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A New Enantioselective Synthesis of N-Arylaziridines by Phase-Transfer Catalysis†

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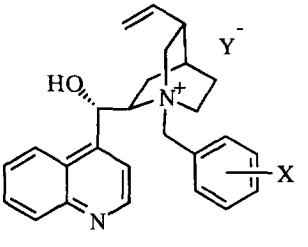
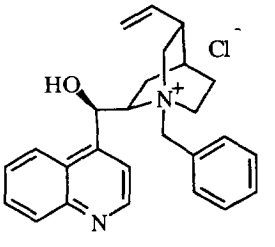
Abstract: Chiral N-arylaziridines are obtained from N-acyl-N-arylhydroxylamines using quaternary salts of *Cinchona* alkaloids as phase-transfer catalysts. Copyright © 1996 Elsevier Science Ltd

Chiral aziridines are important compounds in asymmetric synthesis.[1] They have been successfully used as chiral auxiliaries, chiral ligands for transition metals and chiral substrates in the preparation of biologically active species such as amino acids, β-lactams and alkaloids.[1] In spite of many useful methodologies available for chiral aziridines, most of them require chiral substrates or reagents. An efficient catalytic synthesis of chiral N-tosylaziridines has been developed by Masamune[2], Jacobsen[3] and Evans.[4] Recently, Jacobsen[5] has reported a catalytic asymmetric method for N-arylaziridines with enantiomeric excesses up to 67% but in poor yields.

Here we report a new catalytic enantioselective method for N-arylaziridines based on the quaternary salts **1** of *Cinchona* alkaloids as phase-transfer catalysts.[6] Our group has previously described[7] N-acyl-N-arylhydroxylamines and O-acyl-N-arylhydroxylamines as efficient aziridinating agents of electron deficient olefins. We have now explored this reaction in chiral phase-transfer conditions obtaining aziridines in moderate to good yields and enantiomeric excesses up to 61% (Tables 1 and 2).[8]



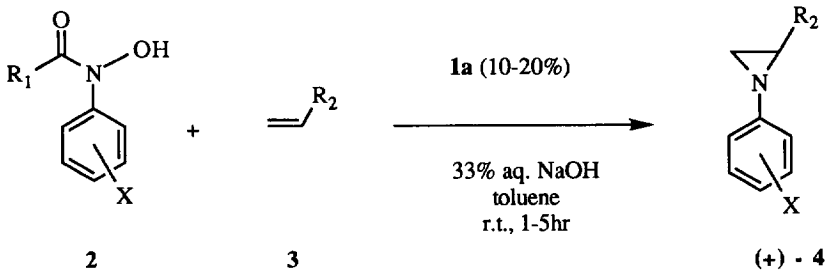
1a: X=4-CF_3, Y=Br
1b: X=3,4-Cl_2, Y=Cl
1c: X=H, Y=Cl



1d

† *This paper is dedicated to Professor Alberto C. Ralha on the occasion of his 75th birthday.*

Table 1. Asymmetric Aziridination of Electron-Deficient Olefins by Hydroxamic Acids



2 3 (+) - 4

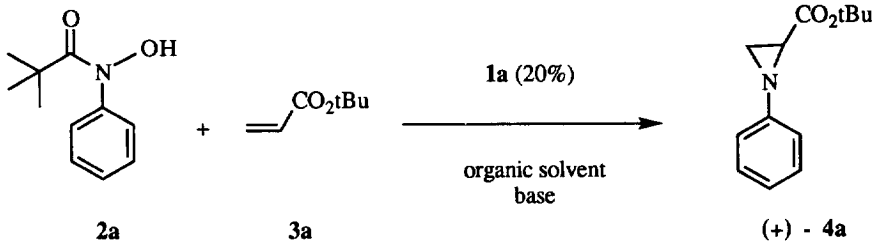
Entry	Hydroxamic Acid R1		X	Olefin R2		Aziridine Yield[a]	E.e.[b]	$[\alpha]_D^{20}$
1	**2a**	tBu	H	**3a**	CO_2tBu	**4a** 79%	45%	+66° (c 1.06)[c]
2	**2b**	tBu	4-Me	**3a**	CO_2tBu	**4b** 50%	51%	+84° (c 0.64)[c]
3	**2c**	tBu	4-Br	**3a**	CO_2tBu	**4c** 50%	36%	+46° (c 0.56)[c]
4	**2d**	tBu	3-Me	**3a**	CO_2tBu	**4d** 40%	43%	+69° (c 0.60)[c]
5	**2e**	tBu	3-Br	**3a**	CO_2tBu	**4e** 28%	16%	+20° (c 0.84)[c]
6	**2f**	tBu	4-NO_2	**3a**	CO_2tBu	**4f** 0%	-	-
7	**2g**	Ph	H	**3a**	CO_2tBu	**4a** 23%	53%	-
8	**2a**	tBu	H	**3b**	SOPh	**4g** 45%	19%, 11%[d]	-

[a] Isolated yields after chromatography; [b] e.e. were measured by HPLC[9a] with a chiral column (Chiralcel® OD); absolute configurations were not assigned; [c] Optical rotations were determined in CH_2Cl_2; [d] e.e. for minor and major diastereomers respectively (ratio 1/19).

Both the enantioselectivity and the yields were found to be sensitive to structural modifications in the reactants. Namely, the substitutions in the N-aromatic moiety of the hydroxamic acids **2** substantially affected the results (Table 1, entries 1-6). On the other hand, the stereoselectivity seems not to be significantly influenced by the acyl group in **2** (Table 1, entries 1 and 7). The aziridination of t-butyl acrylate has also been performed by O-pivaloyl-N-phenylhydroxylamine instead of N-pivaloyl-N-phenylhydroxilamine (**2a**) obtaining the aziridine (+)-**4a** with practically the same e.e. (52%) and lower yield (12%, due to the well-known[10] instability of the O-acyl-N-arylhydroxylamine).

Different solvents and base concentrations have been tried and the results summarized in Table 2. The role played by the solvent is well illustrated by entries 1-5, with the maximum e.e. being obtained in the less polar solvents. Most probably polar solvents weaken the ionic interaction between the catalyst and the anionic aziridinating agent (a similar effect has been previously observed[6a,c]). Lower concentrations of base gave the highest e.e. (61%, entry 7) but the yield drastically dropped (entries 5-7). Reducing the temperature to 0 °C the reaction was not complete after 6 days and the product was isolated in 39% yield and 40% e.e. Use of LiOH or KOH instead of NaOH did not change the e.e. but reduced the yields.

Table 2. The Effect of Base Concentration and Solvent on Asymmetric Aziridination



2a 3a (+) - 4a

Entry	Organic Solvent	Base	4a Yield[a]	E.e.
1	no solvent	NaOH 33%	62%	21%[b]
2	ethyl ether	NaOH 33%	66%	4%[c]
3	dichloromethane	NaOH 33%	29%	34%[b]
4	cyclohexane	NaOH 33%	61%	50%[b]
5	toluene	NaOH 33%	79%	45%[d]
6	toluene	NaOH 20%	18%	57%[c]
7	toluene	NaOH 9%	12%	61%[b]

[a] isolated yields after chromatogrphy [b] measured by ^{1}H NMR with Eu(tfc)$_3$;[9b] [c] measured by optical rotation; [d] measured by chiral HPLC.[9a]

The possibility of a simultaneous non-catalyzed path leading to achiral aziridines was excluded when we observed no reaction of **2a** with t-butyl acrylate (**3a**) in the absence of catalyst (and typical reaction conditions) either in toluene or Et_2O at 25 °C . We also observed that the e.e. of aziridine **4a** was conserved in typical reaction medium after 2 days.

Finally we explored slightly modified catalysts. N-[3,4-(dichloro)-benzyl]cinchoninium chloride[6c] (**1b**) and N-benzyl-cinchoninium chloride[6] (**1c**) catalyzed the formation of aziridine (+)-**4a** in 14% yield (32% e.e.) and 18% yield (18% e.e.) respectively, suggesting that the electronic properties of the benzyl substructure are essential in the catalysis mechanism.

Cinchonidinium and cinchoninium halides have been described[6b,d,f,g] as "pseudoenantiomers" in the sense that the two families give origin to opposite enantiomers in phase-transfer catalyzed reactions. To our surprise we obtained the same major enantiomer of **4a** with the same e.e. (18%) and yield (18%) when N-benzyl-cinchonidinium chloride (**1d**) or N-benzyl-cinchoninium chloride (**1c**) were used. This shows that the hydroxy group in the catalyst is not involved in any significant extent in the enantiotopic differentiation of the olefin.

For the aziridinating agent to distinguish between the two faces of the olefin a chiral environment (generated by the catalyst) should be present. The results here reported suggest that, beyond ionic forces, there are $\pi-\pi$ interactions between the benzyl group of the catalyst and the aryl group of the hydroxylamine responsible for binding the two species. The acyl group of the aziridinating species should be positioned away from the catalyst given the insensitivity of the e.e. to it. Further experiments are underway to secure more insight into the mechanism.

In conclusion, we developed a useful new catalytic method for chiral N-arylaziridines employing inexpensive compounds and simple procedures.

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8. Representative experimental procedure: A mixture of N-phenyl-N-pivaloyl-hydroxilamine (**2a**) (100 mg, 0.52 mmol), 8 mL of toluene, 1 mL of 33% wt. aqueous NaOH, t-butyl acrylate (**3a**) (0.76 mL, 10 eq.) and catalyst **1a** (28 mg, 0.1 eq.) was magnetically stirred under nitrogen at room temperature and more catalyst (28 mg, 0.1 eq.) was added after 2.5 hr. 2 hr later the toluene and non-reacted olefin were evaporated *in vacuo* and the residue was taken up in ether (15 mL), washed with water (3 x 20 mL), the layers were separated and the ether layer was dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* . The aziridine **4a** was purified by preparative layer chromatography on silica gel eluting with hexane-ethyl acetate (4:1).

   All new compounds were adequately characterized by elemental analysis or accurate mass measurements. Their spectral data (IR and ^1H NMR) are in complete accordance with the assigned structures.
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