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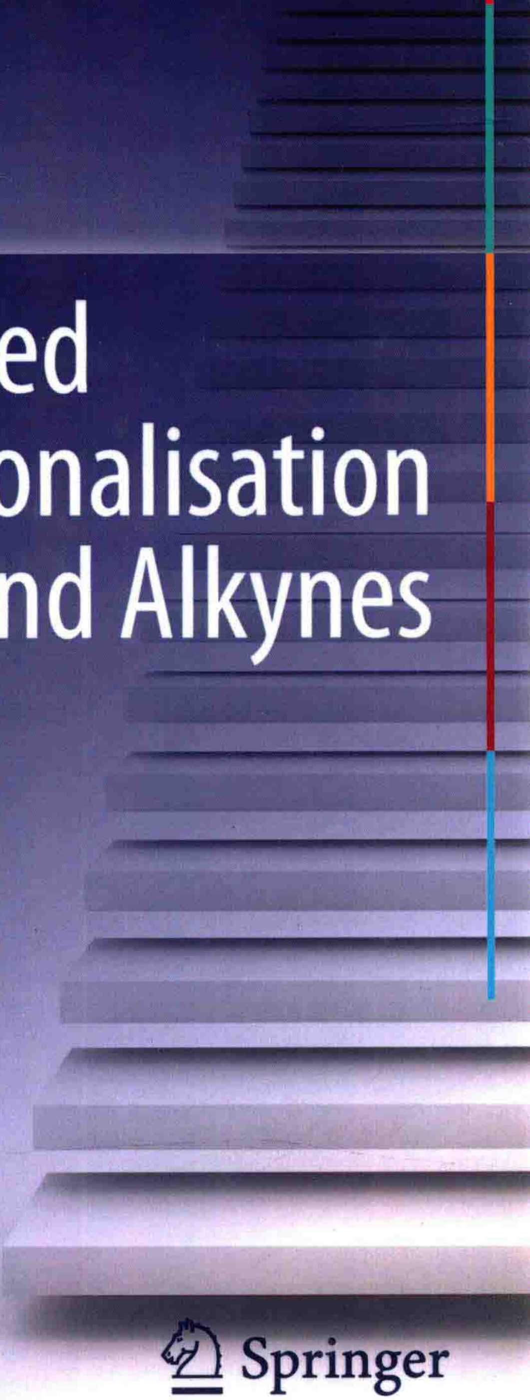
Mark Greenhalgh

Iron-Catalysed Hydrofunctionalisation of Alkenes and Alkynes



Springer

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Iron-Catalysed Hydrofunctionalisation of Alkenes and Alkynes

Doctoral Thesis accepted by
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2. *Chemo-, Regio-, and Stereoselective Iron-Catalysed Hydroboration of Alkenes and Alkynes.*
Greenhalgh, M. D.; Thomas, S. P. *Chem. Commun.* **2013**, *49*, 11230–11232.

3. *Iron-Catalysed Chemo-, Regio-, and Stereoselective Hydrosilylation of Alkenes and Alkynes Using a Bench-Stable Iron(II) Pre-Catalyst.*
Greenhalgh, M. D.; Frank D. J.; Thomas, S. P. *Adv. Synth. Catal.* **2014**, *356*, 584–590.

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Greenhalgh, M. D.; Kolodziej, A.; Sinclair F.; Thomas, S. P. *Organometallics* **2014**, *33*, 5811–5819.

5. *Broad Scope Hydrofunctionalization of Styrene Derivatives Using Iron-Catalyzed Hydromagnesiation.*
Jones, A. S.; Paliga, J. F.; **Greenhalgh, M. D.;** Quibell, J. M.; Steven, A. Thomas, S. P. *Org. Lett.* **2014**, *16*, 5964–5967—Highlighted in *Synfacts* **2015**, *11*, 186.

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Supervisor's Foreword

It is a great pleasure to be able to introduce the Ph.D. work of Dr. Mark Greenhalgh, the quality of which has been recognised by its inclusion in the Springer Thesis Series. Mark was an exceptional Ph.D. student who completed an unparalleled body of work during his Ph.D at Edinburgh. The work in Mark's thesis has been published at the highest level, and his results and ideas have led to three industry-funded Ph.D. studentships and grant income in excess of £1 million.

Mark's thesis deals with the development and application of sustainable homogenous iron catalysts in chemical synthesis. With an ever-growing global demand for sustainability, the development of catalytic processes for fine and bulk chemical synthesis is of paramount importance to satisfy the continued worldwide reliance on the chemical industry for manufactured commodity products. Many of the processes used to make these products however are heavily reliant on precious metal catalysts, such as rhodium, platinum and palladium. These metals are scarce and expensive, with their prices highly sensitive to supply restrictions. The increasing pressure on the supply and demand of these resources has been recognised by the EU, with a sustainable basis for the life-cycle of minerals identified as a primary objective over the coming years. Research into the use of inexpensive and earth abundant alternatives is therefore required to meet these international goals. Iron is the fourth most abundant element in the earth's crust, non-toxic, environmentally benign and inexpensive. These attractive attributes have been recognised with a recent effort by internationally leading research groups to investigate the use of iron-based catalysts in chemical synthesis.

This thesis details research efforts into the development of iron-catalysed hydrosilylation, hydroboration and hydromagnesiation reactions with excellent referencing and scientific argument. The work has focussed on providing methodologies that use only commercially available materials and non-specialised techniques, with the intention that the developed science could be widely adopted by the chemical community. To this end, the in situ reduction of iron-pre-catalysts has been developed and used to enable air- and moisture-stable methodologies. It provides not only an in-depth review of the area, but offers a level of insight well beyond that expected from a Ph.D. student. In short, Mark was one of the unique students whom does not work for you, but works with you. As should be apparent from the quality of the thesis presented here, I fully believe Mark to be a rising star and future research leader.

Edinburgh, UK
March 2016

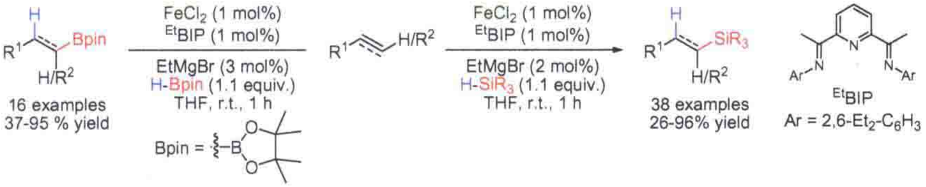
Dr. Stephen Thomas

Abstract

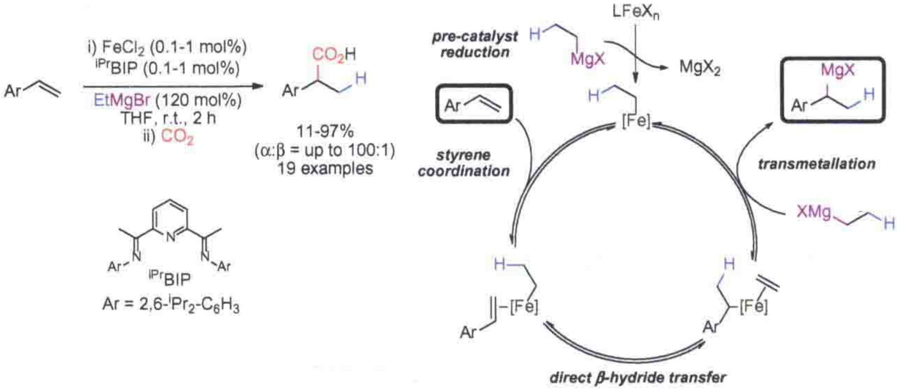
The iron-catalysed hydrofunctionalisation of alkenes and alkynes has been developed to give a range of functionalised products with control of regio-, chemo- and stereochemistry. Using a bench-stable iron(II) pre-catalyst, the hydrosilylation, hydroboration, hydrogermylation and hydromagnesiation of alkenes and alkynes has been achieved.

Iron-catalysed hydrosilylation, hydroboration and hydrogermylation of terminal, 1,1- and 1,2-disubstituted alkyl and aryl alkenes and alkynes was developed, in which the active iron catalyst was generated in situ (Scheme 1). Alkyl and vinyl silanes and pinacol boronic esters were synthesised in good to excellent yield in the presence of a range of functional groups. Catalyst loadings as low as 0.07 mol% were demonstrated, along with catalyst turnover frequencies of up to 60,000 mol h^{-1}.

The iron-catalysed formal hydrocarboxylation of a range of styrene derivatives has been developed for the synthesis of α-aryl carboxylic acids using carbon dioxide and ethylmagnesium bromide as the stoichiometric hydride source



Scheme 1 Iron-catalysed hydrosilylation and hydroboration of alkenes and alkynes



Scheme 2 Iron-catalysed hydromagnesiation of styrene derivatives

(Scheme 2). Detailed mechanistic studies have shown this reaction proceeds by iron-catalysed hydromagnesiation to give an intermediate benzylic organomagnesium reagent. The nature of the active catalyst and reaction mechanism have been proposed.

Preface

The ability to synthesise molecules in a controlled manner is essential for the development of products used in everyday life, such as plastics, fabrics, fertilisers and pharmaceuticals. With ever-growing global chemical demand and energy consumption, the development of efficient, energy-saving synthetic processes is of paramount importance. Catalysis offers the single most powerful method that can be used to improve the yield and efficiency of molecular synthesis whilst also reducing waste and energy consumption. Iron is one of the most abundant elements on earth and therefore is the ideal choice as a catalyst for future applications.

This work developed novel reactions catalysed by an inexpensive, non-toxic and environmentally benign iron catalyst. The controlled and efficient synthesis of a range of molecular structures was achieved. Experiments have provided insight into how these reactions work, which should not only provide a greater understanding of the science involved, but also direct future developments towards highly efficient catalysts and catalytic processes.

Abbreviations

18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
atm.	Atmospheres
$\mathrm{BAr}^{\mathrm{F}}_{4}$	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BDPP	2,4-Bis(diphenylphosphino)pentane
BIP	Bis(imino)pyridine
bMepi	1,3-Bis(6′-methyl-2′-pyridylimino)isoindolate
Bn	Benzyl
BOX	Bis(oxazoline)
Bpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
Bu	Butyl
COD	1,5-Cyclooctadiene
COE	Cyclooctene
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
DACH	1,2-Diaminocyclohexane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCT	Dibenzo[*a*,*e*]cyclooctatetraene
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,2-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
E	Element
ee	Enantiomeric excess
EI	Electron impact

equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron-withdrawing group
GCMS	Gas chromatography mass spectrometry
HMBC	Heteronuclear multiple bond correlation
HMDS	Bis(trimethylsilyl)amide
HPLC	High-performance liquid chromatography
HRMAS	High-resolution magic angle spinning
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IR	Infrared
J	Coupling constant in Hz
L	Ligand
m.p.	Melting point
M	Metal
Me	Methyl
Mes	Mesityl
NBS	*N*-Bromosuccinimide
NMP	*N*-Methylpyrrolidine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
ox	Oxalate
Ph	Phenyl
PHOX	Phosphinooxazoline
Pr	Propyl
py	Pyridine
Rf	Retention factor
r.t.	Room temperature
TBAF	Tetrabutylammonium fluoride
Terpy	Terpyridine
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TOF	Turnover frequency
TON	Turnover number
Tr	Triphenylmethyl
Ts	*para*-Toluenesulfonyl
UV	Ultraviolet

Contents

Chapter 1
Introduction

Abstract The development of efficient and sustainable catalytic methodologies for the construction of complex molecular frameworks is essential for the advancement of synthetic chemistry. The hydrofunctionalisation of alkenes and alkynes can be used for the construction of carbon-carbon and carbon-heteroatom bonds, and represent a potentially 100 % atom-economic process. Transition-metal-catalysed hydrofunctionalisation reactions have therefore found numerous applications in industrial and fine chemical synthesis for the introduction of new functionality in a controlled manner. This chapter introduces the state-of-the-art in this field of chemistry, with a particular focus on methods using inexpensive first row transition-metal catalysts.

The development of efficient and sustainable methodologies for the construction of complex molecular frameworks is essential for the advance of synthetic chemistry. Catalysis can be used to improve the yield and efficiency of these processes whilst also reducing waste and energy consumption, and can give products in high and tuneable chemo- regio- and stereoselectivity.

Transition-metal-catalysed cross-coupling reactions are one of the most versatile methods for the controlled construction of carbon–carbon and carbon–heteroatom bonds (Scheme 1.1) [1]. Cross-coupling reactions are highly applicable to fine chemical synthesis due to the wide range of coupling partners available and considerable literature precedent for these reactions. The hydrofunctionalisation of alkenes and alkynes is an alternative approach to the construction of carbon–carbon and carbon–heteroatom bonds, and represents a potentially 100 % atom-economic process (Scheme 1.1) [2]. Alkenes and alkynes are readily available, diversely-functionalised, bench-stable reagents, which are not intrinsically hazardous [3]. The introduction of new functionality in a controlled manner results in an increase in molecular complexity and presents an opportunity for further synthetic manipulations. Transition-metal-catalysed hydrofunctionalisation reactions have therefore found numerous applications in industrial and fine chemical synthesis.

Late transition-metals, generally those from groups 8–10, have been the most commonly applied catalysts in these processes. Depending upon the oxidation-state of the transition-metal catalyst used, and the polarisation of the hydrogen-heteroatom

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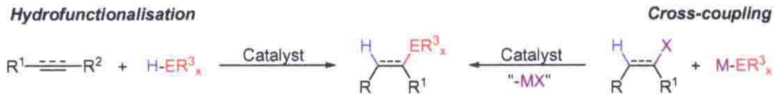
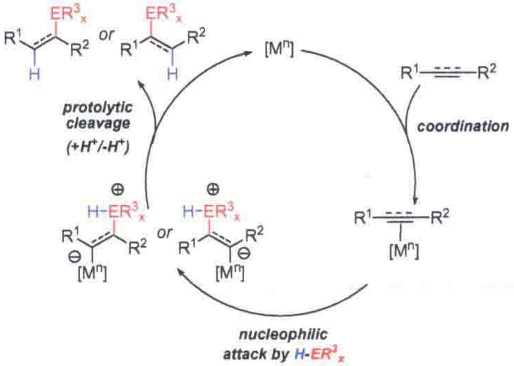


Scheme 1.1 Cross-coupling reactions and the hydrofunctionalisation of alkenes and alkynes using a hydrofunctionalisation reagent (H-ER^3_x) as alternative approaches to molecular synthesis

bond of the hydrofunctionalisation reagent, two general approaches have been used for the transition-metal-catalysed hydrofunctionalisation of alkenes and alkynes. In both cases, coordination of the alkene or alkyne to the transition-metal catalyst is essential for activation of the carbon–carbon multiple bond.

Coordination of an alkene or alkyne to a high oxidation-state late transition-metal catalyst can render the alkene or alkyne more susceptible to nucleophilic attack [4]. For hydrofunctionalisation methodologies where the hydrofunctionalisation reagent is nucleophilic in nature (hydroamination, hydroalkoxylation, etc.), addition of the hydrofunctionalisation reagent to the coordinated alkene or alkyne can give a metal-alkyl or metal-vinyl intermediate, respectively (Scheme 1.2). The hydrofunctionalisation product is then released following protolytic cleavage of the metal-carbon bond (protodemetallation). The metal-alkyl or metal-vinyl intermediate may also be formed through an inner-sphere mechanism, following insertion of the coordinated alkene or alkyne into a metal-heteroatom bond [5].

For hydrofunctionalisation methodologies where the hydrofunctionalisation reagent is not intrinsically nucleophilic (hydrosilylation, hydroboration, etc.), the main approach is to use a low oxidation-state transition-metal catalyst, which can undergo oxidative addition into the hydrogen–heteroatom bond (Scheme 1.3). Insertion of the coordinated alkene or alkyne into either the metal–hydrogen or metal–heteroatom bond gives a metal-alkyl/vinyl intermediate. Reductive elimination of the carbon-heteroatom or carbon–hydrogen bond gives the product of hydrofunctionalisation, and regenerates the low oxidation-state transition-metal catalyst. Hydrosilylation has been proposed to occur by both pathways depending upon the transition-metal catalyst used. Olefin addition into the metal–hydride bond followed by carbon–silicon bond reductive elimination is known as the 'Chalk–



Scheme 1.2 Hydrofunctionalisation of alkenes and alkynes through coordination to a transition-metal catalyst and external attack by a nucleophilic hydrofunctionalisation reagent (H-ER^3_x)