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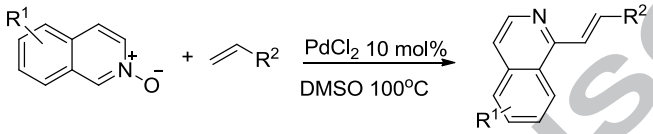

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Palladium-catalyzed external-oxidant-free coupling reactions between isoquinoline/quinoline *N*-oxides with olefins

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ABSTRACT

A convenient and efficient approach for the synthesis of 1-alkenylisoquinolines and 2-alkenylquinolines was developed via palladium-catalyzed coupling reactions between isoquinoline/quinoline *N*-oxides with olefins under external-oxidant-free conditions. Biological evaluation revealed that some of the obtained 1-alkenylisoquinolines exhibited in vitro antiproliferative activities on human-derived prostate, breast, esophageal, and stomach cancer cell lines.

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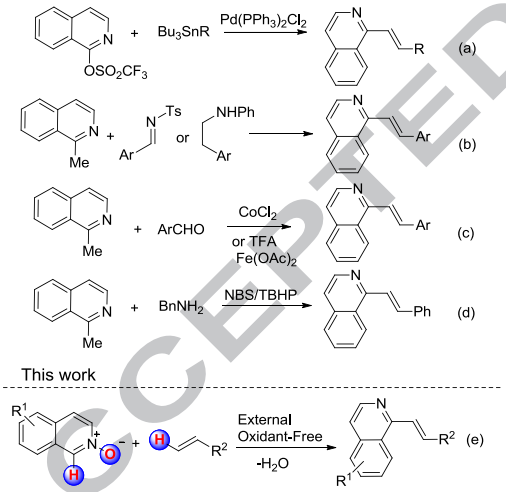
Isoquinoline is a common structural motif found in a wide range of natural products with remarkable pharmacological properties.[1] In particular, 1-alkenylisoquinolines as a privileged scaffold, have attracted attention because of their wide activities as antibacterial, anticancer as well as enzyme inhibitor.[2] On the other hand, they have emerged as significant and versatile building blocks for the synthesis of biologically-active molecules.[3] Therefore, synthetic protocols that enable convenient access to 1-alkenylisoquinolines are of great importance and numerous attempts have been made by organic chemists in the past decades.[4]

Early in 1981, Papadopoulos described a successful palladium-mediated coupling of 1-isoquinolyl triflate with organostannanes (Scheme 1a).[5] Very recently, the synthesis of 1-alkenylisoquinolines was applicable by using substituted 1-methylisoquinoline. For example, Wang and Tian reported the reactions of 1-methylisoquinoline with *N*-sulfonyl aldimines or secondary amines (Scheme 1b).[6] Teo and Uozumi reported cobalt or iron-catalyzed alkenylation of 1-methylisoquinoline with aldehydes via C-H functionalization (Scheme 1c).[7] Wang realized an easy access to biologically active 1-styrylisoquinolines through direct deamination and benzylic C(sp3)–H bond activation under metal-free conditions (Scheme 1d).[8] However, the limited availability of substituted 1-methylisoquinolines and 1-isoquinolyl triflate narrows their range of use. Moveover, compared to substituted 1-methylisoquinolines, substituted isoquinoline *N*-oxides are more obtainable through oxidation of isoquinoline.[9] On the basis of these findings, practical methods for the direct alkenylation of isoquinolines at 1-positions would be highly desirable and enrich the structural diversity of 1-alkenylisoquinolines (Scheme 1e).

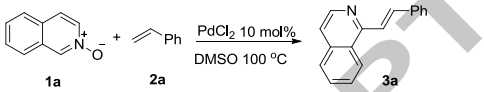


Scheme 1. Construction of 1-alkenylisoquinolines with different strategies.

Optimization of the reaction conditions was carried out using isoquinoline *N*-oxides with styrene as the model substrates. Some screening results are shown in Table 1. As summarized, it was found that using DMSO as solvent gave the best result, whereas other solvents, such as 1,4-dioxane, DMF, NMP, DME, Xylene were less effective or ineffective (entries 1–6). With an attempt to improve the yield of the reaction, further efforts related the influence of various palladium sources were examined. While with $PdBr_2$, $Pd(OAc)_2$ and $Pd(PPh_3)_2(OAc)_2$ the yields were unsatisfactorily low (entries 8–10), $Pd(TFA)_2$ provided **3a** in 71% yield (entry 7). With $PdSO_4$ as the catalyst, only trace of the product **3a** was detected (entry 11). $PdCl_2$ was the most suitable catalyst and resulted in the desired product **3a** being obtained in 77% yield (entry 12). In addition, obviously decreased yields were obtained while further attempt to adjusting the reaction concentration, time and temperature (entries 13–17). A screening of additives such as Py, PPh_3, 1,10-phenanthroline and TFA was also conducted, but provided no improvements (entries 18–21). Therefore, we decided to use condition in entry 12 as the standard reaction conditions.

Table 1

Screening and optimization of the reaction conditions



entry[a]	Cat.(10 mol%)	additive (equiv.)	Solvent(mL)	Time (h)	Yield[b] (%)
1	$PdCl_2$	—	1,4-dioxane (1)	10	28
2	$PdCl_2$	—	DMF (1)	10	32
3	$PdCl_2$	—	NMP (1)	10	30
4	$PdCl_2$	—	DME (1)	10	26
5	$PdCl_2$	—	DMSO (1)	10	50
6	$PdCl_2$	—	Xylene (1)	10	trace
7	$Pd(TFA)_2$	—	DMSO (1)	20	71
8	$PdBr_2$	—	DMSO (1)	20	30
9	$Pd(PPh_3)_2(OAc)_2$	—	DMSO (1)	20	59
10	$Pd(OAc)_2$	—	DMSO (1)	20	42
11	$PdSO_4$	—	DMSO (1)	20	trace
12	**$PdCl_2$**	**—**	**DMSO (1)**	**20**	**77**
13	$PdCl_2$	—	DMSO (1)	30	73
14	$PdCl_2$	—	DMSO (0.5)	20	55
15	$PdCl_2$	—	DMSO (1.5)	20	58
16	$PdCl_2$	—	Neat	20	31
17[c]	$PdCl_2$	—	DMSO (1)	20	63
18	$PdCl_2$	Py (0.2)	DMSO (1)	20	41
19	$PdCl_2$	PPh_3 (0.2)	DMSO (1)	20	52
20	$PdCl_2$	1,10-phenanthroline (0.2)	DMSO (1)	20	24
21	$PdCl_2$	TFA (1)	DMSO (1)	20	35

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), catalyst (10 mol%), solvent (0.5-1.5 mL).

[b] Isolated yield.

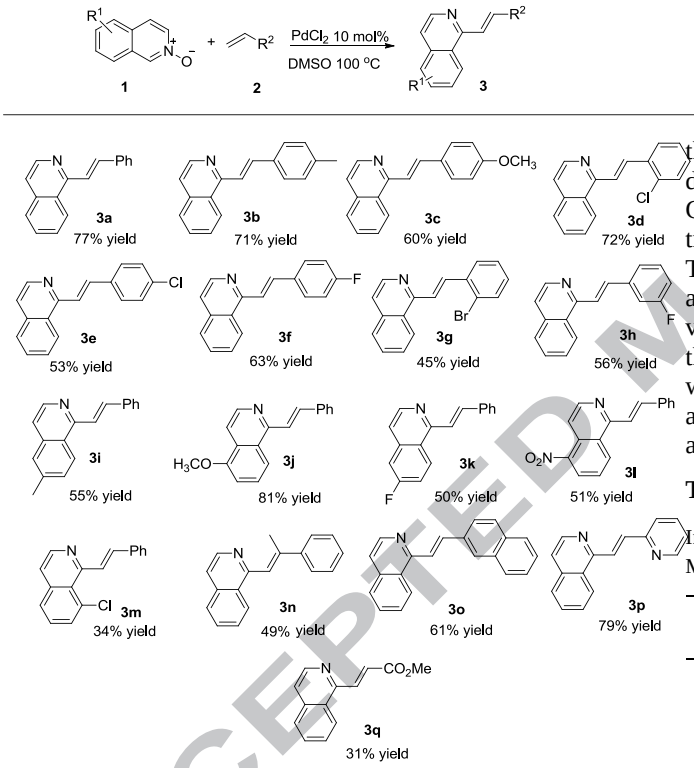
[c] The reaction was performed at 120°C.

After successfully identifying the optimal reaction conditions for the synthesis of 1-alkenylisoquinolines, we turned our attention to the substrate scope and generality. As depicted in Table 2, the reaction can tolerate a variety of functional groups at the o, m, p position of styrene. The coupling of isoquinoline *N*-oxides with olefins with electron-donating (CH_3, OCH_3) and electron-withdrawing groups (F, Br, Cl) on the aromatic ring were smoothly alkenylated at the 1-position to afford the corresponding products **3a-3h** in moderate to good yields. Notably, the tolerance of the chloro and bromo group under these

coupling conditions offer versatile synthetic functionalization for further elaboration. Futhermore, a broad range of isoquinoline *N*-oxides were screened. To our delight, The coupling between styrene and isoquinoline *N*-oxides derivatives with substituent group (CH_3, OCH_3, F, NO_2) at the 5, 6-position were found to be favored affording the desired products **3i-3l**. Steric effects in the isoquinoline *N*-oxides turned out to be stronger, and a sharp decrease yield of 34% **3m** was obtained when 8-Chloroisoquinoline *N*-oxide was employed. Meanwhile, the scope of the reaction was expanded with its compatibility with polycyclic, heterocyclic olefins and acrylates. Either 2-vinylnaphthalene or 2-vinylpyridine could be successfully applied, furnishing the desired products **3o** and **3p** in good yields. Methyl acrylate could also be applied, providing the corresponding product **3q** in 31% yield.

Table 2

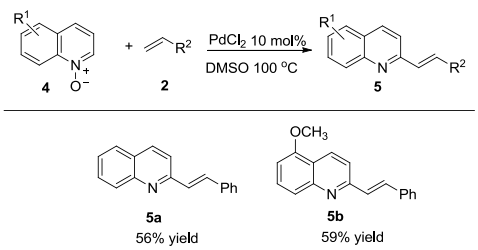
Synthesis of 1-alkenylisoquinolines[ab]



[a] Reaction was performed with **1** (0.5 mmol), **2** (2.5 mmol) and $PdCl_2$ (10 mol%) in 1 mL DMSO at 100 °C for 20h.

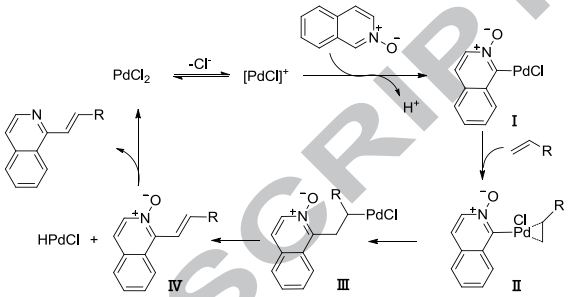
[b] Isolated yield.

With the established facile approach to the synthesis of 1-alkenylisoquinolines in hand, we wondered that this method might offer valuable 2-alkenylquinolines[10] if quinoline *N*-oxides was employed instead of isoquinoline *N*-oxides under similar conditions. As predicted, the coupling reactions of quinoline *N*-oxides with styrene worked well, giving the expected products **5a-5b** in moderate yields.



Scheme 2. Synthesis of 2-alkenylquinolines

A plausible mechanism for the reaction is depicted in Scheme 3. C1-palladated species **I** is formed via electrophilic addition of *N*-oxide and subsequent rearomatization. Then coordination of the palladium complex **I** with olefins followed by insertion of C=C bond gives intermediate **III**. Palladium hydride and intermediate **IV** are released from β-H elimination of **III**. Finally, products and $PdCl_2$ are obtained through oxidation of palladium hydride by intermediate **IV** to complete the catalytic cycle.



Scheme 3. Plausible mechanism for the transformation

In addition, compounds **3c-3f**, and **3o-3p** were evaluated for their in vitro antiproliferative activity on a panel of four human-derived tumor cell lines, using the conventional MTT assay. Compound 5-fluorouracil, a drug which is widely used in the treatment of cancer in clinic, was used as the positive control. The data in Table 3 show that compounds **3e**, **3p** displayed antiproliferative activities against MGC803 and MCF7 with IC_{50} values of 12.82±1.60 and 19.64±1.89 μM, respectively, better than the positive control compound 5-fluorouracil. The result well supports our approach to entry into new potentially antiproliferative agents, based on the framework of 1-alkenylisoquinolines.

Table 3

In vitro antiproliferative activity of **3c-3f**, and **3o-3p** on DU145 (prostate), MCF7 (breast), EC109 (esophageal), MGC803 (stomach) cancer cell lines

Compound	IC_{50} (μmol)			
	DU145	MCF7	EC109	MGC803
3c	115.37±5.67	85.49±4.23	>125	83.22±5.12
3d	>125	>125	109.84±4.25	>125
3e	106.45±5.47	64.83±3.25	21.56±2.84	12.82±1.60
3f	>125	>125	>125	>125
3o	>125	47.05±3.40	121.04±4.51	38.87±3.69
3p	38.30±4.09	19.64±1.89	48.31±4.80	81.08±5.49
5-Fluorouracil	24.36±0.33	22.52±0.21	10.43±0.09	20.67 ± 1.79

In conclusion, a novel and straightforward way for the construction of 1-alkenylisoquinolines and 2-alkenylquinolines via palladium-catalyzed coupling reaction between isoquinoline/quinoline *N*-oxides with olefins has been found. External-oxidant-free conditions make this approach very attractive. In addition, some compounds have been proven to possess antitumor activity by MTT assay which demonstrated the value of this method. Further library construction and antitumor activity tests are underway in our group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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