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Stereoselective S_N2-Substitutions Using Polyfunctional Lithium Arylcuprates Prepared by an Iodine–Copper Exchange

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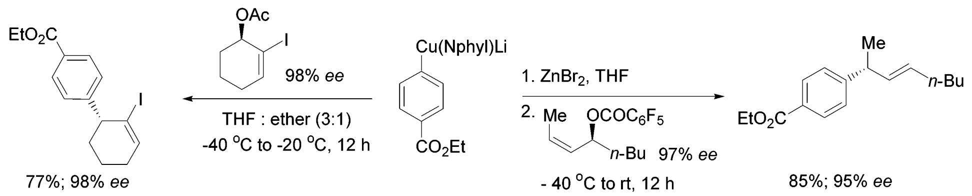
ABSTRACT



Polyfunctional mixed lithium arylcuprates of the type (FG-Ar)($PhMe_2CCH_2$)CuLi obtained via iodine– or bromine–copper exchange with ($PhMe_2CCH_2$)$_2$CuLi react with cyclic 2-iodoallylic acetates with high S_N2 selectivity. The addition of $ZnBr_2$ changes this selectivity and allows the performance of highly regioselective and enantioselective anti S_N2' substitutions using open-chain allylic pentafluorobenzoates.

The use of highly functionalized organometallics considerably enhances the synthetic potential of these reagents.[1] Recently, we have reported an efficient preparation of polyfunctional lithium arylcuprates[2] of the type (FG-Ar)(Neophyl)CuLi **1** (Neophyl = $PhMe_2CCH_2$) from functionalized aryl iodides **2** via an iodine−copper exchange reaction[3] using the bulky lithium cuprate (Neophyl)$_2$CuLi **3**. The Neophyl moiety present in the mixed cuprates of type **1** plays the role of a nontransferable group.[4] Lithium diorganocuprates are powerful nucleophiles and have been extensively used for performing allylic substitutions.[5] Recently, we have shown that chiral 2-iodoallylic alcohol derivatives of type **4** are highly reactive electrophiles that undergo anti S_N2' substitution reactions with a range of zinc−copper reagents (RCu(CN)ZnI), providing chiral products with high enantioselectivity.[6] We have also reported that aryl zinc−copper reagents react with open-chain allylic pentafluorobenzoates providing only the anti S_N2' products allowing an enantioselective synthesis of (+)-ibuprofen.[7] Herein, we wish to report that in the absence of zinc salts, polyfunctionalized aromatic lithium cuprates of type **1** obtained via an iodine−copper exchange undergo a highly stereoselective S_N2 substitution with the allylic acetates **4** leading to chiral products of type **5** (Scheme 1 and Table 1).

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(1) (a) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(2) (a) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263. (b) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229.

(3) (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615. (b) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736.

(4) (a) Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471. (b) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

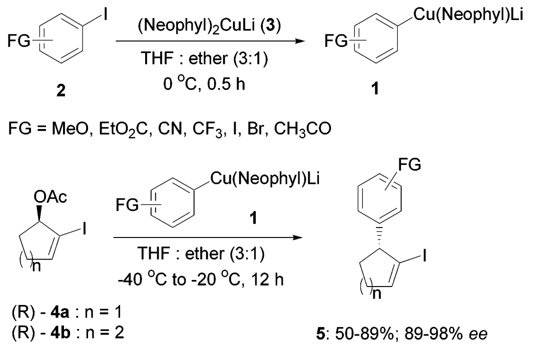
(5) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (c) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1988**, *53*, 1140. (d) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186. (e) Krause N.; Hoffmann-Roder, A.; Canisius, J. *Synthesis* **2002**, 1759. (f) Hoffmann-Roder, A.; Krause N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933.

(6) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059.

(7) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.

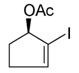
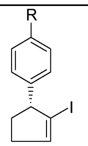
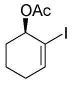
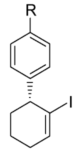
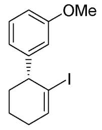
10.1021/ol0362865 CCC: $27.50

Scheme 1. Stereoselective S$_N$2 Substitution of Polyfunctional Lithium Arylcuprates with Cyclic 2-Iodoallylic Acetates



The new polyfunctional arylcopper reagents **1** were prepared by the reaction of aryl iodides **2** with (PhMe$_2$CCH$_2$)$_2$CuLi (1.1 equiv) at −78 °C. The reaction mixture was warmed to 0 °C, which leads to a complete exchange reaction within 0.5 h. In the case of the *p*-cyanophenylcopper reagent **1c**, the precursor was the corresponding bromide (4-bromobenzonitrile). The Br/Cu exchange reaction was performed at room temperature for 0.5 h. The acetates **4a**,**b** were added at −40 °C, and the reaction mixture was stirred at −20 °C for 12 h leading to the products **5a**−**j** in 50−89% yields and excellent enantioselectivities (89−98% ee); see Table 1. (*R*)-2-Iodo-2-cyclopentenyl acetate **4a** (96% ee)[7] reacts with arylcuprates bearing both electron-withdrawing and donating groups (entries 1 and 2 of Table 1) leading to the cyclopentenyl iodides **5a**,**b** in 50−71% yields and 92−96% ee. (*R*)-2-Iodo-2-cyclohexenyl acetate **4b** undergoes the S$_N$2 substitution with better yields (66−89%; entries 3−9) and an excellent transfer of the stereochemical information. A broad range of functional groups can be present in the arylcuprate (CO$_2$Et, CN, CF$_3$, MeO, COCH$_3$). Remarkably, reactive halogenides such as an iodide (entry 6) or a bromide (entry 7) are compatible with the substitution reaction. The resulting chiral dihalogenated products **5f**−**g** (94−96% ee) are versatile building blocks in which the two halogen−carbon bonds can be differentiated in future transformations. Interestingly, the presence of a keto group in the copper reagent **1g** is possible (entry 9). The desired product **5i** is obtained in 67% yield and 89% ee, showing ca. 5% racemization (enantiomer ratio from 99:1 to 95:5). This is may be due to a competitive enolization of the keto group by (Neophyl)$_2$CuLi leading to a new copper bearing an enolate ligand and displaying another chemoselectivity.

Table 1. Reactions of Polyfunctional Copper Organometallics of Type **1** with Various Electrophiles

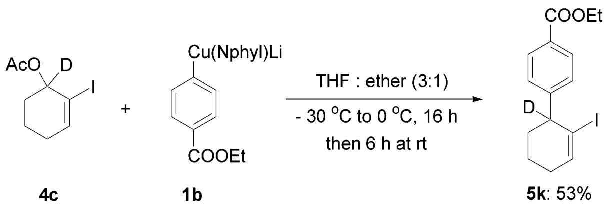
entry	copper reagent (Ar)	allylic acetate (% *ee*)	product of type **5**	yield (%)[a]	*ee* (%)[b]
					
1	*p*-MeOC$_6$H$_4$ (**1a**)	**4a** (96.6)	**5a**: R = OMe	71	92
2	*p*-EtO$_2$CC$_6$H$_4$ (**1b**)	**4a** (96.6)	**5b**: R = CO$_2$Et	50	96
					
3	*p*-EtO$_2$CC$_6$H$_4$ (**1b**)	**4b** (98)	**5c**: R = CO$_2$Et	77	98
4	*p*-NCC$_6$H$_4$ (**1c**)	**4b** (98)	**5d**: R = CN	66	96
5	*p*-F$_3$CC$_6$H$_4$ (**1d**)	**4b** (98)	**5e**: R = CF$_3$	70	94
6	*p*-IC$_6$H$_4$ (**1e**)	**4b** (98)	**5f**: R = I	82	94
7	*p*-BrC$_6$H$_4$ (**1f**)	**4b** (98)	**5g**: R = Br	89	96
8	*p*-MeOC$_6$H$_4$ (**1a**)	**4b** (98)	**5h**: R = OMe	85	95
9	*p*-CH$_3$COC$_6$H$_4$ (**1g**)	**4b** (98)	**5i**: R = COCH$_3$	67	89
10	*m*-MeOC$_6$H$_4$ (**1h**)	**4b** (98)	 **5j**	86	92

[a] Isolated yield of analytically pure product. [b] Enantiomeric excess was determined by HPLC-analysis and chiral-GC. In each case, the racemic product was prepared for calibration.

The S$_N$2 nature of the substitution was established by preparing (*S*)-3-phenylcyclohexene by our method ((i) substitution of (*R*)-**4b** with Ph(Neophyl)CuLi, (ii) *n*-BuLi, −78 °C, then H$_2$O) and measuring its [α_D] (−147.2° (*c* 0.795, benzene, 25 °C). The literature[8] indicates that for (*R*)-3-phenylcyclohexene, [α_D] = +149.7°, benzene, 29 °C. Furthermore, we have prepared 1-*d*-2-iodo-2-cyclohexenyl acetate **4c**[9] and treated it with the mixed lithium cuprate **1b** under our standard conditions. We have observed only the formation of the product **5k** having the deuterium atom at the allylic position 6 (Scheme 2), clearly indicating the occurrence of an S$_N$2 substitution.

We have also examined substitution reactions using 2-methyl-2-cyclohexenyl acetate instead of the iodo-substi-

Scheme 2. Stereoselective S$_N$2 Substitution of **1b** with 1-*d*-2-Iodo-2-cyclohexenyl Acetate



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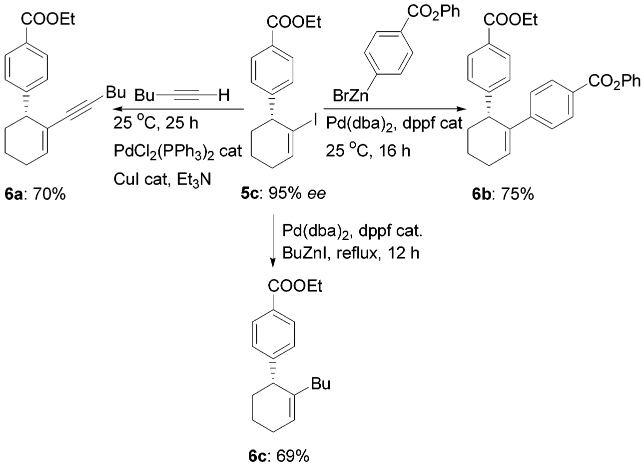
[8] Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Org. Chem.* **1968**, *33*, 4045.

tuted allylic acetate **4b**. We have observed in this case sluggish reactions with loss of stereochemical information. The use of 2-iodo-substituted allylic acetates is therefore essential. Furthermore, we have shown that the iodine in position 2 can be replaced by various groups using cross-coupling reactions (Scheme 3).

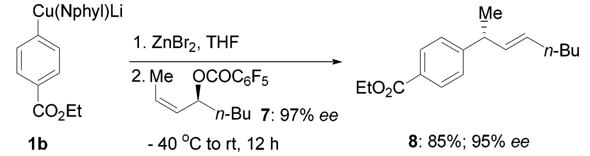
Scheme 3. Cross-coupling Reactions of Compounds of Type **5** in Position 2



Thus, the treatment of cyclohexenyl iodide **5c** (95% ee) with 1-hexyne in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (5 mol %), CuI (5 mol %), and Et_3N (25 °C, 25 h) provides the expected enyne **6a** in 70% yield.[10] Similarly, the reaction of **5c** with 4-carbophenoxyphenylzinc iodide prepared from phenyl 4-iodobenzoate via an iodine−magnesium exchange reaction[11] furnishes, in the presence of $Pd(dba)_2$ (3.5 mol %) and dppf (3.5 mol %) (THF, 25 °C, 16 h), the expected Negishi cross-coupling[12] product **6b** in 75% yield. Finally, the performance of the cross-coupling reaction with BuZnI prepared by the desired insertion of zinc dust in butyl iodide leads,[1a] under the same conditions, to the expected product **6c** in 69% yield (Scheme 3). These cross-coupling reactions indicate that the carbon−iodine bond can be readily transformed to Csp^2-Csp^3, Csp^2-Csp^2, and Csp^2-Csp bonds.

Finally, we examined the nucleophilic substitution of the functionalized arylcuprates of type **1** with chiral open-chain allylic pentafluorobenzoates[13] in the presence of zinc salts. We have indicated above the importance of the presence of zinc salts, which strongly favor the occurrence of S_N2' substitutions. We have found that in the absence of zinc salts, the mixed arylcuprate of type **1** reacts nonregioselectively. However, the addition of zinc bromide (1.0 equiv) allows the performance of a highly stereoselective anti S_N2' substitution as has been observed with zinc−copper reagents prepared from organozinc reagents. Thus, reaction of the lithium cuprate **1b** with a THF solution of $ZnBr_2$ followed by addition of the chiral *cis*-allylic pentafluorobenzoate **7** (97% ee)[14] furnishes, in THF/ether (3:1), only the S_N2' product **8** (85%; 95% ee); Scheme 4.

Scheme 4. Stereoselective Anti S_N2' Substitution of Arylcuprates **1** with Chiral Open-Chain Allylic Pentafluorobenzoates **7**



In summary, we have demonstrated[14] that the new polyfunctional mixed lithium arylcuprates of type **1** react with high stereoselectivity and excellent yields with chiral 2-iodocycloalkenyl acetates of type **4**, affording the S_N2 substitution products. The addition of zinc bromide dramatically changes this behavior and, with an open-chain allylic pentafluorobenzoate, provides only the anti S_N2'-substitution product. We are currently exploring the generality of these allylic reactions as well as their application in natural product synthesis.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] 1-*d*-2-Iodo-2-cyclohexenyl acetate **4c** was prepared in two steps from 2-iodo-2-cyclohexen-1-one: reduction with $NaBD_4$ and $CeCl_3·7H_2O$ in methanol (25 °C, 3 h; 76%) followed by an acylation with Ac_2O in pyridine (83%).

[10] (a) Qing, F.-L.; Gao, W.-Z. *Tetrahedron Lett.* **2000**, *41*, 7727. (b) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

[11] (a) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201. (b) Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* **2003**, 233.

[12] (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Negishi, E.; Matsushita, M.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3822. (c) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683.

[13] Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111.

[14] **Typical Procedure: Preparation of 5c.** A dry and argon-flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of $Nphyl_2CuLi$ (1.1 mmol, 1.1 equiv). Ethyl 4-iodobenzoate (276 mg, 1.0 mmol) was added at −78 °C, and the resulting mixture was kept stirring at 0 °C for 30 min. Then, the reaction was cooled to −40 °C, and (*R*)-2-iodo-cyclohex-2-enyl acetate (266 mg, 1.0 mmol) was added. The resulting mixture was allowed to warm to −20 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, and the mixture was poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 30 mL). The organic fractions were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 10:1) yielded 274 mg (77% yield) of **5c** as a colorless oil.