

Edited by
Barry M. Trost and Chao-Jun Li

Modern Alkyne Chemistry

Catalytic and Atom-Economic
Transformations



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Barry M. Trost and Chao-Jun Li

Modern Alkyne Chemistry

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Modern Alkyne Chemistry

Catalytic and Atom-Economic Transformations

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Contents

List of Contributors XIII

Preface XVII

1	Introduction 1
	<i>Chao-Jun Li and Barry M. Trost</i>
1.1	History of Alkynes 1
1.2	Structure and Properties of Alkynes 2
1.3	Classical Reactions of Alkynes 2
1.4	Modern Reactions 4
1.5	Conclusion 6
	References 7
Part I	Catalytic Isomerization of Alkynes 9
2	Redox Isomerization of Propargyl Alcohols to Enones 11
	<i>Barry M. Trost</i>
2.1	Introduction 11
2.2	Base Catalysis 12
2.3	Ru Catalyzed 15
2.4	Rh Catalysis 20
2.5	Palladium Catalysis 22
2.6	Miscellaneous 24
2.7	Conclusions 25
	References 25
3	Carbophilic Cycloisomerization Reactions of Enynes and Domino Processes 27
	<i>Jean-Pierre Genet, Patrick Y. Toullec, and Véronique Michelet</i>
3.1	Introduction and Reactivity Principles 27
3.1.1	The Reactivity of Carbophilic Lewis Acids in the Presence of Enyne Substrates 27
3.2	Skeletal Rearrangement Reactions in the Absence of Nucleophiles 28
3.2.1	Synthesis of Dienes (1,3- and 1,4-Dienes) 28

3.2.2	Cycloisomerization Reactions Involving Activated Alkene Partners: Conia-Ene Reaction and Related Transformations	32
3.2.3	Formation of Bicyclic Derivatives	37
3.2.3.1	Formation of Bicyclopropanes	37
3.2.3.2	Formation of Bicyclobutenes	41
3.2.3.3	Formation of Larger Rings via Cycloisomerization-Rearrangements	42
3.3	Enyne Domino Processes	44
3.3.1	Domino Enyne Cycloisomerization–Nucleophile Addition Reactions	44
3.3.1.1	Oxygen and Nitrogen Nucleophiles	45
3.3.1.2	Carbon Nucleophiles	54
3.4	Conclusion	61
	References	62

4 Alkyne Metathesis in Organic Synthesis 69

Alois Fürstner

4.1	Introduction	69
4.2	Mechanistic Background and Classical Catalyst Systems	70
4.3	State-of-the-Art Catalysts	75
4.4	Basic Reaction Formats and Substrate Scope	80
4.5	Selected Applications	85
4.5.1	Dehydrohomoancepsenolide	85
4.5.2	Olfactory Macrolides	86
4.5.3	Haliclonacyclamine C	87
4.5.4	Hybridolactone	88
4.5.5	Cruentaren A	88
4.5.6	The Tubulin-Inhibitor WF-1360F	89
4.5.7	Neurymenolide A	91
4.5.8	Leiodermatolide	91
4.5.9	Tulearin C	94
4.5.10	The Antibiotic A26771B	95
4.5.11	Lactimidomycin	96
4.5.12	Citreofuran	97
4.5.13	Polycavernoside	98
4.5.14	Amphidinolide F	99
4.5.15	Spirastrellolide F Methyl Ester	101
4.6	Conclusions	102
	References	108

Part II Catalytic Cycloaddition Reactions 113

5 Alkyne–Azide Reactions 115

Sanne Schoffelen and Morten Meldal

5.1	Introduction	115
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5.2	Reviews on Cu-Catalyzed Azide–Alkyne Cycloaddition	117
5.3	Mechanistic Considerations on the Cu(1) Catalysis	118
5.4	The Substrates for CuAAC	121
5.5	The Environment	124
5.6	Modified 1,2,3-Triazoles and CuAAC Side Reactions	125
5.6.1	Oxidative Couplings of Cu(1)–Triazole Complexes	125
5.6.2	Reactions in the 5-Position of Triazoles	125
5.6.3	Side Reactions due to Substrate Instability	126
5.7	The Catalyst	126
5.7.1	Recent Ligands and their Influence on Cu(1) Catalysis	126
5.7.2	Catalyst Structure–Activity Relationship	128
5.7.3	<i>In Situ</i> Generated CuAAC: Electro-, Photo-, and Self-Induced “Click”	130
5.8	Optimizing Conditions for CuAAC Reactions	131
5.9	CuAAC in Biological Applications	132
5.10	Biocompatibility of the CuAAC Reaction	133
	References	137
6	Catalytic Cycloaddition Reactions	143
	<i>Fiona R. Truscott, Giovanni Maestri, Raphael Rodriguez, and Max Malacria</i>	
6.1	Introduction	143
6.2	(2 + 2) Cycloaddition	143
6.3	(3 + 2) and (2 + 1) Cycloaddition	145
6.4	(4 + 2) Cycloaddition	146
6.5	(5 + 1) and (4 + 1) Cycloadditions	149
6.6	(5 + 2) Cycloaddition	150
6.7	(6 + 2) Cycloaddition	152
6.8	(2 + 2 + 1) Cycloaddition	153
6.9	(2 + 2 + 2) Cycloaddition	155
6.10	(3 + 2 + 1) Cycloaddition	158
6.11	(3 + 2 + 2) Cycloaddition	159
6.12	(4 + 2 + 1) and (4 + 2 + 2) Cycloaddition	160
6.13	(4 + 3 + 2) Cycloaddition	163
6.14	(5 + 2 + 1) and (5 + 1 + 2 + 1) Cycloadditions	163
6.15	(2 + 2 + 1 + 1) and (2 + 2 + 2 + 1) Cycloadditions	164
6.16	(2 + 2 + 2 + 2) Cycloaddition	165
6.17	Conclusions	166
	References	166
Part III	Catalytic Nucleophilic Additions and Substitutions	171
7	Catalytic Conjugate Additions of Alkynes	173
	<i>Naoya Kumagai and Masakatsu Shibasaki</i>	
7.1	Introduction	173
7.2	Metal Alkynylides as Nucleophiles	173

7.2.1	Conjugate Addition of Metal Alkynylides	173
7.2.1.1	Conjugate Addition of Metal Alkynylides to <i>s</i> -cis α,β -Enones	173
7.2.1.2	Conjugate Addition of Metal Alkynylides with a Catalytic Promoter	176
7.2.1.3	Conjugate Addition of Metal Alkynylides with Stoichiometric Promoters	177
7.2.2	Enantioselective Conjugate Addition of Metal Alkynylides	178
7.2.2.1	Use of a Stoichiometric Amount of Chiral Sources	178
7.2.2.2	Catalytic Enantioselective Conjugate Addition of Metal Alkynylides	180
7.3	Direct Use of Terminal Alkynes as Pronucleophiles	182
7.3.1	Direct Catalytic Conjugate Addition of Terminal Alkynes	182
7.3.1.1	Introduction	182
7.3.1.2	Addition to Vinyl Ketones and Acrylates	182
7.3.1.3	Addition to β -Substituted α,β -Enones	184
7.3.2	Enantioselective Direct Catalytic Conjugate Addition of Terminal Alkynes	188
7.4	Summary and Conclusions	196
	References	196
8	Catalytic Enantioselective Addition of Terminal Alkynes to Carbonyls	201
	<i>Barry M. Trost and Mark J. Bartlett</i>	
8.1	Introduction	201
8.2	Metallation of Terminal Alkynes: Formation of Alkynyl Nucleophiles	203
8.2.1	Deprotonation of Terminal Alkynes	203
8.2.2	Oxidative Insertion and Ligand Exchange: Formal Metallation of Terminal Alkynes	205
8.3	Ligand-Catalyzed Alkyne Additions with Stoichiometric Quantities of Metal	207
8.3.1	Addition of Alkynylzinc Nucleophiles to Aldehydes, Ketones, and Imines	207
8.3.2	Titanium-Catalyzed Alkynylation of Aldehydes and Ketones	217
8.3.3	Asymmetric Boron-Catalyzed Alkyne Additions to Aldehydes	222
8.4	Alkyne Additions with Catalytic Amounts of Metal	222
8.4.1	Asymmetric Alkyne Additions to Aldehydes and Ketones Catalyzed by Zinc Salts	222
8.4.2	Indium-Catalyzed Alkyne Additions to Aldehydes	224
8.4.3	Chromium-Catalyzed Alkynylation of Aldehydes with Haloacetylenes	225
8.4.4	Copper-Catalyzed Alkynylation of Aldehydes and Trifluoromethyl Ketones	227
8.4.5	Palladium-Catalyzed Additions to α,β -Unsaturated Carbonyls and Trifluoropyruvate	229

8.4.6	Enantioselective Ruthenium-Catalyzed Alkynylation of Aldehydes	230
8.4.7	Rhodium-Catalyzed Alkynylation of α -Ketoesters	231
8.5	Concluding Remarks	232
	References	233
9	Catalytic Nucleophilic Addition of Alkynes to Imines: The A³ (Aldehyde–Alkyne–Amine) Coupling	239
	<i>Nick Uhlig, Woo-Jin Yoo, Liang Zhao, and Chao-Jun Li</i>	
9.1	A ³ Couplings Involving Primary Amines	239
9.2	A ³ Couplings Involving Secondary Amines	242
9.3	Alkyne Additions with Reusable Catalysts	244
9.4	Asymmetric Alkyne Addition Reactions	246
9.4.1	Asymmetric A ³ -Type Couplings with Primary Amines	246
9.4.2	Asymmetric A ³ -Type Couplings with Secondary Amines	250
9.5	Alkyne Additions to Imines in Tandem Reactions	251
9.5.1	A ³ Coupling with Tandem Cycloisomerizations Involving the Alkyne Triple Bond	252
9.5.2	Tandem Processes Involving Other Transformations of the Alkyne Triple Bond	257
9.5.3	Tandem Processes Involving Decarboxylations	259
9.5.4	Tandem Processes Involving Both the Amine and the Alkyne	260
9.6	Conclusion	262
	References	263
10	The Sonogashira Reaction	269
	<i>Rafael Chinchilla and Carmen Nájera</i>	
10.1	Introduction	269
10.2	Palladium–Phosphorous Catalysts	270
10.2.1	Unsupported Palladium–Phosphorous Catalysts	270
10.2.1.1	Copper-Cocatalyzed Reactions	270
10.2.1.2	Copper-Free Reactions	273
10.2.2	Supported Palladium–Phosphorous Catalysts	274
10.2.2.1	Copper-Cocatalyzed Reactions	274
10.2.2.2	Copper-Free Reactions	275
10.3	Palladium–Nitrogen Catalysts	276
10.3.1	Unsupported Palladium–Nitrogen Catalysts	276
10.3.2	Supported Palladium–Nitrogen Catalysts	277
10.4	N-Heterocyclic Carbene (NHC)-Palladium Catalysts	278
10.4.1	Unsupported NHC-Palladium Catalysts	278
10.4.2	Supported NHC-Palladium Catalysts	279
10.5	Palladacycles as Catalysts	280
10.5.1	Unsupported Palladacycles as Catalysts	280
10.5.2	Supported Palladacycles as Catalysts	281
10.6	Ligand-Free Palladium Salts as Catalysts	282

10.6.1	Unsupported Ligand-Free Palladium Salts as Catalysts	282
10.6.2	Supported Ligand-Free Palladium Salts as Catalysts	283
10.7	Palladium Nanoparticles as Catalysts	283
10.7.1	Unimmobilized Palladium Nanoparticles as Catalysts	283
10.7.2	Immobilized Palladium Nanoparticles as Catalysts	284
10.7.2.1	Copper-Cocatalyzed Reactions	285
10.7.2.2	Copper-Free Reactions	285
10.8	Non-Palladium-Based Catalysts	287
10.9	Mechanistic Considerations	289
10.10	Summary and Conclusions	291
	References	291

Part IV Other Reactions 299

11	Catalytic Dimerization of Alkynes	301
	<i>Sergio E. García-Garrido</i>	
11.1	Introduction	301
11.2	Dimerization of Alkynes Catalyzed by Iron, Ruthenium, and Osmium Complexes	302
11.2.1	Homo-Coupling of Terminal Alkynes	302
11.2.2	Cross-Dimerization of Alkynes	310
11.3	Dimerization of Alkynes Catalyzed by Cobalt, Rhodium, and Iridium Complexes	311
11.3.1	Homo-Coupling of Terminal Alkynes	311
11.3.2	Cross-Dimerization of Alkynes	315
11.4	Dimerization of Alkynes Catalyzed by Nickel, Palladium, and Platinum Complexes	317
11.4.1	Homo-Coupling of Terminal Alkynes	317
11.4.2	Cross-Dimerization of Alkynes	320
11.5	Dimerization of Alkynes Catalyzed by Group 3, Lanthanide, and Actinide Complexes	322
11.6	Dimerization of Alkynes Catalyzed by Titanium, Zirconium, and Hafnium Complexes	325
11.7	Dimerization of Alkynes Catalyzed by Other Compounds	326
11.8	Summary and Conclusions	327
	Acknowledgments	327
	References	328
12	The Oxidative Dimerization of Acetylenes and Related Reactions: Synthesis and Applications of Conjugated 1,3-Diynes	335
	<i>Jean-Philip Lumb</i>	
12.1	Introduction	335
12.2	Syntheses of Conjugated 1,3-Diynes	336
12.3	Scope and Limitation of the Alkyne Dimerization Reaction	338
12.3.1	Choice of Copper Salt	338

12.3.2	Choice of Solvent	339
12.3.3	Substituents on the Alkyne and Basic Additives	339
12.3.4	Additional Metals	340
12.4	Scope and Limitation of Copper-Catalyzed Hetero-Coupling Reactions	340
12.5	The Cadiot–Chodkiewicz Reaction	341
12.6	Palladium-Catalyzed Acetylenic Coupling Reactions	343
12.7	Alternative Methods for the Synthesis of Diynes	344
12.8	Mechanism of Alkyne Homo-Coupling Reactions	344
12.9	Mechanism of Alkyne Hetero-Coupling Reactions	347
12.10	Utility of 1,3-Diynes in the Synthesis of Natural Products	349
12.11	Synthetic Utility of Conjugated 1,3-Diynes	351
12.12	Utility of 1,3-Diynes in Materials Science	355
12.13	Conclusion	359
	References	359
13	The Alkyne Zipper Reaction in Asymmetric Synthesis	365
	<i>Kenneth Avocetien, Yu Li, and George A. O'Doherty</i>	
13.1	Introduction	365
13.2	Mechanism of KNH_2/NH_3 Isomerization	366
13.3	Mechanism of KAPA Isomerization	368
13.4	Applications in Natural Products	370
13.4.1	<i>Galacto</i> -Sugar γ -Lactones	371
13.4.2	<i>Galacto</i> -Sugar δ -Lactones	371
13.4.3	(–)-Apicularen A	371
13.4.4	Milbemycin β_3	373
13.4.5	Cryptocaryols A and B	373
13.4.6	Tricolozin A	374
13.4.7	Elenic Acid	376
13.4.8	Daumone	377
13.4.9	(+)-Broussonetine G	379
13.4.10	Cladospolides A, B, C, <i>iso</i> -Cladospolide B and (<i>ent</i>)-Cladospolide D	379
13.4.11	Shingolipid Analogs	384
13.4.12	Irciniasulfonic Acids	386
13.4.13	Clathculins A and B	386
13.4.14	Cephalosporolide H	387
13.4.15	(+)-Aspicilin	389
13.4.16	Merremoside D	389
13.4.17	Aspergillide B	392
13.5	Conclusion	393
	References	393

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Preface

Alkyne is a basic functionality with “relatively low thermodynamic reactivities” in the classical text of organic chemistry. These classical alkyne reactions often require stoichiometric reagents, which result in low efficiency in chemical syntheses, and “harsh” reaction conditions that cannot tolerate the presence of the various “more reactive functional groups”. The pursuit of synthetic efficiency combined with the recent emphasis of “future sustainability and Green Chemistry,” and the pressing desire for new chemical tools in synthetic biology inspire chemists to uncover new reactions that are catalytic in nature (rather than consuming stoichiometric reagents), occur under ambient conditions (including milder temperature and aqueous media), can tolerate various functional groups, and render “dial-up” reactivity when needed. Alkynes provide the most ideal candidate for such features. While being relatively inert under “classical” conditions, alkynes can be readily “activated” selectively, in the presence of other functional groups and under mild conditions, via transition-metal catalysis through either selective alkyne carbon-carbon triple bond reactions or terminal alkyne C-H bond reactions. Such a unique reactivity allow alkynes to be embedded and be “dialed-up” whenever needed. For the past few decades, modern alkyne chemistry has thus been developed rapidly to feature these characteristics. These developments further focus on atom-economic transformations where minimal or no theoretical by-products are formed. Furthermore, many of these catalytic transformations are orthogonal to biological conditions. These modern catalytic alkyne reactions are much more resource-, time-, and manpower-efficient, and provide an alternative to classical stoichiometric alkyne chemistry. This book comprises a collection of contributions from leading experts and covers various modern catalytic reactions of alkynes. We hope that this focused book will be very helpful not only to students and researchers in chemistry but also to those in material and biological studies and will provide them with tools and opportunities unavailable with classical alkyne chemistry.

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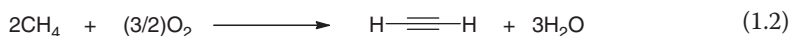
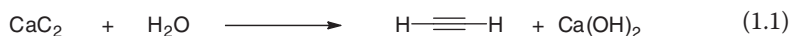
Introduction

Chao-Jun Li and Barry M. Trost

1.1

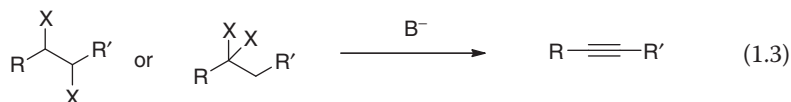
History of Alkynes

Alkyne is one of the fundamental functional groups that established the foundation of organic chemistry [1]. The smallest member of this family, acetylene, was first discovered in 1836 by Edmund Davy [2]. It was rediscovered and named “acetylene” by Marcellin Berthelot in 1860 by passing vapors of organic compounds through a red-hot tube or sparking electricity through a mixture of cyanogen and hydrogen gas. Acetylene is a moderately common chemical in the universe [3], often in the atmosphere of gas giants. In 1862, Friedrich Wöhler discovered the generation of acetylene from the hydrolysis of calcium carbide (Equation 1.1). Acetylene produced by this reaction was the main source of organic chemicals in the coal-based chemical industry era. When petroleum replaced coal as the chief source of carbon in the 1950s, partial combustion of methane (Equation 1.2) or formation as a side product of hydrocarbon cracking became the prevalent industrial manufacturing processes for acetylene. The next member of the family, propyne, is also mainly prepared by the thermal cracking of hydrocarbons. The first naturally occurring acetylic compound, dehydromatricaria ester (**1**), was isolated in 1826 [4] from an *Artemisia* species. Well over 1000 alkyne-containing natural products have been isolated since then, among which many are polyynes-containing natural products isolated from plants, fungi, bacteria, marine sponges, and corals [5].



Dehydromatricaria ester (**1**)

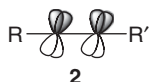
The higher members of alkynes are generally derived from the smaller homologs via alkyne homologation processes of the terminal alkynes (see Equation 1.8, below), while some alkynes are generated through elimination reactions with organic halides under basic conditions (Equation 1.3) [1]. A search in Sci Finder shows that >70 000 terminal alkynes and >10 000 internal alkynes are now commercially available from various sources.



1.2

Structure and Properties of Alkynes

Alkynes contain a tripe bond, composed of a σ -covalent bond formed from two sp -hybridized carbons and two π -bonds resulted from the overlapping of two orthogonal unhybridized p -orbitals on each carbon (2) [1]. Consequently, alkynes are generally rod-like. Cyclic alkynes are less common with benzyne as an important reactive intermediate in organic chemistry [6]. Acetylene is linear and intrinsically unstable under pressure due to its high compressibility as well as its propensity to undergo exothermic self addition reactions. Consequently, acetylene itself can explode violently at high pressure and the safe limit for acetylene is 103 kPa. Thus, acetylene is generally shipped in acetone or dimethyl formamide (DMF) solutions or contained in a gas cylinder with porous filling [7]. Acetylene has been used as a burning fuel and for illumination purposes in the late nineteenth century and early twentieth century [8]. In modern times, alkynes have found a wide range of applications ranging from organic electronic materials, metal-organic frame works (MOF), pharmaceutical agents, and others [9]. The linearity of the alkyne creates strain when an alkyne is part of a ring [10]. In spite of this fact, cyclopentyne, cyclohexyne, and cycloheptyne can be generated at least fleetingly, their existence being confirmed by *in situ* trapping, notably by 1,3-dipolar cycloadditions [11]. Cyclooctyne is still highly strained but has sufficient stability to be isolated and used in click chemistry to study biological processes [12].

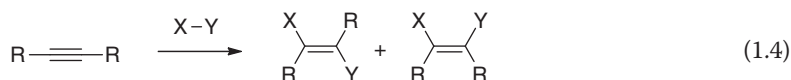


1.3

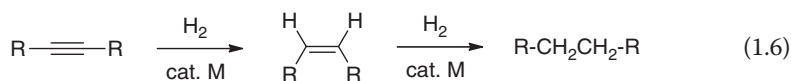
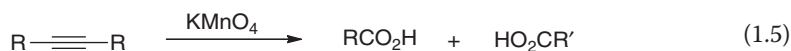
Classical Reactions of Alkynes

The higher degree of unsaturation of alkynes compared to alkenes increases their reactivity toward addition to both alkenes and alkynes. In particular, virtually all additions of HX and RX to alkynes are exothermic. Consequently, these

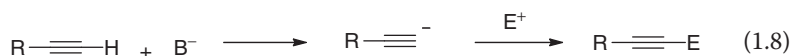
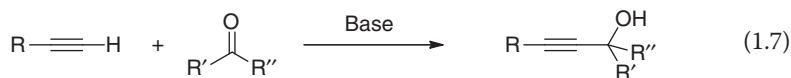
stoichiometric addition reactions have been the basis of most reactions in the classical alkyne chemistry (Equation 1.4) [1]. These classical alkyne addition reactions include the additions of hydrogen, halogens, water, hydrogen halides, halohydrins, hydroborations, and others. With a stoichiometric amount of a strong oxidizing reagent such as KMnO_4 , the addition may be followed by C–C cleavage to give the corresponding acids (Equation 1.5). Less reactive reagents can also be added through the use of a transition-metal catalyst. The unique electronic character of alkynes wherein their HOMO–LUMO gap is rather small makes them especially effective as coordinators to transition metals. Thus, they function as chemoselective functional groups for catalytic transformations. For example, catalytic addition of dihydrogen to alkynes can proceed to either alkenes or alkanes depending on the choice of the catalysts (Equation 1.6) [13]. Further, the hydroalumination [14], hydrosilylation [15], hydrostannylation [16], as well as carboalumination [17] represent important modern advances of the alkyne addition reactions.



X–Y: halogens, HX, HOH, HOCl, HBR_2 , etc.



A second class of reactions pertains to terminal alkynes. Due to the increased s-character, the alkynyl C–H bonds ($\text{p}K_{\text{a}} = 25$) are much more acidic than the corresponding alkenyl C–H bonds ($\text{p}K_{\text{a}} = 43$) and alkyl C–H bonds ($\text{p}K_{\text{a}} > 50$) [18]. Thus, base-promoted additions of terminal alkynes to carbonyl compounds can occur under different basic conditions, a process discovered over a century ago (Equation 1.7). Treatment of terminal alkynes with bases such as lithium amide, butyllithium, or Grignard or zinc reagents generates metal acetylides stoichiometrically, which can then react with different carbon-based electrophiles to produce various higher alkyne homologs in the classical synthetic chemistry (Equation 1.8) [1]. Such processes can be catalyzed to permit deprotonation with much weaker bases as in the coupling with aryl halides under Pd/Cu catalysis (Sonogashira reaction, see Equation 1.13).

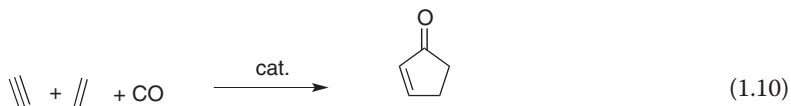


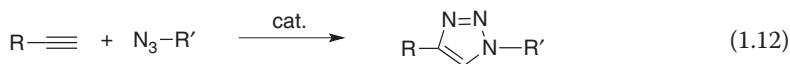
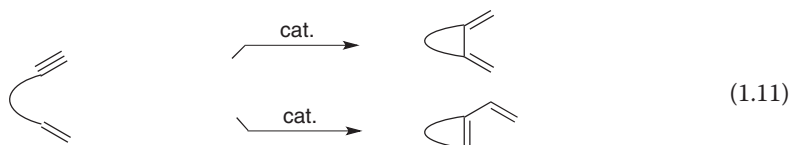
1.4

Modern Reactions

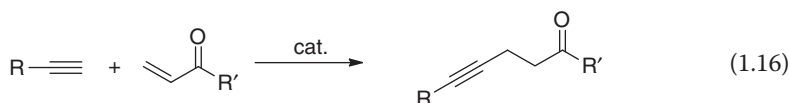
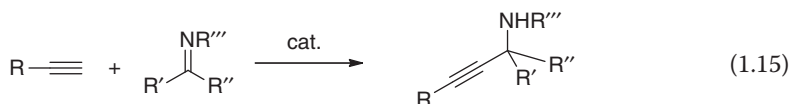
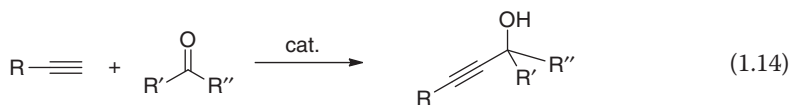
Although the classical stoichiometric addition reactions, alkyne cleavage reactions, and homologation reactions have established the foundation of alkyne chemistry, a rebirth of interest derives from recent concerns regarding societal and ecological sustainability under the mantra of Green Chemistry [19], which emphasizes chemical transformations that are more atom economic [20] and chemoselective, thereby minimizing the use of protecting groups [21]. Furthermore, rapid developments in the field of chemical biology demand chemical transformations that are orthogonal to biological conditions and functionalities in bioorganisms and which can work efficiently under both *in vitro* and *in vivo* biological conditions [22]. Alkynes, being both good π -donors and π -acceptors for transition metals as well as being energy rich, can be effectively activated by a catalyst thereby lowering the energy barrier to proceed to the more stable products while being unreactive toward various biological elements. At the same time, they can be chemoselectively activated in the presence of most typical functional groups (e.g., hydroxyl and carbonyl groups as well as alkenes) and in protic solvents including water [23]. Such triggered reactivities are orthogonal to the classical reactivities and can be tuned to target specific desired reaction sites while maintaining tolerance toward other functionalities through the discrete choice of catalyst, which will greatly simplify the syntheses of complex compounds and allow direct modifications of biomolecules in their native states and ambient environment. Modern developments, in view of atom economy, can be represented by three major classes: (i) catalytic cyclization reactions, (ii) catalytic homologations of terminal alkynes, and (iii) catalytic isomerization reactions of alkyne.

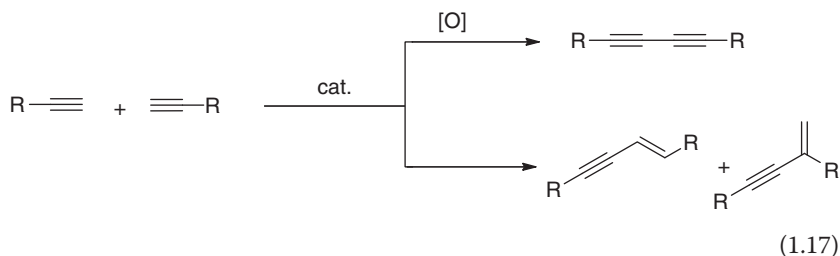
Although alkyne oligomerization was known at a high temperature since the late nineteenth century [2], various cyclization reactions of alkynes catalyzed by transition metals are among the most important developments in modern alkyne chemistry. The most well-known examples include the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions (Equation 1.9) [24], the Pauson–Khand-type reaction of alkyne–alkene–carbon monoxide (Equation 1.10) [25], the enyne cyclization reactions (Equation 1.11) [26], and the 1,3-dipolar cycloaddition such as that with azides (the archetypical Click reaction) (Equation 1.12) [27].



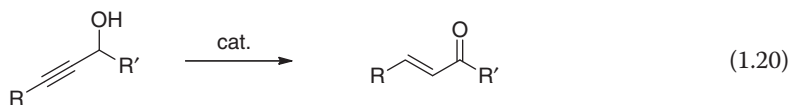
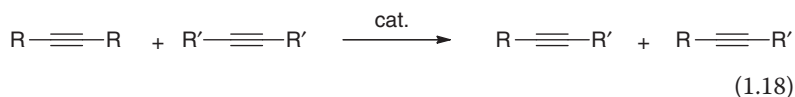


The second major class of modern alkyne reactions is the catalytic transformation of terminal alkyne C–H bonds. Although homologation of terminal alkynes through the reactions of metal acetylides with organic halides is a classical alkyne reaction, such a reaction cannot be applied to aryl and vinyl halides due to their inert nature in nucleophilic substitution reactions. The development of catalytic coupling of terminal alkynes with aryl and vinyl halides (the Sonogashira reaction) has overcome this classical challenge and opened up a new reactivity mode in alkyne homologation (Equation 1.13) [28]. Complimentary to the classical Favorskii reaction (Equation 1.7), the modern development of catalytic direct addition of terminal alkynes to aldehydes provides great opportunities in generating optically active propargyl alcohols (Equation 1.14) [29]. The catalytic direct additions of terminal alkynes to imines (and derivatives) (Equation 1.15) [30] and conjugate addition to unsaturated carbonyl compounds (Equation 1.16) [31] represent other major achievements in modern alkyne reactions. On the other hand, the catalytic oxidative dimerization (Glaser–Hay coupling) [32] and simple alkyne dimerization (Equation 1.17) [33] which date from the late 1800s have become increasingly important in modern synthetic chemistry.





Two additional processes that have much unrealized potential in synthetic chemistry are the alkyne disproportionation (metathesis) and the alkyne redox isomerization reactions. Like the alkene metathesis, the catalytic alkyne–alkyne metathesis reaction retains all functionalities by switching the groups attached to the alkynes (Equation 1.18) [34]. Another unique atom-economic reaction of alkynes that is currently under-utilized but will have a great potential for future development is the “alkyne-zipper reaction” (Equation 1.19) [35]. Such reactions shift readily accessible internal alkyne triple bond to terminal positions for further homologations. A different type of “retaining functionality is found in the redox isomerization of propargyl alcohols to generate conjugated ketones” (Equation 1.20) [36].



1.5

Conclusion

With the recent emphasis on sustainability and the ever increasing needs in synthetic efficiency, alkynes provide a truly unique functionality that is orthogonal to other functional groups, biological conditions, and ambient environment, yet can be selectively triggered to occur in a specific reaction mode with the absence of protecting groups or anhydrous conditions. Such reactions will have great potential to simplify synthetic chemistry and will find wide applications in chemical biology and organic materials. This book, comprising experts on related subjects, provides an overview of developments of modern alkyne reactions. Due to the limit of space, many other important developments in modern alkyne chemistry

such as various catalytic conversions of alkyne triple bonds [37] and alkyne polymerizations [38] have not been covered in this book.

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Part I

Catalytic Isomerization of Alkynes

