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Core-Structure-Motivated Design of a Phosphine-Catalyzed [3 + 2] Cycloaddition Reaction: Enantioselective Syntheses of Spirocyclopenteneoxindoles

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Supporting Information

ABSTRACT: A novel organocatalytic asymmetric [3 + 2] cycloaddition reaction between methyleneindolinones and allylic compounds yielding complex spirocyclopentaneoxindoles has been developed. It provides extraordinary levels of enantioselective control involving a chiral phosphine as a nucleophilic organocatalyst. Simple precursors were used under mild conditions to construct oxindole derivatives with high enantiopurity and structural diversity. This method should be useful in medicinal chemistry and diversity-oriented syntheses of these intriguing compounds.

Inspired by Williams and co-worker's recent pioneering syntheses of prenylated indole alkaloids and the asymmetric total synthesis of (+)- and (−)-versicolamide B,[1] we have developed a simple and efficient approach to the construction of the spirocyclopentaneoxindole scaffold featured in a large number of natural products[2] and drug candidates[3] (Figure 1). The potential clinical significance of these enantiomerically pure backbones has led to a demand for efficient methods for their synthesis. The regioselective and stereoselective preparation of biologically relevant spirooxindoles, which contain several chiral centers including the stereogenic carbon at C3, is challenging and has been addressed in part in elegant studies[4] founded on a few asymmetric transformations, such as cycloaddition processes[5] and the intramolecular Heck reaction.[6] Thus, developing new, highly enantioselective methods for the direct construction of this skeleton is very important.

In recent years, organocatalytic[7] enantioselective domino/cascade reactions[8,9] have been employed for the synthesis of increasingly complex enantiomerically enriched molecules. Although a wide variety of phosphine-catalyzed reactions have been discovered,[10] relatively few enantioselective variants have been reported,[11] and to date there has been only one report concerning the enantioselective synthesis of spirocyclopenteneoxindoles via phosphine catalysis.[11l] Recently, Lu and co-workers reported annulation reactions of Morita−Baylis−Hillman carbonates using a modified allylic phosphonium ylide strategy that provides a reactive functionalized three-carbon synthon,[12a−e] and Zhou reported the asymmetric intramolecular cyclization of these carbonates and olefins with phosphine catalysts.[12g] Encouraged by these results and the fact that methyleneindolinones are highly reactive Michael acceptors,[5,13]

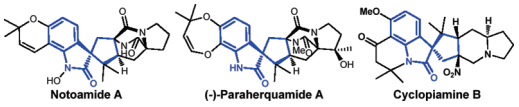

Figure 1. Natural products containing the spirocyclopentaneoxindole scaffold.

Scheme 1. Core-Structure-Motivated Strategy for Spirocyclopentaneoxindole Scaffold Synthesis

we envisioned that spirooxindole skeletons with three stereocenters could be constructed through [3 + 2] cycloaddition reactions between modified allylic compounds and methyleneindolinones catalyzed by chiral phosphine catalysts (Scheme 1). Herein we report the successful implementation of this strategy to provide spirocyclopenteneoxindole derivatives with high enantiopurity and significant opportunities for structural diversification.

We initiated our studies by evaluating the reaction between Boc-protected methyleneindolinone **1a** and Morita−Baylis−Hillman carbonate **2a** using the triarylphosphine (*R*)-BINAP as the catalyst in dichloromethane (DCM) at room temperature (Table 1, entry 1). No product was obtained after 24 h, and **1a** was completely recovered. We assumed that the lack of reaction was due to steric hindrance and the weak nucleophilic ability of the phosphine. Therefore, we turned our attention to more active diphenylphosphine catalysts (entries 2−4). With DIOP as the catalyst, the desired cycloaddition product was obtained in modest yields (entry 2). On the basis of previous reports by Jacobsen[14] and Zhao,[15] we then evaluated some bifunctional phosphine catalysts without success (entries 3 and 4). Biphosphines[16] such as DuPhos derivatives (entry 6) were promising catalysts. (+)-Et-BPE containing a trialkylphosphine moiety proved to be the best candidate for further optimization

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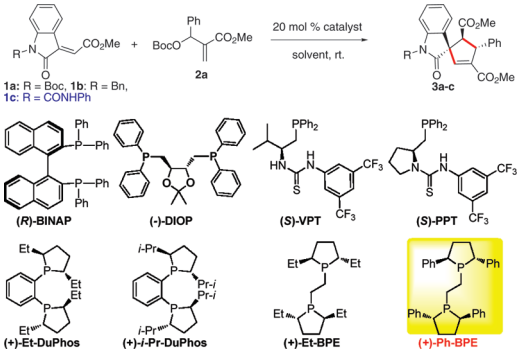
Table 1. Screening of Reaction Conditions[a]



entry	catalyst	1	solvent	t (h)	yield (%)[b]	ee[c]
1	**(*R*)-BINAP**	**1a**	DCM	24	NR	ND
2	**(-)-DIOP**	**1a**	DCM	12	51	52
3	**(*S*)-VPT**	**1a**	DCM	24	39	58
4	**(*S*)-PPT**	**1a**	DCM	24	41	14
5	**(+)-Et-DuPhos**	**1a**	DCM	4	88	4
6	**(+)-*i*-Pr-DuPhos**	**1a**	DCM	12	81	45
7	**(+)-Et-BPE**	**1a**	DCM	1	45	86
8	**(+)-Ph-BPE**	**1a**	DCM	1	84	82
9	**(+)-Ph-BPE**	**1b**	DCM	2	48	97
10	**(+)-Ph-BPE**	**1c**	**DCM**	**1**	**84**	**99**
11	**(+)-Ph-BPE**	**1c**	toluene	4	81	94
12	**(+)-Ph-BPE**	**1c**	Et_2O	1	76	97
13[d]	**(+)-Ph-BPE**	**1c**	DCM	8	81	91
14[e]	**(+)-Ph-BPE**	**1c**	DCM	2	85	99

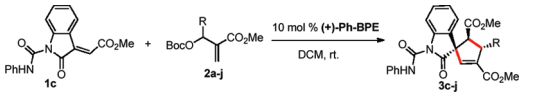
[a] Unless otherwise specified, all reactions were carried out using methyleneindolinone **1a**, **1b**, or **1c** (0.05 mmol, 1 equiv) and allylic compound **2a** (0.075 mmol, 1.5 equiv) with 20 mol % phosphine catalyst at 22 °C. [b] Isolated yields of the major products. Other diastereoisomers were detected by NMR analysis of the crude product. [c] Determined by chiral-phase HPLC analysis. [d] The reaction was conducted at +4 °C. [e] The reaction was carried out using **1c** (0.1 mmol, 1 equiv) and **2a** (0.15 mmol, 1.5 equiv) with 10 mol % catalyst.

(entry 7), as with this catalyst the desired product was obtained with good enantioselectivity (86% ee).

We envisioned that the aromatic $\pi-\pi$ stacking interaction between the catalyst and substrate might have some effect on the stereoselectivity. In the presence of (+)-Ph-PBE, the yield was dramatically improved relative to that of the reaction catalyzed by (+)-Et-BPE, although the enantioselectivity dropped slightly (entry 8). When the protecting group on substrate **1** was Bn rather than Boc, the ee of the reaction catalyzed by (+)-Ph-BPE was improved significantly (entry 9). These results led to design of a substrate containing an amide protecting group, which we hypothesized would form a six-membered ring through hydrogen bonding. With this substrate (**1c**), the desired product was obtained in good yield and excellent enantioselectivity (entry 10), demonstrating that interactions between the substrate and catalyst are crucial. Evaluation of other solvents led to no significant change in the results (entries 11 and 12). Similar results were also obtained when the catalyst loading was decreased to 10 mol % (entry 14).

The generality of the [3 + 2] cycloaddition process was investigated by using various Morita–Baylis–Hillman carbonates (Table 2). Most of the reactions evaluated were completed within 2 h with good yields (63–85%) and enantioselectivities

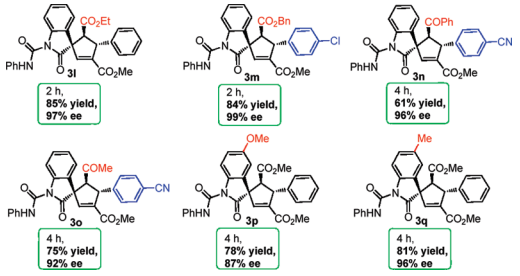
Table 2. Generality of Organocatalytic [3 + 2] Cycloaddition Reactions[a]



entry	R	3	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	**3c**	2	85	99
2	4-Br-Ph	**3d**	1	81	96
3	4-Cl-Ph	**3e**	1	68	95
4	3-Cl-Ph	**3f**	1	73	96
5	4-NO_2-Ph	**3g**	1	81	96
6	4-CN-Ph	**3h**	1	83	96
7	4-OMe-Ph	**3i**	4	66	92
8	2-thiophenyl	**3j**	2	63	91
9[d]	Me	**3k**	12	47	46

[a] All reactions were carried out using **1c** (0.1 mmol, 1 equiv) and **2** (0.15 mmol, 1.5 equiv) with 10 mol % (+)-Ph-BPE in DCM at room temperature (22 °C). [b] Isolated yields of the major products. Other diastereoisomers were detected by NMR analysis of the crude products. Some of drs were estimated as follows: entry 3, dr = 4.1:1:0.2:0.1; entry 7, dr = 3.7:1.0:0.7:0.04; entry 8, dr = 2.3:1.0:0.6:0.1; entry 9, dr = 2.0:1.0:0.2:0.2. [c] Determined by chiral-phase HPLC analysis. [d] For the procedure, see the SI.

Scheme 2. Effect of Methyleneindolinone Substituents



(91–99% ee). The position and electronic properties of the substituent on the aromatic ring had little or no effect on the stereoselectivity. Neutral (entry 1), electron-withdrawing (entries 2–6), and electron-donating (entry 7) groups as well as substrates substituted at different positions on the aromatic ring were good substrates. A substrate with a heteroaromatic group also reacted, affording the corresponding spirocyclopenteneoxindole derivative with excellent enantioselectivity (entry 8). The use of a methyl Morita–Baylis–Hillman carbonate failed to yield the desired product with high enantioselectivity (entry 9).

Further exploration of the substrate scope focused on the methyleneindolinone. As shown in Scheme 2, different substituents in the methyleneindolinone and different esters and ketones yielded the desired products with good selectivity. The absolute configuration of **3m** was determined by X-ray analysis and used together with NMR analysis to establish the relative and absolute configurations of our compounds (see the SI).

To further demonstrate the substrate scope and improve the diastereoselectivity, some Boc-protected methyleneindolinones were tested. However, lower temperatures were needed to achieve the excellent enantioselectivities observed for the amide-protected methyleneindolinones. Boc-protected bispirocyclopenteneoxindoles were obtained in good yields and excellent enantioselectivities in reactions performed at −20 °C for 24 h (Scheme 3). The absolute configuration of **3s** was

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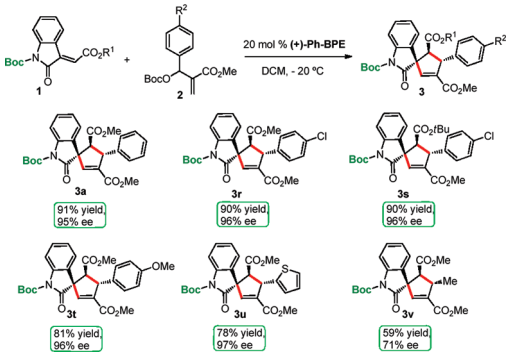
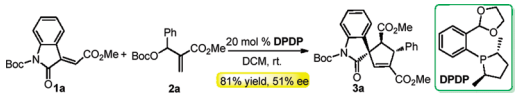
Scheme 3. Boc-Protected Methyleneindolinones



Scheme 4. Deprotection of the Amide Moiety

Scheme 5. Control Experiment for Mechanism Studies



determined by X-ray analysis (see the SI) and found to be in accordance with that of the amide-protected products.

In order to demonstrate the synthetic utility of this method, we developed conditions for deprotection of the amide-protected spirocyclopenteneoxindoles. We were delighted to observe that using KOH and silica gel allowed the amide moiety to be deprotected without affecting the ester functionalities or changing the enantioselectivity (Scheme 4).

While the mechanism of this reaction is not completely elucidated, we believe the second phosphine has a major impact on the stereoselectivity, as evidenced by the reaction with a monophosphine analogue catalyst, DPDP (Scheme 5). We propose the following mechanism based on previous reports of phosphine-catalyzed annulation reactions (Scheme 7).[12b,c] The reaction is initiated by displacement of the carbonate moiety by the phosphine via an addition−elimination mechanism,[12a] which is followed by deprotonation to generate ylide **B**. Regioselective nucleophilic attack on methyleneindolinone **1** by **B** activated by the second phosphine, with subsequent ring closing via intramolecular conjugate addition, affords intermediate **D**. The second phosphine moiety in the catalyst seems to interact with the carbonyl of the methyleneindolinone, since a strong interaction between the catalyst and **1c** (in comparison with **1d**) was observed by ^{31}P NMR spectroscopy (Figure 2). This interaction may explain the lower enantioselectivity obtained for **1d** (Scheme 6). Alternatively, a reversible addition to **1c** might occur. Nucleophilic attack of the carbon bonded to the phosphine would be disfavored because of steric hindrance between the phosphine and the carboxylic ester of **1**. Finally, elimination of the phosphine completes the catalytic cycle, yielding the product **3** and the free catalyst. While further studies need to be performed in order to more fully understand all

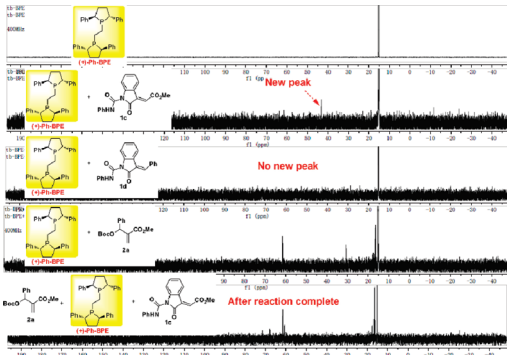
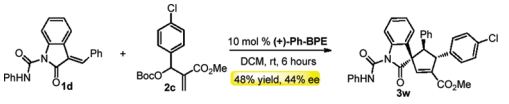
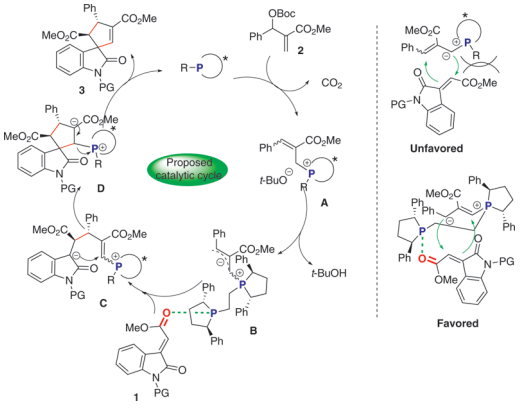


Figure 2. ^{31}P NMR experiments.

Scheme 6. Effect of the Methyleneindolinone Carbonyl Group



Scheme 7. Proposed Mechanism



aspects of the asymmetric induction in this reaction, the trans diastereoselectivity between the carboxylic ester and the phenyl moieties can be explained by the steric hindrance between the two groups in the first nucleophilic attack in going from **B** to **C**. While excellent enantioselectivities were observed for both Boc- and amide-protected oxindoles, the presence of the amide protecting group allowed the reaction to proceed at higher temperatures, probably as a result of the formation of a six-membered ring through intramolecular hydrogen bonding between the amide and the carbonyl of the oxindole, locking the conformation of the substrate.

In summary, we have developed a highly efficient organocatalytic [3 + 2] cycloaddition reaction for the direct construction of spirocyclopenteneoxindole derivatives containing three chiral centers, including one spiro quaternary chiral center. When phosphine was used as the nucleophilic organocatalyst, this straightforward process provided the products with excellent enantioselectivity (up to 99% ee) from simple starting materials and under mild conditions. This strategy will be useful in medicinal chemistry and diversity-oriented synthesis. We believe it to be likely that novel compounds based on spirocyclopenteneoxindole skeletons, such as those prepared here, will provide novel therapeutic agents and useful biological tools.

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■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of all new compounds, HPLC data, X-ray data for **3m** and **3s** (CIF), and complete ref 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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