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Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Phenols

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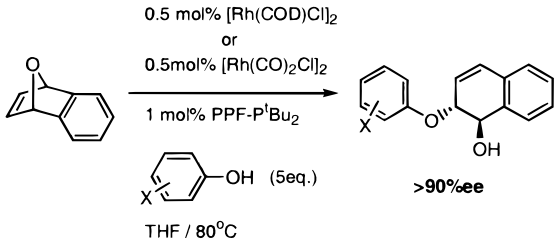
ABSTRACT



The scope of the rhodium-catalyzed asymmetric ring opening reaction of oxabenzonorbornadiene has been extended to include phenolic nucleophiles. The enanatioenriched, functionalized dihydronaphthalene products are highly valuable intermediates for which no other practical methods of preparation are available. A new catalyst system has been developed which allows the use of less reactive *o*-halophenols. The utility of these products has been demonstrated through their application in the synthesis of benzofuran polycyclic materials.

Of the myriad of molecular architectures present in pharmacological agents, certain structures emerge with a higher frequency than others. Among these "privileged structures" is the hydronaphthalene skeleton which can be found in a wide range of compounds possessing diverse biological activities.[1] We recently disclosed a new rhodium asymmetric ring opening (ARO) reaction of oxabicyclic alkenes which produces highly functionalized dihydronaphthalenes in ee's approaching 99%.[2] We now report the extension of this reaction to include phenolic nucleophiles and the development of a new catalyst which allows less reactive *o*-halophenols to induce ring opening. The products of these reactions are interesting in themselves as potential therapeutic agents and are valuable building blocks en route to complex polycyclic skeletal motifs.

Our group has had a long-standing interest in ARO reactions of oxabicyclic alkenes and has previously developed catalytic reductive and alkylative ARO reactions producing enantioenriched dihydronaphthalenols, cyclohexenols, and cycloheptenols.[3] Moinet and Fiaud developed a palladium-catalyzed ARO reaction incorporating aryl groups; however, the hydrophenylated oxabicyclic product predominated.[4] Very recently, we reported an asymmetric rhodium-catalyzed ring opening reaction of oxabenzonorbornadiene with alcohol nucleophiles producing 2-alkoxydihydronaphthalen-1-ols in excellent yields and enantioselectivities (93 to >99% ee). Unlike all other nucleophiles, alcohols under rhodium catalysis give *endo* attack and a *trans* dioxygen relationship. Given the success obtained with alcohols, we sought to expand the scope of this rhodium-catalyzed ARO to include substituted phenols. While phenol nucleophiles have successfully been used in a few transition metal-catalyzed systems,[5] rhodium has never been used as a catalyst with this class of nucleophile, and we have no previous results indicating that phenols are sufficiently nucleophilic

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(2) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* In press

(3) (a) Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107. (b) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *63*, 5246. (c) Lautens, M.; Renaud, J. L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804..

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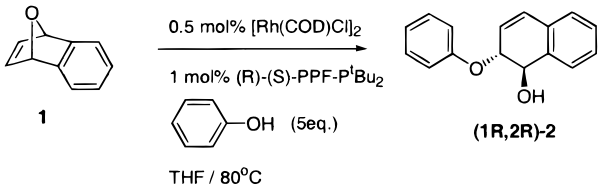
to participate in oxabicyclic ring opening reactions. Extension of this reaction to include phenol nucleophiles would allow facile access to a broad range of enantioenriched dihydronaphalene products which could be further transformed into substituted benzofurans which are themselves pharmaceutically interesting compounds.[6]

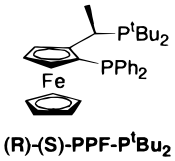
Our initial experiments using $[Rh(COD)Cl]_2$/PPF-P^{t}Bu$_2$ as previously reported with 10 equiv of phenol gave the desired product **2** in near quantitative yield and outstanding enantioselectivity (>99% ee). Subsequent experiments revealed that the amount of phenol could be lowered to 5 equiv with no deleterious effects (Table 1). Below 5 equiv, however, the reactions did not go to completion even after prolonged reaction times, although the enantioselectivity was not adversely affected.

Table 1. Effect of the Number of Equivalents of Phenol Used



Phenol Equiv.	Reaction Time	Yield[a]	ee[b]
10	6 hr	89%	>99%
5	8 hr	91%	>99%
2.5	5 d	35%[c]	>99%
1.5	5 d	10%[c]	>99%

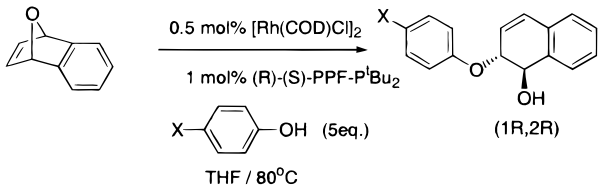
[a] Isolated yield. [b] Ee determined by CSP HPLC. [c] Remainder is unreacted starting material.



(R)-(S)-PPF-P^{t}Bu$_2$

Using these conditions, various *p*-substitiuted phenols were shown to add in high yields and excellent enantioselectivity (Table 2). The reaction proceeded well even when aryl bromides and iodides were used, indicating that the rhodium insertion into the aryl halide bond is slow compared to ring opening. This selectivity permits the preparation of various halo aryl ethers with which further coupling reactions could be performed. An X-ray crystal structure of the 4-bromophenol adduct proved the regiochemistry, the relative stereochemistry, and the absolute configuration of the ring-opened products.

Table 2. ARO with Various *p*-Substituted Phenols

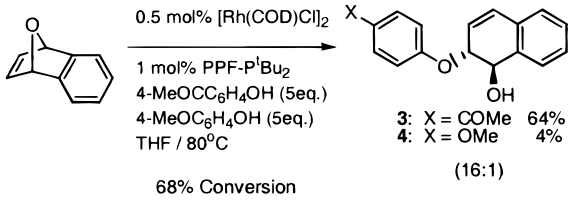


Phenol (X)	Yield(%)[a]	ee(%)[b]
F	92%	97%
Cl	89%	92%
Br	94%	98%
I	92%	98%
$COCH_3$	91%	>99%
CF_3	87%	95%
CH_3	60%	91%
-CN	88%	97%
OMe	85%	95%

[a] Isolated yields. [b] Ee determined by CSP HPLC or formation Mosher's Ester.

We observed significant differences in the relative rates of reaction, with the more acidic phenols adding faster. Sinou made similar observations for the reactivity of phenols in allylic etherification under palladium catalysis.[7] To quantify these observations, we conducted a competition experiment using equimolar amounts of 4-hydroxyacetophenone and 4-hydroxyanisole. At 68% conversion, we observed a 16:1 ratio of **3**:**4** (Scheme 1), confirming that the presence of an electron-withdrawing group on the aromatic ring accelerates the rate of addition.

Scheme 1



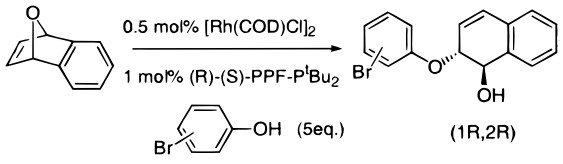
We next examined the effect of other substitution patterns on the reactivity of the phenol. In the case of a bromo substituent, 3- and 4-bromophenol added in high yields and excellent enantioselectivity (Table 3), but 2-bromophenol did not give satisfactory results, adding in only 17% yield after prolonged reaction times. Despite the low conversion, the enantioselectivity was still very high, with the product being produced in 97% ee.

(5) For palladium-catalyzed allylic etherification reactions, see: Muzart, J.; Genet, J. P.; Denis, A. *J. Organomet. Chem.* **1987**, *326*, C23. For enantioselective ring opening of epoxides with Cr(salen) complexes, see: Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086. For the enantioselective ring opening of epoxides with Ga heterobimetallic complexes, see: Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223. For desymmetrization of Baylis–Hillman adducts with palladium, see: Trost, B. M.; Tsui, H. C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534.

(6) Mustafa, A. *Benzofurans*; Wiley Interscience: Toronto, 1974.

(7) Goux, C.; Lhoste, P.; Sinou, D. *Synlett* **1992**, 725.

Table 3. Effect of Phenol Substitution

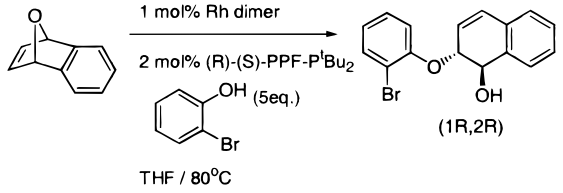


Phenol	Yield(%)[a]	ee(%)[b]
4-Br	94%	98%
3-Br	92%	96%
2-Br	17%[c]	97%

[a] Isolated yield. [b] Ee determined by CSP HPLC. [c] After 24hr reaction time. Remainder is unreacted starting material.

Changing the rhodium source to $[Rh(CO)_2Cl]_2$ increased the yield of the reaction with 2-bromophenol dramatically to 92% and had no detrimental effects on the enantioselectivity (Table 4). It is noteworthy that $[Rh(CO)_2Cl]_2$ is not

Table 4. Effect of Rhodium Source Used



Rh Source	Ligand	Reaction Time	Yield[a](%ee[b])
$[Rh(COD)Cl]_2$	DPPF	24 hr	<10%
$[Rh(CO)_2Cl]_2$	DPPF	24hr	No Reaction[d]
$[Rh(COD)Cl]_2$	PPF-P^{t}Bu$_2$	24 hr	17%[c] (97%ee)
$[Rh(CO)_2Cl]_2$	PPF-P^{t}Bu$_2$	24hr	92% (97%ee)

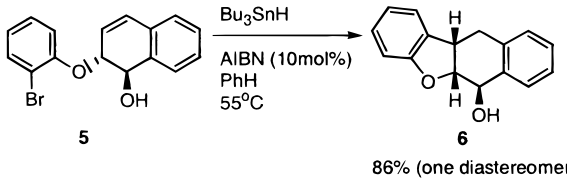
[a] Isolated yield. [b] Ee determined by CSP HPLC. [c] Remainder is unreacted starting material. [d] An insoluble precipitate resulted upon mixing DPPF with the Rh source which did not disolve.

compatible with DPPF under these conditions due to the formation of an insoluble precipitate on mixing the phosphine and the rhodium together.[8]

The enantioselectivity with $[Rh(COD)Cl]_2$/PPF-P^{t}Bu$_2$ with 2-bromophenol is similar to that observed for 3- and 4-bromophenol, which suggests that the catalytically active complex is the same in each case. We reasoned that the poor yield with $[Rh(COD)Cl]_2$ might be due to the rhodium being sequestered from the catalytic cycle by reversible bidentate binding of the 2-halophenol through the oxygen and the bromine atoms. Such a binding pattern has been invoked by Noyori[9] for the ruthenium-catalyzed asymmetric hydrogenation of *o*-bromoacetophenone and by Wills[10] for the rhodium-catalyzed asymmetric hydrosilylation of *o*-chloroacetophenone and *o*-bromoacetophenone.

$[Rh(CO)_2Cl]_2$, upon mixing with certain classes of diphosphines, is known to produce complexes in which one of the carbonyls remains bound.[11] As a result, the $[Rh(CO)_2Cl]_2$/PPF-P^{t}Bu$_2$ catalyst system might have one less vacant coordination site compared to the $[Rh(COD)Cl]_2$ system. This difference could serve to disfavor the bidentate phenol binding that occurs and thus increase the amount of the catalytically active species.

The ring-opened products **5** should be useful for further transformations such as coupling reactions and cyclizations. To demonstrate this concept, **5** was treated with Bu_3SnH and AIBN under high dilution conditions to provide cyclized benzofuran product **6** in 86% yield as one diastereomer (eq 1). The benzofuran skeleton can be found in several



(1)

biologically interesting pharmaceutical agents,[6] and such radical cyclization reactions provide a facile and attractive route to these skeletons in enantioenriched form. We are currently investigating the scope of these transformations which will be reported in our full account of this work.

In conclusion, we have demonstrated that phenols are a useful class of nucleophiles for the rhodium-catalyzed ARO of oxabenzonorbornadiene. While 3- and 4-substituted phenols can be added using the previously reported $[Rh(COD)Cl]_2$/PPF-P^{t}Bu$_2$ catalyst system, the extension to 2-halophenols required a change in the rhodium source to $[Rh(CO)_2Cl]_2$. We propose that the presence of the additional CO ligand on the rhodium prevents the poisoning of the catalyst caused by reversible bidentate binding of the halophenol. The hydronaphthalene and the tetracyclic benzofuran products both belong to biologically important classes of compounds.

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Supporting Information Available: Full characterization details including proton NMR, carbon NMR, IR, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) In our initial studies with alcohol nucleophiles, we found it necessary to change from $[Rh(CO)_2Cl]_2$ to $[Rh(COD)Cl]_2$ as the rhodium source since insoluble precipitates resulted on mixing $[Rh(CO)_2Cl]_2$ with phosphine ligands, which is the case with DPPF in this study. We surmise that this precipitate is due to the formation of dimeric and oligomeric rhodium/phosphine complexes. Fortuitously, this is not the case with the PPF-P^{t}Bu$_2$ ligand.

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