

HETEROCYCLES, Vol. 67, No. 2, 2006, pp. 567 - 574. © The Japan Institute of Heterocyclic Chemistry
Received, 18th August, 2005, Accepted, 10th November, 2005, Published online, 11th November, 2005. COM-05-S(T)74

**EXTENDING THE CONCEPT OF MIXTURES OF CHIRAL
MONODENTATE P-LIGANDS IN ASYMMETRIC Rh-CATALYZED
OLEFIN-HYDROGENATION: USE OF OXAZAPHOSPHOLIDINES**

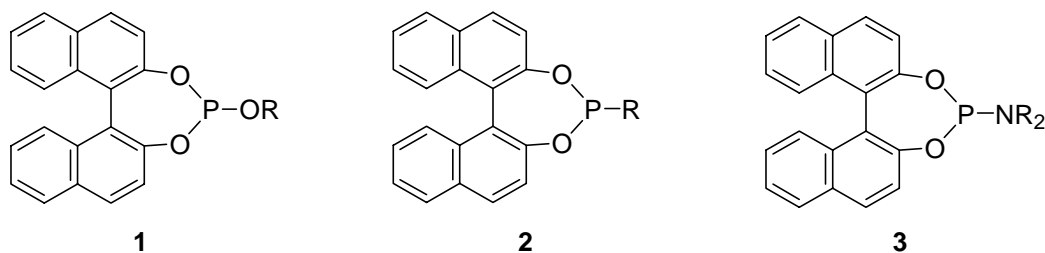
Manfred T. Reetz* and Marek Surowiec

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1,
45470 Mülheim/Ruhr, Germany, e-mail reetz@mpi-muelheim.mpg.de

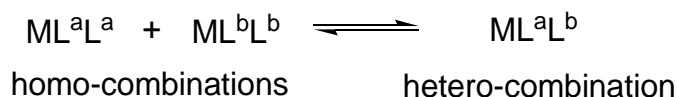
Dedicated to Professor B.M. Trost on the occasion of his 65th birthday.

Abstract – The previously described combinatorial concept of using mixtures of monodentate BINOL-derived phosphites, phosphonites or phosphoramidites as superior ligand systems in Rh-catalyzed asymmetric olefin-hydrogenation has been extended to include chiral oxazaphospholidines. Specifically, the latter were prepared from ephedrine and pseudo-ephedrine according to literature procedures. Mixtures of these P-ligands among themselves or in combination with a BINOL-derived phosphonite lead to enhanced enantioselectivity in the Rh-catalyzed hydrogenation of itaconic acid dimethyl ester (ee up to 89%).

In 2000 three groups reported that certain chiral monodentate P-ligands are well suited in asymmetric Rh-catalyzed olefin-hydrogenation (ee >90%), namely BINOL-derived phosphites (**1**),¹ phosphonites (**2**)² and phosphoramidites (**3**).³ This came as a surprise, because it had been accepted for decades that chelating bidentate diphosphines are necessary for obtaining high enantioselectivity, presumably due to restricted rotational freedom around the Rh-P bonds.⁴ A detailed mechanistic study focusing on phosphites (**1**) was published recently.⁵ On the basis of kinetics, non-linear effects, NMR spectral data and DFT calculations it was shown that in the transition state of the reaction two monodentate P-ligands are bonded to the metal.



Parallel to synthetic^{1,2,6} and mechanistic efforts regarding ligands (**1** - **3**),^{1,2,3,5,6} we proposed in 2002/2003 a new approach to combinatorial asymmetric transition metal catalysis, namely the use of mixtures of chiral monodentate ligands.⁷ Such a process leads to a mixture of three catalysts, the two traditional complexes ML^aL^a and ML^bL^b (termed homo-combinations) and a new complex ML^aL^b (termed hetero-combination) which can be expected to be in equilibrium with one another:



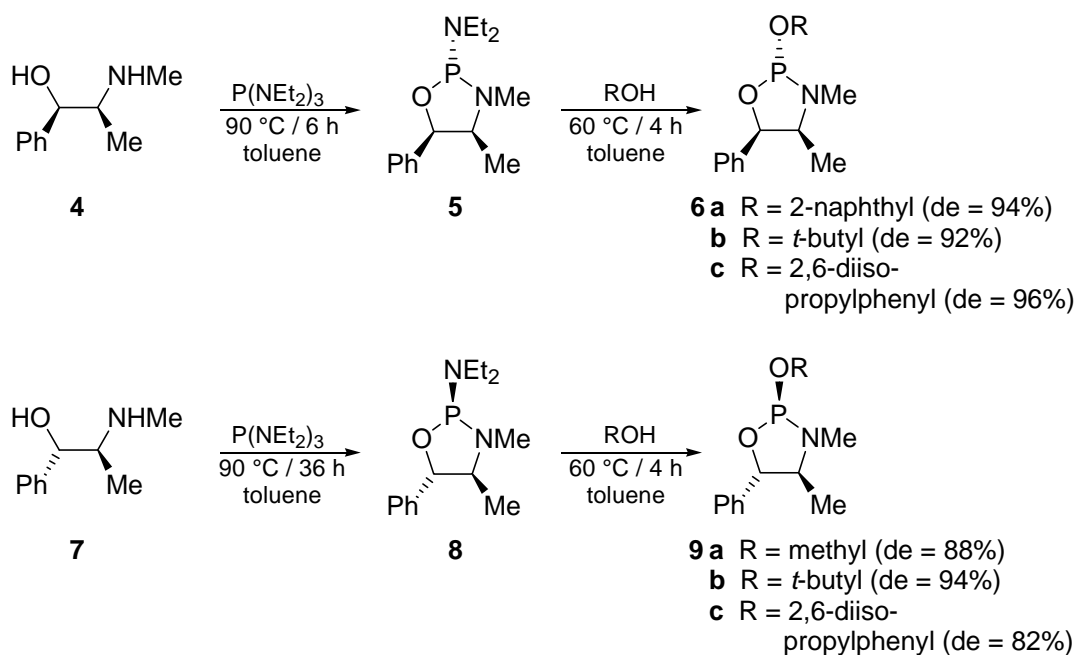
The distribution between the three species is not statistical. Rather, it is dictated by thermodynamics, which means that variation of the L^a/L^b ratio will influence the relative population of the three catalysts or pre-catalysts. If the hetero-combination dominates rate-wise and if it is more enantioselective than the homo-combinations, then enhanced enantioselectivity can be expected.

Although the concept may not appeal to those who strive for well-defined single catalysts, the potential advantage of the concept of using mixtures of monodentate ligands relates to the fact that *high catalyst diversity is generated without the need to prepare new ligands*. In other words, once a set of ligands (library) has been placed on the shelf by commercial acquisition or synthesis, mixing them leads to high numbers of new catalysts. Since rational predictions based on theoretical analyses are not possible presently, an empirical approach is necessary. In our original study we used rather small libraries of ligands (**1**) and (**2**) (less than a dozen) in asymmetric olefin-hydrogenation, yet we were able to find numerous hetero-combinations as hits which exhibit dramatically enhanced enantioselectivity relative to the respective homo-combinations. Following our study, Feringa, de Vries and co-workers reported that mixtures of phosphoramidites (**3**) also lead to enhanced enantioselectivity.⁸

We have recently extended the concept of mixtures of monodentate ligands to include the control of regioselectivity⁹ and diastereoselectivity.¹⁰ In the present study we show that enhancing enantioselectivity is not restricted to the use of mixtures of BINOL-derived P-ligands. Specifically, ephedrine- and pseudo-ephedrine-derived oxazaphospholidines, first prepared by Bernard and Burgada¹¹ and used by Alexakis¹² as ligands in Cu-mediated conjugate addition reactions, result in substantial

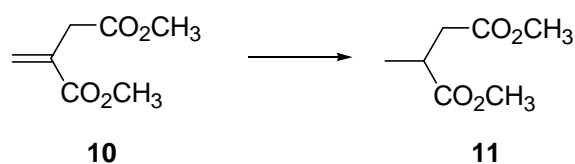
effects when used in combination with the BINOL-derived phosphonite (**2**) ($R = C(CH_3)_3$). The oxazaphospholidines themselves as homo-combinations are not well suited as ligands in Rh-catalyzed hydrogenation.

Following general literature methods,^{11, 12} several ligands were first prepared from ephedrine (**4**) and pseudo-ephedrine (**7**):



Upon treating **4** and **7** with $P(NEt_2)_3$ as shown, compound (**5**) was obtained as a single diastereomer and **8** was formed as a mixture of diastereomers (about 4:1). Since **5** and **8** are somewhat sensitive and require careful handling, purification was not attempted. Rather, the crude forms were subjected to alcoholysis by reaction with ROH in toluene for four hours. Under these conditions the thermodynamically more stable oxazaphospholidines were formed with the configuration at phosphorus as shown in **6** and **9**, respectively. In order to obtain as diastereomerically pure as possible ligands for Rh-catalyzed olefin-hydrogenation, chromatography (Al_2O_3 /pentane) was performed resulting in nearly pure ligands (diastereomeric excess (de) shown above).

Heterocycles (**6**) and (**9**) were then used as ligands in the Rh-catalyzed hydrogenation of itaconic acid dimethyl ester (**10**). In doing so, the standard method^{1, 2, 3} of preparing the pre-catalyst was applied by treating $Rh(cod)_2BF_4$ with two equivalents of a monodentate ligand (**6**) and (**9**), respectively, in dichloromethane. This led to the formation of the pre-catalysts $Rh(\mathbf{6})_2(cod)BF_4$ and $Rh(\mathbf{9})_2(cod)BF_4$.



Not surprisingly, these catalysts resulted in poor enantioselectivity, the ee-value not exceeding 43% (Table 1, Entries 1-6), which does not even match up to the poor performance of the BINOL-derived phosphonite (**2**) ($R = C(\text{CH}_3)_3$) having ee = 56% (Table 1, Entry 7). The combinatorial search was then initiated by first using mixtures of **6a-c**, of **9a-c** and of **6a-c/9a-c** (Table 1, Entries 8-22). The highest enantioselectivity was reached with the hetero-combination **6b/9c** showing ee = 59% (*S*) (Table 1, Entry 19). The individual components (**6b**) and (**9c**) in pure form are less selective (ee = 30% (*S*) and ee = 40% (*R*), respectively) (Table 1, Entries 2 and 6). Thus, although the two homo-combinations induce opposite enantioselectivity, their combination leads to clearly enhanced (*S*)-selectivity. Since in a mixture, all three catalysts are present, these results are remarkable from a theoretical point of view. It strongly suggests that a catalyst system composed of only **6b/9c**, if ligand exchange were not to occur, would show inherently high enantioselectivity, possibly higher than 90%. Theoretically, this might be achievable by designing the proper covalent spacer between **6b** and **9c** with formation of an appropriate bidentate ligand. Interestingly, a second combination **6c/9c** also induces enhanced enantioselectivity (ee = 58% (*R*); Table 1, Entry 22). In this case both respective homo-combinations are (*R*)-selective (Table 1, Entries 3 and 6). Moreover, the two least enantioselective ligands as homo-combinations, namely **6a** (ee = 9% (*R*); Table 1, Entry 1) and **9a** (ee = 0%; Table 1, Entry 4), function in concert with one another in a hetero-combination astonishingly well with ee = 38% (*R*) (Table 1, Entry 14). Of course, these observations have no immediate practical value. Nevertheless, they are significant for theoretical reasons. Moreover, other substrates may behave differently leading to high ees.

Table 1. Rh-catalyzed hydrogenation of itaconate (**10**) (Rh : substrate = 1 : 200, Rh : total ligand = 1 : 2; 1.3 bar H₂; 22 °C; 12 h; dichloromethane). Conversion >95% in all cases.

Entry	Ligand	ee (%)	Configuration of 11
Homo-combinations			
1	6a/6a	9	<i>R</i>
2	6b/6b	30	<i>S</i>
3	6c/6c	43	<i>R</i>
4	9a/9a	0	-

5	9b/9b	15	<i>S</i>
6	9c/9c	40	<i>R</i>
7	<i>(R)</i> - 2 (R = C(CH ₃) ₃)/ <i>(R)</i> - 2 (R = C(CH ₃) ₃)	56	<i>R</i>

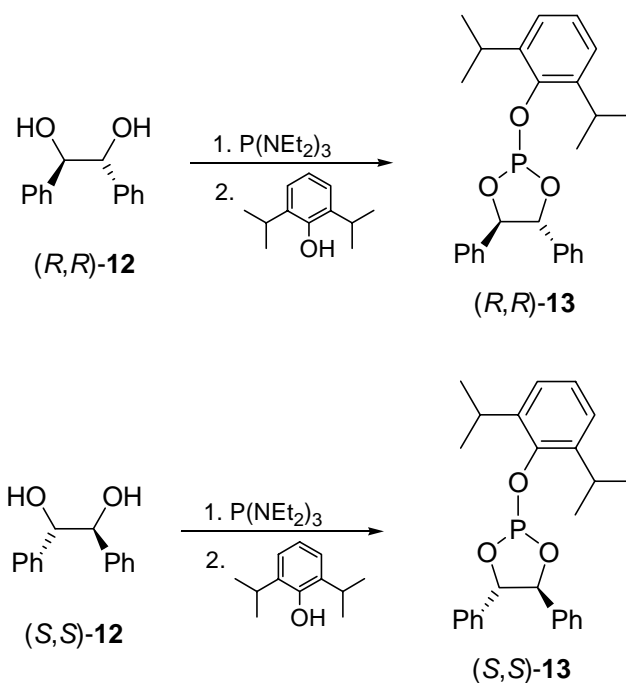
Hetero-combinations

8	6a/6b	12	<i>S</i>
9	6a/6c	8	<i>R</i>
10	6b/6c	15	<i>R</i>
11	9a/9b	23	<i>R</i>
12	9a/9c	26	<i>R</i>
13	9b/9c	36	<i>R</i>
14	6a/9a	38	<i>R</i>
15	6a/9b	24	<i>R</i>
16	6a/9c	0	-
17	6b/9a	7	<i>S</i>
18	6b/9b	35	<i>S</i>
19	6b/9c	59	<i>S</i>
20	6c/9a	24	<i>R</i>
21	6c/9b	33	<i>R</i>
22	6c/9c	58	<i>R</i>
23	<i>(R)</i> - 2 (R = C(CH ₃) ₃)/ 6b	47	<i>R</i>
24	<i>(S)</i> - 2 (R = C(CH ₃) ₃)/ 6b	66	<i>S</i>
25	<i>(R)</i> - 2 (R = C(CH ₃) ₃)/ 6c	44	<i>R</i>
26	<i>(S)</i> - 2 (R = C(CH ₃) ₃)/ 6c	30	<i>S</i>
27	<i>(R)</i> - 2 (R = C(CH ₃) ₃)/ 9b	89	<i>R</i>
28	<i>(S)</i> - 2 (R = C(CH ₃) ₃)/ 9b	52	<i>S</i>
29	<i>(R)</i> - 2 (R = C(CH ₃) ₃)/ 9c	72	<i>R</i>
30	<i>(S)</i> - 2 (R = C(CH ₃) ₃)/ 9c	17	<i>R</i>

It might be argued that some of the hetero-combinations are not optimal because they happen to constitute the mismatched case regarding the absolute configuration of the components. These cases were not checked in the present study. However, in the case of hetero-combinations involving mixtures of oxazaphospholidines and the phosphonite (**2**) (R = C(CH₃)₃), we did in fact study such a potential

phenomenon by using the (*R*)- and (*S*)-form of the BINOL-derived P-ligand. Indeed, the hetero-combination (*R*)-**2** ($R = C(CH_3)_3$)/**9b** led to the highest enantioselectivity in the whole study (ee = 89% (*R*); Table 1, Entry 27), whereas the diastereomeric hetero-combination (*S*)-**2** ($R = C(CH_3)_3$)/**9b** turned out to be considerably less effective (ee = 52% (*S*); Table 1, Entry 28). This contrasts with the performance of pure (*R*)-**2** ($R = C(CH_3)_3$) leading to ee = 56% (*R*) (Table 1, Entry 7).

Finally, it was of interest to test the present oxazaphospholidines in combination with phosphites derived from chiral diols other than BINOL. For this purpose we prepared the C_2 -symmetric phosphites ((*R,R*)- and (*S,S*)-**13**) using the standard procedure as before. Yields of (*R,R*)- and (*S,S*)-**13** were >90%.



Not surprisingly, (*S,S*)-**13** (or the enantiomer) itself is not an effective ligand in the Rh-catalyzed hydrogenation of **10**, resulting in only 43% ee (*R*). In contrast, upon using ligand (**13**) in combination with the pseudo-ephedrine-derived oxazaphospholidine (**9a**) which itself results in ee = 0%, dramatic effects were observed. The hetero-combination **9a**/*(S,S)*-**13** constitutes the matched case leading to ee = 82% (*R*) which is superior to the diastereomeric hetero-combination **9a**/*(R,R)*-**13** (ee = 34% (*S*)).

In conclusion, we have demonstrated for the first time that the original concept of using mixtures of chiral monodentate P-ligands in asymmetric Rh-catalyzed olefin-hydrogenation is not restricted to BINOL-derived ligand systems. The actual enantioselectivities (up to 89% ee) are of little practical utility. However, the effects observed are substantial, which suggests that chiral monodentate P-ligands of the

type (6) and (9) as well as numerous other sorts of chiral monodentate P-ligands need to be studied in mixtures not only when performing olefin-hydrogenation, but also when studying other types of transition metal catalyzed asymmetric reactions. It must also be remembered that such a combinatorial approach not only leads to a dramatic increase in catalyst diversity as shown in Table 1, variation of the $L^a:L^b$ ratio is yet another easily controlled parameter which may generate superior catalyst profiles. Finally, a given "hit" in the hetero-combinatorial library may provide a lead on how to "design" an even better catalyst by joining the two components L^a and L^b covalently by an appropriate spacer with formation of a bidentate ligand. This option would lead back to the traditional concept of single catalysts having chelating bidentate ligands.

ACKNOWLEDGEMENT

Support by the Fonds der Chemischen Industrie is gratefully acknowledged. M.S. thanks the Alexander von Humboldt Foundation for a fellowship.

REFERENCES

1. M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889; M. T. Reetz, G. Mehler, and A. Meiswinkel, patent application DE-A 10027505.2, June 6, 2000 (*Chem. Abstr.*, 2002, **136**, 20159).
2. M. T. Reetz and T. Sell, *Tetrahedron Lett.*, 2000, **41**, 6333; C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, and P. G. Pringle, *Chem. Commun. (Cambridge, U. K.)*, 2000, 961.
3. M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 11539.
4. W. S. Knowles, *Angew. Chem., Int. Ed.*, 2002, **41**, 1998; R. Noyori, *Angew. Chem., Int. Ed.*, 2002, **41**, 2008; E. N. Jacobsen, A. Pfaltz, and H. Yamamoto (Eds.), 'Comprehensive Asymmetric Catalysis', Vol. I-III, Springer, Berlin, 1999.
5. M. T. Reetz, A. Meiswinkel, G. Mehler, K. Angermund, M. Graf, W. Thiel, R. Mynott, and D. G. Blackmond, *J. Am. Chem. Soc.*, 2005, **127**, 10305.
6. See for example: M. T. Reetz, G. Mehler, A. Meiswinkel, and T. Sell, *Tetrahedron Lett.*, 2002, **43**, 7941; M. T. Reetz, *Russ. J. Org. Chem.*, 2003, **39**, 392; H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, and B. L. Feringa, *J. Org. Chem.*, 2005, **70**, 943; A. J. Minnaard, M. van den Berg, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, and

- B. L. Feringa, *Chim. Oggi*, 2001, **19**, 12; M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, and J. G. de Vries, *Adv. Synth. Catal.*, 2003, **345**, 308; Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, and Q.-L. Zhou, *Chem. Commun. (Cambridge, U.K.)*, 2002, 480; A. Bayer, P. Murszat, U. Thewalt, and B. Rieger, *Eur. J. Inorg. Chem.*, 2003, 2614; P. Hannen, H.-C. Militzer, E. M. Vogl, and F. A. Rampf, *Chem. Commun. (Cambridge, U.K.)*, 2003, 2210; Z. Hua, V. C. Vassar, and I. Ojima, *Org. Lett.*, 2003, **5**, 3831.
7. M. T. Reetz, A. Meiswinkel, T. Sell, and G. Mehler, patent application DE-A 10247633.0, October 11, 2002 (*Chem. Abstr.*, 2004, **140**, 381359); M. T. Reetz, T. Sell, A. Meiswinkel, and G. Mehler, *Angew. Chem., Int. Ed.*, 2003, **42**, 790; M. T. Reetz and G. Mehler, *Tetrahedron Lett.*, 2003, **44**, 4593; M. T. Reetz, J.-A. Ma, and R. Goddard, *Angew. Chem., Int. Ed.*, 2005, **44**, 412; M. T. Reetz, *Chim. Oggi*, 2003, **21(10/11)**, 5; M. T. Reetz and X. Li, *Tetrahedron*, 2004, **60**, 9709; M. T. Reetz, G. Mehler, A. Meiswinkel, and T. Sell, *Tetrahedron: Asymmetry*, 2004, **15**, 2165, 3483.
 8. D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, and B. L. Feringa, *Org. Biomol. Chem.*, 2003, **1**, 1087.
 9. M. T. Reetz and X. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 2962.
 10. M. T. Reetz and H. Guo, *Beilstein J. Org. Chem.*, 2005, **1**:3.
 11. D. Bernard and R. Burgada, *Phosphorus*, 1974, **3**, 187; see also J. M. Brunel and B. Faure, *Tetrahedron: Asymmetry*, 1995, **6**, 2353; M. Amedjkouh and P. Ahlberg, *Tetrahedron: Asymmetry*, 2002, **13**, 2229; N. Oka, T. Wada, and K. Saigo, *J. Am. Chem. Soc.*, 2003, **125**, 8307; M. D. K. Boele, P. C. J. Kamer, M. Lutz, A. L. Spek, J. G. de Vries, P. W. N. M. van Leeuwen, and G. P. F. van Strijdonck, *Chem.-Eur. J.*, 2004, **10**, 6232; K. N. Gavrilov, V. N. Tsarev, A. A. Shiryaev, O. G. Bondarev, S. E. Lyubimov, E. B. Benetsky, A. A. Korlyukov, M. Y. Antipin, V. A. Davankov, and H.-J. Gais, *Eur. J. Inorg. Chem.*, 2004, 629; C. Bauduin, D. Moulin, E. B. Kaloun, C. Darcel, and S. Jugé, *J. Org. Chem.*, 2003, **68**, 4293.
 12. A. Alexakis, S. Mutti, and J. F. Normant, *J. Am. Chem. Soc.*, 1991, **113**, 6332; A. Alexakis, J. Frutos, and P. Mangeney, *Tetrahedron: Asymmetry*, 1993, **4**, 2427.