An Efficient Oxidative Cross-Coupling Reaction between C–H and N–H Bonds; A Transition-Metal-Free Protocol at Room Temperature

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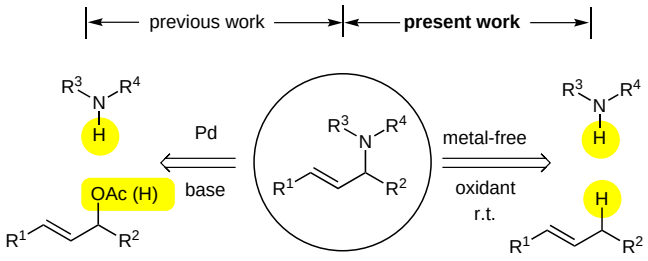
Abstract: A transition-metal-free oxidative coupling of allylic C–H and heterocyclic/aromatic N–H bonds was performed under mild conditions. Promoted by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), up to 99% yield could be achieved.

Key words: metal-free, cross-coupling, oxidative coupling, amination, C–H activation

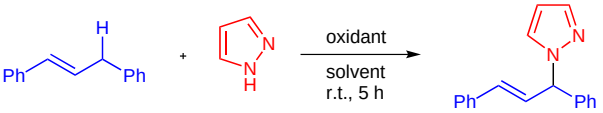
The realm of transition-metal-catalyzed cross-coupling reactions has traditionally required prefunctionalized substrates, either of the electrophilic or nucleophilic partner, for both reactivity and selectivity.[1] Recent revolutionary advancements have focused on the atom-economy issue in the cross-coupling repertoire.[2] Direct C–H bond functionalization, either assisted or catalyzed by transition metals, is a modern direction that is being used to fulfill the spirit of waste minimization.[3] Indeed, it would be highly desirable if a C–H cross-coupling process could be performed in a transition-metal-free environment. In 2010, transition-metal-free coupling reactions between aryl halides (electrophiles) and non-activated arenes (nucleophiles) were independently disclosed by Hayashi/Shirakawa,[4] Lei/Kwong,[5] Shi[6] and others.[7,8] In addition to traditional cross-coupling reactions, oxidative couplings have also received considerable attention.[9]



Scheme 1 Traditional palladium-catalyzed protocol for accessing allylic amines and the proposed new exploration

Allylic amines are important structural motifs in various biologically active and pharmaceutically useful compounds,[10] such as Naftifine (antifungal medicine),[11] and Flunarizine (Ca channel blocker).[12] Moreover, these amines are versatile intermediates for a myriad of synthetic applications.[13] Traditional routes used to access allylic amines often involve Pd-catalyzed allylic substitution (Tsuji–Trost reaction) using allylic acetate as the coupling partner (Scheme 1).[14] The allylic acetate is always from the corresponding allyl alcohol. Given the synthetic potential of the Tsuji–Trost-type reaction, an exploration of non-prefunctionalized coupling partners that could be applicable for this reaction is much warranted (Scheme 1).

Table 1 Initial Screening of the Oxidative C–H/N–H Coupling[a]



1 2 3

Entry	Oxidant (equiv)	Solvent	Yield (%)[b]
1	I_2 (1.0)	dioxane	0
2	DDQ (1.0)	CH_2Cl_2	30
3	BQ (1.0)	CH_2Cl_2	0
4	$PhI(OAc)_2$ (1.0)	CH_2Cl_2	0
5	DDQ (1.0)	$CHCl_3$	25
6	DDQ (1.0)	dioxane	63
7	DDQ (1.0)	toluene	61
8	DDQ (1.0)	THF	53
9	DDQ (1.0)	Et_2O	35
10[c]	DDQ (1.2)	dioxane	90
11[c]	DDQ (1.4)	dioxane	99
12[d]	DDQ (1.4)	dioxane	>99 (93)

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol) and oxidant (as indicated, with respect to **1**), solvent (3 mL), r.t., under air, 5 h. See the Supporting Information for detailed optimization.
[b] GC yield; isolated yield in parentheses.
[c] **2** (0.12 mmol) was used.
[d] **2** (0.12 mmol) was used and the reaction was performed in dioxane (1.0 mL) for 2 h.

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The metal-catalyzed amination of C–H bonds to form new C–N bonds is a current challenge.[15] Despite notable progress that has been made, it would clearly be attractive if these reactions could be carried out in a transition-metal-free manner.[16,17] Very recently, Bao reported the metal-free cross-coupling of 1,3-diarylpropenes with anilines and amides.[18] Herein, we report our further development on the metal-free oxidative coupling between allylic C–H and heterocyclic/aromatic N–H bonds. Notably, 1,3-diarylpropenes can react with N-heterocycles smoothly at a room temperature and up to 99% yield can be achieved.

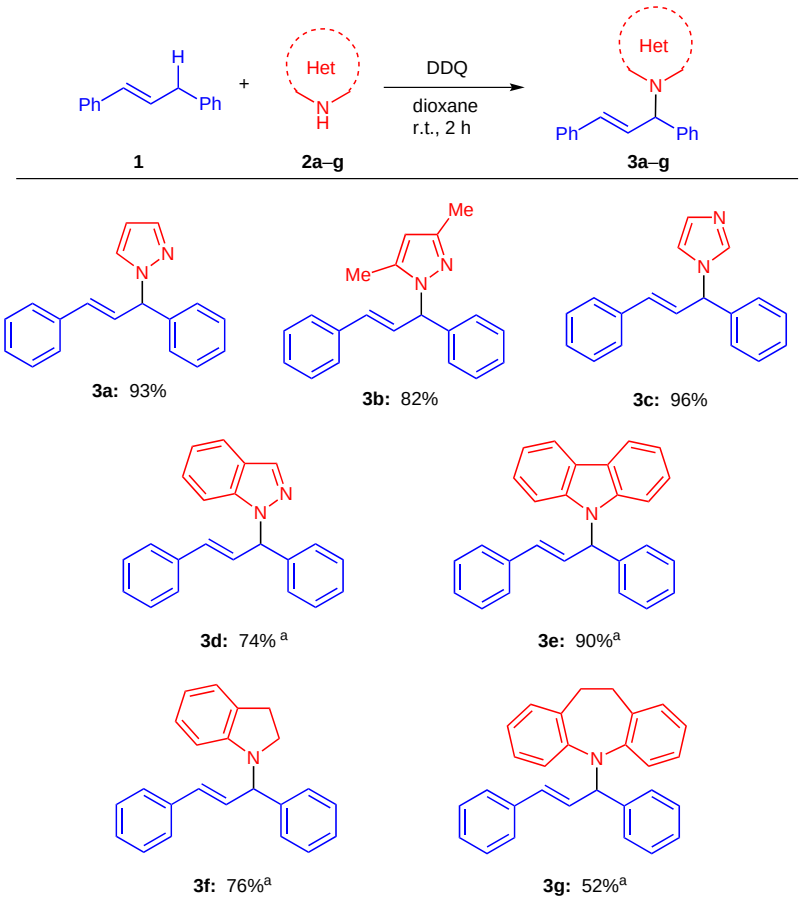
We initially tested the prototypical oxidative coupling using 1,3-diphenylpropene and pyrazole as benchmark substrates (Table 1).[19] A series of commonly available oxidizing agents were examined for their use in generating the desired allylic amine product. In short, DDQ was found to be the most effective oxidant for this reaction (entries 1–4), and dioxane and toluene were the solvents of choice (entries 5–9). Upon investigating the stoichiometry of the oxidant, 1.2–2.0 equivalent of DDQ were found to provide excellent yields (entries 6 and 10–12).

With the optimized reaction conditions in hand, we next examined the scope of the reaction with respect to heterocycles used for the oxidative C–N bond formation (Scheme 2). Substituted pyrazoles provided good product yields (**3b**). Imidazole was found to be a feasible coupling partner (**3c**).[20] Indazole, carbazole and indoline were applicable to generate the corresponding products in good yields (**3d**, **3e** and **3f**), whereas a more sterically hindered coupling partner gave a more moderate yield (**3g**).

In addition to heterocycles, we also examined aniline type substrates **5** (Scheme 3).[21] Coupling partners having a bromo group were found to be applicable (**5c**, **5d** and **5e**), with the bromo moiety remaining intact during the course of the reaction. This serves as a complement to current Pd-catalyzed coupling protocols, which are often incompatible with bromo substituents. Nitro and cyano groups were also tolerated under these reaction conditions (**5f**, **5g** and **5i**), and sterically hindered anilines provided moderate product yields (**5k** and **5n**). Interestingly, the alkynyl aniline was also found to be a feasible substrate (**5o**).

The scope of the reaction with 1,3-diarylpropenes was also investigated (Scheme 4). Product **6** was obtained in 90% yield, and sterically congested 1,3-di(2-methoxyphenyl)propene **7** provided moderate yield (55%). However, the use of 1-[(*E*)-but-1-enyl]benzene as substrate only led to he formation of a trace amount of product.

The functionalization of a C–H bond by an NH_2 group is highly attractive. We therefore attempted to prepare (*E*)-



Scheme 2 Scope of the oxidative coupling between heterocyclic N–H and allylic C–H bonds. *Reagents and conditions*: **1** (0.1 mmol), **2a**–**g** (0.12 mmol), DDQ (0.14 mmol), dioxane (1.0 mL), r.t., under air, 2 h. Isolated yields of **3a**–**g** are reported. [a] The reactions were conducted for 5 h.

1,3-diphenylprop-2-en-1-amine using our methodology (Scheme 5).[22] To our delight, the desired product could be obtained in moderate to good yield.

In summary, we have demonstrated a transition-metal-free oxidative coupling of allylic C–H and aromatic/heterocyclic N–H bonds. This protocol provides rapid access to a variety of allylic amines. No inorganic insoluble base is required. This homogeneous DDQ-promoted system exhibits good functional group tolerance, in which bromo, nitrile, nitro, sulfanyl and alkynyl groups remain intact during the course of reaction. Notably, the free allylic amine can be obtained by using this protocol. Given the attractiveness of the metal-free environment and the favorable reaction conditions (room temperature, 2–5 h), we believe that this method should find widespread use in convergent cross-coupling type organic synthesis. Application of this methodology in micro-channel reactors is under way.

Acknowledgment

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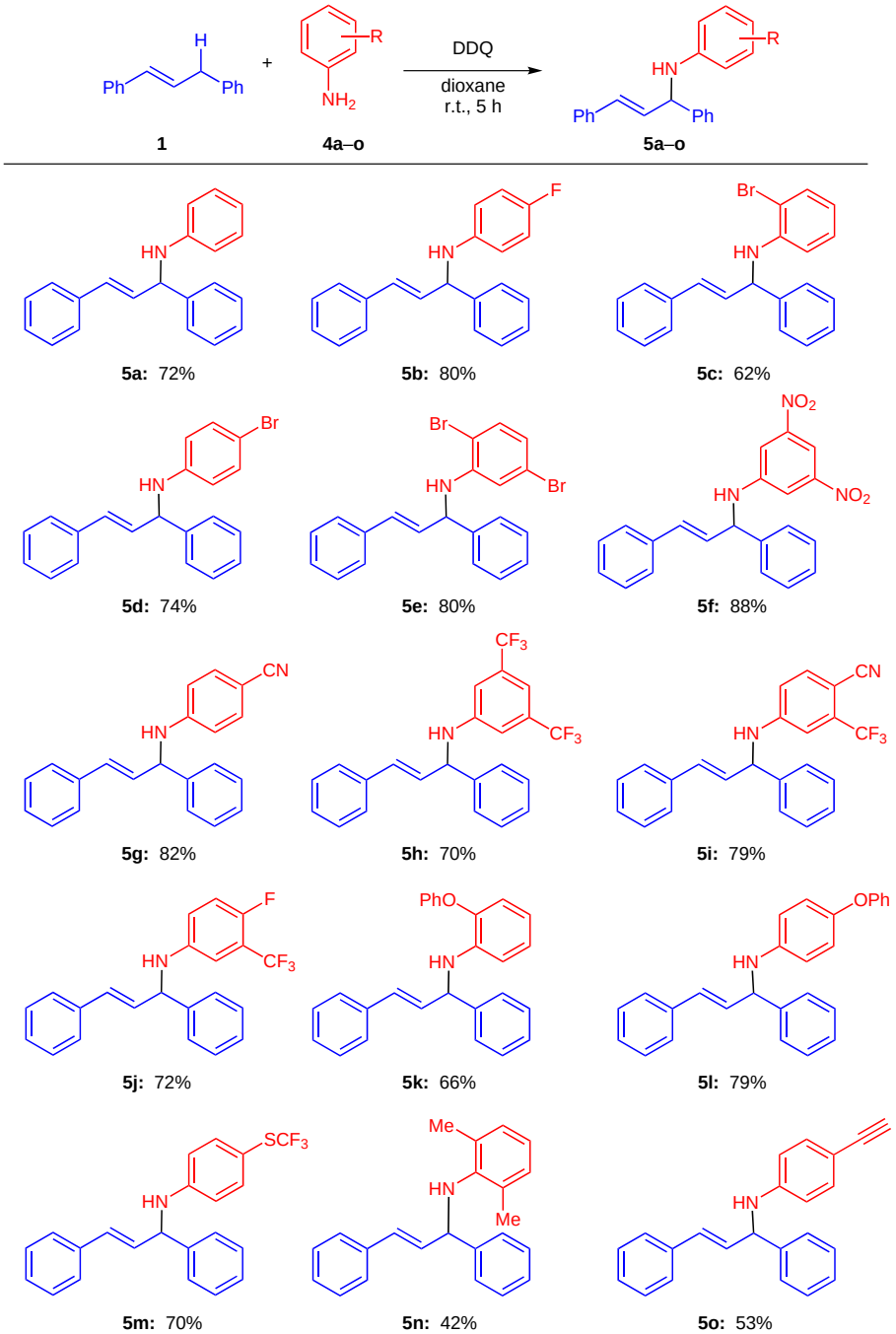
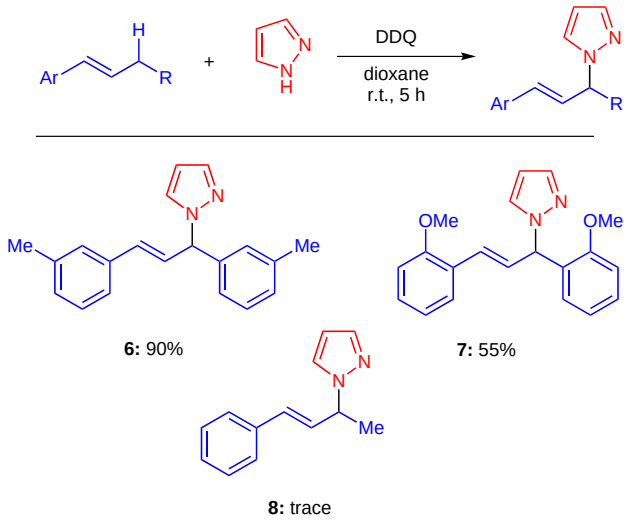
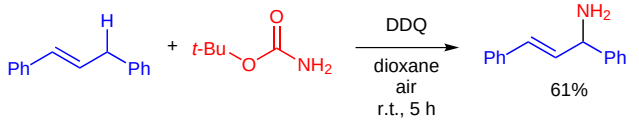


Scheme 3 Scope of the oxidative coupling between aniline N–H and allylic C–H bonds. *Reagents and conditions*: **1** (0.1 mmol), **4a–o** (0.12 mmol) , DDQ (0.14 mmol), dioxane (1.0 mL), r.t., under air, 5 h. Isolated yields are reported.



Scheme 4 Scope of the reaction with substituted 1,3-diarylpropenes



(*E*)-1,3-diphenylprop-2-en-1-amine

Scheme 5 Preparation of (*E*)-1,3-diphenylprop-2-en-1-amine by oxidative C–H/N–H coupling

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) Analytical data of product **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 1.6 Hz, 1 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 7.41–7.23 (m, 10 H), 6.73 (dd, *J* = 7.0, 15.8 Hz, 1 H), 6.45 (d, *J* = 16.0 Hz, 1 H), 6.32 (t, *J* = 2.0 Hz, 1 H), 6.20 (d, *J* = 7.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 139.6, 136.2, 133.9, 128.9, 128.74, 128.67, 128.29, 128.27, 127.54, 127.48, 126.9, 105.8, 67.7. IR: 3060, 3028, 1508, 1495, 1450, 1395, 1280, 1088, 1046, 748, 695 cm^{-1}. HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{16}N_2Na$: 283.1211; found: 283.1198.

(20) Analytical data of product **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.45 (d, *J* = 6.8 Hz, 2 H), 7.41–7.38 (m, 2 H), 7.37–7.34 (m, 2 H), 7.33–7.30 (m, 3 H), 7.12 (dd, *J* = 3.0, 8.2 Hz, 1 H), 6.88 (dd, *J* = 7.0, 15.8 Hz, 1 H), 6.56 (d, *J* = 16.4 Hz, 1 H), 6.52 (d, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 139.0, 136.0, 134.6, 129.0, 128.8, 128.5, 128.4, 127.6, 127.0, 126.9, 126.1, 122.3, 121.9, 121.8, 120.4, 117.9, 69.3. IR: 3059, 3028, 1627, 1513, 1495, 1451, 1390, 1152, 1134, 967, 756, 695 cm^{-1} .

(21) Analytical data of product **5a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.8 Hz, 2 H), 7.39–7.36 (m, 4 H), 7.32–7.29 (m, 3 H), 7.25–7.22 (m, 1 H), 7.17–7.13 (m, 2 H), 6.72 (t, *J* = 7.4 Hz, 1 H), 6.66–6.62 (m, 3 H), 6.41 (dd, *J* = 6.2, 15.8 Hz, 1 H), 5.10 (d, *J* = 6.0 Hz, 1 H), 4.13 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 142.2, 136.8, 131.2, 130.9, 129.3, 129.0, 128.7, 127.8, 127.7, 127.4, 126.7, 117.9, 113.8, 60.8. IR: 3407, 3055, 3025, 1601, 1502, 1449, 1314, 1261, 968, 747, 692 cm^{-1}. HRMS: *m*/*z* $[M - H]^+$ calcd for $C_{21}H_{18}N$: 284.1439; found: 284.1426.

(22) Analytical data of (*E*)-1,3-diphenylprop-2-en-1-amine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.36 (m, 6 H), 7.33–7.28 (m, 3 H), 7.25–7.21 (m, 1 H), 6.61 (dd, *J* = 3.8, 15.8 Hz, 1 H), 6.41–6.30 (m, 1 H), 5.11 (t, *J* = 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 141.3, 136.8, 131.7, 131.5, 130.6, 130.5, 128.7, 127.9, 127.8, 127.2, 126.8, 79.4, 79.3.

(23) Unless otherwise noted, the reaction was carried out as following: To a solution of 1, 4-dioxane (1.0 mL) was added 1,3-diphenylpropenes **1** (0.1 mmol), nitrogen-based nucleophile **2** or **4** (0.12 mmol) and oxidant (0.14 mmol). The reaction mixture was stirred at r.t. for 2–5 h and then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel to yield the desired product.

