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Enantioselective Epoxidation of Dihydroquinolines by Using Iminium Salt Organocatalysts

Philip C. Bulman Page,*[a] David P. Day,[a] and Yohan Chan[a]

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The first examples of asymmetric epoxidation of dihydroquinoline substrates using iminium salt organocatalysts are reported. The 3,4-epoxytetrahydroquinoline products are obtained in good yields and with moderate to good enantioselectivities.

Introduction

The tetrahydroquinoline core motif is commonly found in a wide range of natural products; a recent review on tetrahydroquinolines by Menéndez[1] shows a surge in interest in this area of heterocyclic chemistry, with as many as 400 publications in the last 5 years. Some of the most interesting tetrahydroquinoline-derived natural products have shown potent biological activity, for example benzastatins (C and D) and virantmycin (**1**).[2] The natural products tuberosine B (**2**),[3] and helquinoline (**3**)[4] have recently been isolated, but their biological activity has not yet been reported. Drug molecules containing a tetrahydroquinoline ring system have also been reported to have antiviral (anti-HIV; **4**),[5] antitrypanosomal (**5**),[6] and multidrug resistance (**6**) properties (Figure 1).[7]

Synthesis of racemic or achiral tetrahydroquinolines has been achieved by diverse methodologies.[8] The generation of epoxides from various nitrogen-protected dihydroquinoline substrates has only previously been reported by utilizing *m*-CPBA,[9] or by hydrobromination with aqueous *N*-bromosuccinimide (NBS) followed by base-catalysed elimination.[10]

A limited number of methodologies have been used to achieve the asymmetric synthesis of non-racemic chiral tetrahydroquinolines.[11] Guingant achieved the synthesis of (*R*)-sumanirole, an anti-Parkinson's drug,[12] by using a chiral auxiliary carried on the nitrogen atom of a dihydroquinoline, and *m*-CPBA as the oxidant.[13] The catalytic asymmetric epoxidation of dihydroquinolines has, however, only very rarely been reported. The only examples in the literature were reported by Wuts,[14] in which just one dihydroquinoline was converted into the chiral 3,4-epoxytetrahydroquinoline by using both the Shi[15] and Jacobsen[16] protocols.

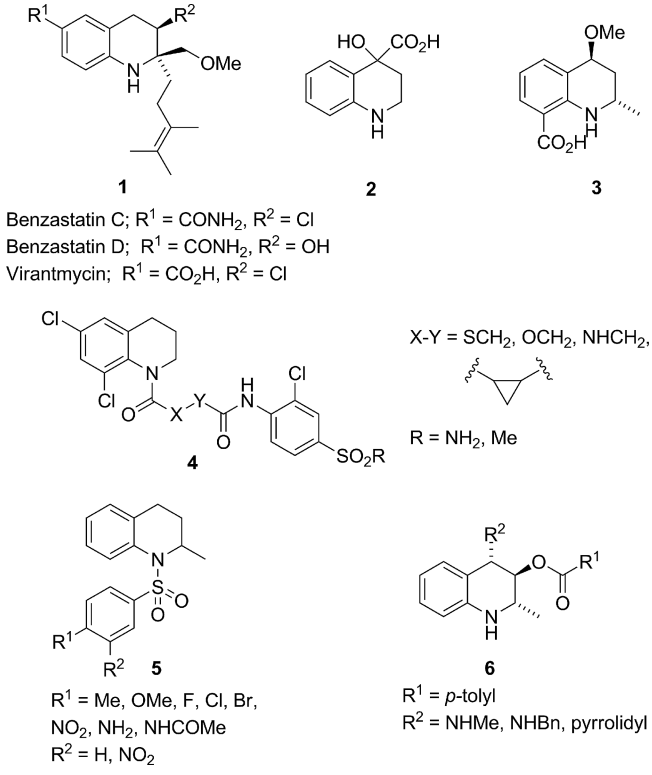

Figure 1. Structures of tetrahydroquinoline-derived natural products and pharmaceuticals.

Oxaziridinium salts, which were first reported by Lusinchi in 1976,[17] are usually prepared in situ by the action of oxone on the corresponding iminium salts. They are highly effective as catalytic oxidants.[18] We have achieved high enantioselectivities in the epoxidation of alkenes by using iminium salt catalysts, such as **7**,[19] **8**,[20] and **9**.[21] Epoxidation of *cis*-alkenes with tetraphenylphosphonium monoperoxysulfate[22] (TPPP) as the stoichiometric

[a] School of Chemistry, University of East Anglia, Norwich Research Park, Norwich, Norfolk NR4 7TJ, U.K.
E-mail: p.page@uea.ac.uk
www.uea.ac.uk/chemistry/people/profile/p-page

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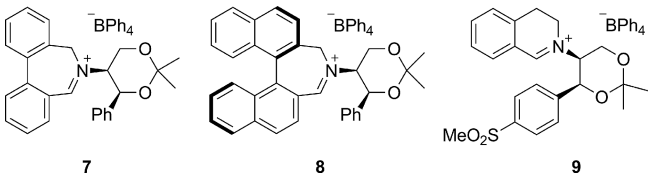
oxidant under non-aqueous conditions was particularly successful;[23] for example, scuteflorin A was obtained with 99% *ee* by using iminium salt **7** (Figure 2).[24]



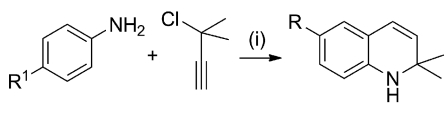
7 **8** **9**

Figure 2. Iminium salt catalysts.

Herein, we describe the first examples of asymmetric epoxidation of dihydroquinolines by using iminium salt catalysis, to afford 3,4-epoxy-tetrahydroquinolines in good conversions, yields and enantioselectivities.

Results and Discussion

Several approaches have been reported for the preparation of racemic or achiral dihydroquinolines.[9,25,26] A number of asymmetric syntheses are also known.[27] By using Ward's methodology,[26] we generated a number of dihydroquinolines **10**–**13** in moderate yields (Scheme 1).



10 R = CN, 30%
11 R = NO_2, 32%
12 R = Cl, 14%
13 R = H, 25%

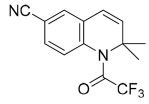
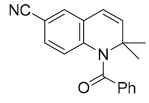
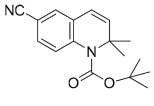
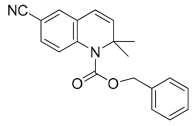
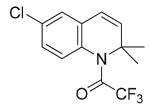
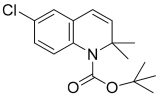
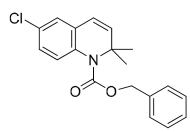
Scheme 1. Reagents and conditions: (i) aniline (1 equiv.), 3-chloro-3-methyl-1-butyne (1 equiv.), copper (I) chloride (1 equiv.), copper powder (1 equiv.), toluene, reflux, 24 h.

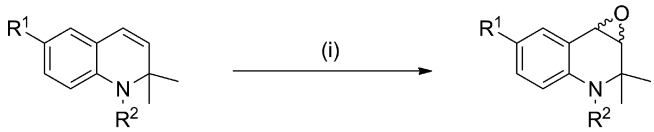
We have observed that dihydroquinolines unprotected at nitrogen are generally unstable to oxidative conditions, but it is possible to generate racemic epoxides from dihydroquinolines with a trifluoroacetyl protecting group and *m*-CPBA as the oxidant.[9] We therefore investigated the incorporation of a number of nitrogen protecting groups (Table 1).

Dihydroquinoline **11**, the nitro derivative, proved unreactive. Dihydroquinoline **13** decomposed under the reaction conditions. We were unable to prepare any *N*-acetyl or *N*-formyl derivatives, but we were able to generate *N*-trifluoroacetyl, benzoyl, BOC, and CBz derivatives from the other substrates. The new nitrogen-protected dihydroquinoline substrates were subjected to epoxidation with *m*-CPBA as the oxidant, to determine their reactivity towards oxidative species, their stability, and to provide racemic standards (Scheme 2, Table 2).

The epoxidation of the various N-protected 6-chloro- and 6-cyano-dihydroquinolines with *m*-CPBA showed that the olefin double bond is reactive towards electrophilic oxygen sources, and the products appear to be stabilized by the electron-withdrawing nature of the protecting groups. In each case, the reaction progress was monitored by ^{1}H NMR spectroscopy of the crude reaction mixture, and, at full conversion, the reactions were worked up and purified by silica gel flash column chromatography. Dihydroquinoline **20** was unreactive.

Table 1. *N*-Protection of dihydroquinolines **10** and **12**.

Starting Material	Product	Conditions	Yield [%]
10	 **14**	TFAA (2 equiv.), Pyridine, CH_2Cl_2, 0 °C to r.t., 1 h	97
	 **15**	*n*BuLi (1.4 equiv.), PhCOCl (1.5 equiv.), THF, −78 °C to r.t., 4 h.	41
	 **16**	*n*BuLi (1.4 equiv.), $(Boc)_2O$ (1.5 equiv.), THF, −78 °C to r.t.	33
	 **17**	*n*BuLi (1.4 equiv.), CbzCl (1.5 equiv.), THF, −78 °C to r.t.	55
12	 **18**	TFAA (2 equiv.), Pyridine, CH_2Cl_2, 0 °C to r.t., 1 h	68
	 **19**	*n*BuLi (1.4 equiv.), $(Boc)_2O$ (1.5 equiv.), THF, −78 °C to r.t.	40
	 **20**	*n*BuLi (1.4 equiv.), CbzCl (1.4 equiv.), THF, −78 °C to r.t.	14



R^1 = CN, Cl
R^2 = C(O)CF_3, C(O)Ph, C(O)O*t*Bu, C(O)CH_2Ph

(52 - 76%)

Scheme 2. Reagents and conditions: (i) *m*-CPBA (2 equiv.), $NaHCO_3$ (4 equiv.), dichloromethane, 0 °C, 24 h.

Table 2. Racemic epoxidation of substrates **14**–**19**.

Substrate	Conv. [%][a]	Yield [%]
14	100	60
15	100	53
16	100	71
17	100	78
18	100	52
19	100	53

[a] All starting material consumed as evaluated by 400 MHz ^{1}H NMR spectroscopy.

Asymmetric epoxidation was then carried out on the nitrogen-protected dihydroquinoline substrates **14**–**20** with catalysts **7**, **8**, and **9** by using two protocols: aqueous, with Oxone as the oxidant (Protocol A, Table 3), and non-aqueous, with TPPP (Protocol B, Table 3). The enantioselectivities ranged from low to good, depending upon the substrate, epoxidation conditions, protecting group, and catalyst used. Background epoxidation was not observed in the absence of catalyst.

Table 3. Epoxidation of N-protected dihydroquinolines **14**–**20**.

Substrate	Catalyst/ Conditions[a]	Time [h]	Yield [%]	Conv. [%][b]	*ee* [%][c]	Abs. config. of the major enantiomer[28]
14	7 A	24	76	97	37	(–)-(3*R*,4*S*)
15	7 A	24	68	89	66	(–)-(3*R*,4*S*)
16	7 A	2	90	100	12	(–)-(3*R*,4*S*)
17	7 A	48	0	0	–	–
18	7 A	24	87	100	22	(–)-(3*R*,4*S*)
19	7 A	0.5	–	–	–	decomposition
20	7 A	24	0	0	–	–
16	8 A	4	70	100	23	(–)-(3*R*,4*S*)
14	9 B	120	10	37	73	(–)-(3*R*,4*S*)
15	9 B	120	< 5	< 5	–	–
17	9 B	120	0	0	–	–
18	9 B	120	13	46	62	(–)-(3*R*,4*S*)

[a] Epoxidation conditions: Protocol A: 5 mol-% catalyst, Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), acetonitrile/water (10:1), 0 °C. Protocol B: 10 mol-% catalyst, TPPP (2 equiv.), dichloromethane, 0 °C. [b] Conversions were evaluated by 400 MHz ^{1}H NMR spectroscopy. [c] Enantioselectivities were determined by chiral HPLC with a Chiralcel ODH column and hexane/2-propanol mixtures as eluent.

By utilizing biphenyl-derived iminium salt **7** under the aqueous conditions, the enantioselectivity varied widely depending on the protecting group attached to the nitrogen atom. When the protecting group was *tert*-butoxycarbonyl (Boc), the enantioselectivities obtained were low (< 25%*ee*). When this group was replaced with a benzoyl protecting group, we observed a dramatic increase in *ee* value; for example, the epoxide derived from substrate 15 was generated in 66%*ee* under these conditions. Carboxybenzyl (Cbz)-protected dihydroquinolines **17** and **20** were unreactive under these conditions, whereas Boc-protected **19** decomposed quickly.

We also observed that changing from the biphenyl moiety of catalyst **7** to the binaphthyl moiety of catalyst **8** afforded one successful example of asymmetric epoxidation, that of substrate **16**, under aqueous conditions, where an improvement in *ee* value of about 10% was recorded. Dihydroquinolines **14** and **17** were unreactive.

When we investigated the effect of changing the catalytic system to a non-aqueous one (Protocol B) with a different complementary catalyst, in this case dichloromethane with dihydroisoquinolinium iminium salt **9**, we observed some of the best enantioselectivities, at the cost of sacrificing conversion to the product. Under these conditions, the substrates tested that provided the highest enantioselectivities were those that contained a trifluoroacetyl protecting group; for example the non-aqueous asymmetric epoxidation of **14** (6-cyano) and **18** (6-chloro) afforded higher enantioselectivities for the epoxide products (62 and 73%*ee*, respectively), but both were obtained at a low conversion (< 50%). When the protecting group was changed from a trifluoroacetyl group to a Cbz- or a benzoyl group, the conversion was poor, even over five days. Use of solvents other than dichloromethane was unsuccessful.

In an attempt to increase the enantioselectivity, we tested a number of the dihydroquinoline substrates under the non-aqueous solvent conditions of protocol B with biphenyl-derived azepinium catalyst **7**. We were surprised to find that substrates **14**, **15**, **17**, and **18** showed no conversion to their corresponding epoxides after one week, as the biphenyl catalysts are the more reactive under aqueous conditions. We have previously observed that binaphthyl catalysts such as **8** provide only very slow epoxidation under non-aqueous conditions.

Figure 3 shows the preferred direction of approach of oxygenation of chromene substrates for all three of the catalysts described here.

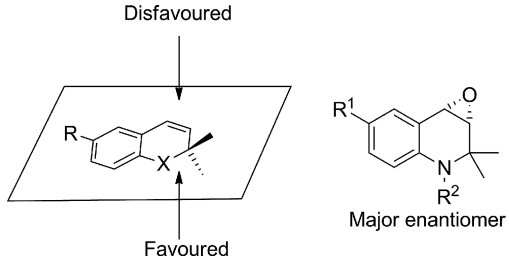


Figure 3. Mnemonic for stereoselectivity and expected major enantiomer.

Conclusions

We have demonstrated the first examples of the asymmetric epoxidation of dihydroquinoline substrates by using iminium salt catalysis, providing the products with up to 73%*ee*. These results show clear potential for the application of the chemistry to the synthesis of tetrahydroquinoline natural products such as virantmycin **1** and helquinoline **3**.

Experimental Section

3-Chloro-3-methylbut-1-yne:[29] Calcium dichloride (23 g, 209 mmol), cuprous chloride (20 g, 204 mmol), copper powder

(0.4 g, 6.67 mmol) and cold concentrated hydrochloric acid (250 mL) were added to a 2 L three-neck flask equipped with a stirrer bar at 0 °C. The solution was left to stir for 5 min at 0 °C and the reaction mixture was purged with argon four times. The corresponding tertiary alcohol (56 g, 667 mmol) was added dropwise over 30 min, and the reaction was left to stir for 1 h at 0–5 °C. The upper organic layer was extracted directly from the reaction, and washed three times with cold concentrated hydrochloric acid (3 × 150 mL). The organic layer was further extracted with cold water (2 × 150 mL), saturated sodium hydrogen carbonate solution (150 mL) and dried on magnesium sulfate to afford the product as a colourless liquid (40 g, 58.4%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.82 (s, 6 H), 2.59 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6, 56.9, 71.9, 86.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = – 2984, 1448, 1368, 1226, 1118, 786 cm^{-1}.

General Procedure for the Formation of 1,2-Dihydroquinolines:[9,26] The required aniline (1 equiv.) and 3-chloro-3-methyl-but-1-yne (1 equiv.) were dissolved in toluene (15 mL/gram of aniline), to which cuprous chloride (1 equiv.) and fine copper powder (1 equiv.) were added to the stirring solution. The reaction was heated under reflux for 24 h. The reaction was cooled, and water (10 mL/gram of aniline) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (10 mL/gram of aniline). The organic layers were combined, and dried over magnesium sulfate. The solvents were removed under reduced pressure. Purification of the crude material by column chromatography on silica gel (ethyl acetate/petroleum ether as the eluent) afforded the dihydroquinolines as crystalline solids or oils.

General Procedure for the Synthesis of *N*-Trifluoroacetyl-1,2-dihydroquinolines: Trifluoroacetic anhydride (2 equiv.) was added dropwise to a stirring solution of dihydroquinoline dissolved in dichloromethane (10 mL/100 mg of dihydroquinoline) and pyridine (1 equiv.) at 0 °C. The reaction was allowed to reach ambient temperature, and after further stirring for one hour, the reaction was quenched with water (5 mL/100 mg of dihydroquinoline). The organic phase was separated and the aqueous phase was extracted with dichloromethane (5 mL/100 mg of dihydroquinoline). The combined organic layers were washed with a copper sulfate solution, brine, and dried with magnesium sulfate. The solvents were removed under reduced pressure. The crude organic mixture was purified by column chromatography on silica gel (ethyl acetate/petroleum ether as the eluent).

General Procedure for the Preparation of Various Nitrogen Protected 1,2-Dihydroquinolines: The desired dihydroquinoline (1 equiv.) was dissolved in anhydrous THF (50 mL/gram of dihydroquinoline) in a flame-dried round-bottomed flask under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C and *n*BuLi (1.4 equiv.) was added slowly over 15 min. The reaction mixture was allowed to stir for 2 h at this temperature. A solution of *tert*-butylcarboxyl anhydride/benzoyl chloride/benzyl chloroformate (1.5 equiv.) in THF (10 mL/gram of dihydroquinoline) was then added dropwise over 15 min. The reaction progress was monitored by TLC. When total disappearance of the starting material was observed, the reaction mixture was quenched with an ammonium chloride solution (10 mL/gram of dihydroquinoline). Ethyl acetate (20 mL/gram of dihydroquinoline) was added, and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (2 × 20 mL/gram of dihydroquinoline). The combined organic layers were then washed with brine (10 mL/gram of dihydroquinoline), dried with sodium sulfate and concentrated under reduced pressure to afford the title compounds as viscous oils/solids.

General Procedure for the Formation of Racemic Epoxides: The required nitrogen-protected dihydroquinoline (1 equiv.) was dissolved in dichloromethane (5 mL/20 mg of dihydroquinoline) and the solution was cooled to 0 °C. *m*-Chloroperbenzoic acid (2 equiv.) and sodium hydrogen carbonate (4 equiv.) were added as one portion. The reaction was allowed to stir at 0 °C until reaction completion was observed by TLC. A saturated solution of sodium hydrogen carbonate (2 mL/20 mg of dihydroquinoline) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 2 mL/20 mg of dihydroquinoline). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel with mixtures of ethyl acetate/petroleum ether/triethylamine as eluents.

General Procedure for the Formation of Chiral Epoxides[30]

Aqueous Conditions: The required nitrogen-protected dihydroquinoline (1 equiv.) and catalyst (5 mol-%) were dissolved in acetonitrile (1 mL/0.05 g of nitrogen protected dihydroquinoline) and water (0.1 mL/0.05 g of nitrogen protected dihydroquinoline) and the mixture cooled to 0 °C. A mixture of Oxone (2 equiv.) and sodium hydrogen carbonate (5 equiv.) was added as a solid in one portion to the mixture with vigorous stirring. The mixture was stirred at 0 °C until complete conversion of the alkene was observed by TLC. Diethyl ether (10 mL/0.05 g of nitrogen protected dihydroquinoline) was added, and the reaction mixture was filtered through a pad of mixed $MgSO_4$ and sodium bisulfite. The solvent was removed under reduced pressure. Pure epoxides were obtained by column chromatography on silica gel with ethyl acetate/petroleum ether/triethylamine as eluents.

Non-aqueous Conditions:[20b] Tetraphenylphosphonium monoperoxysulfate (2 equiv.) was dissolved in dichloromethane (2 mL/0.05 g of TPPP) and the solution cooled to 0 °C. A solution of the iminium salt (10 mol-%) in dichloromethane (0.5 mL/0.05 g of TPPP) was cooled to 0 °C and added dropwise to the solution containing the TPPP over 20 min. The temperature of the reaction vessel was monitored to minimize the increase in temperature during the addition. A solution of the alkene in dichloromethane (0.5 mL/0.05 g of TPPP) was added dropwise. The mixture was stirred at 0 °C with the reaction progress monitored by TLC. Diethyl ether (pre-cooled to the reaction temperature) (20 mL/0.05 g of TPPP) was added to induce precipitation of the remaining oxidant, and the mixture was filtered through Celite. The solvents were removed under reduced pressure. If the reaction does not reach completion the epoxide can be separated from the alkene by column chromatography on silica gel eluting with ethyl acetate/light petroleum.

Acknowledgments

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