Journal of Organometallic Chemistry, 396 (1990) 375–383
Elsevier Sequoia S.A., Lausanne
JOM 21058

Carbonylation (hydroformylation and hydrocarbalkoxylation) and enantioselective carbonylation of some methacrylic acid derivatives

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(Received April 2nd, 1990)

Abstract

The hydroformylation of methyl methacrylate (**1**) or t-butyl methacrylate (**2**) takes place with fair to good chemoselectivity, the regioselectivity depending on the catalyst precursor used. By contrast, methacrylonitrile (**3**), methacrylamide (**4**), and *N*-benzyl-methacrylamide (**5**) undergo hydroformylation followed by subsequent reactions. The formyl product formed is reduced to the corresponding 2-cyano-2-methylpropan-1-ol in the case of **3**, and undergoes cyclization to 2-methyl-2,3-dehydrobutyrolactames for **4** and **5**. Under conditions of hydrocarbalkoxylation in the presence of palladium catalysts, **4** gives 3-methylsuccinimide. In the enantioselective reactions, extents of asymmetric induction of about 20–50% have been obtained.

Introduction

Although the most investigated substrates in hydroformylation or hydrocarboxylation are simple olefinic hydrocarbons [1–4], more recently efforts have been directed towards synthesizing various useful functional compounds and various bifunctional synthons for the synthesis of natural products and biologically active compounds [5,6]. Hydroformylation or hydrocarbonylation can be used as a tool for the synthesis of α-aminoacids when unsaturated amides and imides are the substrate [7–10]. The intramolecular amidocarbonylation of alkenamides yields nitrogen heterocycles of pharmaceutical importance [11]. The scope of the carbonylation reaction has been further extended to the lactam skeleton [12] and to some *N*,*N*-disubstituted amides of unsaturated carboxylic acids [13]. The enantioselective

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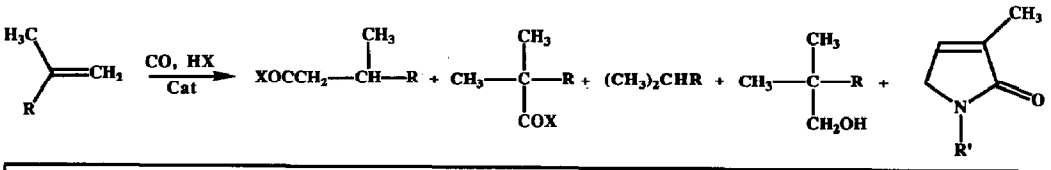
0022-328X/90/$03.50

hydroformylation of unsaturated carboxylic esters has also been studied [10,14]. Carbonylation reactions of functionalyzed olefins are not only of practical importance but also of theoretical interest. It may be possible to identify interactions between the functional groups of the substrate and the catalyst [14,15] that lead to transition states of rigid structure and, therefore, high stereoselectivities. In this paper the hydroformylation and hydrocarbalkoxylation of some methacrylic acid derivatives are discussed.

Results and discussion

The results obtained in the hydroformylation of methyl methacrylate (**1**), t-butyl methacrylate (**2**), methacrylonitrile (**3**), methacrylamide (**4**), and *N*-benzylmethacrylamide (**5**) (Scheme 1) in the presence of rhodium and/or platinum catalyst are reported in Table 1. The hydroformylation of methyl methacrylate (**1**) with [(*R*,*R*)-Diop]Pt($SnCl_3$)Cl [16] (**8**) (Diop denotes [(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis[diphenylphosphine]) as the catalyst precursor gives the less branched isomeric aldehyde **1a** regioselectively, but there is some competitive hydrogenation of the substrate. The rhodium-catalysed reactions, particularly that using the catalyst precursor $[Rh(CO)_2Cl]_2$/(*S*,*S*)-Chiraphos (**7**) (1/4 molar ratio) [17] (Chiraphos is 1,2-dimethyl-1,2-ethanediylbis[diphenylphosphine]), are, in contrast, quite chemoselective. Thus when the catalytic system **7** is used the more branched regioisomeric aldehyde **1b** prevails, whereas use of the unmodified $Rh_4(CO)_{12}$ (**6**) gives almost exclusively the corresponding less branched regioisomer. The enantioselectivity is quite low for the rhodium catalyst **7** (~ 3% asymmetric induction, predominant (*R*)-enantiomer) but fair for the platinum catalyst **8** (37% asymmetric induction, predominant (*S*)-enantiomer). The optical purity and



R =	X =					
$COOCH_3$	H	1a	1b	1c		
	OCH_3	1a'	1b'			
$COOC_4H_9^t$	H	2a	2b	2c		
CN	H		3b	3c	3d	
$CONH_2$	H	4a		4c		4e
	OCH_3	4a'		4c		4e
CONHBz	H	5a		5c		5e

4e: R' = H; 5e: R' = $C_6H_5CH_2$

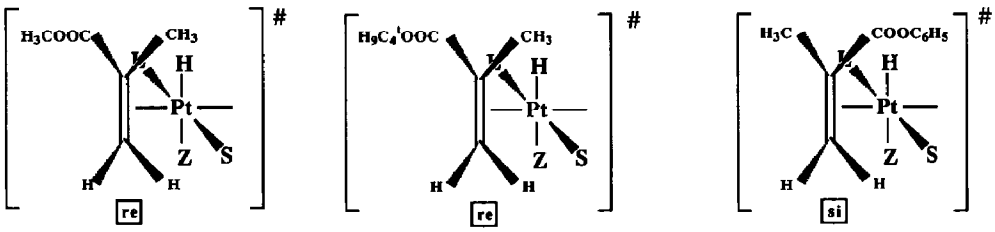
Scheme 1

Table 1

Hydroformylation of some methacrylic acid derivatives with different catalyst precursors [a]

Substrate		Catalyst [b] precursor	Temp. (°C)	p (atm)	Reaction time (h)	Conv. [c] (%)	Products [d]				
							a	b	c	d	e
methyl methacrylate	(1)	6	120	110	78	62	<1	97	3		
methyl methacrylate	(1)	7	100	50	23	52	41	69	<1		
methyl methacrylate [f]	(1)	8	100	80	45	99	83	0	17		
t-butyl methacrylate	(2)	8	100	80	25	40	80	0	20		
methacrylonitril	(3)	7	100	50	105	0					
methacrylonitril	(3)	7	130	160	63	89		<1	43	57	
methacrylamide	(4)	7	120	50	50	97 [e]			53		47
methacrylamide	(4)	8	120	80	240	0 [e]					
methacrylamide	(4)	9	120	50	17	93 [e]			55		45
N-benzylmethacrylamide	(5)	6	120	80	72	99	30		45		25
N-benzylmethacrylamide	(5)	8	120	80	80	99			54		46

[a] Reaction conditions: 30 ml toluene; $p(CO) = p(H_2) = 1:1$; 100 mmol substrate; metal/P = 1/4 (for the rhodium containing in-situ catalysts). [b] **6** = $Rh_4(CO)_{12}$; 7 = $[Rh(CO)_2Cl]_2$/(*S*,*S*)-Chiraphos/NEt_3(1:4:20); **8** = [(*R*,*R*)-Diop]$Pt(SnCl_3)Cl$; **9** = $[Rh(CO)_2Cl]_2/PPh_3/NEt_3$(1:8:20). [c] (mol substrate consumed/mol substrate) × 100; determined by GC and ^{1}H-NMR. [d] (mol product/mol substrate consumed) × 100. [e] 50–65% of the original substrate was polymerized. [f] Compare Ref. 14.



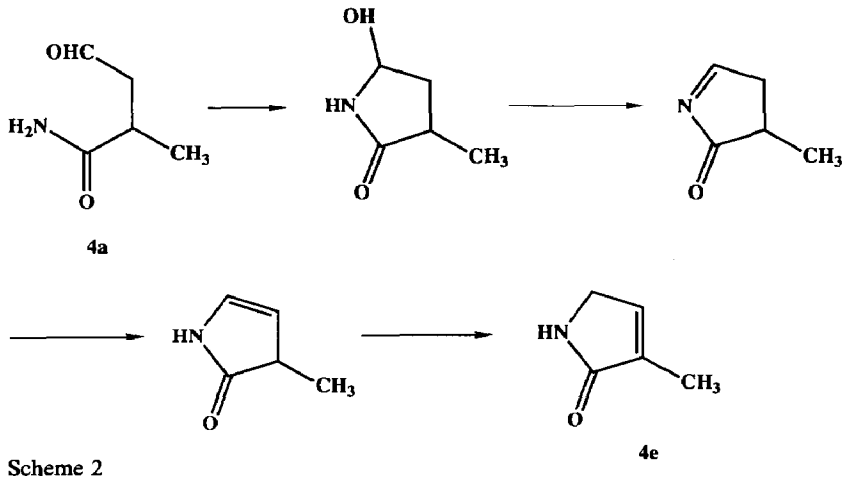
ee 37.2% (*S*)	ee 20.0% (*S*)	ee 23.8% (*R*)
$\Delta G^{\#}$ 557 cal/mol	$\Delta G^{\#}$ 283 cal/mol	$\Delta G^{\#}$ 358 cal/mol
ee 55.5% (*S*)	ee 35.0% (*S*)	ee 49.5% (*R*)
$\Delta G^{\#}$ 800 cal/mol	$\Delta G^{\#}$ 467 cal/mol	$\Delta G^{\#}$ 694 cal/mol

Fig. 1. Type of the enantioface predominantly reacting and the extent of the asymmetric induction in the hydroformylation of some esters of methacrylic acid catalyzed by [(*R*,*R*)-Diop]Pt($SnCl_3$)Cl (**8**) based on a previously proposed model for the transition state [23]. The first set of data was obtained at 100 °C and 80 atm; the second at 50 °C and 200 atm.

the absolute configuration of **1a** were determined for dimethyl methylbutandioate, for which maximum optical rotation and absolute configuration are known [18]. This compound was obtained from the primary hydroformylation product **1a** through oxidation and esterification [19]. Similar regio- and chemo-selectivity was observed in the hydroformylation of t-butyl methacrylate (**2**) catalyzed by **8**. The enantiomeric excess of the produced aldehyde **2a** was ~ 20%, as determined by NMR spectroscopy in the presence of $Eu(tfc)_3$ as the chiral shift reagent. That of the predominant enantiomer (*S*) was determined through conversion of **2a** to methylbutanedioic acid via oxidation and saponification [19]. It is noteworthy that use of the same catalyst precusor **8** under the same reaction conditions leads to predominant formation of the (*R*)-enantiomer (23.8% enantiomeric excess) in the hydroformylation of phenyl methacrylate [14] (Fig. 1).

The hydroformylation of methacrylonitrile (**3**) takes place only under more severe conditions. With **7** as the catalytic system a considerable amount of hydrogenation product **3c** is formed, and some **c3** 2-cyano-2-methylpropan-1-ol (**3d**) was also isolated. The formation of **3d** is probably a consequence of the consecutive hydrogenation of the primary hydroformylation product **3b**, the presence of traces of which could be detected only by linked GC-MS.

Methacrylamide **4** undergoes neither hydroformylation nor hydrogenation at 120 °C under 80 atm of synthesis gas when [(*R*,*R*)-Diop]Pt($SnCl_3$)Cl **8** is the catalyst precursor; a large amount of polymeric material is formed under these conditions. Phosphine-modified rhodium catalysts **7** and **9** (**9** is $[Rh(CO)_2Cl]_2/PPh_3$ with a 1/8 molar ratio) induce formation of the lactame **4e** (Scheme 1) in addition to a rather extensive hydrogenation. However, in this case again much of the substrate (50–65%) is converted into polymeric material. The formation of lactam **4e** can be accounted for in terms of Scheme 2. Formylation of the substrate must



Scheme 2

take place regioselectively at the methylene group; subsequent hemiamide formation, followed by dehydration and isomerization ultimately gives **4e**. Thus, the regioselectivity of the hydroformylation of **4** is the opposite to that observed for **1** and **3** in the presence of the same catalytic system **7**.

Polymeric by-products are not formed under hydroformylation conditions when *N*-benzylmethacrylamide is the substrate. The platinum catalyst precursor **8** gives, along with a rather extensive hydrogenation, about a 50% yield of lactam **5e**, which must be formed in a similar way to **4e**. With $Rh_4(CO)_{12}$ (**6**) as the catalyst precursor **5a**, the possible intermediate in the formation of **5e**, was also detected.

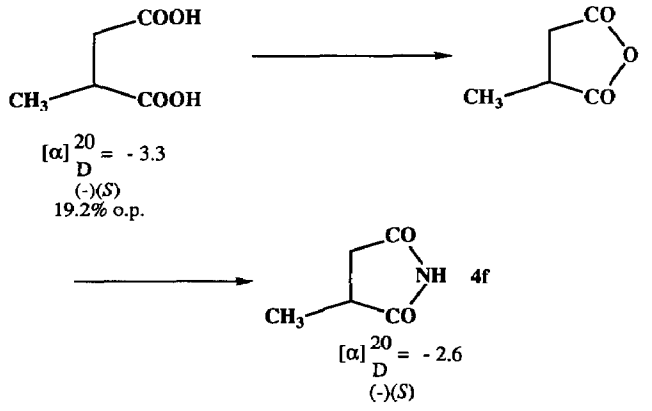
The results obtained in the hydrocarbomethoxylation (Scheme 1, X = CH_3O) of the same substrates with palladium catalysts are shown in Table 2. Methyl methacrylate (**1**) was hydrocarbomethoxylated with either [(*R*,*R*)-Diop]$PdCl_2$ (**10**) or [(*R*,*R*)-Diop-dbp]$PdCl_2$ (**11**) (Diop-dbp is [2,2-dimethyl-1,3-dioxolane-4,5-diylbis(methylene)]bis[5*H*-benzo[*b*]phosphinindole]) as the catalyst precursor. Use of catalyst precursor **10** leads to regiospecific carbonylation to give with > 99% regioselectivity, dimethyl methylsuccinate, as expected [20]. Under the conditions used a fair enantioselectivity is also observed, the (*S*)-enantiomer being formed predominantly with a ~ 38% optical purity. A much lower catalytic activity was observed for catalyst precursor **11**. The reaction in this case is less regioselective, the ratio of dimethyl methylsuccinate to dimethyl dimethylmalonate being 3/1; the enantioselectivity is also lower (~ 9%); the predominant enantiomer produced (*R*) is the opposite of that obtained with the catalytic system **10**. The lower catalytic activity and selectivity of **11** than of **10** was observed previously in the hydrocarbalkoxylation of 2-phenylpropene [21]. However, with this substrate **11** was found to be more enantioselective than **10** under similar conditions, both catalyst precursors producing the same predominant enantiomer. Hydrocarbomethoxylation of methacrylonitrile **3** could not be successfully carried out even under rather severe conditions (140 °C, 480 atm carbon monoxide). This is probably due to the strong coordinating ability of the substrates, which leads to destruction of the catalytic activity of the system. In the hydrocarbomethoxylation of methacrylamide (**4**), the main product formed was methylsuccinimide (**4f**). Only traces of **4a′** i.e., of the direct product of the hydrocarbomethoxylation of **4** were detected through linked

Table 2

Hydrocarbalkoxylation of some methacrylic acid derivatives with $PdCl_2$[(R,R)-Diop] (**10**) as the catalyst precursor [a]

Substrate		Temp. (°C)	p(CO) (atm)	Reaction time (h)	Conv. [c] (%)	Products [d] (%) (e.e., abs. conf.)				
						a′	b′	c	e	f
methyl methacrylate	(**1**)	120	216	22	97	99(37.9; *S*)	1			
methyl methacrylate [b]	(**1**)	120	212	255	12	75(8.7; *R*)	25			
methacrylonitril	(**3**)	140	480	120	0					
methacrylamide	(**4**)	120	203	40	59	<1		25	14	61(37.3; *R*)

[a] Reaction conditions: 1.1 mmol $PdCl_2$[(*R*,*R*)-Diop] (**10**); 100 mmol substrate; 200 mmol methanol; 40 ml benzene. [b] 1.1 mmol $PdCl_2$[(*R*,*R*)-Diop-dbp] (**11**) as the catalyst precursor. [c] and [d] See corresponding footnotes in Table 1.



Scheme 3

GC-MS. The enantioselectivity is very similar to that observed for the reaction of methyl methacrylate (**1**), but the opposite predominant enantiomer is formed. The maximum optical rotation and the relationship between sign of the optical rotation and absolute configuration were determined by reference to methylbutanedioic acid, according to Scheme 3. Some unsaturated lactam **4e** is also formed. More surprising is the formation of the hydrogenation product, **4c**, of the substrate. The possibility that methanol may act as a hydrogen donor in the presence of transition metal catalysts has been previously recognized [22].

Conclusions

Methacrylic esters undergo carbonylation reactions with a good selectivity; for hydroformylation, in particular, the regioselectivity can be controlled to a quite large extent by changing the catalyst precursor. When methacrylonitrile or methacrylamides are the substrates, further reactions take place after hydroformylation; in the simplest case reduction of the aldehyde takes place, otherwise cyclization can occur with formation of saturated or unsaturated lactams.

For the platinum-catalysed hydroformylation of the esters of methacrylic acid with [(*R*,*R*)-Diop]Pt($SnCl_3$)Cl **8**, the type and extent of enantioface selection are compared in Fig. 1. The figure presents a model of the transition state for the formation of the alkyl-complex intermediate that is based on information obtained previously for reactions involving olefinic hydrocarbons [23]. This comparison reveals the interplay of electronic and steric factors on the asymmetric induction processes that take place during hydroformylation.

Experimental

Reagents

The ditertiary phosphines (Diop, Diop-dbp, and Chiraphos) were prepared by published procedures [24–26]. Toluene and benzene were distilled under nitrogen from sodium in the presence of benzophenone. The substrates used (**1**, **3**, and **4**) were Fluka products (purum) and were distilled before use. *N*-Benzyl-methacrylamide (**5**) [27] and t-butyl methacrylate (**2**) [28] were prepared as described previously. The ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker WH 90, Bruker AM

300 WB, or Varian T-60 spectrometer with tetramethylsilane as internal standard. The MS-spectra were recorded on a Hitachi Perkin Elmer RMU-6L spectrometer, in most cases coupled with a GLC apparatus.

High-pressure carbonylation reactions

In a typical hydroformylation a solution of 0.025 mmol of $[Rh(CO)_2Cl]_2$, 0.1 mmol of diphosphine, and 100 mmol of substrate in 30 ml toluene was transferred under nitrogen to a 150 ml stainless steel autoclave. (Solid substrates (**4** and **5**) were put directly into the autoclave). The autoclave was pressurized to the appropriate pressure ($CO/H_2 = 1/1$) and placed in an oil bath with continual agitation by an arm shaker. The pressure was monitored throughout the reaction. After cooling and venting, the solution was removed and immediately analyzed by GLC, then fractionally distilled to allow further characterization of the products.

In the hydrocarbalkoxylation reactions 1 mmol [(*R*,*R*)-Diop]$PdCl_2$ (**10**) and 100 mmol **3** were placed in the autoclave. A solution of 200 mmol of methanol, 40 ml of benzene and 2 drops of hydrochloric acid was sucked into the evacuated autoclave, which was then pressurized with pure carbon monoxide. The subsequent procedure was as described above.

Characterization of the products

The analytical data for **1a**, **1a′** and the determination of their absolute configuration have been reported previously [14]. Characterizations of simple commercial products (e.g. **1c**, **2c**, **3c**) are not described.

*Methyl 2-formyl-2-methyl-propionate (**1b**).* ^{1}H-NMR (60 MHz, $CDCl_3$): 9.64 (s, 1H, C*H*O); 3.8 (s, 3H, OCH_3); 1.39 (s, 6H, CH_3).

*t-Butyl 3-formyl-2-methylpropionate (**2a**).* ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.64 (t, 1H, C*H*O); 2.60-2.80 (m, 2H, CH_2); 2.21-2.28 (m, 1H, C*H*); 1.40 (s, 9H, $(CH_3)_3C$); 1.11 (d, $J = 7.1$ Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 75 MHz):200.5 (*C*HO); 174.0 (*C*OO); 80.8 ($C(CH_3)_3$); 47.1 (CH_2); 34.8 (*C*H); 28.0 ($CH_3)_3C$); 17.1 (CH_3).

*2-Cyano-2-methyl-propanol (**3d**).* ^{1}H-NMR (60 MHz, $CDCl_3$): 3.57 (s, 2H, CH_2); 2.30 (br s, 1H, O*H*); 1.36 (s, 6H, CH_3); ^{13}C-NMR (22.6 MHz, $CDCl_3$): 124.3 (*C*≡N); 68.2 (CH_2); 34.9 (*C*–CN); 22.7 (CH_3).

*3-Methyl-3,4-dehydrobutyrolactam (**4e**).* ^{1}H-NMR (60 MHz, $CDCl_3$): 7.7 (br s, 1H, N*H*); 6.75 (m, 1H, C*H*); 3.92 (m, 2H, CH_2); 1.90 (m, 3H, CH_3); ^{13}C-NMR (22.6 MHz, $CDCl_3$): 175.6 (*C*ONH); 138.3 (*C*H); 134.6 (=*C*CH_3); 46.4 (CH_2); 19.1 (CH_3).

*3-Methylsuccinimide (**4f**).* ^{1}H-NMR (60 MHz, $CDCl_3$): 8.35 (br s, 1H, N*H*); 3.20–2.0 (m, 3H, CH_2C*H*); 1.36 (d, $J = 7.5$ Hz, 3H, CH_3).

*1-Benzyl-3-methyl-3,4-dehydrobutyrolactam (**5e**).* ^{1}H-NMR (300 MHz, $CDCl_3$): 6.60 (m, 1H, =C*H*); 4.56 (s, 2H, CH_2Ph); 3.67 (m, 2H, CH_2N); 1.90 (m, 3H, CH_3).

*N-Benzyl-isobutyramide (**5c**).* ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.5 (br s, 1H, N*H*); 4.35 (d, $J = 5.6$ Hz, 2H, NHCH_2); 2.39 (h, 1H, $J = 6.9$ Hz, C*H*$(CH_3)_2$); 1.13 (d, 6H, $J = 6.9$ Hz, CH($CH_3)_2$). MS (*m*/*z*/r.i.): 177/50 (M^+); 162/8; 107/15; 106/20; 91/100

Acknowledgements

We acknowledge helpful discussions with the late Prof. P. Pino on the "Diplomarbeit" of R.K., and financial support from the Swiss Nationalfonds.

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