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Catalytic Asymmetric Nucleophilic Addition of 3-Vinyl Indoles to Imines

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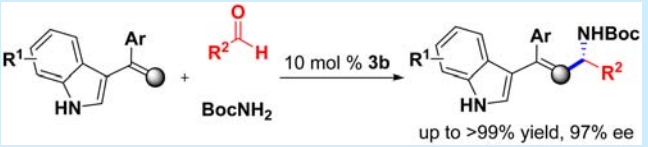
Supporting Information

ABSTRACT: The 3-vinyl indole is used as a nucleophile to react with aromatic and aliphatic imines. Chiral 3-substituted indoles bearing multiple functional groups are produced with up to 99% yield, a 98:2 *E*/*Z* ratio, and 97% ee. A possible mechanism is proposed to explain the observed stereoselectivities. This strategy provides an efficient way for the preparation of novel chiral 3-substituted indoles.



Indole is one of the most widely distributed heterocycles in nature. Substituted indole units not only appear extensively in biologically active natural and unnatural compounds[1] but also have been referred to as "privileged structures" in a large number of drugs.[2] Chiral indoles bearing various substituents at the 3-position are the most popular researched indoles because of their wide range of biological activities. There are two approaches toward the synthesis of optically active 3-substituted indoles. One approach is the use of enantioselective Friedel−Crafts-type reactions of indoles with various electrophiles (Figure 1a, (i)).[3] The other approach is the use of 3-functional indoles, such as 3-indolylmethanols, as reactants for the synthesis of chiral 3-substituted indoles (Figure 1a, (ii));[4] with this approach, many chiral 3-substituted indoles that are difficult to synthesize from indoles can be easily prepared. However, in this respect, 3-indolylmethanols have been the only well-used candidates and are limited in their ability to act as electrophiles because of their molecular structure properties. Therefore, it is valuable to develop new 3-functional indole-involved strategies for the synthesis of structurally diverse chiral 3-substituted indoles. As a part of our continuous research effort,[5] we attempted to discover 3-functional indoles other than 3-indolylmethanol, while aiming to find new reaction models and subsequently enrich the synthetic methodologies for chiral 3-substituted indoles.

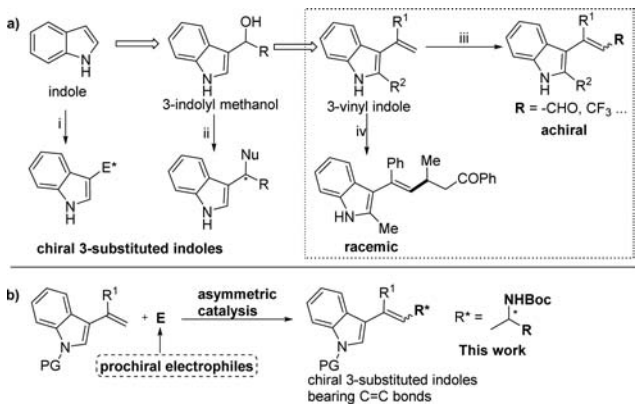


Figure 1. (a) Representative approaches leading to 3-substituted indoles; (b) hypothetical pathway (E = Electrophile, Nu = Nucleophile).

3-Vinyl indole is one of the most important 3-functional indoles, and its derivatives are sophisticated building blocks in the asymmetric synthesis of substituted indoles. Summarily, 3-vinyl indoles have already been successfully used as dienes,[6] dienophiles,[7] and electrophiles[8] in asymmetric catalysis. We noticed that the 3-vinyl indole has been reported as a good nucleophile in the formylation,[9a,b] trifluoromethylation,[9c] alkylation,[9d] and conjugated addition[9e] reactions, leading to the corresponding achiral or racemic 3-subsituted indoles (Figure 1a, (iii−iv)). We envisioned that this nucleophilic property could be used in catalytic asymmetric synthesis for encounters between prochiral electrophiles and 3-vinyl indole, consequently producing a series of new chiral 3-substituted indoles bearing multiple functional groups (Figure 1b). If so, a new application of 3-vinyl indole in catalytic asymmetric synthesis would be achieved. However, there are two challenges in this strategy: the 2-position of 3-vinyl indole can easily participate in the reaction, which will lower the efficiency of preparing chiral 3-substituted indoles, and both of the enantio- and cis/trans- selectivities of the target products need to be improved simultaneously. The benefits and aforementioned challenges stimulated our interest in working on this strategy.

We chose the phenyl substituted 3-vinyl indole **1a** and N-Boc aminal[10] **2a** as reactants, and the well-known group of chiral phosphoric acids[11] as catalysts to validate our hypothesis. We hoped the phenyl of **1a** could prevent the potential cyclization reaction. If so, this transformation will give a concise way leading to the indolyl substituted allylic amines. Many compounds bearing 3-indolyl allylic amine skeletons have

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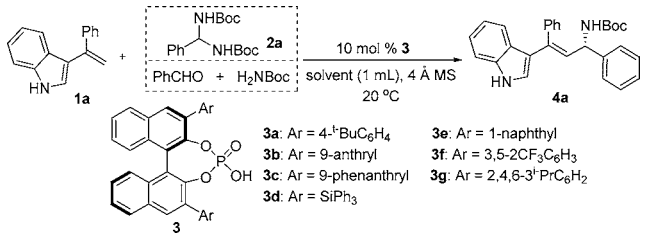
been reported with good biological activities, such as 5-HT2A receptors, selective serotonin reuptake inhibitors, and 5-HT1A antagonists.[12] As expected, in the promotion of 10 mol % phosphoric acid (*R*)-**3a**, the desired product **4a** was obtained in moderate yield; however, there was no enantioselective discrimination observed (Table 1, entry 1). Then, the chiral phosphoric acid catalyst **3b** bearing 9-anthryl was introduced in this reaction, and the product **4a** was generated in 80% yield with 66% ee (Table 1, entry 2). These results indicated that the bulky substituent on the 3,3′-position of catalysts **3** could possibly enhance the enantioselectivity. Then, catalysts **3c**–**g** were examined in this reaction (Table 1, entries 3–7). The catalyst **3b** was the most suitable for this transformation in terms of both yield and enantioselectivity. Accordingly, we further optimized the reaction conditions. The solvent screening indicated that the 1, 2-dichloroethane (DCE) was the best solvent choice in terms of yield, *E*/*Z* ratio, and enantioselectivity (Table 1, entry 12). We found that the additives could affect the reaction outcomes. Specifically, the additive 3 Å MS greatly improved the stereoselectivities (Table 1, entry 14). After optimizing the two-component reaction conditions, we attempted to conduct this reaction in a three-component manner because the aminal **2a** could be formed under acidic conditions. Notably, our experiment was successful, and the product **4a** was obtained in excellent *E*/*Z* ratio and enantioselectivity, albeit the yield decreased slightly (Table 1, entry 15). Then, we further optimized the three-component reaction conditions. When we increased the reactants' concentrations, the yield of **4a** enhanced to 84%, and the *E*/*Z* ratio and enantioselectivity were still maintained at a high level (Table 1, entry 16).

Table 1. Optimization of Reaction Conditions[a]

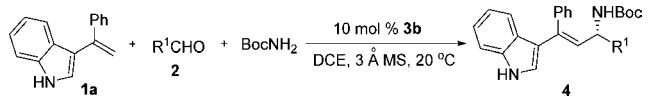


entry	3	solvent	*t* (h)	y (%)[b]	*E*/*Z*[c]	ee (%)[c]
1	**3a**	CH_2Cl_2	47	68	–	0
2	**3b**	CH_2Cl_2	10	80	93:7	66
3	**3c**	CH_2Cl_2	6	75	90:10	54
4	**3d**	CH_2Cl_2	24	<5	–	–
5	**3e**	CH_2Cl_2	40	70	86:14	10
6	**3f**	CH_2Cl_2	42	65	64:36	21
7	**3g**	CH_2Cl_2	97	55	92:8	92
8	**3b**	CCl_4	24	62	96:4	86
9	**3b**	Et_2O	70	10	99:1	5
10	**3b**	$PhCH_3$	70	48	97:3	81
11	**3b**	$CHCl_3$	17	50	98:2	84
12	**3b**	DCE	12	83	97:3	81
13[d]	**3b**	DCE	10	83	94:6	82
14[e]	**3b**	DCE	10	83	97:3	92
15[e,f]	**3b**	DCE	60	70	97:3	92
16[f,g]	**3b**	DCE	50	84	97:3	92

[a]**1a** (0.06 mmol), **2a** (0.05 mmol), 4 Å MS (50 mg). [b]Isolated yield. [c]Determined by HPLC. [d]5 Å MS as additive. [e]3 Å MS as additive. [f]**1a** (0.075 mmol), PhCHO (0.05 mmol), $BocNH_2$ (0.125 mmol). [g]**1a** (0.15 mmol), PhCHO (0.1 mmol), $BocNH_2$ (0.25 mmol), 3 Å MS (100 mg).

With the optimal reaction conditions in hand, we then examined the substrate scope of this three-component reaction. First, various aromatic aldehydes were introduced into this transformation. The electron properties and position of the substituents on the phenyl ring could affect the reaction outcomes. For example, the 4-electron-withdrawing group substituted benzaldehydes were excellent reaction partners in this reaction, producing the corresponding products in high yield and with excellent *E*/*Z* ratios and enantioselectivities (Table 2, entries 2–4). In comparison, the enantioselectivity achieved with 4-Me benzaldehyde was lower (Table 2, entry 5). The 3-substituted benzaldehydes having electron-rich and -deficient functional groups generated the desired products with excellent results (Table 2, entries 6–10), while the *o*-substituted benzaldehydes decreased the enantioselectivities slightly (Table 2, entries 11–12). Subsequently, aliphatic aldehydes were used as acceptors in this transformation as well. We found that cyclohexanecarbaldehyde and pentanal were also suitable reactants, giving the corresponding products in good yields with high *E*/*Z* ratios and enantioselectivities (Table 2, entries 14–15).

Table 2. Substrate Scope with Respect to Aldehydes[a]



entry	4	R^1	*t* (h)	y (%)[b]	*E*/*Z*[c]	ee (%)[d]
1	**4a**	C_6H_5	41	84	97:3	92
2	**4b**	4-ClC_6H_4	36	92	95:5	92
3	**4c**	4-FC_6H_4	28	81	94:6	91
4[e]	**4d**	4-$NO_2C_6H_4$	36	76	93:7	92
5	**4e**	4-MeC_6H_4	48	80	95:5	78
6	**4f**	3-MeC_6H_4	40	82	92:8	93
7	**4g**	3-$MeOC_6H_4$	46	74	97:3	94
8	**4h**	3-FC_6H_4	51	63	98:2	94
9	**4i**	3-ClC_6H_4	29	70	96:4	97
10	**4j**	3-BrC_6H_4	52	62	95:5	96
11	**4k**	2-ClC_6H_4	20	87	89:11	88
12	**4l**	2-FC_6H_4	20	92	94:6	83
13	**4m**	2-naphthyl	37	79	98:2	94
14	**4n**	*c*-hexyl	7.5	91	93:7	96
15	**4o**	*n*-butyl	64	67	85:15	83

[a]**1a** (0.15 mmol), **2** (0.1 mmol), $BocNH_2$ (0.25 mmol). [b]Isolated yield. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC. [e]**3g** as catalyst.

Next, the substrates of 3-vinyl indoles were investigated. The results are listed in Table 3. First, 3-vinyl indoles bearing various substituents on the indole ring were involved in this reaction. We found that both the electron-rich and -deficient indole substituted 3-vinyl indoles produced the corresponding products in excellent results (Table 3, entries 1–4). Then, various 3-vinyl indoles bearing substituted phenyls were examined. The *o*-substituents slightly increased the reaction outcomes. For example, the 2-F phenyl-substituted 3-vinyl indoles generated the product **5e** in excellent yield with a high *E*/*Z* ratio and enantioselectivity (Table 3, entry 5). Either an electron-rich or -deficient substituent was introduced in the 3-position of the phenyl ring of 3-vinyl indole, and the desired

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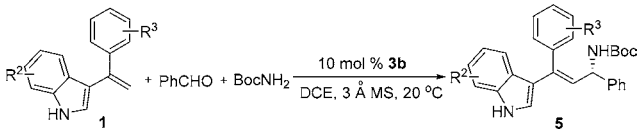
Table 3. Substrate Scope of 3-Vinyl Indoles[a]



entry	5	R^2/R^3	t (h)	y (%)[b]	E/Z[c]	ee (%)[d]
1	**5a**	5-Me/H	47	80	93:7	90
2	**5b**	6-F/H	47	75	97:3	91
3	**5c**	5-Cl/H	36	84	96:4	88
4	**5d**	5-Br/H	47	85	95:5	87
5	**5e**	H/2-F	52	90	98:2	95
6	**5f**	H/3-F	33	88	96:4	89
7	**5g**	H/3-Cl	36	94	98:2	91
8	**5h**	H/3-Me	52	78	96:4	89
9	**5i**	H/3-MeO	47	77	96:4	92
10	**5j**	H/3,5-2Me	40	78	95:5	89
11	**5k**	H/4-F	67	62	97:3	91
12	**5l**	H/4-Cl	52	88	97:3	91
13	**5m**	H/4-Me	23	95	95:5	92
14[e]	**5n**	H/4-Cl	12	98	90:10	83

[a]**1** (0.15 mmol), PhCHO (0.1 mmol), $BocNH_2$ (0.25 mmol). [b]Isolated yield. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC. [e]2-F-PhCHO instead of PhCHO.

compounds **5f–j** were produced with excellent results (Table 3, entries 6–10). Comparable results were obtained when we used 3-vinyl indoles bearing 4-substituted phenyls as donors (Table 3, entries 11–13). We noticed that the 4-Me phenyl-substituted 3-vinyl indole increased the reaction rate greatly (Table 3, entry 13) possibly because the electron-donating property of the 4-Me group increased the nucleophilicity of 3-vinyl indole. The absolute configuration of **5n** (E, S) was established by X-ray single-crystal analysis.[13] The stereochemistries of compounds **4a–o** and **5a–m** were assigned by analogy with those of **5n**.

The possible reaction mechanism was studied. First, the N-Boc protected imine formed *in situ* under the acidic conditions and was activated by phosphoric acid (PA*) through the formation of a H-bond (*int.*-**I**).[11] The possible transition state was explored through a control experiment and nonlinear effect investigation. On one hand, we found the reaction could not proceed when we used the *N*-methyl 3-vinyl indole as the donor (Figure 2a); on the other hand, we detected there

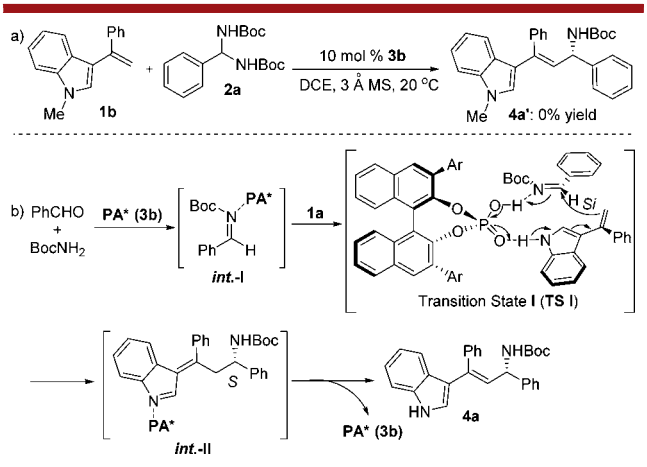
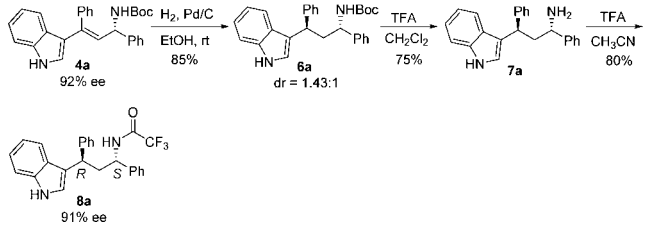


Figure 2. (a) Control experiment. (b) Proposed reaction mechanism.

existed a linear effect between the ee values of the catalyst and products (see the Supporting Information). Based on these results, we speculated that, in the transition state (TS **I**), one catalyst molecule activated the 3-vinyl indole and imine via the formation of hydrogen bonds simultaneously, and the phenyls of 3-vinyl indole and imine were located at the opposite position of the 3,3′-substituents of catalyst **3b** to avoid the steric influence. Then, the 3-vinyl indole attacked the imine at the *Si*-face, producing the intermediate **II** (*int.*-**II**). The final product **4a** was generated via isomerization, and the catalyst **3b** was released (Figure 2b).

The alkenylation products were readily converted into other indole compounds. For example, compound **4a** generated indolyl propylamine **7a** through hydrogenation and deprotection (Scheme 1). Some compounds containing an indolyl

Scheme 1. Synthetic Application



propylamine core have good biological activities.[14] The single crystal of compound **8a** was then prepared and submitted to X-ray analysis for determining the absolute configuration of the new generated chiral center.[13]

In conclusion, 3-vinyl indoles were successfully used as nucleophiles in the catalytic asymmetric synthesis of 3-substituted indoles. The target products bearing multiple functional groups were generated in excellent yields with high E/Z ratios and enantioselectivities under mild reaction conditions. A possible mechanism was proposed to explain the stereoselectivities exhibited in these transformations. Applications of this synthetic strategy to construct chiral 3-substituted indoles in a broad scope are currently underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01880.

Representative experimental procedures and analytical data for all new compounds; X-ray crystalographic data for determination of the configuration of product (PDF)

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Notes

The authors declare no competing financial interest.

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