comes from methanol. The use of O^{18}_2 is to prove that oxygen atom of the amino acetal comes from methanol and not from molecular oxygen (Scheme 2.3, eq. 5). Furthermore, the use of **69a** or **71a** is again to show that 75% deuterium atom is involved in the protonation step of the reaction (Scheme 2.3, eqs 6-7). The reason for H/D exchange may be due to deprotonation and protonation of the reversible steps **2** and **4** (Scheme 2.5).

Probable reasons for 74% H atom observed from ^1H NMR

Scheme 2.3 Isotope labeling experiment

(III) When the reaction was performed in the presence of CD_3OD using compound **70a** as the substrate under the similar reaction conditions, only 67% of **70a** was recovered, and the other three byproducts were also produced although the yield was very low (Scheme 2.4). This result showed that most of steps in this oxidative rearrangement reaction were reversible and this may also be one of the reasons why these byproducts were produced.

Scheme 2.4 Deuterium labeling experiment

On the basis of trapping, control, and isotope labeling experiments, a possible rationalization of this rearrangement was shown in Scheme 2.5.^{46-52,61} In this proposed mechanism, a series of copper-dioxygen species were thought to function as one-electron oxidizing agents toward tertiary amine, enamine **D** and intermediates **B** and **G**. Initially, copper species [LCuⁿ⁺¹] was formed in the catalytic systems of copper salt, molecular oxygen and TMEDA as a bidentate ligand. After electron transfer, deprotonation and electron transfer processes, iminium ion **C** was produced. Subsequently, iminium ion **C** was converted into enamine **D** after deprotonation. Next, electron transfer yielded the cationic radical species **E** and **F**. Nucleophilic attack by methanol on the intermediate **F** and subsequent electron transfer gave the corresponding aziridinium ion **H**. Upon opening of the three-membered ring to form oxocarbenium ion **I**, attack by an additional methanol molecule on the oxocarbenium ion **I** generated the desired product.

⁶¹ (a) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099. (b) Narasaka, K.; Kohno, Y.; Shimada, S. *Chem. Lett.* **1993**, 125.

Scheme 2.5 Proposed mechanism for the oxidative rearrangement of tertiary amines.

2.2.3 SUMMARY

In summary, a novel rearrangement of tertiary amines through aliphatic C–H bond oxidation in dioxygen-copper catalytic systems for the direct synthesis of synthetically useful α -amino acetals was described. Compared with expensive metal catalyst and stoichiometric metal oxidants employed in the traditional methods for C–H bond oxidation, this catalytic system had the obvious advantages of mild reaction conditions and the use of air or oxygen as the oxidant.

2.3 COPPER-CATALYZED OXIDATIVE REARRANGEMENT OF ENAMINES

FOR THE SYNTHESIS OF α -AMINO ACETALS IN MOLECULAR OXYGEN

2.3.1 INTRODUCTION

On the basis of the study of copper-catalyzed oxidative rearrangement of tertiary amines for the synthesis of α -amino acetals and further mechanistic insights, three possible pathways for direct synthesis of α -amino acetals were proposed as shown in Scheme 2.6: (1) oxidative rearrangement of tertiary amines, (2) α -amination of aldehydes with a nucleophilic nitrogen source, and (3) oxidative rearrangement from enamines. Our objective is to realize the synthesis of α -amino acetals with readily removable *N*-protecting groups by examining the three routes using copper-dioxygen catalytic system ($\text{CuBr}_2/\text{TMEDA}/\text{O}_2$).

Scheme 2.6 Different pathways for the synthesis of α -amino acetals

Herein we reported the oxidative rearrangement of enamines with readily removable *N*-protecting groups for direct synthesis of α -amino acetals catalyzed by copper-dioxygen systems. This mild reaction conditions displayed good tolerance towards the functional groups.

2.3.2 RESULTS AND DISCUSSION

We initiated our investigation into the synthesis of α -amino acetals employing $\text{CuBr}_2/\text{TMEDA}/\text{O}_2$ catalytic systems by selecting tertiary amines, secondary amines,

enamines with readily removable *N*-protecting groups as the starting materials. Tertiary amines and secondary amines with readily removable *N*-protecting groups such as benzyl or allyl group were unable to proceed or had the low conversion of the products in CuBr₂/TMEDA/O₂ catalytic systems (Scheme 2.7, eqs. 2.8-2.9). Fortunately, when enamine was subjected to the same reaction conditions, we were able to obtain the desired product in 75% isolated yield (Scheme 2.7, eq. 2.10). These results showed that it was more difficult to form the enamine intermediate when dibenzylhexylamine and dibenzylamine were used as the substrates under the standard conditions.

Scheme 2.7 Different routes for the synthesis of α -amino acetals in CuBr₂/TMEDA/O₂ catalytic systems.

Next, we further explored this oxidative rearrangement for direct synthesis of α -amino acetals from enamines in copper-dioxygen catalytic systems. As revealed in Table 2.3, the reaction did not proceed at all without a copper catalyst (Table 2.3, entry 1). When CuBr₂ or CuI was used alone for this reaction, the desired product was obtained in low (20%) or moderate (45%) yield (Table 2.3, entries 2-3). It was noted

that the complex of CuBr₂/TMEDA was a suitable catalyst, affording the desired product in a yield of 70% (Table 2.3, entry 4).

Table 2.3 Optimization of the reaction conditions^a

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>71b</p> </div> <div style="text-align: center;"> <p>CuBr₂ (0.25 equiv.) TMEDA (0.5 equiv.) MeOH/MeCN = 1 : 4 40 °C, O₂ (1 atm), 2 h</p> </div> <div style="text-align: center;"> <p>72a</p> </div> </div>				
Entry	Catalyst	Ligand	Time (h)	Yield (%) ^b
1	—	—	48	0
2	CuI	—	20	45
3	CuBr ₂	—	20	20
4	CuBr ₂	TMEDA	2	70

^aReaction conditions: enamine (0.5mmol, 1 equiv), copper bromide (0.25 equiv), TMEDA (0.5 equiv), methanol (0.5 mL), acetonitrile (2.0 mL).

^bIsolated yields based on enamine.

Subsequently, a series of enamines with readily removable protecting groups were prepared for direct synthesis of α -amino acetals in copper-dioxygen catalytic systems as shown in Table 2.4. Almost all the enamines were suitable for this reaction, giving the desired products with moderate to good yields. For the enamines with *N*-allyl or benzyl group, this reaction provided the corresponding products in good yields under the standard conditions (Table 2.4, entries 1-3). The enamine with bulky group can also afford the desired product although the yield slightly decreased (Table 2.4, entry 4). This reaction displayed good tolerance to the functional groups, such as, benzyl or allyl groups, double bond. In addition, compared with tertiary amines or secondary amines and aliphatic aldehydes as the starting materials, a shorter time was

required to realize the synthesis of α -amino acetals in copper-dioxygen catalytic systems.

Table 2.4 Scope of the synthesis of α -amino acetals from enamine in molecular oxygen^{a,b}

^aReaction conditions: enamine (0.5 mmol, 1 equiv.), copper(II) bromide (0.25 equiv.), TMEDA (0.5 equiv.), methanol (0.5 mL), MeCN (2 mL) in O₂ (1 atm) at 40 °C for 2 h.

^bIsolated yields based on enamine.

2.3.3 SUMMARY

In summary, an efficient oxidative rearrangement of enamine for direct synthesis of α -amino acetals in copper-dioxygen catalytic system is presented. The mild conditions displayed good tolerance to the functional groups, such as, benzyl or allyl group, double bond.

2.4 CONCLUSION

In this chapter, we successfully applied the copper-dioxygen catalytic systems for the rearrangement of tertiary amines or enamines with readily removable *N*-

protecting groups for the synthesis of α -amino acetals. The common advantages of these reactions are that this process is simple, easy to operate, and the reaction conditions are mild. Furthermore, they displayed good tolerance to the functional groups.

2.5 EXPERIMENTAL SECTION

2.5.1 Copper-Catalyzed Rearrangement of Tertiary Amines through Oxidation of Aliphatic C–H Bonds in Air or Molecular Oxygen: Direct Synthesis of α -Amino Acetals

I. General procedures

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Copper salts and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. Tertiary aliphatic amines **69 (a-k)** were synthesized according to literatures.⁶² Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR. Liquid samples were examined as film

⁶² (a) Ju, Y. H.; Varma, R. S. *Green Chem.* **2004**, 6, 219. (b) Ju, Y. H.; Varma, R. S. *J. Org. Chem.* **2006**, 71, 135.

between NaCl salt plates. HRMS spectra were recorded on a Waters Q – Tof Premier Spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 300, 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.260, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dt (doublets of triplet); m (multiplets); ddt (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

II. Synthesis of (S)-methyl 5-((1-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-yl)(isopropyl)amino)pentanoate (**69I**) and Spectroscopic Information

(S)-Methyl 5-((1-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-yl)(isopropyl)amino)pentanoate (**69I**):

The product was prepared by above general procedure according the literatures,⁶³ to afford product **69I** as light yellowish oil.

⁶³ Smith, C. R.; RajanBabu, T. V. *Org. Lett.* **2008**, *10*, 1657.

¹H NMR (400 MHz, CDCl₃): δ 3.68-3.66 (m, 2H), 3.65 (s, 3H), 3.98-2.99 (m, 1H), 2.61-2.48 (m, 2H), 2.29 (t, *J* = 7.53 Hz, 2H), 2.21-2.17 (m, 1H), 1.84-1.71 (m, 1H), 1.69-1.48 (m, 2H), 1.45-1.22 (m, 2H), 0.98-0.88 (m, 12H), 0.87 (s, 9H), 0.01 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 174.2, 65.2, 62.3, 51.3, 47.9, 45.3, 34.1, 29.9, 28.5, 25.8 (CH₃ x 3), 22.79, 22.77, 21.3, 20.4, 19.3, 18.1, -5.6, -5.8 ppm.

HRMS (ESI, *m/z*): calcd for C₂₀H₄₄NO₃Si⁺ [M+H]⁺ 374.3090, found: 374.3091; [α]_D²⁰ = - 29.9° (*c* = 1.6, CH₂Cl₂).

III. Optimization of the reaction conditions

Table 2.1 Optimization of the reaction conditions.^a

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b	
					70a	70v
1	—	MeCN	40	48	0	0
2 ^c	CuBr ₂	MeCN	40	48	11	0
3	CuBr ₂	MeCN	40	48	51	trace
4 ^{d, e}	CuBr₂	MeCN	40	6	58	trace
5	CuBr ₂	MeOH	40	48	23	trace
6	CuBr ₂	DCE	40	48	17	trace
7	CuBr ₂	THF	40	48	trace	0
8	CuCl ₂	MeCN	40	48	trace	0
9	Cu(OAc) ₂	MeCN	40	48	0	0
10	Cu(OTf) ₂	MeCN	40	48	0	0
11	Cu(acac) ₂	MeCN	40	48	0	0
12	Cu(MeCN) ₄ PF ₆	MeCN	40	48	trace	0
13	CuI	MeCN	40	96	35	17
14	CuBr	MeCN	40	48	trace	0

15	CuCl	MeCN	40	48	0	0
16 ^e	CuBr ₂	MeCN	25	96	42	trace
17^e	CuBr₂	MeCN	40	5	66	trace
18 ^e	CuBr ₂	MeCN	60	5	57	trace
19 ^f	CuBr ₂	MeCN	40	5	63	trace

^aReaction conditions: *N,N*-dicyclohexylbutylamine **69a** (0.5 mmol, 1.0 equiv.), copper catalyst (0.25 equiv.), TMEDA (0.5 equiv.), MeOH (0.2 mL), solvent (2.0 mL), under O₂ atmosphere (1 atm).

^bIsolated yields based on *N,N*-dicyclohexyl-*n*-butylamine.

^cThe reaction was performed without TMEDA, affording the byproduct *N,N*-dicyclohexylformamide with 62% yield.

^dThe reaction was carried out in air.

^eThe reaction was performed using 0.5 mL methanol.

^fThe reaction was performed using 1.0 mL methanol.

Among the various solvents screened (Table 2.1, entries 3 and 5-7), acetonitrile emerged as the best solvent for this reaction, generating the desired product in 51% yield (Table 2.1, entry 3). Other solvents such as methanol, 1,2-dichloroethane (DCE), and tetrahydrofuran (THF) were also screened, but in all cases, the desired α -amino acetal **70a** was obtained in lower yield (Table 2.1, entries 5-7). Other copper catalysts were also screened (Table 2.1, entries 8-15). CuI catalyzed the reaction sluggishly to afford the desired product **70a** and **70v** in 35% and 17% yields, respectively (Table 2.1, entry 13). Other copper salts showed low or even no catalytic activity for this reaction (Table 2.1, entries 8-12 and 14-15). Notably, among the various copper salts investigated, copper (II) was found to exhibit better catalytic activity than copper (I) having the same anion. We also found that the best volume ratio of methanol to acetonitrile was 1 : 4 and 40 °C was the most suitable temperature for this reaction by examining the effect of the volume ratio of MeOH/MeCN and temperature on the yield of α -amino acetal **70a** (Table 2.1, entries 5, 16-19).

IV. General experimental procedure for copper-catalyzed oxidative rearrangement of tertiary aliphatic amines

Typical procedure for the copper-catalyzed oxidative rearrangement of tertiary amines (*N,N*-dicyclohexyl-*n*-butylamine **69a** as an example): *N,N*-dicyclohexyl-*n*-butylamine **69a** (0.118 g, 0.5 mmol) was added to a mixture of CuBr_2 (28 mg, 0.125 mmol), and TMEDA (29 mg, 0.25 mmol) in methanol (0.5 mL, 25 equiv.)/acetonitrile (2.0 mL) in air at room temperature. The mixture was stirred at $40\text{ }^\circ\text{C}$ using O_2 balloon until *N,N*-dicyclohexyl-*n*-butylamine **69a** was completely converted by TLC detection. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70a** as a light yellowish oil (98 mg, 66% yield) and a trace of product **70v** as a light yellowish oil. Then the product **70a** was dissolved in dichloromethane, hexane was added into it and solvent was evaporated to obtain the crystal (CCDC 780728).

***N*-Cyclohexyl-*N*-(1,1-dimethoxybutan-2-yl)cyclohexanamine (70a):**

R_f = 0.79 (hexane: ethyl acetate = 3:1).

mp: 73.5-74.2 °C.

^1H NMR (CDCl_3 , 400 MHz) δ 4.15 (d, J = 2.02 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.74-2.64 (m, 3H), 1.74-1.71 (m, 4H), 1.57-1.17 (m, 16H), 1.05-0.95 (m, 2H), 0.90 (t, J = 7.39 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 112.3, 58.3, 56.64, 56.59, 54.1 (CH x 2), 34.6 (CH_2 x 2), 34.5 (CH_2 x 2), 26.8 (CH_2 x 4), 26.0 (CH_2 x 2), 19.0, 12.4 ppm

FTIR (neat): ν = 2930, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{36}\text{NO}_2^+ [\text{M}+\text{H}]^+$ 298.2746, found: 298.2743.

N-Cyclohexyl-*N*-(1,1-dimethoxypropan-2-yl)cyclohexanamine (70v):

R_f = 0.61 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.04 (d, J = 4.05 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.99-2.93 (m, 1H), 2.67-2.61 (m, 2H), 1.74-1.70 (m, 4H), 1.63-1.51 (m, 6H), 1.36-1.16 (m, 8H), 1.05-0.95 (m, 5H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 111.5, 56.3, 56.1, 54.7 (CH x 2), 51.7, 34.6 (CH_2 x 2), 33.9 (CH_2 x 2), 26.9 (CH_2 x 2), 26.6 (CH_2 x 2), 26.0 (CH_2 x 2), 14.1 ppm

FTIR (neat): ν = 2930, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{34}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 284.2590, found: 284.2597.

***N*-Cyclohexyl-*N*-(1,1-diethoxybutan-2-yl)cyclohexanamine (**70b**):**

The product was prepared by above general procedure and the same chemicals except employing ethanol (0.575 g, 12.5 mmol, 25 equiv.). After 24 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane = 1:100, v/v/v) to afford the desired product **70b** as a light yellowish oil (41 mg, 25% yield) and a trace of compound **70w** as a light yellowish oil.

R_f = 0.82 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.27 (d, J = 2.16 Hz, 1H), 3.86-3.78 (m, 1H), 3.60-3.55 (m, 2H), 3.37-3.29 (m, 1H), 2.78-2.70 (m, 2H), 2.65-2.61 (m, 1H), 1.73-1.71 (m, 4H), 1.57-1.51 (m, 7H), 1.48-1.38 (m, 1H), 1.33-1.16 (m, 14H), 1.04-0.94 (m, 2H), 0.90 (t, J = 7.40 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 109.5, 64.3, 64.2, 58.8, 54.0 (CH x 2), 34.6 (CH_2 x 2), 34.5 (CH_2 x 2), 26.9 (CH_2 x 2), 26.8 (CH_2 x 2), 26.0 (CH_2 x 2), 18.8, 15.7, 15.3, 12.5 ppm

FTIR (neat): ν = 3447, 2930, 1636, 1215, 756 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{40}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 326.3059, found: 326.3062.

***N*-Cyclohexyl-*N*-(1,1-diethoxypropan-2-yl)cyclohexanamine (70w):**

$R_f = 0.76$ (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl₃, 400 MHz) δ 4.16 (d, $J = 3.84$ Hz, 1H), 3.82-3.75 (m, 1H), 3.66-3.50 (m, 2H), 3.47-3.39 (m, 1H), 2.96-2.90 (m, 1H), 2.70-2.64 (m, 2H), 1.73-1.69 (m, 4H), 1.63-1.50 (m, 6H), 1.35-1.16 (m, 14H), 1.05 (d, $J = 6.93$ Hz, 3H), 1.05-0.94 (m, 2H) ppm.

^{13}C NMR (CDCl₃, 100 MHz) δ 109.0, 64.2, 63.9, 54.6 (CH x 2), 52.1, 34.7 (CH₂ x 2), 33.9 (CH₂ x 2), 27.0 (CH₂ x 2), 26.6 (CH₂ x 2), 26.1 (CH₂ x 2), 15.6, 15.3, 13.9 ppm

FTIR (neat): $\nu = 3503, 2928, 1636, 1215, 754\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for C₁₉H₃₈NO₂⁺ [$M+H$]⁺ 312.2903, found: 312.2904.

***N*-Cyclohexyl-*N*-(1,1-dipropoxybutan-2-yl)cyclohexanamine (70c):**

The product was prepared by above general procedure and the same chemicals except employing propanol (0.75 g, 12.5 mmol, 25 equiv.). After 48 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane = 1:100, v/v/v) to afford the desired product **70c** as a light yellowish oil (34 mg, 19% yield).

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

^1H NMR (CDCl₃, 400 MHz) δ 4.26 (d, $J = 2.17$ Hz, 1H), 3.73-3.67 (m, 1H), 3.52-3.41 (m, 2H), 3.26-3.20 (m, 1H), 2.75-2.70 (m, 2H), 2.66-2.62 (m, 1H), 1.73-1.70 (m,

4H), 1.65-1.52 (m, 11H), 1.44-1.35 (m, 1H), 1.32-1.16 (m, 8H), 1.05-0.88 (m, 11H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 109.6, 70.6, 70.4, 58.8, 54.0 (CH x 2), 34.62 (CH₂ x 2), 34.58 (CH₂ x 2), 26.89 (CH₂ x 2), 26.85 (CH₂ x 2), 26.0 (CH₂ x 2), 23.5, 23.2, 19.0, 12.5, 10.8 (CH₃ x 2) ppm

FTIR (neat): ν = 3445, 2930, 1215, 756 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{44}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 354.3372, found: 354.3374.

***N*-(1,1-Bis(pentyloxy)butan-2-yl)-*N*-cyclohexylcyclohexanamine (70e):**

The product was prepared by above general procedure and the same chemicals except employing *n*-pentanol (1.1 g, 12.5 mmol, 25 equiv.). After 48 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane = 1:100, v/v/v) to afford the desired product **70e** as a light yellowish oil (25 mg, 12% yield).

R_f = 0.90 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.24 (d, J = 2.11 Hz, 1H), 3.75-3.69 (m, 1H), 3.55-3.44 (m, 2H), 3.28-3.23 (m, 1H), 2.74-2.69 (m, 2H), 2.65-2.61 (m, 1H), 1.77-1.66 (m, 4H), 1.62-1.16 (m, 32H), 1.04-0.95 (m, 2H), 0.92-0.88 (m, 9H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 109.7, 68.9 (CH x 2), 58.9, 54.0 (CH x 2), 34.64 (CH₂ x 2), 34.58 (CH₂ x 2), 29.9, 29.7, 28.5, 28.4, 26.90 (CH₂ x 2), 26.86 (CH₂ x 2), 26.1 (CH₂ x 2), 22.6, 22.5, 19.0, 14.1 (CH₃ x 2), 12.5 ppm

FTIR (neat): ν = 3460, 2930, 1215, 758 cm^{-1} .

HRMS (ESI, m/z): calcd for $C_{26}H_{52}NO_2^+$ $[M+H]^+$ 410.3998, found: 410.3997.

***N*-Cyclohexyl-*N*-(1,1-dimethoxyhexan-2-yl)cyclohexanamine (70f):**

The product was prepared by above general procedure and the same chemicals except employing *N*-cyclohexyl-*N*-hexylcyclohexanamine **69b** (0.132 g, 0.5 mmol). After 6 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70f** as a light yellowish oil (0.105 g, 65% yield).

R_f = 0.81 (hexane: ethyl acetate = 3:1).

1H NMR (CDCl₃, 400 MHz) δ 4.14 (brs, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.75-2.69 (m, 3H), 1.73-1.72 (m, 4H), 1.57-1.15 (m, 20H), 1.04-0.96 (m, 2H), 0.88 (t, J = 7.24 Hz, 3H) ppm.

^{13}C NMR (CDCl₃, 100 MHz) δ 112.4, 56.69, 56.63, 56.58, 54.1 (CH x 2), 34.6 (CH₂ x 4), 29.9, 26.8 (CH₂ x 4), 26.0 (CH₂ x 2), 25.9, 23.1, 14.2 ppm

FTIR (neat): ν = 2930, 1215, 754, 669, 494 cm⁻¹.

HRMS (ESI, m/z): calcd for $C_{20}H_{40}NO_2^+$ $[M+H]^+$ 326.3059, found: 326.3066.

***N*-Cyclohexyl-*N*-(1,1-dimethoxydodecan-2-yl)cyclohexanamine (70g):**

The product was prepared by above general procedure and the same chemicals except employing *N*-cyclohexyl-*N*-dodecylcyclohexanamine **69c** (0.174 g, 0.5 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70g** as a light yellowish oil (0.125 g, 61% yield).

R_f = 0.83 (hexane: ethyl acetate = 3:1); ^1H NMR (CDCl_3 , 400 MHz) δ 4.14 (d, J = 1.57 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.74-2.71 (m, 3H), 1.57-1.21 (m, 32H), 1.04-0.98 (m, 2H), 0.87 (t, J = 7.01 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 112.4, 56.67, 56.61 ($\text{CH}_2 \times 2$), 54.1 ($\text{CH} \times 2$), 34.59 ($\text{CH}_2 \times 2$), 34.56 ($\text{CH}_2 \times 2$), 31.9, 30.1, 29.7, 29.6 ($\text{CH}_2 \times 2$), 29.4, 27.6, 26.8 ($\text{CH}_2 \times 4$), 26.2, 26.0 ($\text{CH}_2 \times 2$), 22.7, 14.1 ppm

FTIR (neat): ν = 2930, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{26}\text{H}_{52}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 410.3998, found: 410.3998.

Methyl 4-(dicyclohexylamino)-5,5-dimethoxypentanoate (70h):

The product was prepared by above general procedure and the same chemicals except employing methyl 5-(dicyclohexylamino)pentanoate **69d** (0.147 g, 0.5 mmol). After 12 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:2:100, v/v/v) to afford the desired product **70h** as a light yellowish oil (0.106 g, 60% yield).

R_f = 0.65 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.18 (d, J = 1.97 Hz, 1H), 3.64 (s, 3H), 3.42 (s, 3H), 3.41 (s, 3H), 2.85-2.81 (m, 1H), 2.73-2.68 (m, 2H), 2.53-2.28 (m, 2H), 1.87-1.79 (m, 1H), 1.74-1.54 (m, 9H), 1.47-1.45 (m, 2H), 1.33-1.16 (m, 8H), 1.04-0.94 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 174.9, 111.4, 56.4 ($\text{CH}_2 \times 2$), 55.7, 54.1 ($\text{CH} \times 2$), 51.3, 34.6 ($\text{CH}_2 \times 2$), 34.3 ($\text{CH}_2 \times 2$), 31.8, 26.8 ($\text{CH}_2 \times 2$), 26.7 ($\text{CH}_2 \times 2$), 25.9 ($\text{CH}_2 \times 2$), 21.7 ppm

FTIR (neat): ν = 2930, 1730, 1449, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{38}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 356.2801, found: 356.2799.

***N*-(6-Bromo-1,1-dimethoxyhexan-2-yl)-*N*-cyclohexylcyclohexanamine (70i):**

The product was prepared by above general procedure and the same chemicals except employing *N*-(6-bromohexyl)-*N*-cyclohexylcyclohexanamine **69e** (0.172 g, 0.5 mmol). After 6 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70i** as a light yellowish oil (0.109 g, 54% yield).

R_f = 0.75 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.15 (brs, 1H), 3.44-3.39 (m, 8H), 2.74-2.72 (m, 3H), 1.89-1.82 (m, 2H), 1.72-1.64 (m, 5H), 1.57-1.55 (m, 4H), 1.48-1.18 (m, 13H), 1.00-0.98 (m, 2H) ppm

^{13}C NMR (CDCl_3 , 100 MHz) δ 112.2, 56.8, 56.7, 56.5, 54.1 ($\text{CH} \times 2$), 34.6 ($\text{CH}_2 \times 2$), 34.5 ($\text{CH}_2 \times 2$), 34.2, 33.3, 26.8 ($\text{CH}_2 \times 4$), 26.2, 26.0 ($\text{CH}_2 \times 2$), 25.2 ppm

FTIR (neat): ν = 2930, 1449, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $C_{20}H_{39}BrNO_2^+$ $[M+H]^+$ 404.2164, found: 404.2164.

***N*-Cyclohexyl-*N*-(1,1-dimethoxyhex-5-en-2-yl)cyclohexanamine (70j):**

The product was prepared by above general procedure and the same chemicals except employing *N*-cyclohexyl-*N*-(hex-5-enyl)cyclohexanamine **69f** (0.131 g, 0.5 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70j** as a light yellowish oil (98 mg, 61% yield).

R_f = 0.5 (hexane: ethyl acetate = 3:1).

1H NMR ($CDCl_3$, 400 MHz) δ 5.87-5.80 (m, 1H), 5.00 (d, J = 17.18 Hz, 1H), 4.90 (d, J = 10.22 Hz, 1H), 4.15 (d, J = 1.89 Hz, 1H), 3.42 (s, 3H), 3.41 (s, 3H), 2.78-2.70 (m, 3H), 2.28-2.20 (m, 1H), 2.02-1.90 (m, 1H), 1.74-1.72 (m, 4H), 1.57-1.42 (m, 8H), 1.32-1.17 (m, 8H), 1.04-0.95 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.9, 113.6, 112.1, 56.6 (CH_2 x 2), 56.1, 54.1 (CH x 2), 34.6 (CH_2 x 2), 34.4 (CH_2 x 2), 31.6, 26.8 (CH_2 x 4), 26.0 (CH_2 x 2), 25.5 ppm

FTIR (neat): ν = 2930, 1638, 1215, 754, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $C_{20}H_{38}NO_2^+$ $[M+H]^+$ 324.2903, found: 324.2901.

2-(4-(Dicyclohexylamino)-5,5-dimethoxypentyl)isoindoline-1,3-dione (70k):

The product was prepared by above general procedure and the same chemicals except employing 2-(5-(dicyclohexylamino)pentyl)isoindoline-1,3-dione **69g** (0.198 g, 0.5 mmol). After 20 h, the crude product was purified by flash column chromatography (silica gel; diethyl ether/hexane = 2:100, v/v) to afford the desired product **70k** as a light yellowish oil (0.128 g, 56% yield).

R_f = 0.50 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 7.82-7.78 (m, 2H), 7.69-7.64 (m, 2H), 4.12 (d, J = 1.94 Hz, 1H), 3.66-3.62 (m, 2H), 3.40 (s, 3H), 3.73 (s, 3H), 2.76-2.66 (m, 3H), 1.96-1.85 (m, 1H), 1.74-1.34 (m, 13H), 1.27-1.12 (m, 8H), 1.00-0.89 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 168.4 (C x 2), 133.6 (CH x 2), 132.2 (C x 2), 123.0 (CH x 2), 111.8, 56.7, 56.5, 56.2, 54.0 (CH x 2), 38.4, 34.6 (CH_2 x 2), 34.3 (CH_2 x 2), 26.69 (CH_2 x 2), 26.66 (CH_2 x 2), 26.5, 25.9 (CH_2 x 2), 23.3 ppm.

FTIR (neat): ν = 3460, 2930, 1709, 1396, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{41}\text{N}_2\text{O}_4^+$ [$\text{M}+\text{H}$] $^+$ 457.3066, found: 457.3066.

4-(Dicyclohexylamino)-5,5-dimethoxypentyl acetate (**70l**):

The product was prepared by above general procedure and the same chemicals except employing 5-(dicyclohexylamino)pentyl acetate **69h** (0.154 g, 0.5 mmol). After 20 h,

the crude product was purified by flash column chromatography (silica gel; diethyl ether/hexane = 2:100, v/v) to afford the desired product **70l** as a light yellowish oil (0.101 g, 55% yield).

R_f = 0.60 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.15 (d, J = 1.77 Hz, 1H), 4.08-3.98 (m, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 2.75-2.69 (m, 3H), 2.01 (s, 3H), 1.90-1.80 (m, 1H), 1.74-1.71 (m, 4H), 1.57-1.36 (m, 9H), 1.31-1.17 (m, 8H), 1.04-0.94 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 171.3, 112.0, 65.2, 56.8, 56.7, 56.4, 54.0 (CH x 2), 34.6 (CH_2 x 2), 34.4 (CH_2 x 2), 26.73 (CH_2 x 4), 26.67, 25.9 (CH_2 x 2), 22.5, 21.0 ppm.

FTIR (neat): ν = 2930, 1730, 1215, 756, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{40}\text{NO}_4^+$ [$\text{M}+\text{H}$] $^+$ 370.2957, found: 370.2952.

***N*-(1,1-Dimethoxybutan-2-yl)-*N*-isopropylcyclohexanamine (**70m**):**

The product was prepared by above general procedure and the same chemicals except employing *N*-butyl-*N*-isopropylcyclohexanamine **69i** (98 mg, 0.5 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70m** as a light yellowish oil (58 mg, 45% yield).

R_f = 0.67 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.15 (d, J = 2.09 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.33-3.23 (m, 1H), 2.72-2.64 (m, 2H), 1.75-1.72 (m, 2H), 1.61-1.18 (m, 10H), 0.99-0.95 (m, 6H), 0.90 (t, J = 7.43 Hz, 3H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 111.9, 57.7, 56.6, 56.5, 53.5, 44.9, 34.4, 34.3, 26.8, 26.0, 23.5, 23.0, 18.9, 12.4 ppm.

FTIR (neat): ν = 2930, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{32}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 258.2433, found: 258.2433.

***N*-Butyl-*N*-(1,1-dimethoxybutan-2-yl)butan-1-amine (70n):**

The product was prepared by above general procedure and the same chemicals except employing tributylamine **69j** (92.5 mg, 0.5 mmol). After 72 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70n** as a light yellowish oil (15 mg, 12% yield).

R_f = 0.55 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.22 (d, J = 5.44 Hz, 1H), 3.375 (s, 3H), 3.370 (s, 3H), 2.56-2.44 (m, 5H), 1.51-1.42 (m, 1H), 1.41-1.22 (m, 9H), 0.95-0.88 (m, 9H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 107.6, 63.0, 54.71, 54.67, 50.9 ($\text{CH}_2 \times 2$), 32.0 ($\text{CH}_2 \times 2$), 20.5 ($\text{CH}_2 \times 2$), 20.0, 14.2 ($\text{CH}_3 \times 2$), 12.1 ppm.

FTIR (neat): ν = 2930, 1215, 754 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{32}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 246.2433, found: 246.2443.

Methyl 4-(((S)-1-(tert-butyldimethylsilyloxy)-3-methylbutan-2-yl)(isopropyl)amino)-5,5-dimethoxypentanoate (70p):

The product was prepared by above general procedure and the same chemicals except employing (S)-methyl 5-((1-(tert-butyldimethylsilyloxy)-3-methylbutan-2-yl)(isopropyl)amino)pentanoate **69k** (0.186 g, 0.5 mmol). After 48 h, the crude product was purified by flash column chromatography (silica gel; diethyl ether/hexane = 1:100, v/v) to afford the desired product **70p** as a light yellowish oil (0.112 g, 52% yield, 61:39 dr).

One isomer (major):

R_f = 0.72 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.18 (d, J = 1.89 Hz, 1H), 3.72-3.58 (m, 2H), 3.64 (s, 3H), 3.44-3.35 (m, 7H), 3.09-3.05 (m, 1H), 2.59-2.55 (m, 1H), 2.50 (t, J = 7.71 Hz, 2H), 2.00-1.86 (m, 2H), 1.78-1.69 (m, 1H), 1.00 (d, J = 6.64 Hz, 6H), 0.97 (d, J = 6.86 Hz, 3H), 0.92 (d, J = 6.68 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.8, 112.5, 64.3, 61.5, 56.1, 56.0, 54.5, 51.2, 46.1, 31.7, 29.5, 25.9 ($\text{CH}_3 \times 3$), 23.5, 23.4, 22.8, 22.2, 19.8, 18.2, -5.6, -5.8 ppm

FTIR (neat): ν = 3019, 1730, 1215, 756, 669, 484 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{48}\text{NO}_5\text{Si}^+$ $[\text{M}+\text{H}]^+$ 434.3302, found: 434.3298.

$[\alpha]_D^{20}$ = - 31.0° (c = 2.2, CH_2Cl_2).

Another isomer (minor):

R_f = 0.71 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.31 (d, J = 1.44 Hz, 1H), 3.79-3.75 (m, 1H), 3.64 (s, 3H), 3.55-3.51 (m, 1H), 3.50-3.44 (m, 4H), 3.37 (s, 3H), 2.90-2.88 (m, 1H), 2.60-2.48 (m, 2H), 2.40-2.32 (m, 1H), 2.00-1.83 (m, 2H), 1.62-1.63 (m, 1H), 1.03 (d, J = 6.49 Hz, 3H), 0.98 (d, J = 6.76 Hz, 3H), 0.93-0.89 (m, 15H), 0.049-0.045 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.8, 110.4, 64.8, 61.4, 56.6, 56.0, 54.9, 51.3, 45.9, 32.0, 28.3, 25.9 ($\text{CH}_3 \times 3$), 23.6, 22.8, 22.4, 21.9, 20.3, 18.2, -5.6, -5.8 ppm.

FTIR (neat): ν = 3019, 1730, 1215, 756, 669, 484 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{48}\text{NO}_5\text{Si}^+$ $[\text{M}+\text{H}]^+$ 434.3302, found: 434.3298.

***N,N*-Diisobutyl-1,1-dimethoxyhexan-2-amine (70q):**

The product was prepared by above general procedure and the same chemicals except employing *N,N*-diisobutylhex-1-en-1-amine **71a** (0.105 g, 0.5 mmol). After 5 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70q** as a light yellowish oil (85 mg, 62% yield).

R_f = 0.65 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.22 (d, J = 4.67 Hz, 1H), 3.371-3.368 (m, 6H), 2.59-2.55 (m, 1H), 2.34-2.17 (m, 4H), 1.66-1.49 (m, 3H), 1.45-1.24 (m, 5H), 0.90-0.84 (m, 15H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 107.8, 61.6, 60.6 ($\text{CH}_2 \times 2$), 54.8 ($\text{CH}_3 \times 2$), 29.8, 27.2 ($\text{CH} \times 2$), 26.6, 23.0, 21.0 ($\text{CH}_3 \times 2$), 20.8 ($\text{CH}_3 \times 2$), 14.1 ppm.

FTIR (neat): ν = 2955, 1467, 1215, 756, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $C_{16}H_{36}NO_2^+$ $[M+H]^+$ 274.2746, found: 274.2750.

V. Mechanistic study

(1) Isotope labeling experiment

Synthesis of 4-(dicyclohexylamino) butyl-D8 acetate (69l) and Spectroscopic Information

4-(Dicyclohexylamino)butyl-D8 acetate (69l):

The product was prepared by above general procedure according the literatures,⁶⁴ affording the product as colorless oil.

1H NMR (400 MHz, $CDCl_3$): δ 2.48-2.43 (m, 2H), 2.00 (s, 3H), 1.71-1.64 (m, 8H), 1.57-1.54 (m, 2H), 1.23-1.12 (m, 8H), 1.06-0.97 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 57.8 (CH x 2), 31.7 (CH_2 x 4), 26.4 (CH_2 x 4), 26.2 (CH_2 x 2), 20.9 ppm.

HRMS (ESI, m/z): calcd for $C_{18}H_{26}D_8NO_2^+$ $[M+H]^+$ 304.3092, found: 304.3089.

3-(Dicyclohexylamino)-4,4-dimethoxybutyl-D5 acetate (70r):

⁶⁴ Goldsmith, D. J.; Kennedy E.; Campbell, R. G. *J. Org. Chem.* **1975**, *40*, 3571.

The product was prepared by above general procedure and the same chemicals except employing 4-(dicyclohexylamino)butyl-D8 acetate **69l** (0.151 g, 0.5 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane = 0.1:1:100, v/v/v) to afford the desired product **70r** as a light yellowish oil (86 mg, 48% yield).

R_f = 0.60 (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 3.42 (s, 3H), 3.40 (s, 3H), 2.92 (s, 0.74H), 2.72-2.66 (m, 2H), 2.02 (s, 3H), 1.74-1.69 (m, 4H), 1.56-1.54 (m, 4H), 1.50-1.42 (m, 2H), 1.30-1.16 (m, 8H), 1.04-0.94 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 171.2, 56.4 (CH x 2), 54.2 (CH x 2), 52.8, 34.4 (CH₂ x 2), 34.3 (CH₂ x 2), 26.72 (CH₂ x 2), 26.69 (CH₂ x 2), 25.9 (CH₂ x 2), 21.1 ppm.

FTIR (neat): ν = 2930, 1215, 754, 669, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{33}\text{D}_5\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 361.3115, found: 361.3109.

***N*-Cyclohexyl-*N*-(1,1-dimethoxy- ^{13}C 2-butan-2-yl)cyclohexanamine (70s):**

R_f = 0.79 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.16-4.13 (m, 1H), 3.59 (d, $J = 5.96$ Hz, 3H), 3.24 (d, $J = 6.40$ Hz, 3H), 2.73-2.64 (m, 3H), 1.74-1.70 (m, 4H), 1.57-1.17 (m, 16H), 1.05-0.94 (m, 2H), 0.90 (t, $J = 7.40$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 112.2, 56.6, 56.62 ($^{13}\text{CH}_3$), 56.56 ($^{13}\text{CH}_3$), 54.1 (CH x 2), 34.6 (CH_2 x 2), 34.5 (CH_2 x 2), 26.8 (CH_2 x 4), 26.0 (CH_2 x 2), 18.9, 12.4 ppm

FTIR (neat): $\nu = 2930, 1215, 754 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{16}^{13}\text{C}_2\text{H}_{36}\text{NO}_2^+ [\text{M}+\text{H}]^+$ 300.2813, found: 300.2822.

***N*-Cyclohexyl-*N*-(1,1-dimethoxybutan-2-yl)-D7-cyclohexanamine (70t):**

$R_f = 0.79$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 4.14 (s, 1H), 2.73-2.66 (m, 2H), 2.65-2.63 (m, 0.25H), 1.74-1.71 (m, 4H), 1.57-1.17 (m, 16H), 1.05-0.95 (m, 2H), 0.90 (t, $J = 7.40$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 112.1, 58.4, 54.1 (CH x 2), 34.6 (CH_2 x 2), 34.5 (CH_2 x 2), 26.8 (CH_2 x 4), 26.0 (CH_2 x 2), 18.9, 12.4 ppm

FTIR (neat): $\nu = 3447, 2930, 1635, 1215, 752 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{29}\text{D}_7\text{NO}_2^+ [\text{M}+\text{H}]^+$ 305.3185, found: 305.3181.

***N,N*-Diisobutyl-1,1-dimethoxyhexan-D7-2-amine (70u):**

$R_f = 0.65$ (hexane: ethyl acetate = 3:1).

^1H NMR (400 MHz, CDCl_3): δ 4.22 (s, 1H), 2.58-2.51 (m, 0.25H), 2.33-2.17 (m, 4H), 1.66-1.48 (m, 3H), 1.44-1.24 (m, 5H), 0.90-0.84 (m, 15H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 107.6, 60.6 ($\text{CH}_2 \times 2$), 29.8, 27.2 ($\text{CH} \times 2$), 26.5, 23.0, 21.0 ($\text{CH}_3 \times 2$), 20.6 ($\text{CH}_3 \times 2$), 14.1 ppm.

FTIR (neat): $\nu = 3445, 2955, 1633, 1215, 756 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{29}\text{D}_7\text{NO}_2^+ [\text{M}+\text{H}]^+ 281.3185$, found: 281.3189.

(2) Isolation of the intermediate

N,N-dicyclohexyl-*n*-butylamine **69a** (0.118 g, 0.5 mmol) was added to a mixture of CuBr_2 (28 mg, 0.125 mmol), and TMEDA (29 mg, 0.25 mmol) in methanol (0.2 mL)/acetonitrile (2.0 mL) in air at room temperature. The mixture was stirred at 40 °C using O_2 balloon until *N,N*-dicyclohexyl-*n*-butylamine **69a** was completely converted by TLC detection. A white solid (about 10 mg, about 8% yield) was isolated from the reaction mixture by a simple filtration and washed using MeCN (1 mL $\times$ 3). Then the white solid was dissolved in methanol, hexane was added into it, and solvent was evaporated to obtain the crystal ($\text{Cy}_2\text{NH}_2\text{Br}$, CCDC 780729).

Dicyclohexylammonium bromide:

^1H NMR (CD_3OD , 400 MHz) δ 3.23-3.18 (m, 2H), 2.09-2.07 (m, 4H), 1.90-1.86 (m, 4H), 1.75-1.71 (m, 2H), 1.41-1.20 (m, 10H) ppm

^{13}C NMR (CD_3OD , 100 MHz) δ 54.6 ($\text{CH} \times 2$), 30.6 ($\text{CH}_2 \times 4$), 26.2 ($\text{CH}_2 \times 2$), 25.5 ($\text{CH}_2 \times 4$) ppm.

(3) Probable reasons for the formation of compound (70v)

In the mechanistic study, the results of trapping and control experiments (Scheme 2.2, eq. 2.1) supported the existence of the reversible step **1** in the reaction systems. Furthermore, double bond cleavage of enamines (Scheme 2.5, step **3**) using copper-dioxygen catalytic systems had previously been reported. The formation of *N,N*-dicyclohexylformamide and dicyclohexylamine had been detected in the reaction as the byproducts. In order to better understand the formation of compound **70v** (one carbon shortened compound), the following experiments were carried out using one carbon less aldehyde with dicyclohexylamine, the desired compound **70v** (one carbon shortened compound) was obtained.

(4) Experiment for excluding the impossible intermediate

***N*-Cyclohexyl-*N*-(1-methoxybutan-2-yl)cyclohexanamine:**

$R_f = 0.79$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 3.41-3.38 (m, 1H), 3.30 (s, 3H), 3.14 (t, $J = 8.72$ Hz, 1H), 2.75-2.68 (m, 1H), 2.59-2.50 (m, 2H), 1.73-1.70 (m, 4H), 1.58-1.50 (m, 7H), 1.35-1.15 (m, 9H), 1.05-0.94 (m, 2H), 0.89 (t, $J = 7.37$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 77.9, 58.9, 56.2, 54.1 (CH x 2), 34.61 (CH_2 x 2), 34.55 (CH_2 x 2), 26.87 (CH_2 x 2), 26.78 (CH_2 x 2), 25.9 (CH_2 x 2), 23.6, 12.1 ppm

FTIR (neat): $\nu = 3458, 2932, 1663, 1215, 756 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{34}\text{NO}^+ [\text{M}+\text{H}]^+$ 268.2640, found: 268.2649.

not supported process:

2.5.2 Copper-Catalyzed Oxidative Rearrangement of Enamines for the Synthesis of α -Amino Acetals in Molecular Oxygen

I. General procedure:

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Copper salts were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. Enamines **71** were synthesized according to literatures.⁶⁵

II. General experimental procedure for copper-catalyzed oxidative rearrangement of enamine for direct synthesis α -amino acetals under molecular oxygen:

N,N-diallylhex-1-en-1-amine **86b** (90 mg, 0.5 mmol) was added to a mixture of CuBr_2 (28 mg, 0.125 mmol), and TMEDA (29 mg, 0.25 mmol) in methanol (0.5 mL)/acetonitrile (2.0 mL) in air at room temperature. The mixture was stirred at $40\text{ }^\circ\text{C}$ using O_2 balloon for 2 hours. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72a** as a light yellowish oil (85 mg, 70% yield).

N,N-diallyl-1,1-dimethoxyhexan-2-amine (**72a**):

⁶⁵ (a) Hodgson, D. M.; Bray, C. D.; Kindon, N. D.; Reynolds, N. J.; Coote, S. J.; Um, J. M.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 1019. (b) Curphey, T. J.; Hung, J. C. Y. *Chem. Commun.* **1967**, 510. (c) Curphey, T. J.; Hung, J. C. Y.; Chu, C. C. C. *J. Org. Chem.* **1975**, *40*, 607.

R_f = 0.64 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 5.83-5.73 (m, 2H), 5.14 (d, J = 16.80 Hz, 2H), 5.04 (d, J = 10.00 Hz, 2H), 4.24 (d, J = 5.20 Hz, 1H), 3.362-3.359 (m, 6H), 3.26 (dd, J = 14.80, 5.20 Hz, 2H), 3.14 (dd, J = 14.40, 6.94 Hz, 2H), 2.80-2.76 (m, 1H), 1.42-1.37 (m, 3H), 1.36-1.23 (m, 3H), 0.89 (t, J = 7.16 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 138.2 (CH x 2), 115.8 (CH_2 x 2), 107.3, 59.1, 54.8, 54.6, 53.5 (CH_2 x 2), 29.4, 26.3, 22.8, 14.1 ppm

FTIR (neat): ν = 2955, 1641, 1215, 1111, 1074, 918, 758 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{28}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 242.2120, found: 242.2117.

***N*-allyl-*N*-benzyl-1,1-dimethoxyhexan-2-amine (72b):**

Compound **72b** was prepared accordingly to the general experimental procedure using the same chemicals except enamine, *N*-allyl-*N*-benzylhex-1-en-1-amine **71c** (0.114 g, 0.5 mmol) was employed instead. After 2 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72b** as a light yellowish oil (0.105 g, 72% yield).

R_f = 0.69 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.35-7.33 (m, 2H), 7.30-7.26 (m, 2H), 7.24-7.18 (m, 1H), 5.84-5.74 (m, 1H), 5.13 (d, J = 17.20 Hz, 1H), 5.05 (d, J = 10.00 Hz, 1H), 4.31 (d, J = 5.20 Hz, 1H), 3.75 (dd, J = 72.80, 14.00 Hz, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 3.25 (dd, J = 14.20, 5.60 Hz, 1H), 3.17 (dd, J = 14.40, 7.20 Hz, 1H), 2.80-2.76 (m, 1H), 1.52-1.42 (m, 3H), 1.30-1.23 (m, 3H), 0.88 (t, J = 7.20 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.1, 138.1, 128.7 (CH x 2), 128.0 (CH x 2), 126.5, 116.1, 107.3, 58.6, 54.7, 54.5, 54.4, 53.5, 29.3, 26.3, 22.8, 14.1 ppm

FTIR (neat): ν = 3443, 2955, 1641, 1215, 1109, 1072, 758 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 292.2277, found: 292.2273.

***N,N*-dibenzyl-1,1-dimethoxyhexan-2-amine (72c):**

Compound **72c** was prepared accordingly to the general experimental procedure using the same chemicals except enamine, *N,N*-dibenzylhex-1-en-1-amine **71d** (0.139 g, 0.5 mmol) was employed instead. After 2 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72c** as a light yellowish oil (0.128 g, 75% yield).

R_f = 0.67 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.37-7.35 (m, 4H), 7.30-7.27 (m, 4H), 7.23-7.18 (m, 2H), 4.37 (d, J = 5.20 Hz, 1H), 3.74 (dd, J = 50.60, 13.60 Hz, 4H), 3.35 (s, 3H), 3.31 (s, 3H), 2.73-2.68 (m, 1H), 1.59-1.39 (m, 3H), 1.26-1.10 (m, 3H), 0.85 (t, J = 7.60 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.8 (C x 2), 129.0 (CH x 4), 128.0 (CH x 4), 126.6 (CH x 2), 107.5, 57.4, 54.8, 54.5 (CH_2 x 2), 54.3, 29.2, 26.2, 22.7, 14.1 ppm

FTIR (neat): ν = 2955, 1215, 758 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 342.2433, found: 342.2436.

***N,N*-diallyl-1,1-dimethoxy-3-methylbutan-2-amine (72d):**

Compound **72d** was prepared accordingly to the general experimental procedure using the same chemicals except enamine, *N,N*-diallyl-3-methylbut-1-en-1-amine **71f** (82 mg, 0.5 mmol) was employed instead. After 2 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72d** as a light yellowish oil (70 mg, 62% yield).

R_f = 0.74 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 5.84-5.74 (m, 2H), 5.13 (d, J = 17.60 Hz, 2H), 5.03 (d, J = 10.00 Hz, 2H), 4.35 (d, J = 4.44 Hz, 1H), 3.33 (m, 6H), 3.33-3.32 (m, 2H), 3.12-3.06 (m, 2H), 2.51-2.48 (m, 1H), 1.96-1.83 (m, 1H), 0.94 (d, J = 6.80 Hz, 3H), 0.92 (d, J = 6.80 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 138.5 (CH x 2), 115.7 (CH_2 x 2), 106.9, 63.6, 55.1, 54.6, 54.5 (CH_2 x 2), 27.5, 20.9, 20.3 ppm

FTIR (neat): ν = 3456, 2955, 1641, 1215, 1113, 1074, 918, 758 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 228.1964, found: 228.1969.

N-allyl-*N*-(1,1-dimethoxy-3-phenylpropan-2-yl)prop-2-en-1-amine (**72e**):

Compound **72e** was prepared accordingly to the general experimental procedure using the same chemicals except enamine, *N,N*-diallyl-3-phenylprop-1-en-1-amine **71f** (0.106 g, 0.5 mmol) was employed instead. After 2 h, the crude product was purified

by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72e** as a light yellowish oil (70 mg, 51% yield).

R_f = 0.64 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.27-7.14 (m, 5H), 5.65-5.55 (m, 2H), 5.05-4.96 (m, 4H), 4.29 (d, J = 4.80 Hz, 1H), 3.383-3.377 (m, 6H), 3.19 (d, J = 6.00 Hz, 4H), 3.16-3.11 (m, 1H), 2.81 (dd, J = 14.00, 4.40 Hz, 1H), 2.71 (dd, J = 13.80, 8.80 Hz, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.1, 137.8 (CH x 2), 129.5 (CH x 2), 127.8 (CH x 2), 125.5, 116.0 (CH_2 x 2), 106.9, 61.1, 54.8, 54.7, 53.5 (CH_2 x 2), 32.8 ppm

FTIR (neat): ν = 3017, 1215, 1125, 756 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 276.1964, found: 276.1964.

(*Z*)-*N,N*-diallyl-1,1-dimethoxyhept-4-en-2-amine (**72f**):

Compound **72f** was prepared accordingly to the general experimental procedure using the same chemicals except enamine, (4*Z*)-*N,N*-diallylhepta-1,4-dien-1-amine **71g** (95 mg, 0.5 mmol) was employed instead. After 2 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72f** as a light yellowish oil (76 mg, 60% yield).

R_f = 0.69 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 5.83-5.73 (m, 2H), 5.43-5.36 (m, 2H), 5.15 (d, J = 16.00 Hz, 2H), 5.05 (d, J = 10.00 Hz, 2H), 4.26 (d, J = 4.80 Hz, 1H), 3.28 (s, 3H),

3.21 (s, 3H), 3.23-3.21 (m, 4H), 2.91-2.87 (m, 1H), 2.24-2.02 (m, 2H), 2.07-2.02 (m, 2H), 0.96 (t, $J = 7.53$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 138.0 (CH x 2), 131.8, 127.5, 116.0 (CH_2 x 2), 107.0, 59.6, 54.9, 54.7, 53.7 (CH_2 x 2), 24.3, 20.6, 14.2 ppm

FTIR (neat): $\nu = 2963, 1641, 1215, 1113, 1074, 920, 756 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 254.2120, found: 254.2122.

CHAPTER 3

Copper or Indium-Catalyzed α -Amination of Aldehydes with a Nucleophilic Nitrogen

Source

CHAPTER 3 COPPER OR INDIUM-CATALYZED α -AMINATION OF ALDEHYDES WITH A NUCLEOPHILIC NITROGEN SOURCE

3.1 OVERVIEW

Amino acid derivatives are very useful intermediates for the preparation of biologically active molecules.² In particular, to complement those α -amino acids already present in our biological systems, much efforts have been directed towards the synthesis of unnatural analogs.⁴⁻⁹ Therefore, direct introduction of a nitrogen functional group in the α -position of aldehydes for the synthesis of valuable chemicals such as α -amino aldehydes, α -amino acetals and α -amino alcohols stands out to be the most attractive choice. Common strategy for the synthesis of α -amino aldehydes involves the use of enolate reactions with a nitrogen electrophile ($[N]^+$) to afford the desired product (Scheme 3.1).¹⁶⁻²⁵ In contrast, our strategy is to realize the synthesis of α -amino acid derivatives employing a more easily available nitrogen nucleophile ($[N]^-$) *via* the oxidative rearrangement of enamine intermediate (Scheme 3.1).

Scheme 3.1 Different strategy for the synthesis of α -amino aldehydes

In this chapter, we described the synthesis of α -amino acetals using the strategy of α -amination of aldehydes with a nucleophilic nitrogen source by examining the catalytic systems of CuI(Br)-TBHP, InI(Br)-Na₂CO₃·1.5H₂O₂, I₂ (I)-Na₂CO₃·1.5H₂O₂ and RI-Na₂CO₃·1.5H₂O₂. In addition, further mechanistic studies led to the possible rationalization of this reaction.

3.2 CuI(Br)-TBHP CATALYTIC SYSTEM

3.2.1 INTRODUCTION

In Chapter 2, oxidative rearrangement of tertiary amines and enamines with readily removable *N*-protecting groups for the synthesis of α -amino acetals were developed using copper-dioxygen catalytic system (Scheme 3.2). In that study, trapping, control and isotope-labeling experiments led to the proposal of a rearrangement mechanism involving oxidation of aliphatic C–H bonds. However, tertiary and secondary amines with readily removable groups as the starting materials were unable to afford the corresponding α -amino acetals in the copper-dioxygen catalytic systems (CuBr₂/TMEDA/O₂).

Scheme 3.2 Different pathways for the synthesis of α -amino acetals

Taking into account that α -amino acid derivatives with *N,N*-dibenzyl group are not easily epimerized⁶⁶, our objective is to realize the synthesis of α -amino acetals directly employing dibenzylamine as a nucleophilic nitrogen source. Here we report a copper-catalyzed α -amination of aliphatic aldehydes using nucleophilic secondary amines with readily removable *N*-protecting groups as a nitrogen source for the synthesis of α -amino acetals. This reaction can be carried out under very mild conditions, furnishing the desired products in moderate to good yields. Furthermore, easily deprotectable enamine, which is confirmed as the intermediate in this reaction, was also directly converted into α -amino acetals *via* oxidative rearrangement.

3.2.2 RESULTS AND DISCUSSION

In our initial optimization studies, dibenzylamine **73a**, butyraldehyde **74a**, and methanol were selected as the model reaction system. The results are summarized in Table 3.1. When *tert*-butyl hydroperoxide (~5.5 M in decane) was used as the oxidant (Table 3.1, entry 2), the desired product **90a** was obtained in 80% isolated yield. It should be noted that the reaction did not proceed without copper catalyst (Table 3.1, entry 3). Other peroxides such as di-*tert*-butyl peroxide, *tert*-butyl benzoylperoxide were also screened, but the product **90a** was formed either in trace amount (Table 3.1, entry 4) or in low yield (Table 3.1, entry 5). It is noteworthy that the reaction proceeded even at room temperature without a significant decrease in yield (Compare Table 3.1, entry 2 *vs* 6). When the amount of copper(I) iodide was reduced from 0.4 equiv to 0.2 equiv (Table 3.1, entry 7), the reaction still proceeded but a longer reaction time (72 h) was required to furnish the product in 57% isolated yield. We

⁶⁶ (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem. Int. Ed.* **1987**, 26, 1141. (b) Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, 1, 375.

also found that the best volume ratio of methanol to acetonitrile was 1:5, 40 °C was the most suitable temperature for this reaction (Table 3.1, entries 2, 6, 8) and excess of aliphatic aldehyde helped to increase the yield (Table 3.1, entries 2, 9, 10).

Table 3.1. Optimization of reaction conditions using dibenzylamine **73a** and butyraldehyde **74a**^a

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> Bn-NH-Bn 73a </div> <div>+</div> <div style="text-align: center;"> $\text{H-C(=O)-CH}_2\text{CH}_2\text{CH}_3$ 74a </div> <div style="text-align: center;"> $\xrightarrow[\text{MeOH}]{\text{Cu catalyst, Oxidant}}$ </div> <div style="text-align: center;"> $\text{MeO-CH(Me)-CH}_2\text{CH}_2\text{CH}_3$ 75a </div> </div>					
Entry	Catalyst	Oxidant	Temp. (°C)	Time (h)	Yield (%) ^b
1	CuI	O ₂ or air (1 atm)	40	24	0
2	CuI	^t BuOOH	40	24	80
3	—	^t BuOOH	40	24	0
4	CuI	^t BuOO ^t Bu	40	24	trace
5	CuI	^t BuOOBz	40	24	50
6	CuI	^t BuOOH	20	96	75
7 ^c	CuI	^t BuOOH	40	72	57
8 ^d	CuI	^t BuOOH	40	24	50
9 ^e	CuI	^t BuOOH	40	24	70
10 ^f	CuI	^t BuOOH	40	24	62

^aReaction conditions: Dibenzylamine (0.5 mmol, 1.0 equiv.), butyraldehyde (0.75 mmol), copper catalyst (0.4 equiv.), oxidant (1.1 equiv.), methanol (0.4 mL), MeCN (2 mL).

^bIsolated yields based on dibenzylamine.

^cThe reaction was performed using 0.2 equiv. CuI.

^dThe reaction was performed using 0.2 mL MeOH.

^eDibenzylamine (0.5 mmol), butyraldehyde (0.5 mmol).

^fDibenzylamine (0.75 mmol), butyraldehyde (0.5 mmol).

Subsequently, the scope of aliphatic aldehydes for this α -amination reaction was investigated. Most relevant examples are shown in Table 3.2. Apparently all the aldehydes having different functionalities gave the desired products in moderate to good yields under the standard reaction conditions (Table 3.2, entries 1-8). Those aliphatic aldehydes with longer or branched carbon chains were also suitable for this reaction (Table 3.2, entries 2-3) though the isolated yields were slightly lower (Compare Table 3.2, entries 2-3 vs 1). The reaction could also tolerate a wide array of functional groups including double bond (Table 3.2, entries 4-5), *tert*-butyl diphenylsilyl (TBDPS) group (Table 3.2, entry 6), phenyl group (Table 3.2, entry 7) and ester group (Table 3.2, entry 8). Further investigation on the scope of the secondary amines, some secondary amines with readily removable *N*-protecting groups such as allyl or benzyl group were chosen for this α -amination reaction. As shown in Table 3.2, entries 1 and 9, this type of substrates were also suitable for this reaction, affording the products in moderate yields.

Table 3.2 Scope of secondary amines and aliphatic aldehydes^{a,b}

^aReaction conditions: secondary amine **73** (0.5 mmol, 1.0 equiv.), aliphatic aldehyde (0.75 mmol), copper(I) iodide (0.4 equiv.), *tert*-butyl hydroperoxide (~5.5 M in decane) (~1.1 equiv.), methanol (0.4 mL), MeCN (2 mL).

^bIsolated yields based on secondary amine **73**.

It was speculated that the enamine could be a plausible intermediate in these transformations. To probe, the enamine (*N,N*-dibenzylhex-1-en-1-amine, **71d**) with readily removable protecting groups was prepared and subjected to the catalytic conditions. It was found that the enamine was indeed a potential precursor and gave α -amino acetal **72c** in good yield (Scheme 3.3).

Scheme 3.3 Oxidative rearrangement of enamine for the synthesis of α -amino acetal

The following deuterium labeling experiments were carried out to explore the mechanism of this α -amination reaction (Scheme 3.4). Using CD₃OD instead of MeOH, the α -amino acetal containing 57% D atom at α -position was produced (Scheme 3.4, eq. 3.2). In contrast, an aldehyde containing only 12% D atom at α -position was obtained in the absence of CuI and peroxide (Scheme 3.4, eq. 3.3).

Scheme 3.4 Deuterium labeling experiments

On the basis of the results of deuterium labeling experiments (Scheme 3.4) and the study about the cationic radical species from enamine,^{46-52, 61} a possible rationalization of this α -amination reaction was shown in Scheme 3.5. In this proposed process, first, enamine **A** was formed from secondary amine and aliphatic aldehyde. Subsequently, the cationic radical species **B** and **C** were produced *via* electron transfer. Finally, oxidative rearrangement afforded the desired product under the assistance of methanol.

Scheme 3.5 Proposed process for this α -amination of aliphatic aldehydes

3.2.3 SUMMARY

In summary, a copper-catalyzed α -amination of aliphatic aldehydes using nucleophilic secondary amines with readily removable *N*-protecting groups as a nitrogen source for the synthesis of α -amino acetals was described. This reaction can be carried out under very mild conditions, generating the desired products in moderate to good yields. Furthermore, the enamine with readily removable *N*-protecting groups, which was confirmed as the intermediate in this reaction, was also directly converted into α -amino acetal *via* oxidative rearrangement.

3.3 InI(Br)-Na₂CO₃·1.5H₂O₂ CATALYTIC SYSTEM

3.3.1 INTRODUCTION

In the past, most of the interest in indium chemistry was attracted towards the applications of indium (III) complexes and indium metal for organic chemistry. Among them, indium (III) complexes have emerged as the useful Lewis acid catalysts for carbon-carbon bond formation and important organic transformations with notable advantages over other Lewis acids, such as, water stability, recyclability and

operational simplicity. Simultaneously, the applications of indium metal in organic synthesis have also been increasing rapidly. Especially noteworthy was the research areas of organoindium reagent and indium-mediated organometallic chemistry, which was even extensively used in aqueous media.⁶⁷

Despite significant progress in the area of indium metal and indium (III) complexes for a number of chemical transformations, the chemistry of indium in its low oxidation state (I)⁶⁸ is still under exploration. As we know, the solid monohalides InCl, InBr, and InI, among which InI is the most stable, are commercially available. Recently, the monohalides had aroused scientific curiosities with the discovery of inorganic materials, indium cluster and chain compounds, and especially organic and organometallic reagents prepared from the indium monohalides.⁶⁹ For the preparation for organic and organometallic reagents from the indium monohalides, the common method is the oxidative insertion into selected bonds (Scheme 3.6) to afford the corresponding In (III) derivatives. Some examples, the cleavage of homolytic E-E bonds (i)⁷⁰ of peroxides, disulfides, and diselenides, bimetallic compounds containing

⁶⁷ (a) Li, C. J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (b) Kumar, S.; Kaur, P.; Kumar, V. *Current Org. Chem.* **2005**, *9*, 1205. (c) Loh, T.-P.; Chua, G.-L. *Chem. Commun.* **2006**, 2739. (d) Yadav, J. S.; Antony, A.; George, J.; Reddy, B. V. S. *Eur. J. Org. Chem.* **2010**, 591. (e) Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13824.

⁶⁸ (a) Pardoe, J. A. J.; Downs, A. J. *Chem. Rev.* **2007**, *107*, 2. (b)eppe, C. *Current Org. Syn.* **2004**, *1*, 227.

⁶⁹ (a) Araki, S.; Hirashita, T. in *Main Group Metals in Organic Synthesis* (Eds.: Yamamota, H.; Oshima, K.), Wiley-VCH, Weinheim, 2004. (b) Andrews, C. G.; Macdonald, C. L. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7453. (c) Green, S. P.; Jones, C.; Stasch, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8618. (d) Gabbaï, F. P.; Chung, S.-C.; Schier, A.; Krüger, S.; Rösch, N.; Schmidbaur, H. *Inorg. Chem.* **1997**, *36*, 5699. (e) Gabbaï, F. P.; Schier, A.; Riede, J.; Schmidbaur, H. *Inorg. Chem.* **1995**, *34*, 3855. (f) Wright, R. J.; Phillips, A. D.; Hardman, N. J.; Power, P. P. *J. Am. Chem. Soc.* **2002**, *124*, 8538. (g) Hill, M. S.; Hitchcock, P. B.; Pongtavornpinyo, R. *Science* **2006**, *311*, 1904.

⁷⁰eppe, C.; Tuck, D. G. *Can. J. Chem.* **1984**, *62*, 2798.

In-M (M = In, Sn) bonds (ii)⁷¹, alkylindium dihalides (iii)⁷² and α -haloalkyl indium(III) derivatives⁷³, were summarized in Scheme 3.6.

Scheme 3.6 Oxidative insertion into selected bonds to afford the corresponding Indium (III) derivatives

Here InX acts as both the electron pair donor and acceptor, owing to the presence of both free *p* orbitals and a non-bonding lone pair of electrons in a metal orbital.⁷⁴

For the utility of indium (I) compounds in organic synthesis, only several examples using stoichiometric or catalytic indium (I) reagents have been reported. With the aim at further exploration of indium (I) chemistry, some organic reactions mediated or catalyzed by indium (I) compounds are briefly introduced as below.

⁷¹ (a)eppe, C.; Tuck, D. G. *Can. J. Chem.* **1984**, 62, 2893. (b) Khan, M. A.;eppe, C.; Tuck, D. G. *Can. J. Chem.* **1984**, 62, 601. (c) Annan, T. A.; Tuck, D. G. *J. Organomet. Chem.* **1987**, 325, 83.

⁷² (a) Khan, M. A.;eppe, C.; Tuck, D. G. *J. Organomet. Chem.* **1985**, 280, 17. (b)eppe, C.; Tuck, D. G.; Victoriano, L. *J. Chem. Soc., Dalton Trans.* **1982**, 2165.

⁷³ (a) Annan, T. A.; Tuck, D. G.; Khan, M. A.;eppe, C. *Organometallics* **1991**, 10, 2159. (b) de Carvalho, A. B.; de Maurera, M. A. M. A.; Nobrega, J. A.;eppe, C.; Brown, M. A.; Tuck, D. G.; Hernandez, M. Z.; Longo, E.; Sensato, F. R. *Organometallics* **1999**, 18, 99. (c) dos Santos, J. E.;eppe, C.; Brown, M. A.; Tuck, D. G. *Organometallics* **1996**, 15, 2201.

⁷⁴ Aldridge, S. *Angew. Chem. Int. Ed.* **2006**, 45, 8097.

3.3.1.1 INDIUM (I) COMPOUND MEDIATED ORGANIC REACTIONS

The common reactions using stoichiometric amounts of indium (I) reagents are Barbier-type and Reformatsky-type reactions *via* the intermediates of alkylindium (III) dihalides,⁷⁵ palladium or nickel-to-indium transmetalations for propargylation or allylation.⁷⁶ Recently, some examples were developed using indium (I) salts.

THIOALKYLATION

The strategy for the generation of thiolate anions is the insertion of indium(I) iodide into dialkyl disulfides to form bis(thioalkyl)iido-indium complex and subsequent cleavage leading to the formation of thiolate anions. These thiolate anions were used in many organic reactions. For example, facile addition to α, β -unsaturated ketones, aldehydes, carboxylic esters, and nitriles provided the corresponding β -keto or β -cyano sulfides in good to excellent yields (eq. 3.4).⁷⁷

The thiolate anions can be also added to alkyl and acyl halides, affording thioethers and thioesters (eq. 3.5).⁷⁸

⁷⁵ Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, 369, 291.

⁷⁶ (a) Marshall, J. A.; Chobanian, H. R. *J. Org. Chem.* **2000**, 65, 8357. (b) Ohno, H.; Hanaguchi, H.; Tanaka, T. *Org. Lett.* **2000**, 2, 2161. (c) Ohno, H.; Hamaguchi, H.; Tanaka, T. *J. Org. Chem.* **2001**, 66, 1867. (d) Miyabe, H.; Yamaoka, Y.; Naito, T.; Tekemoto, Y. *J. Org. Chem.* **2003**, 68, 6745. (e) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2004**, 69, 1415. (f) Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, 69, 5054.

⁷⁷ Ranu, B. C.; Mandal, T. *Synlett* **2004**, 1239.

⁷⁸ Ranu, B. C.; Mandal, T.; Samanta, S. *Org. Lett.* **2003**, 5, 1431.

R = alkyl/acyl; X = Cl/Br/I

Thiolate anions were also used for other reactions under the assistance of catalyst. The regioselective nucleophilic opening of epoxides by thiolate anions under the assistance of indium(III) chloride leading to β -hydroxyphenyl sulfides was introduced as a typical example (eq. 3.6).⁷⁹ This reaction had the following characteristics: (1) the nucleophilic attack on the less-hindered carbon atom of the terminal alkyl-substituted epoxides, (2) attack on the benzylic carbon of aryl-substituted epoxides, and (3) *trans*-diequatorial β -hydroxysulfides obtained from cyclic epoxides.

R = alkyl/aryl; R¹, R² = H/alkyl/aryl

RADICAL CYCLIZATION

The functionalized tetrahydrofurans were obtained *via* intramolecular cyclization of the aryl substituted α -carbonyl bromo-alkynes using indium (I) iodide as a radical initiator in acetonitrile under sonication in good yields (eq. 3.7).⁸⁰

⁷⁹ Ranu, B. C.; Mandal, T. *Can. J. Chem.* **2006**, *84*, 762.

⁸⁰ Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 2859.

The result that radical quenchers, such as *p*-benzoquinone or TEMPO (2,2,6,6-tetramethylpiperidine oxide), completely arrest the cyclization made this reaction reasonable to be explained as a radical process initiated by InI. In addition, a plausible radical pathway is proposed as shown in Scheme 3.7.

Scheme 3.7 Proposed mechanism for radical cyclization.

3.3.1.2 INDIUM (I) COMPOUND CATALYZED ORGANIC REACTIONS

The catalytic applications of indium (I) compounds in the area of organic synthesis have always been one of the most challenging topics. Up to now, only 1,2-addition to conjugated nitriles under sonication and C–C bond forming reactions by catalytic activation of allylboronate reagents were reported.

3.3.1.2.1 1,2-ADDITION TO CONJUGATED NITRILES

Allyl or benzyl bromides was reacted with α,β -unsaturated nitriles in the presence of 20 mol% of indium(I) iodide under sonication provided the corresponding allylated or benzylated conjugated imines in methylene chloride (eq. 3.8).⁸¹ The advantages of this reaction are as follows: (1) exclusive addition of the allyl or benzyl

⁸¹ Ranu, B. C.; A. Das, *Tetrahedron Lett.* **2004**, 45, 6875.

group to the $C\equiv N$ moiety, (2) catalytic amount of indium (I) iodide, and (3) the efficient and clean reaction with high yield.

3.3.1.2.2 C–C BOND FORMING REACTIONS VIA ACTIVATION OF ALLYLBORONATE REAGENTS

Most recently, Kobayashi and coworkers reported highly efficient C–C bond forming reactions by catalytic activation of allylboronate reagents with low-oxidation state indium(I) catalysts, including allylboration of ketones, allylation of acylhydrazones, unusual C–C bond formations between allylboronates and acetals or ketals, and alkyl-allyl coupling between ethers and an allylborane (Scheme 3.8).^{82, 84-85, 87}

Scheme 3.8 Indium^I catalytic C–C bond forming reactions developed by Kobayashi and coworkers

ALLYLBORATION OF KETONES⁸²

The catalytic activation of pinacolyl allylboronate using indium (I) salt was discovered and was further applied to the allylboration of ketones. The experimental results showed that this efficient reaction of C–C bond formation displayed high functional group tolerance. For the mechanism of this reaction, one possible pathway (dual-activation mechanism) was that indium (I) as a Lewis base activated allylboronate **77** to generate bimetallic allylborate **78** with enhanced nucleophilicity. At the same time, indium (I) might also act as a Lewis acid activator towards ketone **76**. Another might involve allylindium species of type **79** generated from catalytic activation of allylboronate **77** via boron-to-indium transmetalation.⁸³

Figure 3.1 Possible intermediates **76-79** in the indium (I) iodide catalyzed allylation of ketone **76** with **77**.

ALLYLATION OF ACYLHYDRAZONES WITH PINACOLYL ALLYLBORONATE⁸⁴

Indium (I) iodide catalytic α -addition of an α -methylallylboronate to various *N*-acylhydrazones proceeded smoothly to furnish the corresponding *anti* α -adducts in high yields in the presence of an alcohol additive. This reaction showed the

⁸² Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2007**, 46, 5909.

⁸³ Hilt, G.; Smolko, K. I. *Angew. Chem. Int. Ed.* **2001**, 40, 3399.

⁸⁴ Kobayashi, S.; Konishi, H.; Schneider, U. *Chem. Commun.* **2008**, 2313.

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99

of allylsilanes),⁸⁶ the In(I)-catalyzed borono variant displayed α -selectivity. In addition, this reaction was tolerant to a variety of functional groups and was even suitable for propargylation. A transmetalative S_N1 mechanism was also proposed as shown in Scheme 3.10. In the mechanism, a single In^I center acts as a dual catalyst for sequential activation of both reagents.

Scheme 3.10 Proposed transmetalative S_N1 mechanism for C–C bond formations of acetals or ketals with allylboronates

ALLYL-ALLYL COUPLING BETWEEN ETHERS AND ALLYLBORANE⁸⁷

Kobayashi and coworkers further developed alkyl-allyl cross-coupling between ethers and a 9-BBN-derived allylborane. In this reaction, indium(I) triflate was used as the catalyst, affording the desired products in high yields. In addition, it

⁸⁶ (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (b) Braun, M.; Kotter, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 514. (c) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150. (d) Kampen, D.; List, B. *Synlett* **2006**, 2589.

⁸⁷ Dao, H. T.; Schneider, U.; Kobayashi, S. *Chem. Commun.* **2011**, 47, 692.

represented the advantages of (1) broad substrate scope, (2) high functional group tolerance, (3) alkyl-allyl cross-coupling catalyzed by a main group metal, and (4) C–C bond formation with non-carbonyl electrophiles. A transmetalative S_N1 mechanism was proposed as shown in Scheme 3.11. In the mechanism, InOTf plays a dual role. The key step is to activate the C–O bond of ethers as Lewis acid.

Scheme 3.11 Proposed reaction mechanism for alkyl-allyl cross-coupling between ethers and a 9-BBN-derived allylborane

Therefore, the catalytic applications of indium (I) complexes in the area of organic synthesis have been one of the most promising topics. On the other hand, copper-catalyzed oxidative rearrangement of tertiary amines or enamines and α -amination of aliphatic aldehydes for the synthesis of α -amino acid derivatives, which are very useful intermediates for the preparation of biologically active molecules,² were presented in Chapter 2. To the best of our knowledge, indium (I) catalysis for oxidative transformations into the formation of C–C or C–N bond through direct

coupling of organic molecules had not been reported yet. Herein we report an indium-catalyzed α -amination of aliphatic aldehydes using nucleophilic secondary amines with readily removable *N*-protecting groups as a nitrogen source for the synthesis of α -amino acetals. This reaction has the obvious advantages such as simple process, commercially available aliphatic aldehydes and secondary amines as the starting materials and excellent yields. Furthermore, indium catalyst can be recycled four times without obvious loss of catalytic activity.

3.3.2 RESULTS AND DISCUSSION

To begin our study, dibenzylamine **73a**, butyraldehyde **74a**, and methanol were selected as standard starting materials. The results are summarized in Table 3.3. When **73a** and **74a** were treated with sodium percarbonate in methanol/1,4-dioxane (0.5/2, v/v) at 60 °C, no desired product was observed (Table 3.3, entry 1). Interestingly, when In(I)I was used as the catalyst for this reaction (Table 3.3, entry 2), most of the substrate **73a** was converted into the desired product **75a** in 81% isolated yield. Next, we further examined the effect of solvent. DCE and 1,4-dioxane emerged as the best solvents for this reaction, furnishing the desired product in 78% and 81% yields, respectively (Table 3.3, entries 2-5). Other solvents such as acetonitrile, methanol were also screened, but in both cases, only moderate yield of the product was obtained (Table 3.3, entries 4-5). We also found that the best volume ratio of methanol to acetonitrile was 1:4, and 80 °C was the most suitable temperature for this reaction (Table 3.3, entry 6). Other indium salts were also screened (Table 3.3, entries 7-12). In(I)Br, InBr₃ and InI₃ also afforded the desired product in moderate yields (Table 3.3, entries 8, 11-12). Whereas, In(I)Cl, InCl₂ and InCl₃ showed no catalytic activity for this reaction (Table 3.3, entries 7, 9-10). In a word, this α -amination of

aldehydes exhibited the best result while operating at 80 °C using 20 mol% of indium(I) iodide as the catalyst and sodium percarbonate as the oxidant with the volume ratio of methanol to 1,4-dioxane (1:4).

Table 3.3 Optimization of reaction conditions using dibenzylamine **73a** and butyraldehyde **74a**^a

<div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> <chem>c1ccccc1N(c2ccccc2)c3ccccc3</chem> 73a </div> <div>+</div> <div style="text-align: center;"> <chem>CCCC=O</chem> 74a </div> <div style="text-align: center;"> $\xrightarrow[\text{MeOH}]{\text{In catalyst, Oxidant}}$ </div> <div style="text-align: center;"> <chem>CCCC(OC)(OC)N(c1ccccc1)c2ccccc2</chem> 75a </div> </div>					
Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b
1	—	1,4-Dioxane	60	24	0
2	InI	1,4-Dioxane	60	24	81
3	InI	MeCN	60	24	56
4	InI	MeOH	60	24	49
5	InI	DCE	60	24	78
6	InI	1,4-Dioxane	80	12	89
7	InCl	1,4-Dioxane	80	24	0
8	InBr	1,4-Dioxane	80	12	53
9	InCl ₂	1,4-Dioxane	80	24	0
10	InCl ₃	1,4-Dioxane	80	24	0
11	InBr ₃	1,4-Dioxane	80	24	69
12	InI ₃	1,4-Dioxane	80	24	55

^aReaction conditions: Dibenzylamine **73a** (0.5 mmol, 1.0 equiv.), butyraldehyde (0.75 mmol), indium catalyst (0.2 equiv.), sodium percarbonate (1.0 equiv.), methanol (0.5 mL), solvent (2 mL).

^bIsolated yields based on dibenzylamine **73a**.

Subsequently, the optimal reaction conditions were used to investigate the scope of this α -amination of aliphatic aldehydes. As highlighted in Table 3.4, a wide array of aliphatic aldehydes having different functionalities were aminated well using dibenzylamine as a nitrogen source, giving the desired products in good to excellent yields under the standard reaction conditions (Table 3.4, entries 1-9). The length of carbon chain of aldehydes had little effect on this reaction (Table 3.4, entries 1, 3). In contrast, more bulky aldehyde for this reaction led to only moderate yield (Table 3.4, entry 2). Of note was that a variety of the functional groups including double bond (Table 3.4, entries 4-5, 7), ester group (Table 3.4, entries 6-7), *tert*-butyl diphenylsilyl (TBDPS) group (Table 3.4, entry 8), and phenyl group (Table 3.4, entry 9) were also tolerant of this mild oxidation conditions. Further investigation on other secondary amines with readily removable *N*-protecting groups such as allyl or benzyl group for this α -amination reaction showed that this type of substrates were also suitable for this reaction, affording the corresponding products in excellent yields (Table 3.4, entries 10-11).

Table 3.4 Scope for α -amination of aliphatic aldehydes^{a,b}

^aReaction conditions: secondary amine **73** (0.5 mmol, 1.0 equiv.), aliphatic aldehyde (0.75 mmol), indium(I) iodide (0.2 equiv.), sodium percarbonate (1.0 equiv.), methanol (0.5 mL), 1,4-dioxane (2 mL).

^bIsolated yields based on secondary amine **73**.

To further explore the utility of this α -amination in the more complex molecular structures, cyclohexanecarbaldehyde **74k** was chosen for this reaction and this process created a new quaternary carbon centre bearing a C–N bond although the isolated yield was only 35% (Scheme 3.12).

Scheme 3.12 Construction of a new quaternary carbon centre bearing a C–N bond.

On considering the possibility of recycling the indium catalyst, the solid was directly used for the next reaction without further purification after the removal of the supernatant. Gratifying, indium catalyst can be recycled four times without obvious loss of catalytic activity (Figure 3.2).

Figure 3.2 Recycling of indium catalyst. Reaction conditions: Dibenzylamine **73a** (0.5 mmol, 1.0 equiv.), butyraldehyde (0.75 mmol), indium catalyst (0.2 equiv.), sodium percarbonate (1.0 equiv.), methanol (0.5 mL), 1,4-dioxane (2 mL).

Control and deuterium labeling experiments were carried out to explore the possible mechanism of this α -amination using indium catalytic systems. (I) Enamine was regarded as a potential precursor of this reaction. Hence, the enamine **71d** from secondary amine and aldehyde was isolated and then subjected to the catalytic conditions, furnishing the desired product **72c** in excellent yield (Scheme 3.13).

Scheme 3.13 Control experiment

(II) When methanol- d_4 was used in the reaction, a D-labeled α -amino acetal was obtained in good yield under the standard reaction conditions. This implied that two hydrogen atoms at α -position of aldehyde were involved in the reaction. It was noted that only 18% hydrogen atom at α -position was observed from ^1H NMR spectrum (Scheme 3.14).

Scheme 3.14 Deuterium labeling experiments

(III) Equivalent amount of indium salts were used for this reaction without additional oxidant and it was found that when InI was used, only *N,N*-dibenzylbutan-1-amine was produced in 46% yield. On the other hand, trace amount of α -amino acetal **75a** was detected using InI₃ or InBr₃ (Scheme 3.15). Therefore, in the indium catalytic systems, low-oxidation-state InI was supposed to be oxidized to Indium(II) complex, which may function as (1) the single electron transfer (SET) reagent, (2) the electron pair acceptor as these indium salts had free p orbitals, or (3) both SET reagent and electron pair acceptor.⁶⁸⁻⁸⁷

Scheme 3.15 Control experiments

On the basis of the results of control and deuterium labeling experiments, a proposed process of this α -amination was presented in Scheme 3.16. The interaction of enamine **A** and [In^{II}] resulted in the intermediates **B** and **C** through the nucleophilic

attack of methanol. Then, intramolecular transfer of an amino group formed the intermediates **E** and **F**, which can be converted into each other by a proton. Finally, the second nucleophilic attack by methanol on the oxocarbenium ion **E** generated the desired product.

Scheme 3.16 Proposed mechanism for indium-catalyzed α -amination of aldehydes

3.3.3 SUMMARY

In summary, a novel and highly efficient indium^I oxidative catalytic system for the synthesis of α -amino acetals *via* α -amination of aldehydes using nucleophilic secondary amines as a nitrogen source was developed. This reaction has the obvious advantages of simple process, commercially available aldehydes and secondary amines as the starting materials, and excellent yields. In addition, indium catalyst can be recycled four times without obvious loss of catalytic activity.

3.4 CONCLUSION

In this chapter, we studied α -amination of aldehydes using nucleophilic secondary amines with readily removable *N*-protecting groups as a nitrogen source for the synthesis of α -amino acetals in the catalytic systems of CuI(Br)-TBHP and InI(Br)-Na₂CO₃·1.5H₂O₂. This reaction has the advantages of simple process, commercially available aliphatic aldehydes and secondary amines as the starting materials and is also regarded as a synthetic equivalent of C–H functionalization at the α -position of aldehydes. Furthermore, the enamine with readily removable *N*-protecting groups, which is confirmed as the intermediate in this reaction, was also directly converted into α -amino acetal *via* oxidative rearrangement. (1) For the catalytic system of CuI(Br)-TBHP, this reaction can be operated under very mild conditions, affording the desired products in moderate to good yields. (2) In comparison with CuI(Br)-TBHP, the catalytic system of InI(Br)-Na₂CO₃·1.5H₂O₂ displayed better catalytic activity and furnished the desired products in excellent yields. Furthermore, indium catalyst can be recycled four times without obvious loss of catalytic activity.

3.5 EXPERIMENTAL SECTION

3.5.1 CuI(Br)-TBHP Catalytic System

I. General procedures

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Copper salts, and peroxides such as *tert*-butyl hydroperoxide (~5.5 M in decane) (TBHP), di-*tert*-butyl peroxide, and *tert*-butyl benzoylperoxide were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. Secondary amines **73b**⁸⁸ and aliphatic aldehydes **74 (f, h)**⁸⁹ were synthesized according to literatures.

II. Optimization of the reaction conditions^a

Among the various solvents screened (Table 3.1, entries 2 and 11-14), acetonitrile emerged as the best medium for this reaction, rendering the desired product in 80% isolated yield (Table 3.1, entry 2). Other copper catalysts were also examined (Table 3.1, entries 15-20). CuBr and CuBr₂ also catalyzed the reaction to afford the desired product **90a** in moderate yield under the same conditions (Table 3.1, entries 15, 17). Other copper salts such as CuCl, CuCl₂, Cu(OAc)₂ and Cu(OTf)₂ showed low or even no catalytic activities for this reaction (Table 3.1, entries 16, 18-20).

Table 3.1 Optimization of the reaction conditions^a

	73a	74a			75a	
Entry	Catalyst	Oxidant	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b
1	CuI	O ₂ or air (1 atm)	MeCN	40	24	0
2	CuI	<i>t</i> BuOOH	MeCN	40	24	80

⁸⁸ Mukherjee, S.; List, B. *J. Am. Soc. Chem.* **2007**, 129, 11336.

⁸⁹ (a) Huckstep, M.; Taylop, R. J. K. *Synthesis* **1982**, 881. (b) Ciblat, S.; Kim, J.; Stewart, C. A.; Wang, J. Z.; Forgione, P.; Clyne, D.; Paquette, L. A. *Org. Lett.* **2007**, 719.

3	—	^t BuOOH	MeCN	40	24	0
4	CuI	^t BuOO ^t Bu	MeCN	40	24	trace
5	CuI	^t BuOOBz	MeCN	40	24	50
6	CuI	^t BuOOH	MeCN	20	96	75
7 ^c	CuI	^t BuOOH	MeCN	40	72	57
8 ^d	CuI	^t BuOOH	MeCN	40	24	50
9 ^e	CuI	^t BuOOH	MeCN	40	24	70
10 ^f	CuI	^t BuOOH	MeCN	40	24	62
11	CuI	^t BuOOH	MeOH	40	24	50
12	CuI	^t BuOOH	DCE	40	24	48
13	CuI	^t BuOOH	THF	40	24	53
14	CuI	^t BuOOH	DMSO	40	24	51
15	CuBr	^t BuOOH	MeCN	40	24	55
16	CuCl	^t BuOOH	MeCN	40	24	14
17	CuBr ₂	^t BuOOH	MeCN	40	24	67
18	CuCl ₂	^t BuOOH	MeCN	40	24	9
19	Cu(OAc) ₂	^t BuOOH	MeCN	40	24	0
20	Cu(OTf) ₂	^t BuOOH	MeCN	40	24	trace

^aReaction conditions: Dibenzylamine (0.5 mmol, 1 equiv.), butyraldehyde (0.75 mmol), copper catalyst (0.4 equiv.), oxidant (1.1 equiv.), methanol (0.4 mL), solvent (2 mL).

^bIsolated yields based on dibenzylamine.

^cThe reaction was performed using 0.2 equiv. CuI.

^dThe reaction was performed using 0.2 mL MeOH.

^eDibenzylamine (0.5 mmol), butyraldehyde (0.5 mmol).

^fDibenzylamine (0.75 mmol), butyraldehyde (0.5 mmol).

III General experimental procedure for copper-catalyzed α -amination of aliphatic aldehydes

Typical procedure for copper-catalyzed α -amination of aliphatic aldehydes using secondary amines with readily removable *N*-protecting groups as a nitrogen source for

the synthesis of α -amino acetals (dibenzylamine **73a** and butyraldehyde **74a** as a model system): *tert*-butyl hydroperoxide (~5.5 M in decane) (0.1 mL, ~0.55 mmol) was added to a mixture of CuI (38 mg, 0.2 mmol), dibenzylamine **73a** (98 mg, 0.5 mmol), and butyraldehyde **74a** (54 mg, 0.75 mmol) in methanol (0.4 mL)/acetonitrile (2.0 mL) at room temperature. The mixture was stirred at 40 °C until dibenzylamine **73a** was completely converted by TLC detection. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75a** as a light yellowish oil (0.125 g, 80% yield).

***N,N*-dibenzyl-1,1-dimethoxybutan-2-amine (75a):**

R_f = 0.70 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl₃, 400 MHz) δ 7.38-7.36 (m, 4H), 7.30-7.26 (m, 4H), 7.22-7.18 (m, 2H), 4.37 (d, J = 5.16 Hz, 1H), 3.74 (dd, J = 50.34, 13.61 Hz, 4H), 3.35 (s, 3H), 3.32 (s, 3H), 2.65-2.60 (m, 1H), 1.61-1.44 (m, 2H), 0.93 (t, J = 7.43 Hz, 3H) ppm.

^{13}C NMR (CDCl₃, 100 MHz) δ 140.7 (C x 2), 129.0 (CH x 4), 128.0 (CH x 4), 126.6 (CH x 2), 107.4, 59.4, 54.8, 54.44 (CH₂ x 2), 54.38, 19.5, 12.0 ppm

FTIR (neat): ν = 3015, 1452, 1215, 754, 700, 494 cm⁻¹.

HRMS (ESI, m/z): calcd for C₂₀H₂₈NO₂⁺ [$M+H$]⁺ 314.2120, found: 314.2119.

***N,N*-dibenzyl-1,1-dimethoxy-3-methylbutan-2-amine (75b):**

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and 3-methylbutanal **74b** (64 mg, 0.75 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75b** as a light yellowish oil (0.108 g, 66% yield).

R_f = 0.76 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.36 (m, 4H), 7.30-7.26 (m, 4H), 7.22-7.18 (m, 2H), 4.51 (d, J = 4.28 Hz, 1H), 3.77 (dd, J = 102.13, 13.70 Hz, 4H), 3.40 (s, 3H), 3.37 (s, 3H), 2.46-2.43 (m, 1H), 2.05-1.97 (m, 1H), 0.98 (t, J = 6.82 Hz, 3H), 0.83 (t, J = 6.68 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.7 (C x 2), 129.2 (CH x 4), 128.0 (CH x 4), 126.6 (CH x 2), 107.1, 62.5, 55.5 (CH_2 x 2), 55.2, 54.8, 27.2, 20.9, 20.7 ppm

FTIR (neat): ν = 3015, 1215, 754, 700, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 328.2277, found: 328.2273.

N,N-dibenzyl-1,1-dimethoxyoctan-2-amine (**75c**):

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and octanal **74c** (96 mg, 0.75 mmol). After 24 h, the crude product was purified by flash column chromatography

(silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75c** as a light yellowish oil (0.129 g, 70% yield).

R_f = 0.77 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.37-7.35 (m, 4H), 7.30-7.26 (m, 4H), 7.23-7.18 (m, 2H), 4.37 (d, J = 5.03 Hz, 1H), 3.73 (dd, J = 50.95, 13.56 Hz, 4H), 3.35 (s, 3H), 3.32 (s, 3H), 2.73-2.68 (m, 1H), 1.59-1.36 (m, 3H), 1.25-1.17 (m, 5H), 1.15-1.08 (m, 2H), 0.87 (t, J = 7.07 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.8 (C x 2), 129.0 (CH x 4), 128.0 (CH x 4), 126.6 (CH x 2), 107.5, 57.4, 54.8, 54.5 (CH_2 x 2), 54.3, 31.9, 29.4, 26.9, 26.5, 22.7, 14.1 ppm

FTIR (neat): ν = 3015, 1215, 754, 700, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 370.2746, found: 370.2743.

N,N-dibenzyl-1,1-dimethoxypent-4-en-2-amine (**75d**):

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and pent-4-enal **74d** (63 mg, 0.75 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75d** as a light yellowish oil (0.102 g, 63% yield).

R_f = 0.70 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.37 (m, 4H), 7.30-7.26 (m, 4H), 7.21-7.18 (m, 2H), 5.89-5.79 (m, 1H), 5.06 (d, J = 17.14 Hz, 1H), 5.01 (d, J = 10.10 Hz, 1H), 4.38

(d, $J = 4.93$ Hz, 1H), 3.75 (dd, $J = 25.44, 13.56$ Hz, 4H), 3.35 (s, 3H), 3.28 (s, 3H), 2.89-2.84 (m, 1H), 2.44-2.26 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.5 (C x 2), 137.8, 129.0 (CH x 4), 128.0 (CH x 4), 126.7 (CH x 2), 115.5, 107.0, 57.8, 54.7, 54.5, 54.4 (CH_2 x 2), 31.2 ppm

FTIR (neat): $\nu = 3015, 1454, 1215, 754, 700, 494$ cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 326.2120, found: 326.2114.

(Z)-N,N-dibenzyl-1,1-dimethoxyhept-4-en-2-amine (75e):

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and (Z)-hept-4-enal **74e** (84 mg, 0.75 mmol). After 48 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75e** as a light yellowish oil (0.115 g, 65% yield).

$R_f = 0.72$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.36 (m, 4H), 7.30-7.26 (m, 4H), 7.24-7.18 (m, 2H), 5.44-5.36 (m, 2H), 4.38 (d, $J = 4.73$ Hz, 1H), 3.79-3.71 (m, 4H), 3.36 (s, 3H), 3.28 (s, 3H), 2.86-2.81 (m, 1H), 2.44-2.37 (m, 1H), 2.28-2.20 (m, 1H), 2.08-2.01 (m, 2H), 0.93 (t, $J = 7.53$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.6 (C x 2), 131.9, 129.0 (CH x 4), 128.0 (CH x 4), 127.6, 126.7 (CH x 2), 107.3, 58.0, 54.8, 54.6, 54.5 (CH_2 x 2), 24.2, 20.7, 14.2 ppm

FTIR (neat): $\nu = 3017, 1454, 1215, 1072, 756, 699, 498$ cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{23}\text{H}_{32}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 354.2433, found: 354.2443.

***N,N*-dibenzyl-5-(*tert*-butyldiphenylsilyloxy)-1,1-dimethoxypentan-2-amine (75f):**

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and 5-(*tert*-butyldiphenylsilyloxy)pentanal **74f** (0.255 g, 0.75 mmol). After 48 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75f** as a light yellowish oil (0.230 g, 79% yield).

R_f = 0.72 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl₃, 400 MHz) δ 7.66-7.64 (m, 4H), 7.43-7.33 (m, 10H), 7.28-7.17 (m, 6H), 4.38 (d, J = 5.42 Hz, 1H), 3.72 (dd, J = 40.61, 13.45 Hz, 4H), 3.61-3.45 (m, 2H), 3.33 (s, 3H), 3.32 (s, 3H), 2.73-2.68 (m, 1H), 1.86-1.76 (m, 1H), 1.68-1.40 (m, 3H), 1.04 (s, 9H) ppm.

^{13}C NMR (CDCl₃, 100 MHz) δ 140.6 (C x 2), 135.6 (CH x 4), 134.2 (C x 2), 129.4 (CH x 2), 129.1 (CH x 4), 128.0 (CH x 4), 127.5 (CH x 4), 126.7 (CH x 2), 107.4, 63.9, 57.4, 54.7, 54.5 (CH₂ x 2), 54.2, 30.3, 26.9 (CH₃ x 3), 22.8, 19.2 ppm

FTIR (neat): ν = 3017, 1215, 1111, 758, 494 cm⁻¹.

HRMS (ESI, m/z): calcd for C₃₇H₄₈NO₃Si⁺ [$M+H$]⁺ 582.3403, found: 582.3401.

***N,N*-dibenzyl-1,1-dimethoxy-3-phenylpropan-2-amine (75g):**

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and 3-phenylpropanal **74g** (0.100 g, 0.75 mmol). After 48 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75g** as a light yellowish oil (0.129 g, 69% yield).

R_f = 0.72 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.27-7.01 (m, 15H), 4.42 (d, J = 4.38 Hz, 1H), 3.74 (s, 4H), 3.37 (s, 3H), 3.30 (s, 3H), 3.13-3.08 (m, 1H), 2.88-2.86 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.8, 140.3 (C x 2), 129.6 (CH x 2), 128.7 (CH x 4), 128.0 (CH x 6), 126.5 (CH x 2), 125.3, 107.2, 59.6, 54.9, 54.8, 54.4 (CH_2 x 2), 32.6 ppm

FTIR (neat): ν = 3019, 1495, 1454, 1215, 1072, 756, 698, 496 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 376.2277, found: 376.2278.

Methyl 4-(dibenzylamino)-5,5-dimethoxypentanoate (**75h**):

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and methyl 5-oxopentanoate **74h** (97 mg, 0.75 mmol). After 48 h, the crude product was purified by flash column

chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **74h** as a light yellowish oil (0.124 g, 67% yield).

R_f = 0.54 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.33-7.27 (m, 8H), 7.25-7.19 (m, 2H), 4.43 (d, J = 5.53 Hz, 1H), 3.72 (dd, J = 63.86, 13.41 Hz, 4H), 3.55 (s, 3H), 3.363-3.359 (m, 6H), 2.78-2.73 (m, 1H), 2.53-2.26 (m, 2H), 1.86-1.70 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 174.2, 140.2 (C x 2), 129.1 (CH x 4), 128.1 (CH x 4), 126.8 (CH x 2), 106.7, 56.6, 54.8, 54.2 (CH_2 x 2), 53.6, 51.3, 31.1, 21.9 ppm

FTIR (neat): ν = 3017, 1454, 1215, 758, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 372.2175, found: 372.2178.

***N*-allyl-*N*-benzyl-1,1-dimethoxybutan-2-amine (75i):**

The product was prepared by above general procedure and the same chemicals except employing *N*-benzylprop-2-en-1-amine **73b** (74 mg, 0.5 mmol), and butyraldehyde **74a** (55 mg, 0.75 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75i** as a light yellowish oil (92 mg, 69% yield).

R_f = 0.72 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.36-7.34 (m, 2H), 7.30-7.26 (m, 2H), 7.24-7.18 (m, 1H), 5.85-5.75 (m, 1H), 5.15 (d, J = 17.21 Hz, 1H), 5.05 (d, J = 10.10 Hz, 1H), 4.31 (d, J = 5.35 Hz, 1H), 3.75 (dd, J = 72.44, 14.03 Hz, 2H), 3.36 (s, 6H), 3.28-3.15 (m, 2H), 2.72-2.67 (m, 1H), 1.57-1.41 (m, 2H), 0.96 (t, J = 7.41 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.1, 138.1, 128.7 (CH x 2), 128.0 (CH x 2), 126.5, 116.1, 107.3, 60.4, 54.7, 54.5, 54.4, 53.5, 19.7, 12.0 ppm

FTIR (neat): ν = 3017, 1452, 1215, 1065, 756, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 264.1964, found: 264.1965.

***N,N*-dibenzyl-1,1-dimethoxyhexan-2-amine (72c)**: The product was prepared by above general procedure and the same chemicals except employing *N,N*-dibenzylhex-1-en-1-amine **71d** (0.139 g, 0.5 mmol). After 20 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **72c** as a light yellowish oil (0.129 g, 76% yield).

IV. Deuterium labeling experiment

Typical procedure for deuterium labeling experiment (eq. 3.2): *tert*-butyl benzoylperoxide (0.107 g, 0.55 mmol) was added to a mixture of CuI (38 mg, 0.2 mmol), dibenzylamine **73a** (98 mg, 0.5 mmol), and butyraldehyde **74a** (54 mg, 0.75 mmol) in CD_3OD (0.5 mL)/acetonitrile (2.0 mL) at room temperature. The mixture was stirred at 40 $^\circ\text{C}$ for 40 h. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75j** as a light yellowish oil (0.144 g, 80% yield).

***N,N*-dibenzyl-1,1-dimethoxy-D6-butan-D1-2-amine (75j)**:

$R_f = 0.70$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.36 (m, 4H), 7.30-7.26 (m, 4H), 7.23-7.18 (m, 2H), 4.38-4.37 (m, 1H), 3.74 (dd, $J = 49.61, 13.60$ Hz, 4H), 2.64-2.60 (m, 0.43H), 1.59-1.44 (m, 2H), 0.92 (t, $J = 7.43$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.7 (C x 2), 129.0 (CH x 4), 128.0 (CH x 4), 126.6 (CH x 2), 107.2, 59.4, 54.5 (CH_2 x 2), 19.54, 19.43, 12.03, 11.99 ppm

FTIR (neat): $\nu = 3015, 1215, 754, 700, 494\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{33}\text{D}_5\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 361.3115, found: 361.3109.

3.5.2 InI(Br)- $\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$ Catalytic System

I. General procedures

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Indium salts, and sodium percarbonate (available 20-30% H_2O_2) were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. Aliphatic aldehydes **74j**⁹⁰ were synthesized according to literatures.

II. General experimental procedure for indium-catalyzed α -amination of aliphatic aldehydes

⁹⁰ Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, 57, 7771.

Typical procedure for indium-catalyzed α -amination of aliphatic aldehydes for the synthesis of α -amino acetals using secondary amines with readily removable protecting groups as a nitrogen source (dibenzylamine **73a** and butyraldehyde **74a** as a model system): butyraldehyde **74a** (54 mg, 0.75 mmol) was added to a mixture of In(I)I (24 mg, 0.1 mmol), dibenzylamine **73a** (98 mg, 0.5 mmol), and sodium percarbonate (78.5 mg, 0.5 mmol) in methanol (0.5 mL)/1,4-dioxane (2.0 mL) at room temperature. The mixture was stirred at 80°C until dibenzylamine **73a** was completely converted by TLC detection. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75a** (*N,N*-dibenzyl-1,1-dimethoxybutan-2-amine) as a light yellowish oil (0.139 g, 89% yield).

(*E*)-methyl 6-(dibenzylamino)-7,7-dimethoxyhept-2-enoate (75k**):**

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and (*E*)-methyl 7-oxohept-2-enoate **74j** (117 mg, 0.75 mmol). After 24 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane = 1:10) to afford the desired product **75k** as a light yellowish oil (0.149 g, 75% yield).

R_f = 0.42 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.36-7.28 (m, 8H), 7.25-7.21 (m, 2H), 6.90-6.82 (m, 1H), 5.69-5.65 (m, 1H), 4.42 (d, J = 5.09 Hz, 1H), 3.74 (dd, J = 59.48, 13.52 Hz, 4H), 3.71 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 2.75-2.70 (m, 1H), 2.46-2.36 (m, 1H), 2.12-2.02 (m, 1H), 1.71-1.56 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 167.1, 149.8, 140.3 (C x 2), 129.0 (CH x 4), 128.2 (CH x 4), 126.8 (CH x 2), 120.7, 107.0, 57.3, 55.0, 54.45, 54.41 (CH_2 x 2), 51.3, 29.6, 25.1 ppm

FTIR (neat): ν = 3016, 1454, 1215, 758, 700, 494 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{32}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 398.2331, found: 398.2324.

***N,N*-dibenzyl-1-(dimethoxymethyl)cyclohexanamine (75l):**

The product was prepared by above general procedure and the same chemicals except employing dibenzylamine **73a** (98 mg, 0.5 mmol), and cyclohexanecarbaldehyde **74k** (84 g, 0.75 mmol). After 48 h, the crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75l** as a light yellowish oil (62 mg, 35% yield).

R_f = 0.63 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.25-7.22 (m, 4H), 7.18-7.14 (m, 4H), 7.11-7.07 (m, 2H), 4.03 (s, 4H), 4.02 (s, 1H), 3.38 (s, 6H), 1.97-1.93 (m, 2H), 1.77-1.25 (m, 8H) ppm

^{13}C NMR (CDCl_3 , 100 MHz) δ 142.2 (C x 2), 129.0 (CH x 4), 127.7 (CH x 4), 126.0 (CH x 2), 112.0, 63.4, 58.0 (CH_3 x 2), 52.7 (CH_2 x 2), 29.5 (CH_2 x 2), 26.5, 21.1 (CH_2 x 2) ppm

FTIR (neat): ν = 3018, 1215, 756, 698, 496 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{23}\text{H}_{32}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 354.2433, found: 354.2437.

III. Deuterium labeling experiment

Typical procedure for deuterium labeling experiment: butyraldehyde **74a** (54 mg, 0.75 mmol) was added to a mixture of In(I)I (24 mg, 0.1 mmol), dibenzylamine **73a** (98 mg, 0.5 mmol), and sodium percarbonate (78.5 mg, 0.5 mmol) in CD_3OD (0.5 mL)/1,4-dioxane (2.0 mL) at room temperature. The mixture was stirred at 80 $^\circ\text{C}$ for 12 h. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75j'** as a light yellowish oil (0.142 g, 79% yield).

N,N-dibenzyl-1,1-dimethoxy-D6-butan-D1-2-amine (**75j'**):

R_f = 0.70 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.36 (m, 4H), 7.30-7.26 (m, 4H), 7.23-7.18 (m, 2H), 4.38-4.37 (m, 1H), 3.74 (dd, $J = 49.61, 13.60$ Hz, 4H), 2.64-2.60 (m, 0.18H), 1.59-1.44 (m, 2H), 0.92 (t, $J = 7.43$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.7 (C x 2), 129.0 (CH x 4), 128.0 (CH x 4), 126.6 (CH x 2), 107.2, 59.4, 54.5 (CH_2 x 2), 19.54, 19.43, 12.03, 11.99 ppm

FTIR (neat): $\nu = 3015, 1215, 754, 700, 494\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{33}\text{D}_5\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 361.3115, found: 361.3109.

CHAPTER 4

Hypervalent Iodine Catalyzed α -Amination of Aldehydes with a Nucleophilic Nitrogen

Source

CHAPTER 4 HYPERVALENT IODINE CATALYZED α -AMINATION OF ALDEHYDES WITH A NUCLEOPHILIC NITROGEN SOURCE

4.1 OVERVIEW

The first hypervalent iodine compound (Willgerodt's reagent) was synthesized as early as the late 1800's.⁹¹ Recently, these compounds such as IBX and its derivatives had been widely employed as useful mild oxidizing agents in organic synthetic chemistry. Especially over the past two decades, owing to their low toxicity, simple handling, commercial availability, and mild reactivity, hypervalent iodine compounds as the environmentally benign alternatives to rare or toxic heavy metal oxidants had shown high potential for the applications in organic synthesis. A wide range of organic molecules containing functional groups such as olefins, alkynes, enones, silyl enol ethers, sulfides, and phenols could be transformed into very useful compounds under mild conditions using hypervalent iodine as the oxidants. Furthermore, these reagents could be also used for C–H bond activation. However, these oxidations require equal mole quantity and even an excess of the hypervalent iodine reagents. Thus, equimolecular amounts of iodine-containing compounds as waste were produced. In combination of the drawbacks of the explosive sensitivity and poor solubility in common organic solvents, their stoichiometric utility has been limited.⁹²

⁹¹ Willgerodt, C. *J. Prakt. Chem.* **1886**, 33, 154.

⁹² (a) Wirth, T., Ed. *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Topics in Current Chemistry Series 224; Springer: Berlin-Tokyo, 2003. (b) Moriarty, R. M.; Prakash, O. *Hypervalent Iodine in Organic Chemistry: Chemical Transformations*; Wiley-Interscience: 2008. (c) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, 19, 244. (d) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, 44, 3656. (e) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, 48, 9052. (f) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (g) Ochiai, M. *Chem. Rec.* **2007**, 7, 12. (h) Zhdankin, V. V.; Stang, P. J.

In order to overcome these disadvantages, the best choice is to realize the catalytic utilization of hypervalent iodine. As shown in Scheme 4.1, a catalytic cycle was proposed for hypervalent iodine compound. Here ArIX_2 was selected as an example for hypervalent iodine reagents. Firstly, the hypervalent iodine reagent was generated *in situ* under the oxidative conditions. Then, ArIX_2 took part in the oxidative transformation and at the same time, the low valent iodine-containing compound ArI was produced. Finally, the released ArI was successfully reoxidized *in situ* to ArIX_2 .⁹³

Scheme 4.1 Catalytic cycle with hypervalent iodine compounds; Ar = aryl; X = ligand (OH, OAc, OTs, OCOCF_3)

For this catalytic cycle, mild and selective reoxidation conditions are necessary for converting low valent iodine-containing compound formed after the addition-reductive elimination process to hypervalent iodine in the presence of the substrates. However, the efficient and mild transformation from low valent iodine-containing compound to the hypervalent iodine was still scarcely reported. Hence, the

Chem. Rev. **2008**, 108, 5299. (i) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, 63, 7674. (j) Moriarty, R. M. *J. Org. Chem.* **2005**, 70, 2893. (k) Zhdankin, V. V. *J. Org. Chem.* **2011**, 76, 1185. (l) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, 65, 10797. (m) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365.

⁹³ (a) Bell, R.; Morgan, K. J. *J. Chem. Soc.* **1960**, 1209. (b) Moriarty, R. M.; Prakash, O.; Duncan, M. P. *Synthesis* **1985**, 943. (c) Grushin, V. V. *Acc. Chem. Res.* **1992**, 25, 529; (d) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem. Int. Ed.* **2005**, 44, 7065.

construction and utilization of the catalytic systems for realizing the catalytic oxidations for hypervalent iodine is still a challenging topic for chemists.

The first catalytic reaction using hypervalent iodine is the electrolytic *gem*-difluorination of dithioacetals (Scheme 4.2) reported by Fuchigami's group in 1994.⁹⁴ In this reaction, *p*-methoxyiodobenzene is anodically oxidized selectively for the generation of a reactive species difluoro(*p*-methoxyphenyl)- λ^3 -iodane in the presence of $\text{Et}_3\text{N} \cdot 3\text{HF}$.

Scheme 4.2 Catalytic anodic oxidation

The first chemical method for an iodobenzene-catalyzed oxidation was reported by Ochiai's group in 2003. In the reaction, diacyloxy(phenyl)- λ^3 -iodanes was used as real oxidants for α -acetoxylation of ketones and *meta*-chloroperbenzoic acid (*m*CPBA) serves as a terminal oxidant (eq. 4.1).⁹⁵

⁹⁴ Fuchigami, T.; Fujita, T. *J. Org. Chem.* **1994**, *59*, 7190.

⁹⁵ (a) Takeuchi, Y.; Sueda, T.; Ueda, E.; Ochiai, M. Annual Meeting of the Pharmaceutical Society of Japan, Nagasaki, 2003, 28[P1]-I-081. (b) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244.

Afterward, many reactions such as spirocyclizations of phenol derivatives, α -oxygenations of ketones, alcohol oxidation, and other catalytic reactions with iodine (III) or (V), were developed,⁹⁶ employing with commercially available stoichiometric co-oxidants such as *m*CPBA, Oxone[®].

Up until relatively recently there is a high level of interest in (1) the selection of mild and environmentally benign oxidants such as molecular oxygen or hydrogen peroxide as the co-oxidant for generation of active hypervalent iodine species *in situ* and (2) the design of novel chiral iodine-containing compounds and further applications for asymmetric transformations. The following is the latest progress about *in situ* generated organohypervalent iodine or (hypo)iodite as catalyst for organic synthesis.

4.1.1 IN SITU GENERATED CHIRAL ORGANOHYPERVALENT IODINE AS CATALYST

The exploitation of chiral organohypervalent iodine for enantioselective oxidative coupling is still one of the most challenging areas in asymmetric catalysis.⁹⁷

⁹⁶ (a) Minamitsuji, Y.; Kato, D.; Fujioka, H.; Dohi, T. and Kita, Y. *Aust. J. Chem.* **2009**, *62*, 648. (b) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* 2007, 1224. (c) Uyanika, M.; Yasuia, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841. (d) Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251. (e) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315. (f) Farooq, U.; Schäfer, S.; Shah, A. A.; Freudendahl, D. M.; Wirth, T. *Synthesis* **2010**, 1023. (g) Yamamoto, Y.; Togo, H. *Synlett* **2006**, 798. (h) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 6193. (i) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Chem. Commun.* **2006**, 2483. (j) Herrerias, C. I.; Zhang, T. Y.; Li, C.-J. *Tetrahedron Lett.* **2006**, *47*, 13. (k) Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933. (l) Schulze, A.; Giannis, A. *Synthesis* **2006**, 257. (m) Mu, R.; Liu, Z.; Yang, Z.; Liu, Z.; Wu, L.; Liu, Z.-L. *Adv. Synth. Catal.* **2005**, *347*, 1333.

⁹⁷ For the stoichiometric use of chiral hypervalent iodine compounds, see: (a) up to 53 % ee: Imamoto, T.; Koto, H.; *Chem. Lett.* **1986**, 967. (b) up to 56 % ee: Ray III, D.G.; Koser, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 5672. (c) up to 53% ee: Ochiai, M.; Takaoka, Y.; Masaki, Y. *J. Am. Chem. Soc.* **1999**, *121*, 9233. (d) up to 72 % ee: Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519. (e) up to 65% ee: Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T. *Eur. J. Org. Chem.* **2001**, 1569. (f) up to 41% ee: Ladziata, U.; Carlson, J.; Zhdankin, V. V. *Tetrahedron Lett.* **2006**, *47*, 6301. (g) up to 64 % ee: Fujita, M.; Okuno, S.; Lee, H. J.; Sugimura,

After Wirth's research group first reported enantioselective α -tosyloxylation of ketones using chiral iodoarene catalysts (eq. 4.2),⁹⁸ much effort has been devoted to the design of new chiral reagents for asymmetric oxidations aiming at achieving high stereoselectivities.

Some novel reactions catalyzed by chiral hypervalent iodine reagents generated *in situ* with *meta*-chloroperbenzoic acid (*m*CPBA) as a co-oxidant were developed. For example, Quidea *et al.*'s enantioselective hydroxylative dearomatization of phenols (up to 50% ee)⁹⁹ and Altermann *et al.*'s enantioselective α -oxysulfonylation of ketone (up to 44 % ee).¹⁰⁰ Despite their low enantioselectivities and the stoichiometric utility of chiral hypervalent iodine compounds, the catalytic approaches would help us understand the reaction mechanism and the origin of the selectivity in order to better design more effective chiral reagents.

For these oxidative transformations of phenols induced by hypervalent iodine reagents, the two types of key intermediates **80** and **81** were proposed as shown in Scheme 4.3. The intermediate **80** of phenoxy- λ^3 -iodane species was formed after the ligand transfer of the phenolic oxygen atom to the iodine (III) center in the reaction (Scheme 4.3). Subsequently, the attack of a nucleophile on intermediate **80** in an

T.; Okuyama, T. *Tetrahedron Lett.* **2007**, 48, 8691; i) up to 77% ee: Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, 11, 1221.

⁹⁸ (a) Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538. (b) Altermann, S. M.; Richardson, R. D.; Keri Page, T.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Masih Bahar, A.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315.

⁹⁹ Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem. Int. Ed.* **2009**, 48, 4605.

¹⁰⁰ Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Moham-med, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315.

associative manner led to the oxidation to quinone or quinol variants (i.e. cyclohexadienones).¹⁰¹ Alternatively, the dissociation of iodobenzene from intermediate **80** afforded the discrete phenoxenium ions of type **81**. Subsequently, the nucleophile attacked to deliver the product.

Scheme 4.3 The two postulated types of intermediates: **80** and **81**. R, R' = alkyl or alkoxy.

Initial studies on the intermolecular reactions of phenols with nucleophiles concluded that there was no chance for asymmetric induction on the basis of the exclusive formation of the intermediate phenoxenium ion **81** in the reaction.¹⁰² The possibility for asymmetric induction is anticipated, especially from intermediates **80**, while employing enantiopure iodine (III) compounds in the suitable chiral environments.

Lately, Kita and co-workers reported the first enantioselective dearomatization of phenols using new chiral hypervalent iodine (III) reagent **82** with a rigid

¹⁰¹ (a) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (b) Barret, R.; Daudon, M. *Tetrahedron Lett.* **1990**, *31*, 4871. (c) Mal, D.; Roy, H. N.; Hazra, N. K.; Adhikari, S. *Tetrahedron* **1997**, *53*, 2177. (d) Quideau, S.; Looney, M. A.; Pouysegue, L. *Org. Lett.* **1999**, *1*, 1651. (e) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (f) Wood, J. L.; Graeber, J. K.; Njardarson, J. T. *Tetrahedron* **2003**, *59*, 8855.

¹⁰² (a) Kürti, L.; Herczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter, A.; *J. Chem. Soc. Perkin Trans. I* **1999**, 379. (b) Pelter, A.; Ward, R. S.; *Tetrahedron* **2001**, *57*, 273.

spirobiindane backbone.¹⁰³ The high level of the asymmetric induction for constructing a chiral *ortho*-spirolactone structure was achieved with enantiomeric ratios up to 93:7 using a stoichiometric chiral iodine (III) reagent in the presence of acetic acid. When a catalytic amount of **83** (30 mol% based on iodine) together with *m*CPBA was used for this reaction, the enantioselectivity was reduced to 69% ee (Scheme 4.4).

Scheme 4.4 Enantioselective oxidative spirolactonization of 1-naphthols reported by Kita and co-workers.

Ishihara and co-workers designed and synthesized a conformationally flexible C_2 -symmetric iodosylarene catalyst consisting of three units: an iodoaryl moiety (**A**), chiral linkers (**B**), and subfunctional groups (**C**; Scheme 4.5).¹⁰⁴ For iodosylarenes **85** generated in situ from the pre-catalyst **84**, it was thought that the electron-deficient iodine (III) center (σ^* orbital of C–I) of **A** and the Lewis basic group of **C** (lone pair of electrons (n)), such as carbonyl groups **85a** have intramolecular n– σ^* interactions. Alternatively, it was also possible to generate intramolecular hydrogen bonding interactions between the acidic hydrogen of C, C(O)Y–H, and the iodine(III) ligand

¹⁰³ Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3787.

¹⁰⁴ Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2175.

(L, such as an acetoxy group) (**85b**). Based on the intramolecular interactions, the pre-catalyst **84** together with *m*CPBA could also be used for the enantioselective Kita oxidative spirolactonization, affording excellent enantioselectivities (up to 92% ee) (Scheme 4.5). Furthermore, a broader range of substrates were tolerated. Even a 4-benzoylnaphthol derivative could be produced with good enantioselectivity (83% ee), while only racemic product was obtained using Kita's method.

Scheme 4.5 Design of conformationally flexible iodoarene **84** (precatalyst) and iododisylarene **85** (catalyst)

In these ways, the use of this chiral organohypervalent iodine reagent for asymmetric oxidations and further investigations into the transition-state model provide important mechanistic insights into the enantioselective oxidative transformations, and surely contributes to the theoretical design of more effective chiral organohypervalent iodine reagents for organic synthesis.

4.1.2 IN SITU GENERATED (HYPO) IODITE AS CATALYST

The development of new reactions based on Green Chemistry Principles can provide potential benefits for organic synthesis.¹⁰⁵ The recent studies showed that hypervalent iodine compounds were environmentally benign alternatives to rare or toxic metal for oxidative transformations in organic synthesis. However, as shown in Figure 4.1, the iodosoarene-*m*CPBA catalytic system has the drawbacks as follows: (1) harsh reaction conditions, (2) low chemoselectivity (competing with Baeyer–Villiger oxidation), (3) *meta*-chlorobenzoic acid (*m*CBA) generated as waste, and (4) the requirement of excess amounts of carboxylic acids. Therefore, it is very desirable to explore the catalytic applications of hypervalent iodine in combination with the stoichiometric co-oxidant, such as, molecular oxygen or hydrogen peroxide.

Figure 4.1 (Left) In situ-generated aryl- λ^3 - or aryl- λ^5 -iodane catalysis. (Right) In situ-generated hypiodite(I) or iodite(III) catalysis.

Recently, a typical example reported by Ishihara's group was that a catalytic amount of inorganic iodine salt together with molecular oxygen or hydrogen peroxide as the co-oxidant (Figure 4.1) was used as a mild, environmentally benign, and atom-

¹⁰⁵ Anastas, P. T.; Warner, J. C. *Green Chemistry Theory and Practice*; Oxford University Press: New York, 1998.

economical catalytic system for oxidative transformations. The important features of this catalytic system are: (1) metal-free oxidation, (2) milder reaction conditions, (3) high chemoselectivity, (4) wide range of substrates, and (5) water is the only by-product derived from the co-oxidant used.

This catalytic system was successfully applied to the direct α -oxyacylation of carbonyl compounds with carboxylic acids.¹⁰⁶ In the intramolecular (eq. 4.3) and intermolecular (eq. 4.4) oxidative coupling reactions of carbonyl compounds with carboxylic acids, tetra *n*-butylammonium iodide ($n\text{Bu}_4\text{NI}$) was used as a pre-catalyst with commercially available 30% aqueous hydrogen peroxide even at room temperature and *tert*-butyl hydroperoxide (TBHP) as an environmentally benign oxidant, respectively.

Either ammonium hypoiodite ($[\text{Bu}_4\text{N}]^+[\text{IO}]^-$) or iodite ($[\text{Bu}_4\text{N}]^+[\text{IO}_2]^-$) generated *in situ* from ammonium iodide (Bu_4NI) and a co-oxidant was proven to be the active species according to the results of the control experiments. To gain further insight into the reaction, additional control experiments employing the fragmentation of cyclopropylmethyl radicals were carried out (Scheme 4.6). The results suggested that a radical intermediate might be generated in the reaction.¹⁰⁷

¹⁰⁶ Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2011**, 50, 5331.

¹⁰⁷ (a) Griller, D.; Ingold, K. *Acc. Chem. Res.* **1980**, 13, 317. (b) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, 114, 10915.

Scheme 4.6 Control experiments with **75**

Most recently, Ishihara's group successfully realized an enantioselective oxidative cycloetherification of ketophenols to optically active 2-acyl-2,3-dihydrobenzofuran derivatives,¹⁰⁸ which are important structural units in several biologically active molecules.¹⁰⁹ By examining *N*-spiro-type quaternary ammonium iodide pre-catalyst **90** with chiral 3,3'-disubstituted 1,1'-binaphthyl skeletons for this reaction, the best results were provided when the pre-catalyst **90** and hydrogen peroxide as an environmentally benign oxidant were used (Scheme 4.7). In addition, control experiments had also showed that this reaction was catalyzed by in situ-generated chiral quaternary ammonium (hypo)iodite salts.

¹⁰⁸ Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, 328, 1376.

¹⁰⁹ (a) Bowen, D. M.; DeGraw Jr., J. I.; Shah, V. R.; Bonner, W. A. *J. Med. Chem.* **1963**, 6, 315. (b) Céspedes, C. L.; Uchoa, A.; Salazar, J. R.; Perich, F.; Pardo, F. *J. Agric. Food Chem.* **2002**, 50, 2283. (c) Cohen, J. L.; Limon, A.; Miledi, R.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **2006**, 16, 2189.

Scheme 4.7 Enantioselective oxidative cycloetherification of ketophenols to optically active 2-acyl-2,3-dihydrobenzofuran

4.2 $I_2(I^-)-Na_2CO_3 \cdot 1.5H_2O_2$ CATALYTIC SYSTEM

4.2.1 INTRODUCTION

Direct functionalization of molecules *via* transition-metal-free oxidative transformations has always been one of the most challenging research targets.²⁶ Over the past two decades, immense interest was directed on the applications of hypervalent iodine compounds in organic synthesis.⁹²⁻¹⁰⁸ Among them, especially noteworthy is the catalytic utility of hypervalent iodine. Therefore, it is very desirable to apply the catalytic system that involves the pre-catalyst containing an iodine source and stoichiometric co-oxidants for known reactions or the development of new reactions.⁹²⁻¹⁰⁸ On the other hand, α -amino acid derivatives play important roles in many drugs and natural products with biological activities.² However, the

development of novel methodologies for the preparation of these compounds still remain to be a hot research topics in these years. Recently, our group successfully developed copper-catalyzed oxidative rearrangement of tertiary amines or enamines and copper (I) iodide or indium (I) iodide-catalyzed α -amination of aliphatic aldehydes using nucleophilic secondary amines as a nitrogen source for the synthesis of α -amino acetals. As a result, with regard to atom economy and green sustainability, our goal is to provide a much simpler, safer, milder and cleaner process for the synthesis of α -amino acetals through the generation of active hypervalent iodine species *in situ* from readily available and environmentally benign co-oxidants such as molecular oxygen or hydrogen peroxide. Herein we would like to report α -amination of aldehydes with short carbon chain or bulky groups using secondary amines as a nitrogen source for the synthesis of α -amino acetals catalyzed by *in situ* generated hypoiodite with commercially available hydrogen peroxide or sodium percarbonate as the co-oxidant. This novel approach displayed many advantages, such as, metal-free oxidation, milder reaction conditions, more bulky substrates, and non toxic by-product derived from the co-oxidant used.

4.2.2 RESULTS AND DISCUSSION

In the initial optimization study, dibenzylamine **73a**, phenylacetaldehyde **74I** and methanol were selected as the model substrates and molecular iodine as the iodine source was chosen as the pre-catalyst to explore the suitable oxidants and reaction conditions. The typical results were summarized in Table 4.1. After the screening of potential co-oxidant of molecular oxygen, hydrogen peroxide (30 wt% in water), and sodium percarbonate, we found that when molecular oxygen and hydrogen peroxide was used as the co-oxidant for this α -amination, methanol was the most suitable

solvent and generated the desired product **91a** in the yields of 50% and 67% at room temperature, respectively (Table 4.1, entries 1-7). Interestingly, the desired product **91a** was obtained in the yield of 83% using sodium percarbonate as co-oxidant in dichloroethane (DCE) at 40 °C for 16 h (Table 4.1, entry 8). This reaction proceeded smoothly even at room temperature (20 °C) although the yield decreased slightly (Table 4.1, entry 9). Higher temperature (80 °C) resulted in a lower yield (61%) (Compare Table 4.1, entries 10 vs 8-9). As a result, the optimal temperature was found to be 40 °C. The effect of the solvent on the reaction also played an important role. DCE was shown to be the most suitable solvent, furnishing the desired product **91a** in an 83% isolated yield (Table 4.1, entry 8). Whereas, MeCN and 1,4-dioxane only provided moderate yields of 74% and 68% respectively (Table 4.1, entries 12-13). In comparison with molecular oxygen and hydrogen peroxide, only a low yield of 46% was obtained in methanol (Table 4.1, entry 11). The ideal ratio of **73a**:**74l** was established to be 1:1.5 (Table 4.1, entries 9, 14-15). In light of the optimization studies, the optimum conditions for the synthesis of α -amino acetals were the use of sodium percarbonate as the co-oxidant at 40 °C in DCE with the ratio of secondary amine to aldehyde (1:1.5) and the volume ratio of MeOH/DCE (1:4) in the presence of 0.2 equivalent of molecular iodine as the pre-catalyst.

Table 4.1 Optimization of the reaction conditions ^a

BnN(Bn) + O=CCc1ccccc1 >> COC(Cc1ccccc1)N(Bn)Bn

73a **74l** **91a**

Entry	Oxidant (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b
1	O ₂ (1 atm)	DCE	40	16	45

2	O ₂ (1 atm)	DCE	20	24	40
3	O ₂ (1 atm)	MeOH	20	24	50
4	30% H ₂ O ₂ (1.5)	DCE	40	16	41
5	30% H ₂ O ₂ (1.5)	DCE	20	24	39
6	30% H ₂ O ₂ (1.5)	MeOH	40	24	64
7	30% H ₂ O ₂ (1.5)	MeOH	20	24	67
8	Na₂CO₃·1.5 H₂O₂ (1.0)	DCE	40	16	83
9	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	DCE	20	24	79
10	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	DCE	80	24	61
11	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	MeOH	40	16	46
12	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	MeCN	40	16	74
13	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	1,4-Dioxane	40	16	68
14 ^c	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	DCE	40	24	74
15 ^d	Na ₂ CO ₃ ·1.5 H ₂ O ₂ (1.0)	DCE	40	24	61

^aReaction conditions: Dibenzylamine (0.5 mmol, 1.0 equiv.), phenylacetaldehyde (0.75 mmol), iodine (0.2 equiv.), oxidant (1.0 equiv.), methanol (0.5 mL), solvent (2 mL).

^bIsolated yields based on dibenzylamine **73a**.

^cDibenzylamine (0.5 mmol), phenylacetaldehyde (0.5 mmol).

^dDibenzylamine (0.75 mmol), phenylacetaldehyde (0.5 mmol).

Subsequently, we mainly investigated the scope of this α -amination of aldehydes with short carbon chain or bulky group under optimized conditions (Table 4.2). As shown in Table 4.2, the aldehydes with only one secondary carbon were converted into the corresponding α -amino acetals under the standard conditions and even a new C–N bond was directly constructed at the position of tertiary carbon. For the mono-substituted phenylacetaldehydes at the position of the aromatic ring such as methoxy or halo group, this reaction provided the α -amino acetals **91(b-d)** in good yields (75-78%) (Table 4.2, entries 2-4). The aldehyde **74p** with a bigger aromatic group such as naphthyl was also suitable for this reaction and the desired product **91e** was obtained in a moderate yield of 62% (Table 4.2, entry 5). Of note is that this mild condition could tolerate heterocyclic aromatic substituent. For example, the amination

of 2-(thiophen-3-yl)acetaldehyde **74q** afforded α -amino acetal **91f** in a moderate yield of 54% (Table 4.2, entry 6). The reaction was also very effective to branched aldehydes **74b** with an isopropyl group at α -position, which was aminated and provided the desired product **75b** in excellent yield of 82% (Table 4.2, entry 7). It is gratifying that aldehydes with tertiary carbon at the α -position worked well in this reaction and directly created a new quaternary carbon centre bearing a C–N bond, such as, cyclohexane carbaldehyde **74k** and cyclohex-3-ene carbaldehyde **74r** (Table 4.2, entries 8-9). Furthermore, we expanded the scope by investigating the effect of the different functionalities on the secondary amines. The secondary amines with allylic substituent **73(b-c)** or ester functionality **73d** were also suitable for this reaction, affording the corresponding α -amino acetals in moderate yields (Table 4.2, entries 10-12).

Table 4.2 Scope of aldehydes and secondary amines^{a,b}

^aReaction conditions: Secondary amines **73** (0.5 mmol, 1.0 equiv.), aldehydes (0.75 mmol), iodine (0.2 equiv.), sodium percarbonate (1.0 equiv.), methanol (0.5 mL), 1, 2-dichloroethane (2 mL).

^bIsolated yields based on secondary amines **73**.

The secondary amine **73e** with a stereogenic center can also be used for this reaction, furnishing the desired product in a good yield of 78% as a mixture of two diastereomers (1:1). Two optically active α -amino acetals were easily separated by silica-gel column chromatography (Scheme 4.8).

Scheme 4.8 Synthesis of α -amino acetals using chiral secondary amine

In order to better understand the reaction mechanism and the active intermediate involved, the following control experiments were conducted: (I) The enamine **71e** (*N,N*-diallyl-3-methylbut-1-en-1-amine) was utilized for this reaction, affording the desired product **72d** in 70% yield at room temperature under the standard conditions (Scheme 4.9). This showed that enamine was the intermediate of this α -amination.

Scheme 4.9 Control experiment

(II) The reactions with **73a** and **74l** were studied in DCE and methanol at 40 °C using iodized salts of different oxidation states. As shown in Table 4.3, the use of molecular iodine (I_2) and sodium iodate (NaIO_3) did not generate any of the desired product and only trace amount of product was detected using sodium periodate (NaIO_4) (Table 4.3, entries 1 and 3-4). In contrast, when the mixture of molecular iodine and potassium hydroxide was used for the generation of potassium hypoiodite (KIO) *in situ*,¹¹⁰ the desired product was obtained in the yield of 70% (Table 4.3, entry 2). As a result, hypoiodite (IO^-) or iodite (IO_2^-) may be the active intermediate for this reaction.

Table 4.3 Control experiments^a

Entry	Oxidant (equiv.)	Time (h)	Yield (%) ^b
1	I_2 (1.0)	24	0
2	I_2 (1.0) + KOH (2.0)	16	70
3	NaIO_3 (1.0)	24	0
4	NaIO_4 (1.0)	24	trace

^aReaction conditions: Dibenzyldiamine **73a** (0.5 mmol, 1.0 equiv.), phenylacetaldehyde (0.75 mmol), oxidant (1.0 equiv.), MeOH (0.5 mL), DCE (2.0 mL) at 40 °C for 16 h.

^bIsolated yields based on dibenzyldiamine **73a**.

¹¹⁰ Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, 33, 4329.

(III) When the reaction was carried out in the absence of methanol as shown in Scheme 4.10, eq. 4.5, no α -amino aldehyde was detected and only α -iodo aldehyde **92a** was isolated. This showed that (1) in the reaction dibenzylamine was used as the catalyst, not a reactant; (2) hypoiodite acid from the oxidation of molecular iodine led to the formation of the α -iodo iminium ion intermediate and (3) hypoiodite (IO^-) was suggested to be the active intermediate. Meanwhile, further reaction of dibenzylamine with α -iodo aldehyde **92a** in the presence of methanol afforded the desired α -amino acetal (Scheme 4.10, eq. 4.6).

Scheme 4.10 Control experiment

On the basis of these control experiments and the reports about hypervalent iodine chemistry,⁹²⁻¹⁰⁸ a proposed mechanism for *in situ* generated hypoiodite catalytic α -amination of aldehydes was presented in Scheme 4.11. In this proposed mechanism, hypoiodite acid, which was thought to function as one-electron oxidizing reagent or electrophilic reagent, was formed by the oxidation of I_2 or I^- by hydrogen

peroxide in the reaction system. Next, the reaction with enamine **A** provided the iminium ion **B**, which could be explained by control experiment (Scheme 4.10) that H_2O attacked on intermediate **B** to furnish α -iodo aldehyde. Subsequently, methanol attack on iminium ion **B** gave the iodo-substituted intermediate **C** and subsequent intramolecular cyclization afforded aziridinium ion **D**. Finally, additional methanol molecule captured the intermediate, affording the desired product.

Scheme 4.11 Proposed mechanism for α -amination of aldehydes catalyzed by *in situ* generated hypoiodite

4.2.3 SUMMARY

In summary, *in situ* generated hypoiodite catalytic α -amination of aldehydes with short carbon chain or bulky groups was developed through employing commercially available hydrogen peroxide or sodium percarbonate as the co-oxidant. In addition, a mechanism was proposed on the basis of control experiments.

4.3 RI-Na₂CO₃·1.5H₂O₂ CATALYTIC SYSTEM

4.3.1 INTRODUCTION

Direct α -amination of aldehydes using electrophilic or nucleophilic reagents as a nitrogen source has been one of most promising research areas for the construction of α -amino acid derivatives. Most recently, our group focused on metal-catalyzed oxidative transformations into the synthesis of α -amino acetals, such as InI-H₂O₂, CuI-TBHP, and CuBr₂/TMEDA/O₂. Subsequently, in situ generated hypoiodite catalyzed α -amination of aldehydes using nucleophilic secondary amines as a nitrogen source was also investigated. On the other hand, organohypervalent iodine with economical, environmental and scientific advantages had gained tremendous popularity in organic synthesis, especially their catalytic applications in enantioselective synthesis of organic molecules. Therefore, with the expectation to realize the synthesis of enantiopure α -amino acetals, we further explored the potential of organohypervalent iodine, which generated in situ from simple organic compounds with an iodo group under the assistance of environmentally benign co-oxidant, in the synthesis of α -amino acetals.

Herein we report a highly efficient α -amination of aldehydes using nucleophilic secondary amines as a nitrogen source for the synthesis of α -amino acetals in the catalytic systems of the iodo-containing compounds as the pre-catalyst and sodium percarbonate as the co-oxidant. This process is simple, mild, environmentally benign, and transition-metal free.

4.3.2 RESULTS AND DISCUSSION

To begin our study, dibenzylamine **73a**, butraldehyde **74a** and methanol were chosen as the standard substrates to optimize the pre-catalysts and reaction conditions. The results were summarized in Table 4.4. A series of organic compounds with an iodo group were investigated for the transformation with 20 mol% catalytic loading of the pre-catalysts and 1.0 equivalent of sodium percarbonate as the oxidant. Notably, the order of the catalytic activity of the pre-catalyst of iodine-containing compounds was found to be polyfluoro compound with iodo group (heptafluoro-2-iodopropane) > iodo group at 2° position of aliphatic carbon chain > 1° position of aliphatic carbon chain > iodo group in aromatic ring (Table 4.4, entries 1-6). Next, further optimization was carried out through examining the effect of solvents, temperature, and the volume ratio of methanol to 1,4-dioxane on the reaction. As a result, the most suitable reaction conditions were that the reaction was carried out using 20 mol% of heptafluoro-2-iodopropane as the pre-catalyst and 1.0 equivalent of sodium percarbonate as the co-oxidant at 60 °C with the volume ratio of methanol to 1,4-dioxane (1:4).

Table 4.4 Scope of the pre-catalysts for α -amination of aldehydes using dibenzylamine **73a** and butyraldehyde **74a**^a

Entry	Pre-catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b
1		1,4-Dioxane	60	24	84

2		1,4-Dioxane	60	24	55
3		1,4-Dioxane	60	24	46
4		1,4-Dioxane	60	24	78
5		1,4-Dioxane	60	24	trace
6		1,4-Dioxane	60	17	94
7		DCE	60	17	45

^aReaction conditions: Dibenzylamine (0.5 mmol, 1.0 equiv.), butyraldehyde (0.6 mmol), iodine-containing compound (0.2 equiv.), sodium percarbonate (1.0 equiv.), methanol (0.5 mL), solvent (2 mL).

^bIsolated yields based on dibenzylamine **73a**.

With the optimized conditions in hand, a variety of secondary amines and aliphatic aldehydes were found to be suitable for this α -amination of aliphatic aldehydes, giving excellent yields, for example, dibenzylamine and butyraldehyde as shown in Table 4.4, entry 6. Here we mainly introduced the representative results of α -amination of aliphatic aldehydes, which were summarized in Table 4.5, in order to support the further application in the construction of dopamine D1 receptor ligands. As shown in Table 4.5, a variety of secondary amines were suitable for this reaction. Furthermore, the introduction of electron donating or withdrawing groups onto the aromatic ring of the secondary amines almost had no effect on the reactions, affording the desired products in good yields (Table 4.5, entries 2-4, 8-9). The mild reaction conditions displayed tolerance to a variety of functional groups such as phenethyl, 1-naphthylmethyl, and 2-naphthylmethyl (Table 4.5, entries 5-7). Aliphatic aldehyde with shorter carbon chain was used for this reaction and the desired product was

4.3.3 SUMMARY

In summary, highly efficient in situ generated organohypervalent iodine catalyzed α -amination of aldehydes using nucleophilic secondary amines as a nitrogen source for the synthesis of α -amino acetals was studied. This approach displayed the advantages of mild and environmentally benign reaction conditions, non-toxicity, and easy handling.

4.4 CONCLUSION

In this chapter, the transition-metal-free catalytic systems of $I_2(I)$ - $Na_2CO_3 \cdot 1.5H_2O_2$, and $RI-Na_2CO_3 \cdot 1.5H_2O_2$ showed better catalytic activities and broad scope of substrates, especially for the aldehydes with short carbon chain or bulky groups, which afforded no or trace corresponding α -amino acetals in the catalytic systems of $CuI(Br)$ -TBHP and $InI(Br)-Na_2CO_3 \cdot 1.5H_2O_2$. (1) In situ generated hypoiodite catalyzed α -amination of aldehydes with short carbon chain or bulky groups was developed through commercially available hydrogen peroxide or sodium percarbonate as the co-oxidant. In addition, a mechanism was proposed on the basis of control experiments. (2) A highly efficient in situ generated (organo)hypervalent iodine catalyzed α -amination of aldehydes was also investigated for the synthesis of α -amino acetals. This approach displayed the advantages of having mild and environmentally benign reaction conditions, non-toxicity, and easy handling. This catalytic system was developed for the purpose of preparing for α -amino acetals to further construction the potential dopamine D1 receptor ligands.

4.5 EXPERIMENTAL SECTION

4.5.1 I₂(I⁻)-Na₂CO₃·1.5H₂O₂ Catalytic System

I. General procedures

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Molecular iodine and sodium percarbonate (available 20-30% H₂O₂) were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. Secondary amines **73** (**c**, **e**)¹¹¹ and aldehydes **74** (**I-i**)¹¹² were synthesized according to literatures.

II. General experimental procedure for *in situ* generated hypoiodite catalyzed α -amination of aldehydes

Typical procedure for *in situ* generated hypoiodite catalytic α -amination of aldehydes for the synthesis of α -amino acetals (dibenzylamine **73a** and phenylacetaldehyde **74I** as a model system): sodium percarbonate (79 mg, 0.5 mmol) was added to a mixture of iodine (25 mg, 0.1 mmol), dibenzylamine **73a** (98 mg, 0.5 mmol), and phenylacetaldehyde **74I** (90 mg, 0.75 mmol) in methanol (0.5 mL)/dichloroethane (2.0 mL) at room temperature. The mixture was stirred at 40 °C until dibenzylamine **73a**

¹¹¹ (a) Soede-Huijbregts, C.; Laren, M. van; Hulsbergen, F. B.; Raap, J.; Lugtenburg, J. *J. Labelled Cpd. Radiopharm.* **2001**, *44*, 831. (b) Ammon, H. L.; Mariano, P. S.; Dunaway-Mariano, D. *J. Org. Chem.* **1991**, *56*, 7121.

¹¹² (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Ireland, R. E.; Liu, L. B. *J. Org. Chem.* **1993**, *58*, 2899.

was completely converted by TLC detection. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **91a** as light yellow oil (0.150 g, 83%).

***N,N*-dibenzyl-2,2-dimethoxy-1-phenylethanamine (91a) :**

$R_f = 0.68$ (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.41-7.36 (m, 6H), 7.33-7.26 (m, 7H), 7.23-7.19 (m, 2H), 4.96 (d, $J = 7.40$ Hz, 1H), 3.86 (d, $J = 7.39$ Hz, 1H), 3.57 (dd, $J = 50.34, 13.61$ Hz, 4H), 3.74 (s, 4H), 3.21 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.0 (C x 2), 136.3, 129.6 (CH x 2), 129.0 (CH x 4), 128.1 (CH x 4), 128.0 (CH x 2), 127.2, 126.8 (CH x 2), 104.4, 62.4, 54.8, 54.5 (CH_2 x 2), 52.1 ppm

FTIR (neat): $\nu = 3011, 2930, 1495, 1217, 756, 700\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 362.2120, found: 362.2130.

***N,N*-dibenzyl-2,2-dimethoxy-1-(3-methoxyphenyl)ethanamine (91b) :**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 75% yield.

R_f = 0.60 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.42-7.40 (m, 4H), 7.33-7.29 (m, 5H), 7.24-7.20 (m, 2H), 6.89-6.81 (m, 3H), 4.95 (d, J = 7.45 Hz, 1H), 3.84 (s, 3H), 3.83 (d, J = 7.49 Hz, 1H), 3.59 (AB_q, J = 13.46 Hz, 4H), 3.35 (s, 3H), 3.23 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 159.3, 140.1 (C x 2), 137.9, 129.1 (CH x 4), 128.9, 128.1 (CH x 4), 126.9 (CH x 2), 121.9, 115.8, 112.3, 104.4, 62.4, 55.2, 54.9, 54.6 (CH₂ x 2), 52.1 ppm

FTIR (neat): ν = 3011, 1560, 1492, 1217, 756, 700 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 392.2226, found: 362.2230.

***N,N*-dibenzyl-1-(3-chlorophenyl)-2,2-dimethoxyethanamine (91c) :**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 76% yield.

R_f = 0.68 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.39-7.37 (m, 4H), 7.32-7.29 (m, 7H), 7.24-7.20 (m, 2H), 7.18-7.15 (m, 1H), 4.90 (d, J = 7.07 Hz, 1H), 3.83 (d, J = 7.07 Hz, 1H), 3.53 (AB_q, J = 13.48 Hz, 4H), 3.33 (s, 3H), 3.23 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 139.7 (C x 2), 138.6, 133.9, 129.6, 129.2, 129.0 (CH x 4), 128.2 (CH x 4), 127.8, 127.3, 127.0 (CH x 2), 104.5, 62.1, 54.9, 54.5 (CH₂ x 2), 52.6 ppm

FTIR (neat): $\nu = 3011, 1495, 1217, 756, 702 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{27}\text{ClNO}_2^+ [\text{M}+\text{H}]^+$ 396.1730, found: 396.1735.

***N,N*-dibenzyl-1-(4-fluorophenyl)-2,2-dimethoxyethanamine (91d) :**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 78% yield.

$R_f = 0.68$ (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.43-7.41 (m, 4H), 7.35-7.23 (m, 8H), 7.12-7.07 (m, 2H), 4.93 (d, $J = 7.02 \text{ Hz}$, 1H), 3.88 (d, $J = 7.02 \text{ Hz}$, 1H), 3.61 (AB_q, $J = 13.49 \text{ Hz}$, 4H), 3.37 (s, 3H), 3.26 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 162.0 (d, $J = 122 \text{ Hz}$), 139.9 (C x 2), 132.2 (d, $J = 1.75 \text{ Hz}$), 131.1 (d, $J = 3.8 \text{ Hz}$, CH x 2), 129.0 (CH x 4), 128.2 (CH x 4), 126.9 (CH x 2), 114.8 (d, $J = 104.5 \text{ Hz}$, CH x 2), 104.9, 61.7, 54.8, 54.5 (CH_2 x 2), 52.7 ppm.

FTIR (neat): $\nu = 3017, 1603, 1508, 1215, 756, 702 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{27}\text{FNO}_2^+ [\text{M}+\text{H}]^+$ 380.2026, found: 380.2025.

***N,N*-dibenzyl-2,2-dimethoxy-1-(naphthalen-2-yl)ethanamine (91e):**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 62% yield.

$R_f = 0.75$ (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.84-7.78 (m, 2H), 7.67-7.65 (m, 1H), 7.52-7.41 (m, 3H), 7.31-7.18 (m, 11H), 5.14 (d, $J = 7.07$ Hz, 1H), 4.84 (d, $J = 7.09$ Hz, 1H), 3.75 (AB_q, $J = 13.70$ Hz, 4H), 3.53 (s, 3H), 3.15 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.3 (C x 2), 133.95, 133.90, 133.2, 129.2 (CH x 4), 128.6, 128.0 (CH x 4), 127.8, 126.8 (CH x 2), 126.2, 125.5, 125.2, 124.6, 124.4, 105.9, 57.4, 54.8 (CH_2 x 2), 54.3, 53.9 ppm

FTIR (neat): $\nu = 3017, 2378, 1215, 756, 670\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{28}\text{H}_{30}\text{NO}_2^+ [\text{M}+\text{H}]^+$ 412.2277, found: 412.2278.

N,N-dibenzyl-2,2-dimethoxy-1-(thiophen-3-yl)ethanamine (91f) :

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 54% yield.

$R_f = 0.78$ (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.42-7.40 (m, 4H), 7.35-7.30 (m, 5H), 7.25-7.19 (m, 3H), 7.14-7.12 (m, 1H), 4.86 (d, $J = 6.62$ Hz, 1H), 4.00 (d, $J = 6.62$ Hz, 1H), 3.60 (AB_q, $J = 13.50$ Hz, 4H), 3.31 (s, 3H), 3.29 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.1 (C x 2), 137.1, 129.0 (CH x 4), 128.7, 128.2 (CH x 4), 126.9 (CH x 2), 124.6, 123.6, 105.4, 58.1, 54.9, 54.8 (CH_2 x 2), 52.6 ppm

FTIR (neat): $\nu = 3015, 2833, 1217, 756, 700\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_2\text{S}^+ [\text{M}+\text{H}]^+$ 368.1684, found: 368.1676.

***N,N*-dibenzyl-1-(dimethoxymethyl)cyclohex-3-enamine (91g):**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 38% yield at 60 °C.

R_f = 0.83 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.19-7.17 (m, 4H), 7.12-7.08 (m, 4H), 7.05-7.02 (m, 2H), 5.74-5.71 (m, 1H), 5.49-5.46 (m, 1H), 4.26 (s, 1H), 4.05 (AB_q, J = 15.26 Hz, 4H), 3.53 (s, 3H), 3.49 (s, 3H), 2.39-2.22 (m, 3H), 2.03-1.86 (m, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 142.7 (C x 2), 128.6 (CH x 4), 127.5 (CH x 4), 126.7, 125.8 (CH x 2), 124.9, 111.9, 61.7, 59.0, 57.8, 54.3 (CH₂ x 2), 30.4, 27.6, 22.8 ppm

FTIR (neat): ν = 3016, 1215, 756, 702, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 352.2277, found: 352.2280.

***N*-benzyl-*N*-(2,2-dimethoxy-1-phenylethyl)prop-2-en-1-amine (91h) :**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 68% yield.

R_f = 0.69 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.41-7.36 (m, 6H), 7.33-7.26 (m, 7H), 7.23-7.19 (m, 2H), 4.96 (d, J = 7.40 Hz, 1H), 3.86 (d, J = 7.39 Hz, 1H), 3.57 (dd, J = 50.34, 13.61 Hz, 4H), 3.74 (s, 4H), 3.21 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.0 (C x 2), 136.3, 129.6 (CH x 2), 129.0 (CH x 4), 128.1 (CH x 4), 128.0 (CH x 2), 127.2, 126.8 (CH x 2), 104.4, 62.4, 54.8, 54.5 (CH_2 x 2), 52.1 ppm

FTIR (neat): ν = 3017, 1215, 758, 700, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 312.1964, found: 312.1964.

Methyl 2-(benzyl(2,2-dimethoxy-1-phenylethyl)amino)acetate (91i):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 60% yield.

R_f = 0.51 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.43-7.41 (m, 2H), 7.37-7.32 (m, 4H), 7.30-7.19 (m, 4H), 4.72 (d, J = 5.82 Hz, 1H), 4.11 (d, J = 5.81 Hz, 1H), 3.78 (dd, J = 75.70, 13.58 Hz, 2H), 3.63 (s, 3H), 3.42 (s, 3H), 3.41 (dd, J = 154.18, 17.56 Hz, 2H), 3.26 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 172.5, 139.3, 138.0, 129.4 (CH x 2), 128.9 (CH x 2), 128.2 (CH x 2), 128.1 (CH x 2), 127.3, 127.0, 106.1, 65.3, 55.5, 55.0, 54.2, 51.4, 51.1 ppm

FTIR (neat): ν = 3017, 1743, 1217, 770, 700, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 344.1862, found: 344.1866.

***N*-allyl-*N*-(2,2-dimethoxy-1-phenylethyl)prop-2-en-1-amine (91j) :**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 45% yield.

R_f = 0.64 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.34-7.25 (m, 5H), 5.90-5.80 (m, 2H), 5.19-5.10 (m, 4H), 4.23 (d, J = 7.11 Hz, 1H), 3.97 (d, J = 7.10 Hz, 1H), 3.45 (s, 4H), 3.39-3.34 (m, 2H), 3.28 (s, 3H), 2.81-2.76 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 137.1 (CH x 2), 136.4, 129.5 (CH x 2), 127.8 (CH x 2), 127.0, 116.9 (CH₂ x 2), 104.6, 63.9, 54.7, 53.7 (CH₂ x 2), 53.2 ppm

FTIR (neat): ν = 3015, 2930, 1215, 756, 704, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 262.1807, found: 262.1808.

2,2-dimethoxy-*N*-methyl-1-phenyl-*N*-((*R*)-1-phenylethyl)ethanamine (91k) :

One isomer:

Light yellow oil

R_f = 0.59 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.36-7.18 (m, 10H), 4.81 (d, J = 6.68 Hz, 1H), 4.02 (d, J = 6.68 Hz, 1H), 3.73 (q, J = 6.55 Hz, 1H), 3.48 (s, 3H), 3.24 (s, 3H), 2.19 (s, 3H), 1.32 (d, J = 6.58 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 145.7, 138.2, 129.3 (CH x 2), 128.1 (CH x 2), 127.9 (CH x 2), 127.6 (CH x 2), 126.9, 126.6, 105.0, 64.5, 60.4, 54.5, 53.9, 34.5, 18.3 ppm

FTIR (neat): ν = 3016, 1215, 770, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 300.1964, found: 300.1963.

Another isomer:

Light yellow oil

R_f = 0.51 (hexane: ethyl acetate = 4:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.41-7.39 (m, 2H), 7.36-7.32 (m, 4H), 7.29-7.22 (m, 4H), 4.75 (d, J = 6.77 Hz, 1H), 3.84 (d, J = 6.79 Hz, 1H), 3.60 (q, J = 6.71 Hz, 1H), 3.36 (s, 3H), 3.22 (s, 3H), 2.28 (s, 3H), 1.26 (d, J = 6.64 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 145.5, 136.8, 129.8 (CH x 2), 128.3 (CH x 2), 127.73 (CH x 2), 127.69 (CH x 2), 127.0, 126.7, 105.3, 64.9, 61.3, 54.8, 54.0, 33.9, 21.1 ppm

FTIR (neat): ν = 3016, 1215, 770, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 300.1964, found: 300.1963.

Light yellow oil

^1H NMR (CDCl_3 , 400 MHz) δ 9.28 (d, J = 2.63 Hz, 1H), 7.33-7.24 (m, 3H), 7.19-7.17 (m, 2H), 4.71-4.67 (m, 1H), 3.48 (dd, J = 14.66, 7.75 Hz, 1H), 3.19 (dd, J = 14.66, 7.32 Hz, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 191.0, 138.0, 128.9 (CH x 2), 128.7 (CH x 2), 127.2, 38.5, 35.9 ppm

4.5.2 RI-Na₂CO₃·1.5H₂O₂ Catalytic System

I. General procedures

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Pre-catalysts (compounds containing iodo group) and sodium percarbonate (available 20-30% H₂O₂) were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. Secondary amines **73** (**f-o**)¹¹³ were synthesized according to literatures.

II. General experimental procedure for α -amination of aliphatic aldehydes catalyzed by in situ generated organohypervalent iodine.

Typical procedure for α -amination of aliphatic aldehyde for the synthesis of α -amino acetal using secondary amines with as a nitrogen source catalyzed by in situ generated (organo)hypervalent iodine (dibenzylamine **73a** and butyraldehyde **74a** as a model system): sodium percarbonate (79 mg, 0.5 mmol) was added to a mixture of heptafluoro-2-iodopropane (29.6 mg, 0.1 mmol), dibenzylamine **73a** (98 mg, 0.5 mmol), and butyraldehyde **74a** (54 mg, 0.75 mmol) in methanol (0.5 mL)/1,4-dioxane (2.0 mL) at room temperature. The mixture was stirred at 60 °C until dibenzylamine

¹¹³ (a) Venkov, A. P.; Vodenicharov, D. M. *Synthesis*, **1990**, 253. (b) Brishor-Myers Squibb Company. WO 2004/106293 A2, **2004**.

73a was completely converted by TLC detection. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (silica gel; ethyl acetate or diethyl ether/hexane = 1:100) to afford the desired product **75a** (*N,N*-dibenzyl-1,1-dimethoxybutan-2-amine) as light yellowish oil (0.147 g, 94% yield).

***N*-benzyl-1,1-dimethoxy-*N*-methyl-4-phenylbutan-2-amine (91l):**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 77% yield.

R_f = 0.65 (hexane: ethyl acetate = 3:1)

^1H NMR (CDCl_3 , 300 MHz) δ 7.37-7.16 (m, 10H), 4.37 (d, J = 6.00 Hz, 1H), 3.75 (ABq, J = 13.7 Hz, 2H), 3.35 (d, J = 14.49 Hz, 6H), 2.92-2.85 (m, 1H), 2.77-2.66 (m, 2H), 2.28 (s, 3H), 1.79 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 143.0, 140.8, 128.61, 128.59, 128.28, 128.19, 126.69, 125.61, 106.47, 62.8, 59.2, 54.35, 54.14, 37.2, 33.3, 29.1 ppm

FTIR (neat): ν = 3024, 2931, 1600, 1494, 1452, 1363, 1070, 964, 756, 698 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 314.2120, found: 314.2125.

1,1-dimethoxy-*N*-(4-methoxybenzyl)-*N*-methyl-4-phenylbutan-2-amine (91m):

Light yellow oil

R_f = 0.53 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.28-7.13 (m, 7H), 6.87-6.83(m, 2H), 4.35 (d, J = 5.99 Hz, 1H), 3.79 (s, 3H), 3.74 (ABq, J = 13.51 Hz, 2H), 3.33 (d, J = 13.52 Hz, 6H), 2.89-2.82 (m, 1H), 2.76-2.62 (m, 2H), 2.27 (s, 3H), 1.77 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 158.5, 143.0, 132.8, 129.7, 128.6, 128.3, 125.6, 113.6, 106.44, 62.4, 58.6, 55.3, 54.3, 54.1, 36.9, 33.3, 28.9 ppm

FTIR (neat): ν = 3010, 2933, 1610, 1510, 1454, 1363, 1244, 1124, 1035, 964, 754, 667 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{30}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 344.2226, found: 344.2233.

***N*-(4-chlorobenzyl)-1,1-dimethoxy-*N*-methyl-4-phenylbutan-2-amine (91n):**

Light yellow oil

R_f = 0.63 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.28-7.23 (m, 6H), 7.19-7.15 (m, 3H), 4.33 (d, J = 6.02 Hz, 1H), 3.76 (ABq, J = 13.82 Hz, 2H), 3.35 (s, 3H), 3.32 (s, 3H), 2.90-2.81 (m, 1H), 2.73-2.60 (m, 2 H), 2.29 (s, 3H), 1.83-1.74 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 142.8, 139.3, 132.2, 129.9, 128.5, 128.3, 125.7, 106.5, 62.7, 58.6, 54.4, 54.1, 36.9, 33.27, 29.0 ppm

FTIR (neat): ν = 3012, 2933, 1489, 1217, 1122, 1068, 964, 756, 667 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{27}\text{ClNO}_2^+$ $[\text{M}+\text{H}]^+$ 348.1730, found: 348.1741.

1,1-dimethoxy-*N*-methyl-*N*-(4-nitrobenzyl)-4-phenylbutan-2-amine (91o):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 64% yield.

R_f = 0.53 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 8.15 (d, J = 8.66 Hz, 2H), 7.51 (d, J = 8.62 Hz, 2H), 7.20-7.15 (m, 5H), 4.36 (d, J = 6.15 Hz, 1H), 3.91 (ABq, J = 14.9 Hz, 2H), 3.40 (s, 3H), 3.34 (s, 3H), 2.93-2.76 (m, 1H), 2.76-2.65 (m, 2H), 2.29 (s, 3H), 1.89-1.82 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 148.9, 147.0, 142.5, 128.9, 128.5, 128.3, 125.8, 123.5, 106.5, 63.2, 58.8, 54.6, 54.2, 37.2, 33.3, 29.1 ppm

FTIR (neat): ν = 3022, 2935, 1600, 1517, 1452, 1344, 1217, 1124, 1066, 968, 754, 700 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 359.1971, found: 359.1967.

1,1-dimethoxy-*N*-methyl-*N*-(naphthalen-2-ylmethyl)-4-phenylbutan-2-amine (91p):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 62% yield.

$R_f = 0.63$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.84-7.74 (m, 4H), 7.55 (d, $J = 8.74$ Hz, 1H), 7.46-7.43 (m, 5H), 4.41 (d, $J = 6.08$ Hz, 1H), 3.97 (ABq, $J = 13.72$ Hz, 2H), 3.36 (d, $J = 6.00$ Hz), 3.39 (s, 3H), 3.34 (s, 3H), 2.96-2.80 (m, 1H), 2.77-2.67 (m, 2H), 2.32 (s, 3H), 1.84 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 142.9, 138.6, 132.8, 128.6, 128.3, 127.8, 127.7, 127.6, 127.2, 127.0, 125.8, 125.6, 125.4, 106.5, 62.8, 59.5, 54.4, 54.1, 37.2, 33.4, 29.1 ppm

FTIR (neat): $\nu = 3010, 2933, 1600, 1454, 1367, 12115, 1122, 1066, 962, 756, 667$ cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 364.2277, found: 364.2284.

1,1-dimethoxy-*N*-methyl-*N*-(naphthalen-1-ylmethyl)-4-phenylbutan-2-amine

(91q):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 62% yield.

$R_f = 0.68$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 8.26 (d, $J = 8.34$ Hz, 1H), 7.85 (d, $J = 6.00$ Hz, 1H), 7.76 (d, $J = 7.88$ Hz, 1H), 7.49-7.37 (m, 4H), 7.20 (m, 2H), 7.13 (d, $J = 7.60$ Hz, 1H), 7.07 (d, $J = 7.60$ Hz, 2H), 4.42 (d, $J = 5.85$ Hz, 1H), 4.21 (s, 2H), 3.35 (d, $J = 12.5$ Hz, 6H), 2.86-2.72 (m, 2H), 2.56-2.48 (m, 1H), 2.35 (s, 3H), 1.82 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 143.0, 135.7, 133.9, 132.6, 129.4, 128.5, 128.4, 128.2, 127.6, 127.1, 125.5, 125.2, 124.8, 106.7, 62.1, 57.9, 54.6, 54.1, 36.7, 33.4, 28.8 ppm

FTIR (neat): $\nu = 3012, 2933, 1597, 1454, 1217, 1122, 1068, 962, 756, 667 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 364.2277, found: 364.2274.

1,1-dimethoxy-*N*-methyl-*N*-phenethyl-4-phenylbutan-2-amine (91r):

Light yellow oil

$R_f = 0.53$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.30-7.11, 4.26 (d, $J = 5.96 \text{ Hz}$, 1H), 3.31 (d, $J = 7.54 \text{ Hz}$, 6H), 2.90-2.49(m, 7H), 2.41 (s, 3H), 1.73 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 142.9, 141.0, 128.9, 128.6, 128.2, 128.1, 125.8, 125.4, 106.5, 63.4, 56.9, 54.4, 54.3, 37.5, 35.5, 33.0, 28.7 ppm

FTIR (neat): $\nu = 3016, 2949, 1600, 1454, 1373, 1215, 1122, 1068, 756, 669 \text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{30}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 328.2277, found: 328.2277.

***N*-benzyl-1,1-dimethoxy-*N*-methyl-3-phenylpropan-2-amine (91s):**

Light yellow oil

$R_f = 0.65$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.30-7.1.5 (m, 8H), 7.06-7.03 (m, 2H), 4.39 (d, J = 5.62 Hz, 1H), 3.70 (ABq, J = 13.68 Hz, 2H), 3.40 (d, J = 5.52 Hz, 6H), 3.09-3.03 (m, 1H), 2.88-2.80 (m, 2H), 2.29 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 141.2, 140.4, 129.4, 128.5, 128.0, 127.9, 126.5, 125.6, 106.4, 65.2, 59.8, 54.5, 54.4, 37.1, 32.93 ppm

FTIR (neat): ν = 3014, 2933, 1602, 1452, 1367, 1215, 1122, 1074, 966, 756, 667 cm^{-1}

¹.

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 300.1964, found: 300.1962.

***N*-benzyl-*N*-(2,6-dichlorobenzyl)-1,1-dimethoxy-4-phenylbutan-2-amine (91t):**

Light yellow oil

R_f = 0.74 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.27-7.00 (m, 13H), 4.50 (d, J = 4.75 Hz, 1H), 3.77 (ABq, J = 13.01 Hz, 2H), 3.36 (ABq, J = 15.6 Hz, 2H), 3.35 (s, 5H), 2.90-2.76 (m, 2H), 2.44-2.31 (m, 1H), 1.97-1.80 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 143.2, 140.8, 137.2, 135.3, 129.0, 128.7, 128.5, 128.4, 128.2, 127.7, 126.5, 125.4, 107.5, 60.7, 55.3, 54.7, 54.4, 50.6, 33.6, 28.5 ppm.

FTIR (neat): ν = 3014, 2933, 1600, 1435, 1373, 1215, 1136, 1070, 960, 756, 667 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{26}\text{H}_{30}\text{Cl}_2\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 458.1654, found: 458.1665.

***N*-(3,4-dimethoxybenzyl)-1,1-dimethoxy-*N*-methyl-4-phenylbutan-2-amine (91u):**

Light yellow oil

R_f = 0.33 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 300 MHz) δ 7.29-7.16 (m, 5H), 6.99 (s, 1H), 6.85-6.79 (m, 2H), 4.36 (d, J = 5.98 Hz, 1H), 3.87 (s, 6H), 3.75 (ABq, J = 20.21 Hz, 2H), 3.35 (d, J = 14.67 Hz, 6H), 2.91-2.86 (m, 1H), 2.66 (m, 2H), 2.29 (s, 3H), 1.80 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 300 MHz) δ 148.9, 147.8, 142.9, 133.4, 128.5, 128.3, 128.6, 120.5, 111.7, 110.8, 106.4, 62.4, 58.9, 55.9, 55.8, 54.3, 54.1, 37.0, 33.4, 28.9 ppm

FTIR (neat): ν = 3018, 2935, 1512, 1456, 1217, 1136, 1029, 966, 754, 665 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 374.2331, found: 374.2331.

CHAPTER 5

***Constuction of Dihydro-methano-dibenzoazocines and
Dopamine D1 Receptor Ligands***

CHAPTER 5 CONSTRUCTION OF DIHYDRO-METHANO- DIBENZOAZOCINES AND DOPAMINE D1 RECEPTOR

5.1 OVERVIEW

In recent years, much more efforts had been focused on Friedel-Crafts-like alkylations, which could directly construct many structural units in polycyclic natural products or diarylmethane motif consisting of biologically active compounds and pharmaceuticals.¹¹⁴ Traditionally, toxic organo halides together with aluminum chloride were used for the generation of carbocation. As a result, recent research interest in this area is concentrated on the utilization of alcohols with or without protecting groups as a replacement of toxic organo halides.¹¹⁵ Some excellent results¹¹⁶ were reported. For example, many kinds of diarylmethanes and arylheteroarylmethanes were synthesized through iron-catalyzed arylation of benzyl alcohols and benzyl carboxylates as the key step.¹¹⁷ These newly developed methods of Friedel-Crafts-like alkylations showed the advantages of milder reaction conditions and the use of inexpensive and relatively non-toxic catalysts without strong acid. Herein iron(III) chloride mediated Friedel-Crafts double cyclizations for the

¹¹⁴ (a) Skabara, P. J.; Serebryako, I. M.; Perepichka, I. F. *Synth. Met.* **1999**, *102*, 1336. (b) Khan, M. S.; Al-Mandhary, M. R. A.; Al-Suti, M. K.; Ahrens, B.; Mahon, M. F.; Male, L.; Raithby, P. R.; Boothby, C. E.; Kohler, A. *Dalton Trans.* **2003**, 74. (c) Jacob, J.; Oldridge, L.; Zhang, J. Y.; Gaal, M.; List, E. J. W.; Grimsdale, A. C.; Müllen, K. *Curr. Appl. Phys.* **2004**, *4*, 339.

¹¹⁵ (a) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzzello, D.; De Vincentis, F.; Cozzi, P. *Eur. J. Org. Chem.* **2011**, *4*, 647. (b) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (c) Muzart, J. *Tetrahedron* **2008**, *64*, 5815.

¹¹⁶ (a) Olah, G. A.; Krishnamurti, R.; Prakash G. K. S. in *Comprehensive Organic Synthesis*, Vol. 3 (Eds.: Trost, B. M.; Fleming, I.), Pergamon, Oxford, 1991, pp. 293-339. (b) Tsuchimoto, T.; Ozawa, Y.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 4231. (c) Stadler, D.; Bach, T. *Chem. Asian J.* **2008**, *3*, 272. (d) Davoust, M.; Kitching, J. A.; Fleming, M. J.; Lautens, M. *Chem. Eur. J.* **2010**, *16*, 50.

¹¹⁷ Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913.

construction of dihydro-methano-dibenzoazocines and dopamine D1 receptor ligands will be described.

5.2 ONE-POT SYNTHESIS OF DIHYDRO-METHANO-DIBENZOAZOCINES FROM α -AMINO ACETALS VIA INTRAMOLECULAR DOUBLE FRIEDEL-CRAFTS CYCLIZATION

5.2.1 INTRODUCTION

From a 3-dimensional perspective of the generic structure **93** (Figure 5.1), two tetrahydroisoquinoline motifs of 7,12-dihydro-5H-6,12-methano-dibenzo[*c,f*]azocine through a common nitrogen atom constitute a bridged structure.

Figure 5.1 Perspective drawings of dihydro-methano-dibenzoazocines

Owing to the pharmacological properties of dibenzoazocine structural unit in the central nervous system, this class of structural compounds is very useful in the treatment of Alzheimer or Parkinson diseases.¹¹⁸ On the other hand, they are also widely utilized as the potential intermediates for the preparation of alkaloids such as

¹¹⁸ (a) Soine, T. O.; Gisvold, O. *J. Am. Pharm. Assoc., Sci. Ed.* **1944**, 33, 185. (b) Casadio, S.; Pala, G.; Crescenzi, E.; Marazzi-Uberti, E.; Coppi, G.; Turba, C. *J. Med. Chem.* **1968**, 11, 97.

argemonine,^{118a} thalidine,¹¹⁹ isopavines (Scheme 5.1),¹²⁰ and other related structural types.¹²¹

(i) (3,4)-Dimethoxybenzyl bromide, NaHCO_3 , THF/DMSO, reflux, (ii) LiAlH_4 , THF, 0 °C to room temperature, (iii) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C, (iv) AlCl_3 , CH_2Cl_2 , 0 °C to room temperature, (v) RX, acetone, reflux, (vi) *t*-BuOK, dioxane, 80 °C.

Scheme 5.1 Synthesis of O-Methylthalisopavine

Traditionally, the synthesis of dihydro-methano-dibenzoazocines was only limited to the intramolecular acid-catalyzed Friedel-Crafts cyclization of *N,N*-dibenzyl amino acetaldehyde dimethylacetals.¹²² Recently, Hanessian's group reported the synthesis of dihydro-methano-dibenzoazocines with a substituent at C-13 from Friedel-Crafts double cyclizations of *N,N*-dibenzyl α -amino aldehydes, which were prepared from the corresponding natural α -amino acids.¹²³ As presented in Chapter 4, a variety of α -amino acetals can be prepared from commercially available

¹¹⁹ Shamma, M.; Moniot, J. L.; Chinnasamy, P. *Heterocycles* **1977**, 6, 399.

¹²⁰ (a) Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, 62, 6716. (b) Hanessian, S.; Parthasarathy, S.; Mauduit, M. *J. Med. Chem.* **2003**, 46, 34.

¹²¹ (a) Gözler, B. *The Alkaloids* **1987**, 31, 317. (b) Kametani, T. *The Chemistry of the Isoquinoline Alkaloids*; Elsevier: Amsterdam, **1969**.

¹²² (a) Brown, D. W.; Dyke, S. F.; Harky, G.; Sainsbury, M. *Tetrahedron Lett.* **1968**, 2609. (b) Sainsbury, M.; Brown, D. W.; Dyke, S. F.; Harky, G. *Tetrahedron* **1969**, 25, 1881. (c) Bobbitt, J. M.; Shibuya, S. *J. Org. Chem.* **1970**, 35, 1181. (d) Takayama, H.; Takamoto, M.; Okamoto, T. *Tetrahedron Lett.* **1978**, 1307. (e) Hara, H.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull.* **1985**, 33, 2705. (f) Nomoto, T.; Nasui, N.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1646.

¹²³ Hanessian, S.; Mauduit, M.; Demont, E.; Talbot, C. *Tetrahedron* **2002**, 58, 1485.

aldehydes and secondary amines. Therefore, to simplify the routes and broaden the scope of dihydro-methano-diarylazocines, we tried to realize one-pot construction of dihydro-methano-diarylazocines from α -amino acetals employing iron(III) chloride as a milder alternative Lewis acid.¹²⁴

Herein we reported one-pot construction of dihydro-methano-diarylazocines from α -amino acetals through iron (III) chloride-mediated Friedel-Crafts double cyclizations (Scheme 5.2). This method is unrestricted to natural α -amino acids and has more broad applications in organic and medicinal chemistry. In addition, only two steps led to the targeted molecules from commercially available materials.

Scheme 5.2 Proposed routes for the synthesis of dihydro-methano-diarylazocines.

5.2.2 RESULTS AND DISCUSSION

Initially, a variety of the Lewis or proton acids were screened for the synthesis of dihydro-methano-diarylazocines *via* Friedel-Crafts double cyclizations in dichloromethane (DCM) at room temperature by selecting *N,N*-dibenzyl-1,1-dimethoxybutan-2-amine **75a** as the model substrate. It was found that no desired product **93b** was furnished without a Lewis or proton acid (Table 5.1, entry 1). Lewis acids, namely aluminium chloride or indium (III) chloride, were used for this reaction, generating only trace or no product **93b**, respectively (Table 5.1, entries 2-3). Next,

¹²⁴ (a) Miles, W. H.; Nutaitis, C. F.; Anderton, C. A. *J. Chem. Educ.* **1996**, 73, 272. (b) Yu, W.; Wen, M.; Yang, Li.; Liu, Z. L. *Chin. Chem. Lett.* **2002**, 13, 495. (c) Liébert, C.; Brinks, M. K.; Capacci, A. G.; Fleming, M. J.; Lautens, M. *Org. Lett.* **2011**, 13, 3000.

the α -amino acetal **75a** was treated using various proton acids such as trifluoroacetic acid (TFA), trifluoromethanesulfonic acid ($\text{CF}_3\text{SO}_3\text{H}$) in DCM and no desired product **93b** was provided (Table 5.1, entries 4-5). It is gratifying that the desired product **93b** was isolated in a good yield of 71% under the assistance of four equivalents of iron (III) chloride in DCM at room temperature for 3 h (Table 5.1, entry 8). Then, different equivalent of iron(III) chloride was further examined for this Friedel-Crafts cyclization reaction. Only a trace of product **93b** was detected after 15 h when two equivalents of iron (III) chloride were used (Table 5.1, entry 6). Therefore, the optimum equivalent of iron (III) chloride was found to be 4.0 (Table 5.1, entries 6-8).

Table 5.1 Screening of different catalyst^a

75a Catalyst DCM, rt **93b**

Entry	Catalyst (equiv.)	Time (h)	Yield (%) ^b
1	—	24	0
2	InCl_3 (4.0)	24	0
3	AlCl_3 (4.0)	24	trace
4	TFA	24	0
5	$\text{CF}_3\text{SO}_3\text{H}$ (4.0)	24	0
6	FeCl_3 (2.0)	15	trace
7	FeCl_3 (3.0)	3	36
8	FeCl_3 (4.0)	3	71

^aReaction conditions: α -amino acetal **75a** (0.5 mmol, 1.0 equiv.), catalyst (4.0 equiv.), DCM (5 mL).

^bIsolated yields based on α -amino acetal **75a**.

Subsequently, the scope of α -amino acetals for the construction of dihydro-methano-diarylazocines *via* iron (III) chloride-mediated Friedel-Crafts double cyclizations was investigated under the optimized conditions. As shown in Table 5.2, a variety of dihydro-methano-diarylazocines with an appendage at C-13 position were furnished in short reaction time under mild conditions. As the carbon chain at α -position of α -amino acetals was longer (Table 5.2, entry 2 *vs* 3) or more bulky (Table 5.2, entry 2 *vs* 4), the yield of dihydro-methano-diarylazocines decreased under the same conditions (3 h). The α -amino acetals (**91a** and **75l**) at α -position with especially bulky groups were suitable for this reaction, affording the desired products **93 (f, g)** in good yields of 74% and 76% respectively (Table 5.2, entries 6-7). The mild conditions displayed good tolerance to the functional groups such as allyl or benzyl group (Table 5.2, entries 4-6), thus making this reaction more useful in organic and medicinal chemistry. Next, the changing of the aromatic substituents or the length of carbon chain of *N*-protecting group was adopted for the synthesis of unsymmetrical dihydro-methano-diarylazocines in order to add a functional group with the potential for diversification. For an example of the changing of the aromatic substituents, the inseparable isomers **93h** was generated in a good yield of 81% with a ratio of 1:1 as estimated by NMR when the α -amino acetal **91x** with a methoxy group on the aromatic ring was used for this reaction (Table 5.2, entry 8). On the other hand, the α -amino acetal **91y** with a *N*-protecting group of 2-phenylethyl was also suitable for this reaction, affording the desired product **93i** in 80% yield as two isomers in a ratio of 1:1, which were easily separated by silica-gel column chromatography (Table 5.2, entry 9).

Table 5.2 Scope for the synthesis of various dihydro-methano-diarylazocines^{a,b}

^aReaction conditions: α -amino acetal (0.5 mmol, 1.0 equiv.), iron chloride (4.0 equiv.), DCM (5 mL).

^bIsolated yields based on α -amino acetal.

To explore which intermediate may be formed in the synthesis of dihydro-methano-diarylazocines, the α -amino acetal **91z** was prepared and further applied to this Friedel-Crafts reaction. The tetrahydroisoquinoline derivative **94a** was furnished *via* Friedel-Crafts cyclization in a good yield of 70% under the assistance of 2.0 equivalents of iron (III) chloride (Scheme 5.3).

Scheme 5.3 Friedel-Crafts cyclization for the synthesis of tetrahydroisoquinoline derivative

It is noteworthy that the substituted group at C-4 position of tetrahydroisoquinoline derivative **94a** is methoxy, and not hydroxyl. As a result, the synthesis of dihydro-methano-diarylazocines was not α -amino acetal deprotected to α -amino aldehyde, but direct Friedel-Crafts double cyclizations (Scheme 5.4).

Scheme 5.4 Proposed pathway for the synthesis of dihydro-methano-diarylazocines

5.2.3 SUMMARY

In summary, Friedel-Crafts double cyclizations for one-pot construction of dihydro-methano-diarylazocines from α -amino acetals mediated by iron(III) chloride was presented. This approach had the advantages of short routes (two steps) from commercially available secondary amines and aldehydes and iron(III) chloride as a mild mediator for Friedel-Crafts cyclization. A variety of α -amino acetals with different moieties at α -position or substituents on aromatic ring led to a wide range of dihydro-methano-diarylazocines. The development of asymmetric version to

synthesize enantiopure dihydro-methano-diarylazocines and further exploration into complex molecules in organic and medicinal chemistry is currently in progress.

5.3 CONSTRUCTION OF DOPAMINE D₁ RECEPTOR LIGANDS FROM α -AMINO ACETALS VIA INTRAMOLECULAR FRIEDEL-CRAFTS DOUBLE CYCLIZATIONS

5.3.1 INTRODUCTION

In the brain, dopamine functions as an essential neurotransmitter in the central nervous system (CNS) to modulate the movement, cognition, and emotion of human being. Some diseases such as Parkinson and Schizophrenia or psychiatric and neurological disorders may occur if this system is disrupted or manipulated.¹²⁵ Generally, the modulating function is realized through activation of the five distinct receptor subtypes (D₁-D₅), which were classified into 2 families, D₁-like and D₂-like on the basis of their biochemical and pharmacological properties.¹²⁶ The D₁-like receptors (D₁ and D₅) activate adenylyl cyclase, whereas the D₂-like receptors (D₂, D₃, D₄) inhibit adenylyl cyclase.¹²⁷

The therapeutic properties of dopamine D₁ receptor ligands were explored for more than 2 decades until dihydrexidine was synthesized and identified as a selective full dopamine D₁ receptor ligand by Nicholas's group in 1990s (Scheme 5.5).¹²⁸ This

¹²⁵ (a) Missale, C.; Nash, S. R.; Robinson, S. W.; Jaber, M.; Caron, M. G. *Physiol. Rev.* **1998**, *78*, 189. (b) Sidhu, A.; Niznik, H. B. *Int. J. Dev. Neurosci.* **2000**, *18*, 669.

¹²⁶ (a) Garau, L.; Govoni, S.; Stefanini, E.; Trabucchi, M.; Spano, P. F. *Life Sci.* **1978**, *23*, 1745. (b) Kebabian, J. W.; Calne, D. B. *Nature* **1979**, *277*, 93.

¹²⁷ Gingrich, J. A.; Caron, M. G. *Annu. Rev. Neurosci.* **1993**, *16*, 299.

¹²⁸ (a) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756. (b) Kohli, J. D.; Horn, P. T.; Glock, D.; Brewster, W. K.; Nichols, D. E. *Eur. J. Pharmacol.* **1993**, *235*, 31. (c) Lovenberg, T. W.; Brewster, W. K.; Mottola,

compound showed effective antiparkinsonian properties¹²⁹ and the possibility for the healing of cognitive deficits of Schizophrenia.¹³⁰

Scheme 5.5 Synthetic route for dihydrexidine analogues reported by Nicholas and Mailman in 1990s

Since then, there was great interest in the preparation of potential dopamine D1 receptor ligands, especially pharmaceutically active compounds (D1 receptor ligands) in the treatment of psychiatric and neurological disorders. Up to now, reported dopamine D1 receptor ligands are shown in Figure 5.2.¹³¹

D. M.; Lee, R. C.; Riggs, R. M.; Nichols, D. E.; Lewis, M. H.; Mailman, R. B. *Eur. J. Pharmacol.* **1989**, 166, 111.

¹²⁹ (a) Schneider, J. S.; Sun, Z. Q.; Roeltgen, D. P. *Brain Res.* **1994**, 663, 140. (b) Taylor, J. R.; Lawrence, M. S.; Redmond Jr, D. E.; Elsworth, J. D.; Roth, R. H.; Nichols, D. E.; Mailman, R. B. *Eur. J. Pharmacol.* **1991**, 199, 389.

¹³⁰ Goldman-Rakic, P. S.; Castner, S. A.; Svensson, T. H.; Siever, L. J.; Williams, G. V. *Psychopharmacology (Berl)* **2004**, 174, 3.

¹³¹ (a) Berger, J. G.; Chang, W. K.; Clader, J. W.; Hou, D.; Chipkin, R. E.; McPhail, A. T. *J. Med. Chem.* **1989**, 32, 1913. (b) Seiler, M. P.; Hagenbach, A.; Wuethrich, H. J.; Markstein, R. *J. Med. Chem.* **1991**, 34, 303. (c) Hagishita, S.; Shiro, M.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1655. (d) Michaelides, M. R.; Hong, Y. (Abbott Laboratories), US 5597832A, 1997. (e) Wu, W.-L.; Burnett, D. A.; Spring, R.; Greenlee, W. J.; Smith, M.; Favreau, L.; Fawzi, A.; Zhang, H.; Lachowicz, J. E. *J. Med. Chem.* **2005**, 48, 680. (f) Nichols, D.; Cueva, J. *Synthesis* **2009**, 2009, 715.

Figure 5.2 Pharmaceutically active compounds (D1 receptor ligands) used in the treatment of psychiatric and neurological disorders

Recently, some synthetic pathways or methods were developed for the construction of potential dopamine D1 receptor ligands. However, some notable disadvantages such as inaccessible and expensive substrates, relatively harsh reaction conditions, and long reaction routes still existed in the synthetic process. Furthermore, every route led to different compounds and no common scheme prepared for potential dopamine D1 receptor ligands. As a result, the development of a simple, mild, and general method for the construction of a variety of potential dopamine receptor ligands is highly desirable.

On the other hand, as introduced in Chapters 2-4, the synthesis of α -amino acetals using the methods of oxidative rearrangement of tertiary amines or enamines and α -amination of aldehydes has been presented in detail. On the basis of these results, we concluded that the dihydroxidine analogues might be directly constructed from α -amino acetal *via* intramolecular Friedel-Crafts double cyclizations according

to the general retrosynthetic analysis (Scheme 5.6). Meanwhile, organohypervalent iodine catalyzed α -amination of aliphatic aldehydes using nucleophilic secondary amines as a nitrogen source afforded the corresponding α -amino acetals.

Scheme 5.6 A general retrosynthetic analysis of hexahydrobenzo(α)phenanthridine analogue.

Next, we designed the three pathways of inter- and intramolecular Friedel-Crafts cyclizations for the construction of *cis* or *trans*- hexahydrobenzo(α)-

Scheme 5.7 Proposed pathways for the construction of dopamine D1 receptor ligands

-phenanthridine analogues by adjusting the substituted groups of α -amino acetals as highlighted as Scheme 5.7.

Herein, we described the construction of the hexahydrobenzo(α)phenanthridine analogues undergoing α -amination of aliphatic aldehydes using secondary amines as a nitrogen source and subsequent intramolecular Friedel-Crafts double cyclizations mediated by iron(III) chloride as a milder alternative Lewis acid.

5.3.2 RESULTS AND DISCUSSION

In order to further study the construction of potential dopamine D1 receptor ligands from α -amino acetals *via* intramolecular Friedel-Crafts double cyclizations as shown in Scheme 5.6, the α -amino acetals prepared were subjected to different Friedel-Crafts cyclization reaction conditions. The best result was provided when FeCl₃ was used as a mediator in dichloromethane at room temperature. The typical results for the synthesis of dihydrexidine analogues *via* iron(III) chloride mediated intramolecular double Friedel-Crafts cyclizations were summarized in Table 5.3. The desired hexahydrobenzo(α)phenanthridines **95(a-f, i)**, benzonaphthazepine **95g** and tetrahydroindeno[2,1,*c*]-isoquinoline **95h** derivatives were formed in moderate to good yields under the standard conditions (Table 5.3). All the α -amino acetals with electron donating or withdrawing groups on C-4 position on the aromatic ring were suitable for the cyclization reaction although the latter afforded a lower yield (Table 5.3, entries 2-4). Meanwhile, cyclization of α -amino acetal **91n** with a *p*-chloro group on the phenyl ring was also able to give product **95c** in moderate yield (Table 5.3, entry 3). The trends in these results had proven to be consistent with the effects of substituent effects on Friedel-Crafts reactions. If α -amino acetal **91p** was used for this

reaction, C–C bond formation may occur at either C1 or C3 position of α -amino acetal **91p** (Table 5.3, entry 5). Hence, α -amino acetal **91p** was subjected to the standard reaction conditions and the desired products **95e** were furnished in 55% isolated yield (Table 5.3, entry 5). To our delight, the products **95e(1)** and **95e(3)** were easily separated by aluminum oxide column chromatography (Table 5.3, entry 5). In contrast, the product **95f** was exclusively obtained in 82% yield (Table 5.3, entry 6). The benzonaphthazepine **95g** with a seven-membered ring and tetrahydroindeno[2,1,*c*]-isoquinoline **95h** with a five-membered ring can also be furnished by adjusting the length of carbon chain of α -amino acetals in good yields (Table 5.3, entries 7-8). α -Amino acetal with a readily removable protecting group on the nitrogen atom was also suitable for this reaction, affording the desired product with good yield (Table 5.3, entry 9).

Table 5.3 Scope for intramolecular Friedel-Crafts double cyclizations of α -amino acetals^{a,b}

^aReaction conditions: α -amino acetal (0.5 mmol, 1.0 equiv.), iron chloride (4.0 equiv.), DCM (5 mL).

^bIsolated yields based on α -amino acetal.

The structure of hexahydrobenzo(α)phenanthridine **95b** was characterized by X-ray crystallography as highlighted in Figure 4.3. The configuration of **95b** was determined to be *cis*-fused hexahydrobenzo(α)phenanthridine.

Figure 5.3 X-ray configuration of *cis*-fused hexahydrobenzo(α)phenanthridine **95b**

5.3.3 SUMMARY

In summary, a general method for the synthesis of dihydrexidine analogues undergoing α -amination of aldehydes and subsequent intramolecular double Friedel-Crafts cyclizations was developed (Scheme 5.8). The straightforward process and

commercially available starting materials demonstrated the simplicity of the reaction. Further study on the synthesis of *trans*-fused dihydrexidine analogues and asymmetric version and further applications to complex molecules are in progress in our laboratory.

Scheme 5.8 Synthetic routes for the preparation of hexahydrobenzo(α)phenanthridine analogues.

5.4 CONCLUSION

In this chapter, we developed iron(III) chloride mediated Friedel-Crafts double cyclizations for the synthesis of dihydro-methano-diarylazocines and potential dopamine D1 receptor ligands from α -amino acetals. The straightforward process and commercially available starting materials had demonstrated the simplicity of the reaction.

5.5 EXPERIMENTAL SECTION

5.5.1 One-pot Synthesis of Dihydro-methano-dibenzoazocines from α -Amino Acetals *via* Intramolecular Double Friedel-Crafts Cyclization

I. General Procedures

All reactions were carried out without exclusion of air or moisture unless otherwise stated. Iron (III) chloride and Lewis or proton acid were purchased from commercial suppliers, and used directly as received. Commercial solvents and reagents were used without further purification. α -Amino acetals were synthesized according to the procedures of Chapter 4. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and Fluka Analytical 90066 precoated aluminum oxide plate (0.25 mm thickness)].

II. General experimental procedure for one-pot synthesis of dihydro-methano-diarylazocines from α -amino acetals mediated by iron (III) chloride

Typical procedure for one-pot synthesis of dihydro-methano-diarylazocines from α -amino acetals mediated by iron (III) chloride (*N,N*-dibenzyl-1,1-dimethoxybutan-2-amine **75a** in dry DCM as a model system): *N,N*-dibenzyl-1,1-dimethoxybutan-2-amine **75a** (157 mg, 0.5 mmol) was added to a suspension of iron (III) chloride (324 mg, 2 mmol) in dry dichloromethane (5 ml) and was stirred for 3 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (NaHCO_3). The aqueous layer was extracted with DCM, and the combined organic layers were washed with brine, dried over magnesium sulfate (MgSO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel; ethyl acetate/hexane = 1:10, 1:6), affording the desired product **93b** as light yellow oil (0.089 g, 71%).

13-Methyl-7,12-dihydro-5H-6,12-methano-dibenzo[c,f]azocine (93a):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 78% yield.

R_f = 0.39 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 300 MHz) δ 7.25-7.18 (m, 2H), 7.12-7.02 (m, 4H), 7.00-6.93 (m, 2H), 4.31 (AB_q, J = 17.68 Hz, 2H), 4.18 (AB_q, J = 18.35 Hz, 2H), 3.58 (s, 1H), 3.56-3.48 (m, 1H), 1.21 (d, J = 6.90 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 75 MHz) δ 141.7, 138.3, 133.8, 133.5, 128.4, 127.6, 126.3, 126.2, 126.0 (CH x 2), 125.9, 125.6, 60.0, 52.5, 52.2, 41.8, 17.6 ppm

FTIR (neat): ν = 3017, 2972, 1215, 754, 667 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{18}\text{N}^+$ $[\text{M}+\text{H}]^+$ 236.1439, found: 236.1445.

13-Ethyl-7,12-dihydro-5H-6,12-methano-dibenzo[c,f]azocine (93b):

R_f = 0.56 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 500 MHz) δ 7.23-7.19 (m, 2H), 7.08-7.03 (m, 4H), 6.98-6.96 (m, 1H), 6.94-6.92 (m, 1H), 4.30 (AB_q, J = 17.66 Hz, 2H), 4.13 (AB_q, J = 18.34 Hz, 2H),

3.66 (s, 1H), 3.21-3.17 (m, 1H), 1.60-1.52 (m, 1H), 1.46-1.37 (m, 1H), 1.00 (t, $J = 7.42$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz) δ 141.6, 138.5, 134.2, 134.0, 128.1, 127.7, 126.2, 126.1, 126.0 (CH x 2), 125.9, 125.6, 60.1, 58.6, 52.7, 39.9, 24.3, 11.1 ppm

FTIR (neat): $\nu = 3013, 2965, 1215, 756, 665\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{20}\text{N}^+$ $[\text{M}+\text{H}]^+$ 250.1596, found: 250.1590.

13-Octyl-7,12-dihydro-5H-6,12-methano-dibenzo[*c,f*]azocine (93c):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 64% yield.

$R_f = 0.74$ (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 500 MHz) δ 7.24-7.20 (m, 2H), 7.10-7.04 (m, 4H), 7.00-6.94 (m, 2H), 4.31 (AB_q, $J = 17.67$ Hz, 2H), 4.14 (AB_q, $J = 18.33$ Hz, 2H), 3.63 (s, 1H), 3.30-3.27 (m, 1H), 1.56-1.24 (m, 10H), 0.86 (t, $J = 7.00$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz) δ 141.7, 138.6, 134.3, 134.0, 128.2, 127.7, 126.2, 126.1, 126.0 (CH x 2), 125.9, 125.6, 60.1, 57.0, 52.7, 40.4, 31.8, 31.3, 29.3, 26.6, 22.6, 14.1 ppm

FTIR (neat): $\nu = 3017, 2955, 1215, 756, 669\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{28}\text{N}^+$ $[\text{M}+\text{H}]^+$ 306.2222, found: 306.2225.

13-Benzyl-7,12-dihydro-5H-6,12-methano-dibenzo[*c,f*]azocine (93d):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 43% yield.

R_f = 0.50 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 400 MHz) δ 7.34-6.95 (m, 13H), 4.32 (AB_q, J = 17.71 Hz, 2H), 4.25 (AB_q, J = 18.44 Hz, 2H), 3.61-3.57 (m, 1H), 3.55 (s, 1H), 2.94 (dd, J = 13.46, 5.66 Hz, 1H), 2.65 (dd, J = 13.45, 9.69 Hz, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.2, 139.3, 138.3, 133.9, 133.8, 129.1 (CH x 2), 128.4 (CH x 2), 128.3, 127.9, 126.5, 126.23, 126.18, 126.13, 126.10, 126.04, 125.8, 60.2, 58.6, 53.0, 38.8, 38.0 ppm

FTIR (neat): ν = 3017, 2920, 1215, 756, 700, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{23}\text{H}_{22}\text{N}^+$ $[\text{M}+\text{H}]^+$ 312.1752, found: 312.1760.

13-Allyl-7,12-dihydro-5H-6,12-methano-dibenzo[*c,f*]azocine (93e):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 79% yield.

R_f = 0.58 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate);

^1H NMR (CDCl_3 , 400 MHz) δ 7.24-7.19 (m, 2H), 7.12-7.04 (m, 4H), 7.00-6.96 (m, 2H), 5.98-5.87 (m, 1H), 5.10-5.01 (m, 2H), 4.33 (AB_q, J = 17.71 Hz, 2H), 4.16 (AB_q, J = 18.41 Hz, 2H), 3.68 (s, 1H), 3.43-3.39 (m, 1H), 2.36-1.15 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.4, 138.3, 135.8, 134.1, 133.8, 128.2, 127.7, 126.4, 126.2, 126.1, 126.04, 126.01, 125.7, 116.7, 60.2, 56.8, 52.7, 39.8, 36.1 ppm

FTIR (neat): ν = 3017, 2974, 1215, 756, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{20}\text{N}^+$ [$\text{M}+\text{H}$] $^+$ 262.1596, found: 262.1606.

13-Phenyl-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c,f*]azocine (93f):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 74% yield.

R_f = 0.66 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 400 MHz) δ 7.46-7.44 (m, 2H), 7.34-7.30 (m, 2H), 7.24-7.21 (m, 2H), 7.16-7.02 (m, 5H), 6.96-6.92 (m, 1H), 6.77-6.75 (m, 1H), 4.53 (s, 1H), 4.33 (s, 1H), 4.28 (AB_q, J = 17.71 Hz, 2H), 4.18 (AB_q, J = 5.04 Hz, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.4, 140.0, 138.8, 134.7, 134.3, 128.1 (CH x 2), 127.75, 127.72, 127.5 (CH x 2), 126.6, 126.4, 126.3 (CH x 2), 126.1, 125.8 (CH x 2), 60.0, 59.0, 52.7, 38.7 ppm

FTIR (neat): ν = 3017, 2932, 1215, 758 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{20}\text{N}^+$ [$\text{M}+\text{H}$] $^+$ 298.1596, found: 298.1602.

Compound (93g):

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 76% yield.

R_f = 0.66 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 400 MHz) δ 7.20-7.18 (m, 2H), 7.08-7.01 (m, 4H), 6.96-6.94 (m, 2H), 4.20 (AB_q, J = 18.20 Hz, 4H), 3.51 (s, 1H), 1.75-1.56 (m, 5H), 1.53-1.39 (m, 5H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.4 (C x 2), 134.2 (C x 2), 128.2 (CH x 2), 126.2 (CH x 2), 125.9 (CH x 2), 125.4 (CH x 2), 55.3 (CH₂ x 2), 54.4, 45.5, 33.3 (CH₂ x 2), 26.2, 21.9 (CH₂ x 2) ppm

FTIR (neat): ν = 3017, 2933, 1215, 756, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{24}\text{N}^+$ $[\text{M}+\text{H}]^+$ 290.1909, found: 290.1916.

Compound (93i):

One isomer:

Light yellow oil

R_f = 0.73 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 400 MHz) δ 7.30-7.28 (m, 1H), 7.17-7.11 (m, 2H), 7.08-7.00 (m, 4H), 6.93-6.91 (m, 1H), 4.14 (AB_q, J = 17.90 Hz, 2H), 3.67 (s, 1H), 3.45-3.40 (m, 1H), 3.31-3.24 (m, 2H), 3.12-3.05 (m, 2H), 2.25-2.20 (m, 1H), 1.75-1.54 (m, 2H), 1.03 (t, J = 7.38 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 145.4, 141.3, 135.2, 134.9, 131.0, 130.7, 128.8, 126.3, 126.2, 126.1 (CH x 2), 124.6, 62.5, 57.9, 48.8, 48.3, 34.9, 26.8, 11.7 ppm

FTIR (neat): ν = 3017, 2965, 1215, 756, 706, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{22}\text{N}^+$ [$\text{M}+\text{H}$] $^+$ 264.1752, found: 264.1754.

Another isomer:

Light yellow oil

R_f = 0.63 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 400 MHz) δ 7.26-7.24 (m, 1H), 7.16-7.12 (m, 2H), 7.09-7.04 (m, 3H), 7.00-6.98 (m, 1H), 6.91-6.89 (m, 1H), 4.35 (AB_q, J = 17.28 Hz, 2H), 3.80 (d, J = 4.08 Hz, 1H), 3.41-3.34 (m, 1H), 3.25-3.20 (m, 1H), 3.08-3.02 (m, 2H), 2.17-2.13 (m, 1H), 1.56-1.43 (m, 2H), 0.97 (t, J = 7.38 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 142.1, 141.2, 136.6, 136.3, 130.33, 130.26, 130.0, 126.4, 126.3, 126.06, 126.01, 124.5, 59.5, 56.5, 48.6, 48.4, 35.2, 24.4, 11.1 ppm

FTIR (neat): ν = 3017, 2965, 1215, 756, 706, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{22}\text{N}^+$ [$\text{M}+\text{H}$] $^+$ 264.1752, found: 264.1754.

3-Ethyl-4-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (94a):

Light yellow oil

R_f = 0.63 (hexane: ethyl acetate = 4:1, aluminium oxide TLC plate).

^1H NMR (CDCl_3 , 400 MHz) δ 7.40-7.38 (m, 1H), 7.24-7.18 (m, 2H), 7.07-7.05 (m, 1H), 4.31 (d, J = 3.39 Hz, 1H), 3.72 (AB_q , J = 15.85 Hz, 2H), 3.48 (s, 3H), 2.65-2.61 (m, 1H), 2.48 (s, 3H), 1.72-1.53 (m, 2H), 1.02 (t, J = 7.50 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 135.1, 134.1, 128.3, 127.3, 125.9, 125.8, 76.8, 63.6, 57.1, 55.9, 42.5, 18.9, 12.0 ppm

FTIR (neat): ν = 3017, 2965, 1215, 756, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{24}\text{N}^+$ $[\text{M}+\text{H}]^+$ 206.1545, found: 206.1547.

5.5.2 Construction of Dopamine D1 Receptor Ligands from α -Amino Acetals via Friedel-Crafts Cyclization

I. General experimental procedure for the construction of Dopamine D1 receptor ligand derivatives *via* intramolecular double Friedel-Crafts cyclizations mediated by Iron (III) Chloride.

Typical procedure for the synthesis of dihydroexidine analogue from α -amino acetal mediated by FeCl_3 (*N*-benzyl-1,1-dimethoxy-*N*-methyl-4-phenylbutan-2-amine **91I** in dry DCM as a model system): *N*-benzyl-1,1-dimethoxy-*N*-methyl-4-phenylbutan-2-amine **91I** (157 mg, 0.5 mmol) was added to a suspension of iron (III) chloride (324 mg, 2 mmol) in dry dichloromethane (5 mL) and was stirred for 15 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (NaHCO_3). The

aqueous layer was extracted with DCM, and the combined organic layers were washed with brine, dried over magnesium sulfate (MgSO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (aluminum oxide; ethyl acetate/hexane = 1:30), affording the desired product **95a** (97.2 mg, 78%).

6-Methyl-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine (95a):

Light yellow oil

R_f = 0.63 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.30-7.28 (m, 1H), 7.22-7.08 (m, 7H), 4.20 (d, J = 4.49 Hz, 1H), 3.83 (AB_q, J = 15.51 Hz, 2H), 3.19-3.15 (m, 1H), 2.90-2.77 (m, 2H), 2.58 (s, 3H), 2.01-1.94 (m, 1H), 1.82-1.72 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 137.3, 136.8, 136.4, 134.4, 130.8, 128.9, 128.6, 126.4, 126.2, 126.0, 125.8, 125.3, 58.5, 54.2, 42.9, 42.7, 28.0, 20.4 ppm

FTIR (neat): ν = 3016, 2937, 1450, 1381, 1215, 1128, 1037, 908, 754, 667 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{20}\text{N}^+$ $[\text{M}+\text{H}]^+$ 250.1596, found: 250.1604.

2-Methoxy-6-methyl-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine (95b):

This compound was prepared by the general procedure described above and was obtained as light yellow oil. Then the product **95b** was dissolved in dichloromethane, hexane was added into it and solvent was evaporated to obtain the white solid.

R_f = 0.51 (hexane: ethyl acetate = 3:1).

mp: 124.8-125.6 °C

^1H NMR (CDCl_3 , 400 MHz) δ 7.30-7.28 (m, 1H), 7.21-7.12 (m, 3H), 7.02-7.00 (m, 1H), 6.73-6.69 (m, 2H), 4.15 (d, J = 4.59 Hz, 1H), 3.76 (AB_q, J = 15.17 Hz, 2H), 3.71 (s, 3H), 3.17-3.13 (m, 1H), 2.88-2.75 (m, 2H), 2.56 (s, 3H), 1.97-1.93 (m, 1H), 1.78-1.68 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 157.9, 137.9, 137.1, 136.8, 130.8, 129.0, 127.1, 126.6, 126.5, 125.3, 114.3, 111.3, 58.4, 55.1, 53.4, 43.1, 42.8, 28.1, 20.3 ppm

FTIR (neat): ν = 3018, 2937, 1612, 1454, 1377, 1215, 1157, 1037, 756, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{22}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 280.1701, found: 280.1705.

2-Chloro-6-methyl-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine (95c):

Light yellow oil

R_f = 0.63 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.27-7.18 (m, 3H), 7.14-7.09 (m, 3H), 7.01-6.99 (m, 1H), 4.14 (d, $J = 4.44$ Hz, 1H), 3.76 (AB_q, $J = 15.68$ Hz, 2H), 3.18-3.13 (m, 1H), 2.88-2.75 (m, 2H), 2.56 (s, 3H), 1.98-1.91 (m, 1H), 1.73-1.63 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 138.6, 136.7, 136.5, 132.8, 131.8, 130.9, 129.1, 128.4, 127.6, 126.8, 126.1, 125.6, 58.2, 53.3, 42.9, 42.7, 28.0, 19.8 ppm

FTIR (neat): $\nu = 3016, 2937, 1643, 1454, 1373, 1215, 1165, 1097, 908, 754, 667\text{ cm}^{-1}$

¹.

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}^+ [\text{M}+\text{H}]^+$ 284.1206, found: 284.1201.

2-Nitro-6-methyl-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (95d):

Light orange oil

$R_f = 0.44$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 8.05-7.98 (m, 2H), 7.32-7.21 (m, 4H), 7.16-7.14 (m, 1H), 4.24 (d, $J = 4.59$ Hz, 1H), 3.89 (AB_q, $J = 16.98$ Hz, 2H), 3.28-3.20 (m, 1H), 2.86-2.82 (m, 2H), 2.59 (s, 3H), 2.03-1.96 (m, 1H), 1.71-1.61 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 146.7, 142.0, 138.5, 136.5, 135.7, 130.8, 129.3, 127.2 (CH x 2), 125.9, 123.8, 121.0, 57.9, 53.7, 43.0, 42.5, 28.0, 19.5 ppm

FTIR (neat): $\nu = 3018, 2933, 1651, 1523, 1346, 1215, 756, 669\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2^+ [\text{M}+\text{H}]^+$ 295.1447, found: 295.1448.

3-Methyl-1,2,2a,3,4,10c-hexahydrodibenzo[*a,k*]phenanthridine (95e(1)):

Light brown oil

$R_f = 0.55$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.93-7.86 (m, 2H), 7.75 (d, $J = 8.44$ Hz, 1H), 7.49-7.47 (m, 2H), 7.22-7.16 (m, 2H), 7.09-7.05 (m, 1H), 6.87-6.84 (m, 1H), 6.65-6.65 (m, 1H), 4.59 (d, $J = 1.72$ Hz, 1H), 3.91 (AB_q, $J = 16.33$ Hz, 2H), 3.14-3.05 (m, 1H), 2.95-2.88 (m, 2H), 2.46 (s, 3H), 2.33-2.19 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 138.0, 136.9, 133.1, 132.7, 132.2, 131.9, 128.9, 128.5, 128.0, 127.0, 126.3, 125.74, 125.68, 125.1, 125.0, 124.2, 59.7, 58.6, 42.3, 40.2, 26.9, 25.8 ppm

FTIR (neat): $\nu = 2933, 1450, 1215, 1124, 908, 754, 667$ cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{22}\text{N}^+$ $[\text{M}+\text{H}]^+ 300.1752$, found: 300.1754.

7-methyl-5,6,6a,7,8,14b-hexahydrodibenzo[*a,j*]phenanthridine (95e(3)):

Light brown oil

$R_f = 0.53$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.74 (d, $J = 7.85$ Hz, 1H), 7.66 (d, $J = 7.85$ Hz, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.41-7.31 (m, 3H), 7.25-7.17 (m, 3H), 4.94 (d, $J = 1.72$ Hz,

1H), 3.98 (s, 2H), 3.22-3.17 (m, 1H), 2.88-2.84 (m, 2H), 2.63 (s, 3H), 2.00-1.93 (m, 1H), 1.74-1.64 (m, 1H) ppm.

¹³C NMR (CDCl₃, 100 MHz) δ 136.9, 136.6, 136.0, 133.7, 132.4, 132.0, 131.1, 129.1, 127.6, 127.1 (CH x 2), 126.6, 125.45, 125.40, 125.2, 124.4, 59.2, 54.4, 43.2, 43.0, 28.2, 22.1 ppm

FTIR (neat): ν = 2933, 1450, 1215, 1124, 908, 754, 667 cm⁻¹.

HRMS (ESI, m/z): calcd for C₂₂H₂₂N⁺ [M+H]⁺ 300.1752, found: 300.1754.

6-methyl-5,6,6a,7,8,12b-hexahydrodibenzo[*a,i*]phenanthridine (95f):

Light brown oil

R_f = 0.58 (hexane: ethyl acetate = 3:1).

¹H NMR (CDCl₃, 400 MHz) δ 7.87 (d, *J* = 8.31 Hz, 1H), 7.82 (d, *J* = 7.82 Hz, 1H), 7.65 (d, *J* = 8.61 Hz, 1H), 7.53-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.20-7.13 (m, 3H), 4.32 (s, 1H), 4.23 (AB_q, *J* = 16.00 Hz, 1H), 3.27-3.23 (m, 1H), 2.88-2.75 (m, 2H), 2.67 (s, 3H), 2.08-1.91 (m, 2H) ppm.

¹³C NMR (CDCl₃, 100 MHz) δ 138.0, 137.1, 133.4, 131.9, 130.5, 130.4, 128.8, 128.7, 128.5, 127.2, 126.4, 126.10, 126.06, 125.4, 125.2, 122.3, 57.8, 52.6, 43.9, 42.8, 27.5, 20.4 ppm

FTIR (neat): ν = 3016, 1935, 1510, 1450, 1265, 1215, 1128, 1045, 754, 667 cm⁻¹.

HRMS (ESI, m/z): calcd for C₂₂H₂₂N⁺ [M+H]⁺ 300.1752, found: 300.1755.

7-Methyl-6,6a,7,8,9,13b-hexahydro-5H-benzo[d]naphtho[2,1-b]azepine (95g):

Light yellow oil

$R_f = 0.55$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.23-7.18 (m, 2H), 7.16-7.03 (m, 4H), 6.88-6.86 (m, 1H), 6.48-6.46 (m, 1H), 4.53 (d, $J = 3.69$ Hz, 1H), 3.27-3.19 (m, 1H), 3.03-2.75 (m, 6H), 2.47 (s, 3H), 1.94-1.89 (m, 1H), 1.73-1.63 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 141.2, 140.4, 138.8, 137.0, 130.2, 129.4, 128.7, 128.6, 126.5, 126.4, 125.9, 125.8, 63.9, 52.7, 48.8, 44.4, 34.7, 27.7, 22.0 ppm

FTIR (neat): $\nu = 3016, 2937, 1489, 1265, 1215, 1130, 1049, 1006, 754, 667\text{ cm}^{-1}$.

HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{22}\text{N}^+$ $[\text{M}+\text{H}]^+$ 264.1752, found: 264.1744.

6-Methyl-6,6a,7,11b-tetrahydro-5H-indeno[2,1-c]isoquinoline (95h):

Light yellow oil

$R_f = 0.55$ (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.49-7.47 (m, 1H), 7.41-7.39 (m, 1H), 7.26-7.21 (m, 2H), 7.18-7.14 (m, 3H), 7.07-7.05 (m, 1H), 4.38 (d, $J = 6.33$ Hz, 1H), 3.73 (AB_q, $J = 15.29$ Hz, 2H), 3.68-3.63 (m, 1H), 3.23-2.97 (m, 2H), 2.51 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz) δ 144.3, 140.8, 134.7, 133.9, 128.7, 126.8, 126.58, 126.54, 126.45, 126.0, 125.0, 124.4, 65.5, 54.5, 46.9, 43.1, 32.2 ppm

FTIR (neat): ν = 3016, 2937, 1456, 1373, 1265, 1215, 1097, 1031, 968, 754, 667 cm^{-1}

¹.

HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{18}\text{N}^+$ $[\text{M}+\text{H}]^+$ 236.1439, found: 236.1430.

6-(2,6-dichlorobenzyl)-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (95i):

Light yellow oil

R_f = 0.75 (hexane: ethyl acetate = 3:1).

^1H NMR (CDCl_3 , 400 MHz) δ 7.31-7.29 (m, 3H), 7.25-7.17 (m, 2H), 7.15-7.03 (m, 6H), 4.19-3.97 (m, 5H), 3.41-3.36 (m, 1H), 2.88-2.84 (m, 2H), 2.12-2.05 (m, 1H), 1.85-1.75 (m, 1H) ppm

^{13}C NMR (CDCl_3 , 100 MHz) δ 137.6, 136.9, 136.8 (C x 2), 135.0, 134.0, 131.8, 129.2, 128.7, 128.3 (CH x 2), 128.0, 126.5, 126.4, 126.1, 125.5, 125.0, 56.4, 53.3, 50.5, 43.3, 28.9, 18.3 ppm

FTIR (neat): ν = 3018, 2933, 1560, 1435, 1215, 1091, 908, 756, 669 cm^{-1} .

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{N}^+$ $[\text{M}+\text{H}]^+$ 394.1129, found: 394.1123.

APPENDIX

***Copper-Catalyzed Oxidative Alkynylation of
Tertiary Amines in Air***

COPPER-CATALYZED OXIDATIVE ALKINYLYATION OF TERTIARY AMINES IN AIR

1 INTRODUCTION

Nitrogen-containing compounds widely exist in natural products and biomolecules. As a result, the development of novel methods for the construction of them has been one of the most challenging topics in synthetic chemistry.²⁶ Recently, direct functionalization of C–H bond adjacent to a nitrogen atom had attracted considerable attention.²⁷⁻³³ However, as far as we know, sp^3 C–H bond functionalization at the α -position to nitrogen atom using copper catalyst and air as oxidant to couple to alkynes has not been reported.³⁶⁻⁴⁵ Herein, we report that direct cross-coupling reaction of alkynes to the α -position of the nitrogen could be achieved in high efficiency *via* sp^3 C–H bond functionalization at the α -position to nitrogen atom using copper catalyst and air as oxidant under very mild reaction conditions.

2 RESULTS AND DISCUSSION

During our attempts to develop a new [3+2] cycloaddition reaction, we treated phenylacetylene, ethyl benzylideneiminoglycinate, and *N,N*-dicyclohexylmethylamine in the presence of a catalytic amount of CuI (20 mol%) (Scheme 1). Unfortunately, no [3+2] cycloaddition product was detected. However, to our surprise, a trace amount (5% yield) of the direct cross-coupling product **98a** of alkyne and tertiary amine was isolated. We envisaged that **98a** was formed *via* sp^3 C–H bond oxidation at the α -position

to nitrogen followed by coupling with the alkynyl copper reagent where oxygen in air is probably the oxidant.

Scheme 1 Our initial study on copper-catalyzed [3+2] cycloaddition or C–H bond functionalization.

Therefore, we further examined the alkynylation of tertiary aliphatic amines in air. *N,N*-Dicyclohexylmethylamine **96a** and phenylacetylene **97a** were reacted in the presence of various copper complexes and solvents at room temperature in air to optimize the reaction conditions. The results are summarized in Table 1. The effect of the solvent was dramatic under the given catalytic and reaction conditions (Table 1, entries 1-5). Among the various solvents screened, THF and acetonitrile emerged as the best solvents for this reaction, producing the desired product in 76% and 86% yields respectively (Table 1, entries 4-5). Other solvents such as water, 1, 4-dioxane and methanol were also screened, but in all cases, the undesired homocoupling product of phenylacetylene was obtained as the major product (Table 1, entries 1-3). Interestingly, a trace amount of water in the reaction system had no effect on this reaction but too much water in acetonitrile decreased the yield of the product. Other copper catalysts were also screened (Table 1,

entries 7-13). CuI afforded the desired product in 85 % yield although it took longer time (12 h) for the reaction to complete as compared to CuBr₂ (Table 1, entry 11). While CuCl₂ showed moderate catalytic activity (Table 1, entry 7), other Cu(II) salts such as Cu(OAc)₂, Cu(OTf)₂, CuSO₄·5H₂O, (Table 1, entries 8-10), and Cu(I) salts like CuCl and CuBr (Table 1, entries 12-13) showed low catalytic activities. To further improve the yields, various ratios of *N,N*-dicyclohexylmethylamine and phenylacetylene were examined. The best yield was obtained when the *N,N*-dicyclohexylmethylamine/phenylacetylene ratio was 2:1. The yields markedly decreased when the amount of copper bromide was reduced from 0.2 equiv to 0.1 equiv (Table 1, entries 5-6). It is also important to note that the reaction did not proceed without catalyst (Table 1, entry 14). Therefore, our optimal reaction conditions for the alkynylation of tertiary aliphatic amines were as follows: the reaction was carried out in air at room temperature using 20 mol% of copper bromide as the catalyst, acetonitrile as the solvent and the ratio of tertiary amine and alkyne was 2:1.

Table 1 Copper-catalyzed coupling of phenylacetylene **97a** with *N,N*-dicyclohexylmethylamine **96a**: optimization of the reaction conditions^a

C1CCN(C1)C2CCCCC2 + C#CC1=CC=CC=C1 $\xrightarrow[\text{rt, air}]{\text{Cat.}}$ C1CCN(C1)CC#CC1=CC=CC=C1

96a **97a** **98a**

Entry	Cat. (equiv.)	Solvent	Time (h)	Yield (%) ^b
1	CuBr ₂ (0.2)	H ₂ O	24	0
2	CuBr ₂ (0.2)	1,4-dioxane	24	0
3	CuBr ₂ (0.2)	MeOH	24	trace
4	CuBr ₂ (0.2)	THF	5	76

5	CuBr ₂ (0.2)	MeCN	5	86
6	CuBr ₂ (0.1)	MeCN	18	54
7	CuCl ₂ (0.2)	MeCN	24	51
8	Cu(OAc) ₂ (0.2)	MeCN	24	trace
9	Cu(OTf) ₂ (0.2)	MeCN	24	trace
10	CuSO ₄ ·5H ₂ O (0.2)	MeCN	24	0
11	CuI (0.2)	MeCN	12	85
12	CuBr (0.2)	MeCN	24	5
13	CuCl (0.2)	MeCN	24	7
14	—	MeCN	24	0

^aReaction conditions: *N,N*-dicyclohexylmethylamine (2 mmol), phenylacetylene (1 mmol), solvent (4 mL).

^bIsolated yields based on phenylacetylene **97a**.

Subsequently, the scope of tertiary amines for this reaction was investigated. Representative examples are shown in Table 2. It was found that C–H bond of 1° carbon of tertiary amines adjacent to nitrogen atom had better activity than that of 2° carbon (Table 2, entry 4), and C–H bond of 1° carbon also had better activity than that of 3° carbon (Table 2, entries 1-3). Furthermore, tertiary *N*-methylamine with two other 3° carbons adjacent to nitrogen atom resulted in better yields than that with two other 2° carbons (Compare Table 2, entries 1-3 with Table 2, entry 4). The reactivity of the substrate (Table 2, entry 5), containing electron-withdrawing group is relatively inert and no product was obtained in this reaction system. On the basis of the above observations, a tertiary amine with a chiral centre (Table 2, entry 6) was designed and synthesized for this reaction which afforded the desired product in a moderate yield of 59 %.

Table 2 Copper-catalyzed coupling of various tertiary amines **96** with phenylacetylene **97a**^a

$ \begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{N-Me} \\ \diagup \\ \text{R}^2 \\ \mathbf{96 (a-f)} \end{array} + \text{Ph-C}\equiv\text{C-H} \xrightarrow[\text{MeCN, air}]{\text{CuBr}_2 (0.2 \text{ equiv.})} \begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{N} \\ \diagup \\ \text{R}^2 \\ \mathbf{98 (a-f)} \end{array} $					
Entry	Amine	Temp. (°C)	Time (h)	Product	Yield (%) ^b
1		20	5	98a	86
2		20	20	98b	81
3		50	7	98c	57
4		50	12	98d	28
5		50	24	98e	0
6		50	20	98f	59

^aReaction conditions: Tertiary amine **96** (2.0 mmol), phenylacetylene **97a** (1.0 mmol, 1.0 equiv.), acetonitrile (4 mL).

^bIsolated yields based on phenylacetylene **97a**.

Cross-coupling between alkyne and 2° carbon adjacent to nitrogen atom was also investigated. *N*-butyl-*N*-cyclohexylcyclohexanamine **69a** was selected for this reaction. As shown in Scheme 2, the coupling product **98g** was obtained although the yield was only 30%.

Scheme 2 Cross-coupling between phenylacetylene and 2° carbon adjacent to nitrogen atom

To broaden the scope of terminal alkynes used, we carried out the reactions of various terminal alkynes with *N,N*-dicyclohexylmethylamine (Table 3). Almost all the substrates examined under the standard reaction conditions provided the desired products in good to excellent yields. The reactivity of the substituted aromatic alkynes was different depending on the substituted groups. The substituted aromatic alkynes containing electron-deficient groups showed lower reactivity than those containing electron-rich or neutral groups (Compare Table 3, entry 7 with Table 2, entry 1, and Table 3, entry 1). Higher reactivity of those containing neutral groups than electron-rich was observed (compare Table 2, entry 1 with Table 3, entry 1). The aliphatic terminal alkynes showed slightly lower reactivity than the substituted aromatic alkynes containing electron-rich or neutral groups (Table 3, entries 3 and 4). The reactivity of the substrates containing electron-withdrawing groups was relatively inert. The rate of the reaction was very slow, but when the catalytic loading was increased from 0.2 equiv. to 0.5 equiv, the desired products could be obtained in good yields (Table 3, entries 6 and 7). The coupling reaction also tolerated a range of functional groups including a cyclopropyl group (Table 3, entry 2), a TMS or TBS group (Table 3, entries 3 and 5), an ester group (Table 3, entry 8), a nitro group (Table 3, entry 6). Especially noteworthy was that a formyl group which was sensitive to oxidants could also tolerate the reaction conditions (Table 3, entry 7).

Table 3 Copper-catalyzed coupling of *N,N*-dicyclohexylmethylamine **96a** with various terminal alkynes **97**^a

Entry	R ³	Product	Time (h)	Yield (%) ^b
1	4-MeC ₆ H ₄	98h	5	78
2	Cyclopropyl	98i	5	85
3	TBSOCH ₂ CH ₂	98j	8	66
4	PhCH ₂ CH ₂	98k	15	55
5	TMS	98l	12	74 ^c
6	4-O ₂ NC ₆ H ₄	98m	5	84 ^d
7	2-OHCC ₆ H ₄	98n	36	11(67 ^e)
8	EtO ₂ C	98o	48	24 ^f

^aReaction conditions: *N,N*-dicyclohexylmethylamine **96a** (2.0 mmol), alkynes **97** (1.0 mmol, 1.0 equiv.), copper bromide (0.2 mmol), acetonitrile (4 mL).

^bIsolated yields based on alkynes **97**.

^cTwo products (R¹ = TMS, and R¹ = H) were observed in the ratio of 6.6:1 respectively by ¹H NMR analysis.

^{d, e, f}Copper bromide (0.5 mmol).

^e5 hrs.

For the reaction of cross-coupling between alkyne and tertiary amine, tertiary amine was thought to function as (1) the ligand for copper species [LCuⁿ⁺¹] in the system of copper salt and molecular oxygen; (2) the base for the terminal alkyne-copper complex **D**. Based on this, a proposed mechanism was presented in Scheme 3. Firstly, a series of copper-dioxygen species that were formed were used as one-electron oxidizing agents toward tertiary amine, and intermediates **A** and **B**. Thus iminium ion **C** was produced.

Subsequently, the alkynyl-Cu complex **D** attacked on the iminium ion **C** to produce the propargylamine and release the copper catalyst.

Scheme 3 Proposed mechanism for copper-catalyzed alkynylation of tertiary amine.

3 CONCLUSION

In conclusion, we presented a highly efficient copper-catalyzed oxidative alkynylation of tertiary aliphatic amines in air. This process is simple, easy to operate, and the reaction conditions are mild. Furthermore, no additional oxidant and additives were required. In contrast to other reported methods, functional groups which are sensitive to oxidation such as a formyl group can tolerate this very mild reaction conditions. The fact that functional groups which are sensitive to harsh reaction conditions remains intact in our system is of great significance especially if it is used for the synthesis of complex molecules since traditional methods of sp^3 C–H bond activation usually needed strong oxidant or initiator, expensive catalyst or harsh reaction conditions.

4 EXPERIMENTAL SECTION

I. General information

All reactions were carried out in air unless otherwise stated. *N*, *N*-dicyclohexylmethylamine, *N*, *N*-di-*n*-butylmethylamine, copper salts, and all alkynes were purchased from commercial suppliers, and commercial solvents and reagents were used without further purification. *N*, *N*-di-*iso*-propyl methylamine, *N*-methyl-*N*-*iso*-propylcyclohexylamine, and cyclohexyl-*iso*-propyl-carbamic acid *tert*-butyl ester were synthesized according to literatures.¹³²

II. Preparation for tertiary aliphatic *N*-methylamine (96f)

According to the literatures,¹³³ (S)-1-(tert-butyl(methyl)silyloxy)-*N*-isopropyl-*N*, 3-dimethylbutan-2-amine **96f** was synthesized as shown above.

(S)-methyl 2-(isopropyl(methyl)amino)-3-methylbutanoate

¹³² (a) Bhattacharyya, S. *Syn. Commun.* **1995**, 25, 2061. (b) Salmi, C.; Letourneux, Y.; Brunel, J. M. *Lett. Org. Chem.* **2006**, 3, 384. (c) Davies, H. M. L.; Venkataramani, C. *Angew. Chem. Int. Ed.* **2002**, 41, 2197.

¹³³ Anderson, J. C.; Cubbona, R. J.; Harling, J. D. *Tetrahedron: Asymmetry* **2001**, 12, 923.

Light yellow oil

^1H NMR (CDCl₃, 400 MHz) δ 3.66 (s, 3H), 2.94-2.85 (m, 2H), 2.27 (s, 3H), 2.06-1.94 (m, 1H), 1.00-0.98 (m, 6H), 0.94-0.93 (d, J = 9.21, 6.64 Hz, 3H), 0.85-0.83 (d, J = 6.57 Hz, 3H).

^{13}C NMR (CDCl₃, 100 MHz) δ 174.0, 70.1, 53.0, 50.6, 31.3, 27.5, 19.65, 19.63, 19.43, 19.40

(S)-1-(tert-butyldimethylsilyloxy)-N-isopropyl-N, 3-dimethylbutan-2-amine (96f)

Light yellow oil

R_f = 0.42 (Hexane: Ethyl acetate = 3:1)

^1H NMR (CDCl₃, 300 MHz) δ 3.71-3.70 (d, J = 4.76 Hz, 2H), 2.96-2.85 (m, 1H), 2.33-2.28 (m, 1H), 2.26 (s, 3H), 1.89-1.73 (m, 1H), 1.04-1.01 (dd, J = 6.47, 2.44 Hz, 6H), 0.94-0.89 (dd, J = 9.21, 6.74 Hz, 6H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (CDCl₃, 75 MHz) δ 67.4, 61.7, 52.5, 32.3, 28.4, 25.9 (3C), 20.8, 20.7, 20.6, 20.2, 18.2, -5.5, -5.6

FTIR (neat) ν = 2957, 2857, 1464, 1215, 1094, 760 cm⁻¹.

HRMS (ESI) m/z calc. for C₁₅H₃₅NOSi⁺ [M+H]⁺ 274.2566, found 274.2566.

α_D^{20} = -8 (c 1, CH₂Cl₂)

III. General experimental procedure for copper-catalyzed oxidative alkynylation of tertiary aliphatic amines

Tertiary aliphatic amine (2.0 mmol) and terminal alkyne (1.0 mmol) were added to the mixture of CuBr₂ (0.2 mmol) and CH₃CN (4.0 mL) in air at room temperature. The mixture was stirred until the color of the solution turned green. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated. The crude product was purified by flash column chromatography (2-10% ethyl acetate in hexane) to afford the desired product. This procedure is common for Tables 1-3, unless otherwise stated.

N-cyclohexyl-*N*-(3-phenylprop-2-ynyl)cyclohexanamine (98a)

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 86% yield.

R_f = 0.47 (Hexane: Ethyl acetate = 5:1)

¹H NMR (CDCl₃, 400 MHz) δ 7.40-7.37 (m, 2H), 7.29-7.24 (m, 3H), 3.69 (s, 2H), 2.85-2.78 (tt, *J* = 10.92, 2.96 Hz, 2H), 1.91-1.88 (m, 4H), 1.80-1.77 (m, 4H), 1.63-1.60 (m, 2H), 1.42-1.21(m, 8H), 1.17-1.07 (m, 2H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 131.3 (2C), 128.1 (2C), 127.5, 123.8, 89.5, 83.1, 57.4(2C), 35.6, 31.2 (4C), 26.2 (2C), 26.1 (4C)

FTIR (neat) ν = 3015, 2928, 2853, 1489, 1448, 1215, 768 cm^{-1} .

HRMS (ESI) m/z calc. for $\text{C}_{21}\text{H}_{30}\text{N}^+ [\text{M}+\text{H}]^+$ 296.2378, found 296.2356.

***N*-isopropyl-*N*-(3-phenylprop-2-ynyl)cyclohexanamine (98b)**

This compound was prepared by the general procedure described above and was obtained as light yellow oil in 81% yield.

R_f = 0.5 (Hexane: Ethyl acetate = 3:1)

^1H NMR (CDCl_3 , 400 MHz) δ 7.40-7.38 (m, 2H), 7.29-7.26 (m, 3H), 3.67 (s, 2H), 3.35-3.25 (m, 1H), 2.83-2.76 (tt, J = 10.90, 3.17 Hz, 1H), 1.94-1.91 (m, 2H), 1.81-1.78 (m, 2H), 1.64-1.60 (m, 1H), 1.42-1.10 (m, 11H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 131.4 (2C), 128.1 (2C), 127.6, 123.8, 89.2, 83.4, 57.5, 48.2, 35.1, 31.1 (2C), 26.3, 26.1 (2C), 20.7 (2C)

FTIR (neat) ν = 3017, 2932, 1489, 1215, 762, 754 cm^{-1} .

HRMS (ESI) m/z calc. for $\text{C}_{18}\text{H}_{26}\text{N}^+ [\text{M}+\text{H}]^+$ 256.2065, found 256.2056.

***N,N*-diisopropyl-3-phenylprop-2-yn-1-amine (98c)**

Light yellow oil

$R_f = 0.33$ (Hexane: Ethyl acetate = 3:1)

^1H NMR (CDCl_3 , 400 MHz) δ 7.40-7.38 (m, 2H), 7.28-7.24 (m, 3H), 3.65 (s, 2H), 3.30-3.20 (m, 2H), 1.16-1.14 (d, $J = 6.60$ Hz, 12H)

^{13}C NMR (CDCl_3 , 100 MHz) δ 131.3 (2C), 128.1 (2C), 127.6, 123.7, 88.9, 83.4, 48.4 (2C), 34.7, 20.6 (4C)

FTIR (neat) $\nu = 2968, 1489, 1383, 1215, 756\text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{15}\text{H}_{22}\text{N}^+ [\text{M}+\text{H}]^+ 216.1752$, found 216.1746.

***N*-butyl-*N*-(3-phenylprop-2-ynyl)butan-1-amine (98d)**

Light yellow oil

$R_f = 0.6$ (Hexane: Ethyl acetate = 5:1)

^1H NMR (CDCl_3 , 400 MHz) δ 7.45-7.40 (m, 2H), 7.31-7.27 (m, 3H), 3.62 (s, 2H), 2.55-2.51 (t, $J = 7.36$ Hz, 4H), 1.52-1.45 (m, 4H), 1.39-1.30 (m, 4H), 0.95-0.92 (t, $J = 7.32$ Hz, 6H)

^{13}C NMR (CDCl_3 , 100 MHz) δ 131.7 (2C), 128.2 (2C), 127.8, 123.5, 84.9, 84.8, 53.6 (2C), 42.7, 29.7 (2C), 20.7 (2C), 14.1 (2C)

FTIR (neat) $\nu = 2959, 2932, 1489, 1215, 756\text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{17}\text{H}_{26}\text{N}^+ [\text{M}+\text{H}]^+ 244.2065$, found 244.2058.

(S)-1-(tert-butyldimethylsilyloxy)-N-isopropyl-3-methyl-N-(3-phenylprop-2-ynyl)butan-2-amine (98f)

Light yellow oil

$R_f = 0.66$ (Hexane: Ethyl acetate = 20:1)

^1H NMR (CDCl_3 , 400 MHz) δ 7.40-7.37 (m, 2H), 7.29-7.23 (m, 3H), 3.82-3.81 (d, $J = 4.39$ Hz, 2H), 3.76-3.65 (q, $J = 17.71$, 2H), 3.32-3.22 (m, 1H), 2.53-2.49 (m, 1H), 1.97-1.84 (m, 1H), 1.13-1.10 (t, $J = 6.48$ Hz, 6H), 1.02-1.00 (d, $J = 6.71$ Hz, 3H), 0.94-0.92 (d, $J = 6.60$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 131.4 (2C), 128.1 (2C), 127.5, 124.1, 90.6, 82.1, 65.9, 62.3, 49.5, 36.4, 28.4, 25.9 (3C), 22.2, 21.1, 20.3 (2C), 18.2, -5.5, -5.7

FTIR (neat) $\nu = 3017, 2957, 2884, 1462, 1215, 1094, 756\text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{23}\text{H}_{40}\text{NOSi}^+ [\text{M}+\text{H}]^+ 374.2879$, found 374.2865.

$\alpha_D^{20} = -30$ (c 0.2, CH_2Cl_2)

N-cyclohexyl-N-(1-phenylhex-1-yn-3-yl)cyclohexanamine (98g)

Light yellow oil

$R_f = 0.65$ (Hexane: Ethyl acetate = 10:1)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.36-7.33 (m, 2H), 7.30-7.24 (m, 3H), 3.65 (t, $J = 7.47$ Hz, 1H), 2.75-2.68 (m, 2H), 2.16-2.13 (m, 2H), 1.78-1.74 (m, 4H), 1.63-1.18 (m, 16H), 1.10-0.99 (m, 2H), 0.93 (t, $J = 7.35$ Hz, 3H).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 131.2 (2C), 128.2 (2C), 127.3, 124.3, 94.7, 81.9, 55.7 (2C), 47.5, 38.9, 34.8 (2C), 32.3 (2C), 26.9 (2C), 26.7 (2C), 26.2 (2C), 19.9, 14.0

FTIR (neat) $\nu = 3017, 2928, 2407, 1597, 1448, 1215, 756 \text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{24}\text{H}_{36}\text{N}^+ [\text{M}+\text{H}]^+$ 338.2848, found 338.2834.

***N*-cyclohexyl-*N*-(3-*p*-tolylprop-2-ynyl)cyclohexanamine (98h)**

Light yellow oil

$R_f = 0.42$ (Hexane: Ethyl acetate = 5:1)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.29-7.27 (d, $J = 7.94$ Hz, 2H), 7.08-7.06 (d, $J = 7.87$ Hz, 2H), 3.68 (s, 2H), 2.85-2.78 (tt, $J = 10.93, 2.84$ Hz, 2H), 2.31 (s, 3H), 1.91-1.88 (m, 4H), 1.80-1.76 (m, 4H), 1.62-1.59 (m, 2H), 1.47-1.21 (m, 8H), 1.17-1.06 (m, 2H).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 137.4, 131.2 (2C), 128.8 (2C), 123.8, 88.6, 83.2, 57.4 (2C), 35.6, 31.2 (4C), 26.2 (2C), 26.1 (4C), 21.3

FTIR (neat) $\nu = 3019, 2930, 2855, 1508, 1449, 1215, 756 \text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{22}\text{H}_{32}\text{N}^+ [\text{M}+\text{H}]^+$ 310.2535, found 310.2524.

***N*-cyclohexyl-*N*-(3-cyclopropylprop-2-ynyl)cyclohexanamine (98i)**

Light yellow oil

$R_f = 0.44$ (Hexane: Ethyl acetate = 4:1)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 3.40 (s, 2H), 2.74-2.68 (m, 2H), 1.83-1.75 (m, 8H), 1.62-1.59 (m, 2H), 1.33-1.18 (m, 9H), 1.14-1.05 (m, 2H), 0.73-0.59 (m, 4H)

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 86.0, 74.6, 57.2 (2C), 35.1, 31.1 (4C), 26.2 (2C), 26.1 (4C), 7.8 (2C), -0.4

FTIR (neat) $\nu = 3015, 2932, 2855, 1449, 1215, 756 \text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{18}\text{H}_{30}\text{N}^+ [\text{M}+\text{H}]^+ 260.2378$, found 260.2370.

***N*-(5-(tert-butyldimethylsilyloxy)pent-2-ynyl)-*N*-cyclohexylcyclohexanamine (98j)**

Light yellow oil

$R_f = 0.49$ (Hexane: Ethyl acetate = 5:1)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 3.68-3.64 (t, $J = 7.30 \text{ Hz}$, 2H), 3.38 (s, 2H), 2.72-2.66 (m, 2H), 2.36-2.32 (t, $J = 7.29 \text{ Hz}$, 2H), 1.80-1.71 (m, 8H), 1.58-1.55 (m, 2H), 1.33-1.15 (m, 8H), 1.11-1.02 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 80.5, 79.6, 62.1, 57.2 (2C), 35.1, 31.1 (4C), 26.2 (2C), 26.1 (4C), 25.8 (3C), 23.3, 18.2, -5.4 (2C)

FTIR (neat) ν = 2930, 2855, 1449, 1256, 1103, 837, 758 cm^{-1} .

HRMS (ESI) m/z calc. for $\text{C}_{23}\text{H}_{44}\text{NOSi}^+ [\text{M}+\text{H}]^+$ 378.3192, found 378.3192.

***N*-cyclohexyl-*N*-(5-phenylpent-2-ynyl)cyclohexanamine (98k)**

Light yellow oil

R_f = 0.39 (Hexane: Ethyl acetate = 3:1)

^1H NMR (CDCl_3 , 400 MHz) δ 7.30-7.18 (m, 5H), 3.42 (s, 2H), 2.83-2.79 (t, J = 7.49 Hz, 2H), 2.73-2.67 (m, 2H), 2.49-2.46 (t, J = 7.48 Hz, 2H), 1.81-1.74 (m, 4H), 1.61-1.58 (m, 2H), 1.31-1.17 (m, 8H), 1.13-1.04 (m, 2H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 140.9, 128.4 (2C), 128.2 (2C), 126.1, 82.2, 80.0, 57.2 (2C), 35.2, 35.1, 31.1 (4C), 26.3 (2C), 26.2 (4C), 20.9

FTIR (neat) ν = 3017, 2930, 2853, 1450, 1215, 756 cm^{-1} .

HRMS (ESI) m/z calc. for $\text{C}_{23}\text{H}_{34}\text{N}^+ [\text{M}+\text{H}]^+$ 324.2691, found 324.2686.

***N*-cyclohexyl-*N*-(3-(trimethylsilyl)prop-2-ynyl)cyclohexanamine (98l)**

Light yellow oil

$R_f = 0.65$ (Hexane: Ethyl acetate = 5:1)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 3.47 (s, 2H), 2.78-2.71 (tt, $J = 10.80, 3.03$ Hz, 2H), 1.85-1.75 (m, 8H), 1.61-1.58 (m, 2H), 1.35-1.17 (m, 8H), 1.15-1.04 (m, 2H), 0.14 (s, 9H).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 106.7, 87.8, 57.5 (2C), 36.0, 31.2 (4C), 26.3 (2C), 26.2 (4C), -0.1

FTIR (neat) $\nu = 3017, 2926, 2162, 1449, 1249, 841, 775, 742, 756\text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{18}\text{H}_{34}\text{NSi}^+ [\text{M}+\text{H}]^+ 292.2461$, found 292.2461.

***N*-cyclohexyl-*N*-(3-(4-nitrophenyl)prop-2-ynyl)cyclohexanamine (98m)**

Light brown oil

$R_f = 0.55$ (Hexane: Ethyl acetate = 3:1)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.17-8.15 (d, $J = 8.79$, 2H), 7.52-7.50 (d, $J = 8.80$ Hz, 2H), 3.72 (s, 2H), 2.84-2.77 (tt, $J = 10.83, 3.06$ Hz, 2H), 1.90-1.87 (m, 4H), 1.81-1.78 (m, 4H), 1.64-1.61 (m, 2H), 1.41-1.22 (m, 8H), 1.18-1.07 (m, 2H).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 146.6, 132.1 (2C), 130.8, 123.4 (2C), 96.0, 81.7, 57.6 (2C), 35.8, 31.3 (4C), 26.2 (2C), 26.1 (4C)

FTIR (neat) $\nu = 3019, 2932, 2855, 1593, 1518, 1344, 1215, 756\text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_2^+ [\text{M}+\text{H}]^+ 341.2229$, found 341.2216.

2-(3-(dicyclohexylamino)prop-1-ynyl)benzaldehyde (98n)

Light orange oil

$R_f = 0.3$ (Hexane: Ethyl acetate = 5:1)

^1H NMR (CDCl_3 , 400 MHz) δ 10.53 (s, 1H), 7.91-7.89 (d, $J = 8.17$ Hz, 1H), 7.55-7.49 (m, 2H), 7.42-7.38 (m, 1H), 3.77 (s, 2H), 2.86-2.79 (tt, $J = 10.82, 3.10$ Hz, 2H), 1.91-1.88 (m, 4H), 1.81-1.78 (m, 4H), 1.64-1.61 (m, 2H), 1.41-1.21 (m, 8H), 1.18-1.07 (m, 2H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 192.0, 136.1, 133.7, 133.3, 128.0, 127.7, 126.9, 97.4, 78.9, 57.5 (2C), 35.8, 31.3 (4C), 26.2 (2C), 26.1 (4C)

FTIR (neat) $\nu = 3019, 2932, 2855, 1694, 1215, 756\text{ cm}^{-1}$.

HRMS (ESI) m/z calc. for $\text{C}_{22}\text{H}_{30}\text{NO}^+ [\text{M}+\text{H}]^+ 324.2327$, found 324.2313.

Ethyl 4-(dicyclohexylamino)but-2-ynoate (98o)

Light yellow oil

$R_f = 0.6$ (Hexane: Ethyl acetate = 3:1)

^1H NMR (CDCl_3 , 400 MHz) δ 4.24-4.19 (q, $J = 7.14$ Hz, 2H), 3.60 (s, 2H), 2.77-2.71 (m, 2H), 1.84-1.76 (m, 8H), 1.62-1.59 (m, 2H), 1.33-1.19 (m, 11H), 1.16-1.06 (m, 2H).

^{13}C NMR (CDCl_3 , 100 MHz) δ 153.7, 88.6, 75.4, 61.7, 57.4 (2C), 35.0, 31.2 (4C), 26.13 (2C), 25.99 (4C), 14.0

FTIR (neat) ν = 3019, 2932, 2222, 1705, 1215, 756 cm^{-1} .

HRMS (ESI) m/z calc. for $\text{C}_{18}\text{H}_{29}\text{NO}_2^+ [\text{M}+\text{H}]^+$ 292.2277, found 292.2263.

List of Publication

1. Jie-Sheng Tian, Teck-Peng Loh, Copper-Catalyzed Rearrangement of Tertiary Amines through Oxidation of Aliphatic C–H Bonds in Air or Molecular Oxygen: Direct Synthesis of α -Amino Acetals. *Angew. Chem. Int. Ed.* **2010**, 49, 8417-8420.
2. Jie-Sheng Tian, Teck-Peng Loh, Copper-Catalyzed α -Amination of Aliphatic Aldehydes. *Chem. Commun.* **2011**, 47, 5458-5460.
3. Jie-Sheng Tian, Teck-Peng Loh, In situ Generated Hypoiodite Catalyzed α -Amination of Aldehydes. *Manuscript Submitted.* **2011**.

Patent

4. Teck-Peng Loh, Jie-Sheng Tian, New Methodology for the Synthesis of α -Amino Acetals. US 61/361,846, **2010**.

Conference papers

5. Jie-Sheng Tian, Teck-Peng Loh, Copper-Catalyzed Rearrangement of Tertiary Amines via Aliphatic C–H Bonds Oxidation in Air or Molecular Oxygen: Direct Synthesis of α -Amino Acetals. 6th Asian-European Symposium, **2010**, PA14, Singapore.