

Sulfinyl-Mediated Chirality Transfer in
Diastereoselective Claisen
Rearrangements

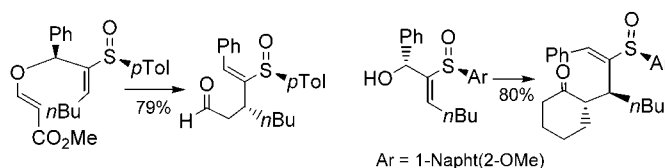
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ABSTRACT



The highly selective Claisen rearrangements of substrates bearing a sulfinyl moiety at C-5 allow for creation of up to two asymmetric centers and preserve a useful vinyl sulfoxide.

Enantiopure sulfoxides are becoming increasingly useful chiral auxiliaries as a result of their ease of preparation, remarkable synthetic versatility, and straightforward removal.¹ In recent years, we have been engaged in the development of novel methodologies involving vinyl sulfoxides,² particularly focusing on strategies that allowed for multiple sulfur-based chirality-transfer operations in acyclic systems.³ Within this context, the Claisen rearrangement was appealing since it is one of the most powerful methods for stereoselective carbon–carbon bond formation.⁴ Furthermore, the development of new enantioselective Claisen protocols is a current problem in organic synthesis,⁵ with the use of

chiral sulfur atoms for that purpose scarcely documented.⁶ In this report we describe the first examples of diastereoselective Claisen rearrangements of readily available substrates bearing a sulfinyl auxiliary at C-5 that take place with good diastereoselectivities and preserve the synthetically useful vinyl sulfoxide moiety.

We envisioned that readily available sulfinyl alcohols **A**⁷ (Scheme 1) could give rise to appropriate substrates **B** to

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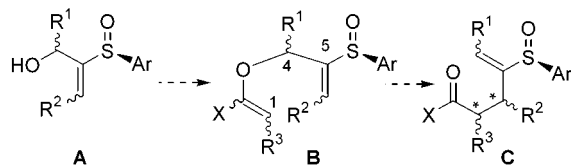
(4) (a) Claisen, B. *Chem. Ber.* **1912**, 45, 3517. For reviews, see: (b) Ziegler, F. *Chem. Rev.* **1988**, 88, 1423–1452. (c) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, pp 827–874. (d) Frauenrath, H. In *Houben-Weyl*; Helmchen, G., Hoffman, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart-New York, 1995; pp 3301–3689.

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(6) (a) Cookson, R. S.; Gopalan, R. *J. Chem. Soc., Chem. Commun.* **1978**, 608. (b) Vatile, J.-M. *Tetrahedron Lett.* **1983**, 24, 1239–1242. (c) Posner, G. H.; Crouch, D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, 56, 6981–6987. (d) Alayrac, C.; Fromont, C.; Metzner, P.; Anh, N. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 371–374. (e) Nowaczyk, S.; Alayrac, C.; Reboul, V.; Metzner, P.; Averbuch-Pouchot, M.-T. *J. Org. Chem.* **2001**, 66, 7841–7848.

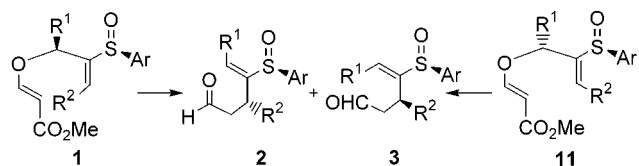
(7) For convenience, most experiments were conducted with racemic sulfoxides. Enantiopure (*E*)-sulfinyl alcohols were prepared (70–80%) from vinyl sulfoxides (Craig, D.; Daniels, K.; McKenzie, A. R. *Tetrahedron* **1993**, 49, 11263–11304) by treatment with LDA and an aldehyde. Racemic (*Z*)-sulfinyl alcohols were prepared (52–60%) from the corresponding alkynyl sulfides (Kabanyane, S. T.; MaGee, D. I. *Can. J. Chem.* **1992**, 70, 2758–2763) by Pd-catalyzed hydrostannylation (Magriotis, P. A.; Brown, J. T.; Scott, M. E. *Tetrahedron Lett.* **1991**, 32, 5047–5051), tin–lithium exchange, condensation with an aldehyde, and diastereoselective oxidation with *m*CPBA. For an enantioselective synthesis of (*Z*)-sulfinyl alcohols, see: Berenguer, R.; Caverio, M.; García, J.; Muñoz, M. *Tetrahedron Lett.* **1998**, 39, 2183–2186.

Scheme 1. Proposed Sulfinyl-Mediated Claisen Rearrangements



test the key rearrangement leading to products **C**, amenable to subsequent regio- and stereocontrolled sulfur-directed transformations. After considerable fruitless experimentation on the Claisen–Ireland protocol,⁸ we shifted our attention to the Claisen–Johnson variant.⁹ It was soon recognized that although the process was viable, its overall efficiency was hampered by the intrinsic lack of geometric control on the enol ether moiety.¹⁰ The use of sulfinyl (*E*)-acrylates, **B** ($X = H$, $R^3 = CO_2Me$),¹¹ seemed an attractive alternative, and indeed they were obtained uneventfully in high yields by known procedures.^{11c}

Scheme 2. Sulfinyl-Mediated Claisen Rearrangements^a



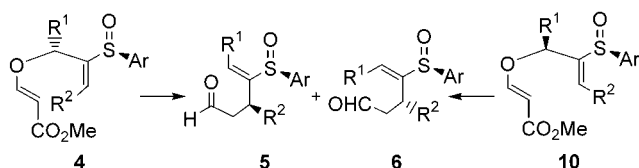
From **(+)-1a**, 130 °C, 60 min, *Z*:*E*, 100:0, **(-)-2a**, 79%

From **1b**, 134 °C, 180 min, *Z*:*E*, 100:0, **2b**, 78%

From **1c**, 130 °C, 75 min, *Z*:*E*, 100:0, **2c**, 79%

From **11a**, 120 °C, 180 min, *Z*:*E*, 8:92, **2a** (8), **3a** (88), 74%

From **11d**, 110 °C, 420 min, *Z*:*E*, 0:100, **3d**, 77%



From **(+)-4a**, 134 °C, 180 min, *Z*:*E*, 73:27, **(-)-5a** (70), **(+)-6a** (23), 73%

From **4b**, 134 °C, 180 min, *Z*:*E*, 74:26, **5b** (73), **6b** (26), 76%

From **4c**, 138 °C, 420 min, *Z*:*E*, 64:36, **5c** (63), **6c** (29), 71%

From **10a**, 126 °C, 150 min, *Z*:*E*, 24:76, **5a** (24), **6a** (73), 74%

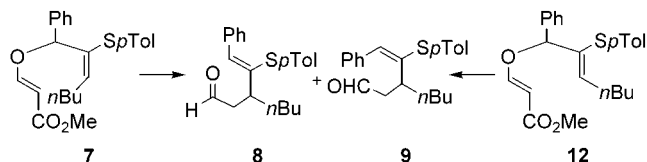
From **10d**, 110 °C, 240 min, *Z*:*E*, 0:100, **6d**, 77%

^a All compounds are racemic unless otherwise noted. Throughout Scheme 2, **a**, Ar = *p*Tol, $R^1 = Ph$, $R^2 = nBu$; **b**, Ar = *p*Tol, $R^1 = Et$, $R^2 = Me$; **c**, Ar = 1-Naphth, $R^1 = Ph$, $R^2 = nBu$; **d**, Ar = 1-Naphth(2-OMe), $R^1 = Ph$, $R^2 = nBu$. *Z*:*E* ratios include two byproducts obtained in some cases; see Supporting Information. Diastereomeric ratios determined by integration of well-resolved signals in the ¹H NMR spectra of the crude reaction mixtures.

The first substrates examined, **1a,b** and **4a,b** (Scheme 2), were selected so as to evaluate the effect of representative R^1 and R^2 groups with a very readily available *p*-tolylsulfinyl auxiliary. The rearrangement and concurrent decarboxylation

took place upon heating (130–134 °C) a solution of the substrate in DMF for relatively short periods of time (60–180 min). Diastereomers **1** gave excellent yields of aldehydes **2** containing a (*Z*)-alkene as single diastereomers. In contrast, diastereomers **4** gave mixtures of rearrangement products **5** and **6** in good yields.¹²

Scheme 3. Influence of the Allylic Center^a



From **7**, 134 °C, 75 min, *Z*:*E*, 93:7, **8** (93), **9** (7), 88%

From **12**, 120 °C, 150 min, *Z*:*E*, 72:28, **8** (72), **9** (28), 80%

^a All compounds are racemic unless otherwise noted.

The rearrangement of sulfide **7** (Scheme 3) was also studied to evaluate the stereodirecting effect of the allylic center in a structurally similar substrate. As expected, the (*Z*)-isomer **8** was obtained with good selectivity (93:7). This suggested a reinforcing relationship of controlling elements for **1** and a nonreinforcing relationship for **4**.¹³

The influence of the geometry of the vinyl sulfoxide moiety was then addressed, and while **10a** (Scheme 2) rearranged smoothly but with low selectivity, diastereomer **11a** gave an 8:88 mixture of products **2a** and **3a**. Also, the corresponding sulfide **12** (Scheme 3) gave a moderately selective mixture in favor of the (*Z*)-sulfide **8**. Therefore, the sulfinyl functionality was providing a remarkable reversal of selectivity by producing predominantly the (*E*)-alkenyl sulfoxides **6a** and **3a**.¹⁴

The influence of the Ar substituent on sulfur was then explored, using the readily available 1-naphthyl and 2-MeO-

(8) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2869–2877. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650–657.

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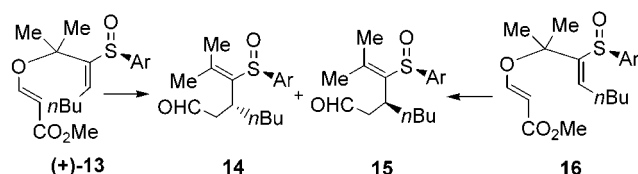
(12) All new products were fully characterized by standard techniques. The optical purity of the final products was established by ¹H NMR analysis with the chiral shift reagent (+)-Eu(tfc)₃. The stereochemistry of rearrangement products **2**, **3**, **5**, and **6** was established by comparison with data for related compounds of secure structure (X-ray analysis^{3a}). For additional stereochemical assignments see Supporting Information.

(13) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

(14) For the only other examples of reversal of *E*-*Z* selectivity in Claisen rearrangements, see: (a) Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 7922–7924. (b) Krafft, M. E.; Dasse, O. A.; Jarrett, S.; Fievre, A. *J. Org. Chem.* **1995**, *60*, 5093–5101.

1-naphthyl moieties.¹⁵ Thus, **1c** (Scheme 2) afforded **2c** as a single isomer, while the less reactive **4c** gave rise to a 63:29 mixture of **5c** and **6c**. In contrast, the more reactive Z series afforded striking results with a 2-MeO-1-naphthyl moiety producing aldehydes **6d** and **3d** as practically single isomers. Finally, the rearrangements of substrates **13** and **16**, bearing geminal dimethyl substitution at C-4, indicate that the sulfinyl moiety alone is capable of efficiently controlling the diastereoselectivity of the process (Scheme 4).

Scheme 4. Influence of the Sulfinyl Moiety^a

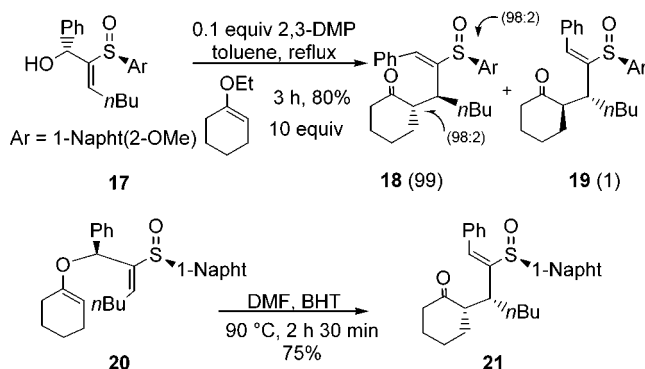


From (+)-**13**, Ar = 1-Napht, 134 °C, 60 min, (+)-**14** (99), **15** (1), 80%
From **16**, Ar = 1-Napht, 134 °C, 60 min, **14** (14), **15** (86), 78%

^a All compounds are racemic unless otherwise noted.

To address the creation of an additional stereocenter the use of cyclohexenyl enol ethers was examined.¹⁶ The treatment of (*Z*)-allylic alcohol **17** with 1-ethoxy-1-cyclohexene in refluxing toluene in the presence of 10% 2,3-dimethylphenol gave adduct **18** as practically a single isomer (Scheme 5). On the other hand, sulfinyl enol ether **20**

Scheme 5. Preparation of Two Consecutive Chiral Centers^a



^a All compounds are racemic unless otherwise noted.

rearranged under exceptionally mild conditions to produce ketone **21**.

These results may be tentatively rationalized in terms of diastereomeric transition states derived from conformers **D–G** (Figure 1), for which an *s-cis* conformation around

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(16) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879–5882.

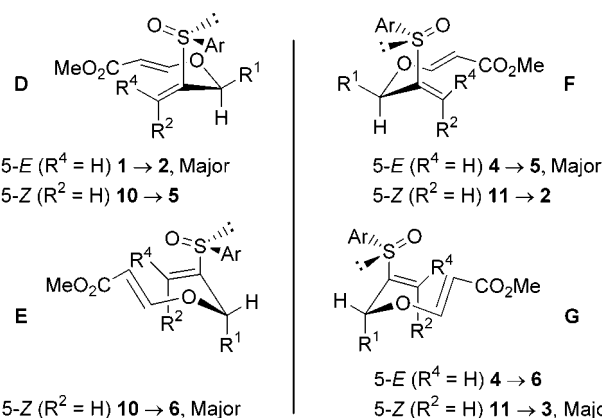


Figure 1. Proposed reactant conformers for sulfinyl-mediated Claisen rearrangements.

the C–S bond is proposed.¹⁷ In the case of 5-*E* substrates (R⁴ = H), **1** displays a reinforcing relationship of stereocontrolling elements with **D** accounting for the observed selectivity, since **E** would have a severe 1,3-diaxial interaction between R¹ and R² and the bulky aryl group pointing toward the incoming vinyl residue. For nonreinforcing diastereomer **4**, the energy difference between **F** and **G** should be smaller than for **1** (**D** and **E**), with **F** being more stable.

The case of 5-*Z* isomers **10–12** was predicted to follow an increased stereodirecting contribution by A^{1,2} strain relative to 1,3-diaxial interactions. Nonetheless, sulfide **12** displayed moderate *Z* selectivity (2.6:1). For diastereomer **10** (R² = H), a nonreinforcing scenario was found, with conformer **E** being favored relative to **D**. Likewise, for **11** (R² = H), **F** and **G** are operative with the latter being substantially more stable. The more hindered 2-MeO-1-naphthyl moiety results in very high stereoselectivity, to produce exclusively the *E* rearrangement products from either diastereomer.

In conclusion, the first examples of Claisen rearrangements of substrates bearing a sulfinyl functionality at C-5 have been described. This strategy allows for creation of up to two asymmetric centers with regeneration of the valuable vinyl

(17) The possibility of boatlike transition states cannot be ruled out. It should be noted that, for a simple (*Z*)-propenyl sulfoxide, the energy difference between the more stable conformers (*s-cis*, C=C/S=O and *s-cis*, C=C/S–) has been evaluated as just –0.4 kcal mol^{–1}. See: Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952–7958.

(18) This methodology entails 3–4 steps, for 5-*E* isomers, or 6–7 steps, for 5-*Z* isomers, from commercially available starting materials. For selected synthetic applications of alkenyl sulfoxides, see: (a) Asymmetric Pauson–Khand: Carretero, J. C.; Adrio, J. *Synthesis* **2001**, 1888–1896. (b) Intermolecular Heck: Díaz Buezo, N.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890–3900. (c) Chiral dipolarophiles: García Ruano, J. L.; Alonso de Diego, S. A.; Martín Castro, A. M.; Martín, M. R.; Rodríguez Ramos, J. H. *Org. Lett.* **2001**, *3*, 3173–3176. (d) Diastereoselective hydrocyanation: García Ruano, J. L.; Cifuentes García, M.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Org. Lett.* **2002**, *4*, 55–57. (e) Intramolecular pyrone-alkene cycloadditions: López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Eur. J.* **2002**, *8*, 884–899.

sulfoxide moiety in an expedient manner.¹⁸ We are currently exploring the scope and limitations of the methodology.

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Supporting Information Available: Experimental procedures and characterization for selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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