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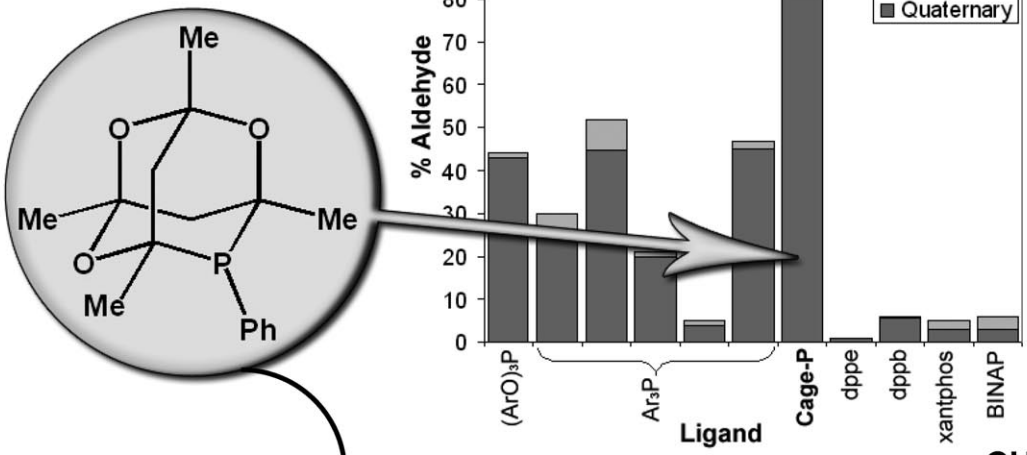
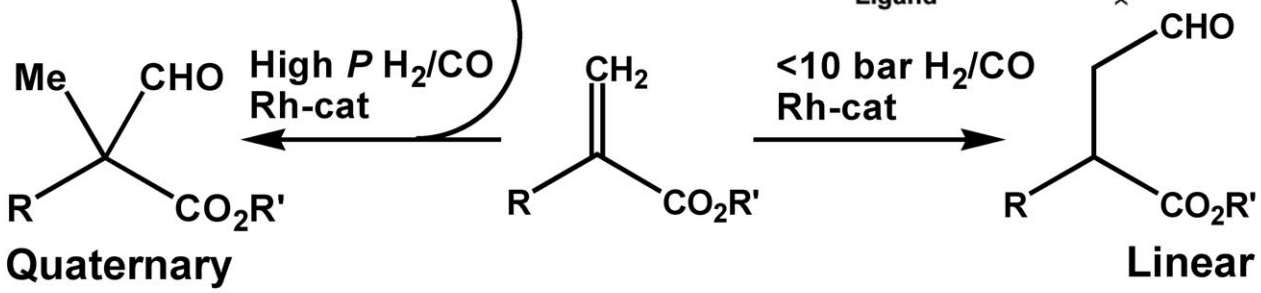
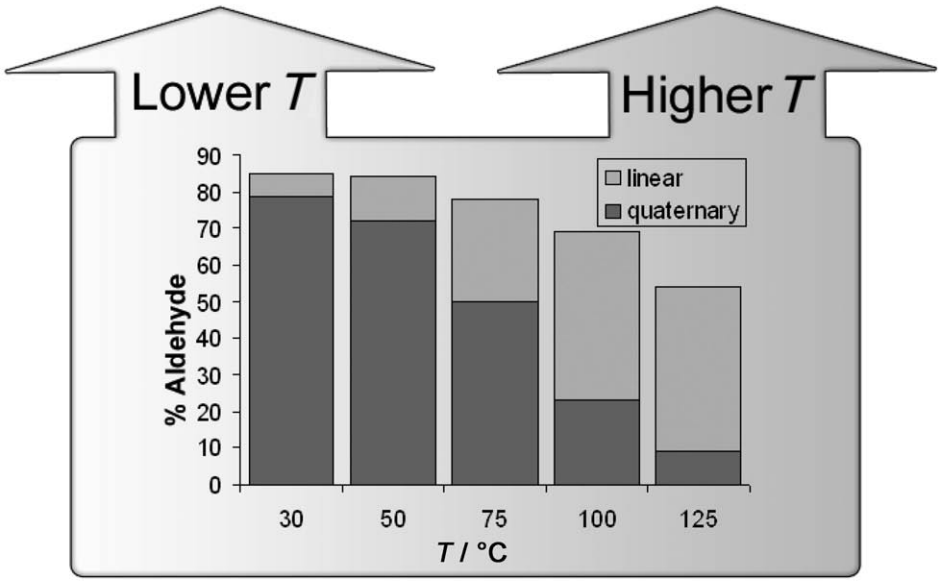
Keuleman's Rule "*In hydroformylation, formyl groups are not produced at quaternary carbon centres*"

Optimal choice of ligand, temperature and pressure makes quaternary hydroformylation practical







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Highly Regioselective Rhodium-Catalysed Hydroformylation of Unsaturated Esters: The First Practical Method for Quaternary Selective Carbonylation

Matthew L. Clarke* and Geoffrey J. Roff[a]

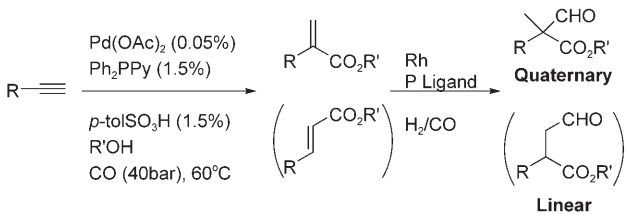
Abstract: Highly regioselective hydroformylation of unsaturated esters can be achieved when a highly reactive, ligand-modified, rhodium catalyst is employed near ambient temperatures (15–50 °C) and pressures over 30 bar. The use of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane shows distinct advantages over other commonly applied phosphanes in terms of reaction rate, and regio- and chemoselectivity. Hydroformylation of a range 1,1-di- and 1,1,2-trisubstituted unsaturated esters yields quaternary aldehydes that are forbidden products according to Keulemans Rule. The aldehydes can be reductively aminated with molecular hydrogen to give β-amino acid esters in high yield. The overall green chemical process involves converting terminal alkynes into unusual β-amino acid esters with only water generated as an essential byproduct. This catalytic system has also been applied to the hydroformylation of simple 1,2-disubstitued unsaturated esters, which have been hydroformylated with excellent α-selectivity and good chemoselectivity for the first time.

Keywords: aldehydes · atom efficiency · homogeneous catalysis · hydroformylation · rhodium

Introduction

One of the challenges facing the chemical industry is to retain the capacity to synthesise complex molecules, while significantly reducing the environmental impact of the synthetic procedures required. The development of selective procedures that do not generate waste products is therefore an important objective that should give process chemists an improved arsenal of clean methodology. Hydroformylation of alkenes is an excellent example of a potentially 100% atom efficient reaction, and has been extensively used in the industrial synthesis of simple linear aldehydes (production is estimated at ~7 million tonnes per annum).[1–4] Enantioselective hydroformylation of some commodity alkenes, such as styrene, vinyl acetate and allyl cyanide, has also been an active topic of research in both academia and industry, with some notable advances in recent years.[5–13] However, despite these precedents, hydroformylation is underused in organic syntheses, with little known about how more complex substrates perform in this reaction.[14–16]

Low-molecular-weight, densely functionalised aldehydes are very important building blocks, in particular for the synthesis of secondary amines. Secondary amines are an extremely common motif in compounds of pharmaceutical interest, with reductive amination the workhorse for their preparation. This research project was therefore aimed towards preparing these building blocks in a highly efficient manner from commodity chemicals (terminal alkynes) with no harmful waste products. The proposed route is shown in Scheme 1 and utilises the potentially 100% atom-efficient



Scheme 1. Palladium-catalysed alkoxycarbonylation followed by hydroformylation.

α-selective alkoxycarbonylation of terminal alkynes developed by Drent and co-workers for methyl methacrylate synthesis from propyne,[17] coupled with the unexplored (potentially 100% atom efficient) hydroformylation of the resulting 1,1-disubstituted esters (Scheme 1).

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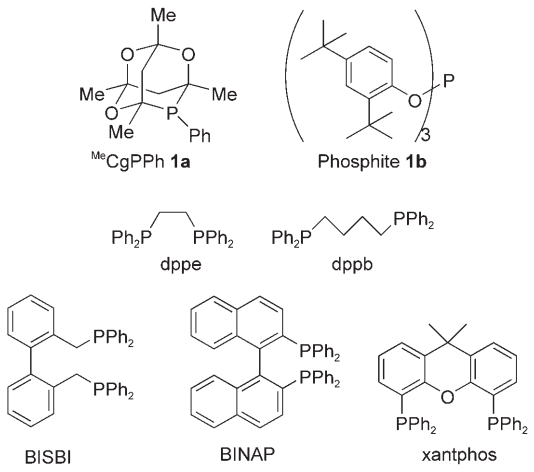
There are two possible regiochemical outcomes from this reaction, a quaternary or linear aldehyde, with the linear product being predicted based on the prevailing dogma in hydroformylation chemistry. The low probability of forming quaternary aldehydes using this methodology is emphasised by the widely quoted Keulemans rule that states: "in hydroformylation, formyl groups are not produced at quaternary carbon centres".[15,16,18,19] However, an inspection of the literature suggested to us that this empirical rule was more of a general observation. In particular, there are a couple of isolated examples of chelation controlled quaternary selective hydroformylation reactions.[20–23] In these examples, the preferential formation of a quaternary rhodium alkyl species stabilised by a second chelate interaction seems the most likely explanation for the selectivity observed. More relevantly, Alper and co-workers had shown that hydroformylation of methyl methacrylate using [Rh(cod)(η^6-C_6H_5-BPh_3)] and dppb (cod = cyclooctadiene, dppb = 1,2-bis(diphenylphosphano)benzene) as ligand gave a 54% yield of the quaternary aldehyde, $Me_2C(CHO)(CO_2Me)$ with 9:1 regioselectivity.[24] This report in particular gave us some hope that a general procedure for quaternary selective hydroformylation of unsaturated esters could be realised if the correct catalyst and reaction conditions could be found.

Results and Discussion

Research described in our preliminary communication demonstrated that quaternary regioselectivity could be obtained providing very reactive rhodium catalysts derived from bulky monophosphite ligands, **1b** were employed. However,



regioselectivity (between 1.7:1 and 13:1) and chemical yield were not quite high enough to be a practical method for synthesis.[25] In an initially unrelated project, we collaborated with the Pringle group to show the remarkably high activity of phenylphosphatrioxaadamantanes (**1a**) in rhodium-catalysed hydroformylation of hex-1-ene.[26] This paper also notes that this easily prepared, air-stable phosphane seemed to hold some advantage in the hydroformylation of methyl atropate in two preliminary reactions under unoptimised conditions. This observation led us to thoroughly investigate the effect of ligands, solvents, temperature, pressure, and substrate in hydroformylation of unsaturated esters, and here we describe how these studies have led to a practical procedure for the synthesis of quaternary substituted aldehydes, and enabled high-yielding α-selective hydroformylation of 1,2-substituted unsaturated esters for the first time.

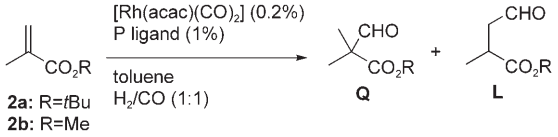
If the hydroformylation of *tert*-butyl methacrylate (**2a**) is performed at high temperatures and low pressure the products were found to be predominantly linear (Table 1 and Scheme 2). Using the cage phosphane catalyst **1a**, *tert*-butyl methacrylate was hydroformylated at 50 °C under 50 bar of syngas with high quaternary/linear selectivity. Recently, Reetz and Li have carried out hydroformylation of *tert*-butyl methacrylate, using mixtures of monodentate phosphorus ligands, although no other substrates were reported.[27] Their results show that the majority of ligands give poor selectivity but several combinations of ligand give similarly excellent regioselectivity.

Hydroformylation of the methyl ester (**2b**) gave even higher selectivity to the quaternary aldehyde. The use of alternative solvents to toluene gave decreased regioselectivity. Since methyl methacrylate is a nonviscous liquid and to

Table 1. Hydroformylation of methyl methacrylate and *tert*-butyl methacrylate.

Alkene	Ligand	Conversion [%][a]	Q/L[a]	Conditions[b]
2a	PPh_3	95	1/3.2	A
2a	PPh_3	51	1/12.0	B
2a	BINAP	23	1/18.0	B
2a	BINAP	25	1/5.1	C
2a	BISBI	91	1/2.9	C
2a	BISBI	25	1/5.0	B
2a	$(PhO)_3P$	95	1/38.0	B
2a	PPh_3	99	11.3/1	D
2a	**1b**	99	1.3/1	D
2a	**1b**	95	1/0.6	E
2a	**1a**	98	14.8/1	D
2b	PPh_3	99	54/1	F
2b	**1b**	99	11/1	F
2b	**1a**	99[c]	45/1	F
2b	**1a**	99[d]	11/1	F
2b	**1a**	99[e]	50/1	F

[a] Determined by proton NMR spectroscopy. [b] Reaction conditions: A) 100 °C, 18 bar, 20 h; B) 100 °C, 8 bar, 20 h; C)100 °C, 18 bar, 40 h; D) 50 °C, 50 bar, 70 h; E) 40 °C, 40 bar, 30 h; F) 50 °C, 50 bar, 20 h. [c] THF used as reaction solvent. [d] DCM used as reaction solvent. [e] 97% isolated yield.



Scheme 2. The hydroformylation of methyl and *tert*-butyl methacrylate.

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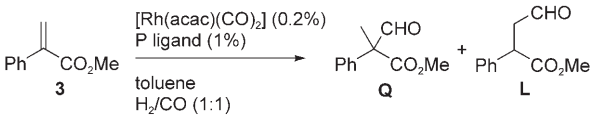
demonstrate the full power of this catalytic system, we hydroformylated neat methyl methacrylate using a substrate/catalyst ratio of 10000 to obtain excellent regioselectivity and almost complete conversion. Analysis of the reaction mixture reveals quaternary aldehyde (95%), linear aldehyde (1.5%) hydrogenated product (1.5%) with only 2% of the methyl methacrylate present.

A thorough examination of the effect of ligands, temperature and pressure in the hydroformylation of methyl atropate (**3**) and esters **4–7** has been carried out (Tables 2 and 3 below). Substrates **3**, **5** and **6** were readily prepared by methoxycarbonylation of the alkynes. Once again, rhodium complexes of **1a** gave by far most impressive results with respect to both regio and chemoselectivity.

For reaction of methyl atropate at 100°C, (Scheme 3; Table 2; entries 11–14), the amount of linear product reduces dramatically with an increase in pressure and the



Scheme 3. Hydroformylation of methyl atropate, **3**.

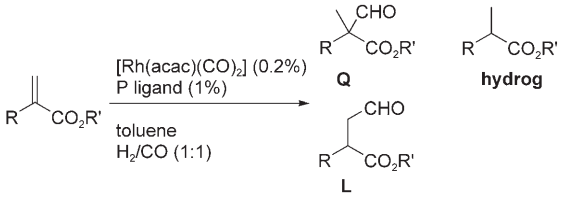
Table 2. Hydroformylation of methyl atropate.

Entry	Ligand	*T* [°C]	*P* [bar]	*t* [h]	Aldehyde [%][a] (% hydrog)	Q/L[a]
1	**1b**	30	50	90	45 (55)	>50/1
2	PPh_3	50	50	20	30 (46)	6/1
3	$(3,5\text{-}(CF_3)_2C_6H_3)_3P$	50	50	20	52 (7)	6.4/1
4	$(4\text{-}Cl\text{-}C_6H_4)_3P$	50	50	20	21 (22)	20/1
5	$(4\text{-anis})_3P$[c]	50	50	20	5 (79)	4.0/1
6	$(4\text{-tolyl})PPh_2$	50	50	20	47 (19)	23/1
7	dppe	50	50	20	1 (16)	>100/1
8	dppb	50	50	20	6 (14)	>100/1
9	xantphos	50	50	20	5	1.5/1
10	BINAP	50	50	20	6	1/1
11	**1a**	100	5	70	45 (55)	1/>100
12	**1a**	100	10	40	60 (30)	1/28
13	**1a**	100	25	24	70 (30)	1/5.3
14	**1a**	100	50	24	76 (24)	1.6/1
15	**1a**	75	50	24	87 (13)	16/1
16	**1a**	50	50	20	90 (10)	44/1
17	**1a**	30	50	90	92[b] (8)	>100/1
18	**1a**	15	50	70	55 (1)	>100/1
19	**1a**	50	25	66	86 (14)	42/1
20	**1a**	50	60	20	86 (14)	41/1

[a] Determined by proton NMR spectroscopy; starting material is the only other chemical making up mass balance. [b] 91% isolated yield. [c] $(4\text{-anis})_3P = (4\text{-MeO-}C_6H_4)_3P$.

amount of hydrogenation is also reduced. In experiments in which the pressure was kept constant (entries 14–18), the amount of linear product and hydrogenation decreased with decreasing temperature. Under optimal conditions hydrogenation was suppressed to 8% with essentially complete quaternary selectivity (entry 17). All other commonly applied monodentate ligands performed badly in this reaction giving relatively low conversions or favouring hydrogenation. Bidentate ligands tested showed very little reactivity.

To demonstrate the scope of this new process, a series of other 1,1-disubstituted alkenes were hydroformylated with high regioselectivity (Scheme 4; Table 3). The hydrogenation byproduct was again a problem in the hydroformylation of dimethyl itaconate (**4**). However, this was essentially eliminated by using phosphane **1a** as ligand.



Scheme 4. Hydroformylation of a range of other 1,2-disubstituted unsaturated esters (see Table 3 footnotes for reaction conditions).

Table 3. Hydroformylation of 1,1-disubstituted alkenes.

Substrate	Conditions[a]	Conversion [%][b] (% hydrog)	Q/L[b]
MeO_2C CO_2Me **4**	A	99 (20)	>100/1
	B	99 (16)	10/1
	C	99 (3)[c]	92/1
*n*Bu CO_2Me **5**	D	99	5.3/1
	C	30[d]	11/1
NC $(CH_2)_2$ CO_2Me **6**	D	>99	6.6/1
	E	>99 (8)[e]	22/1
MeO_2C CO_2Me **7**	A	94[f]	56/1
	B	54[g]	6.2/1
	C	82[h]	48/1

[a] Reaction conditions: 0.2% $[Rh(acac)(CO)_2]$, toluene, A) PPh_3 (1%), 50°C, 50 bar, 20 h; B) **1b** (1%), 50°C, 50 bar, 20 h; C) **1a** (1%), 50°C, 50 bar, 20 h; D) **1a** (1%) 75°C, 75 bar, 70 h; E) **1a** (1%), 50°C, 50 bar, 70 h. [b] Determined by proton NMR spectroscopy. [c] 93% isolated yield. [d] 70% isomerisation product detected. [e] 69% isolated yield. [f] 6% isomerisation product detected. [g] 45% isomerisation detected. [h] 18% isomerisation detected, 62% isolated yield.

A different problem arose in the hydroformylation of methyl α-butylacrylate (**5**) and the diester **7**. The reactions were sluggish and extensive isomerisation to the trisubstituted ester seemed to have taken place. This suggested the possibility that the reaction of **5** proceeds by the hydroformylation of the more stable trisubstituted alkene (**8**) to the same quaternary product (**9**; Scheme 5). When the reaction was stopped after several hours, NMR spectroscopy showed only aldehyde and trisubstituted alkene **8** to be present lending strong support to this proposal. Direct hydroformylation of the trisubstituted alkene was examined by isolating a pure sample of **8** after three hours of treatment with the Rh catalyst and syngas.

Trisubstituted alkenes (Scheme 6; Table 4) are especially problematic substrates for hydroformylation. Breit and co-

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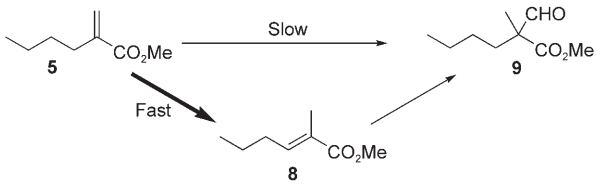
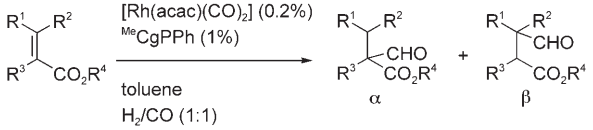


Scheme 5. Proposed isomerisation-hydroformylation.



Scheme 6. Hydroformylation of trisubstituted alkenes (see Table 4 footnotes for reaction conditions).

Table 4. Hydroformylation of trisubstituted alkenes.

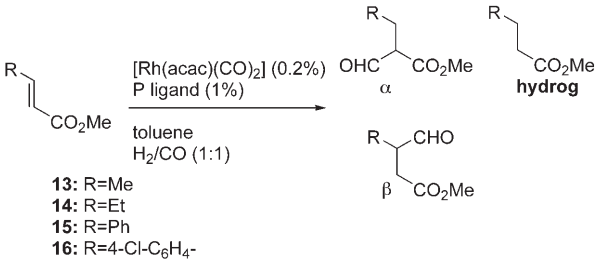
Substrate	Conditions[a]	Conversion [%][b]	α/β[b]
Ph, CO_2Et **10**	A	0	ND
CO_2Me **8**	B	99	10.1/1
Ph, CO_2Me **11**	A	16	12/1
	B	78[c]	7.5/1
CO_2Me **12**	A	48	23/1
	B	99[d]	48/1

[a] Reaction conditions: A)50 °C, 50 bar, 70 h; B)75 °C, 75 bar, 70 h. [b] Determined by proton NMR spectroscopy. [c] 70 % isolated yield, 3 % hydrogenation. [d] 69 % isolated yield.

workers have developed a remarkably active hydroformylation catalyst that gave incredibly high TOF (TOF = turnover frequency) for most substrates.[28] However, hydroformylation of (−)-α-pinene gave only 13 % conversion to the diastereomerically pure linear aldehyde after 16 h emphasising the sluggish nature of the substrates. Methyl tiglate (**12**) has been reported to barely react unless high temperatures are employed and yields below 50 % are observed.[29] It was therefore pleasing to observe that using modified conditions of 75 bar and 75 °C, conversion of **12** to quaternary aldehyde could be achieved using this catalytic system (Table 4). When alkene **8**, previously implicated in hydroformylation of **5**, was examined good quaternary selectivity was observed. A particularly surprising substrate is **11**. In addition to the quaternary aldehyde being disfavoured by Keuleman's rule, it is well established that hydroformylation reactions are normally directed to benzylic positions.[15] However, there is a clear regioselective preference for the quaternary aldehyde. No reaction occurred when **10** was the substrate suggesting that only the 1,1,2-trisubstituted alkenes would react and tetrasubstituted alkenes would most likely be unreactive.

The results show that an ester group has such a strong effect at directing hydroformylation, that disfavoured quaternary aldehydes can be produced with excellent selectivity. The reason this has not been exploited successfully in the past is that the directing effect is somewhat temperature, pressure and ligand dependant and, in particular, is negligible when higher temperatures are employed. Most catalytic systems are ineffective at the temperatures used in this study, with the remarkable difference between other ligands and **1a** evident in Table 2. Finally, it should be noted that the substrates employed are very readily hydrogenated under hydroformylation conditions. The use of ligand **1a** inhibits hydrogenation.

Inspection of the literature reveals that high-yielding regioselective hydroformylation of 1,2-disubsituted unsaturated esters (Scheme 7) has not been possible to date, despite



Scheme 7. Hydroformylation of 1,2-substituted unsaturated esters (see Table 5 footnotes for reaction conditions).

hydroformylation being the cheapest, cleanest route to the fundamental building blocks. We therefore investigated several of these substrates using the new catalyst system and reaction conditions.

A practical process for hydroformylation of methyl crotonate (**13**) has been elusive as phosphane-modified catalysts generally give β-products under the conditions required to achieve full conversion and also suffer from very significant hydrogenation byproduct.[29,30] Our studies, under relatively mild conditions, revealed a high degree of hydrogenation when PPh_3 was used as the ligand (Scheme 7 and Table 5).

Table 5. Hydroformylation of 1-substituted alkenes.

Substrate	Ligand	Conditions[a]	Conversion [%][b] (% hydrog)	α/β[b]
13	PPh_3	C	99 (35)	>100/1
13	**1a**	C	99 (5)[c]	>100/1
13	**1a**	D	99 (3)	>100/1
14	**1a**	D	99 (5)	52/1
15	**1b**	C	99 (14)	5.1/1
15	PPh_3	C	95 (26)	5.6/1
15	**1a**	C	99 (16)	6.0/1
15	**1a**	E	89 (4)	13.8/1
16	**1a**	C	99 (12)[d]	5.9/1

[a] Reaction conditions: A) 15 °C, 50 bar, 20 h; B) 15 °C, 50 bar, 70 h; C) 50 °C, 50 bar, 24 h; D) 40 °C, 75 bar, 90 h, 5:1 CO/H_2 syngas used; E) 30 °C, 80 bar, 60 h, 5:1 CO/H_2 syngas used. [b] Determined by proton NMR spectroscopy. [c] 94 % isolated yield. [d] 64 % isolated yield.

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The influence of the cage phosphane **1a** is dramatic, almost eliminating hydrogenation and retaining near-perfect regioselectivity. Similarly excellent results were obtained in the hydroformylation of **14**. Hydroformylation of methyl crotonate, being a nonviscous liquid was attempted without solvent with substrate/catalyst ratio of 10000. Regioselectivity remained essentially perfect, but more significant hydrogenation (17%) was detected. Hydroformylation of methyl cinnamate (**15**) was also investigated, although studies by Botteghi and Paganelli had shown that the hydrogenation byproduct was more significant than the desired aldehydes with regioselectivity also poor (best α-selectivity: 11% aldehydes with $\alpha/\beta = 2:1$).[31] Our investigation into the α-selective hydroformylation clearly demonstrates that Rh catalysts of the cage phosphane used in conjunction with 50 bar syngas and lower temperature can reduce the amount of hydrogenation byproduct and deliver excellent α-regioselectivity. The regioselectivity could be further increased and hydrogenation further suppressed by using syngas rich in CO (5:1 CO/H_2). Figure 1 shows that this substrate also displays a strong temperature dependence on chemo- and regioselectivity. The analogous cinnamate **16** showed similar selectivity and conversion.

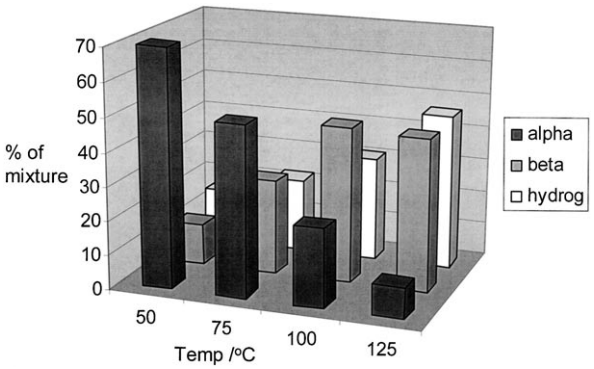
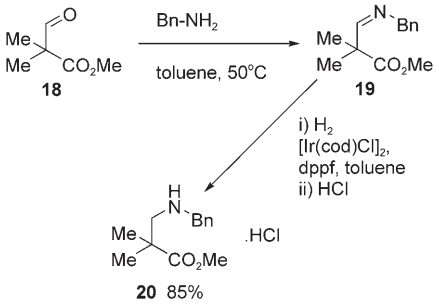


Figure 1. The effect of temperature on regio- and chemoselectivity of hydroformylation of methyl cinnamate.

Reductive amination: β-Amino acids are valuable building blocks in the synthesis of peptidomimetics,[32] therapeutic agents and biologically active compounds.[33,34] Our overall scheme would amount to the conversion of a terminal alkyne into β-amino acid derivative with high yield and only water produced as a necessary byproduct. The catalysts should be removed in the aqueous extraction of the amine salt. To confirm the feasibility of the reductive amination reaction, the aldehyde **18** was readily converted to imine **19** (Scheme 8). The crude imine was hydrogenated in the presence of $[\{Ir(cod)Cl\}_2]$ and dppf (dppf = 1,1′-bis(diphenylphosphano)ferrocene) to a high yield of the amino ester **20**. This result suggests that the quaternary aldehydes produced should be readily reductively aminated using hydrogen, although the direct one-pot route to such compounds via hydroaminomethylation failed to give us the desired compound.[35]



Scheme 8. Reductive amination by imine hydrogenation of one of the quaternary aldehydes.

Conclusion

Aldehydes are fundamental building blocks for organic synthesis. The majority of the aldehydes produced in this paper have been difficult to access in an efficient manner. In the case in which their preparation by hydroformylation has been attempted before, very discouraging results were obtained. We have demonstrated that using phenylphosphatrioxaadamantane as a ligand, a range of unsaturated esters can be hydroformylated with high conversion and regioselectivity to favour the less common α-substituted aldehyde. Keuleman's rule has often been quoted to explain why quaternary aldehydes are not observed in hydroformylation. This paper shows that not only can this class of aldehyde be detected in hydroformylation chemistry, but that methoxycarbonylation followed by hydroformylation represent a clean and practical method for quaternary aldehyde synthesis. Our studies have clearly indicated the necessity for lower reaction temperatures and higher syngas pressure to facilitate such regioselectivity and to reduce the amount of hydrogenation byproducts. It has been demonstrated that β-amino acid derivatives are available in high yield from the aldehydes, thus completing the overall process of synthesising useful chemical building blocks from simple alkynes.

Experimental Section

General: All chemicals and solvents were obtained through commercial sources. Gases were obtained though BOC. Solvents were removed by rotary evaporation on a Heidolph labrota 4000. Flash column chromatography was performed using Davsil silica gel 35–70u 60 A (Fluorochem). NMR were recorded on Bruker Avance 300 instruments. Proton signal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or multiples thereof. Infrared spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR system. Liquids were analysed as films, solids were analysed as KBr discs or nujol mull. Mass spectra were recorded on Waters Micromass LCT fitted with lockspray for accurate mass (ESI) or GCT (CI) instruments. Hydroformylation experiments were carried out in small glass vessels inside stainless steel autoclaves, heated in oil baths and stirred magnetically. The ligands MeCgPPh (**1a**), phosphite **1b**, 1,2-bis(diphenylphosphano)ethane (dppe), 1,2-bis(diphenylphosphano)benzene (dppb), 2,2′-bis[(diphenylphosphano)methyl]-1,1′-biphenyl (BISBI), (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphane) (BINAP), and 9,9-dimethyl-4,5-bis(diphenylphosphano)xanthene,

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(XANTPHOS) were obtained from Strem. The products here have been prepared or detected before by other less efficient methods.[25,30,35–49]

General procedure—alkoxycarbonylation of alkynes:[25] *para*-Toluenesulfonic acid (1.5%) and alkyne were added to solution of $Pd(OAc)_2$ (0.05%), Ph_2PyP (1.5%) in dry methanol. The mixture was transferred to an autoclave and stirred under 40 bar CO at 60°C for 4 h. NMR spectroscopy showed complete conversion in each case. The mixture was diluted with diethyl ether, was washed with saturated NH_4Cl and water, was dried ($MgSO_4$) and was concentrated. The residue was distilled under vacuum to give the desired products in around 60% yield (care had to be taken not sublime any Ph_2PPy, hence the isolated yields are significantly below the conversion).

Methyl atropate (3): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.74$ (s, 3H; CO_2CH_3), 5.81 (s, 1H; CH_2), 6.29 (s, 1H; CH_2), 7.26–7.38 ppm (m, 5H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.2$ (CO_2CH_3), 126.9 (C=CH_2), 128.1128.2, 128.3 (ArCH), 136.7 (ArC), 141.3 (C=CH_2), 167.3 ppm (CO_2CH_3); MS (ES+): m/z: 185 $[M+Na]^+$; IR (film): $\tilde{\nu} = 1615$ (C=C), 1723 cm^{-1} (C=O).

2-Methylenehexanoic acid methyl ester (4): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 7.2$ Hz, 3H; CH_3), 1.25–1.50 (m, 4H; $(CH_2)_2$), 2.28 (t, $J = 8.4$ Hz, 2H; CH_2), 3.73 (s, 3H; CO_2CH_3), 5.51 (s, 1H; =CH_2), 6.11 ppm (s, 1H; =CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3), 22.3, 30.5, 31.6 (CH_2), 51.6 (CO_2CH_3), 124.4 (C=CH_2), 140.8 ppm (*C*=CH_2), *C*O_2CH_3; MS (ES−): m/z: 127 $[M-CH_3]^-$; IR (film): $\tilde{\nu} = 1632$ (C=C), 1723 cm^{-1} (C=O).

5-Cyano-2-methylenepentanoic acid methyl ester (5): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.80$ (quin, $J = 7.7$ Hz, 2H; $CH_2CH_2CH_2$), 2.30 (t, $J = 7.2$ Hz, 2H; CH_2CN), 2.43 (td, $J = 7.7$, 1.0 Hz, 2H; CH_2C=C), 5.6 (q, $J = 1.2$ Hz, 1H; C=CH_2), 6.16 ppm (d, J = 1.2 Hz, 1H; C=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.5$, 24.2, 31.0 (CH_2), 52.0 (CO_2CH_3), 119.3 (CN), 126.6 (C=CH_2), 138.3 (*C*=CH_2), 167.0 ppm (*C*O_2CH_3); MS (ES+): m/z: 176 $[M+Na]^+$; IR (film): $\tilde{\nu} = 1632$ (C=C), 1720 (C=O), 2247 cm^{-1} (CN).

Synthesis of diester (7): Tri-*n*-butylphosphane (723 µl, 0.0029 mol) was added to stirring solution of methylacrylate (10.46 mL, 0.116 mol) and hydroquinone (64 mg, 0.58 mmol) in *tert*-butanol (20 mL). The mixture was heated under reflux for 4 h before treating with 2 M HCl (20 mL) and extracting with diethyl ether. The combined organics were dried ($MgSO_4$) and concentrated. Column chromatography (hexane/EtOAc 4:1) yielded 5.76 g (58%) of a clear oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 2.40–2.60 (m, 4H; $2CH_2$), 3.60 (s, 3H; CO_2CH_3), 3.69 (3s, H; CO_2CH_3), 5.53 (1s, H; C=CH_2), 6.12 ppm (s, 1H; C=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.3$, 32.8 (CH_2), 51.5, 51.8 (CO_2CH_3), 125.9 (C=CH_2), 138 (C=CH_2), 167.0, 173.0 ppm (CO_2CH_3) ; MS (ES+): m/z: 175 $[M+H]^+$; IR (film): $\tilde{\nu} = 1639$ (C=C), 1718 cm^{-1} (C=O).

Synthesis of α-methyl methylcinnamate (9): A mixture of α-methylcinnamic acid (4.05 g, 25.0 mmol) and *para*-toluenesulfonic acid (481 mg, 0.25 mmol) in methanol (50 mL) was heated under reflux for 5 h. The cooled solution was diluted with diethyl ether, was washed with $NaHCO_3$ and brine, and was dried ($MgSO_4$) before concentrating to a white solid (3.30 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.15$ (s, 3H; CH_3), 3.84 (s, 3H; CO_2CH_3), 7.29–7.46 (m, 5H; ArH), 7.72 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 52.1 (CO_2CH_3), 128.3, 128.4, 129.7 (ArC), 135.9 (*C*=CH), 139.0 (C=*C*H), 169.1 ppm (*C*O_2CH_3); MS (ES+): m/z: 199 $[M+Na]^+$; IR (nujol): $\tilde{\nu} = 1633$ (C=C), 1719 cm^{-1} (C=O).

General procedure—rhodium-catalysed hydroformylation using phenylphosphatrioxaadamantane 1a as a ligand: $[Rh(acac)(CO)_2]$ (0.2%) and phosphane (1%) were placed in a clean dry Schlenk tube. The air was displaced with nitrogen and toluene added. The alkene was added and the mixture transferred to an autoclave and stirred under syngas (1:1). The conversion was measured from NMR spectroscopy and isolated yields were obtained through flash chromatography.

Hydroformylation of *tert*-butyl methacrylate (2a): The general procedure was followed using $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), *tert*-butyl methacrylate (0.63 mL, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 50 bar syngas at 50°C for 70 h; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (s, 6H; $(CH_3)_2$), 1.40 (s, 9H; $(CH_3)_3$), 9.57 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.6$ ($(CH_3)_2$), 27.9 (C(*C*$H_3)_3$), 54.3 (*C*$(CH_3)_3$), 171.9 (*C*O_2tBu), 199.5 ppm (CHO); MS (ES+): m/z: 173 $[M+H]^+$; IR (film): $\tilde{\nu} = 1722$ (C=$O_{aldehyde}$), 1743 (C=O_{ester}), 2721, 2825 cm^{-1} (C−$H_{aldehyde}$).

Hydroformylation of methyl methacrylate (2b): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), methyl methacrylate (0.42 mL, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 50 bar syngas at 50°C for 24 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 490 mg (97%) of a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 6H; $(CH_3)_2$), 3.78 (s, 3H; CO_2CH_3), 9.70 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.7$ ($(CH_3)_2$), 52.5 (CO_2CH_3), 53.8 (C), 173.2 (CO_2CH_3), 199.0 ppm (CHO); MS (ES+): m/z: 131 $[M+H]^+$; IR (film): $\tilde{\nu} = 1727$ (C=$O_{aldehyde}$), 1739 (C=O_{ester}), 2725, 2844 cm^{-1} (C−$H_{aldehyde}$).

Hydroformylation of methyl atropate (3): The general procedure was followed with $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol), **1a** (5.6 mg, 0.019 mmol), methyl atropate (314 mg, 1.94 mmol) and toluene (1 mL). The mixture was stirred under 50 bar syngas at 30°C for 90 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 340 mg (91%) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.71$ (s, 3H; CH_3), 3.82 (s, 3H; CO_2CH_3), 7.21–7.49 (m, 5H; ArH), 9.88 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$ (CH_3), 53.2 (CO_2CH_3), 62.5 (C), 127.3, 128.6, 129.6, 136.8 (ArC), 172.5 (CO_2CH_3), 197.0 ppm (CHO); MS (CI): m/z: 193 $[M+H]^+$; HRMS (CI): m/z calcd for $C_{11}H_{13}O_3$: 193.0865; found: 193.0868 $[M+H]^+$; IR (film): $\tilde{\nu} = 1446$, 1495 (C=C_{Ph}), 1720 (C=$O_{aldehyde}$), 1749 (C=O_{ester}), 2727, 2844 cm^{-1} (C−$H_{aldehyde}$).

Hydroformylation of dimethyl itaconate (4): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), dimethyl itaconate (614 mg, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 50 bar syngas at 50°C for 24 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 679 mg (93%) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ (s, 3H; CH_3), 2.80 (s, 2H; CH_2), 3.57 (s, 3H; $CH_2CO_2CH_3$), 3.71 (s, 3H; CO_2CH_3), 9.84 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.6$ (CH_3), 38.5 (CH_2), 52.0, 52.7 (CO_2CH_3), 54.6 (C), 171.1, 172.4 (CO_2CH_3), 199.1 ppm (CHO); MS (ES+): m/z: 189 $[M+Na]^+$; HRMS (ES+): m/z calcd for $C_8H_{12}O_5$: 189.0763; found: 189.0757 $[M+H]^+$; IR (film): $\tilde{\nu} =$ 1718–1746 (br; C=O), 2735, 2852 cm^{-1} (C−$H_{aldehyde}$).

Hydroformylation of methyl α-butylacrylate (5): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), methyl α-butylacrylate (0.415 mL, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 75 bar syngas at 75°C for 70 h. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$ (t, $J = 7.2$ Hz, 3H; CH_3CH_2), 1.05–1.31 (7m, H; CH_3, CH_2CH_2), 1.57–1.86 (m, 2H; CH_2), 3.69 (s, 3H; CO_2CH_3), 9.64 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3), 22.9, 26.3, 34.2 (CH_2), 52.3 (CO_2CH_3), 57.7 (C), 172.8 (CO_2CH_3), 199.7 ppm (CHO); MS (ES+): m/z: 173 $[M+H]^+$; HRMS (ES+): m/z calcd for $C_9H_{16}O_3$: 173.1177; found: 173.1170 $[M+H]^+$; IR (film): $\tilde{\nu} =$ 1722 (C=$O_{aldehyde}$), 1748 (C=O_{ester}), 2733, 2864 cm^{-1} (C−$H_{aldehyde}$).

Hydroformylation of 5-cyano-2-methylenepentanoic acid methyl ester (6): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), 5-cyano-2-methylenepentanoic acid methyl ester (594 mg, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 50 bar syngas at 50°C for 70 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 492 mg (69%) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (s, 3H; CH_3), 1.48–1.65 (m, 2H; CH_2), 1.68–1.99 (m, 2H; CH_2), 2.32 (t, $J = 7.2$ Hz, 2H; CH_2), 3.2 (s, 3H; CO_2CH_3), 9.62 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.8$ (CH_3), 17.9, 21.0, 33.0 (CH_2), 53.1 (CO_2CH_3), 57.6 C), 119.4 (CN), 172.4 (CO_2CH_3), 198.8 ppm (CHO); MS (ES+): m/z: 184 $[M+H]^+$; HRMS (ES+): m/z calcd for $C_9H_{13}NO_3$: 184.0973; found: 184.0981 $[M+H]^+$; IR (film): $\tilde{\nu} = 1721$ (C=$O_{aldehyde}$), 1746 (C=O_{ester}), 2247 (C≡N), 2737, 2846 cm^{-1} (C−$H_{aldehyde}$).

Hydroformylation of 2-methylenepentanedioic acid dimethyl ester (7): The general procedure was followed with $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol), **1a** (5.6 mg, 0.019 mmol), 2-methylenepentanedioic acid dimethyl ester (334 mg, 1.94 mmol) and toluene (1 mL). The mixture was stirred under 50 bar syngas at 50°C for 24 h. Flash column chromatogra-

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phy (SiO_2, hexane/EtOAc 4:1) yielded 260 mg (62%) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (s, 3H; CH_3), 2.03–2.46 (m, 4H; $(CH_2)_2$), 3.66 (s, 3H; $CH_2CO_2CH_3$), 3.77 (s, 3H; CO_2CH_3), 9.70 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.2$ (CH_3), 28.5, 29.0 (CH_2), 51.8, 52.6 (CO_2CH_3), 60.4 (C), 172.1, 172.9 (CO_2CH_3), 198.5 ppm (CHO); MS (ES+): m/z: 203 $[M+H]^+$; HRMS (ES+): m/z calcd for $C_9H_{14}O_5$: 203.0919; found: 203.0928 $[M+H]^+$; IR (film): $\tilde{\nu} = 1717$–1740 (br; C=O), 2735, 2848 cm^{-1} ($C-H_{aldehyde}$).

Hydroformylation of α-methyl methylcinnamate (11): The general procedure was followed with $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol), **1a** (5.6 mg, 0.019 mmol), α-methyl methylcinnamate (341 mg, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 75 bar syngas at 75°C for 70 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 279 mg (70%) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$ (s, 3H; CH_3), 2.99, 3.18 (2d, $J = 13.8$ Hz, 2H; CH_2), 3.65 (s, 3H; CO_2CH_3), 6.99–7.22 (m, 5H; ArH), 9.70 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.4$ (CH_3), 40.7 (CH_2), 52.8 (CO_2CH_3), 59.3 (C), 127.5, 128.8, 130.4, 135.8 (ArC), 172.6 (CO_2CH_3), 199.8 ppm (CHO); MS (ES+): m/z: 207 $[M+H]^+$; HRMS (ES+): m/z calcd for $C_{12}H_{14}O_3$: 207.1021; found: 207.1027; IR (film): $\tilde{\nu} = 1454$, 1497 ($C=C_{Ph}$), 1720 ($C=O_{aldehyde}$), 1742 ($C=O_{ester}$), 2729, 2843 cm^{-1} ($C-H_{aldehyde}$).

Hydroformylation of methyl tiglate (12): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a**(11.3 mg, 0.039 mmol), methyl tiglate (0.46 mL, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 75 bar syngas at 75°C for 70 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 384 mg (69%) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (t, $J = 7.5$ Hz, 3H; CH_3), 1.22 (s, 3H; CH_3), 1.65–1.94 (m, 2H; CH_2), 3.69 (s, 3H; CO_2CH_3), 9.64 ppm (s, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.0$ (CH_2CH_3), 16.5 (CH_3), 27.8 (CH_2), 52.7 (CO_2CH_3), 58.5 (C), 173.1 (CO_2CH_3), 200.2 ppm (CHO); MS (ES+): m/z: 145 $[M+H]^+$; IR (film): $\tilde{\nu} = 1722$ ($C=O_{aldehyde}$), 1750 ($C=O_{ester}$), 2739, 2843 cm^{-1} ($C-H_{aldehyde}$).

Hydroformylation of methyl crotonate (13): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), methyl crotonate (0.41 mL, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 50 bar syngas at 50°C for 24 h. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) yielded 475 mg (94%) of a yellow oil. Aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.4$ Hz, 3H; CH_3), 2.03 (quin, $J = 7.4$ Hz, 2H; CH_2), 3.15 (td, $J = 2.3$, 7.2 Hz, 1H; CH), 3.71 (s, 3H; CO_2CH_3), 9.64 ppm (d, $J = 2.3$ Hz, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.0$ (CH_3), 20.5 (CH_2), 52.7 (CO_2CH_3), 60.1 (CH), 170.3 (CO_2CH_3), 197.7 ppm (CHO); Enol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.95$ (t, $J = 7.4$ Hz, 3H; CH_3), 2.03 (qd, $J = 1.0$, 7.4 Hz, 2H; CH_2), 3.71 (s, 3H; CO_2CH_3), 6.94 (dt, $J = 12.5$, 1.0 Hz, 1H; CHOH), 11.26 ppm (d, $J = 12.5$ Hz, 1H; CHO*H*); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.9$ (CH_3), 21.0 (CH_2), 51.8 (CO_2CH_3), 106.8 (C), 160.6 (CHOH), 173.2 ppm (CO_2CH_3); MS (ES−): m/z: 129 $[M-H]^-$; HRMS (ES−): m/z calcd for $C_6H_9O_3$: 129.0552; found: 129.0549 $[M-H]^-$; IR (film): $\tilde{\nu} = 1671$ ($C=C_{enol}$), 1720 ($C=O_{aldehyde}$), 1740 ($C=O_{ester}$), 3337 cm^{-1} ($O-H_{enol}$).

Hydroformylation of methyl trans-2-pentenoate (14): The general procedure was followed with $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol), **1a** (5.6 mg, 0.019 mmol), methyl trans-2-pentenoate (221 mg, 1.94 mmol) and toluene (1 mL). The mixture was stirred under 75 bar syngas (5:1 CO/H_2) at 40°C for 90 h. Aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.4$ Hz, 3H; CH_3), 1.31–1.60 (m, 2H; CH_2), 1.78 (t, $J = 7.2$ Hz, 2H; CH_2), 3.22 (td, $J = 7.2$, 2.3 Hz, 1H; CH), 3.71 (s, 3H; CO_2CH_3), 9.63 ppm (d, $J = 2.6$ Hz, 1H; CHO); Enol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (t, $J = 7.2$ Hz, 3H; CH_3), 1.31–1.60 (m, 2H; CH_2), 1.96 (t, $J = 7.4$ Hz, 2H; CH_2), 3.71 (s, 3H; CO_2CH_3), 6.93 (dt, $J = 12.5$, 0.8 Hz, 1H; CHOH), 11.31 ppm (d, $J = 12.3$ Hz, 1H; CHO*H*); ^{13}C NMR (both tautomers, 75 MHz, $CDCl_3$): $\delta = 13.5$, 13.7, 20.3, 22.8, 28.7, 29.3, 51.4, 52.4, 58.2, 104.6, 160.8, 168.6, 172.9, 197.3 ppm; MS (ES−): m/z: 144 $[M-H]^-$; HRMS (ES−): m/z calcd for $C_7H_{11}O_3$: 143.0708; found: 143.0708 $[M-H]^-$; IR (film): $\tilde{\nu} = 1737$ ($C=O_{aldehyde}$), 3464 cm^{-1} ($O-H_{enol}$).

Hydroformylation of methyl cinnamate (15): The general procedure was followed with $[Rh(acac)(CO)_2]$ (2 mg, 0.0078 mmol), **1a** (11.3 mg, 0.039 mmol), methyl cinnamate (629 mg, 3.88 mmol) and toluene (2 mL). The mixture was stirred under 50 bar syngas at 50°C for 24 h. Aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.15$ (dd, $J = 5.1$, 6.7 Hz, 2H; CH_2), 3.57 (m, 1H; CH), 3.64 (s, 3H; CO_2CH_3), 7.08–7.24 (m, 5H; ArH), 9.66 ppm (d, $J = 2.1$ Hz, 1H; CHO); Enol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.33$ (s, 2H; CH_2), 3.64 (s, 3H; CO_2CH_3), 6.97 (dt, $J = 12.5$, 1.0 Hz, 1H; CHOH), 7.08–7.24 (m, 5H; ArH), 11.40 ppm (d, $J = 12.8$ Hz, 1H; CHO*H*); ^{13}C NMR (Both tautomers, 75 MHz, $CDCl_3$): $\delta = 32.2$, 33.1, 51.4, 52.6, 60.2, 104.4, 126.2, 126.9, 128.3, 128.4, 128.6, 128.7, 137.4, 140.4, 161.8, 196.4 ppm; MS (ES+): m/z: 193 $[M+H]^+$; IR (film): $\tilde{\nu} = 1446$, 1495 ($C=C_{Ph}$), 1668 ($C=Ce_{nol}$), 1717 ($C=O_{aldehyde}$), 1739 ($C=O_{ester}$), 3334 cm^{-1} ($O-H_{enol}$).

Hydroformylation of methyl 4-chlorocinnamate (16): The general procedure was followed with $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol), **1a** (5.6 mg, 0.019 mmol), methyl 4-chlorocinnamate (381 mg, 1.94 mmol) and toluene (1 mL). The mixture was stirred under 50 bar syngas at 50°C for 24 h. Workup yielded 283 mg (64%) of a pale yellow oil. Aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.10$ (m, 2H; CH_2), 3.58 (m, 1H; CH), 3.64 (s, 3H; CO_2CH_3), 6.97–7.20 (m, 4H; ArH), 9.67 ppm (d, $J = 1.5$ Hz, 1H; CHO); Enol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.30$ (s, 2H; CH_2), 3.66 (s, 3H; CO_2CH_3), 6.97–7.20 (m, 5H; ArH, CHOH), 11.39 ppm (d, $J = 12.6$ Hz, 1H; CHO*H*); ^{13}C NMR (both tautomers, 75 MHz, $CDCl_3$): $\delta = 31.3$, 32.6, 51.6, 52.6, 60.1, 104.0, 128.4, 128.8, 129.8, 130.3, 131.6, 132.8, 136.0, 138.5, 161.9, 172.3, 195.8 ppm; MS (ES+): m/z: 227 $[M+H]^+$; HRMS (ES+): m/z calcd for $C_{11}H_{12}ClO_3$: 227.0475; found: 227.0482 $[M+H]^+$; IR (film): $\tilde{\nu} = 804$ (C−Cl), 1670 ($C=C_{enol}$), 1723 ($C=O_{aldehyde}$), 3449 cm^{-1} ($O-H_{enol}$).

Synthesis of β-amino acid ester 20: A mixture of aldehyde **18** (520 mg, 4 mmol) and benzylamine (471 mg, 4.4 mmol) were stirred in toluene at 50°C overnight. The mixture was concentrated under high vacuum to the crude imine **19**; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (s, 6H; $((CH_3)_2)$, 3.81 (s, 3H; CO_2CH_3), 4.74 (s, 2H; CH_2), 7.27–7.36 (m, 5H; ArH), 7.97 ppm (t, $J = 1.3$ Hz, 1H; CHO).

A mixture of $[Ir(COD)Cl]_2$ (5.4 mg, 0.008 mmol) and 1,1′-bis(diphenylphosphano)ferrocene (dppf; 11.1 mg, 0.02 mmol) was stirred in methanol (2 mL) for 5 min before adding to the crude imine. The mixture was stirred under 60 bar H_2 at 50°C for 24 h. The mixture was concentrated and partitioned between ether and 0.5 M HCl. The acidic layer was made basic and extracted three times into diethyl ether. The combined organics were dried ($MgSO_4$) and concentrated to give 749 mg (85%) of a clear oil. This was converted quantitatively to the hydrochloride salt **20** by treatment with 2 M HCl in diethyl ether and collecting the precipitate. ^{1}H NMR (300 MHz, D_2O): $\delta = 1.14$ (s, 6H; $(CH_3)_2$), 3.06 (s, 2H; CH_2), 3.56 (s, 3H; CO_2CH_3), 4.19 (s, 2H; CH_2Ph), 7.36 (s, 2H; ArH), 7.41 ppm (s, 3H; ArH); (75 MHz, D_2O): $\delta = 22.6$ ($(CH_3)_2$), 41.0 (C), 51.7 (CH_2), 52.8 (CH_2), 52.9 (CO_2CH_3), 129.2, 129.6, 130.2 (ArCH), 129.8 (ArC), 177.6 ppm (CO_2CH_3); MS (ES+): m/z: 222 $[M+H]^+$; IR (film): $\tilde{\nu} = 1743$ (C=O), 3433 cm^{-1} (N−H).

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