CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900722

Matching and Mismatching Effects of Hybrid Chiral Biaxial Bisphosphine Ligands in Enantioselective Hydrogenation of Ketoesters

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Catalytic asymmetric synthesis is a significant component in modern organic chemistry. It has widely been used to produce a number of optically active compounds, from agrochemicals, to pharmaceuticals, to flavors, and fragrances as well as functional materials.[1] One of the most important methods to increase the stereoselectivity of reactions is multiple stereoselectivity (multiple stereodifferentiation, multiple asymmetric induction), when the stereochemical process proceeds under the control of more than one chiral auxiliary.[2] During the last two decades, these double stereoselective strategies have been successfully applied in a variety of reactions, such as Sharpless dihydroxylation, Michael additions, addition to allyl metals, the Reformatsky reaction, the Mukaiyama reaction, photochemical reactions, alkylation, cycloadditions and the synthesis of heteroatom compounds.[2] In contrast, catalytic systems with multiple stereogenic axial elements in chiral ligands are much less explored in transition metal catalyzed asymmetric hydrogenations. The multiple chiral elements in ligands may be situated favorably ("matched") or unfavorably ("mismatched") for stereocontrol when the catalyst interacts with a prochiral substrate. Ultimately, the matched cases may lead to dramatically higher asymmetric induction in the products, whereas the mismatched cases often result in significantly lower selectivity in hydrogenation reactions.[3] Syntheses of these molecules have facilitated a preliminary study of matching and mismatching effects, relating backbone chirality and phosphorus-based chirality with the performance of these ligands in asymmetric catalysis. The most notable achievements of catalytic systems with double asymmetric induction exist in hydrogenation chemistry, focusing primarily on rhodium or ruthenium with bidentate phosphine ligands,[4] in particular, modifications of DIOP,[5] BINAP,[6] dialkylphospholane bis(phospholane) ligands,[7] and many others.[8] As reported, configurational changes in ligands brought by introducing additional chirality are generally unpredictable. There are no reliable predictive models to explain the structural subtleties of catalysts with multiple chiral elements that lead to dramatic changes in stereoselectivities.[9]

As part of our continued interest in the synthesis and use of new chiral bisphosphine ligands in asymmetric catalysis, we have developed a novel class of conformationally rigid C_n-TunePhos ($n=1$–6) by introducing a bridge with variable length to link the chiral atropisometic biaryl groups.[10] This family of TunePhos ligands has proven to be highly efficient in a variety of asymmetric reactions.[11] We envision that changes of relatively flexible alkyl linker in the C_n-TunePhos family with an aromatic group or a bulky chiral bridge may enhance the rigidity and steric hindrance of the structure. Consequently, unique steric or electronic effects and good chiral discrimination could be expected. Herein we report a convenient strategy for the synthesis of a pair of diastereoisomeric forms of ligands **1**, **2** and an analogous ligand **3** in order to assess the effects of stereochemical matching and mismatching interactions upon the structural and catalytic properties of the corresponding ruthenium complexes. Their applications in highly efficient Ru-catalyzed asymmetric hydrogenations for the enantioselective synthesis of α- and β-hydroxy acid derivatives were also explored.

This new series of bisphosphine ligands were prepare as shown in Scheme 1: (*R* or *S*)-2,2′-dichloromethyl-1,1′-binaphthyl (**8**) was synthesized in four steps with high yields from readily accessible starting materials as developed in our group.[12] (*R* or *S*)-2,2′-Bistriflate-1,1′-binaphthyl (**5**) was obtained from (*R* or *S*)-binaphthol with excess trifluoromethane sulfonic anhydride and pyridine in CH_2Cl_2. Kumada-

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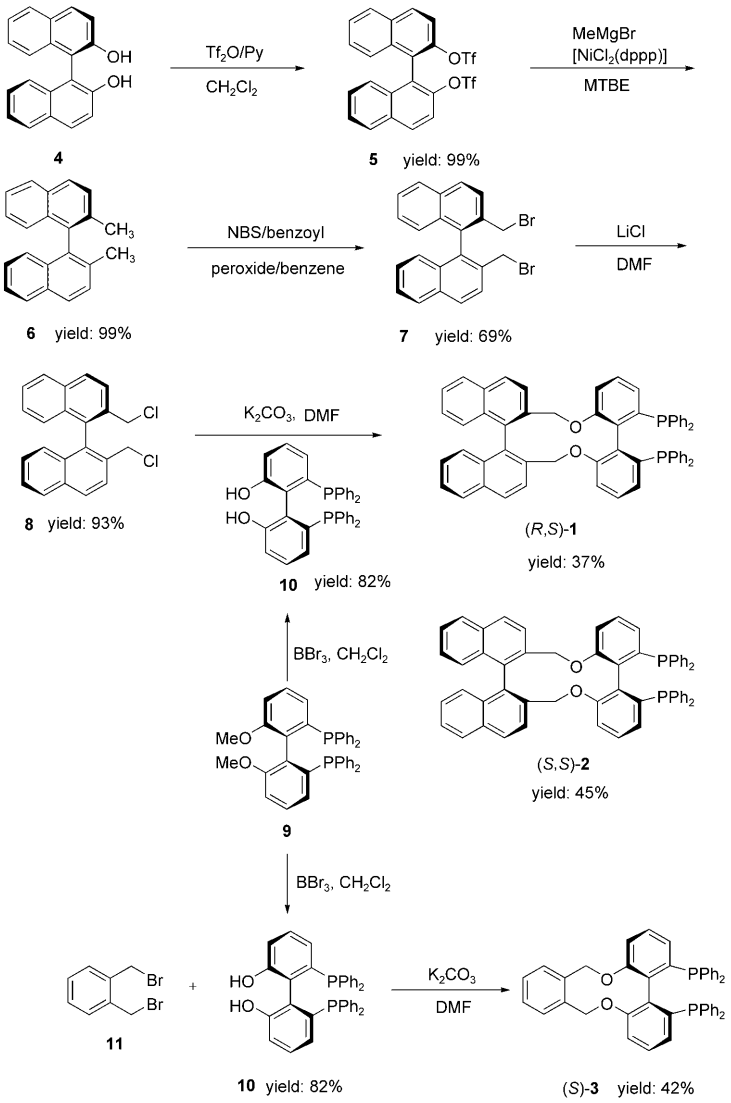
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900722: Experimental procedures and compound characterization data.

type coupling of bistriflate **5** with methylmagnesium bromide gave (*R* or *S*)-2,2′-dimethyl-1,1′-binaphthyl (**6**) almost in a quantitative yield. (*R* or *S*)-2,2′-Dibromomethyl-1,1′-binaphthyl (**7**) was prepared by bromination of **6** with NBS. A simple anion exchange of (*R* or *S*)-2,2′-dibromomethyl-1,1′-binaphthyl (**7**) with LiCl afforded (*R* or *S*)-2,2′-dichloromethyl-1,1′-binaphthyl **8** in 93 % yield. HO-BIPHEP **10** can be prepared after demethylation of enantiomerically pure (*S*)-MeO-BIPHEP.[10] Reaction of **10** with the dichloride compound **8** in the presence of excess anhydrous K_2CO_3 in DMF formed new ligands (*R*,*S*)-**1** or (*S*,*S*)-**2** in moderate yields. Using a similar procedure, we also made the corresponding air-stable chiral monoaxial ligand **3** from the commercially available staring material α,α′-dibromo-*o*-xylene in one step. A key point in the last step of the synthesis was to add 2,2′-dichloromethyl-1,1′-binaphthyl (**8**) dropwise with a syringe pump in 36 h, which dramatically suppressed the intermolecular byproducts. This efficient synthetic route allows us to make the desired hybrid ligands in large scales.



Scheme 1. Synthesis of hybrid chrial biaxial diphosphine ligands.

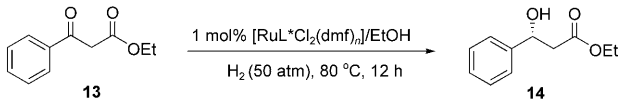
With the availability of diastereomeric bisphosphine ligands **1**, **2** and their analogous ligand **3**, several interesting questions were raised, as also mentioned in Burk's report.[7] For instance, "…could the two diastereomers afford comparative results in catalysis? would significant matching and mismatching effects be associated with the reactivity and selectivity of catalysts bearing the diastereomeric ligands? would the most reactive diastereomeric catalyst also correspond to the most selective catalyst, or would these two properties be independent?…"[7] To address these questions, we have explored these ligands in asymmetric hydrogenation of ketoesters.

Catalysts $[RuL^*Cl_2(dmf)_n]$ **12a–c** (where L* is the corresponding chiral ligand (*R*,*S*)-**1**, (*S*,*S*)-**2** and (*S*)-**3**) were prepared as reddish brown solid from $[RuCl_2(benzene)_2]_2$ and the hybrid ligands in DMF at 100 °C for 30 min.[13] The complexes obtained were used directly in the catalytic reactions.

To compare the catalytic efficiency and selectivity of the two diastereomeric catalyst systems bearing ligands **1** and **2**, we first examined asymmetric hydrogenation of standard β-ketoester substrate **13**, which led to useful pharmaceutical intermediate, (*R*)-3-hydroxyl-3-phenyl propionate **14** (Table 1). Under optimized conditions, the reaction was performed in ethanol at 80 °C under 50 atm hydrogen pressure. All three catalysts were found to be effective for this hydrogenation, giving complete conversion over 12 h with 1 mol % catalyst loading. The enantioselectivities achieved in these reactions were shown in Table 1. Relatively poor enantioselectivity of 78 % *ee* was obtained with catalyst from ligand **1**. The catalyst containing ligand (*S*,*S*)-**2** was found to afford the product **14** with higher enantioselectivity (Table 1, entry 2, 89 % *ee*) under the same reaction conditions, suggesting that this ligand represents the desired matched combination of stereochemical elements. Interestingly, the analogous catalyst bearing the parent BIPHEP backbone with only one chiral axial ligand (*S*)-**3** performed moderately in this reaction (Table 1, entry 3, 83 % *ee*). Another important finding was that in each case *R* enantiomer of product was formed, regardless of the overall backbone stereochemistry. Each of the ligands **1**, **2**, and **3** contains BIPHEP moieties with *S* absolute configuration at the axis. It may be deduced that the chirality of BIPHEP moiety containing diphenyl phosphines influences the absolute stereochemistry observed in hydrogenations when using ligands **1**–**3**. In other words, the chirality of BIPHEP backbone overrides the other bias imposed by the binaphthyl skeleton chirality in these ligands. However, undoubtedly, the binaphthyl linkers in the ligands not only restricted the free rotation of the BIPHEP backbone affording a conformational rigid structure, but also provided a unique chiral environment in the catalytic hydrogenations.

Optically active α-hydroxy acids, β-hydoxy acids and their derivatives represent an important class of building blocks for the synthesis of natural products and biologically active molecules, such as angiotensin converting enzyme inhibitors (ACE): Benazepril, Delapril hydrochloride, and Clopidogre bisulfate.[14]

Table 1. Hydrogenations of β-ketoester with hybrid ligands.

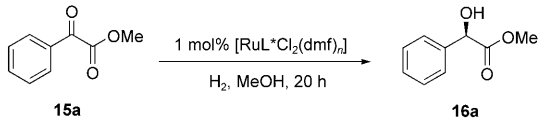


Entry	L*	Conv.	*ee* [%][a]	Configuration[b]
1	**1**	100	78	*R*
2	**2**	100	89	*R*
3	**3**	100	83	*R*

[a] *ee* values were determined by GC on a Chiral select 1000 capillary column. [b] The absolute configuration of **14** was assigned by comparison of the observed optical rotation with reported data.

We next examined the asymmetric hydrogenation of methyl benzoylformate (**15a**) using the ruthenium catalysts bearing the ligands **1** and **2**. The reactions proceeded smoothly under rather harsh conditions (50 atm of hydrogen pressure and 80 °C). As shown in Table 2, a similar trend observed in the asymmetric reduction of substrate **13** was found in the hydrogenation of **15a**, when catalyst [RuL*Cl_2-$(dmf)_n$] **12a** and **12b** were applied in the reaction. In the hydrogenation of α-ketoester **15a**, the superior (matched) ligand system for this reaction was found to be **12b**, which incorporated ligand (*S*,*S*)-**2** (Table 2, entry 2, 88 % *ee*). On the contrary, the catalyst Ru/**1** resulted in a loss of stereocontrol (Table 2, entry 1, 64 % *ee*). Again, the BIPHEP

Table 2. Asymmetric hydrogenation of methyl benzoylformate.



Entry	Catalyst	Solvent	*T* [°C]	H_2 [atm]	Conv. [%]	*ee* [%][a]	Configuration[b]
1	**12a**	MeOH	80	50	100	64	*R*
2	**12b**	MeOH	80	50	100	88	*R*
3	**12c**	MeOH	80	50	100	81	*R*
4	**12a**	MeOH	RT	5	90	85	*R*
5	**12b**	MeOH	RT	5	100	95	*R*
6	**12c**	MeOH	RT	5	100	90	*R*
7	**12b**	CH_2Cl_2	RT	5	<5	N/A	*R*
8	**12b**	acetone	RT	5	<5	N/A	*R*
9	**12b**	EtOAc	RT	5	<5	N/A	*R*
10	**12b**	toluene	RT	5	<5	N/A	*R*
11	**12b**	THF	RT	5	9	58	*R*

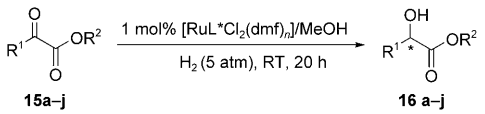
[a] *ee* values were determined by chiral GC (see the Experimental Section). [b] The absolute configurations of products were assigned as *R* by comparison of the observed optical rotation with reported data.

moiety stereochemistry dominated over the backbone chirality, as all catalysts Ru/**1**, Ru/**2** and Ru/**3** afforded methyl mandelate **16a** with *R* absolute configuration.

Further optimization studies showed that the hydrogenation can also proceed smoothly to completion with Ru/**2** catalyst within 20 h under very mild conditions (5 atm of hydrogen pressure and room temperature). This increased the enantioselectivity up to 95 % (Table 2, entry 5). As for the mismatched complex **12a**, the *ee* was improved to 85 % at the cost of the low conversion (Table 2, entry 4). As can be seen from entries 7–11 in Table 2, the solvent effect played an important role in these reactions. Extremely low reactivity was observed in aprotic non-polar solvents such as CH_2Cl_2, EtOAc, THF.

Under the optimized reaction conditions (Table 2, entry 5), a variety of α-aryl substituted α-ketoesters **15a–j** were examined for hydrogenations with [RuL*$Cl_2$$(dmf)_n$] **12b** (Table 3). All selected α-ketoesters were reduced to form chiral α-hydroxy esters with excellent enantioselectivities (94–97 %). The electronic and steric nature of a substituent on the phenyl ring of substrate had little influence on the enantioselectivity and reactivity of the reaction. The enantiomeric excess of **16** was comparable to or better than those obtained when the analogous ligand C_3-TunePhos was used under exactly the same conditions (Table 3).[15] It was noteworthy that, even without acidic additives,[1,3] ligand **2** showed remarkable selectivities compared to BINAP in the hydrogenation of **15**. A key intermediate for the synthesis of ACE inhibitors Benazepril and Delapril hydrochloride[14] was readily accessible via the hydrogenation of ethyl 2-oxo-4-phenylbutyrate with up to 96 % *ee* (Table 3, entry 10). To

Table 3. Asymmetric hydrogenantion of α-aryl substituted α-ketoesters[a].



Entry	Substrate	R^1	R^2	Product	(*S*,*S*)-**2**	*ee* [%][b] (*S*)-C_3-TunePhos
1	**15a**	Ph	Me	**16a**	95	97
2	**15b**	4-F-C_6H_4	Me	**16b**	96	95
3	**15c**	3-F-C_6H_4	Me	**16c**	96	94
4	**15d**	4-Cl-C_6H_4	Me	**16d**	95	93
5	**15e**	4-Br-C_6H_4	Me	**16e**	95	92
6	**15f**	4-Me-C_6H_4	Me	**16f**	94	96
7	**15g**	4-$MeOC_6H_4$	Me	**16g**	97	96
8	**15h**	3-$MeOC_6H_4$	Me	**16h**	96	95
9	**15i**	Me	Me	**16i**	96	85
10	**15j**	Et	Et	**16j**	96	96

[a] Conversions were >99% as indicated by ^{1}H NMR for all entries. [b] *ee* values were determined by chiral GC (see Experimental Section). The absolute configurations of products were assigned as *R* by comparison of the observed optical rotation with reported data.

our best knowledge, these results represent one of the highest enantioselectivities yet achieved yet in the preparation of optically active α-hydroxy acid derivatives using direct asymmetric hydrogenations.

In conclusion, we have endeavored to design and synthesize the ligands containing double chiral axials in a bridging unit in an effort to systematically control the conformation of the backbone structure, while maintaining certain flexibility. In this manner, we not only can maintain high catalytic activity associated with the large bite angle of the diphosphine moiety but also can optimize enantioselectivities

through the enforcement of a dominant backbone conformation with an extra chiral auxiliary of the binaphthyl structure. Moreover, the presence of the chiral binaphthyl auxiliary within a backbone offers the opportunity to prepare diastereomeric ligands that could display the effects of matching and mismatching caused by interactions between the two stereochemical axils within each ligand. Ruthenium catalysts bearing each of the two diastereomeric ligand were examined for effectiveness in hydrogenation reactions. The selectivity data revealed that the matched ligand system was (*S*,*S*)-**2**, which afforded much higher enantioselectivities in hydrogenation of β-ketoesters and methyl benzoylformate, in contrast to the analogous mismatched ligand (*R*,*S*)-**1**. These highly enantioselective hydrogenation reactions provide facile access to optically active α- and β-hydroxy acid derivatives, which are very important chiral building blocks for the syntheses of a variety of natural products and biologically active molecules. Further exploration of the general applications of this class of ligands in transition metal catalyzed asymmetric reactions is under current investigation.

Experimental Section

General hydrogenation procedure: $[Ru(benzene)Cl_2]_2$ (5 mg, 0.01 mmol) and chiral ligand **1**, **2** or **3** (0.021 mmol) were dissolved in degassed DMF (3 mL) in a Schlenk tube and heated to 100 °C under N_2 for 30 min. After the mixture was cooled to 50 °C, the solvent was removed under vacuum to give the catalysts as a reddish brown solid. The catalyst was taken into a glovebox, dissolved in degassed methanol (16 mL), and distributed equally among eight vials. To the catalyst solution was added the substrate (0.25 mmol). The resulting mixture was transferred into an autoclave and charged with H_2 (50 atm for substrate **13** and 5 atm for α-ketoesters **15**). The autoclave was heated at 80 °C for 12 h for β-ketoester or at room temperature for α-ketoester substrates for 20 h. The autoclave was then cooled to room temperature and the H_2 was carefully released. The reaction solution was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC (Gamma dex 225 or Beta dex 390) to determine the enantiomeric excesses.

Acknowledgement

This work was supported by the National Institutes of Health (GM58832).

Keywords: asymmetric catalysis · enantioselectivity · hydrogenation · ruthenium

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Received: March 20, 2009
Published online: June 25, 2009

