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Rhodium catalysed hydroformylation of unsaturated esters ☆

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Abstract—Rhodium catalysed hydroformylation of unsaturated esters has been studied. A pronounced temperature dependence was observed on the regioselectivity and catalytic activity for these reactions, and under the appropriate conditions, it is possible to obtain preferentially either linear or quaternary products. A quaternary selective hydroformylation of methyl atropate to give 1,3-aldehydic esters has also been developed.

1,3-Difunctional and 1,4-difunctional carbonyl compounds are useful intermediates in organic synthesis and pharmaceutical chemistry. A potentially attractive and atom efficient strategy that could produce a wide range of these compounds is alkoxycarbonylation of terminal alkynes, followed by regioselective hydroformylation. The resulting aldehydes should be readily transformable by reductive amination/reduction/oxidation into a range of compounds including amino-alcohols, γ-butyrolactones and diacids. Hydroformylation is well established as an important reaction for bulk chemical synthesis, but in recent years there has been growing interest in the application of this reaction as a functional group tolerant, completely atom efficient C–C bond forming reaction for selective organic synthesis.[1]

Acrylates have been found to be amongst the least reactive substrates in hydroformylation, and consequently studies which demonstrate their high-yielding, selective transformation into 1,3- and 1,4-difunctional compounds are relatively scarce.[2] Furthermore, the formation of potentially valuable chiral 1,3-aldehydic esters from 2-substituted 2-propenoate esters is further disadvantaged by defying the widely quoted Keulemans[1] (empirical) rule, which states that 'in hydroformylation, formyl groups are not produced at quaternary carbon centres'.[3] However, a review of the literature shows that Alper and co-workers have already made some progress in this regard. Hydroformylation of methyl methacrylate (MMA) in the presence of [Rh(COD)(η^6-Ph-BPh$_3$)]/dppb gave a 54% yield of the quaternary aldehyde $Me_2C(CHO)(CO_2Me)$ with a 9:1 selectivity.[4] An earlier paper showed a pronounced temperature and pressure effect on the regioselectivity of MMA hydroformylation: at high pressure and lower temperatures, high selectivity for quaternary Me_2C-$(CHO)(CO_2Me)$ could be obtained using [Rh(PPh$_3$)$_3$(CO)H] as catalyst. Unfortunately, at these lower temperatures (40–60 °C), catalytic activity is compromised.[5] The aim of this study was to understand further the factors affecting rate and selectivity in hydroformylation of the more highly substituted unsaturated esters, which have recently become more accessible using palladium catalysed alkoxycarbonylation. It was envisaged that highly reactive phosphite based catalysts might promote a high yielding regioselective reaction.

In order to discover the ideal ligand and conditions for hydroformylation of unsaturated esters, a range of ligands was screened in the hydroformylation of *tert*-butyl methacrylate (Scheme 1).[2b] Representative results are shown in Table 1. At 100 °C, the linear aldehyde is formed preferentially, but high selectivity is only obtained at low pressures. Phosphine ligands (including the normally highly linear selective BISBI ligand)[6] fail to give either acceptable yields or regioselectivity in this reaction. The use of triphenylphosphite as the ligand gives a near perfect conversion to the linear product (Table 1; entry 7). The use of the bulky phosphite, tdtbpp[7] at 40 °C and 40 bar reverses the selectivity in

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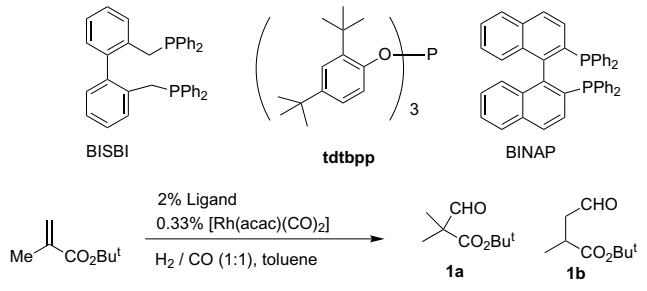
Table 1. Rhodium catalysed hydroformylation of *tert*-butyl methacrylate

Entry	Ligand	Conversion (%)	**1b/1a**	Temperature (°C)	Pressure (bar)	Time (h)
1	Ph_3P	95	3.2/1	100	18	20
2	Ph_3P	51	12.0/1	100	8	20
3	BINAP	23	18.0/1	100	8	20
4	BINAP	25	5.1/1	100	18	40
5	BISBI	91	2.9/1	100	18	40
6	BISBI	25	5.0/1	100	8	20
7	$(PhO)_3P$	95	38.0/1	100	8	20
8	tdtbpp	95	0.6/1	40	40	30

Reactions were carried out in a 100 mL stainless steel autoclave under the conditions described in the Table 1 and Scheme 1. Conversion, GC yields and selectivity were measured using a GC equipped with a FID detector and are measured against biphenyl (20 mol%) added as an internal standard. The identity of the products and the product distributions were further confirmed by ^{1}H NMR integration and EI and CI mass spectrometry.

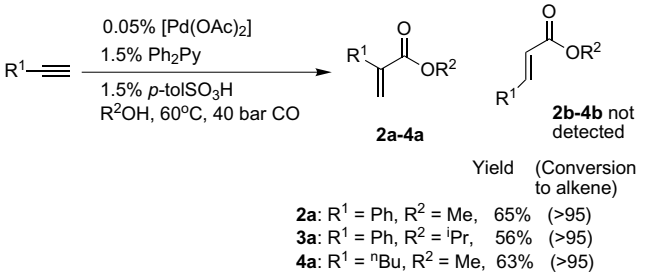


Scheme 1. Ligands used in the hydroformylation of *tert*-butyl acrylate.

favour of the quaternary aldehyde **1a** (Table 1; entry 8, Scheme 1).

Since styrenes tend to favour branched selectivity in rhodium catalysed hydroformylation,[8] it was envisaged that hydroformylation of hitherto unstudied atropate esters might show selectivity for the quaternary aldehyde **5a**. These compounds are potentially useful intermediates for a range of compounds (including, for example, amino-alcohols $Ph(Me)C(CH_2OH)(CH_2NHR)$ that have been investigated as β-adrenoceptor blocking agents).[9]

The atropate type esters **2a** and **3a** were prepared using the catalyst system designed by Drent et al. for carbonylation of propyne.[10] This catalyst gave essentially complete conversion and regioselectivity towards isomers **2a** and **3a**. Some material was unavoidably lost during removal from the autoclave and during vacuum distillation thus giving ~60% yields of pure material (Scheme 2).



Scheme 2. Synthesis of unsaturated esters **2a**–**4a** using palladium catalysed alkoxycarbonylation of alkynes.

The phosphite based catalysts were used for hydroformylation of atropate esters **2a** and **3a** (Scheme 3). These substrates were even less reactive than *tert*-butyl methacrylate and required longer reaction times for complete conversion. A small amount (~10%) of hydrogenation product was also detected in these reactions. However, at lower temperature and higher pressure, it proved possible to form a quaternary carbon centre selectively using rhodium catalysed hydroformylation (Table 2; entry 1, synthesis of **5a**). Some of this material was purified using flash chromatography and showed the expected spectroscopic data for the pure regioisomer **5a**.[11,†] In addition, at 100 °C and low pressure, it was possible to form the linear aldehyde with good selectivity (12:1) using the conditions in Table 2; entry 2. The bulky isopropyl ester proved extremely unreactive in this reaction (higher temperatures than 100 °C were not attempted since tropolate esters are known to polymerise at elevated temperatures). The use of the catalyst system based on tdtbpp did not appear to give any product at all in this case (not shown in Table 2).

In order to investigate the role of the phenyl group in allowing access to the quaternary aldehydes, the hydroformylation of 2-*n*-butyl acrylic acid methyl ester, **4a** (prepared using the Drent methoxycarbonylation reaction) was also attempted using the triphenylphosphite based catalyst system (Table 2; entries 5–7). As can be seen, sufficient quaternary selectivity or conversions in these reactions could not be obtained under the conditions studied. The presence of an aryl group may therefore be advantageous in these reactions.

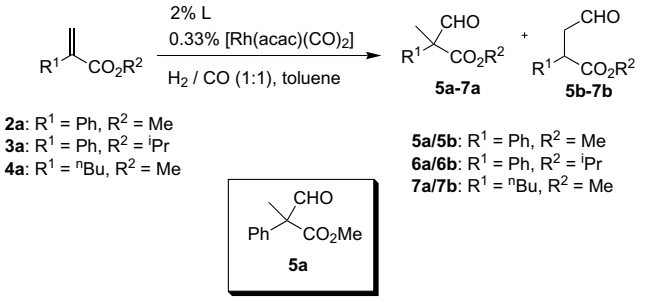
In conclusion, it has been shown that regioselective methoxycarbonylation of phenylacetylene followed by regioselective hydroformylation constitutes a valid method to construct 1,3-dicarbonyl compounds bearing a quaternary carbon centre (and thus contradicting Keulemans rule). Under alternative reaction conditions, it is also possible to prepare 1,4-dicarbonyl compounds of high regioisomeric purity.

† Experimental procedures and selected spectroscopic and characterisation data are available in the supplementary material.

Table 2. Hydroformylation of unsaturated esters **2a**–**4a**

Entry	Alkene	Ligand	Conversion (% hydrog. product)	b/a (a = quaternary product)	Pressure (bar)	Time (h)	Temperature (°C)
1	**2a**	tdtbpp	>98 (13)	1/13	35	70	45
2	**2a**	tdtbpp	>98 (13)	12.2/1	12	40	100
3	**3a**	$(PhO)_3P$	9 (n.d.)	1/2	40	20	40
4	**3a**	$(PhO)_3P$	24 (n.d.)	12/1	8	20	100
5	**4a**	$(PhO)_3P$	49 (<5%)	11/1	8	20	100
6	**4a**	$(PhO)_3P$	15 (n.d.)	1/3.7	32	40	40
7	**4a**	tdtbpp	33 (n.d.)	1/1.7	32	70	50

Reactions were carried out in a 100 mL stainless steel autoclave under the conditions described in the Table 2 and Scheme 3. Conversion, GC yield and selectivity were measured using a GC equipped with a FID detector and are measured against biphenyl (20 mol%) added as an internal standard. Product identities and distributions were further confirmed by ^1H NMR integration and EI and CI mass spectrometry.



Scheme 3. Hydroformylation of esters **2a**–**4a**.

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