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Highly stereoselective hydroformylation of a (2*R*)-2-tert-butyl-Δ^4-1,3-oxazoline derivative

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Abstract

Methyl (2*R*)-2-tert-butyl-Δ^4-1,3-oxazoline-3-carboxylate has been hydroformylated to give methyl (2*R*,4*R*)-2-tert-butyl-4-formyl-oxazolidine-3-carboxylate and methyl (2*R*,5*S*)-2-tert-butyl-5-formyl-oxazolidine-3-carboxylate with up to 99% diastereoselectivities in homogeneous transition-metal-catalysed reactions. A mixture of regioisomers was formed in the presence of rhodium catalysts. Platinum catalysts gave almost exclusively methyl (2*R*,5*S*)-2-tert-butyl-5-formyl-oxazolidine-3-carboxylate. The formyl products obtained are important intermediates for the synthesis of homochiral amino acid derivatives of considerable synthetic value.

1. Introduction

The stereospecific introduction of the formyl group to an olefin is an important goal in synthetic organic chemistry, since the synthetically useful formyl functionality enables further functionalization of the molecule. The asymmetric hydroformylation of olefins containing heteroatoms may result in chiral formyl derivatives of importance as chiral building blocks or biologically active compounds [1,2]. The optical yields achieved are moderate except in a few cases in which optically active ligands (optically active ditertiary phosphines) are used in platinum-catalysed enantioselective hydroformylation of vinyl aromatics and unsaturated esters [3–6]. New stereogenic centres were obtained in the carbonylation of optically active olefins. Simple olefins [7] and unsaturated natural products were transformed to the appropriate formyl diastereomers [8–11].

2. Results and discussion

Chiral building blocks with high e.e. can be obtained in a diastereoselective carbonylation of an optically active molecule containing a preformed stereogenic centre. We report now the diastereoselective hydroformylation of methyl (2*R*)-2-tert-butyl-Δ^4-1,3-oxazoline-3-carboxylate (**1**).

The homogeneous catalytic hydroformylation of **1** under the conventional 'oxo-condition' results in two formyl regioisomers (**2**, **3**) in the presence of a rhodium catalyst (Scheme 1, Table 1). A small amount of **4** is formed under the conditions used. This small extent of hydrogenation (the reaction that usually competes with hydroformylation) is surprising in the light of earlier observations that the amounts of hydrogenation and hydroformylation products are comparable. However, more hydrogenation took place in the case of platinum catalysts and a mixture of dimeric products was formed too (Runs 7 and 8). The side-reactions are strongly suppressed by lowering the reaction temperature (Run 9).

The ratio of formyl regioisomers varies over a wide range depending on the type of the catalyst. The formyl products containing the formyl group on the carbon adjacent to oxygen (**3a**, **3b**) were obtained almost exclusively in the presence of platinum catalysts. The regioselectivity is strongly influenced by the type of the phosphine used in rhodium-catalysed hydroformylation. The formation of **2a**, **2b** and that of **3a**, **3b** are favoured in the presence of monodentate and biden-

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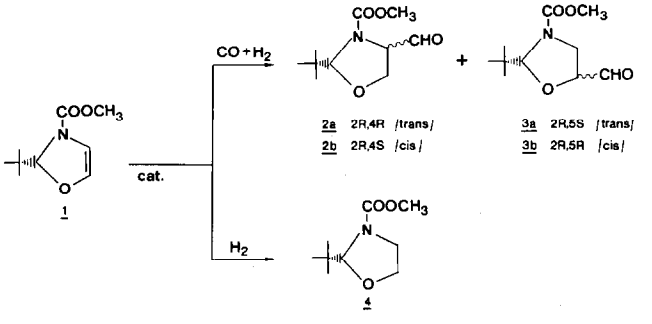
TABLE 1. Hydroformylation of methyl (2*R*)-2*tert*-butyl-Δ^4-1,3-oxazoline-3-carboxylate

Run	Catalyst	Reaction time (h)	Conversion (%)	2 % *trans* / *cis*	3 % *trans* / *cis*	4 %
1	$0.5[Rh(nbd)Cl]_2 + 2.2PPh_3$	12	79	48 **97/3**	31 **96/4**	< 1
2	$0.5[Rh(nbd)Cl]_2 + 2.2PPh_3 + 5\ NEt_3$	14	68	47 **95/5**	21 **90/10**	< 1
3	$0.5[Rh(nbd)Cl]_2$ + DPPB [a]	20	82	28 **98/2**	54 **99/1**	< 1
4	$0.5[Rh(nbd)Cl]_2$ + DPPB	7	62	24 **98/2**	38 **98/2**	< 1
5	$0.5[Rh(nbd)Cl]_2$ + DPPP [b]	20	92	20 **99/1**	71 **99/1**	< 1
6	$0.5[Rh(nbd)Cl]_2$ + DPPE [c]	20	65	22 **98/2**	43 **98/2**	< 1
7	$PtCl_2$(BDPP) [d] + $2SnCl_2$	6	88	< 1	36 **97/3**	15 [e]
8	$PtCl_2$(DPPB) + $2SnCl_2$	15	67	< 1	30 **97/3**	22 [f]
9	$PtCl_2$(DPPB) + $2SnCl_2$ [g]	75	80	< 1	76 **98/2**	3

Reaction conditions: 0.025 mmol catalyst, 15 ml toluene, 100°C, 80 bar $CO/H_2 = 1/1$, 8 mmol substrate.
[a] DPPB = 1,4-bis(diphenylphosphino)butane. [b] DPPP = 1,3-bis(diphenylphosphino)propane. [c] DPPE = 1,2-bis(diphenylphosphino)ethane. [d] BDPP = (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane. [e] 37% side-products. [f] 15% side-products. [g] 50°C.

tate phosphines, respectively. The addition of base to the *in situ* catalytic system has a slight influence on regio- and chemoselectivity (Run 2). (Triethylamine abstracts HCl from hydrido-chlororhodium(III) species resulting in the formation of chlorine-free rhodium(I) complexes.)

The formyl compounds obtained possess new chiral centres generated by carbon–carbon bond formation. The hydroformylation is highly diastereoselective both in the presence of rhodium and platinum catalysts. The *trans*-formyl products (**2a** (2*R*,4*R*) and **3a** (2*R*,5*S*)) were isolated as almost diastereomerically-pure products when rhodium catalysts were used. (It is noteworthy that epimerization at the carbon adjacent to oxygen was observed during NMR studies: the thermodynamically more stable **3a** was formed from **3b**.) The use of chelating biphosphines results in higher diastereoselectivities than that of the monodentate ones (Runs 3–6). The fact, that the modification of the catalysts has only a slight influence on selectivities suggests that the presence of the stereogenic centre bearing the *t*-butyl group is essential in terms of the stereochemical outcome of the hydroformylation reaction.



Scheme 1.

This approach seems to be promising for the synthesis of valuable unnatural α-amino acids and iso-amino acids in enantiomerically pure form after splitting of the heterocycle. The homogeneous catalytic carbonylation (hydroformylation) could serve as a key reaction in the reaction sequence used, and could be superior to most of the classical synthetic methods.

3. Experimental details

3.1. Reagents

The catalytic precursors $[Rh(nbd)Cl]_2$ and $PtCl_2$-(BDPP) were prepared as described previously [12,13].

Toluene was distilled from sodium under argon in the presence of benzophenone. Methyl (2*R*)-2-tert butyl-Δ^4-1,3-oxazoline-3-carboxylate was prepared from (L)-serine according to a published procedure [14,15].

The ^1H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions containing TMS as internal standard on a Varian XL400 spectrometer. The full assignment was based on ^1H–^1H COSY, ^1H–^{13}C HETCOR and DEPT studies. The samples were analysed with a Hewlett Packard 5830A gas chromatograph using an SPB-1 column. The MS spectra were obtained with a Hewlett Packard 5971A GC-MSD spectrometer.

3.2. Hydroformylation experiments

In a typical experiment a solution of 1 mmol of methyl (2*R*)-2-tert-butyl-Δ^4-1,3-oxazoline-3-carboxylate in 20 ml of toluene was transferred under argon to a 100 ml stainless steel autoclave containing 5.8 mg of $[Rh(nbd)Cl]_2$ and 0.0125 mmol of diphosphine. The autoclave was pressurized to the chosen pressure with a 1/1 CO/H_2 mixture, placed in a thermostated electric oven, and agitated with an arm shaker. After cooling and venting of the autoclave, the solution was

analysed by GLC and evaporated to leave an oily residue, which was subjected to column chromatography (silica gel) with ether as eluent. The major (*trans*) diastereomers (**2a** and **3a**) were fully characterized. The *cis* diastereomers (**2b** and **3b**) were identified as minor components in a mixture by ^{1}H NMR (^{1}H–^{1}H COSY) mass spectrometry. (Because of the overlapping patterns of the methylene and methin protons the values of the coupling constants are subject to considerable uncertainty.)

3.3. Characterization of the products

3.3.1. Methyl(2R,4R)-2-tert-butyl-4-formyl-oxazolidine-3-carboxylate (3a)

^{1}H NMR (400 MHz): δ 9.85 (s, 1H, **CHO**); 5.28 (s, 1H, **CH**(^{t}Bu)); 4.37 (dd, 7.9Hz, 9.1Hz, 1H, OC**H**^{a}H^b); 4.30 (dd, 3.5Hz, 7.9Hz, 1H, NC**H**CHO); 4.02 (dd, 3.5Hz, 9.1Hz, 1H, OCH^a**H**^{b}); 3.70 (s, 3H, O**CH**$_3$); 0.965 (s, 9H, C(**CH**$_3$)$_3$); ^{13}C NMR (100.58MHz): δ 196.3 (**CHO**); 159.5 (NCOO); 97.6 (NCO); 68.12 (OCH_2); 65.0 (CCHO); 52.9 (OCH_3); 39.2 (C(CH_3)$_3$); 26.0 (C(**CH**$_3$)$_3$); MS (*m/z* relative intensity): 200/5($M^+ - CH_3$); 186/10($M^+ - C_2H_5$); 158/1000($M^+ - C_4H_9$); Analysis: calculated (found) (%), C: 55.8(56.0); H: 8.0(7.8); N: 6.5(6.7).

3.3.2. Methyl (2R,4S)-2-tert-butyl-4-formyl-oxazolidine-3-carboxylate (2b)

^{1}H NMR (400MHz): δ 9.9 (s, 1H, **CHO**); 5.36 (s, 1H, **CH**(^{t}Bu)); 4.25 (dd, 1H, OC**H**^{a}H^b); 3.2 (dd, 1H, OCH^a**H**^{b}); 3.75 (s, 3H, OCH_3); 0.94 (s, 9H, C(**CH**$_3$)$_3$).

3.3.3. Methyl (2R,5S)-2-tert-butyl-5-formyl-oxazolidine-3-carboxylate (3a)

^{1}H NMR (400MHz); δ 9.65 (d, 1.1Hz, 1H, **CHO**); 5.33 (s, 1H, **CH**(^{t}Bu)); 4.49 (ddd, 1.1Hz, 2.5Hz, 7.9Hz, 1H, OC**H**CHO); 4.28 (dd, 2.5Hz, 11.9Hz, 1H, NC**H**^{a}H^b); 3.72 (s, 3H, O**CH**$_3$); 3.47 (dd, 7.9Hz, 11.9Hz, 1H, NCH^a**H**^{b}); 0.95 (s, 9H,C(**CH**$_3$)$_3$); ^{13}C NMR (100.58 MHz): δ 200.2 (**CHO**); 155.8 (NCOO); 97.3 (NCO); 80.9 (CCHO); 53.0 (OCH_3); 46.2 (NCH_2); 38.1 (C(CH_3)$_3$); 25.2 (C(**CH**$_3$)$_3$); MS (*m/z* relative intensity): 200/10 ($M^+ - CH_3$); 186/60 ($M^+ - C_2H_5$); 158/1000($M^+ - C_4H_9$).

3.3.4. Methyl (2R,5R)-2-tert-butyl-5-formyl-oxazolidine-3-carboxylate (3b)

^{1}H NMR (400MHz): δ 9.7 (s, 1H, **CHO**); 5.45 (s, 1H, **CH**(^{t}Bu)); 4.5 (m, 1H, OC**H**CHO); 4.4 (m, 1H, NC**H**^{a}H^b); 3.96 (m, 1H, NC**H**^{a}**H**^{b}); 3.7 (s, 3H, O**CH**$_3$); 1.04 (s, 9H, C(CH_3)$_3$).

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