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Rhodium-Catalyzed Aldehyde Arylation *via* Formate-Mediated Transfer Hydrogenation: Beyond Metallic Reductants in Grignard-NHK-Type Addition

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Abstract

The first intermolecular carbonyl arylations via transfer hydrogenative reductive coupling are described. Using rhodium catalysts modified by ^tBu₂PMe, 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.

Graphical Abstract

Since the seminal work of Butlerov (1863),^{1a,b} Reformatsky (1887)^{1c} and Grignard (1900),^{1d} the use of preformed organometallic reagents in carbonyl addition has remained a cornerstone of chemical synthesis.² Countless protocols for the addition of non-stabilized

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Notes.

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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 (CrCl₂) pyrophoric (BET₃, ZnEt₂, AlMe₃) or expensive/mass-intensive (R₃SiH).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 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 zinc⁸ (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.

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 PCy₃ (11 mol%) with NaO₂CH (300 mol%) as reductant and Cs₂CO₃ (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, entry 1–8). It was found that the catalyst formed *in situ* from Rh(acac)(CO)₂ (5 mol%) and ^tBu₂PMe (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 dimethoxy ethane (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, entry 11–20). Lower loadings of NaO₂CH 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**, and **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*-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 in these reactions 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 labelling experiments were undertaken (eq. 1–2). Exposure of the aldehyde *deuterio-1a* to 4-iodotoluene **2a** under standard reaction conditions results in the formation of *deuterio-3a*, which completely retains deuterium at the carbinol position (>95:5 ²H) (eq. 1). In a second experiment, aldehyde **1a** and 4-iodotoluene **2a** were subjected to standard reaction conditions using NaO₂CD (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). Rhodium(I)-mediated aryl iodide oxidative addition¹⁵ 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 CO₂ and forms the alkoxyrhodium(III) hydride **IV**. Finally, O-H reductive elimination¹⁶ releases the product of carbonyl arylation and returns rhodium to its low valent form. The role of Cs₂CO₃ appears to extend beyond the deprotonation of ^tBu₂PMe•HBF₄. Lower isolated yields are observed when other carbonate bases are used or the loading of Cs₂CO₃ 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, define a departure from the use of premetallated reagents in chemical synthesis. Future studies will focus on development of a related transfer hydrogenative couplings of vinylic and saturated alkyl halides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). Butlerov A Studien über die Einfachsten Verbindungen der Organischen Chemie., Z. Chem. Pharm 1863, 6, 484–497.(b) Butlerov AZ Sur l'Alcool Pseudobuylique Tertiaire ou Alcool Méthylque triméthylé. Bull. Soc. Chim. Fr 1864, 2, 106–116.(c) Reformatsky S Neue Synthese Zweiatomiger Einbasischer Säuren aus den Ketonen. Ber. Dtsch. Chem. Ges 1887, 20, 1210–1211.(d) Grignard V Sur Quelques Nouvelles Combinaisons Organométalliques du Magnésium et Leur Application à des Synthèses d'alcools et d'hydrocarbures. C R Hebd Séances Acad Sci, Ser C 1900, 130, 1322–1324.
- (2). Comprehensive Organic Synthesis, 2nd ed.; Knochel P; Molander GA, Eds.; Elsevier: Oxford, 2014; Vols. 1 and 2.
- (3). For selected reviews on catalytic enantioselective carbonyl addition, see: (a) Soai K; Shibata T Alkylation of Carbonyl Groups. In Comprehensive Asymmetric Catalysis I-III; Jacobsen EN, Pfaltz A, Yamamoto H, Eds.; Springer-Verlag Berlin Heidelberg: Germany, 1999; Vol. 2, pp 911–922.(b) Kobayashi S; Ishitani H Catalytic Enantioselective Addition to Imines Chem. Rev 1999, 99, 1069–1094.(c) Pu L; Yu H-B Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds. Chem. Rev 2001, 101, 757–824. [PubMed: 11712502] (d) Trost BM; Weiss AH The Enantioselective Addition of Alkyne Nucleophiles to Carbonyl Groups. Adv. Synth. Catal 2009, 351, 963–983.(e) Garcia C; Martin VS Asymmetric addition to ketones: enantioselective formation of tertiary alcohols. Curr. Org. Chem 2006, 10, 1849–1889.(f) Miyaoura N Celebrating 20 Years of SYNLETT-Special Account On Palladium (II)-Catalyzed Additions of Arylboronic Acids to Electron-Deficient Alkenes, Aldehydes, Imines, and Nitriles. Synlett 2009, 2039–2050. (g) Tian P; Dong H-Q; Lin G-Q Rhodium-Catalyzed Asymmetric Arylation. ACS Catalysis 2012, 2, 95–119.
- (4). For selected reviews on metal-catalyzed reductive coupling, see: (a) Montgomery J Nickel-Catalyzed Reductive Cyclizations and Couplings. Angew. Chem. Int. Ed 2004, 43, 3890–3908. (b) Iida H; Krische MJ Catalytic Reductive Coupling of Alkenes and Alkynes to Carbonyl Compounds and Imines Mediated by Hydrogen. Top. Curr. Chem 2007, 279, 77–104.(c) Jeganmohan M; Cheng CH Cobalt- and Nickel- Catalyzed Regio- and Stereoselective Reductive Coupling of Alkynes, Allenes, and Alkenes with Alkenes. Chem. Eur. J 2008, 14, 10876–10886. [PubMed: 18850608] (d) Hassan A; Krische MJ Unlocking Hydrogenation for C–C Bond Formation: A Brief Overview of Enantioselective Methods. Org. Process Res. Devel 2011, 15, 1236–1242. [PubMed: 22125398] (e) Moran J; Krische MJ Formation of C-C. Bonds via Ruthenium Catalyzed Transfer Hydrogenation. Pure Appl. Chem 2012, 84, 1729–1739. [PubMed: 23430602] (f) Moragas T; Correa A; Martin R Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. Chem. Eur. J 2014, 20, 8242–8258. [PubMed: 24905555] (g) Ketcham JM; Shin I; Montgomery TP; Krische MJ Catalytic Enantioselective C-H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. Angew. Chem. Int. Ed 2014, 53, 9142–9150.(h) Everson DA; Weix DJ Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. J. Org. Chem 2014, 79, 4793–4798. [PubMed: 24820397] (i) Nguyen KD; Park BY; Luong T; Sato H; Garza VJ; Krische MJ Metal-catalyzed reductive coupling of olefin-derived nucleophiles: Reinventing carbonyl addition. Science 2016, 354, No. aah5133.(j) Wang X; Dai Y; Gong H Nickel-Catalyzed Reductive Couplings. Top. Curr. Chem 2016, 374, 1.(k) Kim SW; Zhang W; Krische MJ Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier Acc. Chem. Res 2017, 50, 2371–2380. [PubMed: 28792731] (l) Holmes M; Schwartz LA; Krische MJ

Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes, and Enynes with Carbonyl Compounds and Imines. *Chem. Rev* 2018, 118, 6026–6052. [PubMed: 29897740]

- (5). For seminal examples of enantioselective hydrogenative and transfer hydrogenative aldol additions, vinylations, allylations and propargylations, see: (a) Bee C; Han SB; Hassan A; Iida H; Krische MJ Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of Effective Monodentate TADDOL-Like Phosphonite Ligands. *J. Am. Chem. Soc* 2008, 130, 2746–2747. [PubMed: 18266373] (b) Ngai M-Y; Barchuk A; Krische MJ Enantioselective Iridium-Catalyzed Imine Vinylation: Optically Enriched Allylic Amines via Alkyne–Imine Reductive Coupling Mediated by Hydrogen. *J. Am. Chem. Soc* 2007, 129, 12644–12645. [PubMed: 17914825] (c) Kim IS; Ngai M-Y; Krische MJ Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate. *J. Am. Chem. Soc* 2008, 130, 6340–6341. [PubMed: 18444616] (d) Kim IS; Ngai M-Y; Krische MJ Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Allyl Acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition. *J. Am. Chem. Soc* 2008, 130, 14891–14899. [PubMed: 18841896] (e) Kim IS; Han SB; Krische MJ anti-Diastereo- and Enantioselective Carbonyl Crotylation from the Alcohol or Aldehyde Oxidation Level Employing a Cyclometallated Iridium Catalyst: α -Methyl Allyl Acetate as a Surrogate to Preformed Crotylmetal Reagents. *J. Am. Chem. Soc* 2009, 131, 2514–2520. [PubMed: 19191498] (f) Geary LM; Woo SK; Leung JC; Krische MJ Diastereo- and Enantioselective Iridium-Catalyzed Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level: 1,3-Enynes as Allenylmetal Equivalents. *Angew. Chem. Int. Ed* 2012, 51, 2972–2976. (g) Woo SK; Geary LM; Krische MJ Enantioselective Carbonyl Propargylation by Iridium-Catalyzed Transfer Hydrogenative Coupling of Alcohols and Propargyl Chlorides. *Angew. Chem. Int. Ed* 2012, 51, 7830–7834.
- (6). For selected examples of intermolecular Nozaki-Hiyama-Kishi arylation, see: (a) Takai K; Kimura K; Kuroda T; Hiyama T; Nozaki H Selective Grignard-Type Carbonyl Addition of Alkenyl Halides Mediated by Chromium(II) Chloride. *Tet. Lett* 1983, 24, 5281–5284. (b) Fürstner A; Shi N A Multicomponent Redox System Accounts for the First Nozaki–Hiyama–Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc* 1996, 118, 2533–2534. (c) Fürstner A; Shi N Nozaki–Hiyama–Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc* 1996, 118, 12349–12357. (d) Namba K; Wang J; Cui S; Kishi Y Surprisingly Efficient Catalytic Cr-Mediated Coupling Reactions. *Org. Lett* 2005, 7, 5421–5424. [PubMed: 16288521]
- (7). For selected reviews on the Nozaki-Hiyama-Kishi reaction, see: (a) Fürstner A Carbon–Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev* 1999, 99, 991–1046. [PubMed: 11848998] (b) Tian Q; Zhang G Recent Advances in the Asymmetric Nozaki–Hiyama–Kishi Reaction. *Synthesis* 2016, 48, 4038–4049.
- (8). For intermolecular metal-catalyzed aryl halide-aldehyde reductive coupling employing metallic reductants, see: Nickel: (a) Majumdar KK; Cheng C-H Ni(II)/Zn-Mediated Chemoselective Arylation of Aromatic Aldehydes: Facile Synthesis of Diaryl Carbinols. *Org. Lett* 2000, 2, 2295–2298. [PubMed: 10930267] (b) Rayabarapu DK; Chang HT; Cheng C-H Synthesis of Phthalide Derivatives Using Nickel-Catalyzed Cyclization of *o*- Haloesters with Aldehydes. *Chem. Eur. J* 2004, 10, 2991–2996. [PubMed: 15214082] (c) Harnying W; Berkessel A Vinylation of Aldehydes Using Mn/Cr Alloy and a N4- Ligand/NiII- Catalyst. *Chem. Eur. J* 2015, 21, 6057–6061. [PubMed: 25761259] (d) Arendt KM; Doyle AG Dialkyl Ether Formation by Nickel-Catalyzed Cross-Coupling of Acetals and Aryl Iodides. *Angew. Chem. Int. Ed* 2015, 54, 9876–9880. (e) Asachenko AF; Valaeva VN; Kudakina VA; Uborsky DV; Izmer VV; Kononovich DS; Voskoboinikov AZ Coupling of Aromatic Aldehydes with Aryl Halides in the Presence of Nickel Catalysts with Diazabutadiene Ligands. *Russ. Chem. Bull., Int. Ed* 2016, 65, 456–463. (f) Garcia KJ; Gilbert MM; Weix DJ Nickel Catalyzed Addition of Aryl Bromides to Aldehydes to Form Hindered 2° Alcohols. *J. Am. Chem. Soc* 2019, 141, In Press - ja-2018–13709j. (g) Rhodium: Zhou F; Li C-J The Barbier–Grignard-Type Arylation of Aldehydes Using Unactivated Aryl Iodides in Water. *Nature Comm* 2014, 5, 4254.
- (9). For electrochemical intermolecular aryl halide-aldehyde reductive couplings, see: (a) Durandetti M; Périchon J; Nédélec J-Y Nickel- and Chromium-Catalyzed Electrochemical Coupling of Aryl Halides with Arenecarboxaldehydes. *Tet. Lett* 1999, 40, 9009–9013. (b) Durandetti M; Nédélec J-

Y; Perichon J An Electrochemical Coupling of Organic Halide with Aldehydes, Catalytic in Chromium and Nickel Salts. The Nozaki–Hiyama–Kishi Reaction. *Org. Lett* 2001, 3, 2073–2076. [PubMed: 11418052]

- (10). For reviews on the hydrogenolysis of organic halides, see: (a) Pinder AR The Hydrogenolysis of Organic Halides. *Synthesis* 1980, 425–452.(b) Hudlicky M Reduction in Organic Chemistry in *Comprehensive Organic Synthesis*; Trost BM; Fleming I Eds.; Elsevier Ltd, 1991, Vol. 8 pp 895–922.(c) Urbano FJ; Marinas JM Hydrogenolysis of Organohalogen Compounds Over Palladium Supported Catalysts. *J. Mol. Cat. A: Chem* 2001, 173, 329–345.(d) Sheldon RA; van Bekkum H Fine Chemicals through Heterogeneous Catalysis; Wiley-VCH, Weinheim, Germany, 2001, p 415–442.(e) Alonso F; Beletskaya IP; Yus M Metal-Mediated Reductive Hydrodehalogenation of Organic Halides. *Chem. Rev* 2002, 102, 4009–4092. [PubMed: 12428984] (f) Chelucci G; Baldino S; Pinna GA; Pinna, Synthetic Methods for the Hydrodehalogenation of Halogenated Heterocycles. *G. Curr. Org. Chem* 2012, 16, 2921–2945.
- (11). Shin I; Ramgren SD; Krische MJ Reductive Cyclization of Halo-Ketones to form 3-hydroxy-2-oxindoles via Palladium Catalyzed Hydrogenation: a Hydrogen-mediated Grignard addition. *Tetrahedron* 2015, 71, 5776–5780. [PubMed: 26273111]
- (12). For redox-neutral catalytic aryl halide-aldehyde couplings to form ketone products, see: Palladium: (a) Satoh T; Itaya T; Miura M; Nomura M Palladium-Catalyzed Coupling Reaction of Salicylaldehyde with Aryl Iodides via Cleavage of the Aldehyde C–H Bond. *Chem. Lett* 1996, 25, 823–824.(b) Ko S; Kang B; Chang S Cooperative Catalysis by Ru and Pd for the Direct Coupling of a Chelating Aldehyde with Iodoarenes or Organostannanes. *Angew. Chem. Int. Ed* 2005, 44, 455–457.(c) Takemiya A; Hartwig JF Palladium-Catalyzed Synthesis of Aryl Ketones by Coupling of Aryl Bromides with an Acyl Anion Equivalent. *J. Am. Chem. Soc* 2006, 128, 14800–14801. [PubMed: 17105278] (d) Ruan J; Saidi O; Iggo JA; Xiao J Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis. *J. Am. Chem. Soc* 2008, 130, 10510–10511. [PubMed: 18636731] (e) Zanardi A; Mata JA; Peris E Palladium Complexes with Triazolylidene. Structural Features and Catalytic Applications. *Organometallics* 2009, 28, 1480–1483.(f) Adak L; Bhadra S; Ranu BC Palladium(0) Nanoparticle-catalyzed sp² C–H Activation: A Convenient Route to alkyl–aryl Ketones by Direct Acylation of Aryl Bromides and Iodides with Aldehydes. *Tet. Lett* 2010, 51, 3811–3814.(g) Nowrouzi N; Motevalli S; Tarokh D Palladium-Catalyzed Direct C–H Arylation of 2-hydroxybenzaldehydes With Organic Halides in Neat Water. *J. Mol. Cat. A: Chem* 2015, 396, 224–230.(h) Nowrouzi N; Tarokh D PdCl₂/DABCO-Catalyzed Direct Arylation of 2-hydroxybenzaldehydes in H₂O. *J. Iran Chem. Soc* 2016, 13, 1493–1497.(i) Suchand B; Satyanarayana G Palladium-Catalyzed Environmentally Benign Acylation. *J. Org. Chem* 2016, 81, 6409–6423. [PubMed: 27377566] (j) Wakaki T; Togo T; Yoshidome D; Kuninobu Y; Kanai M Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)Aryl Halides via C–H Bond Activation. *ACS Catal* 2018, 8, 3123–3128. (k) Rhodium: Ishiyama T; Hartwig JF A Heck-Type Reaction Involving Carbon–Heteroatom Double Bonds. Rhodium(I)-Catalyzed Coupling of Aryl Halides with N-Pyrazyl Aldimines. *J. Am. Chem. Soc* 2000, 122, 12043–12044.(l) Rao ML; Ramakrishna BS Rhodium-Catalyzed Directing- Group- Assisted Aldehydic C–H Arylations with Aryl Halides. *Eur. J. Org. Chem* 2017, 2017, 5080–5093.(m) Nickel: Huang Y-C; Majumdar KK; Cheng C-H Nickel-Catalyzed Coupling of Aryl Iodides with Aromatic Aldehydes: Chemoselective Synthesis of Ketones. *J. Org. Chem* 2002, 67, 1682–1684. [PubMed: 11871903] (n) Nowrouzi N; Zarei M; Roozbin F First Direct Access to 2-hydroxybenzophenones via Nickel-Catalyzed Cross-Coupling of 2-Hydroxybenzaldehydes with Aryl Iodides. *RSC Adv* 2015, 5, 102448–102453.(o) Photoredox: Zhang X; MacMillan DWC Direct Aldehyde C–H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J. Am. Chem. Soc* 2017, 139, 11353–11356. [PubMed: 28780856] (p) Cobalt: Hu YL; Wu YP; Lu M Co (II)-C12 Alkyl Carbon Chain Multi- Functional Ionic Liquid Immobilized on Nano-SiO₂ Nano-SiO₂@CoCl₃-C12IL as an Efficient Cooperative Catalyst for C–H Activation by Direct Acylation of Aryl Halides with Aldehydes *Appl. Organomet. Chem* 2018, 32, e4096.
- (13). For the magnesium-mediated generation of benzyne from 1-bromo-2-fluorobenzene, see: Wittig G Triptycene. *Org. Synth* 1959, 39, 75.
- (14). For insertion of aldehyde C=O π -bonds into aryl-rhodium σ -bonds and related β -aryl eliminations, see: (a) Krug C; Hartwig JF Direct Observation of Aldehyde Insertion into

Rhodium–Aryl and –Alkoxide Complexes. *J. Am. Chem. Soc.* 2002, 124, 1674–1679. [PubMed: 11853443] (b) Zhao P; Incarvito CD; Hartwig JF Direct Observation of β -Aryl Eliminations from Rh(I) Alkoxides. *J. Am. Chem. Soc.* 2006, 124, 3124–3125.

- (15). For studies on the oxidative addition of aryl halides to rhodium(I) complexes, see: Monophosphine Complexes: (a) Jiao Y; Brennessel WW; Jones WD Oxidative Addition of Chlorohydrocarbons to a Rhodium Tris(pyrazolyl)borate Complex. *Organometallics* 2015, 34, 1552–1566. (b) Townsend NS; Chaplin AB; Abu Naser M; Thompson AL; Rees NH; Macgregor SA; Weller AS Reactivity of the Latent 12- Electron Fragment $[\text{Rh}(\text{PiBu}_3)_2]^+$ with Aryl Bromides: Aryl–Br and Phosphine Ligand C–H Activation. *Chem. Eur. J.* 2010, 16, 8376–8389. [PubMed: 20572181] (c) Chen S; Li Y; Zhao J; Li X Chelation-Assisted Carbon-Halogen Bond Activation by a Rhodium(I) Complex. *Inorg. Chem.* 2009, 48, 1198–1206. [PubMed: 19105736] (d) Douglas TM; Chaplin AB; Weller AS Dihydrogen Loss from a 14-Electron Rhodium(III) Bis-Phosphine Dihydride To Give a Rhodium(I) Complex That Undergoes Oxidative Addition with Aryl Chlorides. *Organometallics* 2008, 27, 2918–2921. (e) Bisphosphine Complexes: Pike SD; Weller AS C–Cl Activation of the Weakly Coordinating Anion $[\text{B}(3,5\text{-Cl}_2\text{C}_6\text{H}_3)_4]^-$ at a Rh(I) Centre in Solution and the Solid-State Dalton Trans 2013, 42, 12832–12835. [PubMed: 23884210] (f) Koenig A; Fischer C; Alberico E; Selle C; Drexler H-J; Baumann W; Heller D Oxidative Addition of Aryl Halides to Cationic Bis(phosphane)rhodium Complexes: Application in C–C Bond Formation. *Eur. J. Inorg. Chem.* 2017, 2040–2047.
- (16). For O–H reductive elimination of metal-bound alkoxides, see: Rhodium: (a) Milstein D Carbon-hydrogen vs. oxygen-hydrogen reductive elimination of methanol from a metal complex. Which is a more likely process? *J. Am. Chem. Soc.* 1986, 108, 3525–3526. (b) Iridium: Glueck DS; Winslow LJN; Bergman RG Iridium Alkoxide and Amide Hydride Complexes. Synthesis, Reactivity, and the Mechanism of Oxygen-Hydrogen and Nitrogen-Hydrogen Reductive Elimination *Organometallics* 1991, 10, 1462–1479. (c) Blum O; Milstein D Direct Observation of O–H Reductive Elimination from Ir^{III} Complexes *Angew. Chem. Int Ed* 1995, 34, 229–231.

Classical C=O Arylation via Arylmetal Reagents **C=O Arylation via Metal Catalyzed Reductive Coupling** **This Work: C=O Arylation via Transfer Hydrogenation**

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

Scheme 1.

Proposed catalytic mechanism for rhodium-catalyzed transfer hydrogenative arylation mediated by formate.

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 ₂ CH	PCy ₃	Dioxane	12
2	Rh(acac)(CO) ₂	NaO ₂ CH	P ^t Bu ₃	Dioxane	25
3	Rh(acac)(CO) ₂	NaO ₂ CH	PPh ₂ Cy	Dioxane	8
4	Rh(acac)(CO) ₂	NaO ₂ CH	dppe	Dioxane	trace
5	Rh(acac)(CO) ₂	NaO ₂ CH	dCype	Dioxane	trace
6	Rh(acac)(CO) ₂	NaO ₂ CH	dippf	Dioxane	trace
7	Rh(acac)(CO) ₂	NaO ₂ CH	dppf	Dioxane	11
8	Rh(acac)(CO) ₂	NaO ₂ CH	^t Bu ₂ PMe	Dioxane	40
9	Rh(acac)(CO) ₂	NaO ₂ CH	^t Bu ₂ PMe	^t AmylOH	64
→ 10	Rh(acac)(CO) ₂	NaO ₂ CH	^t Bu ₂ PMe	DME	72
11	Rh(acac)(CO) ₂	NaO ₂ CH	^t Bu ₂ PMe	DME	n.d. ^b
12	Rh(acac)(CO) ₂	CsO ₂ CH	^t Bu ₂ PMe	DME	17 ^b
13	Rh(acac)(CO) ₂	LiO ₂ CH	^t Bu ₂ PMe	DME	44
14	Rh(acac)(CO) ₂	NH ₄ O ₂ CH	^t Bu ₂ PMe	DME	18
15	Rh(acac)(CO) ₂	^t PrOH	^t Bu ₂ PMe	DME	trace
16	Rh(acac)(CO) ₂	H ₂ (1 atm)	^t Bu ₂ PMe	DME	trace ^c
17	[RhCl(CO) ₂] ₂	NaO ₂ CH	^t Bu ₂ PMe	DME	47
18	[Rh(cod)Cl] ₂	NaO ₂ CH	^t Bu ₂ PMe	DME	27
19	Rh(cod) ₂ BF ₄	NaO ₂ CH	^t Bu ₂ PMe	DME	16
20	Rh(acac)(CO) ₂	NaO ₂ CH	^t Bu ₂ PMe	DME	56 ^d

^aYields are of material isolated by silica gel chromatography. ^tBu₂PMe•HBF₄ was employed as ligand precursor. P^tBu₃ 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 precatalysts was 2.5 mol%. See Supporting Information for further experimental details.

^bReaction was conducted without Cs₂CO₃.

^c75°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

^aAll 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[$\text{RhCl}(\text{CO})_2$]₂ (2.5 mol%) was used.