Homoallylic Sulfones

Synthesis of Homoallylic Sulfones through a Decarboxylative Claisen Rearrangement Reaction**

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The Claisen rearrangement continues to enjoy widespread use as one of the premier carbon–carbon bond-forming reactions in organic synthesis. Contributing to its longstanding preeminence are ease of synthesis of substrates, reliable stereoselectivity based on well-established empirical trends, and adaptability to deliver a range of carbonyl-based functionalities according to the reaction mode selected.[1] We recently began a new research programme aimed towards developing an understanding of the effect on Ireland–Claisen rearrangement[2] stereoselectivity of stereocenters positioned outside but adjacent to the pericyclic array. To this end, we were keen to probe the effect on selectivity of introducing disposable, bulky groups at the α-position of the ketene acetal. Tolylsulfonyl appeared to be a promising choice of group because of its ready incorporation into substrates (by using as starting material commercially available tosylacetic acid), steric bulk, electron-withdrawing nature (in principle thereby facilitating ketene acetal formation), and ease of removal after rearrangement. Prior to commencement of our work there existed a single instance of Ireland–Claisen rearrangement of a ketene acetal derived from an allylic arylsulfonylacetate substrate.[3] In this work Davidson and coworkers generated the ketene acetal under standard conditions, which involves the low-temperature reaction of the ester substrate with LDA followed by chlorotrimethylsilane prior to warming to ambient temperature; sigmatropic rearrangement reached completion in 10 h. Decarboxylation of the derived α-phenylsulfonyl carboxylic acid subsequently took place in a separate step upon heating with weak base. After repeated failures to apply successfully this ketene acetal generation–rearrangement method to structurally simpler substrates, we investigated alternative reaction conditions for the generation of these intermediates. We now report a novel, decarboxylative Claisen rearrangement (DCR) reaction of allyl tosylacetates which yields homoallylic sulfones stereoselectively and in high yields.

The tosylacetate esters **1** required for this study were simply prepared from allylic alcohols and commercially available[4] tosylacetic acid by using standard DCC/DMAP-mediated condensation reactions.[5] Following the failure of conventional ketene acetal forming conditions with lithium diisopropylamide and chlorosilanes, attention was turned to milder methods based on *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate, which we anticipated might provide an effective silylating reagent combination given the acidity of the methylene protons in **1**.[6,7] In the initial phase of the work, solutions of **1** and BSA[8] (1.0 equiv) in toluene together with potassium acetate (0.1 equiv)[9] were heated at reflux for 15 h. Homoallylic sulfones **2** were obtained cleanly and in good to excellent yields upon simple reduced-pressure concentration of the reaction mixtures followed by column chromatography on silica gel. We subsequently found that the same transformations could be carried out on **1** by brief exposure to microwave irradiation in the *presence or absence* of solvent, and that these modified procedures gave similar yields of **2** in most cases where comparison was made. The results of the reactions are collected in Table 1.

Several features of the DCR reactions of **1** are worthy of comment. First, the reaction is tolerant of oxygen and nitrogen substitution (Table 1, entries **4**, **12**, **13**), provided that the heteroatom is fully masked; the nonbenzylated analogue of substrate **1m** failed to undergo DCR reaction. Second, the transformations take place regardless of whether the substrates **1** are derived from primary or secondary (Table 1, entry 11) alcohols, and irrespective of the substitution level of the olefinic carbon atom distal to the oxygen atom within the allylic portion of the substrate (compounds **1g**, **1h**,[10] and **1k** give rise to products **2** that bear quaternary centres). Third, the reactions of **1i** and **1j** are completely stereoselective, and delivery of the (tolylsulfonyl)methyl moiety takes place in an *anti* sense with respect to the more hindered face of the allylic double bond.[11] Finally, in one example (Table 1, entry **12**) a striking level of *acyclic* stereoselectivity was observed in which sulfone **2l** was formed as a 7:1 mixture of diastereoisomers; substrates **1m** and **1n** rearranged with virtually zero selectivity. We have not yet assigned the major diastereomer of **2l**.

During the course of these investigations we became aware of a report of a single instance of a related transformation in which tosylacetic ester **3** was converted into the rearranged, decarboxylated homoallylic sulfone **4** in high yield under strongly basic conditions.[12] It was reasonably postulated that this transformation proceeded via an enolate intermediate, which subsequently rearranged with loss of carbon dioxide in a Carroll-type process.[13] In our hands, treatment of substrate **1a** with NaH in xylenes at reflux resulted in extensive decomposition after 2 h, and at lower temperatures in toluene **2a** was isolated only in low yield (< 10%). In contrast, the more hindered, secondary alcohol-derived substrate **1o** was gradually converted into **2o** in good yield after prolonged exposure to the NaH–toluene conditions (Scheme 1). These findings prompted a more thorough

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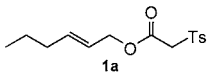
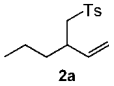
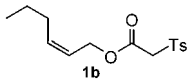
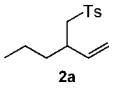
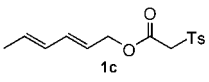
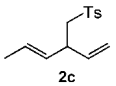
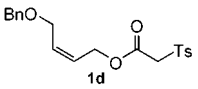
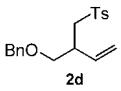
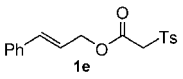
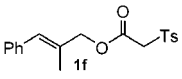
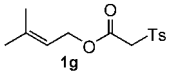
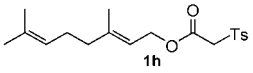
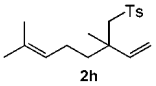
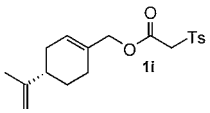
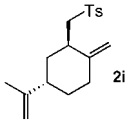
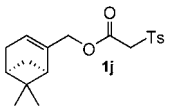
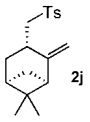
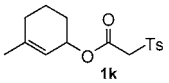
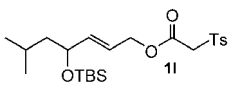
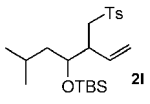
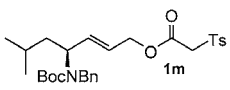
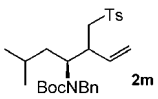
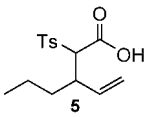
Table 1: Decarboxylative Claisen rearrangement reactions of tosylacetates **1**.

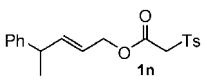
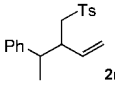
Entry	Substrate	Product	Yield [%] A[a]	B[a]	C[a,b]
1	 **1a**	 **2a**	80	81	92
2	 **1b**	 **2a**	92	–	59
3	 **1c**	 **2c**	90	81	
4	 **1d**	 **2d**	77	–	58
5	 **1e**	 **2e**	74	–	
6	 **1f**	 **2f**	88	–	72
7	 **1g**	 **2g**	88	–	
8	 **1h**	 **2h**	83	89	83
9	 **1i**	 **2i**	89	67	80
10	 **1j**	 **2j**	81	–	80
11[c]	 **1k**	 **2k**	86	–	74
12[c,d]	 **1l**	 **2l**	62	–	
13[e]	 **1m**	 **2m**	74	18	67

examination of the components necessary for the DCR reaction to proceed. Heating of toluene solutions of **1a** in the presence of potassium acetate alone (0.1, 0.5, 1.0 equiv) returned starting material quantitatively. Substitution of BSA with either Me_3SiOAc, $Me_3SiOSiMe_3$, or $(Me_3Si)_2NH$ resulted in complete suppression of the reaction, as did the use of *N*-trimethylsilylacetamide in place of BSA. In contrast, substitution of KOAc with Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or pyrrolidine resulted in the formation of the rearranged but not decarboxylated carboxylic acid product **5** in yields of 70, 56, and 63%, respectively. We propose that **5** was formed by hydrolysis during workup of the corresponding silyl ester presumably formed in the [3,3]-sigmatropic rearrangement step. Exposure of **1a** to BSA alone (1.1 equiv) in toluene at reflux gave **5** in 49% yield. Use of Me_3SiOTf or *t*$BuMe_2SiOTf$ in conjunction with DBU gave **2a** in 15 and 28% yield, respectively, whilst Me_3SiCl–DBU combinations again gave **5**. Finally, exposure of **1a** to a mixture of *N*-trimethylsilylacetamide, *t*BuLi, and Me_3SiOAc gave **2a** in 67% yield; replacing *t*BuLi with KH in this modified reaction returned **2a** in 51% yield.

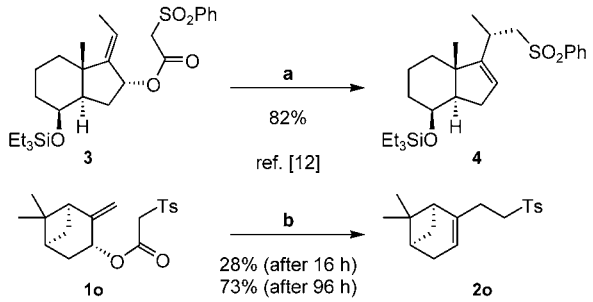

5

We interpret the results described above in terms of a mechanism involving the initial, reversible combination of KOAc and BSA to generate the conjugate base of *N*-trimethylsilylacetamide and Me_3SiOAc. The former species deprotonates **1** and the resultant enolate is silylated by Me_3SiOAc to generate the silyl ketene acetal **A** and regenerate acetate. Following [3,3]-sigmatropic rearrangement of **A** the γ,δ-unsaturated silyl ester **B** is reversibly desilylated by acetate ion, regenerating Me_3SiOAc and giving a carboxylate species; this spontaneously fragments to give CO_2 and the conjugate base of **2**. Finally, this strongly basic intermediate abstracts a proton from *N*-

Table 1: (Continued)

Entry	Substrate	Product	Yield [%] A[a]	B[a]	C[a,b]
14[c,f]	 1n	 2n	63	–	

[a] All reactions were carried out with BSA (1.0 equiv) and KOAc (0.1 equiv). Conditions: A: toluene, 110 °C, 15 h; B: toluene, microwave, 150 °C, 3 min; C: microwave, 150 °C, 3 min. [b] Reactions were carried out in the absence of solvent. [c] Reaction was carried out on racemic substrate. [d] Product was formed as a 7:1 mixture of diastereoisomers. [e] Product was formed as a 1:1 mixture of diastereoisomers. [f] Product was formed as a 3:2 mixture of diastereoisomers. Ts = *p*-toluenesulfonyl; TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl.



Scheme 1. Carroll-type reactions of tosylacetates. a) NaH, xylenes, 140 °C; b) NaH, toluene, 110 °C.

Table 2: Catalytic decarboxylative Claisen rearrangement reactions of tosylacetates **1**.

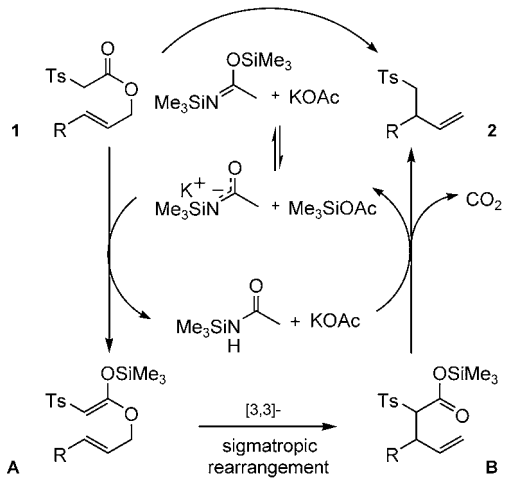
Entry	Substrate	Product	Yield [%] A[a]	B[a]
1	**1a**	**2a**	88	94
2	**1e**	**2e**	92	85
3	**1h**	**2h**	75	87
4	**1j**	**2j**	98	93
5	**1o**	**2o**	91	87

[a] All reactions were carried out with BSA (0.1 equiv) and KOAc (0.1 equiv). Conditions: A: toluene, 110 °C, 15 h; B: toluene, microwave, 150 °C, 3 min.

trimethylsilylacetamide formed in the initial deprotonation event, giving **2** and regenerating the conjugate base of *N*-trimethylsilylacetamide, which enters a subsequent cycle; alternatively, the conjugate base of **2** abstracts a proton *directly* from **1** to generate further nucleophilic enolate. This model is consistent with the results obtained in the reactions carried out with *N*-trimethylsilylacetamide, *t*BuLi or KH, and Me_3SiOAc, which differ only with respect to the mode of generation of the conjugate base of *N*-trimethylsilylacetamide. The proposed mechanism is depicted in Scheme 2.

It was felt that more-conclusive evidence for the proposed catalytic cycle would come from the observation of high-yielding DCR reactions conducted in the presence of substoichiometric amounts of BSA. In the event, substrates **1a**, **1e**, **1h**, **1j**, and **1o** underwent efficient DCR reaction in the presence of only 10 mol % of BSA and potassium acetate. Again, yields of the conventionally and microwave-heated reactions were comparable in all cases studied (Table 2).

In summary, we have uncovered a novel variant of the Ireland–Claisen rearrangement reaction in which the silyl ketene acetals formed in situ undergo sigmatropic rearrangement followed by acetate-induced decarboxylation. To our knowledge, this is the first example of a ketene acetal formation–Claisen rearrangement sequence that utilizes substoichiometric amounts of base and silylating agent.[14] We note that the mildness of the reaction conditions, especially in the catalytic mode, and the apparent compatibility of the transformation with a number of different substrate substitution patterns augur well for its general applicability. Planned future work in this area includes 1) evaluation of the efficiency of DCR reactions of substrates substituted α to the tosyl group, 2) assessment of the sense and level of diastereoselectivity of DCR reactions of chiral tosylacetates such as **1l**, and of analogous sulfoximine-containing substrates; 3) exploration of tandem DCR reactions of the related allylic tosylmalonates; and 4) application of the DCR reaction as a key process in target-oriented natural product synthesis.



Scheme 2. Proposed catalytic cycle for DCR reactions of **1**.

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[1] For a recent, comprehensive review of the Claisen rearrangement, see: A. M. M. Castro, *Chem. Rev.* **2004**, *104*, 2939.
[2] For a recent review of the Ireland–Claisen rearrangement, and leading references, see: M. C. McIntosh, *Tetrahedron* **2002**, *58*, 2905.

[3] A. H. Davidson, N. Eggleton, I. H. Wallace, *J. Chem. Soc. Chem. Commun.* **1991**, 378.
[4] Purchased from Aldrich Chemical Co.
[5] U. Kazmaier, C. Schneider, *Synthesis* **1998**, 1321. DCC = dicyclohexylcarbodiimide; DMAP = 4-(dimethylamino)pyridine.
[6] G. Giambastiani, B. Pacini, M. Porcelloni, G. Poli, *J. Org. Chem.* **1998**, *63*, 804.
[7] B. M. Trost, D. J. Murphy, *Organometallics* **1985**, *4*, 1143.
[8] BSA was purchased from Aldrich Chemical Co. and distilled prior to use.
[9] Reagent-grade potassium acetate used in this study was dried prior to use by heating overnight at 100 °C.
[10] Compound **1h** has been described previously: K. Sato, S. Inoue, T. Sakamoto, *Synthesis* **1981**, 796.
[11] The structure of **2i** was assigned based on the ^{1}H NMR signal corresponding to the allylic methine group. This appeared as a broad multiplet, indicating its equatorial disposition, and therefore the *anti* relationship of the (tolylsulfonyl)methyl and isopropenyl groups. The structure of **2j** was assigned unambiguously by X-ray crystallographic analysis. We thank Dr. Andrew J. P. White (Imperial College) for this determination; full details will be published elsewhere.
[12] M. A. Hatcher, G. H. Posner, *Tetrahedron Lett.* **2002**, *43*, 5009.
[13] For recent reports of highly regioselective, nonregiospecific metal-catalyzed formal Carroll rearrangements, see: E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 2603; for recent applications of the Carroll rearrangement in synthesis, see: M. Defosseux, N. Blanchard, C. Meyer, J. Cossy, *Org. Lett.* **2003**, *5*, 4037; M. E. Jung, B. A. Duclos, *Tetrahedron Lett.* **2004**, *45*, 107; for a review, including an account of asymmetric Carroll rearrangements, see: A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253.
[14] Typical procedure for the DCR of **1**. Conventional thermal conditions: BSA (16.6 μL, 0.07 mmol, 0.1 equiv) and KOAc (6.6 mg, 0.07 mmol, 0.1 equiv) were added to a solution of ester **1a** (200 mg, 0.68 mmol, 1 equiv) in dry toluene (5 mL), and the resulting mixture was heated at 110 °C for 15 h. Concentration under reduced pressure and chromatography (10 % EtOAc/petroleum ether) gave sulfone **2a** (150 mg, 88 %) as a colorless oil. Microwave conditions: KOAc (3.3 mg, 0.03 mmol, 0.1 equiv) was added to a microwave vial followed by ester **1a** (100 mg, 0.34 mmol, 1 equiv), BSA (8.3 μL, 0.03 mmol, 0.1 equiv) and toluene (1 mL). The mixture was heated at 150 °C (250 W) for 3 min. Concentration under reduced pressure and chromatography (10 % EtOAc/petroleum ether) gave **2a** (79 mg, 94 %) as a colorless oil.

