

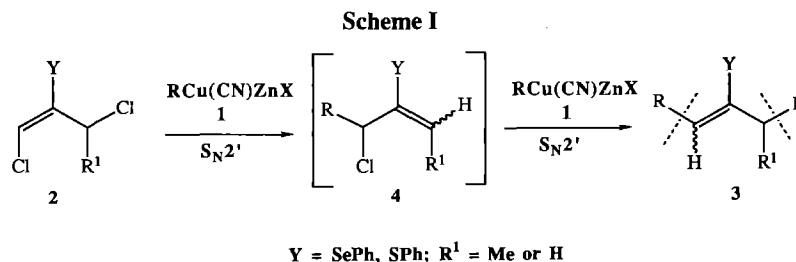
S_N2' Substitutions of 1,3-Dichloropropenes with the Functionalized Copper-Zinc Reagents $RCu(CN)ZnX$

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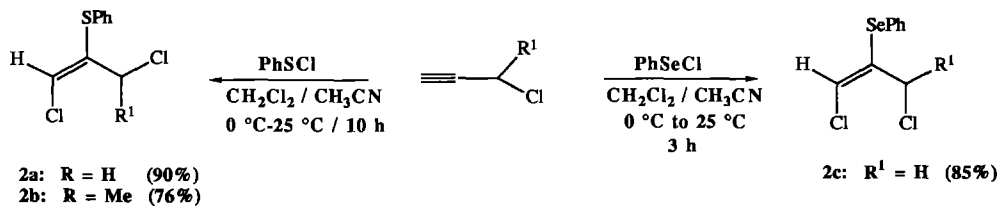
Summary: The addition of benzenesulfonyl (or benzeneselenyl) chlorides to propargylic chlorides affords regio- and stereospecifically (*E*)-1,3-dichloro-2-phenylsulfonyl (or phenylselenyl) propenes (**2a-c**). These new reagents were found to react with excellent S_N2' selectivity with the highly functionalized 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 multicoupling² 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 derivatives⁵ 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-dichloro-



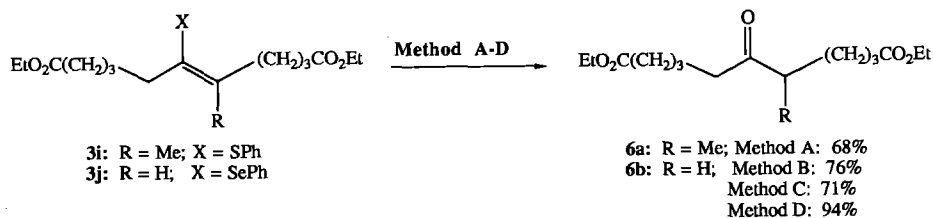
propene (1.0 equiv.) was added at -78 °C to a THF solution of $RCu(CN)ZnX$ (2.5 equiv.). The reaction mixture was warmed to 25 °C (to -10 °C in the case of benzylic copper-zinc reagents). The monitoring of the reaction (GLC analysis) indicates its completion after 3-22 h (see Table I). Besides the desired 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-dibromopropene 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 prepared⁶ by the addition of benzenesulfonyl chloride⁷ or benzeneselenyl chloride⁸ to propargylic chlorides⁹ 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 II



As shown in Table I, a variety of functionalized zinc-copper reagents $\text{RCu}(\text{CN})\text{ZnX}$ 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 $-20\text{ }^\circ\text{C}$ and $-10\text{ }^\circ\text{C}$ (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 $\text{RCu}(\text{CN})\text{ZnX}$ 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 conditions¹¹ 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



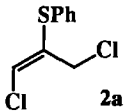
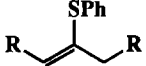
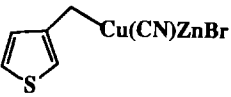

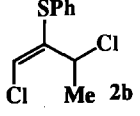
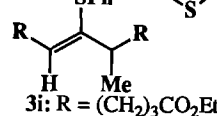
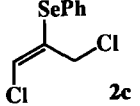
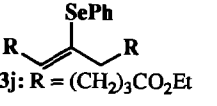
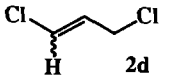
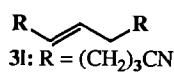
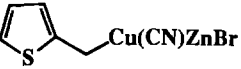
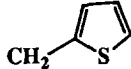
Reaction conditions: Method A: $\text{CF}_3\text{CO}_2\text{H}$, $25\text{ }^\circ\text{C}$, 6 days; Method B: $\text{HCO}_2\text{H}/\text{CH}_2\text{Cl}_2$, $\text{Hg}(\text{OAc})_2$ (1 eq.), $25\text{ }^\circ\text{C}$, 4 days; Method C: $\text{CF}_3\text{CO}_2\text{H}$, $25\text{ }^\circ\text{C}$, 24 h; Method D: $\text{HCO}_2\text{H}/\text{ICH}_2\text{CO}_2\text{H}$, $25\text{ }^\circ\text{C}$, 1 h.

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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 ₂ C-(CH ₂) ₃ -Cu(CN)ZnI	 2a	(25/18)	 3a: R = (CH ₂) ₃ CO ₂ Et	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) ₃ Cu(CN)ZnI	2a	(25/15)	3d: R = (CH ₂) ₃ CN	8/92	85
5	AcO(CH ₂) ₆ Cu(CN)ZnI	2a	(25/15)	3e: R = (CH ₂) ₆ OAc	45/55	76
6	(EtO) ₂ P(O)CH ₂ CH ₂ Cu(CN)ZnBr	2a	(25/ 3)	3f: R = (CH ₂) ₂ P(O)(OEt) ₂	8/92	90
7	PhCH ₂ Cu(CN)ZnBr	2a	(-10/20)	3g: R = CH ₂ Ph	0/100	78
8	 Cu(CN)ZnBr	2a	(-10/16)	3h: R = 	0/100	79
9	EtO ₂ C(CH ₂) ₃ Cu(CN)ZnI	 2b	(25/12)	 3i: R = (CH ₂) ₃ CO ₂ Et	11/89	89
10	EtO ₂ C(CH ₂) ₃ Cu(CN)ZnI	 2c	(25/ 7)	 3j: R = (CH ₂) ₃ CO ₂ Et	20/80	89
11	PhCH ₂ Cu(CN)ZnBr	2c	(-20/14)	3k: R = CH ₂ Ph	3/97	94
12	NC(CH ₂) ₃ Cu(CN)ZnI	 2d	(25/14)	 3l: R = (CH ₂) ₃ CN	87/13	88
13	AcO(CH ₂) ₆ Cu(CN)ZnI	2d	(25/14)	3m: R = (CH ₂) ₆ OAc	70/30	80
14	PhCH ₂ Cu(CN)ZnBr	2d	(-10/16)	3n: R = CH ₂ Ph	100/ 0	94
15	 Cu(CN)ZnBr	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 ¹³C 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-phenylselenenyl-1-propene **2c**. A solution of 2.2 g (11.5 mmol) of benzeneselenenyl chloride (Aldrich) in 10 mL of dry CH₂Cl₂ 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. NH₄Cl solution and brine and dried over MgSO₄. 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 (CDCl₃, 360 MHz) δ 7.52 (m, 2H); 7.32 (m, 3H); 6.54 (s, 1H); 4.30 (s, 2H). (b) Addition of EtO₂C(CH₂)₃Cu(CN)ZnI to **2c** (entry 10 of Table I). A THF solution of 3-carboethoxypropylzinc iodide⁴ (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 phenylselenenyl 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.
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