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Synthesis of Isoquinolines and Pyridines *via* Palladium-Catalysed Iminoannulation of Allenes

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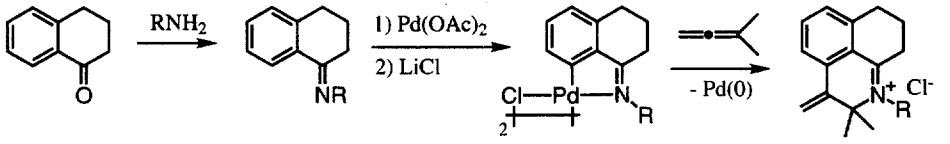
Abstract: Various isoquinolines and pyridines were prepared from aryl- and vinyl halides by a method which involves insertion of an allene into the Pd-C bond and intramolecular nucleophilic attack of the imine.

The use of (π-allyl)palladium complexes as synthetic intermediates is primarily due to their ease of generation by a variety of methods and their accommodation of a wide range of reaction partners (soft and hard carbanions, heteroatom nucleophiles, organotins, carbon monoxide, etc.) to create C-C and carbon-heteroatom bonds in a highly stereo- and regioselective way.[1] The versatility of allenes as substrates in palladium-catalysed processes is demonstrated by the great number of recent publications covering intramolecular[2-4] and intermolecular cyclisations.[5-8] We are interested in the formation of N-heterocycles by iminoannulation of allenes (1,2-dienes). Recently we published results of the formation of N-heterocycles from cyclopalladated α-tetralone ketimines and 1,1-dimethylallene by using stoichiometric palladium, summarised in Scheme 1.[9]



Scheme 1

A recent paper by Larock *et al.*[10] on a palladium-catalysed iminoannulation with internal alkynes to give 3,4-disubstituted pyridines prompted us to disclose our results on the related iminoannulation with allenes.

Since our Pd(II)-mediated reaction in Scheme 1 cannot be made catalytic, due to the difficulty in reoxidising the Pd(0) formed, we turned our attention to a Pd(0)-catalysed version with *ortho*-halide-substituted aryl imines. We first reacted the benzylimine of *o*-iodoacetophenone (**1**) with 1,1-dimethylallene in the presence of 5 mol% of $Pd(OAc)_2$ and 10 mol% of PPh_3 in acetonitrile at 100 °C to produce iminium salt **2** quantitatively (Scheme 2).

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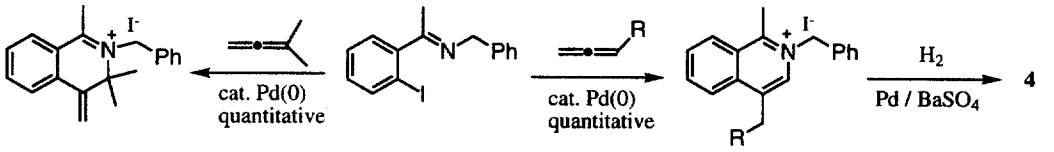
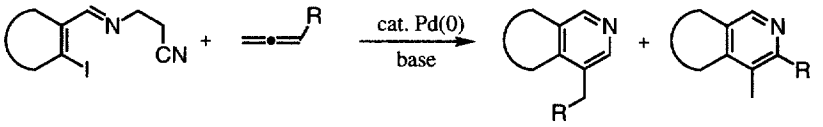


Scheme 2

Iminium salt **2** is formed by attack of the nitrogen on the dimethyl-substituted end of the allene preventing formation of an aromatic system. We therefore turned our attention to mono-substituted allenes. Reaction of imine **1** with several mono-substituted allenes[11] in the presence of 5 mol% of $Pd(OAc)_2$ and 10 mol% of PPh_3 in acetonitrile at 100 °C produced isoquinolinium salts **3** quantitatively (Scheme 2). Hydrogenolysis of the *N*-benzyl group with a catalytic amount of Pd/C or $Pd/BaSO_4$ [12] gave isoquinolines **4** in only very moderate yields (Table 1, entries 1-3). We consequently tried other removable substituents on the imine nitrogen.

With reaction of *N-tert*-butyl imine **5** with $Pd(OAc)_2$ and PPh_3 in the presence of Na_2CO_3 as base, which had also been used by Larock,[10] we obtained the new 4-substituted isoquinolines **6** in moderate to good yields (Table 1, entries 4-6). With vinylic *N-tert*-butyl imines **7**[13,14] (Table 1, entry 7), the pyridinium salt was formed quantitatively, but the *tert*-butyl group was difficult to remove, and only a low yield of the neutral pyridine **8** was obtained.

We now report an easily, by β-elimination removable *N*-substituent, based upon condensation of various aldehydes with 3-aminopropionitrile.[15] The reaction of these imines with 1.5 equiv of a mono-substituted allene in the presence of 5 mol % $Pd(dba)_2$, 5 mol % dppp and 1 equiv of Na_2CO_3 afforded the desired *N*-heterocycles in good to excellent yields[16] (Scheme 3 and Table 1, entries 8-13).



Scheme 3

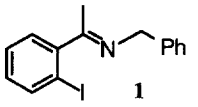
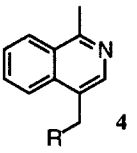
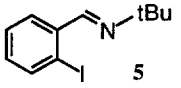
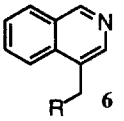
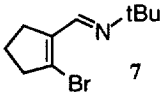
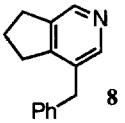
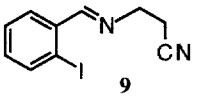
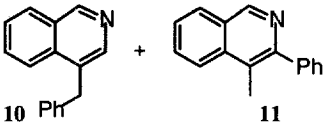
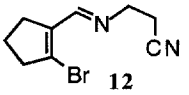
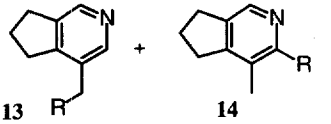
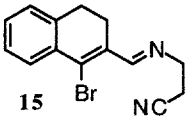
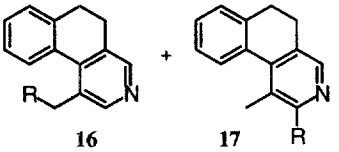
The catalyst is formed *in situ* from $Pd(dba)_2$ and dppp. Initial attempts with 5 mol % $Pd(OAc)_2$ and 10 mol % PPh_3 were less selective for the desired heterocycles. Phosphorus ligands are known to increase the electrophilic nature of π-allylpalladium complexes.[1] Furthermore, the use of bidentate ligands facilitates the formation of cationic π-allylpalladium species which are more electrophilic than neutral complexes and therefore highly reactive toward nucleophiles.[1]

After oxidative addition of the carbon-halogen bond to the palladium, the reaction most likely proceeds *via* a π-allylpalladium intermediate which, after intramolecular nucleophilic attack of the imine onto the allyl carbon, forms a heterocyclic product bearing an exocyclic double bond. This latter product undergoes a 1,3-H shift to form an isoquinolinium salt which loses its *N*-substituent by β-elimination (entries 4-13) or a Pd-catalysed debenzylation (entries 1-3).

The regioselectivity of this annulation is high. In most cases using mono-substituted allenes, only one regioisomer was observed. Formation of 6-membered rings primarily occurred at the less substituted allyl terminus (entries 1-7, 9-10 and 13), although exceptions were found as well (entries 8, 11-12, 14). Probably, steric effects play an important role in the regioselectivity, e.g. the *tert*-butyl substituted imines

lead exclusively to attack at the less substituted end, whereas the 3-aminopropionitrile imines show lower or no regioselectivity, especially in reaction with less bulky allenes (e.g. 1,2-heptadiene, entries 11-12).

Table 1. Synthesis of Nitrogen Heterocycles by the Pd-Catalysed Annulation of Allenes

entry	imine	R	product	% yield[a] (ratio isomers)
	 **1**		 **4**	
1		Cy		10
2		Ph		18
3		nBu		55
4	 **5**	Cy	 **6**	58
5		Ph		80
6		nBu		40
7	 **7**	Ph	 **8**	10
8	 **9**	Ph	 **10** **11**	60 (50 : 50)
9	 **12**	Ph	 **13** **14**	**13**: 76
10		Cy	**13**	83
11		nBu	**13** + **14**	59 [b] (60 : 40)
12	 **15**	nBu	 **16** **17**	85 [b] (50 : 50)
13		Cy		**16**: 70
14		Ph		40 (50 : 50)

[a] Isolated yield. [b] Isolated as an inseparable mixture of isomers.

In summary, we have shown that 3-aminopropionitrile imines of various aldehydes readily cyclise towards isoquinolines and pyridines using mono-substituted allenes. Further studies into the scope of this iminoannulation method are currently under investigation.

Acknowledgement

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References and Notes

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(14) Gilchrist, T. L.; Healy, M. A. M. *Tetrahedron* **1993**, 49, 2543-56.
(15) Horváth, A. *Synthesis* **1995**, 1183-89.
(16) Representative procedure for the annulation of 3-aminopropionitrile aldimines **9**, **12** and **15**:
To a 15 mL sealed tube, flushed with nitrogen, was added palladium bis(dibenzylideneacetone), $Pd(dba)_2$ (0.025 mmol; 5 mol %), diphenylphosphinopropane, dppp (0.025 mmol; 5 mol %), the aryl- or vinylimine (0.50 mmol), the corresponding 1,2-diene (0.75 mmol; 1.5 equiv.), sodium carbonate (0.50 mmol; 1.0 equiv.) and acetonitrile (5 mL). After heating at 100 °C for 16 hours, the reaction was diluted with 30 mL of diethyl ether and washed with 40 mL of saturated ammonium chloride. The organic layer was dried ($MgSO_4$), filtered, concentrated and purified via flash chromatography (silica gel, EtOAc/hexanes as eluents).

4, R=Ph: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.13 (AB, J = 7.8 Hz, 1H), 7.90 (AB, J = 7.8 Hz, 1H), 7.62 (AB_2, J = 7.0 Hz, 1H), 7.57 (AB_2, J = 6.8 Hz, 1H), 7.26-7.15 (m, 5H), 4.36 (s, 2H), 2.97 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.2, 124.0, 121.4, 116.3, 111.3, 109.0, 109.8, 109.3, 108.8, 108.0, 107.60, 107.58, 105.5, 17.6, 3.8; MS (EI, 70eV) *m/z* (relative intensity) 213 (M^+, 100), 176 (35), 156 (100); HRMS calculated for $C_{15}H_{19}N$ 213.1517, found 213.1518.