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Rhodium(II,II) Dimer as an Efficient Catalyst for Aziridination of Sulfonamides and Amidation of Steroids

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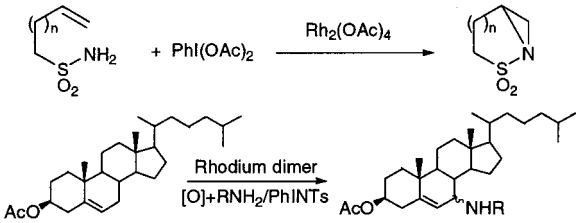
ABSTRACT



Unsaturated sulfonamides underwent direct intramolecular aziridination catalyzed by $Rh_2(OAc)_4$ with $PhI(OAc)_2$ and Al_2O_3 to give the corresponding aziridine products in excellent yields (up to 98%) and with good to excellent conversions. High turnovers (up to 1375) were achieved. The intermolecular rhodium-catalyzed amidation of cholesteryl acetate with PhI═NTs or $PhI(OAc)_2/NH_2R$ as the nitrogen source exhibited both excellent regio- and α-selectivity (α/β ratio up to 9:1).

Nitrogen-atom transfer reactions catalyzed by transition-metal complexes are among the most appealing methodologies for the synthesis of amines and amine derivatives.[1−8] The rhodium(II,II) dimer has been proven to be a versatile catalyst for reactions involving C═C bond addition and C−H bond insertion.[9] In contrast to extensive investigations on C−C bond formation, the application of rhodium(II,II) dimer to C−N bond formation has received significantly less attention

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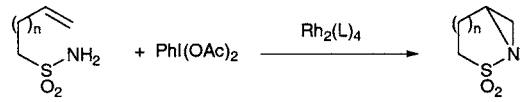
with, to the best of our knowledge, only a handful of publications reported to date.[1b,4,6,8] Furthermore, despite encouraging advances, challenges still remain: first, the turnover number for rhodium(II,II) dimer-catalyzed C−N bond formation remains rather low (<50) and needs to be improved; second, steroid starting materials have thus far received no attention as potential substrates.

Inspired by the work of Breslow[1b] and Du Bois[6] showing that rhodium(II,II) dimers such as $Rh_2(OAc)_4$ can catalyze intramolecular amidation of saturated C−H bonds, we wondered whether these dimers could also be applied to the catalytic intramolecular aziridination of C=C bonds. Pioneering work by Müller showed that iminoiodinanes (derived from unsaturated sulfonamides and $PhI(OAc)_2$) underwent $Rh_2(OAc)_4$-catalyzed intramolecular aziridination to afford the corresponding aziridine **2a** albeit in low yield (about 20%).[4c] Work in our laboratory found that $PhI(OAc)_2$ and RNH_2 (R = *p*-$MeC_6H_4SO_2$, *p*-$NO_2C_6H_4SO_2$) could be used directly as the nitrogen source in intermolecular amidation processes.[5d] More recently, we described one such process of intramolecular amidation of sulfamate esters with high diastereo- and enantioselectivity catalyzed by ruthenium(II) porphyrins.[5h] In light of these results, it was therefore envisaged a "$PhI(OAc)_2$ + RNH_2" amidation protocol to be applicable to a wide variety of RNH_2 compounds and for it to be readily extended to intramolecular aziridination (Scheme 1).

Scheme 1

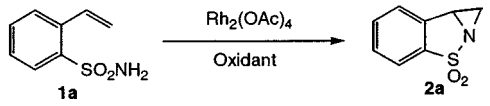


The intramolecular aziridination of **1a** was initially chosen as the model substrate to establish the reaction conditions (Table 1). In the presence of 0.02 equiv of $Rh_2(OAc)_4$, 1.5 equiv of $PhI(OAc)_2$, and 2.5 equiv of Al_2O_3, a variety of solvents were surveyed to ascertain the effect of the reaction medium on yield and conversion. This revealed dichloromethane to be the solvent of choice, furnishing the aziridine **2a** in 83% yield and with near quantitative conversion within 3 h (entry 1).[10] In contrast, reactions conducted in either benzene, acetonitrile, or THF were found to give lower yields or conversions (entries 2−4).

With the solvent of choice established, the effect of changing the oxidant was next examined. In comparing the yield obtained for the model study carried out in CH_2Cl_2 (entry 1), we found that changing the oxidant to iodosylbenzene (PhIO) was detrimental, affording **2a** in 67% yield although having relatively little effect on the conversion (entry 5). The use of 2,6-dichloropyridine *N*-oxide (2,6-Cl_2pyNO) gave no reaction (entry 6).

In turning our attention to the generality of our protocol, a series of unsaturated sulfonamides **1b**−**j** were found to readily undergo intramolecular aziridination to give the corresponding products **2b**−**j** in excellent yields and conversions (Table 2). We were particularly satisfied to find that,

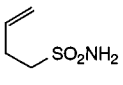
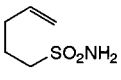
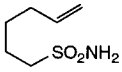
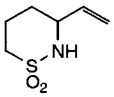
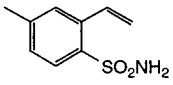
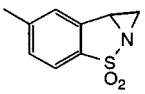
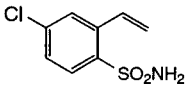
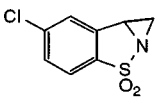
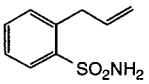
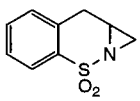
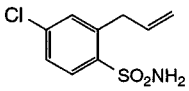
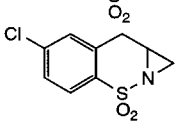
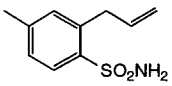
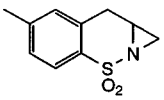
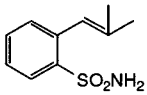
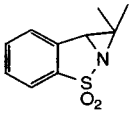
Table 1. Optimization of Reaction Conditions Catalyzed by $Rh_2(OAc)_4$[a]



entry	oxidant	solvent	conversion (%)	yield (%)
1	$PhI(OAc)_2$	CH_2Cl_2	99	83
2	$PhI(OAc)_2$	CH_3CN	63	83
3	$PhI(OAc)_2$	C_6H_6	90	71
4	$PhI(OAc)_2$	THF	85	74
5	PhIO	CH_2Cl_2	95	67
6	2,6-Cl_2pyNO	CH_2Cl_2	0	0

[a] All reactions were performed at 40 °C for 3 h with a $Rh_2(OAc)_4$/**1a**/$PhI(OAc)_2/Al_2O_3$ molar ratio of 0.02:1:1.5:2.5.

Table 2. Intramolecular $Rh_2(OAc)_4$-Catalyzed Aziridination Reactions[a]

entry	substrate		product		conversion(%)	yield(%)
1		**1b**		**2b**	100	97
2		**1c**		**2c**	100	93
3		**1d**		**3**	90	90
4		**1e**		**2e**	85	80
5		**1f**		**2f**	81	74
6		**1g**		**2g**	100	98
7		**1h**		**2h**	91	90
8		**1i**		**2i**	92	91
9		**1j**		**2j**	100	95

[a] Reaction conditions: $Rh_2(OAc)_4$/substrate/$PhI(OAc)_2/Al_2O_3$ = 0.02:1:1.5:2.5; all reactions were performed in CH_2Cl_2 at 40 °C for 3 h.

in a number of cases, product yields and conversions observed were near quantitative (entries 1−2, 6, and 9). Even with substrates **1e**,**f** and **1h**,**i** where it was initially envisaged that the presence of a para substituent on the aromatic ring would be detrimental to the reaction, very good yields and conversions were still observed (entries 4, 5, 7, and 8). Aziridine **2j** was obtained as a crystalline and its structure was determined by X-ray crystal analysis.[11] Albeit not unexpected, only compound **1d** was found not to undergo C=C bond addition, preferring instead to exclusively undergo C−H bond insertion to give vinyllic sultam **3** in 90% yield (entry 3).[7a]

At this juncture, it is worth highlighting the superior nature of the present procedure to previously reported work. In every instance, for example, product yields were found to be significantly higher than those found in work using iminoiodinane intermediates or the analogous copper-catalyzed reactions.[4c,7a] More significantly, the conditions employed allowed for reaction to be achieved with a high turnover number, an important aspect of catalysis. In the presence of 0.02% $Rh_2(OAc)_4$, the intramolecular aziridination of **1g**, for example, afforded **2g** in 55% yield based on 50% conversion with a turnover number of 1375. To the best of our knowledge, this is the highest turnover number ever achieved for rhodium-catalyzed nitrogen atom transfer reactions. Furthermore, this method realized the convenient conversion of unsaturated sulfonamides to cyclic sulfonamides with commercially available reagents (including catalyst, oxidant, and base), waiving the tedious need for initial iminoiodinane preparation. The present procedure can therefore be seen to offer an attractive synthetic route for the synthesis of precursors of sultams, a class of compounds known to exhibit a potent spectrum of bioactivity.[7a,12] It can be envisaged, for example, that further elaboration of compound **1b** (entry 1) would allow access to **4**, potent COX inhibitors,[13a] in significantly improved overall yields, or that of compounds **1g**−**i** (entries 6−8) would lead to the synthesis of **5**, a class of potent calpian I inhibitors, again with significantly improved overall yields to known literature procedures.[13b−c]

In surveying numerous publications describing asymmetric carbene transfer reactions,[9] three chiral rhodium(II,II) dimers were chosen for providing a means of introducing chirality into our intramolecular nitrogen atom delivery reaction (Figure 2). Rh_2(*R*-BNP)$_4$[14] and Rh_2(*R*-ODACA)$_4$[15] showed poor enantioselectivities with ee values less than 5% for the aziridination of substrate **1a**.[16] Doyle's catalyst Rh_2(4*S*-MEOX)$_4$ showed more moderate enantioselectivity with an observed ee value of 49% for the same reaction (54% yield based on 78% conversion). Aziridination of substrates **1g** and **1j** catalyzed by this catalyst, however, gave lower ee values of 21 and 13%, respectively.[17] Nonetheless, this is the first report of an asymmetric intramolecular aziridination reaction catalyzed by rhodium(II,II) dimer complexes and efforts are currently underway to improve the observed enantioselectivities.

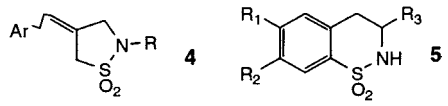


Figure 1. Pharmacologically interesting compounds.

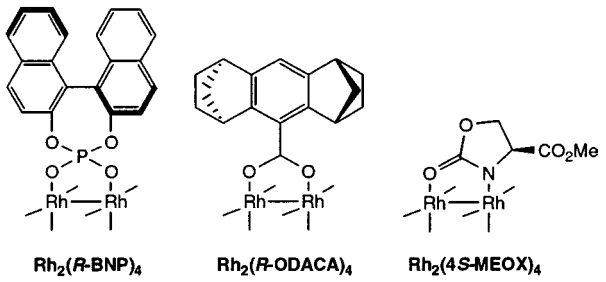


Figure 2. Chiral rhodium complexes used in this work.

Amino steroids have been shown to exhibit noteworthy pharmacological activity, for instance, as anesthetics and enzyme inhibitors in the central nervous system.[18] Previous work by Dauban and Dodd reported a copper-catalyzed aziridination of 11-pregnene-3,20-dione in 53% yield.[7e] Breslow demonstrated that manganese porphyrin catalyzed the amidation of equilenin acetate in 47% yield.[1c] Work previously undertaken in our laboratory had showed that the amidation of cholesteryl acetate catalyzed by ruthenium porphyrin occurred with α-selectivity (α/*β* ratio up to 4.2:1),[5g] while, in contrast, the same reaction catalyzed by ruthenium−salen complexes resulted in *β*-selectivity (*β*/α ratio up to 2.3:1).[5f] It therefore intrigued us to explore the possibility of utilizing rhodium(II,II) dimer catalyst for this reaction (Table 3). Thus, using $Rh_2(OAc)_4$ as the catalyst and PhI=NTs as the nitrogen source, it was found that the

(10) Yield is higher than that of reported by Müller (ref 4c). We noticed that a similar phenomenon occurred upon copper-catalyzed intramolecular aziridination reactions (see refs 7a and 7c).

(11) See Supporting Information.

(12) For a review, see: (a) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry;* Pergamon Press: Oxford, 1990; Vol. 2 Chapter 7.1. For a list of biological applications, see: (b) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.

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(15) Pierson, N.; Fernandez-Garcia, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705.

(16) All asymmetric reactions were performed under the conditions of Table 2. Intramolecular aziridination of **1a** by Rh_2(*R*-BNP)$_4$ afforded conversion of 67% and yield of 64% and that by Rh_2(*R*-ODACA)$_4$ afforded conversion of 88% and yield of 51%.

(17) Aziridination of **1g** afforded conversion of 55% and yield of 82%; aziridination of **1j** afforded conversion of 85% and yield 54%.

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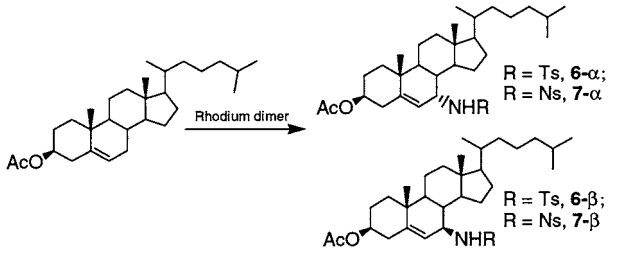
Table 3. Intermolecular Amidation of Cholesteryl Acetate Catalyzed by Rhodium(II,II) Dimer[a]



entry	catalyst	nitrogen source	conversion (%)	yield (%)	α/β[b]
1	$Rh_2(OAc)_4$	PhINTs	30	73	3.4
2	$Rh_2(4S\text{-MEOX})_4$	PhINTs	23	71	4.1
3	$Rh_2(R\text{-ODACA})_4$	PhINTs	28	75	4.8
4	$Rh_2(R\text{-BNP})_4$	PhINTs	21	73	9.0
5	$Rh_2(R\text{-BNP})_4$	$PhI(OAc)_2/NH_2Ts$	20	72	7.8
6	$Rh_2(R\text{-BNP})_4$	$PhI(OAc)_2/NH_2Ns$	25	74	5.1

[a] Reactions were performed in CH_2Cl_2 at 25 °C for 2 h with a catalyst/substrate/PhI═NTs molar ratio of 1:20:40. [b] Determined by ^1H NMR.

amidation of cholesteryl acetate affords the corresponding allylic amidation product **6** with preferential α-selectivity in a ratio of $\alpha/\beta = 3.4$ (entry 1). With previous studies revealing that bulky catalysts could improve α-selectivity, chiral $Rh_2(R\text{-ODACA})_4$, $Rh_2(R\text{-BNP})_4$, and Doyle's catalyst $Rh_2(4S\text{-MEOX})_4$ were examined.[5g] This gave the product with higher α-selectivities of 4.1:1, 4.8:1, and 9:1, respectively (entries 2−4). In employing the "$PhI(OAc)_2/NH_2R$" protocol and switching the nitrogen source to NH_2Ts, product **6** was obtained with lower α-selectivity with a ratio of $\alpha/\beta = 7.8$ (entry 5). Despite this, the scope of the nitrogen source was found to include $NsNH_2$ (Ns = $p\text{-}NO_2C_6H_4SO_2$), furnishing compound **7** again with preferential α-selectivity in a ratio of $\alpha/\beta = 5.1$ (entry 6). The α-selectivity of 9:1 catalyzed by $Rh_2(R\text{-BNP})_4$ with PhI═NTs represents the highest α/β ratio for the amidation of cholesteryl acetate.

In this Letter, we described a rhodium(II,II) dimer-catalyzed aziridination reaction that is both general and high yielding and the use of the same catalyst for the intermolecular amidation of cholesteryl acetate that was achieved with improved α-selectivity. In the case of aziridination, the procedure employed relied upon unsaturated sulfonamides to readily undergo intramolecular aziridination in the presence of $Rh_2(OAc)_4$ and $PhI(OAc)_2$ to give sultam precursors, a class of compounds known to be an essential component for the potent activity observed in a vast array of biologically significant compounds. Efforts are currently underway to develop an enantioselective rhodium-catalyzed version of the present reaction and its application to the total synthesis of a variety of natural products.

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Supporting Information Available: Detailed experimental procedures and characterization data, including X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

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