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The Reaction of the α-Selenium Stabilized Copper Reagents $ArSeCH_2Cu(CN)ZnCl$ with Aldehydes†

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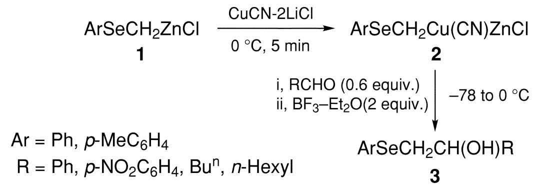
α-Arylseleno-substituted zinc and copper organometallics, in the presence of a Lewis acid, can react with aldehydes, ketones and enals with high chemoselectivity and regioselectivity.

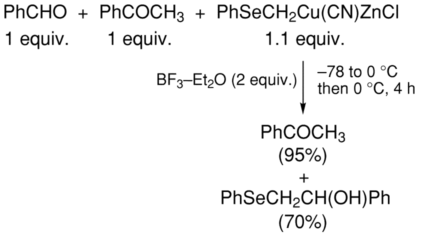
The use of organozinc compounds in organic synthesis has been paid increasing attention recently.[1] Their excellent functional group tolerance, high chemoselectivity and excellent stereoselectivity in many reactions make organozincs ideal organometallic intermediates for the construction of complex polyfunctional molecules. We have already successfully prepared zinc organometallics with an α-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 $BF_3–Et_2O$ (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 $PhSeCH_2Cu(CN)ZnCl$, we obtained 1-phenyl-2-phenylselenoethanol in 70% yield whereas acetophenone was recovered in 95% yield (see Scheme 2).



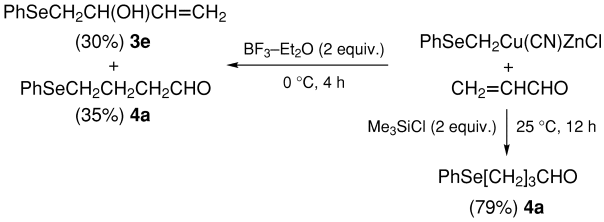
Scheme 1

The reactivity of functionalized copper reagents $RCu(CN)ZnI$ depends strongly on the nature of additives.[3]



Scheme 2

We also find that Lewis acids play an important role in the reaction of $ArSeCH_2Cu(CN)ZnCl$ with α,β-unsaturated aldehydes. Thus, acrolein in the presence of 2 equiv. of $BF_3–Et_2O$ leads to a mixture of the 1,2-adduct (30%) and the 1,4-adduct (35%), whereas in the presence of 2 equiv. of Me_3SiCl, 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]



Scheme 3

In conclusion, the easy preparation of α-seleno-substituted organozinc chlorides **1**, transmetallated to the corresponding copper reagents $ArSeCH_2Cu(CN)ZnCl$ **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 of Me_3SiCl, 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.

Table 1 Products obtained by the addition of copper reagents $ArSeCH_2Cu(CN)ZnCl$ to aldehydes in the presence of Lewis acid

Entry	$ArSeCH_2Cu(CN)ZnCl$	Aldehyde	Reaction conditions[a]	Product[b]	Yield[c] (%)
1	$PhSeCH_2Cu(CN)ZnCl$ **2a**	PhCHO	A	$PhSeCH_2CH(OH)Ph$ **3a**	72
2	**2a**	p-$NO_2C_6H_4CHO$	A	$PhSeCH_2CH(OH)C_6H_4NO_2$-p **3b**	75
3	**2a**	BuCHO	B	$PhSeCH_2CH(OH)Bu$ **3c**	65
4	**2a**	HexCHO	B	$PhSeCH_2CH(OH)Hex$ **3d**	63
5	**2a**	$CH_2{=}CHCHO$	B	$PhSeCH_2CH(OH)CH{=}CH_2$ **3e** + $PhSeCH_2CH_2CH_2CHO$ **4a**	30 35
6	**2a**	$CH_2{=}CHCHO$	C	$PhSeCH_2CH_2CH_2CHO$ **4a**	79
7	p-$TolylSeCH_2Cu(CN)ZnCl$ **2b**	PhCHO	A	p-$TolylSeCH_2CH(OH)Ph$ **3f**	74
8	**2b**	$CH_2{=}CHCHO$	C	p-$TolylSeCH_2CH_2CH_2CHO$ **4b**	75

[a] Reaction conditions A: in the presence of 2 equiv. of $BF_3–Et_2O$, 0 °C, 4 h; B: in the presence of 2 equiv. of $BF_3–Et_2O$, 0 °C, 12 h; C: in the presence of 2 equiv. of Me_3SiCl, 25 °C, 12 h. [b] All products are oils at room temperature. [c] Yields of pure compounds.

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Experimental

^{1}H NMR spectra were recorded in CCl_4 or $CDCl_3$ 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 N_2 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 ^{1}H NMR analysis of hydrolysed reaction aliquots. After 9 h, the peak at δ 4.92 (s, PhSeCH_2Cl) disappeared and the peak at δ 2.27 (s, PhSeCH_3) 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 NH_4Cl (10 ml) and NH_4OH (10 ml), extracted with diethyl ether (2 × 20 ml) and the organic layer was washed with brine and dried with $MgSO_4$. 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. δ_H (CCl_4): 2.65–2.85 (m, 1H, OH), 3.06–3.11 (m, 2H, CH_2Se), 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 ($CDCl_3$): 2.83–3.28 (m, 3H, OH + CH_2Se), 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. $C_{14}H_{13}NO_3Se$ requires C, 52.18; H, 4.07; N, 4.34%.).

1-*Phenylselenohexan*-2-*ol*[7] **3c**.—ν/cm^{-1} 3450, 3085, 2980, 2865, 1590, 1440, 1025, 900, 790, 737, 690. δ_H (CCl_4): 0.88–1.53 (m, 9H, Bu^n), 2.45 (br s, 1H, OH), 2.92–3.18 (m, 2H, CH_2Se), 3.63–3.71 (m, 1H, CHO), 7.23–7.60 (m, 5H, ArH).

1-*Phenylselenooctan*-2-*ol*[8] **3d**.—ν/cm^{-1} 3350, 3090, 3075, 2980, 2942, 2870, 1590, 1448, 1025, 788, 737, 690. δ_H ($CDCl_3$): 0.83–1.60 (m, 13H, n-C_6H_{13}), 2.92–3.10 (m, 2H, CH_2Se), 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-*ol*[9] **3e**.—ν/cm^{-1} 3400, 3095, 3080, 2970, 2865, 1645, 1590, 1440, 1025, 740, 690. δ_H ($CDCl_3$): 2.68 (br s, 1H, OH), 2.90–3.06 (m, 2H, CH_2-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-*Phenylselenobutanal*[10] **4a**.—ν/cm^{-1} 3040, 2940, 2830, 2740, 1735, 1590, 1485, 1440, 1390, 1070, 1020, 730, 685. δ_H ($CDCl_3$): 2.00 (q, 2H, J 7.1, CCH_2C), 2.52 (t, 2H, J 7.1, $CCH_2C{=}O$), 2.86 (t, 2H, J 7.1, $SeCH_2C$), 7.04–7.56 (m, 5H, ArH), 9.74 (s, 1H, CHO).

1-*Phenyl*-2-p-*tolylselenoethan*-1-*ol* **3f**.—ν/cm^{-1} 3440, 3080, 3050, 2950, 2870, 1590, 1490, 1460, 1450, 1200, 1060, 790. δ_H (CCl_4): 2.30 (s, 3H, CH_3Ar), 2.73–2.92 (m, 1H, OH), 3.06–3.17 (m, 2H, CH_2Se), 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. $C_{15}H_{16}OSe$ 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 (CCl_4): 2.03 (q, 2H, J 7.1, CCH_2C), 2.30 (s, 3H, CH_3Ar), 2.50 (t, 2H, J 7.1, $CH_2C{=}O$), 2.97 (*t*, 2H, J 7.1, CCH_2Se), 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. $C_{11}H_{14}OSe$ 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.