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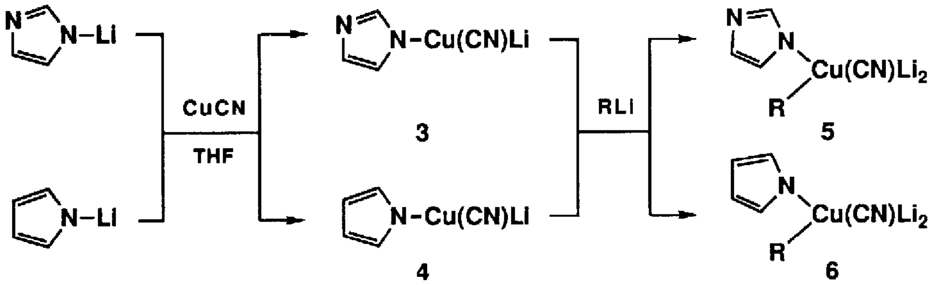
HIGHER ORDER, MIXED CYANOCUPRATES DERIVED FROM N-LITHIOIMIDAZOLE AND PYRROLE: NEW "DUMMY" LIGAND ALTERNATIVES IN ORGANOCOPPER CHEMISTRY

Bruce H. Lipshutz,* Paul Fatheree, William Hagen, and Kirk L. Stevens#
Department of Chemistry
University of California, Santa Barbara, CA 93106
[FAX: 805-893-4120]

Summary: *Treatment of N-lithioimidazole or N-lithiopyrrole with CuCN followed by an organolithium leads to cuprates* $R(Imid)Cu(CN)Li_2$ *and* $R(Pyrr)Cu(CN)Li_2$ *which show "higher order" reactivity relative to* $RCu(CN)Li$.

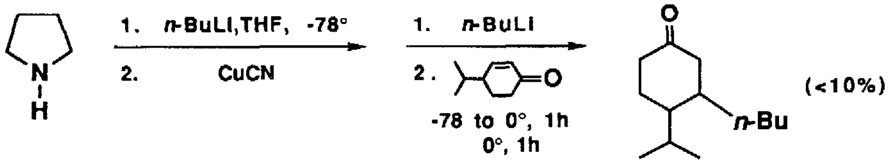
Back in 1987,[1] the lower order (L.O.) cyanocuprate (2-Th)Cu(CN)Li (**1**) derived from 2-lithiothiophene and CuCN was described as a stable (now commercially available), "cuprate-in-a-bottle" precursor to mixed higher order (H.O.) reagents $R(2\text{-}Th)Cu(CN)Li_2$ (**2**). While **1** does provide a convenient source of Cu(I) which calls for only one equivalent of an organolithium to form **2**, reactions of **2** always lead to varying amounts of 2,2'-dithiophene on work-up, which occasionally can complicate product isolation. Moreover, scale-up of reactions involving **1** necessitates handling large quantities of thiophene, which has certain implications associated with sulfur in the molecule. To obviate the issues of ligand homocoupling and sulfur chemistry while remaining within the domain of heteroaromatics, we have investigated nitrogen-containing systems, specifically N-lithiated imidazole and pyrrole, for their potential as non-transferrable groups on copper. We now report that both of these moieties can be utilized in the formation of $R(Imid)Cu(CN)Li_2$ (**5**) and $R(Pyrr)Cu(CN)Li_2$ (**6**), and that they are practical alternatives to 2-lithiothiophene and thus, $R(2\text{-}Th)Cu(CN)Li_2$ (**2**).



Treatment of imidazole in THF with *n*-BuLi affords N-lithioimidazole, which reacts at ambient temperatures with CuCN (or CuCN•2LiCl)[2] to produce a pale green solution. Upon cooling to -78°, particulates are formed to which is added an organolithium (1 eq) to give a pale yellow, homogeneous solution of **5** after slight warming. Metalation of pyrrole in the same fashion followed by exposure to CuCN with slight warming gives a water-white solution which maintains its homogeneity on cooling to -78°. Introduction of 1 eq RLi leads to a pale yellow solution of **6**.

Table 1 shows a representative sampling of reactions of **5**/**6**. The salient features of this methodology include (1) for the two cases examined which compare these H.O. reagents with their L.O. analogs (entries 1a *vs* 1b; 5b *vs* 5c), yields can be significantly lower using the latter species; (2) cuprates **5**/**6** are less reactive than is **2**, as evidenced by the higher temperatures required in these couplings relative to reactions of **2**.[1] This is an expected outgrowth of the heteroatom- rather than carbon-copper bond present in **5**/**6**, seen not only with amido[2] but also with phosphido[3] ligands; (3) the readily prepared[4] vinylfluorosulfonate **11** reacted quite smoothly and efficiently, this new leaving group representing an attractive substitute for the less stable yet more expensive triflate option.[5]

The importance of the aromatic nature of the "dummy" ligand was tested, since, in principle, any dialkylamide could function in a related capacity. Lithiated pyrrolidine, therefore, was converted to the species stoichiometrically related to **5**/**6** using CuCN and *n*-BuLi (as described above). Subsequent addition of a cyclohexenone led to the 1,4-adduct in <10% yield, suggesting that the presence of an amide of this type actually *detracts* from the chemistry of *n*-BuCu(CN)Li (compare with result in Table 1, entry 5c).



Further evidence for the existence of **5**/**6** was sought by focusing on the ability of H.O. cuprates to effect transmetalations of, *e.g.*, vinylic zirconates.[6] Thus, while **6**, R = Me, transformed **7** to the mixed vinylic cuprate **8** and ultimately led to ketone **9**,[7] MeCu(CN)Li did not undergo ligand exchange and hence afforded *none* of the desired adduct. Rather, oxidative dimerization was found to be the major pathway under the influence of the L.O. cuprate.

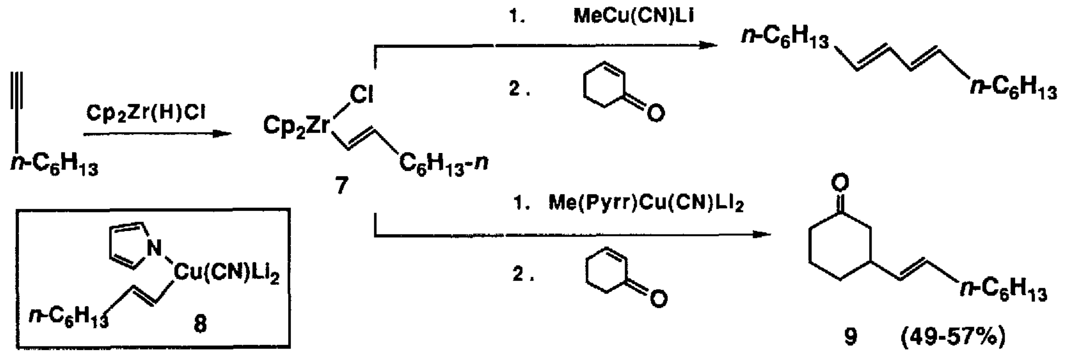
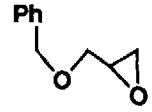
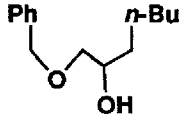
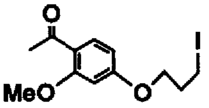
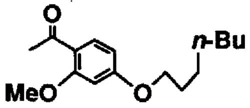
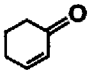
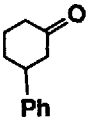
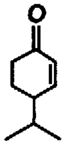
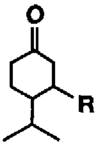
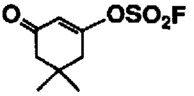
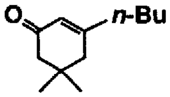
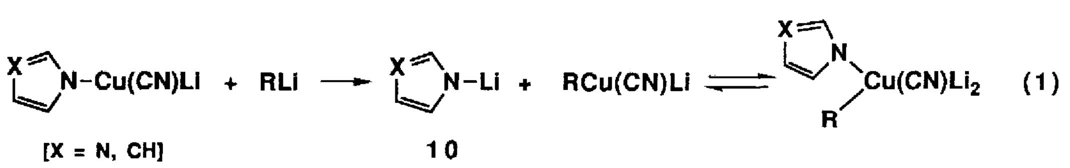


Table 1. Reactions of H.O. cyanocuprates **5** and **6**.

Entry	Substrate	Cuprate	Conditions	Product(s)[a]	Yield(%)[b]
1a		**5**, R = *n*-Bu	-78 to 0°, 4h		82
1b		*n*-BuCu(CN)Li	-78 to 0°, 4h		22[c]
2		**5**, R = *n*-Bu	-78 to 0°, 2h rt, 3h		89
3		**6**, R = *n*-Bu	-78°, 2h rt, 1h		40-50[d]
4		**5**, R = Ph	-78°, 2h		88[e]
5a		*5, R = n-Bu*	*-78°, 2h; 0°, 1h*		*86-88*[e,f]
5b		**6**, R = *n*-Bu	-78 to 0°, 1h; 0°, 1h		81-87[f,g]
5c		*n*-BuCu(CN)Li	-78 to 0°, 1h; 0°, 1h		54-70[h]
5d		**5**, R = Ph	-78°, 0.25h		83[e,i]
6	 **11**	**5**, R = *n*-Bu	-78 to 0°, 2h		94

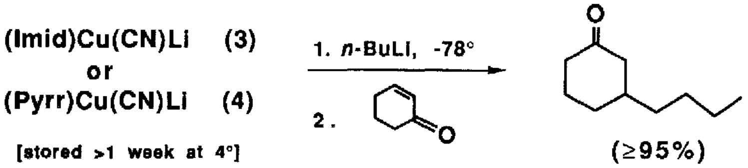
[a] Fully characterized by IR, NMR, MS, and HRMS data. [b] Isolated yields. [c] Starting material (55%) was isolated. [d] The product of iodide reduction (*ca.* 20% by GC) was also formed. [e] BF_3•Et_2O (1 eq) was added. [f] A 99:1 ratio of isomers by GC. [g] Starting material (7-10%) remained by GC. [h] Starting material (10%) remained by GC. [i] An 82:11 mix of isomers by GC.

Low temperature NMR studies on **6**, R = Me, in THF confirmed the presence of a new cuprate, a broadened singlet appearing at δ-1.33. Interestingly, however, the L.O. reagent MeCu(CN)Li (δ-1.44) is the main component in solution (*ca.* 2:1 vs **6**, R = Me). The downfield region correlates with the upfield data, as N-lithiopyrrole is observed (δ5.87, 6.65), while the pyrrole signals in **6** occur at δ5.66 and 6.53. Likewise, **5**, R = Me, displays a new upfield signal at δ-1.26, along with the δ-1.44 peak in *ca.* the same ratio. It therefore appears that **5**/**6** exist (at -78°) as an equilibrium mix according to equation (1), with K_{eq}, as drawn, equal to *ca.* 0.5. The presence of **10** does little to affect the Michael addition chemistry of **5**/**6**, although in some of the slower alkylations, especially when BF_3•Et_2O is present, N-alkylation can be competitive.



(1)

Lastly, the thermal stabilities of both **3** (with LiCl) and **4** (with or without LiCl), as 0.2M solutions in THF, have been briefly examined. Storage of each (Aldrich Sure/Seal™ bottle) in a refrigerator (*ca.* 4°) for just over a week followed by conversion to their respective H.O. cuprates (**5** and **6**, R = *n*-Bu) with *n*-BuLi and introduction of cyclohexenone (1 eq) afforded >95% (by GC analysis) of the Michael product in each case. Thus, as with **1**, these nitrogen-based L.O. cyanocuprates have good shelf-life.



In conclusion, it has been demonstrated that two readily available, heteroaromatic nuclei (imidazole and pyrrole) can serve, in lithiated form, as residual ligands on copper. Although when combined with CuCN and an RLi of one's choosing an equilibrium is established favoring the release of the imidazolide or pyrrolide ligand from the metal, the greater reactivity of the H.O. portion of the mixture can result in enhanced rates of reactions and/or improved yields of products compared to couplings based on L.O. cyanocuprates RCu(CN)Li. From a more pragmatic perspective, reagents **5**/**6** avoid sulfur chemistry and eliminate any need for chromatographic separation of biaryl by-products.[8]

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References and Notes

\# Syntex Fellow, UCSB, 1991-1992.

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5. Other uses of the fluorosulfonate group (*e.g.*, TMSO$_3$SF) will be reported in due course; Lipshutz, B.H., Burgess-Henry, J., Roth, G.P., unpublished work.
6. (a) Lipshutz, B.H., Ellsworth, E.L., *J. Am. Chem. Soc.*, **1990**, 112, 7440; (b) see also, Babiak, K.A., Behling, J.R., Dygos, J.H., McLaughlin, K.T., Ng, J.S., Kalish, V.J., Kramer, S.W., Shone, R.L., *ibid.*, **1990**, 112, 7441.
7. Prior treatment of **7** with 1 eq MeLi, as described in ref. 6a, raised the yield of this reaction to >80%.
8. N-lithiated imidazole can also be stored under argon as a white solid for several weeks and weighed out quickly *in air* without deleterious effects on the cuprate couplings.

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