ChemPubSoc Europe

DOI: 10.1002/chem.201304187

CHEMISTRY
A European Journal
Full Paper

Asymmetric Synthesis

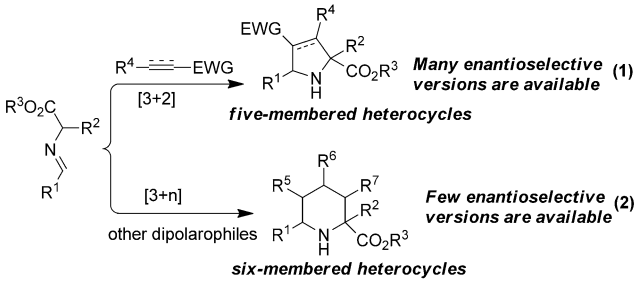
Catalytic Asymmetric Formal [3+3] Cycloaddition of an Azomethine Ylide with 3-Indolylmethanol: Enantioselective Construction of a Six-Membered Piperidine Framework

Feng Shi,* Ren-Yi Zhu, Wei Dai, Cong-Shuai Wang, and Shu-Jiang Tu*[a]

Abstract: A catalytic asymmetric formal [3+3] cycloaddition of 3-indolylmethanol and an in situ-generated azomethine ylide has been established to construct a chiral six-membered piperidine framework with two stereogenic centers. This approach not only represents the first enantioselective cycloaddition of isatin-derived 3-indolylmethanol, but also has realized an unusual enantioselective formal [3+3] cycloaddition of azomethine ylide rather than its common [3+2] cycloadditions. Besides, this protocol combines the merits of a multicomponent reaction and organocatalysis, which efficiently assembles a variety of isatin-derived 3-indolylmethanols, aldehydes, and amino esters into structurally diverse spiro[indoline-3,4′-pyridoindoles] with one all-carbon quaternary stereogenic center in high yields and excellent enantioselectivities (up to 93% yield, >99% enantiomeric excess (*ee*)). Although the diastereoselectivity of the reaction is generally moderate, most of the diastereomers can be separated by using column chromatography followed by preparative TLC.

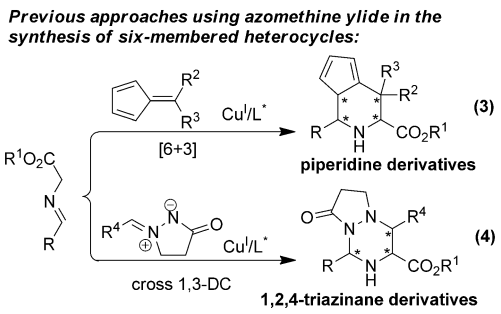
Introduction

The enantioselective 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylides to dipolarophiles has proven to be a powerful tool to synthesize chiral nitrogenous heterocycles.[1] As a result, catalytic asymmetric azomethine ylide-involved 1,3-DCs have achieved elegant developments.[2,3] However, in most of these cycloadditions, electron-deficient olefins[2] or alkynes[3] were employed as dipolarophiles to react with azomethine ylides through a [3+2] reaction mode, which always delivered five-membered heterocycles such as pyrrolidines [Eq. (1)]. In sharp contrast, the enantioselective construction of six-membered heterocycles through azomethine ylide-involved cycloadditions has met with little success [Eq. (2)].



Recently, the two groups of Waldmann[4] and Wang[5] independently discovered the catalytic asymmetric [6+3] cycloadditions of azomethine ylides with fulvenes to provide stereoselective piperidine derivatives [Eq. (3)]. During the preparation of this manuscript, Wang, Guo et al., also reported a chiral Cu^{I}-complex catalyzed cross-1,3-DC between pyrazolidinium ylides and azomethine ylides to give stereoselective 1,2,4-triazinane frameworks [Eq. (4)].[6] In spite of these creative works, the catalytic asymmetric azomethine ylide-involved cycloadditions leading to enantioenriched six-membered heterocyclic architectures are still underdeveloped and thus highly desirable because of the importance of chiral six-membered heterocycles.

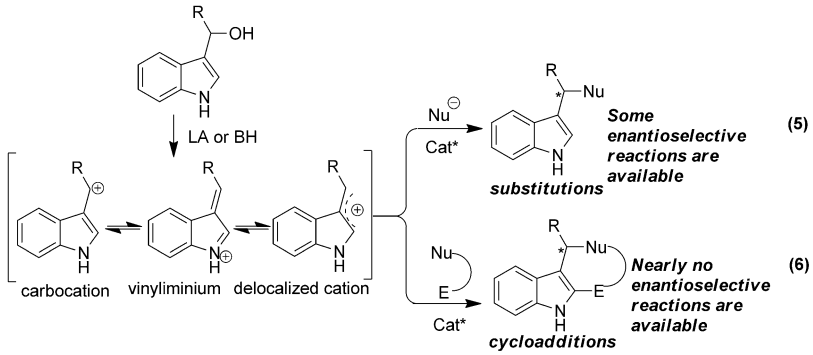
3-Indolylmethanols have recently been recognized as a type of active reaction components for their characteristic of being easily transformed into vinyliminium or carbocation intermediates in the presence of a Lewis or Brønsted acid (LA or BH),[7] which are resonance structures of a delocalized cation. Howev-



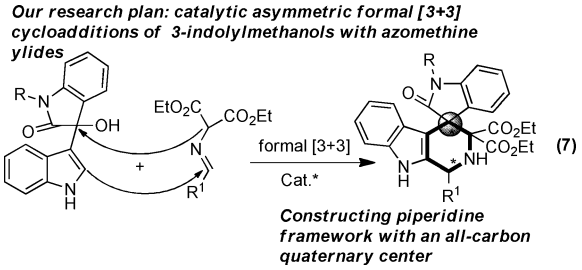
[a] Prof. Dr. F. Shi, R.-Y. Zhu, W. Dai, C.-S. Wang, Prof. S.-J. Tu
School of Chemistry and Chemical Engineering
Jiangsu Normal University
Xuzhou, 221116 (China)
Fax: (+86) 516-83500065
E-mail: fshi@jsnu.edu.cn
laotu@jsnu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304187.

er, previous reports were focused on nucleophilic substitutions of 3-indolylmethanols [Eq. (5)],[8] and hardly any cycloadditions of 3-indolylmethanols have been found in the literature, not to mention their enantioselective transformations [Eq. (6)].[9] Thus, the 3-indolylmethanol-involved cycloaddition, in particular, its enantioselective transformation has become a formidable challenge.



Considering this challenge and the great demand for azomethine ylide-involved cycloadditions leading to six-membered heterocycles, we wondered whether isatin-derived 3-indolylmethanols could be employed as dipolarophiles to undergo catalytic asymmetric formal [3+3] cycloadditions with azomethine ylides in the presence of a chiral catalyst, thereby affording stereoselective spiro[indoline-3,4′-pyridoindoles], in which a six-membered piperidine framework would be constructed with one all-carbon quaternary stereogenic center [Eq. (7)].



On the other hand, our targeted formal [3+3] cycloaddition products, that is, spiro[indoline-3,4′-pyridoindoles], contain two scaffolds of tetrahydropyridoindole and spiro[indoline-piperidine], which exist in a variety of natural products[10] and pharmaceuticals[11] with significant bioactivities such as being MDM2-p53 inhibitors[11a] and sodium channel blockers[11b] (Figure 1), thereby holding great synthetic importance.

We have recently realized a series of chiral phosphoric acid-catalyzed cycloadditions[12] for the synthesis of enantioenriched heterocycles.[13] Inspired by this success and the fact that there have been few reports either on enantioselective cycloadditions of 3-indolylmethanols or on [3+3] cycloadditions of azomethine ylides, we envisioned that isatin-derived 3-indolylmethanols and azomethine ylides could be simultaneously activated by chiral phosphoric acid to undergo enantioselective formal [3+3] cycloadditions, leading to the formation of six-membered piperidine framework and the production of the spiro[indoline-3,4′-pyridoindole] skeleton with multiple stereogenic centers.

In this work, we present the first catalytic asymmetric formal [3+3] cycloadditions of isatin-derived 3-indolylmethanols and in situ-generated azomethine ylide, which directly assembles isatin-derived 3-indolylmethanols, aldehydes, and amino esters into chiral spiro[indoline-3,4′-pyridoindoles] with two stereogenic centers including one all-carbon quaternary center in high yields and excellent enantioselectivities (up to 93% yield, >99% enantiomeric excess (*ee*)).

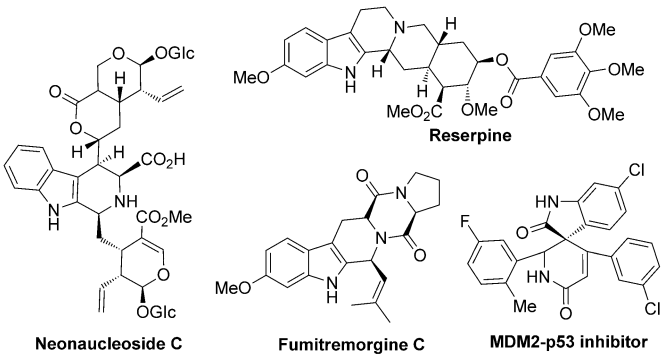


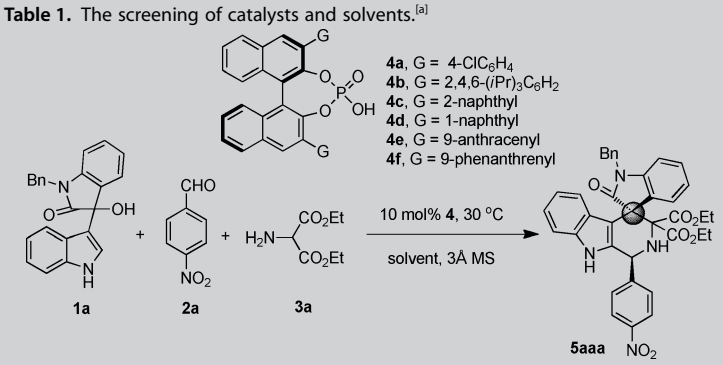
Figure 1. Selected natural products and bioactive compounds containing the core structures of spiro[indoline-3,4′-pyridoindoles]

Results and Discussion

The initial attempt to validate our hypothesis commenced with a three-component reaction of *N*-benzyl isatin-derived 3-indolylmethanol **1a**, 4-nitrobenzaldehyde **2a**, and diethyl 2-aminomalonate **3a** in the presence of 10 mol% of chiral phosphoric acid (CPA) **4a** in toluene at 30 °C (Table 1, entry 1), which smoothly proceeded through the designed formal [3+3] reaction mode although the yield and the stereoselectivity is moderate.

The screening of catalysts revealed that CPA **4f** with the bulky 9-phenanthrenyl group at the 3,3′-positions of the BINOL backbone exhibited higher catalytic activity than the others with regard to enantioselective control (Table 1, entry 6 vs. 1–5), delivering chiral spiro[indoline-3,4′-pyridoindole] **5aaa** with quaternary stereogenic center in 85% *ee*. The subsequent evaluation on solvents in the presence of CPA **4f** disclosed that chlorine-containing alkanes were superior to toluene in terms of enantioselectivity and reactivity (Table 1, entries 7–10 vs. entry 6). Among them, 1,2-dichloroethane (DCE) delivered the

Table 1. The screening of catalysts and solvents.[a]



Entry	4	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	toluene	57 (29)[e]	50:50	56(41)[f]
2	**4b**	toluene	74 (37)[e]	50:50	68(29)[f]
3	**4c**	toluene	58 (39)[e]	67:33	45
4	**4d**	toluene	85 (58)[e]	68:32	80
5	**4e**	toluene	79 (62)[e]	78:22	69
6	**4f**	toluene	69 (53)[e]	77:33	85
7	**4f**	CH_2Cl_2	90 (57)[e]	63:37	97
8	**4f**	$CHCl_3$	83 (46)[e]	56:44	83
9	**4f**	CCl_4	70 (45)[e]	64:36	87
10	**4f**	DCE	85 (54)[e]	63:37	98
11[g]	**4f**	THF	–	–	–
12[g]	**4f**	CH_3CN	–	–	–

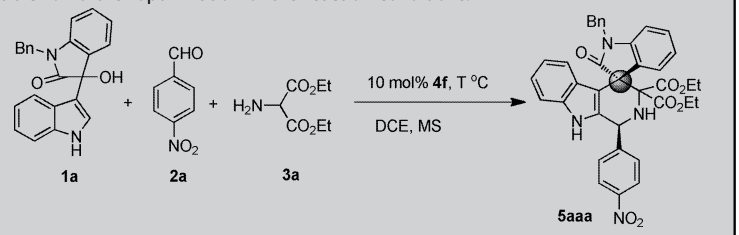
[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in solvent (1.5 mL) with 3 Å MS (100 mg) for 24 h, and the ratio of **1a**/**2a**/**3a** was 1.5:1.2:1. [b] Isolated total yields of two diastereomers. [c] The diastereomeric ratio (d.r.) was determined by HPLC. [d] The *ee* value refers to the major diastereomer **5aaa** and was determined by HPLC. [e] The yield in parentheses refers to that of the major diastereomer **5aaa**. [f] The *ee* value in parentheses refers to another diastereomer **5aaa**′. [g] No desired reaction occurred.

product **5aaa** in high yield of 85% and excellent enantioselectivity of 98% *ee*, albeit with a moderate diastereomeric ratio (d.r.) of 63:37 (Table 1, entry 10). However, using tetrahydrofuran (THF) and acetonitrile as the reaction media failed to facilitate the formal [3+3] cycloaddition, which just gave the azomethine ylide generated from the condensation of **2a** and **3a** (Table 1, entries 11 and 12). Thus, DCE was chosen as the solvent of choice for further investigation.

The further optimization of reaction conditions was concentrated on changing other reaction parameters such as additives, temperature, and the ratio of the reagents to improve the diastereoselectivity of the reaction without the sacrifice of the enantioselectivity and the yield (Table 2). The screening of the molecular sieves (MS) found that no other MS was better than 3 Å MS (Table 2, entries 2 and 3 vs. entry 1). Raising or lowering the reaction temperature could hardly improve the diastereoselectivity (Table 2, entries 4–6 vs. entry 1), and the yield was decreased dramatically at 0 °C (entry 6). At last, the ratio of the reagents was carefully tuned, which included a change in the stoichiometry of both 3-indolylmethanol and the in situ-generated azomethine ylide (Table 2, entries 7–11). However, increasing or decreasing the stoichiometry of 3-indolylmethanol **1a** had no obvious effect on the reaction (Table 2, entries 7–9), and using an excess of **2a** and **3a** at the same time did not benefit the reaction with regard to stereoselectivity (entries 10 and 11). So, the reaction conditions as shown in Table 2, entry 1 were finally selected as the most suitable one for its performance in delivering high yields and excellent enantioselectivity.

To provide a variety of chiral spiro[indoline-3,4′-pyridoindoles] with structural diversity, we then carried out the study on the substrate scope of the formal [3+3] cycloaddition. First, the applicability of the reaction for various N-substituted isatin-derived 3-indolylmethanols **1** was examined. As shown in Table 3, this protocol is amenable to a series of *N*-benzyl isatin-derived 3-indolylmethanols **1a**–**h** with electron-donating or -withdrawing substituents linked to the benzyl group (Table 3, entries 1–8), offering the desired spiro-products in high yields (67–93%) and with excellent enantioselectivities (97–>99% *ee*). Generally speaking, 3-indolylmethanols **1** with electronically rich substituents on the benzyl moiety exhibited better reactivity and enantioselectivity than those with electronically poor substituents (Table 3, entries 2–5 vs. 6–8), and **1c** with a *para*-methyl (*p*Me) group delivered the highest enantioselectivity of >99% *ee* (entry 3). It seemed that the position of the methyl group exerted some effect on the enantiose-

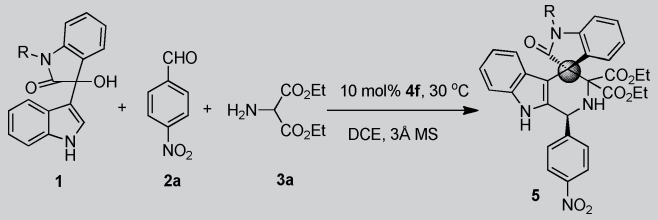
Table 2. Further optimization of the reaction conditions.[a]



Entry	**1a**/**2a**/**3a**	MS	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	1.5:1.2:1	3 Å	30	85 (54)[e]	63:37	98
2	1.5:1.2:1	4 Å	30	68 (41)[e]	60:40	97
3	1.5:1.2:1	5 Å	30	29 (18)[e]	62:38	92
4	1.5:1.2:1	3 Å	45	79 (47)[e]	60:40	97
5	1.5:1.2:1	3 Å	15	70 (44)[e]	63:37	97
6	1.5:1.2:1	3 Å	0	27 (17)[e]	64:36	97
7	2:1.2:1	3 Å	30	88 (51)[e]	58:42	98
8	3:1.2:1	3 Å	30	89 (52)[e]	58:42	96
9	1:1.2:1	3 Å	30	76 (48)[e]	63:37	97
10	1:2.4:2	3 Å	30	94 (56)[e]	60:40	97
11	1:3.6:3	3 Å	30	83 (48)[e]	58:42	97

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale catalyzed by 10 mol% **4f** in DCE (1.5 mL) with MS (100 mg) for 24 h. [b] Isolated total yields of two diastereomers. [c] Determined by HPLC. [d] The *ee* value refers to the major diastereomer **5aaa** and was determined by HPLC. [e] The yield in parentheses refers to that of the major diastereomer **5aaa**.

Table 3. The applicability of the reaction for various N-substituted isatin-derived 3-indolylmethanols **1**.[a]



Entry	5	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**5aaa**	$C_6H_5CH_2$ (**1a**)	85 (54)[e]	63:37	98
2	**5baa**	*p*-*t*Bu$C_6H_4CH_2$ (**1b**)	93 (60)[e]	64:36	98
3	**5caa**	*p*-Me$C_6H_4CH_2$ (**1c**)	79 (49)[e]	62:38	>99
4	**5daa**	*m*-Me$C_6H_4CH_2$ (**1d**)	76 (46)[e]	60:40	98
5	**5eaa**	*o*-Me$C_6H_4CH_2$ (**1e**)	80 (50)[e]	62:38	98
6	**5faa**	*p*-F$C_6H_4CH_2$ (**1f**)	70 (43)[e]	62:38	97
7	**5gaa**	*p*-Br$C_6H_4CH_2$ (**1g**)	67 (40)[e]	60:40	97
8	**5haa**	*m*-Cl$C_6H_4CH_2$ (**1h**)	81 (50)[e]	62:38	98
9	**5iaa**	Ph (**1i**)	58 (34)[e]	58:42	89
10	**5jaa**	Me (**1j**)	83 (42)[e]	50:50	95 (54[f])

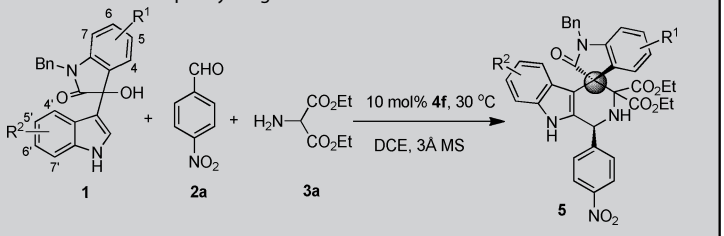
[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale catalyzed by 10 mol% **4f** in DCE (1.5 mL) with 3 Å MS (100 mg) for 24 h, and the ratio of **1**/**2a**/**3a** was 1.5:1.2:1. [b] Isolated total yields of two diastereomers. [c] Determined by ^{1}H NMR spectroscopy except for **5aaa**. [d] The *ee* value refers to the major diastereomer **5** and was determined by HPLC. [e] The yield in parentheses refers to that of the major diastereomer **5**. [f] The *ee* value in parentheses refers to another diastereomer **5′**.

lectivity, because *p*Me-substituted 3-indolylmethanols **1c** offered a higher *ee* value than its *ortho*- and *meta*-methyl-substituted counterparts (Table 3, entry 3 vs. 4 and 5). In addition, *N*-aryl- and *N*-alkyl isatin-derived 3-indolylmethanols as exemplified by **1i** and **1j** could also be utilized to the cycloaddition to generate the corresponding spiro-products, but with decreased reactivity and stereoselectivity (Table 3, entries 9 and 10).

Next, we investigated the generality of the reaction for *N*-benzyl isatin-derived 3-indolylmethanols **1** bearing different substituents at the phenyl rings of both isatin and indole skeletons. As illustrated in Table 4, this approach is applicable to a wide scope of 3-indolylmethanols with various substituents at different position of the two phenyl rings, offering structurally diverse spiro[indoline-3,4′-pyridoindoles] in moderate to high yields of 42–90% and with good to excellent enantioselectivities of 79 to >99% *ee*. Basically, the position of the substituents had an obvious influence on the stereoselectivity of the reaction. As for the isatin moiety, it was found that C5-substituted 3-indolylmethanols were inferior to C6- and C7-substituted ones in stereoselective control (Table 4, entries 6 and 7 vs. 1–5), and C7-substituted 3-indolylmethanols were superior to C6-substituted ones in terms of diastereoselectivity (entries 1–3 vs. 4–5). Among them, 7-methyl 3-indolylmethanol **1m** offered the spiro-product **5maa** in perfect enantioselectivity of >99% (Table 4, entry 3). However, in the case of the indole core, the position of the substituents exerted an opposite effect on the stereoselectivity. Namely, C5′-substituted 3-indolylmethanols were superior to C6′- and C7′-substituted ones with regard to stereoselectivity (Table 4, entries 10 and 11 vs. 8 and 9), whereas C6′-substituted 3-indolylmethanol delivered higher enantioselectivity than the C7′-substituted one (Table 4, entry 9 vs. 8).

Finally, the substrate scope with respect to aromatic aldehydes **2** was explored by the reactions with 3-indolylmethanol **1a** and amino ester **3a** under the optimized reaction conditions. As indicated in Table 5, various aromatic aldehydes **2** substituted with electron-poor, -neutral, or -rich groups were employed to the reaction, which formed a variety of azomethine ylides in situ to participate in the desired formal [3+3] cycloadditions, giving chiral spiro[indoline-3,4′-pyridoindoles] **5** with structural diversity in high yields (73–89%). However, it is evident that the electronic nature of aldehydes imposed some impact on the stereoselectivity of the reaction. Indeed, aromatic aldehydes substituted with electron-withdrawing groups delivered higher enantioselectivities (80 to >99% *ee*) than those substituted with electron-donating or neutral groups, whereas the latter offered better diastereoselectivities (90:10 to

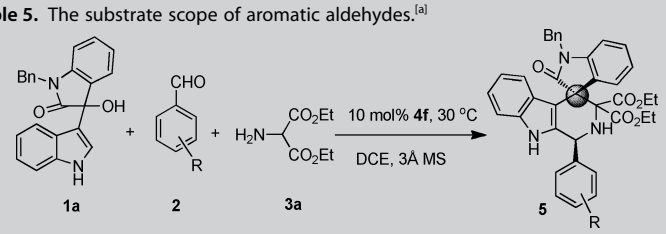
Table 4. The generality of the reaction for various 3-indolylmethanols **1** bearing different substituents at the phenyl rings.[a]



Entry	5	R^1/R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**5kaa**	7-F/H (**1k**)	79 (56)[e]	71:29	97
2	**5laa**	7-Br/H (**1l**)	42 (31)[e]	74:26	96
3	**5maa**	7-CH_3/H (**1m**)	71 (48)[e]	67:33	>99
4	**5naa**	6-Cl/H (**1n**)	54 (33)[e]	62:38	98
5	**5oaa**	6-Br/H (**1o**)	90 (59)[e]	66:34	98
6	**5paa**	5-Cl/H (**1p**)	42 (22)[e]	53:47	94
7	**5qaa**	5-CH_3/H (**1q**)	56 (30)[e]	53:47	93
8	**5raa**	6-Br/7′-CH_3 (**1r**)	66 (22)[e]	33:67	79 (35)[f]
9	**5saa**	6-Br/6′-CH_3 (**1s**)	77 (44)[e]	57:43	87
10	**5taa**	6-Br/5′-CH_3 (**1t**)	66 (40)[e]	60:40	94
11	**5uaa**	6-Br/5′-F (**1u**)	77 (28)[e]	37:63	96 (68)[f]

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale catalyzed by 10 mol% **4f** in DCE (1.5 mL) with 3 Å MS (100 mg) for 24 h, and the ratio of **1**/**2a**/**3a** was 1.5:1.2:1. [b] Isolated total yields of two diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value refers to the major diastereomer **5** and was determined by HPLC. [e] The yield in parentheses refers to that of the major diastereomer **5**. [f] The *ee* value in parentheses refers to another diastereomer **5′**.

Table 5. The substrate scope of aromatic aldehydes.[a]



Entry	5	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**5aaa**	4-NO_2 (**3a**)	85 (54)[e]	63:37	98
2	**5aba**	3-NO_2 (**3b**)	82 (43)[e]	52:48	80 (31)[f]
3	**5aca**	4-CN (**3c**)	73 (40)[e]	55:45	96
4	**5ada**	3,4-Cl_2 (**3d**)	80 (38)[e]	48:52	>99 (75)[f]
5	**5aea**	4-Cl (**3e**)	89 (51)[e]	57:43	94 (83)[f]
6[g]	**5afa**	H (**3f**)	86 (77)[e]	90:10	81
7[g]	**5aga**	4-CH_3O (**3g**)	88 (88)[e]	>95:5	68

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale catalyzed by 10 mol% **4f** in DCE (1.5 mL) with 3 Å MS (100 mg) for 24 h, and the ratio of **1a**/**2**/**3a** was 1.5:1.2:1. [b] Isolated total yields of two diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value refers to the major diastereomers **5** and was determined by HPLC. [e] The yield in parentheses refers to that of the major diastereomer **5**. [f] The *ee* value in parentheses refers to another diastereomer **5′**. [g] The reaction was catalyzed by 10 mol% **4e** in $CHCl_3$ (1.5 mL).

>99:1 d.r.) than the former (Table 5, entries 1–5 vs. 6 and 7). Besides, the position of the substituents also had an effect on the stereoselectivity, since *p*-nitrobenzaldehyde **3a** was far superior to its *meta*-substituted counterpart **3b** in stereoselective control (Table 5, entry 1 vs. 2). It should be mentioned that most of the diastereomers generated from the formal [3+3] cycloadditions can be separated by using column chromatography followed by preparative TLC (see the Supporting Information). However, compounds **5aba** and **5aea** were obtained as inseparable mixtures of two diastereomers, which can hardly be separated even by preparative TLC.

As illustrated in Figure 2, the absolute configuration of spiro[indoline-3,4′-pyridoindole] **5ada** was unambiguously determined to be (1′*S*, 3*S*) by X-ray analysis on its single crystal in >99% *ee*.[14] The configurations of other spiro[indoline-3,4′-pyridoindoles] **5** were assigned by analogy. Besides, to gain some insight into the reaction pathway related to stereoselective control, we also tested the absolute configuration of another diastereomer **5ada′** to be (1′*S*, 3*R*) by the same method (Figure 2).[14]

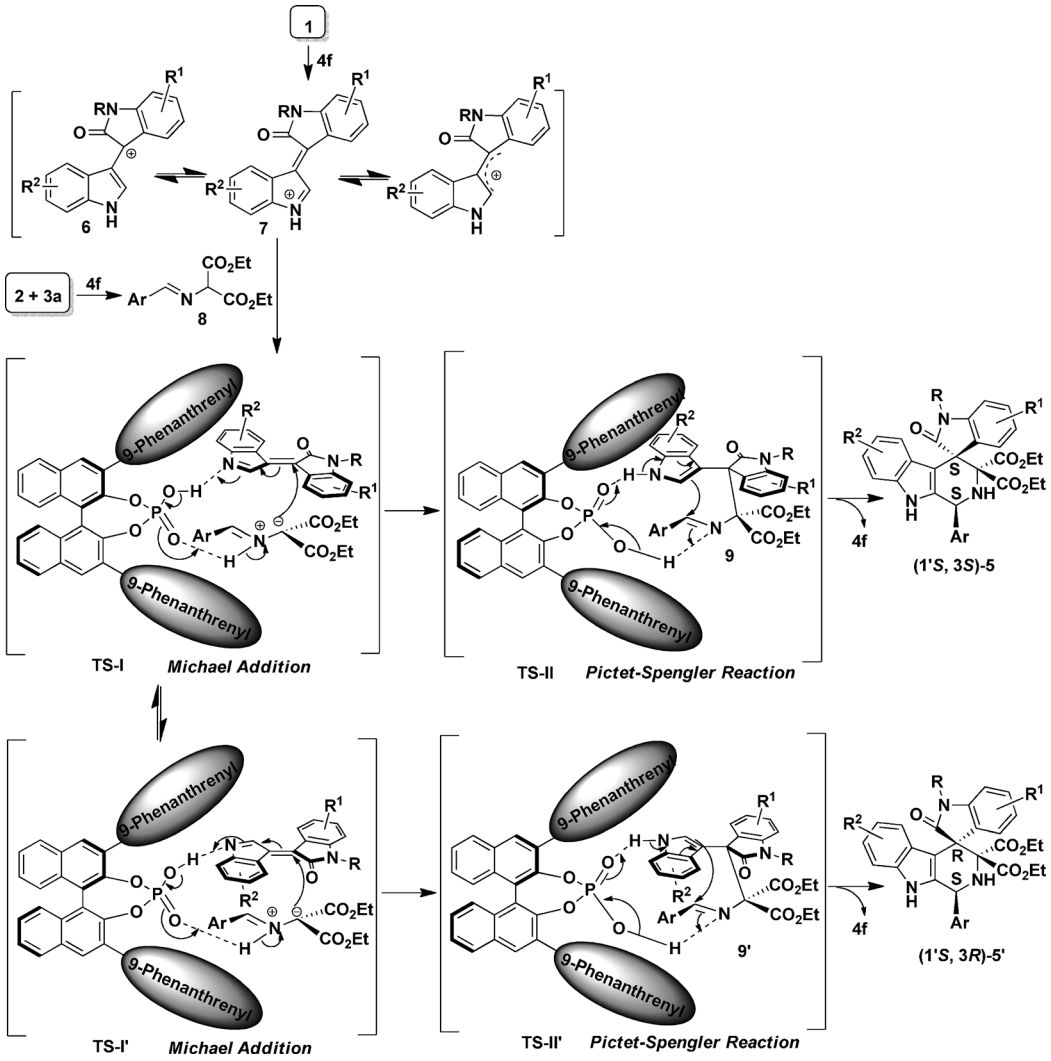
On the basis of our experimental results and previous reports on catalytic asymmetric 3-indolylmethanol-involved reactions[8a,g–h] as well as 1,3-DCs of azomethine ylides catalyzed by CPA,[3a,13a] we suggested a possible reaction mechanism and related transition states to explain the chemistry and stereochemistry of this catalytic asymmetric three-component formal [3+3] cycloaddition (Scheme 1). Initially, the treatment of isatin-derived 3-indolylmethanol **1** with CPA **4f** afforded the corresponding carboncation **6** or vinyliminium **7** intermediate, which transformed into each other in fast equilibrium and served as an efficient electrophilic reagent to react with azomethine ylide **8** generated in situ from the condensation of aldehyde **2** and amino ester **3a**. Then, as illustrated in the transition states (TS) I–II, the formal [3+3] cycloaddition of intermediate **6** or **7** with azomethine ylide **8** might proceed through a sequential Michael addition (TS-I) and Pictet-Spengler reaction (TS-II) to form the desired six-membered heterocyclic skeleton. In the transition states of this reaction, CPA **4f** acted as a Brønsted acid/Lewis base bifunctional catalyst to simultaneously activate both intermediate **7** and azomethine ylide **8** by a hydrogen-bonding interaction. This activation led to an enantioselective formal [3+3] cycloaddition due to the chiral environment created by (*R*)-BINOL backbone and the bulky 3,3′-(9-phenanthrenyl)-substituents of CPA **4f**, thereby offering the experimentally observed (1′*S*, 3*S*)-configured product **5**.

As shown in Figure 2, the two diastereomers of (1′*S*, 3*S*)-**5ada** and (1′*S*, 3*R*)-**5ada′** have different absolute configuration at the 3-position but have the same configuration at the 1′-position, which indicated that there existed little chiral induction and discrimination in the first step of Michael addition. As illustrated in TS-I and TS-I′, The two stereo-modes of nucleophilic substitution of azomethine ylide **8** to vinyliminium **7** had a small difference in steric hindrance and could isomerize to each other, thereby resulting in unsatisfactory diastereoselectivities in some cases. On the contrary, the second step of the Pictet–Spengler reaction of intermediate **9** (TS-II) was proven to be the key step to establish a highly enantioselective formal [3+3] cycloaddition. So, chiral induction and discrimination between CPA **4f** and substrates mainly occurred in the second step, leading to the production of (1′*S*, 3*S*)-**5** with excellent enantioselectivities.

To investigate the role of the N–H group in the indole moiety of 3-indolylmethanol and to testify our proposed activation mode, we performed a control experiment by using *N*-benzyl-protected 3-indolylmethanol **1v** as a substrate (Scheme 2). However, no desired cycloaddition product **5vaa** was observed under the optimal reaction conditions. Instead, a Michael addition product **9vaa** was generated in 38% yield, which indicated that the N–H group of the indole moiety played a crucial role in the reaction to generate formal [3+3] cycloaddition products. On the other hand, the formation of product **9vaa** supported our hypothesis that this formal [3+3] cycloaddition proceeded through a sequential Michael addition/Pictet–Spengler reaction pathway rather than a concerted process.

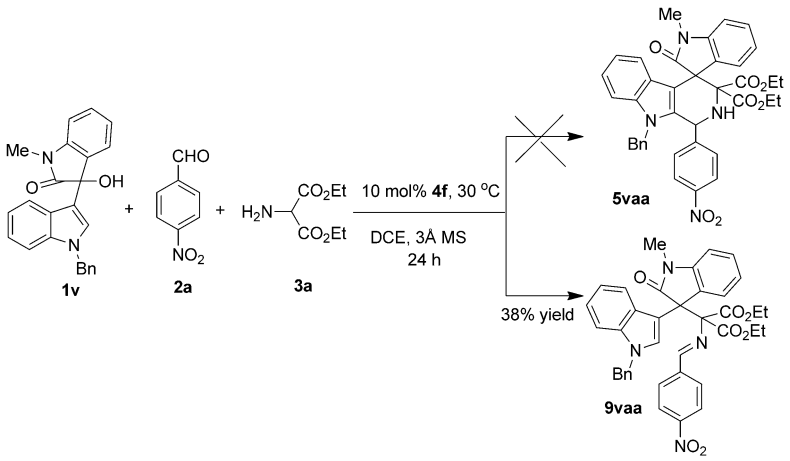
Conclusion

We have established the first catalytic asymmetric formal [3+3] cycloaddition of isatin-derived 3-indolylmethanol and in situ-generated azomethine ylide. This approach not only represents the first enantioselective cycloaddition of isatin-derived 3-indolylmethanol, but has also realized an unusual enantioselective formal [3+3] cycloaddition of azomethine ylide rather than its



Scheme 1. Proposed reaction mechanism and transition states.

common [3+2] cycloadditions, thus constructing a chiral six-membered piperidine framework with two stereogenic centers. Besides, this protocol efficiently assembles a variety of isatin-derived 3-indolylmethanols, aldehydes, and amino ester into structurally diverse spiro[indoline-3,4′-pyridoindoles] with one all-carbon quaternary stereogenic center in high yields and excellent enantioselectivities (up to 93% yield, >99% *ee*). Although the diastereoselectivity of the reaction is generally moderate, most of the diastereomers can be separated by using column chromatography followed by preparative TLC. So, this strategy provides the first enantioselective construction of this type of spiro-architecture, which exists in many natural products and pharmaceuticals.



Scheme 2. Control experiment involving *N*-benzyl-protected 3-indolylmethanol **1v**.

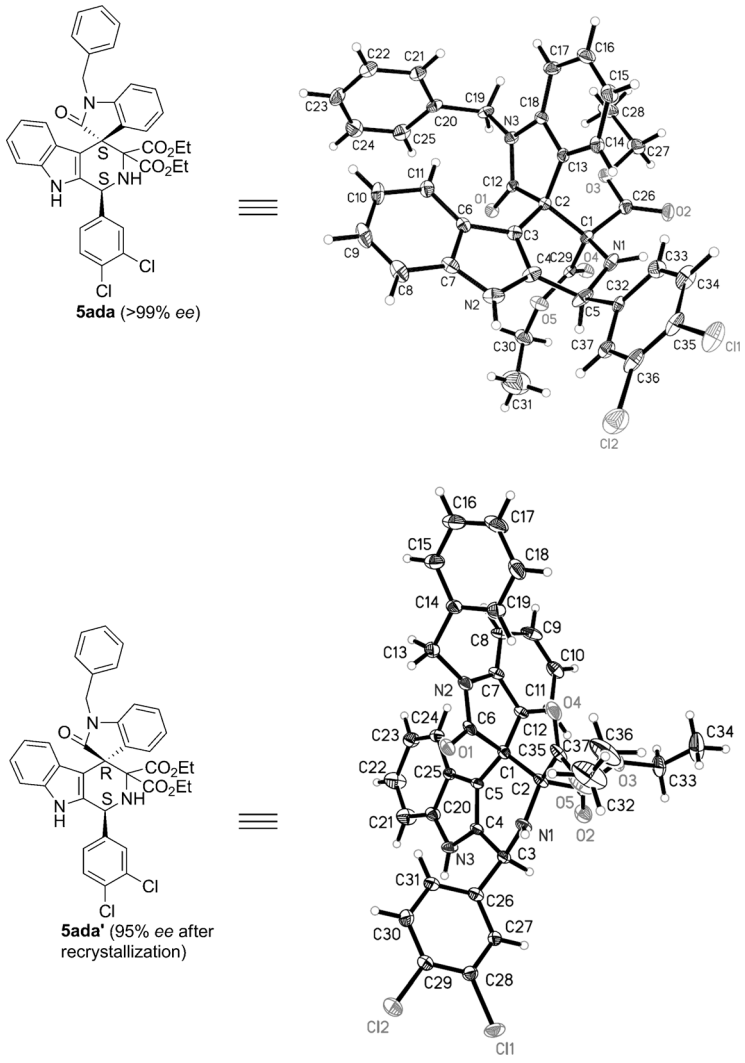


Figure 2. X-ray structures of **5ada** and **5ada′**.

Experimental Section

Representative experimental procedures

Synthesis of (1′*S*, 3*S*)-diethyl 1-(4-bromobenzyl)-1′-(4-nitrophenyl)-2-oxo-1′,2′-dihydrospiro[indoline-3,4′-pyrido[3,4-*b*]indole]-3′,3′(9′*H*)-dicarboxylate (**5gaa**): A solution of aldehyde **2a** (0.12 mmol), amino ester **3a** (0.1 mmol), the catalyst **4f** (0.01 mmol), and 3 Å molecular sieves (100 mg) in DCE (0.5 mL) was stirred at 30 °C for 30 mins. Next, a solution of 3-indolylmethanols **1g** (0.15 mmol) in DCE (1 mL) was added. After being stirred at 30 °C for 24 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1), then preparative thin layer chromatography (toluene/ethyl acetate = 5:1); total yield: 67%; 60:40 d.r.; yield of **5gaa**: 40% as a sticky oil. $[\alpha]_{20}^{D} = +268$ ($c = 0.6$, $CHCl_3$); enantiomeric excess: 97%, as determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70:30, flow rate 1.0 mL min^{-1}, $T = 30$ °C, 254 nm): $t_R = 19.107$ min (major), $t_R = 45.533$ min (minor); ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 9.98$ (s, 1H), 8.37–8.27 (m, 2H), 7.92–7.86 (m, 2H), 7.75–7.68 (m, 3H), 7.67–7.62 (m, 2H), 7.25 (d, $J = 3.9$ Hz, 2H), 7.21 (d, $J = 8.1$ Hz, 1H), 6.95–6.88 (m, 2H), 6.74 (d, $J = 7.9$ Hz, 1H), 6.71–6.63 (m, 1H), 6.17 (d, $J = 3.4$ Hz, 1H), 5.27 (d, $J = 15.0$ Hz, 1H), 5.11 (d, $J = 15.0$ Hz, 1H), 4.28–4.20 (m, 1H), 4.12–4.04 (m, 1H), 3.84 (d, $J = 3.5$ Hz, 1H), 3.76–3.68 (m, 1H), 3.64–3.56 (m, 1H), 1.19 (t, $J = 7.1$ Hz, 3H), 0.67 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.2$, 167.9, 166.6, 148.2, 148.1, 142.4, 136.3, 134.8, 133.4, 131.8, 130.7, 129.9, 128.4, 124.9, 124.2, 123.1, 122.3, 122.1, 120.0, 118.3, 111.1, 108.9, 108.1, 70.9, 61.8, 61.7, 54.6, 52.3, 44.0, 13.8, 13.2 ppm; IR (KBr): $\tilde{\nu} = 3350$, 2928, 1726, 1602, 1520, 1444, 1201, 841, 741 cm^{-1}; ESI FTMS *m/z* calcd for $C_{37}H_{31}BrN_4O_7$: 721.1298 $[C_{37}H_{31}BrN_4O_7-H]^-$; found: 721.1337.

Acknowledgements

We are grateful for financial support from National Natural Science Foundation of China (21372002 and 21232007), Open Foundation of Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials (K201314), PAPD of Jiangsu Higher Education Institutions, and Graduate Students Foundation of Jiangsu Normal University (2013YYB123).

Keywords: asymmetric synthesis · cycloaddition · enantioselectivity · multicomponent reactions · organocatalysis · ylides

[1] a) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825–1872; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2809; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; d) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247–12275; e) W. H. Pearson in *Studies in Natural Product Chemistry, Vol. 1* (Ed.: Atta-Ur-Rahman), Elsevier, Amsterdam, **1998**, p. 323.

[2] For early reports on metal-catalyzed 1,3-DCs, 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 on metal-catalyzed 1,3-DCs, see: c) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428–6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272–4276; 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; for early reports on organocatalyzed 1,3-DCs, see: f) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260–5262; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168–5170; g) I. Ibrahem, R. Rios, J. Vesely, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 6252–6257; h) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691–694; i) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873–9877; for reviews on organo-catalyzed 1,3-DCs, see: j) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; k) H. Pellissier, *Tetrahedron* **2012**, *68*, 2197–2232.

[3] a) F. Shi, S.-W. Luo, Z.-L. Tao, L. He, J. Yu, S.-J. Tu, L.-Z. Gong, *Org. Lett.* **2011**, *13*, 4680–4683; b) F. Shi, Z.-L. Tao, J. Yu, S.-J. Tu, *Tetrahedron: Asymmetry* **2011**, *22*, 2056–2064; c) F. Shi, G.-J. Xing, W. Tan, R.-Y. Zhu, S. Tu, *Org. Biomol. Chem.* **2013**, *11*, 1482–1489; d) F. Shi, R.-Y. Zhu, X. Liang, S.-J. Tu, *Adv. Synth. Catal.* **2013**, *355*, 2447–2458.

[4] M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem.* **2012**, *124*, 9650–9654; *Angew. Chem. Int. Ed.* **2012**, *51*, 9512–9516.

[5] Z.-L. He, H.-L. Teng, C.-J. Wang, *Angew. Chem.* **2013**, *125*, 3006–3010; *Angew. Chem. Int. Ed.* **2013**, *52*, 2934–2938.

[6] a) M.-C. Tong, X. Chen, H.-Y. Tao, C.-J. Wang, *Angew. Chem.* **2013**, *125*, 12603 – 12606; *Angew. Chem. Int. Ed.* **2013**, *52*, 12377 – 12380; b) H. Guo, H. Liu, F.-L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X.-P. Hu, M. Wang, *Angew. Chem.* **2013**, *125*, 12873 – 12877; *Angew. Chem. Int. Ed.* **2013**, *52*, 12641 – 12645.

[7] For a review, see: A. Palmieri, M. Petrini, R. R. Shaikh, *Org. Biomol. Chem.* **2010**, *8*, 1259 – 1270.

[8] For enantioselective substitutions of 3-indolylmethanols, see: a) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4620 – 4623; b) P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem.* **2009**, *121*, 1339 – 1342; *Angew. Chem. Int. Ed.* **2009**, *48*, 1313 – 1316; c) B. Han, Y.-C. Xiao, Y. Yao, Y.-C. Chen, *Angew. Chem.* **2010**, *122*, 10387 – 10389; *Angew. Chem. Int. Ed.* **2010**, *49*, 10189 – 10191; d) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, *2*, 803 – 806; e) J. Xiao, K. Zhao, T.-P. Loh, *Chem. Asian J.* **2011**, *6*, 2890 – 2894; f) J. Xiao, *Org. Lett.* **2012**, *14*, 1716 – 1719; g) L. Song, Q.-X. Guo, X.-C. Li, J. Tian, Y.-G. Peng, *Angew. Chem.* **2012**, *124*, 1935 – 1938; *Angew. Chem. Int. Ed.* **2012**, *51*, 1899 – 1902; h) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 1070 – 1074; *Angew. Chem. Int. Ed.* **2012**, *51*, 1046 – 1050.

[9] For a sole racemic [4+3] cycloaddition, see: a) X. Han, H. Li, R. P. Hughes, J. Wu, *Angew. Chem.* **2012**, *124*, 10536 – 10539; *Angew. Chem. Int. Ed.* **2012**, *51*, 10390 – 10393; for enantioselective reactions, see: b) B. Xu, Z.-L. Guo, W.-Y. Jin, Z.-P. Wang, Y.-G. Peng, Q.-X. Guo, *Angew. Chem.* **2012**, *124*, 1083 – 1086; *Angew. Chem. Int. Ed.* **2012**, *51*, 1059 – 1062; c) J. Huang, S. Luo, L. Gong, *Acta Chim. Sin.* **2013**, *71*, 879 – 883.

[10] a) S. P. Hollinshead, M. L. Trudell, P. Skolnick, J. M. Cook, *J. Med. Chem.* **1990**, *33*, 1062 – 1069; b) J. Garnier, J. Mahuteau, M. Plat, C. Merienne, *Phytochemistry* **1989**, *28*, 308 – 309; c) A. Itoh, T. Tanahashi, N. Nagakura, T. Nishi, *Phytochemistry* **2003**, *62*, 359 – 369.

[11] a) J. Zhang, Z. Zhang, U. S. Pat. Appl. Publ. **2010**, US 20100210674 A1 20100819; b) M. Chafeev, S. Chowdhury, J. Fu, R. Kamboj, D. Hou, S. Liu, PCT Int. Appl., **2008**, WO 2008046084 A2 20080417; c) O.-G. Berge, A. Claesson, B.-M. Swahn, PCT Int. Appl., **2001**, WO 2001005790 A1 20010125.

[12] For early examples, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592 – 1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566 – 1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356 – 5357; for reviews, see: c) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; d) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112; e) M. Terada, *Synthesis* **2010**, 1929; f) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156 – 1171.

[13] a) F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *Chem. Eur. J.* **2012**, *18*, 6885 – 6894; b) F. Shi, G.-J. Xing, R.-Y. Zhu, W. Tan, S. Tu, *Org. Lett.* **2013**, *15*, 128 – 131; c) F. Shi, W. Tan, R.-Y. Zhu, G.-J. Xing, S.-J. Tu, *Adv. Synth. Catal.* **2013**, *355*, 1605 – 1622.

[14] CCDC-967946 (**5ada**) and CCDC-965690 (**5ada'**) 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.

Received: October 27, 2013
Published online on February 2, 2014

