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Synthesis of New N-Heterocycles; Intramolecular Ring Closure with Imines

Jeroen J.H. Diederen, Hans-W. Frühauf*, Henk Hiemstra and Kees Vrieze

Anorganisch Chemisch Laboratorium, Institute of Molecular Chemistry , Universiteit van Amsterdam, Nieuwe Achtergracht 166, NL-1018 WV Amsterdam, The Netherlands

Michel Pfeffer

Laboratoire de Synthèses Métallo-induites, Associé au C. N. R. S., Université Louis Pasteur, 4 Rue Blaise Pascal, F-67070 Strasbourg, France

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Abstract: 1,1-Dimethylallene inserts into the σ Pd-C bond of cyclopalladated α-tetralone ketimines leading to stable new heterocycles after depalladation. Intramolecular attack of an imine on a Pd-allyl complex leads to the formation of iminium salts which may be converted into neutral enamines by base, or amines by hydrogenation with $NaBH_4$. © 1998 Elsevier Science Ltd. All rights reserved.

Various efforts have been made to synthesise cyclic structures in clean and efficient ways.[1] The ability of transition-metal catalysts to exercise control in bond-forming reactions under very mild conditions makes them excellent candidates to facilitate ring formation. π-Allylpalladium chemistry[2-12] has been developed as a powerful tool in organic synthesis by several groups and reviews have appeared by Trost, Tsuji, Oppolzer and Bäckvall on these cyclisation methods. Ring closure with nitrogen nucleophiles on a Pd-allyl moiety has been achieved with amines,[13-17] amides[18,19] and oxims.[20,21] Trost reported a general Pd-catalysed cyclisation of imines with (trimethylsilyl)allylesters to synthesise pyrrolidine-type products. Larock published an elegant general method for regioselective hetero- and carboannulation of 1,2-dienes using functionally substituted aryl halides.[13]

Recently Chengebroyen *et al.* showed that ring closure with pyridine nucleophiles leads to the regioselective formation of new stable pyridinium containing heterocycles.[22] Schiff base ligands have long been known to lead to a large variety of cyclopalladated derivatives whose structural data are closely related to the pyridine derivatives. We wish to report that insertion of 1,1-dimethylallene into the σ Pd-C bond of cyclopalladated α-tetralone ketimines leads indeed to ring closure using imines as nucleophiles with a high degree of regioselectivity. An advantage of imines is the opportunity to form neutral heterocycles by transforming the iminium function into an enamine by using an appropriate base.

α-Tetralone ketimines **a-e** are readily prepared by condensation of α-tetralone with amines. These imines, can be readily cyclopalladated.[23] Cyclopalladation of the N-benzyl tetralone ketimine **e** could in principle also occur at the phenyl ring of the benzyl substituent, but exclusively **1e** is found. Insertion of allenes into σ Pd-C bonds leading to a Pd-allyl complex has been extensively studied by us,[24] and other groups.[25,26] We wanted to study the ability of imines to be effective nucleophiles in ring closure reactions involving cyclopalladated α-tetralone ketimines **1**.

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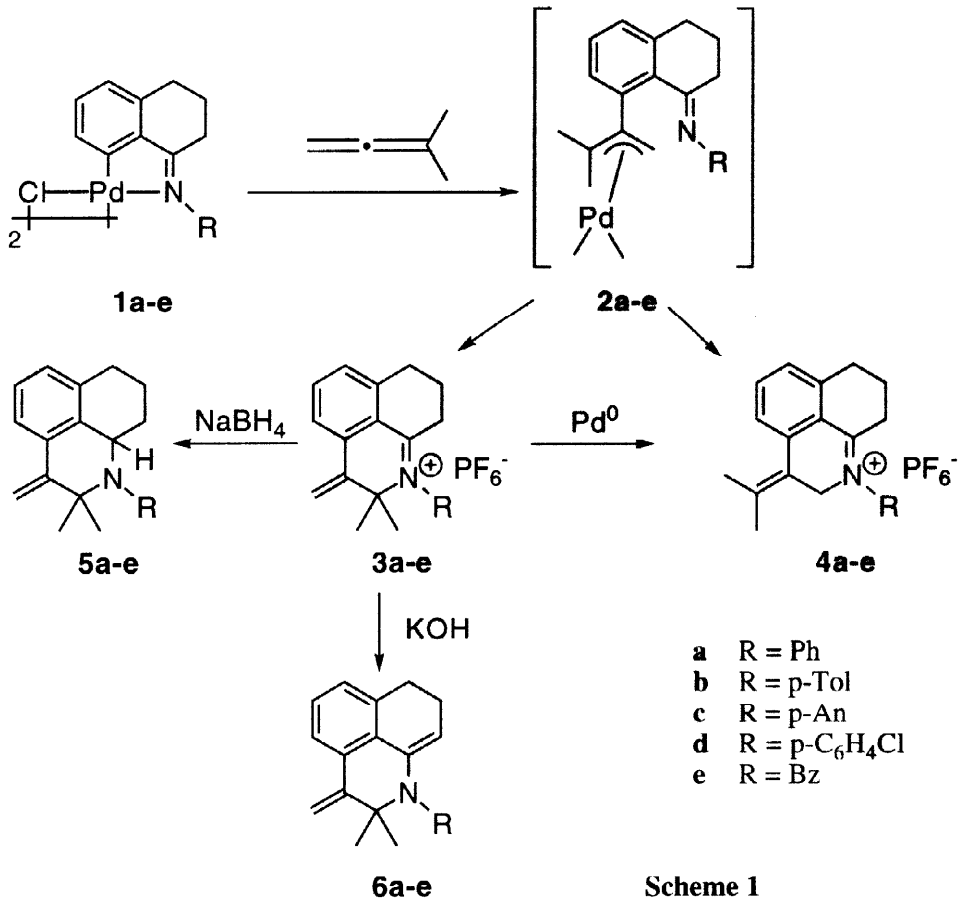
Insertion of 1,1-dimethylallene (DMA) into the σ Pd-C bond of **1** probably leads to the formation of a Pd-allyl intermediate **2** with a very remarkable red-purple colour. We are unable to give structural data of the latter because of its instability and the complex mixture of products formed. Nucleophilic attack of the sp^2 nitrogen atom on the allyl leads to the regioselective formation of novel heterocycles. These iminium salts can be converted to the corresponding enamines by using KOH as a base, or to the amines by a selective hydrogenation of the iminium group with $NaBH_4$. The reactions are summarised in Scheme 1.



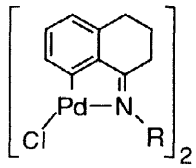
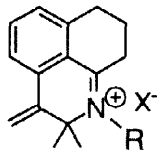
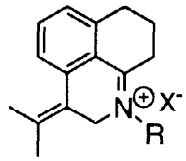
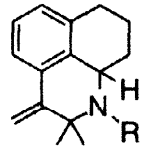
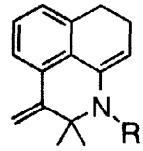
Scheme 1

The cyclopalladated complexes **1a-e** were prepared according to a procedure similar to that of Selvakumar.[23] In general the cyclopalladated derivatives were suspended in dichloromethane and DMA (2.5 equiv) was added to the mixture. The reaction mixtures were stirred at room temperature for 1 day under exclusion of air. The yellow suspension gradually turned into a homogeneous red-purple coloured solution. At this stage the insertion reaction is complete. ^{1}H-NMR analysis of the crude product showed the presence of a Pd-allyl complex **2** and chemical shifts are in accordance with the literature.[22,27] Ring closure towards **3** was achieved by refluxing the reaction mixture in methanol for 15 minutes. Anion exchange with KPF_6 gives the heterocyclic yellow salts in reasonable yields. Refluxing **2** for short times in MeOH without the presence of a Pd^0-source shows a high degree of preference for the kinetic product **3**. Refluxing **3b** in the presence of a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) in MeOH for 18 hours led to complete isomerisation towards the thermodynamically more favoured **4b**.

Reaction of iminium salts **3** with KOH (8 equiv) in MeOH and molecular sieves (4Å) gave after extraction with pentane the neutral enamines **6** as yellow oils in good yields. Products **3** were converted into

the amines by reaction with $NaBH_4$ (3 equiv) in MeOH followed by chromatography over silica gel (9 hexanes/1 ethyl acetate). The results are summarised in Table **1**.

Table 1: Precursors and Heterocyclic Products

entry	Reactants	Yield (**3**+**4**) (%) [a]	Ratio **3**/**4** [b]	Yield (%) [c]	Yield (%) [c]
					
	1	**3**	**4**	**5**	**6**
a	$R = C_6H_5$	60	100/0	74	87
b	$R = p\text{-}CH_3\text{-}C_6H_4$	81	93/7	83	80
c	$R = p\text{-}OCH_3\text{-}C_6H_4$	51	100/0	80	92
d	$R = p\text{-}Cl\text{-}C_6H_4$	79	46/54	60	67
e	$R = CH_2\text{-}C_6H_5$	86	91/9	94	84

a) isolated yield from **1**; $X=PF_6$ b) based upon ^{1}H-NMR data of the mixture c) isolated yield from **3**

The structures of the heterocyclic salts could be unambiguously determined by means of several 2D-NMR techniques (e.g. HH-COSY, NOESY, CH-COSY) and ^{13}C-APT. [28]

From Table **1** it can be seen that nucleophilic attack of the imine nitrogen atom predominantly takes place at the most substituted terminal carbon atom of the allyl group. In general nucleophilic attack of nitrogen nucleophiles (amines, amides) takes place at the sterically least hindered position. Obviously an electronic effect of the two donating methyl groups on the allyl direct the formation of the kinetic product **3**. Two methyl groups can stabilise a positive charge on a Pd-allyl carbon atom.[29] A recent study showed that electron donating substituents on the Pd-allyl terminus make this carbon atom more electron-deficient as seen by ^{13}C-NMR resonances and thus more prone to nucleophilic attack.[30] Only with a suitable Pd^0-source (e.g. $Pd(PPh_3)_4$) and high temperature is isomerisation possible to the thermodynamically more favoured regioisomer **4**.

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References and Notes

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28. ^{1}H-NMR (300 MHz, $CDCl_3$) of **3b**: δ 7.73 (1H, dd, J= 7.5/7.7 Hz), 7.56 (1H, d, J= 7.5 Hz), 7.43 (2H, d, J= 8.2 Hz), 7.40 (1H, d, J= 7.7 Hz), 7.24 (2H, d, J= 8.2 Hz), 5.79 (1H, s), 5.64 (1H, s), 3.01 (2H, t, J= 6.2 Hz), 2.71 (2H, t, J= 6.4 Hz), 2.44 (3H, s), 1.92 (2H, m, J= 6.2/6.4 Hz), 1.51 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178, 147, 142, 141, 138, 136, 134, 131, 130, 125, 123, 121, 117, 67, 33, 28, 25, 21.3, 21.0 Anal. Calcd for $C_{22}H_{24}NPF_6$: C, 59.06; H, 5.41; N, 3.13. Found: C, 57.96; H, 5.35; N, 3.17
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