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Regio- and Stereoselective Copper-Catalyzed Carbozincation Reactions of Alkynyl Sulfoximines and Sulfones

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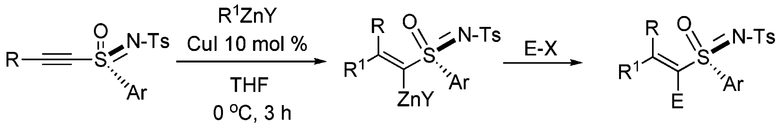
ABSTRACT

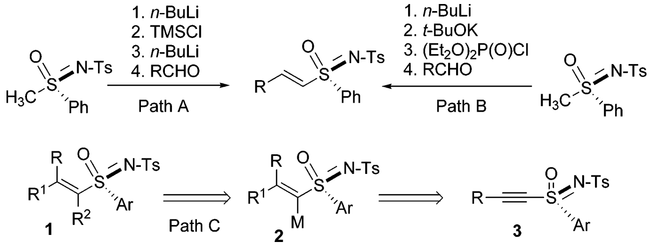


Stereochemically pure polysubstituted vinyl sulfoximines and sulfones are easily prepared by a copper-catalyzed syn carbozincation reaction of the corresponding alkynyl derivatives.

Nonracemic sulfoximines having a stereogenic sulfur atom are well-known in asymmetric synthesis.[1] Particularly, vinyl sulfoximines are an interesting class of compounds, which were used in a large variety of asymmetric transformations such as conjugate additions[1b,2] and pericyclic reactions[3] and as precursors for allylic sulfoximines.[4]

E-Substituted vinyl sulfoximines are easily prepared either by an “in situ Peterson” reaction[5] (Scheme 1, path A) or via metalated hydroxyphosphonate derivatives[6] (Scheme 1, path B). In both cases, yields and *E*-selectivities were excellent (80% yield, >92% *E*). Besides these two protocols, few more preparations of *E*-vinyl-substituted sulfoximines, relying on hydroxyalkylation−elimination sequences of metalated alkyl sulfoximines, were also reported.[7] Surprisingly, straightfor-

Scheme 1. General Preparation of *E*-Substituted Vinyl Sulfoximines



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(1) (a) For recent reviews on the use of sulfoximines in asymmetric catalysis, see: (a) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (b) Harmata, M. *Chemtracts* **2003**, *16*, 660. (c) For a general overview on the chemistry of sulfoximines, see: Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.

(2) (a) Pyne, S. G. *J. Org. Chem.* **1986**, *51*, 81. (b) Pyne, S. G. *Tetrahedron Lett.* **1986**, *27*, 1691. (c) Annunziata, R.; Cinquini, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1684. (d) Pyne, S. G. *J. Chem. Soc., Chem. Commun.* **1986**, 1686.

(3) (a) David, D. M.; Bakavoli, M.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **1995**, *51*, 12393. (b) Craig, D.; Geach, N. J. *Tetrahedron: Asymmetry* **1991**, *2*, 1177. (c) Glass, R. S.; Reineke, K.; Shankli, M. *J. Org. Chem.* **1984**, *49*, 1527. (d) Craig, D.; Geach, N. J.; Pearson, C. J.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 6071.

(4) (a) Erdelmeier, I.; Gais, H.-J.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 935. (b) Günther, M.; Gais, H.-J. *J. Org. Chem.* **2003**, *68*, 8037. (c) Schleusner, M.; Gais, H.-J.; Koep, S.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 7789. (d) Koep, S.; Gais, H.-J.; Raabe, G. *J. Am. Chem. Soc.* **2003**, *125*, 13243. (e) Tiwari, S. K.; Gais, H.-J.; Lindenmaier, A.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Köhler, F.; Günter, M.; Koep, S.; Iska, V. B. R. *J. Am. Chem. Soc.* **2006**, *128*, 7360.

(5) Erdelmeier, I.; Gais, H. J. *Tetrahedron Lett.* **1985**, *26*, 4359.

(6) Craig, D.; Geach, N. J. *Synlett* **1992**, 299.

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ward routes to stereodefined α,β,β′-trisubstituted vinyl sulfoximines of general structure **1** remain unknown. In this communication, we would like to report our preliminary results for an easy preparation of stereodefined polysubstituted vinylsulfoximine derivatives **1**.

Our retrosynthetic analysis for the preparation of **1** shows that it should be easily prepared by a regiospecific syn bisalkylation of substituents R^1 and R^2 on the triple bond of alkynyl sulfoximines **3** (Scheme 1, path C). Accordingly, a regio- and stereoselective carbometalation reaction of **3**, followed by trapping the resulting vinylic organometallic **2** with an electrophile $R^2{-}X$, should be the key reaction for the preparation of tetrasubstituted alkenyl derivatives **1**. Among all the possible candidates for the carbometalation reactions of heterosubstituted alkynes,[8] organocopper derivatives are usually the best candidates[9] because organocopper species are known for their high stereo- and chemoselectivity, which enable them to add smoothly to a large variety of alkynes with high tolerance to many functional groups.[10] However, sulfoximines can be taken as the aza-analogues of sulfones, and the literature shows that the carbocupration of alkynyl sulfones generally leads to two isomers in a variable ratio.[11] The carbometalation reaction of alkynyl sulfoximines **3** was investigated in detail. Our starting material was easily obtained in high yield[12] by reaction of [*N*-(*p*-tolylsulfinyl)imino]phenyliodinane (PhI═NTs)[13] on alkynyl sulfoxide in the presence of a catalytic amount of a copper(II) salt. This imination is stereospecific and occurs with retention of configuration at the sulfur atom.[14] We initially started our investigation by the classical carbocupration reaction of **3a** (Scheme 2 and Table 1). When ethylcopper (prepared from EtMgBr and CuI) was added to alkynyl sulfoximine **3a** in THF at −40 °C, the carbocupration reaction occurred, but two isomers were formed in a 6:1 ratio (Table 1, entry 1). The formation of these two isomers is indeed reminiscent of the carbocupration of acetylenic sulfones.[11]

Scheme 2. Carbometalation Reaction of Alkynyl Sulfoximine **3**

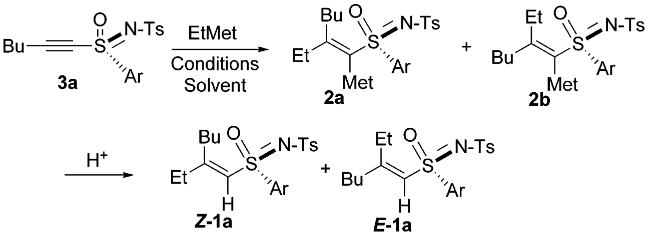

Table 1. Carbometalation Reaction of Alkynyl Sulfoximine **3a**

entry	EtM	solvent	temp (°C), time (h)	*Z*/*E* ratio[e]	yield (%)[d]
1	EtCu	THF	−40, 4	6:1	80
2	EtCu	Et_2O	−40, 4	2:1	70
3	EtCu[a]	THF	−70, 1	4:1	72
4	EtCu[a]	Et_2O	−70, 0.5	1:1	71
5	EtCu[a]	THF/NMP[b]	−50, 1	3:1	90
6	Et_2Cu, MgBr[c]	THF	−60, 0.5	2:1	85
7	RMgBr, CuI (10 mol %)	THF	0, 3	1:1	50
8	Et_2Zn, CuI (10 mol %)	THF	0, 2	100:0	82
9	Et_2Zn, CuI (10 mol %)	Et_2O	rt, 6	100:0	80

[a] The reaction was performed with an excess of CuBr[11a] (CuBr/EtMgBr = 3:1). [b] THF/NMP = 3:1. [c] The structure reflects the stoichiometry rather than the real organometallic species. [d] Yield determined after purification by chromatography on silica gel. [e] Ratio determined by ^1H NMR spectroscopy of the crude mixture.

When the same reaction was performed in a less polar solvent such as Et_2O, the reaction still proceeded but in a 2:1 ratio (Table 1, entry 2). When organocopper (in the presence of excess copper salt,[11a,15] in THF, Et_2O, or a mixture of THF and NMP; Table 1, entries 3, 4, and 5, respectively), alkyl cuprate (Table 1, entry 6), or a copper-catalyzed ethylmagnesiation reaction (Table 1, entry 7) was used, the stereoselectivity was not improved. The two isomers result formally from a syn and anti addition of the organocopper reagent on the triple bond although a subsequent isomerization of the resulting sp^2 organocopper derivative (**2a** into **2b**) cannot be excluded.

Careful analyses of chiral HPLC of racemic and enantioenriched vinyl sulfoximines show that the sulfoximine unit is not racemized in this isomerization process. Only the copper-catalyzed carbozincation[16] reaction led to a single stereoisomer via a syn addition under mild conditions in either THF or Et_2O (Table 1, entries 8 and 9, respectively).

The scope of the reaction is broad in terms of reactive organozinc species which can be used (Scheme 3 and Table 2).

Copper-catalyzed carbozincation reaction proceeds similarly when dialkylzinc (Table 2, entry 1) or alkylzinc halide was used, prepared either from dialkylzinc and 1 equiv of iodine (Table 1, entry 2) or by insertion of zinc dust into

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(7) (a) Craig, D.; Geach, N. J. *Synlett* **1993**, 481. (b) Bailey, P. L.; Clegg, W.; Jackson, R. F. W.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 343. (c) Paley, R. S.; Snow, S. R. *Tetrahedron Lett.* **1990**, *31*, 5853.

(8) For recent reviews on carbometalation, see: (a) Marek, I.; Chinkov, N.; Banon-Tene, D. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; p 395. (b) Banon-Tenne, D.; Marek, I. In Carbometalation Reactions of Zinc Enolate Derivatives. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 2004; p 563. (c) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535.

(9) (a) Chechik-Lankin, H.; Marek, I. *Org. Lett.* **2003**, *5*, 5087. (b) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098.

(10) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(11) (a) Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 14. (b) Fiandanese, V.; Marchese, G.; Naso, F. *Tetrahedron Lett.* **1978**, *19*, 5131. (c) Eisch, J. J.; Behrooz, M.; Galle, J. E. *Tetrahedron Lett.* **1984**, *25*, 4851. (d) Eisch, J. J.; Behrooz, M.; Dua, S. K. *J. Organomet. Chem.* **1985**, *285*, 121. (e) Xie, M.; Huang, X. *Synlett* **2003**, 477. (f) Xie, M.; Wang, J.; Gu, X.; Sun, Y.; Wang, S. *Org. Lett.* **2006**, *8*, 431.

(12) (a) Lacote, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116. (b) For alternative sulfoxide imination procedures, see: Garcìa-Mancheño, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349 and references therein.

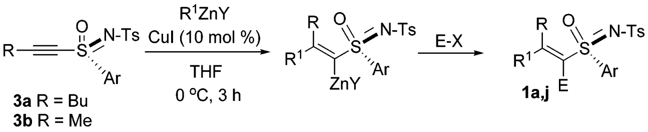
(13) Taylor, S.; Gullick, J.; McMorn, P.; Bethell, D.; Bulman Page, P. C.; Hancock, F. E.; King, F.; Hutchings, G. J. *Top. Catal.* **2003**, *24*, 43.

(14) See experimental procedure for HPLC or GC analyses using chiral stationary phases.

(15) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

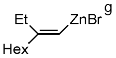
(16) Maezaki, N.; Sawamoto, H.; Yoshigami, R.; Suzuki, T.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1345.

Scheme 3. Copper-Catalyzed Carbozincation Reaction of Alkynyl Sulfoximines



the carbon−iodine bond (Table 2, entry 3). Similarly, the copper-catalyzed carbozincation can be performed from a Grignard reagent or an alkyllithium species if these latters are transmetalated into an organozinc species (Table 1, entries 4 and 9, respectively).

Table 2. Copper-Catalyzed Carbozincation Reaction

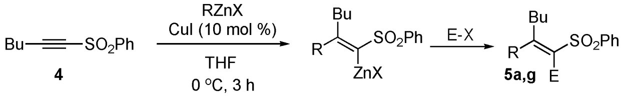
entry	R	R^1ZnY	E−X	E	product	yield (%)[a]
1	**3a**	Et_2Zn	HCl	H	**1a**	82
2	**3a**	EtZnI[b]	HCl	H	**1a**	90
3	**3a**	OctZnI[c]	HCl	H	**1b**	55
4	**3a**	EtZnBr[d]	HCl	H	**1a**	75
5	**3a**	*i*-PrZnBr[d]	HCl	H	**1c**	80
6	**3a**	Me_2Zn	HCl	H	**1d**	83
7	**3a**	PhZnBr[d]	HCl	H	**1e**	85
8	**3b**	Bu_2Zn[e]	HCl	H	**1f**	92
9	**3b**	BuZnBr[f]	HCl	H	**1f**	80
10	**3b**	Et_2Zn	HCl	H	**1g**	90
11	**3a**	$MeOCO(CH_2)_3ZnI$[c]	HCl	H	**1h**	55
12	**3a**	Et_2Zn	I_2	I	**1i**	78
13	**3a**	Et_2Zn	allylBr	allyl	**1j**	65
14	**3a**		HCl	H	**1k**	72
15	**3a**	Hex-CC-ZnBr[f]	HCl	H	**1l**	18

[a] Yields determined after purification by chromatography on silica gel. [b] Prepared from Et_2Zn and I_2. [c] Prepared from the corresponding alkyl iodide and zinc dust. [d] Generated from the corresponding Grignard reagent and $ZnBr_2$. [e] In the presence of CuCN•2LiCl, 10 mol %. [f] Prepared from the corresponding alkyllithium and $ZnBr_2$. [g] Prepared from the corresponding vinyl iodide followed by a iodine−lithium exchange and transmetalation with $ZnBr_2$.

Therefore, most of the classical methods for the preparation of alkylzinc halide derivatives[17] were tested (with different associated salts), and all of them led to the carbometalation reaction of alkynylsulfoximines in very good yields. The nature of the alkyl groups can be extended to secondary alkyl groups (Table 2, entry 5) as well as to the more sluggish methyl and aryl groups (Table 2, entries 6 and 7). Even functionalized alkylzinc iodides undergo the copper-catalyzed carbozincation reaction (Table 2, entry 11).[17] The formation of a discrete organometallic species was checked by iodinolysis and allylation as depicted in Table 2, entries 12 and 13 (formation of **1i** and **1j**, respectively). The allylation reaction implies that the copper salt is used not only as a catalyst for the carbozincation reaction but also for the reaction with electrophiles. The *E*-vinylzinc species, generated by an iodine−lithium exchange followed by a transmetalation reaction with $ZnBr_2$, undergoes the copper-catalyzed carbozincation to lead to the corresponding (*E*,*E*)-dienyl sulfoximines in 72% yield as unique stereoisomer (Table 2, entry 14). In contrast, the addition of alkynylzinc species to alkynylsulfoximine is sluggish and only 18% of the isolated product has been obtained (Table 2, entry 15). The unique stereochemistry of the product was determined by NOE measurement of **1d** and is easily rationalized by a copper-catalyzed syn addition of the organozinc species across the triple bond of the alkynyl sulfoximine.

Having in hand an easy and reproducible protocol for the carbometalation reaction of alkynyl sulfoximines, we decided to investigate also the case of alkynyl sulfones, known to give two isomers by carbocupration reactions.[11] We were pleased to observe that alkynyl sulfones also reacted cleanly with the copper-catalyzed addition of alkylzinc derivatives to lead to a single regio- and stereoisomer in good isolated yields as described in Table 3. Primary and secondary functionalized derivatives react regio- and stereoselectively with alkynyl sulfones.

Table 3. Copper-Catalyzed Carbozincation of Alkynyl Sulfones



entry	RZnX	E−X	E	product	yield (%)[a]
1	Bu_2Zn	HCl	H	**5a**	70
2	Et_2Zn	HCl	H	**5b**	72
3	*i*-PrZnBr[b]	HCl	H	**5c**	92
4	$MeOCO(CH_2)_3ZnI$[c]	HCl	H	**5d**	55
5	Et_2Zn	I_2	I	**5e**	65
6	Et_2Zn	allylBr	allyl	**5f**	60

[a] Yields determined after purification by chromatography on silica gel. [b] Generated from the corresponding Grignard reagent and $ZnBr_2$. [c] Prepared from the corresponding alkyl iodide and zinc dust.

In conclusion, polysubstituted vinyl sulfoximines and sulfones were easily prepared as unique isomers by totally regio- and stereoselective copper-catalyzed carbozincation reactions. The addition is syn, and the resulting sp^2 organometallic can easily react with classical electrophiles. Several applications of this new class of compounds is now underway in our laboratory.

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Supporting Information Available: Experimental procedures with a description of ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.