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A Rhodium IBiox[(−)-menthyl] Complex as a Highly Selective Catalyst for the Asymmetric Hydroarylation of Azabicyles: An Alternative Route to Epibatidine

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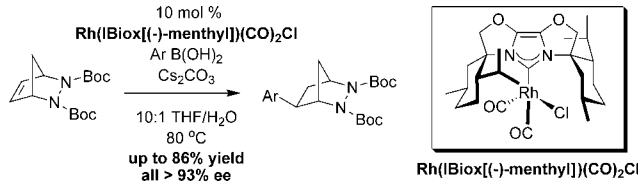
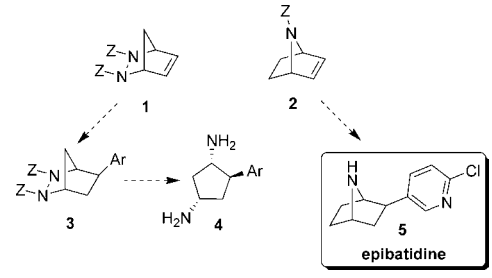
ABSTRACT



The synthesis and characterization of a new chiral rhodium N-heterocyclic carbene complex, Rh(IBiox[(−)-menthyl](CO)$_2$Cl, is reported. In addition, the very high enantioselectivity exhibited by this complex, as a catalyst for the asymmetric hydroarylation of azabicycles, is demonstrated and applied to the synthesis of epibatidine.

Among the most important objectives in the field of synthesis and catalysis is the development of enantioselective methods for the formation of C−C bonds. Metal-catalyzed transformations that can establish the absolute stereochemical configuration of more than one stereocenter in a given target molecule are particularly attractive. One such transformation that has emerged in the past few years involves the desymmetrization of meso heterobicyclic alkenes such as **1** and **2** via transition-metal-catalyzed hydroarylation (Scheme 1).[1] Products such as **3** are potentially valuable intermediates that can undergo reductive N−N bond cleavage to generate functionalized cyclopentane-1,3-diamines,[1a] while the hydroarylation of **2** directly produces 7-azabicyclo[2.2.1] heptane derivatives such as the extremely potent analgesic alkaloid epibatidine.[2]

Scheme 1. Hydroarylation of Azabicycles



Part of the appeal of this method derives from the ease with which azabicycles **1** and **2** can be prepared. In particular,

(1) (a) Bournaud, C.; Chung, F.; Luna, A. P.; Pasco, M.; Errasti, G.; Lecourt, T.; Micouin, L. *Synthesis* **2009**, *6*, 869. (b) Sajisha, V. S.; Anas, S.; John, J.; Radhakrishnan, K. V. *Synlett* **2009**, *18*, 2885. (c) Menard, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2085. (d) Panteleev, J.; Menard, F.; Lautens, M. *Adv. Synth. Catal.* **2008**, *350*, 2893. (e) Yuan, K.; Zhang, T. K.; Hou, X. L. *J. Org. Chem.* **2005**, *70*, 6085. (f) Yao, M. L.; Adiwidjaja, G.; Kaufmann, D. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3375. (g) Storsberg, J.; Nandakumar, M. V.; Sankaranarayanan, S.; Kaufmann, D. E. *Adv. Synth. Catal.* **2001**, *343*, 177.

(2) (a) Carroll, F. I. *Heterocycles* **2009**, *79*, 99. (b) Garraffo, M. H.; Spande, T. F.; Williams, M. *Heterocycles* **2009**, *79*, 207.

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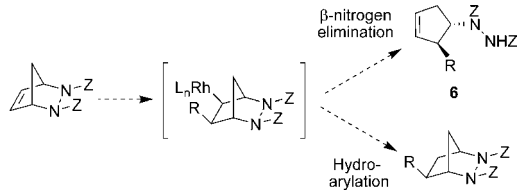
1 can be synthesized in one high-yielding step involving a Diels−Alder reaction between a dialkyl azodicarboxylate and cyclopentadiene,[1c] while **2** is prepared from 3-cyclohexenecarboxylic acid in four high-yielding steps.[3]

We recently reported the first examples of enantioselective hydroarylation of bicyclic hydrazines, where arylboronic acids were coupled to *N*-Boc **1** with very good selectivities of up to 99% ee using $[Rh(COD)OH]_2$ in combination with chiral phosphine ligands such as Josiphos.[1c,d] A competitive process that can occur in this system is the rhodium-catalyzed ring-opening of diazabicycles by β-nitrogen elimination to yield cyclopentene derivatives **6** (Scheme 2). It was found

Scheme 2. Rh-Catalyzed Ring-Opening versus Hydroarylation of Diazabicycles



that by choosing the appropriate phosphine ligand and reaction conditions, either one of the two chemodivergent products could be favored. A limitation of the $Rh(COD)OH]_2$/Josiphos system is that *ortho*-substituted boronic acids are required for high enantioselectivity. Given that the substituted cyclopentane-1,3-diamine structural motif can be found in biologically important compounds such as tRNA ligands[4] and enzyme bisubstrate inhibitors,[5] stereoselective methods for the preparation of compounds such as **4** may prove useful. Therefore, we sought to find an alternative catalyst system exhibiting improved enantiodiscrimination and greater substrate tolerance.

One such family of catalysts that have not been explored in addition reactions with unactivated alkenes are complexes of rhodium that incorporate N-heterocyclic carbenes (NHCs) as ligands. NHCs have become one of the most widely studied classes of ligands next to phosphines, primarily due to their strong σ-donor character, the large steric demand that they can impose about the metal center, and the high stability of the metal−NHC bond.[6] Chiral Rh−NHC complexes have been successfully applied to asymmetric variations of the 1,4-addition of organoboron reagents to enones, the hydrosilylation reaction as well as the hydrogenation of olefins.[7] However, when we subjected the azabicycles to several of the known Rh−NHC complexes we observed low reactivity and selectivity.

A survey of the recent literature led us to consider IBiox[(−)-menthyl] (Figure 1), first prepared by Glorius and

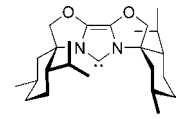


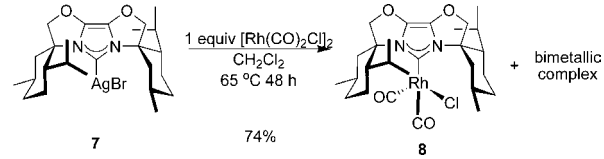
Figure 1. IBiox[(−)-menthyl] NHC ligand devised by Glorius and co-workers.

co-workers,[8] as a potential ligand. The exceeding steric demand imparted by this ligand resulted in high stereoselectivities in the Pd-catalyzed intramolecular α-arylation of aryl chlorides.

To date, IBiox[(−)-menthyl] has not been employed in rhodium chemistry, and therefore, we set out to prepare a discrete complex to ensure that a ligand−Rh species was possible. Indeed, this proved to be more challenging than we expected. Our first attempts were to prepare Rh(IBiox[(−)-menthyl])(COD)Cl from $[Rh(COD)Cl]_2$ using various previously reported methods[7a] for the preparation of Rh−NHC compounds, including heating the NHC precursor IBiox[(−)-menthyl]HOTf with $[Rh(COD)Cl]_2$ in the presence of *t*-BuOK and heating IBiox[(−)-menthyl]AgBr with $[Rh(COD)Cl]_2$. These methods failed to produce any of the desired complex.

We suspected that steric interaction between the COD ligand and the extremely bulky NHC proligand may prevent complexation. Therefore, we looked to $[Rh(CO)_2Cl]_2$ as an alternative. We found that heating the silver precursor **7** with an excess of $[Rh(CO)_2Cl]_2$ produced an inseparable mixture of Rh(IBiox[(−)-menthyl])$(CO)_2$Cl (**8**) and the bimetallic complex [Rh(IBiox[(−)-menthyl])(CO)Cl]$_2$ (∼4:1, respectively) in good yield as an amorphous solid (Scheme 3,

Scheme 3. Synthesis of Rh(IBiox[(−)-menthyl])$(CO)_2$Cl Complex **8**



7 8

Figure 2). Rh−NHC−bis(CO)-chloride complexes are known to reversibly lose a molecule of CO and undergo dimerization in solution over a period of time.[9] Di-μ-chlorido-RhL_n complexes have been employed numerous times as catalyst precursors.[10] Therefore, the mixture of **8** and the bimetallic complex was used in all subsequent reactions without further purification.

(3) Gomez-Sanchez, E.; Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 8656.

(4) Chung, F.; Tisne, C.; Lecourt, T.; Dardel, F.; Micouin, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 4489.

(5) Lombes, T.; Begis, G.; Maurice, F.; Turcaud, S.; Lecourt, T.; Dardel, F.; Micouin, L. *ChemBioChem* **2008**, *9*, 1368.

(6) (a) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev* **2009**, *109*, 3612. (b) *N-Heterocyclic Carbenes in Transition-Metal Catalysis*; Glorius, F., Ed.; Springer: Berlin, 2007. (c) Gade, L. H.; Bellemin-Laponnaz, S. *Top. Organomet. Chem.* **2007**, *21*, 117. (d) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley VCH: Weinheim, 2006. (e) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247.

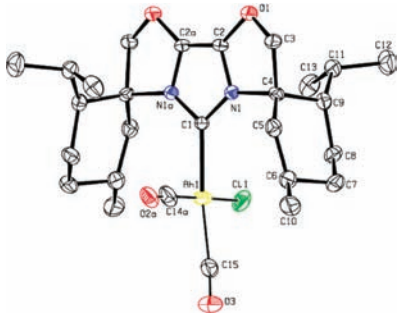
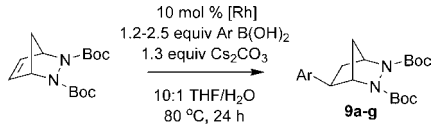
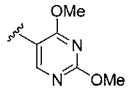
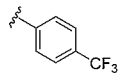


Figure 2. ORTEP depiction of Rh(IBiox[(−)-menthyl])$(CO)_2$Cl complex **8**.

With **8** in hand, we first examined the desymmetrization of diazabicycles with arylboronic acids (Table 1). Using

Table 1. Hydroarylation of *N*-Boc-diazabicycle **1** with Various Boronic Acids



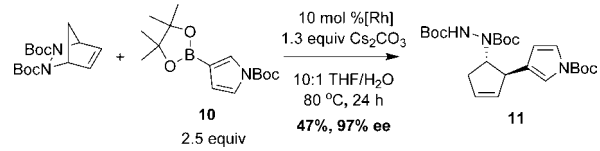
product	Ar	yield[%][a]	*ee* [%][b]
9a		80	94
9b		53	99
9c		26	98
9d		86	95
9e		12	99
9f		83	97

[a] Isolated yield. [b] Determined by chiral HPLC.

reaction conditions similar to those utilized in the Rh−P catalyzed system, it was found that, in general, **8** produced the hydroarylation product in good yield with only trace amounts of the ring-opened cyclopentene being detected by TLC. Most importantly, the reaction proceeded with high ee, all in excess of 90% even in the cases where boronic acids devoid of *ortho*-substituents were used. The low yields obtained for **9c** and **9e** are likely due to unfavorable steric interactions between the *o*-chloro or *o*-methoxy substituent of the boronic acid and the extremely bulky IBiox[(−)-menthyl] ligand, which is in direct contrast with the Rh−P catalysts where the *ortho*-substituent was required. To the best of our knowledge, these are the highest ee's reported to date for the hydroarylation of a bicyclic hydrazine.

The reaction of *N*-Boc-3-pyrrolylpinacolboronic ester[11] **10** with *N*-boc-diazabicycle **1** unexpectedly produced the ring-opened product in moderate yield and very high enantioselectiviy (Scheme 4). This is a somewhat surprising result

Scheme 4. Ring-Opening with *N*-Boc-3-pyrrolylpinacolboronic Ester



given the high yield of hydroarylation product observed when 3-thienylboronic acid was used. Use of the unprotected 3-pyrrolylpinacolboronic ester resulted in no conversion, which we propose to be due to catalyst poisoning by the free amine.

When hydroarylation with phenylboronic acid was carried out in THF/D_2O, a monodeuterated product **9a** was isolated, wherein the deuterium was located on the aromatic ring. This is consistent with the proposal that the reaction proceeds through a 1,4-Rh migration, analogous to the process that we have described previously for the Rh/Josiphos-catalyzed hydroarylation of diazabicycles (Scheme 5). The reaction is slow to initiate in the absence of water, suggesting conversion of L_nRh-Cl **8** to a L_nRh-OH species (**A**) likely precedes transmetalation with the boron reagent. It is known that the transmetalation of boronic acids occurs more readily with L_nRh-OH than with L_nRh-Cl complexes.[10] Following alkene coordination and insertion into the resulting Rh−Ar bond, 1,4-Rh migration occurs via a Rh^{3+} intermediate (**D**) to generate the Rh-Ar species (**E**), which then reacts with 1 equiv of water to liberate the product and regenerate the L_nRh-OH complex (**A**). Incorporation of deuterium occurs upon hydrolysis of the Rh-Ar species (**E**) immediately following the migration step.

In the interest of expanding the scope as well as demonstrating the synthetic potential of this method, we also looked

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(8) (a) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344. (b) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (c) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195. (d) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.

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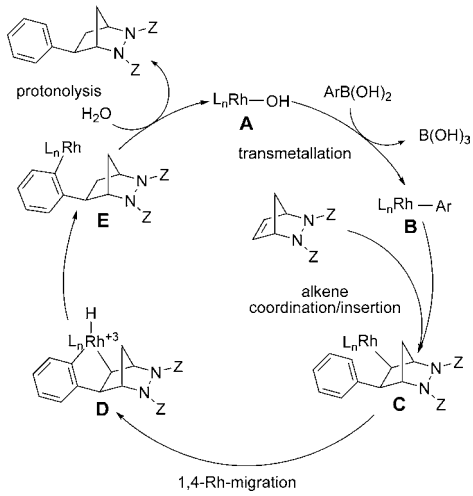
(10) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(11) The pinacolborane ester was used rather than the boronic acid due to the inherent instability of 3-pyrrolylboronic acids.

Scheme 5. Proposed Mechanism for the Rh-Catalyzed Hydroarylation Reaction

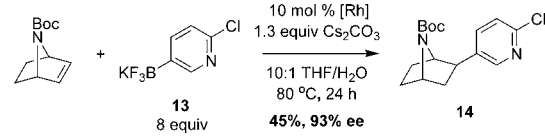


at *N*-Boc-protected 7-azanorbornene **2** as a substrate. Asymmetric hydroarylation of this compound with 2-chloropyridine-5-boronic acid would lead directly to the *N*-Boc-protected alkaloid epibatidine **5**.

Epibatidine is an alkaloid isolated from the skin of a poisonous frog, *Epipedobates tricolor*, and is known to be 200−400 times more potent than morphine.[12] It has been the subject of a number of structure−activity relationship (SAR) studies[13] and total syntheses.[14] Among the most direct and widely applied routes to this molecule and its derivatives is the Pd-catalyzed reductive arylation of substrates such as **2** with aryl iodides.[2,14g] While an asymmetric variant has been reported, the highest observed ee was 81% with a yield of 50%.[14f]

Reaction of *N*-Boc-7-azanorbornene with 2 equiv of *phenyl*boronic acid produced the desired *exo*-hydroarylation product in 69% yield and 93% ee. Unfortunately, reaction with 2-chloropyridine-5-boronic acid generated less than 12% of the *N*-Boc-protected epibatidine, albeit with good enantioselectivity (93% ee). On the basis of the detection of 2-chloropyridine in the crude reaction mixture, it is suspected that the pyridylboronic acid may be more susceptible to proto-deboronation than phenylboronic acid. We therefore tried increasing the number of equivalents of boronic acid, but this failed to improve the yield. Potassium organotrifluoroborates are known to be less prone to undergo protodeboronation and have been used in various rhodium-catalyzed C−C bond-forming processes.[15] Utilizing 8 equiv of potassium trifluoroborate **13** produced the desired *N*-Boc-epibatidine **14** in 45% isolated yield and 93% ee (Scheme 6). Although the yield of **14** is modest, the good selectivity and yield obtained using phenylboronic acid is promising, and further optimization with **13** is underway.

Scheme 6. Synthesis of *N*-Boc Epibatidine[16]



When this reaction was performed in THF/D_2O, a ∼50:50 mixture of **14** having deuterium incorporated in the 4- and 6-positions of the pyridyl ring was produced, which is consistent with a 1,4-Rh migration. Therefore, further elaboration of the epibatidine core in one pot may be possible by taking advantage of this migration.

In summary, we have described the first rhodium complex incorporating IBiox[(−)-menthyl] as a ligand. In addition, we have demonstrated the impressive stereoselectivity that this system provides for the hydroarylation of azabicycles, and as a proof of principle, we have shown that this method can be used to prepare the *N*-Boc-protected alkaloid epibatidine, thus providing an alternative route to this molecule that may be useful for SAR studies. Future investigations will involve expanding the scope of the hydroarylation reaction to other strained alkenes and investigating the application of complex **8** with other Rh-catalyzed reactions.

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Supporting Information Available: Experimental procedures, characterization data, and ^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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(16) Conversion of **14** to epibatidine in 89% yield has been reported; see ref 14a.