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Rhodium-Catalyzed Oxidative C−H Arylation of 2-Arylpyridine Derivatives via Decarbonylation of Aromatic Aldehydes

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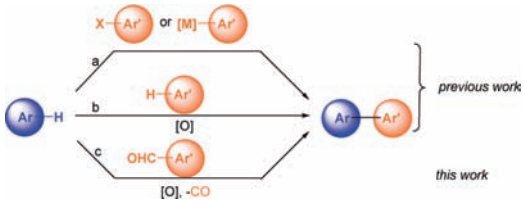
Abstract: A new concept for aryl−aryl coupling that involves oxidative decarbonylative coupling of aryl C−H bonds and readily available aldehydes has been developed, achieving the aryl−aryl union with complete control of reaction sites.

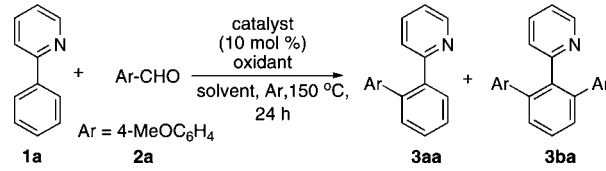
The prevalence and importance of biaryl motifs in natural products, advanced materials, and pharmaceuticals have made the preparation of aryl−aryl bonds among the core interests of organic synthesis for over a century.[1] By far, transition-metal-catalyzed biaryl cross-coupling reactions, which generally employ aryl halides and organometallics as coupling partners, have served as the most common methods for constructing biaryl unions.[2] A variety of other arylation partners involving C−C bond cleavage have also been successfully explored. Among them, Goossen and co-workers[3] reported the cross-coupling reactions of arenecarboxylates with aryl halides through the extrusion of CO_2, which was considered as a major breakthrough in the development of biaryl synthesis. In addition, benzonitrile,[4] α,α-disubstituted arylmethanols,[5] and aryl acid derivatives[6] have also been successfully applied to biaryl synthesis under controlled conditions. In recent years, direct arylations of unactivated arenes with preactivated coupling partners (aryl halides and organometallic reagents) via C−H activation have emerged as attractive alternatives to classical methods (Scheme 1, route a).[7] More recently, more challenging oxidative cross-couplings of two simple arenes have been achieved and developed, affording biaryl products with high atom economy (Scheme 1, route b).[8] While such couplings are conceptually ideal, controlling the regioselectivity of unactivated aryl C−H bonds is still a major challenge. *Herein, we present a new concept for aryl−aryl coupling that involves oxidative decarbonylative coupling of aryl C−H bonds and aldehydes, achieving the aryl−aryl union with complete control of reaction sites (Scheme 1, route c).*

Scheme 1. Arene−Arene Coupling via C−H Activation



On the basis of our previous studies of cross-dehydrogenative-coupling (CDC) reactions[9] and decarbonylative coupling of aldehydes and terminal alkynes,[10] we postulated that readily available aromatic aldehydes could be used as potential arylation partners with arenes via decarbonylative CDC coupling by employing an appropriate oxidant. We began our investigation by testing the reaction of 2-phenylpyridine (**1a**) with anisaldehyde (**2a**) in the presence of catalytic amounts of ruthenium catalyst using *tert*-butyl peroxide (TBP) as oxidant under neat conditions. To our delight, a trace amount of the desired arylation product was detected by GC−MS (Table 1, entry 1). After the catalyst was switched to $(CO)_2Rh(acac)$, the desired product **3aa** was isolated together with biarylated product **3ba** in 28% overall yield (entry 2). Other rhodium catalysts were also tested, and none showed better activities than $(CO)_2Rh(acac)$ (entries 3−6). Among the oxidants examined, only dicumyl peroxide was found to be as effective as TBP (entries 7−9). Because of the higher price of dicumyl peroxide and the difficulty of removing 2-phenylpropan-2-ol after the reaction, TBP was chosen as the oxidant for further optimizations. When the reaction was performed in various solvents, the yield improved significantly (entries 10−13), with chlorobenzene (entry 13) being the best. Shortening the reaction time decreased the yield (entry 14), whereas a longer reaction time did not improve the yield (entry 15). Finally, the use of an additional 0.5 equiv of **2a** increased the yield to 81% (entry 18).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	$[Ru(COD)Cl_2]_n$	TBP	neat	trace
2	$(CO)_2Rh(acac)$	TBP	neat	28[c]
3	$Rh(COD)_2BF_4$	TBP	neat	0
4	$[Rh(COD)Cl]_2$	TBP	neat	11
5	$[(CO)_2RhCl]_2$	TBP	neat	19
6	$RhCl_3$	TBP	neat	18
7	$(CO)_2Rh(acac)$	dicumyl peroxide	neat	27
8	$(CO)_2Rh(acac)$	*tert*-butyl peracetate	neat	13
9	$(CO)_2Rh(acac)$	$(PhCOO)_2$	neat	18
10	$(CO)_2Rh(acac)$	TBP	dioxane	55
11	$(CO)_2Rh(acac)$	TBP	anisole	45
12	$(CO)_2Rh(acac)$	TBP	toluene	48
13	$(CO)_2Rh(acac)$	TBP	PhCl	61
14[d]	$(CO)_2Rh(acac)$	TBP	PhCl	52
15[e]	$(CO)_2Rh(acac)$	TBP	PhCl	58
16[f]	$(CO)_2Rh(acac)$	TBP (1.5 equiv)	PhCl	70
17[f]	$(CO)_2Rh(acac)$	TBP (2.0 equiv)	PhCl	77
18[f]	**$(CO)_2Rh(acac)$**	**TBP (2.5 equiv)**	**PhCl**	**81**
19[f]	$(CO)_2Rh(acac)$	TBP (3.0 equiv)	PhCl	72

[a] Conditions: **1a** (0.1 mmol, 14.6 μL), **2a** (0.25 mmol, 31.0 μL), $(CO)_2Rh(acac)$ (0.01 mmol, 2.6 mg), TBP (0.2 mmol, 37.6 μL), solvent (0.2 mL), argon, 150 °C, 24 h. [b] NMR yield (**3aa** + **3ba**). [c] Isolated yield. [d] For 12 h. [e] For 48 h. [f] **2a** (0.3 mmol, 37.2 μL) was used.

Under the optimized reaction conditions, the scope and generality of this oxidative cross-coupling reaction through decarbonylation of aromatic aldehydes was explored. Electron-rich aromatic aldehydes with a methoxy group at either the para or meta position proved to be good substrates for this transformation, affording the

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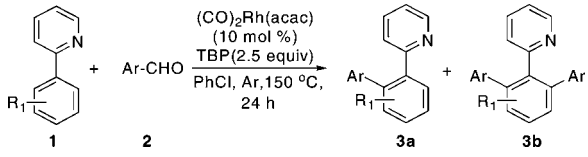
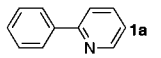
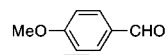
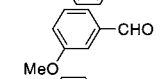
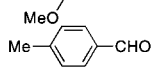
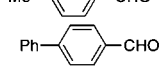
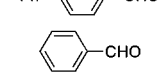
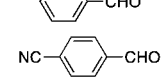
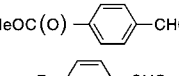
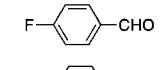
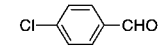
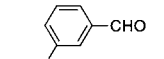
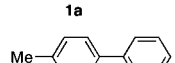
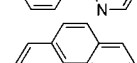
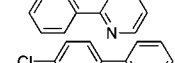
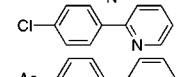
corresponding arylated products in good yields (Table 2, **2a** and **2b**). *p*-Tolualdehyde (**2c**), albeit also effective, furnished the products in moderate yields because of the reaction between the methyl group and the oxidant TBP. 4-Phenylbenzaldehyde (**2d**) and benzaldehyde (**2e**) coupled with 2-phenylpyridine (**1a**) efficiently. Having an electron-withdrawing cyano substituent at the para position, aldehyde **2f** gave a slightly lower yield of decarbonylative coupling products. However, methyl 4-formylbenzoate (**2g**) was found to couple with **1a** efficiently and afforded the desired product in good yield. Notably, the fluoro, chloro, and bromo moieties (commonly used for cross-coupling reactions) in benzaldehydes **2h**, **2i**, **2j**, and **2k** were all tolerated under this novel coupling and afforded the targeted products in moderate to good yields, making further elaborations of the corresponding biaryl products possible. The substituents on the phenyl ring in the 2-arylpyridine derivatives **1b**, **1c**, **1d**, and **1e** did not affect the efficiency of the coupling reactions, and good yields of the desired products were obtained.

A tentative mechanism for this novel coupling is proposed in Scheme 2. Initially, oxidative addition of aldehyde **2** to the Rh(I) center **4** generates species **5**, which undergoes extrusion of CO at elevated temperature to give **6**. Next, **6** reacts with **1a** through C−H bond activation, which is followed by dehydrogenation promoted by TBP to give **7**. Finally, reductive elimination of intermediate **7** affords the target biaryl product **3a** and regenerates the Rh(I) catalyst **4**.

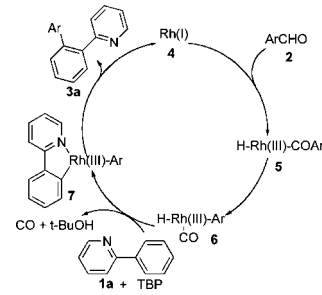
Table 2. Oxidative Decarbonylative Arylation of 2-Arylpyridines[a]



entry	2-arylpyridine	aldehyde		product	yield[b] (%)
1	 **1a**		**2a**	**3aa** + **3ba**	79 (10:9)
2	**1a**		**2b**	**3ab** + **3bb**	82 (10:9)
3	**1a**		**2c**	**3ac** + **3bc**	63 (10:6)
4	**1a**		**2d**	**3ad** + **3bd**	69 (10:8)
5	**1a**		**2e**	**3ae** + **3be**	64 (10:7)
6	**1a**		**2f**	**3af** + **3bf**	67 (10:5)
7	**1a**		**2g**	**3ag** + **3bg**	79 (10:10)
8	**1a**		**2h**	**3ah** + **3bh**	82 (10:8)
9	**1a**		**2i**	**3ai** + **3bi**	70 (10:6)
10	**1a**		**2j**	**3aj** + **3bj**	76 (10:7)
11	**1a**		**2k**	**3ak** + **3bk**	56 (10:18)
12	 **1b**		**2a**	**3al** + **3bl**	87 (10:11)
13[c]	 **1c**		**2a**	**3am**	71
14	 **1d**		**2a**	**3an** + **3bn**	79 (10:9)
15	 **1e**		**2a**	**3ao** + **3bo**	83 (10:10)

[a] Conditions: **1** (0.2 mmol), **2** (0.6 mmol), $(CO)_2Rh(acac)$ (0.02 mmol, 5.2 mg), and TBP (0.5 mmol, 94.0 μL) in PhCl (0.4 mL), argon, 150 °C, 24 h. [b] Isolated yields; the ratios of mono- to bisarylation products determined by ^{1}H NMR analysis are given in parentheses. [c] **1c** (0.2 mmol, 35.8 mg), **2a** (0.3 mmol, 37.2 μL), and TBP (0.25 mmol, 47.0 μL) were used.

Scheme 2. Tentative Mechanism for the Oxidative Arylation of 2-Phenylpyridine with Aryl Aldehydes



In conclusion, we have discovered a novel method for the synthesis of biaryls that employs aromatic aldehydes and 2-arylpyridine derivatives as cross-coupling partners in the presence of an oxidant and proceeds via the extrusion of CO. Aryl halides are tolerated under the reaction conditions. The mechanism and synthetic applications of this aryl−aryl coupling as well as the extension of such a coupling to acrolein derivatives and other substituted benzenes are under further investigation.

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Supporting Information Available: Representative experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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