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Hydrogen Bonding Makes a Difference in the Rhodium-Catalyzed Enantioselective Hydrogenation Using Monodentate Phosphoramidites

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The notion that the chelating structure of bisphosphine ligands is a prerequisite for efficient chiral induction in asymmetric hydrogenation (AH)[1] has recently been challenged by the development of monophosphites,[2] monophosphonites,[3] and monophosphoramidites.[4] Their excellent performance as ligands, relatively simple synthesis from readily available (and cheap) building materials, and good stability continue to provide tremendous interest and potential. Compared to the parent itaconic acid or its dimethyl ester, relatively few catalytic systems have been reported for the AH of β-aryl itaconic acid derivatives.[5] Similarly, AH of the corresponding enol ester to give important α-hydroxy esters has been demonstrated to be more challenging,[1,6] possibly due to their weaker coordinating ability.[1] Moreover, no monodentate phosphine ligands have been described for these substrate classes. We herein report the use of a new generation of the monodentate phosphoramidites, DpenPhos (Scheme 1), for the efficient Rh-catalyzed AH of (*Z*)-methyl α-(acetoxy)acrylates and β-aryl itaconate derivatives. The resulting catalysts are very reactive (TOF up to 400 h^{-1} at $P(H_2)$ = 40 atm),[7] yielding the corresponding products with excellent enantioselectivities (up to >99% ee). The existence of intermolecular hydrogen bonding (HB) between two monodentate ligands in the catalyst is believed to be critical for optimal catalyst performance.

The use of Rh/(*R*,*R*)-**1** or Rh/**3a** for AH of the benchmark substrate (*Z*)-methyl α-(acetoxy)phenylacrylate (**4a**) yielded no product (see Table 1 for conditions).[8] However, replacement of one methyl group in **1** by a proton (**2**) resulted in excellent reactivity under analogous conditions.[9] The modular nature of **2** allowed for facile R group screening (Supporting Information, SI). Catalyst **2b** gave the best results, yielding **6a** in >99% enantiomeric excess (ee). There was a negligible influence with variation of R′ in **2**, with (*R*)- or (*S*)-1-phenylethyl giving **6a** in 96 or 97% ee, respectively. Under optimized reaction conditions, hydrogenation catalyzed by Rh/**2b** of a number of (*Z*)-methyl α-(acetoxy)acrylates afforded the corresponding α-hydroxy esters in excellent ee's (96−99%) (Table 1, entries 1−7).[10] Both β-aliphatic and aromatic groups had little impact on the enantioselectivity.

Similarly, the AH of various β-aryl itaconate derivatives (*E*)-**5a**−**f** was also efficiently catalyzed by Rh/(*R*,*R*)-**2b** under optimized reaction conditions (SI), yielding **7a**−**f** in excellent enantioselectivities (96−99% ee; Table 1, entries 8−13). Electron-withdrawing groups on the aromatic ring showed better reactivity (entries 9 and 10 vs entry 13), while *ortho*-substitution significantly retarded the hydrogenation (entry 12). AH of model substrate **5g** proceeded with a TON[7] of up to 10^5 (entry 14), which is much higher than that catalyzed by the analogous Rh/(*R*,*R*)-**1** complex (TON = 100).[8a]

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Scheme 1. Monophosphorus Ligands Used

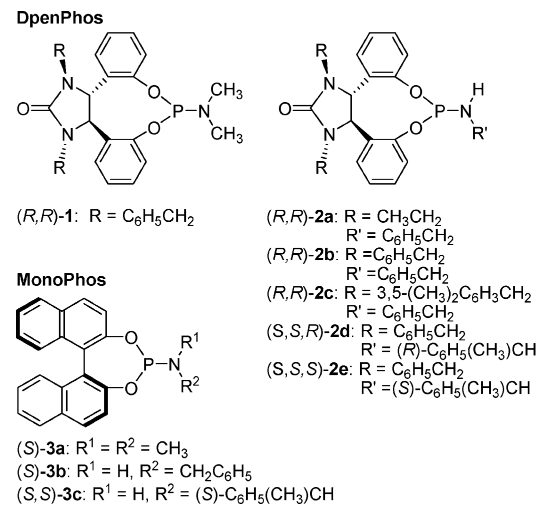
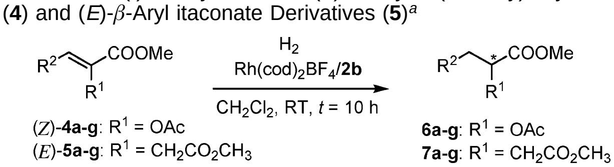


Table 1. Rh(I)-Catalyzed AH of (*Z*)-Methyl α-(acetoxy)acrylates (**4**) and (*E*)-β-Aryl itaconate Derivatives (**5**)[a]



entry	R^2	H_2 (atm)	S/C[b]	ee (%)[c]	config[d]
1	C_6H_5 (**4a**)	60	100	>99	*S*
2	$CH_3(CH_2)_2$ (**4b**)	60	100	99	*S*
3	$(CH_3)_2CH$ (**4c**)	60	100	99	*S*
4	4-FC_6H_4 (**4d**)	60	100	>99	−[e]
5	3-ClC_6H_4 (**4e**)	60	100	96	−[e]
6	2-BrC_6H_4 (**4f**)	60	100	96	−[e]
7	2-naphthyl (**4g**)	60	100	98	−[e]
8	C_6H_5 (**5a**)	40	4000	97	*R*
9	4-FC_6H_4 (**5b**)	40	1000	99	−[e]
10	3-ClC_6H_4 (**5c**)	40	1000	97	*R*
11	2-naphthyl (**5d**)	40	1000	96	*R*
12	2-BrC_6H_4 (**5e**)	40	100	97	−[e]
13	3-$MeOC_6H_4$ (**5f**)	40	100	99	*R*
14	H (**5g**)	30	10^5	94	*R*

[a] Conditions: [Rh(cod)BF_4] = 2 mM; [**2b**] = 4 mM (Rh/**2b** = 1/2); [**4**] = 0.2 M; [**5a**−**f**] = 0.37 M, [**5g**] = 5.0 M. Conversion was always 100% (^{1}H NMR). [b] Substrate/catalyst molar ratio. [c] Determined by chiral HPLC or GC. [d] Absolute configurations determined by $[\alpha]_D$. [e] Not established.

No reaction was observed in the hydrogenation of (*E*)-**5a** using Rh/(*R*,*R*)-**1** or Rh/**3a** catalysts.[11]

We consider the drastic improvement in catalyst performance between Rh/**1** and Rh/**2** to result from HB involving the NH moiety in the latter. ^{1}H NMR spectra of ^{15}N-**2b** (CD_2Cl_2) exhibited no

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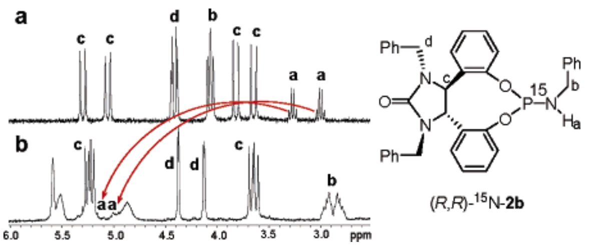

Figure 1. ^{1}H NMR spectra for (*R*,*R*)-^{15}N-**2b** (a) and Rh/^{15}N-**2b** (b) in $CDCl_3$. The downfield shift for the NH protons is shown in red.

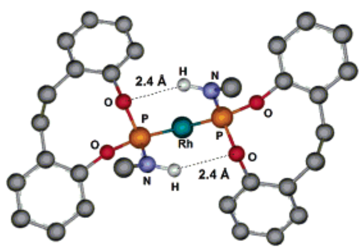

Figure 2. B3LYP/6-31G(d) optimized structure of the Rh/**2b** structural mimic. All C−H hydrogen atoms and COD are omitted for clarity.

change over the concentration range of 0.036−0.68 M. However, upon complex formation, the resonance for the NH moiety significantly shifted downfield from δ 3.12 to 5.08 ppm (Figure 1). Upon addition of CD_3OD (CD_3OD/CD_2Cl_2, 1:4), the NH proton of free ^{15}N-**2b** showed a downfield shift (Δ +0.31 ppm) relative to CD_2Cl_2 and underwent gradual H/D exchange. In contrast, the complexed ligand in the Rh/^{15}N-**2b** complex was unchanged upon addition of CD_3OD, and H/D exchange was ca. 2 times slower under the same conditions.[12] The same behavior was observed for the Rh/^{15}N-**3b** complex (SI). These results clearly show the existence of HB between two constituent **2b** ligands situated adjacently about the Rh metal center in the precatalyst.

To gain an insight into the HB interactions in the Rh/**2b** complex, calculations were performed on a simplified structural mimic (SI). While two potential HB motifs are possible, N−H···N or N−H···O, geometrical optimizations using either starting point converged to the same structure (Figure 2), exhibiting the relatively small inter-ligand bite angle of 89.9° (cf. 94.8° for Rh/**1** complex).[8a,13] Here, the attractive nature of the HB and proximity between participating ligands are expected to subtly influence catalyst structure and reactivity. In the nonpolar reaction environment, such interactions are expected to persist during AH. Although O−H···O=P HB interactions have been observed[14] and self-assembly of complementary HB monophosphines has been developed,[15,16] the present inter-ligand intramolecular HB mode is unique. Further studies of HB effects on reaction parameters and catalysis are currently being pursued.

In conclusion, monodentate phosphoramidite ligands having a primary amine moiety (**2**) were found to display comparable or better efficiency than bisphosphines in Rh-catalyzed AH of challenging substrates. This exceptional reactivity may be attributable to the existence of intermolecular HB between adjacent monophosphoramidite ligands around the Rh metal center. This unique HB interaction provides a new basis for bridging the gap between mono- and bidentate phosphorus ligands.

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Supporting Information Available: Synthesis of ligands, catalysts, and substrates, AH details and optimization, crystal structure of **2b**, NMR analysis, and B3LYP/6-31G(d) calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Under the same conditions using (i) **3a** yielded no product; (ii) **3b** gave ee = 42.5%; and (iii) **3c** gave ee = 41.5%.

(10) For aryl R^2 groups in **4**, Rh/DuPHOS gives ee = 95.6% (highest).[6a]

(11) Use of Rh/**3b** or **3c** gave (*S*)-**7a** in 74.8 and 76.1% ee, respectively.

(12) NOE data were inconclusive due to the pseudo C_2 symmetry of the Rh/**2b** complex on the NMR time scale.

(13) Similarly, Rh/(*S*,*R*)-**3c** displays much higher reactivity than Rh/**3a** for AH of dehydro-α-amino and dehydro-β-amino acid esters. Steric arguments were proposed to explain the enhanced reactivity.[4b,c]

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