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Enantioselective Synthesis of Bicyclopentane-Containing Alcohols via Asymmetric Transfer Hydrogenation

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ABSTRACT: Compounds containing bicyclo[1.1.1]pentane (BCP) adjacent to a chiral centre can be prepared in high enantiomeric excess through the asymmetric transfer hydrogenation (ATH) of adjacent ketones adjacent. In the reduction step, the BCP occupies the position distant from the $\eta^6$-arene of the catalyst. The reduction was applied to the synthesis of a BCP analogue of the antihistamine drug neobenodine.

Compounds which contain a bicyclo[1.1.1]pentane (BCP) are valuable structures for pharmaceutical research. Examples include where a BCP is bioisosteric with a para-substituted aromatic ring, and an alkene. Pellicciari et al. reported the asymmetric synthesis of an amino acid bearing a BCP, prepared via separation of diastereomeric cyanohydrins, which exhibited activity as an mGlu1 receptor antagonist. Compound 1 is a BCP analogue of a $\gamma$-secretase inhibitor, which exhibits improved aqueous solubility and oral absorption characteristics. Compound 2 is a BCP analogue of darapladib, a cardiovascular disease drug in which the isostere exhibited an improved physiochemical profile.

Knochel et al. described the formation of BCP isosteres of alkenes including tazarotene and MPEP, i.e. 3 and 4 respectively, using a coupling of Zn-BCP reagents (formed by the reaction of a Grignard reagent with [1.1.1]propellane) with aromatic and heteroaromatic halides (Figure 1b).

Anderson et al. have reported innovative routes to several BCP derivatives. One example features a versatile synthesis of disubstituted BCP derivatives through the reaction of [1.1.1]propellane with organic iodides under photochemical conditions, followed by an iron-catalyzed Kumada cross-coupling reaction with an aromatic or heteroaromatic Grignard reagent. Syntheses of BCP-flurbiprofen 5 (BCP replacing a fluorinated aromatic ring in the anti-inflammatory drug) and BCP-brequinar 6 (BCP replacing a bridging aromatic ring) were reported.

Aggarwal et al reported the trapping of BCP-containing Grignard reagents with boronic esters to form BCP-boronate complexes (Figure 1b). The methodology was particular effective for the synthesis of alkene-containing derivatives, e.g. 7, and an exam-
ple of an amine-containing derivative, 8, was achieved using a procedure reported by Baran et al. Baran et al. and Qin et al. reported the selective synthesis of functionalised BCP derivatives.

Asymmetric catalytic methods for the synthesis of BCP derivatives have been reported, however not to our knowledge for the formation of adjacent alpha-oxo stereocentres. Therefore we investigated the introduction of a chiral centre adjacent to the group through asymmetric transfer hydrogenation (ATH) of a ketone. This would permit the synthesis of a BCP compounds analogous to benzhydrols and their derivatives as neobendine, carboxamine and levocetizine (antihistamines), in enantiomerically pure form (Figure 2). Benzhydrols and their imine derivatives are challenging substrates for ATH due to the often minimal differences in steric and/or electronic properties of the aryl rings in the precursor benzophenones, although a number of successful strategies have been reported. We reasoned that BCP vs. aromatic or alkyne flanking the ketone in a substrate would offer a greater chance of differentiation due to their contrasting structural properties, and therefore suitable for ATH.

![Figure 2. Potential BCP analogues of antihistamine therapeutics.](image)

**Results and discussion.**

We prepared ketone precursors of the desired alcohols through the reaction of Grignard reagents with [1.1.1]propellane, followed by trapping with an appropriate electrophile (Illustrated in Figure 3a for substrate 10). For the reduction, focussed on the use of the ‘tethered’ catalyst (R,R)-9 (Figure 3b) which we have previously found to be very versatile in ATH applications. [1.1.1]Propellane was initially converted to the ketone via reaction with PhMgBr followed by trapping of the Grignard reagent with PhCOCl. However, a significant amount of benzophenone was also formed, which could not be separated from 10. We found that 10 could be made more cleanly through addition to an aldehyde followed by oxidation with MnO2. ATH of BCP ketone 10 gave the desired alcohol 11 in 97% ee, which confirmed the sharp difference in directing effects between the two groups flanking the ketone. The subsequent X-Ray crystallographic analysis of a chiral derivative (Supporting Information) confirmed that the product configuration was (R), using (R,R)-9. Applying the model previously proposed for ATH indicates that reduction likely proceeds with the BCP distal from the 6-arene (Figure 3c).

The methodology was successfully extended to number of aromatic substrates, and one enone (Figure 4). Alkyl substitution on the aromatic ring was tolerated, giving products of 99% ee for p-substituted substrates and slightly lower for the m-methyl substrate. Substrates containing electron-withdrawing groups such as p-Cl and p-F were reduced in lower ee, possibly reflecting a weaker 6-arene interaction. Substrates containing electron-donating OMe groups were also generally highly enantioselective in reductions (88-96% ee), although a p-phenoxy substrate was reduced in a lower ee of just 85%.
A sharp contrast was exhibited by the formation of the product of ATH of the 2-OMe derivative, i.e. 19, which was reduced in just 2% ee. This result reflects lower enantioselectivities observed for substrates such as 2-methoxy acetophenone. This can be attributed to disruption of the approach of the substrate to the catalyst due to a likely twist of the aromatic ring out of planarity with the ketone. A p-amino substrate was also tolerated, with an alcohol of 97% ee formed, whilst a p-bromo substrate gave the alcohol in 81% ee. Heterocycle-containing substrates were also enantioselectively reduced by ATH, with furan (99% ee), thiophene (99% ee) and pyridine (91% ee) all being compatible with the conditions. The configuration were assigned by analogy with the unsubstituted example, however in the case of the 28, reduced in just 41% ee, the configuration was not established.

We also examined the reductions of ketones flanked by a combination of BCP and an alkyl derivative (Figure 4). We obtained products of high ee; 95-99% in all of the examples tested. Hence the reaction conditions were shown to be tolerant of groups such as p-and o-methoxy, an alkyl group, trimethylsilyl and chloro. An X-ray crystallographic structure of 33 (Supporting Information) served to confirm the configuration as R- when the (R,R) 9 was used in the reductions. This outcome would correspond with the proposed mode of reduction of propargylic ketones by this class of catalyst (Figure 3c).

To highlight the value of the BCP as an isostere of aromatic rings and triple bonds which can facilitate the synthesis of highly enantioselectively enriched products via ATH, we examined the reduction of a range of comparator compounds (Figure 5). Products of only moderate ee were formed. The combination of alkyl vs aromatic in ketones, are also known to be challenging. Known, and important, exceptions are however provided by substrates containing ortho-substituted aromatic rings, which give high ee products due to steric hindrance and electronic differentials between groups.8,9,13b

**Figure 4.** Products of ATH of BCP derivatives of aromatic and alkyl derivatives, using 1 mol% of catalyst (R,R)-9. Conditions are as in Figure 3. Isolated yields are given, conversions were 100% unless otherwise stated. Configurations, other than for 28, were assigned by analogy with (R)-11 or (R)-33.

![Figure 4](image_url)

**Figure 5.** ATH products of non-BCP comparator compounds. a. benzhydrols (configuration not determined), b. dialkynyl ketone reduction products (configuration not determined), c. reported aromatic/alkynyl ketone reduction products. d) reported Ph/tBu ketone. Conversions were 100% unless otherwise stated.

To illustrate the value of the methodology, its application of the to the synthesis of the BCP-neobenodine was undertaken (Figure 6). Intermediate 35 was prepared via the BCP iodide (not isolated). ATH of 35 was undertaken on a 1 mmol scale and gave alcohol 36 of 94% ee in 90% isolated yield. Conversion to the BCP analogue of neobenodine, following the procedure for neobenodine via the amide intermediate,2a,b was successfully completed with minimal loss of ee. In this example the (S,S)-enantomer of catalyst 9 was used in order to form the BCP of the analogous configuration to neobenodine.15

**Figure 6.** Asymmetric synthesis of a BCP containing derivative of neobenodine. The conversion of 35 to (S)-36 was conducted on a 1 mmol scale.

Conclusions
In conclusion, we report a highly enantioselective reduction of BCP-ketones to alcohols using ATH, which we believe represents the first example of a catalytic asymmetric, synthesis of BCP derivatives. Since the BCP group is a known bioisostere of alkynes and aromatic groups, the methodology provides an asymmetric route to analogues of structures which would be challenging to prepare in high ee. The methodology was applied to an efficient asymmetric synthesis of the BCP derivative of neobenodine.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, NMR spectra, X-ray crystallographic data and HPLC data (PDF). The X-ray crystal structural data are available from the Cambridge Crystallographic Data Centre (CCDC) as structures CCDC 2067284 (Figure 4) and CCDC 2067285 (Figure 7) respectively.

**Data sharing statement** The research data (and/or materials) supporting this publication can be accessed at [http://wrap.warwick.ac.uk/TBA](http://wrap.warwick.ac.uk/TBA).

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[15] A change in priority rules means that (S)-BCP-neobenodine is analogous in configuration to (R)-neobenidine.