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Geometrically Selective Synthesis of Functionalized β,β-Disubstituted Vinylic Sulfoxides by Cu-Catalyzed Conjugate Addition of Organozinc Reagents to 1-Alkynyl Sulfoxides

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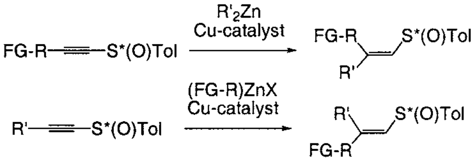
ABSTRACT



A new synthetic method of chiral β,β-disubstituted vinylic sulfoxides bearing various functionalities has been developed by employing Cu-catalyzed conjugate addition of an organozinc reagent to chiral 1-alkynyl sulfoxide. Since the reaction proceeds with very high *syn*-selectivity, both geometric β,β-disubstituted vinylic sulfoxides were stereoselectively synthesized by changing the combination of 1-alkynyl sulfoxide and the organozinc reagent.

Vinylic sulfoxides are well-known chiral building blocks applied to various asymmetric reactions, in which high diastereoselectivity is often realized.[1] In addition, since the sulfinyl group can be converted into various functional groups, vinylic sulfoxides have been employed in many synthetic studies for biologically active natural products. Although some useful methods to synthesize (E)- and (Z)-β-monosubstituted sulfoxides are available,[2] there are few methods for the synthesis of chiral β,β-disubstituted vinylic sulfoxides.[3] One widely used methodology is *syn*-selective conjugate addition of an organocopper reagent to 1-alkynyl sulfoxides.[4] However, the application of this method has been limited to introduction of relatively simple alkyl groups, since organocopper reagents are regularly prepared from reactive organolithium or Grignard reagents. To solve this problem,

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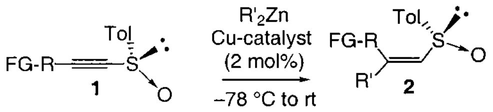
Scheme 1



we investigated Cu-catalyzed carbozincation of the chiral 1-alkynyl sulfoxides with organozinc reagents, which can be prepared straightforwardly from alkyl halides by halogen–zinc exchange reaction. Since several functional groups are compatible with the organozinc reagent as a result of its mild reactivity, a variety of multifunctionalized chiral vinylic sulfoxides could be synthesized by coupling of a functionalized organozinc reagent and 1-alkynyl sulfoxide.[5]

Herein, we present a new efficient method for the geometrically selective synthesis of functionalized chiral β,β-disubstituted vinylic sulfoxides **2** by highly *syn*-selective Cu-catalyzed conjugate addition of organozinc compounds to 1-alkynyl sulfoxides **1** (Scheme 1).

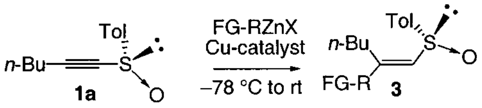
Chiral 1-alkynyl sulfoxides were readily synthesized according to the procedure reported by Kosugi and coworkers.[2d] Table 1 summarizes the reaction of the functionalized 1-alkynyl sulfoxides with dialkylzinc reagents. Upon treatment with Et$_2$Zn (2 equiv) in the presence of catalytic CuI (2 mol %), 1-alkynyl sulfoxide **1a** underwent carbozincation to give a vinylic sulfoxide (*Z*)-**2a** in 97% yield. The reaction proceeded in a *syn*-selective fashion, giving the (*Z*)-isomer exclusively (entry 1).[6] Other Cu-salts such as CuCN and Cu(OTf)$_2$ also catalyzed this reaction to afford (*Z*)-**2** in moderate to good yields (entries 2 and 3).[7] The procedure was applied to the synthesis of various functionalized 1-alkynyl sulfoxides **1b**–**f**. Functional groups such as TBS, Ac, and I are compatible in this reaction. It should be noted that a nucleophile-sensitive acetyl group was not affected under the reaction conditions, and no Cu-catalyzed iodine–zinc exchange reaction[8] was observed (entries 4–6). However, alkynyl sulfoxides **1e** and **1f** bearing a proton and a hindered *t*-Bu group at the β-position, respectively, showed considerably low yields (entries 7 and 8). *syn*-Selective methylation of **1a** was also accomplished using Me$_2$Zn in the presence of CuI catalyst (entry 9).

Table 1. Synthesis of β,β-Disubstituted Vinylic Sulfoxides Using R′$_2$Zn[a]

entry	substrate	FG-R	R′	Cu-catalyst	product (yield, %)
1	**1a**	*n*-Bu	Et	CuI	(*Z*)-**2a** (97)
2	**1a**	*n*-Bu	Et	CuCN	(*Z*)-**2a** (86)
3	**1a**	*n*-Bu	Et	Cu(OTf)$_2$	(*Z*)-**2a** (69)
4	**1b**	TBSO(CH$_2$)$_2$	Et	CuI	**2b** (78)
5	**1c**	AcO(CH$_2$)$_2$	Et	CuI	**2c** (84)
6	**1d**	I(CH$_2$)$_4$	Et	CuI	**2d** (71)
7	**1e**	H	Et	CuI	**2e** (24)[b]
8	**1f**	*t*-Bu	Et	CuI	**2f** (21)
9	**1a**	*n*-Bu	Me	CuI	**2g** (67)[c]

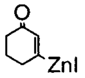
[a] The reactions were carried out in a 1 M solution of the alkyne in THF using R′$_2$Zn (2 equiv) in the presence of Cu-catalyst (2 mol %) at −78 °C to rt unless otherwise stated. [b] (*Z*)-Isomer was produced in 21% yield. [c] The reaction was carried out in a 0.1 M solution.

Scheme 2



A wide range of multifunctionalized organozinc halides can be prepared by halogen–zinc exchange reaction.[9] Next, we investigated the reaction of 1-alkynyl sulfoxide with functionalized organozinc reagents (Scheme 2). The results are shown in Table 2. Organozinc halides were prepared from the corresponding alkyl halides with Zn powder activated with TMSCl and dibromoethane. Upon treatment with allylzinc bromide, the 1-alkynyl sulfoxide **1a** underwent carbozincation in the presence of 2 mol % of CuI, leading to (*E*)-vinylic sulfoxide **3a** in 72% yield as a single product (entry 1). In this case, Cu(OTf)$_2$ was the most efficient

Table 2. Synthesis of β,β-Disubstituted Vinylic Sulfoxides Using Functionalized Organozinc Reagents[a]

entry	FG-RZnX (equiv)	Cu-catalyst (mol%)	product (yield,%)
1	 ZnBr (2)	CuI (2)	**3a** (72)
2	(2)	CuCN (2)	**3a** (73)
3	(2)	Cu(OTf)$_2$ (2)	**3a** (81)
4	BnZnBr (2)	Cu(OTf)$_2$ (2)	**3b** (81)
5	PivOCH$_2$ZnI (3)	Cu(OTf)$_2$ (2)	**3c** (75)
6	EtO$_2$C(CH$_2$)$_3$ZnI (3)	Cu(OTf)$_2$ (2)	**3d** (70)
7	 ZnI (2)	Cu(OTf)$_2$ (2)	**3e** (87)
8	BocNH(CH$_2$)$_3$ZnI (10)	Cu(OTf)$_2$ (2)	**3f** (84)

[a] The reactions were carried out in a 1 M solution of the alkyne in THF using FG-RZnX in the presence of Cu-catalyst at −78 °C to rt.

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(5) Efficient and highly *syn*-selective carbozincation of 1-alkynyl sulfides was reported; see: Rao S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735–5741.

(6) Geometry of the vinylic sulfoxides was determined by NOE experiments.

(7) The reaction of **1a** without Cu-catalyst afforded a β-sulfinylated vinylic sulfoxide via sulfinylzincation along with (*Z*)-**2a**. We have reported the results in a recent communication; see: Maezaki, N.; Yoshigami, R.; Maeda, J.; Tanaka, T. *Org. Lett.* **2001**, *3*, 3627–3629.

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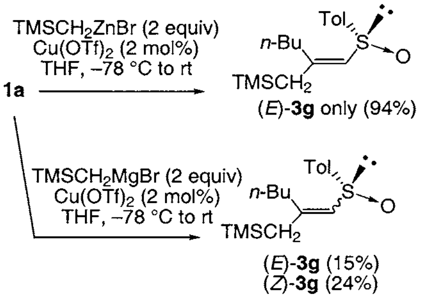
catalyst among the Cu-salts screened to give **3a** in 81% yield (entries 1−3). Using the Cu(OTf)$_2$ catalyst, various functionalized organozinc halides were coupled with the 1-alkynyl sulfoxide **1a** (entries 4−8). The substituents bearing a variety of nucleophile-sensitive functional groups were introduced stereospecifically in moderate to good yields.

The result that the α-sulfinyl vinylzinc intermediate retains the geometry at room temperature is in sharp contrast to the fact that α-sulfinyl vinyllithium isomerizes to a thermodynamically more stable geometric isomer even at −78 °C.[10] The difference between these results presumably arises from the more ionic nature of the carbon−lithium bond than the carbon−zinc bond.

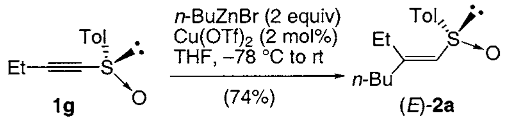
Scheme 3



Scheme 3 shows a comparison of two Cu-catalyzed carbometalations using an organozinc reagent and Grignard reagent, wherein Mg possesses electronegativity between Li and Zn. Although a mixture of geometric isomers (*E*)- and (*Z*)-**3g** was obtained in the reaction with a Grignard reagent, Cu-catalyzed carbozincation provided chiral allylic silane (*E*)-**3g** as the sole geometric isomer. These results obviously exhibit the advantage of organozinc reagents over organomagnesium reagents.[11]

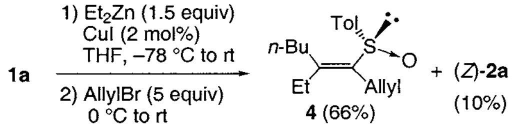
Since the reaction proceeds stereospecifically, it would be applied to stereoselective synthesis of both geometric *β*,*β*-disubstituted vinylic sulfoxides by changing the combination of the *β*-substituent of 1-alkynyl sulfoxide and the organozinc reagent. Thus, the (*E*)-isomer of vinylic sulfoxide (*E*)-**2a** was synthesized in 74% yield by reaction of 1-alkynyl sulfoxide **1g** and *n*-butylzinc bromide in the presence of catalytic Cu(OTf)$_2$ (Scheme 4). Since the corresponding (*Z*)-isomer was synthesized in 97% yield by the CuI-catalyzed conjugate addition of Et$_2$Zn to **1a** (Table 1, entry 1), this method affords a powerful tool for stereoselective synthesis of *β*,*β*-disubstituted vinylic sulfoxides.

Scheme 4



We also found that the vinylzinc intermediate generated by the reaction of **1a** with Et$_2$Zn can be trapped by allyl bromide (5 equiv), giving trisubstituted vinylic sulfoxide **4** in 66% yield along with 10% of (*Z*)-**2a** (Scheme 5).

Scheme 5



Although the yield was moderate, two kinds of substituents were introduced regio- and stereoselectively in a one-pot reaction. Optimization of the yield and the reaction with other electrophiles are in due course, and the results will be reported elsewhere.

In conclusion, we have developed a useful method to synthesize chiral *β*,*β*-disubstituted vinylic sulfoxides with various functionalities via highly *syn*-selective Cu-catalyzed conjugate addition of an organozinc reagent to 1-alkynyl sulfoxide. Further study to explore the scope and limitation of this method is in progress.

Supporting Information Available: Synthetic procedure, characterization data, and spectral data (^{1}H and ^{13}C NMR) of (*Z*)-**2a**, (*E*)-**2a**, and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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