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Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on Her Jubilee

Chiral Monophosphites and Monophosphonites as Ligands in Asymmetric Transition Metal Catalysis*

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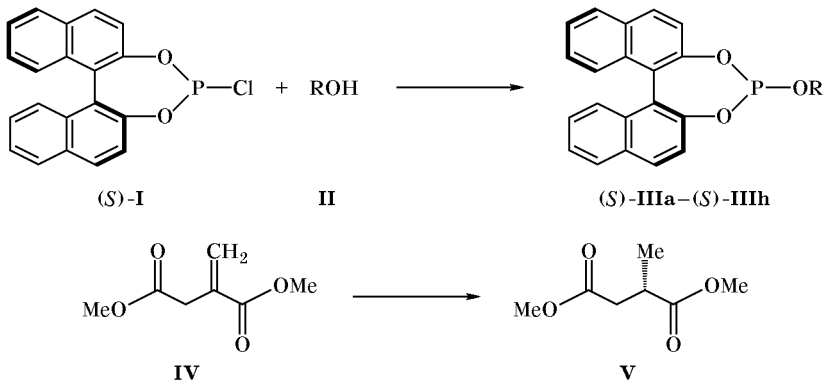
Abstract—Chiral monophosphites and monophosphonites derived from BINOL are more effective ligands in enantioselective rhodium-catalyzed hydrogenation of olefins, as compared to bidentate bis-phosphites. An appreciable increase in enantioselectivity is attained with the use of mixtures of two different monodentate phosphites and phosphonites in rhodium-catalyzed hydrogentation.

Asymmetric transition metal catalysis is of considerable academic and industrial interest [1], as evidenced by the award of the Nobel Prize for Chemistry 2001 to K.B. Sharpless [2], R. Noyori [3], and W.S. Knowles [4]. Many practical, mechanistic, and theoretical advances have been made. One of the long-standing dogmas of asymmetric hydrogenation is the postulate that chelating bidentate ligands (such as chiral diphosphines) are necessary in order to achieve high levels of enantioselectivity (ee > 90%) [1, 3, 4].

As a part of our study of chiral BINOL-derived bidentate bis-phosphites [5], we made an unexpected discovery, namely that analogous monophosphites **III** are better and even cheaper ligands for Rh-catalyzed hydrogenation [6]. Simple alcohols **II** were used as building blocks in the modular synthesis of a number of chiral monophosphites. Scheme 1 shows only a few selected examples, as well as the result of using these simple ligands in the Rh-catalyzed hydrogenation of itaconic acid ester (**IV**). In the original publication [6], a ligand-to-Rh ratio of only 1 : 1 was used, but in fact 2 : 1 is more efficient (the ee values differ only slightly). As can be seen, the ee values range between 35% and 97.8%, depending upon the nature of alcohol **II** which is used in the synthesis of the ligand.

Moreover, a variety of 2-acetamido acrylic acid esters were hydrogenated in a similar way with high

Scheme 1.



III, R = Me (ee 83.4%) (**a**), Et (93.4%) (**b**), *cyclo*-C_6H_{11} (96.8%) (**c**), *t*-Bu (91.4%) (**d**), Ph (97.8%) (**e**), 2,6-$Me_2C_6H_3$ (35.0%) (**f**), *i*-Pr (97.0%) (**g**), 9-fluorenyl (96.0%) (**h**).

* The original article was submitted in English.

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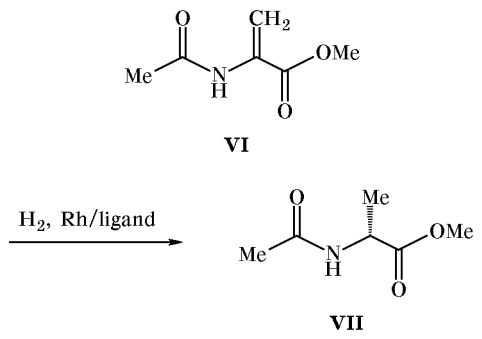
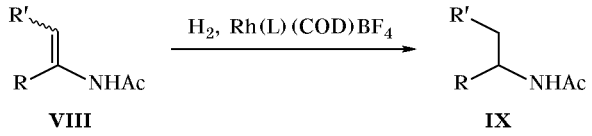
degree of enantioselectivity, as in the case of the parent substrate shown in Scheme 2 [6]. Rhodium-to-substrate ratios of 1:1000 and even 1:5000 can be used in these reactions at room temperature (hydrogen pressure 1.3 atm). The conversion is usually complete.

Scheme 2.



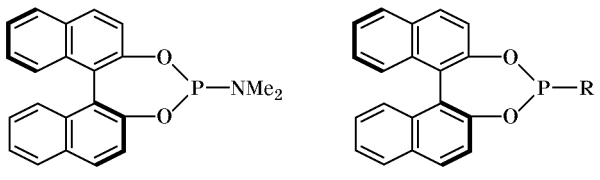
Ligand **IIIa**, ee 76.6%; **IIIb**, 83.6%; **IIIc**, 94.6%; **IIId**, 95.4%; **IIIe**, 78.6%; **IIIf**, 32.4%; **IIIg**, 94.4%; **IIIh**, 92.4%.

Finally, industrially important chiral amines **IX** can also be prepared with high enantioselectivity from *N*-acyl enamines **VIII** [7]. The optimized ee values range from 90% to 98%, depending on the nature of the alcohol component in the chiral monophosphite. These results demonstrate once more the power of the modular nature of these readily accessible ligands. Moreover, the ligands are cheap (only 2% of the cost of BINAP), which makes them very attractive for industrial applications [8].



R = aryl; R′ = H, Me.

Independently, Feringa and co-workers have shown that phosphoramidite **X** is also an excellent ligand in Rh-catalyzed hydrogenation of olefins [9]. Moreover, Pringle [10] and we [11] have reported that analogous



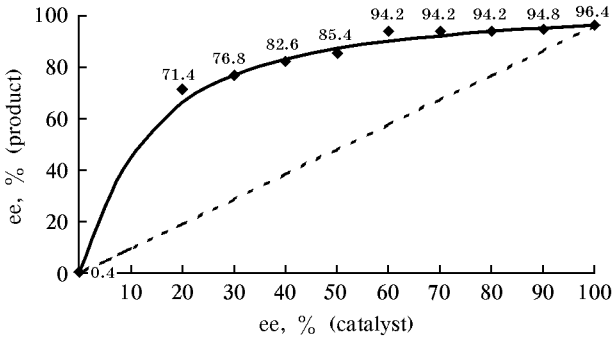
X **XIa–XIf**

XI, R = Me (**a**), Et (**b**), *cyclo*-C_6H_{11} (**c**), *t*-Bu (**d**), Ph (**e**), Cl (**f**).

BINOL-derived monophosphonites **XI** are also interesting ligands, although they are generally less efficient (they exhibit higher activity but ensure slightly lower enantioselectivity).

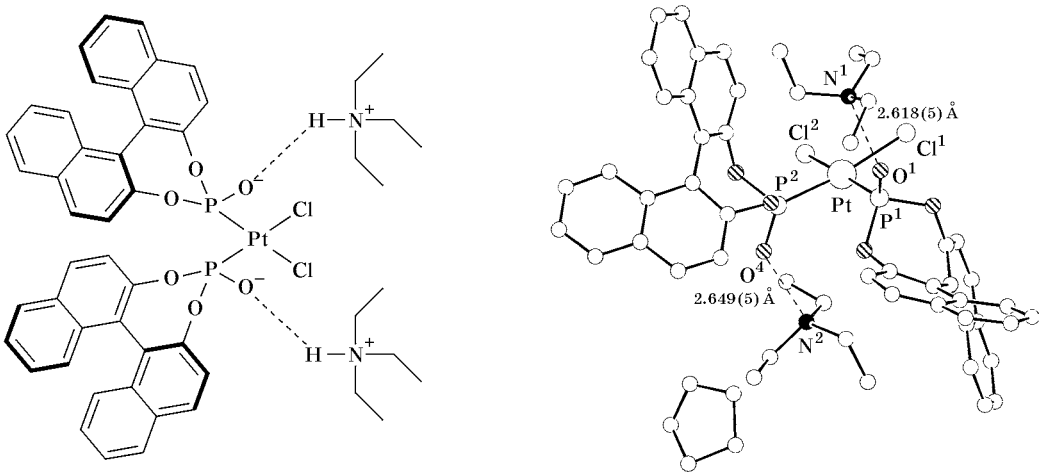
These developments show that the long-standing dogma [1, 3, 4] that chelating (bidentate) ligands are necessary in order to observe high enantioselectivities in hydrogenation no longer pertains. However, the source of high enantioselectivity has not yet been fully illuminated. We have examined the NMR spectra of precatalysts $Rh(L^*_2(COD)BF_4$ and have proven that two chiral monophosphites (L^*) are bonded to rhodium. Moreover, strong nonlinear effects are observed (see figure), suggesting that two monophosphites are attached to the metal in the transition state of hydrogenation and/or in a preequilibrium step [12]. Preliminary kinetic studies showed the following order in the rate of Rh-catalyzed hydrogenation: monophosphonites > monophosphites > monophosphoramidites. In the case of monophosphites turnover numbers of 200000 have been achieved.

These mechanistic advances show that probably two phosphites are bonded to rhodium (as do NMR experiments), but they do not explain the source of enantioselectivity on a molecular basis. Thus, further studies are necessary before final conclusions can be reached. We have not been able to obtain adequate crystals of relevant Rh complexes. However, the X-ray crystal structure of the first metal complex of a BINOL-derived phosphorous acid ester was recently analyzed in our laboratories [13]. It is a Pt complex in which the acidic OH functions are H-bonded to triethylamine. The structure has *cis* arrangement of the two chiral ligands (Scheme 3). It is currently unclear to what extent rotation about the Pt–P bond is reduced or inhibited in complexes of this type, which may bear some resemblance to Rh complexes



Nonlinear effects in the Rh-catalyzed hydrogenation of itaconic acid ester **IV** using monophosphite **IIIg** derived from BINOL and 2-propanol [12].

Scheme 3.

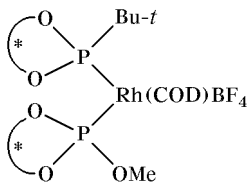


used in hydrogenation. If restricted rotation around the P–metal bonds pertains, then the two mono-P-units simulate a chelating bidentate ligand system, a phenomenon which would explain high enantioselectivity in Rh-catalyzed hydrogenation.

Most recently, we have made an unusual discovery concerning the use of mixtures of two different BINOL-derived monophosphites **III**, two different monophosphonites **XI**, or a mixture of **III** and **XI** [14]. It involves a new concept in the area of combinatorial enantioselective transition metal catalysis. The basic idea concerns the use of mixtures of chiral monodentate ligands. The method is relevant whenever in the transition state of the reaction at least two monodentate ligands (L) are coordinated to the metal (M) of the active catalyst ML_x. For example, in the case of a mixture of two such ligands L^a and L^b, three different catalysts exist in equilibrium with one another, namely two homo-combinations ML^aL^a and ML^bL^b, as well as hetero-combination ML^aL^b. Many examples of homo-combinations are known in the literature, as in the chemistry described above. In contrast, nothing has been published concerning the use of hetero-combinations ML^aL^b as catalysts. Since rapid ligand exchange is likely to occur in most systems, preparation of ML^aL^b in pure form in solution is not expected to be possible. However, a mixture of all three catalysts may well lead to enhanced enantioselectivity provided that ML^aL^b is more active and more selective than either of traditional catalysts ML^aL^a or ML^bL^b. It can also be expected that the relative amounts of the ligands L^a and L^b used may influence the stereochemical outcome.

The Rh-catalyzed hydrogenation of acetamidoacrylic acid ester **VI** in methylene chloride was chosen as test reaction [14]. Initially, the $Rh:L^a:L^b$ ratio was kept constant at 1:1:1. Although not all of the theoretically possible combinations of L^a/L^b were tested, the results summarized in table uncover some remarkable trends, which need to be compared to the most enantioselective homo-combinations.

The results show that certain ligand combinations L^a/L^b lead to notably high enantioselectivities. In the case of two different phosphonites (see table, nos. 15–19), the enantioselectivity is nearly complete (ee = 98%), when one component bears a small substituent R at the phosphorus atom (e.g., methyl group, as in **XIa**) and the other is bulky (nos. 16 and 17). The results show significant improvements relative to the corresponding homo-combinations which lead to ee values of only 92–94% (nos. 1, 3, 4). Acceptable ee values are obtained in the phosphite series (nos. 21–36), but in most cases improvements upon using hetero-combinations are limited. The greatest effect is observed in going from homo-combinations **IIIa** (ee = 76.6%) and **IIIf** (ee = 32.4%) to the hetero-combination based on the same ligands, **IIIa**/**IIIf** (ee = 84.6%) (no. 25). In contrast, the use of proper combinations of phosphonites **XI** and phosphites **III** gives pronounced enhancements in enantioselectivity, especially if a bulky phosphonite (e.g., **XIc** or **XId**) is combined with the least sterically demanding phosphite **IIIa** (nos. 40 and 42), as in the case of **XII**:



XII

Rhodium-catalyzed hydrogenation of methyl 2-acetylamino-2-propenoate (**VI**) [14][a]

Run no.	Ligands	ee, % (configuration)	Run no.	Ligands	ee, % (configuration)
		Homo-combinations			
1	(*R*)-**XIa**/(*R*)-**XIa**	91.8 (*S*)	8	(*S*)-**IIIb**/(*S*)-**IIIb**	83.6 (*R*)
2	(*R*)-**XIb**/(*R*)-**XIb**	94.4 (*S*)	9	(*S*)-**IIIc**/(*S*)-**IIIc**	94.6 (*S*)
3	(*R*)-**XIc**/(*R*)-**XIc**	92.0 (*S*)	10	(*S*)-**IIId**/(*S*)-**IIId**	95.4 (*R*)
4	(*R*)-**XId**/(*R*)-**XId**	93.3 (*S*)	11[c]	(*S*)-**IIIe**/(*S*)-**IIIe**	78.6 (*R*)
5	(*R*)-**XIe**/(*R*)-**XIe**	72.8 (*S*)	12[d]	(*S*)-**IIIf**/(*S*)-**IIIf**	32.4 (*R*)
6[b]	(*R*)-**XIf**/(*R*)-**XIf**	7.4 (*S*)	13	(*S*)-**IIId**/(*S*)-**IIId**	94.4 (*R*)
7	(*S*)-**IIIa**/(*S*)-**IIIa**	76.6 (*R*)	14	(*S*)-**IIIh**/(*S*)-**IIIh**	92.4 (*R*)
		Hetero-combinations			
15	(*R*)-**XIa**/(*R*)-**XIb**	92.6 (*S*)	31	(*R*)-**IIId**/(*R*)-**IIIc**	94.2 (*S*)
16	(*R*)-**XIa**/(*R*)-**XIc**	97.9 (*S*)	32	(*R*)-**IIId**/(*R*)-**IIIe**	92.2 (*S*)
17	(*R*)-**XIa**/(*R*)-**XId**	97.8 (*S*)	33	(*R*)-**IIIe**/(*R*)-**IIIc**	73.6 (*S*)
18	(*R*)-**XIc**/(*R*)-**XId**	94.1 (*S*)	34	(*R*)-**IIId**/(*R*)-**IIIc**	94.6 (*S*)
19	(*R*)-**XId**/(*R*)-**XIe**	75.8 (*S*)	35	(*R*)-**IIId**/(*R*)-**IIId**	94.8 (*S*)
20	(*R*)-**XId**/(*R*)-**XIf**	Racemate	36	(*R*)-**IIId**/(*R*)-**IIIe**	91.2 (*S*)
21	(*R*)-**IIIa**/(*R*)-**IIIb**	80.0 (*S*)	37	(*R*)-**XIa**/(*R*)-**IIIa**	81.9 (*S*)
22	(*R*)-**IIIa**/(*R*)-**IIIc**	76.6 (*S*)	38	(*R*)-**XIa**/(*R*)-**IIIc**	94.4 (*S*)
23	(*R*)-**IIIa**/(*R*)-**IIId**	89.0 (*S*)	39	(*R*)-**XIa**/(*R*)-**IIId**	93.0 (*S*)
24	(*R*)-**IIIa**/(*R*)-**IIIe**	77.4 (*S*)	40	(*R*)-**XIc**/(*R*)-**IIIa**	96.4 (*S*)
25	(*R*)-**IIIa**/(*R*)-**IIIf**	84.6 (*S*)	41	(*R*)-**XIc**/(*R*)-**IIId**	91.8 (*S*)
26	(*R*)-**IIIa**/(*R*)-**IIId**	87.2 (*S*)	42	(*R*)-**XId**/(*R*)-**IIIa**	98.0 (*S*)
27	(*R*)-**IIIb**/(*R*)-**IIIc**	79.0 (*S*)	43	(*R*)-**XId**/(*R*)-**IIIc**	94.6 (*S*)
28	(*R*)-**IIIb**/(*R*)-**IIId**	91.2 (*S*)	44	(*R*)-**XId**/(*R*)-**IIIh**	97.2 (*S*)
29	(*R*)-**IIIb**/(*R*)-**IIIe**	80.8 (*S*)	45	(*R*)-**XIc**/(*R*)-**IIIh**	95.6 (*S*)
30	(*R*)-**IIIb**/(*R*)-**IIIf**	90.0 (*S*)			

[a] Rh-to-substrate ratio 1 : 1000; Rh-to-P ratio 1 : 2; solvent CH_2Cl_2; hydrogen pressure 1.3 bar; temperature 20°C; reaction time 20 h; conversion 100%.

[b] Conversion 1%.

[c] Conversion 93%.

[d] Conversion 62%.

Similar results were observed in the hydrogenation of substituted derivatives of **VI**, itaconic acid dimethyl ester (**IV**), and *N*-acyl enamines **VIII** [14]. Thus, a new principle has been established in combinatorial asymmetric catalysis [15].

To conclude, we have demonstrated that chiral monophosphites and monophosphonites, especially those derived from readily available BINOL, are efficient and cheap ligands for Rh-catalyzed asymmetric hydrogenation of olefins. Their modular synthesis makes structural variation very easy, which means that simple ligand tuning is possible. We have also gone one step further by establishing a new principle in combinatorial asymmetric catalysis, specifically by using mixtures of two different monodentate P-ligands such as BINOL-derived phosphites and phosphonites in Rh-catalyzed hydrogenation. We expect that other reaction types are also amenable to this type of combinatorial optimization. Moreover, mixtures of achiral mono-P-ligands in achiral transformations may also be worthy of study.

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