Asymmetric Catalysis

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Nonlinear Effects in Rh-Catalyzed Asymmetric Olefin Hydrogenation Using Mixtures of Chiral Monodentate P Ligands**

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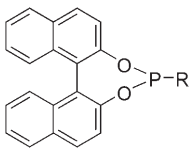
Several years ago three groups reported that certain binaphthol (BINOL)-derived monodentate phosphorus compounds are excellent chiral ligands in Rh-catalyzed olefin hydrogenation, namely, phosphites **1**,[1] phosphonites **1** (R = alkyl, aryl)[2] and phosphoramidites **1**.[3] This came as a surprise



1a R = CH_3
b R = $C(CH_3)_3$

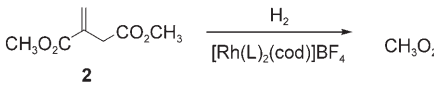
because it had been accepted for decades that chelating bidentate diphosphines are necessary for high enantioselectivity.[4] A recent mechanistic study by our group focused on the phosphites and showed that two monodentate P ligands are bonded to rhodium in the transition state of hydrogenation, which is in accord with NMR data, kinetic investigations, and observations of conventional positive nonlinear effects (NLEs).[5] Such detailed mechanistic investigations have not yet been completed for the catalyst systems involving the analogous phosphonites[2] or phosphoramidites,[3a] but preliminary results point to a similar mechanism.[3b,6]

In 2002, we proposed a new tool in combinatorial asymmetric transition-metal-catalyzed reactions:[7] The use of mixtures of two different chiral monodentate ligands L^a and L^b that led to the presence of three different catalysts in a given reaction mixture, two homo-combinations ML^aL^a and ML^bL^b and one hetero-combination ML^aL^b. If the hetero-combination is more reactive and more enantioselective than either of the homo-combinations, enhanced enantioselectivity will result. We demonstrated this effect in Rh-catalyzed olefin hydrogenation.[7] Thus, the method allows for high catalyst diversity with the possibility of discovering superior catalysts, but without the need to synthesize new ligands. Following our initial report, Feringa and co-workers reported related results using the analogous monodentate phosphoramidites **1**.[8]

Herein, we address for the first time the question of possible NLEs when using such mixtures. The situation is considerably more complex than in the case of classical systems that display conventional NLEs,[9] which means that the usual mathematical treatment does not apply. When varying the enantiomeric purity of L^a from 100 to 0% *ee* (racemate) while keeping the partner ligand pure, for example, L^b_S, six different catalytic reactions need to be considered [Eq. (1)]:

$ML^a_SL^a_S \xrightarrow{k_1}$
$ML^a_RL^a_R \xrightarrow{k'_1}$
$ML^a_RL^a_S \xrightarrow{k_2}$
$\Big|$
$ML^b_SL^b_S \xrightarrow{k_3}$
$ML^a_RL^b_S \xrightarrow{k_4}$
$ML^a_SL^b_S \xrightarrow{k_5}$ (1)

The stereochemical outcome of a given hydrogenation reaction depends upon the inherent enantioselectivity of each of these processes, but also on the relative amounts of catalysts present in the mixture and the six rate constants, which can be expected to be different (except for $k_1 = k'_1$). Because we are unable to separate the homo- from the hetero-complexes and to use the latter without ligand exchange, only k_1 (or k'_1) and k_3 can be measured directly in separate experiments. In the other cases, the rate of product formation results from the combined action of the relevant rate processes. As a model reaction, we chose the Rh-catalyzed hydrogenation of itaconic acid dimethyl ester (**2**), with compounds **1a** and **1b** serving as the two P ligands [Eq. (2)]. In all cases, $[Rh(cod)_2]BF_4$ (cod = cyclooctadiene) was treated with two equivalents of **1** to form $[Rh(L)_2(cod)]$ (L = ligand) complexes as the precatalysts.



CH_3O_2C, CO_2CH_3 $\xrightarrow[[Rh(L)_2(cod)]BF_4]{H_2}$ CH_3O_2C, CO_2CH_3 (2)

2 **3**

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When utilizing the enantiopure homo-combinations [Rh]/(*S*)-**1a** and [Rh]/(*S*)-**1b** in separate experiments, product **3** was shown to have the *S* configuration with 90 and 57% *ee*, respectively.[7b] Upon using a 1:1 mixture of (*S*)-**1a** and (*S*)-**1b**, the *ee* value increased to 96% (*S*).[7b] In the present study, we first varied the enantiopurity of (*S*)-**1a** stepwise from 100 to 0% *ee*, while maintaining 100% *ee* of (*S*)-**1b**. The result of these experiments show that the *ee* value of **3** decreases only slightly from 96 to 92% *ee* (S enantiomer) as the racemic state is approached (Figure 1, black line). Thus, one of the components can be a racemate, and the result from a practical point of view is still acceptable.

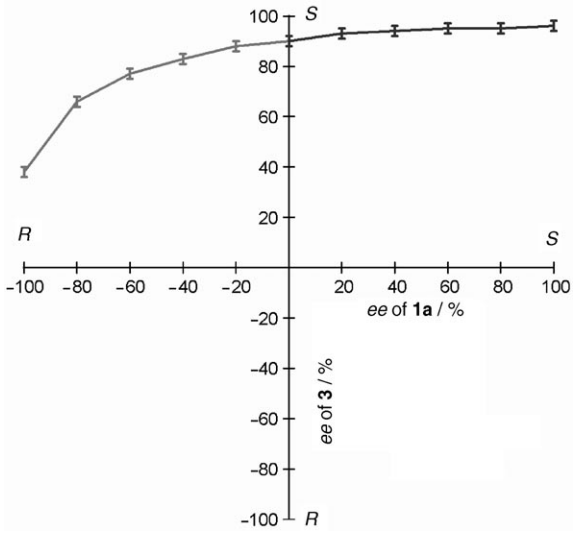


Figure 1. NLE in the Rh-catalyzed hydrogenation of **2** using enantiopure (*S*)-**1b** and **1a** of varying enantiopurity.

It was also of interest to scan the other region of stereochemical space by once again maintaining 100% *S* purity of **1b**, but working in a regime in which the *R* configuration of **1a** dominates, namely, using (*R*)-**1a** at different levels of enantiopurity. The experimental result is also shown in Figure 1 (gray curve). In the extreme case of enantiomerically pure (*R*)-**1a** and (*S*)-**1b** in a mixture, the configuration of **3** remains as *S*, but the *ee* value decreases to 39%. This behavior indicates that the influence of the *tert*-butyl component **1b** dominates the stereochemical outcome.

We then performed the analogous series of experiments in which the enantiopurity of (*S*)-**1a** was maintained at 100% and the *ee* value of **1b** was varied (Figure 2). The results point to a similar behavior when varying the enantiopurity of (*S*)-**1b** from 100 to 0% *ee* (Figure 2, black line). When working in the regime in which more (*R*)- than (*S*)-**1b** is present (gray curve), the quantitative results are somewhat different from those in Figure 1. Nevertheless, the influence of the *tert*-butyl component **1b** dominates again. In this case, the effect finally leads to inversion of configuration, with (*R*)-**3** being formed preferentially with 43% *ee*. This value does not quite correspond to the expected 39% *ee* observed previously in the case of (*R*)-**1a**/(*S*)-**1b**, but may be within experimental error (±2%).

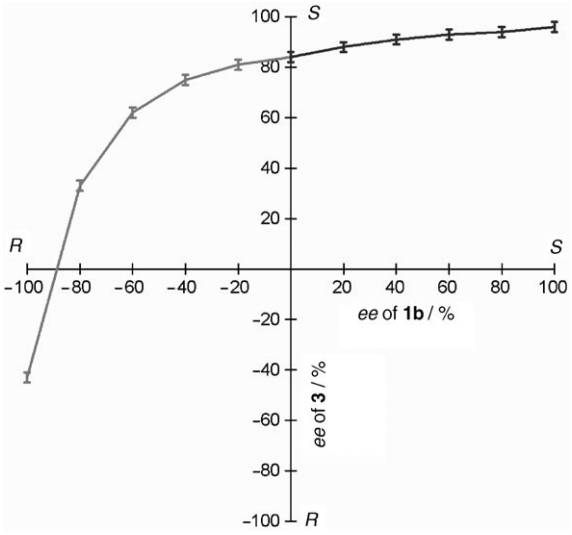


Figure 2. NLE in the Rh-catalyzed hydrogenation of **2** using enantiopure (*S*)-**1a** and **1b** of varying enantiopurity.

To gain some mechanistic insight, we first performed NMR experiments. Upon treating $[Rh(cod)_2]BF_4$ with a 1:1 mixture of (*S*)-**1a** and (*S*)-**1b**, three species were identified by NMR spectroscopy: [Rh{(*S*)-**1a**}$_2$(cod)], [Rh{(*S*)-**1b**}$_2$(cod)], and [Rh{(*S*)-**1a**}{(*S*)-**1b**}(cod)] catalysts in a ratio of 1:1:3, which is not the statistical but rather the thermodynamic value.[6,7b] Of course, once the precatalysts convert into the active species, the ratio may change (which we could not measure). When performing the experiment with a 1:1 mixture of pure (*S*)-**1a** and *rac*-**1b**, a complex NMR spectrum results which displays the same peaks as before in addition to new signals that correspond to diastereomeric complexes. Extensive work is required before a final NMR analysis can be presented.

Kinetic studies of asymmetric catalytic processes are extremely useful in a mechanistic sense and therefore in designing improved catalyst systems.[10] In the present case, the relative rates of hydrogenation of **2** were first measured using the conventional homo-combinations [Rh]/(*S*)-**1a** and [Rh]/(*S*)-**1b**. As shown in Figure 3, the bulky *tert*-butyl ligand (*S*)-**1b** leads to the lowest catalyst activity followed by (*S*)-**1a**. The synthetically useful combination that arises from a mixture of (*S*)-**1a** and (*S*)-**1b** results in the highest rate (Figure 3, red curve), which of course is the result of three reactions. As required by the mixture concept,[7] the two homo-combinations are not only less enantioselective, they are also less active, which is another way of stating that the hetero-combination displays enhanced enantioselectivity and an increased rate. The pure mixed Rh complex of (*S*)-**1a**/(*S*)-**1b**, if it were possible to prepare as the sole species in the reaction, would be even more enantioselective and reactive than the mixture of the three species (the total amount of Rh being constant).

In previous synthetic work regarding the use of mixtures,[6,7] a trend was observed (with exceptions): Hetero-combinations show enhanced enantioselectivity whenever one component is "small" and the other is "large", as in the

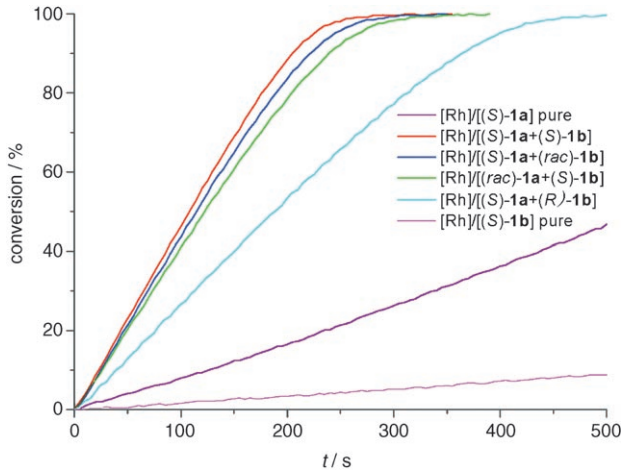


Figure 3. Relative rates of hydrogenation of **2** (Rh/**2** = 1:5000, Rh/**1** = 1:2, **1a**/**1b** = 1:1, 1.3 bar H_2, room temperature, CH_2Cl_2 as the solvent).

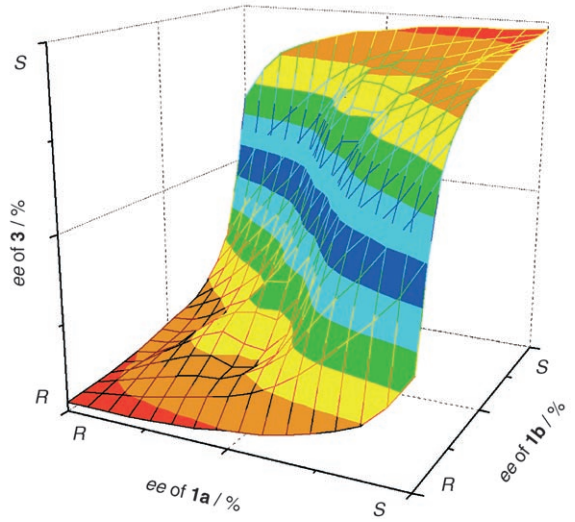
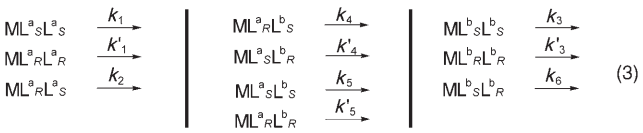


Figure 4. NLE in the Rh-catalyzed hydrogenation of **2** using mixtures of **1a** and **1b**, each with varying degrees of enantiopurity.

present case.[7] Rate enhancement because of this structural feature is observed even when the absolute configurations of the two components are opposite (mismatched), as in the case of (*S*)-**1a**/(*R*)-**1b** (Figure 3, blue curve). Of course, this effect is less pronounced relative to the use of the matched case (*S*)-**1a**/(*S*)-**1b**. The fact that the systems using the racemate of one of the components are more reactive than (*S*)-**1a**/(*R*)-**1b** is now easily understood.

Although the rates of the six individual processes that occur in a system comprising *rac*-**1a**/(*S*)-**1b** (or (*S*)-**1a**/*rac*-**1b**) cannot be measured separately, the results of the kinetic study are in line with the following conclusion: The combination (*S*)-**1a**/(*S*)-**1b** constitutes the most reactive system, all others such as diastereomeric (*S*)-**1a**/(*R*)-**1b** are less able to compete effectively. If the amount of the diastereomeric ligand combination (*S*)-**1a**/(*R*)-**1b** increases in the mixture by using **1b** enriched with the *R* enantiomer, the reaction catalyzed by the respective Rh complex begins to compete and in the extreme case dominates, thus resulting in markedly lower or even opposite enantioselectivity.

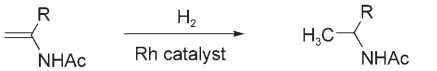
The present results are not only of mechanistic value; they also point to a practical feature, namely, the fact that complete enantiopurity of the ligands is not essential. Indeed, one of the components can even be racemic, with the process still leading to > 92 % *ee*. Although of only partial practical value, we were interested from a theoretical viewpoint to see how the system performs when varying the enantiopurity of both components simultaneously. This means that a total of ten reactions needs to be considered [Eq. (3)].



(3)

The graphic representation of the data of such a systematic search requires a three-dimensional format (Figure 4). It can be seen that the *ee* values vary from 96 % *ee* (*S*) to 96 % *ee* (*R*) in the extremes and that an enantioselectivity of > 90 % *ee* can be achieved even when both components have enantiopurities of only 80 % *ee* and even less (Figure 4, red areas).

The basic phenomenon described above for itaconic acid diester (**2**) was also observed in the case of two other substrates **4a** and **4b** [Eq. (4)], although only a small portion of the data points were collected in these cases (Table 1). For example, in the case of substrate **4b**, racemic **1a** can be used with enantiopure **1b** and the *ee* value is still a respectable 93 % (Table 1, entry 6).



(4)

4a R = Ph
b R = CO_2CH_3

5a R = Ph
b R = CO_2CH_3

Table 1: Asymmetric hydrogenation of olefins **4a**, **b** using ligands **1a**, **b**.

Entry	Ligand	*ee* of **5a** [%][a] (configuration)	*ee* of **5b** [%][b] (configuration)
1	(*S*)-**1a**	76 (*R*)	92 (*R*)
2	(*S*)-**1b**	13 (*R*)	93 (*R*)
3	(*S*)-**1a**/(*S*)-**1b**	95 (*R*)	98 (*R*)
4	(*S*)-**1a**/(*R*)-**1b**	49 (*R*)	82 (*S*)
5	(*S*)-**1a**/*rac*-**1b**	83 (*R*)	62 (*R*)
6	*rac*-**1a**/(*S*)-**1b**	70 (*R*)	93 (*R*)

[a] Conditions: Rh/**4a** = 1:100, Rh/**1** = 1:2, **1a**/**1b** = 1:1, 1.3 bar H_2, room temperature, CH_2Cl_2 as the solvent. [b] Conditions: Rh/**4b** = 1:200, Rh/**1** = 1:2, **1a**/**1b** = 1:1, 1.3 bar H_2, room temperature, CH_2Cl_2 as the solvent.

In summary, we have addressed for the first time the question of nonlinear effects in Rh-catalyzed olefin hydrogenation using a mixture of two different chiral monodentate

P ligands. Apart from the theoretical interest, the results are of practical significance because the ligands do not need to be 100% enantiopure. Indeed, in some cases one of the ligand components can be racemic[11] while still leading to >92% *ee*. It remains to be seen if the molecular basis of the observed kinetic and stereochemical behavior can be uncovered by theoretical studies.

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[11] a) This observation bears some resemblance to our previous work involving a diphosphite composed of a chiral-backbone diol and configurationally fluxional atropisomeric diphenol-derived P heterocycles that lead to three diastereomeric ligand/metal complexes with different kinetic profiles (D. G. Blackmond, T. Rosner, T. Neugebauer, M. T. Reetz, *Angew. Chem.* **1999**, *111*, 2333 – 2335; *Angew. Chem. Int. Ed.* **1999**, *38*, 2196 – 2199; M. T. Reetz, T. Neugebauer, *Angew. Chem.* **1999**, *111*, 134 – 137; *Angew. Chem. Int. Ed.* **1999**, *38*, 179 – 181). Diphenol itself is achiral, but atropisomerism is created in the synthesis of the P heterocycle. This basic phenomenon was reported indepently by Noyori, Mikami, and co-workers in a study in which they describe a Ru complex composed of a chiral diamine and an achiral diphenyl-derived diphosphine; upon complexation, the latter turns into a configurationally fluxional atropisomeric system that leads to two diastereomeric complexes with different reaction rates and enantioselectivity (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). Since these papers appeared, many further examples have been reported, including the extension by Balsells and Walsh who showed that the enantioselectivity of the addition of Et_2Zn to aldehydes catalyzed by a chiral titanium alkoxide can be increased by the addition of "achiral" *meso*-1,2-diamine, which is really a pair of fluxional enantiomers (J. B. Balsells, P. J. Walsh, *J. Am. Chem. Soc.* **2000**, *122*, 1802 – 1803); see also: b) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369 – 3400; c) J. W. Faller, A. R. Lavoie, J. Parr, *Chem. Rev.* **2003**, *103*, 3345 – 3367; d) P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297 – 3344.

