

## Contents

Preface *xi*

Discovery of Catalysis by Nucleophilic Carbenes *xiii*

About the Editor *xvii*

- 1 An Overview of NHCs** *1*  
*Matthew N. Hopkinson and Frank Glorius*
- 1.1 General Structure of NHCs *2*
- 1.1.1 Classes of NHCs and Related Stable Carbenes *2*
- 1.1.2 Structural Features Common to All NHCs *4*
- 1.1.3 Stabilization of the Carbene Center *5*
- 1.2 NHCs as  $\sigma$ -Donating Ligands *7*
- 1.2.1 The Nature of Bonding in NHC Adducts *10*
- 1.2.2 Comparing NHC and Phosphine Ligands *10*
- 1.3 Synthesis of NHCs *11*
- 1.3.1 Generation of the Free Carbene *11*
- 1.3.2 Synthetic Routes Toward Azolium Salt NHC Precursors *12*
- 1.4 Quantifying the Electronic Properties of NHCs *16*
- 1.4.1  $pK_a$  Measurements of Azolium Salts *16*
- 1.4.2 Tolman Electronic Parameter (TEP) *17*
- 1.4.3 NMR Measurements *21*
- 1.4.4 Nucleophilicity and Lewis Basicity *24*
- 1.4.5 Electrochemical Methods *24*
- 1.4.6 Computational Methods *25*
- 1.5 Quantifying the Steric Properties of NHCs *26*
- 1.5.1 Percentage Buried Volume ( $\%V_{\text{bur}}$ ) *27*
- 1.5.2 Steric Maps *29*
- 1.6 Concluding Remarks *30*
- References *30*
- 2 Benzoin Reaction** *37*  
*Steven M. Langdon, Karnjit Parmar, Myron M.D. Wilde, and Michel Gravel*
- 2.1 Background and Mechanism *37*
- 2.2 Standard Conditions and Substrate Scope *40*
- 2.3 Enantioselective Homo-benzoin Reactions *41*

|          |  |            |
|----------|--|------------|
| 2.4      | Cross-benzoin Reactions  | 42         |
| 2.4.1    | Intramolecular Cross-benzoin Reactions   | 42         |
| 2.4.2    | Intermolecular Cross-benzoin Reactions   | 47         |
| 2.5      | Aza-benzoin Reactions  | 51         |
| 2.5.1    | Aza-benzoin Reactions of Aldimines   | 51         |
| 2.5.2    | Aza-benzoin Reactions of Ketimines   | 53         |
|          | References   | 54         |
| <b>3</b> | <b>N-Heterocyclic Carbene-catalyzed Stetter Reaction and Related Chemistry</b>       | <b>59</b>  |
|          | <i>Santigopal Mondal, Santhivardhana R. Yetra, and Akkattu T. Biju</i>               |            |
| 3.1      | Introduction   | 59         |
| 3.2      | Proposed Mechanism of the Stetter Reaction   | 60         |
| 3.3      | Intramolecular Stetter Reaction  | 61         |
| 3.4      | Intermolecular Stetter Reaction  | 68         |
| 3.5      | Cascade Processes Involving Stetter Reaction   | 79         |
| 3.6      | NHC-catalyzed Hydroacylation Reactions   | 82         |
| 3.7      | Conclusion   | 89         |
|          | References   | 89         |
| <b>4</b> | <b>N-Heterocyclic Carbene (NHC)-Mediated Generation and Reactions of Homoenoates</b> | <b>95</b>  |
|          | <i>Vijay Nair, Rajeev S. Menon, and Jagadeesh Krishnan</i>                           |            |
| 4.1      | Homoenoates – An Introduction  | 95         |
| 4.2      | N-Heterocyclic Carbenes (NHCs)   | 97         |
| 4.3      | NHC-Derived Homoenoates – The Beginning  | 98         |
| 4.4      | Mechanistic Pathways Available for NHC-Homoenoates                                   | 100        |
| 4.5      | Reaction of NHC-Homoenoates with Ketones and Ketimines                               | 102        |
| 4.6      | Reaction of NHC-Homoenoates with Michael Acceptors                                   | 108        |
| 4.7      | $\beta$ -Protonation of Homoenoates and Subsequent Reactions                         | 117        |
| 4.8      | Homoenoates in Carbon–Nitrogen Bond Formation  | 122        |
| 4.9      | Domino Reactions of Homoenoates  | 124        |
| 4.10     | New Precursors for Homoenoates   | 126        |
| 4.11     | Conclusion   | 129        |
|          | References   | 129        |
| <b>5</b> | <b>Domino Processes in NHC Catalysis</b>   | <b>133</b> |
|          | <i>Pankaj Chauhan, Suruchi Mahajan, Xiang-Yu Chen, and Dieter Enders</i>             |            |
| 5.1      | Introduction   | 133        |
| 5.2      | Domino Reactions Involving Homoenoate–Enolate Intermediates                          | 134        |
| 5.2.1    | Domino Reactions Involving a Michael/Aldol Reaction Sequence                         | 134        |
| 5.2.2    | Domino Reactions Involving a Michael/Michael Reaction Sequence                       | 138        |
| 5.2.3    | Domino Reactions Involving a Michael/Mannich Reaction Sequence                       | 140        |

|          |  |            |
|----------|--|------------|
| 5.2.4    | Domino Reactions Involving a Homo-aldol/Michael Addition Sequence                                  | 142        |
| 5.3      | Domino Reactions Involving Dienolate–Enolate Intermediates   | 142        |
| 5.4      | Domino Reactions Involving Unsaturated Acyl Azolium–Enolate Intermediates                          | 145        |
| 5.4.1    | Domino Reactions Involving a Michael/Aldol Sequence  | 145        |
| 5.4.2    | Domino Reactions Involving a Michael/Michael Addition Sequence                                     | 149        |
| 5.4.3    | Domino Reactions Involving a Michael/Mannich Reaction Sequence                                     | 152        |
| 5.4.4    | Domino Reactions Involving a Michael/S <sub>N</sub> 2 Reaction Sequence                            | 153        |
| 5.5      | Conclusions and Outlook  | 153        |
|          | References   | 154        |
| <b>6</b> | <b>N-Heterocyclic Carbene Catalysis via the <math>\alpha,\beta</math>-Unsaturated Acyl Azolium</b> | <b>157</b> |
|          | <i>Changhe Zhang and David Lupton</i>  |            |
| 6.1      | Introduction   | 157        |
| 6.2      | Generation of the $\alpha,\beta$ -Unsaturated Acyl Azolium   | 157        |
| 6.3      | Esterification of the $\alpha,\beta$ -Unsaturated Acyl Azolium                                     | 159        |
| 6.4      | [3+ <i>n</i> ] Annulations of the $\alpha,\beta$ -Unsaturated Acyl Azolium                         | 160        |
| 6.4.1    | Annulation with Enolates   | 161        |
| 6.4.2    | Annulation with Eenamines  | 165        |
| 6.4.3    | Annulation with Other Nucleophiles   | 168        |
| 6.5      | [2+ <i>n</i> ] Annulations of the $\alpha,\beta$ -Unsaturated Acyl Azolium                         | 170        |
| 6.5.1    | [2+4] Annulations Terminating in $\beta$ -Lactonization  | 170        |
| 6.5.2    | [2+4] Annulations Terminating in $\delta$ -Lactonization   | 174        |
| 6.5.3    | [2+3] Annulations Terminating in $\beta$ -Lactonization  | 174        |
| 6.5.4    | [2+1] Annulations  | 176        |
| 6.6      | Cascades Involving Bond Formation at the $\gamma$ -Carbon and Acyl Carbon                          | 177        |
| 6.6.1    | Annulations with Ketones and Imines  | 177        |
| 6.6.2    | [4+2] Annulations with Electron-Poor Olefins   | 180        |
| 6.7      | Other Reactions of the $\alpha,\beta$ -Unsaturated Acyl Azolium                                    | 181        |
| 6.8      | Conclusions and Outlook  | 183        |
|          | References   | 183        |
| <b>7</b> | <b>Recent Activation Modes in NHC Organocatalysis</b>  | <b>187</b> |
|          | <i>Zhichao Jin, Xingkuan Chen, and Yonggui R. Chi</i>  |            |
| 7.1      | Introduction   | 187        |
| 7.2      | Activation of Carboxylic Acid Derivatives  | 187        |
| 7.2.1    | $\alpha$ -Carbon Activation of Saturated Carboxylic Esters   | 188        |
| 7.2.2    | $\beta$ -Carbon Activation of $\alpha,\beta$ -Unsaturated Carboxylic Compounds                     | 191        |
| 7.2.3    | Nucleophilic $\beta$ -Carbon Activation of Saturated Carboxylic Esters                             | 195        |
| 7.2.4    | $\gamma$ -Carbon Activation of $\alpha,\beta$ -Unsaturated Carboxylic Esters                       | 198        |
| 7.3      | Radical Reactions Catalyzed by NHC Organic Catalysts   | 199        |
| 7.3.1    | Lessons from Nature  | 199        |

- 7.3.2 Pioneering SET Reactions in NHC Organocatalysis 200
- 7.3.3 NHC-Catalyzed Reductive  $\beta,\beta$ -couplings of Nitroalkenes 201
- 7.3.4 NHC-Catalyzed Benzoylation of Electrophiles 202
- 7.3.5 NHC-Catalyzed  $\beta$ -hydroxylation of  $\alpha,\beta$ -Unsaturated Aldehydes 204
- 7.3.6 Synthesis of Chiral 3,4-diaryl Cyclopentanones Through SET Process 205
- 7.3.7 Polyhalides as Oxidants for NHC-Catalyzed Radical Reactions 206
- 7.3.8 New Mechanisms for Classical Reactions 208
- 7.4 Summary and Outlook into the Future NHC Organocatalysis 209
- References 210

## 8 N-Heterocyclic Carbene-Catalyzed Reactions via Azolium Enolates and Dienolates 213

*Zhao-Fei Zhang, Chun-Lin Zhang, and Song Ye*

- 8.1 Introduction 213
- 8.2 Azolium Enolates from  $\alpha$ -Functionalized Aldehydes 213
  - 8.2.1 Synthesis of Carboxylic Compounds 213
  - 8.2.2 Formal [2+4] Cycloaddition 217
  - 8.2.3 Formal [2+2] Cycloaddition 222
  - 8.2.4 Formal [2+3] Cycloaddition 222
- 8.3 Azolium Enolate from Ketenes 223
  - 8.3.1 Formal [2+2] Cycloaddition 224
  - 8.3.2 Asymmetric Formal [2+3] Cycloadditions 231
  - 8.3.3 Asymmetric Formal [2+4] Cycloadditions 232
  - 8.3.4 Asymmetric Protonation and Halogenation 236
- 8.4 Azolium Enolate from Enals 237
- 8.5 Azolium Enolate from Aldehydes with Oxidant 242
- 8.6 Azolium Enolates from Activated Esters 244
- 8.7 Azolium Enolates from Acids 247
- 8.8 Azolium Dienolate 249
- 8.9 Conclusions and Outlook 257
- References 257

## 9 N-heterocyclic Carbenes as Brønsted Base Catalysts 261

*Jiean Chen and Yong Huang*

References 284

## 10 NHC-Catalyzed Kinetic Resolution, Desymmetrization, and DKR Strategies 287

*Shenci Lu, Si B. Poh, Jun Y. Ong, and Yu Zhao*

- 10.1 Introduction 287
- 10.2 NHC-Catalyzed Acylation 288
  - 10.2.1 Acylation of Aliphatic Alcohols 290
    - 10.2.1.1 Acylation of Aliphatic Alcohols 290
    - 10.2.1.2 DKR Involving Acylation of Alcohols 292
  - 10.2.2 Acylation of Phenols 294

- 10.2.3 Acylation of Amines and Sulfoximines 297
- 10.3 Benzoin and Stetter Reactions 299
  - 10.3.1 Desymmetrization of Achiral Substrates 301
  - 10.3.2 DKR of Racemic Substrates via Benzoin Condensation 302
- 10.4 Annulation Reactions 303
  - 10.4.1 Annulation via Azolium Enolate Addition 303
  - 10.4.2 Annulation via Azolium Homo-enolate Addition 305
  - 10.4.3 Annulation via  $\gamma$ -Addition 305
- 10.5 Conclusion 306
  - Acknowledgments 306
  - References 306
  
- 11 N-Heterocyclic Carbenes for Organopolymerization: Metal-Free Polymer Synthesis 309**  
*Romain Lambert, Joan Vignolle, and Daniel Taton*
  - 11.1 Introduction 309
  - 11.2 Main NHCs and Fundamental Mechanisms of NHC-Induced Polymerization 310
  - 11.3 NHC-Mediated Chain-growth Polymerization 314
    - 11.3.1 Ring-opening Polymerization 314
    - 11.3.2 NHC-OROP (in the Presence of an Initiator) 314
    - 11.3.3 Directly NHC-Mediated ROP (in the Absence of an Initiator): Synthesis of Cyclic vs. Linear Polymers 321
  - 11.4 Reaction with Alkyl (meth)acrylates 328
    - 11.4.1 Basic Nucleophilic Reactivity of Stable Carbenes in the Absence of Initiator 328
      - 11.4.1.1 Ambiphilic Reactivity of Stable Carbenes 331
      - 11.4.1.2 Noncatalytic Reactivity 332
      - 11.4.1.3 Catalytic Reactivity 332
    - 11.4.2 Reactivity of NHCs Toward  $\alpha,\beta$ -Unsaturated Esters in the Presence of Initiators 334
    - 11.4.3 Reactivity of NHCs in Conjunction with a Lewis Acid: Frustrated Lewis Pair-Type Reactivity 335
  - 11.5 NHC-Mediated Step-growth Polymerization 336
  - 11.6 Conclusion 340
    - References 341
  
- 12 N-Heterocyclic Carbene Catalysis in Natural Product and Complex Target Synthesis 345**  
*M. Todd Hovey, Ashley A. Jaworski, and Karl A. Scheidt*
  - 12.1 Introduction 345
  - 12.2 NHC-Catalyzed Benzoin Condensations 345
    - 12.2.1 Synthesis of *trans*-Resorcylic acid 346
    - 12.2.2 Synthesis of (+)-Sappanone B 346
    - 12.2.3 Synthesis of Cassialoin 348
    - 12.2.4 Synthesis of the Kinamycins and the Monomeric Unit of Lomaiviticin Aglycon 349

|          |  |     |
|----------|--|-----|
| 12.2.5   | Synthesis of (–)-Seragakinone A                              | 351 |
| 12.2.6   | Synthesis of Originally Assigned Structure of Pleospdione    | 354 |
| 12.2.7   | Formal Synthesis of Natural Inositols                        | 355 |
| 12.2.8   | Synthesis of (+)-7,20-Diisocyanoadociane                     | 355 |
| 12.3     | The Stetter Reaction   | 357 |
| 12.3.1   | Annulation Reactions   | 358 |
| 12.3.1.1 | Synthesis of Hirsutic Acid C                                 | 358 |
| 12.3.1.2 | Formal Synthesis of Platensimycin                            | 358 |
| 12.3.2   | Fragment Coupling  | 360 |
| 12.3.2.1 | Synthesis of <i>cis</i> -Jasmon and Dihydrojasmon            | 360 |
| 12.3.2.2 | Synthesis of the Core of Atorvastatin                        | 360 |
| 12.3.2.3 | Synthesis of Roseophilin                                     | 361 |
| 12.3.2.4 | Synthesis of <i>trans</i> -Sabinene Hydrate                  | 362 |
| 12.3.2.5 | Synthesis of (+)-Monomorphine I and Related Natural Products | 363 |
| 12.3.2.6 | Synthesis of Haloperidol                                     | 363 |
| 12.3.2.7 | Synthesis of (–)-Englerin A                                  | 364 |
| 12.3.2.8 | Synthesis of Piperodione                                     | 366 |
| 12.4     | NHC-homoenolate Equivalents                                  | 366 |
| 12.4.1   | Synthesis of Salinosporamide A                               | 367 |
| 12.4.2   | Synthesis of Bakkenolides I, J, and S                        | 367 |
| 12.4.3   | Synthesis of Maremycin B                                     | 369 |
| 12.4.4   | Synthesis of Clausenamide                                    | 369 |
| 12.4.5   | Synthesis of (–)-Paroxetine and (–)-Femoxetine               | 370 |
| 12.4.6   | Synthesis of ( <i>S</i> )-Baclofen and ( <i>S</i> )-Rolipram | 371 |
| 12.4.7   | Synthesis of 3-Dehydroxy Secu'amine A                        | 374 |
| 12.5     | NHC-Catalyzed Aroylation Reactions                           | 374 |
| 12.5.1   | Synthesis of Atroviridin                                     | 375 |
| 12.6     | NHC-Catalyzed Redox and Oxidative Processes                  | 376 |
| 12.6.1   | Redox Esterifications  | 376 |
| 12.6.1.1 | Synthesis of (+)-Davanone                                    | 376 |
| 12.6.1.2 | Synthesis of Gelsemoxonine                                   | 377 |
| 12.6.1.3 | Synthesis of (+)-Tanikolide                                  | 378 |
| 12.6.2   | Oxidative Esterification                                     | 379 |
| 12.6.2.1 | Synthesis of (+)-Dactylolide                                 | 379 |
| 12.6.2.2 | Synthesis of Cyanolide A and Clavosolide A                   | 380 |
| 12.6.2.3 | Synthesis of Bryostatin 7                                    | 381 |
| 12.6.3   | Carbon–Carbon Bond Formation                                 | 384 |
| 12.6.3.1 | Synthesis of (–)-7-Deoxyloganin                              | 384 |
| 12.6.4   | Brønsted Base Catalysis                                      | 384 |
| 12.6.4.1 | Synthesis of (1R)-Suberosanone                               | 385 |
| 12.7     | Summary  | 386 |
|          | References   | 386 |