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Asymmetric Construction of Highly Functionalized Spirobarbiturate-Cyclopentenes through Chiral Phosphine-Catalyzed [3+2] Annulation of Morita–Baylis–Hillman Carbonates with Barbiturate-Derived Alkenes

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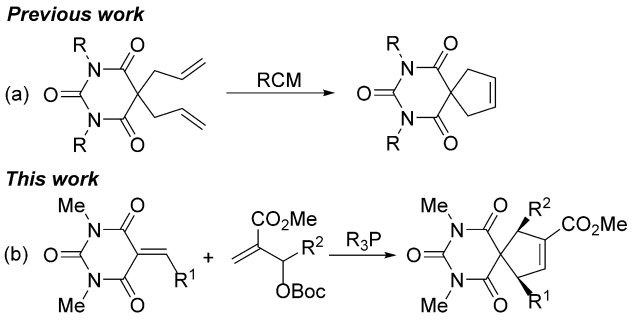
Abstract: A multifunctional chiral phosphine-catalyzed enantioselective [3+2] annulation of Morita–Baylis–Hillman carbonates with barbiturate-derived alkenes has been achieved under mild conditions, providing a variety of chiral spirobarbiturate-cyclopentenes in moderate to excellent yields with moderate to excellent diastereo- and enantioselectivities.

Keywords: alkenes; allenoates; annulation; phosphines; spirobarbiturates

Barbituric acid derivatives are important pharmacological compounds, displaying various activities such as sedative, anesthetic, anxiolytic, anticonvulsant, analeptic, anticancer, anti-AIDS and immunomodulating activities.[1] As a type of barbiturate, spirobarbiturates also showed a range of pharmacological and physiological activities and have attracted much attention.[2,3] Considering functionalized five-membered carbocycles are a common structural motif in medicinally important compounds and natural products,[4] spirobarbiturate-cyclopentenes with the combination of barbiturate and cyclopentene moieties are very appealing in the search for medicinally active compounds. Recently, a synthetic approach to spirobarbiturate-cyclopentenes has been achieved through a ring-closing metathesis (RCM) reaction (Scheme 1).[5] However, this method is not feasible for multi-substituted spirobarbiturate-cyclopentenes. Especially, to the best of our knowledge, an asymmetric construction of spirobarbiturate-cyclopentenes has not been reported. In this context, we considered developing an enantioselective tool to synthesize chiral spirobarbiturate-cyclopentenes through phosphine-catalyzed asymmetric [3+2] annulation of barbiturate-derived alkenes with Morita–Baylis–Hillman (MBH) carbonates.

Phosphine-catalyzed annulation reactions are very powerful methods in the syntheses of carbocyclic and heterocyclic compounds and serve as the key step in the total synthesis of some natural products.[6] Particularly, these annulations have also successfully been applied in the synthesis of complex spirocyclic compounds.[7] Among various annulation reactions, the phosphine-catalyzed [3+2] annulation reaction of MBH carbonates with olefins has emerged as an important tool to synthesize cyclopentenes since Lu first reported a phosphine-catalyzed [3+2] annulation of MBH carbonates as a three-carbon synthon with electron-deficient alkenes.[6j,8] Employing this reaction, a few spirocyclic molecules fused with a cyclopentene moiety have been constructed. Lu, Shi and Barbas independently developed chiral phosphine-catalyzed asymmetric [3+2] annulation reactions of methyleneindolinones with MBH carbonates to prepare

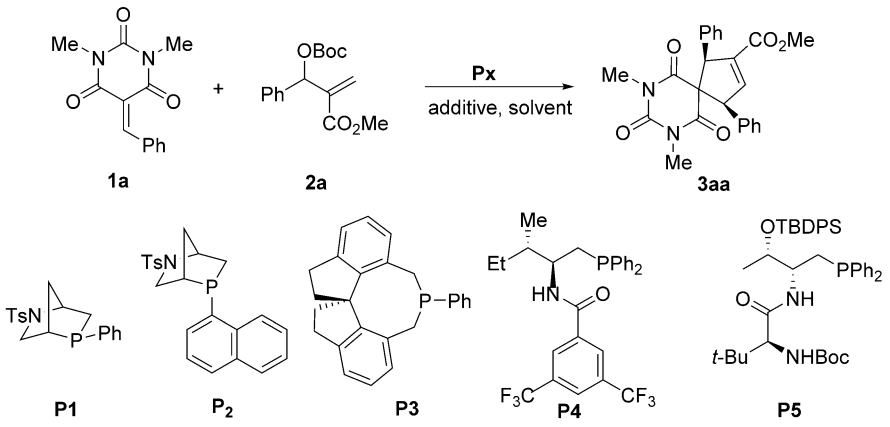


Scheme 1. Synthesis of spirobarbiturate-cyclopentenes.

chiral spirocyclopentene oxindoles.[9] Barbas achieved the asymmetric [3+2] annulation of methylenebenzofuranone with MBH carbonates to give spirocyclopentene benzofuranones.[10] Shi described the asymmetric [3+2] annulation of MBH carbonates with 2-arylideneindane-1,3-diones to provide spirocyclopenteneindenediones.[11] Chen and Liu used MBH carbonates of isatin for the asymmetric [3+2] annulation with alkenes to furnish cyclopentene-fused spirocyclic heterocycles.[12] As part of our continuing efforts on phosphine-catalyzed annulations,[13] herein, we present the multifunctional chiral phosphine-catalyzed asymmetric [3+2] annulations of MBH carbonates with barbiturate-derived alkenes to synthesize enantioenriched spirobarbiturate-cyclopentenes (Scheme 1).

In our initial attempts, we screened different kinds of chiral phosphines in the asymmetric reaction between barbiturate-derived alkene (**1a**) and MBH carbonate (**2a**) in toluene at 80 °C. As shown in Table 1, Kwon phosphines **P1** and **P2**[14] displayed opposing results. With the use of chiral phosphine **P1** as the catalyst, the desired spirobarbiturate-cyclopentene **3aa** was obtained in excellent yield but with moderate enantioselectivity (entry 1). In contrast, chiral phosphine **P2** displayed excellent enantioselectivity but moderate catalytic activity under otherwise identical conditions (entry 2). Spirocyclic chiral phosphine **P3**[15] promoted the reaction to give the product **3aa** in 83% yield albeit with 65% *ee* (entry 3). Satisfactorily, two multifunctional phosphines **P4** and **P5**[16] demonstrated good catalytic capability (entries 4 and 5). Although **P5** delivered better enantioselectivity than **P4** did, **P4** is a preferred catalyst for this reaction in terms of both yield and enantioselectivity (entry 4 *vs.* 5). With **P4** as the catalyst, we next performed solvent screening to improve the enantioselectivity. These experiments revealed that trifluorotoluene was an optimal solvent (entries 6 and 7). In trifluorotoluene, the *ee* value was increased to 93% (entry 7). Using 4 Å MS as an additive, the yield was slightly increased to 80% (entry 8). Since the base has been demonstrated to be favorable to phosphine-catalyzed annulations in the previous report,[17] a catalytic amount of K_2CO_3 was also examined as an additive. To our delight, the yield was indeed marginally enhanced to 85% (entry 9). The base might help in formation of a phosphonium enolate zwitterion from

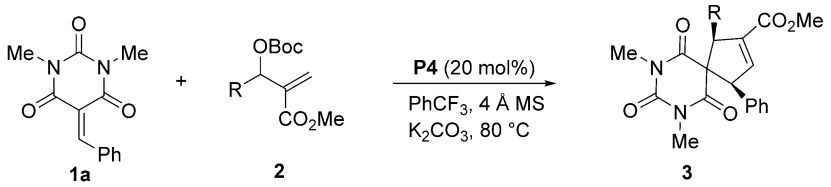
Table 1. Catalyst screen and optimization studies.[a]



Entry	Px	Solvent	Temperature [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**P1**	toluene	80	18	98	37
2	**P2**	toluene	80	18	45	91
3	**P3**	toluene	80	16	83	65
4	**P4**	toluene	80	16	87	85
5	**P5**	toluene	80	16	67	91
6	**P4**	DCE	80	18	76	90
7	**P4**	$PhCF_3$	80	16	76	93
8[d]	**P4**	$PhCF_3$	80	16	80	93
9[e]	**P4**	$PhCF_3$	80	16	85	96

[a] Unless otherwise stated, reactions of **1a** (0.1 mmol) and **2a** (0.12 mmol) were performed in the presence of phosphine (0.02 mmol) in 2 mL of solvent.
[b] Isolated yield. The *dr* is >20:1, determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] 50 mg of 4 Å MS were used as the additive.
[e] 50 mg of 4 Å MS and 20 mol% of K_2CO_3 were used.

Table 2. Scope of MBH carbonates **2**.[a]



Entry	R	Time [h]	3	Yield [%][b]	*ee* [%][c]
1[d]	2-MeC_6H_4 (**2b**)	18	**3ab**	88	91
2	3-MeC_6H_4 (**2c**)	18	**3ac**	99	93
3	4-MeC_6H_4 (**2d**)	16	**3ad**	80	91
4	2-MeOC_6H_4 (**2e**)	16	**3ae**	98	91
5	4-MeOC_6H_4 (**2f**)	17	**3af**	98	93
6	2-FC_6H_4 (**2g**)	18	**3ag**	90	90
7	3-FC_6H_4 (**2h**)	16	**3ah**	80	91
8	4-FC_6H_4 (**2i**)	18	**3ai**	81	91
9	2-ClC_6H_4 (**2j**)	16	**3aj**	97	87
10	3-ClC_6H_4 (**2k**)	18	**3ak**	64	93
11	4-ClC_6H_4 (**2l**)	16	**3al**	86	93
12	2-BrC_6H_4 (**2m**)	20	**3am**	96	85
13	3-BrC_6H_4 (**2n**)	18	**3an**	85	87
14	2-naphthyl (**2o**)	16	**3ao**	87	93
15	2-thienyl (**2p**)	18	**3ap**	90	90
16	*i*-Pr (**2q**)	24	**3aq**	NR[e]	–
17	cyclohexyl (**2r**)	24	**3ar**	NR	–

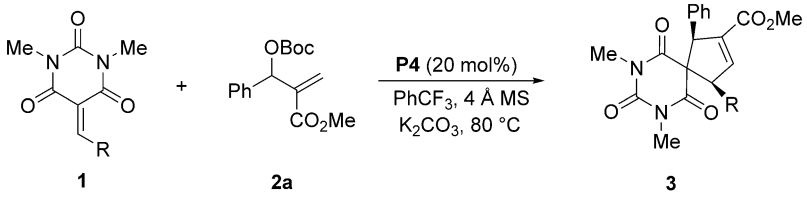
[a] Reactions of **1a** (0.1 mmol) and **2** (0.12 mmol) were performed in the presence of **P4** (0.02 mmol), K_2CO_3 (0.02 mmol) and 50 mg of 4 Å MS at 80 °C in 2 mL of $PhCF_3$.
[b] Isolated yield. Unless otherwise stated, the *dr* is >20:1, determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] *dr* = 10:3.
[e] No reaction.

MBH carbonate, thus slightly increasing the yield. On the basis of the above-mentioned results, the optimized conditions are as follows: reaction of **1a** and **2a** in trifluorotoluene at 80 °C using 20 mol% of **P4** in the presence of 4 Å MS and K_2CO_3.

Under the optimal conditions, the scope of the MBH carbonates **2** in this [3+2] annulation was investigated (Table 2). Generally, whether using electron-rich or electron-deficient aryl-substituted MBH carbonates, the spirocyclic products were obtained in good to excellent yields (64–99%) with good to excellent diastereo- and enantioselectivities (85–93% *ee*) (entries 1–15). The high diastereoselectivities might be attributed to steric hindrance from the phosphine and the special structure of barbiturate ring. The position of the substituent on the benzene ring seemed to have no remarkable influence on the activities and stereoselectivities (entries 1–15). Notably, 2-naphthyl- and 2-thienyl-substituted substrates also reacted efficiently with barbiturate-derived alkene, affording the corresponding spirocyclic products with high yields and excellent *ee* values (entries 14 and 15). Unfortunately, two alkyl-substituted MBH carbonates did not work (entries 16 and 17). The absolute configuration of the spirocyclic products was assigned by an X-ray crystallographic analysis of the product **3al** (entry 11).[18]

Application of the standard conditions to various barbiturate-derived alkenes **1** is summarized in Table 3. Variations of the substituents on the benzene moiety were tolerated. A variety of barbiturate-derived alkenes, regardless of the substitution pattern and electronic nature, worked well to produce the corresponding cycloadducts in high yields (60–99%) with excellent enantioselectivities (91–99% *ee*) (entries 1–13). All products, except **3ca** and **3ka** (entries 3 and 11), were generated with >20:1 diastereomeric ratios. A 2-naphthyl-substituted alkene (**1m**) led to excellent yield, diastereoselectivity and enantioselectivity (86% yield, >20:1 *dr*, 93% *ee*) (entry 14). The 2-furanylalkene **1n** was also compatible with the current system, affording the product **3na** in 99% *ee*, albeit in only 45% yield (entry 15). For phosphine-catalyzed annulation reactions, alkenes bearing aliphatic substituents are generally challenging substrates. In this [3+2] annulation, a cyclohexyl-substi-

Table 3. Scope of barbiturate-derived alkenes **1**.[a]



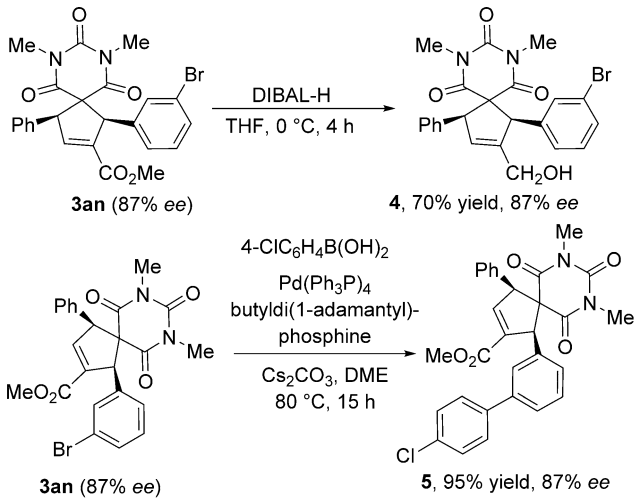
Entry	R	Time [h]	3	Yield [%][b]	*ee* [%][c]
1	Ph (**1a**)	16	**3aa**	85	96
2	2-MeC_6H_4 (**1b**)	16	**3ba**	98	91
3[d]	3-MeC_6H_4 (**1c**)	18	**3ca**	97	99
4	4-MeC_6H_4 (**1d**)	16	**3da**	98	93
5	2-MeOC_6H_4 (**1e**)	18	**3ea**	98	97
6	4-MeOC_6H_4 (**1f**)	18	**3fa**	92	91
7	2-FC_6H_4 (**1g**)	18	**3ga**	87	99
8	4-FC_6H_4 (**1h**)	18	**3ha**	90	91
9	2-ClC_6H_4 (**1i**)	15	**3ia**	60	97
10	4-ClC_6H_4 (**1j**)	15	**3ja**	99	98
11[e]	2-BrC_6H_4 (**1k**)	20	**3ka**	70	99
12	4-BrC_6H_4 (**1l**)	20	**3la**	89	98
14	2-naphthyl (**1m**)	16	**3ma**	86	93
15	2-thienyl (**1n**)	16	**3na**	45	99
16	cyclohexyl (**1o**)	24	**3oa**	30	81

[a] Unless otherwise stated, reactions of **1** (0.1 mmol) and **2a** (0.12 mmol) were carried out in the presence of **P4** (0.02 mmol), K_2CO_3 (0.02 mmol) and 50 mg of 4 Å MS at 80 °C in 2 mL of $PhCF_3$.
[b] Isolated yield. Unless otherwise stated, the *dr* is >20:1, determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] *dr* = 4:1.
[e] *dr* = 4:5.

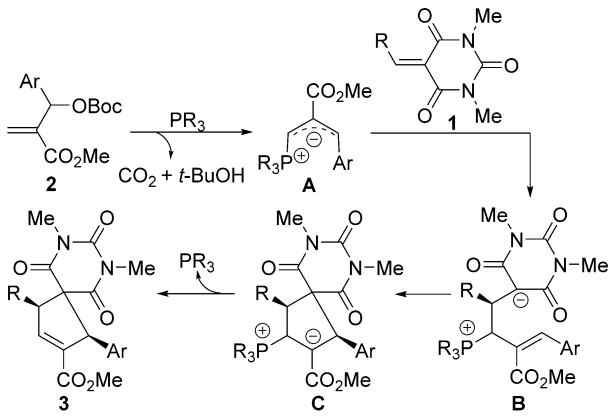
tuted alkene displayed moderate activity, leading to the spirocyclic product **3oa** in 30% yield, but gratifyingly, an 81% *ee* was obtained (entry 16).

The products could further be transformed into other useful compounds (Scheme 2). The spirobarbiturate-cyclopentene **3an** was treated with DIBAL-H in THF at 0 °C for 4 h, giving the reduction product **4** in 70% yield. In the presence of $Pd(Ph_3P)_4$ and butyldi(1-adamantyl)phosphine, the coupling of **3an** with 4-chlorophenylboronic acid proceeded smoothly in 1,1-dimethoxyethane (DME) at 80 °C to afford the corresponding product **5** in 95% yield.

A reasonable mechanism is proposed in Scheme 3. The allylic phosphonium ylide **A** formed from nucleophilic addition of phosphine to MBH carbonate **2** un-



Scheme 2. Synthetic transformations of the product.



Scheme 3. A proposed mechanism.

dergoes a nucleophilic attack from the bottom of the carbon-carbon double bond of the barbiturate-derived alkene to give the phosphonium ylide **B**, which subsequently carries out intramolecular conjugate addition to furnish the [3+2] annulation and afford the phosphonium ylide **C**. Consequent formation of a carbon-carbon double bond and simultaneous ejection of phosphine leads to the annulation product **3**.

In summary, we have developed an efficient method for the asymmetric construction of biologically significant chiral spirobarbiturate-cyclopentenes through chiral phosphine-catalyzed asymmetric [3+2] annulation of MBH carbonates with barbiturate-derived alkenes in moderate to excellent yields with moderate to excellent diastereo- and enantioselectivities. The method will be a useful tool in the synthesis of biologically active compounds for the discovery of novel therapeutic agents.

Experimental Section

General Procedure

Under a nitrogen atmosphere, to a stirred mixture of alkene **1** (0.1 mmol), MBH carbonate **2** (0.12 mmol), K_2CO_3 (0.02 mmol) and 4 Å MS (50 mg) in 2 mL of trifluorotoluene was added chiral phosphine **P4** (11 mg, 0.02 mmol) and the resulting mixture was stirred at 80 °C. Upon completion of the reaction as monitored by TLC, the mixture was concentrated under vacuum. The residue was purified through flash column chromatography (ethyl acetate/petroleum ether) to afford the corresponding annulation product.

Acknowledgements

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[18] CCDC 1470357 (**3al**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.