J|A|C|S COMMUNICATIONS

Published on Web 12/29/2008

Reagent-Controlled Regiodivergent Resolution of Unsymmetrical Oxabicyclic Alkenes Using a Cationic Rhodium Catalyst

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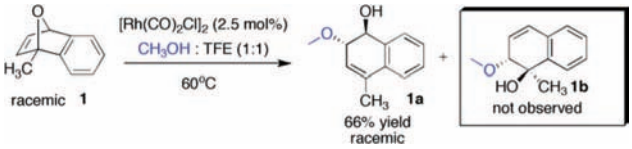
Transition metal catalyzed reactions of oxa- and azabicyclic alkenes have proven extremely useful in the synthesis of materials ranging from biologically active molecules of pharmaceutical interest[1] to polymer components.[2] Many highly efficient asymmetric transformations involving these unique moieties have emerged in the literature[3] as attractive methods to allow rapid access to difficult-to-make hydroxy-dihydronapthalene cores. In our continuing effort to identify useful reactivity profiles in these systems, an enantiomerically pure bridgehead substituted oxabicycle was synthesized[4] and its ring opening chemistry with heteroatom nucleophiles was explored under rhodium catalysis. From our earlier work, it is known that a bridgehead substituted oxabenzonorbornene undergoes Rh-catalyzed addition of methanol with complete substrate control (Scheme 1).[5]

Scheme 1. Substrate Control in Rh-Catalyzed Ring Opening[5]

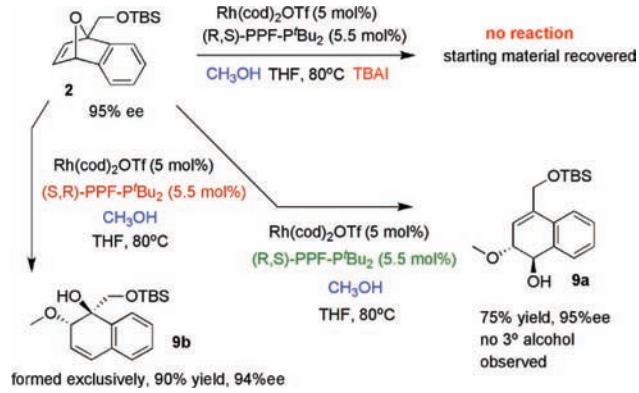


Josiphos type ligands complexed to Rh promote ring opening of meso oxabicyclic and azabicyclic alkenes with heteroatom nucleophiles with very high enantioselectivities. Conventionally, these transformations are carried out with Rh halide complexes, and earlier work in our group has shown that in situ generated Rh iodide complexes[6] (via addition of tetrabutylammonium iodide to the reaction) commonly give the best yields and enantioselectivites in these types of reactions. However, when oxabicycle **2** (Scheme 2) was subjected to our standard ring opening protocol, it was found to be essentially inert. We suspected a more electrophillic catalyst system would be required, and the reaction was attempted using a cationic Rh(I) triflate catalyst in the presence of the (*S*,*R*)-PPF-P^{t}Bu$_2$ Josiphos ligand. Previously we found this complex to be too reactive. Inherent, efficient opening was observed, and moreover only **9b** was observed which is regioisomeric to our earlier studies with achiral ligands. Reacting **2** with the enantiomeric ligand yielded the regioisomer **9a** implying the ligand overrides the inherent preference of the substrate.

In light of the dominant role previously exerted by the substrate, racemic bridgehead substituted oxabicycles were investigated (Scheme 3) and the enantiomers were found to give regioisomeric products implying strong catalyst control.[7] The use of the cationic Rh catalyst has proven to be essential, as replacing the counterion by chloride or iodide does not allow access to **1b** (product type **B**), which arises from the unexpected mode of ring opening.

Our findings imply that a matched/mismatched effect during the oxidative insertion of the Rh ligand complex into the C−O bridgehead bond is operative and responsible for the observed stereoselectivity. (Scheme 4) In all cases, one of the regioisomers

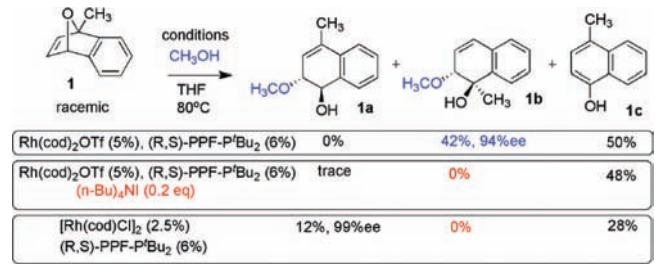
Scheme 2. Reagent Controlled Ring Opening Using Cationic Rh(I)



is produced with very high ee, while the other is formed in lower selectivity. Because the reaction products have two stereocenters, one of which is fixed in the starting material, for one of the products to form in less than perfect ee requires that it originate from the opposite enantiomer of the starting substrate. In general, (Scheme 4) the examples studied give product type **B** as virtually a single enantiomer. This can occur when substrate "R" reacts with the chiral Rh-ligand complex in a matched fashion and breaks the C−O bond in agreement with substrate control. Product type **A** arises from nucleophillic addition via pathway **a**, and pathway **b** (leading to product type **B**) is inoperative. The "S" antipode of the starting material interacts with the chiral catalyst in a mismatched manner, and the inherent reactivity of the substrate participates to a minor extent. The substrate controlled pathway **a′** leads to product **A** with a slight erosion of ee, while ligand control gives rise to product **B** in very high enantiopurity. This model conforms to the trend that the product formed with higher enantioselectivity generally gives a slightly lower yield. Monitoring reaction progress over time using chiral HPLC (entry 4, Table 1) has shown that product ee is constant throughout the reaction, and both enantiomers of the starting material are consumed at very similar rates.

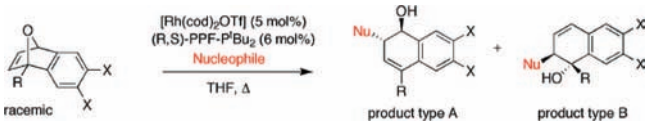
It was found that the degree of enantioselectivity results primarily from the identity of the bridgehead substituent. The unsymmetrical

Scheme 3. Regiodivergent Resolution Resolution Using Cationic Rh(I)



10.1021/ja807942m CCC: $40.75

Table 1. Rh-Catalyzed Divergent Enantioselective Ring Opening

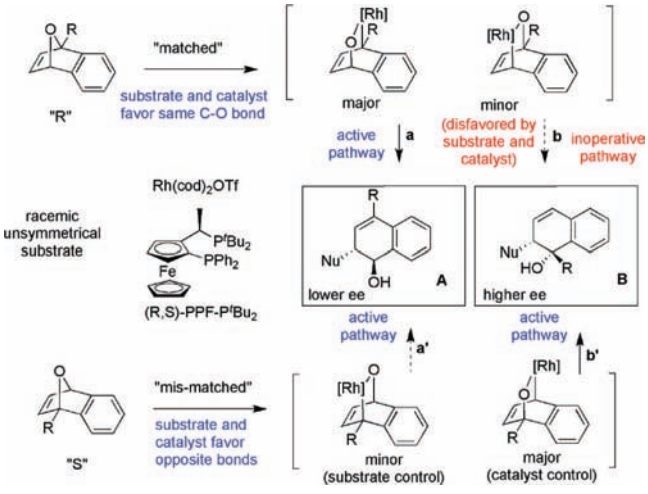


entry	R	X	nucleophile	product A yield (%)	product A ee[d] (%)	product B yield (%)	product B ee[d] (%)
1[b]	CH_3	H	CH_3OH	(50)[a]	-	42	90
2[b]	CH_3	H	Bn_2NH	29	86	32	>99
3[b]	CH_3	H	Et_2NH	48	79[e]	35	>99
4[b]	CH_3	H	$PhNHCH_3$	43	80	35	99
5[c]	CH_3	H		50	75	39	>99
6[c]	CH_3	Br	Bn_2NH	50	83	30	99
7[c]	CH_3	F	Bn_2NH	50	90	45	>99
8[c,f]	CH_3	F		50	90	48	>99
9[b]	CH_2OTBS	H	CH_3OH	27	94	49	81
10[b]	CH_2OTBS	H	Bn_2NH	27	99	32	74
11[b]	CH_2Ph	H	Et_2NH	37	91[e]	32	>99
12[b]	CH_2Ph	H		47	82	36	>99
13[b]	$(CH_2)_2CO_2Et$	H	CH_3OH	41	>99	35	>99

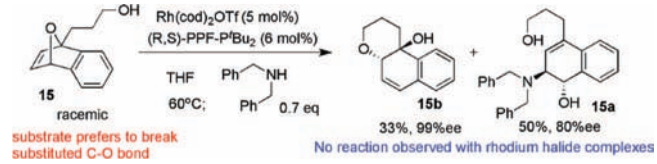
[a] Aromatized naphthol product **1c** was isolated. [b] Reaction performed at 80 °C. [c] Reaction performed at 60 °C. [d] Measured using HPLC analysis with chiral stationary phase columns; conditions are detailed in the Supporting Information. [e] HPLC analysis performed after conversion of the alcohol to the acetate. [f] Relative and absolute stereochemistry assigned by single crystal X-ray analysis.

compounds bearing a methyl group (entries 1−6, Table 1) give product type **A** in moderate to good ee and universally give product type **B** in very high ee. Changing the bridgehead group either leads to a reversal in which regioisomer is formed in high ee (entries 9 and 10, Table 1) or causes both type **A** and **B** products to be formed with very high stereoselectivity (entry 13, Table 1).

Scheme 4. Proposed Pathways Allowing for Observed Stereoselectivity



Scheme 5. Regiodivergent Inter/Intramolecular Parallel Resolution



Tethering a nucleophile to the bridgehead position (Scheme 5) creates a situation wherein one enantiomer undergoes cyclization, whereas the other enantiomer is unable to do so resulting in decomposition. If an external nucleophile is added, then intermolecular opening of the complimentary enantiomer of substrate is observed.

In conclusion, we have demonstrated an unusual mode of reagent control using cationic Rh(I) complexes to resolve racemic bridgehead substituted oxabicyclic alkenes into pairs of regiosiomeric products with high enantioselectivity.

Acknowledgment. We thank NSERC and the University of Toronto for funding of this research. R.W. would like to thank Patricia Perèz-Galan for technical assistance. C.B. thanks the DFG for a postdoctoral fellowship. We also would like to thank Dr. Alan Lough and Dr. Thierry Maris (Université de Montréal) for X-ray analysis.

Supporting Information Available: Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA807942M