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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.

Cyclopentenes 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 cyclopentenes, ring-closing metathesis (RCM) is one of the most attractive options.[8–12] In connection with studies of ring-rearrangement metathesis (RRM) reactions of cyclopentenes for the synthesis of substituted cyclohexenes, 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 ^{1}H 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 conjugating 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 ^{1}H 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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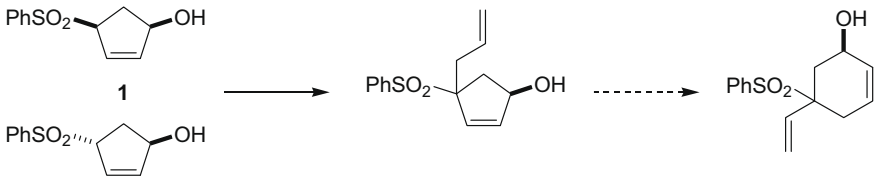
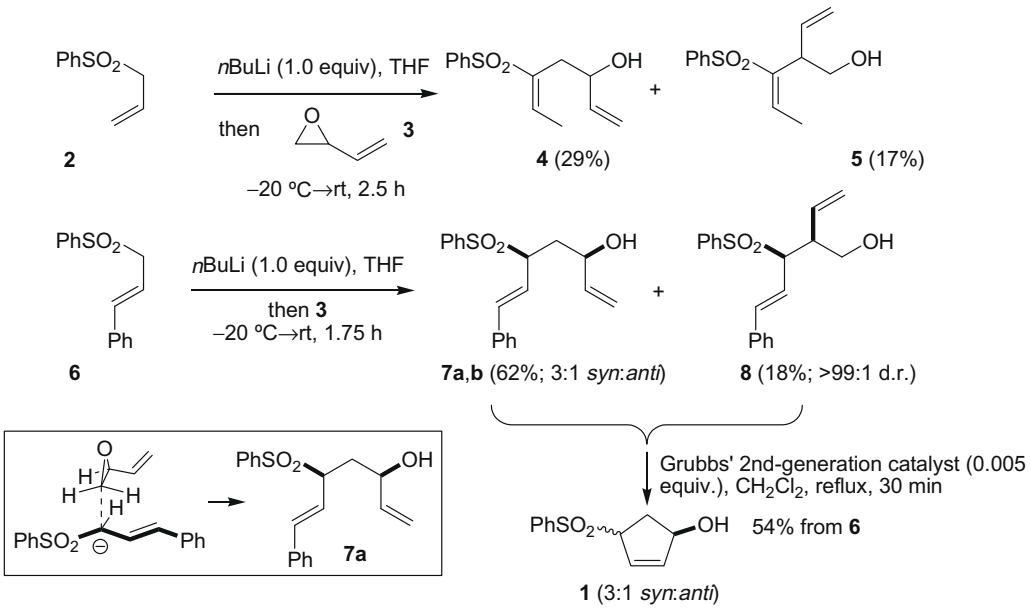


Scheme 1.

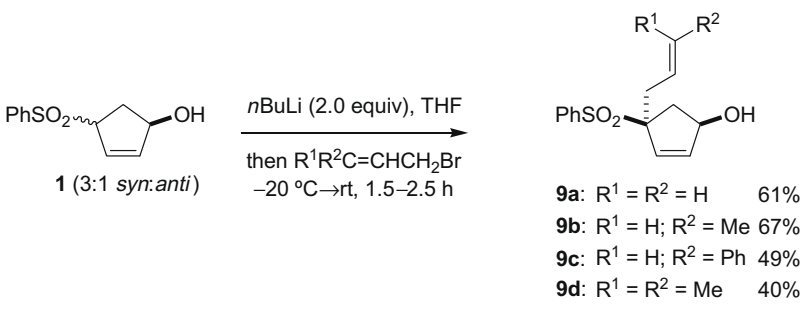


Scheme 2.

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 planar[20] 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 alkoxylithium moiety internally coordinated via a $PhSO_2$ 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···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.

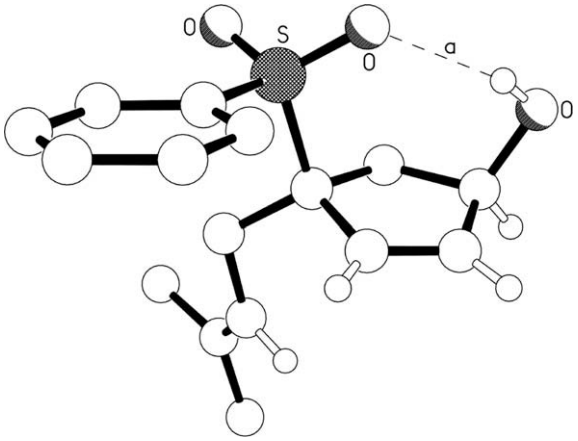


Figure 1. The molecular structure of (±)-9d. The O–H···O hydrogen bond (a) has O···O and H···O separations of 2.9949(18) and 2.16 Å, respectively, with an O–H···O angle of 154°.

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.

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13. *^{1}H NMR data for vinylic sulfones*: Compound **4**: δ_H (270 MHz, $CDCl_3$) 7.86–7.79 (2H, m, *ortho* $PhSO_2$), 7.65–7.45 (3H, m, *para* and *meta* $PhSO_2$), 7.12 (1H, q, *J* 7.0 Hz, C*H*=CSO_2Ph), 5.86–5.72 (1H, m, CH_2=C*H*CHOH), 5.21 (1H, d, *J* 18.0 Hz, *cis* C*H*H=CH), 5.07 (1H, d, *J* 11.0 Hz, *trans* CH*H*=CH), 4.12–4.30 (1H, m, C*H*OH), 2.44–2.38 (2H, m, CH_2CHOH), 1.89 (3H, d, *J* 7.0 Hz, Me), 1.20 (1H, br s, OH); **5**: δ_H (500 MHz, $CDCl_3$) 7.90–7.87 (2H, m, *ortho* $PhSO_2$), 7.64 (1H, m, *para* $PhSO_2$), 7.56–7.53 (2H, m, *meta* $PhSO_2$), 7.16 (1H, q, *J* 7.0 Hz, C*H*=CSO_2Ph), 5.71–5.64 (1H, m, CH_2=C*H*), 4.96 (1H, dd, *J* 10.0, 1.5 Hz, *trans* C*H*H=CH), 4.79 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH*H*=CH), 3.79 (2H, d, *J* 7.5 Hz, CH_2OH), 3.53 (1H, dt, *J* 14.5, 7.5 Hz, C*H*CH_2OH), 1.95 (3H, d, *J* 7.0 Hz, CH_3), 1.28–1.18 (1H, m, OH).
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