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Side-Arm-Promoted Highly Enantioselective Ring-Opening Reactions and Kinetic Resolution of Donor–Acceptor Cyclopropanes with Amines

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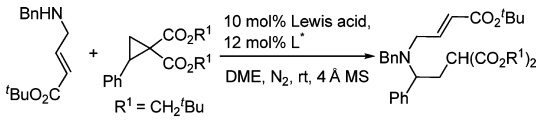
Supporting Information

ABSTRACT: A Ni-catalyzed asymmetric ring-opening reaction of 2-substituted cyclopropane-1,1-dicarboxylates with aliphatic amines has been accomplished using the chiral indane–trisoxazoline (In-TOX) ligand. This highly enantioselective reaction provides an efficient approach to a variety of chiral γ-substituted γ-amino acid derivatives, which are readily transformed into multifunctionalized piperidines and γ-lactams. The single-crystal X-ray structure of the TOX–Ni complex is provided, and the role of the side arm in the chiral ligand is discussed.

The ring-opening reaction of activated donor–acceptor (D–A) cyclopropanes with nucleophiles provides versatile access to various functionalized carbon skeletons.[1−7] Of the strategies developed, Lewis acids have been shown to promote such reactions under mild conditions for most nucleophiles. Amine-initiated nucleophilic ring opening represents a very useful transformation, affording γ-substituted γ-amino acid derivatives.[7] For example, Magolan and Kerr[7d] reported the $Yb(OTf)_3$-catalyzed racemic ring opening of cyclopropane-1,1-dicarboxylates with indoline in the synthesis of a tetracyclic tronocarpine subunit. Later on, the $Ni(ClO_4)_2·6H_2O$- and $La(OTf)_3$-catalyzed ring openings with amines were reported by Lifchits and Charette[7e] and Kotsuki and co-workers,[7f] respectively. Although reactions of D–A cyclopropanes with amines have been developed, most of them invariably require vigorous conditions such as elevated temperature, even in the presence of Lewis acids. This is due to the fact that the complexation of the amine, particularly for aliphatic amines, with the Lewis acid slows the reaction greatly.[7e] Furthermore, to the best of our knowledge, no catalytic asymmetric version of the ring openings with amines has been developed. Herein we describe our efforts on this subject.

As (*S*)-Ph-DBFOX (**L1**) and (*S*)-4-Cl-^{t}Bu-PYBOX (**L2**) have shown excellent behavior in asymmetric annulations of D–A cyclopropanes with nitrones[5a] and aldehydes,[5b] respectively, using 1,1-cyclopropane diester **2a** as a model substrate, we initially employed these two ligands to investigate the asymmetric reaction of **2a** with aliphatic amine **1a** (Table 1, entries 1 and 2). Unfortunately, they both gave unsatisfactory results. We next tested the indane-derived bisoxazoline (BOX) ligand **L3a** with $Ni(ClO_4)_2$, and the product **3aa** was also obtained in poor yield (22%) with poor enantioselectivity (8% ee) after almost 2 days (entry 3). As the complexation of the amine with the Lewis acid is supposed to retard the reaction,[7e] we envisioned that a pendant coordination group in the BOX ligand[8] might modulate the steric and electronic nature of the Ni(II) reactive site (Scheme 1), promoting the complexation and activation of the cyclopropane by interfering with the coordination of the amine.

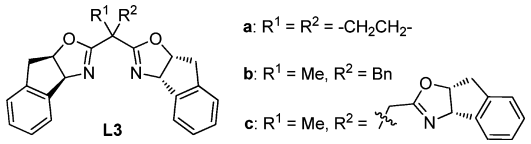
Table 1. Effects of the Ligand (L*) and Lewis Acid[a]



1a 2a 3aa

entry	Lewis acid (M)	ligand (L*)	time (h)	yield (%)[b]	ee (%)[c]
1	$Ni(ClO_4)_2·6H_2O$	**L1**	52	40	58
2	$Ni(ClO_4)_2·6H_2O$	**L2**	46	trace	-
3	$Ni(ClO_4)_2·6H_2O$	**L3a**	46	22	8[d]
4	$Ni(ClO_4)_2·6H_2O$	**L3b**	45	61	13[d]
5	$Ni(ClO_4)_2·6H_2O$	**L3c**	25	72	91
6	$Zn(OTf)_2$	**L3c**	28	NR	-
7	$Fe(ClO_4)_2·6H_2O$	**L3c**	28	NR	-
8	$Cu(OTf)_2$	**L3c**	36	trace	-
9	$Mg(ClO_4)_2·6H_2O$	**L3c**	36	28	7
10[e]	$Ni(ClO_4)_2·6H_2O$	**L3c**	15	90	90

[a]Unless otherwise noted, reactions were carried out under a N_2 atmosphere with **1a** (0.20 mmol), **2a** (0.44 mmol), Lewis acid (0.02 mmol), **L*** (0.024 mmol), and 4 Å molecular sieves (MS) (200 mg) in dimethoxyethane (DME) (2 mL, $[\mathbf{1a}]_0$ = 0.10 M) at rt. [b]Isolated yields. [c]Determined by chiral HPLC. [d]The enantioselectivity was reversed. [e]The reaction was run at 40 °C.



On the basis of this concept, we synthesized ligands **L3b** and **L3c** for comparison. When a benzyl group was introduced as the side arm, the yield was 61% after 45 h of reaction (entry 4). Noticeably, the indane–trisoxazoline (In-TOX) ligand **L3c** bearing a chiral oxazoline group as a coordinating side arm significantly speeded up the reaction, providing **3aa** in 72% yield with 91% ee in 25 h (entry 5).[9] This result suggested a strong effect of the ligand side arm on the reactivity and

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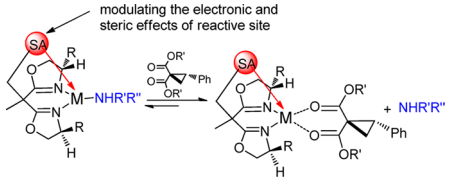
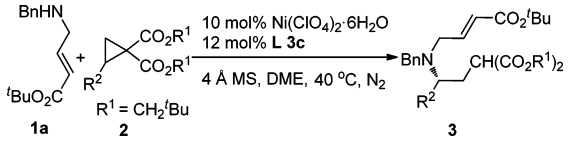
Scheme 1. Strategy for the Reaction of D−A Cyclopropanes with Amines



enantiocontrol in the catalytic asymmetric reaction of D−A cyclopropanes with amines. $Zn(OTf)_2$, $Fe(ClO_4)_2·6H_2O$, and $Cu(OTf)_2$ in combination with **L3c** gave poor results, and the reactions were sluggish (entries 6−8). The Mg complex of **L3c** gave **3aa** in 28% yield with poor enantioselectivity (entry 9). Increasing the reaction temperature from 25 to 40 °C in the case of **L3c**−$Ni(ClO_4)_2$ as the catalyst improved the yield to 90% while almost maintaining the ee after 15 h (entry 10).

The substrate scope was investigated under the optimized conditions (Table 1, entry 10). As shown in Table 2, a series of

Table 2. Reactions of D−A Cyclopropane Diesters with Secondary Amines Catalyzed by L3c−Ni(II)[a]



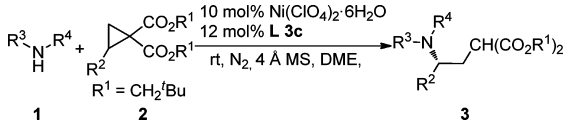
entry	R^2	yield (%)[b]	ee (%)[c]
1	Ph (**2a**)	90 (**3aa**)	90
2	*p*-ClC_6H_4 (**2b**)	88 (**3ab**)	94
3	*p*-BrC_6H_4 (**2c**)	86 (**3ac**)	94
4	3,4-$Cl_2C_6H_3$ (**2d**)	80 (**3ad**)	95
5	*p*-$NO_2C_6H_4$ (**2e**)	75 (**3ae**)	98
6	*p*-MeC_6H_4 (**2f**)	88 (**3af**)	95
7	*m*-MeC_6H_4 (**2g**)	93 (**3ag**)	91
8[d]	*p*-$MeOC_6H_4$ (**2h**)	97 (**3ah**)	94
9[d,e]	*p*-$MeOC_6H_4$ (**2h**)	92 (**3ah**)	93
10	*o*-$MeOC_6H_4$ (**2i**)	59 (**3ai**)	96
11[d]	3,4-$(MeO)_2C_6H_3$ (**2j**)	97 (**3aj**)	92
12[d]	2-thienyl (**2k**)	95 (**3ak**)	94
13[d,f]	PhCH=CH (**2l**)	97 (**3al**)	84
14[f]	CH_2=CH (**2m**)	93 (**3am**)	80

[a]Unless otherwise noted, the reactions were carried out under a N_2 atmosphere with **1a** (0.20 mmol), **2** (0.44 mmol), $Ni(ClO_4)_2·6H_2O$ (0.02 mmol), **L3c** (0.024 mmol), and 4 Å MS (200 mg) in DME (2 mL, $[\mathbf{1a}]_0$ = 0.10 M) at 40 °C. [b]Isolated yields. [c]Determined by chiral HPLC. [d]The reaction was carried out at rt. [e]Catalyst loading = 2 mol %, $[\mathbf{1a}]_0$ = 0.20 M in DME (2 mL). [f]**1a**/**2m** = 1/3.

2-substituted cyclopropanes **2a**−**m** reacted smoothly with aliphatic amine **1a**, affording the corresponding products in up to 97% yield with high enantioselectivity (up to 98% ee). The substituents on the benzene ring of 2-arylcyclopropane diesters had a slight effect on enantioselectivity, and all of them gave >90% ee (entries 1−11). However, the position of the substituent on the aryl group influenced the yield. For example, 2-*p*-$MeOC_6H_4$- and 2-*o*-$MeOC_6H_4$-substituted cyclopropanes **2h** and **2i** both gave excellent ees, but the former showed much better reactivity, probably because of the smaller steric effect relative to the latter (entry 8 vs 10). Notably, for **2h**, when the catalyst loading was reduced to 2 mol %, the corresponding product **3ah** was obtained in 92% yield with 93% ee at room temperature (rt) (entry 9). The reaction could be extended to 2-thienylcyclopropane **2k**, which provided an excellent yield (95%) and enantioselectivity (94% ee) at rt (entry 12). Meanwhile, 2-styryl- and 2-vinyl-substituted cyclopropanes **2l** and **2m** proved to be suitable substrates, delivering yields of 97 and 93% with 84 and 80% ee, respectively (entries 13 and 14).

The generality of various aliphatic amines was then explored (Table 3), and a variety of multifunctionalized compounds that

Table 3. Expansion of the Secondary Amine in the L3c−Ni(II)-Catalyzed Ring Opening of D−A Cyclopropanes[a]



entry	R^3, R^4	R^2	yield(%)[b]	ee (%)[c]
1	Bn, Bn (**1b**)	*p*-$MeOC_6H_4$ (**2h**)	98 (**3bh**)	94
2[d]	Bn, Bn (**1b**)	*p*-$MeOC_6H_4$ (**2h**)	99 (**3bh**)	92
3	Bn, Bn (**1b**)	Furyl (**2n**)	95 (**3bn**)	90
4[e]	Bn, Bn (**1b**)	Furyl (**2n**)	99 (**3bn**)	90
5[f]	Bn, Bn (**1b**)	Ph (**2a**)	71 (**3ba**)	87[10]
6	Bn, CH_2CH_2OTBS (**1c**)	*p*-$MeOC_6H_4$ (**2h**)	94 (**3ch**)	91
7[d]	Bn, CH_2CH_2OTBS (**1c**)	*p*-$MeOC_6H_4$ (**2h**)	98 (**3ch**)	90
8	Bn, CH_2CH_2OTBS (**1c**)	3,4-$(MeO)_2C_6H_3$ (**2j**)	99 (**3cj**)	90
9	Bn, $CH_2CH(OMe)_2$ (**1d**)	3,4-$(MeO)_2C_6H_3$ (**2j**)	99 (**3dj**)	90
10	Bn, CH_2CO_2Et (**1e**)	*p*-$MeOC_6H_4$ (**2h**)	82 (**3eh**)	88
11	Bn, $CH_2CH=CH_2$ (**1f**)	*p*-$MeOC_6H_4$ (**2h**)	85 (**3fh**)	91
12	Ph, $CH_2CH=CH_2$ (**1g**)	*p*-$MeOC_6H_4$ (**2h**)	95 (**3gh**)	91
13	*p*-$MeOC_6H_4CH_2$, $CH_2CH=CH_2$ (**1h**)	*p*-$MeOC_6H_4$ (**2h**)	88 (**3hh**)	90

[a]Unless otherwise noted, the reactions were carried out under a N_2 atmosphere with **1a** (0.20 mmol), **2a** (0.44 mmol), $Ni(ClO_4)_2·6H_2O$ (0.02 mmol), **L3c** (0.024 mmol), and 4 Å MS (200 mg) in DME (2 mL, $[\mathbf{1}]_0$ = 0.10 M) at rt. [b]Isolated yields. [c]Determined by chiral HPLC. [d]Catalyst loading = 2 mol %, $[\mathbf{1}]_0$ = 0.25 M in DME (4 mL). [e]Catalyst loading = 2 mol %, $[\mathbf{1b}]_0$ = 0.10 M in DME (10 mL). [f]Catalyst loading = 5 mol %, 40 °C, **1b**/**2a** = 1/3, $[\mathbf{1b}]_0$ = 0.25 M in DME (4 mL).

could be easily transformed into useful building blocks were obtained. The ring-opening reaction proceeded smoothly with dibenzylamine (**1b**), giving the target products **3bh** and **3bn** in 98 and 95% yield with 94 and 90% ee, respectively (entries 1 and 3). Functionalized benzylamines **1c**−**f** derived from 2-aminoethanol, 2,2-dimethoxyethanamine, bromoacetate, and allyl bromide were well-tolerated in the current system, affording the corresponding versatile γ-substituted γ-amino acid derivatives in 82−99% yield with 88−94% ee (entries 6−11). In particular, the ring opening with aniline-type nucleophile **1g** proceeded very well, providing the desired product **3gh** in 95% yield with 91% ee (entry 12). Remarkably, when the catalyst loading was reduced to 2 mol %, both the yield and the enantioselectivity were almost maintained (entries 1 vs 2, 3 vs 4, and 6 vs 7).

In the current reaction, an excess of the racemic cyclopropane was employed. Further study showed that the excess cyclopropane could be recovered with good ee, suggesting that the present catalysts might be highly efficient for both the asymmetric ring-opening reaction and the kinetic resolution of D−A cyclopropanes. Under optimal conditions, with 1.6 equiv

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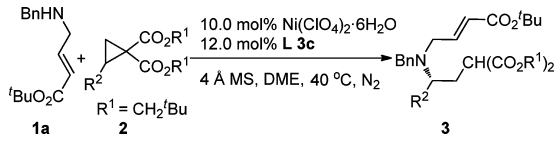
of 2-substituted cyclopropane-1,1-dicarboxylate **2** and 1.0 equiv of amine **1a**, the ring-opening products **3** were obtained in 39–46% yield with 90–97% ee (Table 4). Meanwhile, the

Table 4. Kinetic Resolution of 2-Substituted Cyclopropane Diesters with Secondary Amines Catalyzed by L3c–Ni(II)[a]



entry	2	conversion[b]	(*R*)-2 yield (%)[c]	(*R*)-2 ee (%)[d]	3 yield (%)[c]	3 ee (%)[d]	S[e]
1	**2a**	57	42	93	39	90	18
2	**2b**	55	43	95	40	94	29
3	**2c**	55	46	93	40	97	25
4[f]	**2f**	50	49	88	46	92	47
5	**2g**	57	41	93	42	96	18

[a]Unless otherwise noted, the reactions were carried out under a N_2 atmosphere with **1a** (0.25 mmol), **2** (0.4 mmol), $Ni(ClO_4)_2·6H_2O$ (0.025 mmol), **L3c** (0.03 mmol), and 4 Å MS (250 mg) in DME (2.5 mL, $[2]_0$ = 0.16 M) at 40 °C. [b]Determined by ^{1}H NMR analysis. [c]Isolated yields based on **2**. [d]Determined by chiral HPLC. [e]$S = \ln[(1 - C)(1 - ee^{SM})]/\ln[(1 - C)(1 + ee^{SM})]$ (C = conversion; ee^{SM} = ee of the recovered substrate). [f]0.225 mmol of **1a** was used.

cyclopropanes (*R*)-**2**, which are also important intermediates because of their wide application in organic synthesis,[6] were recovered in 41–49% yield with 88–95% ee. Thus, this method provides easy access to both synthetically useful γ-amino acid derivatives and cyclopropanes with high enantioselectivity.

As observed in the above reaction, the side-arm oxazolinyl group in **L3c** proved to be crucial for regulating the reaction rate and asymmetric induction (Table 1). Though the exact role of the side arm in this reaction is not clear, we developed the model as shown in Figure 1 to explain the effect of the side

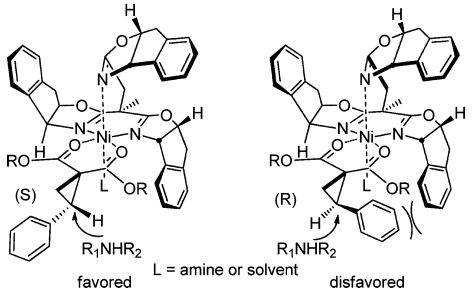
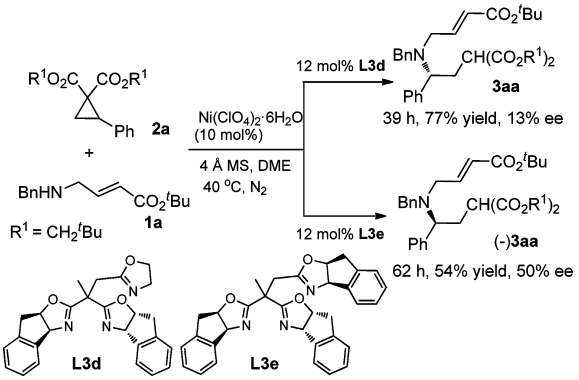


Figure 1. Proposed model for asymmetric induction.

arm on the stereochemical control. In this model, the pendant oxazoline shields the top side, and the catalyst selectively accommodates the *S* enantiomer of the racemic cyclopropane because of the steric repulsion between the phenyl group in the *R* enantiomer and the indanyl moiety of the In-TOX ligand; the bent-forward indane–oxazoline side arm could enhance this preference with the extended aryl moiety. Consequently, the *S* enantiomer is preferentially activated, and subsequent attack of the amine gives the *R* product and leaves the (*R*)-cyclopropane, in complete agreement with the observed results. According to this model, reducing the steric hindrance of the pendant oxazoline group should decrease the enantioselectivity. We thus synthesized **L3d** with a nonsubstituted oxazoline side arm and **L3e** with a side-arm oxazoline having the opposite configuration relative to **L3c** (Scheme 2). As expected, in the control

Scheme 2. Control Experiments Using L3d and L3e



experiment with **L3d**, a dramatic drop in the enantioselectivity was observed (90% ee in Table 1 vs 13% ee in Scheme 2). Notably, ligand **L3e**[9d] gave a 54% yield with 50% ee but with reversed enantioselectivity, suggesting that the configuration of the additional chiral centers in the pendant oxazoline is crucial for the enantioselectivity.

X-ray crystallographic analysis showed that the Ni center in the cationic complex with **L3d** is octahedrally coordinated with the three N atoms of **L3d** and three O atoms from two perchlorate ions (Figure 2). Interestingly, the oxazoline side arm of **L3d** lies on the top of the Ni–bisoxazoline plane, which is completely consistent with the proposed model.

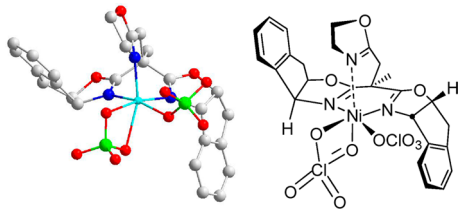
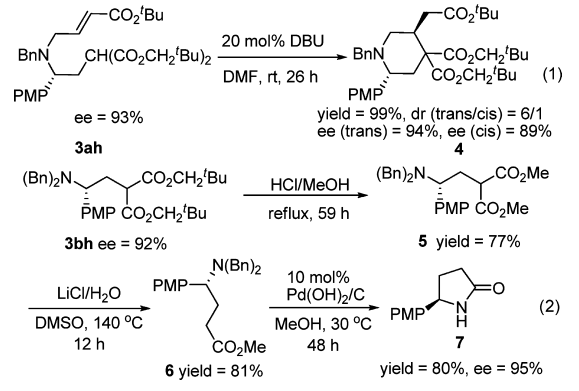


Figure 2. X-ray structure of $[Ni(\mathbf{L3d})](ClO_4)_2$ (H atoms omitted for clarity).

The present reaction is potentially synthetically useful. For example, the product **3ah** was readily transformed into multifunctional piperidine **4** in quantitative yield without loss of ee under mild conditions (eq 1 in Scheme 3). **3bh** was easily

Scheme 3. Transformations of the Ring-Opening Products



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decarboxylated, and the product was deprotected by Pd-catalyzed hydrogenation and cyclized to give optically active γ-lactam **7** (eq 2 in Scheme 3). These products contain important structural motifs found in biologically active compounds.[11] Thus, this reaction provides a facile way to prepare potentially useful building blocks in organic synthesis.

In summary, we have developed the first catalytic enantioselective ring-opening reaction of 2-substituted cyclopropane-1,1-dicarboxylates with multifunctional secondary amines. With the Ni(II) complex of an indene-derived trisoxazoline (In-TOX) ligand, the reaction performed well over a series of substrates, giving the desired products in excellent yield (up to 99%) and enantioselectivity (up to 98% ee) under mild conditions. In this reaction, a strong effect of the ligand side arm was observed, which will be helpful for the modification of BOX ligands in asymmetric catalysis. The single-crystal X-ray structure of the TOX–Ni complex was also obtained, and an asymmetric induction model was developed. This protocol provides a promising method for the synthesis of versatile chiral γ-substituted γ-amino acid derivatives as well as effective kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates. Further investigation of the applications of the current reaction is underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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