Effects of Halide Ligands and Protic Additives on Enantioselectivity and Reactivity in Rhodium-Catalyzed Asymmetric Ring-Opening Reactions

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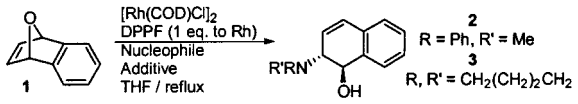
Catalysts containing halide ligands are ubiquitous in asymmetric catalysis. Despite the prevalence of this functionality, halide ligands are often regarded as being of limited importance compared to the chiral ligand.[1] Herein, we report a dramatic halide effect in the rhodium-catalyzed asymmetric ring-opening (ARO) reaction. Three different halide effects are described. Added halide is shown to reverse catalyst poisoning by aliphatic amine nucleophiles, and the nature of the halide is shown to influence the enantioselectivity and reactivity.

We recently reported a rhodium-catalyzed ARO of **1** with alcohols[2] and phenols,[3] producing hydronaphthalenes in high yield and excellent ee. Extension to activated amine nucleophiles was partially successful, but ee's were often significantly lower. Importantly, all efforts to react simple amines under similar conditions failed completely. For example, *N*-methylaniline reacts with **1** to give **2** in 94% yield, whereas no reaction occurs with pyrrolidine (Table 1, entries 1 and 2). To probe this poor reactivity, equimolar amounts of *N*-methylaniline and pyrrolidine were reacted simultaneously. In this case, neither nucleophile reacts, indicating that the more basic aliphatic amine poisons the catalyst (entry 3).[4] Since amines are known to be good ligands for rhodium,[5] it seems likely that the catalyst poisoning is due to irreversible binding of the basic amine to the metal center.

An investigation of the effects of additives revealed that the use of equimolar amounts of pyrrolidine and a proton source such as $Et_3N{\cdot}HCl$ allowed isolation of **3** in 85% yield (entry 4). Further experiments indicated that both the proton and its accompanying counterion were important contributors. For example, addition of camphorsulfonic acid (CSA) gave **3**, but in lower yield with longer reaction time. Addition of Bu_4NCl in the absence of a protic additive also aided the reaction, but less so than $Et_3N{\cdot}HCl$. Using a Bu_4NCl/CSA mixture returned the reaction time to that observed with $Et_3N{\cdot}HCl$ indicating that the chloride and the proton are acting together.[6] Not all halide additives were equally effective. With aliphatic amines, Bu_4NF gave no reaction, Bu_4NBr was more efficient than Bu_4NCl, and Bu_4NI gave the best result (entries 7−10). Again, the addition of CSA in conjunction with Bu_4NI lead to a more rapid consumption of starting material (entries 11 vs 12).

Table 1. Effect of Halide and Protic Additives



entry	nucleophile	additive	time (h)	yield[b] (conv.)
1	*N*-methylaniline	−	0.5	94 (>98)
2	pyrrolidine	−	24	NR
3	*N*-methylanaline	pyrrolidine (5 equiv)	24	NR
4	pyrrolidine	$Et_3N{\cdot}HCl$ (5 equiv)	6	85 (>98)
5	pyrrolidine (10 equiv)	CSA (5 equiv)	25	71 (92)
6	pyrrolidine	Bu_4NCl (5 equiv)	14	79 (91)
7	pyrrolidine	Bu_4NF (5 equiv)	5	NR
8	pyrrolidine	Bu_4NCl (5 equiv)	5	17
9	pyrrolidine	Bu_4NBr (5 equiv)	5	60
10	pyrrolidine	Bu_4NI (5 equiv)	5	85 (>98)
11	pyrrolidine	Bu_4NI (5 equiv)	2	42
12	pyrrolidine	Bu_4NI (5 equiv)/ CSA (1 equiv)	2	81 (>98)
13	dibenzylamine	$Et_3N{\cdot}HCl$ (5 equiv)	6	84
14	dibenzylamine	Bu_4NI (5 equiv)/ CSA (1 equiv)	0.5	91
15	benzylamine	$Et_3N{\cdot}HCl$ (5 equiv)	72	31 (45)
16	benzylamine	Bu_4NI (5 equiv)/ CSA (1 equiv)	6	81 (>98)
17	*p*-methoxybenzylamine	$Et_3N{\cdot}HCl$ (5 equiv)	72	44 (52)
18	*p*-methoxybenzylamine	Bu_4NI (5 equiv)/ CSA (1 equiv)	7	82 (>98)

[a] Conditions: $[Rh(COD)Cl]_2$ (2.5 mol %), dppf (5 mol %), nucleophile (5 equiv), additive (5 equiv) heated in refluxing THF (0.2 M). [b] Isolated yield.

The effect of halide/proton additives was found to be generally applicable for the addition of a variety of aliphatic amines (entries 13−18).[7] While the use of amine hydrochlorides could be employed for secondary amines, only the combination of Bu_4NI and CSA gave quantitative conversion when primary amines were used. The combined use of halides and acid represents a technically simple method for the effective reversal of catalyst poisoning by aliphatic amines.[8]

The use of halide additives also has pronounced effects on the enantioselectivity of the ARO reaction with aliphatic amines. With *p*-methoxybenzylamine, PPF−P^{t}Bu$_2$ gives **4** in 29% ee with Bu_4NCl as the halide additive, and 42% with Bu_4NBr. With Bu_4NI the highest ee's are obtained reaching 72% (Table 2, entries 1 to 3). The best results are obtained by replacing the chloride ligand with iodide prior to the addition of substrates. When this is done, the ee with *p*-methoxybenzylamine and PPF−P^{t}Bu$_2$ is increased to 81% (entry 4). These same conditions were used with dibenzylamine to give **5** in 88% ee (entries 5 to 7). As observed with dppf and pyrrolidine as the nucleophile, no reaction occurs when fluoride is used as the halide additive.

Stabilized amines react in the absence of added protons or halides but still show a remarkable change in enantioselectivity as the halide is varied (Table 3). The best ee's were obtained if the chloride counterion was first removed by the addition of silver triflate (AgOTf) and the halide was added subsequently in the form of ammonium salts. We have extended this observation and can now add soft carbon nucleophiles in high ee when iodide is

(1) Most discussions of halide ligands deal with their removal from the coordination sphere and replacement with noncoordinating anions. For example, see: (a) Evans, D. A.; Murry, J. A.; Von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798. (b) O'Mahoney, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, *4*, 443. For a review of halide effects in asymmetric catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem.*, in press.

(2) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc* **2000**, *122*, 5650.

(3) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677.

(4) We also observed this trend in our rhodium-catalysed ring-opening reactions of vinyl epoxides, see: Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

(5) Wilkinson, G. *Comprehensive Organometallic Chemistry*; Permagon Press, 1982; Vol. 5.

(6) HCl is known to react stoichiometrically with rhodium−amine complexes to generate anionic dihalorhodium species; see: Vallarino, L. M.; Sheargold, S. W. *Inorg. Chim. Acta* **1979**, 36, *243.*

(7) The *trans* relative stereochemistry was proven for the dibenzylamine adduct by X-ray crystal structure analysis.

(8) Experimental evidence supports the hypothesis that the halide additives are acting at the rhodium metal. A crude indication is a change in color of the reaction solution, depending on the halide. Furthermore, no reaction occurs with Bu_4NI, CSA and the rhodium catalyst in the absence of a nucleophile, indicating that the halide is not inducing ring opening with subsequent displacement by the amine.

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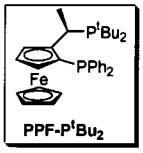
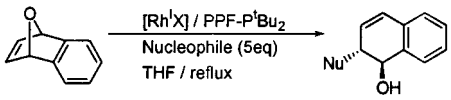
Table 2. Effect of Halide Ligand on Enantioselectivity[a]

Entry	Nucleophile	Halide	Yield[b] (ee[c])
1	*p*-Methoxybenzylamine	Cl	52 (29)
2	*p*-Methoxybenzylamine	Br	67 (42)
3	*p*-Methoxybenzylamine	I	72 (72)
4	*p*-Methoxybenzylamine	I[d]	71 (81)
5	Dibenzylamine	Cl	89 (31)
6	Dibenzylamine	I	86 (74)
7	Dibenzylamine	I[d]	91 (88)



[a] Conditions: 2 mol % $[Rh(COD)Cl]_2$, 5 mol % ligand, 5 equiv nucleophile, 5 equiv halide additive, 1 equiv CSA, 0.2 M in THF. For typical conditions see the Supporting Information. [b] Isolated yield. [c] Ee was determined by CSP HPLC with a Chiralcel OD column. [d] Prior to the addition of the reagents, a halide exchange was performed, see Supporting Information for experimental details.

Table 3. Effect of Counterion on Enantioselectivity[a]



			yield (ee[b])				
entry	nucleophile	product	OTf	F	Cl	Br	I
1	*N*-methylaniline	**2**	93 (96)	91 (96)	92 (74)	90 (78)	97 (92)
2	tetrahydroquinoline	**6**	94 (96)	92 (96)	89 (65)	86 (74)	95 (91)
3	indole	**7**		90 (96)	87 (78)[c]		93 (97)
4	phthalimide	**8**	0[d]	74 (94)	55 (45)[c]	78 (79)	90 (98)
5	dimethylmalonate	**9**	0[d]		56 (51)[c]		97 (98)
6	diethylmalonate	**10**					95 (97)

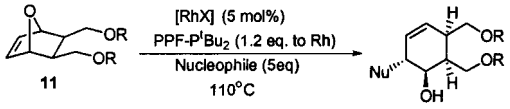
[a] Conditions: prior to the addition of the reagents, a halide exchange was performed, see Supporting Information. $[Rh(COD)Cl]_2$ (0.5 mol %), PPF−P^{t}Bu$_2$ (1.5 mol %), AgOTf (1.5 mol %), R_4NX (2 mol %) 5 equiv nucleophile, 0.2 M in THF. [b] Ee was determined by CSP HPLC with a Chiralcel OD or AD column. [c] Halide exchange was not performed; $[Rh(COD)Cl]_2$ (1 mol %), and PPF−P^{t}Bu$_2$ (2.5 mol %) were dissolved in THF and used directly. [d] Only decomposition to naphthol was observed.

used as the halide ligand (entries 5, 6).[9] Activation of the malonates by deprotonation is not required; in fact, no reaction is observed with the sodium salt.

We have established that the trends were due to the nature of the halide and not due to other factors produced by the halide-exchange protocol. Reaction with *N*-methylaniline and tetrahydroquinoline were performed with a catalyst prepared by simply combining $[Rh(COD)Cl]_2$ and PPF−P^{t}Bu$_2$ *and* with a catalyst where the chloride was first removed with AgOTf and then added back in the form of Bu_4NCl. With both nucleophiles, similar yields and enantioselectivities were obtained with both procedures.

For all of the nucleophiles examined, distinct but nonlinear trends within the halide series are apparent (Table 3). For example, the highest enantioselectivities are observed for F and I. The fact that both F and I perform the best is remarkable since their binding ability to rhodium,[10] their relative *trans*-effect[11] as well as their size are at opposite extremes within the group. With some nucleophiles, the reaction works well with triflates as the only counterion (entries 1 to 3) but the reaction is not as mild or general as the use of iodide counterions since naphthol was observed as the only product in some cases (entries 4, 5). Our preferred protocol uses Bu_4NI as the halide additive.

Table 4. Effect of Halide Ligand on Reactivity[a]



entry	R group[d]	nucleophile	product	yield[b] (% ee[c])
1	Me	*p*-bromophenol	**12**	83 (94)
2	PMB	phenol	**13**	84 (93)
3	PMB	*N*-methylaniline	**14**	93 (95)

[a] Conditions: halide exchange was performed with $[Rh(COD)Cl]_2$ (2.5 mol %), PPF−P^{t}Bu^2 (7.5 mol %), AgOTf (7.5 mol %), and TBAI (10 mol %). See Supporting Information for a detailed procedure. To this was added **16** and nucleophile (5 equiv) followed by heating at 110 °C. [b] Isolated Yield. [c] Ee was determined by CSP HPLC with a Chiralcel OD or AD column. [d] Me = methyl, PMB = *p*-methoxybenzyl.

The choice of halide has also been found to influence the reactivity of the catalyst. Changing the halide ligand from chloride to iodide yields a catalyst that will induce ring opening in the [2.2.1] oxabicycle series as exemplified by **11**. For example, treatment of **11** with catalytic [RhI(PPF−P^{t}Bu$_2$)] and various nucleophiles at 110 °C produces cyclohexenol products in good yield and >90% ee (Table 4).[12] As with **1**, only *trans*-1,2-cyclohexenols are formed when **11** is used. The analogous [RhCl] complex fails to induce a reaction with this substrate.

In conclusion, we have reported three different roles of halide ligands in the rhodium-catalyzed ARO reaction, including overcoming catalyst poisoning, improving the enantioselectivity, and increasing the reactivity. While the role of spectator ligands in neutral systems has been examined,[13] a general appreciation of their influence has not been realized. These results underline the utility of the metal−halide moiety as a tunable functionality in the development of new asymmetric catalysts. We are currently investigating the applicability of halide effects to other systems.

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Note Added after ASAP. There was an error in Table 3 in the version posted ASAP June 29, 2001; the corrected version was posted July 18, 2001.

Supporting Information Available: Experimental details, ^1H and ^{13}C NMR, IR, mass spectroscopy, and other characterization data (PDF) This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The *trans* relative stereochemistry was proven for **2** by X-ray crystal structure analysis. The regio- and relative stereochemistry for the addition of carbon nucleophiles has been determined by X-ray crystal analysis for the use of (phenylsulfonyl)-acetonitrile as the nucelophile.

(10) Vallarino, L. M. *Inorg. Chem.* **1965**, *4*, 161.

(11) Vaska, L.; Peone, J. *J. Chem. Commun*. **1971**, 418.

(12) The absolute stereochemistry was established by X-ray crystallography for the *p*-bromobenzoate of **14**. A full account of the development of these new conditions and their scope will be reported in due course.

(13) (a) Bovens, M.; Togni, A.; Venanzi, L. M. *J. Organomet. Chem.* **1993**, *451* C28−C31. (b) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (d) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc*. **1997**, *119*, 10857. (e) Overman, L. E.; Poon, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 518. (f) Blaser, H.-U.; Buser, H.-P.; Jelett, H. P.; Pugin, B.; Spindler, F. *Synlett* **1999**, *S1*, 867. (g) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 558. (h) Kang, G.-J.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kutney, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1466.