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REACTIONS OF STOICHIOMETRIC HIGHER ORDER, MIXED LITHIO MAGNESIO ORGANOCUPRATES

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Abstract—Novel higher order cuprates, R(2-thienyl)Cu(CN)LiMgBr (**2**), are prepared from the 1 : 1 : 1 combination of CuCN, 2-lithiothiophene and RMgX. Reactions of various members of this new class of reagents are described, including substitution and conjugate addition processes, where the ligand derived from the Grignard reagent is selectively transferred. The effects of added $BF_3 \cdot Et_2O$ are discussed. Some comparison reactions with the corresponding lower order reagents, RCu(CN)MgBr, have also been carried out. Evidence is presented suggesting that species **2**, unlike their dilithio analogs, are not discrete.

INTRODUCTION

Since the early work of Kharasch and Tawney in 1941 on the Cu-catalyzed additions of Grignard reagents to α,β-unsaturated ketones,[1] much of the subsequently developed cuprate chemistry has and continues to favor stoichiometrically defined organolithium-based reagents.[2] Hence, lithio cuprates of both the lower order (L.O., for example, "Gilman" reagents,[3] R_2CuLi) and higher order (H.O.,[4] e.g. "$R_2Cu(CN)Li_2$") persuasion share the majority of the spotlight in synthetic situations where use of a Cu reagent is appropriate. Both systems, however, require the addition of 2 equiv of an organolithium to a Cu(I) salt, only one of which is utilized. The desire to conserve potentially valuable groups has necessitated the development of mixed cuprates, R_TR_RCuLi[2,5] and $R_TR_RCu(CN)Li_2$,[4] which selectively release from Cu a transferable ligand R_T over a residual ligand R_R. Recently, we described a new higher-order mixed cuprate derived from CuCN, 2-lithiothiophene, and an R_TLi, which when combined in a 1 : 1 : 1 ratio presumably form "R_T(2-Th)Cu(CN)Li_2", **1**.[6] These species are highly prone towards delivery of the R_T moiety in substitution reactions of primary and secondary halides and epoxides, although in conjugate addition schemes 1,2-addition of the 2-thienyl group was noted with a number of hindered β,β-disubstituted enones. Fortunately, the use of $BF_3 \cdot Et_2O$ in the presence of **1** circumvents this competing pathway nicely.[7]

These findings notwithstanding, it need be appreciated that the key criterion for applying lithio cuprate technology is the oftentimes limited availability of the lithiated moiety, which is to undergo Li–Cu exchange and ultimately participate in C—C bond formation. Grignard reagents, on the other hand, tend to be more accessible and less expensive than the corresponding lithio derivatives. Thus, in light of the chemistry surrounding dianion salt **1**,[6] a study was undertaken to compare reagents **1** with their mixed lithio magnesio analogs R_T(2-Th)Cu(CN)LiMgBr (**2**). Herein are described some representative substitution and Michael reactions of **2**, the species which we initially *assumed* to form upon the addition of RMgBr and 2-thienyllithium (1 : 1) to 1 equiv of CuCN. In many of these cases involving enones and oxiranes, the effects of added $BF_3 \cdot Et_2O$ are also discussed.

RESULTS

Preparation of R(2-Th)Cu(CN)LiMgBr (**2**) was anticipated to parallel the sequence developed for the dilithio analog, **1**.[6] Thus, metalation of thiophene in THF with 1 equiv of n-BuLi between 0 and 25°[8] followed by addition of this solution to a slurry of CuCN in THF, precooled to −78°, and warming to 0° produces the lower order species 2-ThCu(CN)Li (**3**). Recooling **3** to −78° and introduction of an Et_2O or THF solution of the Grignard reagent (1 equiv), unlike the cases using RLi, most often did not afford homogeneous solutions of **2**. Warming the resulting slurry to 0° usually fails to dissolve the mixed cuprate fully irrespective of R (alkyl, vinyl, aryl) and concentration (0.1–0.4 M). Changing the mode of formation to one which involves the addition of both RMgX and 2-lithiothiophene to a slurry of CuCN in THF or Et_2O followed by warming to effect dissolution of the Cu salt appears to give the same mixture, both in appearance and subsequent coupling reactions. Use of Et_2O as the major or sole solvent in generating **2** leads to a less soluble cuprate, with a brown, sticky mass oftentimes being observed at the bottom of the flask. THF affords a somewhat more homogeneous reagent and is the recommended medium for forming **2**.

These mixed lithio Grignard-derived cuprates are less reactive than their dilithio predecessors, requiring usually higher temperatures or longer reaction times for their couplings. Substitution reactions, as summarized in Table 1, involving primary bromides work well, considering that only *ca* 1.2 equiv of cuprate were used. Moreover, in spite of the relatively high temperatures (0–25°) of this displacement, other potentially receptive functionalities (e.g. a nitrile group) do not effectively compete. Secondary halides, including the more reactive iodides (entry 5), afford only moderate yields.

Epoxides, well-behaved substrates towards both $R_2Cu(CN)Li_2$[9] and R(2-Th)Cu(CN)Li_2,[6] provided a mixed bag of results in their reactions with **2**. A simple monosubstituted case (entry 2) reacted with **2** (R = n-Bu)

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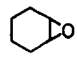
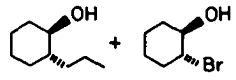
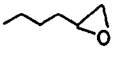
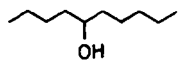
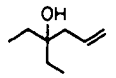
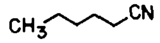
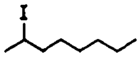
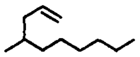
Table 1. Substitution reactions of higher order, mixed lithio magnesio cuprates (**2**)

Entry	Substrate	R_T	Product(s)	Yield
1		$\underline{n}$-C_3H_7		$52+26^a$
2		$\underline{n}$-C_4H_9-		82^b
3		$CH_2{=}CH$-		4^a
4	$Br(CH_2)_4CN$	$CH_2{=}CH$- CH_3-	 	70^a 96^a
5		$CH_2{=}CHCH_2$-		45^a

[a] By quantitative VPC analysis.
[b] Isolated yield.

to give a good yield of the product derived from attack at the least-hindered site. By way of comparison, the lower order species, n-BuCu(CN)MgCl, under otherwise identical conditions, reacted sluggishly, consuming only 60% of the starting epoxide in the same period of time. Cyclohexene oxide (entry 1) gave the known[6] n-propyl-substituted cyclohexanol in essentially the same yield realized using **1** (R = n-Pr). While the major by-product via ring-opening with the dilithio cuprate was cyclohexanone (35%), in this case only 10% was quantitatively determined to be present by GC analysis. Less expected was the corresponding bromohydrin,[10] formed to the extent of 26%, which is suggestive of the potential role of cationic-like intermediates in reactions of **2** not noted previously with **1**. Hence, while **2** appears to be a satisfactory species for effecting substitution reactions at primary centers bearing halogen and for monosubstituted oxiranes, use of a Lewis acid to assist these and more hindered cases results in varying degrees of competitive carbon–halogen bond construction, ' or products apparently of cationic polymerization (Table 1, entry 3).

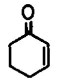
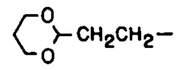
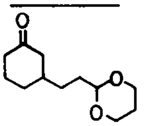
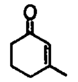
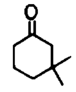
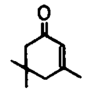
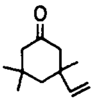
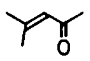
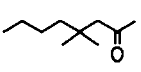
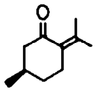
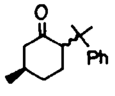
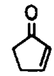
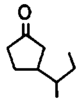
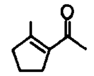
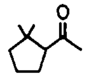
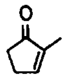
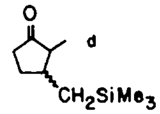
The effects of $BF_3 \cdot Et_2O$ on cuprates **2** themselves can also be quite pronounced. These reagents, which are most often grayish slurries in THF, are rendered far more homogeneous in the presence of $BF_3 \cdot Et_2O$ upon warming to 0°. Interestingly, in time it was found that this aesthetic adjustment has most deleterious consequences for the ensuing reaction. In retrospect, this is not totally unexpected, since previously it had been observed that **1** plus $BF_3 \cdot Et_2O$ begins to decompose at about −20°.[7] Thus, in an effort to solubilize fully what is presumably **2** by warming, reagent decomposition may well occur. Maintaining a heterogeneous mix of **2** and Lewis acid at −78°, however, does provide synthetically useful chemistry where Michael acceptors are concerned.

A representative sampling of the reactions of enones with **2** is illustrated in Table 2. Some trends can be detected from inspection of the data. Unhindered (i.e. α- and β-monosubstituted) enones, e.g. entries 1 and 6, react quite readily at low temperatures, affording 1,4-adducts. The fact that additional carbonyl activation (i.e. with $BF_3 \cdot Et_2O$) is not needed in these cases permits the use of acetal-containing ligands. Thus, a propionaldehyde β-anion equivalent,[11] oftentimes valued for annelation purposes,[12] may be employed (entry 1). Carrying out the coupling in the presence of $BF_3 \cdot Et_2O$ led mostly to recovery of starting cyclohexenone relative to product (7.5 : 1) under otherwise identical conditions, further suggesting the non-compatibility of acetal-containing ligands on Cu with a Lewis acid.

Unsubstituted cyclopentenone (entry 6), not surprisingly, seems to be an especially reactive educt. Yields for the conjugate addition of an s-Bu ligand improved considerably by deviating from use of the otherwise standard, more concentrated cuprate mixtures. Addition of neat enone to a 0.3 M heterogeneous **2** (R = s-Bu) even at ≤ −90°, afforded VPC yields in the 60–65% range. Diluting the cuprate to *ca* 0.1 M *and* cooling the enone in THF prior to introduction (total concentration *ca* 0.09 M) led to the product ketone as a mixture of diastereomers to the extent of 76%.

Aside from these two examples, Michael additions to most of the other unsaturated ketones studied, all of which have either tri- or tetrasubstitution about the olefin, depended heavily on $BF_3 \cdot Et_2O$ to assist in β-carbon–carbon bond formation. The cuprates, formed in THF in the usual manner (*vide supra*) and kept at −78°, were treated with $BF_3 \cdot Et_2O$, producing little visual change. Introduction of the enone occasionally imparted an immediate color change, although the mixture tended to remain heterogeneous throughout the process. Once **2** has been formed in THF, it is possible to remove some solvent *in vacuo* at *ca* 0° (~ 25–

Table 2. Conjugate addition reactions of R_T(2-Th)Cu(CN)LiMgX with enones

Entry	Enone	R_T	Additive	Product(s)	Yield
1			—		85[a]
2		CH_3–	—		29[b]
		CH_3–	$BF_3\cdot Et_2O$		85[b] (89)[c]
3		CH_2=CH–	$BF_3\cdot Et_2O$		75[a] (59)[c]
4		n-C_4H_9–	$BF_3\cdot Et_2O$		77[b] (96)[c]
5		C_6H_5–	—		67[b]
			$BF_3\cdot Et_2O$		59[b]
6		CH_3CH– CH_2CH_3	—		76[b]
7		CH_3–	$BF_3\cdot Et_2O$		73[b]
		CH_3–	—		34[b]
8		Me_3SiCH_2–	$BF_3\cdot Et_2O$		63[a]

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[a] Isolated yield.

[b] By quantitative VPC.

[c] Derived from the corresponding lower order magnesio cuprate.

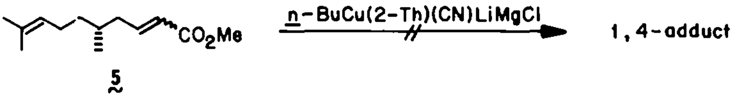
[d] A 3 : 1 mixture of *trans* : *cis*-isomers.

50%) and replace it with dry Et_2O, followed by cooling to −78° and addition of $BF_3\cdot Et_2O$. This partial solvent exchange presumably further activates the Michael acceptor by decreasing the amount of Lewis base present and able to compete for complexation with $BF_3\cdot Et_2O$.

Alkyl, vinyl and aryl groups are all amenable to transfer from Cu to C, and thereby can result in generation of quaternary centers (entries 2–5, 7). Isophorone (entry 3), under the influence of $BF_3\cdot Et_2O$, accepts a vinyl ligand in good yield. Again, the lower order counterpart afforded a substantially lower yield (59%) of conjugate adduct, although 15% starting enone was also recovered. Mesityl oxide (entry 4) and 3-methylcyclohex-2-enone (entry 2) also afford respectable yields of adducts. This latter case, by contrast, gave only 29% of 3,3-dimethylcyclohexanone (vs 85%) when the Lewis acid was omitted. Comparison experiments using the lower order equivalents, contrary to the two prior examples (*vide supra*), gave either superior (mesityl oxide: L.O.: 96%; H.O.: 77%) or comparable results (3-methylcyclohex-2-enone: L.O.: 89% (no BF_3); H.O.: 85%). 2-Methylcyclopentenone (entry 8) reacted with **2**, prepared from Me_3SiCH_2MgBr,[13] giving the β-TMS methyl adduct in 63% isolated yield as a 3 : 1 ratio of *trans* : *cis*-isomers by VPC. Reexposure of this mixture to Et_3N in CH_2Cl_2 at room temperature does not change the relative isomeric content, suggesting that this thermodynamic ratio is probably arrived at under quenching/workup conditions (see Experimental). This coupling is very much akin to the hydroxymethyl anion equivalent recently developed by Tamao and Ishida[14] invoking the CuI-catalyzed addition of an allyldimethylsilylmethyl group, which affords *ca* 2:1 ratios with a substituted cyclohexenone (65%). It cannot, however, be applied to cyclopentenones, suggesting that a stoichiometric reagent such as **2** may be essential in dealing with this highly reactive enone. Pulegone (entry 5), a valuable member of the "chiral pool", serves as the starting point for arriving at 8-phenylmenthol,[15] well known to function as a chiral auxiliary.[16] It is traditionally formed from the CuI-catalyzed addition of PhMgBr (1.5 equiv) in ~ 65% yield. We find that **2** (R = Ph) affords comparable yields of the corresponding menthone as a *ca* 3:1 mixture of *trans* to *cis*-isomers, although somewhat lesser quantities of the Grignard reagent need to be invested (1.25 equiv).

The effects of halide ion were briefly examined via side-by-side comparison of **2** (R = n-Bu) and n-Bu(2-Th)Cu(CN)LiMgCl, **4** (i.e. the cuprates derived from n-BuMgBr and n-BuMgCl, respectively). With regard to cuprate formation, n-Bu(2-Th)Cu(CN)LiMgBr is a noticeably less soluble, gray/tan slurry in THF at *ca* 0.19 M, while the chloro analog **4** is essentially homogeneous. Addition of 1.2 equiv of $BF_3 \cdot Et_2O$ to each at −78°, followed by mesityl oxide (1.0 equiv) and stirring for 30 min afforded 4,4-dimethyl-2-heptanone in slightly higher yield using **4** (77 vs 64%). However, the bromide-containing reaction did show *ca* 8% starting material, suggesting comparable results in terms of efficiency, and that the relative rates may simply reflect the extent to which each reagent is in solution.

Finally, a few experiments were conducted to determine whether unsaturated esters are acceptable reaction partners with **2**. Treatment of methyl ester **5** with **2** (R = n-Bu) at various temperatures, with and without $BF_3 \cdot Et_2O$ present, afforded none of the anticipated, known 1,4-adduct.[4] Aside from some minor impurities (by VPC), essentially all of the starting material was recovered. Thus, it is clear that while the dilithio analog of **2** reacts nicely with this type of substrate,[6] a mixed lithio magnesio cuprate together with an enoate of reduced electrophilicity proves to be a combination not conducive to coupling.



5

DISCUSSION

The results listed in Tables 1 and 2 serve to illustrate that mixed lithio magnesio higher-order reagents can effect many of the valuable coupling reactions in which dilithio cuprates participate. It should also be mentioned that in all cases, limited amounts of reagent (i.e. 1.2–1.4 equiv), and therefore RMgX, were invested and yields may well improve using a greater excess of **2**.

In general, these cuprates are less robust than their dilithio equivalents and are therefore limited in terms of the electrophiles with which they will react. Clearly, the change from lithium to magnesium halide as one of two gegenions has a pronounced affect on stoichiometrically defined higher-order systems, just as it does on lower order organocuprates (i.e. R_2CuLi vs R_2CuMgX).[2]

We found rather intriguing the observation that addition of a solution of RMgX to a solution of 2-ThCu(CN)Li at −78° produces a considerable quantity of floculent, slightly colored material (depending upon RMgX) which dissolves somewhat upon warming to room temperature and then reprecipitates upon cooling to −78°. Using n-Bu(2-Th)Cu(CN)LiMgCl as a model case, the heterogeneous mixture was prepared in a test tube under Ar and centrifuged in the cold ($T \leqslant -50°$) for *ca* 30 min. The supernatant was removed on which a Gilman test[17] was performed at 0°–room temperature, which afforded a distinctly positive result, suggesting the presence of free RMgCl and/or RLi. The aqueous layer upon treatment with a 9:1 mixture of saturated NH_4Cl–concentrated NH_4OH (pH ~ 10) showed the characteristic blue coloration indicative of Cu salts.

The solid material which remains from cuprate generation was also subjected to a Gilman test, which gave a negative result! The aqueous layer upon exposure to NH_4Cl–NH_4OH as above, however, indicated that copper salts were present. Successive washings of the precipitate with fresh solvent followed by analysis of each colored solution flame tested strongly positive for both lithium and copper. Thus, it appears that "R(2-Th)Cu(CN)LiMgX" may not be a discrete species. Further tests of both a chemical and spectroscopic nature (e.g. ^{7}Li-NMR[18]) seem warranted.

Summary

Addition of an equivalent of RMgX to the mixed Gilman reagent 2-ThCu(CN)Li appears to give rise to a heterogeneous mixture which may contain "R(2-Th)Cu(CN)LiMgX" as a reactive component. Halides, epoxides and enones react with these species to afford products reflecting transfer of the R moiety. Lower order analogs, RCu(CN)MgX, may give rise to the desired material with efficiencies on occasion surpassing those realized via higher order reagents. Although these cuprates tend to be less reactive than their dilithio analogs, the use of $BF_3 \cdot Et_2O$ in couplings with unactivated epoxides is precluded due to reagent decomposition. Moreover, with disubstituted cases, halohydrin formation may strongly compete with C—C bond construction. Enones, in particular β,β-disubstituted systems, serve best as Michael acceptors in the presence of $BF_3 \cdot Et_2O$. Interestingly, while R(2-Th)Cu(CN)Li_2 has a strong tendency to transfer a 2-thienyl ligand in a 1,2-sense to hindered enones (without $BF_3 \cdot Et_2O$ present), very little, if any, of this alternative mode of reaction is observed with mixed lithio magnesio cuprates. Since some of these chemical results, including Gilman tests, as well as flame tests on the individual components of these heterogeneous mixtures suggest that "R(2-Th)Cu(CN)LiMgX" is not a single entity, further studies are needed to clarify reagent composition.

EXPERIMENTAL

Materials. CuCN was purchased from Mallinckrodt. Thiophene was purchased from the Aldrich Chemical Company and distilled from CaH_2. n-BuLi was obtained from Ventron and titrated by the method of Watson and Eastham.[19] MeMgBr, n-BuMgCl and vinyl magnesium bromide were bought from Ventron. Allylmagnesium bromide was purchased from Aldrich. Phenylmagnesium bromide and s-butylmagnesium bromide were formed from the corresponding bromides plus Mg metal in refluxing Et_2O. Trimethylsilylmethylmagnesium bromide was prepared using a modification of Sommer's[13] procedure. All Grignard reagents were titrated according to the method of Gilman *et al.*[20] 3-Methylcyclohexenone and pulegone were obtained from Aldrich. 2-Methylcyclopentenone was generously provided by Professor D. Curran (University of Pittsburgh). 2-Methylacetylcyclopentene was prepared according to the procedure of Stowell *et al.*[11] 5-Bromovaleronitrile, 1,1-diethylethylene oxide and 2-iodooctane were obtained as previously noted.[6] Hexene oxide was realized according to the recipe of Emmons and Pagano.[21]

IR spectra were recorded on a Perkin–Elmer 283 spectrometer. ^1H-NMR spectra were obtained using a Varian CFT-20 or Nicolet NT 300 spectrometer at 80 or 300 MHz, respectively. Mass spectra were run on a VG 70-250 instrument. VPC analyses were conducted on a Hewlett–Packard Model 5880A instrument. Quantitative measurements were made using an internal standard.

trans-2-n-*Propylcyclohexanol.* Dry CuCN (97.1 mg, 1.1 mmol) was placed in a 25 ml 2-neck flask, evacuated and purged with argon three times, gently flamed and allowed to cool under vacuum before a final argon purge. THF (0.8 ml) was added via syringe and the slurry cooled to −78°. 2-Thienyllithium was prepared in a 5 ml 2-neck flask from thiophene (94 μl, 1.17 mmol) and n-BuLi (0.45 ml, 2.46 M) in THF at −30° (30 min) and added to CuCN via cannula with a 0.3 ml THF rinse. n-PrMgBr (1.73 ml, 0.64 M) was added via syringe and the mixture warmed to room temp. After recooling to −78°, cyclohexene oxide (100 μl, 1.0 mmol) was added via syringe and allowed to stir for 15 min. After 15 min the temp was raised to 0° for 45 min and then to room temp for 8 h before quenching with a 9:1 soln of sat NH_4Cl–conc NH_4OH, followed by workup in the usual fashion. VPC analysis indicated a 52% yield of product, compared directly with an authentic sample.[6]

5-*Decanol.* 2-Thienyllithium (0.6 mmol) was prepared from thiophene (50 μl, 0.62 mmol) and n-BuLi (0.25 ml, 2.40 M) in THF at −30° (0.4 ml, 30 min) and then added to a precooled (−78°) slurry of CuCN (55 mg, 0.6 mmol) in THF (1.5 ml), followed by n-BuMgCl (0.24 ml, 0.6 mmol). Upon warming to room temp, the mixture dissolved to a green–amber soln with traces of a fluffy white ppt. Recooled to −78°, the mixture thickened to a tan slurry and to it was added the neat epoxide (56 μl, 0.5 mmol). The reaction was warmed to 0° and stirring continued for 4 h followed by quenching and workup in the usual way. Chromatography on SiO_2 with 20% Et_2O/Skelly Solve afforded 63.5 mg (81%) of a clear oil; $R_f = 0.25$.[22]

Hexanenitrile. The cuprate was prepared in the usual manner from CuCN (80.6 mg, 0.90 mmol), 2-lithiothiophene (0.90 mmol), and MeMgBr (0.33 ml, 2.76 M in Et_2O, 0.90 mmol) in dry THF (2.0 ml). To the cold (−78°) mixture was added 5-bromovaleronitrile (70 μl, 0.60 mmol) and the resulting gray slurry was warmed to room temp and stirred at the same temp for 14 h. The mixture was quenched in the usual fashion. Quantitative VPC analysis indicated a yield of 96%. The product co-injects with authentic hexanenitrile and was identical by IR and NMR (available from Aldrich Chem. Co.).

Hept-6-enenitrile. The cuprate was prepared from CuCN (80.6 mg, 0.90 mmol), 2-lithiothiophene (0.90 mmol) and vinylmagnesium bromide (0.47 ml, 1.92 M in THF, 0.90 mmol) in dry THF (2.0 ml). The cuprate was cooled to −78° and 5-bromovaleronitrile (70 μl, 0.60 mmol) was added and the resulting mixture was warmed to 0° where the black soln was stirred at this same temp for 30 min and then warmed to room temp for 14 h. The reaction was quenched in the usual way and quantitative VPC analysis indicated a yield of 70% based on recovered starting material. Column chromatography on SiO_2 with 1:1 Et_2O/Skelly Solve afforded the desired product; IR (neat) cm^{-1} 2940, 2870, 2245, 1430, 995, 912; ^1H-NMR δ 6.1–5.5 (1H, m, X of ABX), 5.2–4.8 (2H, m, AB of ABX), 2.5–1.0 (8H, m); MS (rel. int.) *m/z* 109 (M^+, 2.8), 108 (13.3), 81 (60.2), 69 (53.7), 68 (53.9), 55 (100), 54 (60.8). HRMS calc for $C_7H_{11}N$: 109.0891. Found: 109.0886.

3-[2-(1,3-*Dioxane*)*ethyl*]*cyclohexanone.* CuCN (102 mg, 1.14 mmol) was placed in an oven-dried 2-neck round bottom flask equipped with a magnetic stir bar. The salt was gently flame-dried (30 s) under vacuum and then purged with argon. Dry THF (1.0 ml) was added and the stirred slurry was cooled to −78°. 2-Thienyllithium was prepared in a second 2-neck round bottom flask from thiophene (91 μl, 1.14 mmol) in dry THF (1.0 ml) at −30° to which was added n-BuLi (0.47 ml, 2.44 M in hexanes, 1.14 mmol) and the clear colorless soln was stirred at 0° for 30 min. The preformed 2-thienyllithium was added to the CuCN slurry at −78° and warmed to 0° over 30 min until the tan–brown slurry became clear. The mixture was cooled to −78° and the Grignard reagent derived 2-(2-bromoethyl)-1,3-dioxane[23] (80 μl, 1.42 M in THF, 1.14 mmol) was added dropwise and the resulting mixture was warmed to 0° for 2 min and cooled back to −78°. Cyclohexenone (freshly distilled, 100 μl, 1.03 mmol) was added and the reaction was stirred at -78^c for 2.25 h and quenched by the addition of 5 ml of a 90% NH_4Cl (sat)–10% NH_4OH (conc) soln. After stirring at room temp for 30 min, the soln was worked up in the usual way. Column chromatography on SiO_2 with 1:1 Et_2O/Skelly Solve afforded 186 mg (85%) of product as a clear liquid; IR (neat) cm^{-1} 2960, 2940, 1712, 1408, 1380, 1145, 1008, 942, 895; ^1H-NMR δ 4.51 (1H, t, J = 5.1 Hz), 4.09 (2H, g, J = 5.1 Hz), 3.75 (1H, d of t, J = 2.4 Hz and J = 12.3 Hz), 2.09 (2H, m), 2.0–0.8 (13H, m); MS (rel. int.) *m/z* 213 (M^+ +1, 18), 165 (18.4), 157 (10.5), 138 (14.7), 121 (13.2), 119 (55.6), 110 (16.5), 87 (59.2), 59 (18.3). HRMS calc for $C_{12}H_{20}O_3+1$: 213.1491. Found: 213.1477.

Reaction of MeCu(CN)MgBr *with 3-methylcyclohexenone.* The CuCN (116 mg, 1.3 mmol) was weighed and added to an oven-dried 10 ml 2-neck pear flask along with a stir bar. The ground glass neck was fitted with a "T" top to which argon and vacuum lines were attached. The apparatus was then flame/vacuum-dried and flushed with argon. Et_2O was added and the apparatus was cooled to −78°. Methyl Grignard (0.41 ml, 1.3 mmol) was added and the reaction was warmed to 0° with an ice–water bath to produce a greenish-yellow slurry, and was then cooled back to −78°. $BF_3 \cdot Et_2O$ was added at this point to the mixture with no physical change being observed. After stirring for a few min, the enone was added dropwise, causing a yellow ppt to form. This ppt was much more difficult to deal with in the reaction containing BF_3. The mixture was allowed to stir at -78^c for 1.5 h and then it was quenched at −78° with sat NH_4Cl–NH_4OH soln (9:1, ~ 3 ml). VPC analysis vs α-tetralone indicated a 58% yield of product (40% starting material recovered). The identical reaction without $BF_3 \cdot Et_2O$ afforded an 89% yield of product,[24] with only 3% starting enone leftover.

Reaction of Me(2-Th)Cu(CN)LiMgBr *with 3-methylcyclohexenone.* The CuCN was weighed and placed into the 2-neck pear flask equipped with septa, Teflon tape, stir bar and argon and vacuum lines in place. After flame/vacuum-drying, the flask was flushed with argon. THF (1 ml) was added and the mixture was cooled to −78°. In a separate single-neck flask fitted with two septa and sealed with Teflon tape, THF (1 ml) was added and the flask was cooled to −30°. n-BuLi (0.54 ml, 1.3 mmol) was added followed by thiophene (0.11 ml, 1.4 mmol). This mixture was allowed to stir for 15 min and was cooled to −78° followed by cannula transfer onto the stirring CuCN slurry. This mixture was then warmed to 0° with an ice–water bath until it formed the characteristic "apple juice" soln, and was then cooled back to −78°. Addition of methyl Grignard rendered a thick yellow ppt requiring the use of an external magnet to break it up, allowing the stir bar to stir. Warming this mixture to 0^c formed a tan–yellow slurry. Two ml of Et_2O was added and then the reaction was cooled back to −78°. $BF_3 \cdot Et_2O$ was then added, producing no visible change in the reaction mixture's appearance. Addition of the enone caused the slurry to turn yellow–green. After 1.5 h of stirring at −78^c, the reaction was mustard colored. The mixture was quenched at −78° with 3 ml of a 9 : 1 sat NH_4Cl–NH_4OH (conc) soln and worked up in the usual way. VPC analysis indicated an 85% yield of product.[24]

3,5,5-*Trimethyl-3-vinylcyclohexanone.* Vinyl magnesium bromide (0.73 ml, 1.92 M) was added dropwise to a precooled (−78°) 15 ml 2-neck pear flask containing CuCN (125 mg, 1.40 mmol) and THF (3.0 ml), followed by addition of thienyllithium, prepared from thiophene (116 μl, 1.45 mmol) and n-BuLi (0.46 ml, 2.98 M) in THF at −30° (1.6 ml, 30 min). Warming to room temp yielded a clear green soln which was recooled to −78° to a tan slurry to which $BF_3 \cdot Et_2O$ (172 μl, 1.4 mmol) was added followed by neat isophorone (150 μl, 1.0 mmol). After 1 h at −78°, the reaction was quenched with 3 ml of a 90% NH_4Cl (sat)–NH_4OH (conc) soln. Extractive workup (Et_2O, 3 × 10 ml), drying (Na_2SO_4) and chromatography on silica gel (230–400 mesh) with 20% Et_2O/Skelly Solve afforded 124.6 mg (75%) of a yellow oil, which was identical (NMR, IR, TLC) with authentic material.[6]

Reaction of (vinyl)Cu(CN)MgBr *with isophorone.* Vinyl magnesium bromide (0.73 ml, 1.92 M) was added to a cold (−78^c) slurry of CuCN (126 mg, 1.4 mmol) and THF (4 ml). Warming to room temp for 5 min yielded a tan–yellow semi-dissolved slurry. After recooling to −78°, $BF_3 \cdot Et_2O$ (172 μl, 1.4 mmol) was added followed by isophorone (150 μl, 1.0 mmol). After 1 h at −78°, the black reaction was quenched and extracted in the usual fashion. Chromatography on SiO_2 (20% Et_2O/Skelly Solve; R_f 0.34) afforded 98 mg of the desired product which was identical with authentic material.[6] Also recovered was 24 mg of starting material.

4,4-*Dimethyl-2-octanone.*[25] 2-Thienyllithium (0.6 mmol) was prepared from thiophene (50 μl, 0.62 mmol) and n-BuLi (0.25 ml, 2.50 M) in THF at −30° (0.4 ml, 30 min) and then added to a precooled (−78°) slurry of CuCN (54 mg, 0.6 mmol) in THF (20 ml), followed immediately by n-BuMgCl. Upon warming to room temp, a clear amber soln formed which became a slurry after recooling to −78°. $BF_3 \cdot Et_2O$ (74 μl, 0.60 mmol) was added followed by neat mesityl oxide (57 μl, 0.50 mmol) to give an immediate yellow color and thinning of the mixture. After 30 min at −78^c, the reaction was quenched with 3 ml of a 90% NH_4Cl (sat)–NH_4OH (conc) soln. Quantitative VPC analysis indicated a 77% yield. Workup in the usual fashion followed by chromatography on SiO_2 with 20% Et_2O/Skelly Solve gave a yellow oil; R_f 0.51; ^{1}H-NMR δ 2.32 (2H, s), 2.12 (3H, t), 1.35–1.20 (6H, m), 0.98 (6H, s), 0.90 (3H, t).

Reaction of n-BuCu(CN)MgBr *with mesityl oxide.* BuMgCl (0.24 ml, 2.49 M) was added to a cold (−78°) slurry of CuCN (54 mg, 0.6 mmol) and 1.8 ml of THF. Warming to room temp gave a clear tan soln to which was added, after recooling to −78°, $BF_3 \cdot Et_2O$ (74 μl, 0.6 mmol) followed by mesityl oxide (57 μl, 0.5 mmol). The soln became thick and yellow and the reaction was quenched after 30 min at −78°. VPC analysis indicated a yield of 96%.

8-*Phenylmenthone.*[15] Thiophene (65 ml, 0.81 mmol) was dissolved in 0.81 ml of THF and cooled to −78°. n-BuLi (0.32 ml, 0.76 mmol) was added at −78° followed by warming to 0°. The resulting light yellow soln was added to dry CuCN (68 mg, 0.76 mmol) in 0.75 ml of Et_2O. The mixture was brought to room temp and stirred for 30 min until all the CuCN had dissolved producing a dark tan soln, which was cooled to −78°. Freshly prepared PhMgBr (0.76 mmol, 0.76 ml of Et_2O) was added via cannula to the Cu species producing a heterogeneous slurry, which was warmed to 0° for 5 min, then recooled to −78°. (+)-Pulegone (100 μl, 0.61 mmol) was added, followed by warming to 0° for 30 min, then to room temp for 1 h. The mixture was quenched with 5 ml of a 4 : 1 NH_4Cl (sat)–NH_4OH (conc) mixture. Quantitative VPC analysis indicated a 67% yield of diastereomers. The same procedure employing $BF_3 \cdot Et_2O$ (0.76 mmol) as catalyst added to the cuprate at −78° was found to give a 59% VPC yield of conjugate adducts.[6]

3-s-*Butylcyclopentanone.* Dry CuCN (49.0 mg, 0.54 mmol) was placed in a 25 ml 2-neck flask, evacuated and purged with argon 3 times, gently flamed and allowed to cool under vacuum before a final argon purge. THF (2.5 ml) was added via syringe and the slurry cooled to −78°. 2-Thienyllithium was prepared in a 5 ml pear flask from thiophene (45 μl, 0.54 mmol) and n-butyllithium (0.22 ml, 2.44 M) in THF at −30° (1.0 ml, 30 min) and added to the CuCN via cannula with a 1.0 ml THF rinse. s-BuMgBr (0.63 ml, 0.86 M) was then added and the soln warmed to 0° to give a clear greenish soln. After recooling to −78°, the 2-cyclopentenone (42 μl, 0.50 mmol) in 1.0 ml of THF and cooled to −78° was added via cannula with a 1.0 ml THF (−78°) rinse. The soln was allowed to stir for 1 h at −78°, then quenched with 5 ml of a 10% NH_4OH–NH_4Cl (sat) soln and stirred for 30 min before workup. Quantitative VPC analysis indicated a 76% yield of product of known constitution.[6]

2,2-*Dimethylacetylcyclopentane.* The cuprate was prepared from CuCN (71.9 mg, 0.80 mmol), 2-lithiothiophene (0.80 mmol) and MeMgBr (0.29 ml, 2.76 M in Et_2O, 0.80 mmol) in 1.5 ml of THF. To the cold (−78°) soln was added $BF_3 \cdot Et_2O$ (72.5 μl, 0.59 mmol) and the resulting mixture was stirred at the same temp for 5 min. 1-Acetyl-2-methylcyclopentene[23] was added and the grayish-yellow soln was stirred at −78° for 6 h before quenching and the usual workup. Quantitative VPC analysis indicated a yield of 73%; IR (neat) cm^{-1} 2960, 2880, 1710, 1450, 1360, 1170; ^{1}H-NMR δ 2.61 (1H, t, J = 8.1 Hz), 2.14 (3H, s), 2.0–1.4 (6H, m), 1.20 (3H, s), 0.871 (3H, s); MS (rel. int.) *m/z* 140 (M^+, 0.3), 97 (31.1), 84 (35.6), 82 (23.7), 71 (100), 70 (62.6), 69 (21.2), 55 (88.3). HRMS calc for $C_9H_{16}O$: 140.1565. Found: 140.1547.

The identical reaction was carried out as above, without $BF_3 \cdot Et_2O$, in Et_2O. 1-Acetyl-3-methylcyclopentene was added at −78° and the resulting gray slurry was stirred at the same temp for 8 h, then at 0° for 4 h and at room temp for 11 h. The reaction was quenched in the usual fashion. Quantitative VPC indicated a yield of 34%.

cis *and* trans-*Methyl-3-trimethylsilylmethylcyclopentanone.* To a THF (2 ml) suspension of CuCN (52 mg, 0.6 mmol), thienyllithium, which was prepared from thiophene (0.05 ml, 0.62 mmol) and n-BuLi (0.25 ml, 0.62 mmol) in 1 ml of THF, was added at −78°. Then the mixture was warmed to dissolve CuCN completely. The resultant tan soln was diluted with 1 ml of THF and Grignard reagent (1.24 M in THF, 0.5 ml, 0.62 mmol) was added at −78°. The mixture became heterogeneous. This mixture was warmed to room temp and stirred for 0.5 h. The mixture was recooled to −78° and $BF_3 \cdot Et_2O$ (0.07 ml, 0.6 mmol) and cyclopentenone (0.05 ml, 0.5 mmol) were added successively. At this point the soln became a clear yellow–tan color. After stirring for 2.5 h at −78° the mixture was quenched with NH_4Cl–NH_4OH (9 : 1, 3 ml) and extracted with Et_2O. The extracts were dried (Na_2SO_4) and evaporated. Purification by flash column chromatography (SiO_2, 230–400 mesh; eluted with SS–Et_2O, 9 : 1) to give 60 mg (63% yield) of colorless oil as a 77 : 23 mixture of diastereomers assumed to favor the *trans*-isomer. This ratio did not change upon treatment with Et_3N in CH_2Cl_2 at room temp overnight; IR (neat) cm^{-1} 1745, 1250, 860, 835; ^{1}H-NMR ($CDCl_3$, partial) δ 0.01 (9H, s), 1.00 (CH_3, d, J = 6.3 Hz, major), 0.91 (CH_3, d, J = 7.2 Hz, minor); MS (rel. int.) *m/z* major: 184 (M^+, 16.8), 169 (28.2), 155 (7.0), 127 (5.8), 99 (4.4), 75 (59.1), 73 (100); minor: 184 (17.5), 169 (30.9), 155 (7.9), 127 (6.5), 99 (5.1), 73 (100). HRMS calc for $C_{10}H_{20}OSi$: 184.1283. Found: 184.1288.

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