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cis-Carbocuperation of acetylenic sulfoxides and corresponding applications in the regio- and stereoselective synthesis of polysubstituted vinyl sulfoxides

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Abstract—*cis*-Carbocuperation reaction of monoorganocopper reagent with acetylenic sulfoxides, followed by electrophilic reaction with a variety of electrophiles, provided a regio- and stereoselective method to prepare the versatile polysubstituted vinyl sulfoxides. Sonogashira cross-coupling reaction of the obtained α-iodovinyl sulfoxides with terminal acetylenes was also investigated to afford the versatile conjugate sulfinyl enynes.

Stereoselective synthesis of substituted alkenes has always been an interesting topic in organic synthesis, in which the carbometallation of acetylenes is one of the most efficient routes to stereo-defined alkenes.[1] Among the carbometallation reagents, organocopper reagents have received an especially great deal of attention regarding *cis*-conjugate addition reactions with acetylenic compounds.[2] In the case of functionalized acetylenes, most reactions with organocopper reagents also undergo a facile *cis*-conjugate addition.[3] Substituted vinyl sulfoxides, especially the optically active ones, are very important synthetic intermediates in organic synthesis and have been extensively studied,[4] for the sulfinyl group itself is a potential reaction center. Not only is it a very good leaving group both in ionic[4d] and free radical reactions,[4e] it can also undergo substitution reactions with several organometallic reagents[5] and other conversions.[6] Recently, we and others have reported the hydrozirconation[7] and carbozincation[8] of acetylenic sulfoxides[9] in preparing substituted vinyl sulfoxides. With the knowledge of the advantages of organocopper reagents and the potential synthetic importance of stereo-defined vinyl sulfoxides, we investigated the tandem carbocuperation and electrophilic reaction of acetylenic sulfoxides to extend the stereoselective synthesis of substituted vinyl sulfoxides.

We first studied the reaction of the two component organocopper reagents, that is diorganocopper reagent and monoorganocopper reagent, with acetylenic sulfoxides, in order to examine the regio- and stereochemistry of the Michael addition reaction. As shown in Scheme 1, when the reaction of organocopper reagents with acetylenic sulfoxides was completed at −78 °C, as monitored by TLC, the mixture was quenched with saturated aqueous ammonium chloride at this temperature. The reaction of diorganocopper reagent was rather complicated and no addition product, except for a side-product alkyl tolyl sulfoxide **2** was obtained (Scheme 1, Eq. 1), while the reaction of monoorganocopper reagent gave high yields of addition products **3** (Scheme 1, Eq. 2). Spectroscopic analysis found **3a** to be pure *cis*-addition isomer identical with the known compounds.[10] The above results were consistent with literature reports[10,11] and indicated that monoorganocopper reagents are more suitable Michael addition reagents to acetylenic sulfoxides than diorganocopper reagents, and the addition reaction also exhibits good regio- and stereoselectivity. Thus we used monoorganocopper reagent, prepared in situ from CuI and

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Keywords: Carbocuperation; Acetylenic sulfoxides; Polysubstituted vinyl sulfoxides.

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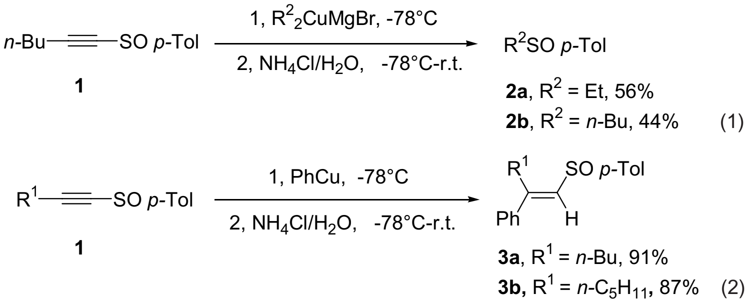


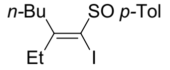
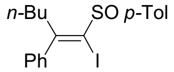
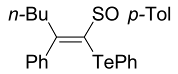
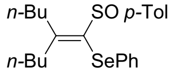
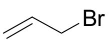
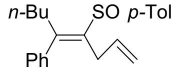
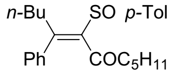
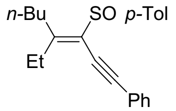
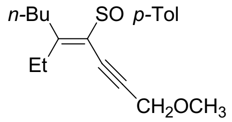
Scheme 1.

1.0 equiv of alkylmagnesium bromide, as the carbocuperation reagent. Various electrophiles were investigated and the results are summarized in Table 1 (Scheme 2).[12]

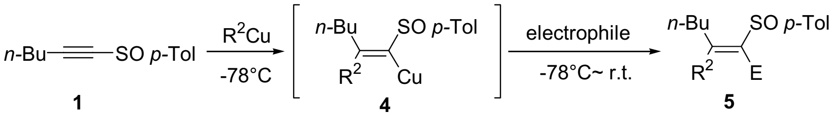
At low temperature, the *cis*-carbocuperation reaction of monoorganocopper reagent with acetylenic sulfoxides afforded the sulfinylvinyl copper intermediate **4** first, and then the intermediate **4** further reacted with different electrophiles to give substituted vinyl sulfoxides **5** (Scheme 2). As shown in Table 1, the reactions of iodine were found to be very effective and afforded high yields of α-iodovinyl sulfoxides (Table 1, entries 1 and 2). Furthermore, the reactions of benzenetellurenyl iodide, benzeneselenyl bromide, and allyl bromide also afforded good yields of α-phenylchalcogenovinyl sulfoxides and sulfinyl 1,4-diene, respectively (entries 3–5). However, the reactions of the vinyl copper intermediate **4** with acyl chloride and acetylenylphenyliodonium tosylates afforded relatively low yields of the products under identical reaction conditions (entries 6–8), which might be attributed to the different effectiveness of different electrophiles in their electrophilic reaction with the vinyl copper intermediate **4**, as no anticipated products were obtained from the reactions of other electrophiles such as methyl iodide, diphenyliodonium chloride or α,β-unsaturated ketones.

Conjugate enynes are typical structure fragments of many natural compounds and their synthesis has also

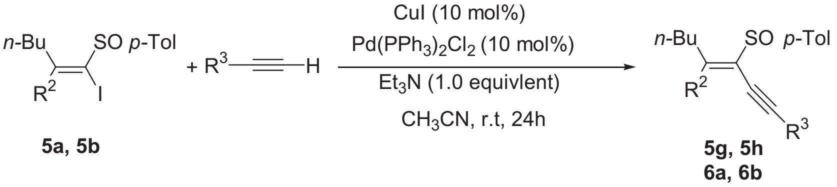
Table 1. Preparation of substituted vinyl sulfoxides from *cis*-carbocuperation of acetylenic sulfoxides

Entry	R^2	Electrophiles	Product	Structure	Yield (%)[a]
1	Et	I_2	**5a**		96
2	Ph	I_2	**5b**		99
3	Ph	PhTeI	**5c**		85
4	*n*-Bu	PhSeBr	**5d**		78
5	Ph		**5e**		89
6	Ph	$C_5H_{11}COCl$	**5f**		51
7	Et	$Ph-\!\!\equiv\!\!-\overset{\oplus}{I}(Ph)OTs^{\ominus}$	**5g**		47
8	Et	$CH_3OCH_2-\!\!\equiv\!\!-\overset{\oplus}{I}(Ph)OTs^{\ominus}$	**5h**		39

[a] Isolated yield based on acetylenic sulfoxides.



Scheme 2.



Scheme 3.

Table 2. Sonogashira cross-coupling reaction of α-iodovinyl sulfoxides with terminal acetylenes

Entry	R^2	R^3	Product	Yield (%)[a]
1	Et	Ph	**5g**	81
2	Et	CH_3COCH_2	**5h**	74
3	Ph	Ph	**6a**	88
4	Ph	CH_3COCH_2	**6b**	71

[a] Isolated yield based on α-iodovinyl sulfoxides.

attracted much interest.[13] Though the above reaction of acetylenic sulfoxides with acetylenylphenyliodonium tosylate afforded low yields of conjugate sulfinyl enynes, the tandem reaction of monoorganocopper reagent, acetylenic sulfoxides, and iodine gave almost quantitative yields of α-iodovinyl sulfoxides. Therefore we further investigated the Sonogashira cross-coupling reaction of α-iodovinyl sulfoxides with terminal acetylenes in the presence of catalytic amount of Pd/Cu(I). As anticipated the conjugate sulfinyl enynes were obtained in good yields (Scheme 3, Table 2).[14]

In conclusion, *cis*-carbocuperation of acetylenic sulfoxides and further reaction with electrophiles provided an efficient, regio- and stereoselective method for the synthesis of a series of potentially useful polysubstituted vinyl sulfoxides. Sonogashira cross-coupling reactions of the obtained α-iodovinyl sulfoxides with terminal acetylenes also provided an effective method to synthesize conjugate sulfinyl enynes.

Acknowledgements

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12. Typical procedure: alkyl or aryl magnesium bromide (0.75 mmol) in dry THF or ether was added at 0 °C to the THF suspension of CuI (0.75 mmol) in a tube reactor under nitrogen and the mixture was stirred for a few minutes to form the monoorganocopper reagent. Then the mixture was cooled to −78 °C and acetylenic sulfoxide (0.5 mmol) in dry THF was injected with a syringe. The reaction mixture was stirred at a temperature not higher than −50 °C for 1 h and then was cooled to −78 °C again. Then the electrophile (0.75 mmol) as listed in Table 1 was added. After the temperature was gradually returned to room temperature, the mixture was washed with saturated

aqueous NH_4Cl and NaCl, extracted with EtOAc, dried over $MgSO_4$. The solvent was evaporated and the residue purified by TLC or flash chromatography to afford the products. No stereoisomer was detected from the analysis of ^1H and ^{13}C NMR spectra. Selected data of compound **5e**: pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, $J = 8.40$ Hz, 2H), 7.36–7.29 (m, 5H), 7.12 (dd, $J = 8.20$ Hz, $J = 1.40$ Hz, 2H), 5.17–5.07 (m, 1H), 4.48 (dd, $J = 13.40$ Hz, $J = 1.40$ Hz, 2H), 4.31 (dd, $J = 17.40$ Hz, $J = 1.40$ Hz, 2H), 3.11–3.04 (m, 1H), 2.94 (dd, $J = 15.60$ Hz, $J = 6.80$ Hz, 1H), 2.90–2.83 (m, 1H), 2.72 (dd, $J = 15.80$ Hz, $J = 6.20$ Hz, 1H), 2.41 (s, 3H), 1.47–1.36 (m, 4H), 0.89 (t, $J = 7.00$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 140.6, 139.9, 139.7, 139.7, 135.7, 129.7, 128.2, 127.6, 127.6, 124.5, 115.3, 36.0, 30.4, 28.9, 22.5, 21.3, 13.8. MS (EI) m/z (%) 339 (M^++1, 100), 321 (16), 139 (12), 115 (18), 91 (41), 77 (12). IR (KBr) cm^{-1} 3055, 2957, 2928, 2865, 1637, 1597, 1491, 1439, 1109, 1082, 1046, 912. Anal. Calcd for $C_{22}H_{26}OS$: C, 78.06; H, 7.74. Found: C, 77.62; H, 7.81.

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14. Typical procedure for the Sonogashira cross-coupling reaction of α-iodovinyl sulfoxides with terminal acetylenes: the mixture of the α-iodovinyl sulfoxides, terminal acetylene (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (10 mol %), and Et_3N (1.0 equiv) in 2 mL CH_3CN was stirred at room temperature for about 24 h. After the completion of the reaction, the mixture was washed with NH_4Cl, abstracted with EtOAc, and dried over $MgSO_4$. The solvent was evaporated and the residue purified by TLC or flash chromatography to afford the products. Selected data of compound **5g**: pale yellow oil. ^1H NMR (100 MHz, $CDCl_3$): δ 7.56 (d, $J = 8.00$ Hz, 2H), 7.32 (d, $J = 8.40$ Hz, 2H), 7.27–7.24 (m, 5H), 2.86–2.72 (m, 2H), 2.57–2.46 (m, 2H), 2.41 (s, 3H), 1.55–1.45 (m, 4H), 1.14 (t, $J = 7.60$ Hz, 3H), 1.00 (t, $J = 6.20$ Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.7, 140.9, 140.2, 131.5, 129.4, 128.3, 128.1, 127.9, 124.7, 122.8, 98.1, 80.6, 31.8, 31.4, 29.3, 22.9, 21.4, 13.9, 12.2. MS (EI) m/z (%) 351 (M^++1, 22), 334 (5), 308 (26), 105 (100), 91 (41), 77 (72). IR (KBr) cm^{-1} 3054, 2958, 2931, 2872, 2200, 1650, 1596, 1490, 1456, 1379, 1330, 1302, 1263, 117, 1145, 1084, 1050. Anal. Calcd for $C_3H_{26}OS$: C, 78.81; H, 7.48. Found: C, 78.49; H, 7.55.