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New synthetic methods based on organozirconium and organocopper chemistry

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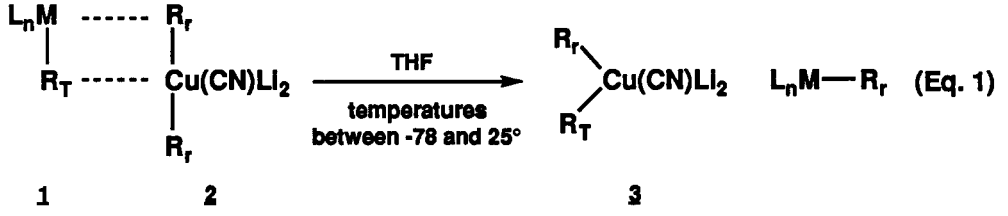
Abstract - Four inter-related topics highlighting recent, unpublished developments on the transmetalation chemistry associated with zirconium and copper reagents are presented.

INTRODUCTION

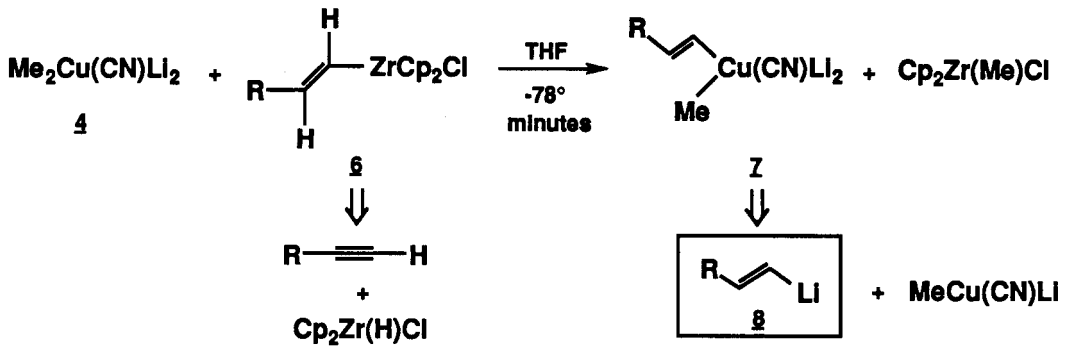
Transmetalation reactions between various organometallic species and equivalent amounts of a higher order (H.O.) cyanocuprate $R_2Cu(CN)Li_2$ have expanded the flexibility associated with cuprate formation (ref 1). These ligand exchange phenomena have been observed to occur efficiently for a number of 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 **3** can then be used to selectively deliver the ligand of interest (R_T) to an organic



[R_T = the desired, transferrable ligand; R_r = a non-transferrable ligand; L_n = n ligands on metal, M]

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.*, $Me_2Cu(CN)Li_2$, **4**) are derivatives of terminal acetylenes which have undergone a standard hydrozirconation reaction (ref. 3) with Schwartz' reagent ($Cp_2Zr(H)Cl$, **5**); *i.e.*, to give vinyl zirconocenes, **6** (Scheme 1). Generation of mixed cuprates **7**, 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.

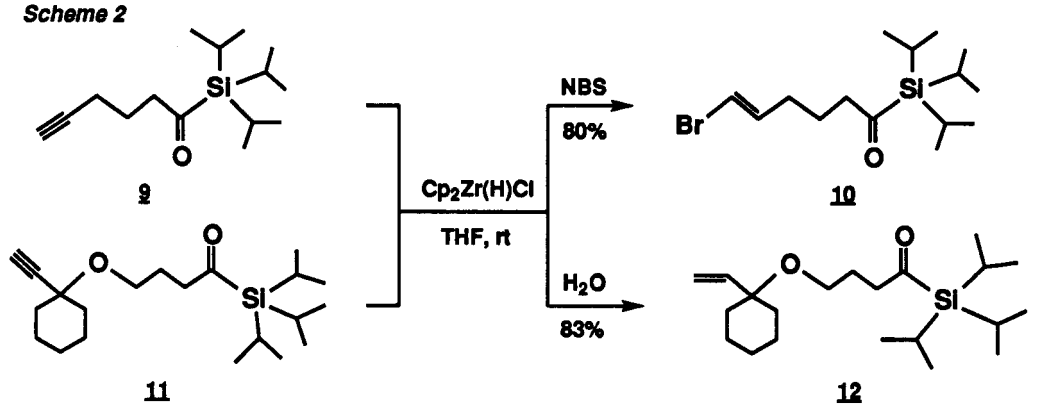
Scheme 1



$Cp_2Zr(H)Cl$: HYDROZIRCONATION vs. CARBONYL REDUCTION

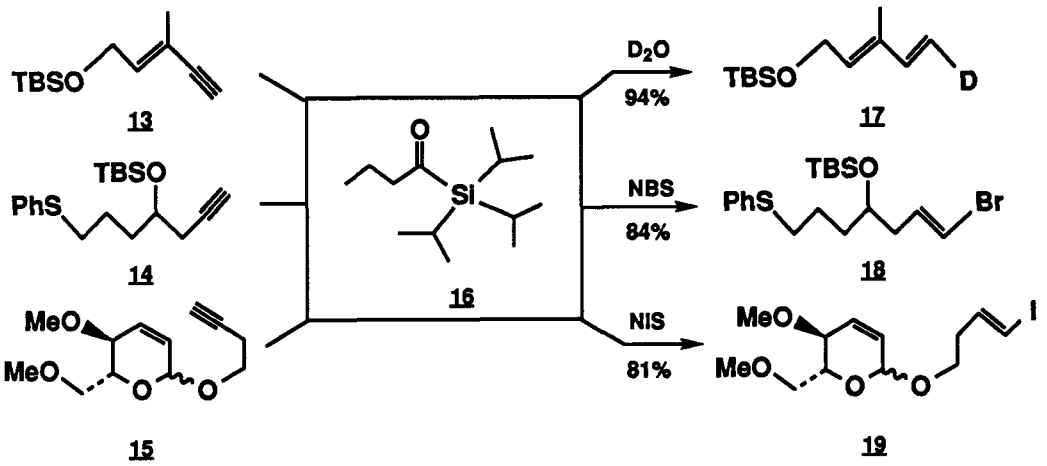
Although the *cis*-addition of Schwartz' reagent across acetylenes, in addition to being efficient, is very highly regio- and stereoselective (ref. 3), there are limitations associated with its use. Perhaps the most noteworthy is its lack of chemoselectivity in the presence of both an acetylene and aldehyde 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 **9** and **11** with an equivalent of $Cp_2Zr(H)Cl$ (**4**) followed by NBS and H_2O, respectively, afforded the olefinic products **10** and **12** (Scheme 2). Attempts at usage of a triethylsilyl analog of **9** led to incomplete conversion; addition of >1 equiv of $Cp_2Zr(H)Cl$ simply led to buildup of the undesired silyl alcohol product.

Scheme 2



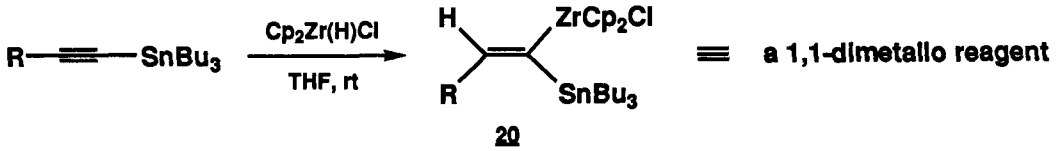
A series of competition experiments was used to test the compatability of a hydrozirconation/ electrophilic trap sequence involving (functionalized) acetylenes in the presence of a TIPS acyl silane. Exposure of a 1:1 mix of each acetylene **13**, **14**, and **15** with TIPS derivative **16** to 1 equiv $Cp_2Zr(H)Cl$, 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.

Scheme 3



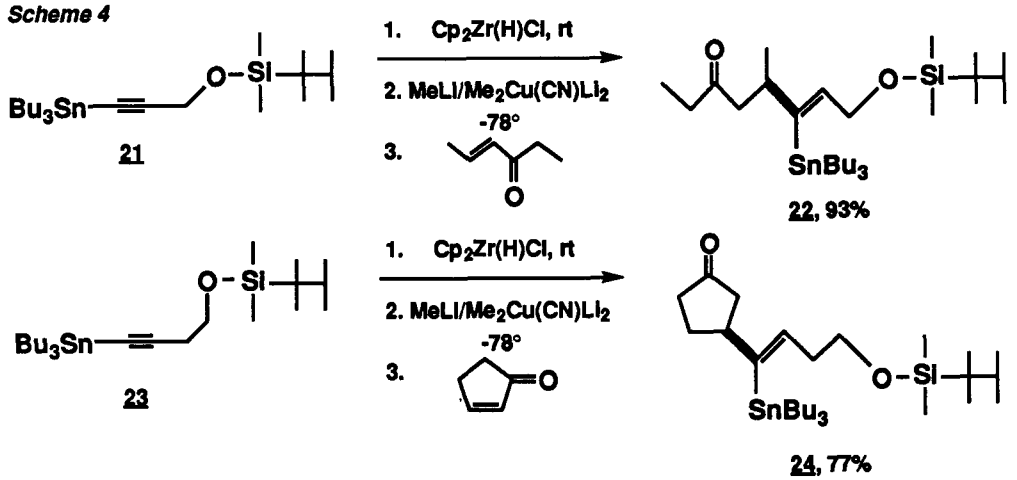
NEW 1,1- DIMETALLO REAGENTS

The addition of $Cp_2Zr(H)Cl$ 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 sp^2 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 $Me_2Cu(CN)Li_2$ on the vinylzirconocene portion in **20** is expected to occur under conditions where



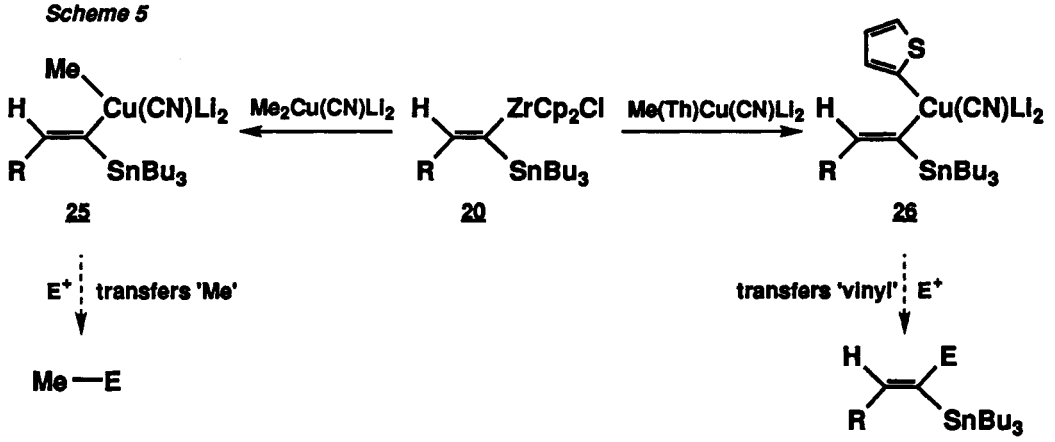
vinylstannanes are inert (ref. 1,2). Indeed, when the tributylstannyl derivative of protected propargyl alcohol (**21**) was hydrozirconated in THF at ambient temperature and then cooled to -78°, introduction of MeLi and preformed $Me_2Cu(CN)Li_2$ followed by cyclopentenone afforded the desired ketone (**22**) in good isolated yield. Likewise, homopropargyl derivative **23** led to vinylstannane **24** (Scheme 4).

Scheme 4

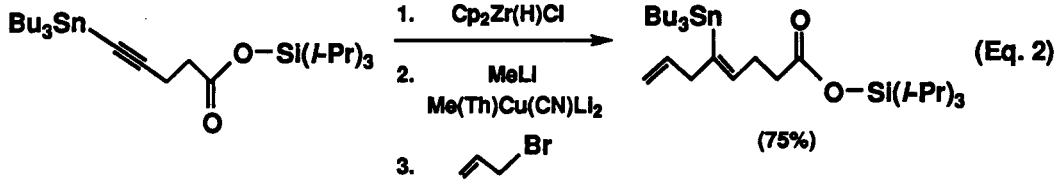


Displacement reactions can also be carried out with cuprates derived from 20, although $Me_2Cu(CN)Li_2$ is *not* a wise choice for this subsequent event since the transmetalated reagent 25 is not selective for vinyl ligand transfer; see Scheme 5 (Ref. 4). By switching to $Me(2\text{-Th})Cu(CN)Li_2$

Scheme 5



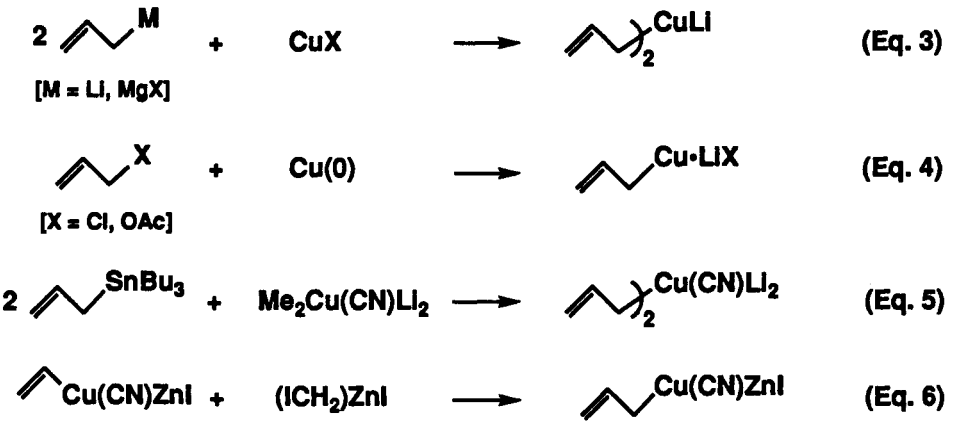
[from MeLi + ThCu(CN)Li; 2-Th = 2-thienyl], mixed cuprate 26 alkylates the desired vinyl ligand using unactivated primary triflates, as well as allylic and benzylic halides; *e.g.*, Eq. 2 (Ref. 8).



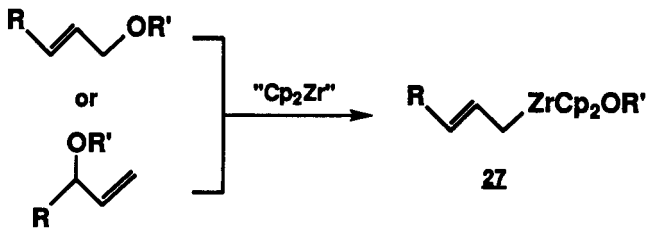
(Eq. 2)

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 H.O. cyanocuprates which take place smoothly at 0° (Eq. 5); and (3) one carbon homologations of L.O vinylic cyanocuprates in the presence of $(ICH_2)ZnI$ or $(ICH_2)_2Zn$ (Eq. 6), have all led to highly reactive forms of these species (Ref. 2).



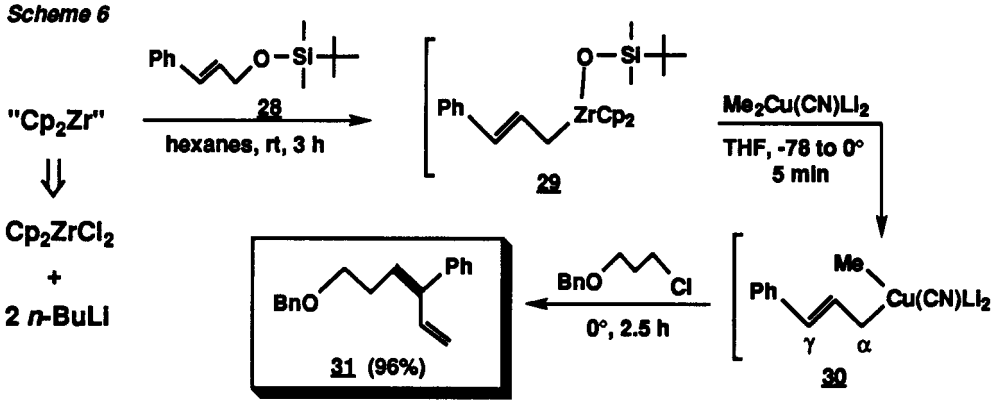
An alternative approach is to consider a ligand exchange between an allylic zirconocene and a H.O. cyanocuprate, which based on related reactions of vinylic (Ref. 9) and allylic stannanes (*cf.* Eq. 5), should be especially facile. Preparation of these starting materials, however, should preferrably 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 "Cp_2Zr" (Ref. 11), which take place efficiently to give reactive allylic zirconocene complexes **27** (Eq. 7).



(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 "Cp_2Zr", zirconocene being formed *in situ* from Cp_2ZrCl_2 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 $Me_2Cu(CN)Li_2$ 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.

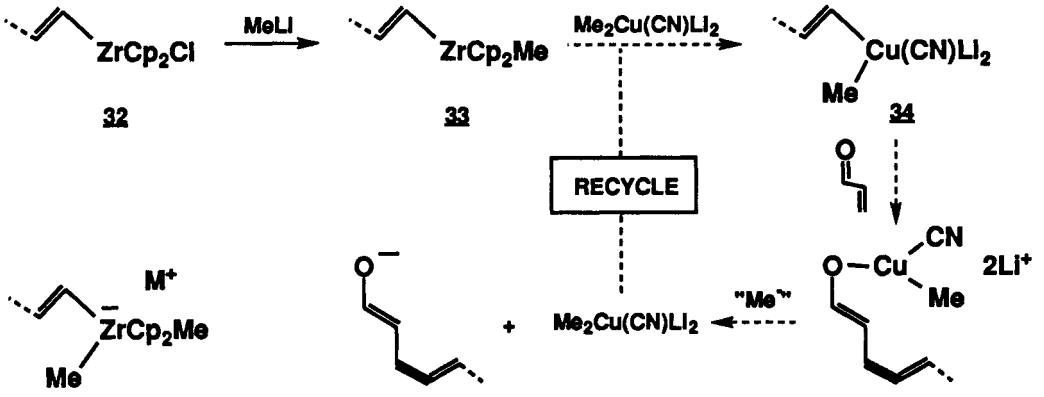
Scheme 6



CYANOCUPRATE - CATALYZED TRANSMETALATION-CONJUGATE ADDITION

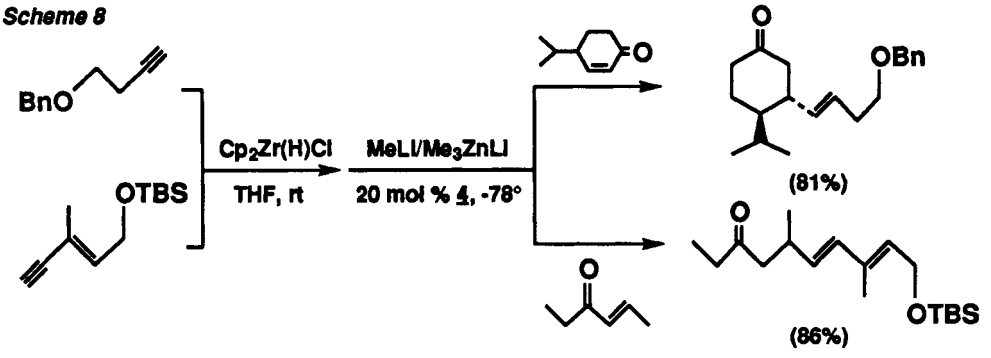
Implicit in the low temperature, rapid conversion of vinylzirconocenes to mixed vinyl cyanocuprates **34** *via* $Me_2Cu(CN)Li_2$ or $Me(Th)Cu(CN)Li_2$ is use of a 1:1 stoichiometry between these reactants. Hence, the 1,4-adduct generated following any conjugate addition of **34** to an enone is likely 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 $Me_2Cu(CN)Li_2$.

Scheme 7



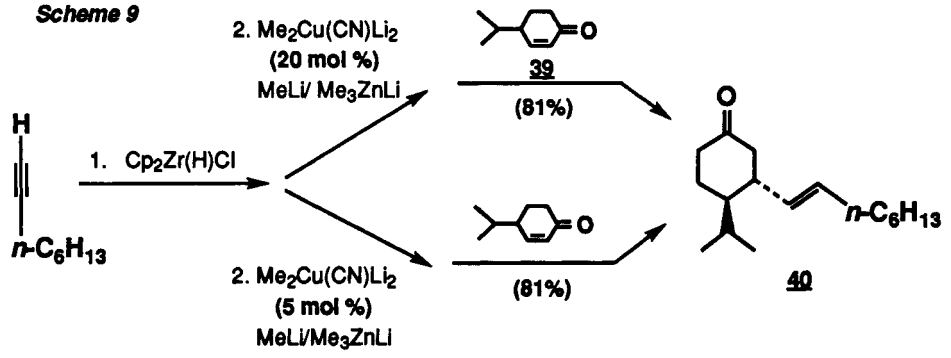
So, what should R-M be? It's properties should be such that it provides a 'soft' form of "Me⁻" yet is capable of a quick ligand exchange with **35**, but cannot itself add in either a 1,2 or 1,4 mode to the substrate enone under conditions where both cuprate **34** is active and the **35** to **36** conversion is facile. The species found which serves beautifully in this capacity is trimethylzincate, Me_3ZnLi, **38** (Ref. 12). Thus, when a vinylzirconocene **32** is exposed to MeLi and 20 mol % $Me_2Cu(CN)Li_2$ (**4**) in THF at -78° in the presence of Me_3ZnLi, 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.

Scheme 8

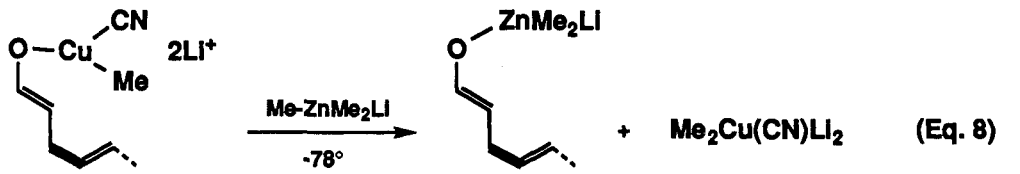


Since the 20 mol % figure was arbitrarily chosen as a starting point, lesser amounts of **4** were tested in terms of effects on reaction rate and yield. Cutting the catalyst concentration down to 5 mol % and extending the reaction time from one to about three hours, in the case of cryptone (**39**) going to product **40**, led to identical yields (Scheme 9).

Scheme 9



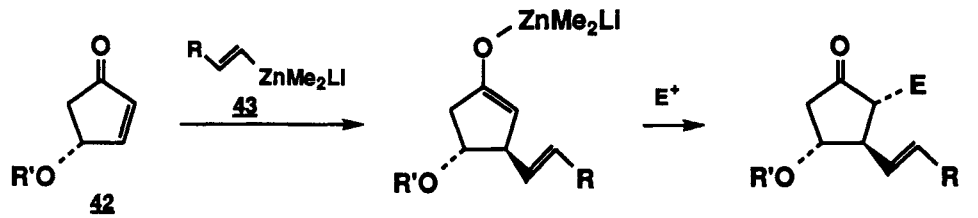
In using Me_3ZnLi as the supply of "Me^-", the implication with respect to the nature of the enolate formed upon Michael addition by **34** followed by transmetalation is that a new zincate, or what might be more commonly thought of as a "zinc enolate", **41** (Eq. 8). What should be appreciated



35 **41**

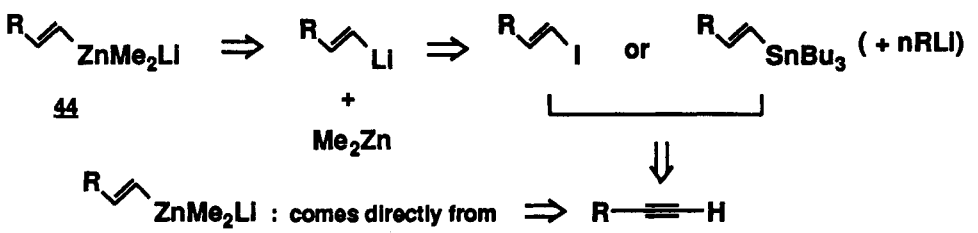
about intermediates **41** is that, unlike their copper counterparts **35** (Ref. 13), they are very reactive toward electrophiles. Indeed, zinc enolates (**41**) are precisely the species involved in Noyori "three-component couplings" (3-CC) using mixed zincates **43** as Michael donors *en route* to the prostaglandin (PG) skeleton; see Scheme 10 (Ref. 14). The prospects for extending this novel cata-

Scheme 10



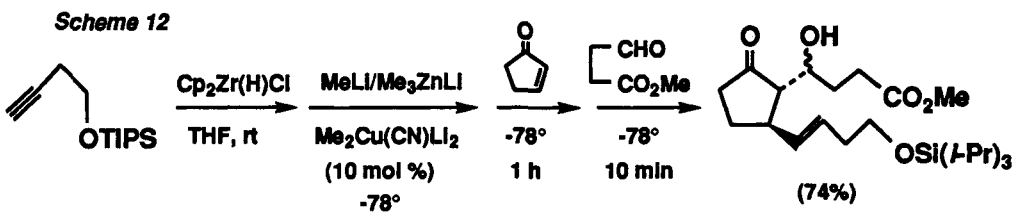
lytic process to include the 3-CC aspect are very exciting, especially given the fact that our chemistry starts at the acetylene stage and does not invoke prior preparation of vinylic iodides or stannanes, or the derived vinyllithiums that go into forming cuprate **34** or zincate **44** (Scheme 11). 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



"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



SUMMARY

It has been demonstrated through the initial use of organozirconium chemistry, in particular relying on hydrozirconation reactions and rearrangements induced by zirconocene ("Cp_2Zr"), 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".

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