Asymmetric Hydroformylation

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Rhodium-Catalyzed Asymmetric Hydroformylation of *N*-Allylamides: Highly Enantioselective Approach to β^2-Amino Aldehydes**

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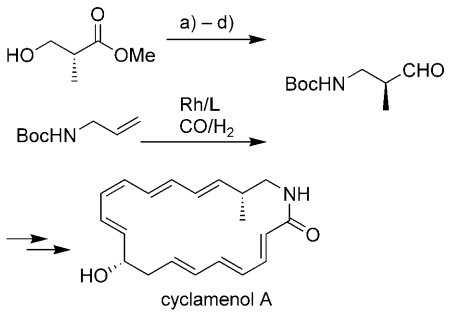
Asymmetric hydroformylation (AHF) has attracted great interest because it can provide enantiomerically pure aldehydes, which are important intermediates for pharmaceuticals and fine chemicals, in an atom efficient manner.[1] Although a number of chiral phosphorus ligands have been developed for the rhodium-catalyzed AHF reaction,[2] the substrates are still limited to simple functionalized terminal olefins without α-hydrogen atoms, such as styrene derivatives and vinyl carboxylates. Expansion of the substrate scope and widening of the application of this methodology is highly desirable.

Chiral β^2-amino aldehydes are important structural elements in natural products.[3] For instance, a Boc (*tert*-butoxycarbonyl)-protected amino aldehyde is a key building block in the synthesis of cyclamenol A (Scheme 1).[4] However, the synthesis of the enantiomerically pure amino aldehyde requires at least four steps, starting from an expensive chiral source, with moderate yields.[4,5] The low efficiency of this synthesis prompted us to seek an alternative approach for synthesizing chiral β^2-amino aldehydes by the direct hydroformylation of *N*-allylamides in a regio- and enantioselective manner.



Scheme 1. Synthesis of chiral β^2-amino aldehydes. a) NH_3, MeOH, NaCN, 50 °C; b) $BH_3{\cdot}Me_2S$, THF, reflux; c) $(Boc)_2O$, Et_3N, MeOH; d) $(COCl)_2$, DMSO, Et_3N. DMSO = dimethyl sulfoxide.

Allylic compounds are particularly challenging substrates for the hydroformylation reaction because of the migration of double bonds.[1] In most cases, the hydroformylation of allylic substrates affords predominantly linear aldehydes, for example, allylbenzene[6] derivatives and allylamines.[7] The hydroformylation reaction of allylic alcohol derivatives to form branched aldehydes has been reported using catalyst-directing phosphine groups that are bound to the substrate,[8] although optically pure aldehydes can only be obtained from chiral substrates.[9] Ojima and co-workers found that the amide group can enhance selectivity for the isoaldehyde product in the hydroformylation of *N*-allylamides through chelation of the carbonyl group to the rhodium center.[10] This preference for branched products encouraged us to use amide moieties as directing groups in the asymmetric hydroformylation reaction, instead of expensive and environmentally unfriendly phosphine groups. Herein, we report a rhodium-catalyzed asymmetric hydroformylation reaction of *N*-allylamides, *N*-allylsulfonamides, as well as other allylic substrates, with excellent enantioselectivity (92–99% *ee*) and a turnover number (TON) of up to 9700; this method provides an alternative, concise, and environmentally friendly route to β^2-amino aldehydes, acids, and alcohols.

We started our investigation using commercially available Boc-protected allyl amine **1a** as a model substrate, as facile removal of the Boc group affords the free β^2-amino aldehyde. We have previously reported that a class of hybrid phosphine–phosphoramidite ligands (yanphos **A**–**C**; Scheme 2), are highly efficient in the asymmetric hydroformylation of styrene, vinyl acetate, and allyl cyanide.[11] The high regio- and enantioselectivity afforded with these catalysts prompted us to consider them in the hydroformylation of **1a**. Two other phosphoramidite ligands and several commercially available chiral ligands (Scheme 2), which were highly efficient in the asymmetric hydroformylation of a variety of functionalized olefins, were also screened. The AHF reactions were carried out with 0.1 mol% catalyst loading and 20 bar CO/H_2 (1:1) gas at 60 °C. The catalyst was prepared in situ by mixing $[Rh(acac)(CO)_2]$ with the ligand in toluene. Under these reaction conditions, all of the linear aldehyde **3a** was transformed into 2-hydroxy pyrrolidine **4a** in quantitative yield, by intramolecular attack of the primary amide on the carbonyl group.[12]

Some representative results are shown in Table 1. With yanphos derivatives as ligands, up to 93% *ee*, full conversion, and good regioselectivity were achieved (Table 1, entries 1–

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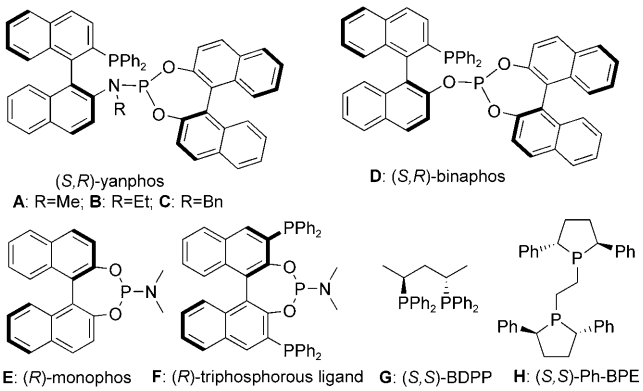
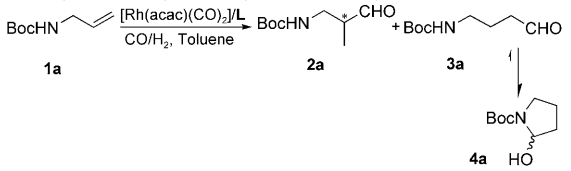


Scheme 2. Chiral ligands for the asymmetric hydroformylation reaction.[14]

Table 1: Asymmetric hydroformylation of *N*-allylamide **1a**.[a]



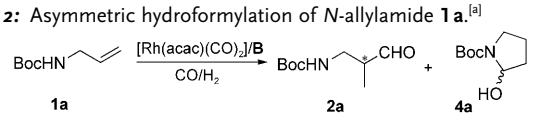
Entry	Ligand	Conversion [%][b]	b/l[b]	*ee* [%][c]
1	A	98	64:36	92(*S*)
2	B	>99	65:35	93(*S*)
3	C	98	64:36	92(*S*)
4	D	99	47:53	78(*S*)
5	E	84	46:54	4(*R*)
6	F	97	62:38	50(*S*)
7	G	43	83:17	56(*R*)
8	H	93	86:14	87(*R*)

[a] Reactions were performed on a 1.0 mmol scale at 60 °C in toluene with substrate/Rh = 1000:1, L/Rh = 4:1, 20 bar CO/H_2 (1:1), and a reaction time of 20 hours. [b] Determined by ^{1}H NMR spectroscopy, b/l (branched/linear ratio) = **2a**/**4a**. [c] Determined by GC analysis using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of the reduced product, *tert*-butyl (3-hydroxy-2-methylpropyl)carbamate, with a literature value; see Ref. [4].

3). Other phosphoramidite ligands, monophos (**E**) and triphosphorus ligand **F**,[13] were also considered but afforded no more than 50% *ee* (Table 1, entries 5 and 6). Binaphos[2a] provided the product in 78% *ee*, but gave less of the desired branched product than the linear one (Table 1, entry 4). Hydroformylation with BDPP and Ph–BPE[2e,14] offered good regioselectivity (83:17 and 86:14, respectively), whilst the enantioselectivity were less satisfying (Table 1, entries 7 and 8).

The success of yanphos **B** encouraged us to investigate the effects of solvent, syngas pressure, and reaction temperature to obtain optimal conditions. Obvious solvent dependency was observed in the AHF reactions catalyzed by rhodium–yanphos complexes (Table 2, entries 1–5). Of the solvents tested, toluene gave the best conversion, regio-, and enantioselectivity. A decrease of the pressure from 20 to 10 bar resulted in a slight increase of the regio- and enantioselectivity, and the inverse was also observed (Table 2, entries 6 and

Table 2: Asymmetric hydroformylation of *N*-allylamide **1a**.[a]



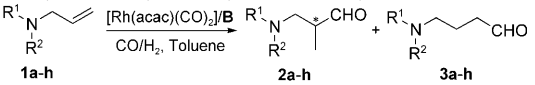
Entry	Solvent	CO/H_2 [bar]	T [°C]	Conversion [%][b]	b/l[b]	*ee* [%][c]
1	benzene	10:10	60	97	62:38	93
2	toluene	10:10	60	>99	65:35	93
3	acetone	10:10	60	88	65:35	83
4	*t*BuOMe	10:10	60	96	60:40	81
5	EtOAc	10:10	60	92	63:37	80
6	toluene	5:5	60	>99	66:34	94
7	toluene	15:15	60	77	65:35	91
8	toluene	5:5	40	61	66:34	94
9	toluene	5:5	80	>99	66:34	91

[a] Reactions were performed on a 1.0 mmol scale with substrate/Rh = 1000:1, **B**/Rh = 4:1, reaction time of 20 hours. [b] Determined by ^{1}H NMR spectroscopy, b/l (branched/linear ratio) = **2a**/**4a**. [c] Determined by GC analysis using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of the reduced product, *tert*-butyl (3-hydroxy-2-methylpropyl)carbamate, with a literature value; see Ref. [4].

7). Lowering the temperature to 40 °C led to a slight increase in *ee* value, but a dramatic decrease in conversion. Likewise, a higher temperature lowered the enantioselectivity (Table 2, entries 8 and 9).

With the optimized reaction conditions in hand (Table 2, entry 6), we examined the scope of the methodology with regards to functional group tolerance. Using a rhodium–yanphos catalyst, a variety of *N*-allylamides, *N*-allylsulfonamides, and *N*-allylphthalimide were hydroformylated with complete conversion, good regioselectivity, and excellent enantioselectivity (>92% *ee*). The functionality on the amide had no effect on the enantioselectivity, but slightly influenced the regioselectivity (Table 3, entries 1–3). For the sulfonamide

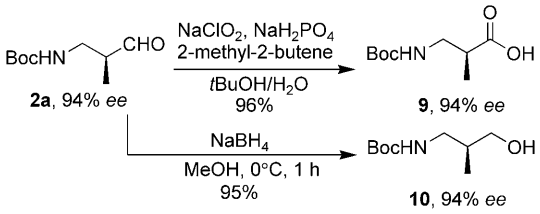
Table 3: Asymmetric hydroformylation of *N*-allylamides **1**.[a]



Entry	R^1	R^2	Conversion [%][b]	b/l[b]	*ee* [%][c]
1	Boc (**1a**)	H	>99	66:34	94
2	Bz (**1b**)	H	>99	78:22	95
3	Ts (**1c**)	H	>99	67:33	94
4	*p*-NO_2PhSO_2 (**1d**)	H	>99	72:28	92
5	*p*-$MeOPhSO_2$ (**1e**)	H	>99	71:29	96
6	Ts (**1f**)	Me	>99	67:33	94
7	Phthaloyl (**1g**)		>99	84:16	96
8	Boc (**1h**)	Boc	>99	72:28	99
9[d]	Boc (**1a**)	H	97	66:34	94

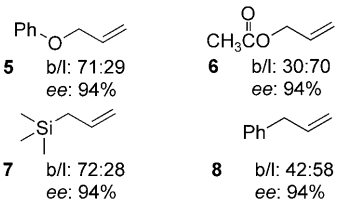
[a] Reactions were performed on a 1.0 mmol scale at 60 °C in toluene with substrate/Rh = 1000:1, **B**:Rh = 4:1, 10 bar CO/H_2 (1:1), reaction time of 20 hours. When R^2 = H, the linear products **3a**–**e** were transformed into their respective 2-hydroxypyrrolidines in quantitative yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC or HPLC analysis using a chiral stationary phase, see the Supporting Information for experimental details. [d] Reaction were performed on a 10.0 mmol scale with substrate/Rh = 10000:1 for 24 hours.

substrates, the electronic properties of the substituents at the *para* position of the phenyl group had a marked effect on the branched/linear selectivity. Electron-rich groups increased the enantioselectivity (Table 3, entries 3–5), whilst introducing a methyl group onto the nitrogen atom of **1c** did not affect the hydroformylation reaction (Table 3, entries 6). However, substrates that contained *N*,*N*-bis(carbonyl) groups showed much better regio- and enantioselectvities. *N*-allylphthalimide afforded 96% *ee* and a branched/linear ratio of 84:16 (Table 3, entry 7). Notably, 99% *ee* was achieved in the hydroformylation of *N*,*N*-bis(Boc)-*N*-allylamine (Table 3, entry 8). To further investigate the reactivity of rhodium–yanphos system in the hydroformylation of *N*-allylamides, a reaction was carried out on a 10.0 mmol scale with substrate/Rh = 10000:1 for 24 hours; 97% conversion (TON = 9700) was achieved without sacrificing the regio- and enantioselectivity (Table 3, entry 9). *N*-Boc-protected β^2-amino aldehyde **2a** was obtained by flash chromatography in 62% yield. Moreover, treatment of **2a** with $NaClO_2$ resulted in β^2-amino acid **9** (96% yield, 94% *ee*), which is an important building block for a number of natural products, such as cryptophycins 1–4.[5] Reduction of aldehyde **2a** provided β^2-amino alcohol **10** (95% yield, 94% *ee*), a starting material for β-methyl carbapenem antibiotics (Scheme 3).



Scheme 3. Synthesis of β^2-amino acids and alcohols.

To further explore the application of this methodology, several other functionalized allylic substrates were utilized in the rhodium–yanphos-catalyzed AHF reaction (Scheme 4).



Scheme 4. Asymmetric hydroformylation of allyl substrates.

The results showed that the functional group on the substrate has no obvious effect on the enantioselectivity, but influenced the branch/linear product ratio. Allyl phenyl ether **5** and allyltrimethylsilane **7** gave comparable results to *N*-allylamide substrates. Allyl acetate **6** and allylbenzene **8** both afforded high enantioselectivity (94%) but showed some linear selectivity.

In conclusion, a variety of allylic substrates have been successfully employed in a rhodium–yanphos-catalyzed hydroformylation reaction under mild conditions, with up to 99% *ee* and 9700 TON. To the best of our knowledge, this is the first example of applying *N*-allylamides and *N*-allylsulfonamides in asymmetric hydroformylation; this reaction provides an alternative catalytic route to β^2-amino aldehydes, acids, and alcohols. Further studies to improve the regio- and enantioselectivity and to explore more applications of this catalyst are underway.

Experimental Section

General procedure for the asymmetric hydroformylation reaction: In a glovebox filled with nitrogen, ligand **B** (0.004 mmol) and [Rh(acac)$(CO)_2$] (0.001 mmol in 0.2 mL toluene) were added to a 2 mL vial. After stirring for 10 minutes, the substrate (1.0 mmol) and additional solvent were added to bring the total volume of the reaction mixture to 1.0 mL. The vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (5 bar) and hydrogen (5 bar) were added sequentially. The reaction mixture was stirred at 60°C (oil bath) for 20 hours. The reaction was cooled and the pressure was carefully released in a well-ventilated fume hood. The conversion and branch/linear ratio were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. The enantiomeric excess was determined either by GC analysis directly, using a chiral stationary phase, or by reducing the aldehyde to the corresponding alcohol with $NaBH_4$, followed by HPLC analysis.

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