Pd-Catalyzed Cyclization of 1-Allyl-2-indolecarboxamides by Intramolecular Amidation of Unactivated Ethylenic Bond

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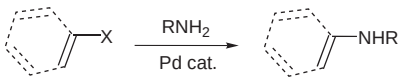
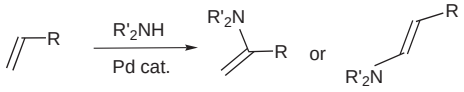
Abstract: The intramolecular Pd(II)-mediated cyclization of 1-allyl-2-indolecarboxamides leads to pyrazino[1,2-*a*]indoles through the conversion of the olefinic C–H bond into a C–N bond by reaction with an amide group. When operating on the allylamide, a domino process was observed with a double C–H functionalization.

Key words: cyclizations, fused-ring systems, indoles, palladium, domino reactions

In recent years there has been increasing interest in palladium-catalyzed C–N bond-forming reactions. As well documented, the Buchwald–Hartwig amination reaction (Equation 1) has had a considerable impact in organic synthesis, despite the need for aryl and vinyl halides as starting substrates.[1] A more versatile methodology, avoiding halogenated compounds, consists of the direct interaction of a nitrogen atom with simple olefins through an oxidative palladium(II)-catalyzed process (Equation 2).[2]



Equation 1

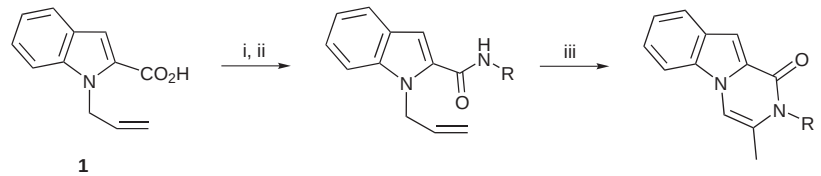


Equation 2

Both protocols have also become important in the functionalization and synthesis of heterocyclic compounds,[3] where in particular the elaboration of the indolyl nucleus has received significant attention.[4] Indole is a versatile and useful tool for the synthesis of a wide range of biologically important molecules, such as alkaloids and natural peptides where the indole nucleus constitutes the core of complex structures.[5]

One research interest in our group concerns the development of Pd-catalyzed processes for the synthesis of indolo-fused polycyclic systems.[6] We have previously described the synthesis of pyrazino[1,2-*a*]indoles by an intramolecular amination reaction employing 1-unsubstituted 2-indolecarboxylic acid allyl-amides.[6c] These synthetically current structures[7] constitute a class of biologically active compounds as serotonin antagonists,[8] protein kinase C inhibitors,[9] DHFR inhibitors,[10] thrombolytics,[11] antileishmanials,[12] GGTase I inhibitors[13] and 5-HT_2 agonists.[14] Here, we report an alternative synthetic approach to the same targets using N-monosubstituted 1-allyl-2-indolecarboxamides and exploiting a Pd(II)-catalyzed intramolecular oxidative process which involves the formation of a C–N bond between the allylic group and the amidic nitrogen atom.

The title amides were easily prepared by converting 1-allyl-2-indolecarboxylic acid (**1**)[15] into the corresponding acyl chloride and subsequent reaction with the amines depicted in Scheme 1.



a: R = phenyl
b: R = 4-methyl-phenyl
c: R = 4-methoxy-phenyl
d: R = 4-nitro-phenyl
e: R = cyclohexyl
f: R = (ethoxycarbonyl)methyl
g: R = benzyl
h: R = (2-furyl)methyl

Scheme 1 Amidation process on 1-allyl-2-indolecarboxamides **2a**–**h**. *Reagents and conditions*: i) $SOCl_2$, toluene, reflux, 4 h; ii) RNH_2, TEA, CH_2Cl_2, r.t., 2 h; iii) $Pd(OAc)_2$ (5 mol%), Na_2CO_3, $Bu_4N^+Cl^-$, 1,4-benzoquinone, DMF, 100 °C, 24 h.

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To realize the Pd-catalyzed intramolecular C–N bond formation, a series of experiments was first screened on the anilide **2a** (Table 1). The best results were observed using 5 mol% of $Pd(OAc)_2$ in the presence of Na_2CO_3, Bu_4NCl and 1,4-benzoquinone (BQ), in DMF as solvent at 100 °C for 24 hours (entry b) which gave the total conversion of the starting amide and the isolation of the pyrazino[1,2-*a*]indole **3a** in 78% yield.[16]

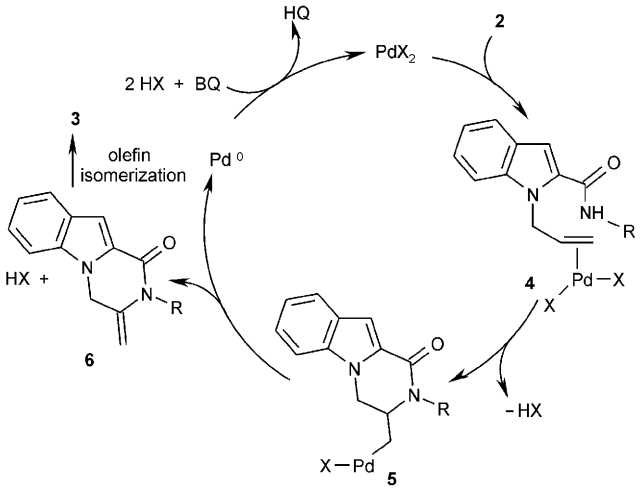
Table 1 Reaction Conditions for Cyclization of **2a**[a]

Entry	Catalyst[b]	Solvent	Base[c]	Oxidant[d]	Yield (%)
a	$Pd(OAc)_2/PPh_3$	DMF	Na_2CO_3	BQ	5
b	$Pd(OAc)_2$	DMF	Na_2CO_3[e]	BQ	78
c	$Pd(OAc)_2$	THF–DMF	*t*-BuOK[e]	BQ	[f]
d	$Pd(OAc)_2$	DMF	Na_2CO_3[e]	MnO_2	69
e	$PdCl_2(CH_3CN)_2$	MeCN		BQ	–
f	$PdCl_2(CH_3CN)_2$	DMF	Na_2CO_3[e]	BQ	28
g	$Pd(OAc)_2$	THF		$CuCl_2$	–
h	$Pd(OCOCF_3)_2$	DMF	Na_2CO_3[e]	BQ	23

[a] Heating at reflux for entries e, g and at 100 °C for other entries for 24 h.
[b] 5 mol%.
[c] 3 Equiv.
[d] 1 Equiv.
[e] In the presence of Bu_4NCl (1 equiv).
[f] Only double-bond isomerization was observed.

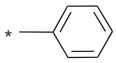
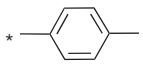
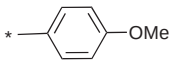
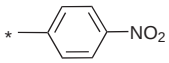
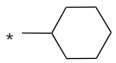
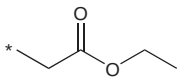
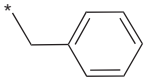
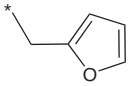
The following facts were established: i) the presence of a base and tetrabutylammonium chloride were essential for the cyclization reaction; the chloride anion plausibly acts as a stabilizing agent in absence of phosphine ligand in the reaction mixture and the cationic portion might act as accelerating agent;[17] ii) the process required the stoichiometric amount of an oxidant in order to achieve reoxidation of the Pd(0) species to Pd(II). The latter evidence demonstrates the need for a Pd(II) species in the catalytic cycle and suggests the following mechanistic sequence. The first formed electrophilic π-olefin palladium(II) complex **4** is able to sustain the intramolecular nucleophilic attack by the deprotonated nitrogen atom of the tethered amide group to afford the σ-complex **5** (Scheme 2). The subsequent β-hydride elimination generates the primary exomethylenic cyclization product **6**, which undergoes an inside double bond migration to give **3a**. This final step produces Pd(0), justifying the need of its reoxidation to Pd(II) to regenerate the catalytic cycle.

In the light of the result obtained with the anilide **2a**, the same amidation reaction was carried out on the substrates **2b**–**h**. Conversions and yields are collected in Table 2. While the behavior of the arylamides **2b**–**d** was analogous to that of **2a**, the alkyl and (hetero)benzylic ones were more reluctant towards the intramolecular C–N bond formation, probably due to the lower NH acidity, and large amounts of starting material remained. Other catalysts and



Scheme 2 Catalytic cycle for amidation process.

Table 2 Conversion and Cyclization Yields of the Carboxamides **2** into the Pyrazino[1,2-*a*]indoles **3**

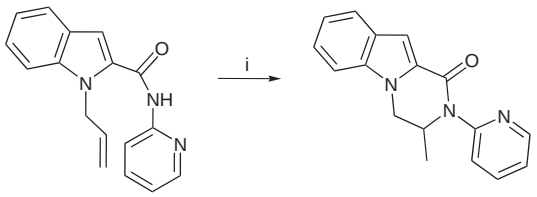
Entry	R	Conversion of **2** (%)[a]	Yield of **3** (%)[b]
a		100	78
b		90	83
c		100	77
d		100	75
e		37	28
f		67	55
g		41	36
h		60	26

[a] Conversion determined by ^1H NMR on the crude reaction mixture.
[b] Yield calculated after chromatography on silica gel column.

bases were tried out to improve the cyclization process of **2e**–**h**. Unfortunately, no better results were attained neither in presence of $Pd(O_2CCF_3)_2$ or $PdCl_2(CH_3CN)_2$ as catalysts nor by using NaH or *t*-BuONa as base. In the latter case, only double bond isomerization was observed.

When the protocol was applied to 1-allyl-2-indolecarboxamides **7** and **9**, bearing a pyridyl or allyl group, respectively, a different behavior was observed.

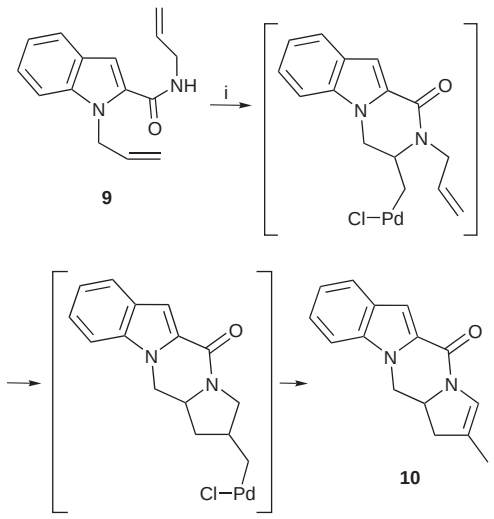
Refluxing the pyridylamide **7** for 48 hours afforded a complex mixture from which only the hydroamidation product **8**[18] was isolated (22% yield) and characterized (Scheme 3). The mechanism path is undefined, even though interference of the pyridyl nitrogen in the Pd elimination from the σ-complex intermediate may be envisaged.



7 **8**

Scheme 3 Hydroamidation of 1-allyl-2-indolecarboxamide **7**. *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), Na_2CO_3, $Bu_4N^+Cl^-$, 1,4-benzoquinone, DMF, 100 °C, 48 h.

Under the standard conditions, only unreacted starting material was recovered on treating allylamide **9**.[19] A search for new reaction conditions to obtain the cyclization path led to an intriguing tetracyclic indole derivative **10**[20] in 28% yield instead of the typical amidation product, as depicted in Scheme 4. Gratifyingly, treatment of **9** with 10 mol% of $PdCl_2(CH_3CN)_2$ as catalyst, a stoichiometric amount of 1,4-benzoquinone in DMF–THF as solvent at 80 °C for 2 hours resulted in a cascade process involving in sequence the intramolecular C–N and C–C bond formations. The Pd-promoted domino process provides for a double C–H functionalization with an oxidative coupling triggered afterwards to the initial amidation step. Longer reaction times led to decomposition of the product.



9 **10**

Scheme 4 Domino process on 1-allyl-2-indolecarboxamide **9**. *Reagents and conditions*: i) $PdCl_2(CH_3CN)_2$ (10 mol%), 1,4-benzoquinone, DMF–THF (1:2), 80 °C, 2 h.

In conclusion, we have developed an alternative synthesis of pyrazino[1,2-*a*]indoles by using the easily accessible 1-allyl-2-indolecarboxamides via intramolecular Pd(II)-catalyzed C–H functionalization. Such a feature is remarkable because C–N bond formation by the way of an amide group is still rare,[21] mostly requiring a powerful electron-withdrawing group (e.g. sulphonyl) on the nitrogen.[22] In the case of the substrate bearing two allylic groups, a domino process was observed with generation of a tetracyclic product. Further studies on the extension of this cascade process are currently underway.

Acknowledgment

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(15) Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418.
(16) **Experimental Procedure.**
A suspension of **2a** (276 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), Na_2CO_3 (318 mg, 3.0 mmol), Bu_4NCl (278 mg, 1.0 mmol) and *p*-benzoquinone (108 mg, 1 mmol) in DMF (10 mL) was stirred for 24 h at 100 °C. The solution was washed with brine (25 mL) and extracted with Et_2O (2 × 25 mL). The organic layer was dried over Na_2SO_4 and taken to dryness under reduced pressure. The residue was chromatographed on a silica gel column with light PE–EtOAc 12:1 as eluent to give **3a**.
Data for 3-Methyl-2-phenyl-2*H*-pyrazino[1,2-*a*]indol-1-one (3a).
Mp 249–250 °C (diisopropyl ether). IR (nujol): 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.95 (3 H, s), 7.24 (1 H, s), 7.29–7.34 (3 H, m), 7.39–7.45 (2 H, m), 7.48–7.56 (3 H, m), 7.68 (1 H, d, *J* = 8.2 Hz), 7.85 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (q), 103.5 (d), 104.1 (d), 110.8 (d), 122.6 (d), 123.0 (s), 123.1 (d), 124.3 (d), 127.4 (s), 128.0 (s), 129.1 (d), 129.4 (d), 129.9 (d), 132.3 (s), 137.9 (s), 158.4 (s). MS: *m/z* = 274 [M^+]. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.97; H, 4.99; N, 10.32.
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(18) **3-Methyl-2-(pyridin-2-yl)-3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-one (8).**
Mp 198–199 °C (diisopropyl ether). IR (nujol): 1678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (3 H, d, *J* = 6.7 Hz), 4.32 (1 H, d, *J* = 12.0 Hz), 4.44 (1 H, dd, *J* = 4.0, 12.0 Hz), 5.43–5.51 (1 H, m), 7.13 (1 H, dd, *J* = 5.0, 7.0 Hz), 7.18–7.24 (1 H, m), 7.34–7.44 (2 H, m), 7.45 (1 H, s), 7.71–7.80 (2 H, m), 8.17 (1 H, d, *J* = 8.4 Hz), 8.47 (1 H, d, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (q), 46.4 (t), 51.5 (d), 107.9 (d), 110.1 (d), 120.1 (d), 120.7 (d), 121.2 (d), 123.2 (d), 125.3 (d), 128.0 (s), 129.2 (s), 137.3 (s), 137.7 (d), 148.1 (d), 152.9 (s), 159.7 (s). MS: *m/z* = 277 [M^+]. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.51; H, 5.27; N, 15.01.
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(20) **2-Methyl-12,12a-dihydro-1*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*a*]indol-5-one (10).**
Oil. IR (nujol): 1657 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 1.83 (3 H, s), 2.59–2.69 (1 H, m), 2.78 (1 H, dd, *J* = 9.2, 15.9 Hz), 3.97 (1 H, dd, *J* = 12.1, 12.2 Hz), 4.52–4.65 (1 H, m), 4.92 (1 H, dd, *J* = 4.4, 12.1 Hz), 6.80 (1 H, s), 7.08 (1 H, s), 7.12 (1 H, dd, *J* = 7.7, 8.3 Hz), 7.31 (1 H, dd, *J* = 7.7, 8.0 Hz), 7.57 (1 H, d, *J* = 8.3 Hz), 7.67 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO): δ = 14.4 (q), 38.8 (t), 45.9 (t), 57.5 (d), 106.6 (d), 109.9 (d), 116.6 (d), 121.1 (d), 122.6 (s), 123.2 (d), 125.0 (d), 128.0 (s), 129.6 (s), 136.8 (s), 169.7 (s). MS: *m/z* 238 [M^+]. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.79; H, 6.01; N, 11.92.
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