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Sidearm as a Control in the Asymmetric Ring Opening Reaction of Donor-Acceptor Cyclopropane†

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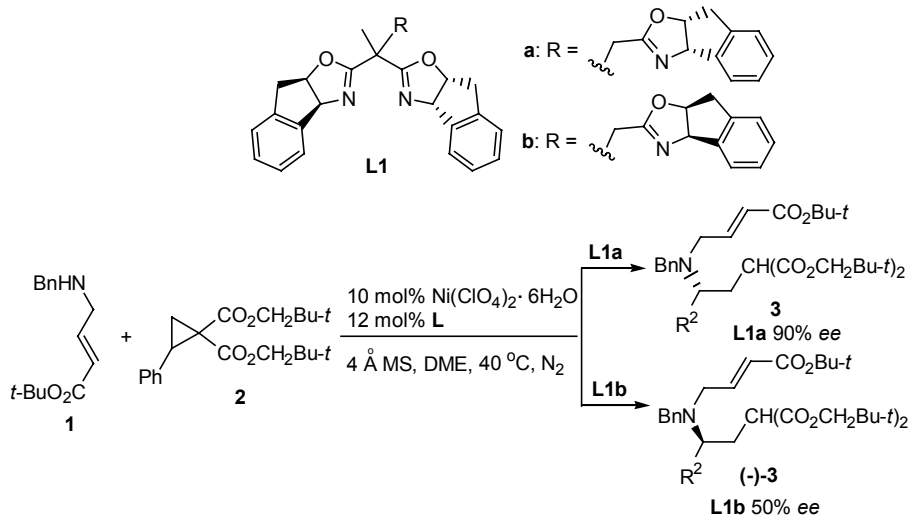
A new type of trisoxazoline and bisthiazoline based ligands have been developed,which are absent of chiral motif on the parent skeleton and containa chiral backbone on sidearm. The ligands promote the amine nucleophilic ring opening reaction of 1,1-cyclopropane diesters smoothly, furnishing the γ-amino acid derivatives in high yield with moderate to good enantioselectivity.

Keywords sidearm, oxazoline, asymmetric, ring opening, cyclopropane

Introduction

In the development of asymmetric catalysts, designing and exploring new ligands that can achieve high enantioselectivity in high efficiency with low cost have always been a goal of the chemists.[1] Recently, we have developed a series of sidearm modified chiral bisoxazoline ligands TOX and SaBOX,[1d,2] which generally behaved superior to the classic bisoxazolines[1e,1i,1j] in some asymmetric reactions in terms of the reactivity and stereoselectivity. For example, in asymmetric Nazarov reaction catalyzed by chiral tris(oxazoline)/Copper(II), we found that the chiral sidearm in different configuration led to different enantioselectivity.[2i] In the ring opening reactions of donor-acceptor cyclopropanes with amines,[3,4] we found that the configuration of the chiral centers in the sidearm is crucial for the enantioselectivity, in which **L1a** prefers to give the (*R*)-product, while **L1b** is favorable for the (*S*) one (Scheme 1).[2o] These results suggest that the chiral backbone of sidearm has a significant influence on the asymmetric induction of reaction. This interesting phenomenon inspired us to explore the role of the chiral sidearm in catalytic asymmetric reactions. Thus, we conceived that it might be possible to design a new ligand that bears a chiral sidearm as the only chiral source in the catalysis, which may give rise to a high efficient asymmetric induction in the ring opening reactions of cyclopropanes with amines. Herein, we wish to present our efforts on this subject.

Scheme 1 Sidearm effect on enantioselectivity



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† Dedicated to Professor Chengye Yuan and Professor Li-Xin Dai on the occasion of their 90th birthdays.

Experimental

Typical procedure for the synthesis of 6a

A mixture of $Ni(ClO_4)_2$•$6H_2O$ (0.02 mmol, 7.3 mg) and the trisoxazoline (**L2c**, 0.024 mmol, 8.4 mg) in dimethoxyethane (DME 2 mL) with activated 4 Å MS was stirred at 40 ℃ for 2 h under nitrogen. Then, the cyclopropane (**4a**, 0.44 mmol, 165.7 mg) and the aliphatic amine (**5a**, 0.20 mmol, 39.5 mg) were added to the mixture of catalyst successively. The resulting suspension was allowed to stir at 40 ℃. Upon disappearance of **5a** as confirmed by thin-layer chromatography, the reaction was filtered through a glass funnel with a thin layer (20 mm) of silica gel (100—200 mesh) with CH_2Cl_2 (approx. 75 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/petroleum, 1/35 to 1/15) to afford the product **6a** (108 mg) as a yellowish oil in 94% yield with 70% *ee* (Chiralcel AD-H, *i*-PrOH/hexanes=5/95, 0.70 mL/min, λ=254 nm: t_R(minor)=9.35 min, t_R(major)=14.04 min); $[\alpha]_D^{20}$ =–53.0° (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37—7.13 (m, 12H), 6.93 (d, *J*=8.4 Hz, 2H), 3.90 (s, 3H), 3.83—3.65 (m, 7H), 3.58 (ABd, *J*=10.4 Hz, 1H), 3.08 (d, *J*=13.6 Hz, 2H), 2.68—2.61 (m, 1H), 2.42—2.35 (m, 1H), 0.88 (s, 9H), 0.84 (s, 9H).

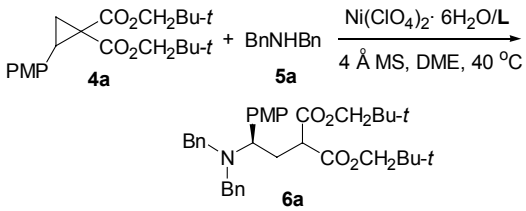
Results and Discussion

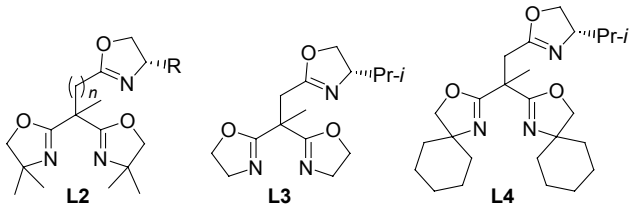
Based on this conception, we initially designed and synthesized a series of trisoxazoline ligands **L2a—i** bearing a chiral oxazoline sidearm and an achiral bisoxazoline parent skeleton.[5] Then we chose the ring opening reaction of cyclopropane **4a** with dibenzylamine **5a** as a model reaction, and screened the ligands by enantioselective control of the reaction at 40℃ in dimethoxyethane (DME). As shown in Table 1, as the size of the R group increased from methyl to *tert*-butyl, the enantioselectivity of the reaction increased first and then decreased obviously (from 35% *ee* to 70% *ee* and then 31% *ee*, Entries 1—5). With *iso*-propyl as R group, the best *ee* value could be achieved (70% *ee*, Entry 3). When a phenyl or a benzyl substituted oxazoline sidearm was used, the cyclopropane **4a** consumed very fast, and the ring opening product **6a** was produced in moderate yields with 18% *ee* and 57% *ee*, respectively (Entries 6 and 7). Lengthen or shorten the bridge of the sidearm destroyed the enantioselectivity dramatically (7% *ee* and 1% *ee*, Entries 8 and 9). When **L3** was employed, the ring opening reaction worked well and the desired product **6a** was obtained in 98% yield with a reversion of enantioselectivity after 7.5 h (Entry 10). **L4** with cyclohexyl groups substituted on the achiral bisoxazoline parent skeleton gave a moderate level of *ee* (56% *ee*, Entry 11).

A range of bisbenzothiazoline ligands **L5a—j** furnished with various chiral oxazoline sidearm were also synthesized[5] and evaluated in the ring opening reaction of cyclopropane with amine (Table 2). Ligand **L5a** with *iso*-propylsubstituted oxazoline as a sidearm delivered 63% *ee* (Entry 1). Bulkier R^3 groups such as *sec*-butyl, *tert*-butyl gave lower *ee* values (Entries 2 and 3). Interestingly, when the oxazoline sidearm was substituted with an aromatic moiety, for example phenyl, benzyl or indenyl, reversed enantioselectivity was observed (Entries 4—6) and the reason is not clear. Increasing the steric hindrance of the oxazoline, led to a dramatic drop of the enantioselectivity (**L5g** vs. **L5a**, 37% *ee* versus 63% *ee*, Entry 7 versus Entry 1). Remarkably, the enantioselectivity of this ring opening reaction is very sensitive to both the size of R^1 group and the structure of the thiazoline moiety (Entries 8—14). Either installing benzyl group as R^1 or furnishing substituent on the *ortho*- or *meta*- position of benzothiazoline would destroy the enantioselectivity (Entries 10—12).

Since the reaction conditions such as the Lewis acids

Table 1 Ligand screening based on trisoxazoline





L2a *n* = 1, R = Me
L2b *n* = 1, R = *i*-Bu
L2c *n* = 1, R = *i*-Pr
L2d *n* = 1, R = *sec*-Bu
L2e *n* = 1, R = *t*-Bu
L2f *n* = 1, R = Ph
L2g *n* = 1, R = Bn
L2h *n* = 0, R = *i*-Pr
L2i *n* = 2, R = *i*-Pr

Entry[a]	L	Time/h	Yield[b]/%	*ee*[c]/%
1	**L2a**	18	82	35
2	**L2b**	16	90	41
3	**L2c**	14.5	94	70
4	**L2d**	10	99	63
5	**L2e**	19	68	31
6	**L2f**	5	55	18
7	**L2g**	7	64	57
8	**L2h**	4	87	7
9	**L2i**	24	26	1
10	**L3**	7.5	98	(–)13
11	**L4**	17	99	56

[a] Conditions: All reactions were carried out under N_2 atmosphere at 40 ℃, **5** (1.0 equiv.), **4** (2.2 equiv.), 10 mol% $Ni(ClO_4)_2$•$6H_2O$, 12 mol% **L2**, $[\mathbf{5}]_0$=0.10 mol•L^{-1}, in DME (2 mL) and 4 Å MS (200 mg). [b] Isolated yield. [c] Determined by chiral HPLC.

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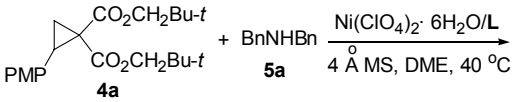
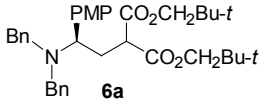
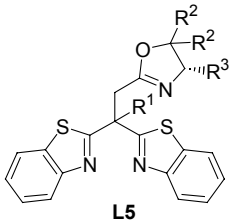
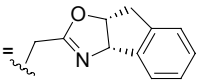
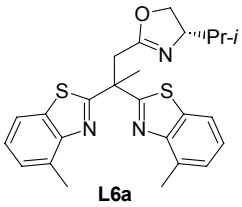
Table 2 Ligand screening based on bisthiazoline

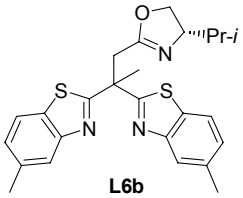






L5a R^1 = Me, R^2 = H, R^3 = *i*-Pr
L5b R^1 = Me, R^2 = H, R^3 = *sec*-Bu
L5c R^1 = Me, R^2 = H, R^3 = *t*-Bu
L5d R^1 = Me, R^2 = H, R^3 = Ph
L5e R^1 = Me, R^2 = H, R^3 = Bn
L5f R^1 = Me, sidearm = 
L5g R^1 = Me, R^2 = Me, R^3 = *i*-Pr
L5h R^1 = H, R^2 = H, R^3 = *i*-Pr
L5i R^1 = Et, R^2 = H, R^3 = *i*-Pr
L5j R^1 = Bn, R^2 = H, R^3 = *i*-Pr



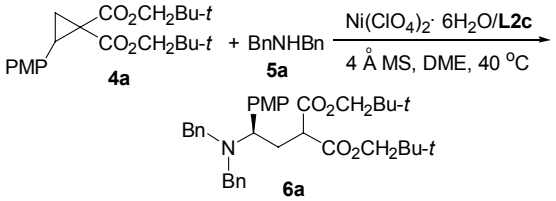


Entry[a]	L	Time/h	Yield[b]/%	*ee*[c]/%
1	**L5a**	17	88	63
2	**L5b**	16	74	60
3	**L5c**	16	36	45
4	**L5d**	16	88	(−)42
5	**L5e**	16	99	(−)29
6	**L5f**	11	29	(−)42
7	**L5g**	12	86	37
8	**L5h**	16	81	(−)12
9	**L5i**	11	96	52
10	**L5j**	12	97	3
11	**L6a**	18.5	96	1
12	**L6b**	19.5	79	8

[a] Conditions: All reactions were carried out under N_2 atmosphere at 40 ℃, **5** (1.0 equiv.), **4** (2.2 equiv.), 10 mol% $Ni(ClO_4)_2$•$6H_2O$ 12 mol% **L2,** $[\mathbf{5}]_0$=0.10 mol•L^{-1} in DME (2 mL) and 4 Å MS (200 mg). [b] Isolated yield. [c] Determined by chiral HPLC.

and the solvents usually affect the yield and the enantioselectivity in asymmetric synthesis. We next focused on investigating a series of metal salts and various commonly used solvents. As shown in Table 3, by using $Co(ClO_4)_2$•$6H_2O$ as Lewis acid, the corresponding product **6a** was obtained in 44% yield and 30% *ee* (Entry 2). $Mn(ClO)_2$•$6H_2O$ and $Mg(ClO_4)_2$•$6H_2O$ led to poor yields with bad enantioselectivity (Entries 3 and 4). Of Lewis acids examined, $Fe(ClO_4)_3$•$6H_2O$, $Zn(OTf)_2$ and $Cu(OTf)_2$ made the reactions sluggish (Table 3, Entries 5—7). With respect to solvent effects, halogenated solvents such as dichloromethane and chloroform speeded up the reaction but with poor *ee* values (94% yield, 27% *ee* and 39% *ee*, Entries 8 and 9). Non-polar solvent such as toluene was also suitable, giving 93% yield and 65% *ee* (Entry 10). In THF and ethyl acetate, 85%—89% yields and moderate enantioselectivities were achieved (58% *ee* and 57% *ee*, Entries 11, 12).

Table 3 Lewis acid and solvent effect

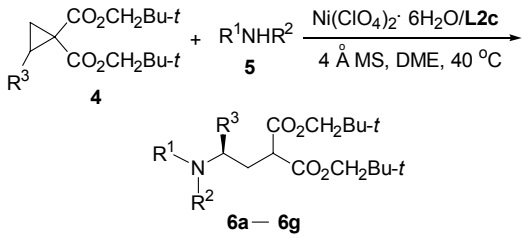


Entry[a]	Lewis acid	Solvent	Time/h	Yield[b]/%	*ee*[c]/%
1	$Ni(ClO_4)_2$•$6H_2O$	DME	14.5	94	70
2	$Co(ClO_4)_2$•$6H_2O$	DME	18	44	30
3	$Mn(ClO)_2$•$6H_2O$	DME	18	12	7
4	$Mg(ClO_4)_2$•$6H_2O$	DME	15.5	33	racemic
5	$Fe(ClO_4)_3$•$6H_2O$	DME	10.5	N.R.	—
6	$Cu(OTf)_2$	DME	10.5	N.R.	—
7	$Zn(OTf)_2$	DME	10.5	N.R.	—
8	$Ni(ClO_4)_2$•$6H_2O$	CH_2Cl_2	3.5	94	27
9	$Ni(ClO_4)_2$•$6H_2O$	$CHCl_3$	10	94	39
10	$Ni(ClO_4)_2$•$6H_2O$	Toluene	10.5	93	65
11	$Ni(ClO_4)_2$•$6H_2O$	THF	15.5	85	58
12	$Ni(ClO_4)_2$•$6H_2O$	EtOAc	10	89	57

[a] Conditions: All reactions were carried out under N_2 atmosphere at 40 ℃, **5** (1.0 equiv.), **4** (2.2 equiv.), 10 mol% metal, 12 mol% **L2c**, $[\mathbf{5}]_0$=0.10 mol•L^{-1} in solvent (2 mL) and 4 Å MS (200 mg). [b] Isolated yield. [c] Determined by chiral HPLC.

With the optimized conditions in hand, the substrate scope of this ring opening reaction was examined. As shown in Table 4, the reaction proceeded smoothly with a range of 1,1-cyclopropane diesters and secondary amines bearing various functional groups such as allyl, silyl ether, acetal and ester were all well tolerated (Entries 1—7). High yields and moderate to good enantioselectivities can be accomplished (74%—99% yields, cyclopropane 29%—70% *ee*). In addition, the phenyl substituted cyclopropane substrate was also examined in the current catalyst system, furnishing the corresponding product in 22% yield with 74% *ee* (Entry 8). However, when $BnNH_2$ was used as nucleophile, poor enantioselectivity was obtained (67% yield, 4% *ee*, Entry 9).

Table 4 Substrate scope



Entry[a]	R^1, R^2	R^3	**6**	Time/h	Yield[b]/%	*ee*[c]/%
1	Bn, Bn	PMP	**6a**	14.5	94	70
2	Bn, $CH_2CH=CH_2$	PMP	**6b**	10.5	76	60
3	Bn, CH_2CH_2OTBS	PMP	**6c**	10.5	77	56
4	Bn, $CH_2CH(OMe)_2$	PMP	**6d**	10	99	53
5	Bn, CH_2CO_2Et	PMP	**6e**	10	74	29
6	Ph, $CH_2CH=CH_2$	PMP	**6f**	10	98	42
7	Bn, Bn	PhCH=CH	**6g**	13.5	99	58
8	Bn, Bn	Ph	**6h**	38	22	74
9	Bn, H	PMP	**6i**	12	67	4

[a] Conditions: All reactions were carried out under N_2 atmosphere at 40 ℃, **5** (1.0 equiv.), **4** (2.2 equiv.), 10 mol% $Ni(ClO_4)_2$•$6H_2O$, 12 mol% **L2c**, $[\mathbf{5}]_0$=0.10 mol•L^{-1} in DME (2 mL) and 4 Å MS (200 mg). [b] Isolated yield. [c] Determined by chiral HPLC.

Conclusions

In summary, we have developed a new type of trisoxazoline and bisthiazoline based ligands with the chiral backbone on sidearm and without chiral motif on the parent skeleton. The ligands promote the amine nucleophilic ring opening reaction of 1,1-cyclopropane diesters smoothly, furnishing the *γ*-amino acid derivatives[6] in high yield with moderate to good enantioselectivity. Further investigation of the role of the sidearm in asymmetric catalysis, as well as the utilization of the new developed ligands in other reactions is still on going in our lab.

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[5] For details, see Supporting information.

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