Asymmetric synthesis of orthogonally protected *trans*-cyclopropane γ-amino acids *via* intramolecular ring closure†

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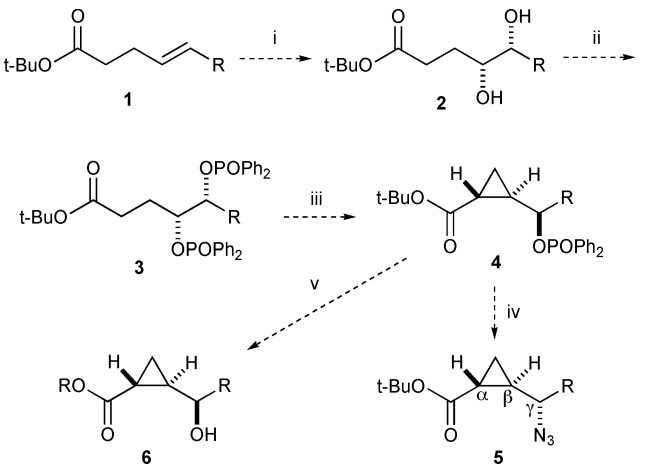
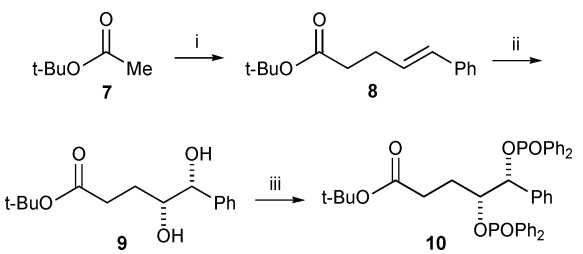
The synthesis of enantiomerically-enriched *trans*-cyclopropane amino- and hydroxy-acids can be achieved by intramolecular ring closure in moderate to good yields. The optically active cyclopropane precursors are easily prepared in a short sequence from inexpensive, commercially available olefins and *tert*-butyl acetate. Several leaving groups and bases were compared for the cyclopropanation step, showing that the diphenylphosphinate and tosyl leaving groups give the best results when used in combination with either LDA or NaHMDS.

Cyclopropane amino acids are an important class of biologically active compounds with unique properties.[1–4] In recent years cyclopropane amino acids have shown promise as therapeutics for the treatment of various neurological diseases and disorders and much research effort has been invested in identifying new drug candidates within this area.[5–15] Moreover, cyclopropane amino acids are useful for studying structure–activity relationships, because in addition to exerting conformational constraints they maintain the hydrophobic character of the linear alkyl chains.[9,13,16,17] The stereocontrolled synthesis of cyclopropanes is challenging and much energy has been devoted to develop new methods for the synthesis of optically active cyclopropane amino acids.[8,17–36] However, there are still many problems associated with the current methodology, particularly the use of transition metals at a late stage of the synthetic sequence, making the rapid identification of new drug candidates costly and difficult. The asymmetric synthesis of cyclopropanes *via* intramolecular ring closure has received less attention. Starting from optically active cyclopropane precursors this approach has been demonstrated to work for lithiated diphenylphosphine oxides displacing mesylates,[37,38] lithiated sulfones displacing tosylates,[39] amide enolates opening cyclic sulfites,[34] and carboxylic ester enolates opening epoxides.[34] We envisaged that the asymmetric synthesis of orthogonally protected *trans*-cyclopropane γ-hydroxy- and amino-acids might be achieved by a short synthetic sequence starting from easily obtained olefins **1** (Scheme 1). Sharpless asymmetric dihydroxylation[40] of olefins **1** gives a wide range of diols **2** with high enantiomeric excess. Double activation of the diols with diphenylphosphinoyl chloride followed by intramolecular ring closure by the carboxylic ester enolates would generate cyclopropanes **4**. Exclusive formation of *trans*-cyclopropanes is expected as the substituents on the new ring prefer to be *anti* in the transition state. The remaining leaving group can finally be displaced with azide to produce protected *trans*-cyclopropane γ-amino acids **5**. Alternatively, transesterification of the phosphinate ester would yield *trans*-cyclopropane γ-hydroxy carboxylic esters **6**. We have previously shown that the diphenylphosphinoyloxy group is a suitable leaving group for the formation of cyclopropanes by intramolecular ring closure and confers a high degree of crystallinity to compounds.[41,42]



Scheme 1 Synthetic outline: i) Sharpless asymmetric dihydroxylation; ii) double activation; iii) base induced cyclisation; iv) displacement with azide; v) double transesterification. R = Et and Ph.

The use of a *tert*-butyl ester prevents lactonisation of the diol during the dihydroxylation step and produces orthogonally protected amino acids. Initially, we synthesised the doubly phosphinoylated cyclopropane precursor **10** from enantiomerically enriched diol **9** (Scheme 2).



Scheme 2 *Reagents and conditions*: i) LDA, HMPA, THF, (*E*)-cinnamyl bromide, −78 °C, 96%; ii) AD-mix-β, 86% (>95% ee); iii) Ph_2POCl, Et_3N, DMAP, CH_2Cl_2, 52%.

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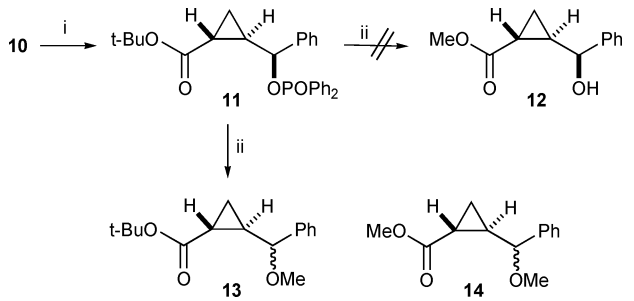
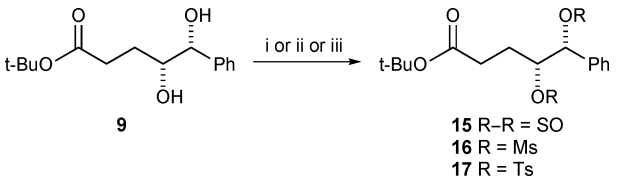
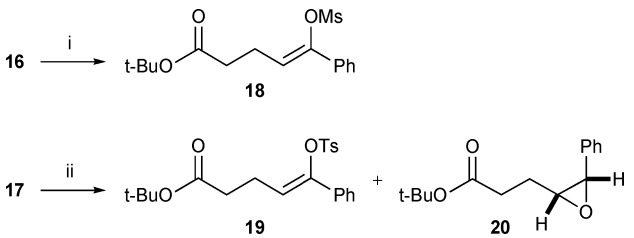
Treatment of bis-phosphinate **10** with LDA or KHMDS in THF only gave small amounts (<10%) of the desired cyclopropane **11**. However, NaHMDS in THF produced the desired cyclopropane in moderate yield and excellent enantiomeric excess (Scheme 3). The purified cyclopropane product was surprisingly stable and could be stored at room temperature for several days with no observed decomposition. Attempted double transesterification with sodium methoxide in methanol to give γ-hydroxy methyl ester



Scheme 3 *Reagents and conditions*: i) NaHMDS, THF, −78 °C to rt, 41% (>95% ee); ii) NaOMe, MeOH, reflux.

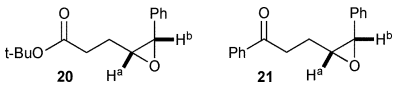


Scheme 4 *Reagents and conditions*: i) $SOCl_2$, pyridine, CH_2Cl_2, **15** 85%; ii) MsCl, pyridine, CH_2Cl_2, **16** 73%; iii) TsCl, pyridine, **17** 72%. SO = cyclic sulfite (*ca* 1:1 mixture of epimers at sulfur).



Scheme 5 *Reagents and conditions*: i) LDA, NaHMDS or KHMDS, THF, −78 °C to rt, 30% with NaHMDS; ii) KHMDS −78 °C to rt **19** 10%, **20** trace, recovered **17** 47%.

Table 1 ^{1}H NMR data for epoxides **20** and **21**

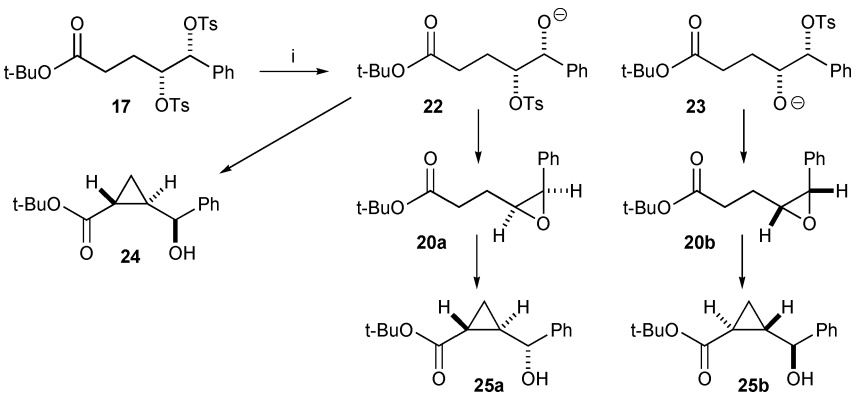


	δ/ppm	J/Hz
20 H^a	3.26	td 6.5 and 4.0
21 H^a	3.37	ddd 7.5, 5.5 and 4.5
20 H^b	4.08	d 4.0
21 H^b	4.14	d 4.0

12 unfortunately resulted in substitution at the benzylic carbon, with loss of stereochemistry to give four cyclopropanes **13** and **14**.

To compare diphenylphosphinate with sulfur-based leaving groups in the ring closure reaction cyclic sulfite **15**, bis-mesylate **16** and bis-tosylate **17** were also synthesised from diol **9** (Scheme 4). Upon treatment with base neither the cyclic sulfite **15** nor bis-mesylate **16** gave cyclopropane, the mesylate producing only the elimination product **18** (30% yield using NaHMDS, Scheme 5). While treatment of the bis-tosylate **17** with LDA also failed to produce any cyclopropane (only starting material was identified in the complex NMR spectrum of the crude product), the crude product from using KHMDS contained, along with elimination product **19**, a small quantity of a compound proposed as epoxide **20**. The epoxide's ^{1}H NMR spectroscopic data are very similar to those of the known phenyl ketone **21** (Table 1).[41]

When bis-tosylate **17** was reacted with NaHMDS two diastereomeric cyclopropanes **24** and **25** were obtained in a 57 : 43 ratio (Scheme 6). We have previously reported the formation of mixtures of *trans*-cyclopropyl phenyl ketones by a related method[41] and the NMR spectra of cyclopropanes **24** and **25** were similar to the those for these cyclopropanes ketone (Scheme 7). Hence, based on this observation and the previously detected epoxide **20** we propose a similar explanation for the outcome of this reaction. In the first step a tosyl group is cleaved by the base (Scheme 6). This could occur either by *ortho*-metalation of the tosyl group followed by elimination of benzyne or by a single electron transfer reduction. Each would produce two regioisomeric mono-tosylates **22** and **23**. Tosylate **22** can cyclise with displacement of the tosylate to give cyclopropane **24** or epoxide **20a**, whereas tosylate **23** can ring close only to form an epoxide **20b**. In a final step the two enantiomeric epoxides can be ring opened by the ester enolate to form the two cyclopropanes **25a** and **25b**.



Scheme 6 *Reagents and conditions*: i) NaHMDS, THF, −78 °C to rt, **24** + **25** 36%.

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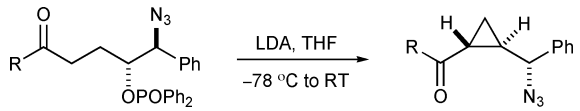
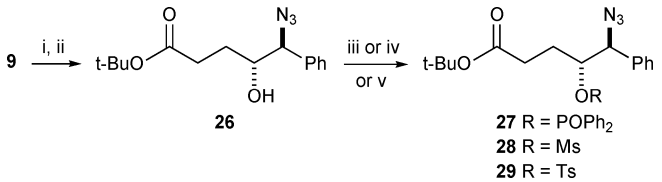


Scheme 7 R = phenyl (95%, >95% ee), furan-2-yl (30%, >96% ee).

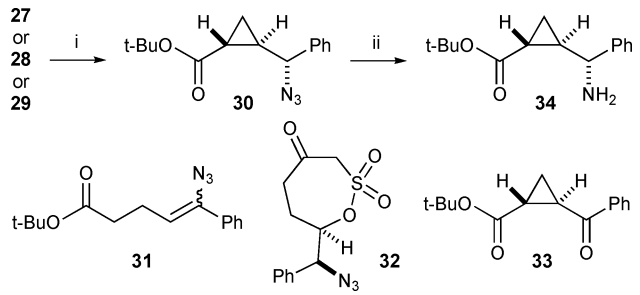
We have previously reported an asymmetric synthesis of *trans*-cyclopropane γ-azido ketones where the cyclopropane is formed *via* intramolecular ring closure by a ketone enolate to displace a diphenylphosphinate leaving group (Scheme 7).[41]

We envisaged circumventing the problems associated with the bis-activation strategy by installing the benzylic azide prior to cyclisation. Hence, diol **9** (Scheme 8) was converted to the cyclic sulfite using thionyl chloride and pyridine in dichloromethane followed by treatment of the crude cyclic sulfite with sodium azide in DMF at 60 °C to give the desired regioisomer of *anti*-azido alcohol **26** exclusively. Activation of alcohol **26** gave cyclopropane precursors **27** to **29** ready for the final cyclisation step.



Scheme 8 *Reagents and conditions*: i) $SOCl_2$, pyridine, CH_2Cl_2; ii) NaN_3, DMF, 60 °C, 65% (2 steps); iii) Ph_2POCl, DMAP, Et_3N, CH_2Cl_2, **27** 67%; iv) MsCl, pyridine, CH_2Cl_2, **28** 94%; v) TsCl, Et_3N, DMAP, CH_2Cl_2, **29** 73%.

Treatment of phosphinate **27** with LDA, NaHMDS or KHMDS in THF resulted in recovery of the starting material, even after prolonged reaction times at room temperature. This was unexpected given the cyclopropanation of the related ketones (Scheme 7).[42] Treatment with potassium *tert*-butoxide produced cyclopropane **30** along with the two geometrical isomers of elimination product **31** (Scheme 9, Table 2). When treated with LDA, mesylate **28** produced the desired cyclopropane **30** as well as side-products **31** and **32**. The formation of a 7-membered cyclic sulfonate **32** shows that the mesyl group is deprotonated by LDA to some extent. A higher yield of cyclopropane was obtained using NaHMDS, but the product again contained elimination product **31**. This side-product could be removed by catalytic hydrogenation to give the free amine **34**. Tosylate **29** gave the desired cyclopropane **30** with lithium and sodium bases in moderate yield and free of any unwanted by-products in the case of the lithium enolate.



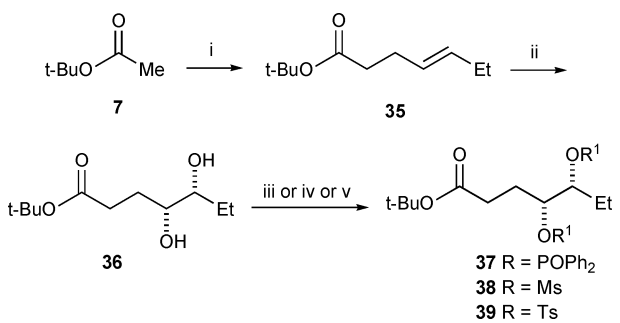
Scheme 9 *Reagents and conditions*: i) see Table 2; ii) $Pd(OH)_2/C$, H_2, MeOH, 91% (>92% ee).

Table 2 Cyclopropanation of phosphinate **27**, mesylate **28** and tosylate **29**

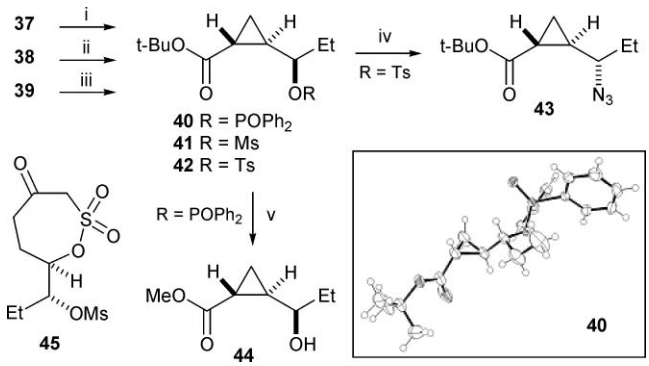
Substrate		Yield (%), isolated			
Substrate	Base[a]	**27/28/29**	**30**	**31**	**32/33**
27	t-BuOK	21[b]	18[b]	61[b]	—
28	LDA	41[b]	36[b]	5[b]	18[b,c]
28	LDA[d]	22	13	[e]	—
28	NaHMDS	14	62	2	—
28	KHMDS	16	44	7	—
29	LDA	—	48	—	—
29	NaHMDS	—	52	—	11[f]
29	KHMDS	63[b]	22[b]	15[b]	—

[a] Reaction conditions: THF, −78 °C to rt. [b] By ^{1}H NMR. [c] Compound **32**. [d] Reaction conditions: THF −78 °C. [e] Observed in ^{1}H NMR spectrum of the crude product. [f] Compound **33**.

Finally, we explored the double activation strategy with a terminal ethyl group. Bis-phosphinate **37**, bis-mesylate **38** and bis-tosylate **39** were synthesised from enantiomerically-enriched diol **36** (Scheme 10). When cyclopropanation of bis-phosphinate **37** was attempted all the reaction conditions produced the desired cyclopropane (Scheme 11). LDA proved to be superior and gave cyclopropane **40** in good yield and excellent enantiomeric excess.



Scheme 10 *Reagents and conditions*: i) LDA, HMPA, THF, −78 °C, 1-bromo-2-pentene, 91%; ii) AD-mix-β, 81%; iii) Ph_2POCl, Et_3N, DMAP, CH_2Cl_2, **37** 74% (>85% ee); iv) MsCl, pyridine, CH_2Cl_2, **38** 67%; v) TsCl, Et_3N, DMAP, CH_2Cl_2, **39** 64%.



Scheme 11 *Reagents and conditions*: i) base, THF, −78 °C to rt giving **40**, LDA: 75% (>96% ee), NaHMDS: 18%, KHMDS: 23%; ii) NaHMDS, THF, −78 °C to rt giving **41** and **45** (**41** : **45** = 3 : 1 by ^{1}H NMR); iii) NaHMDS, THF, −78 °C to rt giving **42**; iv) NaN_3, DMF, 60 °C, 62% (>94% ee, 2 steps from **39**); v) NaOMe, MeOH, reflux, 72%. Inset: X-ray crystal structure of cyclopropane **40** with ellipsoids at 50% probability.

The absolute stereochemistry of cyclopropane **40** was confirmed by X-ray crystallography[43] (Scheme 11). Displacing phosphinate **40** with azide was not possible even under forcing conditions (DMF, 110 °C) and mostly starting material was retrieved. However, double transesterification with sodium methoxide in refluxing methanol gave the desired γ-hydroxy methyl ester **44** in a moderate yield.

Cyclopropanation of bis-mesylate **38** to produce target cyclopropane **41** was best achieved with NaHMDS, although cyclic sulfonate **45** was a by-product. The cyclic sulfonate was assigned as the 7-membered rather than the 8-membered compound due to striking similarities between the ^{1}H NMR spectrum of this compound and the previously isolated 7-membered sulfonate **32** (Scheme 9). Cyclopropane **41** was quite unstable and decomposed during purification. Bis-tosylate **39** cyclised very cleanly using NaHMDS (LDA and KHMDS returned the majority of starting material) and mono-tosylate product **42** could be treated with sodium azide without prior purification to give *trans*-cyclopropane γ-azido ester **43** in good yield and high enantiomeric excess.

In brief, we have demonstrated that one-step intramolecular cyclisation is a useful way of constructing *trans*-cyclopropane products devoid of any *cis*-cyclopropane side-products. The synthetic routes presented herein are short (5–6 steps), starting from cheap, commercially available starting materials, giving orthogonally protected *trans*-cyclopropane γ-amino acids in useful overall yields (19–31%) and high enantiomeric excess (>92% ee). Moreover, when bis-phosphinate activation is employed the method can yield *trans*-cyclopropane γ-hydroxy carboxylic esters with terminal alkyl groups in good yield and high enantiomeric excess.

Acknowledgements

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42 D. J. Fox, S. Parris, D. S. Pedersen, C. R. Tyzack and S. Warren, *Org. Biomol. Chem.*, 2006, DOI: 10.1039/b606874j.
43 Crystal data for **40**. $C_{23}H_{29}O_4P$, $M = 400.43$, triclinic, space group $P1$, $a = 5.8939(2)$, $b = 8.5144(3)$, $c = 11.3355(4)$ Å, $\alpha = 82.108(2)$, $\beta = 87.448(2)$, $\gamma = 82.337(2)^\circ$, $U = 558.23(3)$ Å^3, $Z = 1$, μ(Mo-Kα) $= 0.147$ mm^{-1}, 5699 reflections collected at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3689 unique ($R_{int} = 0.025$); $R_1 = 0.035$, $wR_2 = 0.096$ [$I > 2\sigma(I)$], absolute structure parameter −0.08(8). CCDC reference number 600428. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606879k.

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