

Magnesiation of Electron-Rich Aryl Bromides and Their Use in Nickel-Catalyzed Cross-Coupling Reactions

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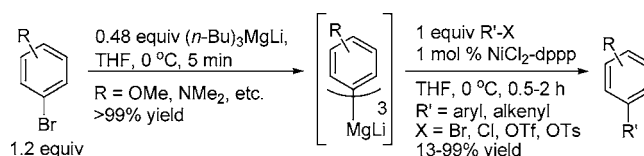
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ABSTRACT



Electron-rich aryl bromides are rapidly converted to the corresponding lithium triaryl magnesiates with $(n\text{-Bu})_3\text{MgLi}$, which undergo efficient nickel-catalyzed Kumada–Corriu cross-coupling reactions with a variety of aryl and alkenyl bromides, chlorides, tosylates, and triflates.

The Kumada–Corriu cross-coupling reaction between Grignard reagents and alkenyl or aryl halides in the presence of nickel-phosphine catalysts is a simple, yet powerful method of direct cross-coupling.¹ While other cross-coupling reactions catalyzed mainly by palladium have become increasingly popular, nickel is much less expensive than palladium² and the nickel-catalyzed Kumada–Corriu coupling is still an effective reaction for substrates whose functional groups are compatible with Grignard reagents. With the ever-increasing diversity of natural products and active pharmaceutical ingredients, there is a demand for access to a variety of non-commercially available Grignard reagents, which may be synthesized via direct magnesium insertion or through halogen–magnesium exchange reactions between alkyl Grignards and aryl and alkenyl halides. However, a major

drawback is that such reactions on electron-rich aryl halides are not trivial and indeed can be quite challenging on some substrates. In some instances, lithium–halogen exchange can also be used to activate the carbon–halogen bond. However, we have found that the corresponding organolithium species are often thermally unstable, requiring the use of cryogenic conditions which can become problematic during scale-up.

Recently, we wanted to investigate the use of electron-rich aryl bromide **1** in Kumada–Corriu couplings by making the corresponding organomagnesium reagent. However, direct Mg insertion attempts or halogen–magnesium exchange with $i\text{-PrMgCl}^3$ or $i\text{-PrMgCl}\cdot\text{LiCl}^4$ failed in our hands. Magnesiation⁵ with $(s\text{-Bu})_2\text{Mg}\cdot\text{LiCl}^6$ proceeded but required long reaction times (12 h) to obtain complete

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(2) For example, 98% NiCl_2 is ca. \$69/mol (\$133/250 g) while 99% PdCl_2 is ca. \$6800/mol (\$5780/150 g). Prices listed are in Canadian dollars. Source: www.sigmaaldrich.com.

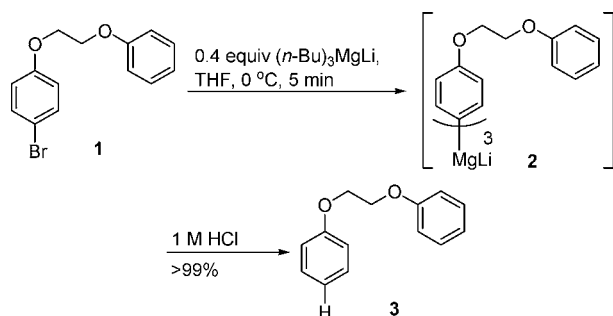
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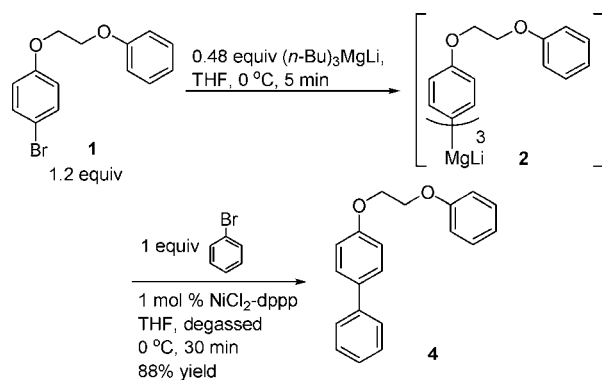
magnesiation. Thus, we decided to turn our attention to the use of the lithium trialkylmagnesiareagent (*n*-Bu)₃MgLi.⁷ Use of 0.4 equiv of (*n*-Bu)₃MgLi (1.2 equiv of Bu[−]) at 0 °C led to rapid and efficient bromine–magnesium exchange⁸ to afford the lithium triarylmagnesiare 2 as evidenced by the disappearance of 1 via LC or GC-MS, whereupon a 1 M HCl quench gave the protonated species 3 (Scheme 1).⁹

Scheme 1. Magnesiation with (*n*-Bu)₃MgLi



The palladium-catalyzed cross-coupling of lithium triarylmagnesiare with aryl bromides has been reported⁹¹ by Mongin and co-workers, for example, between the lithium triarylmagnesiare derived from 3-bromoquinoline and 2-bromopyridine, using 5 mol % of Pd(dba)₂ and dppf to give the cross-coupled biaryl in 56% yield. It was reported that nickel-catalyzed cross-couplings were unsuccessful with aryl bromides and only gave low yields with aryl chlorides. However, in our hands, when a solution of lithium tri-3-quinolylmagnesiare was added to a degassed THF solution containing 2-bromopyridine and 1 mol % of NiCl₂·dppp, the reaction proceeded to give the desired biaryl system in 63% yield. Similarly, when the lithium triarylmagnesiare 2 was added to bromobenzene in degassed THF in the presence of 1 mol % of NiCl₂·dppp, we observed rapid conversion to the desired cross-coupled product 4 in good yield (Scheme 2).

Scheme 2. Ni-Catalyzed Cross-Coupling



To explore the potential of the magnesiation/Ni-catalyzed coupling procedure further, we used 4-bromoanisole

5 as an electron-rich aryl bromide model system to compare standard methods of organomagnesium formation with magnesiation with (*n*-Bu)₃MgLi. As shown in Table 1,

Table 1. Metalation of 4-Bromoanisole

| entry | conditions | time | conversion |
|-------|---|---------|------------|
| 1 | Mg, I ₂ (cat.), THF, reflux | 24–48 h | 100% |
| 2 | <i>i</i> -PrMgCl, THF, 0 °C to rt | 48 h | NR |
| 3 | <i>i</i> -PrMgCl·LiCl, THF, 0 °C to rt | 48 h | NR |
| 4 | (<i>s</i> -Bu) ₂ Mg·LiCl, THF, rt | 8 h | 100% |
| 5 | (<i>n</i> -Bu) ₃ MgLi, THF, 0 °C | <5 min | 100% |

magnesiation with (*n*-Bu)₃MgLi resulted in vastly superior reaction times compared to direct Mg insertion or magnesiation with (*s*-Bu)₂Mg·LiCl. Magnesium exchange reactions with *i*-PrMgCl or *i*-PrMgCl·LiCl did not proceed in our hands.

With an efficient means of obtaining electron-rich lithium triarylmagnesiare, we then went on to investigate the scope of Ni-catalyzed Kumada–Corriu couplings of lithium triarylmagnesiare. A variety of Ni catalysts were evaluated, the results of which are summarized in Table 2. When no

Table 2. Catalyst Study Results

| entry | catalyst | yield of 7 | yield of 8 |
|----------------|---|------------|------------|
| 1 | none | NR | |
| 2 | NiCl ₂ ·(PPh ₃) ₂ | 30% | 20% |
| 3 | NiCl ₂ ·dppe | 50% | 12% |
| 4 | NiCl ₂ ·dppp | 93% | 5% |
| 5 | NiI ₂ ·dppp | 39% | 13% |
| 6 | NiCl ₂ ·(PCy ₃) ₂ | 72% | 18% |
| 7 ^a | NiCl ₂ ·dppp | 82% | 15% |
| 8 | Pd(PPh ₃) ₄ | 3% | ND |
| 9 | PdCl ₂ ·dppb | 10% | 4% |
| 10 | PdCl ₂ ·dppf | 20% | 6% |
| 11 | Co(acac) ₂ | NR | - |

^a Grignard reagent 4-methoxymagnesium bromide used.

catalyst was employed, no reaction was observed and no scrambling between 6 and bromobenzene occurred as

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Table 3. 4-Bromoanisole Lithium Magnesiata Nickel-Catalyzed Cross-Coupling Results

| entry | R-X | yield | entry | R-X | yield | entry | R-X | yield | entry | R-X | yield |
|-------|-----|-------|-------|-----|-------|-------|-----|-------|-------|-----|-------|
| 1 | | 93% | 3 | | 13% | 5 | | 90% | 7 | | 90% |
| 2 | | 70% | 4 | | 99% | 6 | | 88% | 8 | | 72% |
| | | | | | | | | | 9 | | 84% |
| | | | | | | | | | 10 | | 76% |

determined by LC or GC-MS. With nickel-phosphine catalysts, the reactivity followed the generally observed order $\text{NiCl}_2\cdot\text{dppp} > \text{NiCl}_2\cdot\text{dppe} > \text{NiCl}_2(\text{PPh}_3)_2$ as reported by Kumada.^{1a} Homocoupling of the magnesiate **6** forming **8** was always observed in small amounts as a byproduct, as explained by the catalytic cycle proposed by Kumada.^{1a} While the amount of **8** generated seemed to increase as the cross-coupling activity of the catalyst decreased, more importantly, the amount of **8** generated from coupling the lithium triarylmagnesiate with use of $\text{NiCl}_2\cdot\text{dppp}$ was three times less than the amount generated by using the corresponding Grignard reagent (Table 2, entry 4 versus entry 7). Finally, as a further comparison, when Pd catalysts were employed, isolated yields were low (Table 2, entries 8–10), and no reaction was observed with $\text{Co}(\text{acac})_2$ (Table 2, entry 11).¹⁰

With the optimal Ni catalyst, $\text{NiCl}_2\cdot\text{dppp}$, in hand, a variety of aryl and alkenyl bromides, chlorides, tosylates, and triflates were coupled with the lithium magnesiate of 4-bromoanisole, the results of which are summarized in Table 3. While all proceeded to give the desired cross-coupled

product, aryl and alkenyl chlorides gave yields that were lower than those of the corresponding bromides (Table 3, entries 1 and 7 versus entries 2 and 8), while phenyl tosylate (Table 3, entry 3) only gave 13% isolated yield. Less than 10% of homocoupled product **8** was observed in all cases.

Finally, a variety of aryl bromides, both electron-rich and electron-poor, were subjected to the magnesiation and cross-coupling reaction conditions. Results are summarized in Table 4. Magnesiation and cross-coupling occurs quite readily to give good yields of the desired coupled products. In all cases, less than 10% of the homocoupled Ar–Ar was formed with the exception of the electron-poor aryl bromide 1-bromo-4-(trifluoromethyl)benzene (Table 4, entry 8). While magnesiation was still rapid, approximately 20% homocoupled product was obtained. However, this is likely a consequence of the reactivity of electron-poor organomagnesium compounds and not the lithium magnesiate species itself.¹¹

In summary, we have demonstrated that electron-rich aryl bromides can undergo facile and efficient magnesiation with

Table 4. Lithium Magnesiate Nickel-Catalyzed Cross-Coupling Results

| entry | Ar-Br | R-X | yield | entry | Ar-Br | R-X | yield | entry | Ar-Br | R-X | yield |
|-------|-------|-----|-------|-------|-------|-----|-------|-------|--------------------------|-----|------------------|
| 1 | | | 92% | 4 | | | 78% | 7 | | | 80% |
| 2 | | | 89% | 5 | | | 87% | 8 | | | 73% ^a |
| 3 | | | 88% | 6 | | | 87% | 9 | 1 (from Scheme 1) | | 89% |

^a As an inseparable 4:1 mixture of product:4,4'-bis(trifluoromethyl)biphenyl.

(*n*-Bu)₃MgLi more rapidly than with previously reported halogen–magnesium exchange reactions. The resulting

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lithium triarylmagnesiates can undergo Kumada–Corriu nickel-catalyzed cross-couplings with a variety of aryl and alkenyl bromides, chlorides, or sulfonate esters in good yields, building on the arsenal of cross-coupling methods available.

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Supporting Information Available: General procedure and spectral data for compounds **3**, **4**, **7**, and **8** and all entries in Tables 3 and 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) The coupling of 4-(trifluoromethyl)phenylmagnesium bromide with bromobenzene gave similar results (68% yield, 3:1 product:Grignard homocoupling) as entry 8 of Table 4. As expected, the Grignard reagent gave more homocoupled product than the lithium triarylmagnesiate.