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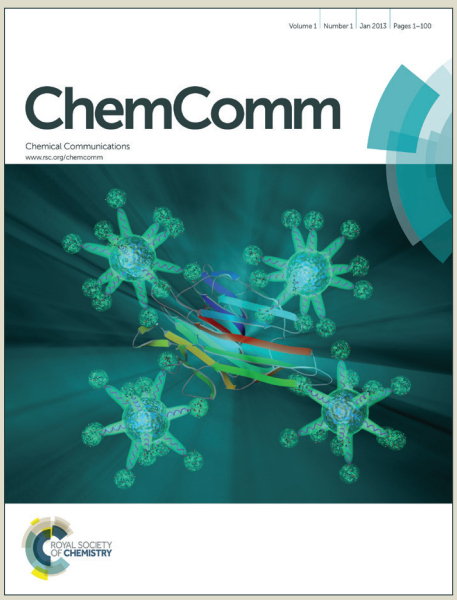

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ARTICLE TYPE

# Organocatalytic Asymmetric Reaction of Indol-2-yl Carbinols with Enamides: Synthesis of Chiral 2-Indole-Substituted 1,1-Diarylalkanes

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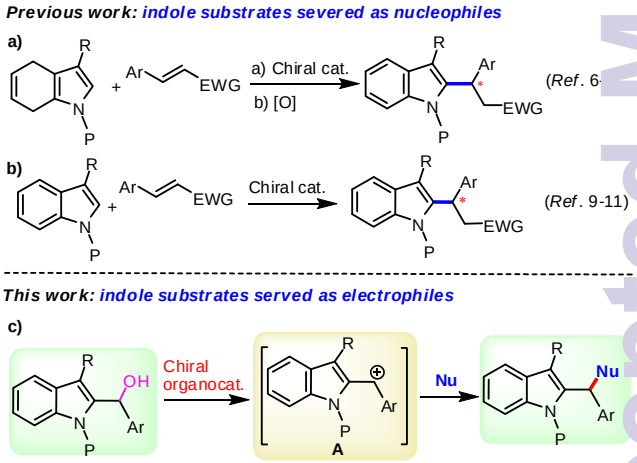
**The chiral phosphoramide-catalyzed asymmetric reaction of indol-2-yl carbinols with enamides is presented. The method provided an efficient and novel way for the synthesis of chiral 2-indole-substituted 1,1-diarylalkane derivatives.**

The 1,1-diarylalkane compounds are prevailing structural motifs in natural products and synthetic molecules for pharmaceuticals and materials.[1] Among them, the heteroaryl-substituted derivatives represent a type of important pharmacophores in medicinal chemistry, particularly those with incorporation of an indole core.[2,3] More significantly, the indole-containing compounds are versatile building blocks in numerous natural products.[4] As a consequence, the enantioselective synthesis of indole-based 1,1-diarylalkanes composes a major theme of recent research in catalytic asymmetric reactions. However, the majority of the investigations have been concentrated on enantioselective synthesis of 3-indole-substituted derivatives.[3,5] The synthesis of 2-indole-substituted analogues remains underdeveloped due to the poor reactivity at indole C2 position. In early studies, the groups of You,[6] Wang,[7] and Du[8] reported the synthesis of 2-indole-substituted 1,1-diarylalkanes by using 4,7-dihydroindole as nucleophile followed by oxidation of the resulting adducts (Scheme 1a). More recently, the groups of Xiao,[9] Feng,[10] and Zhao[11] realized the direct asymmetric Friedel-Crafts reaction at C2 of indole derivatives (Scheme 1b).

All the extant approaches have employed indoles or analogues as nucleophiles. As a result of Martin's[12] and our[13] recent advances in indol-2-yl carbinol chemistry, we devised a strategy by utilizing indole derivatives as electrophiles (Scheme 1c). The new strategy would provide an alternative option for accessing chiral 2-indole-substituted 1,1-diarylalkanes. The successful demonstration of this strategy will be presented herein.




**Scheme 1**. Strategies for the asymmetric synthesis of 2-indole-substitute 1,1-diarylalkanes.

With our experiences on the asymmetric synthesis o diindoylarylmethanes from indol-2-yl carbinols,[13c] we chose chiral phosphoric acids or phosphoramides as the poten catalysts because extensive investigations have witnessed that such Brønsted acids can be versatile catalysts for a wide range of reactions through various activation modes.[14] Moreover, they also carry with them the added advantages of metal free nature and the ease of tuning acidity.[15]

Initially, the reaction of a range of indol-2-yl carbinol derivatives (**1**) and vinylsilyl ether (**2**) was examined, which was assumed to proceed *via* the mono activation mode of ion-pairing or hydrogen-bonding interaction with the presence of phosphoric acids or phosphoramides (Scheme 2a). Unfortunately, a exhaustive screening of various conditions showed that the reaction did not proceed (data not shown). In most cases, a ra d decomposition of **2** was observed. Next, the reaction of indol-2- yl carbinols **1** with enamides **4** was inspected (Scheme 2b). We reasoned that replacement of vinylsilyl ethers with enamid nucleophiles could enable the catalyst to activate both reactant *via* a bifunctional mode through ion-pairing/H-bonding or H bonding/H-bonding interactions.

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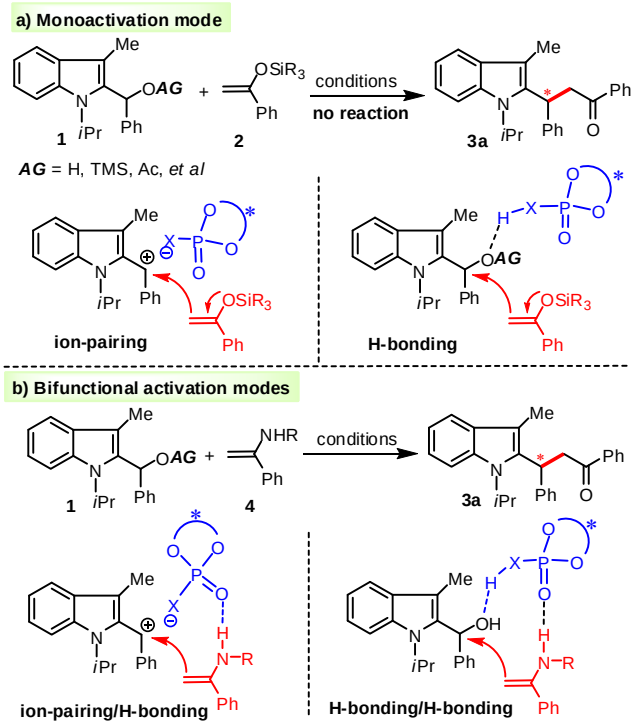
† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, $^1$H-NMR, $^{13}$C-NMR, HRMS, and part of X-ray crystallographic data, and the copies of $^1$H- and $^{13}$C-NMR spectra and HPLC charts. See DOI: 10.1039/b000000x/

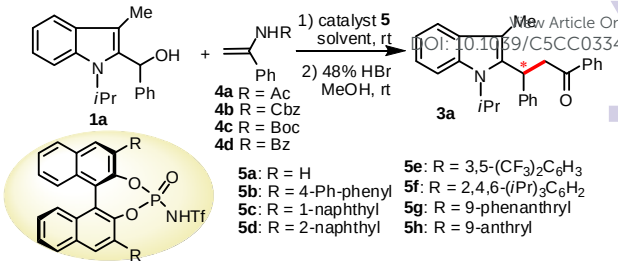



**Scheme 2**. Designed activation modes of indol-2-yl carbinol derivatives with vinlysilyl ethers (a) and enamides (b).

Thus, the reaction of **1a** with various enamide **4** (Table 1) was examined. The results showed that enamides **4a–c** were less effective under various conditions (data not shown). However, **4d** was a promising nucleophile in the presence of phosphoramide **5a** to afford the desired product **3a** in 56% yield and 18% ee in toluene at room temperature (entry 1). A further screening of an array of phosphoramide catalysts (entries 1–8) showed that the BINOL-derived phosphoramide **5g** could be a viable catalyst, providing **3a** in 56% yield and 79% ee (entry 7).

With the optimal catalyst **5g**, a rich variety of solvents were evaluated (entries 9–21). $CHCl_3$ provided the best results in terms of yield, enantioselectivity, and reaction time (entry 14). Having defined the optimal catalyst **5g** and solvent $CHCl_3$ in this way, we optimized the reaction temperature, additives, and concentration (See details in Table S1). It was found that although the enantioselectivities could be increased to 94% ee when the temperature was lowered from room temperature to -10 °C, the yield was dramatically diminished to lower than 30%. At this juncture, the effect of a range of acidic additives including various molecular sieves and Brønsted acids was examined since some prior literatures have demonstrated that the catalytic efficiency of phosphoric acids could be improved with the presence of AcOH.[16] After extensive screening, we eventually found that with the use of 1.5 equiv of *p*-nitrobenzoic acid, the yield of **3a** could be improved substantially to 74% with the maintenance of an excellent enantioselectivity (93% ee) (entry 22). Thus, the optimized conditions for enantioselective synthesis of **3a** are 10 mol% of phosphoramide **5g**, 1.5 equiv of *p*-nitrobenzoic acid in 2 mL $CHCl_3$ solvent.

**Table 1**. Optimization of reaction conditions.[a]



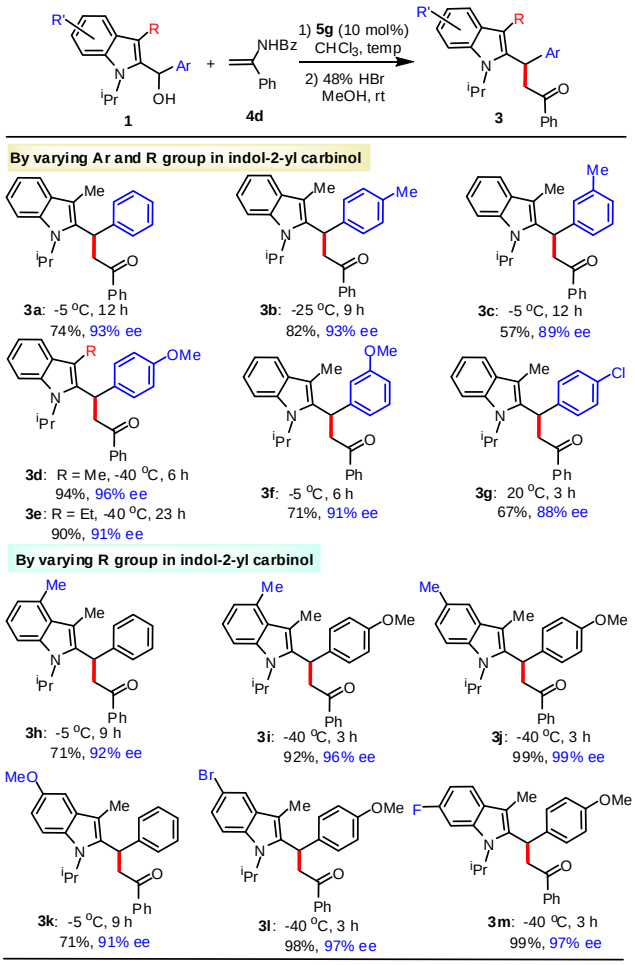



| entry | catalyst | solvent | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | (*R*)-**5a** | toluene | 10 | 56 | 18 |
| 2 | (*R*)-**5b** | toluene | 10 | 51 | 10 |
| 3 | (*R*)-**5c** | toluene | 10 | 50 | 54 |
| 4 | (*R*)-**5d** | toluene | 10 | 49 | 45 |
| 5 | (*R*)-**5e** | toluene | 10 | 65 | 13 |
| 6 | (*R*)-**5f** | toluene | 10 | 29 | 16 |
| **7** | **(*R*)-5g** | toluene | **10** | **56** | **79** |
| 8 | (*R*)-**5h** | toluene | 10 | 49 | 60 |
| 9 | (*R*)-**5g** | benzene | 6 | 45 | 81 |
| 10 | (*R*)-**5g** | PhCl | 3 | 83 | 81 |
| 11 | (*R*)-**5g** | PhF | 10 | 75 | 82 |
| 12 | (*R*)-**5g** | xylene | 6 | 51 | 76 |
| 13 | (*R*)-**5g** | $CH_2Cl_2$ | 3 | 94 | 79 |
| 14 | (*R*)-5g | $CHCl_3$ | 3 | 89 | 86 |
| 15 | (*R*)-**5g** | $(CH_2)_2Cl_2$ | 3 | 82 | 62 |
| 16 | (*R*)-**5g** | $CCl_4$ | 3 | 56 | 75 |
| 17 | (*R*)-**5g** | $Et_2O$ | 10 | 37 | 79 |
| 18 | (*R*)-**5g** | THF | 10 | 25 | 77 |
| 19 | (*R*)-**5g** | dioxane | 10 | 32 | 75 |
| 20 | (*R*)-**5g** | $^t$BuOMe | 10 | 34 | 81 |
| 21 | (*R*)-**5g** | MeCN | 3 | 85 | 9 |
| **22**[d] | **(*R*)-5g** | **$CHCl_3$** | **12** | **74** | **93** |

[a] Unless otherwise noted, the reaction conditions are: **1a** (0.1 mmol), **4d** (0.2 mmol, 2.0 equiv), catalyst **5** (10 mol%) in solvent (2 mL) at room temperature for 10 h; [b] Isolated yield; [c] The ee values were determined by chiral HPLC on a AD-H column; [d] The reaction was performed with the presence of 1.5 equiv of *p*-nitrobenzoic acid in 2 mL $CHCl_3$ at -5 °C.

With the optimized conditions, we next examined the substrat scope (Table 2). A range of indol-2-yl carbinols whose aryl group (Ar) was modified by weak (**3b** and **3c**) or strong (**3d–3f**) electron-donating groups reacted well with enamide **4d**, affording the corresponding 2-indole-substituted 1,1-diarylalkanes in moderately high to high yields (57–94%) as well as good enantioselectivities (88–96%). The *para*-substituted substrates were somewhat more reactive and enantioselective than the *meta*-substituted analogues as shown by a comparison of **3b** *vs.* **3c** and **3d** *vs.* **3f**. In addition, while a somewhat diminished reactivity was observed for a substrate substituted with an electron-withdrawing group (**3g**), satisfactory yield (67%) and high enantioinduction (88% ee) could still be obtained by performing the reaction at 20 °C. The reaction also proceeded efficiently fo indol-2-yl carbinols bearing various R groups in indole ring (**3h–3m**). High to excellent yields (71–99%) as well as excellent enantioselectivities (91–99% ee) were observed for all substrates either by varying the electronic nature or the position of R groups.

**Table 2**. Substrate scope by varying Ar, R and R' group in indol-2-yl carbinols.[a-c]




[a] Unless otherwise noted, the reaction conditions are: **1a** (0.1 mmol), **4d** (0.2 mmol, 2.0 equiv), catalyst **5g** (10 mol%), *p*-nitrobenzoic acid (0.15 mmol, 1.5 equiv) in $CHCl_3$ (2 mL); [b] Isolated yield; [c] The ee values were determined by chiral HPLC.

To extend the scope of the protocol, we further evaluated the reaction by altering the enamide component (Table 3). While a relatively lower yield (70%) and enantioselectivity (82% ee) was observed for the enamide modified by an electron-rich substituent (**3n**, $Ar^1$ = *p*-MeO-$C_6H_4$), other enamides with weak electron-donating Me (**3o**) and electron-withdrawing groups in the phenyl ring periphery such as F (**3p**), Cl (**3q**–**3s**), and Br (**3t**–**3w**) reacted very effectively with different indol-2-yl carbinols. Finally, an examination of the $R^1$ substituents at indole *N*1 revealed that both the reactivity and enantioinduction were sensitive to the electronic and steric nature of $R^1$. For instance, replacement of $^i$Pr group (**3d**) by electron-rich Me (**3x**,) PMB (**3y**), and Bn (**3z**) showed that the enantioselectivities were irregularly decreased, but high yields were still obtained. These observations indicate that $^i$Pr group was suitable for obtaining good enantioinduction under the temporarily optimized conditions. In stark contrast, the reaction was entirely suppressed when an electron-deficient Boc group was attached. The reliablity of the methodology was further exemplified by the gram-scale (up to 1.6 g) synthesis of **3d** and **3t** (**3d**: 95% yield, 95% ee; **3t**: 94% yield, 97% ee). The absolute configuration of the products was assigned to be *R* by X-ray crytallography by converting **3t** into its hydrozone derivative[17] (See SI for details).

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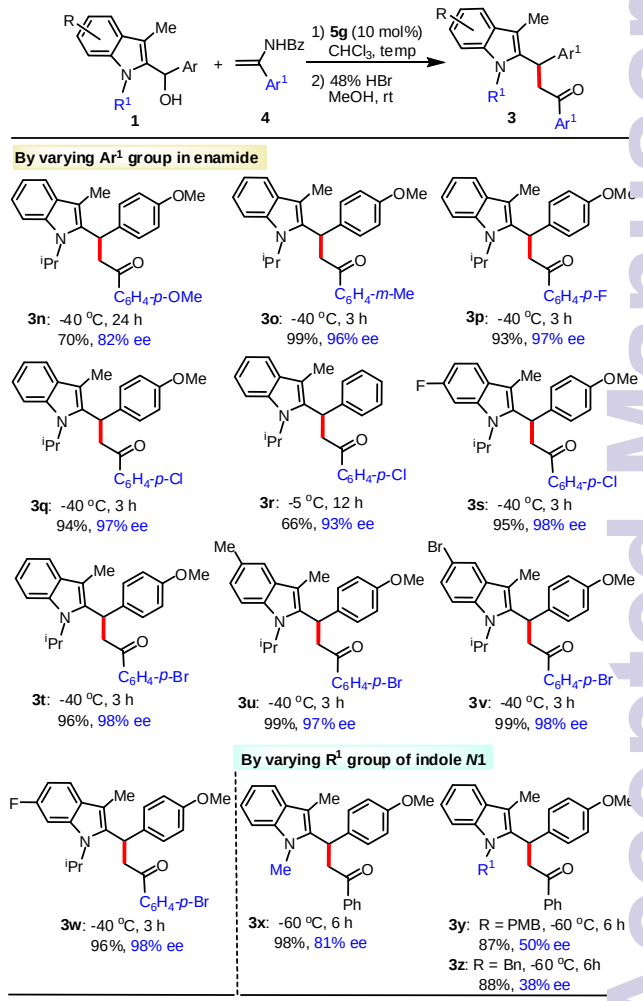
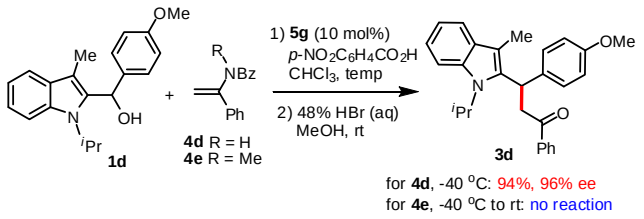
**Table 3**. Substrate scope by varying $R^1$ in indol-2-yl carbinols and $Ar^1$ in enamides.[a-c]



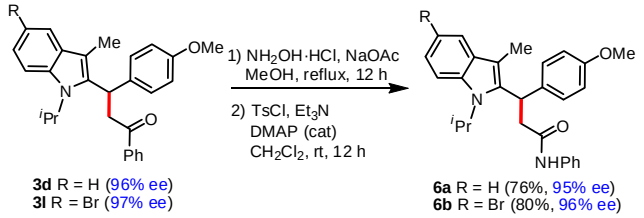

[a] Unless otherwise noted, the reaction conditions are: **1a** (0.1 mmol), **4** (0.2 mmol, 2.0 equiv), catalyst **5g** (10 mol%), *p*-nitrobenzoic acid (0.15 mmol, 1.5 equiv) in $CHCl_3$ (2 mL); [b] Isolated yield; [c] The ee values were determined by chiral HPLC.

We also demonstrated that the use of secondary enamides, i.e., containing N–H bond is vital for this reaction. As illustrated in Scheme 3, **1d** and secondary enamide **4d** could react very smoothly to afford **3d** in excellent yield and enantioinduction. In sharp contrast, ineffective reaction was observed when tertiary enamide **4e** was used in place of **4d**. These results are in good agreement with our proposed bifunctional work mode (Scheme 2b).




**Scheme 3**. Comparison of the reactivity of **4d** and **4e**.

Finally, to demonstrate the synthetic utility of our newly synthesized chiral 2-indole-substituted 1,1-diarylalkanes, **3d** and **3l** were converted into the corresponding amides **6a** and **6b** via a two-step procedure involving oximation of ketone functionality followed by Beckmann rearrangement (Scheme 4). High overall yields were obtained for both compounds. More significantly, the reactions proceeded uneventfully without compromising the enantiomeric purities.




**Scheme 4**. Further derivatization of the synthesized chiral 2-indole-substituted 1,1-diarylalkanes

In conclusion, we have established an organocatalytic protocol for enantioselective synthesis of 2-indole-substituted 1,1-diarylalkanes. The new protocol is compatible with a wide variety of indol-2-yl carbinols and various enamides. Contrary to the reported methods, our strategy has utilized indole derivatives as electrophiles, and thereby offering a new method for accessing chiral 2-indole-substituted 1,1-diarylalkanes. In addition, the synthetic utility of the chiral compounds was also exemplified. An investigation of the biological property of chiral 2-indole-substituted 1,1-diarylalkanes is currently underway.

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17 CCDC 1404860 contains the supplementary crystallographic data o *N*-tosylhydrazone derivative of **3t**.

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The chiral phosphoramide-catalyzed asymmetric reaction of indol-2-yl carbinols with enamides is presented.