Doroszuk J., Musiejuk M., Ponikiewski Ł., Witt D., Convenient and Efficient Diastereoselective Preparation of Functionalized Z -Alkenyl Sulfides, EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, Vol. 2018, Iss. 45 (2018), pp. 6333-6337,

Convenient and efficient diastereoselective preparation of functionalized *Z*-alkenyl sulfides

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Abstract: We have developed an efficient and convenient regio- and stereoselective reduction of the alkynyl sulfides with pinacolborane in the presence of copper (I) chloride to produce (*Z*)-alkenyl sulfides in good and very good yields. The functionalized alkynyl sulfides are readily available based on the reaction of lithium acetylides with thiotosylates under mild conditions.

Introduction

The continuously increasing range of applications for organosulfur compounds has expanded into different fields, from organic synthesis to material science.[1] Among *S*-containing building blocks, one unique functional group is alkynyl sulfides, which contain two carbon atoms connected by a triple bond that are directly substituted with a sulfur atom. The reactivity of this functionality can be useful in organic synthesis. Alkynes have been applied in bulk chemical syntheses based on acetylene gas,[2] in the stereoselective construction of the carbon backbones of natural products[3] and in the metal complex-catalyzed cyclization reactions.[4] In short, alkynyl sulfides can bring together the advantages of sulfur atoms with the exceptionally rich chemistry of alkynes.

Reported methods for the preparation of alkynyl sulfides include reactions based on transition-metal catalysts, such as the copper-catalyzed carbon sulfur coupling between terminal alkynes and disulfides[5] or the use of catalytic rhodium for C-S bond formation by C-H and S-S bond metathesis[6] (Scheme 1). Both alkyne and thiol groups are inherently nucleophilic, thus the umpolung of one of them is necessary for the construction of an alkynyl sulfide. This often requires the use of unselective reagents and harsh reaction conditions, which are not always compatible with sensitive functional groups.[7] Recently, Waser and co-workers developed a thiol-alkynylation procedure that uses hypervalent iodine (ethynylbenziodoxolone, EBX) as the alkyne transfer reagent.[8] This method is highly chemoselective, and a wide range of functional groups are tolerated under the developed conditions. However, the problems associated with the preparation of the hypervalent iodine alkyne transfer reagents are the major disadvantage of the designed transformation. There are also scattered examples in the literature of alkynyl sulfides preparation based on the reaction of thiotosylates with lithium acetylides[9, 10b].

Other practical procedures involve the reaction of a lithium acetylide and an activated thiol or disulfide.[10]

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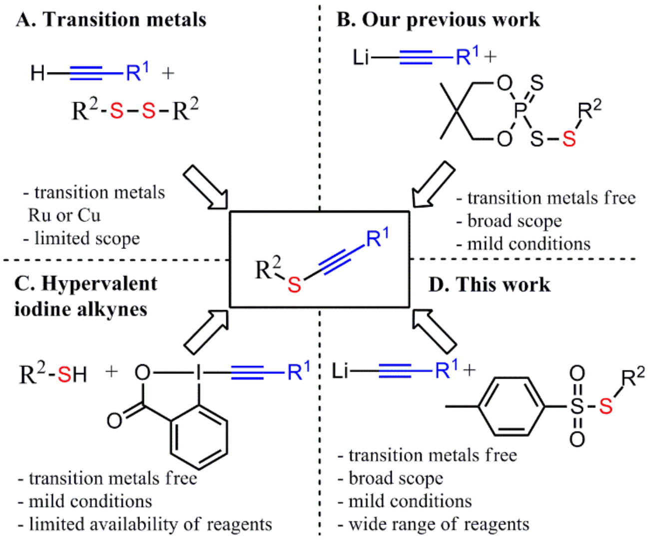


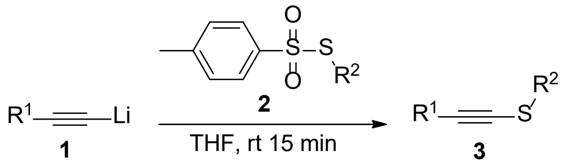
Scheme 1. Previously reported methods for the synthesis of alkynyl sulfides (A-C) and our newly developed approach (D).

Results and Discussion

Previously, we demonstrated the synthesis of functionalized alkynyl sulfides based on the reaction of lithium acetylides with 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-disulfanyl derivatives.[11] These disulfanyl derivatives of phosphorodithioic acid are also convenient substrates for the preparation of α-sulfenylated carbonyl compounds,[12] functionalized phosphorothioates[13] as well as symmetrical and unsymmetrical trisulfanes.[14] The above transformations are based on the electrophilicity of the disulfanyl derivatives, so we extended that approach to the reaction of electrophilic thiotosylate derivatives with lithium acetylides to obtain functionalized alkynyl sulfides under mild conditions.

Herein, we have developed a one-pot synthesis of alkynyl sulfides from various lithium acetylides **1** and thiotosylates **2** (Table 1). The lithium acetylides were generated from the corresponding terminal alkynes and *n*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF. The additional equivalent of *n*-BuLi was added in the case of terminal alkyne **1** and/or thiotosylate **2** possessing acidic functional group (**1c**, **1g** and/or **2c, 2d**). TMEDA was used to prevent the aggregation of lithium acetylides.

Table 1. Reaction of lithium acetylides **1** with thiotosylates **2**[a]

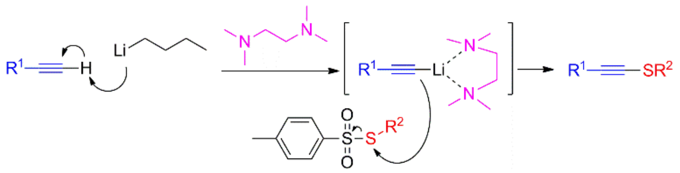


Entry	R^1	R^2	Yield (%)[b]
1	C_6H_5-**1a**	$CH_3(CH_2)_{11}$-**2a**	90 **3aa**
2	C_6H_5-**1a**	$CH_2{=}CH(CH_2)_9$-**2b**	87 **3ab**
3	C_6H_5-**1a**	$HO_2C(CH_2)_{10}$-**2c**	89 **3ac**
4	C_6H_5-**1a**	$HO(CH_2)_{11}$-**2d**	75 **3ad**
5	C_6H_5-**1a**	$C_6H_5CH_2$-**2e**	83 **3ae**
6	C_6H_5-**1a**	4-CH_3-C_6H_4-**2f**	77 **3af**
7	C_6H_5-**1a**	4-CN-C_6H_4-CH_2-**2g**	81 **3ag**
8	C_6H_5-**1a**	4-NO_2-C_6H_4-CH_2-**2h**	84 **3ah**
9	$C_6H_5CH_2OCH_2$-**1b**	$CH_3(CH_2)_{11}$-**2a**	70 **3ba**
10	$C_6H_5CH_2OCH_2$-**1b**	$CH_2{=}CH(CH_2)_9$-**2b**	88 **3bb**
11	$C_6H_5CH_2OCH_2$-**1b**	$HO_2C(CH_2)_{10}$-**2c**	32 **3bc**
12	$C_6H_5CH_2OCH_2$-**1b**	$HO(CH_2)_{11}$-**2d**	62 **3bd**
13	$C_6H_5CH_2OCH_2$-**1b**	$C_6H_5CH_2$-**2e**	67 **3be**
14	$C_6H_5CH_2OCH_2$-**1b**	4-CH_3-C_6H_4-**2f**	74 **3bf**
15	$C_6H_5CH_2OCH_2$-**1b**	4-CN-C_6H_4-CH_2-**2g**	73 **3bg**
16	$C_6H_5CH_2OCH_2$-**1b**	4-NO_2-C_6H_4-CH_2-**2h**	68 **3bh**
17	$BocNHCH_2$-**1c**	$CH_3(CH_2)_{11}$-**2a**	80 **3ca**
18	$BocNHCH_2$-**1c**	$CH_2{=}CH(CH_2)_9$-**2b**	30 **3cb**
19	$BocNHCH_2$-**1c**	$HO_2C(CH_2)_{10}$-**2c**	60 **3cc**
20	$BocNHCH_2$-**1c**	$HO(CH_2)_{11}$-**2d**	61 **3cd**
21	$BocNHCH_2$-**1c**	$C_6H_5CH_2$-**2e**	85 **3ce**
22	$BocNHCH_2$-**1c**	4-CH_3-C_6H_4-**2f**	83 **3cf**
23	$BocNHCH_2$-**1c**	4-CN-C_6H_4-CH_2-**2g**	65 **3cg**
24	$(CH_3)_2CHCH_2CH_2$-**1d**	$CH_3(CH_2)_{11}$-**2a**	61 **3da**
25	$(CH_3)_2CHCH_2CH_2$-**1d**	$CH_2{=}CH(CH_2)_9$-**2b**	56 **3db**
26	$(CH_3)_2CHCH_2CH_2$-**1d**	$CH_3(CH_2)_{11}$-**2a**	90 **3aa**
27	$(CH_3)_2CHCH_2CH_2$-**1d**	$HO_2C(CH_2)_{10}$-**2c**	72 **3dc**
28	$(CH_3)_2CHCH_2CH_2$-**1d**	$HO(CH_2)_{11}$-**2d**	77 **3dd**
29	$(CH_3)_2CHCH_2CH_2$-**1d**	$C_6H_5CH_2$-**2e**	84 **3de**
30	$(CH_3)_2CHCH_2CH_2$-**1d**	4-CH_3-C_6H_4-**2f**	82 **3df**

31	$(CH_3)_2CHCH_2CH_2$-**1d**	4-CN-C_6H_4-CH_2-**2g**	71 **3dg**
32	$(CH_3)_2CHCH_2CH_2$-**1d**	4-NO_2-C_6H_4-CH_2-**2h**	74 **3dh**
33	EtO_2C-**1e**	$CH_3(CH_2)_{11}$-**2a**	82 **3ea**
34	EtO_2C-**1e**	CH_2=$CH(CH_2)_9$-**2b**	71 **3eb**
35	EtO_2C-**1e**	$HO_2C(CH_2)_{10}$-**2c**	79 **3ec**
36	EtO_2C-**1e**	$HO(CH_2)_{11}$-**2d**	76 **3ed**
37	EtO_2C-**1e**	$C_6H_5CH_2$-**2e**	89 **3ee**
38	EtO_2C-**1e**	4-CH_3-C_6H_4-**2f**	73 **3ef**
39	EtO_2C-**1e**	4-CN-C_6H_4-CH_2-**2g**	72 **3eg**
40	EtO_2C-**1e**	4-NO_2-C_6H_4-CH_2-**2h**	81 **3eh**
41	4-CH_3O-2-CH_3-C_6H_3-**1f**	$CH_3(CH_2)_{11}$-**2a**	81 **3fa**
42	4-CH_3O-2-CH_3-C_6H_3-**1f**	CH_2=$CH(CH_2)_9$-**2b**	72 **3fb**
43	4-CH_3O-2-CH_3-C_6H_3-**1f**	$HO_2C(CH_2)_{10}$-**2c**	69 **3fc**
44	4-CH_3O-2-CH_3-C_6H_3-**1f**	$HO(CH_2)_{11}$-**2d**	74 **3fd**
45	4-CH_3O-2-CH_3-C_6H_3-**1f**	$C_6H_5CH_2$-**2e**	80 **3fe**
46	4-CH_3O-2-CH_3-C_6H_3-**1f**	4-CH_3-C_6H_4-**2f**	80 **3ff**
47	4-CH_3O-2-CH_3-C_6H_3-**1f**	4-CN-C_6H_4-CH_2-**2g**	84 **3fg**
48	4-CH_3O-2-CH_3-C_6H_3-**1f**	4-NO_2-C_6H_4-CH_2-**2h**	82 **3fh**
49	3-HO_2C-C_6H_4-**1g**	$CH_3(CH_2)_{11}$-**2a**	68 **3ga**
50	3-HO_2C-C_6H_4-**1g**	CH_2=$CH(CH_2)_9$-**2b**	56 **3gb**
51	3-HO_2C-C_6H_4-**1g**	$HO_2C(CH_2)_{10}$-**2c**	59 **3gc**
52	3-HO_2C-C_6H_4-**1g**	$HO(CH_2)_{11}$-**2d**	54 **3gd**
53	3-HO_2C-C_6H_4-**1g**	$C_6H_5CH_2$-**2e**	62 **3ge**
54	3-HO_2C-C_6H_4-**1g**	4-CH_3-C_6H_4-**2f**	68 **3gf**

[a] Conditions: lithium acetylide **1** (1.0 mmol), TMEDA (1.0 mmol), thiotosylates **2** (1.0 mmol), dry THF (10 mL), rt, 15 min, under N_2.
[b] Isolated yield

The developed method is quite versatile. The presence of additional functional groups, including carbon-carbon double bonds as well as carboxyl, hydroxy, cyano, nitro, amino and ester groups, were well tolerated in the formation of corresponding alkynyl sulfides **3**. Moreover, both starting materials **1** and **2** are readily available and the reaction can be carried out on a larger scale (30-50 mmol) to provide alkynyl sulfides **3** (entries 1, 10, 24, 36, 45, 49) in similar (± 5%) yield reported in Table 1.



Scheme 2. Proposed mechanism for the synthesis of alkynyl sulfide.

Proposed mechanism of these transformation is shown in Scheme 2. Firstly, lithium acetylide is generated from terminal alkyne and *n*-butyllithium. When substrates **1** or **2** with acidic protons were used the additional equivalent of *n*-BuLi was added. These lithium salts are stabilized by presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA). Subsequent nucleophilic substitution on the electrophilic sulfur produced corresponding alkynyl sulfide in good yield.

Single crystals of **3gf** suitable for X-ray diffraction were grown from a saturated chloroform solution (CCDC 1560122). The unit cell of compound **3gf** was a monoclinic system in the space group $P2_1/c$ with four molecules in its elementary cell. The triple bond length between C9 and C8 was 1.207 Å (Figure 1). This is similar to the acetylene bond length (1.203 Å). The angle between C8-S1-C1 was 102.56°.

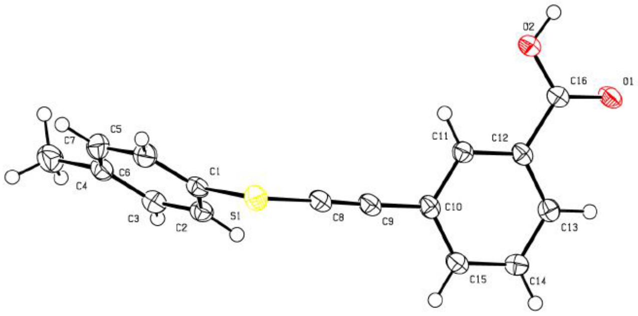
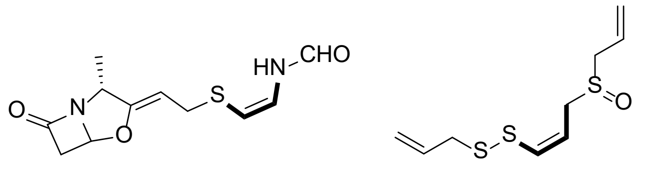


Figure 1. Crystal structure of compound **3gf**.

Due to the growing interest in compounds containing (*Z*)-vinylthio moieties we developed a simple, regio- and stereoselective reduction of alkynyl sulfides to (*Z*)-alkenyl sulfides. Alkenyl sulfides are of interest because they can be used as versatile reagents in organic synthesis.[14] In addition to their interesting reactivity, the alkenyl sulfide functionality is present in many pharmaceutical compounds.[16] The vinyl sulfide moiety is present in ajoene and its derivatives, which are potent antithrombotic agents isolated from garlic (*Alluimsatiuum*).[17] Moreover, a (*Z*)-vinylthio functional group is present in clavulanic acid, which showed β-lactamase-inhibitory activity[18] (Scheme 3). In all cases, the (*Z*)-isomers show better activity than the (*E*)-isomers.

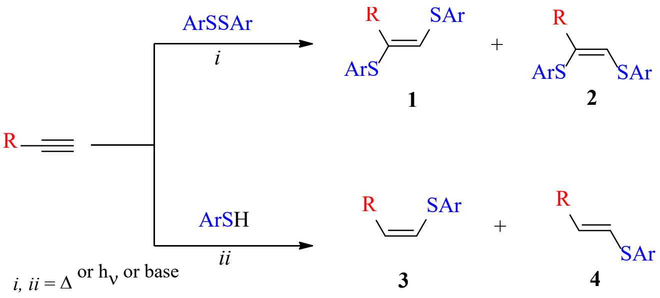


Clavulanic acid derivatives

(Z)-Ajoene

Scheme 3. (*Z*)-vinyl sulfide and disulfane.

Several methods have been developed for the stereoselective synthesis of (*E*)-vinyl sulfides,[19] however, the (*Z*)-isomers are more difficult to prepare. The simplest method for the preparation of vinyl sulfides is based on the addition reactions of thiols or disulfides to acetylenic hydrocarbons. Unfortunately, the addition of disulfides[20] to alkynes usually gave mixture of *Z* and *E* isomers (**1** and **2**), while anti-Markovnikov addition of arylthiols[21] provides a mixture of *Z* and *E* compounds (**3** and **4**) (Scheme 4).

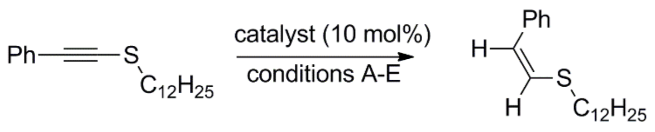


Scheme 4. The addition reactions of thiols and disulfides to terminal alkynes.

A more convenient methodology is based on hydrothiolations of alkynes using catalysts[22] or on transition-metal-catalyzed cross-coupling reactions.[23] In 2005, Yorimitsu and Oshima reported the synthesis of (*Z*)-1-alkenyl sulfides via a cesium-catalyzed hydrothiolation of alkynes in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO).[24] However, this synthetic strategy is only applicable to alkylthiols. Recently, Tang and Li reported the synthesis of (*Z*)-1-alkenyl sulfides by a copper-catalyzed hydrothiolation of alkynes with diaryl disulfides, but the reaction requires a large amount of Rongalite (4 eq) as the radical initiator[25] and is limited to diaryl disulfides. There are also a few methods for the synthesis of alkenyl sulfides via the reduction of alkynyl sulfides. In 2013, Zheng et al. reported the stereoselective preparation of alkenyl sulfides via *syn*-hydrozirconation of alkynyl sulfides by Schwartz reagent.[26] This reaction was used for simple alkynyl sulfides that did not contain additional functional groups. Recently, hydrosilylations of alkynyl sulfides by silane and $[Cp^*Ru(MeCN)_3]PF_6$ as the catalyst have also been reported. After subsequent protodesilylation, (*Z*)-vinyl sulfides were obtained.[27]

In our initial study, we employed alkynyl sulfide **3aa** as a model starting material (Table 2). The most promising reagents and catalysts were examined. Excellent *syn*-addition was observed in the reaction with pinacolborane (HBpin) and CuCl as the catalyst in dry THF (Table 2, entry 5).

Table 2. Conversion of alkynyl sulfide to alkenyl sulfide.



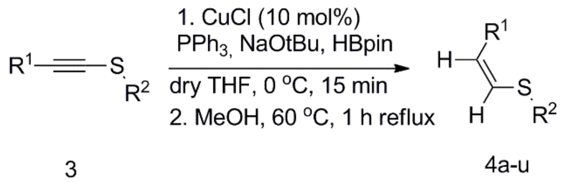
Entry	**Catalyst /reagent**	**Method**	**Yield (%)[a]**	***Z/E*[b]**
1	Schwartz reagent (1 eq.)	A	<5c)	-
2	Hoveyd-Grubbs Catalyst 1st Generation / HCO_2H	B	37d)	-
3	CuCl / catecholborane	C	13	80:20
4	CuCl / pinacolborane	D	30	90:10
5	CuCl / pinacolborane	E	94	100:0

Methods: **A** dichloromethane, rt; **B** $C_{28}H_{45}Cl_2OPRu$ (0.1 eq), NaH (0.2 eq), HCO_2H (50 eq), THF reflux overnight; **C** (i) HBcat (3 eq), CuCl (0.1 eq), PPh_3 (0.1 eq), NaOtBu (0.1 eq), dry THF, (ii) MeOH (6 eq) reflux 1 h; **D** (i) HBpin (3 eq), CuCl (0.1 eq), PPh_3 (0.1 eq), NaOtBu (0.1 eq), dry toluene, 15 min; (ii) MeOH (6 eq) reflux 1 h; **E** (i) HBpin (3 eq), CuCl (0.1 eq), PPh_3 (0.1 eq), NaOtBu (0.1 eq), dry THF, 0 °C, 15 min; (ii) MeOH (6 eq) reflux 1 h.

[a] Isolated yield. [b] *E/Z* ratios of the products were determined by ^1H NMR spectroscopy. [c] Almost no conversion was observed. [d] Observed addition to triple bond, thioester $PhCH_2C(O)SC_{12}H_{25}$ was obtained

Under the optimized conditions, alkynyl sulfides **3** participated in the reduction with good or very good efficiency and excellent regio- and stereoselectivity (Table 3).

Table 3 . Preparation of (Z)-alkenyl sulfides **4** from alkynyl sulfides **3**[a



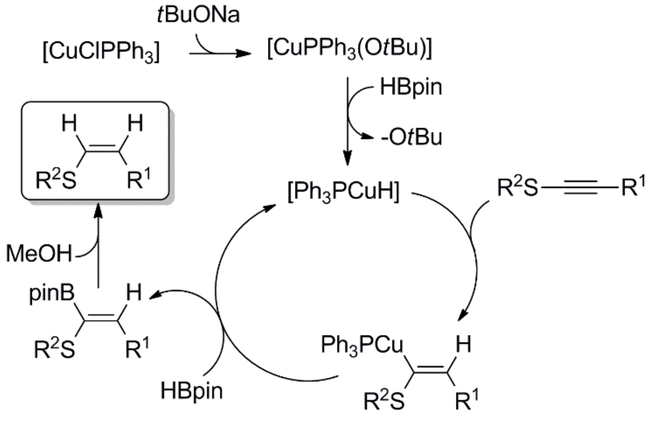
Entry	**R¹**	**R²**	**Yield (%)[b]**	***Z/E*[c]**
1	C_6H_5-	$CH_3(CH_2)_{11}$-	94 **4a**	100:0
2	C_6H_5-	CH_2=$CH(CH_2)_9$-	75 **4b**	100:0
3	C_6H_5-	$CH_3O_2C(CH_2)_{10}$-	89 **4c**	100:0
4	C_6H_5-	4-$CH_3C_6H_4$-SO_2-	50 **4d**	100:0
5	C_6H_5-	$HO(CH_2)_{11}$-	75 **4e**	100:0
6	$C_6H_5CH_2OCH_2$-	$CH_3(CH_2)_{11}$-	90 **4f**	100:0
7	$C_6H_5CH_2OCH_2$-	4-CN-C_6H_4-CH_2-	78 **4g**	100:0
8	BocNHCH_2-	$CH_3(CH_2)_{11}$-	62 **4h**	100:0
9	BocNHCH_2-	$HO(CH_2)_{11}$-	60 **4i**	100:0
10	$(CH_3)_2CHCH_2CH_2$-	$CH_3O_2C(CH_2)_{10}$-	75 **4j**	100:0
11	$(CH_3)_2CHCH_2CH_2$	$HO(CH_2)_{11}$-	61 **4k**	100:0
12	$(CH_3)_2CHCH_2CH_2$	$C_6H_5CH_2$-	82 **4l**	100:0
13	EtO_2C-	$CH_3(CH_2)_{11}$-	87 **4m**	100:0
14	EtO_2C-	4-CH_3-C_6H_4-	87 **4n**	100:0
15	EtO_2C-	4-NO_2-C_6H_4-CH_2-	81 **4o**	100:0
16	4-CH_3O-2-CH_3-C_6H_3-	$CH_3(CH_2)_{11}$-	62 **4p**	100:0
17	4-CH_3O-2-CH_3-C_6H_3-	$HO_2C(CH_2)_{10}$-	59 **4r**	100:0
18	4-CH_3O-2-CH_3-C_6H_3-	4-CN-C_6H_4-CH_2-	79 **4s**	100:0
19	3-HO_2C-C_6H_4-	$CH_3(CH_2)_{11}$-	60 **4t**	100:0

20	3-HO_2C-C_6H_4-	$C_6H_5CH_2$-	76 **4u**	100:0

[a] Conditions: **3** (1.0 mmol), CuCl (0.1 mmol), PPh_3 (0.1 mmol), NaOtBu (0.2 mmol), HBpin (3.0 mmol), dry THF (20 mL), 0°C, 15 min under N_2, then MeOH (6.0 mmol) reflux 1 h. [b] Isolated yield. [c] *E*/*Z* ratio of the product was determined by ^1H NMR spectroscopy

Based on the experimental results, possible catalytic cycles for the Cu-catalyzed hydroboration using HBpin are shown in Scheme 5. PPh_3 and CuCl reacted with NaO*t*Bu to afford [Ph_3PCu(O*t*Bu)]. Subsequent reaction of [Ph_3PCu(O*t*Bu)] with HBpin produced the active catalytic species, appropriate copper hydride [Ph_3PCuH]. *Syn* addition to alkynes sulfide afforded alkenyl copper species that reacted with HBpin to produce corresponding hydroboration product and regenerated active catalytic species [Ph_3PCuH].

Scheme 5. A possible catalytic cycle.



Finally, reaction of alkenyl borane with MeOH provided the (*Z*)-alkenyl sulfide in very good yield and excellent diastereoselctivity.

Conclusions

The mild conditions used herein are tolerant of additional functional groups, including esters (entries 3, 10 and 13-15), ethers (entries 6,7 and 16-18), carbon-carbon double bonds (entry 2), hydroxy group (entries 5, 9, and 11), carboxyl group (entries 17 and 19-20), Boc-amino group (entries 8-9), nitro (entry 15), cyano (entries 7 and 18) and thiotosylate (entry 4). The latter is convenient for the subsequent preparation of (*Z*)-alkenyl disulfanes. The synthesis of unsymmetrical functionalized *Z*-alkenyl disulfanes is under investigation. In conclusion, we developed a convenient and efficient method for preparing alkynyl sulfides under mild conditions based on readily available starting materials. The subsequent reduction of alkynyl sulfides with pinacolborane afforded *Z*-alkenyl sulfides with excellent diastereoselectivity.

Experimental Section

General procedure for the preparation of alkynyl sulfides 3

To a stirred solution of terminal alkyne **1a-g** (1 mmol) and tetramethylethylenediamine (TMEDA) (1 mmol) in anhydrous THF (10 mL) at 0 ºC under an N_2 atmosphere was added dropwise 0.4 mL of 2.5 M solution of BuLi in hexane (1 mmol). After 5 min, the appropriate thiotosylate (**2a-h**, 1 mmol) was added in one portion. The mixture was stirred and warmed to rt for 15 min. Then, the solvent was evaporated, and the residue was dissolved in Et_2O (20 mL), washed with water (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2) to provide corresponding alkynyl sulfide **3** (Table 1).

General procedure for the preparation of (*Z*)-alkenyl sulfides 4

To a mixture of CuCl (0.1 mmol, 0.01 g), PPh_3 (0.1 mmol, 0.027 g), NaOtBu (0.2 mmol, 0.02 g) cooled to 0 °C in dry THF (15 mL) was added HBpin (3 mmol, 0.44 mL). The mixture was stirred for 15 min at 0 °C, and a solution of corresponding alkynyl sulfide **3** (1 mmol) in dry THF (5 mL) was added dropwise. The reaction was monitored by TLC. When all the substrate had been consumed (15 – 60 min), MeOH (6 mmol, 0.25 mL) was added. After stirring at 60 °C for 1 h, the reaction mixture was concentrated, and the residue was purified by column chromatography (SiO_2) to provide *Z*-alkenyl sulfide **4** (Table 3).

Acknowledgements

We gratefully acknowledge the National Science Centre (NCN) for financial support (grant no. 2015/19/B/ST5/03359)

Keywords: alkynyl sulfides; (*Z*)-alkenyl sulfides; hydroboration; thiotosylates; thiols

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