ANGEWANDTE CHEMIE © WILEY-VCH

Carl Glaser was born in 1841 in Kirchheimbolanden in the Rheinpfalz. He started his chemistry studies at the University of Erlangen, where he rapidly developed an interest in the synthesis of tar dyes, which were in high industrial demand at that time. In 1864, he moved to the University of Tübingen to work with Adolph Strecker and, in the same year, obtained his doctoral degree for his experimental investigations of new derivatives of naphthalene. Upon recommendation by Strecker, a former teacher of August Kekulé, Glaser joined the group of Kekulé and participated for several years in the ongoing intensive research on benzene and its derivatives—a field that had just been started with the benzene theory. In 1867, Glaser moved with Kekulé to the Rheinische Friedrich-Wilhelms-Universität Bonn, where he continued his investigations on derivatives of cinnamic acid that he had already started in Tübingen. During this work, he discovered the oxidative coupling of copper alkynylbenzene, the reaction later named after him and which is at the center of this review. Following his habilitation in 1869, Glaser joined the Badische Anilin- & Soda-Fabrik (BASF) and became responsible first for the development, then for the direction of the technical synthesis of alizarine. During his highly successful industrial career, he was in charge of the development of technical production processes for a large series of dyes, including the milestone implementation of a technical synthesis of indigo. He joined the executive board of directors of the company in 1883 and, after his retirement from this position in 1895, was elected to the control board ("Aufsichtsrat"), which he chaired from 1912 to 1920. He died in 1935. (For a more detailed description of the scientific career of Carl Glaser see: R. Anschütz, C. Müller, *Angewandte Chemie* **1927**, *40*, 273 – 300.)

Acetylenic Coupling: A Powerful Tool in Molecular Construction

Peter Siemsen, Robert C. Livingston, and François Diederich*

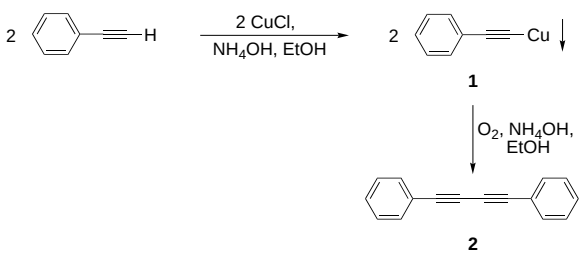
Acetylenic coupling is currently experiencing some of the most intensive study of its long history. Rigid and sterically undemanding di- and oligoacetylene moieties, which are frequently encountered in natural products, are finding increasing application as key structural elements in synthetic receptors for molecular recognition. Interesting electronic and optical properties of extensively π-conjugated systems have spurred research into new linear oligoalkynes and acetylenic carbon allotropes. The synthetic challenges associated with these efforts have in turn spawned new methods. While classical Glaser conditions are still frequently used for homocoupling, the demand for increasingly selective heterocoupling conditions has provided the focus of research over the past decades. These efforts have undoubtedly been hampered by a relatively poor mechanistic understanding of these processes. More recently, palladium-catalyzed coupling methods have led to improvements in both the selectivity and reliability of acetylenic homo- and heterocouplings and paved the way for their application to ever more complicated systems. The variety of acetylenic coupling protocols, the current mechanistic understanding, and their application in natural product and targeted synthesis are discussed comprehensively for the first time in this review, with an emphasis on the most recently developed methods, and their application to the synthesis of complex macromolecular structures.

Keywords: alkynes · C–C coupling · synthetic methods

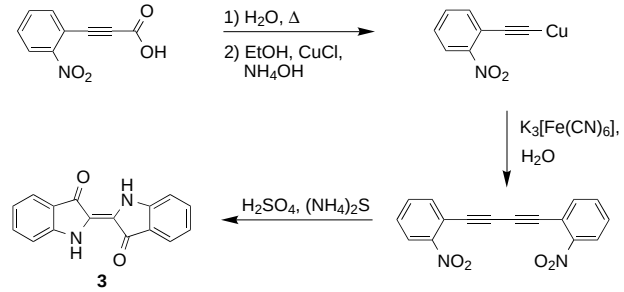
1. Introduction—A Brief Historical Survey

The history of acetylenic coupling began at the University of Bonn with the 1869 observation of Carl Glaser[1] (see p. 2632) that copper(I) phenylacetylide (**1**) exposed to air underwent smooth oxidative dimerization to diphenyldiacetylene (**2**; Scheme 1).

Later the Glaser coupling was extended to various organic compounds possessing a terminal ethynyl group. Baeyer[2a] provided an early demonstration of the synthetic utility of the method in his 1882 synthesis of indigo (**3**; Scheme 2). With the use of potassium ferricyanide as the oxidizing agent,[2b] he simultaneously showed that dioxygen itself is not necessary for the coupling process.



Scheme 1. The first acetylenic coupling described by Glaser.[1]



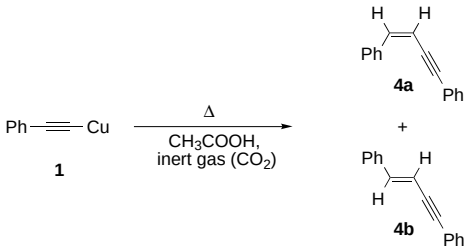
Scheme 2. Indigo synthesis by Baeyer.[2a]

In 1885, Baeyer employed this modified procedure in the preparation of diacetylene and its diiodo and dicarboxylic acid derivatives.[3] Tetraacetylene dicarboxylic acid (HOOC–(C≡C)$_4$–COOH) was also likely generated in these experiments.[3c] In the following years other groups showed that oxidizing agents besides dioxygen[4] or potassium ferricyanide[5] can be employed, including cupric salts,[6–11] potas-

[*] Prof. Dr. F. Diederich, Dipl.-Chem. P. Siemsen, Dr. R. C. Livingston
Laboratorium für Organische Chemie
ETH-Zentrum
Universitätstrasse 16, 8092 Zürich (Switzerland)
Fax: (+41) 1-632-1109
E-mail: diederich@org.chem.ethz.ch

 © WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2000 1433-7851/00/3915-2633 $ 17.50+.50/0

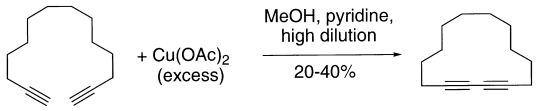
sium permanganate,[12] and peroxides.[13, 14] In 1905, Straus observed that heating copper(I) phenylacetylide (**1**) in acetic acid under inert gas (CO_2) gave linear enynes **4a** and **4b** instead of the expected diphenyldiacetylene (**2**; Scheme 3).[15] Now termed the Straus coupling, this reaction has since become quite generalized,[16, 17] and has even found industrial application in the production of vinylacetylene and divinylacetylene.[18, 19]



Scheme 3. The Straus coupling reaction.[15]

The original Glaser reaction failed to see broad application because of the apparent need to isolate the potentially explosive copper acetylide before oxidation, which was often tedious in view of the poor crystallization properties of most copper salts.[20] Particularly important then was the observation of Zalkind and Aizikovich in 1937 that tertiary alkynols coupled directly in the presence of copper(I) chloride and ammonium chloride to afford the corresponding diacetylene dicarbinols.[21] This method initially failed in the case of primary and secondary alkynols.[22] In 1955, however, Reppe succeeded in the preparation of diprimary and disecondary alkadiynediols by treating the mixture of primary or secondary alkynol, CuCl, and NH_4Cl more intensively with air or dioxygen.[23] Addition of copper(II) acetate was also found to accelerate the reaction, which indicated participation of copper(II) ions in the coupling process. The possibility of forming the copper(I) acetylide in situ paved the way for intensive investigations of the factors influencing the oxidative coupling of various substituted acetylenes,[5, 12, 13, 23–31] which ultimately led to improved convenience and scope of the reaction, and to industrial applications.

A further milestone in the evolution of oxidative acetylenic coupling was the copper(II) salt oxidation in methanolic pyridine introduced in 1956 by Eglinton and Galbraith[32] (Scheme 4). This method proved of great value within a few years of its discovery, and led to the preparation of a variety of new unsaturated macrocycles,[33] including the pioneering annulene syntheses of Sondheimer and co-workers.[34]



Scheme 4. Acetylenic coupling with copper(II) salts in pyridine according to Eglinton and Galbraith.[32]

Another important modification was reported in 1962 by Hay, who performed oxidative acetylenic couplings with O_2 in the presence of catalytic amounts of the bidentate ligand *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and copper(I) chloride (Scheme 5).[35] Enhanced solubility of the reactive species is one major advantage provided by this

P. Siemsen

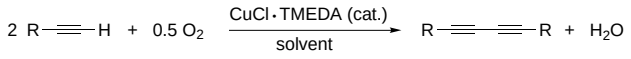
R. Livingston

F. Diederich

Peter Siemsen, born in 1970 in Braunschweig, studied chemistry at the Technische Universität Carolo-Wilhelmina in Braunschweig, from where he received his diploma in 1995. He then joined the group of Prof. F. Diederich as a PhD student, where he is currently doing research on monodisperse platinum-bridged oligomers of tetraethynylethenes.

Robert Livingston, born in 1969 in Seattle, Washington, received his B.A. degree in chemistry from Williams College in 1992. His studies continued in the laboratory of Professor B. M. Trost at Stanford University, where he investigated the redox isomerization of propargylic alcohols. Since receiving his doctorate in 1999 he has conducted research in the group of Professor F. Diederich on the synthesis and polymerization of diethynylallenes.

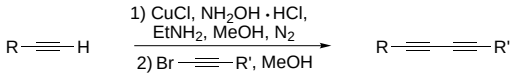
François Diederich, born in 1952 in the Grand Duchy of Luxembourg, received his Ph.D. degree in 1979 from the University of Heidelberg. Following postdoctoral studies at the University of California at Los Angeles (UCLA) from 1979–1981, he was a research associate at the Max-Planck-Institut für medizinische Forschung in Heidelberg. After his Habilitation in 1985, he joined the faculty of the Department of Chemistry and Biochemistry at UCLA where became full professor in 1989. Since April 1992, he has been a professor of organic chemistry at ETH Zürich. He is a member of the Editorial Board for Angewandte Chemie.



Scheme 5. Hay coupling conditions.[35]

method. For example, whereas the copper(I) acetylide of propargyl alcohol precipitates from solutions of copper(I)–pyridine complexes, the use of the soluble copper(I)–TMEDA complex allows the coupling reaction to proceed satisfactorily.

Parallel to the evolution of oxidative homocoupling processes, Chodkiewicz and Cadiot[36] reported in 1957 a potent heterocoupling protocol involving terminal alkyne and 1-bromoacetylene partners in the presence of an amine and catalytic amounts of copper(I) salt (Scheme 6).



Scheme 6. Cadiot–Chodkiewicz heterocoupling conditions.[36]

In Chapter 2 of this review, the scope and limitations of the various acetylenic homo- and heterocoupling methods will be discussed. It will become apparent that, despite the introduction of new methods, the variants of the Glaser homocoupling discussed above and the Cadiot–Chodkiewicz heterocoupling remain the most utilized. Chapter 3 summarizes the current mechanistic understanding of these reactions. Chapter 4 provides selected examples illustrating the wide application of acetylenic coupling in natural product synthesis, construction of molecular receptors, and formation of acetylenic all-carbon and carbon-rich matter.

2. Methods for Acetylenic Homo- and Heterocoupling: Scope and Limitations

Several reviews, now quite outdated, have been published on the Glaser and Cadiot–Chodkiewicz coupling reactions.[37–44] In the meantime, a number of new methods for the synthesis of symmetrically and unsymmetrically substituted 1,3-diynes have been described.

2.1. Copper-Catalyzed Oxidative Homocoupling Reactions—The Glaser Reaction and Related Methods

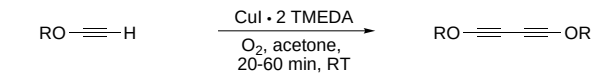
The oxidative coupling of terminal acetylenes has been most extensively investigated. In the original procedure (Scheme 1) a copper(I) acetylide was isolated and subsequently oxidized in air. The method became widely applicable with the finding that the copper(I) derivative, often characterized by poor crystallizability and a tendency to explode in the dry state, can be formed in situ. The influence of various factors, such as the proportion of copper(I) salt, oxidizing agent, pH, time, temperature, solvent, and character of the alkyne, was the subject of numerous investigations. These efforts were reviewed exhaustively by Eglinton and McCrae in 1963[37] and six years later by Cadiot and Chodkiewicz.[39]

The modification by Hay[35] (Scheme 5) presumably represents the most important method for the oxidative coupling to provide linear oligo- and polyacetylenes. In one procedure, the alkyne and catalytic amounts of a copper(I) salt (usually CuCl) are dissolved in the presence of dioxygen in a complexing tertiary amine solvent such as pyridine. More commonly, the coupling is performed in an appropriate solvent such as acetone or *o*-dichlorobenzene using catalytic amounts of the bidentate complexing ligand TMEDA. The latter protocol (O_2, CuCl, TMEDA) is commonly referred to as standard Hay coupling conditions.

By adding a small amount of the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the reaction rate can be accelerated,[43, 45] making it possible to couple even weakly acidic terminal alkynes efficiently. For example, 5-ethynylpyrazole underwent oxidative dimerization under Hay conditions (O_2, CuCl, pyridine) whereas 2-ethynyl-1-methylpyrrole did not, presumably because of the lower acidity of its ethynyl proton.[45] In the presence of catalytic amounts of DBU, however, quantitative dimerization occurred, since the stronger base is more efficient in the deprotonation of the alkyne.

Alkoxyalkynes **5a–f** were found to undergo smooth oxidative dimerization to diynes **6a–f** when a catalyst system consisting of CuI and two equivalents (with regards to CuI) of TMEDA in acetone was used (Table 1).[46] This was attributed to the improved solubility of this catalyst in acetone. Under standard Hay conditions (O_2, CuCl, TMEDA) the conversion was quite inefficient.

Table 1. Preparation of 1,4-dialkoxybuta-1,3-diynes **6a–f** by oxidative coupling.[46]

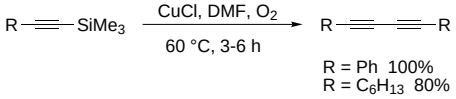


5a	R = *tert*-butyl	**6a**	77 %
5b	R = 1-adamantyl	**6b**	85 %
5c	R = decyl	**6c**	78 %
5d	R = cyclohexyl	**6d**	95 %
5e	R = L-menthyl	**6e**	76 %
5f	R = 2,6-dimethylphenyl	**6f**	65 %

In their investigations of the oxidative dimerization of heterocyclic alkynes, Fritzsche and Hünig[47] found a strong dependency between yield and solvent, and reported the advantageous use of 1,2-dimethoxyethane (DME). Havinga et al.[48] found *o*-dichlorobenzene (ODCB) to be a superior solvent for the oxidative polymerization of 1,8-nonadiyne under Hay conditions (O_2, CuCl, TMEDA) to yield polymers with a molar mass of greater than 20000. Presumably ODCB keeps higher molecular weight oligomers in solution better, thereby ensuring the growth of longer polymers. We observed a similar advantage using this solvent in the oligomerization of platinum-bridged tetraethynylethenes under Hay conditions (Section 4.3). Dichloromethane has been found to be another good solvent for both the oxidant and the polymer formed.[49] In the presence of oxygen-sensitive products or reactants, large excesses of the Hay catalyst (CuCl, TMEDA) have been used to shorten the reaction time.[43, 49]

An interesting procedure, reported by Mori, Hiyama, and co-workers, allows direct coupling of trimethylsilyl-protected

alkynes without previous removal of the protecting groups.[50] A solution of the acetylene is heated together with one equivalent of CuCl in DMF under air or dioxygen to give the coupled product in high yield (Scheme 7). No activator such as fluoride ion was needed to remove the silyl protecting group. This technique allows the efficient dimerization of alkynes which decompose after deprotection, and is also applicable to the synthesis of unsymmetrically substituted diacetylenes (Section 2.2).[51]



Scheme 7. Cu^{I}-promoted oxidative homocoupling of alkynylsilanes.[50]

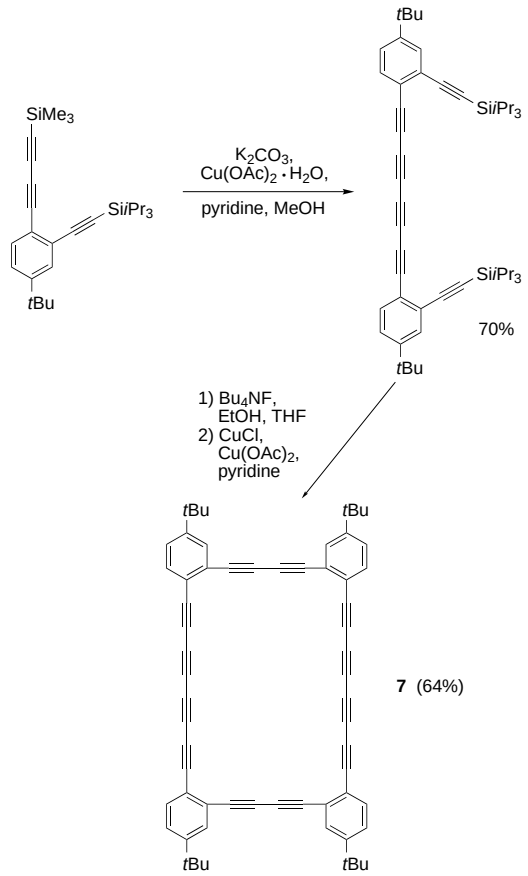
Oxidative coupling reactions are usually the method of choice for the construction of macrocyclic oligoacetylenes containing buta-1,3-diynediyl fragments. In particular the modification by Eglinton and Galbraith (Scheme 4)[32] has been heavily used for this purpose[52] (and less for the construction of linear oligomers[53, 54]). Typically copper(II) acetate is employed, either using pure pyridine as the coordinating solvent, or using cosolvents such as methanol to prevent precipitation of the copper(I) derivatives formed in the course of the reaction.[55] The rate of reaction increases with the concentration of the copper(II) salt.

Several variations of the original Eglinton protocol have been reported, and notably show that pyridine can be substituted entirely. Staab and co-workers used $Cu(OAc)_2$ in pure DMF to form buta-1,3-diynediyl linkages in the key macrocyclization step on the way to benzo-annellated [14]- and [18]annulenes.[56] Berscheid and Vögtle reported high-yielding oxidative cyclodimerizations using $Cu(OAc)_2$ in pure acetonitrile.[57]

A large excess of both CuCl and $Cu(OAc)_2$ in pyridine proved to be highly efficient in intramolecular oxidative dimerizations leading to dehydrobenzo[18]annulenes, as reported by Haley and co-workers.[58a] The same group also used potassium carbonate for the in situ deprotection and coupling of trimethylsilyl-protected alkynes. The application of both methodological advances is illustrated in the synthesis of the dehydrotetrabenzo[32]annulene **7** (Scheme 8).[58b]

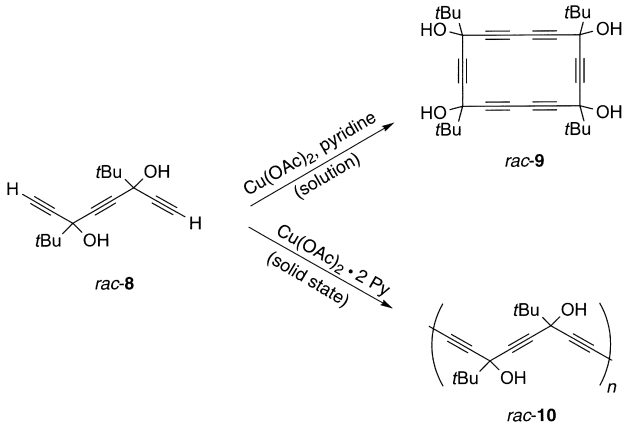
Very recently it was shown that Glaser couplings can be carried out smoothly and in high yield in supercritical carbon dioxide using solid NaOAc instead of amines.[59] Thus, the conversion of phenylacetylene (1 equiv) with $CuCl_2$ (2 equiv) and NaOAc (2 equiv) in supercritical CO_2 in the presence of methanol afforded diphenylbuta-1,3-diyne (**2**) in quantitative yield. Aliphatic alkynes also underwent homocoupling in greater than 90% yield. Control studies showed that the presence of methanol led to large rate enhancements and that reaction rates increased with higher pressures of CO_2.

Oxidative copper-mediated coupling reactions are not limited to homogeneous solutions. Toda and Tokumaru have found them to proceed efficiently and selectively in the solid state.[60] For example, keeping a mixture of powdered copper(I) phenylacetylide (**1**) and $CuCl_2 \cdot 2H_2O$ for 3 h at



Scheme 8. Synthesis of dehydrobenzo[32]annulene **7**.[58b]

room temperature gave diphenylbuta-1,3-diyne (**2**) in 60% yield, whereas the yield of the Glaser reaction in water was only 40%. A remarkable result was observed when the solid-state conditions were applied to the Eglinton procedure. Although the reaction rate was slower in the solid state than in solution, the resulting products differed in some cases. Whereas, for example, the coupling of *rac*-**8** in pyridine (Py) gave the corresponding cyclic dimer *rac*-**9**, the solid-state procedure using the $Cu(OAc)_2 \cdot 2Py$ complex afforded exclusively the linear coupling product *rac*-**10** (Scheme 9). The reaction of optically pure (−)-**8**, however, provided longer



Scheme 9. Oxidative coupling under Eglinton conditions in solution and the solid state.[60]

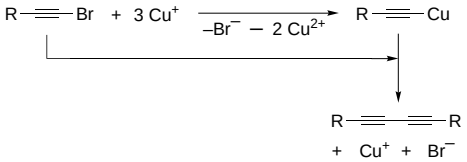
polymers (> 100 monomer units) in solution and only low molecular weight oligomers in the solid state.

In 1995, Baiker and co-workers described another heterogeneous route for the dimerization of phenylacetylene.[61] The coupling was carried out in an autoclave in the presence of sodium hydroxide under enhanced oxygen pressure using Cu-Mg-Al hydrotalcite (a hydroxycarbonate) as the catalyst. This route led, depending on the initial pressure, to yields of diphenylbuta-1,3-diyne (**2**) comparable with those achieved in the conventional Hay synthesis (> 80 %).

2.2. Heterocoupling of Alkynes with 1-Haloalkynes—The Cadiot – Chodkiewicz Reaction and Related Methods

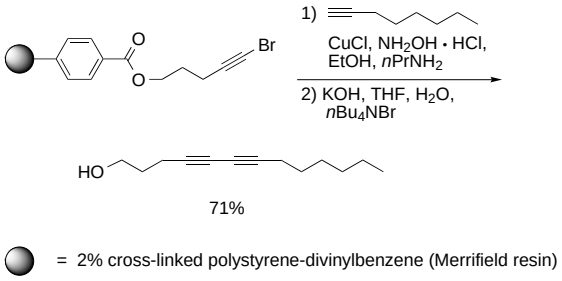
The Glaser reaction and related methods normally give unsatisfactory results for unsymmetrical coupling because of the simultaneous and rather predominant formation of the symmetrical products. Therefore, these techniques have seen little recent application in the synthesis of nonsymmetrical diynes.[62] A solution to this problem, provided by Chodkiewicz and Cadiot,[36] consists of the condensation of terminal alkynes with 1-bromoacetylenes in the presence of a copper(I) salt and a suitable amine (Scheme 6). This method has been used extensively to synthesize a wide range of diacetylenic compounds, and the influence of various factors such as the nature of the base and acetylene, solvent, time, and temperature on the reaction has been investigated in great detail.[37, 39] The method has been applied to the synthesis of numerous aliphatic and aromatic buta-1,3-diynes[63] and tolerates a wide variety of functional groups, including alcohols and polyols,[64] peroxy substituents,[65] quinols,[66] epoxides,[67] amines,[68] acetals,[69] carboxylates,[70] carboxylic esters[71] and amides,[72] disulfides,[73] acetylenic silyl-protecting groups,[74] and even nitroxyl radicals.[75]

Aromatic buta-1,3-diynes[76] are generally obtained in higher yields than their aliphatic counterparts.[39] The terminal alkyne partner for the heterocoupling is particularly suitable if it bears hydrophilic functionality such as hydroxyl, amino, or carboxylate groups.[39] Conjugated alkynes such as buta-1,3-diyne are also suitable as the terminal alkyne component. Apart from bromoalkynes, iodo derivatives[73, 77–79] have also been employed to a minor extent, whereas chloroacetylenes are of little practical importance because of their low reactivity. The former are strongly oxidizing toward copper(I) ions and normally favor self-coupling. This "secondary" Cadiot – Chodkiewicz coupling, often observed with bromoalkynes as well, is considered to proceed by halogen – metal exchange, and can be applied to the synthesis of symmetrical polyacetylenes (Scheme 10).[39]



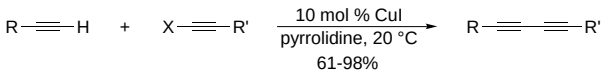
Scheme 10. Halogen – metal exchange and subsequent homocoupling are undesirable side reactions of the Cadiot – Chodkiewicz heterocoupling.[39]

This variant, which occurs primarily as a disturbing side-reaction to the heterocoupling process, can be suppressed by amines and by the use of low concentrations of the copper(I) ion and the haloacetylene.[39, 43] The separate preparation of the copper(I) acetylide proved useful in some cases.[41, 80, 81] Kurth, Schore, and co-workers recently described an interesting polymer-supported technique which inhibits the mutual interaction between haloalkynes and efficiently reduces the self-coupling.[82] The coupling of immobilized chloro- or bromoalkynes with 1-octyne under Cadiot – Chodkiewicz conditions proceeded in high yield and without formation of homocoupled product (Scheme 11), whereas the corresponding conversions in solution gave up to 34 % homocoupled side product.



Scheme 11. Polymer-supported Cadiot – Chodkiewicz heterocoupling efficiently suppresses the self-coupling of the haloacetylene as an undesirable side reaction.[82]

Besides the original Cadiot – Chodkiewicz coupling, which is still important for the synthesis of unsymmetrically substituted di- and polyynes, a number of interesting and complementary variations exist. In 1996, Alami and Ferri reported an efficient copper(I) iodide catalyzed cross-coupling reaction between 1-haloalkynes and terminal alkynes in pyrrolidine (Scheme 12).[83]



X = I, Br

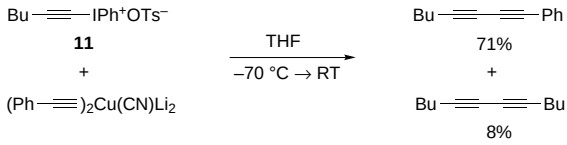
R = C_6H_5, C_5H_{11}, $C_5H_{11}CH(OH)$

R' = CH_2OH, $(CH_2)_2OH$, $(CH_2)_4OH$, $(CH_2)_3Cl$, $(CH_2)_2COOMe$, C_6H_5, C_5H_{11}, CH_2NMe_2

Scheme 12. Copper-catalyzed heterocoupling in pyrrolidine.[83]

Analogous to the Cadiot – Chodkiewicz protocol, they observed low reactivity for the chloro derivatives, whereas the corresponding iodides gave good yields. The reactivity of bromoalkynes could be enhanced by the addition of $[PdCl_2(PPh_3)_2]$ as a cocatalyst. The use of pyrrolidine as the amine solvent gave superior yields and reaction times. Other aliphatic amines gave poor yields, even in the presence of a palladium cocatalyst. The advantages of this procedure are its simplicity and high efficiency, even in the case of acetylenic alcohols, which normally give low yields of cross-coupled product.

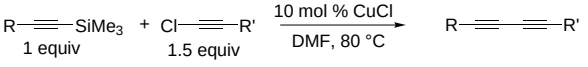
A very mild and efficient cross-coupling of alkynyl(phenyl)-iodonium tosylates such as **11** was described by Kitamura et al.[84] The addition of these tosylates to soluble lithium dialkynylcuprates led to the desired unsymmetrical diacetylenes in good yields and reasonable selectivity with respect to homocoupling (Scheme 13). This mild procedure provides a general alkynylation method for organocopper reagents and is of particular interest for the coupling of highly sensitive alkyne derivatives.



Scheme 13. Cross-coupling of alkynyl(phenyl)iodonium tosylates with alkynylcopper reagents.[84]

In addition to the homocoupling of trimethylsilyl-protected alkynes, Hiyama and co-workers described an analogous heterocoupling of alkynylsilanes and chloroalkynes.[51] The cross-coupling was carried out using catalytic amounts of CuCl and an excess of the haloalkyne in DMF at 80 °C and gave the corresponding unsymmetrically substituted diynes, by silicon to copper exchange, in moderate to high yields (Table 2). Homocoupling of the haloalkynes is clearly suppressed under these conditions and occurs only to a minor extent.

Table 2. Heterocoupling of alkynylsilanes with chloroalkynes.[51]



R	R′	Yield [%][a]
4-MeOC$_6$H$_4$	C$_6$H$_5$	90
4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	97
4-MeCOC$_6$H$_4$	C$_6$H$_5$	69
4-MeCOC$_6$H$_4$	4-MeOC$_6$H$_4$	60
C$_6$H$_5$	4-MeCOC$_6$H$_4$	62
C$_6$H$_5$	4-MeOC$_6$H$_4$	43

[a] GC yield based on the alkynylsilane.

This result is quite remarkable considering that reactions of 1-chloroalkynes with terminal acetylenes often furnish cross-coupled products in poor yields. Since the method can be carried out under neutral conditions without base, it seems to be promising for future applications in modern acetylenic chemistry.

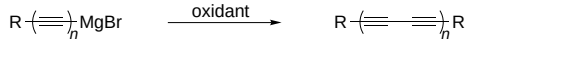
2.3. Coupling Reactions of Alkynyl Grignard Derivatives

Couplings of alkynyl Grignard reagents can be classified as oxidative homocouplings, related to the Glaser coupling, or as nonoxidative heterocouplings with a haloalkyne, analogous to the Cadiot–Chodkiewicz method. These techniques are less widely used than the classical methods, but nevertheless they have led to some significant results in specialized applications.

2.3.1. Oxidative Homocoupling Reactions of Alkynyl Grignard Derivatives

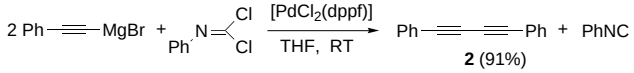
The dimerization of alkynyl Grignard reagents[8, 37–44] in the presence of oxidants such as iodine,[85–87] copper(II) and cobalt salts,[87–90] or nitrobenzene[91] is well known (Table 3), but in view of its limited scope and low tolerance to functional groups, it remains largely of theoretical interest. A small improvement of the limited applicability was reported by Luo and co-workers using 2,3-dichloropropene as the oxidizing agent.[92]

Table 3. Preparation of oligoacetylenes by the oxidative homocoupling of alkynyl Grignard derivatives.



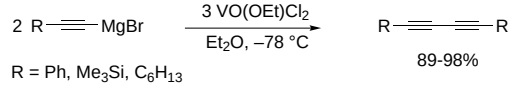
Oligoacetylene	Oxidant	Yield [%]	Ref.
H$_3$C—≡—≡—CH$_3$	C$_6$H$_5$NO$_2$	58	[91]
H$_3$C—(≡—≡)$_2$—CH$_3$	CuCl$_2$	78	[88]
H$_3$C—(≡—≡)$_2$—CH$_3$	I$_2$	66	[87]
C$_4$H$_9$—≡—≡—C$_4$H$_9$	I$_2$, CuCl	70	[89]
C$_6$H$_5$—(≡—≡)$_2$—C$_6$H$_5$	CuCl$_2$	47	[88]
C$_6$H$_5$—≡—≡—C$_6$H$_5$ **2**	CoCl$_2$	42	[88, 89]

The transition metal catalyzed oxidative homocoupling of acetylenic Grignard derivatives has opened up this concept to a larger number of alkyne derivatives. In 1988, Ito et al. described a palladium-catalyzed oxidative coupling reaction of Grignard reagents in the presence of *N*-substituted isocyanide dichlorides (R–N=CCl$_2$) as the reoxidant, which afforded conjugated diynes in high yields (Scheme 14).[93]



Scheme 14. Palladium-catalyzed dimerization of alkynyl Grignard derivatives.[93] dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

Treatment of bis(phenylethynyl)magnesium with iodine in THF in the presence of catalytic amounts of [Pd(acac)$_2$] (acac = acetylacetonate) and PPh$_3$ (4 equiv with respect to the Pd catalyst) also forms diphenylbuta-1,3-diyne (**2**) in 94% yield.[94] Quite recently, Hirao and co-workers reported that the homocoupling of various lithium (Section 2.4) and magnesium acetylides is effectively induced by oxidation with oxovanadium(V) compounds of the type VO(OR)Cl$_2$ under mild conditions (Scheme 15).[95]



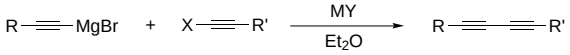
Scheme 15. Oxidative coupling of alkynyl Grignard derivatives in the presence of oxovanadium(v) compounds.[95]

None of these procedures for the oxidative coupling of alkynyl Grignard derivatives has seen widespread application to date.

2.3.2. Heterocoupling of Alkynyl Grignard Derivatives with 1-Haloalkynes

This variant of the Cadiot – Chodkiewicz coupling has been catalyzed by copper(I) and cobalt(II) salts,[37, 39] and was examined in some detail by Weedon and co-workers (Table 4).[89]

Table 4. Heterocoupling of alkynyl Grignard derivatives with 1-haloalkynes.



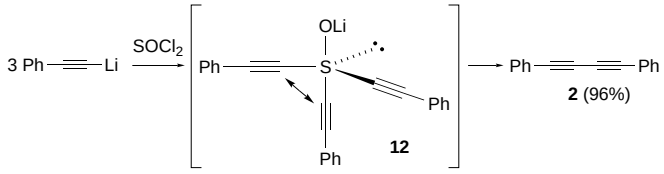
R	R′	X	MY	Yield [%]	Ref.
C_4H_9	C_6H_5	Br	$CoCl_2$	31	[89]
C_6H_5	C_4H_9	I	CuCl	35	[89]
C_6H_5[a]	Cl	Cl	–	33	[96]

[a] $C_6H_5CCMgCl$ was used as the Grignard derivative.

An interesting example was described by Viehe in which dichloroacetylene was coupled with phenylethynylmagnesium chloride to afford the corresponding chlorodiyne in the absence of a catalyst (Table 4).[96] A general problem of the method is homocoupling arising from halogen – magnesium exchange. This lack of selectivity, together with the general disadvantages inherent in the use of Grignard reagents, has hindered the wide use of this cross-coupling protocol in modern organic synthesis.

2.4. Coupling Reactions of Other Organometallic Acetylides

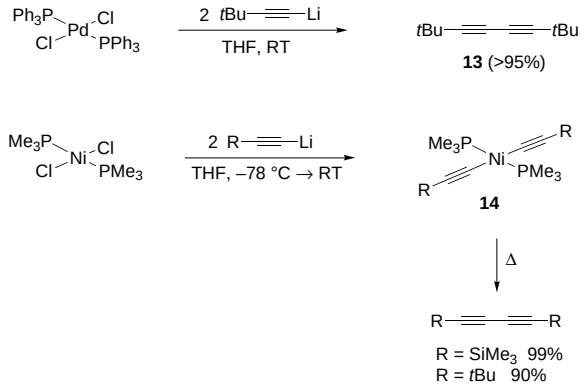
A variety of other organometallic acetylides represent interesting alternatives to the magnesium acetylides discussed in Section 2.3. For early work on oxidative dimerizations of alkali acetylides, the reader is referred to previous review articles.[37, 39] Out of the variety of oxidizing agents employed, thionyl chloride is particularly efficient for the oxidative dimerization of phenyllithium, as described by Oae et al. (Scheme 16).[97] In this conversion, the yield of diphenylbuta-1,3-diyne (**2**) is highest (96%) if the molar ratio of phenylethynyllithium to $SOCl_2$ is 3:1. This finding was explained by the formation of a hypervalent, trigonal-bipyramidal sulfurane intermediate **12** which undergoes reductive elimination



Scheme 16. The homocoupling of phenylethynyllithium in the presence of $SOCl_2$ presumably involves the intermediacy of the hypervalent sulfurane **12**.[97]

through coupling between one equatorial and one axial alkynyl ligand.

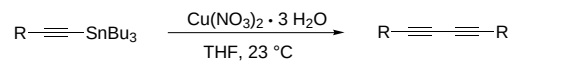
Another strategy for the dimerization of various lithium acetylides involves their addition to nickel or palladium complexes (Scheme 17). Negishi and co-workers found that the reaction of $[PdCl_2(PPh_3)_2]$ with two equivalents of *tert*-butylethynyllithium gave the desired buta-1,3-diyne **13** in greater than 95% yield.[98] Similarly high yields are obtained with nickel complexes.[99, 100] The intermediate *trans*-dialkynylnickel complexes **14a** ($R = SiMe_3$) and **14b** ($R = tBu$) can be isolated and undergo reductive elimination upon heating under argon.



Scheme 17. Homocoupling of alkynyllithium derivatives using palladium[98] and nickel[99, 100] complexes.

Lithium acetylides are often used as precursors for transmetalations which yield alkynyl derivatives that can participate in coupling reactions to provide the corresponding diacetylenes. Among the main group elements, boron,[101, 102] tin,[103] antimony,[104] selenium,[105] and tellurium[106, 107] are well known to provide metalated alkynes which subsequently undergo coupling. Some of these provide potent alternatives to the more established methods. For example, the addition of alkynylstannanes to one equivalent of $Cu(NO_3)_2 \cdot 3H_2O$ or $AgNO_3$ affords the corresponding symmetrical 1,3-diynes in good yields under mild conditions and in short reactions times (10 – 30 min; Table 5).[103] The 85% yield obtained using this procedure for the dimerization of 3-(tetrahydro-2*H*-pyran-2-yloxy)-1-propyne contrasts sharply with the 34% yield obtained under standard Glaser conditions. The Stille-type palladium-catalyzed carbon – carbon bond formation with alkynyltin compounds[108] will be presented later (Section 2.5.2).

Table 5. Formation of 1,3-diynes by a copper(II) nitrate mediated coupling of alkynyltin compounds.[103]

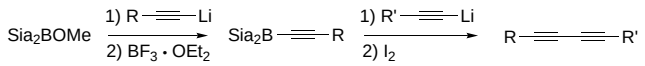


R	Reaction time [min]	Yield [%]
$THPOCH_2$[a]	10	85
C_4H_9	10	60
C_6H_5	30	50
4-MeC_6H_4	10	67

[a] THP = tetrahydro-2*H*-pyran-2-yl.

Oxidation of lithium dialkynyldialkylborates provides an efficient and selective cross-coupling method.[101b, 102] Unsymmetrical lithium dialkynyldialkylborates $Li^+[R''_2B(C{\equiv}CR)(C{\equiv}CR')]^-$ are prepared by the stepwise addition of two different lithium acetylides to dicyclohexyl(methylthio)borane.[101b] The subsequent action of iodine on the borates yields the unsymmetrically substituted conjugated diynes. Symmetrical diacetylenes can also be synthesized by this methodology.[101a] Alternatively, methyl disiamylborinate can be used for the boron-mediated cross-coupling, as demonstrated by Sinclair and Brown (Table 6).[102] This technique provides a procedurally simple alternative to the Cadiot–Chodkiewicz reaction, which requires the preparation of 1-bromoalkynes and is not efficient for the coupling of higher alkynes.

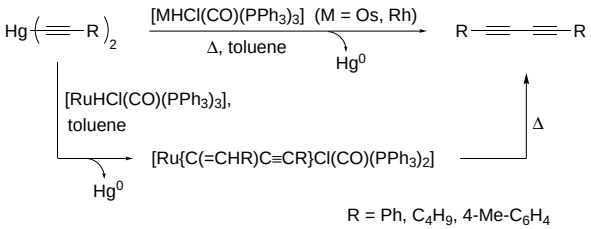
Table 6. Synthesis of conjugated diynes via disiamylalkynylboranes.[102]



R	R′	Yield [%][a]
n-C_6H_{13}	C_2H_5	95 (61)
n-C_6H_{13}	C_6H_{11}	80 (73)
n-C_6H_{13}	C_4H_9	79 (60)
n-C_6H_{13}	C_6H_5	79 (61)

[a] The first number refers to the yield obtained by isolation of the intermediate Sia_2BCCR. The yield in parenthesis refers to a one-pot procedure not involving isolation of any intermediate.

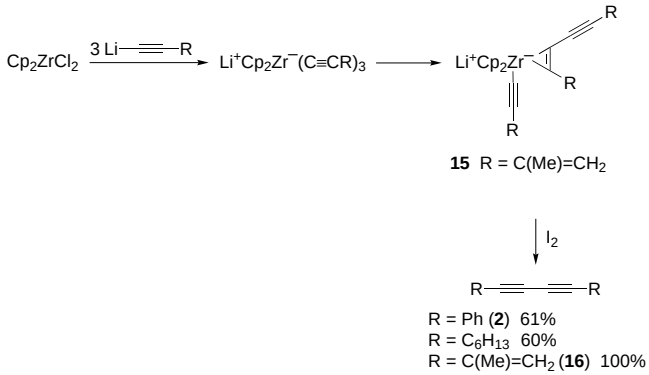
Although bis(alkynyl)mercury compounds emerged early as convenient crystalline derivatives for the characterization of terminal alkynes,[109] their deployment as alkynyl-transfer reagents started relatively late, and has not been extensively studied. Hill and co-workers noted in the course of transalkynylation experiments with bis(alkynyl)mercury compounds that certain platinum group metal complexes catalyze the elimination of mercury under mild conditions to provide buta-1,3-diynes (Scheme 18).[110]



Scheme 18. Catalytic demercuration of bis(alkynyl)mercurials to provide buta-1,3-diynes.[110]

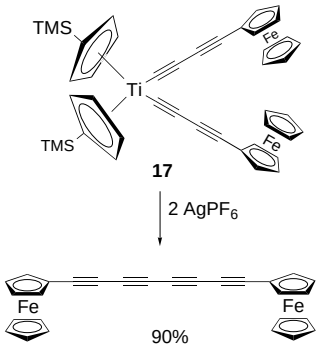
Other transition metals are also known to form alkynyl complexes possessing interesting coupling properties. As early as 1969, Tsutsumi and co-workers reported the formation of diphenylbuta-1,3-diyne in moderate to good yield by treatment of lithium phenylethynylnickel carbonylate ($Li[PhCCNi(CO)_4]$), prepared from PhCCLi and $[Ni(CO)_4]$, with iodine or bromine.[111]

The 1,2-migration reaction of alkynylzirconocenes, described by Negishi and co-workers,[112] represents an efficient carbon–carbon bond formation process which gives symmetrically substituted 1,3-diynes in good to excellent yields. Thus, reaction of zirconocene **15**, formed by treating Cp_2ZrCl_2 with three equivalents of the corresponding lithium acetylide, with iodine (2 equiv) produced buta-1,3-diyne **16** in almost quantitative yield (Scheme 19).



Scheme 19. Buta-1,3-diynes by 1,2-migration reaction of alkynylzirconocenes.[112]

The oxidation of alkynyltitanium compounds generally does not provide diacetylenes in reasonable yields.[113] Two remarkable exceptions were reported quite recently by Hayashi et al.[114] and by Lang and co-workers[115] using titanocenebis(metallocenylacetylide) complexes (metallocenyl = ferrocenyl or ruthenocenyl). The former authors found that complexes such as **17** are readily oxidized with two equivalents of $AgPF_6$ or electrochemically to yield cleanly the acetylenic coupling product (Scheme 20). The electrochemical studies suggested that the reaction is induced by initial oxidation of the metallocenyl units followed by reductive coupling of the two titanocene-bound alkynyl units.



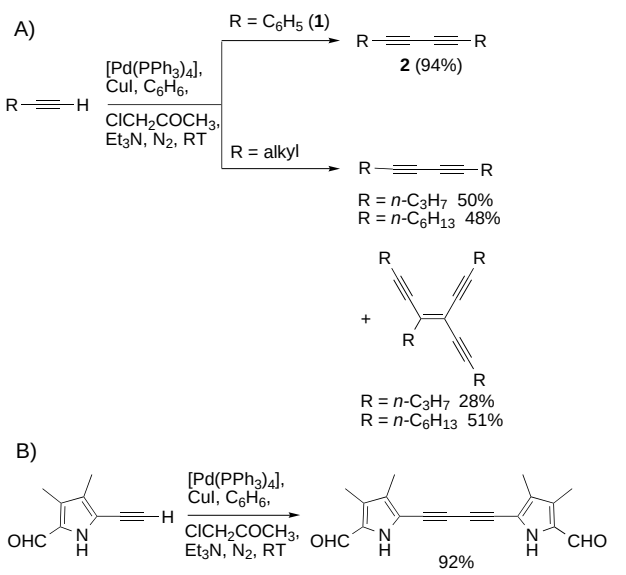
Scheme 20. Reductive coupling induced by metallocene oxidation.[114]

2.5. Palladium-Catalyzed Coupling Reactions of Alkynes and Alkynylstannanes

2.5.1. Palladium-Catalyzed Couplings of Terminal Alkynes

The discovery of palladium-catalyzed coupling reactions more than 30 years ago[116] has initiated explosive growth in the field of organometallic chemistry. An early observation was the formation of symmetric diynes, via dialkynylpalla-

dium intermediates, during couplings between terminal alkynes and aryl or vinyl halides.[117a] In 1985, Rossi et al. optimized this process as a homocoupling method for terminal acetylenes.[117b] Diaryl- and dialkylbuta-1,3-diynes were obtained in moderate to good yields using chloroacetone as the oxidant and a mixture of $[Pd(PPh_3)_4]$ and CuI as the catalyst together with triethylamine (Scheme 21). Whereas aryl-substituted alkynes react exclusively to give the corresponding

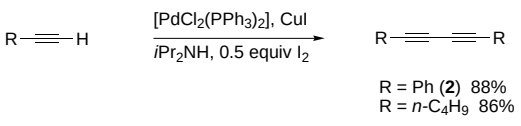


Scheme 21. A) Pd-catalyzed oxidative coupling of terminal alkynes[117b] and B) application to the oxidative dimerization of an alkynylpyrrole.[118]

diynes, aliphatic acetylenes also form 4-alkynylhexa-1,5-diyn-3-enes under these conditions (Scheme 21 A). The efficiency of this method has been underlined quite recently by Kim and co-workers, who reported the oxidative dimerization of an alkynylpyrrole in a notable 92% yield (Scheme 21 B).[118] Consequently, it may represent a good alternative to the Glaser reaction for couplings in nonpolar organic solutions.

A variant of this procedure was described by Kundu et al.[119] These authors used a mixture of $[PdCl_2(PPh_3)_2]$ and CuI as the catalyst in the presence of diisopropylamine while either 4-iodo-2-nitro-resorcinol or dimethyl sulfoxide served as the oxidant. It was found that the reaction proceeds in the absence of CuI, whereas the absence of the palladium catalyst almost completely suppressed the coupling process. Using the same catalyst system but with I_2 as the oxidant proved superior for the homocoupling of aliphatic and aromatic alkynes, as was recently described by Liu and Burton (Scheme 22).[120] A similar system was applied by Kijima and co-workers to the polycondensation of acetylene to yield carbyne fragments (-[C≡C]$_n$-).[121]

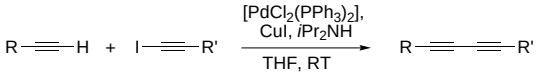
Acetylenic heterocouplings using palladium catalysis are also known. Precedence for the use of 1-haloalkynes in



Scheme 22. Convenient Pd-catalyzed oxidative coupling of both aliphatic and aromatic terminal alkynes.[120]

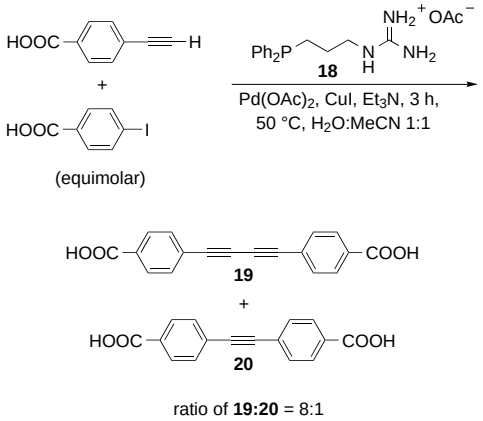
palladium-catalyzed reactions was established by Suzuki and co-workers.[122] In 1991, Wityak and Chan realized a mild and efficient palladium- and copper-mediated coupling of 1-alkynes with 1-iodoalkynes (Table 7).[123] Yields were good to excellent, without any detectable amounts of homocoupling products, even when dioxygen was not rigorously excluded.

Table 7. Pd^0-catalyzed heterocoupling in homogeneous solution.[123]



R	R′	Yield [%]
Ph	$HOCH_2$	79
C_7H_{15}	$HOCH_2$	73
$HOCH_2$	Ph	54
Me_3Si	Ph	91

The design of water-soluble catalytic systems is currently of great interest, since they offer an opportunity for simple and complete product separation from the active catalyst, which is still one of the greatest drawbacks of homogeneous catalysis using transition metals. While studying the reaction between 4-iodobenzoic acid and *p*-carboxyphenylacetylene under aqueous Heck conditions, Dibowski and Schmidtchen found that the conversion in a mixture of acetonitrile and water (1:1) in the presence of the strongly basic guanidinium phosphane ligand **18** provided mainly homocoupled product **19** and only minor amounts of heterocoupled **20** (Scheme 23).[124]

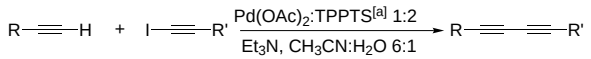


Scheme 23. Pd-catalyzed homocoupling in aqueous solution is preferred under specific conditions over the Heck cross-coupling.[124]

Amatore et al. reported in 1995 an acetylenic cross-coupling reaction with a water-soluble palladium catalyst prepared in situ from palladium(II) acetate and sulfonated triphenylphosphane $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (TPPTS; Table 8).[125] This method works without any copper(I) promoter and is well adapted for the synthesis of unsymmetrically substituted diynes from alkynyl iodides and terminal alkynes.

There have also been a few applications of phase-transfer catalysis in the presence of Pd(0) to the synthesis of 1,3-diynes by acetylenic homocoupling.[126, 127] The use of heterogeneous catalysts is a further strategy to avoid separation problems.

Table 8. Pd-catalyzed cross-coupling in aqueous solution.[125]



R	R′	Yield [%]
$HOC(CH_3)_2$	$CH_3(CH_2)_3$	60
$HOC(CH_3)_2$	Me_3Si	57
$CH_3(CH_2)_4CHOH$	Me_3Si	43
$CH_3(CH_2)_4CHOH$	$H_2NC(C_2H_5)_2$	65

[a] TPPTS = $P(C_6H_4$-m-$SO_3Na)_3$.

Strauss and co-workers reported the homocoupling of phenylacetylene in 71 % yield using palladium on porous glass tubing.[128] This heterogenous catalyst system obviates the use of potentially air- and temperature-sensitive phosphane ligands.[129]

2.5.2. Palladium-Catalyzed Coupling of Alkynylstannanes

The palladium-catalyzed cross-coupling of organostannanes with organohalides or triflates, originally described by Stille and Groh,[130] provides a powerful method for carbon–carbon bond formation.[131] During the total syntheses of the manumycin antibiotics alisamycin[132] and limocrocin,[133] Taylor and co-workers found that the Pd-catalyzed homocoupling of vinylstannanes proceeded smoothly and in high yield under dioxygen or air.[108] This method can also be transferred to alkynylstannanes, as the authors demonstrated with the dimerization of phenylethynylstannane to give diphenylbuta-1,3-diyne (**2**) in 89 % yield (5 mol % $Pd(OAc)_2$, Me_2SO, O_2, RT).

2.6. Other Transition Metal Mediated Alkyne-Coupling Processes

Other transition metals have been applied to acetylenic couplings; however, none of these reactions has gained wide applicability so far. Only one example of a platinum-catalyzed acetylenic coupling has been reported. While investigating carbonylations of alkynyl iodides using a $[PtCl_2(PPh_3)_2]/Et_3N$ system, Watanabe and co-workers observed that 1-iodo-1-octyne underwent sp–sp homocoupling to yield hexadeca-7,9-diyne in 59 % yield.[134]

Takai et al. reported the reductive dimerization of 1-iodo- and 1-chloro-1-alkynes in the presence of two equivalents of chromium(II) chloride.[135] Thus, phenylethynyliodide gives diphenylbuta-1,3-diyne (**2**) in 66 % yield. The reaction is assumed to proceed via intermediate alkynylchromium(III) and dialkynylchromium(IV) compounds, with the latter undergoing reductive elimination to yield homocoupled products.

Conjugated diynes can also be obtained by decarbonylation of the corresponding dialkynylketones using stoichiometric amounts of $[RhCl(PPh_3)_3]$ in boiling xylene, presumably through the intermediacy of dialkynylrhodium complexes.[136] This method affords symmetrical and unsymmetrical diacetylenes, although yields are decent only if the dialkynylketone bears aromatic substituents. Thus, 1,5-diphenylpenta-1,4-diyn-3-one affords **2** in 78 % yield. A rhodium vinylidene complex has been observed to catalyze the disproportionation of phenylacetylene to give diphenylbuta-1,3-diyne (**2**) and styrene.[137, 138]

Takahashi et al. described an intramolecular zirconocene-mediated acetylenic coupling. Treatment of aryl-substituted bis(alkynyl)silanes with $[ZrCp_2Et_2]$ and subsequent addition of two equivalents of iodine provided symmetric diynes in good yields.[139] Thus, **2** was obtained in 95 % yield in the conversion of $(Ph{-}C{\equiv}C)_2SiPh_2$.

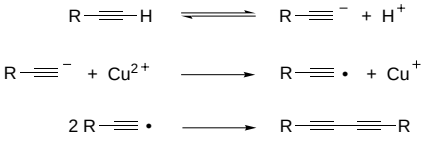
Acetylenic coupling reactions have also been observed within the coordination sphere of some organometallic clusters with the formed buta-1,3-diyne remaining bound to the metal centers.[140–142] Although of considerable mechanistic interest, these reactions have not yet found preparative use.

3. Mechanistic investigations

There have been surprisingly few mechanistic investigations of alkyne couplings, given their wide applicability in synthesis, and the potential for improved conditions that a more complete mechanistic understanding could provide. The classical oxidative alkyne couplings have been the most extensively studied, yet their exact mechanism remains unknown, and the existence of several hypotheses regarding the oxidation state and structure of the postulated intermediary copper acetylides has generated considerable discussion. Here we present an overview of the published investigations and proposed mechanisms for the most commonly employed copper- and palladium-catalyzed couplings.

3.1. Oxidative Couplings

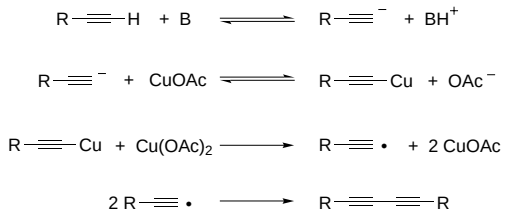
The earliest mechanistic proposals postulated the formation of acetylenic radicals which would then recombine to afford the corresponding diynes. An early kinetic investigation by Klebansky et al. demonstrated that copper(II) ions served as the direct oxidizing agent.[143] They also noted that the rate of coupling was faster in basic media and for more acidic terminal alkynes. In light of these findings, the homolytic bond cleavage proposed earlier by Zalkind and Fundyler[144] was discarded in favor of a heterolytic cleavage followed by the transfer of a single electron to the copper(II) salt (Scheme 24).



Scheme 24. Early proposal for the mechanism of the oxidative acetylenic coupling.[144]

This radical mechanism evolved further with the study of Clifford and Waters in 1963 which showed that copper(I) ions were required for the coupling using $Cu(OAc)_2$ in pyridine in the absence of O_2.[145] They proposed the formation of

copper(I) acetylides which were rapidly oxidized by the transfer of a single electron to copper(II) through an acetate ligand bridge. Decomposition of the resultant copper(II) acetylide and recombination of the free radicals would give the coupled products (Scheme 25).

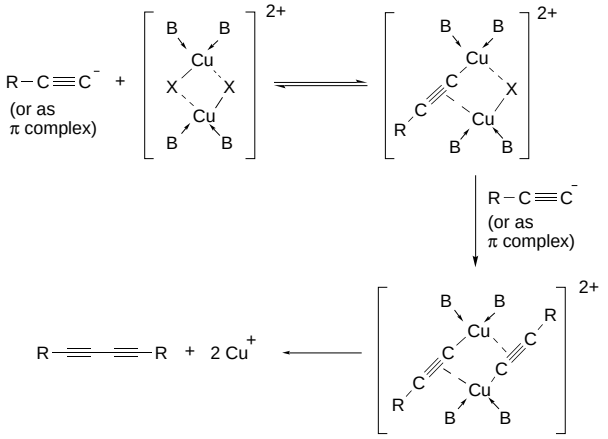


Scheme 25. Mechanism proposed for the oxidative coupling using $Cu(OAc)_2$ in pyridine in the absence of O_2.[145] The coordinating pyridine molecules are omitted.

In the following year, Bohlmann et al. published a landmark study on the rate of dimerization as influenced by the electronic nature of conjugated acetylenes.[146] They found that more acidic acetylenes underwent more rapid dimerization under alkaline conditions, which was consistent with the results of Klebansky et al. However, under acidic conditions (pH 3), an inverse relationship was observed, and the addition of a copper(I) salt became necessary. These observations were explained on the basis of the formation of π complexes between the Cu^I ions and the triple bond, which would activate the alkyne toward deprotonation (Scheme 26). This complexation would be expected to be weaker for the diffuse π systems of polyconjugated substrates, which indeed react more slowly. Klebansky et al. had previously hinted at a similar activation while Clifford and Waters invoked the reversible formation of nonreactive copper–π complexes in a competing nonproductive equilibrium to explain the observed dependence of the reaction rate on the alkyne concentration in their system.

Scheme 26. Acetylene activation by π-complex formation postulated by Bohlmann et al.[146]

Bohlmann et al. also called into question the idea of free radical intermediates, noting that mixtures of electronically different alkynes give predominantly the homocoupled products, whereas no such selectivity would be expected of free radicals. On the basis of the observed second-order dependence of the coupling rate on alkyne concentration, he proposed an alternative dinuclear copper(II) acetylide complex which would collapse directly to the coupled product (Scheme 27). Such an intermediate also rationalized the first-order dependence of the rate on the substrate concentration observed during intramolecular coupling to generate cyclic diynes. Most subsequent mechanistic proposals have discarded free radical intermediates in favor of some variant of this dimeric copper acetylide.[147, 148] Other groups have, however,



Scheme 27. Dimeric copper acetylides were first proposed by Bohlmann et al. as intermediates in the oxidative acetylenic coupling.[146] B = N ligand, for example, pyridine; X = Cl^-, OAc^-.

observed primarily monomeric species under different conditions.[149]

Studies by Fedenok et al. largely confirmed these results. They found that the oxidative coupling rate constant for a range of *para*-substituted phenylacetylenes correlated quantitatively with their Hammett σ constants;[150] that is, reactivity increases with the acidity of the ethynyl proton. The low experimentally determined activation energy of 21 kcal mol^{-1} provided an argument against radical mechanisms and in favor of the simultaneous oxidation and C–C bond formation proposed by Bohlmann et al. However, they found that copper(I) ions played no role in the reaction under their buffered conditions (Et_3N, HOAc, pyridine), and therefore proposed the formation and dimerization of Cu^{II} rather than Cu^I–π complexes.[151]

Later, the same group examined the catalytic coupling in the presence of dioxygen and found that the same mechanism was operative.[152] In buffered alkaline solution (Et_3N, HOAc, pyridine), both the reaction rate and the intensity of the ESR signal for Cu^{II} ions reached saturation above a limiting dioxygen pressure, which provided additional evidence that all the copper was present in the divalent state, with Cu^I only serving as an intermediate electron carrier. The function of dioxygen amounts to the oxidation of Cu^I and regeneration of Cu^{II} ions.

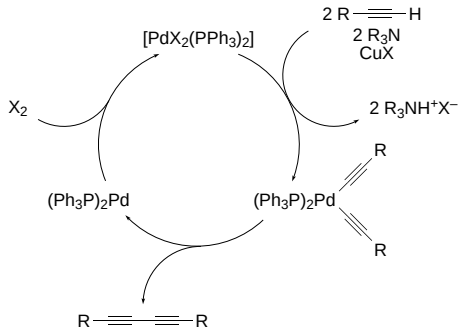
For the catalytic coupling in nonbuffered pyridine, however, they found that reoxidation of Cu^I by dioxygen was significantly slower, and that copper(I) ions were indeed involved in the reaction.[153] While the reaction started slowly, an autocatalytic effect was eventually observed, and this induction period disappeared upon addition of copper(I) chloride. They found that mixtures of copper(I) and copper(II) chloride in the absence of dioxygen in pyridine gave no coupling products unless strong base was added. The use of copper(II) ions, prepared by air oxidation of CuCl, allowed for coupling without the need of additional base. Thus some indeterminate copper(II) salt generated by dioxygen and copper(I) chloride, which the authors dubbed the "oxygen-containing part" of the copper solution, seems to act as the base during the catalytic oxidative coupling in pyridine. Fedenok et al. also noted a complex dependence of the rate

and order of the reaction on the alkyne and copper(I) chloride concentration.[153b]

Temkin and co-workers examined the kinetics of acetylene dimerization in aqueous solutions containing copper(I) and copper(II) chlorides in addition to various background electrolytes (MCl, $M = NH_4^+$, Li^+, Na^+, K^+) to ensure constant activity coefficients of all ions involved.[154] As for many reactions involving copper salts, the presence of other ions in solution had a strong effect on the reaction rate, and even the reaction path. This effect was linked to the activity of the chloride ions, which in turn affects the relative availability of Cu^I and Cu^{II} ions. The authors proposed the involvement of three copper ions (two Cu^I and one Cu^{II}) per alkyne unit in the rate-limiting stage of the oxidative dimerization.[154a] The existence of such higher order complexes has recently been demonstrated by X-ray crystallography in the solid state,[155] where an ethynyl residue was found to undergo π coordination with two Cu^I ions and to form acetylide-type bonds with two other Cu^I centers.

Clearly, the current understanding of the admittedly complex mechanism of copper-mediated oxidative acetylenic coupling remains unsatisfactory. The studies summarized above document that the mechanism is highly dependent on the experimental setup, which makes it difficult to compare the outcome of various kinetic investigations conducted under different conditions. It can be concluded that the mechanism proposed 36 years ago by Bohlmann et al. (Scheme 27) still provides the most reasonable and most accepted picture.

There have been no rigorous mechanistic investigations of the corresponding palladium-catalyzed oxidative coupling procedure. Common to all proposed mechanisms is the formation of an intermediate dialkynylpalladium(II) species and subsequent reductive elimination to generate Pd^0 and the coupled product.[156] The catalytic cycle proposed for oxidative dimerization in the presence of iodine is representative (Scheme 28).[120]

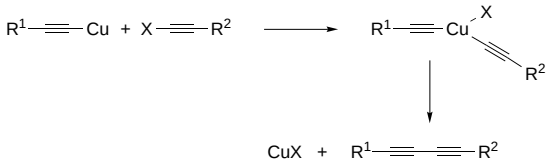


Scheme 28. Mechanism for the palladium-catalyed oxidative homocoupling of terminal alkynes.[120]

The dialkynylpalladium intermediate could conceivably be formed by direct oxidative insertion into the alkyne, ligand displacement by an acetylide anion, or by transmetalation from copper(I) acetylides. The dramatically lower reaction rates in the absence of copper(I) suggest that formation of copper(I) acetylides or alkyne activation towards deprotonation by π complexation to Cu^I ions (Scheme 26) are important processes in the catalytic cycle.[156]

3.2. Nonoxidative Heterocouplings

There have been surprisingly few mechanistic examinations of the copper-catalyzed heterocoupling of alkynes and haloalkynes. This may be due largely to the rapid reaction rates observed for the commonly employed bromoalkynes, which make classical kinetic studies difficult, although some attempts to examine the reaction using the less reactive chloroalkynes have been made.[39] It has been assumed that coupling proceeds through copper(I) acetylides that are formed through one of the mechanisms described above (Section 3.1). Subsequent oxidative addition to the alkynyl halide to generate an intermediate copper(III) species has been proposed (Scheme 29).[39] The fact that similar couplings have been observed for alkynylmagnesium halides, which cannot achieve higher oxidation states, suggests that nucleophilic addition may be a viable alternative.[96]



Scheme 29. Mechanism proposed for the Cadiot–Chodkiewicz heterocoupling.[39]

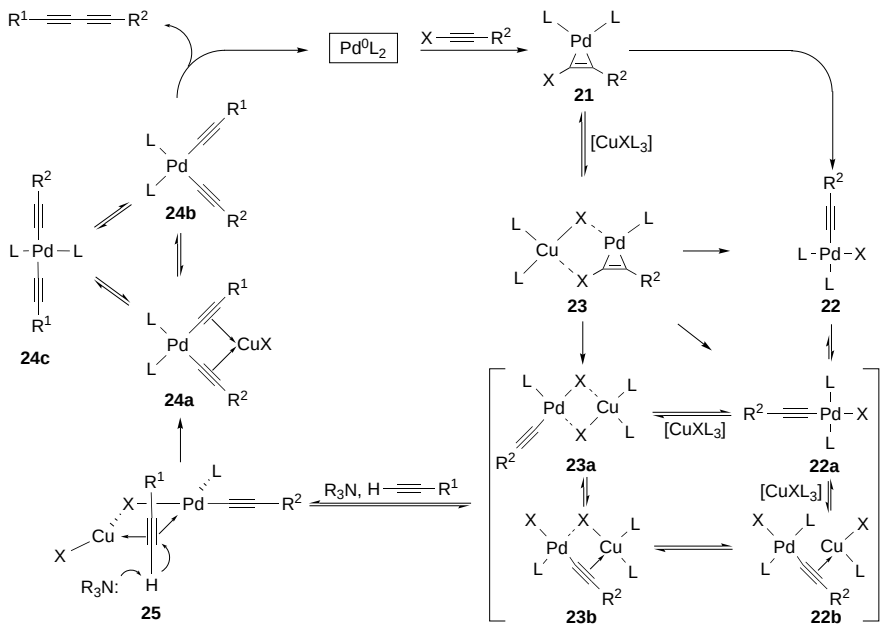
The mechanism of the palladium-catalyzed version was examined by Bugamin et al.[157] and more recently by Cai and Vasella in conjunction with the development of a binomial synthesis of acetylenic oligosaccharides (Section 4.3).[158] ^1H and ^{31}P NMR investigations in the latter study revealed that haloalkynes underwent oxidative addition to Pd(0) via the η^2-palladium complex **21** (Scheme 30). Dramatic acceleration of the rearrangement of **21** to **22** by copper(I) ions suggested the intermediacy of the bimetallic complex **23**. Formation of the dialkynylpalladium complex **24** could proceed through transmetalation of the copper(I) acetylide, for which no evidence was seen in NMR studies, or via complex **25**.

Amatore et al. proposed an alternative mechanism, which involved transmetalation of two alkynylpalladium species, for the formation of the dialkynylpalladium complex **24** in the catalytic cycle (Scheme 31).[125]

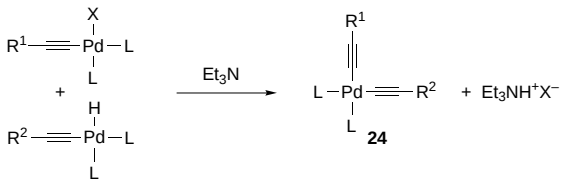
Overall, it becomes apparent that much remains to be understood about the mechanisms of both the oxidative and nonoxidative alkyne coupling processes. Although apparently highly challenging, the search for an improved mechanistic understanding could prove quite rewarding, and provide fertile ground for new method development.

4. Applications of Acetylene Couplings

The far-reaching synthetic applicability of acetylenic coupling methods is impressively demonstrated in various fields of chemistry, such as natural product synthesis, polymer chemistry, and supramolecular chemistry.[159] Because of the size of the subject, it is neither possible nor desirable to give a



Scheme 30. Mechanism proposed by Cai and Vasella for the palladium-catalyzed cross-coupling of alkynes with 1-haloalkynes.[158]



Scheme 31. Transmetalation mechanism proposed by Amatore et al. for the formation of the dialkynylpalladium complex in the palladium-catalyzed cross-coupling of alkynes with 1-haloalkynes.[125]

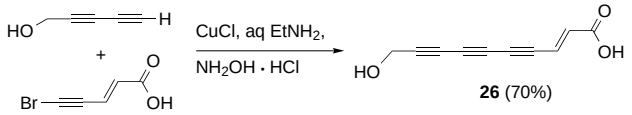
complete survey of every work involving this preparative method. Thus, this section presents only an excerpt with the aim of showing the synthetic utility of alkyne–alkyne coupling reactions, which penetrate the whole of modern chemistry. Besides natural product synthesis, we focus on the field of supramolecular chemistry, where couplings of acetylenes have proven a potent strategy for assembling complex, highly preorganized structures from relatively simple building blocks.

4.1. Synthesis of Natural Products and Analogues

Natural product synthesis was the first domain to employ oxidative coupling reactions of alkynes.[2] In the 1950s, Glaser-type reactions were used in the syntheses of a variety of naturally occurring di- and polyacetylenes.[160] A real breakthrough occurred with the invention of the Cadiot–Chodkiewicz coupling method, which provided more efficient access to unsymmetrically substituted diacetylenes.

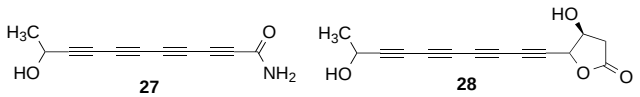
Compounds containing chains of conjugated triple bonds represent a fascinating group of natural products. They show wide distribution in higher plants, from which most natural acetylenes have been isolated,[161] but have also been found in fungi[162] and bacteria.[163] Although a number of excellent reviews have appeared,[31, 160, 164–167] the isolation and synthesis of numerous new polyacetylenic natural products with remarkably diverse functionalization patterns makes an update valuable. Many of these compounds possess interesting biological properties, such as antibacterial,[163, 168] antifungal,[163, 169] pesticidal,[72b, 170] and antitumor activity.[170, 171] For aspects related to biosynthesis and biological activity of polyacetylenic natural products, the reader is referred to the excellent reviews of Bohlmann[167] and BuLock,[165] and to the more recent review by Hansen and Boll.[172]

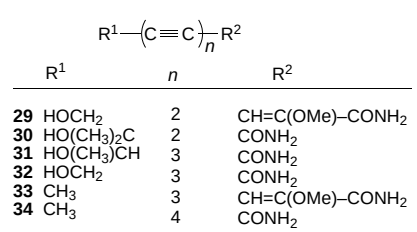
Quite often extreme instability prevents isolation or even spectroscopic investigation of natural polyacetylenes. In such cases their preparation in the laboratory is necessary for structural and biological activity studies. Before the introduction of NMR techniques, Jones and co-workers succeeded in the structure determination of various fungal polyacetylenes, such as triynoic acid **26**, which was prepared by a Cadiot–Chodkiewicz coupling reaction (Scheme 32).[173]



Scheme 32. Synthesis of *trans*-10-hydroxy-dec-2-en-4,6,8-triyn-1-oic acid (**26**).[173]

Sometimes, high instability even prevents total synthesis. In this case, chemical synthesis of more stable analogues is required to elucidate, by spectral comparison, the structure of the natural polyacetylenes. Thus, Bäuerle, Anke, and coworkers found the acetylenic metabolites tetraynamide **27** and tetrayne lactone **28** from the fungus *Mycena viridimarginata* too unstable for isolation and full characterization (Scheme 33).[174] Therefore, they synthesized stable analogues



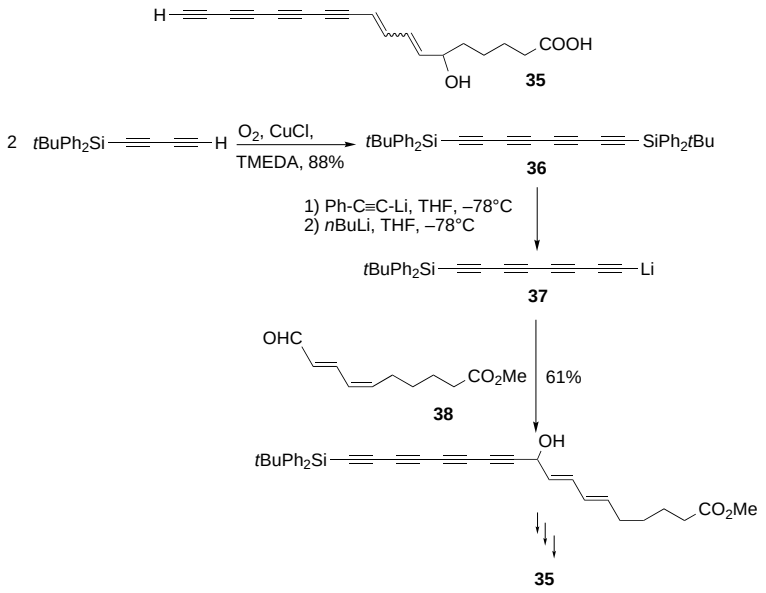


	R^1	n	R^2
29	$HOCH_2$	2	$CH=C(OMe)–CONH_2$
30	$HO(CH_3)_2C$	2	$CONH_2$
31	$HO(CH_3)CH$	3	$CONH_2$
32	$HOCH_2$	3	$CONH_2$
33	CH_3	3	$CH=C(OMe)–CONH_2$
34	CH_3	4	$CONH_2$

Scheme 33. Highly unstable fungal metabolites **27** and **28** and model compounds **29**–**34** prepared for structure elucidation (by spectral comparison).[174]

such as **29**–**34** containing substructures of **27** and **28** by oxidative cross-coupling reactions under Glaser conditions. The tetraacetylenic chromophore in **27** and **28** was subsequently established with confidence on the basis of spectral comparisons between the natural products and the model systems.

A fine example of the synthetic possibilities opened up by combination of acetylenic coupling with selective deprotection techniques was provided by Yamaguchi et al.[163] The authors achieved the total synthesis of caryoynencins (**35**), which are polyyne antibiotics with potent antibacterial activities that can be isolated from cultures of the plant pathogen *Pseudomonas caryophylli*. The tetrayne framework of these molecules was built up efficiently by Hay coupling, and resulted in the formation of the symmetrical building block **36** (Scheme 34). The full carbon skeleton of **35** was subsequently built by addition of lithium acetylide **37**, which

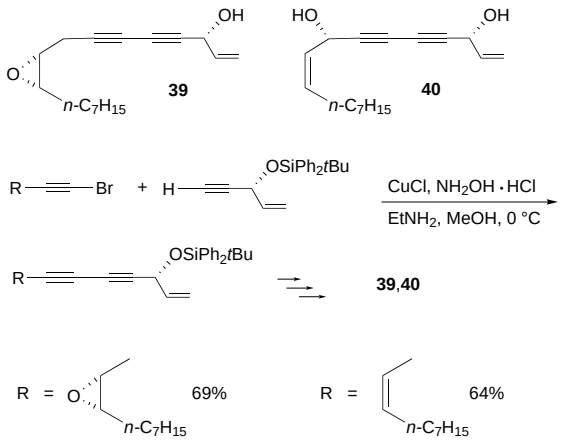


Scheme 34. Construction of the carbon skeleton in the total synthesis of the polyyne antibiotics caryoynencins (**35**).[163] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

was formed by careful mono-deprotection of **36** with phenylethynyllithium, to methyl ester **38**.

The continuing importance of the Cadiot–Chodkiewicz reaction for synthetic access to unsymmetrically substituted natural acetylenes was recently demonstrated by Cai and coworkers with the syntheses of panaxydol (**39**), an antitumor constituent of the *Panax ginseng* plant,[171, 175] and (3*R*,8*S*)-falcarindiol (**40**),[168] which is found in *Umbelliferae* and *Araliaceae* and exhibits anibacterial properties (Scheme 35).

In addition to the syntheses of natural polyacetylenes shown above, alkyne coupling reactions have also been employed as key steps in the preparation of various other biologically interesting compounds, such as allylamines and alkadienylamines (antimycotics),[176] alkynylindoles[177] and indolocarbazoles (antitumor agents),[178] anacyclin and related isobutylamides (insecticides),[72b] alkynyl-substituted steroids (antigestagens),[179] natural unsaturated fatty acids (natural ionophores and defensive substances in rice plants),[180]

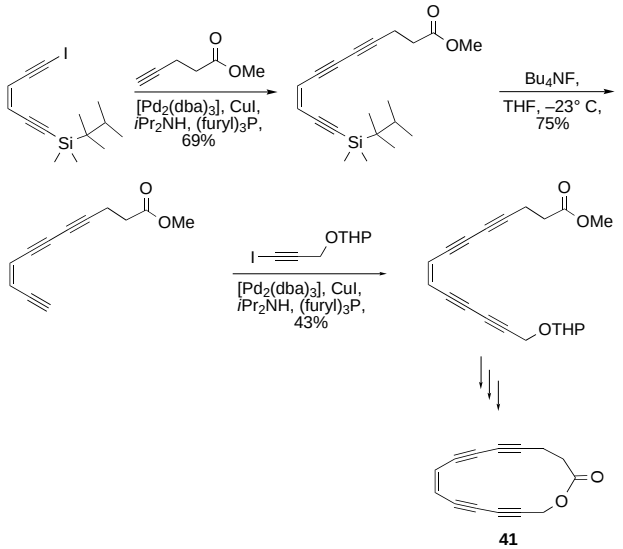


Scheme 35. The Cadiot–Chodkiewicz heterocoupling is the key step in the construction of the carbon framework of panaxydol (**39**)[171] and (3*R*,8*S*)-falcarindiol (**40**).[168]

pheromones,[181] diyne-bridged amino acids,[182] and acetylenic retinoids.[183]

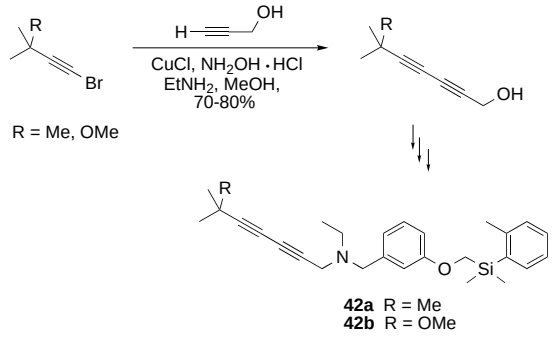
Naturally occurring *cis*-enediynes and unnatural derivatives have received special attention as potent antitumor antibiotics in recent years.[184] Schreiber and co-workers prepared a series of macrocyclic and acyclic *cis*-enetetraynes,[185] but found them remarkably unreactive with respect to the Bergman rearrangement which transforms *cis*-enediynes into benzene-1,4-diradicals, which serve as potent cytotoxic agents.[184c] The *cis*-enetetraynes, such as macrocycle **41** (Scheme 36), were obtained primarily by palladium-catalyzed alkyne cross-coupling reactions, which proved superior in this case to the classical Cadiot–Chodkiewicz conditions.

Another application of the Cadiot–Chodkiewicz cross-coupling in medicinal chemistry can be found in the preparation of the alkynylated benzylamine



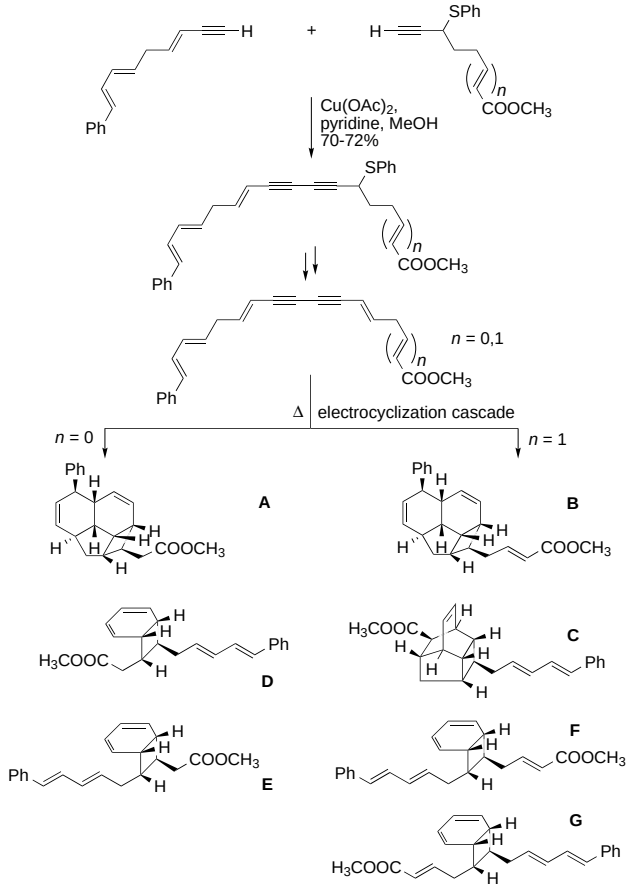
Scheme 36. Synthesis of the macrocyclic enetetrayne **41**.[185] dba = dibenzylideneacetone, THP = tetrahydro-2*H*-pyran.

derivatives **42a** and **42b** (Scheme 37),[186] which are potent inhibitors of squalene epoxidase, a key enzyme in cholesterol biosynthesis and an attractive target in cholesterol-lowering therapy.[187]



Scheme 37. Synthesis of inhibitors of squalene epoxidase.[186]

Another fine example of the use of acetylenic couplings in the preparation of natural products can be found in the synthesis of the endriandric acids, which are isolated from leaves of the Australian plant *Endiandra introrsa*. In a stereocontrolled synthesis starting from buta-1,3-diynes, Nicolaou et al. showed that the biogenesis of the endiandric acids proceeds from achiral precursors by a series of nonenzymatic electrocyclizations (Scheme 38).[188] Such a mechanism had been proposed previously by Black and co-workers.[189]

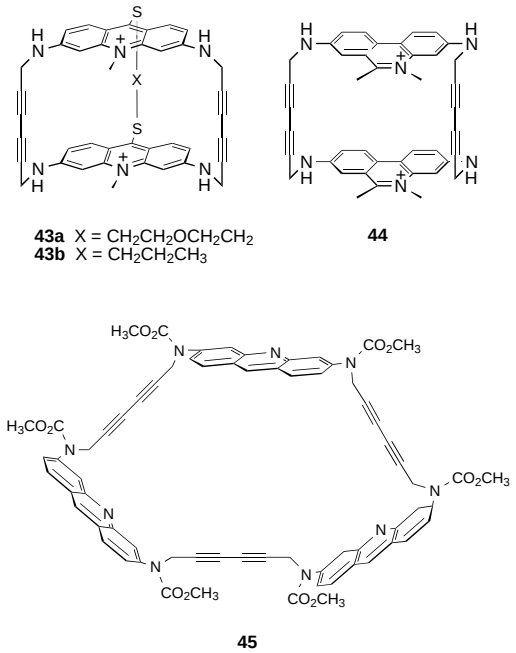


Scheme 38. Synthesis of acetylenic precursors, from which the methyl esters of endriandic acids A–G can be prepared in one step by electrocyclization cascades.[188]

4.2. Molecular Recognition—The Strategy of the Rigid Group

Synthetic cagelike molecules have received much attention as binding pockets in biomimetic systems.[159, 190] Three-dimensional macrocycles are of particular interest because their binding sites are highly defined, which often translates into enhanced affinity and substrate selectivity. Preorganization of macropolycyclic receptors is conveniently achieved by introducing rigid buta-1,3-diynediyl spacers. Furthermore, these systems can be efficiently assembled, often with remarkable yields, by macrocyclization reactions involving multiple acetylenic couplings. Breslow and co-workers reported the formation of a hydrophobic macrobicyclic receptor containing three buta-1,3-diynediyl spacers by a one-pot triple homocoupling of two ethynyl-substituted 1,1,1-triphenylethane moieties. They obtained the desired cage compound, which forms a solid-state inclusion complex with benzene, in a remarkable 35% yield by conducting the triple cyclization in O_2-free pyridine in the presence of both anhydrous CuCl and $CuCl_2$.[191] Many other groups have taken advantage of the preorganizing effect of buta-1,3-diynediyl spacers and the efficiency of acetylenic coupling for the construction of artificial receptors, and this work has been well reviewed quite recently.[159, 190c] In the subsequent survey we focus on recent examples which highlight the utility and selectivity of the most frequently used coupling methods.

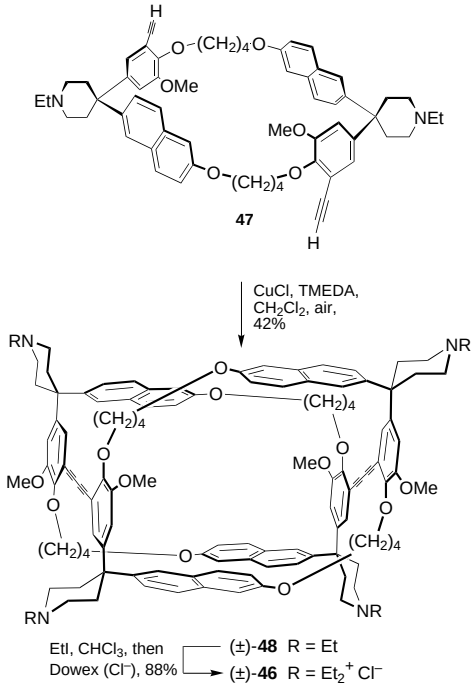
The macrocyclic receptors **43**–**45** (Scheme 39) reported by Lehn and co-workers were synthesized by homocoupling of the corresponding propargyl derivatives, by using the Eglinton method under high dilution (excess $Cu(OAc)_2$, CH_2Cl_2 or acetonitrile, with or without pyridine, under Ar, elevated temperatures).[192, 193] In these systems the buta-1,3-



Scheme 39. Macrocyclic receptors **43**–**45** prepared under Eglinton conditions for the complexation of aromatic substrates by intercalative π–π stacking and for association with nucleic acids by Coulombic and intercalative interactions.[192, 193]

diynediyl bridges serve as rigid spacers that provide cavities for aromatic substrates and nucleotides through intercalative $\pi-\pi$ stacking interactions. Some of these receptors also interact strongly with nucleic acids, presumably by Coulombic interactions with the phosphate backbone, and by intercalation into base-pair stacks.

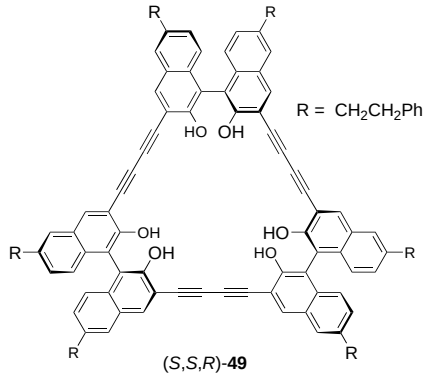
The buta-1,3-diynediyl-linked macrotricyclic receptor (±)-**46** (Scheme 40) was synthesized in our research group with the aim of providing a deep cavity capable of incorporating both the tetracyclic A – D ring system of steroids and parts of the isoprenoidal side chain at C(17).[194a] Recent comprehensive binding studies with a range of steroidal substrates showed that this objective was fully achieved.[194b] Here, the crucial ring closure was achieved by Hay coupling of the diethynylcyclophane **47**, to give (±)-**48** as a single diastereoisomer in a remarkable 42 % yield.



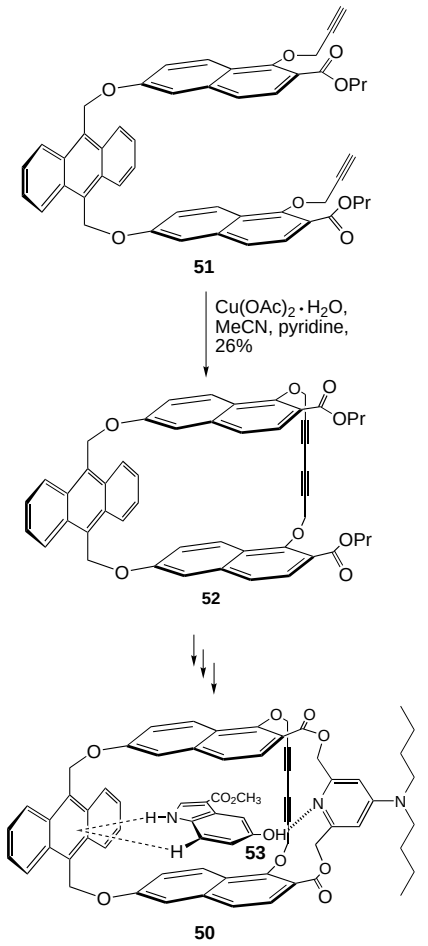
Scheme 40. The Hay coupling of **47** is the key step in the synthesis of the water-soluble steroid receptor (±)-**46**.[194]

Families of trimeric cyclophane receptors, such as (*S*,*S*,*R*)-**49** (Scheme 41) consisting of three butadiyne-bridged optically active 1,1′-binaphthalene units, were also prepared in our group.[195] The macrocyclic scaffolds were constructed using the same Hay conditions as described in Scheme 40. The cavities in these receptors are highly preorganized and (*S*,*S*,*R*)-**49** represents one of the most diastereoselective and enantioselective artificial carbohydrate receptors known. Carbohydrate recognition in these systems occurs in noncompetitive solvents by the guest hydrogen bonding to the convergent array of hydroxyl groups lining the interior of the receptor.

Whitlock and co-workers were the first to take advantage of acetylenic coupling in the construction of preorganized macrocyclic receptors.[190c] An elegant recent development from this group is shown in Scheme 42.[196] In the synthesis of



Scheme 41. The highly diastereo- and enantioselective carbohydrate receptor (*S*,*S*,*R*)-**49** was constructed under Hay conditions.[195b]



Scheme 42. Oxidative coupling under Eglinton conditions in the synthesis of receptor **50**.[196]

50, bis(propargyl) derivative **51** cyclized to **52** by intramolecular oxidative coupling under Eglinton conditions. Receptor **50** is selective for hydroxyindol **53**, which binds in the macrocyclic cavity by a combination of $\pi-\pi$ stacking, C-H $\cdots$ π(aromatic edge-to-face),[197] and OH $\cdots$ N(pyridine) hydrogen-bonding interactions.

Templates have been most successfully used to favor the formation of macrocyclic products during Glaser couplings. Their ability to control the size of macrocycles formed in oxidative alkyne coupling processes was impressively dem-

onstrated by the work of Sanders, Anderson, and Anderson.[198] McCallien and Sanders observed a dramatic influence of the template on product distribution during oligomerization of the dialkynyl-substituted zinc dioxoporphyrin **54**[199] (Scheme 43). Hay coupling of **54** in the absence of templating agents gave primarily the trimeric and tetrameric macrocycles **55b** and **55c**. The addition of bipyridine resulted in exclusive formation of dimeric **55a**, while the presence of 2,4,6-tri(4-pyridyl)triazine and 5,10,15,20-tetrapyridylporphyrin shifted the product distribution towards trimeric **55b** and tetrameric **55c**, respectively.

Macrocycle **55b** and its analogues with different solubility-providing lateral side chains on the porphyrin ring feature a variety of desirable properties, including the binding of various amine ligands,[200] stereoselective catalysis of an *exo*-selective Diels–Alder reaction,[201] and acceleration of acyl transfer in a supramolecular ternary complex.[202] The strategy of templated oxidative coupling has also been extended to the synthesis of other systems, including a ruthenium derivative of **55b**,[203] and more recently of an unusual asymmetric [2]catenane.[204]

Thus, oxidative acetylenic coupling reactions not only provide a simple and effective strategy to create highly preorganized supramolecular structures, but as well open up promising synthetic pathways towards artificial enzymes capable of recognition and catalysis, which remains one of the key objectives in supramolecular chemistry.

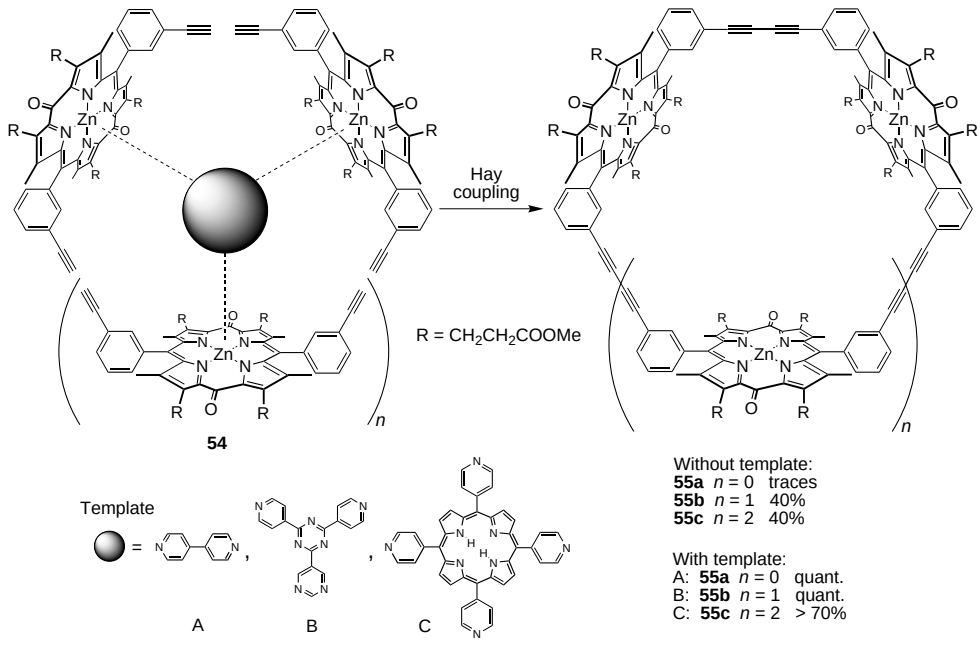
4.3. Synthesis of Linearly π-Conjugated Acetylenic Oligomers and Polymers

The synthesis and properties of conjugated organic oligomers and polymers has been the topic of two recent reviews.[205, 206] Thus, in this section we restrict ourselves to a small excerpt of this rapidly growing field, and describe only a few of the most remarkable results of recent years.

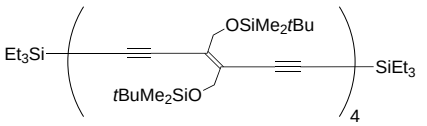
Copper-catalyzed alkyne coupling reactions have proven a potent approach to the preparation of conjugated oligo- and polyacetylenes. The most widely used procedures are oxidative processes, with a clear preference for the Hay method.[207] Controlled polymerization of diethynyl-functionalized monomers to achieve monodisperse oligomers or high molecular weight linear polymers with a well defined, rigid π-conjugated backbone is of significant interest for material scientists, since these systems feature unusual electrooptical properties.[208]

A general synthetic problem in the preparation of monodisperse oligomers and polymers is uncontrolled chain growth during the coupling process, which results in the formation of product mixtures that are difficult to separate, and frequently contain large amounts of insoluble components. Protecting group strategies need to be employed to avoid this problem. This concept was first applied by Walton and co-workers,[209] who used triethylsilyl-protected terminal alkynes in the synthesis of individual polyynes of the type H–(C≡C)$_n$–H with $n = 4-10$ and 12. Both Hay homocouplings[209a] and Cadiot–Chodkiewicz heterocouplings[209b] were successfully applied, in conjunction with protecting group methodology, to the synthesis of these carbyne fragments. Our research group succeeded in the preparation of a series of Et_3Si-endcapped monodisperse poly(triacetylene) (PTA) oligomers containing 4, 8, 12, and 16 monomeric units by a rapid and efficient statistical deprotection-Hay oligomerization sequence starting from an "extended monomer" (Scheme 44). With its 16 C=C double and 32 C≡C triple bonds, and a length of 11.9 nm, hexadecameric PTA **56** is currently the longest linearly fully conjugated molecular wire which does not contain aromatic repeat units.[210]

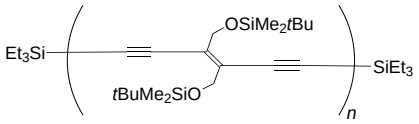
The broad functional group tolerance of oxidative alkyne dimerizations allows great flexibility in the choice of the acetylenic building blocks and easy access to multinanometer-sized structures with electron-donating and -accepting groups that have interesting nonlinear optical properties.[211] Lehn and co-workers reported the formation of reversibly reducible multinanometer-sized molecular rods consisting of poly(phenylthio)-benzene subunits linked by diacetylene bridges.[212] Their synthesis proceeded under either Eglinton or Hay coupling conditions. Wilson and Anderson used the Hay coupling method to synthesize the conjugated tetrapyridylporphyrin dimer **57**, which is capable of binding to two other metalloporphyrin dimers to generate a triple-strand array (Scheme 45).[213] Compound **57** could find interesting appli-



Scheme 43. Dramatic effects of templates on macrocyclic ring size.[199]

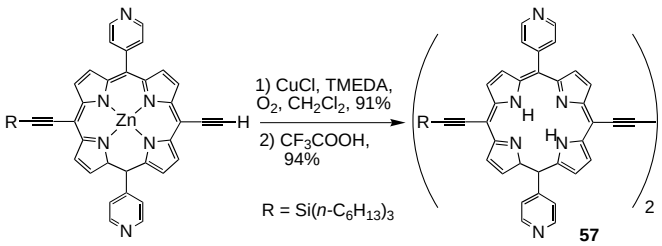


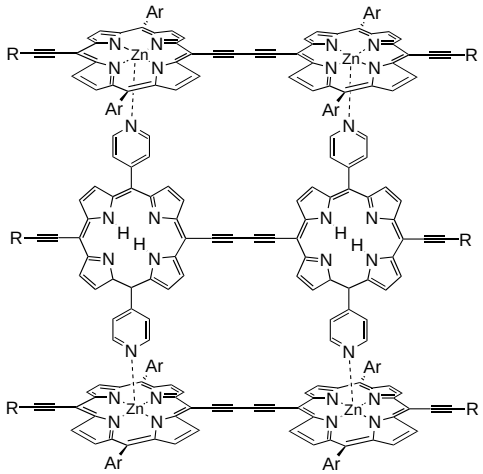
1) NaOH, THF/MeOH 1:1, 20 °C, 20 min
2) CuCl, TMEDA, toluene, molecular sieves (4Å), dry O_2 atmosphere, 2 h, reflux, 1 h



	n	yield
	4	50%
	8	20%
	12	10%
56	16	5%

Scheme 44. Synthesis of PTA oligomers by a statistical deprotection and Hay oligomerization sequence starting from an "extended monomer."[210]

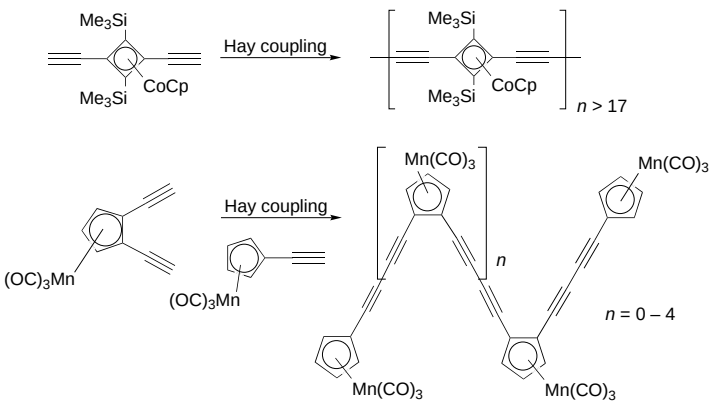




Scheme 45. A conjugated tetrapyridylporphyrin dimer for the self-assembly of a triple strand.[213]

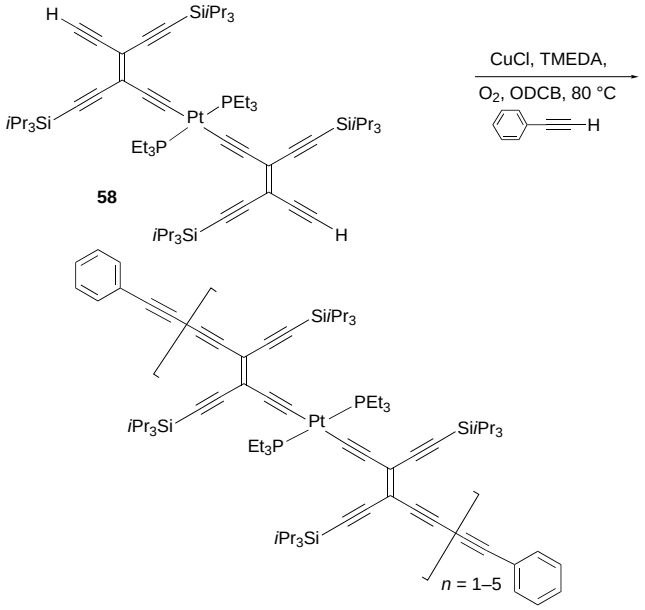
cation for templating diverse oxidative alkyne coupling processes.

Terminal alkynes in organotransition metal complexes also undergo copper-catalyzed couplings.[59, 214] Bunz has employed Hay conditions to prepare molecular rods incorporating cyclobutadiene and cyclopentadienyl–π complexes that have a variety of interesting material properties (Scheme 46).[215, 216]



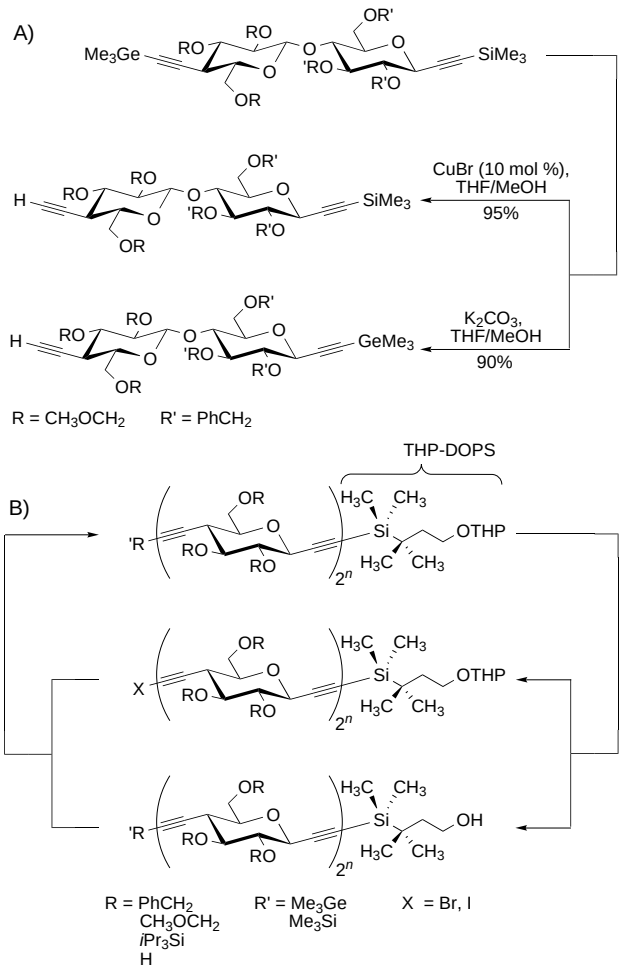
Scheme 46. Organometallic carbon chains assembled by oxidative alkyne coupling.[214–216]

By using transition metals directly as bridging units, we prepared platinum-σ-bis(acetylide) complexes of tetraethynylethenes.[217] They are potent building blocks for longer monodisperse oligomers as a result of their remarkable stability and amazing solubility. Controlled coupling of the bis-deprotected complex **58** under Hay conditions in the presence of phenylacetylene as an end-capping reagent provided oligomers up to the pentamer with a length of 10 nm (Scheme 47).[218]



Scheme 47. Oligomers with a platinum–tetraethynylethene hybrid backbone.[218] ODCB = *o*-dichlorobenzene.

A milestone in the application of copper-catalyzed acetylenic heterocouplings in oligomer preparation is the binomial synthesis of acetylenic oligosaccharides developed by Vasella and co-workers.[219] The synthetic concept consists of consecutive cycles of orthogonal dialkyne deprotection, followed by cross-coupling of the subsequently created haloalkynes with the corresponding terminal alkynes (Scheme 48A and 48B). Two useful sets of orthogonal protecting groups for diacetylenes were introduced in this work by using combinations of



Scheme 48. Two sets of orthogonal alkyne protecting groups and application to the binomial synthesis of acetylenic saccharides .[219]

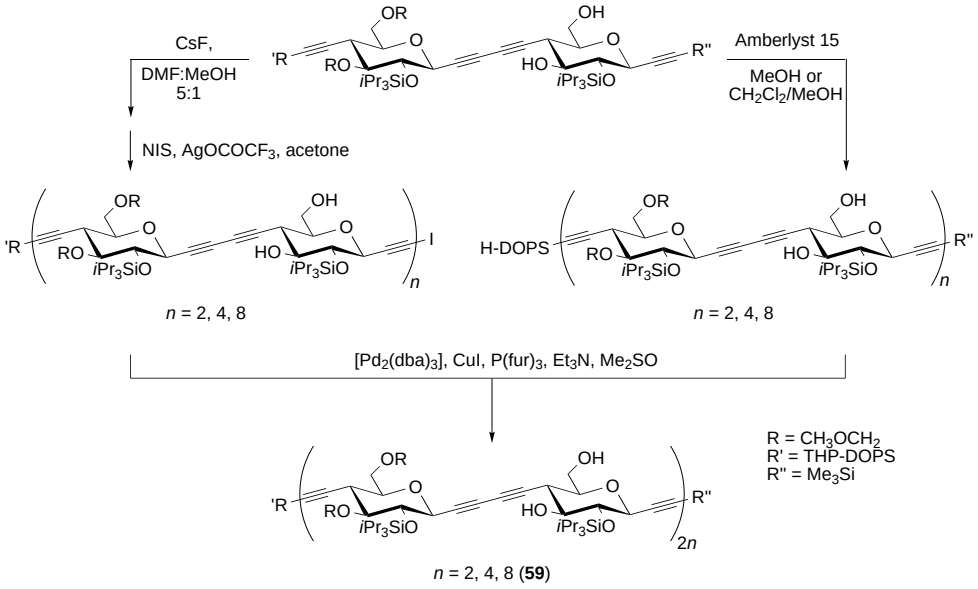
independently removable protective groups, namely Me_3Si with either [dimethyl(oxy)propyl]dimethylsilyl (DOPS)[219b,c] or Me_3Ge groups.[219d]

Quite recently, Vasella and co-workers succeeded in the binomial synthesis of a hexadecameric acetylenic saccharide (**59**), which allowed the evaluation of the structural role of intramolecular hydrogen bonds in cellulose (Scheme 49).[220] Compound **59** shows no sign of aggregation in Me_2SO since the diacetylene bridges, a previously established motif in synthetic saccharides,[221] prevent the formation of specific intramolecular interresidue hydrogen bonds. In contrast, such hydrogen bonds are present in cellulose and are responsible for the aggregation of the natural polysaccharide. This impressive example of controlled oligomerization underlines the important role of alkyne coupling reactions in modern oligomer synthesis.

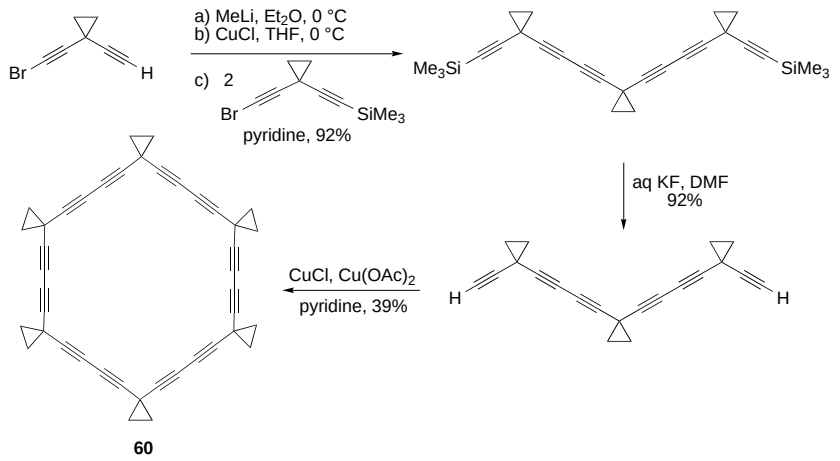
4.4. Cyclic Oligoacetylenes—Towards New Carbon Allotropes

Macrocyclic acetylenic rings have attracted considerable interest in the past. Dehydroannulenes,[34, 52b, 56, 222] and "exploded cycloalkanes" in which −C≡C− ([*n*]pericyclynes) or −C≡C−C≡C− fragments are inserted between each pair of adjacent sp^3-hybridized C atoms in *n*-membered cycloalkanes ($n = 3-6$),[52a, 223] were among the first macrocycles incorporating conjugated oligoacetylene fragments. Our contemporary knowledge of cyclic π-electron conjugation and various forms of aromaticity have been greatly influenced by fundamental studies of these compounds. The Eglinton protocol has been applied most frequently for the synthesis of cyclic oligoacetylenes, although Hay couplings are increasingly used. The size distribution of the cyclic oligomers obtained by the Eglinton or Hay coupling can vary significantly,[224a, 216b] and it is advisable to try both methods to determine which works the best for a given application. More recently, carbon-rich oligoacetylenic rings have attracted particular attention as advanced materials with interesting optoelectronic properties and as precursors to new molecular carbon allotropes. The fascinating perspectives of this research, which relies heavily on acetylenic coupling methodology, has been the subject of several reviews.[224, 225] Therefore, only a few examples of the spectacular molecular architecture generated in this field will be presented here.

In 1995, de Meijere, Scott, and co-workers reported an efficient synthesis of [*n*]rotanes, perspirocyclopropanated macrocyclic oligodiacetylenes that explode violently when struck in the solid state.[226] The synthesis of the hexameric derivative **60**, which in the solid state prefers a chair conformation, is shown in Scheme 50. The macrocyclization



Scheme 49. Binomial synthesis of a hexadecameric acetylenic saccharide.[220]

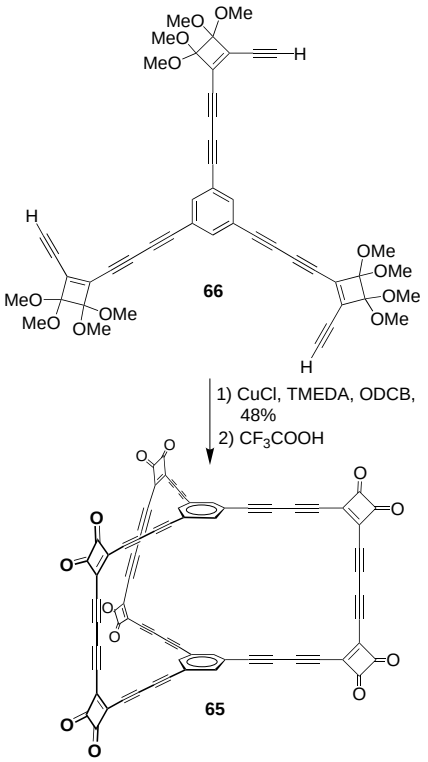


Scheme 50. Synthesis of [6]rotane **60**, a hexameric perspirocyclopropanated macrocyclic diacetylene.[226]

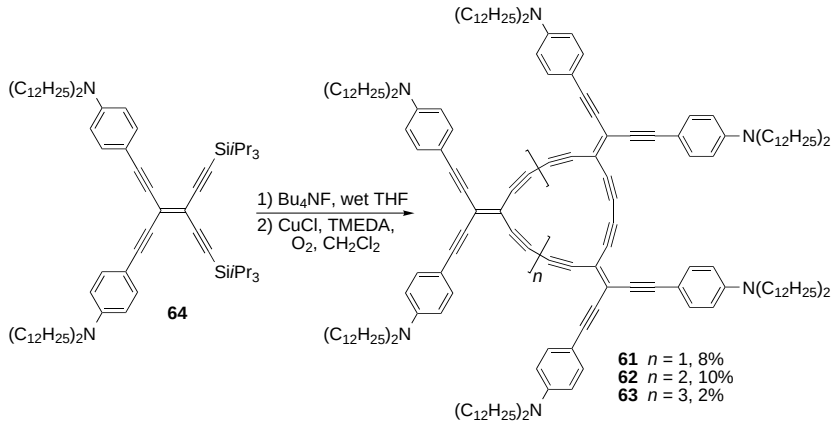
to **60** was performed under Eglinton conditions whereas the precursor alkynes were prepared through repetitive Cadiot–Chodkiewicz coupling.

A great variety of two- and three-dimensional perethynylated all-carbon chromophores have been developed during the past 15 years and are currently being investigated as precursors to all-carbon networks.[224a] Among the largest all-carbon surfaces known are the perethynylated expanded radialenes,[227] which can be conveniently functionalized at the periphery for optimization of their advanced materials properties. Thus *N*,*N*-bis(dodecyl)aniline-functionalized expanded radialenes with all-carbon cores of 30 (**61**), 40 (**62**), and 50 (**63**) C atoms, all featuring unusual electronic properties, were prepared by Hay coupling of the geminally bis-deprotected tetraethynylethene derivative **64** (Scheme 51).[228] The chromophoric properties of these and other related systems[227–229] revealed a poorly developed understanding of macrocyclic cross-conjugation.

On the way to pure molecular carbon allotropes, Diederich, Rubin, and co-workers developed a rational "precursor-approach" to the cyclo[*n*]carbons (cyclo-C_n), which are *n*-membered monocyclic rings of sp-hybridized C atoms with unique electronic structures resulting from two perpendicular systems of conjugated π orbitals. All the macrocyclic precursors to cyclo-C_{18}, cyclo-C_{24}, and cyclo-C_{30} were prepared by oxidative acetylenic coupling, and this work has been extensively reviewed.[224] Subsequent Fourier transform mass spectrometry investigations revealed that the coalescence of these cyclocarbons in ion-molecule reactions could be one pathway to the formation of fullerenes.[230] More direct "precursor-approaches" to the synthesis of buckminsterfullerene (C_{60}) and heterofullerenes were undertaken by the groups of Rubin[231] and Tobe.[232] Rubin et al. prepared macrobicyclic **65** [$C_{60}H_6(CO)_{12}$] by the high-yielding (48% yield) triple Hay coupling of **66** followed by acetal deprotection (Scheme 52). Laser desorption mass spectrometric experiments subsequently showed that the radical anion **65**$^{\bullet-}$ loses its twelve CO residues as well as the six H atoms and rearranges into the buckminsterfullerene anion $C_{60}^{\bullet-}$.



Scheme 52. High-yielding Hay coupling in the synthesis of macrobicyclic **65**, which generates C_{60} ions in mass spectrometric experiments.[231]



Scheme 51. Synthesis of perethynylated expanded radialenes.[228]

A similar "precursor-approach" was described by Tobe et al. who provided mass spectrometric evidence for formation of both $C_{60}^{\bullet-}$ [232a] and the diaza-analogue $C_{58}N_2^{\bullet-}$ [232b] in the gas phase. In these cases, precursors with the same macrobicyclic skeleton as in **65** (the dipyridine analogue was used to generate the diazafullerene) were prepared in

lower yield by Eglinton coupling, which again confirms that it cannot be predicted in advance which oxidative coupling protocol will be the highest yielding one.

These examples readily illustrate the rich variety of molecular construction based on acetylenic coupling that is currently ongoing in synthetic carbon research. A great variety of fullerene – acetylene hybrid systems, in which methanofullerenes are linked by buta-1,3-diynediyl fragments to generate linear and cyclic arrays, have been prepared.[233] Dehydrobenzoannulenes[52b] have attracted additional interest since the recent finding that they can be used for as precursors for carbon nanotubes.[234] Templates will increasingly be used in acetylenic scaffolding[198] to simplify product-purification protocols by avoiding the formation of oligomeric mixtures.[235] Clearly, many of the major research avenues in contemporary organic chemistry rely on acetylenic coupling methodology.

5. Conclusion and Outlook

The rigidity and cylindrical symmetry of oligoalkynes make them valuable as spatially and directionally well-defined structural units in diverse areas of organic chemistry, ranging from the synthesis of natural products and pharmaceuticals, to supramolecular construction, to carbon-rich and all-carbon scaffolding and networking. The applications illustrated above clearly demonstrate the versatility and high functional group tolerance which make alkyne couplings an attractive approach to the construction of complex systems. However, equally clear is that the full potential of this methodology has yet to be realized, and that more general and reliable conditions will be required to meet future synthetic challenges. The optimal conditions for the copper catalyst systems have typically been determined empirically. There is little information and virtually no predictability regarding the control of chain length and the formation of cyclic versus linear products for the oligomerization of terminal diynes. Heterocouplings are frequently complicated by poor reactivity in the case of alkynyl chlorides and by halogen – metal exchange for more reactive substrates. One key to resolving these issues may lie in an improved mechanistic understanding of these processes. Thus, alkyne couplings provide both valuable tools for synthesis as well as ample opportunities for further mechanistic and methodological work.

We thank the ETH research council for generous support of this work and Dr. E. Zass for help with the literature searches.

Received: January 20, 2000 [A 387]

[1] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422 – 424; b) C. Glaser, *Ann. Chem. Pharm.* **1870**, *154*, 137 – 171.

[2] a) A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 50 – 56; b) Baeyer also used this oxidizing agent for the preparation of diphenyldiacetylene and its derivatives: A. Baeyer, L. Landsberg, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 57 – 61.

[3] a) A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 674 – 681 (Baeyer came to the following remarkable conclusion: ".. Man sieht hieraus, dass es aller Wahrscheinlichkeit gelingen wird, noch längere Ketten von Kohlenstoffatomen aufzubauen.. Im günstigen Fall stehen jedenfalls interessante Resultate zu erwarten, da eine derartige Anhäufung von reinen Kohlenstoffatomen aller Wahrscheinlichkeit nach zu neuen Aufschlüssen über die Natur des freien Kohlenstoffs führen dürfte.."("From this one sees that the successful construction of even longer carbon chains is very likely …Even in the simplest cases interesting results can be expected, as such an accumulation of carbon atoms should lead to new insights into the nature of free carbon atoms")); b) A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269 – 2281.

[4] M. D. Cameron, G. E. Benett, *J. Org. Chem.* **1957**, *22*, 557 – 558.

[5] F. J. Brockmann, *Can. J. Chem.* **1955**, *33*, 507 – 510.

[6] The use of copper(II) salts as oxidizing agents was first published in 1897: a) A. A. Noyes, C. W. Tucker, *Am. Chem. J.* **1897**, *19*, 123 – 128; b) see also: A. A. Noyes, C. W. Tucker, *Chem. Zentralbl.* **1897**, *68*, 582 – 583.

[7] F. Straus, L. Kollek, *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 1664 – 1681.

[8] a) M. Nakagawa, *Proc. Jpn. Acad.* **1950**, *26*, 38 – 42; b) M. Nakagawa, *Proc. Jpn. Acad.* **1950**, *26*, 43 – 47.

[9] M. Nakagawa, *J. Chem. Soc. Jpn.* **1951**, *72*, 561 – 566.

[10] A. Vaitiekunas, F. F. Nord, *J. Am. Chem. Soc.* **1954**, *76*, 2733 – 2736.

[11] Y. Odaira, *Bull. Chem. Soc. Jpn.* **1956**, *29*, 470 – 471.

[12] H. H. Schlubach, V. Wolf, *Justus Liebigs Ann. Chem.* **1950**, *568*, 141 – 159.

[13] N. A. Milas, O. L. Mageli, *J. Am. Chem. Soc.* **1953**, *75*, 5970 – 5971.

[14] L. Camici, P. Dembech, A. Ricci, G. Seconi, M. Taddei, *Tetrahedron* **1988**, *44*, 4197 – 4206.

[15] F. Straus, *Justus Liebigs Ann. Chem.* **1905**, *342*, 190 – 265.

[16] a) M. Akhtar, B. C. L. Weedon, *Proc. Chem. Soc.* **1958**, 303; b) M. Akhtar, T. A. Richards, B. C. L. Weedon, *J. Chem. Soc.* **1959**, 933 – 940.

[17] N. Balcioglu, I. Uraz, C. Bozkurt, F. Sevin, *Polyhedron* **1997**, *16*, 327 – 334.

[18] a) J. A. Nieuwland, W. S. Calcott, F. B. Downing, A. S. Carter, *J. Am. Chem. Soc.* **1931**, *53*, 4197 – 4203.

[19] a) M. Rusek, V. Simame, V. Soukenik, *Czech. Pat.* 105, **1962**, 823 – 826; b) see also *Chem. Abstr.* **1964**, 60, 2751.

[20] For a recent publication on the preparation and oxidative coupling of alkynylcopper derivatives, see G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1988**, *53*, 4482 – 4488.

[21] a) Y. S. Zalkind, M. A. Aizikovich, *J. Gen. Chem. USSR* **1937**, *7*, 227 – 233; b) see also Y. S. Zalkind, M. A. Aizikovich, *Chem. Zentralbl.* **1937**, *108*, 4783.

[22] Y. S. Zalkind, I. M. Gverdtsiteli, *J. Gen. Chem. USSR* **1939**, *9*, 971 – 974.

[23] W. Reppe, *Justus Liebigs Ann. Chem.* **1955**, *596*, 1 – 224.

[24] a) K. Bowden, I. Heilbron, E. R. H. Jones, K. H. Sargent, *J. Chem. Soc.* **1947**, 1579 – 1583; b) I. Heilbron, E. R. H. Jones, F. Sondheimer, *J. Chem. Soc.* **1947**, 1586 – 1590.

[25] J. B. Armitage, C. L. Cook, N. Entwistle, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1952**, 1998 – 2005.

[26] J. B. Armitage, C. L. Cook, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1952**, 2010 – 2014.

[27] A. S. Hay, H. S. Blanchard, G. F. Endres, J. W. Eustance, *J. Am. Chem. Soc.* **1959**, *81*, 6335 – 6336.

[28] A. S. Hay, *J. Org. Chem.* **1960**, *25*, 1275 – 1276.

[29] R. A. Raphael, *Proc. Chem. Soc.* **1962**, 97 – 105.

[30] I. D. Campbell, G. Eglinton, *Organic Syntheses Collective Volume 5*, Wiley, New York, **1973**, pp. 517 – 520.

[31] F. Bohlmann in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Dekker, New York, **1969**, chap. 14, pp. 977 – 986.

[32] G. Eglinton, A. R. Galbraith, *Chem. Ind. (London)* **1956**, 737 – 738.

[33] A. Krebs in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Dekker, New York, **1969**, chap. 15, pp. 987 – 1062.

[34] a) Review article: F. Sondheimer, *Pure Appl. Chem.* **1963**, *7*, 363 – 388; b) F. Sondheimer, R. Wolovsky, *J. Am. Chem. Soc.* **1959**, *81*, 1771; c) F. Sondheimer, R. Wolovsky, Y. Amiel, *J. Am. Chem. Soc.* **1962**, *84*, 274 – 284.

[35] A. S. Hay, *J. Org. Chem.* **1962**,*27*, 3320 – 3321.

[36] a) W. Chodkiewicz, P. Cadiot, *C. R. Hebd. Seances Acad. Sci.* **1955**, *241*, 1055 – 1057; b) W. Chodkiewicz, *Ann. Chim. (Paris)* **1957**, *2*, 819 – 869.

[37] G. Eglinton, W. McCrae, *Adv. Org. Chem.* **1963**, *4*, 225 – 328.

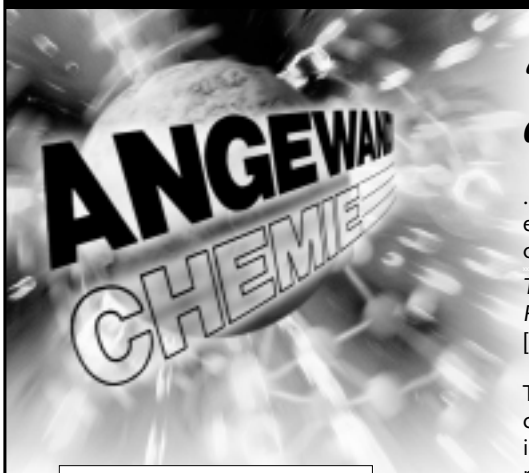
[38] T. F. Rutledge, *Acetylenic Compounds*, Reinhold, New York, **1968**, chap. 6, pp. 245 – 268.
[39] P. Cadiot, W. Chodkiewicz in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Dekker, New York, **1969**, chap. 9, pp. 597 – 647.
[40] W. G. Nigh in *Organic Chemistry*, *Vol. 5: Oxidation in Organic Chemistry*, *Part B* (Ed.: W. S. Trahanovsky), Academic Press, New York, **1973**, pp. 11 – 31.
[41] U. Niedballa, *Methoden Org. Chem. (Houben-Weyl)*, *Vol. 5/2a*, **1977**, pp. 925 – 937.
[42] L. I. Simàndi in *The Chemistry of Functional Groups Supplement C: The Chemistry of Triple-bonded Functional Groups* (Eds.: P. Patai, Z. Rappoport), Wiley, New York, **1983**, chap. 13, pp. 529 – 534.
[43] L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, **1988**, chap. 10, pp. 219 – 227.
[44] K. Sonogashira in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 551 – 561.
[45] S. F. Vasilevsky, H. D. Verkruijsse, L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 529 – 530.
[46] E. Valenti, M. A. Pericas, F. Serratosa, *J. Am. Chem. Soc.* **1990**, *112*, 7405 – 7406.
[47] U. Fritzsche, S. Hünig, *Tetrahedron Lett.* **1972**, 4831 – 4834.
[48] K. E. Knol, L. W. van Horssen, G. Challa, E. E. Havinga, *Polym. Commun.* **1985**, *26*, 71 – 73.
[49] S. Takahashi, E. Murata, K. Sonogashira, N. Hagihara, *J. Polym. Sci. Polym. Chem. Ed.* **1980**, *18*, 661 – 669.
[50] K. Ikegashira, Y. Nishihara, K. Hirabayashi, A. Mori, T. Hiyama, *Chem. Commun.* **1997**, 1039 – 1040.
[51] Y. Nishihara, K. Ikegashira, A. Mori, T. Hiyama, *Tetrahedron Lett.* **1998**, *39*, 4075 – 4078.
[52] For recent reviews on macrocyclic oligoacetylenes, see a) A. de Meijere, S. I. Kozhushkov, *Top. Curr. Chem.* **1999**, *201*, 1 – 42; b) M. M. Haley, J. J. Pak, S. C. Brand, *Top. Curr. Chem.* **1999**, *201*, 81 – 130.
[53] Y. Yto, M. Inouye, M. Murakami, *Chem. Lett.* **1989**, 1261 – 1264.
[54] For a noteworthy application of the Eglinton method in the construction of linear systems, see a) Y. Zhou, J. W. Seyler, W. Weng, A. M. Arif, J. A. Gladysz, *J. Am. Chem. Soc.* **1993**, *115*, 8509 – 8510; b) M. Brady, W. Weng, J. A. Gladysz, *J. Chem. Soc. Chem. Commun.* **1994**, 2655 – 2656; c) T. Bartik, B. Bartik, M. Brady, R. Dembinsky, J. A. Gladysz, *Angew. Chem.* **1996**, *108*, 467 – 469; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 414 – 417; d) B. Bartik, R. Dembinski, T. Bartik, A. M. Arif, J. A. Gladysz, *New J. Chem.* **1997**, *21*, 739 – 750.
[55] G. Eglinton, A. R. Galbraith, *J. Chem. Soc.* **1959**, 889 – 896.
[56] a) U. E. Meissner, B. Meissner, H. A. Staab, *Angew. Chem.* **1973**, *85*, 957 – 958; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 916 – 918; b) H. A. Staab, U. E. Meissner, B. Meissner, *Chem. Ber.* **1976**, *109*, 3875 – 3885; c) H. A. Staab, U. E. Meissner, W. Weinacht, A. Gensler, *Chem. Ber.* **1979**, *112*, 3895 – 3906.
[57] R. Berscheid, F. Vögtle, *Synthesis* **1992**, 58 – 62.
[58] a) J. J. Pak, T. J. R. Weakly, M. M. Haley, *J. Am. Chem. Soc.* **1999**, *121*, 8182 – 8192; b) M. M. Haley, M. L. Bell, J. C. Brand, D. B. Kimball, J. J. Pak, W. B. Wan, *Tetrahedron Lett.* **1997**, *38*, 7483 – 7486.
[59] J. Li, H. Jiang, *Chem. Commun.* **1999**, 2369 – 2370.
[60] F. Toda, Y. Tokumaru, *Chem. Lett.* **1990**, 987 – 990.
[61] S. M. Auer, M. Schneider, A. Baiker, *J. Chem. Soc. Chem. Commun.* **1995**, 2057 – 2058.
[62] In some cases, the yield of unsymmetrical product in Glaser-type couplings can be increased by using a large excess of one coupling component.[41] See for example end-capping oligomerizations under Hay conditions: A. M. Boldi, J. Anthony, V. Gramlich, C. B. Knobler, C. Boudon, J. P. Gisselbrecht, M. Gross, F. Diederich, *Helv. Chim. Acta* **1995**, *78*, 779 – 796.
[63] a) K. Naemura, Y. Hokura, M. Nakazaki, *Tetrahedron* **1986**, *42*, 1763 – 1768; b) T. Ogawa, M. Sotelo, G. Burillo, C. S. Marvel, *J. Polym. Sci. Part C* **1989**, *27*, 167 – 172.
[64] a) E. Barbu, J. Tsibouklis, *Tetrahedron Lett.* **1996**, *37*, 5023 – 5026; b) S. Okada, H. Matsuda, M. Otsuka, N. Kikuchi, K. Hayamizu, H. Nakanishi, M. Kato, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 455 – 461.
[65] A. P. Yuvchenko, K. L. Moiseichuk, E. A. Dikusar, *J. Org. Chem. USSR* **1989**, *25*, 1045 – 1048.
[66] J. C. Cognacq, W. Chodkiewicz, *Bull. Soc. Chim. Fr.* **1966**, 1999 – 2005.
[67] a) D. Grandjean, P. Pale, J. Chuche, *Tetrahedron Lett.* **1992**, *33*, 5355 – 5358; b) D. Grandjean, P. Pale, J. Chuche, *Tetrahedron* **1993**, *49*, 5225 – 5236.
[68] a) S. Ohba, J. F. J. Engbersen, *Tetrahedron* **1991**, *47*, 9947 – 9952; b) R. Rodriguez-Abad, J. Tsibouklis, *Synth. Commun.* **1998**, *28*, 4333 – 4338.
[69] F. Bohlmann, R. Weber, *Chem. Ber.* **1972**, *105*, 3036 – 3040.
[70] a) B. Tieke, G. Lieser, G. Wegner, *J. Polym. Sci. Polym. Chem. Ed.* **1979**, *17*, 1631 – 1644; b) D. Villemin, P. Cadiot, M. Kuétegan, *Synthesis* **1983**, 230 – 231.
[71] a) A. G. Fallis, M. T. W. Hearn, E. R. H. Jones, V. Thaller, J. L. Turner, *J. Chem. Soc.* **1973**, 743 – 749; b) M. Rösner, G. Köbrich, *Angew. Chem.* **1975**, *87*, 715 – 717; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 708 – 709.
[72] a) M. Ahmed, M. Y. Jarrah, E. R. H. Jones, A. F. Magalhães, M. G. Roberts, V. Thaller, *J. Chem. Res. Synop.* **1981**, 262 – 263; b) L. Crombie, A. J. W. Hobbs, M. A. Horsham, R. J. Blade, *Tetrahedron Lett.* **1987**, *28*, 4875 – 4878; c) L. Fomina, A. Vega, S. Fomine, R. Gaviño, T. Ogawa, *Macromol. Chem. Phys.* **1996**, *197*, 2653 – 2663.
[73] M. D. Mowery, C. E. Evans, *Tetrahedron Lett.* **1997**, *38*, 11 – 14.
[74] L. Blanco, H. E. Helson, M. Hirthammer, H. Mestdagh, S. Spyroudis, K. P. C. Vollhardt, *Angew. Chem.* **1987**, *99*, 1276 – 1277; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1246 – 1247.
[75] a) D. W. Wiley, J. C. Calabrese, R. L. Harlow, J. S. Miller, *Angew. Chem.* **1991**, *103*, 459 – 460; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 450 – 452; b) G. P. Hamill, E. A. Yost, D. J. Sandman, *Mol. Cryst. Liq. Cryst.* **1992**, *211*, 339 – 345.
[76] A combination of the Cadiot – Chodkiewicz reaction with the Stille coupling provides a versatile protocol for the synthesis of unsymmetrical diarylbuta-1,3-diynes: A. Godt, *J. Org. Chem.* **1997**, *62*, 7471 – 7474.
[77] N. E. Porter, D. R. Magnin, B. T. Wright, *J. Am. Chem. Soc.* **1986**, *108*, 2787 – 2788.
[78] A. Singh, J. M. Schnur, *Synth. Commun.* **1986**, *16*, 847 – 852.
[79] J. Tsibouklis, C. Pearson, Y.-P. Song, J. Warren, M. Petty, J. Yarwood, M. C. Petty, W. J. Feast, *J. Mater. Chem.* **1993**, *3*, 97 – 104.
[80] R. F. Curtis, J. A. Taylor, *J. Chem. Soc. C* **1971**, 186 – 188.
[81] C. Hartbaum, H. Fischer, *Chem. Ber.* **1997**, *130*, 1063 – 1067.
[82] J. M. Montierth, D. R. DeMario, M. J. Kurth, N. E. Schore, *Tetrahedron* **1998**, *54*, 11741 – 11748.
[83] M. Alami, F. Ferri, *Tetrahedron Lett.* **1996**, *37*, 2763 – 2766.
[84] T. Kitamura, T. Tanaka, H. Taniguchi, P. J. Stang, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2892 – 2893.
[85] V. Grignard, H. Perrichon, *Ann. Chim. (Paris)* **1926**, *5*, 5 – 36.
[86] H. H. Schlubach, V. Franzen, *Liebigs Ann. Chem.* **1951**, *573*, 115 – 120.
[87] J. B. Armitage, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1952**, 2014 – 2018.
[88] H. H. Schlubach, V. Franzen, *Liebigs Ann. Chem.* **1951**, *572*, 116 – 121.
[89] H. K. Black, D. H. S. Horn, B. C. L. Weedon, *J. Chem. Soc.* **1954**, 1704 – 1709.
[90] J. B. Armitage, E. Entwistle, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1954**, 147 – 154.
[91] J. I. Iotsitch, B. I. Orielkine, *Bull. Soc. Chim. Fr.* **1911**, *10*, 647.
[92] Y.-K. Liu, R.-T. Wang, F.-L. Chou, F.-T. Luo, *Bull. Inst. Chem. Acad. Sin.* **1990**, *37*, 43 – 48.
[93] Y. Ito, M. Inouye, M. Murakami, *Tetrahedron Lett.* **1988**, *29*, 5379 – 5382.
[94] U. M. Dzhemilev, A. G. Ibragimov, R. A. Saraev, *Izv. Akad. Nauk SSR Ser. Khim.* **1986**, *2*, 429 – 433.
[95] T. Ishikawa, A. Ogawa, T. Hirao, *Organometallics* **1998**, *17*, 5713 – 5716.
[96] H. G. Viehe, *Chem. Ber.* **1959**, *92*, 3064 – 3075.
[97] S. Oae, Y. Inubushi, M. Yoshihara, *Phosphorus Sulfur* **1995**, *103*, 101 – 110.
[98] a) E. Negishi, T. Takahashi, K. Akiyoshi, *J. Organomet. Chem.* **1987**, *334*, 181 – 194; b) E. Negishi, K. Akiyoshi, T. Takahashi, *J. Chem. Soc. Chem. Commun.* **1987**, 477 – 478.

[99] H. F. Klein, H. Beck-Hemetsberger, L. Reitzel, B. Rodenhäuser, G. Cordier, *Chem. Ber.* **1989**, *122*, 43 – 51.
[100] E. H. Smith, J. Whittall, *Organometallics* **1994**, *13*, 5169 – 5172.
[101] a) A. Pelter, K. Smith, M. Tabata, *J. Chem. Soc. Chem. Commun.* **1975**, 857; b) A. Pelter, R. Hughes, K. Smith, M. Tabata, *Tetrahedron Lett.* **1976**, 4385 – 4388.
[102] J. A. Sinclair, H. C. Brown, *J. Org. Chem.* **1976**, *41*, 1078 – 1079.
[103] S. Ghosal, G. P. Luke, K. S. Kyler, *J. Org. Chem.* **1987**, *52*, 4296 – 4298.
[104] K. Akiba, T. Okinaka, M. Nakatani, Y. Yamamoto, *Tetrahedron Lett.* **1987**, *28*, 3367 – 3368.
[105] J. V. Comasseto, V. Catani, J. T. B. Ferreira, A. L. Braga, *J. Chem. Soc. Chem. Commun.* **1986**, 1067.
[106] M. J. Dabdoub, R. Preto, J. V. Comasseto, S. M. Barros, F. Moussa, *Synth. Commun.* **1990**, *20*, 2181 – 2183.
[107] T. Murai, K. Imaeda, S. Kajita, K. Kimura, H. Ishihara, S. Kato, *Phosphorus Sulfur* **1992**, *67*, 239 – 242.
[108] L. Alcaraz, R. J. K. Taylor, *Synlett* **1997**, 791 – 792.
[109] J. R. Johnson, W. L. McEwen, *J. Am. Chem. Soc.* **1926**, *48*, 469 – 476.
[110] R. B. Bedford, A. F. Hill, A. R. Thompsett, A. J. P. White, D. J. Williams, *Chem. Commun.* **1996**, 1059 – 1060.
[111] I. Rhee, M. Ryang, S. Tsutsumi, *Tetrahedron Lett.* **1969**, 4593 – 4596.
[112] K. Takagi, C. S. Rousset, E. Negishi, *J. Am. Chem. Soc.* **1991**, *113*, 1440 – 1442.
[113] N. Krause, D. Seebach, *Chem. Ber.* **1987**, *120*, 1845 – 1851.
[114] Y. Hayashi, M. Osawa, Y. Wakatsuki, *J. Organomet. Chem.* **1997**, *542*, 241 – 246.
[115] S. Back, H. Pritzkow, H. Lang, *Organometallics* **1998**, *17*, 41 – 44.
[116] a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5526 – 5531; b) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518 – 5526; c) R. F. Heck, *J. Am. Chem. Soc.* **1969**, *91*, 6707 – 6714; d) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
[117] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467 – 4470; b) R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.* **1985**, *26*, 523 – 526.
[118] D. H. Cho, J. H. Lee, B. H. Kim, *J. Org. Chem.* **1999**, *64*, 8048 – 8050.
[119] N. G. Kundu, M. Pal, C. Chowdhury, *J. Chem. Res. Synop.* **1993**, 432 – 433.
[120] Q. Liu, D. J. Burton, *Tetrahedron Lett.* **1997**, *38*, 4371 – 4374.
[121] T. Hattori, M. Kijima, H. Shirakawa, *Synth. Met.* **1997**, *84*, 357 – 358.
[122] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, 3437 – 3440.
[123] J. Wityak, J. B. Chan, *Synth. Commun.* **1991**, *21*, 977 – 979.
[124] H. Dibowski, F. P. Schmidtchen, *Tetrahedron* **1995**, *51*, 2325 – 2330.
[125] C. Amatore, E. Blart, J. P. Genêt, A. Jutand, S. Lemaire-Audoire, M. Savignac, *J. Org. Chem.* **1995**, *60*, 6829 – 6839.
[126] V. Galamb, M. Gopal, H. Alper, *Organometallics* **1983**, *2*, 801 – 805.
[127] M. Vlassa, I. Ciocan-Tarta, F. Margineanu, I. Oprean, *Tetrahedron* **1996**, *52*, 1337 – 1342.
[128] J. Li, A. W.-H. Mau, C. R. Strauss, *Chem. Commun.* **1997**, 1275 – 1276.
[129] Numerous phosphane ligands used in palladium-catalyzed processes are thermally unstable. See for example W. A. Herrmann, C. Brossmer, K. Oefele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989 – 1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844 – 1848.
[130] J. K. Stille, B. L. Groh, *J. Am. Chem. Soc.* **1987**, *109*, 813 – 817.
[131] a) V. Farina in *Comprehensive Organometallic Chemistry*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, 161 – 240; b) T. N. Mitchell in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1997**, 167 – 202.
[132] L. Alcaraz, G. Macdonald, I. Kapfer, N. J. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1996**, *36*, 6619 – 6622.
[133] G. Macdonald, N. J. Lewis, R. J. K. Taylor, *Chem. Commun.* **1996**, 2647 – 2648.
[134] R. Takeuchi, Y. Tsuji, M. Fujita, T. Kondo, Y. Watanabe, *J. Org. Chem.* **1989**, *54*, 1831 – 1836.
[135] K. Takai, T. Kuroda, S. Nakatsukasa, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1985**, *26*, 5585 – 5588.
[136] E. Müller, A. Segnitz, *Liebigs Ann. Chem.* **1973**, 1583 – 1591.
[137] D. H. Berry, R. Eisenberg, *Organometallics* **1987**, *6*, 1796 – 1805.
[138] Ruthenium complexes have been applied to the homodimerization of terminal acetylenes to afford enynes in a reaction similar to the Straus coupling: C. S. Yi, N. Liu, *Synlett* **1999**, 281 – 287.
[139] T. Takahashi, Z. Xi, Y. Obora, N. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 2665 – 2666.
[140] C. M. Forsyth, S. P. Nolan, C. L. Stern, T. J. Marks, A. L. Rheingold, *Organometallics* **1993**, *12*, 3618 – 3623, and references therein.
[141] a) S.-M. Yang, M. C.-W. Chan, K.-K. Cheung, C.-M. Che, S.-M. Peng, *Organometallics* **1997**, *16*, 2819 – 2826; b) Y. Chi, A. J. Carty, P. Blenkiron, E. Delgado, G. D. Enright, W. Wang, S.-M. Peng, G.-H. Lee, *Organometallics* **1996**, *15*, 5269 – 5271.
[142] C.-W. Shiu, Y. Chi, C. Chung, S.-M. Peng, G.-H. Lee, *Organometallics* **1998**, *17*, 2970 – 2976.
[143] A. L. Klebansky, I. V. Grachev, O. M. Kuznetsova, *J. Gen. Chem. USSR* **1957**, *27*, 3008 – 3013.
[144] a) Y. S. Zalkind, Fr. B. Fundyler, *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 128 – 130; b) Y. S. Zalkind, B. M. Fundyler, *J. Gen. Chem. USSR* **1939**, *9*, 1725 – 1728.
[145] A. A. Clifford, W. A. Waters, *J. Chem. Soc.* **1963**, 3056 – 3062.
[146] F. Bohlmann, H. Schönowsky, E. Inhoffen, G. Grau, *Chem. Ber.* **1964**, *97*, 794 – 800.
[147] J. C. Kennedy, J. R. MacCallum, D. H. MacKerron, *Can. J. Chem.* **1995**, *73*, 1914 – 1923.
[148] a) H. J. Kevelam, K. P. de Jong, H. C. Meinders, G. Challa, *Makromol. Chem.* **1975**, *176*, 1369 – 1381; b) G. Challa, H. C. Meinders, *J. Mol. Catal.* **1977**, *3*, 185 – 190.
[149] E. G. Derouane, J. N. Brahm, R. Hubin, *Chem. Phys. Lett.* **1974**, *25*, 243 – 246.
[150] L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1974**, *10*, 934 – 936.
[151] L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1973**, *9*, 1806 – 1809.
[152] L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1976**, *12*, 1385 – 1387.
[153] a) L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1978**, *14*, 1328 – 1333; b) L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1978**, *14*, 1334 – 1337.
[154] a) H. M. Hoan, S. M. Brailovskii, O. N. Temkin, *Kinet. Catal. (Engl. Transl.)* **1994**, *35*, 242 – 246; b) H. M. Hoan, S. M. Brailovskii, O. N. Temkin, *Kinet. Catal. (Engl. Transl.)* **1994**, *35*, 431 – 435.
[155] B. M. Mykhalichko, *Russ. J. Coord. Chem. (Engl. Transl.)* **1999**, *25*, 336 – 341.
[156] H. Alper, M. Saldana-Maldonado, *Organometallics* **1989**, *8*, 1124 – 1125.
[157] N. A. Bumagin, A. B. Ponomarev, I. P Beletskaya, *B. Acad. Sci. USSR* **1984**, *33*, 1433 – 1438.
[158] C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 2053 – 2064.
[159] J. Breitenbach, J. Boosfeld, F. Vögtle in *Comprehensive Supramolecular Chemistry*, *Vol. 2* (Ed.: F. Vögtle), Pergamon, Oxford, **1996**, chap. 2, pp. 29 – 67.
[160] F. Bohlmann, H. Bornowski, C. Arndt, *Fortschr. Chem. Forsch.* **1962**, *4*, 138 – 272, and references therein.
[161] F. Bohlmann, T. Burkhardt, C. Zdero, *Naturally Occurring Acetylenes*, Academic Press, New York, **1973**.
[162] E. H. R. Jones, V. Thaller in *Handbook of Microbiology*, *Vol. 3* (Eds.: A. I. Laskin, H. A. Lechevalier), CRC, Cleveland, **1973**, pp. 63 – 74.
[163] M. Yamaguchi, H.-J. Park, M. Hirama, K. Torisu, S. Nakamura, T. Minami, H. Nishihara, T. Hiraoka, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1717 – 1725.
[164] N. A. Sörensen, *Proc. Chem. Soc. London* **1961**, 98 – 110.
[165] J. D. BuLock, *Prog. Org. Chem.* **1964**, *6*, 86 – 134.
[166] E. R. H. Jones, *Chem. Br.* **1966**, 6 – 13.
[167] F. Bohlmann, *Fortschr. Chem. Forsch.* **1966**, *6*, 65 – 100.
[168] G. Zheng, W. Lu, J. Cai, *J. Nat. Prod.* **1999**, *62*, 626 – 628.
[169] S. C. Shim, T. S. Lee, *J. Org. Chem.* **1988**, *53*, 2410 – 2413.
[170] P. Quayle, S. Rahman, J. Herbert, *Tetrahedron Lett.* **1995**, *36*, 8087 – 8088.
[171] W. Lu, G. Z. Haji, A. Aisa, J. Cai, *Tetrahedron Lett.* **1998**, *39*, 9521 – 9522.
[172] L. Hansen, P. M. Boll, *Phytochemistry* **1986**, *25*, 285 – 293.
[173] J. N. Gardner, E. R. H. Jones, P. R. Leeming, J. S. Stephenson, *J. Chem. Soc.* **1960**, 691 – 697.

[174] R. Jente, F. Bosold, J. Bäuerle, T. Anke, *Phytochemistry* **1985**, *24*, 553 – 559.
[175] An earlier, less efficient synthesis of panaxydol by Cadiot – Chodkiewicz coupling has also been reported: J. Poplawski, J. T. Wrobel, T. Glinka, *Phytochemistry* **1980**, *19*, 1539 – 1541.
[176] a) A. Stütz, G. Petranyi, *J. Med. Chem.* **1984**, *27*, 1539 – 1543; b) A. Stütz, W. Granitzer, S. Roth, *Tetrahedron* **1985**, *41*, 5685 – 5696.
[177] T. A. Prikhodko, V. M. Kurilenko, Z. N. Khlienko, S. F. Vasilevskii, M. S. Shvartsberg, *Izv. Akad. Nauk. SSR Ser. Khim.* **1988**, 120 – 127.
[178] M. G. Saulnier, D. B. Frennesson, M. S. Deshpande, D. M. Vyas, *Tetrahedron Lett.* **1995**, *36*, 7841 – 7844.
[179] E. Ottow, R. Rohde, W. Schwede, R. Wiechert, *Tetrahedron Lett.* **1993**, *34*, 5253 – 5256.
[180] A. V. R. Rao, E. R. Reddy, G. V. M. Sharma, P. Yadagiri, J. S. Yadav, *Tetrahedron Lett.* **1986**, *42*, 4523 – 4532.
[181] P. I. Svirskaya, C. C. Leznoff, W. L. Roelofs, *Synth. Commun.* **1980**, *10*, 391 – 397.
[182] S. Rødbotten, T. Benneche, K. Undheim, *Acta Chem. Scand.* **1997**, *51*, 873 – 880.
[183] a) H. Hopf, N. Krause, *Tetrahedron Lett.* **1985**, *26*, 3323 – 3326; b) N. Krause, H. Hopf, L. Ernst, *Liebigs Ann. Chem.* **1986**, 1398 – 1406.
[184] a) M. D. Lee, G. A. Ellestad, D. B. Borders, *Acc. Chem. Res.* **1991**, *24*, 235 – 243; b) I. H. Goldberg, *Acc. Chem. Res.* **1991**, *24*, 191 – 198; c) K. C. Nicolaou, A. L. Smith in *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, chap. 7, pp. 203 – 283.
[185] D. Elbaum, T. B. Nguyen, W. L. Jorgensen, S. L. Schreiber, *Tetrahedron* **1994**, *50*, 1503 – 1518.
[186] J.-P. Gotteland, I. Brunel, F. Gendre, J. Désiré, A. Delhon, D. Junquéro, P. Oms, J. Halazy, *J. Med. Chem.* **1995**, *38*, 3207 – 3216.
[187] For the inhibition of HMG-CoA reductase, another important enzyme in cholesterol biosynthesis, by polyacetylenic fatty acids, see S. Y. Mhaskar, G. Lakshminarayana, *Synth. Commun.* **1990**, *20*, 2001 – 2009.
[188] a) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, J. Uenishi, *J. Am. Chem. Soc.* **1982**, *104*, 5555 – 5557; b) K. C. Nicolaou, N. A. Petasis, J. Uenishi, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, *104*, 5557 – 5558; c) K. C. Nicolaou, R. E. Zipkin, N. A. Petasis, *J. Am. Chem. Soc.* **1982**, *104*, 5558 – 5560; d) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, *104*, 5560 – 5562.
[189] W. M. Bandaranayake, J. E. Banfield, D. S. C. Black, *J. Chem. Soc. Chem. Commun.* **1980**, 902 – 903.
[190] a) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**; b) C. Seel, A. Galán, J. de Mendoza, *Top. Curr. Chem.* **1995**, *175*, 101 – 132; c) B. J. Whitlock, H. W. Whitlock in *Comprehensive Supramolecular Chemistry*, *Vol. 2* (Ed.: F. Vögtle), Pergamon, Oxford, **1996**, chap. 10, pp. 309 – 324.
[191] D. O'Krongly, S. R. Denmeade, M. Y. Chiang, R. Breslow, *J. Am. Chem. Soc.* **1985**, *107*, 5544 – 5545.
[192] a) S. Claude, J.-M. Lehn, F. Schmidt, J.-P. Vigneron, *J. Chem. Soc. Chem. Commun.* **1991**, 1182 – 1185; b) P. Cudic, M. Zinic, V. Tomisic, V. Simeon, J.-P. Vigneron, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1995**, 1073 – 1075; c) P. Cudic, M. Zinic, V. Skaric, R. Kiralj, B. Kojic-Prodic, J.-P. Vigneron, J.-M. Lehn, *Croat. Chem. Acta* **1996**, *69*, 569 – 611.
[193] A. Lorente, M. Fernández-Saiz, J.-M. Lehn, J.-P. Vigneron, *Tetrahedron Lett.* **1995**, *36*, 8279 – 8282.
[194] a) B. R. Peterson, T. Mordasini-Denti, F. Diederich, *Chem. Biol.* **1995**, *2*, 139 – 146; b) A. Fürer, T. Marti, F. Diederich, H. Künzer, M. Brehm, *Helv. Chim. Acta* **1999**, *82*, 1843 – 1859.
[195] a) S. Anderson, U. Neidlein, V. Gramlich, F. Diederich, *Angew. Chem.* **1995**, *107*, 1722 – 1724; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1596 – 1600; b) A. Bähr, A. S. Droz, M. Püntener, U. Neidlein, S. Anderson, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1998**, *81*, 1931 – 1963.
[196] M. J. Cloninger, H. W. Whitlock, *J. Org. Chem.* **1998**, *63*, 6153 – 6159.
[197] C. A. Hunter, *Chem. Soc. Rev.* **1994**, 101 – 109, and references therein.
[198] For review articles, see a) S. Anderson, H. L. Anderson, J. K. M. Sanders, *Acc. Chem. Res.* **1993**, *26*, 469 – 475; b) J. K. M. Sanders in *Comprehensive Supramolecular Chemistry*, *Vol. 9* (Eds.: J.-P. Sauvage, M. W. Hosseini), Pergamon, Oxford, **1996**, chap. 4, pp. 131 – 164; c) S. Anderson, H. L. Anderson in *Templated Organic Synthesis* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1999**, chap. 1, pp. 1 – 38.
[199] D. W. J. McCallien, J. K. M. Sanders, *J. Am. Chem. Soc.* **1995**, *117*, 6611 – 6612.
[200] H. L. Anderson, S. Anderson, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2231 – 2245.
[201] C. J. Walter, J. K. M. Sanders, *Angew. Chem.* **1995**, *107*, 231 – 233; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 217 – 219.
[202] L. G. Mackay, R. S. Wylie, J. K. M. Sanders, *J. Am. Chem. Soc.* **1994**, *116*, 3141 – 3142.
[203] V. Marvaud, A. Vidal-Ferran, S. J. Webb, J. K. M. Sanders, *J. Chem. Soc. Dalton Trans.* **1997**, 985 – 990.
[204] D. G. Hamilton, L. Prodi, N. Feeder, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1057 – 1065.
[205] J. M. Tour, *Chem. Rev.* **1996**, *96*, 537 – 553.
[206] R. E. Martin, F. Diederich, *Angew. Chem.* **1999**, *111*, 1440 – 1469; *Angew. Chem. Int. Ed.* **1999**, *38*, 1350 – 1377.
[207] a) A. S. Hay, *J. Polym. Sci. Part A* **1969**, *7*, 1625 – 1634; b) for the synthesis of very long oligothiophenes using Eglinton conditions, see H. Nakanishi, N. Sumi, Y. Aso, T. Otsubo, *J. Org. Chem.* **1998**, *63*, 8632 – 8633; c) for other linear couplings under Eglinton conditions, see also reference [54].
[208] a) N. C. Greenham, S. C. Moratti, D. D. C. Bradley, R. H. Friend, A. B. Holmes, *Nature* **1993**, *365*, 628 – 630; b) J. L. Brédas, *Adv. Mater.* **1995**, *7*, 263 – 274.
[209] a) R. Eastmond, T. R. Johnson, D. R. M. Walton, *Tetrahedron* **1972**, *28*, 4601 – 4616; b) R. Eastmond, D. R. M. Walton, *Tetrahedron* **1972**, *28*, 4591 – 4599.
[210] R. E. Martin, T. Mäder, F. Diederich, *Angew. Chem.* **1999**, *111*, 834 – 838; *Angew. Chem. Int. Ed.* **1999**, *38*, 817 – 821.
[211] a) R. R. Tykwinski, F. Diederich, *Liebigs Ann. Chem.* **1997**, 649 – 661; b) R. R. Tykwinski, U. Gubler, R. E. Martin, F. Diederich, C. Bosshard, P. Günter, *J. Phys. Chem. B* **1998**, *102*, 4451 – 4465.
[212] M. Mayor, J.-M. Lehn, K. M. Fromm, D. Fenske, *Angew. Chem.* **1997**, *109*, 2468 – 2471; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2370 – 2372.
[213] G. S. Wilson, H. L. Anderson, *Chem. Commun.* **1999**, 1539 – 1540.
[214] a) U. H. F. Bunz, *Angew. Chem.* **1996**, *108*, 1047 – 1049; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 969 – 971; b) F. Coat, C. Lapinte, *Organometallics* **1996**, *15*, 477 – 479.
[215] U. H. F. Bunz, *Synlett* **1997**, 1117 – 1127.
[216] a) U. H. F. Bunz, *Pure Appl. Chem.* **1996**, *68*, 309 – 312; b) U. H. F. Bunz, *Top. Curr. Chem.* **1999**, *201*, 132 – 161.
[217] a) F. Diederich, R. Faust, V. Gramlich, P. Seiler, *J. Chem. Soc. Chem. Commun.* **1994**, 2045 – 2046; b) R. Faust, F. Diederich, V. Gramlich, P. Seiler, *Chem. Eur. J.* **1995**, *1*, 111 – 117.
[218] P. Siemsen, F. Diederich, unpublished results.
[219] a) J. Alzeer, C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 242 – 264; b) C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 732 – 757; c) C. Cai, A. Vasella, *Helv. Chim. Acta* **1996**, *79*, 255 – 268; d) A. Ernst, L. Gobbi, A. Vasella, *Tetrahedron Lett.* **1996**, *37*, 7959 – 7962; e) T. V. Bohner, R. Beaudegnies, A. Vasella, *Helv. Chim. Acta* **1999**, *82*, 143 – 160.
[220] T. V. Bohner, O.-S. Becker, A. Vasella, *Helv. Chim. Acta* **1999**, *82*, 198 – 228.
[221] a) J. M. J. Tronchet, A.-P. Bonenfant, *Helv. Chim. Acta* **1977**, *60*, 892 – 895; b) J. M. J. Tronchet, A.-P. Bonenfant, *Helv. Chim. Acta* **1981**, *64*, 1893 – 1901.
[222] M. Nakagawa, *Angew. Chem.* **1979**, *91*, 215 – 226; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 202 – 214.
[223] L. T. Scott, M. J. Cooney in *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, pp. 321 – 351.
[224] a) F. Diederich, L. Gobbi, *Top. Curr. Chem.* **1999**, *201*, 43 – 79; b) F. Diederich, *Nature* **1994**, *369*, 199 – 207; c) F. Diederich, Y. Rubin, *Angew. Chem.* **1992**, *104*, 1123 – 1146; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1101 – 1123.
[225] a) B. König, *Top. Curr. Chem.* **1998**, *196*, 91 – 136; b) U. H. F. Bunz, Y. Rubin, Y. Tobe, *Chem. Soc. Rev.* **1999**, *201*, 43 – 79.
[226] A. de Meijere, S. Kozhushkov, T. Haumann, R. Boese, C. Puls, M. J. Cooney, L. T. Scott, *Chem. Eur. J.* **1995**, *1*, 124 – 131.

[227] a) A. M. Boldi, F. Diederich, *Angew. Chem.* **1994**, *106*, 482 – 485; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 468 – 471; b) J. Anthony, A. M. Boldi, C. Boudon, J.-P. Gisselbrecht, M. Gross, P. Seiler, C. B. Knobler, F. Diederich, *Helv. Chim. Acta* **1995**, *78*, 797 – 817.
[228] M. Schreiber, R. R. Tykwinski, F. Diederich, R. Spreiter, U. Gubler, C. Bosshard, I. Poberaj, P. Günter, C. Boudon, J.-P. Gisselbrecht, M. Gross, U. Jonas, H. Ringsdorf, *Adv. Mater.* **1997**, *9*, 339 – 343.
[229] R. R. Tykwinski, *Chem. Commun.* **1999**, 905 – 906.
[230] S. W. McElvany, M. M. Ross, N. S. Goroff, F. Diederich, *Science* **1993**, *259*, 1594 – 1596.
[231] Y. Rubin, T. C. Parker, S. J. Pastor, S. Jalisatgi, C. Boulle, C. L. Wilkins, *Angew. Chem.* **1998**, *110*, 1353 – 1356; *Angew. Chem. Int. Ed.* **1998**, *37*, 1226 – 1229.
[232] a) Y. Tobe, N. Nakagawa, K. Naemura, T. Wakabayashi, T. Shida, Y. Achiba, *J. Am. Chem. Soc.* **1998**, *120*, 4544 – 4545; b) Y. Tobe, H. Nakanishi, M. Sonoda, T. Wakabayashi, Y. Achiba, *Chem. Commun.* **1999**, 1625 – 1626.
[233] a) H. L. Anderson, R. Faust, Y. Rubin, F. Diederich, *Angew. Chem.* **1994**, *106*, 1427 – 1429; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1366 – 1368; b) P. Timmerman, H. L. Anderson, R. Faust, J.-F. Nierengarten, T. Habicher, P. Seiler, F. Diederich, *Tetrahedron* **1996**, *52*, 4925 – 4947; c) P. Timmerman, L. E. Witschel, F. Diederich, C. Boudon, J.-P. Gisselbrecht, M. Gross, *Helv. Chim. Acta* **1996**, *79*, 6 – 20; d) L. Isaacs, P. Seiler, F. Diederich, *Angew. Chem.* **1995**, *107*, 1636 – 1639; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1466 – 1469; e) L. Isaacs, F. Diederich, R. F. Haldiman, *Helv. Chim. Acta* **1997**, *80*, 317 – 342.
[234] a) R. Boese, A. J. Matzger, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1997**, *119*, 2052 – 2053; b) P. I. Dosa, C. Erben, V. S. Iyer, K. P. C. Vollhardt, I. M. Wasser, *J. Am. Chem. Soc.* **1999**, *121*, 10430 – 10431.
[235] a) S. Höger, A.-D. Meckenstock, H. Pellen, *J. Org. Chem.* **1997**, *62*, 4556 – 4557; b) S. Höger, A.-D. Meckenstock, *Tetrahedron Lett.* **1998**, *39*, 1735 – 1736.

+++ THE LINK TO INTERNATIONAL CHEMISTRY +++

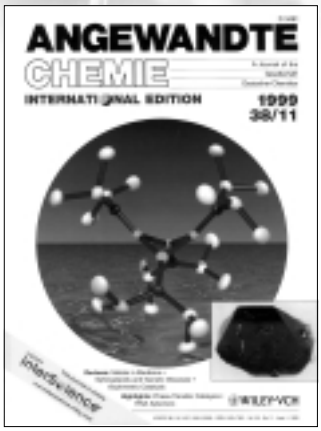


"It is a long time since I have read one issue of a journal [...] which has so much of interest...

...to process R&D chemists and engineers as issue No. 23 in Vol. 36 of *Angewandte Chemie.*

Trevor Laird, Editor of Organic Process Research & Development
[Org. Process Res. Dev. 1998, 2, 64]

The Highlights in *Angewandte* provide concise evaluations of the most important current trends in chemical research.



The most cited Highlights in 1998 are:

- *A.E. Rowan, R.J.M Nolte:* Helical Molecular Programming
- *N. Krause:* Copper-Catalyzed Enantioselective Michael Additions: Recent Progress with New Phosphorus Ligands
- *O. Geis, H.-G. Schmalz:* New Developments in the Pauson - Khand Reaction
- *J.E. Cosgriff, G.B. Deacon:* Another Surprise from Pyrazolate Ligands
- *C. Schneider:* New Polyol Syntheses
- *A.P. Davis:* Tilting at Windmills? The Second Law Survives
- *J.O. Metzger:* Solvent-Free Organic Syntheses
- *H. Frey:* From Random Coil to Extended Nanocylinder: Dendrimer Fragments Shape Polymer Chains
- *J.D. Smith:* Phosphanides of the Heavier Alkali Metals
- *D. Wolf :* High Yields of Methanol from Methane by C-H Bond Activation at Low Temperatures
- *P. Luger:* Large Molecules from the Virtual Bakery - Filling a Gap in Structure Research
- *V. Fehring, R. Selke:* Highly Enantioselective Complex-Catalyzed Reduction of Ketones - Now with Purely Aliphatic Derivations Too

Have your own Highlights every two weeks. Subscribe to *Angewandte* with the Order Form on the last page of this issue.

WILEY-VCH, P.O. Box 10 11 61, 69451 Weinheim, Germany
Phone +49 (6201) 606-328, Fax +49 (6201) 606-348
e-mail: sales-journals@wiley-vch.de, http://www.wiley-vch.de

WILEY-VCH

SCHULZ1299<ACHUNK1>