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Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones

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Conjugate additions of carbon nucleophiles to unsaturated carbonyls constitute an important class of C−C bond forming reactions in organic chemistry. A significant amount of effort has been directed toward the development of Cu-[1] and Rh-catalyzed[2] asymmetric conjugate addition (ACA) of alkylmetal and aryl- and vinylboronic acid reagents to cyclic and acyclic unsaturated carbonyls. Nearly all such studies have focused on transformations that deliver tertiary carbon stereogenic centers. The exception is the recent report by Alexakis and co-workers regarding an efficient Cu-catalyzed procedure[3] for ACA to β-substituted cyclohexenones. Reactions afford all-carbon quaternary stereogenic centers[4] in up to 96% ee. Because of the low substrate reactivity, the more Lewis acidic[3] but less atom-economical trialkylaluminum reagents (versus dialkylzinc reagents) were required in the above study; thus, the investigation involved additions of the more readily available Et_3-Al and (mostly) Me_3Al.

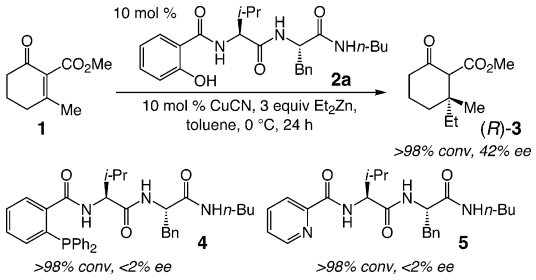
Herein, we disclose a practical method for catalytic ACA of dialkylzinc reagents to cyclic enones that afford quaternary all-carbon stereogenic centers[4] in up to 95% ee. Reactions proceed to >98% conversion with 2 mol % of air-stable CuCN and a new chiral ligand that bears an anthranilic acid-based N-terminus[5] (versus $(CuOTf)_2 \cdot C_6H_6$ and Schiff base phosphines identified previously).[6] Transformations are carried out in undistilled commercial grade toluene. To the best of our knowledge, the present protocol represents the first cases of catalytic enantioselective alkylmetal addition to tetrasubstituted olefins.[7]

We initiated our studies by examining the ability of a range of amino acid-based ligands and Cu salts to promote the ACA of Et_2-Zn to cyclic enone **1** (Scheme 1).[8] These screening studies led us to establish that the combination of CuCN and chiral ligand **2a**, bearing a dipeptide moiety with the N-terminus capped as an *o*-phenoxy amide, delivers the desired product **3** efficiently (>98% conversion, 24 h at 0 °C) and with appreciable enantioselectivity (42% ee; *R* enantiomer major). Use of alternative Cu salts (e.g., $(CuOTf)_2 \cdot C_6H_6$, CuBr) and/or solvents (THF, CH_2Cl_2) results in significantly less selective ACA (<20% ee).[8] Reactions in the presence of the derived phosphine- (e.g., **4**) and pyridyl-based ligands (e.g., **5**) leads to >98% conversion, but **3** is formed in <2% ee.[8] It must be noted that the combination of $(CuOTf)_2 \cdot C_6H_6$ and chiral amino acid-based phosphine ligands, reported previously[6] for ACA of cyclic di- and trisubstituted enones, is ineffective (~50% conversion, <15% ee) in reactions of the present class of substrates.

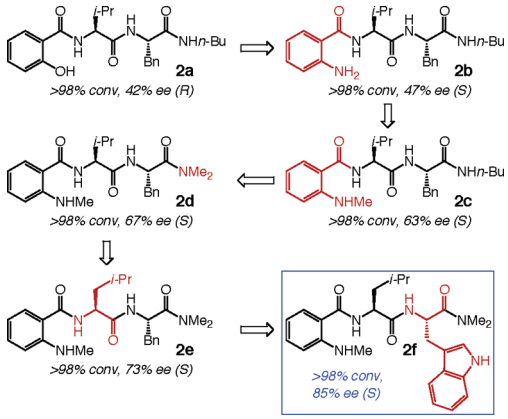
To identify a more effective chiral catalyst, we carried out further optimization studies; the modular nature of the peptidic ligand was exploited in the systematic alteration of each structural unit of the chiral ligand (positional scanning).[9] The results of these investigations are summarized in Scheme 2.

Previous investigations indicate[10] that the present class of chiral amino acid-based ligands complex with the transition metal (including Cu(I)-based systems)[6f] within the N-terminus moiety.

Scheme 1



Scheme 2. Catalyst Optimization through Positional Scanning Studies[a]



[a] The reaction and conditions used are shown in Scheme 1 (10 mol % loading).

Thus, undaunted by the ineffectiveness of **4** and **5** (Scheme 1), we set out to explore more extensively the effect of steric and electronic modifications of the ligand's N-terminus. The resulting screening studies[8] revealed that the combination of CuCN and dipeptide **2b**, where anthranilic acid is used to cap the N-terminus, gives rise to efficient formation of the *opposite product enantiomer* (*S*)-**3** in 47% ee ((*R*)-**3** formed with **2a**). Examination of various derivatives of **2b** indicated that in the presence of **2c** the Cu-catalyzed ACA affords (*S*)-**3** in 63% ee. Subsequent examination of the ligand C-terminus (**2d**) and the two amino acid moieties allowed us to identify **2f** as a chiral ligand that promotes the enantioselective synthesis of (*S*)-**3** in 85% ee (>98% conversion).[11] Further optimization studies led us to determine that treatment of **1** with 2 mol % of **2f**, 2 mol % of CuCN, and 1.5 equiv of Et_2Zn delivers (*S*)-**3** in 82% ee and 89% isolated yield (see entry 1, Table 1; 85% ee with 10 mol % catalyst loading).

With an effective chiral catalyst in hand, identified through screening of ~90 ligand candidates, we examined the scope of the catalytic protocol. The results of these studies are summarized in Table 1; several points regarding these data are noteworthy. (1) Transformations can be performed effectively with five- and six-

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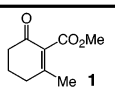
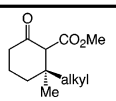
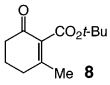
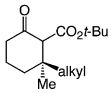
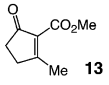
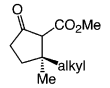
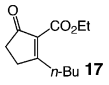
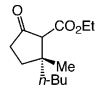
Table 1. Cu-Catalyzed ACA of Dialkylzincs to Tetrasubstituted Enones[a]

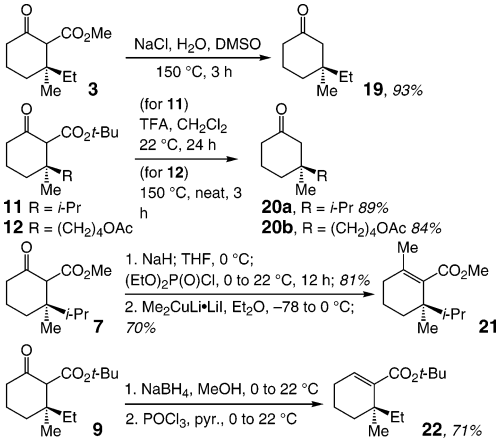
entry	substrate	$(alkyl)_2Zn$	product		T (°C); time (h)	yield (%);[b] ee (%)[c]
1	 **1**	Et_2Zn		**3**	0; 11	89; 82
2		*n*-Bu_2Zn		**6**	−15; 38	>98; 92
3		*i*-Pr_2Zn		**7**	0; 21	76; 86
4	 **8**	Et_2Zn		**9**	0; 27	89; 90
5		*n*-Bu_2Zn		**10**	−15; 43	92; 95
6		*i*-Pr_2Zn		**11**	0; 22	>98; 90
7		$[(AcO(CH_2)_4)]_2Zn$		**12**	−15; 41	74; 95
8	 **13**	Et_2Zn		**14**	0; 21	80; 77
9		*n*-Bu_2Zn		**15**	−15; 43	85; 86
10		*i*-Pr_2Zn		**16**	−15; 40	82; 66
11	 **17**	Me_2Zn		**18**	0; 26	70; 82

[a] Conditions: 2 mol % of **2f**, 2 mol % of CuCN, 1.5 equiv of $(alkyl)_2Zn$ in toluene, undistilled toluene, N_2 atm; except entry 4, 5 mol % of **2f** and CuCN, and entry 11, 5 mol % of **2f**, CuCN, and 3 equiv of Me_2Zn. [b] Isolated yields after silica gel chromatography. [c] Determined by chiral GLC; see the Supporting Information for details.

membered ring substrates and a range of dialkylzinc reagents (commercially available Me_2Zn, Et_2Zn, *n*-Bu_2Zn, and *i*-Pr_2Zn used). Reactions are effective with alkyl as well as *t*-Bu esters (see below for decarboxylations). (2) *All transformations were performed in undistilled toluene*. When purified solvent (passed through Cu and alumina column) is used, significantly lower enantioselectivities are observed.[12] As the requisite Cu salt and ligand are air stable, catalytic ACA can be carried out on the benchtop. Rigorous air exclusion techniques are not required during setup until the addition of dialkylzinc reagent. Such protocols do not lead to significant loss of alkylzinc reagent, as ACA processes proceed to >98% conversion with 1.5 equiv of alkylmetal. (3) Reactions of five-membered ring enones are less selective than six-membered ring substrates (66−86% ee versus 82−95% ee). The examples shown, however, to the best of our knowledge, are the first instances of catalytic ACA to β-disubstituted cyclopentenones. (4) As shown in Table 1, the optimal reaction temperature can be case dependent. For instance, the ACA in entry 9, when performed at 0 and −30 °C, affords **15** in 79 and 57% ee, respectively. (5) In the absence of a chiral ligand, under otherwise identical conditions, conjugate additions proceed readily (>98% conversion). This fact, together with the enantioselectivities in Table 1, suggests that either formation of the Cu−ligand complex is irreversible or that the chiral complex is more effective in promoting addition than CuCN. A potentially relevant experimental observation is that premixing **2f** and CuCN for at least 3 h (22 °C) is required for high enantioselectivity to be obtained. As an example, (*S*)-**3** is formed in only 51% ee (versus 82% ee) when **2f** and CuCN are premixed for 1 h. (6) Initial studies indicate that the present enantioselective protocol can be run on reasonable scale; the reaction in entry 4, when carried out at 0.5 g scale, affords **9** in 87% ee and 76% isolated yield.

Optically enriched ACA products can be functionalized to afford a variety of synthetically useful chiral building blocks (Scheme 3). Decarboxylation of products affords the desired cyclic β,β-dialkyl ketones in high yield under a variety of conditions (**3**→**19** and **11** and **12**→**20a**,**b**, Scheme 3); optically enriched products **20a**,**b** cannot be easily accessed by catalytic ACA of alkylaluminums.[3] The presence of β-ketoester allows access to optically enriched cycloalkenes. For the synthesis of **21**, formation of the derived enol phosphate and treatment with a cuprate reagent delivers the optically enriched unsaturated ester with a tetrasubstituted olefin and an allylic quaternary carbon stereogenic center. A reduction/elimination process gives rise to the corresponding cyclic trisubstituted olefin (e.g., **22**; Scheme 3).

Scheme 3. Representative Functionalizations of ACA Products



In brief, we have identified a chiral ligand (**2f**) that, in the presence of air-stable CuCN, can be used to promote ACA of alkylzincs to tetrasubstituted cyclic enones to afford all-carbon quaternary stereogenic centers. The above attributes should render the present catalytic asymmetric method of notable utility. Study of the full scope of this method and development of catalytic asymmetric additions to β-substituted enones[7] and the related acyclic substrates will be disclosed in due course.

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Supporting Information Available: Experimental procedures and spectral, analytical data for all reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) For example, see: (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363. (d) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (e) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584−4585. (f) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306−5310 and references therein. For reactions with a phosphine ligand bearing an amide N-terminus linkage, see: (g) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279.
(7) The protocol described herein is ineffective with the less activated but also less sterically hindered β-substituted cyclic enones (see ref 3).
(8) See the Supporting Information for details.
(9) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671.
(10) (a) Ref 6f. (b) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599.
(11) The origin of selectivity variations shown in Scheme 2 is unclear at the present time and is the subject of ongoing mechanistic investigations.
(12) For example, the reaction in entry 4, when carried out with purified toluene, affords (*R*)-**9** in 57% ee (versus 90% ee with undistilled toluene). Initial studies suggest that adventitious moisture may be responsible for this unexpected difference; addition of undistilled solvent to purified solvent restores high selectivity. Further studies are in progress.

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