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Metal−Ligand Binding Affinity vs Reactivity: Qualitative Studies in Rh(I)-Catalyzed Asymmetric Ring-Opening Reactions

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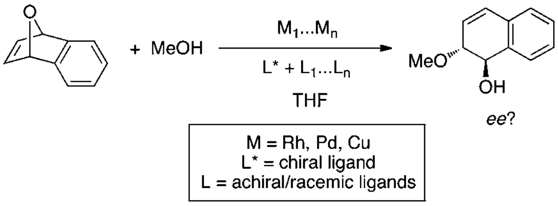
ABSTRACT



Rh(I)-catalyzed asymmetric ring opening (ARO) of oxabenzonorbornadiene is used as a model system to qualitatively study reactions involving multiple metal−ligand interactions. The key feature of this approach is the use of product *ee* as an indicator to quickly gain important information such as the relative ligand binding affinity and relative reactivity of catalysts.

The idea of combining multiple catalysts in a single vessel to facilitate domino reactions has attracted recent attention.[1,2] Whereas various organo-/bio-/metal catalysis combinations are known, the combination of multiple metals and their associated ligands in multicomponent−multicatalyst reactions, $(MC)^2R$, is of particular interest in our research program.[3] Prior studies have involved the use of two or more metals with no added phosphine ligand or a single ligand, thereby minimizing competitive ligand-binding issues. However, in those instances where a domino reaction sequence requires multiple distinct metal complexes each with a specific ligand to carry out the respective transformation, detailed information on competing metal−ligand binding needs to be gained to improve reaction designs. The concept of using a mixture of ligands in transition-metal catalysis to control enantio-, diastereo- and regioselectivities has been successfully demonstrated and extensively studied.[4] A recent example of a Pd catalyst consisting of two biarylphosphine ligands (BrettPhos and RuPhos) for C−N cross-coupling reactions showed superior substrate scope and reactivity.[5] These studies have laid the foundation for understanding complex systems involving multiple metal−ligand interactions.

Our group has reported a domino reaction featuring Rh-catalyzed alkyne arylation and Pd-catalyzed C−N coupling

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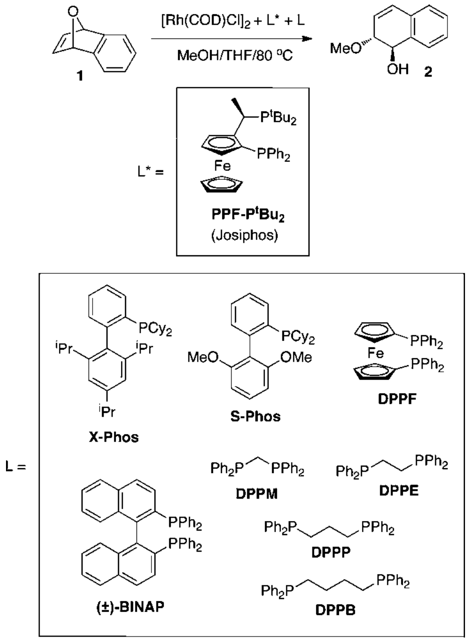
that involved the use of a two-metal/two-ligand (racemic BINAP and X-Phos) catalytic system.[6] Detailed studies to unravel the nature of the ligand−metal interactions were undertaken including ^{31}P NMR. These studies provided useful information, but improved methods for studying the metal−ligand binding were needed as the process we followed was time-intensive. We now report an approach to gain qualitative information on metal−ligand interactions in multimetal/multiligand systems by studying an enantioselective transformation and the effect of added achiral/racemic ligands to identify "interfering" and "non-interfering" ligands for a given reaction.

The Rh-catalyzed asymmetric ring opening (ARO) of oxabicyclic alkenes with heteroatom nucleophiles has been thoroughly studied.[7] The *trans*-1,2-disubstituted dihydronaphthalenol products are obtained with very high enantioselectivities using the chiral Josiphos ligand PPF-P^{t}Bu$_2$.[8] Although Josiphos has been the ligand of choice for the ARO, we had no information on its relative binding affinity and reactivity *in the presence of another achiral ligand.* We envisioned that by employing one metal catalyst with two ligands, chiral (L*) and achiral/racemic (L), in a methanol-induced ARO of oxabenzonorbornadiene **1**, we could use the *ee* of the ring-opened product **2** to gain insight into the binding of the two ligands to the metal center and the relative reactivity of the two complexes (Scheme 1). This hypothesis can be rationalized by two possible limiting cases based on the molar equivalents of metal catalyst (M) to the ligands (L* and L) (Figure 1). Case A includes equimolar equivalents of metal to total ligand (M:L*:L = 2:1:1). In this case, both species ML* and ML will coexist if both ligands can bind and only ML* leads to P*; thus a higher *ee* of the product would indicate a faster *rate* of the reaction from ML*.[9a] Case B includes half molar equivalents of metal to total ligand (M:L*:L = 1:1:1).[9b] In this case, M can preferentially bind to either L* or L creating mixtures of ML*+L or ML+L* which may also exist in equilibrium due to ligand exchange.[10] However, only ML* leads to chiral product P*; thus a higher *ee* of the product would indicate a stronger binding of L* vs L, and/or higher catalytic activity of ML*. This scenario studies the relative binding *affinity* of ligands to the metal center and their reactivity.

Scheme 1. One-Metal/Two-Ligand System in Rh-Catalyzed ARO of Oxabenzonorbornadiene **1** with MeOH



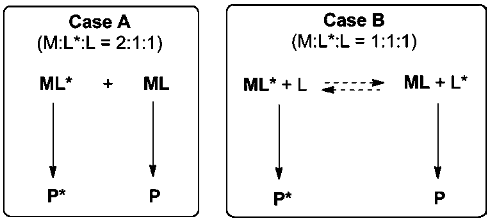


Figure 1. Two possible cases of ligand binding in one-metal/two-ligand systems (* denotes chiral species).

To begin the studies, the chiral PPF-P^{t}Bu$_2$ (Josiphos) ligand and eight mono- and bidentate achiral/racemic phosphine ligands were employed in a series of catalyst competition experiments (Tables 1 and 2). The benchmark

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(9) (a) There also exists a scenario where M does not bind with L; therefore if M is an active catalyst in the reaction it would also contribute to the formation of racemic product P. (b) In the context of Rh-catalyzed ARO using phohspine ligands, M:L = 1:1 implies one Rh binds to two phosphorus atoms.

(10) We assume no doubly bound species ML*L would form due to limited available coordination sites on the Rh center. See ref 7b.

result from Rh/Josiphos-catalyzed ARO was 94% *ee* and 85% yield (Tables 1 and 2, entry 1). The achiral/racemic ligands were tested separately for their activities in the ring-opening reactions under the same conditions. We found that DPPF, DPPB, DPPP, and (±)-BINAP were active ligands to various degrees, whereas S-Phos, X-Phos, DPPM, and DPPE generated inactive catalysts.[11] It should be noted that no catalytic activity was observed using [Rh(COD)Cl]$_2$ in the absence of any added ligand.

The data in Table 1 reveal several interesting observations. The *ee* of the product is minimally affected by DPPM, DPPE, DPPP, DPPF, X-Phos, and S-Phos (entries 2−7). These ligands either fail to bind to Rh or make poorly active catalysts. The effect of (±)-BINAP and DPPB are increasingly pronounced indicating competitive reactivities (entries 8−9), though they clearly form a far less active catalyst than Rh/Josiphos as the *ee*'s remain above 70%. The change from 94% *ee* to 70% *ee* implies ML* is about three times more reactive than ML at 80 °C.[12]

Table 1. Catalyst Competition Studies (Case A) in Rh-Catalyzed ARO Using *Double* Molar Equivalents of Rh to Chiral Ligand (L* = PPF-P^{t}Bu$_2$) and Achiral/Racemic Ligand (L)[a]

entry	L	Rh:L*:L[d]	yield[b] (%)	*ee*[c] (%)
1[e]	–	4:4:0	85	94
2	DPPE	4:2:2	85	94
3	X-Phos	4:2:4	83	94
4	DPPF	4:2:2	55	92
5	DPPM	4:2:2	81	90
6	DPPP	4:2:2	70	90
7	S-Phos	4:2:4	16	90
8	(±)-BINAP	4:2:2	77	84
9	DPPB	4:2:2	76	70

[a] Unless specified otherwise, reactions were run with 0.2 mmol of oxabicycle **1**, 2 mol % [Rh(COD)Cl]$_2$ (i.e., 4 mol % Rh), 2 mol % PPF-P^{t}Bu$_2$, and 2 or 4 mol % L in THF (0.8 mL)/MeOH (0.2 mL) at 80 °C for 1.5 h. The ligands were premixed with a Rh catalyst and substrate **1** at 80 °C for 15 min before MeOH was added. [b] Isolated yield. [c] Measured by HPLC analysis. [d] Mol %. [e] No premixing.

The data in Table 2 permit an exploration of competition of two ligands for the metal when superimposed on the relative reactivity that was observed from data in Table 1. Some ligands such as DPPE, DPPM, X-Phos, and S-Phos bind poorly to Rh, and they tend to give high *ee*'s implying Josiphos binds preferentially and gives more reactive complexes (entries 2−5).[13] In the cases of DPPF and DPPP (entries 7 and 9), they form much less reactive catalysts than Josiphos (cf. Table 1, entries 4 and 6) yet cause more severe *ee* decreases, which suggests that they outcompete Josiphos in binding with Rh. In the cases of (±)-BINAP and DPPB (entries 6 and 8), they also cause a loss in the *ee* likely due to a combination of both competitive binding and catalytic activity as we showed that they form reactive catalysts (cf. Table 1, entries 8−9).

Table 2. Catalyst Competition Studies (Case B) in Rh-Catalyzed ARO Using *Equal* Molar Equivalents of Rh, Chiral Ligand (L* = PPF-P^{t}Bu$_2$), and Achiral/Racemic Ligand (L)[a]

entry	L	Rh:L*:L[d]	yield[b] (%)	*ee*[c] (%)
1[e]	–	4:4:0	85	94
2	DPPE	4:4:4	75	92
3	DPPM	4:4:4	82	89
4	X-Phos	4:4:8	63	88
5	S-Phos	4:4:8	22	86
6	(±)-BINAP	4:4:4	64	80
7	DPPF	4:4:4	71	80
8	DPPB	4:4:4	32	60
9	DPPP	4:4:4	29	52

[a] Unless specified otherwise, reactions were run with 0.2 mmol of oxabicycle **1**, 2 mol % [Rh(COD)Cl]$_2$ (i.e., 4 mol % Rh), 4 mol % PPF-P^{t}Bu$_2$, and4 or 8 mol % L in THF (0.8 mL)/MeOH (0.2 mL) at 80 °C for 1.5 h. The ligands were premixed with a Rh catalyst and substrate **1** at 80 °C for 15 min before MeOH was added. [b] Isolated yield. [c] Measured by HPLC analysis. [d] Mol %. [e] No premixing.

To investigate the possibility of an equilibrium between ML*+L and ML+L* (Figure 1, Case B), we used DPPF in equal molar equivalents as Josiphos and Rh (Table 2 conditions), but the ligands were mixed with the metal sequentially. Two complementary protocols were employed: (A) Premixing Rh and Josiphos at 80 °C for 15 min, then adding DPPF and heating the mixture at 80 °C for 15 min, and finally adding the nucleophile, and the reaction was continued. (B) Premixing Rh and DPPF at 80 °C for 15 min, then adding Josiphos and heating the mixture at 80 °C for 15 min, and finally adding the nucleophile, and the reaction was continued. If no equilibrium existed, then protocol A would give a high *ee* and protocol B would give no *ee*. Instead, protocol A gave the product in 80% *ee* (43% yield) and protocol B gave 84% *ee* (36% yield). As both *ee*'s are very similar to the result when both ligands were mixed with Rh together at the outset (Table 2, entry 7), this is a strong evidence supporting the presence of an equilibrium, i.e. an exchange of ligands on the Rh center.

The complexity of the system was increased by introducing more than one competing achiral ligand (Table 3). The presence of both DPPF and (±)-BINAP in equal molar equivalents to Rh (Case B) gave *ee*'s similar to their stand-alone results (entry 1; cf. Table 2, entries 6−7). Therefore, no additive effects were indicated by these two ligands. However, there seemed to be an additive effect on catalyst reactivity (Case A) from these ligands since the *ee* was decreased compared to their stand-alone results (entry 2; cf. Table 1, entries 4 and 8), possibly due to the fact that Rh/DPPF and Rh/(±)-BINAP were formed and both were reactive catalysts. This result was further demonstrated by using the more reactive Rh/DPPB combination leading to a much lower *ee* (entry 3). On the other hand, adding one more ligand such as (±)-BINAP did not cause a much

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[11] Isolated yields of racemic products from [Rh(COD)Cl]$_2$/L-catalyzed ring-opening reaction of **1** with MeOH:L = DPPF (62%), DPPB (62%), DPPP (29%), (±)-BINAP (21%), S-Phos (< 5%), X-Phos (< 5%), DPPM (< 5%), DPPE (< 5%), none (< 5%).

[12] For $\text{Rate}_{\text{ML*}}:\text{Rate}_{\text{ML}} = 1:1$, product $ee = 94\% \times (1/2) = 47\%$ *ee*. For $\text{Rate}_{\text{ML*}}:\text{Rate}_{\text{ML}} = 3:1$, product $ee = 94\% \times (3/4) = 70.5\%$ *ee*. For $\text{Rate}_{\text{ML*}}:\text{Rate}_{\text{ML}} = 10:1$, product $ee = 94\% \times (10/11) = 85.5\%$ *ee*.

[13] Previously ^{31}P NMR studies showed that Rh did not bind with X-Phos; see ref 6.

Table 3. Catalyst Competition Studies in Rh-Catalyzed ARO Using Multiple Ligands (L* = PPF-P^{t}Bu$_2$)[a]

entry	Rh:L*:L$_1$:L$_2$...L$_n$[d]	yield[b] (%)	*ee*[c] (%)
1	Rh:L*:DPPF:(±)-BINAP (4:4:4:4)	49	78
2	Rh:L*:DPPF:(±)-BINAP (6:2:2:2)	67	80
3	Rh:L*:DPPF:DPPB (6:2:2:2)	76	46
4	Rh:L*:DPPF:(±)-BINAP:DPPB (8:2:2:2:2)	61	44
5	Rh:L*:DPPF:(±)-BINAP:DPPB:DPPP (10:2:2:2:2:2)	76	36
6	Rh:L*:DPPF:(±)-BINAP:DPPM:DPPE (10:2:2:2:2:2)	55	86

[a] Unless specified otherwise, reactions were run with 0.2 mmol of oxabicycle **1**, 2–5 mol % [Rh(COD)Cl]$_2$ (i.e., 4–10 mol % Rh), 2 or 4 mol % PPF-P^{t}Bu$_2$, and 2 or 4 mol % L in THF (0.8 mL)/MeOH (0.2 mL) at 80 °C for 1.5 h. The ligands were premixed with a Rh catalyst and substrate **1** at 80 °C for 15 min before MeOH was added. [b] Isolated yield. [c] Measured by HPLC analysis. [d] Mol %.

further decrease in *ee* (entry 4), due to its moderate catalytic activity. Adding a stronger binding ligand such as DPPP led to a drastic drop in *ee* (entry 5). By replacing DPPB and DPPP with "non-interfering" ligands such as DPPM and DPPE, the *ee* was restored to a similar level as before (entry 6; cf. entry 2). This result was quite remarkable since, even in the presence of five different ligands, Rh preferentially bound with Josiphos to form a very reactive catalyst and produced the ring-opened product with an *ee* of 86%.

To truly mimic a multimetal/multiligand system, we introduced an additional metal (Pd or Cu complex) into the reaction (Table 4).[14] Interestingly, the more reactive Rh/DPPB and the stronger binding DPPP led to minimal *ee* loss in the presence of Pd(OAc)$_2$ at equal molar equivalents (entries 1–2; cf. Table 2, entries 8–9). This result indicated that Pd preferentially bound with DPPB or DPPP creating an inactive catalyst which also eliminated binding of these ligands to Rh, thus leaving the Rh/Josiphos catalyst for product formation.[15] Such preferences in metal–ligand binding was further illustrated in the case where the metal equivalents were doubled (entry 3). Theoretically each metal could bind with both Josiphos and DPPP and would cause a decrease in *ee* or low conversion, yet the result showed Rh/Josiphos and Pd/DPPP were the preferred combinations. In the case of X-Phos, the *ee* was identical to that without Pd(OAc)$_2$ (entry 4; cf. Table 2; entry 4), suggesting a weak binding interaction between Pd and X-Phos. There seemed to be a moderate binding between CuI and DPPP as the *ee* was somewhat higher than previously obtained with Rh alone (entry 6; cf. Table 2, entry 9). The use of other Pd complexes caused a dramatic decrease in yields (entries 5, 7–9) and in some cases *ee*'s. The presence of extra ligands such as PPh$_3$ and dba in the complexes possibly created a mixture of multiple ligated catalytic species, and the Pd(0) complexes could potentially decompose the oxabicycle substrate or facilitate racemic ring opening by insertion into the bridgehead C–O bond.

Table 4. Catalyst Competition Studies in Rh-Catalyzed ARO Using Multiple Metals and Multiple Ligands (L* = PPF-P^{t}Bu$_2$)[a]

entry	Rh:L*:M:L[d]	yield[b] (%)	*ee*[c] (%)
1	Rh:L*:Pd(OAc)$_2$:DPPB (4:4:4:4)	60	94
2	Rh:L*:Pd(OAc)$_2$:DPPP (4:4:4:4)	57	92
3	Rh:L*:Pd(OAc)$_2$:DPPP (8:4:8:4)	37	96
4	Rh:L*:Pd(OAc)$_2$:X-Phos (4:4:4:8)	40	88
5	Rh:L*:PdCl$_2$(PPh$_3$)$_2$:DPPP (4:4:4:4)	18	76
6	Rh:L*:CuI:DPPP (4:4:4:4)	43	66
7	Rh:L*:[Pd(allyl)Cl]$_2$:DPPP (4:4:2:4)	13	54
8	Rh:L*:Pd$_2$dba$_3$:DPPP (4:4:2:4)	19	14
9	Rh:L*:Pd(PPh$_3$)$_4$:DPPP (4:4:4:4)	12	10

[a] Unless specified otherwise, reactions were run with 0.2 mmol of oxabicycle **1**, 2 or 4 mol % [Rh(COD)Cl]$_2$ (i.e., 4 or 8 mol % Rh), 4 or 8 mol % additional metal catalyst, 4 mol % PPF-P^{t}Bu$_2$, and 4 or 8 mol % L in THF (0.8 mL)/MeOH (0.2 mL) at 80 °C for 1.5 h. The ligands and additional metal catalyst were premixed with a Rh catalyst and substrate **1** at 80 °C for 15 min before MeOH was added. [b] Isolated yield. [c] Measured by HPLC analysis. [d] Mol %.

In conclusion, we have developed a method for studying metal–ligand interactions in a multimetal/multiligand system utilizing Rh-catalyzed ARO reactions. Useful qualitative information such as the relative ligand binding affinity and relative reactivity of catalytic species can be gained quickly using the product *ee* as an indicator. We envision that this new concept can be applied to other metal-catalyzed reactions to study metal–ligand compatibility issues, the outcome of which will facilitate designs of new multicatalyst multicomponent reactions, particularly the asymmetric variants.

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Supporting Information Available. Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(14) Analogous competition studies were performed in our one-pot synthesis of chiral dihydrobenzofuran *via* Rh/Pd catalysis: Tsui, G. C.; Tsoung, J.; Dougan, P.; Lautens, M. *Org. Lett.* **2012**, *14*, 5542.

(15) A control experiment showed no reaction with Pd(OAc)$_2$ (4 mol %)/Josiphos (4 mol %) and thus ruled out any contribution of product yield and *ee* from a Pd/Josiphos complex.