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Rh-Catalyzed Asymmetric Hydroformylation of Functionalized 1,1-Disubstituted Olefins

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Supporting Information

ABSTRACT: The first method for the highly enantioselective rhodium-catalyzed hydroformylation of 1,1-disubstituted olefins has been developed. By employing either of the *P*-chirogenic phosphine ligands BenzP* and QuinoxP*, linear aldehydes with β-chirality can be prepared in a highly enantioselective fashion with good chemo- and regioselectivities.

Hydroformylation is one of the most important homogeneously catalyzed processes in industry, as it directly converts inexpensive olefin precursors into their corresponding aldehydes. Of particular interest for the synthesis of fine chemicals is asymmetric hydroformylation (AHF), which allows for the conversion of olefins into optically active aldehydes in a single step.[1] Since the introduction of the Binaphos ligand by Takaya in 1993,[2] the development of chiral phosphorus ligands has significantly facilitated enhanced regio- and enantioselectivity in rhodium-catalyzed AHF.[3−5] Notably, several important applications of olefin hydroformylation to the synthesis of complex molecules have been demonstrated.[6,7b] However, most of the reported methods have been limited to monosubstituted[2−5] and 1,2-disubstituted olefins.[8] In these cases, α-chiral branched aldehydes are formed (Scheme 1). In contrast, AHF of 1,1-disubstituted olefins to provide β-chiral linear aldehydes (as indicated by Keulemans' rule)[9] has been much less extensively investigated and has proven to be a formidable challenge in terms of enantioselectivity.[7,10] In fact, this substrate class has proven to be extremely difficult for a variety of transformations, including asymmetric hydrogenation,[11a,b] epoxidation,[11c,d] and hydroboration.[11e,f] In these reactions, it is often difficult for the chiral catalyst to differentiate between the two enantiotopic faces, so good enantioselectivities are observed only when there is a significant size difference between the two substituents. The AHF of α-alkylacrylate was previously reported by Kollár in the 1980s. However, the reaction employed a $PtCl_2-SnCl_2$ catalyst, which required high syngas pressures (200−250 bar) and long reaction times (90 h) to provide the chiral products with low to modest enantioselectivity in conjunction with significant amounts of hydrogenated side products.[12] In addition, the substrate scope was limited to methacrylate and itaconate. Herein we disclose the first example of a general, highly enantioselective process for the rhodium-catalyzed hydroformylation of α-alkylacrylates that operates under mild conditions.

Our initial studies focused on the AHF of ethyl 2-benzylacrylate (**1**) to give the desired chiral aldehyde product **2a**, with the hopes of discovering not only a highly enantioselective and regioselective transformation but also one that would minimize the formation of undesired side products such as the olefin isomerization product **2c** and the hydrogenation product **2d**.

Scheme 1. AHF of Olefins To Produce Enantioenriched Aldehydes

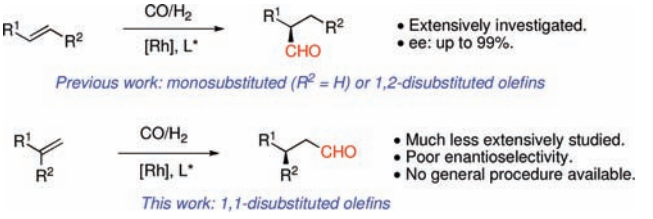
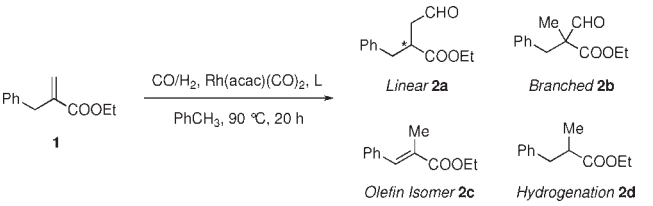


Table 1. Ligand Evaluation for the AHF of Ethyl 2-Benzylacrylate (1)[a,b]



			2a		yield (%)		
entry	ligand	conv (%)	yield (%)	ee (%)[c]	2b	2c	2d
1	**L1**	100	12	16 (*R*)	0	82	6
2	**L2**	100	55	3 (*S*)	5	40	0
3	**L3**	100	11	26 (*S*)	2	71	16
4	**L4**	100	18	4 (*R*)	16	63	0
5	**L5**	100	60	8 (*R*)	6	34	0
6	**L6**	100	43	75 (*R*)	37	12	10
7	**L7**	100	31	82 (*R*)	22	5	42

[a] All reactions were performed at 90 °C in toluene with 10 bar 1:1 CO/H_2, 2.0 mol % $Rh(CO)_2acac$, 2.4 mol % ligand, and 20 h reaction time. [b] GC yields are reported. [c] The ee values were determined by chiral GC. The absolute configurations of **2a** (shown in parentheses) were determined by converting **2a** to the known diethyl ester (see the Supporting Information).

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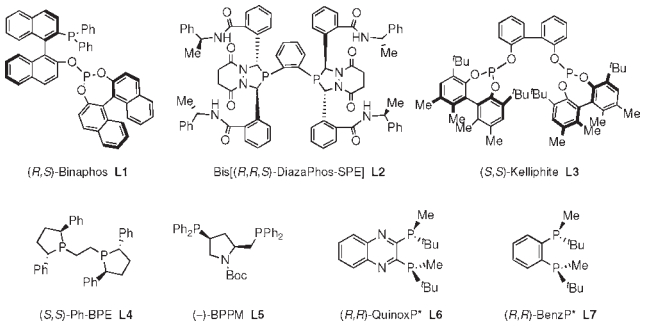

Figure 1. Typical chiral ligands for asymmetric hydroformylation.

The results of an evaluation of ligands for this process are described in Table 1. Among various chiral ligands tested were those previously demonstrated to be successful in AHF, such as Binaphos (**L1**),[2] diazaphospholane (**L2**),[3] Kelliphite (**L3**),[5] Ph-BPE (**L4**),[4] and BPPM (**L5**)[12d] (Figure 1). Not surprisingly, given that 1,1-disubstituted olefins typically display poor reactivity, a 2% loading of the rhodium catalyst and a reaction temperature of 90 °C were required for full conversion of **1** in all cases.[13] The use of Binaphos and Ph-BPE (Table 1, entries 1 and 4), while efficient for the AHF of monosubstituted olefins, gave **2a** in poor yield and with negligible ee. The diazaphospholane- and BPPM-derived catalysts, while displaying excellent reactivity for the desired product, nonetheless failed to exert efficient enantiocontrol (entries 2 and 5). Similarly, application of the diphosphite ligand Kelliphite provided **2a** in poor yield with merely 26% ee (entry 3). We discovered, however, that by moving to ligands bearing chiral information directly on phosphorus, such as the *P*-chirogenic diphosphine QuinoxP* (**L6**), the desired product **2a** could be obtained with 75% ee (entry 6). Furthermore, the structurally related *P*-chirogenic ligand BenzP* (**L7**) gave **2a** in even greater enantiomeric excess (82%; entry 7). It is hypothesized that these structurally rigid *P*-chirogenic ligands are able to bring chiral information closer to the reaction site, rendering them uniquely effective in differentiating between the two olefin substituents.[14]

With these promising results in hand, we sought to optimize the reaction by examining a variety of reaction conditions, as summarized in Table 2. We found that by employing dodecane as the solvent, we could increase the enantioselectivity of product **2a** to 85% (entry 2). However, a considerable amount of hydrogenation product **2d** was still observed. This is presumably a consequence of the electron-withdrawing effect of the phenyl group, which decreases the rate of CO migratory insertion (to afford **2a**), thus enabling the reductive elimination (to afford **2d**) and β-hydride elimination (to afford **2c**) to become competitive. We next focused on varying the total gas pressure and the CO/H_2 ratio in an effort to enhance the rate of formation of **2a** and thus to minimize the side reactions. It is known that an increase in the CO partial pressure corresponds to a decrease in the reaction rate with regard to Rh catalysis,[15] and we indeed observed that by increasing the CO/H_2 ratio to 9:1, a 4% loading of the Rh catalyst was needed for full conversion (entry 3). However, under the same total pressure (10 bar) but with less CO and more H_2 (1:5), the reaction afforded the desired product **2a** in a yield of 63% with 84% ee (entry 4). Under these conditions, only 1% Rh catalyst was needed for full conversion of the starting material. The use of a lower overall pressure (6 bar) of the same 1:5 CO/H_2 mixture

Table 2. Effect of Reaction Conditions on the Yield and Enantioselectivity of the AHF of Ethyl 2-Benzylacrylate (1)[a,b]

					2a		yield (%)		
entry	P (bar) ($CO:H_2$)	T (°C)	[Rh] (%)	conv (%)	yield (%)	ee (%)[c]	2b	2c	2d
1	10 (1:1)	100	2.0	100	35	81	14	7	43
2	10 (1:1)	100	2.0	100	37	85	13	8	43
3	9 (9:1)	100	4.0	100	46	84	11	10	32
4	10 (1:5)	100	1.0	100	63	84	4	16	16
5	6 (1:5)	100	1.0	62	23	83	3	13	23
6	10 (1:5)	90	1.0	100	37	81	4	24	36

[a] Reactions were performed in toluene (entry 1) or dodecane (entries 2–6) with 1–4 mol % $Rh(CO)_2acac$ and (*R,R*)-BenzP* (L/Rh = 1.2). [b] GC yields are reported. [c] Determined by chiral GC.

led to incomplete conversion (entry 5). Lower reaction temperatures were also explored, but both the product yield and ee suffered in this case (entry 6).

With the reaction conditions in hand, we next set out to investigate the substrate scope. In the presence of 1.0% $Rh(CO)_2acac$ and 1.2% BenzP*, a variety of α-alkylacrylates were found to be successful substrates, affording the corresponding linear aldehydes in good to excellent yields with an unprecedented lead of enantioselectivity (Table 3). The AHF of methyl methacrylate provided the corresponding product with 83% ee (entry 1). In the cases of more sterically demanding substrates bearing ethyl, *n*-propyl, benzyl, and the silyloxyalkyl groups, higher ee's of up to 89% could be realized (entries 2–5). The reaction worked particularly well for olefins with secondary alkyl substituents, such as isopropyl, cyclohexyl, and cyclopentyl groups, providing the desired aldehydes in excellent yields with enantioselectivities of 92–94% (entries 6–8). The high yields realized in the examples in entries 6–8 are due to the better regio- and chemoselectivities in comparison with those in entries 1–5. The effect of the bulkier secondary alkyl groups significantly retards the formation of the branched Rh–alkyl intermediate, which would lead to the undesired branched aldehyde and olefin isomer. The 2-isopropyl- and 2-cyclohexyl-1,4-dicarbonyl structures are particularly interesting in that they can be found in many biologically active compounds and active pharmaceutical ingredients (Figure 2).[16] Traditionally, these moieties have been prepared via asymmetric alkylation facilitated by a chiral oxazolidinone auxiliary[17] or via asymmetric hydrogenation with a multistep sequence from 2-isopropylidenesuccinic acid 1-methyl ester.[18] To the best of our knowledge, no synthetic method has been developed to install the stereogenic center catalytically in a single step.

In summary, we have developed the first effective and facile rhodium-catalyzed enantioselective hydroformylation of functionalized 1,1-disubstituted alkenes under mild conditions. In this transformation, the *P*-chirogenic ligands BenzP* and QuinoxP* demonstrated unprecedented stereochemical control in the AHF of α-alkylacrylates. Notably, we were able to minimize the long-standing problem of side reactions by fine-tuning the partial pressures of CO and H_2. In particular, the ability to perform this transformation at acceptably low gas pressure makes it safe for general laboratory use. We expect this

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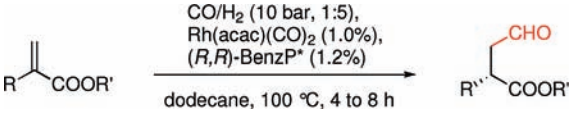
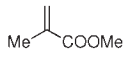
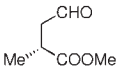
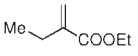
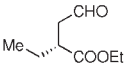
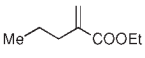
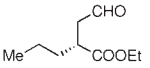
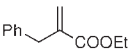
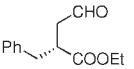
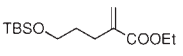
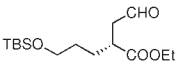
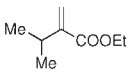
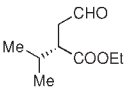
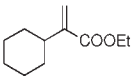
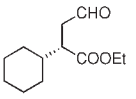
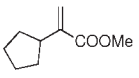
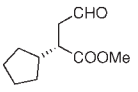
Table 3. Asymmetric Hydroformylation of α-Alkylacrylates[a]



Entry	Olefin	Product	Yield %[b]	ee %[c]
1			54	83
2			68	87
3			63	89
4			60	84
5			62	81
6			91	92
7			84	94
8			85	93

[a] All reactions were performed at 100 °C in dodecane with 10 bar 1:5 CO/H_2, 1.0 mol % $Rh(CO)_2$acac, 1.2 mol % (*R*,*R*)-BenzP*, and 4−8 h reaction time. [b] Isolated yields are reported. Each result shown is the average of two runs in which all of the starting material was consumed. See the Supporting Information for the isolation and characterization of side products. [c] Determined by chiral GC.

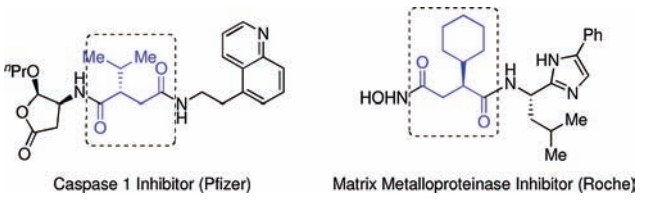


Figure 2. Biologically active compounds containing 2-isopropyl/cyclohexyl-1,4-dicarbonyl moieties.

methodology to broaden the applicability of asymmetric hydroformylation for the synthesis of chiral aldehydes and their derivatives.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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