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Efficient Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzincs to Trisubstituted Cyclic Enones

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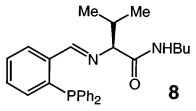
A considerable amount of research has focused on the development of catalytic asymmetric conjugate additions (ACA) of alkylmetals to α,β-unsaturated carbonyls.[1] Previous reports from these laboratories have outlined effective methods for Cu-catalyzed reactions of alkylzincs with disubstituted enones,[2] providing solutions to problems regarding efficient asymmetric additions to cyclopentenones[2a] and acyclic enones.[2b] A number of synthetically important challenges, however, remain unsolved. One relates to the availability of catalytic ACA involving sterically hindered *tri*substituted enones. To the best of our knowledge, there are no existing reports that address this task.[3] Herein we report efficient and highly selective Cu-catalyzed ACA of alkylzincs to trisubstituted unsaturated cyclic ketones. In contrast to previous ACA reactions promoted by amino acid-based chiral ligands,[2] the present transformations are catalyzed by a Schiff base derivative of a *single* amino acid that is commercially available and inexpensive (L- or D-valine). The ligand can be prepared and used directly without isolation and purification to afford high enantioselectivities. The resulting metal enolates can be reacted diastereoselectively to deliver cyclic ketones of high optical purity that bear a quaternary stereogenic center.[4]



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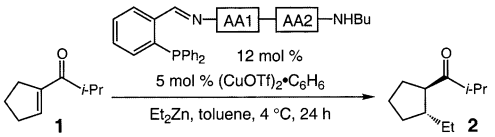
We began our investigation with screening of various amino acid-based ligand candidates.[5] These studies indicated that peptide-based phosphine **3** (Table 1, entry 1) promotes the ACA of Et_2Zn to trisubstituted enone **1** to afford **2** in 85% ee (93% conv after 24 h). The identity of ligand **3** was consistent with previous findings.[2] Also expected was that, as shown in entry 2 of Table 1, substitution of AA1 from L-*t*-Leu to L-Val leads to lowering of selectivity (76 vs 85% ee) and substantial reduction in reactivity (32 vs 93% conv). However, the results shown in entries 3−4 of Table 1 were unanticipated for two reasons: First, insertion of achiral Gly as AA2 in place of L-Phe leads to notable improvement of enantioselectivity (compare entries 3 and 4 to 1 and 2). Second, in contrast to when AA2 is L-Phe (entries 1 and 2), with Gly as the AA2, the ligands bearing L-*t*-Leu (entry 3) and L-Val (entry 4) as AA1 provide comparable reactivity and selectivity. With the positive influence of an achiral AA2, we examined the utility of the derived monoamino acid ligands **7** and **8**, leading us to establish that Schiff base **8** (entry 6) promotes ACA of Et_2Zn to **1** in 96% ee (97% conv). These findings are noteworthy for several reasons: (1) The identity of the optimal ligand varies considerably from the two different dipeptide ligands required for ACA of disubstituted cyclic[2a] or acyclic enones.[2b] (2) The requirement for a single amino acid residue (vs a dipeptide), and that being the inexpensive Val (vs *t*-Leu), renders the present method cost-effective. (3) The data in Table 1 indicate cooperativity between the AA1 and AA2 residues of the dipeptidic chiral ligands.

Table 1. Cooperative Interplay between AA1 and AA2 Moieties of the Chiral Peptide Ligands on Reactivity and Selectivity



1 **2**

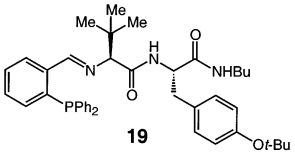
entry	AA1	AA2		conv (%)[a]	ee (%)[b]
1	L-*t*-Leu	L-Phe	**3**	93	85
2	L-Val	L-Phe	**4**	32	76
3	L-*t*-Leu	Gly	**5**	87	93
4	L-Val	Gly	**6**	92	91
5	L-*t*-Leu	−	**7**	>98	83
6	L-Val	−	**8**	97	96

[a] Determined by GLC. [b] Determined by chiral GLC.

The results summarized in Table 2 illustrate that Cu-catalyzed ACA of alkylzincs to a range of cyclic trisubstituted enones are readily promoted by **8**. Although, as expected, reactions proceed more slowly than disubstituted enones,[2a] conversions are high with enantioselectivities ≥95% ee. In many cases isolated yields are lower than percent conversions due to volatility of the products.

Several additional points are noteworthy: (1) Transformations in entries 1−8 and 11−12 (Table 2) afford 1.5−4:1 ratio of anti:syn diastereomers. In contrast, **16a** and **16b** (entries 9 and 10) are formed as 3:1 mixtures of syn:anti isomers. In the case of all cyclopentenyl products, treatment with DBU or Et_3N (MeOH, 22 °C) allows equilibration to the anti isomer (see Table 2).[6] With medium-ring products **18a**−**b**, similar conditions do not lead to improved diastereomeric purity.

(2) All processes in Table 2 are effected in the presence of ligand **8**. Two exceptions are additions to enone **15** (entries 9−10) where **19**[2b] is significantly more efficient (data in entries 9−10, Table 2 relate to reactions catalyzed by **19**). As an example, when **8** is used as the catalyst, **16b** is formed in 95% ee but along with ∼40% of an unidentifiable impurity.[7]



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(3) Six-membered ring trisubstituted enones are inert to catalytic ACA conditions (<5% conv after 12 h). As formerly disclosed,[2b] products expected from cyclohexenyl substrates can be obtained through catalytic additions/intramolecular enolate alkylations of

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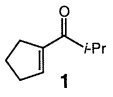
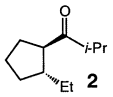
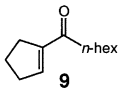
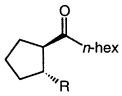
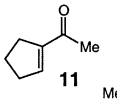
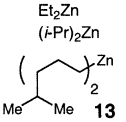
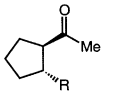
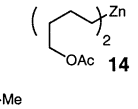
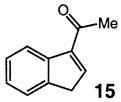
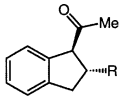
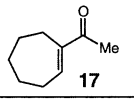
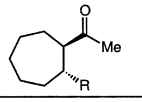
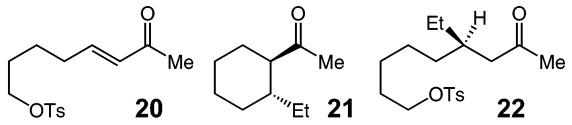
Table 2. Cu-Catalyzed ACA of Alkylzinc Reagents to Cyclic Trisubstituted Enones[a]

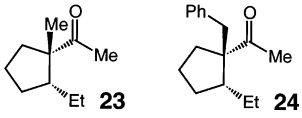
entry	substrate	alkylzinc	product	8,[b] Cu salt (mol %)	conv (%)[c] time (h)	yield (%)[d]	anti:syn (after base)[e]	ee (%);[f] config
1	 **1**	Et_2Zn	 **2**	12, 5.0	>98, 24	77	16:1	96; (–)
2	 **9**	Me_2Zn		**10a** 12, 5.0	87, 48	72	13:1	95; (–)
3		Et_2Zn		**10b** 6.0, 2.5	>98, 12	85	15:1	97; (–)
4		Me_2Zn		**12a** 12, 5.0	79, 24	42	16:1	97; (–)
5		Et_2Zn		**12b** 2.4, 1.0	>98, 6	66	>25:1	97; (–)
6		$(i\text{-Pr})_2Zn$		**12c** 6.0, 2.5	>98, 12	69	>25:1	98; (–)
7	 **11**	 **13**		**12d** 6.0, 2.5	97, 14	84	>25:1	95; (–)
8		 **14**		**12e** 12, 5.0	97, 24	47	>25:1	94; (–)
9	 **15**	Et_2Zn **13**		**16a** 3.6, 1.5	>98, 12	86	16:1	97; (–)
10				**16b** 12, 5.0	>98, 12	75	16:1	>98; (–)
11	 **17**	Et_2Zn **13**		**18a** 6.0, 2.5	98, 12	85	4:1	97; (+)
12				**18b** 12, 5.0	92, 24	65	3:1	98; (+)

[a] Conditions: indicated mol % **8** (except entries 9−10) and $(CuOTf)_2{\cdot}C_6H_6$, 3 equiv of alkylzinc in toluene, 0 °C, indicated duration, N_2 atm. [b] Ligand **8** used in all cases, except entries 9−10, where **19** was employed. [c] Determined by GLC analysis of unpurified reaction mixtures. [d] Isolated yields after purification of conjugate addition products. [e] By GLC and 400 MHz ^1H NMR analysis. Performed by treatment with 1 equiv of DBU in MeOH at 22 °C for 12−24 h (3 equiv of Et_3N used for entries 9−10). [f] By chiral GLC analysis measured for both diastereomers (see the Supporting Information for details).

suitably functionalized acyclic enones such as **20** (to give **21**). The present protocol, however, delivers the corresponding seven-membered ring adducts (see entries 11−12, Table 2). Such products cannot be obtained by the aforementioned tandem approach; reactions of the acyclic enone tosylates (homologue of **20**) only afford acyclic conjugate addition adducts such as **22**.[2b]



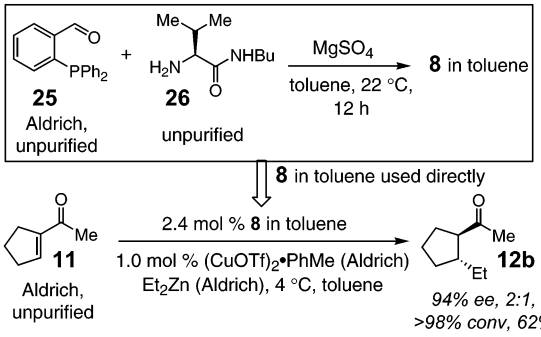
(4) The purported Zn-enolate intermediates react with various alkyl halides. Addition of MeI or $PhCH_2Br$ and DMPU[8] to the reaction of **11** with Et_2Zn (Table 2, entry 5) affords **23** and **24** in 4:1 (65% yield) and >20:1 (70% yield) diastereoselectivity, respectively.



(5) Treatment of a sample of commercially available phosphine **25** (not further purified) with amine **26** (no purification after removal of Boc group) in the presence of $MgSO_4$ leads to a solution of ligand **8** after 12 h (Scheme 1). An appropriate aliquot of this solution was then used to effect the formation of **12b** with commercially available materials **11**, $(CuOTf)_2{\cdot}PhMe$[9] and Et_2Zn (none were purified). The desired product was obtained in 94% ee and 62% yield (compare to entry 5, Table 2; 2:1 prior to equilibration).

Acknowledgment. This work was supported by the NIH (GM-47480).

Scheme 1. Cu-Catalyzed ACA with Commercially Available and Unpurified Materials



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

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(3) For catalytic asymmetric conjugate additions to trisubstituted α,β-unsaturated malonates (<60% ee), see: Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375−1378.
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(6) Equilibration reactions proceed to afford the less volatile products in 70 to >98% isolated yields.
(7) See the Supporting Information for complete data regarding reactions in Table 2 when performed in the presence of **19** (except entries 9 and 10).
(8) See the Supporting Information for experimental details.
(9) Choi, H. Y.; Choi, J. Y.; Yang, H. Y.; Kim, Y. H. *Tetrahedron: Asymmetry* **2002**, *13*, 801−804.

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