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Phosphine-catalyzed asymmetric [4+1] annulation of activated α,β-unsaturated ketones with Morita–Baylis–Hillman carbonates: enantioselective synthesis of spirooxindoles containing two adjacent quaternary stereocenters†

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The asymmetric [4+1] annulation of activated α,β-unsaturated ketones with MBH carbonates catalyzed by bifunctional thiourea–phosphine catalysts derived from an axially chiral binaphthyl scaffold has been developed, giving spirooxindoles with two adjacent quaternary stereocenters in good yields with high enantioselectivities and moderate diastereoselectivities under mild conditions.

Nucleophilic phosphines are widely used as Lewis base catalysts in organic reactions. On the basis of phosphine catalysis, a variety of unique carbo- and heterocyclic frameworks, some of which are commonly present in bioactive natural products and medicinally important compounds, can be easily acquired.[1] It has grown significantly over the past decade and now it is an active area of organocatalysis.[2] Recently, Morita–Baylis–Hillman (MBH) adducts have aroused organic chemists' interest after Lu's pioneering work on the intra- and intermolecular [3+*n*] annulations (*n* = 2, 3, 4, and 6) using MBH carbonates as 1,3-dipoles with various activated alkenes catalyzed by a trivalent phosphine,[3] affording the corresponding cycloadducts in good yields and high regioselectivities under mild conditions.[4] Furthermore, recently some examples of asymmetric [3+2] annulation of MBH carbonates with activated alkenes have also been disclosed.[5] More recently, Zhang, Huang, He and Shi as well as their co-workers have also developed [4+1] annulations utilizing MBH carbonates as 1,1-dipoles to obtain the heterocyclic products in high yields, respectively.[6] In this aspect, we have further developed a series of bifunctional thiourea–phosphine catalysts derived from natural amino acids and applied them in asymmetric [3+2] annulations of MBH carbonates with electron-deficient alkenes, furnishing the corresponding highly functionalized cyclopentenes in good yields and ee values.[7] We have also reported the first highly enantioselective [4+1] annulations between dicyano-2-methylenebut-3-enoates and MBH carbonates catalyzed by chiral bifunctional phosphine, providing an efficient synthesis of highly functionalized cyclopentenes bearing one all-carbon quaternary stereogenic center.[8a] To the best of our knowledge, no asymmetric [4+1] annulation of activated alkenes with MBH carbonates has been further disclosed after our previous report.[8b]

The spirooxindole backbones are commonly present in a number of biologically active compounds as well as natural products.[9] They have recently become one of the most attractive synthetic targets and many kinds of elegant synthetic approaches have been developed for their syntheses.[10] In continuation of our efforts to seek efficient approaches toward the construction of the spirooxindole motif,[11] we wish to report chiral phosphine catalyzed asymmetric [4+1] annulation of MBH carbonates with activated α,β-unsaturated ketones, effectively providing 2*H*-spiro[furan-3,3′-indolin]-2′-one derivatives with two adjacent quaternary stereocenters.

Initially, we examined the reaction of activated α,β-unsaturated ketone **1a** (0.1 mmol) with MBH carbonate **2a** (0.11 mmol, 1.1 equiv.) catalyzed by a bifunctional chiral phosphine catalyst **TP1** derived from a natural amino acid in toluene (2 mL) at room temperature. The desired [4+1] cycloadduct **3a** was obtained in 92% total yield along with 1 : 2 dr within 12 h, the ee value of the major product is 11%, however, the minor product's ee value is 86% (Table 1, entry 1). In order to improve the ee values, multifunctional thiourea–phosphines with more sterically hindered substituents **TP2**, **TP3** and **TP4** were further tested in this reaction, providing the spirooxindole **3a** containing two adjacent quaternary stereocenters in good yields along with moderate stereochemical outcomes (up to 3 : 1 dr and up to 69% ee) (Table 1, entries 2–4). We next utilized bifunctional chiral phosphines derived from an axially chiral binaphthyl scaffold **TP5–TP7** as catalysts for this reaction. **TP6** is the best catalyst in terms of enantioselectivity, affording **3a** in 97% total yield along with 3 : 1 dr, and the major product's ee value is 96% (Table 1, entries 5–7). During the investigation of the nucleophilic phosphine catalysis, we have noticed that substituents in the phosphorus center of chiral phosphine catalysts could remarkably influence the diastereoselectivities,[11j,12] **TP8–TP10** were therefore synthesized and subjected to

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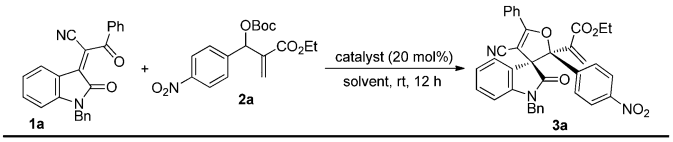
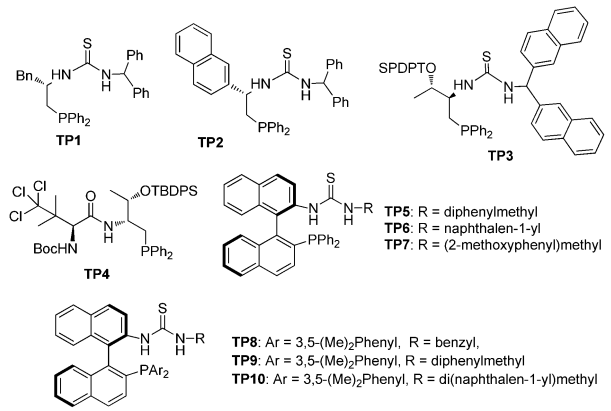
Table 1 Optimization of reaction conditions for the asymmetric [4+1] annulation



Entry[a]	Catalyst	Solvent	Yield[b] (%)	ee (*anti*:*syn*)[c] (%)	dr (*anti*:*syn*)[c] (%)
1	**TP1**	Toluene	92	86/11	1/2
2	**TP2**	Toluene	95	69/2	1/2
3	**TP3**	Toluene	87	50/30	1/2
4	**TP4**	Toluene	86	59/17	1/3
5	**TP5**	Toluene	82	73/58	7/1
6	**TP6**	Toluene	97	96/7	3/1
7	**TP7**	Toluene	94	89/55	2/1
8	**TP8**	Toluene	87	87/10	2/1
9	**TP9**	Toluene	82	73/60	6/1
10	**TP10**	Toluene	96	75/95	6/1
11	**TP6**	DCM	92	96/10	2/1
12	**TP6**	Fluorobenzene	93	64/97	10/1
13	**TP6**	(Trifluoromethyl)benzene	90	56/85	7/1
14	**TP6**	*p*-Xylene	87	65/99	7/1

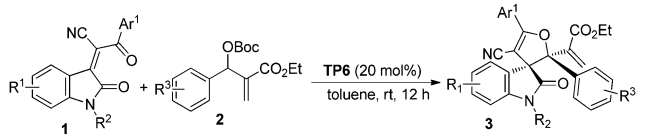


[a] The reaction carried out using **1a** (0.1 mmol), **2a** (0.2 mmol) and catalyst (0.02 mmol) in solvent (2.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

this reaction. It was found that the bifunctional chiral phosphine catalysts **TP8** and **TP9**, having the methyl groups on the 3,5-positions of the benzene ring, showed poor performance in terms of enantioselectivity (Table 1, entries 8 and 9). Increasing the steric hindrance of the thiourea moiety did not further increase the enantioselectivity, affording **3a** in total 96% yield along with 6 : 1 dr, 75% and 95% ee, respectively (Table 1, entry 10). Finally, the solvent effects have also been examined using **TP6** as the catalyst. In dichloromethane (DCM), similar results were obtained, but in fluorobenzene, benzotrifluoride or *p*-xylene, the ee values of **3a** (major diastereomer) decreased remarkably (Table 1, entries 11–14). Therefore, the best reaction conditions have been determined to be **TP6** (20 mol%) in toluene at room temperature within 12 hours.

With the optimized reaction conditions in hand, we next turned our attention to the scope and limitations of this reaction using a variety of activated α,β-unsaturated ketones **1** with MBH carbonates **2**. It was found that a variety of *N*-protected α,β-unsaturated ketones were suitable for this reaction, producing the desired products **3b**, **3c**, **3d** and **3e** in high yields along with

Table 2 Substrate scope of the asymmetric [4+1] annulation of **1** with **2**



Entry[a]	R^1	R^2	Ar^1	R^3	Yield[b] (%)	ee[c] (%)	dr[c] (%)
1	**1b**, H	Me	C_6H_5	**2a**, 4-NO_2	**3b**, 97	98	2/1
2	**1c**, H	MOM	C_6H_5	**2a**, 4-NO_2	**3c**, 92	98	2/1
3	**1d**, H	Allyl	C_6H_5	**2a**, 4-NO_2	**3d**, 99	98	3/1
4	**1e**, H	Ph	C_6H_5	**2a**, 4-NO_2	**3e**, 90	97	2/1
5	**1f**, H[f]	H	C_6H_5	**2a**, 4-NO_2	**3f**, 65	95	3/1[d]
6	**1g**, 5-Me[f]	H	C_6H_5	**2a**, 4-NO_2	**3g**, 61	95	3/1[d]
7	**1h**, 5-F[f]	H	C_6H_5	**2a**, 4-NO_2	**3h**, 58	90	3/1[d]
8	**1i**, 7-Br[f]	H	C_6H_5	**2a**, 4-NO_2	**3i**, 62	96	3/1[d]
9	**1j**, H[f]	H	3-MeC_6H_4	**2a**, 4-NO_2	**3j**, 75	96	4/1[d]
10	**1k**, H[f]	H	4-ClC_6H_4	**2a**, 4-NO_2	**3k**, 51	90	3/1[d]
11	**1a**, H[f]	Bn	C_6H_5	**2b**, 4-Cl_2	**3l**, 90	97	3/1
12	**1a**, H[f]	Bn	C_6H_5	**2b**, 4-CN	**3m**, 98	98	3/1
13	**1a**, H[e]	Bn	C_6H_5	**2d**, 3,4-Cl_2	**3n**, 85	81	1/1
14	**1f**, H[f]	Bn	C_6H_5	**2e**, 3,5-Cl_2	**3o**, 89	96	2/1
15	**1f**, H	Bn	C_6H_5	**2f**, 4-Me	NR		

[a] **1** (0.01 mmol), **1** (0.11 mmol) and **TP6** (0.02 mmol) were stirred in 2 mL of toluene within 12 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR analysis. [e] The reaction mixtures were stirred for 4 days. [f] The reaction mixtures were stirred for 48 h.

moderate de and high ee values (up to 3 : 1 dr, 97–98% ee) (Table 2, entries 1–4). To our delight, as for the *N*-unprotected α,β-unsaturated ketone **1f**, the corresponding [4+1] annulation product **3f** was obtained in 65% yield along with 95% ee and 3 : 1 dr, although the reactivity of **3f** was reduced and the reaction was conducted for 48 h (Table 2, entry 5). When other *N*-unprotected α,β-unsaturated ketones were used in this reaction, the corresponding products were acquired in moderate yields (up to 62% yield) along with excellent enantioselectivities (90–96% ee) and moderate dr values (up to 3 : 1 dr), respectively (Table 2, entries 6–8). When substituents were introduced on the Ar^1 group, the reaction could also proceed smoothly to give the desired products in up to 75% yield and up to 4 : 1 dr (96% ee, respectively) (Table 2, entries 9 and 10). Finally, substrates with electron-withdrawing substituents on the aromatic ring of MBH carbonates were also tested in this reaction, giving the desired products in good yields along with moderate de values and high ee values (Table 2, entries 11–14). Only in the case of MBH carbonate **2e**, the corresponding adduct **3o** was obtained in a relatively low ee value (81% ee), presumably due to the influence of steric hindrance (Table 2, entry 13). Unfortunately, when the methyl group was introduced into the aromatic ring of MBH carbonate, the reactivity of **2f** decreased remarkably with no desired product being formed (Table 2, entry 15).

It should be pointed out that the two diastereoisomers **3f**–**3k** can be isolated by column chromatography and the structures of minor diastereomers **3f′**–**3k′** have also been determined by ^{1}H and ^{13}C NMR spectroscopy, MS and HRMS analyses. The structure of **1c** has been determined by X-ray diffraction to be *Z* configuration and the absolute configuration of **3i** has also been unambiguously determined by X-ray diffraction. Their CIF data are presented in the ESI.†

The plausible mechanism of these [4+1] annulations is proposed in Scheme S1 in the ESI† on the basis of previous literature,[3a,d,6,8,13] and the plausible transition state has also been presented in Fig. S1 in the ESI.†

In conclusion, the asymmetric [4+1] annulation of activated α,β-unsaturated ketones derived from isatin with MBH carbonates catalyzed by chiral bifunctional phosphine has been developed for the first time, which provides highly efficient and enantioselective synthesis of spirooxindoles containing two adjacent quaternary stereocenters. Further efforts are in progress to develop the use of this reaction in organic synthesis.

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