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Diastereo- and enantioselective [3 + 3] cycloaddition of spirocyclopropyl oxindoles using both aldonitrones and ketonitrones

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Optically active spirocyclic compounds play an important role in drug discovery, and new synthetic strategies for the efficient generation of spiro stereocenters are in much demand. Here we report a catalytic enantioselective cycloaddition using spirocyclic donor–acceptor cyclopropanes as a promising approach for the generation of spiro stereocenters. A diastereo- and enantioselective [3 + 3] cycloaddition of spirocyclopropyl oxindoles with both aldonitrones and ketonitrones is developed. The key to reaction development is the activation of spirocyclopropyl oxindoles by a suitable electron-withdrawing *N*-protecting group. This activation approach offers the promise of a general solution to enable spirocyclopropyl oxindoles as synthons for catalytic enantioselective synthesis of spirocyclic oxindoles featuring a C3 spiro stereocenter, a prominent structural motif in drugs and pharmaceutically active compounds. This protocol also constitutes the catalytic enantioselective reaction using unactivated achiral ketonitrones to construct tetrasubstituted carbon stereocenters.

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To enhance the reward in modern probe- and drug-discovery programs, there is a vast demand for synthetic libraries of optically active compounds recapitulating the structural features of privileged scaffolds that widely present in natural products, drugs, and pharmaceutically active compounds[1]. In this context, spirocyclic compounds have found ever-increasing utilization in drug discovery, because the conformational constraints imposed by a spiro-ring fusion often bring about improved biological activities of biomolecules[2, 3]. Therefore, efficient and enantioselective approaches capable of flexible construction of spiro stereocenters would facilitate the buildup of synthetic libraries of optically active spirocyclic compounds, which will help in the search for new lead candidates. However, the catalytic enantioselective synthesis of spirocyclic sterocenters is still a long-standing challenge in synthetic chemistry, especially when a spiro all-carbon quaternary stereocenter[4–6] is involved. Despite the invention of some elegant protocols[7], the exploitation of new synthetic routes for the catalytic enantioselective construction of spiro stereocenters is still highly desirable.

The catalytic enantioselective cycloaddition reactions of doubly activated donor–acceptor (D–A) cyclopropanes[8–13] with different dienes, 1,3-dipoles or dipolarphiles has been established as a powerful approach for the efficient and diverse synthesis of cyclic compounds[14–31]. However, the application of this strategy to construct spirocycles is largely undeveloped, because known successful protocols all rely on the use of 2-substituted cyclopropane-1,1-dicarboxylates and analogous cyclopropyl diketones (Fig. 1a)[14–31]. This is possibly because the geminal ester or ketone groups of such cyclopropanes can effectively stabilize the negative charge in the 1,3-zwitterionic intermediates and facilitate the formation of a well-organized catalyst–substrate complex via bidentate chelation, which is often important for enantiocontrol[20–23]. The use of spirocyclic D–A cyclopropanes for cycloaddition would open new avenues to construct chiral spirocyclic scaffolds (Fig. 1b); however, although an elegant chiral cyclopropane-based version had been reported[32], no successful catalytic enantioselective example is currently known[7–13].

For example, spirocyclopropyl oxindoles represent a class of easily available spirocylic D–A cyclopropanes, but the use of such monoactivated D–A cyclopropanes for enantioselective catalysis is largely unexplored[33]. This is surprising, because as early as in 1999, Carreira et al.[34–37] have successfully utilized unprotected or *N*-benzyl spirocyclopropyl oxindoles to build up the spiro[pyrrolidine-3,3′-oxindole] ring systems via MgI_2-catalyzed annulation with imines. Since the absolute configuration and the substituent of the C3 spiro stereocenters of spirocyclic oxindoles greatly influenced the biological activities[38, 39], it is of current interest to exploit new catalytic enantioselective methods for the synthesis of spirocyclic oxindoles that are prominent structural motifs in natural products and drugs[38–53]. While enantioselective cycloaddition using spirocyclopropyl oxindoles as D–A cyclopropanes constitutes a new entry for diverse synthesis of optically active spirocyclic oxindoles, it is difficult to make use of such monoactivated D–A cyclopropanes, for two reasons. First, with only one amide acceptor group, the activity of spirocyclopropyl oxindoles is not high. Second, a high level of transition state organization is difficult to realize simply by monodentate coordination of the amide group to a chiral Lewis acid. To tackle these two challenges, coupled with our interest in oxindole chemistry[54, 55], we consider activating spirocyclopropyl oxindoles, easily prepared from olefin cyclopropanation using diazooxindoles[55], by installing an electron-withdrawing *N*-protecting group. It may not only improve the stabilization of the negative charge developed at the C3 position of an oxindole via charge separation upon Lewis acid activation, but it may enable the binding of oxindole to chiral catalyst in a bidentate fashion, which is helpful for enantiocontrol. Herein, we demonstrate the power of this approach by a highly diastereo- and enantioselective [3 + 3] cycloaddition of spirocyclopropyl oxindoles and nitrones.

Results

Optimization of the reaction conditions. A variety of activated spirocyclopropyl oxindoles **1c–e** and **2a**, with different electron-withdrawing *N*-protecting groups, were readily prepared in one step from the corresponding unprotected precursor. With these spirocyclic D–A cyclopropanes at hand, we first evaluated their performance in the [3 + 3] cycloaddition reaction using nitrones, because the thus-obtained quaternary spirocyclic oxindoles,

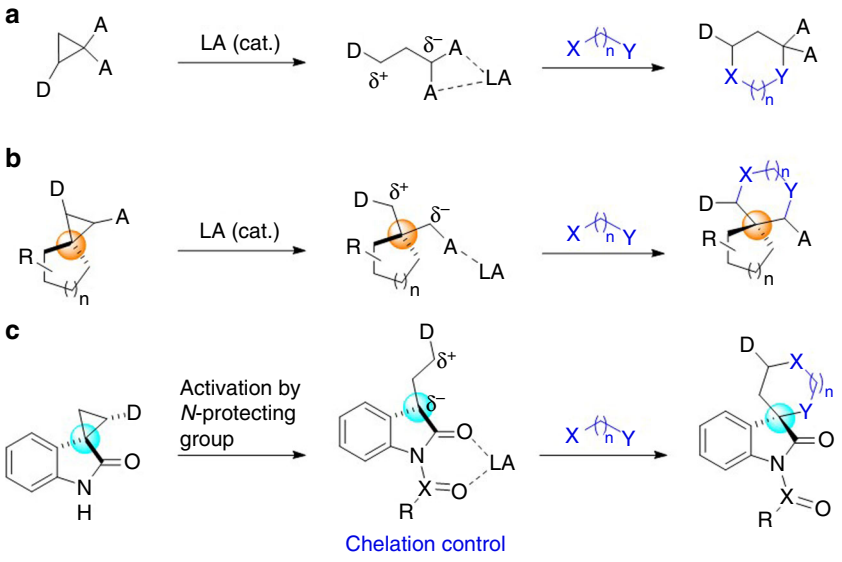
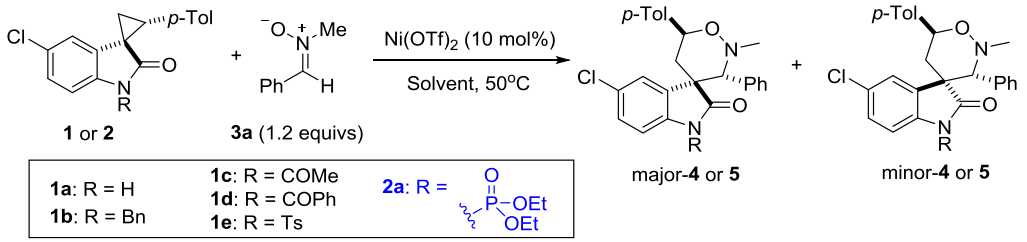


Fig. 1 Enantioselective cycloaddition reactions using D–A cyclopropanes. **a** Well-established cyclic compounds synthesis. **b** Undeveloped spiro stereocenter generation compounds synthesis. **c** Activation of spirocyclopropyl oxindoles for cycloaddition reactions. Donor (D): electron-releasing group; Acceptor (A): electron-withdrawing group (CO_2R or COR)

Table 1 Evaluation of *N*-withdrawing protection group[a]



Entry	1 or 2	Solvent	Adduct	Time (h)	dr[b]	Yield (%)[c]
1	**1a**	DCE	**4a**	48	—	30
2	**1b**	DCE	**4b**	48	—	Nr
3	**1c**	DCE	**4c**	64	5:1	82
4	**1d**	DCE	**4d**	13	6:1	95
5	**1e**	DCE	**4e**	48	11:1	96
6	**2a**	DCE	**5a**	6	>20:1	95
7[d]	**2a**	DCE	**5a**	12	>20:1	87
8[e]	**2a**	DCE	**5a**	3	>20:1	90
9[f]	**2a**	DCE	**5a**	6	>20:1	95(84)

[a]0.1 mmol scale in 1.0 ml of solvent
[b]Determined by ^{1}H NMR analysis
[c]NMR yield using mesitylene as the internal standard
[d]At 40 °C
[e]At 60 °C
[f]With 30 mg 3 Å MS as additive

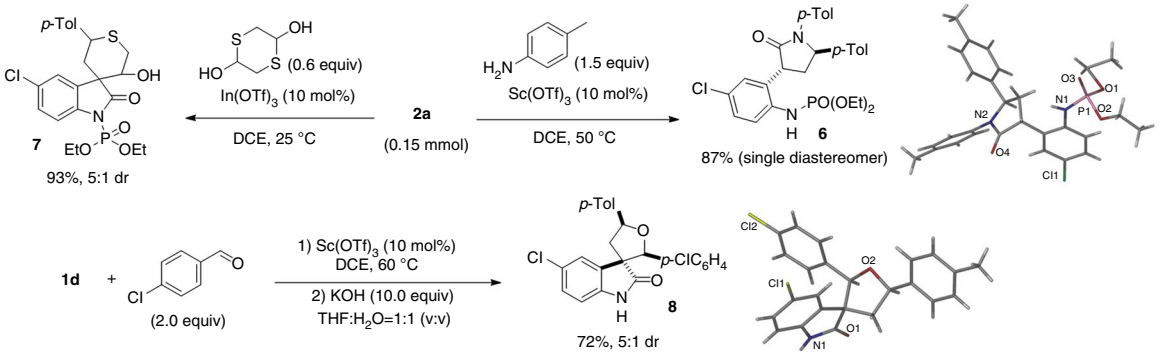
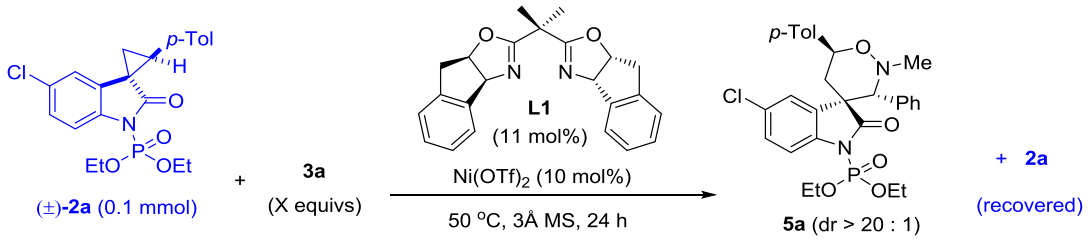


Fig. 2 Other typical reactions of the activated spirocyclopropyl oxindoles. Ring opening reaction of **2a** using *p*-toluidine. Cyclization reaction of **2a** with 1,4-dithiane-2,5-diol. Diploar cycloaddition of **1d** with 4-chlorobenzaldehyde, followed by deprotection using KOH. Isolated yield

merging the structural feature of tetrahydro-1,2-oxazine, are interesting targets for medicinal research. It is worth mentioning that since the pioneering work of Young and Kerr[56], the [3 + 3] cycloaddition reaction of D–A cyclopropanes and nitrones[56–60] has been established as an elegant approach to access tetrahydro-1,2-oxazines, which hold potential as therapeutic agents and as synthons[61–63]. Later, Sibi[18] and Tang[19] independently achieved highly enantioselective versions, which subsequently prompted further studies into catalytic asymmetric synthesis based on D–A cyclopropanes[8–31]. Nevertheless, the use of aliphatic nitrones or ketonitrones for such catalytic enantioselective cycloaddition reactions were undeveloped.

The *N*-protecting group of spirocyclopropyl oxindoles in deed plays an important role in securing high reactivity, as shown in Table 1. All reactions were catalyzed by 10 mol% $Ni(OTf)_2$, using 1,2-dichloroethane (DCE) as solvent at 50 °C. For the screening of Lewis acids, see Supplementary Table 1. Not unexpectedly, the reaction of unprotected oxindole **1a** with nitrone **3a** resulted in a mess, affording the desired adduct **4a** in ca. 30% NMR yield (entry 1, Table 1), and no reaction took place in the case of *N*-benzyl oxindole **1b** (entry 2, Table 1). In contrast, spirocyclopropyl oxindoles **1c** and **1d**, activated by a *N*-acetyl or benzoyl group, exhibited much higher reactivity, giving adducts **4c** and **4d** in high yields (entries 3–4, Table 1). With *N*-*p*-tolylsulfonyl group, oxindole **1e** also worked well with **3a** to give adduct **4e** in high yield and dr value (entry 5, Table 1). Interestingly, *N*-diethoxyphosphoryl oxindole **2a** showed high activity, and the corresponding reaction could complete within 6 h to give adduct **5a** in 95% yield and 20:1 dr (entry 6, Table 1). NMR analysis of these adducts **4** and **5** suggested that the *N*-protecting groups had little influence on the diastereoselectivity; X-ray analysis revealed that the major diastereomer of both *N*-diethoxyphosphoryl and *N*-Ts protected adducts have the same relative configuration. The relative configuration of the minor diastereomer of **4e** was also determined by X-ray analysis, which differed from the major diastereomer at the quaternary center of oxindole (see Supplementary Table 2). These results strongly support our working hypothesis, namely, that it is possible to activate spirocyclopropyl

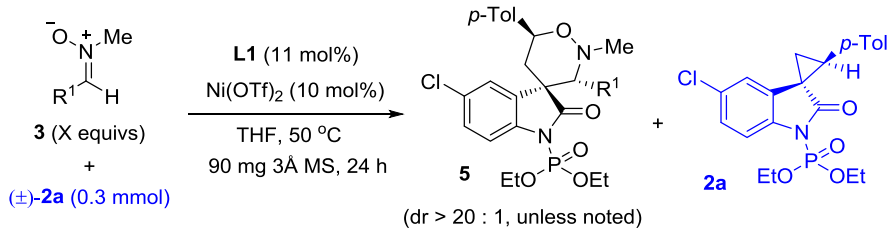
Table 2 Optimization for enantioselective synthesis



Entry	X	Solvent	5a Y/ee (%)[a, b]	2a R/ee (%)[b, c]	s[d] selectivity
1	0.50	DCE	41/92	40/78	7
2	0.50	Toluene	43/96	41/84	10
3	0.50	THF	44/96	48/90	33
4	0.55	THF	49/97	46/96	39

[a]Y/ee: isolated yield and ee value of 5a
[b]Ee value determined by chiral HPLC analysis
[c]R/ee: the recovery and ee value of 2a
[d]$s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$; C refers to the conversion of (±)−2a (1-(yield of recovered 2a))

Table 3 Scope of different nitrones



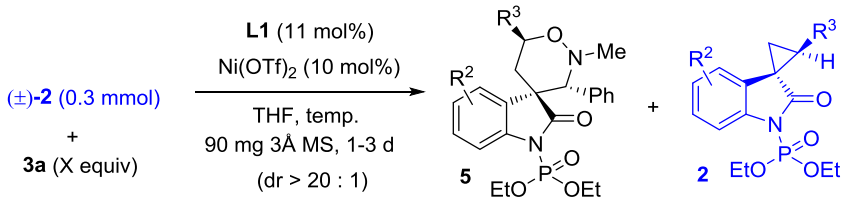
Entry	Nitrone 3	X	5: Y/ee(%)[a, b]	2a: R/ee(%)[b, c]	s[d] selectivity
1	**3a**: R1 = Ph	0.55	**5a**: 42/96	45/97	36
2	**3b**: R^1 = *p*-Tolyl	0.56	**5b**: 45/98	48/97	76
3	**3c**: $R^1 = p\text{-MeOC}_6H_4$	0.55	**5c**: 37/96	42/99	31
4	**3d**: $R^1 = p\text{-ClC}_6H_4$	0.55	**5d**: 41/97	41/97	21
5	**3e**: $R^1 = p\text{-BrC}_6H_4$	0.55	**5e**: 40/97	50/92	79
6	**3f**: $R^1 = p\text{-FC}_6H_4$	0.57	**5f**: 45/95	47/99	80
7	**3g**: $R^1 = m\text{-MeOC}_6H_4$	0.55	**5g**: 46/95	49/90	42
8	**3h**: R^1 = 2-naphthyl	0.56	**5h**: 42/97	48/98	91
9	**3i**: R^1 = 2-furyl	0.56	**5i**: 48/98	44/99	41
10	**3j**: R^1 = 2-thienyl	0.56	**5j**: 42/97	48/90	33
11	**3k**: R^1 = *i*-Pr	0.57	**5k**: 42/93	40/77	7
12[e]	**3l**: R^1 = Cy	0.56	**5l**: 36/90	45/79	11

[a]Y/ee: isolated yield and ee value of **5**
[b]Ee determined by chiral HPLC analysis
[c]R/ee: the recovery and ee value of **2a**
[d]$s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$; *C* refers to the conversion of (±)−**2a** (1-(yield of recovered **2a**))
[e]13:1 dr

oxindoles by installing electron-withdrawing *N*-protecting groups (Fig. 1c).

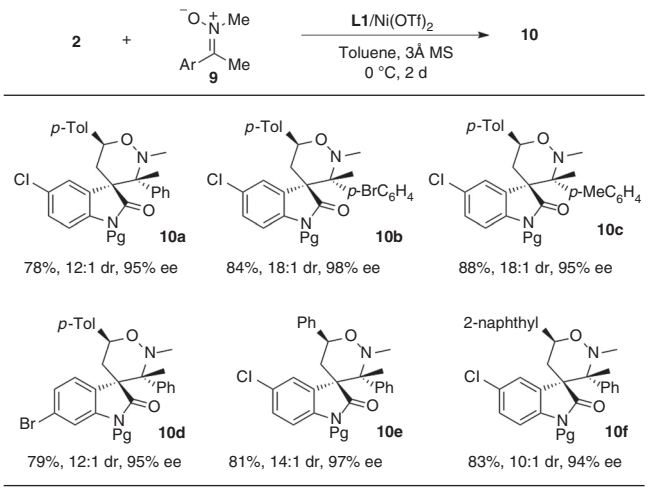
The elaboration of the activated spirocyclopropyl oxindoles. Notably, these activated spirocyclopropyl oxindoles could serve as viable synthons for other typical reactions of D–A cyclopropanes as well (Fig. 2). For example, *N*-diethoxyphosphoryl oxindole **2a** readily underwent ring-opening/cyclization reaction to give 3,5-disubstituted pyrrolidinone **6** in 87% yield, or reaction with 1,4-dithiane-2,5-diol to afford **7** in 93% yield and 5:1 dr. On the other hand, *N*-benzoyl oxindole **1d** was superior in the [3 + 2] cycloaddition with aldehyde. Because deprotection of the adduct occurred in the reaction course, KOH was added to facilitate the removal of protecting group after cycloaddition finished, furnishing unprotected spirocyclic oxindoles **8** in 72% yield with 5:1 dr. The relative configuration of product **6** and **8** was assigned by X-ray analysis. These results implied it possible to adjust *N*-electron-withdrawing group to develop new reactions. It should be noted that *N*-unprotected or *N*-benzyl analogs **1a** and **1b** all failed to participate in the three different kinds of reactions,

Table 4 Scope of spirocyclopropyl oxindoles



Entry	Cyclopropane 2 (R^2, R^3)	X	Temp. (°C)	5: Y/ee(%)[a, b]	2: R/ee(%)[b, c]	s[d] selectivity
1	**2b**: H, *p*-Tolyl	0.57	50	**5m**: 31/95	39/90	11
2	**2c**: 5-F, *p*-Tolyl	0.56	50	**5n**: 40/98	50/92	79
3	**2d**: 5-Br, *p*-Tolyl	0.56	50	**5o**: 44/96	49/99	211
4	**2e**: 6-Br, *p*-Tolyl	0.56	50	**5p**: 38/95	34/99	15
5	**2f**: 5-Me, *p*-Tolyl	0.57	90	**5q**: 34/92	47/70	9
6	**2g**: 5-OMe, *p*-Tolyl	0.57	90	**5r**: 35/90	52/70	15
7	**2h**: 5-Cl, Ph	0.57	60	**5s**: 48/95	48/99	116
8	**2i**: 5-Cl, 4-ClC_6H_4	0.57	70	**5t**: 46/97	48/94	50
9	**2j**: 5-Cl, 2-naphthyl	0.57	60	**5u**: 47/93	44/99	41
10	**2k**: 5-Cl, (*E*)-PhCH=CH	0.54	40	**5v**: 48/90	40/98	21

[a]Y/Ee: isolated yield and ee value of **5**
[b]Determined by HPLC analysis
[c]R/ee: the recovery and ee value of **2**
[d]$s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$; *C* refers to the conversion of (±)-**2** (1-(yield of recovered **2**))



[a] Reaction conditions: $Ni(OTf)_2$ (0.04 mmol), **L1** (0.044 mmol), **2** (0.44 mmol, Pg = $PO(OEt)_2$), and **6** (0.20 mmol) in 2.0 mL of toluene at 0 °C with 3Å MS, under an atmosphere of N_2. [b] Isolated yield based on **9**. [c] For details, see SI.

Fig. 3 Cycloaddition of spirocyclopropyl oxindoles using ketonitrones. Construction of adjacent quaternary and tetrasubstituted carbon stereocenters

confirming the importance of the activation effect of electron-withdrawing *N*-protecting group.

Substrate scope of the reaction. The potential of these activated spirocyclopropyl oxindoles in enantioselective catalysis was further demonstrated by a highly enantioselective [3 + 3] cycloaddition using nitrones. The screening of chiral ligands (see Supplementary Table 3) revealed that bisoxazoline $\mathbf{L_1}$[64]/$Ni(OTf)_2$ complex allowed the synthesis of **5a** in 41% yield and 92% ee (entry 1, Table 2). Gratifyingly, when the reaction solvent was changed from DCE to THF, both adduct **5a** and cyclopropane **2a** were obtained with excellent ee values (entries 1–3, Table 2). By adjusting the amount of nitrone **3a** to 0.55 equiv, adduct **5a** was obtained in 49% yield and 97% ee, with **2a** recovered in 46% yield and 96% ee (entry 4, Table 2). Therefore, the substrate scope was examined using THF as the solvent, in the presence of 10 mol% catalyst $\mathbf{L_1}/Ni(OTf)_2$.

It emerged that both aromatic and aliphatic substituted nitrones were viable substrates for this kinetic resolution, with >20:1 dr values achieved in most cases (Table 3). Both electron-deficient and electron-rich α-aryl nitrones **3a**–**g** worked well to afford the desired adducts **5a**–**g** with excellent ee values (entries 1–7, Table 3). Nitrones **3h**–**j** with a 2-naphthyl, furyl, or 2-thienyl group all afforded the corresponding adducts **5h**–**j** in excellent yields and ee values (entries 8–10, Table 3). In these cases, spirocyclopropyl oxindole **2a** was recovered with an excellent ee value and good yield. Interestingly, aliphatic nitrones **3k**, **l** also gave the desired 1,2-oxazine adducts **5k**, **l** in good yields and with >90% ee; cyclopropane **2a**, however, was recovered with lower ee values (entries 11–12, Table 3). To our knowledge, aliphatic nitrones have not been used for such catalytic enantioselective cycloaddition previously[18, 19, 56–60].

On the other hand, the substituents on oxindole framework of cyclopropane **2** were found to have an influence on the reaction outcome (Table 4). With electron-withdrawing groups on the C5 or C6 positions, oxindoles **2c**–**e** gave the desired adducts **5n**–**p** in 38–44% yield and 95–98% ee, together with the recovery of cyclopropanes **2c**–**e** in good yields and with >90% ee (entries 2–4, Table 4). In contrast, electron-donating groups retarded the reaction. The reactions of **2f**, **g** were run at 90 °C and gave adducts **5q**, **r** with excellent ee values and obviously in lower yields. Cyclopropanes **2f**, **g** were recovered with lower ee values (entries 5 and 6, Table 4). Oxindoles **2h**–**k** with different donor groups (R^3) of the cyclopropane were also tried. As expected, with the R^3 group varying from the *p*-tolyl to phenyl and *p*-chlorophenyl groups, the reaction temperature increased from 50 to 60 and 70 °C (entry 1, Table 3 vs. entries 7–8, Table 4). The adducts **5s**–**v** were all prepared satisfactorily. Cyclopropanes **2h**–**k** were recovered in high yields and excellent ee values (entries 7–10, Table 4).

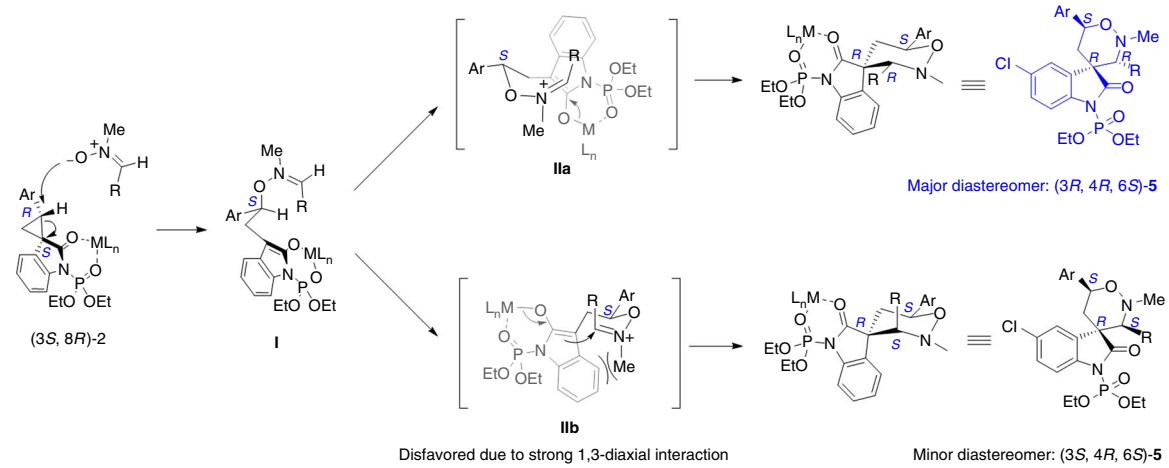


Fig. 4 Working model for the observed 3,6-trans selectivity of adducts **5**. A stepwise annulation mechanism. The favored boat-like transition state **IIa** is possibly stabilized by the cation–π interaction. The chiral-like transition state **IIb** is presumably destabilized by the strong 1,3-diaxial repulsion

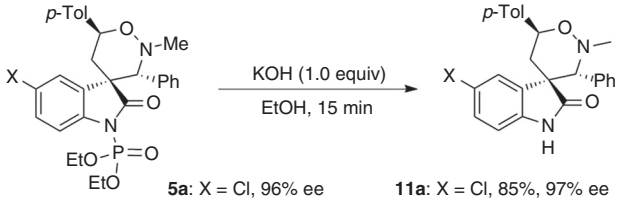


Fig. 5 Deprotection of product **5a** and **5o**. Reaction conditions: **5** (0.1 mmol), KOH (1.0 mmol) in 2.0 mL of EtOH at room temperature. Isolated yield

Notably, acetophenone-derived ketonitrones **9** are also viable substrates, enabling highly stereoselective synthesis of spirocylic oxindoles **10a–f** with adjacent quaternary and tetrasubstituted carbon stereocenters (Fig. 3). It is worth mentioning that enantioselective catalytic reactions based on such unactivated achiral ketonitrones to create tetrasubstituted carbon stereocenters is unprecedented[65], although two protocols using activated ketonitrones have been reported[66, 67].

Proposed working model. The relative configuration of racemic compound **4e** and **5o** was assigned by X-ray analysis. By converting to the corresponding *N*-*p*-tolylsulfonyl analogs, the relative and absolute configuration of compound **5a** and **10a** were also determined by X-ray analysis, as shown in Table 3 and Fig. 3 (for details, see Supplementary Figs. 1 and 2). Those of others were tentatively assigned by NMR analysis. Interestingly, no matter using *N*-*p*-tolylsulfonyl or *N*-diethoxyphosphoryl spirocyclic oxindoles, the cycloaddition reaction with nitrones afforded the major diastereomers of corresponding adducts in which the substituents at C3 and C6 of the tetrahydro-1,2-oxazine bore a *trans* relationship, different from the 3,6-*cis* selectivity of the known [3 + 3] cycloaddition of 2-substituted cyclopropane-1,1-dicarboxylates and nitrones[19, 56]. The observed diastereoselectivity could be rationalized by the following working model involving a stepwise annulation mechanism (Fig. 4). According to previous studies in the Lewis acid catalyzed [3 + n] annulations of D–A cyclopropanes[21, 58], we proposed that the binding of the *N*-diethoxyphosphoryl oxindole **2** to the Lewis acid facilitated the *O*-attack of nitrones at the donor-substituted site of cyclopropane, leading to the reversion at that position, which was consistent with our experiments that under the catalysis of 10 mol% Ni $(OTf)_2$, chiral cyclopropane (3*S*, 8*R*)-**2b** with 90% ee afforded tetrahydro-1,2-oxazine (3*R*, 4*R*, 6*S*)-**5m** as the major product with 90% ee. The stepwise mechanism was also supported by the fact that the ^{1}H NMR analysis of the reaction mixture of nitrone **3a** with *N*-*p*-tolylsulfonyl oxindole **1e** could obviously detect the presence and the gradual disappearance of the intermediate correlating to the nucleophilic *O*-attack of nitrones to the donor-substituted site of cyclopropane (for details, see Supplementary Figs. 15 and 16). The resulting intermediate **I** further underwent an intramolecular Mannich cyclization to afford the desired product with 3,6-*trans* tetrahydro-1,2-oxazine, via a favored boat-like transition state **IIa**, which is possibly stabilized by the cation–π interaction between the iminium species and enolate[68]. The chiral-like transition state **IIb**, leading to the formation of 3,6-*cis* tetrahydro-1,2-oxazine, is presumably destabilized by the strong 1,3-diaxial repulsion between the *N*-methyl group of nitrone and the aromatic framework of oxindole.

Synthetic application. Impressively, our protocol provides a facile access to optically active oxindole-based spirocyclic tetrahydro-1,2-oxazines, and spirocyclopropyl oxindoles as well. It is noteworthy that optically active spirocyclopropyl oxindoles have wide application[33]. On the other hand, the *N*-diphenoxyphosphoryl group of adducts **5** could be readily removed, as evidenced by the conversion of **5a** and **5o** to the corresponding spirocyclic 1,2-oxazine **11a** and **11b** (Fig. 5).

Discussion

In summary, we have demonstrated that spirocyclic oxindoles could be effectively activated by electron-withdrawing *N*-protecting group to serve as D–A cyclopropanes for complexity-generating synthesis. A highly enantioselective [3 + 3] cycloaddition and kinetic resolution of *N*-diethoxyphosphoryl spirocyclopropyl oxindoles is developed, providing a facile access to optically active oxindole-based spirocyclic tetrahydro-1,2-oxazines and spirocyclopropyl oxindoles of wide application[33]. This work also implies that catalytic enantioselective cycloaddition using spirocyclic D–A cyclopropanes is a promising approach for the flexible synthesis of chiral spirocyclic scaffolds. In addition, our work also suggests new synthetic opportunities of ketonitrones in creating tetrasubstituted carbon stereocenters. The evaluation of the biological activities of these spirocyclopropyl oxindoles is now in progress in our laboratories. The application of this strategy to explore other enantioselective cycloaddition additions is now under way in our laboratory.

Methods

General methods. See Supplementary Methods for further details.

General procedure for catalytic enantioselective [3 + 3] cycloaddition of 2 and aldonitrone 3. To a Schlenk tube was sequentially added $Ni(OTf)_2$ (10.7 mg, 0.030 mmol, 10 mol%) and $\mathbf{L_1}$ (11.8 mg, 0.033 mmol, 11 mol%), followed by the addition of anhydrous THF (3.0 ml). After the resulting solution was stirred at 50 °C for 2 h, oxindole **2** (0.30 mmol), nitrone **3**, and MS 3 Å (90 mg) were added successively. The reaction was kept stirring at the temperature indicated in Tables 3 and 4 till the full consumption of **3** by TLC analysis. Then THF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, rapidly passed through a glass funnel with a thin layer (5 mm) of silica gel (100 mesh), washed with CH_2Cl_2, and concentrated under reduced pressure. To determine the dr value of product, the residue was first dissolved in $CDCl_3$, and took some samples to determine diastereoselectivity by ^{1}H NMR analysis. Then the sample for analysis and rest crude product were recombined for column chromatography purification to afford product **5** and recovered spirocyclopropyl oxindole **2**, using DCM/EtOAc (40/1, v/v) as the eluent.

General procedure for catalytic enantioselective [3 + 3] cycloaddition of 2 and ketonitrone 9. To a Schlenk tube was sequentially added $Ni(OTf)_2$ (14.3 mg, 0.040 mmol) and $\mathbf{L_1}$ (15.8 mg, 0.044 mmol), followed by the addition of anhydrous toluene (2.0 ml). After the resulting solution was stirred at room temperature for 2 h and cooled to 0 °C, nitrone **9** (0.2 mmol), oxindole **2** (0.44 mmol), and MS 3 Å (60 mg) were added successively. The reaction was kept stirring at 0 °C for 2 days. Then toluene was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, rapidly passed through a glass funnel with a thin layer (5 mm) of silica gel (100 mesh), washed with CH_2Cl_2, and concentrated under reduced pressure. To determine the dr value of product, the residue was first dissolved in $CDCl_3$, and took some samples to determine diastereoselectivity by ^{1}H NMR analysis. Then the sample for analysis and rest crude product were recombined for column chromatography purification to afford product **10**, using DCM/EtOAc (30/1, v/v) as the eluent.

Data availability. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC-1502102 (racemic major-**4e**), CCDC-1551103 (minor-**4e**), CCDC-1502103 (major-**5o**) CCDC-1502104 (**4e**), CCDC-1502105 (**12a**), CCDC-1523864 (**6**), and CCDC-1523855 (**8**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author on reasonable request.

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Author contributions

J.Z. conceived the idea and supervised the whole project. J.Y. provided fruitful discussion and co-supervised the project. P.-W.X. designed and carried out the experiments. J.-K.L. and L.S. contributed to part experiments. X.-L.Z. performed the X-ray crystal structure assignation. J.Z., P.-W.X. and Z.-Y.C. discussed the results, contributed to writing the manuscript, and commented on the manuscript. All authors approved the final version of the manuscript for submission.

Additional information

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