Cross-Coupling between Functionalized Alkylcopper Reagents and Functionalized Alkyl Halides

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Summary: Functionalized dialkylzincs treated with $Me_2Cu(CN)(MgCl)_2$ in DMPU undergo highly chemoselective cross-coupling reactions with functionalized alkyl iodides or benzylic bromides providing polyfunctional products in good to excellent yields.

The cross-coupling of organometallics FG^1R^1M (M = ZnX, SnR_3, AlR_2, $B(OH)_2$, etc.)[1] with organic halides FG^2R^2X catalyzed by late transition metal complexes (of Pd, Ni) is an excellent method for forming a carbon–carbon bond between functionalized substrates. This reaction proceeds smoothly as long as at least one group (FG^1R^1 or FG^2R^2) bears an unsaturation. In contrast, the Pd-catalyzed cross-coupling reaction between alkyl organometallics and alkyl halides gives only low yields.[2,3] Although alkyl cuprates derived from lithium or magnesium organometallics undergo an efficient substitution reaction with alkyl halides or tosylates,[4] their preparation from organolithiums or Grignard reagents precludes the presence of many functionalities[5] in these compounds and therefore limits the synthetic potential of this cross-coupling.

$$\underset{\mathbf{1}}{(FG^1R^1)_2Zn} \xrightarrow[\text{(2) FG}^2\text{R}^2\text{X } \mathbf{3}\text{, DMPU, −78 to 0 °C, 2 h}]{\text{(1) Me}_2\text{Cu(CN)(MgCl)}_2} \underset{\mathbf{4}}{FG^1R^1R^2FG^2} \qquad (1)$$

The copper species FGRCu(CN)ZnI prepared from alkylzinc halides[6] tolerate the presence of many functionalities, but are unfortunately unreactive toward unactivated primary alkyl halides. Recently, we have found that a wide range of functionalized dialkylzincs $(FG^1R^1)_2Zn$ **1** can be prepared by an iodine–zinc exchange reaction and have demonstrated their utility for performing catalytic enantioselective additions to aldehydes.[7] We wish now to report that the reaction of these functionalized dialkylzincs with $Me_2Cu(CN)(MgCl)_2$ (1 equiv) provides new copper reagents represented tentatively as $(FG^1R^1)_2Cu(CN)(MgX)_2 \cdot Me_2Zn$ **2** which react under mild conditions (−78° to 0 °C, 2h) in polar solvents such as dimethylpropyleneurea (DMPU)[8] with a wide range of functionalized organic halides (FG^2R^2X) **3** providing polyfunctional cross-coupling products of type **4** in good yields (eq 1 and Table I). The coupling reaction shows a remarkable chemoselectivity allowing the presence of ester and cyano groups.

Also, functionalities like a terminal alkyne,[9] a nitroalkane,[10] or a triflamide,[11] which are sensitive toward polar organometallics and readily deprotonated,[9–11] are not affected by the new weakly basic copper reagents **2** (see the preparation of **4e-g** (71–87%); Table I). Interestingly, benzylic bromides which do not react with FGRCu(CN)-ZnX undergo a very clean cross-coupling reaction with the new reagents **2** (see **4i–j**). The use of a polar solvent is required for a smooth reaction; however, DMPU[8] can be replaced by *N*-methylpyrrolidone[12] to give comparable yields.

The performance of the transmetalation of the dialkylzincs **1** with $Me_2Cu(CN)Li_2$[13] instead of $Me_2Cu(CN)$-

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(14) **Typical Procedure: Preparation of 10-Nitro-9-phenyldecyl acetate (4f).** A three-necked flask equipped with a stirring bar, a rubber septa, and an argon inlet was charged with CuCN (5 mg) and 1-acetoxy-4-iodobutane (2.42 g, 10 mmol). Et_2Zn (2.0 mL, 20 mmol) was added, and the reaction mixture was stirred for 5 h at 50 °C. The excess Et_2Zn and formed EtI were removed under vacuum (0.1 mmHg, 50 °C, 1.5 h), and dry THF (5 mL) was added with stirring. The suspension was allowed to settle, and the supernatant liquid was transferred to a THF solution of $Me_2Cu(CN)(MgCl)_2$ (5 mmol, 1 M solution) at −50 °C. The resulting solution was warmed to 0 °C and then cooled to −78 °C, and DMPU (5 mL) was added, followed by 6-iodo-1-nitro-2-phenylhexane (1.00 g, 3 mmol). The reaction was allowed to warm slowly to 0 °C and stirred for 2 h. After workup, drying over $MgSO_4$, and evaporation of the solvents, the residual oil was purified by flash column chromatography (ether–hexanes (1:4)) yielding **4f** (0.80 g, 83% yield) as a clear oil.

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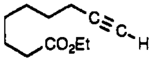
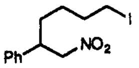
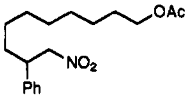
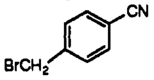
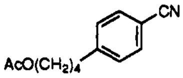
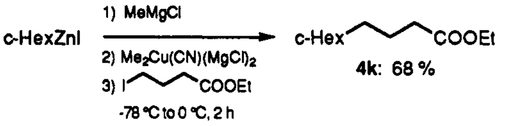
Table I. Cross-Coupling Products 4a–j Prepared from the Reaction of the Zinc–Copper Reagents 2 and the Iodides or Benzylic Bromides 3

entry	$(FGR)_2Cu(CN)(MgX)_2$ 2 (FGR)	alkyl halide 3	product of type 4		yield (%)[a]
1	$AcO(CH_2)_5$	OctI	$AcO(CH_2)_{12}CH_3$	**4a**	80 (77)[b]
2	$AcO(CH_2)_5$	$EtO_2C(CH_2)_3I$	$AcO(CH_2)_8CO_2Et$	**4b**	74 (65)[b]
3	$AcO(CH_2)_5$	$NC(CH_2)_3I$	$AcO(CH_2)_8CN$	**4c**	81
4	$EtO_2C(CH_2)_3$	OctI	$EtO_2C(CH_2)_{10}CH_3$	**4d**	72
5	$EtO_2C(CH_2)_3$	$I(CH_2)_3C{\equiv}CH$		**4e**	71
6	$AcO(CH_2)_4$			**4f**	83
7	$AcO(CH_2)_4$	$PhCH_2N(Tf)(CH_2)_3I$	$PhCH_2N(Tf)(CH_2)_7OAc$	**4g**	87
8	$PhCH_2N(Tf)(CH_2)_3$	$NC(CH_2)_3I$	$PhCH_2N(Tf)(CH_2)_6CN$	**4h**	77
9	$NC(CH_2)_6$	$PhCH_2Br$	$NC(CH_2)_7Ph$	**4i**	93
10	$AcO(CH_2)_3$			**4j**	88

[a] Isolated yields of analytically pure products. [b] Yield obtained using the copper reagent $(FGR)_2Cu(CN)Li_2{\cdot}Me_2Zn$.

$(MgX)_2$ led to inferior results (Table I (**4a–b**)). It is also noteworthy that no methyl transfer is observed with the Grignard-derived copper reagents **2**. Finally, although secondary dialkylzincs are not available by the iodine–zinc exchange reaction, the reaction of c-HexZnI with MeMgCl followed by the addition of $Me_2Cu(CN)(MgCl)_2$ provides a copper reagent which transfers selectively the c-Hex group to alkyl iodides in satisfactory yields (68 % yield; eq 2). The extensive formation of elimination products is observed if secondary iodides are used as electrophiles.



4k: 68 % (2)

In summary, we have developed a highly chemoselective cross-coupling reaction between new functionalized primary or secondary zinc–copper reagents **2** and functionalized primary alkyl halides.[14] Extensions of the method are currently being investigated in our laboratories.

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Supplementary Material Available: Characterization data for new compounds **4a–k** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.