Asymmetric Catalysis

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Highly Enantioselective and Diastereoselective Cycloaddition of Cyclopropanes with Nitrones and Its Application in the Kinetic Resolution of 2-Substituted Cyclopropane-1,1-dicarboxylates**

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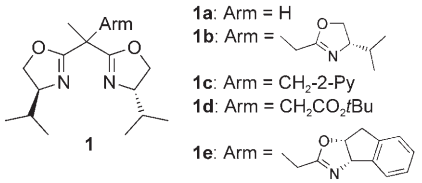
Trisoxazolines[1] have been applied widely in asymmetric catalysis[2] and molecular recognition.[3] In our efforts to develop superior catalysts that are cheap, readily accessible, air stable, and water tolerant, we designed and synthesized the pseudo-C_3-symmetric trisoxazoline **1b** (Scheme 1) by the



Scheme 1. Trisoxazoline (tox) ligands. Py = pyridyl.

sidearm approach, and found that **1b**/Cu^{II} promoted smoothly the highly enantioselective Friedel–Crafts reaction of indoles with arylidene malonates[4] and the Kinugasa reaction.[5] We also described tox/Co^{II}-catalyzed [3+2] cycloaddition reactions between nitrones and alkylidene malonates in which the *endo*/*exo* selectivity could be controlled well by the reaction temperature. Thus, both *cis* and *trans* isoxazolidines could be prepared enantioselectively.[6] Herein, we report that the system tox/Ni^{II} catalyzes the [3+3] cycloaddition of racemic 2-substituted cyclopropane-1,1-dicarboxylates with nitrones to provide ready access to optically active tetrahydro-1,2-oxazine derivatives with high diastereoselectivity and enantioselectivity. Furthermore, this reaction can be employed for the kinetic resolution[7] of 2-substituted cyclopropane-1,1-dicarboxylates to furnish these compounds in optically active form with excellent *ee* values.

Tetrahydro-1,2-oxazine derivatives occur frequently in biologically active compounds[8] and are valuable synthetic intermediates.[9] Among the methods developed for the preparation of such compounds,[10] the [3+3] cycloaddition of donor–acceptor cyclopropanes with nitrones, pioneered by Kerr and co-workers,[11] is a particularly elegant approach. They found that nitrones **3** react smoothly with cyclopropanes **2** in the presence of $Yb(OTf)_3 \cdot x\,H_2O$ to give the *cis* isomers **4** diastereospecifically (see Table 1). Recently, Sibi et al. developed a highly efficient asymmetric version of this reaction.[12] They reported that nitrones react with cyclopropane-1,1-dicarboxylates to afford tetrahydro-1,2-oxazine derivatives with high enantioselectivity in the presence of dbfox/Ni^{II} (10 mol%; dbfox = 4,6-dibenzofurandiyl-2,2'-bisoxazoline). When 2-substituted cyclopropane-1,1-dicarboxylates were used as substrates, and the quantity of the catalyst was increased to 30 mol%, the reactions proceeded smoothly to give the products with high *ee* values but with low diastereoselectivities (the *cis*/*trans* ratio ranged from 1.0:1.4 to 1.0:0.8).

Gratifyingly, we found that diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**2a**) reacted smoothly with nitrone **3a** to furnish the cycloaddition adduct in 99% yield with excellent diastereoselectivity (d.r. > 99:1) in the presence of a catalytic amount of **1b**/$Ni(ClO_4)_2 \cdot 6\,H_2O$. Further studies showed that ligands derived from *i*Pr-box (box = bisoxazoline) influenced strongly both the enantioselectivity and diastereoselectivity of the reaction. The bisoxazoline **1a** without a pendant group gave the desired product with good diastereoselectivity (d.r. 97:3) but only 20% *ee* (Table 1, entry 1). However, when a pyrid-2-yl or oxazolinyl group was introduced as a pendant group, the enantioselectivity was improved to a moderate level, and the high diastereoselectivity was maintained (Table 1, entries 2, 3, and 5). Both excellent enantioselectivity and high diastereoselectivity were observed when the substituent on the nitrogen atom of the nitrone was changed from a phenyl group to a methyl group (Table 1, entry 6). In this case, **4b** was obtained with 95% *ee* and d.r. 11:1 when a catalytic amount of **1e**/$Ni(ClO_4)_2$ was used. Thus, both high enantioselectivity and high diastereoselectivity could be attained by using **1e**/$Ni(ClO_4)_2$ as the catalyst. The ester groups of the 2-phenyl cyclopropane-1,1-dicarboxylate also influenced the enantioselectivity. For example, when **2b** was used instead of **2a**, the *ee* value of the product decreased from 95 to 90% (Table 1, entry 7).

We studied the scope of this reaction in terms of the substrate under the optimal conditions by investigating a variety of nitrones and cyclopropanes with different structures. As shown in Table 2, the ester groups of cyclopropanes **2** slightly influenced the enantioselectivity of the reaction. Benzyl and ethyl diesters reacted with higher enantioselectivity than the corresponding methyl diester (Table 2,

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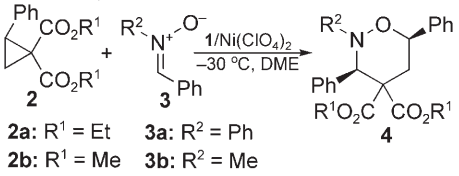
Table 1: Effect of the ligand on the cycloaddition.[a]

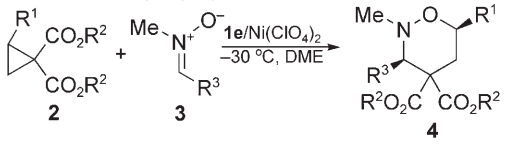


2a: R^1 = Et **3a**: R^2 = Ph
2b: R^1 = Me **3b**: R^2 = Me

Entry	R^1	R^2	**1**	*t* [days]	**4**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Et	Ph	**1a**	4	**4a**	96	97:3	20
2	Et	Ph	**1b**	4	**4a**	99	99:1	55
3	Et	Ph	**1c**	4	**4a**	91	99:1	66
4	Et	Ph	**1d**	4	**4a**	99	94:6	13
5	Et	Ph	**1e**	4	**4a**	99	99:1	57
6	Et	Me	**1e**	4	**4b**	88[e]	11:1	95
7	Me	Me	**1e**	3	**4c**	82[e]	13:1	90
8	Me	Me	**1c**	3	**4c**	77[e]	6:1	88

[a] Reaction conditions: $Ni(ClO_4)_2$ (0.040 mmol), **1** (0.044 mmol), **2** (0.44 mmol), **3** (0.20 mmol), 4-Å molecular sieves; DME = 1,2-dimethoxyethane. [b] Yield of the isolated product. [c] Ratio of isomers (*cis*/*trans*) as determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral phase. [e] Yield of the isolated *cis* isomer.

Table 2: Asymmetric cycloaddition of cyclopropanes with nitrones.[a]



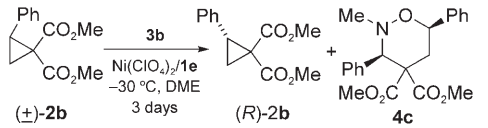
Entry	R^1	R^2	R^3	*t* [days]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	Me	Ph	3	82[e]	13:1	90
2[f]	Ph	Bn	Ph	4	62[e]	10:1	97
3	Ph	Et	Ph	4	88[e]	11:1	95
4	Ph	Et	4-BrC_6H_4	4	85[e]	12:1	97
5	Ph	Et	4-$MeO_2CC_6H_4$	4	97	11:1	97
6	Ph	Et	4-MeC_6H_4	4	80[e]	12:1	96
7	Ph	Et	4-$MeOC_6H_4$	4	92[e]	13:1	90
8	Ph	Et	2-furyl	4	99	13:1	93
9	Ph	Et	styryl	3	76[e]	4:1	92
10[f]	vinyl	Et	Ph	3	88[e]	6:1	80
11[f]	styryl	Et	Ph	5[g]	84	5:1	80
12	Ph	Et	Ph[h]	5	74	11:1	93

[a] Reaction conditions: $Ni(ClO_4)_2$/**1e** = 0.040 mmol/0.044 mmol, **2**/**3** = 0.44 mmol/0.20 mmol, 4-Å molecular sieves. [b] Combined yield of the two diastereomers based on **3**. [c] Ratio of isomers (*cis*/*trans*), determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral phase. [e] Yield of the isolated *cis* isomer. [f] $T = -40$ °C. [g] $t = 5$ h. [h] PhCH=N(O)Bn was used.

entries 1–3). The electronic character of the α-aryl group on the nitrone had a slight effect on the enantioselectivity of the reaction (Table 2, entries 4–7). All reactions of both electron-deficient and electron-rich α-aryl nitrones proceeded with excellent enantio- and diastereoselectivities. A nitrone with an α-furyl group underwent the cycloaddition smoothly with high diastereoselectivity to afford the corresponding 1,2-oxazine product in quantitative yield with a high *ee* value (Table 2, entry 8). A styryl-substituted nitrone reacted to give the cycloaddition product with high enantioselectivity and good diastereoselectivity (Table 2, entry 9). Diethyl 2-vinyl- and 2-styrylcyclopropane-1,1-dicarboxylates reacted smoothly with **3b** to give the desired products with good enantio- and diastereoselectivities (Table 2, entries 10 and 11). Finally, the reaction of an *N*-Bn-substituted nitrone also gave the cycloaddition adduct in good yield with excellent stereoselectivity (Table 2, entry 12).

In the [3+3] cycloaddition reactions described above, an excess of the cyclopropane derivative (2.2 equiv) was used. Interestingly, the remaining cyclopropane could be recovered with a good *ee* value. For example, in the case of entry 1 in Table 2, dimethyl 2-phenylcyclopropane-1,1-dicarboxylate was recovered in 57% yield with 59% *ee* (Scheme 2). These results, together with the importance of cyclopropane-1,1-dicarboxylates as intermediates as a result of their wide application in organic synthesis,[13] encouraged us to explore the kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates. It was found that under optimized conditions the trisoxazoline–Ni$(ClO_4)_2$ catalyst **1e**/Ni$(ClO_4)_2\cdot 6H_2O$ was also an excellent catalyst for the kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates. Simply by changing the ratio of (±)-**2b** to **3b**, a variety of 2-aryl cyclopropane-1,1-dicarboxylates could be resolved efficiently in high yields in the presence of a catalytic amount of **1e**/$Ni(ClO_4)_2\cdot 6H_2O$ (Table 3). This method provides ready access to optically active 2-substituted cyclopropane-1,1-dicarboxylates with excellent enantioselectivities (91–97% *ee*).[14]

Interestingly, optically active **2b** reacted smoothly with nitrone **3b** in the presence of a catalytic amount of $Ni(ClO_4)_2$ without the ligand **1e** to give the tetrahydro-1,2-oxazine **4c** in high yield with the same level of enantiomeric purity as that of the starting material **2b** (Scheme 3). This result further supports the mechanism proposed by Young and Kerr for the [3+3]



2b/**3b** = 2.2:1.0 (*R*)-**2b**: 57% recover, 59% *ee*
4c: 82% yield (*cis*), d.r. = 13:1, 90% *ee*

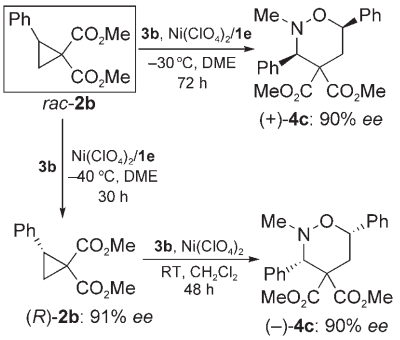
Scheme 2. Reaction of **3b** with excess cyclopropane **2b**.

Table 3: Kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates.[a]

(±)-**2** (*R*)-**2**

X	(±)-**2** [mmol]	**3b** [mmol]	*s*[b]	*t* [h]	*ee* [%][c]	Recovery of **2** [%][d]
Ph	0.40	0.40	16	30	91	43
p-MeC_6H_4	0.40	0.25	97	48	96	49
p-BrC_6H_4	0.40	0.23	81	67	95	49
p-$CF_3C_6H_4$	0.40	0.23	97	168	96	49
p-$NO_2C_6H_4$	0.40	0.23	36	96	97	45
p-ClC_6H_4	0.40	0.23	70	72	94	49
p-$MeOC_6H_4$	0.40	0.23	13	48	92	40

[a] Reaction conditions: $Ni(ClO_4)_2$ (0.040 mmol), **1e** (0.044 mmol), 4-Å molecular sieves. For details, see the Supporting Information. [b] $s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$; *C* refers to the conversion of (±)-**2** (1−(yield of recovered **2**)). [c] Determined by HPLC on a chiral phase. [d] Yield of isolated recovered **2**.



Scheme 3. Synthesis of both enantiomers of the 1,2-oxazine **4c**.

cycloaddition of nitrones with cyclopropanes.[11a] Thus, both enantiomers of the tetrahydro-1,2-oxazine could be prepared from the racemic 2-phenyl cyclopropane-1,1-dicarboxylate: by direct cycloaddition with the nitrone in the presence of a catalytic amount of **1e**/$Ni(ClO_4)_2$ or by **1e**/$Ni(ClO_4)_2$-catalyzed resolution followed by cycloaddition with the nitrone (Scheme 3).

In conclusion, we have developed a highly diastereoselective and enantioselective catalytic cycloaddition of 2-substituted cyclopropane-1,1-dicarboxylates with nitrones in the presence of a trisoxazoline–Ni^{II} catalyst. The diastereoselectivity of the cycloaddition has been improved greatly relative to that of the existing method. The same catalyst **1e**/$Ni(ClO_4)_2$ also proved to be excellent for the kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates. Furthermore, a combination of the asymmetric cycloaddition and the kinetic resolution/cycloaddition provided straightforward access to both enantiomers of tetrahydro-1,2-oxazines. The mild reaction conditions, atom economy, and high stereoselectivity make this reaction potentially useful for organic synthesis.

Experimental Section

Typical procedure for the enantioselective [3+3] cycloaddition: A mixture of $Ni(ClO_4)_2 \cdot 6H_2O$ (0.040 mmol) and the trisoxazoline (0.044 mmol) in dimethoxyethane (1 mL) was stirred at 50 °C for 2 h under nitrogen. The mixture was then cooled to room temperature and added to the cyclopropane diester **2** (0.44 mmol) with a syringe. Activated 4-Å molecular sieves (100 mg) were added to the resulting solution. The mixture was stirred at −30 °C for 30 min, and then the nitrone (0.20 mmol) was added. When the reaction was complete (monitored by TLC), the mixture was passed rapidly through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh), which was then washed with CH_2Cl_2 (50 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography to afford the product.

The general procedure for the kinetic resolution of 2-substituted cyclopropane 1,1-diesters is similar to that for the enantioselective [3+3] cycloaddition. The reaction was carried out at the desired temperature, and the ratio of the nitrone **3b** to the 2-substituted cyclopropane diester (±)-**2** was changed (see Table 3). The reaction was quenched when the conversion of (±)-**2** was equal to or higher than 50% (monitored by ^1H NMR spectroscopy).[15]

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