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Stereoretentive Catalytic [3 + 2]/[3 + 3]-Cycloaddition of Nonracemic Donor−Acceptor Cyclopropanes: Synthesis of Substituted Pyrrolidines and 1,2-Oxazinanes

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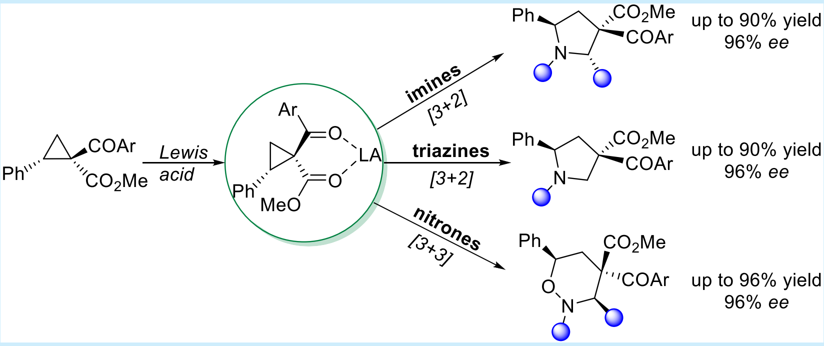

ABSTRACT: A highly enantioselective preparation of substituted pyrrolidines and 1,2-oxazinanes has been achieved via stereoretentive [3 + 2]/[3 + 3]-cycloaddition of nonracemic donor−acceptor cyclopropanes with imines, triazines, and nitrones in good to high yields with broad scope under mild reaction conditions. In comparison with the well-documented approach to donor−acceptor cyclopropane reactions using racemic cyclopropane reactants and a catalyst with chiral ligands, this report features applications of enantioenriched donor−acceptor cyclopropanes as cycloadduct reactants with achiral catalysts.

Donor−acceptor cyclopropanes have been recognized since the late 1970s for their enhanced reactivity in ring-opening reactions with selected nucleophiles,[1] but only in the past 20 years has there been significant recognition that these cyclopropanes could undergo facile cycloaddition reactions.[2] Various aldehydes, vinyl ethers, indoles, imines, nitriles, and nitrones were found to undergo catalytic, mainly [3 + 2]- and [3 + 3]-cycloaddition reactions under mild conditions to form carbocyclic and heterocyclic compounds in high yields.[3] Ligated metal-centered Lewis acids are the effective catalysts, and with chiral ligands they can induce high levels of enantiocontrol.[4]

Because of their ease of access as racemates, the vast majority of catalytic cycloaddition reactions with donor−acceptor cyclopropanes were performed with racemic malonate-derived cyclopropane-1,1-dicarboxylates using Lewis acid catalysts having chiral ligands.[4] Reported uses of nonracemic chiral donor−acceptor cyclopropanes are sparse, and generally limited to single examples. Early in the development of effective donor−acceptor cyclopropanes for cycloaddition, J. Johnson reported that (2*S*)-2-phenylcyclopropane-1,1-carboxylate [(*S*)-**I**, 99% *ee*] underwent Sn(OTf)$_2$-catalyzed cycloaddition with benzaldehyde to produce furan **II** with 96% *ee* (Scheme 1a), which implied that, rather than occurring with ring opening of the cyclopropane prior to bond formation with the aldehyde, the initial bond formation between the aldehyde and cyclopropane preserved enantioselectivity.[5] A similar investigation by M. Kerr revealed the same conclusion for cycloaddition with nitrones at room temperature, but also documented diminished optical purity of the cycloaddition adducts providing evidence for the reversibility of the ring forming event (Scheme 1a).[6] More recently, near complete enantioretention has also been reported for **I** in its cycloaddition reactions with malononitriles,[7] as well as for the palladium-catalyzed [3 + 2]-cycloaddition of chiral vinylcyclopropane analogues of **I** with ketenes.[8] We have reported complete retention of configuration in the formation of spiroketals from cyclopropyl enolates,[9] and a highly enantioselective synthesis of chiral dihydro-3*H*-carbazole-2-carboxylate derivatives by a cyclopentannulation−rearrangement cascade (Scheme 1b).[10] Since the availability of highly enantiomerically enriched donor−acceptor cyclopropanes has

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Scheme 1. Catalytic Transformations of Enantioenriched Cyclopropanes

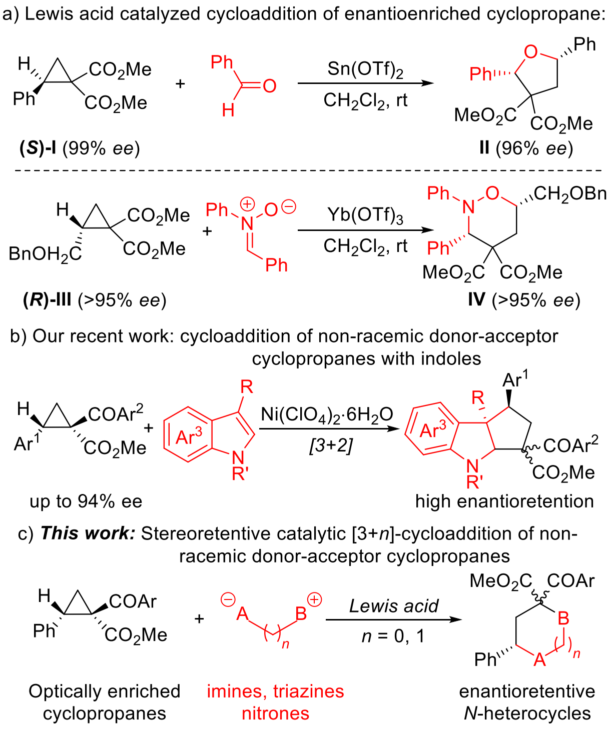
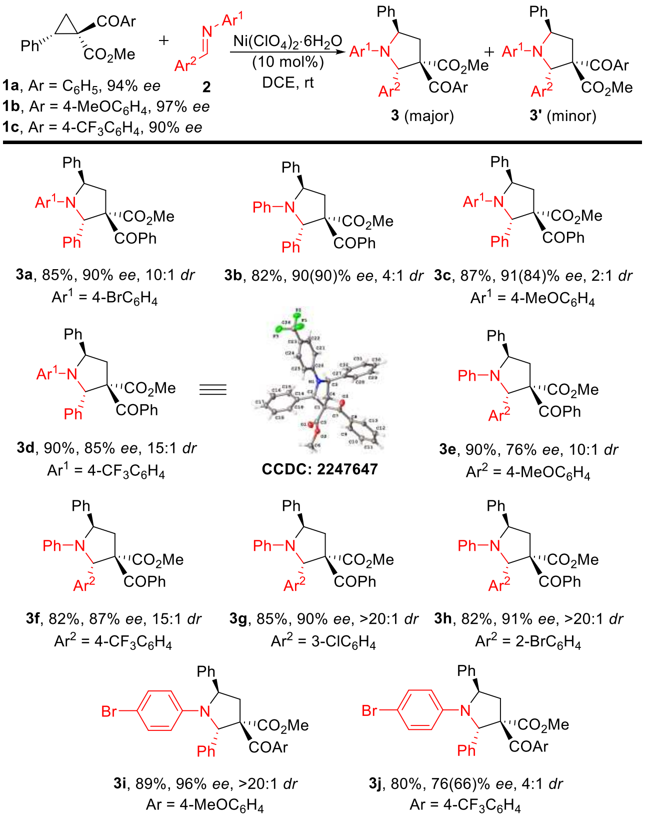


Table 1. Substrate Scope for the Synthesis of Pyrrolidine 3[a]



3a, 85%, 90% *ee*, 10:1 *dr*, Ar^1 = 4-BrC_6H_4

3b, 82%, 90(90)% *ee*, 4:1 *dr*

3c, 87%, 91(84)% *ee*, 2:1 *dr*, Ar^1 = 4-$MeOC_6H_4$

3d, 90%, 85% *ee*, 15:1 *dr*, Ar^1 = 4-$CF_3C_6H_4$

3e, 90%, 76% *ee*, 10:1 *dr*, Ar^2 = 4-$MeOC_6H_4$

3f, 82%, 87% *ee*, 15:1 *dr*, Ar^2 = 4-$CF_3C_6H_4$

3g, 85%, 90% *ee*, >20:1 *dr*, Ar^2 = 3-ClC_6H_4

3h, 82%, 91% *ee*, >20:1 *dr*, Ar^2 = 2-BrC_6H_4

3i, 89%, 96% *ee*, >20:1 *dr*, Ar = 4-$MeOC_6H_4$

3j, 80%, 76(66)% *ee*, 4:1 *dr*, Ar = 4-$CF_3C_6H_4$

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol, 1.2 equiv), $Ni(ClO_4)_2 \cdot 6H_2O$ (3.7 mg, 10.0 mol %), and 4 Å MS (50 mg) in DCE (2.0 mL) at room temperature under an argon atmosphere for 2 h. Isolated yields are given. % *ee* given in parentheses is for diastereomer **3′**.

increased significantly in the past decade, we have been intrigued with a comparison of the two approaches, one using racemic cyclopropane reactants and a catalyst with chiral ligands and the other using enantioenriched cyclopropane reactants with achiral catalysts. Using three transformations as models we now report that very high retention of configuration is generally realized with enantioenriched donor–acceptor cyclopropanes (Scheme 1c).

Highly enantioenriched donor–acceptor cyclopropanes were prepared from 2-diazo-3-ketoesters and styrenes using the dirhodium(II) catalyst $Rh_2(S\text{-}BTPCP)_4$.[10] Only one diastereomer was produced, and its structure was that of the dominant (1*S*,2*S*)-enantiomer.[11] Imines are well-known to undergo Lewis acid catalyzed cycloaddition with donor–acceptor cyclopropanes to form pyrrolidine products,[12] but these reports used achiral or racemic cyclopropanes. Effective construction of pyrrolidine **3a** was realized via nickel(II) perchlorate catalyzed [3 + 2]-cycloaddition of cyclopropane **1a** (94% *ee*) with benzalimine **2a** in dichloroethane (DCE) at room temperature (see Table S1 in SI for details).[11] The configuration at C-5 of **3a** is *R*, demonstrating that addition of **2a** occurs by inversion of configuration.

With the optimal reaction conditions established, the substrate scope with respect to the imine compounds was investigated (Table 1). Various electron-rich and electron-deficient substitutions at the *para*-position on the aniline moiety were all well tolerated, delivering the pyrrolidine products **3a**–**3d** in 82–90% yields with high retention of enantiocontrol (up to 91% *ee*). Moreover, these reactions proceeded smoothly with various substituents on the aryl ring of the benzaldehyde moiety. The reaction could also be applied to *p*-methoxyphenyl, *p*-(trifluoromethyl)phenyl, 3-chlorophenyl, and 2-bromophenyl analogues of imines without a noticeable deterioration in product yield (**3e**–**3h**, 82%–90% yields). A loss of enantioselectivity was found in the formation of **3e** using **2e** (Ar^2 = *p*-$MeOC_6H_4$–) with 10:1 *dr*, but high retention of enantiocontrol (87–91% *ee* from reactant 94% *ee*) and diastereoselectivity (*dr* > 15:1) occurred in reactions forming **3f**–**3h** from imines having electron-withdrawing groups. Reaction of the *p*-methoxyphenyl- (**1b**, 97% *ee*) donor–acceptor cyclopropane with imine **2a** formed the corresponding [3 + 2]-cycloaddition product **3i** in good yield with 96% *ee* and >20:1 *dr*, whereas the *p*-trifluoromethylphenyl- (**1c**, 90% *ee*) donor–acceptor cyclopropane with imine **2a** formed the corresponding [3 + 2]-cycloaddition product **3j** in a modest 80% yield and 76(66)% *ee* with 4:1 *dr*, respectively. The structure of product **3d** was confirmed by single-crystal X-ray diffraction analysis,[13] and other products were assigned by analogy.

Control experiments of cyclopropane **1a** (94% *ee*) without benzalimine **2a** were conducted under the standard conditions. Chiral cyclopropane **1a** was stable during 1 h in the presence of nickel(II) perchlorate. After 2 h, however, another isomer **1a′** was generated in 11% yield with 20% *ee* while cyclopropane **1a** was enantioretentive. By increasing the reaction time to 4 h, the yield of compound **1a′** increased to 16% with similar enantioselectivity. These results (see Table S2 in SI for details) confirm the relative stability of the chiral nonracemic cyclopropane during the cycloaddition reaction.

According to Table 1, diastereoselectivity is reduced (*dr* < 15:1) when Ar^1 has a *para*-substituted electron-donating group

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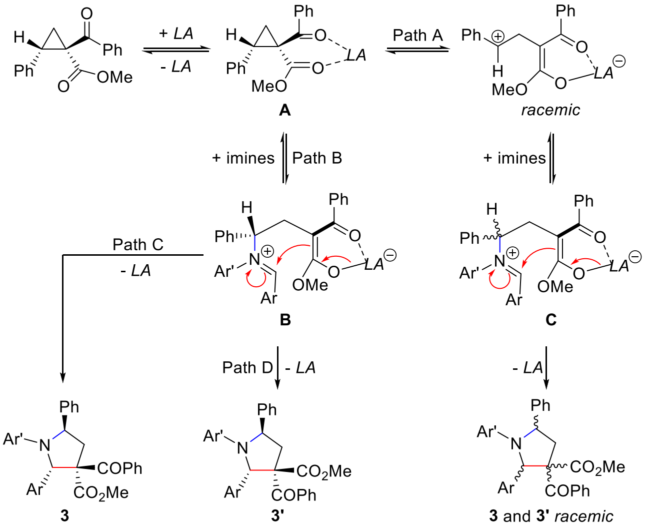
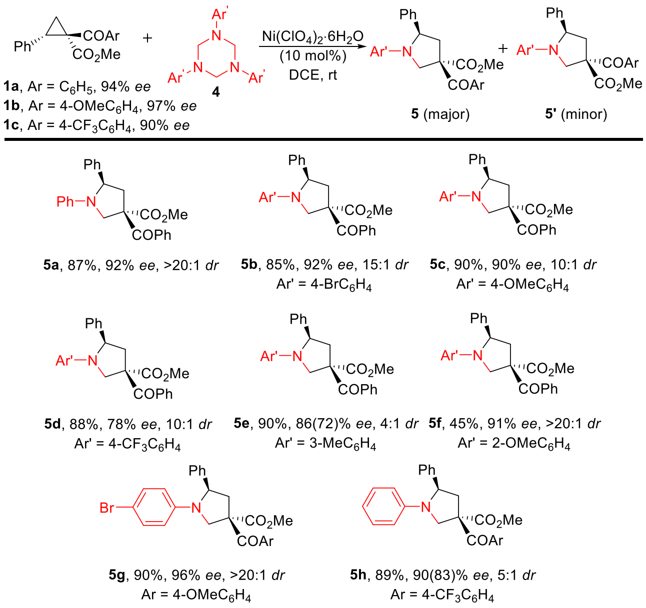
(EDG) or hydrogen (**3b** and **3c**), Ar^2 has a *para*-substituted EDG (**3e**), and Ar has a *para*-substituted electron-withdrawing group (EDG) (**3j**). Enantioretention is reduced when the *para*-substituent of Ar^1 is an EWG (**3d**) and Ar^2 is an EDG (**3e**), but these reductions are small, and when Ar is an EWG (**3j**). Coordination of nickel(II) with the cyclopropyl-β-keto ester forms an activated donor–acceptor cyclopropane complex **A** (Scheme 2) that can racemize (Path A), thereby reducing stereocontrol, or undergo nucleophilic attack by the imine at the 2-position to effect ring opening of the cyclopropane to produce a zwitterionic intermediate **B** (Path B) that can close directly to form product **3** (Path C) with high diastereocontrol or undergo bond rotation that results in diastereomer **3′** (Path D). The racemic Lewis acid coordinated open adduct of **3** is also expected to undergo stepwise cycloaddition, but with low diastereoselectivity and no enantioselectivity. The observed enantioselectivities reflect competition between Path A and Path B.

Scheme 2. Proposed Mechanism for [3 + 2]-Cycloaddition between Donor–Acceptor Cyclopropanes and Imines



1,3,5-Triazinanes are readily available substitutes for unstable formaldimines, and they have found recent applications in the formation of pyrrolidines from their reactions with donor–acceptor cyclopropanes.[14] Their use would provide formation of pyrrolidine structures with a methylene group adjacent to nitrogen instead of an aryl group from the use of benzylideneaniline derivatives **2**. Encouraged by the promising results from the use of **2**, we investigated the scope of reactions employing 1,2,3-triazinanes **4** as imine precursors with donor–acceptor cyclopropanes **1** under the same conditions as reported in Table 1, and these results are reported in Table 2. The amount of formaldimine from triazinane employed was only a 33% molar excess over the molar amount of the donor–acceptor cyclopropane that was used. The cycloaddition reactions occurred smoothly with different substituents on the aryl ring of triazine, forming **5a**–**5d** in high yields with excellent enantioselectivity and diastereoselectivity (up to 90% yield, 92% *ee*, >20:1 *dr*). In the case of triazine **4e** with a methyl group at the 3-position, the pyrrolidine product **5e** was obtained in 4:1 *dr* with 90% yield and 86% *ee*.

Table 2. Substrate Scope for the Synthesis of Pyrrolidine 5[a]



1a, Ar = C$_6$H$_5$, 94% *ee*
1b, Ar = 4-OMeC$_6$H$_4$, 97% *ee*
1c, Ar = 4-CF$_3$C$_6$H$_4$, 90% *ee*

5a, 87%, 92% *ee*, >20:1 *dr*

5b, 85%, 92% *ee*, 15:1 *dr*
Ar' = 4-BrC$_6$H$_4$

5c, 90%, 90% *ee*, 10:1 *dr*
Ar' = 4-OMeC$_6$H$_4$

5d, 88%, 78% *ee*, 10:1 *dr*
Ar' = 4-CF$_3$C$_6$H$_4$

5e, 90%, 86(72)% *ee*, 4:1 *dr*
Ar' = 3-MeC$_6$H$_4$

5f, 45%, 91% *ee*, >20:1 *dr*
Ar' = 2-OMeC$_6$H$_4$

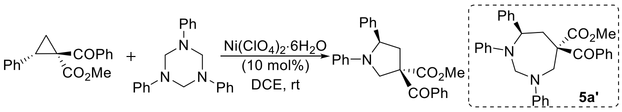
5g, 90%, 96% *ee*, >20:1 *dr*
Ar = 4-OMeC$_6$H$_4$

5h, 89%, 90(83)% *ee*, 5:1 *dr*
Ar = 4-CF$_3$C$_6$H$_4$

[a] Reaction conditions: **1** (0.1 mmol), **4** (0.04 mmol, 0.4 equiv), Ni(ClO$_4$)$_2$·6H$_2$O (3.7 mg, 10.0 mol %), and 4 Å MS (50 mg) in DCE (2.0 mL) at room temperature under an argon atmosphere for 2 h. Isolated yields are given.% *ee* given in parentheses is for diastereomer **5′**.

However, a single diastereoisomer (91% *ee*) was formed in the reaction of *p*-methoxyphenyl triazine, although the product yield was 45%, suggesting the influence of the electron-donating methoxy group on diastereocontrol. Moreover, reactions of the *p*-methoxyphenyl- (**1b**, 97% *ee*) and the *p*-trifluoromethyl-phenyl- (**1c**, 90% *ee*) analogues of donor–acceptor cyclopropane **1** with the triazine compound also formed the corresponding pyrrolidine products in good yields with high retention of enantiocontrol, but very different *dr* ratios.

Werz and co-workers have observed 1,3-bisfunctionalization using similar donor–acceptor cyclopropanes and triazinanes with Sc(OTf)$_3$ as the catalyst.[15] Attempts to prepare the seven-membered ring product **5a′** via [3 + 4]-cycloaddition with cyclopropane **1a** and triazinane **4a** using the Ni(ClO$_4$)$_2$·6H$_2$O catalyst were not successful, and only the [3 + 2]-cycloaddition product was generated with up to 2.0 equiv of triazine (eq 1).



1a, 94% *ee*

4a
1.0 equiv.
2.0 equiv.

5a
88%, 92% *ee*, >20:1 *dr*
85%, 92% *ee*, >20:1 *dr*

To further explore other types of cycloadditions with nonracemic donor–acceptor cyclopropanes, we turned our attention to the use of nitrones as substrates for [3 + 3]-cycloaddition. These reactions have been previously reported with racemic donor–acceptor cyclopropanes.[16] The anticipated 6-membered ring products were observed with very high enantioretention, but generally low diastereocontrol. Optimizations were conducted to enhance the transformation (see Table S3 in SI for details). The best results were obtained when the reaction was catalyzed by Sc(OTf)$_3$ (10.0 mol %) in

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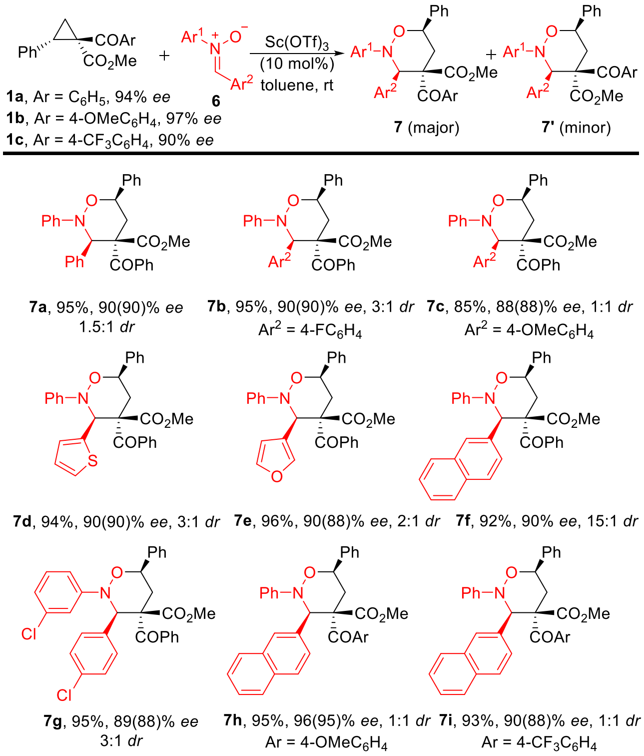
toluene at room temperature for 2 h, leading to **7a** in 95% isolated yield with 79(78)% *ee* and 1.5:1 *dr* from the chiral cyclopropane having 80% *ee.* The substrate scope was then examined under these optimal reaction conditions. As shown in Table 3, the reaction proceeded smoothly with various substitutions on the *para*-position of aryl ring, including electron-neutral (**7a**, 95% yield with 90(90)% *ee*, 1.5:1 *dr*), electron-withdrawing (**7b**, 95% yield with 90(90)% *ee*, 3:1 *dr*), and electron-donating (**7c**, 85% yield with 88(88)% *ee*, 1:1 *dr*) groups. Moreover, comparably high yields and enantiocontrol were obtained for 2-thiophenyl, 3-furyl and 2-naphthyl substituted 1,2-isoxazoles (**7d**−**7f**). In addition, 1,2-oxazinane **7g** was formed in 95% yield with 89(88)% *ee* and 3:1 *dr*. Notably, reactions of the *p*-methoxyphenyl- (**1b**, 97% *ee*) and the *p*-trifluoro-methylphenyl- (**1c**, 90% *ee*) analogues of donor−acceptor cyclopropane **1** with nitrone compound also generated the corresponding 1,2-oxazinane products (**7h** and **7i**) in good yields with high retention of enantiocontrol. To demonstrate the scalability and the practicality of the current method, a 1.0 mmol scale reaction was carried out from which 449 mg of **7a** were isolated (0.94 mmol, 94% yield) with 90(90)% *ee* for the 1.5:1.0 *dr* (see SI for details). The structure of these formed 1,2-oxazinanes was confirmed by single-crystal X-ray diffraction analysis of its fluoro-derivative **7b** (see Figure 1 in SI).[13]

Table 3. Substrate Scope for the Synthesis of 1,2-Oxazinanes 7[a]



1a, Ar = C_6H_5, 94% *ee*
1b, Ar = 4-OMeC_6H_4, 97% *ee*
1c, Ar = 4-$CF_3C_6H_4$, 90% *ee*
6
7 (major)
7' (minor)

7a, 95%, 90(90)% *ee* 1.5:1 *dr*
7b, 95%, 90(90)% *ee*, 3:1 *dr* Ar^2 = 4-FC_6H_4
7c, 85%, 88(88)% *ee*, 1:1 *dr* Ar^2 = 4-OMeC_6H_4
7d, 94%, 90(90)% *ee*, 3:1 *dr*
7e, 96%, 90(88)% *ee*, 2:1 *dr*
7f, 92%, 90% *ee*, 15:1 *dr*
7g, 95%, 89(88)% *ee* 3:1 *dr*
7h, 95%, 96(95)% *ee*, 1:1 *dr* Ar = 4-OMeC_6H_4
7i, 93%, 90(88)% *ee*, 1:1 *dr* Ar = 4-$CF_3C_6H_4$

[a] Reaction conditions: **1** (0.1 mmol), **6** (0.12 mmol, 1.2 equiv), Sc(OTf)$_3$ (5.0 mg, 10.0 mol %), and 4 Å MS (50 mg) in toluene (2.0 mL) at room temperature under an argon atmosphere for 2 h. Isolated yields are given.% *ee* given in parentheses is for diastereomer 7′.

In summary, we have developed Lewis acid catalyzed [3 + 2]- and [3 + 3]-cycloaddition reactions of nonracemic chiral donor−acceptor cyclopropanes with imines, triazines, and nitrones that provide an expeditious synthesis of substituted pyrrolidines and 1,2-oxazinanes derivatives in good to high yields with excellent enantiocontrol under mild reaction conditions with broad substrate generality. Prior reports of these transformations have used racemic cyclopropane reactants with chiral (asymmetric induction) or achiral catalysts, whereas this report features stereoretentive catalytic cycloaddition of enantioenriched donor−acceptor cyclopropanes with achiral catalysts.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00831.

> Experimental procedures and spectroscopic data for all new compounds, and X-ray crystallographic data for **3d** and **7b** (PDF)

Accession Codes

CCDC 2247647−2247648 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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Notes

The authors declare no competing financial interest.

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