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Mixtures of chiral and achiral monodentate ligands in asymmetric Rh-catalyzed olefin hydrogenation: reversal of enantioselectivity

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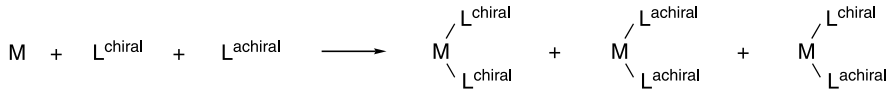
Abstract—The recently described method of combinatorial asymmetric transition metal catalysis based on the use of mixtures of chiral monodentate P-ligands has been extended to include mixtures of chiral and achiral monodentate P-ligands, reversal of enantioselectivity in Rh-catalyzed olefin hydrogenation being possible in appropriate cases.

Recently we described a new concept in the area of combinatorial enantioselective transition metal catalysis which is based on the use of mixtures of chiral monodentate ligands.[1] It is relevant whenever in the transition state of the 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 with one another, namely the two homocombinations ML^aL^a and ML^bL^b as well as the heterocombination ML^aL^b. If ML^aL^b is more reactive and stereoselective than the two homocombinations, then enantioselectivity will be enhanced. Upon screening only a small number of mixtures of chiral BINOL-based monophosphonites[2] and monophosphites[3] in Rh-catalyzed asymmetric olefin hydrogenation, we discovered that certain heterocombinations are in fact highly enantioselective, much more so than either of the relevant homocombinations alone.[1,4]

We now demonstrate that appropriate mixtures of chiral and *achiral* monodentate P-ligands lead to a reversal of the direction of enantioselectivity of Rh-catalyzed olefin hydrogenation. In such systems three different catalysts are again relevant. If the heterocombination is most reactive, it will largely determine the catalytic profile of the system (Scheme 1).

As a model reaction we chose the Rh-catalyzed hydrogenation of the acetamidoacrylate **1**, compounds **3–5** and **6–14** serving as the chiral and achiral P-ligands, respectively. The Rh:P-ligand (total) ratio was adjusted to 1:2, and the ratio of chiral to achiral P-ligand was kept constant at 1:1.



Scheme 1.

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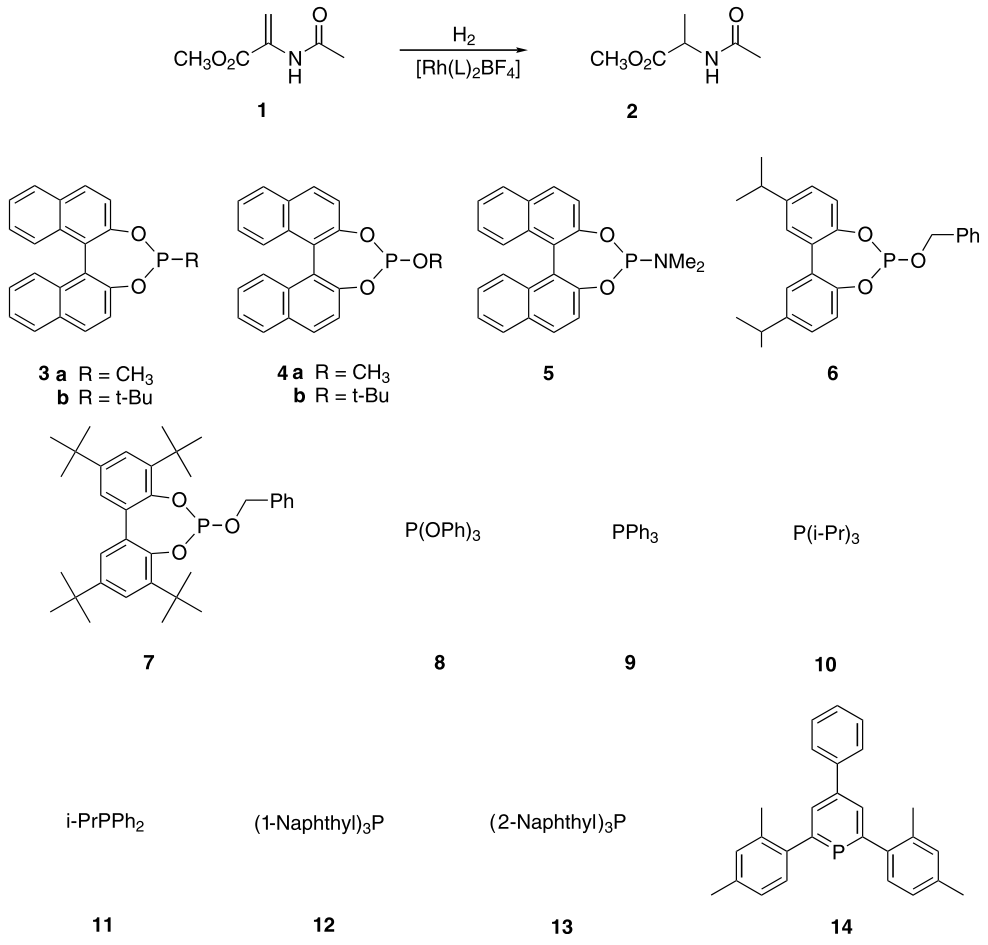

Table 1 reveals some remarkable trends. Large differences in rate are involved as reflected by the different conversions after 24 h of reaction time. In the majority of cases the use of an achiral ligand in combination with a chiral ligand leads to a decrease in enantioselectivity, as might be expected. This also pertains to such ligands as **6** which actually exist as fluxional enantiomeric conformers.[5] In combination with **3b**, for example (Table 1, entry 24), a racemic product is observed. It can be speculated that in the heterocombination two catalysts are involved, namely Rh-complexes of (*R*)-**3b**/(*R*)-**6** and (*R*)-**3b**/(*S*)-**6** which do not lead to improvements, especially in view of the fact that the homocombination **6**/**6** is also involved.

Intriguingly, *reversal* of enantioselectivity is observed in a number of cases (entries 18, 22, 23, 27, 31, 32, 34, 36, 40, 45, 47, and 49). A notable example is the effect of the phosphinine ligand **14**[6] in combination with phosphonite **3a** leading to ee = 58.6% (*R*) in contrast to **3a**/**3a** (ee = 93.0% (*S*)) (entry 1 versus 23). Importantly, when used alone **14** constitutes a catalyst system which is essentially inactive under the reaction conditions (entry 14). Other achiral mono-P-ligands which lead to the reversal of enantioselectivity are certain triarylphosphines as in **4b**/**9** (ee = 45.4% (*R*), entry 45).

The fact that subtle effects must be involved is illustrated by the contrasting behavior of tris(1-naphthyl)- and tris(2-naphthyl)phosphines, **12** and **13**, respectively, the former not exerting any effect (entry 4 versus 48) and the latter causing reversal of enantioselectivity (entry 49). Moreover, the effect is not observed when using Feringa's amidite **5**.[7] However, the present investigation is preliminary, and many more achiral P-ligands and other substrates[8] need to be studied.

In summary, we have extended our original concept of using mixtures of different chiral monodentate ligands[1] to include combinations composed of chiral and achiral monodentate P-compounds. Although further optimization as well as studies directed towards uncovering the reason(s) for reversal of enantioselectivity require further work, the results show that a new and potentially useful concept in combinatorial asymmetric catalysis has emerged.[9–11] Other types of reactions such as hydroformylation should be amenable to this type of catalyst optimization.

Table 1. Rh-catalyzed hydrogenation of **1**[a]

Entry	Ligands	Conversion [%]	ee [%] (config.)
Homocombinations			
1	**3a**/**3a**	100	92.0 (*S*)
2	**3b**/**3b**	100	93.0 (*S*)
3	**4a**/**4a**	100	93.0 (*S*)
4	**4b**/**4b**	100	95.4 (*S*)
5	**5**/**5**	100	96.8 (*S*)
6	**6**/**6**	100	–
7	**7**/**7**	30	–
8	**8**/**8**	100	–
9	**9**/**9**	100	–
10	**10**/**10**	1	–
11	**11**/**11**	99	–
12	**12**/**12**	<1	–
13	**13**/**13**	99	–
14	**14**/**14**	<1	–
Heterocombinations			
15	**3a**/**6**	100	2.8 (*S*)
16	**3a**/**7**	<1	nd
17	**3a**/**8**	100	19.0 (*S*)
18	**3a**/**9**	**100**	**19.6 (*R*)**
19	**3a**/**10**	44	76.0 (*S*)
20	**3a**/**11**	62	41.2 (*S*)
21	**3a**/**12**	82	70.2 (*S*)
22	**3a**/**13**	**100**	**17.5 (*R*)**
23	**3a**/**14**	**20**	**58.6 (*R*)**
24	**3b**/**6**	100	Racemic
25	**3b**/**7**	1	nd
26	**3b**/**8**	100	1.2 (*S*)
27	**3b**/**9**	**76**	**3.2 (*R*)**
28	**3b**/**10**	69	89.2 (*S*)
29	**3b**/**11**	53	32.0 (*S*)
30	**3b**/**12**	24	77.0 (*S*)
31	**3b**/**13**	**100**	**26.2 (*R*)**
32	**3b**/**14**	**9**	**52.6 (*R*)**
33	**4a**/**6**	100	43.2 (*S*)
34	**4a**/**7**	**61**	**6.2 (*R*)**
35	**4a**/**8**	100	34.8 (*S*)
36	**4a**/**9**	**100**	**10.0 (*R*)**
37	**4a**/**10**	100	62.4 (*S*)
38	**4a**/**11**	100	21.0 (*S*)
39	**4a**/**12**	100	42.2 (*S*)
40	**4a**/**13**	**100**	**15.6 (*R*)**
41	**4a**/**14**	97	54.2 (*S*)
42	**4b**/**6**	100	90.0 (*S*)
43	**4b**/**7**	99	63.4 (*S*)
44	**4b**/**8**	100	82.4 (*S*)
45	**4b**/**9**	**100**	**45.4 (*R*)**
46	**4b**/**10**	100	94.2 (*S*)
47	**4b**/**11**	**99**	**21.0 (*R*)**
48	**4b**/**12**	100	95.0 (*S*)
49	**4b**/**13**	**100**	**34.8 (*R*)**
50	**4b**/**14**	100	84.2 (*S*)
51	**5**/**6**	100	84.4 (*S*)
52	**5**/**7**	99	93.2 (*S*)
53	**5**/**8**	100	80.8 (*S*)
54	**5**/**9**	100	64.2 (*S*)
55	**5**/**10**	99	96.8 (*S*)
56	**5**/**11**	99	76.0 (*S*)
57	**5**/**12**	99	97.0 (*S*)
58	**5**/**13**	100	2.8 (*S*)
59	**5**/**14**	100	82.4 (*S*)

[a] (*R*)-BINOL was used in the synthesis of all chiral P-ligands. In all cases the mixture of ligands was treated with $[Rh(cod)_2]BF_4$ in CH_2Cl_2 and hydrogenation was performed at room temperature and 1.3 bar H_2 for 24 h, (Rh:substrate = 1:1000), as previously described using chiral ligands alone.[1]

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9. Our approaches are different from the principle of self-organization of catalysts as for example in the case of Ti-catalysts formed from two different chiral diols used in carbonyl ene-reactions, or the principle of selective activation of racemic catalysts, both described by the pioneering work of Mikami. See: (a) Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem.* **1997**, *109*, 2936–2939; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2768–2771; (b) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613–615.
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