ChemPubSoc Europe

DOI: 10.1002/ejoc.201600680

EurJOC European Journal of Organic Chemistry

Communication

Cross-Coupling

Palladium-Catalyzed Regioselective Dehydrogenative C–H/C–H Cross-Coupling of Pyrroles and Pyridine *N*-Oxides

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Abstract: The palladium-catalyzed cross-dehydrogenative coupling of *N*-alkylpyrroles and pyridine *N*-oxides gave the corresponding pyrrolylpyridine *N*-oxides. $Cu(OAc)_2 \cdot H_2O$ as a co-catalyst with air as the terminal oxidant led to preferential coupling in the β-position, whereas AgOAc as the stoichiometric oxidant resulted in preferential coupling in the α-position. *N*-(Benzyloxymethyl)pyrrole derivatives were deprotected by hydrogenolysis followed by basic hydrolysis.

Introduction

The direct oxidative coupling of two arenes, in which a new carbon–carbon bond is formed at the expense of two carbon–hydrogen bonds (cross-dehydrogenative coupling, CDC), is a particularly attractive synthetic approach to (hetero)biaryls, because it avoids the need for functional groups at the site of coupling.[1e] Hence, the starting materials need to be less functionalized than those used in other cross-coupling reactions and are, therefore, more readily commercially available or easily prepared. One obvious obstacle for an efficient direct C–H/C–H cross-coupling reaction is the presence of several C–H bonds of similar reactivity in the starting material, which could lead to different isomeric products. The other obvious interference is the undesired homocoupling of the starting material. Despite these inherent problems, numerous successful methods for direct cross-coupling reactions have been reported in the last years.[1]

Pyridine *N*-oxides have been used as stable, readily available starting materials in numerous C–H functionalization and C–C bond-forming reactions.[2] Although there is a vast number of examples for the direct arylation of indoles, pyrroles have been used much less often in direct arylations owing to their instability under oxidative conditions and to difficulties in controlling the regioselectivity.[3] There are only a few isolated examples of direct C–H/C–H cross-couplings of pyrrole derivatives with azine *N*-oxides. 2,5-Dimethyl-*N*-phenylpyrrole was coupled with pyridine *N*-oxide by using a palladium catalyst and Ag_2CO_3 as stoichiometric oxidant.[2k] *N*-Tosylpyrrole was β-arylated with pyridine *N*-oxide by using AgOAc as the oxidant.[3r] By using $Cu(OAc)_2$ as a stoichiometric oxidant, *N*-benzylpyrrole was β-arylated with quinoxaline *N*-oxide.[3q] Similarly, *N*-pyridylpyrrole was α-arylated with pyridine *N*-oxide, quinoline *N*-oxide, and quinoxaline *N*-oxide in a chelation-assisted C–H/C–H cross-coupling reaction.[3n] Herein, we report the oxidative cross-coupling of pyridine *N*-oxides and pyrroles with catalyst-controlled regioselectivity.[4]

Results and Discussion

Initially, we tested the reaction of unsubstituted pyridine *N*-oxide (**2a**) with different *N*-substituted pyrroles **1** under conditions previously reported by You et al. for the coupling of pyridine *N*-oxides with thiophenes and furans (Table 1, Entries 1–6).[2j] *N*-Methyl- and *N*-benzylpyrrole were coupled with pyridine *N*-oxide and gave the corresponding products in promising yields with preference for substitution at the β-position of the pyrrole ring (Table 1, Entries 1 and 6), whereas the regioselectivity was decreased for *N*-phenylpyrrole (Table 1, Entry 5). Although *N*-tosylpyrrole showed nearly complete selectivity for the β-coupled product, the yield was low (Table 1, Entry 2), possibly because the electron-withdrawing tosyl (Ts) group decreased the nucleophilicity of the pyrrole ring, which indicated an electrophilic mechanism for the activation of the pyrrole C–H bond. Upon testing an *N*-carbamoyl substituent as a directing group, the proportion of α-arylated pyrrole was increased; however, the yield decreased, and this approach was not pursued any further (Table 1, Entry 3). An *N*-*tert*-butoxycarbonyl (Boc) group was not stable under the reaction conditions, and only a small amount of the unprotected β-arylated product was isolated (Table 1, Entry 4). For further optimization, *N*-benzylpyrrole was chosen. Addition of phosphine ligands improved the regioselectivity, and 1,3-bis(diphenylphosphino)propane (dppp) and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (Dave-Phos) gave the best results (Table 1, Entry 8). Decreasing the loading of the $Cu(OAc)_2 \cdot H_2O$ oxidant to a substoichiometric amount with air as the terminal oxidant decreased the yield and regioselectivity (Table 1, Entry 9). However, the addition of acetic acid restored the regioselectivity and increased the yield,

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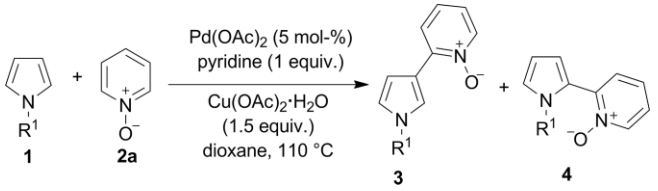
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600680.

Table 1. Optimization of the regioselective heteroarylation of pyrrole.[a]



Entry	R^1	Additive/conditions	Yield[b] [%]	**3/4**
1	Me	CuBr (10 mol-%)	49	80:20
2	Ts	CuBr (10 mol-%)	24	99:1
3	$CONMe_2$	CuBr (10 mol-%)	34	58:42
4	Boc	CuBr (10 mol-%)	13	99:1[c]
5	Ph	CuBr (10 mol-%)	43	67:33
6	Bn	CuBr (10 mol-%)	55	87:13
7	Bn	–	48	83:17
8	Bn	dppp (10 mol-%)	52	92:8
9	Bn	dppp (10 mol-%), $Cu(OAc)_2·H_2O$ (0.5 equiv.)	45	75:25
10	Bn	CuCl (10 mol-%), dppp (10 mol-%), $Cu(OAc)_2·H_2O$ (0.25 equiv.), HOAc (2 equiv.)	67	93:7
11	Bn	bpy (1 equiv.) instead of pyridine	43[d]	50:50
12	Bn	bpy (0.4 equiv.) instead of pyridine, AgOAc (2.3 equiv.) instead of $Cu(OAc)_2·H_2O$	42[d]	20:80

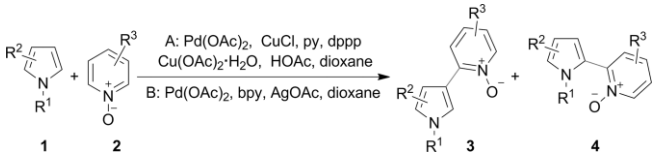
[a] Reaction conditions: **1** (0.25 mmol), **2a** (1 mmol), catalyst (5 mol-%), co-catalyst (10 mol-%), pyridine (0.25 mmol), ligand, oxidant in dioxane (1 mL) at 110 °C for 60 h. [b] Yield of isolated product. [c] Only deprotection products were obtained. [d] Yield was determined by NMR spectroscopy.

which eventually allowed the loading of $Cu(OAc)_2·H_2O$ to be decreased to 0.25 equiv. (Table 1, Entry 10). These conditions appeared to be fairly robust, as displacing the CuCl additive by tetrabutylammonium chloride or NaCl as the chloride source led to similar results, and replacing CuCl by a corresponding amount of $Cu(OAc)_2·H_2O$ only slightly decreased the yield. A subsequent control experiment even showed that the diphosphine could be left out without notable effect (see also Table 2, Entries 24–32). A preliminary screening of the oxidant had indicated that silver salts might lead to preferential C2-arylation.[5] However, even after considerable experimentation, *N*-benzylpyrrole (**1b**) could be α-arylated with pyridine *N*-oxide only in modest yield and regioselectivity by using a catalytic amount of $Pd(OAc)_2$ with 2,2′-bipyridine (bpy) as the ligand and a slight excess of AgOAc as the oxidant (Table 1, Entry 12). Attempts to lower the loading of the silver salt to a substoichiometric amount in combination with a stoichiometric terminal oxidant were unsuccessful.

The substrate scope was probed with a number of substituted pyridine *N*-oxides, which were coupled with *N*-benzylpyrrole (Table 2). With $Cu(OAc)_2·H_2O$ as the co-catalyst (conditions A), pyridine *N*-oxides with a C4 substituent typically gave yields >60 % and regioselectivities >10:1 in favor of β-arylation (Table 2, Entries 1–9). The yields tended to be higher for substrates with electron-withdrawing substituents than for electron-donating substituents (Table 2, Entry 1 vs. 3). This reactivity pattern resembles the trends observed for other palladium-catalyzed arylation reactions of pyridine *N*-oxides.[2f,2g,2h] 4-Cyanopyridine *N*-oxide is the exception (Table 2, Entry 9), with low yield and diminished regioselectivity, possibly because of the coordinating properties of the nitrile group. Pyridine *N*-oxides with substituents in other positions gave lower yields and regioselectivities. In comparison, with AgOAc as a stoichiometric oxidant (conditions B), most yields were in the range of 30–40 % and depended less on the substituent at the pyridine *N*-oxide, whereas the regioselectivities depended more on the substituent and rarely exceeded 1:2 to 1:4 in favor of α-arylation of the pyrrole. Remarkable exceptions were the high regioselectivities in the reactions with quinoline *N*-oxide, isoquinoline *N*-oxide, and pyrazine *N*-oxide (Table 2, Entries 14–16). With 3-bromopyridine *N*-oxide, no product was obtained, because the starting material decomposed under either set of reaction conditions. As expected, with 2,6-lutidine *N*-oxide no coupling product was observed, because both reactive positions of the *N*-oxide ring are blocked. We briefly examined the influence of substituents on the pyrrole ring. Under conditions A, 2-ethyl-*N*-benzylpyrrole led to higher yields (Table 2, Entries 17–20), whereas 2-methoxycarbonyl-*N*-benzylpyrrole led to slightly lower yields (Table 2, Entries 21 and 22), and the regioselectivity remained unaffected for both substrates. 3-Methoxycarbonyl-*N*-benzylpyrrole gave only the α-arylation product in 26 % yield (Table 2, Entry 23). This apparent reversal in regioselectivity likely results simply from the steric influence of the substituent. Under conditions B, the yields of 2-ethyl-*N*-benzylpyrrole remained variable between 20 and 40 %, but the regioselectivity increased considerably. For both sets of conditions, the substituent effect on the yields was consistent with mechanisms such as electrophilic aromatic substitution (S_EAr) or concerted carbometalation (Heck-type), for which the pyrrole acts as the nucleophilic reaction partner.

When we replaced the *N*-benzyl substituent of the pyrrole by an *N*-benzyloxymethyl (BOM; Table 2, Entries 24–30), *N*-(4-methoxy)benzyl (PMB; Table 2, Entry 31) or *N*-3,4-dimethoxybenzyl group (DMB; Table 2, Entry 32), results similar to those previously obtained were found. However, *N*-(2-pyridyl)pyrrole and *N*-(2-pyrimidyl)pyrrole, for which the substituent might act as a directing group, did not give any coupling product. The pyridine *N*-oxide of the coupling products was efficiently deoxygenated to the corresponding pyridine by treatment with PCl_3 (see the Supporting Information, Table S3).[6] Catalytic de-

Table 2. Substrate scope of the oxidative coupling of pyrroles and pyridine *N*-oxides.[a]



1 2 3 4

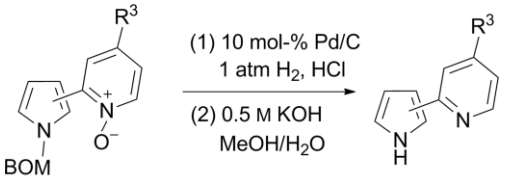
Entry	R^1	R^2	R^3	Yield[b] [%]	**3/4**
1	Bn	H	4-CO_2Et	64 (33)	90:10 (20:80)
2	Bn	H	4-Ph	68 (34)	94:6 (17:83)
3	Bn	H	4-OMe	42 (36)	89:11 (56:44)
4	Bn	H	4-Me	59 (42)	95:5 (43:57)
5	Bn	H	4-*t*Bu	61 (36)	95:5 (25:75)
6	Bn	H	4-COMe	69 (33)	92:8 (20:80)
7	Bn	H	4-OPh	68 (33)	96:4 (20:80)
8	Bn	H	4-CF_3	60 (34)	90:10 (11:89)
9	Bn	H	4-CN	24 (18)	75:25 (20:80)
10	Bn	H	3-CO_2Me	45 (32)	52:48 (25:75)
11	Bn	H	3-Me	45 (21)	75:25 (33:67)
12	Bn	H	2-Me	38 (11)	89:11 (20:80)
13	Bn	H	2-(2-pyridyl)	0 (16)	– (33:67)
14	Bn	H	–[c]	48 (29)	50:50 (10:90)
15	Bn	H	–[d]	50 (28)	75:25 (7:93)
16	Bn	H	–[e]	<5 (25)	– (< 1:99)
17	Bn	2-Et	H	60 (34)	84:16 (20:80)
18	Bn	2-Et	4-CO_2Et	80 (28)	94:6 (< 1:99)
19	Bn	2-Et	4-COMe	74 (22)	91:9 (< 1:99)
20	Bn	2-Et	4-Ph	79 (42)	> 99:1 (9:91)
21	Bn	2-CO_2Me	H	45 (11)	93:7 (33:67)
22	Bn	2-CO_2Me	4-*t*Bu	57 (<5)	>99:1 (–)
23	Bn	3-CO_2Me	H	26 (14)	< 1:99 (< 1:99)
24	BOM	H	H	57[f] (37)	88:12[f] (25:75)
25	BOM	H	4-Ph	51[f] (43)	> 99:1[f] (33:67)
26	BOM	H	4-OMe	67[f] (45)	91:9[f] (55:45)
27	BOM	H	4-Me	60[f] (35)	92:8[f] (57:43)
28	BOM	H	4-*t*Bu	52[f] (37)	> 99:1[f] (33:67)
29	BOM	H	4-CF_3	51[f] (41)	> 99:1[f] (25:75)
30	BOM	H	4-COPh	51[f] (43)	> 99:1[f] (33:67)
31	PMB	H	H	60[f] (35)	93:7[f] (33:67)
32	DMB[g]	H	H	53[f] (33)	90:10[f] (38:62)

[a] Reaction conditions A: **1** (0.25 mmol), **2** (1 mmol), $Pd(OAc)_2$ (5 mol-%), CuCl (10 mol-%), dppp (5 mol-%), $Cu(OAc)_2{\cdot}H_2O$ (25 mol-%), pyridine (1 equiv.), HOAc (2 equiv.) in dioxane(1 mL) at 110 °C for 60 h. Reaction conditions B: **1** (0.25 mmol), **2** (1 mmol), $Pd(OAc)_2$ (5 mol-%), bpy (40 mol-%), AgOAc (2.3 equiv.) in dioxane (1 mL) at 110 °C for 60 h. [b] Yield of isolated product obtained under reaction conditions A. Value in parentheses refers to reaction conditions B. [c] Quinoline *N*-oxide. [d] Isoquinoline *N*-oxide. [e] Quinoxaline *N*-oxide. [f] No dppp was added, CuCl (15 mol-%) used. [g] 3,4-Dimethoxybenzyl.

oxygenation of **4ba** with hydrogen (1 atm, Pd/C, MeOH, r.t.) resulted in only 62 % yield and the formation of unidentified decomposition products. Debenzylation of the *N*-benzylpyrroles proved to be unsuccessful in our hands. Hydrogenation with a catalytic amount of Pd/C resulted only in deoxygenation of the pyridine *N*-oxide, and increasing the pressure resulted in decomposition. Brønsted acids (e.g., H_2SO_4 and HCl) and Lewis acids (e.g., $AlCl_3$) did not convert the starting material. The PMB group could be removed by treatment with a catalytic amount of H_2SO_4 in trifluoroacetic acid, albeit in low yield. The BOM group, however, was successfully removed by catalytic debenzylation with H_2 and Pd/C followed by basic cleavage of the surprisingly stable *N*-hydroxymethyl intermediate (Table 3).

We briefly investigated a possible mechanism for the reaction by H/D exchange experiments and kinetic isotope effect (KIE) measurements (see the Supporting Information). Under conditions A, deuterium was incorporated into the 2- and 3-positions of *N*-benzylpyrrole (**1b**) in a 1:1 ratio and to the same extent as uncatalyzed deuteration occurred (10–15 %). This observation excludes reversible C–H activation of the pyrrole. Under conditions B, however, deuterium was incorporated to a larger extent in a 3:1 ratio favoring the 2-position of the pyrrole ring (65–75 %), which suggests reversible S_EAr-like metalation. Deuterium incorporation into pyridine *N*-oxide (**2a**) occurred only to a small extent and exclusively at the 2-position under both sets of reaction conditions (7 %). For pyridine *N*-oxide, the observed KIEs of $k_H/k_D > 2.0$ are consistent with rate-limiting C–H activation of pyridine *N*-oxide, for example, by a concerted metalation-deprotonation mechanism,[7] under either set of reaction conditions. For the pyrrole, small KIEs of $k_H/k_D \approx 0.9–1.5$ were observed, consistent with electrophilic functionalization of the pyrrole, for example, by S_EAr-like metalation or by carbome-

Table 3. Deprotection of pyrroles.[a]



3 or 4 — 7 or 8

Entry	R^3	2-Arylpyrrole	Yield[b] [%]	3-Arylpyrrole	Yield[b] [%]
1	H	**4ja**	61	**3ja**	74
2	Me	**4je**	88	**3je**	82
3	*t*Bu	**4jf**	71	**3jf**	60
4	OMe	**4jd**	90	**3jd**	84

[a] Reaction conditions: (1) **3** or **4** (0.05 mmol), Pd/C (10 mol-%), H_2 (1 atm), 0.05 M HCl in MeOH/H_2O (2.5 mL). (2) 0.5 M HCl in MeOH/H_2O (2.5 mL). [b] Yield of isolated product.

talation (Heck-type mechanism).[8] Possible explanations for the reagent-dependent regioselectivity might be that the co-oxidant leads to a complete switch in mechanism or that the α- and β-arylation products are formed by different mechanisms. Thus, $Cu(OAc)_2$ might form mixed Cu–Pd clusters,[9] which might lead to carbometalation of the pyrrole. In this case, one would expect preferential addition of the Pd catalyst to the more electron-rich C2 position and arylation of the C3 position. With AgOAc as the oxidant, more electrophilic, possibly cationic Pd intermediates might be formed, which would cause electrophilic palladation of the electron-rich C2 position. Subsequent reductive elimination from the formed pyrrolyl–palladium complex would lead to the observed α-arylation product. The fact that the regioselectivities of pyrrole arylation depend on the pyridine *N*-oxide coupling partner might be an indication that activation of the pyridine *N*-oxide occurs first and that the resulting aryl–palladium complex is involved in the activation of the pyrrole ring. However, dimetallic mechanisms involving separate catalytic cycles for activation of the substrates and a transmetalation step would also be consistent with the experimental observations.[10]

Conclusion

β-Selective arylation of protected pyrroles was achieved by use of $Cu(OAc)_2{\cdot}H_2O$ as an oxidation co-catalyst in a preparatively useful range and comparable to that of other oxidative cross-couplings (also known as CDC reactions) without recourse to sterically demanding *N*-protecting groups. However, α-selective pyrrole arylation without the use of coordinating directing groups cannot be considered a solved problem. While the results with AgOAc as terminal oxidant seem promising, the reaction conditions are hardly practical because of the modest yields and regioselectivities, high catalyst loading, and stoichiometric metal oxidant. Although previously noted,[3b,3c] it is worth reiterating that in this and similar oxidative cross-coupling reactions, not only do the Cu^{II} or Ag^{I} salts serve as oxidants to regenerate the Pd^{II} catalyst, but they also serve distinct and yet to be understood roles in the C–H functionalization process.

Experimental Section

General Procedure for the Oxidative Coupling of Substituted Pyridine *N*-Oxides with Pyrrole Derivatives

Conditions A: A Teflon-capped vial was charged with a stirrer bar, pyridine *N*-oxide (1 mmol, 4 equiv.), $Pd(OAc)_2$ (5 mol-%), CuCl (10 mol-%), dppp (5 mol-%), $Cu(OAc)_2{\cdot}H_2O$ (25 mol-%), pyridine (1 equiv.), AcOH (2 equiv.), and dioxane (0.25 M in substrate), and the mixture was stirred for 10 min. Then, the substituted pyrrole (0.25 mmol, 1.0 equiv.) was added, and the resulting mixture was heated to 110 °C for 60 h and then cooled to room temperature. The mixture was directly purified by flash column chromatography to afford the analytically pure product.

Conditions B: A Teflon-capped vial was charged with a stirrer bar, pyridine *N*-oxide (1 mmol, 4 equiv.), $Pd(OAc)_2$ (5 mol-%), bipyridine (40 mol-%), AgOAc (2.3 equiv.), and dioxane (0.25 M in substrate), and the mixture was stirred for 10 min. Then, the substituted pyrrole (0.25 mmol, 1.0 equiv.) was added, and the resulting mixture was heated to 110 °C for 60 h and then cooled to room temperature. The mixture was directly purified by flash column chromatography to afford the analytically pure product.

Acknowledgments

Funding by the Deutsche Forschungsgemeinschsft (DFG) (grant Tz 68/3-1 to C. C. T.) is gratefully acknowledged. S. L. thanks the China Scholarship Council (CSC) for support by a scholarship.

Keywords: Arylation · Biaryls · Cross-coupling · Palladium · Regioselectivity

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Received: June 3, 2016
Published Online: July 4, 2016

