# Asymmetric Hydroformylation of *Z*-Enamides and Enol Esters with Rhodium-Bisdiazaphos Catalysts

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Ⓢ *Supporting Information*

ABSTRACT: Asymmetric hydroformylation (AHF) of *Z*-enamides and *Z*-enol esters provides chiral, alpha-functionalized aldehydes with high selectivity and atom economy. Rh-bisdiazaphospholane catalysts enable hydroformylation of these challenging disubstituted substrates under mild reaction conditions and low catalyst loadings. The synthesis of a protected analog of L-DOPA demonstrates the utility of AHF for enantioselective, atom-efficient synthesis of peptide precursors.
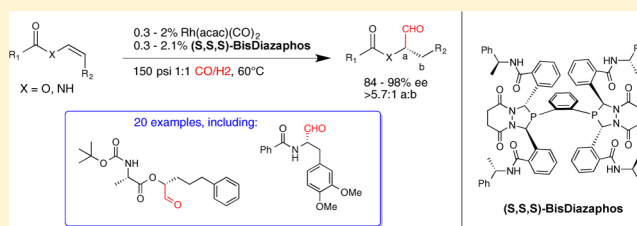
■ INTRODUCTION

Chiral aldehydes are versatile building blocks in organic synthesis. Although the conversion of simple, terminal alkenes into aldehydes by hydroformylation with rhodium catalysts constitutes a long-standing commodity process, applications to the synthesis of chiral aldehydes are less common.[1] The emergence of new chiral catalysts that effect rapid, enantioselective, and regioselective hydroformylation of mono-susbtituted and, to a lesser extent, disubstituted alkenes provides new opportunities for efficient syntheses of chiral aldehydes. In this paper, we demonstrate that disubstituted alkenes comprising *Z*-enol esters and *Z*-enamides undergo efficient hydroformylation with excellent selectivity and functional group tolerance using rhodium catalysts in the presence of the (*S*,*S*,*S*)-bisdiazaphos ligand, **1**.

Effective, modern asymmetric hydroformylation (AHF) technology began with the development of the Rh-(BINAPHOS) catalyst system.[2] Applications of this catalyst demonstrated that useful regio- and enantioselectivities could be effected for a variety of alkenes, especially monosubstituted alkenes. Following these initial demonstrations, several notable ligand systems for AHF have been reported. These ligands include diphosphites such as Chiraphite,[3] mixed phosphine-phosphoramidites such as Yanphos,[4] mixed phosphine-phosphite ligands with small bite angles,[5] Duphos-related diphosphines such as Ph-BPE,[6] and so-called scaffolding monophosphine ligands.[7] Rhodium complexes of the bisdiazaphospholane (BDP; see Figure 1) class of ligands exhibit unusual activity and selectivity in AHF reaction for a broad range of alkene substrates. High (>90% ee) enantioselectivities have been achieved with aryl alkene, 1,3-diene, vinyl acetate, and *N*-vinyl acetamide, dihydrofuran, and other substrates using BDP-derived catalysts.[8]

Effective AHF with disubstituted alkene substrates would expand the strategies available for complex molecule synthesis because AHF provides a fundamentally different disconnection
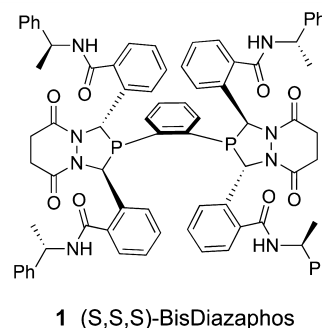

1 (S,S,S)-BisDiazaphos

Figure 1. BDP ligand used for hydroformylation.

than other C−C bond forming reactions. An excellent example is provided by Burke's recent report of a highly efficient synthesis of Patulolide C that features AHF of the *Z*-enol ester **2** (Scheme 1).[8e] Additional examples include the enantioselective synthesis of Garner's aldehyde[9] and Leighton's synthesis of Dictyostatin.[10]

Scheme 1. AHF in the Synthesis of (+)-Patulolide C
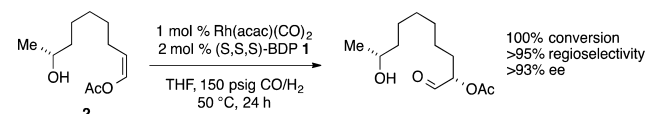
Many simple, *terminal* alkenes have been converted into chiral aldehydes with high selectivity by asymmetric hydroformylation. However, selective AHF of more complex substrates requires effective transformation of more highly substituted alkenes. Prior examples of enantioselective AHF of

Table 1. Some Representative Examples of AHF of 1,1- and 1,2-Disubstituted Alkenes

	Substrate	Ligand	Sub/Cat Ratio	$P_{H2/CO}$ (psi)	T (°C)	t (h)	Conv. (%)	α:β	ee (%)
1		Binaphos[2b]	250	1470	60	50	10	97:3	92
2		BDP 1[8b]	500	150	40	24	37	92:8	94
3		BDP 1[8b]	500	70	40	24	67	-	93
4		Binaphos[2b]	300	1470	60	20	79	96:4	96
5		QuinoxP*[11]	100	145	85	8	46	>100	91
6		BDP 1[8c]	200	140	70	20	99	97:3	90
7		7f	57[a]	50	45	14	77	>100	91

[a]Run with 15 mol % ligand (6.7:1 substrate:ligand) and 0.05 mol % pTsOH as an additive.

Table 2. Asymmetric Hydroformylation of *para*-Substituted Z-Enol Esters (run with 100 mg alkene)

0.3% Rh(acac)(CO)$_2$
0.3% (S,S,S)-BDP
145 psig H$_2$/CO, 24h, 60°C, THF
→ α (major) + β (minor)
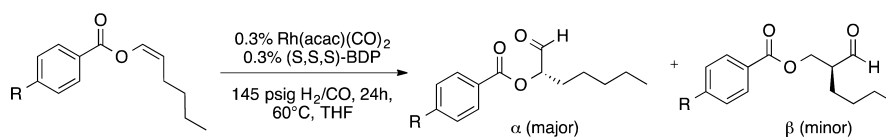
entry	R =	conc. alkene (M)	conv.[a]	α:β[a]	isolated yield	% ee[c]
1[b,e]	H	1.5	>99%	>50:1	92%	97
2[f]	OMe	1.3	>99%	>50:1	84%	96
3	SMe	1.8	>99%	>50:1	85%	90
4	Cl	1.3	>99%	>50:1	88%	96
5	Br	1.3	>99%	>50:1	82%	92
6[d]	CH$_2$Cl	1.5	94%	>50:1	78%	92
7	OH	1.3	93%	>50:1	82%	99

[a]Determined by ^{1}H NMR of crude reaction mixture. [b]Run with 1 g alkene. [c]The ee determined by SFC or HPLC after NaBH$_4$ reduction. [d]0.5% catalyst loading. [e]$[\alpha]^{20}_D = -14.7$ (S), (c = 1.24, CHCl$_3$). [f]The configuration is S as determined by LAH reduction to the diol and comparison of the optical rotation with the previously assigned diol.

disubstituted alkenes with enantioselectivities that exceed 90% ee are given in Table 1.

Application of AHF to 1,2-disubstituted alkenes requires controlling the regioselectivity of CO insertion between two positions that are less sterically differentiated than in monosubstituted or 1,1-disubstituted alkenes. To date, control of regioselectivity has been addressed most effectively for allyl amines and alcohols that are amenable to scaffolding catalysis.[7] Hydroformylation of disubstituted alkenes commonly requires long reaction times and/or high catalyst loading in order to overcome the substrate bulkiness. With Rh-BDP catalysts, AHF of alkenes substituted with inductively electron-withdrawing

groups, such as acetoxy- or acetamido-substituents, generally yield high regioselectivity and good activity.[8c] With the exception of particularly electron-deficient alkenes, AHF of 1,1-disubstituted alkenes is sluggish.[11] A small set of data indicates that the geometry of the double bond of 1,2-disubstituted alkenes also impacts AHF selectivity, with Z-alkenes giving higher regio- and enantioselectivities and faster rates.[2b,8c] Such observations suggest that AHF can be particularly effective for 1,2-disubstituted alkenes comprising (Z)-enol esters and enamides.

■ RESULTS AND DISCUSSION

AHF of Enol Esters. Enol ester substrates are attractive candidates for AHF because the two carbons of the alkene are well-differentiated electronically. Benzoyloxy-substituted alkenes are synthetically accessible as the Z isomer via Ru-catalyzed addition of alkynes to carboxylic acids.[12,13] Hydroformylation of these alkenes in the presence of **1** and Rh(acac)(CO)$_2$, where acac = acetylacetonate, produces only the alpha-substituted, 2-benzoyloxy aldehyde with excellent enantioselectivity (90−99% ee) at low catalyst loadings (0.3%) (Table 2). Results obtained on the gram scale (Table 2, entry 1) are similar to small scale results (Table 2, entries 2−7). Hydroformylation is tolerant of a wide variety of functional groups, including potential catalyst poisoning groups such as thioether, benzylic chloride, and free phenol (Table 2, entries 3, 6, and 7). The substituent in the *para* position has little effect on the hydroformylation activity and all substrates tested give high regio- and enantioselectivity under the screening conditions.

While the results in Table 2 incorporate 24 h reaction times, many substrates go to complete conversion at 60 °C in under 16 h. Significantly, at higher temperatures the reaction time is reduced with no effect on the enantio- or regioselectivity. For (Z)-hex-1-en-1-yl 4′-methoxybenzoate, AHF is complete within 1.5 h at 100 °C, and the resultant aldehyde is produced in 96% ee (Table 3, entry 3). The enantioselectivity only drops modestly when the temperature is further increased to 120 °C.

Table 3. Selectivity of AHF Is Maintained at Higher Temperatures (run with 100 mg alkene)
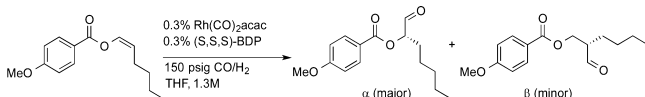
entry	temp (°C)	time (h)	conv.[a]	α:β[a]	% ee[b]
1	60	24	>99%	>50:1	96
2	80	5	>99%	>50:1	96
3	100	1.5	>99%	>50:1	95
4	120	0.5	>99%	>50:1	89

[a]Determined by ¹H NMR of crude reaction mixture. [b]The ee determined by HPLC after NaBH$_4$ reduction.

AHF of enol esters is effective with both acetates and benzoates (Table 4, entry 1). Enol esters derived from enantiopure amino acids of opposite chirality undergo AHF with high diastereoselectivity that is predominately catalyst-controlled, with little match-mismatch effect (Table 4, entries 2 and 3). Trifluoroacetyl enol esters also were investigated, but these undergo undesirable elimination of trifluoroacetic acid under catalytic conditions and give low conversion (37−60%) to the desired product.

AHF of Enamides. Z-Enamides can be synthesized by Ru-catalyzed coupling of primary amides to alkynes.[14] These substrates also undergo AHF with high selectivity for the α-amino aldehyde product. The AHF of enamides is slower than that of the corresponding enol esters (Figure 2), and complete conversion within a day requires higher catalyst loading (1%) at 65 °C.
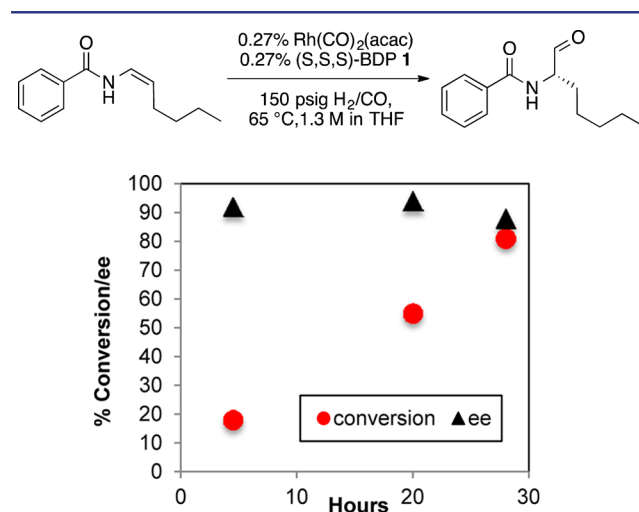

Figure 2. AHF of enamide N-((Z)-1-hexen-1-yl)benzamide with time.

Both E- and Z-enamides were tested under standard AHF conditions of 65 °C and 150 psig CO/H$_2$ (Table 5, entries 1 and 2). Consistent with prior results for propenamide, the Z-enamide gives both higher enantioselectivity and faster rates. Under standard conditions, the AHF of most enamides proceeds with high selectivity and excellent functional group tolerance, including groups that often react with metal catalysts, such as alkyl chlorides and nitriles (Table 5, entries 4 and 5). Important limitations of AHF with bisdiazaphos catalysts are revealed by entries 10 and 11. The α−β unsaturated substrate ethyl-(2-benzamido)ethenoate not only undergoes hydro-

Table 4. AHF of Other Enol Esters (run with 150 psig H$_2$/CO)

Substrate	Product	Conc. alkene	Temp (°C)	Time (h)	Conv.[a]	α:β[a]	Isolated Yield	% ee or de
		1.3 M	60	24	>99%	>50:1	88%	93[b,d]
		1.1 M	60	24	>99%	>50:1	83%	92[a]
		1.1 M	60	24	>99%	>50:1	75%	92[c]

[a]Determined by ¹H NMR of crude reaction mixture. [b]ee determined by HPLC after NaBH$_4$ reduction. [c]Run with (R,R,R)bisdiazaphos. [d]The configuration is S as determined by LAH reduction to the diol and comparison of the optical rotation with the previously assigned diol.

Table 5. Asymmetric Hydroformylation of Enamides (run with 100 mg alkene)

Entry	Substrate	Temp (°C)	Conc. alkene	% Conv.[a]	α: β[a]	%ee[b]
1		65	1.1M	100	>99	85
2		65	1.1M	68	>99	56
3		60	1.0M	87	>99	90
4		60	0.8M	79	14.3	92
5		60	0.8M	100	>99	94
6		55	0.8M	80	>99	84
7[d]		65	1.1M	86	6.3	α: 98 β: 32
8[c]		60	1.1M	100	12.3	α: 90 β: 54
9		60	0.9M	100	21.0	n.d.
10		60	0.9M	70	n.d.	n.d.
11		60	1.8M	27	6.7	n.d.

[a]Determined by ^{1}H NMR of crude reaction mixture. [b]ee determined by HPLC after NaBH$_4$ reduction. [c]$[\alpha]^{20}_D = -103.1$ (S), (c = 1.29, EtOH) for alpha isomer. [d]The absolute configuration was assigned as S after reduction to the alcohol with sodium borohydride and comparison with the previously assigned alcohol.

formylation but also shows extensive hydrogenation of the double bond and degradation of starting material (entry 10). Second, the tertiary amide N-4-phenyl-1-butenylpyrrolidinone hydroformylates at much slower rates than other enamides giving only 27% conversion to aldehyde in 24 h, with extensive isomerization to the E alkene (entry 11).

The N-styryl enamides examined undergo hydroformylation with lower regioselectivity than that seen for enamides with pendant alkyl chains. Presumably this reflects competition between the aryl (which directs formyl insertion in the β position) vs carboxamido (which directs formyl insertion in the α position) directing effects. Because styrene exhibits strong CO-pressure-dependent selectivity, we examined the hydroformylation of N-((Z)-2-phenylvinyl) benzamide as a function of pressure (Figure 3).

As seen for simple styrenes, the regio- and enantioselectivity of (Z)-styreneamides decrease with decreased syngas pressure. Increasing the electron-withdrawing nature of the carboxamide

(trifluoroacetamido vs benzamido) improves the regioselectivity at a given syngas pressure and the trend of increasing regio- and enantioselectivity with increased syngas pressure persevere. Such results demonstrate the importance of manipulating reaction conditions to control selectivity in the hydroformylation of styrenyl substrates.

Synthesis of a L-DOPA Building Block. AHF provides more atom efficient and direct access to highly enantioenriched α-amino aldehydes than methods involving multiple-step reactions and multiple changes in oxidation state to reach the desired aldehyde functionality.[15] Although alpha-substituted aldehydes potentially are susceptible to racemization via enolization, the intrinsically neutral conditions unique to aldehyde synthesis by hydroformylation obviate racemization even at temperatures in excess of 100 °C.[16] As a demonstration of the practical utility of AHF, the synthesis of a protected L-DOPA aldehyde was performed (Scheme 2). While the acid form is accessible through various synthetic methods (the most
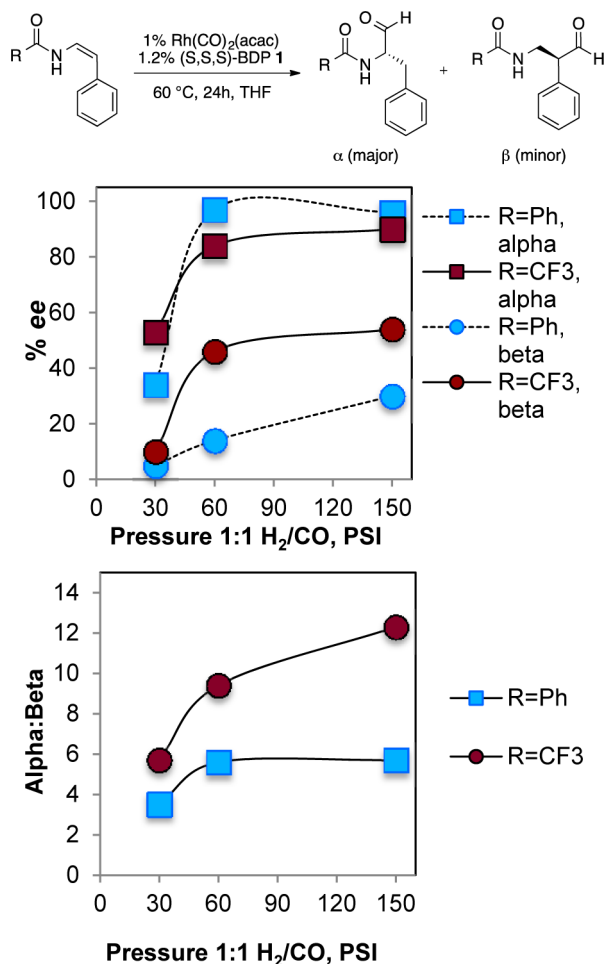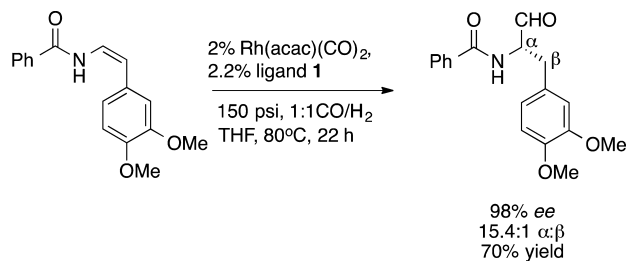
Figure 3. Pressure effects on AHF of styrenyl enamides.

Scheme 2. AHF of Enamides Applied to the Synthesis of Protected analog of L-DOPA Aldehyde[a]

[a]The ee determined by HPLC after NaBH₄ reduction to the alcohol.

notable of which is Knowles' asymmetric hydrogenation), the aldehyde form is a valuable intermediate for formation of peptides and analogs.[17]

The desired *Z*-enamide was synthesized by Ru-catalyzed coupling of benzamide to an alkyne derived from vanillin.[18] Asymmetric hydroformylation of this substrate proceeds cleanly to produce the aldehyde with 98% ee and 15.4:1 branch selectivity. The improved selectivity relative to the styrenyl enamides in Figure 3 is likely due to the electron-donating methoxy substituents on the aryl ring disfavoring acyl formation at the *β* position.[8b]

CONCLUSION

AHF provides a direct, catalytic, and atom-efficient route to useful chiral building blocks, including unnatural amino aldehydes. A variety of Z-enol esters and enamides undergo asymmetric hydroformylation in the presence of **1** and Rh(acac)(CO)₂ to produce α-chiral aldehydes with high regio- and enantioselectivity. Five of the products were determined to have the S configuration by comparison of optical rotations of known compounds; all data are consistent with S configurations for all aldehydes reported herein. These studies highlight critical attributes of the bisdiazaphos hydroformylation catalysts: high intrinsic reactivity (with complete conversion and >90% ee in just 90 min at 0.3 mol % catalyst loading in simple pressure bottles), reliably high enantioselectivities (>90% ee) for a variety of Z-enol esters and enamides, and tolerance of functional groups such as phenols, thioethers, aryl bromides, and benzylic chlorides. For 1,2-disubstituted alkenes with competing regiodirecting substituents, such as styrenyl enamides, increased pressure can effect increased regio- and enantioselectivities for the α-carboxamido aldehyde. Overall, these results significantly expand efficient access to chiral α-functionalized aldehydes.

EXPERIMENTAL DETAILS

General Method for Hydroformylation. Inside a N₂-purged glovebox, an oven-dried 15 mL Ace Glass pressure bottle equipped with a magnetic stir bar was charged with THF stock solutions of Rh(acac)(CO)₂ and BDP ligand 1 using 1000 and 200 µL Eppendorf pipets. The pressure bottle was attached to a pressure reactor and removed from the glovebox, placed in a fume hood, subjected to 5 pressurization (140 psig)/depressurization (15 psig) cycles with syngas to ensure replacement of the dinitrogen atmosphere with syngas, then filled to the appropriate syngas pressure. The solution was allowed to stir at high speed to ensure gas mixing for 30−60 min in an oil bath at the reaction temperature. The reaction vessel was then removed from the oil bath and allowed to cool for 5 min, then the pressure was reduced to <10 psig, and the olefin was injected with a gastight syringe with a 12 in. needle. Solid olefins were injected as a solution in THF. Reactions were run at 0.8−1.3 M final concentration of olefin. The reaction was then repressurized to the reaction pressure after additional pressurization/depressurization cycles and replaced in the oil bath. Upon completion of the reaction, the pressure bottle was removed from the oil bath, allowed to cool to room temperature, and vented in a fume hood. NMR spectra are initially obtained of the crude reaction mixture by adding NMR solvent directly to the reaction mixture. Enantiomeric excess of the hydroformylation product was determined by chiral SFC or HPLC after reduction to the alcohol with NaBH₄.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectral characterization of new compounds, and conditions for determination of enantiomeric excess. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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