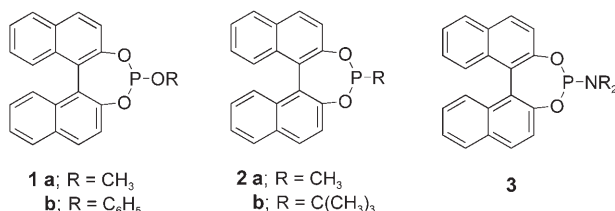


Mixtures of Chiral Phosphorous Acid Diesters and Achiral P Ligands in the Enantio- and Diastereoselective Hydrogenation of Ketimines**

Manfred T. Reetz* and Oleg Bondarev

In 2000, three groups independently reported that 2,2'-dihydroxy-1,1'-binaphthyl (binol) derived monodentate P compounds, namely phosphites of the type **1**,^[1] phosphonites such as **2**,^[2] and phosphoramidites **3**,^[3] are excellent chiral ligands in Rh-catalyzed olefin hydrogenation. Since then this



chemistry has expanded rapidly.^[4,5] It was shown that two monodentate phosphorous ligands bind to Rh in the transition state of the reaction.^[6]

Subsequently we proposed a new tool in combinatorial asymmetric transition-metal (M) catalysis: the use of mixtures of two different chiral monodentate ligands L^a and L^b.^[7] This approach leads to three different catalysts, two homo-combinations ML^aL^a and ML^bL^b and one hetero-combination ML^aL^b. If the latter is more reactive (and/or present in greater amounts) and also more selective than the corresponding homo-combinations, improved catalysts result. We first demonstrated this principle in asymmetric Rh-catalyzed olefin hydrogenation and other reactions,^[7,8] and later extended the concept to include mixtures of chiral and achiral monodentate P ligands.^[9] Other groups have also contributed to this form of combinatorial catalysis,^[10] although the method is still in its infancy.

It has not been possible to make reliable predictions regarding the optimal combination from a set of monodentate ligands, making a combinatorial search necessary. The number of possible hetero-combinations arising from a given library of monodentate ligands increases rapidly when increasing the number (*n*) of its members (Table 1). Mixing ligands pairwise from a relatively large library leads to an "explosion" of catalyst diversity without the need to synthesize any new ligands. In a given collection not all combina-

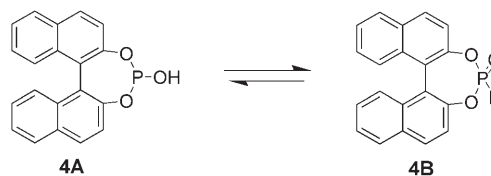
Table 1: Catalyst diversity as a result of mixing ligands L^a and L^b pairwise originating from a library of *n* ligands.

Number of homo-combinations ^[a] (ML ^a L ^a)	Number of hetero-combinations ^[b] (ML ^a L ^b)
20	190
50	1225
100	4950
200	19950
500	124 750

[a] Equivalent to the number of ligands (*n*). [b] Equivalent to $\frac{n(n+1)}{2} - n$.

tions need to be screened^[11] because certain ones can be eliminated on chemical grounds.

Previously we noticed a certain trend in that the optimal combination is often composed of a relatively small ligand L^a and a bulky analogue L^b (with exceptions!).^[7-9] In the case of binol-derived monodentate P ligands of the type **1**, the smallest conceivable residue at P is a hydroxy moiety. This situation suggests the use of the binol-derived P ligand **4A** (which is in equilibrium with the corresponding tautomeric form **4B**; Scheme 1) as the small ligand L^a and some other



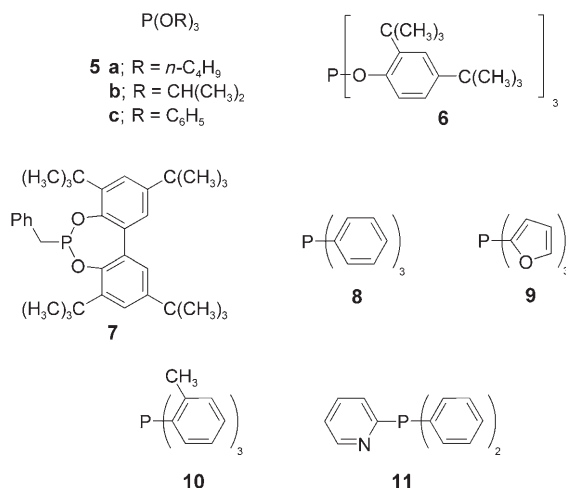
Scheme 1.

sterically more encumbered ligand L^b. Although the equilibrium **4A** $\rightleftharpoons$ **4B** favors **4B**, we have previously shown by X-ray crystallography that transition metals, such as Pt, bind to P in the tautomer **4A**,^[12] in line with numerous previous structural and catalytic studies regarding transition-metal complexes of phosphorous acid diesters and related secondary phosphine oxides.^[13] Moreover, we speculated that such metal complexation acidifies the hydroxy moiety, making possible the protonation and perhaps activation of such substrates as ketimines.^[12]

Herein we report that the use of ligand **4** in combination with certain members of a fairly small library of binol-derived phosphites **1** and phosphonites **2** and especially of achiral P ligands **5–11** leads to remarkably efficient catalyst systems in the Ir-catalyzed diastereo- and enantioselective hydrogenation of imines.^[14] A few combinations of ligands not involving **4** were also tested. All the catalyst systems were generated by

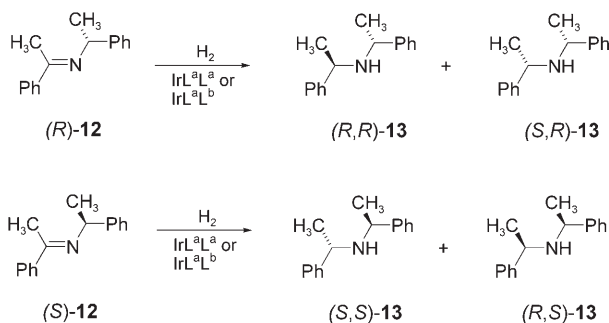
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treating the commercially available salt $[\text{Ir}(\text{cod})\text{Cl}]_2$ (cod = 1,5-cyclooctadiene) with selected P ligands.

We first studied the diastereoselectivity^[15] of the Ir-catalyzed hydrogenation of (*R*)- and (*S*)-**12** (Scheme 2). The



Scheme 2.

Table 2: Diastereoselective Ir-catalyzed hydrogenation of imines (*S*)- and (*R*)-**12** in the presence of homo-combinations of ligands.^[a]

Entry	Imine	Ligand system	Ir:L ^a	Conv. [%]	Diastereomer ratio ^[b]
1	(<i>R</i>)- 12	(<i>S</i>)- 1a	1:2	81	3.8:1
2	(<i>S</i>)- 12	(<i>S</i>)- 1a	1:2	100	3.8:1
3	(<i>R</i>)- 12	(<i>S</i>)- 1b	1:2	76	4.8:1
4	(<i>S</i>)- 12	(<i>S</i>)- 1b	1:2	100	4.7:1
5	(<i>R</i>)- 12	(<i>S</i>)- 2a	1:2	92	3.6:1
6	(<i>S</i>)- 12	(<i>S</i>)- 2a	1:2	100	4.5:1
7	(<i>R</i>)- 12	(<i>S</i>)- 2b	1:2	100	7.0:1
8	(<i>S</i>)- 12	(<i>S</i>)- 2b	1:2	100	7.9:1
9	(<i>R</i>)- 12	(<i>R</i>)- 4	1:2	47	5.1:1
10	(<i>S</i>)- 12	(<i>R</i>)- 4	1:2	100	5.5:1
11	(<i>R</i>)- 12	5a	1:2	70	6.4:1
12	(<i>R</i>)- 12	5b	1:2	83	5.9:1
13	(<i>R</i>)- 12	5c	1:2	94	5.6:1
14	(<i>R</i>)- 12	6	1:2	100	5.3:1
15	(<i>R</i>)- 12	7	1:2	100	11.7:1
16	(<i>R</i>)- 12	8	1:2	100	3.9:1
17	(<i>R</i>)- 12	9	1:2	100	2.6:1
18	(<i>S</i>)- 12	10	1:2	100	5.2:1
19	(<i>R</i>)- 12	11	1:2	100	5.1:1

[a] Solvent: CH_2Cl_2 ; 50 bar H_2 ; Ir:**12** (1:100); 48 h. [b] (*R,R*)-**13**:(*S,R*)-**13** or (*S,S*)-**13**:(*R,S*)-**13**.

results of performing a total of 60 hydrogenations of (*R*)- and (*S*)-**12**, which cover only a small part of chemical space (Table 1), are summarized in Tables 2 and 3.

The data in Tables 2 and 3 are illuminating in several respects, and herein we focus only on the most important points. Firstly, the stereogenic center in the substrate **12** dictates the direction of diastereoselectivity, whereas the nature of the ligands determines the degree of diastereoselectivity, which varies greatly. Thus, if (*R*)-**12** is used as the substrate, the configuration of the newly created stereogenic center in **13** is always *R*, and by the same token (*S*)-**12** leads to the preferential formation of the *S,S* diastereomer. Secondly, diastereoselectivity when using homo-combinations of ligands ranges between 2.6:1 and 11.7:1 (Table 2, entries 1–19), whereas the best hetero-combination leads to a diastereoselectivity of 378.0:1 (Table 3, entry 12). Thus, the positive

Table 3: Diastereoselective Ir-catalyzed hydrogenation of imines (*S*)- and (*R*)-**12** in the presence of hetero-combinations of ligands.^[a]

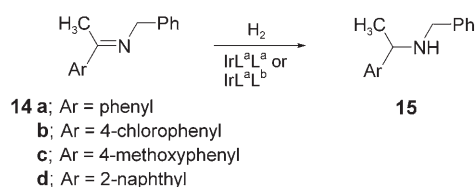
Entry	Imine	Ligand system	Ir:L ^a :L ^b	Conv. [%]	Diastereomer ratio ^[b]
1	(<i>R</i>)- 12	(<i>R</i>)- 4 + 1b	1:1:1	99	5.4:1
2	(<i>S</i>)- 12	(<i>R</i>)- 4 + 1b	1:1:1	100	5.8:1
3	(<i>R</i>)- 12	(<i>R</i>)- 4 + 5a	1:1:1	88	3.8:1
4	(<i>S</i>)- 12	(<i>R</i>)- 4 + 5a	1:1:1	100	8.7:1
5	(<i>R</i>)- 12	(<i>R</i>)- 4 + 5b	1:1:1	86	6.1:1
6	(<i>S</i>)- 12	(<i>R</i>)- 4 + 5b	1:1:1	100	6.0:1
7	(<i>R</i>)- 12	(<i>R</i>)- 4 + 5c	1:1:1	93	4.7:1
8	(<i>S</i>)- 12	(<i>R</i>)- 4 + 5c	1:1:1	100	19.0:1
9	(<i>R</i>)- 12	(<i>R</i>)- 4 + 6	1:1:1	100	1.0:1
10	(<i>S</i>)- 12	(<i>R</i>)- 4 + 6	1:1:1	100	123.0:1
11	(<i>S</i>)- 12	(<i>R</i>)- 4 + 6	1:1:0.5	100	6.0:1
12	(<i>S</i>)- 12	(<i>R</i>)- 4 + 6	1:1:2	100	378.0:1
13	(<i>R</i>)- 12	(<i>R</i>)- 4 + 7	1:1:1	58	4.7:1
14	(<i>S</i>)- 12	(<i>R</i>)- 4 + 7	1:1:1	100	34.0:1
15	(<i>R</i>)- 12	(<i>R</i>)- 4 + 8	1:1:1	100	2.0:1
16	(<i>S</i>)- 12	(<i>R</i>)- 4 + 8	1:1:1	100	71.0:1
17	(<i>R</i>)- 12	(<i>R</i>)- 4 + 9	1:1:1	95	2.5:1
18	(<i>S</i>)- 12	(<i>R</i>)- 4 + 9	1:1:1	100	29.0:1
19	(<i>R</i>)- 12	(<i>R</i>)- 4 + 10	1:1:1	97	4.7:1
20	(<i>S</i>)- 12	(<i>R</i>)- 4 + 10	1:1:1	100	4.4:1
21	(<i>R</i>)- 12	(<i>R</i>)- 4 + 11	1:1:1	90	3.2:1
22	(<i>S</i>)- 12	(<i>R</i>)- 4 + 11	1:1:1	100	22.0:1
23	(<i>S</i>)- 12	(<i>R</i>)- 4 + 11	1:1:2	100	55.0:1
24	(<i>R</i>)- 12	(<i>S</i>)- 1a + 5c	1:1:1	78	6.5:1
25	(<i>S</i>)- 12	(<i>S</i>)- 1a + 5c	1:1:1	100	6.5:1
26	(<i>R</i>)- 12	(<i>S</i>)- 2b + (<i>S</i>)- 2a	1:1:1	91	3.9:1
27	(<i>S</i>)- 12	(<i>S</i>)- 2b + (<i>S</i>)- 2a	1:1:1	100	4.9:1
28	(<i>R</i>)- 12	(<i>R</i>)- 2b + (<i>S</i>)- 2a	1:1:1	100	6.0:1
29	(<i>S</i>)- 12	(<i>R</i>)- 2b + (<i>S</i>)- 2a	1:1:1	100	3.8:1
30	(<i>R</i>)- 12	(<i>S</i>)- 2b + 5a	1:1:1	56	4.0:1
31	(<i>S</i>)- 12	(<i>S</i>)- 2b + 5a	1:1:1	100	5.7:1
32	(<i>R</i>)- 12	(<i>S</i>)- 2b + 5c	1:1:1	62	7.7:1
33	(<i>S</i>)- 12	(<i>S</i>)- 2b + 5c	1:1:1	100	7.9:1
34	(<i>R</i>)- 12	(<i>S</i>)- 2b + 6	1:1:1	100	5.4:1
35	(<i>S</i>)- 12	(<i>S</i>)- 2b + 6	1:1:1	100	1.5:1
36	(<i>R</i>)- 12	(<i>S</i>)- 2b + 8	1:1:1	100	6.0:1
37	(<i>S</i>)- 12	(<i>S</i>)- 2b + 8	1:1:1	100	3.7:1
38	(<i>R</i>)- 12	(<i>S</i>)- 2b + 10	1:1:1	100	5.4:1
39	(<i>S</i>)- 12	(<i>S</i>)- 2b + 10	1:1:1	100	16.5:1
40	(<i>R</i>)- 12	5a + 5c	1:1:1	77	4.7:1
41	(<i>R</i>)- 12	5c + 8	1:1:1	100	8.5:1

[a] Conditions as in Table 2. [b] (*R,R*)-**13**:(*S,R*)-**13** or (*S,S*)-**13**:(*R,S*)-**13**.

effect arising from mixing is enormous. The best catalyst results from a mixture of the Ir salt $[\text{Ir}(\text{cod})\text{Cl}]_2$ (one part), phosphoric acid diester **4A** (one part) and the sterically hindered achiral phosphite **6** (two parts; Table 3, entry 12). If the usual 1:1:1 ratio ($\text{Ir}:\text{L}^a:\text{L}^b$) is employed, diastereoselectivity is lower, but still considerable (123:0:1; Table 3, entry 10). Not only are the enhanced diastereoselectivities relative to those of the respective homo-combinations pronounced, so is the matched/mismatched effect^[16] in several cases. When using the same Ir catalyst derived from (*R*)-**4/6** to hydrogenate the enantiomeric substrate (*R*)-**12**, the reaction turned out to be stereorandom (1.0:1 diastereomer ratio; Table 3, entry 9). Of course, this reaction is stereochemically equivalent to the hydrogenation of (*S*)-**12** using enantiomeric ligand (*S*)-**4**. Another example of a notable matched/mismatched effect is the system involving the phosphite **7** which is actually a fluxional mixture of the *R* and *S* enantiomers (Table 3, entries 13 and 14). In other cases much smaller matched/mismatched effects occur, notably when using ligand **4** alone (Table 2, entries 9 and 10).

Finally, several further hits resulting from other hetero-combinations deserve attention, for example, when using two achiral ligands L^a and L^b . The respective homo-combinations derived from the phosphite **5c** and triphenylphosphine **8** provide low diastereoselectivities of 5.6:1 and 3.9:1, respectively, whereas the corresponding mixture raises the ratio to 8.5:1 (Table 2, entries 13 and 16 versus Table 3, entry 41). Finally, the possible effect of amine additives, such as NEt_3 or pyridine, on the diastereoselectivity when using ligand **4** was studied, but the effect proved to be very small.

We then turned to the enantioselective hydrogenation of prochiral imines **14** (Scheme 3). In this case the size of the



Scheme 3.

ligand library was restricted considerably by choosing only those ligands which had previously displayed the largest effects in enhancing diastereoselectivity, specifically **4** and two simple achiral P ligands **6** and **8** (Table 4).

In these cases again several notable effects were observed. Most importantly, the concept of using hetero-combinations is once more highly successful. For example, in the hydrogenation of imine **14a**, ligand **4** at several Ir:ligand ratios leads at best to an *ee* value of only 45% (Table 4, entry 2), whereas in combination with triphenylphosphine **8** an enantioselectivity of *ee* = 88% was achieved (Table 4, entry 15). The *p*-chloro and *p*-methoxy derivatives **14b** and **14c** behave similarly (Table 4, entries 16–25). Furthermore, in the hydrogenation of **14d**, ligand **4** alone results in almost racemic product **15d** (Table 4, entries 26 and 27), in contrast to the hetero-combination **4/8** which leads to an enantioselectivity

Table 4: Enantioselective Ir-catalyzed hydrogenation of imines **14a–d**.^[a]

Entry	Imine	Ligand system	Ir:L ^a or Ir:L ^a :L ^b	Conv. [%]	<i>ee</i> [%]
Homo-combinations					
1	14a	(<i>R</i>)- 4	1:2	31	18
2	14a	(<i>R</i>)- 4	1:4	21	45
Hetero-combinations					
3	14a	(<i>R</i>)- 4 + 6	1:1:1	94	65
4	14a	(<i>R</i>)- 4 + 6	1:1:2	100	43
5	14a	(<i>R</i>)- 4 + 6	1:2:1	100	76
6	14a	(<i>R</i>)- 4 + 6	1:2:2	100	80
7	14a	(<i>R</i>)- 4 + 6	1:0.5:0.5	100	15
8	14a	(<i>R</i>)- 4 + 6	1:1.5:0.5	100	28
9	14a	(<i>R</i>)- 4 + 8	1:1:1	90	60
10	14a	(<i>R</i>)- 4 + 8	1:1:2	100	83
11	14a	(<i>R</i>)- 4 + 8	1:2:2	100	82
12	14a	(<i>R</i>)- 4 + 8	1:2:1	100	84
13	14a	(<i>R</i>)- 4 + 8	1:3:1	100	82
14	14a	(<i>R</i>)- 4 + 8	1:3:2	100	87
15	14a	(<i>R</i>)- 4 + 8	1:1.5:0.5	100	88
Homo-combinations					
16	14b	(<i>R</i>)- 4	1:2	36	8
17	14b	(<i>R</i>)- 4	1:3	33	30
18	14b	(<i>R</i>)- 4	1:4	36	36
Hetero-combinations					
19	14b	(<i>R</i>)- 4 + 8	1:1:1	78	77
20	14b	(<i>R</i>)- 4 + 8	1:2:1	99	88
21	14b	(<i>R</i>)- 4 + 8	1:2:2	99	90
Homo-combinations					
22	14c	(<i>R</i>)- 4	1:2	39	33
23	14c	(<i>R</i>)- 4	1:3	20	35
Hetero-combinations					
24	14c	(<i>R</i>)- 4 + 8	1:2:1	99	87
25	14c	(<i>R</i>)- 4 + 8	1:2:2	99	92
Homo-combinations					
26	14d	(<i>R</i>)- 4	1:2	100	7
27	14d	(<i>R</i>)- 4	1:4	91	2
Hetero-combinations					
28	14d	(<i>R</i>)- 4 + 6	1:1:1	34	47
29	14d	(<i>R</i>)- 4 + 6	1:2:2	71	72
30	14d	(<i>R</i>)- 4 + 6	1:2:1	82	58
31	14d	(<i>R</i>)- 4 + 8	1:1:1	100	13
32	14d	(<i>R</i>)- 4 + 8	1:2:2	100	91
33	14d	(<i>R</i>)- 4 + 8	1:2:1	96	81
34	14d	(<i>R</i>)- 4 + 8	1:3:1	100	89
35	14d	(<i>R</i>)- 4 + 8	1:3:2	100	92

[a] Conditions as in Table 2; all products **15** have the *S* configuration.

of up to 92% *ee* (Table 4, entry 35). Thus the effect of mixing a chiral and an achiral ligand is dramatic. Overall, the best enantioselectivities achieved when hydrogenating ketimines **14a–d** (88–92% *ee*) compare well with those of recently published catalyst systems.^[14] This study demonstrates once more the power of the combinatorial approach of using mixtures of monodentate ligands.

Experimental Section

General procedure for the hydrogenation using ligand mixtures (ratio $\text{Ir}:\text{L}^a:\text{L}^b = 1:1:1$): A dry 10-mL flask under argon atmosphere was charged with a mixture of a 0.01M solution of the first ligand (0.5 mL) and of a 0.01M solution of the second ligand (0.5 mL) in dry dichloromethane. The solution was treated with a 0.005M solution of

$[\text{Ir}(\text{cod})\text{Cl}]_2$ (0.5 mL) in dichloromethane and stirred for 15 min at room temperature. Then a 0.5 M solution of the imine in dichloromethane (1 mL) was added. The hydrogenation experiments were carried out in a parallel manner using 8 flasks. A dry autoclave under argon atmosphere was charged with 8 flasks. H_2 was blown through, and H_2 at 50 bar was introduced. Hydrogenation was carried out for 48 h. Following dilution, conversion and the diastereomeric ratio were determined by gas chromatography (GC) [HP-5 (Crosslinked 5% PHME Siloxane) 30 m, 0.32-mm ID. **12**: t_{R} 8.34 min, (*S,R*)-**13**: t_{R} 10.42 min, (*R,R*)-**13**: t_{R} 9.86 min]. To determine the *ee*-values, about 1.5 mL of the respective reaction solution was passed through a small amount of silica gel prior to HPLC analysis [**15a**: Chiralcel OD-H, 250 mm, 4.6-mm ID, *n*-heptane/2-propanol (99:1), 0.50 mL min⁻¹, t_{R1} 11.94 min, t_{R2} 13.22 min; **15b**: Chiralpak AD-RH, 125 mm, 4.6-mm ID, acetonitrile/10 mmol triethylammonium acetate (TEAA) pH 7.0 = 60:40, 0.50 mL min⁻¹, t_{R1} 15.32 min, t_{R2} 17.18 min; **15c**: Chiralcel OD-H, 250 mm, 4.6 mm ID, *n*-heptane + 0.1% triethylamine (TEA)/2-propanol (98:2), 0.50 mL min⁻¹, t_{R1} 12.71 min, t_{R2} 16.43 min; **15d**: Chiralcel OD-H, 250 mm, 4.6-mm ID, *n*-heptane (+ 0.1% TEA)/2-propanol (98:2), 0.50 mL min⁻¹, t_{R1} 12.23 min, t_{R2} 13.60 min].

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