

Enantioselective Conjugate Addition of Catalytically Generated Zinc Homoenoate

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Supporting Information Placeholder

ABSTRACT: We report herein an enantioselective conjugate addition reaction of a zinc homoenoate, catalytically generated via ring opening of a cyclopropanol, to an α,β -unsaturated ketone. The reaction is promoted by a zinc aminoalkoxide catalyst generated from Et_2Zn and a chiral β -amino alcohol to afford 1,6-diketones, which undergo, upon heating, intramolecular aldol condensation to furnish highly substituted cyclopentene derivatives with good to high enantioselectivities. The reaction has proved applicable to various 1-substituted cyclopropanols as well as chalcones and related enones. The chiral amino alcohol has proved to enable ligand-accelerated catalysis of the homoenoate generation and its conjugate addition. Positive nonlinear effects and lower reactivity of a racemic catalyst have been observed, which can be attributed to a stable and inactive heterochiral zinc aminoalkoxide dimer.

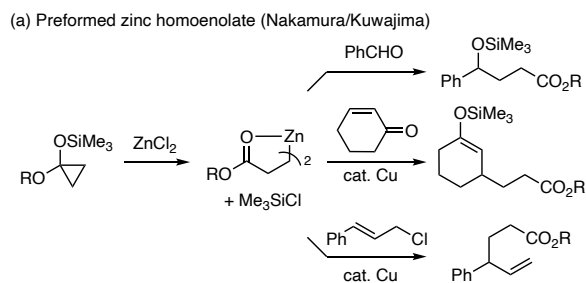
Metal homoenolates represent useful organometallic nucleophiles that allow for umpolung functionalization of the β position of a carbonyl group.¹ Pioneering studies by Nakamura and Kuwajima established 1-alkoxy-1-siloxycyclopropanes as precursors to various main group and transition metal ester homoenolates, among which zinc homoenoate proved to be a particularly versatile nucleophile for fundamental C–C bond forming reactions including 1,2/1,4-addition, allylic substitution, and cross-coupling (Scheme 1a).² Nevertheless, an enantioselective variant of such transformations remains elusive. This is in sharp contrast to the fact that the catalytic enantioselective 1,2/1,4-addition and allylic substitution reactions of simple dialkylzincs have been developed and matured to the level that they now serve as benchmarks for the evaluation of new chiral ligands and catalysts.³ For example, more than 800 and 100 articles can be found for the enantioselective addition of Et_2Zn to benzaldehyde and cyclohexenone, respectively, while no analogous

asymmetric reaction involving a preformed zinc homoenoate has been reported.⁴

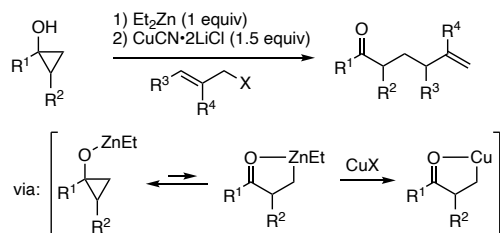
Recently, cyclopropanols have emerged as viable precursors for the in situ-generation of ketone homoenolates.^{1c-f} One of seminal studies in this context is Cha's work on allylic and propargylic substitutions mediated by stoichiometric Et_2Zn in combination with Cu(I) salt, where equilibrium generation of zinc homoenoate from the corresponding cyclopropoxide and its transmetalation to Cu(I) are likely involved (Scheme 1b).⁵ However, such in situ-generated zinc homoenoate has also not been exploited for an enantioselective C–C bond formation.^{6,7}

Herein, we report on an enantioselective conjugate addition (ECA) of a catalytically generated chiral zinc homoenoate to α,β -unsaturated ketones (Scheme 1c).^{8,9} A catalyst generated from Et_2Zn and a chiral β -amino alcohol promotes ring-opening addition of cyclopropanols to chalcone and related enones, which displays the feature of ligand-accelerated catalysis and represents a rare example of transition metal-free ECA of organozinc reagents.¹⁰ Upon heating, the 1,6-diketone products undergo facile intramolecular aldol condensation to afford multisubstituted cyclopentene derivatives with high enantioselectivity.¹¹

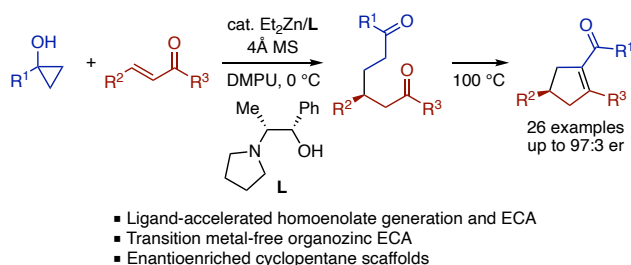
Scheme 1. Generation and C–C Bond-Forming Reactions of Zinc Homoenoate



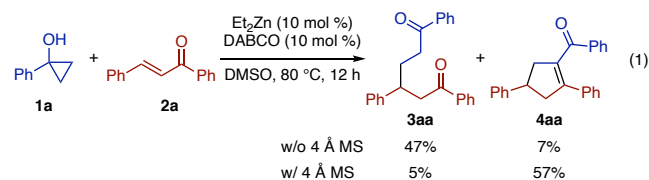
(b) In situ-generated zinc homoenolate (Cha)



(c) **This work:** Catalytically generated chiral zinc homoenolate



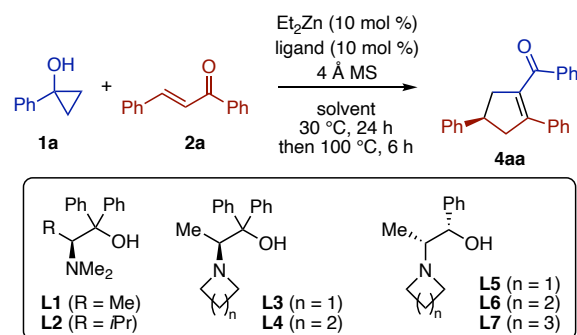
In light of Cha's seminal work on the equilibrium generation of zinc homoenolate from zinc cyclopropoxide,⁵ our first question was whether it is possible to exploit such process for C–C bond formation *catalytic* in zinc. Thus, we initially examined the reaction between 1-phenylcyclopropanol (**1a**) and chalcone (**2a**). Upon brief screening, a catalytic system comprised of Et₂Zn (10 mol %) and DABCO (10 mol %) was found to promote the desired ring-opening conjugate addition in DMSO at 80 °C, affording 1,6-diketone **3aa** in 47% yield along with a small amount of cyclopentene derivative **4aa** as a result of intramolecular aldol condensation of **3aa** (eq 1). By adding molecular sieves 4 Å, the reaction gave **4aa** as the dominant product.



Given the feasibility of zinc-catalyzed generation and conjugate addition of homoenolate from cyclopropanol, we next attempted on rendering the reaction enantioselective. In this respect, we explored a host of chiral β-amino alcohols as ligands, which have found extensive use in the enantioselective addition of

dialkylzincs^{3a} as well as preformed or in situ-generated zinc acetylide.¹² Upon screening of ligands, solvents, and other reaction conditions, a few amino alcohols (**L1**, **L3**, and **L5–L7**) emerged as promising ligands (Table 1, entries 1–7; see also Tables S1 and S2). For example, the reaction of **1a** and **2a** in the presence of Et₂Zn and the norephedrine derivative **L6** (10 mol %) and 4 Å MS in DMSO was performed at 30 °C for 24 h, followed by heating at 100 °C for 6 h, to afford the cyclopentene **4aa** in 73% yield with 87:13 er (entry 6). The use of DMPU as the solvent improved the enantioselectivity to 93:7 er (entry 8). By performing the ECA step at 0 °C for 48 h with an increased catalyst loading (15 mol %), an additional improvement in the yield (89%) and the enantioselectivity (95:5 er) was achieved (entry 9).

Table 1. Zinc-Catalyzed Addition of 1-Phenylcyclopropanol (**1a**) to Chalcone (**2a**)^a



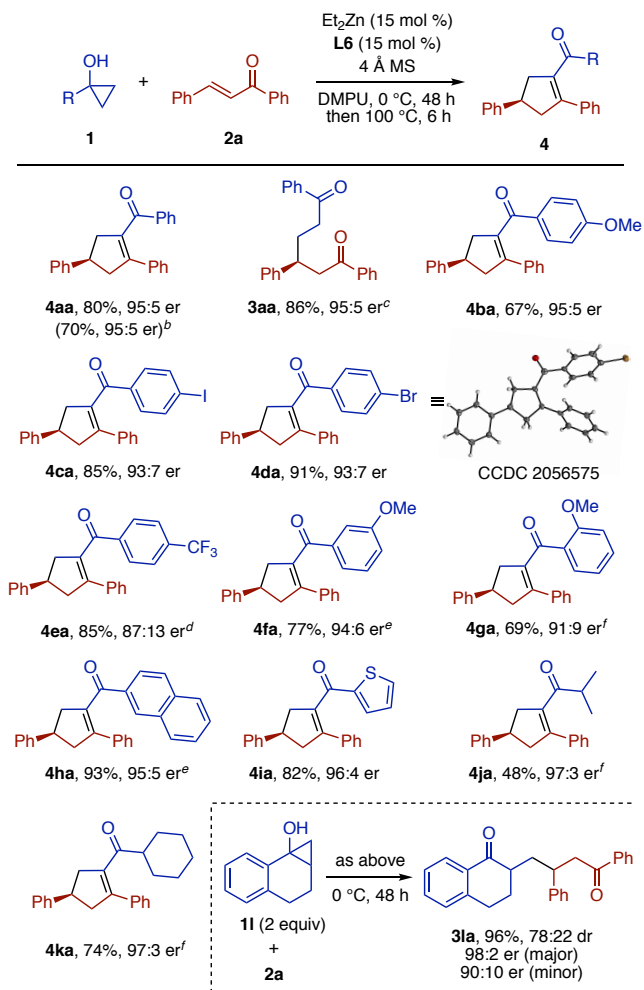
entry	ligand	solvent	yield (%) ^b	er ^c
1	L1	DMSO	88	82:18
2	L2	DMSO	65	47:54
3	L3	DMSO	69	79:21
4	L4	DMSO	63	52:48
5	L5	DMSO	71	77:23
6	L6	DMSO	73	87:13
7	L7	DMSO	50	82:18
8	L6	DMPU	79	93:7
9 ^d	L6	DMPU	89	95:5

^aThe reaction was performed using 0.15 mmol of **1a** and 0.1 mmol of **2a** in 0.3 mL solvent (0.33 M). ^bDetermined by GC using mesitylene as an internal standard. ^cDetermined by chiral HPLC. ^d15 mol % each of Et₂Zn and **L6** was used. The reaction was performed at 0 °C for 48 h and then at 100 °C for 6 h.

With the optimized catalytic system (Table 1, entry 9) in hand, we explored the scope of the present homoenolate ECA. First, a variety of cyclopropanols were subjected to the reaction with chalcone (**2a**) (Scheme 2). Various 1-arylcyclopropanols participated in the ring-opening conjugate addition/intramolecular aldol cascade, thus affording cyclopentenones **4aa–4ha** in moderate to high yields and enantioselectivities with tolerance to methoxy, bromo, iodo, and trifluoromethyl

groups. A modest trend of decreasing enantioselectivity with electron-withdrawing aryl group was observed, as manifested in the case of *para*-trifluoromethyl group (see **4ea**). The absolute configuration of the Br-substituted product **4da** was determined to be (*R*) by X-ray crystallographic analysis. The reaction of **1a** could be performed on a 3 mmol scale without decrease in the enantioselectivity. Importantly, the reaction of **1a** and **2a**, when quenched before the aldol step, gave the 1,6-diketone product **3aa** in good yield with enantioselectivity (95:5 er) identical to that of **4aa**. 1-(2-Thienyl)cyclopropanol also smoothly took part in the reaction to furnish the product **4ia** with 96:4 er. The reactions of 1-alkylcyclopropanols were somewhat sluggish and required higher temperature. Nonetheless, the corresponding cyclopentene products (**4ja** and **4ka**) were obtained with excellent enantioselectivity (97:3 er). A racemic bicyclic cyclopropanol **11** (2 equiv) underwent selective cleavage of the less substituted C–C bond, and afforded the desired conjugate adduct **3la** as a diastereomer mixture (78:22 dr) in 96% yield, with 98:2 and 90:10 ers for the major and minor diastereomers, respectively. Meanwhile, the unreacted **11** was isolated in the form of benzoyl ester in 24% yield (based on **11**) with 96:4 er. This outcome can be rationalized by highly selective kinetic resolution in the ring-opening step and moderately enantioselective conjugate addition of each diastereomeric zinc homoenolate (see Scheme S1).

Scheme 2. Asymmetric Ring-Opening Addition of Various Cyclopropanols to **2a**^a

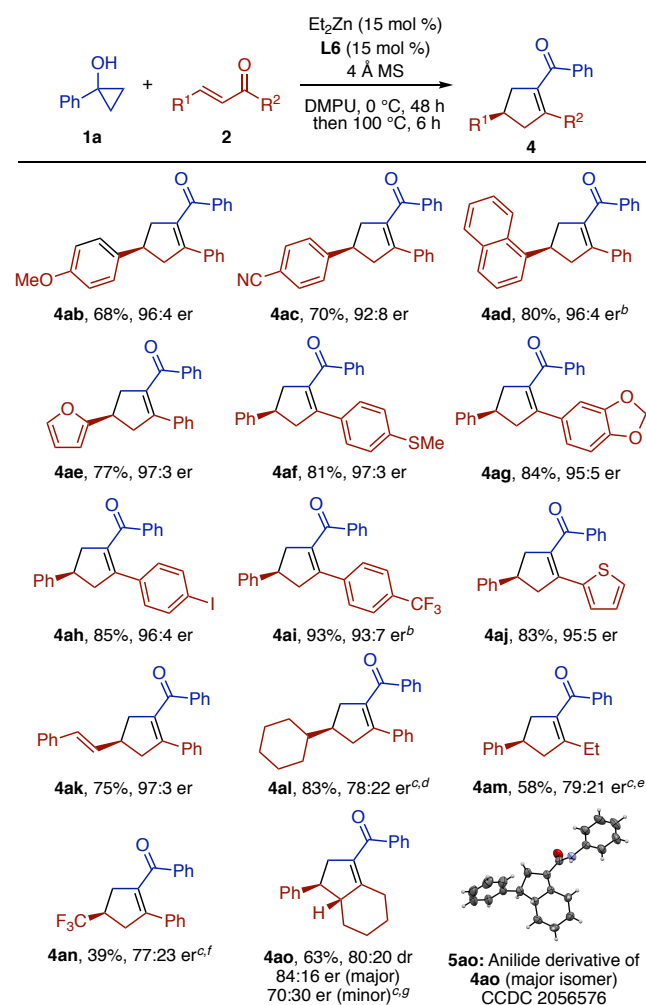


^aThe reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 9. ^b3 mmol-scale reaction. ^cThe reaction was quenched without aldol condensation step. ^dThe ECA step was performed at 30 °C for 12 h. ^eThe ECA step was performed at 0 °C for 72 h. ^fThe ECA step was performed at 30 °C for 48 h.

We next explored the addition of **1a** to various α,β -unsaturated ketones (Scheme 3). Chalcone-type di(hetero)aryl-substituted enones proved to be excellent substrates, affording the corresponding cyclopentenones **4ab–4aj** in moderate to high yields with 92:8 to 96:4 er. A variety of functionalized aryl and heteroaryl groups could be tolerated on both ends of the enone skeleton. An $\alpha,\beta,\gamma,\delta$ -unsaturated ketone underwent selective 1,4-addition of the homoenolate to give the alkenyl-substituted cyclopentene **4ak** with 97:3 er. Meanwhile, enones bearing an alkyl substituent at either the β position or the acyl position failed to participate in the reaction under the standard conditions. Using **L3** as the ligand, such substrates afforded the desired products **4al** and **4am** with moderate enantioselectivities (ca. 80:20 er). β -Trifluoromethyl enone also took part in the reaction, albeit in modest yield and enantioselectivity (see **4an**). The reaction of (*E*)-2-benzylidenecyclohexan-1-one furnished, after 3 h of the aldol condensation step, a

bicyclic product **4ao** as a mixture of diastereomers (80:20 dr) with ers of 84:16 (major) and 70:30 (minor). The relative stereochemistry of the major diastereomer of **4ao** was confirmed by X-ray crystallographic analysis of its anilide derivative **5ao**. Notably, extension of the condensation step for this product resulted in transposition of the C=C bond to the bicyclic juncture to give a tetrasubstituted olefin isomer (66% yield, 50:50 dr and 80:20 er for both diastereomers), presumably via zinc dienolate intermediate (see Scheme S2). Note that the present catalytic system failed to engage cyclic enones such as cyclohexanone as the reaction partner for **1a**.

Scheme 3. Asymmetric Ring-Opening Addition of **1a** to Various Enones^a



^aThe reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 9. ^bThe aldol condensation step was performed at 50 °C for 16 h. ^c**L3** was used instead of **L6**. ^dThe reaction was performed in DMSO at 40 °C for 48 h and then at 100 °C for 6 h. ^eThe ECA step was performed at 30 °C for 48 h. ^fThe ECA step was performed at 30 °C for 24 h. ^gThe aldol condensation step was performed for 3 h.

To gain insight into the ligand effect and the zinc species involved in the present homoenolate ECA, we

performed a series of mechanistic experiments. The model reaction of **1a** and **2a** (performed at 30 °C to facilitate the reaction at low catalyst loadings and/or with low-ee catalysts) was found to display a concentration-dependent nonlinear effects (NLEs; Figure 1a).¹³ Thus, a clear positive NLE was observed with 20 mol % catalyst loading (67 mM [Zn]), while NLE became rather weak upon reducing the catalyst loading down to 10 mol % (33 mM [Zn]). Note that the reaction temperature (30 °C vs 0 °C) and the solvent composition (DMPU vs DMPU/THF) had only minor impact on NLE (see Figures S5 and S6). The ee of **L6** was also found to significantly influence the reaction rate. Thus, the initial rate of the reaction using enantiopure **L6** was found to be more than four times faster than that using racemic **L6** (Figure 1b). These observations suggest the role of homochiral and heterochiral Zn aminoalkoxide dimers as off-cycle species and the reluctance of the latter to dissociate into catalytically active monomeric Zn species (vide infra).^{13b} The ability of the amino alcohol to accelerate the whole reaction process as well as the ring opening step alone was clearly demonstrated by control experiments. Thus, no reaction took place between **1a** and **2a** by omitting **L6** from or replacing **L6** with DABCO in the standard conditions. The reaction of **1a** alone under the standard conditions quantitatively produced propiophenone **1a'** after 48 h, while the ring opening was rather sluggish by omitting **L6** or using DABCO (Figure 1c). Lastly, we probed the solvent effect (DMPU, THF, and their mixed solvents) on the model reaction (Figure 1d). The enantioselectivity proved rather insensitive to the solvent composition. By contrast, the product yield dropped significantly in pure THF (15%) owing to competitive Michael addition of propiophenone enolate to **2a**, while the yield, albeit with some fluctuation, remained substantial ($\geq 50\%$) in the mixed solvents (%THF up to 75%).

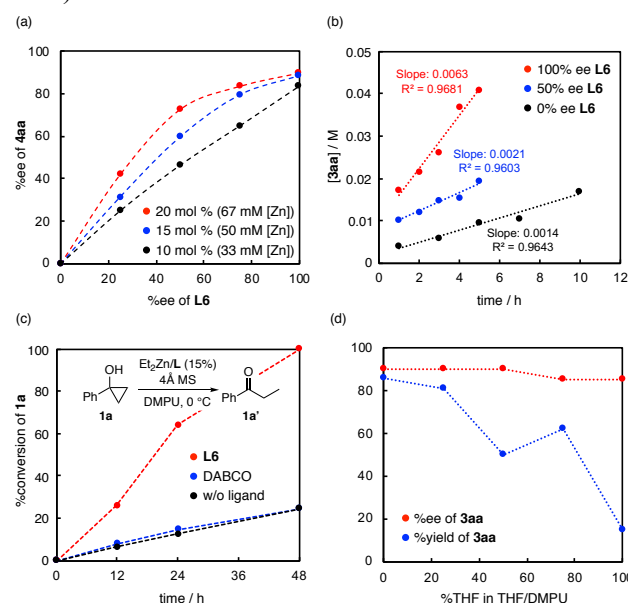
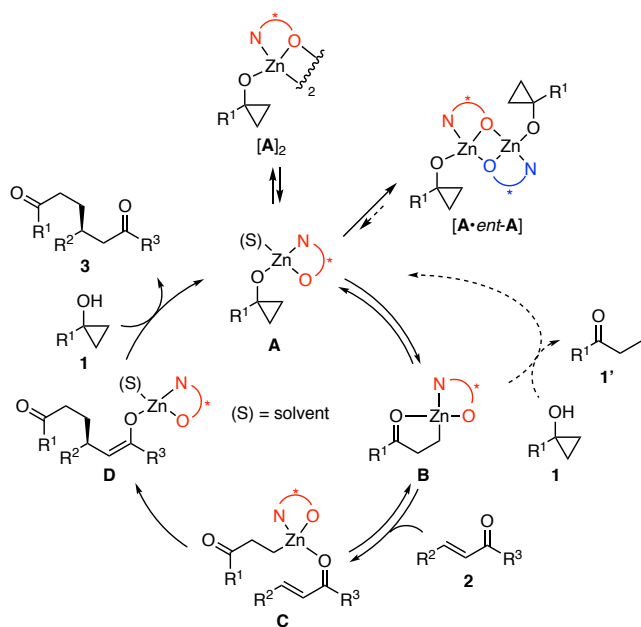


Figure 1. Mechanistic experiments. (a) Nonlinear effects with different catalyst loadings of Et₂Zn/L6 (30 °C, 30 h and 100 °C, 6 h). (b) Initial reaction progress using L6 of different ees (15 mol % catalyst loading, 0 °C). (c) Ring-opening of **1a** alone. (d) Ees and yields of **3aa** in THF/DMPU mixed solvents.

On the basis of the above experiments and the literature knowledge on chiral amino alcohol-catalyzed organozinc addition,^{3a,13b} we propose a catalytic cycle involving a mixed zinc alkoxide **A** derived from Et₂Zn, the amino alcohol, and the cyclopropanol **1** as well as its homochiral and heterochiral dimers ([**A**]₂ and [**A**•*ent*-**A**]; Scheme 4). The monomeric mixed alkoxide **A** would act as a catalytically competent species, undergoing ring-opening to generate the corresponding homoenolate **B**. Upon coordination of the enone **2**, the homoenolate **B** would undergo asymmetric conjugate addition to give a zinc enolate **D**, which would deprotonate **1** to give the 1,6-diketone while regenerating the mixed alkoxide **A**. When there is no enone or ECA is sluggish, the homoenolate **B** can be protonated by **1** to give the corresponding ketone **1'**, which can further participate in enolate Michael addition under zinc catalysis. Based on the solvent effect (Figure 1d), the ability of DMPU as a Lewis base to Zn, rather than its bulk polarity as a solvent, appears to be critical for the preferential CA of the homoenolate over its protonation.

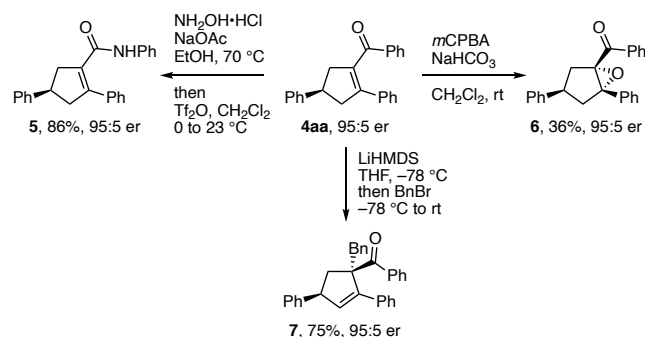
Scheme 4. Possible Catalytic Cycle



Selected transformations of the enantioenriched cyclopentene product **4aa** are shown in Scheme 5. Conversion of the benzoyl group to an anilide moiety via Beckmann rearrangement was achieved through oxime formation and subsequent treatment with Tf₂O, affording the product **5** in good yield. Epoxidation with *m*CPBA provided the tetrasubstituted epoxide **6** in a diastereoselective manner, albeit in a modest yield.

Generation of a dienolate species from **4aa** and LiHMDS was followed by trapping with benzyl bromide, which took place regioselectively at the α position to generate a quaternary stereocenter in the product **7** in a diastereoselective manner.

Scheme 5. Product Transformations



In summary, we have developed an enantioselective ring-opening conjugate addition of cyclopropanols to α,β-unsaturated ketones via catalytic generation of zinc homoenolate. A chiral β-amino alkoxide ligand on zinc accelerates the ring-opening of a cyclopropanol and aids in enantioselective addition of the resulting homoenolate to chalcones and related enones without assistance of transition metal catalyst. The ensuing intramolecular aldol condensation of the 1,6-diketone products allow for facile preparation of multisubstituted cyclopentene derivatives with good to high enantioselectivity. The reaction represents the first example of enantioselective transformation of zinc homoenolate, and also a rare example of asymmetric transformations of metal homoenolates in general. Further development and mechanistic study of synthetic transformations involving catalytically generated metal homoenolates are ongoing in our laboratory.

ASSOCIATED CONTENT

Experimental procedures and characterization data for all the new products (PDF).

Crystallographic data for **4da** (CIF)

Crystallographic data for **5ao** (CIF)

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Notes

The authors declare no competing financial interests.

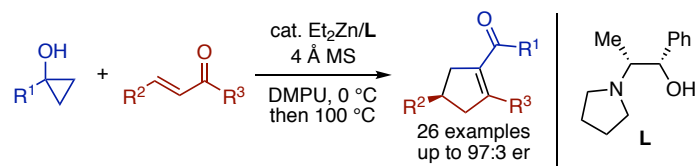
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- Ligand-accelerated, catalytic Zn homoenolate generation
 - TM-free enantioselective organozinc conjugate addition
 - Enantioenriched cyclopentane scaffolds
-