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The Intramolecular, Stereoselective Addition of Sulfoximine Carbanions to α,β-Unsaturated Esters

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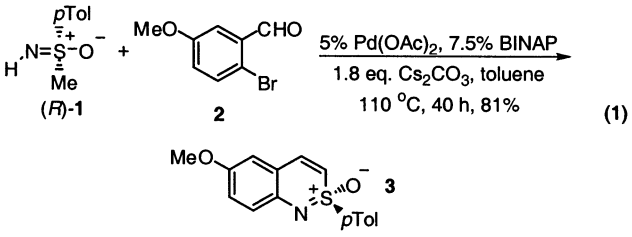
Abstract: *ortho*-Bromocinnamates can be coupled with methyl phenylsulfoximine to afford *N*-arylsulfoximines in excellent yield. Treatment of these products with an amide base results in a completely stereoselective cyclization to afford enantiomerically pure benzothiazines. This reaction is stereospecific.

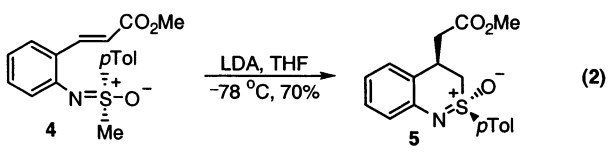
Introduction

As part of our program concerning the synthesis and chemistry of 2,1-benzothiazines,[1] we recently reported the one-pot synthesis of enantiomerically pure benzothiazines via the reaction of enantiomerically pure N−H sulfoximines and *ortho*-bromobenzaldehydes, as shown in eq 1.[2] This process involves



(1)

the Buchwald−Hartwig reaction,[3] followed by an intramolecular condensation. In that report, we also demonstrated a single example of a reaction involving an intramolecular addition of a sulfoximine carbanion to an α,β-unsaturated ester (eq 2). This reaction was completely stereoselective, but it was not clear if the process would be general, nor were any mechanistic details about the reaction known. The study reported herein establishes that such a reaction is general, stereoselective, and stereospecific and can, under the appropriate circumstances, be conducted as a one-pot process involving both carbon−nitrogen and carbon−carbon bond formation.

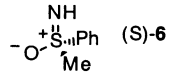


(2)

One motivation for this study centered on the idea that the method, if general, could be used to introduce a stereogenic center adjacent to an aromatic ring, that is, at the benzylic position. The natural and man-made pharmacopoeia is replete with interesting and important structures bearing such a stereogenic center.[4] While to say any methodology can definitively be applied to such a broad range of compounds may be unrealistic, the potential exists for a significant contribution if the initial steps in a methodological development indicate high yields and high levels of stereocontrol.

Results and Discussion

It is important to mention that our work made use of sulfoximine **6**, whose privileged status arises from the fact that it is extremely easy to prepare in enantiomerically pure form.[5] At the outset of this study, it was not clear if we would have to optimize the structure of the sulfoximine to achieve high stereoselection in the conjugate addition step of the process. That this was unnecessary means that this reaction is more than interesting; it is useful.



(S)-**6**

In coupling sulfoximine **6** to various *ortho*-bromocinnamates, we made use of the Buchwald−Hartwig reaction as modified by Bolm for coupling sulfoximines to bromoarenes.[6] In general, this involved refluxing a toluene solution of the bromocinnamate with 5 mol % $Pd(OAc)_2$ in the presence of 7.5 mol % racemic BINAP, 1.4 equiv of Cs_2CO_3, and 1.2 equiv of **6**. This procedure

(1) Harmata, M.; Kahraman, M.; Jones, D. E.; Pavri, N.; Weatherwax, S. E. *Tetrahedron* **1998**, *54*, 9995 and references therein.
(2) Harmata, M.; Pavri, N. *Angew. Chem., Int. Ed.* **1999**, *16*, 2419.
(3) (a) Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Halides and Related Reactions. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, 2002; pp 1051−96. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
(4) Consider, as examples, some compounds seen on perusal of the Merck Index: the *Aspidosperma* alkaloids, estrone and its congeners, tetrahydrocannabinols, podophyllotoxin, morphinoids, calycanthine, chimonanthine, turmerone, viridin, mitomycins, vindoline, teleocidin B_4, pranoprufen, pentazocine, lycoramine, naproxen, and ibuprofen. For a recent reference on the generation of benzylic stereocenters, see: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.
(5) Brandt, J.; Gais, H. *Tetrahedron: Asymmetry* **1997**, *6*, 909.
(6) (a) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *37*, 5731. (b) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169.

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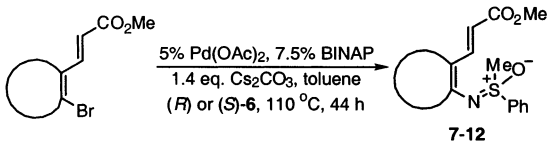
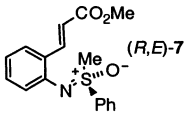
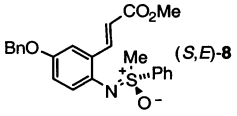
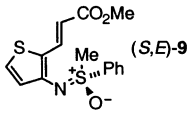
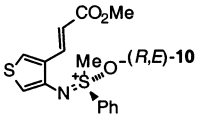
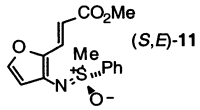
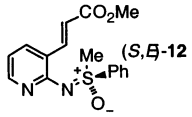
Table 1. Reaction of (*R*)- or (*S*)-**6** with Various *ortho*-Bromocinnamates



7-12

entry	product	yield (%)
1	 (*R*,*E*)-**7**	91
2	 (*S*,*E*)-**8**	93
3	 (*S*,*E*)-**9**	78
4	 (*R*,*E*)-**10**	83
5	 (*S*,*E*)-**11**	96
6	 (*S*,*E*)-**12**	86

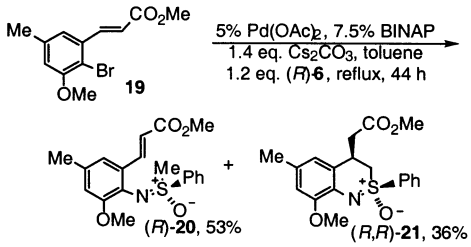
generally afforded high yields of N-arylated sulfoximine using either enantiomer of **6** (Table 1).

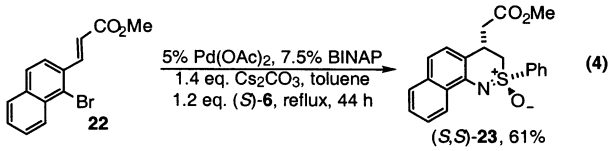
Most gratifyingly, we found that treatment of the sulfoximines with an amide base resulted in the formation of benzothiazines with complete diastereoselectivity (Table 2). Typical reaction conditions involved adding a THF solution of 2 equiv of LDA or LiHMDS in THF to the sulfoximine at −78 °C. Some variation in temperature was explored to assess the effect of this variable on selectivity. None was found. Two substrates could not be cyclized under these conditions. While thiophene **9** afforded benzothiazine **15** in good yield, furan **11** appeared to polymerize when base was added. This problem was circumvented by simply adding the furan to a solution in base, thereby keeping its concentration relatively low. Similarly, pyridine **12** gave either decomposition or side products when treated with base. Inverse addition coupled with rigorous degassing solved this problem, and the desired benzothiazine was obtained in high yield.

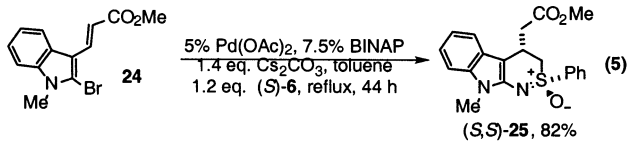
All of the benzothiazines were formed as single stereoisomers. Stereochemical assignments were based on X-ray data obtained for **5**.[2] Other assignments were made on the basis of analogy, based on spectroscopic comparison to **5**.

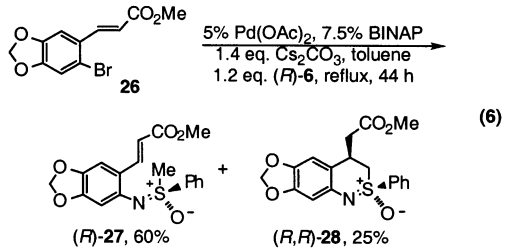
Our rationalization for the outcome of these reactions is based on minimization of steric interactions in the transition state leading to carbon−carbon bond formation. Models suggest that the transition state leading to the observed products is sterically less encumbered than the diastereomeric transition state.

In the course of this work, we discovered that certain *ortho*-bromocinnamates reacted with sulfoximine **6** to give products of both carbon−carbon and carbon−nitrogen bond formation. This was first observed with **19**, whose reaction with **6** afforded a 53% yield of **20** as well as a 36% yield of benzothiazine **21**, with complete stereoselectivity (eq 3). We ascribed the formation of **21** to a buttressing effect, which biased **20** toward a conformation which placed the methyl group of its sulfoximine functionality near the β-carbon of the α,β-unsaturated ester. Equilibrium deprotonation of the sulfoximine to form the corresponding carbanion resulted in some cyclization, due to this proximity effect.



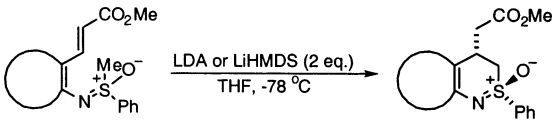




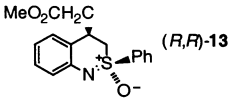
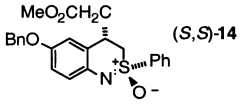
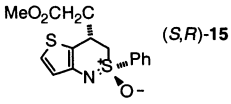
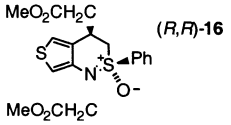
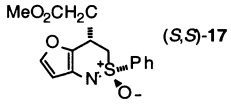
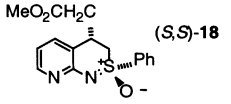


This idea was tested with two other substrates. The reaction of both **22** and **24** with **6** under standard reaction conditions afforded only benzothiazines **23** and **25**, respectively, in a one-pot procedure in good yield (eqs 3 and 4). Thus, it appears that a buttressing effect may be used to create benzothiazines in a single operation. Other effects may also be important, however. For example, the reaction of **26** with **6** gave not only the sulfoximine **27** in 60% yield, but the benzothiazine **28** as well (eq 6). Clearly, no buttressing effect is possible with this system.

Table 2. Reaction of Sulfoximines **7**−**12** with an Amide Base

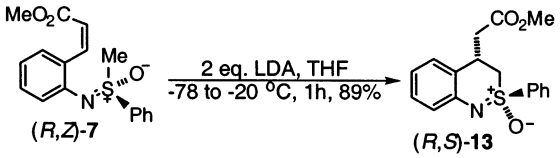


7-12 13-18

entry	educt	product	yield(%)
1	(*R*)-**7**	 (*R*,*R*)-**13**	92[a]
2	(*S*)-**8**	 (*S*,*S*)-**14**	91[a]
3	(*S*)-**9**	 (*S*,*R*)-**15**	91[a]
4	(*R*)-**10**	 (*R*,*R*)-**16**	93[a]
5	(*S*)-**11**	 (*S*,*S*)-**17**	85[b]
6	(*S*)-**12**	 (*S*,*S*)-**18**	77[b]

[a] Prepared by addition of base to sulfoximine. [b] Prepared by addition of sulfoximine to base.

To obtain more information about the base-mediated cyclization step with those substrates requiring two steps to achieve benzothiazine formation, we treated the (*Z*)-cinnamate **7** with LDA (eq 7). Benzothiazine **13** was obtained as the sole product in 89% yield, suggesting that the reaction was stereospecific.



(7)

Conclusion

In summary, we have demonstrated that the intramolecular conjugate addition of sulfoximine carbanions to α,β-unsaturated esters is a powerful method for establishing a stereogenic center at a benzylic position. This methodology has the potential for application to natural product synthesis, especially because a procedure for the reductive removal of the sulfur functionality from benzothiazines is known.[7] The synthesis of molecular scaffolds, establishing the formation of chiral quaternary centers, and exploration of the chemistry of certain chiral benzothiazines themselves are among our immediate goals in further exploring this methodology. Finally, this chemistry is only beginning to be explored. Extensions to other nonbenzenoid systems, using the results obtained thus far as guiding principles, should make possible the synthesis of a wide variety of enantiomerically pure compounds. Further results will be reported in due course.

Acknowledgment. This work was supported by the Petroleum Research Fund, administered by the American Chemical Society, to whom we are grateful. We thank FMC Lithium for a generous gift of the alkyllithium reagents used in this study.

Supporting Information Available: Experimental procedures and copies of the ^{1}H and ^{13}C NMR spectra of **7**−**12**, their precursors, and **13**−**28** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Harmata, M.; Kahraman, M. *Synthesis* **1994**, 142−144.