Ni(II)-Catalyzed Cross-Coupling between Polyfunctional Arylzinc Derivatives and Primary Alkyl Iodides

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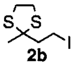
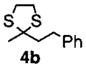
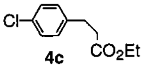
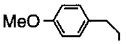
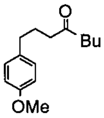
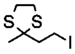
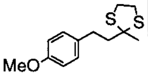
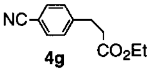
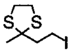
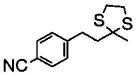
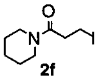
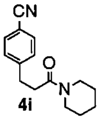
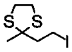
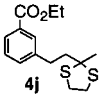
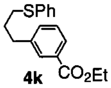
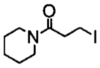
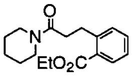
A cross-coupling reaction between organometallics and alkyl halides is an important method for the formation of new carbon−carbon bonds. Many biologically active molecules contain aromatic rings so that the performance of an efficient cross-coupling between C sp^2-hybridized organometallics and alkyl halides is needed. Although the palladium- or nickel-catalyzed cross-coupling between alkyl organometallics RM (M = B, Al, Zn, Mg, etc.) and aryl halides is well-known, the reverse reaction, e.g., the cross-coupling between an aryl organometallic species and an alkyl halide, is far less developed. Aryl-Grignard reagents undergo this cross-coupling in the presence of a copper(I) catalyst, but a moderate functionality compatibility reduces the scope of this reaction.[1] On the other hand, dialkylzincs,[2] which tolerate a broad range of functional groups, require a *stoichiometric amount* of $Me_2Cu(CN)(MgCl)_2$ for cross-coupling reactions with alkyl iodides[3] and arylzinc derivatives react only sluggishly under these conditions, if at all.[4] Recently, we reported a new powerful nickel(II)-catalyzed cross-coupling reaction between dialkylzincs and primary alkyl iodides.[5] We now report that the reaction of arylzinc bromides of type **1** with various alkyl iodides of type **2** in the presence of Ni(acac)$_2$ (10 mol %) and 4-(trifluoromethyl)-styrene[6] (**3**; THF:NMP = 2:1, −15 to −20 °C, 2−5 h) produces highly functionalized cross-coupling products of type **4** in good yields (Scheme 1 and Table 1).

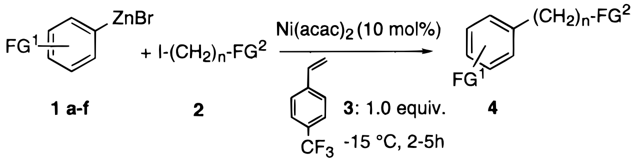
The arylzinc reagents **1** have been generated from polyfunctional aryl-Grignard reagents[7] bearing, for example, an ester function such as **5e** or from aryllithium reagents[8] such as **6d** followed by transmetalation with ZnBr$_2$ (Scheme 2).

Table 1. Polyfunctional Products **4a−l** Obtained by the Ni(II)-Catalyzed Cross-Coupling of Arylzinc Bromides **1a−f** with Alkyl Iodides **2a−f** in the Presence of 4-(Trifluoromethyl)styrene (**3**)

Entry	ArZnBr	I-(CH$_2$)-FG^2	Product of type **4**	Yield (%)^a
1	Ph^b **1a**	PivO(CH$_2$)$_5$I **2a**	PivO(CH$_2$)$_5$Ph **4a**	71
2	Ph^b **1a**	 **2b**	 **4b**	75
3	*p*-Cl-C$_6$H$_4$^{b} **1b**	EtO$_2$C(CH$_2$)$_2$I **2c**	 **4c**	71
4	*p*-MeO-C$_6$H$_4$^{b} **1c**	EtO$_2$C(CH$_2$)$_2$I **2c**	 **4d**	78
5	*p*-MeO-C$_6$H$_4$^{b} **1c**	BuCO(CH$_2$)$_3$I **2e**	 **4e**	72
6	*p*-MeO-C$_6$H$_4$ **1c**	 **2b**	 **4f**	77
7	*p*-NC-C$_6$H$_4$^{b} **1d**	EtO$_2$C(CH$_2$)$_2$I **2c**	 **4g**	75
8	*p*-NC-C$_6$H$_4$^{b} **1d**	 **2b**	 **4h**	80
9	*p*-NC-C$_6$H$_4$^{b} **1d**	 **2f**	 **4i**	71
10	*m*-EtO$_2$C-C$_6$H$_4$^{c} **1e**	 **2b**	 **4j**	72
11	*m*-EtO$_2$C-C$_6$H$_4$^{c} **1e**	PhS(CH$_2$)$_3$I **2d**	 **4k**	75
12	*o*-EtO$_2$C-C$_6$H$_4$^{c} **1f**	 **2f**	 **4l**	72

^{a} Isolated yield of analytically pure products. ^{b} Prepared from the corresponding lithium reagent. ^{c} Prepared from the corresponding magnesium reagent.

Scheme 1



Thus, the treatment of ethyl 3-iodobenzoate (**7e**) with *i*-PrMgBr (1.05 equiv) in THF (−40 °C, 0.5 h) furnishes the highly functionalized[7] Grignard reagent **5e**, which is only stable at or below −40 °C and was reacted with ZnBr$_2$ (1 equiv, THF, −78 °C to room temperature) affording arylzinc bromide **1e**. Similarly 4-bromobenzonitrile (**7d**) was treated with *n*-BuLi (1.6 N solution in hexane, 1.05 equiv, THF, −90 to −100 °C, 20 min) immediately followed by the transmetalation with ZnBr$_2$ (1 equiv, THF, −90 °C to room temperature) leading to arylzinc bromide **1d**. All the arylzinc reagents prepared by these two methods undergo fast and efficient cross-coupling reactions with various polyfunctional primary alkyl iodides. The reaction are complete within a few hours between −15 and −20 °C. A wide range of functional groups is tolerated in both the electrophile and the arylzinc bromide. The presence of polar functional groups such as an ester, amide, or ketone in close proximity to the carbon−iodine bond of **2** did not disturb the cross-coupling (Table 1). The presence of a thioether function enhanced the reaction rate by precoordination of the Ni catalyst to the sulfur atom[9] (entries

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(1) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Nishimura, J.; Yamada, N.; Horiuchi, Y.; Ueda, E.; Ohleayshi, A.; Oku, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2035. (c) Numomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912.

(2) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

(3) Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781.

(4) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

(5) Giovannini, R.; Stüdemann, T.; Dussin, G., Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2387.

(6) The promotor **3** was prepared by the Wittig reaction from the corresponding commercially available *p*-CF$_3$C$_6$H$_4$CHO.

(7) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801.

(8) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983.

(9) (a) Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3350. (b) Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, *27*, 5207. (c) Sustmann, R.; Hopp, P.; Holl, P. *Tetrahedron Lett.* **1989**, *30*, 689. (d) Yamamoto, T.; Abla, M. *J. Organomet. Chem.* **1997**, *535*, 209.

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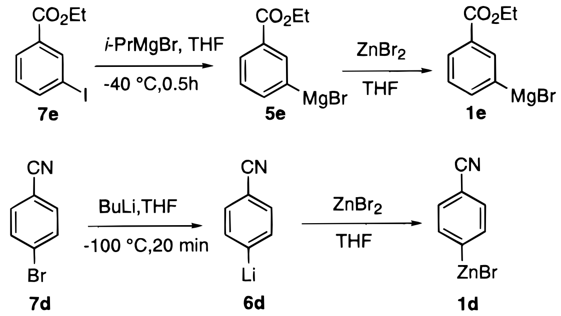
2, 6, 8, 10, and 11). The role of the promotor, **3**, is believed to facilitate the reductive elimination of the Ni(II) intermediate R^1-Ni-R^2 by removing the electron density from the nickel center.[10] The complexation of **3** to the Ni intermediate is essential for the activation and the sterically more hindered 2-(trifluoromethyl)-styrene is far less efficient as promotor for the cross-coupling. In the absence of **3**, considerable amounts of homocoupling products and iodine−zinc exchange products are observed.

Scheme 2



In summary, we have developed a new Ni-catalyzed cross-coupling of various functionalized arylzinc derivatives with primary alkyl iodides. Cross-couplings between C sp^2 organometallics and C sp^3 alkylating agents are seldom and this method should fill this gap.[10]

The study of the scope of this cross-coupling is currently underway.

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Supporting Information Available: Experimental procedures and spectral data for compounds **4a**−**4l** (29 pages, print/PDF). See any current masthead page for ordering information and Web excess instructions. See any current masthead page for ordering information and Web access instructions.

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[10] Typical procedure: (a) **Preparation of ethyl 3-(*p*-cyanophenyl)propionate (4g).** A three-necked flask equipped with a thermometer, a gas inlet, and an addition funnel was charged with 4-bromobenzonitrile (2.27 g, 12.5 mmol) in THF (20 mL). The reaction mixture was cooled to −100 °C and *n*-BuLi (8.7 mL, 12.9 mmol, 1.6 M in hexane) was added over 5 min. A precipitate forms immediately, and the reaction mixture was stirred for 20 min at this temperature. A THF solution of $ZnBr_2$ (6.25 mL, 2.81 g, 12.5 mmol) was slowly added, and the reaction was allowed to warm to room temperature. The reaction mixture was concentrated by evaporation of the solvents under vacuum leading to a ∼1.2 M solution which was transferred at −78 °C to a two-necked flask equipped with an argon inlet and a septum and containing ethyl 3-iodopropionate (1.14 g, 5 mmol), 4-(trifluoromethyl)-styrene (**3**, 0.75 mL, 5 mmol, 1 equiv), and $Ni(acac)_2$ (128 mg, 0.5 mmol, 10 mol %) in THF (1.7 mL and NMP (0.8 mL). The reaction mixture was allowed to warm to −15 °C, was stirred for 5 h, and was worked up as usual affording after flash chromatographical purification (hexanes/ether) the desired product (**4g**): 0.762 g, 75% yield. (b) **Preparation of ethyl 2-(3-oxo-3-piperidinopropyl)benzoate (4l).** A three-necked flask equipped with a thermometer, a gas inlet, and an addition funnel was charged with ethyl 2-iodobenzoate (**7f**: 3.45 g, 12.5 mmol) in THL (20 mL). The reaction mixture was cooled to −40 °C and *i*-PrMgBr (1 M solution in THF, 12.9 mL) was added within 10 min. After 0.5 h, the formation of the arylmagnesium reagent was complete (as checked by iodolysis and hydrolysis of reaction aliquots). The reaction mixture was cooled to −78 °C, a THF solution of $ZnBr_2$ (2.81 g, 6.25 mL, 12.5 mmol) was added, and the reaction mixture as allowed to warm to room temperature. The milky suspension was treated with 1,4-dioxane and stirred for 2 h, leading to a heavy precipitate which was filtered under Ar. The filtrate was concentrated to give a 1.2 M solution. A second two-necked flask equipped with an argon inlet and a septum was charged with $Ni(acac)_2$ (128 mg, 0.5 mmol, 10 mol %), 4-(fluoromethyl)styrene (5 mmol, 0.75 mL), and 1-(3-iodopropyl-1-oxo)piperidine (**2f**, 1.33 g, 5 mmol) and cooled to −78 °C. The solution of the arylzinc reagent was added, and the reaction mixture was warmed to −15 °C and stirred for 5 h. The reaction mixture was worked up a usual and afforded after flash chromatographical purification (hexanes/ether) the desired product (**4l**: 1.041 g, 72% yield).