DOI: 10.1002/chem.201100534

Lewis Base Assisted Brønsted Base Catalysis: Direct Regioselective Asymmetric Vinylogous Alkylation of Allylic Sulfones

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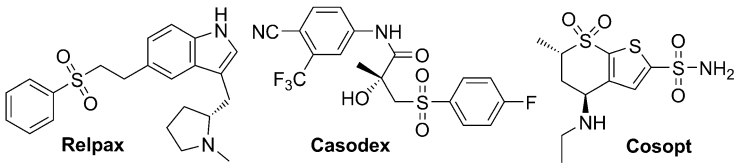
Abstract: A Lewis base assisted Brønsted base catalysis (LBABB) strategy is applied for direct asymmetric vinylogous alkylation of allylic sulfones with Morita–Baylis–Hillman (MBH) carbonates, in which a strong Brønsted base, *tert*-butoxy anion, generated in situ from a tertiary amine catalyst and MBH carbonate, is crucial in activating unstabilized nucleophiles. The γ-regioselective alkylation products were obtained with good to excellent enantiomeric excess values when catalyzed by a modified cinchona alkaloid.

Keywords: alkylation · allylic sulfones · Brønsted bases · Lewis bases · Morita–Baylis–Hillman carbonates

Introduction

The applications of sulfone-containing materials in asymmetric catalysis have recently triggered increasing interest, not only because of their synthetic versatility,[1] but also for their wide distribution in biologically active products,[2] such as the commercial drugs illustrated in Scheme 1.[3] Apart from activating a conjugated double bond for Michael addition,[4] sulfone functionality could stabilize α-carbanions, which allows sulfone-containing alkanes to perform as well as C-nucleophilic reagents. Although significant progress has been made in the past few years, almost all reported asymmetric reactions are confined to sulfones substituted by an α-electron-withdrawing group, especially in the field of metal-free organocatalysis.[5] On the other hand, the utilization of sulfone species possessing a simple functional group, such as allyl phenyl sulfone ($pK_a = 22.5$ in DMSO),[6] the so-called "hard" or unstabilized nucleophile,[7] seems to be a more challenging and formidable task because the removal of the α proton usually needs a much stronger base (*n*BuLi or NaH).[8] To the best of our knowledge, no successful example for such useful synthons has been presented in an asymmetric catalytic manner to date.



Scheme 1. Typical commercial drugs containing sulfone groups.

Inspired by our recent studies on the Lewis basic tertiary amine catalyzed asymmetric allylic alkylation (AAA) reactions with Morita–Baylis–Hillman (MBH) carbonates,[9,10] we recognized that a rather strong Brønsted base, *tert*-butoxy anion (pK_a (*t*BuOH) = 32.2 in DMSO),[6] would be generated in situ in the catalytic cycle, which should be capable of deprotonating a series of otherwise inert nucleophiles. We envisaged that such a catalytic strategy, henceforth abbreviated as Lewis base assisted Brønsted base catalysis (LBABB), would be applicable to the direct vinylogous[11] alkylation of allylic sulfones, as outlined in Scheme 2.

Results and Discussion

The initial reaction of commercially available allyl phenyl sulfone (**2a**) and MBH carbonate **3a** was conducted with 1,4-diazabicyclo[2.2.2]octane (DABCO; **1a**) catalyst in 1,2-dichloroethane (DCE) at 40 °C. The starting materials could be consumed smoothly, but a mixture of γ-selective product **4a** ($E/Z > 99:1$) and α-selective product **5a** (a diastereomeric mixture) was obtained (Table 1, entry 1).[12] Fortunately, the γ-alkylation product **4a** was dominantly produced in 59 % yield after 72 h when catalyzed by a modified cinchona alkaloid **1b**,[13] and more importantly, the enantioselectivity was promising (Table 1, entry 2). To facilitate reactivity, allyl

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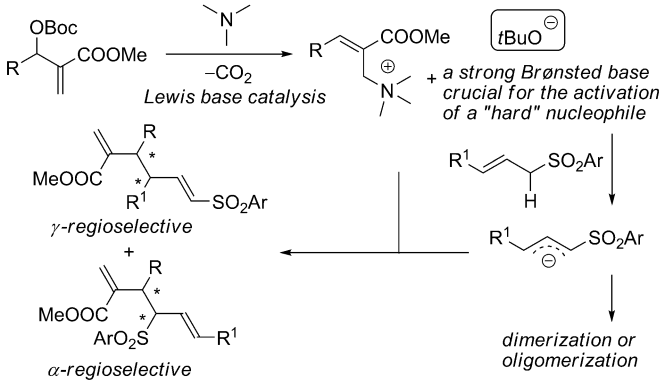
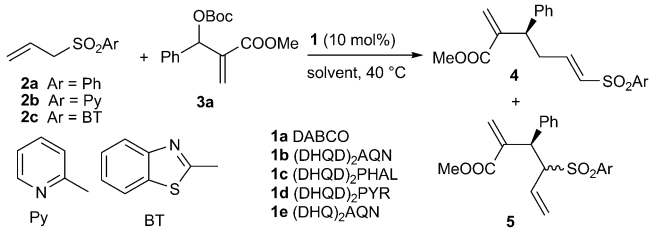
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201100534.



Scheme 2. A LBABB strategy for direct vinylogous alkylation of allylic sulfones. Boc: *tert*-butyloxycarbonyl.

Table 1. Screening studies of vinylogous alkylation of allyl sulfones **2** and MBH carbonate **3a**.[a]



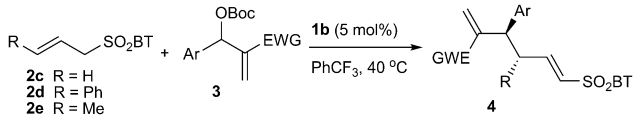
Entry	**1**	**2**	Solvent	*t* [h]	Product (yield [%][b])	*ee* [%][c]
1	**1a**	**2a**	DCE	4	**4a** (60) **5a** (25[d])	–
2	**1b**	**2a**	DCE	72	**4a** (59)	88
3	**1b**	**2b**	DCE	92	**4b** (67)	89
4	**1b**	**2c**	DCE	15	**4c** (77)	89
5	**1c**	**2c**	DCE	72	**4c**, **5c** (<10)	–
6	**1d**	**2c**	DCE	72	**4c**, **5c** (<10)	–
7	**1e**	**2c**	DCE	16	**4c** (77)	−44
8	**1b**	**2c**	toluene	66	**4c** (63)	86
9	**1b**	**2c**	*m*-xylene	66	**4c** (73)	88
10	**1b**	**2c**	$PhCF_3$	22	**4c** (73)	92
11[e]	**1b**	**2c**	$PhCF_3$	65	**4c** (68)	95
12[f]	**1b**	**2c**	$PhCF_3$	48	**4c** (80)	92
13[f,g]	**1b**	**2c**	$PhCF_3$	70	**4c** (70)	90
14[f]	**1e**	**2c**	$PhCF_3$	48	**4c** (68)	−63

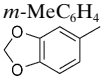
[a] Unless otherwise noted, reactions were performed with **2** (0.05 mmol), **3a** (0.1 mmol), and **1** (10 mol%) in solvent (0.5 mL) at 40°C. $[DHQD]_2AQN$: hydroquinidine (anthraquinone-1,4-diyl) diether; $[DHQD]_2PHAL$: hydroquinidine 1,4-phthalazinediyl diether; $[DHQD]_2PYR$: hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether; $[DHQ]_2AQN$: hydroquinine (anthraquinone-1,4-diyl) diether. [b] Yield of isolated product. [c] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis; *E*/*Z* > 99:1. [d] Diastereomeric ratio (d.r.) = 63:37, determined by ^1H NMR spectroscopic analysis. [e] At RT. [f] At 0.1 mmol scale, with 5 mol% of **1b** in 1 mL of $PhCF_3$. [g] With 2 mol% of **1b**.

sulfones with a more electron-withdrawing heteroaryl group were designed. Although similar results were obtained for 2-pyridyl-substituted sulfone **2b** (Table 1, entry 3), it was pleasing that the reaction could be greatly accelerated for sulfone **2c** with a benzothiazol-2-yl group (Table 1, entry 4). However, the other analogous cinchona alkaloids **1c** and **1d** exhibited very low catalytic activity, and both γ- and α-alkylation products **4c** and **5c** could be detected (Table 1, entries 5 and 6).[14,15] The reaction proceeded efficiently when catalyzed by **1e**, while product **4c** with the opposite configuration was formed in much lower enantioselectivity (Table 1, entry 7). Solvent screening showed that a slower reaction rate was observed in toluene and *m*-xylene (Table 1, entries 8 and 9), but better data were delivered in $PhCF_3$ with regard to reactivity, yield, and enantiocontrol (Table 1, entry 10). When the reaction was conducted at room temperature, the enantioselectivity was slightly improved, but the reaction rate became sluggish (Table 1, entry 11). Finally, it was found that good results could still be obtained with catalyst **1b** (5 mol%; Table 1, entry 12), even at lower catalytic loading (2 mol%; Table 1, entry 13). In addition, the *ee* value was also improved with catalyst **1e** under optimal conditions (Table 1, entry 14).

Consequently, we then examined the substrate scope and limitations of the new vinylogous alkylation reaction. The reaction was performed with catalyst **1b** (5 mol%) in $PhCF_3$ (1 mL) at 40°C. The results are summarized in Table 2. For the reaction of **2c**, an array of MBH carbonates equipped with diverse electron-deficient or -rich aryl or heteroaryl groups have been explored, providing γ-alkylation products **4c**–**4n** in high to excellent enantioselectivities and moderate

Table 2. Substrate scope and limitations.[a]

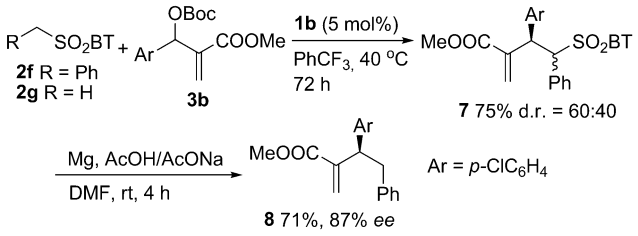


Entry	**2**	Ar	EWG	*t* [h]	Product (yield [%][b])	*ee* [%][c]
1	**2c**	Ph	COOMe	48	**4c** (80)	92
2	**2c**	*p*-ClC_6H_4	COOMe	66	**4d** (69)	98
3	**2c**	*m*-ClC_6H_4	COOMe	71	**4e** (83)	90
4	**2c**	*o*-BrC_6H_4	COOMe	71	**4f** (79)	97
5	**2c**	3,4-$Cl_2C_6H_3$	COOMe	32	**4g** (79)	89
6[d]	**2c**	*p*-$NO_2C_6H_4$	COOMe	61	**4h** (72)	89
7	**2c**	*p*-$MeOC_6H_4$	COOMe	75	**4i** (72)	96
8	**2c**	*m*-MeC_6H_4	COOMe	88	**4j** (82)	95
9	**2c**		COOMe	66	**4k** (74)	93
10	**2c**	1-naphthyl	COOMe	23	**4l** (69)	96
11[e]	**2c**	2-thienyl	COOMe	72	**4m** (77)	94
12[e]	**2c**	2-furyl	COOMe	51	**4n** (67)	83
13	**2d**	Ph	COOMe	64	**4o** (70)	99[f,g]
14	**2e**	Ph	COOMe	69	**4p** (82)	93[f]
15	**2c**	Ph	COMe	31	**4q** (53)	95
16	**2c**	*p*-BrC_6H_4	COMe	24	**4r** (55)	95
17	**2c**	*p*-MeC_6H_4	COMe	24	**4s** (61)	96

[a] Unless otherwise noted, reactions were performed with **2** (0.1 mmol), **3** (0.2 mmol), and **1b** (5 mol%) in $PhCF_3$ (1.0 mL) at 40°C. EWG: electron-withdrawing group. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; *E*/*Z* > 99:1. [d] At 0°C. [e] At RT. [f] D.r. > 99:1, by ^1H NMR spectroscopic analysis. [g] The absolute configuration of **4o** was determined by X-ray analysis (see the Supporting Information).[16] The other products were assigned by analogy.

to good isolated yields (Table 2, entries 1–12). It is noteworthy that the γ-substituted allylic sulfones **2d** and **2e** could be efficiently used, giving the corresponding γ-selective alkylation products **4o** and **4p**, respectively, with remarkable diastereo- and enantioselectivity (Table 2, entries 13 and 14). Additionally, higher reactivity was observed for MBH carbonates derived from methyl vinyl ketone, affording γ-alkylation products **4q**–**4s** with outstanding *ee* values, albeit in modest yields due to some side reactions (Table 2, entries 15–17). It should be noted that unwanted side reactions often occurred when MBH carbonates with β-alkyl substitution were used.

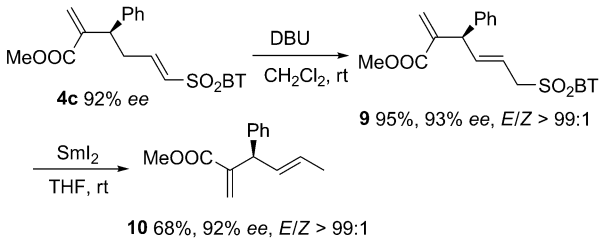
To further illustrate the efficacy of this LBABB strategy, we tested other alkyl-substituted sulfones. As shown in Scheme 3, sulfone **2f** could be smoothly alkylated with



Scheme 3. Expansion of the "hard" alkyl sulfones.

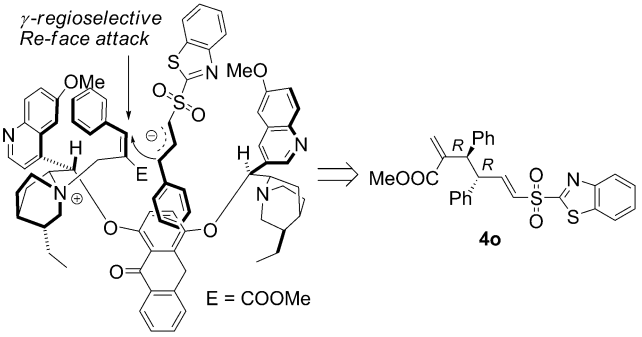
MBH carbonate **3b** by using catalyst **1b**, giving compound **7** as a diastereomeric mixture. Subsequent desulfonylation afforded the allylic benzylation product **8** with high enantiopurity. Nevertheless, the simple sulfone **2g** exhibited no reactivity under the same conditions and remains to be explored further.

Interestingly, the thermodynamic preference for allylic sulfone **9** over its conjugated counterpart **4c** has been observed in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Tandem desulfonylation of **9** with SmI_2 could provide the valuable allylic alkenylation[17] derivative **10**, which is not easily accessible by common synthetic protocols (Scheme 4).



Scheme 4. A formal allylic alkenylation sequence.

Although the conformational ability of dimeric cinchona alkaloids in solution makes it difficult to accurately analyze the transition-state structure of the substrate–catalyst complex, the reaction intermediate for the selective formation of the γ-regioselective substitution product (*R*,*R*)-**4o** with catalyst **1b** is assumed. As shown in Scheme 5, the MBH carbonate, presumably first undergoes Michael-type addition at the nitrogen atom of the quinuclidine, and the resulting complex might be stabilized through π–π stacking between the quinoline moiety and phenyl ring.[18] Such a sandwich-like geometry would effectively block the *Si* face of this complex, thus favoring attack from the *Re* face. In addition, the relatively bulky linkage of **1b** seems to be incompatible with the sulfone moiety, therefore, the less-hindered γ-regioselective product is generated.[14,15]



Scheme 5. Proposed transition state for the formation of product (*R*,*R*)-**4o**.

Conclusion

We have demonstrated that the LBABB strategy is helpful for the direct C–C bond-forming reaction of "hard" nucleophiles, as exemplified in the first asymmetric vinylogous alkylation of allylic sulfones with MBH carbonates. The γ-regioselective products were obtained in high to excellent enantioselectivities and good yields with catalyst **1b**,[14] from which a formal allylic alkenylation procedure has been further developed. We believe that this catalytic strategy will be applicable to more direct asymmetric reactions of diversely structured "hard" nucleophiles,[7] and the results will be reported in due course.

Experimental Section

General procedure for the γ-regioselective alkylation reaction: Sulfone **2c** (23.9 mg, 0.1 mmol), MBH carbonate **3a** (58.4 mg, 0.2 mmol), **1b** (4.3 mg, 5 mol%) in dry $PhCF_3$ (1.0 mL) were stirred at 40 °C, and the reaction was monitored by TLC. After 48 h, the mixture was directly purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give the γ-regioselective alkylation product **4c**.

Compound ***4c***: 80% yield; $[\alpha]_D^{20} = -52.7$ ($c = 1.20$ in $CHCl_3$); 92% *ee*, determined by HPLC analysis (Daicel chiralpak AD, *n*hexane/*i*PrOH = 80/20, 1.0 mL min^{-1}, $\lambda = 254$ nm, $t_{major} = 14.889$ min, $t_{minor} = 16.537$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.66–7.57 (m, 2H), 7.16–7.03 (m, 6H), 6.52 (d, $J = 15.6$ Hz, 1H), 6.33 (s, 1H), 5.62 (s, 1H), 4.06 (t, $J = 8.0$ Hz, 1H), 3.66 (s, 3H), 2.95–2.90 (m, 1H), 2.82–2.76 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 166.6, 166.5, 152.7, 149.4, 141.7, 140.1, 136.8, 129.6, 128.5, 127.8, 127.7, 127.5, 126.9, 125.3, 125.2, 122.2, 51.9, 44.9, 36.3 ppm; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}NO_4S_2$ $[M+H]^+$: 414.0834; found: 414.0839.

General procedure for synthesis of allylic benzylation product 8: Sulfone **2f** (28.9 mg, 0.1 mmol), MBH carbonate **3b** (65.2 mg, 0.2 mmol), and **1b** (4.3 mg, 5 mol%) in dry $PhCF_3$ (1.0 mL) were stirred at 40°C for 72 h. Then, the mixture was directly purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give **7**. The desulfonylation process: Mg powder (24.0 mg, 0.10 mmol) and a solution of AcOH/AcONa (8 M, 0.5 mL) were added to a stirred solution of **7** (33.0 mg, 0.07 mmol) in DMF (1.0 mL) under argon at room temperature. The resulting mixture was stirred at the same temperature for 4 h. The mixture was diluted with Et_2O (5 mL) and the organic layer was isolated. Then, the aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 200:1) to afford the pure desulfonylation product **8**.

Compound **7**: 75% yield; d.r. = 60:40; ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereomer): δ = 8.20 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.63–7.57 (m, 1H), 7.54–7.49 (m, 2H), 7.33–7.27 (m, 2H), 7.20–7.18 (m, 2H), 7.05–6.98 (m, 3H), 6.83–6.81 (m, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 6.08 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 3.71 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer): δ = 165.7, 165.6, 152.2, 139.2, 137.0, 136.0, 132.6, 131.0, 130.5, 129.4, 128.8, 128.5, 128.3, 128.1, 127.8, 127.6, 127.4, 125.4, 122.0, 71.2, 52.0, 48.9 ppm; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{20}ClNO_4S_2Na$ $[M+Na]^+$: 520.0420; found: 520.0422.

Compound **8**: 71% yield; $[\alpha]_D^{20} = -127.1$ (*c* = 0.35 in $CHCl_3$); 87% *ee*, determined by HPLC analysis (Daicel chiralcel OD, *n*hexane/*i*PrOH = 98/2, 1.0 mL min^{-1}, λ = 254 nm, t_{major} = 7.815 min, t_{minor} = 8.641 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.13 (m, 5H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.35 (s, 1H), 5.74 (s, 1H), 4.18–4.15 (m, 1H), 3.66 (s, 3H), 3.20 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.98 ppm (dd, *J* = 13.6, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 142.8, 140.3, 139.3, 132.2, 129.5, 129.0, 128.3, 128.2, 126.1, 124.8, 51.9, 47.5, 40.7 ppm; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{17}ClO_2Na$ $[M+Na]^+$: 323.0815; found: 323.0811.

General procedure for synthesis of alkenylation product 10: DBU (31 μL, 0.21 mmol) was added to a solution of **4c** (288.0 mg, 0.70 mmol, 92% *ee*) in CH_2Cl_2 (10.0 mL). The mixture was stirred at room temperature for 0.5 h and washed with 1 M HCl, water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 10:1) to give intermediate **9**. For the desulfonylation process: a solution of SmI_2 (3 mL, 0.30 mmol; 0.1 M in THF) was slowly added by syringe to a stirred solution of **9** (41.4 mg, 0.10 mmol) dissolved in dry THF (1.0 mL) under argon at room temperature. The resulting mixture was stirred at the same temperature for 0.5 h. The mixture was treated with 1 M HCl (5 mL) and diluted with EtOAc (10 mL). The aqueous phase was separated and extracted with EtOAc (3×10 mL). The combined organic phase was washed with a saturated aqueous solution of sodium thiosulfate, water, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 100:1) to afford **10**.

Compound **9**: 95% yield; $[\alpha]_D^{20} = -33.4$ (*c* = 2.15 in $CHCl_3$); 93% *ee*, determined by HPLC analysis (Daicel chiralcel OD, *n*hexane/*i*PrOH = 70/30, 1.0 mL min^{-1}, λ = 254 nm, t_{minor} = 13.754 min, t_{major} = 19.309 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.19 (m, 1H), 8.00–7.98 (m, 1H), 7.67–7.59 (m, 2H), 7.11–7.08 (m, 3H), 6.94–6.92 (m, 2H), 6.18 (s, 1H), 6.03 (dd, *J* = 15.6 Hz, 7.2 Hz, 1H), 5.44–5.40 (m, 1H), 5.32 (s, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.25–4.22 (m, 2H), 3.63 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 165.0, 152.7, 143.1, 141.4, 139.5, 136.8, 128.4, 128.0, 127.6, 126.8, 126.6, 125.4, 122.3, 116.9, 58.1, 52.0, 49.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}NO_4S_2Na$ $[M+Na]^+$: 436.0653; found: 436.0659.

Compound **10**: 68% yield; $[\alpha]_D^{20} = -57.8$ (*c* = 0.60 in $CHCl_3$); 92% *ee*, determined by HPLC analysis (Daicel chiralcel OD, *n*hexane/*i*PrOH = 98/2, 1.0 mL min^{-1}, λ = 254 nm, t_{minor} = 4.320 min, t_{major} = 6.360 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2H), 7.22–7.17 (m, 3H), 6.32 (s, 1H), 5.70 (ddd, *J* = 16.4 Hz, 7.6 Hz, 1.6 Hz, 1H), 5.58 (s, 1H), 5.43–5.36 (m, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 3.68 (s, 3H), 1.69 ppm (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 143.1, 141.6, 131.6, 128.2, 128.1, 127.2, 126.3, 125.6, 51.7, 49.3, 17.8 ppm; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}O_2Na$ $[M+Na]^+$: 239.1048; found: 239.1053.

General procedure for the one-pot synthesis of α-regioselective conjugated sulfones: The reaction was carried out with sulfone **2c** (23.9 mg, 0.1 mmol), MBH carbonate **3a** (58.4 mg, 0.2 mmol), and **1d** (8.8 mg, 10 mol%) in dry $PhCF_3$ (1.0 mL) at 50°C for 52 h. Then, DBU (4.5 μL, 0.03 mmol) was added and the reaction was stirred at room temperature for 0.5 h. After completion, the mixture was directly purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to give **6a**.

Compound ***6a***: 43% yield; $[\alpha]_D^{20} = -59.0$ (*c* = 0.70 in $CHCl_3$); *E*/*Z* > 99:1; 82% *ee*, determined by HPLC analysis (Daicel chiralpak AD, *n*hexane/*i*PrOH = 90/10, 1.0 mL min^{-1}, λ = 254 nm, t_{major} = 17.462 min, t_{minor} = 19.257 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.0 Hz, 1H), 7.94–7.92 (m, 1H), 7.62–7.53 (m, 3H), 7.13–7.05 (m, 5H), 6.34 (s, 1H), 5.61 (s, 1H), 5.49 (s, 1H), 3.58 (s, 3H), 1.71 ppm (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 166.5, 152.7, 145.8, 140.9, 138.7, 138.0, 137.3, 128.4, 128.3, 127.7, 127.4, 126.9, 125.3, 122.1, 52.2, 44.9, 15.3 ppm; ESI-HRMS: *m*/*z* calcd for $C_{21}H_{19}NO_4S_2Na$ $[M+Na]^+$: 436.0653; found: 436.0653.

Acknowledgements

We are grateful for financial support from the NSFC (20972101 and 21021001) and the National Basic Research Program of China (973 Program) (2010CB833300). We appreciate helpful comments by Diana Chen of My Editor-in-Chief.

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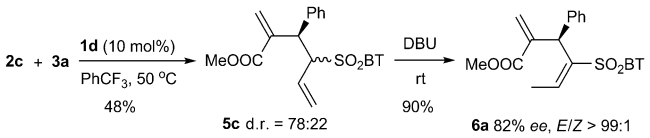

[15] Although the mechanism leading to differently preferred regioselectivity has not yet been determined, we propose that both steric and electronic properties of the catalyst linkage may contribute to the outcome.

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Received: February 17, 2011
Published online: June 30, 2011

