ORGANIC LETTERS

2002
Vol. 4, No. 14
2373−2376

Sulfinyl-Mediated Chirality Transfer in Diastereoselective Claisen Rearrangements

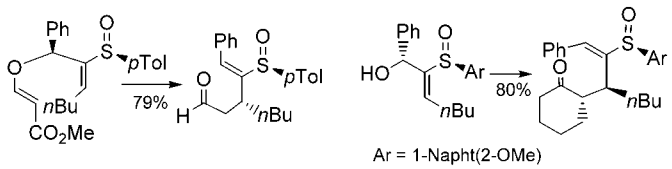
Roberto Fernández de la Pradilla,* Carlos Montero, and Mariola Tortosa

Instituto de Química Orgánica, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain

iqofp19@iqog.csic.es

Received May 1, 2002

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

(1) (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (b) García Ruano, J. L.; Cid de la Plata, M. B. *Top. Curr. Chem.* **1999**, *204*, 1−126. (c) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335−354.

(2) (a) Fernández de la Pradilla, R.; Montero, C.; Priego, J.; Martínez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612−9613. (b) Fernández de la Pradilla, R.; Méndez, P.; Priego, J.; Viso, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1247−1249.

(3) (a) Marino, J. P.; Viso, A.; Lee, J.-D.; Fernández de la Pradilla, R.; Fernández, P.; Rubio, M. B. *J. Org. Chem.* **1997**, *62*, 645−653. (b) Fernández de la Pradilla, R.; Montero, C.; Viso, A. *Chem. Commun.* **1998**, 409−410. (c) Marino, J. P.; Anna, L. J.; Fernández de la Pradilla, R.; Martínez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462−6473.

(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.

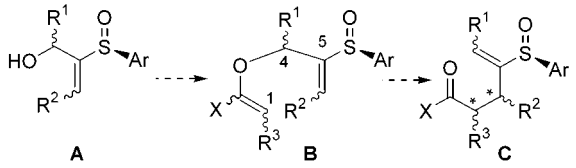
(5) (a) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523−1535. (b) He, S.; Kozmin, S. A.; Rawal, V. *J. Am. Chem. Soc.* **2000**, *122*, 190−191. (c) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911−2912. (d) Enders, D.; Knopp, R.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882. (e) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43−50.

(6) (a) Cookson, R. S.; Gopalan, R. *J. Chem. Soc., Chem. Commun.* **1978**, 608. (b) Vatèle, 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 hydroestannylation (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*)-sulfenyl alcohols, see: Berenguer, R.; Cavero, M.; García, J.; Muñoz, M. *Tetrahedron Lett.* **1998**, *39*, 2183−2186.

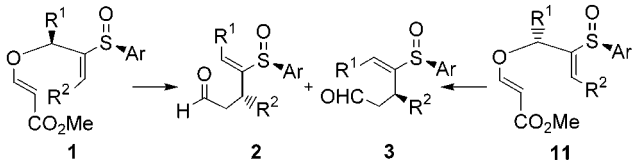
10.1021/ol0261130 CCC: $22.00
Published on Web 06/08/2002

Scheme 1. Proposed Sulfinyl-Mediated Claisen Rearrangements



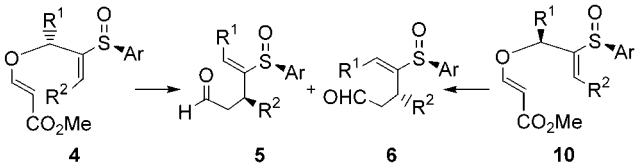
test the key rearrangement leading to products **C**, amenable to subsequent regio- and stereocontrolled sulfur-directed transformations. After considerable fruitless experimentation on the Claisen−Ireland protocol,[8] we shifted our attention to the Claisen−Johnson variant.[9] It was soon recognized 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%



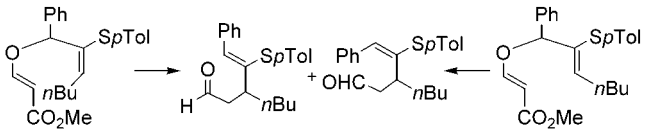
From **(+)-4a**, 134 °C, 180 min, *Z*:*E*, 73:27, **(−)-5a** (70), **(+)-6a** (23), 73%
From **4b**, 134 °C, 180 min, *Z*:*E*, 74:26, **5b** (73), **6b** (26), 76%
From **4c**, 138 °C, 420 min, *Z*:*E*, 64:36, **5c** (63), **6c** (29), 71%

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 = *n*Bu; **b**, Ar = *p*Tol, R^1 = Et, R^2 = Me; **c**, Ar = 1-Naphth, R^1 = Ph, R^2 = *n*Bu; **d**, Ar = 1-Naphth(2-OMe), R^1 = Ph, R^2 = *n*Bu. *Z*:*E* ratios include two byproducts obtained in some cases; see Supporting Information. Diastereomeric ratios determined by integration of well-resolved signals in the ^{1}H 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.

(9) Johnson, W. S.; Werthermann, L.; Barlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743.

(10) Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung. S.; Shanklin Cunningham, P.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976−1985.

(11) (a) Buchi, G.; Vogel, D. E. *J. Org. Chem.* **1983**, *48*, 5406−5408. (b) Vogel, D. E.; Buchi, G. *Org. Synth.* **1988**, *66*, 29−42. (c) Palmisano, G.; D'Anniballe, P.; Santagostino, M. *Tetrahedron* **1994**, *50*, 9487−9494.

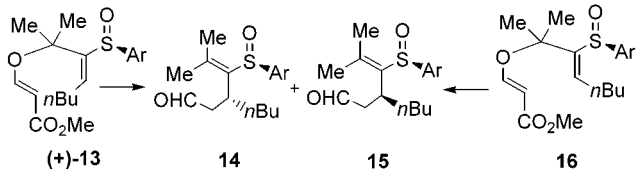
(12) All new products were fully characterized by standard techniques. The optical purity of the final products was established by ^{1}H NMR analysis with the chiral shift reagent (+)-Eu(tfc)$_3$. The stereochemistry of rearrangement products **2**, **3**, **5**, and **6** was established by comparison 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).

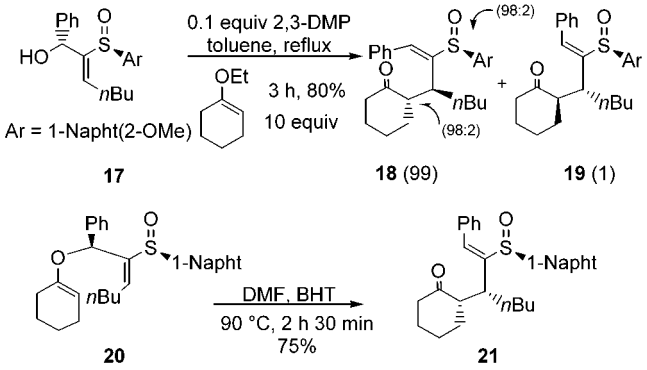
Scheme 4. Influence of the Sulfinyl Moiety[a]



[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

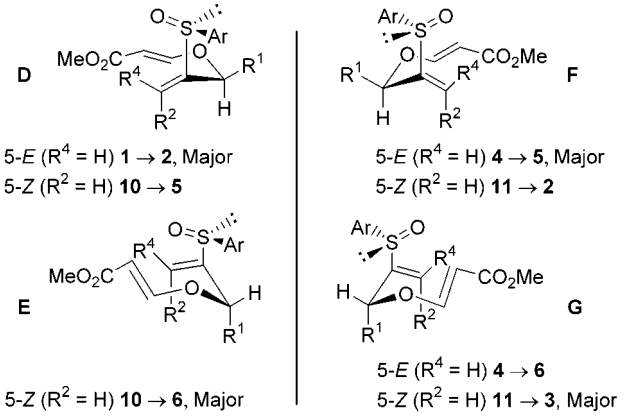


Figure 1. Proposed reactant conformers for sulfinyl-mediated Claisen rearrangements.

the C−S bond is proposed.[17] In the case of 5-*E* substrates (R^4 = 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 R^1 and R^2 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** (R^2 = H), a nonreinforcing scenario was found, with conformer **E** being favored relative to **D**. Likewise, for **11** (R^2 = 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

(15) (a) Watanabe, Y.; Mase, N.; Tateyama, M.; Toru, T. *Tetrahedron: Asymmetry* **1999**, *10*, 737−745. (b) Bell, K. H. *Aust. J. Chem.* **1985**, *38*, 1209−1221.

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

(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.

Acknowledgment. This research was supported by DGI (grants PPQ2000-1330 and BQV2001-0582) and CAM (grant 08.5/0079/2000). We thank CAM and MEC for doctoral fellowships to C.M. and M.T.

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.

OL0261130