Metallacyclobutanes

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Preparation of 2-Azarhodacyclobutanes by Rhodium(I)–Olefin Oxidation**

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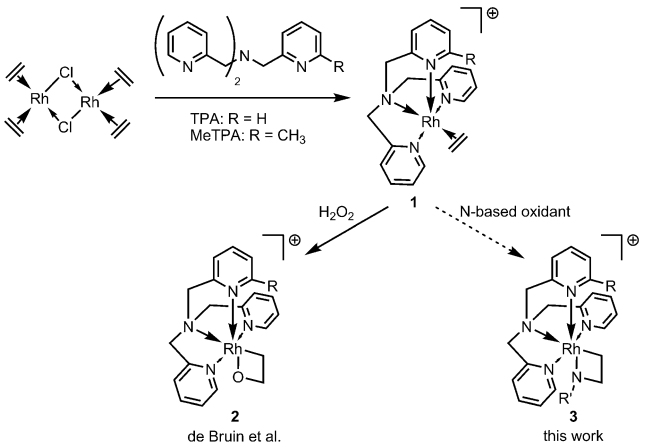
Azametallacyclobutanes have been invoked as intermediates in a number of catalytic reactions. For example, Alper et al. postulated the formation of a transient azarhodacyclobutane intermediate in the rhodium-catalyzed conversion of aziridines to β-lactams.[1] Bergman proposed the intermediacy of azazirconacyclobutenes and azazirconacyclobutanes in the hydroamination of alkynes and olefins, respectively.[2] Reductive elimination from an azaferracyclobutane was postulated by Halfen in the iron-catalyzed aziridination of olefins.[3]

Only a few azametallacyclobutanes have been isolated and characterized. The Bergman group prepared an azairidacyclobutane by C–H activation, ligand displacement, and subsequent deprotonation on an iridium complex.[4] Hillhouse and co-workers discovered that nickel bipyridyl complexes underwent oxidative addition to aziridines, inserting into the least hindered C–N bond. The isolation and complete characterization of these novel azanickelacyclobutanes were reported.[5] Likewise, Wolfe and co-workers demonstrated that azapalladacyclobutanes are intermediates in the isomerization of aziridines to ketimines.[6] Recently, the Hillhouse group reported the intermediacy of an azanickelacyclobutane in a formal [2+2] addition of ethylene to a nickel nitrene complex. Subsequent β-hydride elimination and reductive elimination gave the nitrene insertion product.[7]

We have become interested in the synthesis and reactivity of heteroatom-containing metallacycles, anticipating that these complexes can serve as intermediates in novel chemical transformations.[8] We recently reported that rhodaoxetanes (**2**) undergo transmetalation with organoboronic acids, with the goal of developing catalytic carbohydroxylation.[9] The rhodaoxetanes were originally reported by de Bruin et al. and are easily prepared by oxidation of cationic Rh^I–ethylene complexes with H_2O_2 (Scheme 1, conversion of **1** into **2**).[10] We hypothesized that by changing the oxidant 2-azarhodacyclobutanes could be synthesized from the same Rh^I–ethylene complex. Key to the success of this strategy would be the identification of an appropriate N-based oxidant. We report herein the first examples of isolable azarhodacyclobutanes using *N*-(*p*-toluenesulfonyl)iminophenyliodinane (PhINTs) as the oxidant.[11,12]



Scheme 1. Proposed formation of azarhodacyclobutane **3**.

Complex **1** was exposed to one equivalent of PhINTs in methanol at room temperature. The reaction mixture darkened within minutes from a green to a deep rust-colored, almost black, solution. The ESI mass spectrum of the crude product mixture showed a signal at 590 *m*/*z*, which corresponded to the expected mass of azarhodacyclobutane **3**, consistent with the incorporation of the N-tosyl (tosyl = *p*-toluenesulfonyl) fragment.

We anticipated that azarhodacyclobutane **3** would exhibit a similar ^{1}H NMR spectrum to rhodaoxetane **2**. However, the crude ^{1}H NMR spectrum of **3** was considerably more complicated than that of **2.** Nonetheless, we were able to identify features in the ^{1}H NMR spectrum of the crude reaction mixture that closely resembled signals found in the ^{1}H NMR spectrum of **2.** Specifically, we observed a doublet of triplets in **3** at approximately 2 ppm with a $^2J_{Rh\text{-}H}$ coupling of about 2 Hz. Rhodaoxetane **2** exhibits a doublet of triplets with a similar chemical shift and coupling constants. We also observed a triplet in **3** at about 4 ppm. Rhodaoxetane **2** shows a triplet, again with a similar shift, but slightly farther downfield. The signals in complex **2** correspond to H1 and H2, respectively, in the oxametallacycle (Figure 1). Based on this information, we believed that we had prepared azarhodacyclobutane **3**, as well as a number of by-products.[13]

Attempts to purify the crude material by crystallization, as complexes with Cl^-, BPh_4^-, or PF_6^- counterions, as well as by substitution of tris(2-pyridylmethyl)amine (TPA) for MeTPA as an auxiliary ligand were all unsuccessful. Liquid extraction methods and silica gel column chromatography also failed to purify the product. Gratifyingly, separation by HPLC on a C18 reverse-phase column was effective (14% yield by NMR using 1,3,5-trimethoxybenzene and tetramethylsilane as internal standards, 5% yield of isolated product after

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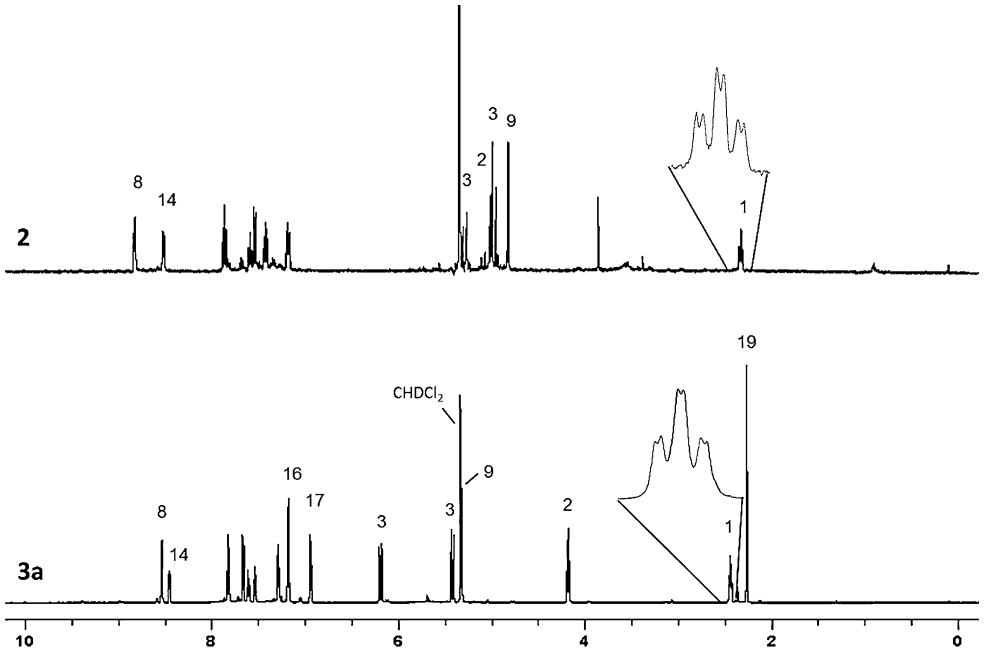
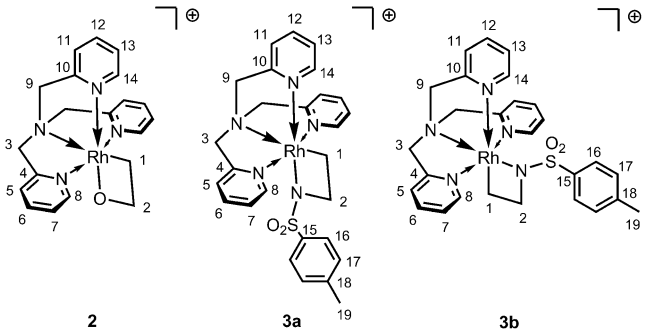


Figure 1. Comparison of ^{1}H NMR spectral data of **2** and **3a** (600 MHz, CD_2Cl_2, 298 K, with a Cl^- counterion).



HPLC). The desired product was isolated, and high-resolution mass spectrometry confirmed the corresponding molecular formula of azarhodacyclobutane **3**.

Two different isomeric structures are possible for **3**, isomers **3a** and **3b**, which differ in the conformation of the N-tosyl moiety with respect to the central amine of the TPA ligand. Although the isolated complex was resistant to crystallization, NMR spectroscopy proved expedient for structural assignments and led us to conclude that we had formed isomer **3a**. It is noteworthy that treatment of **1** with PhINTs in aprotic solvents led to the formation of a mixture of **3a** and **3b** (see below). The ^{1}H NMR spectra of the chloride salts of **2** and **3a** are shown in Figure 1.[14]

Consistent with our expectation, the ^{1}H NMR spectrum of pure **3a** is indeed similar to that of rhodaoxetane **2** (Figure 1 and Table 1).[10] The rhodaoxetane has an octahedral configuration with a plane of symmetry that renders two of the methylpyridyl arms of the TPA ligand equivalent. Therefore, the methylene protons (H9) in the unique methylpyridyl arm, as well as the protons in the oxametallacycle (H1 and H2), are also magnetically equivalent. For complex **3a**, the protons in the azametallacyclobutane ring (H1 and H2) and in the methylene linker of the unique methylpyridyl arm of the ligand (H9) are equivalent. The protons of the two remaining methylpyridyl arms (H3–H8) gave only one set of signals, which integrated to double intensity. These data showed that complex **3** contained the same plane of symmetry and indicated that the inversion of the stereogenic nitrogen center was fast on the NMR timescale.

In close analogy to the rhodaoxetane spectrum, we observed H1 as a doublet of triplets with distinctive Rh coupling (2.44 ppm, dt, 2H, ^3J(H,H) = 7.8 Hz, ^2J(Rh,H) = 2.0 Hz) and H2 as a triplet (4.16 ppm, 2H, ^3J(H,H) = 7.8 Hz). The methylene protons of the equivalent methylpyridyl arms (H3) were diastereotopic and appeared as [AB] doublets at 6.22 ppm and 5.30 ppm (2H, ^2J(H,H) = 15.3 Hz) while the methylene protons in the unique TPA arm (H9) gave a singlet at 5.23 ppm (s, 2H). Further indicative signals were found at 8.54 ppm (d, 2H, ^3J(H,H) = 5.4 Hz, H8) and

Table 1: Tabulated ^{1}H NMR data comparison for **2**, **3a**, and **3b** (600 MHz, CD_2Cl_2, 298 K).[a]

H	**3a**	**3b**	**2**[b]
1	2.44 (dt, 2H, ^3J(H,H) = 7.8 Hz, ^2J(Rh,H) = 2.0 Hz)	1.92 (dt, 2H, ^3J(H,H) = 6.9 Hz, ^2J(Rh,H) = 1.7 Hz)	2.30 (dt, 2H, ^3J(H,H) = 7.5 Hz, ^2J(Rh,H) = 2.4 Hz)
2	4.16 (t, 2H, ^3J(H,H) = 7.8 Hz)	3.95 (t, 2H, ^3J(H,H) = 6.9 Hz)	4.99 (t, 2H, ^3J(H,H) = 7.5 Hz)
3	6.22 (ax) and 5.41 (eq) (d[AB], 2H, ^2J(H,H) = 15.3 Hz)	5.60 (eq) and 4.75 (ax) (d[AB], 2H, ^2J(H,H) = 15.5 Hz)	5.26 (ax) and 4.96 (eq) (d[AB], 2H, ^2J(H,H) = 15.2 Hz)
8	8.54 (d, 2H, ^3J(H,H) = 5.4 Hz)	8.99 (d, 2H, ^3J(H,H) = 5.1 Hz)	8.80 (d, 2H, ^3J(H,H) = 5.4 Hz)
9	5.30 (s, 2H)	5.01 (s, 2H)	4.80 (s, 2H)
14	8.45 (d, 1H, ^3J(H,H) = 7.7 Hz)	10.01 (d, 1H, ^3J(H,H) = 5.3 Hz)	8.49 (d, 1H, ^3J(H,H) = 5.0 Hz)
16	7.20–7.15 (m, 3H; includes H13)	7.37–7.32 (m, 4H)	
17	6.95 (d, 2H, ^3J(H,H) = 7.7 Hz)	7.37–7.32 (m, 4H)	
19	2.27 (s, 3H)	2.44 (s, 3H)	

[a] For full assignment of all ^{1}H and ^{13}C NMR signals, see the Supporting Information; [b] NMR data for complex **2** has previously been reported in [D_6]acetone (Ref. [10]). For direct comparison of our results with this work, we reacquired the spectrum of **2** in CD_2Cl_2.

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8.45 ppm (d, 1H, ^3J(H,H) = 7.7 Hz, H14), corresponding to protons H8 and H14 on the pyridine rings. The aromatic protons of the tosyl moiety, H16 and H17, were observed at 7.20–7.15 ppm (m, 3H; includes H13) and 6.95 ppm (d, 2H, ^3J(H,H) = 7.7 Hz), respectively, while the methyl group, H19 appeared as a singlet at 2.27 ppm (s, 3H) (Table 1).

Further structural evidence was obtained from the $^{13}C\{^1H\}$ NMR spectrum of **3a**. A resonance at 8.1 ppm was attributed to C1, which is one of the metallacycle carbons, and appeared as a doublet with a $^2J_{(Rh\text{-}C)}$ coupling constant of 18.4 Hz. Through the neighboring N–Ts moiety, C2 is deshielded and appeared at 57.9 ppm (Table 2). These data are in good analogy to related azametallacyclobutanes.[5,7]

Table 2: ^{13}C and ^{15}N shifts of **3a** and **3b** acquired by direct- and indirect-detection NMR methods.

	3a		**3b**	
	$^{13}C\{^1H\}$ NMR	$^1H/^{15}N$ HMQC	$^{13}C\{^1H\}$ NMR	$^1H/^{15}N$ HMQC
C1	8.1 (d, $^2J_{(Rh-C)}$ = 18.4 Hz)		1.6 (d, $^2J_{(Rh-C)}$ = 16.1 Hz)	
C2	57.9		57.7	
N(Py)		−155, −156		−145, −114
N(amine)		−338		−350
N(cycle)		−379 (d, $^2J_{(Rh-N)}$ = 14 Hz)		−370

The Rh-coupling observed in both the ^1H and ^{13}C NMR spectra clearly demonstrated the Rh–CH_2 connectivity. A long range $^1H/^{15}N$-correlated HMQC spectrum highlighted the scalar coupling of H1 and H2 with the azarhodacyclobutane nitrogen, for which we could observe a ^{15}N chemical shift of −379 ppm (referenced to CH_3NO_2) by indirect detection (Table 2). Moreover, in a $^1H/^{15}N$-correlated HSQC spectrum modified for long range resonance, a coupling of the azarhodacyclobutane nitrogen to the Rh center with a coupling constant of $^2J_{(Rh\text{-}N)}$ = 14 Hz was observed. The magnitude of this coupling compares well with previously reported five-membered cyclic Rh–toluenesulfonyl-1,2-diphenylethanediamine (Rh–TsDPEN) structures.[15] The approximately 100 ppm lower field chemical shift of the coupling of the nitrogen to the Rh center can be ascribed to the increased ring strain in the four-membered ring of the present structure versus the five-membered ring of Rh–TsDPEN.

Along with the similarities of the ^1H NMR spectra of the product and rhodaoxetane **2**, 2D NOESY spectroscopy gave further insight into the conformation of the azarhodacyclobutane. From this we could determine the following spatial correlations (Table 3). The proton of the metallacycle adjacent to the Rh center (H1) showed cross peaks with H8 and H14 on the equivalent and unique pyridine rings, respectively. Thus, proton H1 must be *trans* to the central TPA amine. Furthermore, H16 on the tosyl group showed correlations with H3, the axial methylene protons in the equivalent methylpyridyl arms, an observation consistent with the N–Ts group being *cis* to the TPA amine, thus confirming the conformation of **3a**.

Table 3: NOESY contacts for **3a** and **3b**.

H	**3a**	**3b**
1	H8, H14	H3, H8 (weak)
2	H8, H14 (weak), H16	H8, H7
3	H5, H16	H1
8	H1, H2	H2
14	H1, H2	H16, H17
16	H2, H3, H8 (weak)	H14

The combined mass spectrometric and NMR spectral data unambiguously prove the assignment of the isolated product as azarhodacyclobutane **3a**.

Having established the structure of **3a**, we were interested in evaluating the reaction conditions for forming this species. We first explored the effect of the solvent. In the presence of protic solvents (CD_3OD, CD_3OD/CD_2Cl_2 1:1, or D_2O) only **3a** was formed. Surprisingly, however, when the reaction was performed in aprotic solvents (CD_2Cl_2, CD_3CN, [D_6]acetone, $CDCl_3$), a mixture of two isomers with 590 m/z was found by HPLC-MS.

Isolation of the second isomer by HPLC was achieved, and rigorous spectroscopic analysis revealed the identity of the compound to be isomer **3b** (Tables 1–3).[16] The presence of protic solvents must either greatly favor the formation of **3a** or inhibit the formation of **3b**.[17] We are currently performing detailed studies on the underlying mechanisms of formation for the two isomers.

NMR yields for **3a** and **3b** were determined based on 1,3,5-trimethoxybenzene and tetramethylsilane as internal standards. In CD_2Cl_2, olefin complex **1** was converted into a 1:1.7 mixture of **3a** and **3b** in a combined yield of 61%. The minor isomer, **3a**, was formed in 22% yield, whereas **3b** was formed in 39% yield. A similar ratio of **3a**/**3b** (1:1.5) was determined by HPLC-MS. The product ratio was independent of the reaction temperature (−78°C, 25°C, 70°C in a sealed tube) and the concentration of the nitrene precursor (1, 2, or 5 equivalents). Importantly, **3a** and **3b** did not interconvert, even at high temperature or with prolonged reaction time (3 days at room temperature). A mixture of **3a** and **3b** was also recovered unchanged after heating for 30 min in either refluxing acetonitrile or water. Heating in DMSO for prolonged periods of time led to gradual decomposition. Notably, no formation of tosyl-aziridine by C–N reductive elimination could be detected.

It is noteworthy that, in the case of H_2O_2 oxidation of **1** in CH_2Cl_2 or CH_3OH, rhodaoxetane **2**, which has the oxetane oxygen *cis* to the central amine of the TPA ligand, was formed exclusively when the reaction was performed at −10°C.[18]

We next focused our attention on the reactivity of azarhodacyclobutanes **3**. These complexes exhibited remarkable thermal stability, presumably owing to their octahedral,

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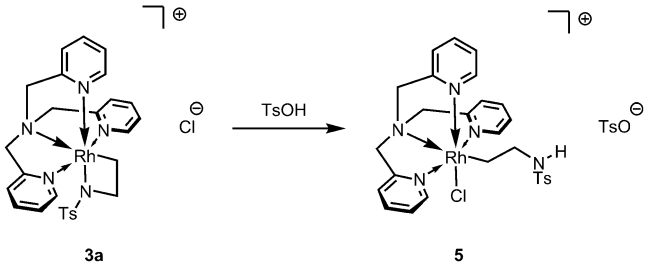
18-electron configuration. We had previously shown that oxarhodacyclobutanes could undergo transmetalation with boronic acids and esters.[8] We anticipated that the azarhodacyclobutanes might exhibit similar reactivity. However, when **3a** and **3b** were exposed to organoboron reagents no reaction was observed over the course of one week. This lack of reactivity can be best explained in light of the proposed transmetalation mechanism with oxarhodacyclobutanes. We surmised that the rhodaoxetane oxygen coordinates to the boron to form a borate complex prior to transmetalation. In the case of azarhodacyclobutanes, coordination would be disfavored by both the steric and electronic effects of the tosyl substituent.

The protonation and subsequent ring opening of rhodaoxetane **2** when treated with acids had been reported by de Bruin et al.[10] We anticipated that **5** could be generated from **3** in the presence of acid and, indeed, treatment of **3a**-Cl with toluenesulfonic acid led to the quantitative formation of a new product (Scheme 2). In analogy to the reported



Scheme 2. Ring opening of **3a** under acidic conditions. Ts = *p*-toluenesulfonyl.

reactivity of oxarhodacyclobutanes, we propose that this ring opening happens after protonation of the ring nitrogen and following displacement by a chloride ligand. The shift of H1 and H2 in the ^{1}H NMR spectrum was indicative of ring opening. Also, the mass spectrum showed a dominant signal at 626 *m*/*z*, with a characteristic chloride isotope pattern. Treatment of **3a**-PF_6 with toluenesulfonic acid in the absence of a strongly coordinating counterion (such as Cl^-) did not lead to ring opening, but allowed for recovery of the azametallacyclobutane.

In summary, we report the preparation and isolation of the first azarhodacyclobutane. Both isomers **3a** and **3b** were characterized by NMR spectroscopy and mass spectrometry and their configurations were unambiguously established by NOE experiments. The effect of solvents on the ratio of **3a** and **3b** has been examined and showed exclusive formation of **3a** in the presence of protic solvents. Preliminary reactivity studies demonstrate that the azarhodacycle can be ring-opened upon treatment with acid. Investigations of the mechanism of formation are underway. We are also currently exploring the formation of substituted azarhodacyclobutanes from higher olefins.

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[14] The ^{1}H NMR spectra of the hexafluorophosphate salts are largely identical, apart from a slight upfield shift of H3 and H9; see the Supporting Information).
[15] A. J. Blacker, S. B. Duckett, J. Grace, R. N. Perutz, A. C. Whitwood, *Organometallics* **2009**, *28*, 1435; the ^{15}N chemical shifts in this publication are referenced to pyridine at 0 ppm; for comparison, we report ^{15}N shifts referenced to pyridine as well as to CH_3NO_2 (IUPAC recommended standard) in the Supporting Information.
[16] Although most of the ^{1}H NMR signals are comparable with **3a**, proton H14 experiences about a 1.5 ppm downfield shift, while H3(eq)is shifted upfield by approximately the same amount, as compared to **3a**. A through space deshielding effect by the tosyl moiety is the likely reason for this observation.
[17] The dielectric constant of the solvent does not appear to play a key role, as mixtures were also obtained in a polar aprotic solvent (acetonitrile).
[18] In the oxidation of **1** to **2** with H_2O_2 at room temperature the formation of a geometric isomer was postulated. This isomer was not further characterized. See Ref. [10a].

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