Synthetic Methods

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Direct Site-Specific and Highly Enantioselective γ-Functionalization of Linear α,β-Unsaturated Ketones: Bifunctional Catalytic Strategy**

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The direct asymmetric γ functionalization of simple unmodified carbonyl compounds has emerged as a powerful, distinct, and atom-economical method offering an efficient entry into functionalized building blocks having high levels of structural complexity.[1] Since the pioneering studies carried out by the groups of Jørgensen, Chen, Melchiorre, and others, different types of vinylogous processes initiated by dienamine intermediates have been studied extensively.[2] However, while there is an ever growing number of documents involving catalytic γ-selective activation of enals, the corresponding reaction embracing enones as γ-type nucleophiles remain comparatively rare. To date, the only example of enantioselective γ functionalization of cyclic enones has been reported by Melchiorre and co-workers who use cyclohexenone derivatives as nucleophilic substrates.[3] Nevertheless, for the γ-site-specific functionalization of linear α,β-unsaturated ketones, which usually act as electrophiles in Michael additions (Figure 1a)[4] or prefer to selectively direct the reaction toward α alkylation (Figure 1b),[5] still represents a longstanding challenge (Figure 1c).

Covalent activation facilitated by chiral amines provides a fascinating platform for stereocontrol in the functionalization at the γ-position of the carbonyl group through dienamine-type intermediates,[2] or even at the ε-position by trienamine catalysis.[6] However, as mentioned before, this strategy works well for HOMO-raising activation of γ- or ε-type nucleophiles equipped with an aldehyde group.[2a–i,6a–f] In the case of enones, the covalent catalytic process was not efficient for such a transformation. More importantly, for the ketones bearing an α′ hydrogen, the regioselectivity problem must be solved, especially for linear enones.[5,7] Very recently, Chen and co-workers used trienamine catalysis to perform a highly efficient asymmetric Diels–Alder reaction with linear 2,4-dienones to give an array of useful cyclohexene products.[8] Still, a "logical and careful design of the dienones" was needed to facilitate the reaction,[9] as it requires an aryl group at the α′-position to the carbonyl group to suppress reaction at the α′ site.

To this end, we envisioned the development of alternative catalytic strategies for the site-selective and stereocontrolled γ functionalization of linear enones.[10] We have recently reported an asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactams and found that the magnesium is prone to activating the γ hydrogen of the carbonyl group (Figure 2a).[11] On this basis, we explored the viability of magnesium catalysis to direct γ deprotonation of linear α,β-unsaturated ketones by introducing an appropriately placed base within the ligand to facilitate the γ-activation process (Figure 2b).

To test our hypothesis, we initially investigated a series of representative salen ligands, either bearing a base or not, in our model reaction. As illustrated in Table 1, the nature of the Brønsted base, such as a tertiary amine or even methoxy

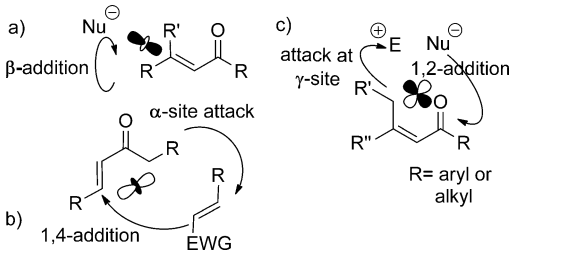

Figure 1. a,b) Previously reported strategies. c) Strategy for γ functionalization of linear enones proposed herein.

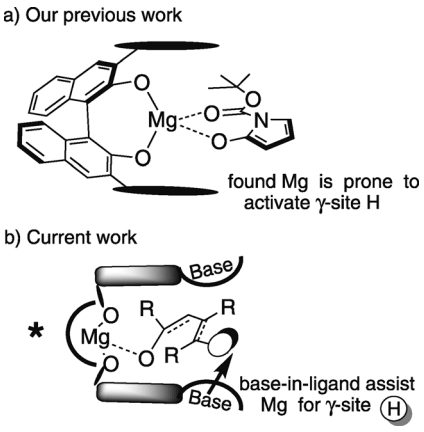

Figure 2. a) Catalyst design reported by our group previously. b) New ligand design reported herein. A base is introduced to assist in the activation of linear enones.

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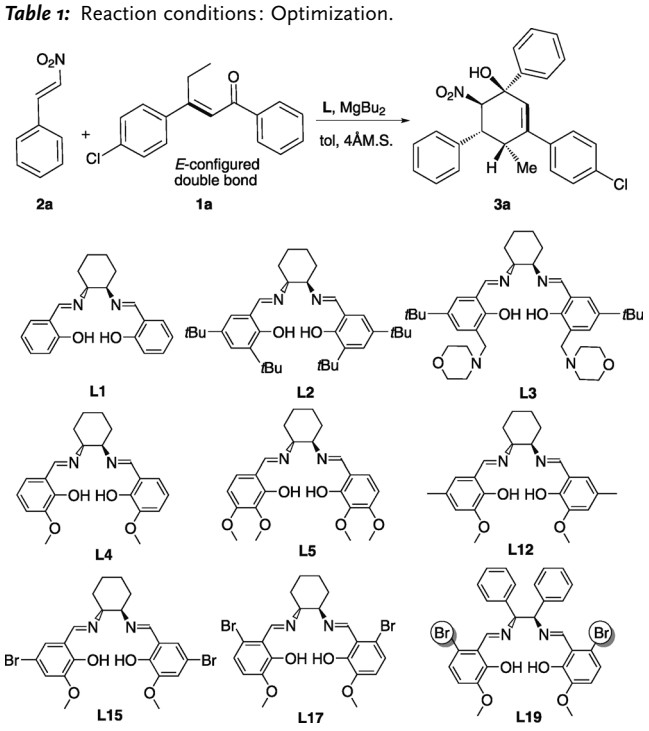
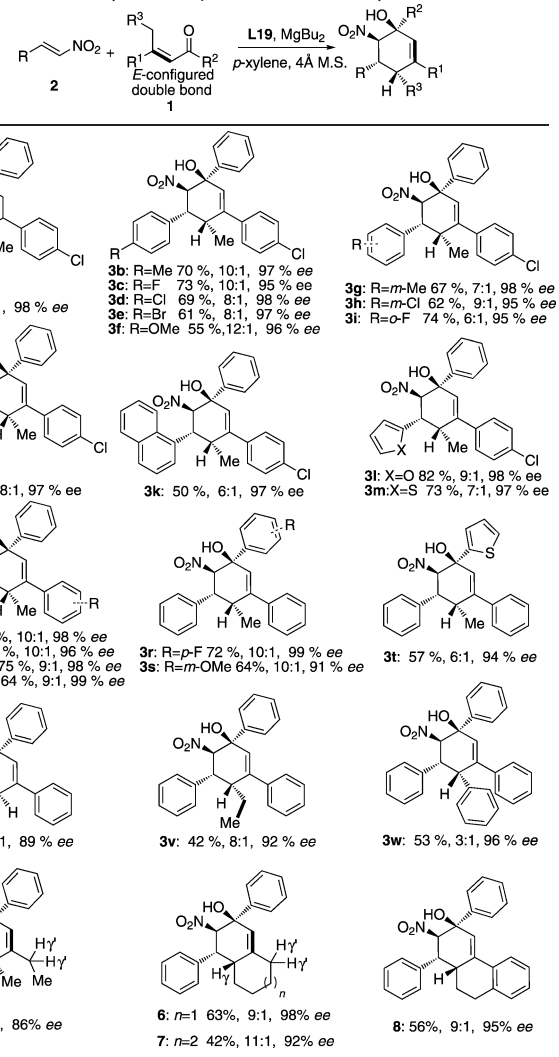
Table 1: Reaction conditions: Optimization.



Entry[a]	Ligand	Yield[b]	d.r.[c]	*ee*[d]
1	**L1**	7	–	–
2	**L2**	< 5	–	–
3	**L3**	48	6:1	68
4	**L4**	52	11:1	85
5	**L5**	50	11:1	39
6	**L12**	53	10:1	82
7	**L15**	62	9:1	80
8	**L17**	63	9:1	88
9	**L19**	59	9:1	92
10[e]	**L19**	64	9:1	98
11[e,f]	**L19**	72	9:1	98

[a] Reactions were performed with 0.2 mmol of **2a** and 0.3 mmol of **1a** in toluene (2.0 mL) in the presence of **L** (20 mol%), $MgBu_2$ (20 mol%), and molecular sieves (M.S.) at 60°C for 24 h. [b] Yield of isolated product. [c] Diastereomeric ratios were determined by ^{1}H NMR (300 MHz) spectroscopy. [d] Enantiomeric excesses of the major diastereomer were analyzed by HPLC analysis using a chiral stationary phase. [e] The reaction was carried out in *p*-xylene. [f] Use 0.4 mmol of **1a** (2.0 equiv).

Table 2: Substrate scope of the γ-functionalization cyclization.[a,b,c,d]



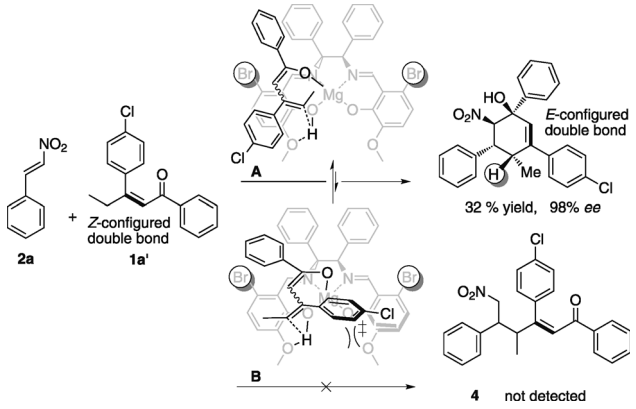
[a] Reactions were performed with 0.2 mmol of **2a** and 0.4 mmol of **1a** in *p*-xylene (2.0 mL) in the presence of **L19** (20 mol%), $MgBu_2$ (20 mol%) and 4 Å molecular sieves (200 mg) at 60°C for 24 h. [b] Yield of isolated product. [c] Diastereomeric ratios were determined by ^{1}H NMR (300 MHz) spectroscopy. [d] Enantiomeric excesses of the major diastereomer were analyzed by HPLC analysis using a chiral stationary phase.

group, introduced to a ligand was helpful for the γ-deprotonation process, probably through assistance from the base near the magnesium center of the catalyst (entries 3 and 4 versus 1 and 2). We turned our efforts to the screening and development of salen-type ligands having such an appended base.[12] This effort led to the identification of the bromine-substituted ligand **L19** as the optimal catalyst, and after optimization of the solvent,[13] the reaction in *p*-xylene afforded good diastereoselectivity (9:1) and high enantiomeric excess of 98% (entries 9 and 10).[14] The use of 2.0 equivalents of the ketone **1a** improved the product (**3a**) yield to 72% yield without loss in the enantioselectivity (entry 11).

Having established the optimized reaction conditions, we explored the scope of this new catalytic, stereoselective γ-functionalization protocol. The representative results are listed in Table 2. Nitroalkenes bearing a variety of aryl groups with either electron-donating or electron-withdrawing substitutents, or heteroaryl groups were well tolerated in this reaction, and the corresponding cyclization products were obtained with high *ee* values and moderate to good yields and diastereoselectivity (**3a**–**m**). However, aliphatic nitroalkenes could not undergo this transformation; the desired products were not detected under our standard reaction conditions. Furthermore, the linear β,β-disubstituted α,β-unsaturated ketones **1** bearing different aryl groups at either the β- or α′-positions were also compatible, thereby leading to the expected products (**3n**–**3t**). Notably, the presence of different substituents at the γ-position of the enones **2** were all tolerated, thus giving excellent *ee* values and moderate

yields (**3u, 3v, 3w**). We then turned our attention to substrates bearing both *Z*-γ- and *E*-γ′-hydrogen atoms to furnish the cyclization product **5** and the bicyclic compounds **6** and **7**. The benzocyclic ring systems **8** could also be obtained with excellent *ee* values and moderate yields. However, the ketones bearing different aliphatic substitutes at the β site and simple disubstituted enones were not tolerated under the present catalytic reaction and only resulted in complex mixtures.[15]

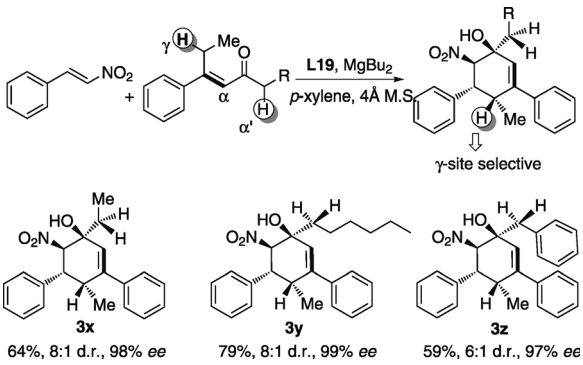
To gain insight into the activation mode of the γ-deprotonation-defining step of the reaction, we employed the (*Z*)-α,β-unsaturated ketone **1a′** under the standard, aforementioned reaction conditions (Scheme 1). We were surprised to observe that the cyclization product **3a** was also



Scheme 1. The cyclization reaction using the (*Z*)-α,β-unsaturated ketone **1a′**

formed with excellent *ee* value and the *Z*-configured double bond in **1a′** resulted in an *E*-configured double bond in **3a**. The product **4**, which maintains the *Z*-configured double bond was not observed. The result suggests that a dienol transition state should exist and the *Z*-configured double bond is transformed into an *E*-configured double bond during the γ-deprotonation process (**A**, Scheme 1). The dienol transition state might be more compatible with the catalysis structure, and a concerted reaction might also proceed smoothly through this favored configuration. Notably, the yield in this transformation was lower, probably owing to the isomerization of the double bond during γ-deprotonation process.

Finally and importantly, an experiment to probe site selectivity was carried out by using β,β-disubstituted α,β-unsaturated linear ketones containing α′ hydrogen atoms (Scheme 2). We were pleased to find complete γ selectivity in preference to the traditional α′ selectivity under our catalytic system (Scheme 2; **3x**, **3y**, **3z**).[16] The highly efficient site selectivity was no doubt determined by the presence of the bifunctional base within the ligand for the magnesium catalysis: 1) Magnesium is a superior metal for activating the γ hydrogen atoms of carbonyl groups, 2) the methoxy group introduced into the ligand might act as a Brønsted base to assist in the γ-deprotonation process, and 3) compared to the α′ site, the γ site might be better positioned to capture the



Scheme 2. Site selectivity demonstration for substrates bearing both α′ and γ hydrogen atoms.

β site of the electrophiles after complex formation with the metal center.

In summary, we have described the first examples of direct site- and enantioselective γ functionalization of linear β,β-disubstituted α,β-unsaturated ketones, thus leading to a variety of optically active cyclohexene frameworks which are not easily accessible using other methodologies. Success of the activation mode, site-specific selectivity, and asymmetric induction relies on the bifunctional base within the ligand. The development of this strategy in other, still challenging γ-functionalization reactions is currently ongoing.

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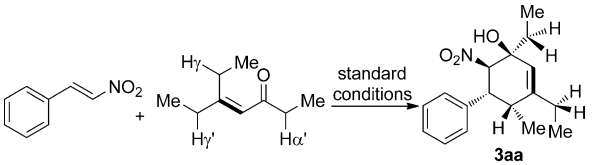
[13] See the Supporting Information for details of the reaction optimization with respect to the ligands and solvents.

[14] See the Supporting Information for details of the X-ray analysis.

[15] See the Supporting Information for some unsuccessful examples of the transformation.

[16] The enone bearing α′, γ, and γ′ hydrogen atoms could also generate the desired cyclization product with a lower *ee* value:



3aa
41%, 5:1 d.r., 50% *ee*