Pergamon

*Tetrahedron Letters*, Vol. 35, No. 35, pp. 6433-6436, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01350-0

# Spectroscopic Studies on Cyanocuprate-Catalyzed 3-Component Couplings: Understanding the Catalytic Cycle

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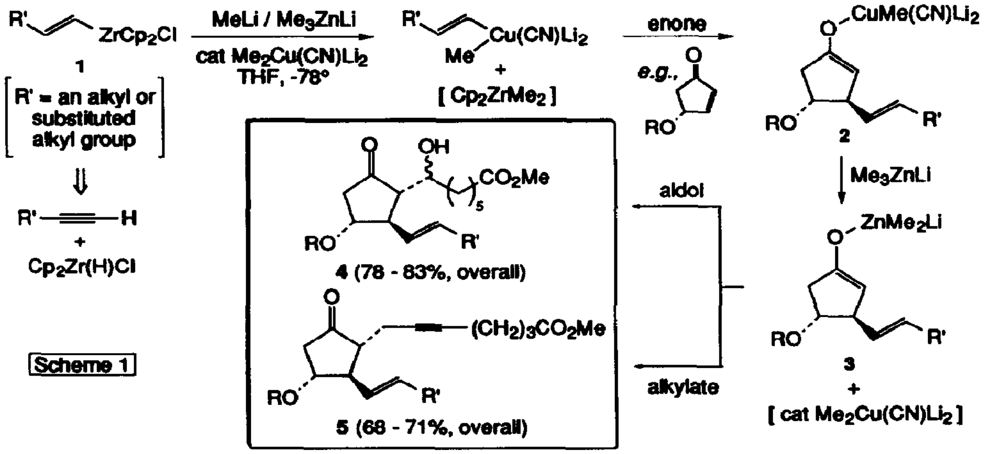
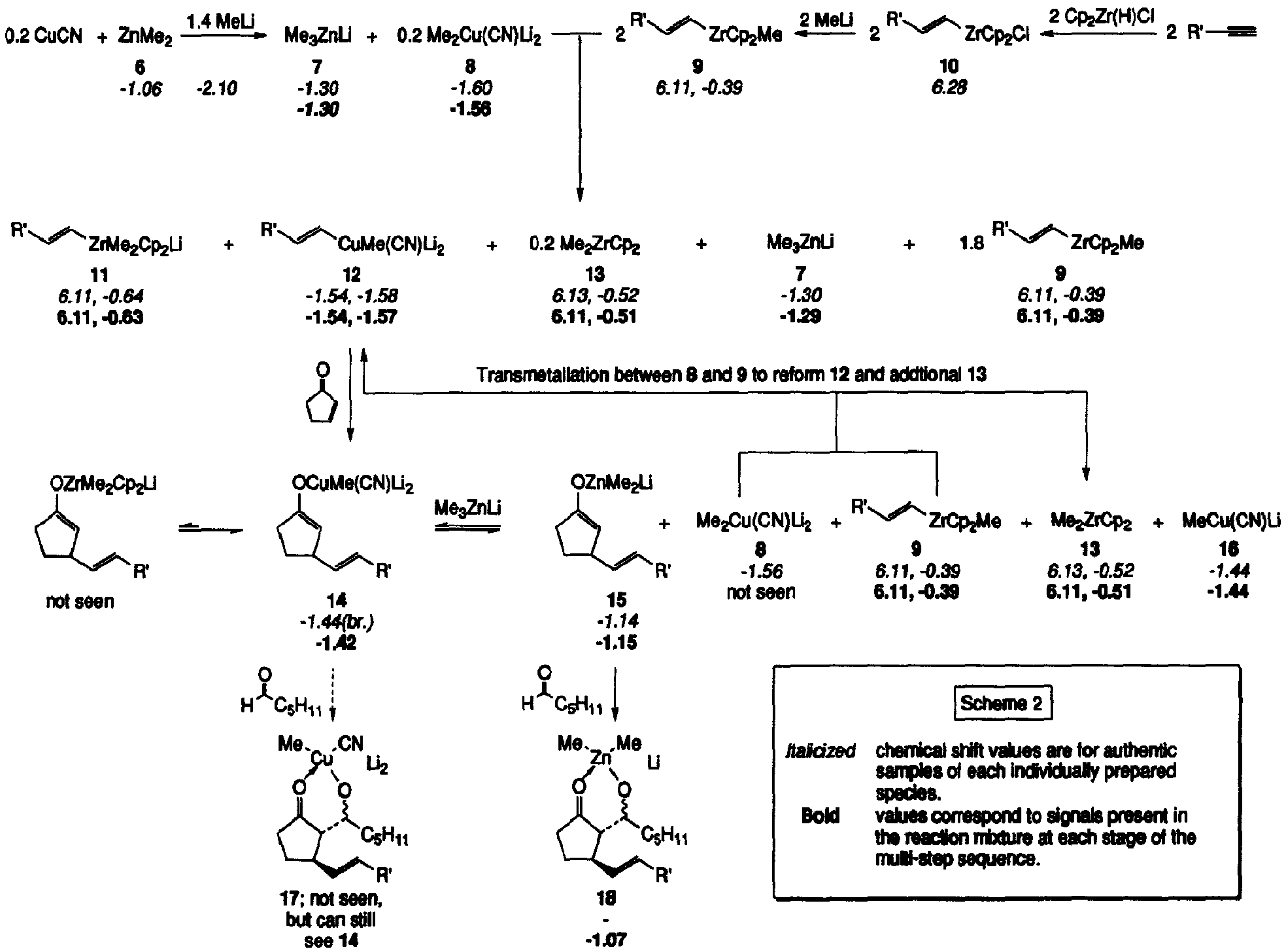
***Summary.*** *Low temperature $^1H$ NMR analysis of a reaction mixture containing a vinylic zirconocene, MeLi, $Me_3ZnLi$, 20 mol % $Me_2Cu(CN)Li_2$ and an enone, reagents which together lead to the Michael delivery of a vinyl ligand, reveals the presence of a zinc enolate, the species likely to be responsible for the subsequent alkylation or aldol reaction as the final step in 3-component couplings.*

In a recent report from these laboratories,[1] a new method for effecting 1,4-addition of a vinylic ligand (in **1**) was described which proceeds through an initial hydrozirconation of a 1-alkyne and utilizes catalytic amounts of higher order cuprate $Me_2Cu(CN)Li_2$ (Scheme 1). It was proposed that the zincate[2] $Me_3ZnLi$ present in the reaction mixture serves to transmetallate the initially formed copper enolate **2**, thereby regenerating the catalyst. The upshot of such a ligand exchange, in principle, is the production a reactive zinc enolate **3**,[3] which should allow for further C-C bond constructions. Indeed, when applied to the cyclopentenone system, both aldol and alkylation reactions leading to **4** and **5**, respectively, can be carried out completing this true 3-component coupling (3-CC) sequence.[4] Alternatively, with an equivalent of $Cp_2ZrMe_2$ presumably present as



**Scheme 1**



**Scheme 2**

| | |
|---|---|
| *Italicized* | chemical shift values are for authentic samples of each individually prepared species. |
| **Bold** | values correspond to signals present in the reaction mixture at each stage of the multi-step sequence. |

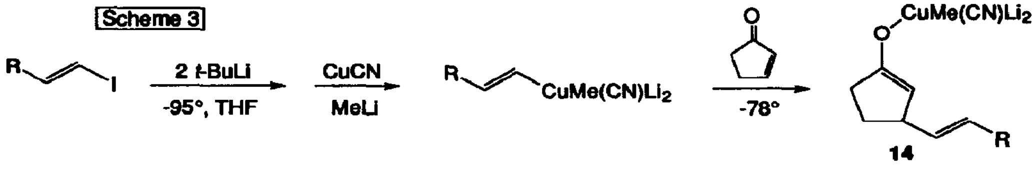
an outgrowth of the initial zirconocene-cuprate transmetallation, a zirconium enolate[5] could be the predominent species, or perhaps a mix of both, as well as Zn or Zr enolates with ligands other than methyl on the metal centers. To better understand the extent to which various species are present and to assess the intermediate(s) likely to be responsible for the final coupling in this 6-step, 1-pot process,[4] we now describe spectroscopic experiments in an effort to gain insight regarding this remarkably efficient combination of reagents.

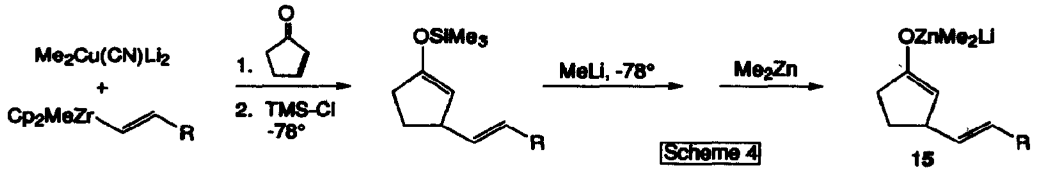
An overview describing the complete sequence and listing the various species observed by $^1$H NMR is illustrated in Scheme 2. *Italicized* chemical shift values under each organometallic represent those recorded for individually prepared samples (*i.e.*, control experiments to establish the identity of compounds observed in the reaction mixture). Those $\delta$ values in **bold** correspond to signals present in the reaction mixture at each stage of the multi-step sequence. Thus, starting with vinyl zirconocene **10**, MeLi supplies the methyl anion which replaces chloride on zirconium, giving a signal at $\delta$ -0.39. The signal due to the cyclopentadienyl groups shifts from $\delta$ 6.28 to $\delta$ 6.11. The other two components, $Me_2Cu(CN)Li_2$, **8** (20 mol %) and $Me_3ZnLi$ (**7**) were prepared from MeLi addition to CuCN (0.20 eq) and $Me_2Zn$ (**6**), respectively. The $Me_2Zn$ ($\delta$ -1.06) signal disappears as those for the cuprate **8** ($\delta$ -1.56) and zincate **7** ($\delta$ -1.30) grow in.

Upon mixing **7**, **8**, and **9** at -78°, transmetallation ensues immediately, leading to the complete loss of cuprate **8**, while zincate **7** remains intact awaiting its role once the newly generated mixed cuprate **12** has delivered its vinyl ligand to an enone (*vide infra*). The by-product of ligand exchange between **8** and **9** is $Cp_2ZrMe_2$ (**13**), which is clearly visible in an amount equal to that of the mixed cuprate **12** formed *in situ* (*i.e.*, 20 mol %). Small amounts of lithio zirconate **11**,[6] which disappear during the subsequent Michael addition, were also confirmed, suggesting further equilibration between **8** and **9**, and possibly **7** as well.

Introduction of the enone begins the process of vinylic ligand transfer and gives rise, as expected, to several new peaks in the $^1$H NMR spectrum. Fortunately, all of these signals are identifiable. Thus, in addition to **9** (prepared originally in excess) and **13** (which builds up from continuous transmetallation between **8** and **9**), singlets at $\delta$ -1.15, -1.42, and -1.44 are present. That these are attributable to zinc enolate **15**, copper enolate **14**, and the lower order cyanocuprate **16**, respectively, can be unequivocally demonstrated again from individual preparations, the spectrum of each being recorded under identical conditions of solvent (THF), reagent concentration, and temperature (-78°) as used in the couplings. Authentic copper enolate **14** was obtained *via* vinyl ligand transfer to cyclopentenone, as illustrated in Scheme 3. Species **15**, on the other hand, was derived from trapping of **14** with $Me_3SiCl$, followed by regiospecific lithium enolate generation and thence exposure to $Me_2Zn$ (Scheme 4). The $\delta$ values for the pure materials were virtually identical

Scheme 3





Scheme 4

to those found from the reaction mixture in all cases (Scheme 2). No other signals due to upfield methyl groups or downfield Cp ligands were noted, further suggesting that a zirconium enolate is not present to any extent observable by 200 MHz NMR.

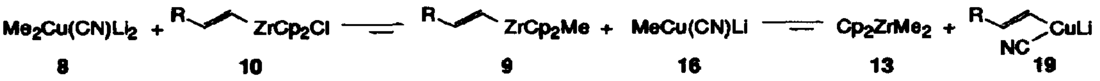
Lastly, quenching of the zinc enolate **15** with an aldehyde should alter the signal at δ -1.15 owing to the likely formation of chelate **18**. In the event, upon introduction of hexanal at -78°, a new peak was observed at δ -1.07, with concommitant loss of signal due to the zinc enolate (Scheme 2).

From these experiments, it is concluded that (1) transmetallation between a higher order cyano-cuprate and vinylic zirconocene is indeed rapid and complete at -78°; (2) zincate Me$_3$ZnLi supplies the methyl ligand to copper which allows for the catalytic cycle to proceed as vinylic zirconocene is converted to Cp$_2$ZrMe$_2$; (3) once the cuprate 1,4-addition is complete, copper situates itself (based on integrations of NMR signals) in part as a copper enolate **14** (14 of 20 mol %) and to a lesser degree (6 of 20 mol %) as a lower order cyanocuprate **16**; after the 3-CC, the same enolate **14** remains, rather than forming chelate **17**, while the signal for **16** disappears; (4) the Me$_3$ZnLi used to effect transmetallation of the copper enolate gives rise predominantly to a zinc enolate rather than a zirconium enolate, which as the major species in solution is likely to be responsible for the final aldol or alkylation step.

**Acknowledgement.** We warmly thank the NSF (CHE 93-03883) for financial support of our programs.

## References and Notes

1. Lipshutz, B.H., Wood, M.R., *J. Am. Chem. Soc.*, **1993**, 115, 12625.
2. Isobe, M., Kondo, S., Nagasawa, N., Goto, T., *Chem. Lett.*, **1977**, 679.
3. Noyori, R., Suzuki, M., *Chem. Tracts; Org. Chem.*, **1990**, 3, 173.
4. Lipshutz, B.H., Wood, M.R., *J. Am. Chem. Soc.*, submitted.
5. Evans, D.A., McGee, L.R., *Tetrahedron Lett.*, **1980**, 20, 3975.
6. The observation that **11** is formed from **8** + **9** strongly suggested that the combination of species **10** and an *equivalent* of cuprate **8** would equilibrate to a mix of **9** + **16** and predominantly **13** + **19**, the latter cuprate being responsible for the 1,4-additons. This is precisely what is observed by $^1$H NMR, which settles the issue raised in some of our earlier transmetallation work where R in **19** contains an electrophilic center; *cf.* Lipshutz, B.H., Keil, R., *J. Am. Chem. Soc.*, **1992**, 114, 7919.



(*Received in USA* 1 *June* 1994; *revised* 7 *July* 1994; *accepted* 11 *July* 1994)