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Enantioselective Hydroformylation of *N*-Vinyl Carboxamides, Allyl Carbamates, and Allyl Ethers Using Chiral Diazaphospholane Ligands

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Abstract: Rhodium complexes of diazaphospholane ligands catalyze the asymmetric hydroformylation of *N*-vinyl carboxamides, allyl ethers, and allyl carbamates; products include 1,2- and 1,3-aminoaldehydes and 1,3-alkoxyaldehydes. Using glass pressure bottles, short reaction times (generally less than 6 h), and low catalyst loading (commonly 0.5 mol %), 20 substrates are successfully converted to chiral aldehydes with useful regioselectivity and high enantioselectivity (up to 99% ee). Chiral Roche aldehyde is obtained with 97% ee from the hydroformylation of allyl silyl ethers. Commonly difficult substrates such as 1,1- and 1,2-disubstituted alkenes undergo effective hydroformylation with 89−97% ee and complete conversion for six examples. Palladium-catalyzed aerobic oxidative amination of allyl benzyl ether followed by enantioselective hydroformylation yields the β^3-aminoaldehyde with 74% ee.

Perfect atom economy, fast rates, and high turnover numbers under mild conditions as well as the synthetic utility of the aldehyde products enable rhodium-catalyzed alkene hydroformylation to be one of the largest homogeneous metal-catalyzed processes, producing billions of pounds of achiral aldehydes per year.[1] In contrast, *enantioselective* hydroformylation is underdeveloped. Relatively few chiral rhodium catalysts effect high selectivity and useable rates for a broad range of substrates.[2,3] Chiral aldehydes are versatile synthetic intermediates, and new catalysts capable of selective asymmetric hydroformylation (AHF) could dramatically impact the synthesis of chiral molecules on research and production scales. We recently demonstrated that Bisdiazaphos **1**, produced in two steps from 1,2-bisphosphino benzene and azine, and $Rh(acac)(CO)_2$ catalyze highly selective hydroformylation of vinyl acetate, allyl cyanide, and styrene derivatives with turnover frequencies approaching 20 000 h^{-1} under mild reaction conditions.[4] In the present study, we demonstrate practical and selective AHF of 20 substrates comprising *N*-vinyl carboxamides, allyl ethers, and allyl carbamates using rhodium catalysts bearing diazaphospholane ligand **1** (Figure 1). These reactions yield important chiral building blocks, including

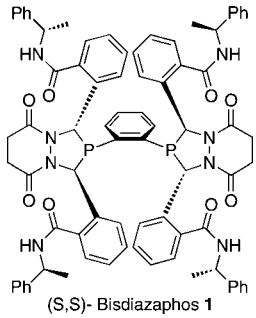


Figure 1. Chiral bisdiazaphospholane ligand used in this study.

Scheme 1. AHF for the Synthesis of 1,2- and 1,3-Aminoaldehydes and 1,3-Alkoxyaldehydes

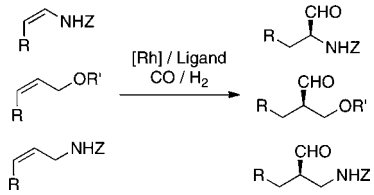
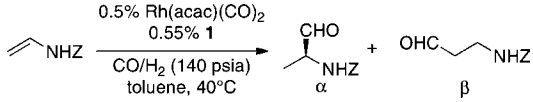
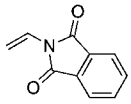
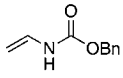
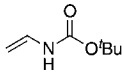
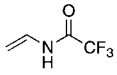


Table 1. Asymmetric Hydroformylation of Monosubstituted Enamides with Ligand **1**[a]



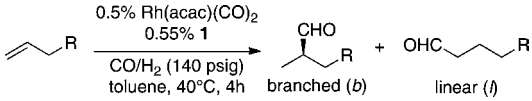
entry	alkene	time (h)	% conv[b]	α:β[b]	% ee[c]
1		4	99	27:1	86
2		6[e]	99	12:1	20
3		8	99	>50:1[d]	95
4		12	99	51:1	94
5		12	99	33:1	99
6		6	99	>50:1[d]	99

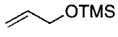
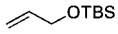
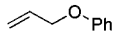
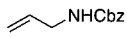
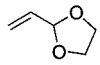
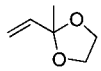
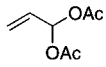
[a] CO/H_2 = 1:1, [alkene] = 0.75 M in toluene. [b] Determined via ^1H NMR spectroscopy. [c] See Supporting Information for determination of enantiomeric excess. [d] Only one product observed via ^1H NMR spectroscopy. [e] 60 °C.

1,2- and 1,3-aminoaldehydes and 1,3-alkoxyaldehydes (Scheme 1), and follow upon the groundbreaking work of Takaya and Nozaki, who first demonstrated that AHF provides ready access to a variety of enantiopure aldehydes.[5,6]

AHF of readily available *N*-vinyl substrates provides an atom economic route to α-amino aldehydes. Under standard conditions of 140 psig synthesis gas (1:1 CO/H_2) in a glass pressure bottle, 0.5 mol % $Rh(acac)(CO)_2$, and 0.55 mol % (*S*,*S*)-Bisdiazaphos **1**, *N*-vinyl acetamide undergoes complete conversion to aldehyde within 4 h at 40 °C (Table 1, entry 1). The internal (α) aldehyde is produced with high regio- (27:1) and stereocontrol (86% ee);

Table 2. Asymmetric Hydroformylation of Allylic Substrates with Ligand **1**[a]



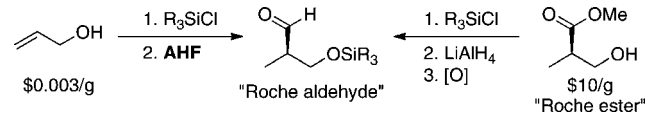
entry	alkene	% conv[b]	b:l[b]	% ee[c]
1		99	1:3.4	95
2		99	2.0:1	97
3		99	2.0:1	96
4		99	2.6:1	96
5		99	4.4:1	86
6		99	4.2:1	92
7		99	2.3:1	96
8		99[d]	7.1:1	93

[a] CO/H_2 = 1:1, [alkene] = 0.75 M in toluene. [b] Determined via ^1H NMR spectroscopy. [c] See Supporting Information for determinaton of enantiomeric excess. [d] 18 h, 0.04% $Rh(acac)(CO)_2$, [diacetoxypropene] = 1 M. Product contained ~25% 1,3-diacetoxy-2-methylprop-1-ene.

hydroformylation of the corresponding *N*-methyl substituted enamide proceeds less successfully (entry 2). Commercially available *N*-vinyl phthalimide reacts with high selectivity, producing the 1,2-aminoaldehyde as the only observed product in 95% enantiomeric excess (entry 3).[7] *N*-Vinyl carbamates also undergo highly selective hydroformylation (entries 4 and 5). *N*-Vinyl trifluoroacetamide[8] proved to be the most reactive and selective substrate, *providing the* α *aldehyde as the only product with 99% enantiomeric excess* (entry 6).

Diazaphospholane ligands are effective for the AHF of *N*- and *O*-functionalized allyl substrates. Regioselective control for these alkenes is challenging; prior work has demonstrated a high preference for the achiral *linear* aldehyde.[5e] For example, the AHF of allyl alcohol using the phosphine-phosphite ligand BINAPHOS yields a 1:9 ratio of branched to linear aldehyde and affords the α aldehyde in 16% ee.[5e] With diazaphospholane ligand **1**, AHF of allyl alcohol proceeds in 95% enantioselectivity, although the regioselectivity still favors the linear aldehyde in a 1:3.4 branched-to-linear ratio (Table 2, entry 1). Analogous allyl *ethers*, however, react with much higher levels of selectivity. Silyl ethers and the phenyl ether react in 99% conversion to afford the chiral 1,3-alkoxyaldehydes with excellent enantioselectivity (96−97%, entries 2−4) and increased levels of regioselectivity (up to 2.6:1). The products of these reactions are 1,3-alkoxy- and 1,3-silyloxyaldehydes, which are common starting materials for the synthesis of biologically active compounds.[9] A prominent example is the Roche aldehyde, which commonly is prepared from the Roche ester (methyl 3-hydroxy-2-methylpropionate) in a three-step sequence (Scheme 2). AHF of allyl silyl ethers with **1** as the ligand proceed with turnover frequencies > 2000 h^{-1} and turnover numbers

Scheme 2. AHF as an Alternate Route to the Roche Aldehyde



exceeding 10 000 at 80 °C.[10] Because of the low cost of allyl alcohol, a commodity chemical, and low catalyst loadings, AHF provides an attractive route to the Roche aldehyde. High pressure is not a prerequisite for effective AHF. For example, AHF of the TBS allyl ether (Table 2, entry 3) at standard loadings and reaction times, but gas pressures of 15 psig and 60 psig *yields complete conversion to aldehydes with selectivities identical to those of reactions performed at 140 psig.*

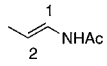
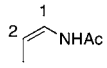
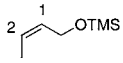
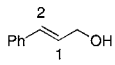
Many other synthetically valuable aldehydes are accessible via AHF. For example, 1,3-aminoaldehydes are synthesized from Cbz-protected allyl amine in 86% enantioselectivity with increased levels of regioselectivity relative to the allyloxy substrates (entry 5). Hydroformylation of α,β-unsaturated carbonyl substrates commonly results in high levels of olefin hydrogenation. This limitation may be overcome, however, by protecting the carbonyl group of acrolein and methyl vinyl ketone as a dioxolane. Hydroformylation of the acrolein derivative with ligand **1** gives the desired aldehyde in 92% ee (entry 6) and 4.2:1 regioselectivity; even higher regioselectivity (7:1) is obtained with acrolein protected as the diacetoxy acetal (entry 8). Similarly useful results were obtained for the vinyl ketone derivative (entry 7). Hydroformylation uniquely provides rapid access to synthetically useful malondialdehyde and related dicarbonyls that are chiral and stable by virtue of having one masked carbonyl and one aldehyde functionality.

Encouraged by the high rates and selectivities for AHF of monosubstituted enamides (cf. Table 1), we investigated the reactivity of disubstituted olefins (Table 3), which commonly proceed at low rates with poor selectivity.[11] The reaction of *trans*-1-acetamido-1-propene is sluggish and exhibits poor regio- and enantioselectivity; however, the *cis* isomer proceeds with 100% conversion under mild conditions to give the α-acetamidoaldehyde with 32:1 regioselectivity and 90% enantioselectivity (entries 1 and 2). Cyclic enamides with four- and five-membered rings proved to be highly reactive and exhibited good levels of enantioselectity (entries 3 and 4). Interestingly, while AHF of the azetidine substrate yielded the 2-formyl regioisomer as the major product (entry 3), hydroformylation of the corresponding five-membered ring was highly regioselective for the 1-formyl product (entry 4). For reasons that are not yet clear, the corresponding six-membered ring was unreactive, even at elevated temperatures (entry 5). Substituted allyl alcohols undergo facile and effective AHF: trimethyl silyl protected *cis*-crotyl alcohol reacts with complete conversion in 15 h at 40 °C (entry 6). In the case of cinnamyl alcohol,[5e] regioselectivity is controlled by the phenyl substituent and affords 1-phenyl-4-hydroxy-butanal in 90% ee as the only product (entry 7).

We also investigated the AHF of 1,1-disubstituted ene-phthalimides, which may be obtained from palladium-catalyzed oxidative imidation of terminal olefins.[12] AHF of these substrates constitutes a novel, efficient route to chiral β^3-aminoaldehydes, originating from simple alkenes (Figure 2).[13]

The AHF reactions yield only the β-aldehyde products, with no α-aldehyde apparent by ^1H NMR spectroscopy.[14] Preliminary results demonstrate that the AHF of an allyl benzyl ether derived ene-phthalimide provides the terminal aldehyde with good levels of chemoselectivity ($\beta:i = 7.1$) and enantioselectivity (74% ee) (eq 1). While the selectivity and rate of this process will presumably vary with the nature of the carboxamide as is seen for *N*-vinyl

Table 3. AHF of 1,2-Disubstituted Olefins with Ligand **1**[a]

entry	alkene	time (h)	temp (°C)	conv (%)[b]	1-formyl: 2-formyl[b]	% ee[c]
1		20	70	66	4.6:1	32
2		20	70	99	32:1	90
3		12	35	99	1:3.6	89
4		15	60	99	10.4:1	97
5		24	100	3	nd	nd
6		18	60	99	1:15	91
7		15	40	99	2.8:1	94
8		16	80	99	<1:50[d]	90

[a] Conditions: 70 °C, 140 psig syn gas (CO/H_2 = 1:1), [alkene] = 0.75 M in toluene, substrate/Rh = 200:1, Ligand/Rh = 1.1:1. [b] Determined via ^{1}H NMR spectroscopy. [c] See Supporting Information for methods used to determine enantiomeric excess. [d] A small amount (6%) of 3-phenyl propanal was observed, presumably arising from isomerization followed by tautomerization to the aldehyde.

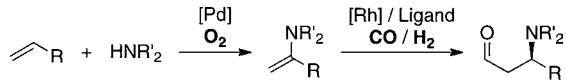
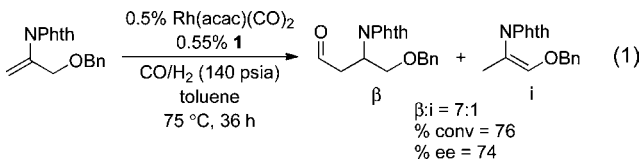


Figure 2. Synthesis of β^3-aminoaldehydes via oxidative amination of unfunctionalized olefins followed by AHF.

carboxamides, this initial example represents a promising future direction for the synthesis of β^3-aminoaldehydes.



(1)

In summary, enantioselective hydroformylation with diazaphospholane ligands enables atom-efficient synthesis of chiral amino- and alkoxyaldehydes from simple substrates under mild conditions. These results, together with previously published examples,[2,4−6] significantly extend the range of chiral aldeydes that can be practically and effectively produced by asymmetric hydroformylation and used in the synthesis of more complex organic molecules.

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Supporting Information Available: Experimental details, characterization data, and conditions for the determination of enantiomeric excess. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Only one aldehyde was observed via ^{1}H NMR spectroscopy.
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(10) Reaction conditions: allyloxy-*tert*-butyldimethylsilane (30 mmol, 4.5 M), $Rh(acac)(CO)_2$ (3 μmol), **1** (3 μmol), 80 °C, 5 h. The reaction proceeded with 99% conversion to aldehydes, $\alpha:\beta$ = 1.8:1, 92% ee. The linear aldehyde can be separated from the branched by flash chromatography to provide the pure chiral aldehyde with no degradation of enantioenrichment.
(11) For example, see: (a) ref 5c. (b) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395–396.
(12) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869.
(13) AHF of methyl *N*-acetamidoacrylate has been demonstrated but was shown to provide exclusively the internal regioisomer: see ref 6d,e.
(14) Refer to the Supporting Information for the investigation of additional substrates.

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