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Substitution Reactions of Aryl *Chlorides* with Organozinc Reagents Catalyzed by Ni(0)

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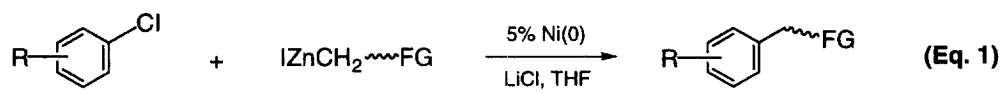
Abstract. *Treatment of substituted aryl chlorides with functionalized organozinc iodides in the presence of catalytic amounts of a soluble Ni(0) source lead to efficient displacement reactions.*

Coupling reactions of aryl bromides, iodides, and pseudo halides (*e.g.*, triflates) with a variety of organometallics have long been under the domain of organopalladium chemistry.[1] Of late aryl chlorides are being aggressively pursued as these educts are usually more accessible, considerably less expensive, and hence, far more attractive insofar as potential use in industrial settings is concerned.[2] In most circumstances Pd(0) is not a sufficiently reactive catalyst for such couplings,[3] thus a shift toward Ni(0) has been made leading to a number of successful substitutions of chloride ion from aryl rings[4] beyond the initial use of Grignards reported by Kumada[5] decades ago. Among the repertoire of organometallics that have come to be especially useful synthetic tools are organozinc reagents,[6] most notably due to their tolerance to internally positioned electrophilic functionality. In this *Letter* we describe our study on the displacement reactions of aryl chlorides by functionalized zinc halides using catalytic amounts of pre-formed Ni(0) (Eq. 1).



(Eq. 1)

[R = alkyl, ether, ester, aldehyde]

[FG = Cl, ester, CN]

Organozinc iodides were prepared in standard fashion as described by Knochel.[6,7] To establish efficacy and gain a sense of conditions required, trial reactions with simple *n*-BuZnI were conducted on aryl chlorides **1** and **2** (Scheme 1). Although each cross-coupling took place under the influence of Ni(0) (prepared from $NiCl_2$ + 2-4 PPh_3 + 2 *n*-BuLi in THF at rt),[8] competing homocouplings to give by-product biaryls were significant (10 - 20%). The inclusion of LiCl in the reaction mixtures,[9] however, served to virtually completely suppress these unwanted side

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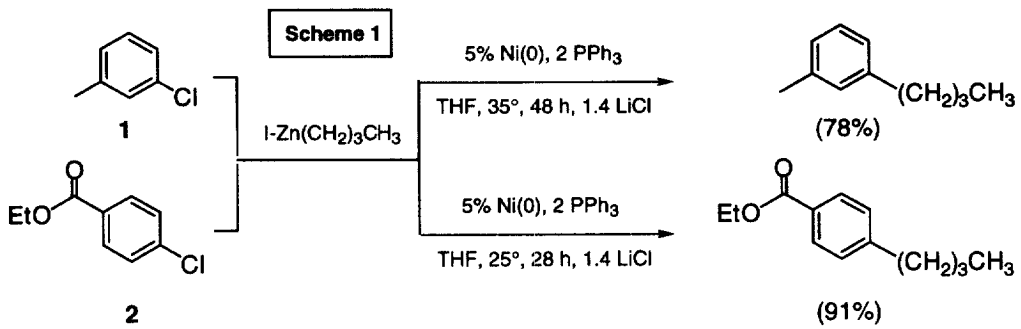
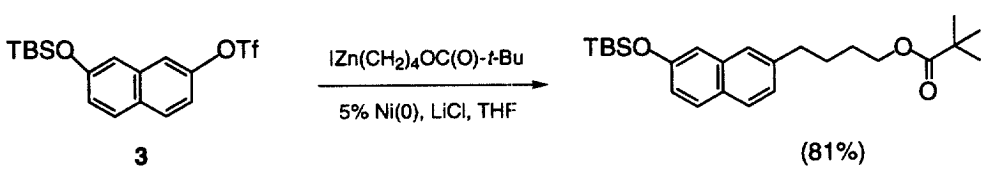
events. Unfortunately, under otherwise identical conditions, seemingly very much related educts would oftentimes not go to completion, and all attempts to force consumption of the aryl chloride were fruitless (*e.g.*, using higher concentrations, more catalyst, varying levels of phosphine(s), higher temperatures, excess zinc reagent, etc.).



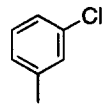
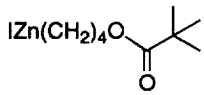
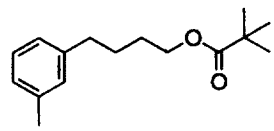
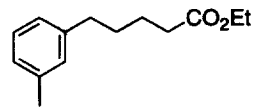
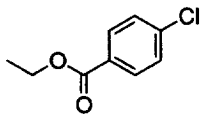
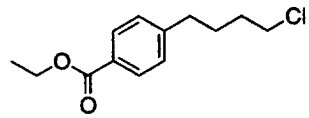
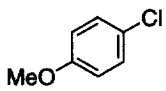
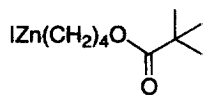
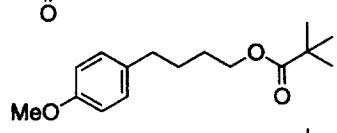
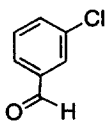
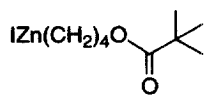
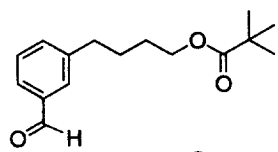
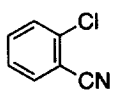
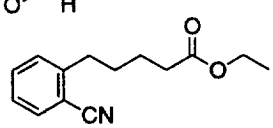
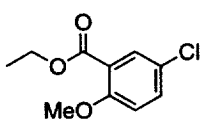
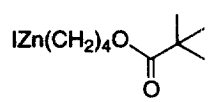
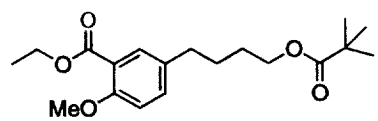
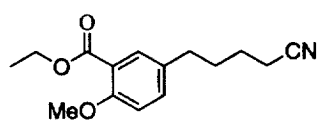
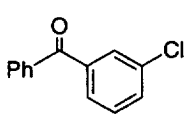
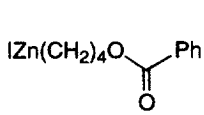
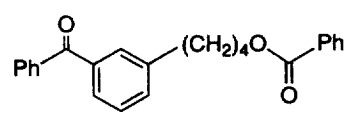
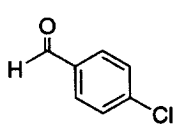
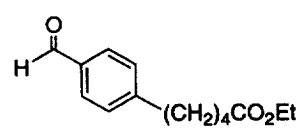
Likewise, attempts to apply this chemistry to functionalized zinc reagents initially met with similar inconsistencies. After considerable time and experimentation it was found that the key to conversion lies in the manner by which the reactants and Ni(0) catalyst are initially handled. That is, by simply combining the RZnI (1.5 eq) and LiCl (1.5 eq) with Ni(0) (5 mol %) at -78° and warming to 0° over 30 minutes, then to rt for 30 minutes followed by heating to 50°C for between 2 to 6 hours, complete consumption of the halide was achieved leading ultimately to good isolated yields of cross-coupling products. Several representative examples are shown in Table 1. Particularly noteworthy is the observation that all groups of varying stereoelectronic impact examined thus far within the aryl chloride partner are tolerated, ranging from the more challenging electron-rich cases (*e.g.*, chloroanisole) to those with electron-poor patterns.[10] Electrophilic centers on the aromatic ring, including an aldehyde residue, are not problematic. Taken together with the variety of electrophilic groups available within the zinc component,[6] highly derivatized aromatics can be expeditiously formed.

Lastly, this method is readily applicable to aryl triflates, as demonstrated with electron-*rich* naphthalene 3, below. In principle, this coupling should proceed as well *via* Pd(0) catalysis;[1,6] however, the numerous virtues of Ni(0) suggest that this metal may be the catalyst of choice.



In summary a mild, efficient, and general method is described[11] for attaching functionalized sp^3-carbon-based residues in the form of organozinc reagents to aromatics *via* displacement of chloride ion. Catalytic amounts of inexpensive Ni(0) efficiently mediate these transformations, by-passing reliance on Pd(0).[12] Further studies of valued cross-coupling

Table 1. Coupling reactions of aryl chlorides with organozinc reagents.

entry	aryl chloride	organozinc reagent[a]	product[b]	yield (%)[c]
1 (a)				92
(b)		$IZn(CH_2)_4CO_2Et$		91
2		$IZn(CH_2)_4Cl$		73
3				82[d]
4				74
5		$IZn(CH_2)_4CO_2Et$		88
6 (a)				79
(b)		$IZn(CH_2)_4CN$		96
7				88
8		$IZn(CH_2)_4CO_2Et$		77

[a]Unless noted all reactions were carried out with 5 mol % Ni(0), and 1.5 eq RZnI. [b]Fully characterized by spectral and HRMS data. [c]Isolated, chromatographically purified material. [d]2.0 equiv of RZnI were used.

reactions driven by nickel(0), including a solid-supported form of this catalyst, will be reported in due course.

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References and Notes

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9. Kubota, H.; Rice, K.C. *Tetrahedron Lett.* **1998**, *39*, 2907.
10. Literature reports on related couplings tend to involve mainly electron-deficient substrates, which are far more prone toward insertion of Ni(0). For an example, see Miller, J.A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441.
11. A representative procedure is as follows (Table 1, entry 1): To a flame-dried 10 mL round-bottom flask was added *bis*(triphenylphosphine)-nickel(II) dichloride (31 mg, 0.047 mmol) and triphenylphosphine (25 mg, 0.094 mmol) under argon at room temperature. THF (1.8 mL) was added followed by *n*-butyllithium (36 µL, 2.58 M in hexanes, 0.094 mmol). To the blood red slurry was then added chlorotoluene (111 µL, 0.94 mmol) and the mixture was cooled to -78°C. Taking care to exclude any zinc dust remaining from the zinc insertion, the iodozinc reagent (0.8 mL, prepared from 1.4 mmol of the 4-iodobutyl pivaloate, 1.75 M in THF)[6,7] containing lithium chloride (57 mg, 1.4 mmol) was slowly added. The mixture was then warmed to 0°C for 0.5 h, rt for 0.5 h, and finally to 50°C for 6 h. HCl (3 mL, 1.0 M) was then added and the mixture extracted with 5 x 5 mL of diethyl ether. The ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and the solvents removed *in vacuo*. The resulting oily residue was chromatographed on silica gel affording 215 mg (92%) of a clear, colorless oil; R_f = 0.42 (hexanes / ethyl acetate, 20/1); IR (neat) 3013, 2958, 2937, 2869, 1728, 1609, 1589, 1480, 1459, 1398, 1365, 1284, 1156, 1037, 936, 879, 780, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 1H), 7.05-6.99 (m, 3H), 4.11 (t, J = 5.6, 2H), 2.64 (t, J = 7.2, 2H), 2.36 (s, 3H) 1.73-1.65 (m, 4H) 1.23 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 178.51, 141.96, 137.77, 129.13, 128.16, 126.49, 125.31, 64.10, 38.66, 28.19, 27.67, 27.15, 21.34; LREIMS 248(3), 146(17), 145(11), 131(22), 119(12), 118(100), 117(10), 105(46), 57(52); HREIMS calcd for $C_{16}H_{24}O_2$ 248.1776; found 248.1780.
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