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Asymmetric synthesis of optically active 2-vinylpyrrolidines and 2-vinylpiperidines by palladium-catalysed cyclisation of amino allylic carbonates

Beata Olszewska, Bogusław Kryczka, Anna Zawisza *

Department of Organic and Applied Chemistry, University of Łódź, Tamka 12, 91-403 Łódź, Poland

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ABSTRACT

Optically active 2-vinylpyrrolidines and 2-vinylpiperidines were synthesised from the corresponding amino allylic carbonates via palladium-catalysed cyclisation. The use of chiral ligands gave the corresponding pyrrolidine and piperidine derivatives having er values from low to moderate.

Saturated nitrogen heterocycles, such as pyrrolidines, piperidines and isoxazolidines, appear as subunits in a broad array of biologically active and medicinally significant molecules.[1] For these reasons, the synthesis of these compounds has been of long-standing interest. Many classical approaches to their construction involve the use of C–N bond-forming reactions such as reductive amination, nucleophilic substitution or dipolar cycloaddition.[2] Although these methods have proved to be quite useful, their substrate scope and functional group tolerance are often limited. In recent years, several powerful new transformations have been developed that involve the use of palladium-catalysed C–N bond-forming reactions for construction of heterocyclic rings.[3]

These transformations frequently occur under mild conditions, tolerate a broad array of functional groups and proceed with high stereoselectivity.

The synthesis of saturated nitrogen heterocycles via Pd-catalysed and other C–N bond-forming reactions can be broadly classified into four categories: (i) amination reactions of alkenes, alkynes and allenes;[2a,2f,4] (ii) 1,3-dipolar cycloadditions;[5] (iii) carbonylation processes;[6] and (iv) intramolecular addition of nitrogen nucleophiles to intermediate π-allylpalladium complexes.[7] A number of different strategies have been employed for the generation of reactive intermediate π-allylpalladium complexes, such as oxidative addition of alkenyl epoxides,[8] allylic acetates[9] and related electrophiles to Pd^0. An important improvement in π-allylpalladium chemistry was achieved by the introduction of allylic carbonates. Carbonates are highly reactive, and more importantly, their reactions can be carried out under neutral conditions.[10]

Extending our previous work on the use of allyl carbonates in the synthesis of *O*-heterocycles,[11] herein we describe our preliminary results obtained on enantioselective Pd-catalysed allylic aminations.

Experiments were performed with methyl and isobutyl carbonates **5a–c** (Scheme 1) using commercially available ligands (Fig. 1).

Substrates **5a–c** were prepared by reduction of bromoesters **1a**,**b** to the corresponding aldehydes[12] followed by elongation of the chain *via* Wittig reaction,[13] reduction to the alcohol **3a**,**b**,[14] condensation with methyl or isobutyl chloroformate and, finally, substitution of the bromine atom with a 4-methylbenzenesulfonamide group (tosyl group).

The cyclisation was first studied with methyl carbonate **5a** as the substrate.[15] Ring-closure of **5a** occurred slowly (48 h) at room temperature in the presence of a catalytic amount of $Pd_2(dba)_3$ associated with the (*R*,*R*)-Trost ligand, providing 2-vinylpyrrolidine **6a**[15,16] as a 45:55 mixture of enantiomers in 94% overall yield (Table 1, entry 1).

Isobutyl carbonate **5b** was more reactive under the same conditions (Table 1, entry 2) and gave product **6a** with the highest yield (98%) and stereoselectivity (40:60 er) in 24 h. Longer chain isobutyl carbonate **5c** was also submitted to this cyclisation procedure in the presence of the (*R*,*R*)-Trost ligand. Pyrrolidine **6b**[15,17] was

* Corresponding author. Tel.: +48 42 6355764; fax: +48 42 6655162.
E-mail address: azawisza@chemia.uni.lodz.pl (A. Zawisza).

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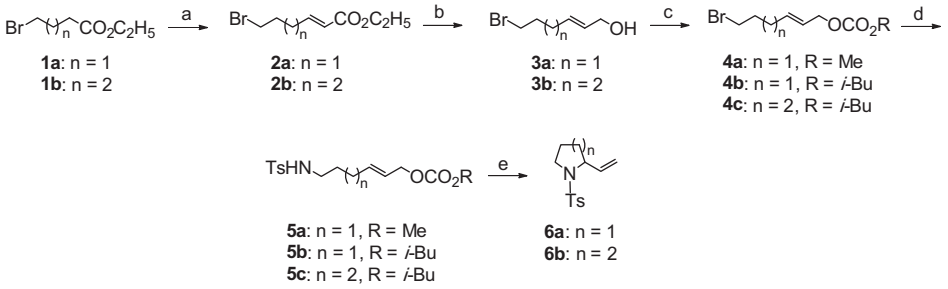

Scheme 1. Pd^0-catalysed synthesis of heterocycles **6a**,**b**; reagents and conditions: (a) 1. DIBAL-H, CH_2Cl_2, −78 °C, 2. $Ph_3P{=}CHO_2C_2H_5$, CH_2Cl_2, rt; (b) DIBAL-H, Et_2O, 0 °C; (c) ROCOCl, C_5H_5N, CH_2Cl_2, 0 °C→rt; (d) TsNHNa, $TsNH_2$, DMSO, 60 °C; (e) [Pd], ligand.

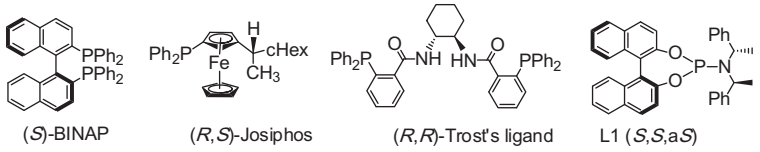

Figure 1. Ligands used in this work.

Table 1
Pd^0-catalysed allylic cyclisation of substrates **5a–c** according to Scheme 1[a]

Entry	Substrate	Ligand	Product	Temp (°C)	Time (h)	Yield (%)[b]	er (%)[c]
1	**5a**	(*R*,*R*)-Trost	**6a**	20	48	94	45:55
2	**5b**	(*R*,*R*)-Trost	**6a**	20	24	98	40:60
3	**5c**	(*R*,*R*)-Trost	**6b**	20	24	99	61:39
4	**5a**	(*S*)-BINAP	**6a**	20	48	97	41:59
5	**5b**	(*S*)-BINAP	**6a**	20	48	97	36:64
6	**5c**	(*S*)-BINAP	**6b**	20	48	45	65:35
7	**5a**	(*R*,*S*)-Josiphos	**6a**	20	96	73	47:53
8	**5a**	(*R*,*S*)-Josiphos	**6a**	60	96	78	46:54
9	**5b**	(*R*,*S*)-Josiphos	**6a**	20	48	87	41:59
10	**5b**	(*R*,*S*)-Josiphos	**6a**	60	48	96	50:50
11	**5c**	(*R*,*S*)-Josiphos	**6b**	20	48	10	66:34
12	**5c**	(*R*,*S*)-Josiphos	**6b**	20	168	82	65:35
13	**5c**	(*R*,*S*)-Josiphos	**6b**	60	72	92	53:47
14	**5a**	L1	**6a**	20	24	0	—
15	**5a**	L1	**6a**	60	24	44	22:78
16	**5b**	L1	**6a**	20	24	99	22:78
17	**5c**	L1	**6b**	20	24	99	90:10

[a] [**5**]:[$Pd_2(dba)_3$]:[ligand] = 40:1:2.2 (4.4), THF.
[b] Yield refers to isolated pure products after column chromatography.
[c] Enantioselectivity (er) was measured by chiral stationary phase HPLC on a chiral IA column (25 cm × 4.6 mm); *i*-propanol/hexane (99:1), flow rate = 0.2 ml min^{-1}, t_R = 23.8 min and t_R = 24.8 min for **6a**; methanol, flow rate = 0.2 ml min^{-1}, t_R = 23.6 min and t_R = 26.4 min for **6b**; the first value corresponds to the enantiomer being eluted first.

obtained in a very good yield (99%) and in a 61:39 ratio (Table 1, entry 3). This Pd^0-catalysed cyclisation was extended to other ligands. Reactions with (*S*)-BINAP required longer reaction times and were characterised by moderate er values of 41:59, 36:64 and 65:35 (**5a**, **5b** and **5c**, respectively), affording quantitative yields of pyrrolidine **6a** (97%) and a moderate yield of piperidine **6b** (45%) (Table 1, entries 4–6). The use of (*R*,*S*)-Josiphos as the chiral ligand and carbonate **5a** afforded **6a** in a good yield of 73% after 96 h but with a very low er value of 47:53 (Table 1, entry 7). Increasing the temperature to 60 °C did not improve the selectivity of the reaction and resulted in only a slight increase in the yield (Table 1, entry 8). Isobutyl carbonate **5b** in the presence of the Josiphos ligand, similar to the results observed in the case of the Trost ligand, gave pyrrolidine **6a** in less time and with a better yield, but with poor enantioselectivity 41:59 (Table 1, entry 9). The same reaction at 60 °C afforded a 1:1 mixture of enantiomers (Table 1, entry 10). Isobutyl carbonate **5c** was less reactive and required a much longer reaction times (Table 1, entries 11–13). Piperidine **6b** was obtained in 10% yield after 48 h and 82% after 168 h as a 65:35 mixture, while at 60 °C, **6b** was obtained in 92% yield after 72 h (53:47 er).

Finally, the asymmetric cyclisation of allylic carbonates **5a–c** was performed in the presence of the phosphorus amidite ligand, L1. The cyclisation of compound **5a** at room temperature did not give the expected product **6a**, but at 60 °C the same reaction afforded a 22:78 mixture of enantiomers in 44% yield after 24 h (Table 1, entries 14–15). The more reactive carbonate **5b**, at room temperature gave quantitatively pyrrolidine **2a** with good selectivity (22:78 er) (Table 1, entry 16). Piperidine **6b** was obtained in 99% yield under the same conditions with an er value of 90:10 starting from allylic carbonate **5c** (Table 1, entry 17).

Table 2 illustrates the influence of the solvent on these intramolecular aminations. The best results were obtained for the reaction carried out in THF. Similar results were observed in toluene.