DOI: 10.1002/chem.201200358

Scaffold-Inspired Enantioselective Synthesis of Biologically Important Spiro[pyrrolidin-3,2′-oxindoles] with Structural Diversity through Catalytic Isatin-Derived 1,3-Dipolar Cycloadditions

Feng Shi,[a] Zhong-Lin Tao,[b] Shi-Wei Luo,*[b] Shu-Jiang Tu,[a] and Liu-Zhu Gong*[b]

Abstract: Catalytic asymmetric construction of the biologically important spiro[pyrrolidin-3,2′-oxindole] scaffold with contiguous quaternary stereogenic centers in excellent stereoselectivities (up to >99:1 d.r., 98% *ee*) has been established by using an organocatalytic 1,3-dipolar cycloaddition of isatin-based azomethine ylides. This protocol represents the first example of catalytic asymmetric 1,3-dipolar cycloadditions involving azomethine ylides generated in situ from unsymmetrical cyclic ketones. In addition, theoretical calculations were performed on the transition state of the reaction to understand the stereochemistry. Preliminary bioassays with these spiro[pyrrolidin-3,2′-oxindole] revealed that several compounds showed moderate cytotoxicity to SW116 cells.

Keywords: cycloaddition · asymmetric synthesis · multicomponent reactions · organocatalysis · spiro compounds

Introduction

The spiro[pyrrolidin-3,2′-oxindole] core is a privileged heterocyclic ring system that is featured in a large family of medicinally relevant compounds exhibiting a wide spectrum of important bioactivities such as antitumor,[1] antidiabetic,[2] antimycobacterial,[3] antimicrobial,[4] antitubercular,[5] and acetylcholinesterase-inhibitory[6] activities. Particularly, as exemplified in Figure 1, compounds of type **I**, **II**, and **III** showed potent antimycobacterial,[3b] antimicrobial,[4c] and antitubercular[5b] activities, respectively.

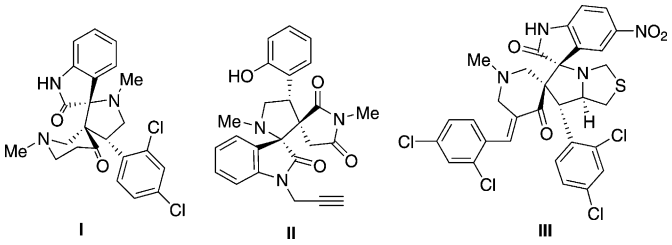


Figure 1. Some biologically important compounds containing the spiro-[pyrrolidin-3,2′-oxindole] core.

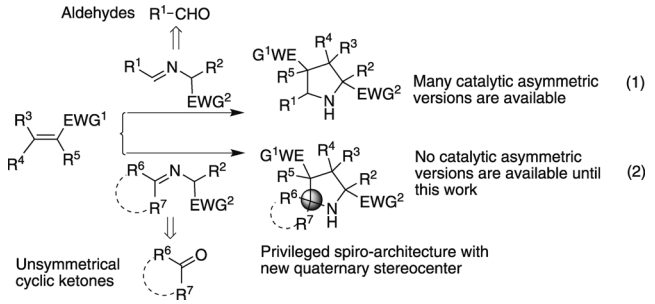
The significant medicinal relevance of such a structural architecture has led to great demand for efficient synthetic methods, especially those producing enantiomerically pure spiro[pyrrolidin-3,2′-oxindole] derivatives. However, the established synthetic approaches are either racemic or require enantiopure starting materials,[3c,4b,c,7] and no catalytic asymmetric approaches have been available to access optically pure spiro[pyrrolidin-3, 2′-oxindole] compounds.[8] As a consequence, the catalytic enantioselective construction of this structurally rigid architecture containing quaternary stereocenters has remained a formidable challenge and is highly desirable.

In the past decades, elegant developments have been described in the field of catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides to electron-deficient olefins by using either chiral metal-based catalysts[9] or organocatalysts [Eq. (1)].[10] The azomethine ylides that participate in these reactions are mostly generated from aldehydes. In contrast, ketones have rarely been applied to 1,3-dipolar cycloadditions as azomethine ylide precursors, presumably due to the low reactivity inherent in both the ketone and the resultant azomethine ylide. So far, catalytic asymmetric 1,3-dipolar cycloaddition reactions involving ketone-based azomethine ylides have occasionally been used in a limited number of metal-catalyzed transformations[11] and in one organocatalytic variant.[10d] However, none of these protocols employed unsymmetrical cyclic ketones [Eq. (2)]. Nevertheless, the application of 1,3-dipolar cycloaddition reactions with ketones, in particular unsymmetrical cyclic ketones, would enable structurally diverse syntheses of spiro-pyrrolidines with concomitant creation of quaternary stereogenic centers and hence holds great synthetic promise.

[a] F. Shi, Prof. S.-J. Tu
School of Chemistry and Chemical Engineering
Xuzhou Normal University
Xuzhou, 221116 (P.R. China)

[b] Z.-L. Tao, S.-W. Luo, Prof. L.-Z. Gong
Hefei National Laboratory for Physical Sciences
at the Microscale and Department of Chemistry
University of Science and Technology of China
Hefei, 230026 (P.R. China)
Fax: (+86) 551-3606266
E-mail: gonglz@ustc.edu.cn
luosw@ustc.edu.cn

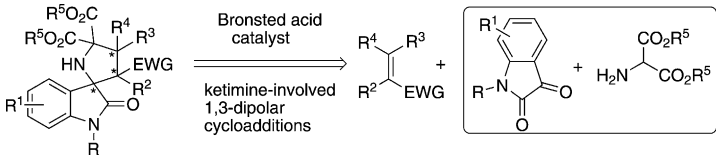
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200358.



Herein, we report the catalytic asymmetric construction of a biologically important spiro[pyrrolidin-3,2′-oxindole] scaffold with multiple contiguous stereogenic centers including one or two quaternary chiral centers by using an organocatalytic 1,3-dipolar cycloaddition reaction with isatins as azomethine precursors, which gives excellent stereoselectivity (up to >99:1 diastereomeric ratio (d.r.) and 98% enantiomeric excess (*ee*))

Results and Discussion

Catalytic asymmetric synthesis of spiro[pyrrolidin-3,2′-oxindole] derivatives: The 1,3-dipolar cycloaddition of electron-deficient olefins with the azomethine ylide generated from isatin provides a straightforward entry to the spiro[pyrrolidin-3,2′-oxindole] scaffold (Scheme 1).

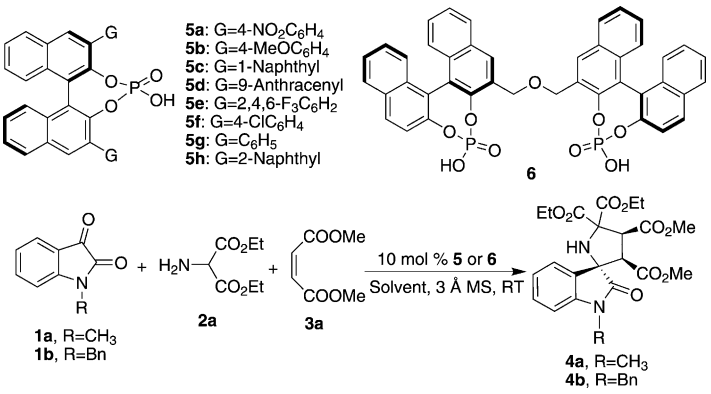


Scheme 1. Strategy used for the construction of the spiro[pyrrolidin-3,2′-oxindole] scaffold with a chiral Brønsted acid catalyst.

We have recently established a series of enantioselective 1,3-dipolar cycloaddition reactions between electron-deficient olefins and azomethine ylides formed from aldehydes using chiral phosphoric acids[12] as catalysts in which a chiral Brønsted acid bonded dipole is involved.[13] Encouraged by these successes and in view of the synthetic importance of developing an enantioselective version of the 1,3-dipolar cycloaddition reaction involving azomethine ylides generated from unsymmetrical cyclic ketones, we envisioned that ketimine-based azomethine ylides could also be activated by the chiral Brønsted acid to undergo enantioselective 1,3-dipolar cycloadditions, leading to the production of the spiro[pyrrolidin-3, 2′-oxindole] skeleton with multiple stereogenic centers.

Optimization of reaction conditions: Our study began with the reaction of 1-methylisatin (**1a**) and diethyl 2-aminomalonate (**2a**) with dimethyl maleate (**3a**) in toluene at room temperature in the presence of 10 mol% chiral phosphoric acids **5** or **6** (Table 1). The results revealed that bisphosphoric acid (Bis-PA) **6** was much superior to other phosphoric acids **5**, delivering 90% *ee* (Table 1, entries 1–8 vs. 9). Interestingly, the reaction with 1-benzylisatin (**1b**) proceeded more efficiently in a higher yield of 78% and enantioselectivity of 93% *ee* under similar conditions (Table 1, entry 10). Thus, this substrate was subsequently employed to optimize the conditions. A survey of solvents revealed that toluene was a suitable reaction media (Table 1, entries 10–14). Changes to the reaction temperature did not enhance the enantioselectivity (Table 1, entries 10 vs. 15 and 16). In addition, tuning other reaction parameters such as substrate ratio and molecular sieves did not deliver higher *ee* values (Table 1, entries 10 vs. 17 and 18). Finally, the presence of 15 mol% **6** was found to facilitate the reaction, delivering a higher yield while maintaining the enantioselectivity (Table 1, entry 19 vs. 10).

Table 1. Screening of catalyst and optimization of conditions.[a]

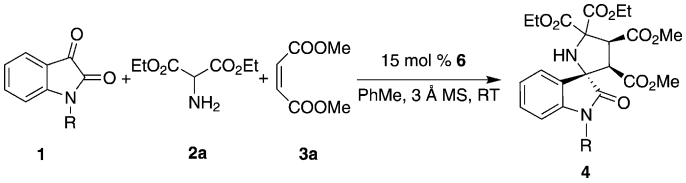


Entry	**4**	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**4aaa**	**5a**	toluene	87	10
2	**4aaa**	**5b**	toluene	87	25
3	**4aaa**	**5c**	toluene	78	13
4	**4aaa**	**5d**	toluene	86	5
5	**4aaa**	**5e**	toluene	73	18
6	**4aaa**	**5f**	toluene	88	25
7	**4aaa**	**5g**	toluene	59	1
8	**4aaa**	**5h**	toluene	92	31
9	**4aaa**	**6**	toluene	54	90
10	**4baa**	**6**	toluene	78	93
11	**4baa**	**6**	THF	12	5
12	**4baa**	**6**	$CHCl_3$	45	92
13	**4baa**	**6**	$(ClCH_2)_2$	16	93
14	**4baa**	**6**	CH_2Cl_2	26	91
15	**4baa**	**6**	toluene	23	77[d]
16	**4baa**	**6**	toluene	87	92[e]
17	**4baa**	**6**	toluene	59	91[f]
18	**4baa**	**6**	toluene	85	91[g]
19	**4baa**	**6**	toluene	88	93[h]

[a] Reagents and conditions (0.1 mmol scale): solvent (1 mL), 3 Å MS (100 mg), 36 h, ratio of **1/2a/3a** 1.2:1:5. [b] Isolated product yield and a single diastereomer was observed unless indicated otherwise. [c] The *ee* value was determined by HPLC analysis. [d] Performed at 0°C. [e] Performed at 40°C. [f] The ratio of **1b/2a/3a** was 1.2:1:10. [g] By using 5 Å MS (100 mg). [h] In the presence of 15 mol% **6**.

Scope of isatins: With the optimal conditions in hand, the generality of the reaction for isatins **1** was then explored with the reactions of diethyl 2-aminomalonate (**2a**) and dimethyl maleate (**3a**). Initially, the effect of N-substituents of isatins **1** on the reaction was investigated. As shown in Table 2, this protocol is amenable to a wide range of isatins with different types of N-substituents, including alkyl, aryl, and benzyl groups, and the products were obtained with high enantioselectivities (up to 94% *ee*). Generally, *N*-benzyl substituted isatin gave higher stereoselectivity than *N*-alkyl or *N*-phenyl derivatives (Table 2, entry 2 vs. 1, 3, and 4). For *N*-benzylisatin derivatives, variation of the substituent on the benzyl moiety had little effect on the enantioselectivity (Table 2, entries 5–9). However, linear *N*-alkyl substituted isatins delivered higher enantioselectivity than the branched and cyclic analogues (Table 2, entry 10 vs. 11 and 12).

Table 2. Effect of N-substituents of isatins **1** on the reaction.[a]



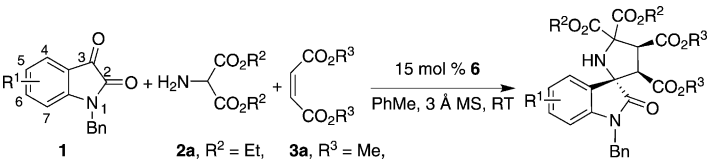
1 2a 3a 4

Entry	4	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4aaa**	Me (**1a**)	77	>99:1	93
2	**4baa**	Bn (**1b**)	88	>99:1	93
3	**4caa**	Ph (**1c**)	90	>99:1	80[e]
4	**4daa**	9-Anthracenyl-CH_2(**1d**)	48	>99:1	88[e]
5	**4eaa**	*p*-*t*Bu$C_6H_4CH_2$(**1e**)	70	>99:1	94
6	**4faa**	*p*-Br$C_6H_4CH_2$ (**1f**)	91	>99:1	92
7	**4gaa**	*o*-Br$C_6H_4CH_2$(**1g**)	62	>99:1	92
8	**4haa**	*p*-F$C_6H_4CH_2$(**1h**)	78	>99:1	92
9	**4iaa**	$C_6F_5CH_2$ (**1i**)	94	>99:1	92
10	**4jaa**	*n*-Hexyl (**1j**)	86	>99:1	92
11	**4kaa**	*i*Pr (**1k**)	89	>99:1	86
12	**4laa**	cyclopentyl (**1l**)	91	>99:1	86

[a] Reagents and conditions (0.1 mmol scale): toluene (1 mL), 3 Å MS (100 mg), 36 h, **1**/**2a**/**3a** ratio 1.2:1:5. [b] Isolated yield. [c] The d.r. was determined by ^{1}H NMR spectroscopic analysis. [d] The *ee* value was determined by HPLC analysis. [e] In the presence of **6** (10 mol%).

The influence of the substituent at the phenyl moiety of isatins **1** on the reaction was then studied (Table 3). Generally, the introduction of an electronically different substituent at C5, C6, or C7 of the isatin was tolerated, with high enantioselectivities ranging from 81 to 98% *ee*. The position of the substituent appeared to exert some influence on the stereoselectivity. Broadly, the C6-substituted isatins provided higher *ee* values than C5-substituted derivatives (Table 3, entry 3 vs. 1 and entry 4 vs. 2), whereas no remarkable difference in the enantioselectivity was observed between the C7- and C6-substituted isatins (Table 3, entry 5 vs. 6). In addition, C5,C6 disubstituted isatins also participated in the reaction with 91% *ee* (Table 3, entry 8). It is noteworthy that d.r. values of more than 99:1 were obtained in all cases.

Table 3. Influence of the substituent at the phenyl moiety of isatins **1** on the reaction.[a]



1 **2a**, R^2 = Et, **2b**, R^2 = Me **3a**, R^3 = Me, **3b**, R^3 = Et 4

Entry	4	R^1	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4maa**	5-F (**1m**)	**3a**	90	>99:1	83
2	**4naa**	5-Me (**1n**)	**3a**	95	>99:1	87
3	**4oaa**	6-F (**1o**)	**3a**	82	>99:1	89
4	**4paa**	6-Me (**1p**)	**3a**	84	>99:1	94
5	**4qaa**	6-Br (**1q**)	**3a**	63	>99:1	94
6	**4raa**	7-Br (**1r**)	**3a**	89	>99:1	96
7	**4saa**	7-CF_3 (**1s**)	**3a**	90	>99:1	96
8	**4taa**	5,6-F_2 (**1t**)	**3a**	86	>99:1	91
9	**4bab**	H (**1b**)	**3b**	84	>99:1	81[e]
10	**4qab**	6-Br (**1q**)	**3b**	52	>99:1	89[e]
11	**4rab**	7-Br (**1r**)	**3b**	77	>99:1	83[e]
12	**4sab**	7-CF_3 (**1s**)	**3b**	86	>99:1	88[e]
13	**4rba**	7-Br (**1r**)	**3a**	72	>99:1	98[f]

[a] Reagents and conditions (carried out with **2a** in 0.1 mmol scale): toluene (1 mL), 3 Å MS (100 mg), 36 h, **1**/**2a**/**3** was 1.2:1:5. [b] Isolated product yield. [c] The d.r. was determined by ^{1}H NMR spectroscopic analysis. [d] The *ee* value was determined by HPLC analysis. [e] The reaction time was 48 h. [f] Compound **2b** was used as a reaction component and in the presence of **6** (25 mol%) and the reaction time was 96 h.

Therefore, this reaction tolerated various isatins to afford spiro[pyrrolidin-3,2′-oxindole] compounds with high enantioselectivities and excellent diastereoselectivities. In addition to dimethyl maleate (**3a**), the use of diethyl maleate (**3b**) as a 1,3-dipolarophile provided high enantioselectivities ranging from 81 to 89% *ee* and excellent diastereoselectivities of more than 99:1 d.r. (Table 3, entries 9–12), although the *ee* values of the spiro[pyrrolidin-3, 2′-oxindole] derivatives synthesized from diethyl maleate (**3b**) were not as high as their counterparts from the reactions with dimethyl maleate (**3a**). Importantly, spiro[pyrrolidin-3,2′-oxindole] **4aaa** could be obtained as a single crystal in more than 99% *ee* after recrystallization; the X-ray analysis of which revealed that the absolute configuration was (2′*S*,3′*R*,4′*S*) (Figure 2).[14] The configurations of other spiro[pyrrolidin-3,2′-oxindole] derivatives generated from maleates were assigned by analogy.

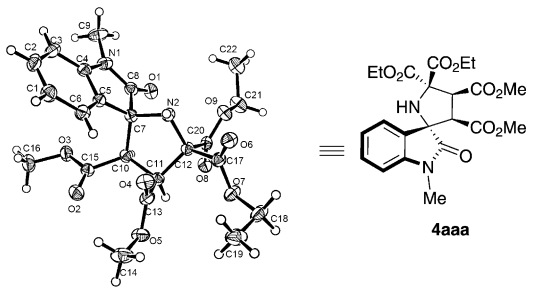


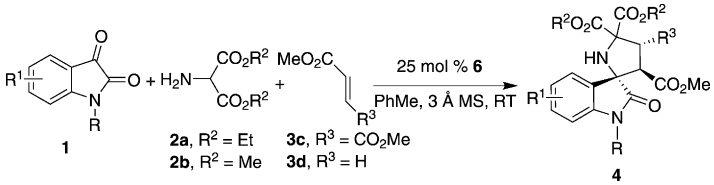
Figure 2. X-ray structure of spiro[pyrrolidin-3,2′-oxindole] **4aaa**.

Scope of 1,3-dipolarophiles: Although fumarates represent challenging dipolarophiles compared with maleates in the asymmetric 1,3-dipolar cycloaddition,[13d] a variety of isatins were accommodated in the 1,3-dipolar cycloaddition with dimethyl fumarate (**3c**) under similar reaction conditions. The presence of 25 mol% of catalyst **6** enabled the generation of spiro[pyrrolidin-3,2′-oxindole] compounds **4bac–wac** with high diastereomeric ratios (30:1 to >99:1 d.r.) and excellent enantioselectivity ranging from 88 to 96% *ee* (Table 4, entries 1–6). The absolute configuration of spiro[pyrrolidin-3,2′-oxindole] **4bac** was assigned as (2′*S*,3′*R*,4′*R*) by X-ray crystallographic analysis (Figure 3).[14] The stereochemistry of the other products were assigned by analogy. Moreover, the 1,3-dipolar cycloaddition of methyl acrylate (**3d**) also proceeded smoothly under similar reaction conditions to produce spiro[pyrrolidin-3, 2′-oxindole] compounds **4bad–wad** with high enantioselectivities of up to 97% *ee* and excellent diastereoselectivities of more than 99:1 d.r. (Table 4, entries 7–11). The use of dimethyl 2-aminomalonate (**2b**) as a reaction component also provided excellent stereochemical outcomes (Table 4, entries 12 and 13).

Importantly, the use of methyl 2-phenylacrylate (**3e**) as a reaction component to participate in the 1,3-dipolar cycloaddition allowed the creation of spiro[pyrrolidin-3,2′-oxindole] derivatives possessing two contiguous quaternary chiral centers, one of which is an all-carbon stereogenic center. However, when the previously optimized conditions for maleates were applied to the reaction involving **3e**, spiro[pyrrolidin-3,2′-oxindole] **4bae** was obtained in an unsatisfactory enantioselectivity (82% *ee*, Table 5, entry 1). Thus, the reaction conditions were reoptimized. Screening of the solvents revealed that chloroform or dichloromethane were more suitable media for the reaction in terms of stereoselectivity; use of these solvents led to higher enantiomeric excesses than those obtained in toluene, however, lower yields were observed (Table 5, entries 2 and 3 vs. 1). The fine-tuning of catalyst loading and reaction temperature revealed that the presence of 25 mol% of catalyst **6** could give high enantioselectivity and reasonable yield in chloroform at room temperature (Table 5, entry 6). Although a slightly improved yield was observed at elevated temperature, this was at the expense of reduced enantioselectivity (Table 5, entry 7). Finally, using a solvent mixture of chloroform and toluene with 1:1 ratio allowed the reaction to proceed in 51% yield with an excellent enantioselectivity of 93% *ee* (Table 5, entry 8).

Under the reoptimized reaction conditions, a variety of isatins were examined in the 1,3-dipolar cycloaddition reaction with methyl 2-phenylacrylate (**3e**). The protocol

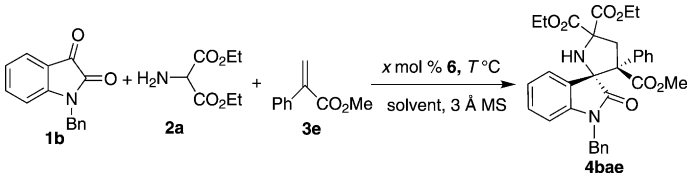
Table 4. The use of dimethyl fumarate (**3c**) and methyl acrylate (**3d**) as 1,3-dipolarophiles for the synthesis of spiro[pyrrolidin-3,2′-oxindoles].[a]



Entry	4	R/R[1]	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4bac**	Bn/H (**1b**)	**3c**	71	40:1	88
2	**4qac**	Bn/6-Br (**1q**)	**3c**	41	>99:1	93
3	**4rac**	Bn/7-Br (**1r**)	**3c**	63	>99:1	95
4	**4uac**	*p*-*t*BuC$_6$H$_4$CH$_2$/6-Br (**1u**)	**3c**	71	30:1	96
5	**4vac**	*p*-*t*BuC$_6$H$_4$CH$_2$/7-Br (**1v**)	**3c**	70	30:1	94
6	**4wac**	*p*-*t*BuC$_6$H$_4$CH$_2$/7-CF$_3$ (**1w**)	**3c**	76	40:1	92
7	**4bad**	Bn/H (**1b**)	**3d**	91	>99:1	87
8	**4qad**	Bn/6-Br (**1q**)	**3d**	44	>99:1	93
9	**4rad**	Bn/7-Br (**1r**)	**3d**	83	>99:1	94
10	**4vad**	*p*-*t*BuC$_6$H$_4$CH$_2$/7-Br (**1v**)	**3d**	86	>99:1	94
11	**4wad**	*p*-*t*BuC$_6$H$_4$CH$_2$/7-CF$_3$ (**1w**)	**3d**	92	>99:1	97
12	**4rbc**	Bn/7-Br (**1r**)	**3c**	46	>99:1	96[e]
13	**4rbd**	Bn/7-Br (**1r**)	**3d**	72	>99:1	96[e]

[a] Reagents and conditions (carried out with **2a** on 0.1 mmol scale): toluene (1 mL), 3 Å MS (100 mg), 60 h, **1**/**2a**/**3** ratio 1.2:1:5. [b] Isolated product yield. [c] The d.r. was determined by ^{1}H NMR spectroscopic analysis. [d] The *ee* value was determined by HPLC analysis. [e] Compound **2b** was used as a reaction component and the reaction time was 96 h.

Table 5. Optimization of reaction conditions for the reactions using methyl 2-phenylacrylate **3e** as 1,3-dipolarophile.[a]



Entry	*x* [mol%]	*T* [°C]	Solvent	Yield [%][b]	*ee* [%][c]
1	15	RT	toluene	64	82
2	15	RT	CH_2Cl_2	27	90
3	15	RT	$CHCl_3$	31	89
4	15	RT	$(ClCH_2)_2$	35	74
5	20	RT	$CHCl_3$	38	91
6	25	RT	$CHCl_3$	46	90
7	25	40	$CHCl_3$	51	88
8	25	RT	$CHCl_3$/toluene = 1:1 *v*/*v*	51	93

[a] Reagents and conditions (0.1 mmol scale): solvent (1 mL), 3 Å MS (100 mg), 72 h, **1b**/**2a**/**3e** ratio 1.2:1:5. [b] Isolated product yield and a single diastereomer was observed unless indicated otherwise. [c] The *ee* value was determined by HPLC analysis.

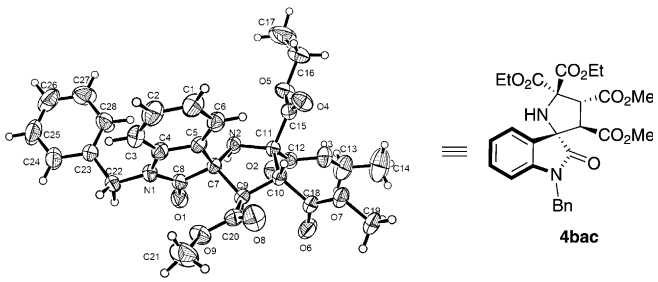
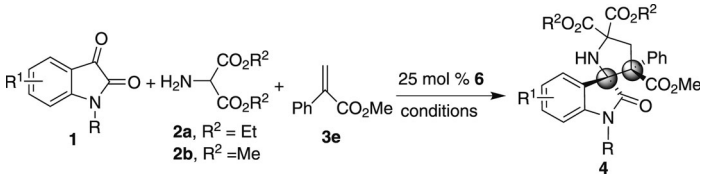


Figure 3. X-ray structure of spiro[pyrrolidin-3,2′-oxindole] **4bac**.

Table 6. The use of methyl 2-phenylacrylate (**3e**) as a 1,3-dipolarophile for the synthesis of spiro[pyrrolidin-3,2′-oxindoles] with two contiguous quaternary chiral centers.[a]



Entry	4	R/R^1	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4bae**	Bn/H (**1b**)	51	>99:1	93
2	**4rae**	Bn/7-Br (**1r**)	52	>99:1	93
3	**4uae**	*p*-*t*BuC$_6$H$_4$CH$_2$/6-Br (**1u**)	53	>99:1	97
4	**4vae**	*p*-*t*BuC$_6$H$_4$CH$_2$/7-Br (**1v**)	51	>99:1	95
5	**4wae**	*p*-*t*BuC$_6$H$_4$CH$_2$/7-CF$_3$ (**1w**)	57	>99:1	95
6	**4rbe**	Bn/7-Br (**1r**)	41	>99:1	95[e]

[a] Reagents and conditions (carried out with **2a** in 0.1 mmol scale): toluene/$CHCl_3$ (1:1 *v*/*v*, 1 mL), 3 Å MS (100 mg), 72 h, **1**/**2a**/**3e** ratio 1.2:1:5. [b] Isolated product yield. [c] The d.r. was determined by ^{1}H NMR spectroscopic analysis. [d] The *ee* value was determined by HPLC analysis. [e] Compound **2b** was used as a reaction component and the reaction time was 96 h.

showed high generality for isatin substrates, and provided spiro[pyrrolidin-3,2′-oxindole] derivatives possessing two contiguous quaternary chiral centers in good yields and with excellent stereoselectivities ranging from 93 to 97% *ee* and more than 99:1 d.r. in all cases (Table 6).

The absolute configuration of spiro[pyrrolidin-3,2′-oxindole] **4bae** was unambiguously determined to be (2′*R*,3′*S*) by X-ray analysis on a single crystal, which was obtained in more than 99% *ee* after recrystallization (Figure 4).[14] The configurations of other spiro[pyrrolidin-3,2′-oxindole] derivatives generated from acrylates were assigned by analogy.

To understand the observed stereochemistry, theoretical calculations were performed on the transition state (TS) of this isatin-derived 1,3-dipolar cycloaddition by using the hybrid density functional theory (DFT) method[15] combined with the 6-31G(d) basis set,[16] as implemented in the Gaussian03 program.[17] Based on our theoretical studies on enantioselective 1,3-dipolar cycloadditions between electron-deficient olefins and azomethine ylide dipoles,[13d] TS models were proposed as shown in Scheme 2 for this catalytic enantioselective

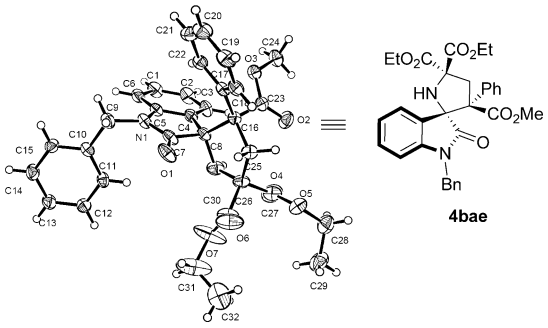
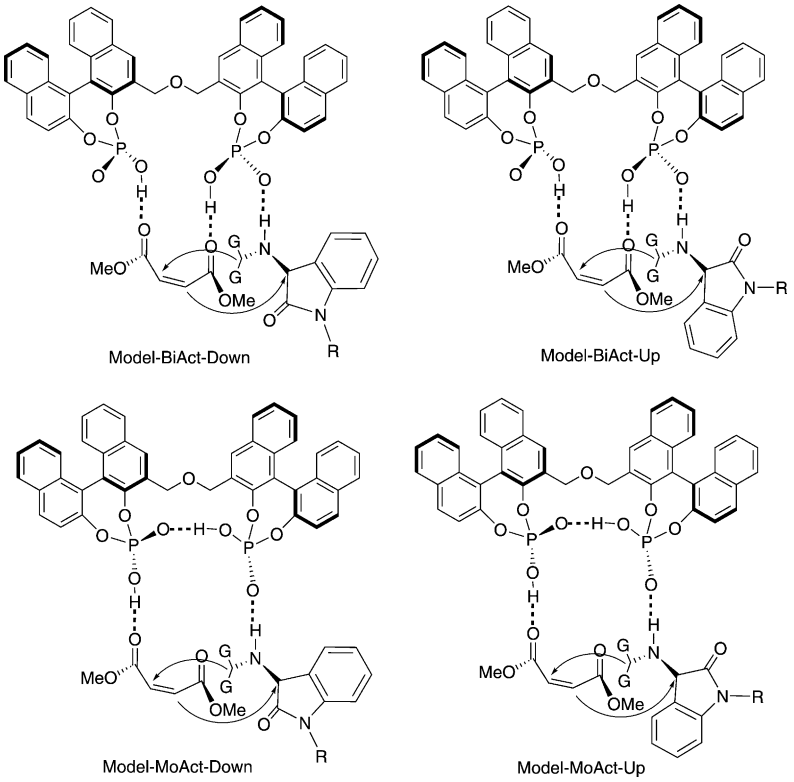


Figure 4. X-ray structure of spiro[pyrrolidin-3,2′-oxindole] **4bae**.

isatin-derived 1,3-dipolar cycloaddition reaction. The bis-phosphoric acid (Bis-PA) is proposed to activate the dipolarophile by forming two hydrogen bonds between its two hydroxyl groups and the two ester carbonyls of maleate and, simultaneously, to activate the dipole by another hydrogen bond between its P=O and the N−H of the azomethine ylide, as illustrated in Model-BiAct. The other way to accelerate this cycloaddition is described as Model-MoAct, in which only one hydrogen bond between the catalyst and the dipolarophile was formed, making the dipolarophile more electronically deficient. Another hydrogen bond between two phosphoric acids may shift the proton between the two phosphate groups to adjust the acidity and basicity of the two phosphoric acids to activate the dipole and dipolarophile more effectively. The dipole of isatin azomethine ylide



Scheme 2. Proposed transition state models for the 1,3-dipolar cycloaddition reaction.

may take two orientations, one is the C=O of isatin *cis* to the N–H and the second is *trans*, as shown as Up or Down in the present models, respectively. To save computational resources, the naphthyl moieties in the catalyst were replaced with phenyl groups and the ethyl esters in the substrate with methyl esters. Furthermore, N–Me was used to replace all N–R groups (Scheme 2).

The located TS structures for the catalytic cycloaddition between maleate and isatin-derived azomethine ylide are shown in Figure 5. The calculated results indicated that the dipole of isatin-derived azomethine ylide, the key intermediate, should take an orientation with the C=O of isatin *trans* to the N–H (Model-Down). In all cases, the TSs with the Up orientation of C=O of isatin was predicted to be less stable than those with C=O Down by about 10 kcal mol^{-1}, probably due to electronic repulsion between the oxygen atoms on C=O and P=O. The repulsive interaction between the C=O and phosphoric oxygen atom may contribute to the clear destabilization in TSs with the Up orientation of C=O.

The located TS structure Model-BiAct-Down-1 represents the most stable TS located, which corresponds to the main product **4aaa** observed experimentally. Model-BiAct-Down-2, corresponding to the enantiomer of the main product, was predicted to be less stable than Model-BiAct-Down-1 by about 4 kcal mol^{-1}. This difference between these two TSs may come from the distinct interaction between the phosphate and the ester group of the dipole. The basic oxygen atom of the ester was slightly removed from the oxygen atom of the phosphate and closer to the positively charged phosphorus atom in Model-BiAct-Down-1, resulting in a favorable ion pair. In contrast, in Model-BiAct-Down-2, the basic oxygen atom of the ester was close to the oxygen atom of the phosphate and far from the positively charged phosphorus atom, resulting in an electronically repulsive interaction. This distinguished ion pair interaction may lead to the high stereoselectivity observed. The Model-MoAct-Down with the single hydrogen-bond activation model was predicted to be less favored by about 6 kcal mol^{-1}.

The hydrogen bond distance between the P=O and H–N is predicted to be 5.68 Å in Model-MoAct-Down-1, which corresponds to the main product **4aaa**. The hydrogen bond between the two phosphoric acids may make the framework of the catalyst too compact to allow access to the relatively bulky substrates, including both maleates and isatin-derived azomethine ylides. In contrast, the electron-rich carbon of the 1,3-dipole attacking the α-carbon of activated maleate, as in Model-MoAct-Down-2, corresponding to the enantiomer of main product, was also predicted to be less favored by approximately 6 kcal mol^{-1}, due to the mismatched polarity and repulsive interaction between the two ester groups of maleate and the dipole. Most likely, the two hydrogen-bond activation model of Model-BiAct-Down has a more flexible framework that enables its active site to open for bulky substrates, such as maleates and isatin-derived azomethine ylides.

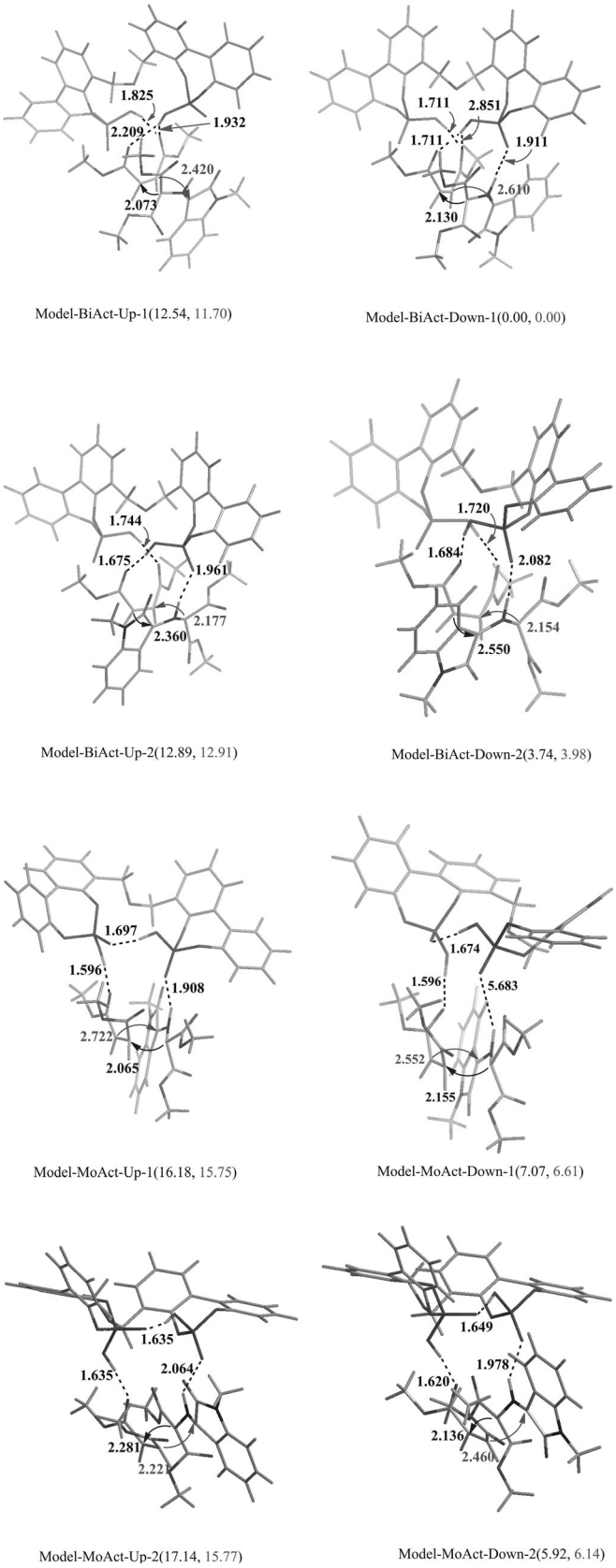


Figure 5. B3LYP/6-31G* optimized transition state structures of the 1,3-dipole cycloaddition reaction of maleate with isatin-derived azomethine ylide and partial crucial bond length parameters (Å). The relative energies in enthalpy (first value) and Gibbs free energy (second value) are shown in parentheses.

For the 1,3-dipolar cycloaddition with acrylate or fumarate as dipolarophile, the TSs should principally adopt Model-MoAct rather than Model-BiAct as shown in Scheme 2, because only one hydrogen bond between the ester group of dipolarophile and the phosphoric acid group of catalyst is formed. The located TS structures are shown in Figure 6. Similar to the case with maleate, the TSs with the Up orientation of the C=O of isatin was predicted to be less stable than that with C=O Down. However, the difference between the two orientations of Up and Down was predicted to be smaller than that in maleate, because the repulsive interaction between the ester group of the dipolarophile and the dipole was reduced both in acrylate, with only one ester group, and fumarate, with the ester group *trans* to the C=O of the isatin. The most stable TS located for acrylate was Model-MoAct-DownA-1 and for fumarate the Model-MoAct-DownF-1 turned out to be most stable, both of which correspond to the main products observed experimentally. In both MoAct-DownA-1 and Model-MoAct-DownF-1, nucleophilic attack of the electron-rich carbon of the 1,3-dipole to the β-carbon of the activated ester group clearly occurs early with a C–C distance of approximately 2.1 Å, compared to the other forming C–C bond distance of approximately 2.7 and 2.6 Å for acrylate and fumarate, respectively. An alternative way to perform the 1,3-dipolar addition was for the electron-rich carbon of the 1,3-dipole to attack the α-carbon of the activated ester group, as shown in TS MoAct-DownA-2 and Model-MoAct-DownF-2, with a forming C–C bond distance of 2.1–2.4 Å; these were evaluated to be less stable than MoAct-DownA-1 by approximately 5 kcal mol^{-1} and then Model-MoAct-DownF-1 by approximately 2 kcal mol^{-1} in Gibbs free energy, respectively. The mismatched polarity should contribute to this higher activation barrier and, because the fumarate seems less mismatched, this results in less difference. The calculated TS structures indicated that this 1,3-dipolar cycloaddition process may still proceed through a concerted pathway, but with one C–C bond formed earlier than the second in the TS to afford the cycloadducts. These TS structures were quite similar to those of other related 1,3-dipolar cycloaddition reactions.[13d] Whereas 2-phenylacrylate was used as the dipolarophile, similar computed results were obtained to those involving acrylate. The located TS structures are shown in Figure 7.

The theoretical studies on the TS models implied that the bisphosphoric acid catalysts with a flexible linkage between the two acid groups make it much easier to recruit bulky substrates and act as a bifunctional catalyst. The dipole and dipolarophile were simultaneously activated by the bisphosphoric acid in this 1,3-dipolar cycloaddition. The differing ion pair interactions between the catalyst and substrates, and either matched or mismatched nucleophilic attack between the activated dipole and dipolarophile resulted in the high stereoselectivity.

Finally, to identify the bioactivity of these new compounds, a number of spiro[pyrrolidin-3, 2′-oxindole] derivatives **4** were selected for in vitro testing of their cytotoxicity against the colon carcinoma cell line SW116.[18] The preliminary bioassay revealed compounds **4raa**, **4uac**, and **4taa** to

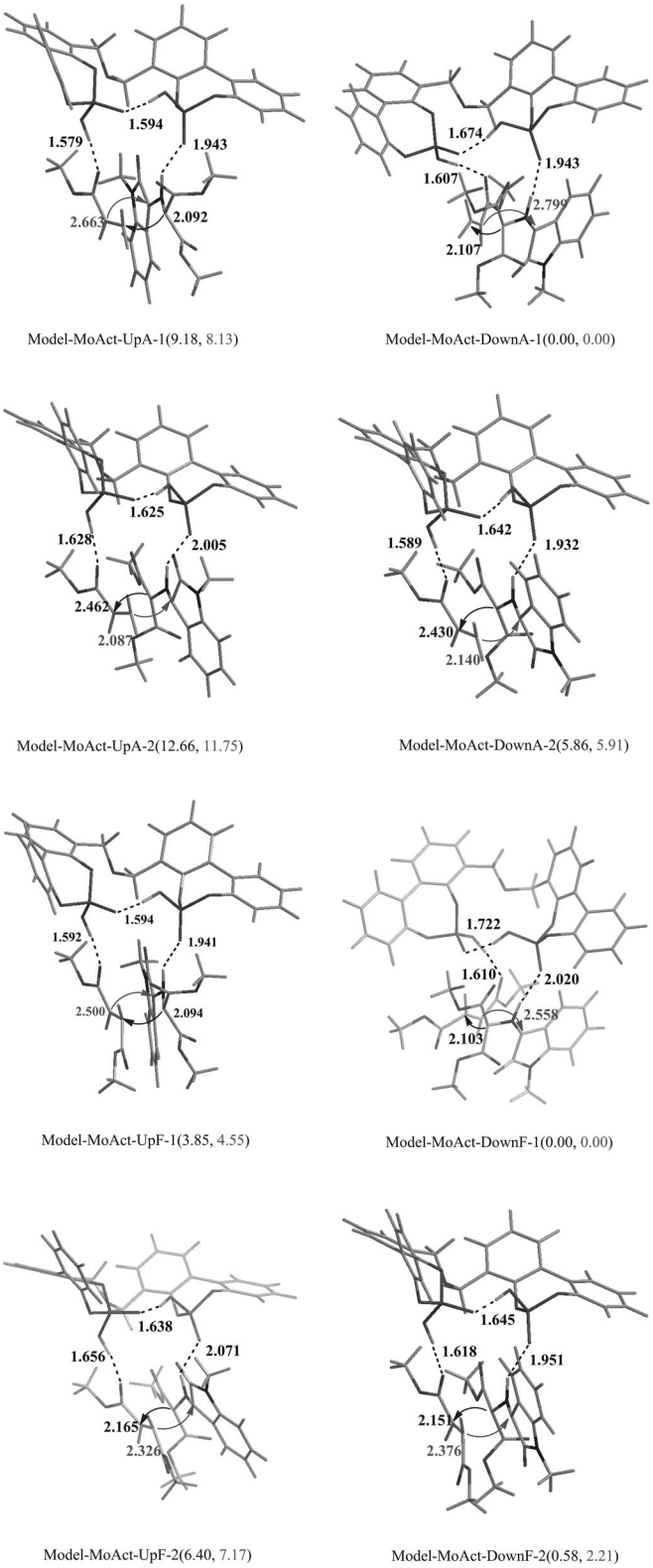


Figure 6. B3LYP/6-31G* optimized transition state structures of isatin-derived azomethine ylide with acrylate or fumarate; partial crucial bond length parameters (Å). The relative energies in enthalpy (first value and Gibbs free energy (second value) are shown in parentheses.

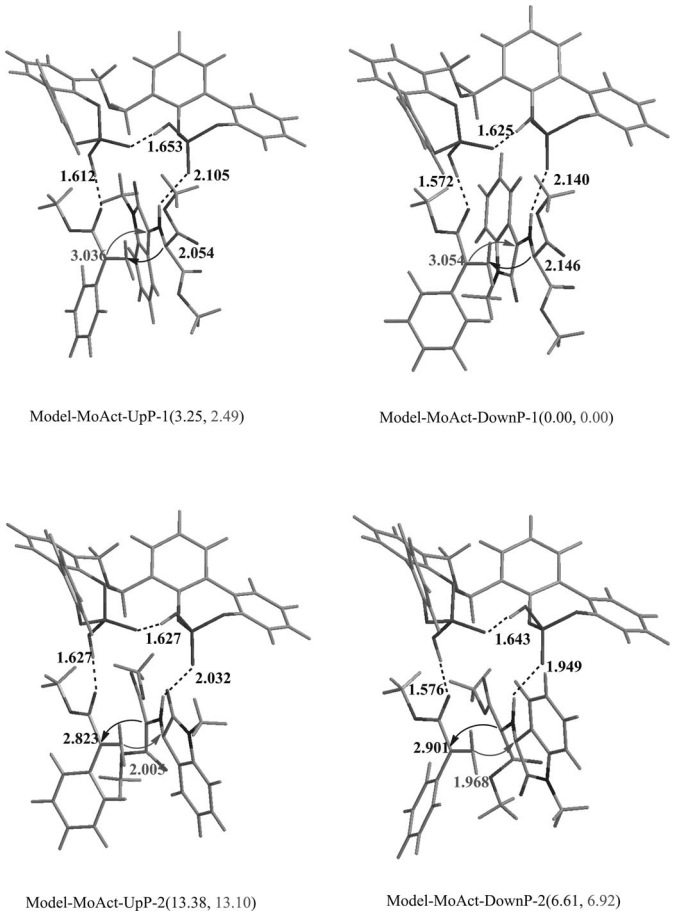


Figure 7. B3LYP/6-31G* optimized transition state structures of isatin-derived azomethine ylide with 2-phenylacrylate; partial crucial bond length parameters (Å). The relative energies in enthalpy (first value) and Gibbs free energy (second value) are shown in parentheses.

have moderate cytotoxicity to SW116 cells, with an inhibition rate of 28.4, 27.6, and 23.6%, respectively, at a concentration of 50 $\mu g\,mL^{-1}$. The results suggest that the spiro[pyrrolidin-3,2′-oxindole] derivatives **4** may have potential in medicinal applications if these compounds are subjected to molecular modulation and further biological studies.

Conclusion

We have established a catalytic, enantioselective route to the biologically important spiro[pyrrolidin-3,2′-oxindole] scaffold with multiple contiguous stereogenic centers including one or two quaternary chiral centers in excellent stereoselectivities (up to >99:1 d.r. and 98% *ee*). Importantly, this transformation represents the first example of a catalytic, asymmetric 1,3-dipolar cycloaddition reaction involving azomethine ylides generated in situ from unsymmetrical cyclic ketones, and provides an unprecedented platform for the preparation of spiro-architectures with concomitant creation of multiple stereogenic centers. The theoretical calculations performed on the transition states of the reaction revealed that the dipole and dipolarophile were simultaneously activated by the bisphosphoric acid in this 1,3-dipolar cycloaddition. The molecular modeling computations on the TS structures suggest that the C=O of isatin should adopt an orientation *trans* to the H–N in the 1,3-dipole to reduce the repulsive interaction between the C=O and phosphoric oxygen atom in the TS. For maleate, the two hydrogen-bond-activation model of Model-BiAct-Down with a more flexible framework is better than the single hydrogen-bond model of Model-MoAct-Down because it allows its active site to open up enough to recruit relatively bulky substrates such as maleates and isatin-derived azomethine ylides. However, when fumarate, acrylate, or 2-phenylacrylate is the dipolarophile, the TSs should principally take the single hydrogen-bond model of Model-MoAct rather than the two hydrogen-bond model of Model-BiAct. The ion pair interaction between the catalyst and substrates, and either matched or mismatched nucleophilic attack between the activated dipole and dipolarophile contributed to the high stereoselectivity of this 1,3-dipolar cycloaddition reaction.

Experimental Section

Typical experimental procedure for the catalytic asymmetric synthesis of spiro[pyrrolidin-3,2′-oxindole] 4aaa: A solution of isatin **1a** (0.12 mmol), amino-ester **2a** (0.1 mmol), catalyst **6** (0.015 mmol), and 3 Å molecular sieves (100 mg) in toluene (0.5 mL) was stirred for 15 min. Dipolarophile **3a** (0.5 mmol) and toluene (0.5 mL) were then added sequentially. After stirring at RT for 36 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resulting solution was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel to afford pure product **4aaa**.

(2′*S*,3′*R*,4′*S*)-5′,5′-Diethyl 3′,4′-dimethyl 1-methyl-2-oxospiro[indoline-3,2′-pyrrolidine]-3′,4′,5′,5′-tetracarboxylate (4aaa): Purified by flash column chromatography (petroleum ether/ethyl acetate = 6:1 then 5:1); reaction time = 36 h; yield: 77%; >99:1 d.r.; white solid; m.p. 111–113 °C; $[\alpha]_D^{20} = -42.4$ (c 0.71, $CHCl_3$); *ee*: 93% determined by HPLC (Daicel Chirapak OD-H; hexane/isopropanol = 80:20; flow rate 1.0 mL min^{-1}; $T = 30$ °C; 254 nm): $t_R = 11.306$ (major), 13.123 min (minor); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.61$ (d, $J = 7.6$ Hz, 1H; ArH), 7.33–7.27 (m, 1H; ArH), 7.07–7.00 (m, 1H; ArH), 6.77 (d, $J = 7.8$ Hz, 1H; ArH), 4.66 (d, $J = 7.9$ Hz, 1H; CH), 4.42–4.24 (m, 4H; $2 \times CH_2$), 3.96–3.90 (m, 2H; CH and NH), 3.79 (s, 3H; CH_3), 3.23 (s, 3H; CH_3), 3.16 (s, 3H; CH_3), 1.31 (t, $J = 7.1$ Hz, 3H; CH_3), 1.28 ppm (t, $J = 7.1$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 178.1$, 171.5, 169.3, 168.5, 167.9, 144.2, 130.1, 127.2, 125.6, 123.1, 107.8, 76.3, 69.5, 62.8, 62.6, 54.8, 52.2, 51.7, 51.1, 26.4, 14.0 ppm; IR (KBr): $\tilde{\nu} = 3346$, 2986, 2952, 1740, 1612, 1473, 1436, 1369, 1217, 1026, 756 cm^{-1}; FTMS (ESI): *m*/*z* calcd. for $C_{22}H_{26}N_2O_9 + H^+$: 463.1711 [*M* + H]; found: 463.1711.

Typical experimental procedure for the catalytic asymmetric synthesis of spiro[pyrrolidin-3,2′-oxindole] 4bae with two contiguous quaternary chiral centers: A solution of isatin **1b** (0.12 mmol), amino ester **2a** (0.1 mmol), catalyst **6** (0.025 mmol), and 3 Å molecular sieves (100 mg) in a solvent mixture of toluene and $CHCl_3$ (1:1 *v*/*v*, 0.5 mL) was stirred for 15 min. The dipolarophile **3e** (0.5 mmol) and further solvent mixture of toluene and $CHCl_3$ (1:1 *v*/*v*, 0.5 mL) were added sequentially. After stirring at RT for 72 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resulting solution was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel to afford pure product **4bae**.

(2′*R*,3′*S*)-5′,5′-Diethyl 3′-methyl 1-benzyl-2-oxo-3′-phenylspiro[indoline-3,2′-pyrrolidine]-3′,5′,5′-tricarboxylate (4bae): Purified by flash column chromatography (petroleum ether/ethyl acetate = 6:1 then 5:1); reaction time = 72 h; yield: 51%; >99:1 d.r.; white solid; m.p. 134–135 °C; $[\alpha]_D^{20}$ = 2.4 (c 0.572, $CHCl_3$); *ee*: 93% determined by HPLC (Daicel Chirapak OD-H; hexane/isopropanol = 90:10; flow rate 1.0 mL min^{-1}; T = 30 °C; 254 nm): t_R = 9.391 (minor), 11.311 min (major); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39 (dd, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H; ArH), 7.27 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H; ArH), 7.22–7.14 (m, 4H; ArH), 7.10–7.04 (m, 3H; ArH), 7.01–6.95 (m, 2H; ArH), 6.87–6.79 (m, 2H; ArH), 6.68 (d, J = 7.7 Hz, 1H; ArH), 4.86 (d, J = 15.5 Hz, 1H; CH), 4.40–4.33 (m, 3H; CH and CH_2), 4.33–4.27 (m, 2H; CH_2), 4.20 (d, J = 15.5 Hz, 1H; CH), 3.95 (s, 1H; NH), 3.61 (s, 3H; CH_3), 3.51 (d, J = 13.7 Hz, 1H; CH), 1.36 (t, J = 7.1 Hz, 3H; CH_3), 1.29 ppm (t, J = 7.1 Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.9, 172.8, 170.8, 170.4, 144.4, 130.3, 128.5, 128.2, 127.7, 127.6, 127.5, 127.4, 125.7, 122.6, 109.3, 74.3, 71.9, 62.7, 62.5, 62.4, 52.4, 44.0, 40.2, 14.2, 14.1 ppm; IR (KBr): $\tilde{\nu}$ = 3546, 3336, 2982, 2926, 1736, 1610, 1467, 1364, 1268, 1232, 1097, 755, 699 cm^{-1}; FTMS (ESI): *m/z* calcd for $C_{32}H_{32}N_2O_7+H^+$: 557.2282 [M+H]; found: 557.2282.

Acknowledgements

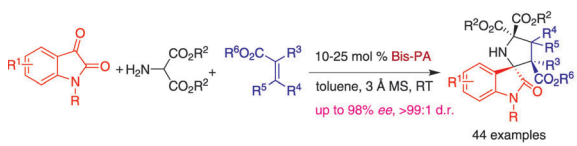
We are grateful for financial support from MOST (973 project 2009CB82530), Ministry of Education and NSFC (20732006, 21002083, 21072181).

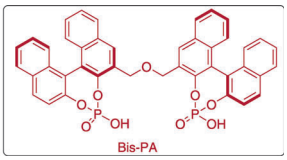
[1] A. S. Girgis, *Eur. J. Med. Chem.* **2009**, *44*, 91–100.
[2] R. Murugan, S. Anbazhagan, S. Sriman Narayanan, *Eur. J. Med. Chem.* **2009**, *44*, 3272–3279.
[3] a) S. U. Maheswari, K. Balamurugan, S. Perumal, P. Yogeeswari, D. Sriram, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7278–7282; b) R. Ranjith Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem.* **2009**, *44*, 3821–3829; c) R. R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, *J. Med. Chem.* **2008**, *51*, 5731–5735; d) R. S. Kumar, S. M. Rajesh, S. Perumal, D. Banerjee, P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem.* **2010**, *45*, 411–422.
[4] a) A. A. Raj, R. Raghunathan, M. R. SrideviKumari, N. Raman, *Bioorg. Med. Chem.* **2003**, *11*, 407–419; b) G. Periyasami, R. Raghunathan, G. Surendiran, N. Mathivanan, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2342–2345; c) A. Thangamani, *Eur. J. Med. Chem.* **2010**, *45*, 6120–6126.
[5] a) P. Prasanna, K. Balamurugan, S. Perumal, P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem.* **2010**, *45*, 5653–5661; b) S. V. Karthikeyan, B. D. Bala, V. P. A. Raja, S. Perumal, P. Yogeeswari, D. Sriram, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 350–353.
[6] M. A. Ali, R. Ismail, T. S. Choon, Y. K. Yoon, A. C. Wei, S. Pandian, R. S. Kumar, H. Osman, E. Manogaran, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7064–7066.
[7] For some transformations from enantiopure starting materials, see: P. Shanmugam, B. Viswambharan, K. Selvakumar, S. Madhavan, *Tetrahedron Lett.* **2008**, *49*, 2611–2615.
[8] For reviews on catalytic asymmetric synthesis of other spiro-oxindoles, see: a) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407 and references cited therein; For selected examples on catalytic asymmetric synthesis of other spiro-oxindoles, see: b) L. E. Overman, M. D. Rosen, *Angew. Chem.* **2000**, *112*, 4768–4771; *Angew. Chem. Int. Ed.* **2000**, *39*, 4596–4599; c) B. M. Trost, M. K. Brennan, *Org. Lett.* **2006**, *8*, 2027–2030; d) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397; e) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758–8759; f) P. Galzerano, G. Bencivenni, F. Pesciaioli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2009**, *15*, 7846–7849; g) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schuermann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735–740; h) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328–15333; i) L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2010**, *46*, 8064–8066; j) W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2011**, *13*, 2472–2475; k) Y.-K. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212–15218; l) L.-T. Shen, P.-L. Shao, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 1943–1948; m) J. Peng, X. Huang, L. Jiang, H.-L. Cui, Y.-C. Chen, *Org. Lett.* **2011**, *13*, 4584–4587; n) K. Mori, T. Yamauchi, J. Maddaluno, K. Nakano, Y. Ichikawa, H. Kotsuki, *Synlett* **2011**, 2080–2084; o) Y.-M. Li, X. Li, F.-Z. Peng, Z.-Q. Li, S.-T. Wu, Z.-W. Sun, H.-B. Zhang, Z.-H. Shao, *Org. Lett.* **2011**, *13*, 6200–6203.
[9] For early reports, see: a) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401; b) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 4410–4412; *Angew. Chem. Int. Ed.* **2002**, *41*, 4236–4238; For reviews, see: c) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428–6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272–6276; d) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887–2902; e) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784–6794 and references cited therein.
[10] a) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260–5262; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168–5170; b) I. Ibrahem, R. Rios, J. Vesely, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 6252–6257; c) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691–694; d) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873–9877.
[11] a) S. Cabrera, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394–16395; b) S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364–5365; c) B. Martín-Matute, S. I. Pereira, E. Pena-Cabrera, J. Adrio, A. M. S. Silva, J. C. Carretero, *Adv. Synth. Catal.* **2007**, *349*, 1714–1724; d) S. Cabrera, R. G. Arrayas, B. Martin-Matute, F. P. Cossio, J. C. Carretero, *Tetrahedron* **2007**, *63*, 6587–6602; e) T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13321–13322; f) C.-J. Wang, G. Liang, Z.-Y. Xue, F. Gao, *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251; g) S. Kobayashi, T. Tsubogo, S. Saito, Y. Yamashita, *Org. Lett.* **2008**, *10*, 807–809; h) R. Robles-Machìn, M. Gonzalez-Esguevillas, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2010**, *75*, 233–236.
[12] For reviews, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; c) M. Terada, *Chem. Commun.* **2008**, 4097–4112; d) M. Terada, *Synthesis* **2010**, 1929–1982.
[13] a) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653; b) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825; c) J. Yu, L. He, X.-H. Chen, J. Song, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4946–4949; d) L. He, X.-H. Chen, D.-N. Wang, S.-W. Luo, W.-Q. Zhang, J. Yu, L. Ren, L.-Z. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 13504–13518; e) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156–1171.
[14] CCDC-845939 (**4aaa**), CCDC-848672 (**4bac**), and CCDC-845940 (**4bae**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.
[15] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652..
[16] P. M. W. Gill, B. G. Johnson, J. A. Pople, M. J. Frisch, *Chem. Phys. Lett.* **1992**, *197*, 499–505.
[17] Gaussian 03, Revision D.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J.

Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

[18] Details of the procedure used to bioscreen **4** is provided in the Supporting Information.

Received: February 2, 2012
Published online: ■■ ▮▮, 2012





The organocatalytic approach: The first catalytic asymmetric construction of a spiro[pyrrolidin-3,2′-oxindole] scaffold with contiguous quaternary stereogenic centers in excellent stereoselectivities has been established (see scheme). This protocol represents the first example of catalytic asymmetric 1,3-dipolar cycloadditions involving azomethine ylides generated in situ from unsymmetrical cyclic ketones.

Asymmetric Synthesis