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A highly regioselective hydroformylation of an α-chiral olefin to produce a versatile trifunctionalised orthogonally protected C5 synthon

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ABSTRACT

This paper describes a highly regioselective hydroformylation of (*R*)-*N*-phthalimido-vinylglycinol, [(*R*)-PVG]. By judicious choice of the reaction conditions, catalyst-controlled preferential formation of the linear regioisomer could be achieved in excellent yield. The hydroformylation product cyclised to a hemi-acetal, which is an orthogonally protected trifunctionalised enantio-enriched C5 synthon. The value of this versatile intermediate was demonstrated by the ready formation of enantio-enriched amino-diols, diamino-alcohols and differentially protected (*R*)-3-aminopiperidine.

Olefin hydroformylation to produce aldehydes is a highly atom-economic process that is widely used in the commodity chemicals industry to produce millions of tonnes per annum of basic feedstocks.[1] Over 70 years of chemical and engineering know-how have been accrued in order to make hydroformylation one of the most heavily used homogenously-catalysed reactions practised today. In spite of this, olefin hydroformylation remains relatively under utilised for the production of fine chemicals and pharmaceutical intermediates. Part of the reason for this is that the majority of the vast wealth of knowledge around the application of this chemistry has been gained from studying the behaviour of very simple terminal alkenes, such as propene. Pharmaceutical intermediates and fine chemicals by their very nature contain more functionality, such as heteroatoms, unsaturated moieties and other reducible groups. Furthermore, the synthesis of these intermediates frequently requires control over the formation of newly generated stereogenic centres. This higher degree of complexity introduces more uncertainty into the outcome of the hydroformylation reactions of such substrates. For the past several years we,[2] and others,[3] have focussed on utilising olefin hydroformylation. This has been achieved in part by expanding the range of available ligands to control chemo-, regio- and stereoselectivity as well as exploring an increased substrate scope.

(*R*)-*N*-phthalimido-vinylglycinol, (*R*)-**1**, is readily available from epoxybutene using a palladium-catalysed dynamic kinetic asymmetric transformation, which has been performed on a kilogram scale using 0.1 mol % of catalyst in 88% ee.[4] Owing to the three distinct functional groups in the four-carbon framework and the defined stereogenic centre, the single enantiomer **1** has been used in the synthesis of a number of natural products and pharmacologically active agents.[5] The presence of the olefin unit, in particular, allows for molecular complexity to be introduced through reactions such as Heck couplings and metathesis. Likewise, we envisaged that hydroformylation of **1** would provide a range of useful synthetic intermediates and undertook studies determining the activity and selectivity of (*R*)-**1** with a variety of hydroformylation catalysts. The results are reported in this paper. We also describe further reactions of the hydroformylation product of (*R*)-**1**, a C_5 orthogonally protected enantio-enriched synthon, which illustrates the potential utility of this versatile intermediate.

The hydroformylation of (*R*)-**1** was examined using several ligands (Fig. 1). We wished to avoid the complication of introducing a new stereocentre which would be observed with the branched aldehyde and, therefore, focussed on formation of the linear regioisomeric product. The achiral bidentate ligands biphephos, **2** and **3**, were chosen because they are generally selective for the desired linear aldehyde. DoverPHOS and triphenyl phosphite were examined in order to ascertain the effects of using monodentate ligands in this reaction. A reaction using no ligand was also undertaken in order to determine the inherent regioselectivity imparted by the substrate. These initial studies were carried out at a molar substrate to catalyst ratio (S/C) of 250 using 10 bar pressure of syngas (1:1 CO/H_2).

The results (Table 1) show that there was no substrate control in this reaction as the ligand-free system provided an equal mixture of the regioisomeric products **4** and **5**, which arise through cyclisation of the aldehydes **6** and **7**, respectively (entry 1). As anticipated, the catalytic system also benefitted from the use of a

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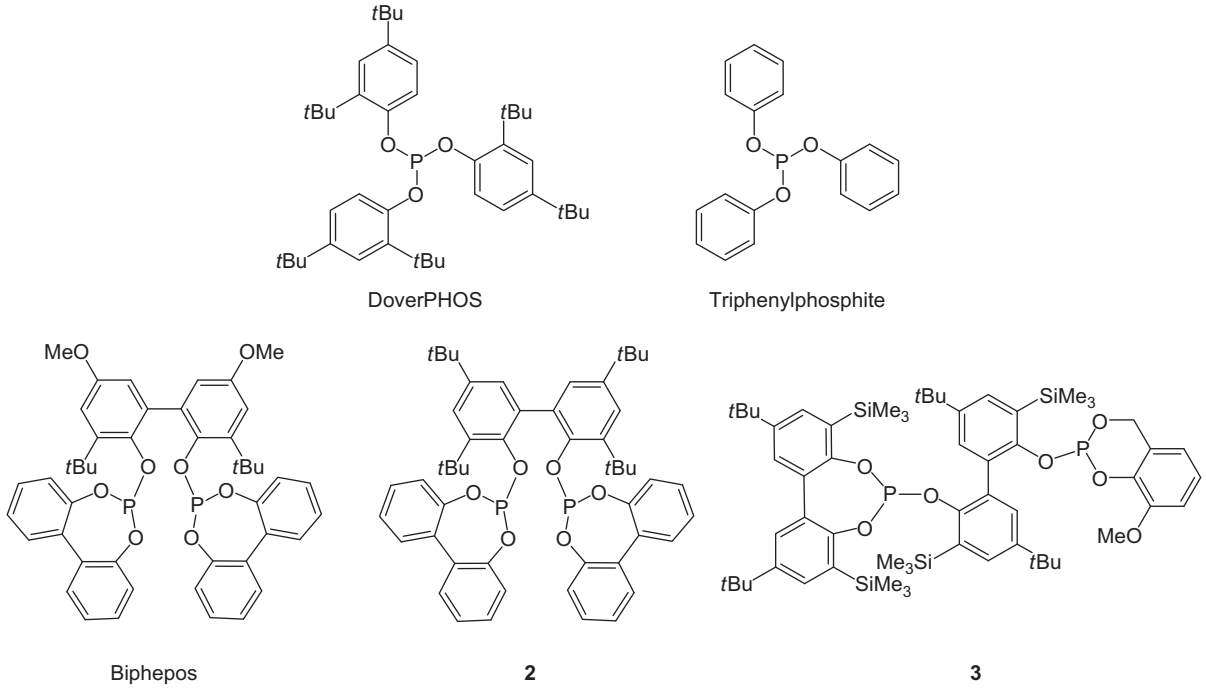
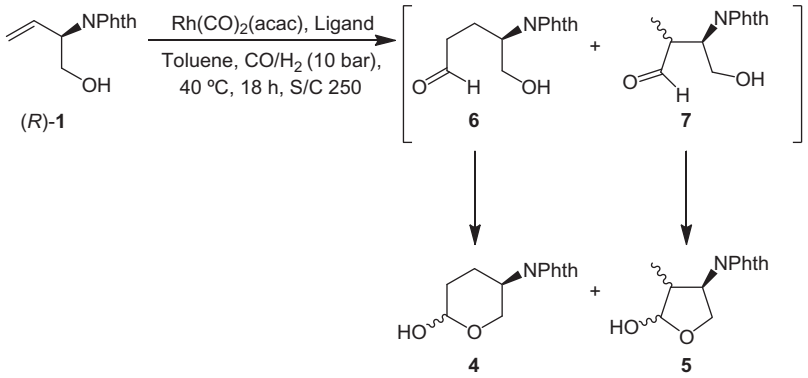


Figure 1. Ligands examined for the hydroformylation of (*R*)-**1**.

Table 1
Hydroformylation of (*R*)-**1**



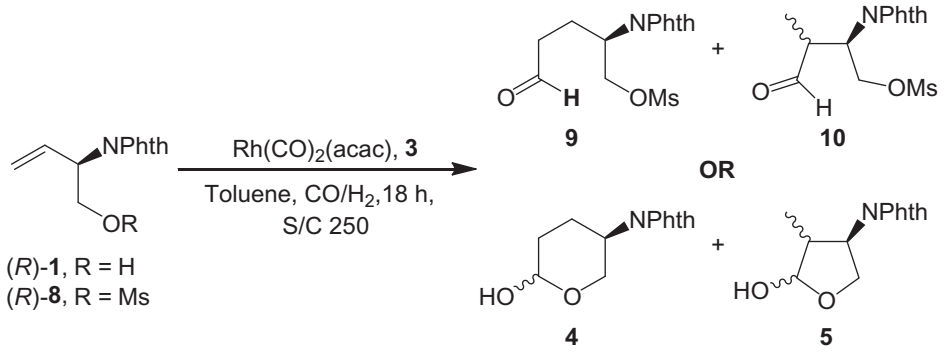
Entry	Ligand	Conv. (%)[a]	**4**:**5**[a]
1	—	16	1:1
2	Biphephos	>95	1:1
3	**2**	>95	2:3
4	**3**	92	7:1
5	DoverPHOS	>95	1:4
6	$P(OPh)_3$	>95	1:2

[a] Determined by ^1H NMR spectroscopy.

ligand in terms of enhanced activity and conversion when compared to the ligand-free system. Ligand **3**, which was developed to favour linear selectivity,[6] was the only example that favoured preferential formation of the desired regioisomer **4** (entry 6).

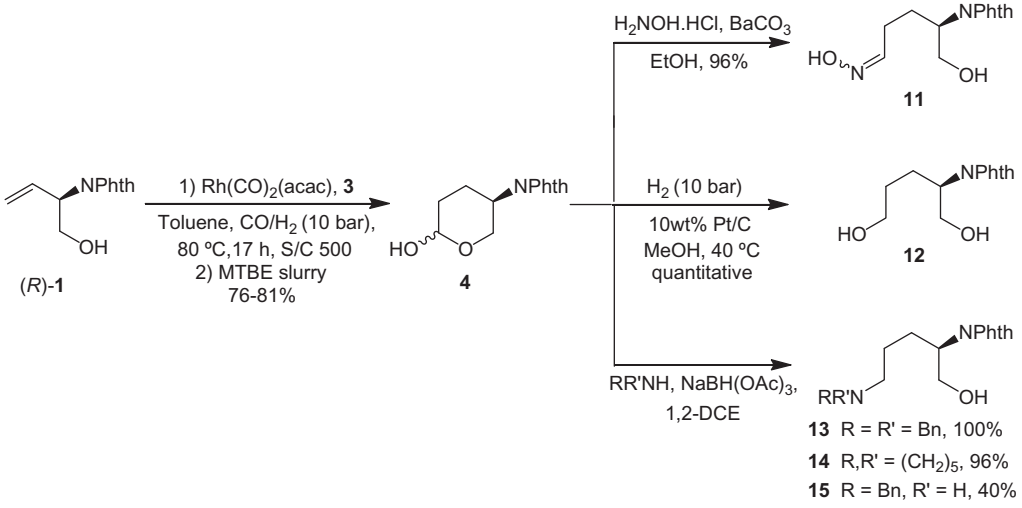
Buoyed by these results we sought to enhance the regioselectivity to favour the linear product by examining the effects of pressure and temperature using the ligand **3** at the same level of overall catalyst loading (Table 2). Some insight into the regiochemical influence of the hydroxy group was probed using both (*R*)-**1** and the mesylate derivative, (*R*)-**8**. Increasing the temperature with (*R*)-**1** gratifyingly provided a higher regioselectivity for the linear product **4** (entry 2), which is in accordance with previous findings.[7] The effect of temperature on the regioselectivity of the reaction using (*R*)-**8** was convoluted by the pressure effects (entry 4). Most noteworthy is that under the same conditions (*R*)-**1** (entry 2) provides a higher level of regioselectivity than (*R*)-**8** (entry 5)

Table 2
Effect of pressure and temperature on the hydroformylation of (*R*)-**1** and (*R*)-**8**



Entry	Substrate	Pressure (bar)	Temp. (°C)	Conv. (%)[a]	**4**:**5** or **9**:**10**[a]
1	(*R*)-**1**	10	40	92	7:1
2	(*R*)-**1**	10	80	>95	16:1
3	(*R*)-**8**	25	40	66	5:1
4	(*R*)-**8**	25	80	>95	4:1
5	(*R*)-**8**	10	80	>95	7:1

[a] Determined by ^{1}H NMR spectroscopy.



Scheme 1. Hydroformylation of (*R*)-**1** and synthetic utility.

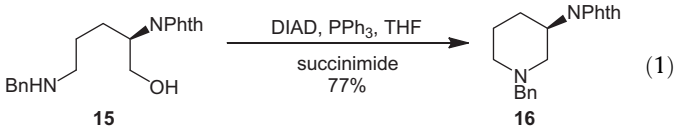
which points to the potential interaction of the hydroxy group in (*R*)-**1** with the catalyst system, and is also consistent with previous findings.[8]

On the basis of these results, the hydroformylation of (*R*)-**1** was carried-out in a single-well pressure vessel in order to study more effectively the effect of a decrease in the catalyst loading (Scheme 1).[9] The hydroformylation took 40 min to reach completion, as determined by syngas uptake, but in order to ensure complete cyclisation the reaction was run for 17 h. Longer reaction times did not have a deleterious effect on the purity of the products and a similar regioselectivity and yield to that previously obtained was observed. The crude reaction mixture consisting of two diastereoisomers of **4** and four diastereoisomers of **5** was purified by trituration using methyl *tert*-butyl ether (MTBE) to provide >95% pure **4** as a 3:2 diastereoisomeric mixture in 76–81% yield. With the stereodefined centre, protected amine and the hemi-acetal functionality being equivalent to a masked aldehyde and alcohol, **4** is a versatile synthon that could potentially be used to produce a diverse array of synthetically-appealing intermediates. Furthermore, the presence of the differentiated functional groups potentially allows for a high degree of control in subsequent reactions in which the stereodefined centre could induce asymmetry.

In order to evaluate the potential of **4** we initially investigated the chemistry of the hemi-acetal functionality. Oximes are known precursors to nitrile oxides and hence isoxazoles and isoxazolines,[10] and treatment of **4** under standard conditions produced the oxime **11** in excellent yield. Reduction of **4** to the amino-diol **12** was achieved using hydrogen in combination with a heterogeneous catalyst as the use of sodium borohydride resulted in the formation of by-products from interaction with the phthalimide group. Reductive amination using sodium triacetoxyborohydride[11] proceeded smoothly to produce the tertiary amines **13** and **14**,

whilst the secondary amine **15** was formed in moderate yield owing to further reaction of this initial product. Nevertheless, these reactions produced enantio-enriched amino-diols and diamino-alcohols in a straightforward fashion.

Enantiopure 3-aminopiperidine is a constituent of several pharmaceutical agents, such as alogliptin[12] and linagliptin,[13] as well as the investigational substances AZD-7762[14] and PCI-32765,[15] amongst others. There are several known procedures to this material based on resolution[16] and use of the chiral pool.[17] Both of these approaches have their limitations and there is a need for new methods to produce enantiopure 3-aminopiperidine. Treatment of **15** under Mitsonobu conditions provided the orthogonally protected 3-aminopiperidine **16** in good yield (Eq. (1)).[18]



15 **16** (1)

In conclusion, this paper reports the highly regioselective hydroformylation of (*R*)-*N*-phthalimido-vinylglycinol, an α-chiral olefin bearing a hydroxy group β to the olefin. The hydroxy group played a role in producing the observed regioselectivity in combination with the appropriate ligand. A simple purification of the hydroformylation product provided access to an orthogonally protected, enantio-enriched, trifunctionalised C_5 synthon. This highly versatile intermediate could provide access to a multitude of product types by exploiting the known chemistry of the functional groups present. We chose to illustrate the potential of this synthon by transformations into amino-diols, a diamino alcohol and an oxime. We also reported the preparation of a differentially protected, enantio-enriched derivative of 3-aminopiperidine. Further work on exploiting the utility of this synthon is ongoing.

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9. *Experimental procedure:* A glass liner was charged with ligand **3** (22 mg, 0.0202 mmol) and secured in a 300 ml pressure vessel. The vessel was charged with nitrogen to a pressure of 10 bar and subsequently vented. This charge/vent cycle was repeated three times. A solution of (acetylacetonato)dicarbonylrhodium(I) in deoxygenated toluene (20 ml of a 0.923 mM solution, 0.0184 mmol) was then added to the pressure vessel, which was subsequently charged with syngas to a pressure of 10 bar and slowly vented. This charge/vent cycle with syngas was repeated two times, after which the vessel was charged with syngas to a pressure of 10 bar, stirring was initiated and the vessel was heated to 40 °C. After 20 min at this temperature, the stirring was stopped and the pressure vessel was vented. A solution of (*R*)-**1** (2.00 g, 9.21 mmol) in deoxygenated toluene (80 ml) was then added to the pressure vessel, which was subsequently charged with syngas to a pressure of 10 bar and then vented. This charge/vent cycle with syngas was repeated two times. The pressure vessel was then charged with syngas to a pressure of 9 bar, stirring was initiated and the solution heated to 80 °C. The pressure within the vessel was maintained between 9 and 10 bar by further addition of syngas, as necessary (stirring was stopped during gas addition). After 90 min, no further uptake of syngas occurred. After 17 h the heating was discontinued and the vessel vented. The vessel was then charged with nitrogen to a pressure of 10 bar and stirred for 20 min and then vented. This charge/stir/vent cycle with nitrogen was repeated three times. The solution was concentrated in vacuo to provide the crude product as a light-tan solid (2.26 g, 99%) as an approximate 16:1 mixture of regioisomers, as determined by ^{1}H NMR analysis. The crude product was purified via trituration by stirring as a suspension in MTBE (30 ml) for 17 h followed by filtration and washing with fresh MTBE (20 ml) to provide **4** as a white solid (1.73 g, 76%) as a 6:4 anomeric mixture. ^{1}H NMR analysis revealed >95% regioisomeric purity.
^{1}H NMR (400 MHz, $CDCl_3$) (major diastereoisomer) δ 7.83 (2H, dd, *J* 8 and 4 Hz), 7.72 (2H, dd, *J* 8 and 4 Hz), 4.92 (1H, ddd, *J* 9, 6 and 2 Hz), 4.43–4.35 (1H, m), 4.26 (1H, t, *J* 12 Hz), 3.90–3.85 (1H, m), 2.96 (1H, d, *J* 2 Hz), 2.60–2.50 (1H, m), 2.13–2.07 (1H, m), 1.94–1.88 (1H, m) and 1.68–1.58 (1H, m); (minor diastereoisomer) δ 7.83 (2H, dd, *J* 8 and 4 Hz), 7.72 (2H, dd, *J* 8 and 4 Hz), 5.32 (1H, m), 4.67 (1H, t, *J* 12 Hz), 4.43–4.34 (1H, m), 3.52 (1H, ddd, *J* 10, 4 and 2 Hz), 2.90–2.79 (1H, m), 2.61–2.50 (1H, m), 2.02–1.96 (1H, m) and 1.68–1.58 (1H, m).
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