Nickel-Catalyzed Addition of Aryl Bromides to Aldehydes To Form Hindered Secondary Alcohols

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Supporting Information

ABSTRACT: Transition-metal-catalyzed addition of aryl halides across carbonyls remains poorly developed, especially for aliphatic aldehydes and hindered substrate combinations. We report here that simple nickel complexes of bipyridine and PyBox can catalyze the addition of aryl halides to both aromatic and aliphatic aldehydes using zinc metal as the reducing agent. This convenient approach tolerates acidic functional groups that are not compatible with Grignard reactions, yet sterically hindered substrates still couple in high yield (33 examples, 70% average yield). Mechanistic studies show that an arylnickel, and not an arylzinc, adds efficiently to cyclohexanecarboxaldehyde, but only in the presence of a Lewis acid co-catalyst (ZnBr₂).

Cross-coupling has revolutionized how molecules are made. However, despite decades-old advancements in the rhodium-catalyzed addition of arylboronic acids to aldehydes and the low functional-group compatibility of organomagnesium and organolithium reagents, a recent analysis of medicinal chemistry patents found that the Grignard reaction remains among the most-used reactions. This is in contrast to couplings with organic halides and alkynes, where cross-coupling approaches have largely supplanted other C–C bond-forming methods. This might be because arylboron reagents require extra steps to synthesize, often via reactive organometallic intermediates (Scheme 1).

A catalytic method for the direct addition of aryl halides to aldehydes would be ideal, but relatively few couplings of this type have been reported. The coupling of aryl iodides with aldehydes in the presence of a reducing agent can be catalyzed by Cr/Ni, Co, and Rh. Aryl bromides are an order of magnitude more abundant than aryl iodides (Scheme 1), but their use in aldehyde arylation remains underdeveloped and a topic of current interest. A major challenge for all of these reductive arylation methods remains couplings with less reactive substrates. There are few examples of couplings with sterically hindered aldehydes and aryl halides. There are even fewer examples of coupling hindered aryl halides with aliphatic aldehydes, perhaps because aliphatic aldehydes are already deactivated toward migratory insertion. We report here a solution to these challenging substrates as well as studies showing that the key bond-forming step occurs by a 1,2-migratory insertion of arylnickel across the aldehyde.

Early experiments focused on coupling a branched aliphatic aldehyde, cyclohexanecarboxaldehyde, with a simple aryl bromide, 4-bromoanisole, because no arylations of this type were known. Confirming Cheng’s earlier report, we also found that reactions with phosphine ligands gave a poor yield (Table 1, entry 1). We next examined a variety of nitrogen ligands, inspired by recent work by Fujihara and Martin with activated carboxyls and Voskoboynikov’s positive results with...

Table 1. Aldehyde Arylation Optimization

| entry | T (°C) | Zn (equiv) | L | yield (%) |
|-------|--------|------------|---|-----------|
| 1     | 80     | 2.5        | L₁ | 3         |
| 2     | 80     | 2.5        | L₃ | 62        |
| 3     | 80     | 2.5        | L₄ | 57        |
| 4     | 80     | 2.5        | L₆ | 62        |
| 5     | 60     | 1.5        | L₆ | 60        |
| 6     | 60     | 1.5        | L₇ | 69 (64)   |
| 7     | 60     | 1.5        | L₁₁| 18        |

Reactions were run on 0.25 mmol scale in 1 mL of THF for 12 h. Yields are corrected GC yields. For additional data on reactions with L₂, L₅, and L₈–L₁₀, see the Supporting Information. Isolated yield after column chromatography.

Received: December 23, 2018 Published: January 29, 2019
Many bidentate and tridentate ligands provided secondary alcohol, but unsubstituted and alkyl-substituted bipyridines provided the highest yield (Table 1, entries 2–6). While we initially screened our reactions at 80 °C, we found that reactions conducted at 60 °C and with less zinc provided nearly the same results (entries 4 and 5). The side reaction that limits the yield of product is pinacol coupling of the aldehyde. The remaining aryl bromide is converted into biaryl and hydrodehalogenated arene.

Adaptation of these conditions to benzaldehyde required only a re-examination of the optimal ligands (Scheme 2). For 4-bromoanisole, 4,4′-di-tert-butyl-2,2′-bipyridine (L4) was optimal (Scheme 2, product 1), but it only provided 17% yield for ethyl 4-bromobenzoate (product 8). We found that terpyridine ligands provided improved results and the tetramethyl PyBox derivative L11 provided the highest yield for this electron-poor aryl bromide (70% yield of 8).

The optimized conditions are applicable to a variety of aldehydes and aryl bromides (Scheme 2). Notable features of the scope are compatibility with both aromatic and aliphatic aldehydes, tolerance for acidic functional groups (4, 5, 25, 27), and the ability to form hindered secondary alcohols (15–22, 28–33). Finally, the chemistry is operationally simple and scales well: 1.67 g of alcohol was synthesized on the benchtop using standard glassware without the need for rigorous exclusion of oxygen.

These results are the state of the art for hindered secondary alcohol synthesis without pre-formed organometallic reagents. There are few previous examples of coupling any aryl bromide with a 2,6-disubsituted aldehyde (21, 22). Although a few couplings with aliphatic aldehydes are known, it is notable that no examples of 2° or 3° aldehydes have been reported (23–33). Addition of hindered aryl groups, even to unhindered aldehydes, is also challenging for published

^{Reactions were conducted on 0.5 mmol scale in 2 mL of THF for 12–16 h. Yields are isolated yields after chromatography on silica gel. X = Br for all substrates unless otherwise noted. ^Isolated yield for a gram-scale reaction using standard glassware.}
methods. As an extreme case, the only other examples of coupling 2,4,6-trisopropylphenyl with aldehydes (as in 20 and 31) utilized aryllithium or arylmagnesium reagents. Finally, this method could be used to form secondary alcohols from the combination of hindered aryl bromides with hindered aldehydes (20 and 28–33).

Given the large improvement in reactivity with sterically hindered substrates compared to previous reports, it would be beneficial to understand the mechanism. Five potential mechanisms have strong precedent in the literature: (1) 1,2-migratory insertion of an aryllnickel(II) intermediate across the aldehyde;\(^{13a,19}\) (2) 1,2-migratory insertion of an aryllnickel(I) intermediate across the aldehyde; (3) in situ formation of a diarylzinc reagent\(^{17}\) that could react with the aldehyde;\(^{24}\) (4) in situ formation of a radical from the aldehyde with subsequent capture by aryllnickel and reductive elimination;\(^{5,15}\) and (5) reaction of a (L)Ni\(^{II}(\mu^{2}-\text{aldehyde})\) species with arylzinc and subsequent reductive elimination.\(^{25}\) For a bisphosphine nickel system, Cheng had suggested migratory insertion via nickel(II) based upon the bisphosphine nickel system, and the Schlenk equilibrium to convert unreactive ArZnBr into reactive Ar\(_2\)Zn will be less favorable with added ZnBr\(_2\). These results appear to rule out direct arylation via diarylzinc reagents.

Second, we considered transmetalation of arylzinc reagents with (L)Ni\(^{II}(\mu^{2}-\text{aldehyde})\), followed by reductive elimination. Reaction of pre-formed (L3)Ni\(^{II}(\text{cod})\) with aldehyde, followed by 4-methoxyphenylnickel bromide formed no addition product (Scheme 3). This rules out the intermediacy of (L3)Ni\(^{II}(\mu^{2}-\text{aldehyde})\) species.

Third, pre-formed (L3)Ni\(^{II}(2\text{-cumyl})\)Br (37) only reacts with cyclohexane carboxaldehyde to form product 29 in the presence of zinc bromide (Scheme 4). This is consistent with arylnickel(II) 1,2-migratory insertion. The role of ZnBr\(_2\) could be to abstract a halide from ZnBr\(_2\) and the Schlenk equilibrium to convert unreactive ArZnBr into reactive Ar\(_2\)Zn. This would likely be low because direct insertion of zinc into aryl bromides is slow—a catalytic reaction run without nickel does not consume any 4-bromoanisole or cyclohexane carboxaldehyde—and the Schlenk equilibrium to convert unreactive ArZnBr into reactive Ar\(_2\)Zn will be less favorable with added ZnBr\(_2\). These results appear to rule out direct arylation via diarylzinc reagents.

A series of studies appears to rule out three of these mechanisms and point to migratory insertion of aryllnickel across the aldehyde (Scheme 3). First, we found that arylzinc reagents react slowly with aldehydes;\(^4\) reagents react slowly with cyclohexane carboxaldehyde to form product 23 (20% yield after 24 h). We do not think that this process is important in catalytic reactions because the amount of product formed is diminished further when catalytic (L3)NiBr\(_2\) is present (10% yield of 23 with equal amounts of bianisole). The amount of diarylzinc present in solution would likely be low because direct insertion of zinc into aryl bromides is slow—a catalytic reaction run without nickel does not consume any 4-bromoanisole or cyclohexane carboxaldehyde—and the Schlenk equilibrium to convert unreactive ArZnBr into reactive Ar\(_2\)Zn will be less favorable with added ZnBr\(_2\). These results appear to rule out direct arylation via diarylzinc reagents.

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Scheme 5. Proposed Mechanism

“Ligand abbreviated for clarity. Conversion of 40 to 41 could proceed by a number of pathways. See discussion.

Migratory insertion of the aryl group into the aldehyde could form an alkoxynickel(II) product or directly release product and form 41. While we have no definitive evidence for either intermediate, alkoxynickel intermediates can lead to the formation of ketone, a side product that is observed in trace amounts, even under optimized conditions.27

In conclusion, the formation of very hindered diarylmethanols and hindered benzyl alcohols by the addition of aryl bromides to aldehydes has been reported for the first time. The simple conditions do not require silicon additives to trap the alcohol or visible light to generate reactive species and can tolerate acidic functional groups. These studies open the door to rapid advancement in the use of carbonyls in metal-catalyzed addition reactions.28

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13709.

Detailed procedures, additional optimization data, and full characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Research reported in this publication was supported by the University of Wisconsin-Madison and the National Institute of General Medical Sciences of the National Institutes of Health under award numbers T32GM008505 (K.J.G.) and S100D020022 (UW Chemistry Instrumentation Center). The authors are indebted to Jill A. Caputo (Univ. of Rochester), Melodie Christensen (Merck), who conducted preliminary studies with phosphine ligands that led to this work, Kai Kang (Univ. of Wisconsin–Madison) for the synthesis of the arynickel(II) complex, and Matthew J. Goldfogel (Univ. of Wisconsin–Madison) for the synthesis of a reductant used in mechanistic studies. We also thank Chiral Technologies (Joe Barendt) for the donation of achiral SFC columns used in this work.

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(15) Recently, MacMillan reported the coupling of aryl bromides with substrates that contain a ketone provided lower yields (product 34 in the Supporting Information, 14% yield). In addition, ethyl 4-bromobenzoate and N-Boc-5-bromoindole provided low yields with cyclohexene carboxaldehyde (products 35 and 36 in the Supporting Information).

(16) Rh-catalyzed arylation with Pd tolerated 2-substituted aldehydes reasonably well (2-iodotoluene, 70%; naphthaldehyde, 57%; o-anisaldehyde, 63% yield). Few examples of hindered aldehydes have been reported for nickel-catalyzed arylation: 2,4-dimethoxybenzaldehyde (12% yield) and 2,4,5-trimethoxybenzaldehyde (93%) have been coupled with PhBr.

(17) Rh-catalyzed arylation with PhCHO does not tolerate a 2-iodotoluene (trace product). Nickel-catalyzed arylation is more tolerant for couplings with PhCHO but varies with the catalyst used. For example, bromosulfonylene was coupled in 98% yield, but the same substrate failed in an earlier study.

(18) Few couplings with aliphatic aldehydes have been reported. The only hindered examples are the nickel-catalyzed coupling of methyl 2-bromobenzoic acid ester with heptanal (38% yield) and butanal (24% yield) and the Rh-catalyzed coupling of 2-phenylpropionaldehyde with isododecene (62% yield).

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(20) Pinacol product grows in with the cross-coupled product. Minor side products observed in early optimization (~10%) resulted from aldehyde reduction and product oxidation to ketone.

(21) Acidic functional groups presented a challenge for Rh-catalyzed arylation (product 4 was formed in only 27% yield). At this time, reactions with substrates that contain a ketone provided lower yields (product 34 in the Supporting Information).

(22) Acidic functional groups presented a challenge for Rh-catalyzed arylation (product 4 was formed in only 27% yield).

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(27) While the ketone derived from 23 was observed in up to 15% yield in our initial studies, less than 3% ketone side product was formed after optimization. Cheng had similarly reported ketone as a side product in ref 13a, and later found this to be the major product at higher temperatures with aryl iodides: see: Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. Nickel-Catalyzed Coupling of Aryl Iodides with Aromatic Aldehydes: Chemoselective Synthesis of Ketones. J. Org. Chem. 2002, 67, 1682–1684.

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