easy to observe tautomers at ambient temperature. In compound **5** we could not observe them in $CDCl_3$ even at −50 °C.

Therefore, the electronic effects of the substituents at position-2 and -5 of the dihydropyrimidine ring play important roles in making possible the observation of individual tautomers.

These findings will facilitate recognition of tautomerism in other dihydropyrimidine derivatives and may serve as a foundation for the investigations of tautomerism of other heterocyclic amidines.

Registry No. 1a, 114790-88-4; **1b**, 114790-93-1; **2a**, 114790-89-5; **2b**, 114790-94-2; **3b**, 114790-90-8; **4a**, 114790-91-9; **5a**, 101645-67-4; **6a**, 114790-92-0.

Supplementary Material Available: Table II (tautomerism of 2-substituted dihydropyrimidine derivatives on the different solvents, concentrations, and temperature) and synthetic methods for compounds **1–6** (5 pages). Ordering information is given on any current masthead page.

Effects of BF_3·Et_2O on Higher Order Organocuprate Reactions: Substrate Activation or Cuprate Modification?†

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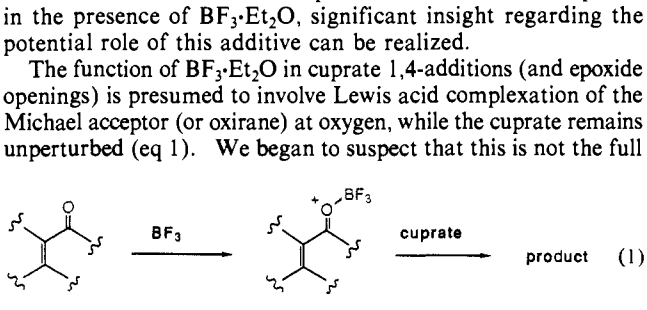
In spite of the vast number of successful applications of organocuprates to synthetic schemes which call for conjugate addition reactions,[2] there are many times when results obtained are simply not satisfactory. Whether due to steric hindrance in the substrate or limited reagent stability or reactivity, cuprate formation by itself does not imply success in subsequent Michael additions. To improve the chances for effecting the desired coupling, it is now common practice to admix either lower order (L.O.) or higher order (H.O.) cuprates[3] with an additive such as BF_3·Et_2O[4] or Me_3SiCl,[5] which oftentimes leads to spectacular increases in rates and yields of reactions. Just how these species effect the solution chemistry of this substrate/reagent combination, however, is still an open matter. We now report that by carrying out both chemical and NMR spectral studies on H.O. cuprates in the presence of BF_3·Et_2O, significant insight regarding the potential role of this additive can be realized.

The function of BF_3·Et_2O in cuprate 1,4-additions (and epoxide openings) is presumed to involve Lewis acid complexation of the Michael acceptor (or oxirane) at oxygen, while the cuprate remains unperturbed (eq 1). We began to suspect that this is not the full

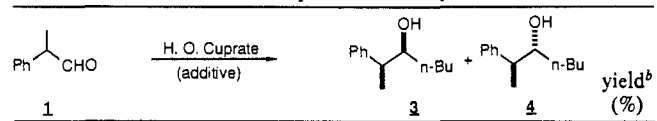


(1)

story, if correct at all, when we examined the 1,2-addition of $Bu_2Cu(CN)Li_2$ (**2**) to aldehyde **1**[6a] under the influence of various additives (see Table I).[6b] The adduct is expected to form a mixture of syn **3** and anti **4** products, providing an internal stereochemical label. As summarized in Table I, although **2** reacts slowly with **1** at −78 °C, an equal amount of **3** and **4** is formed. The same is true for reactions of **2** in the presence of excess BF_3. However, while **2** is totally unreactive (even at room temperature) in the presence of 15-crown-5-ether, the addition of BF_3 to this mixture at −78 °C not only restores activity but also leads to a substantially improved ratio of diastereomers (ca. 10:1 syn:anti by capillary GC).[6b] Moreover, the most reactive reagent combination is in fact the one containing the unreactive cuprate and crown ether, plus BF_3, which consumes aldehyde somewhat faster than does the reactive **2** plus BF_3. Identical results could be obtained by placing the Li^+ sequestering crown ether effect within the cuprate itself by using an acetylenic ligand,[7] as in **5**. That these observations are not consistent with simple carbonyl activation was further strengthened by precomplexing **1** with BF_3 followed by exposure to **5**, which does not give the previously noted 10:1 ratio (see Table I).

To ascertain how the BF_3 must effect the cuprate we turned to low-temperature, high field NMR. H.O. cuprates $Me_2Cu(CN)Li_2$ (**6**), $Me(MeOC(CH_3)_2C{\equiv}C)$-$Cu(CN)Li_2$ (**7**),[8] and Me(2-thienyl)$Cu(CN)Li_2$ (**8**)[8] were studied. Addition of BF_3·Et_2O (2 equiv) to **6** at −90 °C immediately leads to the appearance of

Table I. Addition of H. O. Cuprates to Aldehyde **1**[a]



1	3	4	yield[b] (%)
n-$Bu_2Cu(CN)Li_2$, **2**	1	1	52–72
2 + $4BF_3$	1.3	1	55–65
2 + 15-Cr-5	no reaction		
2 + 15-Cr-5 + $4BF_3$	8–10	1	quant
n-Bu(MeO⟨≡⟩)Cu(CN)Li_2, **5**	no reaction		
5 + $4BF_3$	10–12	1	70
1 + $4BF_3$, then **5**	3	1	20–30
n-Bu(2-Th)$Cu(CN)Li_2$ + $4BF_3$	4	1	50
n-BuCu(CN)Li + $4BF_3$	3.5	1	55
n-BuLi·$2BF_3$	2	1	40

[a] All reactions were run in THF containing 2 equiv of cuprate at −78 °C over a 3-h period. [b] Yields (and ratios of diastereomers) were determined on the crude reaction mixtures by quantitative capillary GC. The remaining mass consisted mostly of starting aldehyde.

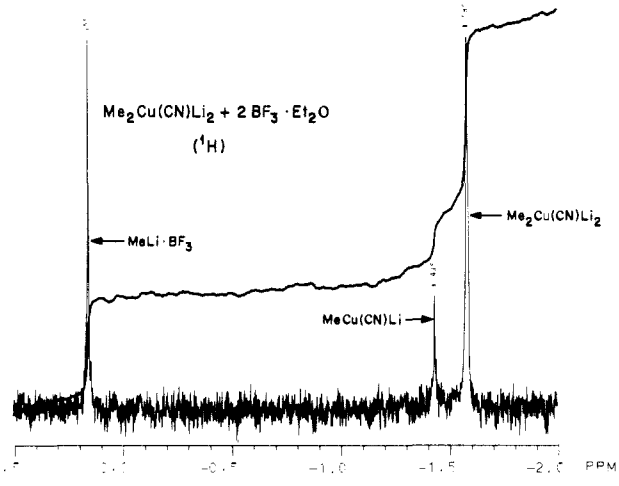


Figure 1. Proton NMR spectrum of $Me_2Cu(CN)Li_2$ + $2BF_3$·Et_2O in THF at −92 °C.

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) A. P. Sloan Fellow, 1984–1988; Dreyfus Teacher-Scholar, 1984–1989.

(2) Posner, G. H. *Org. React.* **1972**, *19*, 1. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

(3) For a review, see: Lipshutz, B. H. *Synth.* **1987**, 325.

(4) The use of BF_3·Et_2O in reactions of organocopper complexes has recently been reviewed; cf.: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.

(5) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025, 4029; Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

(6) (a) The 1,2-addition of cuprates to aldehydes was first noted by Posner: Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106. (b) Yamamoto, Y.; Maruyama, K. *Ibid.* **1985**, *107*, 6411.

(7) Corey, E. J.; Floyd, D. M.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(8) All information regarding this species is in the Supplementary Material.

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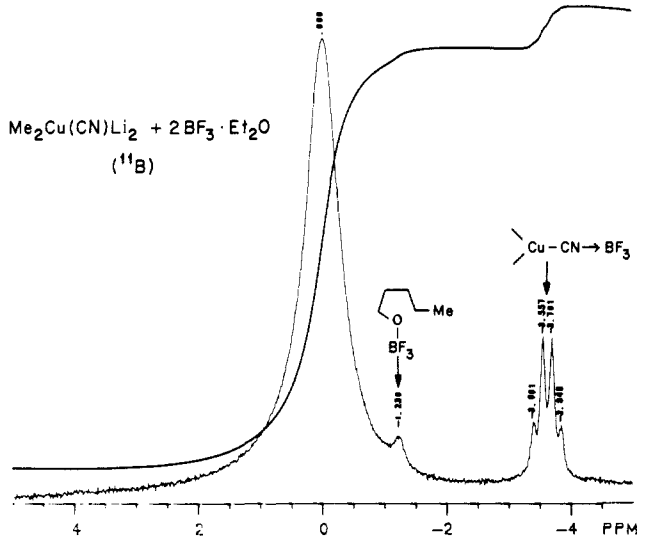


Figure 2. ^{11}B NMR spectrum of $Me_2Cu(CN)Li_2 + 2BF_3{\cdot}Et_2O$ in THF at −70 °C.

two new peaks in the PMR spectrum, in addition to that seen for **6** alone (Figure 1). The new species are identified as the L.O. cuprate MeCu(CN)Li and $MeLi{\cdot}BF_3$.[9] For **7**, which alone shows two methyl singlets suggesting geometrical isomers of a presumed dimer,[10] addition of BF_3 results in essentially complete disappearance of these peaks at −70 °C, with the same two peaks being produced as with **6** but in differing amounts. Cuprate **8** in the presence of BF_3 shows mostly $MeLi{\cdot}BF_3$, plus small amounts of the two signals corresponding to the original cuprate.

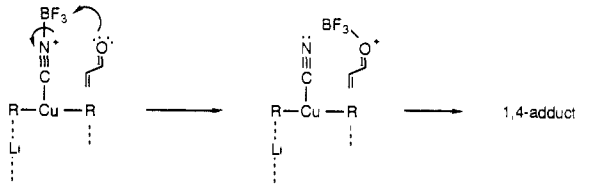
Especially informative data was secured by ^{11}B NMR experiments which shed light not only on the PMR data above but also to the physical location as to some of the BF_3 in the medium. As shown in Figure 2, **6** displays a broad, small signal at δ −1.24, while a stand-alone quartet appears at δ −3.63 (J = 23 Hz). The downfield signal is due to ring opening of THF induced by BF_3, while that at −3.63 ppm *is unequivocally assigned to the Lewis acid on the nitrogen of the nitrile ligand.*[11] With both **7** and **8** the same peaks are present, although with **7** a third signal is observed at −0.54 ppm due to BF_3 complexation of $MeOC(CH_3)_2C{\equiv}C{-}Li$.[8]

These data can be summarized as follows: (1) irrespective of the H.O. cuprate, BF_3 sequesters RLi from the cuprate cluster; (2) with H.O. homocuprates ($R_2Cu(CN)Li_2$), BF_3 rapidly generates an equilibrium as in eq 2; (3) for H.O. mixed cuprates ($RR'Cu(CN)Li_2$), an equilibrium is also established which strongly favors formation of four components, as in eq 3; (4) the BF_3 is

$$R_2Cu(CN)Li_2 + BF_3 \rightleftharpoons RCu(CN)Li + RLi{\cdot}BF_3 \quad (2)$$

$$2RR'Cu(CN)Li_2 + 2BF_3 \rightleftharpoons RCu(CN)Li + R'Li{\cdot}BF_3 + R'Cu(CN)Li + RLi{\cdot}BF_3 \quad (3)$$

situated on the nitrile group as part of the H.O. cuprate.[12] Since the species (in all cases) responsible for the actual chemistry is the H.O. cuprate,[13] a new proposal which accounts for the oftentimes huge increases in reaction rates emerges. That is, rather than as in eq 1, the BF_3 immediately associates (to varying degrees) with the nitrile ligand *within the cuprate* thereby providing strong intra-aggregate activation of the enone, as illustrated below.



In conclusion, with the aid of chemical studies[14] it now seems unlikely that the role of this Lewis acid in accelerating cuprate reactions can be ascribed solely to substrate activation. More definitive information has been gleaned from proton and ^{11}B NMR data on various cuprate/BF_3 solutions. These experiments provide prima facie evidence for cuprate modification *prior to arrival of a substrate* as well as allow for a reasonable alternative explanation of the pronounced effects of $BF_3{\cdot}Et_2O$ on H.O. cuprate reactions.

Acknowledgment. Financial support provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE 87-03757) is gratefully acknowledged.

Supplementary Material Available: Proton NMR spectra for $Me_2Cu(CN)Li_2$, $Me(MeOC(CH_3)_2C{\equiv}C)$-$Cu(CN)Li_2$ (**7**), **7** + $2BF_3{\cdot}Et_2O$, $Me(2\text{-Th})Cu(CN)Li_2$ (**8**), and **8** + $2BF_3{\cdot}Et_2O$ and ^{11}B NMR spectra for **7** + $2BF_3{\cdot}Et_2O$ and **8** + $2BF_3{\cdot}Et_2O$ (4 pages). Ordering information is given on any current masthead page.

(9) Control experiments were conducted to confirm the identity of all of the species arising from the original cuprate solutions upon exposure to $BF_3{\cdot}Et_2O$.

(10) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943. Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1985**, *26*, 5911. See, also: Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098. Hope, H.; Oram, D.; Power, P. P. *J. Am. Chem. Soc.* **1984**, *106*, 1149. Van Koten, G.; Jastrzebski, J. T. B. H.; Muller, F.; Stam, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 697.

(11) Noth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: 1978. Brownstein, S.; Lattremouille, G. *Can. J. Chem.* **1978**, *56*, 2764.

(12) At ca. −75 °C, only a percentage of the nitrile ligand is complexed by BF_3. Upon warming to ca. −55 °C, a significantly greater amount of Lewis acid is irreversibly bound to the CN group, as recooling does not alter the revised (^1H, ^{11}B) NMR spectra.

(13) This seems clear on the basis of (1) comparison data on diastereomer ratios obtained by using the L.O. cyanocuprates plus $BF_3{\cdot}Et_2O$; (2) slightly faster rates of reactions with H.O. versus L.O. cuprates and BF_3 with **1**; (3) ^{11}B NMR spectra of L.O. cyanocuprates and BF_3 which show much less complexation of the Lewis acid with the nitrile ligand.

(14) The role of the crown ether in these reactions is presumably one of enhancing the steric bulk of the reagent via association with the cuprate as the Li^+ adduct. Treatment of $Me_2Cu(CN)Li_2$ with 15-Cr-5 leads to a highly turbid mixture in THF. Addition of BF_3 solubilizes most of the species, the ^{11}B NMR of which is essentially the same as seen with $Me_2Cu(CN)Li_2 + BF_3$. This increase in size would explain the enhanced diastereoselectivity observed.

Antibody Catalysis of Bimolecular Amide Formation†

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The potential for antibodies to accelerate chemical reactions derives from their specific ligand binding function. By designing appropriate substances to be used as haptens, we may elicit antibodies with combining sites that are expedient to enzyme-like activity and specificity.[1] Antibodies to phosphonate esters have been shown to catalyze acyl transfer reactions of carboxylic esters resulting in hydrolysis[2,3] and lactonization.[4]

* Authors to whom correspondence should be addressed.
† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
‡ This is Contribution No. 5326-MB from the Department of Molecular Biology.

(1) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 288. Lerner, R. A.; Tramontano, A. *Sci. Am.* **1988**, *253(3)*, 58–70. Lerner, R. A.; Tramontano, A. *Trends Biochem. Sci.* **1987**, *12*, 427. Tramontano, A.; Janda, K.; Napper, A. D.; Benkovic, S. J.; Lerner, R. A. *Cold Spring Harbor Symp. Quant. Biol.* **1987**, *52*, 91. Schultz, P. G. *Science (Washington, D.C.)* **1988**, *240*, 426.

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