Design and Application of Hybrid Phosphorus Ligands for Enantioselective Rh-Catalyzed Anti-Markovnikov Hydroformylation of Unfunctionalized 1,1-Disubstituted Alkenes

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Design and Application of Hybrid Phosphorus Ligands for Enantioselective Rh-Catalyzed Anti-Markovnikov Hydroformylation of Unfunctionalized 1,1-Disubstituted Alkenes

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ABSTRACT: A series of novel hybrid phosphorus ligands were designed and applied to the Rh-catalyzed enantioselective anti-markovnikov hydroformylation of unfunctionalized 1,1-disubstituted alkenes. By employing the new catalyst, linear aldehydes with β-chirality can be prepared with high yields and enantioselectivities under mild conditions. Furthermore, catalyst loading as low as 0.05 mol% furnished the desired product in good yield and undiminished selectivity, demonstrating the efficiency of this transformation in large-scale synthesis.

Owing to the perfect atom economy, asymmetric hydroformylation (AHF) of alkenes represents one of the most efficient routes for the preparation of chiral aldehydes, which are versatile intermediates for fine chemicals.[1] In this asymmetric transformation, the development of chiral ligands is a key issue, and intensive research efforts have been made in the past decades. Besides the milestone chiral ligands Binaphos[2] and Bis-diazophos[3], a range of chiral phosphorus ligand systems have also been developed for AHF reactions, including Chiraphite,[4] Ph-BPE,[5] YanPhos,[6] and some other phosphorus ligands.[7] Although good regio- and enantioselectivities have been achieved for AHF of monosubstituted and 1,2-disubstituted olefins, in which α-chiral branched aldehydes are formed, AHF of 1,1-disubstituted olefins to provide β-chiral linear aldehydes (as indicated by *Keulemans' empirical rule*)[8] has been much less investigated due to the formidable challenge in terms of enantioselectivity and reactivity. Recently, Buchwald group and Zhang group have reported the Rh-catalyzed asymmetric hydroformylation of an α-alkylacrylate[9] and 1,1-disubstituted allylphthalimides,[10] respectively. However, unlike the AHF of functionalized 1,1-disubstituted olefins, achieving a highly enantioselective AHF of unfunctionalized 1,1-disubstituted olefins becomes more challenging.[1j] Due to a lack of functional groups which can provide binding or affinity interaction with the catalyst, it is very difficult for the catalyst to differentiate the two prochiral faces, which is also a tough issue in other asymmetric transformation, such as hydrogenation,[11] hydroboration,[12] hydroamination[13] and epoxidation.[14] Although this kind of substrate has been studied for a long time in AHF area,[15] there has not been an effective catalytic system that can provide >50% ee of the n-aldehyde in these cases (scheme 1a and 1b).[1j] Herein, we report the design of novel hybrid phosphorus ligands and their application to the Rh-catalyzed AHF of unfunctionalized 1,1-disubstituted alkenes, and linear aldehydes with β-chirality are achieved with high yields (up to 96%) and enantioselectivities (up to 93% ee) under mild conditions.

Our initial studies focused on the AHF of α-methylstyrene (**1a**) to give the desired chiral aldehyde product **2a**, with the expectations of achieving a highly enantioselective transformation. Chiral ligands which are privileged catalysts in the AHF or AH area, such as (*S*,*S*)-Ph-BPE, (*R*c,*S*p)-DuanPhos, (*S*)-BINAP,

Scheme 1. Asymmetric Hydroformylation of Unfunctionalized 1,1-Disubstituted Alkenes

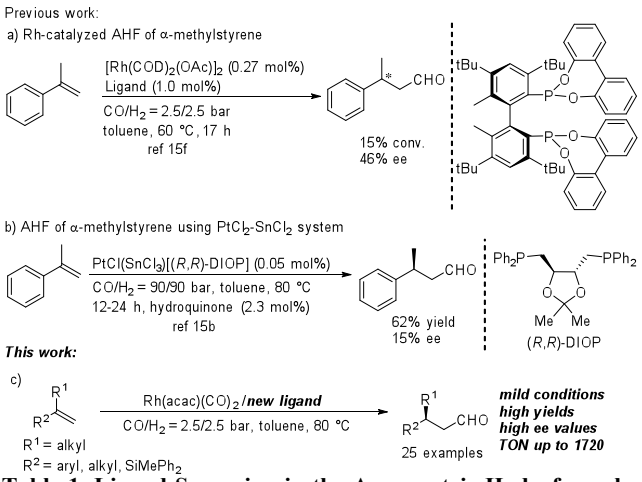
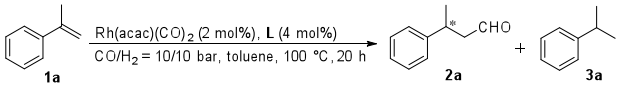


Table 1. Ligand Screening in the Asymmetric Hydroformylation of α-Methylstyrene (1a)[a]



entry	ligand	conv. (%)[b]	yield (%)[b] 2a	yield (%)[b] 3a	ee (%)[c]
1	(*S*,*S*)-Ph-BPE	1	1	<1	-
2	(*R*c,*S*p)-DuanPhos	3	3	<1	-
3	(*S*)-BINAP	<1	<1	<1	-
4	(*R*,*R*)-QuinoxP*	4	4	<1	-
5	XuPhos	2	2	<1	-
6	(*S*,*R*)-YanPhos	17	17	<1	58(*R*)
7	**L1**	7	7	<1	49(*R*)
8	**L2**	5	5	<1	37(*S*)
9	**L3**	40	40	<1	61(*S*)
10	**L4**	35	35	<1	58(*S*)
11	**L5**	**65**	**65**	**<1**	**82(*S*)**
12	**L6**	19	19	<1	55(*S*)

[a]Unless otherwise mentioned, all reactions were performed on a 0.25 mmol scale at 100 °C in 1 mL toluene with substrate/Rh = 50, L/Rh = 2, 20 bar CO/H_2 (1:1), and a reaction time of 20 hours. [b]Determined by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase after $NaBH_4$ reduction. The absolute configuration was assigned by comparing the sign of the optical rotation of (*S*)-**2a** with that reported in the literature, see ref 2 in supporting information.

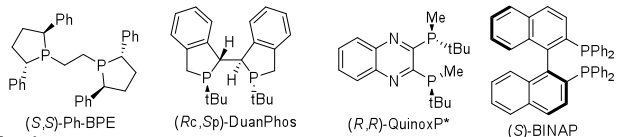
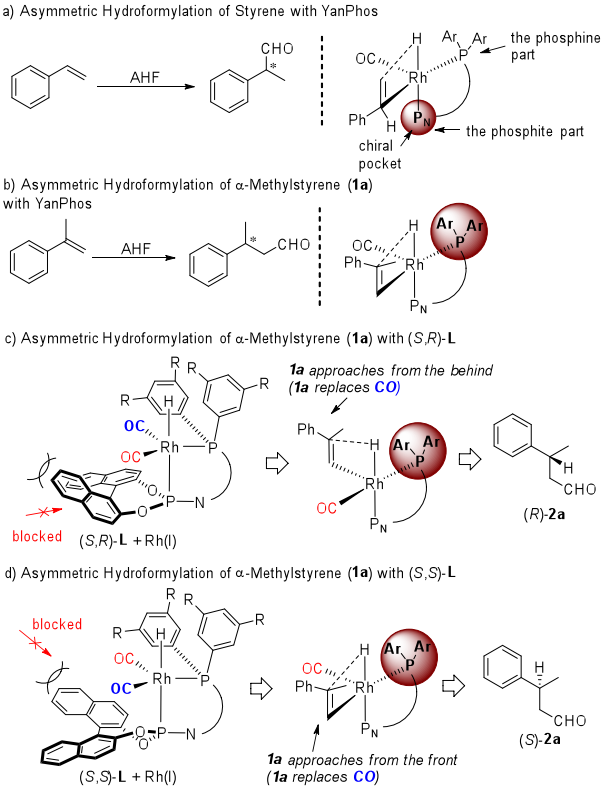


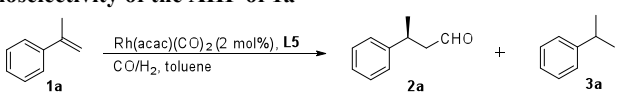
Figure 1. Structures of the Phosphine Ligands for Asymmetric Hydroformylation of 1a.

Scheme 2. Asymmetric Hydroformylation of Styrene and 1a



(*R*,*R*)-QuinoxP*, XuPhos, were tested, but the low conversions (<5%) disclosed that these catalyst systems cannot complete this task (Table 1, entries 1-5). When (*S*,*R*)-YanPhos was employed, 17% yield with 58% ee was given (Table 1, entry 6), which inspired us to a further exploration. Based on previous studies on the mechanism of this transformation,[1j] we know that the hydride adds to the more substituted carbon, and the two groups at C1 of **1a** must orient away from the metal center (scheme 2b), which encumbers the differentiation of the two prochiral faces and is quite different from the AHF of styrene (scheme 2a). Therefore, we supposed that the steric hindrance on the phosphine part of the ligand is a critical factor for the enantioselectivity in the current reaction. Then, **L1** and **L2** were synthesized and tested, but the outcome was unpredictable and puzzling (table 1, entries 7-8).

Table 2. Effect of Reaction Conditions on the Yield and Enantioselectivity of the AHF of 1a[a]



entry	**L**/Rh	T (°C)	CO/H_2 (bar)	t (h)	conv. (%)[b]	yield (%)[b] **2a**	yield (%)[b] **3a**	ee (%)[c]
1	2	100	10/10	20	65	65	<1	82
2	2	100	5/5	20	87	87	<1	82
3	2	100	2.5/2.5	20	97	95	2	82
4	2	100	1/4	20	>99	87	13	81
5	2	100	4/1	20	77	75	2	82
6	1.2	100	2.5/2.5	20	31	30	1	15
7	3	100	2.5/2.5	20	99	98	1	82
8	3	90	2.5/2.5	20	92	91	1	84
9	3	80	2.5/2.5	20	67	66	1	86
10[d]	3	80	2.5/2.5	20	88	86	2	87
11[e]	3	80	2.5/2.5	20	96	94	2	87
12[e]	**3**	**80**	**2.5/2.5**	**48**	**>99**	**98**	**2**	**87**

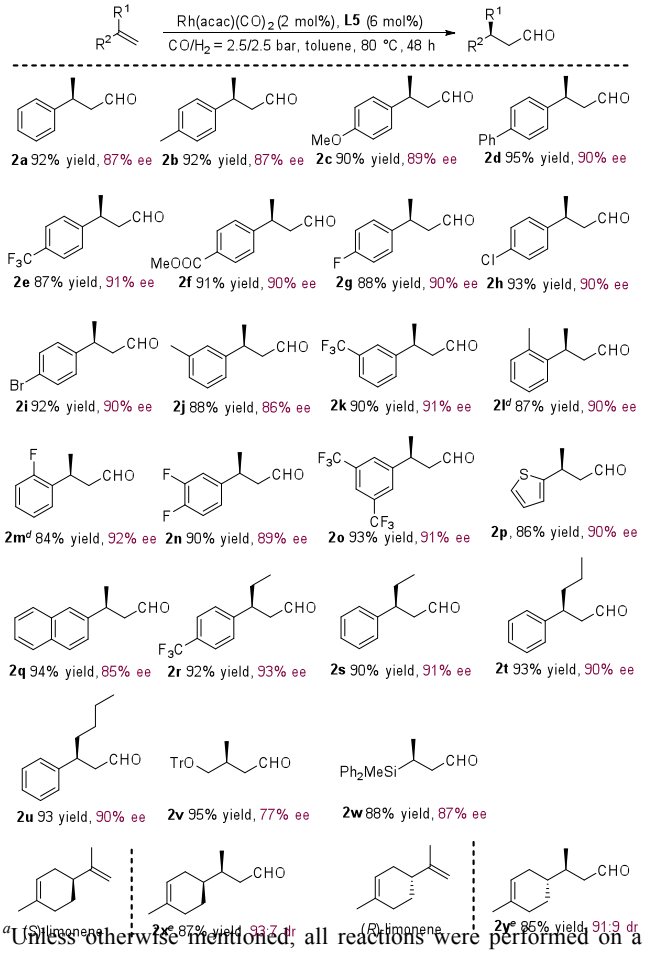
[a]Unless otherwise mentioned, all reactions were performed on a 0.25 mmol scale in 1 mL toluene with substrate/Rh = 50. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase after $NaBH_4$ reduction. The absolute configuration was assigned by comparing the sign of the optical rotation of (*S*)-**2a** with that reported in the literature, see ref 2 in supporting information. [d]0.5 mmol **1a** was used in 1 mL toluene. [e]0.5 mmol **1a** was used in 0.5 mL toluene.

When the steric hindrance on the phosphine increased, the ee values dropped sharply. Interestingly, the opposite enantiomer was obtained when the hindered ligand (**L2**) was used. As the alkene insertion step is the enantioselectivity determining step in Rh-catalyzed AHF,[1j, 2] we focused on the relationship of how **1a** presumably undergoes migratory insertion and the structure of the catalyst.[6a,c] As shown in scheme 2c, when the (*S*,*R*)-ligand was used, the front approach is hindered suggesting that *Re* face attack of **1a** occurs to yield (*R*)-**2a**. In contrast, when **L2** was used, the size of the phosphine prevents a similar mechanism leading to an approach from the front and addition to the *Si* face of **1a** providing (*S*)-**2a**. As a consequence, we speculated that (*S*,*S*)-ligands might be suitable for this reaction as depicted in Scheme **2d**. In this case, **1a** approaches Rh(I) from the front-side and the *Si* face of **1a** is attacked. To test this hypothesis, (*S*,*S*)-**L3**, **L4** and **L5** were prepared and evaluated. In contrast to the (*S*,*R*)-YanPhos system, a much higher conversion with a reversed enantioselectivity was achieved with **L3** (table 1, entry 9). When **L4** was employed, the results were similar to that of **L3** (table 1, entry 10). To our delight, **L5** afforded a moderate yield with 82% ee (table 1, entry 11). The experimental results are consistent with our analysis, and can be summarized as two points: 1) for the AHF of **1a**, (*S*,*S*)-ligands are more suitable than the previous (*S*,*R*)-ligands, which are privileged in the AHF of styrene; 2) in the current system, hindered groups on the phosphine are critical, because they can effectively help deter approach as depicted and improve the differentiation of the two prochiral face of **1a**. As further support, DFT calculations (M06 and B3LYP-D3 methods) suggested that the most stable conformer for (**L5**)Rh(I)H$(CO)_2$ complex preferentially has the phosphoramidite part at the axial position and trans to the hydride (summarized in supporting information).[16] Although the current speculation is reasonable, it should be pointed out that the real catalytic cycle is still unclear. The structure of the phosphite part was also modified (**L6**), but the results was inferior to that of **L3** (table 1, entry 9 *vs* 12).

Inspired by the promising results, we sought to obtain optimal reaction conditions, as summarized in Table 2. We found that lower syngas pressure is beneficial to the conversion, but the hydrogenation product **3a** increased when the CO pressure decreased (entries 1-5). Next, the influence of the **L5**/Rh ratio was investigated. Lowering of the **L5**/Rh ratio gave lower conversion and the ee dropped significantly (entry 6). When the **L5**/Rh ratio rose to 3, a higher yield was achieved (entry 7). Under this ratio (**L5**/Rh = 3), the reaction temperature was screened, and the low

temperature is beneficial to the enantioselectivity albeit with low conversion (entries 7-9). After increasing the concentration of **1a** (entries 10 and 11) and prolonging the reaction time, we obtained full conversion with 98% yield and 87% ee (entry 12).

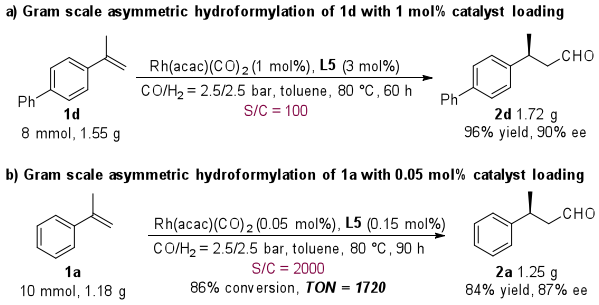
Scheme 3. Rh-Catalyzed Asymmetric Hydroformylation of Unfunctionalized 1,1-Disubstituted Alkenes[a]



[a]Unless otherwise mentioned, all reactions were performed on a 0.5 mmol scale at 80 °C in 0.5 mL toluene with substrate/Rh = 50:1, **L5**/Rh = 3:1, 5 bar CO/H_2 (1:1), and a reaction time of 48 hours. [b]Yield of the isolated product. [c]Determined by HPLC analysis using a chiral stationary phase after $NaBH_4$ reduction. [d]72 h. [e]Diastereoselectivities determined by ^{13}C NMR analysis.

With an optimized set of conditions in hand, we investigated the substrate scope and generality of this transformation. Many functional groups, such as methyl (**2b**), methoxyl (**2c**), phenyl (**2d**), trifluoromethyl (**2e**), esters (**2f**) and halides (**2g-2i**), at the para position of the phenyl group are compatible with this transformation. Substrates with meta-substitution on the phenyl group are also tolerated, and high ee values were obtained (**2j** and **2k**). Because of the added steric hindrance, substrates with ortho-substitution on the phenyl group showed slightly low reactivity, but good yields with excellent enantioselectivities were achieved after prolonged reaction time (**2l** and **2m**). Moreover, the product **2n** and **2o** with disubstituted groups were obtained with high ee values. Substrates containing other aromatic fragments, including thiophenes and naphthalenes, are also accommodated (**2p** and **2q**). Notably, when more challenging substrate (the growth of the alkyl chain makes it more difficult to differentiate the prochiral faces of the substrate) **1r**, **1s**, **1t** and **1u** were employed, high yields with excellent enantioselectivities were obtained as well (**2r-2u**), which demonstrates the good compatibility of this catalytic system. For β-methallyl alcohol, the installation of a trityl protecting group is necessary, which allowed good enantioselectivity to be achieved (**2v**). Furthermore, vinylsilanes underwent hydroformylation to afford highly enantioenriched aldehydes containing stereogenic silicon substituents (**2w**). The ability of the catalytic system to control diastereoselectivity in reactions of enantiopure chiral olefins was also investigated, and the results illustrate that the hydroformylation of (*S*)-limonene and (*R*)-limonene proceeded with excellent catalyst control (**2x** and **2y**).

Scheme 4. Large-Scale Asymmetric Hydroformylation with Lower Catalyst Loading



To demonstrate the synthetic utility of the current methodology, two gram-scale transformations were conducted with lower catalyst loading, as summarized in Scheme 4. Firstly, upon decreasing the catalyst loading to 1 mol%, the asymmetric reaction was conducted, affording the desired aldehyde **2d** in 96% yield with 90% ee (Scheme 4a). Then, a catalyst loading of 0.05 mol% proved sufficient for reactions performed on 10 mmol scale using commercially available α-methylstyrene (**1a**) as the substrate, and 84% yield with undiminished enantioselectivity was obtained (Scheme 4b), demonstrating the efficiency of this transformation in large-scale synthesis.

In conclusion, a new hybrid phosphine-phosphoramidite ligand **L5** has been developed. By employing this new ligand, highly enantioselective Rh-catalyzed anti-Markovnikov hydroformylation of unfunctionalized 1,1-disubstituted alkenes was achieved. This method provides a concise route to the synthesis of aldehydes with β-chirality, which are important intermediates in organic synthesis. Further structural variation of hybrid phosphorus ligands will be developed in the future for asymmetric hydroformylation and other metal-catalyzed transformations.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. 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 interests.

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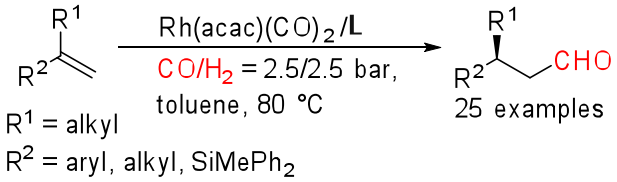
(16) See computational details in Supporting Information.

TOC Graphic:



new chiral ligand ***high ee values***
high yields ***TON up to 1720***