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Mixtures of chiral monodentate phosphites, phosphonites and phosphines as ligands in Rh-catalyzed hydrogenation of *N*-acyl enamines: extension of the combinatorial approach

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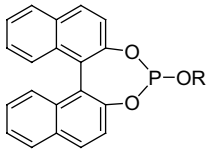
Abstract—Mixtures of BINOL-derived monodentate phosphites and phosphonites have been reacted with Rh-salts to form three (pre)catalysts, which are in equilibrium; two homo-combinations ML^aL^a and ML^bL^b as well as the hetero-combination ML^aL^b. In these cases in which the latter is more active and more enantioselective than the former, enhanced asymmetric induction results in appropriate transition metal catalyzed reactions. This principle has been extended to include mixtures of BINOL-derived monodentate phosphites, phosphonites and phosphines as ligands in the asymmetric Rh-catalyzed hydrogenation of *N*-acyl enamines leading to ee values of >97%.

We recently proposed a new and practical principle in combinatorial asymmetric transition metal catalysis, which is based on the use of two different monodentate P-ligands.[1] The method is relevant whenever in the transition state of a reaction at least two monodentate ligands (L) are coordinated to the metal (M) of the active catalyst ML_x. In the case of a mixture of two such ligands L^a and L^b, three different catalysts exist in equilibrium; specifically the two homo-combinations ML^aL^a and ML^bL^b, as well as the hetero-combination ML^aL^b. Hits in such combinatorial mixtures can be expected if ML^aL^b is more reactive and more enantioselective than the traditional homo-combinations. This concept was illustrated in the Rh-catalyzed hydrogenation of various prochiral olefins, BINOL-derived phosphites **1**[2] and phosphonites **2**[3] serving as the monodentate P-ligands.[1] Thereafter, Feringa et al. extended the area of application by utilizing mixtures of the corresponding phosphoramidites as ligands in Rh-catalyzed hydrogenation[4a] and conjugate addition of phenylboronic acid.[4b]



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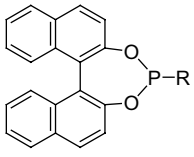

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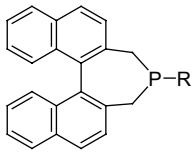

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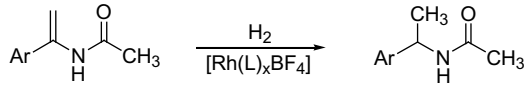
In the industrially important synthesis of chiral amines **5**,[5] we previously restricted our study to a very small library of eight phosphonites **2** and discovered that in the hydrogenation of *N*-acyl enamides[6] **4a** and **b**, the combination of **2a** ($R = CH_3$) and **2b** ($R = C(CH_3)_3$) led to ee values of 96.1% and 97.0%, respectively, which is considerably higher than in the traditional use of the homo-combinations themselves.[1] We herein report that by including previously prepared phosphites **1** in the combinatorial search, highly enantioselective catalysts can be found based on appropriate mixtures of **1** and **2**. Moreover, we show that mixtures composed of the known phosphines **3**[7,8] with **1** or **2** also lead to enhanced enantioselectivities of Rh-catalyzed hydrogenations.



4a Ar = phenyl
4b Ar = 2-naphthyl

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The present results again demonstrate that catalyst diversity can be increased without the necessity to synthesize new ligands.

Using a small library of only five phosphites **1** and three phosphonites **2** in various **1/2** mixtures, two hits were identified in the Rh-catalyzed hydrogenation of substrate **4a** (Table 1, entries 13 and 14). The best one consisted of a mixture of **1b** ($R = CH_2Ph$) and **2b** ($R = C(CH_3)_3$), leading to ee = 97.4% (entry 14). In contrast, the traditional use of the respective homo-combinations **1b** and **2b** in separate experiments resulted in lower ees (91.4% and 13%, respectively, entries 2 and 7). The combination of the sterically smallest methylphosphite **1a** and the sterically largest *t*-butylphosphonite **2b** also gave a hit, but the degree of enantioselectivity (ee = 95.0%) was a little lower (Table 1, entry 13). Thus, the previously observed trend[1] that the optimal catalyst consists of the most bulky ligand L^a and the least bulky ligand L^b does not appear to be completely general.

Table 1. Rhodium-catalyzed asymmetric hydrogenation of enamide **4a** using mixtures of chiral phosphites **1**, phosphonites **2** and phosphines **3**, all derived from (*S*)-BINOL (solvent: CH_2Cl_2; Rh:substrate = 1:500 (250); ligand:Rh = 2:1; 1.3 bar H_2; 20 h; 30 °C) leading to (*R*)-**5a**

Entry	Ligand	Conversion (%)	Ee (%)
Homo-combinations			
1	**1a** $R = CH_3$	100	76.0
2	**1b** $R = CH_2Ph$	100	91.4
3	**1c** $R = C(CH_3)_3$	100	78.0
4	**1d** R = Ph	100	85.4
5	**1e** $R = cC_6H_{11}$	100	84.8
6	**2a** $R = CH_3$	100	75.6
7	**2b** $R = C(CH_3)_3$	83	13.2
8	**2c** $R = cC_6H_{11}$	100	71.8
9	**3a** $R = C(CH_3)_3$	94	24.4
10	**3b** R = Ph	50	14.0
Hetero-combinations			
11	**1a** $R = CH_3$/**1c** $R = C(CH_3)_3$	100	85.2
12	**1d** R = Ph/**1e** $R = cC_6H_{11}$	100	88.6
13	**1a** $R = CH_3$/**2b** $R = C(CH_3)_3$	100	95.0
14	**1b** $R = CH_2Ph$/**2b** $R = C(CH_3)_3$	100	97.4
15	**1c** $R = C(CH_3)_3$/**2a** $R = CH_3$	100	74.4
16	**1c** $R = C(CH_3)_3$/**2c** $R = cC_6H_{11}$	100	53.6
17	**1a** $R = CH_3$/**3a** $R = C(CH_3)_3$	100	89.0
18	**1a** $R = CH_3$/**3b** R = Ph	100	57.2
19	**2a** $R = CH_3$/**3b** R = Ph	100	53.0
20	**2a** $R = CH_3$/**3a** $R = C(CH_3)_3$	100	87.2

Although phosphines **3a** and **3b**[7,8] are not as readily accessible as BINOL derivatives **1** and **2**, we nevertheless used them as components in our combinatorial approach. The homo-combinations **3a/3a** and **3b/3b** lead to ee values of only 24.4% and 14.0%, respectively, in relatively slow reactions (entries 9 and 10). In contrast, the hetero-combinations **1a/3a** and **2a/3a** constituted hits, resulting in ee values of 89.0% and 87.2%, respectively (entries 17 and 20). Although the preparative value of these observations is limited, they are however of theoretical interest.

In the case of naphthyl substrate **4b**, the library of (*S*)-BINOL-derived phosphites was extended to include two diasteromeric ligands **1f** (R = (*R*)-PhEt) and **1g** (R = (*S*)-PhEt) prepared from (*R*)- and (*S*)-2-phenylethanol,[2] respectively. These two ligands had been prepared and used previously in their pure forms as ligands in the Rh-catalyzed hydrogenation of other prochiral olefins, giving rise to very low effects concerning the issue of matched versus mismatched ligand components.[2] In the present case of **4b**, however, ligand **1f**, prepared from (*S*)-BINOL and (*R*)-2-phenylethanol, led to a significantly higher ee (94.0%) than the diastereomeric ligand **1g** derived from (*S*)-BINOL and (*S*)-2-phenylethanol (78.8%) (Table 2, entries 5 and 6). As shown in Table 2, out of a total of only nine hetero-combinations tested, several turned out to be hits, that is, several mixtures showed higher enantioselectivities than the optimal homo-combination. The synthetically most important hits were **1a/2b** (ee = 97.2%, entry 13) and **1f/2b** (ee = 96.8%, entry 15). In both cases one component was phosphonite **2b**, which when used alone in a homo-combination led to racemic product **5b** (entry 3). Interestingly, the hetero-combination of the two phosphites **1c/1f** allowed for a slight enhancement in enantioselectivity (ee = 94.8%; entry 11) relative to the homo-combination **1f/1f** (ee = 94.0%, entry 5), inspite of the fact that the other homo-combination **1c/1c** was completely unselective (racemic **5b**). The diastereomeric hetero-combination **1c/1g** containing the 'mismatched' phosphite **1g** led to an enantioselectivity of only ee = 82.4% (entry 12).

Table 2. Rhodium-catalyzed asymmetric hydrogenation of enamide **4b** using mixtures of chiral phosphites **1** and/or phosphonites **2**, all derived from (*S*)-BINOL (solvent: CH_2Cl_2; Rh:substrate = 1:500; ligand:Rh = 2:1; 1.3 bar H_2; 20 h; 30 °C) leading to (*R*)-**5b**

Entry	Ligand	Conversion (%)	Ee (%)
Homo-combinations			
1	**1a** $R = CH_3$	100	76.0
2	**1b** $R = CH_2Ph$	100	94.0
3	**1c** $R = C(CH_3)_3$	68	*rac*
4	**1e** $R = cC_6H_{11}$	100	85.6
5	**1f** R = (*R*)PhEt	100	94.0
6	**1g** R = (*S*)PhEt	100	78.8
7	**2a** $R = CH_3$	100	78.2
8	**2b** $R = C(CH_3)_3$	100	<3
Hetero-combinations			
9	**1a** $R = CH_3$/**1c** $R = C(CH_3)_3$	100	75.2
10	**1c** $R = C(CH_3)_3$/**1e** $R = cC_6H_{11}$	100	86.8
11	**1c** $R = C(CH_3)_3$/**1f** R = (*R*)PhEt	100	94.8
12	**1c** $R = C(CH_3)_3$/**1g** R = (*S*)PhEt	100	82.4
13	**1a** $R = CH_3$/**2b** $R = C(CH_3)_3$	100	97.2
14	**1e** $R = cC_6H_{11}$/**2b** $R = C(CH_3)_3$	100	86.0
15	**1f** R = (*R*)PhEt/**2b** $R = C(CH_3)_3$	100	96.8
16	**1g** R = (*S*)PhEt/**2b** $R = C(CH_3)_3$	100	84.0
17	**2b** $R = C(CH_3)_3$/**2a** $R = CH_3$	100	97.0

Studies concerning the origin of enhanced activity and enantioselectivity arising from the use of certain hetero-combinations are currently in progress. NMR analysis of the catalyst system derived from the 1:1:1 mixture of

1a, **2b**, and $Rh(cod)_2BF_4$ showed the presence of the two homo-combinations Rh(**1a**)(**1a**)(cod)BF_4 and Rh(**2b**)-(**2b**)(cod)BF_4 and the hetero-combination Rh(**1a**)(**2b**)-(cod)BF_4 in a ratio of 10:14:76.

In summary, we have shown that the combinatorial concept of asymmetric catalysis using mixtures of monodentate ligands[1] can be extended to mixtures of BINOL-derived monophosphites and monophosphonites as ligands in the Rh-catalyzed hydrogenation of *N*-acyl enamines. Since BINOL is currently one of the most inexpensive chiral auxiliary commercially available,[9] modular ligands of the type **1**,[2] **2**[3] and amidite-analogues[4] are industrially viable. Maximum structural diversity while maintaining catalyst activity as well as low costs is a particularly simple goal in the case of the monophosphites **1**,[1,2,10] because an enormously wide range of inexpensive achiral and chiral alcohols are commercially available, which can be used in the synthesis of these modular ligands. Moreover, axially chiral diols[11] other than BINOL or other types of chiral diols[6c] or amino alcohols can also be employed.[1c] The perspectives evolving from our combinatorial approach[1] are practical:[12] As a consequence of mixing two different monodentate P-ligands, a large number of which are already available (and certainly more can be envisioned), catalyst diversity and therefore the probability of discovering highly enantioselective systems increases without the need to synthesize complicated ligands.[1]

References and notes

1. (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem.* **2003**, *115*, 814–817; *Angew. Chem., Int. Ed.* **2003**, *42*, 790–793; (b) Reetz, M. T. *Chim. Oggi* **2003**, *21*(10/11), 5–8; (c) Reetz, M. T.; Meiswinkel, A.; Sell, T.; Mehler, G. Patent application DE-A 102 47 633.0, 2002; (d) Reetz, M. T.; Mehler, G. *Tetrahedron Lett.* **2003**, *44*, 4593–4596.
2. (a) Reetz, M. T.; Mehler, G. *Angew. Chem.* **2000**, *112*, 4047–4049; *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890; (b) Reetz, M. T., Mehler, G.; Meiswinkel, A. Patent application WO 01/94278 A1, 2001; (c) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Feldthusen Jensen, J. *Org. Lett.* **2003**, *5*, 3099–3101.
3. (a) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333–6336; (b) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun. (Cambridge, UK)* **2000**, 961–962.
4. (a) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087–1089; (b) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111–3113.
5. Balkenhohl, F.; Ditrich, K.; Hauer, B.; Ladner, W. *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 381–384.
6. For the synthesis and hydrogenation of *N*-acyl enamides, see: (a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084–6085; (b) Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 5541–5544; (c) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem.* **2002**, *114*, 2454–2456; *Angew. Chem., Int. Ed.* **2002**, *41*, 2348–2350; (d) Rh-catalyzed hydrogenation of *N*-acyl enamines using phosphites **1** as ligands: Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* **2002**, *43*, 7941–7943.
7. (a) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*, 4977–4980; (b) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. *Tetrahedron: Asymmetry* **1994**, *5*, 511–514; (c) Bitterer, F.; Herd, O.; Kühnel, M.; Stelzer, O.; Weferling, N.; Sheldrick, W. S.; Hahn, J.; Nagel, S.; Rösch, N. *Inorg. Chem.* **1998**, *37*, 6408–6417.
8. We thank Prof. M. Beller for samples of **3** ($R = C(CH_3)_3$ and Ph).
9. (*R*)- and (*S*)-BINOL cost about $400/kg for bulk quantities at: (a) Reuter Chemische Apparatebau KG, Freiburg, Germany; (b) Other commercial sources of BINOL are also available.
10. The synthesis of BINOL-derived monophosphites is well known:[2a,b] (a) Ovchinnikov, V. V.; Cherkasova, O. A.; Verizhnikov, L. V. *Zh. Obshch. Khim.* **1982**, *52*, 707–708; *J. Gen. Chem.* **1982**, *52*, 615–616; (b) Bartik, T.; Gerdes, I.; Heimbach, P.; Schulte, H.-G. *J. Organomet. Chem.* **1989**, *367*, 359–370; (c) Heimbach, P.; Bartik, T.; Drescher, U.; Gerdes, I.; Knott, W.; Rienäcker, R.; Schulte, H.-G.; Tani, K. *Kontakte (Darmstadt)* **1988**, *3*, 19–31; (d) Fuji, K.; Kinoshita, N.; Tanaka, K.; Kawabata, T. *Chem. Commun. (Cambridge, UK)* **1999**, 2289–2290; (e) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 2897–2899; (f) Komarov, I. V.; Börner, A. *Angew. Chem.* **2001**, *113*, 1237–1240; *Angew. Chem., Int. Ed.* **2001**, *40*, 1197–1200; (g) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 2897–2899; (h) Adams, D. J.; Chen, W.; Hope, E. G.; Lange, S.; Stuart, A. M.; West, A.; Xiao, J. *Green Chem.* **2003**, *5*, 118–122; (i) Gergely, I.; Hegedüs, C.; Gulyás, H.; Szöllösy, Á.; Monsees, A.; Riermeier, T.; Bakos, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1087–1090; (j) Nakano, D.; Yamaguchi, M. *Tetrahedron Lett.* **2003**, *44*, 4969–4971.
11. (a) Hannen, P.; Militzer, H.-C.; Vogl, E. M.; Rampf, F. A. *Chem. Commun. (Cambridge, UK)* **2003**, 2210–2211; (b) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831–3834.
12. Typical procedure: A dry 50-mL Schlenk flask under an atmosphere of argon is charged with a mixture of a 1.7 mM solution of the first ligand (0.6 mL) and a 1.7 mM solution of the second ligand (0.6 mL) in dry dichloromethane. The solution is treated with a 2.0 mM solution of $[Rh(cod)_2]BF_4$ (0.5 mL) in dichloromethane and stirred for 5 min at room temperature. Then a 0.112 M solution of substrate **4a** in dichloromethane (9 mL) is added. Vacuum is applied three times until the solvent begins to evaporate gently and then hydrogen is introduced. Hydrogenation is carried out at 1.3 bar for 20 h. Following dilution, conversion is determined by NMR spectroscopy. To determine the ee values, about 1.5 mL of the reaction solution can be passed through a small amount of silica gel prior to the GC analysis.