Edited by Marco Bandini and
Achille Umani-Ronchi

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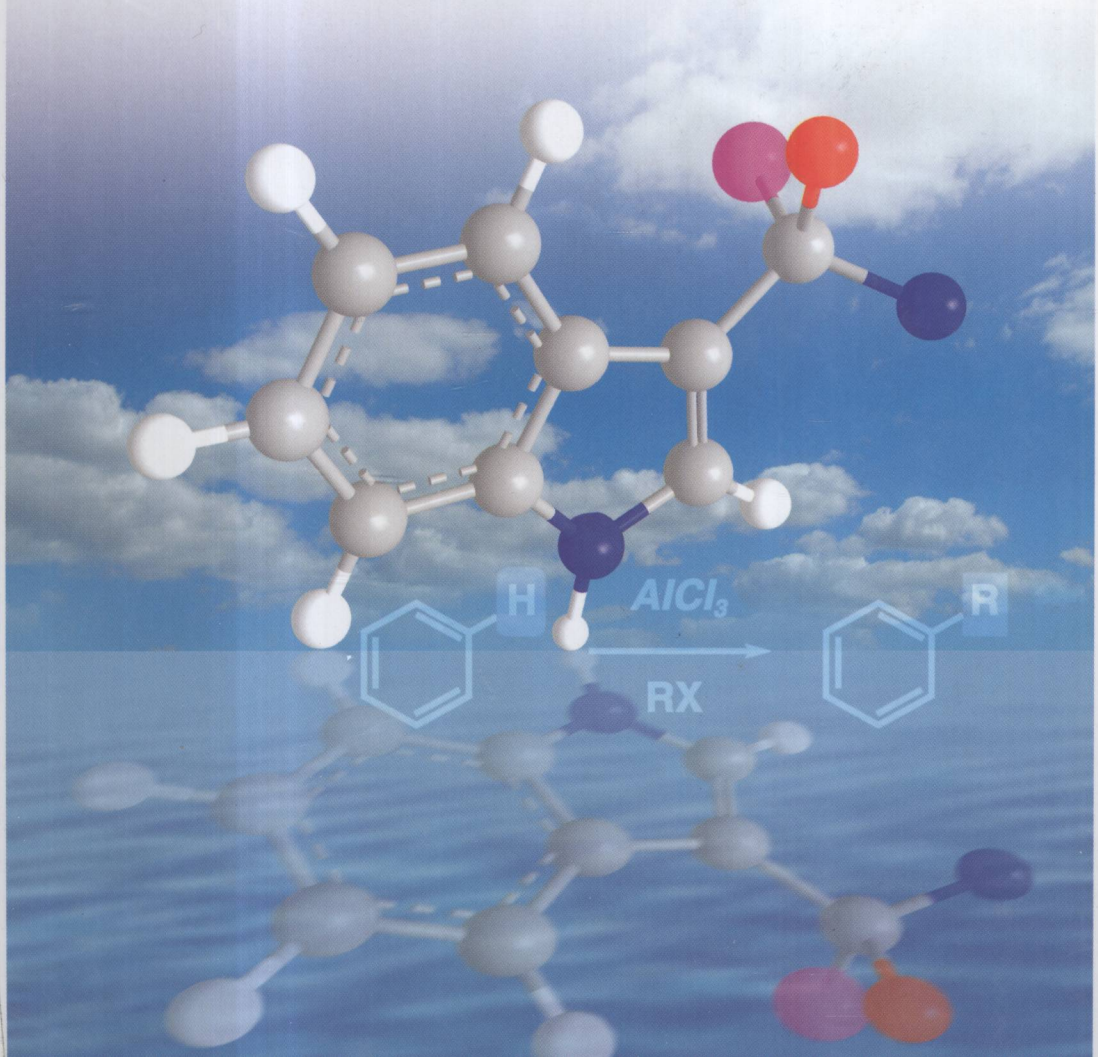
Catalytic Asymmetric Friedel–Crafts Alkylations

With a Foreword by George A. Olah



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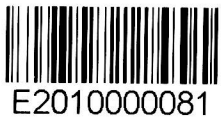

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Marco Bandini and
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Foreword

Charles Friedel, a professor at the Sorbonne in Paris, and James Mason Crafts, his long standing American collaborator from MIT (who later became the President of his institution and founded its renowned graduate school), in 1877 disclosed in a series of papers the discovery of aluminum chloride catalyzed conversion of hydrocarbons. These included alkylation with alkyl halides and other related reactions. Rapid development of the Friedel–Craft-type reaction using a large variety of catalysts made it one of the most versatile and useful fields of organic chemistry.

Marco Bandini has now undertaken to edit, and in no small part write, a most valuable monograph on one of the more recent and important applications of Friedel–Crafts chemistry to catalytic asymmetric alkylations. This clearly is one of the most fascinating and also practical applications of the heritage of Friedel and Crafts applied to the increasingly significant synthesis of asymmetric, optically active compounds. Each chapter was written by leading investigators in the area, covering topics such as Michael Addition, Addition to Carbonyl Compound, Alkylic Akylation, Nucleophilic Substitution on Csp^3 Carbons, Unactivated Alkenes, Catalytic Asymmetric Alkylations in Total Synthesis and Application in Industrial Friedel–Crafts Chemistry.

It is a real pleasure to introduce and recommend to the chemical community, including not only academic and industrial researchers but also other interested chemists, this most useful and stimulating book. It will be I am sure not only of well-deserved interest but also of great practical value to those involved in this significant area of asymmetric synthesis.

Los Angeles, California, October 2008 *George A. Olah*

Catalytic Asymmetric Friedel–Crafts Alkylations. Edited by M. Bandini and A. Umani-Ronchi

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Preface

Friedel–Crafts (FC) alkylation is one of the cornerstones in organic chemistry. Since the pioneering discovery by Charles Friedel and James Mason Crafts in 1887, an impressive number of applications of such a process have appeared for the synthesis of challenging aromatic compounds. Numerous comprehensive treatises on the general aspects of the process, mechanistic details and scope have already been published. In 1963, George A. Olah edited the well referred *Friedel–Crafts and Related Reactions* (1963), a decade later Professor Olah updated his original treatise, producing a monograph entitled *Friedel–Crafts Chemistry*. Almost simultaneously, Royston M. Roberts and Ali A. Khalaf edited their monograph entitled *Friedel–Crafts Alkylation Chemistry*. Other more general monographs focusing on general aspects of aromatic substitutions have appeared later (e.g., *Electrophilic Aromatic Substitution* edited by Roger Taylor in 1990), however, a comprehensive overview addressing strategies to perform catalytic enantioselective FC alkylation is still lacking. With *Catalytic Asymmetric Friedel–Crafts Alkylations* we wish to fill this gap.

Because of the exceptional number of asymmetric FC transformations, we deliberately decided to focus mainly on catalytic enantioselective reactions only (up to July 2008) with a collection of more representative diastereoselective approaches being reported in Chapter 7.

We decided to consider the nature of the electrophilic species as the guideline to creating the chapters of the book. Moreover, the single chapters present further subdivisions for an independent treatment of intramolecular and intermolecular approaches or organometallic and organocatalytic reactions. In our opinion, this choice should help the reader to easily find the necessary information in the articulate scenario of enantioselective FC processes. In doing so, five chapters originated (Chapters 2 to 6) focusing on: conjugate addition to α,β-unsaturated compounds (Chapter 2), direct condensation with carbonyl compounds (Chapter 3), allylic alkylations (Chapter 4), nucleophilic substitution on Csp^3 carbon centers (Chapter 5), and hydroarylation of unactivated carbon–carbon double bonds (Chapter 6).

In Chapter 1, after an introduction to general aspects and the historical background of FC alkylation, a summary of guidelines is reported concerning general

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trends in alkylating agents, chiral catalysts and aromatic systems adopted in catalytic enantioselective aromatic functionalizations.

Chapter 7 has a more target-oriented content. In particular, the authors succeeded in the difficult task of collecting and organizing the plethora of synthetic applications in which asymmetric FC-alkylation is employed as the key step in the total syntheses of natural compounds.

Finally, the tremendous impact of FC processes on actual worldwide chemical industry production is reviewed in Chapter 8. Catalytic enantioselective versions of this class of transformations has not yet been applied to large scale production. However, the ongoing use of innovative catalysts to drive industrial Friedel–Crafts processes towards cleaner and safer production, represents a strong *viaticum* for new developments in the near future.

All the chapters are integrated with a collection of experimental procedures and analytical characterization of model substrates, critically selected by the authors. The presence of these sections will expand the scope of the book to a wide readership such as undergraduate students, graduate students, and researchers both in academia and in industry.

We personally feel indebted to all the authors (we like to call them *friends*) who enthusiastically joined us in the project, providing outstanding contributions. Special mention goes to Professor George A. Olah who kindly agreed to write the foreword.

I (MB) would also like to thank my wife Manuela for putting up with my prolonged absence from the family scene during the editing of this text.

We hope that readers will enjoy reading of the developments in catalytic enantioselective Friedel–Crafts processes presented herein as much as the Editors did during the assembly of the chapters.

Bologna, May 2009

Marco Bandini
Achille Umani-Ronchi

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Contents

Foreword *V*
Preface *XIII*
List of Contributors *XV*

1 General Aspects and Historical Background *1*
Marco Bandini
1.1 Introduction *1*
1.2 General Aspects and Historical Background *3*
1.3 Catalytic Enantioselective FC Reactions: An Introduction *5*
1.3.1 Alkylating Agents *6*
1.3.2 Privileged Catalysts *9*
1.3.3 Aromatic Compounds and Reaction Conditions *13*
References *14*

2 Michael Addition *17*
2.1 Chelating α,β-Unsaturated Compounds *17*
Jesús M. García, Mikel Oiarbide and Claudio Palomo
2.1.1 Chelating Compounds *18*
2.1.1.1 Alkylidene Malonates *19*
2.1.1.2 β,γ-Unsaturated α-Ketoesters *25*
2.1.1.3 α′-Hydroxy Enones *28*
2.1.1.4 α′-Phosphonate Enones *31*
2.1.1.5 α,β-Unsaturated Acyl Compounds *32*
2.1.1.5.1 α,β-Unsaturated Acyl Phosphonates *32*
2.1.1.5.2 α,β-Unsaturated 2-Acyl Imidazoles *34*
2.1.1.6 α,β-Unsaturated Thioesters *39*
2.1.1.7 Nitroacrylates *40*
2.1.1.8 Experimental: Selected Procedures *42*

Catalytic Asymmetric Friedel–Crafts Alkylations. Edited by M. Bandini and A. Umani-Ronchi

ISBN: 978-3-527-32380-7

2.2 Simple α,β-Unsaturated Substrates 49
Giuseppe Bartoli and Paolo Melchiorre
2.2.1 Introduction 49
2.2.1.1 α,β-Unsaturated Aldehydes 50
2.2.1.1.1 Organocatalysis 50
2.2.1.1.2 Organocatalytic Domino Reactions 55
2.2.1.1.3 Experimental: Selected Procedures 57
2.2.1.2 α,β-Unsaturated Ketones 60
2.2.1.2.1 Organometallic Catalysis 60
2.2.1.2.2 Organocatalysis 61
2.2.1.2.3 Experimental: Selected Procedures 64
2.2.2 Intramolecular Approach 65

2.3 Nitroalkenes 67
Luca Bernardi and Alfredo Ricci
2.3.1 Introduction 68
2.3.2 Organocatalytic Enantioselective Reactions 68
2.3.2.1 Friedel–Crafts Alkylation of Indoles 68
2.3.2.1.1 Thiourea Catalysts 69
2.3.2.1.2 Bissulfonamide Catalysts 72
2.3.2.1.3 Phosphoric Acid Catalysts 73
2.3.2.1.4 Synthetic Applications 74
2.3.3 Friedel–Crafts Reactions of Naphthols 75
2.3.3.1 Thiourea Catalysts 75
2.3.4 Addition of 1,2,3-Triazoles 76
2.3.4.1 Cinchona Alkaloids Catalysts 77
2.3.5 Conclusion and Outlook 78
2.3.6 Experimental: Selected Procedures 79
2.3.7 Lewis Acid Catalyzed Enantioselective Reactions 80
2.3.7.1 Friedel–Crafts Reactions of Indoles 81
2.3.7.1.1 Zinc Catalysts 81
2.3.7.1.2 Copper and Aluminum Catalysts 84
2.3.7.2 Friedel–Crafts Reactions of Furans and Pyrroles 88
2.3.7.2.1 Zinc Catalysts 88
2.3.7.3 Conclusion and Outlook 90
2.3.7.4 Experimental: Selected Procedures 91
References 94

3 Addition to Carbonyl Compounds 101
3.1 Aldehydes/Ketones 101
Jia-Rong Chen and Wen-Jing Xiao
3.1.1 Introduction 101
3.1.2 Organometallic Catalysis 102
3.1.2.1 Fundamental Examples and Mechanism 102
3.1.2.1.1 Chiral Titanium (IV) Catalysis 103

3.1.2.1.2 Chiral Bisoxazoline-Cu(II) Catalysis *108*
3.1.2.2 Experiments: Selected Representative Procedures *114*
3.1.3 Organocatalysis *116*
3.1.3.1 Fundamental Examples and Mechanism *116*
3.1.3.2 Experiments: Selected Representative Procedures *118*
3.1.4 Heterogeneous Catalysis *118*

3.2 Imines *119*
Shu-Li You
3.2.1 Catalytic Asymmetric Friedel–Crafts Reaction of Imines *120*
3.2.1.1 Intermolecular Approach *120*
3.2.1.1.1 Organometallic Catalysis *120*
3.2.1.1.2 Organocatalysis *123*
3.2.1.2 Pictet–Spengler Reaction *132*
3.2.2 Selected Procedures *138*
References *140*

4 Nucleophilic Allylic Alkylation and Hydroarylation of Allenes *145*
Marco Bandini and Achille Umani-Ronchi
4.1 Introduction *145*
4.2 Allylic Alkylations *147*
4.2.1 Intermolecular Approach *147*
4.2.1.1 Benzene-Like Compounds *147*
4.2.1.2 Indoles *150*
4.2.1.3 Asymmetric Allylations *152*
4.2.1.4 Experimental: Selected Procedures *155*
4.2.2 Intramolecular Approaches *156*
4.2.2.1 Introduction and Fundamental Examples *156*
4.2.2.2 Experimental: Selected Procedures *159*
4.3 Metallo-Catalyzed Hydroarylation of Allenes *160*
4.3.1 Introduction and Fundamental Examples *160*
4.3.2 Experimental: Selected Procedures *163*
References *164*

5 Nucleophilic Substitution on Csp^3 Carbon Atoms *167*
Marco Bandini and Pier Giorgio Cozzi
5.1 Ring-Opening of Epoxides *168*
5.1.1 Introduction *168*
5.1.2 Enantiomerically Pure Epoxides *169*
5.1.2.1 Introduction *169*
5.1.2.2 Indium(III) Catalysis *172*
5.1.2.3 Mechanism of Indium(III) Catalysis *175*
5.1.2.4 Gold(III) Catalysis *176*
5.1.2.5 Mechanism of Gold(III) Catalysis *177*
5.1.2.6 Experiments: Selected Procedures *177*

5.1.3 Asymmetric Ring-Opening of Racemic and *meso* Epoxides *179*
5.1.3.1 Introduction *179*
5.1.3.2 Salen-Chromium-Catalyzed Kinetic Resolution of Epoxides with Indoles *179*
5.1.3.3 Experiments: Selected Procedures *180*
5.2 Direct Activation of Alcohols *181*
5.2.1 Introduction *181*
5.2.2 Diastereoselective Reactions *182*
5.2.2.1 BF_3-Mediated Reactions *183*
5.2.2.2 Gold(III) Catalysis *184*
5.2.3 Enantioselective Reactions *187*
5.2.3.1 Ruthenium Catalysis *187*
5.2.3.2 Brønsted Acid Catalysis *191*
5.2.3.3 Experiments: Selected Procedures *192*
5.2.3.4 FC Reactions with Chiral Ferrocenyl Compounds *193*
5.2.3.4.1 Indium-Promoted Nucleophilic Substitution with Ferrocene *193*
5.2.3.4.2 "On Water" FC Reactions *194*
5.2.3.4.3 Experiments: Selected Procedures *196*
References *198*

6 Unactivated Alkenes *203*
Ross A. Widenhoefer
6.1 Introduction *203*
6.2 Early Studies *204*
6.2.1 Enantioselective Hydroarylation of Norbornene *204*
6.2.2 Atropselective Alkylation of Biaryls *206*
6.3 Rh(I)-Catalyzed Enantioselective Hydroarylation of Iminoarenes *207*
6.3.1 Catalyst Control *207*
6.3.1.1 Alkylation of Aromatic Ketimines *207*
6.3.1.2 Alkylation of Aromatic Aldimines *209*
6.3.2 Directing Group Control *211*
6.3.2.1 Synthesis of (+)-Lithospermic Acid *211*
6.3.2.2 Optimization and Scope *213*
6.4 Pt(II)-Catalyzed Enantioselective Hydroarylation of Alkenylindoles *214*
6.5 Au(I)-Catalyzed Enantioselective Hydroarylation of Allenylindoles *217*
6.6 Conclusions and Outlook *219*
6.7 Experimental: Selected Procedures *220*
References *221*

7 Catalytic Asymmetric Friedel–Crafts Alkylations in Total Synthesis *223*
Gonzalo Blay, José R. Pedro and Carlos Vila
7.1 Introduction *223*
7.2 Total Synthesis of Indole-Containing Compounds *224*
7.2.1 Synthesis of β-Indolyl-Propanoic Acids *224*
7.2.2 Synthesis of Tryptamine and Tryptophan Analogs *225*

7.2.3 Synthesis of Polycyclic Indoles *228*
7.2.4 Synthesis of 2-Aminomethyl Indoles *229*
7.2.5 Experiments: Selected Procedures *232*
7.3 Total Synthesis of Pyrrole-Containing Compounds *240*
7.3.1 Synthesis of (+)-Heliotridane *240*
7.3.2 Synthesis of the Indolizidine Alkaloids Tashiromine, epi-Tashiromine, Razhinal, Rhazinilam, Leuconolam and epi-Leuconalam *241*
7.3.3 Synthesis of Pyrrolo[1,2-a]pyrazines *242*
7.3.4 Experiments: Selected Procedures *244*
7.4 Friedel–Crafts Alkylation of Furan Derivatives in Total Synthesis *247*
7.4.1 Synthesis of Aminobutenolides *248*
7.4.2 Experiments: Selected Procedures *248*
7.5 Friedel–Crafts Alkylation of Arenes in Total Synthesis *249*
7.5.1 Synthesis of Optically Active Mandelic Acid Derivatives and Aromatic α-Amino Acids *250*
7.5.2 Synthesis of Optically Active Chromanes *250*
7.5.3 Experiments: Selected Procedures *251*
7.6 Asymmetric Synthesis of Natural Products Based on Diastereoselective Friedel–Crafts Reactions *253*
7.6.1 Synthesis of Hapalindole Alkaloids *253*
7.6.2 Synthesis of Acremoauxin A and Oxazinin 3 *255*
7.6.3 Synthesis of (S)-Ketoralac *256*
7.6.4 Synthesis of (−)-Lintetralin *257*
7.6.5 Synthesis of (+)-Erogorgiaene *258*
7.6.6 Synthesis of (+)-Bruguierol C *260*
7.6.7 Synthesis of (−)-Talaumidin *261*
7.6.8 Experiments: Selected Procedures *262*
References *268*

8 Industrial Friedel–Crafts Chemistry *271*
Duncan J. Macquarrie
8.1 Introduction *271*
8.2 Green Chemistry and the Friedel–Crafts Reaction *272*
8.2.1 Green Chemical Assessment of Friedel–Crafts Processes *272*
8.3 Heterogeneous Catalysts for the Friedel–Crafts Reaction *275*
8.3.1 Zeolites *275*
8.3.2 Clays and Other Solid Acids *277*
8.4 Large Scale Hydrocarbon Processing *278*
8.4.1 Ethylbenzene and Cumene *278*
8.4.2 Linear Alkyl Benzenes *279*
8.4.3 Dialkylated Biaryls *280*
8.4.4 Alkylanilines and Related Compounds *280*
8.4.5 Alkylphenol Production *281*
8.4.6 Diarylmethanes *282*
8.4.7 Hydroxyalkylation of Aromatics *282*

8.4.8 Pechmann Syntheses *284*
8.4.9 Use of Epoxides as Alkylating Agents *284*
8.5 Conclusions and Perspectives *286*
References *286*

Index *289*

1
General Aspects and Historical Background

Marco Bandini

Summary

The scope of catalytic enantioselective Friedel–Crafts alkylations is expanding rapidly and since the seminal papers appeared in the mid 1980s, numerous examples featuring enantioselectivities higher than 90% have been published. At present, nearly all the organic compounds displaying electrophilic character have been reacted with aromatic systems in FC-type alkylation reactions. However, the typology of reagents becomes slightly narrower if we limit the survey to approaches that employ chiral catalysts capable of traducing stereochemistry in the final products. Activated as well as unactivated carbon–carbon double bonds and C=X frameworks characterize the most used classes of electrophilic agents, that are generally combined with privileged chiral organometallic and organic catalysts. It is also worth mentioning the actual distribution of enantioselective FC processes based on the type of aromatic system employed. Interestingly, highly reactive electron-rich arenes (pyrrole and indole) still constitute almost 80% of catalytic enantioselective FC-processes, while asymmetric transformations of benzene-like compounds are quite undeveloped.

1.1
Introduction

The Friedel–Crafts (FC) alkylation of aromatic compounds is one of the cornerstones of organic chemistry. Since it was first reported (three consecutive notes appeared in *Comptes Rendus de l'Académie des Sciences* in 1877) [1] by Charles Friedel and James Mason Crafts, countless versions of this process have been reported. In this context, it is worth mentioning that "... one third of worldwide organic chemical production involves aromatic compounds..." [2] with the consequent synthetic interest in their chemical manipulation.

The reaction introduced by the European (CF, Strasbourg, France, 1832–1889) and the youngest American (JMC, Boston, MA, USA, 1839–1917) researchers [3], has always been the subject of lively scientific debate, and one of the most controversial aspects is the definition of the process.

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