Rhodium-Catalyzed Asymmetric Alcoholysis and Aminolysis of Oxabenzonorbornadiene: A New Enantioselective Carbon−Heteroatom Bond Forming Process

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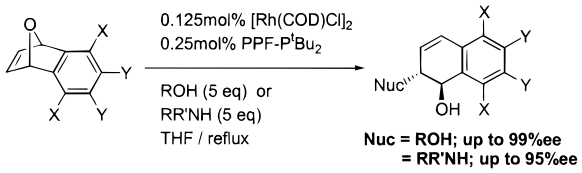
There have been significant advances in the enantioselective synthesis of C−C and C−N bonds via displacement reactions by carbon and nitrogen nucleophiles on η^3-allylpalladium intermediates.[1] Less success has been achieved using alcohols probably due to their poor nucleophilicity.[2,3] The resulting allylic ethers are important synthetic intermediates, thus a general solution to this problem is needed.

We now describe the first rhodium-catalyzed asymmetric ring-opening (ARO) reaction of oxabenzonorbornadienes using alcohol and amine nucleophiles. This reaction generates a new carbon−oxygen or carbon−nitrogen bond via a net intermolecular allylic displacement of the bridgehead oxygen (eq 1). Neutral reaction



conditions and no activation of the nucleophile are features of this methodology. Very high regio- and diastereoselectivity (>99:1), and excellent enantioselectivity (up to 99%ee) are observed. The reaction also produces an unusual stereochemical outcome compared to our prior work on ring openings since the *trans* rather than the *cis* product is formed. Finally we note that very low catalyst loadings (typically 0.25 mol % of the catalytically active rhodium species) make this a practical method as well.

Our recent studies in ARO reactions of oxabicyclic alkenes[4] have resulted in the development of enantioselective reductive[5] and alkylative[6] ARO reactions. However, no ARO reactions have been reported involving heteroatom nucleophiles. Given the prevalence of biologically interesting hydronaphthalene-containing compounds and the diversity of their biological activities, we sought to extend the scope of the ARO methodology such that heteroatomic nucleophiles would be incorporated in the ring-opening step.

Our studies were stimulated by a report of Hogeveen and Middelkoop where a $[Rh(CO)_2Cl]_2$-catalyzed ring-opening reaction of an oxabicyclo[2.2.1]heptadiene with methanol was described.[7] Subsequently, Ashworth and Berchtold established that the stereochemistry of the newly incorporated methoxy functionality was *cis* to the hydroxyl group.[8,9] This stereochemistry is in keeping with our observation of *exo* attack by nucleophiles on other oxabicyclic alkenes.[10]

When we subjected oxabenzonorbornadiene **1** to the Hogeveen and Middelkoop conditions, no reaction was observed; instead a precipitate formed which did not dissolve even upon heating. We reasoned that a more highly polarizing solvent might overcome this problem. Thus, changing the solvent system to a 1:1 mixture of methanol:trifluoroethanol (TFE) and increasing the reaction temperature to 60 °C resulted in the diastereoselective methanolytic ring opening of **1** giving **2** in 70% yield along with a small amount of naphthol. Surprisingly the relative stereochemistry was shown to be *trans* by conversion of **2** to 1,2-dimethoxytetrahydronaphthalene **3** and comparison to authentic samples of *cis*- and *trans*-**3**.[11]

We next investigated the enantioselective variant of this reaction. To incorporate a chiral ligand, the rhodium source was changed from $[Rh(CO)_2Cl]_2$ to $[Rh(COD)Cl]_2$ since insoluble precipitates frequently resulted on mixing $[Rh(CO)_2Cl]_2$ with a phosphine. After examining several achiral ligands, DPPF was found to be the most efficient, giving **2** in 88% yield. It is noteworthy that when the Hogeveen and Middelkoop substrate was subjected to these conditions no reaction occurred, suggesting that the two reactions may proceed by different mechanisms. We tried various chiral ligands based on the ferrocene template,[12] and found JOSIPHOS-type ligands[13] to give the highest ee's. For example, PPF−P^tBu_2 **4** gave **2** in 84% yield and 86% ee at 60 °C. The ee could be significantly improved to 97% when the reaction temperature was increased to 80 °C in accord with similar observations of ee vs temperature in our reductive ARO study.[14]

TFE is not the ideal solvent since it is expensive and toxic. Fortunately, with the $[Rh(COD)Cl]_2$/PPF−P^tBu_2 catalyst, THF gave equally good results. Using these conditions, a wide variety of alcohols react, all in good yields and excellent ee's (Table 1). We were also able to use very low catalyst loadings, typically as low as 0.125 mol % $[Rh(COD)Cl]_2$ and 0.25 mol % PPF−P^tBu_2.

In neat TFE, and in the absence of any other nucleophile, the major product after prolonged reaction time is naphthol with **11** produced in only trace amounts. In THF, however, TFE is readily incorporated as is the very weakly nucleophilic hexafluoroisopropanol (HFIP).

To investigate the effects of substituents on the aromatic ring of **1**, difluoro, methylene dioxy, and dimethyldibromo substrates

(1) For a review on allylic alkylation, see: Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999; Vol. II, p 833. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395 and references therein. For a review on allylic amination, see: Johannsen, M.; Jorgensen, K. A.; *Chem. Rev.* **1998**, *98*, 1689 and references therein.

(2) To achieve efficient catalysis with alcohol nucleophiles, intramolecular delivery of the alcohol is frequently required. For intramolecular examples, see: (a) Sinou, D.; Frappa, I.; Lhoste, P.; Porwanski, S.; Kryczka, B. *Tetrahedron Lett.* **1995**, *36*, 1251. (b) Thorey, C.; Wilken, J.; Henin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5527. (c) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353. (d) Storck, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073. (e) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. For the use of tin alkoxides see: (f) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931. (g) Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558. For the use of cocatalytic trialkylborates as tethers, see: (h) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702.

(3) (a) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1172. (b) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964. (c) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (d) *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Hegedus, L. S., Vol. Ed.; Elsevier Science Ltd.: New York, 1995; Vol. 12, pp 814−817.

(4) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, Vol. 190.

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(6) Lautens, M.; Renaud, J. L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804; Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051.

(7) Hogeveen, H.; Middelkoop, T. B. *Tetrahedron Lett.* **1973**, *190*, 3671.

(8) Ashworth, R. W.; Berchtold, G. A. *Tetrahedron Lett.* **1977**, 339.

(9) We have confirmed the *cis* stereochemistry of Hogeveen and Middelkoop product by X-ray crystal analysis.

(10) Lautens, M. *Synlett* **1993**, 177.

(11) *cis*-**3** was prepared by reaction of 1,2-dihydronaphthalene with OsO_4 followed by dimethylation with dimethyl sulfate. *trans*-**3** was prepared by epoxidation of 1,2-dihydronaphthalene followed by ring opening with hydroxide and dimethylation with dimethyl sulfate.

(12) *Metallocenes*; Togni, A. T., Halterman, R. L., Eds.; Wiley-VCH: New York, 1998; Vol. 2.

(13) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

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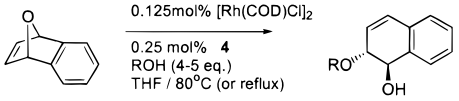
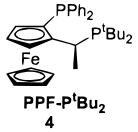
Table 1: ARO of **1** with Various Alcohols



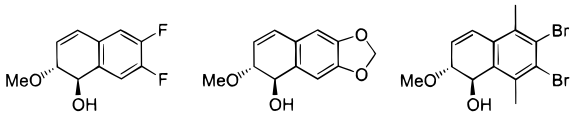
Entry	ROH	Product	Yield(%)	ee(%)[b]
1	MeOH[a]	2	96	97
2	EtOH[a]	5	84	97
3	^{i}PrOH[a]	6	94	93
4	Allyl Alcohol	7	92	>99
5	TMS Ethanol[a]	8	53	95
6	Benzyl Alcohol	9	66	>98
7	PMB Alcohol	10	87	97
8	TFE	11	70	98
9	HFIP	12	90	93



PPF-P^{t}Bu$_2$
4

[a] These reactions have not been optimized. 10 equiv of ROH and 1 mol% of the active catalyst were used. [b] ee determined by formation of Moshers ester or by HPLC analysis with a Chiralcel OD column

were prepared and reacted under the standard conditions with methanol. All gave the corresponding ring-opened products **13**, **14**, and **15** in good yields and excellent ee's, indicating that this reaction is not sensitive to electronic effects.

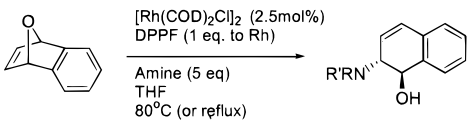


We next investigated the use of nitrogen nucleophiles. It has been previously shown that sulfonamide salts react with allyl carbonates under rhodium catalysis to give retention of absolute configuration.[15] In our case lithiobenzenesulfonamide failed to induce any reaction, whereas benzene sulfonamide gave the desired product in good yield (Table 2, entries 1 and 2). The reaction is quite general, and aromatic amines as well as phthalimide are good nucleophiles. The *trans* stereochemistry was proven for **17** by X-ray crystallography.

We have conducted preliminary studies on the ARO of **1** with nitrogen nucleophiles and obtained encouraging results. Ring opening with toluenesulfonamide and PPF−P^{t}Bu$_2$ occurs in 86% yield and 95% ee (Table 3). With other nucleophiles, BPPFA **21** gives better results than **4** (entries 2 to 4), and thus we anticipate that further modification of the ligand will lead to high ee's.

The mechanism of this transformation is the subject of our current studies. The most likely scenario is *exo* coordination of the rhodium[16] followed by C−O insertion and subsequent displacement of the allyl rhodium species via *endo* nucleophilic attack.

Table 2: Ring Opening with Nitrogen Nucleophiles



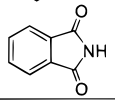
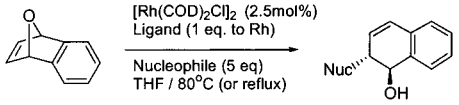
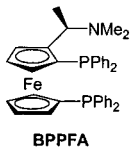
Entry	Amine Nucleophile	Product	Yield
1	$PhSO_2NHLi$	-	NR
2	$PhSO_2NH_2$	16	95%
3	PhNHMe	17	95%
4		18	96%
5		19	77%
6		20	74%

Table 3: ARO with Nitrogen Nucleophiles



Entry	Nucleophile	PPF-P^{t}Bu$_2$	BPPFA
1	$PhSO_2NH_2$	86%(95%ee)	-
2	Phthalimide	83%(45%ee)	64%(74%ee)
3	Indole	87%(73%ee)	81%(79%ee)
4	PhNHMe	96%(74%ee)	94%(74%ee)



BPPFA
21

The products formed by the ring-opening reaction are of particular interest since the hydronaphthalene skeleton is found in a wide range of compounds possessing diverse biological activities.[17−21] To the best of our knowledge, there is no other convenient route to *trans*-1,2-disubstituted dihydronaphthalenol products in enantioenriched form.[22]

In conclusion, we have developed a rhodium-catalyzed ARO of oxabenzonorbornadienes producing *trans*-2-alkoxy- and amino-1,2-dihydro-naphthalen-1-ols in good yield and excellent ee's (up to >99% ee).

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Supporting Information Available: Experimental procedures and characterization data for ring-opened compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000134C

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