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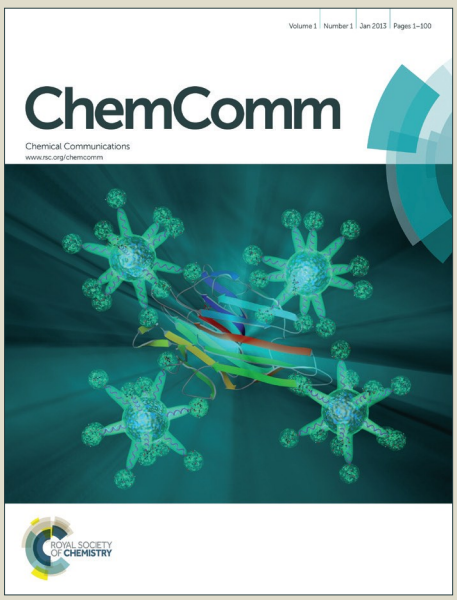

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Communication

Experimental and Mechanistic Analysis of the Palladium-Catalyzed Oxidative C8-Selective C–H Homocoupling of Quinoline *N*-Oxides

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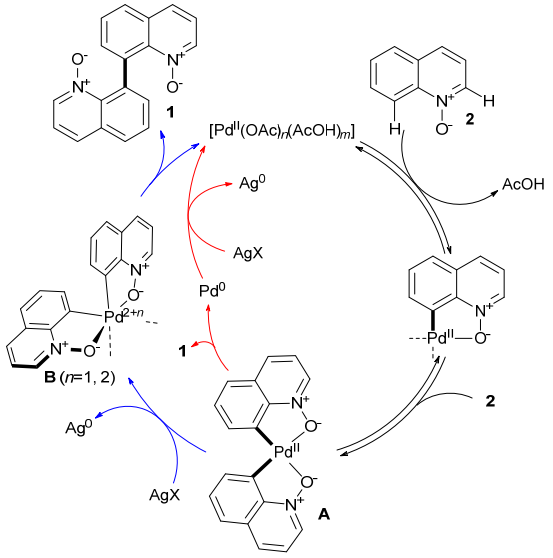
A novel site-selective palladium-catalyzed oxidative C8–H homocoupling reaction of quinoline *N*-oxides has been developed. The reaction affords substituted 8,8'-biquinolyl *N,N'*-dioxides that can be readily converted to a variety of functionalized 8,8'-biquinolyls. Mechanistic studies point to the crucial role of the oxidant and a non-innocent behavior of acetic acid as a solvent.

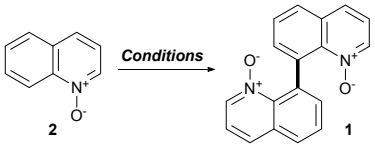
Heteroaryl-heteroaryl bond formation is an important synthetic strategy en route to homo- and heterodimeric structural motifs with applications in catalysis,[1] drug discovery[2] and materials science.[3] Catalytic oxidative C–H homocoupling of heteroarenes is an attractive method of direct biheteroaryl synthesis, as it by-passes prefunctionalization of the heteroarene precursors (e.g. as halides, stannanes or boronic acids). Recent examples of regioselective catalytic oxidative C–H homocoupling of heteroarenes include thiophenes (C2[4]/C3[5]), indoles (C2,[5,6] C2/C3[7]), indolizines (C3),[8] azoles (C2),[9] and furans (C2).[4c] In addition, pyridine and 1,2,3-triazole *N*-oxides undergo oxidative C2–H and C5–H homocoupling reactions, respectively.[10]



Scheme 1. Plausible mechanistic pathways for the oxidative C8–H homocoupling of quinoline *N*-oxides.

We have recently developed a regioselective Pd-catalyzed C8–H arylation of quinoline *N*-oxides.[11,12] Kinetic and DFT computational studies point to the important role of acetic acid as a non-innocent solvent/ligand that directs the turnover-limiting cyclopalladation to the C8 position. It was later observed that certain conditions favor formation of homodimer **1** as a minor by-product (<10% yield), that was hypothesized to be formed by the oxidative C–H homocoupling (Scheme 1). From the synthetic perspective, 8,8'-biquinolyl is a structurally important framework that has been successfully employed in the design of chiral ligands, as shown by Blackmore and co-workers,[13] and is a key structural element of dimeric aporphinoid alkaloids.[14] Mechanistically, Pd-catalyzed oxidative C–H homocoupling reactions remain poorly understood: while a Pd^{II}/Pd^{0} catalytic cycle has generally been postulated,[5] mechanistic evidence suggests that in some cases higher oxidation state Pd species (e.g. a Pd^{IV}/Pd^{II} cycle)[15] can be operative. This paper reports the development and a preliminary mechanistic study of the oxidative C8–H homocoupling of quinoline *N*-oxides.

Table 1. Oxidative C–H homocoupling of quinoline *N*-oxide (**2**).[a]



Entry	Catalyst	Solvent (equiv.)	Oxidant (equiv.)	Yield (%)[b]
1	$Pd(OAc)_2$	AcOH (30)	AgOAc (3)	44
2	$Pd(O_2CCF_3)_2$	AcOH (30)	Ag_3PO_4 (0.5)	32
3	$PdCl_2$	AcOH (30)	Ag_3PO_4 (0.5)	3
4	$Pd(OAc)_2$	AcOH (30)/H_2O (5)	Oxone (2)	12
5	$Pd(OAc)_2$	AcOH (30)/H_2O (5)	$Cu(OAc)_2$ (2)	0
6	$Pd(OAc)_2$	AcOH (15)/H_2O (5)	Ag_3PO_4 (2)	64
7	$Pd(OAc)_2$	AcOH (30)/H_2O (15)	AgOAc (3)	66
8	$Pd(OAc)_2$	AcOH (15)/H_2O (5)	AgOAc (2)	61
9	$Pd(OAc)_2$	AcOH (15)/H_2O (5)	AgOAc (4)	57
10[c]	$Pd(OAc)_2$	AcOH (5)/H_2O (1.5)	AgOAc (4)	82

[a] Reaction conditions: **2** (0.2 mmol), catalyst (10 mol %), oxidant for 12 h at 120 °C. [b] Yields were determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard added prior to work-up. [c] The reaction was carried out on 3.45 mmol scale.

Initial experiments showed that $Pd(OAc)_2$ was superior to other Pd catalysts (Table 1, entries 1–3), and that silver acetate and silver phosphate can both serve as efficient oxidants for the formation of biquinolyl **1**. Other oxidants, e.g. Cu(II) salts, Oxone, $PhI(OAc)_2$, led to low conversions (0–15%). The homocoupling was not observed in other solvents (e.g. *N,N*-dimethylformamide, *tert*-butanol, 1,2-dichloroethane, dioxane) confirming the crucial role of acetic acid in the cyclopalladation. Based on our earlier observation of the accelerating effect of water on C8–H arylation of substrate **2**,[11] reactions were carried out in the acetic acid/water system, and a 57–66% conversion

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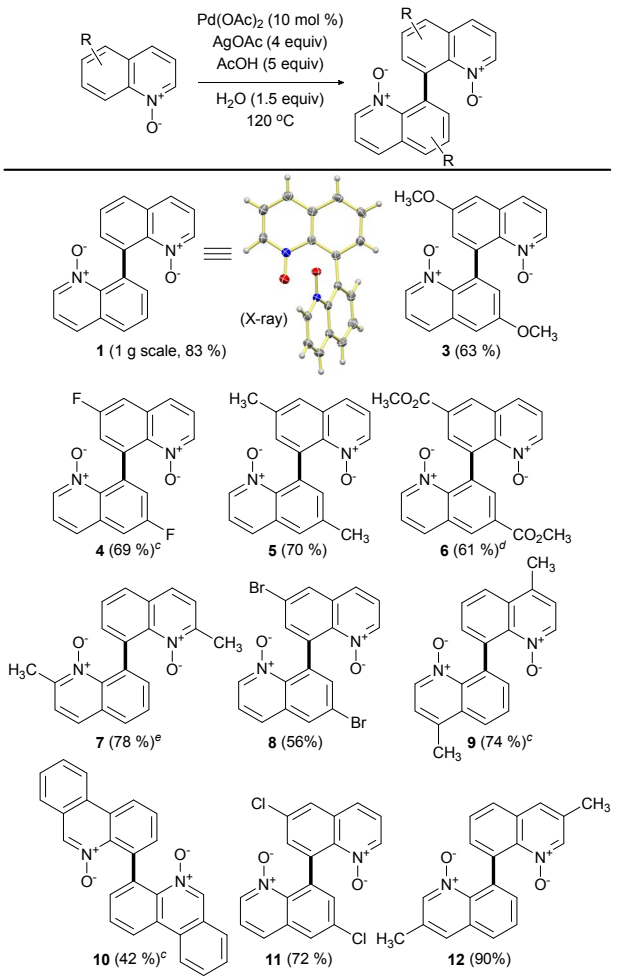
was achieved with a 2–3 : 1 molar ratio of AcOH/H_2O (entries 6–9, Table 1).

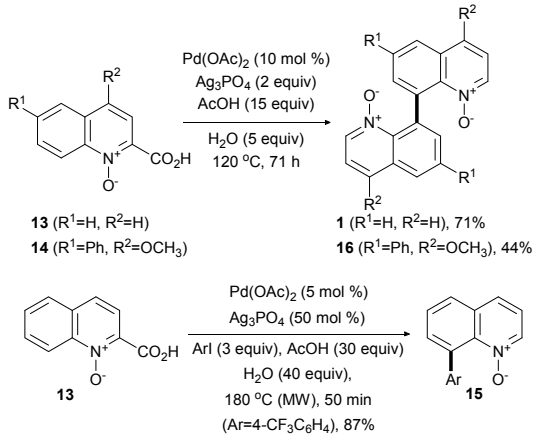
Table 2. Scope of the oxidative C8–H homocoupling reaction.[a,b]



[a] Reaction conditions: *N*-oxide (0.50 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (4 equiv), AcOH (5 equiv), H_2O (1.5 equiv), 120 °C, 12–24 h. [b] The yields are reported for isolated 8,8'-biquinolyl *N,N'*-dioxides. [c] 15 equiv AcOH and 5 equiv H_2O was used. [d] 20 mol % $Pd(OAc)_2$ was used. [e] The reaction was carried out with Ag_3PO_4 (2 equiv.), AcOH (15 equiv), and H_2O (5 equiv).

The conversion was further improved by reducing the amounts of acetic acid and water to 5 and 1.5 equiv, respectively, as a consequence of the increased effective concentrations of the reactants (entry 10). The C–H homocoupling was successfully carried out on a 1 g scale and afforded product **1** in an 83% yield. The reaction can be carried out in the atmosphere of air that has no effect on the conversion. The C8/C2 selectivity is estimated to be >30:1, as no formation of C2-C2 or C2-C8 regioisomers was observed by ^{1}H NMR spectroscopy. The reaction exhibits a broad scope and tolerates a variety of substituents in the quinoline core (Table 2). Halogens, including Br, are well tolerated, and benzylic C–H bonds remain unaffected. 4,7-Dichloroquinoline *N*-oxide did not undergo the C8-dimerization, indicating that C7-substituents may be detrimental to the reaction.

2-Carboxyquinoline *N*-oxide (**13**) underwent a smooth decarboxylation and C8–H homocoupling (Scheme 2). Monitoring of the reaction progress proved that the rapid decarboxylation precedes the dimerization, and the actual substrate for the homocoupling is quinoline *N*-oxide. The facile Ag-catalyzed decarboxylation may be due to the stabilization of the transition state by the electron-withdrawing N–O moiety, as it has been recently rationalized for ortho-substituted benzoic acids.[16] The tandem C2-decarboxylation/C8–H homocoupling process was successfully expanded to the readily available substituted *N*-oxide **14**.

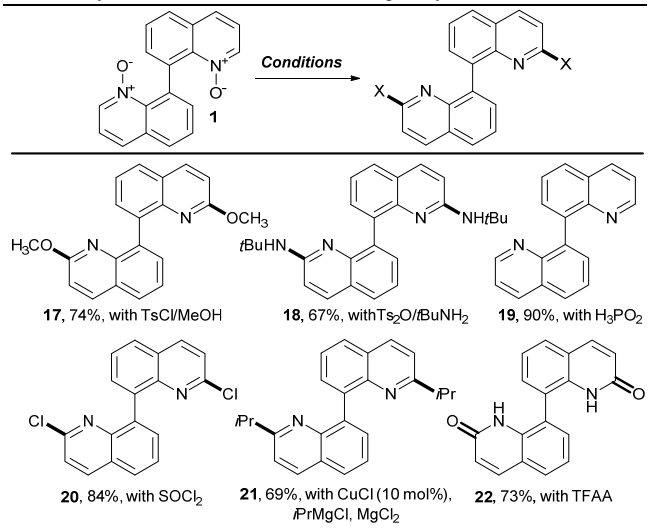


Scheme 2. Tandem C2-decarboxylation/C8–H homocoupling reaction of substituted 2-carboxyquinoline *N*-oxides.

As a corollary, the C8–H arylation of substrate **13** was carried out, and the corresponding cross-coupling product **15** was obtained in an 87% yield. This result compliments Hoarau's Ag- and Cu-mediated, Pd/phosphine-catalyzed C2-selective arylation of 2-carboxyquinoline *N*-oxides.[17]

The *N*-oxide moiety in the homocoupling products can be transformed into a number of functional groups in the C2-position (Table 3). For example, methoxy[18] and *N*-*tert*-butylamino groups[19] were installed in the 2 and 2'-positions in 74% (**17**) and 67% (**18**) yields, respectively.

Table 3. Synthesis of 2,2'-susbtitited 8,8'-biquinolyls from *N*-oxide **1**.



Similarly, a deoxygenation with hypophosphorous acid furnished 8,8'-biquinolyl (**19**), whereas a reaction with thionyl chloride[20] afforded 2,2'-dichloro-8,8'-biquinolyl (**20**) in an 84% yield. In addition, 2,2'-dialkyl-8,8'-biquinolyl **21** was readily obtained by a copper-catalyzed reaction with a Grignard reagent,[21] and 8,8'-biquinolone **22** was formed by a trifluoroacetic anhydride-

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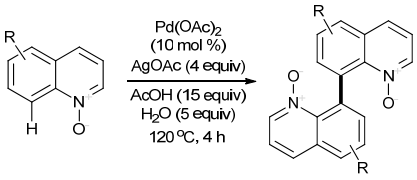
mediated rearrangement.[22] A reaction of **2** with $CF_3Si(CH_3)_3$ in the presence of potassium *tert*-butoxide[23] unexpectedly led to a nearly quantitative conversion to 8,8'-biquinolyl (**19**) presumably due to the increased steric encumbrance in the dimeric *N*-oxide.

The mechanism of the homocoupling reaction was briefly examined by means of kinetic isotope effect and Hammett plot studies. We previously determined by means of H/D-exchange experiments that a highly C8-selective (>30:1) cyclopalladation of **1** occurs in the $Pd(OAc)_2$/AcOH system.



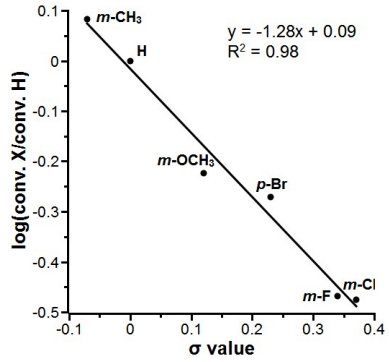


Figure 1. Hammett plot for the oxidative C8–H homocoupling of quinoline *N*-oxide.

It was further determined, that the cyclopalladation was a reversible and turnover-limiting step. It was therefore of interest to compare the mechanistic data for C8–H homocoupling with those for the C8–H arylation. Primary KIE was measured in parallel experiments with substrate **2** in CH_3CO_2H/H_2O, and 2,8-d_2-**2** in CD_3CO_2D/D_2O, respectively. It was determined that the homocoupling proceeded with no primary KIE (k_H/k_D = 1), in contrast to the arylation (k_H/k_D = 2), indicating that the cyclopalladation was not a turnover-limiting step in this case. This result was further supported by the Hammett study (Figure 1) that provided a ρ value of –1.28 for the homocoupling. This ρ value is substantially lower than that observed for the $Pd(OAc)_2$-catalyzed C8-H/D exchange for **2** in AcOH (ρ = –2.98). Furthermore, since no palladacyclic intermediates were isolated or observed by ^{1}H NMR, and the reaction afforded exclusively homocoupling products (e.g. C8-C8 and not C8-C2), the second cyclopalladation step is likely reversible in AcOH under the reaction conditions, and is mechanistically similar to the first cyclopalladation step.[15,24] Hence, the combined KIE, Hammett[25] and kinetic results are more consistent with the reductive elimination as a turnover-limiting step of the reaction. Further, experiments with varied amounts of $Pd(OAc)_2$ in the absence of AgOAc indicate that the reaction does not proceed through a Pd^{II}/Pd^0 catalytic cycle, as no correlation was observed between the concentration of $Pd(OAc)_2$ and conversion of **2**.[26] This result suggests that the oxidation state of palladium that is required for the reductive elimination en route to **1** cannot be accessed in the absence of the Ag^I oxidant,[27] pointing to higher oxidation state pathways as likely mechanistic alternatives.

In conclusion, we have developed a new C8-selective C–H homocoupling of quinoline *N*-oxides. The reaction proceeds with a high degree of site-selectivity to give 8,8'-biquinolyl *N,N'*-dioxides that can serve as precursors to a number of 2,2'-substituted 8,8'-biquinolyls. Preliminary mechanistic analysis points to involvement of the higher oxidation state Pd and the crucial role of acetic acid for the C8-regioselectivity.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b000000x/

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