JOC*Article*

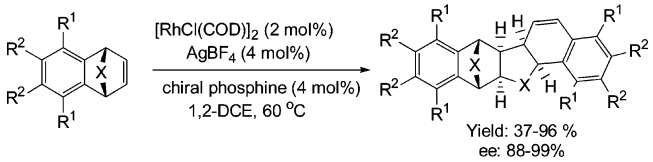
Rhodium-Catalyzed Asymmetric Cyclodimerization of Oxabenzonorbornadienes and Azabenzonorbornadienes: Scope and Limitations

Anna Allen, Paul Le Marquand, Ryan Burton, Karine Villeneuve, and William Tam*

Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, Department of Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1

wtam@uoguelph.ca

Received June 19, 2007



Cationic rhodium(I)-catalyzed cyclodimerization of oxabenzonorbornadienes produced naphtho[1,2-*b*]-furan ring systems in a single step with excellent yields and excellent enantioselectivities. The effect of various Rh(I) catalysts, Ag(I) salts, solvents, and phosphine ligands on the yield and enantioselectivity of the reaction was investigated, and the scope and limitations of this reaction with various oxabicyclic alkenes were studied. Similar results were obtained with the azabenzonorbornadiene analogues, providing the corresponding cyclodimerization products in excellent yields and excellent enantioselectivities.

Introduction

Oxabicyclic alkenes are valuable synthetic intermediates as they can serve as a general template to create highly substituted ring systems. For instance, asymmetric ring opening of these alkenes allows for the formation of several stereocenters in a single step.[1] They are also useful building blocks in molecular architecture.[2] We have recently examined different aspects of ruthenium-catalyzed reactions involving oxabenzonorbornadiene **1a** and found that, depending on the reaction conditions, several products (**2**−**6**) could be obtained (Scheme 1). For example, when oxabenzonorbornadiene **1a** is treated with an alkyne in the presence of the ruthenium catalyst, Cp*Ru(COD)Cl, a [2 + 2] cycloaddition is observed and cyclobutene cycloadduct **2** is formed.[3] When oxabenzonorbornadiene **1a** is treated with the secondary propargylic alcohol **7** in the presence of the neutral Ru catalyst, Cp*Ru(COD)Cl, in MeOH or using a cationic Ru catalyst (e.g., $[CpRu(CH_3CN)_3]PF_6$), isochromene **3** is formed.[4] On the other hand, if the same reaction between **1a** and **7** is carried out with Cp*Ru(COD)Cl in THF, cyclopropane **4** is produced.[5] More recently, we have observed that in the absence of an alkyne, Cp*Ru(COD)Cl catalyzes the isomerization of **1a** to the corresponding naphthalene oxide **5** or naphthol **6**.[6]

(1) For selected examples, see: (a) Lautens, M.; Fagnou, K.; Heibert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (c) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884. (e) Wu, M.-S.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2005**, *70*, 9545. (f) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373. (g) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734. (h) Cabrera, S.; Arrayás, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc. Chem.* **2005**, *127*, 17938. (i) Li, M.; Yan, X.-X.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. *Org. Lett.* **2004**, *6*, 2833 and references therein.

(2) For selected examples of molecular architecture, see: (a) Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Philp, D.; Stoddart, J. F. *Pure Appl. Chem.* **1993**, *65*, 119. (b) Warrener, R. N.; Margetic, D.; Sun, G.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1999**, *40*, 4111. (c) Warrener, R. N.; Butler, D. N.; Margetic, D.; Pfeffer, F. M.; Russell, R. A. *Tetrahedron Lett.* **2000**, *41*, 4671. (d) Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363. (e) Warrener, R. N.; Margetic, D.; Foley, P.; Butler, D. N.; Winling, A.; Beales, K. A.; Russell, R. A. *Tetrahedron* **2001**, *57*, 571. (f) Dalphond, J.; Bazzi, H. S.; Kahrim, K.; Sleiman, H. F. *Macromol. Chem. Phys.* **2002**, *203*, 1988. (g) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.

(3) For our recent studies of Ru-catalyzed [2 + 2] cycloadditions of bicyclic alkenes and alkynes, see: (a) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031. (b) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367. (c) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051. (d) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123. (e) Villeneuve, K.; Tam, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 610. (f) Villeneuve, K.; Riddell, N. G.; Jordan, R. W.; Tsui, G.; Tam, W. *Org. Lett.* **2004**, *6*, 4543. (g) Jordan, R. W.; Khoury, P. R.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2004**, *69*, 8467. (h) Riddell, N. G.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (i) Riddell, N. G.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1943. (j) Liu, P.; Jordan, R. W.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2006**, *71*, 3793. (k) Jordan, R. W.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2006**, *71*, 5830.

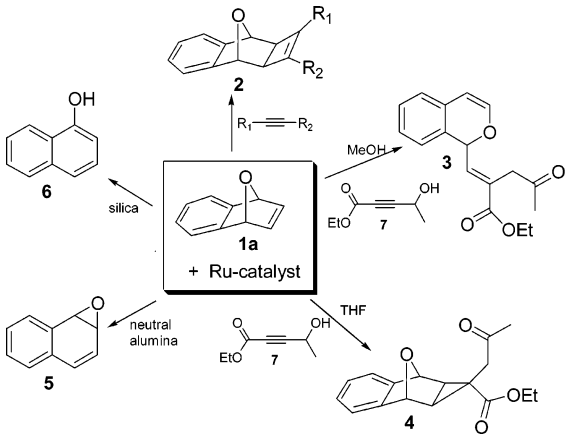
(4) Villeneuve, K.; Tam, W. *Eur. J. Org. Chem.* **2006**, 5499.

(5) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843.

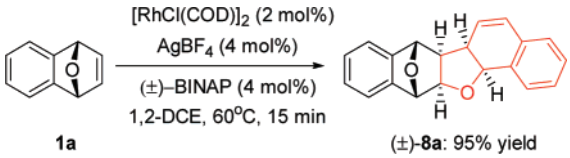
(6) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514.

10.1021/jo7012884 CCC: $37.00
Published on Web 09/20/2007

SCHEME 1. Ru-Catalyzed Reactions of Oxabenzonorbornadiene 1a



SCHEME 2. Rh-Catalyzed Cyclodimerization of Oxabenzonorbornadiene 1a



Since the naphthalene oxide **5** produced contains two stereogenic centers, nucleophilic ring opening of this epoxide would produce a useful synthetic intermediate.[6] An attempt to investigate the asymmetric version of this reaction by the addition of chiral ligands to various Ru catalysts resulted in either no reaction or no asymmetric induction. Since certain rhodium catalysts are known to generate naphthol **6** from oxabenzonorbornadiene **1a**,[1a] we decided to investigate the use of Rh catalysts instead of Ru catalysts. When oxabenzonorbornadiene **1a** was treated with $[RhCl(COD)]_2$ (2 mol %), $AgBF_4$ (4 mol %), and (±)-BINAP (4 mol %) in 1,2-dichloroethane (DCE) at 60 °C, cyclodimerization product (±)-**8a** was formed in 95% isolated yield in 15 min as a single diastereomer, instead of the expected naphthalene epoxide (Scheme 2). Concurrently, the same transformation was discovered by Hayashi and co-workers, using a similar catalytic system (1 mol % $[RhCl(R)\text{-BINAP}]_2$ and 2 mol % $NaBAr^F{}_4$ in DCE at 40 °C, where Ar^F = 3,5-bis-(trifluoromethyl)phenyl).[7] The structure and relative stereochemistry of (±)-**8a** was established by NMR experiments (1D GOESY and 2D COSY)[8] and confirmed by X-ray crystal structure analysis.[9] The absolute stereochemistry was determined through comparison to Hayashi's published results. This unexpected transformation provides a novel and very efficient method for the construction of the naphtho[1,2-*b*]furan ring system (Scheme 2, highlighted in red). This type of naphtho[1,2-*b*]furan ring system is present in a number of biologically important natural products (Figure 1),[10] and multiple step syntheses are usually required to generate such a ring system.[11] More importantly, use of a chiral ligand would possibly produce a chiral naphtho[1,2-*b*]furan ring system, making this novel reaction an especially attractive synthetic method. In fact, when (*R*)-BINAP was employed instead of (±)-BINAP, cyclodimerization product **8a** was formed in 96% ee, vide infra.

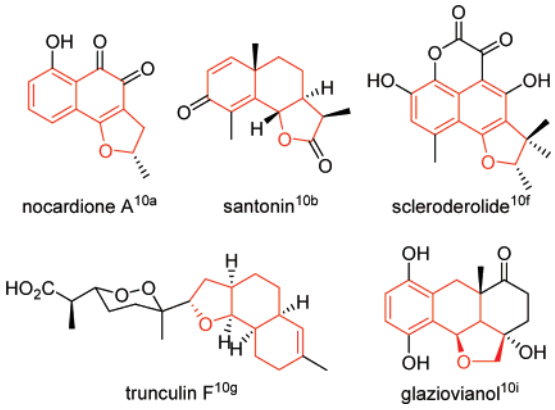


FIGURE 1. Examples of natural products that contain the naphtho-[1,2-*b*]furan ring system.

In recent years, there have been several previous examples of the construction of fused ring systems through dimerization reactions.[12] In 2002, Junjappa and co-workers developed an expedient route to the 1*H*-cyclopenta[*c*]carbazole framework through a cascade of reactions that included the dimerization of the simple indole precursors (eq 1).[12a] Around the same time, Isaccs and co-workers devised a synthetic route to methylene bridged glycoluril dimers, using a variety of glycoluril deriva-

(7) (a) This reaction was discovered by the Ph.D. student Karine Villeneuve on May 9, 2006, and the results were presented in her Ph.D. thesis which was successfully defended on October 20, 2006: Villeneuve, K. Ph.D. thesis, University of Guelph, 2006. (b) During the preparation of this manuscript, a paper closely related to this study (using a slightly different catalyst precursor) appeared: Nishimura, T.; Kawamoto, T.; Sasaki, K.; Tsurumaki, E.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 1492.

(8) GOESY: Gradient enhanced nuclear Overhauser enhancement spectroscopy. See: (a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037. (b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (c) Dixon, A. M.; Widmalm, G.; Bull, T. E. *J. Magn. Reson.* **2000**, *147*, 266.

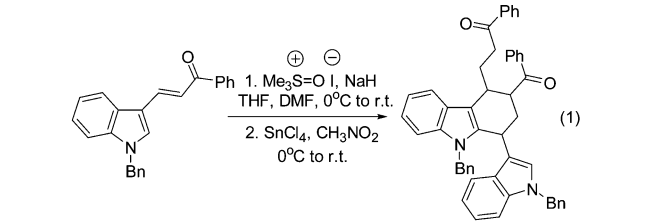
(9) Lough, A. J.; Allen, A.; Tam, W. *Acta Crystallogr.* **2007**, *E63*, o1462−o1463.

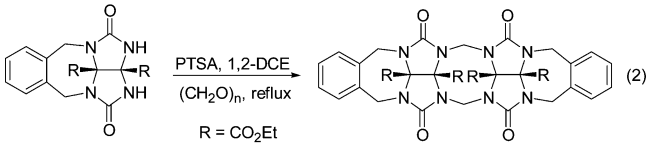
(10) For examples of natural products containing a naphtho[1,2-*b*]furan ring system, see: (a) Otani, T.; Sugimoto, Y.; Aoyagi, Y.; Igarashi, Y.; Furumai, T.; Saito, N.; Yamada, Y.; Asao, T.; Oki, T. *J. Antibiot.* **2000**, *53*, 337. (b) Corey, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 1044. (c) Marco, J. A.; Sanz, J. F.; Falco, E.; Jakupovic, J.; Lex, J. *Tetrahedron* **1990**, *46*, 7941. (d) Hoeksama, H.; Kruger, W. C. *J. Antibiot.* **1976**, *29*, 704. (e) Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128. (f) Tomoda, H.; Tabata, N.; Masuma, R.; Si, S.-Y.; Omura, S. *J. Antibiot.* **1998**, *51*, 618. (g) Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1993**, *46*, 1363. (h) Thomas, R. *Pure Appl. Chem.* **1973**, *34*, 515. (i) da Costa, G. M.; de Lemos, T. L. G.; Pessoa, O. D. L.; Monte, F. J. Q.; Braz-filho, R. *J. Nat. Prod.* **1999**, *62*, 1044. (j) Gaspar-Marques, C.; Simoes, M. F.; Rodriguez, B. *J. Nat. Prod.* **2005**, *68*, 1408.

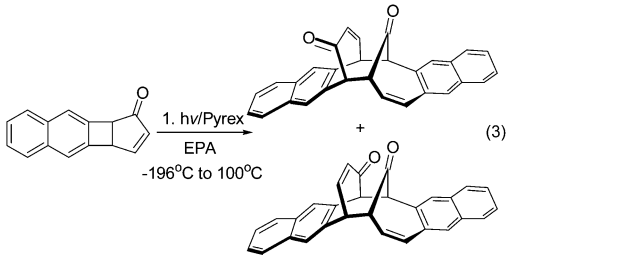
(11) (a) Clive, D. L. J.; Fletcher, S. P. *Chem. Commun.* **2003**, 2464. (b) Kawamata, T.; Nagashima, K.; Nakai, R.; Tsuji, T. *Synth. Commun.* **1996**, *26*, 139. (c) Kraus, G. A.; Chen, L. *Synlett* **1991**, 89. (d) Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756. (e) Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966. (f) Maertens, F.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2004**, 2707. (g) Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282. (h) Brimble, M. A.; Elliott, R. J.; Turner, P. *Tetrahedron* **1998**, *54*, 14053. (i) Takeya, T.; Doi, H.; Ogata, T.; Okamoto, I.; Kotani, E. *Tetrahedron* **2004**, *60*, 9049. (j) Noland, W. E.; Kedrowski, B. L. *J. Org. Chem.* **1999**, *64*, 596.

(12) For examples of the creation of fused ring systems through dimerization reactions, see: (a) Venkatesh, C.; Ila, H.; Junjappa, H.; Mathur, S.; Huch, V. *J. Org. Chem.* **2002**, *67*, 9477. (b) Wu, A.; Chakraborty, A.; Will, D.; Lagona, J.; Damkaci, F.; Ofori, M. A.; Chiles, J. K.; Fettinger, J. C.; Isaacs, L. *J. Org. Chem.* **2002**, *67*, 5817. (c) Ohkita, M.; Sano, K.; Suzuki, T.; Tsuji, T. *Tetrahedron Lett.* **2001**, *42*, 7295. (d) Abakumov, G. A.; Druzhkov, N. O.; Kurskii, Y. A.; Abakumova, L. G.; Shavyrim, A. S.; Fukin, G. K.; Poddel'skii, A. I.; Cherkasov, V. K.; Okhlopkova, L. S. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 2571. (e) Klys, A.; Czardybon, W.; Warkentin, J.; Werstuik, N. H. *Can. J. Chem.* **2004**, *82*, 1769. (f) Abdou, W. M.; Kamel, A. A. *Tetrahedron* **2000**, *56*, 7573.

tives (eq 2).[12b] Tsuji and co-workers achieved the dimerization of naphtho[2,3-*c*]tropone through photochemical treatment of the naphthocyclobutene valence isomer (eq 3).[12c] These are just a few examples of the dimerization strategies available to create fused ring systems.





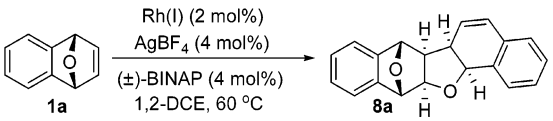


Results and Discussion

Rhodium-Catalyzed Cyclodimerization of Oxabenzonorbornadiene 1a. To explore the scope and limitation of this reaction, we have studied the effect of various Rh(I) catalysts, Ag(I) salts, solvents, and phosphine ligands. Control experiments were initially conducted, and it was found that all components are necessary for the success of this reaction. Omission of a Rh(I) complex leads to no reaction, while use of a neutral Rh(I) complex, rather than cationic, or exclusion of the phosphine ligand results in decomposition of the starting material. Results by Hayashi also confirm the necessity of the cationic Rh(I) species.[7]

After screening through a variety of Rh(I) complexes, it was found that all but one of the chosen catalysts, in their cationic form, promoted the cyclodimerization in good to excellent yields (Table 1). In the case of the chlorobis(cyclooctene)rhodium(I) dimer (entry 8), instead of obtaining the cyclodimerization product **8a**, the reaction provided an alternate isomerized dimer, alcohol **9**, in 43% yield (Scheme 3). It should also be noted that chlorodicarbonylrhodium(I) dimer and Wilkinson's catalyst (entries 2−3) both resulted in slightly lower yields of 79 and 83%, respectively. With the neutral Rh(I) complexes, the catonic forms of the catalysts were generated by the addition of the Ag(I) salt (entries 1−3 and 6−8). Through the evaluation of the Rh(I) catalysts, it can be seen that the best yields were obtained for those catalysts bearing at least one 1,5-cyclooctadiene (COD) ligand (entries 1, 4, 5). In most of the cases, all starting oxabenzonorbornadiene **1a** was consumed within 15 min. The chloronorbornadienerhodium(I) dimer was slightly more sluggish than the majority, requiring a reaction time of 1 h (entry 7), while Wilkinson's catalyst was significantly slower requiring 18 h for the complete consumption of **1a** (entry 3).

TABLE 1. Optimization of Rhodium Catalysts



entry	Rh(I)	time (h)	yield[d] (%)
1	$[RhCl(COD)]_2$	0.25	95
2	$[RhCl(CO)_2]_2$	0.25	79
3[a]	$[RhCl(PPh_3)_3]$	18	83
4[a,b]	$[Rh(COD)_2][BF_4]$	0.25	93
5[a,b]	$[Rh(COD)_2][OTf]$	0.25	93
6	$[RhCl(CH_2{=}CH_2)_2]_2$	0.25	92
7	$[RhCl(NBD)]_2$	1	91
8	$[RhCl(C_8H_{14})_2]_2$	0.25	0[c]

[a] 4 mol % of Rh catalyst was used. [b] No $AgBF_4$ was used. [c] Obtained 43% of **9**. [d] Isolated yield after column chromatography.

SCHEME 3. Generation of Oxabenzonorbornenol 9 with Chlorobis(cyclooctene)rhodium(I) Dimer

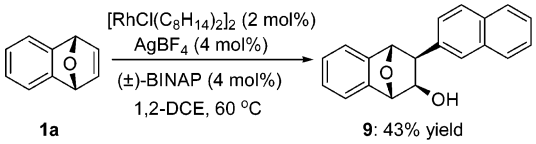
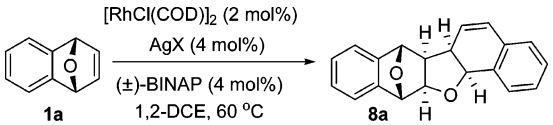


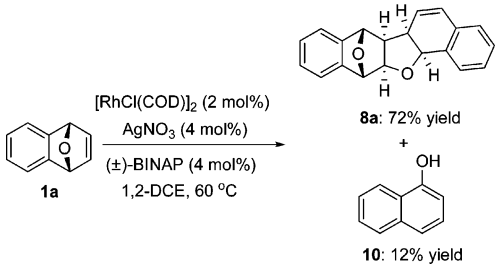
TABLE 2. Optimization of Silver Salts



entry	AgX	time (h)	yield[b] (%)
1	$AgBF_4$	0.25	95
2	$AgNO_3$	8	72[a]
3	$AgSbF_6$	0.25	88
4	AgOTf	0.25	80

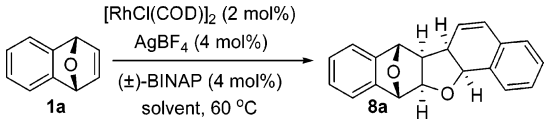
[a] Obtained 12% of 1-naphthol **10**. [b] Isolated yield after column chromatography.

SCHEME 4. Generation of 1-Naphthol Side Product



To test the effect of the counterion of the cationic rhodium catalyst, four common Ag(I) salts were evaluated. All four resulted in the cyclodimerization product **8a** in good to excellent yields (Table 2). The silver tetrafluoroborate salt, used in the original catalytic system, provided a superior yield compared to the other three salts. It should also be noted that in the case of silver nitrate, the reaction also resulted in the isomerization of **1a** to yield 12% of 1-naphthol **10** (Scheme 4). The reaction with silver nitrate was also found to be much slower than with the other three silver salts, requiring 8 h instead of 15 min to go to completion. Slightly lower yields were obtained with silver

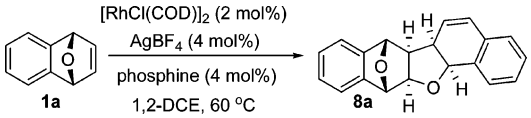
TABLE 3. Optimization of Solvents



entry	solvent	time (h)	yield[b] (%)
1	1,2-dichloroethane	0.25	95
2	toluene	0.25	91
3	THF	0.25	92
4	dichloromethane	0.25	93
5	methanol	0.25	83
6	DMF	0.25	79
7	acetone	0.25	91
8	hexanes	18	29[a]

[a] Obtained 20% of 1-naphthol **10**. [b] Isolated yield after column chromatography.

TABLE 4. Optimization of Nonchiral Ligands



entry	phosphine[12]	time (h)	yield[d] (%)
1	(±)-BINAP	0.25	95
2	dppf	19.5	46[a]
3	dppe	18	0[b,c]
4	PPh_3	18	36[a]
5	PCy_3	18	0
6	P(biphenyl)^{t}Bu$_2$	18	0[a,b]

[a] Recovered 14−42% of **1a**. [b] Obtained 17−48% of 1-naphthol **10**. [c] Obtained 22% alcohol **9**. [d] Isolated yield after column chromatography.

trifluoromethanesulfonate than with silver tetrafluoroborate when using the chloro(1,5-cyclooctadiene)rhodium(I) dimer as the catalyst; interestingly, upon using the similar cationic bis(1,5-cyclooctadiene)rhodium(I) complex, both counterions provide the same yield (Table 1, entries 4−5).

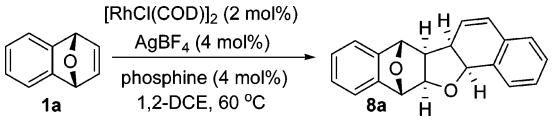
In general, solvent had only a modest effect on the reaction, and good to excellent yields of dimer **8a** were obtained within 15 min (Table 3). Both methanol and DMF (entries 5−6) provided slightly lowered yields of 83 and 79% respectively, although the reaction was still complete within 15 min. All other entries provided yields of 91% or higher, with the exception of hexanes (entry 8). Both the starting oxabenzonorbornadiene **1a** and the catalyst dissolved very poorly in hexanes resulting in a drastically lowered yield of **8a** and a significantly increased reaction time. In addition, 20% of **1a** isomerized to give 1-naphthol **10**.

In contrast to the previously discussed reaction components, the phosphine ligand showed considerable influence on the cyclodimerization of oxabenzonorbornadiene **1a**. Both mono- and bidentate phosphine ligands were evaluated (Table 4). It was found that the BINAP ligand provided significantly better results than any other ligands studied (entry 1). The only other ligands to provide the cyclodimerization product **8a** were diphenylphosphinoferrocene (entry 2) and triphenylphosphine (entry 4); however, these reactions were plagued by low yields and a lack of complete starting material consumption even after 18 h. Diphenylphosphinoethane (entry 3) and 2-(di-*tert*-butylphosphino)biphenyl (entry 6) both resulted in the isomerization of **1a** to yield 1-naphthol **10**, while the diphenylphosphinoethane also provided the isomerized dimer, alcohol **9**. The only alkylphosphine ligand evaluated, tricyclohexylphosphine (entry 5), showed only decomposition of starting materials.

Through the studies described above, it was concluded that although various conditions were found to promote the cyclodimerization of oxabenzonorbornadiene **1a**, the optimal conditions for the racemic cyclodimerization are $[RhCl(COD)]_2$ (2 mol %), $AgBF_4$ (4 mol %), (±)-BINAP (4 mol %), in 1,2-dichloroethane (0.5 M) at 60 °C.

Asymmetric Rhodium-Catalyzed Cyclodimerization of Oxabenzonorbornadiene 1a. With the optimal conditions for the racemic cyclodimerization of oxabenzonorbornadienes determined, the focus was shifted to the development of the asymmetric version. Using the optimized reaction conditions for the cyclodimerization of oxabenzonorbornadiene **1a**, we simply substituted (*R*)-BINAP for the (±)-BINAP to test the initial asymmetric version. We were pleased to find that, along with an excellent yield, the chiral BINAP ligand provided high enantioselectivity (96% ee, Table 5, entry 1).

TABLE 5. Optimization of Chiral Ligands



entry	phosphine[13]	time (h)	yield[f] (%)	ee[g] (%)
1	(*R*)-BINAP	0.5	96	96
2	(*R*)-Tol-BINAP	0.5	86	96
3	(*R*)-3,5-xylyl-BINAP	2	0[a,d]	
4	(*R*,*R*)-Me-Duphos	21	93[b]	68
5	(*S*,*S*)-Chiraphos	2.5	45	60[c]
6	(*R*)-Prophos	2	41[b]	40
7	(*R*,*S*)-Josiphos	24	23[b,d]	37
8	(*S*,*S*)-DIOP	22.5	28[b]	4
9	(*S*,*S*)-Norphos	20	0[d]	
10	(*S*)-Phanephos	21	0[b,d]	
11	(*R*,*R*)-Me-BPE	21.5	0[b,d]	
12	Trost ligand	23	0[e]	

[a] Obtained 25% of alcohol **9**. [b] Recovered 17−61% of **1a**. [c] Opposite configuration. [d] Obtained 3−57% of 1-naphthol **10**. [e] No reaction observed. [f] Isolated yield after column chromatography. [g] The enantiomeric excess (ee) of **8a** was determined by HPLC using a Chiralcel OD-H column.

In order to determine if there was a more suitable ligand for the asymmetric reaction, a variety of chiral ligands were evaluated (Table 5).[13] As the (*R*)-BINAP ligand provided excellent initial results, we were inclined to test other BINAP ligands. While (*R*)-*p*-Tol-BINAP gave identical enantioselectivities as the parent BINAP ligand, the yield was diminished slightly to 86% (entry 2). When changing the ligand to the (*R*)-3,5-xylyl-BINAP, we found that no cyclodimerization product **8a** was obtained; instead, up to 25% of the isomerized dimer, alcohol **9**, and 57% of 1-naphthol **10** were produced (entry 3).

(13) Abbreviations for various phosphine ligands used: dppf, 1,1′-bis(diphenylphosphino)ferrocene; dppe, 1,2-bis(diphenylphosphino)ethane; (*R*)-BINAP, (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; (*R*)-Tol-BINAP, (*R*)-(+)-2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl; (*R*)-3,5-xylyl-BINAP, (*R*)-(+)-2,2′-bis(di(3,5-xylyl)phosphino)-1,1′-binaphthyl; (*R*,*R*)-Me-Duphos, (−)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene; (*S*,*S*)-Chiraphos: (2*S*,3*S*)-(−)-bis(diphenylphosphino)butane; (*R*)-Prophos, (*R*)-(+)-1,2-bis(diphenylphosphino)propane; (*R*,*S*)-Josiphos, (*R*)-(−)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine ethanol adduct; (*S*,*S*)-DIOP, (4*S*,5*S*)-(+)-4,5-bis(diphenylphosphinomethyl)-2,2′-dimethyl-1,3-dioxolane; (*S*,*S*)-Norphos, (2*S*,3*S*)-(+)-2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene; (*S*)-phanephos, (*S*)-(+)-4,12-bis(diphenylphosphino)-[2.2]paracyclophane; (*R*,*R*)-Me-BPE, (+)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)ethane; (*R*)-Trost ligand: (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl).

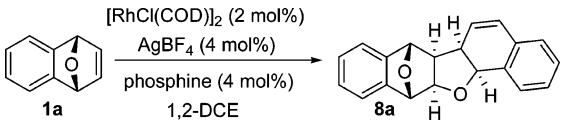
Chiral ligands with other architectures were also screened. (*R*,*R*)-Me-Duphos provided the cyclodimerization product **8a** in an excellent yield of 93%; however, compared to (*R*)-BINAP, the reaction was significantly sluggish and considerably less enantioselective (Table 5, entry 4). Several other chiral ligands also provided **8a**, however, with much lower yields and selectivities, ranging from 28 to 45% and 4−60% ee, respectively (entries 5−8). In addition, in all of these cases the oxabenzonorbornadiene **1a** was not completely consumed. For (*S*,*S*)-Chiraphos and (*R*)-Prophos, reaction times of 24 h were required for complete consumption of the starting material. Extended reaction times also caused the resultant cyclodimerization product **8a** to isomerize to alcohol **9**. Taking heed of this observation, the reaction times were shortened to maximize the yield of **8a** while leaving some oxabenzonorbornadiene **1a** unreacted (entries 5 and 6). For (*R*,*S*)-Josiphos (entry 7) and (*S*,*S*)-DIOP (entry 8), starting material still remained despite allowing the reaction to proceed for up to 24 h. In the case of (*R*,*S*)-Josiphos, a small amount of 1-naphthol **10** was also obtained.

Other chiral ligands were evaluated, but the reaction did not provide the cyclodimerization product **8a** (Table 5, entries 9−12). Total starting material consumption within 20 h for (*S*,*S*)-Norphos (entry 9) provided only 1-naphthol **10** in 35% yield. Both (*S*)-Phanephos (entry 10) and (*R*,*R*)-Me-BPE (entry 11) yielded 1-naphthol **10** and unconsumed starting material after nearly 24 h of reaction time. In the case of (*S*)-Phanephos, a large amount of decomposition was also obtained. The final chiral ligand investigated, the Trost ligand (entry 12), resulted in no reaction as only starting oxabenzonorbornadiene **1a** was observed with no sign of decomposition.

As temperature can have a profound effect on the enantioselectivity of a chiral system, various temperatures were investigated for the most promising chiral ligands (Table 6). The chiral system utilizing the (*R*)-BINAP ligand was evaluated at 60, 40, 25, and 0 °C, while the (*R*)-*p*-Tol-BINAP ligand was evaluated at 60, 40, and 25 °C. The results of these experiments showed that temperature had very little effect on the enantioselectivity of the asymmetric cyclodimerization of oxabenzonorbornadiene **1a**. Cyclodimerizations completed at lower temperatures required progressively longer reaction times.

Through the screening of various chiral ligands, the optimal conditions for the asymmetric cyclodimerization of oxabenzonorbornadiene **1a** was found to be the initial chiral catalytic system: $[RhCl(COD)]_2$ (2 mol %), $AgBF_4$ (4 mol %), and (*R*)-BINAP (4 mol %), in 1,2-dichloroethane (0.5 M) at 60 °C.

TABLE 6. Effect of Temperature on Enantiomeric Ratio



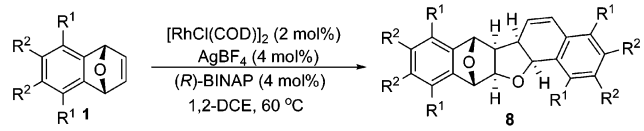
entry	phosphine	*T* (°C)	time (h)	yield[a] (%)	ee[b] (%)
1	(*R*)-BINAP	60	0.5	96	96
2	(*R*)-BINAP	40	1.5	97	96
3	(*R*)-BINAP	25	5	90	96
4	(*R*)-BINAP	0	22	98	96
5	(*R*)-Tol-BINAP	60	0.5	86	96
6	(*R*)-Tol-BINAP	40	2	92	97
7	(*R*)-Tol-BINAP	25	2.5	98	97

[a] Isolated yield after column chromatography. [b] The enantiomeric excess (ee) of **8a** was determined by HPLC using a Chiralcel OD-H column.

Scope of the Reaction. With the optimized conditions for the enantioselective cyclodimerization of oxabenzonorbornadiene **1a** in hand, the scope of the reaction was then investigated using various oxabicyclic substrates. The benzobicyclic alkenes evaluated were prepared through Diels−Alder cycloadditions between furan or pyrroles and the appropriate benzyne species. In each case, the benzynes were generated in situ from either anthranilic acid[14a,b,15a] or halogenated benzenes.[14c−g,15b] We found that the reaction was general for most oxabenzonorbornadienes that contain substituents on the benzene ring. A wide range of yields from 37 to 95% was obtained; however, the enantioselectivities were high, ranging from 88 to 98% ee (Table 7, entries 2−8). In comparison to results reported by Hayashi, divergent results were seen for the dimerizations of **1e** and **1f**. In our study, the yields of these reactions were noticeably lower, and for **1e**, the enantioselectivity was slightly diminished.

Interesting reactivity was observed for some substrates not reported by Hayashi. Surprisingly, oxabenzonorbornadiene **1d** did not provide the corresponding cyclodimerization product, and only 1-naphthol **11a** was obtained in 69% yield (Table 7, entry 4; Scheme 5). This result was not expected as oxabenzonorbornadiene **1c** (entry 3), which only differs in the placement of the methoxy substituents, easily underwent the cyclodimerization to provide the corresponding product **8c** with excellent yield and enantioselectivity. Thus, the position of the substituents on the benzene ring can crucially modify the outcome of this reaction. The naphthol obtained was determined to be the 1-naphthol through conversion to the 1-acetylnaphthol **11b** and subsequent NMR analysis (GOESY).[8] It is also noteworthy that oxabenzonorbornadiene **1g** provided the cor-

TABLE 7. Rh-Catalyzed Asymmetric Cyclodimerization of Benzo-Substituted Oxabenzonorbornadienes



1a: R^1 = H, R^2 = H
1b: R^1 = Me, R^2 = H
1c: R^1 = OMe, R^2 = H
1d: R^1 = H, R^2 = OMe
1e: R^1 = H, R^2 = Br
1f: R^1 = H, R^2 = F
1g: R^1 = F, R^2 = F
1h: R^1-R^2 = -(CH)$_4$-

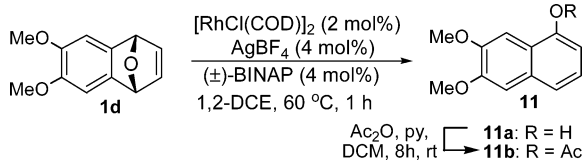
entry	substrate	product	time (h)	yield[c] (%)	ee[d] (%)
1	**1a**	**8a**	0.5	96	96
2	**1b**	**8b**	0.5	77	91
3	**1c**	**8c**	0.5	94	98
4	**1d**	**8d**	0.5	0[a]	
5	**1e**	**8e**	0.5	46	88
6	**1f**	**8f**	0.25	79	97
7	**1g**	**8g**	0.5	37[b]	98
8	**1h**	**8h**	1	95	94

[a] Obtained 69% of **11a** when using (±)-BINAP. [b] Obtained 32% of **12**. [c] Isolated yield after column chromatography. [d] The enantiomeric excess (ee) of **8** was determined by HPLC using a Chiralcel OD-H column.

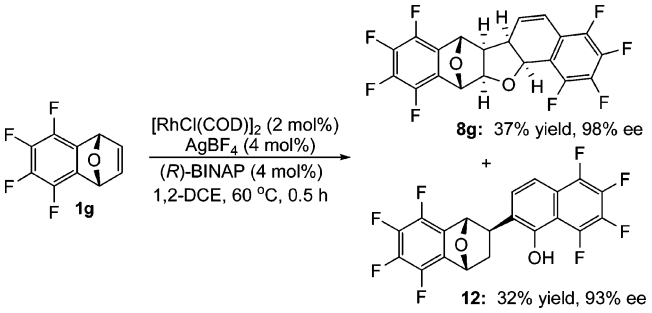
(14) For preparations of oxabenzonorbornadienes, see: (a) Nakayama, J.; Sakai, A.; Hoshino, M. *J. Org. Chem.* **1984**, *49*, 5084. (b) Friedman, L.; Logullo, F. M. *J. Org. Chem.* **1969**, *34*, 3089. (c) Jung, K. Y.; Masato, K. *J. Org. Chem.* **1989**, *54*, 5667. (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884. (e) Lai, Y.-H.; Yong, Y.-L.; Wong, S.-Y. *J. Org. Chem.* **1997**, *62*, 4500. (f) Caster, K. C.; Keck, C. G.; Walls, R. D. *J. Org. Chem.* **2001**, *66*, 2932. (g) Gribble, G. W.; LeHoullier, C. S.; Sibi, M. P.; Allen, R. W. *J. Org. Chem.* **1985**, *50*, 1611. (h) Hart, H.; Bashir-Hashemi, B.; Luo, J.; Meador, M. A. *Tetrahedron* **1986**, *42*, 1641.

(15) For preparations of azabenzonorbornadienes, see: (a) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3645. (b) Cho, Y.-H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837.

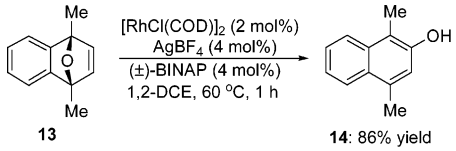
SCHEME 5. Cyclodimerization Attempt of Oxabenzonorbornadiene 1d



SCHEME 6. Cyclodimerization of Oxabenzonorbornadiene 1g



SCHEME 7. Cyclodimerization Attempt of Oxabenzonorbornadiene 13



responding cyclodimerization product **8g** with excellent enantioselectivity (98% ee) in only 37% yield (entry 7). This low yield can be attributed to the generation of a second dimeric product, naphthol dimer **12**, which was obtained in 32% yield (Scheme 6).

Along with oxabenzonorbornadiene substrates with substituted benzenes, we investigated the cyclodimerization of other symmetrical oxanorbornadienes. We attempted the cyclodimerization of C1,C4-substituted oxabenzonorbornadiene **13**; however, no dimer product was observed and only naphthol **14** was isolated in 86% yield (Scheme 7). As only oxabenzonorbornadiene substrates had been investigated, we decided to test the applicability of the reaction to some non-benzo oxabicyclic alkenes. Oxanorbornadiene **15** and oxanorbornene **16** were both subjected to the optimized reaction conditions, but it was found that neither substrate provided the desired cyclodimerization product (Scheme 8). Oxanorbornadiene **15** resulted in two different dimer products, phenol **17** and cyclobutane **18**, obtained in 9 and 39% yields, respectively, also seen in the Hayashi study. Interestingly, phenol **17** has a structure very similar to that of fluorinated naphthol dimer **12** and most likely results through a similar mechanism. In the cases of bicyclic alkenes **1g** and **15**, it seems that the electron-withdrawing abilities of the fluorinated benzene ring of **1g** and the two ester moieties of **15** allowed the reaction to proceed through an alternate pathway, providing the corresponding naphthol or phenol dimerization product. In contrast, oxanorbornene **16** did not provide any kind of dimer, and 39% starting material was recovered after 32 h.

Along with the symmetrical oxabicyclic alkenes evaluated, a number of unsymmetrical oxabicyclic alkenes were also investigated using the optimized cyclodimerization conditions. Unsymmetrical oxabenzonorbornadienes **19a**−**d** and **21**, each

SCHEME 8. Cyclodimerization Attempts of Non-Benzo Oxabicyclic Alkenes

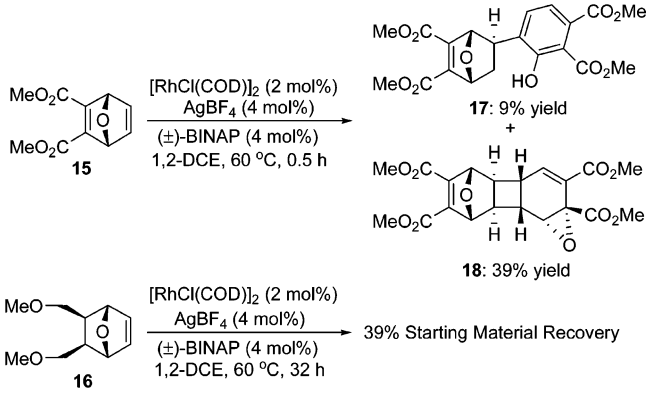
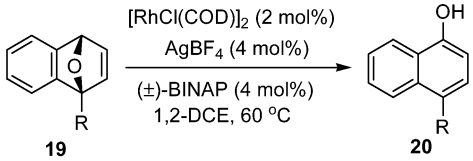


TABLE 8. Evaluation of the Cyclodimerization of Unsymmetrical Oxabenzonorbornadienes

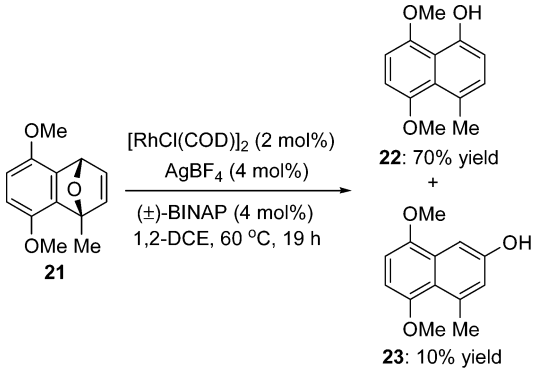


19a: R = CO_2Me
19b: R = Me
19c: R = COMe

entry	substrate	time (h)	yield **20**[a] (%)	recovered **19**[a] (%)
1	**19a**	26	30	70
2	**19b**	1.5	70	0
3	**19c**	26	20	70

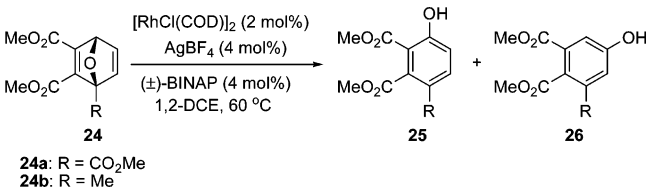
[a] Isolated yield after column chromatography.

SCHEME 9. Generation of Naphthols 22 and 23 from Unsymmetrical Oxabenzonorbornadiene 21



bearing a substituent at the C1 bridgehead position, simply isomerized, leading to the isolation of the corresponding 1-naphthol and, in some cases, recovered oxabenzonorbornadiene (Table 8; Scheme 9). In the case of **21**, the 2-naphthol **23** was also obtained in a 10% yield (Scheme 9). Two non-benzo unsymmetrical oxanorbornadiene substrates (**24a**,**b**) were also evaluated (Table 9). In both cases, no dimerization was observed, quite possibly due to the presence of the C1 substituents. In the case of **24a**, which bears a C1 ester moiety (entry 1), only starting material was isolated after decomposition was observed. However, oxanorbornadiene **24b**, with a C1 methyl substituent, provided the corresponding 1- and 2-naphthols (**25b** and **26b**, respectively) in a 4:1 ratio (**25b**/**26b)** and 65% combined yield.

TABLE 9. Evaluation of the Cyclodimerization of Unsymmetrical Oxanorbornadienes



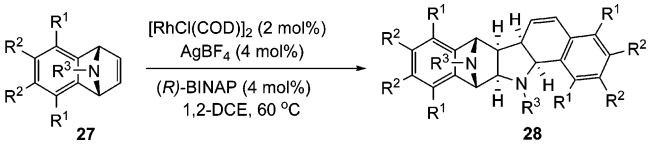
entry	substrate	time (h)	yield **25** + **26**[a] (%)
1	**24a**	1.5	0[b]
2	**24b**	1.5	65[c]

[a] Isolated yield after column chromatography. [b] Recovered 75% of **24a**. [c] Products isolated in a 4:1 (**25**/**26**) ratio.

We then turned our attention to the cyclodimerization of azabenzonorbornadienes (Table 10), providing a wider scope than reported by Hayashi. All substrates evaluated, with the exception of one, provided the corresponding cyclodimerization product **28** in moderate to good yields (54−88%) and with excellent selectivities (94−99% ee). Azabenzonorbornadiene **27b** (entry 2), the only azabicyclic alkene evaluated that did not bear an ester moiety on the bridging nitrogen, did not successfully undergo the cyclodimerization reaction. After 23 h at 60 °C, 76% of azabenzonorbornadiene **27b** was recovered with no apparent product formation; heating to 80 °C for 50 h produced 1-naphthyltosylamine **29** in 30% yield (Scheme 10).

When comparing the reactivity of the oxa- and azabenzonorbornadienes toward the Rh-catalyzed cyclodimerization, it can be seen that the oxabenzonorbornadiene substrates are significantly more reactive than their aza analogues. The oxabenzonorbornadiene substrates require reaction times of just 15 min to 1 h, while the azabenzonorbornadienes required 4−47 h to go to completion. It should also be noted that the less sterically hindering methyl carbamate **27c** (Table 10, entry 3) reacted significantly faster than the corresponding azabenzonorbornadiene **27a** bearing the Boc moiety (entry 1), which indicates that sterics may also be at play.

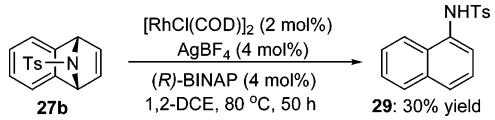
TABLE 10. Rh-Catalyzed Asymmetric Cyclodimerization of Benzo-Substituted Azabenzonorbornadienes



entry	substrate	product	time (h)	yield[b] (%)	ee[c] (%)
1	**27a**	**28a**	20	88	98
2	**27b**	**28b**	23	0[a]	
3	**27c**	**28c**	4	76	98
4	**27d**	**28d**	47	54	99
5	**27e**	**28e**	16	61	94

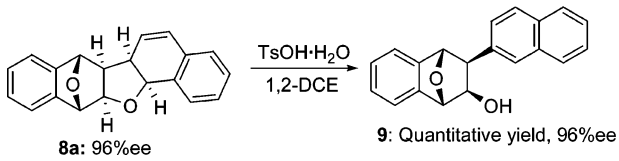
[a] Recovered 76% of **27b**. Heating at 80 °C for 50 h produced 30% 1-naphthyltosylamine **29**. [b] Isolated yield after column chromatography.[c] The enantiomeric excess (ee) of **28** was determined by HPLC using a Chiralcel OD-H column.

SCHEME 10. Generation of 1-Naphthyltosylamine 29



Inspired by the isolation of the alternate isomerized dimer, oxabenzonorbornenol **9**, from the cyclodimerization product **8a**, we attempted to generate this species from the isolated cyclodimerization product. Although disappointing conversion was obtained under basic conditions (no reaction with NaOMe, 20% yield with ^{n}BuLi), we were pleased to find that subjecting **8a** to *p*-toluenesulfonic acid provides **9** in quantitative yield with no degradation of the enantiopurity (Scheme 11).

SCHEME 11. Isomerization of the Cyclodimerization Product 8a to Oxabenzonorbornenol 9

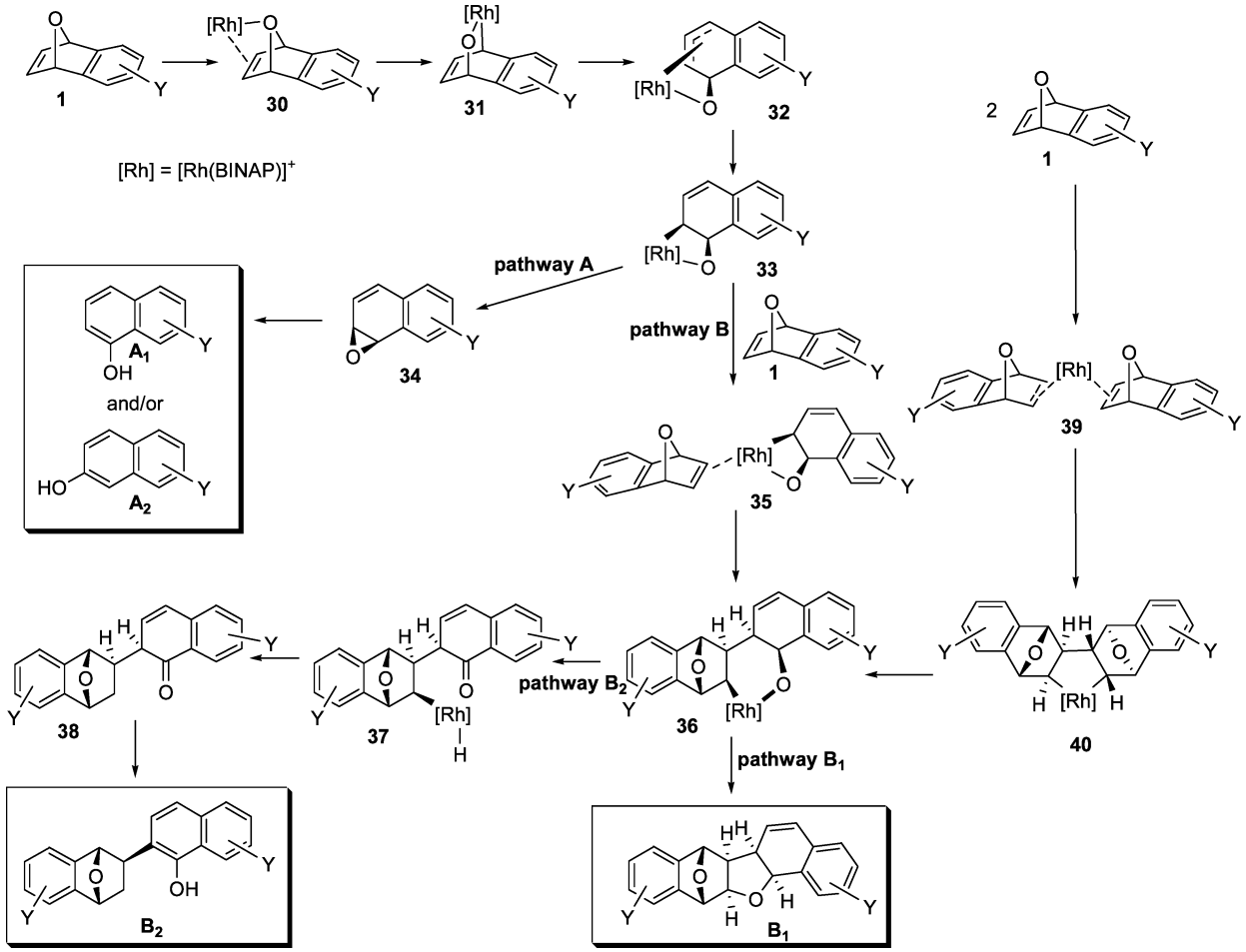


A plausible mechanism has been devised for the formation of the cyclodimerization product $\mathbf{B_1}$, and the side products $\mathbf{A_1}$ (or $\mathbf{A_2}$) and $\mathbf{B_2}$ (Scheme 12). The active catalyst, $[Rh(BINAP)]^+$, is formed through treatment of the precatalyst, $[RhCl(COD)]_2$, with $AgBF_4$ to remove the chloride and then addition of the BINAP ligand, which replaces the COD ligand. The active catalyst is chelated by **1** to form complex **30**. Strain in the oxabicyclic structure is then released through an oxidative insertion of the rhodium into the C−O bond to form complex **31**. This intermediate is in equilibrium with π-allyl complex **32** and metallocycle **33**. As rhodium has the ability to coordinate five species, this allows a second molecule of **1** to coordinate to complex **33** (pathway B), generating complex **35**. A carbometalation can then occur to form the six-membered metallocycle **36**. It is at this point where the mechanistic pathway diverges to provide either the dimerization product $\mathbf{B_1}$ or naphthol $\mathbf{B_2}$. Reductive elimination (pathway B_1) of metallocycle **36** would yield the cyclodimerization product $\mathbf{B_1}$. However, a β-hydride elimination (pathway B_2) can also occur with metallocycle **36**, which leads to the rhodium hydride species **37**. Reductive elimination of **37** would lead to ketone **38** and regeneration of the active catalyst. Compound **38** will then rearomatize via keto−enol tautomerism to provide naphthol $\mathbf{B_2}$. The corresponding naphthol side products $\mathbf{A_1}$ (or $\mathbf{A_2}$) could be formed according to pathway A, which begins with the reductive elimination of complex **33** generating epoxide **34**. Completion of the production of naphthols $\mathbf{A_1}$ (or $\mathbf{A_2}$) from **34** has been previously described.[6]

The formation of naphthol $\mathbf{B_2}$ was only observed during the cyclodimerization of oxabenzonorbornadiene **1g**, providing **12**. Through control experiments, it was determined that **12** was formed directly from **1g**. Dimerization product **8g** was subjected to the both the catalyst conditions and acidic conditions, and in either case, no further reaction was observed.

Cyclodimerization product $\mathbf{B_1}$ could also be formed through an alternate mechanism, proposed by Hayashi and co-workers.[7b] In this mechanism, two molecules of **1** coordinate to the active catalyst, forming **39**, which undergoes an oxidative cyclization to form metallocycle **40**. Subsequent β-oxygen elimination provides metallocycle **36**, which upon reductive elimination provides $\mathbf{B_1}$. Hayashi has also proposed a mechanism for the formation of **17**. Their proposed pathway is analogous to what we have proposed for the formation of dimerization product $\mathbf{B_2}$ (pathway B_2).

SCHEME 12. Proposed Mechanisms



Conclusion

In summary, we have demonstrated that the asymmetric Rh-catalyzed cyclodimerization of oxa- and azabicyclic alkenes can be applied to a wide variety of benzonorbornadiene substrates achieving moderate to excellent yields and excellent enantioselectivities. In our studies, we have also discovered classes of substrates that fail to undergo this reaction, such as those bearing substituents on the bridgehead carbons and non-benzo oxabicyclic alkenes. We have also found substrates bearing strong electron-withdrawing substituents may show differing reactivity and undergo an alternate dimerization pathway.

Experimental

Only representative procedures and characterization of the products are described here. Full details can be found in the Supporting Information.

General Procedure for Rh-Catalyzed Dimerization of Bicyclic Alkenes. Inside an inert atmosphere (Ar) glovebox, $[RhCl(COD)]_2$ (0.02 equiv, 0.00555 mmol) and $AgBF_4$ (0.04 equiv, 0.0111 mmol) were added to an oven-dried vial, dissolved in 1,2-dichloroethane (0.15 mL) and allowed to stir for 20 min. (*R*)-BINAP (0.04 equiv, 0.0111 mmol) was added to the vial as a solid followed by 1,2-dichloroethane (0.15 mL), and the mixture was stirred for an additional 20 min. The bicyclic alkene (1.0 equiv, 0.277 mmol) was then added to the vial as a solid followed by 1,2-dichloroethane (0.30 mL). The mixture was heated to 60 °C and allowed to stir for 15 min to 48 h. The crude mixture was purified by column chromatography.

Cyclodimerization Product 8a (Table 5, Entry 1). Performed according to the general procedure using oxabenzonorbornadiene **1a** (40.9 mg, 0.284 mmol) and heating for 15 min. The crude product was purified by column chromatography (1:4 EtOAc/hexanes, $R_f = 0.49$) to obtain **8a** as an off-white solid (39.2 mg, 0.136 mmol, 96%): mp 164−165 °C; HPLC using a Chiralcel OD-H column, retention times of 24.90 min (minor enantiomer) and 28.79 min (major enantiomer), 96% ee; $[\alpha]^{23}_D$ +208 ($c = 0.57$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, $J = 7.2$ Hz, 1H), 7.32−7.23 (m, 4H), 7.20−7.12 (m, 3H), 6.62 (dd, $J = 9.9$, 2.3 Hz, 1H), 6.03 (dd, $J = 9.9$, 3.0 Hz, 1H), 5.43 (s, 1H), 5.21 (s, 1H), 5.01 (d, $J = 7.2$ Hz, 1H), 4.36 (d, $J = 6.4$ Hz, 1H), 3.31−3.24 (m, 1H), 2.94 (dd, $J = 9.6$, 6.5 Hz, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 146.0, 143.0, 132.4, 131.5, 128.8 (2), 127.4, 127.2, 127.1, 126.8, 126.5, 126.0, 120.5, 119.4, 83.1, 83.0, 81.6, 79.1, 52.4, 39.2; IR (NaCl, cm^{-1}) 3049 (m), 3030 (m), 3003 (m), 2951 (m), 2894 (m), 2850 (m), 1492 (m), 1457 (m), 1320 (w), 1264 (w), 1216 (w), 1061 (s); HRMS (EI) calcd for $C_{20}H_{16}O_2$ (M^+) 288.1150, found 288.1146. Characterized also by 1D GOESY, 2D COSY NMR experiments and X-ray crystal structure analysis.

Cyclodimerization Product 8g (Table 7, Entry 7, $R^1 = R^2$ = F, Scheme 6). Performed according to the general procedure using oxabenzonorbornadiene **1g** (60.9 mg, 0.282 mmol) and heating for 30 min. The crude product was purified by column chromatography to obtain **8g** (1:9 EtOAc/hexanes, $R_f = 0.32$): 22.3 mg, 0.052 mmol, 37%, white solid, mp 194−196 °C dec, HPLC using a Chiralcel OD−H column, retention times of 11.67 min (major enantiomer) and 13.76 min (minor enantiomer), 98% ee; $[\alpha]^{24}_D = +133$ ($c = 0.28$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81 (d, $J = 10.1$ Hz, 1H), 6.13 (dd, $J = 10.1$, 2.4 Hz, 1H), 5.70 (s, 1H), 5.47 (s,

1H), 5.26 (d, J = 7.3 Hz, 1H), 4.42 (d, J = 6.4 Hz, 1H), 3.35 (m, 1H), 3.06 (dd, J = 9.5, 6.5 Hz, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz, observed signals) δ 147.3 (apt d), 144.7 (apt t), 142.2 (m), 141.3 (m), 140.7 (m) 139.7 (m), 138.7 (m), 138.2 (m), 127.4, 127.2 (d, $^2J_{C-F}$ = 17.9 Hz), 124.6 (d, $^2J_{C-F}$ = 18.8 Hz), 116.8, 116.7, 114.2 ($^2J_{C-F}$ = 13.7 Hz), 81.8, 80.8, 76.9, 73.7, 51.6, 38.3; ^{19}F NMR ($CDCl_3$, 377 MHz) δ −147.9 (apt t, J = 20.4 Hz, 1F), −149.3 (apt t, J = 20.6 Hz, 1F), −152.7 (dd, J = 13.6, 20.5 Hz, 1F), −155.4 (dd, J = 13.4, 20.5 Hz, 1F), −160.7 (apt t, J = 19.8 Hz, 1F), −161.1 (apt t, J = 19.7 Hz, 1F), −162.8 (apt t, J = 19.2 Hz, 1F), −164.1 (apt t, J = 20.3 Hz, 1F); IR (NaCl, cm^{-1}) 2958 (m), 2925 (m), 2854 (m), 1507 (m), 1488 (m), 1466 (w), 1423 (w), 1387 (w), 1378 (w), 1292 (w), 1125 (w), 1073 (w), 1046 (w), 1012 (w), 975 (w), 944 (w), 877 (w), 823 (w); HRMS (CI) calcd for $C_{20}H_8F_8O_2$ (M^+) 432.0397, found 432.0390.

Perfluoronaphthol 12 (Scheme 6). Performed according to the general procedure using oxabenzonorbornadiene **1g** (60.9 mg, 0.282 mmol) and heating for 30 min. The crude product was purified by column chromatography to obtain **12** (1:9 EtOAc/hexanes, R_f = 0.51): 19.5 mg, 0.045 mmol, 32%, white solid, mp 156−157 °C, HPLC (Chrial Technologies Chiralcel OB-H column, 99:1 hexanes/2-propanol, 0.05 mL/min, 220 nm) retention times of 194.86 min (major enantiomer) and 235.11 min (minor enantiomer), 93% ee; $[\alpha]^{26}_D$ = +17.9 (c = 0.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J_{H-F} = 9.9 Hz, 1H, OH), 7.56 (dd, J = 8.7, 1.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 5.95 (m, 1H), 5.70 (d, J_{H-F} = 1.6 Hz, 1H), 3.46 (dd, J = 4.7, 8.7 Hz, 1H), 2.29 (m, 1H), 2.20 (m, 1H); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 148.6 (m), 144.9 (m), 143.7 (m), 141.7 (m), 140.4 (m), 139.4 (m), 138.5 (m), 136.0 (m) (preceding signals account for 8 *ipso*-F C), 128.8, 127.0 (d, $^2J_{C-F}$ = 17.8 Hz), 126.9 (d, $^2J_{C-F}$ = 17.0 Hz), 124.9 (*ipso*-OH C), 120.7 (d, $^2J_{C-F}$ = 13.7 Hz), 111.9, 110.6 (m), 81.7, 77.8, 40.3, 35.2; IR (NaCl, cm^{-1}) 3174 (m), 2958 (w), 2924 (m), 2854 (w), 1665 (w), 1622 (w), 1591 (w), 1524 (w), 1507 (m), 1490 (m), 1463 (w), 1411 (m), 1333 (w), 1319 (w), 1309 (w), 1287 (w), 1273 (w), 1252 (w), 1184 (w), 1136 (w), 1114 (w), 1075 (w), 1043 (w), 1020 (w), 987 (w), 972 (w), 923 (w), 903 (w), 876 (w), 854 (w), 816 (w), 804 (w), 761 (w), 719 (w); HRMS (CI) calcd for $C_{20}H_8F_8O_2$ (M^+) 432.0397, found 432.0395. Characterized also by HSQC and 2D COSY NMR experiments.

Cyclodimerization Product 28a (Table 10, Entry 1, $R^1 = R^2$ = H, R^3 = Boc). Performed according to the general procedure using azabenzonorbornadiene **27a** (67.6 mg, 0.278 mmol) and heating for 20 h. The crude product was purified by column chromatography (1:4 EtOAc/hexanes, R_f = 0.39) to obtain **28a** as a light brown solid (59.6 mg, 0.122 mmol, 88%): mp 70 °C dec; HPLC using a Chiralcel OD-H column, retention times of 8.83 min (minor enantiomer) and 13.14 min (major enantiomer), 98% ee; $[\alpha]^{25}_D$ = +47.0 (c = 0.52, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz, 40 °C) δ 7.45−6.85 (m, 8H), 6.57 (br s, 1H), 5.94 (dd, J = 9.7, 5.5 Hz, 1H), 5.52 (d, J = 11.2 Hz, 1H), 4.82 (s, 1H), 4.75 (br s, 1H), 4.17 (br s, 1H), 3.23 (m, 1H), 2.55 (apt t, J = 7.4 Hz, 1H), 1.57 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (APT, HSQC, acetone-d_6, 100 MHz, 40 °C) δ 205.8 (2), 155.6, 137.3, 132.3 (2), 129.7, 128.6, 127.6, 127.4, 127.2, 127.0, 124.8, 122.2, 121.3, 120.5, 80.2, 79.1, 67.4, 64.6, 63.7, 60.1, 53.5, 40.0, 28.8, 28.2; IR (NaCl, cm^{-1}) 3055 (w), 2976 (m), 2931 (m), 1693 (s), 1478 (m), 1456 (m), 1289 (w), 1252 (w), 1229 (w), 1169 (s), 1152, 1113 (m), 941 (w), 785 (w), 752 (w), 737 (w), 702 (w). Anal. Calcd for $C_{30}H_{34}N_2O_4$: C, 74.05; H, 7.04. Found: C, 74.41; H, 6.98.

Oxabenzonorbornenol 9 (Scheme 11). To an oven-dried, round-bottom flask were added **8a** (200.1 mg, 0.694 mmol), *p*-toluenesulfonic acid monohydrate (55.7 mg, 0.293 mmol), and 1,2-dichloroethane (3.5 mL). The mixture was stirred under argon for 5.5 h and then concentrated by rotary evaporation. The crude product was purified using column chromatography (1:4 EtOAc/hexanes, R_f = 0.29) to obtain **9** as a white solid (199.8 mg, 0.693, 99%). Spectroscopic data for **9** was in agreement with values reported in the literature:[7b] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 1H), 7.89 (m, 3H), 7.50 (m, 3H), 7.41 (m, 1H), 7.28 (m, 3H), 5.60 (s, 1H), 5.35 (s, 1H), 4.31 (apt t, J = 7.8 Hz, 1H), 3.44 (d, J = 7.0 Hz, 1H), 1.58 (d, J = 8.8 Hz, 1H); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 146.6, 142.6, 135.0, 133.5, 132.6, 128.6, 127.8, 127.6, 127.54, 127.48 (2), 127.0, 126.4, 126.0, 120.9, 119.1, 86.0, 84.5, 74.2, 51.8; IR (NaCl, cm^{-1}) 3555 (w), 3436 (w), 3052 (w), 2999 (w), 2941 (w), 1632 (w), 1600 (w), 1507 (w), 1460 (w), 1347 (w), 1269 (w), 1213 (w), 1191 (w), 1153 (w), 1068 (m), 995 (w), 982 (w), 942 (w), 907 (w), 826 (m), 810 (m), 784 (w), 757 (m), 741 (m); HRMS (CI) calcd for $C_{20}H_{16}O_2$ (M^+) 288.1150, found 288.1140.

Acknowledgment. This work was supported by NSERC (Canada) and Boehringer Ingelheim (Canada). W.T. thanks Boehringer Ingelheim (Canada) Ltd. for a Young Investigator Award, A.A., P.L., and K.V. thank NSERC for postgraduate scholarships (CGS M, PGS M, and CGS D), and R.B. thanks the Ontario Government for a postgraduate scholarship (OGS).

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

JO7012884