Combinatorial Catalysis

Mixtures of Configurationally Stable and Fluxional Atropisomeric Monodentate P Ligands in Asymmetric Rh-Catalyzed Olefin Hydrogenation**

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Several years ago it was reported that monodentate phosphites,[1] phosphonites,[2] and phosphoramidites[3] derived from 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) are efficient ligands in various Rh-catalyzed asymmetric olefin-hydrogenation reactions (90–99 % *ee*). These observations were surprising, because it had been accepted that chelating bidentate P ligands are generally necessary for high levels of enantioselectivity, probably due to restricted rotation in the Rh complexes. Examples of other types of monodentate P ligands are also known.[4] Preliminary mechanistic results show that two monodentate phosphites (or phosphonites) are bonded to Rh in the transition state of hydrogenation[5] when the precatalyst is $[Rh(cod)(\mathbf{1})_2]BF_4$ (cod = cycloocta-1,5-diene). Based on these results we subsequently demonstrated that the use of a mixture of two different monodentate P ligands constitutes a new and efficient approach to combinatorial asymmetric transition-metal catalysis.[6] Once a library

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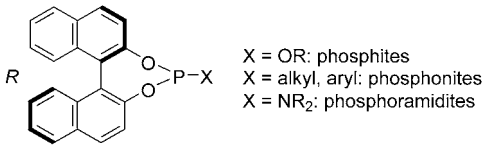
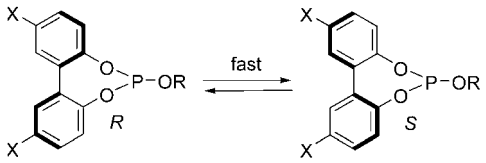
of cheap ligands has been prepared, mixtures result in high catalyst diversity and new ligands are not needed. Although each system actually contains three (pre)catalysts in an (as yet) unpredictable ratio, namely the two homocombinations $[Rh(cod)L^aL^a]BF_4$ and $[Rh(cod)L^bL^b]BF_4$, as well as the heterocombination $[Rh(cod)L^aL^b]BF_4$, enantioselectivities of 95–99% *ee* are often possible, even though the respective homocombinations in pure form result in lower enantioselectivities. Mixtures of BINOL-derived P ligands in combination with a phosphinine (phosphabenzene) or triphenylphosphine cause reversal of enantioselectivity in a few cases.[7]



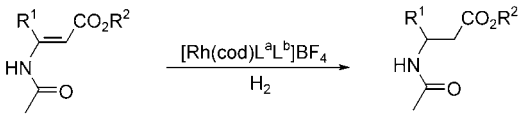
1a X = OMe
b X = *t*Bu

We now show that mixtures of appropriate chiral BINOL-derived phosphonites such as (*R*)-**1b** in combination with certain achiral P ligands or configurationally fluxional atropisomeric phosphites **2** derived from the corresponding achiral biphenols are also excellent ligand systems.



2a X = H; R = CH_3
b X = H; R = CH_2Ph
c X = H; R = *t*Bu
d X = $CH(CH_3)_2$; R = CH_2Ph

Our model reaction was the Rh-catalyzed hydrogenation of β-acylamino acrylate **3a** with formation of the β-amino acid derivative **4a** [Eq. (1)][8] In addition to **2**, the achiral



(1)

3a $R^1 = R^2 = CH_3$
b $R^1 = CH_3$; $R^2 = C_2H_5$
c $R^1 = C_2H_5$; $R^2 = CH_3$
d $R^1 = n\text{-}C_3H_7$; $R^2 = C_2H_5$
e $R^1 = Ph$; $R^2 = C_2H_5$

4

phosphines PMe_3 (**5**), $PiPr_3$ (**6**), and PPh_3 (**7**) as well as the achiral phosphites $P(OMe)_3$ (**8**), $P(OiPr_3)_3$ (**9**), $P(OCH_2tBu)_3$ (**10**), and $P(OPh)_3$ (**11**) were used in combination with (*R*)-**1b** (or (*R*)-**1a**). In all cases $[Rh(cod)_2]BF_4$ was treated with a 1:1 mixture of the two monodentate P ligands (Rh/ligands = 1:2) prior to hydrogenation under standard conditions.[8]

Some remarkable results are listed in Table 1. In particular, the homocombination comprising the *tert*-butylphosphonite (*R*)-**1b** alone leads to only 45% *ee* (*S*) (entry 2), whereas the heterocombination of (*R*)-**1b** and achiral **11** results in 88% *ee* (*S*) (entry 19). Selectivities higher than those obtained with the homocombinations were also observed for several other heterocombinations (entries 7, 8, 11, 16). Dramatic effects emerged when heterocombinations of phosphonite (*R*)-**1b** and configurationally labile atropisomeric phosphites **2a**, **2b**, and **2d** were used; these systems lead to enantioselectivities of 98% *ee* (*S*), 98% *ee* (*S*), and 94% *ee* (*S*), respectively (entries 20, 21, 23).

Table 1: Rh-catalyzed hydrogenation of olefin **3a**.[a] (*R*)-BINOL derivatives led to (*S*)-**4a**.

Entry	Ligand	Conv. [%]	*ee* [%]
	Homocombinations		
1	**1a**	95	75
2	**1b**	83	45
	Heterocombinations		
3	**1a/6**	51	50
4	**1a/7**	92	14
5	**1a/8**	100	30
6	**1a/9**	96	30
7	**1a/10**	100	81
8	**1a/11**	84	79
9	**1a/2a**	83	73
10	**1a/2b**	92	67
11	**1a/2c**	57	83
12	**1a/2d**	97	65
13	**1b/5**	46	51
14	**1b/6**	67	17
15	**1b/7**	98	5
16	**1b/8**	99	84
17	**1b/9**	100	16
18	**1b/10**	89	45
19	**1b/11**	91	88
20	**1b/2a**	100	98
21	**1b/2b**	100	98
22	**1b/2c**	10	7
23	**1b/2d**	99	94

[a] Conditions: 60 bar H_2, CH_2Cl_2, RT, 20 h, Rh/**3a** = 1:50; L^a/L^b = 1:1; Rh/total ligands = 1:2).

A preliminary NMR study of the precatalyst system derived from (*R*)-**1b** and **2a** indicates the existence of a mixture of the two expected homocombinations $[Rh(cod)((R)\text{-}\mathbf{1b})_2]BF_4$ and $[Rh(cod)(\mathbf{2a})_2]BF_4$ in addition to the heterocombination $[Rh(cod)(R)\text{-}\mathbf{1b}(\mathbf{2a})]BF_4$ in a ratio of about 1:1:16 (plus a small amount of unidentified species). However, the situation is in fact more complicated, because those complexes containing the configurationally labile atropisomeric **2a** actually exist as fluxional diastereomers. Thus, the major component in the above mixture exists as a pair of diastereomers in equilibrium [Eq. (2)]. They interconvert so rapidly even at low temperatures that their relative amounts cannot be measured by NMR spectroscopy. In the extreme case only one diastereomeric form is present, but this is rather unlikely.

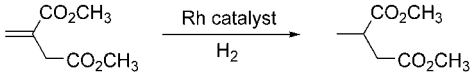
$$[Rh(cod)(R)\text{-}\mathbf{1b}(R)\text{-}\mathbf{2a}]BF_4 \rightleftharpoons [Rh(cod)(R)\text{-}\mathbf{1b}(S)\text{-}\mathbf{2a}]BF_4 \quad (2)$$

We postulate that diastereomer $[Rh(cod)(R)\text{-}\mathbf{1b}(R)\text{-}\mathbf{2a}]BF_4$ constitutes the matched case; cooperativity leads to

a higher hydrogenation rate and to enhanced enantioselectivity. To lend support to this hypothesis, we prepared and tested separately the structurally related heterocombinations composed of two BINOL-derived building blocks, namely [Rh(*R*)-**1b**(*R*)-**1a**]BF_4 and [Rh(*R*)-**1b**(*S*)-**1a**]BF_4, which are configurationally stable diastereomeric complexes. We have already shown that the former precatalyst leads to 99% *ee* (*S*),[8] and we now note that the latter is considerably less effective (40% *ee* (*S*); 84% yield). Of course, it must be remembered that these catalysts cannot be prepared in pure form; in other words, in each case it is the mixture of the two respective homocombinations and the heterocombination that defines the catalytic profile and thus determines the observed enantioselectivity.

The result of our combinatorial search[9] suggested that the heterocombination of **1b** and **2a** may be the optimal ligand system for Rh-catalyzed hydrogenations of β-acylamino acrylates in general. Therefore this combination was tested in the hydrogenation of the other substrates **3b–e** under standard conditions. Indeed, excellent results were obtained: **3b** (96% *ee* (*S*); 90% yield), **3c** (95% *ee* (*S*); 90% yield), **3d** (97% *ee* (*S*); 94% yield;), **3e** (84% *ee* (*R*); 69% yield).

Finally, we performed the hydrogenation of itaconic acid diester **12** (Rh/**12** = 1:1000; Rh/ligand = 1:2; 1.3 bar H_2; RT; 20 h) using the homocombination (*R*)-**1b**, which resulted in only 77% *ee* (*R*) [80% yield, Eq. (3)). For this reason we turned to the corresponding mixtures: The combinations (*R*)-**1b**/**2a** and (*R*)-**1b**/**11** gave essentially identical enantioselectivities (94% *ee* (*R*)) and quantitative yield.



12 **13** (3)

In summary, we have shown for the first time that in Rh-catalyzed olefin-hydrogenation, mixtures comprising a BINOL-derived P ligand in combination with an achiral P compound, or a BINOL-derived P ligand in combination with a chiral but configurationally fluxional biphenol-derived phosphite can result in high enantioselectivity. The latter system is most effective and involves two rapidly interconverting diastereomers; the presumably more reactive *R*/*R* combination shows higher activity and enantioselectivity than the diastereomeric *R*/*S* form. Apart from the theoretical interest, the present results are of practical importance because half of the ligand system is derived from cheap achiral compounds such as biphenol.[10] It remains to be seen if this combinatorial approach can be extended to other reactions and ligand types.[11,12]

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[1] a) M. T. Reetz, G. Mehler, *Angew. Chem.* **2000**, *112*, 4047–4049; *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3890; b) M. T. Reetz, G. Mehler, A. Meiswinkel, Patent Application, WO 01/94278A1, **2001**.

[2] a) M. T. Reetz, T. Sell, *Tetrahedron Lett.* **2000**, *41*, 6333–6336; b) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* **2000**, 961–962.

[3] M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540.

[4] a) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069; b) I. V. Komarov, A. Börner, *Angew. Chem.* **2001**, *113*, 1237–1240; *Angew. Chem. Int. Ed.* **2001**, *40*, 1197–1200; c) M. Ostermeier, J. Prieß, G. Helmchen, *Angew. Chem.* **2002**, *114*, 625–628; *Angew. Chem. Int. Ed.* **2002**, *41*, 612–617; d) Y. Chi, X. Zhang, *Tetrahedron Lett.* **2002**, *43*, 4849–4852; e) W. Chen, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 8737–8740; f) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* **2004**, *69*, 2355–2361; g) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2002**, *114*, 2454–2456; *Angew. Chem. Int. Ed.* **2002**, *41*, 2348–2350; h) Z. Pakulski, O. M. Demchuk, J. Frelek, R. Luboradzki, K. M. Pietrusiewicz, *Eur. J. Org. Chem.* **2004**, 3913–3918; i) T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101–2111; j) F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315–324; k) J. Ansell, M. Wills, *Chem. Soc. Rev.* **2002**, *31*, 259–268.

[5] A. Meiswinkel, Dissertation, Ruhr-Universität Bochum, Germany, **2003**.

[6] a) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814–817; *Angew. Chem. Int. Ed.* **2003**, *42*, 790–793; b) M. T. Reetz, *Chim. Oggi* **2003**, *21*, 5–8; see also: c) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087–1089.

[7] M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593–4596.

[8] M. T. Reetz, X. Li, *Tetrahedron* **2004**, *60*, 9709–9714 and literature cited therein concerning previous work on the hydrogenation of **3**.

[9] The data shown here constitutes only about half of the total combinatorial search. Combinations of phosphonite **1** (X = CH_3) with **2** or **5**–**11** do not result in positive effects.

[10] We have previously shown that certain diphosphites composed of a chiral backbone diol and fluxional atropisomeric biphenol derivatives provide selectivities of up to 99% *ee* in olefin hydrogenation; three rapidly interconverting diastereomers are involved: a) M. T. Reetz, T. Neugebauer, *Angew. Chem.* **1999**, *111*, 134–137; *Angew. Chem. Int. Ed.* **1999**, *38*, 179–181; b) D. G. Blackmond, T. Rosner, T. Neugebauer, M. T. Reetz, *Angew. Chem.* **1999**, *111*, 2333–2335; *Angew. Chem. Int. Ed.* **1999**, *38*, 2196–2199; for related effects see: c) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517–519; *Angew. Chem. Int. Ed.* **1999**, *38*, 495–497; d) M. Diéguez, S. Deerenberg, O. Pàmies, C. Claver, P. W. N. M. van Leeuwen, P. Kamer, *Tetrahedron: Asymmetry* **2000**, *11*, 3161–3166; e) J. W. Faller, A. R. Lavoie, J. Parr, *Chem. Rev.* **2003**, *103*, 3345–3367; f) P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297–3344; g) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369–3400; h) M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón, C. Claver, *Chem. Eur. J.* **2001**, *7*, 3086–3094; i) Z. Luo, Q. Liu, L. Gong, X. Cui, A. Mi, Y. Jiang, *Angew. Chem.* **2002**, *114*, 4714–4717; *Angew. Chem. Int. Ed.* **2002**, *41*, 4532–4535; j) A. Suárez, A. Pizzano, *Tetrahedron: Asymmetry* **2001**, *12*, 2501–2504; k) T. Ooi, Y. Uematsu, M.

Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 1621 – 1624; *Angew. Chem. Int. Ed.* **2002**, *41*, 1551 – 1554; l) C. Monti, C. Gennari, U. Piarulli, *Tetrahedron Lett.* **2004**, *45*, 6859 – 6862; m) H. Horibe, K. Kazuta, M. Kotoku, K. Kondo, H. Okuno, Y. Murakami, T. Aoyama, *Synlett* **2003**, 2047 – 2051; n) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem.* **2004**, *116*, 2480 – 2482; *Angew. Chem. Int. Ed.* **2004**, *43*, 2426 – 2428, and references therein.

[11] Along these lines the use of mixtures of BINOL-derived phosphoramidites **1** ($X = NR_2$) and fluxional atropisomeric phosphoramidites (which we have prepared from biphenol and amines such as dimethylamine and piperidine) offers interesting perspectives.

[12] For more work on combinatorial catalysis see: M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3022–3024; *Angew. Chem. Int. Ed.* **2005**, *44*, 2962–2964.