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Efficient Aziridination of Olefins Catalyzed by Mixed-Valent Dirhodium(II,III) Caprolactamate

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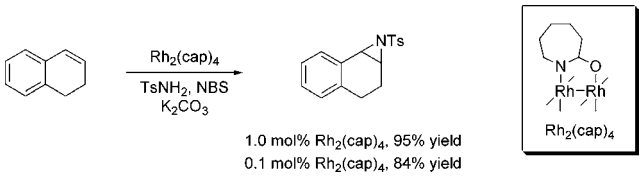
ABSTRACT



A mild, efficient, and selective aziridination of olefins catalyzed by dirhodium(II) caprolactamate [$Rh_2(cap)_4 \cdot 2CH_3CN$] is described. Use of *p*-toluenesulfonamide ($TsNH_2$), *N*-bromosuccinimide (NBS), and potassium carbonate readily affords aziridines in isolated yields of up to 95% under extremely mild conditions with as little as 0.01 mol % $Rh_2(cap)_4$. Aziridine formation occurs through Rh_2^{5+}-catalyzed aminobromination and subsequent base-induced ring closure. An X-ray crystal structure of a Rh_2^{5+} halide complex, formed from the reaction between $Rh_2(cap)_4$ and *N*-chlorosuccinimide, has been obtained.

Olefin aziridination is a powerful approach for the incorporation of nitrogen into organic compounds.[1,2] Largely regarded for their synthetic versatility, aziridines are well suited for ring opening with an assortment of nucleophiles, yielding functionalized amines.[3] Despite their value and utility, however, methods for the direct preparation of aziridines remain limited. Transition metal-catalyzed processes in conjunction with an appropriate nitrene precursor (e.g., iminophenyliodinanes such as TsN═IPh, or in situ variants) have received considerable attention,[4,5] for which catalysis via dirhodium(II,II) complexes (Rh_2^{4+}) holds a prominent position.[6] However, drawbacks in the uses of this methodology arise from high catalyst loadings, limited shelf life of TsN═IPh, competing C−H insertion, and/or poor selectivity. In this communication, we describe a mild, selective, and efficient aziridination protocol that involves catalysis by a mixed-valent dirhodium(II,III) catalyst (Rh_2^{5+}).

We have recently reported that dirhodium(II,II) caprolactamate [$Rh_2(cap)_4$] performs admirably as a catalyst for allylic oxidation.[7] Its effectiveness is derived from its ability to

(1) For a general review of carbon−nitrogen bond formation, see: (a) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 7, p 469.

(2) Selected olefin aziridination reviews, see: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (c) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Phaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 607. (d) Müller, P. In *Advances in Catalytic Processes*; Doyle, M. P., Ed; JAI Press, Inc.: Greenwich, 1997; Vol. 2, p 113.

(3) For a comprehensive review of aziridine ring opening, see: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(4) Selected recent synthesis of aziridines via nitrenes: (a) Dauban, P.; Saniére, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. (b) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481. (c) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530.

(5) Selected enantioselective aziridinations, see: (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (b) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (c) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132. (d) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563.

(6) For Rh_2^{4+}-catalyzed aziridination, see: (a) Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543. (b) Müller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738. (c) Guthikonda, K.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (d) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507. (e) Liang, J. L.; Yuan, S. X.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2003**, *44*, 5917. (f) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019.

(7) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.

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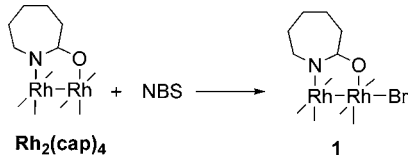
undergo facile atom-transfer redox chemistry (Rh_2^{4+}/Rh_2^{5+}) because of its low one-electron oxidation potential.[8] With similar considerations, we examined the potential of $Rh_2(cap)_4$ as a *bromine* atom-transfer redox catalyst.

Initial studies showed that $Rh_2(cap)_4$ undergoes a one-electron oxidation in the presence of *N*-bromosuccinimide (NBS) to yield paramagnetic complex **1** (Scheme 1).

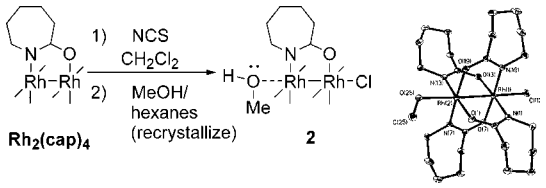
Scheme 1



Evidence includes an oxidative color change (light blue → deep red) in CH_2Cl_2: the UV/visible spectrum of the rhodium complex upon addition of NBS contains a low-energy absorption ($\delta-\delta^*$ transition) at 971 nm ($\epsilon = 930\ M^{-1}\ cm^{-1}$) indicating a Rh_2^{5+} species.[9]

Numerous attempts to obtain crystals of **1** were unsuccessful. However, by replacing NBS with *N*-chlorosuccinimide (NCS), suitable crystals were obtained for X-ray analysis,[10] revealing the dirhodium complex **2** containing an axially bound chlorine (Scheme 2). The spectral properties

Scheme 2

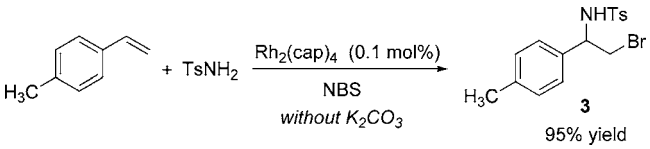


of **2** are consistent with a dirhodium(II,III) complex and thus provide indirect support for **1**.[11]

To determine if $Rh_2(cap)_4$ and NBS could be synthetically useful, we considered bromine-catalyzed aziridination as first advanced by Sharpless.[12] His protocol offers unique advantages over nitrene delivery; however, the catalytic efficiency of phenyltrimethylammonium tribromide and the formation of 1,2-dibromide byproducts were noted limitations.

Efforts using Chloramine-T as a nitrogen source with **1** as a catalyst yielded only trace amounts of aziridine due to catalyst decomposition under the reaction conditions. We then considered the feasibility of a less basic amine derivative to mitigate catalyst destruction. Toward this end, treating 4-methylstyrene (1.0 equiv) in CH_2Cl_2 (0.27 M/olefin) with *p*-toluenesulfonamide (1.1 equiv) and 0.1 mol % $Rh_2(cap)_4$ followed by NBS (1.1 equiv) rapidly gave β-bromosulfonamide **3** in 95% isolated yield (Scheme 3).[13] This result was

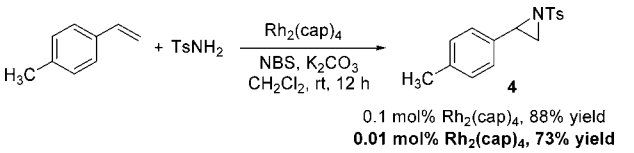
Scheme 3



complementary to a study by Sudalai and co-workers who observed bromoamidation of olefins with $TsNH_2$ and NBS using 5 mol % of various Lewis acids.[14]

We were encouraged by the comparative efficiency of $Rh_2(cap)_4$ for bromoamidation and, looking to convert the product directly to aziridines, conducted the same reaction in the presence of K_2CO_3 (2.1 equiv). Aziridine **4** was produced in 88% isolated yield after 12 h (Scheme 4).

Scheme 4



Further, reducing the amount of catalyst to *only* 0.01 mol % $Rh_2(cap)_4$ (substrate:catalyst = 10 000) gave **4** in 73% yield in 12 h.

This operationally straightforward reaction was readily extended to a variety of olefins (Table 1).[15,16] Aryl- and alkyl-substituted alkenes underwent inter- and intramolecular

(8) $Rh_2(cap)_4 \rightarrow Rh_2(cap)_4^+ < 1$ kcal/mol: Doyle, M. P.; Ren, T. *Progress in Inorganic Chem*istry; Karlin, K., Ed; Wiley: New York, 2001; Vol. 49, p 113.

(9) (a) Cotton, F. A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*; Wiley: New York, 1982; p 390. (b) Cotton, F. A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*, 2nd ed.; Oxford: New York, 1993; p 475.

(10) See Supporting Information for X-ray crystal data.

(11) For Rh_2^{5+} halide complexes containing N−C−N dinuclear bridging ligands, see: (a) Kadish, K. M.; Phan, T. D.; Giribabu, L.; Van Caemelbecke, E.; Bear, J. L. *Inorg. Chem.* **2003**, *42*, 8663. (b) Bear, J. L.; Yao, C. L.; Liu, L. M.; Capdevielle, F. J.; Korp, J. D.; Albright, T. A.; Kang, S. K.; Kadish, K. M. *Inorg. Chem.* **1989**, *28*, 1254.

(12) For bromine-catalyzed aziridination, see: Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. For subsequent studies by other groups, see: (a) Ali, S. I.; Nikalje, M. D.; Sudalai, A. *Org. Lett.* **1999**, *1*, 705. (b) Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2001**, *42*, 1037.(c) Thakur, V. V.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 989. (d) Jain, S. L.; Sharma, V. B.; Sain, B. *Tetrahedron Lett.* **2004**, *45*, 8731.

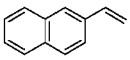
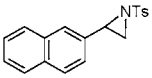
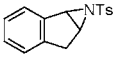
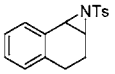
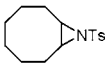
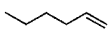
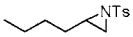
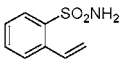
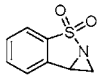
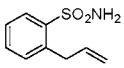
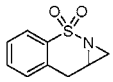
(13) By ^1H NMR, 70% conversion (from 4-methylstyrene into **3**) was observed in only 3 min at 1 mol % $Rh_2(cap)_4$.

(14) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861.

(15) Electron-deficient (methyl-*trans*-cinnamate), trisubstituted (1-methylcyclohexene), and α,α-disubstituted (α-methylstyrene) olefins were not reactive substrates for this protocol.

(16) **Representative Procedure.** A 25 mL flask equipped with a stir bar was charged with olefin (2.72 mmol, 100 mol %), CH_2Cl_2 (10 mL), $TsNH_2$ (2.99 mmol, 110 mol %), K_2CO_3 (5.71 mmol, 210 mol %), and $Rh_2(cap)_4$ (0.0027 mmol, 0.1 mol %). To the mixture was added NBS (2.99 mmol, 110 mol %) in one portion, and the color of the solution immediately turned from light blue to red. The flask was sealed with a septum allowing inclusion of air. After 12 h, silica gel was added to the reaction mixture and the solvent was evaporated. Column chromatography yielded the analytically pure compound.

Table 1. $Rh_2(cap)_4$-Catalyzed Aziridination of Olefins

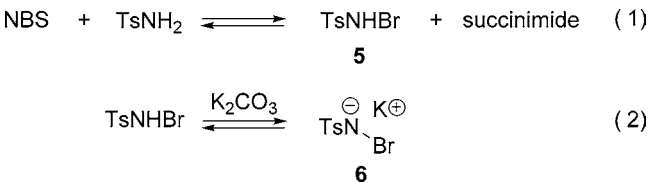
entry	olefin	aziridine	$Rh_2(cap)_4$ (mol%)	yield (%)[a]
1			1.0 0.1	77 62
2			1.0	69[b]
3			1.0	77[b]
4			0.1	65
5			0.1	88
6			1.0 0.1	95 84
7			1.0	74[c]
8			1.0	60[c]
9			1.0	77
10			0.1	86
11			1.0	87

[a] Isolated yield after purification. [b] Under these reaction conditions, aziridine diastereoselectivity was determined by ^{1}H NMR prior to silica purification (entry 2 (trans/cis = 4:1), entry 3 (cis/trans = 7:1)). [c] Using 5 equiv of olefin, yield based on *p*-$TsNH_2$.

aziridination in high yield under these mild conditions. Trans aminobromination occurred exclusively for cycloalkenes prior to aziridine formation, and C−H insertion products were not observed for aliphatic olefins (e.g., entry 8).

A mechanistic proposal for aziridination is presented in Scheme 5. From analysis of a stoichiometric mixture of NBS

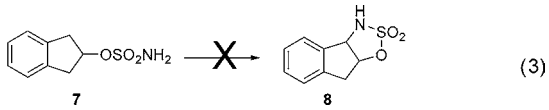
Scheme 5



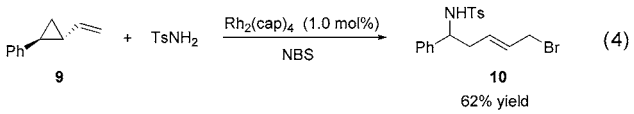
and $TsNH_2$ in solution, we concluded that an equilibrium mixture of *N*-bromo-*p*-toluensulfonamide (TsNHBr, **5**) and succinimide (eq 1) existed. Complete conversion of **5** to NBS was observed by addition of excess succinimide, thereby confirming an equilibrium process. Moreover, addition of $Rh_2(cap)_4$ did not change the equilibrium position.[17]

When excess K_2CO_3 was added to the equilibrium mixture (NBS, TsNHBr/$TsNH_2$, and succinimide), a precipitate was formed concomitant with the disappearance of both NBS and **5** by ^{1}H NMR analysis (eq 2). Because of the low pK_a of **5**,[18] deprotonation shifts the equilibrium toward **6**. Isolation of the precipitate and subsequent ^{1}H NMR analysis in *d*-DMSO indicated that the precipitate was indeed **6**.

We next considered the role of the dirhodium catalyst in the reaction. The observed regioselectivity of **3** is consistent with an ionic addition mechanism (i.e., a bromonium ion intermediate).[19] Evidence against the intermediacy of a nitrene under the conditions described in Scheme 4 and Table 1 was provided by the failure of **7** to undergo C−H insertion under the reaction conditions (eq 3).



A bromonium ion intermediate was further implicated by the use of a radical (and cation) probe **9**[20] that gave only ring-opened product **10** under the reaction conditions with and without K_2CO_3 (eq 4).



These experiments suggest that an ionic mechanism is operative, as opposed to a nitrene process.[21] Further, that a mixed-valent dirhodium(II,III) complex such as **1** is a Lewis acid akin to dirhodium(II,II) carboxamidates[22] is suggested by reaction inhibition in Lewis base solvents such as acetonitrile and THF. Moreover, dirhodium(II,III) methanol complex **2** is capable of catalyzing the hetero-Diels−Alder (HDA) reaction of *p*-nitrobenzaldehyde and 1-methoxy-3-[(trimethylsilyl)oxy]-butadiene (Danishefsky diene). Therefore, we propose that **1** activates residual amounts of **5** and/or NBS, catalyzing electrophilic bromonium ion transfer to an olefin to yield **11** (Scheme 6). Capture with $TsNH_2$ or **6**, gives bromoamide **12**,[23] which can undergo ring closure to give the aziridine.

(17) A small amount of *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) was observed after 24 h.

(18) TsNHCl pK_a = 4.55: Morris, J. C.; Salazar, A. S.; Wineman, M. A. *J. Am. Chem. Soc.* **1948**, *70*, 2036. Rangappa, K. S. *J. Phys. Org. Chem.* **2001**, *14*, 684.

(19) Hassner, A.; Boerwinkle, F. *J. Am. Chem. Soc.* **1968**, *90*, 216.

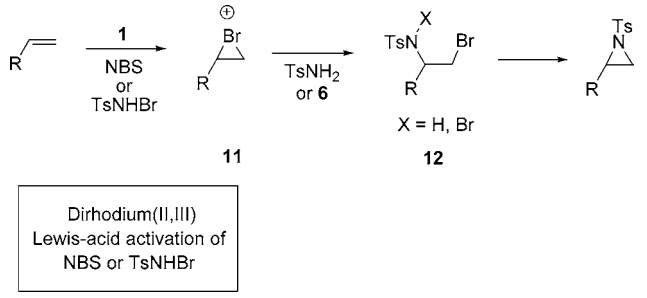
(20) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915.

(21) Bromine atom-transfer via a radical process is not operative, as no bromine addition products were observed when cyclohexene or *p*-methylstyrene was treated with NBS and $Rh_2(cap)_4$ in CH_2Cl_2.

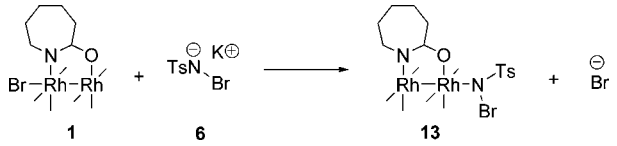
(22) For dirhodium carboxamidates as Lewis acids, see: (a) Doyle, M. P.; Phillips, I. M.; Hu, W. H. *J. Am. Chem. Soc.* **2001**, 123, 5366. (b) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665. (c) Doyle, M. P.; Valenzuela, M.; Huang, P. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5391. (d) Valenzuela, M.; Doyle, M. P.; Hedberg, C.; Hu, W.; Holmstrom, A. *Synlett* **2004**, *13*, 2422. (e) Forslund, R. E.; Cain, J.; Colyer, J.; Doyle, M. P. *Adv. Synth. Catal.* **2005**, *347*, 87.

(23) **12** (R = 4-methylphenyl, X = Br) was independently synthesized by treatment of 4-methylstyrene with *N*,*N*-dibromo-*p*-toluenesulfonamide in CH_2Cl_2. It was found that **12** acts as an electrophilic source of bromine, as treatment with succinimide yields NBS and aminobromide **3** in an equilibrium mixture (see Supporting Information).

Scheme 6



Scheme 7



The metal-based Lewis-acid catalysts for aminobromination reported by Sudalai gave a moderate enhancement in yield for aziridination over a measurable background reaction.[24] Presumably, this is due to the incompatibility of these Lewis acid catalysts and potassium carbonate under the reaction conditions. With the dirhodium(II,II) carboxylates, which do not undergo one-electron oxidation under the reaction conditions, moderate yields of aziridination products were obtained with very low catalyst loadings. Of all the catalysts examined, $Rh_2(cap)_4$ was the most effective.

In addition to the proposed Lewis acid activation, we examined another mechanistic scenario that may be operative in light of the observed substrate reactivity.[15] Due to the known nucleophilicity of Chloramine-T analogues such as **6**, as well as the "through dirhodium" displacement of a halide,[25] we envisioned the possible formation of **13** (Scheme 7). Displacement of bromine from **1** by **6** would give **13** as a metal-bound bromine atom-transfer source. Silver(I) titration experiments identified the presence of chloride ion when **1** was treated with Chloramine-T.[26] In addition, the stoichiometric reaction of **1** with Chloramine-T (2 equiv) and styrene in the absence of potassium carbonate rapidly gave both aminobromination and aziridination products, consistent with the intermediate formation of **13**. Furthermore, bromine atom-transfer from **13** would be a sterically demanding process (as both 1-methylcyclohexene and α-methylstyrene were unreactive). Whether or not there is an extended role for **1** beyond its capacity as a Lewis acid, however, remains uncertain at this time and is currently under investigation.

In summary, we have developed a catalytic olefin aziridination protocol using a multivalent dirhodium catalyst. A selection of olefins has been converted to aziridines in moderate to high yields under extremely mild conditions with as little as 0.01 mol % catalyst. A mechanism has been advanced that suggests that dirhodium(II,III) caprolactamate operates as a Lewis acid catalyst and is capable of generating other potentially useful intermediates. Efforts are underway to develop new applications as well as to probe the nature of catalytic intermediates in mixed-valent dirhodium(II,III) catalysis.

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health (GM 46503). We thank Dr. James Fettinger for X-ray determination and Marcela Valenzuela for catalysis evidence for **2** in the HDA reaction.

Supporting Information Available: X-ray crystallographic data and NMR analysis of reaction intermediates (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Without catalyst, arizidine **3** was obtained in 19% yield. Under the same conditions, other transition metals were examined, giving **3** in moderate yield: CuI (5 mol %, 55%), Mn(II)−salen (5 mol %, 41%), $Rh_2(OAc)_4$ (1 mol %, 42%), $Rh_2(pfb)_4$ (1 mol %, 49%).

(25) For displacement reactions of Rh_2−halides, see: Bear, J. L.; Han, B.; Wu, Z.; Van Caemelbecke, E.; Kadish, K. M. *Inorg. Chem.* **2001**, *40*, 2275.

(26) Silver(I) halide test was performed to detect Br^- as the displacement product of **1** and **6**. Treatment of **1** with $Ag(I)BF_4$ did not yield a precipitate. Treatment of NBS with Chloramine-T in the absence of **1** with $Ag(I)BF_4$ did not yield a precipitate. However, in the presence of Chloramine-T, **1** immediately reacted with $Ag(I)BF_4$ to give a white precipitate determined to be AgCl by its solubility in ammonium hydroxide.