Part I Indium-mediated THP ring formation and
transformation of halo group into hydroxyl group
Part II Palladium-catalyzed direct arylation of
cyclic enamides with arylmetallic reagents

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**PART I: INDIUM-MEDIATED THP RING FORMATION AND
TRANSFORMATION OF HALO GROUP INTO HYDROXYL
GROUP**

**PART II: PALLADIUM-CATALYZED DIRECT ARYLATION
OF CYCLIC ENAMIDES WITH ARYLMETALLIC
REAGENTS**

ZHOU HAI

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2011

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SUMMARY

This thesis comprises of two main parts: indium-mediated THP ring formation and functional group transformation, and palladium-catalyzed direct arylation of cyclic enamides with organometallic reagents via C-H functionalization.

I. ONE-POT TOTAL SYNTHESSES OF THP-RING NATURAL PRODUCTS

A one-pot strategy is devised and applied to the total syntheses of natural products with a THP-ring backbone. A special feature of this one-pot synthesis is the recyclability of the indium complex byproduct generated from the indium-mediated allylation reaction for concurrent catalysis in subsequent steps. Centrolobine and civet cat secretion are synthesized via this new method in overall yields of 58% and 23%, respectively.

II. TRANSFORMATION OF HALO GROUP INTO HYDROXYL GROUP VIA TIN-FREE RADICAL METHOD

Aerobic aqueous transformation of halo group into hydroxyl group via metal-mediated (indium and zinc) free-radical reaction has been achieved under mild neutral reaction condition. This method has also been applied to the conversion of monohalo-, dihalo-, trihalo-, and tetrahalo-carbons into their corresponding products, i.e. alcohol,

carbonyl, acid and carbon dioxide, respectively. In addition, this method has potential application in environmental protection for disposal of halogenated waste solvents and halocarbon-contaminated water supplies.

III. SYNTHESIS OF 4,4-DIHALOTETRAHYDROPYRANS VIA PRINS CYCLIZATION

Indium trihalide-catalyzed synthesis of *cis*-dihalo-2,6,4,4-(*gem*)-disubstituted-tetrahydropyrans via Prins cyclization of aldehydes with halo homoallyl alcohols has been reported firstly. The yields of the reaction varies with different halo-substituents, increasing in the order of I > Br > Cl. Especially the *gem*-diiodo-THP has been obtained in excellent yield up to 96%. The method developed is expected to be applied to construct pyranones, which are important motifs in many natural products.

IV. PALLADIUM(II)-CATALYZED DIRECT ARYLATION OF $C(sp^2)$ -H BONDS

A novel direct coupling of cyclic enamides with arylboronic acid or trialkoxyarylsilane via Pd(II)-catalyzed C-H functionalization has been achieved in good yields (up to 95%).

V. COPPER-FREE, PALLADIUM-CATALYZED SONOGASHIRA CROSS-COUPLING REACTION

A new method of Sonogashira reaction in copper and amine free environment has been developed. This reaction can be applied to different substrates with high yield. It would be a beneficial synthetic tool to construct many complex molecules.

INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
$^{\circ}\text{C}$	degree centigrade
ABq	AB quartet
Ac	acetyl
acac	acetoacetate
AcOH	acetic acid
Ac ₂ O	acetic anhydride
AllylBr	allylbromide
Alloc	allyloxycarbonyl
aq.	aqueous
B:	Lewis base
Bn	benzyl
br s	broad singlet
Bz	benzoyl
Calcld	calculated
Cat.	catalytic
Cbz	benzyloxycarbonyl
CDCl ₃	deuterated chloroform
COSY	correlated spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CH ₂ Cl ₂	dichloromethane
CHCl ₃	chloroform
cm ⁻¹	inverse centimeter
Cy	cyclohexane; cyclohexanyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide

dd	doublets of doublet
ddd	doublets of doublets of doublet
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	diphenylphosphino ferrocenyl
dq	doublets of quartet
dt	doublets of triplet
<i>ee</i>	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electronspray ionization
Et	ethyl
ether	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atomic bombardment
FTIR	Fourier transform infrared spectroscopy
g	gram
Gly	glycine
h	hour
H	hydrogen
hept	heptet
Hex	hexane
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
Ipc	isopinocampheyl

<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constants
kg	kilogram
L.A.	Lewis acid
LDA	lithium diisopropylamide
M	concentration (mol/dm ⁻³)
M ⁺	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxy methyl
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)
NaHMDS	Sodium hexamethyl disilazide
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu	<i>n</i> -butyl
nmr	nuclear magnetic resonance
NMO	4-methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
NOESY	nuclear Overhauser enhancement spectroscopy
N.R.	no reaction
obs.	observed
OTf	trifluoromethanesulfonate
PBr ₃	phosphorus tribromide
PCC	pyridinium chlorochromate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl

PhH	benzene
PhMe	toluene
PMB	<i>p</i> -methoxybenzyl
ppm	parts per million
Py	pyridine
q	quartet
qd	quartets on doublet
quint.	quintet
rt.	room temperature
RBF	round bottom flask
R _f	retention factor
s	singlet
sat'd	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenyl silyl
TBS	<i>tert</i> -butyldimethyl silyl
<i>t</i> -Bu	<i>tert</i> -butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TFA	trifluoroacetic acid
TfOH	triflate acid
Tf ₂ O	Triflate anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMSE	trimethylsilylethyl
TMEDA	N,N,N',N'-tetramethylethylenediamine
TPAP	tetrapropylammonium perruthenate
Ts	<i>p</i> -toluenesulfonyl
T.S.	transition state
vol	volume

PART I

CHAPTER 1

***One-pot Total Syntheses of Natural Products
Containing a THP-ring Backbone: (±)-centrolobine
and (±)-civet cat secretion***

1.1 INTRODUCTION

The growth of organic synthesis, especially of useful compounds, has been facilitated by the many methodologies developed over decades. Among these, one-pot methods are attractive since they generate less waste, minimize isolation of intermediates in multi-step syntheses of complex molecular targets and save time and cost.¹ One-pot reactions can be classified roughly as tandem, domino or cascade reactions, although there is no clear line of demarcation between these terms.² In current literatures, the use of these near-synonymous terms is ambiguous and interchangeable.^{2c} Since there are extremely abundant cases in this important field, this introduction only intends to present a brief taxonomy with typical examples.

1.2 TAXONOMY

Generally speaking, one-pot strategy, including tandem, and domino or cascade reactions, refers to transformation of a reactant through multiple chemical events successively in a single reactor to improve the efficiency of organic synthesis. However, there are still some differences among these terms, which are clarified below with schematic illustration and exemplary cases.

1.2.1 Domino (Cascade) Reaction

¹ (a) Lebel, H.; Ladjel, C.; Brethous, L. *J. Am. Chem. Soc.* **2007**, *129*, 13321-13326. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1-21. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186. (d) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143-2173. (e) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619-1665. (f) Guo, H. C.; Ma, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354-366. (g) Domling, A. *Chem. Rev.* **2006**, *106*, 17-89. (h) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobaslija, M.; McQuade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2899-2906. (i) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266-276. (j) Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602-1634. (k) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967-1983. (l) Catellani, M. *Synlett* **2003**, 298-313. (m) Pamies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247-3261. (n) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215-3229. (o) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195-206. (p) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136. (q) Sheldon, R. A. *Chem. Commun.* **2008**, 3352. (r) Ekoue-Kovi, K.; Wolf, C. *Chem. Eur. J.* **2008**, *14*, 6302. (s) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

² (a) Ajamian, A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754-3760. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365-2379. (c) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329-16332.

A domino reaction is clearly defined by Tietze^{1p} as “a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step”. This type of transformation is also expressed as cascade reaction, although it is not very appropriate. A definitive feature of domino (cascade) reaction is that multiple (≥ 3) sequential elaborations are mediated via a single catalyst and reaction mechanism (Figure 1.1).^{2b} Fogg also noted that domino reaction may undergo in either intermolecular (involving generation of intermediates in the catalytic cycle) or intramolecular way.^{2b} Domino reaction can be classified as cationic, anionic, radical, pericyclic, photochemical, transition-metal induced and so on as well,^{1c,1p} according to the mechanism involved in the initial step. Herein, we prefer to adopt the classification of intermolecular and intramolecular and make a few typical examples of both domino reactions.

Figure 1.1 Schematic illustrations of intermolecular (a) and intramolecular (b) domino reactions.

1.2.1.1 Intramolecular Domino Reaction

Intramolecular domino reactions are very common in vivo, because a great variety of enzymes involve in different steps of reactions. By comparison, it does not

seem to be more feasible in vitro. In this aspect, one of most elegant example is enzyme-catalyzed biosynthesis of steroids starting from squalene epoxide. Four C-C bonds and six stereogenic centers form in the cascade reaction to afford lanosterol in high selectivity (Scheme 1.1).³

Scheme 1.1 Biosynthesis of steroids from squalene epoxide.

Another nice example of intramolecular domino reaction was deployed in the synthesis of polyspirane from palladium catalyzed cycloisomerization of polyenyne.⁴ This process includes three stages: initiation (addition of Pd-H to an acetylene), propagation (intramolecular carbopalladation), and termination (β -hydride elimination). It is worthy to note that regioselectivity of hydropalladation and subsequent carbapalladation are most essential to make this cascade reaction undergo (Scheme 1.2).

Scheme 1.2 Synthesis of polyspirane via Pd-catalyzed cycloisomerization of polyenyne.

Very recently, the first organocatalytic enantioselective polyene cyclization via singly occupied molecular orbital (SOMO) method has been accomplished by MacMillan (Scheme 1.3).⁵ This domino reaction is initiated by single-electron oxidation of chiral enamine intermediate, which is formed by condensation of

³ (a) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025. (c) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171. (d) Corey, E. J.; Virgil, S. C.; Liu, D. R.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 1524.

⁴ Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.

⁵ Rendler, S.; Macmillan, W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

polyenals with amine catalyst under copper triflate as an oxidant. Six-cycle steroidal frameworks have been obtained in excellent enantioselectivity (up to 93% ee) via radical sequence, subsequent oxidation and rearomatization.

1.2.1.2 Intermolecular Domino Reaction

In 2007, Ishihara reported biomimetic halopolycyclization of polyprenoid activated by chiral nucleophilic phosphoramidites to offer a halogenated polycyclic terpenoid in up to 99% enantiomeric and diastereomeric excess (Scheme 1.4).⁶

With the inspiration of biosynthetic way to cholesterol, our group also developed intermolecular chiral acetal-initiated cationic polycyclization at the same

⁶ Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

time. This domino reaction has also been applied to the practical synthesis of terpenoids (Scheme 1.5).⁷

Scheme 1.5 Acetal-initiated intermolecular cationic polyene cyclization.

Yamamoto developed a “super silyl” group for diastereoselective aldehyde cross-aldol cascade reaction to facilitate the construction of β -hydroxy aldehydes (Scheme 1.6).⁸

Scheme 1.6 HNTf₂-catalyzed cascade Mukaiyama aldol reaction.

1.2.2 Tandem Reaction

Tandem reactions are referred to sequential transformation of a substrate that takes place in two (or more) distinct reaction mechanisms without isolation of intermediates. In terms of the catalysis involved, tandem reaction can be further classified as orthogonal, auto and assisted tandem catalysis.^{2b}

1.2.2.1 Orthogonal Tandem Reaction

Mutual independence of sequential reactions is the most distinguished feature for orthogonal tandem reaction. That means two catalytic cycles are manipulated by their distinct catalyst, although both catalysts are present at the outset. With catalyst

⁷ (a) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 10024.

⁸ Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.

A, substrate A is preferably converted to product A, which is then act as substrate B to continue next transformation step with catalyst B to generate product B (Figure 1.2).

Figure 1.2 Illustration of orthogonal tandem reaction. (*additional reagent if required)

Scheme 1.7 shows an elegant example of orthogonal tandem reaction. Treatment of enyne with alkyne diester using Co nanoparticles and Pd as catalysts in three-step one-pot manner to produce tetracyclic fenestranes in 74% yield.⁹ This one-pot reaction is comprised of carbonylative cycloaddition, allylic alkylation and second time carbonylative cycloaddition. Although Pauson-Khand reaction occurs twice in the synthesis of fenestranes, the first one is not real tandem catalysis because palladium catalyst is added after the completion of first step.

Scheme 1.7 Synthesis of fenestranes via tandem allylic alkylation and Pauson-Khand reaction.

⁹ Son, S. U.; Park, K. H.; Chung, Y. K. *J. Am. Chem. Soc.* **2002**, *124*, 6838.

Another beautiful example of orthogonal tandem is the synthesis of branched polyethylenes from a single monomer at the coordinated action of three homogeneous catalysts.¹⁰ In the presence of three catalysts, 1-butene generated from **2** and the distribution of 1-alkenes by use of **3** are incorporated into a branched polyethylenes by titanium catalyst to provide polymer materials with varying properties. The properties of the branched polyethylene are determined by the ratio of the three catalysts (Scheme 1.8).

Scheme 1.8 Synthesis of polyethylenes via triple tandem catalysis

Recently, Goldman reported alkane metathesis which comprises alkane dehydrogenation and olefin hydrogenation (both are acted on by a “pincer”-ligated

¹⁰ Komon, Z. J. A.; Diamond, G. M.; Leclerc, M. K.; Murphy, V.; Okazaki, M.; Bazan, G. C. *J. Am. Chem. Soc.* **2002**, 124, 15280.

iridium complex **1** or **2**), olefin metathesis (mediated by Schrock-type catalyst **3**).¹¹ It is attractive that the metathesis of *n*-hexane provides distribution of C₂ to C₁₅ *n*-alkane products. This method provides a potential access to synthesize artificial fuel.

Scheme 1.9 Alkane metathesis via catalytic tandem alkane dehydrogenation-olefin metathesis.

1.2.2.2 Auto Tandem Reaction

Auto-tandem catalysis is characterized by a single catalyst precursor involved in two or more catalytic cycles with distinct mechanism. The structure of catalyst is essentially conserved, though intermediates will change in different cycle. Catalyst A continues to act on the substrate B, which is also the product A from the transformation of substrate A with catalyst A. Although this category can be subclassified into sequential catalysis and concurrent catalysis sometimes,^{2a} we take them into identity. To reduce side-reactions, it is rather difficult for this type to seek a delicate balance with a single catalyst that ensures two or more different catalytic cycles run at comparable rates without interference with each other (Figure 1.3).

¹¹ Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Bröckhert, M. *Science* **2006**, 312, 257.

Figure 1.3 Illustration of auto tandem reaction. (*Additional reagent if required)

A one-pot synthesis of esters from acid chlorides has been achieved in good yields. This process comprises a selective homogeneous transition-metal-catalyzed Rosenmund-type hydrogenolysis to form aldehyde and catalytic dimerization of the formed aldehyde into an ester (Scheme 1.10).¹²

Scheme 1.10 Synthesis of ester from acid chloride via homogeneous Ru-catalyzed Rosenmund-Tishchenko auto-tandem reactions.

C-C skeleton of expansion of methallylic alcohol has been affected by Knoevenagel condensation of the aldehyde generated from Rh-catalyzed hydroformylation, followed by Rh-catalyzed reduction of the double bond in the product (Scheme 1.11).¹³ In this reaction, the *o*-diphenylphosphinobenzoate acts a directing group to promote *syn* specificity in the hydroformylation step. In addition,

¹² Grushin, V. V.; Alper, H. *J. Org. Chem.* **1991**, 56, 5159.

¹³ Breit, B.; Zahn, S. K. *Angew. Chem. Int. Ed.* **2001**, 40, 1910.

this tandem reaction is preferred for its environmental protection and atom economy: water is the only byproduct.

Scheme 1.11 Sequential catalytic reaction in Hydroformylation-Knoevenagel-hydrogenation of methallylic alcohol.

1.2.2.3 Assisted Tandem Reaction

In assisted tandem catalysis, catalyst A is converted into catalyst B after its function on initial catalytic cycle. This new catalyst allows substrate B which is also the product of original step entering into the second cycle (Figure 1.4).

Figure 1.4 Illustration of assisted tandem reaction. (*Additional reagent if required)

The following assisted tandem reaction works well on alkynes to afford enynes stereospecifically (Scheme 1.12).¹⁴ P^tBu_3 is used to convert the palladium dibromide species which results from first step to $\text{PdBr}_2(\text{P}^t\text{Bu}_3)_2$. The latter one is then reduced to active $\text{Pd}(0)$ species for subsequent Sonogashira coupling.

¹⁴ Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, 4, 4321.

1.3 ONE-POT TOTAL SYNTHESSES OF NATURAL PRODUCTS CONTAINING A THP-RING BACKBONE: (±)-CENTROLOBINE AND (±)-CIVET CAT SECRETION

For the successful implementation of one-pot strategies in natural product synthesis, it is important to maximize the overlap or compatibility factors (such as reagent, catalyst, solvent, and mechanism) of the sequential reactions. There are only a few reports on one-pot total syntheses of natural products from commercially available starting materials, and these still pose a challenge for synthetic chemists.

The *cis*-2,6-disubstituted-tetrahydropyran (THP) ring was featured in a large variety of biologically active natural products such as centrolobine and civet cat secretion (Figure 1.5). Our group, and others, have independently reported the InX₃-

(-)-Centrolobine: Isolated from the heartwood of *Centrolobium robustum* and the stem of *Brosimum potabile*. Exhibits antimicrobial activity and possibly anti-leishmanial effects.

Civet cat secretion: A perfume isolated from glandular secretions of the *Viverra civetta*.

Figure 1.5 Natural products containing tetrahydropyran backbone.

catalyzed Prins cyclization of homoallylic alcohols with aldehydes to produce *cis*-2,6-disubstituted-4-halo-THP products.¹⁶ Subsequent dehalogenation using Bu₃SnH^{16a,c,17} afforded the THP compounds (Scheme 1.14). The disadvantages of this total synthesis

¹⁶ (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, 7, 4491-4494. (b) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, 45, 8387-8390. (c) Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2006**, 47, 1641-1644. (d) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, 40, 1627-1630.

¹⁷ Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, *Org. Lett.* **2002**, 4, 3919-3922

Scheme 1.14 Total synthesis of (-)-Centrolobine in our group.

include protection, deprotection and the use of toxic reagent Bu_3SnH which is difficult to remove from products and unfriendly to environment. One of the efficient alternative reagents for dehalogenation is dihaloindium hydride (Scheme 1.15).¹⁸ An indium hydride (Cl_2InH) was generated by the transmetalation between NaBH_4 and indium(III) trichloride (InCl_3). InCl_3 can be used in catalytic amount with a little excess of NaBH_4 .

Scheme 1.15 Dehalogenation by dihaloindium hydride.

¹⁸ (a) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906-907. (b) Baba, A.; Shibata, I. *Chem. Rec.* **2005**, *5*, 323-335. (c) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003**, *59*, 6627-6635.

Herein, we report the one-pot syntheses of two natural products with a THP ring as the backbone, namely, centrolobine and civet cat secretion, in overall yields of 58% and 23%, respectively. One special feature of this one-pot synthesis is the recyclability of the indium complex byproduct generated from the indium-mediated allylation reaction, for use as the catalyst in subsequent steps. We envisaged that the indium complex byproduct¹⁹ produced from the indium-mediated allylation of aldehydes with allyl bromide would also catalyze the subsequent Prins cyclization and dehalogenation ($\text{NaBH}_4/\text{InX}_3$) (Scheme 1.16).

Scheme 1.16 Proposed hypothesis for constructing a THP ring

To develop a one-pot, three-step synthesis of THP-containing compounds, we needed to screen for the best solvent for each individual step. Our experience with the indium-mediated allylation reaction revealed that water is an excellent solvent for this step.^{19a,b} As water is detrimental for subsequent steps, it is important that the indium-mediated allylation reaction is carried out either under solvent-free conditions or in a minimum amount of water. A detailed solvent screen showed that dichloromethane was the best solvent for the Prins cyclization. On the other hand, THF was found to be the best solvent for the dehalogenation process.

¹⁹ (a) Loh, T. P.; Tan, K. T.; Chng, S. S.; Cheng, H. S. *J. Am. Chem. Soc.* **2003**, *125*, 2958-2963. (b) Loh, T. P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115-9118. (c) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017-7020. (d) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739-1764.

It is important to note that the $\text{NaBH}_4/\text{InX}_3$ system (generated in advance or in situ)²⁰ reduces the 4-iodo and 4-bromo THP compounds efficiently but not the corresponding 4-chloro THP analogue. It was found that 1.5 equiv of InX_3 was essential for the reduction in the third step. Therefore, hydrocinnamaldehyde **1** was subjected to indium-mediated allylation followed by treatment with various aldehydes in a one-pot, three-step process (Table 1.1). The one-pot method worked with a wide variety of aldehydes, including alkyl and aromatic aldehydes, to form THP products **2** in moderate yields. Most substituents on the aromatic aldehydes did not influence the overall yields (entries 1-9). However, the aldehyde with nitro group on the aromatic ring gave no product (entry 10).

²⁰ The preparation of InBr_2H is provided in Experimental Section. Its in situ preparation is very simple. InBr_3 is added to the reaction mixture, followed by the addition of NaBH_4 in portions at rt.

With the reaction conditions established, we applied this method to the one-pot total synthesis of centrolobine, an antibiotic natural product.²¹ The synthesis commenced with allylation of aldehyde **3**²² to give the homoallylic alcohol **4**, followed by Prins cyclization and debromination to produce centrolobine **6** in 58% overall yield (Scheme 1.17).

Scheme 1.17. Total synthesis of (±)-centrolobine via the one-pot method

This one-pot, multiple-step method was also applied to the total synthesis of (6-methyl-2-tetrahydropyranyl) acetic acid **12**, which is a natural product isolated from glandular secretions of the civet cat (*Viverra civetta*),²³ as outlined in Scheme 1.18.

²¹ (a) Boehrsch, V.; Blechert, S. *Chem. Commun.* **2006**, 1968-1970. (b) Chandrasekhar, S.; Prakash, S. J.; Shyamsunder, T. *Tetrahedron Lett.* **2005**, *46*, 6651-6653. (c) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021-2024. (d) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883-3885. (e) Colobert, F.; Des, M. R.; Solladie, G.; Carreno, M. C. *Org. Lett.* **2002**, *4*, 1723-1725.

²² Chen, Y. C.; Muhlrade, A.; Shteyer, A.; Vidson, M.; Bab, I.; Chorey, M. *J. Med. Chem.* **2002**, *45*, 1624-1632.

²³ (a) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, *61*, 11679-11685. (b) Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *Aust. J. Chem.* **1998**, *51*, 9-18. (c) Greenspoon, N.; Keinan, E. *J. Org. Chem.* **1988**, *53*, 3723-3731. (d) Jones, J. B.; Hinks, R. S. *Can. J. Chem.* **1987**, *65*, 704-707. (e) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474-3480. (f) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768-5774.

Scheme 1.18 Total synthesis of (±)-civet cat secretion via the one-pot method

Commercially available acetal **7** was converted into aldehyde **8** by hydrolysis with Amberlyst-15. Subsequent allylation of **8** afforded homoallylic alcohol **9**, which was followed by Prins cyclization and debromination to produce methyl ester **11**. The natural product **12** was obtained by hydrolysis of the ester with lithium hydroxide. This one-pot, five-step method afforded **12** in 23% overall yield.

1.4 CONCLUSION

In conclusion, a one-pot strategy has been successfully designed and applied to the total synthesis of two natural products, ($\pm$)-centrolobine and ($\pm$)-civet cat secretion. This one-pot process provides a practical entry to diverse THP-based natural products and analogues. A special feature of this method is the recyclability of the metal complex byproduct generated from the initial step for catalysis of subsequent steps. Another feature is that no protection/deprotection of the hydroxy group is necessary. Extension to solid-supported synthesis and the application of this one-pot method to the total synthesis of more complex molecules are in progress.

CHAPTER 2

***Aerobic Aqueous Transformation of Halo Group
into Hydroxyl Group via Tin-Free Radical Method***

2.1 INTRODUCTION

The conversion of halides into alcohols is used less often than the reverse conversion in organic synthesis. As a consequence, there are no review and relatively few general methods for this group transformation so far.²⁴ Generally, only activated halides, such as benzyl and allyl halides, can be hydrolysed easily by water or hydroxide ions.²⁵ However, the hydrolysis of non-activated halides is more difficult, and has been achieved using an alternative two-step procedure, that is, initial substitution of the halide by oxygenated nucleophiles, such as acetate or formate, and followed by hydrolysis of ester group.²⁶ Although nucleophilic substitution can usually be facilitated by phase transfer,²⁷ or electrophilic cation like silver salts,²⁸ there are drawbacks in these procedures:

1. High temperature is required for the completion of nucleophilic substitution step, particularly with more inactive halides.
2. The elimination reaction of halide results in side reaction in some cases.

Hence, a free-radical method is an efficiently alternative approach to halide-to-alcohol transformation. This introduction is mainly concentrated on the progress of

²⁴ (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 370. (b) Mitsunobo, O. In *Synthesis of Alcohols and Ethers*, In *Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1993**, 2.

²⁵ Larock, R. C. *Comprehensive Organic Transformation*; VCH Publishers Inc.: New York, **1989**, 481.

²⁶ (a) Alexander, J.; Renyer, M. L.; Veerapanane, H. *Synth. Commun.* **1995**, 25, 3875; and references cited therein. (b) Ruddick, C. L.; Hodge, P.; Houghton, M. P. *Synthesis* **1996**, 1359. (c) Abad, A.; Agullo, C.; Cunat, A. C.; Navarro, I. *Synthesis* **2005**, 3355.

²⁷ (a) Jones, R. A. *Aldrichimica Acta* **1976**, 9, 35. (b) Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, 48, 1360.

²⁸ (a) Gingras, M.; Chan, T. H. *Tetrahedron Lett.* **1989**, 30, 279. (b) Zarraga, M.; Alvarez, E.; Ravelo, J. L.; Rodriguez, V.; Rodriguez, M. L.; Martin, J. D. *Tetrahedron Lett.* **1990**, 31, 1663. (c) Loodworth, A. J.; Tallant Neil, A. J. *Chem. Soc., Chem. Commun.* **1992**, 5, 428. (d) Busque, F.; Cid, P.; de March, P.; Figueredo, M.; Font, J. *Heterocycles* **1995**, 40, 387. (e) Deota, P. T.; Singh, V. *J. Chem. Res., Synop.* **1996**, 258. (f) Liang, X.; Lohse, A.; Bols, M. *J. Org. Chem.* **2000**, 65, 74327. (g) Harmann, H.-J.; Liebscher, J. *Synlett* **2001**, 96. (h) McCullough, K. J.; Tokuhara, H.; Masuyama, A.; Nojima, M. *Org. Biomol. Chem.* **2003**, 1, 1522. (i) Toyonari, I.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, 59, 525.

transformation of alkyl halides into alcohols via free-radical method and aqueous radical dehalogenation.

2.1.1 Direct Radical Transformation of C-X Bonds to C-O Bonds

The first aerobic conversion of carbon-halogen bonds to carbon-oxygen bonds was reported by Nakamura (Scheme 2.1).²⁹ The reaction undergoes via free radical method in presence of stoichiometric 2 equiv of Bu₃SnH and dry air bubbling. This radical nature of the method permits an oxygenative radical cyclization of an olefinic iodide. In addition, a wide range of functional groups are tolerable to this reaction. However, the transformation can only be applied to iodides and activated bromides.

Scheme 2.1 Reductive oxygenation of organic halides.

Further improvement of this transformation was to use catalytic amount of Bu₂(*t*-Bu)SnCl and stoichiometric NaBH₃CN under ultrasonic irradiation.³⁰ A near stoichiometric amount of molecular oxygen could also be employed instead of dry air bubbling (Scheme 2.2).³¹

²⁹ Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980.

³⁰ Sawamura, M.; Kawaguchi, Y.; Sato, K.; Nakamura, E. *Chem. Lett.* **1997**, 705.

³¹ Sawamura, M.; Kawaguchi, Y.; Nakamura, E. *Synlett.* **1997**, 801.

halogen due to steric hindrance (Scheme 2.3).³²

Scheme 2.3 Radical oxygenation of 2-deoxy-2-iodo hexopyranosides with TEMPO.

reduction to afford the hydroxyl pyranosides (Scheme 2.4).³³

Scheme 2.4 Radical substitution of 2-deoxy-2-iodo pyranosides with TEMPO.

³² Moutel, S.; Prandi, J. *Tetrahedron Lett.* **1994**, 35, 8163.

³³ Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 837.

2.2 AQUEOUS RADICAL DEHALOGENATIONS OF ORGANIC HALIDES

2.2.1 Metal Mediated Dehalogenation in Water

Indium has been attracting particular interest from many chemists, due to its unique properties, and reactivity in aqueous media. The first systematic study on indium-mediated dehalogenation was carried out by Ranu.^{34a} A wide range of structurally different α -bromo and α -iodocarbonyl compounds underwent reduction in water, leading to the corresponding dehalogenated products under sonication.^{11a} But simple alkyl and aryl halides remained inert under these conditions. This method was extended to the stereoselective reduction of aryl-substituted *gem*-dibromides, providing primarily the corresponding (*E*)-vinyl bromides.^{34b} However, no stereoselectivity was observed for thiophene- and furan-substituted *gem*-dibromides, whereas alkyl-substituted *gem*-dibromides showed low effectiveness (Scheme 2.5).

Scheme 2.5 Indium-mediated reduction of α -halocarbonyl compounds and aryl-substituted *gem*-dibromides.

The use of micellar solution can enhance the reactivity of certain processes. A catalytic amount of sodium dodecyl sulfate was applied by Kim to indium-mediated reductive dehalogenation of various α -halocarbonyl compounds (Scheme 2.6)³⁵.

³⁴ (a) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1139. (b) Ranu, B.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, 66, 4120.

³⁵ Park, L.; Keum, G.; Kang, S. B.; Kim, K. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4462.

Scheme 2.6 Indium-mediated reduction of α -halocarbonyl compounds in presence of SDS.

Recently, it turned out that indium metal was applicable to the dehalogenation of heteroaromatic halides in water. Common aromatic halides showed low reactivity under the established reaction conditions (Scheme 2.7).³⁶

Scheme 2.7 Indium-mediated reduction of haloheteroaromatics.

Granular iron metal can be used in the reductive dechlorination of two important chloroacetanilide herbicides, alachlor and metolachlor in aqueous solutions at room temperature.³⁷ It was also found to be used in the degradation of another herbicide, Atrazine (Scheme 2.8).³⁸

Scheme 2.8 Iron-mediated reduction of herbicides.

³⁶ Hirasawa, N.; Takahashi, Y.; Fukuda, E.; Sugimoto, O.; Tanji, K. *Tetrahedron Lett.* **2008**, 49, 1492.

³⁷ Eykholt, G. R.; Davenport, D. T. *Environ. Sci. Technol.* **1998**, 32, 1482.

³⁸ Monson, S. J.; Ma, L.; Cassada, D. A.; Spalding, R. F. *Anal. Chim. Acta* **1998**, 373, 153.

Zerovalent zinc plays an important role as a reductant in hydrodehalogenation processes due to its strong reducing ability.³⁹ Even in other types or aqueous reaction such as Barbier reaction, dehalogenated compound is a substantial byproduct with yields up to 71%. Many efforts have been devoted to dehalogenation of carbon tetrachloride using zerovalent zinc in several groups.⁴⁰ The kinetics of these processes was dependent on the surface area of metal, carbon tetrachloride concentration and solution pH, and buffer selection. More interestingly, the system Zn-Cu-DMF-H₂O was applied in selective defluorination of perfluoroarenes under mild conditions (Scheme 2.9).⁴¹

Scheme 2.9 Zinc-mediated selective defluorination.

To demonstrate the dehalogenation ability of zinc in organic synthesis, Kobrina reported the selective reductive dehalogenation of 8-chloro-1,2,3,4,8-pentafluorobicyclo[2.2.2]octa-2,5-dienones with zinc in acetic acid. Successive

³⁹ Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, 102, 4009.

⁴⁰ (a) Warren, K. D.; Arnold, R. G.; Bishop, T. L.; Lindholm, L. C.; Betterton, E. A. *J. Hazard. Mater.* **1995**, 41, 217. (b) Boronina, T.; Klabunde, K. J.; Sergeev, G. B. *Environ. Sci. Technol.* **1995**, 29, 1511. (c) Boronina, T.; Lagadic, I.; Sergeev, G. B.; Klabunde, K. J. *Environ. Sci. Technol.* **1998**, 32, 2614.

⁴¹ (a) Krasnov, V. I.; Platonov, V. E.; Beregovaya, I. V.; Shchegoleva, L. N. *Tetrahedron.* **1997**, 53, 1797. (b) Krasnov, V. I.; Platonov, V. E. *Russ. J. Org. Chem.* **2001**, 37, 517.

hydrodechlorination and hydrodefluorination occurred at the 8-position (Scheme 2.10).⁴²

Scheme 2.10 Zinc-mediated selective and successive dehalogenation.

2.2.2 Non-metal Mediated Dehalogenation in Water

Hypophosphorous acid and its salt are a type of non-metal effective radical reducing agents used extensively in both dehalogenation and deoxygenation. This kind of transformation was first reported by Barton, although the reaction was not carried out initially in aqueous medium (Scheme 2.11).⁴³

Scheme 2.11 H_3PO_2 -mediated dehalogenation.

⁴² Bogachev, A. A.; Kobrina, L. S. *J. Fluorine Chem.* **1998**, 92, 33.

⁴³ (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, 33, 5709. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, 58, 6838. (c) Nambu, H.; Alinejad, A. H.; Hata, K.; Fujioka, H.; Kita, Y. *Tetrahedron Lett.* **2004**, 45, 8927.

Izawa used hypophosphorous acid and its sodium salt as radical reducing agents for halides at the sugar part of nucleosides to afford the corresponding hydrocarbons in aqueous medium (Scheme 2.12).⁴⁴

Scheme 2.12 NaH_2PO_2 -mediated dehalogenation in aqueous medium.

Very recently, β -cyclodextrin (CDs) was adopted as a molecular reactor for free radical dehalogenation in aqueous media. Tetrasubstituted ammonium hypophosphite plays roles as not only an efficient reducing agent, but also a surfactant. Alkyl and aryl halides were subjected to this reaction in the presence of Et_3B and air (Scheme 2.13).⁴⁵

Scheme 2.13 Radical dehalogenation in aqueous β -CD molecular reactor.

By far, tri-*n*-butyltin hydride (TBTH) is the most used radical reducing agent in dehalogenation. But TBTH has practically limited use in organic solvents, due to

⁴⁴ Takamastu, S.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. *Tetrahedron Lett.* **2001**, 42, 7605.

⁴⁵ Johnson, A. E.; Perchyonok, V. T. *Curr. Org. Chem.* **2009**, 13, 914.

its poor solubility. To perform tin radical chemistry in water, Maritra utilized detergents such as sodium dedecyl sulfate (SDS), triton-X-100 or cetyltrimethylammonium bromide to solubilize TBTH in water and therefore attain the dehalogenation in aqueous media. The presence of the detergent is especially necessary for water-insoluble substrates such as 9-bromoanthracene (85% yield of anthracene). Deeper research indicated that no other additive but only NaHCO_3 was enough to achieve the dehalogenation of water-soluble organic halides in water by TBTH. Under these conditions, m-, o-, and p-halobenzoic acids were reduced in high yields (Scheme 2.14).⁴⁶

Scheme 2.14 TBTH-mediated dehalogenation in aqueous medium.

Arylsilane as a radical reducing agent was widely investigated by Yokoyama. This group developed a series of water-soluble organosilane compounds with hydrophilic groups such as an ether group and a hydroxyl group in the side chain. This type of diarylsilanes was applied to the radical reduction of alkyl and aryl halides in aqueous media to give the corresponding dehalogenated products in good yields. The reaction underwent in the presence of triethylborane and air (Figure 2.1).⁴⁷

⁴⁶ (a) Maitra, U.; Sarma, K. D. *Tetrahedron Lett.* **1994**, 35, 7861. (b) Sarma, K. D.; Maitra, U. *Tetrahedron* **1998**, 54, 4965.

⁴⁷ Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1997**, 2519.

Figure 2.1 Reduction of organic halides with diarylsilanes, Et_3B , and H_2O at rt.

$(\text{Me}_3\text{Si})_3\text{SiH}$ was used as a successful reducing reagent in radical dehalogenation in water. The reaction proceeded well with silane, and initiator (ACCN) in aqueous medium at $100\text{ }^\circ\text{C}$ for both hydrophilic and hydrophobic substrates. The only variation is that an amphilic thiol was needed in case of the water-soluble substrates (Scheme 2.15).⁴⁸

Scheme 2.15 $(\text{TMS})_3\text{SiH}$ -mediated dehalogenation in aqueous medium.

⁴⁸ Postigo, A.; Kopsov, S.; Ferreri, C.; Chatgililoglu, C. *Org. Lett.* **2007**, 9, 5159.

2.3 AEROBIC AQUEOUS TRANSFORMATION OF HALO GROUP INTO HYDROXYL GROUP VIA TIN-FREE RADICAL METHOD

Functional group transformations are essential tools in organic synthesis,⁴⁹ of which the transformation of halo group into hydroxyl group is among one of the useful arsenals.⁵⁰ Conventional strategies to convert halogenated compounds to other useful compounds usually employ nucleophilic substitutions via S_N1 and S_N2 mechanisms. However, these are often limited by several constraints such as steric hindrance and electronic effects which affect the reactivity of multihalogenated substrates. Hence, a free radical method could be adopted as an alternative approach. In 1991, Nakamura reported an elegant strategy involving the aerobic conversion of organic halides to alcohols using tin hydride as radical reagent.²⁹⁻³¹ Unfortunately, the application of this method could not be fully exploited, due to its disadvantages of using toxic reagent, water-intolerance, and limited substrate scope (Scheme 2.16). Therefore, a new radical method which can overcome these limitations is highly sought-after.

Scheme 2.16 Reductive oxygenation of organic halides.

Our strategy is to explore a method which involves an aerobic aqueous transformation of halo group into hydroxyl group via metal-mediated tin-free radical reaction under mild reaction conditions. As atmospheric oxygen and water are ubiquitous on Earth, their presence is crucial for subsistence in aerobic organisms

⁴⁹ *Comprehensive Organic Functional Group Transformations*, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Eds., Elsevier, Oxford, 1995.

⁵⁰ Selected examples: (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153. (b) Huang, X.; Batchelor, R. J.; Einstein, F. W. B.; Bennet, A. J. *J. Org. Chem.* **1994**, *59*, 7108. (c) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160. (d) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762. (e) Gingras, M.; Chan, T. H. *Tetrahedron Lett.* **1989**, *30*, 279.

which generate energy via metabolism. Air is a cost-free oxidant, and water is eco-friendly and a universal solvent for life. Hence, it would be extremely favourable if both water and air can be applied in chemical synthesis. Our idea originated from two important aqueous free radical reactions dealing with organic halides (Our group⁵¹ and others⁵² reported indium or zinc mediated Barbier-type addition via single electron transfer (SET) (Scheme 2.17) and Barton's dehalogenation^{43c} process by

Scheme 2.17 Indium or zinc mediated Barbier-type addition.

hypophosphorous acid or its salt). On the basis of this information, a new radical process to convert halo group to hydroxyl group is designed as shown in Scheme 2.18. We envisage that indium or zinc may mediate SET to halide in water to give alkyl free radical, which can then capture the oxygen in air to form a radical intermediate. Hydrogen abstraction and reduction by hypophosphite should provide the final product as an alcohol.

⁵¹ (a) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (b) Loh, T. P.; Li, X. R. *Angew. Chem., Int. Ed.* **1997**, *36*, 980. (c) Shen, Z. L.; Loh, T. P. *Org. Lett.* **2007**, *9*, 5413. (d) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Chem.–Eur. J.* **2008**, *14*, 1875. (e) Shen, Z. L.; Yeo, Y. L.; Loh, T. P. *J. Org. Chem.* **2008**, *73*, 3922. (f) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Tetrahedron Lett.* **2009**, *50*, 1051. (g) Yang, Y. S.; Shen, Z. L.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1209. for reviews, see: (h) Loh, T. P. In *Science of Synthesis*; Yamamoto, H. Ed.; Georg Thieme Verlag: Stuttgart, New York, 2004; pp 413. (i) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739.

⁵² (a) Keh, C. C. K.; Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 4062. for reviews, see: (b) Herreras, C. I.; Yao, X. Q.; Li, Z. P.; Li, C. J. *Chem. Rev.* **2007**, *107*, 2546. (c) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (d) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (e) Miyabe, H.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1267.

Scheme 2.18 Project design and proposed mechanism

We can further extend to geminal multihalogenated compounds, wherein the unstable intermediate formed upon replacement by a hydroxyl group would collapse into a carbonyl, acid and CO_2 in aqueous media (Scheme 2.19). If successful, halogenated hydrocarbons can also act as synthetic equivalents to functional groups such as alcohol, carbonyl and acid with respect to the number of halogen atoms. Herein, we report an efficient and practical aerobic aqueous transformation of halo group into hydroxyl group using a tin-free radical method.

Scheme 2.19 Hypothesis for functional group interconversion

2.3.1 Metal Mediated Transformation of Halide into Alcohol in Water

Our initial studies focused on the conversion of 1-bromoadamantane into 1-adamantanol under different conditions (Table 2.1). The reaction was first carried out in different solvents at 60 °C in the presence of indium and $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$, with air

bubbling. It was gratifying to find that when $\text{H}_2\text{O}-t\text{BuOH}$ (1 : 1) was used as the solvent system, the desired product could be obtained in high yield (75%) (entry 7). To prove that the reaction occurred via free-radical method, 0.5 equiv of galvinoxyl, an efficient free-radical scavenger, was added to the reaction under similar conditions. The reaction was inhibited with only a trace amount of **14a** observed (entry 8). Comparable yield was also obtained using an oxygen balloon instead of air bubbling (entry 9). Zinc was also efficient for this transformation, under air bubbling or oxygen balloon (entries 10-12). However, the reaction performed better in saturated aqueous NH_4Cl solution than in water (entry 11 versus 12). Further investigation indicated that $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ is indispensable for this transformation and the yield would decrease sharply otherwise (entry 6 versus 13).

Table 2.1 Transformation of 1-bromoadamantane into 1-adamantanol under different conditions^a

Entry	Metal	O ₂ source	Solvent (1:1)	Yield (%) ^b
1	In	air bubble	$\text{H}_2\text{O}-\text{EtOH}$	7
2	In	air bubble	$\text{H}_2\text{O}-\text{DMSO}$	25
3	In	air bubble	$\text{H}_2\text{O}-\text{DME}$	27
4	In	air bubble	$\text{H}_2\text{O}-\text{CH}_3\text{CN}$	38
5	In	air bubble	$\text{H}_2\text{O}-\text{DMF}$	43
6	In	air bubble	$\text{H}_2\text{O}-\text{dioxane}$	56
7	In	air bubble	$\text{H}_2\text{O}-t\text{BuOH}$	75
8 ^c	In	air bubble	$\text{H}_2\text{O}-t\text{BuOH}$	trace
9	In	O ₂ balloon	$\text{H}_2\text{O}-t\text{BuOH}$	78
10	Zn	air bubble	sat. aq. $\text{NH}_4\text{Cl}-t\text{BuOH}$	78
11	Zn	O ₂ balloon	sat. aq. $\text{NH}_4\text{Cl}-t\text{BuOH}$	72
12	Zn	O ₂ balloon	$\text{H}_2\text{O}-t\text{BuOH}$	30
13 ^d	In	air bubble	$\text{H}_2\text{O}-\text{dioxane}$	27

^a Reaction conditions unless otherwise specified: metal (3 equiv), $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ (5 equiv), 60 °C, 16 h. ^b Isolated yield. ^c Galvinoxyl (0.5 equiv) was added. ^d Indium (5 equiv), but without addition of $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$.

To investigate the scope of this transformation, various alkyl halides were subjected to the optimized reaction conditions (Table 2.2). Both indium and zinc can mediate the conversion of alkyl halides into alcohols with different oxygen sources (air or oxygen balloon) in moderate to good yields (Table 2.2, entries 2 and 4). Besides alkyl bromide and iodide, alkyl chlorides can also work under the condition, but in relatively low yield of 35% (Table 2.2, entry 1). Secondary and tertiary alkyl halides were transformed into their corresponding alcohols in good yields with this novel method. However, primary halides only gave the product in low yield (Table 2.2, entry 7). This may be due to the well-known fact that primary alkyl free radical intermediate is not stable enough like the secondary and the tertiary ones to be captured by oxygen in the reaction.

Table 2.2 Aerobic aqueous conversion of organic halides to alcohols^a

R-X		M, NaH ₂ PO ₂ ·H ₂ O		R-OH	
13		air, H ₂ O/ ^t BuOH, 60 °C		14	
Entry	R-X	R-OH	Yield / % ^b		
			In ^c	Zn ^d	
1	13a (X = Cl)	14a	34	31	
2	13b (X = Br)	14a	75 (78) ^e	78 (72) ^e	
3	13c (X = I)		54	52	
4	13d	14b	62 (66) ^e	56 (55) ^e	
5	13e	14c	46	61	
6	13f	14d	56 ^f	57 ^e	
7	13g	14e	44	35	
8	13h	14f	47	33	

^a Reaction conditions unless otherwise specified: Metal, NaH₂PO₂·H₂O (5 equiv), H₂O/^tBuOH (1 : 1), air bubble, 60 °C, 16 h. ^b Isolated yield. ^c In (3 equiv). ^d Zn (5 equiv), H₂O/sat. aq. NH₄Cl (1 : 1). ^e Under O₂ balloon. ^f 1,4-dioxane used instead of ^tBuOH.

2.3.2 Metal Mediated Transformation of *gem*-Dihalides into Ketones in Water

With successful establishment of aerobic aqueous transformation of halo group into hydroxyl group via free radical method, we envisioned that this transformation could also be applied to the transformation of geminal dihalo group into the corresponding ketone or aldehyde. It is well known that geminal dihalo at the benzylic position is readily hydrolyzed to ketone or aldehyde (Scheme 2.20).⁵³

Scheme 2.20 Conversion of dihalomethylarenes into the corresponding aldehydes

However, as far as we know, up to now there is still no report on the transformation of geminal dihalo on ‘normal’ carbon into ketone or aldehyde. This may be due to its low reactivity arising from strong stereoelectronic effect just like in CH_2Cl_2 (Figure 2.1).⁵⁴ We hypothesized that our new free-radical method could overcome this drawback.

Figure 2.1 Illustration of the unreactivity of CH_2Cl_2

⁵³ Li, W.; Li, J.; DeVincentis, D.; Mansour, T. S. *Tetrahedron Lett.* **2004**, 45, 1071 and references cited therein.

⁵⁴ Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry* (Oxford, New York, 2001), pp1130-1134.

Following our success with aerobic aqueous transformation of halo group into hydroxyl group via free radical method, *gem*-dihalo-THPs⁵⁵ were next examined under similar conditions in an attempt to obtain *cis*-2,6-disubstituted tetrahydropyran-4-ones.⁵⁶ If successful, this method could be extended to other dihalo-THPs and could also be applied to the synthesis of a wide variety of natural products containing *cis*-2,6-disubstituted tetrahydropyran-4-ones. Examples are Bryostatin 16,⁵⁷ Phorboxazole A,^{56a} Apicularen A,⁵⁸ and Neopeltolide (Figure 2.2).⁵⁹

⁵⁵ For the preparation of 4,4-dihalotetrahydropyrans see next chapter.

⁵⁶ For the other methods of synthesis of pyranones, see (a) III Smith, A. B.; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675. (b) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606. (c) Crimmins, M. T.; Diaz, C. J.; Emmitte, K. A. *Heterocycles* **2004**, *62*, 179. (d) Lee, C. A.; Floreancig, P. E. *Abstracts of Papers, 226th ACS National Meeting*, New York, NY, United States, September 7-11, 2003 (2003).

⁵⁷ Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485.

⁵⁸ Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701.

⁵⁹ (a) Wright A. E.; Botelho, J. C.; Guzmán, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412. (b) Tu, W.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 4567.

Bryostatin 16: Isolated from the marine bryozoan *Bugula neritina*. Exhibit anticancer properties and its potential use in the treatment of Alzheimer's disease, depression and other cognitive impairments.

Neopeltolide: Isolated from a deep-water sponge *Neopeltidae*. Exhibit a potent inhibitor of the in vitro proliferation of the A-549 human lung adenocarcinoma, the NCI-ADR-RES human ovarian sarcoma, and the P388 murine leukemia cell lines, and of the growth of the fungal pathogen *Candida albicans*.

Apicularen A: Isolated from various strains of the myxobacterial genus *Chondromyces*. Exhibit antiproliferative properties against a series of human cancer cells.

Phorboxazole A: Macrolactone with anti-tumour activity

Figure 2.2 Natural products containing pyranones

To optimize the reaction condition for this transformation, *gem*-diiodo-THPs were examined under different conditions to afford *cis*-2,6-disubstituted tetrahydropyran-4-ones (Table 2.3). Both indium and zinc can act as a mediator for the transformation, with the latter giving the product in relatively low yield (Table 2.3, entries 1 versus 2). However, neither of them could work when air bubbling was replaced with oxygen balloon (Table 2.3, entries 3 and 4). Among the water-miscible organic solvents screened, dioxane, acetonitrile and DME afford the highest yields of 51%. This may be a result of the high solubility of the substrates in these solvents (Table 2.3, entries 1 versus 5-7). Herein, we chose DME as the organic solvent for it possesses the lowest toxicity among the three solvents. Hypophosphorous acid could

also be used instead of its salt, albeit with lower yield (Table 2.3, entries 6 versus 8). The reaction cannot work without the addition of any metal or water (Table 2.3, entries 9 and 10). Our investigation also indicated that $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ was very important for this transformation and the yield would decrease sharply otherwise (Table 2.3, entries 6 versus 11). It was also noted that perfluoroalkane failed to increase the yield by improving the oxygen solubility in the reaction mixture (Table 2.3, entry 12). Moreover, *gem*-dichloro-⁶⁰ and *gem*-dibromo-2-phenethyl-6-phenyl-THPs⁵⁵ gave relatively low yields (15% and 38% respectively) under the optimized reaction conditions. (Table 2.3, entries 13 and 14).

Table 2.3 Transformation of 4,4-dihalo-2,6-disubstituted THPs into 2,6-disubstituted tetrahydropyranones under different conditions^a

Entry	X	Metal	Solvent (1:1)	Yield / % ^b
1	I	In	H_2O - <i>t</i> BuOH	44
2	I	Zn	sat. aq. NH_4Cl - <i>t</i> BuOH	27
3 ^c	I	In	H_2O - <i>t</i> BuOH	0
4 ^c	I	Zn	sat. aq. NH_4Cl - <i>t</i> BuOH	0
5	I	In	H_2O -dioxane	51
6	I	In	H_2O -DME	51
7	I	In	H_2O - CH_3CN	51
8 ^d	I	In	H_2O -DME	47
9	I	-	H_2O -DME	0
10	I	In	DME	0
11 ^e	I	In	H_2O -DME	35
12 ^f	I	In	H_2O -DME	50
13	Br	In	H_2O -DME	38
14	Cl	In	H_2O -DME	15

^a Reaction conditions unless otherwise noted: M (3 equiv), $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ (5 equiv), air bubble, 60 °C, 20 h. ^b Isolated yield. ^c O_2 balloon was used instead of air bubbling. ^d H_3PO_2 (5 equiv) was used instead of $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$. ^e Without addition of $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$. ^f Perfluorodecaline (1 equiv) was added.

⁶⁰ Yang, J.; Li, C. J. *Synlett* **1999**, 717.

Investigation showed this transformation performed better in the presence of indium and DME/H₂O (1:1) as solvent. Therefore, a wide variety of *gem*-diiodo-THPs⁵⁵ with different aliphatic and aromatic substituents on the 6 position of the THP ring were examined under optimized condition (Table 2.4). Comparatively higher yields were obtained for most of the substrates (entries 1-7). Interestingly, in the case of the 4-chlorophenyl substituent, a high yield of 71% was obtained, while no reaction was observed with a 4-nitrophenyl substituent (entries 8-9). Besides DME, dioxane is also a suitable solvent for this reaction.

Table 2.4 Transformation of 4,4-diiodo-2,6-disubstituted THPs into 2,6-disubstituted tetrahydropyranones^a

Entry	R	Product	Yield(%) ^b
1	-Ph	16a	51
2	-CH(CH ₂ CH ₃) ₂	16b	43
3	-CH ₂ CH ₂ Ph	16c	45
4	-Cy	16d	50
5		16e	56
6		16f	60
7		16g	52
8		16h	71

Table 2.4 Transformation of 4,4-diiodo-2,6-disubstituted THPs into 2,6-disubstituted tetrahydropyranones^a (continued)

Entry	R	Product	Yield(%) ^b
9			0

^a Reaction conditions unless otherwise specified: indium (3 equiv), NaH₂PO₂·H₂O (5 equiv), air bubble, H₂O-DME (1 : 1), 60 °C, 20 h. ^b Isolated yield.

2.3.3 Metal Mediated Transformation of *gem*-Trihalides into Acids

Next, we extended the method to transform trihaloalkane into acid. Chiral trihalo-1-phenylethanol which could be easily obtained in high optical purity using CBS catalyst is a very useful synthetic intermediate for the preparation of chiral mandelic acid.⁶¹ Corey reported the transformation of this class of compounds by hydrolysis under strong basic conditions to provide mandelic acid with the inversion of configuration.⁶¹ Configuration-retained product could not be prepared directly from trihalo-1-phenylethanol by treatment with silver nitrate, but can be prepared from its corresponding acetate (Scheme 2.21).⁶² It was explained by Mukaiyama in

⁶¹ (a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, 33, 3431. (b) Link, J. O. *Ph. D. Thesis*; Harvard University: USA, **1992**.

⁶² Mukaiyama, T.; Yamaguchi, M.; Kato, J. I. *Chem. Lett.* **1981**, 1505.

Scheme 2.21 Corey's synthesis of mandelic acid with retention and inversion of configuration

his paper that this is due to the stabilization of cationic intermediate by participation of the neighboring acetoxy group.⁶² Using our method, we could synthesize (*R*)-mandelic acid⁶³ with the retention of configuration directly from (*R*)-tribromo-1-phenylethanol (Scheme 2.22).

Scheme 2.22 Transformation of (*R*)-2,2,2-tribromo-1-phenylethanol into (*R*)-mandelic acid via free radical method

2.3.4 Metal Mediated Transformation of *gem*-Tetrahalides into CO₂

This transformation can also be applied to tetrahalogenated compounds. Klabunde proposed a possible method in his paper for the disposal of chlorocarbons-contaminated water by metal-mediated dechlorination.⁶⁴ However, this method failed to completely degrade carbon tetrachloride resulting in a mixture of products (CH₄, CH₃Cl, CH₂Cl₂, and CHCl₃). As hypothesized in Scheme 2.19, carbon tetrahalide would be hydrolyzed automatically to carbon dioxide and inorganic acid if one of the halogen atoms was replaced with hydroxyl group. Studies had shown that carbon tetrabromide could be converted to CO₂ and HBr using our method. To avoid

⁶³ Polavarapu, P. L.; Fontana, L. P.; Smith, H. E. *J. Am. Chem. Soc.* **1986**, *108*, 94.

⁶⁴ Boronina, T.; Klabunde, K. J.; Sergeev, G. *Environ. Sci. Technol.* **1995**, *29*, 1511.

mistaking the atmospheric carbon dioxide in air from the carbon dioxide generated by the reaction, pure oxygen instead of air was bubbled into the mixture of carbon tetrabromide, NaH_2PO_2 , and indium in water-DME (1 : 1) (Scheme 2.23). The generation of white precipitate when gas from the outlet was passed through saturated $\text{Ca}(\text{OH})_2$ solution, gave evidence for the production of CO_2 . The production of hydrobromic acid was also supported by the observation that the pH value of the aqueous layer decreased from 7.14 to 1.79 at the end of reaction and formation of brown precipitate upon addition of AgNO_3 solution. The yield of the reaction was about 35%, calculated based on the amount of AgBr precipitate formed.

Scheme 2.23 Transformation of carbon tetrabromide into carbon dioxide and hydrobromic acid via free radical method

The next challenge will be to transform chlorinated wastes as shown in the scheme below (Scheme 2.24). Using our method, carbon tetrachloride could also be transformed into carbon dioxide and hydrochloric acid in 34% yield under the bubbling of air overnight.

Scheme 2.24 Proposed hypotheses for disposal of halogenated waste solvent

2.4 CONCLUSION

In summary, our studies have shown that aerobic aqueous transformation of halo group into hydroxyl group via metal-mediated (indium and zinc) free-radical reaction could be achieved under mild reaction conditions. This method has also been applied to convert monohalo-, dihalo-, trihalo-, and tetrahalo-carbons into their corresponding products, i.e. alcohol, ketone or aldehyde, acid and carbon dioxide, respectively. In addition, this method has potential application in environmental protection for disposal of halogenated waste solvents and halocarbon-contaminated water supplies.

CHAPTER 3

*Preparation of 4,4-
Dihalotetrahydrotetrapyrans via Indium
Trihalide Catalyzed Prins Cyclization*

3.1 INTRODUCTION

Gem-Dihaloalkanes, especially *gem*-diiodoalkanes are valuable reagents in transition metal catalyzed carbon-carbon bond formation such as Simmons-Smith cyclopropanation⁶⁵ and Takai-Utimoto olefination reactions (Scheme 3.1).⁶⁶ Besides

a) Simmons-Smith Cyclopropanation

b) Takai-Utimoto Olefination

Scheme 3.1 Simmons reaction and Takai reaction

these most notable reactions, the dihaloalkanes are also used in other variety of reactions.⁶⁷ Methods for the preparation of *gem*-difluoro, dichloro, and dibromoalkanes have been widely studied and reviewed.⁶⁸ However, the preparation of *gem*-diiodo-methyl-containing compounds continues to be challenging to organic chemists, due to its relative instability compared to the other *gem*-dihalo species. Nonetheless not many methods are available for this transformation, which provides

⁶⁵ (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (c) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (d) Charette, A. B.; Lemay, J. *Angew. Chem. Int. Ed.* **1997**, *36*, 1090. (e) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.

⁶⁶ (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951. (c) Takai, K.; Kunisada, Y.; Tachibana, Y.; Yamaji, N.; Nakatani, E. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1581. (d) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (e) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2. (f) Johnson, D. V.; Felfer, U.; Griengl, H. *Tetrahedron* **2000**, *56*, 781. (g) Dixon, D. J.; Ley, S. V.; Lohmann, S.; Sheppard, T. D. *Synlett* **2005**, 481.

⁶⁷ (a) Enantioselective synthesis of allenes via RCHI(ZnBu): Varghese, J. P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem.* **2002**, 4154. (b) Diastereoselective addition to aldehydes using RCHI(SmI₂): Matsubara, S.; Yoshioka, M.; Utimoto, K. *Angew. Chem. Int. Ed.* **1997**, *36*, 617. (c) Diastereo-, enantioselective epoxidation via RCHI(MgCl): Schulze, V.; Hoffmann, R. W. *Chem. Eur. J.* **1999**, *5*, 337. (d) Cross coupling via RCHI(ZnI₂): Yoshino, H.; Toda, N.; Kobata, M.; Ukai, K.; Oshima, K.; Utimoto, K.; Matsubara, S. *Chem. Eur. J.* **2006**, *12*, 721. (e) Chain extension via EtZnCHIR: Lin, W.; McGinness, R. J.; Wilson, E. C.; Zercher, C. K. *Synthesis* **2007**, 2404.

⁶⁸ Méndez-Andino, J. L. Dihaloalkanes, R₁R₂C(Hal)₂. In *Comprehensive Organic Functional Group Transformation II*. Kartritzky, A. R.; Taylor, R. J. K. Eds.; Elsevier, 2004; Vol. 4; pp 2-19.

valuable synthetic intermediates for the organic chemist. Since *gem*-diiodide plays an important role in the organic synthesis, existing methods for the preparation of *gem*-diiodoalkanes are presented.

3.2 GENERAL METHODS IN SYNTHESIS OF *GEM*-DIIDOALKANES

3.2.1 Diiodoalkanes from Iodoalkanes

Chiral 1,1-diiodo compounds can be synthesized from 2-deoxy-2-iodo-sugars via an anomeric alkoxy radical fragmentation. The reaction occurred in the presence of (diacetoxyiodo)benzene and iodine under irradiation with two 80 W tungsten filament lamps to produce the corresponding *gem*-diiodo compounds in high yields (Scheme 3.2).⁶⁹

Scheme 3.2 Alkoxy radical fragmentation of halohydrin.

3.2.2 Diiodoalkanes from Simple Diiodoalkanes

Functionalized *gem*-diiodoalkanes have been achieved in excellent yields by utilizing a convenient procedure for NaCHI_2 with alkyl iodides. Various functional group such as olefins, acetals, ethers and silyl ethers, carbamates, and hindered esters are tolerated under the reaction condition. The use of LiCHI_2 allows conversion of benzyl and allyl bromides into diiodide products (Scheme 3.3).⁷⁰

⁶⁹ González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem. Int. Ed.* **2001**, *40*, 2326.

⁷⁰ Bull, J. A.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 8097.

 Scheme 3.3 Synthesis of *gem*-diiodoalkanes by the alkylation of diiodomethane.

3.2.3 Diiodoalkanes from Trihaloalkanes

β,β -Diiodoalkanols can be provided by diiodomethylation of carbonyl compounds. This transformation was carried out by employing diiodomethylsamarium, which is prepared *in situ* from samarium diiodide (Scheme 3.4).⁷¹

 Scheme 3.4 Synthesis of *gem*-diiodoalkanols mediated by the SmI_2 .

3.2.4 Diiodoalkanes from Alkenes

The reaction of α,β -unsaturated aromatic carboxylic acids with *N*-iodosuccinimide (NIS) leads to the corresponding α,α -diiodomethylbenzyl alcohols via TBATFA-catalyzed Hunsdiecker-type halodecarboxylation under mild aqueous conditions. This method is also suitable for the syntheses of α,α -difluoro- and α,α -dichloromethylbenzyl alcohols when the corresponding *N*-halosuccinimide was used (Scheme 3.5).⁷²

⁷¹ Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *Tetrahedron Lett.* **1998**, 39, 1409.

⁷² Naskar, D.; Roy, S. *Tetrahedron* **2000**, 56, 1369.

 Scheme 3.5 Synthesis of *gem*-diiodoalkanol via Hunsdiecker halodecarboxylation.

3.2.5 Diiodoalkanes from Alkynes

Treatment of the alkynes with diisobutylaluminium hydride gives the 1,1-bis(diisobutylalumino)alkane intermediates, which react with iodine to produce the desired *gem*-diiodo products in good yields (Scheme 3.6).⁷³

 Scheme 3.6 Synthesis of *gem*-diiodoalkanol from alkynes

3.2.6 Diiodoalkanes from Aldehydes

The reaction of aldehydes with 1,2-bis(*tert*-butyldimethylsilyl)-hydrazine (BTBSH) catalyzed by scandium trifluoromethanesulfonate leads to the corresponding *N-tert*-butyldimethylsilylhydrazones (TBSHs), which upon reaction with iodine produces the desired *gem*-diiodo compounds. Application of this modified protocol to the Corey lactone provided the expected *gem*-diiodide in 62% yield (Scheme 3.7).⁷⁴

⁷³ (a) Aufauvre, L.; Knochel, P.; Marek, I. *Chem. Commun.* **1999**, 2207. (b) Varghese, J. P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem.* **2002**, 4151.

⁷⁴ Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, 126, 5436.

 Scheme 3.7 Two-step synthesis of *gem*-diiodoalkanols from aldehyde.

3.3 SYNTHESIS OF THP RING VIA PRINS CYCLIZATION

Prins cyclization pathway is a powerful tool to build 2,6-disubstituted tetrahydropyran ring motifs which feature prominently in a wide variety of natural products. Starting from a homoallylic alcohol and an aldehyde mediated by an acid, the pathway goes through the formation of oxonium ion, oxonia-Cope rearrangement and nucleophilic attack to afford a 2,4,6-trisubstituted tetrahydropyran (Scheme 3.8).

Scheme 3.8 Prins cyclization between an aldehyde and a homoallylic alcohol.

Li⁷⁵ demonstrated stoichiometric usage of InCl₃ as Lewis acid to introduce the heteroatom at the 4-position of the THP ring in Prins cyclization (Scheme 3.9). Although 4,4-(*gem*)-dichloroTHP was prepared when using chloro homoallyl alcohol, unfortunately it is still of very little synthetic value, because its application in natural product synthesis remains unexplored.

⁷⁵ (a) Yang, J.; Viswanthan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, 40, 1627. (b) Yang, X. -F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, 66, 739. (c) Yang, J.; Li, C. J. *Synlett* **1999**, 717.

Scheme 3.9 Stoichiometric Prins cyclization in the formation of THP ring.

An interesting investigation was reported by Willis⁷⁶ whereby $\text{BF}_3 \cdot \text{OEt}_2$ mediated Prins cyclization produced the 4-acetyl-THP ring in the presence of acetic acid (Scheme 3.10). The mechanistic proposal for the formation of *meso*-THP side products has also been elaborated in his studies.

 Scheme 3.10 $\text{BF}_3 \cdot \text{OEt}_2$ mediated Prins cyclization

Other precursors such as cyclopropyl carbinols were also used by Yadav⁷⁷ to form 2,4,6-trisubstituted tetrahydropyrans *via* Prins cyclization. Upon treatment with TFA, cyclopropyl carbinol leads to cyclopropyl carbonyl cation which can undergo either ring cleavage to a homoallylic cation⁷⁸ or ring expansion to a cyclobutyl cation⁷⁹ to relieve ring strain. The homoallylic cation via ring-cleavage pathway was stabilized by a silylmethyl functional group.⁸⁰ Subsequent intramolecular nucleophilic attack of the oxonium ion by the intramolecular olefinic part yielded a multiply substituted tetrahydropyran ring (Scheme 3.11).

⁷⁶ (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, 4, 577. (b) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, 5, 2429. (c) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; Simpson, T. J.; Smith, R. W.; King, C. D.; Willis, C. L. *Chem. Commun.* **2001**, 5, 835.

⁷⁷ Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, 126, 8652.

⁷⁸ (a) Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed.* **1968**, 7, 577. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W. Yip, Y. C.; Tanko, J.; Huldicky, T. *Chem. Rev.* **1989**, 89, 165.

⁷⁹ (a) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, 28, 6313. (b) Hardouin, C.; Taran, F.; Doris, E. *J. Org. Chem.* **2001**, 66, 4450.

Scheme 3.11 Prins cyclization using cyclopropyl carbinols.

The rhenium(VII) complex $\text{O}_3\text{ReOSiPh}_3$ was also an effective catalyst for Prins cyclizations of aromatic aldehyde and substituted homoallylic alcohol. The equatorial substituted 4-hydroxytetrahydropyrans are formed in good yields and high selectivity under mild reaction conditions. Electron-rich alcohols are activated for solvolysis by the formation of perrhenate ester (Scheme 3.12).⁸¹

Scheme 3.12 Rhenium(VII)-catalyzed Prins cyclization

Our group developed indium(III)-catalyzed Prins cyclization using trimethylsilyl halides as additives (Scheme 3.13). The crossed 2,4,6-trisubstituted tetrahydropyran products were produced in high yield and selectivity. This method has been successfully applied in the total synthesis of (-)-Centrolobine.⁸²

Scheme 3.13 Indium(III)-catalyzed Prins cyclization

⁸⁰ (a) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, 3, 2717. (b) Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514. (c) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, 43, 2669.

⁸¹ Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, 10, 4839.

⁸² (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, 45, 8387. (b) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, 7, 4491.

3.4 INDIUM(III) TRIHALIDE-CATALYZED SYNTHESIS OF *cis*-2,6-DISUBSTITUTED-4,4-DIHALOTETRAHYDROPYRANS VIA PRINS CYCLIZATION

As described in chapter 2, we have developed a new method to convert *gem*-dihalo-THPs into pyranones which feature extensively in a lot of natural products such as Bryostatin 16, Phorboxazole A, Apicularen A, and Neopeltolide (Figure 3.1).

Figure 3.1 Retrosynthetic strategy for pyranones.

So it is very crucial to seek a synthetic approach to *gem*-dihalo-THPs. Although Li has reported the synthesis of *gem*-dichloro THPs via Prins cyclization, InCl_3 was used in stoichiometric amount.^{75c} Combining the In(III)-catalyzed construction of THP ring developed in our group,⁸² herein we propose a new catalytic version of *gem*-dihalo THPs formation via Prins Cyclization (Scheme 3.14). Activated by Lewis catalyst of indium halides, the oxo-carbenium **Ts1** was formed from a homoallylic alcohol and an aldehyde through subsequent hemi-acetal formation and C-O bond cleavage. Sequential oxonia-Cope rearrangement resulted in the formation of intermediate **Ts2** with a halo-stabilized carbocation and a six-membered ring. Nucleophilic attack of TMSX on carbocation finally afforded a *cis*-2, 6-disubstituted-4,4-dihalo- tetrahydropyran.

Scheme 3.14 Proposed mechanism of indium(III)-catalyzed *gem*-dihalo-THP formation.

We tried to synthesize *cis*-4,4-dihalo-2,6-disubstituted-tetrahydropyrans **15** from 5-halohomoallylic alcohols **17** in the presence of indium trihalide, aldehyde and TMSX (Table 3.1). Solvents screen indicated CH_2Cl_2 is the best solvent for this transformation. With different halo-substituents introduced, *gem*-diiodo-THP could be obtained with the highest yield of 91%. In case of *gem*-dichloro-THP^{75c}, the yield is lowest with much starting material remaining. The yields of reaction increase in the order of $\text{I} > \text{Br} > \text{Cl}$ (Table 3.1, entries 1-3). This may well result from two aspects: (a) The destabilization of carbocation of the transitional state **Ts2** by strong electronegativity of chlorine atom; (b) The nucleophilic attacking capability goes up in same order of $\text{I} > \text{Br} > \text{Cl}$. Meanwhile, NOSEY indicated that the substituents on positions 2 and 6 of the THP ring pose *cis* conformation. In all cases, this method works well with a wide variety of aldehydes, including alkyl and aromatic aldehydes to produce *gem*-diiodo-THP products **15** in high to excellent yields. The substituents on aromatic aldehydes do not have much influence on the yields (Table 3.1, entries 3-11). In addition, mixed *gem*-dihalo-THP can also be synthesized using this method.

Table 3.1 Syntheses of 4,4-dihalo-2,6-disubstituted THPs via Prins cyclization^a (continued)

Entry	R	Product	Yield(%) ^b
11			84

^a Reaction conditions unless otherwise noted: InX_3 (10 mol%), TMSX (1.1 equiv), RCHO (1 equiv), CH_2Cl_2 , rt, overnight. ^b Isolated yield.

3.5 CONCLUSION

In conclusion, indium trihalide-catalyzed synthesis of *cis*-4,4-dihalo-2,6-disubstituted- tetrahydropyrans via Prins cyclization of aldehydes with halo homoallyl alcohols has been reported firstly. The yields of the reaction varies with different halo-substituents, increasing in the order of $\text{I} > \text{Br} > \text{Cl}$. Especially the *gem*-diiodo-THP has been obtained in excellent yield up to 96%. The method developed is expected to be applied to construct pyranones, which are important motifs in many natural products.

PART II

CHAPTER 4

***Direct Arylation of Cyclic Enamides with
Organometallic Reagents: Pd^{II}/Pd⁰ Catalysis***

4.1 INTRODUCTION

Palladium-catalyzed cross-coupling methods are the most valuable synthetic tools among a variety of transition metal catalyzed C-C formation. Particularly, palladium-catalyzed arylation with organohalides and other surrogates are applied extensively to construct biaryl motifs, which are widely represented in many medicinally active natural products. In terms of nucleophilic partner used, they are named as Kumada-Tamao (Grignard reagents), Suzuki-Miyaura (boron), Negishi (zinc), Stille-Migita-Kosugi (tin) and Hiyama (silicon) reactions (Figure 4.1).⁸³ A common feature of these classic catalytic cycles is the formation of aryl palladium (II) intermediate through oxidative addition, which is subsequently to form C-C bonds by functionalization.

Figure 4.1 Pd(0)-catalyzed arylation.

The versatility of these traditional cross-coupling originate from the reactivity of aryl palladium (II) intermediate in catalytic process. The existed C-H bond activation⁸⁴ provided a facile access to straightforward coupling with arene⁸⁵ by viewing C-H bonds as “ubiquitous functionality” (Figure 4.2).

⁸³ (a) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (b) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 10022. (c) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (d) Baudoin, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 1373.

⁸⁴ For reviews on C-H activation, see: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180. (d) Bergman, R. G. *Nature* **2007**, *446*, 391. (e) Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6908.

⁸⁵ For reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (c) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

Figure 4.2 Pd(II)-catalyzed C-H functionalization.

Compared with various functionalizations of aryl halides, the major challenge of palladium-catalyzed aromatic C-H functionalization is its poor selectivity, which limits the utility of this transformation. To overcome this drawback, much effort has been paid to control regioselectivity in the formation of cyclopalladation⁸⁶ of C-H bonds by *ortho* directing group (Figure 4.3). These anchoring groups mainly includes nitrogen-containing groups,⁸⁷ such as pyridinyl, oxazolyl, iminyl, etc., and oxygen-containing groups,⁸⁸ such as acid, ester, acetamino etc..

 Figure 4.3 C-H activation through *ortho* cyclopalladation with directing group.

Another related direct arylation is catalytic oxidative arene cross-coupling, in which neither of aromatic partners needs to be preactivated. In this catalytic process, palladium (II) species demonstrate dual C-H activation behavior (Figure 4.4).

⁸⁶ (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, 87, 3273. (c) Carr, K.; Sutherland, J. K. *J. Chem. Soc. Chem. Commun.* **1984**, 1227. (d) Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, 41, 699. (e) Bore, L.; Honda, T.; Gribble, G. W. *J. Org. Chem.* **2000**, 65, 6278. (f) Webster, C. E.; Fan, Y.; Hall, M. B.; Kunz, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 125, 858. (g) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, 127, 13754. (h) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 16496. (i) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, 129, 6880.

⁸⁷ (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 7330. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, 127, 13154.

Figure 4.4 Pd(II)-catalyzed C-H functionalization.

4.1.1 Other Transition Metal Catalyzed Arylation of $C(sp^2)$ -H Bonds

Although other transitional metal catalyzed C-H activation/C-C bond formation is beyond the scope of this introduction, it is worthwhile highlighting three direct arylations with organometallic reagents, which mark the cornerstones and significant advancements in this field. These reactions are catalyzed by rhodium (I)⁸⁹, ruthenium (II)⁹⁰ and iron (III)⁹¹ respectively (Scheme 4.1).

Scheme 4.1 Other transition metal catalyzed C-H functionalization. a) Rh; b) Ru; c) Fe.

⁸⁸ (a) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961. (b) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* **1997**, 36, 1740. (c) Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, 44, 4046.

⁸⁹ Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439.

⁹⁰ Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, 125, 1698.

4.1.2 Pd(II)-Catalyzed Arylation of $C(sp^2)$ -H Bonds with Organometallic Reagents.

Different from arylation of $C(sp^2)$ -H with organohalides through Pd^{II}/Pd^{IV} or Pd^0/Pd^{II} catalysis, arylation with organometallic reagents adopts Pd^{II}/Pd^0 catalysis (Figure 4.5). Besides regioselectivity aforementioned, another challenging obstacle for this catalytic process is that Pd(II) catalyst is prone to react with organometallic reagents rather than inert C-H bonds, resulting in Pd(0) precipitate and homocoupling of organometallic reagents.

Figure 4.5 Proposed Pd^{II}/Pd^0 catalytic cycle.

In 2006, Yu reported palladium(II)-catalyzed alkylation of oxazoline substrates with organotin reagents, which opens a new chapter for $C(sp^2)$ -H coupling with organometallic reagents via Pd^{II}/Pd^0 catalysis although no aryltin reagent was used (Scheme 4.2).⁹² In this reaction, BQ is not only an oxidant, but also play a vital role in promotion of C-H activation.

Scheme 4.2 Pd(II)-catalyzed C-H coupling with organotin reagents.

⁹¹ Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858.

⁹² Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

Encouraged by the result aforementioned, Yu continued to developed successfully the coupling of pyridine substrates with organoboronic acids, albeit low yield with arylboronic acid.⁹³ Yu also found the cross coupling of carboxylic acids with arylboron partners, in which carboxyl group acts a directing group in reactions (Scheme 4.3).⁹⁴

Scheme 4.3 Coupling of C(SP²)-H with orgaoboron developed by Yu.

Pd(II)-catalyzed arylation via C-H activation further demonstrated by Shi in the coupling of anilides with arylboronic acid⁹⁵ and arylsilanes⁹⁶ (Scheme 4.4). As early study by van Leeuwen,⁹⁷ the reaction of these anilides with palladium(II) proceeds by electrophilic palladation.

⁹³ Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.

⁹⁴ (a) Giri, R.; Mangel, N.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J. Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Wang, D. H.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

⁹⁵ Shi, Z. J.; Li, B. J.; Wan, X. B.; Fang, Z.; Cao, B.; Qin, C. M.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554.

⁹⁶ Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066.

⁹⁷ Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Veies, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

Scheme 4.4 C-H coupling of acetamides with organometallic reagents.

Additionally, one of the most challenging tasks is to widen C-H activation/C-C coupling reaction to the substrates without *ortho* chelating functional groups. Whereas we are encouraged to see that the coupling of electron-rich arenes, indoles and olefins with organoboron⁹⁸ and organotin⁹⁹ (Scheme 4.5). The remaining key challenges of this kind of reactions are how to attain higher selectivity and efficiency and to expand the potential for synthetic applications. The most promising solution to these problems is to design a novel ligand that will impart an appropriate electronic or steric bias on Pd(II) so that selective C(sp²)-H coupling can be accomplished.

⁹⁸ (a) Yang, S. D.; Sun, C. L.; Fang, Z.; Li, B. J.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (b) Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428. (c) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708.

⁹⁹ Kawai, H.; Kobayashi, Y.; Oi, S.; Inoue, Y. *Chem. Commun.* **2008**, 1464.

 Scheme 4.5 Coupling of electron-rich C(SP²)-H with organometallic reagents.

4.1.3 Pd(II)- Catalyzed Dehydrogenative Arylation

Recently, intermolecular cross-dehydrogenative arylation has attracted significant attention. Many efforts have been devoted to eliminate homocoupling side product. The most accepted mechanism for this type of reaction is Pd^{II}/Pd⁰ catalysis as well (Figure 4.6).

Figure 4.6 Proposed $\text{Pd}^{\text{II}}/\text{Pd}^0$ catalytic cycle for dehydrogenative arylation.

The breakthrough in this respect has been made by Lu in $\text{Pd}(\text{II})$ -catalyzed oxidative coupling reactions between two simple electronically unbiased arenes in the presence of $\text{K}_2\text{S}_2\text{O}_8$ (Scheme 4.6).¹⁰⁰ The reaction occurred under mild conditions, although the yields and selectivity of the heterocoupling product versus the homocoupling side product are relatively low.

Scheme 4.6 An early example of oxidative coupling.

Further advancement was accomplished by replacing one of the arenes with electron-rich heterocycles such as indoles¹⁰¹ and benzofurans¹⁰², which improve substantially the selectivity of the heterocoupling reaction (Scheme 4.7). It is worth noting that the leading oxidative cross-coupling work was reported by Itahara in stoichiometric coupling of indole with benzene.¹⁰³

¹⁰⁰ Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, 25, 5973.

¹⁰¹ Stuart D. R.; Fangou, K. *Science* **2007**, 316, 1172.

¹⁰² Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, 9, 3137.

¹⁰³ (a) Itahara, T. *J. Chem. Soc. Chem. Commun.* **1981**, 254. (b) Itahara, T.; Kawasaki, K.; Ouseto, F. *Bull. Chem. Soc. Jpn.* **1984**, 57, 3488. (c) Itahara, T. *J. Org. Chem.* **1985**, 50, 5272. (d) Itahara, T. *J. Org. Chem.* **1985**, 50, 5546. (e) Itahara, T. *Heterocycles* **1986**, 24, 2557.

Scheme 4.7 Coupling of heterocycles with benzene.

Furthermore, directing groups has been employed to suppress homocoupling side product (Scheme 4.8). Sanford elegantly established a highly efficient cross-dehydrogenative coupling reaction using a pyridyl moiety as a directing group.¹⁰⁴ Concurrently, Xia found that ferrocene derivatives with oxazoline as a directing group could undergo oxidative arylation in moderate yields.¹⁰⁵

Scheme 4.8 Dehydrogenative coupling using directing groups.

In addition, acetamino group could also be a valuable directing group for dehydrogenative arylations, as observed by Shi.¹⁰⁶ Remarkably in this transformation, Cu(OTf)₂ was employed in co-catalytic amounts and molecular oxygen was present as the terminal oxidant. Nonetheless, Buchwald achieved palladium-catalyzed oxidative

¹⁰⁴ Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904.

¹⁰⁵ Xia, J. B.; You, S. L. *Organometallics* **2007**, *26*, 4869.

¹⁰⁶ Li, B. J.; Tian, S. L.; Fang, Z.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115.

arylation in the absence of additional metal-containing cocatalyst.¹⁰⁷ Herein, the key elaborations are the use of TFA as solvent and the addition of DMSO to slow palladium black formation (Scheme 4.9).

Scheme 4.9 Aerobic cross-dehydrogenative arylation of anilide.

¹⁰⁷ Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

4.2 DIRECT ARYLATION OF CYCLIC ENAMIDES WITH ARYL BORONIC ACIDS VIA Pd(II)–CATALYZED C–H ACTIVATION

C–C bond formation is vital in organic chemistry. Among the many cross-coupling reactions, Suzuki–Miyaura coupling is one of the most important C–C bond construction protocol employed in the syntheses of commodity chemicals, pharmaceutical compounds and biologically active natural products.¹⁰⁸ One of the main drawbacks associated with this classic palladium-catalyzed cross coupling reaction is the need to use organohalides or other surrogates as substrates. Therefore, many research groups have focused on C–H activation using simple non-halogenated substrates.¹⁰⁹ Recently, formation of C–C bond through aromatic C–H activation via coupling with organoboron reagents (Suzuki-type reaction) assisted by directing group has been reported by several groups.¹¹⁰ However, as far as we know, direct cross-coupling of cyclic enamides via ortho C–H activation using palladium catalyst has not been reported. Herein, we report the highly efficient direct cross-coupling reaction between cyclic enamides and aryl boronic acids using catalytic amount of palladium(II) acetate.

¹⁰⁸ For reviews see : (a) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, 63, 419. (d) Suzuki, A. *J. Organometallic Chem.* **1999**, 576, 147. (e) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 48, 9633.

¹⁰⁹ For recent references: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, 107, 174. (b) Lee, J. M.; Ahn, D. S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. *J. Am. Chem. Soc.* **2006**, 128, 12954. (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, 130, 9254. (d) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2008**, 47, 3219. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, 34, 633. (f) Shilov, A. E.; Shul, pin, G. B. *Chem. Rev.* **1997**, 97, 2879. (g) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, 130, 11270. (h) Wang, D. H.; Wasa, M.; Giri, R.; Yu, J. Q. *J. Am. Chem. Soc.* **2008**, 130, 7190. (i) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, 129, 6066. (j) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc.* **2009**, 131, 1372. (k) Cárdenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, 128, 5033. (l) Chu, J. H.; Chen, C. C.; Wu, M. J. *Organometallics*. **2008**, 27, 5173. (m) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, 130, 3708.

¹¹⁰ (a) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, 128, 78. (b) Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, 128, 12634. (c) Giri, R.; Maugel, N.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J. Q. *J. Am. Chem. Soc.* **2007**, 129, 3510. (d) Shi, Z. J.; Li, B. J.; Wan, X. B.; Fang, Z.; Cao, B.; Qin, C. M.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, 46, 5554. (e) Kakiuchi, F.; Kan, S.; Igi, K.; Chantani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, 125, 1698.

To begin our study, α -tetralone-derived enamide **18a** was chosen to couple with phenylboronic acid **19a** in the presence of $\text{Pd}(\text{OAc})_2$ as a catalyst under various reaction conditions (Table 4.1). Firstly using K_2CO_3 as base and dioxane as solvent, we surveyed the effect of different oxidants. To our delight, the desired product **20a** was obtained along with aromatized coupling product **21a** (92 : 8) in low to excellent yields (entries 1-6). However, $\text{Cu}(\text{OTf})_2$ was found to be the most efficient oxidant for this coupling reaction, yielding the product in 80% yield (entry 6). It is worthy to note that the presence of base is critical to this coupling reaction. Reaction without the use of base leads to intractable products. Furthermore, the substrate readily decomposes under acidic condition. Among the various bases screened (entries 13-17), stronger bases gave the product in high selectivity, but in low yield. For instance,

Table 4.1 Screening conditions for the Pd(II)-catalyzed direct arylation of **18a** with phenylboronic acid^a

Entry	Oxidant	Base	Solvent	Yield(%) ^b (20a : 21a) ^c
1	Ag_2O	K_2CO_3	dioxane	39
2	AgF	K_2CO_3	dioxane	32
3	AgOAc	K_2CO_3	dioxane	34
4	Ag_2CO_3	K_2CO_3	dioxane	30
5	$\text{Cu}(\text{OAc})_2$	K_2CO_3	dioxane	38
6	$\text{Cu}(\text{OTf})_2$	K_2CO_3	dioxane	80
7	$\text{Cu}(\text{OTf})_2$	K_2CO_3	DCE	52
8	$\text{Cu}(\text{OTf})_2$	K_2CO_3	CH_3CN	0
9	$\text{Cu}(\text{OTf})_2$	K_2CO_3	$t\text{-BuOH}$	0
10	$\text{Cu}(\text{OTf})_2$	K_2CO_3	DMSO	0
11	$\text{Cu}(\text{OTf})_2$	K_2CO_3	DMF	29 (50 : 50)
12	$\text{Cu}(\text{OTf})_2$	K_2CO_3	toluene	39 (41 : 59)
13	$\text{Cu}(\text{OTf})_2$	KOAc	dioxane	64 (77 : 23)
14	$\text{Cu}(\text{OTf})_2$	K_3PO_4	dioxane	54 (74 : 26)
15	$\text{Cu}(\text{OTf})_2$	Cs_2CO_3	dioxane	37 (91 : 9)
16	$\text{Cu}(\text{OTf})_2$	KO^tBu	dioxane	23 (96 : 4)
17	$\text{Cu}(\text{OTf})_2$	Na_2CO_3	dioxane	76 (90 : 10)

^a Conditions: 10 mol % $\text{Pd}(\text{OAc})_2$, 2 equiv of **19a**, 2 equiv of oxidant, 2 equiv of base, 80 °C, 16 h. ^b Yields of isolated products. ^c Ratios in parentheses are the ratios of **20a** and **21a** (inseparable), which are calculated by ^1H NMR analysis; other ratios are 92 : 8.

t-BuOK afforded the highest selectivity (96 : 4) albeit with low yield (23%) (entry 16). Solvents also have a strong influence on the yield of the product. As shown in table 4.1, the reaction performed best in the presence of Cu(OTf)₂ as oxidant, K₂CO₃ as base, and dioxane as solvent.

With the optimized reaction conditions in hand, we continued to explore the scope of this Pd(II)-catalyzed C-H arylation process. Different aromatic boronic acids were examined (Table 4.2). This transformation was amenable to various aromatic

Table 4.2 Pd-catalyzed direct arylation of **18a** with various boronic acid **19**^a

Entry	19	20 : 21 ^c	Yield(%) ^b
1	19a	92 : 8	80
2	19b	82 : 18	60
3	19c	95 : 5	75
4	19d	80 : 20	67
5	19e	80 : 20	70
6	19f	86 : 14	57
7	19g	90 : 10	67
8	19h	95 : 5	64
9	19i	88 : 12	68
10	19j	71 : 29	68

^a Conditions: 10 mol % Pd(OAc)₂, 2 equiv of **19**, 2 equiv of Cu(OTf)₂, 2 equiv of K₂CO₃, dioxane, 80 °C, 16 h. ^b Yields of isolated products. ^c The ratios of **20** and **21** (inseparable) are calculated by ¹H NMR analysis.

boronic acids possessing electron-donating or electron-withdrawing groups, furnishing the products in good to excellent yields. Electron-withdrawing group, such as the nitro group, on the phenyl ring of the boronic acid usually helps to increase the selectivity (**20** : **21** = 95 : 5, entry 8). In addition, the position of the substituents on the aromatic ring of the boronic acids also plays a vital role on the selectivity. *Ortho* methyl group provides higher selectivity than *meta* and *para* ones, perhaps arising from steric hindrance (entries 3 vs 4 and 5). *Meta* methoxy group affords better selectivity than *para* one (entries 9 vs 10). This may be due to electronic effect. It should be noted herein that *meta*-methoxy group is electron-withdrawing, whereas the *para* one is electron-donating.

Various cyclic enamides were next investigated (Table 4.3).¹¹¹ This direct arylation could tolerate both mono- and di-substitution on either the phenyl or aliphatic ring of α -tetralone-derived enamides (entries 1-4). Substitution of the aliphatic ring produced very high selectivity of the coupling product (entry 4). In the case of 4-chromanone-derived enamides, this coupling reaction also worked well with various substituents (for substrates **18f-18j**) on either the phenyl or aliphatic ring, providing only product **20**. No aromatized products were observed in all these cases (entries 5–9).

¹¹¹ Preliminary investigation using linear enamides proved futile.

Table 4.3 Pd-catalyzed direct arylation of various cyclic enamides **18** with benzene boronic acid **19a**^a

$ \begin{array}{c} \text{NHAc} \\ \\ \text{R}^1\text{-C}_6\text{H}_4\text{-C} \begin{array}{c} \diagup \text{X} \diagdown \end{array} \\ \text{18} \end{array} + \text{PhB(OH)}_2 \xrightarrow[\text{80 } ^\circ\text{C}]{\text{Pd(OAc)}_2, \text{K}_2\text{CO}_3, \text{Cu(OTf)}_2, \text{Dioxane}} \begin{array}{c} \text{NHAc} \\ \\ \text{R}^1\text{-C}_6\text{H}_4\text{-C} \begin{array}{c} \diagup \text{X} \diagdown \end{array} \text{Ph} \\ \text{20} \end{array} + \begin{array}{c} \text{NHAc} \\ \\ \text{R}^1\text{-C}_6\text{H}_4\text{-C} \begin{array}{c} \diagup \text{X} \diagdown \end{array} \text{Ph} \\ \text{21} \end{array} $			
Entry	18	20 : 21 ^c	Yield(%) ^b
1	18b	86 : 14	82
2	18c	75 : 25	63
3	18d	86 : 14	65
4	18e	96 : 4	69
5	18f	100 : 0	74
6	18g	100 : 0	71
7	18h	100 : 0	70
8	18i	100 : 0	57
9	18j	100 : 0	90

^a Conditions: 10 mol % Pd(OAc)₂, 2 equiv of **19a**, 2 equiv of Cu(OTf)₂, 2 equiv of K₂CO₃, dioxane, 80 °C, 16 h. ^b Yields of isolated products. ^c The ratios of **20** and **21** (inseparable) are calculated by ¹H NMR analysis.

The mechanism of coupling reaction is proposed as shown in Scheme 4.10. With assistance of the acetamino group, six-membered palladacycle **22a** is formed, which transmetalates with phenyl boronic acid. Subsequent reductive elimination leads to product **20** and Pd(0). The Pd(0) species are reoxidized to Pd(II) by Cu(II) to complete the catalytic cycle (path a). The side coupling product **21** may well go through two possible paths (b and c).¹¹² The product **20** may be oxidized by oxidant to give **21** (path c).¹¹³ The other possibility being that starting material **18a** is first oxidized to aromatic acetamide **24**, followed by aromatic C-H activation and C-C coupling via palladacycle **25** to provide dehydrogenated product **21** (path b).¹¹⁴ Similar aromatic C-H activation has been reported by Inoue¹¹⁵ and Shi.^{110d}

Scheme 4.10 Proposed Mechanism of Direct Arylation of Cyclic Enamides

¹¹² For aromatization, see: (a) Silva, L. F.; Siqueira, F. A.; Pedrozo, Jr., E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, 9, 1433. (b) Nino, E.; Avnir, D.; Eisen, M. S.; Blum, J. J. *Sol-Gel Sci. Techn.* **2005**, 35, 159. (c) Wong, W. K.; Chen, X. P.; Chik, T. W.; Wong, W. Y.; Guo, J. P.; Lee, F. W. *Eur. J. Inorg. Chem.* **2003**, 3539. (d) Neumann, R.; Lissel, M. *J. Org. Chem.* **1989**, 54, 4607. (e) Back, T. G.; Chau, Joseph H.-L.; Parvez, M. *Synthesis* **1995**, 162.

¹¹³ An experiment to prove path c: the ratio of coupling products of in Table 4.2 entry 5 (original ratio 80 : 20), under standard phenylation reaction condition for 16 hrs, changed to be 25 : 75.

¹¹⁴ Aromatic acetamide **24** was observed under reaction condition of the direct arylation of **18**, in the absence of organoboronic acid.

¹¹⁵ Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, 46, 4416.

4.3 CONCLUSION

In summary, we have developed a new, selective and direct coupling method to access various cyclic enamides derivatives¹¹⁶ from cyclic enamides and aryl boronic acids via Pd(II)-mediated direct C-H functionalization. Further investigations to expand the scope of the substrates and to understand the mechanism of this coupling reaction are in progress.

¹¹⁶ For their importance and extensive application in asymmetric catalytic hydrogenation, see : (a) Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2912. (b) Renaud, J. L.; Dupau, P.; Hay, A.-E.; Guingouain, M.; Dixneuf, P. H.; Bruneau, C. *Adv. Synth. Catal.* **2003**, 345, 230. (c) Zhang, Z. G.; Zhu, G. X.; Jiang, Q. Z.; Xiao, D. M.; Zhang, X. M. *J. Org. Chem.* **1999**, 64, 1774. (d) Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, 344, 1003. (e) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, 63, 6084. (f) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832.

4.4 PALLADIUM–CATALYZED DIRECT ARYLATION OF CYCLIC ENAMIDES WITH ARYLSILANE VIA SP² C-H ACTIVATION

Hiyama-coupling reaction involving the palladium-catalyzed coupling between organohalides or other surrogates with organosilanes is one of the most useful tool for C-C bond formation.¹¹⁷ Compared with similar coupling reactions using organostannane, Grignard and organoboron reagents, Hiyama coupling holds many advantages such as environmental benignity, atomic efficiency and safe handling. Recently, new C-C bond forming methods via C-H activation have attracted much interest among chemists.^{109, 118} Although many groups have reported direct arylation with organoboronic acids,^{109g, 110} there is still very little studies on the direct coupling using organosilane via C-H functionalization.¹⁰⁹ⁱ Herein, we report the first direct cross-coupling reaction between an enamide and organosilanes via the vinylic C-H bond activation using palladium catalyst.

Recently, our group has successfully developed direct cross-coupling reaction between cyclic enamide and arylboronic acid or acrylate via C-H bond activation. We envisioned the same substrate could also be used in the direct arylation with organosilane reagents. We initiated our investigation by studying the Hiyama-type coupling reaction of 4-chromanone-derived enamide **18f** with (trimethoxy)phenylsilane **26a** in the presence of Pd(OAc)₂ as a catalyst under various reaction conditions (Table 4.4).¹¹¹ In our initial screening of fluoride sources, it is

¹¹⁷ For selected examples, see: (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. (c) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (d) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556. (e) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

¹¹⁸ (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (e) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (f) Chiong, H. A.; Pham, Q. N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (g) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

gratifying to find that AgF could afford the desired product in high yield (entry 4). We hypothesized that AgF not only plays the role as a simple fluoride to activate the organosilane, but also as an oxidant to reoxidize Pd(0) to Pd(II) to fulfill the catalytic cycle. Three equivalents each of both AgF and PhSi(OMe)₃ was found necessary for complete consumption of the substrates (entries 4 vs 5). Other additional inorganic oxidants such as Cu(OAc)₂ were screened with this coupling reaction, but afforded the desired product in low yield. Among the different solvents screened, dioxane is the most suitable for this transformation (entries 4, 6-9). Various palladium species were also examined, but the transformation works well only in the presence of Pd(OAc)₂ as a catalyst (entries 4, 10-13).

Table 4.4 Screening conditions for the Pd(II)-catalyzed direct arylation of **18f** with phenyl trimethoxysilane^a

CC(=O)Nc1ccc2occcc2c1 (**18f**) + COC(OC)c1ccccc1OC (**26a**) $\xrightarrow[\text{Fluoride, solvent, 80 } ^\circ\text{C}]{\text{Pd (10 mol\%)}}$ CC(=O)Nc1ccc2occcc2c1c3ccccc3 (**20aa**)

Entry	Pd	Fluoride	Solvent	Yield(%) ^b
1	Pd(OAc) ₂	CuF ₂	dioxane	12
2	Pd(OAc) ₂	TBAF	dioxane	0
3	Pd(OAc) ₂	CsF	dioxane	0
4	Pd(OAc) ₂	AgF	dioxane	73
5 ^c	Pd(OAc) ₂	AgF	dioxane	61
6	Pd(OAc) ₂	AgF	DCE	30
7	Pd(OAc) ₂	AgF	toluene	25
8	Pd(OAc) ₂	AgF	DMF	44
9	Pd(OAc) ₂	AgF	CH ₃ CN	37
10	Pd(PPh ₃) ₂ Cl ₂	AgF	dioxane	32
11	Pd(OTFA) ₂	AgF	dioxane	47
12	Pd(PhCN) ₂ Cl ₂	AgF	dioxane	51
13	PdCl ₂	AgF	dioxane	18

^a Conditions: 10 mol % Pd(OAc)₂, 3 equiv of **26a**, 3 equiv of Fluoride, 80 °C, 16 h. ^b Yields of isolated products. ^c Conditions: 10 mol % Pd(OAc)₂, 2 equiv of **26a**, 2 equiv of Fluoride, 80 °C, 16 h.

The direct arylation of 4-chromanone-derived enamide **18f** with various trialkoxyarylsilanes was surveyed with 10 mol% of Pd(OAc)₂, 3 equiv of AgF in dioxane (Table 4.5). Compared with trimethoxyphenylsilane, triethoxyphenylsilane was a little less reactive (entries 1 vs 2). The arylated products were obtained in

Table 4.5 Pd-catalyzed direct arylation of **18f** with silyl reagents **26**^a

$ \begin{array}{c} \text{NHAc} \\ \\ \text{C}_6\text{H}_4\text{---O---CH=CH} \\ \text{18f} \end{array} + \text{26 (3 equiv)} \xrightarrow[\text{Dioxane, 80 }^\circ\text{C}]{\text{Pd(OAc)}_2 \text{ (10 mol\%)} \\ \text{AgF (3 equiv)}} \begin{array}{c} \text{NHAc} \\ \\ \text{C}_6\text{H}_4\text{---O---CH=CH---Ar} \\ \text{20} \end{array} $			
Entry	26	20	Yield(%) ^b
1	26a		20fa (73)
2	26b		20fb (66)
3	26c		20fc (51)
4	26d		20fd (54)
5	26e		20fe (55)
6	26f		20ff (56)
7	26g		20fg (50)
8	26h		20fh (40)

^a Conditions: 10 mol % Pd(OAc)₂, 3 equiv of **26**, 3 equiv of AgF, 80 °C, 16 h. ^b Yields of isolated products.

moderate to high yields via the coupling with different triethoxyarylsilane possessing electron-donating or electron-withdrawing groups on the phenyl ring. The position of these substituents has a great influence on this transformation. *Meta* and *para* substituents introduced on the phenyl ring of phenylsilane could afford the coupling products in good yields. However, *ortho* substituted ones hardly give the desired products, perhaps due to steric hindrance. It is noteworthy that chloro substituent on the phenylsiloxane exhibit tolerance toward this coupling reaction, which could serve as a handle for further transformation (entry 5).

To examine the scope of this direct arylation, various cyclic enamides were subjected to the reaction conditions (Table 4.6). Both electron-donating and electron-withdrawing groups on the phenyl ring of 4-chromanone-derived enamides **18** afforded the coupling products in moderate to excellent yields (entries 1-4). Notably as well, chloro group on the phenyl ring of enamide which tolerated the reaction condition could also be used for further transformation (entry 4). Substitution on the alicyclic ring of enamides could also be applied to give the coupling products, but in relatively low yields. Particularly for the substrate disubstituted on the alicyclic ring, the yield was only 19% (entry 6). This may well result from large steric hindrance to the adjacent vinylic C-H position of the enamide. In addition, application of this transformation to α -tetralone-derived enamides also produced the desired product in high yields (entries 7 and 8).

Table 4.6 Pd-catalyzed direct arylation of various cyclic enamides **18** with phenyl trimethoxysilane **26a**^a

$ \begin{array}{c} \text{NHAc} \\ \\ \text{R}^1\text{-C}_6\text{H}_3\text{-C} \\ \\ \text{X} \\ \textbf{18} \end{array} + \text{PhSi(OMe)}_3 \textbf{26a} \xrightarrow[\text{Dioxane, 80 }^\circ\text{C}]{\text{Pd(OAc)}_2 \text{ (10 mol\%)} \\ \text{AgF (3 equiv)}} \begin{array}{c} \text{NHAc} \\ \\ \text{R}^1\text{-C}_6\text{H}_3\text{-C-Ph} \\ \\ \text{X} \\ \textbf{20} \end{array} $			
Entry	18	20	Yield(%) ^b
1	18f	20fa (73)	
2	18h	20ha (72)	
3	18i	20ia (47)	
4	18g	20ga (95)	
5 ^c	18k	20ka (43)	
6	18j	20ja (19)	
7 ^u	18e	20ea (81)	
8 ^u	18a	20aa (43)	

^a Conditions: 10 mol % Pd(OAc)₂, 3 equiv of **26a**, 3 equiv of Fluoride, 80 °C, 16 h. ^b Yields of isolated products. ^c 55% of starting material was recovered. ^d some aromatized by-product of starting material was observed in the reaction.

Although there is the possibility of Heck-type reaction pathway for this coupling reaction, we believe that the reaction may go through palladation of cyclic enamides, which is similar to the mechanism of direct arylation of enaminones^{109m} and that of aromatic C-H activation reported by Inoue¹¹⁵ and Shi¹⁰⁹ⁱ, as depicted in Scheme 4.11. Assisted by the acetamino group, six-membered palladacycle **22f** is first formed. Next, with activation by fluoride, aryl group from siloxane **26** is transmetalated with palladacycle **22f** to give palladium species **23f**, which upon reductive elimination produced the cross-coupling product and Pd(0). Pd(0) is then reoxidized to Pd(II) by Ag(I) to fulfill the catalytic cycle.

Scheme 4.11 Proposed Mechanism of Direct Arylation of Cyclic Enamides

4.5 CONCLUSION

In conclusion, we have developed a palladium-catalyzed direct cross-coupling method for arylation of cyclic enamides with trialkoxyarylsilanes via C-H activation to produce a wide variety of enamides derivatives.¹¹⁶ The future studies will focus on its potential application and understanding of the mechanism of this transformation.

APPENDIX

***Copper-free Palladium-catalyzed Sonogashira
Cross-coupling Reaction Using Cesium Hydroxide
as an Activator***

1.1 INTRODUCTION

The Sonogashira reaction, which refers to palladium-catalyzed cross coupling between alkenyl or aryl halides and terminal alkynes, in presence of copper(I) cocatalyst, is a booming method to synthesize arylalkynes and enynes that exist widely in natural products, organic materials and pharmaceuticals (Scheme 1).¹¹⁹

Scheme 1. Typical Sonogashira reaction.

Since the pioneer studies¹²⁰ on this coupling reaction in 1975, Sonogashira reaction has seen significant development. It is noteworthy that even primary and second halides have been alkynylated using a Sonogashira procedure recently.¹²¹ Although the addition of copper salts as cocatalysts can accelerate greatly the reaction, the main drawback is that it often generates homocoupling byproducts of terminal alkynes (Glaser coupling product). Many efforts have been devoted to reduce this problematic side reaction in the absence of copper salt. Those copper-free Sonogashira coupling reaction frequently need harsh condition and the use of excess amine (often even as solvent), which diminishes the economical and environmental

¹¹⁹ (a) Chinchilla, R.; Nájera, C. *Chem.Rev.* **2007**, *107*, 874. (b) Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*; Elsevier: Oxford, 2004; p 293. (c) Sonogashira, K. In *Metal-catalyzed cross-coupling Reactions*; Diederich, F.; de Meijera, A.; Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1. p 319. (d) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (e) Negishi, E.; Anastasia, L. *Chem.Rev.* **2003**, *103*, 1979. (f) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; de Meijere, A.; Eds.; Wiley-Interscience: New York, 2002; p 493. (g) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (h) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127. (i) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M. Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 3, p 521.

¹²⁰ (a) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

¹²¹ (a) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. (b) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925.

advantages. Hence, the development of procedures aiming to eliminate both copper and amine has been pursued in the last decades. This introduction only covers recent developments in the palladium-phosphorous-complex-catalyzed copper-free Sonogashira cross coupling reaction, although this coupling reaction can also be catalyzed by other palladium complex such as palladium-nitrogen, *N*-heterocyclic carbene-palladium complex and palladacycle catalyst so on.

1.2 MECHANISTIC ASPECTS

The exact mechanism of the copper-cocatalyzed Sonogashira reaction is unclear. But this reaction is believed to undergo through two independent catalytic cycles: the Pd-cycle and the Cu-cycle (shown in Scheme 2). The generally accepted Pd-cycle is based on a fast oxidative addition of organohalide to the real reactive Pd catalyst generated from the initial Pd complex. Then this cycle would connect with the Cu-cycle. Thus, the copper acetylide formed in presence of the copper(I) salt would transmetalated into R^1PdXL_2 to generate a Pd species, which on reductive elimination affords the final coupled alkyne with regeneration of the catalysts.

Scheme 2. Proposed mechanism of copper-cocatalyzed Sonogashira reaction.

The mechanism of copper-free Sonogashira coupling is also equivocal. The first step would undoubtedly be the oxidative addition of organohalide to the Pd(0) complex. However, the second step is still poorly understood. Generally employed amines are not strong enough to deprotonate the alkyne. It is supposed that the formation of π -alkyne-Pd complex as shown in Scheme 3 would make the ligated alkyne proton more acidic for easier deprotonation.¹²²

Scheme 3. Proposed mechanism of copper-free Sonogashira reaction.

¹²² Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, 5, 4191.

1.3 PALLADIUM-PHOSPHORUS COMPLEXES

1.3.1 Unsupported Palladium-Phosphorus Complexes

The traditionally used catalysts in Sonogashira reaction are palladium-phosphorus complexes such as $\text{Pd}(\text{PPh}_3)_4$ and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$. Besides, the catalysts with bidentate ligands such as $\text{Pd}(\text{dppf})\text{Cl}_2$, $\text{Pd}(\text{dppp})\text{Cl}_2$, and $\text{Pd}(\text{dppe})\text{Cl}_2$ are also commonly employed.

The first example of copper-free procedures may trace back to 1986. The copper-free coupling of enol triflates with terminal alkynes was catalyzed by 5 mol % $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ at 60 °C,¹²³ and it was found later that excess use of cyclic amines could accelerate the coupling reaction.¹²⁴ In 2003, it was reported that copper-free Sonogashira coupling of activated aryl bromide and aryl iodide catalyzed by $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ at 70 °C in piperidine.¹²⁵ This copper-free method has been applied recently to the cross-coupling of 2-haloselenophenes with terminal alkynes (Scheme 4).¹²⁶ In addition, $\text{Pd}(\text{PPh}_3)_4$ generated in situ in the presence of triethylamine has been employed in the copper-free coupling of 10-bromoanthracene^{127a} or vinyl tosylates with terminal alkyne,¹²⁸ and recently using K_3PO_4 as a base for the coupling of aryl halides.^{127b}

Scheme 4. Cu-free coupling of 2-bromoselenophene and propargyl alcohol

¹²³ Cacchi, S.; Morera, E.; Ortat, G. *Synthesis* **1986**, 320.

¹²⁴ Alami, M.; Ferri, F.; Linstumelle, G. *Tetrahedron Lett.* **1993**, 34, 6403.

¹²⁵ Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, 44, 8653.

¹²⁶ Soares do Rego Barros, O.; Favero, A.; Nogueira, C. W.; Menezes, P. H.; Zeni, G. *Tetrahedron Lett.* **2006**, 47, 2179.

¹²⁷ (a) Wan, C. W.; Burghart, A.; Chen, J.; Bergstrom, F.; Johansson, L. B. A.; Wolford, M. F.; Kim, T. G.; Topp, M. R.; Hochstrasser, R. M.; Burgess, K. *Chem.-Eur. J.* **2003**, 9, 4430. (b) Shirakawa, E.; Kitabata, T.; Otsuka, H.; Tsuchimoto, T. *Tetrahedron* **2005**, 61, 9878.

¹²⁸ Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. *Tetrahedron Lett.* **2002**, 43, 6673.

More electron-rich phosphane ligand such as $P(tBu)_3$ and $Pd_2(dba)_3$ have been used in a Cu-free coupling of aryl bromides at room temperature.¹²⁹ Even the system $PdCl_2-(PCy_3)_2$ ¹³⁰ and $Pd(OAc)_2-BINAP$ ¹³¹ could be used in copper-free coupling of aryl chlorides using a carbonate as base at 100 °C. The combination related bulky electron-rich *o*-biphenylphosphane **27** and $Pd(PhCN)_2Cl_2$ has been used the cross-coupling of aryl chlorides and even aryl tosylates with terminal alkynes using Cs_2CO_3 as base, in which copper(I) iodide can inhibit product formation.¹³² Other palladium-phosphorus complexes such as $[Pd(\eta^3-C_3H_5)Cl_2]$ -ferrocenyl phosphane **28**,¹³³ $Pd_2(dba)_3 \cdot CHCl_3$ -phosphadamantane **29**,¹³⁴ and $Pd(OAc)_2$ -bisaminomethylphosphane **30**¹³⁵ have been applied in the copper-free Sonogashira reaction (Scheme 5).

Scheme 5. Related phosphorous ligands used in Cu-free Sonogashira coupling

To avoid the use of copper as cocatalyst, Mori employed Ag_2O , TBAF, TBAOH as activators for the Sonogashira reaction in the presence of $Pd(PPh_3)_4$ or

¹²⁹ Böhm, V. P. H.; Hermann, W. A. *Eur. J. Org. Chem.* **2000**, 3679.

¹³⁰ Yi, C.; Hua, R. *J. Org. Chem.* **2006**, 71, 2535.

¹³¹ Juo, Y.; Gao, H.; Li, Y.; Huang, W.; Lu, W.; Zhang, Z. *Tetrahedron* **2006**, 62, 2465.

¹³² Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, 42, 5993.

¹³³ Hierso, J. C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. V. *Org. Lett.* **2004**, 6, 3473.

¹³⁴ Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, 69, 5082.

$\text{Pd}_2(\text{dba})_3$ as a catalyst at 60 °C.¹³⁶ More interestingly, tetrabutylammonium acetate could be used as a base in ligand-, and copper-free Sonogashira reaction of aryl iodides, using $\text{Pd}(\text{OAc})_2$ as catalyst in DMF at room temperature.¹³⁷

Hydrophilic phosphane ligands have been designed for water-soluble palladium complexes in the homogeneous aqueous-phase Sonogashira reaction. The combination of $\text{Pd}(\text{OAc})_2$ and lithium carboxylate-containing phosphane **31** has allowed copper-free Sonogashira coupling reaction in aqueous acetonitrile. One illustrative example is the coupling reaction between *o*-iodinated benzyl alcohol and phenylacetylene (Scheme 6).¹³⁸ The other active water-soluble palladium catalyst is obtained by the combination of biphenyl sulfonated phosphane **32** and $\text{PdCl}_2(\text{MeCN})_2$, which allowed a high yielding Cu-free Sonogashira reaction of aryl chlorides and bromides, with Cs_2CO_3 as a base in aqueous acetonitrile at 60-100 °C (Scheme 6).¹³⁹

Scheme 6. Hydrophilic phosphane ligands used in Cu-free Sonogashira coupling

¹³⁵ Mery, D.; Heuzé, K.; Astrue, D. *Chem. Commun.* **2003**, 1934.

¹³⁶ (a) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, 2, 2935. (b) Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* **2001**, 649. (c) Ahmed Mohamed, M. S.; Sekiguchi, A.; Shimada, T.; Kawashima, J.; Mori, A. *Bull. Chem. Soc. Jpn.* **2005**, 78, 327.

¹³⁷ Urganokar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, 69, 5752.

¹³⁸ Genin, E.; Amengual, R.; Michelet, V.; Savignae, M.; Jutand, A.; Neuville, L.; Genet, J. P. *Adv. Synth. Catal.* **2004**, 346, 1733.

1.3.2 Supported Palladium-Phosphorus Complexes

Supported palladium-phosphorus complex is a solution to the problem with the recovery of costly catalyst, especially in large-scale reaction. To date, an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium-phosphorus complex **33** has been employed in water for the copper-free Sonogashira coupling of aryl halides in high yields (Scheme 7).¹⁴⁰

Scheme 7. Resin-supported palladium-phosphine complex in Sonogashira reaction

1.4 COPPER-FREE, PALLADIUM-CATALYZED SONOGASHIRA REACTION OF ARYL HALIDE WITH TERMINAL ALKYNES USING CESIUM HYDROXIDE AS AN ACTIVATOR

The Sonogashira reaction which involves the sp^2 - sp C-C bond formation is a very useful and powerful tool for the preparation of aryl internal alkynes in organic synthesis.^{119,120} The classical palladium-catalyzed Sonogashira coupling reactions of terminal alkynes and aromatic halides involve the usage of two catalysts, a zerovalent palladium complex and a halide salt of copper(I). The palladium complex activates the organic halides by oxidative addition into the carbon-halogen bond and gives palladium(II) intermediate after which it then undergoes transmetallation with the alkynyl copper (generated from the terminal alkyne base, and copper iodide). The coupling of the two organic ligands in reductive elimination gives the product and regenerate the palladium(0) catalyst.

¹³⁹ Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.

¹⁴⁰ Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71.

However, the presence of copper(I) as cocatalyst will always result in dimerization of alkyne side product. To avoid drawbacks, we are interested to develop copper and amine-free Sonogashira reaction despite the fact that there are already a few papers on this copper and amine free Sonogashira reaction. Knochel reported cesium hydroxide catalyzed alkynylation of aldehydes and ketones, in which alkynes can be activated by cesium hydroxide to generate a stable organometallic species (Scheme 8, equation 1).¹⁴¹ We hypothesized cesium hydroxide can also be applied to Sonogashira reaction to replace copper and amine (Scheme 8, equation 2).

Scheme 8. Hypothesis of Sonogashira reaction using CsOH as activator

With iodobenzene and phenylacetylene in the presence of 5% mol palladium complex and CsOH.H₂O, we started to explore the reaction. Using a catalytic amount of CsOH (0.1 equiv) in the reaction, we are delighted to find a desired product in low yield. In attempting to optimize the reaction by increasing the amount of CsOH, we realized that 1 eq of CsOH is sufficient (Table 1, Entries 2, 3 and 5). The reaction proceeds in the yield of 67% in the solvent of THF/H₂O (9:1), but a little low yield in anhydrous solvent. Higher yield can be obtained in normal THF (82%). Therefore, it can be concluded the presence of little water is beneficial to this reaction (Table 1, Entries 1, 3 and 4). Among the palladium complexes screened, Pd(PPh₃)₄ is the best catalyst (Table 1, Entry 3 and 6).

¹⁴¹ Tzlis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, 38, 1463.

Table 1. Different kinds of conditions for Sonogashira Reaction^a

Entry	Reaction Condition	Yield (%) ^b
1	Pd(PPh ₃) ₄ (5 mol%), CsOH (1 equiv), THF (anhyd.)	60
2	Pd(PPh ₃) ₄ (5 mol%), CsOH (0.1 equiv), THF	10
3	Pd(PPh ₃) ₄ (5 mol%), CsOH (1 equiv), THF	82
4	Pd(PPh ₃) ₄ (5 mol%), CsOH (1 equiv), THF/H ₂ O (9:1)	67
5	Pd(PPh ₃) ₄ (5 mol%), CsOH (1.2 equiv), THF	75
6	PdCl ₂ (PPh ₃) ₂ (5 mol%), CsOH (1 equiv), THF	48

^a The reaction was carried out at 60 °C. ^b Yields of isolated products.

With our developed method, both aryl iodide and bromide can give products, but the latter afforded lower yield (Table 2, Entries 1 vs. 2, 3 vs. 4). The results also showed iodide with electron donating group such as methoxy, on phenyl ring gives an excellent yield up to 92%. Iodide with electron withdrawing group such as nitro can also give a high yield (Table 2, Entries 3-6).

Table 2. Copper-, amine- free, Sonogashira couplings of various halides with phenylacetylene^a

Entry	ArX	Yield (%) ^b
1		82
2		36
3		92
4		61
5		75
6		76

^a Conditions: 5 mol% Pd(PPh₃)₄, 1 equiv of CsOH.H₂O, 1 equiv of ArX, 60 °C. ^b Yields of isolated products.

Continuing with our developed method, we attempted to use various types of acetylene: alkyl and aromatic groups. As for alkyl acetylene, it can be tolerant to different functional groups such as hydroxyl, amine and ketone groups. Especially the one with amino group gives a higher yield of 92% (Table 3, Entry 3). Aromatic acetylene can also give high desired product (Table 3, Entries 5 and 6).

Table 3. Ligand-, Copper-, Sonogashira Couplings of Aliphatic terminal alkynes with Iodobenzene^a

Entry	R	Yield (%) ^b
1	HOCH ₂ -	63
2	HO(CH ₂) ₂ -	36
3	NH ₂ CH ₂ -	92
4	CH ₃ CO-	61
5	4-Cl-C ₆ H ₄ -	79
6	2-CH ₃ -C ₆ H ₄ -	93

^a Conditions: 5 mol% Pd(PPh₃)₄, 1 equiv of CsOH.H₂O, 1 equiv of terminal alkynes, 60 °C. ^b Yields of isolated products.

With success in exploring a new method to construct the internal acetylene by copper-free Sonogashira reaction, we have proposed a plausible mechanism (Scheme 9). CsOH react with phenylacetylene to form a cesium acetylide. Meanwhile iodobenzene undergoes oxidative addition with zerovalent palladium to form Pd(II) intermediate. The two intermediates then undergo transmetallation and the resulting intermediate proceeded with reductive elimination to give a product with regeneration of Pd(0).

Scheme 9. Plausible mechanism for copper-free Sonogashira reaction

1.5 CONCLUSION

In short, we have developed a new method of Sonogashira reaction in copper and amine free environment. This reaction can be applied to different substrates with high yield. It would be a beneficial synthetic tool to construct many complex molecules.

CHAPTER 5

Experimental Section

5.1 GENERAL INFORMATION

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in flame-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 °C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under “Chromatography”). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 °C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 °C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego¹⁴². Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with

traces of moisture *in vacuo* followed by subsequent purging with nitrogen. Acrolein and crotonylaldehyde were freshly distilled prior to usage.

Triethylamine, toluene and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. DMF was distilled over Linde type 4A molecular sieve prior to usage. 1*N* and 4*N* hydrochloric acid was diluted from concentrated 37% solution using deionised water. 3*M* sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F₂₅₄ pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, potassium permanganate solution or ceric molybdate solution followed by heating on a hot plate.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 mm) and freshly distilled solvents. Columns were packed as slurry of silica gel in hexane/CH₂Cl₂ and equilibrated with the appropriate solvent/solvent mixture prior to use. The solute was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

¹⁴² Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between NaCl salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as c and was calculated as grams per milliliters (g / 100 mL) whereas the solvent was indicated in parentheses (c , solvent).

Mass Spectroscopy

Mass spectrometry was performed by the staffs in the Division of Chemistry and Biological Chemistry of the Nanyang Technological University. MS (EI) spectra were recorded on a Thermo Finnigan Polaris Q GCMS. MS (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. HRMS (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and HRMS were reported in units of mass of charge ratio (m/z).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and

500 NMR spectrometers. Boron (^{11}B) nuclear magnetic resonance and fluorine (^{19}F) nuclear magnetic resonance were performed on a Bruker Avance 300 NMR spectrometer.

Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, CDCl_3 (^1H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet).

Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplets), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and ddt (doublet of doublet of triplets). Coupling constants (J) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by $n\text{H}$.

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 8.0 software.

5.2 One-Pot Total Syntheses of Natural Products Containing a THP-Ring Backbone: (±)-Centrolobine and (±)-Civet cat Secretion

Table 5.1 Effect of solvents on the one-pot and two-steps synthesis of **2a**^a

Entry	Solvent A	Solvent B	Overall Yield/% ^c
1	ethyl acetate	ethyl acetate	45
2	toluene	toluene	0
3	Et ₂ O	Et ₂ O	44
4 ^b	Et ₂ O	Et ₂ O	49
5	hexane	hexane	0
6	dioxane	dioxane	16
7	diglyme	diglyme	38
8	CH ₃ CN	CH ₃ CN	8
9	neat	THF	59
10	DCM	CH ₃ CN	54
11	DCM	THF	74
12 ^b	DCM	THF	73

^a 1st step: InBr₃ 0.1 mmol, TMSBr 1.1 mmol, benzaldehyde 0.95 mmol, **1** 1mmol, solvent A 2mL; 2nd step: InBr₃ 1.5 mmol, NaBH₄ 2 mmol, solvent B 2 mL. ^b HInBr₂ was prepared in situ. ^c Yields were based on benzaldehyde.

A Typical Procedure for the Preparation of HInBr₂ (Generated in Advance)

To a suspension of InBr₃ (0.29 g, 0.83 mmol) in anhydrous THF (2 mL), was added NaBH₄ (42 mg, 1.10 mmol) in portions at -78 °C under nitrogen. After being stirred for 5 minutes at -78 °C, the heterogeneous solution was warmed up to rt. and stirred for 5 mins for being used directly in reactions. The molar amount of HInBr₂ prepared was calculated as an equivalent to InBr₃.

General Procedure for One-pot, Three-step Synthesis of 2 (Table 1.1)

To a mixture of **1** (0.1 g, 0.75 mmol, 1.0 eq.), water (80 μ L, 4.5 mmol, 6.0 eq.), indium powder (0.13 g, 1.13 mmol, 1.5 eq.), was added dropwise allyl bromide (0.11 g, 0.89 mmol, 1.2 eq.) at 0 °C. The mixture was continued to be stirred for 2 h at rt.. After removal of excess allyl bromide by rotatory evaporator, the residue was dissolved in CH₂Cl₂ (2 mL). To the solution was added aldehyde (0.71 mmol, 0.95 eq.) in one portion at r.t., followed by addition dropwise of TMSBr (110 μ L, 0.83 mmol, 1.1 eq.) at 0 °C. After stirring for 2 hrs at r.t., CH₂Cl₂ was removed by rotatory evaporator to get a residue which was dissolved again in anhydrous THF (3 mL). InBr₃ (0.4 g, 1.13 mmol, 1.5 eq.) was added in one portion followed by addition of NaBH₄ (57 mg, 1.5 mmol, 2 eq.) in small portions under nitrogen (or added the solution to the HInBr₂ prepared according the procedure above). The mixture was stirred for 2 h at rt., and quenched by addition of 1N HCl aqueous solution. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was rinsed with saturated NaHCO₃ aqueous solution and brine subsequently. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated to get a residue which was purified by flash chromatography eluting with EE/Hex = 1/100, 1/50, to get pure product **2**.

2-phenethyl-tetrahydro-6-phenyl-2H-pyran

R_f = 0.85 (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.41 – 7.16 (m, 10H), 4.35 (dd, $J = 11.3$ Hz, 2.1 Hz, 1H), 3.49 – 3.43 (m, 1H), 2.83 – 2.72 (m, 1H), 1.98 – 1.76 (m, 4H), 1.68 – 1.60 (m, 2H), 1.59 – 1.31 (m, 3H);

^{13}C NMR (75 MHz, CDCl_3): δ 162.3, 143.6, 142.5, 128.5, 128.3, 128.2, 127.0, 125.8, 125.6, 79.3, 77.1, 38.1, 33.5, 31.7, 31.3, 24.1;

FTIR (neat): 3061, 3026, 2934, 2857, 1602, 1495, 1452, 1387, 1306, 1209, 1088, 1045, 908, 750, 698, 552 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_1$ $[\text{M}]^+$: 266.1665. Found: 266.1663;

2-ethyl -tetrahydro-6- phenethyl -2*H*-pyran

$R_f = 0.87$ (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.28 – 7.16 (m, 5H), 3.25 – 3.10 (m, 2H), 2.80 – 2.66 (m, 2H), 1.88 – 1.76 (m, 2H), 1.71 – 1.65 (m, 1H), 1.59 – 1.42 (m, 5H), 1.28 – 1.13 (m, 2H), 1.00 (t, $J = 7.4$ Hz, 3H);

^{13}C NMR (300 MHz, CDCl_3): δ 142.6, 128.6, 128.2, 125.6, 79.3, 76.5, 38.1, 31.8, 31.8, 31.4, 29.5, 23.7, 10.3;

FTIR (neat): 3061, 3026, 2932, 2859, 2843, 1603, 1495, 1454, 1439, 1371, 1321, 1202, 1084, 1036, 1005, 897, 748, 698, 484 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_1$ $[\text{M}]^+$: 218.1665. Found: 218.1668;

2-(pentan-3-yl) -tetrahydro-6- phenethyl -2H-pyran

$R_f = 0.86$ (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.27 – 7.16 (m, 5H), 3.24 – 3.12 (m, 2H), 2.86 – 2.60 (m, 2H), 1.86 – 1.16 (m, 13H), 0.91 – 0.87 (m, 6H);

^{13}C NMR (75 MHz, CDCl_3): δ 142.7, 128.5, 128.2, 125.5, 79.3, 76.8, 45.8, 38.3, 32.0, 31.8, 28.6, 24.0, 21.4, 21.2, 11.2, 11.0;

FTIR (neat): 3061, 3026, 2959, 2932, 2872, 1603, 1454, 1439, 1379, 1317, 1200, 1084, 1049, 893, 746, 698 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_1$ $[\text{M}]^+$: 260.2135. Found: 260.2146;

2,6-diphenethyl-tetrahydro -2H-pyran

$R_f = 0.83$ (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.31 – 7.17 (m, 10H), 3.28 – 3.20 (m, 2H), 2.91 – 2.81 (m, 2H), 2.77 – 2.67 (m, 2H), 1.94 – 1.66 (m, 5H), 1.65 – 1.38 (m, 3H), 1.30 – 1.20 (m, 2H);

^{13}C NMR (75 MHz, CDCl_3): δ 142.5, 128.5, 128.3, 125.6, 76.7, 38.2, 31.9, 31.8, 23.7;

FTIR (neat): 3061, 3024, 2932, 2857, 2834, 1603, 1495, 1454, 1323, 1198, 1082, 1043, 750, 698, 476 cm^{-1} ;

HRMS (EI) m/z Calcd for $C_{21}H_{26}O_1$ $[M]^+$: 294.1978. Found: 294.1975;

2-cyclohexyl-tetrahydro-6- phenethyl -2*H*-pyran

R_f = 0.87 (10:1 hexane/diethyl ether)

1H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.16 (m, 5H), 3.22 – 3.14 (m, 1H), 2.98 – 2.90 (m, 1H), 2.80 – 2.67 (m, 2H), 2.14 – 2.08 (m, 1H), 1.85 – 1.66 (m, 8H), 1.65 – 1.34 (m, 3H), 1.33 – 1.21 (m, 5H), 1.20 – 0.95 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 128.6, 128.2, 125.5, 82.2, 76.5, 43.3, 38.2, 32.0, 31.8, 29.5, 29.0, 28.7, 26.7, 26.3, 26.1, 23.8;

FTIR (neat): 3061, 3026, 2926, 2851, 1603, 1450, 1384, 1325, 1202, 1088, 1042, 907, 883, 756, 698, 546 cm^{-1} ;

HRMS (EI) m/z Calcd for $C_{19}H_{28}O_1$ $[M]^+$: 272.2135. Found: 272.2135;

2-(naphthalene-1-yl)-tetrahydro-6- phenethyl -2*H*-pyran

R_f = 0.64 (10:1 hexane/diethyl ether)

1H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 7.4 Hz, 1H), 7.82 (d, J = 16.6 Hz, 1H), 7.72 (d, J = 23.2 Hz, 1H), 7.66 – 7.44 (m, 1H), 7.30 – 7.17 (m,

1H), 5.06 (d, $J = 10.4$ Hz, 1H), 3.70 – 3.63 (m, 1H), 2.88 – 2.72 (m, 2H), 2.08 – 1.71 (m, 7H), 1.47 – 1.42 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3): δ 142.5, 138.9, 133.8, 130.7, 128.7, 128.5, 128.3, 127.7, 125.6, 125.6, 125.5, 125.3, 123.7, 123.0, 77.7, 76.7, 38.2, 32.5, 31.8, 31.6, 24.3;

FTIR (neat): 3059, 3026, 2934, 2855, 2245, 1942, 1599, 1454, 1439, 1317, 1261, 1196, 1082, 1038, 908, 799, 777, 733, 698, 648, 563, 473 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{23}\text{H}_{24}\text{O}_1$ $[\text{M}]^+$: 316.1822. Found: 316.1824;

2-(4-methoxyphenyl)-tetrahydro-6-phenethyl-2H-pyran

$R_f = 0.58$ (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.33 – 7.16 (m, 7H), 6.88 (d, $J = 8.6$ Hz, 2H), 4.30 (dd, $J = 11.2$ Hz, 1.9 Hz, 1H), 3.80 (s, 3H), 3.49 – 3.41 (m, 1H), 2.84 – 2.66 (m, 2H), 1.99 – 1.20 (m, 8H);

^{13}C NMR (75 MHz, CDCl_3): δ 158.7, 142.5, 135.9, 128.5, 128.2, 127.0, 125.6, 113.6, 79.0, 77.2, 55.3, 38.1, 33.3, 31.7, 31.3, 24.0;

FTIR (neat): 3061, 3024, 2999, 2932, 2855, 2835, 1614, 1514, 1495, 1441, 1302, 1246, 1175, 1080, 1038, 908, 831, 810, 748, 700, 583 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_2$ $[\text{M}]^+$: 296.1771. Found: 296.1775;

2-phenethyl-tetrahydro-6-*o*-tolyl-2*H*-pyran

$R_f = 0.88$ (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.30 – 7.13 (m, 9H), 4.31 (dd, $J = 11.2$ Hz, 1.9 Hz, 1H), 3.49 – 3.40 (m, 1H), 2.85 – 2.69 (m, 2H), 2.33 (s, 3H), 1.97 – 1.76 (m, 4H), 1.67 – 1.46 (m, 3H), 1.41 – 1.30 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3): δ 142.6, 140.7, 136.6, 128.9, 128.5, 128.2, 125.8, 125.6, 79.3, 77.1, 38.1, 33.5, 31.7, 31.3, 24.1, 21.1;

FTIR (neat): 3061, 3024, 2932, 2857, 1603, 1516, 1495, 1454, 1385, 1306, 1207, 1186, 1082, 1043, 908, 804, 746, 698, 534 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{20}\text{H}_{24}\text{O}$ $[\text{M}]^+$: 280.1822. Found: 280.1821;

2-(4-chlorophenyl)-tetrahydro-6-phenethyl-2*H*-pyran

$R_f = 0.86$ (10:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ 7.28 – 7.16 (m, 9H), 4.32 (dd, $J = 11.2$ Hz, 2.2 Hz, 1H), 3.50 – 3.40 (m, 1H), 2.90 – 2.65 (m, 2H), 1.97 – 1.76 (m, 4H), 1.67 – 1.60 (m, 2H), 1.50 – 1.25 (m, 2H);

^{13}C NMR (75 MHz, CDCl_3): δ 142.4, 142.2, 132.7, 128.5, 128.3, 128.3, 127.1, 125.6, 78.7, 77.2, 38.0, 33.6, 31.7, 31.1, 23.9;

FTIR (neat): 2922, 2853, 1493, 1456, 1375, 1088, 1042, 1015, 841, 804, 698 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_1\text{Cl}_1$ $[\text{M}]^+$: 300.1274. Found: 300.1272;

General Procedure for One-pot, Three-step Total Synthesis of Centrolobine

To a mixture of **3** (0.1 g, 0.67 mmol, 1 eq.), water (72 μL , 4.02 mmol, 6 eq.), indium powder (0.12 g, 1 mmol, 1.5 eq.) in THF (72 μL), was added dropwise allyl bromide (71 μL , 0.8 mmol, 1.2 eq.) at 0 $^\circ\text{C}$. The mixture was continued to be stirred for 2 h at rt.. After removal of excess allyl bromide and THF by rotatory evaporator, the residue was dissolved in CH_2Cl_2 (2 mL). To the solution was added *p*-Anisaldehyde (89 mg, 0.64 mmol, 0.95 eq.) in one portion at rt., followed by addition dropwise of TMSBr (97 μL , 0.74 mmol, 1.1 eq.) at 0 $^\circ\text{C}$. After stirring for 2 hrs at rt., CH_2Cl_2 was removed by rotatory evaporator to get a residue which was dissolved again in anhydrous THF (3 mL). InBr_3 (0.36 g, 1 mmol, 1.5 eq.) was added in one portion followed by addition of NaBH_4 (51 mg, 1.34 mmol, 2 eq.) in small portions under nitrogen (or added the solution to the HInBr_2 prepared according the procedure above). The mixture was stirred for 2 h at rt., and quenched by addition of 1N HCl aqueous solution. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was rinsed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to get a residue which was purified by flash chromatography eluting with EA/Hex = 1/10, 1/6, 1/4 to get pure product **6** (0.12 g, 58%).

4-(2-(tetrahydro-6-(4-methoxyphenyl)-2H-pyran-2-yl)ethyl)phenol, Centrolobine

$R_f = 0.48$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 7.31 (d, $J = 8.5$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 8.5$ Hz, 2H), 4.94 (s, 1H), 4.30 (dd, $J = 11.2$ Hz, 1.8 Hz, 1H), 3.80 (s, 3H), 3.48 – 3.40 (m, 1H), 2.73 – 2.63 (m, 2H), 2.05– 1.49 (m, 7H), 1.40 – 1.25 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3): δ 158.7, 153.5, 135.8, 134.6, 129.5, 127.1, 115.1, 113.6, 79.1, 77.2, 55.3, 38.3, 33.3, 31.2, 30.7, 24.0;

FTIR (neat): 3383, 3013, 2936, 2858, 2839, 1614, 1514, 1454, 1441, 1246, 1036, 830, 766 cm^{-1} ;

HRMS (EI) m/z Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3$ $[\text{M}]^+$: 312.1711. Found: 312.1720;

General Procedure for One-pot, Multiple-step Total Synthesis of Civet Cat Secretion

A mixture of dimethyl acetal **7** (100 mg, 0.67 mmol, 1 eq.), amberlyst-15 (60 mg), and water (120 mg, 6.75 mmol, 10 eq.) in acetone (3 mL) was refluxed overnight. The acetone was removed by rotatory evaporator and replaced with THF (2 mL) instead. To the mixture, were added indium powder (0.12 g, 1 mmol, 1.5 eq.) and allyl bromide (71 μL , 0.8 mmol, 1.2 eq.) at 0 $^\circ\text{C}$, and the reaction was continued to be stirred for 2 h at rt.. After removal of excess allyl bromide and THF by rotatory evaporator, the residue was dissolved in CH_2Cl_2 (2 mL). To the solution was added

acetaldehyde (38 μ L, 0.67 mmol, 1 eq.) in one portion at rt., followed by addition dropwise of TMSBr (0.1 mL, 0.74 mmol, 1.1 eq.) at 0 $^{\circ}$ C. After stirring for 2 hrs at r.t., CH_2Cl_2 was removed by rotatory evaporator to get a residue which was dissolved again in anhydrous THF (3 mL). InBr_3 (0.36 g, 1 mmol, 1.5 eq.) was added in one portion followed by addition of NaBH_4 (51 mg, 1.34 mmol, 2 eq.) in small portions under nitrogen (or added the solution to the HInBr_2 prepared according the procedure above). The mixture was stirred for 2 h at rt., and a solution of lithium hydroxide monohydrate (85 mg, 2.03 mmol, 3.0 eq.) in water (0.33 mL) was added. The reaction was stirred for 4 h at rt., then diluted with water (10 mL) and washed with ethyl ether (2 x 10 mL) to remove organic impurities. The aqueous layer was acidified by addition of 1N HCl aqueous solution, and extracted with ethyl ether (3 x 10 mL). The combined organic layer was rinsed with brine and dried over anhydrous Na_2SO_4 , filtered and concentrated to get a residue which was purified by flash chromatography eluting with EA/Hex = 1/4, 1/2 to get pure product **12** (25 mg, 23%).

(6'-methyl-2'-tetrahydropyranyl) acetic acid, Civet Cat Secretion

$R_f = 0.73$ (10:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$)

^1H NMR (300 MHz, CDCl_3): δ 3.79 – 3.74 (m, 1H), 3.59 – 3.52 (m, 1H), 2.54 (t, $J = 7.5$ Hz, 2H), 1.87 – 1.81 (m, 1H), 1.65 – 1.61 (m, 3H), 1.30 – 1.22 (m, 2H), 1.20 (d, $J = 6.2$ Hz, 3H);

^{13}C NMR (75 MHz, CDCl_3): δ 74.6, 73.9, 41.1, 32.7, 30.7, 29.7, 23.1, 22.0;

FTIR (neat): 3458 – 3387, 2968, 2931, 2860, 2849, 1714, 1385, 1292, 1205, 1070 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_8\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 158.0937. Found: 158.0933;

5.3 Aerobic Aqueous Transformation of Halo Group into Hydroxyl Group via Tin-Free Radical Method

General Procedure for the Transformation of 1-Bromo-adamantane into 1-Adamantanol [CAS: 768-95-6] via Free Radical Method (Table 2.1)

To a solution of 1-bromoadamantane (142 mg, 0.66 mmol) dissolved in an organic solvent (40 mL) in a 100 mL two-necked round bottom flask equipped with a condenser, was added water (40 mL). After air was bubbled in for 10 minutes, indium or zinc powder (1.98 mmol) and sodium hydrophosphite monohydrate (0.21 g, 1.98 mmol) was added into the mixture. The reaction mixture was heated to 60 °C and stirred vigorously overnight while air was bubbled in or under oxygen balloon. After reaction, the mixture was extracted using diethyl ether (3 x 20 mL), washed with brine, dried over anhydrous magnesium sulphate, and filtered. The filtrate was

evaporated to obtain the crude product. The crude product was purified by silica gel column chromatography (eluent: ethyl acetate / hexane 1/3) to get the desired product. The corresponding spectroscopic data is in accordance with those reported in the literature for 1-adamantanol. $R_f = 0.35$ (3:1 hexane/ethyl acetate)

General Procedure for the Transformation of Organohalides into Alcohols via Free Radical Methods (Table 2.2)

To a solution of organic halides **13** (0.40 mmol) dissolved in *tert*-butanol (40 mL) in a 100 mL two-necked round bottom flask equipped with a condenser, was added water or saturated NH_4Cl aqueous solution (40 mL). After air was bubbled in for 10 minutes, indium or zinc powder (1.20 mmol) and sodium hydrophosphite monohydrate (0.21 g, 2.0 mmol) was added into the mixture. The reaction mixture was heated to 60 °C and stirred vigorously for 16 h while air was bubbled in. After reaction, the mixture was extracted using diethyl ether (3 x 20 mL), washed with brine, dried over anhydrous magnesium sulphate, and filtered. The filtrate was evaporated to obtain the crude product. The crude product was purified by silica gel column chromatography (eluent: ethyl acetate / hexane 1/10) to get the desired product **14**.

General procedure for transformation of 4,4-dihalo-2,6-disubstituted THPs into 2,6-disubstituted tetrahydropyranones under different conditions (Table 2.3)

To a solution of 4,4-diiodo-THP **15a-c** (0.66 mmol) dissolved in an organic solvent (40 mL) in a 100 mL two-necked round bottom flask equipped with a condenser, was added water (40 mL). After air was bubbled in for 10 minutes, indium or zinc powder (1.98 mmol) and sodium hydrophosphite monohydrate (0.21 g, 1.98 mmol) was added into the mixture. The reaction mixture was heated to 60 °C and stirred vigorously overnight while air was bubbled in or under oxygen balloon. After reaction, the mixture was extracted using diethyl ether (3 x 20 mL), washed with brine, dried over anhydrous magnesium sulphate, and filtered. The filtrate was evaporated to obtain the crude product. The crude product was purified by silica gel column chromatography (eluent: ethyl acetate / hexane 1/3) to get the desired product **16a**.

General procedure for the preparation of pyranones via free radical method (Table 2.4)

To a solution of 4,4-diiodo-THP **15** (0.29 mmol) dissolved in 1,2-dimethoxyethane (40 mL) in a 100 mL two-necked round bottom flask equipped with a condenser, was added water (40 mL). After air was bubbled in for 10 minutes, indium (0.17 g, 1.45 mmol) and sodium hydrophosphite monohydrate (0.15 g, 1.45 mmol) was added into the mixture. The reaction mixture was heated to 60 °C and stirred vigorously for 16 h while air was bubbled in. After reaction, the mixture was extracted using diethyl ether (3 x 20 mL), washed with brine, dried over anhydrous magnesium sulphate, and filtered. The filtrate was evaporated to obtain the crude product. The crude product was purified by silica gel column chromatography (eluent: ethyl acetate / hexane 1/10) to get the desired product **16**.

Cis-2-phenethyl-6-phenyldihydro-2H-pyran-4(3H)-one

$R_f = 0.2$ (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (41 mg, 51%).

^1H NMR (300 MHz, CDCl_3) δ 7.51-7.15 (m, 10H), 4.63 (dd, $J_1 = 3.1$ Hz, $J_2 = 11.2$ Hz, 1H), 3.78-3.71 (m, 1H), 2.90-2.50 (m, 6H), 2.23-2.06 (m, 1H), 1.95-1.88 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ 206.71, 141.37, 140.90, 128.61, 128.43, 127.97, 125.97, 125.57, 78.40, 76.15, 49.45, 47.70, 37.86, 31.46.

FTIR (neat, cm^{-1}) 3026.31, 2927.94, 2860.43, 1714.72, 1494.83, 1454.33, 1348.24, 1253.73, 1138.00, 1056.99, 752.24, 698.23.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$: 281.1542, found 281.1539.

Cis-2-(pentan-3-yl)-6-phenethyldihydro-2H-pyran-4(3H)-one

$R_f = 0.36$ (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (34 mg, 43%).

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.25 (m, 2H), 7.21-7.17 (m, 3H), 3.52-3.45 (m, 2H), 2.89-2.81 (m, 1H), 2.75-2.67 (m, 1H), 2.37-2.21 (m, 4H), 2.01-1.91 (m, 1H), 1.83-1.74 (m, 1H), 1.60-1.38 (m, 4H), 1.34-1.25 (m, 1H), 0.91 (q, $J = 6.7$ Hz, 6H);

^{13}C NMR (100 MHz, CDCl_3) δ 208.29, 141.55, 128.41, 128.38, 125.90, 78.43, 75.77, 48.07, 45.83, 45.26, 38.04, 31.58, 21.24, 21.17, 11.12, 11.09;

FTIR (neat, cm^{-1}) 2960.73, 2931.80, 2873.94, 1716.65, 1496.76, 1454.33, 1327.03, 1286.52, 1236.37, 1149.57, 1095.57, 1062.78, 1029.99, 748.38, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$: 275.2011, found 275.2000.

Cis-2,6-diphenethyldihydro-2H-pyran-4(3H)-one

$R_f = 0.18$ (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (40 mg, 45%).

^1H NMR (300 MHz, CDCl_3) δ 7.32-7.18 (m, 10H), 3.56-3.46 (m, 2H), 2.90-2.83 (m, 2H), 2.81-2.72 (m, 2H), 2.38-2.20 (m, 4H), 2.05-1.96 (m, 2H), 1.86-1.77 (m, 2H);

^{13}C NMR (75 MHz, CDCl_3) δ 207.14, 141.40, 128.42, 128.39, 125.96, 75.76, 47.87, 37.96, 31.62;

FTIR (neat, cm^{-1}) 3024.38, 2924.09, 2856.58, 1716.65, 1494.83, 1454.33, 1327.03, 1278.81, 1236.37, 1130.29, 1087.85, 1055.06, 750.31, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$: 309.1855, found 309.1854.

Cis-2-cyclohexyl-6-phenethyldihydro-2H-pyran-4(3H)-one

R_f = 0.3 (15:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (41 mg, 50%).

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.25 (m, 2H), 7.21-7.17 (m, 3H), 3.50-3.43 (m, 1H), 3.29-3.23 (m, 1H), 2.88-2.81 (m, 1H), 2.77-2.69 (m, 1H), 2.42-2.37 (m, 1H), 2.33-2.19 (m, 3H), 2.10-2.03 (m, 1H), 2.01-1.92 (m, 1H), 1.82-1.74 (m, 3H), 1.71-1.64 (m, 2H), 1.55-1.46 (m, 1H), 1.32-1.15 (m, 3H), 1.12-0.98 (m, 2H).;

^{13}C NMR (100 MHz, CDCl_3) δ 208.12, 141.50, 128.43, 128.37, 125.89, 81.08, 75.51, 48.12, 45.40, 43.29, 38.00, 31.54, 28.95, 28.49, 26.40, 25.97, 25.87;

FTIR (neat, cm^{-1}) 2924.09, 2852.72, 1720.50, 1450.43, 1325.10, 1271.09, 1157.29, 1122.57, 1089.78, 1058.92, 842.89, 748.38, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$: 287.2011, found 287.2006.

Cis-2-(naphthalen-1-yl)-6-phenethyldihydro-2H-pyran-4(3H)-one

$R_f = 0.18$ (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (54 mg, 56%).

^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, $J = 8.2$ Hz, 1H), 7.89 (d, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.70 (d, $J = 7.1$ Hz, 1H), 7.55-7.48 (m, 3H), 7.31-7.23 (m, 2H), 7.21-7.16 (m, 3H), 5.32 (dd, $J_1 = 2.6$ Hz, $J_2 = 11.3$ Hz, 1H), 3.95-3.87 (m, 1H), 2.93-2.71 (m, 4H), 2.57-2.45 (m, 2H), 2.18-2.08 (m, 1H), 2.01-1.91 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 206.87, 141.35, 136.19, 133.76, 130.11, 128.96, 128.63, 128.43, 128.40, 126.29, 125.97, 125.71, 125.49, 122.97, 76.54, 75.70, 48.59, 47.88, 37.97, 31.48;

FTIR (neat, cm^{-1}) 3059.10, 3024.38, 2924.09, 2858.51, 1714.72, 1600.92, 1516.26, 1494.83, 1454.33, 1332.81, 1267.23, 1240.23, 1136.07, 1082.07, 1053.13, 910.40, 798.53, 777.31, 732.95, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{23}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$: 331.1698, found 331.1692.

Cis-2-(4-methoxyphenyl)-6-phenethyldihydro-2H-pyran-4(3H)-one

$R_f = 0.15$ (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (54 mg, 60%).

^1H NMR (400 MHz, CDCl_3) δ 7.33-7.24 (m, 4H), 7.20-7.17 (m, 3H), 6.93 (d, $J = 8.7$ Hz, 2H), 4.57 (dd, $J_1 = 3.9$ Hz, $J_2 = 10.3$ Hz, 1H), 3.82 (s, 3H), 3.75-3.68 (m, 1H), 2.89-2.72 (m, 2H), 2.63-2.52 (m, 2H), 2.46-2.35 (m, 2H), 2.12-2.03 (m, 1H), 1.93-1.83 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 206.94, 159.34, 141.38, 133.02, 128.42, 126.98, 125.95, 113.97, 78.16, 76.08, 55.29, 49.34, 47.69, 37.85, 31.44;

FTIR (neat, cm^{-1}) 2953.02, 2931.80, 2858.51, 2837.29, 1716.65, 1612.49, 1514.12, 1454.33, 1350.17, 1303.88, 1249.87, 1176.58, 1138.00, 1053.13, 1033.85, 910.40, 831.32, 732.95, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{23}\text{O}_3$ $[\text{M}+\text{H}]^+$: 311.1647, found 311.1646.

Cis-2-phenethyl-6-*p*-tolylidihydro-2H-pyran-4(3H)-one

$R_f = 0.18$ (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (44 mg, 52%).

^1H NMR (400 MHz, CDCl_3) δ 7.31-7.23 (m, 4H), 7.22-7.15 (m, 5H), 4.58 (dd, $J_1 = 3.2$ Hz, $J_2 = 11$ Hz, 1H), 3.75-3.67 (m, 1H), 2.89-2.72 (m, 2H), 2.64-2.51 (m, 2H), 2.43-2.38 (m, 2H), 2.36 (s, 3H), 2.13-2.03 (m, 1H), 1.93-1.83 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 206.88, 141.39, 137.93, 137.73, 129.25, 128.42, 125.93, 125.58, 78.36, 76.08, 49.42, 47.71, 37.85, 31.43, 21.12;

FTIR (neat, cm^{-1}) 3026.31, 2922.16, 2858.51, 1716.65, 1516.05, 1496.76, 1454.33, 1344.38, 1309.67, 1288.45, 1253.73, 1240.23, 1138.00, 1053.13, 810.10, 748.38, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$: 295.1698, found 295.1720.

Cis-2-(4-chlorophenyl)-6-phenethyldihydro-2H-pyran-4(3H)-one

R_f = 0.23 (10:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (65 mg, 71%).

^1H NMR (400 MHz, CDCl_3) δ 7.38-7.25 (m, 6H), 7.21-7.16 (m, 3H), 4.59 (dd, J_1 = 2.6 Hz, J_2 = 11.6 Hz, 1H), 3.76-3.69 (m, 1H), 2.87-2.75 (m, 2H), 2.62 (dt, J_1 = 1.8 Hz, J_2 = 14.3 Hz, 1H), 2.52-2.36 (m, 3H), 2.14-2.04 (m, 1H), 1.95-1.86 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 206.19, 141.25, 139.40, 133.70, 128.77, 128.46, 128.40, 126.92, 126.01, 77.69, 76.19, 49.35, 47.60, 37.79, 31.45;

FTIR (neat, cm^{-1}) 3026.31, 2947.23, 2926.01, 2860.43, 1716.65, 1492.90, 1454.33, 1344.38, 1300.02, 1278.81, 1238.30, 1139.93, 1087.85, 1055.06, 1014.56, 910.40, 817.82, 748.38, 734.88, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{O}_2\text{Cl}$ $[\text{M}+\text{H}]^+$: 315.1152, found 315.1159.

Typical Procedure for Transformation of (*R*)-2,2,2-Tribromo-1-phenylethanol into (*R*)-Mandelic acid [CAS: 611-71-2] via Free Radical Method

To a solution of (*R*)-2,2,2-tribromo-1-phenylethanol (0.3 g, 0.84 mmol) dissolved in *tert*-BuOH (40 mL) in a 100 mL two-necked round bottom flask equipped with a condenser, was added water (40 mL). After air was bubbled in for 10 minutes, indium (0.39 g, 3.36 mmol) and sodium hydrophosphite monohydrate (0.45 g, 4.2 mmol) was added into the mixture. The reaction mixture was heated to 60 °C and stirred vigorously for 20 h while air was bubbled in. After the reaction, the mixture was basified with 1 N NaOH solution, and washed with diethyl ether (3 x 20 mL). The aqueous layer was acidified with 6 N HCl, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulphate, and filtered. The filtrate was evaporated to obtain the crude product. The crude product was rinsed with a tad of cold CH₂Cl₂ to give colorless crystals (52 mg, 41%). $[\alpha]_{\text{D}}^{21} -137^\circ$ (c = 0.86, EtOH); lit: $[\alpha]_{\text{D}}^{18} -151^\circ$ (c = 1, EtOH) *R*-enantiomer. The corresponding spectroscopic data matched those reported in the literature for (*R*)-Mandelic acid. *R_f* = 0.2 (5:1 methanol/ethyl acetate)

Typical Procedure for Transformation of Carbon Tetrabromide into Carbon Dioxide and Hydrobromic Acid via Free Radical Method

To a solution of carbon tetrabromide (332 mg, 1 mmol) dissolved in 1,2-dimethoxyethane (40 mL) in a 100 mL two-necked round bottom flask equipped with a condenser (from which, a tube was connected into a conic flask containing sat. $\text{Ca}(\text{OH})_2$ solution), was added water (40 mL), indium (344 mg, 3 mmol) and sodium hydrophosphite monohydrate (318 mg, 3 mmol). The reaction mixture was heated to 60 °C and stirred vigorously for 2 h while oxygen was bubbled in. White precipitate was formed slowly in sat. $\text{Ca}(\text{OH})_2$ solution. After the reaction, the mixture was filtered to get filtrate, which was then washed using diethyl ether (3 x 20 mL). The pH of aqueous layer was detected with pH meter. pH dropped sharply from 7.54 to 1.79. Then excess 0.5 M AgNO_3 was added into aqueous solution and brown precipitate was formed. The brown precipitate was collected by filtration and dried over vacuum desiccators overnight (259 mg, 35%).

Typical Procedure for Transformation of Tetrachloro Methane into Carbon Dioxide and Hydrochloric Acid via Free Radical Method

To a solution of tetrachloro methane (154 mg, 1 mmol) dissolved in 1,2-dimethoxyethane (40 mL) in a 100 mL two-necked round bottom flask equipped with

a condenser (from which, a tube was connected into a conic flask containing sat. $\text{Ca}(\text{OH})_2$ solution), was added water (40 mL), indium (344 mg, 3 mmol) and sodium hydrophosphite monohydrate (318 mg, 3 mmol). The reaction mixture was heated to 60 °C and stirred vigorously for 4 h while oxygen was bubbled in. A little of white precipitate was formed slowly in sat. $\text{Ca}(\text{OH})_2$ solution. Then air instead of pure oxygen, was bubbled into the reaction overnight. After reaction, the mixture was filtered to get filtrate, which was evaporated to remove organic solvent and then washed using diethyl ether (3 x 20 mL). The pH value of aqueous layer decreased from 7.54 to 2-3. Then excess 0.5 M AgNO_3 was added into aqueous solution and white precipitate was formed. The white precipitate was collected by filtration and dried over vacuum desiccators overnight (200 mg, 34%).

5.4 Indium(III) Trihalide-Catalyzed Synthesis of *cis*-2,6-Disubstituted-4,4-Dihalotetrahydropyrans via Prins Cyclization

Preparation of substrates 17:¹⁴³

Scheme for preparation of 5-chloro-1-phenylhex-5-en-3-ol:

¹⁴³ (a) Oda, Y.; Matsuo, S.; Saito, K. *Tetrahedron Lett.* **1992**, 33, 97. (b) Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, 49, 172.

Typical procedure for the preparation of 5-chloro-1-phenylhex-5-en-3-ol.

To a mixture of hydrocinnamaldehyde (1.41 g, 10.5 mmol), and zinc powder (1.37 g, 21 mmol, 2 equiv) in water (4 mL), toluene (3.9 mL), and acetic acid was added dropwise 2,3-dichloropropene (2.33 g, 21 mmol, 2 equiv) at 45 °C. The reaction continued to be stirred for 2 hrs. The suspension was filtered through Celite and the precipitate was washed with ether. The combined filtrates were washed with 7% aqueous Na₂CO₃ solution, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography to give **17a** (1.47 g, 66%) as a colorless oil.

5-chloro-1-phenylhex-5-en-3-ol

R_f = 0.73 (4:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (1.47 g, 66%).

¹H NMR (300 MHz, CDCl₃) δ 7.32-7.18 (m, 5H), 5.28 (d, *J* = 0.9 Hz, 1H), 5.24 (d, *J* = 0.8 Hz, 1H), 4.00-3.93 (m, 1H), 2.86-2.68 (m, 2H), 2.50-2.47 (m, 2H), 1.85-1.76 (m, 3H);

¹³C NMR (75 MHz, CDCl₃) δ 141.74, 139.21, 128.42, 128.38, 125.90, 115.19, 68.08, 47.33, 38.16, 31.97;

FTIR (neat, cm^{-1}) 3348.42, 3026.31, 2941.44, 2920.23, 2858.51, 1635.64, 1494.83, 1454.33, 1130.29, 1078.21, 1053.13, 887.26, 748.38, 700.16, 644.22;

HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{OCl}$ $[\text{M}+\text{H}]^+$: 211.0890, found 211.0890.

General scheme for preparation of 5-halo-1-phenylhex-5-en-3-ol:

General procedure for the preparation of 5-halohomoallylic alcohols.

To a mixture of hydrocinnamaldehyde (1.41 g, 10.5 mmol), and tin powder (3.74 g, 31 mmol, 3 equiv) in an ether-water (each 14 mL), were added a few drops of an aqueous HBr solution and 2,3-dihaloropropene¹⁴⁴ (15.8 mmol, 1.5 equiv). The reaction continued to be stirred overnight at rt.. The suspension was filtered through Celite and the precipitate was extracted with ether three times. The combined organic layers were washed with 7% aqueous Na_2CO_3 solution, dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by column chromatography to give **17b-c** as colorless oil.

¹⁴⁴ Preparation of 3-bromo-2-iodopropene, see Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.*, **2004**, 126, 12248.

5-bromo-1-phenylhex-5-en-3-ol

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

The title compound was obtained by flash chromatography (2.1 g, 80%).

^1H NMR (300 MHz, CDCl_3) δ 7.32-7.15 (m, 5H), 5.69 (d, $J = 1.5$ Hz, 1H), 5.54 (d, $J = 1.5$ Hz, 1H), 4.02-3.92 (m, 1H), 2.89-2.64 (m, 2H), 2.59-2.54 (m, 2H), 1.86-1.77 (m, 3H);

^{13}C NMR (75 MHz, CDCl_3) δ 141.73, 130.44, 128.43, 128.39, 125.90, 119.77, 68.55, 49.39, 38.00, 31.99;

FTIR (neat, cm^{-1}) 3400.50, 3030.17, 2908.65, 1629.85, 1454.33, 1419.61, 1195.87, 1116.78, 1045.42, 893.04, 758.02, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{OBr}$ $[\text{M}+\text{H}]^+$: 255.0385, found 255.0385.

5-iodo-1-phenylhex-5-en-3-ol

$R_f = 0.78$ (4:1 hexane/ethyl acetate)

The title compound was obtained by flash chromatography (1.4 g, 45%).

^1H NMR (300 MHz, CDCl_3) δ 7.32-7.15 (m, 5H), 6.16 (d, $J = 0.9$ Hz, 1H), 5.84 (d, $J = 0.9$ Hz, 1H), 3.99-3.89 (m, 1H), 2.89-2.60 (m, 2H), 2.57-2.43 (m, 2H), 1.87-1.77 (m, 3H);

^{13}C NMR (75 MHz, CDCl_3) δ 141.95, 128.92, 128.63, 128.59, 107.55, 69.50, 53.10, 37.96, 32.22;

FTIR (neat, cm^{-1}) 3392.79, 3024.38, 2927.94, 1616.35, 1494.83, 1454.33, 1118.71, 1076.28, 1051.20, 898.83, 748.38, 700.16;

HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{OI}$ $[\text{M}+\text{H}]^+$: 303.0246, found 303.0239.

General reaction scheme for 4,4- dihaloTHP via Prins cyclization:

General Procedure:

To a mixture of 5-halohomoallylic alcohol **17** (1.65 mmol), aldehyde (1.65 mmol), and InX_3 (0.17 mmol) in CH_2Cl_2 (2 mL), was added dropwise TMSX (1.82 mmol) at 0 °C. After stirring overnight at rt, The reaction was then quenched by addition of saturated aqueous NaHCO_3 . The mixture was extracted with ethyl acetate (3×20 mL). The combined organic layer was rinsed with brine. The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue which was purified by flash chromatography eluting with 1 : 50 diethyl ether : hexane solvent system, to afford pure product **15** as a colorless liquid.

Cis-4,4-dichloro-2-phenethyl-6-phenyltetrahydro-2H-pyran

$R_f = 0.78$ (20:1 hexane/ethyl ether)

Cis-4,4-dichloro-2-phenethyl-6-phenyltetrahydro-2H-pyran: The title compound was obtained by flash chromatography (0.28 g, 51%).

^1H NMR (300 MHz, CDCl_3) δ 7.46-7.16 (m, 10H), 4.73 (dd, $J_1 = 2.0$ Hz, $J_2 = 11.0$ Hz, 1H), 3.90-3.81 (m, 1H), 2.86-2.68 (m, 3H), 2.56 (dt, $J_1 = 2.1$ Hz, $J_2 = 13.8$ Hz, 1H), 2.30 (dd, $J_1 = 11.0$ Hz, $J_2 = 13.9$ Hz, 1H), 2.18 (dd, $J_1 = 10.8$ Hz, $J_2 = 13.8$ Hz, 1H), 2.05-1.91 (m, 1H), 1.90-1.77 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3) δ 141.62, 140.56, 128.50, 128.42, 127.87, 125.91, 125.82, 87.53, 75.92, 73.72, 52.94, 50.92, 36.81, 31.54;

FTIR (neat, cm^{-1}) 3026.31, 2924.09, 2866.22, 1494.83, 1454.33, 1155.36, 1089.78, 1062.78, 775.38, 754.17, 698.23, 597.93, 561.29;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{21}\text{OCl}_2$ $[\text{M}+\text{H}]^+$: 335.0969, found 335.0971.

Cis-4,4-dibromo-2-phenethyl-6-phenyltetrahydro-2H-pyran

$R_f = 0.80$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.45 g, 65%).

^1H NMR (300 MHz, CDCl_3) δ 7.39-7.16 (m, 10H), 4.76 (dd, $J_1 = 1.9$ Hz, $J_2 = 10.7$ Hz, 1H), 3.94-3.86 (m, 1H), 2.91 (dt, $J_1 = 2.1$ Hz, $J_2 = 14.3$ Hz, 1H), 2.87-2.80 (m, 1H), 2.78-2.70 (m, 2H), 2.51 (dd, $J_1 = 10.7$ Hz, $J_2 = 14.2$ Hz, 1H), 2.40 (dd, $J_1 = 10.6$ Hz, $J_2 = 14.1$ Hz, 1H), 2.03-1.94 (m, 1H), 1.88-1.87 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3) δ 141.63, 140.37, 128.53, 128.44, 127.89, 125.95, 125.86, 76.61, 74.46, 64.56, 55.71, 53.61, 36.61, 31.59;

FTIR (neat, cm^{-1}) 3026.31, 2916.37, 2864.29, 1494.83, 1454.33, 1153.43, 1089.78, 1060.85, 754.17, 698.23, 557.43;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{21}\text{O}^{81}\text{Br}_2$ $[\text{M}+\text{H}]^+$: 426.9918, found 426.9939.

Cis-4,4-diiodo-2-phenethyl-6-phenyltetrahydro-2H-pyran

$R_f = 0.70$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.78 g, 91%).

^1H NMR (400 MHz, CDCl_3) δ 7.38-7.16 (m, 10H), 4.64 (dd, $J_1 = 1.6$ Hz, $J_2 = 10.3$ Hz, 1H), 3.84-3.76 (m, 1H), 2.91 (dt, $J_1 = 1.9$ Hz, $J_2 = 12.7$ Hz, 1H), 2.86-2.68 (m, 3H), 2.50 (dd, $J_1 = 10.3$ Hz, $J_2 = 14.4$ Hz, 1H), 2.39 (dd, $J_1 = 10.2$ Hz, $J_2 = 14.3$ Hz, 1H), 2.05-1.94 (m, 1H), 1.90-1.78 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 141.61, 139.84, 128.46, 128.41, 127.79, 125.91, 125.86, 77.74, 75.59, 60.09, 57.86, 35.90, 31.57, 0.63;

FTIR (neat, cm^{-1}) 3026.31, 2949.16, 2926.01, 2860.43, 1492.90, 1452.40, 1143.79, 1087.85, 1058.92, 908.47, 752.24, 732.95, 698.23, 551.64, 499.56;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{21}\text{OI}_2$ $[\text{M}+\text{H}]^+$: 518.9682, found 518.9656.

Cis-4,4-diiodo-2-(pentan-3-yl)-6-phenyltetrahydro-2H-pyran

$R_f = 0.84$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.68 g, 80%).

^1H NMR (500 MHz, CDCl_3) δ 7.32-7.15 (m, 5H), 3.59-3.52 (m, 1H), 3.50-3.45 (m, 1H), 2.83-2.75 (m, 1H), 2.70-2.62 (m, 3H), 2.29-2.20 (m, 2H), 1.89-1.84 (m, 1H), 1.72-1.67 (m, 1H), 1.51-1.36 (m, 4H), 1.29-1.22 (m, 1H), 0.90 (q, $J = 7.4$ Hz, 6H);
 ^{13}C NMR (125 MHz, CDCl_3) δ 141.80, 128.40, 128.38, 125.85, 77.89, 75.45, 58.68, 55.75, 44.19, 36.06, 31.69, 21.48, 21.41, 11.24, 10.97, 3.67;

FTIR (neat, cm^{-1}) 2960.27, 2930.86, 2873.42, 1496.29, 1453.86, 1146.69, 1075.81, 748.87, 734.40, 698.72, 519.82, 496.67;

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{27}\text{OI}_2$ $[\text{M}+\text{H}]^+$: 513.0151, found 513.0142.

Cis-4,4-diiodo-2,6-diphenyltetrahydro-2H-pyran

$R_f = 0.64$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.73 g, 81%).

^1H NMR (400 MHz, CDCl_3) δ 7.34-7.15 (m, 4H), 3.62-3.54 (m, 2H), 2.88-2.76 (m, 2H), 2.74-2.61 (m, 4H), 2.29 (dd, $J_1 = 10.2$ Hz, $J_2 = 14.4$ Hz, 2H), 1.98-1.84 (m, 2H), 1.79-1.66 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3) δ 141.64, 128.41, 125.92, 75.37, 58.46, 35.98, 31.72, 1.39;

FTIR (neat, cm^{-1}) 3024.38, 2947.23, 2858.51, 1494.83, 1452.40, 1143.79, 1070.49, 908.47, 734.88, 696.30, 528.50;

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{25}\text{OI}_2$ $[\text{M}+\text{H}]^+$: 546.9995, found 547.0006.

Cis-2-cyclohexyl-4,4-diiodo-6-phenyltetrahydro-2H-pyran

$R_f = 0.80$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.74 g, 86%).

^1H NMR (500 MHz, CDCl_3) δ 7.35-7.20 (m, 5H), 3.59-3.53 (m, 1H), 3.34-3.28 (m, 1H), 2.87-2.79 (m, 1H), 2.77-2.64 (m, 3H), 2.33-2.24 (m, 2H), 2.10-1.97 (m, 1H), 1.95-1.87 (m, 1H), 1.82-1.64 (m, 5H), 1.52-1.46 (m, 1H), 1.31-1.15 (m, 3H), 1.13-1.05 (m, 2H).;

^{13}C NMR (125 MHz, CDCl_3) δ 141.73, 128.42, 128.37, 125.85, 80.37, 75.16, 58.71, 56.19, 41.52, 36.00, 31.65, 29.01, 28.77, 26.43, 26.01, 25.90, 3.41;

FTIR (neat, cm^{-1}) 2924.11, 2851.30, 1495.81, 1450.48, 1147.17, 1091.24, 1063.27, 908.00, 733.92, 698.24, 516.06;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{27}\text{OI}_2$ $[\text{M}+\text{H}]^+$: 525.0151, found 525.0127.

Cis-4,4-diiodo-2-(naphthalene-1-yl)-6-phenyltetrahydro-2H-pyran

$R_f = 0.56$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.90 g, 96%).

^1H NMR (300 MHz, CDCl_3) δ 8.01 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 7.7$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 7.1$ Hz, 1H), 7.60-7.44 (m, 3H), 7.30-7.16 (m, 5H), 5.39 (d, $J = 9.8$ Hz, 1H), 4.02-3.93 (m, 1H), 3.17-3.08 (m, 1H), 2.87-2.71 (m, 3H), 2.55-2.44 (m, 2H), 2.11-1.98 (m, 1H), 1.96-1.84 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3) δ 141.63, 135.45, 133.64, 129.87, 128.98, 128.42, 128.23, 126.37, 125.93, 125.62, 125.55, 123.15, 122.52, 76.09, 75.10, 59.31, 58.15, 36.01, 31.63, 1.09;

FTIR (neat, cm^{-1}) 3059.61, 3025.37, 2949.67, 2927.00, 2861.42, 1495.33, 1453.37, 1143.80, 1087.38, 1059.41, 908.00, 799.50, 777.32, 731.51, 698.24, 504.39;

HRMS (ESI) m/z calculated for $\text{C}_{23}\text{H}_{23}\text{OI}_2$ $[\text{M}+\text{H}]^+$: 568.9838, found 568.9847.

Cis-4,4-diiodo-2-(4-methoxyphenyl)-6-phenyltetrahydro-2H-pyran

$R_f = 0.37$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.68 g, 75%).

^1H NMR (400 MHz, CDCl_3) δ 7.31-7.23 (m, 4H), 7.21-7.16 (m, 3H), 6.89 (d, $J = 8.7$ Hz, 2H), 4.58 (d, $J = 9.4$ Hz, 1H), 3.83-3.73 (m, 1H), 3.80 (s, 3H), 2.89-2.65 (m, 4H), 2.50 (dd, $J_1 = 4.3$ Hz, $J_2 = 14.4$ Hz, 1H), 2.38 (dd, $J_1 = 4.2$ Hz, $J_2 = 4.3$ Hz, 1H), 2.03-1.92 (m, 1H), 1.87-1.76 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 159.21, 141.62, 132.01, 128.40, 127.24, 125.89, 113.85, 77.44, 75.60, 60.02, 57.86, 55.31, 35.90, 31.56, 0.93;

FTIR (neat, cm^{-1}) 3024.89, 2951.11, 2930.86, 2861.42, 1612.50, 1509.79, 1453.37, 1303.89, 1249.88, 1175.14, 1144.76, 1059.89, 908.96, 825.54, 733.44, 698.72, 541.52;
HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{23}\text{O}_2\text{I}_2$ $[\text{M}+\text{H}]^+$: 548.9788, found 548.9758.

Cis-4,4-diiodo-2-phenethyl-6-p-tolyltetrahydro-2H-pyran

$R_f = 0.73$ (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.75 g, 85%).

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.13 (m, 9H), 4.60 (d, $J = 9.6$ Hz, 1H), 3.82-3.74 (m, 1H), 2.90-2.65 (m, 4H), 2.49 (dd, $J_1 = 10.3$ Hz, $J_2 = 14.4$ Hz, 1H), 2.38 (dd, $J_1 = 10.3$ Hz, $J_2 = 14.4$ Hz, 1H), 2.35 (s, 3H), 2.03-1.93 (m, 1H), 1.86-1.73 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 141.63, 137.52, 136.88, 129.11, 128.40, 125.86, 77.66, 75.55, 60.09, 57.89, 35.90, 31.56, 21.14, 0.93;

FTIR (neat, cm^{-1}) 3024.89, 2950.15, 2920.25, 2860.94, 1514.62, 1495.33, 1453.37, 1144.76, 1064.72, 908.96, 812.04, 734.40, 698.72, 521.75;

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{23}\text{OI}_2$ $[\text{M}+\text{H}]^+$: 532.9838, found 532.9802.

Cis-2-(4-chlorophenyl)-4,4-diiodo-6-phenethyltetrahydro-2H-pyran

R_f = 0.60 (20:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.7 g, 77%).

^1H NMR (400 MHz, CDCl_3) δ 7.35-7.15 (m, 9H), 4.61 (dd, $J_1 = 1.5$ Hz, $J_2 = 10.3$ Hz, 1H), 3.82-3.74 (m, 1H), 2.86 (dt, $J_1 = 2.0$ Hz, $J_2 = 14.4$ Hz, 1H), 2.83-2.65 (m, 3H), 2.43 (dd, $J_1 = 10.4$ Hz, $J_2 = 14.4$ Hz, 1H), 2.37 (dd, $J_1 = 10.4$ Hz, $J_2 = 14.4$ Hz, 1H), 2.04-1.92 (m, 1H), 1.87-1.77 (m, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 141.49, 138.32, 133.49, 128.60, 128.43, 128.38, 127.22, 125.95, 77.06, 75.65, 59.92, 57.70, 35.83, 31.56, -0.30;

FTIR (neat, cm^{-1}) 3025.37, 2950.15, 2928.45, 2861.90, 1490.99, 1453.37, 1144.76, 1088.34, 1063.27, 1014.57, 908.00, 821.20, 730.54, 698.72, 510.66;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{OClI}_2$ $[\text{M}+\text{H}]^+$: 552.9292, found 552.9174.

***Cis*-4,4-diiodo-2-(4-nitrophenyl)-6-phenethyltetrahydro-2*H*-pyran**

$R_f = 0.34$ (10:1 hexane/ethyl ether)

The title compound was obtained by flash chromatography (0.78 g, 84%).

^1H NMR (300 MHz, CDCl_3) δ 8.22 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.6$ Hz, 2H), 7.33-7.16 (m, 5H), 4.74 (d, $J = 9.2$ Hz, 1H), 3.87-3.78 (m, 1H), 2.91 (dt, $J_1 = 2.0$ Hz, $J_2 = 14.4$ Hz, 1H), 2.83-2.70 (m, 3H), 2.47-2.34 (m, 2H), 2.08-1.96 (m, 1H), 1.92-1.80 (m, 1H);

^{13}C NMR (75 MHz, CDCl_3) δ 147.39, 146.97, 141.33, 128.48, 128.35, 126.52, 126.02, 123.69, 76.78, 75.80, 59.59, 57.49, 35.74, 31.59, -1.83;

FTIR (neat, cm^{-1}) 3025.37, 2950.15, 2928.93, 2861.90, 1602.86, 1519.92, 1495.33, 1346.81, 1144.76, 1062.79, 908.96, 850.13, 749.35, 733.92, 698.24, 508.25;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{I}_2$ $[\text{M}+\text{H}]^+$: 563.9533, found 563.9551.

5.5 Direct Arylation of Cyclic Enamides with Aryl Boronic Acids via Pd(II)–Catalyzed C-H Activation

Preparation of substrates:¹⁴⁵

¹⁴⁵ (a) Zhang, Z.-G.; Zhu, G.-X.; Jiang, Q.-Z.; Xiao, D.-M.; Zhang, X.-M. *J. Org. Chem.* **1999**, *64*, 1774. (b) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (c) Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; De Vries, A. H. M.;

General reaction scheme for preparation of cyclic enamides:

General procedure for the preparation of oxime .

A mixture of cyclic ketone (41 mmol), NaOAc (4.04 g, 49.2 mmol, 1.2 equiv) and hydroxylamine hydrochloride (3.42 g, 49.2 mmol, 1.2 equiv) in methanol (20 mL) was stirred for 2 h at 60 °C. The reaction mixture was allowed to be cooled to r.t., before diluting with EA (75 mL). 2N NaOH (20 mL) was added prior to removal of solvents in vacuo. The residue was redissolved in water (60 mL) and EA (120 mL).

De Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, 344, 1003. (d) Zhao, H. ; Vandenbossche, C. P. ; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, 10, 505.

The aqueous layer was extracted with additional EA (70 mL). The combined organic layer was washed with brine (70 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to afford the ketoxime for next step directly.

General procedure for preparation of acetamide.

To a solution of oxime and acetic anhydride (12 mL, 12.6 g, 123 mmol, 3 equiv) in DMF (60 mL) was added iron powder (6.9 g, 123 mmol, 3 equiv), the reaction was initiated by adding 2 drops of chlorotrimethylsilane under nitrogen. The reaction mixture was stirred at 70 °C overnight. TLC showed that the reaction was complete. After being cooled to r.t., the reaction mixture was diluted with water and extracted with EA, washed with water, brine and dried over Mg₂SO₄. Final product was obtained after purified by column chromatography eluting with 1 : 1 EA : Hex solvent system.

General reaction scheme for cross-coupling of cyclic enamides with arylboronic acids:

General Procedure :

Cyclic enamide **18** (0.27 mmol), Pd(OAc)₂ (6.7 mg, 0.03 mmol, 10 mol%), Cu(OTf)₂ (0.2 g, 0.54 mmol, 2 equiv), K₂CO₃ (75 mg, 0.54 mmol, 2 equiv), arylboronic acid **19** (0.54 mmol, 2 equiv) and anhydrous 1,4-dioxane (4 mL) were added to a 8 mL vial. The vial was then capped tightly and stirred for 10 minutes at room temperature, and

Table 4.2, entry 2:

$R_f = 0.48$ (1:1 hexane/ethyl acetate)

20b and **21b** were obtained as a mixture, which is inseparable by flash chromatography (51 mg, 60%).

N-(3, 4-dihydro-2,2'-binaphthyl-1-yl)acetamide (**3b**):

^1H NMR (500 MHz, DMSO) δ 9.13 (s, 1H), 8.01-7.10 (m, 11H), 2.92 (t, $J = 7.8$ Hz, 2H), 2.81 (t, $J = 7.8$ Hz, 2H), 1.89 (s, 3H);

^{13}C NMR (75 MHz, DMSO) δ 169.19, 138.30, 136.48, 135.36, 133.99, 133.31, 132.88, 132.00, 129.09, 127.82, 127.38, 127.15, 127.09, 126.25, 126.13, 125.91, 125.78, 125.60, 122.94, 29.21, 27.30, 22.44;

FTIR (neat, cm^{-1}) 3234.62, 1653.00, 1629.85, 1529.55, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 314.1545, found 314.1543.

N-(2,2'-binaphthyl-1-yl)acetamide (**21b**)

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 312.1388, found 312.1391.

Table 4.2, entry 3:

$R_f = 0.70$ (1:1 hexane/ethyl acetate)

N-(2-*o*-tolyl-3, 4-dihydronaphthalen-1-yl)acetamide (**20c**):

¹³C NMR (100 MHz, DMSO) δ 168.53, 140.51, 135.73, 135.35, 134.75, 133.15, 129.84, 129.03, 127.53, 127.15, 126.95, 126.86, 126.18, 125.25, 122.88, 29.08, 27.41, 22.35, 19.61;

HRMS (ESI) m/z calculated for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1545, found 278.1538.

HRMS (ESI) m/z calculated for $C_{19}H_{18}NO$ $[M+H]^+$: 276.1388, found 276.1380.

20d + **21d** (20d : 21d) = (80 : 20)

20d and **21d** were obtained as a mixture, which is inseparable by flash chromatography (50 mg, 67%).

¹H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 7.27-7.10 (m, 8H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.31 (s, 3H), 1.89 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.21, 137.66, 136.15, 135.20, 134.25, 133.46, 128.76, 128.53, 128.23, 127.02, 126.91, 126.19, 122.81, 29.16, 27.25, 22.43, 20.77;
FTIR (neat, cm^{-1}) 3250.05, 1654.92, 1625.99, 1521.84, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 278.1545, found 278.1548.

N-(2-*o*-tolynaphthalen-1-yl)acetamide (**21d**)

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 276.1388, found 276.1391.

Table 4.2, entry 5:

R_f = 0.70 (1:1 hexane/ethyl acetate)

20e and **21e** were obtained as a mixture, which is inseparable by flash chromatography (53 mg, 70%).

N-(2-*m*-tolyl-3,4-dihydronaphthalen-1-yl)acetamide (**20e**):

^1H NMR (400 MHz, DMSO) δ 9.02 (s, 1H), 7.27-7.01 (m, 8H), 2.85 (t, J = 7.9 Hz, 2H), 2.66 (t, J = 7.9 Hz, 2H), 2.31 (s, 3H), 1.88 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.25, 140.60, 136.95, 135.26, 134.37, 133.42, 128.53, 127.85, 127.71, 127.59, 127.08, 127.00, 126.22, 124.23, 122.90, 29.17, 27.27, 22.38, 21.09;

FTIR (neat, cm^{-1}) 3221.12, 1654.92, 1624.06, 1602.85, 1523.76, 721.38.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 278.1545, found 278.1539.

N-(2-*o*-tolynaphthalen-1-yl)acetamide (**21e**)

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 276.1388, found 276.1389.

Table 4.2, entry 6:

$R_f = 0.52$ (1:1 hexane/ethyl acetate)

20f and **21f** were obtained as a mixture, which is inseparable by flash chromatography (52 mg, 57%).

N-(2-(biphenyl-4-yl)-3,4-dihydronaphthalen-1-yl)acetamide (**20f**):

^1H NMR (400 MHz, DMSO) δ 9.12 (s, 1H), 7.80-7.65 (m, 4H), 7.60-7.54 (m, 1H), 7.52-7.43 (m, 4H), 7.40-7.32 (m, 1H), 7.23-7.12 (m, 3H), 2.88 (t, $J = 7.8$ Hz, 2H), 2.71 (t, $J = 7.8$ Hz, 2H), 1.92 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.29, 139.76, 139.72, 138.59, 135.32, 133.68, 133.31, 128.97, 128.93, 128.81, 127.70, 127.40, 127.10, 126.48, 126.22, 126.19, 122.93, 29.01, 27.23, 22.46;

FTIR (neat, cm^{-1}) 3269.34, 1660.71, 1622.13, 1514.12, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$: 340.1701, found 340.1698.

N-(2-(biphenyl-4-yl)-naphthalen-1-yl)acetamide (**21f**)

HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 338.1545, found 338.1535.

Table 4.2, entry 7:

$R_f = 0.78$ (1:1 hexane/ethyl acetate)

20g and **21g** were obtained as a mixture, which is inseparable by flash chromatography (54 mg, 67%).

N-(2-(4-chlorophenyl)-3, 4-dihydronaphthalen-1-yl)acetamide (**20g**): The title compounds were obtained as an off-white solid (54 mg, 67%).

^1H NMR (300 MHz, DMSO) δ 9.07 (s, 1H), 7.65-7.30 (m, 4H), 7.30-7.00 (m, 4H), 2.86 (t, $J = 7.7$ Hz, 2H), 2.65 (t, $J = 7.7$ Hz, 2H), 1.89 (s, 3H);

^{13}C NMR (75 MHz, DMSO) δ 169.15, 139.54, 135.33, 133.05, 131.32, 129.04, 128.91, 128.16, 127.97, 127.26, 127.13, 126.24, 122.94, 28.84, 27.11, 22.41;

FTIR (neat, cm^{-1}) 3282.84, 1656.85, 1622.13, 1517.98, 769.60, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{17}\text{NOCl}$ $[\text{M}+\text{H}]^+$: 298.0999, found 298.0986.

N-(2-(4-chlorophenyl)naphthalen-1-yl)acetamide (**21g**)

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{15}\text{NOCl}$ $[\text{M}+\text{H}]^+$: 296.0842, found 296.0846.

Table 4.2, entry 8:

$R_f = 0.50$ (1:1 hexane/ethyl acetate)

20h and **21h** were obtained as a mixture, which is inseparable by flash chromatography (53 mg, 64%).

N-(2-(3-nitrophenyl)-3, 4-dihydronaphthalen-1-yl)acetamide (**20h**):

¹³C NMR (75 MHz, DMSO) δ 169.18, 147.58, 142.44, 135.56, 133.69, 132.70, 131.93, 130.14, 129.64, 127.71, 127.25, 126.34, 123.16, 121.77, 121.62, 28.53, 27.05, 22.39;

HRMS (ESI) m/z calculated for $C_{18}H_{17}N_2O_3$ $[M+H]^+$: 309.1239, found 309.1241.

HRMS (ESI) m/z calculated for $C_{18}H_{15}N_2O_3$ $[M+H]^+$: 307.1083, found 307.1087.

20i and **21i** were obtained as a mixture, which is inseparable by flash chromatography (54 mg, 68%).

¹H NMR (400 MHz, DMSO) δ 9.04 (s, 1H), 7.30-6.81 (m, 8H), 3.74 (s, 3H), 2.85 (t, *J* = 7.9 Hz, 2H), 2.66 (t, *J* = 7.9 Hz, 2H), 1.89 (s, 3H);

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FTIR (neat, cm^{-1}) 3232.70, 1660.71, 1624.06, 1593.20, 1583.56, 1521.84, 1220.94, 1174.65, 1035.77, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 294.1494, found 294.1489.

N-(2-(3-methoxyphenyl)naphthalen-1-yl)acetamide (**21i**)

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 292.1338, found 292.1338.

Table 4.2, entry 10:

$R_f = 0.51$ (1:1 hexane/ethyl acetate)

20j and **21j** were obtained as a mixture, which is inseparable by flash chromatography (54 mg, 68%).

N-(2-(4-methoxyphenyl)-3,4-dihydronaphthalen-1-yl)acetamide (**20j**):

^1H NMR (300 MHz, DMSO) δ 9.00 (s, 1H), 7.30-6.70 (m, 8H), 3.77 (s, 3H), 2.85 (t, $J = 7.7$ Hz, 2H), 2.64 (t, $J = 7.7$ Hz, 2H), 1.90 (s, 3H);

^{13}C NMR (75 MHz, DMSO) δ 169.22, 158.22, 135.12, 134.00, 133.58, 132.74, 130.00, 128.41, 127.80, 127.02, 126.77, 122.72, 113.39, 55.06, 29.21, 27.28, 22.45;
FTIR (neat, cm^{-1}) 3275.13, 1656.85, 1606.70, 1512.19, 1246.02, 1178.51, 1033.85, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 294.1494, found 294.1482.

N-(2-(4-methoxyphenyl)naphthalen-1-yl)acetamide (**21j**)

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 292.1338, found 292.1333.

Table 4.3, entry 1:

$R_f = 0.41$ (1:1 hexane/ethyl acetate)

20k and **21k** were obtained as a mixture, which is inseparable by flash chromatography (65 mg, 82%).

N-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)acetamide (**20k**):

^1H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 7.45-7.20 (m, 5H), 7.05 (d, $J = 8.5$ Hz, 1H), 6.80 (s, 1H), 6.74 (dd, $J = 8.5, 2.3$ Hz, 1H), 3.76 (s, 2H), 2.84 (t, $J = 7.9$ Hz, 2H), 2.65 (t, $J = 7.9$ Hz, 2H), 1.87 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.16, 158.46, 140.86, 137.14, 131.42, 128.40, 127.92, 127.09, 126.65, 126.28, 124.38, 112.92, 111.25, 55.08, 29.10, 27.67, 22.43;

FTIR (neat, cm^{-1}) 3192.19, 1649.14, 1597.06, 1523.76, 1240.23, 1143.79, 1033.85;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 294.1494, found 294.1491.

N-(6-methoxy-2-phenylnaphthalen-1-yl)acetamide (**21k**)

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 292.1338, found 292.1335.

Table 4.3, entry 2:

$R_f = 0.45$ (1:3 hexane/ethyl acetate)

20l and **21l** were obtained as a mixture, which is inseparable by flash chromatography (55 mg, 63%).

N-(6,7-dimethoxy-2-phenyl-3, 4-dihydronaphthalen-1-yl)acetamide (**20l**):

^1H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 7.40-7.32 (m, 5H), 6.86 (s, 1H), 6.70 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.79 (t, $J = 7.9$ Hz, 2H), 2.63 (t, $J = 7.9$ Hz, 2H), 1.88 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.69, 148.56, 147.38, 141.42, 132.17, 128.87, 128.81, 128.42, 127.55, 127.14, 126.64, 112.02, 108.49, 56.28, 55.80, 29.93, 27.39, 22.91;

FTIR (neat, cm^{-1}) 3238.48 (weak), 1649.14, 1604.77, 1508.33, 1288.45, 1259.52, 1149.57, 1047.35, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 324.1600, found 324.1594.

N-(6,7-dimethoxy-2-phenylnaphthalen-1-yl)acetamide (**21l**)

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 322.1443, found 322.1443.

Table 4.3, entry 3:

$R_f = 0.27$ (1:1 hexane/ethyl acetate)

20m and **21m** were obtained as a mixture, which is inseparable by flash chromatography (51 mg, 65%).

N-(5,7-dimethyl-2-phenyl-3, 4-dihydronaphthalen-1-yl)acetamide (**20m**):

^1H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 7.49-7.22 (m, 5H), 6.88 (s, 1H), 6.82 (s, 1H), 2.75 (t, $J = 7.8$ Hz, 2H), 2.64 (t, $J = 7.8$ Hz, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 1.87 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.16, 140.89, 134.10, 134.01, 133.66, 133.27, 130.62, 129.78, 128.76, 127.94, 127.07, 126.84, 121.49, 28.95, 23.00, 22.46, 20.92, 19.00;

FTIR (neat, cm^{-1}) 3234.62, 1647.21, 1600.92, 1537.27, 763.81, 723.31;

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$: 292.1701, found 292.1697.

N-(5,7-dimethyl-2-phenylnaphthalen-1-yl)acetamide (**21m**)

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 290.1545, found 290.1549.

Table 4.3, entry 4:

$R_f = 0.51$ (1:1 hexane/ethyl acetate)

20n and **21n** were obtained as a mixture, which is inseparable by flash chromatography (52 mg, 69%).

N-(4-methyl-2-phenyl-3,4-dihydronaphthalen-1-yl)acetamide (**20n**):

^1H NMR (400 MHz, DMSO) δ 9.05 (s, 1H), 7.49-7.14 (m, 9H), 3.15-2.95 (m, 1H), 2.92-2.79 (m, 1H), 2.50-2.36 (m, 1H), 1.87 (s, 3H), 1.26 (d, $J = 6.9$ Hz, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.27, 140.92, 140.29, 132.66, 128.01, 127.38, 127.11, 126.93, 126.12, 125.75, 123.06, 36.86, 31.45, 22.44, 19.62;

FTIR (neat, cm^{-1}) 3234.62, 1664.57, 1600.92, 1537.27, 723.31;

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 278.1545, found 278.1546.

N-(4-methyl-2-phenyl-3, 4-dihydronaphthalen-1-yl)acetamide (**21n**)

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 276.1388, found 276.1393.

Table 4.3, entry 5:

$R_f = 0.49$ (1:1 hexane/ethyl acetate)

N-(3-phenyl-2*H*-chromen-4-yl)acetamide (**20o**):

The title compound was obtained by flash chromatography (53 mg, 74%).

^1H NMR (400 MHz, DMSO) δ 9.21 (s, 1H), 7.49-7.29 (m, 5H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 7.6$ Hz, 1H), 6.94 (t, $J = 7.6$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 5.07 (s, 2H), 1.92 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.46, 153.81, 135.96, 129.25, 128.34, 127.82, 127.76, 127.17, 126.21, 123.78, 122.31, 121.30, 115.46, 68.55, 22.45;

FTIR (neat, cm^{-1}) 3234.62, 1664.57, 1600.92, 1537.27, 1209.37, 1037.70, 1004.91, 723.31;

HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 266.1181, found 266.1179.

Table 4.3, entry 6:

$R_f = 0.75$ (1:1 hexane/ethyl acetate)

N-(6-chloro-3-phenyl-2*H*-chromen-4-yl)acetamide (**20p**):

The title compound was obtained by flash chromatography (58 mg, 71%).

^1H NMR (400 MHz, DMSO) δ 9.26 (s, 1H), 7.43-7.34 (m, 5H), 7.22 (d, $J = 7.7$ Hz, 1H), 7.05 (s, 1H), 6.90 (d, $J = 7.7$ Hz, 1H), 5.11 (s, 2H), 1.93 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.61, 152.57, 135.50, 129.22, 128.73, 128.40, 128.13, 127.17, 125.17, 124.11, 123.07, 117.34, 68.74, 22.46;

FTIR (neat, cm^{-1}) 3234.62, 1664.57, 1600.92, 1537.27, 1209.37, 1089.78, 1004.91, 763.81, 723.31, 702.09;

HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{Cl}$ $[\text{M}+\text{H}]^+$: 300.0791, found 300.0788.

Table 4.3, entry 7:

$R_f = 0.62$ (1:1 hexane/ethyl acetate)

N-(6-methyl-3-phenyl-2*H*-chromen-4-yl)acetamide (**20q**):

The title compound was obtained by flash chromatography (53 mg, 70%).

^1H NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.41-7.28 (m, 5H), 6.98 (d, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.76 (d, J = 8.1 Hz, 1H), 5.02 (s, 2H), 2.23 (s, 3H), 1.92 (s, 3H);
 ^{13}C NMR (100 MHz, DMSO) δ 169.39, 151.68, 136.10, 129.91, 129.61, 128.29, 127.79, 127.73, 127.12, 126.28, 123.93, 122.14, 115.24, 68.53, 22.47, 20.43;
 FTIR (neat, cm^{-1}) 3248.13, 1654.92, 1631.78, 1523.76, 1209.37, 1012.63, 721.38;
 HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 280.1338, found 280.1337.

Table 4.3, entry 8:

R_f = 0.68 (1:1 hexane/ethyl acetate)

N-(6-fluoro-3-phenyl-2*H*-chromen-4-yl)acetamide (**20r**):

The title compound was obtained by flash chromatography (44 mg, 57%).

^1H NMR (400 MHz, DMSO) δ 9.26 (s, 1H), 7.43-7.31 (m, 5H), 7.04-6.97 (m, 1H), 6.92-6.84 (m, 2H), 5.07 (s, 2H), 1.93 (s, 3H);
 ^{13}C NMR (100 MHz, DMSO) δ 169.60, 156.98 (d, J = 234.8 Hz), 149.88, 135.16, 129.18, 128.39, 128.06, 127.17, 125.61 (d, J = 2.0 Hz), 123.94 (d, J = 8.0 Hz), 116.73 (d, J = 8.2 Hz), 115.30 (d, J = 23.2 Hz), 110.08 (d, J = 24.9 Hz), 68.73, 22.45;
 FTIR (neat, cm^{-1}) 3153.61, 1635.64, 1622.13, 1531.48, 1517.98, 1280.73, 1249.87, 1172.72, 1014.56, 721.38;
 HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{F}$ $[\text{M}+\text{H}]^+$: 284.1087, found 284.1090.

Table 4.3, entry 9:

$R_f = 0.45$ (1:3 hexane/ethyl acetate)

N-(6, 7-dimethoxy-2, 2-dimethyl-3-phenyl-2*H*-chromen-4-yl)acetamide (**20s**):

The title compound was obtained by flash chromatography (86 mg, 90%).

^1H NMR (400 MHz, DMSO) δ 8.78 (s, 1H), 7.40-7.25 (m, 3H), 7.17 (d, $J = 7.2$ Hz, 2H), 6.58 (d, $J = 11.6$ Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 1.72 (s, 3H), 1.34 (s, 6H);

^{13}C NMR (100 MHz, DMSO) δ 168.75, 150.12, 146.95, 142.87, 136.47, 133.82, 128.59, 127.91, 127.20, 126.24, 113.22, 108.06, 101.25, 78.66, 56.37, 55.70, 26.52, 22.28;

FTIR (neat, cm^{-1}) 3259.70, 1651.31, 1643.35, 1616.35, 1504.48, 1361.74, 1292.31, 1261.45, 1203.58, 1161.15, 1138.00, 1080.14, 999.13, 860.25, 752.24, 725.23, 698.23, 590.22;

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 354.1705, found 354.1696.

5.6 Palladium–Catalyzed Direct Arylation of Cyclic Enamides with Arylsilane via sp^2 C-H Activation

Preparation of substrates:¹⁴⁵

General reaction scheme for preparation of cyclic enamides:

General procedure for the preparation of oxime .

A mixture of cyclic ketone (41 mmol), NaOAc (4.04 g, 49.2 mmol, 1.2 equiv) and hydroxylamine hydrochloride (3.42 g, 49.2 mmol, 1.2 equiv) in methanol (20 mL) was stirred for 2 h at 60 °C. The reaction mixture was allowed to be cooled to r.t., before diluting with EA (75 mL). 2N NaOH (20 mL) was added prior to removal of solvents in vacuo. The residue was redissolved in water (60 mL) and EA (120 mL). The aqueous layer was extracted with additional EA (70 mL). The combined organic layer was washed with brine (70 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to afford the ketoxime for next step directly.

General procedure for preparation of acetamide.

To a solution of oxime and acetic anhydride (12 mL, 12.6 g, 123 mmol, 3 equiv) in DMF (60 mL) was added iron powder (6.9 g, 123 mmol, 3 equiv), the reaction was initiated by adding 2 drops of chlorotrimethylsilane under nitrogen. The reaction mixture was stirred at 70 °C overnight. TLC showed that the reaction was complete. After being cooled to r.t., the reaction mixture was diluted with water and extracted with EA, washed with water, brine and dried over Mg₂SO₄. Final product was obtained after purified by column chromatography eluting with EA : Hex (1/2, 1)solvent system.

General reaction scheme for cross-coupling of cyclic enamides with arylsiloxanes:

General Procedure:

Cyclic enamide **18** (0.27 mmol), Pd(OAc)₂ (6.7 mg, 0.03 mmol, 10 mol%), arylsiloxane **26** (0.81 mmol, 3 equiv) and anhydrous 1,4-dioxane (4 mL) were added to a 8 mL vial. Then AgF (0.1 g, 0.81 mmol, 3 equiv) was added into the vial. The vial was capped tightly and stirred for 10 minutes at room temperature, and then heated for 16 h at 80 °C in an oil bath and the progress of the reaction was monitored by thin-layer chromatography. After removal of the solvent, the residue was purified by flash chromatography to give pure products **20**.

Table 4.5, entry 1:

R_f = 0.49 (1:1 hexane/ethyl acetate)

N-(3-phenyl-2*H*-chromen-4-yl)acetamide (**20fa**): The title compound was obtained by flash chromatography (52 mg, 73%).

¹H NMR (400 MHz, DMSO) δ 9.21 (s, 1H), 7.49-7.29 (m, 5H), 7.18 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.07 (s, 2H), 1.92 (s, 3H);

¹³C NMR (100 MHz, DMSO) δ 169.46, 153.81, 135.96, 129.25, 128.34, 127.82, 127.76, 127.17, 126.21, 123.78, 122.31, 121.30, 115.46, 68.55, 22.45;

FTIR (neat, cm⁻¹) 3234.62, 1664.57, 1600.92, 1537.27, 1209.37, 1037.70, 1004.91, 723.31;

HRMS (ESI) m/z calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181, found 266.1179.

Table 4.5, entry 3:

R_f = 0.45 (2:1 hexane/ethyl acetate)

N-(3-(4-methoxyphenyl)-2*H*-chromen-4-yl)acetamide (**20fc**): The title compound was obtained by flash chromatography (41 mg, 51%).

1H NMR (300 MHz, DMSO) δ 9.16 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 6.5 Hz, 1H), 7.00-6.81 (m, 4H), 5.04 (s, 2H), 3.77 (s, 3H), 1.94 (s, 3H);

^{13}C NMR (75 MHz, DMSO) δ 169.43, 158.82, 153.60, 128.90, 128.54, 128.04, 127.52, 125.22, 123.57, 122.51, 121.24, 115.35, 113.76, 68.57, 55.14, 22.47.

FTIR (neat, cm^{-1}) 3230.77, 1651.07, 1641.42, 1525.69, 1512.19, 1292.31, 1249.87, 1215.15, 1178.51, 1026.13, 1004.91, 819.75, 761.88, 721.38, 665.44;

HRMS (ESI) m/z calculated for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1287, found 296.1283.

Table 4.5, entry 4:

R_f = 0.35 (2:1 hexane/ethyl acetate)

N-(3-*p*-tolyl-2*H*-chromen-4-yl)acetamide (**20fd**): The title compound was obtained by flash chromatography (41 mg, 54%).

¹H NMR (300 MHz, DMSO) δ 9.16 (s, 1H), 7.30-7.03 (m, 6H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.04 (s, 2H), 2.31 (s, 3H), 1.92 (s, 3H);

¹³C NMR (75 MHz, DMSO) δ 169.38, 153.70, 137.19, 132.96, 129.05, 128.85, 127.68, 127.03, 125.74, 123.66, 122.38, 121.24, 115.37, 68.53, 22.43, 20.80;

FTIR (neat, cm⁻¹) 3232.70, 1654.92, 1639.49, 1512.19, 1037.70, 1006.84, 813.96, 763.81, 721.38.

HRMS (ESI) *m/z* calculated for C₁₈H₁₈NO₂ [M+H]⁺: 280.1338, found 280.1334.

Table 4.5, entry 5:

R_f = 0.60 (2:1 hexane/ethyl acetate)

N-(3-(4-chlorophenyl)-2*H*-chromen-4-yl)acetamide (**20fe**): The title compound was obtained by flash chromatography (45 mg, 55%).

¹H NMR (400 MHz, DMSO) δ 9.23 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.06 (s, 2H), 1.93 (s, 3H);

¹³C NMR (100 MHz, DMSO) δ 169.35, 153.86, 134.89, 132.84, 129.48, 128.98, 128.35, 126.70, 126.31, 123.84, 122.07, 121.34, 115.01, 68.25, 22.49;

FTIR (neat, cm⁻¹) 3224.98, 1651.07, 1633.71, 1519.91, 1338.60, 1274.95, 1213.23, 1091.71, 1039.63, 1008.77, 817.82, 761.88, 721.38, 665.44;

HRMS (ESI) m/z calculated for $C_{17}H_{15}NO_2Cl$ $[M+H]^+$: 300.0791, found 300.0795.

Table 4.5, entry 6:

R_f = 0.30 (2:1 hexane/ethyl acetate)

N-(3-*m*-tolyl-2*H*-chromen-4-yl)acetamide (**20ff**): The title compound was obtained by flash chromatography (42 mg, 56%).

1H NMR (400 MHz, DMSO) δ 9.18 (s, 1H), 7.32-7.06 (m, 6H), 6.93 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.05 (s, 2H), 2.31 (s, 3H), 1.92 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.44, 153.78, 137.42, 135.88, 129.17, 128.45, 128.20, 127.81, 127.69, 126.11, 124.29, 123.77, 122.36, 121.28, 115.43, 68.56, 22.40, 21.04;

FTIR (neat, cm^{-1}) 3230.77, 1651.07, 1635.64, 1600.92, 1519.91, 1309.67, 1273.02, 1217.08, 1035.77, 1004.91, 786.96, 763.81, 721.38, 704.02, 623.01;

HRMS (ESI) m/z calculated for $C_{18}H_{18}NO_2$ $[M+H]^+$: 280.1338, found 280.1336.

Table 4.5, entry 7:

R_f = 0.53 (2:1 hexane/ethyl acetate)

N-(3-(4-fluorophenyl)-2*H*-chromen-4-yl)acetamide (**20fg**): The title compound was obtained by flash chromatography (38 mg, 50%).

¹H NMR (300 MHz, DMSO) δ 9.21 (s, 1H), 7.43 (t, J = 8.1 Hz, 2H), 7.30-7.05 (m, 4H), 6.94 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 5.06 (s, 2H), 1.93 (s, 3H);

¹³C NMR (75 MHz, DMSO) δ 169.41, 161.49 (d, J = 243.6 Hz), 153.79, 132.34 (d, J = 3.7 Hz), 129.35 (d, J = 7.8 Hz), 129.30, 126.83, 126.27, 123.75, 122.17, 121.31, 115.42 (d, J = 5.4 Hz), 115.10, 68.43, 22.45;

FTIR (neat, cm⁻¹) 3232.70, 1662.64, 1637.56, 1521.84, 1508.33, 1280.73, 1222.87, 1161.15, 1037.70, 1020.34, 1006.84, 829.39, 763.81, 721.38;

HRMS (ESI) m/z calculated for C₁₇H₁₅NO₂F [M+H]⁺: 284.1087, found 284.1098.

Table 4.5, entry 8:

R_f = 0.49 (2:1 hexane/ethyl acetate)

N-(3-(3-methoxyphenyl)-2*H*-chromen-4-yl)acetamide (**20fh**): The title compound was obtained by flash chromatography (32 mg, 40%).

¹H NMR (300 MHz, DMSO) δ 9.21 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.22-7.08 (m, 2H), 6.98-6.83 (m, 5H), 5.06 (s, 2H), 3.75 (s, 3H), 1.93 (s, 3H);

¹³C NMR (75 MHz, DMSO) δ 169.46, 159.10, 153.81, 137.21, 129.38, 129.26, 127.74, 126.29, 123.79, 122.27, 121.29, 119.43, 115.43, 113.63, 112.64, 68.50, 55.05, 22.45;

FTIR (neat, cm^{-1}) 3182.55, 1664.57, 1639.49, 1591.27, 1583.56, 1531.48, 1344.38, 1226.73, 1033.85, 1008.77, 761.88, 721.38, 665.44;

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 296.1287, found 296.1288.

Table 4.6, entry 2:

R_f = 0.62 (1:1 hexane/ethyl acetate)

N-(6-chloro-3-phenyl-2*H*-chromen-4-yl)acetamide (**20ha**): The title compound was obtained by flash chromatography (54 mg, 72%).

^1H NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.41-7.28 (m, 5H), 6.98 (d, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.76 (d, J = 8.1 Hz, 1H), 5.02 (s, 2H), 2.23 (s, 3H), 1.92 (s, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.39, 151.68, 136.10, 129.91, 129.61, 128.29, 127.79, 127.73, 127.12, 126.28, 123.93, 122.14, 115.24, 68.53, 22.47, 20.43;

FTIR (neat, cm^{-1}) 3248.13, 1654.92, 1631.78, 1523.76, 1209.37, 1012.63, 721.38;

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 280.1338, found 280.1337.

Table 4.6, entry 3:

R_f = 0.68 (1:1 hexane/ethyl acetate)

N-(6-fluoro-3-phenyl-2*H*-chromen-4-yl)acetamide (**20ia**): The title compound was obtained by flash chromatography (36 mg, 47%).

¹H NMR (400 MHz, DMSO) δ 9.26 (s, 1H), 7.43-7.31 (m, 5H), 7.04-6.97 (m, 1H), 6.92-6.84 (m, 2H), 5.07 (s, 2H), 1.93 (s, 3H);

¹³C NMR (100 MHz, DMSO) δ 169.60, 156.98 (d, *J* = 234.8 Hz), 149.88, 135.16, 129.18, 128.39, 128.06, 127.17, 125.61 (d, *J* = 2.0 Hz), 123.94 (d, *J* = 8.0 Hz), 116.73 (d, *J* = 8.2 Hz), 115.30 (d, *J* = 23.2 Hz), 110.08 (d, *J* = 24.9 Hz), 68.73, 22.45;

FTIR (neat, cm⁻¹) 3153.61, 1635.64, 1622.13, 1531.48, 1517.98, 1280.73, 1249.87, 1172.72, 1014.56, 721.38;

HRMS (ESI) *m/z* calculated for C₁₇H₁₅NO₂F [M+H]⁺: 284.1087, found 284.1090.

Table 4.6, entry 4:

R_f = 0.75 (1:1 hexane/ethyl acetate)

N-(6-chloro-3-phenyl-2*H*-chromen-4-yl)acetamide (**20ga**): The title compound was obtained by flash chromatography (77 mg, 95%).

¹H NMR (400 MHz, DMSO) δ 9.26 (s, 1H), 7.43-7.34 (m, 5H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 5.11 (s, 2H), 1.93 (s, 3H);

¹³C NMR (100 MHz, DMSO) δ 169.61, 152.57, 135.50, 129.22, 128.73, 128.40, 128.13, 127.17, 125.17, 124.11, 123.07, 117.34, 68.74, 22.46;

FTIR (neat, cm⁻¹) 3234.62, 1664.57, 1600.92, 1537.27, 1209.37, 1089.78, 1004.91, 763.81, 723.31, 702.09;

HRMS (ESI) m/z calculated for $C_{17}H_{15}NO_2Cl$ $[M+H]^+$: 300.0791, found 300.0788.

Table 4.6, entry 5:

R_f = 0.35 (2:1 hexane/ethyl acetate)

N-(6-fluoro-2-methyl-3-phenyl-2*H*-chromen-4-yl)acetamide (**20ka**): The title compound was obtained by flash chromatography (35 mg, 43%).

1H NMR (400 MHz, DMSO) δ 9.14 (s, 1H), 7.40-7.32 (m, 5H), 7.04-6.98 (m, 1H), 6.94-6.83 (m, 2H), 5.34 (q, J = 6.2 Hz, 1H), 1.87 (s, 3H), 1.25 (d, J = 6.4 Hz, 3H);

^{13}C NMR (100 MHz, DMSO) δ 169.49, 156.79 (d, J = 233.8 Hz), 147.98, 135.71, 134.89, 128.32, 127.94, 127.83, 124.70 (d, J = 1.8 Hz), 123.07 (d, J = 8.0 Hz), 117.35 (d, J = 7.7 Hz), 115.44 (d, J = 23.1 Hz), 109.98 (d, J = 24.9 Hz), 74.45, 22.40, 19.00; FTIR (neat, cm^{-1}) 3232.70, 1660.71, 1649.14, 1519.91, 1288.45, 1247.94, 1174.65, 813.96, 761.88, 721.38, 698.23, 665.44;

HRMS (ESI) m/z calculated for $C_{18}H_{17}NO_2F$ $[M+H]^+$: 298.1243, found 298.1242.

Table 4.6, entry 6:

R_f = 0.45 (1:3 hexane/ethyl acetate)

N-(6, 7-dimethoxy-2, 2-dimethyl-3-phenyl-2*H*-chromen-4-yl)acetamide (**20ja**): The title compound was obtained by flash chromatography (18 mg, 19%).

¹H NMR (400 MHz, DMSO) δ 8.78 (s, 1H), 7.40-7.25 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 6.58 (d, J = 11.6 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 1.72 (s, 3H), 1.34 (s, 6H);
¹³C NMR (100 MHz, DMSO) δ 168.75, 150.12, 146.95, 142.87, 136.47, 133.82, 128.59, 127.91, 127.20, 126.24, 113.22, 108.06, 101.25, 78.66, 56.37, 55.70, 26.52, 22.28;

FTIR (neat, cm⁻¹) 3259.70, 1651.31, 1643.35, 1616.35, 1504.48, 1361.74, 1292.31, 1261.45, 1203.58, 1161.15, 1138.00, 1080.14, 999.13, 860.25, 752.24, 725.23, 698.23, 590.22;

HRMS (ESI) m/z calculated for C₂₁H₂₄NO₄ [M+H]⁺: 354.1705, found 354.1696.

Table 4.6, entry 7:

R_f = 0.51 (1:1 hexane/ethyl acetate)

N-(4-methyl-2-phenyl-3, 4-dihydronaphthalen-1-yl)acetamide (**20ea**): The title compound was obtained by flash chromatography (61 mg, 81%).

¹H NMR (400 MHz, DMSO) δ 9.05 (s, 1H), 7.49-7.14 (m, 9H), 3.15-2.95 (m, 1H), 2.92-2.79 (m, 1H), 2.50-2.36 (m, 1H), 1.87 (s, 3H), 1.26 (d, J = 6.9 Hz, 3H);

¹³C NMR (100 MHz, DMSO) δ 169.27, 140.92, 140.29, 132.66, 128.01, 127.38, 127.11, 126.93, 126.12, 125.75, 123.06, 36.86, 31.45, 22.44, 19.62;

FTIR (neat, cm⁻¹) 3234.62, 1664.57, 1600.92, 1537.27, 723.31;

HRMS (ESI) m/z calculated for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1545, found 278.1546.

Table 4.6, entry 8:

R_f = 0.46 (1:1 hexane/ethyl acetate)

N-(2-phenyl-3,4-dihydronaphthalen-1-yl)acetamide (**20aa**): The title compound was obtained by flash chromatography (31 mg, 43%).

1H NMR (400 MHz, DMSO) δ 9.04 (s, 1H), 7.48-7.11 (m, 9H), 2.86 (t, J = 7.9 Hz, 2H), 2.67 (t, J = 7.9 Hz, 2H), 1.88 (s, 3H).;

^{13}C NMR (75 MHz, DMSO) δ 169.21, 140.67, 135.28, 134.35, 133.36, 128.58, 127.96, 127.08, 126.93, 126.21, 122.88, 29.17, 27.24, 22.40;

FTIR (neat, cm^{-1}) 3277.06, 1651.07, 1622.13, 1523.76, 767.67, 702.09;

HRMS (ESI) m/z calculated for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1388, found 264.1379.

5.7 Copper-Free, Palladium-Catalyzed Sonogashira Reaction of Aryl Halide with Terminal Alkynes using Cesium Hydroxide as an Activator

General reaction scheme for Cu-free Sonogashira reaction:

General procedure for the Cu-free Sonogashira reaction.

To a solution of acetylene (0.49 mmol), aromatic halide (0.49 mmol) and Pd(PPh₃)₄ (0.025 mmol) in THF (2 mL), CsOH.H₂O (0.49 mmol). The resulting mixture was heated at 60 °C and stirred overnight. The reaction was diluted with ether, followed by filtration to get rid of ppt. Filtrate was concentrated by the rotatory evaporator to get residue which was purified by flash chromatography to get pure product.

4-phenylbut-3-yn-1-ol

R_f = 0.56 (1:3 hexane/ethyl acetate)

¹H NMR (400 MHz, CDCl₃) δ 7.43-7.40 (m, 2H), 7.30-7.26 (m, 3H), 3.82 (t, *J* = 4.62 Hz, 2H), 2.70 (t, *J* = 4.68 Hz, 2H), 1.86 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 131.61, 128.22, 127.91, 123.27, 86.31, 82.42, 61.11, 23.77.

3-phenylprop-2-yn-1-amine

R_f = 0.20 (1:3 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3) δ 7.42-7.40 (m, 2H), 7.30-7.29 (m, 3H), 3.65 (s, 2H);

^{13}C NMR (100 MHz, CDCl_3) δ 131.50, 128.23, 128.00, 123.15, 90.09, 82.42, 32.12.

1-bromo-4-(phenylethynyl)benzene

R_f = 0.82 (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 7.57-7.47 (m, 4H), 7.44-7.34 (m, 5H);

^{13}C NMR (100 MHz, CDCl_3) δ 133.00, 131.59, 131.57, 128.49, 128.38, 122.89, 122.45, 122.23, 90.48, 88.28.

1-chloro-4-(phenylethynyl)benzene

R_f = 0.72 (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 7.57-7.51 (m, 2H), 7.50-7.44 (m, 2H), 7.39-7.31 (m, 5H);

^{13}C NMR (100 MHz, CDCl_3) δ 134.27, 132.82, 131.62, 128.71, 128.50, 128.41, 122.95, 122.17, 121.18, 90.34, 88.25.

1-methyl-4-(phenylethynyl)benzene

$R_f = 0.75$ (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 7.54-7.51 (m, 2H), 7.43 (d, $J = 8.04$, 2H), 7.34-7.32 (m, 3H), 7.15 (d, $J = 7.83$, 2H), 2.36 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 138.36, 131.52, 131.47, 129.09, 128.29, 128.04, 123.45, 120.15, 89.53, 88.69, 77.42, 77.00, 76.58, 21.49.

1-methoxy-4-(phenylethynyl)benzene

$R_f = 0.76$ (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 7.52-7.46 (m, 4H), 7.32 (d, $J = 6.92$, 3H), 6.88 (d, $J = 8.52$, 2H), 3.82 (s, 3H).

^{13}C NMR (400 MHz, CDCl_3) δ 159.59, 133.04, 131.43, 128.29, 127.91, 123.57, 115.36, 113.98, 89.34, 88.04, 55.28.

3-phenylprop-2-yn-1-ol

$R_f = 0.45$ (1:3 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3) δ 7.45-7.43 (m, 2H), 7.41-7.30 (m, 3H), 4.50 (s, 2H), 1.78 (s, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 131.65, 128.48, 128.29, 122.49, 87.15, 85.69, 51.63.

1-(4-(phenylethynyl)phenyl)ethanone

$R_f = 0.78$ (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, $J = 6.27$, 2H), 7.61 (d, $J = 6.27$, 2H), 7.56-7.54 (m, 2H), 7.37 (t, $J = 2.40$, 3H), 2.61 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 197.30, 136.15, 131.71, 131.66, 128.78, 128.41, 128.24, 128.17, 122.61, 92.68, 88.57, 26.59.

1-nitro-4-(phenylethynyl)benzene

$R_f = 0.21$ (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 8.23 (d, $J = 8.84$, 2H), 7.67 (d, $J = 8.84$, 2H), 7.58-7.55 (m, 2H), 7.40-7.39 (m, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 146.99, 132.28, 131.85, 130.28, 129.29, 128.55, 123.66, 122.11, 94.71, 87.55.

1-methyl-2-(phenylethynyl)benzene

$R_f = 0.76$ (30:1 hexane/ CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ 7.56-7.55 (m, 2H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.38-7.34 (m, 3H), 7.25-7.24 (m, 2H), 7.18 (dd, $J_1 = 4.6$ Hz, $J_2 = 7.8$ Hz, 1H), 2.54 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 140.21, 131.80, 131.49, 129.40, 128.33, 128.28, 128.10, 125.59, 123.50, 123.0, 93.28, 88.30, 20.70.

1,2-diphenylethyne

$R_f = 0.82$ (30:1 hexane/ CH_2Cl_2)

^1H NMR (300 MHz, CDCl_3) δ 7.56-7.51 (m, 4H), 7.40-7.31 (m, 6H);

^{13}C NMR (75 MHz, CDCl_3) δ 131.59, 128.33, 128.24, 123.25, 89.35.

List of Publication

1. Zhou, H.; Xu, Y. H.; Chung, W. J.; Loh, T. P. Palladium-Catalyzed Direct Arylation of Cyclic Enamides with Arylsilane via sp^2 C-H Activation *Angew. Chem., Int. Ed.* **2009**, 48, 5355-5357.
2. Zhou, H.; Chung, W. J.; Xu, Y. H.; Loh, T. P. Direct Arylation of Cyclic Enamides via Pd(II)-Catalyzed C-H Activation *Chem. Commun.* **2009**, 3472-3474.
3. Zhou, H.; Loh, T. P. One-Pot Total Syntheses of Natural Products Containing a THP-Ring Backbone: ($\pm$)-Centrolobine and ($\pm$)-Civet Cat Secretion *Tetrahedron Lett.* **2009**, 50, 4368-4371.
4. Zhou, H.; Chung, W. J.; Loh, T. P. Indium Trihalide Catalyzed 4,4-Dihalotetrahydropyrans via Prins Cyclization *manuscript in preparation*.
5. Zhou, H.; Ong, X. J.; Loh, T. P. Copper-, and Ligand-Free, Palladium-Catalyzed Sonogashira Coupling Reaction Activated by Cesium Hydroxide *manuscript in preparation*.
6. Zhou, H.; Chung, W. J.; Soh, Y. N.; Loh, T. P. Aerobic Aqueous Transformation of Alkyl Halides into Alcohols via Tin-Free Radical Method *manuscript in preparation*.
7. Zhou, H.; Chung, W. J.; Soh, Y. N.; Loh, T. P. Aerobic Aqueous Transformation of Gem-dihalides into Ketones via Tin-Free Radical Method *manuscript in preparation*.

Conferences

1. Zhou, H.; Loh, T. P. *Aerobic Aqueous Transformation of Halo Group into Hydroxyl Group via Tin-Free Radical Method*. 6th Asian-European Symposium on Metal Mediated Efficient Reactions, Singapore, June 7-9, 2010.
2. Zhou, H.; Loh, T. P. *Palladium-Catalyzed Direct Arylation of Cyclic Enamides via sp^2 C-H Functionalization*. 6th Asian-European Symposium on Metal Mediated Efficient Reactions, Singapore, June 7-9, 2010.
3. Zhou, H.; Loh, T. P. *One-Pot Total Syntheses of Natural Products Containing a THP-Ring Backbone: ($\pm$)-Centrolobine and ($\pm$)-Civet Cat Secretion*. 6th Asian-European Symposium on Metal Mediated Efficient Reactions, Singapore, June 7-9, 2010.
4. Zhou, H.; Loh, T. P. *Exploration of a One-Pot Method to Natural Product Synthesis: Total Syntheses of ($\pm$)-Centrolobine and ($\pm$)-Civet Cat Secretion*. International Symposium on Catalysis and Fine Chemicals, Singapore, December 16-21, 2007.