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LETTERS

Use of α-chlorosulfides in indium promoted C–C couplings: easy entry into the stereoselective formation of epoxy alkynes

Gregory Engstrom,[†] Meisha Morelli,[‡] Carolyn Palomo and Thomas Mitzel *
Department of Chemistry, Trinity College, 300 Summit Street, Hartford, Connecticut, 06106 USA

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Abstract

The use of α-chlorosulfide compounds to control stereoselectivity in indium promoted C–C couplings occurs smoothly at room temperature under aqueous and mixed aqueous/organic conditions. Use of the halide to control *syn*/*anti* ratios simplifies the indium promoted coupling with respect to earlier studies and is used to gain entry into stereocontrolled epoxy alkynes in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: indium couplings; epoxy alkynes; stereocontrol.

Use of indium mediated Barbier reactions to form C–C bonds has become a new and exciting area of chemical synthesis.[1] Indium metal has been shown to form chelates in aqueous solutions, thus allowing for good stereocontrol in the formation of coupling products, an attribute utilized in a variety of procedures.[1] Past studies have utilized placement of a chiral center containing an electron donating group α- to a carbonyl functionality to control stereochemistry of product formation.[2] While these studies have met with good success, formation of an α-chiral center is often not trivial, and the instability of these molecules can make isolation and purification an arduous process. We now report a much less complicated system to control stereochemistry using a novel sulfide–indium species derived from α-chlorosulfide reagents.

Reaction of α-chlorosulfide species with magnesium metal to promote C–C bond formations was described by Normant in the 1960s.[3] Further studies revealed the versatility of having a sulfur atom present,[4] and that reactions of this type could be accelerated if a phenyl ring was attached to the sulfur atom.[5] More recently this preparation has been used successfully with lithium and chromium metal,[6] however, there are relatively few examples which utilize direct metallation of the chloride species.

Synthetic versatility offered by α-chloroheteroatomic species, coupled with the effectiveness and ease of use of indium metal, led us to believe that this would be a good system for use in the stereocontrolled

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* Corresponding author. Fax: (860) 297-5129; e-mail: tmitzel@mail.trincoll.edu

[†] Current address: Fulbright College of Arts and Sciences, Department of Chemistry and Biochemistry, 115 Chemistry Building, University of Arkansas, Fayetteville, AR, 72701, USA.

[‡] Current address: Amherst College, Amherst, MA 01002-5000, USA.

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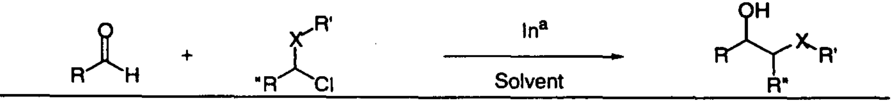
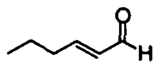
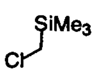
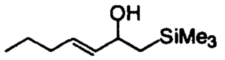
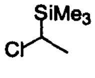
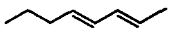
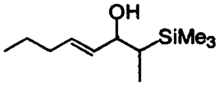
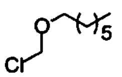
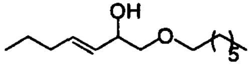
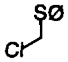
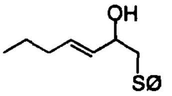
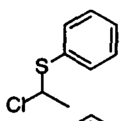
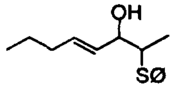
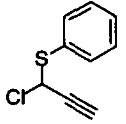
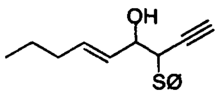
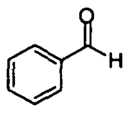
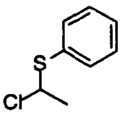
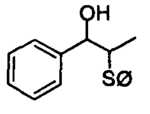
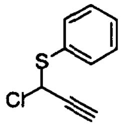
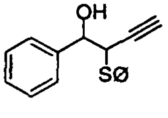
Table 1
Initial studies probing the feasibility of indium promoted reactions with α-chlorosulfides



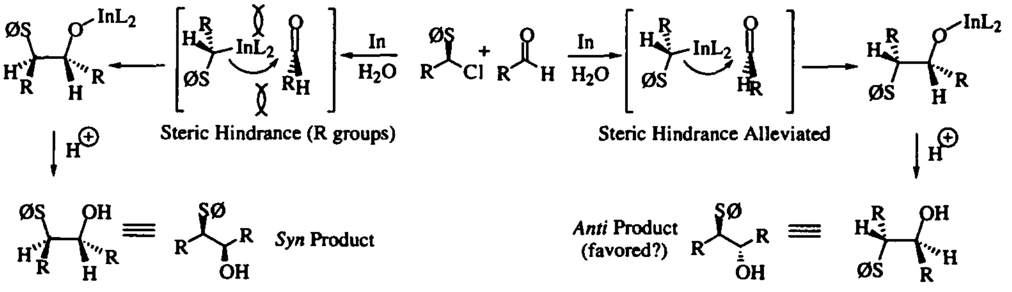
	Aldehyde	Halide	Solvent	Product	Ratio (syn/anti)	Yields
1			H_2O			NR
2			DMF			65 %
3			H_2O			49 %
4			DMF			66%
5			H_2O			59 %
6			H_2O/DMF			75 %
7			DMF			86 %
8			H_2O			86 %
9			H_2O/DMF			88 %
10			H_2O		40:60	65%
11			DMF		58:42	70%
12			$H_2O/InCl_3$		54:46	65%
14			$DMF/InCl_3$		61:39	70%
15			H_2O		34:66	68%
16			DMF/H_2O		32:68	68%
17			$H_2O/InCl_3$		**78:22**	85%
18			$H_2O/DMF/InCl_3$		76:24	84%
19			H_2O		**25:75**	84%
20			DMF/H_2O		29:71	73%
21			$H_2O/InCl_3$		77:23	87%
22			$H_2O/DMF/InCl_3$		**78:22**	81%
23			H_2O		30:70	70%
24			DMF/H_2O		**20:80**	83%
25			$H_2O/InCl_3$		78:22	87%
26			$H_2O/DMF/InCl_3$		**88:12**	84%

[a] Reactions were run at room temperature for a period of 1-20 hours. The ratio of reagents was as follows: 1.0:1.5:1.1 (Aldehyde : halide : Indium). The reaction was run at 0.1 M with respect to the amount of In.

formation of C–C bonds. Early studies were undertaken to determine the feasibility of indium promoted C–C bond formation using α-chloroheteroatomic species, and involved silyl-, thio-, and oxy-species as shown in Table 1, entries **1–9**.

As Table 1 describes, this reaction was quite successful with a number of systems. An interesting aberration is shown in entry **3** where in situ elimination of the silyl group occurred under fully aqueous conditions presumably via elimination under acidic conditions created as the reaction proceeded. Highest yields were realized under aqueous conditions, or conditions containing 50:50 mixtures of water and dimethylformamide. Reactions carried out using dimethylformamide as the sole solvent required pre-mixing of indium metal with the α-chlorosulfide species. This mixture was heated to 50°C for one hour, cooled, and the aldehyde added. Yields were generally lower utilizing this methodology and no stereocontrol over product formation was witnessed. Attempts to carry out this reaction at room temperature in the absence of water as a co-solvent resulted in very little product formation and this route was not pursued any further. It was determined from these initial studies that products obtained from chlorosulfide compounds in an aqueous or mixed solvent system returned superior and cleaner reaction mixtures with respect to the systems we tested. Based on these studies, we chose to pursue this arena further with regard to stereoselective control utilizing the α-chlorosulfide species. Results of the second set of studies are shown in Table 1, entries **10–26**.[7]

As revealed by ^{1}H NMR studies, *anti*-selectivity was witnessed in these systems with highest ratios evidenced in an aqueous solvent (entries **19**, **23**, and **24**). A suggested mechanism for *anti*-selection is shown in Scheme 1.

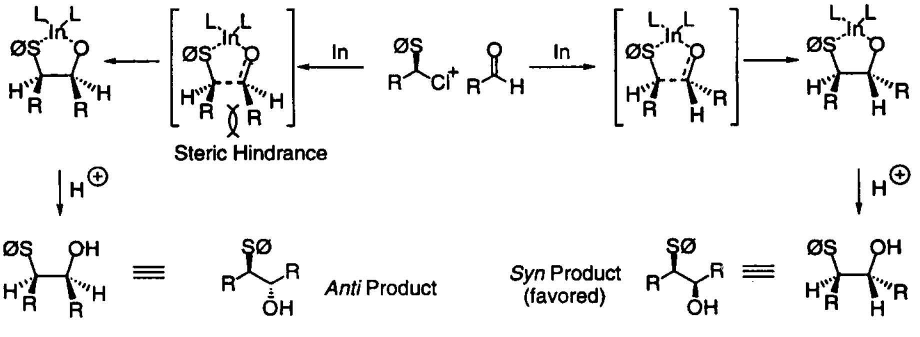


Scheme 1.

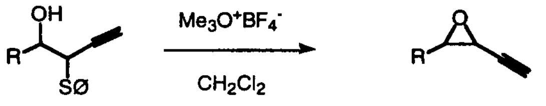
It is proposed that this mechanism proceeds by a non-chelated route and is governed by sterics. The two heteroatoms will align *anti*- to each other, eliminating electron–electron repulsion, as shown in both possible pathways. Following Scheme 1 along the left-hand pathway, it is noticed that the R groups of the aldehyde and indium species will be oriented *gauche*. Steric hindrance encountered via this pathway will raise the energy sufficiently to favor the right-hand pathway in which most steric interactions have been alleviated. Entries **15–18** and **23–26** are very interesting for more than just their witnessed stereocontrol as it is noted that the alkyne functional group is retained. Alkyne moieties have been shown to rearrange to allenes in C–C bond formations using metal promoters.[8] One exception was shown by Chan with bromo-alkyne systems.[8b] The sigma withdrawing capacity of a sulfur atom in α-chlorosulfide anions helps to stabilize the intermediate such that charge buildup is located in the propargyl position. As a result, rearrangement to an allene is not witnessed, allowing for isolation of the more versatile epoxy alkyne.

In an attempt to form *syn* products, indium chloride ($InCl_3$) was utilized during the initial phase of this reaction. It was thought a Lewis acid would complex with the reagents as shown in Scheme 2, favoring a mechanistic pathway that leads to a *syn* isomer. Reversal of stereoselectivity was indeed witnessed when $InCl_3$ was used as shown in entries **21**, **22**, **25**, and **26**. Selectivity of the propargyl system increased to 88:12, with the *syn* product favored under these conditions. It should be noted, once again, that no rearrangement to an allene is seen upon workup. The more synthetically versatile alkyne group is once again retained in our final product.[7]

Preservation of the alkyne functional group allowed use of our coupling products (entries **15–18** and **23–26**) as an entry into formation of epoxy alkynes which are prevalent in a variety of natural products of interest.[9] Conversion of the β-hydroxy thio ether to an epoxide was carried out using trimethyloxoniumtetrafluoroborate (Eq. 1), in good yields, furnishing the desired epoxide with no loss of stereocontrol.[10,11]



Scheme 2.



(1)

In conclusion, use of α-chloro sulfides allows for an easy method to form C–C bonds with good stereocontrol and further allows easy entry into formation of epoxy alkynes, synthetically useful building blocks in a variety of natural products.[9] Further studies including expansion of R-groups to test the versatility of this system are currently in progress.

Acknowledgements

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7. Diastereomeric products resulting from coupling of hexenal with the α-chlorosulfide were not separable by column chromatography, however, diastereomeric products resulting from coupling of benzaldehyde with the α-chlorosulfide were separable by column chromatography (hexanes:ethyl acetate 100:1) to give pure compounds.
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10. Example of reaction conditions for epoxy alkyne formation (benzaldehyde coupling product): To a stirring mixture of 80 mg (0.314 mmol) of the β-hydroxy thio ether in 5 mL of dichloromethane was added 52 mg (0.35 mmol) of trimethyloxoniumtetrafluoroborate. The solution was stirred at room temperature for 8 hours at which time thin layer chromatography revealed the absence of staring material. A solution of 7% sodium hydroxide (5 mL) was added with stirring for 15 minutes, the layers separated, and the organic layer dried over magnesium sulfate. The solvent was removed at room temperature and the crude material was purified via flash column chromatography (silica gel, 100:1 hexanes:ethyl acetate) to give a colorless oil. Yields were in the 65–80% range.
11. Previous use of trimethyloxoniumtetrafluoroborate: Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 3803.