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Organocatalytic Synthesis of Spiro[pyrrolidin-3,3′-oxindoles] with High Enantiopurity and Structural Diversity

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Abstract: The privileged spiro[pyrrolidin-3,3′-oxindole] derivatives exhibit important biological activities. An enantioselective organocatalytic approach to the rapid synthesis of spiro[pyrrolidin-3,3′-oxindole] derivatives with high enantiopurity and structural diversity is described. The asymmetric catalytic three-component 1,3-dipolar cycloaddition of a broad range of methyleneindolinones with aldehydes and amino esters in the presence of chiral phosphoric acid provides spirooxindole derivatives in high yield with unusual regiochemistry and excellent stereoselectivities (up to 98% ee) under mild conditions. The straightforward construction of spirooxindole skeletons with high stereo- and regioselectivity suggests a new avenue to medicinal chemistry and diversity-oriented synthesis. Theoretical calculations disclosed that both the azomethine ylide and the methyleneindolinone are hydrogen-bonded with the phosphoric acid, which accounted for the high enantio- and regioselectivity and indicated that the unusual regioselectivity results from the stabilization stemming from the favorable $\pi-\pi$ stacking interaction between the oxo-indole ring and the conjugated esters.

Introduction

The spiro[pyrrolidin-3,3′-oxindole] ring system constitutes the core structural element found in a large family of natural alkaloids and unnatural compounds exhibiting important biological activities as exemplified by those shown in Figure 1.[1,2] For example, the spirotryprostatins A and B were isolated from the fermentation broth of *Aspergillus fumigatus* and have been shown to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells.[3] The significant biological activity and recent synthetic advances of these natural products have encouraged the development of biologically promising analogues that are often more efficacious and selective than the original natural products,[4−6] as exemplified by MI-219,[4] a potent, highly selective, and orally active inhibitor of the interaction between the tumor suppressor p53 and the E3 ubiquitin ligase MDM2. The privileged spirooxindole skeletons have high potential as core elements for the development of related compounds leading to medicinal agents.[2a]

The significance of these heterocyclic motifs has led to a demand for efficient synthetic methods, particularly those producing enantiomerically pure spiro[pyrrolidin-3,3′-oxindoles]. Numerous elegant transformations have been developed for the construction of these structural skeletons,[2] which usually employ either enantiopure starting materials or multistep reactions to construct the optically active spirooxindole skeletons. Williams reported another approach to access the optically pure spiro[pyrrolidin-3,3′-oxindoles] in the synthesis of spirotryprostatin B.[7] This chiral auxiliary-induced three-component 1,3-dipolar cycloaddition reaction of methyleneindolinones **1** with azomethine ylides proved to be an attractive synthetic method, regiospecifically providing spiro[pyrrolidin-3,3′-oxindole] derivatives of type **4** (Scheme 1).[4,6,7] Although these were elegant and creative strategies toward the construction of spirooxindole architecture, the directly catalytic asymmetric approach to access optically pure spiro[pyrrolidin-3,3′-oxindoles] has met with little success.[8] Consequently, an enantioselective catalytic method for the direct construction of spirooxindole skeletons

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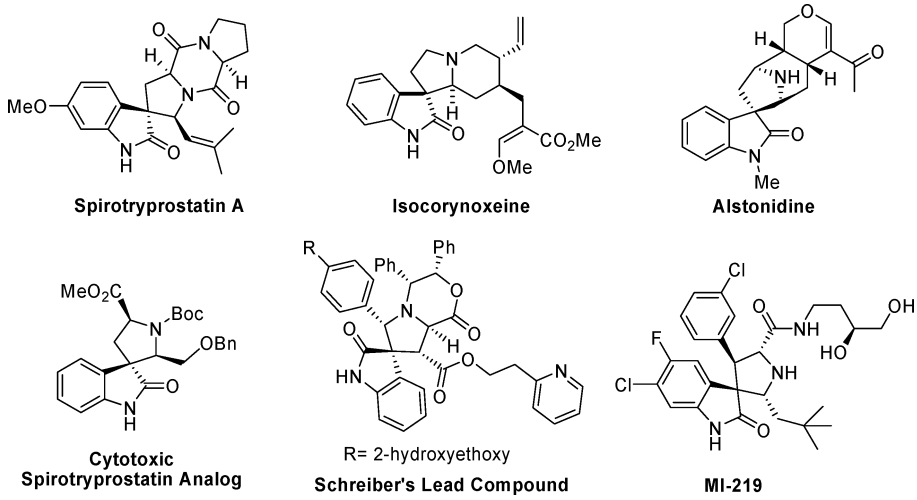
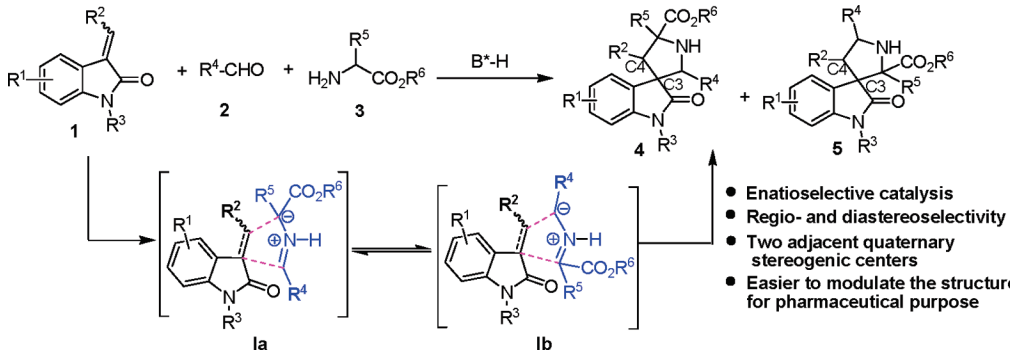


Figure 1. Biologically important molecules containing spiro[pyrrolidin-3,3′-oxindole].

Scheme 1. 1,3-Dipolar Cycloaddition Reactions for Synthesis of Spiro[pyrrolidin-3,3′-oxindole] Derivatives



in one pot is highly desirable with respect to synthetic efficiency and atom economy.

Recently, chiral phosphoric acids have been widely used as organocatalysts in the activation of imines[9,10] and carbonyl compounds[11] for stereoselective transformations. We have recently reported the chiral phosphoric acid catalyzed 1,3-dipolar addition reactions providing five-membered heterocycles.[12] Encouraged by these achievements, we proposed 1,3-dipolar cycloaddition reactions between azomethine ylides and methyleneindolinones catalyzed by chiral phosphoric acid to construct the spirooxindole skeleton with concomitant generation of stereogenic centers in high levels of stereoselectivity (Scheme 1). However, several challenges are associated with the directly catalytic asymmetric construction of the spirooxindole structure *in one cycloaddition step*. First, it was more difficult to control the regioselectivity at the C3 and C4, as two sites of regiochemistry may result from this type of cycloaddition according to previous reports.[13] Moreover, a unique spiro quaternary stereogenic center at C3 site is created, which, in having six substituents on the pyrrolidine ring, is more sterically congested

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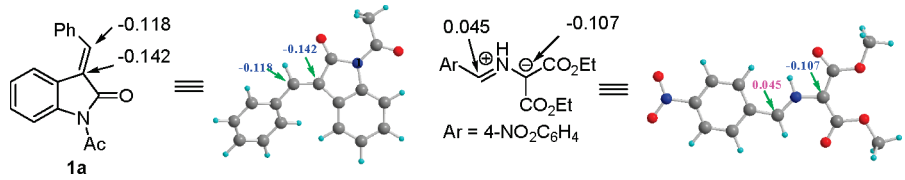
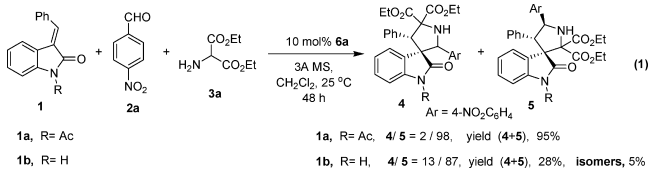


Figure 2. Computed natural bond orbital (NBO) charges of **1a** and a dipole by B3LYP/6-31G* method.

as compared to chiral auxiliary-induced dipolar addition reactions.[4,7] Nonetheless, it is a greater challenge to control the high diastereoselectivity, in consideration of the simultaneous creation of two quaternary centers at the pyrrolidine ring.[14] In addition, it has been unclear whether the chiral Brønsted acid activated the azomethine ylide alone to control the stereochemistry or whether both substrates were required to achieve high asymmetric induction.[10,11] Herein, we report the first asymmetric catalytic 1,3-dipolar cycloaddition between an azomethine ylide and methyleneindolinones with concomitant creation of two adjacent quaternary stereogenic centers[14] for the rapid synthesis of spiro[pyrrolidin-3,3′-oxindole] derivatives with high enantiopurity and structural diversity. The highly stereoselective construction of spirooxindole skeletons with unusual regioselectivity suggests a new avenue of great importance to medicinal chemistry and diversity-oriented synthesis.[6,15] In addition, theoretical calculations on the transition states have been carried out to explain the unusual regioselectivity and high enantioselectivity.

Results and Discussion

1,3-Dipolar Cycloaddition Reaction To Construct Spirooxindole Skeletons. We initially believed that the asymmetric catalytic 1,3-dipolar cycloaddition reaction of methyleneindolinones **1** with azomethine ylides would be an elusive objective because no catalysts have been reported to effect this reaction although numerous asymmetric catalytic procedures for 1,3-dipolar cycloaddition reaction have been described.[16,17] In consideration of the above-mentioned challenges, we selected (*E*)-1-acetyl-3-benzylideneindolinone (**1a**) as a dipolarophile on the supposition that the acetyl group on the nitrogen atom would enhance the polarizability of the dipolarophile and contribute to the high regioselectivity. Moreover, the acetyl group on the nitrogen atom served to reduce the energy of the lowest unoccupied molecular orbital (LUMO) of the dipolarophiles and consequently increased the reactivity of the methyleneindolinone.



Indeed, (*E*)-3-benzylideneindolinone (**1b**), usually used as a dipolarophile in chiral auxiliary-induced dipolar addition reactions,[4,6] showed low reactivity, providing moderate regioselectivity and accompanying other isomers, while (*E*)-1-acetyl-3-benzylideneindolinone (**1a**) reacted with 4-nitrobenzaldehyde and diethyl aminomalonate (**3a**) under the catalysis of phosphoric acid **6a** in dichloromethane at 25 °C smoothly and produced the desired compounds in a high yield (eq 1). Interestingly, the regiochemistry is independent of the electron distribution over two carbon atoms of the C−C double bond of (*E*)-3-benzylideneindolinone. The calculations show that in the (*E*)-3-benzylideneindolinone **1a** the carbon bonded to phenyl is more electronically poor than the other one and in azomethine ylide, formed from 4-nitrobenzaldehyde and diethyl aminomalonate, the carbon next to the two esters is negatively charged (Figure 2); therefore **4a** should be dominantly formed according to the regulations obtained from previous reports on the 1,3-dipolar addition of azomethine ylides to unsymmetrical electronically poor olefins.[16,18] However, we observed a major product **5a**, implying that the regiochemistry is not directed by the electronic effect but by some other factors. Notably, this finding is quite unusual because a very limited number of intermolecular 1,3-dipolar addition reactions have been reported with the regioselectivity opposite to that directed by the electronic effect.[19] Moreover, the chemistry represents thus far the sole enantioselective catalytic cycloaddition involving methyleneindolinone dipolarophiles to straightforwardly access the optically active spiro[pyrrolidin-3,3′-oxindole] derivatives.

Screening of the BINOL-derived phosphoric acids **6** revealed that the presence of either highly sterically congested or less bulky substituents on the catalysts were deleterious to the enantioselectivity (Table 1, entries 1−5). 3,3′-*β*-Naphthyl phosphoric acid **6f** was found to effect the most enantioselective cycloaddition (entry 6, >93/7 rr, 93% *ee*). However, in our earlier studies, the bis-phosphoric acid, which delivered a high *ee* in the 1,3-dipolar cycloaddition of azomethine ylides to maleates,[12a] exhibited poor stereoselectivity (93% yield, 2% ee). A survey of solvents revealed that dichloromethane was most suitable for the reaction. Lowering the reaction temperature did not enhance the enantioselectivity (entry 12), while conducting the reaction at room temperature provided the best results (entry 13).

With the optimal conditions in hand, we investigated the generality for the scope of aldehydes (Table 2). In the asymmetric catalytic 1,3-dipolar addition, a wide range of aromatic and aliphatic aldehydes were tolerated and provided high yields

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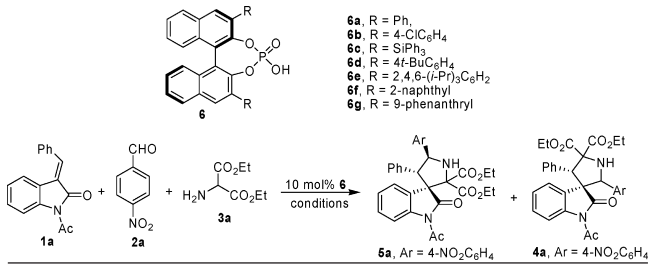
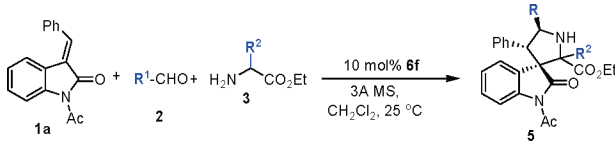
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (**6**)	solvent	temp (°C)	yield (%)[b]	*rr*[c]	*ee* (%)[d]
1	**6a**	CH_2Cl_2	0	89	95/5	22
2	**6b**	CH_2Cl_2	0	85	95/5	40
3	**6c**	CH_2Cl_2	0	90	99/1	5
4	**6d**	CH_2Cl_2	0	95	95/5	2
5	**6e**	CH_2Cl_2	0	89	99/1	0
6	**6f**	CH_2Cl_2	0	91	97/3	93
7	**6g**	CH_2Cl_2	0	79	99/1	83
8	**6f**	$CHCl_3$	0	73	97/3	78
9	**6f**	$(CH_2Cl)_2$	0	40	99/1	83
10	**6f**	$PhCH_3$	0	83	99/1	84
11	**6f**	THF	0	77	99/1	−4
12	**6f**	CH_2Cl_2	−10	94	95/5	90
13	**6f**	CH_2Cl_2	25	94	>99/1	93[e]

[a] The reaction was carried out on a 0.2 mmol scale with 3 Å MS (300 mg) at 0 °C for 72 h, and the ratio of **1a/2a/3a** was 2.0/1.2/1.0. [b] Isolated yield. [c] The *rr* refers to the regiomeric ratio of **5a/4a** and was determined by ^{1}H NMR. [d] The *ee* was determined by HPLC. [e] The ratio of **1a/2a/3a** was 1.2/1.2/1.0, and the reaction time was 24 h. [f] Benzaldehyde was used as a reaction component.

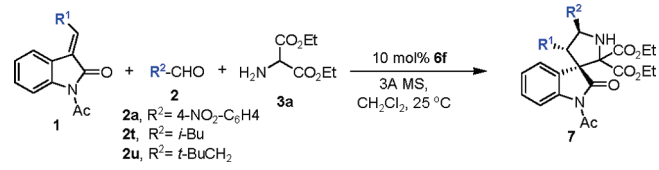
Table 2. Scope of Aldehydes and Amino Esters[a]



entry	R (**2**)	R^2 (**3**)	**5**	yield (%)[b]	*rr*[c]	*ee* (%)[d]
1	3-$NO_2C_6H_4$ (**2b**)	CO_2Et (**3a**)	**5b**	96	>99/1	93
2	2-$NO_2C_6H_4$ (**2c**)	CO_2Et (**3a**)	**5c**	91	>99/1	92
3	4-CNC_6H_4 (**2d**)	CO_2Et (**3a**)	**5d**	93	>99/1	91
4	3-CNC_6H_4 (**2e**)	CO_2Et (**3a**)	**5e**	91	>99/1	91
5	4-BrC_6H_4 (**2f**)	CO_2Et (**3a**)	**5f**	96	>99/1	87
6	2-BrC_6H_4 (**2g**)	CO_2Et (**3a**)	**5g**	89	>99/1	90
7	4-ClC_6H_4 (**2h**)	CO_2Et (**3a**)	**5h**	97	>99/1	88
8	2,4-$(NO_2)_2C_6H_3$ (**2i**)	CO_2Et (**3a**)	**5i**	97	>99/1	98
9	2,3-$Cl_2C_6H_3$ (**2j**)	CO_2Et (**3a**)	**5j**	94	>99/1	94
10	3,4-$Cl_2C_6H_3$ (**2k**)	CO_2Et (**3a**)	**5k**	93	>99/1	90
11	2-Cl-4-FC_6H_3 (**2l**)	CO_2Et (**3a**)	**5 L**	96	>99/1	90
12	3-F-4ClC_6H_3 (**2m**)	CO_2Et (**3a**)	**5m**	97	98/2	89
13	2-F-3-ClC_6H_3 (**2n**)	CO_2Et (**3a**)	**5n**	93	>99/1	89
14	Ph (**2o**)	CO_2Et (**3a**)	**5o**	87	>99/1	85
15	4-MeC_6H_4 (**2p**)	CO_2Et (**3a**)	**5p**	95	95/5	82
16	4-$MeOC_6H_4$ (**2q**)	CO_2Et (**3a**)	**5q**	86	87/13	81
17	*n*-Pr (**2r**)	CO_2Et (**3a**)	**5r**	71	>99/1	91
18	*n*-Bu (**2s**)	CO_2Et (**3a**)	**5s**	59	>99/1	86
19	*i*-Bu (**2t**)	CO_2Et (**3a**)	**5t**	89	>99/1	93
20	*t*-$BuCH_2$ (**2u**)	CO_2Et (**3a**)	**5u**	90	>99/1	92
21	4-$NO_2C_6H_4$ (**2a**)	Ph (**3b**)	**5v**	85	>99/1	82[e]
22	4-$NO_2C_6H_4$ (**2a**)	4-ClC_6H_4 (**3c**)	**5w**	80	>99/1	85[e]
23	4-$NO_2C_6H_4$ (**2a**)	4-FC_6H_4 (**3d**)	**5x**	90	>99/1	84[e]

[a] The reaction was carried out on a 0.2 mmol scale with 3 Å MS (300 mg) for 24−96 h, the ratio of **1a/2/3a** was 1.2/1.2/1. [b] Isolated yields. [c] The *rr* refers to the regiomeric ratio of **5/4** and was determined by ^{1}H NMR. [d] The *ee* was determined by HPLC. [e] The reaction with **3** (Arylglycine methyl ester) in the presence of 20 mol % **6f** at 35 °C, giving >95/5 exo/endo, with a ratio of **1a/2a/3** of 2/1.2/1.

Table 3. Asymmetric Cycloaddition Reactions of Substituted Methyleneindolinones Catalyzed by **6f**[a]



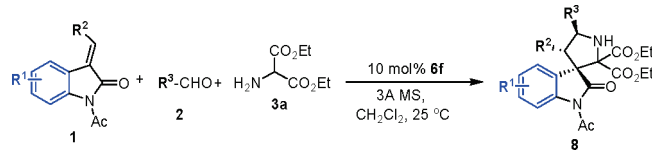
entry	**7**	**2**	R^1	*rr*[c]	yield (%)[b]	ee (%)[d]
1	**7a**	**2a**	4-CNC_6H_4	>99/1	95	91
2	**7b**	**2a**	4-$MeO_2CC_6H_4$	>99/1	93	92
3	**7c**	**2a**	4-BrC_6H_4	>99/1	97	91
4	**7d**	**2a**	4-FC_6H_4	>99/1	91	93
5	**7e**	**2a**	4-ClC_6H_4	>99/1	94	92
6	**7f**	**2a**	4-$MeOC_6H_4$	>99/1	96	92
7	**7g**	**2a**	4-MeC_6H_4	>99/1	92	90
8	**7h**	**2a**	2-FC_6H_4	>99/1	97	81
9	**7i**	**2a**	2-ClC_6H_4	>99/1	95	86
10	**7j**	**2a**	3-ClC_6H_4	>99/1	93	90
11	**7k**	**2a**	3,4-$Cl_2C_6H_4$	>99/1	91	90
12	**7l**	**2a**	2-naphthyl	>99/1	90	92
13	**7m**	**7a**	1-naphthyl	>99/1	92	98
14	**7n**	**2a**	2-furanyl	95/5	74	93
15	**7o**	**2a**	(*E*)-PhCH═CH	83/17	82	90
16	**7p**	**2a**	*i*-Bu	89/11	94	89
17	**7q**	**2a**	*n*-Pr	80/20	94	83
18	**7r**	**2t**	4-MeC_6H_4	>99/1	88	82
19	**7s**	**2t**	4-ClC_6H_4	>99/1	94	92
20	**7t**	**2t**	4-FC_6H_4	>99/1	89	93
21	**7u**	**2u**	3-ClC_6H_4	>99/1	94	88

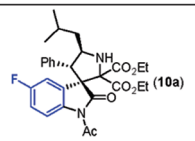
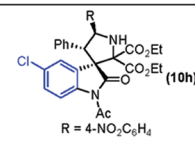
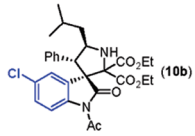
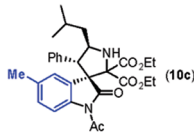
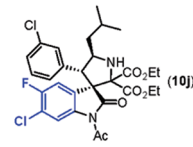
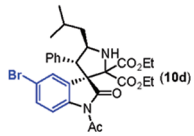
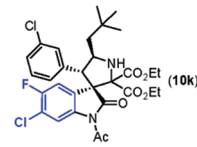
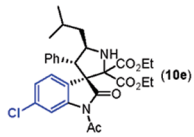
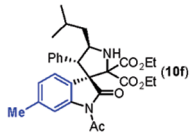
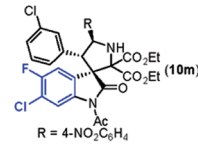
[a] The reaction was carried out on a 0.2 mmol scale with 3 Å MS (300 mg) for 24−96 h, the ratio of **1/2/3a** was 1.2/1.2/1. [b] Isolated yields. [c] The *rr* refers to the regiomeric ratio and was determined by ^{1}H NMR. [d] The *ee* was determined by HPLC.

and regioselectivities. The electronically deficient benzaldehydes afforded higher stereoselectivity than the electronically rich and neutral derivatives (entries 1−13 vs 14−16), but the electronically rich benzaldehydes gave lower regioselectivity (entries 15 and 16). Significantly, aliphatic aldehydes, including linear enolizable variants such as *n*-butyraldehyde and *n*-pentanal, were good reaction partners to give the desired products in good to high yields and with excellent regio- and enantioselectivity (>99/1 rr, 86−93% *ee*, entries 17−20). α-Arylglycine methyl esters could also undergo the cycloaddition with 4-nitrobenzaldehyde and (*E*)-1-acetyl-3-benzylideneindolinone (**1a**) to regiospecifically give rise to spiro[pyrrolidin-3,3′-oxindoles] **5v−x** bearing two adjacent quaternary stereogenic centers (entries 21−23). These outcomes are particularly significant in view of the challenges in the construction of quaternary stereogenic centers.[14]

Further exploration of the substrate scope was focused on methyleneindolinone derivatives bearing various substituents at the carbon−carbon double bond (Table 3). The protocol was applicable to either aromatic, aliphatic, or vinyl substituted eneindolinones. For benzylideneindolinone derivatives, variation at the *para*-substituent of the benzylidene moiety had little effect on the enantioselectivity (entries 1−7). In contrast, *ortho*-substituents of benzylideneindolinones were deleterious to the stereoselectivity. Thus, 1-acetyl-3-(2-fluorobenzylidene)indolinone and 1-acetyl-3-(2-chlorobenzylidene)indolinone gave 81% and 86% *ee*, respectively (entries 8−9), lower than those of their structural analogues (entries 1−7, 10, and 11). Naphthalenylmethyleneindolinones participated in the cycloaddition reactions to give the products with up to 98% *ee* (entries 12−13). 1-Acetyl-3-(2-furanylmethylene)indolinone afforded

Table 4. Generality of Asymmetric Cycloaddition Reactions for the Indolinone Moiety of Methyleneindolinones[a]



Entry	8	Yield,[b] % *ee*[c]	Entry	8	Yield,[b] % *ee*[c]
1	 (10a)	87% yield, 92% *ee*	7	 (10h) R = 4-$NO_2C_6H_4$	91% yield, 92% ee
2	 (10b)	94% yield, 92% ee	8	 (10i) R = 4-$NO_2C_6H_4$	86% yield, 91% ee
3	 (10c)	95% yield, 93% ee	9	 (10j)	73% yield, 86% ee
4	 (10d)	90% yield, 92% ee	10	 (10k)	80% yield, 88% ee
5	 (10e)	94% yield, 91% ee	11	 (10l) R = 4-$NO_2C_6H_4$	91% yield, 89% ee
6	 (10f)	89% yield, 93% ee	12	 (10m) R = 4-$NO_2C_6H_4$	94% yield, 87% ee

[a] The reaction was carried out on a 0.2 mmol scale with 3 Å MS (300 mg) for 24−96 h, giving regiospecific products; the ratio of **1/2/3a** was 1.2/1.2/1. [b] Isolated yields. [c] The *ee* was determined by HPLC.

93% *ee* (entry 14). 1-Acetyl-3-((*E*)-3-phenylallylidene)indolinone and two species of 1-acetyl-3-(alkyl)indolinones underwent clean cycloaddition reactions with good enantioselectivities, but the regioselectivity was comparably lower (entries 15−17). In addition to aromatic aldehydes, the less reactive aliphatic aldehydes were also good reaction components for methyleneindolinone derivatives. Thus, a number of benzylideneindolinones reacted with 3-methylbutanal and 3,3-dimethylbutanal in high yields and enantioselectivities (entries 18−21).

The generality of the reaction condition for the substituents on the indolinone moiety of the methyleneindolinones was also investigated (Table 4). Variation of the electronic properties of the substituents at either C5 or C6 of methyleneindolinones was tolerable with high yields ranging from 86% to 95% and enantioselectivities ranging from 91% to 93% *ee* (entries 1−8). The cycloaddition reactions with methyleneindolinones substituted at both C5 and C6 proceeded cleanly to afford spiro[pyrrolidin-3,3′-oxindoles] in good yields and stereoselectivities (entries 9−12). The presence of chlorine or fluorine at either C5 or C6 of the spiro derivatives is very important for pharmacological activity.[4] Thus, these spiro[pyrrolidin-3,3′-oxindole] derivatives will provide promising candidates for chemical biology and drug discovery. The relative and absolute configurations of **8d** were assigned by the X-ray analysis (see Supporting Information).

Theoretical Study of the Transition Structures and Mechanism Considerations. We performed theoretical calculations on the transition state to explain the unusual regioselectivity and high enantioselectivity observed in these reactions.[20] As shown in Figure 3, the best transition structure for the three-component 1,3-dipolar cycloaddition reaction is TS-1, wherein both the methyleneindolinone and the azomethine ylide are hydrogen-bonded with the hydroxyl proton and phosphoryl oxygen of the catalyst, which serve respectively as Brønsted acid and Lewis base to activate the two substrates simultaneously.[10,11] The hydroxyl group appears to be a better hydrogen-bond donor as indicated

(20) All calculations were performed with the Gaussian 03 program.

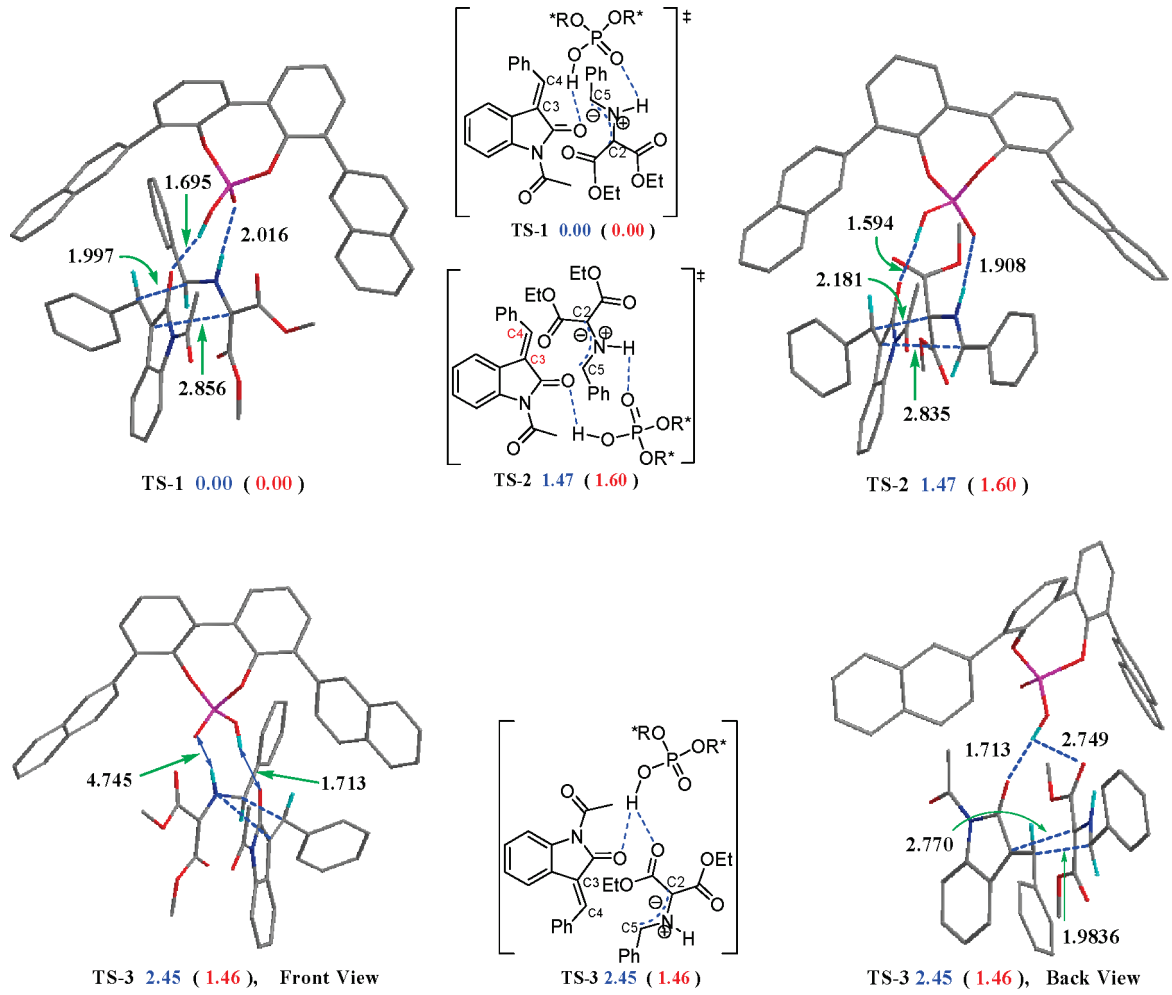
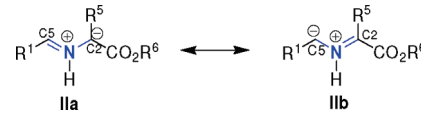


Figure 3. Located transition state structures and relative energies expressed in terms of enthalpy and of free energy in parentheses via B3LYP/6-31G* calculations (distances in angstrom and energies in kcal/mol). Most H atoms are removed for clarity.

by the shorter hydrogen bond in all cases. TS-1, which leads to the formation of the major product observed experimentally, is found to be more stable than TS-2, which corresponds to the minor product with regioselectivity opposite to the major product, presumably due to the stabilization stemming from the favorable $\pi-\pi$ stacking interaction between the oxo-indole ring and the conjugated esters in TS-1 (the distance between the oxo-indole ring and the conjugated esters is only ~3.0 Å).[21] TS-3, which leads to the formation of the enantiomer of the major product, is considerably less stable than TS-1 in energy. Moreover, in TS-3 the distance of P═O···H—(N) is as much as 4.745 Å, unable to allow the formation of a hydrogen bond for the activation of the azomethine ylide; therefore the azomethine ylide is less activated than that in TS-1, resulting in a slower 1,3-dipolar addition to generate the minor enantiomer.

As reported previously in the relevant reactions, the azomethine ylide can present as two zwitterionic resonance forms **IIa** and **IIb**.[22] On the basis of the DFT calculations and the regioselectivity observed experimentally, we proposed that two zwitterionic azomethine ylide resonance forms might exist in the present 1,3-dipolar cycloaddition reactions and be responsible for the regioselectivity of the cycloaddition reaction of azomethine ylide with unsymmetrical dipolarophiles.

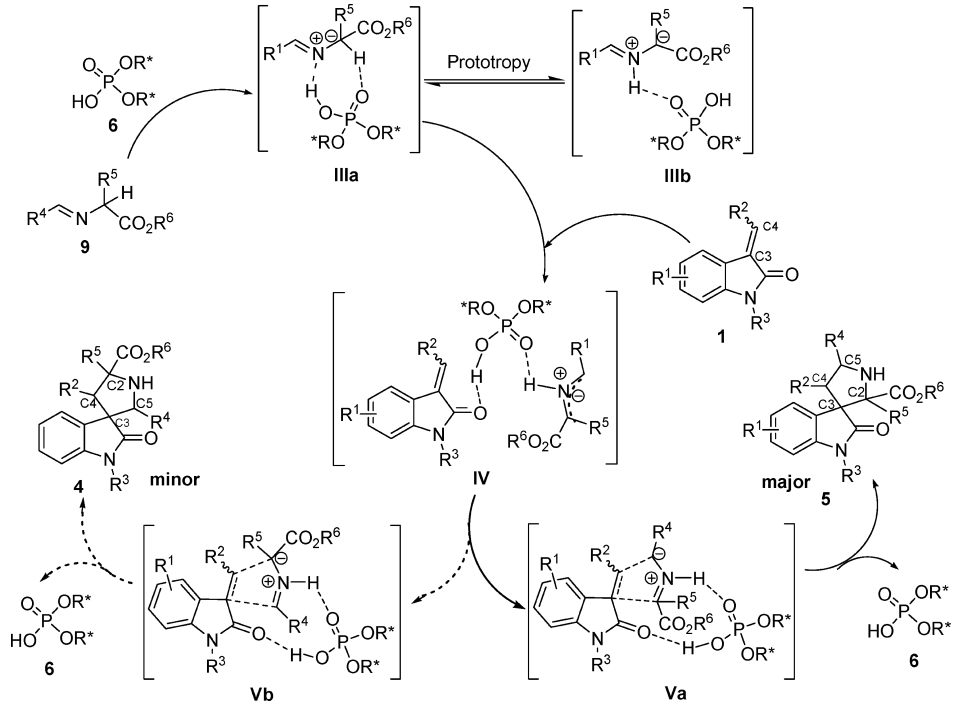


The two zwitterionic resonance forms **IIa** and **IIb** were confirmed by the theoretical calculations (Figure 3). As indicated by the located transition state structures in TS-1, the C4—C5 bond is formed earlier than the C2—C3 bond, as the distance of C4—C5 is shorter than that of C2—C3 by ~0.86 Å. In TS-3, the C4—C5 bond is also formed in the initial stage of the reaction. In the transition states TS-1 and TS-3, the azomethine ylide served as the zwitterionic resonance form **IIb**, reacting with methyleneindolinones to afford spiro[pyrrolidin-3,3′-ox-

(21) (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books; Sausalito, CA, 2005. (b) Demeshko, S.; Dechert, S.; Meyer, F. *J. Am. Chem. Soc.* **2004**, *126*, 4508. (c) The aromatic stacking interaction between the aryl groups to fix the geometry in chiral phosphoric acid catalysis; see: Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756.

(22) (a) The proposed zwitterionic resonance forms are similar to the principal resonance forms of the carbanion intermediate in transamination reactions; see: Martell, A. E. *Acc. Chem. Res.* **1989**, *22*, 115. (b) For the zwitterionic resonance forms of azomethine ylides, also see: 16a, 16b.

Scheme 2. Proposed Mechanism for the Regiospecific 1,3-Dipolar Reaction of Methyleneindolinones with Azomethine Ylides under the Catalysis of the Chiral Brønsted Acid



indole] derivatives of type **5** (Scheme 2). However, in TS-2, the distance of the forming C2−C4 bond is shorter than C3−C5 by ∼0.65 Å, indicating that the C2−C4 bond is formed earlier than the latter, with the azomethine ylide serving as zwitterionic resonance form **IIa**, giving the opposite regiomer of type **4**. Although the azomethine ylide form **IIb** in TS-1 is not usually proposed in 1,3-dipolar cycloaddition reactions,[7] TS-1 is favored due to its lower enthalpy of ∼1.47 kcal mol^{-1} compared to TS-2 (Figure 3).

The proposed mechanism for the reaction course of this cycloaddition reaction is summarized in Scheme 2. The 1,3-dipolar cycloaddition reaction started with a condensation of the aldehyde with amino esters, to give an imine **9**. The chiral phosphoric acid and the imino ester are able to form a chiral azomethine ylide **IIIa**, which principally undergoes a 1,2-prototropic process to form **IIIb** (Scheme 2).[23] Either the chiral azomethine ylide **IIIa** or **IIIb** reacts with the methyleneindolinone (**1**) to generate an intermediate **IV**, wherein the hydroxyl proton and the phosphoryl oxygen of the chiral phosphoric acid would form double hydrogen bonding interactions with the methyleneindolinone and the azomethine ylide dipole, respectively.[10,11] The resulting reaction intermediate **IV** undergoes a 1,3-dipolar cycloaddition reaction, regiospecifically yielding spiro[pyrrolidin-3,3′-oxindole] derivatives **5** via the transition state **Va** (Scheme 2), as suggested by DFT calculation. In contrast, the minor regiomer **4** was given by the reaction via the energetically less favored transition state **Vb**.

(23) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.

Conclusion

In summary, we have reported an unprecedented asymmetric catalytic three-component 1,3-dipolar cycloaddition of a broad range of methyleneindolinones with aldehydes and amino esters by using a phosphoric acid as the chiral catalyst. This reaction is so far the sole catalytic synthesis of spiro[pyrrolidin-3,3′-oxindole] derivatives with high enantioselectivity and structural diversity. This new, straightforward protocol for rapid construction of the privileged spirooxindole architecture has great usefulness in medicinal chemistry and diversity-oriented synthesis[2a,4,6] and, thus, may lead to further development of related compounds as potential medicinal agents. Theoretical calculations disclosed that both the azomethine ylide and the methyleneindolinone are hydrogen-bonded with the phosphoric acid, which accounted for the high enantio- and regioselectivity and indicated that the unusual regioselectivity results from the stabilization stemming from the favorable $\pi-\pi$ stacking interaction between the oxo-indole ring and the conjugated esters. We will next focus on the evaluation of the biological activity of the molecules obtained from this method.

Acknowledgment. We are grateful for financial support from NSFC (20732006), MOST (973 program 2009CB825300), Ministry of Education, and CAS. We also thank Dr. Zhenyu Li for his early calculation on the electron density of **1a**.

Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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