Highly Diastereoselective Asymmetric Thio-Claisen Rearrangements

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The Claisen rearrangement has evolved into one of the most powerful transformations for the stereoselective formation of carbon−carbon bonds.[1] Compared to the more familiar oxygen version, the "thio-Claisen" rearrangement has been little investigated,[2] particularly its asymmetric version, wherein the chirality resides in the amino portion of the starting thioamide. The asymmetric thio-Claisen rearrangements investigated to date suffer from low diastereofacial selectivity as a consequence of free rotation around the C−N bond in the *N*,*S*-ketene acetal intermediate (Scheme 1).[3] The sole exception comes from the work of Meyers et al., wherein the rigid bicyclic thiolactam framework prevents rotation around the C−N bond of the *N*,*S*-ketene acetal intermediate.[4] Described below are the first examples of asymmetric thio-Claisen rearrangements of systems containing C_2-symmetric amines, which proceed with good to exceptionally high diastereoselectivities.[5]

The decision to use a C_2-symmetric amine as the chiral auxiliary for the thio-Claisen rearrangement was based on the following considerations. First, deprotonation of a tertiary thioamide is known to produce the *Z*-thioenolate with very high selectivity.[2c] Second, there is a strong preference for the chairlike transition state in the Claisen rearrangement.[1] Finally, the use of a C_2-symmetric auxiliary was expected to preclude the rotomer issue mentioned above, since both rotomers[6] would be identical. Taken together, these factors meant the thio-Claisen rearrangement using a C_2-symmetric amine would proceed primarily through only two low-energy transition states, **A** and **B**, of which the former was expected to be favored for steric reasons (Figure 1).

The required thioamide substrate, (−)-**1**, was readily prepared via a two-step sequence from (+)-*trans*-2,5-diphenylpyrrolidine.[7] Acylation of the amine with propionyl chloride (Et_3N, CH_2Cl_2, 92%) followed by thionation with Lawesson's reagent (PhMe, reflux, 98%) afforded enantiopure thioamide (−)-**1**.[8] Compound

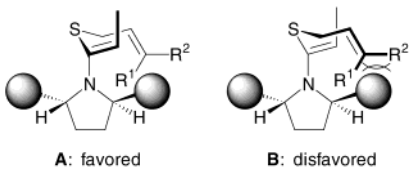


Figure 1.

Scheme 1

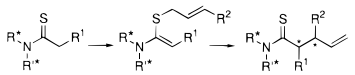
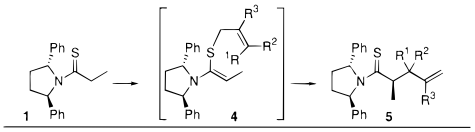


Table 1. Thio-Claisen Rearrangements Giving One New Stereogenic Center



entry	allylating agent	conditions[a]	product	% yield[b]	de[c]
1		-78 °C to room temp	**5a**	98	9.8:1 (81%)
2		-78 °C to room temp	**5b**	100	7.7:1 (77%)
3		reflux, 6h	**5c**	89	>200:1 (>99%)
4		reflux, 6h	**5d**	91	>100:1 (>98%)

[a] THF, *n*-BuLi, −78 °C; add allylic bromide, then warm to the conditions indicated. [b] Isolated yield. [c] The diastereoselectivities (de) were determined by HPLC.

(−)-**1** was deprotonated with *n*-BuLi at −78 °C, and the resultant *Z*-thioenolate was treated with the allyllic bromide.[2c] Rearrangement of the *N*,*S*-ketal intermediate was carried out by warming the reaction mixture to room temperature or, when necessary, to reflux.

The first group of asymmetric thio-Claisen rearrangements to be examined were selected so as to produce one new stereogenic center (Table 1). Upon treatment of the enolate of **1** with allyl bromide or methallyl bromide and allowing the reaction mixture to warm to room temperature, the thio-Claisen rearrangements took place readily and afforded the expected products, **5a** and **5b**, in nearly quantitative yields. The product from allyl bromide was obtained as a 9.8:1 ratio of diastereomers (81% de), and that from methallyl bromide was obtained in a 7.7:1 ratio (77% de).[9] The absolute configuration of the newly created centers for both rearrangement products was established by correlation with authentic samples of the amides prepared via Evans's chiral oxazolidinone alkylation methodology.[10] This correlation confirmed that the observed diastereoselectivity originated from the facial bias imposed by the chiral auxiliary in **4**, with the rearrangement proceeding predominantly via transition state **A** (Figure 1).

The results from the next two examples studied were striking. After alkylation of the thioamide enolate with 4-bromo-2-methyl-2-butene and warming the reaction mixture to room temperature, the intermediate *N*,*S*-ketene acetal remained unrearranged. To promote the rearrangement, the reaction mixture was heated to reflux for 6−7 h. Despite the higher temperature, the rearrange-

(1) (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 827. (b) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (d) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43.

(2) (a) Schuijl, P. J. W.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 929. (b) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881. (c) Tamaru, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631. (d) Metzner, P. *Synthesis* **1992**, 1185.

(3) (a) Welch, J. T.; Eswarakrishnan, S. *J. Am. Chem. Soc.* **1987**, *109*, 6716. (b) Reddy, K. V.; Rajappa, S. *Tetrahedron Lett.* **1992**, *33*, 7957. (c) Jain, S.; Sinha, N.; Dikshit, D. K.; Anand, N. *Tetrahedron Lett.* **1995**, *36*, 8467.

(4) Lemieux, R. M.; Devine, P. N.; Mechelke, M. F.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 3585 and references therein.

(5) We had earlier found *trans*-2,5-diphenylpyrrolidine to be a superb chiral auxiliary for dienes in Diels−Alder reactions. See: (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562.

(6) Of the infinite number of rotomers possible, only the two shown allow optimum stabilizing delocalization between the sp^2-hybridized nitrogen lone pair and the enamine π-bond.

(7) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asymmetry* **1995**, *6*, 409.

(8) The enantiomeric excess of the thioamide was >99% based on chiral HPLC comparison with (±)-**1**. Reviews on Lawesson's reagent: (a) Voss, J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 1, p 530. (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

(9) Determined by HPLC comparison with authentic samples. See Supporting Information.

(10) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(11) The absolute configuration was assigned by analogy with the rearrangement products with allyl bromide and methallyl bromide (Table 1, entries 1 and 2).

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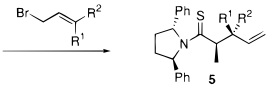
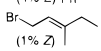
Table 2. Rearrangements Producing Two New Stereogenic Centers



entry	allylating agent	conditions[a]	product	% yield[b]	*syn*:*anti*	de (major)
1	 (3% *Z*)	-78 °C to room temp	**5e**	93	1:41	76%(*anti*)
2	 (3% *E*)	reflux, 3h	**5f**	92	>30:1	>99%(*syn*)
3		-78 °C to room temp	**5g**	100	<1:100	66%(*anti*)
4	 (4% *E*)	reflux, 8h	**5h**	86	>30:1	>99%(*syn*)
5	 (1% *Z*)	reflux, 9h	**5i**	81	<1:50	>99%(*anti*)
6	 (1% *E*)	reflux, 9h	**5j**	88	>50:1	>99%(*syn*)

[a] THF, *n*-BuLi, −78 °C; add allylic bromide, then warm to the conditions indicated. [b] Isolated yield. [c] The diastereoselectivities (de) were determined by HPLC.

ment proceeded with excellent diastereoselectivity and afforded thioamide **5c** as a single diastereomer (by HPLC).[9] Similarly high selectivity was observed for the alkylative rearrangement using (2-bromo-ethylidene)-cyclohexane.[9]

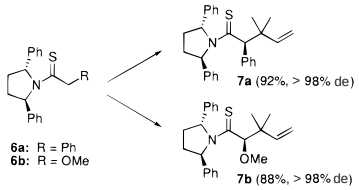
The observed high diastereoselectivity for entries 3 and 4, as well as the difference in the level of selectivity between entries 1, 2 and entries 3, 4, can be understood by inspection of molecular models (Figure 1). Of the two likely transition states, **A** and **B**, the former is expected to be of lower energy because the allylic group is positioned in the open face of the C_2-symmetric chiral auxiliary, on the side away from the proximal phenyl group on the pyrrolidine ring. Transition state **B** is disfavored since it has the allyllic group in close proximity to the pyrrolidine phenyl group. The steric problem is particularly severe when there is a "*Z*-oriented" substituent on the allylic sulfide (R^1 in Figure 1). The other two substituents, R^2 and R^3, are pointed away from the phenyl group in the transition state and are not expected to greatly affect the diastereoselectivity (e.g., entry 2).

The above analysis brings out a novel and unique aspect of the present work: *It is the "Z-oriented" substituent—and it only—that is of paramount importance for realizing high diastereoselectivity*. To test this proposition, we examined the alkylative rearrangement of *E*- and *Z*-crotyl bromides (Table 2). The rearrangement with *E*-crotyl bromide took place upon warming the reaction mixture to room temperature and gave a 97.6:2.4 ratio of anti and syn diastereomers, respectively (entry 1).[9] The asymmetric induction for the major (anti) diastereomer was 7.5:1, very similar to that observed with allyl bromide.[11] The intermediate formed upon alkylation with *Z*-crotyl bromide rearranged much more slowly than that with *E*-crotyl bromide and required heating to reflux for 3 h. As predicted, the diastereomeric excess (de) of the syn product was exceptionally high (entry 2).[12]

The results from the alkylation rearrangement using *E*- and *Z*-cinnamyl bromides (Table 2, entries 3 and 4) paralleled those with the crotyl bromides. As expected, the rearrangement with *E*-cinnamyl bromide proceeded with high anti selectivity, but the de of the anti diastereomer was only modest (4.9:1). The stereochemistry of the rearrangement products was assigned

(12) The small amount of the anti diastereomers arises primarily from the *E*-bromide (ca. 3% by NMR) present in the alkylating agent. If corrected for the contamination by the *E*-isomer, the syn:anti selectivity for the rearrangement is >99%.

Scheme 2



analogously to that with the crotyl bromides. Gratifyingly, the thio-Claisen rearrangement of the *Z*-cinnamyl bromide alkylation product proceeded with exceedingly high syn:anti and facial selectivities.[12]

The examples shown in entries 5 and 6 are most interesting: two stereogenic centers, of which one is quaternary, are produced with almost complete diastereocontrol. Indeed, the present chemistry is particularly well suited for the synthesis of quaternary stereogenic centers because the intermediate *N*,*S*-ketene acetal would necessarily have a *Z*-oriented substituent.

Finally, the present thio-Claisen chemistry appears to have considerable scope. We have examined the alkylative rearrangement of two additional thioamides, **6a** and **6b** (Scheme 2). Both rearrangements proceeded in high yields and afforded the thio-Claisen products with excellent diastereoselectivity (>98% by NMR).

In summary, we have investigated several thio-Claisen rearrangements using a C_2-symmetric pyrrolidine[13] as the removable chiral auxiliary.[14] The rearrangements proceed with high syn:anti selectivities and good to excellent asymmetric induction. In particular, the rearrangements of allylic units possessing a substituent cis to the allylic sulfide take place with exceptionally high diastereoselectivity, among the highest reported for any Claisen rearrangement. A simple, predictive model is provided to explain the extraordinary asymmetric inductions observed.

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Supporting Information Available: Details for preparations and characterizations of all new compounds, including copies ^{1}H NMR and ^{13}C NMR spectra, along with HPLC analysis of diastereoselectivity (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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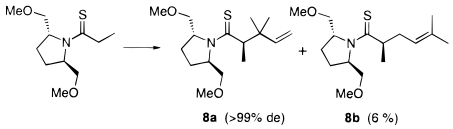
(13) We have also examined the thio-Claisen rearrangement using the commercially available auxiliary, (*R*,*R*)-(−)-2,5-bis(methoxymethyl)pyrrolidine. Treatment of the enolate of the thioamide with HMPA (3 equiv), followed by addition of 4-bromo-2-methyl-2-butene and heating the reaction mixture to reflux, afforded the expected thio-Claisen product with excellent diastereoselectivity (>99%). The product (92% total yield) contained about 6% of the direct alkylation product, produced as a single diastereomer.



(14) The chiral auxiliary can be cleaved from the thio-Claisen products under reductive hydrolysis conditions. For example, (−)-(2*R*,3*S*)-2-methyl-3-phenyl-4-penten-1-ol was obtained in 64% overall yield from thioamide **5h** as shown below. The alcohol was obtained with >30:1 syn:anti ratio. Mosher ester analysis (NMR) indicated the ee to be >97% (see Supporting Information for details).