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Highly Stereoselective Synthesis of Terminal Chloro-Substituted Propargylamines and Further Functionalization

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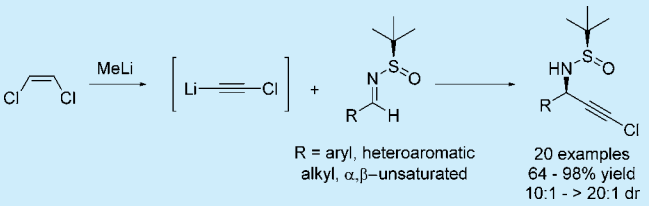
Supporting Information

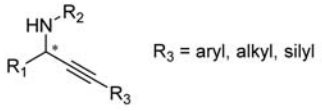
ABSTRACT: The highly stereoselective addition of lithiated chloroacetylene, derived *in situ* from *cis*-1,2-dichloroethene and methyl lithium, to Ellman chiral *N*-*tert*-butanesulfinyl imines is reported. The reaction proceeds in high yield (up to 98%) and with excellent diastereoselectivity (up to >20:1) for a variety of aryl, heteroaromatic, alkyl, and α,β-unsaturated imine substrates. Transformations of the terminal chloro-substituted propargylamine products are described in which lithium−halogen exchange yields nucleophilic acetylides that can be quenched to yield terminal alkynes or intercepted by carbon electrophiles.



The asymmetric addition of chemically diverse alkynes to imines is an important goal in synthetic organic chemistry due to the utility of optically active propargylamines in the synthesis of a variety of natural products, heterocycles, and bioactive compounds.[1] In light of their synthetic potential, many strategies for the stereoselective synthesis of propargylamines have been developed. Featuring predominately in this methodology are several classes of catalytic systems including copper-catalyzed alkyne additions to imines in the presence of chiral tridentate ligands (e.g., Pybox)[2] or chiral Bronsted acids;[3] copper-catalyzed three-component couplings of aldehydes, amines, and alkynes in the presence of chiral ligands;[4] and the addition of zinc acetylides to imines in the presence of chiral amino alcohol and BINOL-based ligands.[5] In addition to asymmetric catalysis, diastereoselective addition of metal acetylides to chiral imines is also a robust method for the synthesis of chiral propargylic amines.[6] In particular the addition of lithium acetylide,[7] alkynyl Grignard,[8] and aluminum acetylide[9] reagents to Ellman *N*-*tert*-butanesulfinyl (*N*-*t*-BS) imines has been studied extensively and the utility of this approach has been demonstrated in the synthesis of complex molecules.[8] Alternate strategies to access optically active propargylamines including kinetic resolution,[10] biocatalytic syntheses,[11] and radical alkynylation[12] have also been recently developed.

To date, optically active propargylamines prepared using these methods bear aryl, alkyl, or silyl alkyne substituents (Figure 1). We envisioned that propargylic amines **1** bearing an acetylenic halogen constitute a useful class of propargylamines as the halogen provides access to additional modes of acetylene reactivity. Indeed, terminal halo-substituted propargylamines have been used in route to more complex molecular structures;[13] however, preparation of these substrates requires halogenation of propargylamines bearing a terminal alkyne which in turn must be prepared from a terminal acetylene precursor[13] (Figure 1). Thus, a direct method for the stereoselective synthesis of terminal halo-substituted propargylamines would constitute a significant advance in making these molecules more readily accessible. In light of the absence of such a method for the preparation of terminal halo-substituted propargylamines (racemic or asymmetric), and the synthetic potential of this class of propargylamines, we have developed a highly stereoselective method for the synthesis of these molecules and have initiated investigations into their synthetic utility.

Chiral propargylamines directly accessible with current methodology.



Current access to terminal halo-substituted propargylamines.

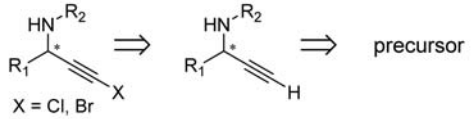


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Figure 1. Directly accessible classes of chiral propargylamines and current method to access terminal halo-substituted propargylamines.

The addition of halogenated acetylenes to imine electrophiles is hampered by the limited commercial availability and volatility of the haloacetylenes, as only chloroacetylene is commercially available and is a gas at room temperature. However, reaction of commercially available 1,2-dihaloethenes with organolithium reagents efficiently generates lithiated haloacetylides *in situ*[14a] via E2 elimination and deprotonation as shown in Scheme 1. As lithiated haloacetylides generated in this manner have been

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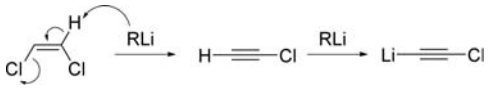
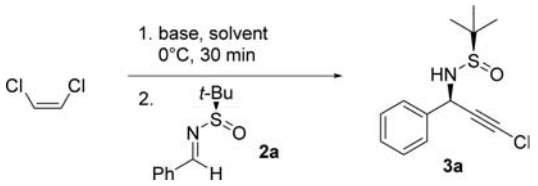
Scheme 1. *In Situ* Generation of Lithiated Chloroacetylide



shown to be effective nucleophiles with carbonyl electrophiles,[14] we envisioned that this approach could be applied in the diastereoselective addition to chiral imines. Due to the good diastereoselectivities observed in the addition of lithium acetylides to Ellman *N*-*t*-BS imines (up to >99:1 dr)[7] and the success of a similar strategy by Poisson and co-workers in the addition of lithiated ynol ethers (derived from dichloroenol ethers) to *N*-*t*-BS imines,[7b] we chose to explore the use of these chiral imines to access optically active terminal halo-substituted propargylamines.

We began our studies by testing the addition of lithiated chloroacetylene generated in Et_2O from *cis*-1,2-dichloroethene[15] and MeLi (1.6 M in Et_2O) at 0 °C[14a] to phenyl *N*-*t*-BS imine **2a** as shown in Table 1. We were pleased to find that

Table 1. Optimization of Reaction Conditions for Addition of Lithium Chloroacetylide to Ellman Imine 2a[a]



entry	base	solvent	yield (%)[b]	dr[c]
1	MeLi[d]	Et_2O	81	>20:1
2	MeLi[d]	toluene	71	>20:1
3	MeLi[d]	THF	66	15:1
4	MeLi[d]	hexanes	37[e]	>20:1
5	MeLi[d]	CH_2Cl_2	–	–
6	**MeLi[d]**	**1,4-dioxane**	**95**	**>20:1**
7	*n*-BuLi[f]	1,4-dioxane	89	>20:1
8	LDA[g]	1,4-dioxane	58	>20:1
9	LiHMDS[h]	1,4-dioxane	57	15:1
10	LiHMDS[i]	1,4-dioxane	92	>20:1
11	MeLi[d,j]	1,4-dioxane	92	>20:1
12	MeLi[d,k]	1,4-dioxane	trace	N.D.

[a]Reaction conditions: *cis*-1,2-dichloroethene (1.5 mmol) dissolved in solvent (1.0 mL) and cooled to 0 °C. A solution of base (1.5 mmol) was added, and reaction was stirred at 0 °C for 30 min to generate lithiated chloroacetylide. A solution of imine **2a** (0.5 mmol) in solvent (1.0 mL) was added, and the reaction was stirred for 1.5 h allowing it to warm to rt. [b]Isolated yield. [c]Determined by analysis of crude ^{1}H NMR spectra. [d]1.6 M soln in Et_2O. [e]3 h, 45% yield. [f]2.5 M soln in hexanes. [g]Prepared from diisopropylamine (1.5 mmol) and *n*-BuLi (1.5 mmol, 2.5 M soln in hexanes) in 1,4-dioxane (1 mL). [h]1.0 M soln in THF. [i]1.0 M soln in hexanes. [j]2-fold dilution: lithiated chloroacetylide formed in 2.0 mL of 1,4-dioxane, and imine **2a** was added in 2.0 mL of 1,4-dioxane. [k]Solution of imine (0.5 mmol) precomplexed with $BF_3{\cdot}Et_2O$ (0.55 mmol).

the reaction proceeded in good yield (81%) and excellent stereoselectivity (dr >20:1) with complete consumption of the imine within 1.5 h. The stereochemistry of the amine stereocenter was assigned in analogy to the accepted model for lithium acetylide additions to *N*-*t*-BS imines[7] and was later confirmed through comparison of an analog derived from a terminal chloro-substituted propargylamine to a known compound.[16] Screening reaction solvents revealed that THF decreased the diastereoselectivity of the reaction (entry 3) while hexanes severely diminished reactivity (entry 4). CH_2Cl_2 was found to be an unsuitable solvent (entry 5). Excellent yield (95%) and diastereoselectivity (>20:1) were achieved with 1,4-dioxane (entry 6).

Having identified 1,4-dioxane as the optimal solvent several bases were tested. Use of *n*-BuLi (2.5 M in hexanes, entry 7) afforded similar results to MeLi, while use of LDA significantly diminished the isolated yield (entry 8). LiHMDS, shown to be an effective base in the addition of lithium acetylides to *N*-*t*-BS imines,[7a] was also tested. LiHMDS (1.0 M in THF) negatively affected diastereoselectivity (entry 9); however, LiHMDS (1.0 M in hexanes) displayed high stereoselectivity and good yield (entry 10). Dilution of the reaction mixture by 2-fold (entry 11) did not significantly impact reactivity or diastereoselectivity.

The use of $BF_3{\cdot}OEt_2$ as a Lewis acid additive was also tested, as this has been shown to reverse the diastereoselectivity of the reaction in related additions with the reaction presumably proceeding through an open transition state.[7b,c] However, use of $BF_3{\cdot}OEt_2$ with our optimized conditions resulted in the formation of only a trace amount of product (entry 12). Finally, we also explored whether the optimal reaction conditions in entry 6 could be utilized with 1,2-dibromoethene in order to access terminal bromo-substituted propargylamines. Unfortunately, no desired product was obtained when 1,2-dibromoethene (commercially available as a mixture of *cis* and *trans* isomers) was used.

Having identified the use of *cis*-1,2-dichloroethene and MeLi in 1,4-dioxane (entry 6) as the optimal reaction conditions we then explored the substrate scope of the transformation as shown in Table 2. Good to excellent yields (64−98%) and diastereoselectivities (10:1−>20:1) were obtained for a range of aromatic, heteroaromatic, alkyl, and α,β-unsaturated *N*-*t*-BS imines (Table 2). For aryl derivatives the reaction tolerated electron-donating and -withdrawing substituents and substitution at the *ortho*-, *meta*-, and *para*-positions. Interestingly, lower diastereoselectivities were observed for *ortho*-substituted phenyl derivatives bearing a chlorine or methoxy group (entries 1 and 7), but this effect was not observed with the *ortho*-methyl group (entry 5). Heterocycles were also tolerated in the reaction (entries 9 and 10), although furyl derivative **3k** was obtained with the lowest observed diastereoselectivity (10:1, entry 10). It is possible that imines **2b**, **2h**, and **2k** exhibit lower diastereoselectivity due to competing coordination of lithium chloroacetylide by the proximal 2-position heteroatom, which may partially disrupt the chair transition state responsible for the high stereoselectivity in the other products.[17]

Reaction of alkyl *N*-*t*-BS imines proceeded in uniformly high yield and dr for straight-chain, branched, and cyclic substrates (entries 11 to 18) with the exception of isobutyl compound **3n** (entry 13). For this substrate, diminished diastereoselectivity (14:1) and significant side product formation were observed in analysis of the crude ^{1}H NMR. Finally, reactions of α,β-unsaturated *N*-*t*-BS imines were also found to proceed with good selectivity and yield (entries 19 and 20). Pleasingly, the reaction was scalable and could be performed on gram scale (5 mmol imine) for **3a** and **3l** with no erosion of diastereoselectivity and comparable yields to those reported in Tables 1 and 2 (93% and 88% respectively).

Having determined the scope of the reaction, we next turned our attention to exploring the utility of the terminal chloro-substituted propargylamines. Treatment with *n*-BuLi (2.5

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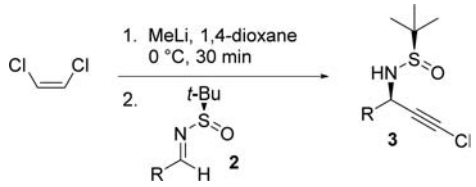
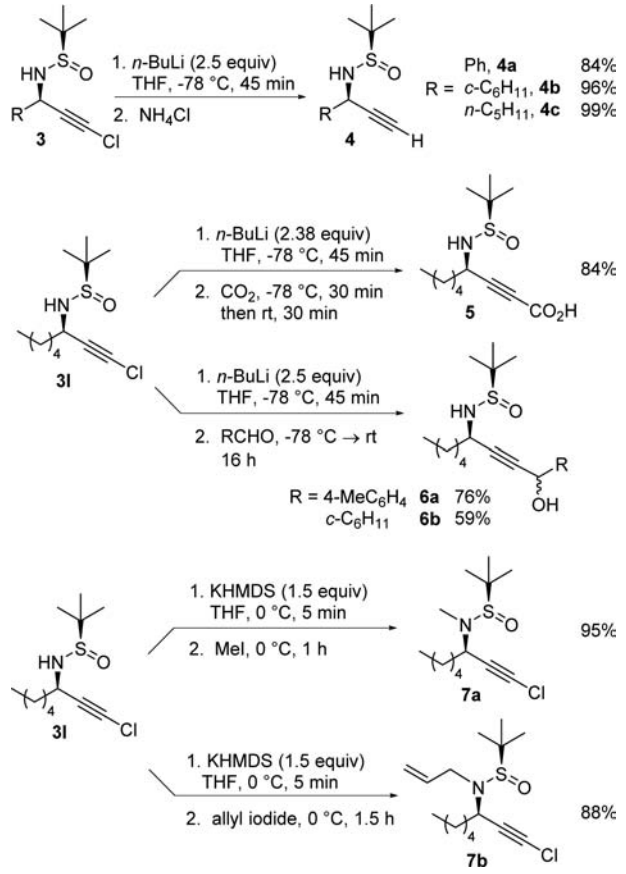
Table 2. Substrate Scope for Addition of Lithium Chloroacetylide to Ellman Imines 2[a]



entry	R	product	yield (%)[b]	dr[c]
1	2-ClC_6H_4	**3b**	86	14:1
2	3-ClC_6H_4	**3c**	71	19:1
3	4-ClC_6H_4	**3d**	64	>20:1
4	4-FC_6H_4	**3e**	80	>20:1
5	2-MeC_6H_4	**3f**	90	>20:1
6	4-MeC_6H_4	**3g**	82	>20:1
7	2-$MeOC_6H_4$	**3h**	84	13:1
8	4-$MeOC_6H_4$	**3i**	74	>20:1
9	3-thienyl	**3j**	75	>20:1
10	2-furyl	**3k**	77	10:1
11	*n*-C_5H_{11}	**3l**	82	>20:1
12	*n*-C_7H_{15}	**3m**	98	>20:1
13	^{i}Bu	**3n**	73	14:1
14	^{i}Pr	**3o**	83	>20:1
15	^{t}Bu	**3p**	91	19:1
16	*c*-C_6H_{11}	**3q**	93	>20:1
17	*c*-C_5H_9	**3r**	90	>20:1
18	$PhCH_2CH_2$	**3s**	95	>20:1
19	PhCH=CH	**3t**	77	19:1
20	MeCH=CH	**3u**	96	>20:1

[a]Reaction conditions from Table 1, entry 6. [b]Isolated yield. [c]Determined by analysis of crude ^{1}H NMR spectra.

Scheme 2. Transformations of Terminal Chloro-Substituted Propargylamines



equiv) at −78 °C effected lithium−halogen exchange to afford an intermediate dianion. Quenching with saturated aqueous NH_4Cl led to the corresponding terminal acetylenes in good yield (84−99%, Scheme 2). Compound **4b** matched the reported compound[16] in all aspects (^{1}H NMR, ^{13}C NMR, optical rotation), allowing verification of the stereochemistry at the propargylic carbon. Notably this approach to optically active terminal propargylamines serves as an alternative among a handful of methods providing access to these substrates.[18]

More interestingly, the intermediate lithium acetylide could be intercepted with carbonyl electrophiles such as CO_2 or aldehydes to furnish the corresponding carboxylic acid (**5**) or propargylic alcohol derivatives (**6a**/**6b**) in moderate to good yield (Scheme 2). This strategy is a significant improvement over previous methods to access these classes of compounds which typically rely on silyl acetylenes as the terminal acetylene surrogate and require separate deprotection and deprotonation steps to generate the acetylene nucleophile.[19] Considering that the yields reported for deprotonation of terminal propargylamines and addition to aldehydes are moderate (typically ∼50%),[19] the use of chloro-substituted propargylamines represents an attractive improvement over current methods used in the synthesis of molecules such as **6a** and **6b**. Finally, we have demonstrated that the acetylenic chlorine can be left intact while selectively alkylating the nitrogen atom as demonstrated in derivatives **7a** and **7b**. Substrates similar to **7b** represent an important scaffold for cyclization reactions,[20] and the acetylenic halogen is often desired for these substrates[13a] and in related cyclizations.[21]

In summary we have developed a method for the direct stereoselective synthesis of terminal chloro-substituted propargylamines. Notably the method uses commercially available materials, operates at easily accessible temperatures (0 °C), is scalable (5 mmol scale), and is applicable for a range of aromatic, heteroaromatic, alkyl, and *α,β*-unsaturated *N*-*t*-BS imines. We have also demonstrated the useful reactivity of this class of propargylamines, showing efficient access from these substrates to terminal acetylenes, carboxylic acid and propargylic alcohol derivatives, and *N*-alkylated compounds maintaining the acetylenic chlorine. Studies toward developing methods for the stereoselective synthesis of terminal bromo-substituted propargylamines and further applications of this intriguing class of molecules are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02408.

Proposed transition state explaining stereoselectivity, experimental procedures and characterization data, crude ^{1}H NMR spectra for dr determination, and ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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