



Highly diastereoselective allylation reactions of dilithiated 4-(phenylsulfonyl)-cyclopent-2-enol

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ABSTRACT

A two-step synthesis of 4-(phenylsulfonyl)cyclopent-2-enol using epoxide ring-opening and ring-closing alkene metathesis is described. Treatment of the dianion of 4-(phenylsulfonyl)cyclopent-2-enol with allylic bromides gave the corresponding alkylated products with excellent to complete diastereoselectivity.

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Cyclopentenones continue to be the subject of significant research interest,^{1–3} which stems from their importance both in synthesis method development and as intermediates in natural product synthesis.^{4–7} Amongst the many methods developed for the assembly of cyclopentenones, ring-closing metathesis (RCM) is one of the most attractive options.^{8–12} In connection with studies of ring-rearrangement metathesis (RRM) reactions of cyclopentenones for the synthesis of substituted cyclohexenones, we became interested in the lithiation and stereoselective allylation of 4-(phenylsulfonyl)cyclopent-2-enol **1**. Our intention was to convert the allylated congeners of **1** into their cyclohexene isomers using RRM (Scheme 1). This Letter describes highly the diastereoselective allylation reactions of **1**, and provides further examples of chirality transfer in the ring-opening reactions of strained heterocycles by sulfone-stabilised carbanionic nucleophiles.

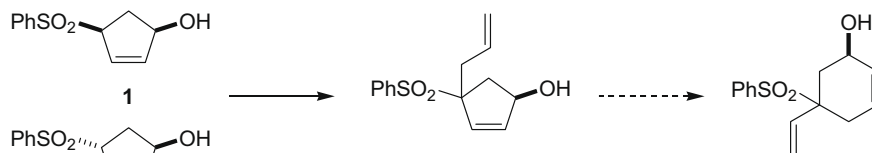
Initial attempts to make **1** involved the reaction of lithiated allylsulfonylbenzene **2** with butadiene monoxide **3**; the anticipated diene product would be subjected to ring-closing alkene metathesis to provide the cyclopentene. However, under the conditions shown, a 1.7:1 mixture (determined by ¹H NMR analysis) of vinylic sulfones **4** and **5** was formed (Scheme 2).¹³ Although the double-bond stereochemistry was not rigorously proved, the assignment of *E*-geometry followed from our previous studies of vinylic sulfones possessing methyl groups in the β-position;¹⁴ similar results were reported by Cheng et al.¹⁵ This unwanted double bond migration was suppressed effectively by the introduction of a conjugat-

ing group at the γ-position of the sulfone nucleophile: treatment of **3** with lithiated cinnamylsulfonylbenzene **6** gave a 3.5:1 mixture of allylic sulfones **7a,b** and **8** in 80% combined yield.¹⁶ This indicates significantly enhanced regioselectivity in the reaction with **3** of the more sterically demanding nucleophile Li-**6** compared with Li-**2**. Compound **7** was formed as a 3:1 mixture of diastereoisomers. Assignment of the structure **7a** to the major isomer followed from the conversion, using Grubbs' second-generation catalyst, of the 3:1 mixture of **7** into a 3:1 mixture of **1**, the major component of which was identical to *syn*-4-(phenylsulfonyl)cyclopent-2-enol formed in 42% yield by the Pd(0)-catalysed reaction of sodium phenylsulfinate with cyclopentadiene monoxide.^{17,18} The predominant formation of **7a** may be rationalised in terms of the minimisation of steric interactions between the phenylsulfonyl and vinyl groups in the nucleophile and electrophile, respectively. In contrast, regioisomer **8** was formed with complete diastereoselectivity (Scheme 2). We have assigned the structure shown since it would arise via the less sterically congested transition state in a manner similar to **7a**; additionally, the stereochemistry shown corresponds to that observed in our studies of reactions of lithio-**6** with a vinylaziridine, where the adduct structure was unequivocally assigned by X-ray crystallographic analysis.¹⁹ As regioisomers **7** and **8** were difficult to separate on large scales, a procedure was developed whereby the crude reaction mixture of **7a,b** and **8** was subjected directly to the subsequent RCM step: **1** was obtained as a 3:1 *syn:anti* mixture (determined by ¹H NMR spectroscopic analysis) in 54% overall yield starting from **45 g** of **6**.

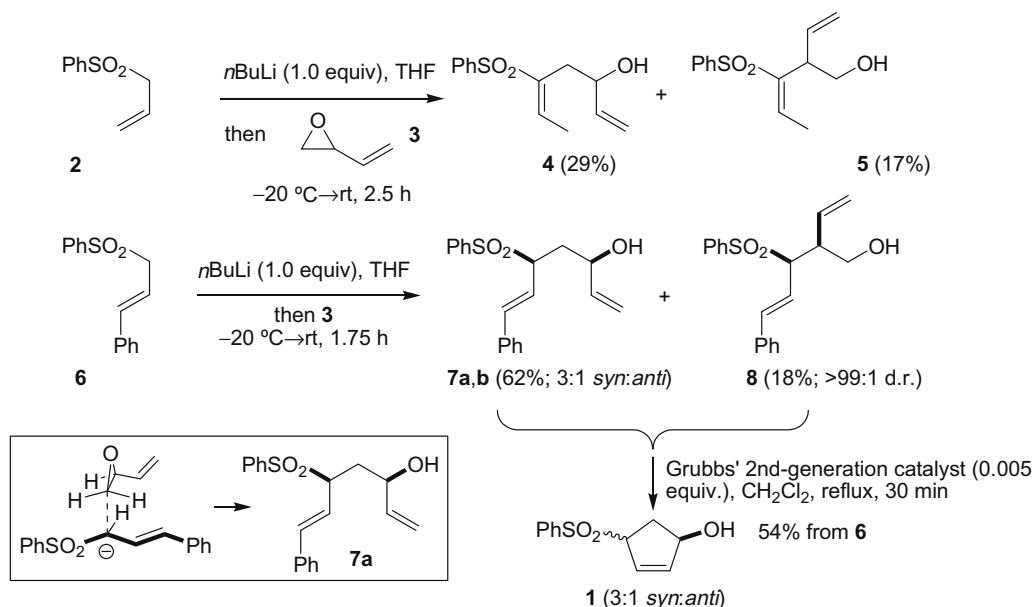
Next, α-alkylation reactions of the cyclopentenols **1** were investigated. Exposure of the 3:1 mixture of *syn* and *anti* **1** to a twofold

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Scheme 1.

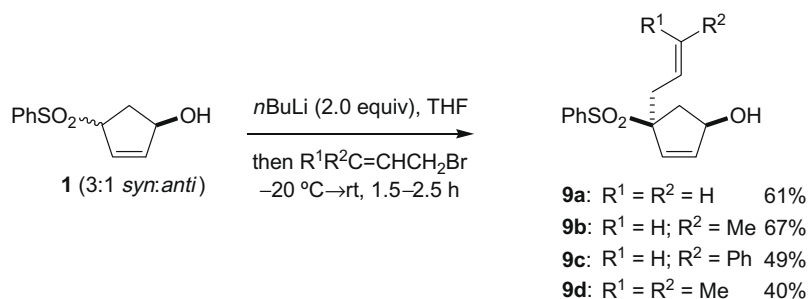


Scheme 2.

excess of *n*BuLi was followed by the addition of one equivalent of electrophile. Allylation reactions of the dianion of **1** were found to be highly or completely stereoselective in the four cases studied. Doubly deprotonated **1** reacted smoothly with 3-bromo-1-propene to give a 10:1 mixture of cyclopentenols **9a**. Similar reactions using (*E*)-1-bromo-2-butene and (*E*)-(3-bromoprop-1-enyl)benzene were observed, giving **9b** and **9c**, respectively; in these cases complete stereoselectivity was observed. Combination of dilithiated **1** with (*E*)-1-bromo-3-methyl-2-butene gave a single, crystalline substitution product **9d**. X-ray crystallographic analysis showed that allylation had occurred *anti* to the hydroxy group, and this stereochemistry was inferred also for the major/exclusive products from the other three reactions (Scheme 3). In no case were any by-products detected corresponding to the conjugate elimination from the dianion of **1**.

The selectivity observed in these processes is striking. This may be a consequence of simple steric hindrance, where the electrophile approaches a planar²⁰ allylic sulfone α -carbon atom in an *anti* sense with respect to the solvated, and therefore bulky lithiated oxygen atom. Alternatively, the geometry of the carbanionic centre may deviate significantly from planar geometry, with the alkoxy-lithium moiety internally coordinated via a PhSO₂ oxygen–lithium interaction.^{21–25} The molecular structure of **9d** provided some support for the latter hypothesis, showing an intramolecular hydrogen-bond between the pro-*S* sulfone oxygen atom [with respect to the (1*R*,4*S*) enantiomer shown] and the alcohol –OH (Fig. 1).²⁶ This suggests that an analogous S=O $\cdots$ Li–O interaction would be feasible if the dianion of **1** were significantly pyramidalised.²⁰

In summary, we have developed a facile two-step sequence for the synthesis of 4-(phenylsulfonyl)cyclopent-2-enol **1** using



Scheme 3.

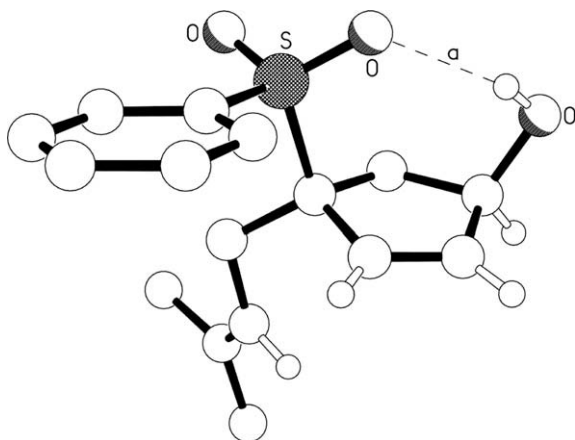


Figure 1. The molecular structure of (±)-9d. The O–H...O hydrogen bond (a) has O...O and H...O separations of 2.9949(18) and 2.16 Å, respectively, with an O–H...O angle of 154°.

epoxide ring-opening and ring-closing alkene metathesis as the key steps. The dilithio dianion of **1** undergoes highly diastereoselective allylation reactions, the selectivity of which may be explained in terms of a planar, solvated or pyramidalised, internally coordinated sulfone α -carbanion. In addition, the stereoselective formation of **7** and **8** in the reaction of Li-**6** with **3** demonstrates that as with the analogous aziridines, chirality transfer may be achieved in the ring-opening reactions of epoxides by sulfone-stabilised carbanions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.10.074](https://doi.org/10.1016/j.tetlet.2009.10.074).

References and notes

1. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 1.
2. Hudlicky, T.; Reed, J. W. *Comprehensive Organic Synthesis*. In Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991.
3. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, 95, 1293.
4. Satyanarayana, J.; Basaveswara Rao, M. V.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1996**, 37, 3565. and references cited therein.
5. Herndon, J. W.; Hill, D. K.; McMullen, L. A. *Tetrahedron Lett.* **1995**, 36, 5687.
6. Schaudt, M.; Blechert, S. J. *Org. Chem.* **2003**, 68, 2913.
7. Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, 69, 7284.
8. Fujimure, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, 118, 2499.
9. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, 62, 7310.
10. Kingsbury, J. S.; Garber, S. B.; Giftos, J. M.; Gray, B. L.; Okamoto, M. M.; Farrer, R. A.; Fourkas, J. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, 40, 4251.
11. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, 54, 4413.
12. Donohoe, T. J.; Rosa, C. P. *Org. Lett.* **2007**, 9, 5509.
13. ¹H NMR data for vinylic sulfones: Compound **4**: δ_{H} (270 MHz, CDCl₃) 7.86–7.79 (2H, m, *ortho* PhSO₂), 7.65–7.45 (3H, m, *para* and *meta* PhSO₂), 7.12 (1H, q, *J* 7.0 Hz, CH=CSO₂Ph), 5.86–5.72 (1H, m, CH₂=CHCHOH), 5.21 (1H, d, *J* 18.0 Hz, *cis* CHH=CH), 5.07 (1H, d, *J* 11.0 Hz, *trans* CHH=CH), 4.12–4.30 (1H, m, CHOH), 2.44–2.38 (2H, m, CH₂CHOH), 1.89 (3H, d, *J* 7.0 Hz, Me), 1.20 (1H, br s, OH); **5**: δ_{H} (500 MHz, CDCl₃) 7.90–7.87 (2H, m, *ortho* PhSO₂), 7.64 (1H, m, *para* PhSO₂), 7.56–7.53 (2H, m, *meta* PhSO₂), 7.16 (1H, q, *J* 7.0 Hz, CH=CSO₂Ph), 5.71–5.64 (1H, m, CH₂=CH), 4.96 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CHH=CH), 4.79 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CHH=CH), 3.79 (2H, d, *J* 7.5 Hz, CH₂OH), 3.53 (1H, dt, *J* 14.5, 7.5 Hz, CHCH₂OH), 1.95 (3H, d, *J* 7.0 Hz, CH₃), 1.28–1.18 (1H, m, OH).
14. Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron* **1999**, 55, 13471.
15. Cheng, W. C.; Wong, M.; Olmstead, M. M.; Kurth, M. J. *Org. Lett.* **2002**, 4, 741.
16. ¹H NMR data for **7a**: δ_{H} (270 MHz, CDCl₃) 7.83 (2H, d, *J* 8.0 Hz, *ortho* PhSO₂), 7.60 (1H, t, *J* 8.0 Hz, *para* PhSO₂), 7.54 (2H, t, *J* 8.0 Hz, *meta* PhSO₂), 7.26–7.24 (5H, m, PhCH), 6.30 (1H, d, *J* 16.0 Hz, PhCH=CH), 5.99–5.82 (2H, m, PhCH=CH and CH₂=CH), 5.23 (1H, dd, *J* 16.0, 5.5 Hz, *cis* CHH=CH), 5.13 (1H, dd, *J* 10.5, 5.5 Hz, *trans* CHH=CH), 4.13–4.03 (2H, m, CHSO₂Ph and CHOH), 2.33 (1H, ddd, *J* 20.5, 11.0, 3.0 Hz, CHHCHOH), 1.96 (1H, ddd, *J* 20.5, 11.0, 3.0 Hz, CHHCHOH), 1.55–1.52 (1H, d, *J* 3.5 Hz, OH).
17. (a) Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, 33, 423; (b) Buckley, S. L. J.; Harwood, L. M.; Macías-Sánchez, A. J. *ARKIVOC* **2002**, VIII, 46; (c) Galkina, A.; Buff, A.; Schulz, E.; Hennig, L.; Findeisen, M.; Reinhard, G.; Oehme, R.; Welzel, P. *Eur. J. Org. Chem.* **2003**, 4640.
18. ¹H NMR data for syn-**1**: δ_{H} (270 MHz, CDCl₃) 7.90 (2H, d, *J* 7.0 Hz, *ortho* PhSO₂), 7.67 (1H, t, *J* 7.0 Hz, *para* PhSO₂), 7.57 (2H, t, *J* 7.0 Hz, *meta* PhSO₂), 6.36–6.35 (1H, m, CH=CHCHOH), 5.74–5.73 (1H, m, CH=CHCHOH), 4.72–4.70 (1H, m, CHSO₂Ph), 4.16–4.01 (1H, m, CHOH), 2.26–2.21 (2H, m, CH₂).
19. Carballares, S.; Craig, D.; Hyland, C. J. T.; Lu, P.; Mathie, T.; White, A. J. P. *Chem. Commun.* **2009**, 451.
20. Gais, H. J.; Vollhardt, J.; Hellmann, G.; Paulus, H.; Lindner, H. J. *Tetrahedron Lett.* **1988**, 29, 1259.
21. Arnett, E. M.; Nichols, M. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, 112, 7059.
22. Shimizu, M.; Takebe, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* **1996**, 37, 7387.
23. Sutjianto, A.; Curtiss, L. A. *J. Phys. Chem. A* **1998**, 102, 96.
24. Chivers, T.; Downard, A.; Glenn, P. A. *Inorg. Chem.* **1998**, 37, 5708.
25. Baboul, A. G.; Redfern, P. C.; Sutjianto, A.; Curtis, L. A. *J. Am. Chem. Soc.* **1999**, 121, 7220.
26. Crystal data for (±)-**9d**: C₁₆H₂₀O₃S, *M* = 292.38, monoclinic, *P*2₁/c (no. 14), *a* = 17.906(4), *b* = 6.3895(18), *c* = 12.901(4) Å, β = 99.06(2)°, *V* = 1457.6(7) Å³, *Z* = 4, *D*_{calc} = 1.332 g cm⁻³, μ (Cu-K α) = 2.012 mm⁻¹, *T* = 173 K, colourless block-like needles, Oxford Diffraction Xcalibur PX Ultra diffractometer; 2803 independent measured reflections (*R*_{int} = 0.0314), *F*² refinement, *R*₁(obs) = 0.0313, *wR*₂(all) = 0.0931, 2362 independent observed absorption-corrected reflections [*I*(*F*_o) > 4 σ (*I*(*F*_o))], 2 θ _{max} = 142°, 188 parameters. CCDC 749015.