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An Asymmetric Allylic Alkylation–Smiles Rearrangement–Sulfinate Addition Sequence to Construct Chiral Cyclic Sulfones

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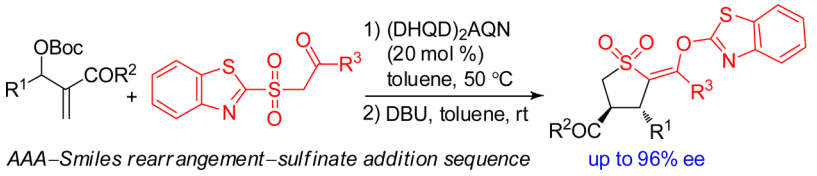
ABSTRACT



AAA–Smiles rearrangement–sulfinate addition sequence up to 96% ee

An asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates and β-keto sulfones was investigated by the catalysis of modified cinchona alkaloids, whose products underwent a Smiles rearrangement–sulfinate addition cascade to furnish highly functionalized five-membered cyclic sulfones in moderate to excellent enantioselectivity and good diastereoselectivity after treatment with DBU.

Chiral cyclic sulfones are the key scaffolds in a number of pharmaceutically important compounds and natural products as those exemplified in Figure 1,[1] which exhibit broad biological activities such as inhibiting HIV-1 protease, hepatitis C virus, influenza neuraminidase, and human carbonic anhydrase II, etc. They have also been utilized as versatile intermediates in diverse synthetic transformations,[2] such as Ramberg–Bäcklund rearrangement to chiral olefins.[3] Although an array of catalytic protocols have been developed for the construction of acyclic chiral sulfones,[4] production of chiral cyclic sulfones remains a challenging problem, and most reported methodologies rely on utilizing chiral starting materials.[5] To the best of our knowledge, the catalytic versions of chiral cyclic sulfones are very limited up to date, except that a notable example was presented by Anderson and co-workers through Ir-catalyzed asymmetric hydrogenation of prochiral unsaturated cyclic sulfones.[6]

Recently, an asymmetric allylic alkylation (AAA) reaction with racemic Morita–Baylis–Hillman (MBH) carbonates or acetates catalyzed by a chiral tertiary amine or phosphine has provided an efficient approach to produce multifunctional chiral compounds, which could be further applied to synthesize diverse cyclic frameworks.[7] In our

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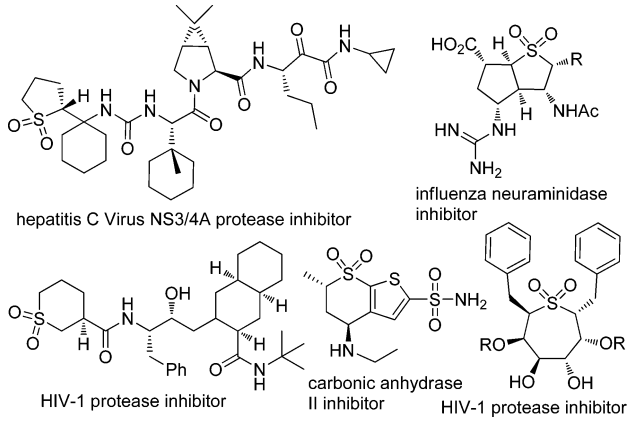
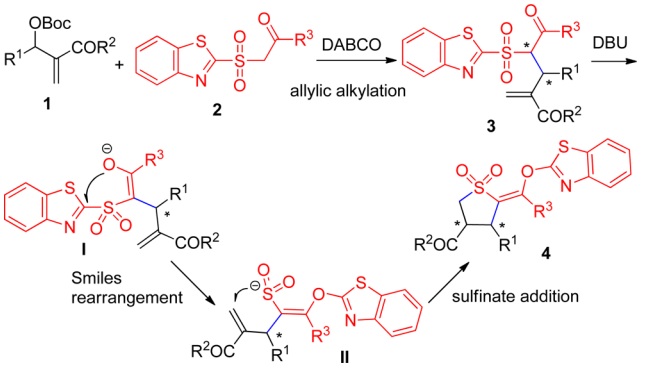


Figure 1. Biologically active compounds containing a cyclic sulfone motif.

continuing efforts to expand this catalytic strategy,[8] we are interested in the assembly of MBH carbonates **1** and nucleophilic β-keto sulfones **2** containing a benzothiazol-2-yl moiety.[9] It was revealed that the alkylation intermediate **3** from the catalysis of DABCO (1,4-diazabicyclo-[2.2.2]-octane) could undergo an intramolecular Smiles rearrangement[10] in the presence of a stronger base such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). In contrast to the usual elimination of one molecular SO_2 that involves in Julia–Kocienski-type reaction,[9,11] the in situ generated sulfinate anion[12] of intermediate **II** attacks α,β-unsaturated carbonyl system, furnishing multifunctional five-membered cyclic sulfones in a quite straightforward and efficient manner, as outlined in Scheme 1.

Scheme 1. Allylic Alkylation–Smiles Rearrangement–Sulfinate Addition Sequence to Cyclic Sulfones



After discovering this interesting reaction sequence, we systematically investigated the asymmetric allylic alkylation of β-keto sulfones **2a** with MBH carbonates **1a** catalyzed by modified cinchona alkaloid in order to access chiral sulfone **4a**.[7,8] Commercially available $(DHQD)_2PYR$ (20 mol %) exhibited acceptable catalytic activity at 50 °C in 1,2-dichloroethane (DCE). A trace amount of cyclic sulfone product **4a** was detected under such asymmetric catalytic conditions, while full conversion of allylic alkylation intermediate **3a** to **4a** could be realized after treatment with DBU in toluene at ambient temperature. Good diastereoselectivity (5.7:1) was observed for the crude cyclic sulfone product,[13] while the pure major diastereomer *anti*-**4a** could be smoothly separated in moderate yield and with modest enantioselectivity (Table 1, entry 1). Subsequently, a few solvents were screened (entries 2–7) for AAA reaction, and better results were attained in toluene (entry 6). $(DHQD)_2PHAL$ gave the similar data (entry 8); pleasingly, higher yield and enantioselectivity were gained by using $(DHQD)_2AQN$ as the catalyst (entry 9). $(DHQ)_2AQN$ produced the product with an opposite configuration to that of $(DHQD)_2AQN$, but only a fair ee value was obtained (entry 10). The reaction could be significantly accelerated at higher 70 °C catalyzed by $(DHQD)_2AQN$, while both isolated yield and ee were slightly reduced for product **4a** (entry 11). On the other hand, sulfones **2** with other substitutions, such as *N*-phenyltetrazole, were also investigated, but either inferior results were given or the later Smiles rearrangement could not be promoted by adding DBU.[14]

With the optimal conditions in hand, an array of MBH carbonates and β-keto sulfones containing a benzothiazol-2-yl moiety were explored. The AAA reactions were conducted in toluene catalyzed by 20 mol % of $(DHQD)_2AQN$ at 50 °C. Then intermediates **3** were isolated, and subsequent Smiles rearrangement–sulfinate addition cascade was promoted by

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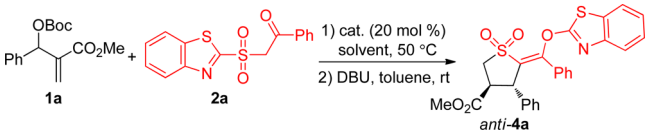
(13) The similar dr values (about 5:1) were observed in DCM or THF.

(14) For more details, see the Supporting Information.

Table 1. Screening of Conditions for AAA–Smiles Rearrangement–Sulfinate Addition with MBH Carbonate **1a** and β-Keto Sulfone **2a**[a]



entry	cat.	solvent	t (h)[b]	yield (%)[c]	ee (%)[d]
1	$(DHQD)_2PYR$	DCE	65	67	70
2	$(DHQD)_2PYR$	$CHCl_3$	70	72	70
3	$(DHQD)_2PYR$	CH_3CN	72	20	79
4	$(DHQD)_2PYR$	THF	85	67	75
5	$(DHQD)_2PYR$	dioxane	90	65	75
6	$(DHQD)_2PYR$	toluene	70	73	79
7	$(DHQD)_2PYR$	$PhCF_3$	50	80	76
8	$(DHQD)_2PHAL$	toluene	67	75	78
9	$(DHQD)_2AQN$	toluene	65	82	90
10	$(DHQ)_2AQN$	toluene	96	70	−46
11[e]	$(DHQD)_2AQN$	toluene	32	77	88

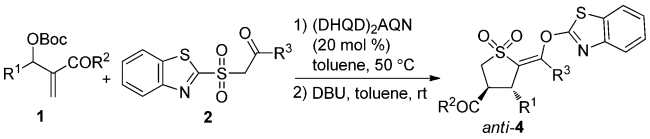
[a] Unless noted otherwise, reactions were performed with 0.2 mmol of **1a**, 0.1 mmol of **2a**, 20 mol % of cat. in 0.5 mL of solvent at 50 °C. Then the intermediate was isolated and treated with DBU in toluene at room temperature for 8 h. [b] For AAA step. [c] Isolated yield for two steps. [d] By chiral HPLC analysis. [e] At 70 °C. $(DHQD)_2PYR$: hydroquinidine 2,5-diphenyl-4,6-pyrimi-dinediyl diether; $(DHQD)_2PHAL$: hydroquinidine 1,4-phthalazinediyl diether; $(DHQD)_2AQN$: hydroquinidine anthraxquinone-1,4-diyl diether; $(DHQ)_2AQN$: hydroquinine anthraxquinone-1,4-diyl diether.

DBU in toluene at ambient temperature. Such two reactions could not be carried out in a one-pot procedure, because DBU would catalyze the allylic alkylation of a small amount of remaining MBH carbonates and β-keto sulfones, which would significantly decrease the ee values of the final cyclic sulfone products. The results are summarized in Table 2. In general, MBH carbonates bearing a variety of aryl or heteroaryl groups could be well tolerated. The similar diastereoselectivity was observed in the crude sulfone mixtures, and the major *anti*-isomers could be separated in moderate to good yields and with high enantioselectivity (Table 2, entry 1–13). Nevertheless, a MBH carbonate with an alkyl group exhibited much lower reactivity. Although excellent diastereoselecvitiy was observed in the cyclization, the corresponding cyclic sulfone **4n** was obtained in low yield and enantioselectivity (entry 14). On the other hand, it was found that β-keto counterparts with diverse aryl or heteroaryl groups could be smoothly applied (entries 15–19), and good data was still delivered for a simple methyl-substituted one (entry 20). Finally, a MBH carbonate derived from methyl vinyl ketone was tested, and product **4u** was isolated in good yield and with excellent enantioselectivity (entry 21).

As outlined in Figure 2, single crystals suitable for X-ray crystallographic analysis were fortunately obtained from enantiopure *anti*-**4j**; thus, its chemical structure and absolute configuration could be unambiguously determined.

It was pleasing that the benzothiazol-2-yl moiety of products **4** could be smoothly removed. As illustrated in Scheme 2, the alkenyl ether group of **4j** was efficiently

Table 2. Substrate Scope for AAA–Smiles Rearrangement–Sulfinate Addition with MBH Carbonates **1** and β-Keto Sulfones **2**[a]



entry	R^1	R^3	t (h)[b]	dr[c]	yield (%)[d]	ee (%)[e]
1	Ph	Ph	65	5.7:1	**4a**, 82	90
2	2-ClC_6H_4	Ph	72	5.7:1	**4b**, 74	96
3	2-BrC_6H_4	Ph	72	6.0:1	**4c**, 80	94
4	3-ClC_6H_4	Ph	72	6.0:1	**4d**, 75	92
5	4-ClC_6H_4	Ph	65	6.0:1	**4e**, 80	89
6	4-BrC_6H_4	Ph	65	6.0:1	**4f**, 78	88
7[f]	3,4-$Cl_2C_6H_3$	Ph	72	5.7:1	**4g**, 72	91
8	3-MeC_6H_4	Ph	96	5.7:1	**4h**, 83	93
9	4-MeC_6H_4	Ph	96	5.7:1	**4i**, 78	93
10	4-$MeOC_6H_4$	Ph	96	6.0:1	**4j**, 72	92
11	2-naphthyl	Ph	72	6.0:1	**4k**, 78	96
12	2-furyl	Ph	65	5.0:1	**4l**, 65	88
13	2-thienyl	Ph	72	6.0:1	**4m**, 68	91
14	*n*-propyl	Ph	96	19:1	**4n**, 45	52
15	Ph	4-ClC_6H_4	60	6.0:1	**4o**, 70	89
16	Ph	3-BrC_6H_4	96	6.0:1	**4p**, 76	86
17	Ph	4-MeC_6H_4	96	6.0:1	**4q**, 72	90
18[f]	Ph	2-naphthyl	96	6.0:1	**4r**, 78	91
19[f]	Ph	2-thienyl	72	5.0:1	**4s**, 70	90
20	Ph	Me	96	6.0:1	**4t**, 65	84
21[g]	Ph	Ph	72	6.0:1	**4u**, 75	96

[a] Unless noted otherwise, reactions were performed with 0.2 mmol of MBH carbonate **1** derived from methyl acrylate, 0.1 mmol of β-keto sulfone **2**, 20 mol % of $(DHQD)_2AQN$ in 0.5 mL of toluene at 50 °C. Then the intermediate was isolated and treated with DBU in toluene at room temperature for 8 h. [b] For AAA step. [c] Determined by ^1H NMR analysis of the crude product. [d] Isolated yield for two steps. [e] By chiral HPLC analysis. [f] At 30 °C. [g] R^2 = Me.

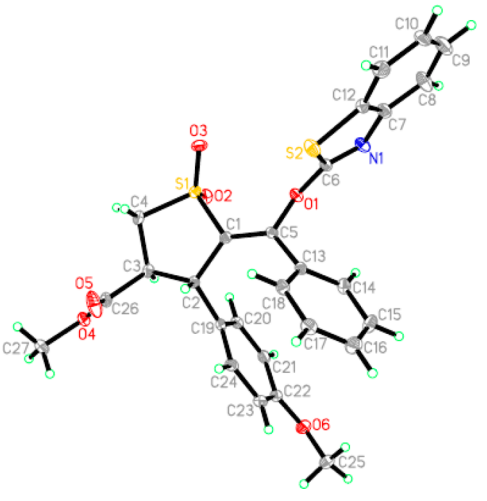
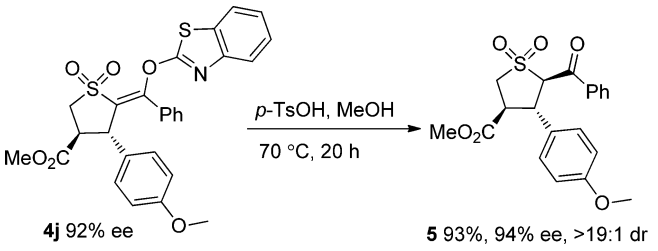


Figure 2. X-ray structure of enantiopure *anti*-**4j**.

Scheme 2. Hydrolysis of Alkenyl Ether Group



hydrolyzed by *p*-TsOH in methanol at 70 °C, cleanly producing cyclic sulfone **5** with exclusive diastereoselectivity and retained enantiopurity. The relative configuration of the newly formed chiral center could be assigned by NOE analysis.[14] The multifunctionalities of **5** might provide more opportunities for organic synthesis.

In conclusion, we have investigated the asymmetric allylic alkylation of β-keto benzothiazol-2-yl sulfones with Morita–Baylis–Hillman carbonates catalyzed by modified cinchona alkaloids. The chiral intermediates underwent intramolecular Smiles rearrangement by subsequent treatment with organic base DBU, and an unusual intramolecular sulfinate addition was followed to give cyclic sulfone products with dense functionalities in high enantioselectivity and with good diastereoselectivity. The benzothiazol-2-yl moiety could be efficiently removed in a traceless manner; thus, the reported sequence provides a formal [3 + 2] annulation process to construct useful five-membered cyclic sulfones from readily available starting materials. More results will be reported in due course.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, CIF file of enantiopure *anti*-**4j**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.