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Chiral rhodium(II,II) dimers catalyzed enantioselective intramolecular aziridination of sulfonamides and carbamates

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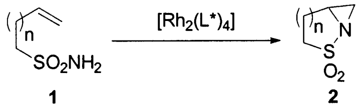
Abstract—The asymmetric intramolecular aziridination of unsaturated sulfonamides and carbamates catalyzed by chiral dirhodium(II,II) complexes were achieved in good yields (up to 95%) and enantioselectivity (up to 76% e.e.).

Transition-metal catalyzed nitrogen-atom transfer reactions are among one of the most powerful strategies for the synthesis of amines and amine derivatives.[1–10] However, in contrast to the extensive investigations on carbene insertions to C=C and C–H bonds, the applications of metal catalysts for analogous nitrene insertion reactions remain sparse.[1–5] Breslow[1] and Du Bois[3] had described dirhodium(II,II) complexes with bridging carboxylate ligands such as [$Rh_2(CH_3CO_2)_4$] catalyzed amidation of saturated C–H bonds. The same catalytic systems were shown by Müller and co-workers to mediate aziridination of C=C bonds by iminoiodinanes.[2] More recently, we reported the intramolecular aziridination of unsaturated sulfonamides **1** catalyzed by [$Rh_2(CH_3CO_2)_4$]. The corresponding cycloadducts **2** were furnished in high yields (up to 98%) and with high product turnovers.[5] Herein we describe the realization of an enantioselective version of this protocol that is potentially useful for effecting intramolecular aziridination of these compounds in a stereocontrolled manner (Scheme 1).



1 **2**

Scheme 1. Enantioselective intramolecular aziridination of acyclic sulfonamides catalyzed by chiral rhodium dicarboxylates.

The intramolecular aziridination of acyclic sulfonamide **1a** was chosen as the model reaction to establish the optimum conditions for introducing chirality into our intramolecular nitrogen atom delivery reaction (Table 1). In the presence of 1.5 equiv. of PhIO in a solution of C_6H_6, the effect of several different chiral dirhodium(II,II) catalysts that are commonly used for asymmetric C–C bond formations were surveyed (Fig. 1). The chiral rhodium catalysts were prepared by literature methods[11–13] or purchased from commercial sources.[14,15] This revealed [Rh_2(4*S*-MEOX)$_4$][14] (0.02 equiv.) to be the catalyst of choice, furnishing the aziridine **2a** with an observed e.e. value of 75% and in 65% yield based on 90% conversion (entry 1). Similar enantioselectivities were observed for reactions with catalyst loading increasing to 5 and 10 mol% (entries 2–3). In contrast, reactions conducted with the catalysts [Rh_2(4*S*-TCPTTL)$_4$][13] and [Rh_2(4*S*-MPPIM)$_4$][15] were found to give lower e.e. values (entries 7–8). It was interesting to note that whilst the analogous reaction of **1a** with $PhI(OAc)_2$ as the oxidant in C_6H_6 gave **2a** with a slightly lower e.e. value, in other solvent systems markedly lower e.e. values were obtained (entries 4–6). Furthermore, the use of $PhI(OAc)_2$ in combination with either [Rh_2(*R*-BNP)$_4$][11] or [Rh_2(*R*-ODACA)$_4$][12] catalyst was found to give **2a** with close to no chiral induction (entries 9–10).

In turning attention to the generality of the present protocol, i.e. '[Rh_2(4*S*-MEOX)$_4$]+PhIO', the enantioselective intramolecular aziridination of a series of unsaturated sulfonamides **1b–i** were examined (Table 2). Thus, in the presence of [Rh_2(4*S*-MEOX)$_4$] (10 mol%) and 1.5 equiv. of PhIO, acyclic sulfonamides **1b–f**[16]

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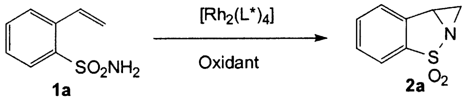
Table 1. Optimization of reaction conditions catalyzed by $Rh_2(L^*)_4$[a]



1a → **2a**

Entry	Catalyst	Oxidant	Solvent	Yield (%)[b,c]	E.e. (%)[d]
1	$[Rh_2(4S\text{-MEOX})_4]$	PhIO	C_6H_6	65 (90)	75
2	$[Rh_2(4S\text{-MEOX})_4]$[e]	PhIO	C_6H_6	65 (90)	76
3	$[Rh_2(4S\text{-MEOX})_4]$[f]	PhIO	C_6H_6	66 (90)	76
4	$[Rh_2(4S\text{-MEOX})_4]$	$PhI(OAc)_2$	C_6H_6	62 (80)	69
5	$[Rh_2(4S\text{-MEOX})_4]$	$PhI(OAc)_2$	CH_3CN	51 (32)	23
6	$[Rh_2(4S\text{-MEOX})_4]$	$PhI(OAc)_2$	CH_2Cl_2	78 (54)	49
7	$[Rh_2(4S\text{-MPPIM})_4]$	PhIO	C_6H_6	60 (10)	50
8	$[Rh_2(4S\text{-TCPTTL})_4]$	PhIO	C_6H_6	61 (52)	57
9	$[Rh_2(R\text{-BNP})_4]$	$PhI(OAc)_2$	CH_2Cl_2	64 (67)	4
10	$[Rh_2(R\text{-ODACA})_4]$	$PhI(OAc)_2$	CH_2Cl_2	51 (88)	3

[a] Reaction conditions: catalyst:substrate:oxidant = 0.02:1:1.5, 5°C, 8 h.
[b] Isolated yield.
[c] Yield in parentheses denotes conversion.
[d] E.e.s determined by HPLC using a chiral OD column.
[e] 5 mol% catalyst was used.
[f] 10 mol% catalyst was used.

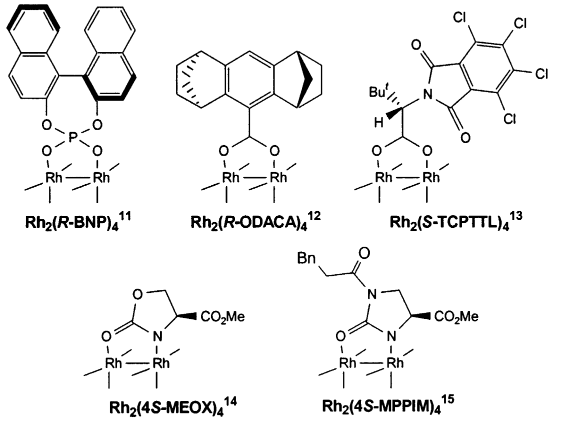
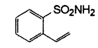
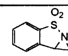
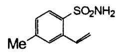
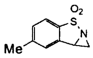
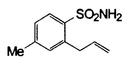
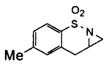
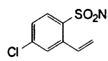
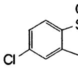
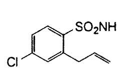
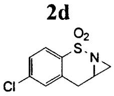
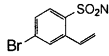
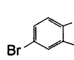
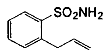
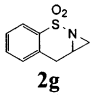
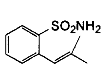
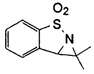
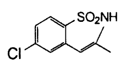
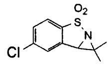


Figure 1. Chiral dirhodium(II,II) catalysts used in this work.

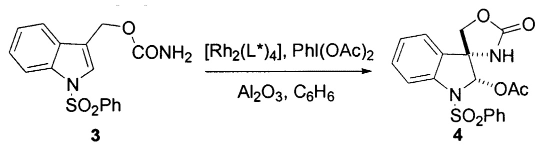
containing either an electron-donating or electron-withdrawing group at the *para*-position on the aromatic ring gave the corresponding aziridines **2b**–**f**[17] in good yields (up to 75%) and with e.e. values up to 74% (entries 2–6). Only in the case of aziridine **2d** was HPLC analysis unable to determine the e.e. accomplished for this reaction (entry 4). Nevertheless, the aziridination of **1g** was achieved in 71% isolated yield based on 70% conversion and with an e.e. value of 57% (entry 7). Furthermore, reaction of the trisubstituted alkene **1h** was observed to furnish **2h** in 81% yield based on 95% conversion and in 64% e.e. (entry 8). Likewise, reaction of *p*-chloro-*o*-(2-methylpropenyl)benzenesulfonamide **1i**[18] gave the corresponding aziridine product **2i**[19] in 95% isolated yield and with an e.e. value of 63% (entry 9). The analogous reactions of **1c** and **1h** carried out with a lower catalyst loading of 2 mol% of $[Rh_2(4S\text{-MEOX})_4]$ were observed to give **2c** and **2h** with e.e.

Table 2. Intramolecular aziridination of acyclic sulfonamides catalyzed by $[Rh_2(4S\text{-MEOX})_4]$[a]

Entry	Substrate 1	Product 2	Conversion (%)	Yield (%)[b]	E.e. (%)[c]
1	 **1a**	 **2a**	66	90	76
2	 **1b**	 **2b**	55	71	74
3	 **1c**	 **2c**	44	73	55
4	 **1d**	 **2d**	60	70	-[d]
5	 **1e**	 **2e**	57	68	67
6	 **1f**	 **2f**	22	74	75
7	 **1g**	 **2g**	70	71	57
8	 **1h**	 **2h**	95	81	64
9	 **1i**	 **2i**	93	95	63

[a]Reaction conditions: catalyst:substrate:PhIO = 0.1: 1: 1.5, C_6H_6, 5°C, 8h. [b]Isolated yield. [c]E.e.'s determined by HPLC using a chiral OD column. [d]E.e. could not be determined by HPLC analysis.

Table 3. Concomitant intramolecular aziridination and nucleophilic ring-opening of **3**[a]



Entry	Catalyst	Conversion (%)	Yield (%)[b]	E.e. (%)[c]
1	[Rh_2(4*S*-MEOX)$_4$][d]	50	74	53
2	[Rh_2(4*S*-MEOX)$_4$][e,f]	48	71	33
3	[Rh_2(*R*-BNP)$_4$][f]	95	86	8
4	[Rh_2(4*S*-TCPTTL)$_4$]	70	55	3
5	[Rh_2(*R*-ODACA)$_4$][f]	85	90	11
6	[Rh_2(4*S*-MPPIM)$_4$]	–	Trace	–

[a] Reaction conditions: catalyst:carbamate **3**:PhI(OAc)$_2$:Al$_2$O$_3$ = 0.05:1:1.5:2.5, 5°C, C_6H_6, 8 h.

[b] Isolated yield.

[c] E.e.s determined by HPLC using a chiral OD column.

[d] 10 mol% catalyst was used.

[e] 2 mol% catalyst was used.

[f] Reaction conducted at 40°C.

values of 46 and 32%, respectively. One reason for the decreased e.e. values could possibly lay in the instability of the catalysts under the reaction conditions employed.

To highlight the synthetic utility of the present stereoselective amidation protocol, the intramolecular aziridination of indole carbamate **3** was examined (Table 3). In the presence of 10 mol% of [Rh_2(4*S*-MEOX)$_4$], 1 equiv. of PhI(OAc)$_2$ and 2.5 equiv. of Al_2O_3, oxazolidinone **4** was afforded in 74% yield based on 50% conversion. More importantly, under these conditions concomitant aziridination and nucleophilic ring opening gave **4**, a synthetically useful precursor of medicinally important vicinal amino alcohols,[4b] which was observed with an e.e. value of 53% (entry 1). The use of the same catalyst at a lower catalyst loading (2 mol%) and at an elevated temperature was found to give similar product yield and conversion but the indole product **4** was obtained in 33% e.e. (entry 2). Likewise, whilst product yields and conversions were maintained for the analogous reactions catalyzed by [Rh_2(*R*-BNP)$_4$], [Rh_2(4*S*-TCPTTL)$_4$] and [Rh_2(*R*-ODACA)$_4$] (up to 90%), significantly lower product e.e. values were obtained for these reactions (entries 3–5). The [Rh_2(4*S*-MPPIM)$_4$] catalyzed reaction of **3** was the only instance where trace product formation was detected (entry 6).

In summary, we have found a mild and straightforward enantioselective method for the synthesis of optically enriched sultams and an indole oxazolidine. Efforts are currently underway to improve the moderate to good e.e. values accomplished by the present protocol through ligand modification and the development of new and robust dirhodium(II,II) catalysts. The results of these findings and their applications to the total synthesis of a variety of natural products will be reported in due course.

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X.-Q.; Zhu, N.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563; (h) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465; (i) Zhang, J.-L.; Che, C.-M. *Org. Lett.* **2002**, *4*, 1911.

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14. [Rh_2(4*S*-MEOX)$_4$] is commercially available from Sigma-Aldrich, order no.: 45,953-4, CAS no.: 167693-36-9.
15. [Rh_2(4*S*-MPPIM)$_4$] is commercially available from Acros, order no.: 30255-0250, CAS no.: 171230-55-0.
16. Selected data for **1f**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=$ 8.02 (d, $J=6.8$ Hz, 1H), 7.56 (m, 2H), 7.33 (m, 1H), 5.75 (d, $J=16.2$ Hz, 1H), 5.55 (d, $J=9.8$ Hz, 1H), 4.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=137.3$, 133.4, 129.5, 128.8, 128.2, 126.8, 120.4, 118.5; MS (EI): 262 (M^+); HRMS (EI) calcd. for $C_8H_9NO_2S$ (M^+-Br) 183.0354, found: 183.0354.
17. Selected data for **2f**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=$ 7.71 (d, $J=7.4$ Hz, 1H), 7.62 (m, 2H), 4.14 (t, $J=4.4$ Hz, 1H), 2.88 (d, $J=3.8$ Hz, 1H), 2.36 (d, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=138.1$, 133.7, 130.7, 126.9, 125.8, 124.0, 44.5, 43.3; MS (EI): 260 (M^+); HRMS (EI) calcd for $C_8H_7NO_2S$ (M^+-Br) 181.0198, found: 181.0197.
18. Selected data for **1i**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 7.93 (d, $J=8.4$ Hz, 1H), 7.32 (m, 2H), 6.65 (s, 1H), 4.82 (s, 2H), 1.99 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=141.0$, 139.0, 138.8, 132.1, 129.2, 128.1, 127.1, 121.3, 26.5, 19.9; HRMS (EI) calcd for $C_{10}H_{12}ClNO_2S$: 245.0277, found: 245.0269.
19. Selected data for **2i**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 7.61 (d, $J=8.1$ Hz, 1H), 7.53 (m, 2H), 4.07 (s, 1H), 1.54 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=139.8$, 136.3, 130.8, 129.5, 126.2, 123.3, 57.6, 54.1, 26.9, 14.5; HRMS (EI) calcd for $C_{10}H_{10}ClNO_2S$: 243.0121, found: 243.0119.