The Reaction of the α -Selenium Stabilized Copper Reagents ArSeCH₂Cu(CN)ZnCl with Aldehydes[†]

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 α -Arylseleno-substituted zinc and copper organometallics, in the presence of a Lewis acid, can react with aldehydes, ketones and enals with high chemoselectivity and regioselectivity.

The use of organozinc compounds in organic synthesis has been paid increasing attention recently.¹ Their excellent functional group tolerance, high chemoselectivity and excellent stereoselectivity in many reactions make organozincs ideal organometallic intermediates for the construction of complex polyfunctional molecules. We have already successfully prepared zinc organometallics with an a-selenium functional group and using CuCN-2LiCl have transmetallated them to the corresponding copper reagents.² Their reaction with acyl chlorides has achieved satisfactory results. Herein, we report the results of their reaction with aldehydes.

We found that copper reagent 2 (1 equiv.) reacts in the presence of BF₃-Et₂O (2 equiv.) with various aldehydes (0.6 equiv.) in THF at 0 °C (4–12 h) to furnish the α -selenium functionalized secondary alcohols 3 in good yields (63-75%) (see Scheme 1 and Table 1). Aromatic aldehydes show the greatest reactivity (4 h at 0 °C) (see entries 1, 2 and 7 of Table 1). However, for aliphatic aldehydes a longer reaction time (12 h at 0 °C) is required (see entries 3 and 4 of Table 1). Under our conditions, ketones do not react with copper reagents 2. On treating a 1:1 mixture of benzaldehyde and acetophenone with PhSeCH₂Cu(CN)ZnCl, we obtained 1-phenyl-2-phenylselenoethanol in 70% yield whereas acetophenone was recovered in 95% yield (see Scheme 2).

CuCN-2LiCl ArSeCH₂ZnCl ArSeCH₂Cu(CN)ZnCl 0 °C. 5 min 1 2 i, RCHO (0.6 equiv.) -78 to 0 °C ii, BF₃-Et₂O(2 equiv.) Ar = Ph, p-MeC₆H₄ ArSeCH₂CH(OH)R $R = Ph, p-NO_2C_6H_4, Bu^n, n-Hexyl$ 3

Scheme 1

reactivity of functionalized copper reagents The RCu(CN)ZnI depends strongly on the nature of additives.²



We also find that Lewis acids play an important role in the reaction of ArSeCH₂Cu(CN)ZnCl with α,β -unsaturated aldehydes. Thus, acrolein in the presence of 2 equiv. of BF₃-Et₂O leads to a mixture of the 1,2-adduct (30%) and the 1,4-adduct (35%), whereas in the presence of 2 equiv. of Me₃SiCl, only the 1,4-adduct is obtained in 79% yield (see Scheme 3 and entries 5, 6 and 8 of Table 1). Zinc and copper organometallics therefore possess better regioselectivity than the known organolithium reagents.⁴



In conclusion, the easy preparation of a-selenosubstituted organozinc chlorides 1, transmetallated to the corresponding copper reagents ArSeCH₂Cu(CN)ZnCl 2 with their good reactivity, can react with aldehydes in good yields whereas ketones remain almost intact in a 1:1 mixture of the two electrophiles. Furthermore, in the presence

Table 1 Products obtained by the addition of copper reagents ArSeCH₂Cu(CN)ZnCl to aldehydes in the presence of Lewis acid

Entry	ArSeCH ₂ Cu(CN)ZnCl	Aldehyde	Reaction conditions ^a	Product ⁶	Yield ^c (%)
1	PhSeCH ₂ Cu(CN)ZnCl 2a	PhCHO	А	PhSeCH ₂ CH(OH)Ph 3a	72
2	2a	<i>p</i> -NO ₂ C ₆ H ₄ CHO	А	$PhSeCH_2CH(OH)C_6H_4NO_2-p$ 3b	75
3	2a	BuCHO	В	PhSeCH ₂ CH(OH)Bu 3c	65
4	2a	HexCHO	В	PhSeCH ₂ CH(OH)Hex 3d	63
5	2a	CH ₂ =CHCHO	В	$PhSeCH_2CH(OH)CH=CH_2$ 3e + PhSeCH_2CH_2CH_2CHO 4a	30 35
6	2a	CH ₂ =CHCHO	С	PhSeCH ₂ CH ₂ CH ₂ CHO 4a	79
7 8	<i>p</i> -TolylSeCH ₂ Cu(CN)ZnCl 2b 2b	PhCHO CH ₂ =CHCHO	A C	<i>p</i> -TolylSeCH ₂ CH(OH)Ph 3f <i>p</i> -TolylSeCH ₂ CH ₂ CH ₂ CHO 4b	74 75

^aReaction conditions A: in the presence of 2 equiv. of BF₃-Et₂O, 0 °C, 4 h; B: in the presence of 2 equiv. of BF₃-Et₂O, 0 °C, 12 h; C: in the presence of 2 equiv. of Me₃SiCl, 25 °C, 12 h. ^bAll products are oils at room temperature. ^cYields of pure compounds.

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of Me₃SiCl, the reaction with enals takes place only in the form of a 1,4-addition. Their reaction towards other carbon electrophiles is currently being investigated in our laboratory.

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Experimental

¹H NMR spectra were recorded in CCl₄ or CDCl₃ on a JEOL PMX 60si spectrometer using tetramethylsilane as internal standard. Chemical shifts are reported as δ in ppm. *J* are reported in Hz. IR spectra were obtained on a PE683 spectrometer. Mass spectra (MS) were recorded on a HP5989A mass spectrometer. Elemental analyses were performed on a Carlo-Erba 1106. Tetrahydrofuran (THF) was distilled from sodium-benzophenone, immediately before use. Chloromethyl selenides were prepared according to the literature.⁵ Aldehydes were redistilled under the protection of N₂ prior to use. The remaining chemicals were obtained from commercial sources. All reactions were performed under a nitrogen atmosphere.

General Procedure for the Preparation of Phenylselenomethylzinc Chlorides 1.--A dry three-necked flask equipped with a magnetic stirring bar and a thermometer under nitrogen was charged with zinc dust (0.29 g, 4.5 mmol) and flushed three times with nitrogen. A solution of 1,2-dibromoethane (0.03 g, 0.15 mmol) in THF (2 ml) was then added. The resulting zinc suspension was gently heated to boiling and then cooled again to room temperature. The same activation process was repeated twice and chlorotrimethylsilane (0.03 g, 0.15 mmol) was added. After 10 min of stirring at room temperature, a solution of chloromethyl phenyl selenide (0.31 g, 1.5 mmol) in THF (2 ml) was added dropwise over 10 min. The reaction mixture was stirred for 9 h at 25 °C. The reaction process was monitored and the yield was estimated by ¹H NMR analysis of hydrolysed reaction aliquots. After 9 h, the peak at δ 4.92 (s, PhSeCH₂Cl) disappeared and the peak at δ 2.27 (s, PhSeCH₃) reached a maximum, approximately 75% yield. The excess zinc was allowed to settle and the resulting clear solution was ready to use for further transformation.

Conversion of Seleno-substituted Organozinc Chloride 1 to the Corresponding Copper Reagents 2 and Reaction with Aldehydes.—A dry flask equipped with a magnetic stirring bar was charged under nitrogen with lithium chloride (0.13 g, 3.0 mmol; previously dried under vacuum at 130 °C for 2 h) and copper cyanide (0.13 g, 1.5 mmol) and was flushed three times with nitrogen. The mixture was dissolved in 2 ml of dry THF. The resulting yellowish solution was cooled to -78 °C and the zinc reagent 1, prepared as described above, was slowly added via a cannula. The reaction mixture was allowed to warm to 0 °C for 5 min and then cooled again to -78 °C. After the aldehyde (0.67 mmol) and the appropriate Lewis acid (2.2 mmol) had been added, the mixture was allowed to warm to 0 °C (or 25 °C) and maintained at this temperature for 4 h in the case of the aromatic aldehydes, and for 12 h for the aliphatic aldehydes. Then the mixture was treated with a saturated solution of NH₄Cl (10 ml) and NH₄OH (10 ml), extracted with diethyl ether $(2 \times 20 \text{ ml})$ and the organic layer was washed with brine and dried with MgSO₄. The solvents were evaporated and the product was separated from the residue through preparative TLC (silica gel) with cyclohexane-ethyl ether (4:1) as eluent. Yields are shown in Table 1.

1-*Phenyl*-2-*phenylselenoethan*-1-*ol*⁶ **3a**.— ν/cm^{-1} 3440, 3080, 2950, 1590, 1490, 1460, 1200, 1050, 730, 700. $\delta_{\rm H}$ (CCl₄): 2.65–2.85 (m, 1H, OH), 3.06–3.11 (m, 2H, CH₂Se), 4.45–4.68 (m, 1H, CHO), 7.00–7.50 (m, 10H, ArH).

1-p-*Nitrophenyl-2-phenylselenoethan*-1-*ol* **3b**.—*ν*/cm⁻¹ 3440, 3090, 2940, 1610, 1590, 1520, 1480, 1440, 1350, 1190, 1060, 900, 730, 680. δ_H (CDCl₃): 2.83–3.28 (m, 3H, OH + CH₂Se), 4.70–4.92 (m, 1H, CHO), 7.13–7.60 (m, 7H, ArH), 8.13 (d, 2H, ArH). MS: *m*/*z* 323 and 321 (M⁺),‡ 172, 169, 157, 152, 136, 93 (Found: C, 51.83; H, 3.99; N, 4.04. C₁₄H₁₃NO₃Se requires C, 52.18; H, 4.07; N, 4.34%.).

1-Phenylselenohexan-2-ol⁷ 3c.— ν/cm^{-1} 3450, 3085, 2980, 2865, 1590, 1440, 1025, 900, 790, 737, 690. $\delta_{\rm H}$ (CCl₄): 0.88–1.53 (m, 9H, Buⁿ), 2.45 (br s, 1H, OH), 2.92–3.18 (m, 2H, CH₂Se), 3.63–3.71 (m, 1H, CHO), 7.23–7.60 (m, 5H, ArH).

1-Phenylselenooctan²-ol⁸ 3d.—ν/cm⁻¹ 3350, 3090, 3075, 2980, 2942, 2870, 1590, 1448, 1025, 788, 737, 690. $\delta_{\rm H}$ (CDCl₃): 0.83–1.60 (m, 13H, *n*-C₆H₁₃), 2.92–3.10 (m, 2H, CH₂Se), 3.30 (br s, 1H, OH), 3.37–3.80 (m, 1H, CHO), 7.16–7.73 (m, 5H, ArH).

4-Phenylselenobut-1-en-3-ol⁹ **3e**. $-\nu/cm^{-1}$ 3400, 3095, 3080, 2970, 2865, 1645, 1590, 1440, 1025, 740, 690. $\delta_{\rm H}$ (CDCl₃): 2.68 (br s, 1H, OH), 2.90–3.06 (m, 2H, CH₂-Se), 4.04–4.16 (m, 1H, CH-O), 5.02 (dd, 1H, *J* 10, 2), 5.15 (dd, 1H, *J* 16, 2), 5.80 (ddd, 1H, *J* 16, 10, 6), 7.12–7.60 (m, 5H, ArH). 4-Phenylselenobutanal¹⁰ **4a**. $-\nu/cm^{-1}$ 3040, 2940, 2830, 2740,

4-*Phenylselenobutanal*¹⁰ **4a**.— ν/cm^{-1} 3040, 2940, 2830, 2740, 1735, 1590, 1485, 1440, 1390, 1070, 1020, 730, 685. $\delta_{\rm H}$ (CDCl₃): 2.00 (q, 2H, *J* 7.1, CCH₂C), 2.52 (t, 2H, *J* 7.1, CCH₂C=O), 2.86 (t, 2H, *J* 7.1, SeCH₂C), 7.04–7.56 (m, 5H, ArH), 9.74 (s, 1H, CHO).

1-Phenyl-2-p-tolyselenoethan-1-ol **3f**.— ν/cm^{-1} 3440, 3080, 3050, 2950, 2870, 1590, 1490, 1460, 1450, 1200, 1060, 790. $\delta_{\rm H}$ (CCl₄): 2.30 (s, 3H, CH₃Ar), 2.73–2.92 (m, 1H, OH), 3.06–3.17 (m, 2H, CH₂Se), 4.43–4.66 (m, 1H, CHO), 6.96 (d, 2H), 7.23–7.59 (m, 5H), 7.68–7.85 (m, 2H), MS: m/z 292 and 290 (M⁺),‡ 186, 171, 169, 107, 91 (Found: C, 61.49; H, 5.85. C₁₅H₁₆OSe requires C, 61.85; H, 5.54%).

4-p-*Tolylselenobutanal* **4b**.— ν/cm^{-1} 3095, 3085, 2940, 2830, 2740, 1735, 1590, 1485, 1440, 1390, 1070, 1020, 790. δ_{H} (CCl₄): 2.03 (q, 2H, *J* 7.1, CCH₂C), 2.30 (s, 3H, CH₃Ar), 2.50 (t, 2H, *J* 7.1, CH₂C=O), 2.97 (*t*, 2H, *J* 7.1, CCH₂Se), 6.97 (d, 2H, *J* 8), 7.40 (d, 2H, *J* 8), 9.69 (s, 1H, CHO). MS: *m*/*z* 242 and 240 (M⁺),‡ 213, 198, 186, 185, 171, 44, 29. (Found C, 55.12; H, 5.80. C₁₁H₁₄OSe requires C, 54.77; H, 5.85%).

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^{\$}Selenium-containing compounds exhibit the characteristic isotopic family in their mass spectra 74 Se(0.87), 76 Se(9.02), 77 Se(7.58), 78 Se(23.52), 80 Se(49.82), 82 Se(9.19%), but only the peaks due to the isotopes 80 Se and 78 Se are reported here.