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## Accepted Article

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# Enantioselective Cyclopropanation of 4-Nitroisoxazole Derivatives

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**Abstract.** The present study reports an asymmetric organocatalytic cascade reaction of 4-nitroisoxazole derivative with *α,β*-unsaturated aldehydes catalysed by chiral secondary amine. Using this approach, 1,2,3-trisubstituted cyclopropane products were obtained in isolated yields up to 98% with moderate diastereoselectivities, and enantiopurity up to 99% *ee*. Moreover, this synthetic protocol can be used for further applications, as shown by a set of additional transformations of the corresponding cyclopropanes and by the formal synthesis of GABA ligands.

**Keywords:** Asymmetric catalysis; Organocatalysis; Heterocycles; Cyclization; Domino reactions

The smallest cycloalkanes – cyclopropanes – are a group of compounds commonly used in modern organic synthesis[1] to prepare not only bioactive compounds but also natural molecules, such as terpenes, pheromones, unusual amino and fatty acids or their metabolites.[2] Unsurprisingly, several cyclopropanes are available in the pharmaceutical market, showing a wide range of biological activities, from enzyme inhibition to antifungal, antimicrobial, antibiotic, antibacterial, antitumor or antiviral activity (Figure 1, A).[3] Considering the high potential of the cyclopropane scaffold in medicinal chemistry, considerable research has focused on the development of efficient methods for the synthesis of enantiomerically enriched cyclopropanes.

Since the pioneering studies by Simmons and Smith,[4] and later by Nozaki,[5] a common strategy to build a chiral cyclopropane motif has consisted of [2+1] cycloaddition between olefins and carbenes or metal-carbenoids.[6] In addition, several radical processes have also been successfully used to prepare chiral cyclopropanes.[8] Currently, although this research area is dominated by transition-metal catalysis and biocatalysis,[7] the increasing popularity of organocatalysis has prompted organic chemists to perform asymmetric synthesis of cyclopropanes using an organocatalytic approach.[9] Among these approaches, one of the most commonly applied organocatalytic concept is based on Michael-initiated ring closing (MIRC) cyclopropanation using aminocatalysis and non-covalent catalysis.[10] Cyclopropanation based on iminium-enamine activation involves a conjugate addition to an electrophile producing an enamine, which then undergoes an intramolecular ring closure.[7f] MIRC cyclopropanation can be performed as cascade Michael/*α*-alkylation reaction between *α,β*-unsaturated aldehydes activated by chiral secondary amines and readily enolisable nucleophiles such as *α*-halogenated malonates,[11] bromonitroalkanes,[12] electron-deficient benzyl halides[13] and sulfurylides.[14]

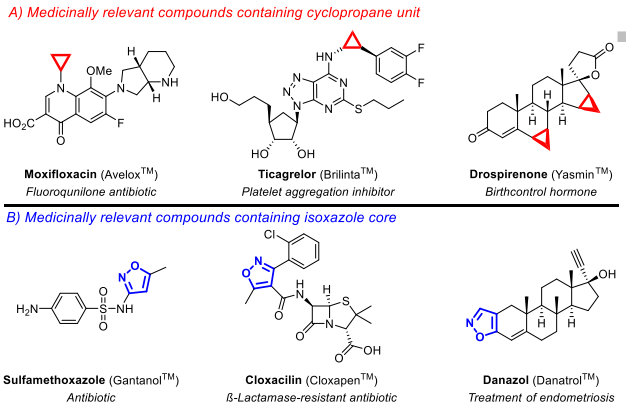


**Figure 1.** Examples of medicinally relevant compounds

The isoxazole moiety is an important class of five-membered heterocycles. This structural motif has been consistently used as a versatile building block in organic synthesis.[15] Moreover, several drugs and natural products contain an isoxazole moiety (Figure 1, B).[16] Interestingly, the first synthesis of optically active isoxazole derivatives using metal-free functionalization of 4-nitro-5-styrylisoxazoles was reported by Adamo, in 2009.[17] To date, several enantioselective organocatalytic additions to 4-nitro-5-styrylisoxazoles have been developed,[18] including

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cyclopropanation with *α*-halogenated malonates [19] or other cyclizations using diverse soft nucleophiles.[20] Recently, the nucleophilic character of 3,5-dimethyl-4-nitroisoxazole was revealed in an enantioselective addition to enals.[21] In addition, hard nucleophiles, such as $OH^-$ or $CF_3^-$, react *via* addition to the electrophilic carbon at the 5-position of the isoxazole ring.[22] Conversely, the methyl substituent at the 5-position reacts with soft electrophiles due to its nucleophilic character caused by the nitro group at the 4-position.[23] Interestingly, the reactivity of readily available 5-halomethyl-4-nitroisoxazoles has not been studied yet.

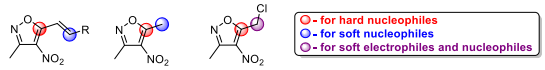
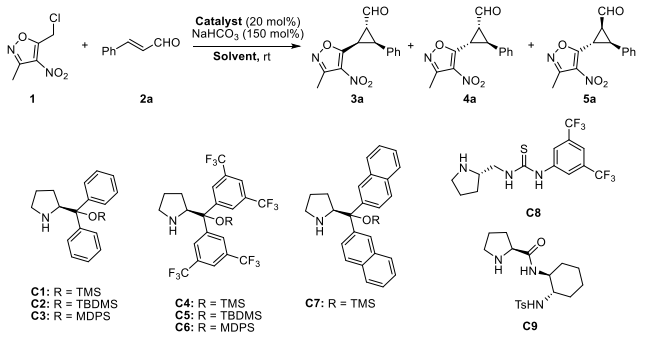



**Figure 2.** Reactivity of 3,5-dimethyl-4-nitroisoxale, 4-nitro-5-styrylisoxazoles and 5-(chloromethyl)-3-methyl-4-nitroisoxazole

In sharp contrast to the well-developed MIRC cyclopropanation of *α,β*-unsaturated aldehydes with various nucleophiles, organocatalytic MIRC cyclopropanation between *α,β*-unsaturated aldehydes and 5-(chloromethyl)-3-methyl-4-nitroisoxazole for the preparation of 1,2,3-trisubstituted cyclopropanes remains unpublished despite their natural occurrence and relevant biological activity.

We began our study by mixing readily accessible 5-(chloromethyl)-3-methyl-4-nitroisoxazole[24] (**1**) and *trans*-cinnamaldehyde (**2a**) in the presence of a chiral Hayashi-Jørgensen catalyst (**C1**) and triethylamine for trapping HCl, producing, as expected, **3a**, **4a** and **5a**, in a moderate combined yield, with good enantioselectivities (entry 1, Table 1). The enantiomeric purity of diastereomers **3a**, **4a** and **5a** was determined by HPLC of the more stable Wittig reaction adducts **6a**, **7a** and **8a**, respectively (see SI file for further information). Similar results of MIRC cyclopropanation between **1** and **2a** were also assessed when using other organic bases, such as 2,6-lutidine or Hünig's base (entries 2, 3). In turn, the model reaction conducted with $NaHCO_3$ provided the corresponding products with a better isolated yield (entry 4). When using the more sterically demanding diphenylprolinol catalysts **C2** and **C3** (entries 5 and 6), the enantioselectivities were increased, and the yields were up to 77%. Other prolinol-based catalysts, such as the *O*-silylated *bis*(3,5-trifluoromethyl)-diphenyl prolinols **C4**-**C6** (Jørgensen catalysts) provided slightly higher diastereoselectivities, albeit with a significantly reduced enantiomeric enrichment of product **5a** (entries 7-9). We also tested other prolinol catalysts, including bifunctional catalysts combining a proline-based secondary amine with thiourea or with a diamine unit (**C8** and **C9**), but the enantiocontrol of the reaction was almost entirely lost (entries 11, 12). For more details, see Tables **S1**-**S4** in the SI file.

**Table 1.** Screening of catalysts and other optimization studies




| Entry[a] | Cat. | Solvent | Time (h) | Dr[b] | Yield[c] (%) | *ee*[d] (%) |
|---|---|---|---|---|---|---|
| 1[e] | **C1** | DCM | 15 | 1.9/1/1.4 | 43 | 90/89/69 |
| 2[f] | **C1** | DCM | 15 | 1.3/1/1.3 | 41 | 94/89/73 |
| 3[g] | **C1** | DCM | 15 | 1.9/1.0/1 | 36 | 92/86/77 |
| 4 | **C1** | DCM | 15 | 1.2/1.1/1 | 74 | 96/86/81 |
| 5 | **C2** | DCM | 15 | 1.4/1.0/1 | 61 | 97/92/90 |
| 6 | **C3** | DCM | 15 | 2.4/1.0/1 | 77 | 99/98/98 |
| 7 | **C4** | DCM | 40 | 1.6/1.3/1 | 84 | 95/98/60 |
| 8 | **C5** | DCM | 15 | 5.2/4.5/1 | 88 | 98/99/75 |
| 9 | **C6** | DCM | 40 | 5.6/4.4/1 | 95 | 99/99/74 |
| 10 | **C7** | DCM | 15 | 2.1/1.0/1 | 30 | 99/84/78 |
| 11 | **C8** | DCM | 15 | 1.3/1.1/1 | 30 | -1/10/23 |
| 12 | **C9** | DCM | 85 | 1.4/1.5/1 | 59 | 24/-14/53 |
| 13 | **C5** | MeCN | 3 | 3.2/5.1/1 | 94 | 97/98/38 |
| 14 | **C3** | MeCN | 15 | 1.6/1/1.0 | 88 | 98/94/93 |
| 15 | **C3** | $Et_2O$ | 15 | 2.3/1/1.4 | 78 | 99/99/92 |
| 16 | **C3** | Toluene | 15 | 3.2/1/1.3 | 37 | 99/99/99 |
| 17[h] | **C3** | DCM | 15 | 1.4/1/1.0 | 96 | 98/98/96 |

[a] Reactions were conducted with **1** (0.3 mmol), **2a** (0.6 mmol), $NaHCO_3$ (0.45 mmol) and 20 mol% catalyst in 1.0 ml solvent at rt. [b] Determined by $^1$H-NMR analysis of the crude reaction mixture, (**3a**/**4a**/**5a**). [c] Isolated combined yield. [d] Determined by chiral HPLC analysis of methyl esters after Wittig reaction (**6a**/**7a**/**8a**). [e] Using triethylamine. [f] Using 2,6-lutidine. [g] Using *N,N*-diisopropylethylamine. [h] Using 15 mol% catalyst. TMS – trimethylsilyl, TBDMS – *tetr*-butyldimethylsilyl, MDPS – methyldiphenylsilyl.

After optimizing the reaction conditions, we began exploring the scope of this organocatalytic cyclopropanation reaction by varying the aldehyde **2** (Table 2). We assessed the effect of the electronic properties of the substituents at the aromatic ring on reactivity and on stereochemical outcome. In almost every case, corresponding cyclopropanes **3**, **4** and **5** were obtained in high isolated yields (80-98%) with enantioselectivities ranging from 80% to 99% *ee* and diastereoselectivities from 1.3/1/1 to 2.5/1/1.2. Cyclopropanes derived from aldehydes bearing halogen or other electron-withdrawing groups in the *para* position of the aromatic ring (entries 4-6 and 11, 12) were obtained in high yields (73-92%), with enantioselectivities ranging from 83 to 99% (typically higher than 95%) and with diastereoselectivities of up to 1.9/1/1.1). Cyclopropanes derived from an aldehyde with electron-donating groups in the *para*

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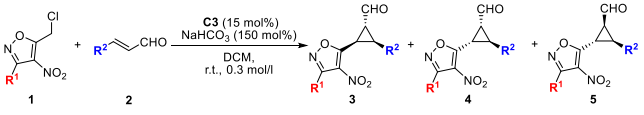
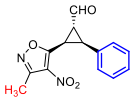
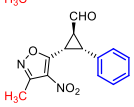
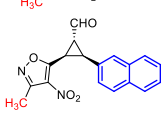
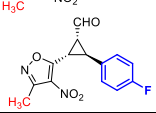
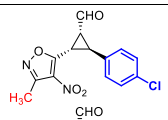
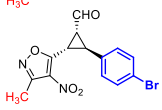
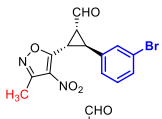
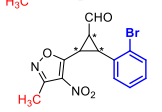
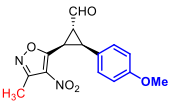
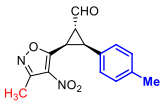
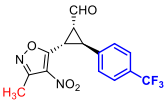
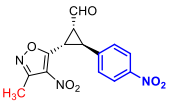
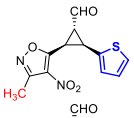
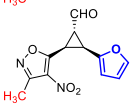
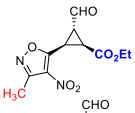
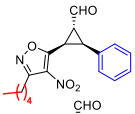
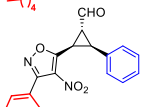
position were prepared with similar efficiency and selectivity. Only the reaction with the *p*-methoxycinnamic aldehyde afforded the minor diastereomer **4h** with a significantly reduced enantiocontrol (*ee* = 79%, entry 9). Conversely, the diastereomer **4i** (*p*-tolyl, entry 10) with the same configuration was obtained with 95% enantiopurity. High reactivity and stereocontrol were also reached when using *ortho*- and *meta*-substituted aromatic aldehydes (entries 7,8). For example, the *meta*-brominated aldehyde **2f** provided all cyclopropanes in high yield (80%) and in an almost enantiopure form for every diastereomer (99%/98%/99% *ee*). In addition to aromatic aldehydes, heteroaromatic aldehydes were explored (entries 13, 14). Interestingly, diastereomers **5l** and **4m** were obtained with slightly reduced enantioselectivities of 76% and 75% *ee*, respectively. Moreover, we were able to purify the diastereomer **3l** from the starting aldehyde only by HPLC. Furthermore, we tested aliphatic *α,β*-unsaturated aldehydes and ethyl (*E*)-4-oxobut-2-enoate (**2n**). Enal **2n** provided the corresponding products with high yields and enantioselectivities, whereas the aliphatic enals bearing *γ*-protons provided a complex mixture with only traces of the desired products (entry 16). Subsequently, we examined various isoxazoles **1** under optimised reaction conditions. The reaction between *trans*-cinnamaldehyde and isoxazole with a longer aliphatic chain at the 3-position afforded the corresponding cyclopropanes **3o**, **4o**, **5o** in high yields and with high enantioselectivity, albeit with reduced diastereocontrol. Similar results were obtained when treating *trans*-cinnamaldehyde with 5-(chloromethyl)-3-phenyl-4-nitroisoxazole (entry 18). Further variations of a key isoxazole derivative **1**, such as changing the nitro group to other electron-withdrawing groups, such as cyano, trifluoromethyl and ester groups, were not tested due to difficulties in preparing the designed starting materials.

**Table 2.** Substrate scope of the cyclopropanation reaction

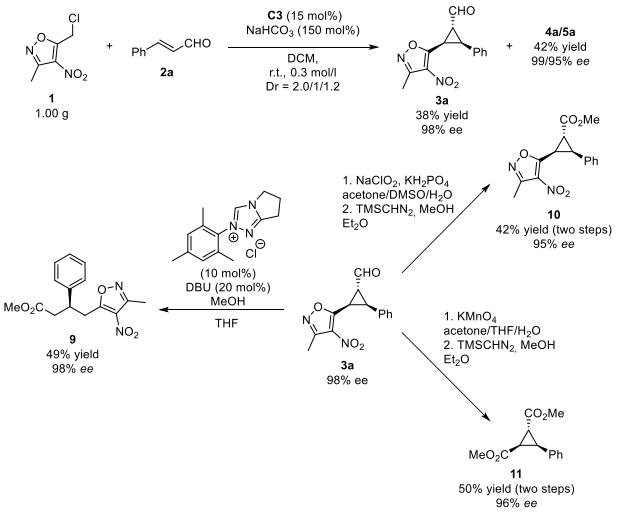



| Entry[a] | Isolated pure diast.[b] | | Time (h) | Dr[c] | Yield (%)[d] (yield of pure dia) | *ee* (%)[e] |
|---|---|---|---|---|---|---|
| 1 |  | **3a** | 15 | 1.4/1/1.0 | 96 (40) | 98/98/96 |
| 2[f] |  | *ent*-**3a** | 15 | 1.5/1/1.0 | 92 (39) | 98/97/95 |
| 3 |  | **3b** | 96 | 1.3/1/1.0 | 97 (40) | 96/99/81 |
| 4 |  | **4c** | 24 | 1.9/1/1.1 | 82 (20) | 99/97/85 |
| 5 |  | **4d** | 24 | 1.7/1/1.2 | 73 (18) | 99/94/94 |
| 6 |  | **4e** | 24 | 1.6/1/1.0 | 92 (27) | 98/97/83 |
| 7 |  | **4f** | 24 | 1.4/1.0/1 | 80 (21) | 99/98/99 |
| 8 |  | **3g** **4g** **5g** | 24 | 1.4/1/1.9 | 72 (23/17/32) | 95/88/80 |
| 9 |  | **3h** | 20 | 1.9/1/1.3 | 93 (42) | 97/79/95 |
| 10 |  | **3i** | 26 | 2.5/1/1.2 | 82 (41) | 98/95/94 |
| 11 |  | **4j** | 18 | 1.6/1/1.0 | 88 (24) | 99/96/93 |
| 12 |  | **4k** | 24 | 1.7/1.2/1 | 98[g] (n.d.)[h] | 98/98/88 |
| 13 |  | **3l** | 30 | 1.6/1/1.0 | 52[g] (n.d.)[h] | 97/97/76 |
| 14 |  | **3m** | 24 | 1.6/1/1.7 | 78 (29) | 87/75/93 |
| 15 |  | **3n** | 18 | 1.7/1/1.4 | 78 (34) | 94/87/86 |
| 16 |  | - | 120 | n.d. | traces | n.d. |
| 17 |  | **3o** | 18 | 1.0/1/1.1 | 84[g] (23) | 99/96/83 |
| 18 |  | **3p** | 18 | 1.1/1/1.1 | 85 (27) | 98/93/89 |

[a] Reactions were conducted with **1** (0.3 mmol), **2** (0.6 mmol), $NaHCO_3$ (0.45 mmol) and **C3** (20 mol%) in DCM (1.0 ml) solvent at rt. [b] Isolated after column chromatography. [c] Determined by 1H-NMR analysis of the crude reaction mixture, (**3**/**4**/**5**). [d] Isolated combined yield. [e] Determined by chiral HPLC analysis of methyl esters after Wittig reaction (**6**/**7**/**8**). [f] Using catalyst *ent*-**C3.** [g] NMR yield for **3**/**4**/**5.** [h] Inseparable mixture with starting material or other by-products (typically isolable after Wittig reaction).

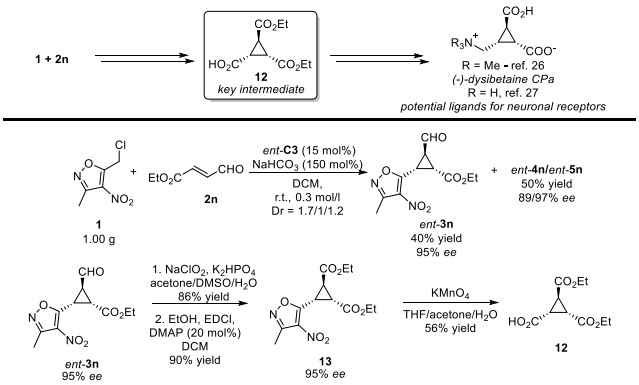
To test the developed organocatalytic system on a large scale, 1.00 g isoxazole **1** was used to perform the cyclopropanation reaction, obtaining the products in 80% yield, with same enantioselectivities (98%/99%/95% *ee*) and with slightly increased diastereoselectivities (Scheme 1). The applicability of the resulting cyclopropanes was demonstrated in the set of transformations described in Scheme 1. The regioselective opening of cyclopropane **3a** by NHC-catalysed redox esterification[25] afforded ester **9**

in 49% yield, with 98% enantiopurity. Similarly, when aldehyde **3a** was selectively oxidized by Pinnick oxidation and subsequently methylated using trimetylsilyl-diazomethane, the yield and enantiopurity were 42% and 95% *ee*, respectively. We were also able to transform the isoxazole ring into carboxylic acid by treatment with $KMnO_4$. Under these conditions, the aldehyde moiety was also oxidized to carboxylic acid. The resulting dicarboxylic acid was converted into dimethyl ester **11** in 50% yield and without significantly changing the enantiomeric purity.




**Scheme 1.** Gram-scale experiment and other transformations of cyclopropane **3a**

Lastly, we demonstrated the value of synthesized 1,2,3-trisubstituted cyclopropanes **3** for the synthesis of a naturally occurring compound, (-)-dysibetaine CPa.[26, 27] This compound and its desmethyl analogue stand out as potential ligands for neuronal receptors such as $\gamma$-aminobutyric acid (GABA) receptors, as they incorporate a GABA motif.[28] The enantioenriched key intermediate **12** can be prepared from ethyl (*E*)-4-oxobut-2-enoate (**2n**) using an *ent*-**C3**-catalysed cyclopropanation protocol, followed by Pinnick oxidation, EDC-mediated esterification and oxidation with $KMnO_4$ (Scheme 2).




**Scheme 2.** Formal total synthesis of (-)-dysibetaine CPa and its desmethyl analogue

The relative configuration of all diastereomers **3**, **4** and **5** prepared by MIRC cyclopropanation was determined by 1D NOE NMR spectroscopy (for more details, see the SI file). In addition, the absolute configuration of diastereomers **3** and **4** was ascertained by X-ray diffraction analysis of methyl ester *ent*-**6a** (prepared from cyclopropyl carbaldehyde *ent*-**3a** using Wittig olefination) and cyclopropyl carbaldehyde **4j**.[29] The configuration of *ent*-**6a** and **4j** was assigned as (1*S*, 2*R*, 3*S*) and (1*R*, 2*S*, 3*S*), respectively (Figure 3, for details, see the SI file).

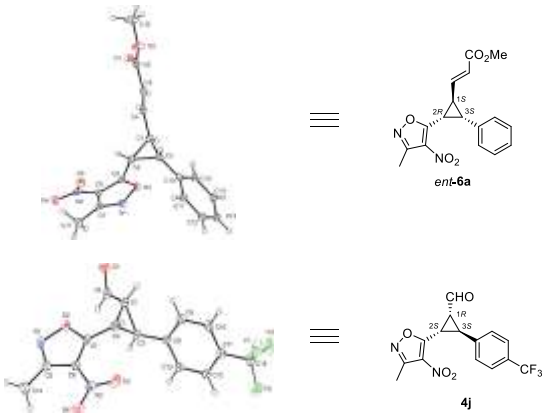
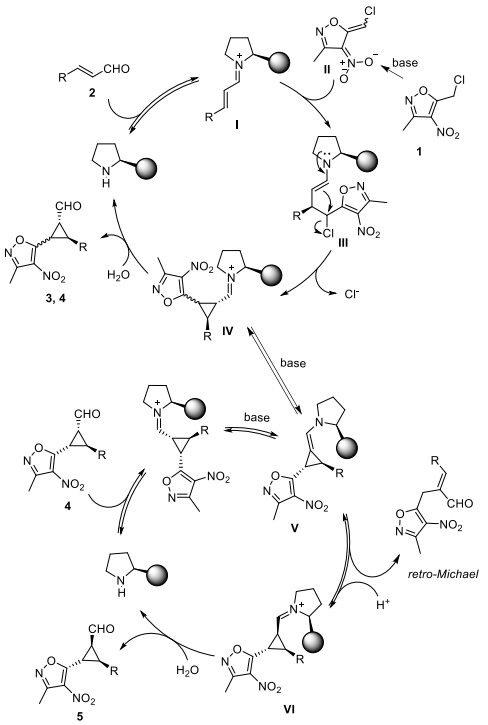



**Figure 3.** X-ray structures of cyclopropanes *ent*-**6a** and **4j**.

Based on absolute configurations and previous reports,[11a, 12c] a mechanism is proposed, as shown in Scheme 3. We hypothesize that this reaction proceeds through two aminocatalytic cycles. Initially, the formed iminium ion **I** with a shielded *Si*-face is stereoselectively attacked by the isoxazole nucleophile **II**. This step is followed by an intramolecular ring-closing alkylation of enamine with a benzylic-type chloride. In the final stage of the first catalytic cycle, the iminium ion **IV** is hydrolysed to cyclopropane products **3** and **4**, releasing a secondary amine. In turn, the formation of diastereomer **5** can proceed either by enamine **V** formation *via* iminium **IV** deprotonation or *via* condensation of **4** with a secondary amine catalyst. Due to sterical hindrance of the diaryl((trialkylsilyl)oxy)methyl group present in the

secondary amine, enamine **V** is protonated from the *Re*-face, thereby affording the iminium ion **VI**. Subsequent hydrolysis produces the diastereomer **5**. The second catalytic cycle is also crucial for the formation of retro-Michael products, through a cyclopropane cleavage competing with the protonation of **V**.




**Scheme 3.** Plausible reaction mechanism

In summary, we have developed an enantioselective organocatalytic cyclopropanation of readily available 4-nitroisoxazole derivatives with *α,β*-unsaturated aldehydes. The reaction is catalysed by a chiral secondary amine, affording chiral 1,2,3-trisubstituted cyclopropanes in high yields and enantioselectivities. This synthetic protocol can be used for further applications, as shown by a set of additional transformations of the corresponding cyclopropanes and by the formal synthesis of GABA ligands.

## Experimental Section

The catalyst **C3** (20.2 mg, 0.045 mmol, 0.15 eq.) was added to a solution of the corresponding *α,β*-unsaturated aldehyde **2** (0.6 mmol, 2.0 eq.) in DCM (1.0 ml). The mixture was stirred for 10 minutes at room temperature. Then, $NaHCO_3$ (37.8 mg, 0.45 mmol, 1.5 eq.) and compound **1** (53.1 mg, 0.3 mmol, 1.0 eq.) were added. The reaction was stirred for the indicated time (TLC control). After completing the reaction, the solvents were evaporated. The crude product was purified by column chromatography (eluting by hexane/EtOAc mixtures).

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# Enantioselective Cyclopropanation of 4-Nitroisoxazole Derivatives

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