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Enantioselective synthesis of *N*-heterocycles via intramolecular Pd(0)-catalysed allylic amination

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ABSTRACT

An efficient and stereoselective synthesis of pyrrolidine-, piperidine-, and azepane-type *N*-heterocycles is described by the intramolecular Pd(0)-catalysed cyclisation of amino allylic carbonates. The use of chiral ligands gave the corresponding heterocyclic derivatives having er values that were from moderate to good.

1. Introduction

Nitrogen heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules.[1] For these reasons the efficient stereoselective construction of these molecules, particularly in a catalytic enantioselective manner, has been of long-standing interest. Several powerful new transformations have been developed that involve the use of transition metal-catalysed *C*–*N* bond-forming reactions for the construction of heterocyclic rings. These transformations frequently occur under mild conditions, tolerate a broad array of functional groups and proceed with high stereoselectivity.

Recently, a variety of late transition metal complexes based on Pt[2] and Rh, in which the enantioselective hydroamination of unactivated alkenes with amines has been presented.[3] Futhermore, Ir,[4] Pd,[5] Au,[6] and Cu[7] based catalysts have been reported as catalysts for intramolecular hydroamination.

Intramolecular cyclisation of allenes with tethered amines in the presence of a transition metal catalyst represents a second route for generating nitrogen-containing heterocycles. These transformations have been developed with metal salts or complexes of Zr, Ti,[8] Cu,[9] lanthanides,[10] Pd,[11] Au,[12] Ag,[13] and Hg.[14]

The intramolecular enantioselective amination of allylic alcohols with amines or carbamates has also attracted attention as a route to functionalised nitrogen heterocycles, and methods employing catalysts based on Au,[15] Bi,[16] Pd,[17] Ru,[18] Hg, Sn, Ga, Bi, and Fe[16,19] have been reported.

The groups of Helmchen have reported enantioselective intramolecular amination of allylic acetates and carbonates catalysed by Ir complexes.[20] This method gave 2-vinylpyrrolidine and 2-vinylpiperidine derivatives in good yields and ee values of >90%.

By extending our previous work on the use of allyl carbonates in the synthesis of *O*- and *N*-heterocycles,[21] in this paper we report results on enantioselective intramolecular Pd(0)-catalysed allylic amination.

2. Results and discussion

2.1. Synthesis of the starting materials

The starting allylic carbonates **5a**–**i** were prepared according to Scheme 1.

The reduction of bromoesters **1a**–**c** to the corresponding aldehydes,[22] followed by elongation of the chain via the Wittig reaction[23] afforded unsaturated esters **2a**–**c** in 75, 72, and 70% yields, respectively. Compounds **3a**–**c** were obtained in 85, 98, and 76% yields, respectively, by the reduction of esters **2a**–**c** with DIBAL–H in diethyl ether.[24]

Condensation of these alcohols with methyl or isobutyl chloroformate at 0 °C afforded allylic carbonates **4a**–**e** in 82–96% yield. Finally, substitution of the bromine atom with a 4-methylbenzenesulfonamide group (tosyl group), benzyl group,

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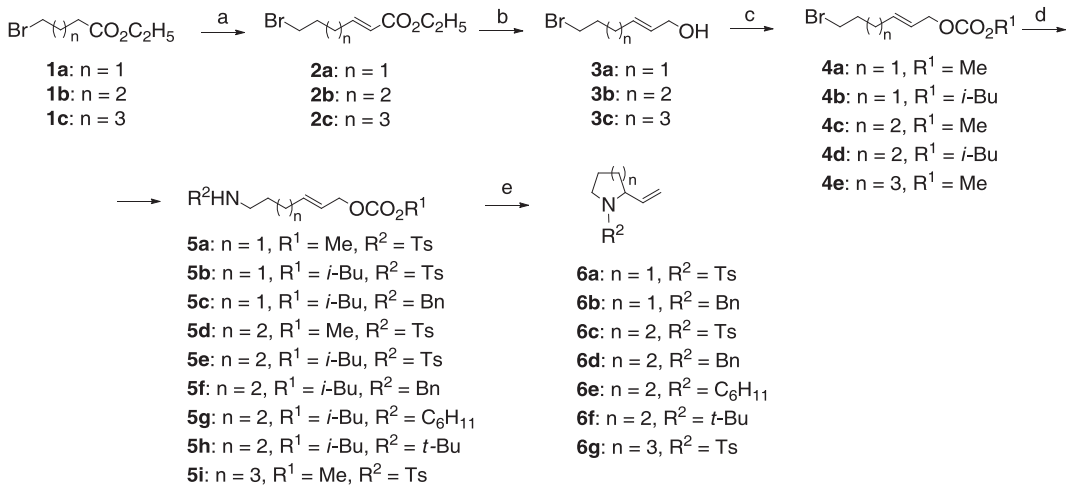

Scheme 1. Pd^0-catalysed synthesis of heterocycles **6a**–**g**. Reagents and conditions: (a) 1. DIBAL–H, CH_2Cl_2, −78 °C, 2. $Ph_3P{=}CHCO_2C_2H_5$, CH_2Cl_2, rt; (b) DIBAL–H, Et_2O, 0 °C; (c) R^1OCOCl, C_5H_5N, CH_2Cl_2, 0 °C→rt; (d) TsNHNa, $TsNH_2$, DMSO, 60 °C or R^2NH_2, *i*-Pr_2EtN, DMF, rt for R^2=Bn, C_6H_{11}, *t*-Bu; (e) $Pd_2(dba)_3$, ligand.

cyclohexyl or *tert*-butyl group gave corresponding amino-carbonates **5a**–**i** (45–85% yield).

2.2. Pd(0)-catalysed cyclisation of allylic carbonates 5a–i

The cyclisation was first studied with methyl carbonate **5a** as the substrate. The ring-closure of **5a** occurred readily in THF at room temperature in the presence of a catalytic amount of $Pd_2(dba)_3$ and PPh_3, which provided exclusively 1-tosyl-2-vinylpyrrolidine **6a**[21b] in 98% yield (Table 1, entry 1). Under the same conditions isobutyl carbonate **5b** quantitatively gave pyrrolidine **6a** (Table 1, entry 2). The cyclisation of *N*-benzyl carbonate **5c** occurred slowly at room temperature and provided 1-benzyl-2-vinylpyrrolidine **6b**[15b,20d,25] in 95% yield (Table 1, entry 3). Longer chain, methyl and isobutyl carbonates **5d** and **5e** were also submitted to this cyclisation procedure, 1-tosyl-2-vinylpiperidine **6c**[21b] was obtained in a very good yield after 30 min in both cases (97 and 98%, respectively, Table 1, entries 4 and 5). The reaction with *N*-benzyl carbonate **5f** required a longer reaction time (48 h) but gave an *N*-benzyl derivative of piperidine **6d**[15b,20d,25] in 98% yield (Table 1, entry 6). The cyclisation of compound **5g** at room temperature did not give the expected product **6e**. The same reaction at 60 °C afforded 1-cyclohexyl-2-vinylpiperidine **6e** in 56% yield after 20 h (Table 1, entries 7 and 8). The formation of *N*-*tert*-butyl-2-vinylpiperidine **6f** was never observed in the cyclisation of allylic carbonate **5h** (Table 1, entries 9 and 10). Finally, we studied the Pd(0)-catalysed cyclisation of allylic carbonate **5i**. Azepane **6g** was obtained in 70% yield after 24 h at 20 °C (Table 1, entry 11).

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

Entry	Substrate	Product	*T* [°C]	Time [h]	Yield[b] [%]
1	**5a**	**6a**	20	0.5	98
2	**5b**	**6a**	20	0.5	99
3	**5c**	**6b**	20	24	95
4	**5d**	**6c**	20	0.5	97
5	**5e**	**6c**	20	0.5	98
6	**5f**	**6d**	20	48	99
7	**5g**	**6e**	20	24	0
8	**5g**	**6e**	60	24	56
9	**5h**	**6f**	20	48	0
10	**5h**	**6f**	60	48	0
11	**5i**	**6g**	20	24	70

[a] [**5**]/[$Pd_2(dba)_3$]/[PPh_3]=40:1:4.4, THF.
[b] Yield refers to isolated pure products after column chromatography.

2.3. Pd(0)-catalysed asymmetric cyclisation

Asymmetric cyclisation was performed only with *N*-tosyl and *N*-benzyl isobutyl carbonates **5b**, **5c**, **5e** and **5f**. The results presented in Table 1 and our previous studies[21b,c] have shown that using isobutyl carbonates as a starting material gave higher reactivities and selectivities in comparison with methyl carbonates. Several types of ligands were selected for testing.

Phosphines were the first class of ligands (Fig. 1) applied to the Pd(0)-catalysed allylic substitutions (Table 2, entries 1–10). Ring-closure of **5b** occurred slowly (48 h) at room temperature in the presence of (*S*)-Binap and provided 1-tosyl-2-vinylpyrrolidine **6a** as a 41:59 mixture of enantiomers in 97% overall yield (Table 2, entry 1). Longer chain isobutyl carbonate **5e** was less reactive under the same conditions and gave piperidine **6c** in 45% yield and in a 65:35 ratio (Table 2, entry 2). Carbonate **5b** in the presence of the Josiphos ligand, similar to the results observed for (*S*)-Binap, gave pyrrolidine **6a** in good yield (87%) and with an enantioselectivity ratio of 41:59 (Table 2, entry 3).

The same reaction at 60 °C afforded a 1:1 mixture of enantiomers (Table 2, entry 4). Isobutyl carbonate **5e** was less reactive and required a much longer reaction time (Table 2, entries 5–7). *N*-Tosyl piperidine **6c** was obtained in 10% yield after 48 h and 82% after 168 h as a 65:35 mixture, while at 60 °C **6c** was obtained in 92% yield after 72 h (53:47 er). The same reaction in the presence of the Walphos–phosphines ligand derived from ferrocene–afforded a 1:1 mixture of enantiomers (Table 2, entry 8). The trifluoromethyl derivative of Walphos was more reactive and gave a product of intramolecular allylic amination **6c** in a higher yield (81%) and was enantioselective (69:31). Asymmetric cyclisation of *N*-tosyl carbonate **5e** was also carried out in the presence of the phosphine-amine ligand PPM. This cyclisation gave piperidine **6c** in 64% yield and a very low er value of 53:47.

Phosphorus amidites were second class of ligands used for the construction of heterocyclic rings (Table 2, entries 11–16). The cyclisation of compounds **5b** at room temperature in the presence of L1(*S*,*S*,a*S*) gave pyrrolidine **6a** (99% yield) with good selectivity (22:78 er) (Table 2, entry 11). Piperidine **6c** was obtained in 99% yield under the same conditions with an er value of 90:10 starting from allyl carbonate **5e** (Table 2, entry 12). Lowering the temperature to 0 °C and −20 °C improved the selectivity of the reaction, and an er of 93:7 and 92:8, respectively (Table 2, entries 13 and 14). We also tried to cyclise **5e** in the presence of phosphorus amidite ligand L2(*R*,*R*,*R*), which is different from the L1(*S*,*S*,a*S*) of 2,5-