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Thomas M. Gøgsig

New Discoveries on the β-Hydride Elimination

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Thomas M. Gøgsig

New Discoveries on the β-Hydride Elimination

Doctoral Thesis accepted by
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Parts of this thesis have been published in the following journal articles:

Studies on the Heck Reaction with Alkenyl Phosphates: Can the 1,2-Migration Be Controlled? Scope and Limitations. Ebran, J.-P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931.

Studies on the 1,2-Migrations in Pd-Catalyzed Negishi Couplings with JosiPhos Ligands. Lindhardt, A. T.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 135.

Heteroaromatic Tosylates as Electrophiles in Regioselective Mizoroki-Heck Couplings with Electron Rich Olefins. Gøgsig, T. M.; Lindhardt, A. T.; Dekhane, M.; Grouleff, J.; Skrydstrup, T. *Chem. Eur. J.* **2009**, *15*, 5950.

Mild and Efficient Nickel-Catalyzed Heck Reactions with Electron-Rich Olefins. Gøgsig, T. M.; Kleimark, J.; Nilsson Lill, S.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443.

Carbonylative Heck Reactions Using CO Generated ex Situ in a Two-Chamber System. Hermange, P.; Gøgsig, T. M.; Lindhardt A. T.; Taaning R. H.; Skrydstrup T. *Org. Lett.* **2011** *13*, 2444.

Furthermore, seven scientific papers related to this work have been published and referenced throughout the thesis. Several of the papers have been highlighted by distinguished researchers. For example, the palladium 1,2-migration has been highlighted by Professor Ian J. S. Fairlamb (*Eur. J. Org. Chem.* **2009**, 4011) and Professor Zhang-Jie Shi (*Chem. Eur. J.* **2011**, *17*, 1728). The latter also covered the regioselective Heck reaction (Chapter 5), the iron catalyzed cross couplings (*Org. Lett.* **2009**, *11*, 4886), the nickel catalyzed Suzuki coupling of alkenyl phosphates (*Chem. Commun.* **2006**, 4137) and the Kumada coupling using ligand-free conditions (*J. Org. Chem.* **2009**, 74, 3536). In addition, the work regarding the direct vinylation strategy (*J. Org. Chem.* **2008**, *73*, 3404) has been highlighted by Professor Paul Knochel (*Synfacts* **2008**, 754) and Professor Scott E. Denmark (*Chem. Commun.* **2009**, 20).

Supervisors' Foreword

It is a great pleasure for us to write this introduction for truly an outstanding Ph.D. graduate, Dr. Thomas M. Gøgsig, who graduated from Aarhus University in November 2011. Thomas M. Gøgsig has been involved in the development of a number of significant transition metal-catalyzed reactions for the synthesis of organic compounds. Organic-based compounds are central for the economic growth of Europe, as chemical industries, which produce plastics, fuels, pharmaceuticals, rubber, cosmetics, detergents, coatings, dyestuffs, and agrochemicals, all rely on synthetic organic chemistry for their production. Most modern, high-tech materials are composed of organic compounds. Clearly, the availability of organic compounds produced by synthetic organic chemists is critically important for our high standard of living. An important area of organic chemistry is catalysis, which represents a very efficient means of synthesizing organic compounds. There are many different types of catalysts, but for those, which are composed of transition metals (38 elements in groups 3 through 12 of the periodic table), these represent some of the most important chemical entities for catalyzing the synthesis of organic molecules. The award of three Nobel Prizes in chemistry to this field in just the last decade truly reflects its importance (2001: For asymmetric metal-catalyzed reactions; 2005: For the development of metal-catalyzed metathesis reactions; 2010: For the discovery of palladium-catalyzed carbon–carbon bond forming reactions). Fundamental research from Academia is undoubtedly the main driving force for such discoveries as seven of the nine recipients of the Nobel Prize in catalysis are affiliated to a university. The unearthing of new elementary properties of transition metal based reagents has led to a greater comprehension of the reactivity of such catalysts, where its scientific outcome has in many cases provided new catalytic processes.

The scientific contributions from the Ph.D. work of Thomas M. Gøgsig falls specifically into this category. Thomas M. Gøgsig has worked in a very competitive area of expertise dealing with the discovery or improvement of a number of transition metal-catalyzed transformations, including (a) studies on Pd-catalyzed 1,2-migration reactions, (b) Pd-catalyzed Heck reactions employing heteroaromatic tosylates, (c) Ni-catalyzed Heck reactions, and (d) Pd-catalyzed carbonylation reactions

employing ex-situ generated stoichiometric carbon monoxide. In all of this work, Thomas M. Gøgsig has shown excellent maturity as a chemist, dramatically improving the scope of the above-mentioned reactions and providing important mechanistic information that will, no doubt, help others to improve even further the outcome of these processes. Furthermore, the many publications from the work of Thomas M. Gøgsig have been published in leading international chemistry journals such as *J. Am. Chem. Soc.* and *Angew. Chem. Int. Ed.* In addition to these publications, two patent applications have also been submitted and Thomas M. Gøgsig has also been a key player in the setup of a new startup company SyTracks which is marketing some of Thomas M. Gøgsig's research discoveries. Certainly, the productivity of the thesis is highly impressive and many of his publications are key references within a very competitive field.

Prof. Troels Skrydstrup
Prof. John F. Hartwig

Preface

The author has been part of the OChem Graduate School Program, Aarhus University, and financially supported by the Faculty of Science. The work presented in this dissertation has primarily been performed at the Department of Chemistry, Aarhus University in the period August 2007–August 2011 under the supervision of Professor Troels Skrydstrup. The work presented in Chap. 4 relies on experiments conducted at the Chemical and Life Sciences Laboratory, University of Illinois at Urbana-Champaign, United States, under the supervision of Professor John F. Hartwig.

In Chap. 1, a presentation of the underlying principles of the organometallic chemistry involved in this dissertation is given.

Chapters 2 and 3 describe an extension of the palladium 1,2-migration in the Heck reaction discovered by Skrydstrup and coworkers. This work was performed in collaboration with Dr. Jean-Philippe Ebran and Dr. Anders Thyboe Lindhardt.

Chapter 4 describes the mechanistic studies on the palladium 1,2-migration in the Negishi and Kumada couplings, which were conducted under the guidance of Professor John F. Hartwig. The work has not been published so far.

In Chap. 5, a presentation of the related regioselective Heck reaction of heteroaromatic tosylates is given. The work was conducted in collaboration with Dr. Anders Thyboe Lindhardt, Dr. Mouloud Dekhane from AstraZeneca, and B.Sc. Julie Grouleff.

Chapter 6 describes a newly developed nickel-catalyzed Heck reaction. This work was performed in collaboration with Dr. Anders Thyboe Lindhardt and B.Sc. Signe Korsager. The computational part was conducted by the group of Professor Per-Ola Norrby; Dr. Jonatan Kleimark; and Dr. Sten Nilsson-Lill.

Chapter 7 describes the recently discovered carbonylative Heck reaction using a two-chamber system. The work was conducted in collaboration with Dr. Philippe Hermange, Dr. Anders Thyboe Lindhardt, and Dr. Rolf H. Taaning.

A representative selection of experimental details regarding the unpublished results presented in Chap. 4 and the nickel-catalyzed Heck reaction (Chap. 6) are also included in the appendices.

Denmark, July 2011 Thomas M. Gøgsig

Acknowledgments

First and foremost I would like to thank Professor Troels Skrydstrup for his guidance throughout the years and for the many hours of instructive discussions. I am very grateful to him for giving me the opportunity to work as a Ph.D. student and the liberty to pursue the questions generated by the research conducted in his laboratories. I would like to extend special thanks to my colleague and friend Dr. Anders Thyboe Lindhardt for the many successful collaborations and for proofreading this dissertation. In addition, I am very grateful to the former and present members of Group 107 for creating a relaxed but educational environment. I would like to highlight the following persons who have all participated and contributed to the research I have been involved in: Rolf H. Taaning, Jean-Philippe Ebran, Philippe Hermange, Delphine Gauthier, Lina Søbjerg, Signe Korsager, Dennis U. Nielsen, Klaus M. Bjerglund, Mette L. H. Mantel, Daniel Lupp, Kim L. Jensen, and Stephan Beckendorf.

I am deeply appreciative to Professor John F. Hartwig for allowing me to join his group for five months at the University of Illinois, Urbana-Champaign and for giving me the opportunity to learn from his expertise and comprehensive knowledge on organometallic chemistry. In this regard, I would like to thank the Hartwig Group for welcoming me and my wife. Thanks to Brad P. Carrow, Cass Richers, Christo Sevov, Seth Marquard, Alexey G. Sergeev, Ramesh Giri, Zheng Huang, David Huang, and especially Nan Holda.

Finally, I would like to express my sincere gratitude to my family at both ends of Denmark and for their kind help in times of need. Thanks to you Agnethe and for your untiring patience with me and to you Augusta for your sparkling smiles in the early mornings.

Contents

Abbreviations

Ac	Acetyl
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bs	Broad singlet
calcd	Calculated
CBz	Carbobenzyloxy
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
Cy_2NMe	*N*,*N*-dicyclohexyl-*N*-methylamine
Cp	Cyclopentadienyl
d	Duplet
dba	*trans*,*trans*-dibenzylidene acetone
DBU	1,8-diazabicycloundec-7-ene
DFT	Density functional theory
DIPEA	Diisopropyl ethyl amine
DMF	*N*,*N*-dimethyl formamide
Dmphen	2,9-Dimethyl-1,10-phenanthroline
DMSO	Dimethylsulfoxide
D*i*PrPF	1,1′-bis(diisopropylphosphino)ferrocene
DPPPe	1,2-bis(diphenylphosphino)pentane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1′-bis(diphenylphosphino)ferrocene
DPPBz	1,2-Bis(diphenylphosphino)benzene
D*t*BPF	1,1′-bis(di*tert*-butylphosphino)ferrocene
EDG	Electron donating group
ee	Enantiomeric excess
EWG	Electron-withdrawing group
equiv	Equivalent
Fe	Iron