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Direct Site-Selective Arylation of Enamides via a Decarboxylative Cross-Coupling Reaction

Nicolas Gigant, Laëtitia Chausset-Boissarie, and Isabelle Gillaizeau*

Institut de Chimie Organique et Analytique, UMR 7311 CNRS, rue de Chartres, Université d'Orléans, F-45067 Orléans Cedex 2, France

isabelle.gillaizeau@univ-orleans.fr

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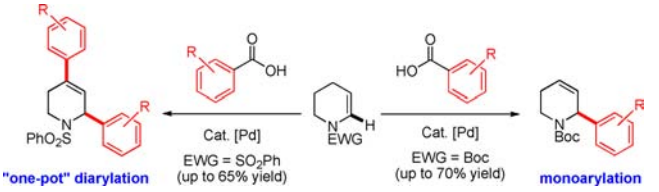
ABSTRACT



An efficient Pd-catalyzed decarboxylative cross-coupling reaction of simple enamides was achieved. Depending on the choice of the nitrogen-protecting group, a site-selective synthesis of mono- or diarylated framework(s) was performed under mild conditions. This unprecedented reactivity could be applied to the synthesis of a range of 2- or 2,4-diarylated nitrogen-containing bioactive derivatives.

The screening of libraries of small organic molecules to discover new potential drugs or to detect an interaction with proteins for instance has become one of the most important challenges for the organic chemist.[1] "Diversity-Oriented Synthesis" (DOS) first introduced by Schreiber and co-workers in 2000[2] is perhaps the most promising strategy to improve the number of compounds in order to find a lead for medicinal chemistry programs,[3] as it enables considerable molecular diversity to be generated in only a few steps starting from simple materials. At the heart of DOS are the synthetic methods required for the efficient generation of complex molecular scaffolds. This diversity can be rapidly obtained by carbon−carbon bond-forming reactions. Indeed, catalyzed cross-coupling is currently one of the most powerful methods in the construction of carbon frameworks, and during the past decade in particular, benzoic acids have emerged as viable coupling partners toward oxidative decarboxylative couplings.[4] These species can be considered as the synthetic equivalents of aryl halides and have several advantages, principally their availability, low cost, and stability. In 2002, Myers et al. reported the first palladium-catalyzed coupling of arene carboxylic acids with olefinic substrates in a decarboxylative Heck-type reaction.[5] This concept was further expanded by Goossen[6] and others,[7] and more especially for the arylation of a range of substrates. Despite significant advances in this chemistry, some limitations emerge when the process combines both decarboxylative cross-coupling and carbon−hydrogen bond activation.[4a]

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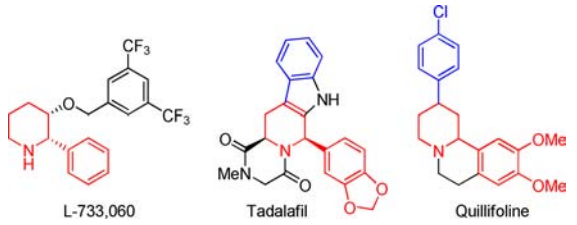
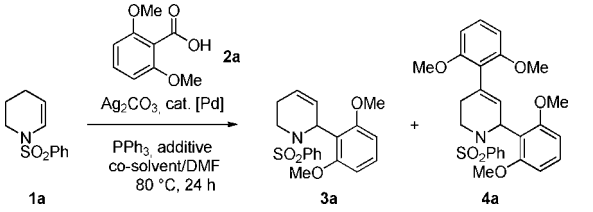


Figure 1. Representative examples of 2-aryl- or 2,4-diaryl-piperidines.

Enamides are stable enamine surrogates and are important key intermediates for the synthesis of small but complex nitrogen containing compounds; recently, they have been involved in several metal catalyzed reactions.[8] Among these reactions, direct C3 dehydrogenative functionalization of nonaromatic enamides was recently described with alkenes[9] or arenes[10] and direct C2 functionalization was extensively reported by Xiao's team starting from aryl chlorides[11] and Park with pinacol arylboronates.[12] Recently, we have been engaged in the development of a regioselective oxidative C−H bond functionalization program starting from nonaromatic enamides.[9,13] In pursuit of this goal, we wish herein to report our results in this area involving the decarboxylative cross-coupling reaction of aryl carboxylic acids, for the synthesis of arylated nitrogen containing frameworks. We expect this new method to be broadly applicable to the synthesis of natural products and medicinal agents (Figure 1).[14]

Guided by recent advances in this area, our representative attempts are summarized in Table 1. We first selected the simple cyclic enamide **1a** and 2,6-dimethoxybenzoic acid as a coupling partner, in the presence of Ag_2CO_3, a catalytic amount of $Pd(OAc)_2$, PPh_3 as a phosphine ligand, and DMSO as a cosolvent in DMF at 80 °C for 24 h (Table 1, entry 1). By applying these conditions at the outset of our study, only a trace amount of the attempted product was identified. Surprisingly, adding propionic acid to enhance the electrophilic ability of the palladium intermediate led to a mixture of the expected monoarylated product **3a** in combination with the diarylated product **4a** (as a **3a:4a** 30:70 ratio) in a promising global yield of 47% (entry 2). This result showed that the second cross-coupling reaction proceeds faster than the first one. It is noticeable that this diarylated framework is the key scaffold of some bioactive substances such as the β-carboline alkaloids tadalafil or quillifoline (Figure 1). As the choice of solvent is known to control the decarboxylation rate,[4b,7b,7f,16c] our next attempt was to use TMSO in place of DMSO (entry 3) as a cosolvent; an increase in the yield of product **3a** to 21% and **4a** to 51% was thus observed.

Table 1. Optimization of Direct Mono- or Diarylation onto Enamide **1a**[a]



entry	**2a** (equiv)	catalyst	cosolvent	additive	yield **3a** (%)[b]	yield **4a** (%)[b]
1	3	$Pd(OAc)_2$	DMSO	none	trace	trace
2	3	$Pd(OAc)_2$	DMSO	$EtCO_2H$	14	33
3	3	$Pd(OAc)_2$	TMSO	$EtCO_2H$	21	51
4	3	$Pd(OAc)_2$	TMSO	none	19	34
5	3	$Pd(OAc)_2$	TMSO	$tBuCO_2H$	trace	trace
6[c]	3	$Pd(OAc)_2$	TMSO	$EtCO_2H$	0	0
7[d]	3	$Pd(OAc)_2$	TMSO	$EtCO_2H$	0	0
8	5	$Pd(OAc)_2$	TMSO	$EtCO_2H$	trace	65
9[e]	1	$Pd(OAc)_2$	TMSO	$EtCO_2H$	trace	trace
10	5	$Pd(TFA)_2$	TMSO	$EtCO_2H$	trace	26
11	5	$Pd(MeCN)_2Cl_2$	TMSO	$EtCO_2H$	trace	trace

[a] Reaction conditions unless otherwise specified: **1a** (1 equiv), **2a**, Ag_2CO_3 (2 equiv), Pd(II) catalyst (10 mol %), PPh_3 (0.5 equiv), cosolvent (2.4 equiv), additive (0.5 equiv) in DMF at 80 °C for 24 h. [b] Yield of pure product after purification by column chromatography. [c] The reaction was conducted without PPh_3. [d] The reaction was carried out in a sealed tube. [e] Ag_2CO_3 (1 equiv) was used.

Modifications of both the additive and of the phosphine ligand were unsuccessful (entries 4−6). The low yields observed in these cases resulted from a degradation reaction in addition to the formation of side products arising from degradation and/or homocoupling.[15] Degradation also occurred when the process was carried out under pressure (entry 7). With selective transformations noted as a key challenge in organic chemistry, in order to favor the formation of diarylated scaffolds **4a**, the amount of carboxylic acid was increased. The use of 5 equiv of **2a** led gratifyingly to the corresponding piperidine core **4a**,

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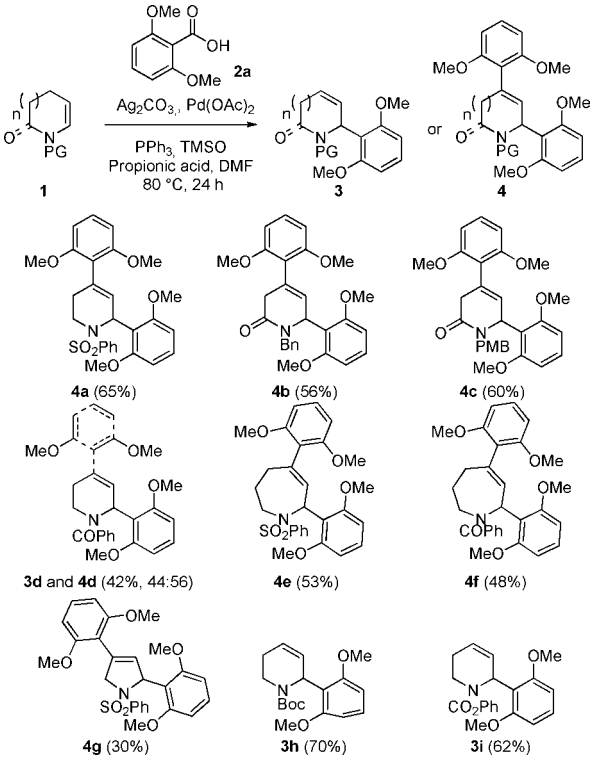
isolated as the sole compound in 65% yield (entry 8). Unfortunately, by using only 1 equiv of **2a**, no selectivity was observed and the monoarylated product **3a** was not isolated due to a lack of conversion (entry 9). Other palladium sources were also tested but with no overall improvement (entries 10–11).

Scheme 1. Influence of the Protecting Group for the Direct Mono- or Diarylation of Enamides **1**[a]



[a] Reaction conditions: **1** (1 equiv), **2a** (5 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), PPh_3 (0.5 equiv), TMSO (2.4 equiv) and propionic acid (0.5 equiv) in DMF at 80 °C for 24 h. Yield of pure product after purification by column chromatography in parentheses.

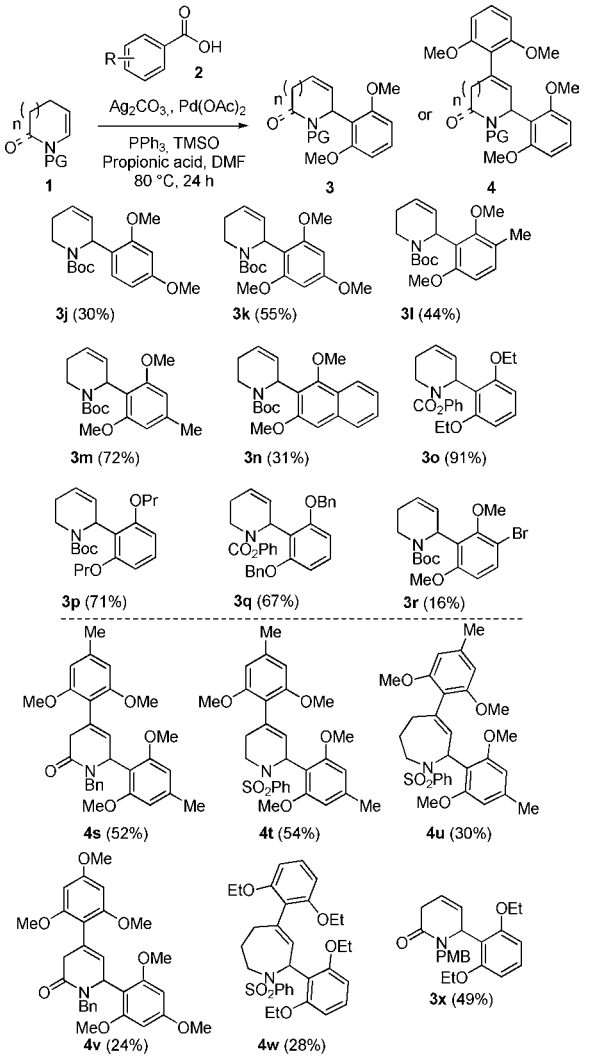
With a set of optimized conditions in hand, we next examined various simple enamides in the Pd-decarboxylative cross-coupling reaction with electron-rich 2,6-dimethoxybenzoic acid as the coupling partner (Scheme 1). It is important to mention that to date and to the best of our knowledge, direct arylation cross-coupling has not been reported in the literature on nonaromatic enamides. We found that the endoenamide **1b** or **1c** was converted to the corresponding diarylated compound **4b** or **4c** with good yields *via* a one-pot double cross-coupling process. Starting from the latter, further functionalization could be envisaged by introducing diversity *via* the lactam function. It should also be noted that the electronic density on the benzyl protecting group had no influence on the reaction selectivity. Unfortunately, the reaction was not selective with enamide **1d**; an inseparable mixture of mono- and diarylated products (respectively **3d** and **4d**) was obtained in moderate yield. Diversification was also introduced with five- or seven-membered ring systems. Double cross-coupling occurred with enamides **1e**, **1f**, and **1g** in fair to good yields. For the five-membered ring, a low yield was associated with a degradation reaction. Surprisingly, we were pleased to find that, starting from enamide **1h** bearing a Boc protecting group, the corresponding 2-arylpipiridine core **3h** was isolated as the sole compound in 70% yield. The same behavior was also observed with enamide **1i** bearing a phenyl carbamate group. With this strategy, we were now able to perfectly control the mono- or difunctionalization of the enamides thanks to the electronic density of the protecting group on the nitrogen atom. Performing the reaction with strong electroattractive protecting groups favored the double direct cross-coupling process while less electroattractive protecting groups such as carbamates favored the mono-cross-coupling reaction.

Moreover, we examined the direct arylation for the synthesis of various arylpiperidine skeletons (Scheme 2). The reaction tolerates a range of polyfonctionalized electron-rich *ortho*-methoxy-substituted benzoic acids in good to excellent yields (**3k**–**m**). Naphtalen derivative **3n** is also compatible under these conditions. Moreover, other benzoic acids bearing *ortho*-electron donating groups gave us the desired frameworks **3o**–**q** in high yields. Different aryl carboxylic acids were then tested under optimized conditions on enamide **1h** bearing a Boc-nitrogen protective group (Scheme 2). The reaction tolerated a range of polyfunctionalized electron-rich alkoxy-substituted or weak electron-donating alkyl-substituted benzoic acids in good to excellent yields (**3j**–**q**). The particular substitution pattern of the phenyl ring of these carboxylic acids affected the yield (**3m** versus **3l**, **3j** versus **3h**).[16] It is noteworthy that attempts to test the reaction with *meta*- or *para*-alkoxy substituted benzoic acid derivatives were not satisfactory. Naphtalen derivative **3n** is also compatible in these conditions. Electron-defficient aryl carboxylic acids underwent a cross-coupling reaction to afford the corresponding arylated product **3r**, albeit in low yield. When the electronic density decreased on the aromatic core, the direct cross-coupling arylation was less efficient. Finally, we focused our last efforts on the synthesis of 2,4-diarylpiperidines with success. Frameworks **4s**–**w** were isolated with moderate to good yields for a double direct C2,C4 dehydrogenative functionalization. It is interesting to note that with specific enamide **1c** we can control the monoaddition with the use of more hindered substituents to afford **3x** in moderate yield. Beyond this elegant method, the obtained products could be easily further functionalized for the synthesis of small but more complex heterocyclic systems.

Given that the exact mechanism of decarboxylative coupling is still not clear, a plausible catalytic cycle is proposed in Scheme 3. After generation of a Pd(II) species and formation of a Pd(II)-carboxylate complex, an aryl Pd(II) intermediate was created *via* extrusion of CO_2. Subsequent carbopalladation of enamide **1a**, followed by β-hydride elimination, gave both compound **2a** and the Pd-hydride species. Thanks

(16) For selected examples: (a) Xiang, S.; Cai, S.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 4608–4611. (b) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506–5509. (c) Cornella, J.; Sanchez, C.; Banawa, D.; Larrosa, I. *Chem. Commun.* **2009**, 7176–7178.

Scheme 2. Direct Arylation with Various Aryl Carboxylic Acids[a]

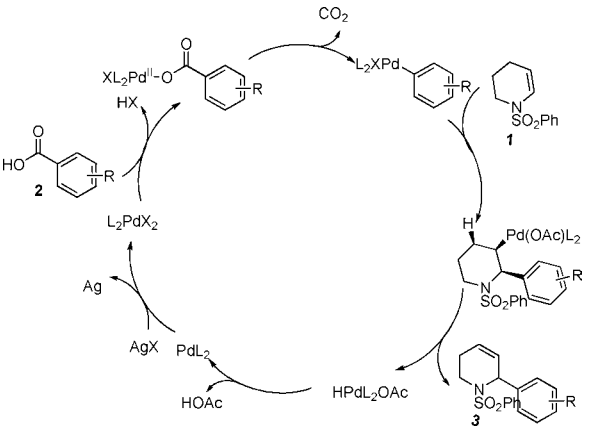


[a] Reaction conditions: **1** (1 equiv), **2** (5 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), PPh_3 (0.5 equiv), TMSO (2.4 equiv) and propionic acid (0.5 equiv) in DMF at 80 °C for 24 h. Yield of pure product after purification by column chromatography in parentheses.

to elimination of acetic acid and oxidation by silver carbonate, the latter was converted to the reactive Pd(II) form. We conjecture that a second catalytic cycle is involved in the formation of the diarylated product **4a**. In order to evaluate the role of silver salt in this process, we carried out the reaction in the absence of Ag_2CO_3 and by using stoichiometric amounts of $Pd(OAc)_2$.[17] The desired scaffold **4a** was thus isolated in 41% yield accompanied by some impurities. Without a palladium source, the use of Ag_2CO_3 alone was not effective for the coupling, showing that this salt is not the key reagent in the decarboxylation step. In this case, starting material was recovered accompanied by a small amount of decarboxylated derivative which led us to suggest that the decarboxylation is mediated by palladium on electron-rich carboxylic acids.[5]

(17) The use of other sources of oxidant such as $Cu(OAc)_2$, $CuCl_2$, or benzoquinone was not successful.

Scheme 3. Proposed Catalytic Cycle for the Direct Monoarylation of Enamides **1**



In conclusion, this report describes an original direct mono- or diarylation reaction of cyclic enamides *via* a Pd-catalyzed decarboxylative cross-coupling process under mild conditions. We have developed a new site-selective arylation that can control the number of functionalizations at either the C2 or C2−C4 positions by involving an electronic strategy thanks to nitrogen protecting groups. This approach also represents a simple and convenient one-pot route for the synthesis of polyarylated piperidinic systems, and the synthesis of potential biological products is currently being explored in our laboratory. An enantioselective approach using a chiral ligand and/or a chiral catalyst could also be envisaged.

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Supporting Information Available. Full characterization details including ^1H and ^{13}C NMR, IR, MS, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.