Transition-Metal-Catalyzed Functionalization of Aryl C-H Bonds via a Cross-Dehydrogenative-Coupling Process

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Abstract

This thesis is an investigation on the functionalization of aryl C-H bonds in the presence of transition-metal catalysts and oxidants.

In the first part of this thesis, an oxidative amidation of 2-arylpyridine derivatives and 1-methylindoles with a variety of amides is described. Copper(I) bromide is used as catalyst and *tert*-butyl peroxide (TBP) is employed as oxidant. High regioselectivity of this amidation process is achieved through chelation-assisted aryl C-H activation.

In the second part of this thesis, a new concept is described for aryl-aryl coupling that involves oxidative decarbonylative coupling of aryl C-H bonds and readily available aldehydes and forms the aryl-aryl union with complete control of reaction sites. This process is catalyzed by $(CO)_2Rh(acac)$, along with TBP as an oxidant.

The third and final part of this thesis describes a novel ruthenium- and copper-catalyzed domino reaction between alkynols and aldehydes, which affords 5-olefinated 3,4-dihydropyran derivatives efficiently with only water as the byproduct.

Résumé

Ce manuscrit de thèse présente l'étude de la fonctionnalisation de liaisons C-H aryliques catalysée par des complexes de métaux de transition en présence d'un oxydant.

Dans une première partie est décrite la réaction d'amidation oxydante de dérivés de 2-arylpyridine et de 1-méthylindole par une variété d'amides. Le bromure de cuivre(I) est utilisé comme catalyseur et le peroxyde de *tert*-butyle (TBP) comme oxydant. Dans ces conditions, une excellente régiosélectivité est obtenue pour cette transformation grâce à la présence d'un groupe directeur qui permet l'assistance par chélation de l'activation de la liaison C-H.

Au cours de la deuxième partie est abordé un nouveau concept pour la synthèse de motifs aryl-aryl, impliquant une séquence décarbonylation/couplage oxydant. Cette réaction permet la formation d'un composé biaryle à partir d'arènes et d'aldehydes aromatiques aisément accessibles avec un contrôle total des sites réactionnels. Elle est catalysée par le complexe $(CO)_2Rh(acac)$ en présence de TBP comme oxydant.

La troisième et dernière partie de cette thèse présente une nouvelle réaction domino catalysée par des complexes de ruthénium et de cuivre qui permet l'obtention de 3,4-dihydropyranes substitués en position 5 à partir d'aldéhydes et d'hydroxyalcynes avec la formation d'eau comme unique sous-produit.

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Abbreviations

AA	ascorbic acid
Ac	acetyl
acac	acetylacetone
APCI	atmospheric-pressure chemical ionization
Ar	aryl or argon
atm	atmosphere
Boc	butoxycarbonyl
BQ	1,4-benzoquinone
br	broad (^{1}H-NMR)
t-Bu	*tert*-butyl
Bz	benzoyl
cat	catalyst
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet (^{1}H-NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	*trans,trans*-dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

de	diastereomeric excess
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
Eq	equation
equiv	equivalent
Et	ethyl
GC-MS	gas chromatography-mass spectrometry
h	hour
HPMV	$H_4PMo_{11}VO_{40}$
HQ	hydroquinone
HRMS	high-resolution mass spectrometry
Hz	Hertz
i-Pr	iso-propyl
IBX	2-iodoxybenzoic acid
Ile	isoleucine
IR	infrared spectroscopy
L	ligand
Leu	leucine
m	mutiplet (^{1}H-NMR)
M	metal
m	meta

mp	melting point
Me	methyl
MeSaI	3-methylsalicylate
min	minute
MS	molecular sieve
MW	microwave
n-hept	*n*-heptyl
2-naph	2-naphthyl
NMR	nuclear magnetic resonance spectroscopy
[O]	oxidant
OTf	trifluoromethanesulfonate
p	para
PG	protecting group
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthaloyl
Piv	pivaloyl
ppm	parts per million
rt	room temperature
s	singlet (^{1}H-NMR)
SEM	[2-(trimethylsilyl)ethoxy]methyl
SET	single electron transfer
t	triplet (^{1}H-NMR)

TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetyl
THF	tetrahydrofuran
TM	transition metal
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Trp	tryptophan
Ts	tosyl
Val	valine

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Chapter 1

Introduction

This dissertation focuses on the subjects of C-H bond functionalization and domino reactions, both of which can be considered under the banner of "Green Chemistry". In this chapter, I will discuss a general introduction of primary concepts regarding the entire dissertation, including Green Chemistry, catalysis, C-H bond activation, and domino reactions.

1.1 Green Chemistry

As an organic chemistry researcher working in an academic laboratory, we do have some knowledge of lab safety considerations and awareness of environmental protection issues. We know the dangers of fatal sodium nitrite and highly poisonous osmium tetraoxide, which should be handled with appropriate precautions. We know the hazards to our health if exposed to toxic solvents, like benzene and pyridine, and normally we should set up experiments and perform work-up in fume hoods. However, we may not know how these toxins collected in waste-containers from different labs are finally disposed of, and whether the poisonous vapor removed by fume hoods gets appropriate disposal before going to its final destination, the atmosphere. Furthermore, we often do not know in detail how chemicals are made in industry and how their chemistry developed in academic laboratories affects the biosphere.[1] A serious problem that we have been faced

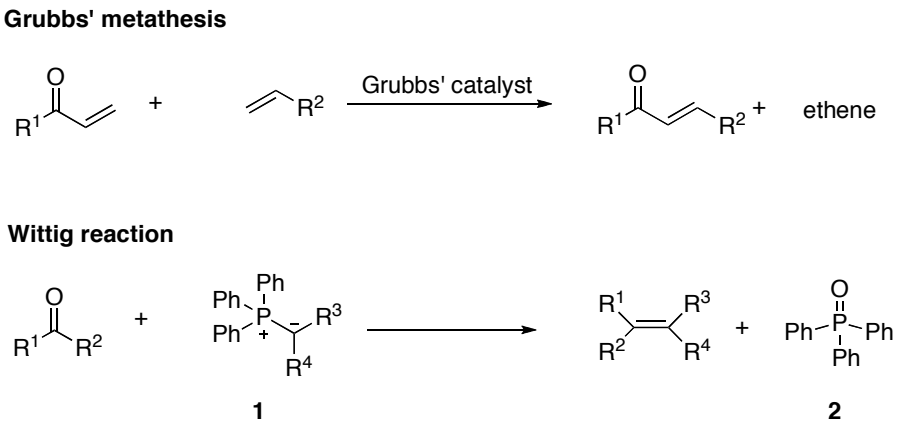
with is that the current chemical manufacture is not sustainable across the world and our modern society almost totally relies on the products of the chemical industry.[2] A new approach is urgently needed to make chemistry greener.

Green Chemistry, also called Sustainable Chemistry, is defined as "the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances."[3,4] The theme of this concept is elucidated by The Twelve Principles introduced in 1998 by Paul Anastas and John Warner.[5] This new approach has been acting as a guideline for the design of new chemical products and processes, from research laboratories to industry plants.

In the past fifty years, phenomenal advances have been made in the area of synthetic organic chemistry, accompanied with the establishment of a powerful and versatile synthetic toolbox for organic chemists. However, academic chemists are still struggling to develop new methodologies, design new synthetic routes, and optimize current approaches, in order to achieve the syntheses of complex molecules from simple starting materials in an efficient and convenient way.[6] To our delight, a couple of fascinating branches of organic synthesis have been introduced and become the subject of intense research in recent years, among which catalytic reactions,[7] C-H activation,[8] and domino reactions[9] have abstracted great interests due to their green potentials.

1.2 Catalysis

Catalysis itself is one of The Twelve Principles of Green Chemistry and catalytic reactions are naturally preferred in Green Chemistry. Firstly, a catalytic reaction generally proceeds with a lower activation energy, which implies that less energy is consumed. Secondly, the regenerability of catalysts helps avoid the use of stoichiometric amounts of reagents and thus reduce the generation of waste. Finally, in the presence of catalysts, products can be obtained with greater selectivity and thus the formation of corresponding byproducts can be minimized. For example, the Grubbs' catalyst allows the construction of C-C double bonds, which plays an important role for the ring formation of complex molecules. Compared with the traditional Wittig reaction which requires the preparation of phosphonium salts **1** and produces a large amount of waste **2**, the Grubbs' metathesis usually employs simple terminal alkenes as substrates and generates gaseous ethene as the only byproduct (Scheme 1.1).

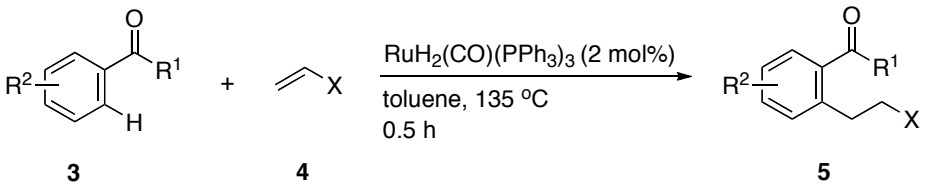


Scheme 1.1 Comparison of the Grubbs' metathesis and the Wittig reaction

1.3 C-H bond activation

Synthetic organic chemists are always concerned with the reactivity and selectivity of an organic transformation. It is true that C-H bonds are traditionally considered unreactive, but it has been well demonstrated theoretically and experimentally that C-H bonds can be activated through coordination to certain transition-metal catalysts and further transformed into a wide variety of functional groups. In addition to avoiding the use of activated precursors for classical cross-coupling strategies and reducing the production of toxic byproducts, C-H bond functionalization also provides a novel approach to construct complex molecules from cheap and abundant starting materials with high atom-efficiency. Over the last decade, we have witnessed a tremendous increase of research projects launched in this area and rapid and extensive progress made.[10] Herein, a few milestones will be chosen and discussed in detail, providing a general overview of the accomplishments achieved in this research area and showing its development trend as well.

In 1993, as one of the seminal reports of transition-metal-catalyzed C-C bond formation via C-H activation, Murai *et al.* demonstrated that the cleavage of C-H bonds in aromatic systems could be achieved in the presence of an organic ruthenium complex

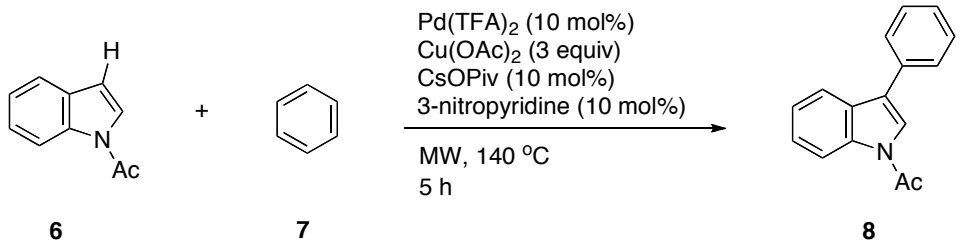


3 **4** **5**

Scheme 1.2 Ru-catalyzed *ortho*-alkylation of arenes

$RuH_2(CO)(PPh_3)_3$, leading to further addition to alkenes and affording *ortho*-alkylated products efficiently (Scheme 1.2).[11] Notably, this work successfully demonstrated a carbonyl group in substrates **3** as a directing group and made the activation of *ortho*-C-H bond favorable, achieving *ortho*-alkylation products **5** with high regioselectivity. This pioneering work really opened a door for organic chemists to gain the "holy grail" of organometallic chemistry.

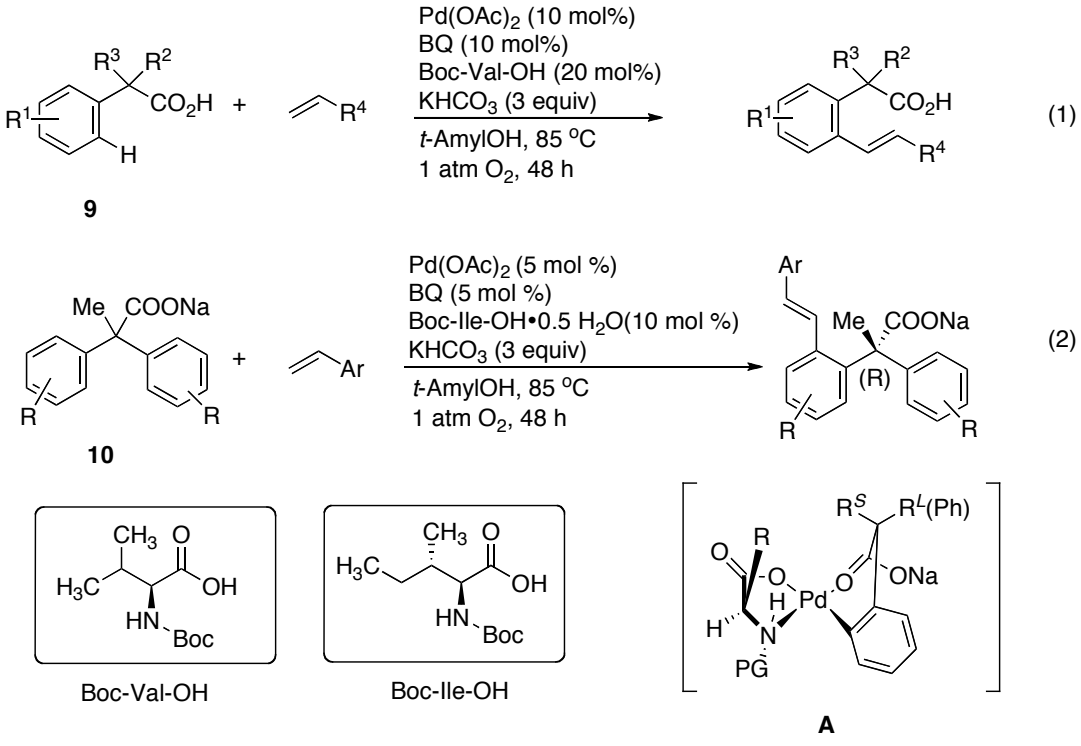
Palladium-catalyzed cross-coupling reactions are considered having one of the biggest impacts on how organic compounds are made. Three pioneers, Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki were awarded jointly the Nobel Prize in chemistry in 2010. These classical cross-coupling reactions require the use of organohalides and organometallic reagents, and produce a stoichiometric amount of metal waste upon the completion of the cross-coupling processes. In 2007, Stuart and Fagnou reported a novel oxidative cross-coupling reaction of *N*-acetylindoles **6** and benzenes **7**, completely avoiding the use of organohalides and organometallic reagents (Scheme 1.3).[12] This work not only solved the problem of a selective cross-coupling of two aromatic compounds without each compound also coupling with itself to produce undesired products,[13] but



Scheme 1.3 Oxidative cross-coupling of unactivated arenes

also achieved good regioselectivity, ensuring selective coupling at a specific site on each molecule with more than one-type of C-H bonds.

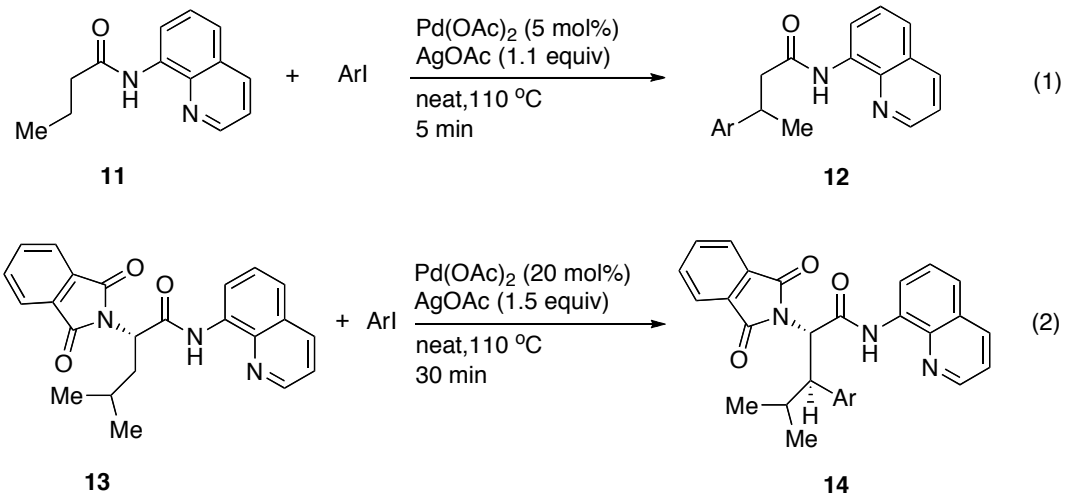
The issue of selectivity is paramount in the development of all C-H bond functionalization methods. To some extent, a high selectivity means good yields of desired products and simple purification procedures. In 2010, the Yu group developed an operational Mizoroki-Heck reaction via carboxylate-directed Pd(II)-catalyzed aryl C–H activation (Scheme 1.4, Eq. 1).[14] This oxidative C-H olefination employed oxygen as a terminal oxidant and eliminated the need for prior halogenation, which is a requisite for the standard Mizoroki-Heck reaction. Given that the regioselective introduction of a halide onto an arene is not always straightforward, this novel approach succeeded in



Scheme 1.4 Ligand-enabled aryl C-H olefination

selectively installing the olefin motifs onto the *ortho*-position of extensive phenylacetic acid substrates **9**. Furthermore, the same group demonstrated that the more challenging Pd(II)-catalyzed enantioselective C-H olefination of diphenylacetic acids **10** could be achieved in the presence of monoprotected amino acid ligands (Scheme 1.4, Eq. 2).[15] **A** was the proposed transition state that rationalized the introduction of chirality to the final product. This new method featured a promising synthetically useful Pd-catalyzed enantioselective C-H activation reaction.

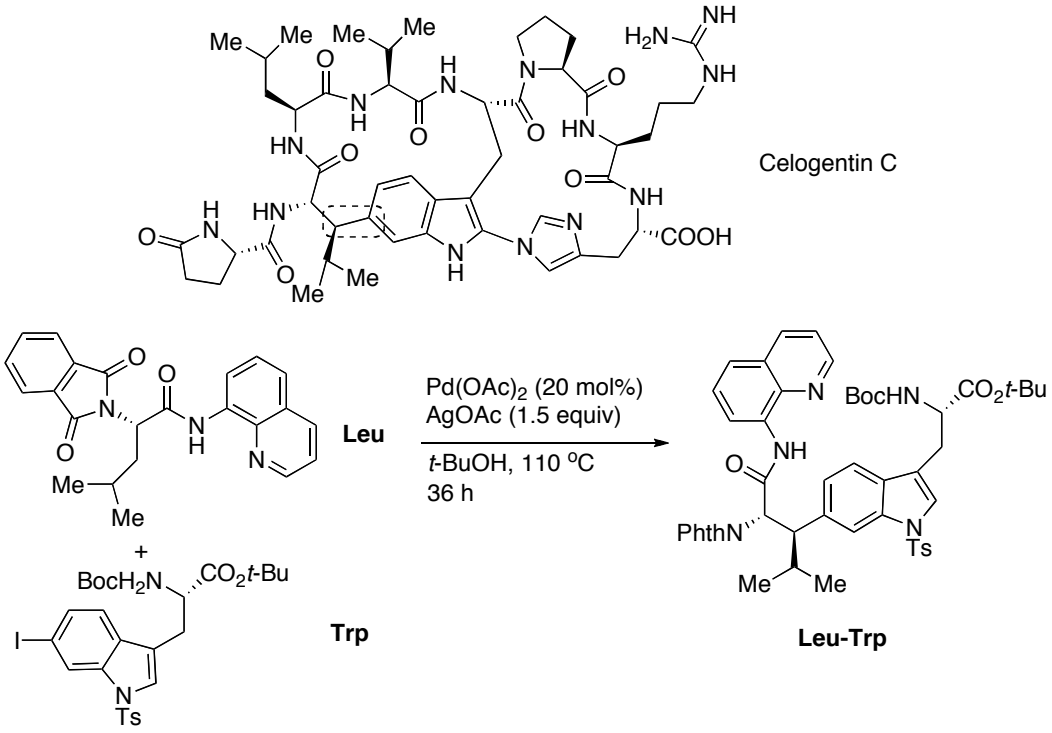
Like any famous reaction proved as a powerful tool for the total synthesis of natural products or complex molecules, C-H activation must undergo such a true test of its synthetic utility. In 2005, Daugulis *et al.* developed a $Pd(OAc)_2$-catalyzed arylation of sp^3 C-H bonds of amides **11** and high regioselectivity was achieved through the chelation assistance of a pyridine auxiliary (Scheme 1.5, Eq. 1).[16] Later, when this method was applied to chiral α-amino acid derivatives **13** with minor modifications, a stereoselective



Scheme 1.5 Pyridine-directed arylation of the β-C-H bond of amides

arylation process was achieved and the product **14** was obtained as a single diastereomer in a high yield (Scheme 1.5, Eq. 2).[17]

The application of this stereoselective C-H activation to the synthesis of natural products was envisioned by Chen and Feng, who recently succeeded in the total synthesis of Celogentin C[18] that was isolated from the seeds of *Celosia argentea* and found to possess biological activities (Scheme 1.6).[19] One challenge to synthesize this molecule is the construction of Leu-Trp linkage with high stereoselectivity, which was successfully accomplished by employing a $Pd(OAc)_2$/AgOAc/*t*-BuOH system. The desired Leu-Trp union was obtained as a single diastereomer in a high yield, which set up a solid base for the accomplishment of this total synthesis.

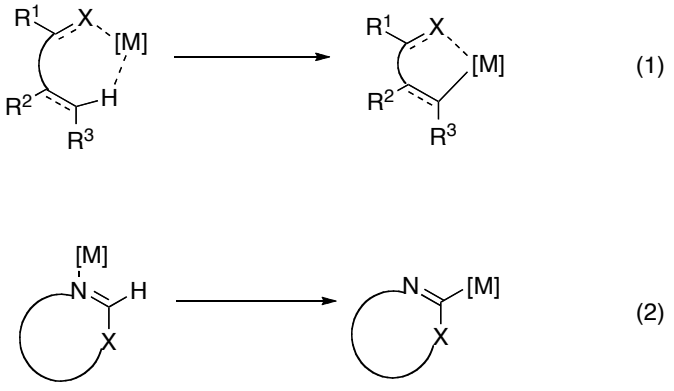


Scheme 1.6 Total synthesis of Celogentin C involving C-H activation

In summary, C-H activation provides an alternative to classical organic reactions based on functional group transformations, and the generality and practicability of this novel chemistry are still under investigations.

1.4 Heteroatom-directed C-H bond activation

The inherent subtle reactivity difference of the prevalent C-H bonds in organic compounds makes the selective activation of these bonds a challenge. One successful strategy involves the use of a proximal heteroatom that serves as a directing group through coordinating to a metal center, which makes the C-H activation an intramolecular process and entropically favorable. Generally, there are two mechanistically distinct reaction pathways. In one case, the heteroatom coordinates to a metal center, facilitating the activation of a proximal C-H bond and the formation of a five- or six-membered intermediate (Scheme 1.7, Eq. 1). In this case, carbonyl,[20] imimo,[21] amino,[22] and pyridyl[23] have been well explored as directing groups. In the other case, the heteroatom

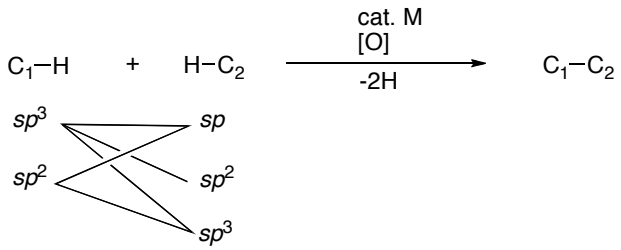


Scheme 1.7 Modes of heteroatom-directed C-H activation

of a heterocycle initially coordinates to a metal center without the formation of cyclic intermediate (Scheme 1.7, Eq. 2). In this case, a wide variety of *N*-heterocycles have been explored as substrates for C-H functionalization.[24]

1.5 Cross-dehydrogenative-coupling (CDC)

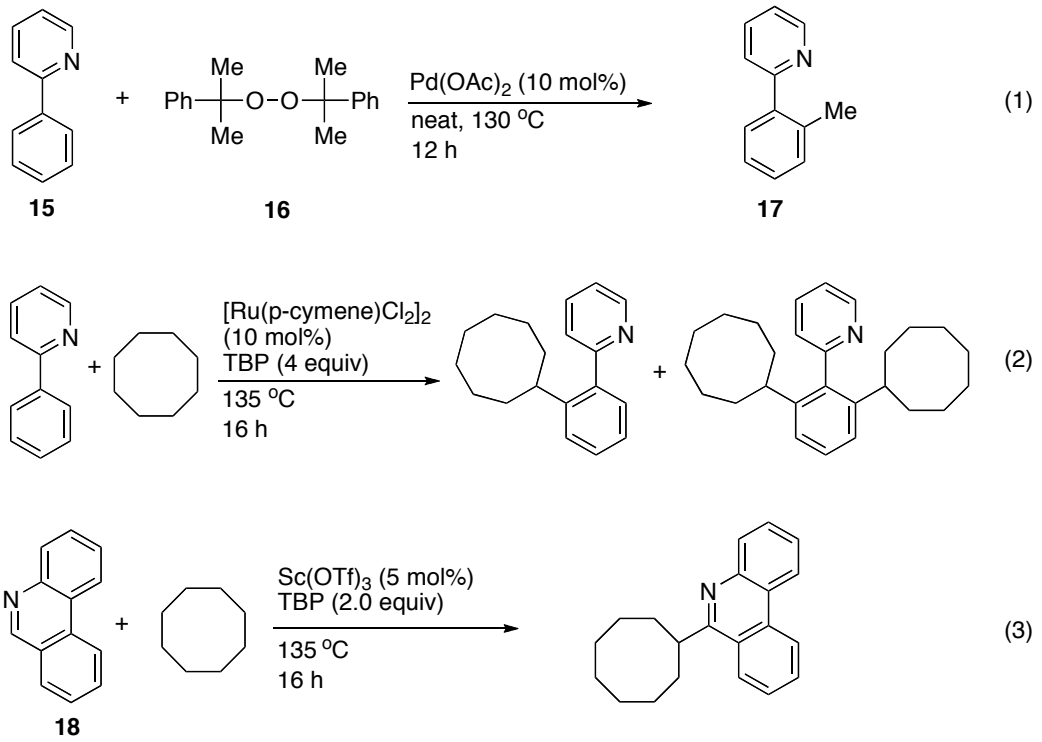
In the past several years, the Li group has presented a novel approach to construct carbon-carbon directly from two different C-H bonds under oxidative conditions (Scheme 1.8).[25] Simple and cheap copper and iron salts can often be used as catalysts. In some cases, molecular oxygen can be used as a terminal oxidant and the reaction can be conducted in aqueous media.[26]



Scheme 1.8 Cross-dehydrogenative-coupling reactions

Among others, it has been demonstrated that direct functionalization of aryl C-H bonds to form C-C bonds worked well under the CDC reaction conditions. Firstly, Zhang reported a $Pd(OAc)_2$-catalyzed methylation of 2-phenylpyridine derivatives **15** by using dicumyl peroxide **16** as both oxidant and methylation reagents (Scheme 1.9, Eq. 1).[27] Later, Deng successfully extended this method to the alkylation of 2-phenylpyridines **15** (Scheme 1.9,

Eq. 2)[28] and quinolines **18** (Scheme 1.9, Eq. 3)[29] by adding alkanes to the reaction mixtures and using *tert*-butyl peroxide (TBP) as an oxidant.

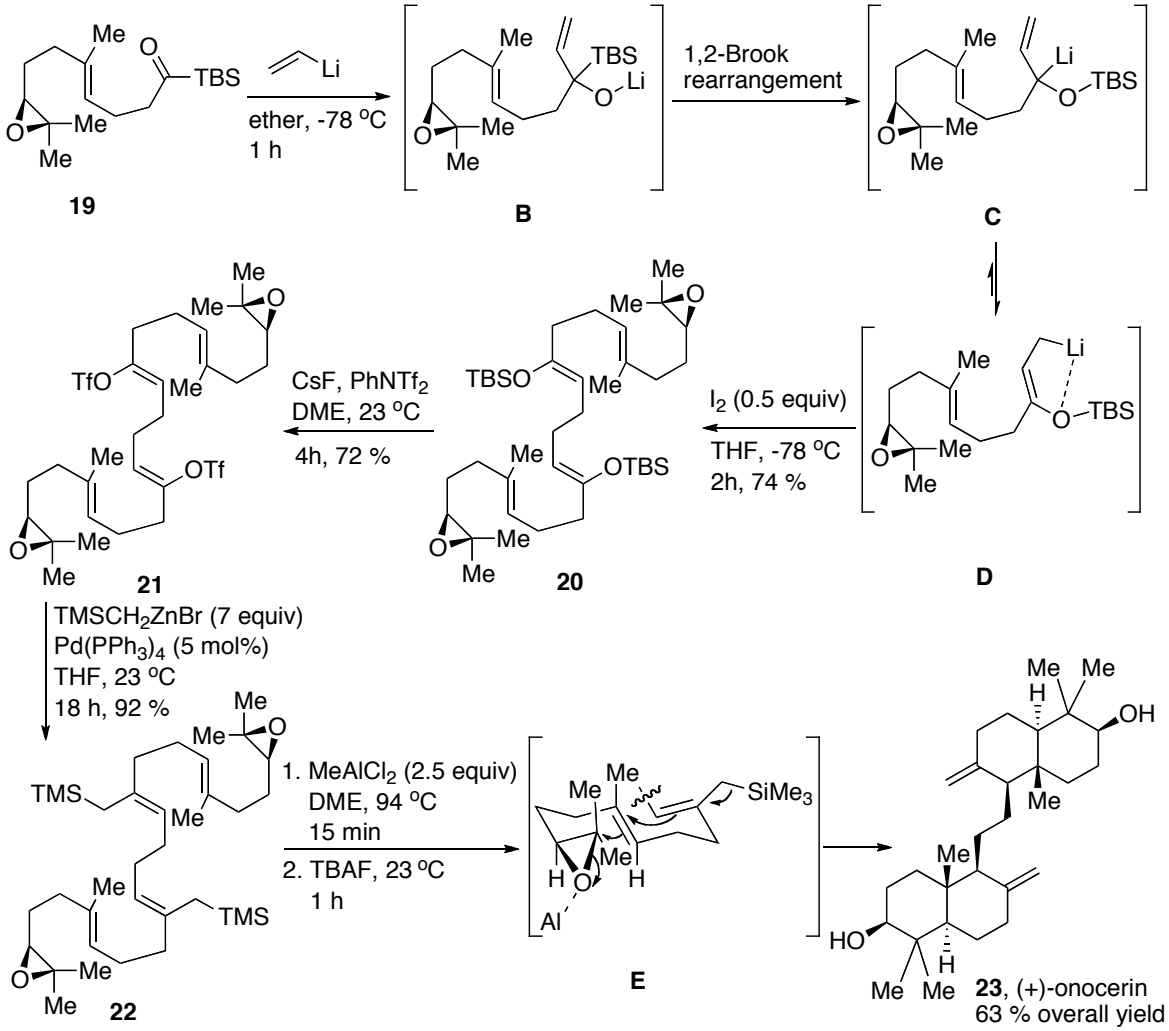


Scheme 1.9 Functionalization of aryl C-H bonds via a CDC process

1.6 Domino reactions

A domino reaction is a consecutive series of organic reactions in one single operation without isolating the intermediates, changing the reaction conditions, or adding reagents.[30] Compared to the classical stepwise synthesis of organic compounds, domino reactions usually allow the construction of complex molecules in an extraordinarily efficient way, which makes the application of domino reactions to natural product syntheses particularly attractive to organic chemists.[31] The great power of domino

reactions has been well demonstrated by the accomplishments of many total syntheses of natural products with considerable structural and stereochemical complexity. Herein, Corey's concise total synthesis of (+)-α-onocerin will be chosen as a representative example to discuss in detail.[32] In 2002, Corey *et al.* presented an elegant total synthesis of (+)-onocerin **23** involving two domino reactions (Scheme 1.10). The starting enantiopure epoxy ketone **19** was treated with vinyllithium in ether at -78 °C for 1 h, followed by the



Scheme 1.10 Corey's total synthesis of (+)-onocerin

addition of an I_2 solution in THF. After workup the dimer **20** was obtained in 74 % yield. This rapid and efficient construction of **20** was believed to occur via a domino reaction. Firstly, the nucleophilic addition of vinyllithium to ketone **19** afforded alkoxide **B**, which transformed to chelated *Z*-allylic lithium intermediate **D** via a 1,2-Brook rearrangement and allylic rearrangement. Then dimerization occured upon the addition of I_2, furnishing **20** in good yield. Protecting groups switching from TBS to TMS was accomplished through general procedures (**20→22**). Exposure of **22** to 2.5 equiv of $MeAlCl_2$ in DME at -94 °C for 15 min followed by treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF at 23 °C for 1 h, the final target molecule **23** was obtained in 63 % yield. This final domino reaction allowed the formation of four rings, four carbon-carbon bonds, and six new stereogenic centers in just one step.

References

(1) M. Poliakoff, P. T. Anastas, *Nature*, **2001**, *413*, 257.

(2) M. Poliakoff, P. Licence, *Nature*, **2002**, *419*, 880.

(3) (a) P. T. Anastas, J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998. (b) I. T. Horváth, P. T. Anastas, *Chem. Rev.* **2007**, *107*, 2167.

(4) P. T. Anastas, T. C. Williamson, in *Green Chemistry: Designing Chemistry for the Environment*, American Chemical Series Books, Washington, DC, 1996, pp. 1–20.

(5) P. T. Anastas, J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, 1998, pp. 30.

(6) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature*, **2007***, 446*, 404.

(7) (a) I. T. Horváth, in *Encyclopedia of Catalysis*, Wiley-VCH Verlag GmbH, Weinheim, 2003. (b) B. Cornils, W. A. Hermann, M. Muhler and C.-H. Wong, in *Catalysis from A to Z*, Wiley-VCH Verlag GmbH, Weinheim, 2007.

(8) (a) S. Murai, in *Activation of Unreactive Bonds and Organic Synthesis,* Topics in Organometallic Chemistry, Springer-Verlag, Berlin Heidelberg, 1999, vol. 3. (b) K. Goldberg, A. S. Goldman, in *Activation and Functionalization of C–H Bonds,* ACS Symposium Series, Oxford University Press, 2004. (c) Y. Fujiwara, C. Jia, *Pure Appl. Chem.* **2001**, *73*, 319. (d) J. A. Labinger, J. E. Bercaw, *Nature*, **2002**, *417*, 507. (e) R. G. Bergman, *Nature,* **2007**, *446*, 391. (f) C. I. Herrerias, X. Yao, Z. Li, C.-J. Li, *Chem. Rev*. **2007**, *107*, 2546.

(9) (a) P. J. Parsons, C. S. Penkettand, A. J. Shell, *Chem. Rev*. **1996**, *96*, 195. (b) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun*. **2003**, 551. (c) A. Padwa, *Pure Appl. Chem.* **2004**, *76*, 1933. (d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(10) (a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731. (b) C.-H. Jun, C. W. Moon, H. Lee, D.-Y. Lee, *J. Mol. Catal. A* **2002**, *189*, 145. (c) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826. (d) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 212. (e) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077. (f) Y. J. Park, C.-H. Jun, *Bull. Korean Chem. Soc.* **2005**, *26*, 871. (g) F. Kakiuchi, *Top. Organomet. Chem.* **2007**, *24*, 1. (h) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173. (i) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013. (j) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013. (k) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (l) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061. (m) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev*. **2010**, *110*, 624. (n) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654. (o) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev*. **2009**, *38*, 2447. (p) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074. (q) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun*. **2010**, *46*, 677. I T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110,* 1147.

(11) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.

(12) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172.

(13) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047.

(14) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315.

(15) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460.

(16) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(17) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.

(18) Y. Feng, G. Chen, *Angew. Chem., Int. Ed.* **2010**, *49*, 958.

(19) J. Kobayashi, H. Suzuki, K. Shimbo, K. Takeya, H. Morita, *J. Org. Chem.* **2001**, *66*, 6626.

(20) For selected recent reports, see: (a) D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676. (b) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898. (c) R. Martinez, M.-O. Simon, R. Chevalier, C. Pautigny, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2009**, *131*, 7887. (d) Y.-X. Jia, E. P. Kündig, *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (e) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem., Int. Ed.* **2009**, *48*, 1830. (f) H. Zhou, Y.-H. Xu, W.-J. Chung, T.-P. Loh, *Angew. Chem., Int. Ed.* **2009**, *48*, 5355. (g) H. Zhou, W.-J. Chung, Y.-H. Xu, T.-P. Loh, *Chem. Commun.* **2009**, 3472.

(21) (a) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123. (b) N. Yoshikai, A. Matsumoto, J. Norinder, E. Nakamura, *Angew. Chem., Int. Ed.* **2009**, *48*, 2925.

(22) H. He, W.-B. Liu, L.-X. Dai, S.-L. You, *J. Am. Chem. Soc.* **2009**, *131*, 8346.

(23) For selected recent reports, see: (a) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113. (b) L. Ackermann, A. Althammer, R. Born, *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (c) X. D. Zhao, Z. K. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 8136. (d) S.

J. Gu, C. Chen, W. Z. Chen, *J. Org. Chem.* **2009**, *74*, 7203. (e) T. Kochi, S. Urano, H. Seki, E. Mizushima, M. Sato, F. Kakiuchi, *J. Am. Chem. Soc.* **2009**, *131*, 2792. (f) X. D. Zhao, E. Dimitrijevic, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466.

(24) For selected examples, see: (a) B. S. Lane, M. A. Brow, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996. (c) B. B. Touré, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979. (d) J. C. Lewis, S. H. Wiedemann, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2004**, *6*, 35. (e) J. C. Lewis, J. Y. Wu, R. G. Bergman, J. A. Ellman, *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (f) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972. (g) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748. (h) D. R., Jr. Gauthier, J. Limanto, P. N. Devine, R. A. Desmond, R. H., Jr. Szumigala, B. S. Foster, R. P. Volante, *J. Org. Chem.* **2005**, *70,* 5938. (i) F. A. Zhuravlev, *Tetrahedron Lett.* **2006**, *47*, 2929.

(25) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.

(26) (a) O. Basle, C.-J. Li, *Green Chem.* **2007**, *9*, 1047. (b) O. Basle, C.-J. Li, *Org. Lett.*, **2008**, *10*, 3661.

(27) Y. Zhang, J. Feng, C.-J. Li, *J. Am. Chem. Soc.* **2008**, *130*, 2900.

(28) G. Deng, L. Zhao, C.-J. Li, *Angew. Chem., Int. Ed.* **2008**, *47*, 6278.

(29) G. Deng, C.-J. Li, *Org. Lett,* **2009**, *11*, 1171.

(30) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

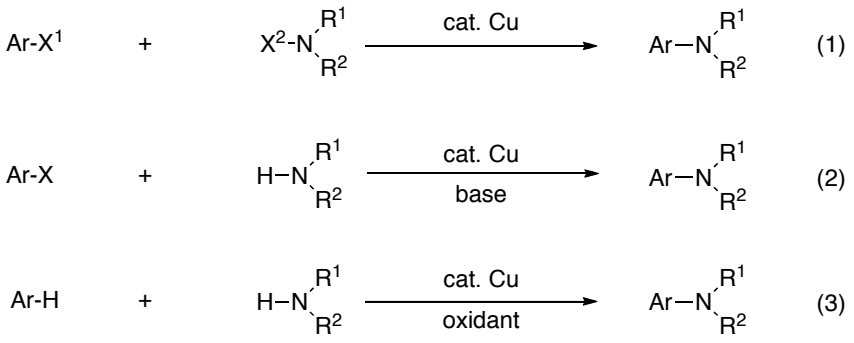
(31) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(32) Y. Mi, J. V. Schreiber, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 11290.

Chapter 2

Copper-Catalyzed Oxidative Amidation of 2-Arylpyridine Derivatives

Carbon-nitrogen bonds are one of the most abundant bonds in organic compounds, including pharmaceuticals, agrochemicals, dyes and ligands.[1] Significant effort has been made to develop new methodologies for the synthesis of C-N bonds.[2] Over the past few decades, transition-metal-mediated- or catalyzed- C-N coupling reactions have been extensively investigated, providing a versatile and efficient tool to construct C-N bonds.[3] Recently, explorations toward more economical and environmentally benign catalysts have led to various pioneering advances in Cu-mediated and -catalyzed C-N bond formation processes. Among them, examples involving the use of R^1R^2N-X and organometallic reagents have been reported (Scheme 2.1, Eq. 1). More generally, aryl halides and pseudohalides have been widely explored as aryl donors (Scheme 2.1, Eq. 2). Recently, the direct amination of aryl C-H bonds has emerged as a powerful alternative, which principally requires the use of an oxidant (Scheme 2.1, Eq. 3).

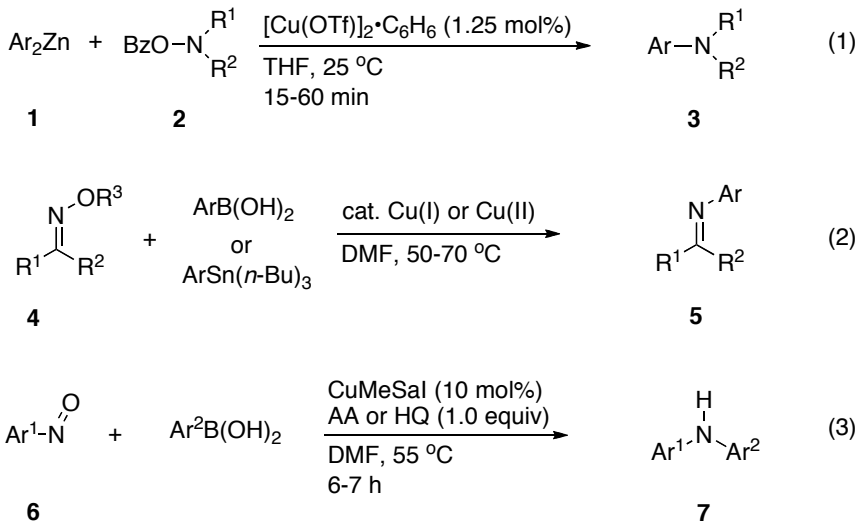


Scheme 2.1 Cu-catalyzed C-N coupling

In this chapter, a concise review relevant to aryl C-N bond formation will be presented with selected examples. The discovery and development of a new copper-catalyzed amidation reaction involving aryl C-H activation will be discussed in detail.

2.1 Cu-catalyzed electrophilic amination of organometallic reagents

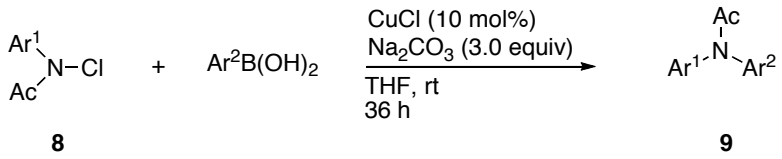
Electrophilic amination of organometallic reagents by R^1R^2N-X has not received significant attention, although it is conceptually feasible. The Johnson group studied the coupling of N-O derivatives and diorganozinc reagents. They demonstrated that *O*-benzoyl hydroxylamines **2** could be used as electrophiles, which underwent smooth coupling with diarylzinc reagents **1** and afforded tertiary amines in good yields (Scheme 2.2, Eq. 1).[4] This method has been improved to include a zinc-free version.[5]



Scheme 2.2 Cu-catalyzed C-N coupling of N-O derivatives and organometallic reagents

The Liebeskind group also successfully explored the coupling reactions of other N-O derivatives with organometallic reagents. They reported that *O*-acyl ketoximes **4** could be used as good substrates for the *N*-imination of both arylboronic acids and organostannanes (Scheme 2.2, Eq. 2) and this method tolerates various functional groups.[6] It was believed that the oxidative insertion of Cu(I) into the weak N-O bonds of **4** played a crucial role in this transformation. Later, the same group also employed the nitroso aromatics **6** as C-N coupling partners with arylboronic acids (Scheme 2.2, Eq. 3).[7]

Recently, Lei *et al.* hypothesized that *N*-chloroamides **8** could be very promising amination reagents due to the ease of preparation and the high activities of the N-Cl bond, which resulted in a novel Cu-catalyzed amination of arylboronic acids under mild conditions (Scheme 2.3).[8] Notably, the chloro, bromo, and iodo moieties on the phenyl rings of both amides and arylboronic acids could be tolerated under the reaction conditions.



Scheme 2.3 Cu-catalyzed amination of arylboronic acids with *N*-chloroamides

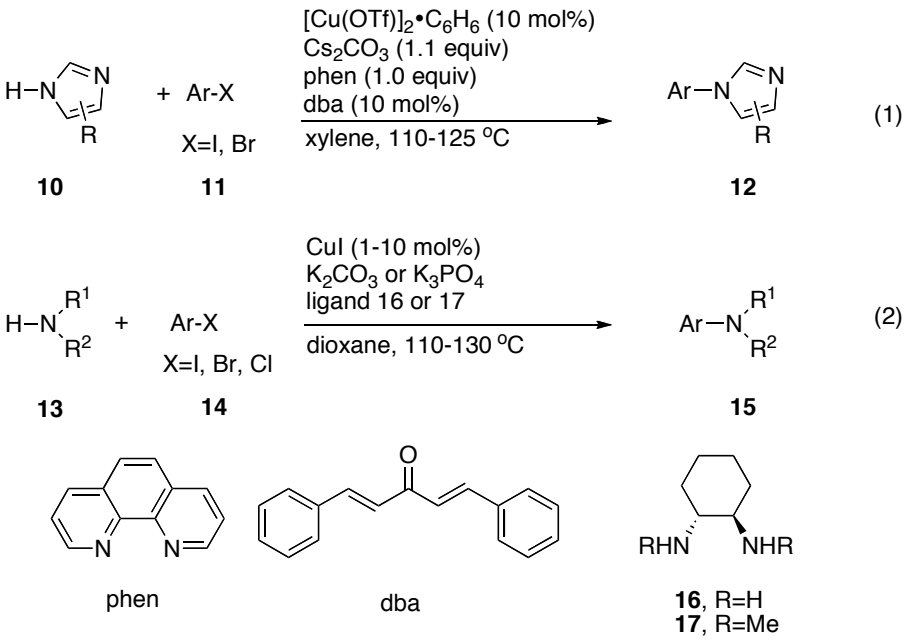
2.2 Cu-catalyzed amination of aryl halides and pseudohalides

The C-N coupling reaction can be traced back to the beginning of last century, when seminal Ullmann-type reactions were discovered. Since then, copper salts have been

dominantly reported as catalysts for these coupling reactions.

2.2.1 Cu-catalyzed amination of aryl halides

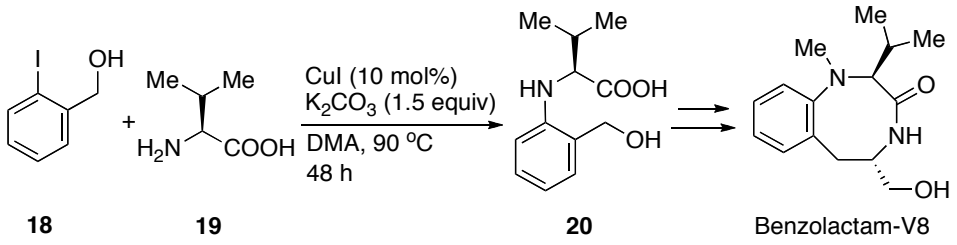
In the classical Ullmann-type C-N coupling reactions, copper salts were initially used as catalysts to form C-N bonds from aryl halides and amines.[9] Buchwald and co-workers reported one of the first modern Cu-catalyzed C-N coupling reactions. They demonstrated that $[Cu(OTf)]_2$•benzene could efficiently catalyze the reaction between imidazoles **10** and arylhalides **11**, including aryl iodides and aryl bromides (Scheme 2.4, Eq. 1).[10] It was found that the addition of 1,10-phenanthroline (phen) and *trans,trans*-dibenzylideneacetone (dba) was crucial to the success of this transformation. This process could be conducted at relatively low temperatures and was effective for a wide variety of substrates with high yields of desired products. This pioneering work has witnessed a



Scheme 2.4 Cu-catalyzed amination of arylhalides

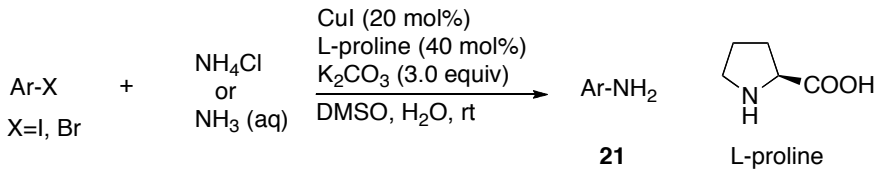
tremendous development of this research area. Since then, they have made further important contributions to the introduction of a general synthesis of aryl C-N bonds. In 2001, they presented a general and efficient *N*-arylation of amides **13** and nitrogen heterocycles with aryl halides (Scheme 2.4, Eq. 2).[11] This protocol employed CuI as catalyst, K_2CO_3 or K_3PO_4 as base, and simple diamines **16** or **17** as ligand. Notably, aryl chlorides were successfully explored as good arylation substrates and the amine components could be extend to various amides, amines, and nitrogen heterocycles.

Optically pure α-amino acids are some of the most important building blocks in organic synthesis, the application of which in C-N coupling reactions and further complex molecule syntheses is always of great interest to organic chemists. Ma *et al.* reported a general CuI-catalyzed C-N coupling reaction of aryl halides with α-amino acids.[12] Compared to the classical Ullmann-type reaction conditions, the accelerating effect induced by α-amino acids has allowed the coupling reaction to occur at significantly lower temperatures. Furthermore, the application of this method to the coupling of *orth*-iodobenzoic acid derivative **18** and L-valine **19** resulted in an efficient preparation of **20**, which was a key intermediate for the synthesis of benzolactam-V8 (Scheme 2.5).



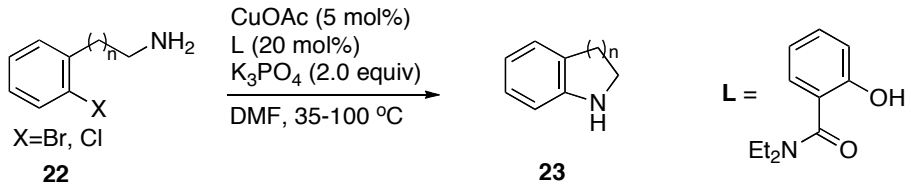
Scheme 2.5 Synthesis of benzolactam-V8 based on Cu-catalyzed C-N coupling

Recently, the cheap and stable NH_4Cl solid was utilized as an ammonia surrogate in the Cu-catalyzed amination of aryl halides, affording aniline derivatives efficiently (Scheme 2.6).[13] It was found that this process could proceed at room temperature due to the accelerating effect of L-proline as ligand.



Scheme 2.6 Cu-catalyzed amination of aryl halides with ammonium salts

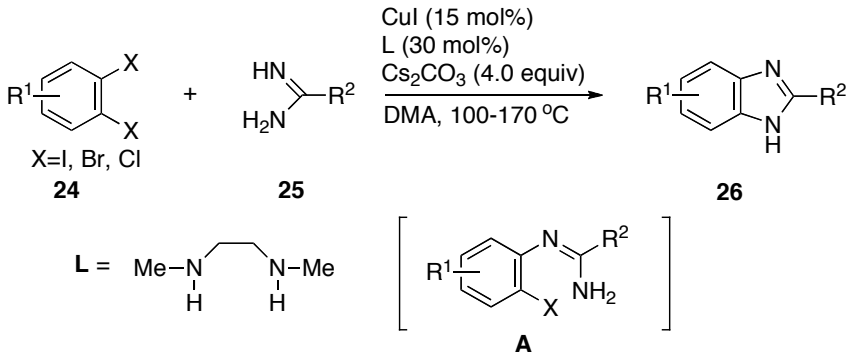
In addition to the formation of a C-N bond based on cross-coupling reactions, intramolecular processes have also been achieved in the presence of copper catalysts, which provides an efficient route to the synthesis of *N*-containing heterocycles. Buchwald *et al.* demonstrated that the cyclization of *ortho*-bromo or *ortho*-chlorophenethylamines **22** worked well in the presence of CuOAc as a catalyst, providing easy access to nitrogen heterocycles **23** (Scheme 2.7).[14]



Scheme 2.7 Intramolecular Cu-catalyzed amination of arylhalides

Recently, Deng *et al.* reported a CuI-catalyzed tandem double amination of 1, 2 dihalobenzene **24** with substituted guanidines **25**, allowing the preparation of

benzimidazole derivatives **26** in one step from simple starting materials (Scheme 2.8).[15] They believed this transformation occured through intermediate **A**, which was the product of a classical intermolecular C-N coupling reaction.

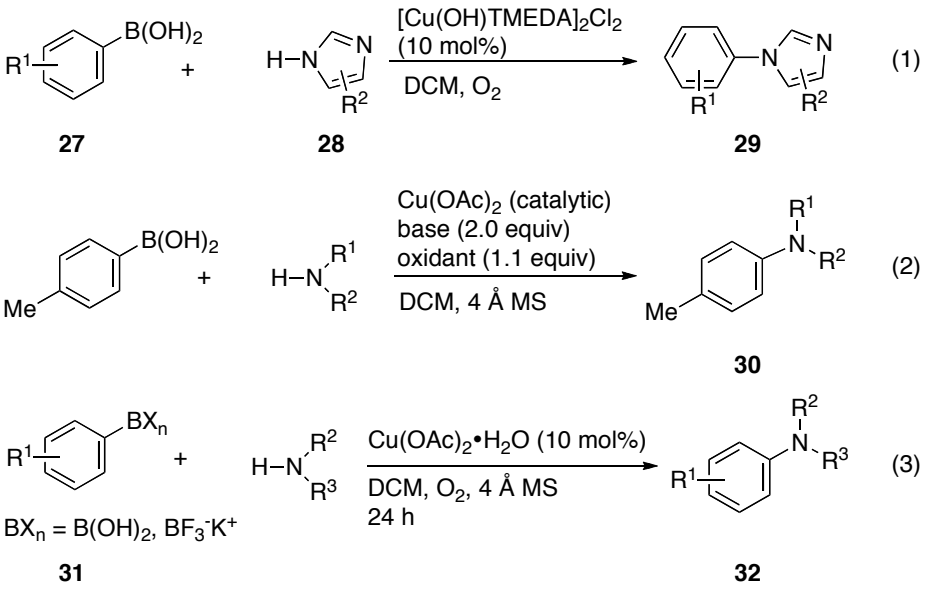


Scheme 2.8 Tandem aminations of 1,2-dihalobenzens with guanidines

2.2.2 Cu-catalyzed amination of aryl pseudohalides

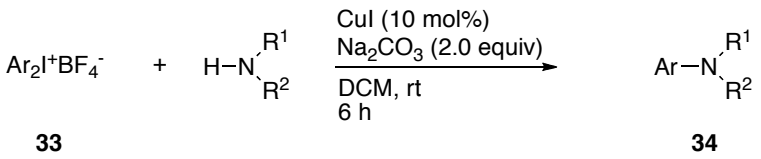
Other arylation reagents instead of aryl halides have also been explored as Cu-catalyzed C-N coupling partners. In 1998, Chan-Lam-Evans reactions were introduced for the formation of aryl C-N bonds by using arylboronic acids as aryl donors.[16] However, a stoichiometric amount of copper salts was required. Later, catalytic versions were developed, also involving copper salts as catalysts. The first example was introduced by Collman and Zhong, which demonstrated that C-N coupling of aryl boronic acids with imidazoles **28** could be achieved in the presence of a catalytic amount of $[Cu(OH)TMEDA]_2Cl_2$ (Scheme 2.9, Eq. 1).[17] Lam *et al.* reported a $Cu(OAc)_2$-catalyzed example, which could be applied to more general amine substrates (Scheme 2.9, Eq. 2).[16b] Later, Quach and Batey improved this method by extending the substrate scope to

both potassium aryltrifluoroborate salts **31** and a wide variety of amine derivatives, avoiding the use of any base and ligand (Scheme 2.9, Eq. 3).[18]



Scheme 2.9 Cu-catalyzed amination of arylboronic reagents

Aryliodonium salts **33** have also been used as arylation reagents in the presence of a catalytic amount of CuI (Scheme 2.10).[19] One advantage of this method is that this process can be conducted under mild conditions, making it feasible for a wide variety of amine substrates due to functional group tolerance.



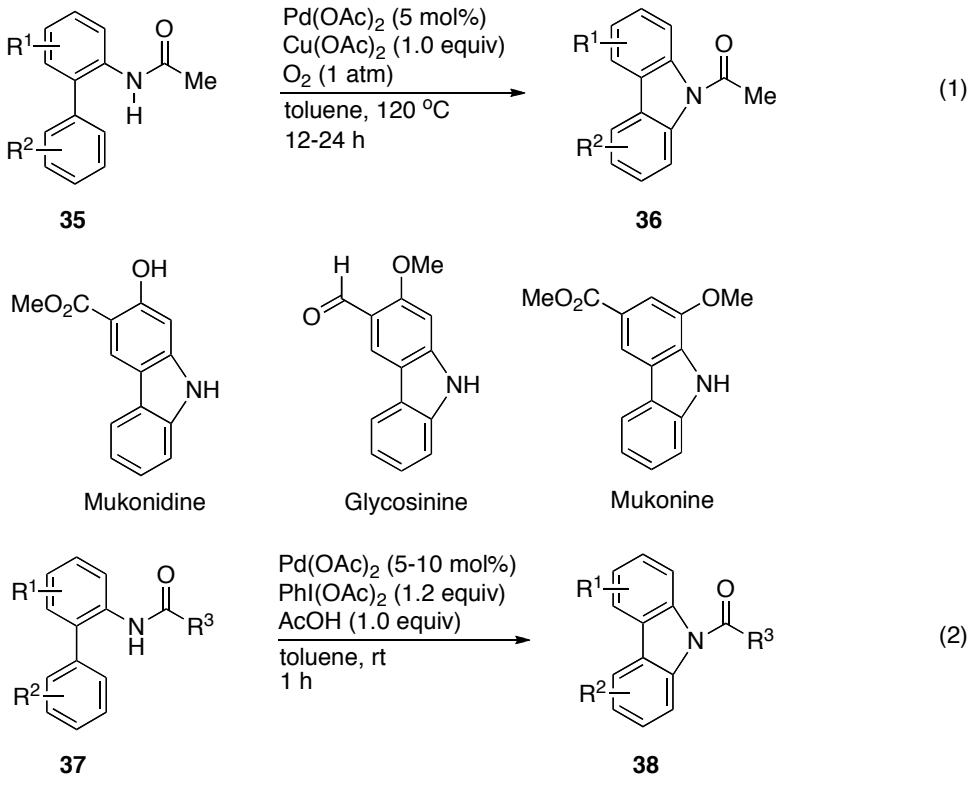
Scheme 2.10 Cu-catalyzed amination of aryliodonium salts

2.3 Oxidative amination of unactivated arenes

The great success of C-C bonds formation via C-H activation encourages organic chemists to explore its feasibility for the formation of C-N formation, which has resulted in considerable progress in this research area. Herein, we will focus on the oxidative aryl C-N coupling processes based on aryl C-H bonds activation.

2.3.1 Intramolecular oxidative amination of unactivated arenes

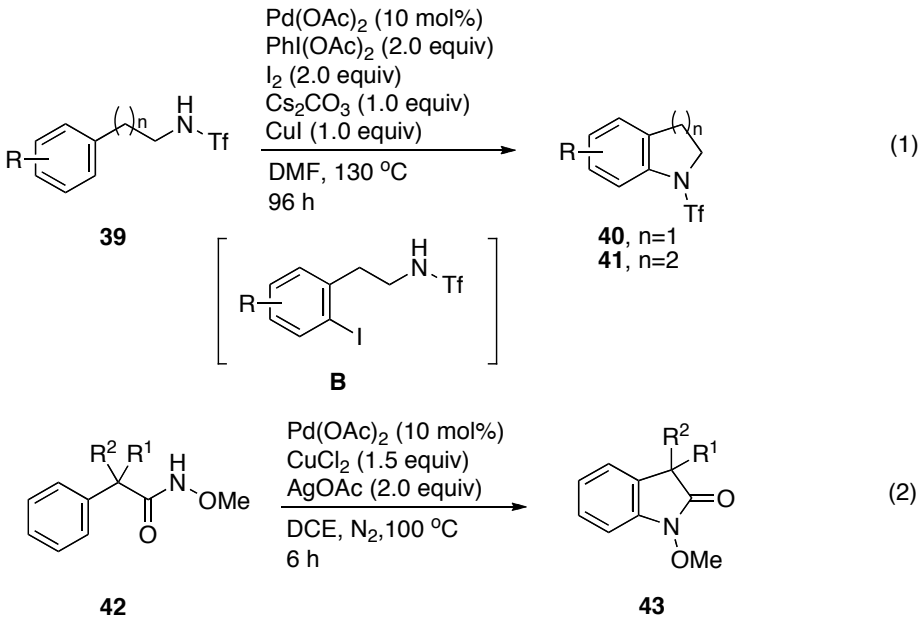
Compared with traditional methods, intramolecular C-N coupling reactions via C-H activation provide a straightforward access to the synthesis of *N*-containing heterocycles. In 2005, the Buchwald group developed a new method for the efficient preparation of



Scheme 2.11 Pd-catalyzed synthesis of substituted carbazoles

carbazoles **36** from 2-phenylacetanilide derivatives **35** via a tandem C-H activation and C-N coupling process (Scheme 2.11, Eq. 1).[20] This method can be applied to an extensive scope of substrates, affording desired products in high yields. This transformation was believed to proceed via a Pd(0)-Pd(II) catalytic cycle. The application of this protocol in the synthesis of natural products was also accomplished, such as mukonidine, glycosinine, and mukonine (Scheme 2.11, Eq. 1).[21] Later, Gaunt *et al.* reasoned that reductive elimination from a high oxidation state Pd(IV) center would more readily facilitate C-N bond formation and successfully disclosed an ambient Pd(II)-catalyzed C-H bond amination process (Scheme 2.11, Eq. 2).[22]

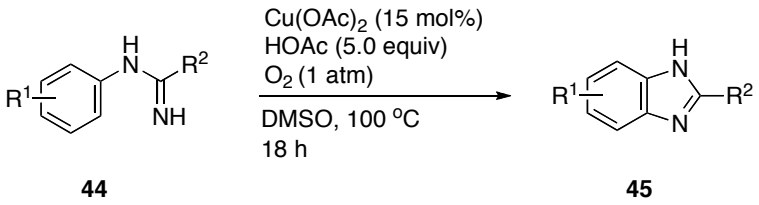
In 2008, the Yu group presented a direct construction of indolines **40** and tetrahydroisoquinolines **41** from arylamines **39** (Scheme 2.12, Eq. 1). They demonstrated



Scheme 2.12 Pd-catalyzed synthesis of indolines, isoquinolines and lactams

that a tandem Pd(II)-catalyzed iodination and Cu-catalyzed C-N coupling occurred via the intermediate **B**, affording the final cyclization products.[23] Later, a more practical version was developed, which employed amide substrates **42** and avoided the use of base and I_2 (Scheme 2.12, Eq. 2).[24]

Copper complexes have been rarely reported as effective catalysts for the direct oxidative C-N coupling reactions. In 2008, Buchwald *et al.* reported that $Cu(OAc)_2$ could catalyze the formation of benzimidazoles **45** via the cyclization of amidines **44** (Scheme 2.13).[25] It was realized that the addition of AcOH was crucial to this transformation. Notably, oxygen could be used as an oxidant and the reaction could be conducted in air.

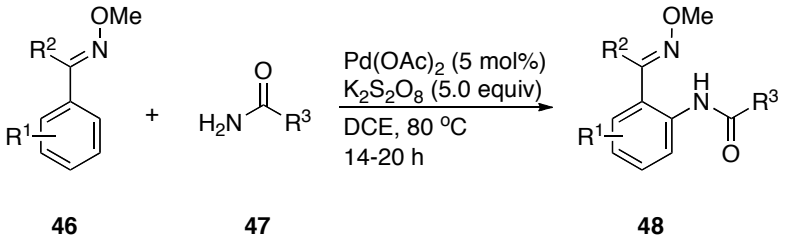


Scheme 2.13 Cu-catalyzed synthesis of benzimidazoles from amidines

2.3.2 Intermolecular oxidative amination of unactivated arenes

In the case of intermolecular C-N coupling reactions, a pre-installed directing group is generally essential to control the regioselectivity of the C-H activation process. In 2006, Che *et al.* reported a Pd-catalyzed amidation of unactivated arenes **46**, employing oxime as the directing group (Scheme 2.14).[26] Under their optimal reaction conditions, various primary amides **47** turned out to be effective substrates, affording exclusive *ortho*-

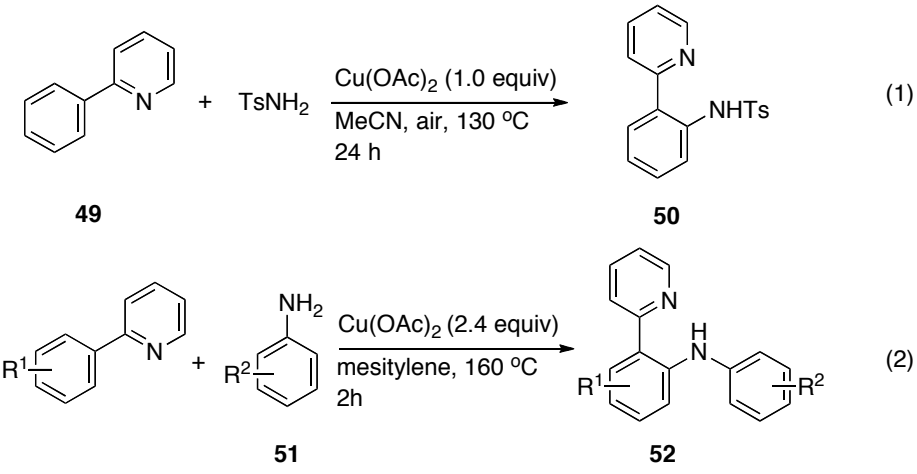
amidation products **48** in high yields. However, this method is not applicable to benzamide, 2° amides and 1°/2° amines.



46 **47** **48**

Scheme 2.14 Pd-catalyzed *ortho*-amidation of aromatic oximes

At the early stage of C-H activation development, 2-phenylpyridine derivatives have been widely used as substrates. The Yu group reported an example of amination of 2-phenylpyridine **49** with $TsNH_2$ in the presence of a stoichiometric amount of $Cu(OAc)_2$ (Scheme 2.15, Eq. 1).[27] Later, the Chatani group was able to extend this method to other amine substrates **51**, although the yields were low (Scheme 2.15, Eq. 2).[28]

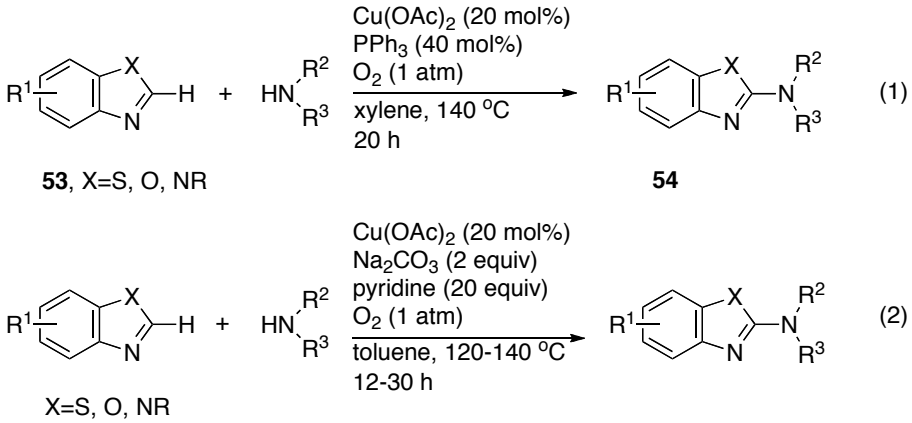


49 **50**

51 **52**

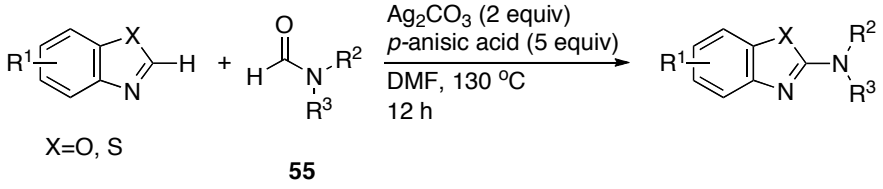
Scheme 2.15 Cu-mediated oxidative amination of 2-phenylpyridines

Recently, Cu-mediated oxidative amination of nitrogen heterocycles **53** has been achieved under aerobic conditions. In the method developed by the Mori group, a PPh_3 ligand was essential (Scheme 2.16, Eq. 1).[29] A similar report presented by Schreiber *et al.* revealed that both organic and inorganic base played an important role under their optimal reaction conditions (Scheme 2.16, Eq. 2).[30]



Scheme 2.16 Cu-catalyzed oxidative amination of heterocyclic C-H bonds

In 2009, a novel silver mediated amination strategy was developed by the Chang group, which employed formamides **55** as nitrogen donors through an acid-promoted decarbonylation process (Scheme 2.17).[31]



Scheme 2.17 Ag-mediated direct amination of benzoxazoles

2.4 Copper-catalyzed oxidative amidation of 2-arylpyridine derivatives

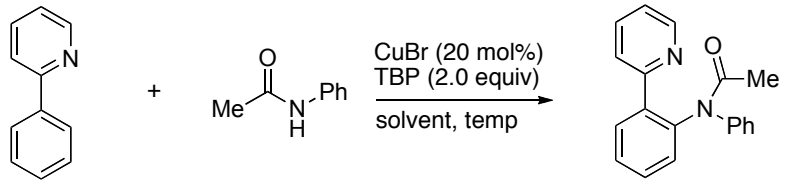
2.4.1 Background

As illustrated above, the transition-metal-catalyzed direct amination of unactivated arenes, in the presence of an appropriate oxidant, has served as an important tool to construct aryl C-N bonds. Among them, cheap copper salts as catalysts are of great interest to organic chemists. Meanwhile, arylamide has been recognized as an important structural motif for biological studies.[32] Herein, we present a Cu-catalyzed direct and highly site-selective amidation of 2-arylpyridine derivatives through a cross-dehydrogenative-coupling (CDC) process, which can serve as a novel approach to modify amides and directly produce various biologically useful arylamide derivatives.

2.4.2 Optimization of reaction conditions

We began our studies by examining the reaction of 2-phenylpyridine **49a** with acetanilide **56a** in dioxane by using CuBr (20 mol%) as catalyst and *tert*-butyl peroxide (TBP) as an oxidant. To our delight, the desired *ortho*-amidated product **57a** was isolated in fair yield (Table 1, entry 1) and its molecular structure was confirmed by X-ray crystallography (Figure 2.1). Oxygen was also found to be an effective oxidant, although the yield was only moderate (entry 3). Later, when the reaction was performed in benzene, it afforded the corresponding amidation product in 56% yield (entry 4). Increasing the substrate concentration improved the yield to 67% (entry 5). A higher temperature led to a decreased yield possibly due to the decomposition of product (entry 6), whereas a longer reaction time at a lower temperature did not significantly improve the yield (entry 7).

Table 2.1 Optimization of reaction conditions[a]



49a **56a** **57a**

entry	solvent	temp (°C)	yield[b] (%)
1	dioxane	120	45(32)
2[c]	dioxane	120	trace
3[d]	dioxane	120	31
4	benzene	120	56
5[e]	benzene	120	67
6[e]	benzene	130	27
7[e,f]	benzene	100	50
8[g]	benzene	120	80 (71)
9	DMSO	120	trace
10	DMF	120	0
11	toluene	120	44
12	xylene	120	25
13[h]	neat	120	92 (87)

[a] Unless otherwise noted, all reactions were performed under standard reaction conditions: 2-phenylpyridine **49a** (31 mg, 0.2 mmol), acetanilide **56a** (54 mg, 0.4 mmol), TBP (74 μL, 0.4 mmol), solvent (0.6 mL), oil bath for 16 h. [b] ^{1}H-NMR yields using an internal standard; isolated yields were in parenthesis. [c] Oxidant: *tert*-butyl hydroperoxide (5.0-6.0 M solution in decane, 73 μL, 0.4 mmol). [d] Oxidant: O_2 (1 atm). [e] Reactions in benzene (0.2 mL). [f] 48 h. [g] **49a** (47 mg, 0.3 mmol), **56a** (27 mg, 0.2 mmol), benzene (0.1 mL). [h] **49a** (47 mg, 0.3 mmol), **56a** (27 mg, 0.2 mmol).

To further optimize the reaction conditions, we decided to change the ratio of the two substrates, since the *ortho*-bromination product of 2-phenylpyridine was found to be a major side product. When 1.5 equivalents of **49a** were used, the yield was increased up to 80% (entry 8). When the reaction was carried out in other solvents, no good results were obtained (entries 9-12). An excellent yield (92%) was obtained when the reaction was carried out under neat conditions (entry 13).

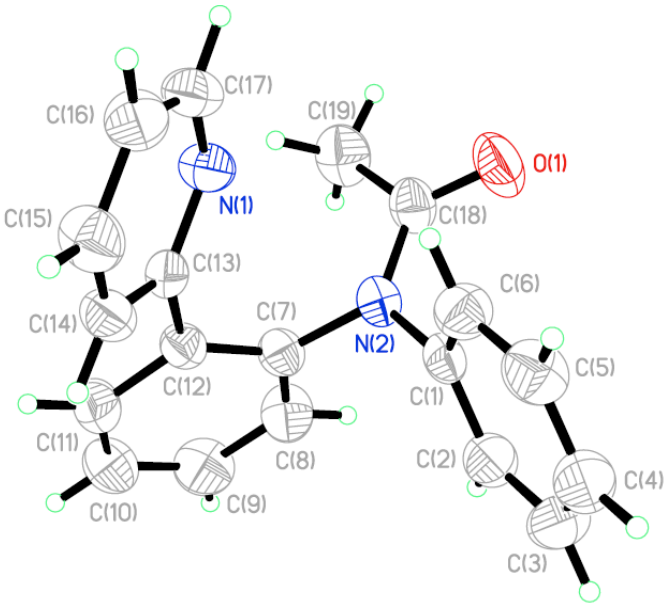


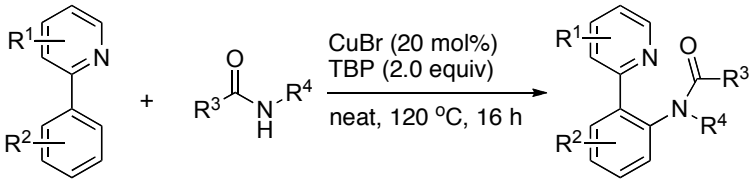
Figure 2.1 ORTEP representation of the molecular structure of **57a**

2.4.3 Scope of the oxidative amidation of 2-arylpyridines

With the optimal reaction conditions in hand, we then explored the scope and generality of this transformation (Table 2.2). Both 1° and 2° amides were found to be effective substrates for the *ortho*-amidation of **49a**. With an *ortho*-methoxy substituted phenyl ring, the amide **56b** gave a reasonable yield of the arylation product, although it is more

sterically hindered (entry 2). It is possible that coordination of the methoxy group to Cu facilitated the amidation process. The amide bearing phenyl with an electron-withdrawing group at *para*- position formed the product in good yield (entry 3). Notably, the chloro, bromo and iodo moieties on arylamides were all well tolerated under these reaction conditions and afforded the target products in good yields (entries 4-8**),** which makes further elaborations of the corresponding amidation products readily. Substituents either on the pyridine ring or phenyl ring of **49** did not significantly affect the efficiency of the transformation (entries 8 and 9). The desired product was obtained in excellent yield with sterically hindered benzoquinoline **49d** with a rigid skeleton (entry 10). *N*-Methylbenzamide **56h** also turned out to be a suitable substrate (entry 11). Simple 1° amides **56i** and **56j** were not good substrates under neat conditions. However, the amidation products **57l** and **57m** were obtained in comparatively lower yields when benzene was employed as solvent (entries 12 and 13). It might be explained that the nucleophilicity of 1° amides is not as good as that of 2° amides.

Table 2.2 Amidation of 2-arylpyridine[a]



49 **56** **57**

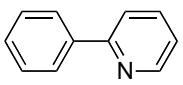
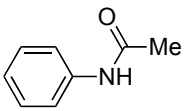
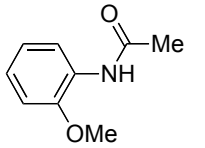
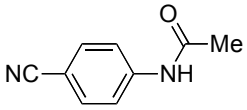
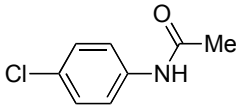
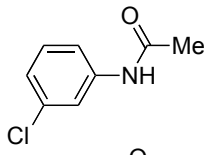
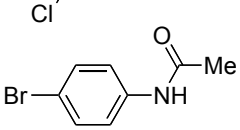
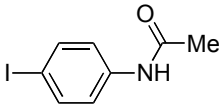
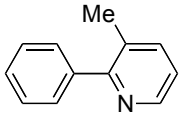
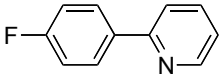
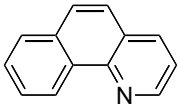
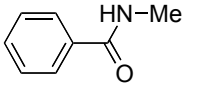
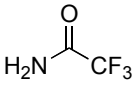
entry	2-arylpyridine		amide		yield **57** %[b]
1		**49a**		**56a**	**57a** (87)

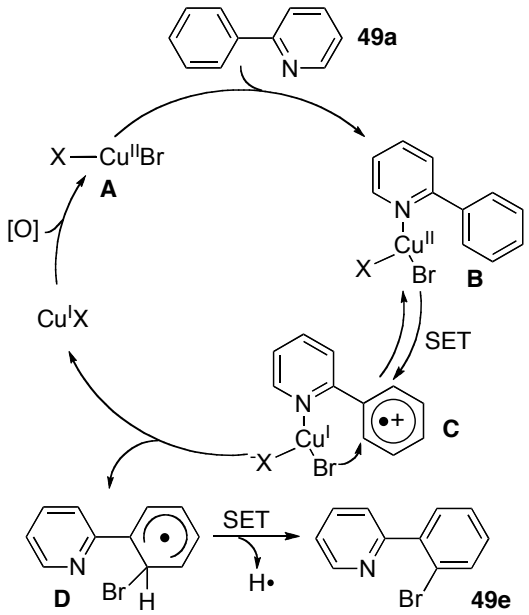
Table 2.2 (continued)

entry	2-arylpyridine	amide		yield **57** %[b]
2	**49a**		**56b**	**57b** (63)
3	**49a**		**56c**	**57c** (70)
4	**49a**		**56d**	**57d** (79)
5	**49a**		**56e**	**57e** (90)
6	**49a**		**56f**	**57f** (83)
7	**49a**		**56g**	**57g** (78)
8	 **49b**	**56f**		**57h** (70)
9	 **49c**	**56a**		**57i** (76)
10	 **49d**	**56a**		**57j** (90)
11	**49a**		**56h**	**57k** (83)
12	**49a**		**56i**	**57l** (49)[c]
13	**49a**	NH_2Ts	**56j**	**57m** (37)[c]

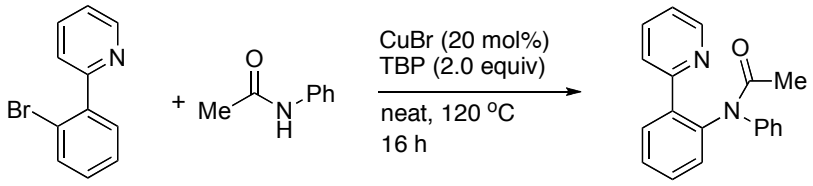
[a] All reactions performed under standard reaction conditions: 2-arylpyridine (**49**, 0.6 mmol), amide (**56**, 0.4 mmol), TBP (148 μL, 0.8 mmol), 120 °C for 16 h. [b] Isolated yields based on amides. [c] In benzene (0.2 mL).

2.4.4 Proposed mechanism of the oxidative amidation of 2-arylpyridines

In terms of the mechanism of the amidation of 2-arylpyridine, since 2-(2-bromophenyl)pyridine **49e** was isolated as a major side product, it was proposed that a bromination of 2-phenylpyridine **49a** occurred first through a single electron transfer (SET) process and the formation of the cation-radical intermediate **C** was the rate-limiting step (Scheme 2.18).[27] A subsequent Ullmann-type coupling of **49e** with amide **56a** afforded the final product,[33] which worked well under the same reaction conditions (Scheme 2.19). The observed high *ortho*-selectivity was achieved through chelation methodology in the presence of a directing group and, notably, no diamidation product was observed.



Scheme 2.18 Proposed mechanism for the bromination of 2-phenylpyridine



49e **56a** **57a,** 75%

Scheme 2.19 Cu-catalyzed amidation of 2-(2-bromophenyl)pyridine

2.4.5 Conclusions

In conclusion we have developed a novel method for the direct and highly regioselective amidation of 2-arylpyridine derivatives in the absence of a specialized ligand or a base. This new method requires only inexpensive CuBr as catalyst and *tert*-butyl peroxide as oxidant, and can tolerate aryl halides.

2.4.6 Experimental section

General experimental details

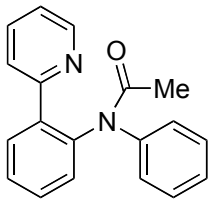
Arylacetamides **56b-56g** were prepared by reacting the corresponding anilines with acetyl chlorides in water and CH_2Cl_2, followed by aqueous 1M NaOH work-up, extraction with CH_2Cl_2, and recrystallization from Hexane/EtOAc.[34] *N*-Methylbenzamide **56h** was synthesized by treating benzoyl chloride with methylamine (large excess) in ether, followed by recrystallization from ether/hexane.[35] 3-Methyl-2-phenylpyridine **49b** and 2-(4-fluorophenyl)pyridine **49c** were prepared through the Suzuki coupling of the corresponding boronic acids and 2-bromopyridines following a literature procedure.[36] 2-(2-bromophenyl)pyridine **49e** was prepared by treating 2-phenylpyridine with NBS

catalyzed by $Pd(OAc)_2$.[37] Other reagents were commercially available and used as received. All reagents were weighed and handled in air.

^1H and ^{13}C-NMR spectra were recorded on Varian 400 and 500 MHz spectrometers in $CDCl_3$ solutions and chemical shifts (δ, ppm) were determined with internal solvent signal as reference (7.26 for ^1H-NMR and 77.0 for ^{13}C-NMR). HRMS were made by McGill University. Flash column chromatography was performed on EMD Silica Gel 60 with an appropriate solvent system (see details below). X-ray diffraction data were measured on a D8 diffractometer (Bruker, Billerica, MA). Melting points were measured on Gallenkamp melting point apparatus (MF-370).

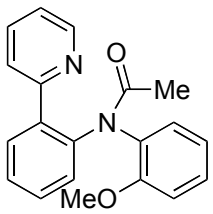
General experimental procedures and characterizations

A mixture of 2-arylpyridine (0.6 mmol), CuBr (11.5 mg, 0.08 mmol, 20 mol%), amide (0.4 mmol) and *tert*-butyl peroxide (TBP, 148 μL, 0.8 mmol) was combined and sealed in a 5 mL conical vial with a Teflon lined cap. The vial was heated at 120 ^oC in an oil bath for 16 h and then cooled to room temperature. The resulting mixture was diluted with EtOAc and filtered through a plug of silica gel eluting with EtOAc. The filtrate was concentrated *in vacuo* with a rotary evaporator and the residue was purified by column chromatography on silica gel. When amides NH_2COCF_3 (45 mg, 0.4 mmol) and NH_2Ts (68 mg, 0.4 mmol) were used as substrates, benzene was required as a solvent (0.2 mL) and other conditions were not changed.



N-Phenyl-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57a**

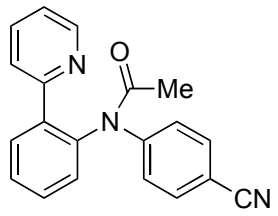
57a was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56a** (54 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57a** (a mixture of two rotamers) as a light orange solid (100 mg, 87 %), mp 124-125 °C. IR: ν_{max} 3055, 3012, 1664, 1582, 1491, 1367, 1328, 768, 746, 696, 650 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.63 (br s, 1H), 7.73-6.98 (m, 12H), 2.08-1.92 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.0, 157.9, 156.5, 149.6, 149.1, 143.4, 142.2, 141.0, 140.7, 139.2, 136.3, 131.4, 130.8, 130.3, 129.7, 129.1, 128.6, 128.2, 127.6, 127.1, 125.2, 125.1, 123.9, 123.3, 122.3, 24.4, 22.8. HRMS exact mass calc'd for $C_{19}H_{17}ON_2$ ([M+H]) *m/z*: 289.1335; found *m/z*: 289.1325.



N-(2-Methoxyphenyl)-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57b**

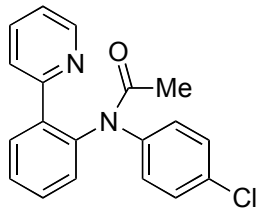
57b was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56b** (66 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57b** (a mixture of two rotamers) as a colorless oil (80 mg, 63 %). IR: ν_{max} 3050, 3005, 1667, 1585, 1495, 1461, 1424, 1368, 1327, 1276, 1239, 1025, 792, 747, 696, 644 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.69

(s, 1H), 7.77-7.10 (m, 8H), 6.96-6.57 (m, 3H), 3.85-3.75(m, 3H), 2.08-1.81 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 172.2, 171.4, 158.3, 157.4, 154.8, 154.6, 149.6, 149.0, 141.5, 140.9, 138.9, 138.7, 136.4, 136.3, 132.6, 131.0, 130.6, 130.1 129.4, 129.0, 128.7, 128.6, 128.2, 127.9, 127.5, 124.2, 123.8, 122.3, 122.1, 121.2, 120.6, 112.0, 111.6, 55.5, 55.4, 23.3, 21.9. HRMS exact mass calc'd for $C_{20}H_{19}O_2N_2$ ([M+H]) *m/z*: 319.1441; found *m/z*: 319.1430.



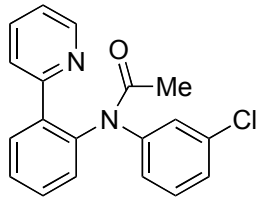
N-(4-Cyanophenyl)-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57c**

57c was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56c** (64 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57c** as a light yellow oil (88 mg, 70 %). IR: ν_{max} 3056, 3006, 2224, 1676, 1599, 1585, 1501, 1365, 1289, 836, 795, 744, 673 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.60 (dd, *J*=4.0 Hz, 0.8 Hz, 1H), 7.64-7.53 (m, 4H), 7.41-7.37 (m, 3H), 7.22-7.12 (m, 4H), 2.10 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 171.2, 156.3, 149.5, 146.2, 139.8, 139.1, 136.6, 132.2, 131.5, 130.4, 130.0, 129.3, 125.0, 123.2, 122.5, 118.7, 107.7, 24.7. HRMS exact mass calc'd for $C_{20}H_{16}ON_3$ ([M+H]) *m/z*: 314.1288; found *m/z*: 314.1278.



N-(4-Chlorophenyl)-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57d**

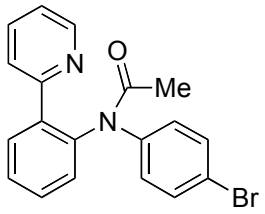
57d was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56d** (68 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57d** (a mixture of two rotamers) as a yellow oil (102 mg, 79 %). IR: ν_{max} 3054, 1670, 1584, 1488, 1470, 1443, 1366, 1315, 1299, 1285, 1090, 1013, 826, 748, 727, 708, 665 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.62 (br s, 1H), 7.74-6.89 (m, 11H), 2.09-1.89 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.0, 156.4, 149.5, 149.0, 140.6, 139.0, 136.4, 131.4, 130.8, 130.3, 129.8, 129.3, 128.8, 128.2, 126.4, 123.9, 123.2, 122.4, 24.4, 22.7. HRMS exact mass calc'd for $C_{19}H_{16}ON_2Cl$ ([M+H]) *m/z*: 323.0946; found *m/z*: 323.0934.



N-(3-chlorophenyl)-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57e**

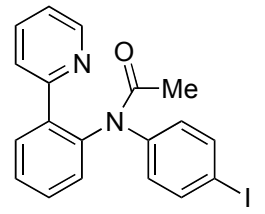
57e was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56e** (68 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57e** (a mixture of two rotamers) as a yellow oil (116 mg, 90 %). IR: ν_{max} 3060, 1665, 1584, 1470, 1369, 1328, 1300, 922, 784, 770, 754, 732, 689, 679 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.64 (s, 1H), 7.60-6.84 (m,

11H), 2.08 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.0, 156.4, 149.5, 143.2, 140.5, 139.1, 136.4, 133.7, 131.3, 130.3, 129.8, 129.0, 128.9, 128.0, 127.4, 125.5, 125.2, 123.3, 122.4, 24.4, 22.9. HRMS exact mass calc'd for $C_{19}H_{16}ON_2Cl$ ([M+H]) *m/z*: 323.0946; found *m/z*: 323.0944.



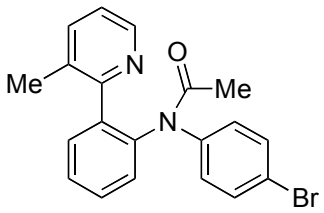
N-(4-Bromophenyl)-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57f**

57f was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56f** (92 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57f** (a mixture of two rotamers) as a yellow oil (122 mg, 83 %). IR: ν_{max} 3055, 1669, 1584, 1485, 1366, 1315, 1297, 1010, 896, 822, 794, 747, 716, 660 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.63 (br s, 1H), 7.62-7.22 (m, 9H), 6.97-6.86 (m, 2H) 2.09-1.91 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.0, 156.4, 149.6, 141.2, 140.6, 139.1, 136.5, 136.2, 132.3, 131.4, 131.2, 130.3, 129.8, 129.3, 128.9, 127.9, 126.8, 123.9, 123.3, 122.4, 118.3, 24.4, 22.8. HRMS exact mass calc'd for $C_{19}H_{16}ON_2Br$ ([M+H]) *m/z*: 367.0417; found *m/z*: 367.0430.



N-(4-Iodophenyl)-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57g**

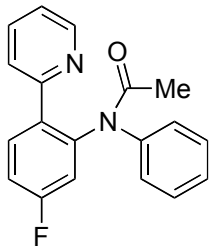
57g was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56g** (111 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57g** (a mixture of two rotamers) as a light yellow solid (129 mg, 78 %), mp 115-116 °C. IR: ν_{max} 3046, 1669, 1586, 1484, 1471, 1426, 1375, 1327, 1007, 822, 796, 749, 716, 709 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.63 (br s, 1H), 7.62-7.23 (m, 9H), 6.85-6.75 (m, 2H), 2.07-1.92 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.0, 156.4, 149.6, 141.9, 140.5, 139.1, 138.3, 137.2, 136.5, 131.4, 131.2, 130.3, 129.8, 128.9, 127.9, 127.1, 126.8, 123.8, 123.2, 122.4, 89.5, 24.4, 22.7. HRMS exact mass calc'd for $C_{19}H_{16}ON_2I$ ([M+H]) *m/z*: 415.0302; found *m/z*: 415.0286.



N-(4-Bromophenyl)-*N*-(2-(3-methylpyridin-yl)phenyl)acetamide **57h**

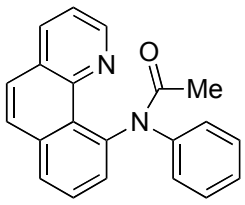
57h was prepared from 2-arylpyridine **49b** (102 mg, 0.6 mmol) and amide **56f** (92 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57h** (a mixture of two rotamers) as a light yellow solid (107 mg, 70 %), mp 95-96 °C. IR: ν_{max} 2928, 1679, 1572, 1489, 1449, 1366, 1318, 1303, 1068, 1010, 828, 800, 772 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.47-8.35 (m, 1H), 7.55-7.13 (m, 9H), 6.51-6.50 (m, 1H), 2.24-2.18 (m, 3H), 1.69-1.53 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.2, 155.8, 146.7, 145.9, 141.1, 140.3, 139.0, 138.0, 137.8, 132.1, 132.0, 131.0, 130.5, 129.6, 129.2, 128.9, 128.3, 127.6, 127.0, 122.8,

122.4, 118.7, 24.1, 22.7, 19.1, 18.3. HRMS exact mass calc'd for $C_{20}H_{18}ON_2Br$ ([M+H]) *m/z*: 383.0577; found *m/z*: 383.0564.



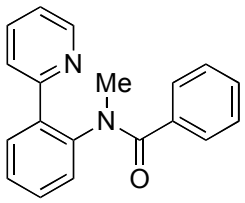
N-(5-Fluoro-2-(pyridin-2-yl)phenyl)-*N*-phenylacetamide **57i**

57i was prepared from 2-arylpyridine **49c** (104 mg, 0.6 mmol) and amide **56a** (54 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57i** (a mixture of two rotamers) as a light yellow solid (93 mg, 76 %), mp 69-70 °C. IR: ν_{max} 3058, 3009, 1672, 1605, 1590, 1565, 1493, 1465, 1428, 1412, 1368, 1328, 1301, 1209, 1151, 827, 787, 760, 736, 693, 654 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.62 (br s, 1H), 7.74-7.55 (m, 2H), 7.23-7.07 (m, 9H), 2.08-1.90 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 170.9, 170.6, 163.8, 161.8, 157.2, 155.7, 149.7, 149.2, 143.0, 142.3, 142.0, 136.5, 135.3, 132.8, 132.1, 129.3, 128.4, 127.7, 125.3, 123.9, 123.2, 122.3, 117.3, 116.3, 116.1, 115.9, 114.9, 24.3, 22.8. HRMS exact mass calc'd for $C_{19}H_{16}ON_2F$ ([M+H]) *m/z*: 307.1241; found *m/z*: 307.1232.



N-(Benzo[*h*]quinolin-10-yl)-*N*-phenylacetamide **57j**

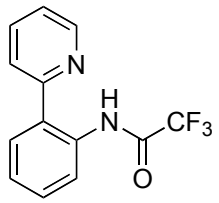
57j was prepared from 2-arylpyridine **49d** (108 mg, 0.6 mmol) and amide **56a** (54 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57j** (a mixture of two rotamers) as a white solid (112 mg, 90 %), mp 152-153 °C. IR: ν_{max} 3048, 1668, 1621, 1594, 1564, 1492, 1423, 1371, 1331, 1297, 976, 834, 776, 758, 724, 702, 671, 648 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 9.01-8.93 (m, 1H), 8.16-7.04 (m, 12H), 2.34-1.89 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 172.4, 171.1, 149.0, 148.1, 145.8, 145.7, 144.8, 142.9, 140.9, 140.7, 136.1, 135.9, 135.6, 135.5, 131.1, 129.9, 129.2, 129.0, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.3, 127.3, 126.9, 126.7, 126.6, 126.3, 125.7, 124.9, 122.0, 121.7, 24.1, 23.5. HRMS exact mass calc'd for $C_{21}H_{17}ON_2$ ([M+H]) *m/z*: 313.1323; found *m/z*: 313.1335.



N-Methyl-*N*-(2-(pyridin-2-yl)phenyl)benzamide **57k**

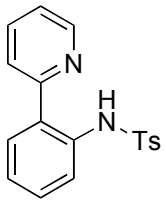
57k was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56h** (54 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:2) to afford **57k** (a mixture of two rotamers) as a light yellow solid (96 mg, 83 %), mp 95-96 °C. IR: ν_{max} 3057, 2922, 2853, 1632, 1596, 1575, 1465, 1423, 1369, 1303, 794, 747, 719, 701, 655, 630 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.60 (d, *J*=4.0 Hz, 1H), 7.67 (td, *J*=8.0 Hz, 1.5 Hz, 1H), 7.47 (d, *J*=7.5 Hz, 1H), 7.35 (td, *J*=7.5 Hz, 1.0 Hz, 1H), 7.28 (q, *J*=8.0 Hz, 2H), 7.22 (dd, *J*=7.0 Hz, 5.0 Hz,

1H), 7.15 (t, *J*=8.0 Hz, 2H), 7.02-6.96 (m, 4H), 3.41 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 170.1, 156.6, 149.7, 142.7, 137.6, 136.5, 135.4, 131.0, 129.5, 128.7, 128.3, 127.6, 127.2, 123.1, 122.0, 38.8. HRMS exact mass calc'd for $C_{19}H_{17}ON_2$ ([M+H]) *m/z*: 289.1335; found *m/z*: 289.1325.



2,2,2-Trifluoro-*N*-(2-(pyridin-2-yl)phenyl)acetamide **57l**

57l was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56i** (45 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (CH_2Cl_2/Hexane = 1:3) to afford **57l** (52 mg, 49 %).[38] ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 14.43 (br s, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.59 (d, *J*=8.5 Hz, 1H), 7.91-7.86 (m, 2H), 7.81 (d, *J*=7.5 Hz, 1H), 7.47 (t, *J*=7.8 Hz, 1H), 7.34-7.27 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 157.1, 155.1(q, *J*=37.0 Hz), 147.1, 138.2, 136.0, 130.5, 128.3, 125.2, 125.2, 122.4, 122.3, 121.9, 116.2 (q, *J*=286.8 Hz).



4-Methyl-*N*-(2-(pyridin-2-yl)phenyl)benzenesulfonamide **57m**

57m was prepared from 2-arylpyridine **49a** (93 mg, 0.6 mmol) and amide **56j** (68 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column

chromatography (CH_2Cl_2/MeOH = 16:1) to afford **57m** (48 mg, 37 %).[27] ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.47 (d, *J*=4.8 Hz, 1H), 7.63-7.56 (m, 3H), 7.45-7.34 (m, 3H), 7.23 (d, *J*=8.4 Hz, 2H), 7.14 (td, *J*=7.2 Hz, 1Hz), 6.97 (d, *J*=8.0 Hz, 2H), 2.33 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 154.3, 149.3, 146.6, 144.9, 135.8, 133.9, 131.6, 131.3, 129.9, 129.3, 128.1, 127.6, 125.1, 124.0, 122.0, 21.6.

References

(1) (a) Lawrence, S. A. *Amines: Synthesis Properties and Applications*; Cambridge University Press: Cambridge, 2004. (b) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: New York, 1984. (c) Patai, S. *The Chemistry of Amines, Nitroso, Nitro and Related Groups*; John Wiley & Sons: Chichester, 1996.

(2) For selected reviews, see: (a) T. Müller, K. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795. (b) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054. (c) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

(3) For reviews, see: (a) J. F. Hartwig, In *Handbook of Organopalladium Chemistry for Organic Synthesis*; E. Negishi, Ed.; Wiley: New York, 2002. (b) L. Jiang, Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 699. (c) D. Surry, S. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (d) C. Mauger, G. Mignani, *Aldrichim. Acta* **2006**, *39*, 17.

(4) (a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 364. (c) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219.

(5) M. J. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521.

(6) Y. Yu, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2004**, *6*, 2631.

(7) S. Liu, Y. Yu, L. S. Liebeskind, *Org. Lett.* **2007**, *9*, 1947.

(8) C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, A. Lei, *Angew. Chem., Int. Ed.* **2008**, *47*, 6414.

(9) H.B. Goodbrand, N.-X. Hu, *J. Org. Chem.* **1999**, *64*, 670.

(10) A. Kiyomori, J.-F. Marcoux, S. L. Buchwald, *Tetrahedron Lett.* **1999**, *40*, 2657.

(11) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald *J. Am. Chem. Soc.* **2001**, *123,* 7727.

(12) D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(13) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052.

(14) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793.

(15) X. Deng, H. McAllister, N. S. Mani, *J. Org. Chem.* **2009**, *74*, 5742.

(16) (a) P. Y. S. Lam, D. Bonne, G. Vincent, C. G. Clark, A. P. Combs, *Tetrahedron Lett.* **2003**, *44*, 1691. (b) P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon, P.K. Jadhav, *Tetrahedron Lett.* **2001**, *42*, 3415. (c) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941. (d) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937. (e) D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933.

(17) J. P. Collman, M. Zhong, *Org. Lett.* **2000**, *2*, 1233.

(18) T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 4397.

(19) S.-K. Kang, S.-H. Lee, D. Lee, *Synlett.* **2000**, *7*, 1022.

(20) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560.

(21) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7603.

(22) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 16184.

(23) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2008**, *47*, 6452.

(24) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058.

(25) G. Brasche, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 1932.

(26) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048.

(27) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(28) T. Uemura, S. Imoto, N. Chatani, *Chem. Lett.* **2006,** *35*, 842.

(29) D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Org. Lett.* **2009**, *11*, 1607.

(30) Q. Wang, S. L. Schreiber, *Org. Lett.* **2009**, *11*, 5178.

(31) S. H. Cho, J. Y. Kim, S. Y. Lee, S. Chang, *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.

(32) G. N. Tew, D. Liu, B. Chen, R. J. Doerksen, J. Kaplan, P. J. Carroll, M. L. Klein, W. F. DeGrado, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5110.

(33) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581.

(34) Seganish, W. M.; DeShong, P. *J. Org. Chem*. **2004**, *69*, 6790.

(35) S. Hanada, T. Ishida, Y. Motoyama, H. Nagashima, *J. Org. Chem*. **2007**, *72*, 7551.

(36) A. F. Littke, C. Y. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

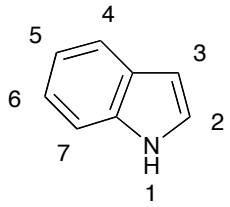
(37) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483.

(38) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048.

Chapter 3

Copper-Catalyzed Oxidative Amidation of 1-Methylindoles

Indole is a popular component of fragrances and also a precursor to many pharmaceuticals, agrochemicals, pigments and materials.[1] Enormous efforts have been devoted to the development of the synthesis and functionalization of this core aromatic compound.[2] Indole is commonly considered as an electron-rich heteroaromatic system, acting as a highly reactive nucleophile. The most reactive position of indole towards electrophiles is the C3 site and the C2 position is also available under certain conditions (Scheme 3.1). In this chapter, a concise review of the amination of indole at the C3 and C2 sites will be presented, as well as a novel Cu-catalyzed oxidative amidation of 1-methylindoles with high regioselectivity.

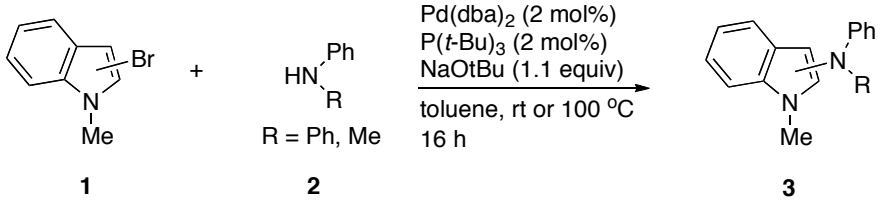


Scheme 3.1 The structure of indole and its numbering system

3.1 Direct amination of indole

The palladium-catalyzed amination of aryl halides has emerged as an important tool for the amination of indoles. In 2003, Hartwig *et al.* reported a comprehensive study of the

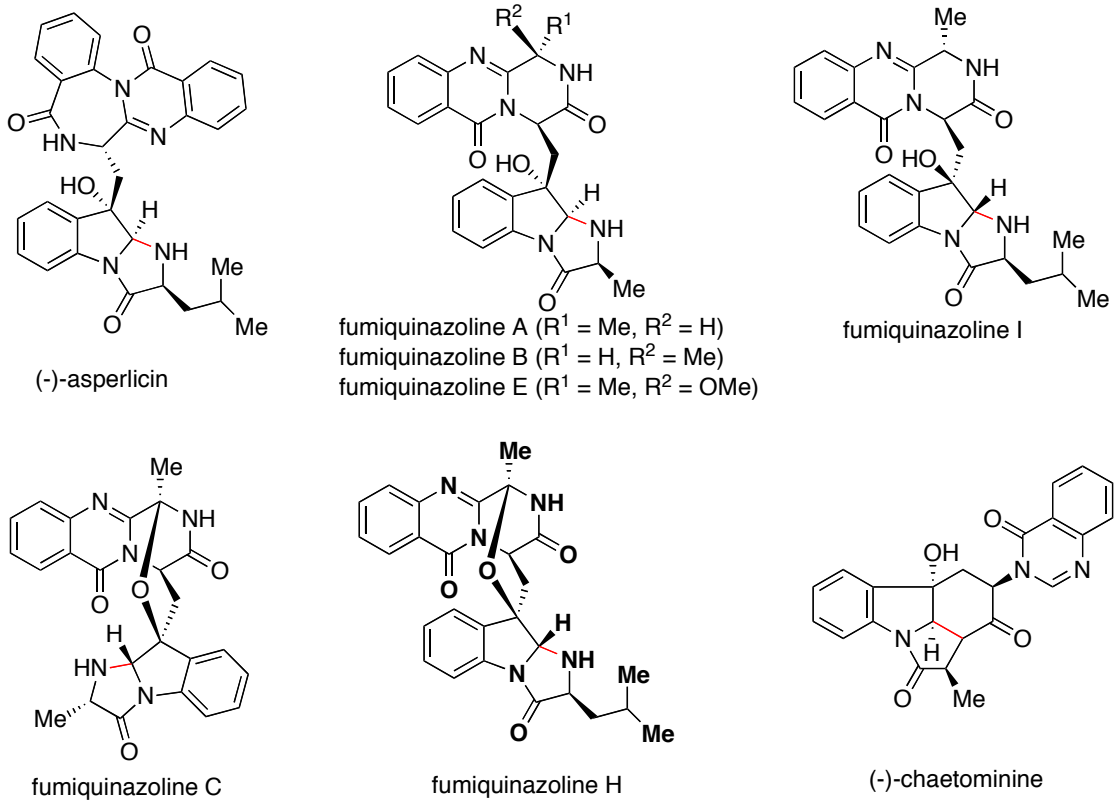
palladium-catalyzed amination of five-membered heterocyclic halides.[3] Specifically, under their optimal reaction conditions, protected 1-methylindole bromides **1** showed high reactivity towards amines **2**, affording desired products **3** in good yields (Scheme 3.2). Interestingly, 2-bromo indoles provided products in slightly higher yields than 3-bromo indoles.



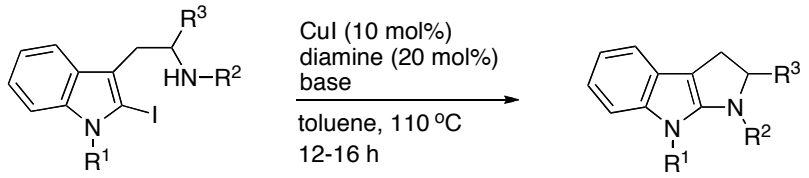
Scheme 3.2 Pd-catalyzed amination of bromo-1-methylindole

The direct functionalization of indoles has also been successfully applied to the synthesis of indole-containing natural products. Based on the intramolecular Pd-catalyzed amination of indole halides, the Snider group has reported several total synthesis of indole-containing natural products (Scheme 3.3), including (-)-asperlicin,[4] fumiaquinazoline A,[5] B,[5] C,[6] E,[6] H,[6] and I,[5] and (-)-chaetominine.[7]

Similar transformations catalyzed by copper(I) have also been reported. Evano *et al.* demonstrated that CuI could efficiently catalyze the cyclization of *N*-protected iodo-trytophans **4**, affording pyrroloindoles **5** in moderate to high yields (Scheme 3.4).[8] 2 Equiv of K_2CO_3 or K_3PO_4 as base and 20 mol% of diamines as ligand were required for this transformation.



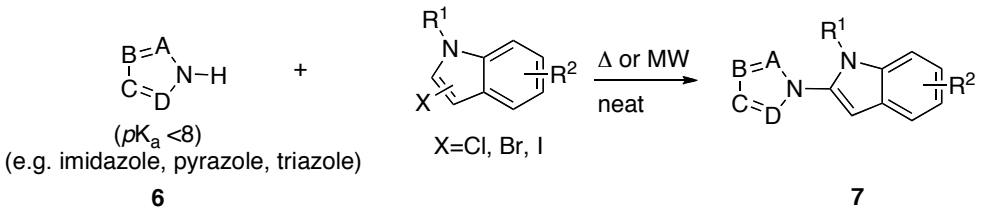
Scheme 3.3 Total synthesis of natural products based on amination of indoles



Scheme 3.4 Cu-catalyzed cyclization of iodo-tryptophans

Recently, Poirier and co-workers have developed a metal-free strategy for the coupling of 2- and 3-haloindoles with azoles **6**, which employed the use of heating or microwave under neat conditions (Scheme 3.5).[9] The coupling products **7** were obtained in moderate to high yields. Interestingly, free indoles without any protecting group turned out to be

effective substrates for this transformation. The coupling of azoles with 3-halodindoles also afforded 2-amination products, unless the C2-site of indoles was blocked.



Scheme 3.5 Metal-free coupling of azoles with 2- and 3-haloindoles

3.2 Copper-catalyzed oxidative amidation of 1-methylindoles

3.2.1 Background

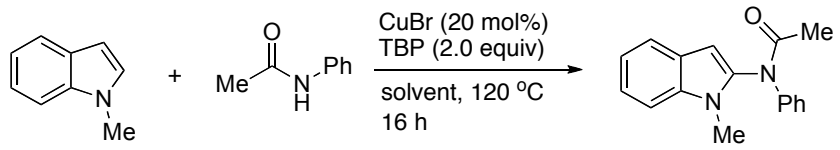
As discussed in chapter 2, the direct amidation of 2-arylpyridine derivatives were achieved by using CuBr as a catalyst and TBP as an oxidant, which encouraged us to extend this method to other aromatic substrates. Among them, indole is of great interest due to its high reactivity and its potential application in the pharmaceutical industry. To the best of our knowledge, the direct amidation of indoles has not been reported. Herein, we presented such a process involving CuBr/*t*-butylperoxide (TBP) as a catalytic system.

3.2.2 Optimization of reaction conditions

To our surprise, when applying the modified reaction conditions of chapter 2.3.2 to 1-methylindole **8a**, the desired amidation product **10a** was obtained in 60% yield (Table 3.1, entry 1) with extremely high C2 selectivity.[10] It was found that benzene as a solvent was essential for this transformation. Other solvents were also tested, however none gave

better results than benzene (entries 2-7). Under neat conditions, the yield was low and the indole decomposed (entry 8).

Table 3.1 Optimization of reaction conditions[a]



8a **9a** **10a**

entry	solvent	^{1}H-NMR yield (%)
1	benzene	64
2	chlorobenzene	33
3	toluene	15
4	xylene	trace
5	dioxane	trace
6	DMSO	0
7	$ClCH_2CH_2Cl$	trace
8	neat	27

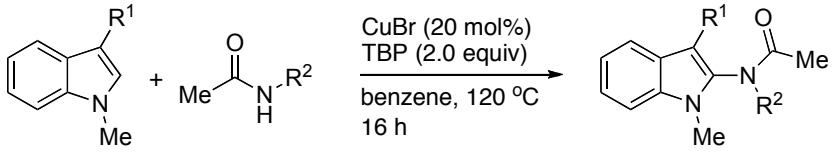
[a] 1-Methylindole **8a** (40 mg, 0.3 mmol), CuBr (6 mg, 0.04 mmol, 20 mol%), acetanilide **9a** (27 mg, 0.2 mmol) and TBP (74 μL, 0.4 mmol) in solvent (0.1 mL).

3.2.3 Scope of the oxidative amidation of 1-methylindole

With the optimal reaction conditions in hand, we then examined the scope of this amidation process. The methoxy group at *ortho*-position of phenyl bearing amide facilitated the formation of amidation product (Table 3.2, entry 3**)** while no significant effect was observed with the *para*-substituted derivative **9b** (entry 2). 1, 3-Dimethylindole **8b** also served as a suitable substrate, affording amidation product **10d** in

reasonable yield (entry 4). Similar to the amidation of 2-arylpyridine, halide moieties of amides were unaffected under these conditions (entries 5-8). However, electron-withdrawing cyano group either on the phenyl ring of acetanilide **9h** or on that of 1-methylindole **8c** suppressed the reaction completely (Scheme 3.6). In addition, simple 1° amides, **9i** and **9j**, as well as *N*-methylbenzamide **9k** were not reactive (Scheme 3.6).

Table 3.2 Amidation of 1-methylindole[a]



8 **9** **10**

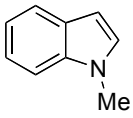
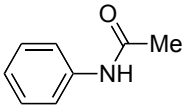
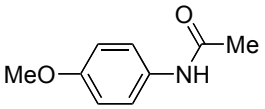
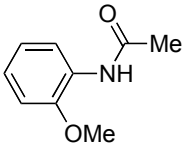
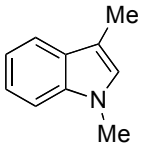
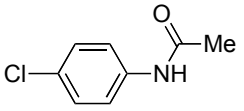
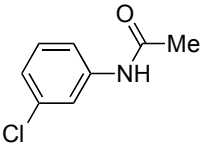
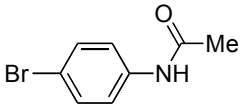
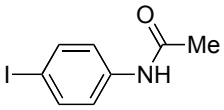
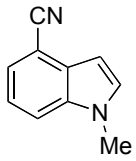
entry	1-methylindole	amide	yield **10** %[b]
1	 **8a**	 **9a**	**10a** (60)
2	**8a**	 **9b**	**10b** (54)
3	**8a**	 **9c**	**10c** (70)
4	 **8b**	**9a**	**10d** (52)
5	**8a**	 **9d**	**10e** (44)
6	**8a**	 **9e**	**10f** (36)

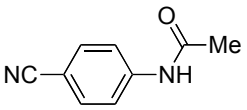
Table 3.2 (continued)

entry	1-methylindole	amide		yield **10** %[b]
7	**8a**		**9f**	**10g** (48)
8	**8a**		**9g**	**10h** (60)

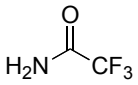
[a] All reactions were performed under standard reaction conditions: 1-methylindole (**8**, 0.6 mmol), amide (**9**, 0.4 mmol), TBP (148 μL, 0.8 mmol), benzene (0.2 mL), 120 °C for 16 h. [b] Isolated yields based on amides.



8c

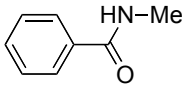


9h



9i

9j



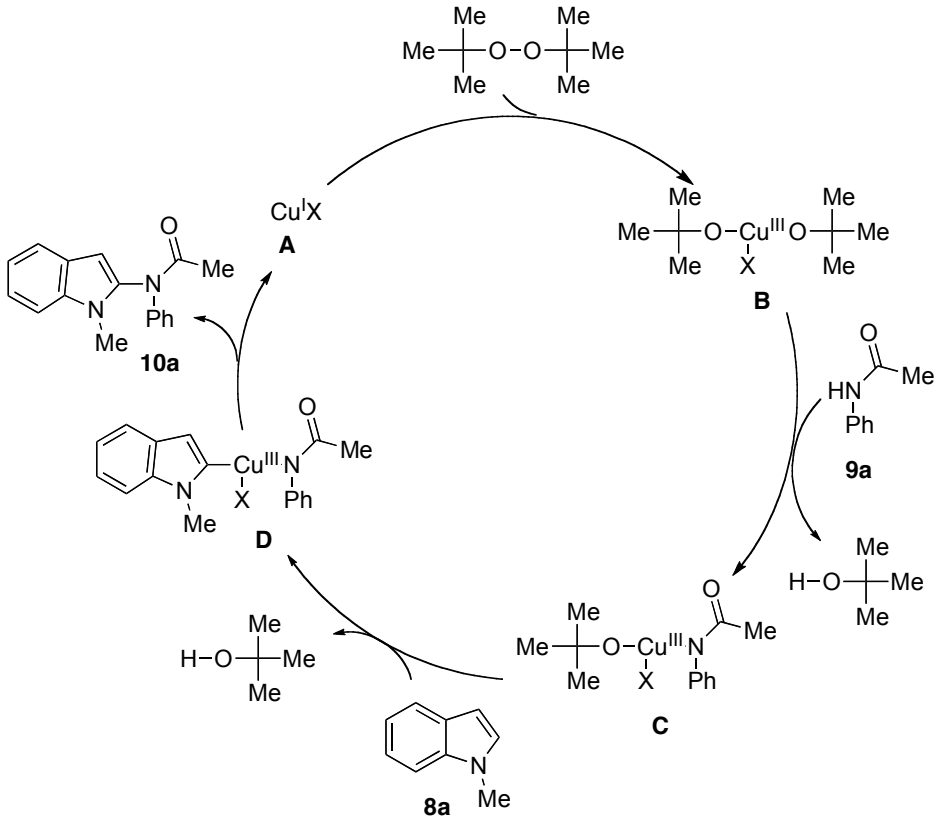
9k

Scheme 3.6 Ineffective substrates for the amidation of 1-methylindole

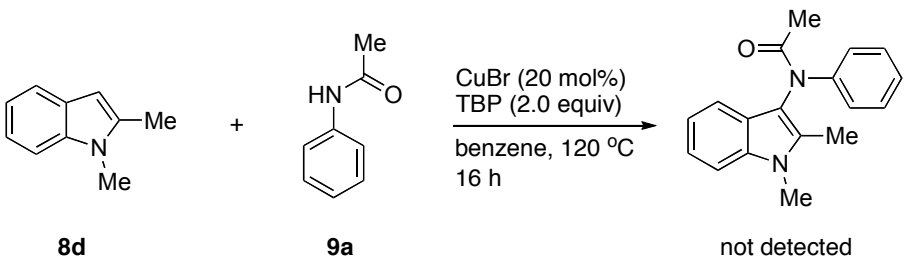
3.2.4 Proposed mechanism for the oxidative amidation of 1-methylindole

Although the mechanism of the Cu-catalyzed oxidative Ar-H and N-H coupling is not clear, based on previous studies of Cu mediated amination,[11] arylation,[12] and CDC reactions,[13] a tentative mechanism was proposed to rationalize this Cu-catalyzed oxidative amidation of 1-methylindole (Scheme 3.7). Low oxidation state Cu(I) **A** first inserts into the weak O-O bond of TBP to generate intermediate **B**, which reacts with

amide **9a** to form Cu(III) species **C** and alcohol. Reaction of **C** with 1-methylindole **8a** leads to the formation of another equivalent of alcohol and species **D**, which undergoes reductive elimination to generate final amidation product **10a** and Cu(I) **A**. However, the reason for high C2-selectivity of this process is still not clear at this stage. It seems that C3 is not reactive to amide, since no amidation product was obtained when 1, 2-dimethylindole **8d** was tested as a substrate (Scheme 3.8).



Scheme 3.7 Tentative mechanism for the amidation of 1-methylindole



8d **9a** not detected

Scheme 3.8 The reactivity of 1,2-dimethylindole towards acetanilide

3.2.5 Conclusions

In conclusion we have developed a novel method for the direct and highly regioselective amidation of 1-methylindoles in the absence of a specialized ligand or a base. This new method requires only inexpensive CuBr as catalyst, and can tolerate aryl halides..

3.2.6 Experimental section

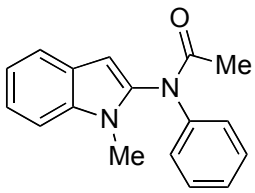
General experimental details

All reagents were commercially available and used as received. All reagents were weighed and handled in air.

^{1}H and ^{13}C-NMR spectra were recorded on Varian 400 and 500 MHz spectrometers in $CDCl_3$ solutions and chemical shifts (δ, ppm) were determined with internal solvent signal as reference (7.26 for ^{1}H-NMR and 77.0 for ^{13}C-NMR). HRMS were made by McGill University. Flash column chromatography was performed on EMD Silica Gel 60 with an appropriate solvent system (see details below). Melting points were measured on Gallenkamp melting point apparatus (MF-370).

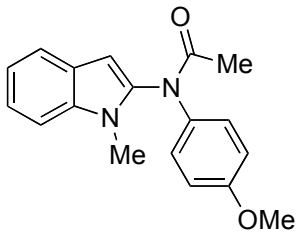
General experimental procedures and characterizations

A mixture of 1-methylindole **8** (0.6 mmol), CuBr (11.5 mg, 0.08 mmol, 20 mol%), amide **9** (0.4 mmol) and TBP (148 μL, 0.8 mmol) in benzene (0.2 mL) was sealed in a 5 mL conical vial with a Teflon lined cap. The vial was heated at 120 ^{o}C in an oil bath for 16 h and then cooled to room temperature. The resulting mixture was diluted with EtOAc and filtered through a plug of silica gel eluting with EtOAc. The filtrate was concentrated *in vacuo* with rotary evaporator and the residue was purified by column chromatography on silica gel.



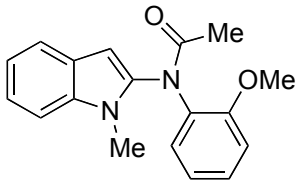
N-(1-Methyl-1*H*-indol-2-yl)-*N*-phenylacetamide **10a**

10a was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9a** (54 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10a** as an orange oil (63 mg, 60 %). IR: ν_{max} 3055, 1683, 1549, 1484, 1464, 1432, 1366, 1281, 749, 734, 694, 682, 663 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.64 (d, *J*=8.0 Hz, 1H), 7.40-7.27 (m, 6H), 7.23-7.16 (m, 2H), 6.56 (s, 1H), 3.60 (s, 3H), 2.13 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.3, 136.7, 135.1, 129.0, 126.3, 125.3, 122.5, 121.0, 120.3, 119.7, 109.9, 109.6, 100.0, 28.9, 23.4. HRMS exact mass calc'd for $C_{17}H_{17}ON_2$ ([M+H]) *m/z*: 265.1335; found *m/z*: 265.1327.



N-(4-Methoxyphenyl)-*N*-(1-methyl-1*H*-indol-2-yl)acetamide **10b**

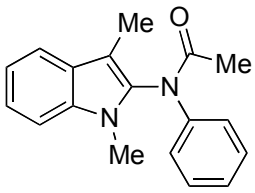
10b was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9b** (66 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (Ether/Hexane = 3:1) to afford **10b** as a yellow oil (64 mg, 54 %). IR: ν_{max} 3052, 3003, 2933, 2836, 1680, 1550, 1506, 1463, 1367, 1289, 1243, 1031, 830, 750, 732, 664 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.62 (br s, 1H), 7.31-7.27 (m, 4H), 7.16 (br s, 1H), 6.87-6.86 (d, *J*=5.0 Hz, 2H), 6.56 (br s, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.5, 157.6, 137.0, 135.1, 133.6, 126.6, 126.3, 122.6, 121.0, 120.3, 114.2, 109.6, 99.8, 55.4, 28.9, 23.2. HRMS exact mass calc'd for $C_{18}H_{19}O_2N_2$ ([M+H]) *m/z*: 295.1441; found *m/z*: 295.1432.



N-(2-Methoxyphenyl)-*N*-(1-methyl-1*H*-indol-2-yl)acetamide **10c**

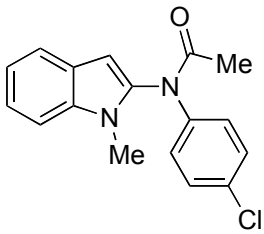
10c was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9c** (66 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10c** (a mixture of two rotamers) as a yellow oil (82 mg, 70 %). IR: ν_{max} 3053, 2928, 2838, 1682, 1546, 1496, 1463, 1433, 1367, 1299, 1275, 1239, 1022, 830, 750, 732, 664 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H

7.60-7.50 (m, 1H), 7.36-6.93 (m, 7H), 6.57-6.32 (m, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 2.08 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 172.3, 171.3, 154.7, 154.5, 137.7, 135.1, 131.8, 130.0, 129.7, 129.2, 128.9, 128.4, 126.4, 122.3, 121.5, 121.2, 121.0, 120.9, 120.6, 120.1, 119.5, 112.3, 112.1, 109.6, 109.4, 99.1, 96.7, 55.7, 55.5, 29.7, 29.5, 22.3, 22.1. HRMS exact mass calc'd for $C_{18}H_{19}O_2N_2$ ([M+H]) *m/z*: 295.1441; found *m/z*: 295.1432.



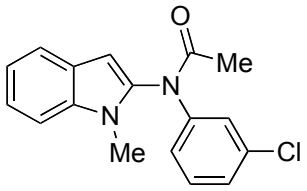
N-(1,3-dimethyl-1*H*-indol-2-yl)-*N*-phenylacetamide **10d**

10d was prepared from 1, 2-dimethylindole **8b** (87 mg, 0.6 mmol) and amide **9a** (54 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10d** as a white solid (58 mg, 52 %), mp 160-161 °C. IR: ν_{max} 2914, 1681, 1466, 1433, 1366, 1296, 764, 739, 698, 672 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.63 (d, *J*=7.5 Hz, 1H), 7.33-7.30 (m, 6H), 7.20-7.18 (m, 2H), 3.56 (s, 3H), 2.33 (s, 3H), 2.06 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.3, 140.8, 134.7, 133.6, 128.9, 126.7, 125.9, 124.3, 122.8, 119.6, 119.4, 109.4, 107.1, 28.9, 23.2, 8.4. HRMS exact mass calc'd for $C_{18}H_{19}ON_2$ ([M+H]) *m/z*: 279.1492; found *m/z*: 279.1485.



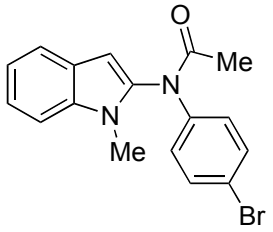
N-(4-Chlorophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)acetamide **10e**

10e was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9d** (68 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10e** as an orange oil (52 mg, 44 %). IR: ν_{max} 3054, 2927, 1686, 1551, 1488, 1467, 1367, 1304, 1092, 1011, 828, 750, 734, 714, 667 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.65 (d, *J*=8.0 Hz, 1H), 7.34-7.29 (m, 6H), 7.21-7.19 (m, 1H), 6.56 (br s, 1H), 3.57 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.2, 139.4, 136.1, 135.2, 131.6, 129.1, 126.2, 122.8, 121.2, 120.5, 110.0, 109.7, 100.2, 28.9, 23.4. HRMS exact mass calc'd for $C_{17}H_{16}ON_2Cl$ ([M+H]) *m/z*: 299.0946; found *m/z*: 299.0935.



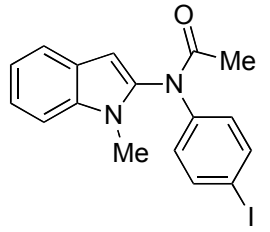
N-(3-chlorophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)acetamide **10f**

10f was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9e** (68 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10f** as an orange oil (43 mg, 36 %). IR: ν_{max} 3056, 2929, 1687, 1589, 1470, 1365, 1285, 1264, 778, 740, 687, 670, 658, 614 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.65 (d, *J*=8.0 Hz, 1H), 7.42 (s, 1H), 7.34-7.29 (m, 2H), 7.28-7.23 (m, 2H), 7.21-7.17 (m, 2H), 6.57 (br s, 1H), 3.58 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.2, 142.0, 135.9, 135.2, 134.5, 129.8, 126.3, 126.2, 125.2, 123.1, 122.8, 121.1, 120.5, 109.7, 100.3, 28.9, 23.4. HRMS exact mass calc'd for $C_{17}H_{16}ON_2Cl$ ([M+H]) *m/z*: 299.0946; found *m/z*: 299.0942.



N-(4-Bromophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)acetamide **10g**

10g was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9f** (86 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10g** as an orange oil (66 mg, 48 %). IR: ν_{max} 3055, 2932, 1683, 1551, 1484, 1466, 1432, 1365, 1303, 1280, 1009, 824, 750, 734, 706, 665 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.64 (d, *J*=8.0 Hz, 1H), 7.44 (d, *J*=8.5 Hz, 2H), 7.32-7.28 (m, 2H), 7.26-7.19 (m, 3H), 6.56 (br s, 1H), 3.56 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.52, 140.0, 136.0, 135.2, 132.0, 126.6, 126.2, 122.8, 121.1, 120.5, 119.4, 109.7, 100.2, 28.9, 23.5. HRMS exact mass calc'd for $C_{17}H_{16}ON_2Br$ ([M+H]) *m/z*: 343.0441; found *m/z*: 343.0428.



N-(4-Iodophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)acetamide **10h**

10h was prepared from 1-methylindole **8a** (79 mg, 0.6 mmol) and amide **9g** (104 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **10h** as orange oil (94 mg, 60 %). IR: ν_{max} 3053, 2933, 1686, 1550, 1482, 1365, 1305, 1280, 1005, 821, 750, 733, 705, 665 cm^{-}

[1]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.64 (d, *J*=4.5 Hz, 1H), 7.32-7.27 (m, 2H), 7.19 (d, *J*=2.0 Hz, 1H), 7.14-7.12 (m, 2H), 6.56 (br s, 1H), 3.56 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 171.2, 140.7, 138.0, 135.9, 135.1, 132.0, 126.8, 126.2, 122.8, 121.1, 120.4, 109.7, 100.2, 28.9, 23.5. HRMS exact mass calc'd for $C_{17}H_{16}ON_2I$ ([M+H]) *m/z*: 391.0302; found *m/z*: 391.0287.

References

(1) (a) R. J. Sundberg in *The Chemistry of Indoles*, Academic Press, New York, 1970. (b) R. K. Brown in *Indoles* (Ed.: W. J. Houlihan), Wiley-Interscience, New York, 1972.

(2) "Indole and its Derivatives": J. A. Joule in *Science of Synthesis* (Houben-Weyl Methods of Molecular Transformations), Vol. 10 (Ed.: E. J. Thomas), Thieme, Stuttgart, 2000, chap. 10.13.

(3) M. W. Hooper, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2003**, *68*, 2861.

(4) F. He, B. M. Foxman, B. B. Snider, *J. Am. Chem. Soc.* **1998**, *120,* 6417.

(5) B. B. Snider, H. Zeng, *Org. Lett.* **2000**, *2*, 4103.

(6) B. B. Snider, H. Zeng, *J. Org. Chem.* **2003**, *68*, 545.

(7) B. B. Snider, X. Wu, *Org. Lett.* **2007**, *9*, 4913.

(8) A. Coste, M. Toumi, K. Wright, V. Razafimahaléo, F. Couty, J. Marrot, G. Evano, *Org. Lett.* **2008**, *10*, 3841.

(9) M. Poirier, S. Goudreau, J. Poulin, J. Savoie, P. L. Beaulieu, *Org. Lett.* **2010**, *12*, 2334.

(10) Only one isomer was isolated, and both NMR and GC-MS did not detect the presence of other isomers.

(11) D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Org. Lett.* **2009**, *11*, 1607.

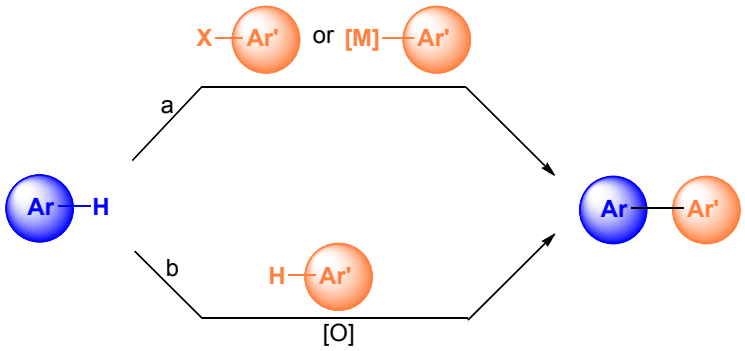
(12) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc*. **2008**, *130*, 8172.

(13) Y. Zhang, J. Feng, C.-J. Li, *J. Am. Chem. Soc*. **2008**, *130*, 2900.

Chapter 4

Rhodium-Catalyzed Oxidative C-H Arylation of 2-Arylpyridine Derivatives via Decarbonylation of Aromatic Aldehydes

The prevalence and importance of biaryl motifs in natural products, advanced materials, and pharmaceuticals have made the preparation of aryl-aryl bonds among the core interests of organic synthesis for over a century.[1] By far, transition-metal-catalyzed biaryl cross-coupling reactions, which generally employ aryl halides and organometallic reagents as coupling partners, have served as the most common methods for constructing biaryl unions.[2] In recent years, direct arylations of unactivated arenes with preactivated coupling partners (aryl halides and organometallic reagents) via C-H activation have emerged as attractive alternatives to classical methods (Scheme 4.1, route a).[3] More recently, more challenging oxidative cross couplings of two simple arenes have been achieved and developed, affording biaryl products with high atom economy (Scheme 4.1, route b).[4] In addition, a variety of other arylation partners involving C-C bond cleavage have also been successfully explored. In this chapter, a concise review of transition-metal-catalyzed oxidative coupling of two simpler arenes and biaryl formation involving carbon-based leaving groups will be presented.



Scheme 4.1 Arene-arene coupling via C-H activation

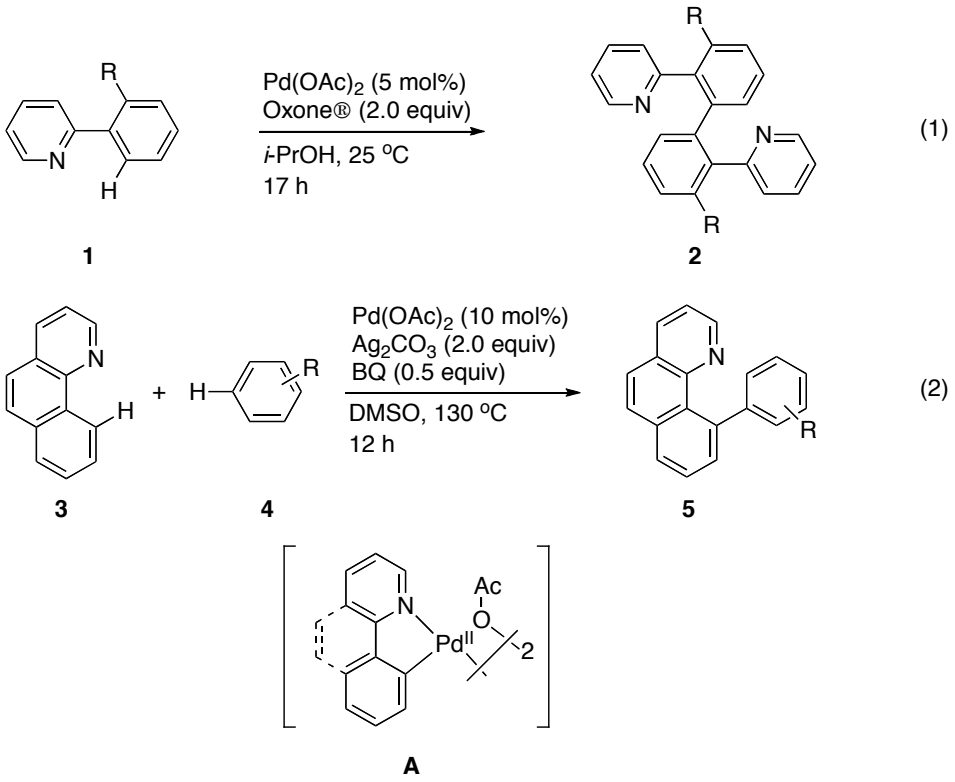
4.1 Transition-metal-catalyzed oxidative coupling of arenes

Theoretically, the ideal approach for constructing the biaryl linkage is through oxidative formation of the C–C bond from two simple arenes. However, it is still a big challenge to control the regioselectivity of aryl C-H activation.

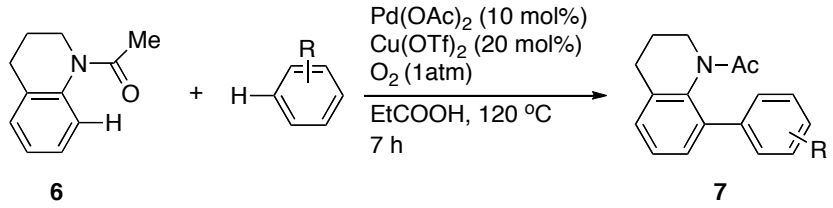
4.1.1 Directed oxidative coupling of arenes

A solution to this challenge is through the use of a directing group. The Sanford group has developed a method for Pd-catalyzed oxidative cross coupling of arenes based on pyridyl-directed C-H activation. Firstly, the homo-coupling of 2-arylpyridine derivatives **1** was achieved by using Oxone® as an oxidant (Scheme 4.2, Eq. 1).[5] Notably, biaryl products **2** were obtained with high *ortho*-regioselectivity and bromo-motif could be tolerated under their optimal reaction conditions. Later, a highly regioselective cross-coupling version was presented,[6] which was promoted by the use of benzoquinone (Scheme 4.2, Eq. 2). Investigation of the mechanism of this novel Pd-catalyzed oxidative coupling of arenes revealed that the formation of a cyclometallated intermediate **A** (Scheme 4.2) played an important role in the highly regioselective C-H activation

process,[7] which had been demonstrated in their previous aryl C-H functionlization chemistry.[8]



Scheme 4.2 Pd-catalyzed oxidative coupling of 2-arylpyridine derivatives

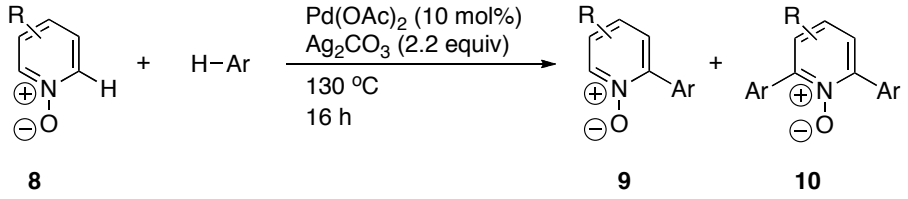


Scheme 4.3 Pd-catalyzed oxidative arylation of *N*-acetanilides

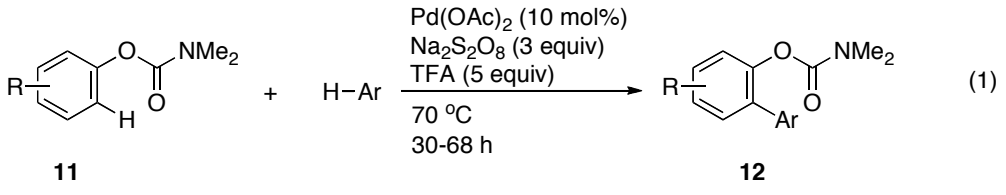
Shi *et al.* successfully explored the oxidative arylation of *N*-acetanilides **6** bearing a carbonyl directing group.[9] Inexpensive $Cu(OTf)_2$ was used as a co-catalyst with

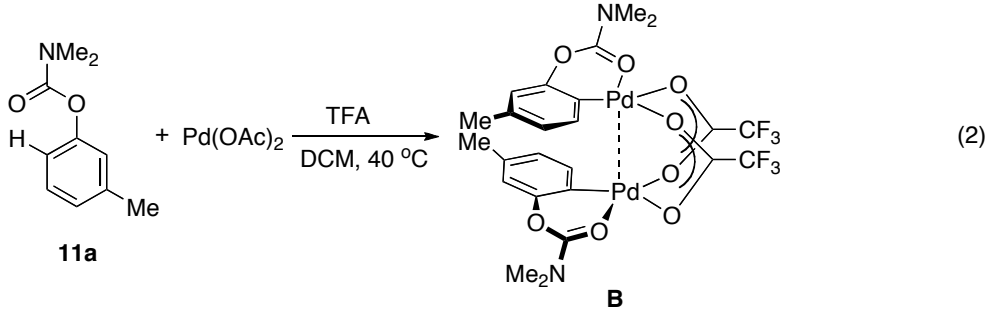
$Pd(OAc)_2$ and O_2 was used as the terminal oxidant. This method provided a straightforward access to the construction of fully functionalized carbazole derivatives.

The Chang group demonstrated that the oxygen of pyridine *N*-oxide **8** could act as a good directing group for the activation of *ortho*-C-H bonds (Scheme 4.4).[10] In the presence of a catalytic amount of $Pd(OAc)_2$ and 2.2 equiv of Ag_2CO_3, efficient arylations of pyridine *N*-oxides were achieved, affording both monoarylated and biarylated products **9** and **10**.



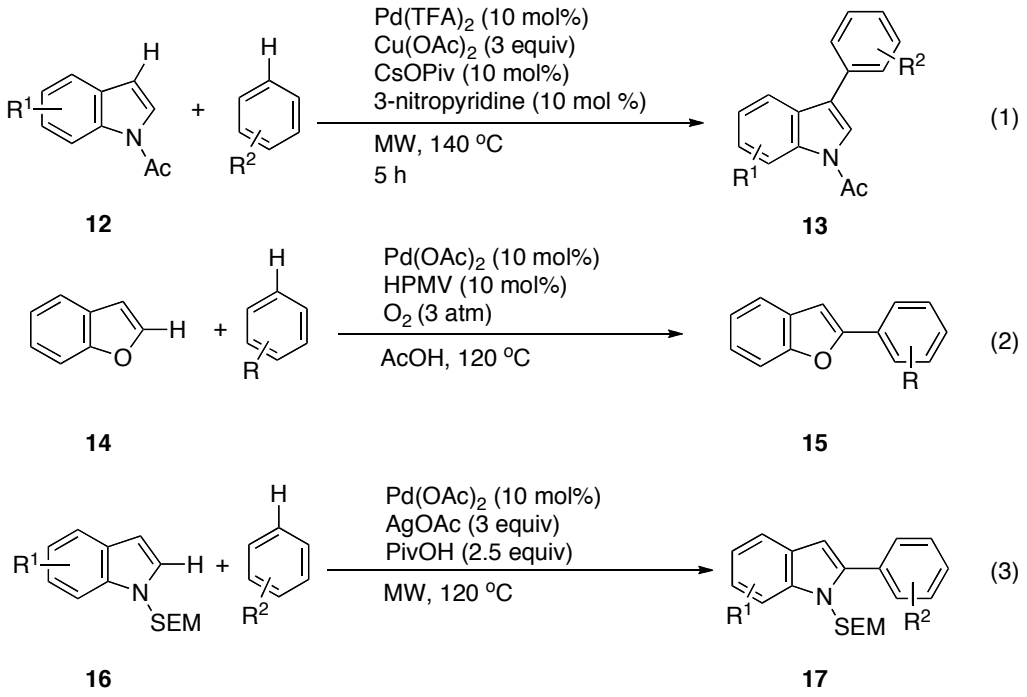
Scheme 4.4 Pd-catalyzed oxidative arylation of pyridine *N*-oxides





Scheme 4.5 Pd-catalyzed oxidative arylation of *O*-phenylcarbamates

Recently, Dong *et al.* reported that *O*-phenylcarbamates **11** could be used as good substrates for oxidative arylations with simple arenes (Scheme 4.5, Eq. 1).[11] It was found that the addition of trifluoroacetic acid (TFA) was critical for the successful cyclopalladation of *O*-phenylcarbamates, forming a trifluroacetate-bridged bimetallic Pd complex **B**. This Pd complex was obtained through treating *O*-phenylcarbamate **11a** with TFA and $Pd(OAc)_2$ in DCM at 40 ^oC and characterized by X-ray crystallography (Scheme 4.5, Eq. 2).



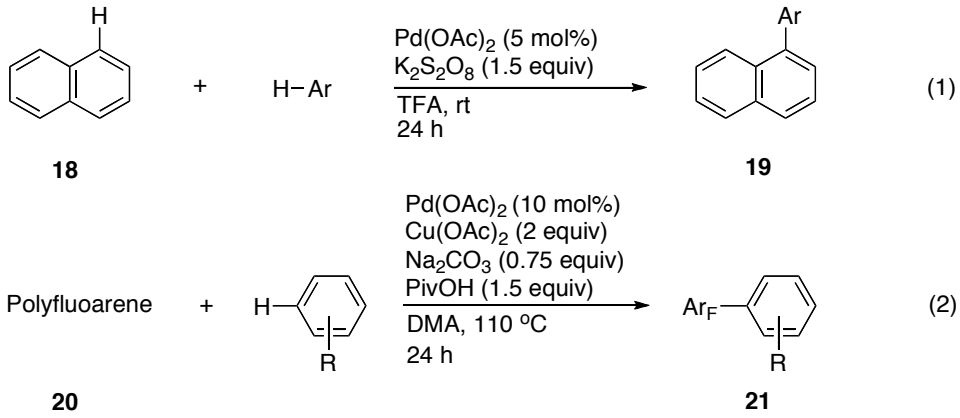
Scheme 4.6 Pd-catalyzed oxidative arylation of indoles and benzofuran

As discussed in chapter 1, the Fagnou group reported a remarkable solution to the coupling of unactivated *N*-acetylindoles **12** and benzenes (Scheme 4.6, Eq. 1). [12] Later, the Deboef group reported that benzofurans **14** could also be effective substrates, although affording cross-coupling products **15** with high C2-selectivity in moderate

yields (Scheme 4.6, Eq. 2).[13] When changing *N*-protecting group from acetyl to alkyl (SEM) group, they achieved a highly regioselective C2-arylation process (Scheme 4.6, Eq. 3).[14]

4.1.2 Undirected oxidative coupling of arenes

The oxidative cross-coupling of two simple arenes, both of which have no directing groups, is a challenge to organic chemists. Under such situations, the regioselectivity of the cross-coupling process completely relies on the minute reactivity difference of C-H bonds and steric hindrance affect of reactive sites. Lu *et al.* chose naphthalene **18** as oxidative coupling substrates with simple benzenes (Scheme 4.7, Eq. 1).[15] They found that the cross-coupling products **19** were obtained with a high selectivity against the formation of homo-coupling products, although the yields were low. In addition, a high regioselectivity for the formation of products **19** was achieved. Inspired by the previously reported arene cross-coupling reactions, Wei and Su hypothesized that Pd-catalyzed cross-coupling between two arenes with distinct electronic property might be achieved under controlled reaction conditions. When electron-deficient polyfluorobenzenes **20** were chosen as a coupling partner, the arylation products **21** were obtained in moderate to good yields (Scheme 4.7, Eq. 2).[16] Mechanism study through the determination of the values of the kinetic isotope effects (KIEs) for both coupling partners revealed that the C-H bond cleavage of simple arenes is the rate-limiting step for this transformation.

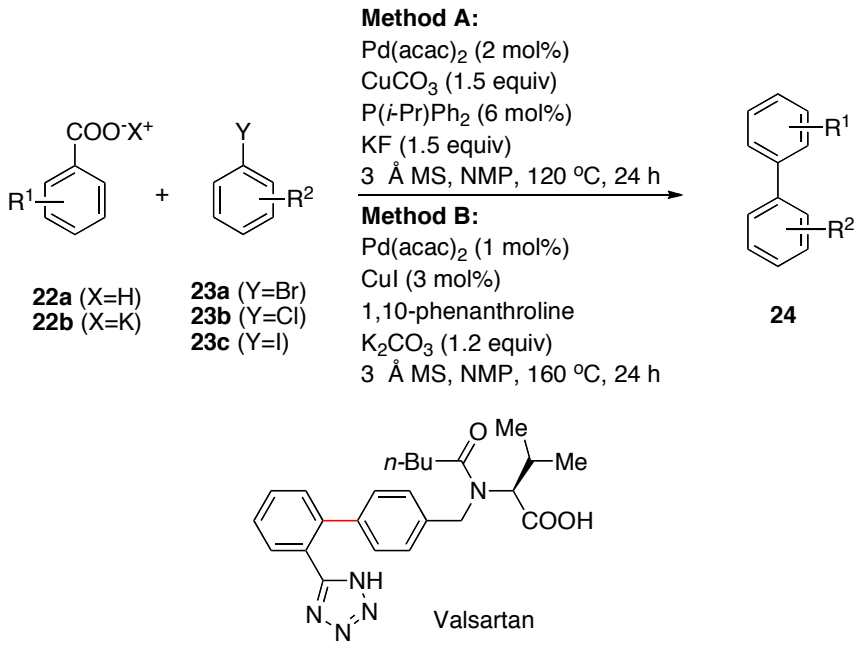


Scheme 4.7 Pd-catalyzed oxidative arylation of arenes without directing groups

4.2 Biaryl formation involving carbon-based leaving groups

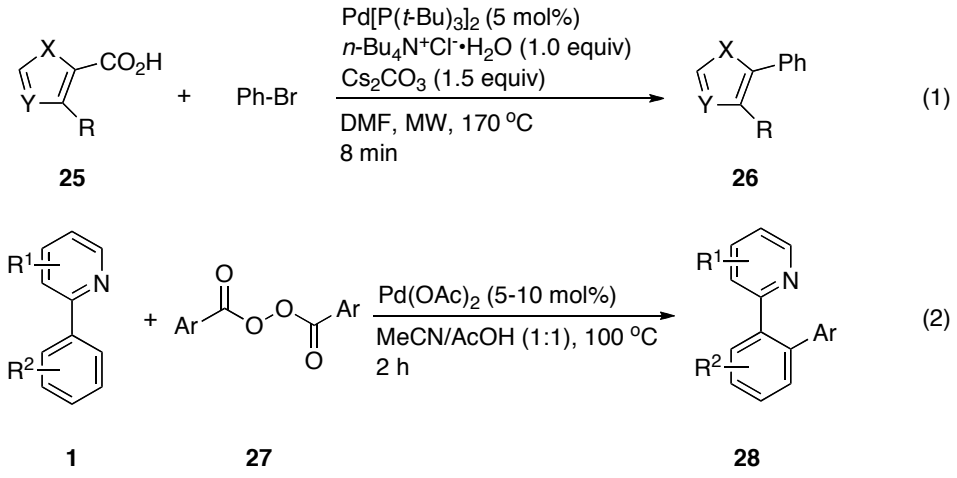
4.2.1 Decarboxylative biaryl synthesis

The Gooßen group reported the cross-coupling reactions of arenecarboxylates with arylhalides through the extrusion of CO_2, which was considered a major breakthrough in the development of biaryl synthesis.[17] Firstly, they introduced a bimetallic catalyst system for the cross-coupling reaction of arenecarboxylic acids **22a** with aryl bromides **23a**. The original protocol required the use of a stoichiometric amount of the copper salt (Scheme 4.8, method **A**) but it was improved to include a Cu-catalyzed version (method **B**).[18] Later, this method was further developed and the substrate scope was extended to potassium carboxylates **22b** [19] and aryl chlorides **23b** and aryl iodides **23c**.[20] Furthermore, this method led to an efficient synthesis of Valsartan from simple starting materials.[21]



Scheme 4.8 Pd-catalyzed decarboxylative biaryl synthesis

An independent report from Forgione *et al.* demonstrated that heteroaromatic carboxylic acids **25** could be used as coupling partners through a Pd-catalyzed decarboxylation process, affording biaryl products **26** in moderate to high yields (Scheme 4.9, Eq. 1).[22]

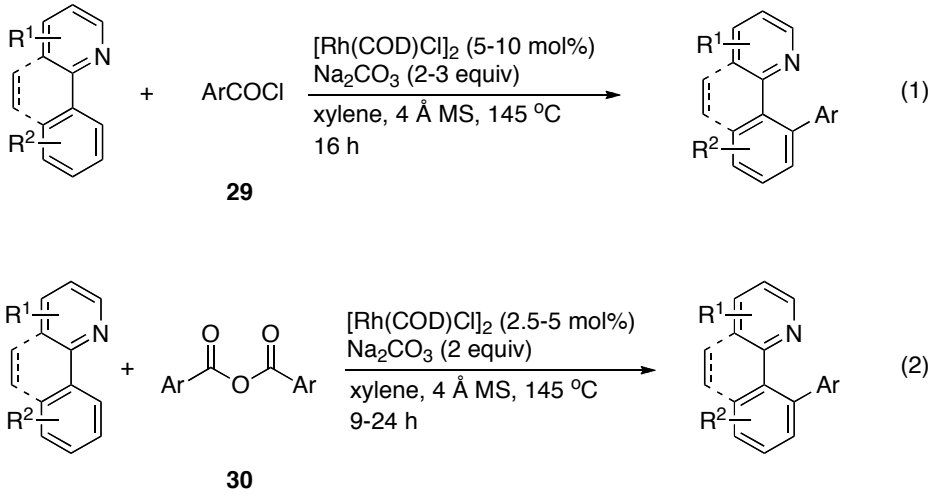


Scheme 4.9 Pd-catalyzed arylation through decarboxylation

It was found that the addition of tetrabutylammonium chloride hydrate was crucial to this transformation. In 2009, Yu *et al.* reported that aryl acylperoxides could release CO_2 upon heating and form aryl radical, which was further installed onto 2-arylpyridines **1** in the presence of a catalytic amount of $Pd(OAc)_2$ (Scheme 4.9, Eq. 2).[23]

4.2.2 Decarbonylative biaryl synthesis

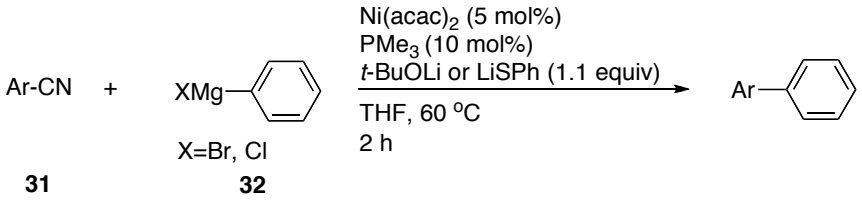
The pioneering work from the Yu group demonstrated that aryl acylchlorides **29** could be used as arylation reagents through the extrusion of CO (Scheme 4.10, Eq. 1).[24] It was found that $[Rh(COD)Cl]_2$ was the optimal catalyst for this novel transformation, and the addition of 4 Å MS could remarkably improve the arylation efficiency. Later, the same group continued their contribution to this area by using arylanhydrides **30** as coupling partners (Scheme 4.10, Eq. 2).[25] Similar reaction conditions with minor modification were found to be effective for this transformation.



Scheme 4.10 Rh-catalyzed arylation through decarbonylation

4.2.3 Biaryl formation involving other C-based leaving groups

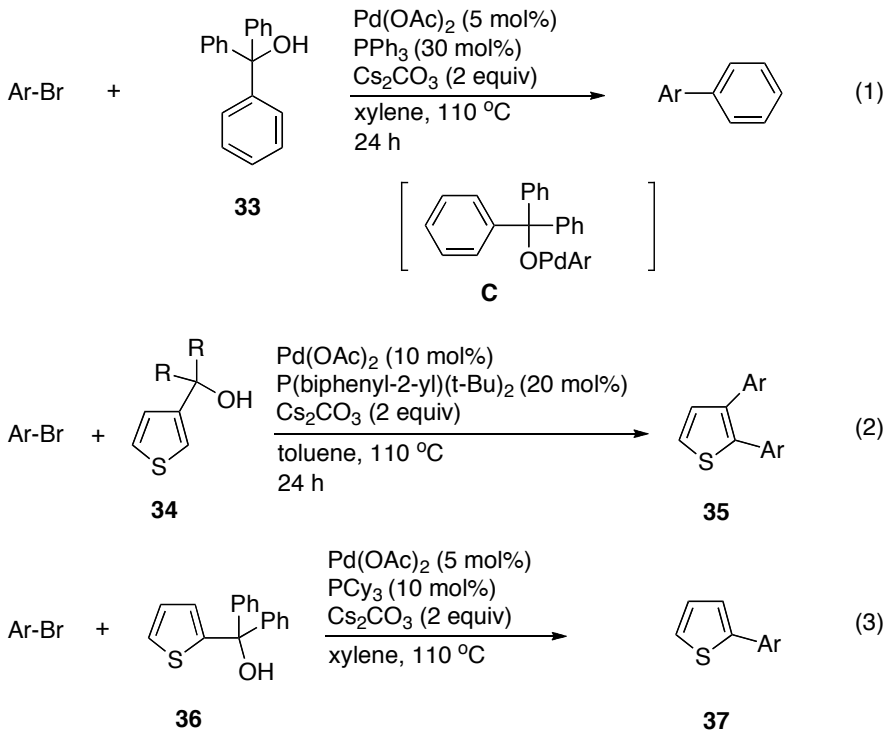
The organometallic reaction involving the cleavage of C-CN bonds has been reported[26] and its application to the synthesis of biaryl unions has been demonstrated. Miller *et al.* disclosed the cross-coupling reaction of various benzonitriles **31** with aryl Grignard reagents **32** (Scheme 4.11).[27] Low-valent nickel catalyst was required for the activation of aryl-CN bonds, and the addition of strong base *t*-BuOLi or PhSLi was crucial to suppress the competing attack of Grignard reagents at the nitrile carbon.



Scheme 4.11 Biaryl formation by activation of aryl-CN bonds

In 2001, Miura *et al.* first introduced α,α-disubstituted arylmethanols **33** as arylation reagents (Scheme 4.12, Eq. 1).[28] They suggested the initial formation of an arylpalladium(II) alcoholate species **C**, which served as a critical intermediate for the arylation process through β cleavage and reductive elimination of benzophenone. However, a significant amount of *ortho*-arylated side products was obtained due to the efficient directing affect of the benzylic hydroxyl group. This method was later extended to the arylation of α,α-disubstituted 3-thiophenemethanols **34,** affording 2,3-diarylated products **35** (Scheme 4.12, Eq. 2).[29] In 2007, Bíró and Kotschy achieved a high selective arylation of α,α-disubstituted benzo[*b*]thien-2-ylmethanols **36** (Scheme 4.12, Eq. 3).[30] The formation of *ortho*-arylated products was suppressed by using a bulky phosphine

ligand PCy_3 for inducing the β-carbon elimination.



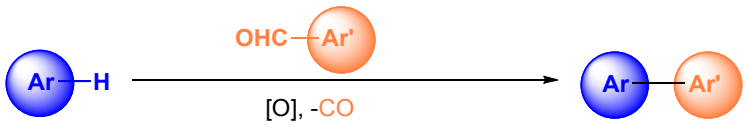
Scheme 4.12 Pd-catalyzed cross coupling of aryl carbinols and aryl halides

4.3 Rhodium-catalyzed oxidative C-H arylation of 2-arylpyridine derivatives via decarbonylation of aromatic aldehydes

4.3.1 Background

As discussed above, while the cross-coupling of two simple arenes is conceptually ideal, controlling the regioselectivity of unactivated aryl C-H bonds still remains a challenge. Herein, we present a new concept for aryl-aryl coupling that involves oxidative decarbonylative coupling of aryl C-H bonds and aldehydes, achieving the aryl-aryl union with complete control of reaction sites (Scheme 4.13). On the basis of our previous

studies of cross-dehydrogenative-coupling (CDC) reactions[31] and decarbonylative coupling of aldehydes and terminal alkynes,[32] we postulated that readily available aromatic aldehydes could be used as potential arylation partners with arenes via a decarbonylative CDC process by employing an appropriate oxidant.

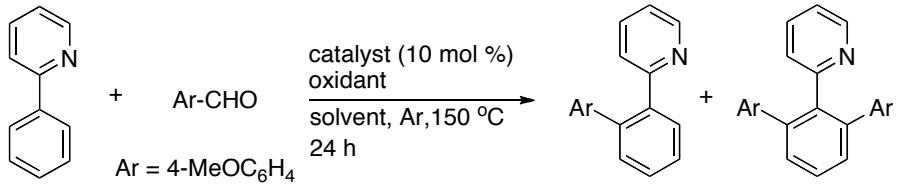


Scheme 4.13 Oxidative decarbonylative coupling of aryl C-H bonds

4.3.2 Optimization of reaction conditions

We began our investigation by testing the reaction of 2-phenylpyridine **1a** with anisaldehyde **38a** in the presence of catalytic amounts of ruthenium catalyst using *tert*-butyl peroxide (TBP) as oxidant under neat conditions. To our delight, a trace amount of the desired arylation product was detected by GC-MS (Table 4.1, entry 1). After the catalyst was switched to $(CO)_2Rh(acac)$, the desired product **39aa** was isolated together with biarylated product **39ba** in 28% overall yield (entry 2). Other rhodium catalysts were also tested, however none showed better activities than $(CO)_2Rh(acac)$ (entries 3-6). Among the oxidants examined, only dicumyl peroxide was found to be as effective as TBP (entries 7-9). Because of the higher price of dicumyl peroxide and the difficulty of removing 2-phenylpropan-2-ol after the reaction, TBP was chosen as the oxidant for further optimizations. When the reaction was performed in various solvents, the yield improved significantly (entries 10-13), with chlorobenzene (entry 13) being the best. Shortening the reaction time decreased the yield (entry 14), whereas a longer reaction time did not improve the yield (entry 15). Finally, the use of an additional 0.5 equiv of **38a** increased the yield to 81% (entry 18).

Table 4.1 Optimization of reaction conditions[a]



1a **38a** **39aa** **39ba**

entry	catalyst	oxidant	solvent	yield (%)[b]
1	$[Ru(COD)Cl]_2$	TBP	neat	trace
2	$(CO)_2Rh(acac)$	TBP	neat	28[c]
3	$Rh(COD)BF_4$	TBP	neat	0
4	$[Rh(COD)Cl]_2$	TBP	neat	11
5	$(CO)_4RhCl$	TBP	neat	19
6	$RhCl_3$	TBP	neat	18
7	$(CO)_2Rh(acac)$	dicumyl peroxide	neat	27
8	$(CO)_2Rh(acac)$	*tert*-butyl peracetate	neat	13
9	$(CO)_2Rh(acac)$	$(PhCOO)_2$	neat	18
10	$(CO)_2Rh(acac)$	TBP	dioxane	55
11	$(CO)_2Rh(acac)$	TBP	anisole	45
12	$(CO)_2Rh(acac)$	TBP	toluene	48
13	$(CO)_2Rh(acac)$	TBP	PhCl	61
14[d]	$(CO)_2Rh(acac)$	TBP	PhCl	52
15[e]	$(CO)_2Rh(acac)$	TBP	PhCl	58
16[f]	$(CO)_2Rh(acac)$	TBP (1.5 equiv)	PhCl	70
17[f]	$(CO)_2Rh(acac)$	TBP (2.0 equiv)	PhCl	77
18[f]	**$(CO)_2Rh(acac)$**	**TBP (2.5 equiv)**	**PhCl**	**81**
19[f]	$(CO)_2Rh(acac)$	TBP (3.0 equiv)	PhCl	72

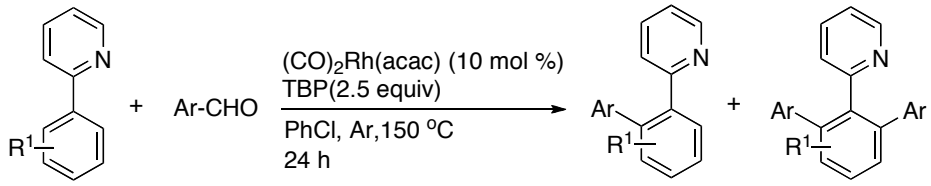
[a] **1a** (14.6 μL, 0.1 mmol), **38a** (31.0 μL, 0.25 mmol), $(CO)_2Rh(acac)$ (2.6mg, 0.01 mmol), TBP (37.6 μL, 0.2 mmol,), solvent (0.2 mL), argon, 150 °C, 24 h. [b] ^{1}H-NMR yield (**39aa**

+**39ba**). [c] Isolated yield. [d] 12 h. [e] 48 h. [f] **38a** (0.3 mmol, 37.2 μL).

4.3.3 Scope of oxidative decarbonylative arylation of 2-arylpyridines

Under the optimized reaction conditions, the scope and generality of this oxidative cross-coupling reaction through decarbonylation of aromatic aldehydes was explored. Electron-rich aromatic aldehydes with a methoxy group at either the *para* or *meta* position proved to be good substrates for this transformation, affording the corresponding arylated products in good yields (Table 4.2, **38a** and **38b**). *p*-Tolualdehyde **38c**, albeit also effective, furnished the products in moderate yields because of the reaction between the methyl group and the oxidant TBP. 4-Phenylbenzaldehyde **38d** and benzaldehyde **38e** coupled with 2-phenylpyridine **1a** efficiently. Having an electron-withdrawing cyano substituent at the *para* position, aldehyde **38f** gave a slightly lower yield of decarbonylative coupling products. However, methyl 4-formylbenzoate **38g** was found to couple with **1a** efficiently and afforded the desired product in good yield. Notably, the fluoro, chloro, and bromo moieties (commonly used for cross-coupling reactions) in benzaldehydes **38h**, **38i**, **38j**, and **38k** were all tolerated under this novel coupling and afforded the targeted products in moderate to good yields, making further elaborations of the corresponding biaryl products possible. The substituents on the phenyl ring in the 2-arylpyridine derivatives **1b**, **3**, **1c**, and **1d** did not affect the efficiency of the coupling reactions, and good yields of the desired products were obtained.

Table 4.2 Oxidative decarbonylative arylation of 2-arylpyridines[a]



1 **38** **39a** **39b**

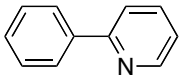
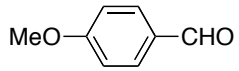
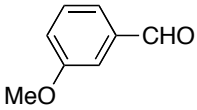
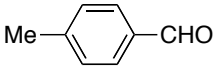
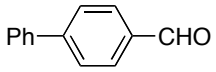
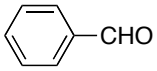
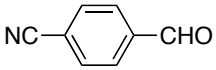
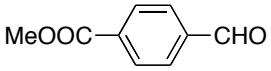
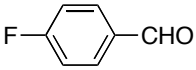
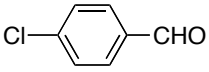
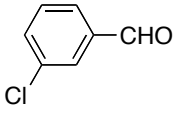
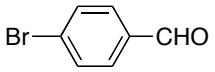
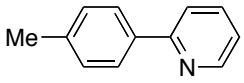
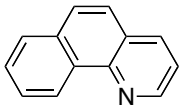
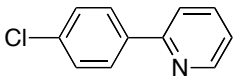
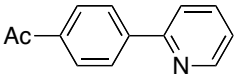
entry	2-arylpyridine	aldehyde		product	yield[b] (%)
1	 **1a**		**38a**	**39aa** + **39ba**	79 (10:9)
2	**1a**		**38b**	**39ab** + **39bb**	82 (10:9)
3	**1a**		**38c**	**39ac** + **39bc**	63 (10:6)
4	**1a**		**38d**	**39ad** + **39bd**	69 (10:8)
5	**1a**		**38e**	**39ae** + **39be**	64 (10:7)
6	**1a**		**38f**	**39af** + **39bf**	67 (10:5)
7	**1a**		**38g**	**39ag** + **39bg**	79 (10:10)
8	**1a**		**38h**	**39ah** + **39bh**	82 (10:8)
9	**1a**		**38i**	**39ai** + **39bi**	70 (10:6)
10	**1a**		**38j**	**39aj** + **39bj**	76 (10:7)

Table 4.2 (continued)

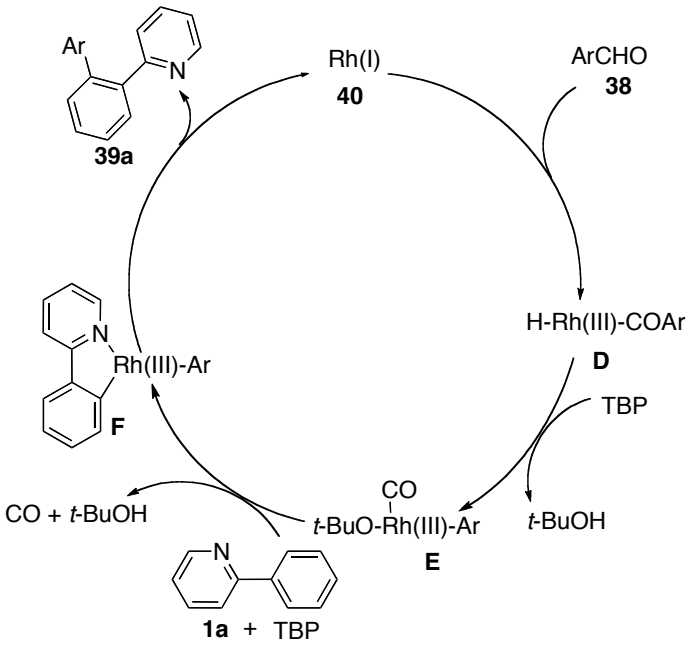
entry	2-arylpyridine	aldehyde		product	yield[b] (%)
11	**1a**		**38k**	**39ak** + **39bk**	56 (10:18)
12		**1b**	**38a**	**39al** + **39bl**	87 (10:11)
13[c]		**3**	**38a**	**39am**	71
14		**1c**	**38a**	**39an** + **39bn**	79 (10:9)
15		**1d**	**38a**	**39ao** + **39bo**	83 (10:10)

[a] Conditions: **1** (0.2 mmol), **38** (0.6 mmol), $(CO)_2Rh(acac)$ (0.02 mmol, 5.2 mg) and TBP (0.5 mmol, 94.0 μL) in PhCl (0.4 mL), argon, 150 °C, 24 h. [b]Isolated yield, with ratio (in parentheses) of mono/bisarylation products determined by ^{1}H-NMR analysis. [c] **3** (0.2 mmol, 35.8 mg), **38a** (0.3 mmol, 37.2 μL) and TBP (0.25 mmol, 47.0 μL).

4.3.4 Tentative mechanism for the oxidative arylation of 2-phenylpyridine with aromatic aldehydes

A tentative mechanism for this novel coupling is proposed in Scheme 4.14. Initially, oxidative addition of aldehyde **38** to the Rh(I) center **40** generates species **D**, which undergoes dehydrogenation promoted by TBP to give **E**. Next, **E** reacts with **1a** through C-H bond activation, which is followed by dehydrogenation and extrusion of CO at elevated temperature to give **F**. Finally, reductive elimination of intermediate **F** affords

the target biaryl product **39a** and regenerates the Rh(I) catalyst **40**.



Scheme 4.14 Tentative mechanism for the oxidative arylation of 2-phenylpyridine with aromatic aldehydes

4.3.5 Conclusions

In conclusion, we have discovered a novel method for the synthesis of biaryls that employs aromatic aldehydes and 2-arylpyridine derivatives as cross-coupling partners in the presence of an oxidant and proceeds via the extrusion of CO. Aryl halides are tolerated under the reaction conditions.

4.3.6 Experimental section

General experimental details

2-(4-Chlorophenyl)pyridine **1c** and 1-[4-(pyridin-2-yl)phenyl]ethanone **1d** were prepared

through the Suzuki coupling of the corresponding boronic acids and 2-bromopyridines following a literature procedure.[33] Other reagents were commercially available and used as received. All reagents were weighed and handled in air.

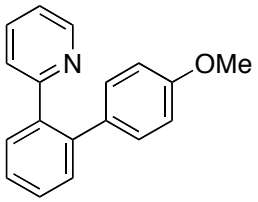
^{1}H and ^{13}C-NMR spectra were recorded on Varian 300, 400 and 500 MHz spectrometers in $CDCl_3$ solutions and chemical shifts (δ, ppm) were determined with internal solvent signal as reference (7.26 for ^{1}H–NMR and 77.0 for ^{13}C–NMR). HRMS analyses were made at the Chemistry Department of McGill University. Flash column chromatography was performed on EMD Silica Gel 60 with an appropriate solvent system (see details below).

General experimental procedures and characterizations

$(CO)_2Rh(acac)$ (0.02 mmol, 5.2 mg) was weighed in air, sealed in a 5 mL conical vial with a Teflon lined cap, and flushed with argon. Then, 2-phenylpyridine **1a** (29.2 μL, 0.2 mmol), anisolealdehyde **38a** (74.5 μL, 0.6 mmol), *tert*-butyl peroxide (94 μL, 0.5 mmol) and chlorobenzene (0.4 mL) were added through syringes into the vial, which was subsequently heated at 150 ^{o}C in an oil bath for 24 h with stirring and then cooled to room temperature. The resulting mixture was diluted with EtOAc and washed with saturated aq. $NaHCO_3$ solution and dried over $MgSO_4$. Solvents were removed *in vacuo* with a rotary evaporator and the residue was purified by column chromatography on silica gel.

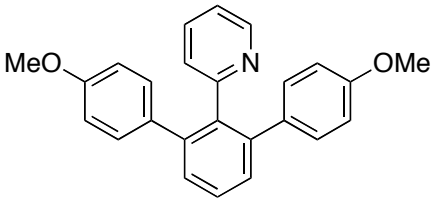
Solid 2-arylpyridine derivatives (**3**, **1c** and **1d**) and aromatic aldehydes (**38d**, **38f**, **38g**,

38i and **38k**) were added together with Rh-catalyst. For substrate **3**, only 1.5 equivalents of **38a** (37.2 μL, 0.3 mmol) and 1.25 equivalents of TBP (47.0 μL, 0.25 mmol) were used.



2-(4'-methoxybiphenyl-2-yl)pyridine **39aa**

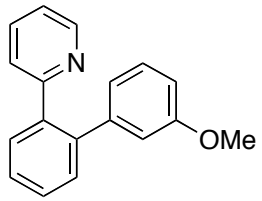
39aa was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39aa**[34] as a light yellow oil (22 mg, 42 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.64 (d, *J*=4.8 Hz, 1H), 7.69-7.66 (m, 1H), 7.46-7.38 (m, 4H), 7.12-7.10 (m, 1H), 7.07 (dt, *J*=8.8 Hz, 2.0 Hz, 2H), 6.90 (d, *J*=8.0 Hz, 1H), 6.78 (dt, *J*=8.8 Hz, 2.0 Hz, 2H), 3.79 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C 159.4, 158.5, 149.4, 140.1, 139.4, 135.2, 133.7, 130.7, 130.5, 130.4, 128.5, 127.3, 125.4, 121.3, 113.5, 55.6.



2-[2,6-bis(4-methoxyphenyl)phenyl]pyridine **39ba**

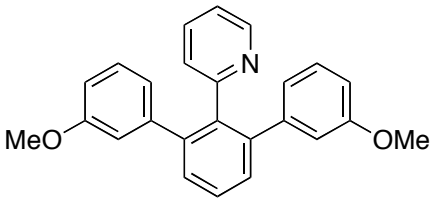
39ba was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column

chromatography (EtOAc/Hexane = 1:3) to afford **39ba**[34] as a light yellow solid (27 mg, 37 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.35 (dd, *J*=4.4 Hz, 0.8 Hz, 1H), 7.50-7.46 (m, 1H), 7.41 (s, 1H), 7.39 (d, *J*=1.2 Hz, 1H), 7.33 (td, *J*=7.6 Hz, 2.0 Hz, 1H), 7.00 (dt, *J*=8.8 Hz, 2.0 Hz, 4H), 6.94-6.91 (m, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.69 (dt, *J*=8.8 Hz, 2.0 Hz, 2H), 3.75 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C 159.2, 158.0, 148.6, 141.4, 138.4, 135.0, 134.0, 130.6, 129.2, 128.1, 126.8, 120.8, 113.1, 55.1.



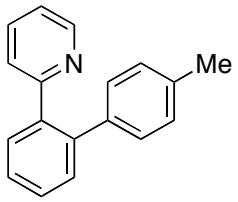
2-(3'-methoxybiphenyl-2-yl)pyridine **39ab**

39ab was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38b** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39ab**[35] as a light yellow oil (22 mg, 43 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.64 (d, *J*=4.0 Hz, 1H), 7.70-7.69 (m, 1H), 7.46 (s, 3H), 7.40 (t, *J*=7.5 Hz, 1H), 7.15 (t, *J*=7.5 Hz, 1H), 7.11 (t, *J*=5.0 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 6.77 (d, *J*=7.5 Hz, 2H), 6.68 (d, *J*=1.5 Hz, 1H), 3.63 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.3, 159.2, 149.4, 142.7, 140.5, 139.5, 135.2, 130.4, 130.3, 129.0, 128.5, 127.7, 125.3, 122.2, 121.3, 114.9, 112.9, 55.1.



2-[2,6-bis(3-methoxyphenyl)phenyl]pyridine **39bb**

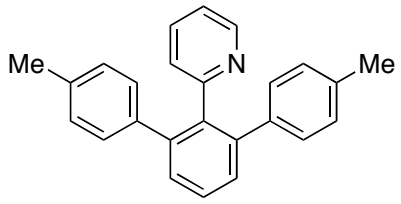
39bb was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38b** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39bb**[36] as a light yellow solid (29 mg, 39 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.36 (d, *J*=4.5 Hz, 1H), 7.53-7.50 (m, 1H), 7.48 (s, 1H), 7.46 (d, *J*=1.5 Hz, 1H), 7.34 (td, *J*=7.5 Hz, 1.5 Hz, 1H), 7.09 (t, *J*=7.5 Hz, 2H), 6.96-6.92 (m, 2H), 6.75 (d, *J*=7.5 Hz, 2H), 6.70 (dd, *J*=8.0 Hz, 2.0 Hz, 2H), 6.61 (s, 2H), 3.58 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.1, 158.8, 148.5, 142.9, 141.7, 138.4, 135.0, 129.4, 128.7, 128.2, 126.7, 122.1, 120.9, 114.7, 112.9, 55.0.



2-(4'-methylbiphenyl-2-yl)pyridine **39ac**

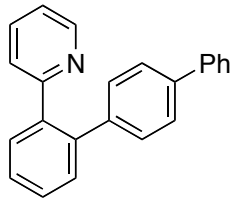
39ac was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38c** (72 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:4) to afford **39ac**[37] as a light yellow oil (19 mg, 39 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.64 (d, *J*=4.4 Hz, 1H), 7.70-7.67 (m, 1H), 7.46-7.42 (m, 3H), 7.39 (td, *J*=8.0 Hz, 1.6 Hz, 1H), 7.12-7.09 (dd, *J*=6.6 Hz, 1.4 Hz, 1H), 7.05 (s, 4H), 6.91-6.89 (d, *J*=8.0 Hz, 1H), 2.32 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C

159.4, 149.4, 140.5, 139.4, 138.3, 136.3, 135.2, 130.5, 130.5, 129.5, 128.8, 128.5, 127.4, 125.4, 121.3, 21.1.



2-[2,6-bis(4-methylphenyl)phenyl]pyridine **39bc**

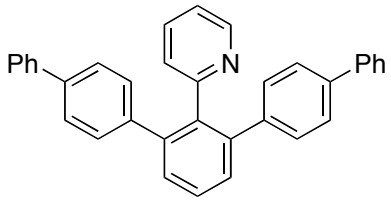
39bc was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38c** (72 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:4) to afford **39bc**[37] as a light yellow solid (16 mg, 24 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.34 (d, *J*=4.8 Hz, 1H), 7.51-7.47 (m, 1H), 7.42 (s, 1H), 7.40 (d, *J*=1.2 Hz, 1H), 7.32 (td, *J*=7.6 Hz, 1.6 Hz, 1H), 6.99-6.94 (m, 9H), 6.91-6.88 (m, 1H), 2.27 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.2, 148.5, 141.7, 138.6, 138.4, 135.8, 134.9, 129.5, 129.3, 128.3, 128.1, 126.8, 120.8, 21.0.



2-(biphenyl-2-yl)pyridine **39ad**

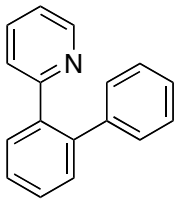
39ad was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38d** (109 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39ad** as a light yellow solid (23 mg, 38 %). IR: ν_{max} 3046, 1583, 1480, 1457, 1422, 851, 774, 760, 743, 731, 700, 614 cm^{-}

[1]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.65 (d, *J*=4.0 Hz, 1H), 7.73-7.71 (m, 1H), 7.60 (dd, *J*=8.5 Hz, 1.5 Hz, 2H), 7.50-7.48 (m, 5H), 7.45-7.40 (m, 3H), 7.34 (t, *J*=7.5 hz, 1H), 7.25 (t, *J*=7.5 Hz, 2H), 7.12 (ddd, *J*=7.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 6.97 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.2, 149.5, 140.5, 140.3, 140.1, 139.5, 139.3, 135.3, 130.5, 130.4, 130.1, 128.7, 128.6, 127.7, 127.3, 126.9, 126.7, 125.4, 121.4. HRMS exact mass calc'd for $C_{23}H_{18}N$ ([M+H]): 308.1434; found *m/z*: 308.1429.



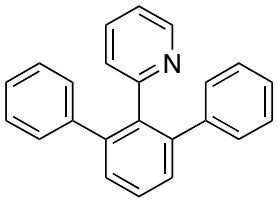
2-[2,6-bis(4-phenylphenyl)phenyl]pyridine **39bd**

39bd was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38d** (109 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39bd** as a white solid (28 mg, 31 %). IR: ν_{max} 3027, 1588, 1486, 1453, 1006, 840, 808, 765, 745, 731, 694, 617 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.35 (d, *J*=4.5 Hz, 1H), 7.56 (d, *J*=7.0 Hz, 5H), 7.52 (d, *J*=7.0 Hz, 2H), 7.42-7.39 (t, *J*=7.5 Hz, 8H), 7.35-7.30 (m, 3H), 7.18 (d, *J*=8.0 Hz, 4H), 6.97-6.92 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.9, 148.7, 141.5, 140.7, 140.6, 138.9, 138.6, 135.0, 130.0, 129.6, 128.7, 128.3, 127.2, 126.9, 126.9, 126.3, 121.0. HRMS exact mass calc'd for $C_{35}H_{26}N$ ([M+H]): 460.2060; found *m/z*: 460.2061.



2-(biphenyl-2-yl)pyridine **39ae**

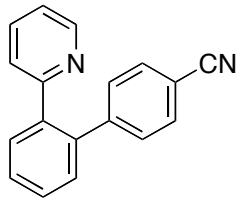
39ae was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38e** (64 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:4) to afford **39ae**[34] as a light orange solid (18 mg, 38 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.64 (d, *J*=4.5 Hz, 1H), 7.70 (t, *J*=4.3 Hz, 1H), 7.48-7.43 (m, 3H), 7.38 (td, *J*=7.5 Hz, 1.5 Hz, 1H), 7.25-7.23 (m, 3H), 7.17-7.15 (m, 2H), 7.10 (dd, *J*=6.8 Hz, 5.3 Hz, 1H), 6.88 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C 159.2, 149.4, 141.3, 140.6, 139.4, 135.2, 130.5, 130.5, 129.7, 128.5, 128.0, 127.6, 126.7, 125.4, 121.3.



2-(2,6-diphenylphenyl)pyridine **39be**

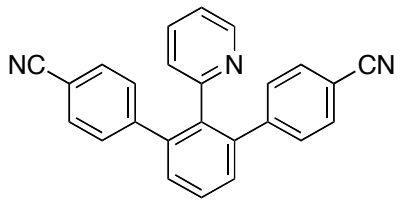
39be was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38e** (64 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:4) to afford **39be**[34] as a light yellow solid (16 mg, 26 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, *J*=4.4 Hz, 0.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.46 (s, 1H), 7.45 (d, *J*=1.6 Hz, 1H), 7.30 (td, *J*=7.6 Hz, 1.6 Hz, 1H), 7.17-7.14 (m, 6H), 7.11-7.09 (m, 4H), 6.93-6.87(m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.9,

148.5, 141.8, 141.6, 138.5, 134.8, 129.6, 129.5, 128.2, 127.6, 126.8,126.2, 120.8.



2-(4'-cynobiphenyl-2-yl)pyridine **39af**

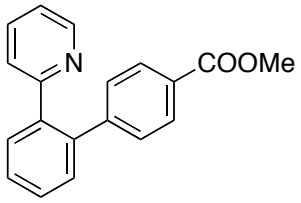
39af was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38f** (79 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (DCM/Ether = 20:1) to afford **39af**[38] as a white solid (23 mg, 45 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.59 (d, *J*=4.0 Hz, 1H), 7.68 (dd, *J*=6.0 Hz, 1.5 Hz, 1H), 7.54-7.47 (m, 5H), 7.41 (dd, *J*=6.5 Hz, 2.0 Hz, 1H), 7.24 (s, 2H), 7.16 -7.14 (m, 1H), 6.96 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.6, 149.6, 146.4, 139.6, 138.8, 135.7, 131.8, 130.7, 130.3, 130.2, 128.8, 128.7, 125.0, 121.8, 118.9, 110.4.



2-[2,6-bis(4-cynophenyl)phenyl]pyridine **39bf**

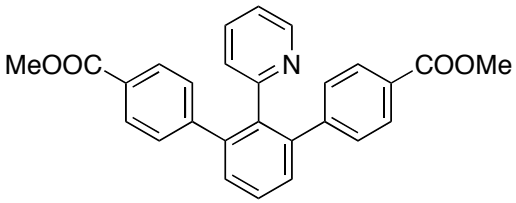
39bf was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38f** (79 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (DCM/Ether = 20:1) to afford **39bf**[39] as a white solid (16 mg, 22 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.33 (d, *J*=4.5 Hz, 1H), 7.60 (t, *J*=7.5 Hz, 1H), 7.48 (s, 2H), 7.46 (d, *J*=7.0 Hz, 4H), 7.37 (t, *J*=7.5 Hz, 1H), 7.19 (d, *J*=7.0 Hz, 4H), 7.01 (t, *J*=5.5 Hz,

1H), 6.82 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 157.4, 149.1, 146.0, 140.4, 138.4, 135.5, 131.6, 130.2, 130.1, 128.8, 126.6, 121.8, 118.7, 110.5.



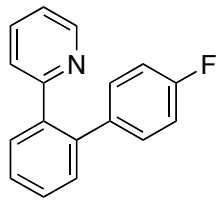
2-(4'-methoxycarbonylbiphenyl-2-yl)pyridine **39ag**

39ag was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38g** (98 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39ag** as a white solid (23 mg, 40 %). IR: ν_{max} 3001, 2950, 1723, 1705, 1608, 1586, 1434, 1426, 1286, 1274, 1110, 1102, 859, 783, 776, 759, 748, 727, 704, 616 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.61 (d, *J*=5.0 Hz, 1H), 7.91 (d, *J*=8.5 Hz, 2H), 7.71-7.69 (m, 1H), 7.52-7.48 (m, 2H), 7.45-7.43 (m, 1H), 7.41-7.40 (m, 1H), 7.23 (d, *J*=8.5 Hz, 2H), 7.12 (dd, *J*=7.5 Hz, 5.0 Hz, 1H), 6.90 (d, *J*=8.0 Hz, 1H), 3.90 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 167.0, 158.9, 149.5, 146.2, 139.6, 139.6, 135.5, 130.6, 130.3, 129.7, 129.3, 128.6, 128.4, 128.3, 125.2, 121.6, 52.1. HRMS exact mass calc'd for $C_{19}H_{16}O_2N$ ([M+H]): 290.1176; found *m/z*: 290.1174.



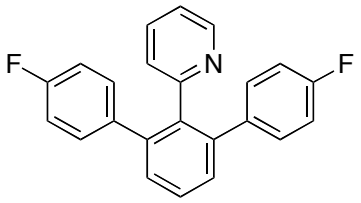
2-[2,6-bis(4-methoxycarbonylphenyl)phenyl]pyridine **39bg**

39bg was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38g** (98 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39bg**[40] as a white solid (33 mg, 39 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.29 (d, *J*=4.5 Hz, 1H), 7.83 (d, *J*=8.0 Hz, 4H), 7.56 (t, *J*=7.5 Hz, 1H), 7.48 (d, *J*=7.5 Hz, 2H), 7.30 (t, *J*=8.0 Hz, 1H), 7.16 (d, *J*=8.0 Hz, 4H), 6.93 (t, *J*=6.0 Hz, 1H), 6.85 (d, *J*=7.5 Hz, 1H), 3.87 (S, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 167.0, 158.0, 148.8, 146.2, 141.0, 138.4, 135.2, 129.8, 129.6, 129.0, 128.4, 128.1, 126.7, 121.4, 52.0.



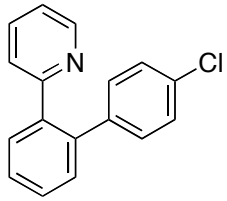
2-(4'-fluorobiphenyl-2-yl)pyridine **39ah**

39ah was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38h** (74 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39ah**[37] as a light yellow solid (23 mg, 46 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.62 (d, *J*=5.0 Hz, 1H), 7.69-7.67 (m, 1H), 7.48-7.45 (m, 2H), 7.44-7.39 (m, 2H), 7.12-7.09 (m, 3H), 6.95-6.89 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 161.9 (d, *J*=244.8 Hz), 159.1, 149.5, 139.5, 137.3 (d, *J*=3.3 Hz), 135.3, 131.2 (d, *J*=7.8 Hz), 130.5, 130.4, 128.5, 127.7, 125.2, 121.4, 115.0 (d, *J*=21.3 Hz).



2-[2,6-bis(4-fluorophenyl)phenyl]pyridine **39bh**

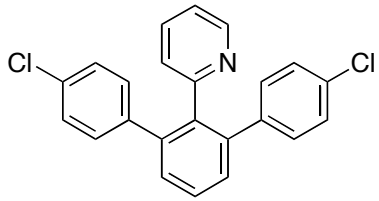
39bh was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38h** (74 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39bh**[37] as a light yellow solid (25 mg, 36 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.34 (d, *J*=4.5 Hz, 1H), 7.51 (td, *J*=7.5 Hz, 1.0 Hz, 1H), 7.42 (d, *J*=8.0 Hz, 2H), 7.33 (t, *J*=7.5 Hz, 1H), 7.06-7.04 (m, 4H), 6.96-6.93 (m, 1H), 6.86-6.82 (m, 5H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 161.6 (d, *J*=244.8 Hz), 158.6, 148.7, 140.9, 138.6, 137.4 (d, *J*=3.3 Hz), 135.1, 131.1 (d, *J*=8.4 Hz), 129.5, 128.2, 126.7, 121.1, 114.6 (d, *J*=20.8 Hz).



2-(4'-chlorobiphenyl-2-yl)pyridine **39ai**

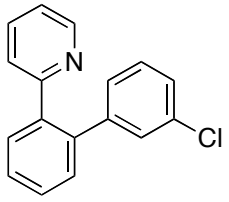
39ai was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38i** (84 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39ai**[38] as a light orange solid (23 mg, 44 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.62 (d, *J*=4.5 Hz, 1H), 7.69-7.67 (m, 1H), 7.48-7.39 (m, 4H), 7.20 (d, *J*=9.0 Hz, 2H), 7.13 (m, 1H), 7.08 (d, *J*=9.0 H, 2H), 6.92 (d, *J*=7.5

Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.0, 149.5, 139.8, 139.5, 139.3, 135.4, 132.8, 130.9, 130.5, 130.3, 128.6, 128.2, 127.9, 125.2, 121.5.



2-[2,6-bis(4-chlorophenyl)phenyl]pyridine **39bi**

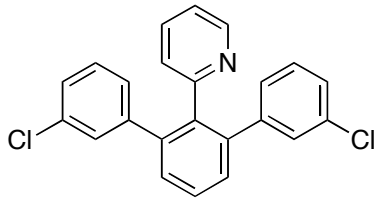
39bi was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38i** (84 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39bi**[41] as a light yellow solid (20 mg, 26 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.35 (d, *J*=4.5 Hz, 1H), 7.52 (t, *J*=7.5 Hz, 1H), 7.42 (d, *J*=7.5 Hz, 2H), 7.35 (t, *J*=7.5 Hz, 1H), 7.13 (d, *J*=8.0 Hz, 4H), 7.01 (d, *J*=8.0 Hz, 4H), 6.97 (dd, *J*=7.0 Hz, 6.0 Hz, 1H), 6.85 (d, *J*=7.5 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.3, 148.8, 140.7, 139.8, 138.4, 135.3, 132.5, 130.8, 129.6, 128.4, 127.9, 126.6, 121.3.



2-(3'-chlorobiphenyl-2-yl)pyridine **39aj**

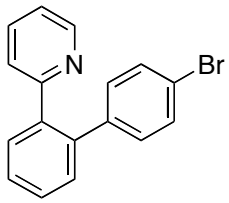
39aj was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38j** (84 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39aj**[38] as a light orange solid (24 mg,

45 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.63 (d, *J*=4.5 Hz, 1H), 7.70-7.68 (m, 1H), 7.50-7.40 (m, 4H), 7.22-7.19 (m, 2H), 7.14 -7.11 (m, 2H), 6.97 (dd, *J*=9.5 Hz, 7.5 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.8, 149.5, 143.2, 139.5, 139.1, 135.4, 133.9, 130.5, 130.3, 129.5, 129.2, 128.6, 128.1, 128.0, 126.8, 125.2, 121.5.



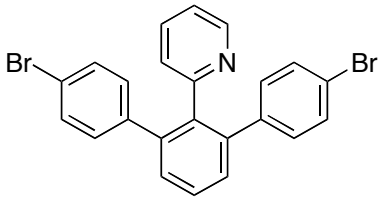
2-[2,6-bis(3-chlorophenyl)phenyl]pyridine **39bj**

39bj was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38j** (84 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39bj** as a light yellow oil (23 mg, 31 %). IR: ν_{max} 3054, 1591, 1563, 1480, 1455, 1403, 1082, 889, 778, 748, 699, 618 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.36 (d, *J*=4.5 Hz, 1H), 7.53 (t, *J*=7.5 Hz, 1H), 7.44 (d, *J*=7.5 Hz, 2H), 7.37 (td, *J*=8.0 Hz, 1.5 Hz, 1H), 7.14-7.12 (m, 4H), 7.06 (t, *J*=8.0 Hz, 2H), 6.98 (dd, *J*=7.5 Hz, 5.0 Hz, 1H), 6.93 (d, *J*=7.5 Hz, 2H), 6.88 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.0, 148.7, 143.1, 140.5, 138.5, 135.2, 133.6, 129.7, 129.6, 128.8, 128.4, 127.8, 126.6, 126.6, 121.3. HRMS exact mass calc'd for $C_{23}H_{16}NCl_2$ ([M+H]): 376.0654; found *m/z*: 376.0656.



2-(4'-bromobiphenyl-2-yl)pyridine **39ak**

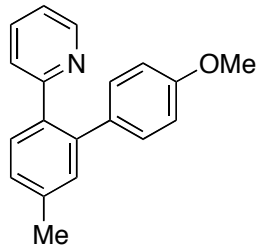
39ak was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38k** (111 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:4) to afford **39ak**[38] as a white solid (12 mg, 20 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.62 (dd, *J*=5.0 Hz, 0.5 Hz, 1H), 7.68-7.67 (m, 1H), 7.49 -7.43 (m, 3H), 7.41-7.39 (m, 1H), 7.36 (dt, *J*=9.0 Hz, 2.0 Hz, 2H), 7.13 (ddd, *J*=7.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 7.02 (dt, *J*=9.0 Hz, 2.0 Hz, 2H), 6.92 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.0, 149.5, 140.3, 139.5, 139.3, 135.5, 131.3, 131.2, 130.6, 130.3, 128.6, 128.0, 125.2, 121.5, 121.0.



2-[2,6-bis(4-bromophenyl)phenyl]pyridine **39bk**

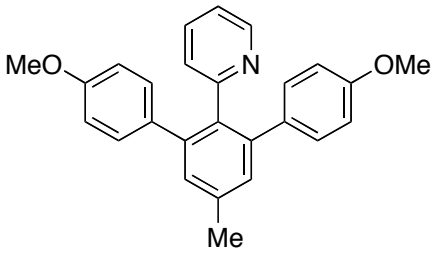
39bk was prepared from 2-arylpyridine **1a** (31 mg, 0.2 mmol) and aldehyde **38k** (111 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:4) to afford **39bk** as a light orange solid (33 mg, 36 %). IR: ν_{max} 3046, 2923, 1588, 1561, 1488, 1453, 1422, 1386, 1068, 1007, 823, 798, 786, 757, 749, 722, 632, 619 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.35 (dd, *J*=4.5 Hz, 1.0 Hz, 1H), 7.52 (td, *J*=7.5 Hz, 1.0 Hz, 1H), 7.41 (d, *J*=7.0 Hz, 2H), 7.36 (t, *J*=7.5

Hz, 1H), 7.27 (d, *J*=7.5 Hz, 4H), 6.99-6.98 (m, 1H), 6.96 (d, *J*=7.5 Hz, 4H), 6.85 (d, *J*=8.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.2, 148.8, 140.8, 140.3, 138.3, 135.3, 131.2, 130.8, 129.6, 128.4, 126.6, 121.3, 120.8. HRMS exact mass calc'd for $C_{23}H_{16}NBr_2$ ([M+H]): 463.9644; found *m/z*: 463.9649.



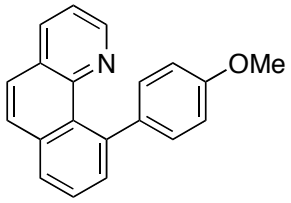
2-(4'-methoxy-5-methylbiphenyl-2-yl)pyridine **39al**

39al was prepared from 2-arylpyridine **1b** (34 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39al** as a yellow oil (23 mg, 41 %). IR: ν_{max} 3001, 2927, 2835, 1606, 1587, 1512, 1496, 1460, 1428, 1289, 1243, 1176, 1029, 829, 786, 747, 692, 622 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.63 (d, *J*=4.0 Hz, 1H), 7.59 (d, *J*=8.0 Hz, 1H), 7.37 (t, *J*=7.5 Hz, 1H), 7.24 (d, *J*=9.0 Hz, 2H), 7.07 (d, *J*=7.5 Hz, 3H), 6.87 (d, *J*=8.0 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.4, 158.5, 149.3, 140.0, 138.3, 136.6, 135.1, 133.9, 131.1, 130.7, 130.5, 128.0, 125.4, 121.0, 113.5, 55.2, 21.2. HRMS exact mass calc'd for $C_{19}H_{18}ON$ ([M+H]): 276.1383; found *m/z*: 276.1380.



2-[2,6-bis(4-methoxyphenyl)-4-methylphenyl]pyridine **39bl**

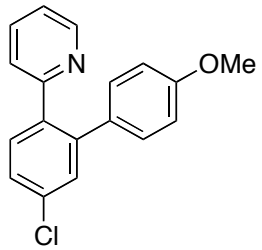
39bl was prepared from 2-arylpyridine **1b** (34 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:3) to afford **39bl** as a light yellow solid (35 mg, 46 %). IR: ν_{max} 2931, 1608，1511, 1290, 1248, 1179, 1033, 829, 799, 748 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.34 (d, *J*=4.5 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 1H), 7.22 (s, 2H), 7.00 (d, *J*=8.5 Hz, 4H), 6.91 (t, *J*=6.0 Hz, 1H), 6.85 (d, *J*=7.5 Hz, 1H), 6.68 (d, *J*=8.0 Hz, 4H), 3.74 (s, 6H), 2.46 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 159.4, 158.0, 148.5, 141.3, 137.7, 135.8, 134.9, 134.2, 130.6, 129.9, 126.9, 120.6, 113.1, 55.1, 21.2. HRMS exact mass calc'd for $C_{26}H_{24}O_2N$ ([M+H]): 382.1802; found *m/z*: 382.1799.



10-(4-methoxyphenyl)benzo[*h*]quinoline **39am**

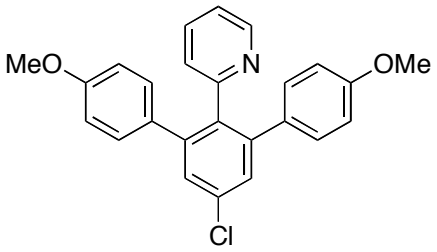
39am was prepared from 2-arylpyridine **3** (36 mg, 0.2 mmol) and aldehyde **38a** (41 mg, 0.3 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39am**[42] as a light yellow solid (40 mg, 71 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.48 (dd, *J*=4.0 Hz, 1.6 Hz, 1H), 8.09 (dd, *J*=8.0 Hz, 1.6 Hz, 1H), 7.91 (dd, *J*=8.0 Hz, 0.8 Hz, 1H), 7.85 (d, *J*=8.8 Hz, 1H), 7.69 (d, *J*=8.8

Hz, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.55 (dd, *J*=7.2 Hz, 1.2 Hz, 1H), 7.33 (q, *J*=4.0 Hz, 1H), 7.30 (dt, *J*=8.4 Hz, 2.0 Hz, 2H), 6.96 (dt, *J*=8.4 Hz, 2.0 Hz, 2H), 3.91 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C 157.9, 146.9, 146.9, 141.3, 138.9, 135.2, 135.0, 131.7, 129.8, 129.1, 128.3, 127.7, 127.2, 127.0, 125.9, 121.0, 112.8, 55.3.



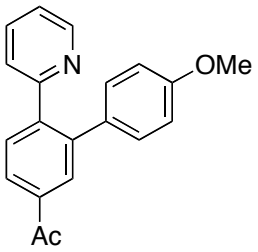
2-(5-chloro-4'-methoxybiphenyl-2-yl)pyridine **39an**

39an was prepared from 2-arylpyridine **1c** (38 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39an** as an orange oil (24 mg, 41 %). IR: ν_{max} 2935, 2836, 1681, 1608, 1584, 1513, 1456, 1430, 1290, 1242, 1177, 1024, 833, 790, 750 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.63 (d, *J*=5.0 Hz, 1H), 7.62 (d, *J*=8.5 Hz, 1H), 7.41-7.38 (m, 3H), 7.13-7.10 (m, 1H), 7.05 (d, *J*=8.0 Hz, 2H), 6.86 (d, *J*=7.5 Hz, 1H), 6.78 (d, *J*=8.0 Hz, 2H), 3.88 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.9, 158.3, 149.5, 141.8, 137.8, 135.3, 134.3, 132.4, 131.9, 130.6, 130.2, 127.3, 125.3, 121.5, 113.7, 55.2. HRMS exact mass calc'd for $C_{18}H_{15}ONCl$ ([M+H]): 296.0837; found *m/z*: 296.0838.



2-[2,6-bis(4-methoxyphenyl)-4-chlorophenyl]pyridine **39bn**

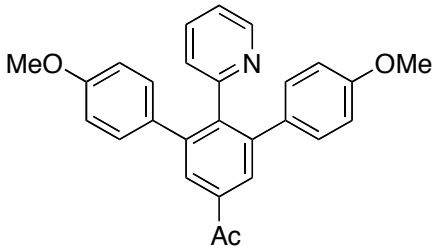
39bn was prepared from 2-arylpyridine **1c** (38 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:5) to afford **39bn** as a light yellow solid (30 mg, 38 %). IR: ν_{max} 2932, 2835, 1607, 1510, 1288, 1246, 1178, 1029, 826, 800, 749 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.35 (d, *J*=4.5 Hz, 1H), 7.39 (s, 2H), 7.33 (td, *J*=7.5 Hz, 1.5 Hz, 1H), 6.98 (d, *J*=8.5 Hz, 4H), 6.93 (dd, *J*=7.0 Hz, 5.5 Hz, 1H) 6.83 (d, *J*=8.0 Hz, 1H), 6.69 (d, *J*=8.5 Hz, 4H), 3.74 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 158.4, 158.3, 148.7, 143.1, 137.0, 135.1, 133.6, 132.8, 130.5, 128.8, 126.7, 121.0, 113.2, 55.1. HRMS exact mass calc'd for $C_{25}H_{21}O_2NCl$ ([M+H]): 402.1255; found *m/z*: 402.1258.



2-(5-acyl-4'-methoxybiphenyl-2-yl)pyridine **39ao**

39ao was prepared from 2-arylpyridine **1d** (39 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:1) to afford **39ao** as an orange oil (25 mg, 41 %). IR: ν_{max} 3001, 2930, 2835, 1680, 1607, 1584, 1513, 1292, 1244, 1176, 1022, 831, 790,

748, 602 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.61 (dt, *J*=4.0 Hz, 1.0 Hz, 1H), 8.01-7.99 (m, 2H), 7.78 (dd, *J*=5.5 Hz, 3.0 Hz, 1H), 7.43 (td, *J*=7.5 Hz, 2.0 Hz, 1H), 7.14 (ddd, *J*=7.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 7.09 (dt, *J*=8.5 Hz, 2.5 Hz, 2H), 6.92 (d, *J*=7.5 Hz, 1H), 6.80 (dt, *J*=8.5 Hz, 2.5 Hz, 2H), 3.79 (s, 3H), 2.66 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 197.9, 158.9, 158.3, 149.6, 143.6, 140.6, 136.9, 135.4, 132.7, 130.9, 130.7, 130.5, 127.0, 125.3, 121.9, 113.7, 55.2, 26.8. HRMS exact mass calc'd for $C_{20}H_{18}O_2N$ ([M+H]): 304.1332; found *m/z*: 304.1327.



2-[2,6-bis(4-methoxyphenyl)-4-acylphenyl]pyridine **39bo**

39bo was prepared from 2-arylpyridine **1d** (39 mg, 0.2 mmol) and aldehyde **38a** (82 mg, 0.6 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:1) to afford **39bo** as a light yellow solid (34 mg, 42 %). IR: ν_{max} 3039, 3000, 2933, 2837, 1681, 1606, 1510, 1293, 1244, 1229, 1176, 1029, 830, 802, 776, 753, 622 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.37 (d, *J*=4.0 Hz, 1H), 7.97 (s, 2H), 7.36 (t, *J*=7.5 Hz, 1H), 7.02 (d, *J*=8.5 Hz, 4H), 6.96 (t, *J*=7.5 Hz, 1H), 6.87 (d, *J*=7.5 Hz, 1H), 6.71 (d, *J*=8.5 Hz, 4H), 3.75 (s, 6H), 2.67 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 197.9, 158.4, 158.4, 148.7, 142.8, 142.1, 136.6, 135.2, 133.1, 130.6, 128.9, 126.4, 121.2, 113.3, 55.1, 26.8. HRMS exact mass calc'd for $C_{27}H_{24}O_3N$ ([M+H]): 410.1751; found *m/z*: 410.1753.

References

(1) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.

(2) For recent reviews, see: (a) A. de Meijere, F. Diederich, Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH, Weinheim, 2004. (b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(3) For reviews and recent examples, see: (a) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263. (b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev*. **2007**, *107*, 174. (c) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrich. Acta* **2007**, *40*, 35. (d) B. J. Li, S. D. Yang, Z. J. Shi, *Synlett* **2008**, 949. (e) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev*. **2009**, *38*, 2447. (f) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074. (g) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun*. **2010**, 46, 677. (h) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110,* 1147. (i) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242. (j) F. Pogan, P. H. Dixneuf, *Adv. Synth. Catal.* **2009**, *351*, 1737.

(4) For reviews, see: J. A. Ashenhurst, *Chem. Soc. Rev*. **2010**, *39*, 540.

(5) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047.

(6) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904.

(7) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 9651.

(8) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047.

(9) B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem., Int. Ed.* **2008**, *47*, 1115.

(10) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254.

(11) X. Zhao, C. S. Yeung, Vy M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837.

(12) (a) D. R. Stuart, K. Fagnou, *Science*, **2007**, *316*, 1172. (b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072.

(13) (a) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett.* **2007**, *9*, 3137. (b) S. Potavathri, A.S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann, B. DeBoef, *Tetrahedron Lett.* **2008**, *49*, 4050.

(14) S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. LeBris, B. DeBoef, *J. Am. Chem. Soc.* **2010**, *132*, 14676.

(15) R. Li, L. Jiang, W. Lu, *Organometallics* **2006**, *25,* 5973.

(16) Y. Wei, W. Su, *J. Am. Chem. Soc.* **2010**, *132*, 16377.

(17) (a) L. J. Gooßen, K. Gooßen, N. Rodriguez, M. Blanchot, C. Linder, B. Zimmermann, *Pure Appl. Chem.* **2008**, *80*, 1725. (b) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.

(18) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662.

(19) L. J. Gooßen, B. Zimmermann, T. Knauber, *Angew. Chem., Int. Ed.* **2008**, *47*, 7103.

(20) L. J. Gooßen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824.

(21) L. J. Gooßen, B. Melzer, *J. Org. Chem.* **2007**, *72*, 7473.

(22) P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006***, 128*, 11350.

(23) W.-Y. Yu, W. N. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174.

(24) (a) X. Zhao, Z. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 8136. (b) W. Ye, N. Luo, Z. Yu, *Organometallics* **2010**, *29*, 1049.

(25) W. Jin, Z. Yu, W. He, W. Ye, W.-J. Xiao, *Org. Lett.* **2009**, *11*, 1317.

(26) M. Tobisub, N. Chatani, *Chem. Soc. Rev.* **2008**, *37*, 300.

(27) (a) J. A. Miller, *Tetrahedron Lett.* **2001**, *42*, 6991. (b) J. A. Miller, J. W.; Penny, J. A. Dankwardt, *Synthesis* **2003**, 1643.

(28) Y. Terao, H. Wakui, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc*. **2001**, *123*, 10407.

(29) M. Nakano, T. Satoh, M. Miura, *J. Org. Chem.* **2006**, *71*, 8309.

(30) A. B. Bíró, A. Kotschy, *Eur. J. Org. Chem.* **2007**, 1364.

(31) (a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335. (b) O. Baslé, J. Bidange, Q. Shuai, C.-J. Li*, Adv. Synth. Catal.* **2010**, *352*, 1145.

(32) (a) X. Guo, J. Wang, C.-J. Li, *J. Am. Chem. Soc.* **2009**, *131*, 15092. (b) X. Guo, J. Wang, C.-J. Li, *Org. Lett.* **2010**, *12*, 3176.

(33) T. Tagata, M. Nishida, *J. Org. Chem.* **2003**, *68*, 9412.

(34) F. Pogan, P. H. Dixneuf, *Adv. Synth. Catal.* **2009**, *351*, 1737.

(35) N. Luo, Z. K. Yu, *Chem. Eur. J.* **2010**, *16*, 787.

(36) F. Yang, Y. Wu, Y. Li, B Wang, J. Zhang, *Tetrahedron* **2009**, *65*, 914.

(37) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579.

(38) W.-Y. Yu, W. N. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174.

(39) I. Oezdemir, S. Demir, B. Cetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H.

(40) P. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2009**, *11*, 1871.

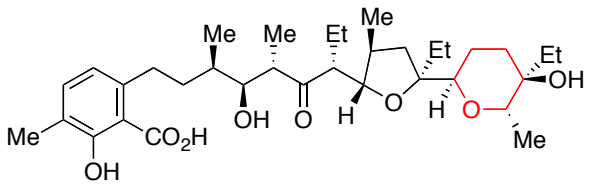
(41) L. Ackermann, A. Althammer, R. Born, *Tetrahedron* **2008**, *64*, 6115.

(42) X. Zhao, Z. K. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 8136.

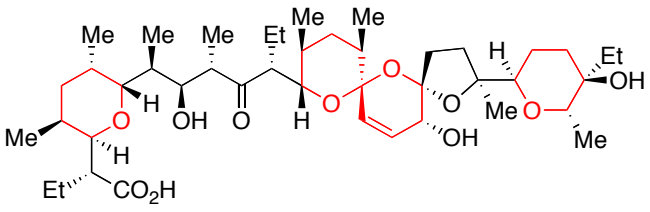
Chapter 5

A Novel Approach to Dihydropyran Derivatives via a Ruthenium- and Copper-Catalyzed Domino Reaction between Alkynols and Aldehydes

Tetrahydropyrans and dihydropyrans have been found to be pivotal structures in a wide variety of natural products and pharmaceuticals and many efforts have been made towards the synthesis of these compounds.[1] Polyether antibiotics, such as Lasalocid A and Narasin, the main structure features of which are tetrahydropyrans and dihydropyrans, have attracted considerable attention due to their biological activity and commercial value (Scheme 5.1).[2]



Lasalocid A



Narasin

Scheme 5.1 Representatives of polyether antibiotics

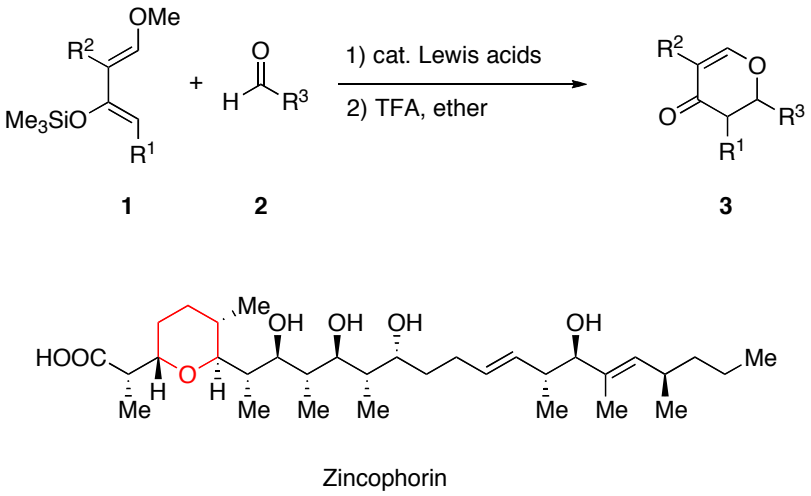
Specifically, the construction of dihydropyran motifs, also highly useful synthons, is particularly attractive since the olefin function of these compounds could serve as useful building blocks for further transformation to polysubstituted tetrahydropyrans.[3] In this chapter, a concise review of the synthesis of dihydropyrans will be discussed. In addition, a novel ruthenium- and copper-catalyzed domino reaction between alkynols and aldehydes will be presented, which provides a straightforward access to 5-olefinated 3,4-dihydropyran derivatives.

5.1 Synthesis of dihydropyrans

5.1.1 Hetero Diels-Alder reactions

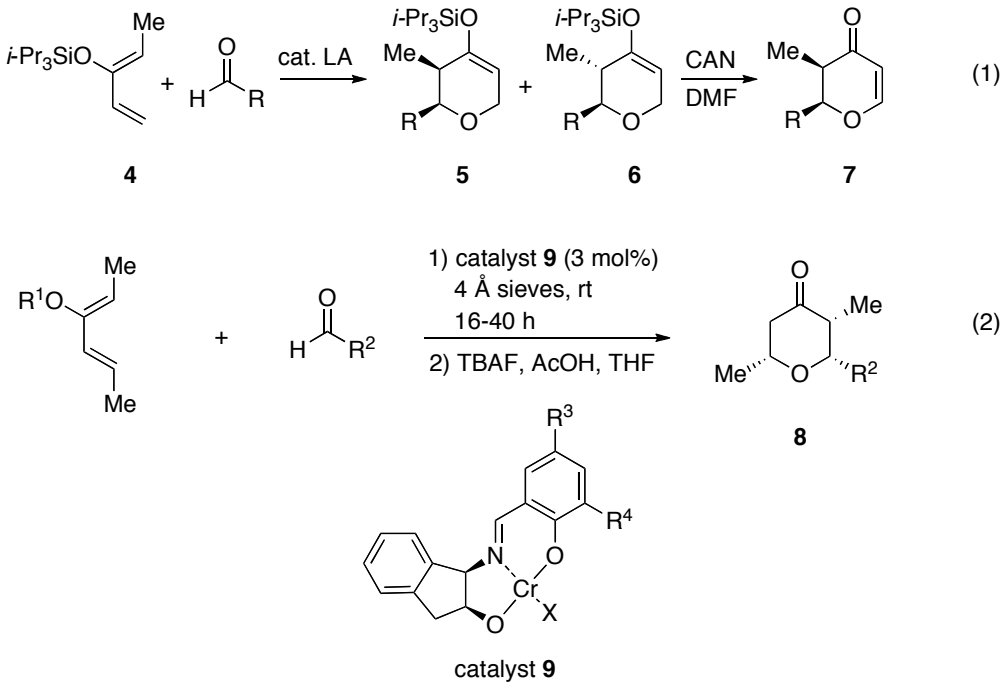
One powerful method for the preparation of dihydropyrans is the hetero Diels-Alder reaction (HDA) of dienes with aldehydes or electron-rich alkenes with α,β-unsaturated carbonyl compounds.

Danishefsky and his colleagues realized Lewis acid (LA)-catalyzed HDA reactions between dienes **1** and aldehydes **2**, affording dihydropyrones **3**, a precursor of dihydropyrans (Scheme 5.2).[4] The electron-donating effects of the 1- and 3-oxygen functions endowed the high reactivity of dienes **1** and allowed the HDA reaction occur under mild reaction conditions, making further development of stereoselective versions promising. This novel methodology was promptly applied to the synthesis of zincophorin[5] and other natural products.[6]



Scheme 5.2 HDA reaction of dienes and aldehydes

The application of asymmetric catalysis to this protocol has made it an even more powerful synthetic tool. In 1996, Evans and Nelson reported a stereoselective synthesis of dihydropyran-4-ones **7** via a formal HDA reaction of the monoactivated (triisopropylsilyl)oxy diene **4** with an array of aldehydes (Scheme 5.3, Eq. 1).[7] Lewis acids Me_2AlCl or BF_3•OEt_2 can catalyze this transformation, affording the isolable enol ether products **5** and **6** with high diastereoselectivity. The treatment of the dominant *cis*-diastereoisomer **5** with ceric ammonium nitrate (CAN) at 0 ^oC furnished the *cis*-2, 3-disubstituted dihydropyran-4-ones **7** in excellent yields. Later, the Jacobsen group developed a highly enantio- and diastereoselective HDA reaction of similar substrates by using chiral tridentate chromium(III) catalysts **9**, providing tetrahydropyranones **8** with 3 stereocenters after desilylation (Scheme 5.3, Eq. 2).[8]

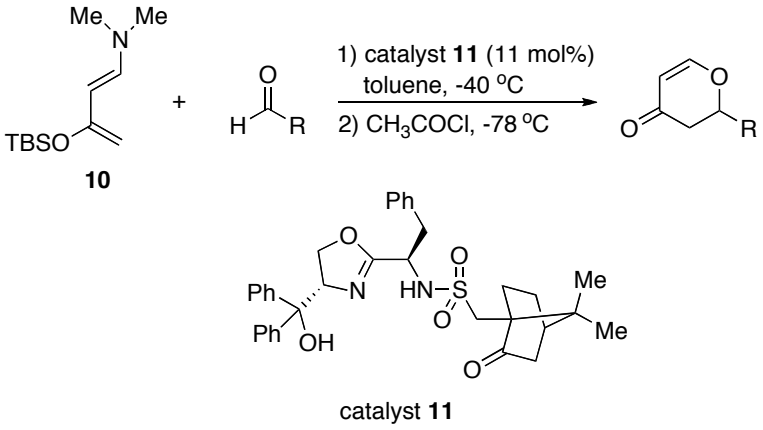


Scheme 5.3 Stereoselective synthesis of dihydropyrans via HDA reactions

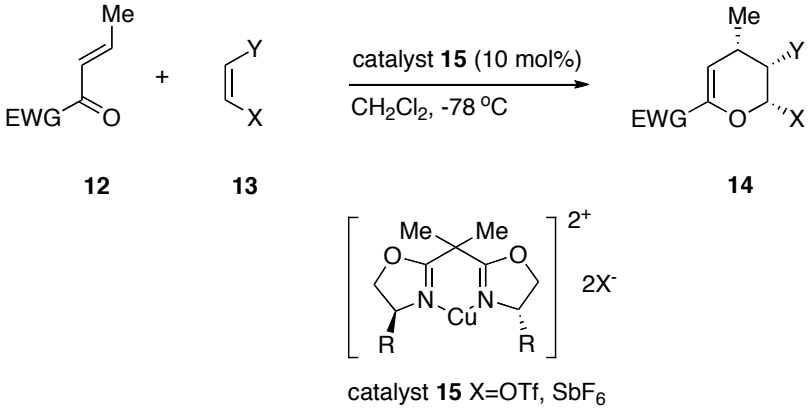
Recently, Sigman and Rajaram devised an organo catalyst **11** (Scheme 5.4) based on an amine-functionalized oxazoline, which possessed two hydrogen bond donating arms.[9] This molecule turned out to be a good catalyst for enantioselective HDA reactions of dienes **10** and aldehydes, finally affording dihydropyranones in good yields with high enantioselectivity.

A different approach to dihydropyrans involving HDA reactions has been developed by using electron-rich alkenes and α,β-unsaturated carbonyl compounds as starting materials. Evans *et al.* demonstrated that, in the presence of a catalytic amount of Cu(II) complexes, the HDA reaction of α,β-unsaturated carbonyl compounds **12** and alkenes **13** afforded dihydropyrans **14** in good yields with excellent stereoselectivity (Scheme 5.5).[10]

Heterodienes with electron-withdrawing groups at the carbonyl group were effective substrates.



Scheme 5.4 Enantioselective HDA reaction promoted by organo catalysts

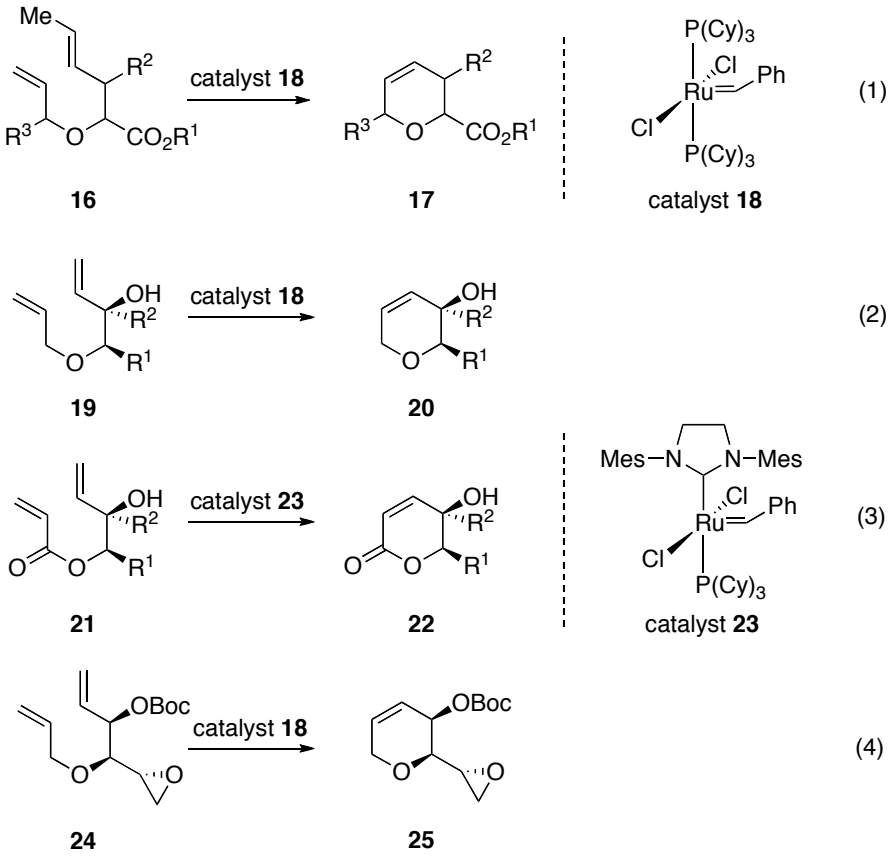


Scheme 5.5 Cu-catalyzed enantioselective synthesis of dihydropyrans

5.1.2 Ring-closing olefin metathesis

Grubbs' catalyst has been considered as a versatile tool for the synthesis of cyclic alkenes, and also has been widely used for the construction of dihydropyran derivatives.

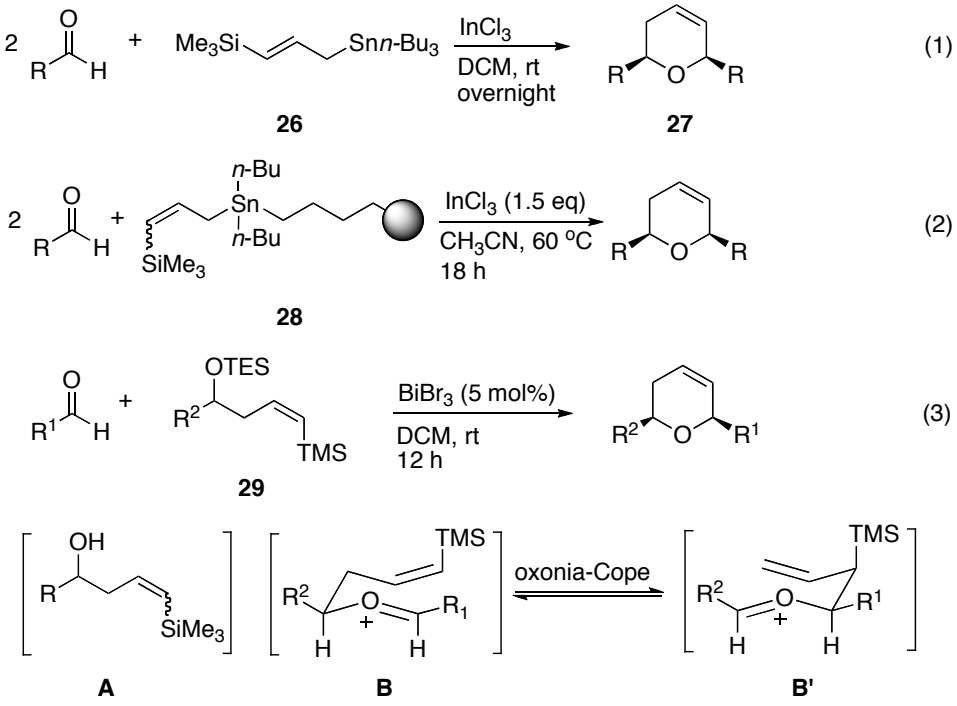
Among them, Burke *et al.* reported a ring-closing metathesis (RCM) of diene substrates **16** containing an α-alkoxy-γ,δ-unsaturated ester, affording dihydropyran derivatives **17** in good yields (Scheme 5.6, Eq. 1).[11] The first-generation Grubbs' catalyst **18** was effective for this transformation. The Schmidt group reported a similar process by using dienes **19** bearing a free allylic hydroxyl group as substrates (Scheme 5.6, Eq. 2).[12] However, the second-generation catalyst **23** was required for the RCM of dienes **21** containing one electron-deficient double bond (Scheme 5.6, Eq. 3). One advantage of this protocol is that it can tolerate a wide variety of functional groups, and the same group has also achieved the RCM of dienes **24** with an epoxide substitutent (Scheme 5.6, Eq. 4).[13]



Scheme 5.6 Synthesis of dihydropyrans via ring-closing metathesis

5.1.3 Prins-cyclization

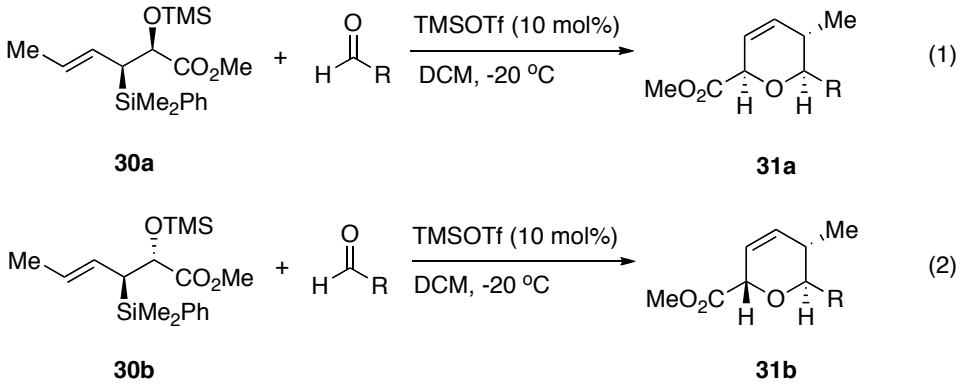
The Li group disclosed an $InCl_3$-mediated Prins-cyclization process of 2 equivalents of aliphatic aldehydes with 3-trimethylsilylallyltributylstannane **26**, affording functionalized dihydropyrans **27** with high *cis*-stereoselectivity (Scheme 5.7, Eq. 1).[14] A similar report was by presented by Zammattio and his colleagues, who employed insoluble polymer supported stannane reagents **28** as substrates for the Prins-cyclization reaction. Whatever the *E* or *Z* configuration of the vinylsilane, *cis* stereoselective dihydropyrans were obtained (Scheme 5.7, Eq. 2).[15] It was elucidated that this reaction proceeded via the intermediate γ-silylated homoallylic alcohol **A**, which was isolated and characterized. Lian and Hinkle further explored a $BiBr_3$-catalyzed cyclization of (*Z*)-1-trimethylsilyl-4-triethylsilyloxybutene **29** with aldehydes and obtained dihydropyrans with *cis*



Scheme 5.7 Synthesis of 2,6-disubstituted dihydropyrans via Prins-cyclization

stereoselectivity as well (Scheme 5.7, Eq. 3).[16] The *cis* stereoselectivity of this Prins-cyclization could be rationalized by the formation of chair like (*E*)-oxocarbenium ion transition states **B** and **B'**, on which the R groups adopted equatorial positions in order to minimize the 1,3 diaxial interactions.

Huang and Panek demonstrated that, when chiral crotylsilanes **30** were used, 2,6-disubstituted dihydropyans **31** were obtained with high stereoselectivity and the configuration of the silane reagent controls the stereochemical course of the cyclization (Scheme 5.8),[17] which could be rationalized through an *anti*-S_E' mode of addition.[18]

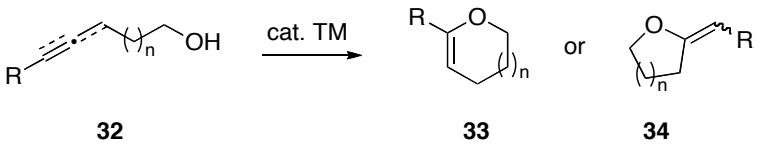


Scheme 5.8 TMSOTf-catalyzed annulation of chiral crotylsilanes

5.1.4 Cycloisomerization

Recently, transition-metal-catalyzed formal addition of a hydroxyl bond across an unsaturated C-C bond has provided an efficient route for the synthesis of oxygen-containing heterocycles, converting the starting materials into final products with 100% atom-efficiency.[19] Generally, in the presence of a transition-metal catalyst, alkynes or

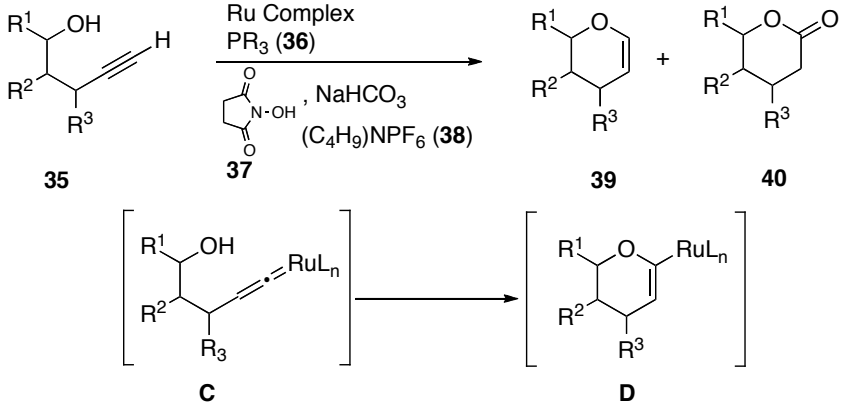
allene tethered to alcohols **32** undergo cycloisomerization to form endo- cyclic enol ethers **33** or exo-enol ethers **34** (Scheme 5.9).



32 **33** **34**

Scheme 5.9 Transition-metal-catalyzed formation of *O*-containing heterocycles

In terms of the synthesis of 3,4-dihydropyrans starting with alkynols, various catalytic systems have been developed. Trost and Rhee discovered a ruthenium-catalyzed cyclization of alkynols **35**, affording a mixture of dihydropyran **39** and lactone **40** (Scheme 5.10).[20] The ratio of these two products could be changed through the modification of the catalytic system. Lower loadings of the Ru complex, ligand **36**, and oxidant **37** favored the formation of dihydropyran products **39**. It was believed that this novel reaction occurred via a key rutheniumvinylidene intermediate **C**, which underwent a nucleophilic addition and afforded the dihydropyran **39** after protonation.

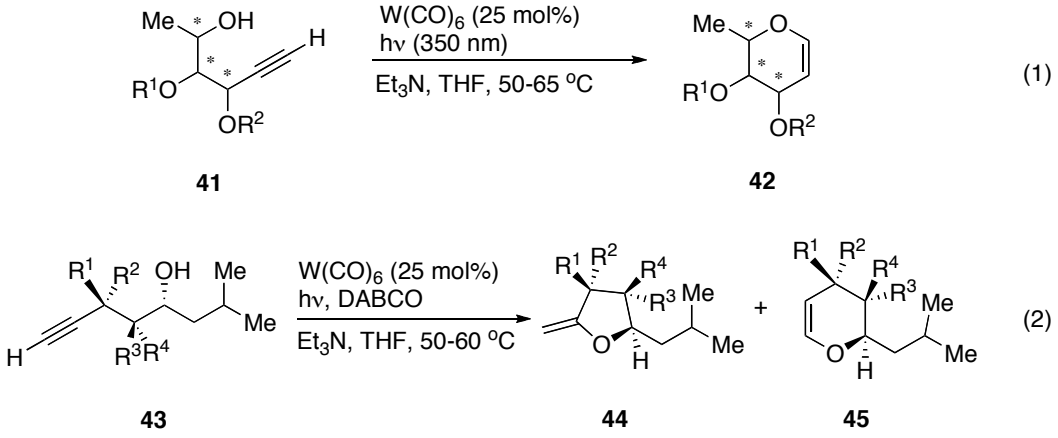


35 **37** **39** **40**

C **D**

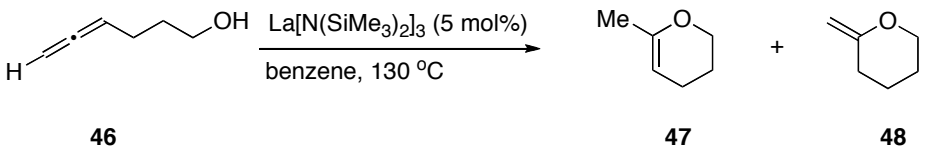
Scheme 5.10 Ru-catalyzed cyclization of alkynols

McDonald *et al.* disclosed, when photolyzed at 350 nm, $W(CO)_6$ could catalyze the cycloisomerization of highly functionalized terminal alkynyl alcohols **41** to *endo*-cyclic enol ethers **42** in high yields (Scheme 5.11, Eq. 1).[21] Tertiary amines (triethylamine or DABCO) were essential for this reaction and chiral substrates afforded corresponding enol ethers with out any epimerization. Wipf and Graham have also reported a similar catalytic system. However, this tungsten-catalyzed cycloisomerization of **43** afforded a mixture of *exo*-enol ethers **44** and dihydropyrans **45** (Scheme 5.11, Eq. 2).[22]



Scheme 5.11 W-catalyzed cycloisomerization of alkynols

Recently, Marks *et al*. reported the synthesis of 6-methylated dihydropyrans together with its isomer of *exo*-cyclic enol ethers, via a lanthanide-catalyzed cyclization of allenyl alcohol **46** (Scheme 5.12).[23] Endo-cyclic enol ethers **47** was obtained as a major isomer together with a minor exo-isomer **48**.



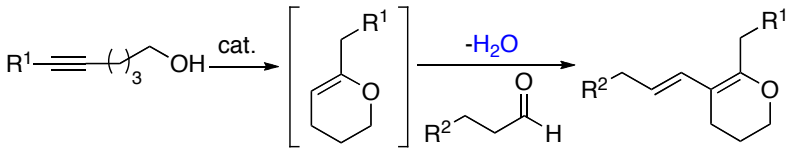
46 47 48

Scheme 5.12 La-catalyzed cycloisomerization of allenyl alcohols

5.2 Ruthenium- and copper-catalyzed domino reaction between alkynols and aldehydes

5.2.1 Background

As discussed above, highly selective syntheses of 6-substituted 3,4-dihydropyran directly from 5-hexyn-1-ol derivatives still remain a big challenge. It is even more challenging to cascade such cyclizations with a further catalytic reaction. Herein, we present a novel transition-metal-catalyzed domino alkynol cyclization and C-C bond formation with aldehydes to afford 5-olefinated 3,4-dihydropyran derivatives efficiently (Scheme 5.13).



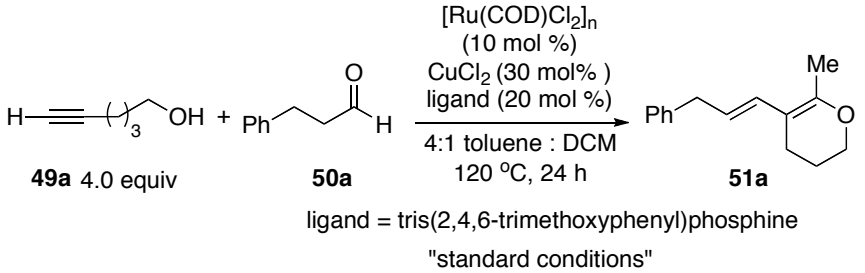
Scheme 5.13 A novel dihydropyran synthesis

5.2.2 Optimization of reaction conditions

Previously, we reported a Ru-catalyzed decarbonylative addition of aldehydes to alkynes,[24] and unexpectedly when the "standard conditions" were applied to terminal

alkynol **49a** and hydrocinnamaldehyde **50a**, an unknown product was isolated in good yield (Table 5.1, entry1). With 4-nitrohydrocinnamaldehyde (**50d**) as an aldehyde the product was characterized by X-ray crystallography as **51d**, which has an unusual 5 (*E*) – olefinated 3,4-dihydropyran (Figure 5.1). To further optimize the reaction conditions, various factors affecting this transformation were examined. The use of a phosphine ligand was found to be important but not essential, without which the yield was decreased (entry 2). In the absence of $[Ru(COD)Cl_2]_n$, **51a** was obtained in less than 5 % yield (entry 3). Without the addition of $CuCl_2$, only a trace amount of product was detected by GC-MS (entry 4). When the reaction was conducted at lower temperatures, lower yields were obtained (entries 5). Pre-stirring of the catalyst in DCM was found to be quite important and shortening this procedure decreased the yield (entry 6). Reducing the amount of the alkynol **49a** resulted in lower yields of products (entries 7-10). In addition, when the reaction was run in a shorter time, the product was obtained in a slightly lower yield (entry 11). Finally, it was realized that the "standard conditions" turned out to be the optimal reaction conditions for this novel transformation.

Table 5.1 Factors influencing the domino reaction of aldehydes and alkynols[a]



entry	change from the "standard conditions"	yield (%)[b]
1	none	78 (72)

Table 5.1 (continued)

entry	change from the "standard conditions"	yield (%)[b]
2	no ligand	20
3	no $[Ru(COD)Cl_2]_n$	<5
4	no $CuCl_2$	trace[c]
5	100 °C	29
6	pre-stirred for 1 h	54
7	alkynol (1.5 equiv)	10
8	alkynol (2.0 equiv)	11
9	alkynol (2.5 equiv)	20
10	alkynol (3.0 equiv)	19
11	16 h	57

[a] Conditions: $[Ru(COD)Cl_2]_n$ (0.01 mmol, 2.8 mg), $CuCl_2$ (0.03 mmol, 4.1 mg), and ligand (0.02 mmol, 10.6 mg) were pre-stirred in DCM (0.1 mL) under argon at rt for 24 h. Then, **49a** (0.4 mmol, 45.2 μL), **50a** (0.1 mmol, 15.0 μL), and toluene (0.4 mL) were added under argon and heated at 120 °C for 24 h. [b] ^{1}H-NMR yields using an internal standard; isolated yields are given in parenthesis. [c] Determined by GC-MS.

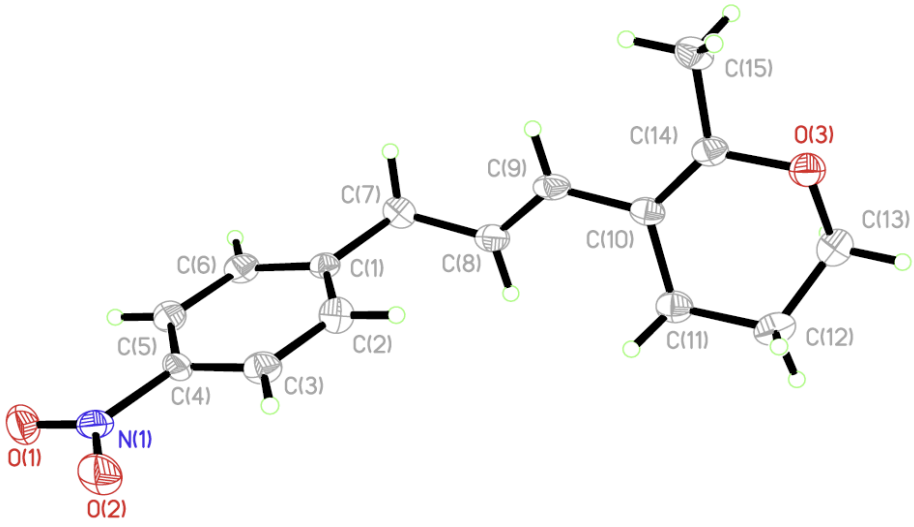
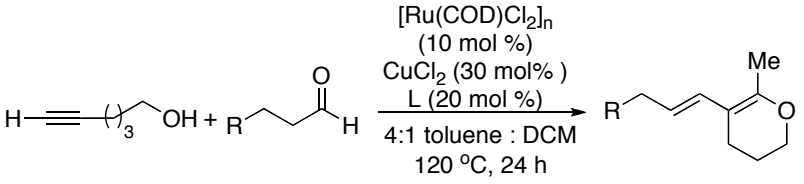


Figure 5.1 ORTEP representation of the molecular structure of **51d**

5.2.3 Scope of the domino reaction of aldehydes and alkynols

Under the "standard conditions", the scope and generality of this domino reaction was explored. An electron-rich methoxy substituent at the *para*-position of the hydrocinnamaldehyde showed similar reactivity toward the alkynol (Table 5.2, entry 2). *para*-Brominated hydrocinnamaldehyde **50c** appeared to be a good substrate for this transformation, furnishing the desired product in a good yield without affecting the bromo-motif (entry 3). Having a strong electron-withdrawing nitro group at the para-position, aldehyde **50d** afforded the product in a reasonable yield (entry 4). When aldehyde **50e** was employed as the substrate, the desired product was obtained in a slightly lower yield (entry 5). Interestingly, aldehyde **50f**, with an additional double bond conjugated to the phenyl ring, still gave a fair yield of the desired product (entry 6). Long-chain aliphatic aldehyde **50g** also turned out to be an effective substrate, albeit in a lower yield (entry 7).

Table 5.2 Synthesis of dihydropyrans from aldehydes and **49a**[a]



49a **50** **51**

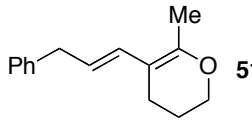
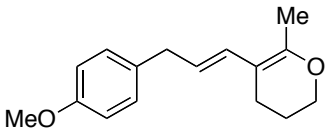
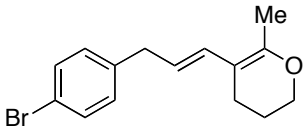
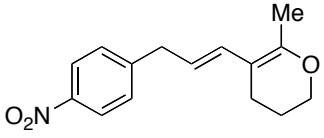
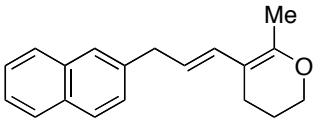
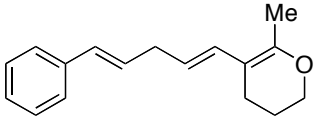
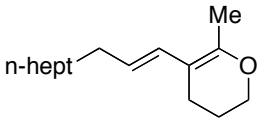
entry	R		product	yield[b] (%)
1	C_6H_5	**50a**	 **51a**	72

Table 5.2 (continued)

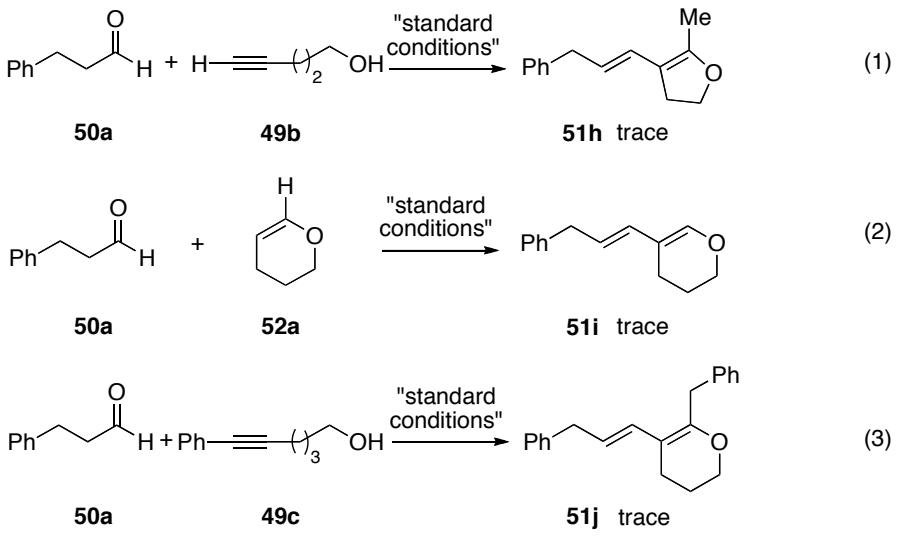
entry	R		product	yield[b] (%)
2	4-$MeOC_6H_4$	**50b**	 **51b**	70
3	4-BrC_6H_4	**50c**	 **51c**	74
4	4-$NO_2C_6H_4$	**50d**	 **51d**	50
5	2-naph	**50e**	 **51e**	65
6	C_6H_5CHCH	**50f**	 **51f**	52
7	n-hept	**50g**	 **51g**	46

[a] **49a** (0.8 mmol, 90.4 μL) and **50** (0.2 mmol) under "standard conditions". [b] Isolated yields (average of two runs).

5.2.4 Mechanism

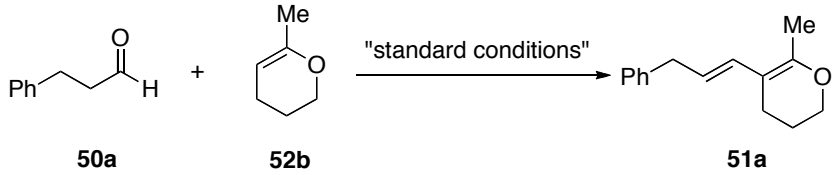
To understand this novel Ru- and Cu-catalyzed domino reaction between alkynols and aldehydes, the mechanism for the product formation was briefly explored. Firstly, the

reactivity of other alkynols toward hydrocinnamaldehyde was investigated under the "standard conditions". The use of 4-pentyn-1-ol **49b**, instead of **49a**, provided only a trace amount of desired product **51h** as detected by GC-MS (Scheme 5.14, Eq. 1), suggesting that the formation of 5-membered enol ether was not favoured. Direct reaction of dihydropyran (DHP) **52a** (reported as a cycloisomerization product of **49b** in the presence of a certain ruthenium catalyst[7]) with aldehyde **50a** showed a similar reactivity (Scheme 5.14, Eq. 2). In addition, the reaction of phenyl-substituted alkynol **49c** with aldehyde **50a** also afforded only a trace amount of the product (Scheme 5.14, Eq. 3). Secondly, 6-methylated DHP **52b**, which we hypothesized to be an intermediate for this transformation, was tested under the "standard conditions" and the desired product **51a** was obtained successfully (Table 5.3, entry 1). Furthermore, it was found that $CuCl_2$ was essential for the formation of **51a** (entry 2), without which no product was obtained. In the absence of $[Ru(COD)Cl_2]_n$ the desired product still formed with a slightly reduced yield (entry 3).



Scheme 5.14 The reactivity of **50a** with other substrates

Table 5.3 Effect of catalyst on the reaction between **50a** and 6-methylated DHP **52b**[a]

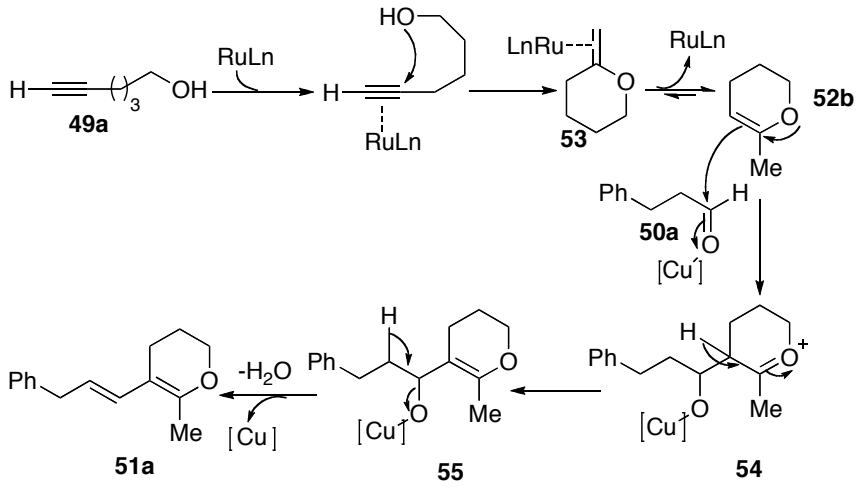


50a **52b** **51a**

entry	change from the "standard conditions"	yield[b] (%)
1	none	39
2	no $CuCl_2$	0
3	no $[Ru(COD)Cl_2]_n$	19

[a] **50a** (15 μL, 0.1 mmol) and **52b** (0.4 mmol, 20-40 wt. % in hexane) under "standard conditions". [b] ^{1}H-NMR yields using an internal standard (average of two runs).

Based on these results and previous studies of transition-metal catalyzed cycloisomerization of alkynols,[20] a tentative mechanism was proposed to rationalize this Ru- and Cu-catalyzed domino reaction between aldehydes and alkynols as follows: A ruthenium-catalyzed cyclization of alkynol **49a** generated exo-6-membered enol ether **53**, which can readily isomerize to a more stable endo-cyclic enol ether **52b**, also in the presence of ruthenium catalysts.[25] This might explain why internal alkynol **49c** was not a good substrate, since its exo-enol ether intermediate with a double bond conjugated to the phenyl ring is relatively stable compared to its endo-isomer. Next, in the presence of $CuCl_2$, which acted as a Lewis acid, an aldol-type reaction between the enol ether **52b** and the aldehyde **50a** occurred, followed by a dehydration upon which the final product **51a** was formed.



Scheme 5.15 Tentative mechanism for the reaction between **49a** and **50a**

5.2.5 Conclusions

A novel domino reaction between alkynols and aldehydes in the presence of catalytic amounts of $[Ru(COD)Cl_2]_n$ and $CuCl_2$ was developed. The reaction provides an effective method to prepare 5-olefinated-3, 4-dihydropyran derivatives. A tentative mechanism was proposed involving a domino alkynol cyclization, olefin migration, aldol type reaction and dehydration.

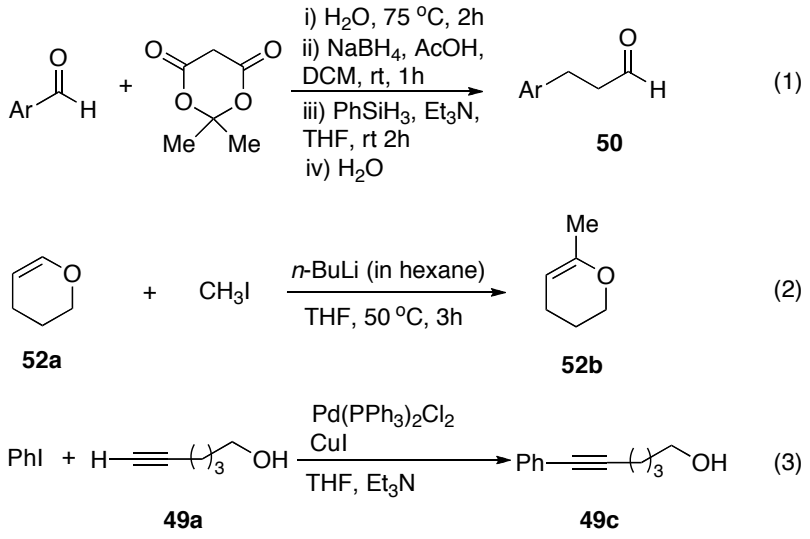
5.2.6 Experimental section

General experimental details

Hydrocinnamaldehyde derivatives **50b**, **50c**, **50d**, **50e**, and **50f** were prepared from corresponding aromatic aldehydes following literature procedures (Scheme 5.16, Eq. 1).[26] **52b** was synthesized from the methylation of *3,4*-dihydro-2*H*-pyran and it was obtained as an azeotropic mixture in hexane by fractional distillation (Scheme 5.16, Eq. 2). **49c**

was prepared from **49a** via Sonogashira coupling with iodobenzene following literature procedures (Scheme 5.16, Eq. 3).[27] Other reagents were commercially available and used as received. All reagents were weighed and handled in air.

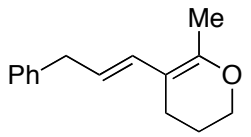
^{1}H and ^{13}C-NMR spectra were recorded on Varian 300, 400 and 500 MHz spectrometers in $CDCl_3$ solutions and chemical shifts (δ, ppm) were determined with internal solvent signal as reference (7.26 for ^{1}H-NMR and 77.0 for ^{13}C-NMR). HRMS were made by McGill University. X-ray diffraction data were measured on a D8 diffractometer (Bruker, Billerica, MA). Melting points were measured on Gallenkamp melting point apparatus (MF-370). Flash column chromatography was performed on EMD Silica Gel 60 with an appropriate solvent system (see details below).



Scheme 5.16 Preparation of starting materials

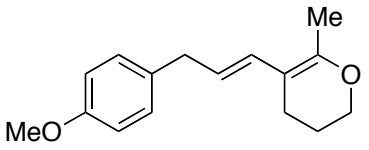
General experimental procedures and characterizations

A mixture of $[Ru(COD)Cl_2]_n$ (0.02 mmol, 5.6 mg), $CuCl_2$ (0.06 mmol, 8.2 mg), and tris(2,4,6-trimethoxyphenyl)phosphine (0.04 mmol, 21.2 mg) in DCM (0.2 mL) was stirred under argon at room temperature for 24 h. Then, **49a** (0.4 mmol, 90.4 μL), **50a** (0.2 mmol, 30.0 μL), and toluene (0.8 mL) were added under argon and heated at 120 ^oC for 24 h. After the reaction, the mixture was first cooled to room temperature. Then it was diluted with DCM and filtered through a plug of silica gel eluting with DCM. The filtrate was concentrated *in vacuo* with a rotary evaporator and the residue was purified by flash column chromatography on silica gel.



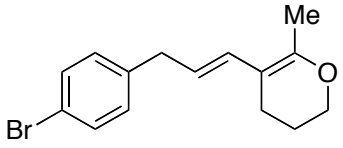
(*E*)-6-methyl-5-(3-phenylprop-1-enyl)-3,4-dihydro-2*H*-pyran **51a**

51a was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50a** (27 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:50) to afford **51a** as a colorless oil (31 mg, 72 %). IR: ν_{max} 3430, 2936, 1709, 1668, 1452, 1243, 1173, 1059, 1000, 910, 732, 698, 665 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.29 (t, *J*=7.5 Hz, 2H), 7.22-7.18 (m, 3H), 6.36 (d, *J*=15.5 Hz, 1H), 5.52-5.46 (m, 1H), 3.95 (t, *J*=5.5 Hz, 2H), 3.45 (d, *J*=7.0 Hz, 2H), 2.12 (t, *J*=6.5 Hz, 2H), 1.90 (s, 3H), 1.89-1.84 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 150.0, 141.4, 129.3, 128.5, 128.4, 125.9, 122.1, 106.5, 65.8, 39.7, 22.4, 21.0, 16.5. HRMS (APCI) exact mass calc'd for $C_{15}H_{19}O$ ([M+H]) *m/z*: 215.1430; found *m/z*: 215.1431.



(*E*)-5-(3-(4-methoxyphenyl)prop-1-enyl)-6-methyl-3,4-dihydro-2*H*-pyran **51b**

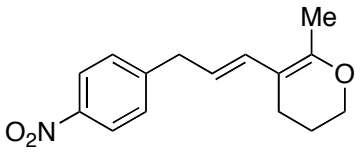
51b was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50b** (33 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:30) to afford **51b** as a colorless oil (34 mg, 70 %). IR: ν_{max} 3423, 2935, 1713, 1668, 1610, 1510, 1441, 1300, 1244, 1174, 1031, 999, 910, 823, 729 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.13 (t, *J*=8.5 Hz, 2H), 6.84 (d, *J*=8.0 Hz, 2H), 6.34 (d, *J*=15.5 Hz, 1H), 5.49-5.44 (m, 1H), 3.94 (t, *J*=5.5 Hz, 2H), 3.79 (s, 3H), 3.39 (d, *J*=6.5 Hz, 2H), 2.11 (t, *J*=6.5 Hz, 2H), 1.90 (s, 3H), 1.87-1.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 157.8, 149.8, 133.4, 129.4, 129.0, 122.5, 113.7, 106.5, 65.8, 55.2, 38.8, 22.4, 21.0, 16.5. HRMS (APCI) exact mass calc'd for $C_{16}H_{21}O_2$ ([M+H]) *m/z*: 245.1536; found *m/z*: 245.1538.



(*E*)-5-(3-(4-bromophenyl)prop-1-enyl)-6-methyl-3,4-dihydro-2*H*-pyran **51c**

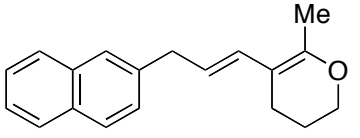
51c was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50c** (43 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:50) to afford **51c** as a colorless oil (43 mg, 74 %). IR: ν_{max} 3406, 2925, 1709, 1646, 1486, 1386, 1265, 1179, 1069, 1010, 804 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.40 (dt, *J*=8.5 Hz, 2.5 Hz, 2H), 7.08 (d, *J*=9.0 Hz, 2H),

6.35 (d, *J*=15.0 Hz, 1H), 5.45-5.39 (m, 1H), 3.95 (t, *J*=5.0 Hz, 2H), 3.39 (d, *J*=7.0 Hz, 2H), 2.10 (t, *J*=6.0 Hz, 2H), 1.89 (s, 3H), 1.87-1.84 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 150.3, 140.4, 131.4, 130.2, 129.8, 121.2, 119.6, 106.4, 65.8, 39.0, 22.3, 21.0, 16.6. HRMS (APCI) exact mass calc'd for $C_{15}H_{18}OBr$([M+H]) *m/z*: 293.0536; found *m/z*: 293.0536.



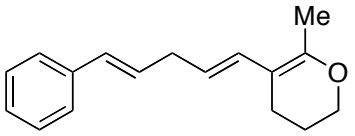
(*E*)-6-methyl-5-(3-(4-nitrophenyl)prop-1-enyl)-3,4-dihydro-2*H*-pyran **51d**

51d was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50d** (36 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:25) to afford **51d** as a yellow solid (26 mg, 50 %), MP 40-42 ^{o}C. IR: ν_{max} 2917, 1646, 1507, 1341, 1265, 1174, 1067, 955, 935, 853, 724, 696, 665 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 8.14 (d, *J*=8.7 Hz, 2H), 7.36 (d, *J*=8.7 Hz, 2H), 6.39 (d, *J*=15.3 Hz, 1H), 5.45-5.35 (m, 1H), 3.95 (t, *J*=5.1 Hz, 2H), 3.54 (d, *J*=6.9 Hz, 2H), 2.10 (t, *J*=5.9 Hz, 2H), 1.90 (s, 3H), 1.87-1.83 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 150.9, 149.4, 146.4, 130.9, 129.2, 123.7, 119.6, 106.2, 65.8, 39.5, 22.3, 21.0, 16.6. HRMS (APCI) exact mass calc'd for $C_{15}H_{18}O_3N$([M+H]) *m/z*: 260.1281; found *m/z*: 260.1281.



(*E*)-6-methyl-5-(3-(naphthalen-2-yl)prop-1-enyl)-3,4-dihydro-2*H*-pyran **51e**

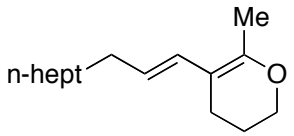
51e was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50e** (37 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:50) to afford **51e** as a light yellow oil (34 mg, 65 %). IR: ν_{max} 3406, 2924, 1710, 1644, 1600, 1385, 1264, 1182, 1071, 956, 938, 855, 812, 746, 646 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.80 (dd, *J*=15.0 Hz, 8.5 Hz, 3H), 7.65 (s, 1H), 7.44 (td, *J*=7.0 Hz, 1.5 Hz, 2H), 7.37 (dd, *J*=8.5 Hz, 1.5 Hz, 1H), 6.44 (d, *J*=15.5 Hz, 1H), 5.59-5.53 (m, 1H), 3.96 (t, *J*=5.0 Hz, 2H), 3.62 (d, *J*=7.0 Hz, 2H), 3.14 (t, *J*=6.0 Hz, 2H), 1.92 (s, 3H), 1.90-1.85 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 150.1, 138.9, 133.7, 132.1, 129.5, 127.9, 127.6, 127.4, 126.4, 125.8, 125.1, 121.9, 106.5, 65.8, 39.9, 22.4, 21.0, 16.6. HRMS (APCI) exact mass calc'd for $C_{19}H_{21}O$([M+H]) *m/z*: 265.1587; found *m/z*: 265.1587.



6-methyl-5-((1*E*,4*E*)-5-phenylpenta-1,4-dienyl)-3,4-dihydro-2*H*-pyran **51f**

51f was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50f** (32 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:50) to afford **51f** as a light yellow oil (25 mg, 52 %). IR: ν_{max} 3397, 3024, 2926, 1705, 1644, 1447, 1386, 1265, 1182, 1109, 1069, 963, 732, 693 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.36 (d, *J*=7.0 Hz, 2H), 7.29 (t, *J*=7.0 Hz, 2H), 7.20 (t, *J*=7.0 Hz, 1H), 6.41 (d, *J*=16.0 Hz, 1H), 6.36 (d, *J*=15.5 Hz, 1H), 6.27-6.22 (m, 1H), 5.43-5.37 (m, 1H), 3.96 (t, *J*=4.5 Hz, 2H), 3.03 (d, *J*=7.0 Hz, 2H), 2.14 (t, *J*=6.5 Hz, 2H), 1.90 (s, 3H), 1.88-1.87 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 150.0, 137.8,

130.1, 129.5, 129.3, 128.5, 126.9, 126.0, 120.8, 106.6, 65.8, 36.7, 22.4, 21.0, 16.5. HRMS (APCI) exact mass calc'd for $C_{17}H_{21}O$ ([M+H]) *m/z*: 241.1587; found *m/z*: 241.1588.



(*E*)-5-(dec-1-enyl)-6-methyl-3,4-dihydro-2*H*-pyran **51g**

51g was prepared from alkynol **49a** (79 mg, 0.8 mmol) and aldehyde **50g** (31 mg, 0.2 mmol) following the above general procedure. The mixture was purified by column chromatography (EtOAc/Hexane = 1:50) to afford **51g** as a colorless oil (22 mg, 46%). IR: ν_{max} 3438, 3280, 2918, 2851, 1740, 1671, 1466, 1371, 1226, 1110, 1069, 999, 977, 938, 848, 720 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 6.25 (d, *J*=15.5 Hz, 1H), 5.38-5.32 (m, 1H), 3.94 (t, *J*=5.0 Hz, 2H), 2.12-2.07 (m, 4H), 1.88 (s, 3H), 1.87-1.84 (m, 2H), 1.39-1.35 (m, 2H), 1.28 (br s, 10H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 149.1, 127.8, 124.1, 106.6, 65.7, 33.4, 31.9, 30.2, 29.5, 29.3, 29.3, 22.7, 22.5, 21.0, 16.5, 14.1. HRMS (APCI) exact mass calc'd for $C_{16}H_{29}O$ ([M+H]) *m/z*: 237.2213; found *m/z*: 237.2216.

Reference

(1) (a) M. C. Elliot, E. Williams, *J. Chem. Soc.*, *Perkin Trans. 1* **2001**, 2303. (b) I. Paterson, C. De Savic, M. Tudge, *Org. Lett.* **2001**, *3*, 3149. (c) D. J. Faukner, *Nat. Prod. Rep.* **2000**, *17*, 7. (d) M. C. Elliot, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291. (e) M. C. Elliot, *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175. (f) D. J. Faukner, *Nat. Prod. Rep*. **1997**, *14*, 259. (g) Y. J. Class, P. Deshong, *Chem. Rev.* **1995**, *95*, 1843. (h) R. D. Norcross, I. Paterson, *Chem. Rev.* **1995**, *95*, 2041. (i) T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309.

(2) (a) J. W. Westley, *Polyether Antibiotics:Naturally Occurring Acid Ionophores,* Vols I and II. Marcel Dekker, New York (1982). (b) G. R. Painter, B. C. Pmesman, *Top. Curr. Chem.* **1982***, 101,* 83. (c) B. C. Pressman, E. I. Harris, W. S. Jagger, J. M. Johnson, *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 1949. (d) J. W. Westley, *Annu. Rev. Med. Chem.* **1975**, *10,* 246. (e) J. W. Weatley, *Adv. Appl. Microbial.* **1977**, *22,* 172. (f) B. C. Pressman, *Annu. Rev. Biochem.* **1976**, *45*, 501. (g) M. D. Ruff, *Polyether Antibiotics: Naturally Occurring Acid Ionophores* (Edited by J. W. Westley), Vol. I, Ch. 6. Marcel Dekker, New York (1982).

(3) (a) L. Coppi, A. Ricci, M. Taddei, *J. Org. Chem.* **1988**, *53*, 913. (b) C. J. Li, W. C. Zhang, *Tetrahedron* **2000**, *56*, 2403. (c) B. Schmidt, M. Westhus, *Tetrahedron* **2000**, *56*, 2421.

(4) (a) M. Bednarski, S. J. Danishefsky, *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) S. J. Danishefsky, M. P. DeNinno, *Angew. Chem., Int. Ed.* **1987**, *26*, 15.

(5) S. J. Danishefsky, H. G. Selnick, R. E. Zelle, M. P. DeNinno, *J. Am. Chem. Soc.* **1988**, *110*, 4368.

(6) S. J. Danishefsky, C. I. Maring, *J. Am. Chem. Soc.* **1985**, *107,* 1269.

(7) P. A. Evans, J. D. Nelson, *J. Org. Chem.* **1996,** *61,* 7600.

(8) A. G. Dossetter, T. F. Jamison, E. N. Jacobsen, *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.

(9) S. Rajaram, M. S. Sigman, *Org. Lett.* **2005**, *7*, 5473.

(10) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122,* 1635.

(11) S. D. Burke, R. A. Ng, J. A. Morrison, M. J. Alberti, *J. Org. Chem.* **1998**, *63*, 3160.

(12) H. Wildemann, P. Dunkelmann, M. Muller, B. Schmidt, *J. Org. Chem.* **2003**, *68*, 799.

(13) B. Schmidt, S. Nave, *J. Org. Chem.* **2006**, *71*, 7364.

(14) G. S. Viswanathan, J. Yang, C.-J. Li, *Org. Lett.* **1999**, *1*, 993.

(15) G. Fraboulet, V. Fargeas, M. Paris, J.-P. Quintard, F. Zammattio, *Tetrahedron* **2009**, *65*, 3953.

(16) Y. Lian, R. J. Hinkle, *J. Org. Chem.* **2006**, *71*, 7071.

(17) H. Huang, J. S. Panek, *J. Am. Chem. Soc.* **2000**, *122,* 9836.

(18) (a) V. G. Matassa, P. R. Jenkins, A. Kumin, L. Damm, J. Schreiber, D. Felix, E. Zass, A. Eschenmoser, *Isr. J. Chem*. **1989**, *29*, 321. (b) S. E. Denmark, E. J. Weber, T. M. Wilson, *Tetrahedron* **1989**, *45*, 1053.

(19) (a) F. Alonso, I. P. Beletsaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079. (b) F. E. McDonald, *Chem. Eur. J.* **1999**, *5*, 3103. (c) B. Weyershausen, K. H. Dötz, *Eur. J. Inorg. Chem.* **1999**, 1057. (d) M. A. Tius, In *Modern Allene Chemistry*; N. Krause, A. S. K.

Hashmi, Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. *2*, pp 834-838. (e) K. Tani, Y. Kataoka, In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001; pp 171-216. (f) P. A. Bartlett, In *Asymmetric Synthesis*; J. D. Morrisson, Eds.; Academic Press: New York, 1984; Vol. 3, p 455.

(20) B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 2528.

(21) (a) Y. Sheng, D. G. Musaev, K. S. Reddy, F. E. McDonald, K. Morokuma, *J. Am. Chem. Soc.* **2002**, *124*, 4149. (b) F. E. McDonald, K. S. Reddy, Y. Díaz, *J. Am. Chem. Soc.* **2000**, *122,* 4304.

(22) P. Wipf, T. H. Graham, *J. Org. Chem.* **2003**, *68*, 8798.

(23) (a) S. Seo, X. Yu, T. J. Marks, *J. Am. Chem. Soc.* **2009**, *131*, 263. (b) X. Yu, S. Seo, T. J. Marks, *J. Am. Chem. Soc.* **2007**, *129*, 7244.

(24) (a) X. Guo, J. Wang, C.-J. Li, *Org. Lett.* **2010**, *12*, 3176. (b) X. Guo, J. Wang, C.-J. Li, *J. Am. Chem. Soc.* **2009**, *131*, 15092.

(25) C.-J. Li, D. Wang, D.-L. Chen, *J. Am. Chem. Soc.* **1995**, *117*, 12867.

(26) Frost, C. G.; Hartley, B. C. *J. Org. Chem.* **2009**, *74*, 3599.

(27) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett*. **2003**, *5*, 2989.

Conclusions and Claims to Original Knowledge

Through the transition-metal-catalyzed activation of aryl C-H bonds, we have developed a series of oxidative amidation and arylation reactions of simple arenes. In addition, a novel domino reaction between alkynols and aldehydes was presented.

An oxidative amidation of 2-arylpyridine derivative with high regioselectivity has been developed by using cheap copper(I) bromide as catalyst and *tert*-butyl peroxide as oxidant. This simple solvent-free procedure provides an easy access to the preparation of *N*-biarylated amides without the addition of a specific ligand or a base. This method has been successfully extended to the amidation of 1-methylindoles, which is of great interest due to the biological activity of indole. Notably, aryl halides could be tolerated under the amidation process, which makes further elaborations of the amidation products readily.

An oxidative arylation of 2-arylpyridine derivatives with aromatic aldehydes through a decarbonylation process has been achieved. This novel method for the synthesis of biaryl unions could be applied to an extensive substrate scope of aromatic aldehydes and 2-arylpyridines.

An unusual ruthenium-and copper-catalyzed reaction between alkynols and aldehydes has been disclosed, which affords 5(*E*)-olefinated 3,4-dihydropyran derivatives

efficiently. A brief mechanistic study revealed that this novel reaction might proceed via a domino process.

During the course of this thesis, the following articles were published:

1. Zhou, L.; Shuai, Q.; Jiang, H.-F.; Li, C.-J. *Chem. Eur. J.* **2009**, *15*, 11668.

2. Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632.

3. Baslé, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145.

4. Shuai, Q.; Yang, L.; Guo, X.; Baslé, O.; Li, C.-J. *J. Am. Chem. Soc.* **2010**, *132*, 12212.

5. Dou, X.; Shuai, Q.; He, L.-N.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352,* 2437.

6. Feng, C.; Liu, Y.; Peng, S.; Shuai, Q.; Deng, G.; Li, C.-J. *Org. Lett.* **2010**, *12*, 4888.

7. Dou, X.; Shuai, Q.; He, L.-N.; Li, C.-J. *Inorganica Chimica Acta*, **2011**, *369,* 284.

8. Yang, L.; Zeng, T.; Shuai, Q.; Guo, X.; Li, C-J. *Chem. Commun.* **2011**, *47*, 2161.

9. Xiao, F.; Shuai, Q.; Zhao, F.; Baslé, O.; Deng, G.; and Li, C-J. *Org. Lett.* **2011**, *13,* 1614.

10. Shuai, Q.; Guo, X.; Chua, Z.; Bohle, D. S.; Li, C.-J. *in preparation*.

Author Contributions

Chapters 2 and 3: **Qi Shuai** contributed to project design, optimization of reaction conditions, synthesis and characterization of desired products and co-wrote the paper. **Guojun Deng** contributed to the preparation of compounds **49b**, **49c**, **56b**, **56c**, **9b** and **9c**. **Zhijie Chua** and **D. Scott Bohle** contributed to X-ray data analysis of compound **57a**. **Chao-Jun Li** contributed to project design, data analysis and co-wrote the paper.

Chapter 4: **Qi Shuai** contributed to project design, optimization of reaction conditions, synthesis and characterization of desired products and co-wrote the paper. **Luo Yang**, **Xiangyu Guo**, and **Olivier Baslé** contributed to project design. **Chao-Jun Li** contributed to project design, data analysis and co-wrote the paper.

Chapter 5: **Qi Shuai** contributed to project design, optimization of reaction conditions, synthesis and characterization of desired products and co-wrote the paper. **Zhijie Chua** and **D. Scott Bohle** contributed to X-ray data analysis of compound **51d**. **Xiangyu Guo** contributed to project design. **Chao-Jun Li** contributed to project design, data analysis and co-wrote the paper.

Appendix

1. X-ray structure parameters for compound **57a** in chapter 2

Table 1. Crystal data and structure refinement for sq1m1.

Identification code	sq1m1
Empirical formula	C19 H16 N2 O
Formula weight	288.34
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 12.8384(15) A alpha = 90 deg. b = 12.3142(14) A beta = 90 deg. c = 18.970(2) A gamma = 90 deg.
Volume	2999.0(6) A^3
Z, Calculated density	8, 1.277 Mg/m^3
Absorption coefficient	0.080 mm^-1
F(000)	1216
Crystal size	0.80 x 0.70 x 0.60 mm
Theta range for data collection	2.15 to 28.24 deg.
Limiting indices	-16<=h<=16, -15<=k<=16, -24<=l<=23
Reflections collected / unique	25160 / 3579 [R(int) = 0.0855]
Completeness to theta = 28.24	96.4 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3579 / 0 / 199
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.1071
R indices (all data)	R1 = 0.1064, wR2 = 0.1318
Largest diff. peak and hole	0.216 and -0.220 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for sq1m1.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	786(1)	1590(1)	1460(1)	41(1)
N(2)	1636(1)	-587(1)	1717(1)	37(1)
O(1)	1381(1)	-512(1)	2889(1)	62(1)
C(1)	788(1)	-1336(1)	1622(1)	35(1)
C(2)	975(2)	-2370(2)	1377(1)	47(1)
C(3)	159(2)	-3083(2)	1285(1)	57(1)
C(4)	-839(2)	-2772(2)	1434(1)	57(1)
C(5)	-1031(2)	-1738(2)	1673(1)	53(1)
C(6)	-219(2)	-1016(2)	1766(1)	45(1)
C(7)	2194(1)	-271(2)	1091(1)	37(1)
C(8)	3087(2)	-837(2)	911(1)	51(1)
C(9)	3594(2)	-631(2)	284(1)	59(1)
C(10)	3211(2)	140(2)	-169(1)	56(1)
C(11)	2327(2)	715(2)	10(1)	47(1)
C(12)	1803(1)	527(1)	642(1)	35(1)
C(13)	849(1)	1167(1)	810(1)	34(1)
C(14)	79(1)	1323(2)	312(1)	43(1)
C(15)	-796(2)	1904(2)	491(1)	52(1)
C(16)	-866(2)	2338(2)	1155(1)	50(1)
C(17)	-60(2)	2166(2)	1613(1)	47(1)
C(18)	1859(2)	-199(2)	2374(1)	43(1)
C(19)	2714(2)	620(2)	2432(1)	56(1)

Table 4. Bond lengths [A] and angles [deg] for sq1m1.

N(1)-C(17)	1.330(2)
N(1)-C(13)	1.341(2)
N(2)-C(18)	1.365(2)
N(2)-C(1)	1.439(2)
N(2)-C(7)	1.441(2)
O(1)-C(18)	1.216(2)
C(1)-C(2)	1.377(3)
C(1)-C(6)	1.378(2)
C(2)-C(3)	1.378(3)
C(2)-H(2A)	0.9300
C(3)-C(4)	1.367(3)
C(3)-H(3A)	0.9300
C(4)-C(5)	1.374(3)
C(4)-H(4A)	0.9300
C(5)-C(6)	1.382(3)
C(5)-H(5A)	0.9300
C(6)-H(6A)	0.9300
C(7)-C(8)	1.385(2)
C(7)-C(12)	1.394(2)
C(8)-C(9)	1.378(3)

C(8)-H(8A)	0.9300
C(9)-C(10)	1.372(3)
C(9)-H(9A)	0.9300
C(10)-C(11)	1.380(3)
C(10)-H(10A)	0.9300
C(11)-C(12)	1.394(2)
C(11)-H(11A)	0.9300
C(12)-C(13)	1.490(2)
C(13)-C(14)	1.380(2)
C(14)-C(15)	1.375(3)
C(14)-H(14A)	0.9300
C(15)-C(16)	1.370(3)
C(15)-H(15A)	0.9300
C(16)-C(17)	1.369(3)
C(16)-H(16A)	0.9300
C(17)-H(17A)	0.9300
C(18)-C(19)	1.495(3)
C(19)-H(19A)	0.9600
C(19)-H(19B)	0.9600
C(19)-H(19C)	0.9600

C(17)-N(1)-C(13)	117.18(15)
C(18)-N(2)-C(1)	119.82(14)
C(18)-N(2)-C(7)	123.70(15)
C(1)-N(2)-C(7)	116.46(14)
C(2)-C(1)-C(6)	119.63(18)
C(2)-C(1)-N(2)	120.22(16)
C(6)-C(1)-N(2)	120.14(16)
C(1)-C(2)-C(3)	120.00(19)
C(1)-C(2)-H(2A)	120.0
C(3)-C(2)-H(2A)	120.0
C(4)-C(3)-C(2)	120.5(2)
C(4)-C(3)-H(3A)	119.8
C(2)-C(3)-H(3A)	119.8
C(3)-C(4)-C(5)	119.8(2)
C(3)-C(4)-H(4A)	120.1
C(5)-C(4)-H(4A)	120.1
C(6)-C(5)-C(4)	120.2(2)
C(6)-C(5)-H(5A)	119.9
C(4)-C(5)-H(5A)	119.9
C(1)-C(6)-C(5)	119.94(18)
C(1)-C(6)-H(6A)	120.0
C(5)-C(6)-H(6A)	120.0
C(8)-C(7)-C(12)	120.23(16)
C(8)-C(7)-N(2)	118.58(16)
C(12)-C(7)-N(2)	120.99(15)
C(7)-C(8)-C(9)	120.67(19)
C(7)-C(8)-H(8A)	119.7
C(9)-C(8)-H(8A)	119.7
C(10)-C(9)-C(8)	119.92(19)
C(10)-C(9)-H(9A)	120.0
C(8)-C(9)-H(9A)	120.0
C(9)-C(10)-C(11)	119.69(19)
C(9)-C(10)-H(10A)	120.2
C(11)-C(10)-H(10A)	120.2
C(10)-C(11)-C(12)	121.60(18)
C(10)-C(11)-H(11A)	119.2
C(12)-C(11)-H(11A)	119.2

C(7)-C(12)-C(11)	117.89(16)
C(7)-C(12)-C(13)	122.55(15)
C(11)-C(12)-C(13)	119.56(16)
N(1)-C(13)-C(14)	122.20(16)
N(1)-C(13)-C(12)	116.82(15)
C(14)-C(13)-C(12)	120.97(16)
C(13)-C(14)-C(15)	119.17(17)
C(13)-C(14)-H(14A)	120.4
C(15)-C(14)-H(14A)	120.4
C(16)-C(15)-C(14)	119.00(18)
C(16)-C(15)-H(15A)	120.5
C(14)-C(15)-H(15A)	120.5
C(15)-C(16)-C(17)	118.23(18)
C(15)-C(16)-H(16A)	120.9
C(17)-C(16)-H(16A)	120.9
N(1)-C(17)-C(16)	124.19(18)
N(1)-C(17)-H(17A)	117.9
C(16)-C(17)-H(17A)	117.9
O(1)-C(18)-N(2)	121.10(18)
O(1)-C(18)-C(19)	121.69(18)
N(2)-C(18)-C(19)	117.21(16)
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for sq1m1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	43(1)	44(1)	37(1)	-5(1)	-1(1)	5(1)
N(2)	36(1)	40(1)	33(1)	5(1)	1(1)	0(1)
O(1)	76(1)	78(1)	33(1)	9(1)	-1(1)	-21(1)
C(1)	40(1)	39(1)	27(1)	6(1)	1(1)	1(1)
C(2)	53(1)	45(1)	43(1)	1(1)	2(1)	7(1)
C(3)	77(2)	42(1)	53(1)	-6(1)	-6(1)	-2(1)
C(4)	63(2)	60(1)	48(1)	-1(1)	-4(1)	-18(1)
C(5)	42(1)	66(2)	51(1)	-3(1)	3(1)	-5(1)
C(6)	43(1)	45(1)	48(1)	-2(1)	4(1)	1(1)
C(7)	34(1)	41(1)	36(1)	1(1)	3(1)	1(1)
C(8)	42(1)	53(1)	57(1)	7(1)	7(1)	10(1)
C(9)	44(1)	65(1)	67(2)	-5(1)	20(1)	10(1)
C(10)	55(1)	64(1)	50(1)	-1(1)	23(1)	-2(1)
C(11)	53(1)	48(1)	41(1)	6(1)	7(1)	-1(1)
C(12)	36(1)	37(1)	32(1)	0(1)	2(1)	0(1)
C(13)	40(1)	30(1)	32(1)	4(1)	4(1)	-1(1)
C(14)	51(1)	46(1)	33(1)	-1(1)	-1(1)	7(1)
C(15)	49(1)	62(1)	45(1)	3(1)	-8(1)	13(1)
C(16)	48(1)	49(1)	52(1)	1(1)	7(1)	14(1)
C(17)	54(1)	47(1)	39(1)	-8(1)	5(1)	6(1)
C(18)	43(1)	48(1)	37(1)	9(1)	-6(1)	-1(1)
C(19)	49(1)	66(1)	52(1)	7(1)	-12(1)	-7(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for sq1m1.

	x	y	z	U(eq)
H(2A)	1652	-2587	1274	56
H(3A)	288	-3781	1120	69
H(4A)	-1385	-3259	1374	68
H(5A)	-1710	-1523	1772	63
H(6A)	-351	-315	1925	54
H(8A)	3348	-1363	1216	61
H(9A)	4195	-1013	169	70
H(10A)	3545	275	-595	67
H(11A)	2075	1240	-298	56
H(14A)	152	1038	-140	52
H(15A)	-1332	2000	168	62
H(16A)	-1447	2740	1290	59
H(17A)	-107	2472	2060	56
H(19A)	2799	827	2917	84
H(19B)	2540	1248	2157	84
H(19C)	3352	311	2261	84

Table 8. Torsion angles [deg] for sq1m1.

C(18)-N(2)-C(1)-C(2)	-117.35(19)
C(7)-N(2)-C(1)-C(2)	64.0(2)
C(18)-N(2)-C(1)-C(6)	63.6(2)
C(7)-N(2)-C(1)-C(6)	-115.05(18)
C(6)-C(1)-C(2)-C(3)	-0.8(3)
N(2)-C(1)-C(2)-C(3)	-179.80(16)
C(1)-C(2)-C(3)-C(4)	0.1(3)
C(2)-C(3)-C(4)-C(5)	0.5(3)
C(3)-C(4)-C(5)-C(6)	-0.4(3)
C(2)-C(1)-C(6)-C(5)	0.9(3)
N(2)-C(1)-C(6)-C(5)	179.93(16)
C(4)-C(5)-C(6)-C(1)	-0.3(3)
C(18)-N(2)-C(7)-C(8)	87.0(2)
C(1)-N(2)-C(7)-C(8)	-94.4(2)
C(18)-N(2)-C(7)-C(12)	-98.2(2)
C(1)-N(2)-C(7)-C(12)	80.5(2)
C(12)-C(7)-C(8)-C(9)	-0.7(3)
N(2)-C(7)-C(8)-C(9)	174.13(19)
C(7)-C(8)-C(9)-C(10)	-0.3(3)
C(8)-C(9)-C(10)-C(11)	0.9(3)
C(9)-C(10)-C(11)-C(12)	-0.5(3)
C(8)-C(7)-C(12)-C(11)	1.1(3)
N(2)-C(7)-C(12)-C(11)	-173.65(16)
C(8)-C(7)-C(12)-C(13)	-179.63(17)
N(2)-C(7)-C(12)-C(13)	5.6(3)
C(10)-C(11)-C(12)-C(7)	-0.5(3)
C(10)-C(11)-C(12)-C(13)	-179.76(18)

C(17)-N(1)-C(13)-C(14)	0.6(3)
C(17)-N(1)-C(13)-C(12)	179.67(16)
C(7)-C(12)-C(13)-N(1)	47.4(2)
C(11)-C(12)-C(13)-N(1)	-133.28(18)
C(7)-C(12)-C(13)-C(14)	-133.47(19)
C(11)-C(12)-C(13)-C(14)	45.8(2)
N(1)-C(13)-C(14)-C(15)	-1.9(3)
C(12)-C(13)-C(14)-C(15)	179.03(17)
C(13)-C(14)-C(15)-C(16)	1.8(3)
C(14)-C(15)-C(16)-C(17)	-0.5(3)
C(13)-N(1)-C(17)-C(16)	0.9(3)
C(15)-C(16)-C(17)-N(1)	-0.9(3)
C(1)-N(2)-C(18)-O(1)	3.2(3)
C(7)-N(2)-C(18)-O(1)	-178.19(17)
C(1)-N(2)-C(18)-C(19)	-176.89(16)
C(7)-N(2)-C(18)-C(19)	1.7(3)

Table 9. Hydrogen bonds for sq1m1 [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

2. X-ray structure parameters for compound 51d in chapter 5

Table 1. Crystal data and structure refinement for qs1maa.

Identification code	qs1maa
Empirical formula	C15 H17 N O3
Formula weight	259.30
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.8172(7) A alpha = 86.792(6) b = 7.9768(11) A beta = 76.305(6) c = 11.8718(11) A gamma = 64.131(
Volume	646.21(12) A^3
Z, Calculated density	2, 1.333 Mg/m^3
Absorption coefficient	0.093 mm^-1
F(000)	276
Crystal size	0.60 x 0.30 x 0.05 mm
Theta range for data collection	1.77 to 20.48 deg.
Limiting indices	-7<=h<=7, -7<=k<=7, -11<=l<=11
Reflections collected / unique	2306 / 1233 [R(int) = 0.0295]
Completeness to theta = 20.48	95.7 %
Absorption correction	None
Max. and min. transmission	0.9954 and 0.9464
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1233 / 0 / 172
Goodness-of-fit on F^2	1.185
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1009
R indices (all data)	R1 = 0.0715, wR2 = 0.1085
Largest diff. peak and hole	0.209 and -0.207 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for qs1maa.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)

O(1)	1139(4)	8005(4)	7586(3)	31(1)
O(2)	2070(4)	6217(4)	6052(2)	35(1)
O(3)	5711(3)	12520(3)	-1613(2)	26(1)
N(1)	1727(5)	7691(5)	6532(4)	26(1)
C(1)	2530(5)	11856(5)	4468(4)	19(1)
C(2)	2837(5)	10195(5)	3971(4)	25(1)
C(3)	2591(5)	8819(5)	4634(4)	25(1)
C(4)	2021(5)	9123(5)	5815(4)	21(1)
C(5)	1695(5)	10754(6)	6339(4)	25(1)
C(6)	1952(5)	12106(5)	5662(4)	23(1)
C(7)	2831(6)	13351(5)	3739(3)	25(1)
C(8)	2765(6)	13210(5)	2507(4)	24(1)
C(9)	4246(6)	12885(5)	1605(4)	23(1)
C(10)	4221(6)	12717(5)	399(4)	20(1)
C(11)	2381(5)	12794(5)	168(3)	25(1)
C(12)	2618(6)	12396(5)	-1101(3)	28(1)
C(13)	3790(5)	13304(6)	-1815(4)	29(1)
C(14)	5754(6)	12498(5)	-465(4)	22(1)
C(15)	7737(5)	12185(5)	-401(4)	28(1)

Table 3. Bond lengths [A] and angles [deg] for qs1maa.

O(1)-N(1)	1.225(4)
O(2)-N(1)	1.228(4)
O(3)-C(14)	1.370(5)
O(3)-C(13)	1.427(4)
N(1)-C(4)	1.453(5)
C(1)-C(6)	1.380(5)
C(1)-C(2)	1.380(5)
C(1)-C(7)	1.504(5)
C(2)-C(3)	1.370(5)
C(2)-H(2A)	0.9300
C(3)-C(4)	1.368(5)
C(3)-H(3A)	0.9300
C(4)-C(5)	1.367(5)
C(5)-C(6)	1.366(5)
C(5)-H(5A)	0.9300
C(6)-H(6A)	0.9300
C(7)-C(8)	1.487(5)
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-C(9)	1.317(5)
C(8)-H(8A)	0.9300
C(9)-C(10)	1.451(5)
C(9)-H(9A)	0.9300
C(10)-C(14)	1.332(5)
C(10)-C(11)	1.502(5)
C(11)-C(12)	1.508(5)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-C(13)	1.491(5)
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(14)-C(15)	1.479(5)
C(15)-H(15A)	0.9600
C(15)-H(15B)	0.9600
C(15)-H(15C)	0.9600
C(14)-O(3)-C(13)	114.3(3)

O(1)-N(1)-O(2)	122.8(3)
O(1)-N(1)-C(4)	118.9(4)
O(2)-N(1)-C(4)	118.3(4)
C(6)-C(1)-C(2)	118.1(4)
C(6)-C(1)-C(7)	120.5(4)
C(2)-C(1)-C(7)	121.4(4)
C(3)-C(2)-C(1)	121.5(4)
C(3)-C(2)-H(2A)	119.2
C(1)-C(2)-H(2A)	119.2
C(4)-C(3)-C(2)	118.5(4)
C(4)-C(3)-H(3A)	120.8
C(2)-C(3)-H(3A)	120.8
C(3)-C(4)-C(5)	121.7(4)
C(3)-C(4)-N(1)	119.3(4)
C(5)-C(4)-N(1)	119.1(4)
C(6)-C(5)-C(4)	118.9(4)
C(6)-C(5)-H(5A)	120.5
C(4)-C(5)-H(5A)	120.5
C(5)-C(6)-C(1)	121.3(4)
C(5)-C(6)-H(6A)	119.3
C(1)-C(6)-H(6A)	119.3
C(1)-C(7)-C(8)	114.3(3)
C(1)-C(7)-H(7A)	108.7
C(8)-C(7)-H(7A)	108.7
C(1)-C(7)-H(7B)	108.7
C(8)-C(7)-H(7B)	108.7
H(7A)-C(7)-H(7B)	107.6
C(9)-C(8)-C(7)	125.0(4)
C(9)-C(8)-H(8A)	117.5
C(7)-C(8)-H(8A)	117.5
C(8)-C(9)-C(10)	125.9(4)
C(8)-C(9)-H(9A)	117.0
C(10)-C(9)-H(9A)	117.0
C(14)-C(10)-C(9)	121.9(4)
C(14)-C(10)-C(11)	121.3(4)
C(9)-C(10)-C(11)	116.8(4)
C(10)-C(11)-C(12)	111.5(3)
C(10)-C(11)-H(11A)	109.3
C(12)-C(11)-H(11A)	109.3
C(10)-C(11)-H(11B)	109.3
C(12)-C(11)-H(11B)	109.3
H(11A)-C(11)-H(11B)	108.0
C(13)-C(12)-C(11)	109.2(3)
C(13)-C(12)-H(12A)	109.8
C(11)-C(12)-H(12A)	109.8
C(13)-C(12)-H(12B)	109.8
C(11)-C(12)-H(12B)	109.8
H(12A)-C(12)-H(12B)	108.3
O(3)-C(13)-C(12)	110.2(3)
O(3)-C(13)-H(13A)	109.6
C(12)-C(13)-H(13A)	109.6
O(3)-C(13)-H(13B)	109.6
C(12)-C(13)-H(13B)	109.6
H(13A)-C(13)-H(13B)	108.1
C(10)-C(14)-O(3)	123.2(3)
C(10)-C(14)-C(15)	128.8(4)
O(3)-C(14)-C(15)	108.0(3)
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for qs1maa.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	39(2)	34(2)	23(2)	5(2)	-6(2)	-19(2)
O(2)	53(2)	24(2)	37(2)	2(2)	-12(2)	-23(2)
O(3)	25(2)	27(2)	27(2)	2(1)	-7(1)	-12(1)
N(1)	24(2)	28(3)	35(3)	7(2)	-13(2)	-16(2)
C(1)	15(2)	22(3)	22(3)	1(2)	-5(2)	-8(2)
C(2)	25(2)	22(3)	24(3)	-2(2)	-4(2)	-8(2)
C(3)	25(2)	19(3)	32(3)	1(2)	-9(2)	-10(2)
C(4)	22(2)	19(3)	24(3)	9(2)	-8(2)	-12(2)
C(5)	30(3)	27(3)	23(3)	0(2)	-7(2)	-16(2)
C(6)	28(2)	18(3)	27(3)	-3(2)	-8(2)	-12(2)
C(7)	24(2)	24(3)	25(3)	1(2)	-3(2)	-11(2)
C(8)	22(3)	24(3)	30(3)	4(2)	-8(2)	-12(2)
C(9)	22(3)	18(3)	35(3)	7(2)	-11(2)	-13(2)
C(10)	20(3)	15(3)	27(3)	2(2)	-5(2)	-9(2)
C(11)	25(2)	21(3)	30(3)	2(2)	-7(2)	-11(2)
C(12)	24(3)	24(3)	36(3)	-2(2)	-11(2)	-9(2)
C(13)	31(3)	28(3)	29(3)	1(2)	-10(2)	-11(2)
C(14)	24(3)	17(3)	28(3)	1(2)	-8(2)	-11(2)
C(15)	28(3)	28(3)	31(3)	2(2)	-4(2)	-17(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic
displacement parameters (A^2 x 10^3) for qs1maa.

	x	y	z	U(eq)
H(2A)	3220	10005	3167	30
H(3A)	2807	7703	4289	30
H(5A)	1303	10940	7143	30
H(6A)	1734	13218	6014	28
H(7A)	4089	13293	3757	30
H(7B)	1830	14559	4082	30
H(8A)	1588	13364	2363	29
H(9A)	5413	12750	1755	28
H(11A)	1317	14022	411	30
H(11B)	2043	11886	622	30
H(12A)	3277	11060	-1279	34
H(12B)	1343	12877	-1278	34
H(13A)	3874	13125	-2631	35
H(13B)	3149	14634	-1616	35
H(15A)	7797	12176	398	42
H(15B)	8020	13168	-769	42
H(15C)	8680	11008	-790	42

Table 6. Torsion angles [deg] for qs1maa.

C(6)-C(1)-C(2)-C(3)	-0.4(5)
C(7)-C(1)-C(2)-C(3)	179.0(3)
C(1)-C(2)-C(3)-C(4)	0.2(5)
C(2)-C(3)-C(4)-C(5)	0.1(5)
C(2)-C(3)-C(4)-N(1)	179.2(3)
O(1)-N(1)-C(4)-C(3)	-177.0(3)
O(2)-N(1)-C(4)-C(3)	2.5(5)
O(1)-N(1)-C(4)-C(5)	2.1(5)
O(2)-N(1)-C(4)-C(5)	-178.3(3)
C(3)-C(4)-C(5)-C(6)	-0.2(6)
N(1)-C(4)-C(5)-C(6)	-179.3(3)
C(4)-C(5)-C(6)-C(1)	0.1(6)
C(2)-C(1)-C(6)-C(5)	0.2(5)
C(7)-C(1)-C(6)-C(5)	-179.2(3)
C(6)-C(1)-C(7)-C(8)	-159.8(3)
C(2)-C(1)-C(7)-C(8)	20.8(5)
C(1)-C(7)-C(8)-C(9)	-115.7(4)
C(7)-C(8)-C(9)-C(10)	179.1(3)
C(8)-C(9)-C(10)-C(14)	175.9(4)
C(8)-C(9)-C(10)-C(11)	-4.4(6)
C(14)-C(10)-C(11)-C(12)	5.9(5)
C(9)-C(10)-C(11)-C(12)	-173.8(3)
C(10)-C(11)-C(12)-C(13)	-39.2(4)
C(14)-O(3)-C(13)-C(12)	-51.8(4)
C(11)-C(12)-C(13)-O(3)	63.1(4)
C(9)-C(10)-C(14)-O(3)	-173.3(3)
C(11)-C(10)-C(14)-O(3)	6.9(6)
C(9)-C(10)-C(14)-C(15)	7.2(6)
C(11)-C(10)-C(14)-C(15)	-172.6(4)
C(13)-O(3)-C(14)-C(10)	16.7(5)
C(13)-O(3)-C(14)-C(15)	-163.7(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for qs1maa [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)