Asymmetric Catalysis

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Unprecedented Selectivity via Electronic Substrate Recognition in the 1,4-Addition to Cyclic Olefins Using a Chiral Disulfoxide Rhodium Catalyst**

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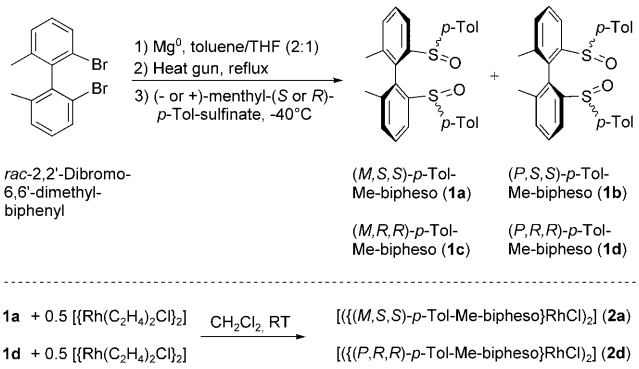
The importance of asymmetric synthesis as a tool for obtaining enantiomerically pure compounds has been fully acknowledged by the chemical community. Metal-catalyzed asymmetric reactions provide one of the most elegant ways to introduce chiral information into a substrate, and the success of such systems relies on identification of efficient, chiral ligand–metal complexes.[1] A survey of the nature of these ligands shows that the overwhelming majority bind the metal through phosphorous, nitrogen, or oxygen atoms. In the last few years, chiral diene ligands have also appeared in combination with rhodium and iridium catalysis.[2] Perhaps because organic sulfur-containing compounds often poison metals, catalysts that contain sulfur–metal bonds have to date played a relatively minor role in (asymmetric) catalysis.[3]

We very recently started an investigation into the potential of sulfoxide-based compounds as ligands in asymmetric late-transition-metal chemistry. Especially appealing properties of such compounds are their nontoxicity and air and moisture stability, their inherent chirality at the sulfur center, as well as their easy synthetic access in enantiomerically pure form. An analogue of binap (1,1′-binaphthalene-2,2′-diyl-bis(diphenylphosphine)) that we called *p*-Tol-binaso (1,1′-binaphthalene-2,2′-diyl-bis(*p*-tolylsulfoxide)) was synthesized in our group and showed very encouraging results in the rhodium-catalyzed 1,4-addition of boronic acids to α,β-unsaturated compounds.[4] Pioneered by Miyaura, Hayashi, and co-workers a decade ago, this reaction represents a very straightforward entry into useful chiral organic building blocks and has emerged as an important methodology in organic synthesis.[5,6]

Building upon our previous results and in analogy to research done with diphosphines, we decided to modify the atropisomeric backbone to test its impact on reactivity and selectivity of the rhodium precatalyst. To do so, we chose biphemp (dimethylbiphenyl-2,2′-diyl-bis(diphenylphosphine)) as our template and synthesized the racemic dibromo derivative using well-established methods.[7] Subsequent generation of the di-Grignard species[8,9] and reaction with commercially available (− or +)-menthyl-(*S* or *R*)-*p*-Tol-sulfinate led to the isolation of *p*-Tol-Me-bipheso (**1**) as a mixture of diastereomeric pairs. The respective diastereomers were separated by simple column chromatography to give the pure ligands **1a**/**1b** and **1c**/**1d** in 50–60 % yields (Scheme 1).



Scheme 1. Synthesis of the *p*-Tol-Me-bipheso ligand and rhodium complexes thereof.

Ligand (*M*,*S*,*S*)-*p*-Tol-Me-bipheso (**1a**) or (*P*,*R*,*R*)-*p*-Tol-Me-bipheso (**1d**) was then treated with the rhodium ethylene dimer [{Rh(C_2H_4)$_2$Cl}$_2$] in methylene chloride. Subsequent concentration and layering with THF gave complexes **2a** and **2d** as red crystals in high yield (90–95 %). Diastereomers **1b** and **1c** of the ligand do not bind well to the dimeric rhodium precursor. In these cases, the relative orientation of the tolyl groups hinders formation of the dimer, a phenomenon that was observed earlier for atropisomeric diphosphine ligands incorporating bulky aromatic groups on the phosphorous atoms.[10]

To unambiguously assign the stereochemistry of the present system and to better understand the binding situation of sulfoxides, crystal structure analyses of one of the ligands (**1a**) and its corresponding rhodium complex **2a** were performed (Figure 1). For comparison, we also synthesized and crystallized the analogous diphosphine complex [({(*S*)-biphemp}RhCl)$_2$] (**3**, see the Supporting Information).[11] As can be seen from the most important bond lengths and angles (Supporting Information, Table S1), the structures of the

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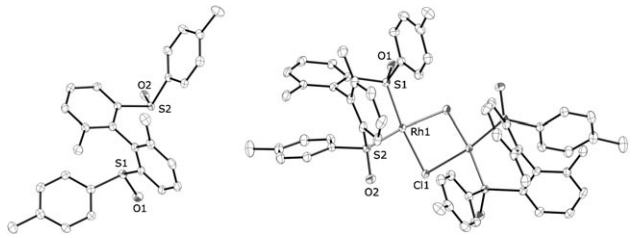


Figure 1. Displacement ellipsoid views of (*M*,*S*,*S*)-*p*-Tol-Me-bipheso (left, **1a**) and [({(*M*,*S*,*S*)-*p*-Tol-Me-bipheso}RhCl)$_2$] (right, **2a**). Ellipsoids set at 50% probability.

disulfoxide and diphosphine compounds are similar. The sulfur–rhodium and phosphorus–rhodium bond lengths as well as the intermetallic separations in the two dimers are almost identical. Probably the most important difference arises from the slightly shorter bonds between the sulfoxide moieties and the backbone carbon skeleton. This structural feature leads to a more open S-Rh-S bond angle in both the Me-bipheso and the binaso rhodium complex,[4] while it maintains the dihedral angle between the planes of the atropisomeric backbone units at a very similar value to that of the corresponding diphosphine systems (Supporting Information, Table S1).[12,13] Finally, coordination of the sulfoxide moiety to the metal leads to a shortening of the S=O bond, a phenomenon that gives a qualitative indication of the donor abilities of sulfoxides.

To quantify to what extent sulfoxide ligands are able to donate electron density to rhodium, we synthesized cationic carbonyl complexes of general formula $[(L\text{-}L)Rh(CO)_2]^+$ (where L-L is one of the investigated bidentate sulfoxide or analogous phosphine ligands) by treating $[\{Rh(CO)_2Cl\}_2]$ with the chelating ligand in the presence of $AgBF_4$ (see the Supporting Information). The surprising results of this study (Table 1) show that the carbonyl stretching frequencies of the

Table 1: Comparison of the σ-donor properties of disulfoxides and diphosphines in $[(L\text{-}L)Rh(CO)_2]^+$ complexes.

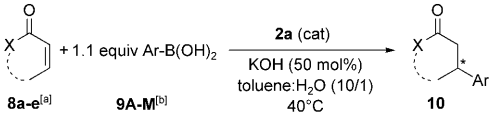
Rhodium complex	$\nu_{(CO)}$ [cm^{-1}][a]
[{(*M*,*S*,*S*)-*p*-Tol-Me-bipheso}Rh(CO)$_2$]BF$_4$ (**4a**)	2058
[{(*P*,*S*,*S*)-*p*-Tol-Me-bipheso}Rh(CO)$_2$]BF$_4$ (**4b**)	2057
[{(*M*,*R*,*R*)-*p*-Tol-binaso}Rh(CO)$_2$]BF$_4$ (**5**)	2056
[{(*S*)-biphemp}Rh(CO)$_2$]BF$_4$ (**6**)	2071
[{(*rac*)-binap}Rh(CO)$_2$]BF$_4$ (**7**)	2071

[a] Thin film, solid IR spectroscopy; average value $(\nu_s+\nu_{as})/2$.

complexes with sulfoxide ligands are lower than for the corresponding phosphine compounds. Contrary to our expectations, aryl disulfoxides *p*-Tol-Me-bipheso and *p*-Tol-binaso are therefore clearly more electron-donating than their aryl diphosphine counterparts biphemp and binap. To our knowledge, this study represents the first measure of σ donation for sulfoxides and indicates to which degree this ligand class has been neglected in the past. The results might also shed some light onto recent studies by Milstein and co-workers that show surprising stoichiometric reactivities with iridium disulfoxide complexes.[14]

Precatalyst **2a** was then tested in the Miyaura–Hayashi reaction of 2-cyclohexen-1-one (**8a**) with phenylboronic acid (**9A**) using previously established reaction conditions (toluene/H_2O/KOH at 40 °C). It soon became clear that in terms of activity towards substrate **8a**, the Me-bipheso ligand is superior to binaso and, as a consequence, an average of only half of the catalyst loading is needed for full conversion within short reaction times (Table 2, entries 1–14). In absolute terms, only 0.25–0.50 mol% **2a** (0.5–1 mol% Rh) is required, a finding that puts this system above most of the catalytic systems tested to date, which routinely need 3 mol% Rh for good reactivity. Furthermore, degradation of the aryl boronic acids does not occur during catalysis and allows the use of stoichiometric amounts of the coupling partner (normally, 2–5 equivalents have to be used). Albeit less efficiently, cyclic substrates **8b**, **8c**, and **8d** were also coupled successfully and in high yield. Probably more impressive than the high activity displayed by precatalyst **2a** is the selectivity with which this disulfoxide catalyst operates for cyclic unsaturated substrates.

Table 2: Disulfoxide rhodium precatalyst **2a** in the 1,4-addition of aryl boronic acids to α,β-unsaturated substrates.



8a-e[a] **9A-M**[b] **10**

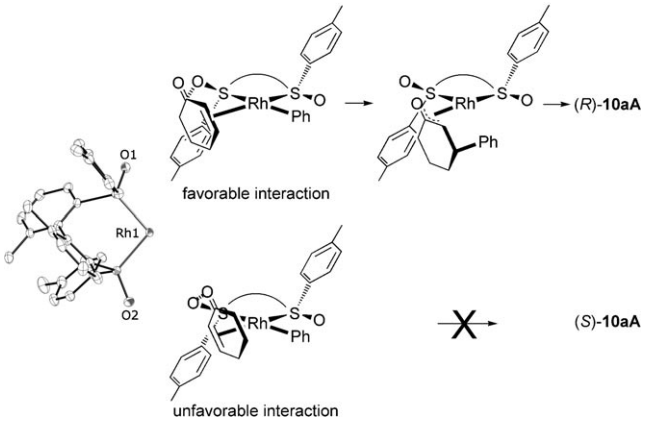
Entry	8	9	mol% **2a**	*t* [h][c]	Yield [%][d]	*ee*[e] [%]
1	**8a**	**9A**	0.5	<0.5	98 (**10aA**)	>99 (*R*)
2	**8a**	**9A**	0.25	0.5	98 (**10aA**)	>99 (*R*)
3[f]	**8a**	**9A**	0.25	0.5	98 (**10aA**)	>99 (*S*)
4	**8a**	**9B**	0.5	1.5	91 (**10aB**)	>99
5	**8a**	**9C**	0.5	0.5	88 (**10aC**)	99
6	**8a**	**9D**	0.5	3	95 (**10aD**)	99
7	**8a**	**9E**	0.25	2	88 (**10aE**)	99
8	**8a**	**9F**	0.5	0.75	96 (**10aF**)	>99
9	**8a**	**9G**	0.5	<0.5	96 (**10aG**)	>99
10	**8a**	**9H**	0.5	1.5	98 (**10aH**)	99
11	**8a**	**9I**	0.25	1.5	80 (**10aI**)	>99
12	**8a**	**9J**	0.25	3	98 (**10aJ**)	>99
13	**8a**	**9K**	0.5	1.5	92 (**10aK**)	>99
14	**8a**	**9M**	0.5	1	95 (**10aM**)	99
15	**8b**	**9A**	1	2	94 (**10bA**)	98
16	**8c**	**9A**	0.5	6	98 (**10cA**)	98
17	**8c**	**9F**	1	2	82 (**10cF**)	97
18	**8d**	**9L**	1	1	46 (*cis*-**10dL**)	97
					48 (*trans*-**10dL**)	95
19[g]	**8e**	**9K**	2.5	5.5	43 (**10eK**)	20

[a] **8a** = 2-cyclohexen-1-one, **8b** = 2-cyclopenten-1-one, **8c** = 5,6-dihydro-2*H*-pyran-2-one, **8d** = 6-methyl-2-cyclohexen-1-one, **8e** = *trans*-1,3-diphenyl-2-propenone. [b] Ar = Ph (**9A**), 4-$CH_3C_6H_4$ (**9B**), 4-ClC_6H_4 (**9C**), 4-FC_6H_4 (**9D**), 4-$CH_3OC_6H_4$ (**9E**), 3-$CH_3C_6H_4$ (**9F**), 3-$CF_3C_6H_4$ (**9G**), 3-ClC_6H_4 (**9H**), 3-FC_6H_4 (**9I**), 3-$CH_3OC_6H_4$ (**9J**), 1-naphtyl (**9K**), 2-naphtyl (**9L**), 1-pyrene (**9M**). [c] Reaction is stopped after full conversion or when no further conversion is observed as determined by GC-MS. [d] Yield of isolated product after column chromatography. [e] Determined by HPLC analysis with chiral columns (Daicel Chiralcel OD-H, OJ-H, OB). [f] Using [({(*P*,*R*,*R*)-*p*-Tol-Me-bipheso}RhCl)$_2$] (**2d**) as catalyst. [g] 2.2 equiv **9K**.

The enantiomeric excesses reported in Table 2 are superior to any catalytic system we are aware of for the 1,4-addition to substrate **8a**. All of the aryl boronic acids tested can be coupled with at least 99% *ee*, and in most cases where selectivities exceed this value, the minor isomer cannot be detected at all by HPLC and we can assume that only one enantiomer is generated. Selectivities for the addition of aryl boronic acids to **8b**, **8c**, and **8d** are almost as high and among the best reported to date.[6] Preliminary results concerning the addition of 1-naphthylboronic acid (**9K**) to a linear α,β-unsaturated ketone (*trans*-1,3-diphenyl-2-propenone, **8f**), however, were disappointing (Table 2, entry 19). Both the reactivity and the enantioselectivity drop dramatically under the reaction conditions used.

With these data in hand, we turned our attention to possible reactivity and selectivity pathways for precatalyst **2a**, especially in view of the fact that the catalytic cycle for the 1,4-addition reaction with binap rhodium has been studied in detail by Hayashi and co-workers.[15] Important information was gathered regarding the initial step leading to the active, monomeric rhodium hydroxo catalyst species by comparing the activities of disulfoxide and diphosphine rhodium dimers with chloro and hydroxo bridges (Table 3). Several conclusions can be drawn from the results obtained. First of all, the diphosphine compounds are distinctly less active and selective than the systems incorporating disulfoxides. Secondly, with (*S*)-biphemp as a ligand, the transformation from the chloro-bridged dimer **3** to the active species is clearly more difficult than formation of the monomeric [Rh]–OH species by dimer dissociation from **12**. The inverse trend is observed with disulfoxide ligand **1a**, where the catalytic run performed using **2a** is faster and more efficient than when starting with **11a**. Finally, selectivities with the hydroxo-bridged species are somewhat lower for both ligand classes.

The stereochemical pathway of the Miyaura–Hayashi reaction is well-documented and arises from the possible approach pathways of the olefinic substrate to the [Rh]–Ph species. The model for enantioselection in this and in the overwhelming majority of metal-mediated asymmetric reactions is based on the assumption that the substrates approach the metal so as to minimize steric interactions with the protruding R groups of the chiral ligand structure.[16] However, the present system is devoid of any significant steric crowding around the metal center, with both *p*-tolyl groups on the sulfoxide units oriented away from the metal center and parallel to the atropisomeric backbone (see partial view of **2a** in Scheme 2).[17] As a viable working model, we therefore propose that selectivity arises from favorable or unfavorable electronic interactions of the prochiral substrate molecules with the oxygen atoms on the sulfoxide moieties. Accordingly, the olefinic double bond of 2-cyclohexen-1-one (**8a**) coordinates to rhodium, placing the carbonyl carbon atom in close proximity to the sulfoxide oxygen atom, and migratory insertion would then form the stereogenic carbon center with absolute configuration (*R*), as observed. In contrast, an unfavorable electronic situation arises when the enone approaches the metal center from its opposite face, and the (*S*) product is therefore not produced. Obviously, the model we propose herein is speculative, and we are currently trying to synthesize rhodium precursors in which both diastereomers of a given atropisomeric backbone of ligand **1** can be compared (**1a** vs. **1c** and **1b** vs. **1d**).[18,19]

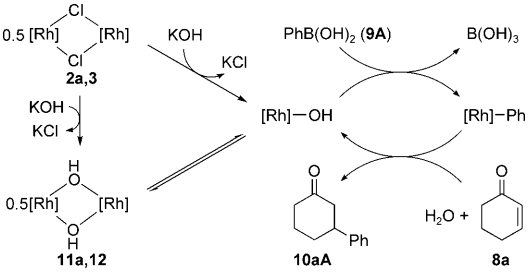


Scheme 2. Partial view of complex **2a** (left) and proposed origin of enantioselectivity (right).

To conclude, *p*-Tol-Me-bipheso, a chelating disulfoxide ligand based on the biphemp structure, shows unprecedented selectivity in the 1,4-addition of aryl boronic acids to cyclic α,β-unsaturated ketones and esters while allowing the use of low catalyst loadings and stoichiometric amounts of expensive boronic acid. As *p*-Tol-Me-bipheso represents only the second chelating chiral sulfoxide ligand to be used successfully in asymmetric metal-mediated catalysis, the very fact that it can outperform well-established ligand entities points to the enormous potential of these new sulfur-based ligands.

Comparing disulfoxide ligands with their diphosphine counterparts revealed important trends and differences. Contrary to our expectation, disulfoxides are better σ-donating ligands than diphosphines for the present rhodium

Table 3: Reaction network of the rhodium-catalyzed 1,4-addition of phenylboronic acid (**7a**) to 2-cyclohexen-1-one (**9A**) and catalytic results obtained.



Precatalyst (0.5 mol%)[a]	*t* [h]	Yield [%]	*ee* [%]
2a	< 0.5	98[b,c]	> 99
[{(**1a**)RhOH}$_2$] (**11a**)	2	91[b,c]	98
[({(*S*)-biphemp}RhCl)$_2$] (**3**)[e]	48	58[b,d]	90
[({(*S*)-biphemp}RhOH)$_2$] (**12**)	24	96[b,c]	58

[a] Conditions employed are identical to Table 2, entry 1. [b] Yield of isolated product after column chromatography. [c] Reaction is stopped after full conversion. [d] Incomplete conversion. [e] A run at elevated temperature (100°C, 1 h) gave 83% yield and 84% *ee*.

systems. Furthermore, a study of precatalyst activation unveiled distinctly different reactivity patterns for the two ligand classes, showing all the while that the Me-bipheso ligand is clearly superior to biphemp. Probably most intriguing is the fact that an unusual electronic recognition between the sulfoxide moieties and the prochiral substrate appears to be responsible for the unparalleled selectivity of the present catalytic system. This latter finding is now being thoroughly investigated as part of our ongoing efforts in the area of chiral sulfoxide-mediated catalytic studies.

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[16] Sometimes, such as in the present catalytic transformation, only one bulky substituent is enough for efficient chiral recognition, see Refs. [6n] and [6s].

[17] In biphemp (or binap) the S=O bond is exchanged for a P-phenyl group. It is this very group that is invoked as being responsible for enantioselection in these atropisomeric systems. For recent reviews on binap and its derivatives, see: a) W. J. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) M. Berthod, G. Mignani, G. Woodward, M. Lemaire, *Chem. Rev.* **2005**, *105*, 1801; c) H. Shimizu, I. Nagasaki, T. Saito, *Tetrahedron* **2005**, *61*, 5405.

[18] Cationic complexes of the formula $[Rh(L\text{-}L)(cod)]^+$ (cod = 1,5-cyclooctadiene) have been obtained with all four ligands (**1a**–**1d**), but unfortunately, catalytic results with these and the carbonyl-containing complexes **4a**/**4b** of Table 1 were poor.

[19] It is possible that the lack of reactivity and selectivity for the open-chain enone **8e** is linked to the mode of operation of catalyst **2a**. More detailed studies are underway.

