

Preface *xi*

Discovery of Catalysis by Nucleophilic Carbenes *xiii*

About the Editor *xvii*

<b>1</b>	<b>An Overview of NHCs</b>	<b>1</b>
	<i>Matthew N. Hopkinson and Frank Glorius</i>	
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
<b>2</b>	<b>Benzoin Reaction</b>	<b>37</b>
	<i>Steven M. Langdon, Karnjit Parmar, Myron M.D. Wilde, and Michel Gravel</i>	
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 Homoenolates</b>	<b>95</b>
	<i>Vijay Nair, Rajeev S. Menon, and Jagadeesh Krishnan</i>	
4.1	Homoenolates – An Introduction	95
4.2	N-Heterocyclic Carbenes (NHCs)	97
4.3	NHC-Derived Homoenolates – The Beginning	98
4.4	Mechanistic Pathways Available for NHC-Homoenolates	100
4.5	Reaction of NHC-Homoenolates with Ketones and Ketimines	102
4.6	Reaction of NHC-Homoenolates with Michael Acceptors	108
4.7	$\beta$ -Protonation of Homoenolates and Subsequent Reactions	117
4.8	Homoenolates in Carbon–Nitrogen Bond Formation	122
4.9	Domino Reactions of Homoenolates	124
4.10	New Precursors for Homoenolates	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 Homoenolate–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 Benzylation 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 Homoenolate 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 <i>trans</i> -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 (+)-Monomorine 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