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MORE HIGHLY MIXED, HIGHER ORDER CYANOCUPRATES "R_T(2-thienyl)Cu(CN)Li_2". EFFICIENT REAGENTS WHICH PROMOTE SELECTIVE LIGAND TRANSFER

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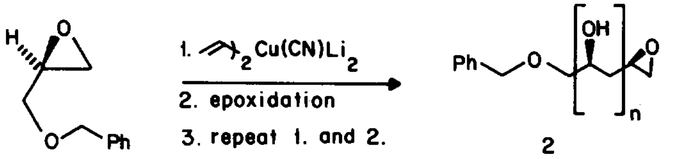
Summary

The combination of an organolithium (R_TLi) and 2-lithiothiophene (2-thienyl) with CuCN forms a new reagent, "R_T(2-thienyl)Cu(CN)Li_2." This species selectively transfers the R_T ligand in substitution reactions with epoxides and halides. In conjugate addition processes, the cuprate reacts with unhindered substrates, while β,β-disubstituted cases unexpectedly afford products resulting from 1,2-addition of the thiophene group. The prospects for use of these reagents in the synthesis of polyene macrolide antibiotics are discussed.

Introduction

In applying higher order, mixed cuprate technology [1] (i.e., $R_2Cu(CN)Li_2$, **1**, from 2 RLi + CuCN) to the formation of an all *syn*-1,3-polyol network **2** characteristic of the polyene macrolides [2] (e.g., Roflamycoin, **3**), it was recognized that a related strategy could be invoked for coupling of this unit with a functionalized polyene. Clearly, participation of a vinyl organometallic intermediate **4** in cuprate formation would be required. As **4** would necessitate its own preparation, there was tremendous incentive to devise a modified protocol wherein only one equivalent of **4** need be utilized in cyanocuprate generation, yet which would encourage selective



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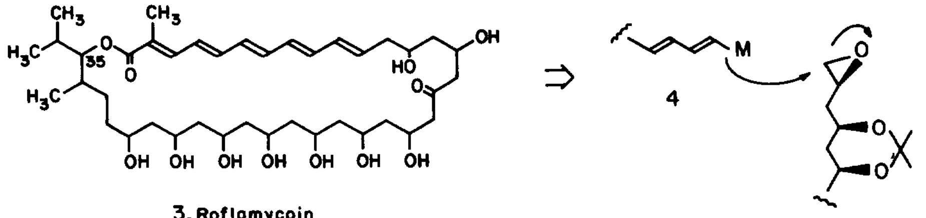
ligand transfer from copper to carbon [3] in opening an epoxide **5**. Unfortunately, as



3, Roflamycoin

4

5

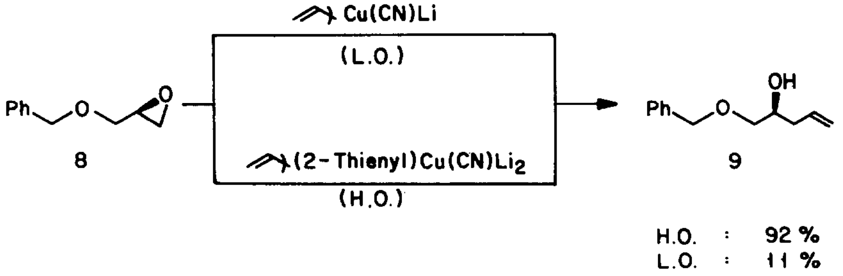
recently discussed [4], use of a simple methyl group (from MeLi) in the form of $R_T(CH_3)Cu(CN)Li_2$ (R_T = vinyl) is not satisfactory, as the methyl ligand is preferentially released from copper. Hence, an extensive listing of other potential second, non-transferable or "dummy" ligands, R_R, was screened based on steric (e.g., $(CH_3)_3CCH_2$) or electronic (e.g., $CF_3CF_2CF_2$ [5]) grounds. Attempted couplings of (vinyl)$R_RCu(CN)Li_2$ with model substrate 2-iodooctane led, in general, to either no reaction or the product of reduction (i.e., octane). Ultimately, the 2-thienyl group was examined (i.e., R_T(2-thienyl)Cu(CN)Li_2, **6**, R_T = vinyl), and found to exhibit excellent properties as an R_R not only in substitution reactions of oxiranes and halides, but in many conjugate addition processes as well. Use of this moiety in this context is precedented in the work of Ullenius [6], where conjugate addition reactions of lower order cuprates R_T(2-thienyl)CuLi were studied. Herein we present the results of our study on the synthetic utility of mixed organocuprates **6**.

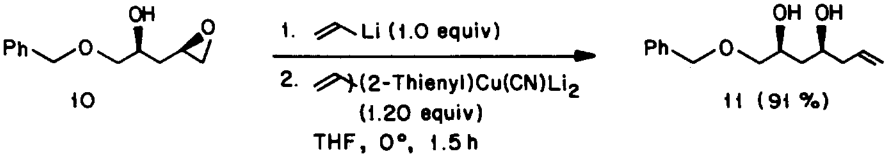
Results

Metalation of thiophene occurs readily in Et_2O [6] or THF at 0°C using n-BuLi. The resulting 2-lithio derivative, upon addition to CuCN (1 equiv.) at 0°C affords a homogeneous and quite thermally stable lower order cuprate, presumably (2-thienyl)Cu(CN)Li, **7**. Cooling to −78°C is followed by the addition of R_TLi, resulting in formation of the higher order reagent, usually unchanged in appearance. This process appears to be rapid as the substrate may be introduced at the same temperature without delay.

Immediate attention focussed on the delivery of a vinyl group, as a model, to chiral, monosubstituted epoxides of type **8** and **10**. Treatment of **8** with 1.09 equivalents of cyanocuprate **6**, R_T = vinyl, in THF at 0°C for 2.5 h afforded a 92% isolated yield of homoallylic alcohol **9**. By contrast, the corresponding lower order reagent derived from CuCN plus vinyllithium (1 equiv.) under otherwise identical conditions gave only 11% of **9**, with the remaining mass accounted for in starting material. Likewise, exposure of **10** to the same higher order cuprate, following initial oxyanion formation via vinyllithium, led to the olefinic 1,3-diol **11** to the extent of 91% after filtration through silica gel. Hence, it would appear on the basis of these results, TLC and VPC data, and related examples (vide infra) that little, if any, thiophene transfer is occurring.

In order to evaluate the "scope and limitations" of reagents **6**, a series of substitution reactions was investigated. As illustrated in Table 1, other epoxides (entries 1–4) as well as halides (entry 6) react efficiently with 1.10–1.25 equivalents of cuprate **6** containing either an alkyl- or vinyllithium-derived ligand, as R_T. Not





surprisingly, cyclohexene oxide (entry 3) gave a moderate yield of secondary alcohol along with over 30% of the product of rearrangement, cyclohexanone. An essentially identical result was realized using n-Pr$_2$Cu(CN)Li$_2$, suggesting that reagent reactivity and/or composition was not at fault. Similar competing pathways have been noted with these epoxides using other organocopper complexes [7,8], while the cyclopentene oxide system presents no such complication [9]. The increased stability of **6**, R_T = vinyl, allows substitution to occur at a secondary, unactivated center bearing iodine (entry 5), since somewhat elevated temperatures, longer times, and slightly more reagent than with **1** [10] were required. Transfer of a secondary center to a primary carbon containing bromine (entry 6) occurs readily.

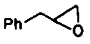
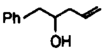
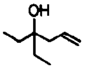
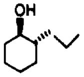
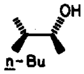
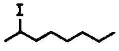
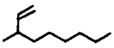
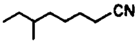
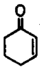
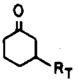
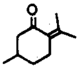
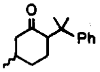
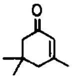
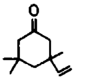
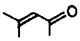
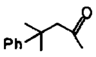
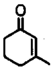
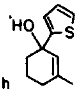
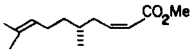
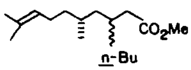
The success of the mixed 2-thienyl-containing cyanocuprates **6** in effecting displacements encouraged us to briefly explore their chemistry with α,β-unsaturated ketones and esters. We were delighted to find that while cyclohexenone reacts with n-Bu(Me)Cu(CN)Li$_2$ to afford a 11–12/1 ratio of n-butyl to methyl transfer [11], **6**, R_T = n-Bu (entry 7) gives 3-n-butylcyclohexanone essentially as the only product of 1,4-addition. However, in going to more hindered systems, in particular β,β-disubstituted cases (entries 8–11), the yields dropped considerably relative to those obtained using R$_2$Cu(CN)Li$_2$ [12]. Quite unexpectedly, the competing mode of reaction is 1,2-addition of the 2-thienyl group! Indeed, with 3-methylcyclohexenone (entry 11), a high yield of the tertiary alcohol was isolated. Fortunately, less reactive enoates (entry 12) with a mono β-substitution pattern [13] react to afford high yields of 1,4-adduct.

Discussion

The results in Table 1 raise several issues worthy of comment. As for reagents **6**, although various ligands R_T may be incorporated, the preparation of **7** is carried out prior to the commitment of any (potentially valuable) R_TLi. As with MeCu(CN)Li [4], **7** is soluble at low temperatures such that addition of a cold solution (where necessary) of R_TLi to form **6** will occur without compromising either the thermal stability or stereochemical integrity of R_TLi. Once formed, cuprates **6** are quite stable species, even more so than are their predecessors **1** [10]. Hence, their reactivity profile is such that usually somewhat higher reaction temperatures (vs. those for **1**)

TABLE I

Reactions of R_T(2-thienyl)Cu(CN)Li_2 with Organic Substrates

Entry	Substrate	R_T (equiv)	Conditions	Product(s)	Yield (%)[a]
1		 (1.25)	Et_2O/THF 0°, 1 h		90
2		 (1.20)	Et_2O/THF rt, 4h		71
3		n-Pr(1.10)	THF/Et_2O -78→0° 1 h		55[b]
4		n-Bu(1.20)	Et_2O/THF rt, 9h		77[b]
5		 (1.50)	THF, 31°, 18h		67[b]
6		s-Bu (1.10)	THF, -78→0° 1 h		82
7		n-Bu(1.20) Ph (1.29)	THF, -78°, 0.25h Et_2O, -78°, 0.33h		83(>95)[b] 80
8		Ph(1.20)	Et_2O, -78→0° 0.75h		63
9		(1.42)	Et_2O/THF -78→0° 1h		49[b]
10		Ph(1.20)	Et_2O/THF -50°, 1 h -25°, 0.25h		51
11		t-Bu(1.30)	Et_2O -20°, 0.75h		87
12		n-Bu(1.10)	Et_2O, -78°→ rt, 2h		89

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[a] Isolated yields, unless stated otherwise. [b] By quantitative VPC.

are mandated for achieving reasonable rates of reaction.

The explanation for the high degree of selectivity of ligand transfer [3,14] is certainly open to debate. It may be attributable to the opportunities which exist for both *dπ* * and *dd* backbonding between copper and the heteroaromatic thiophene group, or copper and sulfur, respectively. However, the former situation also presents itself in $R_T(Ph)Cu(CN)Li_2$, yet phenyl transfer, in most cases, is facile [12]. Moreover, the fact that 2-furyl ligands couple [15] with various substrates suggests that sulfur is playing a key role. Still, it is not obvious whether this atom is acting as a two-electron donor, thereby occupying the fourth coordination site on copper (in place of, presumably, THF [16]), or whether the entire cluster and aggregation state have been altered to accommodate this ligand.

The results from the Michael additions of **6** (Table 1) would seem to support the latter possibility. As the steric demands of the enone increase, considerable 1,2-addition takes place by the 2-thienyl group. This is completely contrary to our earlier results on the identical substrates using cuprates **1**, where exclusive 1,4-addition occurs [12]. Moreover, it is difficult to see why a copper(I) dianion would prefer, most blatantly in the case of entry 11, to release the 2-thienyl residue [16] leaving behind the far less favorable (i.e., less stable) lower order cuprate t-BuCu(CN)Li [17]. Interestingly, this phenomenon is not manifested in substitution reactions, where one could envision competing eliminations, reductions, and rearrangements perhaps due to free RLi. While these points remain at this time unanswered, we have found a practical solution to this problem of thiophene 1,2-addition, which relies on carbonyl activation with Lewis acids [18]. The applications of this methodology to polyene macrolide synthesis will be reported in due course. Further studies aimed at addressing these concerns, in particular using spectroscopic techniques (e.g., ^{7}Li NMR [19]) are underway.

Conclusions

The (initial) goal of developing a copper-based organometallic (for epoxide openings) which will allow the selective transfer of valuable vinylic ligands has been reached. Reagent **6**, stoichiometrically represented by "R_T(2-thienyl)Cu(CN)-Li_2" and derived from inexpensive, available precursors, is quite reactive toward primary halides, secondary iodides, mono- and di-substituted epoxides, as well as unhindered enones and enoates. Thus, this species provides a solution to the long-standing concern over R_TLi conservation expressed in our original report [10] and continuously noted by others [3,7,8a,14].

Experimental

2*S*-(−)-Benzyl-2-hydroxypent-4-enyl ether (**9**). Thiophene (88 μl, 1.1 mmol) was added to THF (1 ml) in a 10 ml, 2-neck pear flask, at −78°C, followed by n-butyllithium (0.39 ml, 1.1 mmol). The ice bath was removed and the temperature slowly (ca. 5 min) raised to 0°C where stirring was continued for 30 min. The faint yellow anion was then transferred, via cannula, into a 15 ml, 2-neck flask containing CuCN (89.6 mg, 1 mmol) and THF (1 ml), which was previously purged with argon and cooled to −78°C. Warming to 0°C produced a light tan solution which was recooled to −78°C where vinyllithium (0.5 ml, 1 mmol) was injected, with immediate warming to 0°C (no change visible). In a separate 10 ml pear flask, the epoxide (149 mg, 0.91 mmol) was dissolved in THF (1 ml), cooled to −30°C and transferred, via cannula, into the precooled (−78°C) cuprate. The temperature was maintained at 0°C for 2.5 h, followed by quenching with 5 ml of a 90% saturated NH_4Cl/conc NH_4OH solution. Extractive workup (Et_2O, 2 × 10 ml), drying over Na_2SO_4, and chromatography on silica gel (230–400 mesh) with 40% Et_2O/skelly solve afforded 141 mg (92%) of a clear liquid; $R_f = 0.33$ (1/1 Et_2O/skelly solve); b.p. 90°C (0.1 mmHg), $[\alpha]_D - 2.2°$ ($c = 3$, $CHCl_3$); IR (neat) cm^{-1} 3400, 3070, 3030, 1640, 1100, 740, 700; ^1H NMR ($CDCl_3$) δ 7.33 (5H, s), 5.90–5.75 (1H, m), 5.1 (2H, m), 4.55 (2H, s), 3.90 (1H, m), 3.6–3.4 (2H, m), 2.41 (1H, d, J 3.3 Hz), 2.26 (2H, t, J 6.9 Hz). Mass spectrum, m/e (relative intensity): 192 (1.06), 92(24.89), 91(100); Exact mass found: 192.1161; $C_{12}H_{16}O_2$ calcd.: 192.1150.

2*S*,4*S*-(−)-Benzyl-2,4-dihydroxyhept-6-enyl ether (**11**). Thiophene (29 μl, 0.36 mmol) was added to THF (0.5 ml) in a 15 ml, 2-neck pear flask at −78°C, followed by n-butyllithium (0.13 ml, 0.36 mmol). The Dry Ice bath was replaced with a 0°C bath, and stirring was continued for 0.5 h. The light yellow solution was transferred, via cannula, into a 15 ml, 2-neck flask containing CuCN (31 mg, 0.336 mmol) and THF (0.5 ml) under argon at −78°C. Warming to 0° produced a light tan solution which was recooled to −78°C where vinyllithium (0.168 ml, 0.336 mmol) was injected. The cuprate was warmed to 0°C for a brief period (~ 2 min), then recooled to −78°C. In a separate 15 ml, 2-neck pear flask, the epoxy alcohol (60 mg, 0.28 mmol) was dissolved in THF (0.5 ml) and cooled to −78°C where 1 equiv. vinyllithium (0.14 ml, 0.28 mmol) was added. Stirring was continued at the same temperature for 15 min, then at 0°C for 0.5 h. The substrate was next transferred, via cannula, into the precooled (−78°C) cuprate, followed by warming to 0°C. After 1.5 h at 0°C, 5 ml of a 90% NH_4Cl (satd)/10% NH_4OH(conc) solution was injected as quench. Extractive workup with EtOAc (3 × 10 ml) and drying over $MgSO_4$ was followed by chromatography on silica gel (230–400 mesh) with Et_2O to afford 60 mg (91%) of a clear oil ($R_f = 0.35$, Et_2O).

The diastereomers were separated by chromatography on silica gel (230–400 mesh, 20% acetone/skelly solve); IR (neat) cm^{-1} 3400, 3080, 3040, 1640, 1100, 760, 700; *Anti* isomer; $R_f = 0.18$; ^1H NMR ($CDCl_3$): δ 7.33 (5H, s), 5.8 (1H, m), 5.14 (2H, m), 4.56 (2H, s), 4.15 (1H, m), 3.98 (1H, m), 3.60–3.38 (2H, m), 2.71 (1H, s), 2.41 (1H, s), 2.25 (2H, m), 1.40–1.20 (2H, m); *Syn* isomer; $[\alpha]_D$ −1.2° ($c = 10.05$, $CHCl_3$); $R_f = 0.28$; ^1H NMR ($CDCl_3$): δ 7.33 (5H, s), 5.81 (1H, m), 5.12 (2H, m), 4.55 (2H, s), 4.06 (1H, m), 3.93 (1H, m), 3.5–3.3 (2H, m), 3.23 (1H, s), 3.15 (1H, s), 2.24 (2H, t, J 6.6 Hz), 1.47–1.40 (2H, m); mass spectrum, m/e (relative intensity): 236 (1.6), 219 (11.2), 181 (6.6), 119 (5.1), 91 (84.1), 87 (18.1), 31 (100); Exact mass found: 236.1419; $C_{14}H_{20}O_3$ calcd.: 236.1411.

5-Phenylpenten-4-ol (entry 1). Dry CuCN (45.8 mg, 0.5 mmol) was placed in a 10 ml 2-neck flask, evacuated and purged with argon three times, gently flame dried at vacuum and purged with argon. Et_2O (0.8 ml) was added via syringe and the stirred slurry cooled to −78°C. 2-Thienyllithium (0.5 mmol) was prepared from thiophene (43 μl, 0.54 mmol) and n-butyllithium (0.18 ml, 2.78 *M*) in THF at −30°C (0.2 ml, 30 min) and added via cannula to the CuCN with a 0.2 ml Et_2O rinse. Warming to room temperature for 5–10 min yielded a two phase solution to which was added, after recooling to −78°, vinyllithium (0.25 ml, 2.0 *M*). Warming to room temperature gave a white over amber 2-phase mixture. The epoxide was introduced at

-78°C and the reaction warmed to 0°C. After 1 h it was quenched and worked up in the usual way. The product was isolated in 90% yield (58.7 mg) by chromatography on silica gel with 20% EtOAc/skelly solve; TLC: $R_f = 0.45$ (20% EtOAc/skelly solve); IR (neat) cm^{-1} 3400, 3065, 3030, 1642, 1605, 740, 695; ^{1}H NMR, δ 1.78 (1H, s), 2.17–2.39 (2H, m), 2.65–2.89 (2H, m), 2.65–2.89 (2H, ddd), 3.80–4.0 (1H, m), 5.05–5.26 (2H, m), 5.80–5.94 (1H, m), 7.21–7.36 (5H, m); mass spectrum, *m/e* (relative intensity): 121 (39), 103 (27), 92 (100), 91 (48), 77 (10); exact mass found: 162.1063; $C_{11}H_{14}O$ calcd.: 162.1044.

4-Ethylhexen-4-ol (entry 2). Dry CuCN (43.3 mg, 0.49 mmol) was placed in a 10 ml 2-neck flask and evacuated and purged with argon (3x), then flamed gently under vacuum and allowed to cool before a final argon purge. Et_2O (0.7 ml) was added via syringe and the slurry was cooled to -78°C. 2-Thienyllithium was prepared in a 5 ml 2-neck flask from thiophene (40 μl, 0.5 mmol) and n-butyllithium (0.17 ml, 2.78 *M*) in THF at -30°C (0.2 ml, 20 min) and transfered via cannula onto the CuCN slurry. Upon warming to room temperature the CuCN dissolved completely to give a two phase mixture of white liquid over a brown oil. This mixture was then recooled to -78°C where vinyllithium (0.24 ml, 2.0 *M*) was added and again the mixture was warmed to room temperature for 1 min and recooled to -78° where the epoxide was added neat (48 μl, 0.40 mmol) and the reaction was allowed to warm to room temperature. After 4 h, the reaction was quenched and worked up in the usual way. A yield of 71% was determined via quantitative gas chromatographic analysis, along with ca. 30% starting material also being detected. A pure sample of the product is obtained by chromatography an silica gel with 1/1 Et_2O/skelly solve; $R_f = 0.45$. Spectral data were in full agreement with that obtained earlier [20].

trans-2-n-Propylcyclohexanol (entry 3). Copper cyanide (97.1 mg, 1.1 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 sec) under vacuum and then purged with argon. Dry THF (1.0 ml) was added and the slurry was cooled to -78°C. 2-Thienyllithium was prepared in a second 2-neck round bottom flask from thiophene (94.1 μl, 1.18 mmol) in dry Et_2O (1.3 ml) at -30°C to which was added n-BuLi (0.44 ml, 2.53 *M* in hexanes, 1.1 mmol) and the clear colorless solution was stirred at room temperature for 30 min. n-Propyllithium (0.66 ml, 1.66 *M* in Et_2O, 1.1 mmol) was added to the CuCN slurry at -78° and warmed to 0°C over 30 min until the tan-brown slurry became clear. The reaction mixture was cooled to -78°C and the thienyllithium was added via cannula with the resulting mixture being stirred at 0°C for 15 min and then cooled to -78°C. Freshly distilled cyclohexene oxide (100 μl, 1.0 mmol) was added and the reaction was warmed to 0°C over 1 h and quenched by the addition of 5 ml of a 90% NH_4Cl (sat.)/10% NH_4OH (conc.) solution. After stirring at room temperature for 30 min, the solution was worked up in the usual way. The crude material (VPC yield: 55%) was chromatographed on silica gel using 2/1 skelly solve/Et_2O; IR (neat) cm^{-1} 3370, 1058, 1045, 1023, 929; ^{1}H NMR, δ 3.20 (1H, m), 2.00–0.80 (17H, m); mass spectrum, *m/e* (relative intensity) 125(2.1), 124(19.8), 99(17.3), 96(31.0), 95(41.4), 81(49), 57(100); exact mass found: 141.1295; ($C_9H_{18}O - 1$; Chem. ionization, $P + 1 - H_2$) calcd.: 141.1311; found: 125.1343; C_9H_{17} ($P + 1 - H_2$) calcd.: 125.1356.

Opening of *cis*-2-butene oxide (entry 4). Thiophene (82 μl, 1.02 mmol) was added to THF (0.6 ml) in a 10 ml, 2-neck pear flask at -78°C, followed by n-butyllithium (0.36 ml, 1.0 mmol). The temperature was slowly (ca. 5 min) raised to 0°C where stirring was continued for 30 min. The light yellow solution was transferred, via cannula, into a precooled (−78°C) 15 ml 2-neck round bottom flask containing CuCN (89.6 mg, 1 mmol) and Et_2O (0.6 ml). Et_2O (0.2 ml) was subsequently used to wash in the pear flask. Warming to 0°C resulted in a light tan solution which was recooled to −78°C where n-butyllithium (0.36 ml, 1 mmol) was injected. Warming to 0°C and recooling to −78°C was followed by injection of the epoxide (78 μl, 0.9 mmol). Stirring was continued at room temperature for 9 h, followed by quenching with 5 ml of a 90% NH_4Cl (satd.) 10% NH_4OH (conc.) solution. Quantitative VPC analysis indicated formation of 3-methyl-2-heptanol [4] in 77% yield.

3-Methylnonene (entry 5). Dry CuCN (68.2 mg, 0.76 mmol) was placed in a 10 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 (0.5 ml) was added via syringe and the slurry cooled to −78°C. 2-Thienyllithium was prepared in a 5 ml 2-neck flask from thiophene (66 μl, 0.82 mmol) and n-butyllithium (0.29 ml, 2.63 M) in THF at −30°C (0.3 ml, 30 min) and added to the CuCN via cannula with a 0.2 ml THF rinse. With warming to room temperature, the CuCN dissolved to give a clear amber solution. After recooling to −78°, vinyllithium (0.37 ml, 2.0 *M*) was added followed by 2-iodooctane. The reaction was warmed to 31°C (H_2O bath heated only by a magnetic stirrer motor) for 18 h before quenching and the usual workup. Quantitative VPC analysis indicates a yield of 67% [4].

6-Methyloctanenitrile (entry 6). The cuprate was prepared from CuCN (84.4 mg, 0.94 mmol), 2-lithiothiophene (0.94 mmol), and s-BuLi (1.12 ml, 0.84 *M*, 0.94 mmol) in 1.5 ml THF. To the cold (−78°C) solution was added 5-bromovaleronitrile (100 μl, 0.86 mmol). After ca. 5 min at this temperature, the solution was slowly warmed to 0°C with stirring continued for a total of 1 h. Workup in the usual fashion followed by chromotography on SiO_2 with 1/1 Et_2O/skelly solve afforded 97.6 mg (82%) product; TLC: R_f (1/1 Et_2O/skelly solve) 0.67; IR (neat) cm^{-1} 2250; ^1H NMR, δ 2.34 (2H, t, *J* 7.1 Hz), 1.62 (2H, m), 1.55–1.05 (6H, m) 1.0–0.75 (7H, m); mass spectrum, *m/e* (relative intensity): 138 (4.1, M^+-1), 124 (26), 111 (36), 110 (97), 96 (20), 82 (26), 69 (52), 54 (100); Anal. found: C, 77.76; H, 12.56; N, 9.92; $C_9H_{17}N$ calcd.: C, 77.62; H, 12.31; N, 10.07%.

3-n-Butylcyclohexanone (entry 7, R_T = n-Bu). Dry CuCN (0.6 mmol) was placed in a 10 ml 2-neck flask and three times evacuated and purged with argon, then gently flamed under vacuum and allowed to cool before a final argon purge. THF (1.0 ml) was added via syringe and the slurry cooled to −78°C. 2-Thienyllithium was prepared in a dry 5 ml 2-neck flask from thiophene (52 μl, 0.65 mmol) and n-butyllithium (0.22 ml, 2.78 *M*) in THF at −30°C (0.3 ml, 30 min) and added via cannula to the CuCN slurry with a 0.2 ml THF rinse. Upon warming to room temperature, the CuCN dissolved to yield a clear amber solution which was then cooled to −78°C and n-butyllithium (0.22 ml, 2.78 *M*) was added. The mixture is warmed to 0°C for 1 min and recooled to −78°C where the cyclohexenone was added (49 μl, 0.5 mmol) to give a sudden yellowing which dissipated within 5 min. The reaction was quenched after 15 min at −78°C and worked up in the usual manner. Quantitative VPC indicated a yield in excess of 95%. The product (60.8 mg, 83%) was isolated by chromatography on silica gel with 10% EtOAc/skelly solve; TLC: $R_f = 0.35$. Spectral data were identical to that obtained earlier [11].

3-Phenylcyclohexanone [21] (entry 7, R_T = Ph). Thiophene (65 μl, 0.81 mmol) was dissolved in Et_2O (0.75 ml) and cooled to −78°C. n-BuLi (0.75 mmol, 2.78 *M* in hexane) was added and the mixture taken to 0°C for one hour, recooled to −78°C and added via cannula to dry CuCN (67 mg, 0.75 mmol) in 0.75 ml Et_2O. The heterogeneous mixture was taken to room temperature for 20 min, then recooled to −78°C. PhLi (0.75 mmol, 2.22 *M* in cyclohexane) was added followed by warming to 0°C for 5 min, cooling to −78°C and addition of neat 2-cyclohexenone (56 μl, 0.58 mmol). The mixture was stirred for 20 min, then quenched and worked up in the usual way. Chromatography on SiO_2 (25% Et_2O/skelly solve) afforded 80 mg (80%) of a clear oil; R_f (25% Et_2O/skelly solve) 0.26; IR(neat) cm^{-1} 3030, 3020, 2940, 1712, 1605; ^1H NMR δ 1.70–2.57 (8H, m), 3.00 (1H, m), 7.22 (5H, m); mass spectrum, *m/e* (relative intensity) 174 (100, M^+), 131 (71), 117 (91), 104 (68), 42 (28).

8-Phenylmenthone (entry 8). Thiophene (60 μl, 0.75 mmol) was dissolved in 0.75 ml of Et_2O and cooled to −78°C. n-BuLi (0.75 mmol) was added and the solution warmed to ca. −35°C for one hour, recooled to −78°C and added via cannula to dry CuCN (66.8 mg, 0.75 mmol) in 0.75 ml of Et_2O. This mixture was warmed to 0°C and stirred until homogeneous. The solution was taken to −78°C and PhLi (0.74 mmol) was added, followed by warming to 0°C for 5 min, then recooling to −78°C. Pulegone (95 μl, 0.58 mmol) was added neat and the mixture was slowly warmed to 0°C. After 45 min the mixture was quenched and worked up in the usual fashion. Chromatography on SiO_2 (5% Et_2O/skelly solve; $R_f = 0.24, 0.28$) afforded 85 mg (63%) of a clear oil which was identical (NMR, IR, TLC) with authentic material [22].

Conjugate addition to isophorone (entry 9). Thiophene (82 μl, 1.02 mmol) was added to THF (0.5 ml) in a 10 ml 2-neck pear flask at −78°C, followed by dropwise addition of n-butyllithium (0.36 ml, 1 mmol). Stirring was continued at −78°C for 5 min, then at 0°C for 30 min. The light yellow solution was then transferred, via cannula, into a precooled (−78°C) 15 ml 2-neck round bottom flask containing CuCN (89.6 mg, 1 mmol) and Et_2O (0.5 ml), with a wash of 0.4 ml Et_2O. Warming to 0°C gave a light tan clear two-phase solution which was recooled to −78°C. Vinyllithium (0.50 ml, 1 mmol) was injected, with warming to 0°C and recooling to −78°C which produced no visible change. Isophorone (104 μl, 0.7 mmol) was added neat, dropwise, with stirring continued at −78°C for 2 h, −50°C for 0.5 h, and 0°C for 1 h. Quenching with 5 ml of a 90% NH_4Cl (satd.)/NH_4OH (conc.) solution was followed by VPC analysis which indicated a 49% yield [11].

4-Methyl-4-phenyl-2-pentanone (entry 10). CuCN (55 mg, 0.6 mmol) was placed with a magnetic stir bar in a 10 ml 2-neck flask, evacuated and purged with argon three times, gently flame dried under vacuum and allowed to cool before a final argon purge. Et_2O (1.0 ml) was added via syringe and the slurry cooled to −78°C. 2-Thienyllithium (0.6 mmol) was prepared in a dry 5 ml 2-neck flask from thiophene (52 μl, 0.65 mmol) and n-butyllithium (0.22 ml, 2.78 *M*) in THF at −30°C (0.3 ml, 45 min) and then added to the CuCN slurry with a 0.2 ml Et_2O rinse. This mixture was allowed to warm to room temperature for several minutes to yield a fully dissolved bi-phasic solution of colorless liquid over an amber oil. After recooling to −50°C, phenyllithium (0.27 ml, 0.6 mmol) was added. The solution was again warmed to room temperature and then recooled to −50°C whereupon mesityl oxide (57 μl, 0.5 mmol) was added. After 1 h at −50°C and 15 min at −25°C, the reaction was quenched and worked-up in the usual way. Quantitative VPC analysis indicated a 51% yield of product [11].

Attempted conjugate addition with 3-methylcyclohexenone (entry 11). Thiophene (0.08 ml, 1 mmol) was added to THF (0.4 ml) in a 10 ml, 2-neck pear flask at −78°C, followed by n-butyllithium (0.36 ml, 1 mmol). Stirring was continued at the same temperature for 15 min, then at 0°C for 0.5 h. The light yellow solution was next transferred, via cannula, into a slurry of Et_2O (0.8 ml) and CuCN (89.6 mg, 1 mmol) with a wash of 0.2 mL Et_2O. Warming to 0°C resulted in a two phase, clear-tan solution which was recooled to −78°C. t-Butyllithium (0.37 ml, 0.75 mmol) was injected slowly, with the temperature raised to 0°C for 5 min. Recooling to −78°C caused the solution to thicken to a slurry. The enone (85 μl, 0.75 mmol) was added neat and dropwise whereupon a red solution formed immediately. Stirring was continued at −20°C for 0.75 h, followed by quenching, workup, and chromatography of the crude material on silica gel (230–400 mesh) with 1/1 Et_2O/skelly solve to collect 126 mg (87%) of a clear oil; $R_f = 0.5$ (1/1 Et_2O, skelly solve); IR (neat) cm^{-1} 3380, 2950, 1635, 700; ^1H NMR ($CDCl_3$) 1.372 (3H, s), 1.5–2.0 (4H, m), 2.3–2.6 (2H, m), 6.05 (1H, s), 6.9–7.2 (3H, m); mass spectrum, *m/e* (relative intensity) 194 (12.5, M^+), 179 (23.4), 176 (43.2), 161 (15.0), 128 (12.2), 97 (14.7), 78 (100); exact mass found: 194.0760; $C_{11}H_{14}OS$ calcd.; 194.0789.

5S-Methyl 3-n-butyl-5,9-dimethyldec-9-enoate (entry 12). The mixed cuprate was formed using CuCN (54 mg, 0.61 mmol), 2-lithiothiophene (0.61 mmol), and n-BuLi (0.24 ml, 2.53 *M*, 0.61 mmol) in 1.4 ml Et_2O. The unsaturated ester (121 μl, 0.55 mmol) was added to the cold (−78°C) cuprate, the solution from which was slowly warmed to room temperature and stirred there for 2 h. Quenching and workup as previously described followed by chromatography on SiO_2 with 5% Et_2O/pentane afforded 131 mg (89%) product; TLC: R_f (10% Et_2O/skelly solve) 0.60; IR (neat) cm^{-1} 1745, 1165, 1020; ^1H NMR, δ 5.09 (1H, m), 2.45–2.20 (3H, m), 2.1–1.8 (3H, m), 1.80–0.80 (25H, m); mass spectrum, *m/e* (relative intensity) 268 (2.78, M^+) 238 (1.05), 237 (5.47), 218 (4.66), 194 (35.16), 69 (100); exact mass found: 268.2406; $C_{17}H_{32}O_2$ calcd.: 268.2402.

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