ARTICLE

Phosphine-Catalyzed Enantioselective [4 + 1] Annulation of Oxindoles with Allenic Ketones for the Construction of Spirocyclopentene oxindoles

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A phosphine-catalyzed enantioselective [4 + 1] annulation between allenic ketones and oxindoles has been developed. This annulation reaction makes use of allenic ketones as a dielectrophilic C4 synthon and oxindoles as a nucleophilic C1 reaction partner. A range of 3-spirocyclopentene-2-oxindoles with a quaternary stereogenic center were prepared in high yields and with excellent enantioselectivities. Synthetic elaborations of the [4 + 1] annulation product led to a facile total synthesis of (+)-debromoflustramide B.

Spirooxindoles are important molecular skeletons that are often found in natural products and active pharmaceutical ingredients (API).[1] In particular, spirooxindoles bearing a five-membered ring structure are one of the most common structural motifs. As shown in Figure 1, cyclopiamine B, marcfortine A and brevianamide A belong to prenylated indole alkaloids family which possess a diverse range of bioactivities including anti-tumor, anthelmintic, insecticidal, antibacterial and calmodulin-inhibition properties.[2] Compound MI-5 is an inhibitor designed from a natural lead compound, which demonstrated excellent anti-tumor activity.[3] While synthetic methods for the preparation of spirooxindoles containing a 5-membered heterocycle have been well investigated,[4,5] on the other hand, strategies to access 5-membered carbocyclic spirooxindoles are less developed.

Over the past two decades, phosphine catalysis has been firmly established as a powerful synthetic tool for the creation of cyclic structural motifs.[6] By employing isatin-derived imines as a reaction partner, phosphine-catalyzed [3 + 2] annulation with allenes/MBH adducts led to effective formation of chiral 3,2'-pyrrolidinyl spirooxindoles.[7] When the asymmetric synthesis of 5-membered carbocyclic spirooxindoles is concerned, there were only a handful of literature reports. In 2010, Marinetti et al.[8] developed an asymmetric [3 + 2] annulation between allenoates and isatin derived alkenes for the production of carbocyclic spirooxindoles (scheme 1, a). Subsequently, we,[9] and the Barbas group,[10] disclosed highly enantioselective [3 + 2] annulations between MBH adducts and isatin-derived alkenes for the construction of optically enriched 3-spirocyclopentene-2-oxindoles (Scheme 1, b). More recently, the Chen group[11] made use of isatin-derived MBH derivatives in phosphine-mediated [3 + 2] annulation reaction to construct spirooxindoles containing a five-membered carbocyclic structure. (scheme 1, c). Notably, all the above approaches required the utilization of isatin derivatives as the starting material, making synthetic approaches less flexible. We question whether simple 2-oxindoles could be employed as the starting material via phosphine activation to access five-membered carbocyclic spirooxindoles. We reckon that there are two key considerations: 1) the weak nucleophilicity of the 3-position of 2-oxindoles dictates the importance of selecting suitable electrophilic reaction partners; 2) cyclization modes other than [3 + 2] annulations would have to be devised to access the desired product. In the past decade, our group has been actively investigating asymmetric phosphine catalysis.[12] Very recently, we introduced a new type of allenic ketone as a

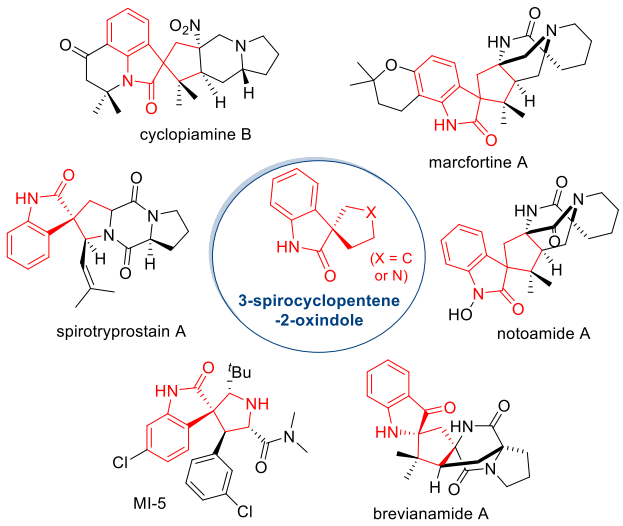

Figure 1. Natural products containing a 3-spirocyclopentene-2-oxindole motif.

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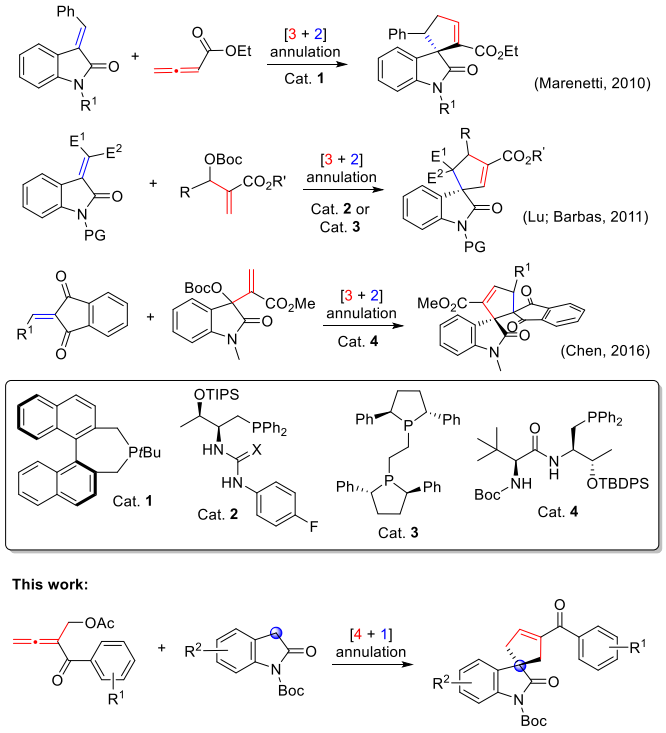
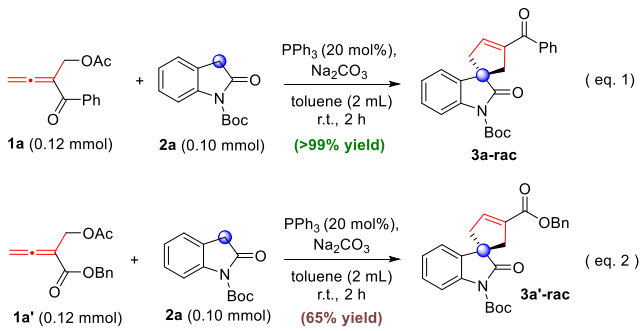
dielectrophilic C4 synthon, and demonstrated its utilization in phosphine catalyzed enantioselective [4 + 2] annulation reaction.[13] We reasoned such dielectrophilic allene ketone partner with enhanced electrophilicity may be used in conjunction with non-decorated oxindole to promote a novel annulation reaction. Herein, we document a highly enantioselective [4 + 1] annulation between 2-oxindoles and an allenic ketone for the efficient preparation of optically enriched 3-spirocyclopentene-2-oxindoles.

Scheme 1. Strategies for the construction of spirocyclopentene oxindoles via phosphine catalysis

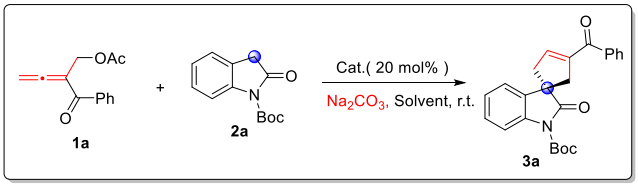


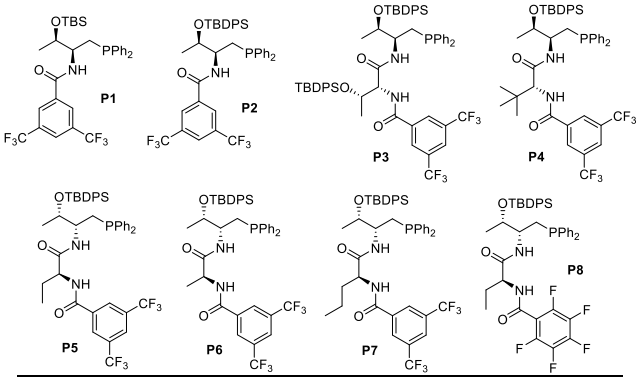
We started our investigation by comparing reactivities of our allenic ketone and Tong's allenoate[14] in the projected [4 + 1] annulation reactions with oxindole substrate. Whereas the reaction between oxindole **2a** and allenic ketone **1a** catalyzed by triphenylphosphine furnished the annulation product in quantitative yield (eq. 1), the reaction employing allenoate **1a'** under otherwise identical conditions afforded the annulation product in 65% yield (eq. 2). This confirmed that allenic ketone is essential for the projected transformation, as its high electrophilicity allows the employment of relatively weak-nucleophilic oxindoles in phosphine-mediated annulation reaction.



Next, we focused on the development of the enantioselective [4 + 1] annulation reaction between oxindoles **2a** and allenic ketones **1a**. While L-thr-derived phosphine–amide catalysts **P1** and **P2** were poor catalysts (entries 1 and 2), thr-based dipeptide phosphines were much more effective (entries 3–8), and among which, phosphine **P8** was most efficient in inducing asymmetry. A quick solvent screening identified *t*-butyl methyl ether (TBME) as the solvent of choice (entries 9–13). The enantioselectivities of the reaction were further enhanced by running the reaction at lower temperatures (entries 14–18). At last, when the reaction was performed at -35 °C in TBME, the desired [4 + 1] annulation product **3a** was formed in high yield with 92% *ee* (entries 16–17). Notably, when the optimized reaction condition were applied to allenoate substrate **1a'** (eq. 2), no reaction was observed, further confirming the reactivity difference between allenic ketone and allenoate. A gram scale reaction was also performed, with a good chemical yield and well-maintained enantioselectivity (entry 19).

Table 1. Reaction screening[a]





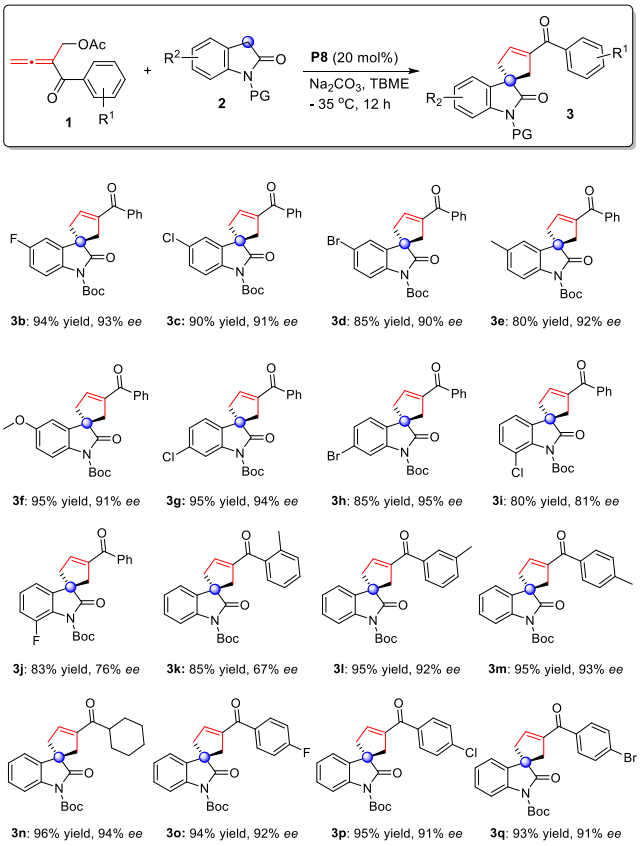
Entry	Cat.	Solvent	t [h]	T (°C)	Yield (%)[b]	*ee* (%)[c]
1	**P1**	CH_2Cl_2	2	r.t.	99	-9
2	**P2**	CH_2Cl_2	2	r.t.	99	-11
3	**P3**	CH_2Cl_2	2	r.t.	99	-64
4	**P4**	CH_2Cl_2	2	r.t.	98	-53
5	**P5**	CH_2Cl_2	2	r.t.	98	74
6	**P6**	CH_2Cl_2	2	r.t.	98	71
7	**P7**	CH_2Cl_2	2	r.t.	98	66
8	**P8**	CH_2Cl_2	2	r.t.	98	75

9	**P8**	THF	2	r.t.	80	84
10	**P8**	Toluene	2	r.t.	99	85
11	**P8**	1,4-dioxane	2	r.t.	85	70
12	**P8**	Ether	2	r.t.	98	87
13	**P8**	TBME	2	r.t.	98	88
14	**P8**	TBME	4	0	98	88
15	**P8**	TBME	6	-25	95	90
16	**P8**	TBME	12	-35	95	92
17	**P8**	TBME	24	-40	93	92
18[d]	**P8**	TBME	12	-35	87	92
19[e]	**P8**	TBME	12	-35	71	92

[a]Reactions were performed with **1a** (0.12 mmol), **2a** (0.10 mmol), Na_2CO_3 (0.10 mmol), and the catalyst (0.02 mmol) in solvent specified (2 mL) at temperatures specified. [b]Yields of isolated products. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Catalyst loading decreased to 10 mol%. [e]**1a** (4.8 mmol), **2a** (4 mmol), Na_2CO_3 (4 mmol), and the catalyst (0.8 mmol) in TBME (20 mL). TBME: *tert*-butyl methyl ether.

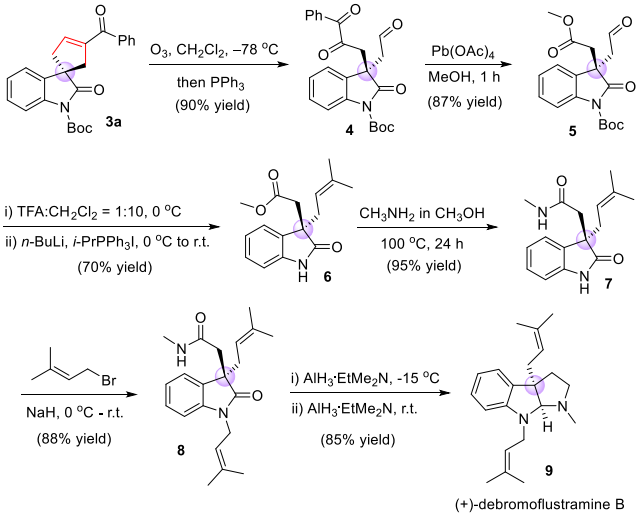
After identifying the best conditions, we proceeded to establish the substrate scope (Scheme 2). The annulation reaction was applicable to various 2-oxindoles, tolerating different types of substituents and electronic nature of groups on the oxindole ring (**3b**–**3h**). Moreover, allenic ketones containing different aryl moieties could also be employed. Substrates bearing *ortho*-, *meta*-, or *para*-methyl substituted, or different halogen atom-substituted phenyl rings (**3k**–**3m**, & **3o**–**3q**) were well-tolerated. In addition, a cyclohexyl-containing allenic ketone (**3n**) was found to be suitable as well. This annulation did not work well for certain types of substrates, when 7-substituted oxindoles (**3i** and **3j**), or an allenic ketone with an ortho-substituent (**3k**) were employed, enantioselectivities of the reactions dropped dramatically. In all the other examples examined, the [4 + 1] annulation products were obtained in very good yields and with excellent enantioselectivities. When the unprotected oxindole or oxindoles with *N*-methyl or *N*-benzyl group were employed, no desired [4 + 1] annulation product was observed.

To demonstrate synthetic utility of this novel annulation reaction, we carried out an asymmetric total synthesis of (+)-debromoflustramie B (Scheme 3). The [4 + 1] annulation product **3a** was subjected to ozonolysis to furnish intermediate **4**, which was oxidized by lead tetraacetate to form ester **5**. After cleavage of the *N*-Boc group, a Wittig reaction afforded terpenyl **6**. The subsequent amidation with methylamine and an *N*-alkylation led to the formation of **7**. Followed by protecting the oxindole with 1-bromo-3-methylbut-2-ene afford **8**. At last, treatment of **8** with $AlH_3{\cdot}EtMe_2N$, induced reductive cyclization to yield tricyclic lactam, which was further reduced to give natural product (+)-debromoflustramie B (**9**) with an overall yield of 38.9%. The absolute configuration of which was confirmed by comparing the optical rotation of our synthetic (+)-debromoflustramie B with the value reported in the literature.[15]



Scheme 2. Reaction scope. Reactions were performed with **1** (0.12 mmol), **2** (0.1 mmol), Na_2CO_3 (0.10 mmol), and **P8** (0.02 mmol) in TBME (2 mL) at -35 °C. Yields refer to isolated products. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Scheme 3. Total synthesis of (+)-debromoflustramine B



In conclusion, we developed a novel asymmetric [4 + 1] annulation by utilizing allenic ketones as a C4 dielectrophilic reaction partner, allowing simple oxindole to be utilized as a C1 reaction component. Remarkably, 3-spirocyclopentene-2-oxindoles containing a quaternary stereogenic center were constructed via a simple one-step operation, in very high chemical yields and with excellent enantioselectivities. Furthermore, the power of synthetic strategy reported herein was demonstrated in a concise total synthesis of (+)-debromoflustramine B. We believe the excellent electrophilicity of allenic ketone-derived C4 synthon will find more applications in phosphine catalysis, enabling the discovery of novel catalytic processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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