Cross-Coupling

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Heterogeneous Rhodium-Catalyzed Aerobic Oxidative Dehydrogenative Cross-Coupling: Nonsymmetrical Biaryl Amines

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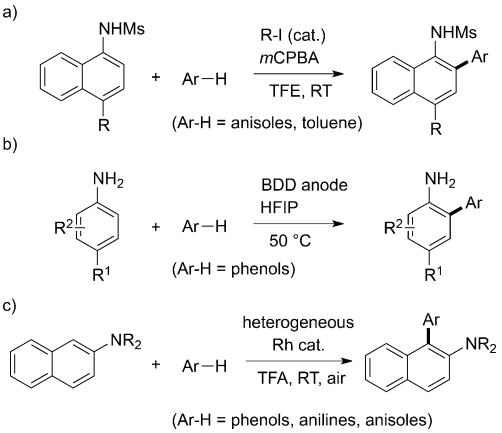
Abstract: *The first heterogeneously catalyzed oxidative dehydrogenative cross-coupling of aryl amines is reported herein. 2-Naphthylamine analogues were reacted with various electron-rich arenes using a heterogeneous Rh/C catalyst under mild aerobic conditions, thus affording nonsymmetrical biaryl amines in excellent yields with high selectivities. This reaction provides a mild, operationally simple, and efficient approach for the synthesis of biaryls which are important to pharmaceutical and materials chemistry.*

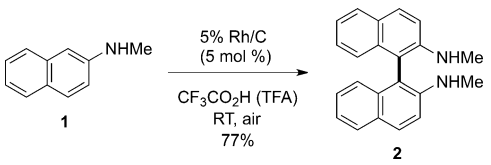
Heterogeneous metal catalysts are critical to the synthesis of fine chemicals and functional materials owing to their advantages such as high efficiency, robustness, and facile recyclability and reusability.[1,2] Biaryls are privileged structures found in many natural products, pharmaceuticals, and liquid crystals. The direct arylation through C–H bond activation has become one of the most attractive synthetic strategies to produce symmetrical and nonsymmetrical biaryls, because the reactants do not have to be prefunctionalized, and because of the atom and step economy.[3,4] However, only few examples of direct arylation using heterogeneous catalysts have been reported. In 2013, Glorius and co-workers reported the first heterogeneously catalyzed direct arylation with aryl chlorides and aryliodonium salts.[5] There still remains ample room to develop heterogeneous metal-catalyzed C–H bond activation strategies.

Among direct arylation methods, oxidative C–H/C–H cross-coupling between two distinct arenes, also known as cross-dehydrogenative coupling (CDC), is an efficient and promising strategy to synthesize a variety of biaryls.[6] However, the oxidative cross-coupling between two arenes with similar chemical and physical properties, such as phenol–phenol or aniline–aniline coupling, are still difficult because of the concomitant formation of homocoupling products and thus only limited success has been reported until recently.[7–9] In particular, oxidative cross-coupling of aryl amines remains largely unexplored because aryl amines are easily oxidized, and thus generate many side products. Recently Kita and co-workers have reported the metal-free oxidative cross-coupling of *N*-Ms-protected aryl amines using organoiodine catalysts in combination with *m*CPBA (Scheme 1 a).[8e] Waldvogel and co-workers have developed electrochemical oxidative phenol–aniline cross-coupling with high selectivity (Scheme 1 b).[9e] Despite these advances, there remains no general method for aniline–aniline cross-coupling.[10] Furthermore, replacement of the stoichiometric oxidant with molecular oxygen represents an important advance and thus direct catalytic cross-coupling using molecular oxygen as the only oxidant is highly desirable.[11] Herein, we demonstrate the first heterogeneously catalyzed aerobic oxidative dehydrogenative cross-coupling of aryl amines (Scheme 1 c). Our methodology enables a concise and convenient preparation of nonsymmetrical biaryls using air or oxygen at room temperature.



Scheme 1. Aryl–aryl bond formation by cross-coupling of aryl amines. BDD = boron-doped diamond, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, *m*CPBA = *m*-chloroperbenzoic acid, TFA = trifluoroacetic acid, TFE = 2,2,2-trifluoroethanol.

Recently, we found that rhodium on carbon functions as an excellent catalyst for the oxidative homocoupling of the aryl amine **1** under mild reaction conditions to provide the dehydrodimer **2** in a high yield (Scheme 2).[12] Notably, this reaction can be carried out with low catalyst loading using air as a terminal oxidant, which is especially advantageous



Scheme 2. Heterogeneous Rh/C-catalyzed homocoupling of aryl amines.

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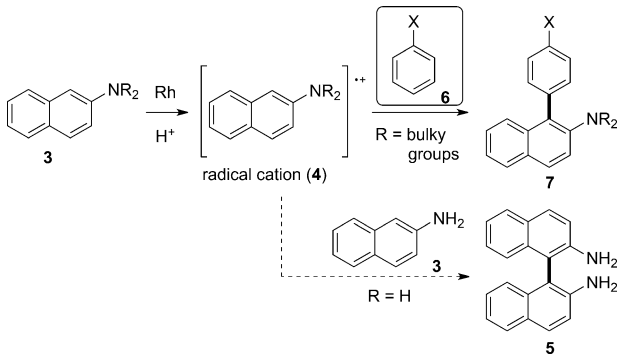
because previous methods usually require a stoichiometric amount of metal salts or oxidants.[13] Thus, we envisioned extending the homocoupling to a heterogeneously catalyzed CDC reaction. Based on our previous results, the aryl amines **3** can be oxidized by a rhodium catalyst to afford the radical cation **4**, which reacts with **3** to give the dehydrodimer **5** (Scheme 3). Thus, we hypothesized that the homocoupling could be suppressed if **3** had sterically hindered substituents on the amino group, thus the resulting radical cations **4** would preferentially react with sterically less hindered arenes (**6**) to provide the cross-coupled biaryls **7**.

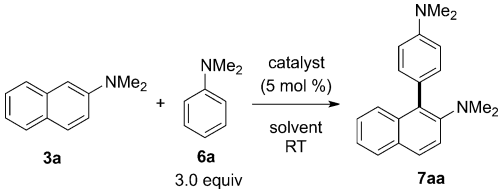


Scheme 3. Working hypothesis for cross-coupling of aryl amines.

If the nucleophilicity of **3** toward radical cations can be controlled by electronic and steric effects, the cross-coupling of **3** should be enabled. Thus, we selected *N*,*N*-dimethylamino-2-naphthalene (**3a**) as a substrate with a bulky amino group and examined the effects of various catalysts in the cross-coupling of **3a** with 3 equivalents of **6a** in trifluoroacetic acid (TFA) under oxygen (Table 1). In the presence of 5% Rh/C (5 mol % of rhodium),[14] the desired cross-coupled product **7aa** was obtained in 85% along with a small amount of the dehydrodimer of **3a** (entry 2). No reaction was observed in the absence of catalysts (entry 1). With Rh/Al_2O_3, the yield of **7aa** was dramatically decreased because of the slow conversion (entry 3). While other heterogeneous catalysts resulted in low yields and poor selectivities (entries 4–11), Pt/C afforded a superior yield of **7aa** (entry 8).[15] Under aerobic conditions, cross-coupling between **3a** and **6a** resulted in a decreased yield of **7aa** because of the slow conversion (entry 12). When the reaction temperature was elevated to 60°C (entry 13) or 5 equivalents of **6a** were employed (entry 14), the cross-coupling proceeded more efficiently to give **7aa** in 84% and 78%, respectively. We also assessed several solvents (entries 15 and 16) and found that TFA was the most effective, probably because of its ability to stabilize radical cation intermediates.[16]

With the optimized reaction conditions in hand, we investigated the cross-coupling using various 2-naphthylamines (Table 2). When the *N*,*N*-diethylamino analogue **3b** and piperidino analogue **3c** were employed, their homocoupling products were not observed and the desired products **7ba** (84%) and **7ca** (93%), respectively, were obtained. Furthermore, even using a small amount of **6a**, the reaction of

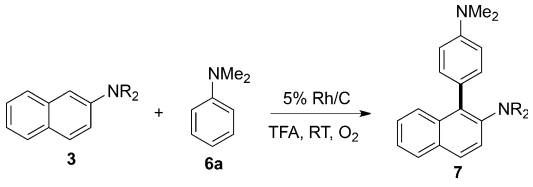
Table 1: Optimization for dehydrogenative cross-coupling of the aryl amine **3a**.



Entry	Catalyst	Solvent	air/O_2	*t* [h]	Yield [%][a]	**7aa**/dehydro dimer of **3a**
1	–	TFA	O_2	80	n.r.	–
2	5% Rh/C	TFA	O_2	16	85	10.9:1
3	5% Rh/Al_2O_3	TFA	O_2	42	9	2.0:1
4	5% Ru/C	TFA	O_2	46	23	10.0:1
5	5% Ru/Al_2O_3	TFA	O_2	42	4	2.6:1
6	10% Pd/C	TFA	O_2	42	6	6.3:1
7	5% Pd/Al_2O_3	TFA	O_2	17	36	1.4:1
8	5% Pt/C	TFA	O_2	12	90	>20:1
9	5% Pt/Al_2O_3	TFA	O_2	20	55	6.3:1
10	PtO_2	TFA	O_2	80	9	2.6:1
11	3% Cu/C	TFA	O_2	40	12	16.7:1
12	5% Rh/C	TFA	air	33	59	14.3:1
13[b]	5% Rh/C	TFA	air	5	84	18.7:1
14[c]	5% Rh/C	TFA	air	26	78	16.7:1
15[d]	5% Rh/C	AcOH	air	24	<10	0.5:1
16[d]	5% Rh/C	CH_2Cl_2	air	24	n.r.	–

[a] Yield of isolated product. [b] 60°C. [c] 5.0 equiv of **6a** was used. [d] 1.5 equiv of **6a** was used. n.r. = no reaction.

Table 2: Dehydrogenative cross-coupling of various aryl amines.[a]

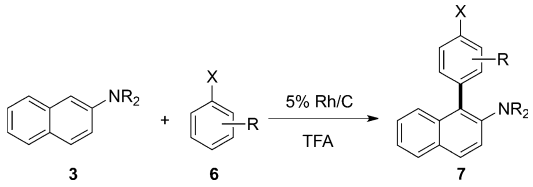


	3a	**3b**	**3c**	**3d**	**3e**	**3f**
NR_2	NMe_2	NEt_2			$NiPr_2$	
7	**7aa**	**7ba**	**7ca**	**7da**		**7fa**
Yield [%]	85	84	93 (92)[b]	79	trace	19
cross/homo	10.9:1	>20:1	>20:1	11.2:1	–	1:1.3
t [h]	16	43	22	50	45	4

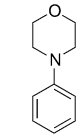
[a] Reaction conditions: **3**, **6a** (3.0 equiv), 5% Rh/C (5 mol%), TFA, RT, O_2. Yield is that of the isolated product. [b] The yield given within parentheses was obtained using 1.5 equiv of **6a** at 50°C.

3c provided an excellent yield of **7ca**. The morpholino analogue **3d** also afforded **7da** in good yield but the selectivity was not better than that with **3c**. In contrast, the reaction of the *N*,*N*-diisopropylamino analogue **3e** was very sluggish owing to the steric hindrance of the bulky amino group and the pyrrolidino analogue **3f** resulted in a sharp decrease in the yield of **7fa**. Probably, since pyrrolidine is less sterically hindered than diethylamino and piperidino groups, the homocoupling of **3f** proceeded faster.[17] These results revealed the effect of amino substituents on the selectivity of

Table 3: The cross-coupling of aryl amines with aromatic nucleophiles.[a]

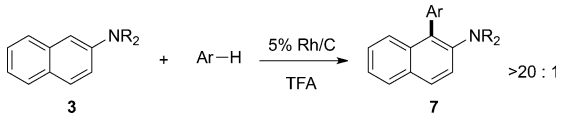


3 6 7

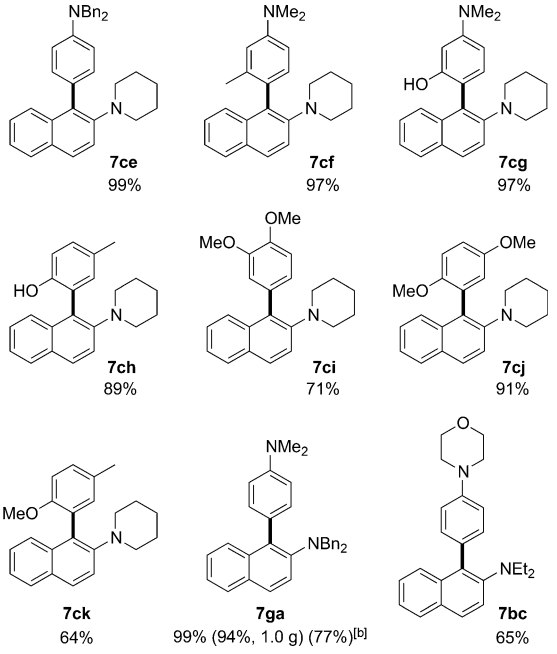
6	7	NMe_2 (3a) yield[c] [%]	cross/homo	7	Piperidino (3a) yield[c] [%]	cross/homo
 6b	7ab	97	>20:1	7cb	89	>20:1
 6c	7ac	42	2.1:1	7cc	95	>20:1
 6d	7ad	26	0.78:1	7cd	92	>20:1

[a] Reaction conditions: **3**, **6** (3.0 equiv), 5% Rh/C (5 mol%), TFA, 60°C, air. [b] Conducted at RT under O_2. [c] Yield of isolated product.

Table 4: Scope of dehydrogenative cross-coupling of aryl amines.[a]



3 7



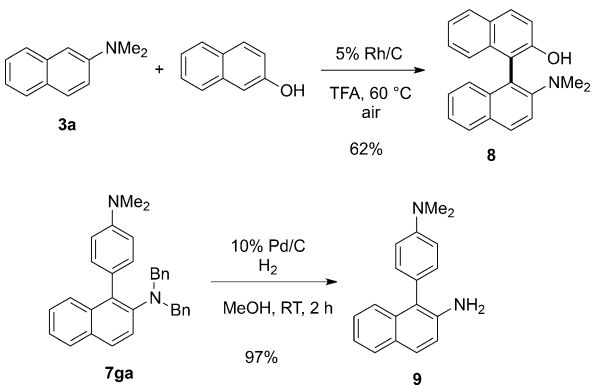
[a] Reaction conditions: **3**, Ar-H (3.0 equiv), 5% Rh/C (5 mol%), TFA, 60°C. Yield is that of the isolated product. [b] 5% Rh/C (0.27 mol% of rhodium).

the reaction. Consequently, **3b** and **3c** afforded the most efficient and selective cross-coupling.

Next, we examined the cross-coupling of **3a** and **3c** with several electron-rich arenes (**6**; Table 3). Phenols were also good coupling partners. The coupling between **3a** and **3c** with phenol **6b** afforded **7ab** and **7cb**, respectively, in excellent yields. However, the coupling between **3a** and either *N*-phenylmorpholine (**6c**) or 2-methylanisole (**6d**) were less selective and resulted in decreased yields of **7ac** and **7ad**, respectively. In contrast, the cross-coupling of **3c** with either **6c** or **6d** proceeded selectively to give **7cc** (95%) and **7cd** (92%), respectively. Probably, since **6c** and **6d** were less nucleophilic than **6a** and **6b**, the difference in nucleophilicity between **3a** and **6c** (or **6d**) became smaller and thus the relative amount of homocoupling of **3a** increased.[18,19] Since **3c** is less nucleophilic than **3a** as a result of the large piperidino group, even **6c** and **6d** function as more powerful nucleophiles toward **3c** and the high selectivity is obtained when using **3c**. These insights support our hypothesis shown in Scheme 1.[20] The steric hindrance of the aryl amines and the nucleophilicity of coupling partners are important to obtain the cross-coupled product rather than the homocoupling product.

Since excellent selectivity was observed with **3c**, we investigated the scope of the CDC (Table 4). Various substituted anilines and phenols were reacted with **3c** to give the cross-coupled biaryls **7ce**, **7cf**, **7cg**, and **7ch** in excellent yields and selectivities. Several anisoles also afforded good yields of **7ci**, **7cj**, and **7ck**. *N*,*N*-Dibenzylamino-2-naphthalene (**3g**) and **3b** reacted with anilines to give the corresponding **7ga** and **7bc** efficiently. The reaction of **3g** on a large scale also proceeded in excellent yield, and was comparable to that on a small scale. Furthermore, even using 0.27 mol% of 5% Rh/C, **7ga** was obtained in good yield and the turnover number (TON) reached up to 280.[21]

To demonstrate the potential applications of the present cross-coupling, the preparation of versatile 1,1′-binaphthyl-based ligands was examined (Scheme 4). Cross-coupling of **3a** with an excess of 2-naphthol proceeded to give the NOBIN analogue **8** in 62%.[22] The *N*,*N*-dibenzyl group of **7ga** was easily removed by Pd/C-catalyzed hydrogenolysis to give **9** in 97%. Since the resulting primary amino group can be used for



Scheme 4. Synthetic utility of the developed cross-coupling reactions.

further transformations, our methodology provides efficient access to a variety of biaryls.[23]

In conclusion, we developed the first heterogeneous, catalytic, aerobic cross dehydrogenative coupling of aminonaphthalenes with electron-rich arenes to provide nonsymmetrical biaryls in high yields and selectivities. This reaction provides a mild and operationally simple approach for the synthesis of biaryl amines. Further studies regarding the synthetic applications and mechanistic details are underway in our laboratory.

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[21] The preliminary recycling experiment for the cross-coupling of **3g** with **6a** in the presence of recovered 5% Rh/C at 50°C under

oxygen (1 atm) provided 93% of **7ga**. This result revealed that Rh/C can be reused in the present reaction.

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