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Stacey L. McDonald

Copper-Catalyzed Electrophilic Amination of sp^2 and sp^3 C—H Bonds

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Doctoral Thesis accepted by
Duke University, Durham, NC, USA

Springer

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Supervisor's Foreword

It is my great pleasure to introduce Dr. Stacey L. McDonald's work for publication in Springer Theses. The importance of nitrogen-containing molecules is evident in biomedical research and drug discovery; 874 of 1035 FDA-approved small-molecule drugs contain at least one N-atom. In the past few decades, the development of new and efficient amination methods has made a broad impact on organic synthesis, material science, and drug discovery. Among different approaches for the C–N bond formation, direct amination of C–H bonds offers an attractive and potentially more effective route.

The thesis of Stacey L. McDonald explores the amination of C–H bonds using electrophilic amino sources for the synthesis of α-amino carboxyl acid and α-amino phosphonic acid derivatives as well as a wide range of amino arenes and heteroarenes. A crucial technical innovation demonstrated in this thesis is the implementation of a direct H–Zn exchange that allows for the formation of organozinc intermediates that are suitable for copper-catalyzed amino transfer reactions. Selective H–Zn exchange on a broad range of C–H bonds, including both sp^2 and sp^3 C–H bonds, has been achieved by the use of strong and non-nucleophilic bases $Zn(tmp)_2$ or tmpZnCl•LiCl. Success in developing the direct and efficient access to diverse and novel amine-containing structures is highly valuable. These new amination methods will greatly expand the chemical diversity and space of available amine skeletons and will contribute to future advances in material science, medicinal chemistry, and drug discovery. Simultaneously, these findings in Stacey's amination work have inspired further work in the research group where we are exploring the applicability of selective H–Zn exchange in conjugation with different electrophilic partners for a general and powerful platform for C–H functionalization.

Stacey L. McDonald's thesis is written in a very clear style and is accompanied by a good review of previous electrophilic amination work for the synthesis of different alkyl and aryl amines. Exciting advancements in this thesis will be of interest to a broad audience ranging from organometallics to heterocyclic and organophosphorus chemistry.

Durham, NC
March 2016

Prof. Qiu Wang, Ph.D.

Abstract

The wide presence of C–N bonds in biologically and pharmaceutically important compounds continues to drive the development of new C–N bond-forming transformations. Among the different strategies, electrophilic amination is an important synthetic approach for the direct formation of C–N bonds. Compared to electrophilic amination of organometallic reagents, direct amination of C–H bonds will provide a potentially more effective route toward C–N bond formation. Toward this, we proposed an electrophilic amination of C–H bonds via their reactive organometallic surrogate intermediates. Specifically, we are interested in organozinc intermediates and their in situ formation from C–H bonds.

This dissertation reports our development of direct amination of various C–H bonds using an H–Zn exchange/electrophilic amination strategy as a rapid and powerful way to access a variety of functionalized amines. We were able to achieve C–H zincation using strong, non-nucleophilic bases $Zn(tmp)_2$ or tmpZnCl•LiCl and subsequent electrophilic amination of the corresponding zinc carbanions with catalytic copper and *O*-benzoylhydroxylamines as the electrophilic nitrogen source. With such a one-pot procedure, the synthesis of various amines from C–H bonds has been achieved, including α-amination of esters, amides, and phosphonates. Direct amination of heteroaromatic and aromatic C–H bonds has also been developed in good to high yields. It is important to note that mild reactivity of organozinc reagents offers a good compatibility with different functional groups, such as esters, amides, and halides.

Success in developing direct and efficient syntheses of these various amines is highly valuable. These new amination methods will greatly expand the chemical diversity and space of available amine skeletons and will contribute to future advances in material science, medicinal chemistry, and drug discovery.

Parts of this thesis have been published in the following journal articles:

McDonald, S. L.; Hendrick, C. E.; Bitting K. J.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroaromatic and Aromatic C–H Bonds via TMPZnCl·LiCl Mediated Metalation," *Org. Synth.* **2015**, *92*, 356−372.

McDonald, S. L.; Wang, Q. "α-Amination of Phosphonates: A Direct Synthesis of α-Amino Phosphonic Acids and Their Derivatives," *Synlett* **2014**, *25,* 2233−2238. (invited contribution)

McDonald, S. L.; Hendrick, C. E.; Wang, Q. "Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes via C–H Zincation," *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670. (highlighted in Synfacts)

McDonald, S. L.; Wang, Q. "Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives," *Angew. Chem. Int. Ed.* **2014**, *53*, 1867–1871. (highlighted in Synfacts)

McDonald, S. L.; Wang, Q. "Selective α-amination and α-acylation of esters and amides *via* dual reactivity of *O*-acylhydroxylamines toward zinc enolates," *Chem. Comm.* **2014**, *50*, 2535−2538.

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I would also like to extend my gratitude to my research advisor, Qiu Wang. Thank you for taking me in and pushing me to be the best scientist I could be each and every day. Your guidance and encouragement over the past 3 years have been greatly appreciated. It has been a distinct privilege working with you, and I am extremely grateful for this experience.

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Contents

Abbreviations

Ac	Acetate
acac	Acetylacetone
Ar	Aryl
bipyr	2,2′-Bipyridine
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BPO	Benzoyl peroxide
Bu	Butyl
Bz	Benzoyl
Cbz	Carboxybenzyl
cod	Cyclooctadiene
Cp	Cyclopentadienyl
DCE	Dichloroethane
DCM	Dichloromethane
DG	Directing group
DMA	Dimethylacetamide
DMEDA	*N,N′*-Dimethylethylenediamine
DMF	Dimethylformamide
dppbz	1,2-Bis(diphenylphosphino)benzene
dpppen	1,2-Bis(diphenylphosphino)pentane
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
Et	Ethyl
ICy•BF_4	1,3-Dicyclohexylimidazolium tetrafluoroborate salt
IMes•HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
iPr	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
i-Pr	Isopropyl
iPr•HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide

LDA	Lithium diisopropylamide
Me	Methyl
MeCN	Acetonitrile
n-BuLi	*n*-Butyl lithium
NCS	*N*-Chlorosuccinimide
Ph	Phenyl
phen	1,10-Phenanthroline
pivOH	Pivalic acid
Pr	Propyl
RBF	Round-bottomed flask
rt	Room temperature
SIMes•HBF_4	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
tmp	2,2,6,6-Tetramethylpiperidide
TMSCl	Chlorotrimethylsilane
trisyl	2,4,6-Triisopropylbenzene
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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