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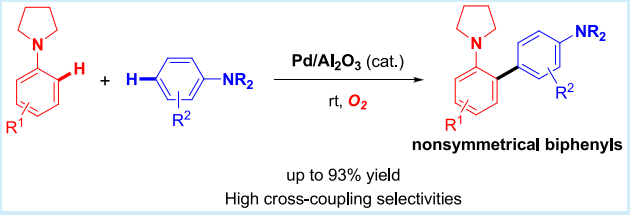
# A Highly Selective Palladium-Catalyzed Aerobic Oxidative Aniline–Aniline Cross-Coupling Reaction

Kenji Matsumoto,* Satoshi Takeda, Tsukasa Hirokane, and Masahiro Yoshida

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, 180 Nishihama-Boji, Yamashiro-cho, Tokushima 770-8514, Japan

Supporting Information

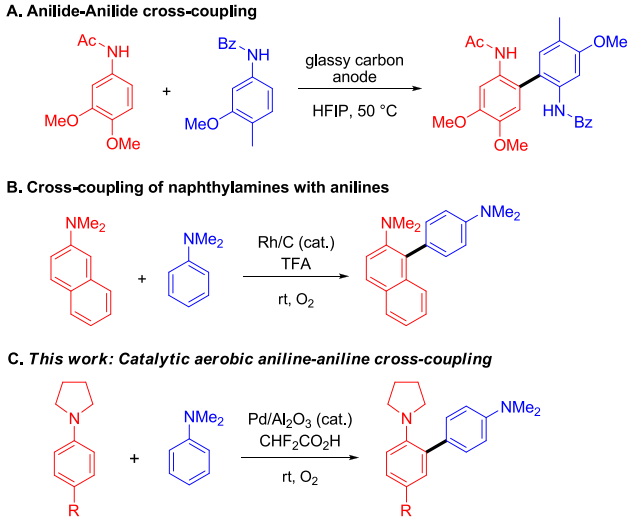
**ABSTRACT:** The first catalytic oxidative aniline–aniline cross-coupling reaction using oxygen as the terminal oxidant is reported. Anilines possessing a pyrrolidino group can be preferentially oxidized under mild aerobic conditions and reacted with other anilines to afford a variety of nonsymmetrical 2-aminobiphenyls with high selectivities. A heterogeneous palladium catalyst is used for the dehydrogenative cross-coupling of anilines with structurally diverse arenes. This reaction does not require stoichiometric oxidants and is an economical and environmentally friendly method.






Nonsymmetrical biaryls are fundamental scaffolds for natural products, catalysts, and industrial materials.[1] In particular, 2-aminobinaphthyls (NOBINs) are prominent functionalized nonsymmetrical biaryls that are used in asymmetric catalysis and are key sources of chiral ligands.[2] Furthermore, 2-aminobiphenyls are widely found in biologically active natural products and pharmaceuticals, such as anticancer agents and anti-HIV agents,[3] and are also employed for the expeditious preparation of key terpene indole alkaloid intermediates.[4] Consequently, many synthetic approaches for the efficient construction of the biaryl linkage in nonsymmetrical 2-aminobiaryls have been developed.[5] Among them, the direct oxidative (dehydrogenative) cross-coupling of aryl amines is the most promising strategy for the preparation of nonsymmetrical 2-aminobiaryls, mainly because the approach circumvents the necessity for substrate prefunctionalization and delivers high atom and step economies.[6] The catalytic oxidative coupling of naphthols and phenols has been well-studied, and the selective cross-coupling has also been reported.[7,8] In contrast, the oxidative coupling of aryl amines has received less attention, and the catalytic methods available for these coupling reactions are still limited because of the facile oxidation of aryl amines, which can lead to the formation of undesired competitive products.[9−11] Recently, Kita and co-workers reported a catalytic oxidative cross-coupling of *N*-sulfonyl anilides with electron-rich arenes using hypervalent iodine reagents.[11a] However, catalytic cross-couplings of different aryl amines with similar chemical properties, such as aniline–aniline or anilide–anilide cross-couplings, remain highly challenging and suffer from low coupling selectivities due to the small differences in the oxidation potentials of the coupling partners. Although Waldvogel and co-workers developed an interesting electrochemical oxidative anilide–anilide cross-coupling (Scheme 1A),[12] unprotected anilines are unsuitable for such electrochemical reactions because of their high tendency for anodic overoxidation.

**Scheme 1. Oxidative Cross-Coupling of Aryl Amines**




We previously studied heterogeneous metal-catalyzed aerobic oxidative couplings[13] and developed reactions for the homocoupling and selective cross-coupling of aryl amines for the preparation of symmetrical and nonsymmetrical 2-aminobiaryls in high yields (Scheme 1B).[14] Despite these advances, there have been no reports on the catalytic aniline–aniline cross-coupling reaction. Continuing our interest in this area, we sought to develop the catalytic cross-coupling of two different anilines. Since molecular oxygen is considered the ideal oxidant, the direct oxidative cross-coupling of anilines using molecular oxygen as the sole oxidant is highly desirable.[15] Herein we demonstrate the first catalytic dehydrogenative aniline–aniline cross-coupling reaction with

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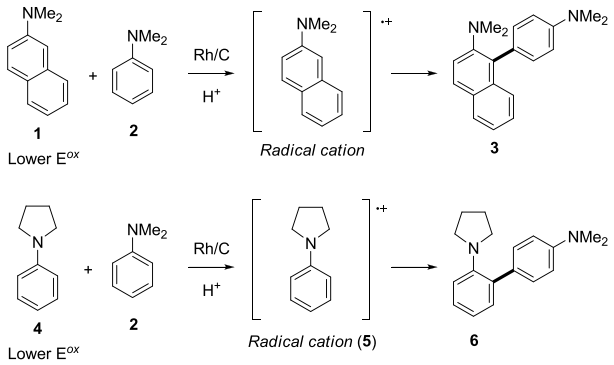
a heterogeneous palladium catalyst under mild aerobic conditions (Scheme 1C).[16]

For the selective aniline−aniline cross-coupling to be successful, overoxidation and homocoupling need to be prevented. In our previous report on the naphthylamine−aniline cross-coupling reaction,[14b] the lower oxidation potential of naphthylamine **1** due to its extended conjugation compared to that of *N*,*N*-dimethylaniline (**2**) allowed its preferential oxidation in the presence of **2** to facilitate the formation of cross-coupled product **3** with high selectivity (Scheme 2). A difference in the oxidation potentials of the two

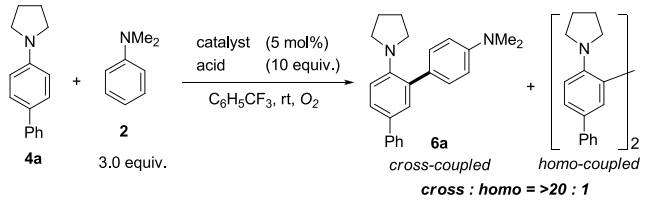
**Scheme 2. Working Hypothesis for the Catalytic Dehydrogenative Aniline−Aniline Cross-Coupling Reaction**




anilines would therefore clearly enable the desired aniline−aniline cross-coupling to take place. Since the pyrrolidino group is a highly powerful electron-donating substituent,[17] we hypothesized that *N*-aryl pyrrolidine **4** would have a lower oxidation potential than **2**, which could promote its selective oxidation to afford radical cation **5**.[18] The preferential reaction of **5** with the less sterically hindered aniline **2** would provide nonsymmetrical 2-aminobiphenyl **6** instead of the homocoupling products.

Thus, *N*-(4-biphenyl)pyrrolidine (**4a**) was selected as the substrate for optimization of the aniline−aniline cross-coupling reaction with **2** using oxygen as the terminal oxidant (Table 1). In a previous study,[14a,b] we found that a heterogeneous Rh/C catalyst could effectively promote the oxidative coupling of aryl amines, and the use of a suitable acid was effective for preventing side reactions such as overoxidation. Building on these conditions, we attempted the cross-coupling of **4a** and **2** with 5 mol % Rh/C in the presence of trifluoroacetic acid (TFA) and observed the selective formation of the desired cross-coupled product **6a** in 55% yield with no detectable formation of the product from homocoupling of **4a** (entry 1). We subsequently examined the effect of various acids on this reaction and found difluoroacetic acid to be the most efficient under the standard conditions (entries 2−4). The use of another rhodium catalyst, $Rh/Al_2O_3$, delivered **6a** in a lower yield (entry 5). While catalysis with Pt/C and $Pt/Al_2O_3$ afforded unsatisfactory results because of competitive reactions, the $Pd/Al_2O_3$-catalyzed reaction proceeded efficiently to afford **6a** in 82% yield (entries 6−9). In contrast, Ru/C and Cu/C were found to be less active (entries 10 and 11). Neither the catalyst nor difluoroacetic acid alone was able to afford the desired product (entries 12 and 13). When a smaller amount of **2** was used, the yield decreased to 51%, although the reaction proceeded efficiently (entry 14). It was therefore apparent that the combination of $Pd/Al_2O_3$ and difluoroacetic

**Table 1. Optimization of the Catalytic Aniline−Aniline Cross-Coupling Reaction**[a]




| entry | catalyst | acid | time (h) | yield (%) |
|---|---|---|---|---|
| 1 | 5% Rh/C | TFA | 74 | 55 |
| 2 | 5% Rh/C | MsOH | 53 | 6 |
| 3 | 5% Rh/C | $CHF_2CO_2H$ | 46 | 62 |
| 4 | 5% Rh/C | $CH_3CO_2H$ | 46 | no reaction |
| 5 | 5% $Rh/Al_2O_3$ | $CHF_2CO_2H$ | 45 | 28 |
| 6 | 5% Pt/C | $CHF_2CO_2H$ | 5 | 2 |
| 7 | 5% $Pt/Al_2O_3$ | $CHF_2CO_2H$ | 3.5 | 31 |
| 8 | 5% Pd/C | $CHF_2CO_2H$ | 54 | 59 |
| 9 | 5% $Pd/Al_2O_3$ | $CHF_2CO_2H$ | 23 | 82 |
| 10 | 5% Ru/C | $CHF_2CO_2H$ | 112 | no reaction |
| 11 | 5% Cu/C | $CHF_2CO_2H$ | 70 | no reaction |
| 12 | 5% $Pd/Al_2O_3$ | – | 97 | no reaction |
| 13 | – | $CHF_2CO_2H$ | 23 | no reaction |
| 14[b] | 5% $Pd/Al_2O_3$ | $CHF_2CO_2H$ | 23 | 51 |

[a] **4a**, **2** (3 equiv), catalyst (5 mol %), acid (10 equiv), $C_6H_5CF_3$, rt, $O_2$. Isolated yields are presented. [b] 1.5 equiv of **2** was used.

acid was the most effective catalytic system for this cross-coupling reaction under mild aerobic conditions.[19]

With the optimized conditions in hand, we subsequently investigated the scope of the cross-coupling reaction using various *N*-aryl pyrrolidines (Scheme 3). When the *p*-*tert*-butyl-substituted aniline was employed, the desired product **6b** was obtained in 92% yield with no detectable formation of the homodimer. The reactions of anilines possessing electron-donating substituents such as methoxy, phenoxy, and 2-acetoxyethyl groups at the *para* position also proceeded to afford **6c−e**, respectively, in good to moderate yields with high cross-coupling selectivities. When the reaction rate was too low, the rate and yield could generally be improved by increasing the amount of acid. An aniline with an electron-withdrawing ester substituent was also tolerated, affording **6f** in 74% yield despite the use of TFA as the solvent. Furthermore, 3-fluorine-substituted aniline reacted with **2** to provide **6g** in 90% yield. Other 3,4-disubstituted anilines were also efficiently cross-coupled to afford the desired products (**6h−j**) in high regioselectivities.

Having achieved excellent yields with high cross-coupling selectivities using **4**, we investigated the dehydrogenative cross-coupling reaction using various electron-rich arenes (Scheme 4). Thus, various substituted anilines were reacted with **4a** and **4b** to afford **7a**, **7b**, **7c**, **7e**, and **7f** in good yields with high selectivities. Among them, 3-substituted anilines were suitable coupling partners, affording **7c**, **7e**, and **7g** in excellent yields. However, no reaction occurred with *N*-phenylmorpholine because of its low nucleophilicity. The presence of an amide group was also tolerated, and the reaction with acetaminophen afforded **7h** in 66% yield. On the basis of these remarkable results, we then conducted the cross-coupling of **4b** with various phenols and anisoles. The cross-coupling reaction using 2,6-dimethylphenol yielded the desired product **7i** in 80% yield, while the reactions at the *ortho* positions of 4-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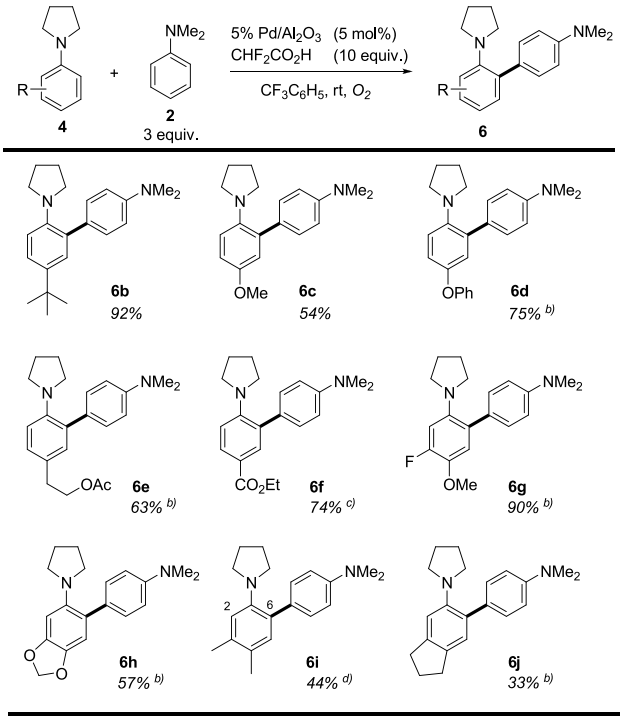
**Scheme 3. Cross-Coupling of Various *N*-Aryl Pyrrolidines with *N*,*N*-Dimethylaniline[a]**



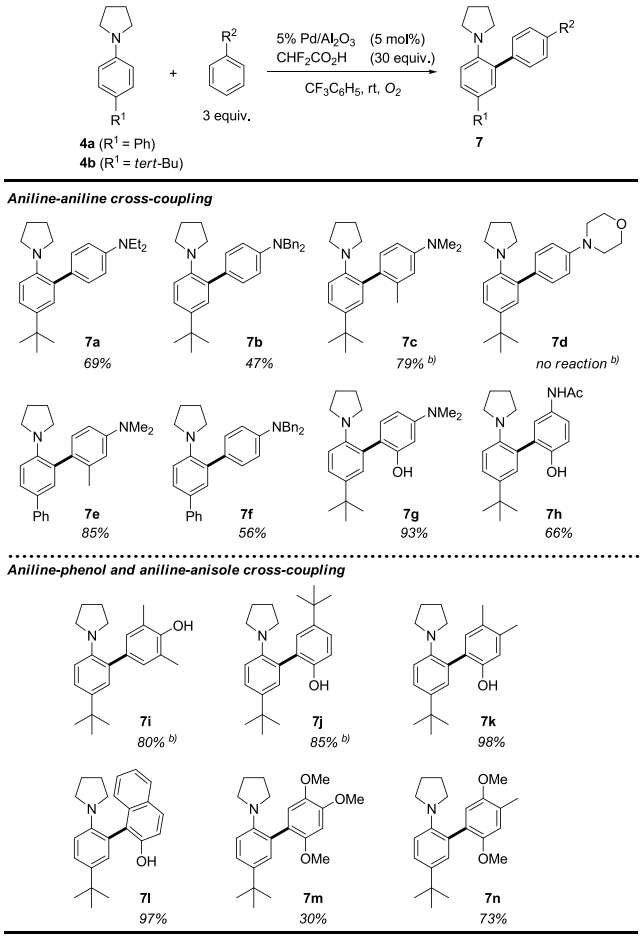

[a]Reaction conditions: **4**, **2** (3 equiv), 5% $Pd/Al_2O_3$ (5 mol %), $CHF_2CO_2H$ (10 equiv), $CF_3C_6H_5$, rt, $O_2$. Isolated yields are presented. [b]30 equiv of $CHF_2CO_2H$ was used. [c]TFA was used. [d]6-isomer:2-isomer = 16:1.

substituted phenols and 2-naphthol afforded **7j–l** in excellent yields with perfect selectivities. When the highly activated anisole 1,2,4-trimethoxybenzene was used, the yield of **7m** decreased to 30% because of the preferential homocoupling of the anisole. To our delight, the reaction with 2,5-dimethoxytoluene proceeded well to afford **7n** in 73% yield. These results therefore indicate that the reaction has a broad substrate scope and that *N*-aryl pyrrolidines can be cross-coupled with a wide range of electron-rich arenes such as anilines, phenols, and anisoles in an efficient manner.

To demonstrate the potential application of the present cross-coupling reaction, the late-stage modification of a pharmaceutical agent was examined (Scheme 5). The cross-coupling of **4b** with estrone, which is a known estrogen receptor agonist, proceeded smoothly under the standard conditions to give optically active **7o** in 78% yield in a highly selective manner. The structure of **7o** was unambiguously assigned by X-ray analysis. These nonsymmetrical 2-amino-biphenyls are expected to have broad utilities as catalyst ligands and organocatalysts and in drug discovery.

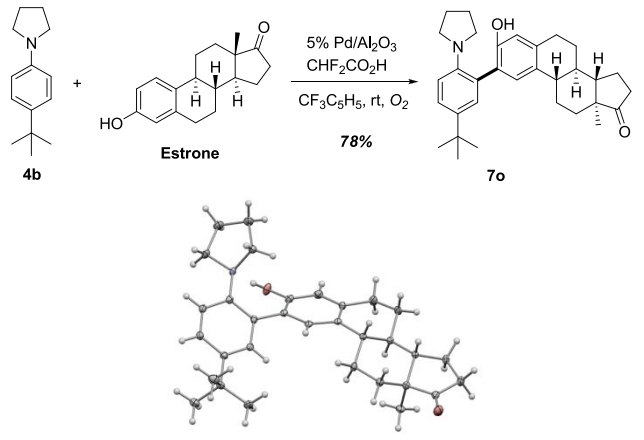
To gain insight into the reaction mechanism, several control experiments were then conducted (Scheme 6). Initially, the reaction was performed under an air or argon atmosphere; however, the yields of **6a** decreased dramatically in both cases, suggesting that oxygen is critical for promoting the present heterogeneous metal-catalyzed cross-coupling reaction. Subsequently, we found that when the radical trapping agent TEMPO was added under the standard conditions, the reaction failed to produce the desired product. With the use of galvinoxyl as an alternative radical trapping reagent, the

**Scheme 4. Cross-Coupling of *N*-Aryl Pyrrolidines with Various Arenes[a]**




[a]Reaction conditions: **4**, arene (3 equiv), 5% $Pd/Al_2O_3$ (5 mol %), $CHF_2CO_2H$ (30 equiv), $CF_3C_6H_5$, rt, $O_2$. Isolated yields are presented. [b]10 equiv of $CHF_2CO_2H$ was used.

**Scheme 5. Synthetic Utility of the C–H/C–H Cross-Coupling Reaction**




cross-coupling reaction was once again completely inhibited. These results suggested that a radical cation is likely involved as a reactive species under the reaction conditions employed herein. Furthermore, the *N*,*N*-dimethylamino analogue **8** and piperidino analogue **9** failed to afford the expected products,



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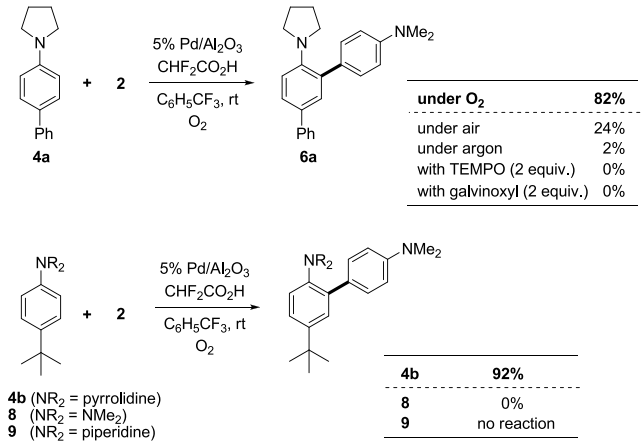
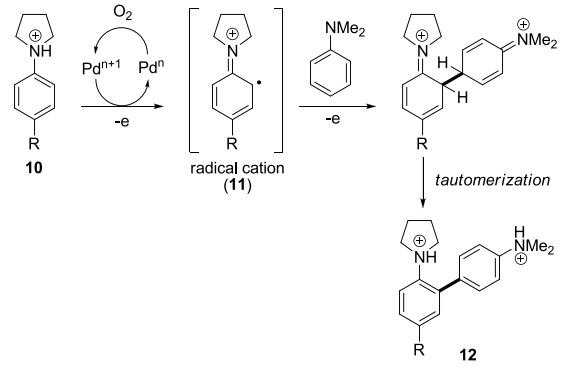
**Scheme 6. Control Experiments To Probe the Mechanism of the Cross-Coupling Reaction**




indicating the significant effect of the amine substituent in achieving a highly selective and efficient aniline−aniline cross-coupling. On the basis of these results, a proposed mechanism is presented in Scheme 7. More specifically, ammonium ion **10**

**Scheme 7. Proposed Mechanism**




undergoes a one-electron transfer reaction with the palladium catalyst, resulting in the formation of radical cation intermediate **11** and the reduced palladium species.[20,21] Radical cation **11** then couples preferentially with the other less sterically hindered aniline, and subsequent tautomerization affords the cross-coupled product **12** with excellent selectivity since the bulky amino group on the aniline suppresses homocoupling at the ortho position. In contrast, since the dimethylamino and piperidino groups are more bulky but less nucleophilic than pyrrolidine,[22] the homo- and cross-coupling reactions of **8** and **9** do not proceed. The *para* substituents of **10** were also necessary for the efficient cross-coupling and required to prevent the homocoupling of radical cation **11** at the *para* position. Subsequently, molecular oxygen oxidizes the reduced catalyst, regenerating the active palladium metal.

In conclusion, we have successfully developed the first heterogeneously catalyzed aerobic oxidative aniline−aniline cross-coupling reaction, which provides nonsymmetrical 2-aminobiphenyls in high yields and selectivities. The presented method operates under mild conditions, displays a broad scope, and allows the synthesis of a range of substituted and optically active 2-aminobiphenyls in good to excellent yields. The combination of the heterogeneous catalyst with oxygen as a terminal oxidant provides an economical and environmentally friendly alternative to previously reported methods. Further studies of the synthetic applications of our method and additional mechanistic details are underway, and the results will be presented in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02527.

Experimental details and $^{1}$H NMR and $^{13}$C NMR spectra (PDF)

### Accession Codes

CCDC 1936765 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: kmatsumoto@ph.bunri-u.ac.jp

### ORCID

Kenji Matsumoto: 0000-0002-0294-7092


### Notes

The authors declare no competing financial interest.

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