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C7-Functionalized Indoles

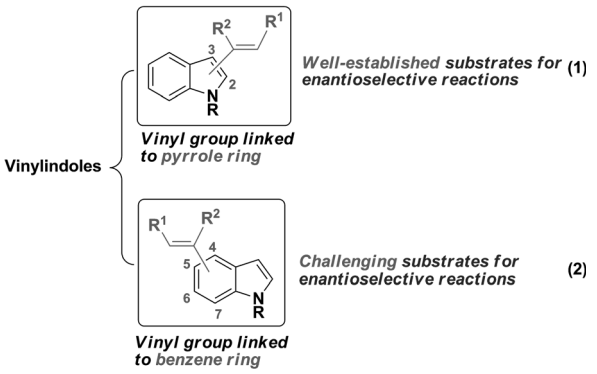
Organocatalytic Asymmetric Cascade Reactions of 7-Vinylindoles: Diastereo- and Enantioselective Synthesis of C7-Functionalized Indoles

Feng Shi,* Hong-Hao Zhang, Xiao-Xue Sun, Jing Liang, Tao Fan, and Shu-Jiang Tu[a]

Abstract: The first catalytic asymmetric cascade reaction of 7-vinylindoles has been established by the rational design of such substrates. Cascade reactions with isatin-derived 3-indolylmethanols in the presence of a chiral phosphoric acid derivative allow the diastereo- and enantioselective synthesis of C7-functionalized indoles as well as the construction of cyclopenta[*b*]indole and spirooxindole frameworks (all >95:5 d.r., 94–>99% *ee*). This approach not only addresses the great challenge of the catalytic asymmetric synthesis of C7-functionalized indoles, but also provides an efficient method for constructing biologically important cyclopenta[*b*]indole and spirooxindole scaffolds with excellent optical purity. Investigation of the reaction pathway and activation mode has suggested that this cascade reaction proceeds through a vinylogous Michael addition/Friedel–Crafts process, in which dual H-bonding activation of the two reactants plays a crucial role.

Introduction

Indole represents one of the most intriguing heterocyclic motifs, and constitutes the core structures of numerous natural products and pharmaceuticals.[1] As a result, the synthesis of functionalized indoles, especially in a diastereo- and enantioselective manner, has attracted great interest in the chemical community.[2] In this context, vinylindoles have been recognized as versatile reactants for the stereoselective synthesis of functionalized indoles by making use of the reactivity of the vinyl group and the nucleophilicity of the indole moiety. In most cases, 2-vinylindoles[3] or 3-vinylindoles,[4] bearing vinyl groups on the more reactive pyrrole ring, have been employed as substrates for catalytic asymmetric reactions, thus achieving enantioselective synthesis of C2- or C3-functionalized indoles [Eq. (1) in Scheme 1]. However, in sharp contrast, vinylindoles with vinyl groups attached at the C4–C7 positions of the less active benzene ring have been scarcely utilized as reactants in catalytic asymmetric reactions,[5] and as a result enantioselective synthesis of C4 to C7-functionalized indoles has remained underdeveloped [Eq. (2) in Scheme 1]. The challenge relating to enantioselective transformations involving such vinylindoles mainly stems from three issues. Firstly, such vinylindoles are difficult to prepare. Secondly, vinyl groups in the C4- to C7-positions show relatively low reactivity and remote enantioselective control. Thirdly, there is competing nucleophilicity between the C2- or C3-position and the vinyl group.



Scheme 1. Profile of vinylindoles employed in catalytic enantioselective reactions.

Recently, Bernardi, Fochi, and co-workers employed 4-vinylindoles in catalytic asymmetric cascade reactions with enals in the presence of a chiral amine catalyst, which afforded C3,C4-annulated indoles with excellent diastereo- and enantioselectivities (Scheme 2).[5c] Apart from this elegant work, progress has been limited, and the development of catalytic asymmetric reactions involving C4 to C7-vinylindoles is still highly desirable yet rather challenging, and requires specific synthetic design.

Scheme 2. Previous work using 4-vinylindoles in catalytic asymmetric reactions.

[a] *Prof. Dr. F. Shi, H.-H. Zhang, X.-X. Sun, J. Liang, T. Fan, Prof. S.-J. Tu*
School of Chemistry and Chemical Engineering
Jiangsu Normal University, Xuzhou, 221116 (China)
E-mail: fshi@jsnu.edu.cn

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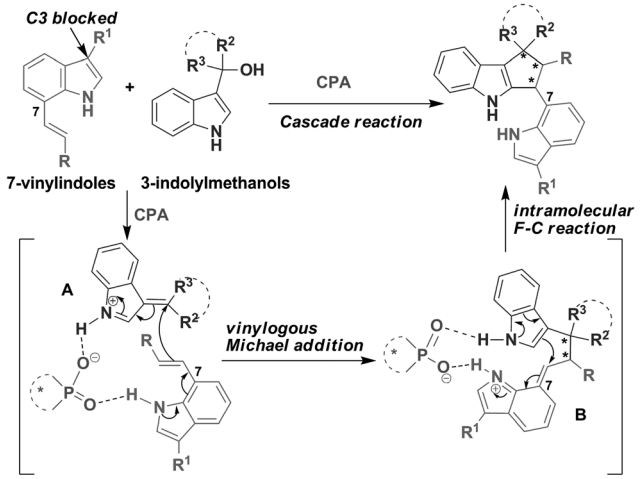
Considering this challenge, we have designed a new class of 7-vinylindoles as promising reactants for stereoselective syntheses of C7-functionalized indoles by making use of the 7-vinyl group (Scheme 3). In our design, an alkyl blocking group



Scheme 3. Design of catalytic asymmetric cascade reactions involving 7-vinylindoles.

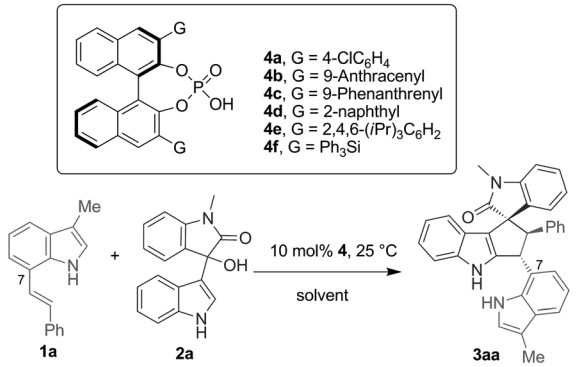
is introduced at the more reactive C3-position of the indole core so as to avoid competition between this site and the 7-vinyl group in nucleophilic additions. Organocatalytic asymmetric domino reactions,[6] particularly chiral phosphoric acid[7] (CPA)-catalyzed cascade reactions, have proven to be robust methods for synthesizing optically pure molecules and realizing enantioselective transformations in a single step. Furthermore, 3-indolylmethanols show great potential in catalytic enantioselective reactions as suitable acceptors of Michael addition after being transformed into vinyliminium intermediates in the presence of an acid.[8–10] Inspired by these successes and our interest in CPA-catalyzed asymmetric cascade reactions,[9l,10c,11] we envisaged that appropriate 7-vinylindoles could, in principle, undergo enantioselective cascade reactions with 3-indolylmethanols in the presence of CPA, thus achieving stereoselective synthesis of C7-functionalized indoles (Scheme 3). In this design, 7-vinylindoles and vinyliminium **A** generated from the 3-indolylmethanol would be simultaneously activated by CPA through H-bonding interaction to perform the first step of vinylogous Michael addition. The transient intermediate **B** could then further undergo the second step of intramolecular Friedel–Crafts (F-C) reaction, again under the catalysis of CPA, thus completing the stereoselective synthesis of C7-functionalized indoles by the construction of a chiral cyclopenta[*b*]indole framework. This structure is also present in many natural alkaloids and bioactive molecules.[12]

Herein, we report the first catalytic asymmetric cascade reactions of 7-vinylindoles, which have been accomplished through the rational design of such substrates. Such cascade reactions with 3-indolylmethanols in the presence of a chiral phosphoric acid allow the diastereo- and enantioselective synthesis of C7-functionalized indoles as well as the construction of cyclopenta[*b*]indole and spirooxindole frameworks (all >95:5 d.r., 94–>99% *ee*).

Results and Discussion

Initially, considering the significance and the challenge in constructing a chiral 3,3′-spirooxindole scaffold with a spiro-quaternary stereogenic center,[13] the cascade reaction of 7-vinylindole **1a** with isatin-derived 3-indolylmethanol **2a** was employed as a model reaction to test our hypothesis as well as to construct a spirooxindole structure (Table 1). As expected, the

Table 1. Screening of catalysts and solvents.[a]



Entry	Cat.	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	toluene	24	>95:5	98
2	**4b**	toluene	19	>95:5	98
3	**4c**	toluene	23	>95:5	96
4	**4d**	toluene	56	>95:5	96
5	**4e**	toluene	trace	–	–
6	**4f**	toluene	trace	–	–
7	**4d**	EtOAc	15	>95:5	90
8	**4d**	$CHCl_3$	30	>95:5	94
9	**4d**	1,4-dioxane	trace	–	–
10	**4d**	CH_3CN	trace	–	–
11	**4d**	*o*-xylene	24	>95:5	94
12	**4d**	*m*-xylene	29	>95:5	94
13	**4d**	*p*-xylene	27	>95:5	94
14	**4d**	C_6H_5F	27	>95:5	95
15	**4d**	C_6H_5Br	18	>95:5	95

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in solvent (1 mL) for 12 h, and the mole ratio of **1a**/**2a** was 1.2:1. [b] Isolated yield. [c] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR and HPLC. [d] The enantiomeric excess (*ee*) was determined by HPLC.

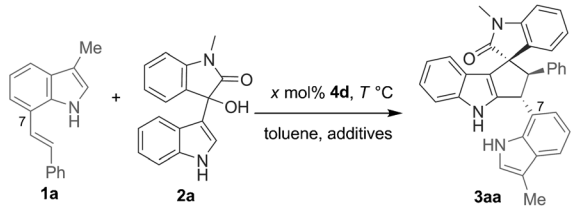
cascade reaction in the presence of CPAs **4a**–**4d** indeed afforded the desired C7-functionalized product **3aa** with concomitant construction of the spirooxindole framework with excellent diastereo- and enantioselectivities (entries 1–4). However, the yields in these cases were generally low, and CPAs **4e** and **4f** failed to catalyze the cascade reaction (entries 5 and 6). Monitoring of the reaction by TLC revealed that 3-indolylmethanol **2a** was easily transformed into a complex mixture in the presence of acidic catalysts, and that a small amount of by-product was generated through nucleophilic substitution at

the C2 position of 7-vinylindole **1a** with 3-indolylmethanol **2a**, thus accounting for the low yield of the desired product **3aa**. This result also indicated that the relatively low reactivity of the 7-vinyl group was an inherent challenge in the synthesis of C7-functionalized indoles. Among the tested catalysts, CPA **4d** with β-naphthyl groups at the 3,3′-positions exhibited the highest catalytic activity in terms of yield (entry 4). Hence, in the presence of CPA **4d**, various solvents, including an arene, ester, haloalkane, ether, and nitrile, were utilized in the model reaction. The results showed toluene, an arene-type solvent, to be far superior to the others in terms of both reactivity and enantioselectivity (entry 4 versus entries 7–10). Then, various other arene-type solvents were evaluated in the model reaction, but in all cases lower product yields were obtained compared to that in toluene (entries 11–15 versus entry 4). Therefore, toluene was chosen as the optimal solvent for further optimization of the conditions.

To improve the yield without compromising the enantioselectivity, subsequent optimization of the reaction conditions was focused on temperature, additives, reagent ratio, and catalyst loading (Table 2). Neither lowering nor elevating the reaction temperature improved the yield or the stereoselectivity (entries 2 and 3 versus entry 1). Because the vinyliminium intermediate was generated by dehydration of 3-indolylmethanol **2a**, some additives such as molecular sieves (MS) and anhydrous sodium sulfate were added to the reaction system as water absorbers (entries 4–8). It was found that the addition of anhydrous sodium sulfate improved the yield to some extent (entry 8 versus entry 1). Subsequently, the ratio of reagents **1a** and **2a** was modified, but no further improvement in the yield was obtained (entries 9–11). Moreover, the effect of catalyst loading on the reaction was investigated (entries 12–14), which revealed that 5 mol% of **4d** could catalyze the reaction just as well as 10 mol% of **4d** (entry 12 versus entry 1), but that increasing the catalyst loading could improve the yield and the enantioselectivity (entries 13 and 14 versus entry 1). Finally, a catalyst loading of 15 mol% **4d** was regarded as optimal for its good performance in raising the yield to 68% with a retained excellent stereoselectivity of >95:5 d.r. and 96% *ee* (entry 13).

Having established the optimal reaction conditions, the applicability of this catalytic asymmetric cascade reaction to the stereoselective synthesis of C7-functionalized indoles and the construction of cyclopenta[*b*]indole-containing spirooxindole frameworks was firstly examined by using a series of 7-vinylindoles **1** with different terminal substituents (Table 3). As indicated in entries 1–7, this protocol was amenable to substrates **1a**–**1g** bearing phenyl groups with either electron-donating or electron-withdrawing substituents at different positions of the ring, affording the desired products in moderate to good yields with excellent stereoselectivities (all >95:5 d.r., 96–>99% *ee*). The electronic nature of these substituents clearly had some effect on the reactivity, because electron-donating groups gave much higher yields than electron-withdrawing groups (entries 2–4 versus 5–7). The position of the substituents also seemed to exert some influence on the reactivity since a methyl group in a *meta* position led to a higher prod-

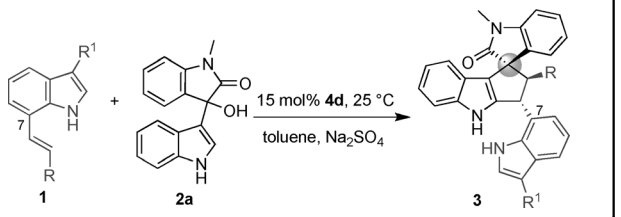
Table 2. Further optimization of the reaction conditions.[a]



Entry	*x*	Additives	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	10	–	25	56	>95:5	96
2	10	–	0	32	>95:5	96
3	10	–	50	48	>95:5	96
4	10	3 Å MS	25	34	>95:5	98
5	10	4 Å MS	25	57	>95:5	94
6	10	5 Å MS	25	54	>95:5	94
7	10	$MgSO_4$	25	56	>95:5	96
8	10	Na_2SO_4	25	62	>95:5	96
9[e]	10	Na_2SO_4	25	25	>95:5	96
10[f]	10	Na_2SO_4	25	43	>95:5	94
11[g]	10	Na_2SO_4	25	38	>95:5	90
12	5	Na_2SO_4	25	55	>95:5	96
13	15	Na_2SO_4	25	68	>95:5	96
14	20	Na_2SO_4	25	69	>95:5	99

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in toluene (1 mL) with additives (100 mg) for 12 h, and the mole ratio of **1a**/**2a** was 1.2:1. [b] Isolated yield. [c] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR and HPLC. [d] The enantiomeric excess (*ee*) was determined by HPLC. [e] The mole ratio of **1a**/**2a** was 1:2. [f] The mole ratio of **1a**/**2a** was 2:1. [g] The mole ratio of **1a**/**2a** was 3:1.

Table 3. The applicability of 7-vinylindoles to the cascade reaction.[a]



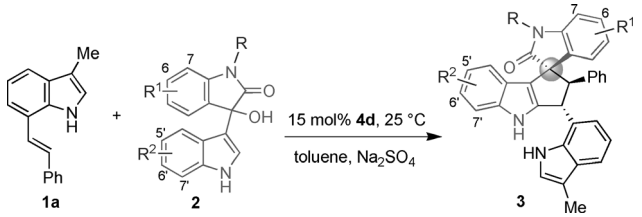
Entry	**3**	R/R^1 (**1**)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3aa**	C_6H_5/Me (**1a**)	68	>95:5	96
2	**3ba**	*m*-MeC_6H_4/Me (**1b**)	78	>95:5	>99
3	**3ca**	*p*-MeC_6H_4/Me (**1c**)	63	>95:5	99
4	**3da**	*p*-*t*BuC_6H_4/Me (**1d**)	65	>95:5	99
5	**3ea**	*m*-FC_6H_4/Me (**1e**)	43	>95:5	97
6	**3fa**	*m*-ClC_6H_4/Me (**1f**)	47	>95:5	99
7	**3ga**	*p*-BrC_6H_4/Me (**1g**)	41	>95:5	>99
8	**3ha**	Me/Me (**1h**)[e]	56	>95:5	94
9	**3ia**	Et/Me (**1i**)[f]	43	>95:5	98
10[g]	**3ja**	H/Me (**1j**)	17	>95:5	97
11	**3ka**	C_6H_5/Et (**1k**)	65	>95:5	>99

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale catalyzed by 15 mol% **4d** in toluene (1 mL) with sodium sulfate (100 mg) at 25 °C for 12 h, and the mole ratio of **1**/**2a** was 1.2:1. [b] Isolated yield. [c] The d.r. was determined by ^{1}H NMR. [d] The *ee* was determined by HPLC. [e] A mixture of *E*/*Z* isomers (*E*/*Z* = 2:1) was employed in the reaction. [f] A mixture of *E*/*Z* isomers (*E*/*Z* = 1.6:1) was employed in the reaction. [g] Catalyzed by 15 mol% ***ent*-4d**.

uct yield than a methyl group in the *para* position (entry 2 versus entry 3). More importantly, this method could be applied to 7-vinylindoles **1h** and **1i** bearing terminal alkyl groups, giving the respective products with excellent diastereo- and enantioselectivities (entries 8 and 9). However, when unsubstituted (R = H) 7-vinylindole **1j** was utilized in the reaction, the desired product **3ja** was generated in very low yield, albeit with high stereoselectivity (entry 10), which could be ascribed to the fact that substrate **1j** is readily decomposed in the presence of an acidic catalyst. Furthermore, the methyl group at the C3-position of 7-vinylindole could be changed to an ethyl group without affecting the efficacy of the desired reaction (entry 11).

Next, the substrate scope with respect to isatin-derived 3-indolylmethanols **2** was studied by performing reactions with 7-vinylindole **1a**. As shown in Table 4, a wide range of isatin-derived 3-indolylmethanols **2** with various substituents at different positions of the isatin or indole moiety could be employed as suitable reaction partners in the cascade reaction, giving structurally diverse C7-functionalized products **3** in generally acceptable yields with high stereoselectivities (all >95:5 d.r., 95–>99% *ee*). These substrates exhibited essentially no significant differences in stereoselectivity, but showed some obvious differences in reactivity. Specifically, this approach was applicable to *N*-alkyl- or *N*-benzyl-substituted substrates, but the former (**2a** and **2b**) showed much higher reactivity than the latter (**2c**) (entries 1 and 2 versus entry 3). Furthermore, this method proved to be suitable for a variety of substrates with different substituents at varied positions of the isatin moiety (entries 4–6) or the indole core (entries 7–12), although the electronic nature and the position of the substituents had a delicate and irregular effect on the reactivity.

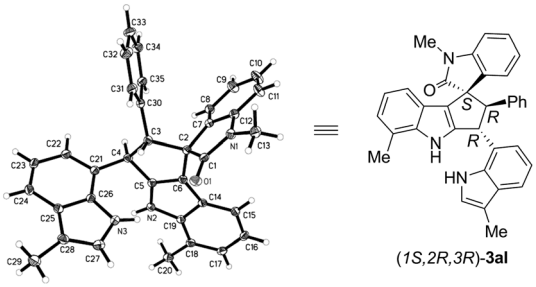
Table 4. The substrate scope of isatin-derived 3-indolylmethanols.[a]



Entry	3	R/R[1]/R[2] (2)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3aa**	Me/H/H (**2a**)	68	>95:5	96
2[e]	**3ab**	*i*Pr/H/H (**2b**)	61	>95:5	>99
3	**3ac**	Bn/H/H (**2c**)	41	>95:5	97
4	**3ad**	Bn/6-F/H (**2d**)	43	>95:5	98
5	**3ae**	Me/7-F/H (**2e**)	64	>95:5	98
6	**3af**	Bn/7-Me/H (**2f**)	40	>95:5	98
7	**3ag**	Me/H/5′-Me (**2g**)	50	>95:5	99
8	**3ah**	Bn/H/5′-MeO (**2h**)	56	>95:5	99
9	**3ai**	Me/H/6′-F (**2i**)	61	>95:5	95
10	**3aj**	Bn/H/6′-Cl (**2j**)	41	>95:5	98
11	**3ak**	Bn/H/7′-Me (**2k**)	43	>95:5	>99
12	**3al**	Me/H/7′-Me (**2l**)	62	>95:5	95

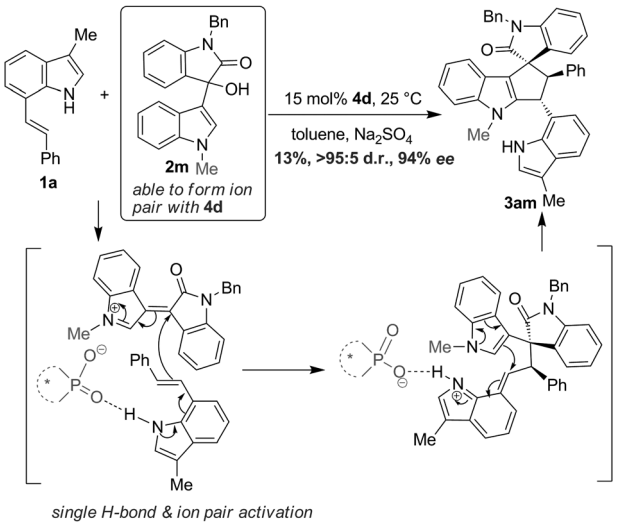
[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale catalyzed by 15 mol% **4d** in toluene (1 mL) with sodium sulfate (100 mg) at 25 °C for 12 h, and the mole ratio of **1a**/**2** was 1.2:1. [b] Isolated yield. [c] The d.r. was determined by ^{1}H NMR. [d] The *ee* was determined by HPLC. [e] Catalyzed by 15 mol% ***ent*-4d**.

The absolute configuration of C7-functionalized product **3al** (>99% *ee* after recrystallization) was unambiguously determined as (1*S*,2*R*,3*R*) by single-crystal X-ray diffraction analysis (Scheme 4).[14] The absolute configurations of the other spiro-products **3** were assigned by analogy.

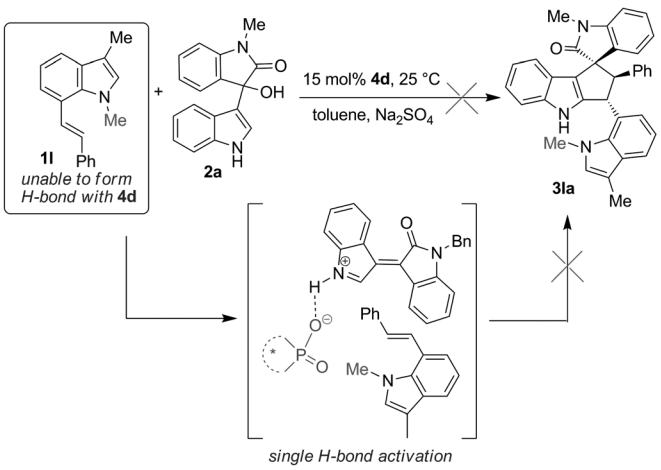


Scheme 4. The absolute configuration of product **3al**.

To gain insight into the activation mode of the catalyst towards the substrates in the catalytic asymmetric cascade reaction, some control experiments were carried out (Schemes 5 and 6). Firstly, *N*-methyl-protected 3-indolylmethanol **2m** was employed as a substrate instead of its N-unprotected counterpart **2c** (Table 4, entry 3) in the reaction under the optimal conditions. The desired product **3am** was thereby obtained with excellent diastereo- and enantioselectivity (>95:5 d.r., 94% *ee*), albeit in a very low yield of 13% (Scheme 5). This result indicated that the N–H group of the indole moiety of the 3-indolylmethanol played an important role in controlling the reactivity, but that its absence had little influence on the stereoselectivity. Although the vinyliminium species derived from substrate **2m** could not form an H-bond with CPA due to



Scheme 5. Control experiment using N-protected 3-indolylmethanol **2m**.



Scheme 6. Control experiment using N-protected 7-vinylindole **1l**.

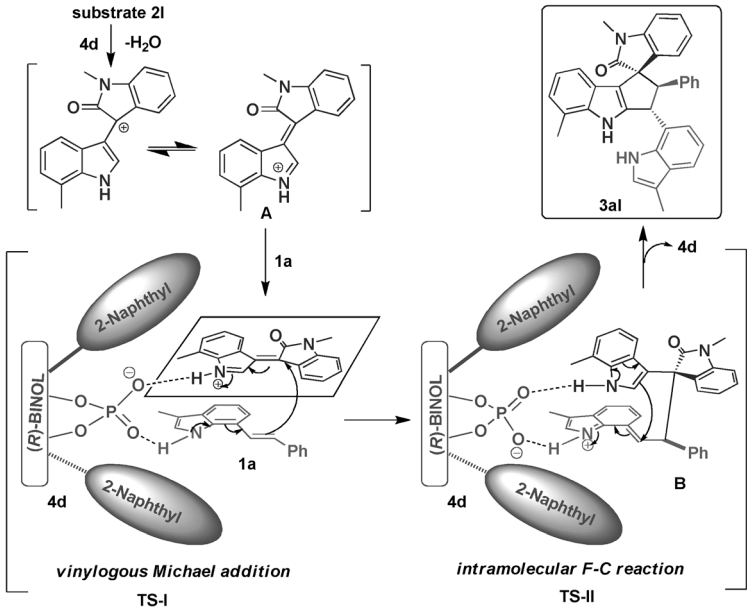
the absence of an N–H group, it was still able to form an ion pair with the CPA anion. Besides, the CPA could interact through H-bonding with reactant **1a**. Hence, the dual activation mode of H-bonding as well as ion-pair interaction between the catalyst and the two reactants contributed to the excellent stereoselectivity obtained. However, because the ion-pair interaction was much weaker than the H-bond, the N-protected substrate **2m** exhibited much lower reactivity than N-unprotected substrate **2c**.

Next, *N*-methyl-protected 7-vinylindole **1l** was utilized as a reactant in place of N-unprotected analogue **1a** (Table 4, entry 1) in the reaction under the standard conditions (Scheme 6). However, none of the desired product **3la** was generated, which indicated that the N–H group of the 7-vinylindole played a crucial role in the designed cascade reaction.[15] Specifically, in the absence of this N–H group, the CPA could not form an H-bond with the 7-vinylindole and thus failed to activate the 7-vinyl group. Although the CPA could interact with the vinyliminium species through H-bonding, this single H-bond activation mode was insufficient to induce the cascade reaction. Hence, the activation of 7-vinylindoles through H-bond formation was a decisive factor for the reaction.

Based on the experimental results, we proposed possible transition states and an activation mode to account for the chemistry and stereochemistry of the cascade reaction, as exemplified by the formation of C7-functionalized product **3al**. As shown in Scheme 7, in the presence of catalyst **4d**, isatin-derived 3-indolylmethanol **2l** was readily converted into a carbocation and a vinyliminium intermediate (**A**), which could establish an H-bond and an ion-pair interaction with the CPA anion. Simultaneously, 7-vinylindole **1a** was also activated by the same catalyst through an H-bond, rendering the C7-vinyl group more nucleophilic, thus facilitating the first step of vinylogous Michael addition to generate a transient intermediate **B** (**TS-I**). Then, still under the dual H-bond activation of the same catalyst, this intermediate underwent an intramolecular Friedel–Crafts (F-C) reaction to restore the original aromatic indole structure (**TS-II**), thereby leading to the synthesis of C7-functionalized indoles and construction of the spirooxindole scaffold. During this cascade process, a highly diastereo- and enantioselective vinylogous Michael addition/intramolecular F-C reaction occurred because of the chiral environment created by the (*R*)-BINOL backbone and the 3,3′-substituents of CPA **4d**, which resulted in the experimentally observed (1*S*,2*R*,3*R*)-configured product **3al**.

Conclusion

We have established the first catalytic asymmetric cascade reaction of 7-vinylindoles following the rational design of such substrates. Their cascade reactions with isatin-derived 3-indolylmethanols in the presence of chiral phosphoric acid allow the diastereo- and enantioselective synthesis of C7-functionalized indoles as well as the construction of cyclopenta[*b*]indole and spirooxindole frameworks (all >95:5 d.r., 94–>99% *ee*). This approach not only addresses the great challenge in catalytic asymmetric synthesis of C7-functionalized indoles, but also provides an efficient method for constructing biologically important cyclopenta[*b*]indole and spirooxindole scaffolds with excellent optical purity. Investigation of the reaction pathway and the activation mode has suggested that this cascade reaction proceeds via a vinylogous Michael addition/Friedel–Crafts process, in which dual H-bond activation of the two reactants plays a crucial role. This synthetic strategy may expedite the design of substrates and cascade reactions based on different activation modes for developing stereoselective syntheses of C7-functionalized indoles.



Scheme 7. Proposed transition states of the cascade reaction.

Experimental Section

Typical experimental procedure for the catalytic asymmetric cascade reaction leading to stereoselective synthesis of C7-functionalized indole and spirooxindole 3 aa: In air, toluene (1 mL) was added to a mixture of 7-vinylindole **1 a** (0.12 mmol), 3-indolylmethanol **2 a** (0.1 mmol), catalyst **4 d** (0.015 mmol), and sodium sulfate (100 mg). After being stirred at 25 °C for 12 h, the reaction mixture was filtered to remove sodium sulfate and the collected solid was washed with ethyl acetate. The combined filtrate and washings were concentrated under reduced pressure to leave the crude product, which was purified by flash column chromatography on silica gel to afford pure **3 aa**.

(1*S*,2*R*,3*R*)-1′-Methyl-3-(3-methyl-1*H*-indol-7-yl)-2-phenyl-3,4-dihydro-2*H*-spiro(cyclopenta[*b*]indole-1,3′-indolin)-2′-one (3 aa): Flash column chromatography, eluting with petroleum ether/ethyl acetate (6:1), after a reaction time of 12 h yielded 33.6 mg (68%) of **3 aa**; >95:5 d.r.; colorless solid, m.p. 176.0–177.4 °C; $[\alpha]_{20}^{D}=-305.5$ ($c=0.31$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.44$ (s, 1H), 7.76 (s, 1H), 7.54 (dd, $J=7.4$, 1.1 Hz, 1H), 7.10–6.92 (m, 12H), 6.89–6.82 (m, 2H), 6.79–6.72 (m, 2H), 5.39 (d, $J=8.4$ Hz, 1H), 5.23 (d, $J=8.3$ Hz, 1H), 3.37 (s, 3H), 2.31 ppm (d, $J=0.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=180.9$, 145.8, 142.9, 141.0, 137.4, 133.9, 130.6, 129.6, 128.2, 127.9, 127.8, 126.9, 125.9, 123.0, 122.8, 122.6, 122.3, 121.9, 120.2, 118.7, 118.6, 118.0, 117.9, 112.0, 110.9, 107.7, 66.3, 60.5, 48.8, 26.7, 9.6 ppm; IR (KBr): $\tilde{\nu}=3378$, 3055, 2919, 1697, 1611, 1492, 1469, 1449, 1349, 1375, 1313, 1248, 1126, 1089, 1057, 1021, 907, 806, 740, 696 cm^{-1}; ESI FTMS: exact mass calcd for $[C_{34}H_{27}N_3O+Na]^+$: m/z 516.2052; found: m/z 516.2052; enantiomeric excess: 96%, determined by HPLC (Daicel Chirapak IA, hexane/isopropanol, 70:30, flow rate 1.0 mL min^{-1}, $T=30$ °C, 254 nm): $t_R=5.11$ min (minor), $t_R=11.64$ min (major).

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Keywords: asymmetric synthesis · cascade reactions · organocatalysis · spirooxindole · vinylindoles

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FULL PAPER

C7-Functionalized Indoles

F. Shi, H.-H. Zhang, X.-X. Sun, J. Liang, T. Fan, S.-J. Tu*

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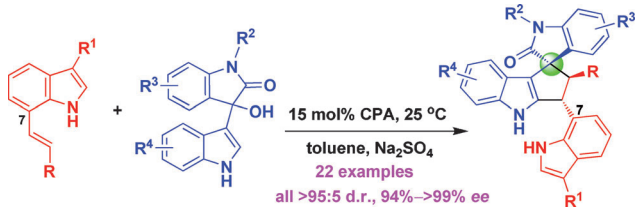
Organocatalytic Asymmetric Cascade Reactions of 7-Vinylindoles: Diastereo- and Enantioselective Synthesis of C7-Functionalized Indoles



Cascade reactions of 7-vinylindoles: The first catalytic asymmetric cascade reaction of 7-vinylindoles has been established by the rational design of such substrates. Cascade reactions with isatin-derived 3-indolylmethanols catalyzed by chiral phosphoric acid (CPA; see scheme) allow the diastereo- and enantioselective synthesis of C7-functionalized indoles as well as the construction of cyclopenta[*b*]indole and spirooxindole frameworks (all >95:5 d.r., 94–>99% *ee*).