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Asymmetric intramolecular Pd(II)-catalysed amidocarbonylation of unsaturated amino alcohols

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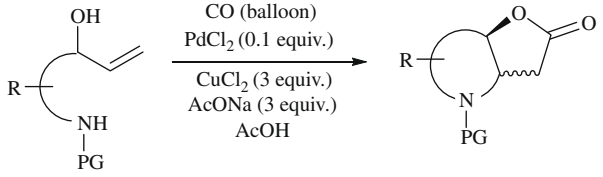
ABSTRACT

The first example of an asymmetric carbonylative bicyclisation of racemic N-protected 1-amino-pent-4-ene-3-ols (±)-**1** catalysed by palladium(II) with chiral bis(oxazoline) ligands was investigated. The kinetic resolution of (±)-**1** in the presence of chiral catalyst, *p*-benzoquinone in acetic acid under carbon monoxide atmosphere afforded enantiomerically enriched derivatives of 2-oxa-6-azabicyclo[3.3.0]octan-3-ones (*R*,*R*)-**2** and (*S*,*S*)-**2**, respectively.

1. Introduction

The intramolecular palladium(II)-catalysed carbonylation of unsaturated polyols is an important transformation of alkenes into bisheterocyclic lactones.[1] Early examples of this domino reaction; Pd(II)-promoted cyclisation—intramolecular amidocarbonylation were described for 3-hydroxypent-4-enyl- and 5-hydroxyhex-6-enylamides providing *cis*- and/or *trans*-fused bicyclic lactones, and involving the pyrrolidine-[2] and/or piperidine[2,3] structural motif, respectively (Scheme 1). Such a transformation of enantiomerically pure substrates has found numerous applications as the key step in the total syntheses of natural compounds and useful chirons containing saturated azaheterocyclic skeleton (Geissman–Waiss lactone,[4] homo-DLX,[5] homo-L-*ido*-DMAP,[5] homo-l-DNJ,[6] homo-L-*ido*-l-DNJ,[6] calvine and epicalvine[7]).



R = OH, protected OH (OP), H
PG = Ts, Z, Boc, Bn

Scheme 1. Intramolecular Pd(II)-catalysed amino/amidocarbonylation of unsaturated amino alcohols.

For the synthesis of the enantiomerically pure N-protected (1*R*,5*R*)-2-oxa-6-azabicyclo[3.3.0]octane-3-one (+)-**2** (N-protected Geissman–Waiss lactone[8]), which is an important intermediate in the synthesis of a number of necine bases[9] (pyrrolizidine alkaloids), the application of enantioselective palladium(II)-catalysed bicyclisation as the key reaction offers an asymmetric alternative to the existing synthetic routes.[10] Following reports on the non-enantioselective carbonylation of unsaturated aminopolyols,[1g,5–7] and/or of racemic[2,3] and enantiomerically pure,[4] simple amino alcohols, we attempted to extend this to a kinetic resolution of racemic N-protected 1-aminopent-4-ene-3-ols (±)-**1**.

Typically, the carbonylation of alkenyl amino alcohols is catalysed by 10 mol % of the palladium(II)-salt in the presence of an oxidant ($CuCl_2$, *p*-benzoquinone, $CuCl_2/O_2$). Generally, the most efficient catalytic system for the intramolecular amino/amidocarbonylation of unsaturated aminopolyols, originally developed for the Wacker process, contains palladium(II) chloride as a catalyst, copper(II) chloride as an oxidant and sodium acetate in acetic acid as a buffer, the reaction taking place under a carbon monoxide atmosphere (balloon) at room temperature. The N-protected 1-aminopent-4-ene-3-ols **1** afforded under these reaction conditions the corresponding 2-oxa-6-azabicyclo[3.3.0]octan-3-ones **2** in good yields[2–7] following the usual *cis*-ring formation pattern, but an asymmetric version of this type of reaction has not been reported so far. To the best of our knowledge, previously reported work on related asymmetric Wacker-type oxidations have been limited to the monocyclisation of alkenols and alkynols.[11] Sasai et al.[12] described an enantioselective intermolecular amidocarbonylation of pentenyl amine derivatives catalysed by Pd(II)-chiral SPRIX—complexes to form pyrrolidin-2-yl-acetic methyl esters in good yields with moderate enantioselectivity. There is no report in the literature, related to the enantioselective carbonylative bicyclisation of unsaturated amino alcohols. Recently, we have reported on the asymmetric intramolecular oxycarbonylation of unsaturated diols catalysed by chiral palladium(II) complexes.[13] The kinetic resolution of racemic pent-4-ene-1,3-diol in the

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presence of $Pd(OAc)_2$-{(*R*,*S*)-indabox}, *p*-benzoquinone in acetic acid under carbon monoxide atmosphere afforded enantiomerically enriched (1*R*,5*R*)-2,6-dioxabicyclo[3.3.0]octan-3-one in 29% yield and 62% ee.

Herein, we report a study on the enantioselectivity of carbonylative bicyclisation of N-protected 1-aminopent-4-ene-3-ols (±)-**1** promoted by chiral Pd(II) complexes.

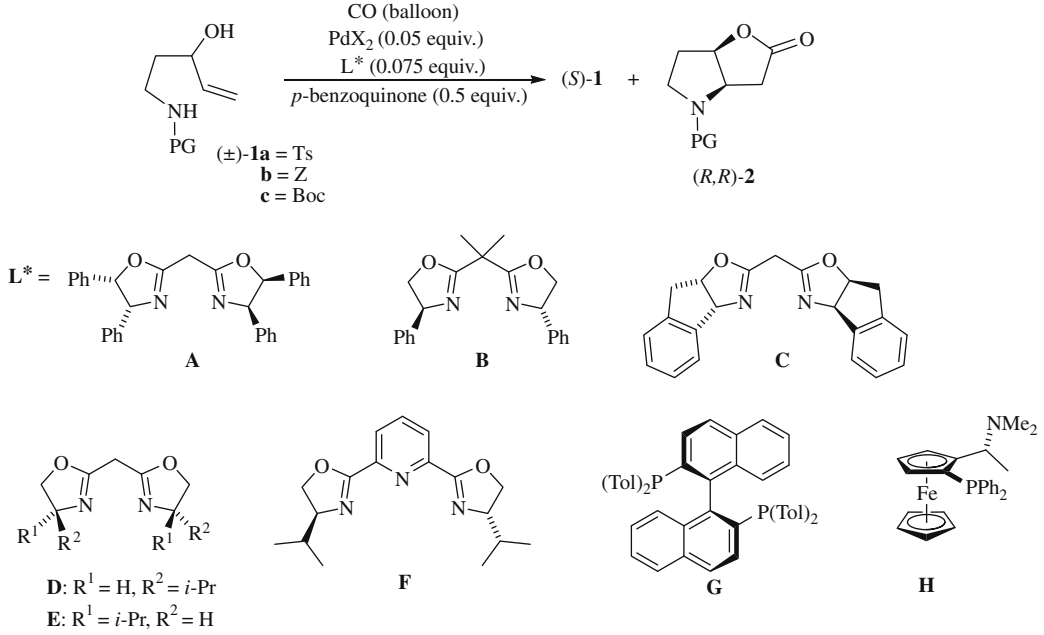
2. Results and discussion

Having obtained preliminary results on the use of chiral Pd(II)-complexes in the oxycarbonylative kinetic resolution of pent-4-ene-1,3-diol,[13a] we focused on the asymmetric Pd(II)-catalysed amidocarbonylation of alkenyl amines. In the case of the amino alkenols, the nature of the amino-protecting group had been found to be essential for optimal adjustment of the N-nucleophilicity, in order to favour the cyclisation step over the competing *N*-Pd complexation.[2–5] We had proposed to use *p*-toluenesulfonyl, benzyloxycarbonyl and *tert*-butyloxycarbonyl, respectively, as N-protecting groups in order to decrease the affinity of amino function to Pd(II)-species. The substrates, N-protected amino alcohols (±)-**1**, were obtained from acetonitrile adopting a known route. Following the reaction sequence, a condensation of acetonitrile lithium enolate with acrolein,[14] $LiAlH_4$-mediated reduction of nitrile[15] and a final protection of amino group with TsCl,[16] ZCl[17] and Boc_2O,[18] respectively, amides (±)-**1** were readily prepared in good yields [(±)-**1a** (32%), (±)-**1b** (41%), (±)-**1c** (29%) overall]. We then prepared lactones (±)-**2** as racemic standards for GC analysis. Thus, amino alcohols (±)-**1** were submitted to amidocarbonylation, carried out under standard conditions,[2–5] that is, with palladium(II) chloride, copper(II) chloride and sodium acetate in acetic acid under carbon monoxide atmosphere at normal pressure and room temperature. The corresponding pyrrolidinolactones (±)-**2a**–**c** were obtained in 90%, 88% and 89% yield, respectively, with noteworthy chemo-, regio- and *cis*-diastereoselectivity. The structures of (±)-**2a**–**c** were established using NMR spectroscopy. All the spectroscopic and physical data of our samples were in good agreement with those reported in the literature.[3,4,19]

Next, we have examined several palladium(II) salts, chiral ligands and reoxidants for the bicyclisation of (±)-**1a**–**c** (Scheme 2). Initially, the optimised catalytic system for the kinetic resolution of unsaturated 1,3-diols was examined.[13] Racemic 1-tosylaminopent-4-ene-3-ol (±)-**1a** was chosen as a model substrate for screening the reaction conditions (Table 1). The transformation was carried out with different chiral PdX_2–(**L***) complexes, *p*-benzoquinone in acetic acid under a carbon monoxide atmosphere (balloon). Chiral palladium(II)-complexes were generated in situ from PdX_2 and a slight excess of chiral ligands **L***. In accordance with the kinetic resolution process, the 50% conversion was maintained by use of 0.5 equiv of *p*-benzoquinone. Conversion control was made by GC using HP5 (30 m, id 0.25 mm, film thickens 0.125 μm) stationary phase. The bicyclic product **2** was separated by flash chromatography and the enantiomeric excess determined by GC analysis with a ChirasilDex (permethylated-β-cyclodextrin) stationary phase (2.5 m, id 0.25 mm, film thickens 0.25 μm).

As shown in Table 1, the reaction catalysed with $PdCl_2$–(**L***) (entries 1, 6, 11, 14) and $Pd(BF_4)_2$–(**L***) complexes (entries 3, 13 and 16) afforded only racemic lactone **2a**. Moderate selectivities were achieved using $Pd(OAc)_2$-[bis(oxazolines) A, B, C] (entries 2, 5 and 7) catalysts. It is apparent that the catalytic activity of the palladium complexes in the present reaction was strongly dependent upon the nature of the anionic part of the catalyst. Generally, the enantioselectivity of the reaction was increased by the use of bis(oxazolines)-ligands **A**–**E**. The best selectivity (66% ee) was noted with $Pd(OAc)_2$-{(*R*,*S*)-indabox} (entry 7), however the transformation proceeded with low conversion. The use of palladium catalysts with ligands **A**, **B**, **D** and **E** under the same reaction conditions furnished product **2a** in comparable yields (14–21%), but with lower enantioselectivities (34–60% ee, entries 2, 5, 8 and 9). It is significant, that the reaction proceeding in the presence of *S*-configured bis(oxazoline) **E** provided enriched lactone (−)-**2**, while the opposite enantiomer **D** preferred the formation of (+)-**2**. The PdX_2-complexes with ligands **F**–**H** have been shown to be inactive as catalysts for the transformation (entries 10–16).

Based on the results with *N*-tosyl derivative (±)-**1a**, our attention was turned to the screening of the other suitable protected amino alcohols (Table 2). The choice of 1-benzyloxycarbonyl- and 1-*tert*-butyloxycarbonylaminopent-4-ene-3-ols (±)-**1b**,**c** gave us an advantage of straightforward determination of the absolute



Scheme 2. Kinetic resolution of N-protected 1-aminopent-4-ene-3-ols (±)-**1** in the asymmetric Pd(II)-catalysed amidocarbonylation.

Table 1
Kinetic resolution of 1-tosylaminopent-4-ene-3-ol (±)-**1a** in the asymmetric Pd(II)-catalysed amidocarbonylation

Entry	X	Ligand	Conditions	Conversion (%)	Yield[a] (%)	ee[b] (%)	$[\alpha]_D$ (25 °C) (*c*, $CHCl_3$)
1	Cl	**A**[c]	25 °C, 48 h	37	26	0	—
2	AcO	**A**[c]	17 °C, 41 h	22	21	60	−28 (0.21)
3	BF_4	**A**[c]	20 °C, 45 h	52	33	26	−11 (0.12)
4	Cl	**B**[c]	20 °C, 120 h	16	14	26	+13 (0.12)
5	AcO	**B**[c]	17 °C, 48 h	33	26	40	—
6	Cl	**C**[c]	20 °C, 96 h	30	21	0	—
7	AcO	**C**[c]	16 °C, 17 h	25	21	66	−32 (0.17)
8	AcO	**D**[20]	20 °C, 21 h	17	15	34	+23 (0.14)
9	AcO	**E**[20]	20 °C, 42 h	22	21	34	−22 (0.15)
10	AcO	**F**[c]	40 °C, 24 h	23	23	9	+4.3 (0.21)
11	Cl	**F**[c]	40 °C, 32 h	42	36	0	—
12	AcO	**H**[21]	20 °C, 48 h	32	30	15	—
13	BF_4	**H**[21]	20 °C, 48 h	20	16	9	—
14	Cl	**G**[c]	22 °C, 24 h	100	92	0	—
15	AcO	**G**[c]	40 °C, 96 h	<5	—	0	—
16	BF_4	**G**[c]	19 °C, 240 h	<5	—	0	—

[a] Isolated yield after flash column chromatography.
[b] Enantiomeric excesses were determined using gas chromatography with chiral stationary phase (see Section 4).
[c] Commercially available.

Table 2
Kinetic resolution of N-protected 1-aminopent-4-ene-3-ol (±)-**1a**,**b**,**c** in asymmetric Pd(II)-catalysed amidocarbonylation

Entry	Diol	Ligand	Conditions	Conversion (%)	Yield[a] (%)	ee[b] (%)	Lactone
1	(±)-**1b**	**C**	BQ (0.5 equiv), AcOH, 22 °C, 48 h	22	20	62	(*R*,*R*)-**2b**[c]
2	(±)-**1b**	**C**	BQ (0.5 equiv), AcOH, 28 °C, 42 h	11	8	68	(*R*,*R*)-**2b**
3	(±)-**1b**	**A**	BQ (0.5 equiv), AcOH, 27 °C, 42 h	20	18	73	(*R*,*R*)-**2b**
4	(±)-**1a**	**C**	BQ (0.5 equiv), THF, 22 °C, 192 h	<5	—	—	—
5	(±)-**1a**	**C**	BQ (0.5 equiv), CH_2Cl_2, 27 °C, 42 h	<5	—	—	—
6	(±)-**1a**	**—**	BQ (1.0 equiv), AcOH, 25 °C, 91 h	>95	76	0	(±)-**2a**
7	(±)-**1a**	**A**	BQ (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), ligand (0.12 equiv), AcOH, 29 °C, 24 h	50	40	60	(-)-**2a**
8	(±)-**1a**	**—**	Duroquinone (1.0 equiv), AcOH, 25 °C, 192 h	—	—	—	—
9	(±)-**1a**	**—**	Tetrachlorobenzoquinone (1.0 equiv), AcOH, 29 °C, 312 h	—	—	—	—
10	(±)-**1a**	**A**	BQ (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), ligand (0.12 equiv), CH_2Cl_2/AcOH (1:1), −15 °C, 144 h	5	—	26	(−)-**2a**
11	(±)-**1c**	**A**	BQ (1.0 equiv), CH_2Cl_2, 29 °C, 24 h	71	65	26	(*R*,*R*)-**2c**
12	(±)-**1c**	**C**	BQ (1.0 equiv), CH_2Cl_2, 20 °C, 48 h	85	68	33	(*R*,*R*)-**2c**

[a] Isolated yield after flash column chromatography.
[b] Enantiomeric excesses were determined using gas chromatography with chiral stationary phase (see Section 4).
[c] $[\alpha]_D^{25} = -40$ (*c* 0.21, $CHCl_3$).

configuration of known lactones **2b**,**c**, together with the pleasing option of N-deprotection to Geissman–Waiss's precursor by hydrogenolysis (Scheme 2). The absolute configuration of the lactones **2b**,**c** was assigned by comparison of the specific rotation value with the literature data {for (*R*,*R*)-**2b**: $[\alpha]_D^{25} = -122$ (*c* 4.7, $CHCl_3$);[4] $[\alpha]_D^{24} = -115$ (*c* 1.12, $CHCl_3$);[9f,22] $[\alpha]_D^{32} = -170$ (*c* 0.7, $CHCl_3$);[23] for (*S*,*S*)-**2b**: $[\alpha]_D^{25} = +123$ (*c* 1.14, $CHCl_3$);[4] $[\alpha]_D^{26} = +123$ (*c* 1.14, $CHCl_3$);[9f,22] $[\alpha]_D^{28} = +109$ (*c* 1.10, MeOH);[24] for (*R*,*R*)-**2c**: $[\alpha]_D^{31} = -127$ (*c* 0.4, CH_2Cl_2);[10o] $[\alpha]_D^{27} = -131$ (*c* 1.0, $CHCl_3$);[10p] $[\alpha]_D^{20} = -150$ (*c* 0.5, $CHCl_3$);[25] for (*S*,*S*)-**2c**: $[\alpha]_D^{27} = +96$ (*c* 0.43, CH_2Cl_2);[10m] $[\alpha]_D^{28} = +134$ (*c* 1.02, $CHCl_3$)[26]}. In the next set of experiments, the catalytic system and solvent was scrutinised using the most effective $Pd(OAc)_2$-{(*R*,*S*)-indabox (**C**)} and $Pd(OAc)_2$-{2,2′-methylenebis[(4*R*,5*S*)-4,5-diphenyloxazolin-2-yl] (**A**)} catalysts (see Table 2). First, we looked at the nature of amino-protecting group of substrates (±)-**1b**,**c** to compare the selectivity with that observed for N-tosylated alcohol (±)-**1a** and found the benzyloxycarbonyl moiety to be an equally suitable one (62–73% ee, entries 1–3) in contrast with *tert*-butyloxycarbonyl (entries 11 and 12). It is notable that the attempts to perform the bicyclisation of **1a** to **2a** using dichloromethane or tetrahydrofuran as solvents failed totally (entries 4 and 5). Next, we decided to investigate the relative stoichiometry of reagents used in the reaction and we found that the catalytic system containing $Pd(OAc)_2$ (0.1 equiv), ligand (0.14 equiv) and *p*-BQ (1.0 equiv), with respect to substrate (±)-**1a**, increased the conversion and yield of the reaction (entries 6 and 7). Finally, the choice of reoxidant was inspected: the replacement of *p*-benzoquinone by either duroquinone or tetrachlorobenzoquinone had a detrimental effect on the desired transformation of **1** to **2** and only complex reaction mixtures were obtained (entries 8 and 9). Unfortunately, when the reaction was performed at lower temperature (−15 °C), it did not improve the enantioselectivity (entry 10).

3. Conclusions

In conclusion, we have developed an enantioselective amidocarbonylative bicyclisation of alkenyl aminoalcohols catalysed by in situ prepared chiral palladium(II) complexes. This is the first example of a kinetic resolution process of racemic unsaturated amino alcohols of the title reaction. The N-protected 2-oxa-6-azabicyclo[3.3.0]octan-3-ones (*R*,*R*)-**2b** and (−)-**2** (derivatives of the Geissman–Waiss lactone) were obtained in 20–40% yields with 60–73% ee. Further studies to improve the performance of asymmetric catalysts for this transformation are now currently under way.

4. Experimental

4.1. A typical procedure for asymmetric amidocarbonylation of N-protected 1-amino-pent-4-ene-3-ols (±)-1 with $(L^*)Pd(OAc)_2$ and $(L^*)PdCl_2$

A chiral ligand (0.075–0.12 equiv) in CH_2Cl_2 (1 mL) was added to the solution of $Pd(OAc)_2$, or $Pd(MeCN)_2Cl_2$ (0.025–0.1 equiv) in CH_2Cl_2 (1 mL), respectively. The mixture was stirred for 15 min to give a clear solution and CH_2Cl_2 was removed in vacuo. The resulting chiral palladium complex was dissolved in glacial AcOH (2 mL), and substrate (±)-1 (1.0 equiv, 0.42 mmol) and *p*-benzoquinone (0.5–1.0 equiv) in AcOH (2 mL) were added. The flask was purged with CO from a balloon and the reaction mixture was vigorously stirred until the deposition of black palladium was observed (approx. 1–2 days). The solvent was evaporated and the crude product purified by flash column chromatography.

4.2. Asymmetric amidocarbonylation of (±)-1 with $(L^*)Pd(BF_4)_2$ and $(L^*)PPh_3Pd(BF_4)_2$

A chiral ligand (0.12 equiv) in CH_2Cl_2 (1 mL) was added to a solution of $Pd(MeCN)_2Cl_2$ (0.1 equiv) in CH_2Cl_2 (1 mL). The mixture was stirred for 15 min to give a clear solution. This solution was added to a mixture of $AgBF_4$ (0.2 equiv) in CH_2Cl_2 (1 mL). Precipitated AgCl was removed and the filtrate was concentrated. In the synthesis of $(L^*)PPh_3Pd(BF_4)_2$, in addition PPh_3 (0.1 equiv) was added and stirred for 30 min before concentration in vacuo. The solid was dissolved in glacial AcOH (2 mL), and substrate (±)-1 (1.0 equiv, 0.42 mmol) and *p*-benzoquinone (0.5–1.0 equiv) in AcOH (2 mL) were added. The flask was purged with CO from the balloon and the mixture was stirred vigorously until black palladium was observed (approx. two days). The solvent was then evaporated and the crude product purified by flash column chromatography. The spectroscopic and physical data were in good agreement with those reported.[3,4,19]

The general conversion control of purified products was performed on Agilent 5980 series II gas chromatograph equipped with split/splitless injector (250 °C, split ratio 1:50) and FID detector (250 °C). Hydrogen with optimal velocity 40 cm/s was used as a carrier gas. The oven was operated under temperature programme 180 °C (25 min)–10 °C/min–240 °C (5 min). The enantiomeric excess was determined using the same gas chromatograph using hydrogen with velocity 85 cm/s a carrier gas and temperature programme 60 °C (2 min)–3.5 °C/min–190 °C.

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