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Remote Asymmetric Induction in Organocopper Conjugate Additions to 3-Ketoacrylates.

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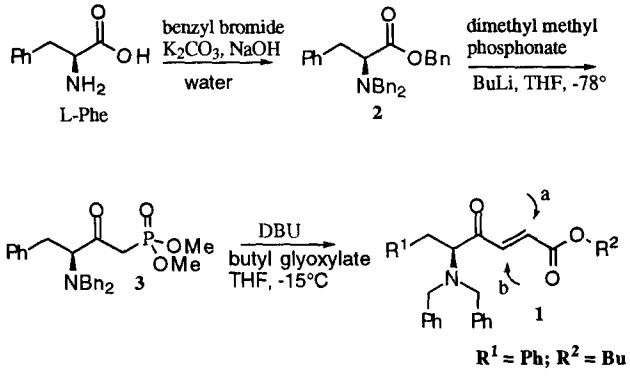
Abstract: Remote asymmetric induction has been achieved in the conjugate addition of organocopper reagents to a novel 3-ketoacrylate system, **1**. Conjugate additions proceed in moderate to good yield and with high regio- and stereoselectivity in the presence of diethylaluminum chloride. Copyright © 1996 Elsevier Science Ltd

Organocopper reagents have been used extensively for effecting conjugate addition reactions to simple activated olefins (*e. g.*, unsaturated ketones and esters).[1] Over the past twenty five years factors including the reduction potential of the substrate, the "order" and nature of the ligands associated with the organocopper/cuprate reagent, the coordinating ability of the solvent and the presence or absence of active Lewis acids have all been shown to exert profound effects on the reactivity and efficiency of these processes.[1,2,7] In contrast, conjugate additions to 1, 2-doubly activated olefins have been studied to a much lesser extent, undoubtedly because of the extra complications associated with formal two electron reductions and, in certain cases, the inability to control regio- and stereoselectivity.[3,7] In this communication, we report that a special class of doubly activated olefins, *i. e.*, chiral, non-racemic 3-ketoacrylates, undergoes highly regio- and stereoselective conjugate addition reactions when exposed to the appropriate combination of a Lewis acid and an organocopper reagent.

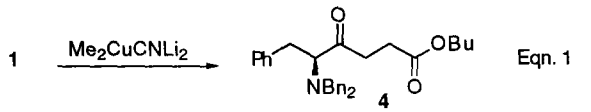
Because of its ready accessibility and the large steric demands exerted by its resident N,N-dibenzylamino group, substrate **1** ((5S)-5-N,N-dibenzylamino-4-oxo-6-phenyl-hex-2-enoic acid, butyl ester) appeared to be an ideal candidate for sorting through the regiochemical and stereochemical issues which arise regarding organocopper conjugate additions to 1,2-doubly activated olefins. We hypothesized that, based on electronic consideratons, 1,4 addition to the "enone" (Path A) would be favored over 1,4 addition to the "enoate" (Path B) (Scheme 1). In addition, we hoped that the bulkiness of the N,N-dibenzylamino group would be sufficient to simultaneously limit the rotamer populations around the hinge bonds adjacent to the carbonyl group and block one face of the "enone" moiety, thereby allowing the addition to take place in a diastereoselective manner. While precedents exist for the successful use of N,N-dibenzylamino groups for controlling the stereoselectivity at adjacent centers[4], much less is known about the extent to which this effect can be extended to more distant sites in substrates. In this regard, perhaps the closest analogy for remote functionalizations is our earlier work on aldol reactions of N,N-dibenzylamino ketones in which we demonstrated that high levels of asymmetric induction could be achieved four carbons away from the chiral center.[5]

Substrate **1** was synthesized in three steps from L-phenylalanine (Scheme 1). Several related compounds have been synthesized by other groups using similar methodology.[6] Tribenzylation of L-phenylalanine in 64 % yield, followed by addition of the lithium anion of dimethyl methylphosphonate produced phosphonate **3** ((3S)-3-N,N-dibenzylamino-2-oxo-4-phenyl-butylphosphonic acid, dimethyl ester) in 81% yield. Subsequent Wadsworth-Emmons condensation of **3** with butyl glyoxylate resulted in desired substrate **1** in 87% yield. Chiral HPLC analysis demonstrated that no racemization occurred during the preparation of substrate **1**.



Scheme 1

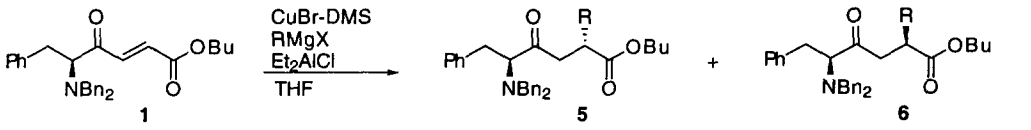
Initially, substrate **1** was exposed to several commonly-used organocopper/cuprate reagents including Me_2CuLi and $Me_2CuCNLi_2$. Clean reduction of the double bond resulted on exposure to $Me_2CuCNLi_2$ (Eqn 1) and **4** was also a major product observed in the more complicated mixture which resulted from exposure to Me_2CuLi. Since substrate **1** is an electron deficient system, we concluded that reduction of the olefin via two electron transfer was reasonable[7] and instead turned our attention to traditionally less reactive organocopper reagents.



We hypothesized that an alkylcopper and substrate **1** might possess the right combination of oxidation and reduction potential respectively to effect conjugate addition. Unfortunately, exposure to several organocopper reagents (RCu) and Lewis acid/organocopper reagent combinations did not lead to any significant quantities of 1, 4 addition product. However, in the presence of diethylaluminum chloride and an organocopper reagent moderate to good yields of highly regioselective (i.e., Path A) conjugate addition products were obtained (Table 1). Moderate yields are partially due to the presence of reduction product **4** in the reaction mixtures. By far, the most intriguing observation was the high levels of regio and stereocontrol that are attainable. These high diastereoselectivites are achievable for both alkyl and aryl substituents. Attempts to add more bulky secondary and tertiary alkyl substituents were unsuccessful or low yielding.

In order to verify the regio- and stereochemistry of **5a-e**, **5a** was reduced to **7a** and cyclized to give crystalline **8a**. An X-ray crystal structure of **8a** confirmed regio and stereochemistry consistent with product **5a**. Reduction of the conjugate addition adducts to the corresponding alcohols proceeds with high diastereoselectivity.[4] The major by-product observed is the corresponding lactones. Lactonization can be completely effected with catalytic glacial acetic acid in refluxing toluene.[8]

Table 1. Organocopper Conjugate Additions with Diethylaluminum chloride



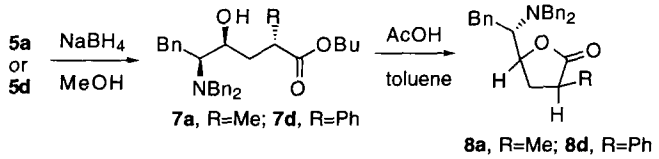
5a, R=Me; **5b**, R=Et; **5c**, R=Bu
5d, R=Ph; **5e**, R=pMeOPh

6a, R=Me; **6b**, R=Et; **6c**, R=Bu
6d, R=Ph; **6e**, R=pMeOPh

Entry	RMgX	Conditions	Isolated %Yield **5a-e**[a]	Ratio **5:6**
1	MeMgBr	A	45 (64)	92:8[b]
2	EtMgBr	A	38 (64)	91:9[c]
3	BuMgCl	B	45 (60)	93:7[c]
4	PhMgBr	C	60 (65)	94:6[c]
5	pMeOPhMgBr	C	37 (47)	92 :8[c]

Conditions: A 1.5 equiv. of "RCu" and Et_2AlCl at -78. B 1.5 equiv. of "RCu" and Et_2AlCl at -90. C 2.0 equiv. of " RCu" and Et_2AlCl at -20. [a]Note that yields in parentheses reflect the isolated yield of **5** plus that amount of **5** estimated by ^1H NMR to be in remaining mixed fractions collected after a single purification. [b] Ratio determined by ^1H NMR anaylsis. [c] Ratio determined by HPLC analysis.

Table 2. Reduction and Lactonization of Conjugate Addition Products



7a, R=Me; **7d**, R=Ph

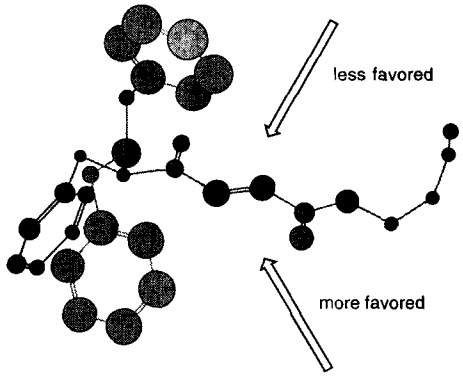
8a, R=Me; **8d**, R=Ph

R	% Yield 7	% Yield 8
Methyl	60	98
Phenyl	75	82

We hypothesize that the diethylaluminum chloride is probably acting as a Lewis acid which activates the "enone" portion of **1** for conjugate addition. In order to gain insight into the mechanism of the reaction and a rationale for the high levels of regio and stereoselectivity observed, an X-ray crystal structure of **1** was obtained (Figure 1).[9] We further hypothesize that in solution one of the benzyl groups of the N,N dibenzyl moiety hinders attack from the the top face of the enone as suggested by the solid state structure. Thus, attack

of the organocopper reagent would be at the electronically more reactive position beta to the enone and on the opposite face of the N,N dibenzyl group.

Figure 1



In conclusion, we have investigated organocopper conjugate additions to a novel substrate and clarified the issues of regio and stereochemistry relevant to this system. The high diastereoselectivities observed at a center remote from the N,N dibenzyl group in an acyclic system are especially intriguing and further studies are in progress on this system. In addition, this methodology may be useful in the future toward the syntheses of posssible protease inhibitors and dipeptide isosteres.

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#. Questions regarding X-ray structures may be addressed to this author.

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9. X-ray structure of **1** was obtained from a racemic sample of **1** as the enantiomerically-pure compound is not crystalline. Hydrogen atoms were omitted from structure for clarity.

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