Dihydroisoquinolinium salts: catalysts for asymmetric epoxidation

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A range of dihydroisoquinolinium salts has been prepared and tested as asymmetric epoxidation catalysts in an investigation of the reaction mechanism and the factors affecting enantioselectivity in this process.

Introduction

Optically active epoxides are important building blocks in asymmetric synthesis.[1] Due to their high versatility, they have frequently been employed as key intermediates in synthesis. In addition, the epoxide functionality is itself found as part of the structure of many biologically active compounds and natural products.[2] Over recent years, a number of research groups around the world have worked towards the development of methodologies to access chiral epoxides with high enantioselectivity. The greatest impact in the construction of chiral epoxides has been made with the introduction of catalytic systems. The most popular precursors remain olefins, but approaches have been also made which involve carbonyl compounds as the starting materials.[3] Undoubtedly the best-known catalytic process is that of Sharpless for the epoxidation of allylic alcohols, usually with greater than 90% ee.[4]

Attempts have also been made to mimic the biosynthetic pathway of epoxide formation using cytochrome P450 analogues, which are based on chiral porphyrin–transition metal complexes.[5] Although a plethora of chiral complexes based upon cyclic polyamines/polyimines has been synthesized,[6] the enantioselectivities have remained low. Limited generality has been observed, styrenes usually being the best substrates, and this restricts the applicability of the method.[7]

Chiral salen complexes of transition metals,[8] which bear some similarity to porphyrin systems, have been developed by Jacobsen,[9] Katsuki and others as catalysts for asymmetric epoxidation. A high degree of substrate specificity is observed however, for example, tetrasubstituted[10] and acyclic *E*-alkenes[11] tend to give lower ees than trisubstituted and aryl alkenes.[12] More seriously, the reaction is not stereospecific, leading to loss of the geometry around the former double bond, particularly in the case of aryl alkene substrates. Jacobsen and co-workers have, however, developed a modification to allow the generation of *trans* epoxides as the major products derived from *Z*-alkene substrates by addition of cinchona alkaloid-derived salts.[13]

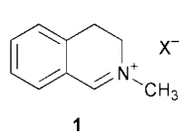
Catalytic asymmetric epoxidation has also been studied using purely organic molecules as the mediators. Chiral peracids are of limited value for asymmetric epoxidation,[14] and an asymmetric version of the analogous Payne epoxidation procedure, mediated by nitrile and hydrogen peroxide, has provided high ees only when using as mediator a nitrile derived from a relatively inaccessible chiral helicene.[15]

The Julia–Colonna asymmetric epoxidation reaction employs alkaline hydrogen peroxide and a chiral polypeptide derived from a naturally occurring amino acid, typically leucine. Good to excellent enantioselectivities are obtained, but essentially only for α,β-unsaturated ketone substrates with aryl substituents. Further, the process is not homogeneous, but multiphasic. These features again limit the potential of this method as a synthetic tool for the construction of chiral epoxides from a more general pool of substrates.[16]

Chiral dioxiranes, generated by the reaction of Oxone™ (Caroate) with chiral ketones, have also been developed as reagents for asymmetric epoxidation.[17] Until recently, however, the enantioselectivities obtained with these chiral oxidants were only moderate.[18] Over the last three years, independent work by Yang, Shi, and Armstrong has identified chiral ketones whose derived dioxiranes are among the best chiral epoxidizing agents. Yang and co-worker's C_2 symmetric ketone in the presence of alkaline Oxone™, was shown to epoxidize *trans*-stilbene with 84% ee.[19] Under similar conditions, Armstrong and Hayter's chiral α-fluoro ketone mediates epoxidation of triphenylethylene with 83% ee.[20] Shi and co-worker's fructose derived chiral ketone catalyses the asymmetric epoxidation of a wide variety of alkenes, including allylic and homoallylic alcohols and ethers, with good to excellent enantioselectivities.[21]

Oxaziridines are the nitrogen analogues of dioxiranes, and constitute an important class of organic oxidants under non-aqueous conditions. Indeed, Davis and co-worker's oxaziridines[22] and related systems[23] are very successful in the asymmetric oxidation of sulfides to sulfoxides, but are much less successful with less potent nucleophilic substrates such as alkenes.

Oxaziridinium salts, a related electrophilic oxygen source first reported in 1976,[24] and subsequently investigated by Lusinchi and co-workers,[25] have been shown to be extremely reactive for oxygen transfer to nucleophilic substrates, including sulfides and alkenes.[26] These organic salts were prepared either by quaternization of the corresponding oxaziridines or by peracid oxidation of iminium salts. More importantly, dihydroisoquinolinium salts **1** were shown to catalyse the epoxidation of simple olefins, the corresponding racemic oxaziridinium salts **2** (R = R′ = H) being presumed to be the active oxidants.[27]



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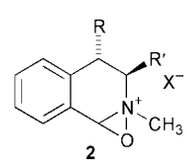

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The first enantiomerically pure oxaziridinium salt **2** (R = Ph, R′ = Me; X = BF_4^-) was prepared by quaternization of an oxaziridine derived from a chiral imine, prepared in turn in four steps from norephedrine.[28] This salt was shown to induce asymmetric epoxidation of alkenes, and furthermore the corresponding iminium salt was shown to catalyse epoxidation using Oxone™ as the stoicheiometric oxidant; ees of up to *ca.* 40% have been obtained. No *cis*-epoxide products are observed, suggesting a single-step oxygen transfer process. More recently, Aggarwal and Wang have reported the similar catalytic asymmetric epoxidation of simple alkenes mediated by a binaphthalene-derived iminium salt.[29] This system provided 1-phenylcyclohex-1-ene oxide with 71% ee and *trans*-stilbene oxide with 31% ee, also with complete retention of stereochemistry. Armstrong and co-workers have shown that even acyclic iminium salts can catalyse epoxidation by Oxone™.[30]

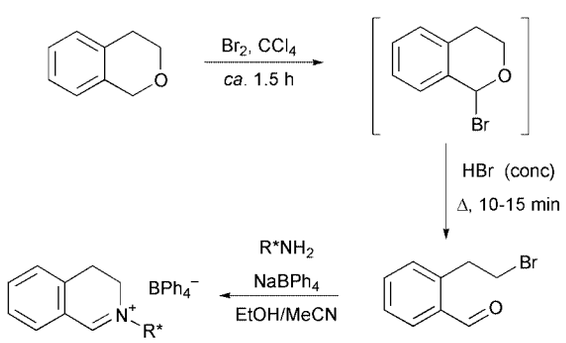
Perhaps because this process is relatively new, no thorough investigation of the parameters involved in this class of catalytic asymmetric process has yet been reported. We have previously described our approach to a new type of cyclic chiral iminium salt containing the asymmetric centres in an exocyclic substituent at nitrogen, and these iminium salts have been successfully employed in the catalytic asymmetric epoxidation of simple alkenes.[31] Herein we describe our examination of some of the parameters that influence the yield, enantioselectivity and reaction rate, and we discuss a possible mechanistic rationale for the process.

Results and discussion

Catalyst design and synthesis

The exocyclic group attached to the nitrogen atom of the oxaziridinium salt is invariably methyl or ethyl in the examples published prior to our own work and discussed above. The approach we have taken towards the design of this class of chiral catalysts is entirely different in concept. We reasoned that attachment of the controlling asymmetric centres (*e.g.* on exocyclic carbon atoms) to the iminium nitrogen atom would bring the asymmetric centre of the catalyst nearer to the site of the reaction, and might therefore be expected to lead to higher ees. Our preliminary experiments revealed that acyclic iminium salts derived for example from benzaldehyde and 2,4-dichlorobenzaldehyde do not promote the desired reaction to any reasonable extent because of their instability towards hydrolysis under the alkaline conditions employed in the reaction. These findings are in accord with the work of Armstrong *et al.*[30] We therefore chose cyclic iminium salts for investigation, and we selected the dihydroisoquinolinium nucleus as a basis for study.

Formally, such catalysts might be prepared through condensation of primary amines with a bromoaldehyde as shown in Scheme 1, a hitherto little-explored synthetic approach,[32] but

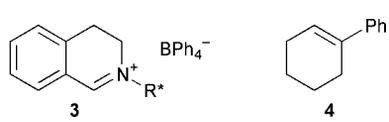


Scheme 1

one with the great advantage that a wide variety of readily available chiral primary amines can be used. The key intermediate, 2-(2-bromoethyl)benzaldehyde, was prepared according to the procedure of Rieche and Schmitz:[33] Bromination of isochromane yields the expected 1-bromoisochromane which may be isolated by distillation if required. Treatment of the initial product with concentrated aqueous HBr furnishes the desired bromoaldehyde in good yield (85%); it may also be purified by distillation, but the crude product (*ca.* 80% pure, contaminated principally by 2-vinylbenzaldehyde) can be used with equal success in most cases. Cyclocondensation directly with the appropriate amine takes place, generally at room temperature, to give the iminium salts in good yields.

This sequence has proved invaluable for the screening of asymmetric catalysts derived from a wide variety of chiral amines. Furthermore, the overall process employed in the synthesis of the catalyst is rapid, inexpensive, involves simple synthetic steps, does not require chromatography, and is easily scaled up. The catalyst preparations described below have been performed on scales of up to 70 g without any difficulties.

Chiral primary amines react smoothly and rapidly with 2-(2-bromoethyl)benzaldehyde to furnish the corresponding dihydroisoquinolinium bromide salts. These organic salts, with a few exceptions, are oils, and difficulties were encountered on attempting to purify them by conventional methods. This problem was solved by counter-anion exchange, which takes place readily simply by addition of an appropriate inorganic salt to the reaction mixture before work up. Fluoroborate, hexafluorophosphate, perchlorate, and periodate salts of these derivatives did not prove ideal, but the tetraphenylborate salts **3**, produced



3 **4**

by use of sodium tetraphenylborate, were most suitable: they are all solids, with the degree of crystallinity varying with the alkyl group of the parent amine. As a consequence of a side reaction, the elimination of hydrogen bromide from the bromoethyl moiety of the precursor, the yields are generally between 30 and 80%. Very hindered amines give inferior conversions, typically of the order of 20–30%, presumably due to their increased tendency to act as bases rather than nucleophiles, and indeed increased amounts of 2-vinylbenzaldehyde (and the corresponding imine) are observed in these cases. Nevertheless, the very small quantities required to catalyse the desired reactions more than compensate for the moderate yields and cost of some of the chiral amines screened. Typically, for the epoxidation of 1-phenylcyclohex-1-ene on a 3 mmol scale, less than eight milligrams of most catalysts were used for quantitative conversions within 1 hour. Overall, the synthesis of the catalyst and the asymmetric synthesis of epoxides together may usually be completed within eight hours.

Epoxidation reactions

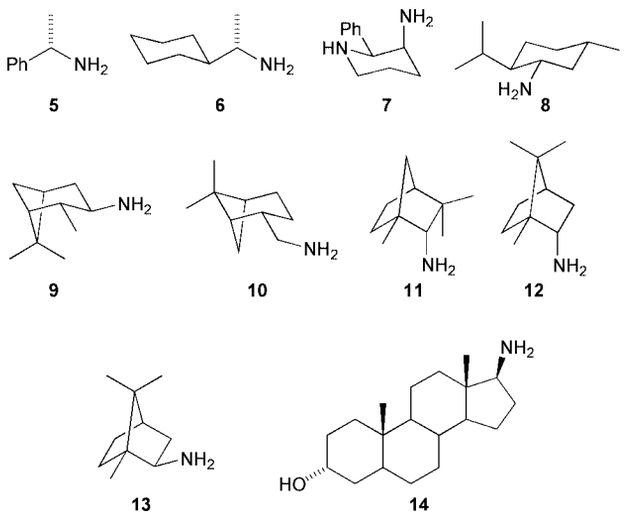
After some experimentation, optimum conditions were established for the catalytic asymmetric epoxidation of 1-phenylcyclohex-1-ene **4**: 0 °C in water–acetonitrile (1 : 1); typically 0.5 to 10 mol% of the dihydroisoquinolinium salt; two equivalents of Oxone™ and four equivalents of sodium carbonate. The results are summarized in Table 1 for a selection of primary amines **5**–**14**. Reactions were in general complete within the one hour timescale allowed, entries c and g (fenchyl) † being exceptions. It is important to note that blank reactions carried out in parallel under the same conditions, in the presence of Oxone™, but without catalyst, gave no reaction over up to eight hours when four equivalents of sodium carbonate were present.

† The IUPAC name for fenchyl is 1,3,3-trimethylbicyclo[2.2.1]heptyl; for myrtanyl is 6,6-dimethylbicyclo[2.2.1]hept-2-ylmethyl; for isobornyl is *exo*-bornyl and for isopinocampheyl is 2,6,6-trimethylbicyclo-[3.1.1]heptyl.

Table 1 Epoxidation of 1-phenylcyclohex-1-ene with dihydroisoquinolinium tetraphenylborate salts derived from chiral amines[a]

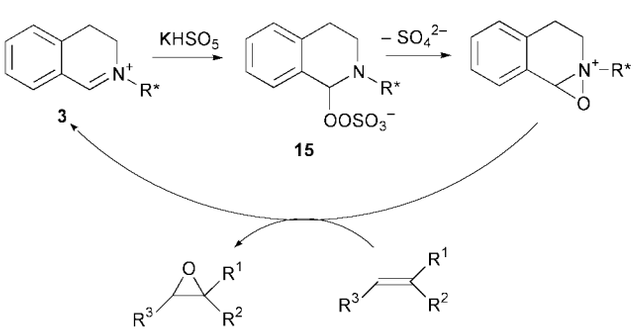
Entry	Amine precursor[39]	Catalyst load (mol%)	Yield (%)	Ee (%)[40]	Configuration[41]
a	**5**	5.0	54	0	
b	**6**	5.0	70	0	
c	**7**	1.0	39	25	(−)-(*S*,*S*)
d	**8**	0.5	63	19	(+)-(*R*,*R*)
e	**9**	0.5	68	27	(+)-(*R*,*R*)
f	**10**	0.5	66	12	(−)-(*S*,*S*)
g	**11**	0.5	45	32	(+)-(*R*,*R*)
h	**12**	0.5	60	18	(+)-(*R*,*R*)
i	**13**	0.5	58	8	(+)-(*R*,*R*)
j	**14**	0.5	47	14	(−)-(*S*,*S*)

[a] Conditions: 4 equiv. Oxone™; 8 equiv. Na_2CO_3; 0 °C; H_2O–MeCN 1 : 2; reactions were monitored by TLC.



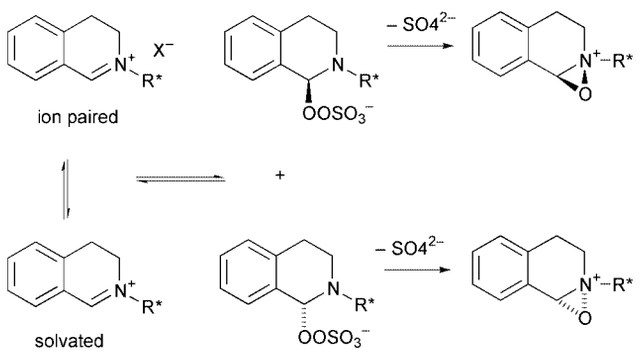
There is therefore no significant competition under these reaction conditions from achiral epoxidation processes, such as Payne-type oxidation mediated by the acetonitrile solvent, and indeed the epoxidation reaction does proceed in dichloromethane as solvent in the absence of acetonitrile.

A possible catalytic cycle for an oxaziridinium ion as the oxidative intermediate is depicted in Scheme 2. The first stage is



Scheme 2

the formation of an initial adduct **15**, uncharged at nitrogen, formed by (probably reversible) nucleophilic attack of the oxidant on the iminium salt **3**; this reaction would be expected to be retarded in polar solvents. This is followed by irreversible expulsion of sulfate to give the oxaziridinium ion, a reaction which would be expected to be accelerated in polar solvents, but which is we believe the rate-determining step under our reaction conditions. Oxygen may then be transferred to a substrate in a subsequent step, the rate of which would not be expected to have any great solvent dependence. An interesting but complicating feature of these processes is that it is not one but two diastereoisomeric oxaziridinium salts which may be formed, by attack of oxidant at the *Si* or *Re* face of the iminium species



Scheme 3

(Scheme 3). Each may deliver the oxygen atom to either of the prochiral faces of the alkene substrate with a different degree of enantiocontrol, and they may be in competition for the alkene substrate. Further, even if oxaziridinium ion is the oxidative intermediate, it remains unclear whether these epoxidation reactions proceed through spiro or planar transition states,[34] although recent theoretical work provides evidence for the spiro transition state.[35]

With the first two entries in Table 1, using the structurally simplest amines, no asymmetric induction was observed, and it became clear that a conformationally more defined and rigid system was required to impart reasonable enantioselectivities. The catalyst corresponding to entry c (the *cis*-3-amino-2-phenylpiperidine system) appears to decompose under the reaction conditions, perhaps accounting for the incomplete conversion. Acyclic iminium salts are unstable towards hydrolysis under our reaction conditions. It may be in this case that the cyclization to give the iminium salt is less favourable due to steric and/or conformational restrictions in the piperidine derivative.

Both camphor-based (entries h, i) and menthyl (entry d) systems gave disappointing ees, although these are two of the more common systems upon which chiral auxiliaries and catalysts have been based, often imparting high selectivity. The factors which determine enantioselectivities remain unclear, since the myrtanyl† system (entry f), which has its asymmetric centres relatively remote from the reaction site, provides greater selectivity than does the isobornyl† system (entry i). It is clear from the cases examined that increased steric hindrance near the reaction site is important, but is not the only factor which governs enantioselectivity. For example, the fenchyl derivative (entry g), which is the most sterically demanding, gave the best enantioselectivity under these conditions, albeit at the expense of the apparent rate of the process. The *N*-(isopinocampheyl)† dihydroisoquinolinium salt (entry e), which has considerably less steric requirements than the fenchyl, is however almost as selective, although in a faster reaction. Further, it is significantly more selective than the camphor, menthyl and steroidal systems, all of which are of similar or higher steric demand,

Table 2 Effect of counter-ion on epoxidation of 1-phenylcyclohex-1-ene with dihydroisoquinolinium salts derived from amine **9**[a]

Entry	Counter-ion	Ee (%)[40]	Configuration[41]
a	BPh_4	40	(+)-(*R*,*R*)
b	BF_4	28	(+)-(*R*,*R*)
c	PF_6	28	(+)-(*R*,*R*)
d	ClO_4	20	(+)-(*R*,*R*)
e	IO_4	35	(+)-(*R*,*R*)

[a] Conditions: 5 mol% catalyst; 2 equiv. Oxone™; 4 equiv. Na_2CO_3; 0 °C; H_2O–MeCN 1:1; reactions were monitored by TLC. Reactions were judged to be complete when all alkene had been consumed (≤45 min in all cases).

despite the similarity in the yields obtained after a one hour reaction time between all these systems.

The reaction parameters

An examination of some of the reaction parameters was carried out in order to optimize the reaction conditions with respect to the enantioselectivity of the oxygen transfer process. The isopinocampheylamine derivative exhibited one of the best profiles in terms of ees and rates; further, both enantiomeric forms of the chiral amine are commercially available. For these reasons it was chosen as the model catalyst for optimization studies and for investigation of parameters that may influence the enantioselectivity of the catalytic reaction.

Effect of counter-ion. Although in several cases we were unable to isolate tetrafluoroborate salts by anion exchange of the iminium bromides, the isopinocampheylamine-derived dihydroisoquinolinium salt was successful in forming precipitates with a variety of counter-ions. Thus, in addition to the original tetraphenylborate, the corresponding tetrafluoroborate, hexafluorophosphate, perchlorate and periodate salts were also prepared. The latter two were formed in somewhat better yields than the fluorine-containing examples.

All of the salts were tested in the asymmetric catalytic epoxidation of 1-phenylcyclohex-1-ene (Table 2). A catalyst loading of 5 mol% was used in 1:1 water–acetonitrile solvent in the presence of two equivalents of Oxone™ and four equivalents of sodium carbonate at 0 °C. The enantioselectivities obtained exhibited an interesting trend. The periodate salt produced an enantioselectivity (35%) comparable to those obtained with the tetraphenylborate species (40% ee), while the fluoride-containing counter-ions afforded lower ees (28%). The perchlorate salt furnished inferior enantioselectivities (20% ee). All of the salts however invariably produced the same enantiomer of the epoxide product (*R*,*R*) as the major component, and all of the reactions were complete within the same time scale, *ca*. 45 minutes. Control experiments were carried out to prove that neither perchlorate nor periodate were acting as oxidants towards either the substrate or the iminium salt under the reaction conditions. Although the differences in ees observed are not large, they are reproducible, and this behaviour would be consistent with the existence of the catalyst in the reaction medium as ion pairs, with the tightness of electrostatic bonding depending upon the relative polarizability of each counter-ion. Single crystal X-ray analysis of the isopinocampheyl tetraphenylborate catalyst suggests the presence of π-stacking between the dihydroisoquinoline unit and one phenyl group of the counter-ion. Presumably the counter-ion moderates the intrinsic enantioselectivity of the oxaziridinium species by providing an additional contribution to the activation barrier leading to the two diastereoisomeric transition states.

Effect of the solvent system. An increase in water to acetonitrile ratio is accompanied by an increase in the reaction rate. The effect is more pronounced when small amounts of catalysts are used. Thus, with the isopinocampheylamine derivative (entry e) (0.5 mol%), the yield of 1-phenylcyclohex-1-ene oxide was approximately 30% after one hour at 0 °C when a 1:1 ratio of the two solvent was used, but the yield was essentially quantitative at 2:1 (water–acetonitrile). Reducing the amount of Oxone™ and base by a factor of 2 (*i.e.* using one equivalent of Oxone™ and two equivalents of sodium carbonate), resulted in incomplete conversion after one hour in the improved (2:1) solvent system. In accord with previous suggestions,[17,19,21,36] this may result from competitive decomposition of Oxone™ under the basic conditions, and hence, in a faster reaction, more of the unstable oxidant is consumed in the desired oxygen transfer process. Higher catalyst loadings accelerate the rate of the reaction to an extent that outweighs the effect of water content. Thus, when the water content was varied successively from 10 to 50 to 66 and finally to 90% in acetonitrile with 5 mol% catalyst loading (perchlorate salt), all reactions indicated complete consumption of 1-phenylcyclohex-1-ene within 20 minutes. This change in solvent composition did not however influence the enantioselectivity of the reaction: for example, all reactions of the perchlorate salt in acetonitrile–water produced 1-phenylcyclohex-1-ene oxide with 18–20% ee with remarkable consistency.

This dramatic effect of the presence of water on the rate of the reaction is perhaps a result of increasing Oxone™ solubilization with increasing water concentration, such that nucleophilic attack by persulfate on the iminium species is speeded up, leading to a concentration effect coupled with better solvation of departing sulfate ion.

Such an apparent rate change without change in enantioselectivity suggests that the rate-determining step does not involve oxygen transfer to the substrate, *i.e.* that the subsequent enantiocontrolling oxygen transfer to alkene is not the rate-determining step under these conditions, and is consistent with the catalytic cycle outlined in Scheme 2.

We have briefly investigated any potential correlation of reaction rates and extent of asymmetric induction with the polarity of the co-solvent, as this could prove useful in clarification of the reaction mechanism and therefore the factors that control the enantioselectivity of the process. The co-solvents used were selected so that they differed significantly in dielectric constant (ε, indicated by the values in brackets): dichloromethane (8.9), trifluoroethanol (26.7), acetonitrile (37.5), water (78.4), formamide (111).

The epoxidation of 1-phenylcyclohex-1-ene with the isopinocampheyl catalyst (entry e) (10 mol%) was tested using these co-solvents with water in 1:1 ratio (Table 3). In order also to examine the counter-ion effect, the catalyst was tested both as its perchlorate and tetraphenylborate salts (20 and 40% ee respectively, in acetonitrile). The perchlorate salt exhibited an interesting trend. In trifluoroethanol, it mediated the epoxidation of 1-phenylcyclohex-1-ene within 30 minutes with quantitative conversion and 26% ee, while in dichloromethane the reaction was unusually slow (50% conversion after three hours), but the ee of the epoxide was still increased to 33%. In formamide however there was no reaction, and this was also the case for the tetraphenylborate salt. The lack of reaction in formamide regardless of the counter-ion involved perhaps suggests that the iminium species are too well stabilized/solvated, and the possibility of an irreversible attack by the formamide cannot be dismissed. Oddly, while the reaction proceeds slowly in DMF (65% conversion after 4 hours), the epoxide product is racemic. The tetraphenylborate salt mediated the same reaction in trifluoroethanol within the expected time scale (20–30 minutes) and with the same ee as the perchlorate salt (26%). In the chlorinated solvent system however, no reaction was manifested even after three hours. The difference in reactivity for both counter-ions with dichloromethane as the co-solvent reflects the poor miscibility of the two solvents, which must severely

Table 3 Effect of cosolvents on epoxidation of 1-phenylcyclohex-1-ene with dihydroisoquinolinium salts derived from amine **9**[a]

Entry	Cosolvent	Counter-ion	Time/h	Conversion (%)	Ee (%)[40]	Configuration[41]
a	CH_2Cl_2	ClO_4	3	50	33	(+)-(*R*,*R*)
b	CF_3CH_2OH	ClO_4	0.5	100	26	(+)-(*R*,*R*)
c	CH_3CN	ClO_4	0.5	100	20	(+)-(*R*,*R*)
d	H_2NCHO	ClO_4	3	0	—	
e	CH_2Cl_2	BPh_4	3	0	—	
f	CF_3CH_2OH	BPh_4	0.5	100	26	(+)-(*R*,*R*)
g	CH_3CN	BPh_4	0.5	100	40	(+)-(*R*,*R*)
h	H_2NCHO	BPh_4	3	0	—	

[a] Conditions: 10 mol% catalyst; 2 equiv. Oxone™; 4 equiv. Na_2CO_3; 0 °C; H_2O–solvent 1 : 1; reactions were monitored by TLC. Conversion measured by ^1H NMR spectroscopy.

limit the availability of the inorganic oxidant in the organic phase.

The epoxidation reaction was also tested using the periodate salt in trifluoroethanol, and again produced the epoxide with 26% ee, leading inexorably to the conclusion that since the other parameters were kept constant, generation of a trifluoroethoxide counter-ion may occur in all three cases under the reaction conditions (pK_A of CF_3CH_2OH = 12.37).[37]

Effect of temperature. The effect of this parameter on the reaction is also difficult to study over a wide range. This is partly due to the instability of Oxone™ under alkaline conditions, which increases at higher temperatures, and partly due to the freezing point of aqueous solvent mixtures and to reagent solubility below 0 °C.

When the solvent system used was of high acetonitrile to water ratio (1 : 1), the reaction at −10 °C was sluggish as the solubility of the inorganic oxidant and base in water is dramatically decreased at that temperature. As indicated above, we have found that a high water content in the solvent system does not adversely affect the enantioselectivities and also speeds up the reaction; we therefore repeated the oxidation at −10 °C using an increased proportion of water (3 : 1 water–acetonitrile); a separate acetonitrile phase is seen at both 0 and −10 °C. Oxidation of 1-phenylcyclohex-1-ene mediated by the isopinocampheylamine-derived dihydroisoquinolinium tetraphenylborate salt (5 mol%) resulted, within 45 minutes, in complete consumption of the starting material, and afforded the corresponding epoxide in slightly improved yield. The enantioselectivity (*ca.* 35%) was very little reduced below that obtained at 0 °C (40%).

In order to double check on the apparent insensitivity of the reaction selectivity to temperature, the oxidation was also conducted at a lower catalyst loading. Thus, with 0.5 mol% of the same catalyst, the selectivities exhibited at 0 and −10 °C were again essentially the same (26–28% ee). In the absence of the cooling bath, the temperature of the reaction mixture reaches up to 32 °C, perhaps due to the exothermicity of the neutralization of Oxone™ by the sodium carbonate, and ambient temperature is then slowly attained. When the oxidation was repeated over this temperature range (27–32 °C), negligible conversion to the epoxide after 1 hour was detected. This unexpected failure of the catalysed process at moderately increased temperature may be due to instability of the oxaziridinium species or of Oxone™ at higher temperatures.[38] Indeed, in catalytic processes for alkene epoxidation where Oxone™ is used as the stoicheiometric oxidant (*e.g.* mediated by oxaziridinium salts or dioxiranes), reactions performed at above 0 °C are rare.[17–21] We have observed that Oxone™ gradually loses its efficacy on storage, even when kept cool.

Effect of catalyst loading. Catalyst loading was expected to be an important parameter in the reaction system in relation to conversion and perhaps also enantiomeric excess. The relationship in Fig. 1 was obtained for the isopinocampheyl derivative

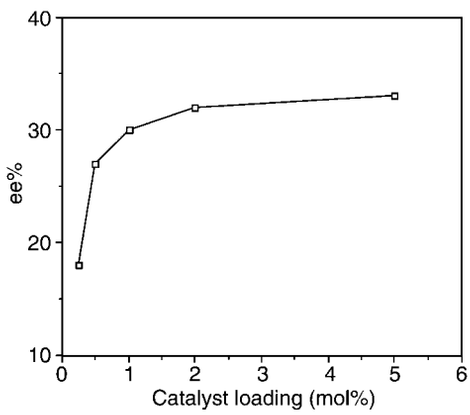


Fig. 1

using a fixed concentration of 1-phenylcyclohex-1-ene as substrate; it indicates that the enantioselectivity increases with increasing catalyst concentration, reaching a maximum at around 2 mol%.

The variation of ee in Fig. 1 suggests that the oxidation pathway is in some way dependent upon the mediator concentration, giving low enantioselectivity at lower catalyst loadings. However, as indicated above, blank reactions, carried out in the presence of Oxone™ but without catalyst under the same conditions gave no reaction. In the absence of any such achiral oxidation process, this behaviour is consistent with a breakdown of catalyst–counter-ion ion pairs at low catalyst concentration. Two diastereoisomeric adducts are possible upon (probably reversible) reaction of the catalyst with persulfate; the ratio of these diastereoisomeric adducts may vary with the degree of ion pairing in the catalyst. This ratio would be reflected in the ratio of the diastereoisomeric oxaziridine salts formed from the adducts by the irreversible loss of sulfate, presumed to be the rate determining step, and would affect the ee observed as enantioselectivity in the (fast) epoxidation step then arises from competition between these diastereoisomeric oxaziridine salts for the two enantiotopic faces of the alkene (Scheme 3). Doubling the alkene concentration from one to two molar while keeping the equivalence of base constant and the catalyst loading fixed at 5 mol% had a negligible effect upon the rate and enantioselectivity of the process, again supporting the conclusion that the alkene is not involved in the rate-determining step.

Effect of substrate structure. The isopinocamphenylamine-derived catalyst described here was tested with several aryl alkenes **16**–**21** as substrates (Table 4), chosen to provide a range of alkene substitution patterns. It is interesting that this system appears to offer a similar pattern of substrate structure–enantioselectivity relationship to that of the previously described iminium salt-catalysed epoxidation systems of Lusinchi and Aggarwal; thus *trans*-stilbene is a poor substrate, and 1-phenylcyclohex-1-ene the best, of those tested with our system.

Table 4 Epoxidation of unfunctionalized aryl alkenes with dihydroisoquinolinium salt derived from amine **9**[a]

Entry	Alkene	Yield (%)	Ee (%)[40]	Configuration[41]
a	**16**	68	8	(+)-(*R*)
c	**17**	75	10[42]	(+)-(*R*,*R*)[b]
d	**18**	72	15	(+)-(*R*,*R*)
e	**19**	43	5	(+)-(*S*)
f	**4**	68	40	(+)-(*R*,*R*)
g	**20**	34	3	(+)-(1*S*,2*R*)
h	**21**	73	20–63[43]	(−)[c]

[a] Conditions: 5 mol% catalyst; 2 equiv. Oxone™; 4 equiv. Na_2CO_3; 0 °C; H_2O–MeCN 1:1; reactions were monitored by TLC. Reactions were judged to be complete when all alkene had been consumed (≤45 min in all cases). [b] 10 mol% catalyst. [c] Absolute configuration unknown.

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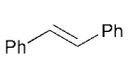
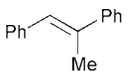
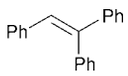


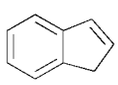
17



18



19



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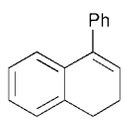

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Conclusion

In conclusion, we have examined a range of dihydroisoquinolinium salt epoxidation catalysts, effective at catalyst loadings as low as 0.5 mol%, providing up to *ca*. 40% ee in the epoxidation of alkenes. Investigation of some of the reaction parameters has thrown some light on the reaction mechanism, including the conclusion that the enantiocontrolling step involving transfer of oxygen to the substrate is not rate-determining. This conclusion suggests that the prospects for optimization of the process are good, since tuning of enantioselectivity may be possible without adverse effects upon the overall rate.

Experimental

General

Light petroleum ether (bp 40–60 °C), was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulfate or chloride. Dichloromethane was distilled over phosphorus pentaoxide or calcium hydride. Tetrahydrofuran was distilled under a nitrogen atmosphere from the sodium–benzophenone ketyl radical or from lithium aluminium hydride. Triethylamine and diisopropylethylamine were stored over potassium hydroxide pellets. Commercially available reagents were used as supplied, without further purification, unless otherwise stated. Air- and moisture-sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240 °C. This was allowed to cool in a desiccator over self-indicating silica gel pellets, under a nitrogen atmosphere. The reactions were carried out under a slight positive static pressure of nitrogen. Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230–400 mesh). Thin layer chromatography (TLC) was carried out on glass or aluminium plates coated with a silica gel layer of 0.25 mm thickness, containing fluorescer. Compounds were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate.

Microanalyses were performed on Carlo Erba or Perkin-Elmer instruments. Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at 589 nm, at the temperatures indicated and are reported in units of 10^{-1} deg cm^2 g^{-1}. Melting points were carried out on an Electrothermal-IA 9100 apparatus and are uncorrected. Infrared absorption spectra were recorded on a Perkin-Elmer FT-IR spectrometer Paragon 2001 instrument in the range of 4000–600 cm^{-1}. Mass spectra were recorded using Kratos MS-80 or JEOL-SX102 instruments using the electron impact ionization technique. Electrospray mass spectrometry was carried out using a Hewlett Packard Autoplatform instrument or by the EPSRC National Service. Proton nuclear magnetic resonance spectra were recorded on Bruker AC 200, AC 250, AC 300, and DPX 400 instruments, operating at 200.10, 250.13, 300.17, and 400.13 MHz respectively. Carbon-13 nuclear magnetic resonance spectra were recorded on Bruker AC 250 and DPX 400 instruments, operating at 62.86 and 100.62 MHz respectively.

Enantiomeric excesses were determined either by ^{1}H NMR spectroscopy in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [(+)-Eu(hfc)$_3$], as the chiral shift reagent, or by chiral HPLC analysis using Chiracel OD and Chiracel OJ columns mounted on a TSP Thermo-Separating-Products Spectra Series P200 instrument. The solvent system used was hexane–propan-2-ol (90:10 or 95:5), operating at a flow rate of 0.50 mL per minute, (pump pressure equivalent to *ca.* 80–135 psi), with the UV detector set at 254 nm.

2-(2-Bromoethyl)benzaldehyde[33]

Bromine (60 g, 0.37 mol) was added slowly over a period of 10 minutes to an ice cooled solution of isochromane (50 g, 0.37 mol) in carbon tetrachloride (200 mL) with stirring. After the exothermic reaction subsided, the cooling bath was removed and the dark brown solution heated under reflux until the reaction mixture became pale yellow, and liberation of HBr ceased (*ca.* 1.5 hours). The solution was then allowed to reach ambient temperature and the solvent removed under reduced pressure. To the yellow oil obtained (1-bromoisochromane), aqueous hydrobromic acid (48%, 75 mL) was added and the reaction mixture heated under reflux. After 10–15 minutes the solution was allowed to cool and extracted with diethyl ether (4 × 50 mL). The organic extracts were washed with water (2 × 30 mL) and dilute aqueous sodium bicarbonate, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure furnished crude 2-(2-bromoethyl)benzaldehyde as an orange oil approximately 85–90% pure (67.5 g, 65% yield). Analytically pure samples may be obtained by distillation under reduced pressure at *ca.* 150 °C and 0.5 mbar; chromatography is not recommended. Both the crude and the distilled compound can be used in the synthesis of dihydroisoquinolinium salts. ν_{max}/cm^{-1} (neat) 2742, 1697, 1600, 1575, 1260, 1193, 755; δ_H ($CDCl_3$, 400 MHz) 3.54–3.63 (4 H, m), 7.33 (1 H, d, *J* 8.0 Hz), 7.48 (1 H, t, *J* 7.5 Hz), 7.54 (1 H, t, *J* 8.0 Hz), 7.80 (1 H, d, *J* 7.5 Hz), 10.14 (1 H, s); δ_C (62.50 MHz) 33.17, 36.70, 128.10, 132.51, 134.14, 134.33, 134.88, 140.95, 193.33; *m*/*z* 211.98370; calcd for C_9H_9BrO: 211.98373.

General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl)benzaldehyde and primary amines

A solution of the amine or amino alcohol in ethanol (10 mL per g of amine) is added dropwise to 2-(2-bromoethyl)benzaldehyde (1.2 equiv.; 1.8 equiv. if crude material is used), externally cooled using an ice bath. The reaction mixture is stirred for a few hours or overnight (depending on the amine used) while attaining ambient temperature. A solution of sodium tetraphenylborate (or any other anion exchanging salt, 1.10 equiv.) in the minimum amount of acetonitrile is added in one portion, and after 5 minutes the organic solvents are evaporated under reduced pressure. Ethanol is added to the residue, followed by water. The resulting solid is collected by filtration and

washed with additional ethanol followed by diethyl ether. If no solid materializes after the addition of water the suspension is allowed to settle, the ethanol–water phase is decanted, and the residue is macerated in hot ethanol. The organic salt may then precipitate but in rare cases does so only upon slow cooling of the hot alcoholic solution. If solubility problems arise, small amounts of acetonitrile may be added during this process.

(−)-2-[(1*S*)-1-Phenylethyl]-3,4-dihydroisoquinolinium tetraphenylborate

Amine **5** (1.00 g, 8.26 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (3.00 g, 14 mmol) according to the general procedure to give the salt as a pale yellow solid (1.92 g, 42%), mp 168–169 °C. $[a]_D^{20}$ −9.4 (*c* = 1.57, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1647, 1605, 1572; δ_H (CD_3CN, 400 MHz) 1.82 (3 H, d, *J* 6.9 Hz), 2.99 (2 H, t, *J* 7.6 Hz), 3.65–3.71 (2 H, m), 5.24 (1 H, q, *J* 6.8 Hz), 6.82 (4 H, t, *J* 7.2 Hz), 6.97 (8 H, t, *J* 7.4 Hz), 7.25–7.29 (8 H, m), 7.37 (1 H, d, *J* 7.6 Hz), 7.45 (5 H, m), 7.54 (1 H, t, *J* 7.6 Hz), 7.75 (1 H, t, *J* 7.6 Hz), 7.83 (1 H, d, *J* 7.6 Hz), 8.97 (1 H, s); δ_C (100 MHz) 17.61, 24.57, 46.96, 68.86, 121.53, 124.34, 125.30, 127.22, 127.96, 128.10, 129.05, 129.29, 130.83, 133.77, 135.37, 136.73, 138.01, 163.51, 164.57; *m*/*z* 236.14190; calcd for $C_{17}H_{18}N$: 236.14392.

(+)-(−)-2-[(1*S*)-1-Cyclohexylethyl]-3,4-dihydroisoquinolinium tetraphenylborate

Amine **6** (1.00 g, 7.86 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (3.00 g, 14 mmol) according to the general procedure to give the salt as a colourless solid (2.55 g, 58%), mp 178–180 °C. $[a]_D^{20}$ +22.5 (*c* = 1.36, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1641, 1603, 1573; δ_H (CD_3CN, 400 MHz) 1.00–1.04 (1 H, m), 1.18–1.27 (3 H, m), 1.44 (3 H, d, *J* 2.7 Hz), 1.60–1.79 (6 H, m), 1.92–1.94 (1 H, m), 3.16 (2 H, t, *J* 7.9 Hz), 3.83–3.87 (3 H, m), 6.83 (4 H, t, *J* 7.2 Hz), 6.98 (8 H, t, *J* 7.4 Hz), 7.25–7.29 (8 H, m), 7.44 (1 H, d, *J* 7.6 Hz), 7.51 (1 H, t, *J* 7.6 Hz), 7.74–7.79 (2 H, m), 8.67 (1 H, s); δ_C (100 MHz) 14.71, 24.41, 24.96, 25.17, 25.24, 27.89, 29.33, 39.55, 45.24, 72.60, 121.48, 124.21, 125.33, 128.00, 128.12, 133.48, 135.44, 136.96, 137.93, 163.53, 165.15; *m*/*z* 242.19090; calcd for $C_{17}H_{24}N$: 242.19086.

(+)-2-[(1*R*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate

exo-Bornylamine **13** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a colourless solid (0.65 g, 17%), mp 196–197 °C. $[a]_D^{20}$ +6.9 (*c* = 1.22, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1649, 1601, 1572; δ_H (CD_3CN, 400 MHz) 0.84 (3 H, s), 0.89 (3 H, s), 1.12 (3 H, s), 1.25–1.31 (1 H, m), 1.36–1.40 (1 H, m), 1.67–1.72 (1 H, m), 1.85–1.91 (2 H, m), 1.97 (1 H, t, *J* 4.3 Hz), 2.39–2.48 (1 H, m), 3.06–3.14 (2 H, m), 3.81–3.87 (1 H, m), 3.89–3.95 (2 H, m), 6.82 (4 H, t, *J* 7.2 Hz), 6.98 (8 H, t, *J* 7.4 Hz), 7.25–7.29 (8 H, m), 7.41 (1 H, d, *J* 7.6 Hz), 7.50 (1 H, t, *J* 7.6 Hz), 7.75 (1 H, t, *J* 7.6 Hz), 7.81 (1 H, d, 7.6 Hz), 8.81 (1 H, s); δ_C (100 MHz) 11.92, 19.09, 19.92, 24.52, 25.84, 33.19, 36.95, 44.39, 47.99, 50.92, 52.00, 77.91, 121.44, 124.64, 125.31, 127.89, 128.07, 133.71, 135.38, 135.45, 137.91, 163.57, 164.20; *m*/*z* 268.20690; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*S*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate

endo-Bornylamine **12** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a colourless solid (1.00 g, 26%), mp 198–200 °C. $[a]_D^{20}$ −33.2 (*c* = 1.53, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1645, 1600, 1575; δ_H (CD_3CN, 400 MHz) 0.96 (3 H, s), 0.98 (3 H, s), 1.00 (3 H, s), 1.22–1.28 (1 H, m), 1.47–1.51 (2 H, m), 1.65–1.70 (1 H, m), 1.85–1.91 (2 H, m), 2.29–2.36 (1 H, m), 3.11 (2 H, t, *J* 7.8 Hz), 3.81–3.88 (2 H, m), 4.24–4.27 (1 H, m), 6.82 (4 H, t, *J* 7.2 Hz), 6.97 (8 H, t, *J* 7.7 Hz), 7.25–7.28 (8 H, m), 7.44 (1 H, d, *J* 7.6 Hz), 7.51 (1 H, t, *J* 7.6 Hz), 7.75 (1 H, t, *J* 7.6 Hz), 7.85 (1 H, d, *J* 7.7 Hz), 8.67 (1 H, s); δ_C (100 MHz) 13.03, 17.35, 18.63, 24.59, 26.32, 26.63, 31.24, 43.85, 50.11, 51.54, 51.63, 76.34, 121.44, 124.63, 125.31, 127.90, 128.05, 133.71, 135.38, 137.19, 137.87, 163.49, 164.71; *m*/*z* 268.20660; calcd for $C_{19}H_{26}N$: 268.20651.

(+)-2-[(1*R*,2*R*,4*S*)-1,3,3-Trimethylbicyclo[2.2.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate

(+)-*endo*-Fenchylamine **11** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a colourless solid (2.33 g, 61%), mp 153–155 °C. $[a]_D^{20}$ +12.5 (*c* = 1.50, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1649, 1605, 1577; δ_H (CD_3CN, 400 MHz) 1.04 (3 H, s), 1.29 (6 H, s), 1.40–1.93 (7 H, m), 3.15 (2 H, t, *J* 8.0 Hz), 3.89–3.92 (2 H, m), 3.65 (1 H, s), 6.83 (4 H, t, *J* 7.2 Hz), 6.98 (8 H, t, *J* 7.5 Hz), 7.25–7.29 (8 H, m), 7.43 (1 H, d, *J* 7.6 Hz), 7.52 (1 H, t, *J* 7.6 Hz), 7.76 (1 H, t, *J* 7.6 Hz), 7.91 (1 H, d, *J* 7.6 Hz), 8.75 (1 H, s); δ_C (62.50 MHz) 18.48, 20.30, 24.34, 24.94, 25.52, 30.74, 40.56, 44.25, 48.07, 49.29, 51.25, 83.48, 121.50, 124.36, 126.43, 127.93, 128.10, 134.03, 135.87, 137.09, 137.98, 163.50, 164.94; *m*/*z* 268.20650; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate

Isopinocampheylamine **9** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a colourless solid (2.67 g, 70%), mp 238–240 °C. $[a]_D^{20}$ −24.7 (*c* = 1.36, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1639, 1600, 1574, 735, 710; δ_H (CD_3CN, 400 MHz) 1.12 (3 H, s), 1.18 (3 H, d, *J* 7.0 Hz), 1.33 (3 H, s), 1.95–2.00 (3 H, m), 2.12–2.15 (2 H, m), 2.42–2.60 (2 H, m), 3.24 (2 H, t, *J* 7.6 Hz), 4.08 (2 H, t, *J* 7.7 Hz), 4.54 (1 H, m), 6.86 (4 H, t, *J* 7.2 Hz), 7.01 (8 H, t, *J* 7.4 Hz), 7.28–7.32 (8 H, m), 7.49 (1 H, d, *J* 7.5 Hz), 7.56 (1 H, t, *J* 7.6 Hz), 7.80–7.84 (2 H, m), 9.09 (1 H, s); δ_C (100 MHz) 18.71, 22.15, 25.00, 26.95, 31.38, 33.07, 38.72, 39.66, 40.76, 44.62, 46.73, 89.18, 121.46, 124.71, 125.32, 127.93, 128.12, 133.42, 135.49, 136.96, 137.89, 163.55, 166.44; *m*/*z* 268.20590; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium periodate

Isopinocampheylamine **9** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a yellow solid (2.00 g, 67%), mp 159–161 °C (dec.). $[a]_D^{20}$ −14.5 (*c* = 3.50, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1648, 1608, 1576, 844; δ_H, δ_C (CD_3CN, 400 and 100 MHz respectively) identical with tetraphenylborate derivative within 0.06 ppm (except for the tetraphenylborate signals); *m*/*z* 268.20600; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium hexafluorophosphate

Isopinocampheylamine **9** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a colourless solid (1.56 g, 58%), mp 239–241 °C. $[a]_D^{20}$ −34.8 (*c* = 2.3, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1646, 1608, 1576, 877, 834; δ_H, δ_C (CD_3CN, 400 and 100 MHz respectively) identical with tetraphenylborate derivative within 0.09 ppm (except for the tetraphenylborate signals); *m*/*z* 268.20610; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium tetrafluoroborate

Isopinocampheylamine **9** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol)

according to the general procedure to give the salt as a colourless solid (1.20 g, 52%), mp 186–188 °C. $[\alpha]_D^{20}$ −33.6 (c = 2.5, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1645, 1606, 1577, 1062, 933, 776, 767; δ_H, δ_C (CD_3CN, 400 and 100 MHz respectively) identical with tetraphenylborate derivative within 0.07 ppm (except for the tetraphenylborate signals); *m*/*z* 268.20600; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium perchlorate

Isopinocampheylamine **9** (1.00 g, 6.52 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a colourless solid (1.47 g, 63%), $[\alpha]_D^{20}$ −36.0 (c = 2.4, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1645, 1606, 1576, 1086, 1051, 768, 623; δ_H, δ_C (CD_3CN, 400 and 100 MHz respectively) identical with tetraphenylborate derivative within 0.05 ppm (except for the tetraphenylborate signals); *m*/*z* 268.20590; calcd for $C_{19}H_{26}N$: 268.20651.

(−)-2-[(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl]-3,4-dihydroisoquinolinium tetraphenylborate

Menthylamine **8** (1.00 g, 6.44 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a pale yellow solid (1.44 g, 38%), mp 166–168 °C. $[\alpha]_D^{20}$ −28.1 (c = 1.71, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1643, 1605, 1576; δ_H (CD_3CN, 400 MHz) 0.79 (3 H, d, *J* 6.9 Hz), 0.94 (3 H, d, *J* 6.8 Hz), 0.96 (3 H, d, *J* 6.5 Hz), 1.21–1.25 (1 H, m), 1.45–1.49 (1 H, m), 1.51–1.68 (2 H, m), 1.70–1.82 (3 H, m), 1.84–2.00 (2 H, m), 3.13 (2 H, t, *J* 7.9 Hz), 3.83–3.89 (3 H, m), 6.81 (4 H, t, *J* 7.1 Hz), 6.98 (8 H, t, *J* 7.4 Hz), 7.25–7.28 (8 H, m), 7.42 (1 H, d, *J* 7.1 Hz), 7.50 (1 H, t, *J* 7.3 Hz), 7.74–7.77 (2 H, m), 8.74 (1 H, s); δ_C (100 MHz) 14.30, 19.87, 20.81, 22.33, 24.56, 26.01, 31.23, 32.93, 72.97, 121.47, 124.47, 125.31, 127.99, 128.13, 133.50, 135.44, 137.09, 138.06, 163.53, 165.76; *m*/*z* 270.22220; calcd for $C_{19}H_{28}N$: 270.22216.

(−)-2-{[(1*S*,2*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl]-methyl}-3,4-dihydroisoquinolinium tetraphenylborate

Myrtanylamine **10** (1.00 g, 6.52 mol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.5 g, 11.7 mmol) according to the general procedure to give the salt as a pale green solid (2.87 g, 75%), mp 173–174 °C. $[\alpha]_D^{20}$ −10.7 (c = 1.80, CH_3CN); ν_{max}/cm^{-1} (Nujol) 1651, 1604, 1574; δ_H (CD_3CN, 400 MHz) 1.13 (3 H, s), 1.28 (3 H, s), 1.57–1.58 (1 H, m), 1.94–2.05 (6 H, m), 2.47–2.49 (1 H, m), 2.65–2.67 (1 H, m), 3.13 (2 H, t, *J* 7.9 Hz), 3.83–3.86 (4 H, m), 6.87 (4 H, t, *J* 7.2 Hz), 7.02 (8 H, t, *J* 7.4 Hz), 7.29–7.33 (8 H, m), 7.46 (1 H, d, *J* 7.3 Hz), 7.54 (1 H, t, *J* 7.3 Hz), 7.77–7.80 (2 H, m), 8.68 (1 H, s); δ_C (100 MHz) 18.23, 22.05, 24.31, 24.95, 26.60, 32.25, 37.70, 37.91, 40.59, 42.89, 47.97, 65.62, 121.46, 124.14, 125.32, 128.03, 128.05, 133.30, 135.76, 136.49, 137.90, 163.54, 165.77; *m*/*z* 268.20650; calcd for $C_{19}H_{26}N$: 268.20651.

(+)-2-[(2*S*,3*S*)-2-Phenylhexahydropyridin-3-yl]-3,4-dihydroisoquinolinium tetraphenylborate

(2*S*,3*S*)-*cis*-3-Amino-2-phenylpiperidine **7** (1.00 g, 5.68 mmol) was treated with crude 2-(2-bromoethyl)benzaldehyde (2.20 g, 10.3 mmol) according to the general procedure to give the salt as a yellow solid (1.38 g, 40%), mp 172–174 °C (dec.). $[\alpha]_D^{20}$ +141.6 (c = 1.11, CH_3CN); ν_{max}/cm^{-1} (Nujol) 3320, 1634, 1603, 1576; δ_H (CD_3CN, 400 MHz) 1.91–1.98 (1 H, m), 2.24–2.33 (4 H, m), 2.47 (1 H, br s), 2.66–2.70 (1 H, m), 2.88–2.97 (2 H, m), 3.24 (1 H, m), 3.39 (1 H, m), 4.10 (1 H, m), 4.22 (1 H, m), 4.37 (1 H, m), 5.47 (1 H, br s), 6.88 (4 H, t, *J* 7.0 Hz), 7.02 (8 H, t, *J* 7.2 Hz), 7.26–7.36 (12 H, m), 7.40–7.42 (2 H, m), 7.49 (1 H, t, *J* 7.2 Hz), 7.72–7.79 (2 H, m), 9.86 (1 H, s); δ_C (100 MHz) 18.62, 24.40, 27.29, 45.71, 51.28, 61.52, 68.09, 121.51, 124.02, 125.36, 125.75, 127.72, 127.96, 128.07, 128.67, 133.65, 135.50, 136.24, 137.78, 139.07, 163.52, 167.40; *m*/*z* 291.18850; calcd for $C_{20}H_{23}N_2$: 291.18611.

(−)-2-[(3*R*,10*S*,13*S*,14*R*,17*S*)-3-Hydroxy-10,13-dimethyl-perhydrocyclopenta[*a*]phenanthren-17-yl]-3,4-dihydroisoquinolinium tetraphenylborate

Amine **14** (1.50 g, 5.15 mmol) was treated with 2-(2-bromoethyl)benzaldehyde (2.00 g, 9.38 mmol) according to the general procedure to give the salt as a colourless solid (0.41 g, 11%), mp 125–127 °C. $[\alpha]_D^{20}$ −1.2 (c = 1.33, CH_3CN); ν_{max}/cm^{-1} (Nujol) 3420, 1644, 1605, 1578; δ_H (CD_3CN, 400 MHz) 0.74 (3 H, s), 0.79 (3 H, s) 1.11–1.93 (22 H, m), 2.44 (1 H, m), 3.13 (2 H, m), 3.87–3.92 (4 H, m), 6.82 (4 H, t, *J* 7.2 Hz), 6.98 (8 H, t, *J* 7.4 Hz), 7.25–7.29 (8 H, m), 7.47 (1 H, d, *J* 7.3 Hz), 7.51 (1 H, t, *J* 7.4 Hz), 7.76–7.79 (2 H, m), 8.78 (1 H, s); δ_C (100 MHz) 10.92, 11.24, 20.07, 22.75, 24.13, 24.87, 28.10, 28.55, 32.02, 32.64, 35.37, 35.59, 35.84, 36.68, 38.82, 46.15, 51.34, 52.88, 53.92, 65.27, 79.72, 121.68, 124.68, 125.46, 128.18, 128.34, 133.82, 135.64, 137.37, 138.10, 163.48, 164.43; *m*/*z* 406.31100; calcd for $C_{28}H_{40}NO$: 406.31097.

General procedure for the catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts

Oxone™ (2 equiv.), is added to an ice-cooled solution of sodium carbonate (4 equiv.) in water (12 mL per 1.20 g of sodium carbonate or as appropriate to adjust the MeCN–H_2O ratio) with vigorous stirring, and the resulting foaming suspension is stirred for *ca*. 5 minutes until most of the effervescence subsides. The iminium salt (5–10 mol% with respect to the substrate) is added as a solution in acetonitrile (7 mL per 100 mg of catalyst), followed by the alkene substrate (1 equiv.), also as a solution in acetonitrile to adjust the MeCN–H_2O ratio (5 mL per 400 mg of alkene). Solid substrates are added directly to the reaction mixture after addition of further acetonitrile (5 mL per 400 mg of alkene). The suspension is stirred at 0 °C until the substrate is completely consumed as indicated by TLC. The reaction mixture is diluted with water until most of the inorganic material dissolves, and extracted four times with diethyl ether. The organic extracts are washed with water and brine, and then dried over sodium sulfate. Filtration and evaporation of the solvents provides the crude epoxides. Chromatography on a short column of silica gel, eluting initially with light petroleum to remove non polar impurities and/or unreacted parent alkene, followed by light petroleum–ethyl acetate (95 : 5), affords the purified epoxides.

1-Phenylcyclohexene oxide [12,44–46]

Treatment of 1-phenylcyclohex-1-ene **4** (0.50 g, 3.15 mmol) according to the general procedure afforded the epoxide as a colourless oil (0.36 g, 68%). ν_{max}/cm^{-1} (neat) 3084, 1602, 1495, 1446, 1359, 1249, 1173, 1132, 1079, 1030, 993, 974; δ_H ($CDCl_3$, 250 MHz) 1.22–1.35 (1 H, m), 1.53–1.64 (3 H, m), 1.99–2.06 (2 H, m), 2.16–2.18 (1 H, m), 2.26–2.32 (1 H, m), 3.10 (1 H, t, *J* 2.0 Hz), 7.28–7.44 (5 H, m); δ_C (62.50 MHz) 19.78, 20.09, 24.69, 28.15, 60.13, 61.84, 125.26, 127.12, 128.20, 142.80.

1-Phenyl-3,4-dihydronaphthalene oxide [42,47]

Treatment of 1-phenyl-3,4-dihydronaphthalene **21** (1.00 g, 4.85 mmol) according to the general procedure afforded the epoxide as a pale yellow solid (0.78 g, 72%), mp 104–106 °C (lit. 94–97 °C). ν_{max}/cm^{-1} (Nujol) 1602, 1486, 1307, 1155, 1074, 1042, 953; δ_H ($CDCl_3$, 250 MHz) 2.10 (1 H, td, *J* 13.7, 5.8 Hz), 2.49–2.60 (1 H, m), 2.77 (1 H, dd, *J* 15.5, 5.6 Hz), 2.98–3.06 (1 H, m), 3.71 (1 H, d, *J* 3.1 Hz), 7.11–7.31 (4 H, m), 7.45–7.61 (5 H, m); δ_C (62.50 MHz) 22.14, 25.43, 60.89, 62.98, 125.95, 127.68, 127.87, 128.07, 128.18, 128.58, 129.82, 134.99, 137.45, 138.82.

trans-Stilbene oxide [28,42,48,49]

Treatment of *trans*-stilbene **17** (1.00 g, 5.33 mmol) according to the general procedure afforded the epoxide as a colourless solid (0.82 g, 76%), mp 66–67 °C (lit. 61–63 °C). ν_{max}/cm^{-1} (Nujol) 1601, 1492, 1284, 1176, 1157, 1094, 1072, 1025; δ_H ($CDCl_3$, 400 MHz) 3.84 (2 H, s), 7.28–7.37 (10 H, m); δ_C (100 MHz) 63.28, 125.98, 128.62, 129.31, 137.60.

trans-α-Methylstilbene oxide [18]

Treatment of *trans*-α-methylstilbene **18** (1.00 g, 5.15 mmol) according to the general procedure afforded the epoxide as a colourless oil (0.64 g, 55%). ν_{max}/cm^{-1} (neat) 3061, 1602, 1495, 1449, 1381, 1279, 1157, 1118, 1065, 1027, 980; δ_H ($CDCl_3$, 400 MHz) 1.46 (3 H, s), 3.96 (1 H, s), 7.30–7.46 (10 H, m); δ_C (100 MHz) 17.14, 63.48, 67.52, 125.57, 126.92, 127.70, 127.93, 128.60, 129.21, 136.36, 142.75.

Indene oxide [50–52]

Treatment of indene **20** (0.50 g, 4.31 mmol) according to the general procedure afforded the epoxide as a colourless oil (0.30 g, 52%). ν_{max}/cm^{-1} (neat) 3027, 2917, 1482, 1464, 1390, 1372, 1232, 1183, 1142, 829, 758, 745, 723; δ_H ($CDCl_3$, 200 MHz) 2.97 (1 H, dd, *J* 18.1, 2.7 Hz), 3.21 (1 H, d, *J* 17.6 Hz), 4.13 (1 H, t, *J* 3.0 Hz), 4.26 (1 H, dd, *J* 2.8, 1.1 Hz), 7.14–7.29 (3 H, m), 7.49 (1 H, dd, *J* 6.6, 1.7 Hz); δ_C (100 MHz) 34.62, 57.64, 59.09, 125.22, 126.12, 126.28, 128.59, 140.99, 143.64.

2,2,3-Triphenylethylene oxide [21,43,53]

Treatment of triphenylethylene **19** (1.00 g, 3.90 mmol) according to the general procedure afforded the epoxide as a colourless oil which slowly solidified (0.44 g, 42%), mp 66–67 °C (lit. 75 °C). ν_{max}/cm^{-1} (neat) 3062, 3030, 2957, 2925, 2856, 1605, 1596, 1499, 1471, 1448, 1262, 1221, 741, 698, 621; δ_H ($CDCl_3$, 250 MHz) 4.40 (1 H, m), 7.10–7.47 (15 H, m); δ_C (62.50 MHz) 68.03, 68.34, 126.33, 126.75, 127.50, 127.55, 127.64, 127.70, 127.78, 127.83, 127.95, 128.20, 128.62, 135.42, 135.88, 141.12.

α-Methylstyrene oxide [15,54]

Treatment of α-methylstyrene **16** (1.00 g, 8.47 mmol) according to the general procedure afforded the epoxide as a colourless oil (0.72 g, 64%). ν_{max}/cm^{-1} (neat) 3034, 2958, 2929, 2872, 1604, 1496, 1447, 1381, 1343, 1061, 1027, 860, 759, 699; δ_H ($CDCl_3$, 250 MHz) 0.86 (3 H, d, *J* 6.6 Hz), 2.79 (1 H, dd, *J* 5.4, 0.8 Hz), 2.96 (1 H, d, *J* 5.4 Hz), 7.24–7.38 (5 H, m); δ_C (62.50 MHz) 21.74, 56.66, 56.93, 125.23, 127.37, 128.25, 129.00.

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41 Absolute configuration of major enantiomer of product. Absolute configurations were assigned by comparison of the sign of optical rotation with literature values.

42 This figure differs from that reported in our communication (see ref. 31).

43 In contrast to our earlier report (see ref. 31) the epoxide is in this case formed in the reaction mixture with 20% ee; a fractional crystallization occurs when using our standard work-up, resulting in isolation of the epoxide with up to 63% ee.

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