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EFFECTS OF LEWIS ACIDS ON HIGHER ORDER, MIXED CUPRATE COUPLINGS

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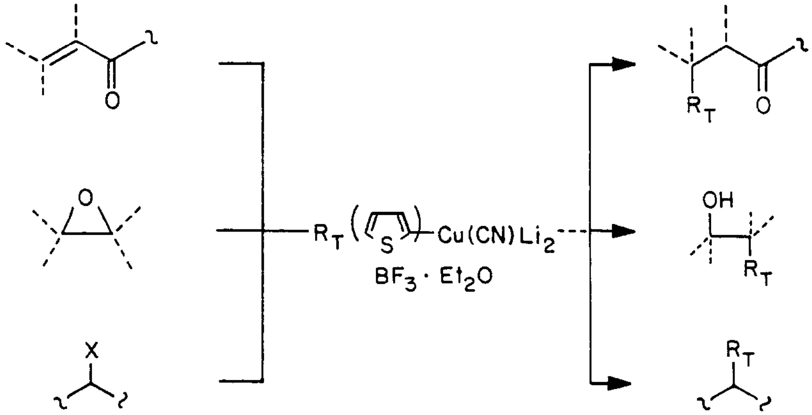
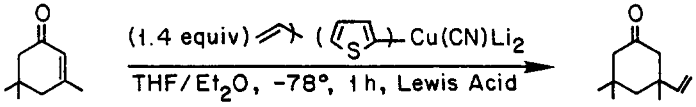
SUMMARY: *The presence of $BF_3 \cdot Et_2O$ in reactions of $R_2Cu(CN)Li_2$ and R_T(2-thienyl)$Cu(CN)Li_2$ with epoxides and α,β-unsaturated ketones leads to dramatic enhancements in reaction rates and/or product yields relative to those observed in the absence of this Lewis Acid.*

In tracing the evolutionary course of organocuprate chemistry, tremendous emphasis has been placed on developing mixed Gilman reagents R_TR_RCuLi, such that only one equivalent of a potentially valuable organolithium species, R_TLi, need to be invested in reagent formation.[2] Unfortunately, cuprate reactivity is usually sacrificed to some degree relative to homocuprates R_2CuLi.[3] During our investigations of the more robust higher order cyanocuprates, $R_2Cu(CN)Li_2$, 1,[4] we recognized the corresponding need for the more highly mixed species $R_TR_RCu(CN)Li_2$, the chemistry of which (with R_R = 2-thienyl) has recently been described.[5] In this report, we present the results of a study on the effects of Lewis Acids on CuCN-derived lithio cuprates.



As shown in Table I, the extent of conjugate addition of a vinyl ligand, under the influence of a Lewis Acid (1 equiv vs enone), to isophorone was monitored under a given set of conditions. Most acids were compatible with the cuprate, however, $TiCl_4$, $ZnCl_2$, and $SnCl_4$ all formed insoluble gums upon addition to R_T(2-thienyl)Cu(CN)Li_2, 2, R_T = vinyl, at -78°C. Only $BF_3 \cdot Et_2O$ afforded the desired cyclohexanone to any significant degree. Trimethylborate was also of no consequence, as was its use essentially as co-solvent.[6]

Table I. Effects of Various Lewis Acids on the Reaction:

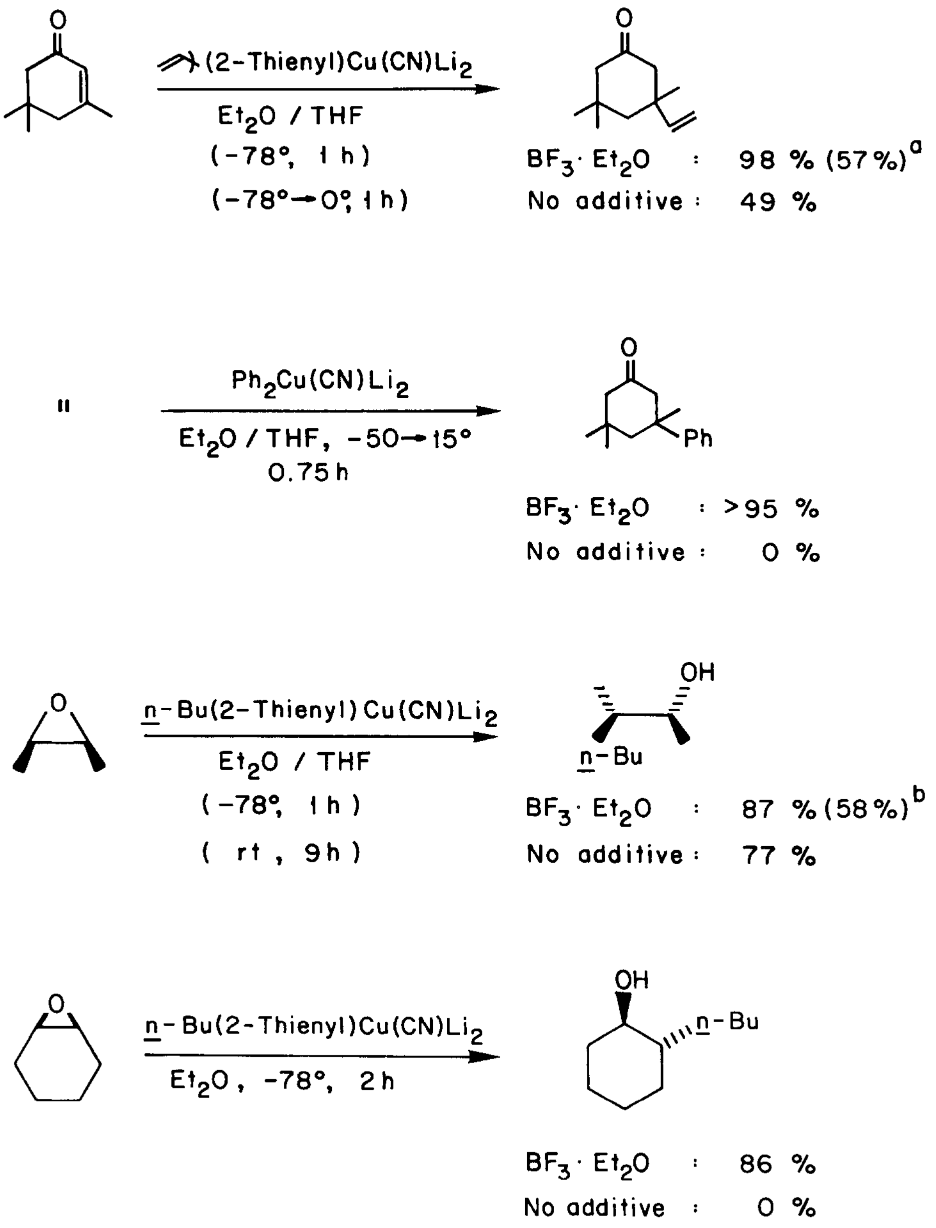


Entry	Lewis Acid	% Product[a,b]
1	none	< 5
2	$EtAlCl_2$	12
3	Et_2AlCl	8
4	$LiClO_4$	0
5	LiBr	4
6	$TiCl_4$	0
7	$Ti(O{-}\langle)_4$	0
8	$ZnCl_2$	0
9	$SnCl_4$	0
10	$BF_3 \cdot Et_2O$	98
11	$B(OCH_3)_3$	1
12	AlF_3	0

[a] By quantitative VPC analysis. [b] In all cases, the remaining mass was starting material.

Considering the dramatic effect of $BF_3 \cdot Et_2O$ (entry 10) compared to the control reaction (entry 1), its potential as an additive was probed in greater detail, which has lead to the following observations: (1) one full equivalent is required, as use of 0.52 equiv afforded a 52% yield of conjugate adduct, while 0.26 equiv gave the ketone to the extent of 28% (by VPC); (2) performing the reaction in 100% THF does not alter the reaction outcome, in spite of the well-known impact of this solvent on reactions of this type; [7,8] (3) the thermal stability of the 2/$BF_3 \cdot Et_2O$ combination appears to be excellent at temperatures below -25°C;[9] (4) utilization of $BF_3 \cdot Et_2O$ provides no advantage in couplings of 2 with secondary halides; (5) following 1,4-addition, all attempts to trap the (presumably) boron enolate with EtI have thus far been unsuccessful.

SCHEME I.



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[a] Yield from reaction of Cu(CN)Li + $BF_3 \cdot Et_2O$; [b] From displacement reaction using n-BuCu(CN)Li + $BF_3 \cdot Et_2O$.

In light of this information, we set out to compare and contrast the reactions of both 1/ and 2/$BF_3 \cdot Et_2O$ on epoxides and enones without the assistance of a Lewis Acid. Scheme I illustrates four representative examples. Most noteworthy is the successful 1,4-addition of a phenyl group to BF_3-activated isophorone. Without $BF_3 \cdot Et_2O$, essentially none of the desired material is formed, only starting material and 1,2-adduct being recovered. In the case of *cis*-2-butene oxide, the difference in rates of reaction is remarkable. Similar findings were noted for cyclohexene oxide, which is oftentimes not well-behaved toward cuprate reagents.[7a,10]

In summary, a general study[11] concerning the influence of Lewis Acids, in particular, on reactions of higher order cuprates has been conducted. It has been found that $BF_3 \cdot Et_2O$, as noted by others,[12,13] stands alone in its ability to compensate for somewhat reduced mixed cuprate reactivity *via* substrate activation (i.e., for oxiranes and enones). The applications of these advances in organometallic chemistry to natural products synthesis[14] will be reported in due course.

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8. We have noted, however, that the initial color changes accompanying introduction of the substrate in Et_2O/THF do not occur in the absence of Et_2O.
9. Above this temperature, the reagent begins to darken and significantly loses its efficacy [e.g., after warming over 30 min to 0°C, 15% ketone (Table I) was formed after adding isophorone].
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