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C_3-Symmetric Chiral Trisimidazoline: Design and Application to Organocatalyst

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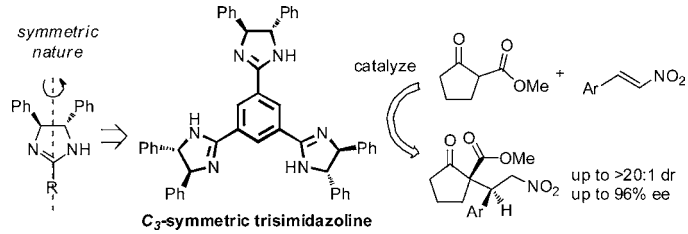
ABSTRACT



C_3-symmetric chiral trisimidazoline was designed and synthesized as a new entry of organocatalyst with the concept of constructing C_3-symmetric molecules with three C_2-symmetric chiral components, and the application of this novel catalyst to asymmetric conjugate addition of β-ketoesters to nitroolefins was described.

One of the key challenges in organic chemistry is to design and develop a new catalyst scaffold.[1] Imidazolines are structural analogues of oxazolines, which are one of the widely used structures for chiral ligands,[2] and various substituents can be introduced on the nitrogen atom for tuning the steric environment and electron density. Therefore, their use as chiral ligands has recently been developed.[3] Meanwhile, their use as organocatalysts has not been significantly explored, though they have great potential due to their basicity, nucleophilicity, and the Brønsted acidity of their salts (Figure 1i).[4] There are only a few asymmetric reactions with imidazolines as an organocatalyst such as the Diels−Alder reactions (as acid catalysts)[4a,b] and the Morita Baylis−Hillman reactions (as nucleophilic base catalysts).[4c] However, no high enantioselectivity has been achieved. In addition, despite the fact that there has been much attention regarding C_3-symmetric molecules in the area of molecular recognition, chiral ligands, and material science,[5,6] applications to organocatalysts are rare.[7] We now report the first highly enantioselective reaction

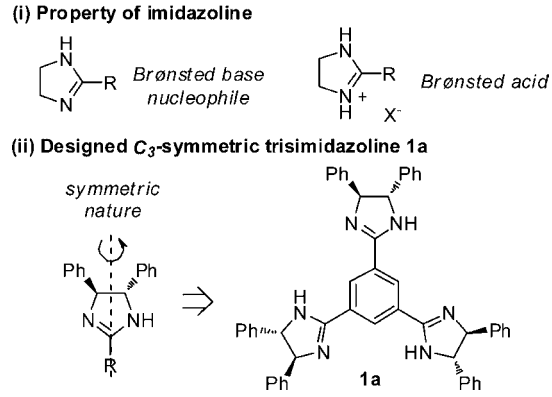


Figure 1. Design of the catalyst.

(1) *Comprehensive Asymmetric Catalysis*; Jacobsenm, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg: Germany, 1999; Vols. 1−3.

(2) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(3) Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2009**, *351*, 489.

(4) (a) Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661. (b) Akalay, D.; Dürner, G.; Bats, J. W.; Bolte, M.; Göbel, M. W. *J. Org. Chem.* **2007**, *72*, 5618. (c) Xu, J.; Guan, Y.; Yang, S.; Ng, Y.; Peh, G.; Tan, C.-H. *Chem. Asian J.* **2006**, *1*, 724. (d) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, *7*, 3461. (e) Annamalai, V. R.; Linton, E. C.; Kozlowski, M. C. *Org. Lett.* **2009**, *11*, 621.

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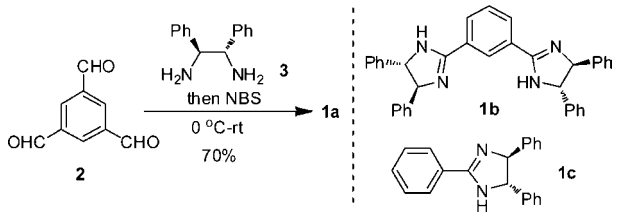
using imidazolines as an organocatalyst, i.e., the newly designed C_3-symmetric chiral trisimidazoline **1a** (Figure 1ii), with the concept of constructing C_3-symmetric molecules with three C_2-symmetric chiral components, as a Brønsted base catalyst[8] for the enantioselective conjugate addition of α-substituted β-ketoesters to nitroolefins.

Imidazolines derived from C_2-symmetric diamines, such as chiral 1,2-diphenyl ethylenediamine, have a symmetrical structure. To utilize the symmetric nature of imidazolines, we designed the C_3-symmetric trisimidazoline **1a** (Figure 1ii): three-imidazoline rings were substituted on the 1-, 3-, and 5-positions of the benzene ring. Since the interesting molecular recognition of trisimidazoline derived from ethylenediamine was reported to form 1:3 complexes with carboxylic acids or tetrazoles,[9] we expected that **1a** would have good interactions between the reaction substrates and provide a unique chiral environment. We chose the β-ketoester as a substrate assuming that the enolate of the β-ketoester and trisimidazoline **1a** could form a complex through hydrogen-bonding interactions. The conjugate addition of α-substituted β-ketoesters to nitroolefins was initially studied, because this reaction is very attractive from the point of constructing quaternary and tertiary stereocenters in one step.[10,11]

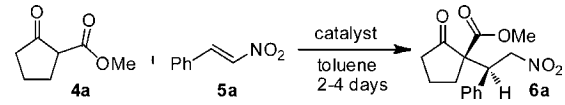
The C_3-symmetric trisimidazoline **1a** was readily prepared by a one-pot condensation−oxidation procedure developed by us[12] from trialdehyde **2** and chiral diamine **3** with NBS (Scheme 1). In the same way, bisimidazoline **1b** and monoimidazoline **1c** were also prepared for comparison.

Scheme 1. Preparation of Trisimidazoline **1a** (left) and Structures of Bisimidazoline **1b** and Monoimidazoline **1c** (right)



The reaction of methyl 2-oxocyclopentanecarboxylate (**4a**) and β-nitrostyrene (**5a**) was examined to evaluate the imidazoline catalysts **1a**−**c** (5 mol %) (Table 1). To our

Table 1. Evaluation of the Imidazolines **1a**−**c**[a]



entry	cat.	loading (mol %)	yield (%) (dr)	ee (%)[b]
1	**1a** (tris)	5	94 (18:1)	89
2	**1b** (bis)	5	91 (18:1)	61
3	**1c** (mono)	5	29 (5:1)	1
4	**1a** (tris)	2.5	97 (18:1)	90
5	**1b** (bis)	7.5	90 (16:1)	67
6[c]	**1a** (tris)	5	95 (20:1)	95

[a] Unless otherwise noted, the reaction was carried out with **4** (0.14 mmol) and **5** (0.21 mmol) with **1** in toluene (0.47 mL) at rt. [b] Ee of major diastereomer is shown. [c] −10 °C.

delight, the C_3-symmetric trisimidazoline **1a** had a good enantioselectivity (entry 1, 89% ee). A moderate selectivity was obtained with bisimidazoline **1b** (entry 2, 61% ee), while monoimidazoline **1c** produced an almost racemic product (entry 3, 1% ee). The reduction of the loading of **1a** and the increase of **1b** did not have significant influence on the selectivity: 2.5 mol % of **1a** afforded **6a** in 90% ee (entry 4) and 7.5 mol % of **1b** afforded **6a** in 67% ee (entry 5). These results indicated that at least two imidazolines on the benzene ring were essential for this reaction and the structure of trisimidazoline **1a** was much more effective than that of bisimidazoline **1b**. Encouraged by these results, we screened several solvents to optimize the conditions using **1a**. Details are shown in the Supporting Information, and less polar solvents tended to produce a good enantioselectivity but a protic solvent, such as MeOH, resulted in a poor selectivity (4% ee). After the optimization, lowering the reaction temperature to −10 °C led to a further improvement of the enantioselectivity (entry 6, 95% ee) with high diastereoselectivity.

With the optimized reaction conditions in hand, the generality of the reactions using the several nitroolefins and β-ketoesters was investigated (Table 2). The reaction of β-ketoester **4a** with different substituted aromatic nitroolefins, such as electron-rich, electron-poor, bulky, and heteroaromatic ones, afforded the corresponding adducts in good yields with high diastereo- and enantioselectivities (entries 1−7).

(5) For reviews, see: (a) Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248. (b) Gibson, S. E.; Castaldi, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4718. (c) Moberg, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4721. (d) Gibson, S. E.; Castaldi, M. P. *Chem. Commun.* **2006**, 3045.

(6) Interesting molecular recognitions and chiral ligands with C_3-symmetric trisoxazolines were reported. For examples, see: (a) Kim, S.-G.; Kim, K.-H.; Jung, J.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2002**, *124*, 591. (b) Ahn, K. H.; Ku, H.-Y.; Kim, Y.; Kim, S.-G.; Kim, Y. K.; Son, H. S.; Ku, J. K. *Org. Lett.* **2003**, *5*, 1419. (c) Gade, L. H.; Bellemin-Laponnaz, S. *Chem.—Eur. J.* **2008**, *14*, 4142.

(7) Han, J.; Wu, H.; Teng, M.; Li, Z.; Wang, Y.; Wang, L.; Pan, Y. *Synlett* **2009**, 933.

(8) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

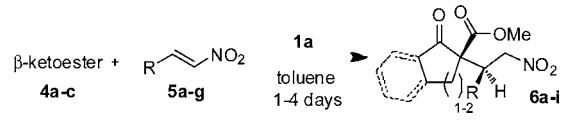
(9) (a) Kraft, A.; Fröhlich, R. *Chem. Commun.* **1998**, 1085. (b) Kraft, A.; Osterod, F.; Fröhlich, R. *J. Org. Chem.* **1999**, *64*, 6425. For another interesting propery of trisimidazolines, see: (c) Nam, S. R.; Kim, H.-J.; Sakamoto, S.; Yamaguchi, K.; Hong, J.-I. *Tetrahedron Lett.* **2004**, *45*, 1339–1342. (d) Yan, L.; Wang, Z.; Chen, M.-T.; Wu, N.; Lan, J.; Gao, X.; You, J.; Gau, H.-M.; Chen, C.-T. *Chem.—Eur. J.* **2008**, *14*, 11601–11609.

(10) For selected reviews on asymmetric 1,4-addition, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(11) For selected recent examples with organocatalysts, see: (a) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (d) Zhang, Z.-H.; Dong, X.-Q.; Chen, D.; Wang, C.-J. *Chem.—Eur. J.* **2008**, *14*, 8780. (e) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195. (f) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437. (g) Jiang, X.; Zhang, Y.; Liu, X.; Zhang, G.; Lai, L.; Wu, L.; Zhang, J.; Wang, R. *J. Org. Chem.* **2009**, *74*, 5562.

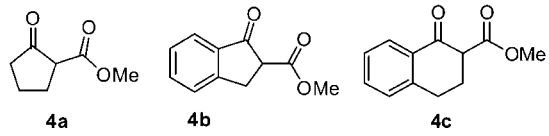
(12) (a) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197. (b) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638. For our related works, see: (c) Murai, K.; Morishita, M.; Nakatani, R.; Kubo, O.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 8947. (d) Murai, K.; Morishita, M.; Nakatani, R.; Fujioka, H.; Kita, Y. *Chem. Commun.* **2008**, 4498.

Table 2. Generality[a]



entry	4	R	6	yield (%) (dr)	ee (%)[d]
1	**4a**	Ph (**5a**)	**6a**	95 (>20:1)	95
2[b]	**4a**	4-MeOC$_6$H$_4$ (**5b**)	**6b**	94 (>20:1)	93
3	**4a**	4-ClC$_6$H$_4$ (**5c**)	**6c**	91 (>20:1)	96
4[b]	**4a**	4-FC$_6$H$_4$ (**5d**)	**6d**	95 (>20:1)	94
5[b]	**4a**	2-MeC$_6$H$_4$ (**5e**)	**6e**	79 (16:1)	94
6	**4a**	2-ClC$_6$H$_4$ (**5f**)	**6f**	96 (>20:1)	93
7	**4a**	2-thienyl (**5g**)	**6g**	95 (>20:1)	90[e]
8	**4b**	Ph (**5a**)	**6h**	99 (4:1)	74[f]
9[c]	**4c**	Ph (**5a**)	**6i**	71 (>20:1)	89

β-ketoester



4a **4b** **4c**

[a] Unless otherwise noted, the reaction was carried out with **4** (0.14 mmol) and **5** (0.21 mmol) with **1a** (0.007 mmol) in toluene (0.47 mL) at −10 °C. [b] 0 °C. [c] 10 mol % of **1a**, rt. [d] Ee of major diastereomer is shown. [e] Absolute and relative configurations were not determined. [f] Absolute configuration was not determined.

The indanone carboxylate **4b** and tetralone carboxylate **4c** were also applicable (entries 8 and 9). Most of the products **6** were reported compounds and proposed stereochemistries in the literature[11b,d] were shown as the scheme in Table 2.

On the basis of the results of the reaction with trisimidazoline **1a**, bisimidazoline **1b**, or monoimidazoline **1c** (see, Table 1, entries 1−3), two imidazolines on the benzene ring were involved in the enantioselective addition. Since imidazolines would work as Brønsted bases, they could activate the β-ketoesters. Once the imidazolines were protonated, they could work as proton donors. Therefore, we assume that the following two activation models i and ii are possible (Figure 2): (i) the β-ketoester could be activated through interactions with the two imidazolines to discriminate the enantiotopic face of the enolate and (ii) the β-ketoester and nitroolefin could be activated by one imidazoline, respectively. In both models, one imidazoline (ring a, Figure 2) should work as a Brønsted base and another imidazoline (ring b, Figure 2) as a proton donor. The importance of the hydrogen atom on the nitrogen of **1a** was supported by the low selectivity of the reaction in MeOH and the control experiment with *N*-Me trisimidazoline **1d** (Scheme 2); the reaction of **4a** and **5a** with **1d** afforded **6a** in 26% ee and the reaction with **1d** was much slower than that with **1a**.[13]

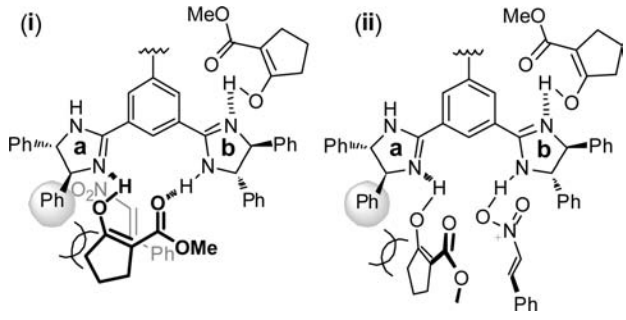
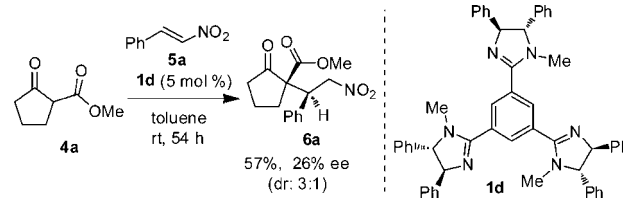


Figure 2. Possible transition states.

Scheme 2. Control Experiment with *N*-Me Trisimidazoline **1d**



The beneficial effect of the C_3-symmetry of **1a** was assumed to create three equally aligned reaction sites surrounded by two imidazolines providing a better chiral environment. On the other hand, in the case of bisimidazoline **1b**, the reaction could proceed in a space outside of the possible reaction site surrounded by two imidazolines and be catalyzed by one of the two imidazolines, though the details need to be investigated.

In summary, we have designed the C_3-symmetric trisimidazoline **1a** as a new organocatalyst, and demonstrated that it catalyzes the asymmetric conjugate addition of β-ketoesters to nitroolefins. This is the first highly enantioselective reaction with imidazolines as organocatalyst. The superiority of the C_3-symmetric structure on the imidazoline catalyst was also demonstrated. The efficiency as an organocatalyst could be regarded as one of the new functionalities of C_3-symmetric molecules and the design principle constructing C_3-symmetric molecules with three C_2-symmetric chiral components could be applicable to other organocatalysts. Additional investigations to clarify the mechanism and its applications to other reactions are currently underway.

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Supporting Information Available: Experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) When **1a** was used, the reaction time was 48 h (Table 1, entry 1), while when **1d** was used, the reaction was not completed and stopped in 54 h.