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(*R*,*R*)-2,5-Diphenylpyrrolidine: Diastereoselective Radical Addition to the Derived Methacrylamide

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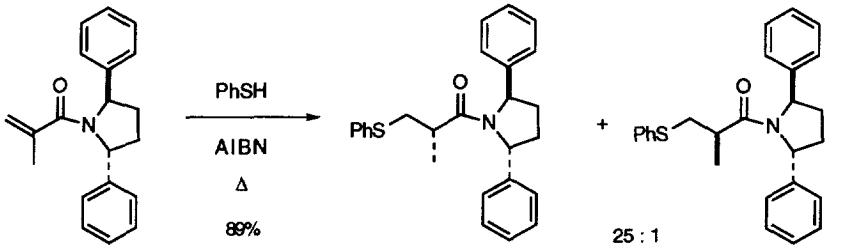
Abstract: Radical addition of thiophenol to the methacrylamide **1** proceeds with high diastereoselectivity, to give **2** and **3** in a ratio of 25:1. © 1997 Elsevier Science Ltd.

Chong recently reported[2,3] the preparation of (*R*, *R*)-2,5-diphenylpyrrolidine in high enantiomeric purity. In a parallel effort, we also had been intrigued by the selectivity that might be induced by this readily available chiral amine, and had been investigating its preparation and reactions. We now report that radical addition to the derived methacrylamide **1** proceeds with excellent diastereoselectivity, to give **2** and **3** in a ratio of 25:1.



1 **2** **3**

Porter has reported[4a] diastereoselective radical transformations α to the carbonyl of amides prepared from *trans*-2,5-dimethylpyrrolidine, and Giese has reported[4b] diastereoselective radical additions to the derived methacrylamide. In both cases, appreciable diastereoselectivity (up to 17 : 1) was observed. While these results were encouraging, the *trans*- 2,5-dimethylpyrrolidine is difficult to prepare,[5] and is volatile and so difficult to handle.

The corresponding *trans*- 2,5-diphenylpyrrolidine is less volatile than the *trans*- 2,5-dimethylpyrrolidine, and so is more practical both to prepare and to recycle.[2,3] We reasoned that as the phenyl groups are sterically more demanding than methyl groups, the *trans*- 2,5-diphenylpyrrolidine might also be more highly directing.

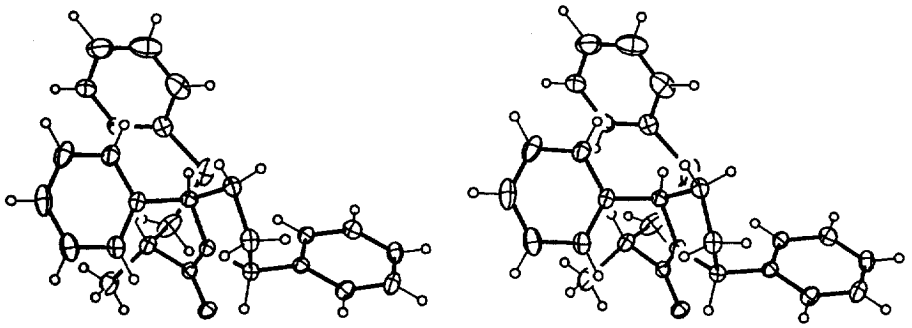


Figure 1. Stereoview of the X-ray crystal structure of the major diastereomer **2**.

Acylation of (*R, R*)-*trans*-2,5-diphenylpyrrolidine[2,3] with methacryloyl chloride in the presence of Et3N gave the corresponding methacrylamide **1** (87%). Heating of **1** with thiophenol (2.25 eq) in toluene at 100°C overnight in the presence of AIBN (0.25 eq) gave clean conversion to a mixture of **2** and **3**.[6] Integration of the ^{1}H NMR spectrum of the mixture of products showed a ratio of 25:1, with the major (more polar) diastereomer **2** at δ 4.9, and the minor (less polar) diastereomer **3** at δ 5.3. These diastereomers were readily separated by silica gel chromatogaphy. The major diastereomer (**2**) was recrystallized from MTBE, and the structure was established by X-ray analysis (**Fig. 1**).[7]

It is striking that substantial diastereoselectivity was observed even at 100°C for hydrogen atom transfer to the intermediate radical from addition to **1**. This suggests that *trans* 2,5-diphenylpyrrolidine will indeed be a useful auxiliary for inducing diastereoselectivity at the position α to the amide carbonyl.

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References and Notes:

(1) Undergraduate research participant, University of Delaware.

(2) Chong, J.M.; Clarke, I.S.; Kock, I.; Olback, P.C.; Taylor, N.J. *Tetrahedron: Asymmetry* **1995**, *6*, 409.

(3) Chong reported the isolation of the mesylate of 1,4-diphenyl-1,4-butanediol, and subsequent cyclization with allylamine. We have found that the yield of the product N-allylpyrrolidine is better if the allylamine is added directly to the mesylation reaction mixture.

(4) (a) Porter, N.A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A.T. *J. Am. Chem. Soc.* **1991**, *113*, 7002. (b) Giese, B.; Hoffmann, U.; Roth, M.; Veit, A.; Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445.

(5) Beak, P.; Kerrick, S.T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116* 3221 and references cited therein.

(6) **2**: TLC R_f (20% MTBE/pet. ether, two dev.) = 0.25; ^{1}H NMR (δ): 7.3 (m, 13 H); 6.9 (d, J=6.8 Hz, 2H); 5.5 (d, J=8.8 Hz, 1H); 4.9 (d, J=5.6 Hz, 1H); 3.1 (m, 1H); 2.9 (m, 1H); 2.7 (m, 1H); 2.5 (m, 2H); 1.7 (m, 2H); 0.9 (d, J=5.0 Hz, 3H). ^{13}C NMR (δ): u: 174.8, 144.1, 143.4, 136.7, 32.8, 30.8 d: 129.5, 129.1, 128.9, 128.6, 126.9, 126.4, 125.9, 125.8, 125.7, 62.8, 62.7, 38.1, 27.2. IR (cm^{-1}): 2922, 1644, 1460, 1377. **3**: TLC R_f = 0.33; ^{1}H NMR (δ): 7.3 (m, 10 H); 7.0 (m, 3H); 6.8 (m, 2H); 5.5 (d, J=7.5 Hz, 1H); 5.3 (d, J=6.2 Hz, 1H); 3.1 (m, 1H); 2.8 (m, 1H); 2.6 (m, 2H); 2.4 (m, 1H); 1.8 (m, 2H); 1.3 (d, J=4.4 Hz, 3H).

(7) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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