Regio- and Stereoselective Copper-Catalyzed Addition of Aromatic and Aliphatic Thiols to Terminal and Internal Nonactivated Alkynes

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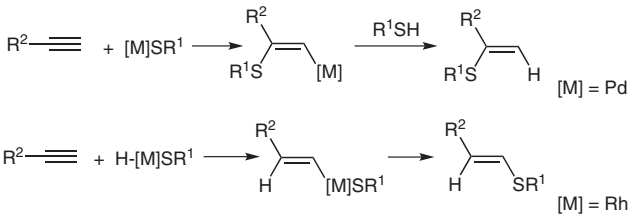
Abstract: The CuI-catalyzed regio- and stereoselective hydrothiolation of terminal and internal alkynes affords (*Z*)-β-alkenylsulfides. The following isomerization of the *Z*-isomers into *E*-isomers catalyzed by CuI is described.

Key words: hydrothiolation, alkynes, copper catalyst, stereoselective anti-Markovnikov addition, isomerization

Considerable attention is being focused on the regio- and stereoselective synthesis of vinyl sulfides in recent years. Vinyl sulfides are important building blocks in organic synthesis used as precursors for aldehyde and ketone formation,[1] electronically active poly(vinylene sulfide)s,[2] as reagents in cross-coupling,[3] Heck,[4] and cycloaddition reactions,[5] in the synthesis of polydentate P,S-ligands,[6] as ligands for CH activation[7] and allylic alkylation,[8] as equivalents of enolate anions,[9] and Michael acceptors.[10] Many natural products with useful biological and pharmacological properties contain an alkenyl sulfide fragment.[11]

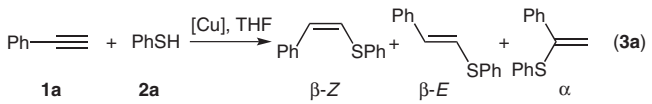
The addition of thiols to terminal alkynes, catalyzed by transition metals,[12] lanthanides and actinides,[13] allows to obtain alkenyl sulfides with high regioselectivity, forming either α- (Markovnikov addition) or β-isomers (anti-Markovnikov addition). Formation of the α-isomer involves the insertion of alkyne into M–SR bond followed by the protonolysis of the C–M bond (M = Pd).

Stereoselective *syn*-addition leading to the anti-Markovnikov product, for instance in the reaction catalyzed by $RhCl(PPh_3)_3$, begins with the insertion of alkyne into H–



Scheme 1

Table 1 Effects of [Cu] Catalyst on Addition of PhSH to Phenyl Acetylene



Entry[a]	Catalyst	Conversion (%), 20 °C, 48 h	Isomeric ratio of **3a** (%)[b]			Conversion (%), 40 °C, 3 h	Isomeric ratio (**3a**), (%)[b]		
			β-*Z*	β-*E*	α		β-*Z*	β-*E*	α
1	none	60	70	30	0	62	68	32	0
2	CuI	80	90	10	0	93	93	7	0
3	CuBr	0	–			0	–		
4	CuCl	0	–			0	–		
5	Cu_2O	73	60	18	22	80	45	37	18
6	$Cu(OAc)_2$[c]	10	100	0	0	–	–		
7	$CuSO_4$	85	40	30	30	90	28	53	18

[a] *Reaction conditions:* PhSH (0.5 mmol), phenyl acetylene (0.5 mmol), THF (0.25 mL), [Cu] (3 mol%).
[b] Determined by ^1H NMR.
[c] Formation of polymers at 40 °C was observed.

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M bond with the following reductive elimination (Scheme 1).[12g,i,l,m,q]

It should be pointed out that the β-isomer can be also obtained in simple base-catalyzed addition reactions[14] as well as in thermal or photochemical radical processes,[15] which, however, are usually not stereoselective.

A recent trend towards replacing precious metal complexes, which, moreover, have to be presynthesized, with cheap and easily available copper complexes or salts,[12a,16] prompted us to examine the possibility of the copper-catalyzed hydrothiolation of alkynes. Copper complexes are known to have good affinity towards triple bond and therefore can activate it (as Lewis acids) towards nucleophilic attack.

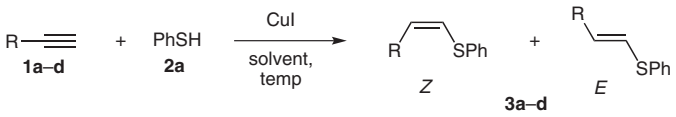
Using the reaction of thiophenol with phenyl acetylene as a model we tested several copper salts and found that only CuI gave a good result (Table 1) improving the yield and selectivity of the noncatalyzed reaction.

It is interesting that in the case of Cu_2O and $CuSO_4$ the yield is also high, but the selectivity is poor. The reactions catalyzed by CuI were studied for thiophenol with several alkynes in different solvents and at different temperatures (Table 2).

Though the addition of thiols to alkynes can be performed without copper catalyst, especially in the case of PhSH and phenylacetylene, the addition of CuI significantly changes the stereochemistry of the reaction, showing that the catalytic process predominates.

In fact we have found that the reaction of thiophenol with phenylacetylene without solvent in the presence of 3 mol% CuI at room temperature gives the same result as the reaction without catalyst, the same yield and same selectivity (*Z*/*E* = 3:1, Table 1, entry 1 and Table 2, entry 1).

Table 2 CuI-Catalyzed Addition of Thiophenol to Terminal Alkynes[24]



R: Ph (**a**); *n*-Bu (**b**); CH_2NMe_2 (**c**); CH_2OH (**d**)

Entry[a]	Alkyne	Solvent, additive (mol%)	Temp (°C)	Time (h)	Yield (%)[b]	*Z*/*E* ratio of **3**[c]
1	**1a**	none	20	48	60	3:1[12f,16f,19] **3a**
2	**1a**	none, Et_3N (20)	40	4	100	100:0 **3a**
3	**1a**	none, TMEDA (20)	40	4	80	100:0 **3a**
4	**1a**	THF	20	48	80	6.1:1 **3a**
5	**1a**	THF, Et_3N (20)	20	48	70	100:0 **3a**
6	**1a**	DMF	40	6	100	49:1 **3a**
7	**1a**	*i*-AmOH, ethylene glycol (10:1)	40	6	100	1:6.1 **3a**
8	**1a**	*i*-AmOH, ethylene glycol (10:1)	80	4	100	1:49 **3a**
9	**1b**	DMF	80	1	90	20:1[15l,22a,b] **3b**
10	**1b**	*i*-AmOH, ethylene glycol (10:1)	80	1	90	1:4 **3b**
11	**1c**	THF or DMF	40	4	100	0:100[20] **3c**[26]
12	**1d**	THF	40	4	100	1:10[12r,21] **3d**[27]

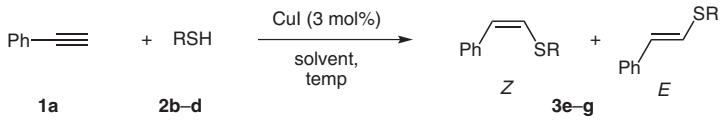
[a] *Reaction conditions:* PhSH (1 mmol), alkyne (1 mmol), solvent (0.25 mL), CuI (3 mol%).
[b] Isolated yield.
[c] Determined by ^1H NMR.

However, the yield and *Z* selectivity increased by addition of 20 mol% Et_3N or TMEDA at 40 °C possible due to solubility of CuI (Table 2, entries 2 and 3). The addition of Et_3N acts in the same way in THF to form *Z*-isomer as the only product (Table 2, entry 5). In DMF at 40 °C the reaction proceeds fast and with high stereoselectivity (Table 2, entry 6). The stereochemistry of reaction can be changed completely by using a protic solvent. Thus the studied reaction in the mixture of *i*-AmOH–ethylene glycol (10:1) at 40 °C gives 100% yield and predominantly the *E*-isomer (Table 2, entry 7). Increasing the temperature up to 80 °C leads to an increase in the *E*/*Z* ratio (49:1, Table 2, entry 8).

The same regularity was observed for aliphatic alkynes. The reaction of hexyne-1 with PhSH at 80 °C in DMF and *i*-AmOH–ethylene glycol (10:1) gives the same yield of the product **3b**, but the selectivity is fully converted from a *Z*/*E* ratio of 20:1 into 1:4 (Table 2, entries 9 and 10). The reactions of *N*,*N*-dimethylpropargyl amine and propargyl alcohol with PhSH revealed the strong influence of the functional group capable to coordinate the metal on the selectivity of reaction. For these alkynes the *E*-isomer is formed as the only isomer (Table 2, entry 11 for CH_2NMe_2) and predominantly (Table 2, entry 12 for CH_2OH) even in THF.

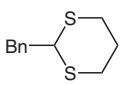
Several aliphatic thiols were studied in the reaction with phenylacetylene. For all thiols the yield of the products are high but the reaction needs high temperature for the reaction with PhSH (Table 3). CuI-catalyzed reactions of aliphatic thiols and phenylacetylene in THF and DMF proceed with high yields and *Z*-stereoselectivity (Table 3, entries 1, 2, 5–7). In 1,3-propanedithiol only one SH

Table 3 CuI-Catalyzed Addition of Aliphatic Thiols to Phenylacetylene



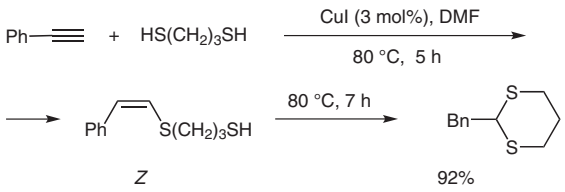
1a **2b–d** **3e–g**

3e R = Bn
3f R = Hex
3g R = $HS(CH_2)_3$

Entry[a]	Thiol **2** (*R*)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	*Z*/*E* ratio of **3**[c]
1[32]	**2b** Bn	DMF	80	2	72	10:1[12q,14c,23a,b] **3e**
2		THF	50	6	70	12:1
3		*i*-AmOH, ethylene glycol (10:1)	80	2	70[d]	1:4
4		*i*-AmOH, ethylene glycol (10:1)	80	4	88[d]	1:10
5	**2c** Hex	DMF	80	2	90	15:1[23a] **3f**[25]
6		DMF	80	4	97	4:1
7		THF	50	4	90	16:1
8		*i*-AmOH, ethylene glycol (10:1)	80	2	90	1.3:1
9		*i*-AmOH, ethylene glycol (10:1)	80	4	96	1:5
10[e]	**2d** $HS(CH_2)_3SH$	DMF	80	5	100	100:0[17] **3g**[28]
11		THF	50	5	97	100:0
12		*i*-AmOH, ethylene glycol (10:1)	80	5	85	4:1
13		none	80	5	90	1.3:1
14		DMF	80	12	92	 **3h**[17,29]

[a] *Reaction conditions:* Thiol (1 mmol), alkyne (1 mmol), CuI (3 mol%), solvent (0.5 mL).
[b] Isolated yield
[c] *Z*/*E* isomeric ratio determined by ^1H NMR
[d] Formation of disulfide observed
[e] *Reaction conditions:* Thiol (1 mmol), alkyne (2 mmol), solvent (0.5 mL), CuI (6 mol%).

group takes part in the reaction and only *Z* isomer is formed (Table 3, entries 10, 11), on further heating (80 °C, 7 h) the reaction leads to the intramolecular heterocyclization and the formation of 2-benzyl-1,3-dithiane (**3h**, Scheme 2).[17]



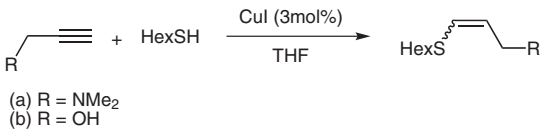
Scheme 2

In the protic solvent, as it was with thiophenol, formation of the *E*-isomer is observed (Table 3, entries 3, 4, 8, 9). The *E*/*Z* ratio increases with time and at higher reaction temperatures. In the reaction of HexSH with phenylacetylene, even in a protic solvent, both isomers are formed in roughly equal amounts, while after keeping the reaction mixture at 80 °C for four hours the *E*/*Z* ratio reaches 5:1 (Table 3, entries 8 and 9). For benzylthiol the initial *E*/*Z* ratio of 4:1 (2 h) changes to 10:1 (4 h, Table 3, entries 3 and 4), the *E*-isomer appears also for 1,3-propaneditiol (Table 3, entry 12).

As follows from the data in Table 3, the yield of alkyl-β-styrylsulfides was near to quantitative in all solvents, the stereoselectivity depends on the solvent. The reaction without solvent is not stereoselective for all thiols (Table 3, entry 13).

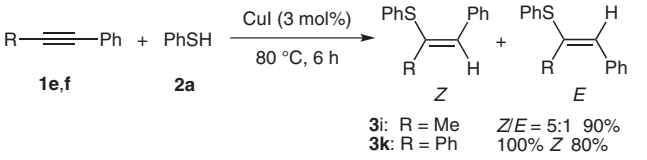
Special trial experiments showed that aliphatic thiols do not react with aliphatic alkynes without copper catalyst under similar conditions. The lower reactivity of alkylthiols becomes especially pronounced in the reaction with *N*,*N*-dimethylpropargyl amine and propargyl alcohol in THF.

The product yield for *N*,*N*-dimethylpropargylamine reaches 40% at 80 °C in 12 hours, while for the propargyl alcohol it is even lower (Scheme 3).



Scheme 3 *Reaction and conditions*: (a) 12 h, 80 °C, 40%, *E* = 100%;(b) 4 h, 50 °C, <10%, *E*/*Z* = 3:1.

It is known that hydrothiolation of internal alkynes is much more difficult to carry out than terminal alkynes. However, the CuI-catalyzed hydrothiolation of methylphenylacetylene and diphenylacetylene with PhSH proceed very smoothly without solvent at 80 °C and high regio- and stereoselectivety to give only one isomer in the case of R = Ph (apparently *Z*),[15b] and mainly the *Z*-isomer in the case of R = Me (Scheme 4).[12i,15b,l,16b,18]



Scheme 4

The obtained data shows clearly that the CuI-catalyzed hydrothiolation of alkynes can serve as a useful preparative method for the synthesis of various *Z*-β-alkenylsulfides.

Earlier it has been shown that (*Z*)-alkenylsulfides have been obtained in the reaction of arylpropiolic acid with RSH in the presence of CuI and Cs_2CO_3. The reaction was not stereoselective for PhSH, though for other RSH *Z* stereoselectivity was observed.[12n] In our opinion, under the conditions described in the work[12n] decarboxylation of arylpropiolic acid takes place, and the reaction proceeds with the phenylacetylene formed.

The transition-metal-catalyzed hydrothiolation, if it goes against Markovnikov rule, proceeds as *syn* addition leading to the *E*-isomer. On the other hand as we have shown in this paper the *Z*-isomer can be isomerized into the *E*-isomer under heating or increasing the time of the reaction in the presence of CuI and thiols. Without CuI increasing the reaction time or its temperature almost no effect on the *Z*/*E*-isomer ratio has been observed (Table 4). However, in the presence of CuI and especially in a protic solvent (Table 4) the amount of the *E*-isomer increases reaching in some cases 100%.

In summary, a regio- and stereoselective method is developed for the synthesis of *Z*-β-isomers of alkenylaryl(alkyl)sulfides based on the CuI-catalyzed hydrothiolation of alkynes. The following isomerization of the *Z*-isomers into *E*-isomers, also catalyzed with CuI, allows to obtain the *E*-isomers of alkenylsulfides. CuI ap-

Table 4 Thermal and CuI-Catalyzed Isomerization of Ethenyl Sulfides in *i*-AmOH–Ethylene Glycol (10:1)

Entry[a]	Ethenyl sulfide **3**	Starting *Z*/*E* ratio	Temp (°C)	Time (h)	*Z*/*E* ratio (A)[b]	*Z*/*E* ratio (B)[b]
1	**3a**	2.4:1	85	2	2.0:1	1:6
			85	4	1.8:1	0:100
2	**3i**[30]	2.5:1	85	2	2.2:1	1:1
			85	4	2.0:1	1:10
			85	6	1.9:1	1:30
3	**3f**	1.9:1	85	4	1.8:1	1:1.3
			100	6	1.7:1	1:4.2[c]
4	**3f**	1.9:1	85	4	1.7:1	1:2.5
			100	6	1.6:1	1:10[c]

[a] *Z*/*E* ratio determined by ^{1}H NMR analysis.
[b] Conditions A: heating; conditions B: heating with 1 equiv of thiol and 3 mol% CuI.
[c] HexSCH=CHPh is partly decomposed.

parently acts as a Lewis acid and activates the triple bond towards *trans*-nucleophilic addition.

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(24) The products **3a**,[12r,16f,19] **3c**,[20] **3d**,[12r,21] **3b**,[15l,22a,b] **3e**,[12q,14c,23a,b] **3f**,[23a] **3g**,**h**,[18] **3i**,[12i,15b,l,16b,17] **3k**,[15b,31] were identified according to published data. The *Z*/*E* isomeric ratio for **3i** and **3k** was determined by ^{1}H NMR and ^{13}C NMR spectroscopy.

(25) **Typical Experimental Procedure for the CuI-Catalyzed Hydrothiolation of the Alkynes**

To a mixture of phenylacetylene (**1a**, 0.102 g, 1 mmol), CuI (0.006 g, 3 mol%) in DMF (0.5 mL) was added HexSH (**2c**, 0.118 g, 1 mmol) under an argon atmosphere, the mixture was stirred at 80 °C for 2 h and then evaporated under vacuum. The resulting oil was diluted with $CHCl_3$ and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (EtOAc–hexane, 5:95) to afford hexyl-(2-styryl)sulfide (**3f**,[23a] 0.198 g, 90%; *Z*/*E* = 15:1 by NMR) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 7.46–7.15 (m, 5 H, Ph), 6,39 (d, $^3J_{HH}$ = 10.5 Hz, 1 H, PhCH=), 6.20 (d, $^3J_{HH}$ = 10.5 Hz, 1 H, =CHS), 2.72 (t, $^3J_{HH}$ = 7.4 Hz, 2 H, CH_2S), 1.65 (m, 2 H), 1.38 (m, 2 H), 1.28 (m, 4 H), 0.87 (t, 3 H, CH_3); δ (*E*-isomer) = 7.34–7.16 (m, 5 H, Ph), 6.72 (d, $^3J_{HH}$ = 16.0 Hz, 1 H, PhCH=), 6.46 (d, $^3J_{HH}$ = 16.0 Hz, 1 H, =CHS), 2.79 (t, $^3J_{HH}$ = 7.4 Hz, 2 H, CH_2S), 1.69 (m, 2 H), 1.43 (m, 2 H), 1.31 (m, 4 H), 0.90 (t, 3 H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (*Z*-isomer) = 136.94, 128.45, 128.02, 127.57, 126.55, 125.59, 35.80, 31.27, 30.10, 28.15, 22.43, 13.93; δ (*E*-isomer) = 136.98, 128.48, 128.05, 127.60, 126.35, 125.05, 32.52, 31,25, 29.23, 28.36, 22.41, 13.96.

(26) **(*E*)-*N*,*N*-Dimethyl-3-(phenylthio)-2-propenylamine (3c)**[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.50 (m, Ph), 6.39 (dt, $^3J_{HH}$ = 16.0 Hz, J_{HH} = 1.4 Hz, 1 H, =CHS), 5.87 (dt, $^3J_{HH}$ = 16.0 Hz, J_{HH} = 1.4 Hz, 1 H, =CHC), 3.23 (d, J_{HH} = 8.0 Hz, 2 H, CH_2N), 2.36 (s, 6 H, CH_3N). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 135.57, 128.93, 128.84, 128.11, 126.55, 126.36, 57.10, 44.91. Anal. Calcd for $C_{11}H_{15}NS$: C, 68.37; H, 7.81; N, 7.25. Found: C, 68.25; H, 8.00; N, 7.38.

(27) **3-(Phenylthio)prop-2-en-1-ol (3d, *E*/*Z* = 5:1)**[12r,21]

***E*-Isomer**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.49 (m, 5 H, Ph), 6.43 (dt, $^3J_{HH}$ = 14.0 Hz, J_{HH} = 1.4 Hz, 1 H, =CHS), 5.93 (dt, $^3J_{HH}$ = 1.4 Hz, 1 H, =CHC), 4.16 (d, $^2J_{HH}$ = 7.15 Hz, 2 H, H_2CO), 2.15 (br s, 1 H, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 132.99, 130.93, 129.96, 128.98, 127.36, 127.05, 63.07.

***Z*-Isomer**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.49 (m, 5 H, Ph), 6.33 (dt, $^3J_{HH}$ = 8.0 Hz, J_{HH} = 1.2 Hz, 1 H, =CHS), 5.90–5.96 (m, 1 H, =CHC), 4.34 (d, $^2J_{HH}$ = 7.12 Hz, 2 H, H_2CO), 2.13 (br s, 1 H, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.88, 129.58, 129.04, 128.98, 127.36, 126.91, 59.65. Anal. Calcd. for $C_9H_{10}OS$: C, 65.06; H, 6.02. Found: C, 65.26; H, 6.19.

(28) **(*Z*)-3-(2-Styrylthio)propanethiol (3g)**[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.48 (m 5 H, Ph), 6.44 (dd, $^3J_{HH}$ = 10.8 Hz, 1 H, =CHPh), 6.17 (dd, $^3J_{HH}$ = 10.8 Hz, 1 H, =CHS), 2.84–2.93 (m, 2 H, $=CSCH_2$), 2.57–2.63 (m, 2 H, H_2CSH), 1.82–1.97 (m, 2 H, CCH_2C), 1.34 (t, $^3J_{HH}$ = 7.0 Hz, 1 H, SH). ^{13}C NMR (100.6 MHz, $CDCI_3$): δ = 137.20, 129.16, 128.66, 128.25, 126.91 126.74, 41.61, 30.60, 25.64.

(29) **2-Benzyl-1,3-dithiane (3h)**[17]

^{1}H NMR (400 MHz, $CDCI_3$): δ = 7.25–7.31 (m, 5 H, Ph), 4.25 (t, 1 H, SCH_2S), 2.94 (d, 2 H, H_2CPh), 2.73 (m, 4 H, SCH_2C), 2.05 (m, 1 H), 1.88 (m, 1 H). ^{13}C NMR (100.6 MHz, $CDCI_3$): δ = 137.20, 129.16, 128.25, 126.91, 48.82, 41.59, 30.60, 25.60.

(30) **1-Phenyl-2-(phenylthio)propene (3i,**[12i,15b,l,16b,18] ***Z*/*E* = 5:1)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.55 (21 H, m), 6.69 (1 H, s, *Z* form), 2.12 (3 H, s, *E* form, 0.17), 2.01 (3 H, s, *Z* form, 0.83). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (*Z*) = 136.72, 133.50, 131.98, 131.57, 130.79, 128.98, 128.82, 127.96, 127.12, 126.91, 25.55; δ (*E*) = 137.04, 133.83, 131.96, 131.41, 130.69, 129.03, 128.62, 128.21, 127.33, 126.69, 19.49.

(31) **(*Z*)-1,2-Diphenyl-1-(phenylthio)ethene (3k)**[15b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (1 H, d, *J* = 7.6 Hz), 7.62 (1 H, d, *J* = 7.8 Hz), 6.92–7.52 (13 H, m), 6.79 (1 H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.83, 137.86, 136.64, 135.64, 134.56, 132.25, 129.74, 129.44, 129.00, 128.58, 128.10, 127.95, 127.36, 125.73.

(32) **Typical Procedure for the Thermal and CuI-Catalyzed *Z*- to *E*-Isomerization of Alkenyl Sulfides**

In each of two Schlenk tubes under argon atmosphere were placed phenyl-(2-styryl)sulfide (*Z*/*E* = 2.4:1, 0.106 g, 0.5 mmol). In one of the Schlenk tubes were added thiophenol (**2a**, 0.055 g, 0.05 mmol), and CuI (0.006 g, 3 mol%). Both tubes were heated at 85 °C. The changes of the *Z*/*E* ratio was inspected by ^{1}H NMR spectroscopy. After 4 h without PhSH and CuI the ratio was *Z*/*E* = 1.8:1, with CuI and thiol only 100% *E*-isomer **3a** was observed (Table 3, entry 1).

