Transannular, decarboxylative Claisen rearrangement reactions for the synthesis of sulfur-substituted vinylcyclopropanes†

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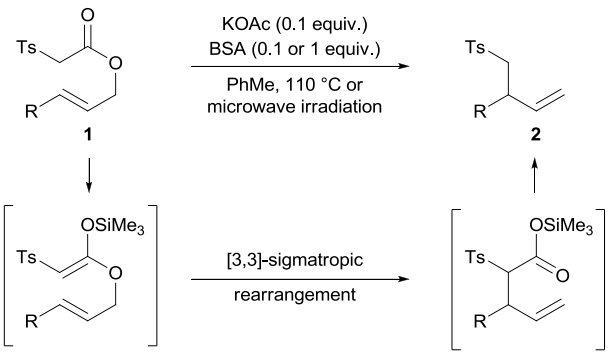
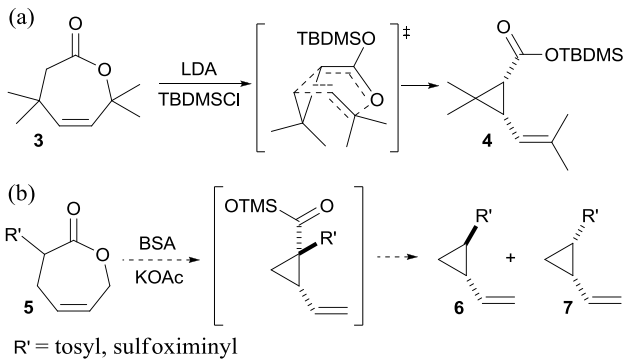
Unsaturated ε-lactones bearing an α-arylsulfonyl or α-arylsulfoximinyl substituent undergo stereoselective transannular decarboxylative Claisen rearrangement to give substituted vinylcyclopropanes.

Since the first report nearly 40 years ago, the Ireland–Claisen rearrangement[1] has become a mainstay of organic synthesis, due to its ability to deliver the products of reliably regiospecific and stereoselective C–C bond formation.[2] The decarboxylative Claisen rearrangement (dCr) reaction is a catalysed variant[3] of the Ireland–Claisen rearrangement which has been developed in our laboratory. In this reaction, exposure of allylic sulfonylacetates **1** to *N,O*-bis(trimethylsilyl)acetamide (BSA) and KOAc under relatively mild conditions allows access to homoallylic sulfones **2** in good to excellent yields (Scheme 1).[4,5] We have demonstrated the utility of the dCr reaction in diverse synthetic contexts, including dearomatisation of heteroaromatic substrates,[6] *de novo* synthesis of pyridines[7] and natural product total synthesis.[8] We have also studied the relationship between substrate structure and reactivity in the dCr reaction of tosylmalonate substrates.[9,10,11]



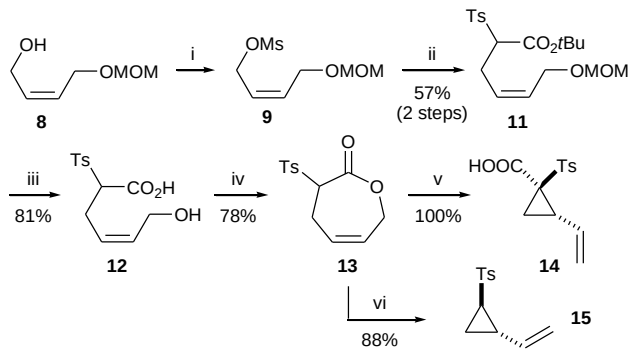
Scheme 1 Decarboxylative Claisen rearrangement reaction.

This communication presents an application of the dCr methodology to α-sulfonyl and α-sulfoximinyl ε-lactones. We envisaged that such cyclic substrates would be able to undergo ring contraction by means of a transannular dCr, to give 2-vinylcyclopropylsulfones and -sulfoximines respectively. Claisen rearrangements of α-unsubstituted ε-lactones have been reported by Funk[12] and Knight.[13] These reactions gave products having *cis*-disposed carboxylic acid and alkenyl groups (e.g. **4**), arising from the imposition of (*E*)-geometry on silyl ketene acetal formation,[14] and the constraint of the subsequent rearrangement to a single accessible boat-like transition state (Scheme 2a). In the present work, the relative stereochemistry of the decarboxylated cyclopropanes is dictated by the protonation of the cyclopropyl anion arising from decarboxylation, and was not precedented (Scheme 2b).



Scheme 2 Non-decarboxylative precedent is stereospecific.

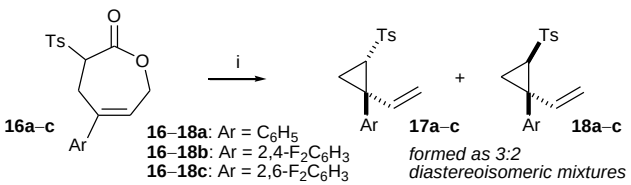
The first substrate studied was the readily accessible α-tosyl-ε-lactone **13**. Monoprotected diol **8** was mesylated, and the resultant sulfonate ester **9** used to alkylate the sodium enolate of *t*-butyl tosylacetate **10**; subsequent deprotection and cyclisation gave **13**. Subjection of **13** to dCr conditions at room temperature gave carboxylic acid **14** in quantitative yield. Under more forcing conditions, cyclopropylsulfone **15** was the sole product obtained; we ascribe the complete *trans* selectivity to anion equilibration to the less sterically-hindered product (Scheme 3).



Scheme 3 Synthesis and rearrangement of α-tosyl-ε-lactone **13** *Reagents and conditions* (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) $TsCH_2CO_2tBu$ (**10**), NaH, THF, rt; (iii) aq. HCl (2 M), MeCN, heat, 2 h; (iv) DIC, CH_2Cl_2, rt, 16 h; (v) BSA (1.0 equiv.), KOAc (0.1 equiv.), CH_2Cl_2, rt, 16 h; (vi) BSA (1.0 equiv.), KOAc (0.1 equiv.), DMF, microwave, 160 °C, 10 min.

It seems likely that the facile nature of the Ireland–Claisen rearrangement of **13** in comparison with those of acyclic allylic tosylacetates stems from the favoured adoption of the reactive conformation because of the constraints on the vinylic and allylic moieties imposed by the ring. Presumably, spontaneous decarboxylation is disfavoured in comparison with the malonate substrates studied previously in the dCr reaction, because of the lesser degree of stabilisation of incipient negative charge α- to the sulfur atom. Additionally, the C–C bond to be cleaved upon extrusion of CO_2 is unusually strong due to orbital rehybridisation in the cyclopropane ring.

This chemistry allows access also to cyclopropanes possessing quaternary centres. Subjection of substrates **16a-c** (prepared from the corresponding monoprotected *Z*-allylic mesylates in a manner analogous to **13**, using either *t*-butyl or methyl tosylacetate†) to microwave-assisted dCr conditions once again provided decarboxylated cyclopropylsulfones **17a–c** and **18a–c** in good yield (Scheme 4, Table 1). Mixtures (3:2) of **17** and **18** were formed in all cases, as evidenced by ^{1}H nmr analysis: in **17a**–**c**, the olefinic –C*H*=CH_2 signals appeared some 0.8 ppm downfield from the corresponding resonances in **18a**–**c**. The moderate diastereoselectivity is ascribed to steric interactions of the tosyl group with a quaternary centre substituent, which are present regardless of the relative configuration of the sulfone-bearing carbon atom.



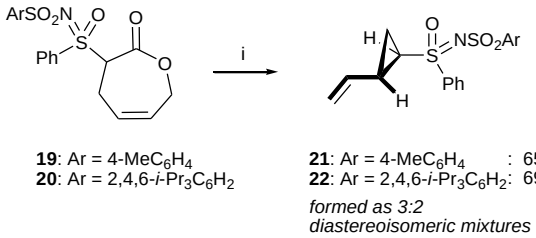
Scheme 4 *Reagents* and *conditions* (i) 1.0 equiv BSA, 0.1 equiv KOAc, DMF, microwave, 160 °C, 10 min.

Table 1 dCr reactions of α-tosyl-γ-aryl-ε-lactones.

Substrate	Ar	Products	Total yield (%)[a]
16a	–C_6H_5	**17a** + **18a**	87
16b	–2,4-$C_6H_3F_2$	**17b** + **18b**	75
16c	–2,6-$C_6H_3F_2$	**17c** + **18c**	82

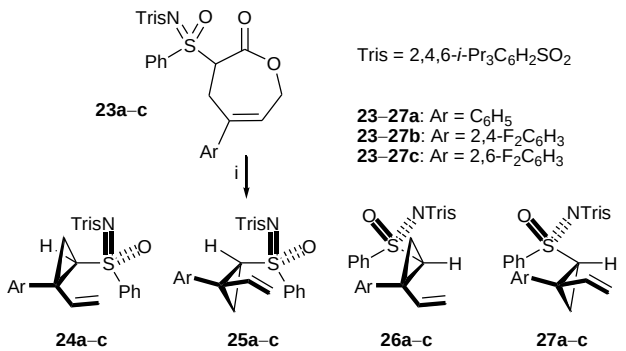
[a] Isolated yield. Ratio **17**:**18** = 3:2 in each instance.

The final part of this study looked at asymmetric induction from stereocentres outside the pericyclic array. In our previous work,[15] diastereomeric ratios of up to 87:13 had been realised for acyclic substrates analogous to **1** bearing an *N*-trisylsulfoximinoyl group in place of the sulfone. Initial experiments focussed on substrates **19** and **20**; these are chiral-at-sulfur analogues of the sulfone-containing substrate **13**, and were synthesised in analogous manner, using the corresponding sulfoximine-substituted acetate ester in place of tosylacetates.[16] Disappointingly, although dCr reactions of **19** and **20** gave respectively the cyclopropylsulfoximines **21** and **22** in good yield and with complete *anti* selectivity, in both cases the products were formed as 3:2 diastereoisomeric mixtures; the major isomers were not assigned (Scheme 5).



Scheme 5 Non-selective dCr reactions of **19** and **20** *Reagents and conditions* (i) BSA (1.0 equiv.), KOAc (0.1 equiv.), DMF, microwave, 160 °C, 10 min.

In an effort to enhance diastereomeric ratios by increasing the steric demand within the allylic motif, the more highly-substituted substrates **23a**–**c** were evaluated as chiral analogues of **16**; these compounds were synthesised analogously to **13** and **16**.[17] The dCr reactions of **23** each gave mixtures of four diastereoisomers **24**–**27**. In each case, the resolution of vinylic signals in the ^{1}H nmr spectra of crude dCr reaction products allowed unambiguous evaluation of the stereoselectivities, and was again invaluable in structure assignment.† In isomers **24** and **25** having *syn* vinyl and sulfoximine groups, double doublets characteristic of the internal vinyl protons again appeared between 0.5 and 0.8 ppm downfield from those in the two *anti* isomers **26** and **27**, presumably because of anisotropic deshielding by the sulfoximine moiety. These relative stereochemical assignments were supported in the case of products **24b–27b** (Ar = 2,4-$F_2C_6H_3$) by the observation of nOe enhancements, which indicated proximity of the sulfoximine α-methine proton to the vinyl group in the case of the major *anti* isomer **26b**, and to the difluorophenyl group in the case of *syn* isomers **24b** and **25b**. The stereochemistry of the minor *syn* isomer **25b** was unequivocally assigned by X-ray crystallographic analysis,[18] and the structure of major *syn* isomer **24b** was inferred accordingly. The structures of the major and minor *anti* isomers followed from those of the *syn* compounds, since the configuration of the quaternary centre is set during the pericyclic process, and is unaffected by the subsequent *in situ* decarboxylation step. The dCr reactions of **23a**–**c** are shown in Scheme 6, and the results collected in Table 2.



Scheme 6 dCr Reactions of **23** *Reagents and conditions* (i) BSA (1.0 equiv.), KOAc (0.1. equiv.), DMF, microwave, 160 °C, 10 min.

Table 2 dCr reactions of α-sulfoximinyl-γ-aryl-ε-lactones **23**.

Substrate	Ar	Products	Ratio[a]	Yield (%)[b]
23a	C_6H_5	**24a**:**25a**:**26a**:**27a**	44:22:26:7	78
23b	2,4-$C_6H_3F_2$	**24b**:**25b**:**26b**:**27b**	44:16:33:7	70
23c	2,6-$C_6H_3F_2$	**24c**:**25c**:**26c**:**27c**	49:11:36:4	71

[a] Ratios based on ^{1}H nmr analysis of crude products

[b] Isolated yield.

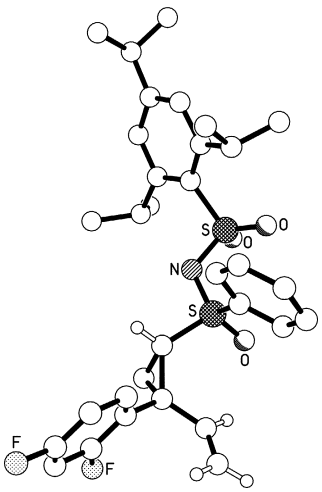
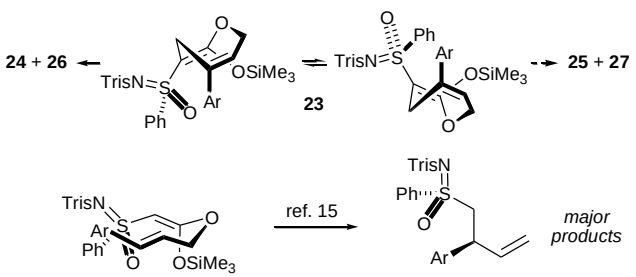


Fig. 1 The molecular structure of **25b**.

Inspection of the results in Table 2 reveals that the ratios of *syn* to *anti* products ([**24**+**25**]:[**26**+**27**]) vary between 2:1 and 1.25:1. More importantly, the ratios [**24**+**26**]:[**25**+**27**] are indicative of asymmetric induction from the sulfoximine group, since these pairs of compounds arise through C–C bond formation taking place with the same topicity. Thus, rearrangement of **23a** took place with an overall diastereoisomeric ratio (d.r.) of *ca.* 70:30, while that of **23b** and **23c** showed d.r.s of 77:23 and 85:15 respectively. The sense of asymmetric induction evident in the major products is the same as that observed previously in reactions of acyclic substrates,[15] taking into account the necessary boat-like geometry of the reacting conformation (Scheme 7). It is noteworthy that the d.r. is greatest for substrate **23c**, which has the sterically most demanding Ar group.



Scheme 7 Reactive conformations of **23**

In summary, we have described the first transannular decarboxylative Claisen rearrangements, and have demonstrated their use in the stereoselective formation of quaternary centres. Extension of this methodology to larger rings, and use in total synthesis will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and full spectroscopic data for all novel compounds, crystallographic data for compound **25b**. See DOI: 10.1039/b000000x/

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15 D. Craig, F. Grellepois and A. J. P. White, *J. Org. Chem.*, 2005, **70**, 6827.
16 Substrate **19** was synthesised as the R_S enantiomer; substrate **20** was synthesised as the S_S enantiomer.
17 Substrates **23a**–**c** were synthesised as racemic mixtures.
18 *Crystal data for* **25b**: $C_{32}H_{37}F_2NO_3S_2$, M = 585.75, orthorhombic, *Pca*2$_1$ (no. 29), a = 11.4277(3), b = 11.7915(3), c = 22.8410(5) Å, V = 3077.82(13) Å^3, Z = 4, D_c = 1.264 g cm^{-3}, μ(Mo-Kα) = 0.218 mm^{-1}, T = 173 K, colourless platy needles, Oxford Diffraction Xcalibur 3 diffractometer; 6964 independent measured reflections (R_{int} = 0.0560), F^2 refinement, R_1(obs) = 0.0472, wR_2(all) = 0.0918, 4734 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], $2\theta_{max}$ = 61°], 366 parameters. The absolute structure of **25b** was determined by a combination of R-factor tests [R_1^+ = 0.0472, R_1^- = 0.0479] and by use of the Flack parameter [x^+ = 0.00(6), x^- = 1.00(6)]. CCDC **xxxxxx**.