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Asymmetric Hydroformylation of an Enantiomerically Pure Bicyclic Lactam: Efficient Synthesis of Functionalised Cyclopentylamines

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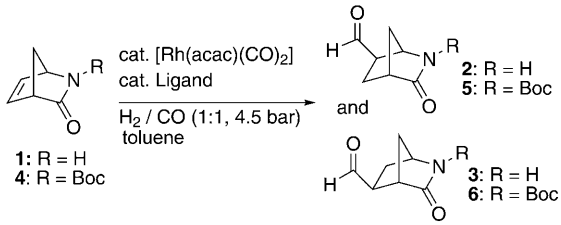
Hydroformylation of alkenes is one of the most industrially important applications of transition metal catalysis.[1] Until recently, the most significant applications were focussed on linear selective hydroformylations of simple terminal alkenes, delivering aldehydes and products available from aldehydes for the commodity chemicals industry. For many years, the hydroformylation of more functionalised alkenes that would deliver the high-value products needed for organic synthesis was studied to a lesser degree, in part due to concerns regarding the control of regioselectivity, poor substrate scope and in the case of asymmetric catalysis, generally quite low enantioselectivity.[2] Consequently, asymmetric hydroformylation is under-exploited in organic synthesis,[3] despite the relatively recent discovery of some potentially useful enantioselective catalysts.[4–14] Enantioselective hydroformylation catalysts have generally been "benchmarked" for controlling selectivity in the hydroformylation of styrene derivatives and vinyl acetate. One of our objectives has been to demonstrate that this technology can be exploited in the synthesis of a wide range of useful chiral building blocks and hopefully encourage the widespread use of this potentially very clean, convenient and economic method for asymmetric C–C bond formation. Although internal alkenes can be sluggish hydroformylation substrates, strained alkenes often show good reactivity, as demonstrated by recent studies on the hydroformylation of norbornene and bicyclic hydrazines.[15] Therefore, we turned our interest to attempting hydroformylation of the bicyclic lactam azabicyclo-[2.2.1]hept-5-en-3-one (**1**) (see Scheme 1), because there is a significant demand for functionalised cyclopentylamines that potentially could be accessed by using this reaction. This demand arises from the widespread use of carbocyclic nucleoside analogues in medicinal chemistry;[16] a considerable range of compounds of this general type are biologically active, including clinically applied drugs and drug candidates, most notably, the widely applied nucleoside analogue reverse transcriptase inhibitor Abacavir, used to treat HIV and AIDS. In this communication, we report the successful enantioselective hydroformylation of a bicyclic lactam, and show two examples where the products can be easily converted into functionalised cyclopentylamines in enantiomerically pure form.[17]



Scheme 1. Asymmetric hydroformylation of bicyclic lactams (acac = acetylacetone).

The enantiomerically pure bicyclic lactam **1** is produced very efficiently on a multi-tonne scale by Chirotech.[18] We began our study by investigating if there was any diastereocontrol when this substrate was subjected to hydroformylation either as the free amide or as the Boc-protected analogue (Boc = *tert*-butoxycarbonyl). These studies revealed that it was a straightforward substrate to hydroformylate in terms of reaction rate, and that the reaction is completely *exo*-selective, as determined by NOE NMR measurements (see the Supporting Information). The selectivity of the hydroformylation reaction is reflected in the ratio of re-

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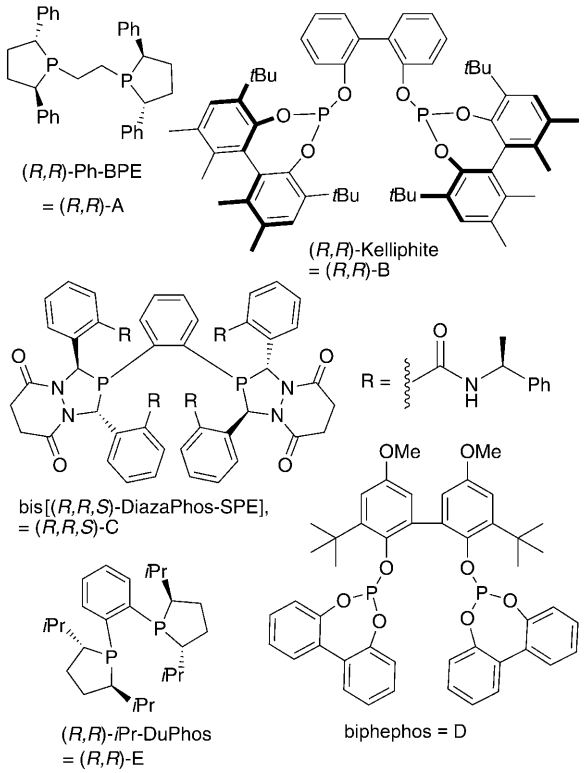
gioisomers produced and the regioselectivity is derived from selective binding of one enantioface of the alkene.

Our studies using achiral ligands show that there is essentially no substrate-controlled regioselectivity in these reactions (Table 1, entries 1–3). These three reactions were also hampered by the appearance of a precipitate that is insoluble in all solvents tested and was not characterised because it this was not observed in other experiments. Fortunately, when our studies moved towards the use of enantiomerically pure catalysts in this hydroformylation, no chemoselectivity issues and high selectivity can be observed (only) if Kelliphite, (*R*, *R*)-B (Scheme 2), is used as ligand.

Table 1. Hydroformylation of NH lactam **1**.[a]

Entry	Ligand[b]	*t* [h]	*T* [°C]	Yield[c] **2** + **3** [%]	**2/3**
1	PPh_3	3	50	40	1:1.1
2	DPPF[c]	3	50	48	1:1.25
3	D	3	50	37	1.5:1
4	(*S*,*S*)-A	1.5	50	31	1:3
5	(*R*,*R*)-A	1.5	50	27	1.5:1
6	(*R*,*R*,S)-C	2	50	>99	1:1.7
7	(*R*,*R*)-B	5	35	>99	9:1
8	(*R*,*R*,S)-C	5	35	95	1:1.6
9	(*R*,*R*)-B	5	20	>99[d]	9.4:1
10	(*S*,*S*)-B	5	20	>99[d]	1:6.3

[a] Reactions run in toluene by using 0.4 mol% Rh catalyst and 0.5% chiral ligand at 4.5 bar initial pressure of syngas. See the Supporting Information for detailed conditions. [b] The structures of ligands A–E are shown in Scheme 2. [c] **2** + **3** represents the conversion to aldehyde products as determined by ^{1}H NMR spectroscopy against tetraethylsilane as internal standard. Conversion of alkenes > 99% except entries 4 (31%) and 5 (27%). [c] DPPF = 1,1′-bis-diphenylphosphino-ferrocene. [d] No internal standard and only desired products formed in entries 9 and 10.



Scheme 2. Ligands A–E as identified in Table 1 and Table 2.

The *N*-Boc alkene was also hydroformylated readily, giving slightly higher selectivity. It is noteworthy that despite being a di-substituted alkene, lactam **4** was hydroformylated quantitatively within 1 h at 50°C (Table 2, entry 1) and that the reaction operates at 20°C, giving complete *exo* selectivity and a synthetically useful ≈10:1 ratio of isomers (Table 2, entry 9). The selectivity observed with Kelliphite contrasts quite starkly with all other ligands examined (Table 2). There is almost no matching effect here with opposite configuration ligands giving similar and opposing selectivities (Table 2, compare entries 3 and 7).

Table 2. Hydroformylation of *N*-Boc lactam **4**.[a]

Entry	Ligand[b]	*t* [h]	Yield **5**+**6**[c] (%)	**5/6**
1	(*R*,*R*)-B	1	>99	7.5:1
2	(*R*,*R*,*S*)-C	1	>99	1:2.6
3	(*R*,*R*)-B	3	>99	7.3:1
4	D	3	90	1:1.2
5	DPPF	3	98	1:1.2
6	(*S*,*S*)-E	3	27	1:3.2
7	(*S*,*S*)-B	3	>98	1:8.6
8	(*R*,*R*)-B[d]	15	>99	9.4:1
9	(*S*,*S*)-B[d]	15	>99	1:10.1

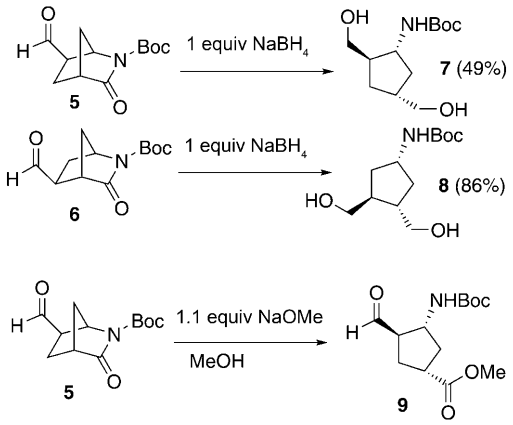
[a] Reactions run in toluene by using 0.4 mol% Rh catalyst and 0.5% chiral ligand at 4.5 bar initial pressure of syngas. See the Supporting Information for detailed conditions. [b] The structures of ligands A–E are shown in Scheme 2. [c] **5** + **6** represents the conversion to aldehyde products as determined by ^{1}H NMR spectroscopy against tetraethylsilane as internal standard, and matches conversion of alkene (complete chemoselectivity). [c] T = 20°C.

The reactivity observed in the screening studies appeared quite promising, so the potential for scale-up was confirmed with a reaction using 15 g of enantiopure alkene (1.2 M concentration) and just 0.02 mol% catalyst at 4.5 bar pressure. This was complete (> 99% conversion) within 18 h at 50°C. The *exo* isomer was produced with a slightly lower **5**/**6** ratio of 7.1:1. A single crystallisation of this product gave 9 g (58%) of purified enantiopure aldehyde and upgraded the **5**/**6** ratio to over 25:1.

In order to demonstrate that these aldehydes could be manipulated into various useful compounds, we have begun

to examine their transformation into pharmacophores and useful building blocks. Treatment of isomer **5** with sodium borohydride results in the reduction of the aldehyde and reductive ring opening of the lactam to give the Boc-protected amino-diol, **7**. If the other enantiomer of Kelliphite is used in the hydroformylation, subsequent tandem reduction–reductive lactam opening gives the regioisomer **8**. Compound **8** is an intermediate and the main pharmacophore in a subnanomolar HSV-1 inhibitor that was previously prepared as a racemate in nine steps.[16i,j]

In order to deliver a functionalised chiral intermediate with the carbonyls groups at different oxidation levels, basic methanolysis was carried out (Scheme 3). Preliminary ef-



Scheme 3. Tandem reduction–reductive ring opening or ring opening by methanolysis of the hydroformylation product **5** is possible.

forts show that this reaction proceeds quantitatively but caused 8% of epimerisation in the crude product. The epimer was essentially removed by a single un-optimised recrystallisation from boiling diethyl ether to give **9** with 28% yield (**9**/epi-**9** > 30:1).

In summary, the use of the correct chiral ligand enables an asymmetric hydroformylation of an enantiopure, protected, bicyclic lactam to take place with high selectivity. Two aldehydes can be produced with very high productivity and therefore this protocol could be suitable for larger scale application if desired. These aldehydes can be converted into enantiopure functionalised cyclopentylamines. These procedures should be of use in the synthesis of a variety of cyclopentylamines that could be used as carbocyclic nucleoside analogues. Full optimisation of the catalytic procedure and product isolation, along with further demonstrations of the synthetic utility of these aldehydes will be investigated in due course.

Experimental Section

Full experimental details, characterisation data and assignments are available in the Supporting Information.

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Keywords: alkenes · carbocycles · carbocyclic nucleoside analogues · carbonylation · enantioselective catalysis · ring-opening

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