

Nickel-Catalyzed Cross-Coupling Reaction of Aryl Fluorides and Chlorides with Grignard Reagents under Nickel/Magnesium Bimetallic Cooperation

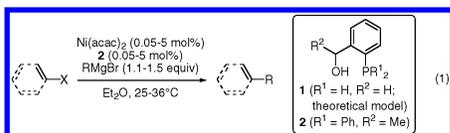
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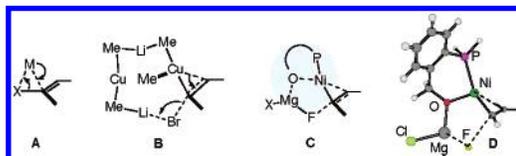
It has been generally accepted that the group 10 metal-catalyzed substitution reaction of an aryl or a vinyl halide with a main group organometallic reagent takes place via three-centered activation of the R–X bond by the d¹⁰ metal atom (A), where the role of the main group metal atom has not been explored.^{1,2} Our recent study on a much related reaction of the group 11 d¹⁰ species, lithium diorganocuprate(I), suggested, however, an energetically preferred open transition state (TS, B), where the lithium(I) atom activates the leaving X group to assist the C–X bond cleavage.³ Given the similarity of groups 10 and 11 chemistry, we conjectured on such a synergistic scenario in the group 10 catalysis. We report herein that a new phosphine ligand **2** capable of holding nickel and magnesium atoms together (shadowed in C) accelerates the nickel-catalyzed cross-coupling reaction of Grignard reagents.⁴ With this ligand, we achieved the cross-coupling reaction with aryl fluorides and aryl chlorides in higher efficiency than previously reported catalytic systems, and even polyfluoro and polychloro aromatics that have so far been known as poor electrophiles in such reactions.^{5–7} In addition to the high reactivity, this catalysis shows intriguing chemoselectivity; that is, aryl fluorides react faster than triflates or sulfides.

On the basis of our experience in organocopper chemistry,⁸ we carried out a series of model calculations to find that the anion of a hydroxy phosphine **1** facilitates the cooperative C–F bond activation.⁹ The formation of a vinyl nickel(II) intermediate from vinyl fluoride can be achieved with a 6.4 kcal/mol activation energy through a transition state (TS) D, while a three-centered oxidative addition reaction with a model Ni(0) complex, Ni(H₂PCH₂CH₂-PH₂), without any magnesium salt requires an activation energy of 35.5 kcal/mol (see Supporting Information for more details of the computational results).



To our satisfaction, the triphenylphosphine derivative bearing an *o*-(1-hydroxyethyl) group on one of the phenyl groups (**2**), which was designed after **1**, effected efficient cross-coupling of Grignard reagents with a variety of substrates in ether (eq 1, Table 1). In the presence of 1 mol % of Ni(acac)₂ (acac = acetylacetonato) and **2**, 4-fluoro- and 4-chlorotoluene reacted with PhMgBr (1.1 equiv) in less than 1 h at room temperature in ether to give 4-methylbiphenyl in 94–97% yield (entries 1 and 2). The reaction gave a small amount (3–4%) of the homocoupling product of the Grignard reagent. Note that PPh₃ was entirely ineffective under the same conditions, and that bulky or electron-rich phosphines (such as P(*t*-Bu)₃)¹ or bidentate phosphines (such as 1,3-bis(diphenylphosphino)propane (dppp)) are reported to be not very effective for the

Chart 1. Monometallic (A) and Bimetallic (B–D) Modes of C(sp²)–X Bond Activation^a



^a The model TS of C–F bond activation (D) was obtained by density functional calculations (B3LYP/LANL2DZ for Ni, 6-31G(d) for the rest).

Table 1. Ni/2-Catalyzed Cross-Coupling of Grignard Reagent with Aryl Fluorides and Other Electrophiles^a

| entry | substrate | RMgBr | catalyst (mol%) | time (h) | product | %yield ^b |
|-------|-------------------------------------|--------|--|----------|--------------------------------------|--|
| 1 | Me-C ₆ H ₄ -X | R = Ph | 1 | 1 | Me-C ₆ H ₄ -Ph | 94 (X = F) |
| 2 | | | 1 | 1/3 | | 97 (X = Cl) ^c |
| 3 | | | 0.2 | 3 | | 91 (X = Br) ^c |
| 4 | | | 0.05 | 2 | | 98 (X = I) ^c |
| 5 | | | 1 | 1 | | 80 (X = OTf) ^{c,d} |
| 6 | | | 1 | 1 | | 5 (X = SMe) ^{c,e} |
| 7 | | R = Ph | 0.2 | 2 | | 96 |
| 8 | | R = Ph | 1 | 1 | | 93 (Y = OMe) 87 (Y = NMe ₂) |
| 10 | | R = Ph | 1 | 9 | | 93 (Y = OMe) |
| 11 | | | 1 | 5 | | 96 (Y = Me) |
| 12 | | R = Ph | 1 | 1 | | 97 |
| 13 | | R = Me | R = 4-MeC ₆ H ₄ | 1 | 12 | 97 (Y = OMe) ^f |
| 14 | | | R = 4-MeOC ₆ H ₄ | 2.5 | 12 | 94 (Y = Me) ^g |
| 15 | | | R = 2-MeC ₆ H ₄ | 5 | 48 | 27 (Y = OMe) ^{g,h} |
| 16 | | | R = Me | 5 | 4 | 67 (Y = Me) ^{g,i} |
| 17 | | R = Ph | 0.05 | 3 | | 95 ^c |
| 18 | | R = Ph | 0.05 | 5 | | 100 (X = Br) ^c |
| 19 | | | 0.05 | 5 | | 17 (X = OTf) ^c |

^a The reaction was carried out on a 1 mmol scale as described in eq 1 using 1.1 equiv of Grignard reagent unless otherwise noted. ^b Isolated yield unless otherwise noted. ^c The yield was determined by GC or ¹H NMR with an internal standard. ^d 12% starting material recovery. ^e 88% starting material recovery. ^f 1.2 equiv of Grignard reagent was used. ^g 1.5 equiv of Grignard reagent was used. ^h The reaction temperature was 40 °C. ⁱ The reaction was carried out in THF at 60 °C.

same transformation.^{5,6} Aryl bromide and iodide needed the catalyst loading of only 0.2–0.05% to achieve the same reaction rate (entries 3 and 4).

Aryl triflates and sulfides are generally more reactive than fluorides in group 10 metal catalysis.^{10,11} This is supported by the calculations in that the activation energy for oxidative addition of methyl vinyl sulfide to Ni(H₂PCH₂CH₂PH₂) (without magnesium salt) is 21.8 kcal/mol, while it is 35.5 kcal/mol for vinyl fluoride. Under the present condition, however, they are less reactive. With 1% catalyst and 1 h reaction time, the conversion of tolyl triflate was not complete and that of tolyl sulfide was poor (entries 5 and 6). Only with 5% catalyst, the latter substrate gave the coupling product in 62% yield after 24 h, accompanied by 4,4'-dimethylbi-

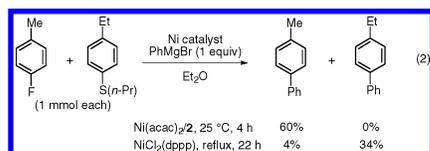
Table 2. Ni/2-Catalyzed Arylation of Aryl Polyfluorides and Polychlorides^a

| entry | substrate | RMgBr (equiv) | catalyst (mol%) | time (h) | product | %yield ^b |
|-------|-----------|---|-----------------|----------|---------|----------------------------|
| 1 | | R = Ph (2.1) | 0.5 | 1 | | 92 (p-isomer) |
| 2 | | (2.1) | 1 | 2 | | 92 (m-isomer) |
| 3 | | (2.5) | 5 | 48 | | 85 (o-isomer) |
| 4 | | R = Ph (3.5) | 2.5 | 2 | | 88 |
| 5 | | R = Ph (3.5) | 2.5 | 5 | | 88 |
| 6 | | R = 4-MeC ₆ H ₄ (3.5) | 2.5 | 2 | | 91 (X = H) 80 (X = OMe) |
| 7 | | R = Ph (4.0) | 5 | 48 | | 89 ^c |
| 8 | | R = 4-MeC ₆ H ₄ (3.5) | 5 | 24 | | 85 |
| 9 | | R = Ph (5.5) | 7.5 | 96 | | 58 ^{c,d} |

^a The reaction was carried out at 0.5–1 mmol scale at room temperature unless otherwise noted. ^b Isolated yield. ^c The reaction temperature was 45 °C (bath temp). ^d The rest of the product consisted of ca. 2:3 mixture of 1-chloro-2,4,5-triphenylbenzene and 1,2,4-triphenylbenzene.

phenyl (homocoupling of the sulfide, 16%) and toluene (reduction, 10%). Thus, the reaction was found to become faster in an order of X = SMe < OTf < F < Cl < Br < I.

Competition experiments were carried out. The reaction of an equimolar mixture of 4-fluorotoluene, 1-ethyl-4-propylthiobenzene, and PhMgBr in the presence of **2** afforded 4-methylbiphenyl (60%) and none of 4-ethylbiphenyl (the aryl sulfide was entirely recovered) (eq 2), while the same reaction in the presence of dppp gave more of the latter than the former. Interestingly, the Ni/**2**-catalyzed reaction was much slower in the presence of the sulfide than in its absence (Table 1, entry 1), suggesting that the sulfide is a preferred ligand to the catalyst but does not take part in the coupling reaction.



The reaction with vinyl chlorides and bromides was efficient and requires less than 0.05 mol % catalysis (entries 17 and 18), while reaction with enol triflates was sluggish (entry 19) and required 1 mol % of catalyst to achieve 88% yield after 5 h.

Electron-deficient (entry 7), electron-rich (entries 8–10), and ortho-substituted (entries 10–12) aryl fluorides gave the cross-coupling product in high yield. No sign of C–O bond cleavage was found (entries 8, 10, and 13–15), though aryl ethers have been known to be good substrates in nickel catalysis.^{6b,12}

Electron-rich aryl Grignard reagents reacted rapidly and cleanly (entries 13 and 14). A phenyl Grignard reagent bearing a 4-trifluoromethyl group resulted largely in Grignard homocoupling. MeMgBr was found to be less reactive (entry 16), and BuMgCl reduced the fluoride rather than giving the cross-coupling product.

Polychloro and fluoroaromatics took part in the coupling reaction rather efficiently (Table 2). Entries 1–3 show the conversion of *o*-, *m*-, and *p*-difluorobenzene into the corresponding terphenyls by the use of a nearly stoichiometric amount of a phenyl Grignard reagent. Triarylation of 1,3,5-trifluoro and chlorobenzene took place smoothly (entries 4 and 5). The methoxy group in 2,4,6-trichloroanisole remained intact in the triarylation reaction (entry 6). 1,2,4-

Trichlorobenzene required refluxing conditions (in ether; the use of THF slowed the conversion) to give the sterically hindered 1,2-diphenyl substitution (entry 7). In a similar vein, we consider that steric effect causes selective production of 1,3-diphenylated compound in entry 8. Even the 1,2,4,5-tetraphenylation could be achieved, albeit in moderate yield (entry 9).

In summary, we have designed a new bidentate ligand **2** on the basis of an assumption that the C–F bond cleavage is a turnover-limiting step of the nickel-catalyzed reaction of aryl fluorides, and hence, the bimetallic synergy accelerates the reaction. Though the reported synthetic results do not necessarily prove this hypothesis, the high reactivity and the chemoselectivity, in particular, are consistent with the assumption. Probing the generality of the hypothesis will be the next step of our study. The new catalytic system does not accelerate the equivalent palladium-catalyzed reaction between Grignard and arylating reagents, suggesting that the turnover-limiting step is different in the palladium catalysis. In addition to its synthetic merit, the high reactivity of the new catalytic system may suggest new ways to scavenge environmentally noxious polychloro aromatics. Though the ligand **2** was employed here as its racemate, we consider that its optically active counterpart would be worthwhile to examine in the future.

Supporting Information Available: Experimental and computational details, and full citation of ref 9 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA056327N