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Creation of bispiro[pyrazolone-3,3′-oxindoles] *via* a phosphine-catalyzed enantioselective [3 + 2] annulation of the Morita–Baylis–Hillman carbonates with pyrazoloneyldiene oxindoles†

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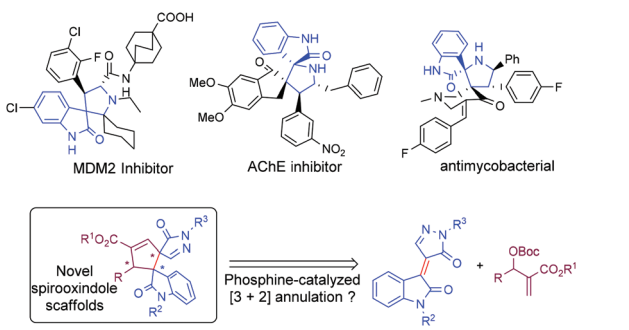
A [3 + 2] annulation between the Morita–Baylis–Hillman (MBH) carbonates and pyrazoloneyldiene oxindoles catalyzed by **(*S*)-SITCP** has been developed. Structurally novel bispiro[pyrazolone-3,3′-oxindoles] containing two contiguous quaternary stereogenic centers were created in excellent yields, in a diastereospecific and highly enantioselective manner.

Spirooxindoles represent a huge family of privileged structural motifs that are widely present in natural products and biologically active molecules.[1] In this context, architecturally complex spirooxindoles containing two vicinal all-carbon quaternary stereogenic centers are the most challenging and intriguing molecular architectures, which pose great challenges to synthetic chemists. Pyrazolones and their derivatives, interesting synthetic intermediates, are widely recognized as important building blocks in medicinal chemistry.[2] In our ongoing research in medicinal chemistry, we became interested in uncovering novel molecular structures that possess anti-cancer activities. We aimed to design novel spirooxindole scaffolds that comprise both oxindole and pyrazolone moieties.[3] In view of a broad spectrum of biological activity profiles of these two subunits, we anticipate that the resulting spirooxindole-pyrazolone framework will not only be structurally novel, but also may have unique/promising biological profiles (Scheme 1).

The synthesis of spirooxindole-pyrazolone is a challenging task, as there are two spirocyclic structures and two vicinal quaternary stereogenic centers packed in a crowded space.[4] To develop an asymmetric synthesis to access such molecules, we envisaged that a phosphine-catalyzed [3 + 2] annulation may be utilized. The past decade has witnessed an astonishing development of asymmetric phosphine catalysis,[5] and undoubtedly, phosphine-catalyzed annulation reactions represent one of the most effective approaches for the construction of ring systems. In particular, phosphine-catalyzed enantioselective [3 + 2] annulations are extremely useful for the synthesis of highly functionalized five-membered cyclic products.[6] Despite the common employment of mono-, di-, or tri-substituted alkenes in phosphine-catalyzed asymmetric annulation reactions, it is really unusual to have tetra-substituted alkenes as reaction partners. Very recently, we disclosed a phosphine-catalyzed [3 + 2] annulation of isoindigos and allenes for the creation of spirocyclic bisindoline alkaloid core structures.[7] We envisioned that tetra-substituted activated alkenes derived from oxindole and pyrazolone may serve as excellent C_2 synthons; the electron-withdrawing oxindole and pyrazolone moieties will render sufficient activation to the double bond flanked by the two heteroaryl subunits. For the



Scheme 1 Constructing novel spirooxindole motifs.

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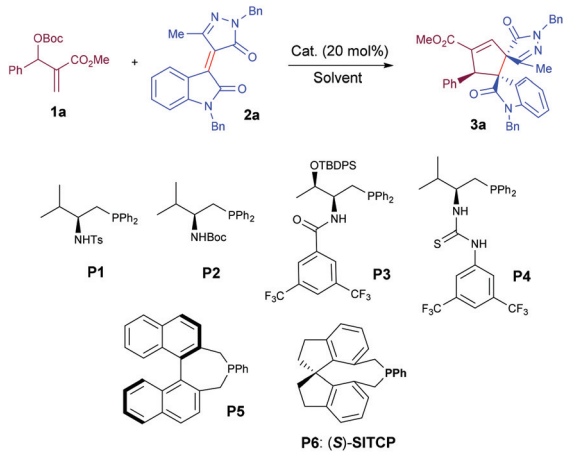
selection of C_3 synthons, we chose the Morita–Baylis–Hillman (MBH) adducts as they are readily accessible, chemically stable, and structurally diverse. Compared with allene counterparts, the MBH adducts are much less commonly employed as reaction partners in phosphine-catalyzed enantioselective [3 + 2] annulation processes, likely due to their lower tendency to form active phosphonium ylides upon phosphine attack. To the best of our knowledge, there was only one example reporting the use of tetra-substituted alkenes in [3 + 2] annulation with the MBH adducts; the employment of α,α-dicyanoalkenes led to the formation of products with two contiguous quaternary centers, including one stereogenic center.[8] Herein, we disclose a highly enantioselective [3 + 2] annulation of the MBH carbonates with tetra-substituted alkenes derived from oxindole and pyrazolone, delivering structurally novel bispiro[pyrazolone-3,3′-oxindoles] bearing two vicinal all-carbon quaternary stereocenters.

We began our investigation by examining the reaction between the MBH carbonate **1a** and pyrazoloneyldiene oxindole **2a**, employing different phosphine catalysts (Table 1). In the presence of triphenylphosphine, the projected [3 + 2] annulation proceeded smoothly to furnish the desired bispiro[pyrazolone-3,3′-oxindole] **3a** in 99% yield, and as a single diastereomer (entry 1). We next evaluated the asymmetric version of this reaction by employing amino acid-derived bifunctional phosphine catalysts, which were demonstrated to be extremely powerful and versatile in a wide range of asymmetric transformations.[9] However, we were very disappointed to discover that such catalysts performed poorly in this reaction. In the presence of tosyl-derived **P1**, the desired product was obtained in 80% yield, but without any enantioselectivity (entry 2). The employment of other bifunctional phosphines led to the products in very low chemical yields and poor enantioselectivities (entries 3–5). We then turned our attention to more nucleophilic, C_2-symmetric chiral phosphine catalysts. While binaphthyl-based C_2-symmetric phosphine **P5** was completely ineffective (entry 6), we were delighted to discover that **(*S*)-SITCP** exerted excellent asymmetric induction; the desired product was obtained with 95% ee, albeit in 25% yield (entry 7). Running the reaction at 60 °C and adding K_2CO_3 (20 mol%) as an additive improved the yield dramatically to 72%, without erosion of enantioselectivity (entry 8). Solvent screening revealed that dioxane is the best solvent (entries 9–12). Reducing the catalyst loading to 10 mol% or decreasing the temperature to 40 °C resulted in lower chemical yields, without affecting the enantioselectivities (entries 13 and 14). Under the optimized reaction conditions, the reaction reached completion in 3 hours, affording the spirooxindole product **3a** in 95% yield and 95% ee (entry 10).[10]

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	T/°C	Time/h	Yield[b] (%)	ee[d] (%)
1	PPh_3	Toluene	r.t.	72	99	—
2	**P1**	Toluene	r.t.	72	85	0
3	**P2**	Toluene	r.t.	72	17	11
4	**P3**	Toluene	r.t.	72	12	40
5	**P4**	Toluene	r.t.	72	28	50
6	**P5**	Toluene	r.t.	72	<5	—
7	**(*S*)-SITCP**	Toluene	r.t.	72	25	95
8[c]	**(*S*)-SITCP**	Toluene	60	6	72	95
9[c]	**(*S*)-SITCP**	THF	60	3	90	93
10[c]	**(*S*)-SITCP**	**Dioxane**	**60**	**3**	**95**	**95**
11[c]	**(*S*)-SITCP**	MTBE	60	24	50	95
12[c]	**(*S*)-SITCP**	CH_3Cl	60	24	60	95
13[c,e]	**(*S*)-SITCP**	Dioxane	60	8	81	95
14[c]	**(*S*)-SITCP**	Dioxane	40	12	60	95

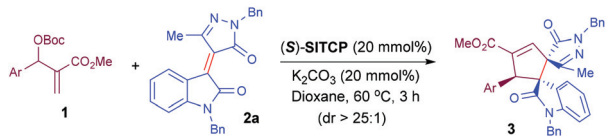
[a] Reactions were performed with **1a** (0.15 mmol), **2a** (0.1 mmol), solvent (0.5 mL) and a catalyst (0.02 mmol) under the conditions specified, and dr ratios were >25 : 1 for all cases. [b] Isolated yield. [c] K_2CO_3 (0.02 mmol) was used as an additive. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The catalyst loading was 10 mol%.

With the optimized reaction conditions in hand, the substrate scope of **(*S*)-SITCP** catalyzed [3 + 2] annulations between various MBH carbonates **1** and pyrazoloneyldiene oxindole **2a** was examined, and the results are summarized in Table 2. All the substrates decorated with electron-donating or electron-withdrawing groups on the benzene ring of the MBH carbonates **1** underwent the annulations smoothly, affording the bispiro[pyrazolone-3,3′-oxindoles] **3** in good to excellent yields (76–99%) along with excellent stereoselectivities (dr >25 : 1, 85–97% ee) (entries 1–14). Furthermore, 1-naphthylaldehyde-derived and 2-thienylaldehyde-derived MBH carbonates were both found to be good substrates, and the corresponding bispiro[pyrazolone-3,3′-oxindoles] **3o** & **3p** were obtained in high yields and with excellent ee values (entries 15 & 16).

The reaction scope with regard to different pyrazoloneyldiene oxindoles was next examined (Scheme 2). The reaction is well tolerant of different substituted pyrazoloneyldiene oxindoles, and excellent enantioselectivities and chemical yields were attainable (**3q–3s**). Methylated isatin-derived pyrazoloneyldiene oxindole could also be used, furnishing tricyclic spiro products in excellent yields (86–99% yields) and enantioselectivities (97–99% ee) (**3t–3w**). When formaldehyde or isatin derived MBH carbonate was employed, no reaction was observed (**3x** & **3y**).[11] The absolute configuration of the products was determined on the basis of X-ray crystallographic analysis of **3f**.

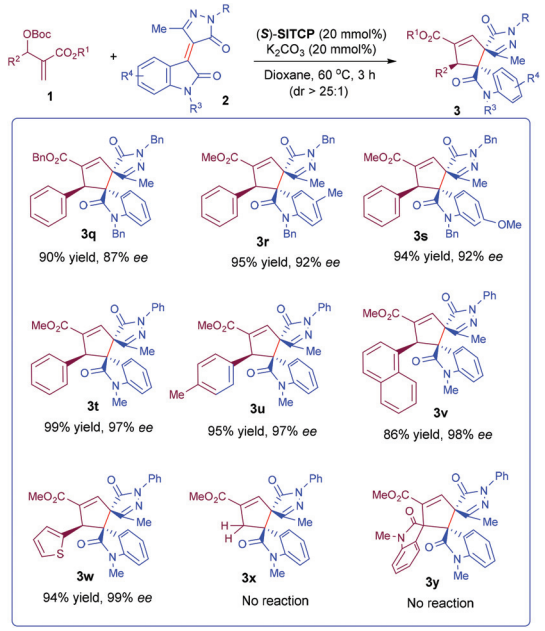
A plausible mechanism is illustrated in Scheme 3. The reaction starts with phosphine attack on the MBH carbonate to

Table 2 Employing different MBH carbonates[a]

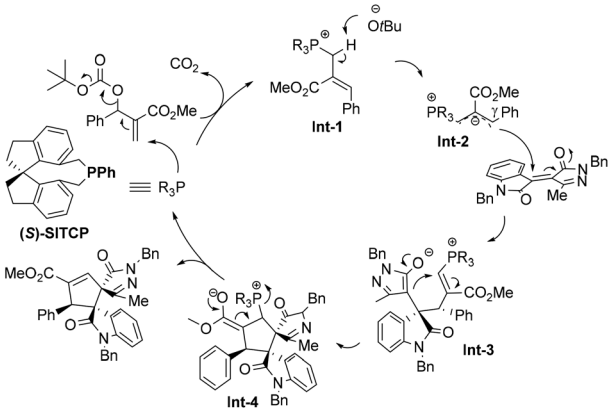


Entry	Ar	3	Yield[b] (%)	ee[c] (%)
1	Ph	**3a**	95	95
2	4-MeC_6H_4	**3b**	77	93
3[d]	4-$MeOC_6H_4$	**3c**	76	92
4	4-FC_6H_4	**3d**	85	90
5	4-ClC_6H_4	**3e**	97	91
6	4-BrC_6H_4	**3f**	94	92
7	4-$NO_2C_6H_4$	**3g**	99	90
8	4-$CF_3C_6H_4$	**3h**	88	91
9	3-MeC_6H_4	**3i**	89	94
10[d]	3-$OMeC_6H_4$	**3j**	96	94
11	3-ClC_6H_4	**3k**	92	93
12	3-BrC_6H_4	**3l**	97	92
13	2-ClC_6H_4	**3m**	87	90
14	2,4-$Cl_2C_6H_3$	**3n**	90	85
15	1-Naphthyl	**3o**	80	96
16	2-Thienyl	**3p**	95	97

[a] Reactions were performed with **1** (0.15 mmol), **2a** (0.1 mmol), dioxane (0.5 mL), K_2CO_3 (0.02 mmol) and **(*S*)-SITCP** (0.02 mmol) under the conditions specified. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction time was 12 h.



Scheme 2 Further scope of the reaction. Reaction conditions: The MBH carbonates **1** (0.15 mmol), alkenes **2** (0.1 mmol), dioxane (0.5 mL), K_2CO_3 (0.02 mmol) and **(*S*)-SITCP** (0.02 mmol) in dioxane, 60 °C, 3 h; the dr ratios were determined by ^1H NMR analysis of the crude products; yields refer to the isolated yields, the ee values were determined by chiral HPLC analysis on a chiral stationary phase.



Scheme 3 Proposed mechanism.

create phosphonium **Int-1**, which was deprotonated by the *in situ* generated *tert*-butoxide to form ylide **Int-2**. The subsequent addition to the more electron-deficient carbon of pyrazoloneyldiene oxindole then affords the advanced intermediate **Int-3**, and cyclization next takes place to deliver the spiro product, with the regeneration of a phosphine catalyst.

Conclusions

In conclusion, we have disclosed an unprecedented [3 + 2] annulation between the MBH carbonates and pyrazoloneyldiene oxindoles catalyzed by **(*S*)-SITCP**. Structurally novel bispiro[pyrazolone-3,3′-oxindoles] containing two contiguous quaternary stereogenic centers were created in excellent yields, in a diastereospecific and highly enantioselective manner. Biological activities of this class of structurally novel spirooxindole compounds, especially their potential anti-cancer activities, are currently being investigated in our laboratories.

Experimental

Typical procedure for the preparation of bispiro[pyrazolone-3,3′-oxindoles]

To a dried round bottle flask with a magnetic stirring bar under N_2 at room temperature were added MBH carbonates **1** (0.1 mmol) and pyrazoloneyldiene oxindoles **2** (0.12 mmol), followed by the addition of anhydrous dioxane (0.5 mL) and K_2CO_3 (0.02 mmol). Catalyst **P6** (0.02 mmol, 7.1 mg) was then introduced, and the reaction mixture was stirred for 2–12 hours at 60 °C. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 7 : 1) on silica gel to afford products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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10 While pyrazoloneyldiene oxindole bearing a free NH displayed low reactivity, *N*-Boc/*N*-Ac pyrazoloneyldienes showed poor stereoselectivities in the annulation.

11 We speculate that the key carbanion (**Int-2**) could not be efficiently formed without resonance contribution from the aryl moiety, which may account for the lack of reactivity of the formaldehyde-derived MBH carbonate in the cyclization.