Asymmetric Catalysis

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Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu–Peptide Complexes**

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In recent years, a considerable amount of effort has been expended on the development of catalytic methods for asymmetric conjugate additions (ACA) of alkyl metal reagents to unsaturated carbonyls.[1] Research in these laboratories has led us to identify amino acid based phosphanes, such as **1**–**3** (Scheme 1), as chiral ligands for use in Cu-

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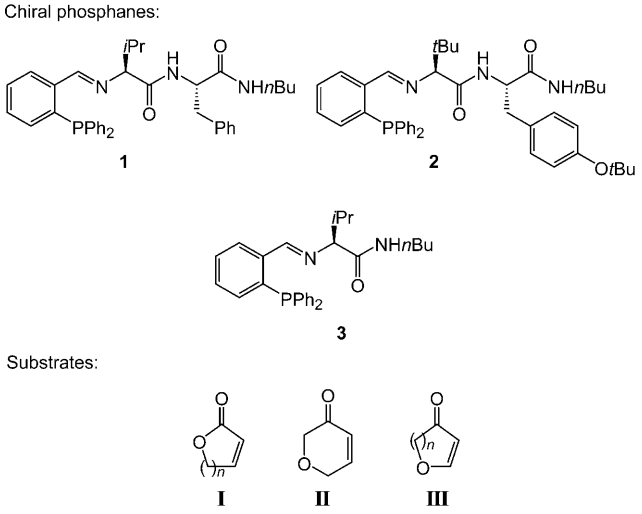


Scheme 1. Chiral amino acid based phosphanes used for Cu-catalyzed asymmetric conjugate additions (ACA) to various heterocyclic enones.

catalyzed ACA processes involving dialkylzinc reagents.[2] However, the majority of investigations have focused on transformations of unsaturated ketones;[2,3] more recently, a number of studies have involved Cu-catalyzed ACA of nitroalkenes.[4]

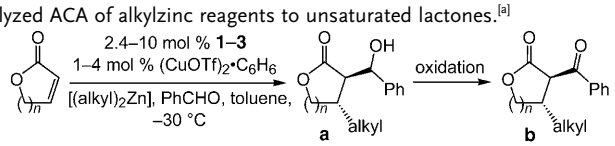
Catalytic ACA reactions of the less reactive cyclic or acyclic unsaturated carboxylic esters (e.g., **I**, Scheme 1) have received far less attention.[5] A number of studies have addressed the problem of catalytic additions of dialkylzinc reagents to unsaturated lactones.[6–8] In spite of high enantioselectivities (>90% *ee*) in select instances, the above disclosures address only reactions of one or two substrates (**I**, $n=1$ or 2) or nucleophiles (typically [Et_2Zn]; less frequently [Me_2Zn]). Due to complications that will be clarified later, in a number of cases, isolated yields are not indicated (only % conversion disclosed).[6a,b,d] In addition, two reports provide examples of Cu-catalyzed ACA of Grignard reagents to lactones (**I**, $n=2$);[9a–b] in one disclosure,[9a] high catalyst loading is required (32 mol%; 5–92% *ee*) and the other[9b] offers only a single example (82% *ee*). To the best of our knowledge, a report regarding catalytic ACA of an alkyl metal reagent to substrate types **II** or **III** (Scheme 1) has not appeared.

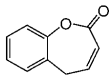
Herein, we disclose the first effective and general protocol for catalytic ACA of dialkylzinc reagents to unsaturated furanones and pyranones of varying steric and electronic properties (i.e., **I**–**III**, Scheme 1). Enantioselective additions proceed in the presence of optically pure phosphanes **1**–**3** to afford the desired products in high isolated yield and in up to >98% *ee*. We report the synthesis of catalytically active Cu^I–peptide complexes that are air stable, can be prepared from commercially available Cu salts and utilized after storage for at least a week.

Phosphanes **1**–**3** can be used to effect efficient and enantioselective ACA of alkylzinc reagents to small and medium ring unsaturated lactones (Table 1). A variety of dialkylzinc reagents, including the sterically demanding [$(i\text{Pr})_2Zn$] (entries 2 and 5) as well as the less reactive [Me_2Zn] can be employed (entries 3 and 7). To obtain high yield, reactions must be carried out in the presence of an aldehyde;[10] this is presumably due to adventitious ketene formation or intermolecular Michael addition if the enolate intermediate is not trapped in situ. The resulting aldol adduct can be oxidized to afford the corresponding diketone (>98% *anti*), or, as represented by the formation of **15** and **16** (Scheme 2), converted to the derived optically enriched β-alkyl carbonyl by an efficient retro-aldol process.

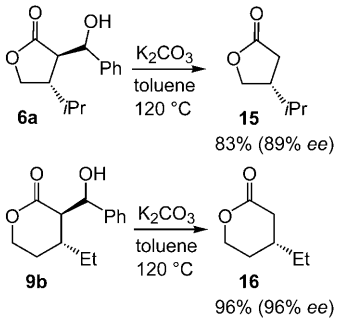
This phase of our studies pointed to a chiral ligand hierarchy: First, the simplest phosphane **3** was examined; in cases where ACA was sluggish, the more potent **1** was utilized (e.g., <10% conversion with 10 mol% **3** vs. >98% conversion with **1** in entry 7). Chiral phosphane **2** was employed when ACA products from reactions with **1** were judged not to

Table 1: Cu-catalyzed ACA of alkylzinc reagents to unsaturated lactones.[a]



Entry	Substrate		[(alkyl)$_2$Zn]	Ligand (mol%)	mol% Cu salt	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1		4	[Et_2Zn]	**2** (10)	4	**5b**	48	67	97
2			[$(i\text{Pr})_2Zn$]	**1** (10)	4	**6b**	48	85	89
3[d]		7	[Me_2Zn]	**1** (10)	4	**8b**	48	40	>98
4			[Et_2Zn]	**3** (2.4)	1	**9b**	6	90	96
5			[$(i\text{Pr})_2Zn$]	**2** (2.4)	1	**10b**	12	91	90
6			[{$Me_2CH(CH_2)_3$}$_2$Zn]	**3** (2.4)	1	**11b**	12	78	96
7		12	[Me_2Zn]	**1** (10)	4	**13b**	12	66	98
8			[Et_2Zn]	**3** (10)	4	**14b**	6	84	94

[a] Reactions were carried out under N_2. Oxidation step: PCC (pyridinium chlorochromate; 2.1 equiv), NaOAc, celite, 4-Å molecular sieves, CH_2Cl_2; products **a** are obtained in 0–60% *de*; see the Supporting Information for details. [b] >98% conversion in all cases, except entry 3 (65–70%); conversion determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified products. Isolated yields for the ACA/aldol addition step; isolated yields for oxidations are >85%. [c] Determined by chiral HPLC analysis; see the Supporting Information for details. [d] Reaction was carried out at −15 °C.

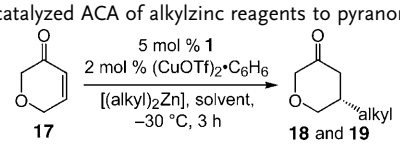


Scheme 2. Unmasking of ACA products.

be of sufficient optical purity (e.g., **5b** formed in 84% *ee* in the presence of ligand **1** vs. 97% *ee* with phosphane **2**).

As illustrated in entries 1 and 4 of Table 2, under conditions identical to those used for reactions of lactones (see Table 1), Cu-catalyzed ACA of pyranone **17** proceed to

Table 2: Cu-catalyzed ACA of alkylzinc reagents to pyranone **17**.[a]



17 **18** and **19**

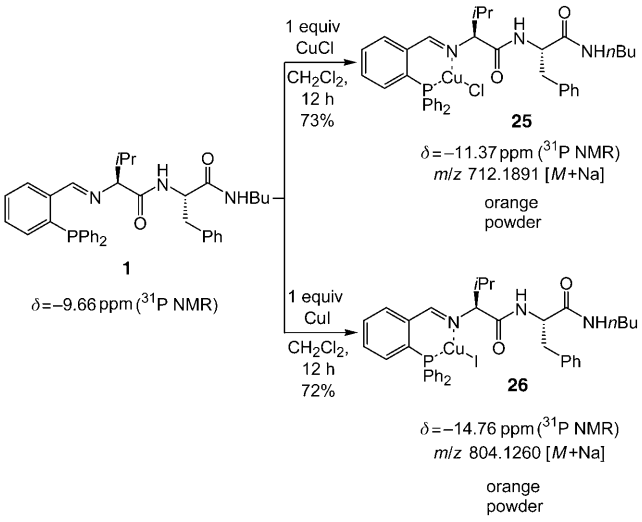
Entry	[(alkyl)$_2$Zn]	Solvent	Product	Yield [%][b]	*ee* [%][c]
1	[Et$_2$Zn]	toluene	**18**	n.d.	64
2	[Et$_2$Zn]	Et$_2$O	**18**	n.d.	72
3	[Et$_2$Zn]	THF	**18**	66	98
4	[Me$_2$Zn]	toluene	**19**	n.d.	56
5	[Me$_2$Zn]	THF	**19**	58	>98

[a] Reactions were carried out under N_2. [b] Isolated yields after silica gel chromatography. [c] All enantioselectivities determined by chiral GLC analysis; see the Supporting Information for details. n.d. = not determined.

>98% conversion but with inferior enantioselectivity (64% and 56% *ee*). We surmised that the diminished asymmetric induction might be due to the neighboring Lewis basic oxygen atom directing the enantioselective addition of an alkyl–copper complex to the electronically activated ketone.[11] Accordingly, we examined the effect of coordinating solvents to disrupt the purported O→Cu chelation. As illustrated in entries 3 and 5 of Table 2, when the catalytic ACA are performed in THF **18** and **19** are generated in ≥98% *ee*; as shown in entry 2, the less Lewis basic Et$_2$O does not have as pronounced an effect. Remarkably, in the case of the more electron rich unsaturated lactones (Table 1), there is <2% conversion when THF is used as the solvent.

Next, we turned our attention to the least electrophilic class of ACA substrates (**III**, Scheme 1). As the data summarized in Table 3 indicate, amino acid based chiral phosphanes are effective with this group of heterocyclic enones: ACA products are formed efficiently in ≥98% *ee*. As was the case with transformations involving unsaturated lactones, the presence of an aldehyde trap is required (to circumvent β elimination or intermolecular Michael addition). A similar ligand hierarchy, as mentioned for studies summarized in Table 1, holds here as well. Unlike reactions in Table 1, the products **a** of the three-component asymmetric process, are generated in high diastereoselectivity (80 to >98% *de*), and, as with transformations in Table 1, can be converted to ACA products **b** in high yield (Table 3).

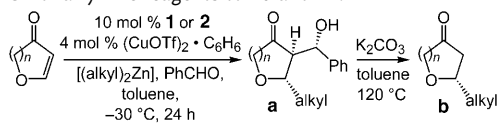
With an effective protocol for ACA of alkylzinc reagents to substrate classes **I**–**III** in hand, we focused our efforts on gaining insight regarding the nature of the chiral Cu complex. In this context, our efforts to synthesize and isolate a complex derived from a peptide phosphane and (CuOTf)$_2$·C$_6$H$_6$ was unsuccessful (presumably due to sensitivity of the Cu–triflate complexes). However, as depicted in Scheme 3, we have been



Scheme 3. Preparation of air-stable chiral Cu complexes **25** and **26**.

able to prepare the complexes derived from reaction of phosphane **1** with CuCl and CuI. Thus, treatment of unpurified commercial samples of CuCl and CuI with **1** at ambient temperature results in the formation of orange powders. These air-stable Cu complexes,[5c] for which we propose structures **25** and **26**, have been characterized spectroscopically (Scheme 3).[12] As the representative data summarized in Table 4 illustrate, not only are **25** and **26** effective ACA catalysts (entries 2 and 4), these chiral Cu complexes deliver improved enantioselectivity compared to when catalysts are prepared in situ (entries 1 and 3, Table 4). Higher catalyst loading (8 vs. 2 mol% in Table 1) is needed for reactions promoted by **25** and **26** (vs. **1**–**3**), likely due to lower activity of metal halide versus triflate complexes. Complex **25** is less stable than iodide **26**; whereas a week-old sample of **26** (stored in

Table 3: Cu-catalyzed ACA of alkylzinc reagents to **20** and **22**.[a]



Entry	Substrate		[(alkyl)$_2$Zn]	Ligand	Product	Conv. [%][b]	Yield [%][c]	*ee* [%][d]	*de* [%][e]	Product	Yield [%][c]
1		**20**	[Et$_2$Zn]	**1**	**21a**	>98	68	>98	>98	**21b**	74
2		**22**	[Et$_2$Zn]	**2**	**23a**	80	63	>98	80	**23b**	92
3			[(*i*Pr)$_2$Zn]	**2**	**24a**	71	54	98	80	**24b**	84

[a] Reactions were carried out under N_2. [b] Conversion determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified products. [c] Isolated yields after silica gel chromatography. [d] Enantioselectivities determined by chiral GLC or HPLC analysis; see the Supporting Information for details. [e] See the Supporting Information for stereochemical assignments.

Table 4: Representative ACA catalyzed by **25** and **26**.[a]

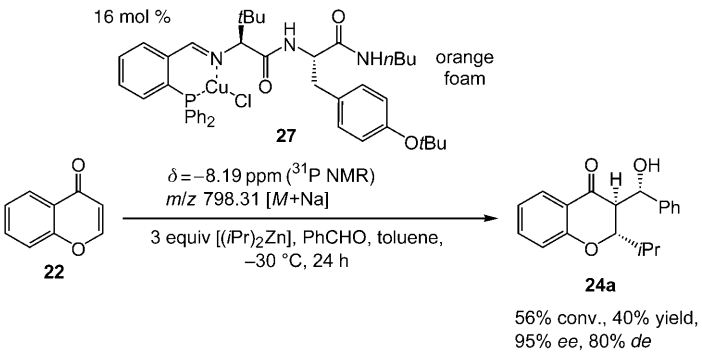
7 $\xrightarrow[2)\ \text{PCC, NaOAc}]{1)\ 8\,\text{mol}\%\ \text{catalyst, [Et}_2\text{Zn], PhCHO}}$ **9b**

Entry	Catalyst	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	**1** + CuCl	92	51	90
2	**25**	92	87	94
3	**1** + CuI	57	24	63
4	**26**	92	74	89

[a] [Et_2Zn] (3 equiv), −30 °C, toluene, 12 h, N_2. [b] Conversion determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Isolated yields after silica gel chromatography; oxidations proceed in ≈90% isolated yield. [d] Enantioselectivities determined by chiral HPLC analysis.

air) promotes ACA with equal efficiency and enantioselectivity, a similar batch of **25** affords **9b** in 87% yield and 72% *ee* (vs. 94% with a freshly prepared sample).

An additional example, shown in Equation (1), illustrates that isolation of Cu-peptide chiral complexes is not limited to



(1)

the derivatives of phosphane **1**. Thus, in the presence of **27** (16 mol%), derived through reaction of **2** ($\delta = -10.7$ ppm, ^{31}P NMR) with CuCl (1 equiv, CH_2Cl_2, 22 °C; 84% yield), heterocyclic enone **22** can be converted to **24a** in 95% *ee* and 80% *de*. Similar to reactions with **25** and **26**, the copper chloride complex is less effective than when the chiral catalyst is prepared in situ from $(CuOTf)_2{\cdot}C_6H_6$ and phosphane **2** (see entry 3, Table 3).

In summary, we report the first generally effective method for catalytic ACA of dialkylzinc reagents to unsaturated furanones and pyranones with different steric and electronic properties. The present method significantly enhances the general utility of Cu-catalyzed ACA of alkylmetal reagents to unsaturated carbonyls. Synthesis, isolation, and characterization of catalytically active and air-stable chiral Cu–peptide complexes **25**–**27** enhance the practical utility of these protocols and set the stage for future mechanistic investigations.

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[12] See the Supporting Information for details.

