Combinatorial Catalysis

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

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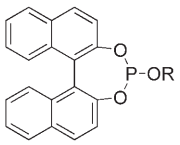
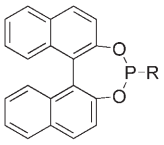
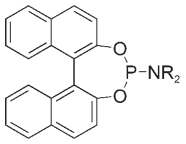
In 2000, three groups independently reported that 2,2′-dihydroxy-1,1′-binaphthyl (binol) derived monodentate P compounds, namely phosphites of the type **1**,[1] phosphonites such as **2**,[2] and phosphoramidites **3**,[3] are excellent chiral ligands in Rh-catalyzed olefin hydrogenation. Since then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



1 a; R = CH_3
b; R = C_6H_5



2 a; R = CH_3
b; R = $C(CH_3)_3$



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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.

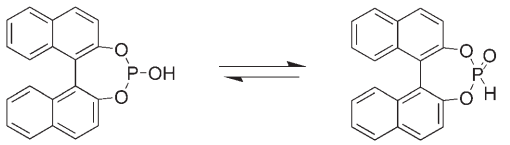
It has not been possible to make reliable predictions regarding the optimal combination from a set of monodentate ligands, making a combinatorial search necessary. The number of possible hetero-combinations arising from a given library of monodentate ligands increases rapidly when increasing the number (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 combinations need to be screened[11] because certain ones can be eliminated on chemical grounds.

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^aL^a)	Number of hetero-combinations[b] (ML^aL^b)
20	190
50	1225
100	4950
200	19950
500	124750

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

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



4A **4B**

Scheme 1.

sterically more encumbered ligand L^b. Although the equilibrium **4A**⇄**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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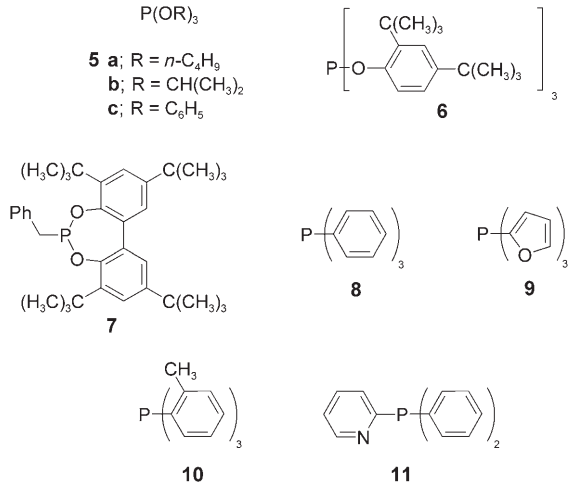
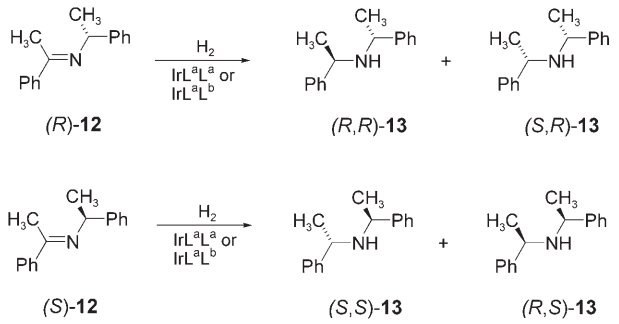


treating the commercially available salt [{Ir(cod)Cl}$_2$] (cod = 1,5-cyclooctadiene) with selected P ligands.

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	(*R*)-**12**	(*S*)-**1a**	1:2	81	3.8:1
2	(*S*)-**12**	(*S*)-**1a**	1:2	100	3.8:1
3	(*R*)-**12**	(*S*)-**1b**	1:2	76	4.8:1
4	(*S*)-**12**	(*S*)-**1b**	1:2	100	4.7:1
5	(*R*)-**12**	(*S*)-**2a**	1:2	92	3.6:1
6	(*S*)-**12**	(*S*)-**2a**	1:2	100	4.5:1
7	(*R*)-**12**	(*S*)-**2b**	1:2	100	7.0:1
8	(*S*)-**12**	(*S*)-**2b**	1:2	100	7.9:1
9	(*R*)-**12**	(*R*)-**4**	1:2	47	5.1:1
10	(*S*)-**12**	(*R*)-**4**	1:2	100	5.5:1
11	(*R*)-**12**	**5a**	1:2	70	6.4:1
12	(*R*)-**12**	**5b**	1:2	83	5.9:1
13	(*R*)-**12**	**5c**	1:2	94	5.6:1
14	(*R*)-**12**	**6**	1:2	100	5.3:1
15	(*R*)-**12**	**7**	1:2	100	11.7:1
16	(*R*)-**12**	**8**	1:2	100	3.9:1
17	(*R*)-**12**	**9**	1:2	100	2.6:1
18	(*S*)-**12**	**10**	1:2	100	5.2:1
19	(*R*)-**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 stereogeneic 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]

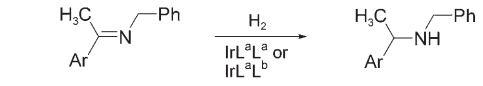
Entry	Imine	Ligand system	Ir:L[a]:L[b]	Conv. [%]	Diastereomer ratio[b]
1	(*R*)-**12**	(*R*)-**4**+**1b**	1:1:1	99	5.4:1
2	(*S*)-**12**	(*R*)-**4**+**1b**	1:1:1	100	5.8:1
3	(*R*)-**12**	(*R*)-**4**+**5a**	1:1:1	88	3.8:1
4	(*S*)-**12**	(*R*)-**4**+**5a**	1:1:1	100	8.7:1
5	(*R*)-**12**	(*R*)-**4**+**5b**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



14a; Ar = phenyl
b; Ar = 4-chlorophenyl
c; Ar = 4-methoxyphenyl
d; Ar = 2-naphthyl

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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 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.

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

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

Experimental Section

General procedure for the hydrogenation using ligand mixtures (ratio Ir:L^a: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

[{Ir(cod)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% PH ME 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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