Synthesis of Asymmetric *N*-Arylaziridine Derivatives Using a New Chiral Phase-Transfer Catalyst

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Abstract: Substituted *N*-arylaziridine derivatives were synthesized in an enantioselective manner from *N*-acyl-*N*-arylhydroxylamine and electron deficient olefins using chiral phase-transfer catalysts (CPTCs) derived from cinchona alkaloids. The structures of the CPTCs were ascertained through various spectral techniques such as FT-IR, ¹H NMR, ¹³C NMR, and mass spectroscopy, as well as elemental analyses. The efficiency and chiral behavior of a range of CPTCs were studied with respect to both yield and ee. The chemical yields were in the range of 24–92% and ee was 29–95%. It was observed that the *S*-enantiomers were more predominant than the *R*enantiomers with cinchonidine as catalyst; whereas the *R*-enantiomers were more predominant in the case of cinchonine based CPTC. We propose here a suitable mechanism for the formation of chiral aziridines as well as optimized procedures for a range of *N*arylaziridine derivatives.

Key words: enantioselection, cinchona alkaloid, aziridine, hydroxamic acids, electron deficient olefins

The ability of aziridines to undergo highly regio- and stereoselective ring-opening reactions makes them valuable in organic synthesis.¹ This ability is also known in nature, where a number of molecules possessing an aziridine ring have been shown to exhibit potent biological activity, which is intimately associated with the reactivity of the strained heterocycle. For example, various forms of mitomycin, together with porfiromycin and mitiromycin,² represent an important class of naturally occurring mitosanes, isolated from soil extracts of Streptomyces verticillatus.³ These mitosanes exhibit both anti-tumor and antibiotic activity, their anti-tumor properties result from their ability to cross-link DNA.² Structure-activity relationships have identified the aziridine ring as being essential for antitumor activity and many research studies have concentrated on synthesizing derivatives of these natural products with increased potency.⁴

A number of synthetic aziridines have also been shown to exhibit useful biological properties.^{5,6} Novel antitumor agents related to mitosanes and mytomycins have recently been synthesized and demonstrated to possess activity against a variety of cancers.⁷ Thus aziridine derivatives are worthy targets for a synthetic organic chemist and it is essential that efficient methods exist for the facile synthesis of a range of structurally diverse aziridines, with the added requirement that any available method should also allow enantioselective aziridine formation. The significance of the aziridines and their derivatives depend on their high reactivity giving a variety of ring-opened or ring-expanded nitrogen containing compounds. Particularly, the presence of electron-withdrawing group on the aziridine nitrogen plays a key role in the ring-opening reactions, affecting both the regio- and stereoselectivity.⁸ Though, numerous methods are available to prepare aziridines or substituted aziridines, the utilization of chiral phase-transfer catalyst (CPTC) is still in its infancy. It is also known that the enantioselective synthesis of aziridines is of much significance due to its significant applications in medicinal chemistry.

In the last 30 years the field of asymmetric catalysis has become the subject of extensive research activity, resulting in the development of naturally occurring cinchona alkaloids as chiral auxiliaries. Cinchona alkaloids have a veritable history in the field of asymmetric synthesis owing to their firmly established ability to induce chirality. Hence, they have been widely used in asymmetric syntheses both in homogeneous and heterogeneous reactions.⁹ These catalysts have shown broad application in mediating a variety of synthetically useful transformations with high selectivities.9c Particularly, CPTC has been dominated by cinchona and its derivatives¹⁰ although the other quaternary ammonium salts¹⁰ and metal catalysts¹¹ have been reported recently for the asymmetric synthesis. Reactions such as carbon-carbon bond formation,^{12,13} alkylation,^{14a-d} Darzen reaction,^{14e-h} Michael addition,^{14i,j} aldol condensation,^{14k} and α -hydroxylation of ketones^{14l} were performed in the recent past using different CPTCs. CPTC has also been used to control diastereoslectivity, as demonstrated by the highly effective and practical synthesis of HIV protease inhibitors by nitro-aldol reactions of aldehydes with nitromethane.

The synthesis of chiral aziridines was reported by Jacobsen¹⁵ and Evans¹⁶ using copper catalysts with chiral dinitrogen ligands. Recently Jacobsen et al.¹⁷ studied the synthesis of chiral aziridines using bisoxazolines copper(I) complex and reported an ee up to 67% with a modest chemical yield. Joao Aires-de-sousa et al.¹⁸ have reported a new enantioselective method for the synthesis of N-aryl aziridines using *N*-benzyl cinchona alkaloid derivative as a soluble CPTC. Their study concluded that the *O*-pivaloyl-*N*-phenylhydroxylamines and *N*-pivaloyl-*N*-

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phenylhydroxylamines are efficient aziridinating agents of electron deficient olefins. They reported different chiral aziridines using cinchona alkaloid-derived CPTC; but here the chemical yield is 79% with ee up to 61%.



Scheme 1 Synthesis of aziridine derivatives

In this paper, our main focus of attention has been devoted to the synthesis of efficient and new CPTCs. This in turn could improve the reaction yield and enantiomeric efficiency. Furthermore, it is also our aim to explore the possibilities of *N*-acyl-*N*-arylhydroxylamines **1** (Scheme 1) as efficient aziridinating agents due to the presence of electron deficient atoms. As a first step, CPTC 7 was synthesized from 2-hydroxy-3-chloromethyl-5-methyl benzaldehyde (4) and cinchonidine 5 in acetonitrile at 20 °C. The resulting mixture was stirred with *p*-toluene sulfonylchloride to give CPTC 9-O-[p-toluenesulfonyl-N-(3formyl-5-methyl-2-hydroxybenzyl)]cinchonidinium chloride (7; 91%). Similarly cinchonine derived CPTC 10, 9-O-[p-toluenesulfonyl-N-(3-formyl-5-methyl-2-hydroxybenzyl]cinchonium chloride was also prepared in 85% yield following the same experimental methodology as in 7 (Scheme 2). In order to examine the catalytic efficiency of these two chiral quaternary ammonium CPTCs 7 and 10; they were used individually to effect the aziridination reaction of different hydroxamic acids 1 with different olefins 2 in a biphasic system with various solvents in the presence of 10-30% aqueous NaOH/KOH solutions. The relative and absolute configurations of the aziridine product **3** were assigned by analyses of their ¹H NMR spectra. The ee of the N-aryl aziridine products were measured using chiral HPLC analysis. All the asymmetric aziridination reactions were carried out using commercially available hydroxamic acids/substituted hydroxamic acid as substrate with a view to improving the yields (92%) and also ee (up to 95%) in the presence of our CPTCs (Table 1).

The influence of base (NaOH or KOH) at different concentrations (10–30% w/v) and solvents with different polarities (MeOH, Et_2O , and toluene) for the aziridination reaction was also studied to determine their effect on the chemical yield and ee. The amount of aziridine derivatives and their corresponding ee under different reaction conditions are presented in Tables 1 and 2. The result reveals that changing the base from NaOH to KOH as well as varying their concentration has a remarkably influence on the reactions (Table 1). For example, the aziridine yield and ee obtained in the presence of NaOH is much higher than in the case of KOH due to the stronger ionic interaction between Na⁺ and the *N*-acyloxy anions **13** compared to the K⁺ ion. Similarly, a higher yield and ee was observed in the presence of low concentrations of aqueous NaOH (Table 1, entries 1–3). This is probably due to the decomposition of CPTC in the presence of high concentrations of NaOH. Similar results have been reported for C- and O-alkylations of *C*-benzyl and benzyl ethers, respectively, using tetrabutylammonium hydrogen sulfate as a soluble phase transfer catalyst.¹⁹

 Table 1
 Effect of Base and its Concentration on the Aziridination

$\begin{array}{c} OH \\ \downarrow \\ Ph \end{array} + = CO_{2^{t}-Bu} \\ CO_{2^{t}-Bu} \\ CPTC 10 \end{array} + \begin{array}{c} OOt-Bu \\ N \\ OTC 10 \\ OTC 10$						
Entry	Aqueous Base	Concentration (%, w/v)	Yield (%)	ee (%)	Configuration	
1	NaOH	10	84	95	R	
2	NaOH	20	75	85	R	
3	NaOH	30	46	73	R	
4	КОН	10	38	26	R	
5	КОН	20	32	15	R	
6	КОН	30	24	-	_	

The change of solvent is an important factor in the aziridination reaction (Table 2). The yield and ee have been found to increase in the order of methanol < diethylether < toluene. The decreased product yield/ee in highly polar solvents such as methanol or diethylether may due to the higher degree of solvation of CPTCs; as a result the efficiency of the catalyst is decreased. In the case of toluene, which is a low polar solvent, the degree of solvation of CPTCs is considerably less. So the degree of decay due to solvation of CPTCs is minimized/ignored.

 Table 2
 The Effect of Solvent on Yield and Enantiomeric Excess

OH Ph	I COt-Bu	CO ₂ t-Bu <u>s</u>	20% aq NaOH/ solvent CPTC 7	N N	Ot-Bu
Entry	Solvent	3	Yield (%) ee (%)	Configuration
1	Toluene	2.4	92	94	S
2	Et ₂ O	4.2	56	58	S
3	MeOH	32.63	47	42	S

The product yields and ee for a range of aziridinations are presented in Table 3. These results reveal that the stereochemical course of the aziridination reaction depends on the stereochemistry/molecular assembly of the different



Scheme 2 Formation of various intermediates/molecular assembly to enantioselective aziridinating reaction under CPTCs condition

reactants and CPTCs. Furthermore, the results proved that the stereochemical course of the aziridination reaction mainly depends on the stereochemistry of the N-phenyl-*N*-hydroxamic acid derivatives **1** as can be seen when a number of electron deficient olefins 2 underwent reaction in the presence of CPTCs 6, 7, 9, and 10. The increased yield and ee of each reaction can be mainly attributed to an effective contact ion-pair formed between the positive quaternary ammonium ions (R_4N^+) and the CPTC (6, 7, 9, and 10) with N-acyloxy anion 13 due to electrostatic attraction and also the same attraction between R_4N^+ of all the CPTCs with the π -bond present on the α - and β -carbons of the acrylate olefin 2 (15, Scheme 2).²⁰ Similarly, a decrease in the aziridination product yield and ee may be due to the formation of a hydrogen bond between the reactants (13 and 2) and the free hydroxyl group present at the $C_0(O)$ -position of the CPTCs 6 and 9 (Scheme 2, 16, 17). In these studies it was established that the O-tosyl derivative of the catalysts (7 and 10) is far superior in forming the aziridine in high yield (92%) and ee (95%) compared to the O-acryloyl derivative already reported.²¹ Here also the mechanistic considerations are the same namely the prevention of hydrogen bonding at the C₀-position of the catalysts 7 and 10 due to O-derivatization thus resulting in high yield and ee.

In order to improve the yield and ee further, we synthesized $C_0(O)$ -protected cinchona derived CPTCs by tosylation. To the best of our knowledge there is no report available for $C_{9}(O)$ -tosylated and N-substitution of 3formyl-5-methyl-2-hydroxybenzyl cinchona derived compound as CPTCs. The reaction yield and ee for the reaction catalyzed by 7 and 10 for all the aziridination reactions were observed to be higher (Table 3, entries 3a-o,) than for catalysts 6 and 9. This is because, the free OH present at the C(9)-position of catalyst 7 and 10 has been derivatized as a tosylate as a result, it facilitates the formation of N-arylated aziridine. Furthermore, the other possibility of hydrogen bonding between the free OH present in the phenol moiety of the catalyst and N-acyloxy anion or carbonyl oxygen (olefin) may also be ignored due to intramolecular hydrogen bonding with the adjacent formyl group (Figure 1, 18). Therefore, the α - and β -carbons of the olefinic double bond and N-acyloxy anion are brought closer towards (in bonding distance) the R₄N⁺ site of catalysts 7 and 10 through electrostatic attraction of the π bond and ion-pair formation, respectively. This is possible due to the absence of hydrogen bonding between the catalyst and substrates. The formation of the R- and S-isomer is then solely dependent on chiral transfer between substrate and catalysts.

In cinchonium CPTC 10 the molecular assembly during chiral exchange would be attributed to the formation of an ion-pair between R_4N^+ and *N*-acyloxy anion 13, with the quinoline part of catalyst 10 serving as the platform for the aromatic ring of substrate 1 (Scheme 2).

Similarly, for the other substrates, the olefin is again oriented towards the R_4N^+ site of the catalyst ($R_4N^+ \pi$ -electrostatic attraction). The molecular assembly when arranged in such a manner leads to the formation of R-isomers, as observed earlier.²¹ In the case of a reaction catalyzed by cinchonidinium CPTC, 7 must also undergo similar molecular assembly/orientation in such a manner on the other side, which would lead to the S-isomer of aziridine derivatives. The increased/decreased chemical yields/ees of the reaction is mainly due to the presence of electron-donating/withdrawing group on the N-aromatic moiety of the hydroxamic acid 1. It is clear from Table 3 that the yield and ee of aziridines increases when electrondonating groups are present on the aromatic moiety (Table 3, 3b, 3f, 3o-q). In contrast, the presence of an electron withdrawing group (Table 3, 3e, 3j, 3m), resulted in lower yield due to the N-acyloxy anion 13 being generated in smaller quanities.



Ion-pair formed between R_4N^+ of CPTC's with the *N*-acyloxy anion as a result of electrostatic attraction; there is also electrostatic attraction between R_4N^+ and the π -bond of the olefins



Hydrogen bonding between the electrophilic $\alpha\text{-carbon}$ of the olefin with the free -OH present at the C_9 (O) position of catalysts 6 and 9





Figure 1

 Table 3
 Asymmetric Aziridination of N-Aryl Hydroxamic Acids with Electron-Deficient Olefins

Product	Hydroxamic acids		Olefins	CPTC	Aziridines	Aziridines	
	\mathbf{R}^1	Х	\mathbb{R}^2	(10 mol%)	Yield ^a (%)	ee (%)	Configuration
3 a	<i>t</i> -Bu	Н	CO ₂ - <i>t</i> -Bu	7	79	94	S
3b	<i>t</i> -Bu	4-OMe	CO ₂ - <i>t</i> -Bu	10	92	95	R
3c	<i>t</i> -Bu	4-Cl	CO ₂ - <i>t</i> -Bu	10	86	85	R
3d	<i>t</i> -Bu	3-Br	CO ₂ - <i>t</i> -Bu	7	87	76	S
3e	<i>t</i> -Bu	4-COOH	Ph	10	53	75	R
3f	<i>t</i> -Bu	4-OH	SOPh	10	77	82	R
3g	<i>t</i> -Bu	Н	CO ₂ - <i>t</i> -Bu	10	56	88	R
3h	<i>t</i> -Bu	4-Br	CO ₂ - <i>t</i> -Bu	7	79	87	S
3i	Ph	4-Me	CO ₂ Me	7	85	79	S
3j	Ph	4-NO ₂	CO ₂ - <i>t</i> -Bu	7	41	43	S
3k	t-Bu	4-Br	CO ₂ Me	10	49	76	R
31	Ph	4-Me	CO ₂ - <i>t</i> -Bu	10	69	85	R
3m	<i>t</i> -Bu	$4-NO_2$	CO ₂ - <i>t</i> -Bu	10	92	89	R



Hydrogen bonding between *N*-acyloxy anion and free -OH present at the C_9 (O) position of catalysts **6** and **9**



Intramolecular hydrogen bonding between the phenolic -OH of the benzyl moiety and adjacent aldehyde group

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Table 3 Asymmetric Aziridination of N-Aryl Hydroxamic Acids with Electron-Deficient Olefins (continued)

Product	Hydroxamic acids		Olefins	CPTC	Aziridines		
	\mathbb{R}^1	Х	R ²	(10 mol%)	Yield ^a (%)	ee (%)	Configuration
3n	<i>t</i> -Bu	4-Br	CO ₂ - <i>t</i> -Bu	7	70	_	_
30	<i>t</i> -Bu	4-Me	CO ₂ - <i>t</i> -Bu	10	65	90	R
3р	<i>t</i> -Bu	4-Me	CO ₂ - <i>t</i> -Bu	6	24	29	S
3q	<i>t</i> -Bu	4-Me	CO ₂ - <i>t</i> -Bu	9	31	32	R

^a Isolated yield after chromatography.

The present study has shown that N-arylaziridines can be successfully synthesized. We also reported two different stable new CPTCs, 7 and 10. The structure of both these CPTCs was confirmed using various spectral techniques like FT-IR, ¹H NMR, ¹³C NMR, and mass spectroscopy. The potential and asymmetric property of the catalysts was examined by employing them in the synthesis of various asymmetric N-arylaziridines. The chiral induction efficiency of the different reactions was determined by chiral HPLC analysis. The optimum conditions for the reaction were a low concentration (10% w/v) of aqueous NaOH, a solvent with a low dielectric constant like toluene, and an electron-donating group present on the N-aryl group on the hydroxamic acid. It was proven that catalyst 7 favors the formation of the S-enantiomer and catalyst **10** favors the R-enantiomer based on their racemization analysis of the products using HPLC. The convenient synthetic procedures described here should facilitate the syntheses and application of more of these derivatives.

Materials were obtained as follows, cinchonine (Fluka), cinchonidine (Fluka), N-acyl-N-arylhydroxylamine (Lancaster, K), p-TsCl (Merck), 5-methyl salicylaldehyde (Merck), paraformaldehyde (Merck), all olefins were commercial samples. All solvents were distilled prior to use. IR spectra were recorded on JASCO-FT-IR model 5300 spectrometer using a KBr pellet. ¹H NMR (300 and 200 MHz) and ¹³C NMR (75 and 50 MHz) spectra were recorded in CDCl₃ on a Bruker AC-200 spectrometer using TMS as an internal standard. Elemental analyses were recorded on Perkin-Elmer 240-CHN analyzer. Optical rotations were measured with an Autopol IIautomatic polarimeter at r.t. For TLC analysis, plates coated with silica gel were run in hexane-EtOAc and were developed in an iodine chamber. Column chromatography was performed under gravity with silica gel (100-200 mesh). The racemization products of various N-arylaziridines were analyzed by HPLC using a chiral pircle column with hexane-dioxane (100:0.5) at a flow rate of 0.5mL/ min.

3-Chloromethyl-5-methyl-2-hydroxybenzaldehyde (4)

To a mixture of 5-methyl salicylaldehyde (5 g, 16.5 mmol), paraformaldehyde (1.43 g, 48.64 mmol) and concd HCl (25 mL) were added, followed by concd H_2SO_4 (5–6 drops). The solution was refluxed for 2 h and then HCl gas was passed through the reaction mixture, which was then refluxed for another 2 h. The temperature of the reaction mixture was allowed to cool to r.t. The orange product obtained, was filtered and washed with HCl (2 × 10 mL), dried, and recrystallized from CHCl₃–THF; yield: 4.7g (73%).

FT-IR: 3420, 2200, 1730, 1220, 720 cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ = 2.1 (s, 3 H), 3.2 (s, 2 H), 5.2 (s, 1 H), 7.1 (m, 1 H), 7.34 (m, 1 H), 9.6 (s, 1 H).

 ^{13}C NMR (50 MHz): δ = 11.45, 20.27, 40.61, 122.10, 124.64, 131.81, 136.77, 156.32, 193.30.

N-(3-Formyl-5-methyl-2-hydroxybenzyl)cinchonidinium Chloride (6)

A mixture of cinchonidine (5; 3.0 g, 10.19 mmol) and 3-chloromethyl-5-methyl-2-hydroxybenzaldehyde (4; 1.88 g, 10.18 mmol) in MeCN (50 mL) was stirred at r.t. for 36 h. The solution was washed with a small amount of sat. NaHCO₃ solution (10 mL) and the organic layer was dried, the crude residue was purified by column chromatography (EtOH–cyclohexane, 3:7); yield: 4.35 g (89%).

FT-IR: 3442, 2837, 1730, 1620, 1075 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.72–1.76 (m, 4 H), 2.23 (br s, 1 H), 2.32 (s, 3 H), 2.77–2.85 (m, 1 H), 3.13–3.17 (m, 1 H), 3.20–3.25 (m, 4 H), 4.05–4.12 (q, 1 H, *J* = 6 Hz), 4.5–4.54 (m, 2 H), 4.96–5.03 (t, 2 H, *J* = 10.5 Hz), 5.10–5.13 (d, 1 H, *J* = 9.0 Hz), 5.73–5.76 (m, 1 H), 7.30–7.98 (m, 8 H), 9.45 (s, 1 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 21.7, 22.6, 27.4, 31.6, 36.3, 36.5, 55.2, 60.8, 66.4, 68.1, 79.7, 114.3, 119.5, 121.7, 123.3, 125.4, 125.8, 126.3, 128.4, 129.8, 127.1, 131.2, 137.1, 140.7, 144.6, 148.2, 159.5, 157.3, 187.2.

MS: m/z (%) = 444.20 (M⁺).

Anal. Calcd for C₂₈H₃₁ClN₂O₃: C, 70.21; H, 6.52; N, 5.84. Found C, 70.18; H, 6.48; N, 5.77.

9-*O*-[*p*-Toluenesulfonyl-*N*-(3-formyl-5-methyl-2-hydroxybenzyl)]cinchonidinium Chloride (7)

N-(3-Formyl-5-methyl-2-hydroxybenzyl)cinchonidinium chloride (6; 2.5g, 5.22 mmol), *p*-TsCl (1.8g, 9.44 mmol), DMF–CH₂Cl₂ (40 mL, 1:1), and K₂CO₃ (0.9g, 6.52 mmol) were refluxed for 36 h. Then the solution was washed with a solution of MgSO₄ (2 × 15 mL) and then with H₂O (50 mL). The organic layer was separated and concentrated; the white solid was recrystallized from EtOH; yield: 4.22 g (98%).

FT-IR: 3443, 1725, 1670 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.23 (s, 6 H), 1.60–1.64 (m, 1 H), 3.82–3.87 (m, 2 H), 3.55–1.63 (m, 11 H), 4.95 (s, 1 H), 5.23–5.30 (m, 2 H), 5.90–6.05 (m, 1 H), 6.70–8.98 (m, 12 H), 9.87 (s, 1 H).

¹³C NMR (75 MHz, CDCl₃): δ = 20.2, 20.5, 28.7, 31.73, 34.22, 38.95, 61.45, 61.65, 62.78, 64.33, 76.32, 114.66, 119.75, 123.56, 125.67, 126.42, 128.54, 128.72, 128.74, 129.85, 130.76, 130.73, 131.93, 137.10, 142.49, 143.33, 143.65, 148.12, 148.16, 150.03, 156.20, 190.16.

MS: m/z = 599.17 (M⁺).

Anal. Calcd for $C_{35}H_{37}ClN_2O_5S\colon C,\,66.31;\,H,\,5.83;\,N,\,4.42.$ Found: C, 66.28; H, 5.83; N, 4.39.

N-(3-Formyl-5-methyl-2-hydroxybenzyl)cinchonium Chloride (9)

A mixture of cinchonine (8; 2.6 g, 8.84 mmol) and 3-chloromethyl-5-methyl-2-hydroxybenzaldehyde (4; 0.93 g, 5.4 mmol) in MeCN (50 mL) was stirred at r.t. for 24 h. Then the solution was washed with sat. NaHCO₃ solution (10 mL), dried over MgSO₄, the organic layer was concentrated, and the residue was recrystallized from CCl_4 -cyclohexane (1:1); yield: 3.21 g (91.9%).

FT-IR: 3440, 2210, 1725, 1218 cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$): $\delta = 1.69-1.75$ (m, 4 H), 2.02 (s, 1 H), 2.35 (s, 3 H), 2.78-2.88 (m, 1 H), 3.13-3.16 (m, 1 H), 3.22-3.26 (m, 4 H), 4.03 (q, 1 H, J = 8.6 Hz), 4.50-4.55 (m, 2 H), 4.95-5.04 (m, 3 H), 5.72-5.74 (m, 1 H), 7.25-7.32 (m, 1 H), 7.42-7.51 (m, 6 H), 8.02-8.07 (m, 1 H), 8.63-8.70 (m, 1 H), 9.40 (s, 1 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 21.2, 21.2, 28.5, 30.6, 38.2, 38.7, 55.2, 61.2, 65.4, 69.3, 79.7, 114.4, 119.7, 121.6, 123.6, 125.4, 125.8, 126.3, 128.4, 128.8, 129.1, 130.2, 137.1, 140.7, 143.6, 148.2, 149.5, 156.3, 190.2.

MS: *m*/*z* = 445.20.

Anal. Calcd for $C_{28}H_{31}ClN_2O_3$: C, 70.21; H, 6.52; N, 5.84. Found: C, 70.20; H, 6.51; N, 5.83.

9-*O*-[*p*-Toluenesulfonyl-*N*-(3-formyl-5-methyl-2-hydroxybenzyl)]cinchonium Chloride (10)

N-(3-Formyl-5-methyl-2-hydroxybenzyl)cinchonium chloride (**9**; 2.24 g, 4.8 mmol), *p*-TsCl (1.5 g, 8.02 mmol), DMF–CH₂Cl₂ (45 mL, 8:1), and K₂CO₃ (0.7 g, 5.07 mmol) were refluxed for 36 h. Then the solution was first washed with a solution of MgSO₄ (25 mL) and then with H₂O (50 mL). The organic layer was separated, concentrated, and the residual white solid was recrystallized from EtOH; yield: 2.8 g (90%).

FT-IR: 3400, 2210, 1710, 1220 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): $\delta = 1.30$ (s, 6 H), 1.62–1.64 (m, 1 H), 3.20–3.40 (m, 2 H), 3.50–3.90 (m, 11 H), 4.90 (s, 1 H), 5.20–5.60 (m, 2 H), 5.90–6.10 (m, 1 H), 6.70 (m, 1 H), 6.97–6.99 (m, 1 H), 7.24–7.26 (m, 1 H), 7.40–7.44 (m, 2 H), 7.50–7.70 (m, 2 H), 7.81–7.84 (m, 2 H), 8.90 (s, 1 H), 10.23 (s, 1 H).

¹³C NMR (75 MHz, CDCl₃): δ = 20.7, 21.4, 28.5, 30.72, 38.12, 38.93, 61.45, 61.55, 63.78, 65.33, 76.3, 114.67, 119.92, 123.56, 125.67, 126.42, 127.84, 128.7, 128.74, 129.75, 130.7, 130.73, 131.9, 137.10, 140.49, 143.33, 143.6, 148.1, 148.16, 149.0, 156.20, 190.02.

MS: *m*/*z* = 599.19.

Anal. Calcd for $C_{35}H_{37}CIN_2O_5S$: C, 66.32; H, 5.84; N, 4.42. Found: C, 66.32; H, 5.82; N, 4.40.

Aziridines 3; General Procedure

A solution of *N*-arylhydroxylamines (1 mmol) and electron-deficient olefin (1 mmol) in toluene (10 mL) containing a suspension of 10% aq NaOH (6 mmol) was stirred at r.t. for 2 h. The progress of the reaction was monitored by TLC. When no arylhydroxylamine **1** was detected, the reaction mixture was then filtered and the filtrate was concentrared to dryness. The residue was purified by column chromatography (hexane–EtOAc, 90:10). Analytical samples were obtained by crystallization of the residue.

tert-Butyl-1-phenylaziridine-2-carboxylate (3a)

Yield: 84%; mp 125.5–126.5 °C.

FT-IR: 1178, 1460, 1720, 3100 cm⁻¹.

¹H NMR: δ = 1.40 (s, 9 H), 1.96 (d, 2 H, *J* = 7.2 Hz), 2.42 (t, 1 H), 6.58–7.08 (m, 5 H).

 ^{13}C NMR: δ = 29.1, 29.8, 43.2, 73.4, 113.3, 118.6, 129.4, 144.2, 172.4.

MS: m/z = 220.10.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.14; H, 7.76; N, 6.38. Found: C, 71.13; H, 7.76; N, 6.36.

tert-Butyl-1-(4-methoxyphenyl)aziridine-2-carboxylate (3b)

Yield: 1.3 g (89%); yellowish oil; $[a]_D^{20}$ +20 (*c*, 0.84, CH₂Cl₂). FT-IR: 1170, 1465, 1715, 3080 cm⁻¹.

¹H NMR: δ = 1.38 (s, 9 H), 1.93–1.95 (m, 2 H), 2.44 (t, 1 H), 3.74 (s, 3 H), 6.47–6.50 (m, 2 H), 6.57–6.60 (m, 2 H).

 ^{13}C NMR: δ = 28.7, 29.9, 43.6, 56.0, 73.8, 114.3, 115.1, 136.8, 151.6, 172.6.

MS: m/z = 251.15.

Anal. Calcd for $C_{14}H_{19}NO_{3:}$ C, 67.46; H, 7.64; N, 5.62. Found: C, 67.45; H, 7.63; N, 5.61.

tert-Butyl-1-(4-chlorophenyl)aziridine-2-carboxylate (3c) Yield: 79%; yellow oil; $[\alpha]_D^{20}$ +20 (*c* 0.87, CH₂Cl₂).

FT-IR (KBr): 1174, 1470, 1710, 3090 cm⁻¹.

¹H NMR: δ = 1.40 (s, 9 H), 1.92–1.95 (m, 2 H), 2.42–2.44 (m, 1 H), 6.53–6.56 (m, 2 H), 7.05–7.13 (m, 2 H).

¹³C NMR: δ = 28.4, 29.6, 43.7, 73.6, 112.4, 114.5, 129.9, 142.6, 175.3.

MS: *m*/*z* = 253.09.

Anal. Calcd for $C_{13}H_{16}CINO_{2:}$ C, 61.49; H, 6. 31; N, 5.52. Found: C, 61.47; H, 6.31; N, 5.50.

tert-Butyl-1-(3-bromophenyl)aziridine-2-carboxylate (3d) Yield: 90%; yellow oil; $[\alpha]_D^{20}$ +20 (*c* 0.80, CH₂Cl₂).

¹H NMR: δ = 1.41 (s, 9 H), 2.40 (t, 1 H, *J* = 5.2 Hz), 1.96 (d, 2 H, *J* = 7.3 Hz), 6.53–6.56 (m, 1 H), 6.76–6.79 (m, 2 H), 6.96–6.99 (m, 1 H).

 ^{13}C NMR: δ = 29.1, 29.8, 43.2, 73.3, 112.2, 116.4, 121.3, 124.1, 131.7, 146.7, 172.0.

MS: *m*/*z* = 297.04.

Anal. Calcd for C₁₃H₁₆BrNO₂: C, 52.36; H, 5.41; N, 4.70. Found: C, 52.35; H, 5.39; N, 4.70.

4-(2-Phenylaziridin-1-yl)benzoic Acid (3e)

Yield 86%; $[\alpha]_D^{20}$ +20 (*c* 0.86, CH₂Cl₂).

¹H NMR: δ = 1.91–1.94 (m, 2 H), 2.42 (m, 1 H), 6.81–6.86 (m, 2 H), 7.08–7.16 (m, 5 H), 7.93–7.96 (m, 2 H), 11.13 (s, 1 H).

¹³C NMR: δ = 36.5, 43.7, 73.4, 113.0, 120.7, 128.2, 128.8, 131.0, 137.4, 149.7, 172.1.

MS: m/z = 241.10.

4-(2-Benzenesulfinylaziridine-1-yl)phenol (3f)

Yield: 2.6 g (97%); yellow oil; ee: 82% (77% yield, Chiral HPLC); $[\alpha]_{D}^{20}$ +20 (*c* 0.67, CH₂Cl₂).

FT-IR: 1175, 1465, 3100, 3600 cm⁻¹.

 ^1H NMR: δ = 1.91–1.95 (m, 2 H), 2.70–2.74 (m, 1 H), 5.10 (s, 1 H), 6.42–6.49 (m, 4 H), 7.48–7.51 (m, 2 H), 7.30–7.34 (m, 1 H), 7.64–7.66 (m, 2 H).

¹³C NMR: δ = 31.9, 63.4, 114.5, 116.6, 123.5, 129.7, 130.8, 137.1, 146.8, 147.4.

MS: *m*/*z* = 260.59.

Anal. Calcd for $C_{14}H_{13}NO_2S;\,C,\,64.78;\,H,\,5.02;\,N,\,5.40.$ Found: C, 64.77; H, 5.02; N, 5.38.

Methyl-1-(p-tolyl)aziridine-2-carboxylate (3i)

Yield: 74%; yellow oil.

¹H NMR: δ = 1.93–1.97 (m, 2 H), 2.35 (s, 3 H), 2.44 (m, 1 H), 3.63 (s, 3 H), 6.48–6.50 (m, 2 H), 6.86–8.89 (m, 2 H).

¹³C NMR: δ = 20.9, 29.9, 43.5, 50.2, 113.1, 127.2, 130.3, 141.6, 172.4.

MS: *m*/*z* = 192.05.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.05; H, 6.85; N, 7.30.

tert-Butyl-1-(4-nitrophenyl)aziridine-2-carboxylate (3m)

Yield: 90%; $[\alpha]_D^{20}$ +20 (*c* 0.86, CH₂Cl₂).

¹H NMR: δ = 1.38 (s, 9 H), 1.89–1.93 (m, 2 H), 2.42–2.50 (m, 1 H), 6.85 (dd, 2 H, *J* = 4.8 Hz), 8.00–8.11 (dd, *J* = 4.8 Hz).

¹³C NMR: δ = 28.7, 29.6, 44.1, 73.7, 114.0, 124.5, 137.2, 151.5, 175.7.

MS: *m*/*z* = 265.07.

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.10; H, 6.08; N, 10.58.

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