Organic LETTERS

Letter

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Enantioselective Synthesis of Spirobarbiturate-Cyclohexenes through Phosphine-Catalyzed Asymmetric [4 + 2] Annulation of Barbiturate-Derived Alkenes with Allenoates

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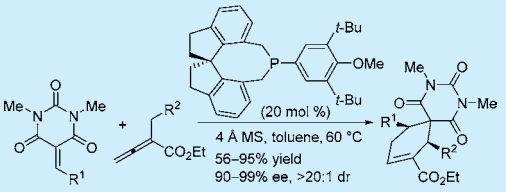
Supporting Information

ABSTRACT: An enantioselective synthesis of pharmaceutically important spirobarbiturates has been achieved via spirocyclic chiral phosphine-catalyzed asymmetric [4 + 2] annulation of barbiturate-derived alkenes with allenoates. With the use of this tool, various spirobarbiturate-cyclohexenes are obtained in good to excellent yields with excellent diastereo- and enantioselectivities. A wide range of α-substituted allenoates and barbiturate-derived alkenes were tolerated.

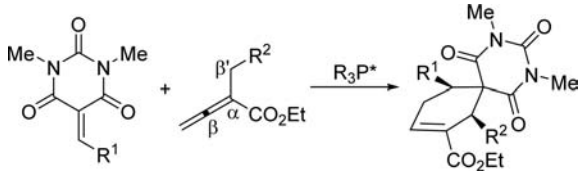


Barbiturates, namely barbituric acid derivatives, are well-known as an important class of central nervous system depressants, acting as sedatives, anesthetic, anxiolytic, and anticonvulsant agents.[1] Their additional pharmacological potential has also been exploited as analeptics, immunomodulating, anti-AIDS, and anticancer agents.[2] As a privileged medicinal scaffold, the barbituric acid scaffold has been incorporated in more than 5000 pharmacologically active compounds.[3] Among these compounds, spirobarbiturates display various useful pharmacological and physiological activities and have attracted much attention.[4] Many synthetic methods for spirobarbiturates have been developed;[5] however, an enantioselective synthesis has never been reported and is highly desirable.

Since functionalized cyclohexenes are key substructures in many natural products and bioactive molecules,[6] it is very significant to synthesize chiral spirobarbiturate-cyclohexenes in which the cyclohexene moiety is fused at the 5-position of the barbituric nucleus. Generally, spirobarbiturates were constructed with the use of barbituric acid building block as the starting material, which is an easily accessible feedstock material. For construction of cyclohexene fused at the barbituric acid scaffold, a synthetic strategy based on the annulation reaction of barbiturate-derived alkenes is simple and feasible. Among various annulation reactions, phosphine-catalyzed asymmetric [4 + 2] annulation of activated alkenes with allenoates provides an alternative access to multisubstituted cyclohexenes, which are difficult to be prepared through a Diels–Alder reaction.[7,8] Although nucleophilic phosphine-catalyzed asymmetric annulation reactions have been intensely studied in the past decade and have emerged as a very useful tool for generating chiral carbo- and heterocyclic compounds[9] and the total synthesis of natural products,[10] chiral phosphine-catalyzed [4 + 2] annulation of activated alkenes with allenoates evolved very slowly and only very limited examples had been reported.[8] Moreover, in those successful reactions, the allenoate scope was extremely narrow, generally being limited to very active and special α-(alkoxycarbonylmethyl)allenoates.[8,11] Therefore, developing phosphine-catalyzed asymmetric [4 + 2] annulation of alkenes with allenoates represents a challenging task. The barbiturate-derived alkenes are ideal candidates for phosphine-catalyzed asymmetric [4 + 2] annulation, as they not only exhibit high activity but also provide a favorable moiety for stereoselective control. Their asymmetric [4 + 2] annulation with allenoates might overcome the narrow substrate scope, giving very diverse spirobarbiturate-cyclohexenes. Herein, we report an enantioselective synthesis of chiral spirobarbiturate-cyclohexenes through phosphine-catalyzed enantioselective [4 + 2] annulation of barbiturate-derived alkenes with allenoates (Scheme 1).

In the initial screening studies, we found that, in the presence of achiral phosphine, [4 + 2] annulation proceeded smoothly at 60 °C to give the desired product **3aa** as a major diastereomer

Scheme 1. Phosphine-Catalyzed [4 + 2] Annulation of Alkenes with Allenoates

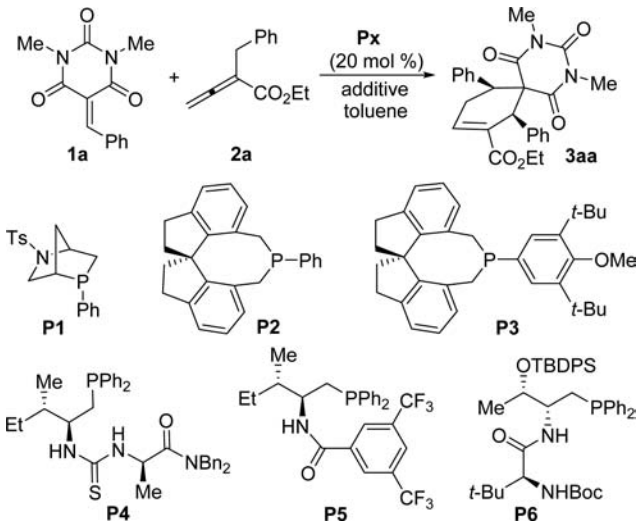


Received: January 24, 2016
Published: March 3, 2016

DOI: 10.1021/acs.orglett.6b00239
Org. Lett. 2016, 18, 1302–1305

(Table 1, entries 1–2). Next, various chiral phosphines were screened to develop the asymmetric reaction. Kwon phosphine

Table 1. Evaluation of the Reaction Conditions[a]



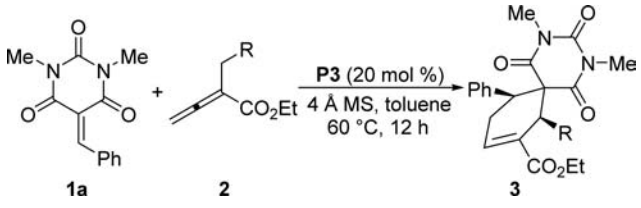
entry	Px	additive	t/°C	t/h	yield (%)[b]	ee (%)[c]
1	Ph_3P	–	60	24	68	–
2	$EtPPh_2$	–	60	18	98	–
3	**P1**	–	80	48	35	6
4	**P2**	–	60	24	62	83
5	**P3**	–	60	12	86	96
6	**P4**	–	60	24	13	11
7	**P5**	–	60	24	36	10
8	**P6**	–	60	18	65	25
9	**P3**	4 Å MS	60	12	93	98
10	**P3**	4 Å MS	40	48	48	99
11[d]	**P3**	4 Å MS	60	12	85	94
12[e]	**P3**	4 Å MS	60	48	63	95
13[f]	**P3**	4 Å MS	60	48	56	96

[a]Unless indicated otherwise, reactions were carried out in 2 mL of toluene using 0.1 mmol of **1a**, 0.12 mmol of **2a**, and 70 mg of 4 Å MS in the presence of 20 mol % of phosphine. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The dr is >20:1, determined by ^{1}H NMR analysis of the crude product. [d]10 mol % of **P3**. [e]5 mol % of **P3**. [f]1 mol % of **P3**.

P1 displayed moderate catalytic activity and poor enantioselectivity (entry 3). To our delight, spirocyclic chiral phosphines **P2** and **P3** demonstrated satisfactory catalytic capability (entries 4–5).[12] Particularly, **P3** catalyzed the reaction to give the product **3aa** in 86% yield and 96% ee (entry 5). In comparison, three multifunctional phosphines **P4**–**P6** could only deliver poor to moderate catalytic activities and poor enantioselectivities (entries 6–8).[13] With **P3** as the catalyst, further optimization of the reaction conditions was attempted. Using 4 Å molecular sieves as an additive, the yield of **3aa** was markedly increased to 93% with an excellent 98% ee (entry 9). Decreasing the temperature to 40 °C slightly enhanced ee to 99%, but a long reaction time was required, simultaneously leading to a remarkably lower 48% yield (entry 10). When the catalyst loading was decreased to 10, 5, and even 1 mol %, respectively, the enantioselectivity still remained at a high level, although the yield could be impaired (entries 11–13).

Under the optimized conditions, the substrate scope of α-substituted allenoates (**2**) was investigated (Table 2). A variety

Table 2. Scope of Allenoate 2[a]



entry	2	3	yield (%)[b]	ee (%)[c]
1	Ph (**2a**)	**3aa**	93	98
2	2-MeC_6H_4 (**2b**)	**3ab**	86	92
3	3-MeC_6H_4 (**2c**)	**3ac**	94	98
4	4-MeC_6H_4 (**2d**)	**3ad**	92	95
5	3-$OMeC_6H_4$ (**2e**)	**3ae**	84	98
6	4-t-BuC_6H_4 (**2f**)	**3af**	90	96
7	2-FC_6H_4 (**2g**)	**3ag**	85	94
8	3-FC_6H_4 (**2h**)	**3ah**	91	96
9	4-FC_6H_4 (**2i**)	**3ai**	88	98
10	3-ClC_6H_4 (**2j**)	**3aj**	94	97
11	4-ClC_6H_4 (**2k**)	**3ak**	93	96
12	2-BrC_6H_4 (**2l**)	**3al**	87	90
13	3-BrC_6H_4 (**2m**)	**3am**	92	97
14	4-BrC_6H_4 (**2n**)	**3an**	91	96
15	3-$CF_3C_6H_4$ (**2o**)	**3ao**	93	97
16	4-$CF_3C_6H_4$ (**2p**)	**3ap**	90	96
17	2-naphthyl (**2q**)	**3aq**	95	97
18	CO_2Et (**2r**)	**3ar**	67	97
19	H (**2s**)	**3as**	62	90

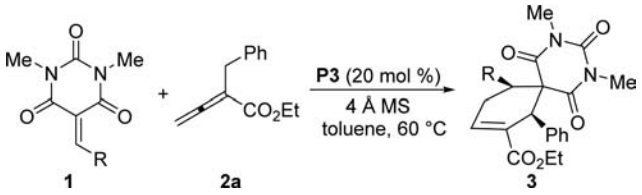
[a]Unless indicated otherwise, reactions were carried out in 2 mL of toluene using 0.1 mmol of **1a**, 0.12 mmol of **2**, and 70 mg of 4 Å MS in the presence of 20 mol % of **P3**. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The dr is >20:1, determined by ^{1}H NMR analysis of the crude product.

of α-substituted allenoates (**2a**–**2p**) bearing electron-rich, -neutral, and -deficient aromatic moieties underwent asymmetric [4 + 2] annulation reaction, giving the corresponding products (**3aa**–**3ap**) in high yields (84–94%) and with excellent enantioselectivities (90–98%) (entries 1–16). The naphthyl substituted allenoate **2q** also reacted smoothly with the alkene **1a** to afford the product **3aq** in 95% yield and 97% ee (entry 17). The α-(ethoxycarbonylmethyl)allenoate **2r** underwent the reaction to give the product **3ar** in 67% yield and 97% ee (entry 18). It is notable that α-methyl-substituted allenoate (**2s**) is a compatible substrate, leading to the desired product **3as** in 62% yield and 90% ee (entry 19).

We next explored the scope of barbiturate-derived alkenes. As summarized in Table 3, a series of aromatic alkenes, irrespective of their electronic properties and substitution patterns, were reacted to give products **3** in high yields with excellent enantioselectivities (entries 1–19). The fused aromatic and heteroaromatic alkenes such as 2-naphthyl, 2-furanyl, and 2-thienyl alkenes (**1u**–**1w**) were also tolerated and yielded products (**3ua**–**3wa**) in 83–91% yields with 92–98% ee (entries 20–22). Notably, a styryl alkene **1x** worked efficiently to give the product **3xa** in 92% yield and 93% ee (entry 23). Satisfactorily, the alkene scope could be further expanded to the alkyl substituted substrate **1y**, which delivered product **3ya** in 56% yield with 90% ee (entry 24). The absolute configuration of products **3** was assigned by single-crystal X-ray analysis of the product **3oa** (see SI).[14]

DOI: 10.1021/acs.orglett.6b00239
Org. Lett. 2016, 18, 1302–1305

Table 3. Scope of Barbiturate-Derived Alkene 1[a]

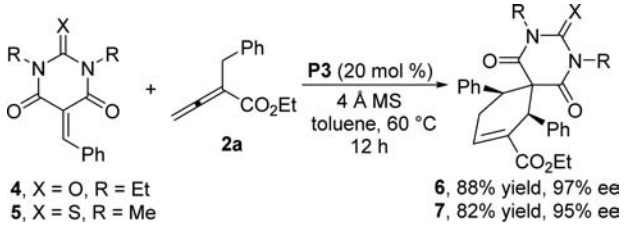


entry	1	t/h	3	yield (%)[b]	ee (%)[c]
1	3-MeC$_6$H$_4$ (**1b**)	12	**3ba**	86	98
2	4-MeC$_6$H$_4$ (**1c**)	12	**3ca**	91	98
3	2-MeOC$_6$H$_4$ (**1d**)	12	**3da**	81	95
4	3-MeOC$_6$H$_4$ (**1e**)	12	**3ea**	84	98
5	4-MeOC$_6$H$_4$ (**1f**)	12	**3fa**	92	99
6	4-EtC$_6$H$_4$ (**1g**)	12	**3ga**	95	99
7	4-PhC$_6$H$_4$ (**1h**)	12	**3ha**	88	95
8[d]	2-FC$_6$H$_4$ (**1i**)	48	**3ia**	72	90
9	3-FC$_6$H$_4$ (**1j**)	12	**3ja**	88	96
10	4-FC$_6$H$_4$ (**1k**)	12	**3ka**	85	96
11	3-ClC$_6$H$_4$ (**1l**)	12	**3la**	91	93
12	4-ClC$_6$H$_4$ (**1m**)	12	**3ma**	94	96
13	3-BrC$_6$H$_4$ (**1n**)	12	**3na**	92	93
14	4-BrC$_6$H$_4$ (**1o**)	12	**3oa**	92	97
15	3-NO$_2$C$_6$H$_4$ (**1p**)	48	**3pa**	76	94
16	4-NO$_2$C$_6$H$_4$ (**1q**)	48	**3qa**	80	92
17	3-CF$_3$C$_6$H$_4$ (**1r**)	12	**3ra**	95	96
18	4-CF$_3$C$_6$H$_4$ (**1s**)	12	**3sa**	93	95
19	3-CNC$_6$H$_4$ (**1t**)	48	**3ta**	75	94
20	2-naphthyl (**1u**)	12	**3ua**	91	98
21	2-furanyl (**1v**)	12	**3va**	83	92
22	2-thienyl (**1w**)	12	**3wa**	85	98
23	styryl (**1x**)	12	**3xa**	92	93
24	cyclohexyl (**1y**)	12	**3ya**	56	90

[a]Unless indicated otherwise, reactions were carried out in 2 mL of toluene using 0.1 mmol of **1**, 0.12 mmol of **2a**, and 70 mg of 4 Å MS in the presence of 20 mol % of **P3**. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The dr is >20:1, determined by ^{1}H NMR analysis of the crude product. [d]The reaction was performed at 100 °C.

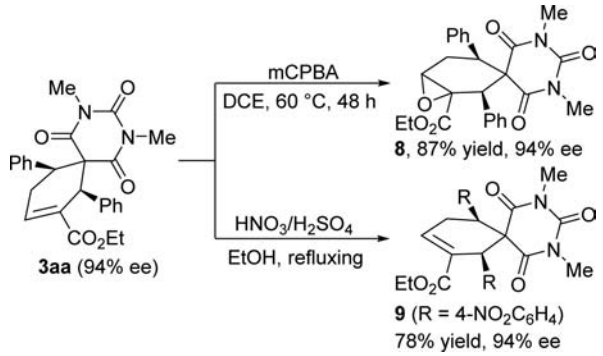
As shown in Scheme 2, under the standard reaction conditions, an ethyl barbiturate derived alkene (**4**) reacted

Scheme 2. Scope of Activated Alkenes



with allenoate **2a** to give spirobarbiturate-cyclohexene **6** in 88% yield and 97% ee. In particular, a thio-barbiturate-derived alkene (**5**) provided the product **7** in 82% yield and 95% ee. Further elaboration of products was briefly explored (Scheme 3). By treatment of **3aa** with mCPBA in 1,2-dichloroethane at 60 °C for 48 h, epoxidation of carbon−carbon double bond was achieved to give a tricyclic heterocycle in 87% yield with 94% ee (its absolute configuration had not been determined), which could be a valuable precursor for the synthesis of novel optically active compounds. With the use of HNO_3/H_2SO_4, nitration of

Scheme 3. Elaboration of Products



spirobarbiturate **3aa** occurred in refluxing ethanol to give dinitro substituted product **9** in 78% yield with 94% ee.

In summary, we have achieved an enantioselective synthesis of pharmaceutically important spirobarbiturate-cyclohexenes through spirocyclic chiral phosphine-catalyzed asymmetric [4 + 2] annulation of barbiturate-derived alkenes with allenoates. Using this tool, the biologically useful spirobarbiturate-cyclohexenes are obtained in good to excellent yields with excellent diastereo- and enantioselectivities. The reaction tolerated a broad scope of allenoates and barbiturate-derived alkenes bearing various substituents, providing an important alternative tool for the enantioselective synthesis of chiral cyclohexene derivatives. For the first time, the allenoate scope of the phosphine-catalyzed asymmetric allene−alkene [4 + 2] annulation was expanded to include diverse α-substituted allenoates. This reaction represents important progress in the chiral phosphine-catalyzed asymmetric [4 + 2] annulation of allenoates with alkenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00239.

Experimental procedure, characterization data, HPLC analysis dada, NMR spectra and X-ray crystallographic data (PDF)

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Author Contributions

§H.L. and Y.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the NSFC (21372256 and 21572264).

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DOI: 10.1021/acs.orglett.6b00239
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(11) In ref 8a, when the isatin-derived alkene was used as the substrate, two allenoates bearing electron-poor aromatic rings at the β'-position also worked, however, the reaction was not applicable to an electron-neutral phenyl ring at the β'-position.

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(14) Crystallographic data for **3oa** have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 1431960.

DOI: 10.1021/acs.orglett.6b00239
Org. Lett. 2016, 18, 1302−1305