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Chiral Phosphoric Acid-Catalyzed C6 Functionalization of 2,3-Disubstituted Indoles for Synthesis of Heterotriarylmethanes

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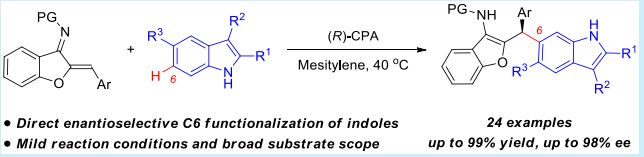
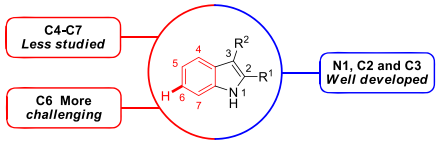
ABSTRACT: The direct regio- and enantioselective C6 functionalization of 2,3-disubstituted indoles with azadienes has been developed using chiral phosphoric acid as catalyst, providing a convenient approach to synthesize the optically active heterotriarylmethanes with excellent yields, broad substrate scope, and up to 98% ee. Mechanistic studies revealed that *N*-alkylation of 2,3-disubstituted indoles with azadienes would be reversible, and enantioselective C6 functionalization could be enabled.



Indoles belong to a class of nitrogen-containing heteroaromatics and have been recognized as privileged structure scaffolds due to their prevalence in natural products as well as pharmaceutical molecules.[1] Therefore, the synthesis of functionalized indoles has attracted considerable attention and various protocols have been developed.[2,3] Among them, the asymmetric functionalization of indoles is one of the most straightforward and efficient approaches for the preparation of chiral indole derivatives, and has achieved great progress.[3] Due to the inherent activity of the pyrrole ring, the asymmetric functionalization reactions usually occur at the N1, C2, and C3 positions of indoles (Scheme 1).[3] As opposed to the well-developed N1, C2, and C3 functionalization of indoles, the enantioselective C−H functionalization at the low active C4−C7 positions of the fused benzene ring has been less studied (Scheme 1), and the majority of them were realized by introducing guiding groups.[3] Notably, the direct enantioselective C6 functionalization of indoles could be regarded as a more challenging task (Scheme 1).[3] There are few examples of direct racemic C6 functionalization of indoles. In 2014, You and co-workers described scandium triflate-catalyzed direct C6 functionalization of 2,3-disubstituted indoles with aziridines.[4a] Subsequently, Brønsted acid-catalyzed and gallium triflate-catalyzed direct C6 functionalization of indoles were reported.[4b−e] To the best of our knowledge, only one direct asymmetric C6 functionalization of 2,3-disubstituted indole was disclosed. In 2019, Zhang and co-workers illustrated chiral phosphonic acid-catalyzed C6 functionalization of 2,3-disubstituted indoles with isatin-derived *N*-Boc ketimines.[5] Hence, it is highly desirable to explore the direct asymmetric C6 functionalization of indoles.

Scheme 1. Enantioselective Functionalization of Indoles



Aurone-derived azadienes are important highly active electrophilic intermediates in organic synthesis due to the driving force of rearomatization, and have received tremendous attention. In recent years, numerous catalytic asymmetric reactions of aurone-derived azadienes for the construction of chiral benzofuran derived compounds have been successfully developed.[6,7] As our contiguous exploration of the application of azadienes, we concentrated on organocatalytic asymmetric reactions of azadienes.[7f−i] Previously, we successfully realized chiral phosphoric acid-catalyzed C3-functionalization of indoles with azadienes (Scheme 2a).[7i] In order to diversify the direct enantioselective C6 functionalization of indoles, we envisioned the combination of 2,3-disubstituted indoles and aurone-derived azadienes in the presence of chiral phosphoric acid to facilitate enantioselective C6 functionalization of indoles. The key for this functionalization reaction is the control of regioselectivity including N1 and C6 selectivity. Due to the high reactivity of azadienes, the *N*-alkylation products would undergo retro-*aza*-Michael addition. Thus, *N*-alkylation of 2,3-disubstituted indoles with azadienes would be reversible and the challenging enantioselective C6 functionalization could be enabled (Scheme 2b). Herein, we reported the direct regio- and enantioselective C6 functionalization of 2,3-disubstituted indoles with azadienes, providing a facile access to optically active heterotriarylmethanes, which are essential motifs in natural products and biologically active molecules.[8]

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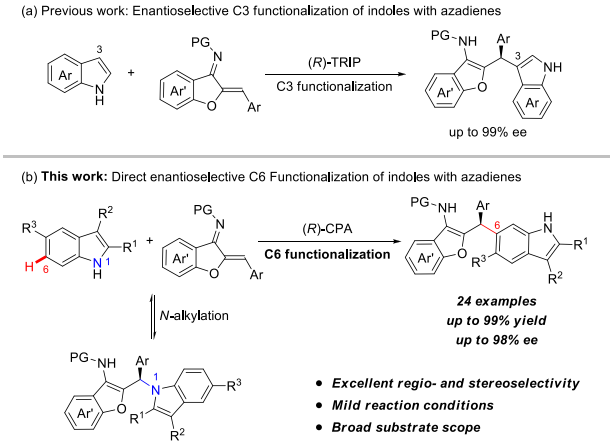
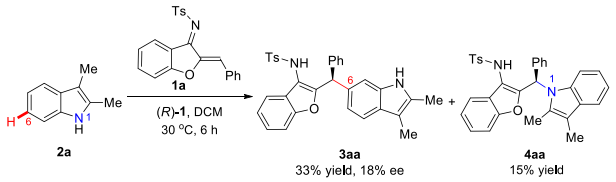
Scheme 2. Enantioselective Functionalization of Indoles with Azadienes



To test our hypothesis, we initially explored enantioselective functionalization of 2,3-dimethylindole **2a** with azadiene **1a** in the presence of chiral phosphoric acid (*R*)-**1** with dichloromethane at 30 °C. Pleasingly, the transformation conducted smoothly in 6 h. The desired C6 functionalized product **3aa** was obtained in 33% yield and 18% ee; simultaneously, *N*-alkylation product **4aa** could also be achieved in 15% yield (Scheme 3). It was worth to note that *N*-alkylation product

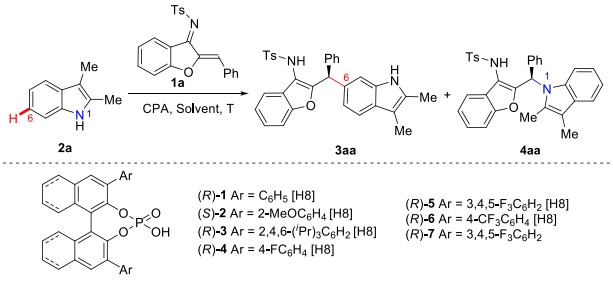
Scheme 3. Initial Exploration



4aa was not very stable and could undergo retro-*aza*-Michael addition to give the starting materials, which was in accordance with our prediction. The structure of product **4aa** was determined by derivatization (for details, see Supporting Information).

Considering that *N*-alkylation of 2,3-dimethylindole **2a** with azadiene **1a** could be reversible, the reaction time was prolonged to 24 h to improve the reactivity of C6 functionalization. As expected, the yield of C6 functionalized product **3aa** was improved slightly and the yield of *N*-alkylation product **4aa** decreased to 3% (Table 1, entry 1). Subsequently, a series of chiral phosphoric acids were evaluated extensively. When fluoro-substituted chiral phosphoric acid (*R*)-**4** was used as catalyst, the yield was improved obviously, and no *N*-alkylation product **4aa** was observed (entry 4). Encouraged by this result, we screened fluoro-substituted chiral phosphoric acids. H8-BINOL-derived fluorinated chiral phosphoric acid (*R*)-**5** was the most favorable catalyst in view of yield and enantioselectivity (entry 5). Various solvents were examined, and it was found that the solvent played a crucial role on the reactivity and enantioselectivity. No desired product was observed with tetrahydrofuran as solvent, and the yield dropped in toluene (entries 8−9). Mesitylene proved to be the most suitable solvent, providing C6 functionalized product **3aa** in 82% yield and 88% ee (entry 10). To further improve the reactivity of C6

Table 1. Optimization of the Reaction Conditions



entry[a]	solvent	CPA	*T* (°C)	3aa/4aa yield (%)[b]	3aa ee (%)[c]
1	DCM	(*R*)-**1**	30	36/3	18
2	DCM	(*S*)-**2**	30	37/2	3
3	DCM	(*R*)-**3**	30	44/−	3
4	DCM	(*R*)-**4**	30	63/−	24
5	DCM	(*R*)-**5**	30	80/−	40
6	DCM	(*R*)-**6**	30	61/−	38
7	DCM	(*R*)-**7**	30	88/−	24
8	THF	(*R*)-**5**	30	trace/−	−
9	Toluene	(*R*)-**5**	30	49/−	71
10	Mesitylene	(*R*)-**5**	30	82/−	88
11	Mesitylene	(*R*)-**5**	0	61/−	78
12	Mesitylene	(*R*)-**5**	40	>95/−	90
13	Mesitylene	(*R*)-**5**	50	>95/−	90
14[d]	Mesitylene	(*R*)-**5**	40	>95/−	86
15[e]	Mesitylene	(*R*)-**5**	40	98/−	90

[a]Conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), CPA (10 mol %), solvent (4.0 mL), 24 h. [b]Determined by NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by HPLC. [d]Mesitylene (2.0 mL). [e]11 h, isolated yield.

functionalization, the effect of reaction temperature was tested. When the reaction temperature was increased to 40 °C, the desired C6 functionalized adduct was furnished in excellent yield and enantioselectivity (entries 11−13). Finally, the reaction concentration was also investigated. Increasing the concentration could cause the slight decrease in enantioselectivity (entry 14). On the basis of screening conditions described above, the use of fluorinated chiral phosphoric acid (*R*)-**5** as catalyst in mesitylene at 40 °C was determined to be the optimal reaction conditions.

With the optimized reaction conditions, the substrate scope of azadienes was examined (Scheme 4). In general, an array of aurone-derived azadienes performed the direct enantioselective C6 functionalization of indoles smoothly. The tolerance of different protective groups on nitrogen was investigated and the transformation was successful for sulfonylimines **1a−1c** with moderate to high enantioselectivities. For azadienes with methyl substituent at the 5- or 6-position of benzofuryl ring, the target products **3da** and **3ea** were obtained in 91% and 87% ee, respectively. The steric properties of the substituents on the aromatic ring had slight influence on yields and enantioselectivities. For the substrate containing trifluoromethyl substituent at the *para* position, the corresponding C6 functionalization product **3ma** resulted in 66% ee. The moderate enantioselectivity might be ascribed to the electronic effects. The absolute configuration of product (+)-**3na**, which was recrystallized from chloroform and *n*-hexane, was unambiguously assigned as *S* by X-ray crystallographic analysis.[9]

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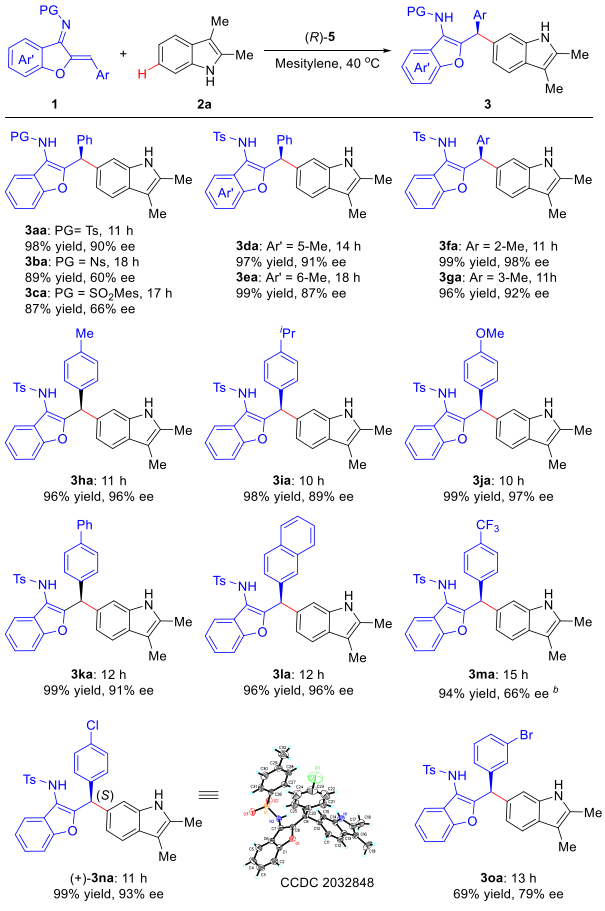
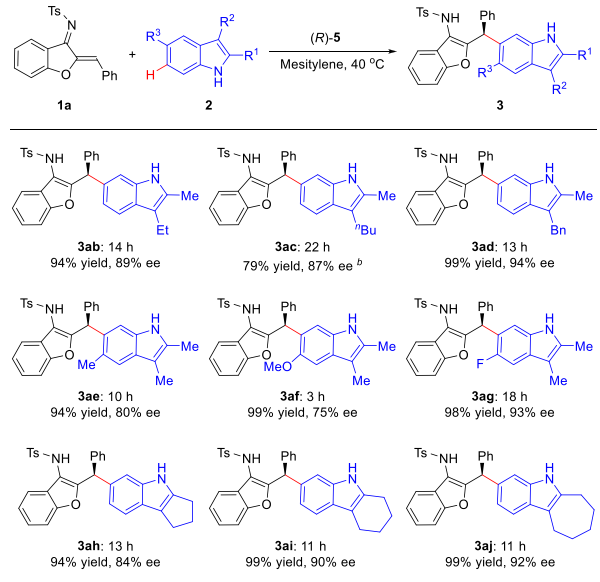
Scheme 4. Substrate Scope of Azadienes[a]



[a]Conditions: azadienes **1** (0.10 mmol), 2,3-dimethylindole **2a** (0.12 mmol), CPA (*R*)-**5** (10 mol %), mesitylene (4.0 mL), 40 °C. [b]50 °C.

Next, we evaluated the substrate scope of 2,3-disubstituted indoles. As depicted in Scheme 5, a plethora of 2,3-disubstituted indoles were suitable reaction partners, giving the desired products in moderate to good enantioselectivities. 3-Benzyl-substituted indole **2d** was prior to 3-alkyl-substituted indoles **2b**−**2c** in view of enantioselectivity for this conversion. For 2,3-disubstituted indoles with electron-donating groups on the 5-position, moderate enantioselectivities were achieved. The C6 functionalization of 2,3-dimethyl-5-fluoroindole **2g** with azadiene conducted well, providing the product **3ag** in 98% yield and 93% ee. Notably, the ring-fused indoles **2h**−**2j** could also exhibit pleasing results. For instance, seven fused ring indole **2j** underwent the reaction successfully with excellent enantioselectivity.

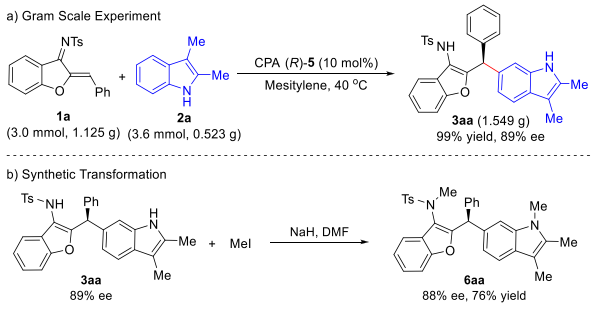
Scheme 5. Substrate Scope of 2,3-Disubstituted Indoles[a]



[a]Conditions: azadiene **1a** (0.10 mmol), indoles **2** (0.12 mmol), CPA (*R*)-**5** (10 mol %), mesitylene (4.0 mL), 40 °C. [b]50 °C.

To demonstrate synthetic potential of this chiral phosphoric acid-catalyzed direct C6 functionalization of 2,3-disubstituted indoles, a gram-scale reaction of azadiene **1a** (1.125 g) with 2,3-dimethylindole **2a** was performed. Satisfyingly, the transformation conducted well under the standard conditions to afford the corresponding product **3aa** in 99% yield and 89% ee without loss of yield and enantioselectivity (Scheme 6a). Next,

Scheme 6. Gram Scale Experiment and Synthetic Transformation



the utility of this strategy has been demonstrated in synthetic transformation reaction. The treatment of **3aa** with iodomethane afforded methylated product **6aa** in moderate 76% yield and without the loss of enantioselectivity (Scheme 6b).

In order to gain the insight of the reaction mechanism, several control experiments were carried out (Scheme 7). When *N*-methyl protected 2,3-dimethylindole **2k** was used to react with azadiene **1a** under the standard conditions, C6 functionalized product **3ak** could be achieved in only 40% yield and 67% ee (Scheme 7a). This result indicated that the hydrogen-bonding interaction between the free N−H moiety of indole and the phosphoryl oxygen atom of chiral phosphoric acid catalyst played a vital role in the control of enantioselectivity. Subjection of *N*-alkylation product **4aa** to the standard conditions, C6 functionalized product **3aa** was obtained in 84% yield and 88% ee (Scheme 7b), demonstrating that the *N*-alkylation could be reversible and enantioselective C6 functionalization could be facilitated. To further identify that *N*-alkylation products could undertake retro-*aza*-Michael addition, we conducted the reaction of azadiene **1a** with 2,3-dimethyl-6-chloroindole **2l** under the standard conditions. In this case, *N*-alkylation product **4al** was delivered in 38% yield (Scheme 7c). The structure of **4al** was determined by X-ray via derivatization (for details, see Supporting Information). Then, the crossover experiment of *N*-alkylation product **4al** and 2,3-dimethylindole **2a** was performed under the standard conditions. This reaction resulted in C6 functionalized product **3aa** in 54% yield with 75% ee and *N*-alkylation product **4al** in 38% recovery (Scheme 7d).

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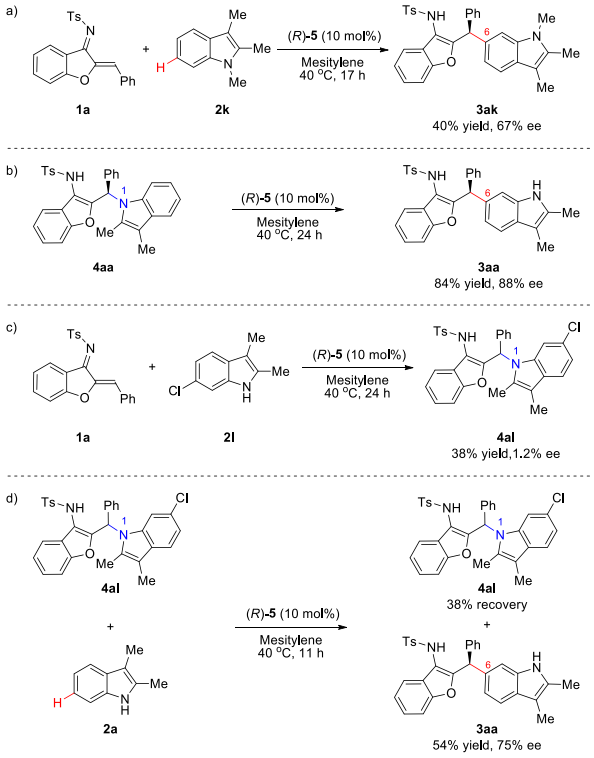
Scheme 7. Control Experiments



On the basis of the above experimental results, we proposed a plausible stereocontrol model for the enantioselective C6 functionalization of indoles with azadienes using chiral phosphoric acid (*R*)-**5** as catalyst (Figure 1). The chiral

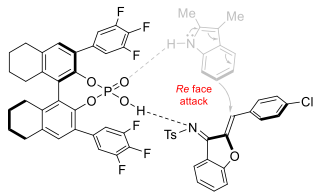


Figure 1. Proposed stereocontrol model.

phosphoric acid served as bifunctional organocatalyst. The hydroxyl group of chiral phosphoric acid had hydrogen-bonding interaction with the ketimine moiety of substrate azadiene, simultaneously, the phosphoryl oxygen atom of chiral phosphoric acid activated indole. The *si*-face of azadiene was shielded by the 3,4,5-trifluoro-phenyl groups at the 3,3′-positions of the catalyst. Therefore, the reaction was more likely to take place at the *re*-face of azadiene, giving *S*-configured heterotriarylmethane product.

In summary, we successfully developed a challenging direct enantioselective C6-functionalization of 2,3-disubstituted indoles, in contrast to the well-established N1, C2, and C3 functionalization of indoles. An efficient chiral phosphoric acid-catalyzed direct C6-functionalization of 2,3-disubstituted indoles with aurone-derived azadienes provided a range of chiral heterotriarylmethanes in high yields with excellent enantioselectivities and regioselectivities. Mechanistic studies suggested that *N*-alkylation of 2,3-disubstituted indoles with azadienes would be reversible and enantioselective C6 functionalization could be enabled. Further studies on the exploration of this strategy to develop enantioselective C6-functionalization of indoles are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04002.

General information, optimization results, general procedures, characterization data, and spectra, X-ray data (PDF)

Accession Codes

CCDC 2023468 and 2032848 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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