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Completely Regioselective Hydroformylation of Methyl N-Acetamidoacrylate by Chiral Rhodium Phosphine Catalysts.

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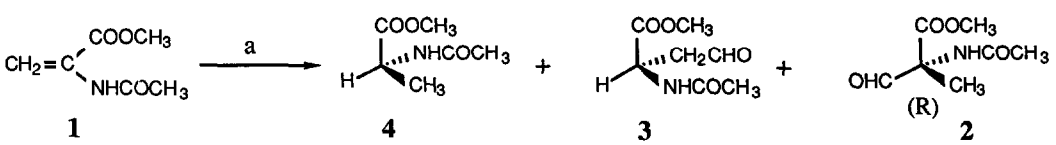
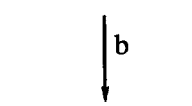
Abstract: The asymmetric hydroformylation of methyl N-acetamidoacrylate (MAA; **1**) is efficiently catalysed by $HRh(CO)(PPh_3)_3$ in the presence of a chiral chelating diphosphine. The reaction proceeds with complete positional selectivity affording in high yield the more branched aldehyde where the formyl group is bound to a chiral quaternary carbon atom. Enantiomeric excesses up to 60% are obtained with DIOP as chiral ligand.

In recent years the rhodium catalysed hydroformylation of nitrogen substituted olefins attracted attention as a powerful synthetic tool for the preparation of valuable polyfunctional synthons[1]. Unsaturated alkyl-[2] and acyl-[3] amines, imides[4], mono- and di- substituted amides[5] and lactams[6] have been used as substrates and fair to good asymmetric inductions have been recorded in the enantioselective process. There have been no reports, to our knowledge, on the hydroformylation of dehydroaminoacid derivatives like the title compound. This seems rather surprising in view of the enormous amount of work carried out on the asymmetric hydrogenation of this substrate with Wilkinson-type catalysts and of the excellent enantioselectivities recorded in this process.[7] The aldehydes **2** and **3**, arising from the hydroformylation of MAA (Scheme), are both synthetic intermediates of great potential for which several applications in organic synthesis can be devised. This prompted us to undertake this investigation.

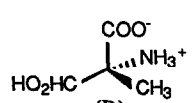


1 **4** **3** **2**



a) CO/H_2 (1:1) 100 atm; 80 °C; 70 h
$HRh(CO)(PPh_3)_3$ / Chelating Diphosphine

b) $NaBH_4$ / THF, 25 °C, 4 h; then HCl 1:1, reflux 6 h.



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Under typical hydroformylation conditions (80°C; 80-100 atm total pressure; H_2/CO 1: 1), in the presence of rhodium phosphine catalysts, MAA undergoes three different reactions: CO insertion to afford an

aldehyde; hydrogen addition to afford methyl N-acetylalaninate (MAL; **4**) and polymerization. The relative extent of these competitive processes can be quite different and is markedly dependent on several parameters.

Hydrogenation and, to a lower extent, polymerization were the exclusive or the largely prevalent reaction paths with most rhodium derivatives we have screened as potential catalysts. This list includes mononuclear derivatives such as $RhCl_3$ or $Rh(CO)Cl(PPh_3)_2$, **7**; dimeric species like $[RhL_2Cl]_2$ (L = CO or ethylene; L_2 = 1,5-cyclooctadiene or norbornadiene) and polynuclear carbonyl clusters such as $Rh_6(CO)_{16}$. With the exception of **7**, these derivatives did not produce any detectable amount of aldehyde from MAA irrespective of the hydroformylation conditions employed. Only the phosphino complex **7**, in the presence of two moles of (-)-DIOP, produced a trace of aldehyde **2** (2% by GLC) together with almost racemic MAL. A more significative amount of **2** (40%) was obtained when $HRh(CO)(PPh_3)_3$ **6** was employed as catalyst. A systematic study with this precursor pointed out two general features of this reaction. First, under hydroformylation conditions, the insertion of carbon monoxide, when it occurs, takes place with complete positional selectivity on the more substituted carbon of MAA affording, as the exclusive formyl derivative, the aldehyde **2**, where a quaternary asymmetric carbon atom is originated through a carbon-carbon bond formation. In all the experiments, the isomeric aldehyde **3**, if formed, was not present in detectable amounts. Second, the chemoselectivity of the reaction is extremely capricious and, beside the catalytic precursor, also the structure of the additional phosphine ligand has a dramatic influence on the aldehyde yield.

Table 1. Hydroformylation of MAA catalysed by $HRh(CO)(PPh_3)_3$, **6**.

Ligand[a]	L/6	2(%)
-	-	40
PPh_3	4	38
PPh_3	10	55
PBu_3	4	0
DPM	2	38
DPE	2	7
DPP	2	54
DPB	2	64
DME	2	17
DPFe	2	43
DIOP	2	91
DIOP	4	90

a) DPM, DPE, DPP, DPB: bisdiphenylphosphinomethane, -ethane, -propane, -butane. DME: bisdimethylphosphinoethane. DPFe: 1,1'-bisdiphenylphosphinoferrocene.

Table 2. Asymmetric hydroformylation of MAA with $HRh(CO)(PPh_3)_3$ and (-)-DIOP[b]

DIOP/6	T (°C)	H_2/CO	e.e.[d]
1	80	1	11
2	80	1	28
4	80	1	38
6	80	1	38
4	80	4	38
4	80	10	44
4	80	20	44
4	60	10	47
4	40	10	54
4	30	10	59
4[c]	80	1	23

b) Reaction conditions as below but benzene (20 ml) as solvent. c) Solvent MEK. d) Determined by GLC. Prevailing configuration (R).

EXPERIMENTAL. MAA (1 g), $HRh(CO)(PPh_3)_3$ (0.064 g) and the required amount of phosphine were introduced in a stainless steel autoclave. The air was evacuated, methyl ethyl ketone (20 ml) was introduced by suction and the vessel was pressurized with CO/H_2 at room temperature (100 atm). After 70 h at 80°C, the solvent was removed and the residue was chromatographed on silica. Aldehyde **2** was purified by distillation: b.p.140-150°C at 10 Pa. ^1H NMR (δ, $CDCl_3$): 1.7 (s, CH_3); 2.2 (s, CH_3CO); 4.0 (s, OCH_3); 9.8 (s, CHO). IR (nujol; cm^{-1}): 3280 s; 1729 s; 1656 b. MS: m/z 173 (1%, M^+). The e.e's were determined on crude samples

by GLC on a Chirasil-Val capillary column (50m; 0.25 i.d.; Alltech) operated at 149°C with a HP 5890A instrument using a FID detector and Helium (80 KPa) as carrier. Retention times (m): 18.5 (S); 19.0 (R). Alternatively, base line separation of the resonance at δ 2.2, allowing an accurate integration of the separate peaks, could be obtained in the NMR using Eu(hfc)3 as a chiral shift reagent.

The data reported in Table 1 point out that the extent of aldehyde formation increases as the phosphine basicity decreases and as the size of the chelate ring of bidentate ligands increases. High selectivities, equal or higher than 90%, were recorded only with DIOP and strictly related ligands such as DIOCOL[8]. With the same ligands, satisfactory yields of **2** (80-85%) could be obtained also when using as catalytic precursor rhodium(I) dicarbonyl acetylacetonate. Selectivities somewhat lower (50-70%) were attained with DIOP and the chlororhodium derivative **7** when triethylamine (40 moles per Rh) was present in the reaction mixture. Surprisingly, addition of the same base to $HRh(CO)(PPh_3)_3$ completely prevented the hydroformylation of MAA and led to quantitative production of racemic MAL.

The enantioselectivity of the reaction was found critically dependent also on the structure of the chiral diphosphine and in this case again the best results were obtained with DIOP and DIOCOL which gave almost identical results. (S,S)-CHIRAPHOS[9] gave only racemic MAL in 30-40% yield. This was the main product also in the experiments carried out in the presence both of the proline derived ligands[10] BPPM and PPM (94 and 70%, respectively) and of the phosphinamides[11] PNPP and (-)menthyl-PNPP (60 and 80%, respectively). The e.e.'s of aldehyde **2** in these runs were not higher than 10% obtained with BPPM. Improved selectivities, but still low e.e.'s were observed with (S)-BINAP[12] (45 and 7%, respectively), (1S,2S)-DIPMC[13] (75 and 0%, respectively) and (S,S)-SKEWPHOS[14] (86 and 11%, respectively).

With DIOP, the influence of several parameters on the extent of the asymmetric induction was investigated in some detail and the results are summarized in Table 2. Lowering the reaction temperature and reducing the solvent polarity resulted in a sharp increase of the enantioselectivity and in a slight improvement of the chemoselectivity up to 95-97%. Hydrogen rich mixtures had a beneficial effect on the reaction rate which increased roughly four times on going from 1:1 to 20:1 ratio. Noticeably, this was not detrimental for the yield of aldehyde which, on the contrary, slightly improved on increasing the hydrogen content up to 10:1 (95 vs. 90%) and decreased only upon further increments (80% at 20:1). Lowering the total pressure, on the contrary, increased the extent of hydrogenation and ultimately at atmospheric pressure only MAL (9% e.e.) was obtained. This last compound was produced in good enantiomeric excess (65%) as the exclusive reaction product when the hydroformylation was carried out in the presence of $PtCl(SnCl_3)$[(-)-DIOP][15]

In summary, under optimum conditions, more than 90% isolated yield of **2** with about 50% e.e. could be obtained in 70h at 60°C operating at MAA/Rh = 100 and H_2/CO = 10. Higher e.e.'s (≈60%) required much longer times and resulted in a slightly lower yield. It should be noted that this enantioselectivity, albeit not exceptional, is the highest attained so far in the asymmetric hydroformylation with rhodium catalysts. Better e.e.'s have been obtained on different substrates by Parrinello and Stille[4] with Pt/Sn chiral catalysts. In that case, however, conversions were not complete and the regioselectivity for the branched aldehyde was usually poor (≈35%). As a consequence, the chemical yields of the desired product were low and not comparable with ours.

The rhodium catalysed hydroformylation of methyl methacrylate can afford very high yields of the branched aldehyde, but a small amount of linear isomer is always formed[16] and the reaction conditions are quite different from ours. Very high selectivities for the branched isomer, but poor e.e.'s have been recently reported

for aryl substituted ethylenes[17]. We may speculate that polydentate binding of MAA to rhodium is occurring and that this chelation effect may be largely responsible for the regio- and stereo-selectivity observed.

Right handed samples of **2** were catalytically decarbonylated with $Rh(DPP)_2Cl$[18] to give (S)-MAL. Although the reaction was markedly affected by racemization, this allowed to establish that the prevailing enantiomer obtained with (-)DIOP has the (R) configuration and to extrapolate for this $[\alpha]_{Dmax}$ + 34±2 (c 2, acetone). (+)-(R)-**2** was readily converted into (-)-(R)-α-methylserine **5** (Scheme), isolated in crystalline form (m.p. 263-5°C) by ion exchange chromatography. This simple transformation is illustrative of the scope of aldehyde **2** in the synthesis of organic compounds of biological interest. Addition of suitable organometallic reagents to the formyl group should provide a straightforward synthetic method, racemization free, for the preparation of α-methylamino acids derivatives of known configuration. As the opposite enantiomer should be obtained in few steps by addition to the ester function followed by elaboration of the protected formyl group, this points out the synthetic utility of aldehyde **2** as a synthon of dissimetrized methyl aminomalonic acid.

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