Synthesis of enantioenriched α-chiral bicyclo[1.1.1]pentanes

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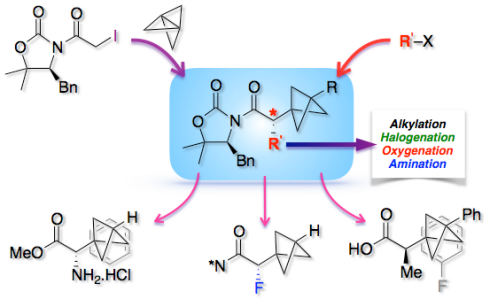
Supporting Information Placeholder



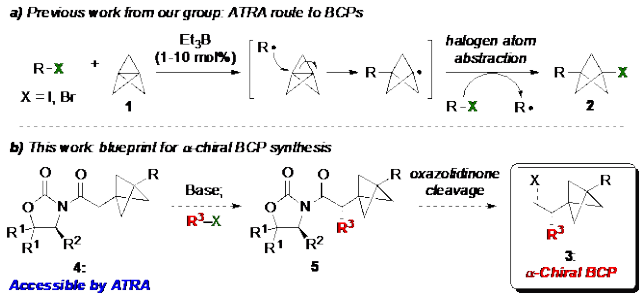
ABSTRACT: Bicyclo[1.1.1]pentanes (BCPs), useful surrogates for *para*-substituted arenes, alkynes and *tert*-butyl groups in medicinal chemistry, are challenging to prepare when featuring stereogenic centres adjacent to the BCP. We report the development of an efficient route to α-chiral BCPs, via highly diastereoselective asymmetric enolate functionalization. We also describe the application of this chemistry to the synthesis of BCP analogues of phenylglycine and tarenflurbil, the single enantiomer of the NSAID flurbiprofen.

Bicyclo[1.1.1]pentanes (BCPs)[1] are widely recognised as useful surrogates for 1,4-disubstituted benzene rings,[2] alkynes,[3] and *tert*-butyl groups[4] in drug design.[5] While a number of methods are available for the preparation of BCP-containing molecules,[6] the synthesis of BCPs featuring adjacent stereogenic centres (α-chiral BCPs) remains a significant challenge. The few known examples focus on the synthesis of phenylglycine BCP analogues;[7] however, a general and practical approach to enantioenriched α-chiral BCPs remains elusive.

We recently disclosed an efficient route to highly functionalized disubstituted BCP derivatives *via* atom transfer radical addition (ATRA) reactions.[8] Using triethylborane as an initiator, radicals derived from readily available alkyl halides effect ring opening of tricyclo[1.1.1.0^{1,3}]pentane (**1**, Scheme 1a), affording 1-halo-3-substituted BCPs **2**. This process is particularly effective and rapid for electron-deficient radicals derived from α-halo carbonyls; we recognized that this could enable a general, stereoselective strategy to access α-chiral BCPs (**3**, Scheme 1b) *via* reactions of enantioenriched ATRA-derived α-BCP oxazolidinones (**4**). Here we describe the realization of this route, which allows installation of a wide range of substituents adjacent to the BCP, together with high-yielding removal and recovery of the auxiliary, and application of the methodology to the synthesis of BCP analogues of phenylglycine, and the NSAID tarenflurbil.

Our studies began with a survey of reactivity of various BCP oxazolidinones (**4a-f**, Table 1). These could be accessed *via* ATRA

Scheme 1. Strategy for enantioenriched BCP synthesis

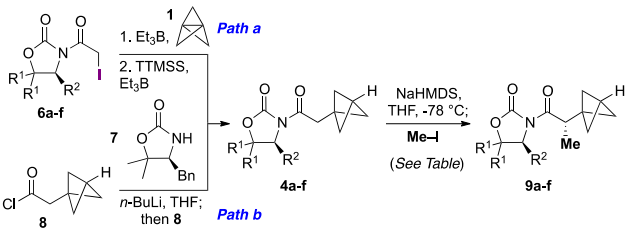


a Previous work involving triethylborane-initiated ATRA approach to 1-halo-3-substituted BCPs. **b** The approach to α-chiral BCPs described in this work.

reaction of the α-iodooxazolidinones **6a-f** (Path a), followed by deiodination using $(Me_3Si)_3SiH$ (TTMSS). **4f** was also prepared by acylation of oxazolidinone **7** with acid chloride **8** (Path b); this latter route was readily performed on multigram scale (1.8 g of **4f** obtained from 1.33 g of **8**, 63%). We quickly found that the reaction conditions and substitution pattern of the auxiliary proved crucial to reaction efficiency: sodium enolates[9] of commonly used oxazolidinones **4a-c** (R^1 = H,

entries 1–3) gave modest yields (with the exception of **4c**, featuring a benzyl substituent) or *dr*s (with the exception of *iso*-propyl substituted **4a**) in alkylations with iodomethane. 'SuperQuat' auxiliaries (R^1 = Me/Ph, entries 4-6) were next

Table 1. Reaction Optimization[a]



entry	substrate	R^1	R^2	product, yield (%)[b]	*dr*[c]
1	**4a**	H	i-Pr	**9a**, 36	>20:1
2	**4b**	H	Ph	**9b**, 29	3:1
3	**4c**	H	Bn	**9c**, 85	14:1
4	**4d**	Me	Ph	**9d**, 50	>20:1
5	**4e**	Ph	Bn	**9e**, 22	>20:1
6	**4f**	**Me**	**Bn**	**9f, 84**	**>20:1**

[a] Alkylation conditions: NaHMDS (1.1 equiv.), THF, -78 °C, 30 min; MeI (3.0 equiv.), -78 °C, 1–6 h. Reactions performed on 0.15 mol scale. [b] Isolated yield [c] *dr* determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; ratio of *S*:*R* isomers assigned by analogy to products **9j**, **9l** and **9s**, the structures of which were determined by X-ray crystallography (see below).

examined, which can not only deliver enhanced stereocontrol, but also improve auxiliary cleavage / recycling efficiency.[10] To our delight, this fine-tuning of the oxazolidinone scaffold led to the formation of adducts **9d-f** as single diastereomers, with the benzyl-substituted oxazolidinone **4f** giving **9f** in high yield and exceptional stereoselectivity.

Having identified optimal enolate functionalization conditions, the scope of the process was explored using substrate **4f** (Figure 1). A wide range of electrophiles were successfully installed, with the products isolated in high yields and as single diastereomers in nearly all cases. Alkyl halides bearing saturated and unsaturated aliphatic chains (**9g-l**) and heterocycles (**9m**, **n**) were all well-tolerated; in most cases, alkylation occurred smoothly at -78 °C, with warming to 0 °C necessary for less reactive electrophiles (**9g**, **9h**). **4f** also underwent aldol chemistry: for example, reaction of the dibutylboron enolate derived from **4f** with benzaldehyde afforded adduct **9o** in excellent yield and selectivity at the α-stereocenter (98%, *dr* 1:1.5 at the hydroxyl-bearing stereocenter). Alternatively, use of 1,3,5-trioxane as a formaldehyde equivalent, with $TiCl_4$ and Hünig's base, enabled hydroxymethylation to form **9p**. Consistent yields were observed on scale-up to 1.33 mmol scale for this product (54%), and also methylated product **9f** (80%).

The direct introduction of heteroatoms also proved possible: **4f** could be fluorinated with high diastereoselectivity using NFSI as the electrophile (**9q**, 85%, 13:1 *dr*), which is of interest given the importance of fluorinated motifs in drug development.[11] The analogous bromination (**9r**) proceeded with low selectivity using *N*-bromosuccinimide, but surprisingly the same product was isolated with high diastereoselectivity (78%, 13:1 *dr*) on reaction with 2-(bromomethyl)-5-nitrofuran, instead of the expected heterocycle installation. α-Hydroxylation and hydrazinylation were achieved using the Davis oxaziridine and *di-tert*-butyl azodicarboxylate as respective electrophiles, with **9s** and **9t** formed as single diastereomers and in excellent yields (80 and 98%). Finally, 1,3-

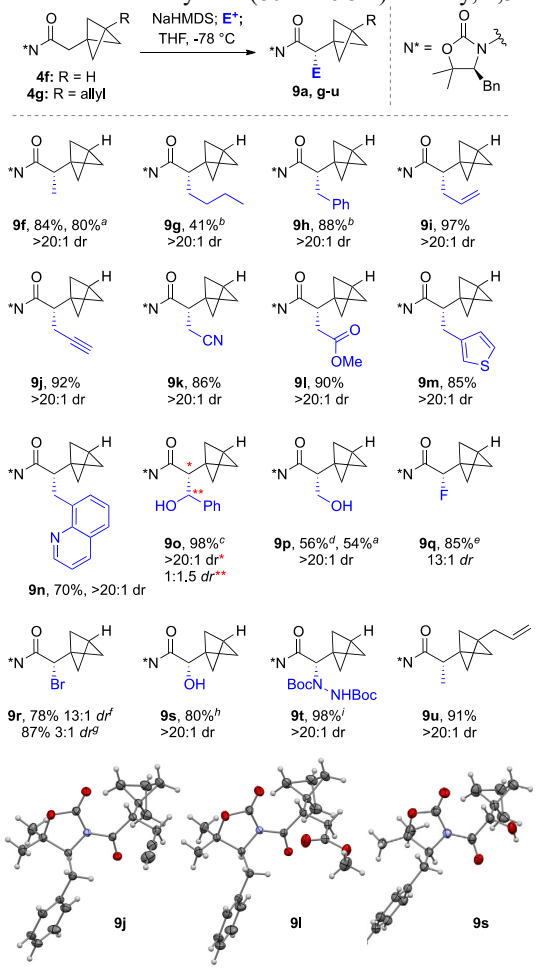
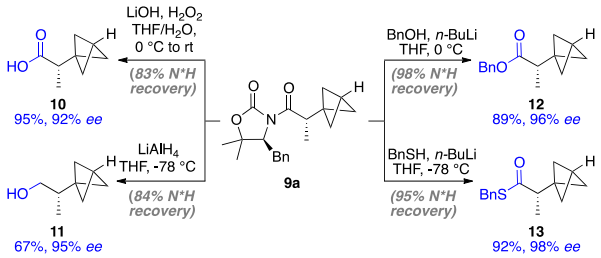


Figure 1. Synthesis of α-chiral BCPs. Reaction conditions unless stated otherwise: **4** (0.15 mmol, 1.0 equiv.), NaHMDS (1.1 equiv.), THF, -78 °C, 30 min; electrophile E^+ (3.0 equiv.). Reaction times varied with the electrophile; see the Supporting Information for details. [a] Reaction conducted on 1.33 mmol scale (0.42 g); [b] -78 °C→ 0 °C (12 h). [c] **4f**, *n*-Bu_2BOTf (1.1 equiv.), *i*-Pr_2EtN (1.2 equiv.), CH_2Cl_2, 0 °C, 30 min; PhCHO (1.1 equiv.), -78 °C, 3.5 h. [d] $TiCl_4$ (1.0 equiv.), CH_2Cl_2, 0 °C, 10 min; *i*-Pr_2EtN (1.1 equiv.), 40 min; 1,3,5-trioxane (1.2 equiv.), $TiCl_4$ (1.0 equiv.), 3 h. [e] E^+ = NFSI (1.3 equiv.), 3 h. [f] E^+ = 2-(bromomethyl)-5-nitrofuran, 2 h. [g] E^+ = NBS, 4 h. [h] NaHMDS (1.2 equiv.); 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (1.5 equiv.), 20 min. [i] E^+ = *di-tert*-butyl azodicarboxylate (1.3 equiv.), 5 min.

disubstituted BCP compounds could be accessed by construction of the corresponding disubstituted BCP oxazolidinone prior to diastereoselective alkylation (**9u**, 91%).[3] The structures of **9j**, **9l** and **9s** were determined by X-ray crystallographic analysis,[12] and the stereochemistry of all other products was assigned by analogy. The BCP was observed to position itself on the opposite face to the oxazolidinone benzyl group in all three structures, demonstrating its potential utility as a conformational control element, as well as a useful motif in drug design.

Crucially, the SuperQuat oxazolidinone was readily cleaved to access functional groups that enable further manipulation of the chiral BCP products (Scheme 2). These transformations included hydrolysis (**10**), reduction (**11**), and transesterification (**12**, **13**); all products were obtained in high yields and excellent enantiopurity, with the oxazolidinone being recovered in good yield.

Scheme 2. Removal of the SuperQuat auxiliary to access enantioenriched BCP building blocks



The diastereoselective enolate functionalization chemistry provides opportunities for the synthesis of α-chiral BCP analogues of bioactive compounds (Scheme 3). The methodology was first utilized in the synthesis of a BCP analogue of phenylglycine, where methanolysis of **9t** to give ester **14**, followed by deprotection of the Boc groups and Pt-catalyzed hydrogenation,[6d, 6j] afforded the BCP analogue **15** of L-(+)-α-phenylglycine methyl ester hydrochloride in 78% yield from **9t**. We also targeted the asymmetric synthesis of an analogue of a pharmaceutical featuring a benzylic stereocentre. Tarenflurbil, the (*R*)-enantiomer of the NSAID flurbiprofen, was selected for this purpose. This synthesis commenced with acid **16**, which was converted to the acyl oxazolidinone **17** as outlined in Table 1 path b. Diastereoselective enolate methylation proceeded in high yield and exceptional stereoselectivity (91%, *dr* >20:1), affording BCP-tarenflurbil **18** after hydrolytic cleavage of the oxazolidinone (86%).

In conclusion, we have developed a general method to access bicyclo[1.1.1]pentanes featuring stereogenic centres adjacent to the BCP, via the diastereoselective functionalization of SuperQuat oxazolidinone BCP derivatives. The substituent scope includes saturated and unsaturated carbon chains, carbonyls, heterocycles and heteroatoms; we also demonstrated the facile cleavage of this auxiliary, which delivers enantioenriched BCP products with high *ee*. We further established the first examples of direct asymmetric ATRA reactions to prepare enantioenriched BCPs. This methodology was applied to the synthesis of BCP analogues of phenylglycine and tarenflurbil. This chemistry opens many opportunities for the synthesis of chiral BCP derivatives, which are likely to be of high value to the pharmaceutical and agrochemical industries.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra (pdf), CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

There are no conflicts to declare.

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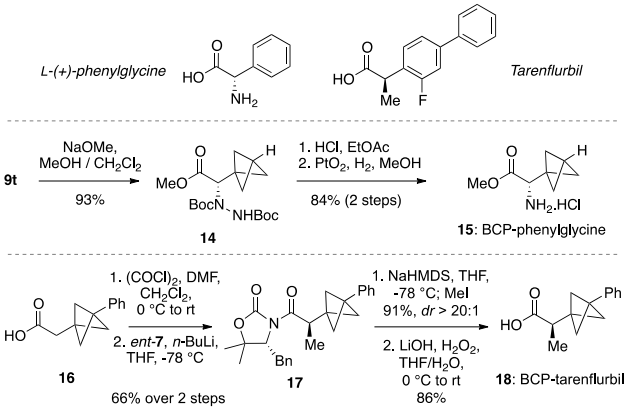
Scheme 3. Synthetic Applications



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(12) Low temperature single crystal X-ray diffraction data for **12j**, **12l** and **12s** were collected with a (Rigaku) Oxford Diffraction Su-

perNova A diffractometer at 150K. All data were reduced using CrysAlisPro, solved using SuperFlip [L. Palatinus, G. Chapuis, *J. Appl. Crystallogr.* **2007**, *40*, 786-790] and the structures were refined using CRYSTALS.[P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, *36*, 1487; R. I. Cooper, A. L. Thompson, D. J. Watkin, *J. Appl. Crystallogr.* **2010**, *43*, 1100-1107]. The Flack(x) parameter [H. D. Flack, *Acta Crystallogr. A* **1983**, *39*, 876-881; H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143-1148] was refined in all cases; see the Supporting Information (CIF) for further details. CCDC 1888813-1888815 contains the Supplementary crystallographic data for this paper.