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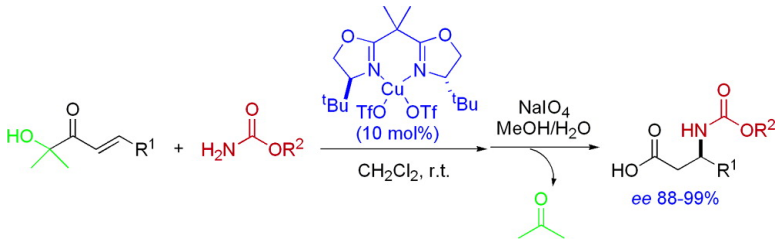

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Catalytic Enantioselective Conjugate Addition of Carbamates

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Interest in the synthesis of optically active β-amino acids[1] arises due to their presence in a variety of natural products,[2] including β-lactams,[3] and because of the promise shown by β-peptides as biostable peptidomimetics.[4] While the Mannich-type reaction between azomethines and enolates is a powerful method for constructing this functionality,[5] the conjugate addition of amines and their synthetic equivalents to α,β-unsaturated carbonyls constitutes another practical, direct, and flexible strategy toward this goal.[1,6] Recent advances in this direction include the conjugate addition of amines,[7] aldoximes,[8] and masked forms of ammonia such us hydrazoic acid,[9] trimethylsilyl azide,[10] and hydroxylamines[11] promoted by catalytic quantities of certain chiral metal complexes[7−11] and even simple peptides.[9] Catalytic activation of α,β-unsaturated carbonyls toward reaction with weaker nitrogen nucleophiles such as carbamates has, however, proven to be more difficult, and indeed it was only very recently that this reaction could be realized catalytically through the use of certain Brønsted[12] and Lewis acids.[13] While these recent methods directly afforded useful N-protected β-amino carbonyl adducts, asymmetric variants of this reaction, which are of potentially great practical importance, have until now remained elusive. Here we report the first highly enantioselective conjugate addition reactions of carbamates to enones catalyzed by chiral Lewis acids.

It has been postulated that a major obstacle to the development of Lewis acid-catalyzed enantioselective conjugate additions of carbamates is the possibility for alternative nonselective pathways to be catalyzed by Brønsted acids (protons) resulting from hydrolysis of Lewis acids in reaction media.[14] We surmised that one way of minimizing these competing pathways might be to use chelating α,β-unsaturated carbonyl templates capable of preferentially coordinating to oxophilic metal centers rather than protons.[15] We recently hypothesized that α'-hydroxy enones coordinate to Lewis acids (i.e., Evans bis-(oxazoline)−copper complexes) in a very efficient manner, probably through a 1,4-metal binding pattern, and successfully applied this principle to enantioselective Diels−Alder reactions.[16] Accordingly, it was expected that this sytem might be equally effective in the context of asymmetric conjugate addition reactions of carbamates.

Initial screening reactions carried out with α'-hydroxy enone **1a** and benzyl carbamate **2** in the presence of 10 mol % of several chiral Lewis acids, Table 1, revealed that using catalyst **9** β-amino-protected carbonyl adduct **11a** was indeed formed in an impressive 86% isolated yield and, most notably, with 96% ee. Significant changes were not observed with catalyst **10**, but catalysts **6**−**8** were found to be less efficient in terms of either reactivity or enantioselectivity.

Table 2 shows that reacting carbamate **2** (2 mol equiv) with a variety of β-alkyl-substituted α'-hydroxy enones (bearing both linear and branched aliphatic chains) in the presence of 10 mol % catalyst **9** affords the corresponding N-protected β-amino carbonyls **11** in regularly high yields and excellent enantioselectivities. Other alkyl carbamates such as **3**−**5** were also reactive under these conditions, and indeed when *tert*-butyl carbamate **3** was used, the Boc-protected adducts were produced after considerably shorter reaction times and the yields even increased slightly. Reactions were generally carried out at ambient temperature in methylene chloride,[17] although for enone **1g**, which bears the bulky *tert*-butyl group, refluxing conditions were required. Interestingly, no detrimental effect on enantioselectivity was observed in this instance. Unfortunately, enones bearing β-aryl substituents proved to be unreactive even under forcing conditions.[18]

To assess the key role played by the achiral template in these reactions, complementary assays using enoyl derivatives **15** and **16**, two typical substrates used in enantioselective conjugate addition reactions, were performed. While enone **1c** reacted with benzylcarbamate **2** in the presence of catalyst **9** to provide **11c** in 83%

Table 1. Reaction of α'-Hydroxy Enone **1a** [$R^1 = PhCH_2CH_2$] with Benzylcarbamate **2** Promoted by Representative Bis(oxazoline)−Metal Complexes

				product **11a**	
catalyst	R	MX_n	time, h	yield, %[a]	ee, %[b]
6	^{t}Bu	$Mg(OTf)_2$	144	no reaction[c]	
7	^{t}Bu	$Zn(OTf)_2$	144	no reaction[c]	
8	Ph	$Cu(OTf)_2$	72	49[d]	83
9	^{t}Bu	$Cu(OTf)_2$	72	86	96
10			40	90	98

[a] Isolated yield after column chromatography. [b]Determined by HPLC. [c]Starting material recovered. [d]Not optimized.

Table 2. Enantioselective Conjugate Addition of Carbamates to α'-Hydroxy Enones **1** Catalyzed by Complex **9**[a]

compd **1**	R^1	carbamate	time (h)	product	yield (%)[b]	ee (%)[c]
a	$Ph(CH_2)_2$	**2**	71	**11a**	86	96
		3	18	**12a**	92	88
		4	118	**13a**	51[d]	99
		5	142	**14a**	74	96
b	$CH_3(CH_2)_5$	**2**	62	**11b**	66	92
		3	18	**12b**	76	96
c	CH_3CH_2	**2**	66	**11c**	83	96
d	$(CH_3)_2CHCH_2$	**2**	68	**11d**	71	96
		3	22	**12d**	87	98
e	$(CH_3)_2CH$	**2**[e]	67	**11e**	53	98
f	*c*-C_6H_{11}	**2**[e]	96	**11f**	57	94
		3	100	**12f**	85	91
g	$(CH_3)_3C$	**2**[f]	96	**11g**	65	94

[a] Reactions performed on a 2 mmol scale with a ratio of **1**:carbamate:**9** = 1:2:0.1. [b]Isolated yield after column chromatography. [c]Determined by HPLC using Chiralpak AD, AS, and Chiralcell OD columns (see Supporting Information for details). [d]Volatile compound. [e]Performed with 20 mol % catalyst. [f]Reaction carried out at refluxing conditions.

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Scheme 1. Chemical Elaboration of Adducts onto Optically Pure N-Protected β-Amino Acids

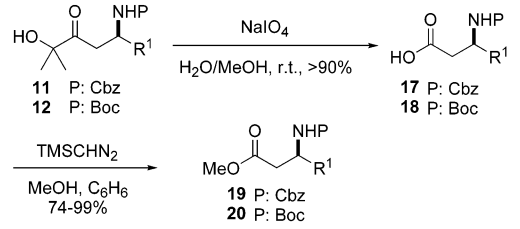
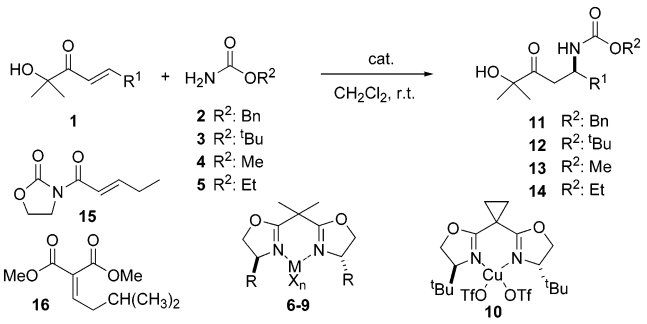


Chart 1



yield and 96% ee, *N*-enoyl oxazolidinone **15** proved to be totally unreactive. The alkyledene malonate **16** was more reactive, and under the above conditions the corresponding addition product could be obtained in 80%, albeit in racemic form.

The excellent enantioselectivity observed in these reactions is of particular interest in that it provides, through oxidative cleavage of the acyloin moiety, optically pure N-protected β-alkyl-β-amino acids. For example, treatment of Cbz adducts **11a** and **11d** with sodium metaperiodate in a methanol−water mixture afforded **17a** and **17d** in 96 and 91% yields, respectively. Similarly, treatment of the Boc adducts **12a** and **12d** under the same conditions afforded acids **18a** and **18d** in 99 and 92% yields. Of considerable practical importance is the fact that these transformations yield acetone as the only byproduct. The absolute configuration of acid **17d** and of the methyl ester derivatives **19d**, **20a**, and **20d** was determined by comparison of the optical rotations with published values and by chemical correlation.[19] The configuration for the remaining adducts was assigned by analogy.

In conclusion, we have demonstrated for the first time that asymmetric catalytic conjugate addition of carbamates with high enantiocontrol is feasible. In particular, chiral bis(oxazoline)copper complexes catalyze the addition reaction of carbamates and α'-hydroxy enones to yield products with ees uniformly above 92%.[20] Further work to expand this catalytic system to other asymmetric reactions is under investigation.

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Supporting Information Available: Complete experimental procedures, determination of stereoisomeric mixtures, ^{1}H and ^{13}C spectra, and HPLC chromatograms (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In acetonitrile, which is the solvent of choice for Cu(II)-catalyzed conjugate additions of carbamates (see ref 13b), the asymmetric reaction did not proceed. THF was also found to be ineffective (<5% conversion after 2 days). Diethyl ether generally showed results comparable to those attained in methylene chloride, although in certain instances the enantioselectivity was essentially perfect (for example, product **11a** 92% yield, ≥99% ee; **11b**, 95% yield, ≥99% ee).
(18) For problems inherent to the conjugate addition of N-nucleophiles to β-aryl enoyl systems, and a solution to them, see: ref 11c. Also see: ref 11e−g.
(19) See Supporting Information for details.
(20) At the present stage, proposals for consistent catalytic cycle and transition-state models seem premature. One reviewer has suggested an eight-membered transition state involving copper coordination.

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