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Tertiary amine-promoted enone aziridination: investigations into factors influencing enantioselective induction

Alan Armstrong [a,*], Robert D. C. Pullin [a], Chloe R. Jenner [a], Klement Foo [a], Andrew J. P. White [a], James N. Scutt [b]

[a] *Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK*
[b] *Syngenta Ltd, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, UK*

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ABSTRACT

trans-N-Unsubstituted aziridines were synthesised (up to 77% ee) via a chiral tertiary amine-promoted nucleophilic aziridination of α,β-unsaturated ketones utilising in situ generated *N–N* ylides (aminimines). A wide range of chiral tertiary amines were synthesised and evaluated, allowing structure–activity relationships to be drawn. The most efficient promoter for asymmetric aziridination, quinine, was assessed with several enones to ascertain the effect of substrate structure on product ee, while the intermediate hydrazinium salt was characterised by X-ray crystallography.

1. Introduction

Aziridines are present in several biologically active natural products[1] as well as representing versatile building blocks for synthetic manipulation,[2–4] and their enantioselective preparation is therefore an important challenge.[2] Whilst several strategies for aziridine synthesis are in principle available, a potentially powerful approach involves the direct enantioselective transfer of a nitrene equivalent to an alkene precursor. Indeed, the addition of electrophilic metal nitrenoids to alkenes has been well documented.[2] These reactions have proved applicable to the enantioselective aziridinations of styrenes,[3] α,β-unsaturated compounds including cinnamate esters,[4] chalcones[5] and more recently vinyl ketones.[6] On the other hand, the direct enantioselective preparation of aziridines from alkenes via the use of nucleophilic nitrene equivalents has, until relatively recently, received less attention. Phase-transfer catalysts have been employed with nucleophilic nitrene equivalents for the aziridination of certain electron-deficient alkenes but, in general, only moderate levels of asymmetric induction have thus far been realised.[7] More recently, the use of both primary and secondary aminocatalysts, via presumed iminium activation, has led to the enantioselective preparation of aziridines from α,β-unsaturated aldehydes[8] and -ketones,[9] and notably excellent levels of enantioselectivity can be observed. However, the previously reported methods usually deliver *N*-protected aziridines; in the case of metal nitrenoids, this commonly means *N*-sulfonylaziridines, protecting groups that can be difficult to remove. In contrast, racemic *N*-unsubstituted aziridines can be prepared using *N–N* ylides (referred to in the literature as aminimines or aminimides) as nucleophilic nitrene equivalents. This type of aziridination was first reported by Ikeda in 1980,[10] and subsequent studies by both ourselves[11] and Xu[12] have shown that aminimines generated by the deprotonation of pre-formed hydrazinium salts can effect the aziridination of a variety of aromatic α,β-unsaturated ketones (chalcones) in high yields. The co-product of these aziridination reactions is a tertiary amine. A significant development came when it was demonstrated independently by both Shi[13] and ourselves[14] that aziridination can be effected via the in situ amination of tertiary amines in the presence of a base. The tertiary amine promoter is typically *N*-methylmorpholine (NMM) (25–100 mol %) and in our work, the electrophilic nitrogen source is *O*-diphenylphosphinyl hydroxylamine **1** ($DppONH_2$). This is suggested to form the reactive *N–N* ylide in situ, delivering the aziridine via a conjugate addition-ring-closure process (Scheme 1). We have shown that a variety of α,β-unsaturated carbonyl compounds can be aziridinated to give *trans-N*-unsubstituted aziridines diastereoselectively.[14–16] Developing enantioselective versions of these processes by replacing NMM with a chiral amine is of great potential interest and importance. We initially reported[14] a preliminary result with a single chiral amine, quinine: (*E*)-chalcone **2a** was aziridinated with a promising level of asymmetric induction (56% ee). This prompted the further studies described herein, in which a wider range of chiral tertiary amines and substrates was evaluated.

2. Results and discussion

Our previous studies of (*E*)-chalcone aziridination with $DppONH_2$ showed that aziridination does not take place in the

* Corresponding author. Tel.: +44 02075945876.
E-mail address: A.Armstrong@imperial.ac.uk (A. Armstrong).

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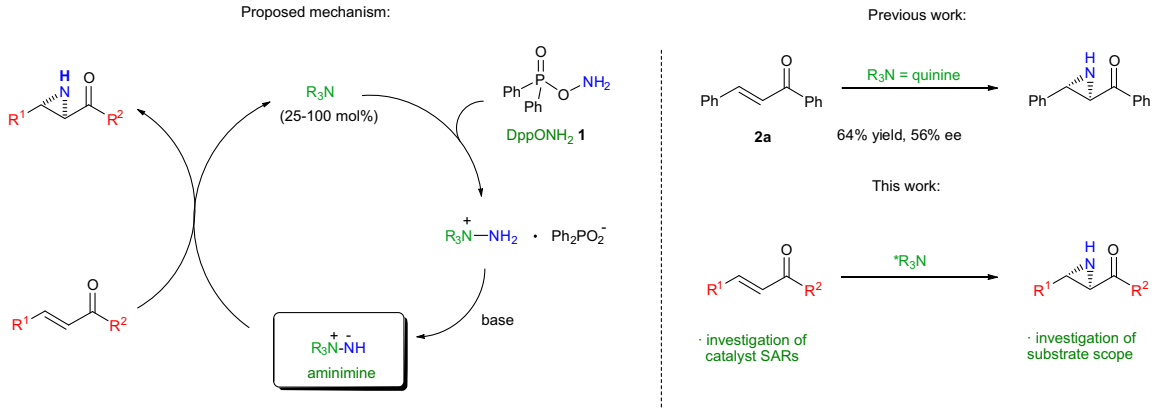
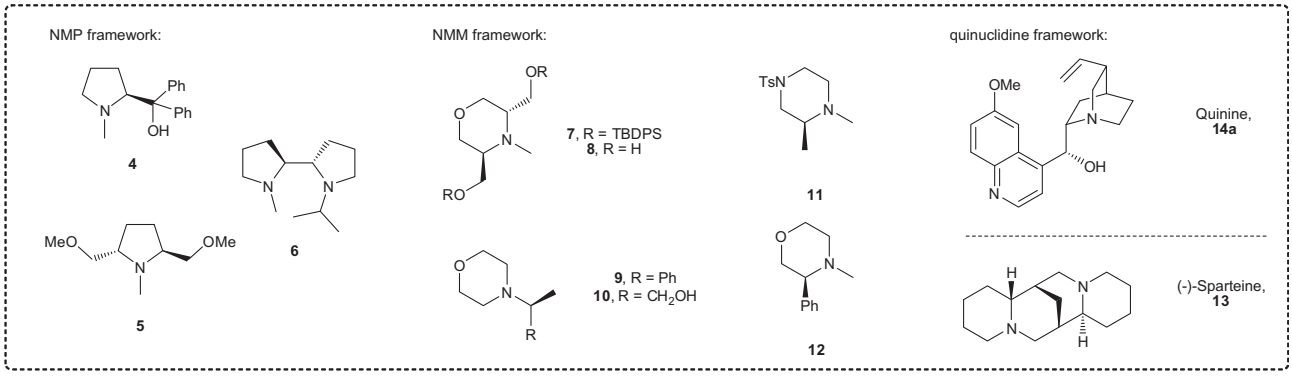
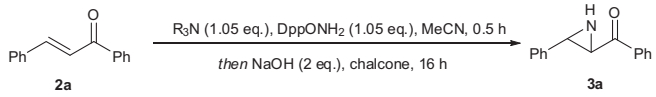


Scheme 1. Organocatalytic alkene aziridination using *N*-*N* ylides.

Table 1
Initial screening of chiral tertiary amines as promoters for the asymmetric aziridination of chalcone **2a**





Entry[a]	R_3N	Yield[b] (%)	ee[c] (%)	Aziridine enantiomer[d]
1	**4**	75	4	(2*S*,3*R*) (+)
2	**5**	<5	—	—
3	**6**	81	6	(2*S*,3*R*) (+)
4	**7**	<5	—	—
5	**8**	5	14	(2*S*,3*R*) (+)
6	**9**	<5	—	—
7	**10**	12	<5	(2*S*,3*R*) (+)
8	**11**	67	23	(2*R*,3*S*) (−)
9	**12**	<5	—	—
10	(−)-Sparteine, **13**	23	37	(2*S*,3*R*) (+)
11	Quinine, **14a**	59	46	(2*R*,3*S*) (−)
12[e]	Quinine, **14a**	64	56	(2*R*,3*S*) (−)

[a] Reactions performed on a 0.12–0.24 mmol scale.
[b] Isolated yield after purification by column chromatography.
[c] Enantiomeric excess (ee) measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H) (2*S*,3*R*, t_R = 13.1 min, 2*R*,3*S*, t_R = 15.0 min).
[d] Configuration of the major enantiomer was determined by comparison to the literature.[17]
[e] NaH/*i*-PrOH was used as the base, CH_2Cl_2 as the reaction solvent.[14]

absence of the tertiary amine promoter and that cyclic (aliphatic) tertiary amines generally provided higher yields of aziridine than acyclic tertiary amines.[14] Thus we identified the *N*-methylmorpholine (NMM), *N*-methylpyrrolidine (NMP) and quinuclidine frameworks as effective tertiary amines promoters for aziridination (Scheme 1).[14] In our search for a chiral tertiary amine capable of delivering asymmetric aziridination, we began by surveying readily accessible chiral derivatives of these frameworks, selecting (*E*)-chalcone **2a** as our model substrate (Table 1).

Based on the NMP framework, various pyrrolidine derivatives were screened, which included **4**, C_2-symmetric derivative **5** and diamine **6**.[18] However, only low levels of asymmetric induction were observed in all cases (<10% ee) and with varying levels of reactivity (entries 1–3). Switching to the NMM framework, a diverse range of chiral NMM derivatives were synthesised, including C_2-symmetric NMMs[19] **7** and **8**, chiral *N*-pendant morpholines[20] **9** and **10**, 3-substituted NMM[21] **12** and chiral piperazine **11**. However, with the exception of piperazine **11**, the reactivities of these

1,4-heterocycles were low, which we found to be closely related to steric hindrance around the *N*-centre. In all cases, levels of asymmetric induction were also low (up to 23% ee) (entries 4–9). The commercially available alkaloid (−)-sparteine **13** was also screened but again provided a low yield of aziridine (23%) and only moderate levels of asymmetric induction (37% ee) (entry 10). The cinchona alkaloid quinine **14a** however, based upon the reactive quinuclidine framework, showed promising levels of both reactivity (59%) and asymmetric induction (46% ee) (entry 11). As indicated in our initial report, this could be improved upon by using NaH/*i*-PrOH as the base with CH_2Cl_2 as the reaction solvent (entry 12).[14] In light of this promising result and the ready access to several cinchona alkaloid derivatives either commercially or via synthetic modification, we decided to continue our investigations with this class of tertiary amine, seeking to explore the effects of structural modification on the enantioselectivity (Table 2).

Pseudoenantiomeric quinidine **14b** was found to promote aziridination in a lower yield but comparable ee (50% ee) to quinine **14a** and, as expected, was selective for the opposite aziridine enantiomer (entry 2 vs 1). Cinchonidine **15a** and cinchonine **15b**, devoid of the 6-methoxy group on the quinoline ring, gave lower levels of ee (42% and 41% ee, respectively) (entries 3 and 4). Hydro-quinine **16a** and –quinidine **16b** were also less effective promoters in terms of both yield and ee compared to their parent vinyl derivatives (entries 5 and 6 vs 1 and 2). Quincorine **17a** and quincoridine **17b**, devoid of the C9-stereocentre and quinoline moiety, both gave racemic aziridines indicating the importance of these groups in terms of asymmetric induction (entries 7 and 8).

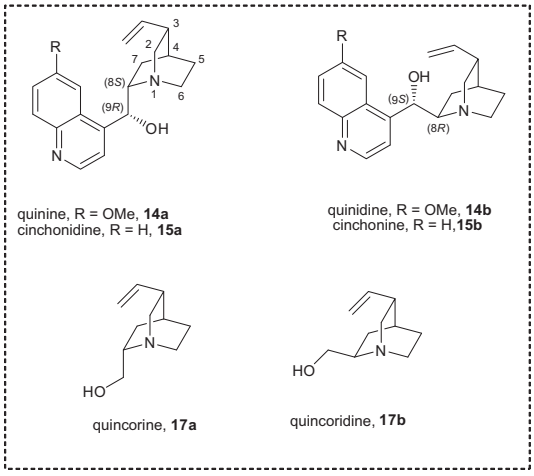
In light of the apparent importance of the C9-substituent, we decided to screen a range of C9-modified quinine derivatives. Several of these were prepared (Scheme 2).

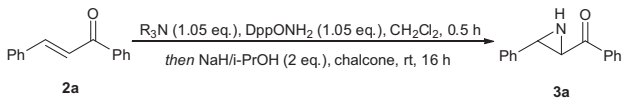
Following reported procedures, we initially prepared *O*-Me derivative **18**,[22] alkylated derivative **19**,[23] oxidised quininone **20**[24] and the fluorinated cinchona alkaloids **21a** and its 9-epimer **21b**.[25] To allow testing of the importance of the C9-configuration, we also prepared 9-epi-quinine **22** by hydrolysis of the mesylate of the quinine according to conditions reported by Hoffmann.[26] Similarly, the 9-epi primary amine **23b** was obtained from quinine following literature procedures reported by Brunner,[27] via inversion with diphenylphosphoryl azide (DPPA), followed by an in situ Staudinger reduction. Amine **23b** then served as precursor to the corresponding C9-epi acetamide **24b**, sulfonamide **25b** and thiourea derivative **26**.[28,29] In order to complement this C9-epi series of hydrogen bond donor alkaloids, the corresponding members of the natural C9-series were also synthesised. The required substitution of 9-epi-quinine **22** with inversion to give amine **23a** proved challenging; indeed, attempted synthesis by following the protocols adopted for the corresponding 9-epi-amino-derivative **23b** failed to afford any detectable traces of the desired compound but instead yielded the elimination product **27** (single geometric isomer; configuration not assigned). Modified reaction conditions involving prolonged heating after addition of DPPA did afford amine **23a**, although in low yield (22%). Further functionalisation then provided the novel *N*-acyl **24a** and *N*-tosyl **25a** derivatives.

These cinchona alkaloid derivatives were screened for the aziridination of chalcone (Table 3). The two compounds with sp^2-hybridisation at C9, ketone **20** and alkene **27**, did not significantly promote aziridination (entries 1 and 2). All of the C9-epi-derivatives, irrespective of the C9-substituent, afforded very low enantioselectivities (<14% ee, entries 3–8). Yields were also generally very low, with the exception of the C9-epi-amino compound **23b**.[30,31] In this particular case, a possible explanation for the low enantioselectivity could be that amination with $DppONH_2$ proceeded on the primary amine; however, ^{1}H NMR experiments in the absence of enone suggested that only the tertiary amine was being aminated. Overall, these poor results with C9-epi-derivatives suggest that the natural cinchona alkaloid C8–C9 relative configuration is essential for the reactivity and enantioselectivity.

Returning to derivatives with the natural C9-configuration, we were disappointed that a very low conversion was observed with the C9-fluoride **21a** (entry 9). The C9-amine **23a** was more encouraging (entry 10): a moderate yield (42%) and enantioselectivity (35% ee) was observed. Interestingly, the major aziridine configuration was the opposite to that observed with quinine itself, which may indicate a role for the quinine 9-hydroxyl as a hydrogen bond donor to the enone substrate (see later for discussion). However, the acetamide **24a** and sulfonamide **25a** derivatives, also bearing potential hydrogen bond donors, were essentially inactive, suggesting that steric hindrance at C9 is detrimental to reactivity (entries 11 and 12). In order to further probe the role of the C9 hydroxyl, we tested the C9-OMe derivative **18**, which has previously been employed in an organocatalytic cyclopropanation reaction involving *C*–*N* ylides.[22] The introduction of the methyl group at the 2-position of the quinoline ring was suggested to lower the nucleophilicity of the quinoline nitrogen, thus favouring reaction at the quinuclidine nitrogen. Conceivably, the incomplete conversion in our aziridination chemistry using quinine could also be due in part to competing amination at the quinoline nitrogen (notwithstanding the observation, noted earlier, that amine **23b** appeared to be aminated selectively at the quinuclidine centre). However, **18** displayed both poor reactivity and also poor levels of asymmetric induction as a promoter for aziridination (entry

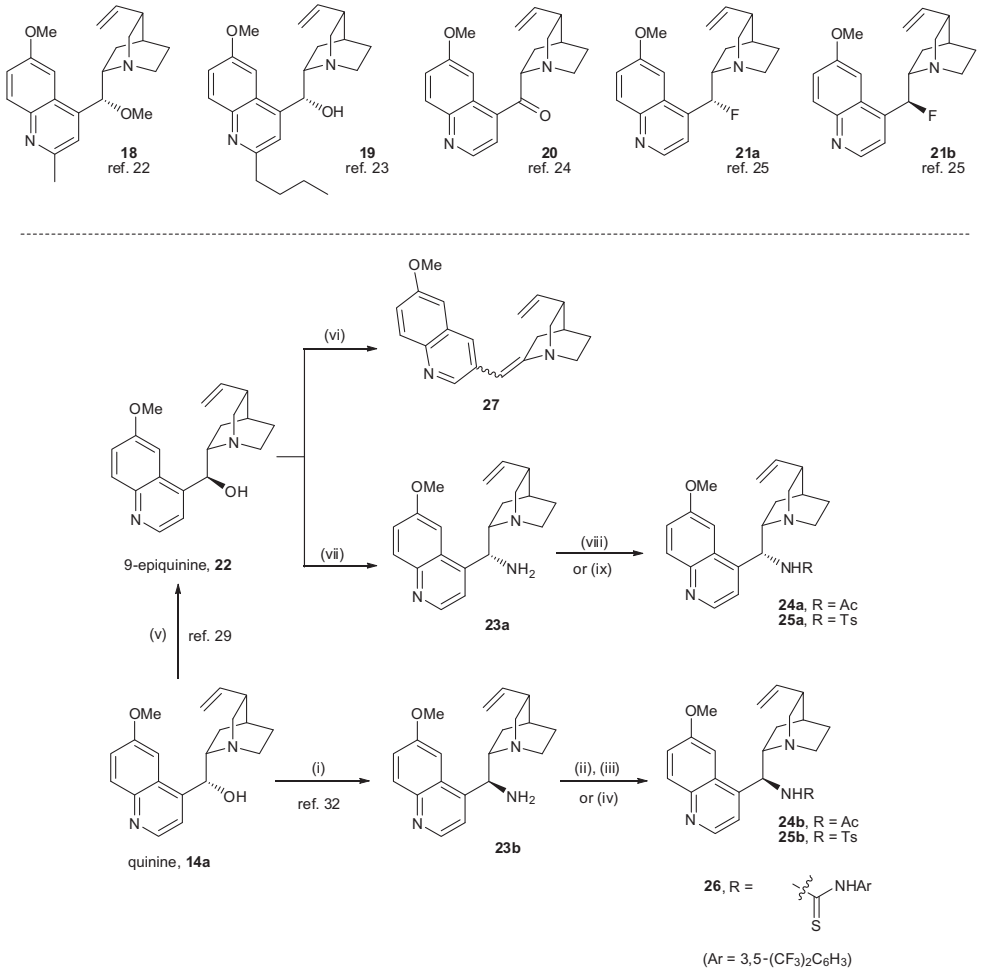
Table 2
Screening of commercially available cinchona alkaloids for the asymmetric aziridination of chalcone





Entry[a]	R_3N	Yield[b] (%)	ee[c] (%)	Aziridine enantiomer[d]
1	Quinine, **14a**	64	56	(2*R*,3*S*) (−)
2	Quinidine, **14b**	31	50	(2*S*,3*R*) (+)
3	Cinchonidine, **15a**	38	42	(2*R*,3*S*) (−)
4	Cinchonine, **15b**	42	41	(2*S*,3*R*) (+)
5	Hydroquinine, **16a**	49	50	(2*R*,3*S*) (−)
6	Hydroquinidine, **16b**	32	30	(2*S*,3*R*) (+)
7	Quincorine, **17a**	44	0	—
8	Quincoridine, **17b**	85	0	—

[a] Reactions performed on a 0.12 mmol scale.
[b] Isolated yield after purification by column chromatography.
[c] Enantiomeric excess (ee) measured by HPLC analysis.
[d] Configuration of major enantiomer determined by comparison to the literature.[17]



Scheme 2. Synthesis of C9-functionalised cinchona alkaloids. Reagents and conditions: (i) PPh_3, DIAD, $(PhO)_2P(O)N_3$, THF, rt, 3 h; PPh_3, 50 °C, 1 h; H_2O, rt, 16 h, 55%; (ii) AcCl, Et_3N, CH_2Cl_2, 0 °C to rt, 18 h, 78%; (iii) K_2CO_3, TsCl, CH_2Cl_2, rt, 16 h, 69%; (iv) 3,5-$(CF_3)_2C_6H_3NCS$, THF, rt, 18 h, 62%; (v) MsCl, Et_3N, THF, 70 °C, 4 h, 98%; L-tartaric acid, H_2O, 100 °C, 1 h, 79%; (vi) PPh_3, DIAD, $(PhO)_2P(O)N_3$, THF, rt, 3 h; PPh_3, 50 °C, 1 h; H_2O, rt, 16 h, 47%; (vii) PPh_3, DIAD, $(PhO)_2P(O)N_3$, THF, rt to 45 °C 5 h; PPh_3, 45 °C, 1 h; H_2O, rt, 16 h, 22%; (viii) AcCl, Et_3N, CH_2Cl_2, 0 °C to rt, 18 h, 83%; (ix) K_2CO_3, TsCl, CH_2Cl_2, rt, 16 h, 71%.

Table 3
Asymmetric aziridination of chalcone with C9-modified quinine derivatives

Entry[a]	R_3N	C9-substituent	C9 config.[b]	Yield[c] (%)	ee[d] (%)	Aziridine enantiomer[e]
1	**20**		—	16	<5	(2*S*,3*R*) (+)
2	**27**		—	<5	—	—
3	**22**	OH	Epi	28	11	(2*S*,3*R*) (+)
4	**23b**	NH_2	Epi	62	<5	(2*S*,3*R*) (+)
5	**24b**	NHAc	Epi	8	14	(2*S*,3*R*) (+)
6	**25b**	NHTs	Epi	<5	—	—
7	**26**	C(S)NHAr	Epi	<5	—	—
8	**21b**	F	Epi	8	10	(2*S*,3*R*) (+)
9	**21a**	F	Natural	<5	—	—
10	**23a**	NH_2	Natural	42	35	(2*S*,3*R*) (+)
11	**24a**	NHAc	Natural	<5	—	—
12	**25a**	NHTs	Natural	<5	—	—
13[f]	**18**	OMe	Natural	8	7	(2*R*,3*S*) (−)
14	**19**	OH	Natural	38	37	(2*R*,3*S*) (−)

[a] Reactions performed on a 0.12–0.14 mmol scale using the conditions shown in Table 2.
[b] Relative to quinine.
[c] Isolated yield after purification by column chromatography.
[d] Enantiomeric excess (ee) measured by HPLC analysis.
[e] Configuration of major enantiomer determined by comparison to the literature.[17]
[f] NaOH was used as the base.

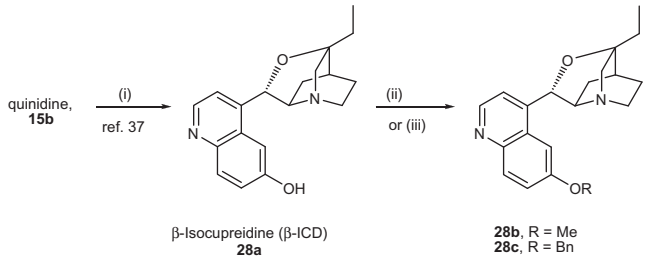
13). The related derivative **19**, also bearing a 2-alkyl substituent on the quinoline but now possessing the free C9 hydroxyl functionality, showed greater activity and selectivity as a promoter for the aziridination (38%, 37% ee) (entry 14), although surprisingly its performance was worse than that of its parent, quinine (compare Table 2, entry 1).

Considering further modification of the cinchona alkaloid motif, we were interested in derivatives that may be less conformationally flexible, yet without presenting undue steric hindrance around the reacting quinuclidine *N*-centre, which we believed to be a problem with many C9-functionalised derivatives. β-Isocupreidine (β-ICD) **28a**, which possesses a rigid tricyclic structure, was an attractive option and it and its derivatives have been shown to be effective catalysts for enantioselective Morita-Baylis-Hillman reactions.[32] β-ICD **28a** was obtained from quinidine **14b** via procedures described by Hatakeyama.[33] Since this process not only promotes cyclisation but also demethylates the quinoline methoxy group, methyl ether **28b** and the novel benzyl ether **28c** were also prepared (Scheme 3). All were then screened for the aziridination of chalcone (Table 4).

β-ICD **28a** promoted aziridination with low yield (28%) and extremely poor ee (5% ee) (entry 1). However, under the basic reaction conditions, the phenolic moiety of β-ICD is likely to be deprotonated and this competing consumption of base may affect the desired deprotonation of the in situ generated hydrazinium salt required for the ylide formation (see Scheme 1). The methyl ether **28b** circumvents this problem and showed a substantial increase in both yield (54%) and ee (37% ee) of the aziridine product (entry 2). The sterically bulkier aromatic *O*-benzyl ether **28c** again provided a moderate yield (47%) with a slight increase in ee (43% ee) (entry 3). Interestingly, the configuration of the major aziridine afforded with the amines **28b** and **28c** was the opposite of that afforded by their parent, quinidine. This may again support the possible role of the quinine/quinidine C9-hydroxyl as a hydrogen bond donor (vide infra).

After extensive screening of chiral tertiary amines, quinine remained the most favourable promoter in terms of asymmetric induction in the aziridination reaction and so we were keen to investigate potential relationships between the substrate structure and product enantioselectivity. Quinine was therefore screened with a range of electron-rich and electron-poor chalcones (Table 5).

Asymmetric induction was found to be lowered for substrates with electron withdrawing substituents (entries 4, 5 and 8). However, higher enantiomeric excesses were observed when electron donating groups were present at the ketone aromatic (entries 6 and 7), with 4-methoxyphenyl aziridine **3f** being obtained in 66% ee. To probe this effect further, a variety of enones possessing electron rich heteroaromatics at the ketone were also screened with quinine (Table 6).



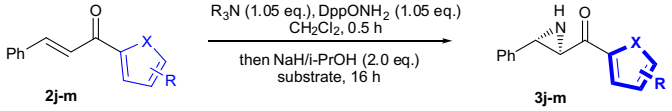
Scheme 3. Synthesis of β-isocupreidine **28a** and derivatives **28b–c**. Reagents and conditions: (i) KBr, 85% H_3PO_4, 100 °C, 10 d, 54%; (ii) $TMSCHN_2$, C_6H_6/MeOH (3:2), rt, 3 h, 43%; (iii) NaH, THF, 0 °C, 10 min, BnBr, TBAI, 0 °C to 40 °C, 16 h, 20%.

Table 4
Asymmetric aziridination of chalcone with β-isocupreidine **28a** and derivatives **28b–c**

Entry[a]	R_3N	Yield[b] (%)	ee (%)[c]	Aziridine enantiomer[d]
1	**28a**	28	5	(2*R*,3*S*) (−)
2	**28b**	54	37	(2*R*,3*S*) (−)
3	**28c**	38	43	(2*R*,3*S*) (−)

[a] Reaction performed on a 0.12 mmol scale using the conditions shown in Table 2.
[b] Isolated yield after purification by column chromatography.
[c] Enantiomeric excess (ee) measured by HPLC.
[d] Configuration of major enantiomer determined by comparison to the literature.[17]

Table 6
Asymmetric aziridination of heteroaromatic-substituted enones with quinine

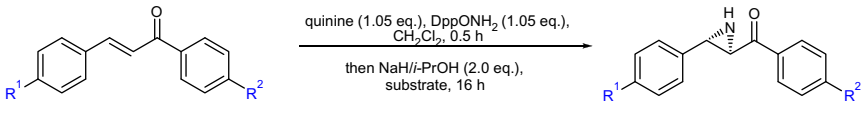


R_3N = quinine, **14a**

Entry[a]	R	Aziridine	Yield[b] (%)	ee[c,d] (%)
1	2-Furyl	**3j**	41	71 (−)
2	2-Thiophenyl	**3k**	47	72 (−)
3	4-Methyl-2-Thiophenyl	**3l**	46	77 (−)
4	5-Chloro-2-thiophenyl	**3m**	27	64 (−)

[a] Reaction performed on a 0.11–0.22 mmol scale.
[b] Isolated yield after purification by column chromatography.
[c] Enantiomeric excess (ee) measured by HPLC.
[d] The configuration of the major enantiomer assigned as (2*R*,3*S*) by analogy to the aziridination of chalcone with quinine.

Table 5
Asymmetric aziridination of electron-rich and electron-poor chalcones with quinine



Entry[a]	R^1	R^2	Aziridine	Yield[b] (%)	ee[c,d] (%)
1	H	H	**3a**	64	56 (2*R*,3*S*) (−)
2	MeO	H	**3b**	35	55 (−)
3	Me	H	**3c**	55	52 (−)
4	Cl	H	**3d**	54	48 (−)
5	NO_2	H	**3e**	43	37 (−)
6	H	MeO	**3f**	48	66 (−)
7	H	Me	**3g**	68	59 (−)
8	H	Cl	**3h**	62	46 (−)

[a] Reaction performed on a 0.12–0.13 mmol scale.
[b] Isolated yield after purification by column chromatography.
[c] Enantiomeric excess (ee) measured by HPLC.
[d] The configuration of the major enantiomer assigned as (2*R*,3*S*) in analogy to the aziridination of chalcone with quinine.

With heteroaromatic enones **2j–m**, the observed levels of asymmetric induction (64–77% ee) were found to be consistently higher than that of chalcone **2a** (56% ee) in the aziridination. The more electron rich aromatics (entries 1–3) afforded products with higher ee than the 5-chloro-2-thiphenyl system (entry 4). The 4-methyl-2-thiophenyl derivative **3l** afforded the highest ee to date (77% ee) (entry 3). These results indicate that varying the ketone aromatic substituent is a productive approach to improving the enantioselectivity.

Despite screening a range of tertiary amine promoters, none of these afforded a higher enantioselectivity than quinine itself. Rational improvement requires a more detailed study of the mechanism of the reaction. While this is presumed to involve a stepwise conjugate addition of the aminimine intermediate to the enone followed by ring closure, we currently do not know which of these steps is rate/product determining. The addition step may be irreversible and enantiomer determining; alternatively, it may be reversible, with the enantioselectivity being controlled by the relative rates of ring closure of diastereomeric intermediates. The observation that electron poor enones are generally more reactive[11] suggests that the addition step is more likely to be rate- and enantiomer determining. Consideration of the ground state conformation of the aminimine may therefore be relevant. The preferred conformation of quinine itself is the so called *anti-open* conformation, both in solution[34] and the solid state[35] (where *anti* denotes a C4′a–C4′–C9–C8 torsion angle of +90 deg, and *open* indicates an N1–C8–C9–C4′ torsion angle of 180 deg). We were pleased to be able to isolate the precursor to our likely aminimine intermediate, the *N*-aminated quinine **29**, as its tetraphenylborate salt, crystals of which were suitable for analysis by X-ray crystallography.[36] The conformation of *N*-aminoquininium **29** was found to be similar to that of the parent quinine, that is, *anti-open* (Fig. 1). While the conformation of the aminimine intermediate may differ, particularly in the transition state, this information may prove useful in future catalyst design. In constructing a TS-model based on this structure, a key question is whether the C9-hydroxy group acts as a hydrogen bond donor towards the enone substrate. Jørgensen has postulated this mode of hydrogen bonding in the transition state of aza-Michael additions of hydrazones to cyclic enones promoted by various cinchona alkaloids.[37] In attempting to gain evidence for this interaction from our own results, unfortunately the most direct hydroxyl replacements, the 9-fluorocompound **21a** and the dimethylated quinine **18**, both afforded very low yields (Table 3). However, tentative support for the H-bond comes from the results with the 9-amino derivative **23a**, where a sterically comparable but much weaker H-bond donating C9-substituent than the hydroxyl afforded the opposite major aziridine enantiomer to the quinine itself. The observation that β-ICD derivatives **28**, which are conformationally locked in the 'open' conformation, but devoid of the C9-hydroxyl, give the opposite major aziridine enantiomer relative to their parent, quinidine, is also consistent with this idea. On this basis, we propose a tentative TS-model to account for the observed major aziridine enantiomer

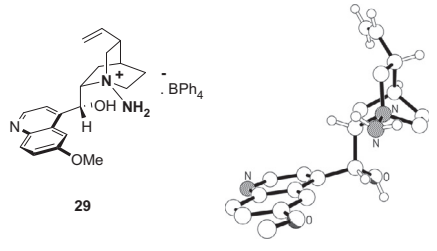


Figure 1. X-ray crystal structure of the cation present in the crystals of *N*-aminoquininium tetraphenylborate **29**.[36]

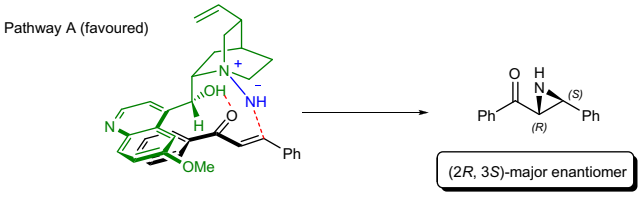


Figure 2. Proposed model for asymmetric aziridination with quinine.

(Fig. 2). This model places the substrate C1-aromatic group in close proximity to the quinoline ring, which is consistent with the observed importance of this substrate substituent (as seen in Table 6).

3. Conclusion

In conclusion, a detailed examination of the factors affecting the enantioselective tertiary amine-promoted nucleophilic aziridination of α,β-unsaturated ketones utilising in situ generated *N–N* ylides (aminimines) has been conducted. We have prepared and screened a wide range of structurally diverse chiral tertiary amines and evaluated them as enantioselective organocatalysts. Quinine was the most favourable promoter examined in terms of asymmetric induction. Through structural derivatisation, correlations between substrate structure and observed levels of enantioselectivity and analysis of the preferred conformation of a reaction intermediate we have been able to propose a preliminary transition state model for enantioselective aziridination. In terms of future catalyst development, this TS-model suggests that variation of the quinoline ring to optimise the interaction with enone substituents may be a fruitful endeavour. In addition, further structural variation on the β-ICD framework merits future investigation.

4. Experimental

4.1. General

Anhydrous acetonitrile and benzene were used as commercially supplied; methanol, CH_2Cl_2 and THF were purified by passage through an alumina solvent purification column. DMF was dried over $MgSO_4$ before distillation under reduced pressure over 4 Å molecular sieves. All commercial reagents were used as supplied unless otherwise stated. Reactions were run under a positive pressure of argon in oven dried glassware with magnetic stirring. Reaction temperatures were recorded as bath temperatures. Flash column chromatography was carried out using silica gel, particle size 40–60 μm. Analytical thin layer chromatography (TLC) was performed using glass backed plates pre-coated with silica gel 60 F254. Melting points were obtained using a hotplate microscope and are uncorrected. Infrared analyses were recorded using ATR. NMR analyses were recorded at 400 or 500 MHz in $CDCl_3$ or D_4-MeOD as specified. Chemical shifts are quoted in ppm relative to TMS (as referenced to residual solvent, for example, $CHCl_3$ δ_H 7.26 or $CDCl_3$ δ_C 77.0), with coupling constants quoted in Hz and reported to the nearest 0.1 Hz (^{1}H NMR). ^{13}C assignments, where given, are based on HSQC, HMBC and DEPT-135 experiments. Mass spectrometry analyses were carried out using CI^+ (NH_3), ES^+ or EI^+. Specific rotations (α') were recorded on a polarimeter, cell path length (l) 0.5 dm, at the stated temperature (°C) and concentration (c) measured in units of g/100 mL; specific rotations were converted to optical rotations $[\alpha]_D$ via the equation: $[\alpha]_D = (100.\alpha')/(l.c)$. The enantiomeric excesses (ee) of the aziridines prepared were measured by HPLC analysis (conditions: 93:7 hexane/IPA; 0.8 mL/min; 254 nm; AD-H column).

4.2. Preparation of tertiary amine catalysts

(−)-Sparteine and cinchona alkaloids **14**–**17a**,**b** were obtained commercially and used as supplied. Amines **4**,[38] **9**,[20] alkaloids **18**,[22] **19**,[23] **20**,[24] **22**,[26] **23b**,[27] **26**[28] and **28a**[33] were prepared according to literature procedures, with data in agreement with those reported. All other tertiary amines were prepared, according to the following procedures.

4.2.1. (2*S*,5*S*)-2,5-Bis(methoxymethyl)-1-methylpyrrolidine 5

Formaldehyde (0.12 mL, 1.57 mmol, 37% aqueous) was added to a solution of commercially available (2*S*,5*S*)-(+)-2,5-bis(methoxymethyl)pyrrolidine (50 mg, 0.31 mmol) in MeOH (5 mL) and stirred for 5 min. Next, Pd/C (10 mg, 10% wt.) was added in one portion and the mixture was stirred under an atmosphere of H_2 for 15 h. The reaction mixture was then filtered through Celite and washed with CH_2Cl_2. The filtrate was then concentrated in vacuo and purified by flash column chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to afford **5** (38.1 mg, 70%) as a pale yellow oil; $[\alpha]_D^{28} = -51.4$ (*c* 0.55, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3360, 2970, 2875, 1660, 1465, 1115, 900; δ_H (400 MHz, $CDCl_3$) 3.52 (2H, dd, *J* 10.1 and 5.1, C*H*$_2$OMe), 3.45 (2H, dd, *J* 10.1 and 4.3, C*H*$_2$OMe), 3.38–3.35 (2H, m, 2 × C*H*CH$_2$OMe), 3.35 (6H, s, 2 × °C*H*$_3$), 2.64 (3H, s, NC*H*$_3$), 2.10–2.05 (2H, m, C*H*$_2$CH), 1.77–1.74 (2H, m, CHC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 72.9, 63.8, 59.2, 35.9, 26.8; *m*/*z* (CI$^+$ (NH_3)) 174 (MH$^+$, 100%); HRMS (CI$^+$ (NH_3)) MH$^+$ calculated for $C_9H_{20}NO_2$ 174.1494, observed 174.1494.

4.2.2. (*S*)-2-((*S*)-1-Isopropylpyrrolidin-2-yl)-1-methylpyrrolidine 6

Formaldehyde (0.12 mL, 1.57 mmol, 37% aqueous) was added to a solution of (2*S*,5*S*)-(+)-2,5-bis(methoxymethyl)pyrrolidine (50.5 mg, 0.28 mmol) (prepared and donated by the laboratories of Alexakis[18]) in MeOH (5 mL) and stirred for 5 min. Next, Pd/C (10 mg, 10% wt.) was then added in one portion and the mixture was stirred under an atmosphere of H_2 for 15 h. The reaction mixture was then filtered through Celite and washed with CH_2Cl_2. The filtrate was then concentrated in vacuo and purified by flash column chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to afford **6** (35 mg, 65%) as a pale yellow oil; $[\alpha]_D^{20} = -62.8$ (*c* 0.51, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2962, 2854, 2812, 1452, 1365, 1330, 1260, 1177, 1116, 1068, 978, 917, 873; δ_H (400 MHz, $CDCl_3$) 3.19–3.02 (4H, m, NC*H*$_2$ and 2 × C*H*N), 2.60–2.53 (2H, m, NC*H*$_2$), 2.42 (3H, s, NC*H*$_3$), 2.22 (1H, m, C*H*(CH$_3$)$_2$), 1.85–1.61 (8H, m, 4 × CH$_2$), 1.18 (3H, d, *J* 6.7, CH(C*H*$_3$)$_3$), 1.18 (3H, d, *J* 6.7, CH(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 68.0, 61.3, 57.9, 50.6, 47.4, 41.7, 26.4, 26.2, 23.9, 23.1, 21.9, 15.5; *m*/*z* (CI$^+$ (NH_3)) 197 (MH$^+$, 25%), 285 (100); HRMS (CI$^+$ (NH_3)) MH$^+$ calculated for $C_{12}H_{25}N_2$ 197.2018, observed 197.2022.

4.2.3. 4-Methyl-(3*R*,5*R*)-3,5-bis(*tert*-butyldiphenylsiloxymethyl) morpholine 7

At first, Pd(OH)$_2$/C (20 mg, 20% wt.) was added to a solution of (3*R*,5*R*)-3,5-bis(*tert*-butyldiphenylsiloxymethyl)morpholine (prepared according to the procedures of Sasaki[19]) (187 mg, 0.30 mmol), formaldehyde (0.1 mL, 3.6 mmol, 37% aqueous) and acetic acid (0.1 mL, 1.8 mmol) in methanol (5 mL) and was stirred under the presence of H_2 at room temperature and atmospheric pressure for 3 h. The catalyst was then filtered off and the filtrate concentrated in vacuo before the addition of saturated aqueous Na_2CO_3 solution (10 mL) and water (10 mL). The aqueous layer was separated and extracted with $CHCl_3$, washed with a saturated aqueous sodium chloride solution (10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/hexane) afforded **7** (156 mg, 81%) as a colourless oil; R_f: (5% EtOAc/hexane) 0.40; $[\alpha]_D^{18} = +37.2$ (*c* 0.86, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3071, 2930, 2889, 1960, 1891, 1825, 1730, 1667, 1590, 1472, 1428, 1391, 1361, 1307, 1275, 1260, 1112 br, 1022, 1000, 937, 824, 739, 701, 614, 505; δ_H (400 MHz, $CDCl_3$) 7.66–7.63 (8H, m, 8 × PhH), 7.45–7.34 (12H, m, 12 × PhH), 3.82–3.75 (4H, m, 2 × C*H*$_2$OR), 3.69–3.63 (4H, m, 2 × C*H*$_2$OR), 2.66 (2H, br, 2 × C*H*N), 2.13 (3H, s, NC*H*$_3$), 1.03 (18H, s, 2 × SiC(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 135.5, 133.4, 129.7, 127.7, 69.0, 60.3, 59.5, 40.10, 26.8, 19.1; *m*/*z* (EI$^+$) 637 (M$^+$, 3%), 368 (100); HRMS (ES$^+$) MH$^+$ calculated for $C_{39}H_{52}NO_3Si_2$ 638.3486, observed 638.3488.

4.2.4. (3*S*,5*S*)-3,5-Bis(hydroxymethyl)-4-methylmorpholine 8

Tetra-*n*-butylammonium fluoride in THF (3.5 mL of a 1 M solution) was added to a stirred solution of morpholine **7** (310 mg, 0.48 mmol) in THF (1.5 mL) at 0 °C. The mixture was then allowed to warm to room temperature and stirred overnight. The solution was concentrated in vacuo and purified by flash column chromatography (10% MeOH/EtOAc) to afford **8** (63 mg, 80%) as a colourless oil; R_f: (20% MeOH/EtOAc) 0.20; $[\alpha]_D^{22} = +30.4$ (*c* 1.25, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3312 br, 2958, 2886, 2861, 1574, 1457, 1365, 1270, 1125, 926, 883, 844, 774, 698; δ_H (400 MHz, $CDCl_3$) 3.86 (2H, dd, *J* 10.8 and 5.7, C*H*$_2$OR), 3.79 (2H, dd, *J* 11.6 and 6.1, C*H*$_2$OR), 3.73 (2H, dd, *J* 11.6 and 3.5, C*H*$_2$OR), 3.64 (2H, dd, *J* 11.2 and 3.4, C*H*$_2$OR), 3.12 (2H, br), 2.84 (2H, br), 2.51 (3H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 67.9, 58.8, 58.2, 38.5; *m*/*z* (EI$^+$) 161 (M$^+$, 2%), 130 (M$^+$ –CH$_2$OH, 100); HRMS (ES$^+$) MH$^+$ calculated for $C_7H_{16}NO_3$ 162.1130, observed 162.1129.

4.2.5. (*S*)-2-Morpholin-4-yl-propan-1-ol 10

Prepared using (*S*)-2-aminopropanol by following the reported procedure for the synthesis of **9** by Oda;[20] yellow oil; R_f: (1% MeOH/CH_2Cl_2) 0.50; $[\alpha]_D^{22} = +40.4$ (*c* 0.94, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3436 br, 2968, 2860, 1453, 1265, 1156, 1114, 1038, 960, 916, 872, 849, 731; δ_H (400 MHz, $CDCl_3$) 3.76–3.66 (4H, m, 2 × C*H*$_2$OR), 3.42 (1H, dd, *J* 10.4 and 5.0, C*H*HOH), 3.32 (1H, t, *J* 10.4, CH*H*OH), 2.77 (1H, m, NC*H*(CH$_2$OH)), 2.69–2.62 (2H, m, C*H*$_2$NR$_2$), 2.39–2.43 (2H, m, C*H*$_2$NR$_2$), 0.92 (3H, d, *J* 6.7, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 67.3, 62.1, 60.3, 48.1, 9.5; *m*/*z* (EI$^+$) 145 (M$^+$, 2%), 114 (M$^+$ –CH$_2$OH, 100); HRMS (ES$^+$) MH$^+$ calculated for $C_7H_{16}NO_2$ 146.1181, observed 146.1186.

4.2.6. (2*S*)-1,2-Dimethyl-4-(*para*-toluenesulfonyl)piperazine 11

Triethylamine (190 µl, 1.37 mmol) was added to a solution of commercially available (*S*)-(+)-2-methylpiperazine (125 mg, 1.25 mmol) in CH_2Cl_2 (7 mL) at 0 °C and stirred for 5 min. *p*-Toluenesulfonyl chloride (238 mg, 1.25 mmol) was then added and the mixture was stirred for 1 h at 0 °C before being allowed to warm to room temperature and stirred for a further 4 h. Water was then added and the aqueous layer was separated and extracted with CH_2Cl_2, before being washed sequentially with 1 M HCl (50 mL), water (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated in vacuo to afford tosyl piperazine, (3*S*)-3-methyl-1-[(4-methylbenzene)sulfonyl]piperazine (310 mg, 97%) as a white solid. The product could be used without further purification; mp 138.5–141 °C (acetone); $[\alpha]_D^{23} = +38.9$ (*c* 0.93, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3352, 2971, 2922, 2863, 2821, 1605, 1452, 1325, 1165, 1133, 1121, 997, 914, 861, 811, 754s, 655; δ_H (500 MHz, DMSO-d_6) 7.61–7.59 (2H, m, 2 × Ar*H*), 7.47–7.44 (2H, m, 2 × Ar*H*), 3.41–3.37 (2H, m, C*H*$_2$NTs), 2.85 (1H, dt, *J* 12.1 and 2.8, C*H*$_2$NTs), 2.68–2.60 (2H, m, 3-*H* and C*H*HN(H)), 2.41 (3H, s, ArC*H*$_3$), 2.06 (1H, td, *J* 11.3 and 3.1, CH*H*N(H)), 1.70 (1H, t, *J* 10.8, C*H*HN(H)), 0.90 (3H, d, *J* 6.4, 3-(C*H*$_3$)); δ_C (126 MHz, DMSO-d_6) 143.4, 131.9, 129.7, 127.5, 52.3, 49.5, 45.9, 44.3, 20.9, 18.8; *m*/*z* (CI$^+$) 255 (MH$^+$, 100%), 99 (M$^+$ –Ts, 10); HRMS (CI$^+$) MH$^+$ calculated for

$C_{12}H_{19}N_2O_2S$ 255.1167, observed 255.1164. $Pd(OH)_2/C$ (50 mg, 20% wt.) was added to a solution of the tosyl piperazine (123 mg, 0.48 mmol), formaldehyde (0.13 mL, 4.8 mmol, 37% aqueous) and acetic acid (0.14 mL, 2.4 mmol) in methanol (5 mL) and was stirred under the presence of hydrogen at room temperature and atmospheric pressure for 4 h. Next, the solution was filtered and the filtrate concentrated in vacuo before the addition of a saturated aqueous Na_2CO_3 solution (10 mL) and water (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2, washed with a saturated aqueous sodium chloride solution (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford **11** (99 mg, 77%) as a white solid. The product could be used without further purification; mp 106-108°C; $[\alpha]_D^{23} = +48.9$ (*c* 0.45, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 2968, 2860, 2801, 1596, 1453, 1359, 1339, 1304, 1285, 1242, 1166, 1152, 1126, 1062, 1020, 992, 968, 925, 813, 802, 761, 710, 655; δ_H (400 MHz, $CDCl_3$) 7.61 (2H, d, *J* 8.2, 2 × Ar*H*), 7.31 (2H, d, *J* 7.9, 2 × Ar*H*), 3.54 (1H, m, C*H*HX), 3.46 (1H, dt, *J* 11.0 and 2.5, 3-C*H*), 2.75 (1H, dt, *J* 11.4 and 2.9, C*H*HX′), 2.46 (1H, td, *J* 11.1 and 2.7, CH*H*X), 2.41 (3H, s, CH_3), 2.34 (1H, td, *J* 11.3 and 3.0, CH*H*X′), 2.23 (3H, s, ArCH_3), 2.19 (1H, m, 2-*H*), 2.06 (1H, t, *J* 10.8, 3-H*H*), 1.01 (3H, d, *J* 6.3, 2-(CH_3)); δ_C (100 MHz, $CDCl_3$) 143.6, 132.0, 129.6, 127.8, 56.8, 54.3, 52.1, 46.0, 42.0, 21.5, 16.6; *m*/*z* (EI$^+$) 268 (M^+, 20%), 113 (M^+ –Ts, 100); HRMS (EI$^+$) M^+ calculated for $C_{13}H_{20}N_2O_2S$ 268.1245, observed 268.1239.

4.2.7. (3*S*)-3-Phenyl-*N*-methylmorpholine 12

Phenol (360 mg, 3.82 mmol) and 45% HBr/AcOH (1.6 mL) were added to a solution of (3*S*)-3-phenyl-4-(*para*-toluenesulfonyl)morpholine (35 mg, 0.11 mmol) (prepared according to the procedures of Aggarwal[21]) at 0 °C, before being warmed to room temperature and stirred for 16 h. The reaction was cooled to 0 °C and 20% aqueous NaOH was cautiously added. The mixture was then diluted with Et_2O, the organic layer was separated and extracted, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (15% MeOH/CH_2Cl_2) afforded the deprotected morpholine, (3*S*)-3-phenylmorpholine (19.4 mg, quant.) as a colourless oil; R_f: (15% MeOH/CH_2Cl_2) 0.35; $[\alpha]_D^{24} = +36.8$ (*c* 0.87, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3429, 2962, 2848, 2789, 1493, 1449, 1350, 1289, 1232, 1116, 1037, 984, 904, 880, 794, 756, 700, 650, 590; δ_H (400 MHz, $CDCl_3$) 7.42–7.26 (5H, m, 5 × Ph*H*), 3.94 (1H, dd, *J* 10.1 and 3.2), 3.88 (1H, dd, *J* 11.3 and 2.9), 3.84 (1H, dd, *J* 11.3 and 3.3), 3.69 (1H, td, *J* 11.3 and 2.7), 3.45 (1H, t, *J* 10.5), 3.12 (1H, td, *J* 11.6 and 3.3), 3.00 (1H, br dt, *J* 11.6); δ_C (100 MHz, $CDCl_3$) 139.8, 128.5, 127.9, 127.2, 73.2, 66.9, 60.4, 46.3; HRMS (ES$^+$) M^+ calculated for $C_{10}H_{14}NO$ 164.1075, observed 164.1064. Next, $Pd(OH)_2/C$ (10 mg, 20% wt.) was added to a solution of the deprotected morpholine (18.5 mg, 0.11 mmol), formaldehyde (0.1 mL, 3.6 mmol, 37% aqueous) and acetic acid (0.1 mL, 1.8 mmol) and stirred under the presence of hydrogen at room temperature and atmospheric pressure for 5 h. The solution was then filtered and the filtrate concentrated in vacuo before the addition of a saturated aqueous Na_2CO_3 solution (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2, washed with a saturated aqueous sodium chloride solution (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc/hexane) afforded **12** (16.2 mg, 83%) as a colourless oil; R_f: (30% EtOAc/hexane) 0.25; $[\alpha]_D^{24} = +31.9$ (*c* 0.69, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3004, 2985, 2912, 2857, 2840, 1622, 1499, 1447,1274, 1255, 1219, 1202, 1108, 1079, 1004, 925, 848, 744; δ_H (400 MHz, $CDCl_3$) 7.34–7.27 (5H, m, 5 × Ph*H*), 3.92 (1H, 3-*H*), 3.80 (1H, td, *J* 11.5 and 1.4, 2-*H*H), 3.72 (1H, dd, *J* 11.6 and 3.3), 3.41 (1H, t, *J* 10.9, 2-H*H*), 3.08 (1H, dd, *J* 10.3 and 3.1), 2.85 (1H, d, *J* 11.8), 2.43 (1H, td, *J* 11.7 and 3.4), 2.08 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 128.5, 128.1, 127.8, 127.4, 73.0, 69.3, 67.2, 55.5, 43.6; *m*/*z* (CI$^+$) 178 (MH$^+$, 100%); HRMS (CI$^+$) MH$^+$ calculated for $C_{11}H_{16}NO$ 178.1232, observed 178.1234.

4.2.8. 9-Fluoro(9-deoxy)-quinine 21a

The title compound was obtained by washing the corresponding dihydrochloride salt (prepared and donated by the laboratories Gilmour[25]) with 1 M aqueous NaOH. The solution was diluted with CH_2Cl_2 and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated in vacuo to afford amine **21a** (14.7 mg) as a colourless oil; $[\alpha]_D^{23} = -31.1$ (*c* 0.90 $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3350, 2950, 2900, 1600, 1575, 1500, 1450, 1400, 1250, 1200, 1100, 1050, 1000, 900, 850, 800, 750, 600; δ_H (400 MHz, $CDCl_3$) 8.77 (1H, d, *J* 4.5, Ar*H*), 8.04 (1H, d, *J* 9.2, Ar*H*), 7.46 (1H, d, *J* 4.5, Ar*H*), 7.39 (1H, dd, *J* 9.2 and 2.7, Ar*H*), 7.16 (1H, br s, Ar*H*), 6.50 (1H, br d, *J* 48.6, 9-C*H*F), 5.70 (1H, m, C*H*=CH_2), 5.00–4.94 (2H, m, C=C*H*$_2$), 3.97 (3H, s, CH_3), 3.49 (1H, m, C*H*), 3.32–3.21 (2H, m, 2 × C*H*), 2.86 (1H, m, C*H*), 2.78 (1H, m, C*H*), 2.39 (1H, m, C*H*), 1.90–1.78 (3H, m, 3 × C*H*), 1.63 (1H, m, C*H*), 1.50 (1H, m, C*H*); δ_C (100 MHz, $CDCl_3$) 158.3, 147.3, 144.3, 141.6, 140.7, 131.9, 125.4 (d, $^3J_{F,C}$ 5.5), 122.2, 117.4 (d, $^3J_{F,C}$ 11.2), 115.1, 100.7, 92.5 (d, $^1J_{F,C}$ 174.0), 59.3 (d, $^2J_{F,C}$ 21.6), 56.5, 56.1, 43.4 (d, $^3J_{F,H}$ 5.6), 39.2, 27.6, 26.9, 20.0 (d, $^3J_{F,C}$ 5.5); δ_F (376 MHz, $CDCl_3$) −198.1; HRMS (ES$^+$) MH$^+$ calculated for $C_{20}H_{24}N_2OF$ 327.1868, observed 327.1873.

4.2.9. 9-Fluoro(9-deoxy)-epiquinine 21b

The title compound was obtained by washing the corresponding dihydrochloride salt (prepared and donated by the laboratories of Gilmour[25]) with 1 M aqueous NaOH. The solution was diluted with CH_2Cl_2 and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated in vacuo to afford amine **21b** (15.6 mg) as a colourless oil; $[\alpha]_D^{23} = +25.3$ (*c* 1.19, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 2936, 2865, 1621, 1508, 1475, 1455, 1433, 1361, 1227, 1081, 1029, 981, 911, 853, 748, 717, 635; δ_H (400 MHz, $CDCl_3$) 8.77 (1H, d, *J* 4.4, Ar*H*), 8.05 (1H, d, *J* 9.1, Ar*H*), 7.42–7.38 (3H, m, 3 × Ar*H*), 5.86 (1H, dd, *J* 48.4 and 9.2, 9-C*H*F), 5.76 (1H, m, C*H*=CH_2), 5.04–4.95 (2H, m, C=C*H*$_2$), 3.94 (3H, s, CH_3), 3.53 (1H, m, C*H*), 3.35–3.25 (2H, m, 2 × C*H*), 2.89 (1H, m, C*H*), 2.79 (1H, m, C*H*), 2.31 (1H, m, C*H*), 1.72 (1H, m, C*H*), 1.63–1.59 (2H, m, 2 × C*H*), 1.41 (1H, m, C*H*), 0.94 (1H, dd, *J* 13.6 and 7.7, C*H*); δ_C (100 MHz, $CDCl_3$) 157.8, 147.1, 144.7, 141.2, 140.2 (d, $^2J_{F,C}$ 18.5), 131.7, 126.8 (d, $^4J_{F,C}$ 1.3), 121.7, 120.0 (d, $^3J_{F,C}$ 6.8), 114.4, 101.6, 91.2 (d, $^1J_{F,C}$ 179.4), 59.0 (d, $^2J_{F,C}$ 19.5), 55.7, 55.4, 41.3, 39.2, 27.7, 27.0, 24.3 (d, $^3J_{F,C}$ 4.4); δ_F (376 MHz, $CDCl_3$) −176.4 (dd, $^2J_{F,H}$ 48.9 and $^3J_{F,H}$ 11.3); HRMS (ES$^+$) MH$^+$ calculated for $C_{20}H_{24}FN_2O$ 326.1873, observed 327.1871.

4.2.10. 9-Amino-(9-deoxy)-quinine 23a

9-Epiquinine, **22**, (1.03 g, 3.70 mmol) and PPh_3 (1.16 g, 4.44 mmol) were dissolved in THF (23 mL) and the solution was cooled to 0 °C and diisopropyl azodicarboxylate (1.10 mL, 5.55 mmol) was added dropwise. After 5 min, diphenyl phosphoryl azide (1.20 mL, 5.55 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 1 h and then at 45 °C for 2 h. Next, PPh_3 (1.16 g, 4.44 mmol) was added in one portion and the mixture was heated at 45 °C until the visible evolution of nitrogen had ceased. Next, H_2O (2 mL) was added and the solution was stirred for a 16 h at room temperature. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 and 1 M aqueous HCl (1:1, 100 mL). The aqueous phase was washed with CH_2Cl_2 and basified with conc. aqueous NH_3, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a yellow oil. The crude oil was then purified by mass triggered reverse phase chromatography (0.05% NH_3HOAc in MeCN/H_2O) and finally washed with saturated aqueous K_2CO_3 solution, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated in vacuo to afford **23a** (263 mg, 22%) as a pale orange oil; $[\alpha]_D^{19} = -55.1$ (*c* 0.65, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3275 br, 2937, 2863, 1620, 1589, 1508, 1472, 1431, 1358, 1226, 1028, 911, 827, 713; δ_H (400 MHz, $CDCl_3$) 8.74 (1H, d, *J* 4.6, Ar*H*), 8.01 (1H, d, *J*

9.2, Ar*H*), 7.45 (1H, d, *J* 2.6, Ar*H*), 7.37–7.34 (2H, m, 2 × Ar*H*), 5.91 (1H, m, C*H*=CH$_2$), 5.08–5.02 (2H, m, CH=C*H*$_2$), 4.70 (1H, br d, *J* 6.3, 9-C*H*NH$_2$), 3.97 (3H, s, C*H*$_3$), 3.21 (1H, q, *J* 8.4), 3.08 (1H, br), 3.06 (1H, dd, *J* 13.7 and 10.0), 2.58 (1H, m), 2.30 (1H, br), 2.12 (1H, m), 2.05–1.47 (2H, br, N*H*$_2$), 1.91 (1H, m), 1.69 (1H, m), 1.58–1.49 (2H, m); δ_C (100 MHz, CDCl$_3$); 157.8, 149.1, 147.9, 144.8, 141.7, 132.0, 127.6, 121.2, 118.3, 114.6, 101.2, 60.6, 56.2, 55.7, 53.6, 42.0, 39.6, 27.8, 27.7, 26.2; *m*/*z* HRMS (ES$^+$) MH$^+$ calculated for $C_{20}H_{26}N_3O$ 342.2076, observed 324.2065.

4.2.11. 9-*N*-Acetamido-(9-deoxy)-9-quinine 24a

Amine **23a** (30 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1 mL) and triethylamine (0.19 mL, 1.4 mmol) and the solution was cooled to 0 °C. Acetyl chloride (10 μL) in CH_2Cl_2 (1 mL) was then added dropwise over 10 min. The reaction was then stirred at room temperature for 18 h. Next CH_2Cl_2 (1.5 mL) was added, the organic solution washed with saturated aqueous Na_2CO_3 (3 × 10 mL), dried over Na_2SO_4 and the solvent removed in vacuo. Purification by flash column chromatography on silica gel (25% MeOH/EtOAc) afforded **24a** (30 mg, 83%) as a colourless oil; $[\alpha]_D^{22} = -35.3$ (*c* 1.4, CHCl$_3$); ν_{max}/cm^{-1}(ATR) 3566, 2926, 1652, 1558, 1373, 1228, 1028; δ_H (400 MHz, CDCl$_3$) 8.67 (1H, d, *J* 4.6, Ar*H*), 7.95 (1H, d, *J* 9.2, Ar*H*), 7.63 (1H, d, *J* 2.7, Ar*H*), 7.34 (1H, dd, *J* 9.2 and 2.7, Ar*H*), 7.31 (1H, d, *J* 4.6, Ar*H*), 6.01–5.87 (3H, m, C*H*=CH$_2$, 9-C*H*NH and N*H*), 5.14–5.10 (2H, m, CH=C*H*$_2$), 3.97 (3H, s, C*H*$_3$), 3.67 (1H, m, 8-*H*), 3.12 (1H, dd, *J* 13.7 and 10.0, 2-*H*H), 2.92–2.84 (1H, m, 6-*H*H), 2.76 (1H, m, 2-H*H*), 2.58 (1H, m, 6-H*H*), 2.32 (1H, br, 3-*H*), 2.04 (1H, m, 7-*H*H), 1.94 (3H, s, COC*H*$_3$), 1.88 (1H, m, 4-*H*), 1.76 (1H, m, 5-*H*H), 1.55–1.47 (2H, m, 7-H*H* and 5-H*H*); δ_C (100 MHz, CDCl$_3$) 169.7 (C), 158.2 (C), 147.5 (CH), 144.8 (C), 144.5 (C), 142.0 (CH), 131.5 (CH), 128.4 (C), 122.2 (CH), 119.1 (CH), 114.5 (CH$_2$), 101.5 (CH), 57.5 (CH), 55.9 (CH), 55.8 (CH$_2$), 49.4 (CH), 41.4 (CH$_2$), 39.5 (CH), 27.5 (CH$_2$), 27.5 (CH), 25.4 (CH$_2$), 23.3 (CH); *m*/*z* (EI$^+$) 365 (M$^+$, 2%) 136 (100%); HRMS (EI$^+$) M$^+$ calculated for $C_{22}H_{27}N_3O_2$ 365.2103, observed 365.2105.

4.2.12. 9-*N*-Acetamido(9-deoxy)-9-epiquinine 24b

Amine **23b** (35 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (0.7 mL) and triethylamine (0.22 mL, 1.6 mmol) and the solution was cooled to 0 °C. Acetyl chloride (11 μL) in CH_2Cl_2 (0.3 mL) was then added dropwise over 10 min. The reaction was then stirred at room temperature for 18 h. Next, CH_2Cl_2 (1.5 mL) was added, the organic solution washed with saturated aqueous Na_2CO_3 (3 × 10 mL), dried over Na_2SO_4 and the solvent removed in vacuo. Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded **24b** (29 mg, 78%) as a yellow oil; $[\alpha]_D^{22} = +16.6$ (*c* 0.7, CHCl$_3$); ν_{max}/cm^{-1} (ATR) 3245, 2960, 2927, 1650, 1508, 1027, 800, 665; δ_H (400 MHz, CDCl$_3$) 8.73 (1H, d, *J* 4.5, Ar*H*), 8.02 (1H, d, *J* 9.2, Ar*H*), 7.69 (1H, d, *J* 2.1, Ar*H*), 7.39 (1H, dd, *J* 9.2 and 2.1, Ar*H*), 7.33 (1H, d, *J* 4.5, Ar*H*), 6.76 (1H, br, N*H*), 5.75 (1H, m, C*H*=CH$_2$), 5.37 (1H, br s, 9-C*H*NH), 5.02–4.97 (2H, m, CH=C*H*$_2$), 3.99 (3H, s, C*H*$_3$), 3.28 (1H, dd, *J* 13.7 and 10.2, 2-*H*H), 3.20–3.10 (2H, br m, 8-*H* and 6-*H*H), 2.79–2.69 (2H, m, 6-H*H* and 2-H*H*), 2.31 (1H, br m, 3-*H*), 1.98 (3H, s, COC*H*$_3$), 1.68–1.61 (3H, m, 2 × 5-*H* and 4-*H*), 1.47 (1H, br t, *J* 10.5, 7-*H*H), 0.92 (1H, br dd, *J* 13.5 and 6.2, 7-H*H*); δ_C (100 MHz, CDCl$_3$) 170.1 (C), 157.8 (C), 147.5 (CH), 145.1 (C), 144.8 (C), 141.1 (CH), 131.7 (CH), 128.3 (C), 121.7 (CH), 119.2 (CH), 114.6 (CH$_2$), 101.9 (CH), 59.5 (CH), 56.0 (CH$_2$), 55.6 (CH), 51.1 (CH), 40.9 (CH$_2$), 39.4 (CH), 27.8 (CH$_2$), 27.3 (CH), 26.2 (CH$_2$), 23.2 (CH); *m*/*z* (EI$^+$) 365 (M$^+$, 2%), 136 (100); HRMS (EI$^+$) M$^+$ calculated for $C_{22}H_{27}N_3O_2$ 365.2103, observed 365.2100.

4.2.13. *N*-(*p*-Toluenesulfonyl)-9-amino(9-deoxy)-quinine 25a

p-Toluenesulfonyl chloride (136 mg, 0.71 mmol) was added in one portion to a solution of amine **23a** (166 mg, 0.51 mmol) and K_2CO_3 (138 mg, 0.61 mmol) in CH_2Cl_2 (4 mL) at room temperature and stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2, filtered to remove solid K_2CO_3 and washed with saturated aqueous Na_2CO_3 solution. The organic layer was then separated, dried (Na_2SO_4), filtered and concentrated in vacuo to afford an orange residue. Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded **25a** (174 mg, 71%) as a white solid; R_f: (5% MeOH/CH_2Cl_2) 0.30; mp 75–78 °C; $[\alpha]_D^{22} = +96.6$ (*c* 0.58, CHCl$_3$); ν_{max} (ATR)/cm^{-1} 3285, 3083, 2942, 2871, 1622, 1600, 1510, 1450, 1318, 1223, 1155, 1091, 1029, 912, 811, 664; δ_H (400 MHz, CDCl$_3$) 8.47 (1H, d, *J* 4.6, Ar*H*), 7.80 (1H, d, *J* 9.2, Ar*H*), 7.25 (1H, dd, *J* 9.2 and 2.5 Ar*H*), 7.22–7.18 (4H, m, 4 × Ar*H*), 6.63 (2H, d, *J* 8.1, 2 × Ar*H*), 5.85 (1H, m, C*H*=CH$_2$), 5.16 (1H, br, 9-C*H*NTs), 5.04–5.00 (2H, m, CH=C*H*$_2$), 3.95 (3H, s, °C*H*$_3$), 3.30 (1H, br, C*H*), 3.17–2.88 (2H, br, 2 × C*H*), 2.68–2.47 (2H, br, 2 × C*H*), 2.27 (1H, br, C*H*), 2.16 (1H, br, C*H*), 2.09 (3H, s, ArC*H*$_3$), 1.89 (1H, br, C*H*), 1.81–1.60 (2H, br, 2 × C*H*), 1.51 (1H, br, C*H*); δ_C (126 MHz, CDCl$_3$) 157.6, 147.0, 144.5, 144.1, 142.8, 140.9, 136.5, 131.1, 128.3, 127.2, 126.3, 121.4, 118.8, 114.8, 101.0, 60.1, 56.0, 55.8, 54.1, 41.8, 39.1, 27.4, 26.9, 25.8, 21.0; HRMS (ES$^+$) MH$^+$ calculated for $C_{27}H_{32}N_3O_3S$ 478.2164, observed 478.2157.

4.2.14. *N*-(*p*-Toluenesulfonyl)-9-amino(9-deoxy)-9-epiquinine 25b

p-Toluenesulfonyl chloride (77 mg, 0.41 mmol) was added in one portion to a solution of amine **23b** (88 mg, 0.27 mmol) and K_2CO_3 (45 mg, 0.33 mmol) in CH_2Cl_2 (6 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2, filtered, to remove solid K_2CO_3 and washed with saturated aqueous Na_2CO_3 solution (3 × 10 mL). The organic layer was then separated, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a white residue. Purification by flash column chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) afforded **25b** (89 mg, 69%) as a white solid; R_f: (5% MeOH/CH_2Cl_2) 0.30; mp 64.5–67 °C; $[\alpha]_D^{22} = +49.1$ (*c* 1.43, CHCl$_3$); ν_{max} (ATR)/cm^{-1} 3211, 2927, 2871, 1621, 1593, 1508, 1477, 1323, 1228, 1154, 1091, 1030, 987, 915, 854, 813, 728, 661; δ_H (400 MHz, $C_2D_2Cl_4$, 403 K) 8.61 (1H, d, *J* 4.4, Ar*H*), 8.01 (1H, d, *J* 9.0, Ar*H*), 7.54 (1H, br, Ar*H*), 7.41–7.33 (3H, m, 3 × Ar*H*), 7.28 (1H, br, Ar*H*), 6.92 (1H, br d, *J* 7.5, Ar*H*), 5.73 (1H, m, C*H*=CH$_2$), 5.05–5.00 (2H, m, CH=C*H*$_2$), 4.84 (1H, br), 4.01 (3H, s, C*H*$_3$), 3.35 (1H, dd, *J* 13.8 and 10.1), 3.20 (1H, br), 3.05 (1H, m), 2.88–2.76 (2H, m), 2.39 (1H, br), 2.29 (3H, s, ArC*H*$_3$), 1.75 (1H, m), 1.69–1.64 (2H, m), 1.42 (1H, m), 0.97 (1H, m); δ_C (126 MHz, $C_2D_2Cl_4$, 403 K) 158.7, 146.7, 144.1, 142.4, 137.6, 136.7, 136.7, 131.4, 128.1, 127.4, 126.4, 121.9, 121.6, 117.0, 102.0, 58.6, 56.3, 54.2, 41.2, 36.4, 29.3, 27.2, 24.6, 24.1, 20.6; *m*/*z* (CI$^+$) 478 (M$^+$, 95%), 189 (100), 309 (98); HRMS (ES$^+$) M$^+$ calculated for $C_{27}H_{32}N_3O_3S$ 478.2164, observed 478.2174.

4.2.15. (3*R*,4*S*)-8-[(6-Methoxyquinolin-4-yl)methylene]-5-vinylquinuclidine 27

9-Epiquinine, **22**, (150 mg, 0.46 mmol) and PPh$_3$ (145.5 mg, 0.55 mmol) were dissolved in THF (3 mL) and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (100 μL, 0.51 mmol) was then added in one portion before the dropwise addition of diphenyl phosphoryl azide (119 μL, 0.55 mmol) in THF (1 mL). The mixture was allowed to warm to room temperature and stirred for 3 h before the addition of PPh$_3$ (242 mg, 0.92 mmol) in one portion and the mixture was heated at 50 °C for 3 h. Next, H_2O (1 mL) was added and the solution was stirred for 16 h at room temperature. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 and 1 M aqueous HCl (1:1, 10 mL). The aqueous phase was washed with CH_2Cl_2 and basified with concentrated aqueous NH_3, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (7% MeOH/EtOAc) afforded **27** (63.4 mg, 47%) as a colourless oil; R_f: (7% MeOH/EtOAc) 0.45; $[\alpha]_D^{22} = +55.2$ (*c* 0.58, CHCl$_3$); ν_{max}

(ATR)/cm^{-1} 2933, 2865, 1619, 1579, 1506, 1468, 1430, 1357, 1257, 1227, 1106, 1084, 1031, 913, 840, 729, 713, 676; δ_H (400 MHz, $CDCl_3$) 8.70 (1H, d, *J* 4.6, Ar*H*), 7.97 (1H, d, *J* 9.2, Ar*H*), 7.82 (1H, d, *J* 4.6, Ar*H*), 7.33 (1H, dd, *J* 9.1 and 2.7, Ar*H*), 7.27 (1H, s, Ar*H*), 6.42 (1H, s, C*H*=CR$_2$), 5.98–5.89 (1H, br m, C*H*=CH$_2$), 5.10–5.05 (2H, m, CH=C*H*$_2$), 3.95 (3H, s, C*H*$_3$), 3.28 (1H, dd, *J* 13.8 and 9.5), 3.07–2.93 (2H, m), 2.80–2.71 (2H, m), 2.44–2.38 (2H, m), 2.02–1.99 (1H, m), 1.73–1.65 (2H, m); δ_C (100 MHz, $CDCl_3$) 157.3, 154.3, 147.9, 144.6, 140.8, 139.7, 131.5, 127.7, 121.5, 120.9, 114.8, 1114.4, 102.1, 55.5, 53.78, 47.8, 39.7, 30.5, 29.7, 27.2; *m*/*z* (CI$^+$) 307 (MH$^+$, 100%); HRMS (CI$^+$) MH$^+$ calculated for $C_{20}H_{23}N_2O$ 402.1810, observed 402.1815.

4.2.16. *O*-Methyl-β-isocupreidine 28b[33]

(Trimethylsilyl)diazomethane (0.11 mL of a 2.0 M solution in hexanes, 0.21 mmol) was added dropwise to a solution of **28a** (50 mg, 0.16 mmol) in benzene/MeOH (2 mL, 3:2) and stirred for 3 h at room temperature. After this time, the reaction was concentrated in vacuo and the residue purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford **28b** (22.4 mg, 43%) as a colourless oil; R_f: (5% MeOH/CH_2Cl_2) 0.60; $[\alpha]_D^{22} = -8.7$ (*c* 0.69, MeOH) {lit.[33] $[\alpha]_D^{19} = -8.2$ (*c* 1.02, MeOH)}; δ_H (400 MHz, $CDCl_3$) 8.78 (1H, d, *J* 4.5, Ar*H*), 8.01 (1H, d, *J* 9.2, Ar*H*), 7.71 (1H, d, *J* 4.4, Ar*H*), 7.34 (1H, dd, *J* 9.2 and 2.6, Ar*H*), 7.17 (1H, d, *J* 7.2, Ar*H*), 5.96 (1H, s, C*H*OR), 3.97 (3H, s, OC*H*$_3$), 3.62 (1H, d, *J* 13.5), 3.56 (1H, d, *J* 6.0), 3.06–3.03 (2H, m), 2.71 (1H, d, *J* 13.5), 2.17 (1H, m), 1.80 (1H, m), 1.73–1.62 (3H, m, C*H*$_2$CH$_3$ and 1 × C*H*), 1.55 (1H, m), 1.28 (1H, dd, *J* 12.6 and 6.3), 1.03 (3H, t, *J* 7.4, –CH$_2$C*H*$_3$). All data were in agreement with those reported.[33]

4.2.17. *O*-Benzyl-β-isocupreidine 28c

At first, NaH (7.7 mg, 60% dispersion in mineral oil, 0.19 mmol) was added to a solution of **28a** (40.0 mg, 0.13 mmol) in THF (1 mL) at 0 °C and stirred for 10 min. Benzyl bromide (16.8 μL, 0.14 mmol) was then added dropwise to the solution before the addition of TBAI (7 mg, 0.02 mmol). The mixture was then heated to 40 °C and stirred for 20 h. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded **28c** (10.5 mg, 20%) as a colourless oil; R_f: (5% MeOH/CH_2Cl_2) 0.35; $[\alpha]_D^{22} = +10.3$ (*c* 0.58, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 2942, 2878, 1619, 1597, 1509, 1456, 1225, 1010, 909, 853, 730; δ_H (400 MHz, $CDCl_3$) 8.76 (1H, d, *J* 4.5, Ar*H*), 8.04 (1H, d, *J* 9.2, Ar*H*), 7.72 (1H, d, *J* 4.3, Ar*H*), 7.54–7.52 (2H, m, 2 × Ar*H*), 7.45–7.30 (5H, m, 5 × Ar*H*), 5.96 (1H, s, C*H*OR), 5.28 (1H, d, *J* 11.5, C*H*HPh), 5.22 (1H, d, *J* 11.5, CH*H*Ph), 3.62 (1H, d, *J* 13.4), 3.52 (1H, d, *J* 5.6), 3.07–3.00 (2H, m), 2.72 (1H, d, *J* 13.5), 2.18 (1H, m), 1.81–1.50 (5H, m, C*H*$_2$CH$_3$ and 3 × C*H*), 1.27 (1H, dd, *J* 12.6 and 6.3), 1.05 (3H, t, *J* 7.4, –CH$_2$C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 157.0, 147.7, 144.1, 142.7, 136.5, 131.9, 128.5, 128.0, 127.9, 126.4, 122.0, 119.4, 102.1, 77.0, 72.9, 70.6, 56.3, 54.6, 46.6, 32.9, 27.4, 24.0, 23.4, 7.3; HRMS (ES$^+$) MH$^+$ calculated for $C_{26}H_{29}N_2O_2$ 401.2229, observed 401.2238.

4.3. Preparation of aromatic α,β-unsaturated ketones

All were obtained from commercial sources and used as supplied with the exception of **2j**,**l**,**m** which were prepared according to the procedures outlined:

4.3.1. (*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one) 2j[39]

2-Acetyl furan (0.54 g, 4.9 mmol) in EtOH (5 mL) was added slowly to KOH (15 mL, 10% aqueous) at 0 °C and stirred for 15 min. Benzaldehyde (0.50 mL, 4.9 mmol) was then added and the mixture was allowed to stir for a further 15 min at 0 °C before being warmed to room temperature and stirred for 20 h. The reaction was then diluted with water (10 mL), neutralised with HCl (10% aqueous) and extracted with EtOAc. The organic extracts were then washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexane) afforded enone **2j** (0.86 g, 88%) as a colourless solid; mp 84–86 °C (lit.[39], 81–83 °C); δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 15.8, PhC*H*=CH), 7.63–7.61 (3H, m, 3 × Ar*H*), 7.45 (1H, d, *J* 15.8, PhCH=C*H*), 7.40–7.38 (3H, m, 3 × Ar*H*), 7.34 (1H, m, Ar*H*), 6.57 (1H, m, Ar*H*); *m*/*z* (CI$^+$ (NH_3)) 199 (MH$^+$, 100%); HRMS (CI$^+$ (NH_3)) MH$^+$ calculated for $C_{13}H_{11}O_2$ 199.0759, observed 199.0762. All data were in agreement with those previously reported.[39]

4.3.2. (*E*)-1-(4-Methylthiophen-2-yl)-3-phenylprop-2-en-1-one 2l

Following the procedure for the synthesis of **2j**; using 2-acetyl-4-methylthiophene (0.5 mL, 4.4 mmol) and benzaldehyde (0.45 mL, 4.4 mmol), with flash column chromatography purification (2% EtOAc/hexane) afforded enone **2l** (0.72 g, 72%) as an off-white solid; mp 96-98 °C; ν_{max}/cm^{-1}(ATR) 1645, 1599, 1572, 1424, 1230; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* 15.6, PhC*H*=CH), 7.69 (1H, br s, Ar*H*), 7.66–7.63 (2H, m, 2 × Ar*H*), 7.43–7.41 (3H, m, 3 × Ar*H*), 7.42 (1H, d, *J* 15.6, PhCH=C*H*), 7.27 (1H, br s, Ar*H*), 2.33 (3H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 182.0 (C), 145.0 (C), 143.8 (CH), 139.1 (C), 134.8 (C), 134.0 (CH), 130.6 (CH), 130.0 (CH), 129.0 (CH), 128.5 (CH), 121.6 (CH), 15.7 (CH); *m*/*z* (CI$^+$ (NH_3)) 229 (MH$^+$, 100%); HRMS (CI$^+$ (NH_3)) MH$^+$ calculated for $C_{14}H_{13}OS$ 229.0687, observed 229.0685.

4.3.3. (*E*)-1-(5-Chlorothiophen-2-yl)-3-phenylprop-2-en-1-one 2m

Following the procedure for the synthesis of **2j**; using 2-acetyl-5-chlorothiophene (0.5 g, 3.1 mmol) and benzaldehyde (0.32 mL, 3.1 mmol), with flash column chromatography purification (3% EtOAc/hexane) afforded enone **2m** (0.35 g, 45%) as a white solid; mp 94-96 °C; ν_{max}/cm^{-1} (ATR) 1645, 1592, 1576, 1424, 1233; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 15.6, PhC*H*=CH), 7.61 (1H, d, *J* 4.1, Ar*H*), 7.58–7.56 (2H, m, 2 × Ar*H*), 7.38–7.37 (3H, m, 3 × Ar*H*), 7.30 (1H, d, *J* 15.6, PhCH=C*H*), 6.95 (1H, d, *J* 4.1, Ar*H*); δ_C (100 MHz, $CDCl_3$) 180.9 (C), 144.4 (CH), 144.3 (C), 139.7 (C), 134.4 (C), 131.4 (CH), 130.8 (CH), 129.0 (CH), 128.6 (CH), 127.8 (CH), 120.2 (CH); *m*/*z* (CI$^+$ (NH_3)) 249 (MH$^+$, 100%); HRMS (CI$^+$ (NH_3)) MH$^+$ calculated for $C_{13}H_{10}OSCl$ 249.0141, observed 249.0141.

4.3.4. General procedure for the aziridination α,β-unsaturated ketones with quinine

All reactions were performed on a 0.11–0.24 mmol scale according to the following procedure: DppONH$_2$ (1.05 equiv) was added to a solution of amine quinine (1.05 equiv) in CH_2Cl_2 (0.06 M in substrate) at room temperature and the mixture stirred for 0.5 h. Next, NaH (60% dispersion in mineral oil, 2 equiv), *i*-PrOH (2 equiv) and enone (1 equiv) were added sequentially and the mixture was allowed to stir at room temperature for 16 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution and the aqueous layer separated and extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography afforded the desired aziridine. Enantiomeric excess (ee) was measured by HPLC analysis (conditions: 93:7 hexane:IPA, 0.8 mL/min, 254 nm, AD-H).

4.3.5. (2*R*,3*S*)-Phenyl-(3-phenylaziridin-2-yl)methanone 3a[14]

Using chalcone **2a** (25 mg, 0.12 mmol) afforded aziridine **3a** (18.0 mg, 64%) as a white solid; R_f: (10% EtOAc/hexane) 0.50; mp

99–101 °C (lit.[14] 99–101 °C); $[\alpha]_D^{22} = -139$ (*c* 0.66, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, *J* 8.8, 2 × PhH), 7.62 (2H, t, *J* 7.4, 2 × PhH), 7.49 (1H, t, *J* 7.6, PhH), 7.39–7.30 (5H, m, 5 × PhH), 3.52 (1H, dd, *J* 2.3, 2-CHN), 3.18 (1H, dd, *J* 2.5, 3-CHN), 2.68 (1H, br, NH); *m*/*z* (EI^+) 233 (M^+, 80%), 206 (100), 105 (100); Assay of enantiomeric excess: (t_R (minor) = 13.1 min, t_R (major) = 15.0 min) 56% ee. All data were in agreement with those reported for the racemate.[14]

4.3.6. ((2*R*,3*S*)-3-(4-Methoxyphenyl)aziridin-2-yl)phenyl methanone 3b[14]

Using 4-methoxychalcone **2b**, (31 mg, 0.13 mmol), afforded aziridine **3b** (12 mg, 35%) as a viscous orange oil; $[\alpha]_D^{22} = -379.3$ (*c* 0.12, MeOH); δ_H (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* 7.4, 2 × ArH), 7.64 (1H, t, *J* 7.4, ArH), 7.52 (2H, t, *J* 7.9, 2 × ArH), 7.32 (2H, d, *J* 8.7, 2 × ArH), 6.92 (2H, d, *J* 8.7, 2 × ArH), 3.84 (3H, s, OCH_3), 3.50 (1H, br, CHNH), 3.16 (1H, br, CHNH), 2.67 (1H, br, NH); *m*/*z* (CI^+ (NH_3)) 254 (MH^+, 100%); HRMS (CI^+ (NH_3)) MH^+ calculated for $C_{16}H_{16}NO_2$ 254.1181, observed 254.1185; Assay of enantiomeric excess: (t_R (minor) = 23.3 min, t_R (major) = 26.7 min) 55% ee. All data were in agreement with those previously reported for the racemate.[14]

4.3.7. ((2*R*,3*S*)-3-(4-Methylphenyl)aziridin-2-yl)phenyl methanone 3c[14]

Using 4-methylchalcone **2c**, (29 mg, 0.13 mmol), afforded aziridine **3c** (17 mg, 55%) as a cream solid; mp 106–108 °C (lit.[14], 106–07 °C); $[\alpha]_D^{22} = -99.4$ (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02–8.01 (2H, m, 2 × ArH), 7.63 (1H, m, ArH), 7.52–7.49 (2H, m, 2 × ArH), 7.30–7.28 (2H, m, 2 × ArH), 7.21–7.19 (2H, m, 2 × ArH), 3.51 (1H, br, CHNH), 3.17 (1H, br, CHNH), 2.68 (1H, br, NH), 2.39 (3H, s, CH_3); *m*/*z* (CI^+ (NH_3)) 238 (MH^+, 100%); HRMS (CI^+ (NH_3)) MH^+ calculated for $C_{16}H_{16}NO$ 238.1232, observed 238.1241; Assay of enantiomeric excess: (t_R (minor) = 13.3 min, t_R (major) = 16.0 min) 52% ee. All data were in agreement with those previously reported for the racemate.[14]

4.3.8. ((2*R*,3*S*)-3-(4-Chlorophenyl)aziridin-2-yl)phenyl methanone 3d[13]

Using 4-chlorochalcone **2d**, (32 mg, 0.13 mmol), afforded aziridine **3d** (18 mg, 54%) as a white solid; mp 88–90 °C (lit.[13], 88–90 °C); $[\alpha]_D^{22} = -147.5$ (*c* 0.8, MeOH); δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, *J* 7.1, 2 × ArH), 7.65 (1H, t, *J* 7.1, ArH), 7.52 (2H, t, *J* 7.9, 2 × ArH), 7.37–7.32 (4H, m, 4 × ArH), 3.47 (1H, dd, *J* 7.8 and 2.2 CHNH), 3.17 (1H, dd, *J* 9.3 and 2.2 CHNH), 2.70 (1H, br m, NH); *m*/*z* (CI^+ (NH_3)) 258 (MH^+, 100%); HRMS (CI^+ (NH_3)) calculated for $C_{15}H_{13}NOCl$ 258.0686, observed 258.0689; Assay of enantiomeric excess: (t_R (minor) = 16.3 min, t_R (major) = 27.9 min) 48% ee. All data were in agreement with those previously reported for the racemate.[13]

4.3.9. ((2*R*,3*S*)-3-(4-Nitrophenyl)aziridin-2-yl)phenyl methanone 3e[13]

Using 4-nitrochalcone, **2e**, (33 mg, 0.13 mmol) afforded aziridine **3e** (15 mg, 43%) as a yellow solid; mp 139–141 °C (lit.[13], 141-143 °C); $[\alpha]_D^{22} = -103.3$ (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.25–8.23 (2H, m, 2 × ArH), 8.02–8.00 (2H, m, 2 × ArH), 7.66 (1H, m, ArH), 7.58–7.51 (4H, m, 4 × ArH), 3.53 (1H, dd, *J* 7.8 and 2.1, CHNH), 3.28 (1H, dd, *J* 8.8 and 2.1, CHNH), 2.80 (1H, br, NH); *m*/*z* (CI^+ (NH_3)) 269 (MH^+, 100%); HRMS (CI^+ (NH_3)) MH^+ calculated for $C_{15}H_{13}N_2O_3$ 269.0926, observed 269.0928; Assay of enantiomeric excess: (t_R (minor) = 37.2 min, t_R (major) = 76.3 min) 37% ee. All data were in agreement with those previously reported for the racemate.[13]

4.3.10. ((2*R*,3*S*)-3-Phenylaziridin-2-yl)-4-methoxyphenyl methanone 3f[14]

Using 4′-methoxychalcone, **2f**, (31 mg, 0.13 mmol) afforded aziridine **3f** (16 mg, 48%) as a white solid; mp 71–72 °C (lit.[14], 71–73 °C); $[\alpha]_D^{22} = -138.9$ (*c* 0.36, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02–8.00 (2H, m, 2 × ArH), 7.39–7.28 (5H, m, 5 × ArH), 6.99–6.97 (2H, m, 2 × ArH), 3.90 (3H, s, OCH_3), 3.48 (1H, dd, *J* 8.0 and 2.3, CHNH), 3.17 (1H, dd, *J* 9.3 and 2.3, CHNH), 2.66 (1H, dd, *J* 9.3 and 8.0, NH); *m*/*z* (CI^+ (NH_3)) 254 (MH^+, 100%); HRMS (CI^+ (NH_3)) MH^+ calculated for $C_{16}H_{16}NO_2$ 254.1181, observed 254.1185; Assay of enantiomeric excess: (t_R (minor) = 32.2 min, t_R (major) = 42.2 min) 66% ee. All data were in agreement with those previously reported for the racemate.[14]

4.3.11. ((2*R*,3*S*)-3-Phenylaziridin-2-yl)-4-methylphenyl methanone 3g[14]

Using 4′-methylchalcone **2g**, (29 mg, 0.13 mmol) afforded aziridine **3g** (21 mg, 68%) as an off-white solid; mp 87–89 °C (lit.[14], 89–90 °C); $[\alpha]_D^{22} = -169.6$ (*c* 0.63, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.93–7.91 (2H, m, 2 × ArH), 7.39–7.28 (7H, m, 7 × ArH), 3.51 (1H, dd, *J* 8.0 and 2.3, CHNH), 3.18 (1H, dd, *J* 9.3 and 2.3, CHNH), 2.70–2.66 (1H, br, NH), 2.45 (3H, s, CH_3); *m*/*z* (CI^+ (NH_3)) 238 (MH^+, 100%); HRMS (CI^+ (NH_3)) MH^+ calculated for $C_{16}H_{16}NO$ 238.1232, observed 238.1239; Assay of enantiomeric excess: (t_R (minor) = 16.0 min, t_R (major) = 21.5 min) 59% ee. All data were in agreement with those previously reported for the racemate.[14]

4.3.12. ((2*R*,3*S*)-3-Phenylaziridin-2-yl)-4-chlorophenyl methanone 3h[14]

Using 4′-chlorochalcone **2h**, (32 mg, 0.13 mmol) afforded aziridine **3h** (20 mg, 62%) as a white solid; mp 76–78 °C (lit.[14], 75–77 °C); $[\alpha]_D^{22} = -128.0$ (*c* 0.63, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.97–7.95 (2H, m, 2 × ArH), 7.50–7.49 (2H, m, 2 × ArH), 7.40–7.34 (5H, m, 5 × ArH), 3.48 (1H, br, CHNH), 3.21 (1H, br, CHNH), 2.66 (1H, br, NH); *m*/*z* (CI^+ (NH_3)) 258 (MH^+, 100%); HRMS (CI^+ (NH_3)) MH^+ calculated for $C_{15}H_{13}NOCl$ 258.0686, found 258.0690; Assay of enantiomeric excess: (t_R (major) = 16.6 min, t_R (minor) = 17.7 min) 46% ee. All data were in agreement with those previously reported for the racemate.[14]

4.3.13. ((2*R*,3*S*)-3-Phenylaziridin-2-yl)(furan-2-yl) methanone 3j

Using enone **2j**, afforded aziridine **3j** (10 mg, 41%) as a white solid; mp 82–84 °C; $[\alpha]_D^{22} = -395.3$ (*c* 0.4, MeOH); ν_{max}/cm^{-1}(ATR) 1648, 1565, 1468, 1399, 1282, 1002, 764; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 1.2, ArH), 7.38–7.33 (6H, m, 6 × ArH), 6.62 (1H, dd, *J* 3.5 and 1.6, ArH), 3.46 (1H, d, *J* 2.1, CHNH), 3.28 (1H, d, *J* 2.1, CHNH), 2.54 (1H, br, NH); δ_C (100 MHz, $CDCl_3$) 184.4 (C), 152.2 (C), 147.5 (CH), 138.3 (C), 128.5 (CH), 127.8 (CH), 126.3 (CH), 118.5 (CH), 112.7 (CH), 43.6 (CH), 43.4 (CH); *m*/*z* (CI^+ (NH_3)) 214 (M^+, 100%); HRMS (CI^+ (NH_3)) M^+ calculated for $C_{13}H_{12}NO_2$ 214.0868, observed 214.0871. Assay of enantiomeric excess: (t_R (minor) = 18.3 min, t_R (major) = 34.2 min) 71% ee.

4.3.14. ((2*R*,3*S*)-3-Phenylaziridin-2-yl)(thiophen-2-yl) methanone 3k

Using enone **2k**, afforded aziridine **3k** (23 mg, 47%) as a white solid; mp 114–116 °C; $[\alpha]_D^{26} = -319.0$ (*c* 0.79, MeOH); ν_{max}/cm^{-1} (ATR) 1645, 1523, 1500, 1420, 1261, 960; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, dd, *J* 4.0 and 0.9, ArH), 7.76 (1H, dd, *J* 5.1 and 0.9, ArH), 7.39–7.31 (5H, m, 5 × ArH), 7.19 (1H, dd, *J* 5.1 and 4.0, ArH), 3.42 (1H, d, *J* 2.2, CHNH), 3.29 (1H, d, *J* 2.2, CHNH), 2.45 (1H, br, NH); δ_C (125 MHz, $CDCl_3$) 188.2 (C), 142.8 (C), 138.2 (C), 134.8 (CH), 132.9 (CH), 128.5 (CH), 128.5 (CH), 127.8 (CH), 126.2 (CH), 44.3 (CH), 43.2 (CH); *m*/*z* HRMS (ES^+) MH^+ calculated for $C_{13}H_{12}NOS$

230.0647, observed 230.0640. Assay of enantiomeric excess: (t_R (minor) = 22.8 min, t_R (major) = 26.8 min) 72% ee.

4.3.15. ((2*R*,3*S*)-3-Phenylaziridin-2-yl)(4-methylthiophen-2-yl) methanone 3l

Using enone **2l**, afforded aziridine **3l** (12 mg, 46%) as a yellow oil; $[\alpha]_D^{23} = -536.4$ (*c* 0.22, MeOH); ν_{max}/cm^{-1} (ATR) 1644, 1421, 1266, 1213, 756; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, Ar*H*), 7.38–7.32 (6H, m, 6 × Ar*H*), 3.37 (1H, d, *J* 2.0, C*H*NH), 3.26 (1H, d, *J* 2.0, C*H*NH), 2.31 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 188.2 (C), 142.3 (C), 139.4 (C), 138.3 (C), 134.8 (CH), 130.8 (CH), 128.5 (CH), 127.9 (CH), 126.2 (CH), 44.3 (CH), 43.2 (CH), 15.6 (CH); *m*/*z* (CI^+ (NH_3)) 244 (M^+, 100%); HRMS (CI^+ (NH_3)) M^+ calculated for $C_{14}H_{14}NOS$ 244.0796, observed 244.0807. Assay of enantiomeric excess: (t_R (minor) = 18.5 min, t_R (major) = 25.4 min) 77% ee.

4.3.16. (2*R*,3*S*)-3-Phenylaziridin-2-yl)(5-chlorothiophen-2-yl) methanone 3m

Using enone **2m**, afforded aziridine **3m** (16 mg, 27%) as a white solid; mp 83–85 °C; $[\alpha]_D^{22} = -311.1$ (*c* 0.54, MeOH); ν_{max}/cm^{-1} (ATR) 1634, 1427, 1271, 1019, 833; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 4.1, Ar*H*), 7.40–7.33 (5H, m, 5 × Ar*H*), 7.01 (1H, d, *J* 4.1, Ar*H*), 3.32 (1H, d, *J* 2.1, C*H*NH), 3.28 (1H, d, *J* 2.1, C*H*NH), 2.25 (1H, br, N*H*); δ_C (125 MHz, $CDCl_3$) 187.3 (C), 141.3 (C), 141.1 (C), 138.0 (C), 132.5 (CH), 128.6 (CH), 128.0 (CH), 128.0 (CH), 126.2 (CH), 43.8 (CH), 43.4 (CH); *m*/*z* HRMS (ES^+) MH^+ calculated for $C_{13}H_{11}NOSCl$ 264.0252, observed 264.0252. Assay of enantiomeric excess: (t_R (major) = 15.9 min, t_R (minor) = 20.2 min) 64% ee.

4.4. Preparation of *N*-aminoquininium tetraphenylborate 29

At first, $DppONH_2$ (180 mg, 0.77 mmol) was added in one portion to a stirred solution of quinine (250 g, 0.77 mmol) in THF (5 mL). A thick white precipitate formed after 5 min of stirring and THF (10 mL) was added to the mixture and stirred for 2 h. The mixture was then filtered and the residue was dried under vacuum to afford *N*-aminoquininium diphenylphosphinate as a white powder (0.19 g, 44%). A portion of the phosphinate (120 mg, 0.22 mmol) was dissolved in H_2O (20 mL) and a solution of $NaBPh_4$ (81 mg, 0.24 mmol) in H_2O (1.2 mL) was added to the mixture and a white solid precipitated out immediately. The mixture was left to stir for 40 min and then filtered and dried under reduced pressure overnight to afford *N*-aminoquininium tetraphenylborate **29** (77 mg, 54%) as a white solid; mp 115–120 °C; ν_{max}/cm^{-1} (ATR) 3200 br, 3055, 2961, 1621, 1589, 1509, 1472, 1429, 1242, 1137, 1073, 1031, 910, 859, 734, 707; δ_H (400 MHz; $CDCl_3$) 8.72 (1H, d, *J* 4.5, Ar*H*), 8.05 (1H, d, *J* 9.3, Ar*H*), 7.85 (1 h, m, Ar*H*), 7.55–7.65 (8H, m, 8 × Ph*H*), 7.45–7.36 (2H, m, 2 × Ar*H*), 7.12–7.20 (8H, m, 8 × Ph*H*), 6.93–7.0 (4H, m, 4 × Ph*H*), 5.63 (1H, s, 9-C*H*), 5.38 (1H, m, C*H*=CH_2), 5.07–4.98 (2H, m, CH=CH_2), 4.34 (1H, m, –C*H*–), 3.93 (3H, s, OCH_3), 3.56 (1H, m, –C*H*–), 3.28 (1H, m, –C*H*–), 3.18 (1H, m, –C*H*–), 2.86 (1H, m, –C*H*–), 2.74 (1H, m, –C*H*–), 2.17 (2H, m, 2 × –C*H*–), 2.02 (1H, m, –C*H*–), 1.88 (1H, m, –C*H*–), 1.42 (1H, m –C*H*–); δ_C (100 MHz; $CDCl_3$) 164.8, 158.6, 147.2, 143.6, 142.9, 136.1, 135.6, 131.7, 128.4, 126.3, 125.3, 122.4, 121.8, 119.0, 118.2, 100.7, 71.6, 67.1, 63.6, 58.2, 55.9, 38.8, 25.9, 25.6, 19.7, 18.6; *m*/*z* (ES^+) 340 (MH^+ -Ph_4B, 100%); HRMS (ES^+) calculated for $C_{20}H_{26}N_3O_2$ 340.2025, observed 340.2037.

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References

1. For a review see: Lowden, P. A. S. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; p 399.
2. For a review see: (a) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905; (b) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693; (c) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509; (d) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
3. For a review see: (a) Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chem. Asian J.* **2007**, *2*, 248; (b) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245; (c) Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2002**, *67*, 2101; (d) Subbarayan, V.; Ruppel, J. V.; Zhu, S.; Perman, J. A.; Zhang, X. P. *Chem. Commun.* **2009**, 4266.
4. For selected examples see (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328; (b) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450; (c) Wang, X.; Ding, K. *Chem. Eur. J.* **2006**, *12*, 4568.
5. Ma, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2005**, *70*, 10155.
6. Fukunaga, Y.; Uchida, T.; Ito, Y.; Matsumoto, K.; Katsuki, T. *Org. Lett.* **2012**, *14*, 4658.
7. For examples see (a) Aires-de-Sousa, J.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1996**, *37*, 3183; (b) Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron: Asymmetry* **2002**, *12*, 3349; (c) Fioravanti, S.; Mascia, M. G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2004**, *60*, 8073; (d) Murugan, E.; Siva, A. *Synthesis* **2005**, 2022; (e) Minakata, S.; Murakami, Y.; Tsuruoka, R.; Kitanaka, S.; Komatsu, M. *Chem. Commun.* **2008**, 6363.
8. For examples see: (a) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329; (b) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem. Eur. J.* **2011**, *17*, 7904; (c) Deiana, L.; Zhao, G.-L.; Lin, S.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 3201; (d) Desmarchelier, A.; Pereira de Sant'Ana, D.; Terrasson, V.; Campagne, J. M.; Moreau, X.; Greck, C.; Marcia de Figueiredo, R. *Eur. J. Org. Chem.* **2011**, 4046; (e) Vesely, J.; Ibrahem, I.; Zhao, G. L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778.
9. (a) Menjo, Y.; Hamajima, A.; Sasaki, N.; Hamada, Y. *Org. Lett.* **2011**, *13*, 5744; (b) Jiang, H.; Holub, N.; Anker Jørgensen, K. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20630; (c) De Vincentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. *Chem. Asian J.* **2010**, *5*, 1652; (d) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703.
10. Ikeda, I.; Machii, Y.; Okahara, M. *Synthesis* **1980**, 650.
11. Armstrong, A.; Carbery, D. R.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Synlett* **2006**, 2504.
12. Xu, J.; Jiao, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1491.
13. Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 8005.
14. Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351.
15. Armstrong, A.; Ferguson, A. Beilstein. *J. Org. Chem.* **2012**, *8*, 1747.
16. Armstrong, A.; Pullin, R. D. C.; Jenner, C. R.; Scutt, J. N. *J. Org. Chem.* **2010**, *75*, 3499.
17. Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178.
18. Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.
19. Dave, R.; Sasaki, N. A. *Org. Lett.* **2004**, *6*, 15.
20. Kawaguchi, M.; Ohashi, J.; Kawakami, Y.; Yamamoto, Y.; Oda, J. *Synthesis* **1985**, 701.
21. Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3784.
22. Johansson, C. C. C.; Bremeyer, N.; Ley, S. V.; Owen, D. R.; Smith, S. C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6024.
23. Hintermann, L.; Schmitz, M.; Englert, U. *Angew. Chem. Int. Ed.* **2007**, *46*, 5164.
24. Hutchison, D. R.; Khau, V. V.; Martinelli, M. J.; Nayyar, N. K.; Peterson, B. C.; Sullivan, K. A. *Org. Synth.* **1998**, *75*, 223.
25. Bucher, C.; Sparr, C.; Schweizer, W. B.; Gilmour, R. *Chem. Eur. J.* **2009**, *15*, 7637.
26. Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2085.
27. Brunner, H.; Bügler, J.; Nuber, B. *Tetrahedron Asymmetry* **1995**, *6*, 1699.
28. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.
29. For a review see: Connon, S. J. *Chem. Commun.* **2008**, 2499.
30. For aminocatalytic epoxidations of cyclic enones using salts of **23b** see: Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070.
31. For aminocatalytic epoxidations of acyclic enones using salts of **23b** see: Reisinger, C. M.; Wang, X. W.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 8112.
32. For a review see: Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614.
33. Nakano, A.; Kawahara, S.; Akamatsu, S.; Morokuma, K.; Nakatani, M.; Iwabuchi, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron* **2006**, *62*, 381.

34. (a) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121; (b) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.
35. Pniewska, B.; Suszko-Purzycka, A. *Acta. Cryst.* **1989**, *C45*, 638.
36. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 863857. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
37. Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3565.
38. Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879.
39. Demir, A. S.; Sesenoglu, Ö.; Ülkü, D.; Arici, C. *Helv. Chim. Acta* **2004**, *87*, 106.

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