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Enantioselective Conjugate Addition of Catalytically Generated Zinc Homoenolate

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Cite This: J. Am. Chem. Soc. 2021, 143, 4775–4781
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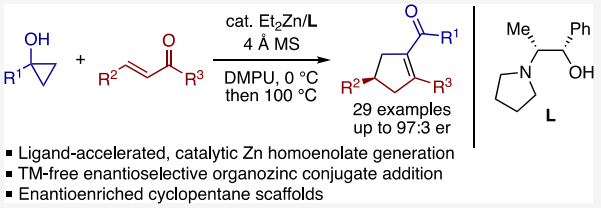
ABSTRACT: We report herein an enantioselective conjugate addition reaction of a zinc homoenolate, catalytically generated via ring opening of a cyclopropanol, to an α,β-unsaturated ketone. The reaction is promoted by a zinc aminoalkoxide catalyst generated from Et_2Zn and a chiral β-amino alcohol to 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 homoenolate 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.



INTRODUCTION

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 homoenolate 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 homoenolate has been reported.[4]

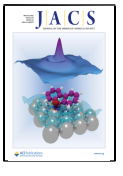
Recently, cyclopropanols have emerged as viable precursors for the in situ generation of ketone homoenolates.[1c−f] One of seminal studies in this context is Cha's work on allylic and propargylic substitutions mediated by stoichiometric Et_2Zn in combination with Cu(I) salt, where equilibrium generation of zinc homoenolate from the corresponding cyclopropoxide and its transmetalation to Cu(I) are likely involved (Scheme 1b).[5] However, such in situ generated zinc homoenolate 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 homoenolate 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]

RESULTS AND DISCUSSION

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 a 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 composed of Et_2Zn (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 to render the reaction

Received: January 23, 2021
Published: March 16, 2021



https://doi.org/10.1021/jacs.1c00869
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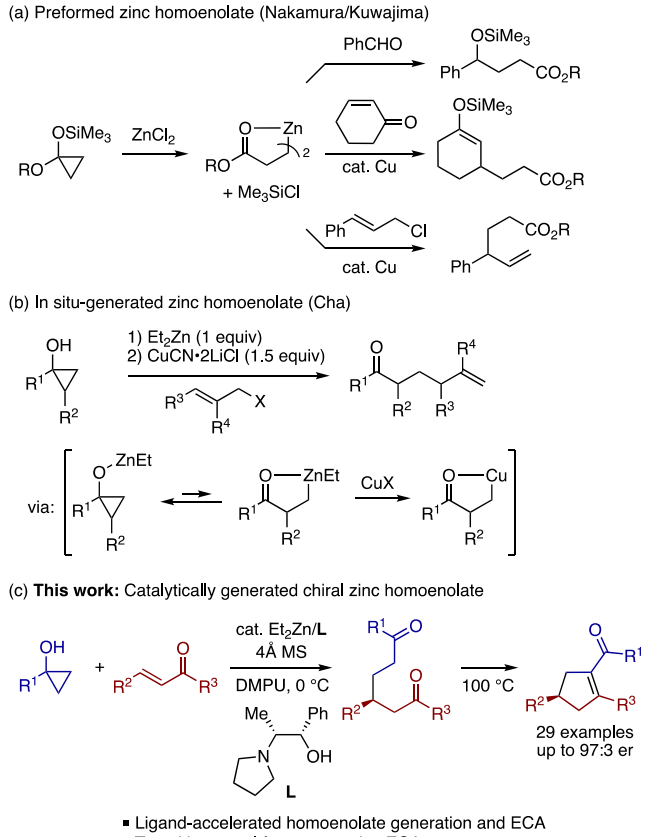
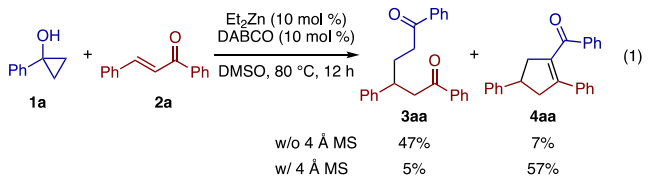
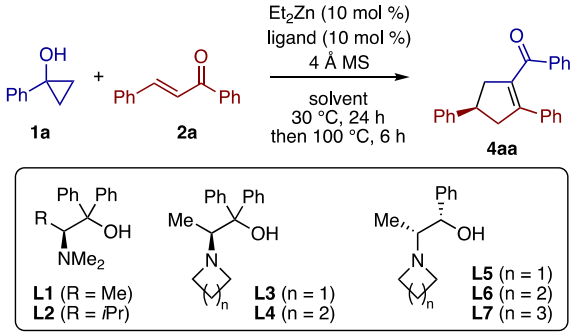
Scheme 1. Generation and C−C Bond-Forming Reactions of Zinc Homoenolate





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] In view of the relevance of five-membered ring scaffolds in bioactive compounds,[11] we focused on the formation of the cyclopentene product rather than the 1,6-diketone. In doing so, the effect of kinetic resolution in the aldol condensation step (see Table S1) was eliminated by forcing it to complete under harsh conditions (typically 100 °C, 6 h). 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 Et_2Zn and the norephedrine derivative **L6** (10 mol % each) 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

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

[a]The reaction was performed using 0.15 mmol of **1a** and 0.1 mmol of **2a** in 0.3 mL of solvent (0.33 M). [b]Determined by GC using mesitylene as an internal standard. [c]Determined by chiral HPLC. [d]15 mol % each of Et_2Zn and **L6** was used. The reaction was performed at 0 °C for 48 h and then at 100 °C for 6 h.

yield (89%) and the enantioselectivity (95:5 er) was achieved (entry 9).

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 cyclopentenes **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 the *p*-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 a 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**. This underlines that the enantiomeric ratio of **4aa** solely reflects the ECA step despite the feasibility of kinetic resolution during the intramolecular aldol condensation (see Table S1). 1-(2-Thienyl)-cyclopropanol and 1-(1-cyclohexenyl)cyclopropanol also smoothly took part in the reaction to furnish the desired products **4ia** and **4ja**, respectively, with 96:4 er. The reactions of 1-(*sec*-alkyl)cyclopropanols were somewhat sluggish and required higher temperatures. Nonetheless, the corresponding cyclopentene products (**4ka** and **4la**) were obtained with excellent enantioselectivity (97:3 er). In contrast, the reaction of 1-pentylcyclopropanol produced a mixture of inseparable products, as indicated by GC analysis prior to aldol condensation. The formation of the desired ECA product

https://doi.org/10.1021/jacs.1c00869
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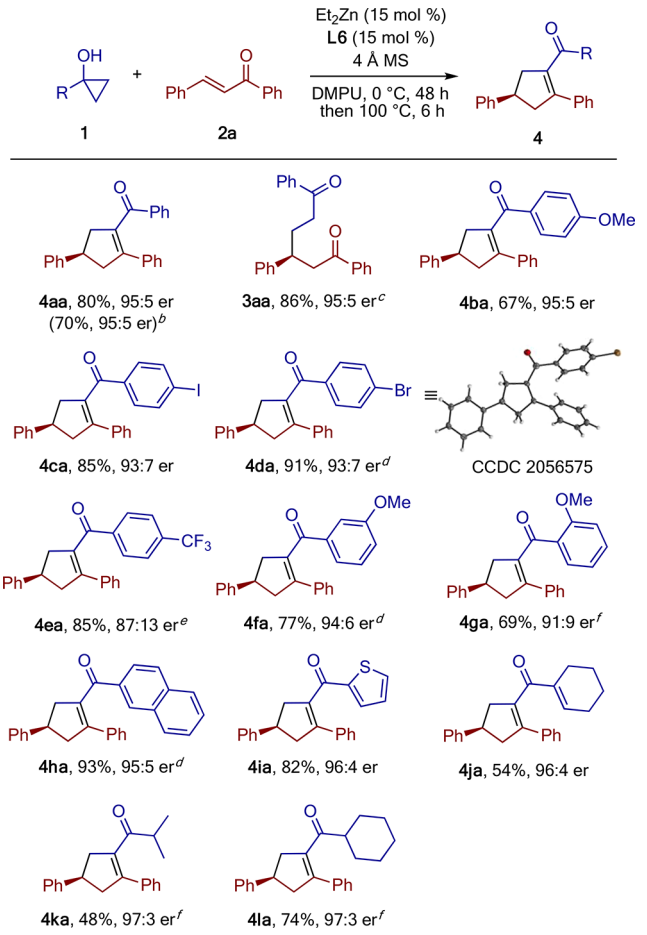
Scheme 2. Asymmetric Ring-Opening Addition of Various Cyclopropanols to 2a[a]

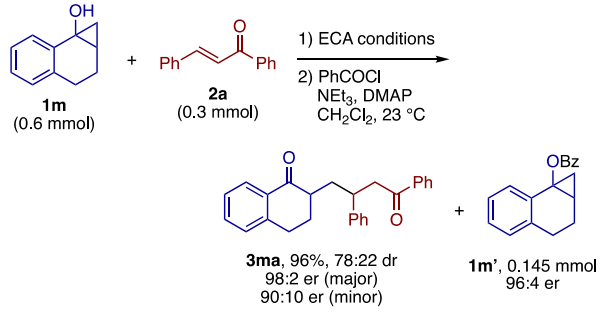


[a]The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 9. [b]3 mmol scale reaction. [c]The reaction was quenched without aldol condensation step. [d]The ECA step was performed at 0 °C for 72 h. [e]The ECA step was performed at 30 °C for 12 h. [f]The ECA step was performed at 30 °C for 48 h.

along with other bimolecular products (e.g., enolate Michael adduct) was suggested but not unambiguously confirmed.

A racemic bicyclic cyclopropanol **1m** (2 equiv) underwent selective cleavage of the less substituted C−C bond and afforded the desired conjugate adduct **3ma** as a diastereomer mixture (78:22 dr) in 96% yield, with 98:2 and 90:10 ers for the major and minor diastereomers, respectively (Scheme 3). Meanwhile, the unreacted **1m** was isolated in the form of benzoyl ester **1m′** in 24% yield (based on **1m**) with 96:4 er.

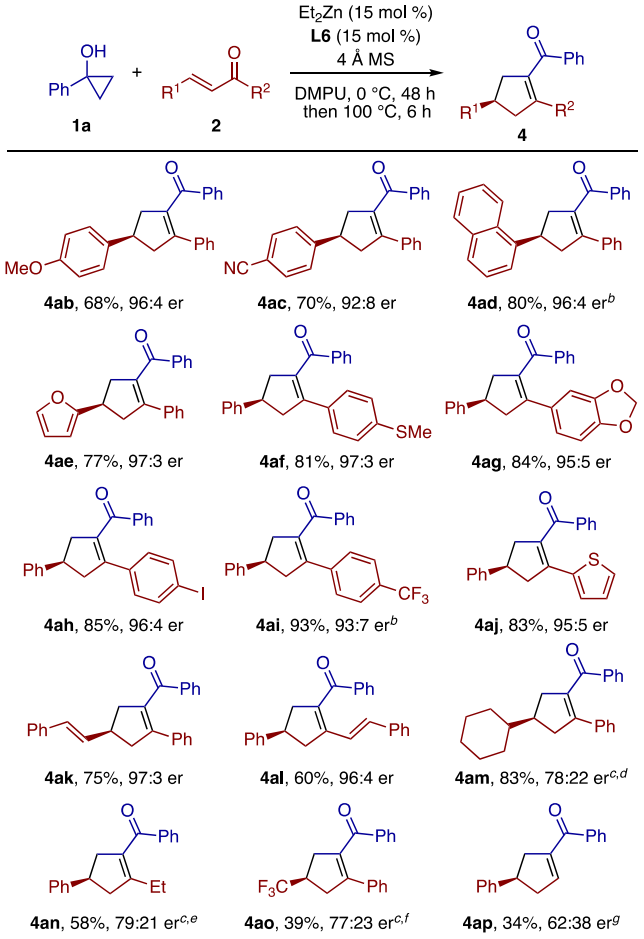
Scheme 3. Addition of Bicyclic Cyclopropanol 1m to 2a



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).

We next explored the addition of **1a** to various α,β-unsaturated ketones (Scheme 4). Chalcone-type di(hetero)-

Scheme 4. Asymmetric Ring-Opening Addition of 1a to Various Enones[a]



[a]The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 9. [b]The aldol condensation step was performed at 50 °C for 16 h. [c]**L3** was used instead of **L6**. [d]The reaction was performed in DMSO at 40 °C for 48 h and then at 100 °C for 6 h. [e]The ECA step was performed at 30 °C for 48 h. [f]The ECA step was performed at 30 °C for 24 h. [g]The ECA and aldol steps were performed at 60 °C for 12 h.

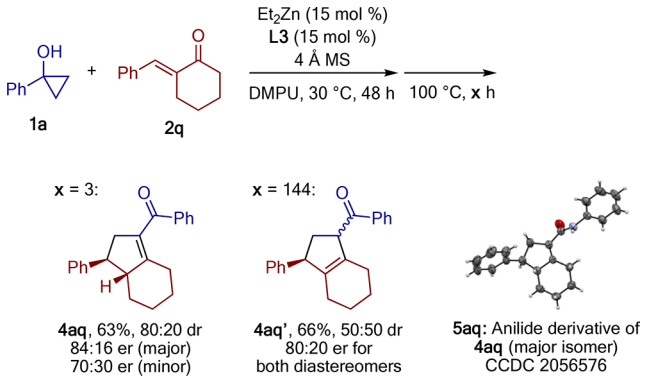
aryl-substituted enones proved to be excellent substrates, affording the corresponding cyclopentenes **4ab**−**4aj** in moderate to high yields with 92:8 to 96:4 er. A variety of functionalized aryl and heteroaryl groups could be tolerated on both ends of the enone skeleton. An α,β,γ,δ-unsaturated ketone underwent selective 1,4-addition of the homoenolate to give the alkenyl-substituted cyclopentene **4ak** with 97:3 er. Dibenzylideneacetone selectively afforded the monoconjugate addition product, which cyclized into the cyclopentene **4al** with equally high enantioselectivity (96:4 er). Unlike these examples, 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

https://doi.org/10.1021/jacs.1c00869
J. Am. Chem. Soc. 2021, 143, 4775−4781

substrates afforded the desired products **4am** and **4an** with moderate enantioselectivities (ca. 80:20 er). *β*-Trifluoromethyl enone also took part in the reaction, albeit in modest yield and enantioselectivity (see **4ao**). GC analysis of the reaction mixture prior to aldol condensation indicated the formation of other bimolecular products. Cinnamaldehyde was also found to undergo the homoenolate conjugate addition, affording the disubstituted cyclopentene **4ap** in diminished yield and enantioselectivity.

The reaction of (*E*)-2-benzylidenecyclohexan-1-one furnished, after 3 h of the aldol condensation step, a bicyclic product **4aq** as a mixture of diastereomers (80:20 dr) with ers of 84:16 (major) and 70:30 (minor) (Scheme 5). The relative

Scheme 5. Addition of 1a to (*E*)-2-Benzylidenecyclohexan-1-one



stereochemistry of the major diastereomer of **4aq** was confirmed by X-ray crystallographic analysis of its anilide derivative **5aq**. 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 **4aq′** (66% yield, 50:50 dr and 80:20 er for both diastereomers), presumably via a zinc dienolate intermediate (see Scheme S2). Note that other types of Michael acceptors such as cyclohexenone, methyl cinnamate, and *β*-nitrostyrene failed to undergo homoenolate conjugate addition under the achiral reaction conditions (see eq 1). As such, we did not explore the feasibility of their homoenolate ECA at this time.

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 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]). Furthermore, the reaction procedure was found to have a slight but non-negligible influence on NLE. Thus, while the above NLE experiments were set up according to the general procedure, which involves sequential addition (without a break longer than 15s) of Et_2Zn, **2a**, and **1a** to a mixture of **L6** and 4 Å MS in DMPU, aging of a mixture of **L6** and Et_2Zn for 10 min at room temperature prior to the addition of **1a** and **2a** slightly enhanced the NLE (Figure S5). On the other hand, the reaction temperature (30 vs 0 °C) and the solvent composition (DMPU vs DMPU/THF) had only a minor impact on NLE (see Figures S6 and S7). The ee of **L6**

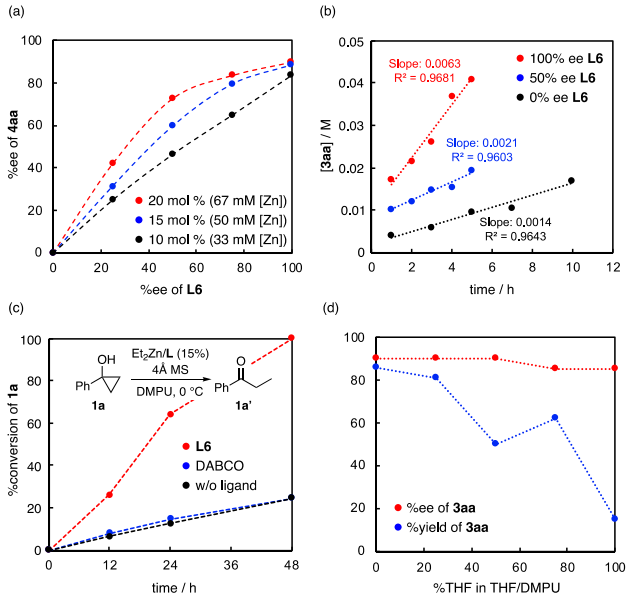


Figure 1. Mechanistic experiments. (a) Nonlinear effects with different catalyst loadings of Et_2Zn/**L6** (30 °C, 30 h and 100 °C, 6 h). (b) Initial reaction progress using **L6** of different ees (15 mol % catalyst loading, 0 °C). (c) Ring-opening of **1a** alone. (d) Ees and yields of **3aa** in THF/DMPU mixed solvents.

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). Note that the reaction mixtures appeared clear and homogeneous regardless of using enantiopure or racemic **L6**. Apart from these observations under the actual reaction conditions in DMPU, we found that mixing racemic **L6** and Et_2Zn in Et_2O immediately generated a white precipitate, which was a signature of the formation of insoluble heterochiral aggregates,[14] while a mixture of enantiopure **L6** and Et_2Zn in Et_2O formed a homogeneous solution. These observations may suggest that, in highly polar and Lewis basic DMPU, both homochiral and heterochiral Zn aminoalkoxide dimers form as soluble species and that the latter is reluctant to dissociate into catalytically relevant 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 under 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). We also 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 (≥50%) in the mixed solvents (%THF up to 75%).

It is well established that a 1:1 mixture of Et_2Zn and chiral *β*-amino alcohol gives rise to homochiral and heterochiral ethylzinc aminoalkoxide dimers, depending on the enantiomeric composition of the ligand.[13b] The heterochiral dimer is

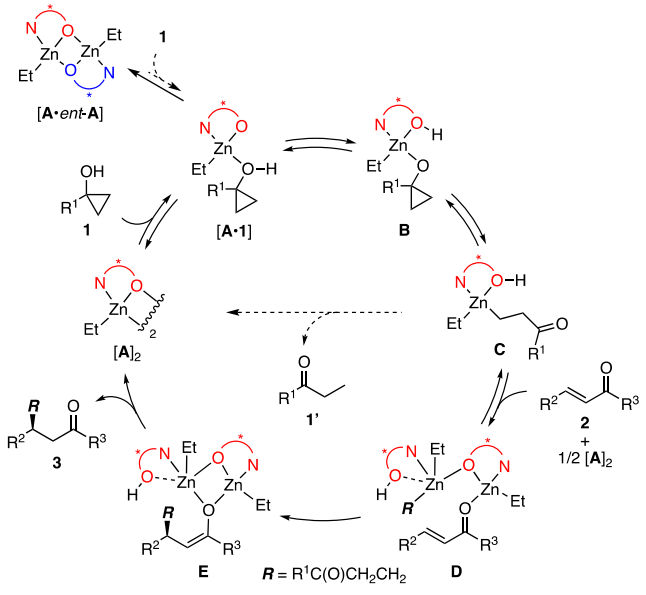
https://doi.org/10.1021/jacs.1c00869
J. Am. Chem. Soc. 2021, 143, 4775−4781

often much more stable and reluctant to dissociate into monomers, which is responsible for NLE in Et_2Zn addition to aldehyde. A question relevant to the present reaction system is what happens to such ethylzinc aminoalkoxide dimers upon exposure to cyclopropanol. In attempts to address this question, we measured ^{1}H NMR spectra of zinc species formed by mixing **L6** and Et_2Zn in a 1:1 ratio followed by another alcohol (1 equiv; *t*BuOH, *i*PrOH, or MeOH) as a model of the cyclopropanol substrate (see Figures S8−S11). Except for the case using MeOH, the ^{1}H NMR spectra showed clearly resolved quartet (~0.6 ppm) and triplet (~1.6 ppm) signals that could be assigned to an ethyl group on Zn. This observation indicates that ethylzinc aminoalkoxide [(**L6**-H)ZnEt] resists protonation of the remaining ethyl group by a bulky alcohol such as *t*BuOH and *i*PrOH, which should also be the case for the tertiary cyclopropanol substrates used in the present reaction. Similar observations have been made for the reluctance of [LZnEt] species toward protonation of the Zn−Et bond by alcohol.[15] Note also that, a sample prepared by mixing Et_2Zn and *t*BuOH first, followed by **L6**, gave rise to a ^{1}H NMR spectrum close to that of the above-mentioned experiment. This suggests that the initially formed (*t*BuO)-ZnEt underwent deprotonation of **L6** with *t*BuO rather than Et, thus generating [(**L6**-H)ZnEt] and *t*BuOH.

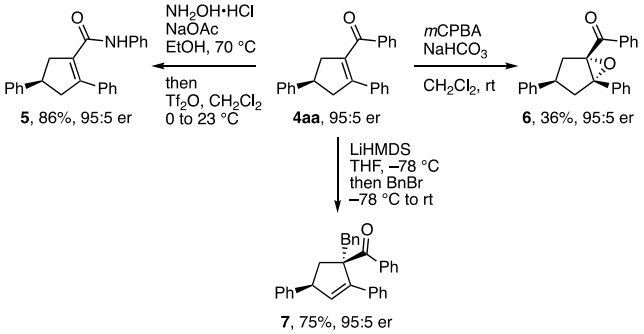
Given the reluctance of bulky alcohols to protonate the Zn−Et bond of [(**L6**-H)ZnEt], we speculate that the formation of a mixed zinc bisalkoxide species such as [(**L6**-H)(**1**-H)Zn] in the present reaction system is less likely and that a zinc cyclopropoxide species would form as a transient rather than resting species via reversible protonation of the aminoalkoxide ligand. With this conjecture, and on the basis of the above NLE and other experiments as well as the literature knowledge on chiral amino alcohol-catalyzed organozinc addition,[3a,13b] we suggest a tentative catalytic cycle as illustrated in Scheme 6. Coordination of the cyclopropanol **1** would break down the homochiral ethylzinc aminoalkoxide dimer $[\mathbf{A}]_2$ into a monomeric species [**A**·**1**]. Deprotonation of the cyclopropyl OH with the internal aminoalkoxide base would reversibly generate a cyclopropoxide species **B**, which would further undergo ring-opening to generate the corresponding homoenolate **C**. Association of the homoenolate **C** with the aminoalkoxide **A** and the enone **2** would generate a bimetallic species **D**,[16] followed by delivery of the homoenolate to give an enolate species **E**.[17] Proton transfer from the amino alcohol to the enolate would furnish the conjugate adduct **3** while regenerating the aminoalkoxide dimer $[\mathbf{A}]_2$. The heterochiral dimer [**A**·*ent*-**A**], preferentially formed when using racemic ligand, would be reluctant to dissociate into the monomer [**A**·**1**]. When there is no enone or ECA is sluggish, the homoenolate **C** could be protonated, possibly via internal proton transfer from the amino alcohol, to give the corresponding ketone **1′**, which could further participate in enolate Michael addition under zinc catalysis. On the basis of 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. Thus, we speculate that coordination of DMPU to zinc would assist in dissociation of the dimeric species and/or increasing the nucleophilicity of the homoenolate.

Selected transformations of the enantioenriched cyclopentene product **4aa** are shown in Scheme 7. Conversion of the benzoyl group to an anilide moiety via Beckmann rearrangement was achieved through oxime formation and subsequent treatment with Tf_2O, 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 6. Possible Catalytic Cycle



Scheme 7. Product Transformations



CONCLUSION

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 a transition-metal catalyst. The ensuing intramolecular aldol condensation of the 1,6-diketone products allows 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 mecha-

https://doi.org/10.1021/jacs.1c00869
J. Am. Chem. Soc. 2021, 143, 4775−4781

nistic study of synthetic transformations involving catalytically generated metal homoenolates are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00869.

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

Accession Codes

CCDC 2056575−2056576 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c00869

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministry of Education (Singapore) and Nanyang Technological University (MOE2016-T2-2-043 and RG101/19). We thank Dr. Yongxin Li (Nanyang Technological University) for his assistance with the X-ray crystallographic analysis.

■ DEDICATION

This article is dedicated to Professor Eiichi Nakamura on the occasion of his 70th birthday and in recognition of his seminal contribution to the chemistry of metal homoenolates.

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(16) Alternatively, the aminoalkoxide oxygen of **A** may form a hydrogen bond with the amino alcohol OH of the homoenolate **C** to give a different association complex. For such a complex, one may conceive a mechanism involving concerted proton transfer from **C** to **A** along with the nucleophile delivery. In any case, the bimetallic mechanism for the conjugate addition remains speculative and warrants further investigation.
(17) Note that the model reaction between **1a** and **2a** under the standard conditions did not give any trace of a byproduct arising from conjugate addition of the ethyl group to **2a**.

https://doi.org/10.1021/jacs.1c00869
J. Am. Chem. Soc. 2021, 143, 4775−4781