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Asymmetric reduction of azirines; a new route to chiral aziridines

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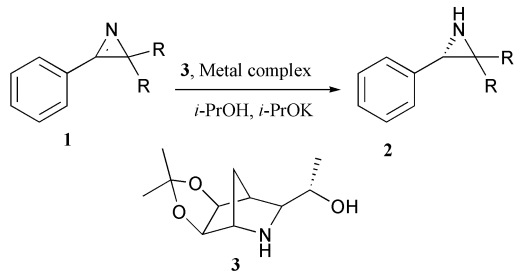
The first enantioselective reduction of aromatic 2*H*-azirines yields aziridines in up to 70% ee, using the aminoalcohol-$[RuCl_2(p\text{-cymene})]_2$ catalyzed asymmetric transfer hydrogenation reaction.

Chiral aziridines are useful synthetic intermediates in organic synthesis since large ring-strain can facilitate regio- and stereoselective ring-opening of the three-membered heterocycle.[1] Many nitrogen containing biologically interesting molecules can be synthesized from aziridines that are made from either enantiomerically pure starting material or through asymmetric synthesis.[2,3] Catalytic enantioselective aziridination of alkenes and imines have been developed into useful synthetic tools but high enantiomeric excess can only be obtained for a limited set of substrates.[4] An alternative route from readily available starting materials to chiral aziridines is therefore desirable. 3-Substituted 2*H*-azirines are highly strained molecules with an unsaturated C=N moiety that can react with nucleophiles.[5] These prochiral substrates serve as precursors to aziridines and can be synthesized on a multigram scale, starting from the corresponding olefin.[6] We here disclose the first enantioselective reduction of azirines that introduces a new route to chiral aziridines (Scheme 1).

Chiral amines can be obtained from enantioselective reduction of prochiral imines.[7] Attempts to reduce azirine **1** using different transition metal complexes did not give the desired aziridine **2**. However, when experiments were performed using the transfer hydrogenation reaction with *i*-PrOH as the hydrogen donor, the results were promising.[8] This reaction has been developed into an attractive complement to hydrogenation, and aromatic ketones can be reduced in more than 95% enantiomeric excess, using a number of catalysts.[9,10] Cyclic imines can be reduced with high stereoselectivity if the more potent formic acid–triethylamine (5:2) mixture is used.[11] The presence of this hydrogen donor was found to cause decomposition of azirine **1**.

We have previously reported that amino alcohol **3** is a very active and selective ligand for aromatic ketone reduction.[12] This bicycle was used as the ligand for the stereoselective reduction of azirine **1**, catalyzed by the metal complexes shown in Table 1.†

The catalyst derived from $[RuCl_2(p\text{-cymene})]_2$ gave (*S*)-2-phenylaziridine in 70% ee and was chosen for further optimization (Table 1, entry 3). Using this catalyst, the reaction could be performed at 0 °C giving **2** in 78% ee but with lower yield because of by-product formation (Table 1, entry 4).



Scheme 1 Asymmetric reduction of azirine **1**.

Table 1 Asymmetric transfer hydrogenation of **1** (R = H)[a]

Entry	Metal complex	Time[b]	Yield	Ee[c]
1	$[IrClCp^*]_2$	15	51	3
2	$[RhClCp^*]_2$	15	41	10
3	$[RuCl_2(p\text{-cymene})]_2$	2	80	70
4	$[RuCl_2(\text{mesityl})]_2$	120	34	43
5	$[RuCl_2(HMB)]_2$	—	—	—
6[d]	$[RuCl_2(p\text{-cymene})]_2$	60	56	78
7[e]	$[RuCl_2(p\text{-cymene})]_2$	2	93	64
8[f]	$[RuCl_2(p\text{-cymene})]_2$	5	70	70
9[g]	$[RuCl_2(p\text{-cymene})]_2$	2	85	67
10[h]	$[RuCl_2(p\text{-cymene})]_2$	5	83	65
11[i]	$[RuCl_2(p\text{-cymene})]_2$	2	86	50

[a] Reactions were performed on a 1.0 mmol scale in a 0.1 M *i*-PrOH solution with ligand : base : substrate : Ru 4 : 5 : 100 : 1 at room temperature. [b] Reaction times are in minutes as determined by TLC. [c] Determined on Chiralcel OD-H column. [d] Performed at 0 °C. [e] 1 M in *i*-PrOH. [f] 0.05 M in *i*-PrOH. [g] Performed in 9 mL of CH_2Cl_2 and 1 mL of *i*-PrOH. [h] Toluene : *i*-PrOH 9 : 1. [i] Performed in CH_3CN : *i*-PrOH 9 : 1.

To investigate concentration effects, reductions were run with different substrate concentrations in *i*-PrOH. Surprisingly, the stereoselectivity decreased in a 1 M solution but performing the reaction in a 0.05 M solution did not have any effect on the stereoselectivity (Table 1, entry 9,10). No racemization of **2** was observed after stirring the reaction mixture overnight.

Since the reaction could be performed in a 1 M solution using only 1 mL of *i*-PrOH, we investigated the possibility of diluting the reaction mixture to a 0.1 M solution with another solvent to study solvent effects. Toluene, acetonitrile and THF were tested but the effect on reaction times and ees proved to be of limited importance, and gave slightly lower enantiomeric excess (Table 1, entry 9–11).

Next, we studied the influence of substituents on reactivity and selectivity. Compounds with substituents on the arene or in the 2-position of the azirine moiety were synthesized and reduced under the optimized conditions.

As seen in Table 2, the stereoselective outcome of the reaction was strongly influenced by substituents on the aromatic

Table 2 Asymmetric transfer hydrogenation of azirines[a]

Entry	Ar	R	Time[b]	Yield	Ee[c]
1	C_6H_5	H	2	80	70
2	*o*-ClC_6H_4	H	2	83	56
3	*m*-ClC_6H_4	H	2	78	58
4	*p*-ClC_6H_4	H	2	81	44
5	*p*-BrC_6H_4	H	2	92	50
6	*m*-$CH_3C_6H_4$	H	5	75	65
7	*p*-$CH_3C_6H_4$	H	5	83	72
8	2,4,6-MeC_6H_2	Me	5	89	57
9	*p*-$CH_3OC_6H_4$	H	10	72	0
10	2-Naphthyl	H	10	92	50
11	C_6H_5	Me	—	—	—

[a] Reactions performed on a 1 mmol scale at room temperature for 2–10 minutes with S/C 100. [b] Minutes (TLC). [c] Determined on Chiralcel OD-H column.

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ring and by the bulkiness of the alkyl group. Chloro- and bromo-substituted aromatic azirines were reduced in 44 to 58% enantiomeric excess (Table 2, entries 2–5). Methyl substitution at the *m*- and *p*-positions on the aromatic ring yielded aziridines with 65 and 72% ee respectively (Table 2, entries 6,7). Surprisingly, a methoxy substituent in the *p*-position has a dramatic negative influence on selectivity and yields the product as a racemate (Table 2, entry 9). As shown in entry 11, increased steric hindrance on the aliphatic group inhibits reduction. This is probably due to lack of flexibility in this type of azirine. Our attempts to reduce aliphatic azirines have failed. These substrates proved to be less stable and difficult to isolate.

In agreement with the Noyori mechanism, preliminary mechanistic experiments indicate that a *N*–H moiety in the ligand is necessary for reduction. Alkylation of the nitrogen (Me) on **3** inhibits reaction. This suggests that a mechanism involving a concerted addition of a proton and a hydride from the catalyst is operating, as is the case in the asymmetric transfer hydrogenation of aromatic ketones.[13]

In conclusion, chiral aromatic aziridines can be obtained from the asymmetric transfer hydrogenation of azirines. Azirine **1** is reduced with 70% enantiomeric excess which is comparable to the stereoselectivity reported for aziridination of styrene.[4] Other methods to reduce 2*H*-azirines are currently under investigation.

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Notes and references

† A typical procedure: to a dry 25 mL Schlenk flask equipped with a magnetic stirrer and Ar atmosphere, were added $[RuCl_2(p\text{-cymene})]_2$ (2.5 μmol, 1.53 mg) and amino alcohol **3** (20 μmol, 4.27 mg) followed by 2 mL of *i*-PrOH (freshly distilled over CaH_2). The reaction mixture was stirred for 15 min at rt and another 6 mL of *i*-PrOH was added followed by *i*-PrOK (25 μmol, 25 μL, 1 M solution in *i*-PrOH). The substrate (1.0 mmol) in 2 mL of *i*-PrOH was added dropwise and the reaction was followed by TLC. The reaction was quenched by the addition of 2 drops of water and the solvent removed by distillation. The red oil was filtered through a short plug of SiO_2 (1 g) with pentane–Et_2O. The ee was determined on a Chiralcel OD-H column with a UV detector and a flow rate of 0.5 mL min^{-1} using hexane : *i*-PrOH 90 : 10.

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