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EVALUATION OF A CHIRAL ARYL AUXILIARY DESIGN FOR SULFUR: CONSTRUCTION OF AUXILIARY-MODIFIED REAGENTS AND STEREOSELECTION IN SULFOXIDE FORMATION

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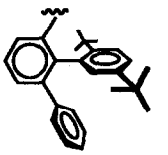
Summary: *Compounds possessing thiol, sulfide, and sulfoxide functionality attached to chiral auxiliary fragment 1 can be synthesized from halogenated aromatics 2 and 3. In the sulfoxides, auxiliary 1 can define the sulfinyl configuration in either relative sense depending on whether sulfinyl configuration is established under kinetic or thermodynamic control.*

The invention of enantioselective carbon-carbon bond formation methodology is currently a high priority goal of synthesis research. Sulfur is a particularly attractive reaction focus, in this regard, owing to the diversity of carbon-carbon bond forming reactions it mediates.[2] While most previous efforts to develop enantioselective sulfur-mediated reactions have located stereogenicity at sulfur, we have been interested in an auxiliary-based approach to facilitate the recycling of reagent absolute stereochemistry. Herein we outline the synthesis of racemic substances with sulfur functionality appended to the monodentate chiral auxiliary fragment **1**, and illustrate the way in which auxiliaries of this type can control the relative stereoselection that must underlie their involvement in enantioselective chemistry.

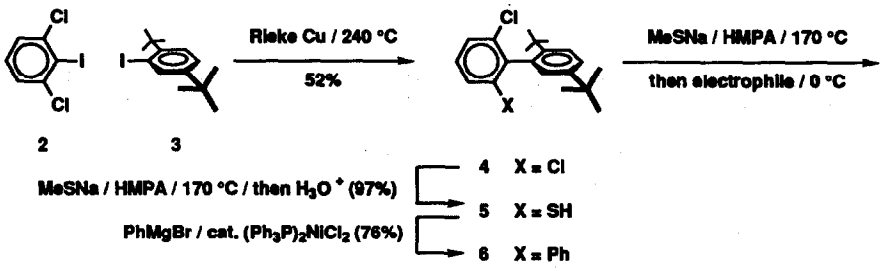


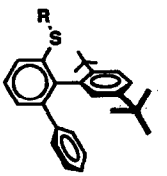
1

The construction of reagents bearing **1** proceeded through biaryl **4**[3] and terphenyl **6** (Scheme I). Although we planned initially to produce **4** through nickel-catalyzed chemistry developed by Kumada,[4] treatment of **2**[5] and the Grignard reagent derived from **3**[6] with various phosphine-ligated nickel dichloride catalysts, as required by that approach, gave products that arose from halogen-metal exchange, i.e. **2** decomposed and **3** was reformed. On the other hand, when 2,6-dichlorobromobenzene and 1,2,3-trichlorobenzene were paired with the Grignard reagent derived from **3** under similar conditions, no reaction occurred in either case. Instead, **4** could be synthesized through the Ullmann coupling[7] indicated, which involved Rieke copper.[8] The differential reactivity of **2** and **3** in the Ullmann reaction allows the latter to be used in excess to optimize heterocoupling; recovery of **3** is efficient since its homocoupling is impeded. Regarding the installation of the phenyl substituent that restricts biaryl rotation,[9] again we had intended to make use of the Kumada chemistry, but changed course after **4** proved to be unreactive toward phenylmagnesium halide in the presence of nickel catalysts, and the mono-Grignard reagent derived from **4** failed to attack bromobenzene under similar conditions. In the alternative route developed, **4** was converted[10] to chlorothiol **5**, which underwent a nickel-catalyzed reaction with phenylmagnesium bromide that led through thiol substitution[11] to **6**. We conclude from our experience with these nickel-catalyzed processes that the sulfur substitution chemistry developed by the Wenkert group is far less sensitive to steric congestion than is the analogous halide substitution chemistry.[12]

The final operation in the synthesis of reagents based on **1** required a second application of the reaction between aryl chlorides and sodium methylthiolate employed in the formation of **5**. However since the product of this reaction prior to aqueous work up is the sodium arylthiolate, it can be quenched *in situ* with a variety of electrophiles. Eight such examples are listed in Scheme I. Electrophiles that failed in this thiolate capture protocol included cyclopentenone and cyclohexenone (polymerization of the enones

Scheme I





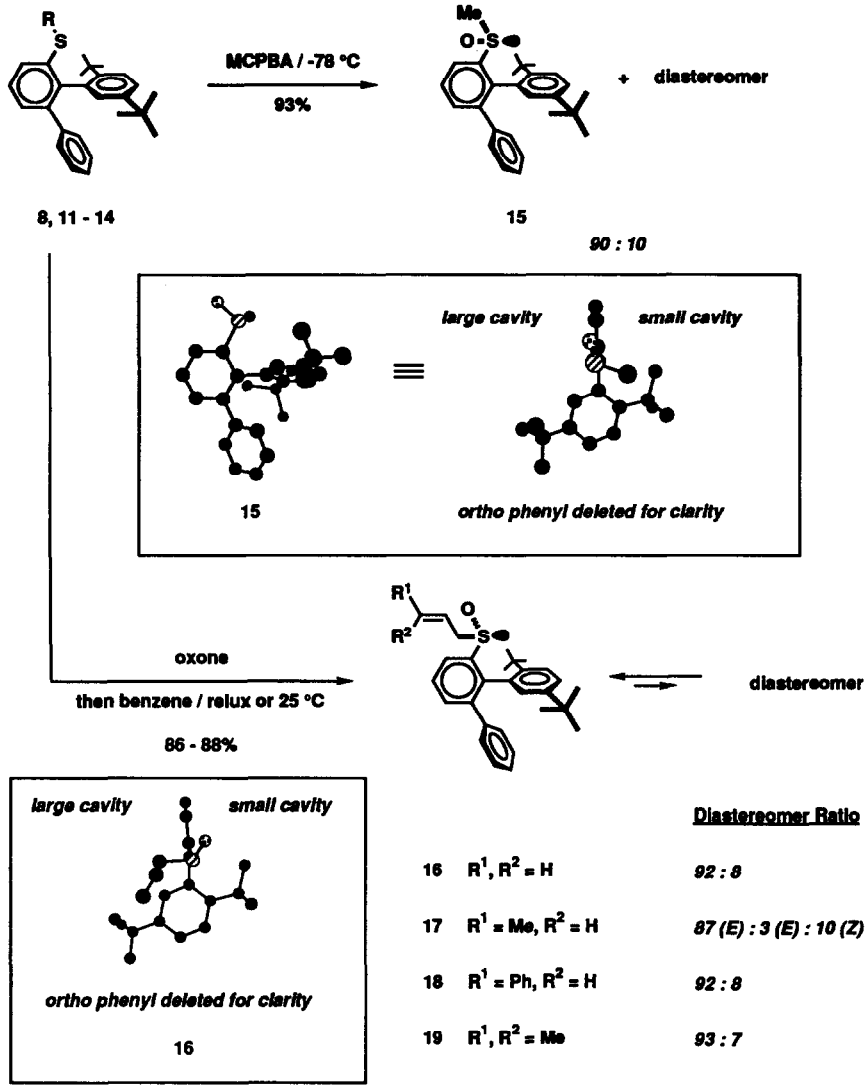
Electrophile		R	Yield
H_3O^+	7	H	97%
Methyl iodide	8	Me	96%
n-Hexyl iodide	9	*n*-Hexyl	96%
Ethyl bromoacetate	10	CH_2CO_2Et	82%
Allyl iodide	11	CH_2	86%
Crotyl bromide	12	CH_2 Me (10% Z)	85%
Cinnamyl bromide	13	CH_2 Ph	77%
Prenyl bromide	14	CH_2 Me Me	85%

occurred), and cyclohexene oxide (no reaction or unfavorable equilibrium). Thus 7 - 14 are available through four operations from the halogenated aromatics 2 and 3 in overall yields of 29 - 37%.

To gauge the effectiveness of auxiliary 1 in controlling stereoselection in the vicinity of sulfur, the conversions of 8 and 11 - 14 to their corresponding sulfoxides were investigated (Scheme II). In the case of 8, low temperature MCPBA oxidation gave with 90% stereoselection the diastereomer indicated; a single recrystallization removed the minor diastereomer. Since this process is a kinetically controlled one, it seems likely that external reagent attack occurs within the large cavity region defined by the *o-tert*-butyl substituent in a reactive rotamer that projects the methyl substituent into the small cavity region; see the crystallographically determined structure of 15[1] depicted in Scheme II.

In contrast, oxone oxidation[13] of 11 - 14 followed by equilibration of the sulfoxides so produced through the sulfoxide-sulfenate rearrangement[14] provided similar degrees of diastereoselection, but in the opposite sense. In these thermodynamically controlled cases, it is clear that it is the more sterically demanding allylic substituent that chooses to reside in the large cavity; see the

Scheme II



		Diastereomer Ratio
16	R^1, R^2 = H	92 : 8
17	R^1 = Me, R^2 = H	87 (E) : 3 (E) : 10 (Z)
18	R^1 = Ph, R^2 = H	92 : 8
19	R^1, R^2 = Me	93 : 7

model of allyl sulfoxide **16**.[15] Crotyl sulfoxide **17** is noteworthy in that heating it in refluxing benzene or storing it at room temperature as the solid for several weeks or in solution for several days led to an increase in the amount of Z isomer. Relatively brief equilibration of its sulfur configuration at room temperature maintained the non-equilibrium olefin geometrical composition incorporated through alkylation with commercially available crotyl bromide in the previous step. This experience suggests that the significant difference in the rates of configurational equilibration at the sulfur center and geometrical equilibration of the olefin in γ-substituted allylic sulfoxides[14] will allow the preservation of E geometry in reagents prepared, for example, from geometrically pure *E*-2-alken-1-ol derivatives. Configurationally defined sulfoxides form the basis of much useful asymmetric synthesis methodology.[2] Sulfoxides **16 - 19** undergo regio- and diastereoselective conjugate additions to cyclopentenone and, in the case of **19**, to cyclohexenone.[16]

Finally, auxiliary **1** represents but the first generation of a general design. In order to shorten the synthesis of reagents and to enhance the stereoselectivities they effect, we anticipate that modification of the *tert*-butyl-bearing ring will be necessary. For example, the removal of the distal *tert*-butyl substituent, a synthetic convenience associated with design **1**, and alteration of the proximal substituent will better differentiate the sizes of the large and small cavities, and will produce a structurally simpler auxiliary. These optimization efforts are underway, and will precede the development of optically active reagents.[17]

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