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Cyanocuprates Convert Carboxylic Acids Directly into Ketones

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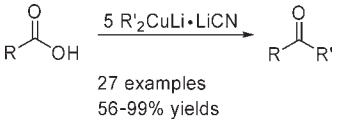
ABSTRACT



Carboxylic acids were converted directly in 56−99% yields into methyl, *n*-butyl, and isopropyl ketones using excess cyanocuprates $R_2CuLi \cdot LiCN$. A substrate with a stereocenter α to the carboxylic acid was converted into ketones with very little loss of enantiomeric purity. A variety of functional groups were tolerated including aryl bromides. This direct transformation of a carboxylic acid into ketone with minimal tertiary alcohol formation is proposed to involve a relatively stable copper ketal tetrahedral intermediate.

Conversion of a carboxylic acid into a ketone is a fundamental transformation in organic chemistry.[1−4] This functional group change is usually performed indirectly by activating the carboxylic acid into an acyl chloride[5−8] or into a Weinreb amide[9−11] and then by nucleophilic attack of an organometallic species such as an organocopper, organolithium, or Grignard reagent. Conversion of a carboxylic acid directly into a ketone, however, can be achieved in one step using at least 2 equiv of an organolithium reagent,[12−17] but very often formation of much tertiary alcohol occurs. Furthermore, organolithium reagents reacting directly with α-chiral nonracemic carboxylic acids (i.e., 2-substituted alkanoic acids) can cause significant unwanted α-deprotonation of the methine hydrogen atom and thus ultimate loss of α-stereochemical purity.[15,18] We have discovered recently and now report that cuprates, formed in situ from organolithium reagents and cuprous cyanide[19−23] in a 2:1 ratio, convert carboxylic acids directly and cleanly into ketones with much less formation of tertiary alcohols and with much less erosion of α-stereochemical purity than with the corresponding organolithium reagents.

Treatment of 50 mg of (*S*)-2-phenylbutyric acid (98.5% ee by chiral HPLC) with 5 equiv of cyanocuprate $Me_2CuLi \cdot LiCN$ in Et_2O produced the corresponding methyl ketone **1a** in 99% yield and with only 0.2% loss of ee (98.5% → 98.3%) (Scheme 1A). This reaction was performed also on gram scale (1.5 g of isolated product) producing methyl ketone **1a** in 93% yield and with only 0.5% loss of ee (98.5% → 98.0%). In contrast, treatment of (*S*)-2-phenylbutyric acid with 2.1 equiv of MeLi yielded 66% methyl ketone **1a** and 4% dimethyl tertiary alcohol

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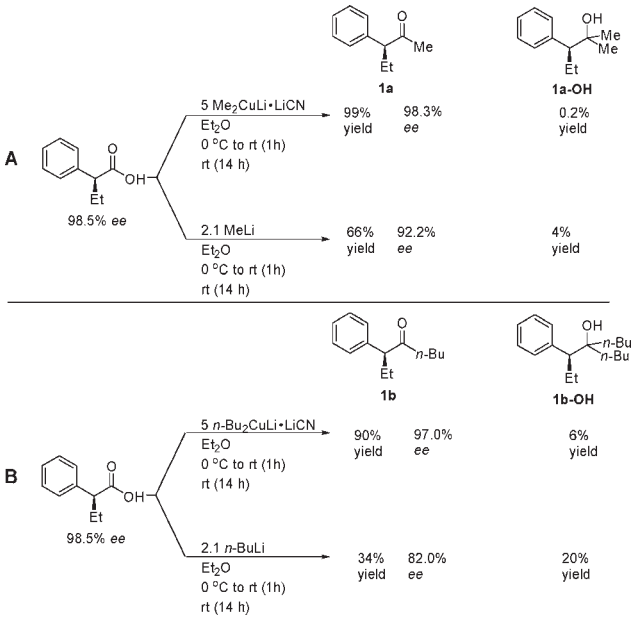
1a-OH with a significant decrease in enantiomeric excess (98.5% → 92.2%) of methyl ketone **1a**. *n*-Butyl ketone **1b** was prepared in 90% yield by treating (*S*)-2-phenylbutyric acid with 5 equiv of *n*-$Bu_2CuLi \cdot LiCN$ in Et_2O with only a 1.5% loss of enantiomeric excess (98.5% → 97.0%) (Scheme 1B). By comparison, *n*-butyl ketone **1b** was prepared in 34% yield and 82.0% ee by treating (*S*)-2-phenylbutyric acid with 2.1 equiv of *n*-BuLi, corresponding to a 3-fold drop in yield and a substantial loss of ee as compared to the cyanocuprate protocol; the starting carboxylic acid was recovered in 30% yield upon acidic workup.

Other copper(I) sources (CuI, CuBr·DMS, and CuSPh) were tested, and only CuI gave any methyl ketone product (~10%). The use of cuprates derived from Grignard reagents was also investigated, but unacceptable amounts (20–40%) of tertiary alcohol were observed. Room temperature was found to be optimal; when the cyanocuprate reaction was held at 0 °C or lower, little or no reaction occurred. Though as few as 3.5 equiv of $Me_2CuLi \cdot LiCN$ produced methyl ketone in approximately 75% yield, the use of 5 equiv of cyanocuprate was found to be optimal for maximizing ketone formation. Substrate scope was tested comparing this new cyanocuprate reaction and the literature alkyllithium protocol (Figure 1, yields in parentheses

Scheme 1. Yields and ee's are the average of quadruplicate experiments.



are for RLi reactions). Although there is no universal literature protocol (equivalents of RLi range from 2 to 5 and temperature from −78 °C to reflux),[12–17] the alkyllithium reaction conditions we chose were intended to maximize ketone formation and to minimize tertiary alcohol formation. Quenching protocols also were screened including inverse addition of the reaction mixture into cold dilute HCl;[16] no effect on stereochemistry or on ketone/tertiary alcohol ratio was observed as a function of quenching protocol. In all cases, ketones synthesized using a cyanocuprate were isolated in higher yields (1.5- to 3-fold increase) than those synthesized from the corresponding alkyllithium and in most cases required no purification after aqueous workup.

Benzoic acid was converted cleanly in 91–97% yields into methyl (**2a**), *n*-butyl (**2b**), and isopropyl (**2c**) ketones using the corresponding cyanocuprate. Ester methyl benzoate, however, was converted into a tertiary alcohol using excess $Me_2CuLi \cdot LiCN$. 4-Fluoro-, 2-fluoro-, and 4-chlorobenzoic acids were converted into the corresponding methyl (**3a**, **4a**, **5a**) and *n*-butyl (**3b**, **4b**, **5b**) ketones without breaking the carbon–halogen bond. Also, most noteworthy, 4- and 3-bromobenzoic acids were converted into bromophenyl methyl ketones **6a** and **7a** without breaking the carbon–bromine bond. All halogenated benzoic acids shown in Figure 1 are known to undergo *ortho*-lithiation in the presence of alkyllithium reagents,[24–26] a side reaction that is effectively suppressed by utilizing a cyanocuprate reagent.

4-Methoxybenzoic acid and 2-picolinic acid, two substrates that are also prone to *ortho*-lithiation by organolithium reagents,[27–29] were converted cleanly into the corresponding ketones **8a, 8b**, and **9a** in high yields using this cyanocuprate procedure. 1,3-Thiazole-4-carboxylic acid was transformed into methyl ketone **10a** in 74% yield using $Me_2CuLi \cdot LiCN$; however, when the same acid was treated with MeLi, complete decomposition of the thiazole ring was observed.

3-Phenylpropionic acid was converted cleanly into the corresponding methyl (**11a**), *n*-butyl (**11b**), and isopropyl (**11c**) ketones in 86–99% yields. Attempts to treat 3-phenylpropionic acid with $Ph_2CuLi \cdot LiCN$ were unsuccessful at yielding phenyl ketone. This result can be attributed to the instability of $Ph_2CuLi \cdot LiCN$ at room temperature, where the cuprate readily decomposes into biphenyl.[30,31] Also, treatment of 3-phenylpropionic acid with *t*-$Bu_2CuLi \cdot LiCN$ yielded the *tert*-butyl ketone in only 17% yield with the remaining mass balance being unreacted carboxylic acid. Other carboxylic acids, such as cyclohexylacetic, cyclohexylcarboxylic, phenylacetic, and the sterically hindered 2-phenylisobutyric acids, were converted into methyl ketones **12a**, **13a**, **14a**, and **15a** and *n*-butyl ketones **12b**, **13b**, and **14b** in 56–99% yields. Treatment of phenylalanine with $Me_2CuLi \cdot LiCN$ yielded only recovered starting material upon aqueous workup.[32]

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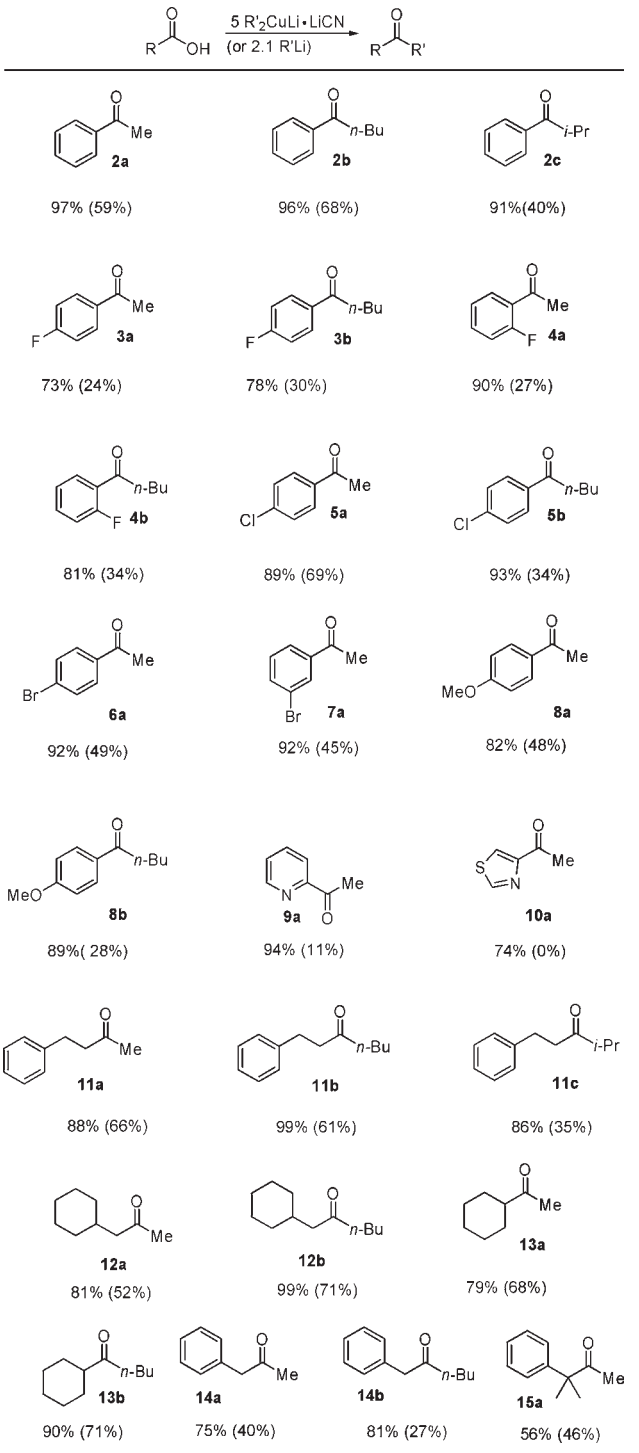
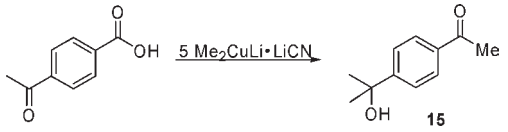


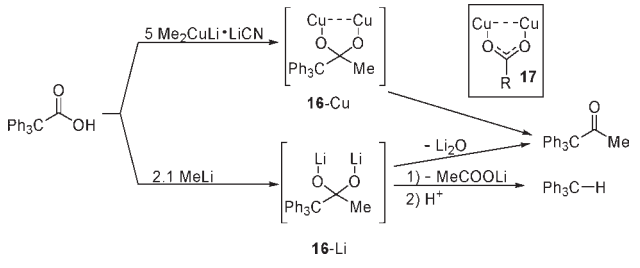
Figure 1. Yields in parentheses are for RLi reactions.

Some mechanistic insight was gained from the treatment of 4-acetylbenzoic acid and of triphenylacetic acid with $Me_2CuLi \cdot LiCN$. When treated with $Me_2CuLi \cdot LiCN$, 4-acetylbenzoic acid yielded mainly keto-alcohol **15** (Scheme 2). This result implies that the ketone formed from the treatment of a carboxylic acid with $Me_2CuLi \cdot LiCN$ is not formed until aqueous workup. This was further corroborated when acetophenone was treated with $Me_2CuLi \cdot LiCN$ and yielded exclusively 2-phenyl-2-propanol in less than 1 h, a product not observed when benzoic acid is treated with $Me_2CuLi \cdot LiCN$. Also, when triphenylacetic acid was treated with $Me_2CuLi \cdot LiCN$ no triphenylmethane was produced. However, upon treatment with methyllithium, as expected from literature precedent,[33] triphenylacetic acid was converted into triphenylmethane in 28% yield. Scheme 3 is proposed as a rationale for these results. We propose the intermediacy of ketal tetrahedral intermediate **16-Cu**, structurally similar to copper(I) carboxylate **17** in which X-ray crystallography shows an attractive cupriophilic Cu−Cu interaction with the two carboxylate oxygens bridging two copper atoms.[34−36] The ketal tetrahedral intermediate **16-Cu** (additional ligands on copper are not shown) apparently is sufficiently more stable than the corresponding dilithio species **16-Li** to avoid fragmentation into triphenylmethyllithium which, after protonation, would produce triphenylmethane (Scheme 3). Years ago, we reported that copper(I) enolates are less basic and less reactive than the corresponding lithium enolates.[37] Thus, it seems likely that ketal tetrahedral intermediate **16-Cu**, being more stable than **16-Li**, is less prone to fragment into a ketone during the course of the reaction or upon acidic workup while cuprate is still present to consume the ketone and to form tertiary alcohol. This increased stability of ketal tetrahedral intermediate **16-Cu** relative to that of **16-Li** appears to be the fundamental basis for success of the new method we describe here achieving cuprate conversion of carboxylic acids directly into ketones with minimal formation of tertiary alcohols.

Scheme 2



Scheme 3



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In conclusion, we report the clean transformation of carboxylic acids into methyl, *n*-butyl, and isopropyl ketones in high yields utilizing cyanocuprate reagents. A substrate with a stereocenter α to the carboxylic acid was converted by cyanocuprates into ketones with very little loss of enantiomeric purity. This new cyanocuprate procedure did not cleave the carbon−halogen bond in halobenzoic acids. Furthermore, halobenzoic acids, prone to ortho-lithiation by organolithium reagents, were converted by cyanocuprates in high yields into the corresponding halophenyl ketones. We propose that the success of this cyanocuprate conversion of carboxylic acids directly into ketones is due to the intermediacy of a relatively stable copper ketal tetrahedral intermediate, the role of which is under further investigation.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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