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Palladium-catalyzed C–H alkenylation of quinoxaline *N*-oxide enabled by a mono-*N*-protected amino acid

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ABSTRACT

The efficient alkenylation of quinoxaline *N*-oxide was achieved *via* Pd-catalyzed C–H activation, using the assistance of a mono-*N*-protected amino acid. Further deoxygenation of the 2-styrylquinoxaline-*N*-oxides yielded the corresponding styrylquinoxaline derivatives.

Introduction

Quinoxaline is a privileged benzodiazine heterocycle, present as a key structural element in several biologically active compounds.[1,2] It exhibits a wide spectrum of biological activities, including antibacterial, antiprotozoal, anticancer, and antidepressant effects.[3–7] Although quinoxaline rarely occurs in Nature, it is widely distributed in biologically important synthetic molecules that include many known drugs such as Quinacilin, Brimonidine, and Varenicline (Fig. 1).[8] Besides neutral quinoxalines, mono- and di-*N*-oxide derivatives have also been described in the literature as exhibiting bioactivity against a diverse range of targets.[9–12]

Quinoxaline ring substituents, found in biologically active compounds, are normally introduced before the heterocyclization step. However, in recent years, new strategies for ring functionalization have received increasing attention from the synthetic community.[13] *trans*-Styrylquinoxalines can be considered as isosteres of stilbenes, which are widely present in natural compounds exhibiting a wide range of biological activities,[14–18] and chemical modifications strategies for this core could be useful for medicinal chemistry applications. Styrylquinoxalines are generally prepared by the aldol-type condensation of methyl quinoxaline derivatives with aromatic aldehydes (Scheme 1).[19,20] Recently Zhang and co-workers reported the synthesis of 2-styrylquinoxaline from quinoxaline *N*-oxide by direct C–H activation using iodine (Scheme 1).[21]

Considering the importance of the quinoxaline scaffold in medicinal chemistry, the functionalization of quinoxaline is an important strategy for expanding the chemical space and producing innovative compounds for drug discovery programs. C–H activation is a promising approach for functionalization of the quinoxaline core.[22] Among the various methods for direct functionalization *via* C–H bond activation, the Fujiwara-Moritani reaction is an important strategy for the olefination of aromatic compounds.[23–25] Importantly, this reaction has also been recently used for the olefination of diazines.[26,27]

Azine *N*-oxides possess increased α-hydrogen acidity and nucleophilicity, conferring good reactivity and selectivity to this heterocyclic class. This strategy has been used by several groups, who have developed important methodologies for the direct C–H functionalization of pyridine rings.[28–37] Among them, Cho and co-workers performed a palladium-catalyzed alkenylation using azine *N*-oxides and acrylates (Scheme 2).[26] Inspired by this methodology and in an attempt to expand the quinoxaline chemical space for medicinal chemistry purposes, we herein describe the C–H alkenylation of quinoxaline *N*-oxide (Scheme 2). The present study highlights the importance of ligands in the catalytic activity of Pd(II) in the Fujiwara-Moritani reactions.

Results and discussion

We began our study by investigating the synthesis of (*E*)-2-styrylquinoxaline 1-oxide **3a** using the best conditions reported by Cho and co-workers[26] (Table 1, entry 1).

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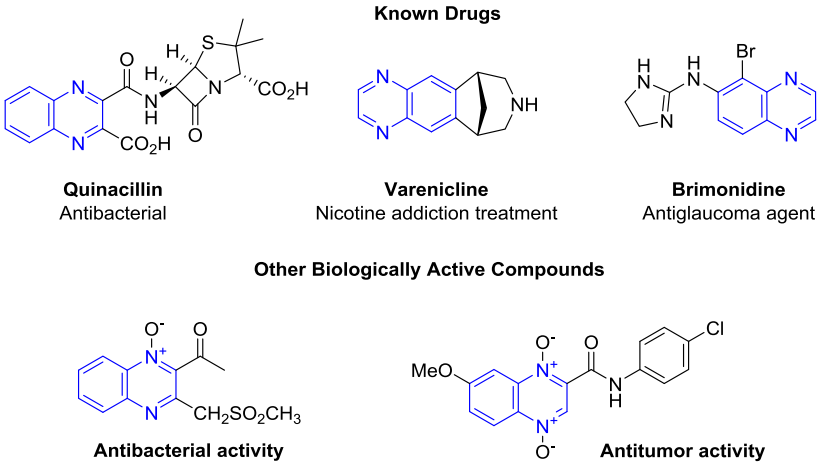
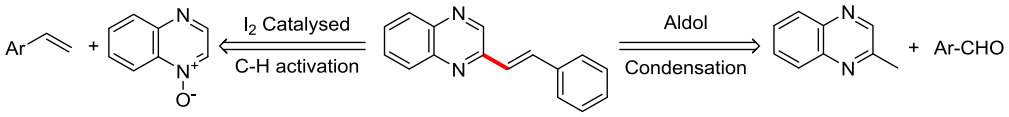
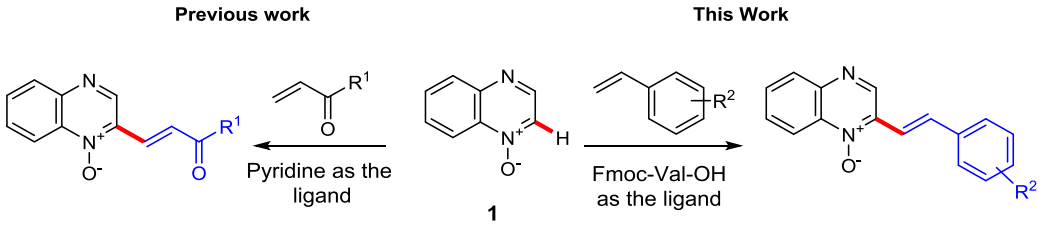


Fig. 1. Commercially available drugs and other biologically active compounds containing the quinoxaline core.



Scheme 1. Synthetic strategies to obtain 2-styryl quinoxalines.



Scheme 2. Palladium-catalyzed Fujiwara-Moritani reaction using quinoxaline *N*-oxide and styrenes and acrylates.

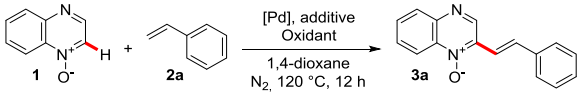
When other solvents were used, such as 2-propanol, acetonitrile, DMSO, DMF, and toluene (Table S1, entries 2–6; ESI), no improvement in yield was observed. Moderate yields were also obtained when 1,4-dioxane was used with different sources of Pd(II) (Table 1, entries 2–4). The use of bidentate ligands such as 1,10-phenanthroline (Phen) and 4,4-di-*tert*-butyl-2,2-bipyridyl (BBBPY) were found to decrease the yields of the olefination product (Table 1, entries 5 and 6) compared to the pyridine ligand (Table 1, entry 1). Subsequently, different amino acids were used as ligands (Table 1, entries 7–10). Among these, Fmoc-Val-OH gave the best result (Table 1, entry 10). Several oxidants were also screened in order to improve the yield (Table 1, entries 10–14). Use of silver acetate led to the highest yield of (*E*)-2-styrylquinoxaline *N*-oxide (Table 1, entry 14,). Upon investigating the different ratios of quinoxaline *N*-oxide/styrene (Table 1, entries 15–18), the 4:1 ratio was found to be optimal. Reduction in the amount of the additive led to a considerable decrease in the yield (Table 1, entries 19–21); in the absence of an additive, a poor yield was obtained (Table 1, entry 22). Furthermore, no reaction was possible without an oxidant or a palladium source (Table 1, entries 23 and 24).

After establishing the optimal reaction conditions (Table 1, entry 14,), the scope and limitations of the protocol were investigated (Scheme 3). Typically, when silver acetate was used as the oxidant, it was possible to obtain the desired product in good to excellent yield, even with bromine-substituted styrene **3e**. However, silver carbonate was found to be a better oxidant than silver acetate for synthesizing compounds **3c** and **3f** (Scheme 3).

Quinoxaline *N*-oxide proved to be an ideal substrate for the Fujiwara-Moritani coupling and presented specific reactivity of the *N*-oxide functionality at the *ortho* position. The remarkable ability of the mono-*N*-protected amino acid (Fmoc-Val-OH) to accelerate Pd(II)-catalyzed oxidative C–H cross-coupling reactions, first discovered by Yu and co-workers, was also observed in this study.[38,39]

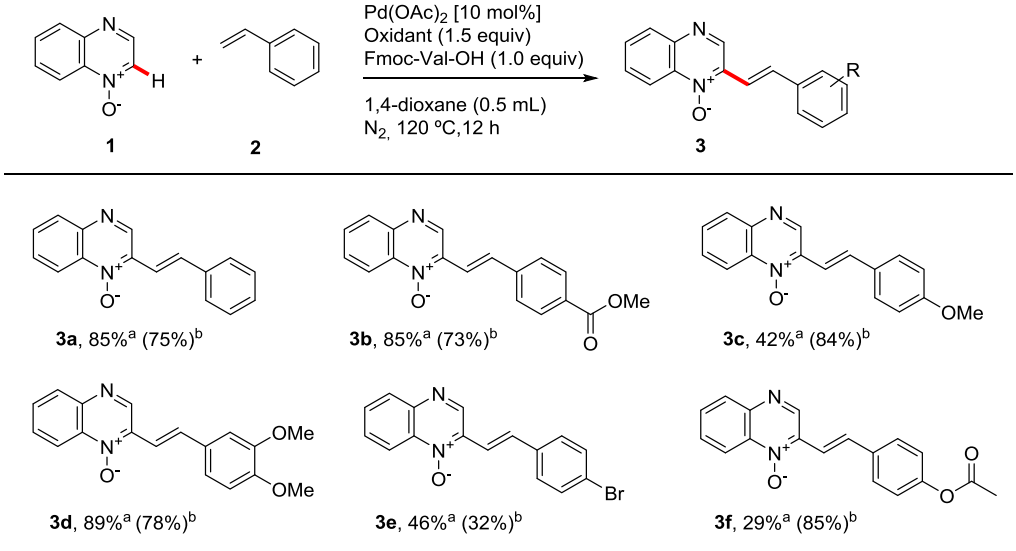
A probable reaction mechanism has been proposed (Scheme 4) based on the experimental results obtained from this work and the extensive experimental and computational studies described in the literature.[38,40,41] It is proposed that palladium(II) acetate initially forms a complex with the *N*-protected amino acid, with both the –NH and carboxylate groups coordinating with the Pd center in a bidentate manner. Subsequently, this Pd-complex coordinates with the oxygen at the *N*-oxide and reversible ligand exchange takes place by concerted metalation/deprotonation (CMD), forming complex **C** (Scheme 4), which is relatively stable due to the formation of a hydrogen-bond between the acetic acid ligand and the anionic oxygen. That the coordination occurs with the *N*-oxide moiety and not with nitrogen was verified by the experimental observation that the neutral quinoxaline did not yield the alkenylated product (result not showed). Finally, coordination of Pd to the styrene followed by carbopalladation leads to complex **E** (Scheme 4), which forms the quinoxaline **3**, substituted at the

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Additive	Oxidant	Yield **3a** (%)[b]
1	$Pd(OAc)_2$	Pyridine	Ag_2CO_3	64
2	$Pd(acac)_2$	Pyridine	Ag_2CO_3	23
3	$PdCl_2(PPh_3)_2$	Pyridine	Ag_2CO_3	38
4	PdI_2	Pyridine	Ag_2CO_3	29
5	$Pd(OAc)_2$	BBBPY	Ag_2CO_3	30
6	$Pd(OAc)_2$	Phen	Ag_2CO_3	11
7	$Pd(OAc)_2$	L-proline	Ag_2CO_3	–
8	$Pd(OAc)_2$	Fmoc-Ala-OH	Ag_2CO_3	53
9	$Pd(OAc)_2$	Fmoc-Gly-OH	Ag_2CO_3	54
10	$Pd(OAc)_2$	Fmoc-Val-OH	Ag_2CO_3	75
11	$Pd(OAc)_2$	Fmoc-Val-OH	$K_2O_8S_2$	18
12	$Pd(OAc)_2$	Fmoc-Val-OH	Ag_2O	74
13	$Pd(OAc)_2$	Fmoc-Val-OH	$Cu(OAc)_2$	75
14	**$Pd(OAc)_2$**	**Fmoc-Val-OH**	**AgOAc**	**85**
15[c]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	85
16[d]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	61
17[e]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	42
18[f]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	28
19[g]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	70
20[h]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	67
21[i]	$Pd(OAc)_2$	Fmoc-Val-OH	AgOAc	50
22	$Pd(OAc)_2$	–	AgOAc	45
23	–	Fmoc-Val-OH	AgOAc	–
24	$Pd(OAc)_2$	Fmoc-Val-OH	–	Traces

[a] Reagents and conditions: **1** (4.0 equiv.), solvent (0.5 mL), palladium catalyst (10 mol%), additive (1.0 equiv.), oxidant (1.5 equiv.), **2a** (1.0 equiv.), 120 °C, 12 h.
[b] Isolated Yield.
[c] **1**:**2a** = 5:1.
[d] **1**:**2a** = 3:1.
[e] **1**:**2a** = 2:1.
[f] **1**:**2a** = 1:1.
[g] Additive 50 mol%.
[h] Additive 30 mol%.
[i] Additive 15 mol%.



Scheme 3. Scope for the reaction between quinoxaline *N*-oxide and styrenes.

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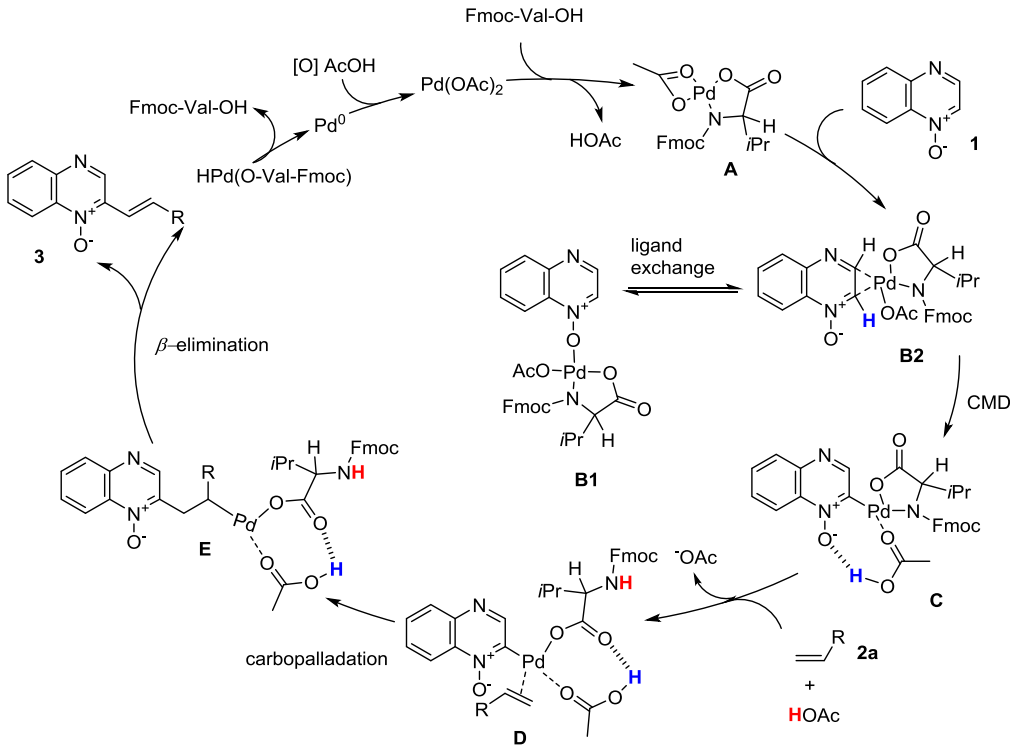
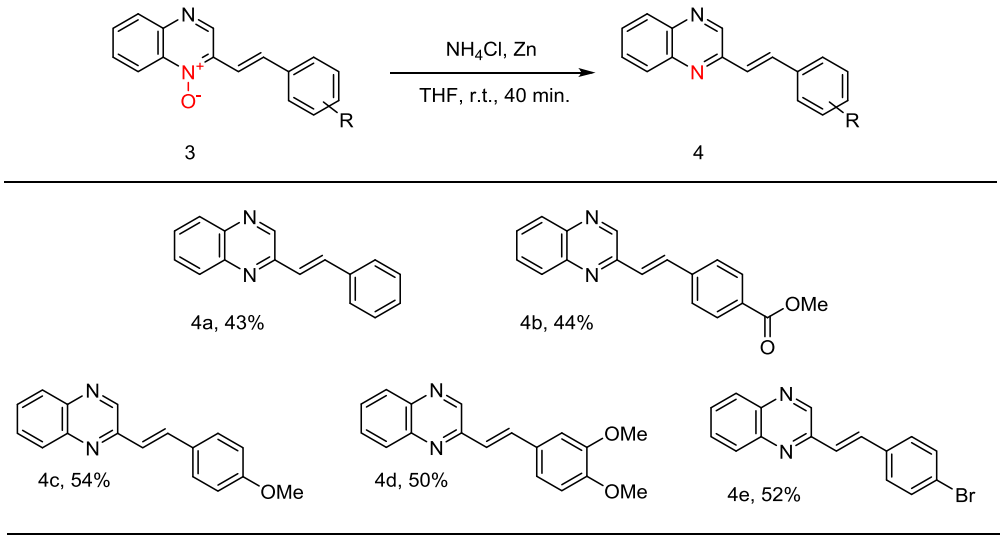


Scheme 4. Proposed mechanism for quinoxaline *N*-oxide alkenylation by the Fujiwara-Moritani reaction.[38,40,41]



Scheme 5. Deoxidation of quinoxaline *N*-oxide derivatives.

α-position to the *N*-atom, after β-elimination (Scheme 4), and the Pd returns to the catalytic cycle.

In order to evaluate the reactivity of these compounds under reductive conditions, the respective styrylquinoxaline-*N*-oxides were reduced using Zn in the presence of NH_4Cl to obtain the corresponding styrylquinoxalines **4a–e** (Scheme 5).[42] Although moderate yields were observed, the generation of the deoxygenated quinoxaline products highlighted the suitability of the present route to obtain functionalized quinoxalines (Scheme 5).

Conclusion

A practical and useful Fmoc-Val-OH ligand/palladium-catalyzed system was described for the C–H alkenylation of quinoxaline *N*-oxide to obtain six novel 2-styrylquinoxaline *N*-oxides in moderate to good yields. Considering the results presented herein, along with data available in the literature, a rational pathway for this reaction was fully described. Furthermore, efficient reduction of the 2-styrylquinoxaline *N*-oxides to styrylquinoxaline was also successfully accomplished.

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A. Supplementary data

Supplementary data (synthetic procedures; optimization study synthetic procedures; optimization study) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.05.054.

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