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Iron Porphyrin-Catalyzed Olefination of Ketenes with Diazoacetate for the Enantioselective Synthesis of Allenes

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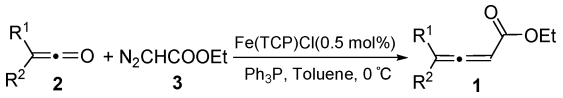
The Wittig reaction and its variants are the most powerful approaches for constructing carbon−carbon double bonds in organic synthesis due to their unambiguous positioning and good stereoselectivity.[1] Of the recent developments,[2−4] much attention has been paid to ylide olefination of aldehydes[3] and ketones[4] under neutral conditions by transition metal complex-catalyzed decomposition of diazo compounds to generate ylide in situ. In our studies on ylide reactions in organic synthesis,[2b−e,5] we are interested in developing an efficient method for the synthesis of allenes via olefination of ketenes, unstable carbonyl compounds,[6] with diazoacetate in the presence of transition metal complex. Fortunately, we found that such an olefination process could be achieved smoothly in the presence of PPh_3 and 0.5 mol % of tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(TCP)Cl). In particular, when chiral phosphine was used, optically active allenes could be prepared with high enantioselectivities in high yields. In this communication, we wish to report the preliminary results.

Allenes are of great importance due to their occurrence[7] in natural products and biologically active compounds, and they are valuable intermediates[8] in organic synthesis. Although many synthetic methods have been developed, a practical and mild process, in particular, for the synthesis of optically active ones,[9] is still a challenge. Gratifyingly, it was found that allenic ester **1a** could be synthesized in nearly quantitative yield when the reaction of 2-phenylprop-1-en-1-one with ethyl diazoacetate was carried out in toluene at 0 °C in the presence of PPh_3 and 0.5 mol % of Fe(TCP)Cl (Table 1, entry 1). Further studies showed that a variety of ketenes with different structures are good substrates for this olefination. As shown in Table 1, pure disubstituted ketenes gave good to excellent yields (entries 1−8). Disubstituted ketenes, prepared in situ from acyl chlorides without further purification, also worked well to afford the trisubstituted allenes in good yields (entries 9 and 10). A one-pot strategy has also been developed for some unstable ketenes. For example, 4-monosubstituted and 4,4-disubstituted allenic esters **1k**−**1o** could be obtained in good yields when Et_3N and acyl chloride were added sequentially[10] into the ylide generated in situ from phosphine and diazoacetate (entries 11−15). Thus, various 4-monosubstituted and 4,4-disubstituted allenic esters could be synthesized (even in gram scale, entry 2 in Table 1) by the current protocol.

For the olefination of aldehydes with diazo compounds catalyzed by transition metal complex, there are two mechanistic pathways in the literature,[3,4] as shown in Scheme 1, depending on the metal complex. In the case of Fe(TCP)Cl employed, Woo and his coworkers[3g,4a] documented that the mechanism involved the formation of a free ylide (Path B in Scheme 1). On the basis of this mechanistic insight, it is envisaged that chiral allenes could be prepared enantioselectively just by the use of chiral phosphine instead of triphenylphosphine. To our delight, a variety of optically active allenic esters could be synthesized with excellent enantioselectivities (93−98% ee) in high yields by employing chiral diphosphine compound **4** under the optimal conditions, as shown in Table 2.[11] These results also proved clearly that the mechanism of the present olefination involves the generation of an ylide through catalytic transfer of an iron(II) carbene ligand to phosphine.

Compound **4** is a diphosphine, and the molar ratio of EDA to **4** used in the current reaction is 2:1. Therefore, both monoylide **6a** and diylide **6b** are possible intermediates of this reaction. To elucidate the real intermediate, ylides **6a** and **6b** were synthesized

Table 1. Olefination of Ketenes with EDA Catalyzed by Fe(TCP)Cl[a]



entry	R^1	R^2	method	**1**	yield (%)[b]
1	Ph	Me	A	**1a**	99
2	Ph	Et	A	**1b**	99 (94[d])
3	Ph	*i*-Pr	A	**1c**	99
4	Ph	*n*-Bu	A	**1d**	98
5	*p*-Cl−C_6H_4	Et	A	**1g**	98
6	*p*-MeO−C_6H_4	Et	A	**1h**	92
7	*o*-Me−C_6H_4	Et	A	**1i**	95
8	COOEt	*i*-Bu	A	**1j**	83
9[c]	Ph	allyl	A	**1e**	53
10[c]	Ph	3-butenyl	A	**1f**	75
11	*n*-C_5H_{11}	H	B	**1k**	77
12	*n*-$C_{10}H_{21}$	H	B	**1l**	80
13	Ph	H	B	**1m**	56
14	Br	Me	B	**1n**	59
15	*n*-Bu	Et	B	**1o**	74

[a] For detailed procedures of methods A and B, please see the Supporting Information. [b] Isolated yield. [c] Ketenes were prepared in situ. [d] In 7 mmol scale, and 0.25 mol % of Fe(TCP)Cl was used.

Scheme 1. Possible Pathways for the Olefination of Aldehydes via Transition-Metal-Catalyzed Decomposition of Diazoacetate

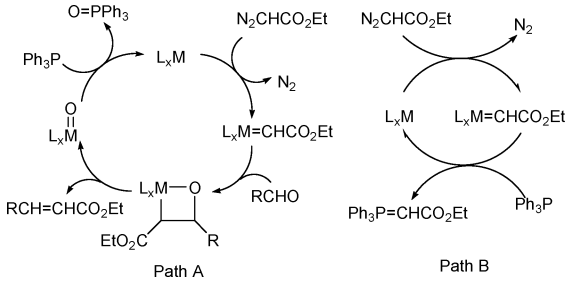


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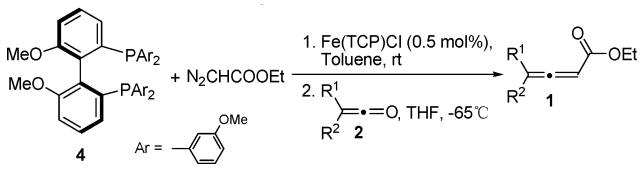
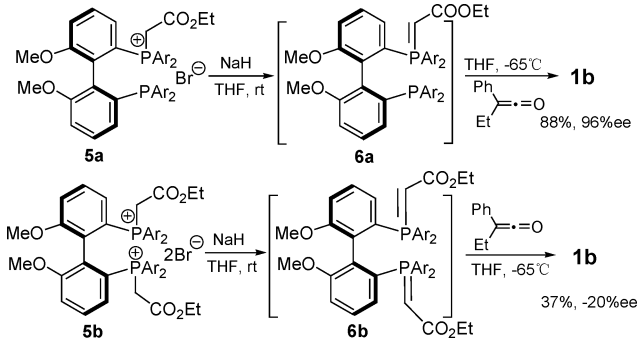
Table 2. Enantioselective Synthesis of Allenes[a]



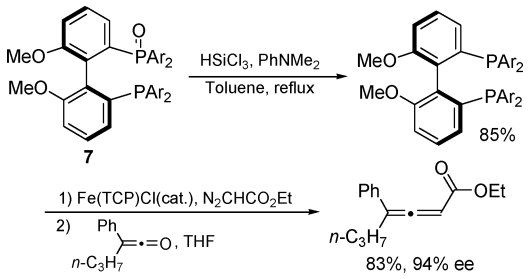
entry	R^1	R^2	**1**	yield (%)[b]	ee (%)[c]
1	Ph	Me	**1a**	72	93
2	Ph	Et	**1b**[d]	90	97
3	Ph	*n*-Pr	**1r**	87	93
4	*o*-Me−C_6H_4	Et	**1i**	86	97
5	*p*-MeO−C_6H_4	Et	**1h**	81	96
6	*p*-Cl−C_6H_4	Et	**1g**	83	97
7	*p*-Br-C_6H_4	Et	**1s**	80	98

[a] For detailed procedures, please see the Supporting Information. [b] Isolated yield. [c] Determined by chiral HPLC. [d] **1b** was assigned as *S*-configuration by comparing its optical rotation with the literature.

Scheme 2. Effects of Ylides on the Synthesis of Chiral Allene **1b**



Scheme 3. Phosphine Recovered and Reused



from their corresponding salts **5a** and **5b**, respectively. It was found that ylide **6a** gave the desired product **1b** in 88% yield with 96% ee, which is consistent with the experimental observation (entry 2, Table 2). However, diylide **6b** afforded the enantiomer of **1b** in 37% yield with −20% ee. These results, together with the fact that 83% of monophosphine oxide **7** was isolated in the reaction of 2-phenylpent-1-en-1-one with ylide generated in situ (entry 3 in Table 2), showed clearly that the monoylide **6a** is the intermediate and further confirmed the mechanism Woo et al. proposed. Noticeably, the recovered chiral phosphine oxide could be readily reduced by $HSiCl_3$ and reused. For example, **1r** could be obtained with 94% ee in 83% yield using the recovered compound **4** as the phosphine (Scheme 3), comparable to the results when phosphine **4** was first used (entry 3 in Table 2).

In summary, we have developed an efficient method for the synthesis of allenes under neutral conditions by olefination of ketenes with EDA in the presence of Ph_3P and catalytic Fe(TCP)-Cl for the first time. We have also realized its asymmetric version and found that, by employing chiral phosphine instead of PPh_3, chiral allenes could be synthesized with high enantioselectivities (93−98% ee) in good yields, providing an easy access to optically active allenic esters. In addition, the results described here confirmed that the mechanism involves ylide olefination. The high enantioselectivity, the neutral condition, and the fact that the phosphine could be recovered and reused make the current method potentially useful in organic synthesis.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For detailed procedure, please see Supporting Information.

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Asymmetric Catalysis

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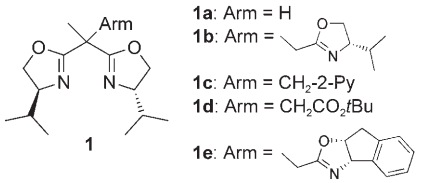
Highly Enantioselective and Diastereoselective Cycloaddition of Cyclopropanes with Nitrones and Its Application in the Kinetic Resolution of 2-Substituted Cyclopropane-1,1-dicarboxylates**

*Yan-Biao Kang, Xiu-Li Sun, and Yong Tang**

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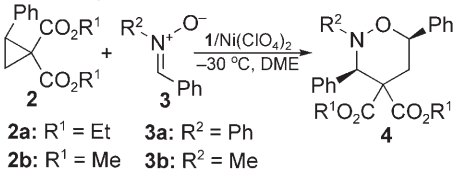
Table 1: Effect of the ligand on the cycloaddition.[a]

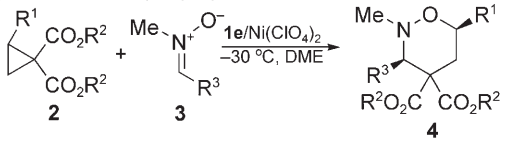


2a: R^1 = Et **3a**: R^2 = Ph
2b: R^1 = Me **3b**: R^2 = Me

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]



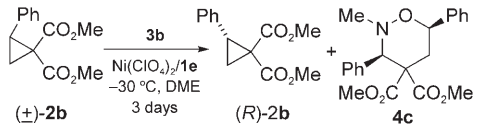
Entry	R^1	R^2	R^3	*t* [days]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	Me	Ph	3	82[e]	13:1	90
2[f]	Ph	Bn	Ph	4	62[e]	10:1	97
3	Ph	Et	Ph	4	88[e]	11:1	95
4	Ph	Et	4-BrC_6H_4	4	85[e]	12:1	97
5	Ph	Et	4-$MeO_2CC_6H_4$	4	97	11:1	97
6	Ph	Et	4-MeC_6H_4	4	80[e]	12:1	96
7	Ph	Et	4-$MeOC_6H_4$	4	92[e]	13:1	90
8	Ph	Et	2-furyl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

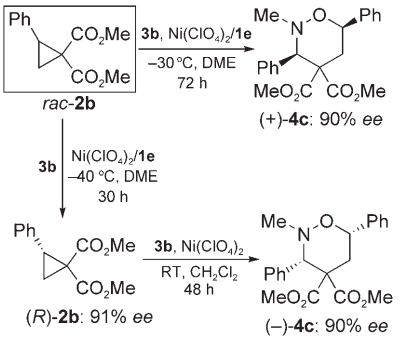
Scheme 2. Reaction of **3b** with excess cyclopropane **2b**.

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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