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Published on 11 June 2014. Downloaded by WASHBURN UNIVERSITY on 28/10/2014 04:33:18.

Cite this: *Chem. Commun.*, 2014, **50**, 8605

Received 13th May 2014,
Accepted 9th June 2014

DOI: 10.1039/c4cc03605k

www.rsc.org/chemcomm

Chiral phosphoramide-catalyzed enantioselective synthesis of 2,3′-diindolylarylmethanes from indol-2-yl carbinols and indoles†

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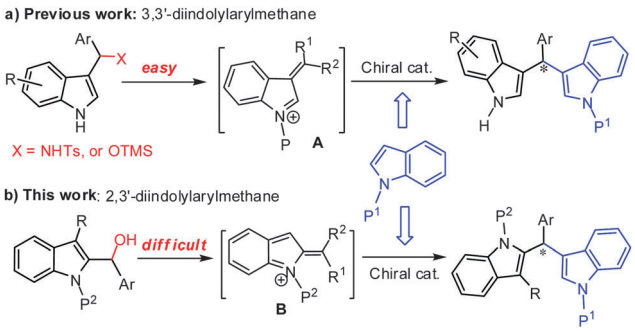
We present the first asymmetric reaction of indol-2-yl carbinols with indole derivatives catalyzed by chiral phosphoramides for the enantioselective synthesis of 2,3′-diindolylarylmethanes in excellent yields of over 90% as well as high enantioselectivity of up to 96% ee.

Hetero-triarylmethanes are unique structural motifs and have a broad range of applications in areas such as materials science, biochemistry, and pharmaceuticals.[1] Among which, diindolylarylmethanes represent appealing hetero-triarylmethanes due to their highly promising therapeutic utility as anticancer agents[2] against an array of cancer cell lines such as breast,[3a] prostate,[3b] colon,[3c] pancreatic,[3d] acute myelogenous leukemia,[3e] bladder,[3f] and endometrial cancer cell lines.[3g] Despite these important advances, the biological properties of the chiral derivatives remain unexplored due to the lack of effective methods for enantioselective synthesis of such compounds. However, numerous studies have witnessed that the biological activity of a molecule, including that of the hetero-triarylmethanes,[4] is dramatically influenced by its chirality. It is therefore highly desired to establish some methods for the enantioselective synthesis of diindolylarylmethanes for activity evaluation.

So far, a few protocols for the enantioselective synthesis of 3,3′-diindolylarylmethanes have been developed *via* the Friedel–Crafts-type reaction of indol-3-yl carbinol derivatives (Scheme 1a).[5] In addition, the synthesis of other 3-substituted chiral indole derivatives using indol-3-yl carbinol analogues has also been frequently reported.[6] However, to the best of our knowledge, methods for the asymmetric synthesis of 2,3′- or 2,2′-diindolylarylmethanes as well as the chemistry of indol-2-yl substrates have not been achieved (Scheme 1b). This is due to the distinctive chemistries associated with indoles. Namely, indole C-2 exhibits a much lower nucleophilicity than that at the C-3 position.[7] On the other hand, the formation of electrophilic indol-2-yl cation species **B** from indol-2-yl derivatives is more difficult to compare with that of indol-3-yl cation **A**.[8]



Scheme 1 Protocols for the enantioselective synthesis of 3,3′-diindolylarylmethanes, (a); and 2,3′-diindolylarylmethanes, (b).

We took particular interest in these challenging issues and initiated a project to investigate the enantioselective synthesis of 2,3′-diindolylarylmethanes by using indol-2-yl carbinol derivatives as the electrophiles (Scheme 1b). Initial evaluation on the feasibility of the protocol through the reaction of **8a** and indole **9a** for the synthesis of **10a** showed that, among an array of BINOL-based chiral Brønsted acids such as (thio)phosphoramides (**11**), (thio)phosphoric acids (**12**), and imidodiphosphoric acids (**13**), phosphoramides **11**[9] might be promising catalysts (Table 1). The reaction could be completed very rapidly within *ca.* 10 min at room temperature to give **10a** in excellent yield of higher than 90% and moderate enantioselectivity of *ca.* 40% ee in several low polarity solvents (see entry 1 in Table 1 for representative data). In comparison, phosphoric acids **12** and imidodiphosphoric acids **13**, which have been shown to be powerful catalysts for indol-3-yl carbinol derivatives,[5,6] were far less effective for indol-2-yl carbinol **8a**.[10] More interestingly, among a range of catalysts **11** being examined, the simplest catalyst (***R*)-11a** (R = H, X = O) derived from the unsubstituted BINOL, exhibited a much better and reversed enantioinducing

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, ^{1}H- and ^{13}C-NMR, and HRMS data, and the copies of ^{1}H- and ^{13}C-NMR spectra, and HPLC chart. See DOI: 10.1039/c4cc03605k

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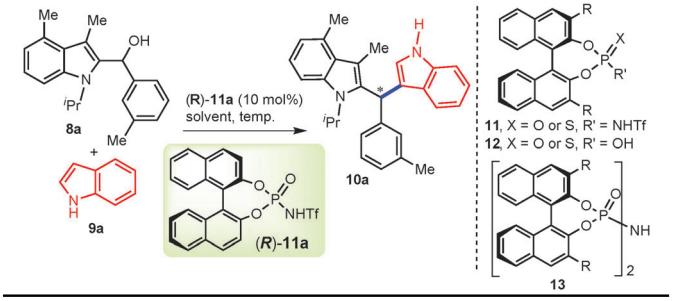
Table 1 Optimization of the reaction conditions[a]



Entry	T (°C)	Solvent	Additive	Yield[b] (%)	ee[c] (%)
1	rt	Toluene	—	90	46
2	−30	Toluene	—	92	75
3	−40	Toluene	—	94	82
4	−50	Toluene	—	93	89
5	**−60**	**Toluene**	**—**	**92**	**91**
6	−70	Toluene	—	94	80
7	−40	ClC_6H_5	—	88	67
8	−40	FC_6H_5	—	90	50
9	−40	F_5C_6H	—	57	27
10	−40	DCM	—	92	42
11	−40	Acetone	—	74	13
12	−40	MeCN	—	62	0
13	−60	Toluene	3 Å MS	90	90[d]
14	−60	Toluene	4 Å MS	90	89[d]
15	−60	Toluene	H_2O	95	90[e]

[a] Reaction conditions: indol-2-yl carbinol **8a** (0.05 mmol), indole **9a** (0.05 mmol), catalyst (***R*)-11a** (10 mol%) in solvent (2 mL) for 10 min to 4 h. [b] Yield of isolated product. [c] The ee value was determined by HPLC on an AD-H column. [d] In the presence of a 60 wt% molecule sieve. [e] In the presence of 10.0 equiv. of water.

ability as compared to the 3,3′-disubstituted (R ≠ H) catalysts.[10] Here, although the reasons for such an unusual observation await a detailed clarification, the results imply that the reaction mechanism of indol-2-yl carbinol substrates is somewhat different from other types of reactions catalyzed by BINOL-based phosphoric acids or phosphoramides,[5,6,9,11] since for most of the reported asymmetric transformations, the incorporation of bulk substituents at the 3,3′-position to increase the steric shielding or π–π interaction was an essential requirement for inducing good enantioselectivity.

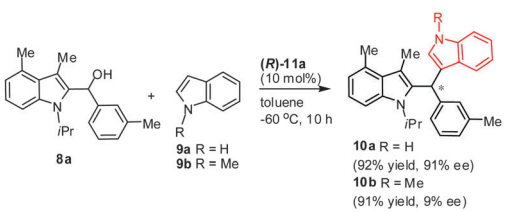
Thus, owing to the promising asymmetric catalytic ability, and the indisputable advantage for easy preparation of **11a**, we carried out a detailed optimization of the reaction parameters by using this catalyst. The enantioselectivity increased gradually upon lowering the temperature and reached up to 91% ee at −60 °C (entries 1–5). Somewhat surprisingly, the ee value reduced to 80% when the temperature was further lowered to −70 °C (entry 6). These observations suggest that a boundary reaction temperature exists for producing the best enantioselectivity although the reasons are not clear at this stage. Of note, although the enantioselectivity was considerably influenced by the reaction temperature, the catalytic activity was less affected by the temperature since all the reactions could proceed smoothly to afford **10a** in excellent yields within 10 min to 4 h at different temperatures in toluene.

We then examined the effect of solvents on this reaction. The results showed that the enantioselectivity dropped off markedly when the polarity of the solvents was increased from toluene (entry 3), *via* chlorobenzene (entry 7) and fluorobenzene (entry 8) to pentafluorobenzene (entry 9), and was almost lost in high polar solvents such as acetone and MeCN (entries 11 and 12). The observation of such a strong solvent effect strongly demonstrates that the ion-pairing interaction[11] between an indole iminium cation species **B** (Scheme 1b) or a benzhydryl-type carbocation[12] and a phosphoramide anion should be involved in the reaction cycle. Finally, considering that a molecule of water is generated during the reaction, we investigated the effect of water on the reaction. Only negligible influence was observed both on yield and enantioselectivity either in the presence of molecular sieves (entries 13 and 14) or by the external addition of a large excess amount of water (entry 15).

Thus, an extensive screening of various reaction parameters led to the establishment of the optimized conditions for the asymmetric synthesis of 2,3′-diindolylarylmethanes. The reaction with 10 mol% of **(*R*)-11a** in toluene at −60 °C afforded the product **10a** in 92% yield and 91% ee (entry 5). Furthermore, the use of 1 : 1 substrates and the absence of extra additives, as well as the generation of water as the sole by-product makes this protocol simple, clean, and atom-economical. In addition, the use of the most readily available catalyst represents an added bonus.

For a better understanding of the working model of the asymmetric transformation, we carried out additional control experiments (Scheme 2). High enantioinduction was achieved for the reaction of indol-2-yl carbinol **8a** with N–H free indole **9a** (91% ee, **10a**). In stark contrast, the enantioselectivity dropped down dramatically to 9% ee for **10b** when N–Me protected indole **9b** was used as a nucleophile although the yield was not influenced. These results suggested that, in addition to the exemplified ion-pairing interaction between the catalyst and cation species **B**, the intermolecular H-bonding interaction between the catalyst and the N–H free indole nucleophile may also play a crucial role in high enantioselectivity. In fact, the important role of H-bonding interactions has been frequently proposed in chiral phosphoric acid or phosphoramide-catalyzed asymmetric reactions.[11,13] These results would provide important information for the design and development of other new asymmetric reactions related with indol-2-yl carbinol substrates.

Next, we investigated the scope and limitation of the protocol. First, an array of indol-2-yl carbinols **8** bearing different R^1, R^2, R^3, and Ar groups was reacted with indole **9a** (Table 2). An excellent yield (>90%) as well as high to excellent enantioselectivity (up to 96% ee) was obtained for indol-2-yl carbinols modified by a Me group (R^1) at C-4, C-5, and C-6 positions (**10a–10g**). In addition, various R^2 substituents such as Me (**10a–10g**), Et (**10h–10j**), and



Scheme 2 Control experiments.

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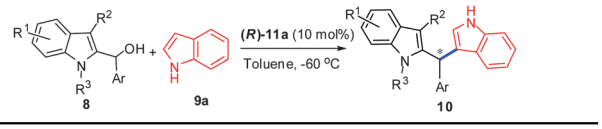
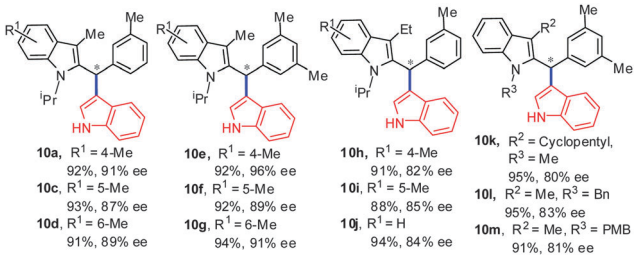
Table 2 Enantioselective reaction of various indol-2-yl carbinols **8** with indole **9a**[a]



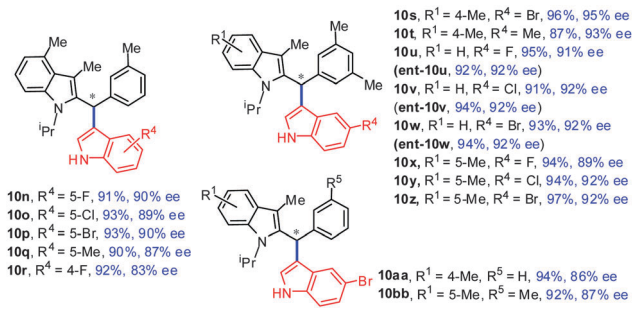


[a] Reaction conditions: indol-2-yl carbinols **8** (0.1 mmol), indole **9a** (0.1 mmol), catalyst (***R***)-**11a** (10 mol%) in toluene (4 mL) at −60 °C for 3–10 h, yield of isolated products; ee % was the average value of two runs and was determined by HPLC on AD-H, OD-H, or OJ-H column (see ESI for details); the reaction time was not optimized.

cyclopentyl (**10k**) were also compatible, although a bulkier R^2 group led to a somewhat decreased enantioselectivity. Finally, an array of R^3 groups such as iPr (**10a–10j**), Me (**10k**), Bn (**10l**), and PMB (**10m**) was also viable. These results exemplified that the reaction exhibits a broad substrate scope for indol-2-yl carbinol electrophiles.

To further demonstrate the broad generality and reliability of the protocol, we examined the asymmetric reaction by varying the indole nucleophiles **9**. The results are summarized in Table 3. Typically, indole nucleophiles with a variety of substituents such as 5-F, Cl, Br, Me, and 4-F reacted smoothly with **8a** to deliver the corresponding diindolylarylmethanes **10n–10r** both in good yield and enantioselectivity. Furthermore, a flexible combination of various indol-2-yl carbinols **8** and indole nucleophiles **9** showed that all the combinations could also proceed very cleanly and efficiently under the optimized conditions to afford the desired products **10s–10bb**

Table 3 Enantioselective reaction of a free combination of various indol-2-yl carbinols **8** with indoles **9**[a]



[a] Reaction conditions: indol-2-yl carbinols **8** (0.1 mmol), indoles **9** (0.1 mmol), catalyst (***R***) or (***S***)-**11a** (10 mol%) in toluene (4 mL) at −60 °C for 3–12 h. Isolated yield; ee % was the average value of two runs and was determined by HPLC on an AD-H or OD-H column; the reaction time was not optimized.

in excellent yields (>90%) as well as high ee values (86–95%). These results unambiguously exemplified that the asymmetric reaction presented herein also displays a broad substrate scope for indole nucleophiles. Finally, by replacing the catalyst (***R***)-**11a** with (***S***)-**11a**, the corresponding enantiomers could also be synthesized uneventfully in identically high yields and enantioselectivities as seen from the data of **10u–10w** *vs.* *ent*-**10u**-*ent*-**10w**. These results would facilitate a clear investigation into the effect of chirality on anticancer properties.

In summary, we have developed a novel methodology that has realized the asymmetric reaction of the inherently challenging indol-2-yl carbinols. The protocol exhibits a broad compatibility for these substrates and can proceed in a very simple, clean, and atom-economical manner in the presence of the most readily available BINOL-based phosphoramides as catalysts. The unprecedented chiral 2,3′-diindolylarylmethane compounds synthesized in this work are interesting candidates for the discovery of new anticancer drugs. In addition, the established interaction model should be useful for the *de novo* design of other types of asymmetric reactions related with indol-2-yl carbinols. Currently, we are screening the anticancer activity of the synthesized chiral diindolylarylmethanes and exploring new conditions for the enantioselective reaction of indol-2-yl carbinols with other appropriate π-nucleophiles. In addition, the determination of the absolute configuration of the products and the clarification of the reasons for why the unsubstituted catalyst **11a** afforded a better and reversed enantioselectivity as compared to the 3,3′-disubstituted catalysts are also the focus of our current studies.

Financial support from NSFC (21272225), and Key Lab of Synthetic Chemistry of Natural Substances, SIOC, is acknowledged.

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