Tetrahedron Letters, Vol.31, No.13, pp 1829-1832, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

S_N2' Substitutions of 1,3-Dichloropropenes with the Functionalized Copper-Zinc Reagents RCu(CN)ZnX

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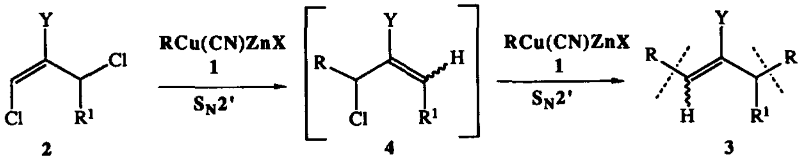
Summary: The addition of benzenesulfenyl (or benzeneselenyl) chlorides to propargylic chlorides affords regio- and stereospecifically (E)-1,3-dichloro-2-phenylsulfenyl (or phenylselenyl) propenes (2a-c). These new reagents were found to react with excellent S_N2' selectivity with the highly functionalized copper-zinc reagents RCu(CN)ZnX, affording polyfunctional vinylic-thioethers or -selenides of type 3. The acidic hydrolysis of 3 furnishes symmetrical ketones in good yields.

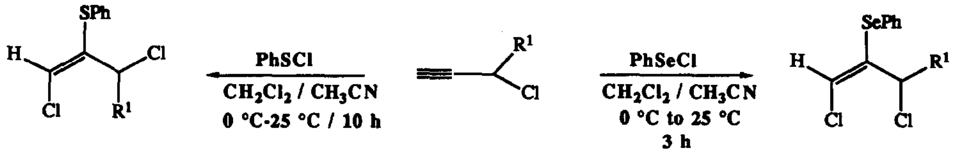
Many functionalized allylic compounds have proven to be versatile reagents for organic synthesis.[1] 1,3-Dihalopropenes are potentially interesting multicoupling[2] reagents, since two successive S_N2' substitutions would allow a 1,3-*bis*-functionalization of the allylic system. Unfortunately a comprehensive literature search shows that 1,3-dihalopropenes usually undergo only S_N2 substitutions leading to terminal vinylic halides which are unreactive towards further substitution.[3] We have found during a general study on the reactivity of the functionalized copper-zinc organometallics RCu(CN)ZnX[4] **1** that these copper derivatives[5] react with a high S_N2' selectivity (> 98%) with various 1,3-dichloropropenes **2** to afford functionalized olefins of type **3**[6] (see Scheme I and Table I). Typically the 1,3-dichloropropene (1.0 equiv.) was added at -78 °C to a THF solution of RCu(CN)ZnX (2.5 equiv.). The reaction mixture was warmed to 25 °C (to -10 °C in the case of benzylic copper-zinc reagents). The monitoring of the reaction (GLC analysis) indicates its completion after 3-22 h (see Table I). Besides the desired 1,3-disubstituted allylic products $R{-}CH{=}C(Y){-}CH_2{-}R$ **3**, less than 3% of 1,1-disubstituted allylic derivatives of type **5** ($R_2CH{-}C(Y){=}CH_2$) was detected in the crude reaction mixture. In strong contrast, the use of 1,3-di*bromo*propene leads to the formation of appreciable amounts of compounds **5** (6-30%). This behaviour may be explained by the easy isomerization of the intermediate allylic *bromide* (compare with **4**; Scheme I) rather than by a low regioselectivity of the reaction of RCu(CN)ZnX with allylic bromides. The 1,3-dichloro allylic compounds **2a-c** were prepared[6] by the addition of benzenesulfenyl chloride[7] or benzeneselenyl chloride[8] to propargylic chlorides[9] in a mixture of dichloromethane and acetonitrile (3-10 h; 25 °C)[6]. These additions are regio- and stereospecific, affording only the (*E*)-isomers in high yields (76-90%); see Scheme II.

Scheme I



Y = SePh, SPh; R^1 = Me or H

Scheme II

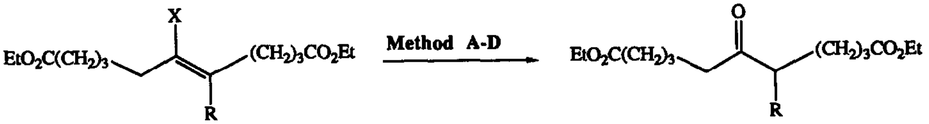


2a: R = H (90%)
2b: R = Me (76%)

2c: R^1 = H (85%)

As shown in Table I, a variety of functionalized zinc-copper reagents RCu(CN)ZnX containing ester-, nitrile- or phosphonate groups react in high yields. The reaction can be extended to the more reactive and thermally less stable benzylic and heterocyclic copper-zinc reagents by performing the coupling reactions between -20 °C and -10 °C (see entries 7,8,11,14, and 15). The alkenyl thio- and seleno-ethers produced have predominantly the (Z) configuration, whereas mainly (E)-olefins result from the addition of RCu(CN)ZnX to 1,3-dichloropropene.[10] Remarkably, benzylic and heterobenzylic copper-zinc reagents afford almost exclusively one double bond isomer (see entries 7,8,11,14 and 15). Several of the functionalized vinylic thioethers and selenides can be converted under various reaction conditions[11] to ketones by using formic or trifluoroacetic acid as solvent. A mixture of iodoacetic and formic acid was found especially efficient for the hydrolysis of the selenium derivative **3j** to the ketone **6b** (see Scheme III). The new allylic 1,3-dichlorides **2a-2c** belong to a new class of useful $a^2/a^{2'}$ multicoupling reagents[2,12] allowing a highly regioselective 1,3-difunctionalization of allylic systems. Extensions of this methodology are currently underway in our laboratories.

Scheme III



3i: R = Me; X = SPh
3j: R = H; X = SePh

6a: R = Me; Method A: 68%
6b: R = H; Method B: 76%
Method C: 71%
Method D: 94%

Reaction conditions: Method A: CF_3CO_2H, 25 °C, 6 days; Method B: HCO_2H/CH_2Cl_2, $Hg(OAc)_2$ (1 eq.), 25 °C, 4 days; Method C: CF_3CO_2H, 25 °C, 24 h; Method D: HCO_2H/ICH_2CO_2H, 25 °C, 1 h.

Acknowledgment: We thank the Chemistry Department of the University of Michigan and the Horace H. Rackham School of Graduate Studies of the University of Michigan, the National Institutes of Health (GM 41908) and the Donors of the Petroleum Research Fund, administered by the American Chemical Society for their generous support of this work.

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1. (a) Trost, B.M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1; (b) Molander, G.A.; Schubert, D.C. *J. Am. Chem. Soc.* **1987**, *109*, 6877; (c) Heathcock, C.H.; Smith, K.M.; Blumenkopf, T.A. *J. Am. Chem. Soc.* **1986**, *108*, 5023; (d) Beak, P.; Kempf, D.J.; Wilson, K.D. *J. Am. Chem. Soc.* **1985**, *107*, 4745; (e) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261; (f) Auvray, P.; Knochel, P.; Normant, J.F. *Tetrahedron* **1988**, *44*, 4495.
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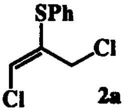
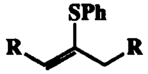
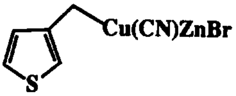
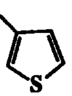
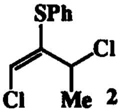
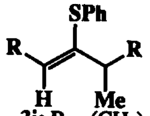
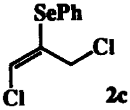
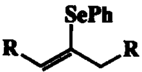
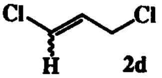
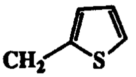
Table I. Products of Type 3 Obtained by the Reaction of the 1,3-Dichloropropenes **2a-d** with the Copper-Zinc Reagents RCu(CN)ZnX.

Entry	RCu(CN)ZnX	1,3-dichloro-derivative	Reaction Conditions (temp (°C)/time (h))	Product of Type 3	*E/Z* ratio	Yield (%)[a]
1	$EtO_2C-(CH_2)_3-Cu(CN)ZnI$	 **2a**	(25/18)	 **3a**: R = $(CH_2)_3CO_2Et$	21/79	88
2	c-HexCu(CN)ZnI	**2a**	(25/22)	**3b**: R = c-Hex	44/56	88
3	BuCu(CN)ZnI	**2a**	(25/14)	**3c**: R = Bu	40/60	89
4	$NC(CH_2)_3Cu(CN)ZnI$	**2a**	(25/15)	**3d**: R = $(CH_2)_3CN$	8/92	85
5	$AcO(CH_2)_6Cu(CN)ZnI$	**2a**	(25/15)	**3e**: R = $(CH_2)_6OAc$	45/55	76
6	$(EtO)_2P(O)CH_2CH_2Cu(CN)ZnBr$	**2a**	(25/ 3)	**3f**: R =$(CH_2)_2P(O)(OEt)_2$	8/92	90
7	$PhCH_2Cu(CN)ZnBr$	**2a**	(-10/20)	**3g**: R = CH_2Ph	0/100	78
8		**2a**	(-10/16)	**3h**: R = 	0/100	79
9	$EtO_2C(CH_2)_3Cu(CN)ZnI$	 **2b**	(25/12)	 **3i**: R = $(CH_2)_3CO_2Et$	11/89	89
10	$EtO_2C(CH_2)_3Cu(CN)ZnI$	 **2c**	(25/ 7)	 **3j**: R = $(CH_2)_3CO_2Et$	20/80	89
11	$PhCH_2Cu(CN)ZnBr$	**2c**	(-20/14)	**3k**: R = CH_2Ph	3/97	94
12	$NC(CH_2)_3Cu(CN)ZnI$	 **2d**	(25/14)	 **3l**: R = $(CH_2)_3CN$	87/13	88
13	$AcO(CH_2)_6Cu(CN)ZnI$	**2d**	(25/14)	**3m**: R = $(CH_2)_6OAc$	70/30	80
14	$PhCH_2Cu(CN)ZnBr$	**2d**	(-10/16)	**3n**: R = CH_2Ph	100/ 0	94
15		**2d**	(-10/15)	**3o**: R = 	100/ 0	84

[a] All yields refer to isolated yields of analytically pure products. Satisfactory spectral data (IR, ^1H and ^{13}C NMR, mass spectra and high resolution mass spectra) were obtained for all new compounds.

3. 1,3-Dihalopropenes (X = Cl or Br) are known to undergo substitution reactions with various nucleophiles. However, only the S_N2 substitution products are usually obtained: (a) Julia, M; Blasioli, C. *Bull. Soc. Chim. Fr. (Part 2)* **1976**, 1941; (b) LeBorgne, J.-F. *J. Organomet. Chem.* **1976**, *122*, 129; (c) Larcheveque, M.; Valette, G.; Cuvigny, T. *Tetrahedron* **1979**, *35*, 1745; (d) Savignac, P.; Breque, A.; Mathey, F.; Varlet, J.-M.; Collignon, N. *Synth. Comm.* **1979**, *9*, 287; (e) Ochiai, M.; Fujita, E. *J. Chem. Soc. Chem. Comm.* **1980**, 1118; (f) Schulze, K.; Richter, F.; Weisheit, R.; Krause, R.; Muhlstadt, M. *J. Prakt. Chem.* **1980**, *322*, 629; (g) Alexakis, A.; Chapdelaine, M.J.; Posner, G.H.; Runquist, A.W. *Tetrahedron Lett.* **1978**, 4205; (h) Nishiyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1981**, *22*, 5289; (i) Reich, H.J.; Clark, M.C.; Willis, Jr., W.W. *J. Org. Chem.* **1982**, *47*, 1618; (j) Schuda, P.F.; Heimann, M.R. *J. Org. Chem.* **1982**, *47*, 2484; (k) Gawley, R.E.; Termine, E.J. *J. Org. Chem.* **1984**, *49*, 1946; (l) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J.C. *J. Am. Chem. Soc.* **1984**, *106*, 2105; (m) Singh, R.K. *Synthesis* **1985**, 54.
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5. An alternative mechanism consisting of two successive S_N2 substitutions: the first at an allylic position and the second at a vinylic position can be ruled out, since we observed that vinylic chlorides are inert toward a substitution with the reagents RCu(CN)ZnX. However alkenyl iodides react slowly at higher temperatures (40-50 °C; C. Retherford, P. Knochel, work in progress). S_N2' allylation reactions of organozinc compounds in the presence of a catalytic amount of a copper (I) salt have been reported: (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056; (b) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418; (c) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155.
6. *Typical Procedure.* (a) Preparation of 1,3-dichloro-2-phenylselenyl-1-propene **2c**. A solution of 2.2 g (11.5 mmol) of benzeneselenyl chloride (Aldrich) in 10 mL of dry CH_2Cl_2 was added at -20 °C to 1.05 g (14 mmol) of propargyl chloride in 20 mL of dry acetonitrile. The reaction mixture was allowed to warm to 25 °C and was stirred for 3 h. After the addition of 200 mL of ether, the reaction mixture was sequentially washed with a sat. NH_4Cl solution and brine and dried over $MgSO_4$. Evaporation of the solvents affords 2.608 g (85% yield) of a pure yellow-orange oil which has a purity greater than 98% (contains 1.6% of diphenyldiselenide) and was used directly in the next step. ^1H NMR ($CDCl_3$, 360 MHz) δ 7.52 (m, 2H); 7.32 (m, 3H); 6.54 (s, 1H); 4.30 (s, 2H).
   (b) Addition of $EtO_2C(CH_2)_3Cu(CN)ZnI$ to **2c** (entry 10 of Table I). A THF solution of 3-carboethoxypropylzinc iodide[4] (4.6 mL, 8 mmol) was added at -30 °C to 6 mL of a THF solution containing 720 mg (8 mmol) of copper cyanide and 680 mg (16 mmol) of lithium chloride. The resulting yellow-grey solution was stirred 5 min at 0 °C and cooled back to -78 °C. A solution of 1.06 g (4 mmol) of **2c** in 2 mL of THF was added and the reaction mixture was allowed to warm to 25 °C. The reaction was monitored by GLC analysis which indicated its completion after 6 h. After a standard work-up procedure the resulting crude oil, which contained 1% of the 1,1-disubstitution product of type **5**, was purified by flash chromatography to afford 1.50 g (89% yield) of the desired 1,3-disubstitution product **3j** (see entry 10 of Table I).
7. The addition of phenylsulfenyl chloride to allylic and propargylic dihalides has been reported: (a) Hopkins, P.B.; Fuchs, P.L. *J. Org. Chem.* **1978**, *43*, 1208; (b) Pariza, R.J.; Fuchs, P.L. *J. Org. Chem.* **1983**, *48*, 2304; (c) Pariza, R.J.; Fuchs, P.L. *J. Org. Chem.* **1985**, *50*, 4252; (d) Bridges, A.J.; Fischer, J.W. *J. Org. Chem.* **1984**, *49*, 2954; (e) Back, T.G.; Krishna, M.V.; Muralidharan, K.R. *J. Org. Chem.* **1989**, *54*, 4146.
8. For the addition of phenylselenyl chloride to alkynes and allenes see: (a) Kataev, E.G.; Mannafov, T.G. *Zh. Org. Khim.* **1970**, *6*, 1971; (b) Garralt, D.G.; Beaulieu, P.L.; Ryan, M.D. *Tetrahedron* **1980**, *36*, 1507; (c) Halazy, S.; Hevesi, L. *Tetrahedron Lett.* **1983**, *24*, 2689.
9. 3-Chloro-1-butyne has been prepared in two steps from 3-butyne-2-ol: (i) TsCl, KOH, ether (79%); (ii) LiCl, DMSO (65%) see: Brandsma, L. *Preparative Acetylenic Chemistry*, **1988**, Elsevier, Amsterdam, Oxford, New York.
10. The stereochemistry of the double bond of compounds **3i**, **3j** and **3n** has been established by NOE experiments. See also: Corey, E.J.; Shulman, J.I. *J. Org. Chem.* **1970**, *35*, 777.
11. (a) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357; (b) Marino, J.P.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 1; (c) Petragnani, N.; Rodrigues, R.; Comasseto, J.V. *J. Organomet. Chem.* **1976**, *114*, 281; (d) Comasseto, J.V. Petragnani, N.J. *Organomet. Chem.* **1978**, *152*, 295.
12. Seebach, D. *Angew. Chem.* **1979**, *91*, 259; ibid, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

(Received in USA 6 February 1990)