

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

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S 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 arynickel, and not an arylzinc, adds efficiently to cyclohexanecarboxaldehyde, but only in the presence of a Lewis acid co-catalyst (ZnBr_2).

Cross-coupling has revolutionized how molecules are made.¹ However, despite decades-old advancements in the rhodium-catalyzed addition of arylboronic acids to aldehydes^{2,3} 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.^{1b} This is in contrast to couplings with organic halides and alkenes, where cross-coupling approaches have largely supplanted other C–C bond-forming methods.¹ 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.^{4,5} The coupling of aryl iodides with aldehydes in the presence of a reducing agent can be catalyzed by Cr/Ni,⁶ Co,⁷ and Rh.^{8,9} Aryl bromides are an order of

magnitude more abundant than aryl iodides (Scheme 1),¹⁰ but their use in aldehyde arylation remains underdeveloped^{11–13} and a topic of current interest.^{14,15}

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 aldehydes¹⁶ and aryl halides.¹⁷ There are even fewer examples of coupling hindered aryl halides with aliphatic aldehydes, perhaps because aliphatic aldehydes are already deactivated toward migratory insertion.^{18,19} 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 arynickel across the aldehyde.

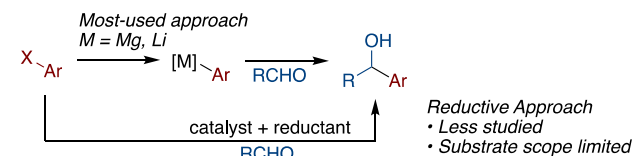
Early experiments focused on coupling a branched aliphatic aldehyde, cyclohexane carboxaldehyde, with a simple aryl bromide, 4-bromoanisole, because no arylations of this type were known. Confirming Cheng's earlier report,^{13a} we also found that reactions with phosphine ligands gave a poor yield (Table 1, entry 1). We next examined a variety of nitrogen ligands, inspired by recent work by Fujihara and Martin with activated carbonyls⁴ 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) ^b
7	60	1.5	L11	18

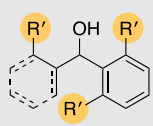
L1 $\text{Ph}_2\text{P}-\text{CH}_2-\text{CH}_2-\text{PPh}_2$
L3 R = H
L4 R = 4-^tBu
L6 R = 4-Me
L7 R = 5-Me
L11

Scheme 1. Aldehyde Arylation Strategies



This study

- Abundant aryl bromides
- Simple conditions
- R = aryl and 2°/3° aliphatic
- sterically hindered substrates



Aryl Commercial Availability

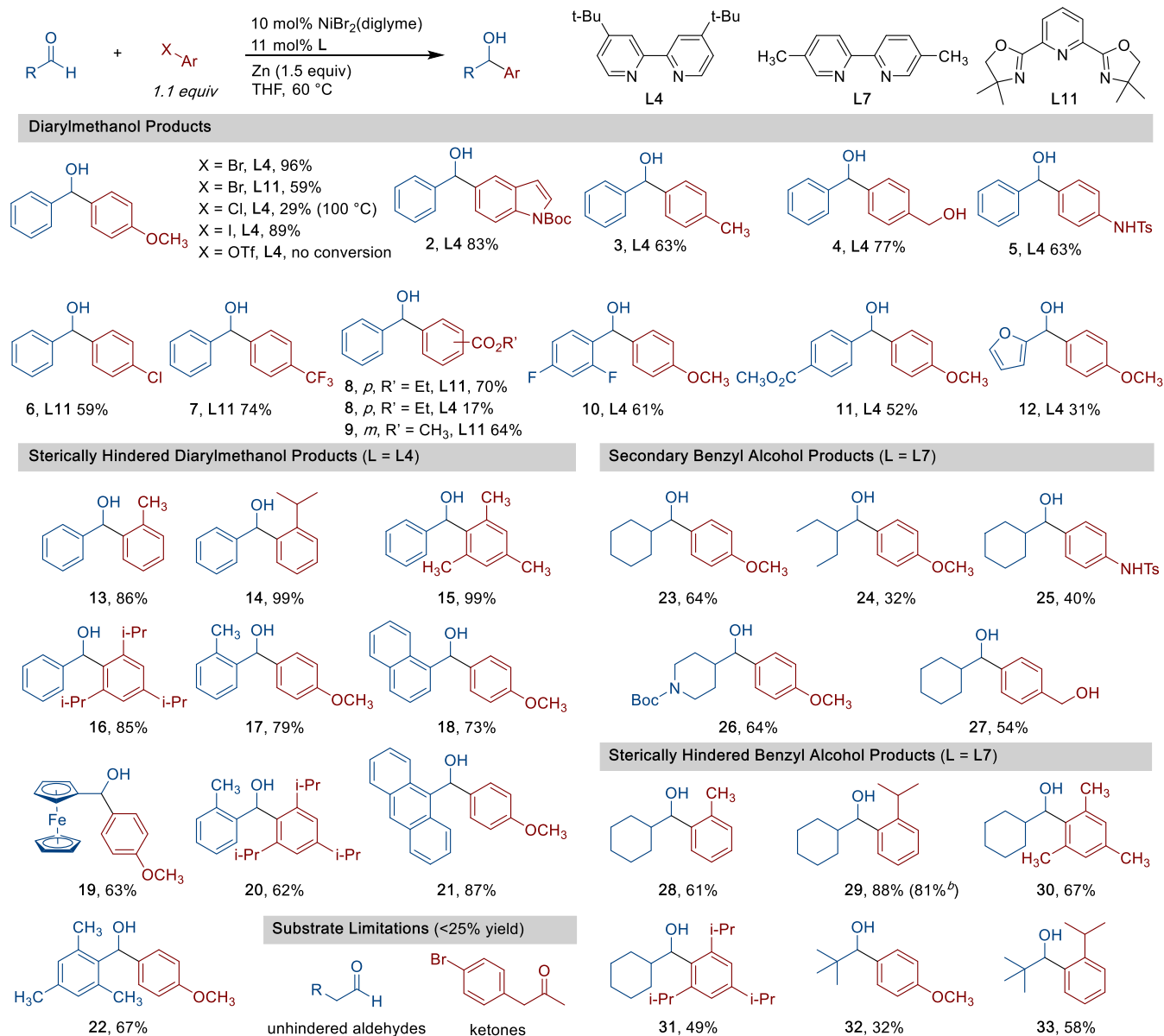
B(OH)_2	8.5×10^3
I	8.1×10^4
Br	6.4×10^5

^aReactions 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. ^bIsolated yield after column chromatography.

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Scheme 2. Substrate Scope



^aReactions 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. ^bIsolated yield for a gram-scale reaction using standard glassware.

aromatic aldehydes.^{13d} Many bidentate and tridentate ligands provided secondary alcohol 23, 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 23 is pinacol coupling of the aldehyde.²⁰ 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),²¹ and the ability to form hindered secondary alcohols (15–22, 28–33).²² Finally, the chemistry is operationally simple and scales well: 1.67 g of alcohol 29 was synthesized on the benchtop using standard glassware without the need for rigorous exclusion of oxygen.

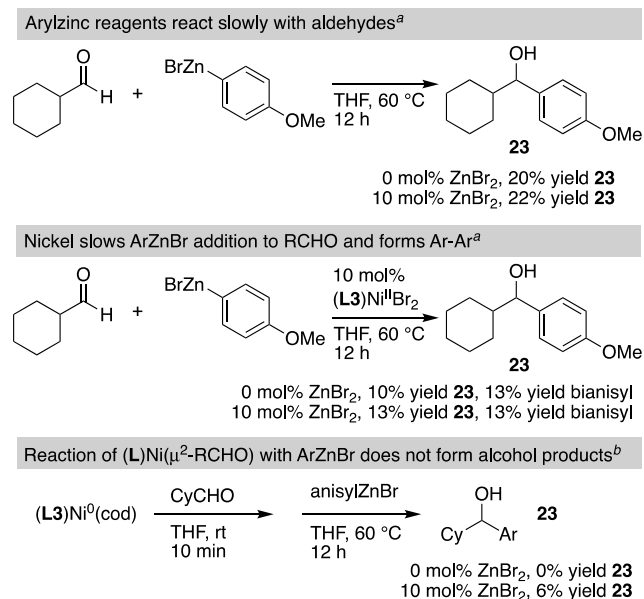
These results are the state of the art for hindered secondary alcohol synthesis without pre-formed organometallic reagents. We could find no previous examples of coupling any aryl bromide with a 2,6-disubstituted aldehyde (21, 22). Although a few couplings with aliphatic aldehydes are known, it is notable 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

methods. As an extreme case, the only other examples of coupling 2,4,6-triisopropylphenyl 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 arylnickel(II) intermediate across the aldehyde;^{13a,19} (2) 1,2-migratory insertion of an arylnickel(I) intermediate across the aldehyde; (3) in situ formation of a diarylzinc reagent²³ that could react with the aldehyde;²⁴ (4) in situ formation of a radical from the aldehyde with subsequent capture by arylnickel and reductive elimination;^{9,15} and (5) reaction of a (L)Ni^{II}(μ²-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 finding that a mixture of Ni(cod)₂ with **L1**, benzaldehyde, and bromoanisole only formed alcohol product when zinc bromide was present.^{13a} Considering the differences in ligand and reactivity observed, it was not clear if this hypothesis could be extended to our system.

A series of studies appears to rule out three of these mechanisms and point to migratory insertion of arylnickel across the aldehyde (Scheme 3). First, we found that arylzinc

Scheme 3. Reactivity of Arylzinc Bromide



^aReaction conducted at 0.18 M ArZnBr with a 1:1 ratio of ArZnBr/CyCHO. ^bReaction conducted with a 1:1:1 ratio of [Ni]/CyCHO/ArZnBr.

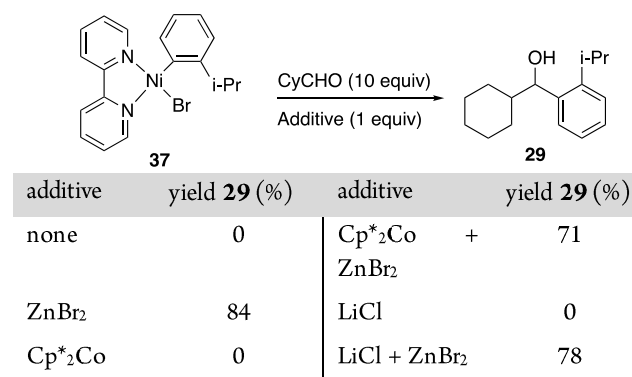
reagents react slowly with cyclohexane carboxaldehyde to form product **23** (20% yield after 24 h). We do not think that this process is important in catalytic reactions because the amount of product formed is diminished further when catalytic (L3)NiBr₂ is present (10% yield of **23** with equal amounts 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 Ar₂ZnBr into reactive Ar₂Zn will be less favorable with added ZnBr₂. These results appear to rule out direct arylation via diarylzinc reagents.

Second, we considered transmetalation of arylzinc reagents with (L)Ni^{II}(μ²-aldehyde), followed by reductive elimination. Reaction of pre-formed (L3)Ni⁰(cod) with aldehyde, followed by 4-methoxyphenylzinc bromide formed no addition product (Scheme 3). This rules out the intermediacy of (L3)Ni^{II}(μ²-aldehyde) species.

Third, pre-formed (L3)Ni^{II}(2-cumyl)Br (**37**) only reacts with cyclohexane carboxaldehyde to form product **29** in the presence of zinc bromide (Scheme 4). This is consistent with

Scheme 4. Stoichiometric Reactions of (L)Ni^{II}(Ar)Br^a



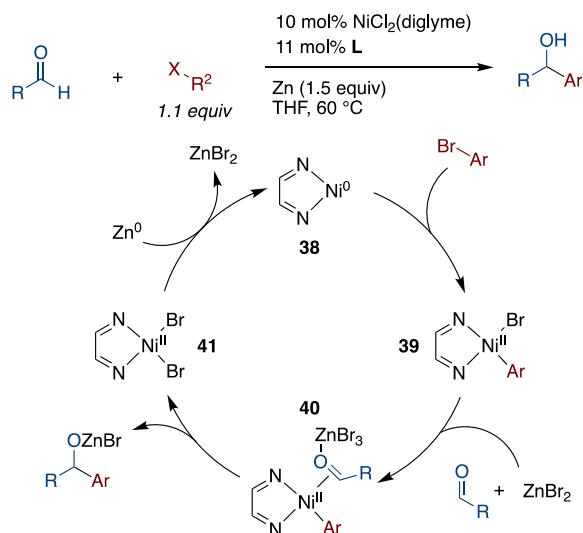
^aReactions were run at 0.0125 M in [Ni] in THF at 60 °C for 12 h. Yield is corrected GC yield. See Supporting Information for additional experiments and full details.

arylnickel(II) 1,2-migratory insertion. The role of ZnBr₂ could be to abstract a halide from **37** to form [(L)Ni^I(Ar)]ZnBr₃,^{23b} accelerate migratory insertion via σ-coordination of the carbonyl oxygen, or both. Finally, these conditions are not consistent with formation of an alkyl radical from the aldehyde because arylnickel(II) **37** is not sufficiently reducing.

To examine the possibility that reduction of **37** is accelerated by abstraction of bromide by ZnBr₂, we also examined the addition of a strong single-electron reductant that would not have a strong halide affinity or be able to form an arylmetal reagent, Cp*₂Co.²⁶ This reaction resulted in no product formation, in sharp contrast with the studies of Fujihara with similar arylnickel(II) complexes and CO₂.^{4a} When Cp*₂Co and ZnBr₂ were both added to the reaction of (L3)Ni^{II}(2-cumyl)Br with cyclohexane carboxaldehyde, product was formed, but in diminished yield compared to the reaction without reductant. While we cannot rule out the intermediacy of arylnickel(I), at this time we think an arylnickel(II) is more likely.

Based upon these experiments, we propose the mechanism in Scheme 5. Reduction of the nickel pre-catalyst forms **38**, and oxidative addition of Ar–Br forms **39**. The pinacol side product appears to arise from **38** because it was formed in larger amounts in experiments that started with nickel(0) or in experiments that generated nickel(0) in situ (Scheme 3 and Supporting Information). Arylnickel(II) **39** interacts with ZnBr₂ and aldehyde to form a reactive intermediate, here depicted with zinc coordination to the aldehyde as **40**. 1,2-

Scheme 5. Proposed Mechanism



^aLigand 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 alkoynickel(II) product or directly release product and form **41**. While we have no definitive evidence for either intermediate, alkoynickel 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 benzylic 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.

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(16) Rh-catalyzed arylation with PhI tolerated 2-substituted aldehydes reasonably well (2-iodotoluene, 70%; naphthaldehyde, 57%; *o*-anisaldehyde, 63% yield).⁸ Few examples of hindered aldehydes have been reported for nickel-catalyzed arylation: 2,4-dimethoxybenzaldehyde (12% yield)^{13a} and 2,4,5-trimethoxybenzaldehyde (93%)^{13d} have been coupled with PhBr.

(17) Rh-catalyzed arylation with PhCHO does not tolerate a 2-iodotoluene (trace product).⁸ Nickel-catalyzed arylation is more tolerant for couplings with PhCHO but varies with the catalyst used. For example, bromomesitylene was coupled in 98% yield,^{13d} but the same substrate failed in an earlier study.^{13a}

(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)^{13b} and the Rh-catalyzed coupling of 2-phenylpropionaldehyde with iodobenzene (62% yield).⁸

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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).⁸

(22) At this time, reactions with substrates that contain a ketone provide lower yields (product 34 in the Supporting Information, 14% yield). In addition, ethyl 4-bromobenzoate and *N*-Boc-5-bromoindole provided low yields with cyclohexane carboxaldehyde (products 35 and 36 in the Supporting Information).

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