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# 1,4-Diynes from alkynyl–propargyl coupling reactions

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**Abstract**

This review deals with state-of-the-art propargylation of metal-alkynyls. After outlining the importance of the –C≡C–Csp$^3$–C≡C– sequence in organic and organometallic molecules, processes for obtaining these 'skipped diynes' from metal-alkynyls (or metal acetylides –C≡C–[M]) and propargyl electrophiles (X–CR$_1$R$_2$–C≡C– or X=CR–C≡C–) are classified according to the nature of the metal (M = Li, Na, K, Mg, Cu, Zn, Al, Si, –CMe$_2$OAl(OR)$_2$, ...) and to the hybridization state of the electrophilic carbon (sp$^3$, sp$^2$). The allenic/propargylic regioselectivity being crucial, emphasis is placed on methods resorting to pre-complexation of the propargylic moiety with transition-metals: $\eta^2/\eta^3$ coordination with cobalt, and $\eta^1$ coordination with ruthenium are specifically discussed. Whenever such processes have been used for definite synthetic purposes, the ultimate target is mentioned. For comparison, alternative routes to skipped diynes are illustrated by a few recent examples.


*Keywords:* Skipped diynes; Acetylide; Propargylation; 1,4-Diynes; Alkynes complexes

## 1. Introduction and scope

The 1,4-diyn-1,5-diyl unit, where a sp$^3$ carbon center separates two triple bonds, is the central function of the so-called *skipped diynes*. Its specific consideration is relevant with respect to three standpoints.

i) In bioorganic chemistry, just like isoprene is the branched C$_5$ brick of terpenes, 1,4-pentadiyne could be regarded as a linear C$_5$ brick occurring in natural products [1]. Its allenyne tautomeric form was also recognized early in mycomycin and other natural molecules [2]. From a synthetic point of view, the brick mainly appears as a common hydrogenable precursor of *cis*-unsaturated fatty acids, arachidonic acids, leukotrienes, prostaglandins etc.

ii) In general synthetic organic and organometallic chemistry, 1,4-pentadiyne is a hydrocarbon equivalent of 1,2,4,5-pentatetraol. It is an attractive synthon for versatile construction and functionalization of new carbon skeletons. For example, it served as a link in fullerene–acetylene hybrids [3a], was introduced in strained carbon rings, via its double coordinating ability towards Co$_2$(CO)$_6$ units [3b], and exhibits original organometallic chemistry, e.g. with hydridoazavinilidene ruthenium clusters [3c].

iii) In physical organic chemistry, the long known tautomeric instability of 3-unsubstituted derivatives, with respect to allenynes [4], might be partly controlled by double homoconjugation of the orthogonal π systems through the sp$^3$ carbon center. The VSEPR geometry of the C$_5$ skeleton is indeed planar, and the question of homoconjugation is general for all derivatives, and especially for pericyclynes [5]. Very recently, the possibility of Bergman-like cycloaromatization of the penta-1,4-diyn-3-yl anion to a cyclopentadienyl anion has been theoretically envisioned [6].

While catalytic methods for Csp–Csp (Glaser, Eglington, Hay, Cadiot-Chodkiewicz) [7b] and Csp–Csp$^2$ (Sonogashira) [7c] bond formation are widely documented, methods for Csp–Csp$^3$ bond formation mainly rely on classical ionic routes [7a,7d,7e]. Three main pathways

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to skipped diynes are therefore currently envisioned, depending on the strategy for introducing the sp–sp–$sp^3$–sp–sp hybridization sequence and the propargylic C–C bond (Scheme 1).

i) In route C, the hybridization sequence is introduced *after* the construction of the $C_5$ skeleton. This alternative route will be merely illustrated by recent relevant examples at the end of this review.
ii) In routes A and B, the hybridization sequence and the propargylic bond are installed *simultaneously*. Owing to the acidity of acetylenic protons, the metal-alkynyl route A is by far the most natural, and henceforth is our central concern. The alternative propargyl-metal route B, an 'umpolung' of route A, is however exemplified at the end of this report.

On the other hand, the selectivity is a priori affected by the possibility of propargyl–allenyl isomerization or 'mesomerization' when the $Csp^3$ center corresponds to CHR or $CH_2$ group [4].

This review thus focuses on recent advances in the direct preparation of $sp^3$-skipped diynes from metal-alkynyls (or metal acetylides) and propargylic electrophiles via route A. Preparation of vinylidene $sp^2$-skipped diynes from haloenynes is thoroughly covered by specific reviews on Sonogashira coupling reactions [7c,7e], and remains beyond the scope of this report [8]. Likewise, preparation of oxo $sp^2$-skipped diynes R–C≡C–C(=O)–C≡C–R′ (e.g. from R–C≡C–COCl and $Me_3Si$–C≡C–$SiMe_3$ under Friedel-Craft conditions) will not be considered [9].

In the first part, classical procedures from free propargyl electrophiles are reviewed and classified according to: (i) the starting hybridization state of the electrophilic center ($sp^3$ in substitution processes, $sp^2$ in addition processes); and (ii) the metal counterpart of the acetylide. Procedures resorting to Lewis acid activation are highlighted. In the second part, procedures resorting to pre-complexation of the propargylic electrophile with transition metal are discussed in detail. The treated reactions were often reported as particular applications of more general processes: procedures compatible with both alkynyl *and* propargyl reactants are emphasized.

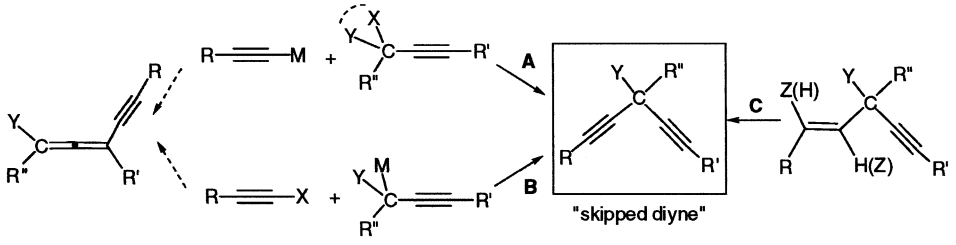
## 2. Free propargylic electrophiles

### 2.1. $sp^3 \rightarrow sp^3$ Substitution processes

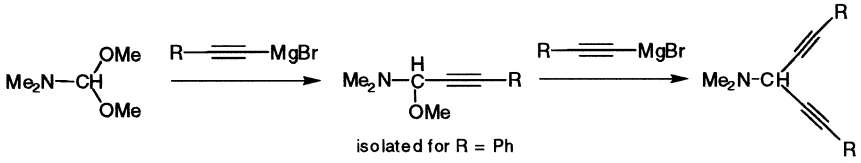
#### 2.1.1. Monometallic metal-alkynyl systems

*2.1.1.1. Lithium-, sodium- and magnesium-alkynyls.* Early examples of direct substitution appeared in 1933, when 1,5-disubstituted alka-1,4-diynes were prepared from sodium acetylene [10]. Since that time, few direct substitutions of propargyl halides with lithium and magnesium acetylides have been reported. This procedure generally leads to moderate yields [11], although few exceptions are found [12]. In particular, a double substitution of methoxy groups of a dialkylaminoacetal was reported to take place with up to 82% yield (Scheme 2) [13]. Similar results were obtained through an addition–elimination process from R–C≡C–MgBr and the iminium salt Cl–CH=$NMe_2^+X^-$ (except for R = $SiMe_3$) (see Section 2.2.1) [13].

*2.1.1.2. Copper-alkynyls.* Preformed Group 11 metal acetylides, such as silver acetylides, were claimed to react not efficiently with propargyl chlorides and bromides [14]. Under coupling conditions however, the Cu(I)-promoted Csp–Csp Cadiot–Chodkiewicz cou-




Scheme 1. Regiochemical ambiguity and main routes to skipped diynes. Route A: metal-alkynyl+propargyl electrophile. Route B: metal-propargyl+alkynyl electrophile. Route C: elimination from alkene precursors.




Scheme 2. Double substitution of methoxy groups by Grignard acetylides [13].

Table 1
Influence of the amine base in Cadiot's CuCl-catalyzed alkynyl–propargyl coupling reactions (Scheme 3) [15]

| Reagents | Products | Amines | Selectivity in β-diyne (%) |
|---|---|---|---|
| $HOCH_2–C≡CH + ClCH_2C≡CH$ | $HOCH_2–C≡C–CH_2–C≡CH$ | $NH_4OH$ | 5 |
| $Me(HO)CH–C≡CH + ClCH_2–C≡C–Me$ | $Me(HO)CH–C≡C–CH_2–C≡C–Me$ | $t$-$BuNH_2$ | 95 |
| $Me_2C(OH)–C≡CH + ClCH_2–C≡C–Me$ | $Me_2C(OH)–C≡C–CH_2–C≡C–Me$ | $t$-$BuNH_2$ | 95 |
| $Me_2C(OH)–C≡CH + ClCH(Me)–C≡C–Me$ | $Me_2C(OH)–C≡C–CH(Me)C≡C–Me$ | $N$-Methyl-morphine | 75 |

pling reaction [7b] can be generalized to $Csp–Csp^3$ coupling reactions. Thus, reactions of terminal alkynes with $X–CH_2–C≡C–R'$ electrophiles ($R' \neq H$) in the presence of CuCl catalyst (ca. 5%) and an amine base (1.2 equivalents) afford 1,4-pentadiynes [15]. Likely due to steric effects, when the propargyl is itself a terminal alkyne ($R' = H$), the regioselectivity is reversed to the allenic product. The amine promotes the formation of the copper-alkynyl reagent and traps the resulting HX residue (Table 1). *tert*-Butylamine gives satisfactory results, but other bulky bases such as DBU were also reported [16] (Scheme 3).

### 2.1.2. Bimetallic metal-alkynyl systems

*2.1.2.1. Magnesium–copper systems.* After unsuccessful attempts to promote propargylation of magnesium acetylides in the presence of various metal salts ($CdCl_2$, $AgNO_3$, $MnCl_2$, $CoCl_2$, $FeCl_2$), it was early recognized that primary propargyl halides and pseudo-halides can be readily converted to 1,4-pentadiynes by reaction with magnesium–copper acetylide systems [17]. The procedure has been then widely utilized under either stoichiometric or catalytic conditions [18].

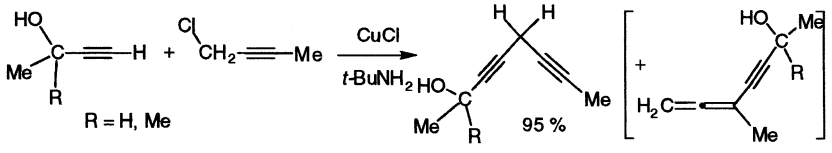
In the presence of a stoichiometric amount of copper(I), the reaction rate is enhanced by addition of HMPA which dissolves the copper salt [19].

In the presence of a catalytic amount of copper(I) chloride, THF appears as a solvent of choice [20]. Absence of copper or use of diethylether as solvent results in lower yields (e.g. the yield in 1-phenyl-penta-1,4-diyne from phenylethynylmagnesium bromide and propargyl bromide drops from 57 to ca. 25%). Neutral workup conditions are also required in order to prevent isomerization to the allenyne product.

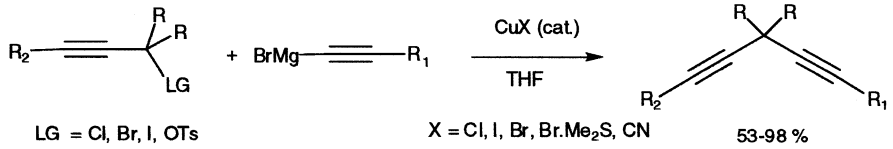
Many analogous CuX-catalyzed propargylation of Grignard acetylides (X = Cl, Br, I, CN) with different leaving groups LG = Cl [21], Br [22], I [23], OTs [24] have been reported (Scheme 4).

The CuCl-catalyzed method has been used sequentially for the preparation of linear skipped polyynes containing terminal acetylene groups (Scheme 5) [25].

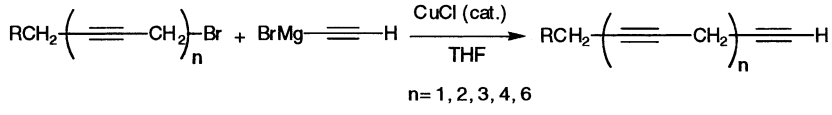
Most substrates are *primary* halides. Scott and de Meijere, however, applied this principle for the substitu-



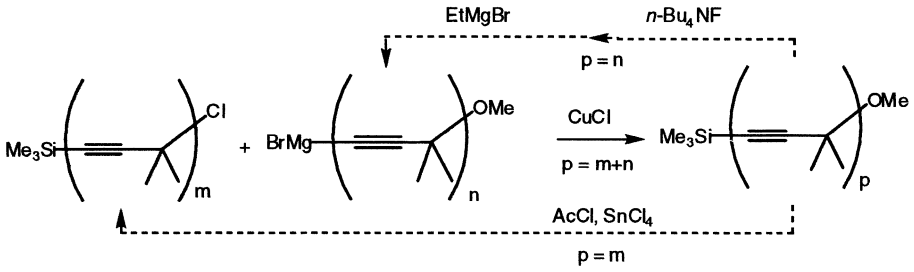

Scheme 3. Cadiot's CuCl-catalyzed coupling of alkynes with primary propargyl halides [15].



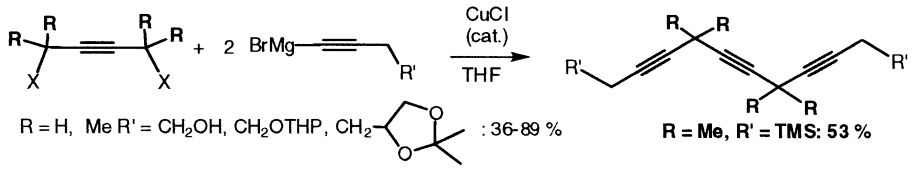

Scheme 4. CuX-catalyzed propargylation of Grignard acetylides. Representative examples are: R = H, Me; $R_1 = CH_2OTHP$, H, $(CH_2)_2OMgBr$, TMS, $t$-Bu, $CH_2TMS$, CH=CHCH(Et)OMgBr, CH=CH–$CH_2OCH$=CHOEt, $(CH_2)_2OTHP$, $CH_2–C≡C–C_8H_{17}$, $CH_2–C≡C–C_9H_{19}$, $CH_2–C≡C–C_{10}H_{21}$. $R_2$ = H, $CH_2TMS$, TMS, $C_5H_{11}$, $(CH_2)_2OSi(t\text{-}Bu)Ph_2$, $(CH_2)_7CO_2H$, $(CH_2)_2Br$, $(CH_2)_4OTHP$, $C_8H_{17}$, $C_9H_{19}$, $C_{10}H_{21}$, $CH_2–CH=CH_2$ [20–26].




Scheme 5. Sequential application of the CuCl-catalyzed coupling of Grignard acetylides with propargyl bromides [25].




Scheme 6. Scott's procedures for coupling Grignard acetylides with tertiary propargyl chlorides [26].




Scheme 7. One-pot Cu(I)-catalyzed bispropargylic disubstitution by Grignard acetylides [17,26,27].

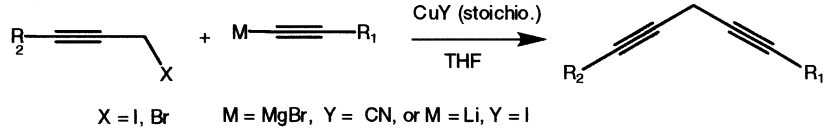
tion of *tertiary* propargyl chlorides (Scheme 6) in either step-by-step or block-to-block preparations of linear precursors of permethylated pericyclynes [26]. Nevertheless, the authors had to resort to another Csp–Csp$^3$ coupling procedure for the final ring closing step (see below, Scheme 19).

Likewise, double CuCl-catalyzed substitutions of bispropargylic dichlorides and dibromides were carried out under one-pot conditions (Scheme 7) [17,27]. Scott and de Meijere applied their method for substituting tertiary propargylic chlorides with Grignard acetylides in a bispropargylic version [26].

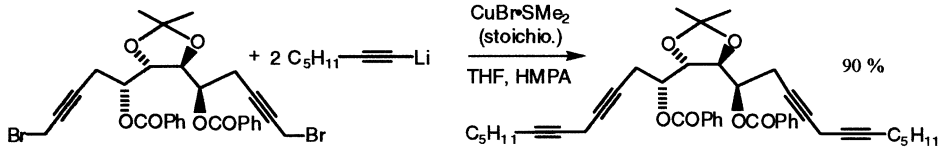
*2.1.2.2. Lithium–copper systems.* In the presence of stoichiometric amounts of copper(I), propargyl halides react efficiently with *lithium* acetylides (Scheme 8) [28].

The lithium procedure was successfully applied in a one-pot double substitution of a well defined ω-bispropargylic dibromide for the synthesis of 9-HETE (Scheme 9) [29].

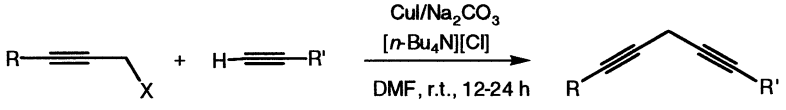
*2.1.2.3. Sodium/potassium–copper systems.* In 1992, Jeffery *et al*. reported on a convenient procedure for coupling primary propargyl halides with terminal alkynes in the presence of copper(I) salts [30]. Preliminary




Scheme 8. Copper-catalyzed propargylic substitutions by either lithium or magnesium acetylides [28].




Scheme 9. En route to 9-HETE, double CuCl-catalyzed propargylic substitution by a lithium acetylide [29].




Scheme 10. Jeffery–Gueugnot–Linstrumelle procedure [31].

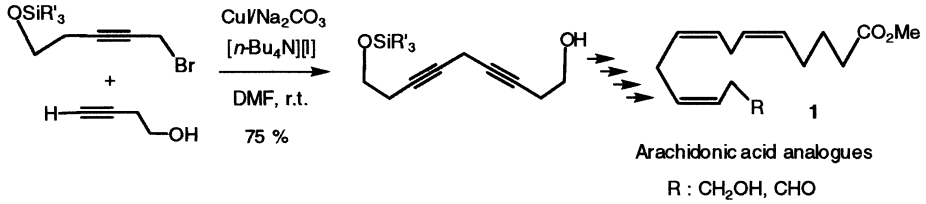
Table 2
Examples of Jeffery–Gueugnot–Linstrumelle procedures for the coupling of alkynes with various primary propargyl halides (conditions in Scheme 10) [31]

| X | R | R′ | Yield (%) |
|---|---|---|---|
| Cl | $-CH_2OH$ | $-C_5H_{11}$ | 91 |
| Br | $-SiMe_3$ | $-(CH_2)_3COOMe$ | 76 |
| I | $-CH_2CH_3$ | $-CH_2OH$ | 84 |
| OTs | $-CH_2CH_3$ | $-CH_2OH$ | 76 |

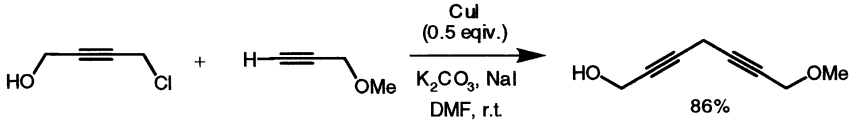
deprotonation of the alkyne with strong metal-alkyl bases (EtMgBr, *n*-BuLi, ...) is no longer required. Instead, reversible deprotonation is induced in situ by sodium carbonate. The reaction yield is improved by adding tetrabutylammonium chloride in the medium. In most cases, copper iodide is added in *stoichiometric* amounts with respect to primary propargyl bromides (Scheme 10, Table 2) [31].

The role of the ammonium salt is not clearly established, but it was shown that chloride can be replaced for iodide. Recently, this procedure has been frequently used, e.g. for the synthesis of HEPE ((8*R*)-hydroxy-eicosa-(5*Z*, 9*E*, 11*Z*, 14*Z*, 17*Z*)-pentaenoic acid) [32], pheromones [33] and arachidonic acid analogues **1** depicted in Scheme 11 [34].

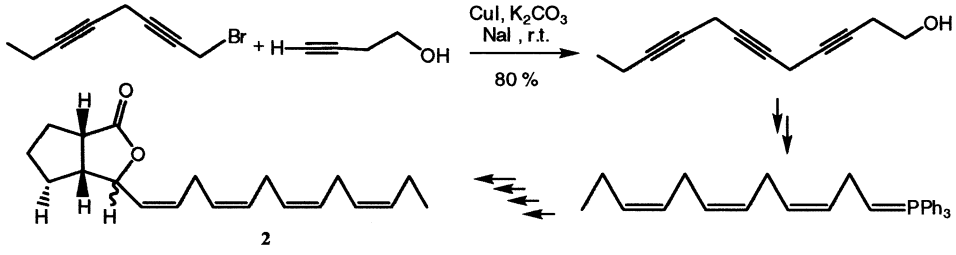
In 1993, Pivnitsky and coworkers replaced tetrabutylammonium halides for sodium iodide, and sodium carbonate for potassium carbonate (66–92% yield) [35]. In 1998, Parrain and Santelli reported on a systematic study of this reaction (Scheme 12) [36]. Under optimized conditions, the propargylic–allenic coupling ratio figures up to ca. 90/10. The regioselectivity is dependent on the nature of the copper salt, the temperature, and the nature of the leaving group. The authors highlight the prevalent role of DMF as solvent for dissolving the cuprous salt. The reaction can also be conducted in water, albeit in much lower yields. Use of stoichiometric amounts of copper leads to slightly better yields, but the work-up is then more tedious. The conditions are compatible with all kinds of substituents at the alkynyl and primary propargyl reactants.



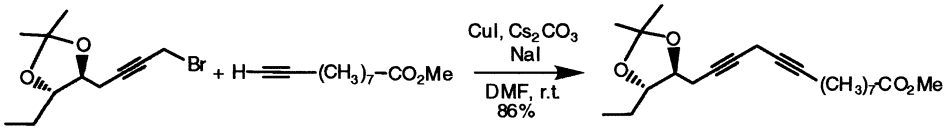

Scheme 11. Application of the iodide-modified Jeffery–Gueugnot–Linstrumelle procedure [31].



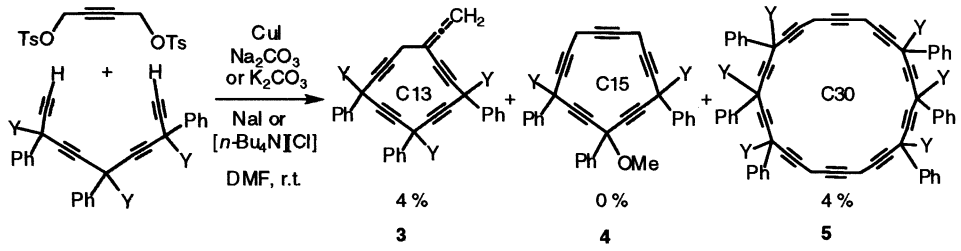

Scheme 12. Parrain–Santelli optimized conditions for alkynyl–propargyl coupling [36].




Scheme 13. Synthesis of bacillariolide via NaI-modified Pivnitsky–Parrain–Santelli alkynyl–propargyl coupling [40].




Scheme 14. Cesium–copper system for alkynyl–propargyl coupling in the presence of NaI [42].




Scheme 15. Synthesis of C13 and C30 cyclic skipped polyynes **3** and **5** [43].

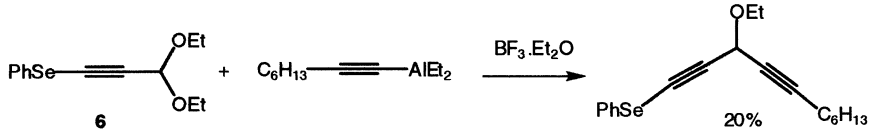
The sodium iodide procedure was recently used for the synthesis of linoleic acid [37], pheromones [38], lipoxygenase substrates [39], a polyene fragment of bacillariolide **2** (Scheme 13) [40], and other fatty acid derivatives [41]. In some examples, cesium carbonate has also been used in place of sodium or potassium carbonate (Scheme 14) [42].

A cyclizing version of this reaction has been attempted for the preparation of a functional [5]pericyclyne **4** from 1,4-ditosyloxybut-2-yne and an undecatetrayne precursor [43]. Beside several acyclic skipped polyynes, two cyclic products were isolated (Scheme 15). An *exo*-allenic isomer **3** was the sole product resulting from a $S_{N'}$ Csp–Csp coupling process. The latter is likely driven by ring strain effects. A [10]pericyclyne dimer **5** (a functional 'ring carbomer' of cyclodecane) resulted from a 'normal' copper-catalyzed $Csp^3$–Csp coupling process in basic media. The starting tetrayne was prepared by sequential nucleophilic addition of lithium-alkynyls to PhCOCl (see Section 2.2.1).

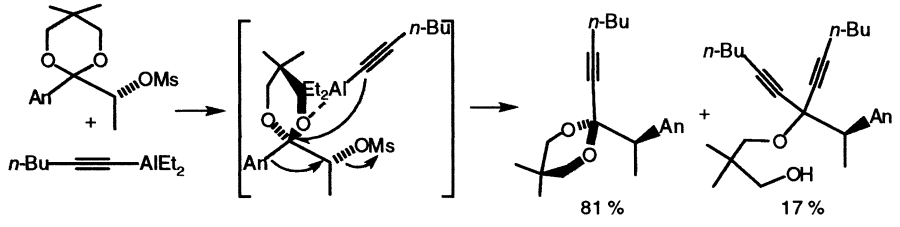
*2.1.2.4. Alkynylalanes.* Alkynylalanes are rather soft nucleophiles, but react with propargylic cations under $S_N1$ conditions. In the presence of $BF_3{\cdot}OEt_2$, benzenesulfenyl- or benzeneselenenylpropynal diethylacetal (**6**) thus affords 1,4-diyne products in moderate yield [44]. The second ethoxy group is not substituted (Scheme 16).

A skipped diyne side-product was also obtained from alkynylalanes. It results from a selective process involving an opening of a cyclic ketal and a migration-assisted $Csp^3$–Csp bond formation (Scheme 17) [45].

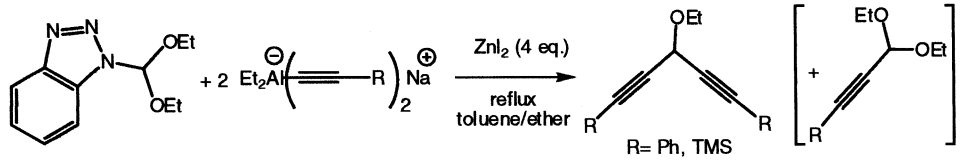
Anionic aluminum-alkynyls are stronger nucleophiles than alkynylalanes. In 1999, Katritzky and coworkers [46] took advantage of the good leaving group properties of the benzotriazole unit to prepare skipped pentadiynes from benzotriazole–ether substrates in 75–95% yield. The reaction was run in the presence of four equivalents of $ZnI_2$, which likely acts as a Lewis acid (Scheme 18). They observed that dialkynylaluminates confer a better chemoselectivity than lithium-alkynyls. Depending on the conditions, two different



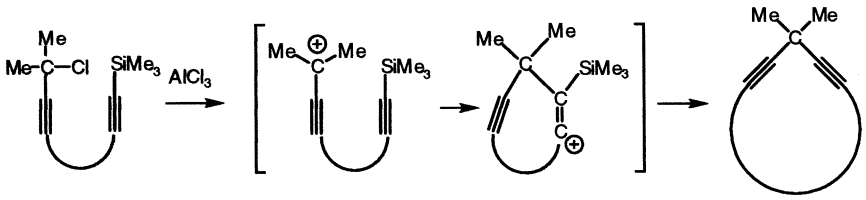

Scheme 16. Substitution of a propargylic alkoxy group with alkynylalane under $S_N1$ conditions [44].




Scheme 17. Formal double substitution by alkynylalane reagents. The migrating group is An = *p*-MeO–$C_6H_4$ [45].



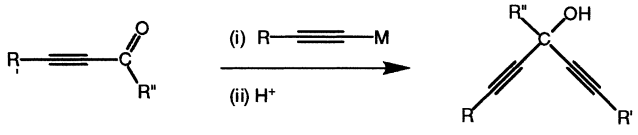

Scheme 18. Double substitution of benzotriazole and ethoxy groups with alkynylaluminates [46].



Scheme 19. Scott's ring-closing alkynyl–propargyl coupling procedure for the synthesis of permethylated [5] and [6]pericyclynes [47].

selectivities are possible. In presence of a single equivalent of aluminate and only two equivalents of $ZnI_2$ at lower temperature, monosubstitution of the benzotriazole affords propynaldiethylacetal derivatives in quantitative yield.

*2.1.2.5. Alkynylsilanes–$AlCl_3$.* The metallic character of silicon is not sufficient to promote alkynyl transfer to a neutral propargylic center. In the presence of $AlCl_3$ however, a stabilized 'nacked' tertiary carbocation is generated, and attack of trimethylsilylalkynes then proceeds [47]. This reaction is the key-step of Scott's synthesis of permethylated pericyclynes. It is here remarkable that 'classical' copper(I)-catalyzed substitution of tertiary propargyl halides by alkynylmagnesium bromides (which were used for the synthesis of skipped polyyne precursors: Section 2.1.2, Scheme 6) turned out to be unsuccessful in the intramolecular version. Nonetheless, larger ring sizes resulted in lower yields (from 35% to 1.5%) (Scheme 19).



Scheme 20. 1,2-Addition of metal-alkynyls to oxopropargylic substrates.

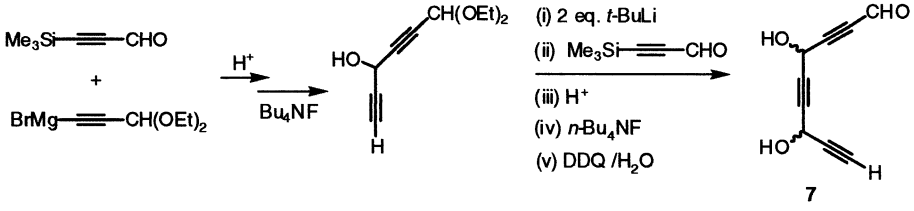
## 2.2. $sp^2 \rightarrow sp^3$ Addition processes

### 2.2.1. Lithium, sodium and magnesium-alkynyls

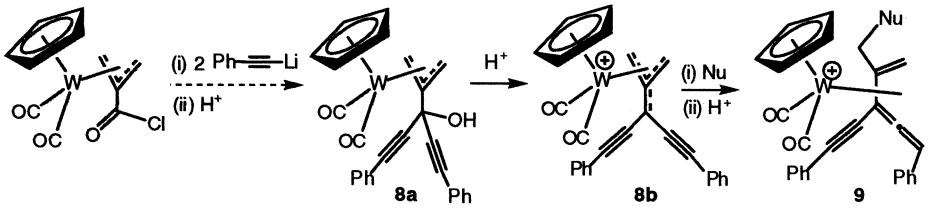
Lithium, sodium and Grignard acetylides add to alkynyl carbonyl compounds in a 1,2-regioselective manner to give dialkynylmethanol derivatives (Scheme 20). The method is commonly used with lithium acetylides and aldehydes [48], ketones [49], esters [50], acylchlorides [51], anhydrides [52] or carbonates [53]. Sodium [54] or Grignard [55] acetylides can also be utilized. Some representative examples are hereafter selected.

For example, the reaction with propargylic aldehydes was applied twice for preparing secondary skipped triynediols **7**, which were regarded as potential precursors of unsubstituted carbo[6]cyclitol and $[C,C]_6$-carbobenzene (Scheme 21) [56].

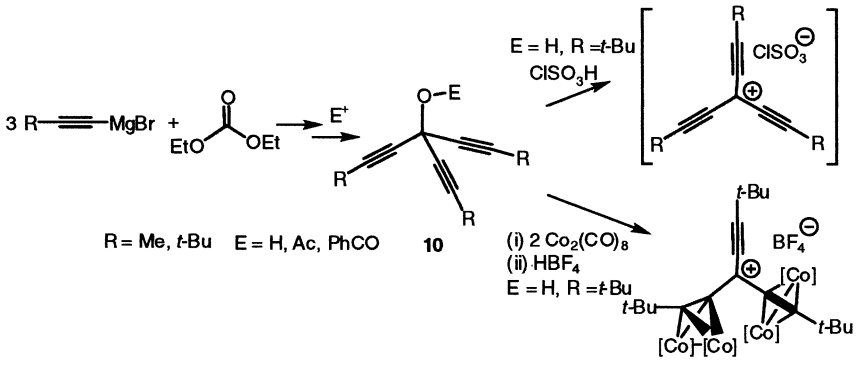
*Bisadditions* of acetylides to esters [57a] and acylchlorides [43,57b] are widely exemplified. The conditions are compatible with sensitive substrates, such as tungstenum carbonyl complexes: the α-dialkynyl-trimethylenemethane ligand in complex **8b** thus served as a precursor of the alkynyl-vinylallene ligands in complex **9** [58]. Although no detail is given, the precursor **8a** was likely synthesized by a general method based on the addition of two equivalents of an organolithium reagent to an acylchloride ligand (Scheme 22) [59].



Scheme 21. Reactions of lithium and magnesium acetylides with propargylic aldehydes [56].



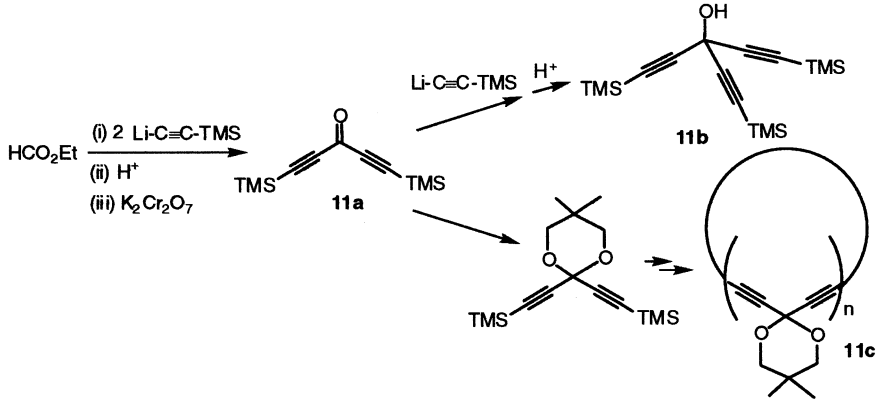
Scheme 22. Addition of two equivalents of lithium-alkynyl to an acylchloride ligand [58,59].



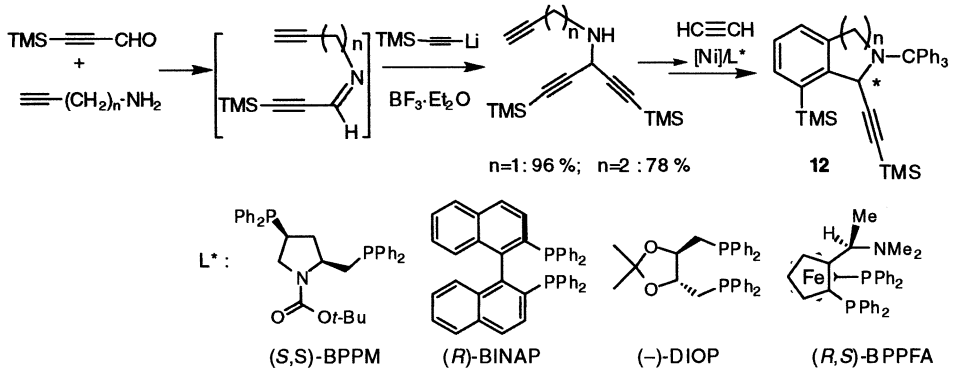

Scheme 23. Syntheses of triethynylmethanol derivatives and their cations. [Co] = $Co(CO)_3$ [60,61].

*Trisadditions* of acetylides are useful for the synthesis of triethynylcarbinol derivatives. In 1924, Ivitzky already prepared tris(*tert*-butylethynyl)methanol from phosgene and sodium-*tert*-butylacetylene [60]. In 1974, Miller and coworkers obtained the same product and the analogous tris(1-propynyl)methanol (**10**) from diethylcarbonate and three equivalents of the corresponding alkynylmagnesium bromide. Esters and carbocations were then generated from these carbinols (Scheme 23) [53]. The procedure was improved by Mellikyan et al. who prepared tris(*tert*-butylethynyl)methanol in 55% yield. This allowed them for resolving the first X-ray crystal structure of a $Co_2(CO)_6$-protected (triply) propargylic cation (see Section 3) [61].

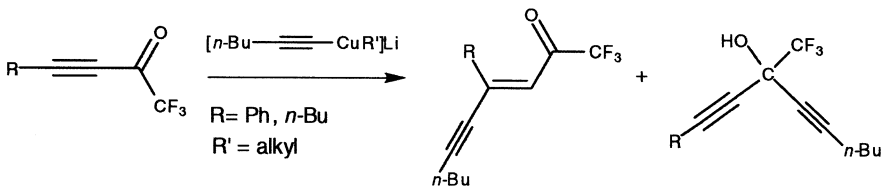
Triethynylmethanol and derivatives **11b** were also synthesized in three steps by addition of alkynyllithium to trimethylsilylpropynal, oxidation, and addition of a second equivalent of alkynyllithium to the dialkynylketone **11a** (Scheme 24) [62]. Attempts to quaternize the central carbon by a fourth acetylenic unit failed, and the synthesis of tetraethynylmethane was achieved much later by Feldman *et al*. (see Section 4.2). Dialkynylketone **11a** was also used by Bunz under its dioxolane



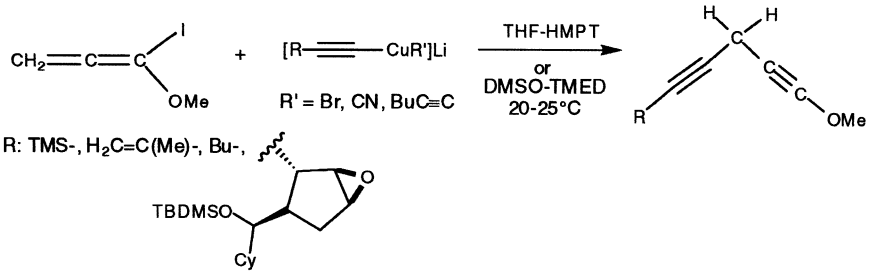

Scheme 24. Preparation of dialkynylketone **11a** and its conversion to skipped polyynes [62,63].




Scheme 25. Addition of lithium trimethylsilylacetylide to imines, and application to the synthesis of isoindolines and isoquinolines [64].




Scheme 26. 1,2-Addition of alkynylcuprates to trifluoromethylalkynylketones [65].




Scheme 27. Skipped diynol ethers from alkoxyiodoallenes and alkynylcuprates [66,67].

ketal form for the preparation of oxygen-substituted expanded pericyclynes **11c** (Scheme 24) [63].

Acetylenic imine derivatives also undergo nucleophilic attack by anionic acetylides. We previously mentioned the reaction of the iminiochloride $ClCH{=}NMe_2^+$ (Section 2.1.1) [13]. In the presence of borontrifluoride etherate, alkynyllithiums add to acetylenic imines (*in situ* prepared from propargylic aldehydes) [64]. The triyne products then served as substrates for nickel-catalyzed asymmetric cyclotrimerization with acetylene, to give isoindolines and isoquinolines **12** (Scheme 25).

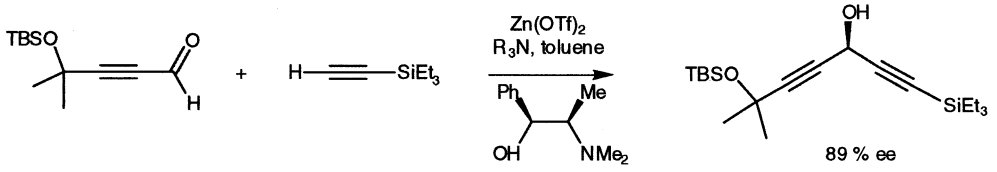
### 2.2.2. Alkynylcuprates

Organocuprates generally react with unsaturated carbonyl compounds in a 1,4-regioselective manner. Thus lithium-alkynyl cuprates react with α,β-acetylenic ketones to give enynones, although dialkynylcarbinols resulting from a competitive 1,2-addition were obtained as minor products [65]. In the case of highly electrophilic propargylic trifluoromethylketones, 1,2-addition is the major process. It is noteworthy that the alkynyl ligand of the cuprate is here transferred preferentially to the alkyl ligand (Scheme 26).

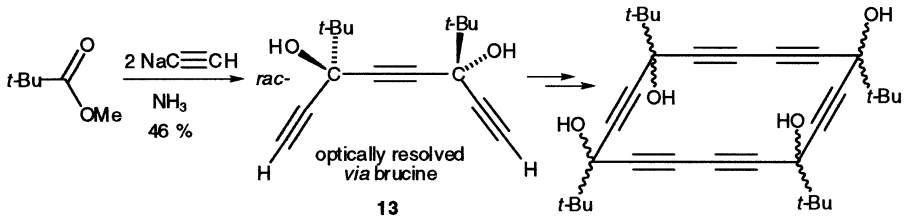
Alkynylcuprates also react with terminal iodoallenes in a 1,4-regioselective manner to give skipped diynes in good yields (71–86% yield, Scheme 27) [66]. Corey and De applied this method for the preparation of hybridalactone [67].

### 2.2.3. Zinc-alkynyls

In 2000, Carreira *et al*. disclosed a general enantioselective method for preparing optically active alkynylcarbinols from zinc-alkynyls and aldehydes in the presence of (+)- or (−)-*N*-methylephedrine [68]. In one example, the conditions turn out to be compatible




Scheme 28. Carreira's enantioselective synthesis of a secondary dialkynylcarbinol from a zinc-alkynyl [68].




Scheme 29. Resolved skipped triyndiol **13** and its application to the synthesis of a semi-expanded [4]pericyclyne [69].

with propynal substrates, affording a chiral dialkynylcarbinol in 89% ee (Scheme 28).

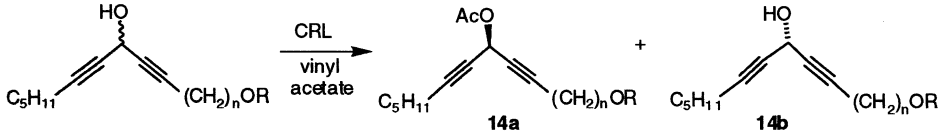
To emphasize the importance of this discovery, let us remark that asymmetric dialkynylcarbinols are 'weakly chiral' compounds: the difference between the two alkynyl substituents is indeed repelled to the γ-position from the stereogenic center. Racemic dialkynylcarbinols prepared by classical additions (Section 2.2.1) were previously resolved either chemically or enzymatically. A skipped triyndiol **13** was thus obtained as a single *dl* diastereoisomer by addition of sodium acetylene to *tert*-$BuCO_2R$, and its optical resolution was achieved by recrystallization of a complex of the (−) enantiomer with brucine (Scheme 29) [69].

Chattopadhyay [70] and Yadav [71] reported on *Candida rugosa* lipase (CRL)-mediated resolutions of racemic dialkynylcarbinols (obtained by addition of $RO(CH_2)_n$–C≡C–Li to $C_5H_{11}$–C≡C–CHO). CRL presents a good selectivity for the (*S*)-alcohol, affording (*S*)-acetate **14a** and unreacted (*R*)-alcohol **14b**. The optically pure dialkynylmethanol products were then converted to lipoxygenase substrates and to a cytotoxic principle of a marine sponge (Scheme 30).

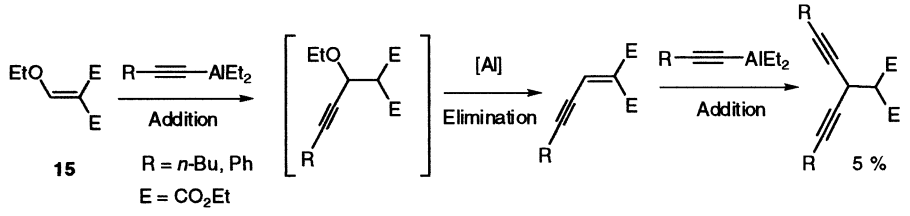
Let us also mention an asymmetric synthesis of a chiral dialkynylcarbinol via a chiral alkynyl-epoxyalcohol. The second triple bond was here generated by elimination (route C, see Section 4.2, Scheme 50).

### 2.2.4. Aluminum-alkynyls

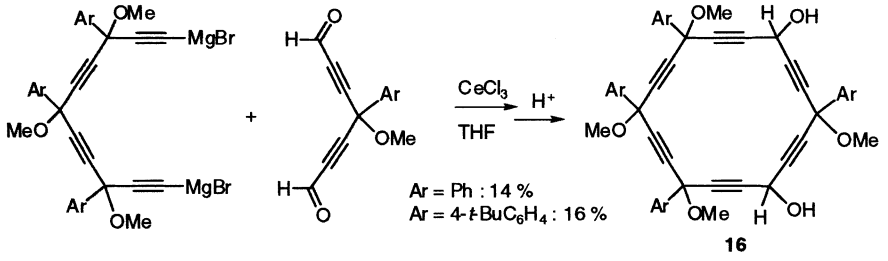
1,4-Diynes were obtained as side-products from alkynyldiethylalanes and ethoxymethylenemalonate **15**, via an addition–elimination–addition process [72]. After the first step, aluminum likely acts as a Lewis acid promoting elimination of ethanolate. A second equivalent of alkynylalane then adds to the enyne intermediate to give the (undesired) skipped diyne.



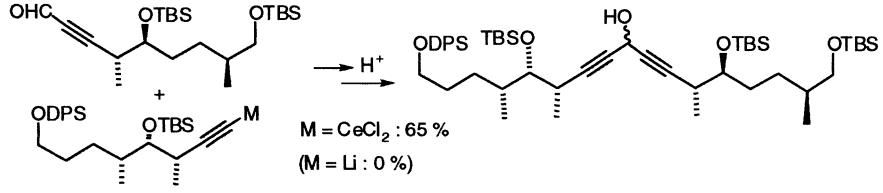

Scheme 30. Lipase-mediated optical resolution of chiral dialkynylcarbinols [70,71].



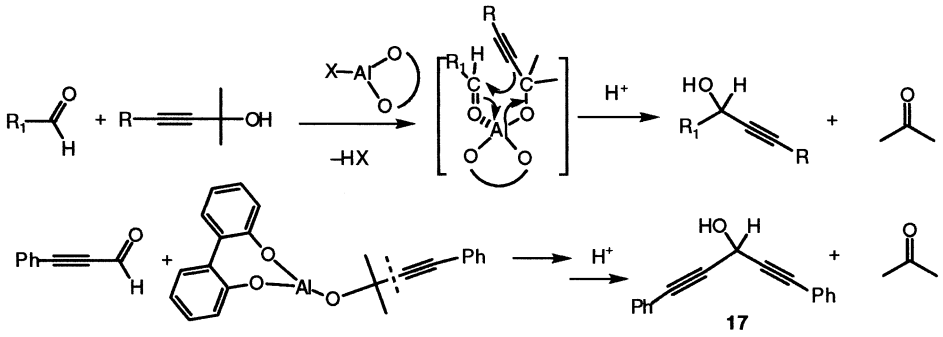

Scheme 31. Skipped diynes through Michael-type additions of alkynylalanes [72].




Scheme 32. Cerium-assistance in the key-step of Ueda's synthesis of functional [6]pericyclynes [57].




Scheme 33. Cerium effect in the addition of acetylides to propargylic aldehydes (Marshall's synthesis of tautomycin) [74].




Scheme 34. Maruoka's alkynyl transfer from a tertiary propargylic alcohol to aldehydes, and in particular to phenylpropynal [75].

Using lithium as a less acidic countercation of the acetylide, the elimination step (and therefore the second addition step) does not proceed (Scheme 31).

### 2.2.5. Cerium-alkynyls

Sometimes, direct nucleophilic attacks of metal-alkynyls to sensitive aldehydes such as propargylic aldehydes, may lead to substantial decomposition. Transmetallation of lithium or magnesium for cerium results in a reduced reactivity of the alkynyl group, and prevents the formation of by-products. The cerium effect has been highlighted by Ueda and coworkers in their preparation of functional [6]pericyclynes **16** via a cyclizing double addition of ω-diacetylides to bispropargylic dialdehydes (Scheme 32). While lithium diacetylides did not afford the desired product, magnesium diacetylides alone gave **16** in 6% yield only. Transmetallation of MgBr for $CeCl_2$ resulted in improved yields [57].

A similar reaction of an ester substrate with two equivalents of cerium-alkynyl ($CeCl_2$–acetylide, prepared from lithium acetylide and $CeCl_3$) was reported [73]. Very recently, Marshall and Yanik also reported on the determining effect of the use of a cerium-alkynyls in a key-step for the synthesis of tautomycin (Scheme 33) [74].

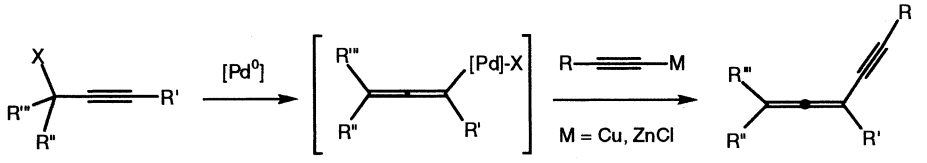
### 2.2.6. 'Aluminum–acetonium'-alkynyls

A chemoselective method for the preparation of secondary propargylic alcohols from aldehydes and tertiary propargylic alcohols has been recently disclosed by Maruoka and coworkers [75]. The principle and the experimental conditions are closely related to those of the Meerwein–Ponndorf–Verley reduction of carbonyl compounds by aluminum-promoted hydrogen transfer from isopropanol. Instead of a hydride, an alkynylide is here transferred, and acetone is released (Scheme 34). The reaction can be thus formally regarded as a nucleophilic attack of the 'aluminum–acetonium salt of a terminal alkyne'. The aluminum-activated alkynyl–carbon bond thus reacts just as an alkynyl–metal bond. As an application, bis(phenylethynyl)methanol (**17**) was prepared in 54% yield from phenylpropynal and 2-(phenylethynyl)-2-propanol in the presence of five equivalents of (2,2′-diphenolato)methylaluminum at room temperature (Scheme 34).

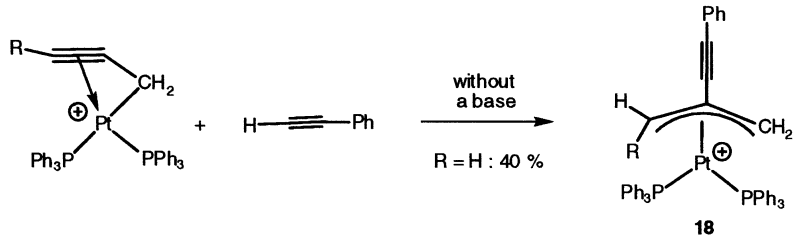
## 3. Transition metal-coordinated propargylic electrophiles

### 3.1. General trends in the reactivity of allenyl and propargyl metal complexes with acetylides

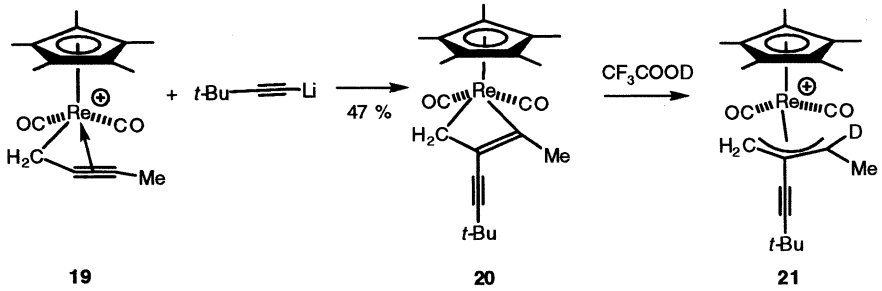
The generation of free propargylium cations requires strong Brønsted or Lewis acids, but complexation of the propargylium unit in transition metal complexes allows for stabilization [76]. When the complexing agent is a di- or tri-nuclear cluster of cobalt, molybdenum or ruthenium carbonyl units, the carbenium center preserves some electrophilic reactivity [77]. Before tackling a survey of the reactivity of these complexes with alkynyl nucleophiles, let us emphasize that general electrophilic propargylation is much less advanced than the equivalent allylation: no general catalytic method is indeed available. By comparison with allylic acetates, propargylic acetates, carbonates, and halides indeed react with Pd(0) complexes to afford σ-$\eta^1$-allenyl Pd(II) complexes. The latter react with various nucleophiles as allenylation catalysts (Scheme 35). No propargylation is observed. In particular, copper or zinc acetylides




Scheme 35. Reactivity of propargyl pseudohalides with Pd(0) complexes, and subsequent $S_N'$ attack of acetylides [78].




Scheme 36. Regioselective addition of neutral phenylacetylene to cationic π-propargyl platinum complexes [83].




Scheme 37. Casey's addition of lithium *tert*-butylacetylide to a cationic π-propargyl rhenium complex [84].

regioselectively afford the allenyne product at the expense of the propargylyne product [78].

The coordination chemistry of versatile allenyl and propargyl ligands with various second and third row transition metals has been recently reviewed by Wojcicki [79]. Their $\eta^3$ 'haptomeric' form [80], is equivalent to the long studied π-allyl ligands [81]. Chen thus considered the formers as a new class of potent organometallic carbon electrophiles [82]. Their electrophilic regioselectivity is however quite different from that occurring in π-allyl palladium complexes. Thus, cationic π-propargyl platinum complexes are stable, but undergo nucleophilic attack at the central carbon atom, albeit not in a catalytic manner (Scheme 36). In particular, phenylacetylene reacts with $[(\eta^3\text{-RCCCH}_2)\text{Pt}(\text{PPh}_3)_2]^+$ in the absence of any base, to afford the alkynyl-substituted π-allyl complex **18** [83].

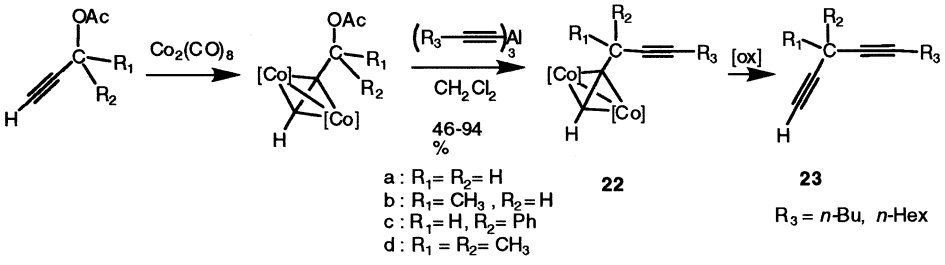
Finally, Casey *et al*. recently reported that cationic $\eta^3$-propargyl rhenium complex **19** reacts with lithium *tert*-butylacetylide with the same regioselectivity. A thermally unstable neutral rhenacyclobutene complex **20** was characterized and readily protonated to a $\eta^3$-allyl complex **21** (Scheme 37) [84].

### 3.2. Dicobalthexacarbonyl propargylium complexes

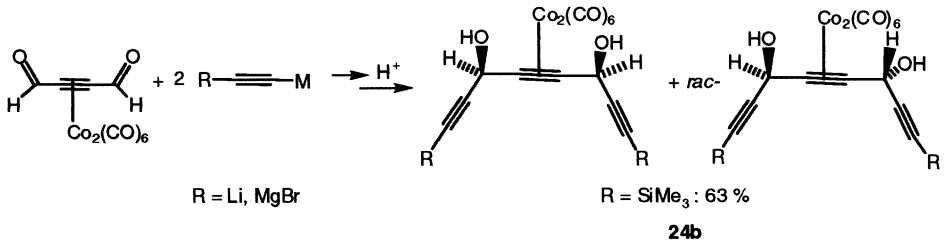
#### 3.2.1. Substitution

Reaction of propargylic alcohols, ethers and esters with $Co_2(CO)_8$ affords $\eta^2$-$Co_2(CO)_6$ alkyne complexes, and subsequent addition of a Brønsted or Lewis acid brings leads to the formation of stabilized Nicholas' propargylium complexes [85]. Then, attack of *neutral* nucleophiles takes place exclusively at the propargylium center: the $Co_2(CO)_6$ unit not only stabilizes the cation, but also protects the Csp allenic center from the incoming nucleophile. Likely due to competitive attack at the metal carbonyl ligands, *anionic* C-nucleophiles such as lithium or magnesium carbanions do not react selectively. By contrast, *neutral* C-nucleophiles such as allylsilanes, enolethers, electron-rich arenes, etc. lead to the propargylated product [76,77].

While alkynylsilanes do not react with Nicholas' complexes (e.g. $(\eta^2\text{-BnOCH}_2\text{C}{\equiv}\text{CCH}_2\text{OBn})\text{Co}_2(\text{CO})_6$) in the presence of $BF_3{\cdot}OEt_2$ [86], alkynylalanes directly afford the expected $\eta^2$-1,4-diyne cobalt complex **22** [87]. Aluminum intervenes both as a Lewis acid and as the counterpart of the alkynyl nucleophile (Scheme 38). This




Scheme 38. Nicholas' $Co_2(CO)_6$-mediated propargylation of tris(alkynyl)aluminum [87].



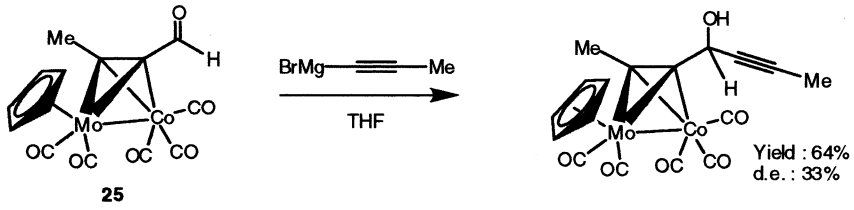

Scheme 39. Double attack of lithium and magnesium bromide-alkynyls at the carbaldehyde function of the $Co_2(CO)_6$ complex of acetylenedicarbaldehyde, **24a** [89].

situation was already encountered in the reaction of alkynylalanes with free propargyl electrophiles (see Sections 2.1.2 and 2.2.3). The free skipped diynes **23** can be then quantitatively released by oxidative demetallation (e.g. with CAN). The process is compatible with all substitution patterns at the propargylic center.

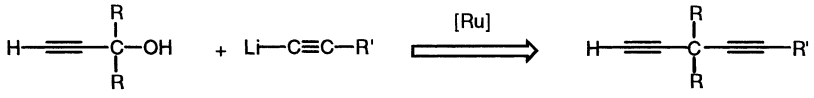
A quaternary dialkynyldimethylmethane derivative was thus obtained in 48% yield.

### 3.2.2. Addition

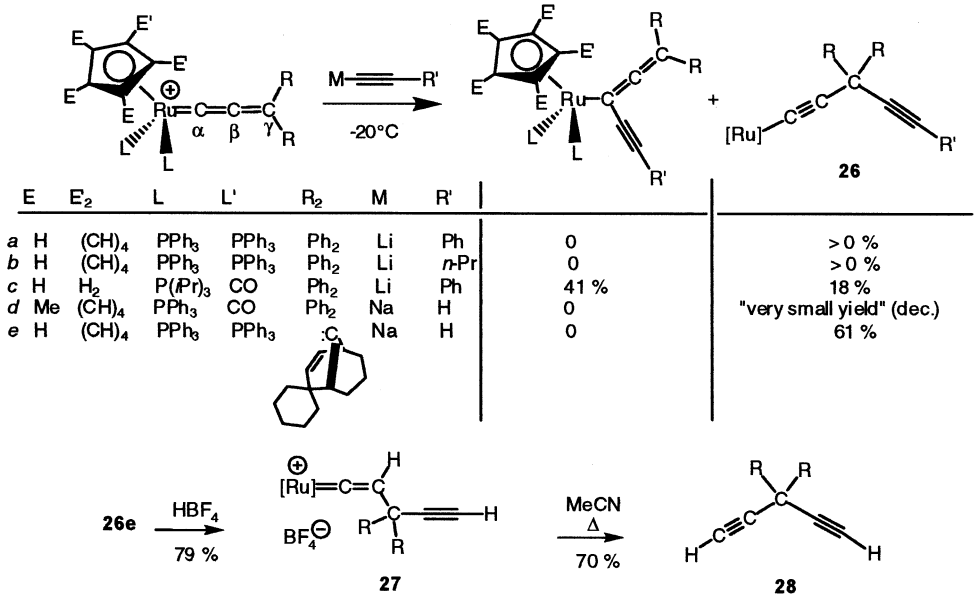
The $Co_2(CO)_6$ complex of acetylenedicarbaldehyde **24a** does not exhibit any cobalt-induced prepolarization




Scheme 40. Stereoselective attack of a disymmetrical Mo–Co complex of butynal by a Grignard acetylide [90].




Scheme 41. Gimeno's principle for the preparation of skipped diynes from propargylic alcohols and metal-alkynyls [91].




Scheme 42. Applications of Gimeno's principle for the synthesis of skipped diynes via allenylidene(ruthenium) intermediates [91–93].

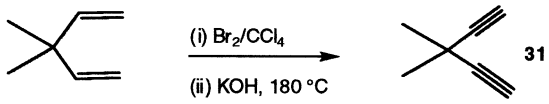
of the CH=O bond [88,89]. However, despite a possible competition for the metal carbonyl groups, lithium and magnesium acetylides regio- and stereoselectively attack at the carbaldehyde center to give skipped triynediol complexes **24b** in moderate to low yields, with a preferred *meso* configuration (Scheme 39).

An *oxo*propargylic binuclear cobalt–molybdenum complex **25** was reported to undergo regio- and stereoselective attack by a Grignard acetylide [90]. Though not confirmed by an X-ray crystal structure of the product, the bulky cyclopentadienyl ligand of molybdenum is anticipated to disfavor an attack from the same side of the butynal ligand (Scheme 40).

### 3.3. Ruthenium allenylidene complexes

Allenylidene ruthenium complexes exhibit a sequence of three alternate electrophilic and nucleophilic carbon centers. In 1994, Gimeno and coworkers used this pseudopropargylic function as a substrate for nucleophilic attack by lithium-alkynyls (Scheme 41). Although attack could *a priori* occur at either the Cα or Cγ center, the Cγ center is regioselectively affected (Scheme 42) [91].

In 1997, Esteruelas *et al*. showed that the regioselectivity is driven by the steric and electronic nature of auxiliary ligands, and observed attack at both the γ and α positions. The reaction afforded the first complex bearing an (alkynyl)allenyl ligand [92]. The same year, Gimeno and coworkers used a similar procedure to isolate a tertiary dialkynylmethane derivative with ruthenium-alkynyl substituent **26** [93]. Since direct demetallation of the ruthenium-alkynyl complex was unsuccessful, an intermediate vinylidene–ruthenium complex **27** was first generated. The free diethynylmethane derivative **28** was then released after exchange with acetonitrile at reflux (Scheme 42).




Scheme 45. Preparation of 3,3-dimethyl-penta-1,4-diyne (**31**) by double dehydro-bromination [98].

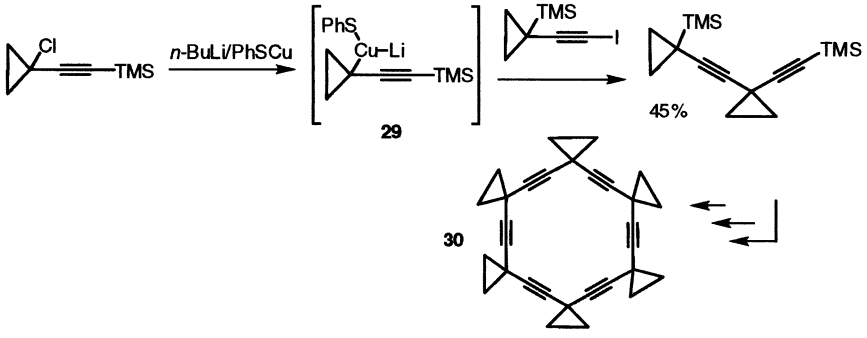
## 4. Recent illustrations of alternative routes to 1,4-diynes

### 4.1. Umpolung of 'natural' alkynyl–propargyl coupling reactions (route B, Scheme 1)

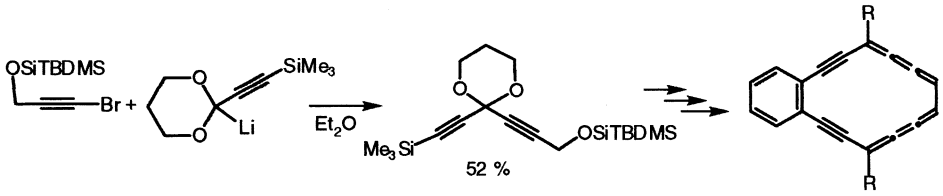
In their synthesis of spiro-substituted [6]pericyclyne **30**, de Meijere, Scott and coworkers utilized a regioselective head-to-tail coupling of two analogous propargylic units, namely a propargyl(phenylthio)lithium cuprate **29** and a iodoalkyne (Scheme 43) [94].

The same principle was used by Kuwatani and Ueda for the synthesis of a precursor of octadehydro[14]annulenes (Scheme 44). The reaction is a formal umpolung of the reverse natural addition of R–C≡C–MgBr to O=CH–C≡C–R′ [95].

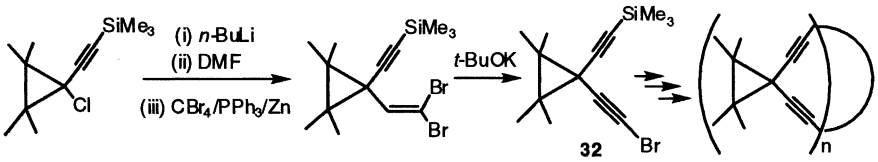
To the best of our knowledge, it is worth noting that despite a reported unsuccessful attempt [57], there is no example of reaction of iodoalkynes with propargylic aldehydes under Takai–Oshima–Nozaki–Kishi conditions, namely in the presence of $CrCl_2$. The *in situ* metal–iodine exchange would however classify the reaction under the heading of route A (Scheme 1) [96].



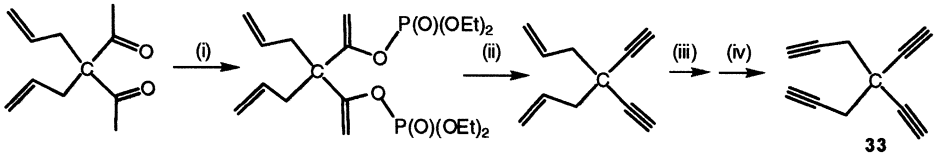

Scheme 43. Scott's synthesis of hexaspirotriacontahexayne **30** [94].




Scheme 44. Kuwatani's propargyl-alkynyl umpolung for the synthesis of octadehydro[14]annulenes.




Scheme 46. Preparation of dialkynylcyclopropanes for the synthesis of cyclic oligodiacetylenes [99].

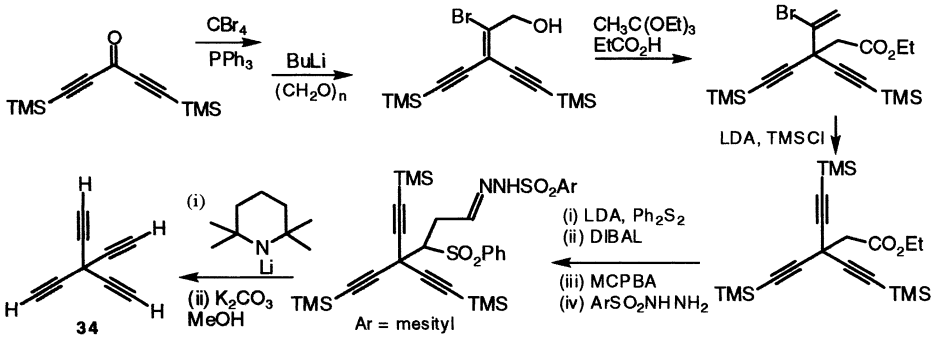


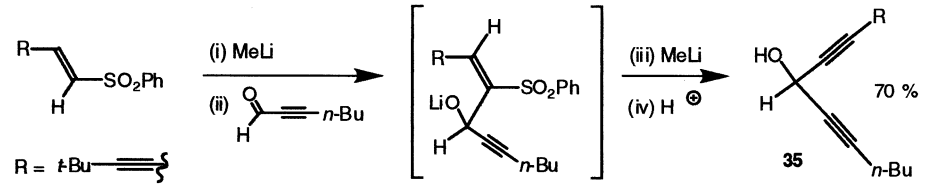

Scheme 47. Synthesis of diallyl- and dipropargyl-diethynylmethanes. (i) LDA, then $ClP(O)(OEt)_2$. (ii) LDA, then HCl. (iii) $Br_2$, −78 °C: selective bromination of the double bonds. (iv) $NaNH_2$, then HCl [100].

### 4.2. Elimination reactions from alkene precursors (route C, Scheme 1)

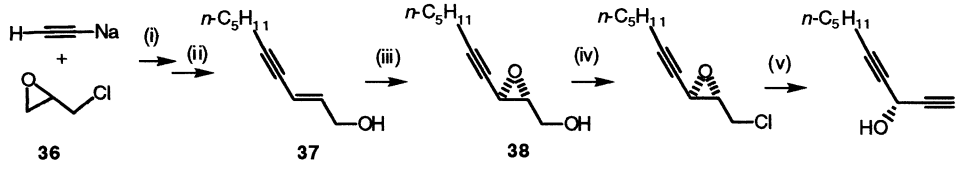
Although skipped diynes have been also obtained by deconjugation of 1,3-pentadiynes via the polylithiated base $C_5Li_5$ [97a] or by photocycloaddition of 1,3,5-hexatriynes with 2,3-dimethyl-2-butene [97b], most of them are alternatively produced by elimination processes from less unsaturated linear $C_5$ precursors. The classical bromination/dehydrobromination procedure can be thus applied twice in a row, albeit under severe conditions, for the direct preparation of 3,3-dimethyl-penta-1,4-diyne (**31**) (Scheme 45) [98].

Let us also mention de Meijere's preparation of a disymmetrical 1,4-diethynylcyclopropane brick **32** for the ultimate synthesis of macrocyclic oligodiacetylenes (Scheme 46) [99].




Scheme 49. One-pot synthesis of dialkynylcarbinols by base-induced dehydrosulfonylation [104].




Scheme 50. Synthesis of an optically pure dialkynylcarbinol. (i) Liq. $NH_3$, then $H^+$. (ii) $LiNH_2$, then $n$-$C_5H_{11}Br$. (iii) $Ti(OiPr)_4$–(+)-DIPT–$t$-BuOOH. (iv) $PPh_3$–$CCl_4$–$NaHCO_3$. (v) LDA–THF [105].

Terminal alkynes can also result from Negishi's 'dehydration' of methylketones [100]. For example, this procedure is allowed for the preparation of quaternary dialkynylmethane derivatives **33** (Scheme 47).

Alternatively, the triple bond can be generated by base-induced dehydrosulfonylation. In 1993, this method has been used to introduce the last propargylic ethynyl unit in Feldman's synthesis of the long sought tetraethynylmethane **34** [101]. By contrast, attempts at classical dehydrochlorination failed, giving an allene-diyne product [102]. Despite its intrinsic unstability, tetraethynylmethane **34** could be used in further transformations [103]. As a remarkable feature of this synthesis, the third propargylic triple bond and the skeleton of the fourth one are simultaneously formed by an original cyclic reaction (Scheme 48).

Dehydrosulfonylation can also occur *in situ*. In one example, the $C_5$ core was generated by addition of an alkenylsulfone anion to a propargylic aldehyde. *In situ* MeLi-induced elimination leads to the 1,4,6-triyne **35** (Scheme 49) [104].

As a last example, a multistep preparation of optically pure dialkynylcarbinols is based on an elimination process from chlorhydrins [105a] (for optical resolutions of chiral dialkynylmethanol derivatives, see Section 2.2.3). The central bond of the $C_5$ precursor was here formed from sodium acetylide and epichlorhydrin **36** [105b]. The allylic enynol **37** was then converted to a chiral epoxyalcohol **38** by Sharpless epoxidation. Compound **38** was then chlorinated, opened, and finally dehydrochlorinated and dehydrated (Scheme 50).

## 5. Conclusion

The above reactions show that despite a wide demand for various synthetic purposes, no universal methodology for alkynyl–propargyl coupling is prevalent. Clearly, the discovery of a general catalytic method for $Csp^3$–Csp coupling—and especially for alkynyl–propargyl coupling—is a challenge for the future. The growing interest for the design of new carbon-rich molecules [106] will surely motivate efforts in this direction.

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