

Palladium-catalysed Cyclisation–Amination of Allenes–Effect of Base on Regioselectivity of Formation of Allylic Amines

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The palladium catalysed cyclisation of aryl iodides onto proximal allenes occurs at the centre carbon atom of the allene forming a five- or six-membered rings and generating a π -allyl intermediate. The regiochemistry of attack of secondary amines on the π -allyl intermediate is sensitive to added inorganic base, steric effects and the nature of the adjacent heteroatom.

As part of continuing studies on the scope of our palladium catalysed cascade cyclisation–anion capture methodology,^{1,2} we have been evaluating the synthetic utility of cyclisation of aryl iodides onto 1,2-dienes with capture by secondary amines (Scheme 1).

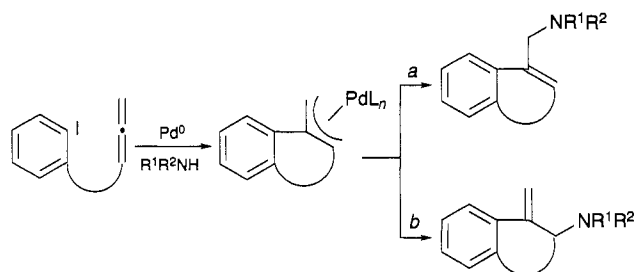
Cyclisation onto 1,2-dienes normally occurs at the centre carbon of the allene moiety,^{2,3} except when such cyclisations involve three- vs. four-membered ring formation.† Cyclisation onto the centre carbon of the allene moiety generates a π -allylpalladium(II) species which offers two possible sites of attack for the secondary amine [Scheme 1, paths (a) and (b)]. We now report on the effect of additives on the regioselectivity of such amination processes.

Cyclisation of **1** (MeCN, 80 °C) using a catalyst system comprising 10 mol% Pd(OAc)₂, 20 mol% PPh₃ and K₂CO₃ (1 mol) in the presence of amine **2** afforded **3** (91%) over 28 h. Repeating the reaction but replacing K₂CO₃ by Ag₂CO₃ (1 mol) afforded **4** (77%) over 6 h. Monitoring (¹H NMR) of the

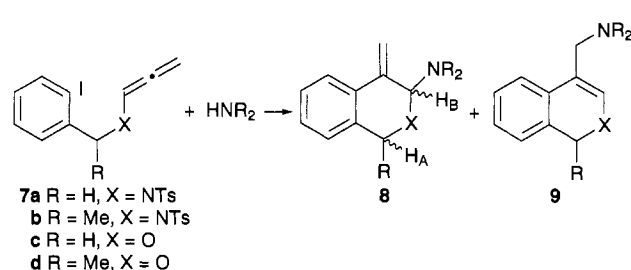
reaction employing K₂CO₃ as base showed that mixtures of **3** and **4** are present initially [time (**3**:**4**): 2 h (2.5:1), 4 h (4:1), 24 h (8:1), 28 h (>10:1); an additional 10 mol% of Pd(OAc)₂ was added after 24 h]. In accord with these results **1** reacts with the same catalyst system and amine **5** using K₂CO₃ as base over 12 h to give only **6** (60%), Scheme 2.

A similar series of reactions were carried out on allenes **7a–d** employing amines **2**, **5**, Et₂NH and piperidine (Scheme 3, Table 1).

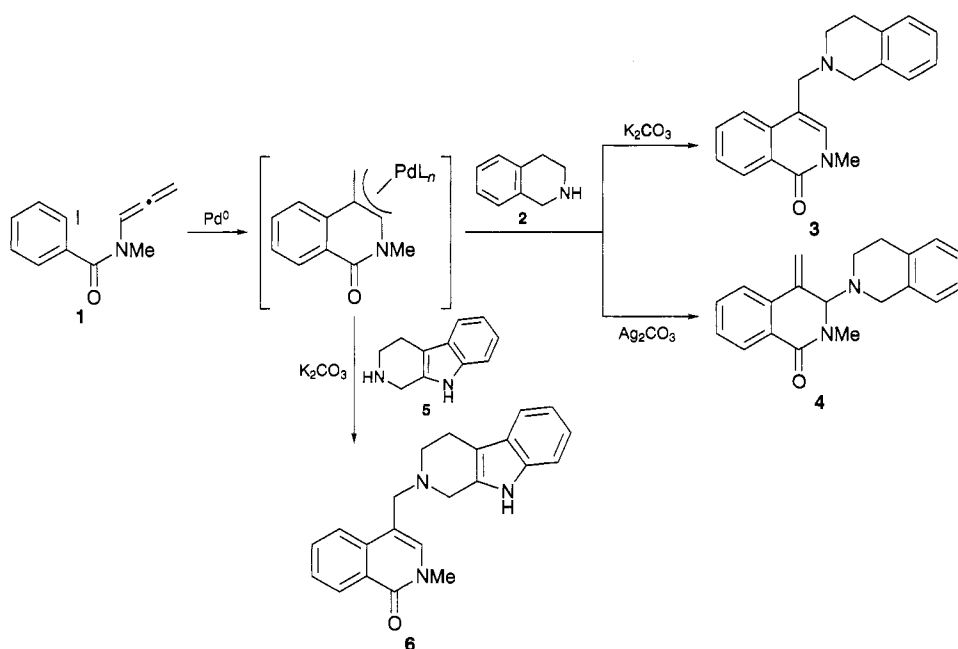
Reaction of **7a** with the same catalyst system using Ag₂CO₃ as base and amine **2** gave a mixture of **8a** and **9a** (NR₂ = tetrahydroisoquinoliny) in which the former was the minor component (Table 1), suggesting that the bulky Ts group was impeding attack at the π -allyl site proximal to the NTs group. Monitoring the reaction (0.5, 1.5 and 4 h) showed the ratio of **8a** to **9a** remained essentially unchanged. Repeating the reaction using K₂CO₃ as base gave **9a** as the sole product. As expected **7b** reacts with **2**, piperidine and Et₂NH using K₂CO₃ as base, to



Scheme 1



Scheme 3



Scheme 2

Table 1 Product distribution from reactions of **7a–d** with secondary amines^a

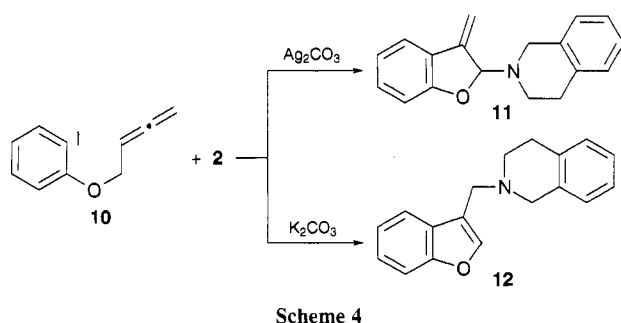
Allene 7	Amine	Base	8:9	Yield (%) ^b
a	2	Ag ₂ CO ₃	1 : 3.8	59
a	2	K ₂ CO ₃	— 100	91
b	2	K ₂ CO ₃	— 100	96
b	piperidine	K ₂ CO ₃	— 100	93
b	Et ₂ NH	K ₂ CO ₃	— 100	88
c	2	K ₂ CO ₃	100 —	36
c	2	Ag ₂ CO ₃	100 —	88
c	piperidine	Ag ₂ CO ₃	100 —	70
d	2	Ag ₂ CO ₃	100 —	78 ^c

^a Conditions: **7** (0.6 mmol), Pd(OAc)₂ (10 mmol%), PPh₃ (20 mmol%) inorganic base (2 equiv.), MeCN (7 ml) and amine (1.3–1.5 equiv.), boiled under reflux for 4 h under N₂. ^b Isolated yield. ^c Reaction time 2 h.

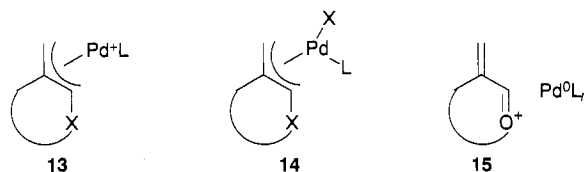
Table 2 Influence of temperature on the diastereoselectivity for the conversion of **7d** to **8d**^a

T/°C	t/h	cis:trans ^{b,c}	Yield (%) ^d
80	2	3:1	78
25	2	8:1	87
0	4	11:1	—

^a Reactant and catalyst ratios as for Table 1. Ag₂CO₃ employed as base in all reactions. ^b Diastereoisomer ratios determined from the ¹H NMR spectra of the reaction mixtures. ^c Note that workup by chromatography on silica affords a 1:1 mixture of diastereoisomers. ^d Isolated yield.



give **9b** (NR₂ = tetrahydroisoquinolyl, piperidinyl or Et₂N) in excellent yield (Table 1). Allene **7c** reacts with **2** or piperidine in the presence of K₂CO₃ or Ag₂CO₃ to give only **8c** (NR₂ = tetrahydroisoquinolyl or piperidinyl) with Ag₂CO₃ producing a substantial increase in yield over K₂CO₃ for **8c** (NR₂ = tetrahydroisoquinolyl). The presence of a methyl substituent in the tether results in the formation of a diastereoisomeric mixture when **7d** is cyclised to **8d** (NR₂ = tetrahydroquinolyl) in good yield (Table 1) using Ag₂CO₃ as base.



The *cis*–*trans* diastereoisomer mixture is, as might be expected, sensitive to the temperature of the reaction (Table 2). NOE data on the major diastereoisomer of **8d** (irradiation of H_A effects a 12% enhancement of the signal for H_B) established the *cis*-stereochemistry.

The regiospecificity of cyclisation of **7c/7d** to **8c/8d** irrespective of the inorganic base contrasts with the behaviour of **10** which reacts (MeCN, 60 °C, 6 h) with **2** in the presence of Ag₂CO₃ to give **11** (83%) whilst when the base is K₂CO₃ (MeCN, 80 °C, 6 h) it gives **12** (71%), Scheme 4.

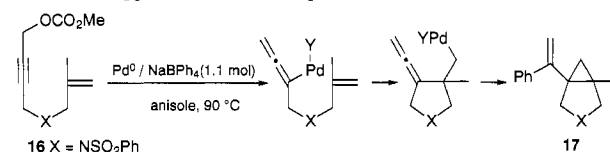
The reactions employing Ag₂CO₃ as base are believed to proceed *via* the cationic complex **13** which promotes nucleophilic attack at the most electron deficient allylic centre adjacent to X and prevents any subsequent rearrangement. Reactions employing K₂CO₃ as base are believed to proceed *via* **14** or the corresponding neutral bridged binuclear complex. In these cases the two allylic termini are less strongly differentiated and rearrangement to the more stable, less sterically hindered, allylic amine can occur. Steric effects can perturb this reactivity pattern (*e.g.* **7a**, Table 1) whilst the anomalous behaviour of **7c/7d** may reflect equilibration of the π-allyl complexes with **15** which undergoes Michael addition of the secondary amines.

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Footnote

† A typical example is the cascade cyclisation-anion capture of **16** to **17** (55%) (R. Grigg and D. Wilson, unpublished work).



References

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