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Catalytic Enantioselective Synthesis of Quaternary All-Carbon Stereogenic Centers. Preparation of α,α′-Disubstituted β,γ-Unsaturated Esters through Cu-Catalyzed Asymmetric Allylic Alkylations

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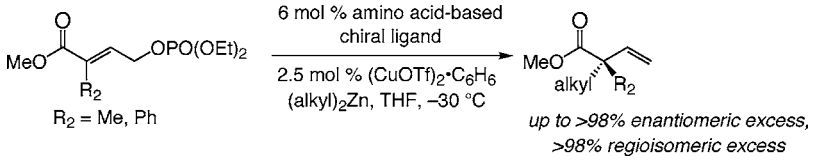
ABSTRACT



Peptide-based chiral ligands, readily prepared from commercially available materials, are used to promote Cu-catalyzed asymmetric allylic alkylations of α,β-unsaturated esters bearing a γ-phosphate with various alkylzinc reagents. These transformations lead to the formation of α,α′-dialkyl-β,γ-unsaturated esters in high yields as well as high regio- (re) and enantioselectivities (ee).

Development of efficient protocols for catalytic enantioselective synthesis of quaternary all-carbon stereogenic centers is an important and challenging goal in modern organic synthesis.[1] A related class of transformations that are of particular synthetic utility includes reactions that generate a quaternary carbon stereogenic site adjacent to a carbonyl group. A number of studies in the past few years have aimed to provide solutions to this problem. Among strategies[2] that have resulted from such efforts are those involving Pd-catalyzed arylations,[3] allylations,[4] Heck reactions[5] and carbonylations,[6] metallocene-catalyzed acylations,[7] Cr-catalyzed alkylations,[8] and Rh-,[9] Pd-,[10] and La-catalyzed[11] conjugate additions.

All of the above approaches involve addition of a metal enolate to a carbon electrophile,[12] and *cyclic* metal enolates are employed in nearly all instances. An alternative approach

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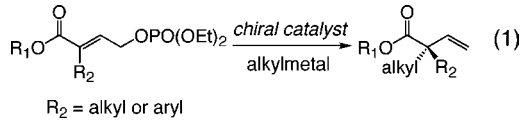
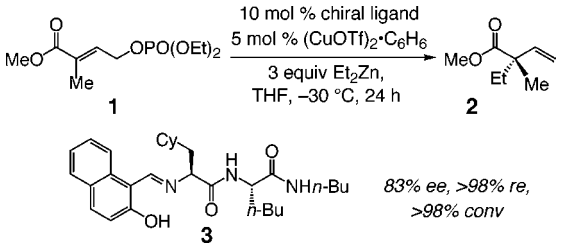
that involves a carbonyl-containing electrophile and would deliver the alkyl group as a nucleophile is illustrated in eq 1.[13] Catalytic asymmetric allylic alkylation[14,15] of α,β-unsaturated esters, bearing a trisubstituted olefin and a leaving group at the γ position, may afford the desired all-carbon stereogenic center in the optically enriched or pure form. Importantly, this strategy provides access to optically enriched *acyclic* products that can be easily modified in a variety of ways as a result of the presence of the carboxylic ester and the terminal olefin. Herein, we disclose the results of our studies toward the development of the catalytic asymmetric protocol summarized in eq 1.



We initiated our studies by investigating the feasibility of the proposed catalytic asymmetric alkylation under the conditions outlined recently by us for enantioselective additions of alkylzincs to the derived allylic phosphates bearing a disubstituted olefin (R_2 = H in eq 1). As illustrated in Scheme 1, we established that in the presence of 10 mol

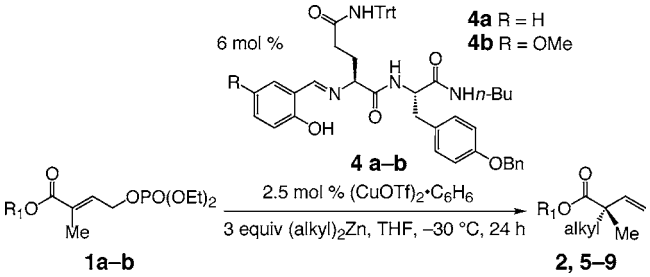
Scheme 1. Initial Studies on Cu-Catalyzed Allylic Alkylations



% of dipeptide Schiff base **3** and 5 mol % of $(CuOTf)_2$•C_6H_6 unsaturated ester **1** undergoes efficient alkylation (>98% conv) to afford **2**, bearing the desired quaternary all-carbon stereogenic center, in 83% ee and >98% re (regioisomeric excess; S_N2'/S_N2).

Next, to identify a more efficient and selective catalyst, we carried out ligand screening studies, taking advantage of the facile modularity[16] of the peptide-based class of chiral Schiff bases. Approximately 90 ligand candidates were synthesized on solid support,[17] cleaved, and tested for their ability to promote the Cu-catalyzed enantioselective alkylation depicted in Scheme 1. These investigations led us to identify **4a** and **4b** as the more attractive alternatives to **3**. Thus, as illustrated in entries 1−2 of Table 1, Cu-catalyzed

Table 1. Enantioselective Cu-Catalyzed Allylic Alkylations



entry	R_1		$(alkyl)_2Zn$	ligand	prod	yield[a] (%)	re[b] (%)	ee[c] (%)
1	Me	**1a**	Et_2Zn	**4a**	**2**	52[d]	>98	90
2	Me	**1a**	Et_2Zn	**4b**	**2**	43[d]	>98	87
3	Me	**1a**	$[Me_2CH(CH_2)_3]_2Zn$	**4a**	**5**	80	>98	88
4	Me	**1a**	$[AcO(CH_2)_4]_2Zn$	**4a**	**6**	78	60	77
5	Me	**1a**	$[AcO(CH_2)_4]_2Zn$	**4b**	**6**	78	78	77
6	Me	**1a**	i-Pr_2Zn	**4a**	**7**	90	80	46
7	*t*-Bu	**1b**	Et_2Zn	**4a**	**8**	79	>98	>98
8	*t*-Bu	**1b**	$[AcO(CH_2)_4]_2Zn$	**4b**	**9**	77	>98	83

[a] Isolated yields after silica gel chromatography; all reactions proceeded to >98% conversion. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra. [c] Determined by chiral GLC analysis of the derived carboxylic acid (β-Dex column for entries 1−3 and 7) or conversion to the derived MPTA ester followed by 400 MHz ^{1}H NMR analysis. [d] Low yields due to product volatility.

asymmetric alkylation of **1** with Et_2Zn in the presence of **4a** and **4b** leads to the formation of **2** in 90% and 87% ee, respectively (>98% conversion and re with both chiral ligands).

Additional data regarding Cu-catalyzed enantioselective allylic alkylations of methyl ester **1a** and *tert*-butyl ester **1b** are summarized in Table 1. Several features of these data

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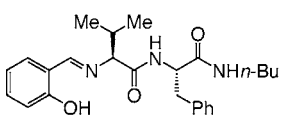
(17) See the Supporting Information for details.

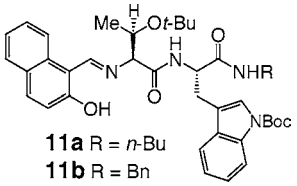
are noteworthy: (i) Catalytic alkylations are not limited to reactions of Et_2Zn and can be efficiently carried out in the presence of the more sterically hindered alkylmetals (entries 3−6 and 8) or those that bear heteroatom substituents (entries 4, 5 and 8). However, as the example in entry 6 indicates, addition with a secondary alkylzinc reagent leads to the formation of the desired product with lower optical purity. (ii) Comparison of entries 1 with 7 and 4 with 8 indicates that catalytic alkylations are more enantioselective with the sterically bulky *tert*-butyl ester **1b**. (iii) Overall, chiral ligands **4a** and **4b** should together be considered as optimal. In certain cases, **4a** delivers a more selective transformation (compare entries 1 and 2), but there are also instances, as exemplified by the outcome of reactions in entries 4 and 5, that **4b** is the superior chiral ligand (78% vs 60% re with 77% ee in both cases).

The Cu-catalyzed asymmetric reactions described above allow access to all-carbon quaternary stereogenic centers that bear alkyl substituents (in addition to the carboxylic ester and the newly generated vinyl group). Due to the significance of corresponding aryl-containing compounds in the enantioselective synthesis of biologically active molecules (see Scheme 2 for an example), we set out to investigate the feasibility of applying the present protocol to the asymmetric synthesis of this class of molecules. Our attempts to identify conditions that lead to efficient catalytic asymmetric additions of Ph_2Zn resulted only in low conversions (<30% conversion after 24 h) and enantioselectivities.

An alternative approach to the synthesis of the corresponding aryl-containing compounds would involve catalytic asymmetric alkylation of aryl-substituted substrates, such as **12a** (see Table 2). Initial studies indicated that addition of Et_2Zn in the presence of 10 mol % of chiral ligand **4a** (5 mol % of $(CuOTf)_2{\cdot}C_6H_6$ at −15 °C) leads to 52% conversion after 24 h to afford **13** in 23% ee and 60% re. Reaction with ligand **3** proved to be more facile (>98% conversion) but equally nonselective (29% ee and <2% re). However, since the same transformation in the presence of ligand **10** proceeds to 92% conv after 24 h and affords **13** in 48% ee and >98% re, we initiated a ligand screening study in search of an effective ligand for Cu-catalyzed alkylations of **12a**.



10

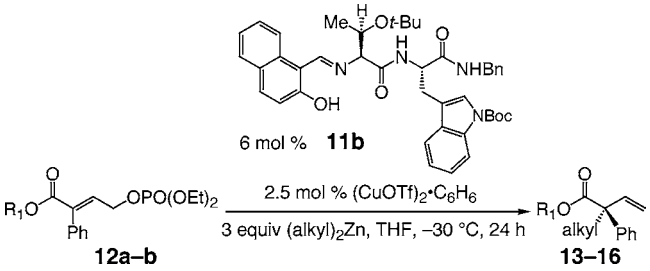


11a R = *n*-Bu
11b R = Bn

Screening studies (involving ∼90 candidates) led us to establish that in the presence of dipeptide **11a**, β,γ-unsaturated ester **13** can be obtained efficiently (>98% conversion in 24 h) and in 79% ee and >98% re. To improve enantioselectivity, and based on recent observations regarding the effect of the amide terminus on asymmetric induction, we examined the catalytic activity of a dozen chiral dipeptides[17] related to **11a** but with altered secondary amide groups. These studies pointed to benzyl amide **11b** as the most optimal.[18] Thus, as illustrated in entry 1 of Table 2, in the presence of 6 mol % of **11b** and 2.5 mol % of the Cu(I) triflate salt, alkylation of **12a** with Et_2Zn proceeds to >98% conversion in 24 h to afford **13** in >98% re and 86% ee. In a similar fashion, as shown in entry 2 of Table 2, **14** is obtained in >98% re and 94% ee. Catalytic asymmetric alkylations of *tert*-butyl ester **12b** is more sluggish but affords the desired products in >98% re. In contrast to reactions of methyl-substituted olefin **1b** (vs **1a**), reactions of the more sterically hindered **12b** are somewhat less enantioselective than reactions of methyl ester **12a**.

It is important to note that ligand **11b** is significantly less effective ligand than **4a**,**b** in Cu-catalyzed enantioselective additions to **1a**; as an example, in the presence of 6 mol % of **11b** methyl ester **2** is formed in only 31% ee (>98% re, >98% conversion after 24 h at −30 °C). Moreover, catalytic alkylations of **1a**,**b** with a chiral dipeptide bearing a benzyl amide terminus that is derived from **4a** does not lead to improved enantioselection; conversion of **1a** to **2** in the presence of such a ligand (under conditions shown in Table 1) leads to isolation of the desired product in 77% ee (vs 90% with **4a** and 87% with **4b**). Such variations in the identity of the optimal ligand should not come as a surprise. Change of substrate structure, in which a smaller Me group has been exchanged for a larger Ph unit, may well be expected to require an altered chiral pocket for effective asymmetric induction. The versatility of the amino acid-based chiral ligands is partly because the structure of the catalyst can be adjusted so that high selectivity can be achieved even

Table 2. Enantioselective Cu-Catalyzed Allylic Alkylations of Olefins Bearing a Phenyl Substituent



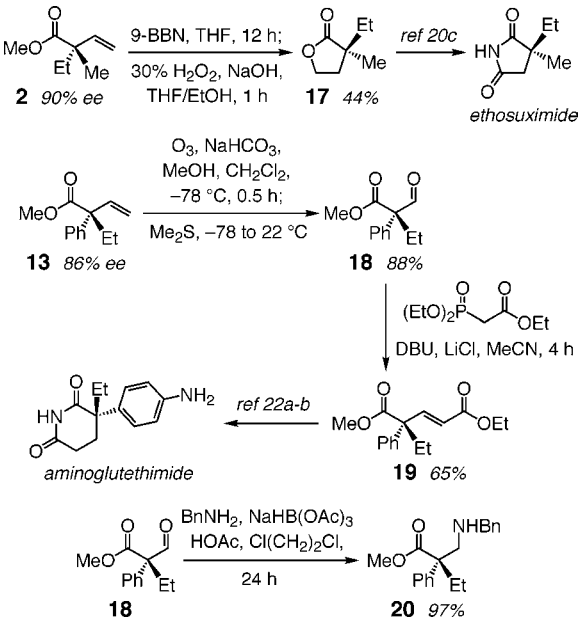
12a–b **13–16**

entry	R_1		$(alkyl)_2Zn$	product	yield[a] (%)	re[b] (%)	ee[c] (%)
1	Me	**12a**	Et_2Zn	**13**	95	>98	86
2	Me	**12a**	Me_2Zn	**14**	85	>98	94
3	*t*-Bu	**12b**	Et_2Zn	**15**	80	>98	79
4	*t*-Bu	**12b**	Me_2Zn	**16**	87[d]	>98	89

[a] Isolated yields after silica gel chromatography; all reactions proceeded to >98% conversion. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra. [c] Determined by chiral GLC (Chiraldex-GTA column for entry 1) or chiral HPLC (Chiralcel OJ column for entries 2−4). Reaction carried out with 12 mol % of **11b** and 5 mol % of Cu salt at −15 °C.

(18) For other instances, where modification of the amide terminus of an amino acid-based ligand has resulted in significant improvements in enantioselectivity of metal-catalyzed reactions, see: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019. (b) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829−2832.

Scheme 2. Representative Applications of the Cu-Catalyzed Enantioselective Method to the Preparation of Biologically Active Molecules



with substrates that present different steric challenges.[19] Thus, if high selectivities and yields are to be obtained with different classes of substrates, a (small) collection—rather than a single optimal catalyst—might be required. This scenario may be viewed as superior to one where a single chiral catalyst is available but selectivities vary widely and are at times not at synthetically useful levels.

As was mentioned above, the products of the asymmetric Cu-catalyzed alkylation can be easily manipulated en route to the synthesis of a range of biologically active molecules that bear quaternary carbon stereogenic centers. Several representative examples are illustrated in Scheme 2. Hydroboration of optically enriched **2** leads to the formation of lactone **17**, which has been converted to ethosuximide.[20] Alternatively, conversion of **13** to optically enriched aldehyde **18**, followed by a routine olefination affords unsaturated diester **19**, which has been converted to aminoglutethimide AG,[21] a highly efficient aromatase inhibitor that has been used effectively against breast cancer in post-menopausal women.[22] Conversion of **18** to **20** underlines the utility of the products obtained through the present protocol to the synthesis of optically enriched β-amino acids that bear an all-carbon quaternary center.[23]

In summary, we disclose an efficient Cu-catalyzed protocol for the preparation of acyclic β,γ-unsaturated esters that bear an all-carbon quaternary stereogenic center α to the carbonyl group. We demonstrate that the presence of the ester and olefin functional groups present a large number of possibilities for functionalization of the optically enriched products (including conversion to various heterocycles). The present protocol thus allows access to versatile nonracemic chiral molecules that should find utility in organic synthesis and cannot be readily prepared by alternative methods.

Future studies will focus on development of other catalytic alkylation reactions that generate quaternary carbon stereogenic centers as well as those that utilize alternative alkylmetal reagents.

Acknowledgment. This paper is fondly dedicated to the memory of the late Professor Murray Goodman, a pioneer in the field of peptide chemistry. Financial support was generously provided by the NIH (GM-47480).

Supporting Information Available: Experimental and analytical data for substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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