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Palladium-catalyzed *ortho*-olefination of 2-arylpyrrolidines: A tool for increasing structural complexity in nitrogen heterocycles☆

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ABSTRACT

The dual role of the (2-pyridyl)sulfonyl unit as directing functionality and readily removable *N*-protecting group has enabled an efficient and practical transformation of 2-arylpyrrolidine derivatives into more complex tricyclic frameworks via palladium-catalyzed *ortho*-olefination with electron deficient alkenes and subsequent cyclization upon *N*-deprotection under mild conditions. The key cross coupling step in the presence of *N*-fluoro-2,4,6-trimethylpyridinium triflate ([F+]) as the terminal oxidant is both highly efficient and tolerant to a variety of steric and electronic changes at both coupling partners. By adequate choice of reductive conditions, the *N*-sulfonyl deprotection can be directed to the selective formation of benzo-fused pyrrolizidine or fused pyrrolidino-benzazapine frameworks.

1. Introduction

Nitrogen-containing heterocyclic compounds are privileged structures in terms of biological activity and continues to inspire the development of new methods for their synthesis and functionalization.[1] Introducing complexity and diversity on a core molecule is crucial for facilitating lead discovery and optimization in medicinal chemistry. Toward that goal, the metal catalyzed C–H alkenylation of nitrogen heterocycles has attracted much current interest as a unique tactic for rapidly increasing structural complexity due to the synthetic versatility of the newly incorporated alkenyl group.[2,3] Introducing a directing group on a N atom has become a commonly used strategy to ensure site-selectivity, thereby leading to great progress in this area.[4] However, to take full advantage of the synthetic potential of this strategy, directing groups must have the ability to be readily removed under conditions that are compatible with the presence of sensitive alkenyl groups. This is not always achievable and often removal of the *ortho*-directing group from the product requires prior derivatization of the newly incorporated alkene, which is a feat that often limits the transformation's synthetic utility. Additionally, controlling mono-vs. disubstitution selectivity is a continuing challenge in this type of processes.[5]

Our research group has pioneered the use of the (2-pyridyl) sulfonyl unit (SO_2Py) as a weakly coordinating and readily removable directing group in metal-catalyzed C–H functionalization reactions.[6] The dual protecting and directing role of SO_2Py in C–H functionalization was first demonstrated by achieving an efficient and general Pd-catalyzed C2-alkenylation of indoles and pyrroles with both electron-poor and non-activated alkenes (Scheme 1a).[6a,b] This strategy has also been applied to the Pd-catalyzed *ortho*-C–H alkenylation of *N*-alkylated aniline, benzylamine, phenethylamine and γ-arylpropylamine derivatives with electron-poor alkenes (Scheme 1b).[6c,j] More recently, this concept was extended to the

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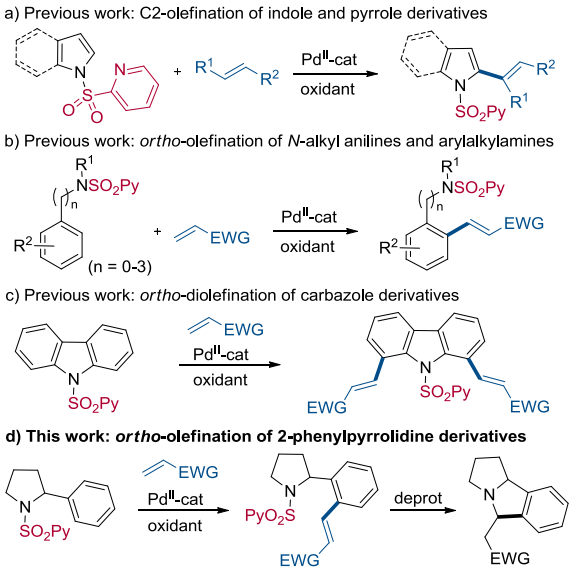


Scheme 1. N–SO_2Py directing group in Pd-catalyzed direct C–H olefination of nitrogen heterocycles.

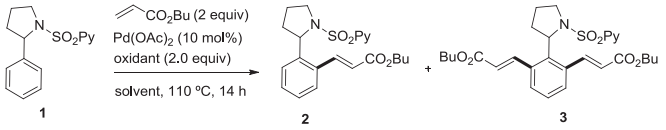
regiocontrolled direct Pd-catalyzed C1/C8-diolefination of carbazoles (Scheme 1c).[6d]

Driven by our continued interest in the development of practical methods based on catalytic C–H functionalization for the assembly of nitrogen-containing heterocyclic architectures from simple precursors, we envisioned that the 2-arylpyrrolidine unit[7] could provide an ideal platform for iterative *ortho*-selective C–H alkenylation and subsequent cyclization leading to more complex polycyclic ring systems such as benzo-fused pyrrolizidines (Scheme 1d). It is important to note that the benzopyrrolizidine motif forms the core of many natural products with pharmacological relevance.[8,9] In this pursuit, we describe herein an efficient method for the *ortho*-olefination of 2-aryl-*N*-(2-pyridyl)sulfonylpyrrolidines with electron-deficient alkenes and their derivatization into heterocyclic systems of increased complexity such as benzo-fused pyrrolizidines or pyrrolidino-benzazepines by appropriate choice of *N*-deprotection conditions.

2. Results and discussion

At the outset of our study, we studied the alkenylation of the N–SO_2Py-protected parent 2-phenylpyrrolidine **1** with butyl acrylate, taking as the basis for reaction optimization the conditions previously established for the *ortho*-olefination of benzylamine derivatives.[6c] The results of this study are presented in Table 1. The reaction of **1** with butyl acrylate (2 equiv) in the presence of $Pd(OAc)_2$ (10 mol%) and *N*-fluoro-2,4,6-trimethylpyridinium triflate ([F$^+$], 2 equiv) as oxidant in DCE at 110 °C for 14 h led to the clean formation of the expected olefination product **2** with complete conversion and very good mono-/disubstitution selectivity (**2**/**3** = 92:8, entry 1). The superiority of [F$^+$] as oxidant was demonstrated upon evaluation of a handful of oxidants of different oxidizing ability. $PhI(OAc)_2$ proved also to be an effective stoichiometric oxidant for this reaction, although incomplete conversion was observed (67%, entry 2). Other oxidants used in Pd-catalyzed C–H activation processes such as $K_2S_2O_8$, Oxone or $Ce(SO_4)_2$ provided unpractical conversions (9–24%, entries 3–5). No product was detected when the reaction was performed in the presence of $Cu(OAc)_2$, a weaker oxidant widely used in Pd-catalyzed C–H olfefinations that have been proposed to occur through catalytic

Table 1
Optimization studies in the model olefination of substrate 1 [a].



Entry	Oxidant	Solvent	Conversion %[b]	2/3[b]
1	[F$^+$][c]	DCE	>97	92:8
2	$PhI(OAc)_2$	DCE	67	>95:<5
3	$K_2S_2O_8$	DCE	24	>95:<5
4	Oxone	DCE	11	>95:<5
5	$Ce(SO_4)_2$	DCE	9	>95:<5
6	$Cu(OAc)_2$	DCE	<3	–
7	[F$^+$][c]	Toluene	45	>95:<5
8	[F$^+$][c]	1,4-Dioxane	35	>95:<5
9	[F$^+$][c]	DMSO	25	>95:<5
10	[F$^+$][c]	DMF	76	>95:<5
11	[F$^+$][c]	AcOH	90	90:10
12[d]	[F$^+$][c]	DCE	>97 (85)[e]	>95:<5
13[d,f]	[F$^+$][c]	DCE	70	>95:<5
14[d,g]	[F$^+$][c]	DCE	40	>95:<5

[a] Reaction conditions: **1** (0.15 mmol), butyl acrylate (0.30 mmol), $Pd(OAc)_2$ (0.015 mmol), oxidant (0.30 mmol), solvent (1.5 mL), 110 °C, 14 h under N_2.
[b] Determined by ^{1}HNMR.
[c] [F$^+$] = *N*-fluoro-2,4,6-trimethylpyridinium triflate.
[d] Reaction performed in the presence of 1.2 equiv (0.18 mmol) of butyl acrylate.
[e] Isolated yield of the mono-olefination product after chromatographic purification.
[f] In the presence of 5 mol% of $Pd(OAc)_2$.
[g] In the presence of 2 mol% of $Pd(OAc)_2$.

cycles based on Pd^{II}/Pd^0 redox shuttles (entry 6).[3] In contrast, the powerful oxidant [F$^+$] has been used in Pd-catalyzed C–H transformations such as fluorination, trifluoromethylation, and aminations, for which a key stage of the proposed cycle is the oxidation of a Pd^{II} intermediate into high-valent Pd^{III} or Pd^{IV} intermediates.[10]

A solvent screening revealed DCE as the most effective reaction media. Other aprotic solvents of varied polarity such as toluene, 1,4-dioxane or DMSO failed to provide a conversion beyond 45% (entries 7–9), whereas the use of DMF resulted in a boost in conversion up to 76% (entry 10). In accordance with the suggested important role of polar acidic solvents in the acceleration of cyclopalladation processes,[11] the model reaction of **1** with butyl acrylate in AcOH resulted in 90% conversion, albeit a slightly diminished mono-/disubstitution selectivity was observed (**2**/**3** = 90:10, entry 11). The higher efficiency observed in the chlorinated solvent DCE can be plausibly ascribed to the presence of small amounts of HCl upon partial decomposition. Finally, we were glad to find that the di-*ortho*-olefination process was almost completely suppressed by reducing the amount of alkene to 1.2 equiv without any appreciable impact in reactivity, thereby providing the desired mono-alkenylation product **2** in 85% isolated yield (entry 12). In constrast, decreasing the palladium catalyst loading to 5 mol% and 2 mol% resulted in incomplete conversions (entries 13 and 14, respectively).

The unique directing role of the N–SO_2Py unit was illustrated through a control experiment showing that no reaction was produced when the analogue *N*-tosylated 2-phenylpyrrolidine **4** was submitted to the reaction with butyl acrylate under otherwise identical reaction conditions, resulting in the exclusive recovery of starting material (Scheme 2).

With an efficient and selective *ortho*-alkenylation protocol in hand, we next set out to investigate the scope of alkenylation of substrate **1** with various electron-deficient alkenes (Scheme 3). Not only acrylates, but also phenyl vinyl sulfone and dimethyl vinyl