Copper-Mediated Synthesis of Natural and Unnatural Products

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Abstract

The true value of organotransition metal reagents and reactions in organic synthesis is measured by the extent of their usage in the synthesis of complicated natural products. From this point of view, the importance of the organocopper reagents is comparable to that of palladium reagents. This chapter highlights some of the most important advances in this field published from about 1995 onwards, as several excellent reviews [1] already cover papers published before then.

Applications of organocopper reagents and reactions to natural product synthesis are classified by reaction type: conjugate addition, SN2 substitution, SN2' substitution, 1,2-metalate rearrangement, and carbocupration.

9.1 Conjugate Addition

Conjugate addition [2] to Michael acceptors is the most important and useful reaction in organocopper chemistry, and the reaction is often used as the key step in the synthesis of numerous natural and unnatural products. Perhaps one of the most efficient methods for the synthesis of quaternary carbon centers is organocopper-mediated conjugate addition to β,β-disubstituted enones.

An example of the construction of quaternary carbon can be seen in a synthetic approach to forskolin (1) [3]. Forskolin, a highly oxygenated labdane diterpene, exhibits a broad range of physiological activities thanks to its ability to activate adenylyl cyclase. Hanna’s group’s synthetic strategy (Scheme 9.1) involved an intramolecular Diels–Alder cyclization of trienone 2, which should have assembled the A and B rings of the tricyclic forskolin skeleton simultaneously. The approach failed to give the desired product, however, owing to the steric bulkiness of the system. In order to overcome this difficulty, the construction of the forskolin framework from tricyclic ketone 4 by 1,4-addition of methyl copper reagent was successfully investigated. Subsequent treatment of 4 with MeCu–BF₃ in ether, according to Yamamoto’s procedure [4], provided 3 in 62% yield.
One of the advantages of conjugate addition is that it may be used to introduce sp² carbon side chains, for example in the synthesis of (−)-morphine (5) [5]. Opium alkaloids of the (−)-morphine type have long represented challenges for natural products synthesis because of their complex molecular architecture, involving a dense network of three carbocycles and two heterocycles containing five vicinal stereogenic carbons. One of these stereocenters (C13) is a quaternary benzylic carbon atom and therefore difficult to create. The synthetic strategy of Mulzer’s group [6] was the first to provide a functionalized phenanthrene derivative of type 7, with a correctly substituted aromatic ring A, and then to employ conjugate addition of an sp²-unit (vinyl group) to establish this quaternary benzylic stereocenter (Scheme 9.2). The conjugate addition of a vinyl cuprate to 7, with activation of the vinyl cuprates by chlorotrimethylsilane (TMSCl) [7], was troubled by low yields of 8 and by a non-polar C₂ symmetrical dimer byproduct. As a subsequent refinement, the simple vinyl magnesiocuprate (CH₂–CH)₂CuMgCl [8], in the absence of TMSCI, afforded precursor 8 as a single diastereomer in 91% yield without any dimeric byproducts. This chirally economic asymmetric total synthesis is linear...
Another of the merits of organocopper reagents is the high degree of stereocontrol in conjugate addition. The polypropionate pathway is a biosynthetic route to important classes of antibiotics and the basic structures of a number of natural products. In practice, each propionate-derived stereocenter [9] can be constructed individually by adopting the aldol condensation in its numerous asymmetric versions [10]. The alternative method, which consists of the stereocontrolled addition of a cuprate to an enantiopure \( \gamma \)-alkoxy-\( \beta \)-unsaturated ester followed by hydroxylation of the corresponding enolate, has been reported by Hanessian et al. [11], who applied this method to the construction of the C19–C28 acyclic chain of rifamycin S [12] [12]. This simple strategy, shown in Scheme 9.3, is admirable, with sequential reactions proceeding in a stereocontrolled fashion through iterative cycles of

\[ \text{Scheme 9.2.} \]
cuprate additions, hydroxylations, Wittig chain extensions, and Mitsunobu reactions. This simple approach can give rise to all the combinations of stereotriads shown as types 9, 10, and 11.

In the case at hand, the \(\gamma\)-alkoxy-\(\alpha,\beta\)-unsaturated esters 13, 15, 17, and 19 were treated with lithium dimethylcuprate in the presence of excess TMSCl in THF at \(-78^\circ C\), producing the adducts 14, 16, 18, and 20 in 95, 85, 83, and 86% yields, respectively (Scheme 9.4). It was thus possible to assemble the acyclic C19–C28 subunit 21 of rifamycin S (12), which represents the longest sequence of contiguous propionate-derived units among the macrolides and ansa antibiotics. The strategy has also successfully been applied to the syntheses of the (all propionate)-derived segments of such natural products as bafilomycin A1 [13], hygrolitin [14], elaiophylin [15], and scytophytin C [16].

Scheme 9.4.

Conjugate addition of organocopper reagents has also been used to introduce multifunctional groups in the final carbon–carbon bond-forming step. The immunosuppressant FK-506 (25) [17] was noteworthy in its activity, which was found
to be approximately 100 times higher than that of cyclosporin A, the favored drug at that time [18]. In the total synthesis of 25, by Ireland et al., addition of a vinyl cuprate was a key step [19]. Their strategy was to couple two large building blocks, the “top half” and “bottom half” fragments (Scheme 9.5), and conjugate addition of the bottom half vinyl iodide 23 to the top half spiroenone 22 was investigated in this context. Use variously of lower order cuprates and homo- and mixed-cyano-Gilman cuprates [20] gave the desired adduct 24 in yields no better than 30–40%. An improved methodology involved the use of a dummy group, hexynylcopper, as its bis-HMPT complex [21]. This reaction required only 1.1 equiv. of the vinyl lithium derived from 23, and gave a 70% yield of the ketone 24. High facial selectivity was formed and no diastereomeric conjugate addition products were formed [22]. The success of this coupling procedure provides an ideal solution to the problems of trisubstituted olefin synthesis that had been prominent in previous syntheses [23].

Another example is found in the total synthesis of iso[7]-levuglandin D₂ (30) by Salomon et al. [24]. The cyanocuprate 27 was prepared by transmetalation of multifunctional vinylstannane 26 with Me₃CuLi-LiCN [Scheme 9.6] [25]. Addition of the enone 28 to the multifunctional vinylcuprate 27 provided the conjugate addition product 29 in 65% yield (based on the enone consumed).
A typical one-pot, three-component coupling sequence can be found in the preparation of the prostaglandin skeleton [26] in a remarkably rapid fashion by the conjugate addition of an organocopper reagent to a substituted cyclopentanone, followed by enolate trapping. That chemistry is not discussed here though, since there have been many excellent reviews in the past ten years [1, 27]. Yamamoto et al. first accomplished three-component coupling using organocopper compounds in the field of \(\beta\)-lactam synthesis [28], the key steps being addition of nitrogen nucleophiles to enoates with the aid of copper amides and subsequent enolate trapping with an electrophile. Palomo et al. have recently reported an alternative synthetic method [29]. Their strategy was based on an efficient combination of three reactants, in the form of addition of organocuprate reagents to \(\alpha,\beta\)-unsaturated carboxylic acid derivatives and subsequent condensation of the resulting enolates with an imine, as shown in Scheme 9.7. Treatment, for example, of the Gilman reagent Me\(_2\)CuLi with N-enoyl-sultam 31, followed by one-pot enolate trapping with the imine, produced a 57% chemical yield of the cis \(\beta\)-lactam adduct 32, with high diastereoselectivity (98:2), and in excellent enantiomeric purity (>99% ee). The stepwise process, by way of metal enolates generated by deprotonation, provided the expected adduct in lower chemical yields and with poorer diastereomeric and enantiomeric ratios than those attained using this method.
9.2 SN2 Substitution [30]

As well as conjugate additions, SN2 substitution reactions with organocopper reagents are frequently used in various synthetic processes. In a total synthesis of brevetoxin B [33], an active principle of the poisonous waters associated with the red tide phenomenon, substitution on an sp2 carbon center by a functional organocopper reagent is employed as one of the key reactions (Scheme 9.8) [31]. To carry out the formation of the D ring, alkyl iodides 35 and 36 were transformed into their lithio derivatives by halogen-metal exchange with t-BuLi and into the cyano-Gilman reagents R(2-thienyl)CuLi/C1LiCN [32], which coupled easily with the lactone-derived enol triflate 34 to afford desired oxepenes 38 and 39 in 50% and 49% yields, respectively. In view of the lack of stereoselectivity in these substitution reactions, the orthoester iodide 37 was prepared and utilized in order to improve the stereochemical outcome of the process. Its coupling with the enol triflate 34 by way of the cyanocuprate afforded 40 in an 85% total yield and with a diastereoselectivity of ca. 2.4:1 in favor of the desired stereoisomer. The diastereoselectivity is quite superior to that obtained in the two preceding cases. It should be noted here the use of the solvent system Et2O:THF:HMPA (1:1:1) in this coupling reaction was important for the stereoselectivity observed. Compound 40 was converted to the DEFG lactone segment in several steps.

SN2 substitution using organocopper reagents is an efficient method for the synthesis of 3-substituted olefins. In the synthesis of farnesyl diphosphate analogues (43, 45) as potential inhibitors of the enzyme protein-farnesyl transferase, for example, organocopper methodology was compared with the Stille reaction [33] and the Suzuki reaction [34], frequently used in the coupling of vinyl triflates with
a variety of organotin nucleophiles and boronic acids to introduce functional groups onto sp² carbon atoms [35]. In this case, neither of these palladium-catalyzed coupling reactions was amenable to the introduction of a cyclopropyl or t-buty1 nucle-
ophile. On the other hand, treatment of vinyl triflate 41 with 1.5 equiv. of \( i\text{-BuCu(CN)Li} \) in ether at \(-78 \, ^\circ\text{C}\) for 1 h produced the desired ester 42 in 68% yield (Scheme 9.9). Coupling of 41 with the lower order cyclopropyl cyanocuprate reagent at \(-78 \, ^\circ\text{C}\) for 1.5 h also afforded 44, in 71% yield. The double bond geometry was maintained during all these cuprate coupling reactions, and none of the undesired but more stable trans isomers of 42 and 44 were isolated.

In a total synthesis of cdc25A protein phosphatase inhibitor dysidiolide (46) [37], substitution on an sp\(^3\) carbon center by vinyl cuprate was used to accom-
plish elaboration of the side chain (Scheme 9.10) [38]. The C-1 side chain was set in place by means of iodide displacement with the vinyl cuprate derived from 2-lithiopropene (10 equiv. of 2-bromopropene, 21 equiv. of t-BuLi, 5 equiv. of CuI, Et₂O, −30 to 0 °C, then 0 °C for 30 min) to afford 48 in 97% yield.

Several groups have recently accomplished various intramolecular and intermolecular Stille-type reactions [39] with the aid of a copper(I) salt in the absence of palladium catalysts, with transmetalation of organostannanes with the copper(I) salt serving to generate organocopper(I) species [40]. To explore the cephalosporin analogues as β-lactam antibiotics possessing high antibacterial activity, a non-palladium Stille-type reaction was used in the synthesis of C(3)-substituted Δ³-cephems [41]. Treatment of the 3-halomethyl-Δ³-cephems 49 with tributylvinyltin (1.5 equiv.) and copper chloride (1.0 equiv.) in the presence of terpyridine (1.0 equiv., added for coordinative stabilization of the generated vinylcopper species) in N-methyl-2-pyrroldinone at room temperature predominantly afforded the 3-allyl-Δ³-cephem 50 in 68% yield (Scheme 9.11). Copper-promoted reactions with allenyltributyltin, allyltributyltin, and styryltributyltin were also successfully applied to the synthesis of cephem derivatives, giving the desired coupling products in 84%, 61%, and 50% yields, respectively.
$S_{N}2$ Reactions with epoxides and aziridines are also synthetically useful. An example of epoxide cleavage with an organocopper reagent with $sp^3$ carbon moieties is the enantioselective synthesis of (3S,4S)-4-methyl-3-heptanol (53), an elm bark beetle ($Scolytus multistriatus$) pheromone [42]. The chiral epoxy oxazolidine 51, prepared from ($R$)-phenylglycinol, reacted with a propylmagnesium bromide-derived cuprate at $-70^\circ C$ to afford the oxazolidine 52 in 74% yield (Scheme 9.12). Compound 52 was converted into the target molecular 53 by conventional procedures.

Epoxide ring-opening with transfer of an $sp^2$ carbon moiety was applied in a short synthesis [44] of eicosanoid 56 [45], relevant in marine prostanoid biosynthesis (Scheme 9.13). Homooallyl alcohol 55 was obtained in good yield from 54 by use of a cyano-Gilman alkenylcuprate [46].

Cleavage of aziridines has been employed in the asymmetric total synthesis of pancretatin 57 [47], a compound that is the object of considerable attention thanks to its broad spectrum of antineoplastic activities [48]. The chemistry of vinylaziridines has for the most part been confined to their use in rearrangement sequences resulting in functionalized pyrrolines. Hence, because of the lack of data concerning the ring-opening of vinylaziridines with carbon nucleophiles,
there was a need for a preliminary study of the opening of aziridines with different organometallic species. According to this, whereas lithium diphenylcyanocuprate only shows anti-$S_N2$ substitution, organometallic reagents predominantly react by syn-$S_N2'$ substitution; no explanation for this divergent reactivity is given. Ortho-
lithiation \[49\] of a dimethylamide species \(58\), followed by cuprate formation according to Lipshutz et al. \[50\], provided the required cyano-Gilman reagent \(59\) (Scheme 9.14). The reaction between \(59\) and the activated aziridine \(60\) gave a 75\% yield of the product \(61\). This is the first example of the preparation of cyano-Gilman cuprates by amide group-directed \emph{ortho}-metalation.

\begin{equation}
\begin{aligned}
\text{Scheme 9.14.}
\end{aligned}
\end{equation}

9.3 \emph{S_{\text{N}2'}} Substitution \[51\]

Organocuprates react rapidly with allylic halides (or acetates), propargyl halides (or acetates), and vinyloxiranes, frequently with \emph{S_{\text{N}2'}} regioselectivity. The reaction ordinarily takes place with \emph{anti} (with respect to the leaving group) stereochemistry.
In an alternative synthesis of pancratistatin (57) by Trost et al. [52], (Scheme 9.15) addition of the Grignard reagent 63 [53] to a mixture of the azide 62 and copper cyanide reproducibly gave the desired adduct 64. Because of the difficulties associated with purification of adduct, the overall yield of the two steps (the next being dihydroxylation of the olefin) was 62%.

Scheme 9.15.

When an allylic carbamate is employed as a substrate, on the other hand, syn substitution occurs [54]. For example, two efficient synthetic routes to 1α,25-dihydroxy-16-ene-vitamin D₃ (65) and its analogues have been developed (Scheme 9.16) [55]. In route A, the CD side chain fragments 67 and 69 were prepared by SN₂₀₀₀ syn substitution of allylic carbamates 66 and 68 with R₅Cu₃Li₂, and the triene unit was then constructed by coupling with the A ring fragment. In route B, SN₂₀₀₀ syn allylation of the carbamate moiety took place on the intermediates 70 and 72, already possessing the vitamin D triene unit, to afford the precursors 71 and 73. Both routes gave the desired allyl products in high yields.

In syntheses of the potent tetrapeptide mimetic farnesyl transferase inhibitors B956 (80) and B957 (81), the double bond pairs were constructed by application of iterative Nozaki–Hiyama–Kishi (NHK) and cuprate SN₂₀₀₀ reactions (Scheme 9.17) [56]. The preparation of the precursor 75 for the Ibuyaka–Yamamoto SN₂₀₀₀ replacement reaction [57] was carried out starting from 74, by means of the already mentioned NHK reaction [58]. The construction of the olefinic moiety of the peptide isostere 76 was effected by copper-mediated displacement with alkyl nucleophiles. In practice, anti-SN₂₀₀₀ diastereoselectivity with high E olefin selectivity was observed for the first iteration, on treatment of 75 with the reagent produced by addition of BF₃·Et₂O to a mixture of i-PrMgCl and CuCN. In the second iteration, the unusual Z olefin 78 – not the E olefinic product 79 expected from the normal anti pathway – was obtained as the major isomer from the SN₂₀₀₀ reaction of 77, again prepared through an NHK sequence. Compounds B956 and B957 were prepared in high yields from 78 and 79 by the usual sequence, both with >95% purity. This iterative NHK reaction followed by SN₂₀₀₀ substitution thus demonstrates the widespread utility of organocopper reagents in the preparation of olefinic peptide mimetics of other interesting peptides.
Scheme 9.16. Copper-Mediated Synthesis of Natural and Unnatural Products
Scheme 9.17.

The propargyl structure of PDE IV inhibitor SB 222618 (82) was prepared with the aid of a regioselective SN2' substitution of the allenic compound 83 (Scheme 9.18) [59]. The most critical step in the synthesis of 82 is the preparation of the intermediate 85. Aryl copper reagent 84 was prepared as the substitution partner, since it is known that Vermeer-type organocopper species [60] of formula R(CuMgBr)2–LiBr exhibit good regioselectivity in SN2' reactions [61]. Treatment of 84 with the bromoallene 83 gave the desired propargyl product 85 in 60% yield.

Aziridine cleavage based on an SN2' reaction was used for the synthesis of peptides bearing \( E \) alkene dipeptide isosteres, a novel class of potent bombesin receptor antagonists [62]. Treatment of the vinylaziridine 86 (Scheme 9.19) with isobutyl and isopentyl magnesium cyanocuprates in THF at \(-78^\circ C\) for 30 min. stereospecifically gave the desired \( E \) alkene isosteres 87 in high isolated yields [63].
A 1,2-metalate rearrangement of a higher order cuprate, known as a Kocienski rearrangement [64], was used as a key step in the synthesis of the marine anti-inflammatory sesterterpenoid manoalide 95 (Scheme 9.20) [65]. Treatment of the alkenyl lithium 89 (prepared from the alkenylstannane 88 with s-BuLi in a diethyl ether-pentane mixture) with the homocuprate 91 (produced from iodoalkane 90) gave the iodoalkene 94 in 72% overall yield from 88. The reaction proceeds as fol-
lows. The cuprate reagent 92 is first formed from 89 and 91, and 1,2-metalate rearrangement then takes place as shown by the arrows in 92 to give 93. Iodonolysis of 93 results in 94.

Scheme 9.20.

The “western part” 97 of tylosin aglycon (96), a 16-membered macrolide, has also been synthesized using this Kocienski metalate rearrangement [66]. Treatment of the lithiated dihydrofuran 99 with the stannyl cuprate [67] obtained from Bu3SnLi and CuCN, followed by MeI alkylation, exclusively gave the E vinyl stannane 100, in 80% yield. In the last stage, stannyl cupration [68] of the deprotected enyne diol 101 afforded the desired (E, E) stannyl diene 97 in 85% yield.

The advantage of this strategy is thus the subsequent trapping of the metalate rearrangement product to provide a clean, efficient, and highly stereoselective route to the trisubstituted alkenes.
Scheme 9.21.

Copper-Mediated Synthesis of Natural and Unnatural Products

**Tylonolide (tylosin aglycon)**

**Western Part**

**Eastern Part**

1. **(Bu$_3$Sn)$_2$CuLi-LiCN**
2. Mel
   - Kocienski rearrangement

**TIPS** = trisopropylsilyl

**Scheme 9.21.**
The carbocupration of alkynes occurs in a cis fashion to afford the synthetically useful cis alkenyl products. Recently, copper-mediated introduction of heteroatoms such as stannyl and silyl groups has become frequently used in place of introduction of carbon units as an efficient strategy to build important precursors in syn-
thesis. The synthesis of stipiamide 102 [70], possessing anti-HIV and antifungal activities, was accomplished with high selectivity in a single operation, using sequential tin-copper syn additions [71] of tributylstannyl cuprate to acetylene, followed by conjugate addition to ethyl propionate. The stannyl cuprate was prepared first, by treatment of hexabutylditin with butyllithium, methyllithium, and copper cyanide in THF at −78 °C [72] (Scheme 9.22). Excess acetylene gas was added directly to the cold solution, and ethyl propionate was then added. After quenching with methanol [73], the diene ester 103, intended as the precursor for a Stille coupling, was obtained in 82% yield based on ethyl propionate, with greater than 25:1 Z,E,Z,E,Z selectivity. The stipiamide (E,E,Z,E,E) olefin structure was subsequently achieved, using the Stille coupling as the final step.

As described above, many copper-mediated reactions play important roles in the syntheses of natural and unnatural products. To date natural product syntheses using organocopper reagents have been accomplished, and will undoubtedly be increasing greatly from now on.

References


See, for example, T. Mukaiyama, Org. React. 1982, 28, 203–331.


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Appl. Chem. 1990, 62, 1931–1940;