Enantioselective Synthesis of Allenamides *via* Sulfimide [2,3]-Sigmatropic Rearrangement

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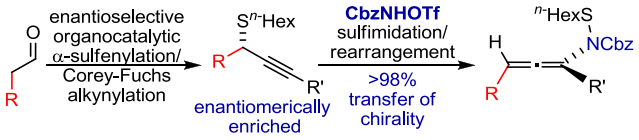
ABSTRACT



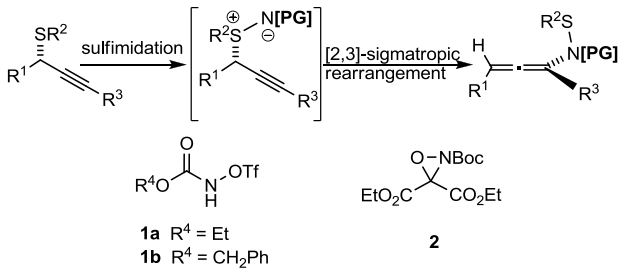
Abstract: Chiral allenamides are prepared with high levels of enantiomeric purity by [2,3]-sigmatropic rearrangement of propargylic sulfimides. The required branched propargylic sulfides are prepared by an enantioselective organocatalytic aldehyde alpha-sulfenylation followed by Corey-Fuchs alkynylation.

The chemistry of allenamides is currently attracting considerable interest[1] and several potentially useful synthetic transformations have been studied. For example, allenamides have been used in [2+2],[2,3] [3+2],[4] [4+2],[3,5] [4+3],[6] and Pauson-Khand[7] cycloadditions, radical cyclizations,[8] acid-[9] and gold-[10] catalyzed intramolecular cyclizations, and various processes proceeding *via* epoxidation.[11] Amongst several methods for allenamide synthesis,[12] the most popular is base-catalyzed isomerization of propargylic amines.[5b,13] This method has been used to make allenamides bearing a chiral auxiliary[5a,14] and has been adapted to give allenamides with an additional, axial element of chirality with high diastereoselectivities.[15] More recently, Hsung[16] and Trost[17] independently published copper-catalyzed coupling reactions of allenyl halides with various nitrogen nucleophiles. Hsung's work is notable as it includes the first example of enantiomerically enriched allenamides with respect to axial chirality without any external chiral elements. However, a limitation is the lack of methods for preparing the allenyl halide precursors in high ee.[18] It would therefore be beneficial to develop a general method of preparing axially chiral allenamides without the need for chiral auxiliaries.

In connection with an ongoing research program in our laboratory on the synthesis and reactions of sulfimides,[19-21] we recently[22] described the synthesis of allenamides via [2,3]-sigmatropic rearrangement[23] of propargylic sulfimides generated *in situ* by amination of the corresponding propargylic sulfides using the novel aminating agent **2**, developed in our laboratory (Scheme 1). This rearrangement was first reported by Tamura and Ikeda[24] who used the aminating agent $EtO_2CNHOTf$ **1a** and was more recently studied by Van Vranken[25] using an Fe(II)-catalyzed sulfimidation with $BocN_3$. Our previously published results,[22] as well as Van Vranken's work, suffered from the limitation that high yields could only be obtained for propargylic sulfides without further α-substitution. We attributed this limitation in our own work to competing N vs. O transfer from **2**. Furthermore, the possibility of central-to-axial transfer of chirality in this reaction has not been studied and would provide an efficient synthesis of axially chiral allenamides. Here we report new amination conditions which give good yields for the amination/ rearrangement of α-branched substrates as well as an asymmetric organocatalytic approach for the synthesis of the α-branched propargylic sulfide precursors, allowing an

effective route to enantiomerically enriched axially chiral allenamides.

Scheme 1. Synthesis of allenamides *via* sulfimidation/ [2,3]-sigmatropic rearrangement



In order to find higher-yielding conditions for allenamide synthesis, we began our investigation by exploring some of the most commonly used reagents for sulfimidation,[26] namely chloramine-T[27] and PhINTs.[28] Although we found a small improvement in the yield of allenamide from amination/rearrangement of challenging α-branched sulfide **3b** (e.g. Table 1: 31% **5b** for PhINTs (entry 5) c.f. 13% **4b** using **2** (entry 2)) these results were unsatisfactory. Noting Ikeda and Tamura's 1981 report[24] of the reagent $EtO_2CNHOTf$ **1a** for sulfimidation, in particular a single example of high yielding sulfimidation/[2,3]-sigmatropic rearrangement of phenyl propargyl sulfide, we felt that this type of reagent might suit our purposes if we could prepare an analogue with a synthetically more useful N-protecting group. Although we were not successful in preparing the Boc-protected variant, we were able to synthesize the Cbz analogue of this reagent using a similar method to the one reported by Ikeda and Tamura – preparation of the thallium salt of the corresponding *N*-hydroxycarbamate, followed by treatment with triflic anhydride. Although the CbzNHOTf **1b** thus prepared proved to be unstable to attempted purification, the crude material was found to effect efficient sulfimidation of a range of simple aryl and alkyl sulfides (see Supporting Information). It was then tested in the sulfimidation/ rearrangement of **3b**. Upon treatment with **1b** followed by aqueous sodium bicarbonate, the desired allenamide **6b** was obtained in 54% yield (Table 1, entry 6).

Encouraged by this result, a series of α-branched propargylic sulfides **3c-j** was prepared to establish the scope of the reaction. Pleasingly, we were able to isolate the corresponding allenamides **6c-i** in 47%-84% yield (Table 2). The results indicate that the more sterically demanding α-substituents such as isopropyl (entry 7) are tolerated. Several different acetylenic substituents could also be tolerated, including CH_2OH, methyl, phenyl and iodine. Interestingly, in the case of the acetylenic ester **3j**, the isolated product was the alkyne **7**, presumed to arise from isomerization of the initially formed allenamide.

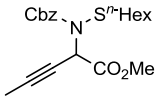


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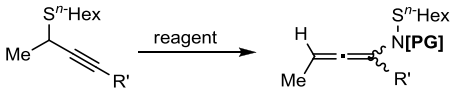
Table 1. Sulfimidation/rearrangement using different sulfimidation reagents.

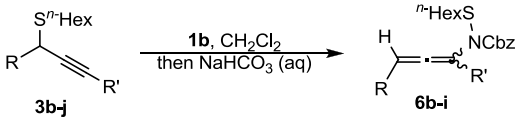


3 **4-6**

entry	**3**	R′	reagent	**[PG]**	**4-6**	yield (%)[a]
1	**a**	H	**2**[b]	Boc	**4a**	37[c]
2	**b**	Me	**2**[b]	Boc	**4b**	13[c]
3	**a**	H	Chloramine-T[d]	Ts	**5a**	49
4	**b**	Me	Chloramine-T[d]	Ts	**5b**	29
5	**b**	Me	PhINTs[e]	Ts	**5b**	31
6	**b**	Me	**1b**[f]	Cbz	**6b**	54

[a] After column chromatography. [b] CH_2Cl_2, -78 °C to rt. [c] see ref 22. [d] MeCN, -15 °C to 0 °C. [e] MeCN, $Cu^{I}OTf$·PhMe (2:1 complex) cat, rt [f] CH_2Cl_2, rt, 1 h, then $NaHCO_3$ (aq) 16 h.

Table 2. Synthesis of allenamides from α-branched propargylic sulfides, **3a-h**.



3b-j **6b-i**

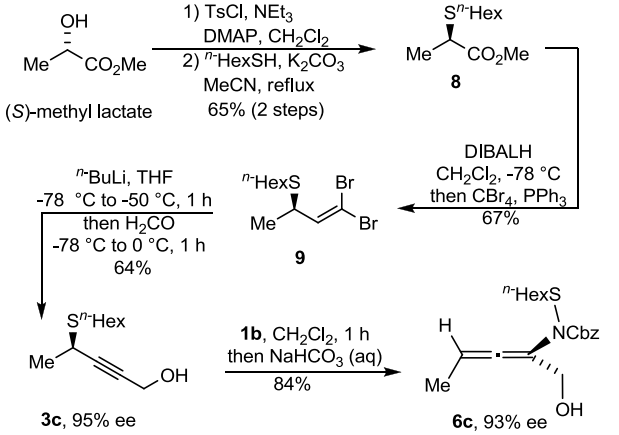
entry	R	R′	**3/6**	yield (%)[a]
1	Me	Me	**b**	54
2	Me	CH_2OH	**c**	84
3	Me	I	**d**	63
4	Me	Ph	**e**	47
5	Et	H	**f**	65
6	Et	CH_2OH	**g**	81
7	*i*-Pr	H	**h**	71
8	Bn	CH_2OH	**i**	74
9	Me	CO_2Me	**j**	-[b]

[a] After column chromatography. [b] Alkyne **7** was isolated in 48% yield; only a trace of the desired allenamide, **6j** was isolated.

In order to pursue the enantioselective synthesis of allenamides, a reliable method to prepare enantiomerically enriched propargylic sulfides was now required. We first developed a route starting from a chiral pool starting material, (*S*)-methyl lactate (Scheme 2). Tosylation and S_N2 displacement by hexanethiol gave methyl ester **8**.[20] To avoid racemization of the intermediate aldehyde, a one-pot reduction/alkynylation method was now considered necessary. The Corey-Fuchs synthesis was chosen as the most versatile alkynylation method since the resulting lithium acetylide may be quenched *in situ* with a variety of electrophiles. DIBAL-H reduction of **8** followed by *in situ* dibromoolefin formation[29] gave **9** in 67% yield. The dibromoolefin **9** was

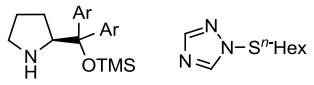
treated with *n*-BuLi followed by paraformaldehyde to give propargylic sulfide **3c**, which was of 95% ee according to HPLC analysis of the corresponding Mosher's ester. Reaction of enantiomerically enriched **3c** with **1b** under the same conditions as before gave **6c** with 93% ee (chiral HPLC), demonstrating >98% conservation of enantiomeric purity in the rearrangement.

Scheme 2. Synthesis of enantiomerically enriched allenamide **6c** from (*S*)-methyl lactate.



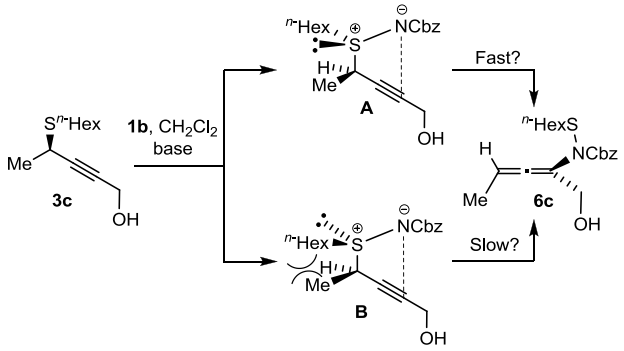
The absolute configuration of the allenamide product has not been determined unambiguously, but is assigned based on the expected suprafacial nature of the rearrangement, as observed for other propargylic [2,3]-sigmatropic processes.[30] Although a mixture of diastereomeric sulfimide intermediates **A** and **B** is possible due to the formation of a stereocenter at sulfur, the stereochemical course of the rearrangement is likely to be determined solely by the carbon chiral centre.[31] As depicted in Scheme 3, it might be expected that diastereomer **B**, which would suffer from a steric interaction between the α- and *S*-hexyl substituents in the reactive conformation, would undergo rearrangement more slowly than **A**. We have some evidence that diastereomeric sulfimide intermediates are indeed formed and undergo rearrangement at different rates. Thus, in the reaction of racemic sulfide **3b** with **1b**, ^{1}H NMR analysis of the reaction mixture before the addition of base indicated the presence of a ca. 3:2 mixture of diastereomeric azasulfonium salts. One hour after addition of base, ^{1}H NMR showed the desired allene product **6b** as well as the sulfimide, now as a single diastereomer. A prolonged reaction time after addition of base was required for full conversion to **6b**.

Although the demonstration of effective chirality transfer was pleasing, the chiral pool approach used for the asymmetric synthesis of propargylic sulfide **3c** is limited to α-methyl substitution. We therefore wished to develop a more general route. Prompted by our recently published preparation of allylic sulfides,[21] we envisaged organocatalytic α-sulfenylation of aldehydes followed by alkynylation. An adapted version of Jørgensen's[32] method using the prolinol organocatalyst **10** and the sulfur electrophile **11** was employed in the α-sulfenylation step.



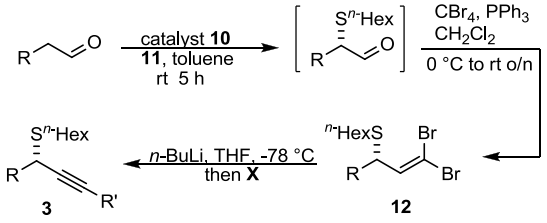
10 Ar = 3,5-$(CF_3)_2$-C_6H_3 **11**

Scheme 3.



For the alkynylation, the Corey-Fuchs reaction was again chosen – the dibromoolefination initially being performed *in situ* after the organocatalytic α-sulfenylation step to avoid the need to isolate the potentially racemizable intermediate α-sulfenyl aldehyde. Unfortunately, with this procedure, the yield of dibromoolefins **12a-c** was compromized by the formation of by-products (see Supporting Information). Better results were obtained by filtering the sulfenylation reaction mixture over silica prior to the addition of the dibromoolefination reagents, and yields of 52-59% could be achieved (Table 3). Treatment of **12a-c** with *n*-BuLi and an electrophile (water or paraformaldehyde) then gave **3f-i** in 50-83% yield.

Table 3. Synthesis of enantiomerically enriched sulfides **3f-i** via organocatalytic α-sulfenylation of aldehydes

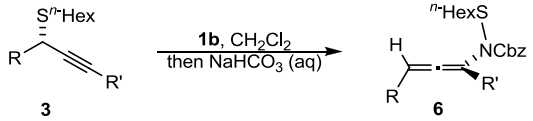


entry	R	**12**	yield (%)[a,b] **12**	**X**	R′	**3**	yield (%)[b] **3**
1	Et	**a**	52	H_2O	H	**f**	62
2	Et	**a**	52	CH_2O	CH_2OH	**g**	83
3	*i*-Pr	**b**	59	H_2O	H	**h**	72
4	Bn	**c**	54	CH_2O	CH_2OH	**i**	50

[a] Reaction mixture filtered over silica prior to dibromoolefination step. [b] Yield after column chromatography.

These enantiomerically enriched propargylic sulfides **3f-i** were then subjected to our sulfimidation conditions and the enantiomeric purity of the resulting chiral allenamides **6f-i** determined by chiral HPLC (Table 4). The ee levels (81-89%) were good, although slightly lower than usually observed in organocatalytic α-sulfenylation of aldehydes.[21, 32] In view of the high levels of chirality transfer seen for the chiral pool-derived substrate **3c**, it is likely that this reflects the tendency of the intermediate α-sulfenyl aldehydes to undergo racemization rather than a loss of enantiomeric purity during the rearrangement.

Table 4. Sulfimidation/rearrangement of enantiomerically enriched propargylic sulfides **3**.



entry	R	R′	3/6	yield (%)[a]	ee (%)[b]
1	Et	H	**f**	76	87
2	Et	CH_2OH	**g**	83	88
3	^{i}Pr	H	**h**	71	89
4	Bn	CH_2OH	**i**	74	81

[a] After column chromatography. [b] Determined by chiral HPLC.

In conclusion, we have demonstrated for the first time that chiral propargylic sulfides undergo amination/[2,3]-sigmatropic rearrangement with a high level of chirality transfer, affording enantiomerically enriched allenamides. As part of the work, we developed the novel sulfimidation reagent **1b** bearing a synthetically useful carbamate protecting group, as well as a new approach for the synthesis of the propargylic sulfide precursors using organocatalysis. Further development of the method and study of synthetic applications of the allenamide products is currently underway.

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Supporting Information Available General experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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