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Palladium-catalyzed double allylic alkylation of indole-2-hydroxamates: easy access to pyrazino[1,2-*a*]indole derivatives

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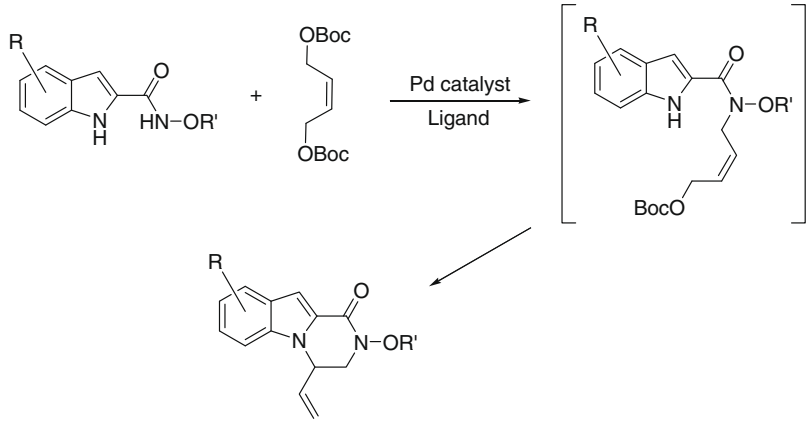
ABSTRACT

The synthesis of pyrazino[1,2-*a*]indoles via a palladium-catalyzed double allylic alkylation of indole-2-hydroxamates is described. The reaction conditions are very mild and allow for a wide variety of substitutions on the indole core.

Over the years, pyrazino-indoles have been shown to be important templates in medicinal chemistry. They have found various applications such as antidepressant[1], anti-inflammatory[2] and anti-obesity[3] agents. Most methods described for their synthesis are either lengthy or use conditions that are not compatible with many functional groups. We report herein mild and versatile conditions for the synthesis of pyrazino[1,2-*a*]indoles via palladium-catalyzed double allylic alkylation of indole-2-hydroxamate.

In light of some recent work published by Trost[4] and our group[5] on the palladium-catalyzed allylic alkylation (Pd-AA) of 2-bromopyrrole, we envisioned that a similar methodology might be applicable to indole-2-hydroxamates, thus providing a quick access to pyrazino-indoles (Scheme 1).

To assess the feasibility of this strategy, we first performed the reaction using conditions that were developed by Trost's group in the synthesis of Agelastatin A.[4] Unfortunately, treating **1** and **2** with $Pd_2(dba)_3{\cdot}CHCl_3$, Trost's ligand[6] and HOAc in DCM gave no desired product. However, when using conditions previously used in our laboratory for the Pd-AA of 2-bromopyrrole (Table 1, entry 1), we were pleased to observe, albeit in low yield, the desired product. Interestingly, we also observed side product **4** arising from the alkylation of a second hydroxamate rather than the desired intramolecular displacement by the indole. It is worth noting that no alkylation at C-3 of the indole nor any of the possible eight-membered rings that could arise from the substitution on the terminal carbon of the chain during the second alkylation were observed.



Scheme 1. One-pot approach to pyrazino[1,2-*a*]indoles.

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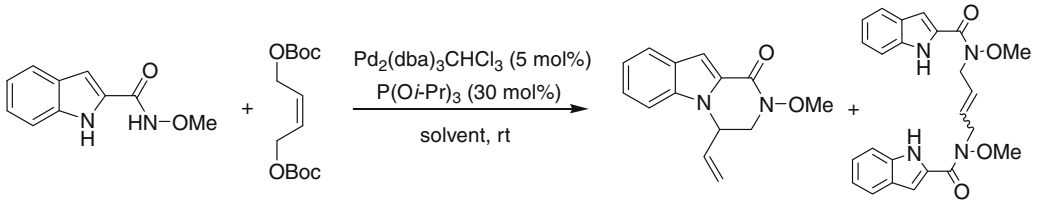
Table 1
Optimisation of solvent and additives



Entry	Solvent	Equiv of **2**	Additive	Yield **3**[a] (%)	Yield **4**[a] (%)
1	Toluene	1.5	None	28	20
2	DMF	1.5	None	21	8
3	EtOH	1.5	None	28	18
4	THF	1.5	None	7	19
5	MeCN	1.5	None	27	10
6	DCE	1.5	None	64	11
7	DCM	1.5	None	69	9
8	DCM	1.0	None	37	27
9	DCM	1.3	None	57	13
10	DCM	1.8	None	60	10
11	DCM	1.5	HOAc[b]	57	16
12	DCM	1.5	DIPEA[c]	62	14
13	DCM	1.5	Cs_2CO_3[c]	16	16
14	DCM	1.5	LiCl[c]	0	0

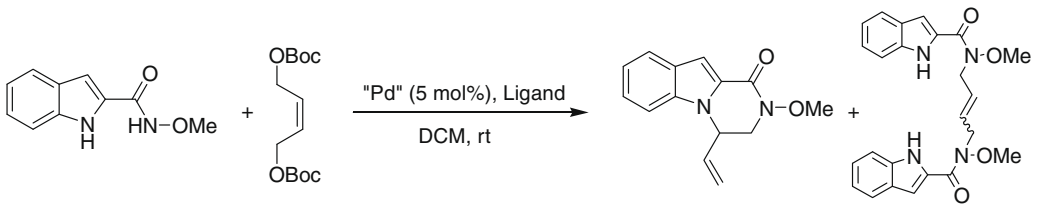
[a] Yields determined by HPLC.
[b] 10 mol %.
[c] 1.0 equiv.

A rapid screen of solvents (Table 1, entries 1–7) showed that DCE and DCM were the preferred solvents for this reaction, giving the desired product in 64% and 69% yield, respectively.

With DCM as the solvent, the amount of dicarbonate **2** used was examined (Table 1, entries 7–10). Increasing the amount of electrophile **2** from 1 to 1.5 equiv diminished the amount of side product **4** and increased the amount of the desired product. However, further increases to 1.8 equiv and higher did not result in any improvement in yield and the reaction became much slower. This behaviour may be explained by the excess electrophile sequestering the catalyst, thus slowing down the reaction. Several additives were also tested, such as HOAc (which had previously proven beneficial),[4] but none showed any improvement to the reaction (entries 11–14).

When examining the palladium source, we observed that both $Pd_2(dba)_3$ and $Pd(dba)_2$ gave good yields of the desired product. However Pd/C, $Pd(OAc)_2$, $Pd(P(tBu)_3)_2$ and $[Pd(C_3H_5)Cl]_2$ gave no conversion. Among the various ligands tested, $P(O\text{-}iPr)_3$ gave the best results while alkyl phosphines displayed no conversion to product (Table 2, entries 1–7). By modifying the amount of ligand, it was found that an increasing ratio of ligand/Pd up to 2.7 gave increased conversion with no significant further increase at higher ratios. (Table 2, entries 8–12).

Table 2
Optimisation of reaction conditions



Entry	Catalyst	Ligand	Ratio Ligand/Pd	Yield **3**[a] (%)	Yield **4**[a] (%)
1	**$Pd_2(dba)_3{\cdot}CHCl_3$**	**P(O*i*-Pr)$_3$**	**2.7**	**69**	**9**
2	$Pd(dba)_2$	P(O*i*-Pr)$_3$	2.7	65	9
3	$Pd_2(dba)_3{\cdot}CHCl_3$	$P(OPh)_3$	2.7	26	16
4	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	2.7	45	10
5	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*t*-Bu)$_3$	2.7	0	0
6	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*n*-Bu)$_3$	2.7	0	0
7	$Pd_2(dba)_3{\cdot}CHCl_3$	dppp	2.7	0	0
8	$Pd_2(dba)_3{\cdot}CHCl_3$	P(O*i*-Pr)$_3$	1.5	*Trace*	0
9	$Pd_2(dba)_3{\cdot}CHCl_3$	P(O*i*-Pr)$_3$	2.0	56	11
10	$Pd_2(dba)_3{\cdot}CHCl_3$	P(O*i*-Pr)$_3$	2.5	66	11
11	$Pd_2(dba)_3{\cdot}CHCl_3$	P(O*i*-Pr)$_3$	3.0	68	10
12	$Pd_2(dba)_3{\cdot}CHCl_3$	P(O*i*-Pr)$_3$	4.0	70	9

[a] Yields determined by HPLC

With a suitable set of reaction conditions developed, we next sought to determine the effect of the hydroxamate substituent. To our knowledge, since it was first reported by Trost[4], methyl and benzyl hydroxamates are the only hydroxamates that have been successfully used in Pd-AA. It was envisaged that increasing the bulkiness of the O-substituent would disfavour the formation of by-product **4**. Indeed, as shown in Table 3, when the size of the substituent was increased from Me to *i*-Pr to *t*-Bu the yield of the product improved from 58% to 78% to 81%.

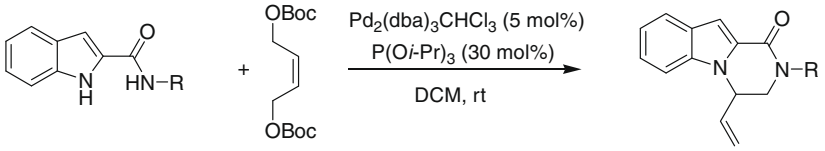
When an alkyl amide was used (Table 3, entry 5), no reaction occurred, demonstrating that the enhanced nucleophilicity provided by the neighbouring oxygen atom (α-effect)[7] is mandatory for the reaction to proceed.

The scope of the methodology was then extended to substituted indole-2-hydroxamates. We were pleased to observe that the reaction proceeded smoothly for a wide variety of substituents on the indole (Table 4). More specifically, electron-donating, electron-withdrawing as well as conjugating groups were all tolerated at various positions. It is of special interest that a bromine atom (Table 4, entry 9) does not react under the reaction conditions and thus offers a good handle for subsequent elaboration of this substrate under transition-metal-catalyzed coupling conditions. Furthermore, every position of the indole could be substituted without affecting the outcome of the reaction.

Finally, the corresponding primary amide and secondary amine are easily accessible via cleavage of the N–O bond using samarium iodide[8] followed by reduction of the carbonyl group with $LiAlH_4$ in ethyl ether (Scheme 2).

In conclusion, a general method 9 for the synthesis of pyrazino[1,2-*a*]indole derivatives has been developed. The reaction

Table 3
Optimisation of hydroxamate substituent

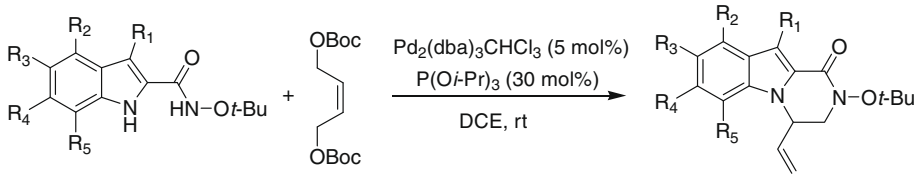


1 **2** **3**

Entry	**R**	Yield[a] (%)
1	OMe	58
2	OBn	72
3	O*i*-Pr	78
4	**O*t*-Bu**	**81**
5	DMB[b]	0

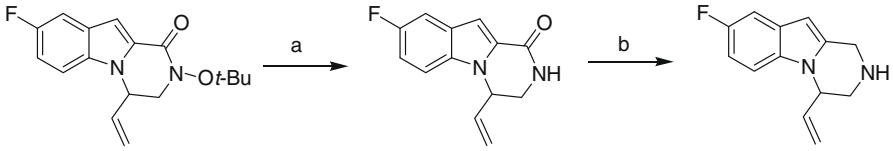
[a] Isolated yield.
[b] DMB = 2,4-dimethoxybenzyl.

Table 4
Indole substrate scope



1 **2** **3**

Entry	R_1	R_2	R_3	R_4	R_5	Isolated yield (%)
1	H	H	H	H	H	81
2	H	H	OMe	H	H	70
3	H	H	Cl	H	H	72
4	H	H	F	H	H	75
5	H	H	CO_2Et	H	H	55
6	Me	H	OMe	H	H	65
7	H	H	H	CN	H	70
8	H	H	Me	H	Me	88
9	H	Br	Cl	H	H	60



Scheme 2. Reagents and conditions: (a) SmI_2, THF, 0 °C, 20 min, 91%; (b) LAH, Et_2O, reflux, 90%.

conditions are very mild, taking place at room temperature under catalytic conditions and allow for a wide variety of substitutions on the indole core.

Work is currently underway in our laboratory to develop an asymmetric version of this reaction.

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9. *General procedure for the palladium-catalyzed allylic alkylation*: To a stirred solution of indole-2-hydroxamate[10] (1.0 equiv) and 2-butene-1,4-di-*tert*-butyldicarbonate (1.5 equiv) in DCM or DCE (0.1 M) was added a pre-stirred solution of $Pd_2(dba)_3CHCl_3$ (0.05 equiv) and $P(OiPr)_3$ (0.3 equiv) in DCM or DCE. The reaction was stirred at room temperature until completion as determined by HPLC. The crude reaction mixture was then concentrated and purified by silica gel chromatography.
10. The indole-2-hydroxamates were prepared according to a modified version of Gissot, A.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 6925. To a stirred mixture of ethyl-5-chloroindole-2-carboxylate (1.0 equiv) and O-*t*-butylhydroxylamine hydrochloride (1.2 equiv) in THF (0.2 M) at −78 °C was added dropwise LiHMDS 1 M THF solution (5 equiv). The solution was stirred at −20 °C for 1 h. Work-up followed by trituration in 10% ether/hexanes afforded the product in 95% yield. In some cases the hydroxamates were synthesised using indole-2-carboxylic acid and hydroxlamines via standard peptidic coupling.