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Cross-Coupling

Pd-Catalyzed Decarboxylative Cross-Coupling of 2-Carboxyazine *N*-Oxides with Various (Hetero)aryl Halides

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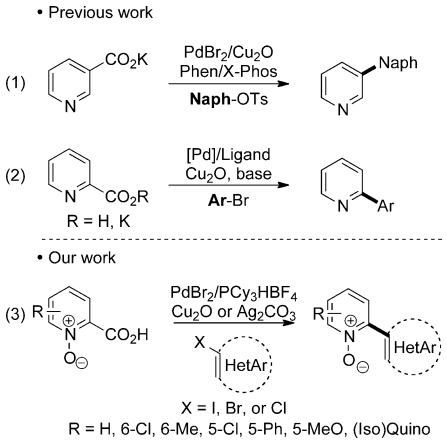
Abstract: Decarboxylative cross-coupling reactions of substituted 2-carboxyazine *N*-oxides, with a variety of (hetero)aryl halides, by bimetallic Pd^0/Cu^I and Pd^0/Ag^I catalysis are reported. Two possible pathways, a conventional bimetallic-catalyzed decarboxylative arylation, as well as a protodecarboxylative/direct C–H arylation sequence have been considered. These methods provide the first general decarboxylative arylation methodology for the 2-carboxyazine series.

Transition-metal-catalyzed cross-coupling reactions represent a highly attractive method in synthetic chemistry for C–C bond formation.[1] Nevertheless, these "traditional" cross-coupling reactions possess several disadvantages, such as the use of stoichiometric organometallic reagents, which are often air and moisture sensitive. In this context, carboxylic acids represent an alternative for the selective in situ generation of organometallic species by the transition-metal-mediated extrusion of CO_2.[2] These masked organometallic building blocks are generally inexpensive, stable, easy to handle, easy to store, readily available, and more environmentally friendly. Since the first example of transition-metal-mediated decarboxylative biaryl coupling reported by Nilsson,[3] significant progress has been made towards the Pd-catalyzed arylation of aromatic,[2g,h] and electron-rich heteroaromatic, carboxylic acids.

To date, the use of π-deficient heteroaryl carboxylic acids as coupling partners remains a substantial challenge owing to the difficulty associated with accessing metalated azinyl intermediates.[1b] In 2008, the Gooßen group reported a first and unique example of the decarboxylative cross-coupling of nicotinate with naphthyltosylate (Scheme 1, [Eq. (1)]).[9] More recently, the Wu and Stoltz research groups achieved the bimetallic Pd^0/Cu^I-catalyzed decarboxylative coupling of unsubstituted 2-azynylcarboxylic acids by using only aryl bromides as coupling partners (Scheme 1, [Eq. (2)]).[10]



Scheme 1. Decarboxylative cross-coupling reactions of azine derivatives.

Recent calculations and studies of this dual catalysis (Pd/Cu or Pd/Ag) revealed that the decarboxylative metalation likely proceeds by means of an *ipso*-interaction of the metal (Cu^I or Ag^I) on the carboxylate function, and could be facilitated by the electron-withdrawing effect of a heteroatom at the *ortho*-position.[11,12] Thus, we supposed that the N-oxidation of azinylcarboxylic acids may dramatically favor the decarboxylative metalation by enhancing the HOMO populations, along with the electron density, at the C2 position. Moreover, N-oxidation of azines is one of the most employed activation methods to introduce various substituents at the C2 position.[13] Notably, azine *N*-oxides are highly effective in Pd-catalyzed carbonate-assisted direct C–H arylation with halides.[14]

Herein, we report the first decarboxylative cross-coupling reactions of substituted carboxyazine *N*-oxides with a variety of (hetero)aryl halides as electrophiles by bimetallic Pd^0/Cu^I or Pd^0/Ag^I catalysis, offering a straightforward synthetic route to 2-(hetero)arylazine *N*-oxides, and circumventing the preformation of unstable 2-azinyl organometallic species (Scheme 1, [Eq. (3)]). Two mechanisms have been considered; 1) the conventional bimetallic-catalyzed decarboxylative cross-coupling reaction (Figure 1, cycles A and C)[2,15,16] and 2) the direct C–H arylation of the protodemetalated N-oxide substrate (Figure 1, cycles B and C).[17–21]

Quinaldic acid *N*-oxide (**1a**) was selected as a model substrate and *p*-tolylhalides **2a**,**b** as coupling partners. A set of experiments was carried out by using standard bimetallic $PdBr_2$ (10 mol%)/Ag_2CO_3 (one equivalent) or Cu_2O (one equivalent)

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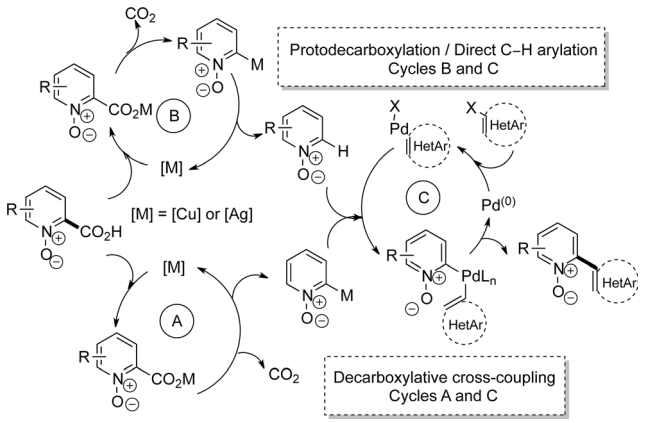
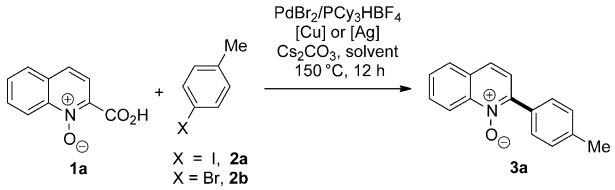


Figure 1. Possible mechanisms for the decarboxylative cross-coupling of azine *N*-oxides with aryl halides.

Table 1. Pd-catalyzed decarboxylative cross-coupling of quinaldic acid *N*-oxide **1a** under various reaction conditions.[a]



Entry	Additive [(equiv)]	*p*-Tol-X	Solvent	Yield [%][b]
1	Ag_2CO_3 (1.0)	I	DMF	56
2	Cu_2O (1.0)	Br	DMF	40
3	Ag_2CO_3 (1.0)	I	1,4-dioxane	91, 79[d]
4	Ag_2CO_3 (1.0)	Br	1,4-dioxane	78
5	Cu_2O (1.0)	I	1,4-dioxane	40
6	Cu_2O (1.0)	Br	1,4-dioxane	85, 50[d]
7	Ag_2CO_3 (1.0)	I	1,4-dioxane	78[c]
8	Cu_2O (1.0)	Br	1,4-dioxane	83[c]
9	Cu_2O (0.5)	Br	1,4-dioxane	85[c]
10	Cu_2O (0.2)	Br	1,4-dioxane	80[c]

[a] $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Cs_2CO_3 (3 equiv), **1a** (2 equiv), **2a**–**b** (0.3 mmol), additive, solvent (1.5 mL), 150 °C. [b] Yield based on isolated product after flash chromatography. [c] 1.5 equiv of **1a**. [d] Scale up, 1.5 mmol of halide under optimized conditions.

catalytic systems, in DMF at 150 °C, depending on the nature of the halide.[2] The formation of desired product **3a** was observed in 40–56% yield under both co-catalysis conditions by using PCy_3HBF_4 (Cy = cyclohexyl) as a ligand and Cs_2CO_3 as a base (Table 1, entries 1 and 2).

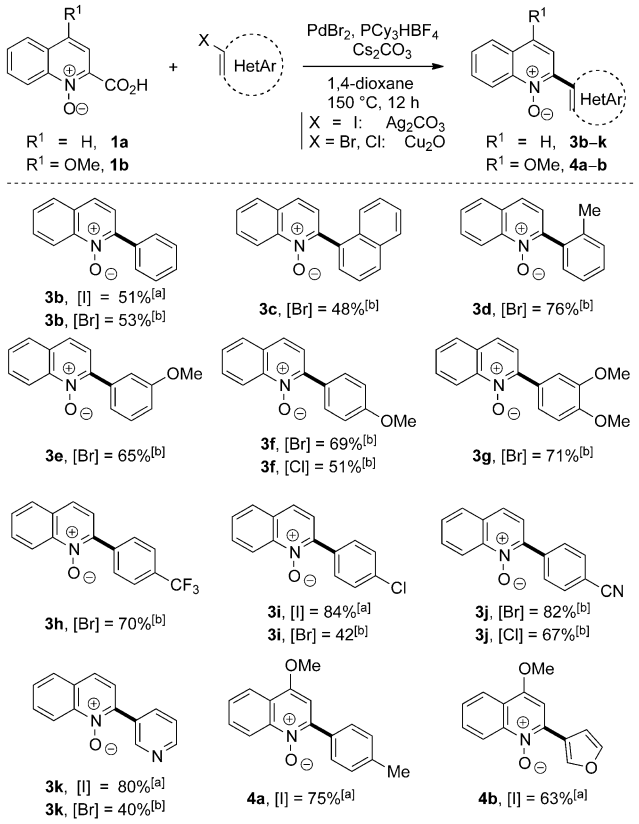
At this stage, the major challenge to improve the yield was to circumvent the competitive protodecarboxylation side reaction. In accordance with the observations of Glorius et al.,[22] we found that the use of 1,4-dioxane as a solvent dramatically improved the yields under both silver and copper co-catalysis (Table 1, entries 1–3 and 6). After screening various parameters (e.g. ligands, palladium sources, and bases),[23] the best results were obtained by using $PdBr_2$ (10 mol%) in the presence of Cs_2CO_3 with PCy_3HBF_4 (10 mol%) (Table 1, entries 3–6). We were pleased to find that these decarboxylative coupling reactions are applicable under both copper and silver co-catalysis, regardless of the nature of the halide (Table 1, entries 3–6). However, aryl iodides are better coupling partners under the Ag-mediated reaction conditions, whereas the Cu-catalyzed transformation works well with aryl bromides (Table 1, entries 3 and 6). We then observed that two equivalents of acid **1a** are required to achieve an efficient Pd^0/Ag^I-catalyzed decarboxylative reaction (Table 1, entries 3 and 7). On the other hand, lowering the amount of Cu_2O from stoichiometric to catalytic (20 mol%) amounts, along with decreasing the amount of acid **1a** from 2 to 1.5 equivalents, did not affect the efficiency of the Pd^0/Cu^I-catalyzed decarboxylative process (Table 1, entries 8–10). Interestingly, the optimized protocols were also easily scaled up from 0.3 to 1.5 mmol without a large decrease in yield (Table 1, entries 3 and 6).

To determine the catalytic cycle that operates between the conventional decarboxylative arylation and the protodecarboxylation/C–H arylation (Figure 1, cycles A and C or B and C), direct C–H arylations of quinoline *N*-oxide were performed under both copper- and silver-mediated decarboxylative arylation procedures.[24] The expected product, **3a**, was obtained in a very poor 12% yield with *p*-tolylbromide as a coupling partner under the copper-mediated procedure, whereas with silver as co-catalyst, C2 arylated **3a** was synthetized in 17 and 93% yields with *p*-tolylbromide and -iodide, respectively. With these results, we can suggest that both decarboxylative coupling methods proceed mainly through the conventional decarboxylative cross-coupling mechanism pathway (Figure 1, cycles A and C).

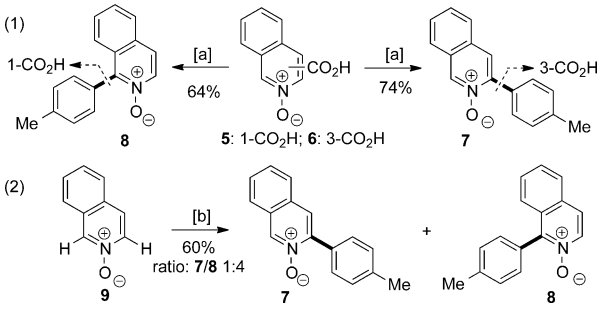
With the optimized conditions in hand, the scope of the decarboxylative coupling was undertaken by using quinaldic acid *N*-oxides **1a** and **1b** with a broad range of aryl halides, bearing electron-donating or -withdrawing groups (Scheme 2). We were pleased to observe the formation of the desired C2-arylated products, **3b**–**k** and **4a**,**b**, in reasonable to good yields, with (hetero)aryl iodides under the silver-mediated process, as well as with (hetero)aryl bromides and chlorides under copper co-catalysis (Scheme 2). Remarkably, the electronic and steric hindrance effects of both coupling partners have no influence on the success of the decarboxylation reaction.

To further examine the versatility of this methodology, the decarboxylative arylation was attempted with the isoquinolinic acid *N*-oxides **5** and **6** (Scheme 3). Unfortunately, the desired product could not be detected under the above optimized conditions owing to a lack of solubility of the acid in 1,4-dioxane. Nevertheless, switching the solvent to DMF afforded the expected arylated isoquinolinic *N*-oxides **7** and **8** in good yields under the silver-mediated process (Scheme 3, [Eq. (1)]). Remarkably, the transformations were regiospecific at the carboxy-position site. The exclusive formation of C3-arylated isoquinoline *N*-oxide **7**, from the 3-carboxyisoquinoline acid *N*-oxide **6**, proves that the silver-mediated decarboxylative cross-coupling of isoquinolinic acid *N*-oxides **5** and **6** proceeds only through the conventional mechanism (Figure 1, cycles A and C).

Moreover, the unselective C1/C3 arylation of isoquinoline *N*-oxide **9** by direct C–H arylation with *p*-tolyliodide **2a** under



Scheme 2. Scope of the decarboxylative cross-coupling reaction with various (hetero)aryl halides and quinaldic acid *N*-oxides: [a] $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Ag_2CO_3 (1 equiv), Cs_2CO_3 (3 equiv), **1a–b** (2 equiv), HetAr–I or HetAr–Br (1 equiv), 1,4-dioxane (0.2 M), 150 °C, 12 h. [b] $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Cu_2O (20 mol%), Cs_2CO_3 (3 equiv), **1a–b** (1.5 equiv), HetAr–Br or HetAr–Cl (1 equiv), 1,4-dioxane (0.2 M), 150 °C, 12 h. [c] Yield based on isolated product after flash chromatography.



Scheme 3. Decarboxylative cross-coupling reactions with isoquinoline–carboxylic acid *N*-oxides **5**–**6**: [a] $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Ag_2CO_3 (1 equiv), K_2CO_3 (3 equiv), **5**–**6** (2 equiv), **2a** (1 equiv), DMF (0.2 M), 150 °C, 12 h. [b] $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Ag_2CO_3 (1 equiv), K_2CO_3 (3 equiv), **9** (2 equiv), **2a** (1 equiv), DMF (0.2 M), 150 °C, 12 h.

the silver-mediated conditions confirm our mechanistic hypothesis (Scheme 3, [Eq. (2)]). By contrast, the protodecarboxylation became the main side reaction under the copper-mediated process and surprisingly, the subsequent direct C–H arylation of the in-situ-generated isoquinoline *N*-oxide was completely inefficient.

To better understand the ability of the azinyl–copper intermediate to undergo a competitive side protonation, instead of being involved in the transmetalation step (Figure 1, cycles A and C), DFT calculations[25] were carried out, following the Liu's model,[26–27] to highlight the decarboxylative metalation pathway under Cu^I and Ag^I catalysis. For a better estimation of the energy gain brought by the N-oxide function, picolinic acid and its N-oxide were examined as substrate models (Figure 2).

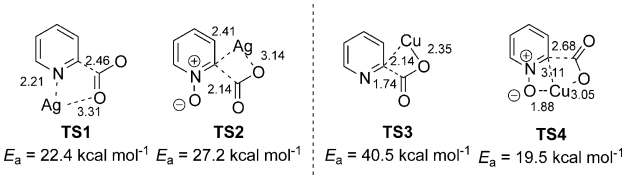
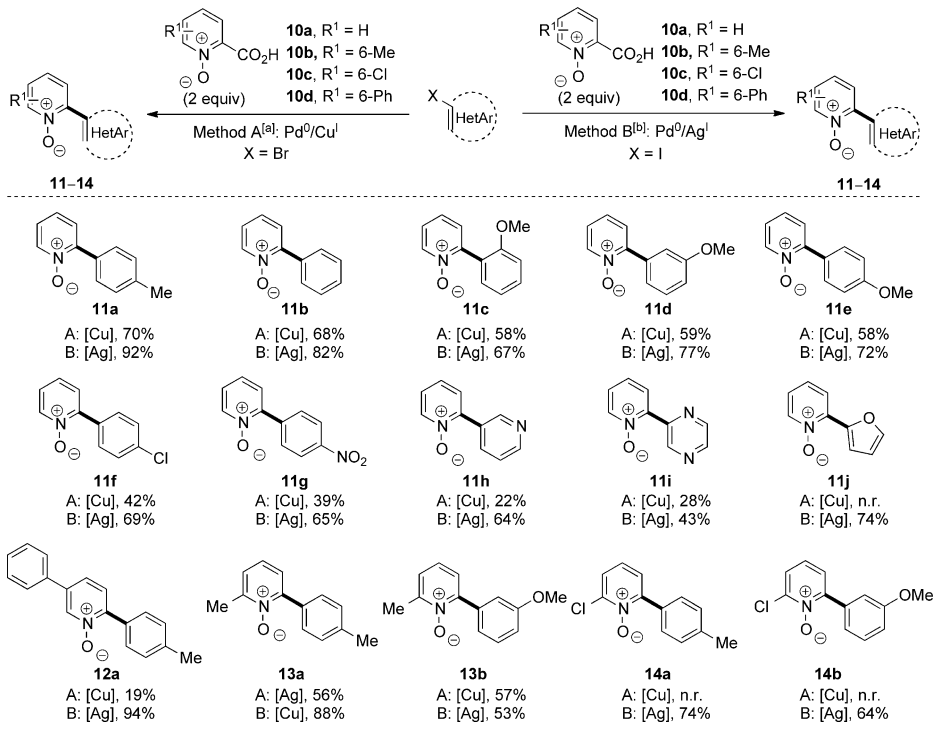


Figure 2. Transition states investigated by DFT calculations for the decarboxylative–metalation step.[25]

Contrary to our initial expectations, we found that the CO_2Ag–pyridine complexation (**TS1**) facilitates the extrusion of CO_2 by better cooperative assistance than the standard concerted *ipso*-decarboxylative metalation on pyridine *N*-oxide (**TS2**), thus decreasing the activation energy from 27.2 to 22.4 kcal mol^{-1} (Figure 2). Surprisingly, this specific pyridine–metal interaction was not found under the copper-assisted pathway, explaining that the *ipso*-decarboxylative metalation proceeds with a higher (40.5 kcal mol^{-1}) activation energy (Figure 2, **TS3**). Unexpectedly, an additional interaction between the N-oxide group and copper species is observed by DFT calculations. This interaction spectacularly diminishes the activation energy to 19.5 kcal mol^{-1} (Figure 2, **TS4**). Nevertheless, in spite of the better assistance of the copper versus silver catalysis in the decarboxylative metalation step (**TS3** versus **TS2**), we observed that silver catalysis may proceed only through the conventional decarboxylative coupling in the picolinic acid *N*-oxide series. This paradox suggests that the two catalytic cycles operating in conventional decarboxylative coupling (Figure 1, cycle A and C) might occur simultaneously under silver catalysis, but not under copper catalysis. As a consequence, the accumulation of the highly sensitive azinyl–copper intermediate favors the side protonation and the protodecarboxylation/direct C–H arylation pathway (Figure 1, cycles B and C). Therefore, silver catalysis was found to be much more adequate in achieving the conventional decarboxylative coupling reaction because the azinyl–silver intermediate is generated more slowly, and is less sensitive to protonation,[18b] than the azinyl–copper intermediate. The azinyl–silver intermediate is highly reactive in the subsequent transmetalation step with the iodo-arylpalladium complexes because of the high stability of the silver iodide.

At this stage, we sought to investigate the decarboxylative cross-coupling with various picolinic acid *N*-oxides (**10a–d**, Scheme 4). As previously observed with the isoquinolinic acid *N*-oxides series, the effectiveness of the copper-mediated decarboxylative arylation was significantly improved, from 22 to

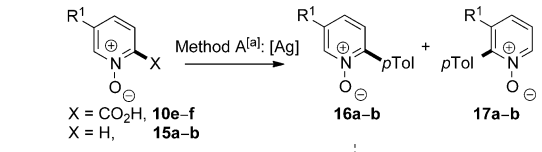


Scheme 4. Decarboxylative cross-coupling reactions with various picolinic acids: [a] HetAr–Br (1 equiv), $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Cu_2O (50 mol%), Phen (50 mol%)K_2CO_3 (3 equiv), **10a–d** (2 equiv), DMF (0.2 M), 150 °C, 12 h. [b] HetAr–I (1 equiv), $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Ag_2CO_3 (1 equiv), Cs_2CO_3 (3 equiv), **10a–d** (2 equiv), 1,4-dioxane (0.2 M), 150 °C, 12 h. [c] Yield based on isolated product after flash chromatography (n.r. = no reaction).

70% yield, with picoline acid *N*-oxide **10a** and *p*-tolylbromide **2b**, by switching the base and solvent from Cs_2CO_3/1,4-dioxane to K_2CO_3/DMF, and by adding phenanthroline. With these new conditions in hand, the majority of C2-arylated pyridines, **11b–g**, were obtained in reasonable to good yields (Scheme 4). Concerning the mechanistic pathway, the use of more convenient K_2CO_3-based experimental conditions to achieve the Fagnou direct C–H arylation of pyridine *N*-oxide,[14] combined with our previous observation that the azinyl–Cu^I intermediate is sensitive to protonation in DMF, showed that the copper co-catalyzed process proceeds mainly through a protodecarboxylative/direct C–H arylation sequence (Figure 1, cycle B and C). This suggestion was also consistent with the fact that the decarboxylative heteroarylation proceeds in low yield, whereas the reaction failed with 2-bromofuran.[28]

From our previous results with quinaldic and isoquinolinic acid *N*-oxides, we observed that our optimized Cs_2CO_3-based bimetallic Pd^0/Ag^I catalysis methodology appeared to be more efficient and general than the K_2CO_3-based Pd^0/Cu^I method for the decarboxylative (hetero)arylation. This observation was confirmed with a set of experiments with picolinic acid *N*-oxide (**10a**) and *p*-tolyliodide (**2a**) under the optimized conditions; the silver-mediated process gave an excellent 92% yield of 2-*p*-tolylpyridine *N*-oxide (**11a**, Scheme 4). Good results were then obtained with a variety of electronically different (hetero)aryl iodides, providing the corresponding C2-arylated pyridines, **11b–g**, in significantly better yields than those observed through the copper-mediated process (Scheme 4). Remarkably, the procedure is reasonably efficient when applied to the decarboxylative heteroarylation of picolinic acid *N*-oxides **10a**, affording 2-(hetero)aryl pyridines, **11h–j**, in moderate yields (Scheme 4).

Finally, the scope of picolinic acid *N*-oxide was also successfully extended to two series of unsymmetrical picolinic acids substituted at the C6 (**10b–c**, Scheme 4) and C5 (**10d–f**) positions (Scheme 4 and Scheme 5). To the best of our knowledge, these reactions represent the first examples of decarboxylative arylation of substituted azinic acids. The better efficiency and versatility of the silver-mediated process compared to the copper-mediated process suggested that the reaction proceeds through the conventional decarboxylative (hetero)arylation mechanism (Figure 1, cycles A and C). This hypothesis was then confirmed with the high regioselectivity observed at the carboxy-function site during the decarboxylative cross-coupling of the unsymmetrical models **10e–f**. By contrast, the direct C–H arylation of the 3-methoxy- and 3-chloropyridine *N*-oxides **15a–b**,[29] reinvestigated under our experimental conditions, led exclusively to the C2-arylated pyridine isomers **17a–b** in reasonable yields,[30] instead of the C6 isomers (**16a–b**), during the decarboxylative process (Scheme 5).



	· Our work (X = CO_2H)		· Direct C–H Arylation (X = H)	
	Yield (%)[b]	Ratio **16** : **17**	Ratio **16** : **17**	Yield (%)[b]
R^1 = OMe	A: 51%, **16a**	99 : trace	trace : 99	A: 81%, **17a**
R^1 = Cl	A: 43%, **16b**	99 : trace	trace : 99	A: 79%, **17b**

Scheme 5. Decarboxylative arylation of unsymmetrical substituted azinic acids. [a] $PdBr_2$ (10 mol%), PCy_3HBF_4 (10 mol%), Ag_2CO_3 (1 equiv), Cs_2CO_3 (3 equiv), **2a** (1 equiv), **10e–f** (2 equiv), 1,4-dioxane (0.2 M), 150 °C, 12 h. [b] Yield based on isolated product after flash chromatography.

In conclusion, we have disclosed the first Pd-catalyzed decarboxylative (hetero)arylations of 2-carboxyazine *N*-oxides with copper and silver species as co-catalysts. This innovative methodology tolerates a broad range of azine *N*-oxides and (hetero)aryl halides substituted by electronically different groups.

Moreover, this method provides novel, general, and selective access to important 2-(hetero)arylazine compounds, which are found in many natural products, drug molecules, and materials. During our study, two possible pathways, the conventional bimetallic-catalyzed decarboxylative arylation as well as the protodecarboxylative/direct C–H arylation sequence have been considered. Finally, we can conclude that the decarboxylative transformation of azine *N*-oxides is an additional and complementary method to C–H functionalization, in which the regioselectivity is easily controlled by the position of the carboxylic acid functional group.

Acknowledgements

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Keywords: 2-carboxyazine *N*-oxides · catalysis · cross-coupling · palladium

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[25] All DFT calculations were performed with the Gaussian 09 package with the B3LYP functional. The basis set was TZVP for C, H, N, P, O and DGDZVP for Pd, Cu and Ag. Geometries were optimized in vacuo and subsequent frequency calculations were carried out to check the stationary points on the potential energy surface and to perform thermodynamic energy corrections (see the Supporting Information for more details).
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[29] For the C2/C6 regioselectivity concerning the direct arylation on the unsymmetrical pyridine *N*-oxides, see ref. [14c] and [14g].
[30] This high selectivity for the direct C–H arylation reactions at the C2 position is unprecedented and the Fagnou procedure was found to be less selective with this model. This point is under investigation.

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