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Rhodium-Catalyzed Aldehyde Arylation via Formate-Mediated Transfer Hydrogenation: Beyond Metallic Reductants in Grignard/Nozaki−Hiyami−Kishi-Type Addition

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Supporting Information

ABSTRACT: The first intermolecular carbonyl arylations via transfer hydrogenative reductive coupling are described. Using rhodium catalysts modified by ^{t}Bu$_2$PMe, sodium formate-mediated reductive coupling of aryl iodides with aldehydes occurs in a chemoselective fashion in the presence of protic functional groups and lower halides. This work expands the emerging paradigm of transfer hydrogenative coupling as an alternative to preformed carbanions or metallic reductants in C═X addition.

Since the seminal work of Butlerov (1863),[1a,b] Reformatsky (1887),[1c] and Grignard (1900),[1d] the use of pre-formed organometallic reagents in carbonyl addition has remained a cornerstone of chemical synthesis.[2] Countless protocols for the addition of non-stabilized carbanions and their equivalents (e.g., arylboron reagents)[3f,g] to carbonyl compounds and imines now exist, including enantioselective methods.[3] Nevertheless, the requisite organometallic nucleophiles complicate large-volume applications due to issues of safety, the frequent requirement of cryogenic conditions, and the separation/disposal of metallic byproducts. While metal-catalyzed reductive coupling represents an alternative to discrete organometallic reagents in carbonyl addition, the terminal reductants often utilized in such processes are metallic (Zn, Mn), toxic ($CrCl_2$), pyrophoric (BEt_3, $ZnEt_2$, $AlMe_3$), or expensive/mass-intensive (R_3SiH).[4] Using hydrogen, 2-propanol, and formic acid, which are relatively benign, inexpensive, low-molecular-weight reductants, diverse catalytic enantioselective carbonyl and imine reductive coupling reactions were developed in our laboratory,[4b,d,e,g,i,l] including aldol additions,[5a] vinylations,[5b] allylations,[4l,5c−e] and propargylations.[4l,5f,g] *Here, we report the first examples of intermolecular carbonyl arylation via metal-catalyzed transfer hydrogenation, representing the first intermolecular carbonyl−aryl halide reductive couplings beyond metallic reductants* (Figure 1).[6,7]

Aside from the Nozaki−Hiyami−Kishi reaction,[6,7] surprisingly few intermolecular metal-catalyzed aryl halide−aldehyde reductive couplings have been reported, all of which are mediated by elemental zinc[8] (or an Mn−Cr alloy)[8c] or are conducted electrochemically.[9] Reductive aldehyde arylations via hydrogenation or transfer hydrogenation have not been described, almost certainly due to competing hydrogenolysis of the aryl halide.[10] Despite this lack of precedent, a hydrogen-mediated Grignard-type cyclization was recently developed in our laboratory.[11] While these conditions were not applicable to intermolecular carbonyl reductive couplings, related redox-neutral aryl halide−aldehyde couplings to form ketone products have been reported.[12] In these processes, Ar−X oxidative addition is followed by carbonyl insertion to form a metal alkoxide, which upon β-hydride elimination and H−X reductive elimination returns the metal to its low-valent form. It was posited that interception of the metal alkoxide derived upon carbonyl arylation by 2-propanol or a formate salt might enable reductive arylation to form secondary alcohol products.

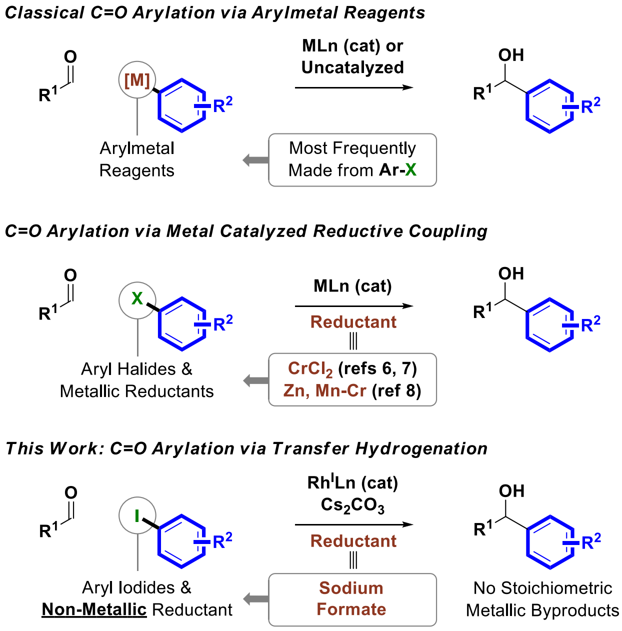

Figure 1. Classical carbonyl arylation and related catalytic reductive couplings.

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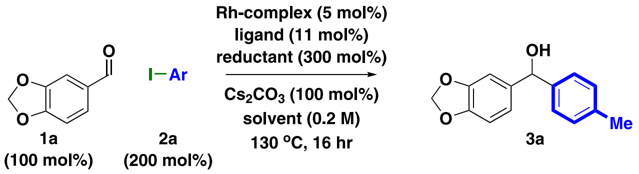
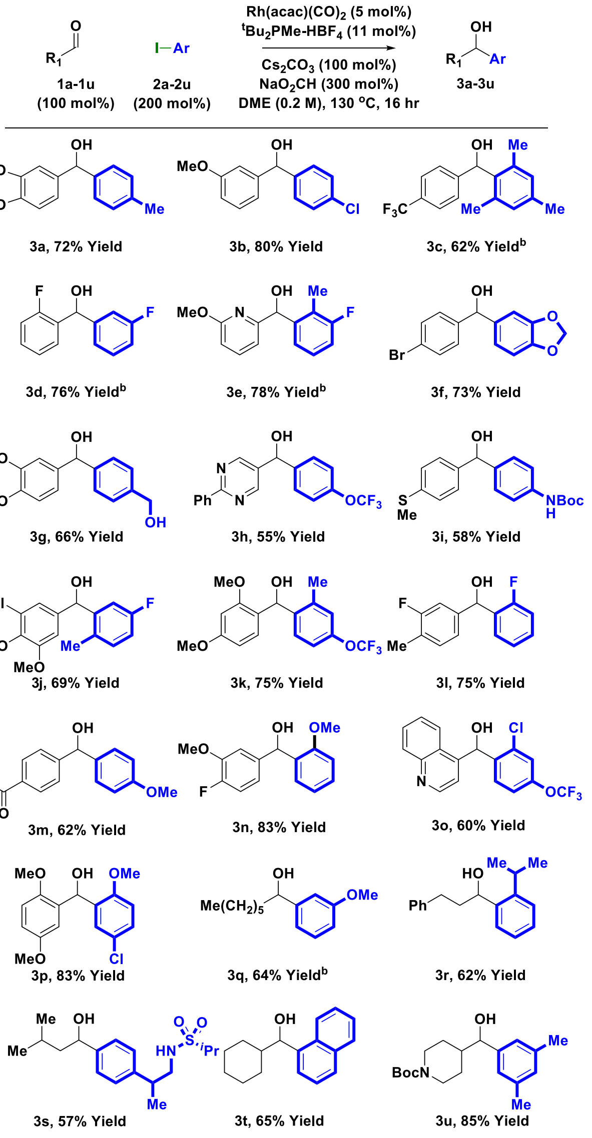
Table 1. Selected Optimization Experiments in the Rhodium-Catalyzed Transfer Hydrogenative Aldehyde Arylation[a]



entry	catalyst	reductant	ligand	solvent	yield (%)
1	$Rh(acac)(CO)_2$	NaO_2CH	PCy_3	Dioxane	12
2	$Rh(acac)(CO)_2$	NaO_2CH	P^tBu_3	Dioxane	25
3	$Rh(acac)(CO)_2$	NaO_2CH	PPh_2Cy	Dioxane	8
4	$Rh(acac)(CO)_2$	NaO_2CH	dppe	Dioxane	trace
5	$Rh(acac)(CO)_2$	NaO_2CH	dCype	Dioxane	trace
6	$Rh(acac)(CO)_2$	NaO_2CH	dippf	Dioxane	trace
7	$Rh(acac)(CO)_2$	NaO_2CH	dppf	Dioxane	11
8	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	Dioxane	40
9	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	^{t}AmylOH	64
➡ 10	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	DME	72
11	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	DME	n.d.[b]
12	$Rh(acac)(CO)_2$	CsO_2CH	$^tBu_2PMe$	DME	17[b]
13	$Rh(acac)(CO)_2$	LiO_2CH	$^tBu_2PMe$	DME	44
14	$Rh(acac)(CO)_2$	NH_4O_2CH	$^tBu_2PMe$	DME	18
15	$Rh(acac)(CO)_2$	^{i}PrOH	$^tBu_2PMe$	DME	trace
16	$Rh(acac)(CO)_2$	H_2 (1 atm)	$^tBu_2PMe$	DME	trace[c]
17	$[RhCl(CO)_2]_2$	NaO_2CH	$^tBu_2PMe$	DME	47
18	$[Rh(cod)Cl]_2$	NaO_2CH	$^tBu_2PMe$	DME	27
19	$Rh(cod)_2BF_4$	NaO_2CH	$^tBu_2PMe$	DME	16
20	$Rh(acac)(CO)_2$	NaO_2CH	$^tBu_2PMe$	DME	56[d]

[a] Yields are of material isolated by silica gel chromatography. $^tBu_2PMe{\cdot}HBF_4$ was employed as ligand precursor. P^tBu_3 was used as a 1.0 M solution in toluene. Lithium formate was used as the monohydrate. The loading of bidentate ligands was 5.5 mol%. The loading of dimeric rhodium pre-catalysts was 2.5 mol%. See Supporting Information for further experimental details. [b] Reaction was conducted without Cs_2CO_3. [c] 75 °C in DME or 130 °C in diglyme. [d] **2a** (150 mol%).

Table 2. Rhodium-Catalyzed Transfer Hydrogenative Coupling of Aldehydes 1a−1u and Aryl Iodides 2a−2u To Form Products of Reductive Arylation, 3a−3u[a]



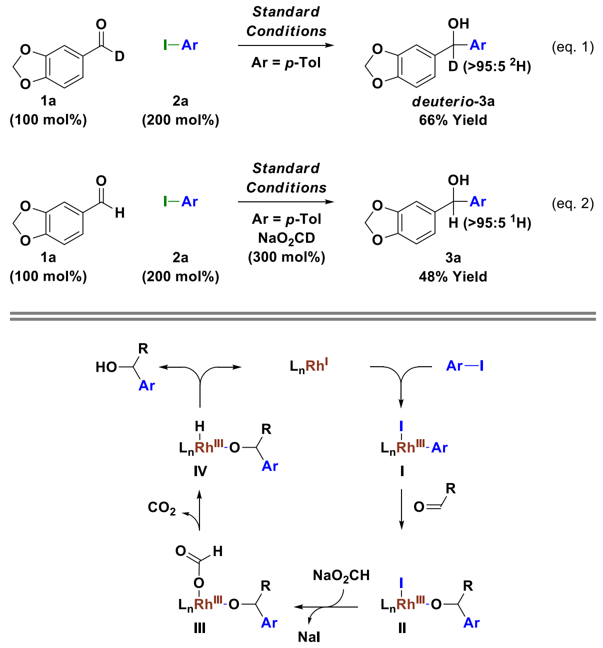
3a, 72% Yield
3b, 80% Yield
3c, 62% Yield[b]
3d, 76% Yield[b]
3e, 78% Yield[b]
3f, 73% Yield
3g, 66% Yield
3h, 55% Yield
3i, 58% Yield
3j, 69% Yield
3k, 75% Yield
3l, 75% Yield
3m, 62% Yield
3n, 83% Yield
3o, 60% Yield
3p, 83% Yield
3q, 64% Yield[b]
3r, 62% Yield
3s, 57% Yield
3t, 65% Yield
3u, 85% Yield

[a] All reactions were performed on a 0.20 mmol scale. Yield of material isolated by silica gel chromatography. See Supporting Information for further experimental details. [b] $[RhCl(CO)_2]_2$ (2.5 mol%) was used.

With this strategy in mind, piperonal **1a** (100 mol%) and 4-iodotoluene **2a** (200 mol%) were exposed to 2-propanol or sodium formate in the presence of diverse palladium or rhodium complexes. Using the catalyst derived from $Rh(acac)(CO)_2$ (5 mol%) and PCy_3 (11 mol%) with NaO_2CH (300 mol%) as reductant and Cs_2CO_3 (100 mol%) as base in dioxane (0.2 M) at 130 °C, the desired reductive coupling product **3a** was formed in 12% isolated yield (Table 1, entry 1). A range of other ligands were evaluated under these conditions (Table 1, entries 1−8). It was found that the catalyst formed *in situ* from $Rh(acac)(CO)_2$ (5 mol%) and $^tBu_2PMe$ (11 mol%) delivered the benzhydryl alcohol **3a** in 40% isolated yield (Table 1, entry 8). Increased efficiencies were observed for reactions conducted in *tert*-amyl alcohol (Table 1, entry 9) and dimethoxyethane (Table 1, entry 10), which provided 64% and 72% isolated yields of **3a**, respectively. Deviation from the latter conditions did not improve the yield of **3a** (Table 1, entries 11−20). Lower loadings of NaO_2CH or **2a** decreased the isolated yield of **3a**. NHC-modified rhodium complexes did not promote reductive coupling.[8g]

To evaluate reaction scope, optimal conditions identified for the formation of **3a** were applied to aldehydes **1a−1u** and aryl iodides **2a−2u** (Table 2). Both aromatic (**1a−1p**) and aliphatic aldehydes (**1q−1u**) underwent reductive coupling efficiently, and diverse functional groups, including those that are incompatible with main-group organometallic reagents, were tolerated. As illustrated in the formation of compounds **3b**, **3f**, **3j**, **3o**, and **3p**, aryl iodides may be activated in the presence of aryl chlorides and bromides. Additionally, as illustrated by the formation of **3c−3e**, **3h**, **3j−3l**, **3n**, and **3o**, fluorine-containing functional groups are tolerated. Notably, 2-fluoro- and 2-chloro-containing 1-iodobenzenes **2l** and **2o** were converted to adducts **3l** and **3o**, respectively, without competing aryne formation.[13] The formation of products **3g**, **3i** and **3s**, which incorporate alcohol, carbamate, and sulfonamide groups, respectively, demonstrates the tolerance of acidic OH- and NH-containing functional groups. Adducts **3e**, **3h**, and **3o**, which incorporate aromatic *N*-heterocycles, are formed efficiently, as are adducts **3i** and **3m**, which contain methyl sulfide and methyl ester moieties. The tolerance of *ortho*-substituted iodides, as demonstrated by the formation of adducts **3c**, **3e**, **3j−3l**, **3n−3p**, **3r**, and **3t**—in particular the formation of adduct **3c**, derived from an *ortho,ortho*-

Scheme 1. Proposed Catalytic Mechanism for Rhodium-Catalyzed Transfer Hydrogenative Arylation Mediated by Formate



disubstituted mesityl iodide—is also notable. Finally, linear and branched aliphatic aldehydes were converted to adducts **3q**−**3u** without competing aldol dimerization. The primary side reactions observed are reduction of the aldehyde, dehydrohalogenation, or reductive dimerization of the aryl iodide and ketone formation.[12]

To gain insight into the catalytic cycle, deuterium labeling experiments were undertaken (eqs 1 and 2 in Scheme 1). Exposure of the aldehyde *deuterio*-**1a** to 4-iodotoluene **2a** under standard reaction conditions resulted in the formation of *deuterio*-**3a**, which completely retains deuterium at the carbinol position (>95:5 ^{2}H) (eq 1). In a second experiment, aldehyde **1a** and 4-iodotoluene **2a** were subjected to standard reaction conditions using NaO_2CD (eq 2). The product **3a** did not incorporate deuterium. These results refute intervention of ketone intermediates that might arise via β-hydride elimination from the rhodium alkoxide derived upon carbonyl insertion into the aryl−rhodium bond.[14] Exposure of aryl ketones to the standard reaction conditions results in only trace quantities of carbonyl reduction product.

Based on the collective data, the following catalytic cycle is proposed (Scheme 1, bottom). Rhodium(I)-mediated aryl iodide oxidation addition[15] delivers the arylrhodium(III) complex **I**. Aldehyde coordination precedes insertion of the aldehyde C═O bond into the metal−aryl bond to form the rhodium(III) alkoxide **II**.[14] Counterion exchange provides the rhodium(III) formate complex **III**, which upon β-hydride elimination releases CO_2 and forms the alkoxyrhodium(III) hydride **IV**. Finally, O−H reductive elimination[16] releases the product of carbonyl arylation and returns rhodium to its low-valent form. The role of Cs_2CO_3 appears to extend beyond the deprotonation of ^{t}Bu$_2$PMe·HBF$_4$. Lower isolated yields are observed when other carbonate bases are used or the loading of Cs_2CO_3 is decreased. Studies aimed at elucidating more precise details of the reaction mechanism are underway.

In summary, we report the first example of reductive carbonyl arylation using a non-metallic reductant, sodium formate. This process is non-cryogenic and can be applied in the presence of functional groups that are typically not compatible with traditional main-group organometallic reagents. This work, along with other hydrogen-transfer-mediated carbonyl reductive couplings developed in our laboratory, defines a departure from the use of pre-metalated reagents in chemical synthesis. Future studies will focus on development of related transfer hydrogenative couplings of vinylic and saturated alkyl halides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13652.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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