New synthetic methods based on organozirconium and organocopper chemistry

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Abstract - Four inter-related topics highlighting recent, unpublished developments on the transmetalation chemistry associated with zirconium and copper reagents are presented.

INTRODUCTION

Transmetalation reactions between various organometallic species and equivalent amounts of a higher order (H.O.) cyanocuprate $R_2Cu(CN)Li_2$ have expanded the flexibility associated with cuprate formation (ref 1). These ligand exchange phenomena have been observed to occur efficiently for a number of metals, including Zn, Al, Te, Sn, and Zr, in each case the transmetalation taking place under mild (ambient temperature or below) conditions (ref 2); see Eq. 1. The resulting mixed cuprates 2 can then be used to selectively deliver the ligand of interest (RT) to an organic substrate. All of the starting metal-organics $R_TML_n$ (1) which participate thus far in subsequent carbon-carbon bond forming reactions of 3 contain $R_T$ = a vinylic group. The vinyl organometallics most prone toward exchanges with H.O. cuprates, 2, (e.g., Me$_2$Cu(CN)Li$_2$, 4) are derivatives of terminal acetylenes which have undergone a standard hydrozirconation reaction (ref. 3) with Schwartz' reagent (Cp$_2$Zr(H)Cl, 5); i.e., to give vinyl zirconocenes, 6 (Scheme 1). Generation of mixed cuprates 2, which selectively transfer the vinyl group, can thus be accomplished without recourse to traditional approaches involving lithiated intermediates, 8 (ref. 4). This presentation will focus on both new and related transformations initially involving organozirconium chemistry, followed directly by transmetalations to copper.

\[ L_nM \quad \downarrow \quad \text{THF} \quad \downarrow \quad \text{temperatures between -78 and 25°C} \]
\[ R_T \quad \text{Cu(CN)Li}_2 \quad \text{Cu(CN)Li}_2 \quad L_nM \quad - \quad R_T \quad (\text{Eq. 1}) \]

[R$_T$ = the desired, transferrable ligand; R$_r$ = a non-transferrable ligand; L$_n$ = n ligands on metal, M]
Although the cis-addition of Schwartz' reagent across acetylenes, in addition to being efficient, is very highly regio- and stereoselective (ref. 3), there are limitations associated with its use. Perhaps the most noteworthy is its lack of chemoselectivity in the presence of both an acetylene and aldehyde or ketone, where competitive 1,2-addition of hydride readily takes place (ref. 5). Since most of our transmetalations involve hydrozirconation as a first step, normally it would not be possible for the alkynyl substrate to harbor either of these sensitive functionalities. We have endeavored, therefore, to find an appropriate carbonyl surrogate which would eliminate this alternative mode of addition, yet allow for its conversion to several carbonyl derivatives of one's choosing. The group that has been found which fulfills this requirement is the triisopropylsilylcarbonyl moiety (i.e., an acyl silane), prepared according to literature routes (ref. 6). Treatment of each of the 1-alkynes 2 and 11 with an equivalent of Cp₂Zr(H)Cl (4) followed by NBS and H₂O, respectively, afforded the olefinic products 8 and 12 (Scheme 2). Attempts at usage of a triethylsilyl analog of 9 led to incomplete conversion; addition of >1 equiv of Cp₂Zr(H)Cl simply led to buildup of the undesired silyl alcohol product.

A series of competition experiments was used to test the compatibility of a hydrozirconation/electrophilic trap sequence involving (functionalized) acetylenes in the presence of a TIPS acyl silane. Exposure of a 1:1 mix of each acetylene 13, 14, and 15 with TIPS derivative 16 to 1 equiv Cp₂Zr(H)Cl, followed by addition of an electrophile, gave only products 17-19 along with recovered 16 (ca. 90%), in good isolated yields (Scheme 3). From these examples, together with the known conversions of acyl silanes to aldehydes, acyclic ketones, acids, etc. (ref. 6), it should now be possible to effect hydrozirconations on otherwise hydride-sensitive carbonyl groups using the TIPS moiety both as a steric shield and residue easily interchanged for other functional groups.
NEW 1,1-DIMETALLO REAGENTS

The addition of Cp₂Zr(H)Cl across a trialkylstannyl acetylene (R'-C≡C-SnR₃) has recently been shown to afford, upon proton quenching, Z-vinylstannanes (ref. 7). The regiochemistry of this process is such that zirconium is localized on the resulting sp² carbon bearing the R₃Sn moiety. Intermediates 20, in principle, are then subject to sequential manipulations of each metal, being formally stereo-defined 1,1-dianion equivalents. A H.O. cuprate-based transmetalation using Me₂Cu(CN)Li₂ on the vinylzirconocene portion in 20 is expected to occur under conditions where vinylstannanes are inert (ref. 1,2). Indeed, when the tributylstannyl derivative of protected propargyl alcohol 21 was hydrozirconated in THF at ambient temperature and then cooled to -78°C, introduction of MeLi and preformed Me₂Cu(CN)Li₂ followed by cyclopentenone afforded the desired ketone 22 in good isolated yield. Likewise, homopropargyl derivative 23 led to vinylstannane 24 (Scheme 4).
Displacement reactions can also be carried out with cuprates derived from 26, although Me₂Cu(CN)Li₂ is not a wise choice for this subsequent event since the transmetalated reagent 25 is not selective for vinyl ligand transfer; see Scheme 5 (Ref. 4). By switching to Me(2-Th)Cu(CN)Li₂

Scheme 5

Me
H
\[ \text{Me}_{2}\text{Cu(CN)Li}_2 \rightarrow \text{Me}(\text{2-Th})\text{Cu(CN)Li}_2 \]

[from MeLi + ThCu(CN)Li; 2-Th = 2-thienyl], mixed cuprate 26 alkylates the desired vinyl ligand using unactivated primary triflates, as well as allylic and benzylic halides; e.g., Eq. 2 (Ref. 8).

\[
\text{Bu}_3\text{Sn} + \text{O-Si}(\text{t-Pr})_3 \rightarrow \text{Bu}_3\text{Sn} \text{O-Si}(\text{t-Pr})_3 \quad (\text{Eq. 2})
\]

ALLYLIC CUPRATES DIRECTLY FROM ALLYLIC ETHERS

Methods for generating allylic cuprates traditionally involve initial metathesis reactions between allylic lithiums or Grignard reagents; see Eq. 3 (Ref. 4). More recently, inroads which include (1) oxidative addition of Rieke copper to allylic chlorides and acetates (Eq. 4); (2) transmetalations between allylic stannanes and H₂O cyanocuprates which take place smoothly at 0° (Eq. 5); and (3) one carbon homologations of L₂ vinyl cyanocuprates in the presence of (ICH₂)ZnI or (ICH₂)₂Zn (Eq. 6), have all led to highly reactive forms of these species (Ref. 2).

\[
\begin{align*}
\text{M} + \text{CuX} & \rightarrow \text{CuLi} \\ 
\text{X} + \text{Cu(0)} & \rightarrow \text{Cu-LIX} \\ 
\text{SnBu}_3 + \text{Me}_2\text{Cu(CN)Li}_2 & \rightarrow \text{Cu(CN)Li}_2 \\ 
\text{Cu(CN)ZnI} + (\text{ICH}_2)\text{ZnI} & \rightarrow \text{Cu(CN)ZnI}
\end{align*}
\]

(Eq. 3) (Eq. 4) (Eq. 5) (Eq. 6)
An alternative approach is to consider a ligand exchange between an allylic zirconocene and a H.O. cyanocuprate, which based on related reactions of vinylic (Ref. 9) and allylic stannanes (cf. Eq. 5), should be especially facile. Preparation of these starting materials, however, should preferrably not require another allylic organometallic precursor, but rather take advantage of some unique feature of organozirconium chemistry. Recently, Taguchi and co-workers (Ref. 10) have described just such a development involving rearrangement reactions of allylic ethers, initiated by "Cp2Zr" (Ref. 11), which take place efficiently to give reactive allylic zirconocene complexes 22 (Eq. 7).

In a preliminary study to assess the reactivity of 27 toward H.O. cuprates, a silyl ether of cinnamyl alcohol (28) was treated with "Cp2Zr", zirconocene being formed in situ from Cp2ZrCl2 and two equivalents of n-BuLi in THF (-78° for 1 h, then warmed to room temperature for 3 h). The presumed allylic zirconocene complex 29 was then treated with one equivalent of Me2Cu(CN)Li2 at -78°, warmed to 0° briefly, and then the mixture allowed to react with a primary chloride at this temperature. After the reaction was complete in a matter of a few hours, an excellent yield of the allylated electrophile 31 was realized (Scheme 6). The regiochemistry of allylic cuprate (30) attack, as expected (Ref. 2), was at the γ-site.

**Scheme 6**

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\[
\begin{aligned}
\text{"Cp2Zr"} & \quad \text{hexanes, rt, 3 h} \\
\downarrow & \\
\text{Cp2ZrCl2} + 2 \text{n-BuLi} & \rightarrow 29 (96\%) \\
\end{aligned}
\]
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**CYANOCUPRATE - CATALYZED TRANSMETALATION-CONJUGATE ADDITION**

Implicit in the low temperature, rapid conversion of vinylzirconocenes to mixed vinyl cyanocuprates 34 via Me2Cu(CN)Li2 or Me(Th)Cu(CN)Li2 is use of a 1:1 stoichiometry between these reactants. Hence, the 1,4-adduct generated following any conjugate addition of 34 to an enone is likely to be a copper/lithium enolate 35 (Scheme 7). In an effort to reduce the amount of copper associated with this process (i.e., make the conversion catalytic in copper), what is needed is another organometallic (R-M) which will effectively supply a methyl anion to react with and thereby free enolate 35 from copper, regenerating the starting H.O. cuprate for recycling back into the transmetalation sequence. Clearly, use of MeMgX or MeLi is not an attractive option, since R-M itself must be compatible with the α,β-unsaturated ketone. Moreover, a hard source of "Me-" might interact with the vinylzirconocene, the resulting ate complex 37 reducing the amount of methyl anion available to attack 35 and reform Me2Cu(CN)Li2.
So, what should R-M be? It's properties should be such that it provides a 'soft' form of "Me-'" yet is capable of a quick ligand exchange with 35, but cannot itself add in either a 1,2 or 1,4 mode to the substrate enone under conditions where both cuprate 34 is active and the 35 to 36 conversion is facile. The species found which serves beautifully in this capacity is trimethylzincate, Me3ZnLi, (Ref. 12). Thus, when a vinylzirconocene 32 is exposed to MeLi and 20 mol % Me2Cu(CN)Li2 (4) in THF at -78° in the presence of Me3ZnLi, the subsequent introduction of an enone over the course of ca. one hour affords the 1,4-adduct in yields routinely ranging between 80-90%. Two representative examples are shown in Scheme 8.

Since the 20 mol % figure was arbitrarily chosen as a starting point, lesser amounts of 4 were tested in terms of effects on reaction rate and yield. Cutting the catalyst concentration down to 5 mol % and extending the reaction time from one to about three hours, in the case of cryptone (39) going to product 40, led to identical yields (Scheme 9).
In using Me$_2$ZnLi as the supply of "Me-", the implication with respect to the nature of the enolate formed upon Michael addition by 34 followed by transmetalation is that a new zincate, or what might be more commonly thought of as a "zinc enolate", 41 (Eq. 8). What should be appreciated about intermediates 41 is that, unlike their copper counterparts 35 (Ref. 13), they are very reactive toward electrophiles. Indeed, zinc enolates 41 are precisely the species involved in Noyori "three-component couplings" (3-CC) using mixed zinicates 43 as Michael donors en route to the prostaglandin (PG) skeleton; see Scheme 10 (Ref. 14). The prospects for extending this novel cata-

**Scheme 10**

\[
\begin{align*}
\text{R} & \text{ZnMe}_2\text{Li} \quad \xrightarrow{\text{E}^+} \quad \text{R} \text{ZnMe}_2\text{Li} \\
\text{R} & \text{O} \\
\end{align*}
\]

lytic process to include the 3-CC aspect are very exciting, especially given the fact that our chemistry starts at the acetylene stage and does not invoke prior preparation of vinylic iodides or stannanes, or the derived vinylolithiums that go into forming cuprate 34 or zincate 44 (Scheme 11). According to the scenario pictured in Scheme 7, the end point should correspond to a buildup of a zinc enolate 41 (cf. Eq. 8), and hence, in principle, all that should be needed at this stage is to add

**Scheme 11**

\[
\begin{align*}
\text{ZnMe}_2\text{Li} & \quad \xrightarrow{\text{E}^+} \quad \text{ZnMe}_2\text{Li} \\
\text{Me}_2\text{Zn} & \quad \xrightarrow{\text{Me}_2\text{ZnLi}} \quad \text{SnBu}_3 \quad (+ n\text{RLi}) \\
\text{R} & \quad \xrightarrow{\text{Me}_2\text{ZnLi}} \quad \text{R} \\
\end{align*}
\]

"E" (e.g., cf. Scheme 10). The two types of "E" of importance in PG syntheses are (1) aldehydes, and (2) propargylic halides and sulfonates (Ref. 15). We have utilized the former in assessing this new approach to PG's. As illustrated in Scheme 12, this technology does permit realization of a true, 1-pot, 3-component coupling.

**Scheme 12**

\[
\begin{align*}
& \text{Cp}_2\text{Zr(HCl)} \quad \xrightarrow{\text{THF, rt}} \quad \text{MeLi/Me}_2\text{ZnLi} \\
& \text{Me}_2\text{Cu(CN)Li}_2 \quad \text{(10 mol %)} \\
& \text{THF, rt} \quad \text{-78°} \quad \text{1 h} \\
& \xrightarrow{\text{CHO CO}_2\text{Me}} \quad \text{OH} \quad \text{CO}_2\text{Me} \\
& \text{OSi(δ-Pr)₃} \\
& \text{(74%)}
\end{align*}
\]
SUMMARY

It has been demonstrated through the initial use of organozirconium chemistry, in particular relying on hydrozirconation reactions and rearrangements induced by zirconocene ("Cp₂Zr"), that transmetalations of ligands from zirconium to copper are facile and can lead to cyanocuprate reagents highly capable of carbon-carbon bond formation. Processes resulting in transfer of vinylstannane residues, as well as allylic and vinylic ligands, have been developed. Methodology associated with the latter group utilizes catalytic amounts of copper and shows strong potential as a novel means of effecting, in a single flask operation, "three-component couplings".

REFERENCES