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Formate-Mediated Cross-Electrophile Reductive Coupling of Aryl Iodides and Bromopyridines

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Dedicated to Professor Barry M. Trost on the occasion of his 80th birthday.

Abstract: Two catalytic systems for the formate-mediated cross-electrophile reductive coupling of aryl iodides with 6-bromopyridines are described. Using homogenous rhodium or heterogeneous palladium catalysts, the products of reductive biaryl cross-coupling could be formed in moderate yield with excellent levels of chemoselectivity.

Keywords: cross-electrophile coupling · reductive coupling · rhodium · palladium · formate

Metal-catalyzed cross-couplings have opened vast volumes of chemical space.[1] Nevertheless, a major liability associated with their use is the requirement of premetalated nucleophiles, which are often prepared through multi-step protocols involving numerous sacrificial reagents. Metal-catalyzed cross-electrophile reductive coupling[2,3] avoids the use of premetalated reagents, however, such processes typically utilize elemental zinc or manganese as reductants, which generates stoichiometric quantities of metallic byproducts. Additionally, the activated surface of such zero-valent metals poses serious safety issues, which is not ideal for large volume applications.[4] Clearly, metallic reductants are as problematic as the premetalated reagents they are intended to replace.

Use of safe, abundant, low molecular weight reductants such as elemental hydrogen, 2-propanol or sodium formate in metal-catalyzed cross-electrophile reductive coupling would enable process-relevant transformations of this type. Precedent can be found in palladium-catalyzed reductive biaryl homo-couplings that employ elemental hydrogen,[5] 2-propanol,[6] ascorbic acid[7] and formate[8a–d,f] as terminal reductants. A rhodium-catalyzed reductive biaryl homo-coupling mediated by formate also has been disclosed.[8c] Studies on the use of organic reductants in metal-catalyzed cross-electrophile reductive coupling are also few in number, and include the use of tetrakis(dimethylamino)ethylene (TDAE),[9,10] which is relatively expensive, poly(ethylene glycol),[11] hydrazine,[12] strained 1,2-diols (via retro-pinacol reaction)[13] and diisopropylethylamine (via photoredox catalysis).[14]

In connection with the discovery and development of reductive C–C couplings promoted by hydrogenation, transfer hydrogenation and hydrogen auto-transfer,[15] we recently described a series of formate-mediated carbonyl reductive couplings of aryl iodide,[16a] vinyl bromide[16b] and vinyl triflate[16c] pronucleophiles. The ability to promote reductive couplings of aryl halide partners prompted an investigation into related formate-mediated cross-electrophile reductive couplings. Here, we report two promising catalytic systems for the formate-mediated cross-electrophile reductive coupling of 4-iodoansiole with 6-bromo-2-picoline based on rhodium and palladium (Figure 1).

Utilizing conditions previously developed in our laboratory for rhodium-catalyzed transfer hydrogenative aryl-aldehyde couplings,[16a] 4-iodoanisole **1a** and 6-bromo-2-picoline **2a**

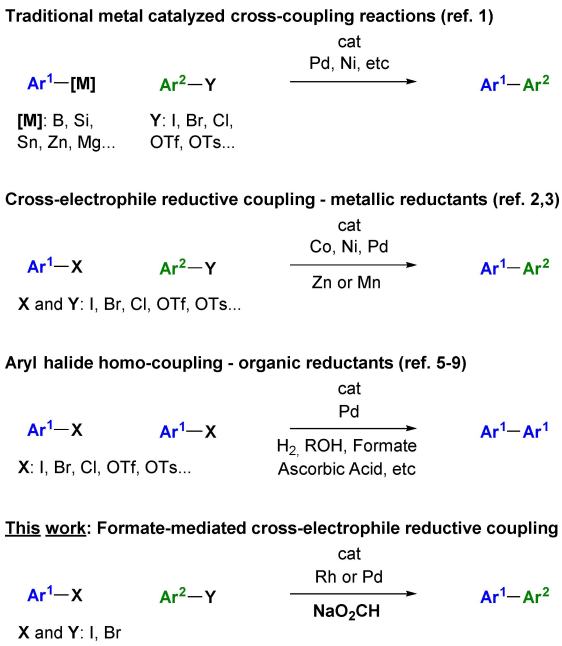

Figure 1. Construction of new carbon-carbon bonds *via* various methods of cross coupling.

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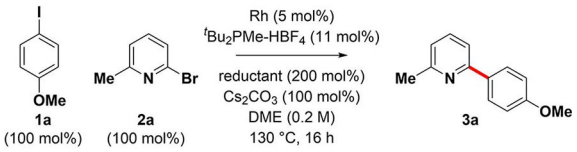
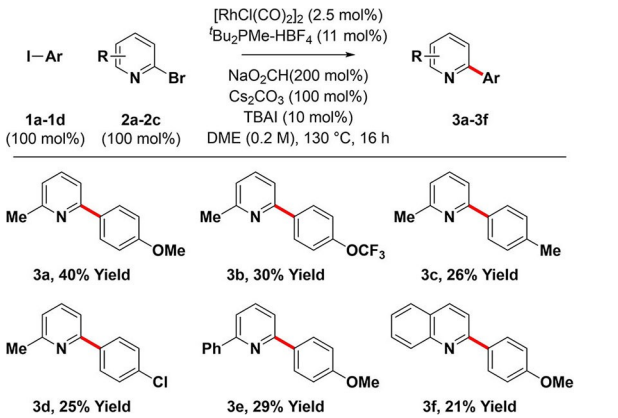
Table 1. Selected optimization experiments in the formate-mediated cross-electrophile coupling of 4-iodoanisole **1a** and 6-bromo-2-picoline **2a** catalyzed by rhodium.[a]



Entry	Rh catalyst	reductant	additive (mol%)	yield (%)
1	$Rh(CO)_2(acac)$	NaO_2CH	-	25
2	$Rh(CO)_2Cp^*$	NaO_2CH	-	20
3	$[RhCl(CO)_2]_2$	NaO_2CH	-	33
4	$[RhCl(CO)_2]_2$	CsO_2CH	-	20
5	$[RhCl(CO)_2]_2$	KO_2CH	-	20
6	$[RhCl(CO)_2]_2$	HCO_2H:Et_3N (5:2)	-	25
7	$[RhCl(CO)_2]_2$	HCO_2H:DIPEA (5:2)	-	22
8	$[RhCl(CO)_2]_2$	NaO_2CH	Bu_4NI (10)	40

[a] Yields are of material isolated by silica gel chromatography. The loading of dimeric rhodium precatalysts was 2.5 mol%.

Table 2. Rhodium-catalyzed formate-mediated cross-electrophile coupling of aryl iodides **1a–1d** and bromopyridines **2a–2c**.[a]

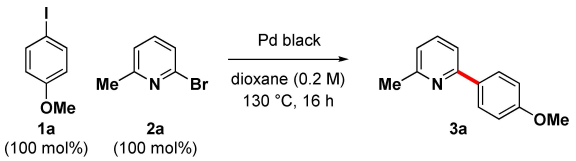


[a] Yields are of material isolated by silica gel chromatography. See supporting information for further experimental details.

undergo cross-electrophile reductive coupling to form biaryl **3a** in 25% yield (Table 1, Entry 1). Only trace amounts (< 5%) of the homo-coupling products were detected. The major side product of the reaction is dehalogenation of the starting materials **1a** and **2a** to give anisole and 2-picoline, respectively. Other commercially available rhodium precatalysts were evaluated, and it was found that complexes lacking carbonyl ligands delivered only trace amounts of the cross-coupling product **3a** along with dehalogenated starting materials. Evaluation of other organic reductants, such as 2-propanol, hydroquinone, and formic acid, failed to deliver significant quantities of hetero-coupling product. Other formate salts provided the product, however in slightly decreased yields (Table 1, Entries 4–7). Lewis basic and acidic additives failed to increase the yield, although upon introduction of tetrabutylammonium iodide (10 mol%) the cross-coupling product **3a** could be obtained in 40% yield (Table 1, Entry 8). Other iodide salts (e.g. KI, NaI, etc.) did not have the same favorable effect. Additionally, a wide variety of mono- and bidentate phosphine and NHC ligands were evaluated under these conditions, however similar or worse levels of conversion were observed. Variation of base also failed to increase yield. Lower reaction temperatures decreased conversion, while elevated reaction temperatures proved to be of little benefit. Evaluation of other aryl iodides and bromopyridines under these conditions selectively furnished the cross-coupling products in modest yields due to competing dehalogenation of the starting materials (Table 2).

Inspired by a report from Sasson and co-workers[5] in which palladium on carbon was utilized in the presence of hydrogen gas to affect aryl halide homo-coupling, palladium-catalyzed cross-electrophile reductive couplings were explored. Initial screening utilizing palladium on carbon in combination with hydrogen gas (1 atm) as reductant and triethylamine (200 mol%) as base provided the cross-coupling product in low yields. Similar results were observed when utilizing palladium black (Table 3, Entry 1). Encouraged by the effect of additives in the rhodium-based catalyst system, diverse additives were screened. Again, tetrabutylammonium iodide was found to increase the yield of **3a**, although super-stoichiometric quantities were required (Table 3, Entry 2). As with the rhodium-based catalyst system, only trace amounts of the homo-coupling products were observed and dehalogenation of the starting materials **1a** and **2a** accounted for the remainder of the mass balance. Control experiments revealed that triethylamine, and not hydrogen, served as the reducing agent (Table 3, Entries 3 and 4). This led to the evaluation of other organic reductants. While reactions conducted using 2-

Table 3. Selected optimization experiments in the formate-mediated cross-electrophile coupling of 4-iodoanisole and 6-bromo-2-picoline catalyzed by Pd black.[a]

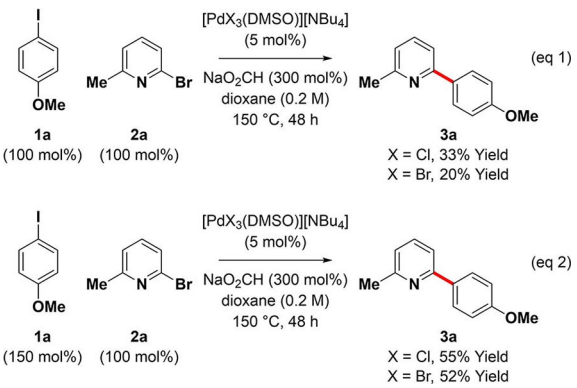


Entry	Pd (mol%)	reductant (mol%)	additive (mol%)	Yield (%)
1	10	H_2 (1 atm); Et_3N (200)	-	12
2	10	H_2 (1 atm); Et_3N (200)	Bu_4NI (200)	32
3	10	H_2 (1 atm)	Bu_4NI (200)	0
4	10	Et_3N (200)	Bu_4NI (200)	42
5	10	2-PrOH (200)	Bu_4NI (200)	18
6	10	NaO_2CH (200)	Bu_4NI (200)	45
7	10	NaO_2CH (300)	Bu_4NI (200)	52
8	10	NaO_2CH (300)	Bu_4NI (100)	40
9	5	NaO_2CH (300)	Bu_4NI (200)	51
10	1	NaO_2CH (300)	Bu_4NI (200)	55

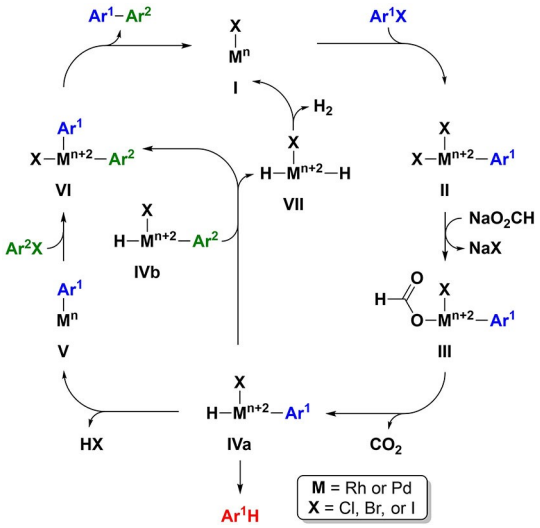
[a] Yields were determined by ^1H NMR of crude reaction mixtures using trimethoxybenzene as an internal standard. Select experiments were duplicated and NMR yields were in close alignment with yields of material isolated by silica gel chromatography.

propanol were less efficient (Table 3, Entry 5), a 45% yield of the cross-coupling product **3a** was obtained using sodium formate (Table 3, Entry 6). Subsequent optimization experiments focused on sodium formate due to its tractability and low cost. Increasing the loading of formate salt, the cross-coupling product **3a** could be obtained in 52% yield (Table 3, Entry 7). Interestingly, decreased loadings of tetrabutylammonium iodide resulted in lower yields of **3a** (Table 3, Entry 8). Finally, it was observed that the loading of palladium black could be decreased without compromising the yield of **3a**. In fact, similar yields could be observed at catalyst loadings as low as 1 mol% (Table 3, Entries 9 and 10). Additionally, use of 2-bromoquinoline in place of 6-bromo-2-picoline resulted in formation of the cross-coupling product in 53% yield (see Supporting Information).

The requirement of TBAI in these reactions suggested its potential role in creating a new active catalyst when combined with the palladium(0) source. Hence, a series of anionic palladium complexes $[PdX_3(DMSO)][NBu_4]$ (X=Cl, Br) were prepared[17] and evaluated as catalysts in the cross-electrophile reductive coupling of 4-iodianisole **1a** with 6-bromo-2-picoline **2a** (Eq 1). The cross-coupling product **3a** was formed in moderate yields. Utilizing a slight excess of 4-iodoanisole under otherwise identical conditions gives the cross-coupling product **3a** in 55% yield (Eq 2). In both cases the primary side products result from dehalogation of **1a** and **3a** to form anisole and 2-picoline, respectively, and not biaryl homo-coupling. These data corroborate intervention of anionic palladium complexes as catalysts. Such anionic palladium species are known to participate in aryl halide oxidative addition with enhanced rates in comparison to corresponding neutral palladium(0) species.[18]



The indicated general catalytic mechanism is one of several that could be proposed based on the collective data (Scheme 1). Aryl halide oxidative addition to either rhodium (I) or anionic palladium(0) **I** followed by ligand exchange with formate gives intermediate **III**. β-Hydride elimination releases carbon dioxide and forms the hydride complex **IVa**, which engages in HX reductive elimination to generate either arylrhodium(I) or anionic arylpalladium(0) complexes **V**. Alternatively, carbon-hydrogen reductive elimination from intermediate **IVa** generates the observed dehalogenation side-



Scheme 1. Proposed catalytic mechanism for the rhodium- or anionic palladium-catalyzed cross-electrophile coupling.

products. A second aryl halide oxidative addition can then occur to give the bis(aryl) rhodium(III) or anionic palladium (II) intermediate **VI**. Reductive elimination releases the cross-coupling product and regenerates complex **I** to close the catalytic cycle. The bis(aryl) species **VI** might also form through alternate mechanism involving reversible transmetalation between complementary arylmetal intermediates **IVa** and **IVb**. In this case, elimination of diatomic hydrogen from intermediate **VII** would be required to close the catalytic cycle. Reductive elimination from complexes containing one electron-rich aryl group and electron-poor aryl group is kinetically preferred,[19] which may account for the preferential formation of cross-coupling (vs homo-coupling) products.

In summary, we have demonstrated the potential of two distinct catalytic systems for formate-mediated cross-electrophile reductive coupling of 4-iodianisole **1a** and 6-bromo-2-picoline **2a**. Our current set of conditions provide the desired cross-coupling product **3a** in up to 55% yield accompanied by only trace quantities of homo-coupling product. Studies toward improved catalytic systems for formate-mediated cross-electrophile reductive coupling are currently underway.

Acknowledgements

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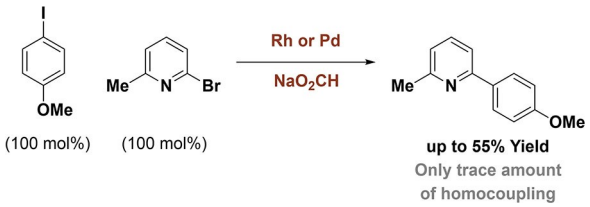

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