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Asymmetric Synthesis of α,α-Dibranched Propargylamines by Acetylide Additions to *N-tert*-Butanesulfinyl Ketimines

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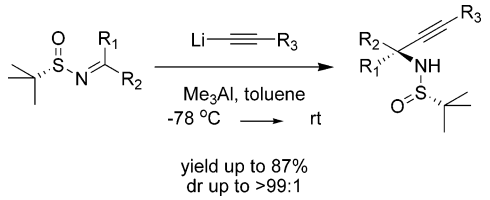

Addition of lithium acetylides prepared from 1-pentyne, phenylacetylene, and trimethylsilylacetylene to diverse *N-tert*-butanesulfinyl ketimines affords a range of α,α-dibranched propargyl sulfinamides in generally good yields (up to 87%) and with high diastereoselectivities (up to >99:1). Acidic cleavage of the *tert*-butanesulfinyl group provides the free α,α-dibranched propargylamines.

Propargylamines are important intermediates in the synthesis of many drugs, drug leads, and natural products,[1] and therefore, considerable effort has been dedicated to the development of efficient asymmetric methods for their construction. Although a number of efficient approaches for the synthesis of enantiomerically enriched α-branched propargylamines have been reported,[2,3] very few methods are applicable to the asymmetric synthesis of α,α-dibranched propargylamines and these are limited to a narrow set of structural types.[4−6] In the context of the synthesis of potent, nonpeptidic cathepsin S inhibitors, we required efficient entry to enantiomerically pure α,α-dibranched propargylamines.[5] Here, we report a general method for the asymmetric synthesis of these compounds by the addition of lithium acetylides to *N*-sulfinyl ketimines with uniformly high diastereoselectivity.[7]

We previously reported the asymmetric synthesis of tertiary carbinamines by the dropwise addition of the Me_3Al complex of *N-tert*-butanesulfinyl ketimines to solutions of alkyl-, vinyl-, and aryllithiums in hydrocarbon solvents.[7,8] Accordingly, *N-tert*-butanesulfinyl ketimines (**1**) were first prepared in good yields according to the previously described method (Scheme 1).[9] The 1,2-addition of lithium acetylides to *N*-sulfinyl ketimines (**1**) was performed by dropwise addition of a −78 °C solution of **1** and Me_3Al in toluene to a solution of in situ generated lithium acetylide precooled to −78 °C (Scheme 2). Uniformly high diastereoselectivities were observed for a broad range of ketimine and acetylide inputs, and additions to a majority of the *N*-sulfinyl ketimines proceeded in good yields (Table 1). For those substrate combinations where a minor diastereomer was obtained, purification by chromatography readily provided the diastereomerically pure major isomer. The stereochemical assignment for the major diastereomer of the addition reactions is based on an X-ray crystal structure of inhibitor **3** (Figure 1) that was cocrystallized with the cysteine protease cathepsin S at 1.5 Å resolution.[10] This assignment is consistent with the sense of induction observed for the addition of alkyl- and

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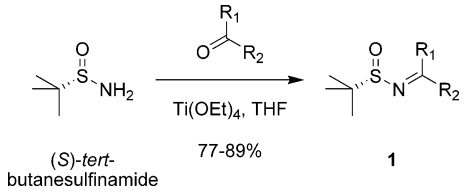
TABLE 1. 1,2-Additions of Alkynyllithiums to *N*-Sulfinyl Ketimines 1

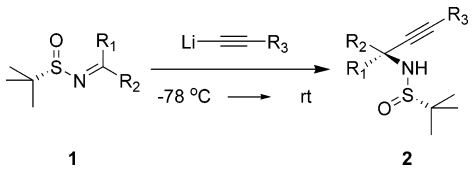
	N-sulfinyl ketimine **1**			alkynyllithium addition		propargyl sulfinamide **2**		
entry	compound	R_1	R_2	R_3	conditions	compound	dr	yield (%)
1	**1a**	methyl	*iso*-propyl	*n*-propyl	toluene w/Me_3Al	**2a**	>99:1[a]	71[b]
2	**1a**	methyl	*iso*-propyl	phenyl	toluene w/Me_3Al	**2b**	95:5[a]	74[b]
3	**1a**	methyl	*iso*-propyl	TMS	toluene w/Me_3Al	**2c**	>99:1[a]	87[b]
4	**1b**	methyl	*tert*-butyl	TMS	toluene w/Me_3Al	**2d**	>99:1[a]	81[b]
5	**1c**	methyl	cyclohexyl	TMS	toluene w/Me_3Al	**2e**	>99:1[a]	73[b]
6	**1d**	methyl	*trans*-4-methylcyclohexyl	TMS	toluene w/Me_3Al	**2f**	>99:1[a]	80[b]
7	**1e**	methyl	*cis*-4-methylcyclohexyl	TMS	toluene w/Me_3Al	**2g**	97:3[a]	85[b]
8	**1f**	ethyl	cyclohexyl	TMS	toluene w/Me_3Al	**2h**	90:10[c]	80[b]
9	**1f**	ethyl	cyclohexyl	TMS	toluene	**2h**	89:11[c]	60[b]
10	**1g**[d]	methyl	*n*-butyl	TMS	toluene w/Me_3Al	**2i**	95:5[a]	46[b]
11	**1h**	methyl	phenyl	TMS	toluene w/Me_3Al	**2j**	86:14[c]	20[e]
12	**1h**	methyl	phenyl	TMS	toluene	**2j**	89:11[c]	11[e]
13	**1h**	methyl	phenyl	TMS	THF	**2j**	ND	<5[e]

[a] Diastereomeric ratio was determined by HPLC assay. [b] Isolated yield of diastereomerically and analytically pure material after chromatography. [c] Diastereomeric ratio was determined by NMR analysis. [d] *N*-Sulfinyl ketimine **1g** exists as a 5:1 mixture of *E* and *Z* isomers. [e] Yield determined by NMR analysis using hexamethylbenzene as an external standard.

SCHEME 1



SCHEME 2



aryllithium reagents to *N*-sulfinyl ketimines.[8] Inhibitor **3** was prepared by the reaction of a derivative of propargylamine **2c** and an α-azido acid via a copper-catalyzed 1,3-dipolar cycloaddition.

n-Propylethynyllithium and phenylethynyllithium were added to *N*-sulfinyl ketimine **1a** generating the respective propargyl sulfinamide products **2a** and **2b**, in good yield and with high diastereoselectivity (Table 1). (Trimethylsilyl)ethynyllithium was also added to a number of *N*-sulfinyl ketimines with good yields and diastereoselectivities seen for a range of substrates. The α-branched isopropyl (**1a**), *tert*-butyl (**1b**), cyclohexyl (**1c**), and *trans*-4-methylcyclohexyl (**1d**) *N*-sulfinyl ketimines provided the desired products in high yields and without any detectable minor diastereomer (entries 4−7). The α-branched *cis*-4-methylcyclohexyl *N*-sulfinyl ketimine **1e** also reacted in good yield and with high diastereoselectivity to give propargyl sulfinamide **2g**. Interestingly, the minor diastereomer proved to be propargyl sulfinamide **2f** on the basis of NMR and HPLC comparisons.

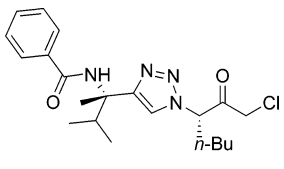
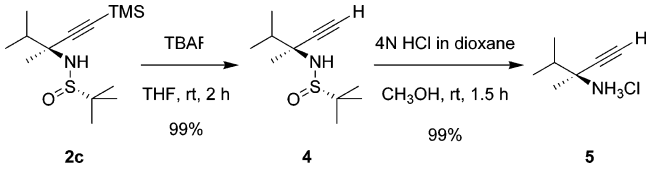


FIGURE 1. Cathepsin S inhibitor derived from propargyl sulfinamide **2c**.

SCHEME 3



This minor byproduct presumably formed by competitive and reversible α-deprotonation of the *N*-sulfinyl ketimine to give the thermodynamically favored *trans*-4-methylcyclohexylsulfinyl ketimine epimer followed by acetylide addition.

Additionally, the more sterically hindered *N*-sulfinyl ketimine **1f** reacted in good yield with only a modest drop in diastereoselectivity to give propargyl sulfinamide **2h**. In this example, we also see the effect of the Me_3Al Lewis acid on conversion to product. Although only a modest drop in the diastereoselectivity was observed without the Me_3Al additive, a significant drop in the yield occurred (entry 8 vs entry 9).

An anomalously low yield was seen for the non-α-branched *N*-sulfinyl ketimine **1g** and the aryl-substituted *N*-sulfinyl ketimine **1h**, with competitive deprotonation to form the metalloenamine likely hampering the reaction progress as evidenced by the large amount of recovered starting *N*-sulfinyl ketimine upon reaction workup. Neither removal of Me_3Al (entry 12) nor use of THF as solvent (entry 13) improved the yield of the product.

Reaction of the trimethylsilyl-functionalized propargyl sulfinamide products with tetrabutylammonium fluoride (TBAF) readily provides the synthetically useful terminal acetylenes as demonstrated for the conversion of sulfinamide **2c** to the terminal acetylene **4** in near quantitative yield (Scheme 3). The *N*-*tert*-butanesulfinyl group also may be cleaved under acidic methanolysis conditions to give the free amine hydrochloride salt in near quantitative yield, as illustrated for the conversion of **4** to the propargylamine hydrochloride salt **5** (Scheme 3).

In conclusion, additions of acetylide nucleophiles to *N*-*tert*-butanesulfinyl ketimines provide a general and efficient method for the asymmetric synthesis of α,α-dibranched propargylamines, with good yields and high diastereoselectivities observed for a range of acetylides and *N*-sulfinyl ketimine starting materials.

(10) PDB ID: 2H7J. Also see: Patterson, A. W.; Wood, W. J. L.; Ellman, J. A. *J. Med. Chem.*, submitted.

Experimental Section

General Procedure for the 1,2-Addition of Alkynyllithiums to *N*-*tert*-Butanesulfinyl Ketimines with Me_3Al. To a 0.85 M solution of alkyne (3.0−3.5 equiv) in toluene at −78 °C was added butyllithium (2.2 equiv) as a solution in hexanes. The resulting solution was stirred for ca. 15 min before a stirred −78 °C toluene solution of *N*-sulfinyl ketimine **1** (1.0 equiv, 0.35 M) and Me_3Al (1.2 equiv) was slowly added via cannula. Stirring was continued at −78 °C for 2 h, and then the solution was allowed to warm to room temperature over 4 h. Stirring was continued at room temperature for 10−30 h before the mixture was cooled in an ice−water bath. Saturated aqueous Na_2SO_4 was added dropwise until gas was no longer evolved upon addition. The slurry was filtered, and the filter cake was rinsed with EtOAc. The filtrate was dried (Na_2SO_4), filtered, and concentrated. The diastereomeric ratio was determined by HPLC or by NMR with hexamethylbenzene as an external standard. If the starting *N*-sulfinyl ketimine was not fully reacted, the crude material was dissolved in CH_3OH and a 1 M aqueous solution of CH_3CO_2H (2:1 ratio) was added. The solution was stirred at room temperature for 8−12 h to hydrolyze the *N*-sulfinyl ketimine. The resulting slurry was then concentrated to remove the CH_3OH, and brine was added. The slurry was then extracted three times with ethyl acetate, dried with Na_2SO_4, filtered, and concentrated. Chromatography afforded the diastereomerically pure propargyl sulfinamides **2**.

(*Ss*,*S*)-(+)-*N*-(1-Isopropyl-1-methyl-3-trimethylsilanyl-prop-2-ynyl)-2-methylpropanesulfinamide (2c). The general procedure was followed with a mixture of 13.0 mL of (trimethylsilyl)ethyne (93.6 mmol), 36.0 mL of butyllithium (68.6 mmol, 1.9 M in hexanes), 5.90 g of *N*-sulfinyl ketimine **1a** (31.2 mmol), and 3.55 mL of Me_3Al (37.0 mmol) in 193 mL total volume of toluene. The diastereomeric ratio was determined to be >99:1 by HPLC assay. Hydrolysis followed by purification by silica gel chromatography (hexane/ethyl acetate = 2:1) provided diastereomerically pure propargyl sulfinamide **2c** (7.81 g, 87%) as a white solid: mp 64−66 °C; $[\alpha]^{20}_D = +54.0$ (*c* 1.0, $CHCl_3$); IR 758, 839, 1010, 1025, 1248, 2174, 2957, 3103 cm^{-1}; ^1H NMR (400 MHz) δ 0.15 (s, 9H), 1.00 (d, $J = 6.8$, 3H), 1.03 (d, $J = 6.8$, 3H), 1.20 (s, 9H), 1.43 (s, 3H), 1.93 (septet, $J = 6.8$, 1H), 3.22 (s, 1H); ^{13}C NMR (100 MHz) δ −0.2, 17.1, 17.8, 22.5, 25.3, 38.2, 56.1, 57.7, 88.9, 108.0. Anal. Calcd for $C_{14}H_{29}NOSSi$: C, 58.48; H, 10.17; N, 4.87. Found: C, 58.77; H, 10.37; N, 5.13.

(*Ss*, *S*)-(+)-*N*-(1-Isopropyl-1-methyl-prop-2-ynyl)-2-methylpropanesulfinamide (4). To a 0.1 M solution of propargyl sulfinamide **2c** (5.10 g, 17.7 mmol) in 180 mL of THF cooled in an ice−water bath was added 16.8 g of TBAF (53.2 mmol). The solution was stirred for 2 h at room temperature, and then the solution was poured into saturated aqueous NH_4Cl with rapid stirring. The resulting suspension was transferred to a separatory funnel and extracted three times with Et_2O. The combined organic portions were dried (Na_2SO_4), filtered, and concentrated. Silica gel chromatography (hexane/ethyl acetate = 1:1) provided propargyl sulfinamide **4** (3.77 g, 99%) as a white solid: mp 98−100 °C; $[\alpha]^{20}_D = +72.1$ (*c* 1.0, $CHCl_3$); IR 1015, 1031, 1382, 2104, 2953, 3210, 3262 cm^{-1}; ^1H NMR (400 MHz) δ 0.92 (d, $J = 6.8$, 3H), 0.95 (d, $J = 6.8$, 3H), 1.10 (s, 9H), 1.37 (s, 3H), 1.82 (septet, $J = 6.8$, 1H), 2.37 (s, 1H), 3.18 (s, 1H); ^{13}C NMR (100 MHz) δ 16.9, 17.4, 22.3, 25.0, 38.1, 55.8, 56.6, 72.8, 85.8. Anal. Calcd for $C_{11}H_{21}NOS$: C, 61.35; H, 9.83; N, 6.50. Found: C, 61.52; H, 10.13; N, 6.64.

(*S*)-(+)-1-Isopropyl-1-methyl-prop-2-ynylamine Hydrochloride (5). To a 0.15 M solution of propargyl sulfinamide **4** (3.77 g, 17.5 mmol) in 120 mL of CH_3OH was added 13.0 mL of 4 M HCl in 1,4-dioxane (52.5 mmol). The solution was stirred for 1.5 h and concentrated to yield propargylamine **5** (2.55 g, 99%) as a white solid: dec 245 °C; $[\alpha]^{20}_D = +2.1$ (*c* 1.0, CH_3OH); IR 556, 708, 1385, 1513, 1608, 2117, 2873 (br), 3221 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.93 (d, $J = 6.8$, 3H), 0.97 (d, $J = 6.8$, 3H), 1.60 (s, 3H), 2.10 (septet, $J = 6.8$, 1H), 3.30 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 17.8, 17.9, 24.5, 37.7, 56.9, 78.1, 81.5. Anal. Calcd for $C_7H_{14}NCl$: C, 56.94; H, 9.56; N, 9.49. Found: C, 57.01; H, 9.79; N, 9.27.

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Supporting Information Available: General experimental methods; synthesis and compound characterization for *N*-sulfinyl ketimines **1**; and specific reaction conditions and complete compound characterization of propargyl sulfinamides **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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