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Chemo- and diastereoselective cyclopropanation of allylic amines and carbamates

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ABSTRACT

A highly chemo- and diastereoselective protocol for the cyclopropanation of tertiary allylic amines with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] is described. The high levels of diastereoselectivity observed in these reactions may be attributed to chelation of the nitrogen atom to the zinc reagent, which then transfers a methylene unit to the *syn*-face of the olefin. Furthermore, a stereodivergent protocol for the cyclopropanation of a range of allylic carbamates has been developed, which provides access to both diastereoisomers of the corresponding cyclopropanes with very high levels of diastereoselectivity: cyclopropanation with the Wittig–Furukawa reagent [$Zn(CH_2I)_2$] proceeds under chelation control to give the corresponding *syn*-product, whilst reaction with Shi's carbenoid proceeds under steric control to give the corresponding *anti*-cyclopropane, in >95:5 dr in both cases.

1. Introduction

The cyclopropane motif is found in a wide range of natural products.[1] These range from very simple structures such 1-aminocyclopropanecarboxylic acid **1**, a biosynthetic precursor of the plant hormone ethylene,[2] to polycyclopropanated structures, such as the cholesteryl ester transfer protein inhibitor U-106305 **2**, isolated from the fermentation broth of *Streptomyces* sp. UC 11136 (Fig. 1).[3] In addition to being present in structures of wide-ranging complexity, the cyclopropane motif is also found in secondary metabolites from a variety of biosynthetic pathways. These include polyacetates, fatty acids, amino acids, polyether antibiotics, terpenoids, steroids and alkaloids.[4]

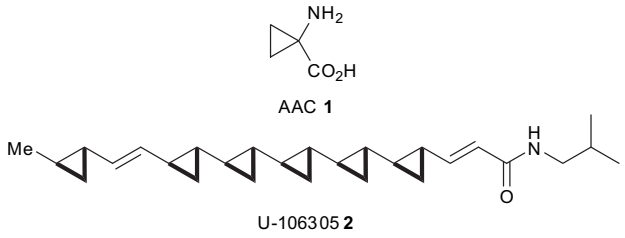

Fig. 1. Natural products containing the cyclopropane motif.

Although a wide range of methods have been developed to facilitate the stereoselective synthesis of cyclopropanes the area has been broadly dominated by three principal methods: (i) transition-metal catalysed decomposition of diazo compounds followed by addition to an olefin;[5–7] (ii) Michael-initiated ring closure (MIRC)[8,9] and (iii) the cyclopropanation of olefins with halomethyl metal reagents.[10,11] The Simmons–Smith cyclopropanation reaction has been one of the most widely used methods to promote the stereospecific conversion of an olefin into a cyclopropane for over 50 years,[12] and new classes of highly reactive zinc carbenoids have been developed, in particular over the past decade.[13] As such, the efficient cyclopropanation of isolated and electron poor double bonds is now possible, and the substrate scope of the reaction is therefore immensely broad.[10b] Diastereoselective cyclopropanation employing a zinc carbenoid, relying upon delivery of the incoming methylene group by the binding of an allylic hydroxyl group to the zinc atom, has long been exploited. Other groups including α,β-unsaturated acetals,[14] amides[15] and boronates[16] have also been shown to enable diastereoselective reaction. Although allylic amines have the same potential for directing cyclopropanation, the competing formation of a zinc-complexed ammonium ylide often thwarts cyclopropanation.[17] The diastereoselective Simmons–Smith cyclopropanation of allylic amines[18] using N-protecting groups bearing free hydroxyl moieties to promote cyclopropanation has recently been reported: Aggarwal et al.[19] demonstrated that treatment of **3** [derived from (1*R*,2*R*)-pseudoephredrine] with $Zn(CH_2I)_2$ gave the corresponding cyclopropane **4** in 95% yield and >99:1 dr whilst Katigiri et al.[20] reported that cyclopropanation of **6** [derived from (*S*)-1,2-epoxy-3,3,3-trifluoropropane]

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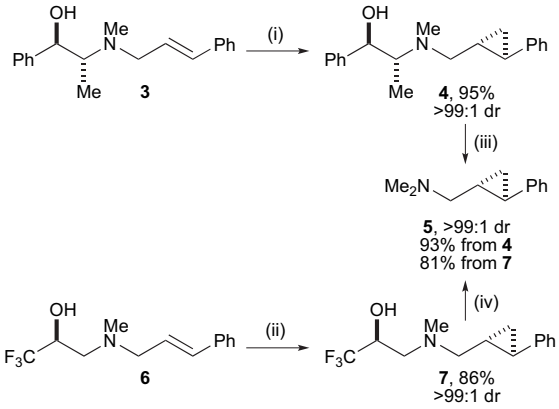
can be achieved to give **7** in 86% yield and >99:1 dr. One disadvantage of these approaches, however, is the relatively harsh reaction conditions required for removal of the *N*-substituent (via quarternization with MeI followed by treatment with base), which therefore inherently limits this methodology to the preparation of the corresponding *N*,*N*-dimethyl protected derivatives such as **5** (Scheme 1).



Scheme 1. Reagents and conditions: (i) $Zn(CH_2I)_2$, CH_2Cl_2, 0 °C, 2 days; (ii) $Zn(CH_2I)_2$, CH_2Cl_2, −5 °C, 1 h; (iii) MeI, 6 days then NaH, THF, reflux, 3.5 h; (iv) MeI, EtOH, reflux, 16 h then KO^{t}Bu, 18-crown-6, THF, rt, 24 h.

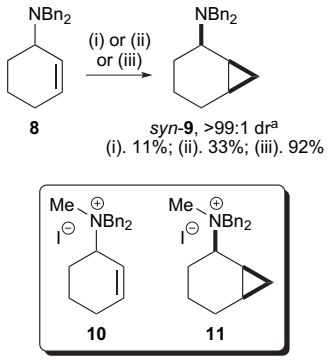
As part of an ongoing research programe directed towards the chemo- and stereoselective functionalisation of allylic amines at the olefin,[21–23] we became interested in the potential of allylic amines as substrates for the Simmons–Smith reaction. In this manuscript we report our full investigations into the cyclopropanation of allylic amines and their derivatives; part of this work has been communicated previously.[21]

2. Results and discussion

2.1. Cyclopropanation of 3-(*N*,*N*-dibenzylamino)cyclohexene: model studies

Initial studies focussed on cyclopropanation of our model substrate 3-(*N*,*N*-dibenzylamino)cyclohexene **8**.[24] Attempted cyclopropanation of **8** with the Wittig–Furukawa reagent $[Zn(CH_2I)_2]$[25] or Denmark's reagent $[Zn(CH_2Cl)_2]$[26] proceeded with almost complete consumption of starting material,[27] giving a low mass return of cyclopropane *syn*-**9** (>99:1 dr) as the only product in 11 and 33% isolated yield, respectively. Although no other products were isolated from these reactions, comparison of the ^{1}H NMR spectra of the crude reaction mixtures with those of authentic samples of *N*-methyl ammonium species **10** (prepared in quantitative conversion via treatment of **8** with MeI in MeCN at 40 °C for 2 days) and **11** (prepared via treatment of **9** with $Zn(CH_2I)_2$)[28] revealed that N-methylation was the major deleterious side-reaction in this system and accounts for the poor mass return. Cyclopropanation of **8** with the more reactive Shi's carbenoid $[CF_3CO_2ZnCH_2I]$,[13a] however, proceeded with full conversion to give *syn*-**9** in 92% isolated yield and >99:1 dr (Scheme 2).[29,30] The relative *syn*-configuration within **9** was proven unambiguously by single crystal X-ray analysis of the corresponding tetrafluoroborate salt **9**·HBF_4 (Fig. 2). This stereochemical outcome is presumably a result of initial binding of the zinc carbenoid by the nitrogen atom, followed by rapid intramolecular cyclopropanation.

A series of competition experiments was designed to probe further the hypothesis that the high *syn*-diastereoselectivity observed during the cyclopropanation of **8** was a result of a chelation



Scheme 2. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 1 h; (ii) Et_2Zn, ICH_2Cl, CH_2Cl_2, rt, 1 h; (iii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h. [[a]crude and purified].

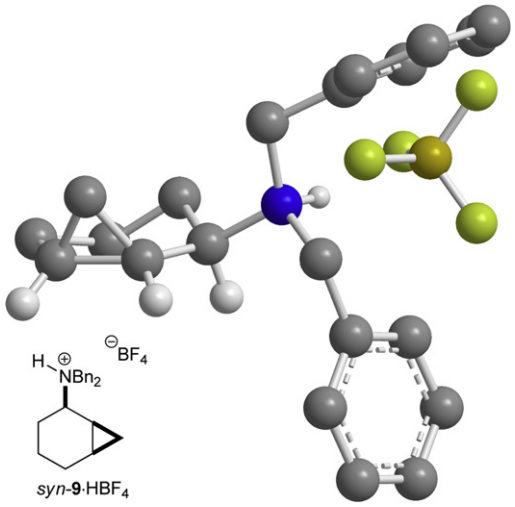
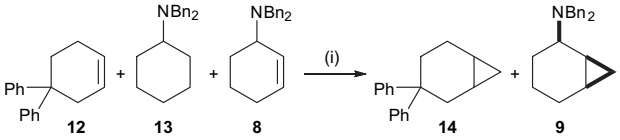


Fig. 2. Chem 3D representation of the single crystal X-ray structure of **9**·HBF_4 (some H atoms have been omitted for clarity).

controlled mechanism. 4,4-Diphenylcyclohex-1-ene **12** and *N*,*N*-dibenzylcyclohexylamine **13** were chosen as mimics for the olefin and tertiary amino functionalities within allylic amine **8**, respectively;[31] cyclohexene was deemed to be unsuitable for this purpose as its volatility (bp 83 °C), or indeed the volatility of the corresponding cyclopropane, would mean that accurate determination of the product distributions from any competition experiments would be extremely problematic. It was hoped that the *gem*-diphenyl group within **12** would significantly reduce this volatility, whilst being remote enough so as to not suppress the cyclopropanation reaction. Reaction of either **8** or **12** with 2.0 equiv of Shi's carbenoid $[CF_3CO_2ZnCH_2I]$ for 30 min resulted in essentially complete conversion (>98%) to give cyclopropanes *syn*-**9** (>99:1 dr) and **14**, respectively. The same reactions were then conducted in the presence 1.0 equiv of **13** (as an external tertiary amine) in each case. Reaction of **8** under these conditions resulted in >98% conversion to *syn*-**9** (>99:1 dr), whereas in the case of **12** cyclopropane **14** was produced in only 8% conversion. The observation that the rate of non-directed cyclopropanation of **12** is reduced by the presence of a tertiary amine is consistent with co-ordination of the nitrogen atom to zinc, stabilizing the carbenoid and reducing its reactivity.[32] In addition, the observation that the cyclopropanation of allylic amine **8** is not hindered by the presence of a tertiary amine suggests that chelation controlled cyclopropanation is taking place in this case. Furthermore, when an equimolar mixture of allylic amine **8** and olefin **12** was treated with 2.0 equiv of Shi's carbenoid for 30 min *syn*-**9** (>99:1 dr) was produced in >98% conversion, whereas only 9%

conversion to **14** was observed. An interesting observation is that in the case of cyclopropanation of **12** in the presence of amine **13**, 1.0 equiv of amine is able to inhibit 2.0 equiv of carbenoid. This suggests that the carbenoid is likely to be present as a dimer. In support of this, the reaction was repeated with 4.0 equiv of carbenoid, which resulted in >98% conversion to **14** after 30 min; this result is consistent with the amine sequestering 2.0 equiv of the carbenoid, leaving the other 2.0 equiv to effect cyclopropanation of **12** (Scheme 3).



12 (equiv)	13 (equiv)	8 (equiv)	$CF_3CO_2ZnCH_2I$ (equiv)	Coversion to 14 (%)	Coversion to 9 (%)[a]
0	0	1	2	--	>98
1	0	0	2	>98	--
1	1	0	2	8	--
0	1	1	2	--	>98
1	0	1	2	9	>98
1	1	0	4	>98	--

Scheme 3. Reagents and conditions: (i) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, 0 °C to rt, 30 min. [[a]>99:1 dr].

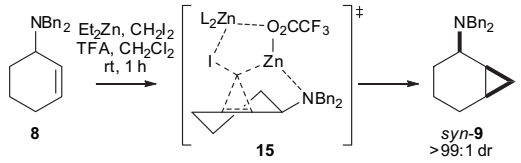
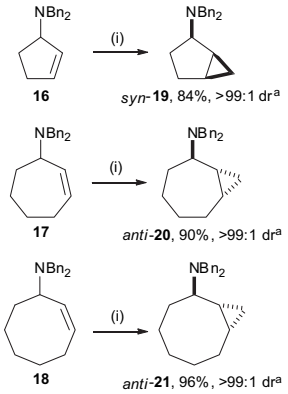


Fig. 3. Proposed transition state model **15** for the directed cyclopropanation of allylic amine **8** with Shi's carbenoid. [L=ligand].

These data are consistent with the cyclopropanation of allylic amine **8** proceeding via transition state model **15** where a dimeric zinc species derived from Shi's carbenoid [$CF_3CO_2ZnCH_2I$] is chelated to the nitrogen atom such that the carbenoid may be delivered to the *syn*-face of the double bond, producing *syn*-**9** with very high diastereoselectivity (Fig. 3).[33]

2.2. Cyclopropanation of 5-, 7- and 8-membered ring allylic amines

Having shown that the cyclopropanation of our model substrate **8** proceeds with excellent diastereoselectivity when Shi's carbenoid [$CF_3CO_2ZnCH_2I$] is employed, the scope of the reaction with respect to the corresponding 5-, 7- and 8-membered ring allylic amines **16**–**18**[34] was next investigated. Thus, treatment of the five-membered ring substrate **16** with Shi's carbenoid afforded *syn*-**19** in 84% yield and >99:1 dr. The relative *syn*-configuration within **19** was assigned by analogy to the stereochemical outome observed upon cyclopropanation of the six-membered ring substrate **8** (giving *syn*-**9**), and this assignment was further supported by ^{1}H NMR NOE analysis. This stereochemical outcome is consistent with our observations concerning the ammonium directed oxidation of five-membered ring substrate **16**[22c] and may be rationalised by coordination of the nitrogen atom to the zinc reagent followed by intramolecular delivery of the methylene unit to the *syn*-face, although minimisation of torsional strain in the transition state may also contribute.[35] Reaction of the 7- and 8-membered ring substrates **17** and **18** with $CF_3CO_2ZnCH_2I$ gave *anti*-**20** and *anti*-**21** in 90 and 96% yield, respectively, and in >99:1 dr in each case (Scheme 4). The relative *anti*-configurations within **20** and **21** were proven unambiguously by single crystal X-ray analyses (Figs. 4 and 5). These results are consistent with the high levels of *anti*-diastereoselectivity observed in our studies concerning the epoxidations of **17** and **18** by *m*-CPBA in the presence of Cl_3CCO_2H.[22c] The high degree of *anti*-diastereoselectivity in the cyclopropanation of **18** parallels the cyclopropanation of *cis*-cyclooct-2-en-1-ol,[36,37] which has also been reported as proceeding with complete *anti*-diastereoselectivity; the accepted explanation for *anti*-cyclopropanation in this case is that, in the preferred low-energy chair-boat conformation[38] of the cyclooctene ring, addition reactions can only occur on the sterically more accessible face of the olefin, which is not blocked by the rest of the ring. Indeed, in the solid-state both allylic amine **18**[39] and *anti*-cyclopropane **21** display chair-boat conformations, with the *N*,*N*-dibenzylamino group occupying a pseudobowsprit position. The high level of *anti*-diastereoselectivity observed in the



Scheme 4. Reagents and conditions: (i) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h. [[a]crude and purified].

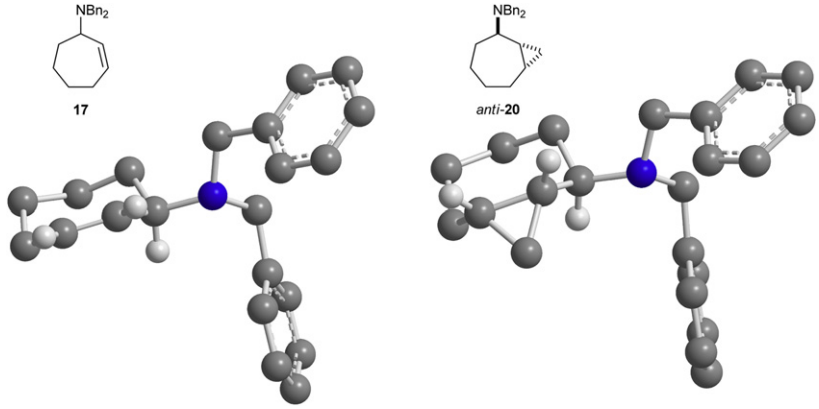


Fig. 4. Chem 3D representations of the single crystal X-ray structures of allylic amine **17** and *anti*-cyclopropane **20** (some H atoms have been omitted for clarity).

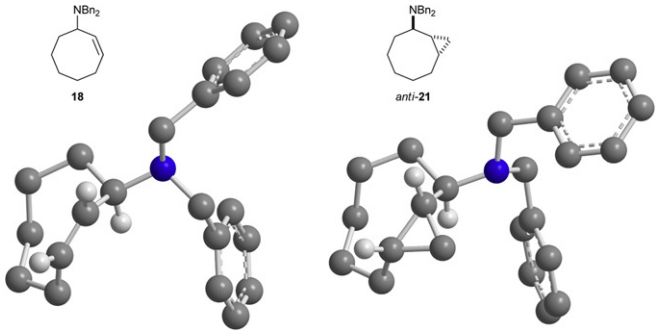


Fig. 5. Chem 3D representations of the single crystal X-ray structures of allylic amine **18** and *anti*-cyclopropane **21** (some H atoms have been omitted for clarity).

cyclopropanation of **17**, however, is in contrast to the poorly diastereoselective cyclopropanation of cyclohept-2-en-1-ol with either the Simmons–Smith[40] (Zn/Cu, CH_2I_2) or Molander[41] (Sm/Hg, CH_2I_2) reagents; in these cases the low diastereoselectivities suggest that the seven-membered ring is conformationally ill-defined, consistent with the known conformational lability of cycloheptene itself.[42] The sterically-demanding *N*,*N*-dibenzylamino group may therefore be enforcing a more well-defined ground state conformation, which is reflected in the transition state for the cyclopropanation of **17** and the stereochemical outcome may therefore be simply ascribed to reaction on the least hindered face. In the solid-state structures of both allylic amine **17**[43] and *anti*-cyclopropane **20** the seven-membered ring adopts a chair-type conformation, and it has been shown that both cycloheptene[42] and cycloheptene oxide[44] favour this conformation in solution. Therefore, chelation of the nitrogen atom to zinc resulting in chelation controlled cyclopropanation of neither **17** nor **18** need be invoked to explain the high diastereofacial selectivity, but may still be involved in stabilizing the transition state, especially when the relatively close proximity of the *N*,*N*-dibenzylamino group to the *anti*-face of the olefin is considered (Figs. 4 and 5).

2.3. Cyclopropanation of acyclic allylic amines

The effects of 1,2- and 1,3-allylic strain within the diastereoselective cyclopropanation reaction manifold were assessed by reaction of a range of acyclic *N*,*N*-dibenzyl substituted allylic amines **24**–**31** with Shi's carbenoid. The synthesis of the requisite substrates **24**–**31** employed the addition of a range of Grignard reagents to α-benzotriazolyl substituted amines **22** and **23**[45] to give allylic amines **24**–**31** in moderate to good yield and, where applicable, in sufficiently high diastereoisomeric purity (Scheme 5).

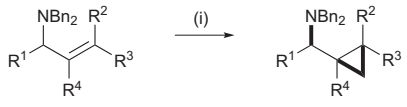
22 R^1 = Ph
23 R^1 = ^{i}Pr

24-31

Product	R^1	R^2	R^3	R^4	Yield %	dr (*E*):(*Z*)
24	Ph	Me	H	H	75	9:91
25	Ph	Me	Me	H	93	--
26	Ph	Me	H	Me	87	4:96
27	Ph	Me	Me	Me	40	--
28	^{i}Pr	Me	Me	H	88	--
29	Ph	H	Me	H	38	>99:1
30	Ph	H	H	H	92	--
31	Ph	H	H	Me	quant	--

Scheme 5. Reagents and conditions: (i) RMgX, PhMe, 50 °C, 2 h.

Treatment of substrates **24**–**28** with Shi's carbenoid gave cyclopropanes **32**–**36** as single diastereoisomers (>99:1 dr) in typically high yield, although the reaction of (*E*)-**29** (which experiences far less 1,3-allylic strain than **24**–**28**) with Shi's carbenoid proceeded to give 92% conversion to **37** in 89:11 dr, which was isolated in 60% yield (Scheme 6).[46] The relative configurations within **33** and **36** were unambiguously established by single crystal X-ray analyses (Figs. 6 and 7), and the relative configurations within the remaining cyclopropanes **32**, **34**, **35** and **37** were assigned by analogy.



24-29 **32-37**

Allylic amine	R^1	R^2	R^3	R^4	Product	Yield %	dr[a]
24	Ph	Me	H	H	**32**	66	>99:1
25	Ph	Me	Me	H	**33**	88	>99:1
26	Ph	Me	H	Me	**34**	71	>99:1
27	Ph	Me	Me	Me	**35**	37	>99:1
28	^{i}Pr	Me	Me	H	**36**	79	>99:1
29	Ph	H	Me	H	**37**[b]	60	89:11

Scheme 6. Reagents and conditions: (i) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h. [[a]crude and purified; [b]92% conversion].

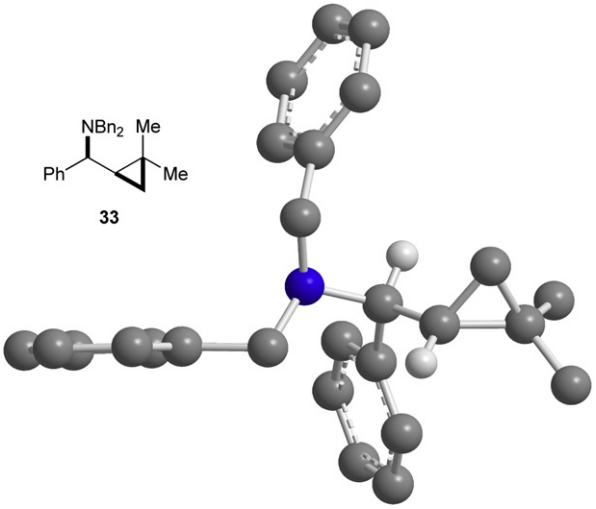


Fig. 6. Chem 3D representation of the single crystal X-ray structure of **33** (some H atoms have been omitted for clarity).

Treatment of allylic amines **30** and **31** (which contain a terminal olefin) with the deuterium labelled analogue of Shi's carbenoid [$CF_3CO_2ZnCD_2I$] gave cyclopropanes **39** and **41** in 72 and 94% yield, and 70:30 and 58:42 dr, respectively; comparable yields of the unlabelled cyclopropanes **38** and **40** were obtained upon reaction of **30** and **31** with $CF_3CO_2ZnCH_2I$ (Scheme 7).[47]

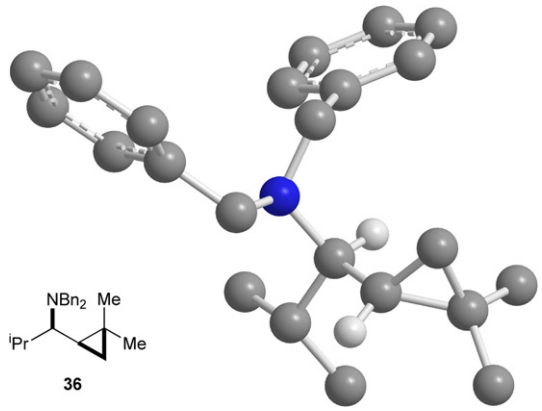
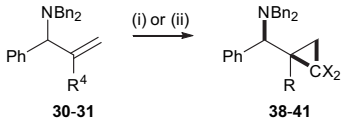


Fig. 7. Chem 3D representation of the single crystal X-ray structure of **36** (some H atoms have been omitted for clarity).



Allylic amine	R^4	Product	X	Yield %	dr[a]
30	H	**38**	H	73	--
30	H	**39**	D	72[b]	70:30
31	Me	**40**	H	94	--
31	Me	**41**	D	94	58:42

Scheme 7. Reagents and conditions: (i) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h; (ii) Et_2Zn, CD_2I_2, TFA, CH_2Cl_2, rt, 3 h. [[a]crude and purified; [b]86% conversion].

1,3-Allylic strain is minimised within the solid-state conformations of **33** and **36**, and it may also be reasoned that the corresponding allylic amines adopt a similar conformation in solution. The stereochemical outcome (and high levels of diastereoselectivity) observed in the cyclopropanation of acyclic allylic amines **24**–**28** is consistent with transition state model **43** in which 1,3-allylic strain is minimised and cyclopropanation occurs under chelation control (Fig. 8). The lower diastereoselectivity observed upon cyclopropanation of **29** (89:11 dr), **30** (70:30 dr) and **31** (58:42 dr) reflects their increased conformational freedom due to a decrease in 1,3-allylic strain.

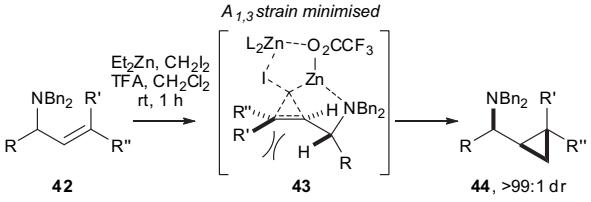
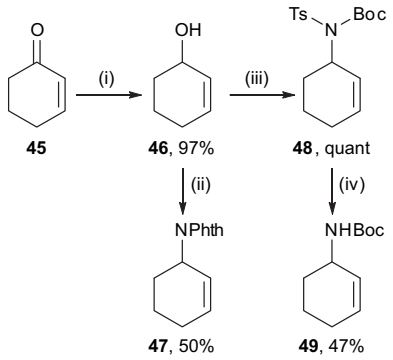


Fig. 8. Proposed transition state model for the directed cyclopropanation of acyclic allylic amines **24**–**28** with Shi's carbenoid.

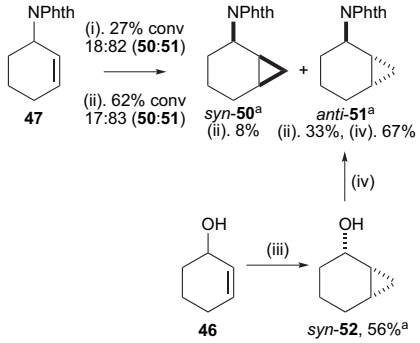
2.4. Cyclopropanation of allylic imides, carbamates, amides and sulfonamides

The N-protecting groups were next varied, in order to probe the possibility of preparing the corresponding *anti*-cyclopropanes. Representative substrates **47** and **49** were chosen for initial screening. Thus, cyclohexenone **45** was reduced under Luche conditions to give allylic alcohol **46** in 97% yield. Subsequent Mitsunobu reaction with either phthalimide or *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide gave **47** and **48** in 50% and quantitative yield, respectively. Finally, **48** was treated with sodium naphthalide to afford *tert*-butyl carbamate **49** in 47% yield (Scheme 8).



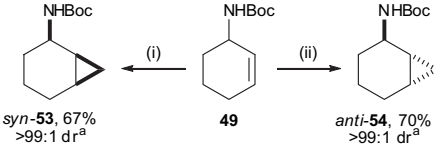
Scheme 8. Reagents and conditions: (i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (ii) phthalamide, PPh_3, DEAD, THF; (iii) TsNHBoc, PPh_3, DEAD, THF, rt, 24 h; (iv) sodium naphthalide, THF, rt, 3 h. [NPhth=phthalimido].

Reaction of **47** with $Zn(CH_2I)_2$ proceeded to 27% conversion (after 3 h), giving an 18:82 mixture of *syn*-**50**/*anti*-**51**,[48] whereas reaction of **47** with $CF_3CO_2ZnCH_2I$ under identical conditions gave 62% conversion to a 17:83 mixture of *syn*-**50**/*anti*-**51**, from which *syn*-**50** and *anti*-**51** were isolated as single diastereoisomers (>99:1 dr) in 8 and 33% yield, respectively. The relative configuration within *anti*-**51** was initially established via independent chemical synthesis from cyclohex-2-enol **46**:[49] cyclopropanation of allylic alcohol **46** with Denmark's reagent [$Zn(CH_2Cl)_2$] gave *syn*-**52** in 56% yield and >99:1 dr. Installation of the phthalimido group and inversion of configuration was then achieved by Mitsunobu reaction of *syn*-**52** with phthalimide to give *anti*-**51** in 67% yield and >99:1 dr (Scheme 9). Subsequent single crystal X-ray analysis of *syn*-**50** allowed its relative configuration (and therefore also the relative configuration within *anti*-**51**) to be unambiguously assigned.[50] Although the diastereoselectivity of cyclopropanation appears to be predominantly a result of steric control, competing chelation by one of the carbonyl groups may give rise to the minor product *syn*-**50**.



Scheme 9. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 3 h; (ii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 3 h; (iii) Et_2Zn, ICH_2Cl, CH_2Cl_2, rt, 1 h; (iv) phthalimide, PPh_3, DEAD, THF, rt, 24 h. [[a]Isolated in >99:1 dr; NPhth=phthalimido].

Cyclopropanation of allylic carbamate **49** was next investigated. Treatment of **49** with the Wittig–Furukawa reagent [$Zn(CH_2I)_2$] was found to give *syn*-cyclopropane **53** in >99:1 dr[51] and 67% isolated yield, whereas treatment of **49** with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] gave the corresponding *anti*-cyclopropane **54** in 70% yield and >99:1 dr (Scheme 10). The relative configurations



Scheme 10. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 3 h; (ii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 3 h. [[a]crude and purified].

within *syn*-**53** and *anti*-**54** were established via chemical correlation (vide infra).

The complementary diastereoselectivities of this reaction are postulated to be a result of initial formation of an intermediate zinc complex by deprotonation of the N*H* proton of the carbamate. In the case of $Zn(CH_2I)_2$ the co-ordinated zinc carbenoid **55** is able to effect intramolecular cyclopropanation of the double bond to give *syn*-**53**, whereas with $CF_3CO_2ZnCH_2I$ a second equivalent of the zinc reagent is required to undergo intermolecular cyclopropanation of the double bond by approach to the least hindered face of **56**, giving the corresponding *anti*-cyclopropane **54** (Fig. 9).[52]

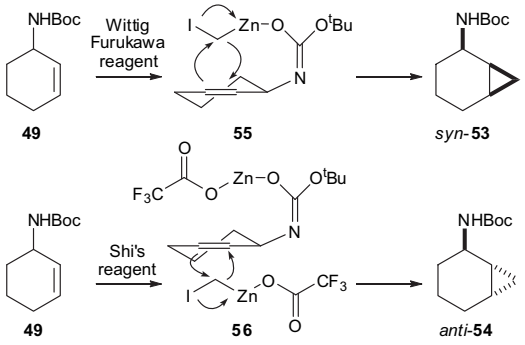
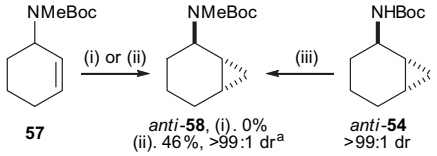


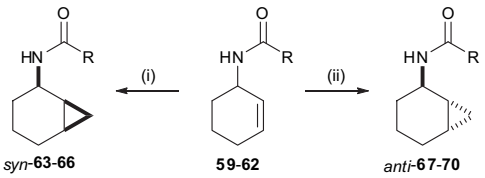
Fig. 9. Proposed mechanistic rationale for the stereodivergent cyclopropanation of allylic carbamate **49** with either $Zn(CH_2I)_2$ or $CF_3CO_2ZnCH_2I$.

Consistent with this hypothesis, treatment of allylic carbamate **49** with 1.0 equiv of $Zn(CH_2I)_2$ gave 37% conversion to *syn*-**53** after 1 h, whereas analogous treatment of **49** with 1.0 equiv of $CF_3CO_2ZnCH_2I$ gave no observable cyclopropanation products. Moreover, treatment of the corresponding *N*-methyl-*N*-Boc protected substrate **57**[23] with 2.0 equiv of $Zn(CH_2I)_2$ gave no reaction. When 2.0 equiv of $CF_3CO_2ZnCH_2I$ was employed, however, *anti*-**58** was isolated in 46% yield and >99:1 dr. In order to corroborate this stereochemical assignment, an authentic sample of *anti*-**58** was prepared via N-methylation of *anti*-**54** (Scheme 11).



Scheme 11. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 1 h; (ii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h; (iii) NaH, MeI, THF, 0 °C, 16 h. [^{a}crude and purified].

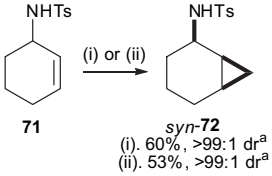
A range of other carbamates **59**–**61**[53] were next subjected to the optimised cyclopropanation conditions. In each case, treatment of carbamates **59**–**61** with the Wittig–Furukawa reagent $[Zn(CH_2I)_2]$ gave the corresponding *syn*-cyclopropanes **63**–**65** in >99:1 dr, whereas similar treatment of **59**–**61** with Shi's carbenoid $[CF_3CO_2ZnCH_2I]$ gave the corresponding *anti*-cyclopropanes **67**–**69** in ≥95:5 dr. Furthermore, this stereodivergent protocol also proved to be applicable to the cyclopropanation of allylic amides: treatment of benzamide **62** with the Wittig–Furukawa reagent gave *syn*-**66** in quantitative yield and >99:1 dr and treatment of **62** with Shi's carbenoid gave *anti*-**70** in 80% yield and >99:1 dr (Scheme 12). The relative configurations within *syn*-**65** and *anti*-**69** were initially assigned by ^{1}H NMR NOE analyses. In particular, *anti*-**69** exhibited a strong enhancement between C(2)*H* and C(7)H_A. Crucially, this enhancement was absent for *syn*-**65**, which instead showed a strong enhancement between N*H* and C(7)H_A. Subsequent chemical correlation studies unambiguously confirmed the assigned relative configurations within *syn*-**65** and *anti*-**69**; the relative configurations within the remaining cyclopropanated products **63**, **64**, **66**, **67**, **68** and **70** were assigned by analogy to those of the *N*-Boc and *N*-Cbz protected analogues **53**, **54**, **65** and **69**.



	R	Yield %	dr^a		R		R	Yield %	dr^a
63	OMe	99	>99:1	**59**	OMe	**67**	OMe	83^b	98:2
64	OPh	99	>99:1	**60**	OPh	**68**	OPh	75^c	95:5
65	OBn	84	>99:1	**61**	OBn	**69**	OBn	89	98:2
66	Ph	quant	>99:1	**62**	Ph	**70**	Ph	80^d	>99:1

Scheme 12. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 1 h; (ii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h. [^{a}crude and purified; ^{b}88% conversion; ^{c}80% conversion; ^{d}92% conversion].

Surprisingly, cyclopropanation of *N*-tosyl protected **71** with either the Wittig–Furukawa reagent $[Zn(CH_2I)_2]$ or Shi's carbenoid $[CF_3CO_2ZnCH_2I]$ gave the same product *syn*-**72** in 60 and 53% yield, respectively, and in >99:1 dr in each case (Scheme 13). The relative *syn*-configuration within **72** was initially established by ^{1}H NMR NOE studies and was then unambiguously established by single crystal X-ray analysis (Fig. 10).



Scheme 13. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 1 h; (ii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 12 h. [^{a}crude and purified].

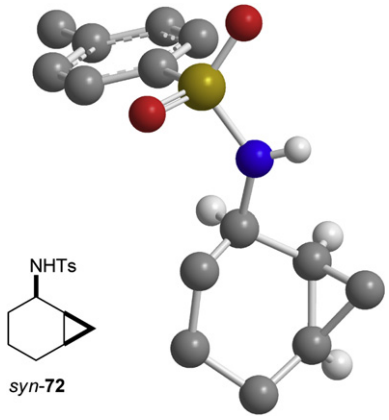
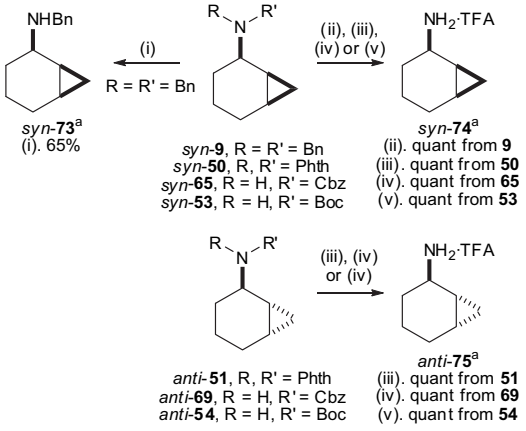


Fig. 10. Chem 3D representation of the single crystal X-ray structure of *syn*-**72** (some H atoms have been omitted for clarity).

2.5. *N*-Deprotections

In order to confirm the assigned relative configurations within these cyclopropanated products and to demonstrate the utility of this protocol in synthesis, deprotection of the *N*,*N*-dibenzyl, phthalimido, *N*-Cbz and *N*-Boc protected substrates was undertaken. It was found that under 1 atm of hydrogen, in the presence of Pd/C, selective mono-debenzylation of *syn*-**9** could be achieved allowing isolation of *syn*-**73** in 65% yield. Under more forcing conditions (5 atm) hydrogenolysis of *syn*-**9**, followed by treatment with TFA, gave *syn*-**74** in quantitative yield; in each case, no products arising

from cleavage of the cyclopropane ring were observed. Deprotection of the phthalimido groups within *syn*-**50** and *anti*-**51** was achieved upon treatment with hydrazine, giving *syn*-**74** and *anti*-**75** (after treatment with TFA) in quantitative yield and >99:1 dr in each case. Deprotection of the *N*-Cbz protected substrates *syn*-**65** and *anti*-**69** via hydrogenolysis also gave *syn*-**74** and *anti*-**75** (following treatment with TFA), both in quantitative yield and >99:1 dr; again no products arising from cleavage of the cyclopropane ring were observed in either case. Cleavage of the *N*-Boc protecting groups within *syn*-**53** and *anti*-**54** was achieved upon treatment with TFA giving *syn*-**74** and *anti*-**75** directly, in quantitative yield and >99:1 dr in each case (Scheme 14). These studies therefore allowed for the relative configurations within **53**, **54**, **65** and **69** to be unambiguously assigned.

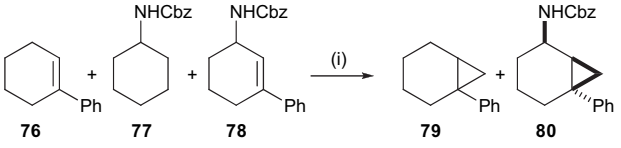


Scheme 14. Reagents and conditions: (i) H_2 (1 atm), Pd/C (50 wt %), MeOH/H_2O/AcOH (40:4:1), rt, 16 h; (ii) H_2 (5 atm), Pd/C (50% w/w), MeOH/H_2O/AcOH (40:4:1), rt, 12 h; (iii) NH_2NH_2, MeOH, reflux, 12 h; (iv) H_2 (1 atm), MeOH/EtOAc (4:1), rt, 1 h; (v) TFA, CH_2Cl_2, rt, 1 h. [[a]Isolated in >99:1 dr; NPhth=phthalimido].

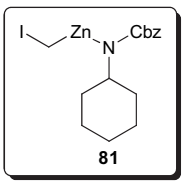
2.6. Cyclopropanation of allylic carbamates: mechanistic investigations

Having proposed that *syn*-cyclopropanation of the allylic carbamates occurs via intramolecular cyclopropanation, whereas *anti*-cyclopropanation occurs via intermolecular cyclopropanation, we wished to design a series of competition experiments to verify this hypothesis. We have recently reported the application of this stereodivergent cyclopropanation protocol in the syntheses of *trans*-SCH-A[54] and its epimer *cis*-SCH-A[11b] via the cyclopropanation of a C(3)-aryl substituted allylic carbamate[21b] in which C(3)-phenyl substituted allylic carbamate **78** was employed as a model system for reaction optimisation. Commercially available 1-phenylcyclohexene **76** (bp 251–253 °C) was selected as a suitable mimic for the olefin functionality within C(3)-phenyl substituted allylic carbamate **78**.[55] In addition, it was proposed that **77**[56] could be used as a mimic for the carbamate functionality within **78**. Reaction of 1-phenylcyclohexene **76** with 1.0 equiv of $Zn(CH_2I)_2$ for 60 min resulted in 13% conversion to cyclopropane **79**, whilst reaction with 2.0 equiv of $Zn(CH_2I)_2$ resulted in 20% conversion to **79**. Under identical conditions reaction of **76** in the presence of 1.0 equiv of carbamate **77** resulted in 24% conversion to **79** when 1.0 equiv of $Zn(CH_2I)_2$ was used and 44% conversion to **79** with 2.0 equiv of $Zn(CH_2I)_2$. The increased reactivity of **76** in the presence of carbamate **77** can be rationalized by the formation of intermediate iodomethylzinc amide **81** which, due to the electron withdrawing nature of the carbamate functionality, is postulated to be a more reactive carbenoid than $Zn(CH_2I)_2$, consistent with the observations of Shi et al.[13c] It should be noted, however, that the observed rate of intermolecular cyclopropanation mediated by iodomethylzinc amide **81** is still significantly slower than that observed for the cyclopropanation of allylic carbamate **78**,[57] consistent with intramolecular cyclopropanation in the latter case. In support of this hypothesis, cyclopropanation of 1-phenylcyclohexene **76** in the presence of 1.0 equiv of allylic carbamate **78** was next investigated. Reaction with 1.0 equiv of $Zn(CH_2I)_2$ resulted in 17% conversion of **76** to **79** and 96% conversion of **78** to **80**,[58] whereas reaction with 2.0 equiv of $Zn(CH_2I)_2$ resulted in 59% conversion of **76** to **79** and >98% conversion of **78** to **80** (Scheme 15). Moreover, further kinetic studies[59] revealed that cyclopropanation of **78** with 2.0 equiv of $Zn(CH_2I)_2$ was found to reach completion after only 25 min, whereas treatment of **76** with 2.0 equiv of $Zn(CH_2I)_2$ for 25 min only produced **79** in 27% conversion. These results strongly suggest that **78** reacts via an intramolecular cyclopropanation step, since the reaction rate is significantly higher than that observed for intermolecular cyclopropanation in the presence of an external carbamate (the ratio of **79**/**80** is ~1:8 respectively after 10 min).

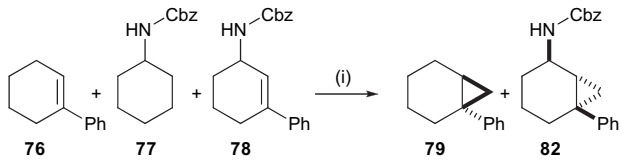
The same series of experiments were next performed with $CF_3CO_2ZnCH_2I$, in order to probe the proposed intermolecular nature of the *anti* selective cyclopropanation reaction manifold. Reaction of 1-phenylcyclohexene **76** with 1.0 equiv of $CF_3CO_2ZnCH_2I$ resulted in 53% conversion to **79**, whilst cyclopropanation of **76** with 2.0 equiv of $CF_3CO_2ZnCH_2I$ proceeded to give **79** in 95% conversion. In the presence of 1.0 equiv of carbamate **77**, reaction of **76** with 1.0 equiv of $CF_3CO_2ZnCH_2I$ gave **79** in only 4% conversion, consistent with 1.0 equiv of $CF_3CO_2ZnCH_2I$ being consumed by deprotonation of carbamate **77** to form intermediate **83**, whereas reaction with 2.0 equiv of $CF_3CO_2ZnCH_2I$ proceeded to give **79** in 72% conversion. As expected, reaction of **76** in the presence of allylic carbamate **78** and only 1.0 equiv of $CF_3CO_2ZnCH_2I$ resulted in extremely low conversion to either **79** or **82**. Reaction of **76** and **78** with 2.0 equiv of $CF_3CO_2ZnCH_2I$ resulted in 53% conversion of **78** to **82** and 61% conversion of **76** to **79**. Importantly, the carbenoid appears to show no strong preference for cyclopropanation of substrate **78** over 1-phenylcyclohexene **76**, consistent with an intermolecular rather than intramolecular cyclopropanation mechanism in each case (Scheme 16). These experiments support



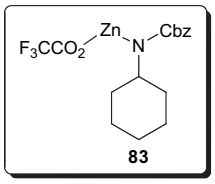
76 (equiv)	77 (equiv)	78 (equiv)	$Zn(CH_2I)_2$ (equiv)	Conversion to 79 (%)	Conversion to 80 (%)[a]
1	0	0	1	13	0
1	0	0	2	20	0
1	1	0	1	24	0
1	1	0	2	44	0
1	0	1	1	17	96
1	0	1	2	59	>98
0	0	1	2	0	>98



Scheme 15. Reagents and conditions: (i) $ZnEt_2$, CH_2I_2, CH_2Cl_2, rt, 60 min. [[a]>99:1 dr].



76 (equiv)	77 (equiv)	78 (equiv)	$F_3CCO_2ZnCH_2I$ (equiv)	Conversion to 79 (%)	Conversion to 82 (%)[a]
1	0	0	1	53	0
1	0	0	2	95	0
1	1	0	1	4	0
1	1	0	2	72	0
1	0	1	1	4	3
1	0	1	2	61	53



Scheme 16. Reagents and conditions; (i) $ZnEt_2$, CH_2I_2, TFA, CH_2Cl_2, rt, 60 min. [[a]>99:1 dr].

the proposed rationale that *syn*-cyclopropanation arises through chelation control whilst *anti*-cyclopropanation arises from a sterically directed intermolecular reaction.

3. Conclusion

In conclusion, a highly chemo- and diastereoselective protocol for the cyclopropanation of a range of cyclic and acyclic tertiary allylic amines employing Shi's carbenoid [$CF_3CO_2ZnCH_2I$] has been developed. The high levels of diastereoselectivity observed in these systems may be rationalised by chelation of the nitrogen atom to the carbenoid, which is then delivered to the *syn*-face of the olefin. In addition, the reaction of a range of cyclic allylic amides and carbamates with either the Wittig–Furukawa reagent [$Zn(CH_2I)_2$] or Shi's carbenoid provides access to both *syn*- and *anti*-diastereoisomers of the corresponding cyclopropanes, respectively, in high dr. This stereodivergent protocol is consistent with co-ordination of the zinc carbenoid to the nitrogen atom followed by either (i) intramolecular *syn*-cyclopropanation in the case of Zn $(CH_2I)_2$ or (ii) intermolecular *anti*-cyclopropanation by a second equivalent of the zinc reagent in the case of $CF_3CO_2ZnCH_2I$.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs et al.[60] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.2. General experimental procedures

4.2.1. General procedure 1: cyclopropanation with the Wittig–Furukawa reagent [$Zn(CH_2I)_2$]. CH_2I_2 (4.0 equiv) was added dropwise to a stirred solution of $ZnEt_2$ (1.0 M in hexanes, 2.0 equiv) in CH_2Cl_2 (0.5 M w.r.t. substrate) at −78 °C. The resultant mixture was vigorously stirred at 0 °C for 15 min resulting in the formation of a white precipitate. The requisite substrate (1.0 equiv) was then added to the reaction mixture, either neat or as a solution in CH_2Cl_2. The reaction mixture was stirred at rt for the specified time then satd aq Na_2EDTA (~1 mL/mmol) was added. The resultant mixture was vigorously stirred for 5 min then diluted with CH_2Cl_2 (~10 mL/mmol) and satd aq $NaHCO_3$ (~10 mL/mmol). The aqueous layer was extracted with three portions of CH_2Cl_2 and the combined organic extracts were dried and concentrated in vacuo.

Safety note: The preparation of $Zn(CH_2I)_2$ on a large-scale (>8 mmol) has been reported to be potentially explosive.[61] The modified procedure described above appears to significantly reduce the chance of explosion, and has been performed numerous times on large-scale (>20 mmol) without incident. The principal difference is the careful addition of CH_2I_2 to $ZnEt_2$ at −78 °C, which allows the gradual exothermic formation of $Zn(CH_2I)_2$.

4.2.2. General procedure 2: cyclopropanation with Shi's carbenoid [$CF_3CO_2ZnCH_2I$]. CH_2I_2 (4.0 equiv) was added dropwise to a stirred solution of $ZnEt_2$ (1.0 M in hexanes, 2.0 equiv) in CH_2Cl_2 (0.5 M) at −78 °C and the resultant mixture was allowed to stir at 0 °C for 15 min resulting in the formation of a white precipitate. TFA (2.0 equiv) was then added to the mixture resulting in the rapid formation of a homogeneous colourless solution which was allowed to stir at 0 °C for 15 min. The requisite substrate (1.0 equiv) was added to the mixture, either neat or as a solution in CH_2Cl_2. The resultant mixture was stirred at rt for the specified time then satd aq Na_2EDTA (~1 mL/mmol) was added. The resultant mixture was vigorously stirred for 5 min then diluted with CH_2Cl_2 (~10 mL/mmol) and satd aq $NaHCO_3$ (~10 mL/mmol). The aqueous layer was extracted with three portions of CH_2Cl_2 and the combined organic extracts were dried and concentrated in vacuo.

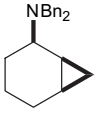
4.2.3. General procedure 3: synthesis of acyclic allylic amines. Method A: The requisite Grignard reagent (1.5 equiv) was added via syringe to a stirred solution of the requisite α-benzotriazole (1.0 equiv) in

PhMe (0.4 M) at rt. The resultant suspension was stirred at 50 °C for 2 h then allowed to cool to rt before satd aq NH_4Cl was carefully added. The resultant mixture was diluted with Et_2O and the aqueous layer was extracted with three portions of Et_2O. The combined organic extracts were washed sequentially with 1.0 M aq NaOH and brine, then dried and concentrated in vacuo.

Method B: The requisite vinyl bromide (1.5 equiv) was added dropwise to a stirred suspension of Mg turnings (1.5 equiv) and I_2 (cat) in THF (0.5 M) at rt. The resultant suspension was gently heated to initiate Grignard formation at which point the solution turned colourless. The reaction mixture was heated at reflux for 2 h (or until all the Mg had been consumed), then allowed to cool to rt before being transferred to a stirred solution of α-benzotriazole (1.0 equiv) in PhMe (0.25 M) at rt. The resultant suspension was stirred at 50 °C for 2 h then allowed to cool to rt before satd aq NH_4Cl was carefully added. The reaction mixture was then diluted with Et_2O and the aqueous layer was extracted with three portions of Et_2O. The combined organic extracts were washed sequentially with 1.0 M aq NaOH and brine, then dried and concentrated in vacuo.

4.2.4. General procedure 4: synthesis of allylic carbamates and amides. The requisite alcohol (1.0 equiv), either neat or as a solution in either THF or 1,4-dioxane, was added to a stirred solution of $Bi(OTf)_3$ (0.05 equiv), KPF_6 (0.05 equiv), $MgSO_4$ (~150 mg/mmol) and the requisite amide or carbamate (1.5 equiv) in THF or 1,4-dioxane (0.1–0.2 M) at rt. The resultant mixture was allowed to stir at rt for the specified time, then filtered through a pad of Celite (eluent Et_2O or EtOAc). The filtrate was then concentrated in vacuo.

4.3. (1*RS*,2*SR*,3*RS*)-*N*,*N*-Dibenzylbicyclo[4.1.0]heptan-2-amine 9

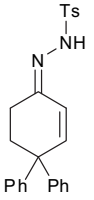


Following General procedure 2, **8**[24] (277 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (0.15 mL, 2.0 mmol) were reacted in CH_2Cl_2 (2.0 mL) for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1), **9** as a colourless oil (268 mg, 92%, >99:1 dr); ν_{max} (film) 2930 (C–H), 1494, 1453; δ_H (400 MHz, $CDCl_3$) 0.26–0.30 (1H, m, C(7)H_A), 0.62–0.68 (1H, m, C(7)H_B), 0.75–0.84 (1H, m, C(6)*H*), 0.97–1.08 (3H, m, C(1)*H*, C(4)H_A, C(3)H_A), 1.16–1.25 (1H, m, C(5)H_A), 1.36–1.42 (1H, m, C(4)H_B), 1.45–1.53 (1H, m, C(3)H_B), 1.73–1.80 (1H, m, C(5)H_B), 3.00–3.09 (1H, m, C(2)*H*), 3.64 (2H, d, *J* 14.1, N(CH_APh)$_2$), 3.69 (2H, d, *J* 14.1, N(CH_BPh)$_2$), 7.09–7.13 (2H, m, *Ph*), 7.18–7.22 (4H, m, *Ph*), 7.31–7.33 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.7 (*C*(6)), 11.2 (*C*(7)), 12.7 (*C*(1)), 22.5 (*C*(3)), 23.8 (*C*(4), *C*(5)), 54.4 (*C*(2), N(*C*H_2Ph)$_2$), 126.6, 128.2, 128.6 (*o*,*m*,*p*-*Ph*), 141.4 (*i*-*Ph*); *m*/*z* (ESI$^+$) 292 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}N^+$ ([M+H]$^+$) requires 292.2065, found 292.2065.

4.3.1. X-ray crystal structure determination for ***9***·HBF_4. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[62]

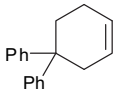
X-ray crystal structure data for **9**·HBF_4 [$C_{21}H_{26}BF_4N$]: M=379.25, monoclinic, space group $P\ 2_1/c$, a=9.3534(2) Å, b=15.3985(3) Å, c=13.8619(4) Å, β=100.7273(9)°, V=1961.62(8) Å^3, Z=4, μ=0.100 mm^{-1}, colourless plate, crystal dimensions=0.1×0.1×0.1 mm. A total of 4489 unique reflections were measured for $5<\theta<27$ and 2693 reflections were used in the refinement. The final parameters were wR_2=0.146 and R_1=0.057 [$I>3.0\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 783809. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4. 4,4-Diphenyl-2-cyclohexenone tosylhydrazone 85



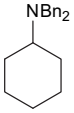
A solution of tosylhydrazide (825 mg, 4.43 mmol) in PhMe (5 mL) was added to a stirred solution of 4,4-diphenyl-2-cyclohexen-1-one **84** (1.00 g, 4.03 mmol) in MeOH (10 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo and the residue was dissolved in EtOAc (25 mL). The resultant solution was washed with H_2O (3×10 mL) then dried and concentrated in vacuo to give **85** as a pale yellow solid (1.62 g, 96%);[63] mp 165 °C (dec) (lit.[63] mp 191–192 °C); δ_H (400 MHz, $CDCl_3$) 2.23 (2H, t, *J* 6.3, C(5)H_2), 2.41–2.46 (2H, m, C(6)H_2) overlapping 2.44 (3H, s, CH_3), 6.37 (1H, d, *J* 10.2, C(2)*H*), 6.60 (1H, d, *J* 10.2, C(3)*H*), 7.15–7.38 (12H, m, *Ar*), 7.66 (1H, br s, N*H*), 7.85 (2H, d, *J* 8.3, *Ar*).

4.5. 4,4-Diphenylcyclohex-1-ene 12



Catechol borane (0.23 mL, 2.2 mmol) was added to a stirred solution of **85** (833 mg, 2.0 mmol) in $CHCl_3$ (5 mL) at 0 °C and the resultant mixture was stirred at rt for 2 h. NaOAc·$3H_2O$ (816 mg, 6.0 mmol) was then added and the reaction mixture was heated at 60 °C for 1 h before being allowed to cool to rt. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried and concentrated in vacuo. Purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 20:1 gradient elution) gave **12** as a white solid (351 mg, 75%);[63] mp 59–60 °C (lit.[63] mp 62–63 °C); δ_H (400 MHz, $CDCl_3$) 1.77–1.83 (2H, m, C(5)H_2), 2.38 (2H, t, *J* 6.1, C(6)H_2), 2.61–2.64 (2H, m, C(3)H_2), 5.64–5.70 (1H, m, C(1)*H*), 5.85–5.90 (1H, m, C(2)*H*), 7.15–7.29 (10H, m, *Ph*).

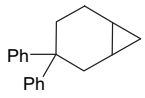
4.6. (*RS*)-*N*,*N*-Dibenzylcyclohexanamine 13



A mixture of cyclohexylamine **86** (0.44 mL, 4.0 mmol) and BnBr (0.96 mL, 8.0 mmol) in 0.5 M aq NaOH (17.6 mL, 8.8 mmol) was heated at 80 °C (microwave) for 30 min. The reaction mixture was then allowed to cool to rt and extracted with EtOAc (3×15 mL).

The combined organic extracts were then dried and concentrated in vacuo. Purification by flash column chromatography (30–40 °C petrol/EtOAc, 1:0 to 5:1 gradient elution) gave **13** as a white solid (940 mg, 84%);[64] mp 61–62 °C (lit.[64] mp 62 °C); δ_H (400 MHz, $CDCl_3$) 1.13–1.44 (6H, m, 6×CH_2), 1.81–1.89 (2H, m, 2×CH_2), 1.95–2.01 (2H, m, 2×CH_2), 2.56 (1H, tt, *J* 11.6, 3.4, C*H*NBn_2), 3.72 (4H, s, N(CH_2Ph)$_2$), 7.25–7.28 (2H, m, *Ph*), 7.34–7.49 (8H, m, *Ph*).

4.7. (*RS*,*RS*)-3,3-Diphenylbicyclo[4.1.0]heptane 14

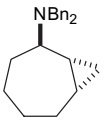


Following General procedure 2, **12** (28 mg, 0.10 mmol), $ZnEt_2$ (0.2 mL, 0.2 mmol), CH_2I_2 (30 μL, 0.4 mmol) and TFA (15 μL, 0.2 mmol) were reacted in CH_2Cl_2 (0.2 mL) for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1), **14** as a colourless oil (30 mg, quant); ν_{max} (film) 3055, 2995, 2935, 2860 (C–H), 1600, 1495, 1465, 1110, 1020, 765, 740, 700; δ_H (400 MHz, $CDCl_3$) 0.12–0.16 (1H, m, C(7)H_A), 0.66 (1H, app t, *J* 8.8, 4.5, C(7)H_B), 0.82 (1H, app tt, *J* 9.3, 5.0, C(6)*H*), 1.19–1.23 (1H, m, C(1)*H*), 1.44 (1H, app tt, *J* 13.5, 5.3, C(5)H_A), 1.65 (1H, app dd, *J* 15.0, 2.6, C(2)H_A), 1.81–1.86 (1H, m, C(5)H_B), 1.96 (1H, app td, *J* 13.2, 4.5, C(4)H_A), 2.13 (1H, app ddt, *J* 13.1, 5.0, 2.6, C(4)H_B), 2.95 (1H, app ddd, *J* 15.0, 9.2, 2.8, C(2)H_B), 7.13–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.4, 9.6 (*C*(1) and *C*(6)), 10.7 (*C*(7)), 19.8 (*C*(5)), 30.2 (*C*(4)), 38.1 (*C*(2)), 45.0 (*C*(3)), 125.4, 125.5, 126.6, 127.9, 128.0, 128.6 (*o*,*m*,*p*-*Ph*), 146.9, 152.0 (*i*-*Ph*); *m*/*z* (FI^+) 248 ($[M]^+$, 100%); HRMS (FI^+) $C_{19}H_{20}^+$ ($[M]^+$) requires 248.1572, found 248.1565.

4.8. (1*RS*,2*SR*,3*RS*)-*N*,*N*-Dibenzylbicyclo[3.1.0]hexan-2-amine 19

Following General procedure 2, **16**[34] (263 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (0.15 mL, 2.0 mmol) were reacted in CH_2Cl_2 (2.0 mL) for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1), **19** as a yellow oil (233 mg, 84%, >99:1 dr); ν_{max} (film) 3027, 2928, 2864, 2799 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 0.31–0.36 (1H, m, C(6)H_A), 0.56 (1H, app q, *J* 4.0, C(6)H_B), 1.18–1.24 (2H, m, C(5)*H*, C(3)H_A), 1.28–1.32 (1H, m, C(1)*H*), 1.61–1.66 (1H, m, C(3)H_B), 1.69–1.74 (2H, m, C(4)H_2), 3.41–3.46 (1H, m, C(2)*H*), 3.71–3.78 (4H, m, N(CH_2Ph)$_2$), 7.22–7.27 (2H, m, *Ph*), 7.33 (4H, app t, *J* 7.4, *Ph*), 7.42 (4H, d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.1 (*C*(6)), 15.1 (*C*(5)), 17.8 (*C*(1)), 23.0 (*C*(3)), 25.5 (*C*(4)), 55.9 (N(CH_2Ph)$_2$), 63.3 (*C*(2)), 126.5, 128.0, 128.8 (*o*,*m*,*p*-*Ph*), 140.7 (*i*-*Ph*); *m*/*z* (ESI^+) 278 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{24}N^+$ ($[M+H]^+$) requires 278.1903, found 278.1901.

4.9. (1*RS*,2*RS*,7*SR*)-*N*,*N*-Dibenzylbicyclo[5.1.0]octan-2-amine 20

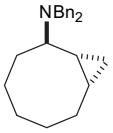


Following General procedure 2, **17**[34] (1.00 g, 3.43 mmol), $ZnEt_2$ (6.86 mL, 6.86 mmol), CH_2I_2 (1.10 mL, 13.7 mmol) and TFA (0.51 mL, 6.86 mmol) in CH_2Cl_2 (7 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 99:1 gradient elution), **20** as a white crystalline solid (940 mg, 90%, >99:1 dr); mp 43–45 °C; ν_{max} (KBr) 3025, 2920, 2850 (C–H), 1495, 1455, 1125, 1030, 975, 740, 700, 665; δ_H (400 MHz, $CDCl_3$) 0.08 (1H, q, *J* 4.7, C(8)H_A), 0.48–0.57 (1H, m, C(6)H_A), 0.72–0.78 (1H, m, C(7)*H*), 0.90 (1H, app td, *J* 8.0, 4.3, C(8)H_B), 0.97–1.13 (2H, m, C(1)*H* and C(4)H_A), 1.20–1.29 (1H, m, C(5)H_A), 1.65–1.76 (2H, m, C(3)H_A, C(5)H_B), 1.87–1.92 (1H, m, C(4)H_B), 1.98–2.03 (1H, m, C(3)H_B), 2.08–2.14 (1H, m, C(6)H_A), 2.22 (1*H*, t, *J* 9.8, C(2)*H*), 3.75 (4H, s, N(CH_2Ph)$_2$), 7.21–7.25 (2H, m, *Ph*), 7.32 (4H, app t, *J* 7.4, *Ph*), 7.45 (4H, app d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.8 (*C*(7)), 15.6, 15.6 (*C*(1), *C*(8)), 28.9 (*C*(5)), 30.1 (*C*(4)), 31.1 (*C*(6)), 35.5 (*C*(3)), 54.2 (N(CH_2Ph)$_2$), 61.4 (C(2)), 128.1, 128.5, 128.5 (*o*,*m*,*p*-*Ph*), 141.1 (*i*-*Ph*); *m*/*z* (CI^+) 306 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{22}H_{28}N^+$ ($[M+H]^+$) requires 306.2222, found 306.2233.

*4.9.1. X-ray crystal structure determination for **20**.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[62]

X-ray crystal structure data for **20** [$C_{22}H_{27}N$]: M=305.46, monoclinic, space group C 2/c, a=25.5945(4) Å, b=9.9031(2) Å, c=14.6450(2) Å, β=104.7501(8)°, V=3589.67(10) Å^3, Z=8, μ=0.065 mm^{-1}, colourless plate, crystal dimensions=0.05 ×0.05×0.1 mm. A total of 4068 unique reflections were measured for 5<θ<27 and 4068 reflections were used in the refinement. The final parameters were wR_2=0.116 and R_1=0.070 [I>−3.0σ(I)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 783810. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.10. (1*RS*,2*RS*,8*SR*)-*N*,*N*-Dibenzylbicyclo[6.1.0]octan-2-amine 21



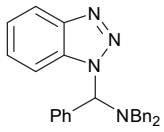
Following General procedure 2, **18**[34] (916 mg, 3.0 mmol), $ZnEt_2$ (6.0 mL, 6.0 mmol), CH_2I_2 (0.97 mL, 12.0 mmol) and TFA (0.45 mL, 6.0 mmol) in CH_2Cl_2 (6 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 9:1 gradient elution), **21** as a white crystalline solid (920 mg, 96%, >99:1 dr); mp 80–82 °C; ν_{max} (KBr) 3060, 2925, 2850 (C–H), 1490, 1455, 1125, 1025, 905, 745, 700, 665; δ_H (400 MHz, $CDCl_3$) 0.03–0.06 (1H, m, C(9)H_A), 0.36–0.46 (1H, m, C(7)H_A), 0.69–0.84 (3H, m, C(1)*H*, C(8)*H* and C(9)H_B), 0.97–1.05 (1H, m, C(5)H_A), 1.23–1.33 (1H, m, C(6)H_A), 1.42–1.69 (5H, m, C(3)H_A, C(4)H_2, C(5)H_B and C(6)H_B), 1.77–1.82 (1H, m, C(3)H_B), 1.87–1.95 (1H, m, C(7)H_B), 2.24 (1H, app dt, *J* 10.4, 3.3, C(2)*H*), 3.63 (2H, d, *J* 13.8, N(CH_APh)$_2$), 3.84 (2H, d, *J* 13.8, N(CH_BPh)$_2$), 7.22–7.25 (2H, m, *Ph*), 7.32 (4H, app t, *J* 7.4, *Ph*), 7.44 (4H, app d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.9 (*C*(9)), 15.3, 17.5 (*C*(1), *C*(8)), 25.4 (*C*(4)), 27.0 (*C*(5)), 28.6 (*C*(7)), 29.9 (*C*(6)), 30.7 (*C*(3)), 54.2 (N(CH_2Ph)$_2$), 55.8 (*C*(2)), 126.6, 128.1, 128.7 (*o*,*m*,*p*-*Ph*), 141.3 (*i*-*Ph*); *m*/*z* (ESI^+) 320 ($[M+H]^+$,

100%); HRMS (CI^+) $C_{23}H_{30}N^+$ ($[M+H]^+$) requires 320.2378, found 320.2375.

*4.10.1. X-ray crystal structure determination for **21**.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[62]

X-ray crystal structure data for **21** [$C_{23}H_{29}N$]: M=319.49, monoclinic, space group $P\,2_1/c$, a=12.1237(3) Å, b=10.8303(2) Å, c=14.6175 (3) Å, β=95.1731(11)°, V=1911.51(7) Å^3, Z=4, μ=0.063 mm^{-1}, colourless plate, crystal dimensions=0.1×0.1×0.2 mm. A total of 4334 unique reflections were measured for $5<\theta<27$ and 3204 reflections were used in the refinement. The final parameters were wR_2=0.179 and R_1=0.079 [$I>3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 783811. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.11. (*RS*)-1-[α-(Dibenzylamino)benzyl]benzotriazole 22

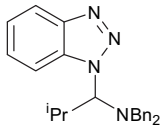


A solution of benzaldehyde (10.1 mL, 100 mmol), dibenzylamine (19.2 mL, 100 mmol) and benzotriazole (11.9 g, 100 mmol) in MeOH/Et_2O (1:1, 100 mL) was stirred at rt for 30 min, then the resultant homogeneous solution was stored at 0 °C for 16 h resulting in the precipitation of a white solid. The mixture was then filtered and the solid residue was triturated with cold Et_2O to give **22** (3:1 mixture of regioisomers) as a white solid (35.3 g, 87%).

Data for mixture: mp 144–146 °C (lit.[65] mp 153°C).

Data for major isomer: δ_H (400 MHz, $CDCl_3$) 3.51 (2H, d, J 14.2, N(CH_APh)$_2$), 4.26 (2H, d, J 14.2, N(CH_BPh)$_2$), 6.85 (1H, s, PhC*H*), 7.25–7.45 (18H, m, *Ar*), 8.19 (1H, d, J 8.2, *Ar*).

4.12. (*RS*)-*N*-(1-Benzotriazol-1-yl-2-methylpropyl) dibenzylamine 23

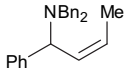


A solution of isobutyraldehyde (9.13 mL, 100 mmol), dibenzylamine (19.2 mL, 100 mmol) and benzotriazole (11.9 g, 100 mmol) in MeOH/Et_2O (1:1, 100 mL) was stirred at rt for 30 min, then the resultant homogeneous solution was stored at 0 °C for 16 h resulting in the precipitation of a white solid. The mixture was then filtered and the solid residue was triturated with cold Et_2O to give **23** (2:1 mixture of regioisomers) as a white solid (29.8 g, 81%).

Data for mixture: mp 96–98 °C (lit.[66] mp 83–85°C).

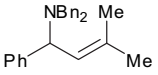
Data for major isomer: δ_H (400 MHz, $CDCl_3$) 0.48 (3H, d, J 6.5, CHMe_A), 1.39 (3H, d, J 6.5, CHMe_B), 3.01–3.14 (1H, m, C*H*Me$_2$), 3.21–3.30 (4H, m, N(CH_2Ph)$_2$), 5.09 (1H, d, J 10.6, *CH*CHMe$_2$), 7.06–7.09 (1H, m, *Ar*), 7.27–7.50 (11H, m, *Ar*), 7.97–8.00 (1H, m, *Ar*), 8.11–8.13 (1H, m, *Ar*).

4.13. (*RS,Z*)-*N,N*-Dibenzyl-1-phenylbut-2-ene-1-amine 24



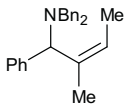
Following General procedure 3, **22** (2.02 g, 5.00 mmol), (*Z*)-1-bromoprop-1-ene (0.64 mL, 7.5 mmol) and Mg (182 mg, 7.5 mmol) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **24** as a white solid (1.23 g, 75%, 91:9 dr);[67] mp 53–55 °C; ν_{max} (film) 3027 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 1.51 (3H, d, J 5.8, C(4)H_3), 3.53 (2H, d, J 14.8, N(CH_APh)$_2$), 3.78 (2H, d, J 14.8, N(CH_BPh)$_2$), 4.67 (1H, d, J 9.8, C(1)*H*), 5.84 (1H, app t, J 10.2, C(2)*H*), 5.99 (1H, m, C(3)*H*), 7.25–7.46 (13H, m, *Ph*), 7.61 (2H, app d, J 7.6, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (*C*(4)), 53.8 (N(CH_2Ph)$_2$), 58.4 (*C*(1)), 126.8 (*C*(3)), 128.2 (*C*(2)), 126.8, 126.9, 128.1, 128.2, 128.7, 128.9 (*o,m,p-Ph*), 140.2, 140.4 (*i-Ph*); m/z (ESI^+) 328 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{26}N^+$ ($[M+H]^+$) requires 328.2060, found 328.2059.

4.14. (*RS*)-*N,N*-Dibenzyl-3-methyl-1-phenylbut-2-en-1-amine 25



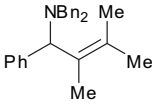
Following General procedure 3, **22** (2.02 g, 5.00 mmol) and 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 15.0 mL, 7.5 mmol) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **25** as a pale yellow oil (1.59 g, 93%); ν_{max} (film) 3027 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 1.54 (3H, s, C(3)Me_A), 1.94 (3H, s, C(3)Me_B), 3.57 (2H, d, J 13.8, N(CH_APh)$_2$), 3.77 (2H, d, J 13.8, N(CH_BPh)$_2$), 4.58 (1H, d, J 9.8, C(1)*H*), 5.60 (1H, d, J 9.8, C(2)*H*), 7.25–7.28 (3H, m, *Ph*), 7.34–7.41 (6H, m, *Ph*), 7.47 (4H, d, J 7.6, *Ph*), 7.61 (2H, app d, J 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(3)Me_A), 26.2 (C(3)Me_B), 53.9 (N(CH_2Ph)$_2$), 60.1 (*C*(1)), 121.5 (*C*(3)), 126.7, 126.7, 128.1, 128.2, 128.7, 128.7 (*o,m,p-Ph*), 136.7 (*C*(2)), 140.4, 143.1 (*i-Ph*); m/z (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{28}N^+$ ($[M+H]^+$) requires 342.2216, found 342.2217.

4.15. (*RS,Z*)-*N,N*-Dibenzyl-2-methyl-1-phenylbut-2-en-1-amine 26



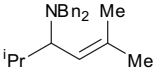
Following General procedure 3, **22** (1.01 g, 2.50 mmol), (*Z*)-2-bromobut-2-ene (0.38 mL, 3.75 mmol) and Mg (91 mg, 3.75 mmol) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **26** as a colourless oil (740 mg, 87%, 96:4 dr); ν_{max} (film) 3027, 2925 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$), 1.87 (3H, d, J 6.8, C(4)H_3), 1.97 (3H, s, C(2)*Me*), 3.86 (2H, d, J 14.6, N(CH_APh)$_2$), 4.03 (2H, d, J 14.6, N(CH_BPh)$_2$), 5.05 (1H, s, C(1)*H*), 5.61 (1H, q, J 6.8, C(3)*H*), 7.43–7.46 (3H, m, *Ph*), 7.51–7.60 (10H, m, *Ph*), 7.78 (2H, d, J 7.6, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(4)), 19.6 (C(2)*Me*), 52.8 (N(CH_2Ph)$_2$), 63.9 (*C*(1)), 124.2 (*C*(3)), 126.9, 126.9, 128.3, 128.3, 128.5, 129.5 (*o,m,p-Ph*), 136.6 (*C*(2)), 138.8, 142.1 (*i-Ph*); m/z (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{28}N^+$ ($[M+H]^+$) requires 342.2216, found 342.2217.

4.16. (*RS*)-*N*,*N*-Dibenzyl-2,3-dimethyl-1-phenylbut-2-en-1-amine 27



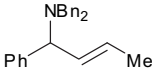
Following General procedure 3, **22** (2.02 g, 5.00 mmol), 2-bromo-3-methylbut-2-ene (0.87 mL, 7.5 mmol) and Mg (182 mg, 7.5 mmol) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol), **27** as a yellow oil (713 mg, 40%); ν_{max} (film) 3027, 2923 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 1.87 (3H, s, C(3)Me_A), 1.89 (3H, s, C(2)*Me*), 2.03 (3H, s, C(3)Me_B), 3.89 (2H, d, *J* 14.4, N(CH_APh)$_2$), 4.00 (2H, d, *J* 14.4, N(CH_BPh)$_2$), 5.12 (1H, s, C(1)*H*), 7.45–7.49 (4H, m, *Ph*), 7.54–7.61 (9H, m, *Ph*), 7.81 (2H, app d, *J* 7.6, *Ph*); δ_C (400 MHz, $CDCl_3$) 14.0 (C(2)*Me*), 21.1 (C(3)Me_A), 21.7 (C(3)Me_B), 53.2 (N(CH_2Ph)$_2$), 66.1 (*C*(1)), 126.7, 126.9, 128.3, 128.3, 128.4, 129.5 (*o*,*m*,*p*-*Ph*), 128.8 (*C*(3)), 129.0 (*C*(2)), 139.1, 143.0 (*i*-*Ph*); *m*/*z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}N^+$ ([M+H]$^+$) requires 356.2373, found 356.2377.

4.17. (*RS*)-*N*,*N*-Dibenzyl-2,5-dimethylhex-4-en-3-amine 28



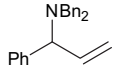
Following General procedure 3, **23** (1.85 g, 5.00 mmol) and 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 15.0 mL, 7.5 mmol) in PhMe (25 mL) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol), **28** as a white solid (1.35 g, 88%); mp 42–44 °C; ν_{max} (KBr) 3025, 2955, 2920 (C–H), 1495, 1455, 1100, 1070, 1030, 975, 740, 700; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.6, C(2)Me_A), 1.27 (3H, d, *J* 6.6, C(2)Me_B), 1.56 (3H, s, C(5)Me_A), 1.88–1.93 (1H, m, C(2)*H*), 1.96 (3H, s, C(5)Me_B), 2.93 (1H, app t, *J* 10.4, C(3)*H*), 3.42 (2H, d, *J* 14.2, N(CH_APh)$_2$), 3.95 (2H, d, *J* 14.2, N(CH_BPh)$_2$), 5.29 (1H, d, *J* 10.6, C(4)*H*), 7.30–7.33 (2H, m, *Ph*), 7.41 (4H, app t, *J* 7.5, *Ph*), 7.55 (4H, app d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(5)Me_A), 20.7 (C(2)Me_2), 26.2 (C(5)Me_B), 30.4 (*C*(2)), 53.9 (N(CH_2Ph)$_2$), 62.9 (*C*(3)), 122.4 (*C*(4)), 126.6, 128.2, 128.7 (*o*,*m*,*p*-*Ph*), 136.0 (*C*(5)), 141.1 (*i*-*Ph*); *m*/*z* (CI$^+$) 264 ([M–C_3H_7]$^+$, 100%), 308 ([M+H]$^+$, 10%); HRMS (CI$^+$) $C_{22}H_{30}N^+$ ([M+H]$^+$) requires 308.2378, found 308.2364.

4.18. (*RS*,*E*)-*N*,*N*-Dibenzyl-1-phenylbut-2-ene-1-amine 29



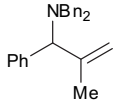
^{t}BuLi (1.7 M in pentane, 8.82 mL, 15.0 mmol) was added to a stirred solution of (*E*)-1-bromoprop-1-ene (0.64 mL, 7.5 mmol) in Et_2O (30 mL) at −78 °C and the resultant mixture was stirred for 1 h at −78 °C. Solid $MgBr_2 \cdot OEt_2$ (1.55 g, 6.00 mmol) was then added and the reaction mixture was allowed to warm to 0 °C over 30 min, and was then added to a solution of **22** (2.02 g, 5.0 mmol) in PhMe (30 mL) at 0 °C via cannula. The resultant mixture was stirred at 0 °C for 2 h then satd aq NH_4Cl (20 mL) was added. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic extracts were washed with 1.0 M aq NaOH (30 mL) and brine (30 mL), then dried and concentrated in vacuo. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **29** as a white solid (621 mg, 38%, >99:1 dr); mp 60–61 °C; ν_{max} (KBr) 3025 (C–H), 1495, 1450, 1030, 975, 745, 700, 665; δ_H (400 MHz, $CDCl_3$) 1.97 (3H, d, *J* 7.1, C(4)H_3), 3.65 (2H, d, *J* 13.7, N(CH_APh)$_2$), 3.81 (2H, d, *J* 13.7, N(CH_BPh)$_2$), 4.37 (1H, d, *J* 8.6, C(1)*H*), 5.70–5.79 (1H, m, C(3)*H*), 5.84–5.90 (1H, m, C(2)*H*), 7.34 (3H, app q, *J* 7.0, *Ph*), 7.42–7.47 (6H, m, *Ph*), 7.55 (4H, d, *J* 7.1, *Ph*), 7.66 (2H, d, *J* 7.8, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (*C*(4)), 53.9 (N(CH_2Ph)$_2$), 64.7 (*C*(1)), 126.8, 126.9, 128.2, 128.2, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 129.0 (*C*(2)), 130.5 (*C*(3)), 140.4, 142.6 (*i*-*Ph*); *m*/*z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N^+$ ([M+H]$^+$) requires 328.2060, found 328.2056.

4.19. (*RS*)-*N*,*N*-Dibenzyl-1-phenyl-prop-2-en-1-amine 30



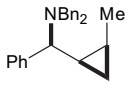
Following General procedure 3, **22** (2.02 g, 5.00 mmol) and vinylmagnesium chloride (1.6 M in THF, 4.69 mL, 7.5 mmol) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **30** as a yellow oil (1.45 g, 92%); ν_{max} (film) 3027 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 3.56 (2H, d, *J* 13.8, N(CH_APh)$_2$), 3.70 (2H, d, *J* 13.8, N(CH_BPh)$_2$), 4.30 (1H, d, *J* 8.6, C(1)*H*), 5.24 (1H, dd, *J* 17.2, 1.0, C(3)H_A), 5.48 (1H, dd, *J* 10.1, 1.0, C(3)H_B), 6.09–6.18 (1H, m, C(2)*H*), 7.23–7.29 (3H, m, *Ph*), 7.32–7.39 (6H, m, *Ph*), 7.44 (4H, d, *J* 7.3, *Ph*), 7.53 (2H, d, *J* 7.6, *Ph*); δ_C (100 MHz, $CDCl_3$) 53.7 (N(CH_2Ph)$_2$), 65.2 (*C*(1)), 119.4 (*C*(3)), 126.8, 127.0, 128.1, 128.2, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 135.3 (*C*(2)), 140.0, 141.4 (*i*-*Ph*); *m*/*z* (ESI$^+$) 314 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{24}N^+$ ([M+H]$^+$) requires 314.1903, found 314.1899.

4.20. (*RS*)-*N*,*N*-Dibenzyl-2-methyl-1-phenylprop-2-en-1-amine 31



Following General procedure 3, **22** (809 mg, 2.00 mmol) and *iso*-propenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol) were reacted to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **31** as a yellow oil (655 mg, quant); ν_{max} (film) 3027 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 1.79 (3H, s, C(2)*Me*), 3.50 (2H, d, *J* 14.4, N(CH_APh)$_2$), 3.81 (2H, d, *J* 14.4, N(CH_BPh)$_2$), 4.30 (1H, s, C(1)*H*), 5.02 (1H, app br s, C(3)H_A), 5.16 (1H, app br s, C(3)H_B), 7.25–7.28 (2H, m, *Ph*), 7.33–7.41 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (C(2)*Me*), 53.4 (N(CH_2Ph)$_2$), 70.1 (*C*(1)), 114.3 (*C*(3)), 126.8, 127.0, 128.0, 128.2, 128.8, 129.4 (*o*,*m*,*p*-*Ph*), 138.9, 139.3 (*i*-*Ph*), 145.6 (*C*(2)); *m*/*z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N^+$ ([M+H]$^+$) requires 328.2060, found 328.2061.

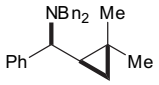
4.21. (1*RS*,1′*SR*,2′*RS*)-*N*,*N*-Dibenzyl-1-(2′-methylcyclopropyl)-1-phenylmethanamine 32



Following General procedure 2, **24** (327 mg, 1.0 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (0.15 mL, 2.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol), **32** as a white solid (226 mg, 66%, >99:1 dr); mp 48–50 °C; ν_{max} (KBr) 3027, 2919, 2833, 2805 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 0.35 (1H, app q, *J* 5.0, C(3′)H_A), 0.77 (3H, d, *J* 6.3, C(2′)*Me*), 0.96–1.02 (1H, m, C(2′)*H*), 1.09–1.17 (1H, m, C(3′)H_B), 1.38–1.47 (1H, m, C(1′)*H*), 3.46

(1H, d, *J* 10.6, C(1)*H*), 3.66 (2H, d, *J* 13.6, N(C*H*$_A$Ph)$_2$), 3.93 (2H, d, *J* 13.6, N(C*H*$_B$Ph)$_2$), 7.28–7.53 (13H, m, *Ph*), 7.63 (2H, d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.3 (*C*(3′)), 13.0 (*C*(2′)), 13.5 (C(3′)*Me*), 14.2 (*C*(1′)), 54.0 (N(*C*H$_2$Ph)$_2$), 60.7 (*C*(1)), 126.7, 126.8, 127.9, 128.2, 128.8, 128.8 (*o*,*m*,*p*-*Ph*), 140.8, 142.7 (*i*-*Ph*); *m*/*z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}N^+$ ([M+H]$^+$) requires 342.2216, found 342.2215.

4.22. (1*RS*,1′*SR*)-*N*,*N*-Dibenzyl-1-(2′,2′-dimethylcyclopropyl)-1-phenylmethanamine 33

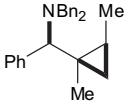


Following General procedure 2, **25** (171 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **33** as a white solid (156 mg, 88%, >99:1 dr); mp 60–62 °C; ν_{max} (film) 3027 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 0.47 (1H, app t, *J* 4.9, C(3′)*H*$_A$), 0.68 (3H, s, C(2′)*Me*$_A$), 0.85 (1H, dd, *J* 8.3, 4.3, C(3′)*H*$_B$), 1.14–1.20 (1H, m, C(1′)*H*), 1.18 (3H, s, C(2′)*Me*$_B$), 3.42 (1H, d, *J* 10.6, C(1)*H*), 3.63 (2H, d, *J* 13.6, N(C*H*$_A$Ph)$_2$), 3.82 (2H, d, *J* 13.6, N(C*H*$_B$Ph)$_2$), 7.22–7.30 (3H, m, *Ph*), 7.34 (4H, app t, *J* 7.4, *Ph*), 7.40 (2H, app t, *J* 7.6, *Ph*), 7.45 (4H, d, *J* 7.4, *Ph*), 7.52 (2H, app d, *J* 7.6, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (*C*(2′)), 20.0 (C(2′)*Me*$_A$), 20.4 (*C*(3′)), 22.1 (C(2′)*Me*$_B$), 27.4 (*C*(1′)), 53.9 (N(*C*H$_2$Ph)$_2$), 61.6 (*C*(1)), 126.6, 126.7, 127.8, 128.2, 128.6, 128.7 (*o*,*m*,*p*-*Ph*), 140.7, 143.0 (*i*-*Ph*); *m*/*z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}N^+$ ([M+H]$^+$) requires 356.2372, found 356.2372.

4.22.1. X-ray crystal structure determination for ***33****.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[62]

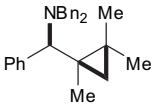
X-ray crystal structure data for **33** [$C_{26}H_{29}N$]: *M*=353.51, orthorhombic, space group *F* 2 *d d*, *a*=9.02980(10) Å, *b*=19.3438(3) Å, *c*=49.1328(3) Å, *V*=8582.06(19) Å^3, *Z*=16, μ=0.063 mm^{-1}, colourless plate, crystal dimensions=0.05×0.05×0.3 mm. A total of 2589 unique reflections were measured for 5<θ<27 and 2029 reflections were used in the refinement. The final parameters were wR_2=0.042 and R_1=0.034 [*I*>3.0σ(*I*)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 783812. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.23. (1*RS*,1′*SR*,2′*RS*)-*N*,*N*-Dibenzyl-1-(1′,2′-dimethylcyclopropyl)-1-phenylamine 34



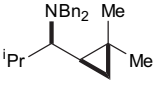
Following General procedure 2, **26** (171 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **34** as a colourless oil (127 mg, 71%, >99:1 dr); ν_{max} (film) 3061, 3027, 2960 (C–H), 1493, 1452; δ_H (400 MHz, $CDCl_3$) 0.30–0.33 (1H, m, C(3′)*H*$_A$), 0.60–0.65 (1H, m, C(2′)*H*), 0.77–0.80 (1H, m, C(3′)*H*$_B$), 0.98–1.01 (3H, m, C(2′)*Me*), 1.33 (3H, s, C(1′)*Me*), 3.61 (1H, s, C(1)*H*), 3.88 (2H, d, *J* 14.2, N(C*H*$_A$Ph)$_2$), 4.08 (2H, d, *J* 14.2, N(C*H*$_B$Ph)$_2$), 7.30–7.52 (13H, m, *Ph*), 7.77 (2H, d, *J* 6.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1 (C(2′)*Me*), 19.4 (*C*(2′)), 20.8 (*C*(1′)), 22.8 (*C*(3′)), 23.3 (C(1′)*Me*), 53.8 (N(*C*H$_2$Ph)$_2$), 65.0 (*C*(1)), 126.6, 126.7, 128.0, 128.2, 129.0, 129.5 (*o*,*m*,*p*-*Ph*), 139.9, 142.6 (*i*-*Ph*); *m*/*z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}N^+$ ([M+H]$^+$) requires 356.2373, found 356.2375.

4.24. (*RS*,*RS*)-*N*,*N*-Dibenzyl-1-phenyl-1-(1′,2′,2′-trimethylcyclopropyl)methanamine 35



Following General procedure 2, **27** (178 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 19:1), **35** as a yellow oil (68 mg, 37%, >99:1 dr); ν_{max} (film) 3027 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 0.39 (1H, d, *J* 4.4, C(3′)*H*$_A$), 0.44 (1H, d, *J* 4.4, C(3′)*H*$_B$), 0.93 (3H, s, C(2′)*Me*$_A$), 1.08 (3H, s, C(2′)*Me*$_B$), 1.36 (3H, s, C(1′)*Me*), 3.68 (1H, s, C(1)*H*), 3.82 (2H, d, *J* 14.4, N(C*H*$_A$Ph)$_2$), 4.00 (2H, d, *J* 14.4, N(C*H*$_B$Ph)$_2$), 7.23–7.46 (13H, m, *Ph*), 7.63 (2H, app d, *J* 7.6, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(1′)*Me*), 19.1 (*C*(2′)), 22.7 (C(2′)*Me*$_A$), 23.3 (C(2′)*Me*$_B$), 25.0 (*C*(1′)), 29.2 (*C*(3′)), 53.9 (N(*C*H$_2$Ph)$_2$), 66.4 (*C*(1)), 126.5, 126.6, 127.9, 128.1, 128.8, 129.2 (*o*,*m*,*p*-*Ph*), 140.0, 142.8 (*i*-*Ph*); *m*/*z* (ESI$^+$) 370 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}N^+$ ([M+H]$^+$) requires 370.2529, found 370.2528.

4.25. (*RS*,*RS*)-*N*,*N*-Dibenzyl-1-(2′,2′-dimethylcyclopropyl)-2-methylpropan-1-amine 36



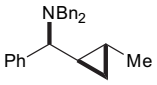
Following General procedure 2, **28** (307 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (0.15 mL, 2.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol), **36** as a white crystalline solid (252 mg, 79%, >99:1 dr); mp 63–65 °C; ν_{max} (KBr) 3060, 3025, 2950 (C–H), 1495, 1455, 745, 700; δ_H (400 MHz, $CDCl_3$) 0.63–0.67 (2H, m, C(3′)*H*$_A$, C(1′)*H*), 0.70–0.74 (1H, m, C(3′)*H*$_B$), 0.92 (3H, s, C(2′)*Me*$_A$), 0.95 (3H, d, *J* 6.7, C(2)*Me*$_A$), 1.08 (3H, d, *J* 6.7, C(2)*Me*$_B$), 1.15 (3H, s, C(2′)*Me*$_B$), 1.86–1.94 (1H, m, C(2)*H*), 2.07–2.12 (1H, m, C(1)*H*), 3.81 (2H, d, *J* 13.5, N(C*H*$_A$Ph)$_2$), 3.97 (2H, d, *J* 13.5, N(C*H*$_B$Ph)$_2$), 7.28–7.32 (2H, m, *Ph*), 7.38 (4H, app t, *J* 7.4, *Ph*), 7.47 (4H, app d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(2′)), 18.3 (*C*(3′)), 20.1, 21.5 (C(2)*Me*$_2$), 21.6 (C(2′)*Me*$_A$), 26.4 (*C*(1′)), 27.2 (*C*(2′)*Me*$_B$), 32.0 (C(2)), 55.1 (N(*C*H$_2$Ph)$_2$), 61.9 (*C*(1)), 126.7, 128.1, 129.2 (*o*,*m*,*p*-*Ph*), 141.1 (*i*-*Ph*); *m*/*z* (CI$^+$) 278 ([M−C_3H_7]$^+$, 100%), 322 ([M+H]$^+$, 10%); HRMS (CI$^+$) $C_{23}H_{32}N^+$ ([M+H]$^+$) requires 322.2535, found 322.2525.

4.25.1. X-ray Crystal Structure Determination for ***36****.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[62]

X-ray crystal structure data for **36** [$C_{23}H_{31}N$]: *M*=321.51, triclinic, space group *P*−1, *a*=9.3589(2) Å, *b*=10.0571(2) Å, *c*=10.6726(3) Å,

α=102.2247(9)°, β=95.2451(9)°, γ=92.1221(9)°, V=976.01(4) Å^3, Z=2, μ=0.062 mm^{-1}, colourless plate, crystal dimensions=0.2×0.2×0.2 mm. A total of 4430 unique reflections were measured for 5<θ<27 and 3112 reflections were used in the refinement. The final parameters were wR_2=0.043 and R_1=0.040 [I>3.0σ(I)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 783813. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.26. (1*RS*,1′*SR*,2′*SR*)-*N*,*N*-Dibenzyl-1-[2′-methylcyclopropyl]-1-phenylmethanamine 37



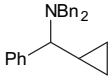
Following General procedure 2, **29** (164 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **37** as a pale yellow oil (102 mg, 60%, 89:11 dr).

Data for mixture: ν_{max} (film) 3060, 3025, 2950 (C–H), 1495, 1450, 1120, 1070, 1030, 745, 700; *m*/*z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{28}N^+$ ([M+H]$^+$) requires 342.2216, found 342.2213.

Data for major isomer: δ_H (400 MHz, $CDCl_3$) 0.33–0.40 (1H, m, C(2′)*H*), 0.61–0.65 (1H, m, C(3′)H_A), 0.70–0.74 (1H, m, C(3′)H_B), 1.03–1.10 (1H, m, C(1′)*H*), 1.15 (3H, d, *J* 6.1, C(2′)*Me*), 3.11 (1H, d, *J* 9.8, C(1)*H*), 3.68 (2H, d, *J* 13.6, N(CH_APh)$_2$), 3.88 (2H, d, *J* 13.6, N(CH_BPh)$_2$), 7.26–7.51 (13H, m, *Ph*), 7.58 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.4 (*C*(2′)), 14.9 (*C*(3′)), 18.6 (*C*(1′)), 18.7 (C(2′)*Me*), 54.0 (N(CH_2Ph)$_2$), 66.2 (*C*(1)), 126.7, 126.7, 127.9, 128.2, 128.7, 128.7 (*o*,*m*,*p*-*Ph*), 140.6, 142.7 (*i*-*Ph*).

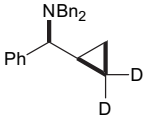
Data for minor isomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.30 (3H, d, *J* 6.1, C(2′)*Me*).

4.27. (*RS*)-*N*,*N*-Dibenzyl-1-cyclopropyl-1-phenylmethanamine 38



Following General procedure 2, **30** (157 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 19:1), **38** as a pale yellow oil (119 mg, 73%); ν_{max} (film) 3026 (C–H), 1493, 1453; δ_H (400 MHz, $CDCl_3$) 0.01–0.03 (1H, m, C(2′)H_A), 0.52–0.62 (2H, m, C(2′)H_B, C(3′)H_A), 0.81–0.88 (1H, m, C(3′)H_B), 1.30–1.39 (1H, m, C(1′)*H*), 3.01 (1H, d, *J* 9.8, C(1)*H*), 3.67 (2H, d, *J* 13.8, N(CH_APh)$_2$), 3.93 (2H, d, *J* 13.8, N(CH_BPh)$_2$), 7.27–7.34 (3H, m, *Ph*), 7.38 (4H, app t, *J* 7.6, *Ph*), 7.45 (2H, app t, *J* 7.6, *Ph*), 7.50 (4H, app d, *J* 7.1, *Ph*), 7.60 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.0 (*C*(2′)), 6.7 (*C*(3′)), 10.8 (*C*(1′)), 54.1 (N(CH_2Ph)$_2$), 67.2 (*C*(1)), 126.8, 128.0, 128.2, 128.2, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 140.6, 142.4 (*i*-*Ph*); *m*/*z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N^+$ ([M+H]$^+$) requires 328.2060, found 328.2064.

4.28. (*RS*,*RS*)-*N*,*N*-Dibenzyl-1-(2′,2′-dideuteriocyclopropyl)-1-phenylmethanamine 39



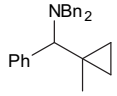
Following General procedure 2, **30** (157 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CD_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 3 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 19:1), **39** as a pale yellow oil (118 mg, 72%, 70:30 dr).

Data for mixture: ν_{max} (film) 3060, 3025, 2805 (C–H), 1600, 1495, 1455, 1120, 1070, 1030, 970, 910, 745, 700; *m*/*z* (ESI$^+$) 330 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{24}D_2N^+$ ([M+H]$^+$) requires 330.2185, found 330.2175.

Data for major isomer: δ_H (400 MHz, $CDCl_3$) −0.02 (1H, app t, *J* 4.9, C(3′)H_A), 0.57 (1H, dd, *J* 8.3, 4.6, C(3′)H_B), 1.30–1.39 (1H, ddd, *J* 9.7, 8.3, 5.0, C(1′)*H*), 3.01 (1H, d, *J* 9.8, C(1)*H*), 3.67 (2H, d, *J* 13.8, N(CH_APh)$_2$), 3.93 (2H, d, *J* 13.8, N(CH_BPh)$_2$), 7.27–7.34 (3H, m, *Ph*), 7.38 (4H, app t, *J* 7.6, *Ph*), 7.45 (2H, app t, *J* 7.6, *Ph*), 7.50 (4H, d, *J* 7.1, *Ph*), 7.60 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.0 (*C*(3′)), 10.8 (*C*(1′)), 54.1 (N(CH_2Ph)$_2$), 67.2 (*C*(1)), 126.8, 128.0, 128.2, 128.2, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 140.6, 142.4 (*i*-*Ph*).[68]

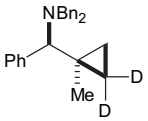
Data for minor isomer: δ_H (400 MHz, $CDCl_3$) 0.52–0.62 (1H, app t, *J* 4.6, C(3′)H_A), 0.82 (1H, dd, *J* 7.7, 4.6, C(3′)H_B), 1.30–1.39 (1H, m, C(1′)*H*), 3.01 (1H, d, *J* 9.8, C(1)*H*), 3.67 (2H, d, *J* 13.8, N(CH_APh)$_2$), 3.93 (2H, d, *J* 13.8, N(CH_BPh)$_2$), 7.27–7.34 (3H, m, *Ph*), 7.38 (4H, app t, *J* 7.6, *Ph*), 7.45 (2H, app t, *J* 7.6, *Ph*), 7.50 (4H, d, *J* 7.1, *Ph*), 7.60 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 6.7 (*C*(3′)), 10.8 (*C*(1′)), 54.1 (N(CH_2Ph)$_2$), 67.2 (*C*(1)), 126.8, 128.0, 128.2, 128.2, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 140.6, 142.4 (*i*-*Ph*).[68]

4.29. (*RS*)-*N*,*N*-Dibenzyl-1-(1′-methylcyclopropyl)-1-phenylmethanamine 40



Following General procedure 2, **31** (164 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1), **40** as a yellow oil (160 mg, 94%); ν_{max} (film) 3026, 2951 (C–H), 1493, 1452; δ_H (400 MHz, $CDCl_3$) 0.17–0.19 (1H, m, C(2′)H_A), 0.46–0.52 (3H, m, C(2′)H_B, C(3′)H_2), 1.16 (3H, s, C(1′)*Me*), 3.08 (1H, s, C(1)*H*), 3.72 (2H, d, *J* 14.5, N(CH_APh)$_2$), 3.98 (2H, d, *J* 14.5, N(CH_BPh)$_2$), 7.26–7.30 (2H, m, *Ph*), 7.33–7.38 (8H, m, *Ph*), 7.40–7.45 (3H, m, *Ph*), 7.52 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*(2′)), 16.5 (*C*(3′)), 18.2 (*C*(1′)), 19.8 (C(1′)*Me*), 52.7 (N(CH_2Ph)$_2$), 71.0 (*C*(1)), 126.7, 126.8, 127.9, 128.1, 129.2, 129.2 (*o*,*m*,*p*-*Ph*), 138.9, 141.5 (*i*-*Ph*); *m*/*z* (ESI$^+$) 342 ([M+H$^+$], 100%); HRMS (ESI$^+$) $C_{25}H_{28}N^+$ ([M+H]$^+$) requires 342.2216, found 342.2209.

4.30. (*RS*,*RS*)-*N*,*N*-Dibenzyl-1-(1′-methyl-2′,2′-dideuteriocyclopropyl)-1-phenylmethanamine 41



Following General procedure 2, **31** (164 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CD_2I_2 (0.16 mL, 2.0 mmol) and TFA

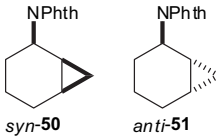
(70 μL, 1.0 mmol) in CH_2Cl_2 (1.0 mL) were reacted for 3 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 19:1), **41** as a pale yellow solid (108 mg, 63%, 58:42 dr).

Data for mixture: mp 57–59 °C; ν_{max} (KBr) 3060, 3025, 2960, 2810 (C–H), 1600, 1495, 1450, 1120, 1070, 1030, 910, 775, 750, 700; *m/z* (ESI$^+$) 344 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{26}D_2N^+$ ([M+H]$^+$) requires 344.2342, found 344.2335.

Data for major isomer: δ_H (400 MHz, $CDCl_3$) 0.46–0.52 (2H, m, C(3′)H_2), 1.16 (3H, s, C(1′)*Me*), 3.08 (1H, s, C(1)*H*), 3.72 (2H, d, *J* 14.5, N(CH_APh)$_2$), 3.98 (2H, d, *J* 14.5, N(CH_BPh)$_2$), 7.26–7.30 (2H, m, *Ph*), 7.33–7.38 (8H, m, *Ph*), 7.40–7.45 (3H, m, *Ph*), 7.52 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (*C*(3′)), 18.2 (*C*(1′)), 19.8 (C(1′)*Me*), 52.7 (N(CH_2Ph)$_2$), 71.0 (*C*(1)), 126.7, 126.8, 127.9, 128.1, 129.2, 129.2 (*o*,*m*,*p*-*Ph*), 138.9, 141.5 (*i*-*Ph*).[68]

Data for minor isomer: δ_H (400 MHz, $CDCl_3$) 0.17–0.19 (1H, m, C(3′)H_A), 0.46–0.52 (1H, m, C(3′)H_B), 1.16 (3H, s, C(1′)*Me*), 3.08 (1H, s, C(1)*H*), 3.72 (2H, d, *J* 14.5, N(CH_APh)$_2$), 3.98 (2H, d, *J* 14.5, N(CH_BPh)$_2$), 7.26–7.30 (2H, m, *Ph*), 7.33–7.38 (8H, m, *Ph*), 7.40–7.45 (3H, m, *Ph*), 7.52 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*(3′)), 18.2 (*C*(1′)), 19.8 (C(1′)*Me*), 52.7 (N(CH_2Ph)$_2$), 71.0 (*C*(1)), 126.7, 126.8, 127.9, 128.1, 129.2, 129.2 (*o*,*m*,*p*-*Ph*), 138.9, 141.5 (*i*-*Ph*).[68]

4.31. (1*RS*,2*SR*,3*SR*)- and (1*RS*,2*RS*,3*SR*)-2-Phthalimidobicyclo[4.1.0]heptane *syn*-50 and *anti*-51

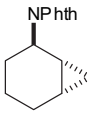


Following General procedure 2, **47**[23,69] (455 mg, 2.00 mmol), $ZnEt_2$ (4.0 mL, 4.0 mmol), CH_2I_2 (0.64 mL, 8.0 mmol) and TFA (0.30 mL, 4.0 mmol) in CH_2Cl_2 (4.0 mL) were reacted for 3 h to give a 17:83 mixture of *syn*-**50** and *anti*-**51**, respectively, in addition to 38% returned starting material. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave *syn*-**50** (38 mg, 8%, >99:1 dr) and *anti*-**51** (311 mg, 33%, >99:1 dr) as white solids.

Data for syn-**50**: mp 140–142 °C; ν_{max} (KBr) 2947 (C–H), 1707 (imide); δ_H (400 MHz, $CDCl_3$) 0.65–0.71 (1H, m, C(7)H_A), 0.89 (1H, app q, *J* 5.2, C(7)H_B), 1.03–1.12 (2H, m, C(1)*H*, C(6)*H*), 1.23–1.36 (1H, m, C(4)H_A), 1.45–1.55 (2H, m, C(5)H_A, C(3)H_A), 1.63–1.72 (1H, m, C(4)H_B), 1.97–2.02 (1H, m, C(5)H_B), 2.09–2.19 (1H, m, C(3)H_B), 4.72–4.77 (1H, m, C(2)*H*), 7.68–7.70 (2H, m, *Ar*), 7.81–7.83 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*(6)), 11.2 (*C*(7)), 14.8 (*C*(1)), 23.0 (*C*(5)), 23.3 (*C*(3)), 23.9 (*C*(4)), 49.6 (*C*(2)), 123.0 (*C*(3′), *C*(4′)), 132.2 (*C*(2′), *C*(5′)), 133.7 (*C*(1′), *C*(6′)), 168.9 (*C*=O); *m/z* (FI$^+$) 241 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{15}H_{15}NO_2^+$ ([M]$^+$) requires 241.1103, found 241.1111.

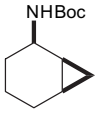
Data for anti-**51**: mp 130–132 °C; ν_{max} (KBr) 2940 (C–H), 1709 (imide); δ_H (400 MHz, $CDCl_3$) 0.18 (1H, app q, *J* 5.3, C(7)H_A), 0.62–0.68 (1H, m, C(7)H_B), 1.01–1.13 (2H, m, C(1)*H*, C(4)H_A), 1.18–1.25 (1H, m, C(6)*H*), 1.51–1.58 (2H, m, C(4)H_B, C(3)H_A), 1.75–1.91 (3H, m, C(3)H_B, C(5)H_2), 4.28 (1H, app dd, *J* 11.5, 5.7, C(2)*H*), 7.69–7.71 (2H, m, *Ar*), 7.82–7.84 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 9.3 (*C*(7)), 11.3 (*C*(6)), 14.5 (*C*(1)), 18.1 (*C*(4)), 22.3 (*C*(5)), 27.0 (*C*(3)), 47.9 (*C*(2)), 123.1 (*C*(3′), *C*(4′)), 132.1 (*C*(2′), *C*(5′)), 133.8 (*C*(1′), *C*(6′)), 168.2 (*C*=O); *m/z* (FI$^+$) 241 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{15}H_{15}NO_2^+$ ([M]$^+$) requires 241.1103, found 241.1110.

4.32. (1*RS*,2*RS*,3*SR*)-2-Phthalimidobicyclo[4.1.0]heptane 51



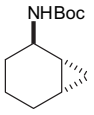
PPh_3 (1.44 g, 5.50 mmol), **52**[70] (561 mg, 5.00 mmol) and DEAD (0.87 mL, 5.50 mmol) were added to a stirred solution of phthalimide (809 mg, 5.50 mmol) in THF (100 mL) at rt. The resulting mixture was stirred at rt for 24 h then concentrated in vacuo. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 19:1) gave **51** as a white solid (600 mg, 50%, >99:1 dr); mp 130–132 °C.

4.33. *tert*-Butyl (1*RS*,2*SR*,6*SR*)-bicyclo[4.1.0]heptan-2-ylcarbamate 53



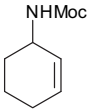
Following General procedure 1, **49**[23,71] (197 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol) and CH_2I_2 (0.32 mL, 4.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 3 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1), **53** as a white solid (141 mg, 67%, >99:1 dr); mp 41–43 °C; ν_{max} (film) 3343 (N–H), 2933 (C–H), 1701 (C=O); δ_H (500 MHz, $CDCl_3$) 0.04–0.06 (1H, m, C(7)H_A), 0.48–0.52 (1H, m, C(7)H_B), 0.77 (1H, app q, *J* 11.6, C(3)H_A), 1.02–1.07 (1H, m, C(6)*H*), 1.11–1.20 (2H, m, C(1)*H*, C(4)H_A), 1.28–1.36 (2H, m, C(5)H_A, C(4)H_B), 1.42 (9H, br s, CMe_3), 1.69 (1H, br s, C(3)H_B), 1.84–1.87 (1H, m, C(5)H_B), 3.98 (1H, br s, C(2)*H*), 4.53 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 7.8 (*C*(7)), 11.6 (*C*(6)), 15.5 (*C*(1)), 21.5 (*C*(4)), 23.0 (*C*(5)), 27.5 (*C*(3)), 28.4 (CMe_3), 46.5 (*C*(2)), 78.8 (CMe_3), 155.3 (*C*=O); *m/z* (ESI$^+$) 270 ([M+MeCN+NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{21}NNaO_2^+$ ([M+Na]$^+$) requires 234.1465, found 234.1465.

4.34. *tert*-Butyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]heptan-2-ylcarbamate 54



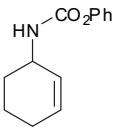
Following General procedure 2, **49**[71] (197 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (150 μL, 2.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 3 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1), **54** as a white solid (148 mg, 70%, >99:1 dr); mp 40–42 °C; ν_{max} (film) 3333 (N–H), 2933 (C–H), 1703 (C=O); δ_H (500 MHz, $CDCl_3$) −0.03–0.02 (1H, m, C(7)H_A), 0.52–0.57 (1H, m, C(7)H_B), 0.70–0.74 (1H, m, C(1)*H*), 0.83–0.88 (1H, m, C(6)*H*), 0.99–1.03 (1H, m, C(4)H_A), 1.06–1.12 (1H, m, C(3)H_A), 1.24–1.32 (1H, m, C(4)H_B), 1.37 (9H, br s, CMe_3), 1.39–1.44 (1H, m, C(3)H_B), 1.51–1.56 (1H, m, C(5)H_A), 1.68–1.75 (1H, m, C(5)H_B), 3.71 (1H, br s, C(2)*H*), 4.76 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 9.2 (*C*(7)), 9.7 (*C*(6)), 16.3 (*C*(1)), 16.9 (*C*(4)), 24.8 (*C*(5)), 28.0 (*C*(3)), 28.4 (CMe_3), 46.4 (*C*(2)), 78.9 (CMe_3), 155.2 (*C*=O); *m/z* (ESI$^+$) 270 ([M+MeCN+NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{21}NNaO_2^+$ ([M+Na]$^+$) requires 234.1465, found 234.1465.

4.35. Methyl (*RS*)-cyclohex-2-en-1-ylcarbamate 59



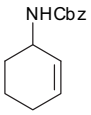
Following General procedure 4, **46** (980 mg, 10.0 mmol), Bi(OTf)$_3$ (328 mg, 0.50 mmol), KPF_6 (92 mg, 0.50 mmol), methyl carbamate (1.13 g, 15.0 mmol) and $MgSO_4$ (~1.5 g) in THF (50 mL) were reacted for 16 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 9:1 gradient elution), **59** as a white solid (1.21 g, 78%);[72] mp 25–26 °C; δ_H (400 MHz, $CDCl_3$) 1.47–1.55 (1H, m, CH_2), 1.56–1.66 (2H, m, CH_2), 1.84–1.92 (1H, m, CH_2), 1.94–2.00 (2H, m, CH_2), 3.64 (3H, s, O*Me*), 4.18 (1H, br s, C(1)*H*), 4.75 (1H, br s, N*H*), 5.58 (1H, dd, *J* 9.9, 2.0, C(2)*H*), 5.78–5.83 (1H, m, C(3)*H*).

4.36. Phenyl (*RS*)-cyclohex-2-en-1-ylcarbamate 60



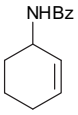
Following General procedure 4, **46** (980 mg, 10.0 mmol), Bi(OTf)$_3$ (328 mg, 0.5 mmol), KPF_6 (92 mg, 0.5 mmol), phenyl carbamate (2.06 g, 15.0 mmol) and $MgSO_4$ (~1.5 g) in THF (50 mL) were reacted for 16 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0 to 9:1 gradient elution), **60** as a white solid (1.23 g, 57%); mp 108–110 °C; ν_{max} (KBr) 3330 (N–H), 3020, 2930, 2870 (C–H), 1735 (C=O), 1530, 1495, 1340, 1210, 975, 725, 665; δ_H (400 MHz, $CDCl_3$) 1.61–1.70 (3H, m, C(5)H_2, C(6)H_A), 1.95–2.04 (3H, m, C(4)H_2, C(6)H_B), 4.29–4.50 (1H, m, C(1)*H*), 5.03 (1H, d, *J* 6.8, N*H*), 5.69–5.71 (1H, m, C(2)*H*), 5.88–5.93 (1H, m, C(3)*H*), 7.15 (2H, app d, *J* 7.7, *Ph*), 7.20 (1H, app t, *J* 7.5, *Ph*), 7.36 (2H, app t, *J* 7.7, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (C(5)), 24.8 (*C*(6)), 29.6 (*C*(4)), 46.6 (*C*(1)), 127.4 (*C*(2)), 121.6, 125.2, 129.3 (o,*m*,*p*-*Ph*), 131.1 (*C*(3)), 151.0 (*i*-*Ph*), 153.8 (*C*=O); *m*/*z* (ESI$^+$) 276 ([M+MeCN+NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{15}NNaO_2^+$ ([M+Na]$^+$) requires 240.0995, found 240.0997.

4.37. Benzyl (*RS*)-cyclohex-2-en-1-ylcarbamate 61



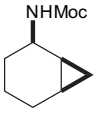
Following General procedure 4, **46** (980 mg, 10.0 mmol), Bi(OTf)$_3$ (328 mg, 0.5 mmol), KPF_6 (92 mg, 0.5 mmol), benzyl carbamate (2.27 g, 15.0 mmol) and $MgSO_4$ (~1.5 g) in THF (50 mL) were reacted for 16 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 9:1 gradient elution), **61** as a white solid (1.92 g, 83%);[73] mp 65–67 °C; δ_H (400 MHz, $CDCl_3$) 1.01–1.93 (3H, m, CH_2), 1.45–1.64 (3H, m, CH_2), 4.22 (1H, br s, C(1)*H*), 5.02–5.09 (2H, m, OCH_2Ph), 5.39 (1H, br s, N*H*), 5.58 (1H, d, *J* 9.9, C(2)*H*), 5.74–5.79 (1H, m, C(3)*H*), 7.23–7.29 (5H, m, *Ph*).

4.38. (*RS*)-*N*-(Cyclohex-2-en-1-yl)benzamide 62



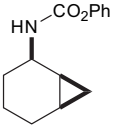
Following General procedure 4, **46** (980 mg, 10.0 mmol), Bi(OTf)$_3$ (328 mg, 0.50 mmol), KPF_6 (92 mg, 0.50 mmol), benzamide (1.82 g, 15.0 mmol) and $MgSO_4$ (~1.5 g) in THF (50 mL) were reacted for 16 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0 to 9:1 gradient elution), **62** as a white solid (570 mg, 28%);[74] mp 96–98 °C (lit.[74] mp 102–104 °C); δ_H (400 MHz, $CDCl_3$) 1.57–1.72 (3H, m, CH_2), 1.93–2.02 (3H, m, CH_2), 4.64–4.70 (1H, m, C(1)*H*), 5.62–5.68 (1H, m, C(2)*H*), 5.85–5.90 (1H, m, C(3)*H*), 6.34 (1H, d, *J* 7.5, N*H*), 7.36–7.40 (2H, m, *Ph*), 7.44–7.48 (2H, m, *Ph*), 7.75–7.78 (1H, m, *Ph*).

4.39. Methyl (1*RS*,2*SR*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 63



Following General procedure 1, **59** (155 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol) and CH_2I_2 (0.32 mL, 4.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1), **63** as a colourless oil (167 mg, 99%, >99:1 dr); ν_{max} (film) 3320 (N–H), 3015, 2930, 2855 (C–H), 1700 (C=O), 1540, 1460, 1250, 1045, 780, 645; δ_H (400 MHz, $CDCl_3$) 0.05 (1H, app q, *J* 5.2, C(7)H_A), 0.49 (1H, td, *J* 8.8, 4.7, C(7)H_B), 0.76 (1H, m, C(3)H_A), 1.00–1.18 (3H, m, C(1)*H*, C(4)H_A, C(6)*H*), 1.24–1.38 (2H, m, C(4)H_B, C(5)H_A), 1.64–1.72 (1H, m, C(3)H_B), 1.82–1.89 (1H, m, C(5)H_B), 3.60 (3H, s, O*Me*), 3.97–4.04 (1H, m, C(2)*H*), 4.78 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 7.8 (*C*(7)), 11.6 (*C*(1)), 15.4 (*C*(6)), 21.5 (*C*(4)), 22.9 (*C*(5)), 27.3 (*C*(3)), 47.0 (*C*(2)), 51.7 (O*Me*), 156.4 (*C*=O); *m*/*z* (ESI$^+$) 192 ([M+Na]$^+$, 80%), 361 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{15}NNaO_2^+$ ([M+Na]$^+$) requires 192.0995, found 192.0998.

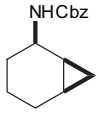
4.40. Phenyl (1*RS*,2*SR*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 64



Following General procedure 1, **60** (217 mg, 1.0 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol) and CH_2I_2 (0.32 mL, 4.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 9:1), **64** as a white solid (229 mg, 99%, >99:1 dr); mp 101–103 °C; ν_{max} (KBr) 3310 (N–H), 2930 (C–H), 1705 (C=O), 1535, 1495, 1215, 1020, 990, 795, 665; δ_H (400 MHz, $CDCl_3$) 0.17 (1H, app t, *J* 5.1, C(7)H_A), 0.61 (1H, app t, *J* 8.7, 4.7, C(7)H_B), 0.86–0.95 (1H, m, C(3)H_A), 1.11–1.29 (3H, m, C(1)*H*, C(4)H_A, C(6)*H*), 1.33–1.45 (2H, m, C(4)H_B, C(5)H_A), 1.81–1.89 (1H, m, C(3)H_B), 1.89–1.99 (1H, m, C(5)H_B), 4.11–4.19 (1H, m, C(2)*H*), 5.07–5.08 (1H, m, N*H*), 7.11–7.21 (3H, m, *Ph*), 7.36 (2H, app t, *J* 7.8, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.9 (*C*(7)), 11.8 (*C*(6)), 15.3 (*C*(1)), 21.4 (*C*(4)), 22.9 (*C*(5)), 27.3 (*C*(3)), 47.5 (*C*(2)), 121.6,

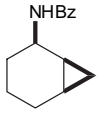
125.1, 129.2 (o,*m*,*p*-*Ph*), 151.1 (*i*-*Ph*), 153.9 (*C*=O); *m*/*z* (ESI$^+$) 232 ([M+H]$^+$, 40%), 485 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{17}NNaO_2^+$ ([M+Na]$^+$) requires 254.1151, found 254.1154.

4.41. Benzyl (1*RS*,2*SR*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 65



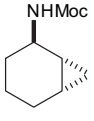
Following General procedure 1, **61** (231 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol) and CH_2I_2 (0.32 mL, 4.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1), **65** as a white solid (206 mg, 84%, >99:1 dr); mp 48–50 °C; ν_{max} (KBr) 3330 (N–H), 2935, 2360 (C–H), 1695 (C=O), 1530, 1240, 1045, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.09 (1H, q, *J* 5.1, C(7)H_A), 0.51–0.57 (1H, m, C(7)H_B), 0.78–0.87 (1H, m, C(3)H_A), 1.06–1.14 (1H, m, C(6)*H*), 1.14–1.25 (2H, m, C(1)*H*, C(4)H_A), 1.28–1.42 (2H, m, C(5)H_A, C(4)H_B), 1.70–1.79 (1H, m, C(3)H_B), 1.86–1.96 (1H, m, C(5)H_B), 4.06–4.15 (1H, m, C(2)*H*), 4.88 (1H, d, *J* 6.3, N*H*), 5.11 (2H, s, CH_2Ph), 7.30–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.9 (*C*(7)), 11.7 (*C*(6)), 15.4 (*C*(1)), 21.5 (*C*(4)), 22.9 (*C*(5)), 27.4 (*C*(3)), 47.2 (*C*(2)), 66.4 (O*C*H_2Ph), 128.0, 128.2, 128.5 (o,*m*,*p*-*Ph*), 136.7 (*i*-*Ph*), 155.7 (*C*=O); *m*/*z* (ESI$^+$) 268 ([M+Na]$^+$, 40%), 304 ([M+NH_4+MeCN]$^+$, 100%), 513 ([2M+Na]$^+$, 30%); HRMS (ESI$^+$) $C_{15}H_{19}NNaO_2^+$ ([M+Na]$^+$) requires 268.1308, found 268.1309.

4.42. (1*RS*,2*SR*,6*SR*)-*N*-(Bicyclo[4.1.0]hept-2-yl)benzamide 66



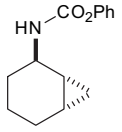
Following General procedure 1, **62** (201 mg, 1.0 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol) and CH_2I_2 (0.32 mL, 4.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 7:3 to 1:1 gradient elution), **66** as a white solid (215 mg, quant, >99:1 dr); mp 122–124 °C; ν_{max} (KBr) 3295 (N–H), 1625 (C=O), 1535, 665; δ_H (400 MHz, $CDCl_3$) 0.21 (1H, app q, *J* 5.2, C(7)H_A), 0.62 (1H, td, *J* 8.7, 4.6, C(7)H_B), 0.87–0.96 (1H, m, C(3)H_A), 1.13–1.22 (1H, m, C(6)*H*), 1.24–1.35 (2H, m, C(1)*H*, C(5)H_A), 1.40–1.48 (2H, m, C(4)H_2), 1.85–1.92 (1H, m, C(5)H_B), 1.95–2.01 (1H, m, C(3)H_B), 4.51–4.58 (1*H*, m, C(2)*H*), 6.07 (1H, br s, N*H*), 7.42–7.52 (3H, m, *Ph*), 7.77–7.80 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.0 (*C*(7)), 11.6 (*C*(6)), 15.4 (*C*(1)), 21.6 (*C*(4)), 23.0 (*C*(5)), 27.0 (*C*(3)), 46.0 (*C*(2)), 127.0, 128.4, 131.1 (o,*m*,*p*-*Ph*), 135.0 (*i*-*Ph*), 166.9 (*C*=O); *m*/*z* (ESI$^+$) 216 ([M+H]$^+$, 40%), 238 ([M+Na]$^+$, 40%), 453 ([2M+Na]$^+$, 100%), 668 ([3M+Na]$^+$, 60%); HRMS (ESI$^+$) $C_{14}H_{17}NNaO^+$ ([M+Na]$^+$) requires 238.1202, found 238.1200.

4.43. Methyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 67



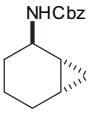
Following General procedure 2, **59** (100 mg, 0.64 mmol), $ZnEt_2$ (1.93 mL, 1.93 mmol), CH_2I_2 (0.31 mL, 3.87 mmol), TFA (0.15 mL, 1.93 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 4 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0 to 9:1 gradient elution), **67** as a white crystalline solid (90 mg, 83%, 98:2 dr); mp 50–52 °C; ν_{max} (KBr) 3305 (N–H), 1690 (C=O), 1540, 1255, 1095, 665; δ_H (400 MHz, $CDCl_3$) 0.01–0.05 (1H, m, C(7)H_A), 0.59 (1H, td, *J* 9.2, 4.9, C(7)H_B), 0.73–0.79 (1H, m, C(1)*H*), 0.87–0.95 (1H, m, C(6)*H*), 1.00–1.09 (1H, m, C(4)H_A), 1.13–1.22 (1H, m, C(3)H_A), 1.27–1.37 (1H, m, C(4)H_B), 1.42–1.49 (1H, m, C(3)H_B), 1.55–1.61 (1H, m, C(5)H_A), 1.77 (1H, app dq, *J* 13.7, 6.9, C(5)H_B), 3.62 (3H, s, O*Me*), 3.79–3.85 (1H, br m, C(2)*H*), 5.08 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 9.2 (*C*(7)), 9.7 (*C*(6)), 16.1 (*C*(1)), 16.7 (*C*(4)), 22.6 (*C*(5)), 27.9 (*C*(3)), 46.8 (*C*(2)), 51.7 (O*Me*), 156.3 (*C*=O); *m*/*z* (ESI$^+$) 170 ([M+H]$^+$, 25%), 192 ([M+Na]$^+$, 40%), 339 ([2M+H]$^+$, 30%), 361 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{15}NNaO_2^+$ ([M+Na]$^+$) requires 192.0995, found 192.0999.

4.44. Phenyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 68



Following General procedure 2, **60** (100 mg, 0.46 mmol), $ZnEt_2$ (1.38 mL, 1.38 mmol), CH_2I_2 (0.22 mL, 2.76 mmol) and TFA (0.11 mL, 1.38 mmol) in CH_2Cl_2 (1.5 mL) were reacted for 4 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0 to 9:1 gradient elution), **68** as a white solid (80 mg, 75%, 95:5 dr); mp 110–112 °C; ν_{max} (KBr) 3320 (N–H), 2930 (C–H), 1710 (C=O), 1540, 1490, 1215, 690, 665; δ_H (400 MHz, $CDCl_3$) 0.12 (1H, app q, *J* 5.3, C(7)H_A), 0.69 (1H, td, *J* 9.2, 5.0, C(7)H_B), 0.87–0.93 (1H, m, C(1)*H*), 0.97–1.05 (1H, m, C(6)*H*), 1.11–1.20 (1H, m, C(4)H_A), 1.25–1.37 (1H, m, C(3)H_A), 1.37–1.46 (1H, m, C(4)H_B), 1.54–1.73 (2H, m, C(3)H_B, C(5)H_A), 1.87 (1H, app dq, *J* 13.7, 6.8, C(5)H_B), 3.97 (1H, app q, *J* 6.3, C(2)*H*), 5.36 (1H, br d, *J* 6.9, N*H*), 7.14–7.21 (3H, m, *Ph*), 7.36 (2H, app t, *J* 7.8, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.4 (*C*(7)), 9.7 (*C*(6)), 16.0 (*C*(1)), 16.8 (*C*(4)), 22.7 (*C*(5)), 27.7 (*C*(3)), 47.1 (*C*(2)), 121.6, 125.2, 129.2 (o,*m*,*p*-*Ph*), 151.1 (*i*-*Ph*), 153.8 (*C*=O); *m*/*z* (ESI$^+$) 232 ([M+H]$^+$, 30%), 290 ([M+MeCN+NH_4]$^+$, 60%), 485 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{17}NNaO_2^+$ ([M+Na]$^+$) requires 254.1151, found 254.1163.

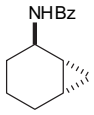
4.45. Benzyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 69



Following General procedure 2, **61** (231 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (150 μL, 2.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 4 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1), **69** as a white solid (218 mg, 89%, 98:2 dr); mp 44–45 °C; ν_{max} (KBr) 3330 (N–H), 2935 (C–H), 1700 (C=O), 1530, 1240, 1090, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.09 (1H, app d, *J* 5.0, C(7)H_A), 0.63–0.68 (1H, m, C(7)H_B), 0.80–0.85 (1H, m, C(1)*H*), 0.92–0.97 (1H, m, C(6)*H*), 1.06–1.13 (1H, m, C(4)H_A), 1.20–1.26 (1H, m, C(3)H_A), 1.37 (1H, dd, *J* 13.2, 6.9, C(4)H_B), 1.50–1.54 (1H, m, C(3)H_B), 1.60–1.66 (1H, m, C(5)H_A), 1.79–1.84 (1H, m, C(5)H_B), 3.89–3.93 (1H, m, C(2)*H*), 5.08–5.18 (3H, m, N*H*, OCH_2Ph), 7.29–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.3 (*C*(7)), 9.7 (*C*(6)), 16.1 (*C*(1)), 16.8 (*C*(4)), 22.7 (*C*(5)), 27.9 (*C*(3)), 46.9 (*C*(2)), 66.5 (O*C*H_2Ph), 128.0, 128.1, 128.5 (o,*m*,*p*-*Ph*), 136.7 (*i*-*Ph*), 155.7 (*C*=O); *m*/*z* (ESI$^+$) 268 ([M+Na]$^+$, 60%), 304.2 ([M+NH_4+MeCN]$^+$, 100%), 513

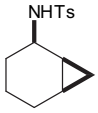
([2M+Na]$^+$, 80%); HRMS (ESI$^+$) $C_{15}H_{19}NNaO_2^+$ ([M+Na]$^+$) requires 268.1308, found 268.1308.

4.46. (1*RS*,2*RS*,6*SR*)-*N*-(Bicyclo[4.1.0]hept-2-yl)benzamide 70



Following General procedure 2, **62** (201 mg, 1.0 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol), CH_2I_2 (0.32 mL, 4.0 mmol) and TFA (0.15 mL, 2.0 mmol) in CH_2Cl_2 (2.0 mL) were reacted for 6 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 7:3 to 1:1 gradient elution), **70** as a white solid (173 mg, 80%, >99:1 dr); mp 128–130 °C; ν_{max} (KBr) 3310 (N–H), 3060, 2930 (C–H), 1630 (C=O), 1540, 1490, 1320, 1270, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.10 (1H, app q, *J* 5.3, C(7)H_A), 0.64 (1H, td, *J* 9.2, 4.9, C(7)H_B), 0.81–0.87 (1H, m, C(1)*H*), 0.91–0.98 (1H, m, C(6)*H*), 1.06–1.14 (1H, m, C(4)H_A), 1.26–1.43 (2H, m, C(3)H_A, C(4)H_B), 1.53–1.67 (2H, m, C(3)H_B, C(5)H_A), 1.75–1.84 (1H, m, C(5)H_B), 4.25–4.30 (1H, m, C(2)*H*), 6.74 (1H, d, *J* 7.6, N*H*), 7.34–7.38 (2H, m, *Ph*), 7.41–7.45 (1H, m, *Ph*), 7.78–7.80 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.3 (*C*(7)), 9.9 (*C*(1)), 15.9 (*C*(6)), 17.1 (*C*(4)), 22.7 (*C*(5)), 27.8 (*C*(3)), 45.8 (*C*(2)), 127.0, 128.4, 131.2 (*o*,*m*,*p*-*Ph*), 135.0 (*i*-*Ph*), 166.7 (*C*=O); *m*/*z* (ESI$^+$) 274 ([M+NH_4+MeCN]$^+$, 100%), 453 ([2M+Na]$^+$, 70%); HRMS (ESI$^+$) $C_{14}H_{17}NNaO^+$ ([M+Na]$^+$) requires 238.1202, found 238.1209.

4.47. (1*RS*,2*RS*,6*SR*)-*N*-(Bicyclo[4.1.0]heptan-2-yl)-4′-methylbenzenesulfonamide 72



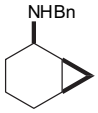
Method A: Following General procedure 1, **71**[23,75] (251 mg, 1.00 mmol), $ZnEt_2$ (2.0 mL, 2.0 mmol) and CH_2I_2 (0.32 mL, 4.0 mmol) in CH_2Cl_2 were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0 to 3:1 gradient elution), **72** as a white solid (160 mg, 60%, >99:1 dr); mp 68–70 °C; ν_{max} (KBr) 3260 (N–H), 3065, 3005, 2935, 2860 (C–H), 1600, 1450, 1325 (SO_2N), 1160 (SO_2N), 1095, 1070, 930, 815, 670; δ_H (400 MHz, $CDCl_3$) 0.09 (1H, app q, *J* 5.3, C(7)H_A), 0.42 (1H, app td, *J* 8.8, 4.9, C(7)H_B), 0.82–0.93 (2H, m, C(1)*H*, C(3)H_A), 0.96–1.13 (2H, m, C(4)H_A, C(6)*H*), 1.20–1.36 (2H, m, C(4)H_B, C(5)H_A), 1.56–1.62 (1H, m, C(3)H_B), 1.77–1.84 (1H, m, C(5)H_B), 2.41 (3H, s, C(4′)*Me*), 3.69 (1H, ddt, *J* 10.5, 7.8, 5.5, C(2)*H*), 4.90 (1H, d, *J* 7.7, N*H*), 7.28 (2H, d, *J* 8.4, C(3′)*H*, C(5′)*H*), 7.81 (2H, d, *J* 8.4, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 8.1 (*C*(7)), 12.4 (*C*(6)), 15.8 (*C*(1)), 21.5 (*C*(4)), 21.6 (C(4′)*Me*) 22.6 (*C*(5)), 28.3 (*C*(3)), 50.3 (*C*(2)), 127.0 (*C*(2′), *C*(6′)), 129.6 (*C*(3′), *C*(5′)), 138.7 (*C*(4′)), 143.0 (*C*(1′)); *m*/*z* (ESI$^-$) 264 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}NNaO_2S^+$ ([M+Na]$^+$) requires 288.1029, found 288.1032.

Method B: Following General procedure 2, **71** (126 mg, 0.50 mmol), $ZnEt_2$ (1.0 mL, 1.0 mmol), CH_2I_2 (0.16 mL, 2.0 mmol) and TFA (0.07 mL, 1.0 mmol) in CH_2Cl_2 were reacted for 1 h to give, after purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0 to 3:1 gradient elution), **72** as a white solid (70 mg, 53%); mp 66–68 °C.

4.47.1. X-ray Crystal Structure Determination for 72. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[62]

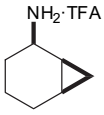
X-ray crystal structure data for **72** [$C_{14}H_{19}NO_2S$]: *M*=263.36, monoclinic, space group *P* $2_1/c$, *a*=10.0211(5) Å, *b*=12.9160(7) Å, *c*=11.1049(6) Å, β=105.377(4)°, *V*=1385.88(13) Å^3, *Z*=4, μ=0.228 mm^{-1}, colourless plate, crystal dimensions=0.12×0.24×0.37 mm. A total of 3073 unique reflections were measured for $5<\theta<27$ and 2129 reflections were used in the refinement. The final parameters were wR_2=0.068 and R_1=0.083 [$I>1.5\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 783814. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.48. (1*RS*,2*SR*,3*RS*)-*N*-Benzylbicyclo[4.1.0]heptan-2-amine 73



Pd/C (10% wt, 29 mg) was added to a degassed solution of **9** (58 mg, 0.20 mmol) in MeOH/H_2O/AcOH (40:4:1, 2 mL) and the resultant suspension was stirred under H_2 (1 atm) for 16 h. The reaction mixture was then filtered through Celite (eluent MeOH) and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3×10 mL) then dried and concentrated in vacuo to give **73** as a pale yellow oil (28 mg, 65%, >99:1 dr); ν_{max} (film) 2930, 2857 (C–H), 1454; δ_H (400 MHz, $CDCl_3$) 0.19 (1H, app q, *J* 5.3, C(7)H_A), 0.53–0.59 (1H, m, C(7)H_B), 0.78–0.90 (1H, m, C(3)H_A), 1.06–1.22 (3H, m, C(1)*H* and C(6)*H*, C(4)H_A), 1.35–1.45 (2H, m, C(5)H_A, C(4)H_B), 1.52 (1H, br s, N*H*), 1.62–1.68 (1H, m, C(3)H_B), 1.88–1.94 (1H, m, C(5)H_B), 3.08–3.13 (1H, m, C(2)*H*), 3.88 (1H, d, *J* 12.9, NCH_APh), 3.96 (1H, d, *J* 12.9, NCH_BPh), 7.24–7.27 (1H, m, *Ph*), 7.32–7.38 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.5 (*C*(7)), 11.6 (*C*(1)), 15.7 (*C*(6)), 21.6 (*C*(4)), 23.8 (*C*(5)), 27.9 (*C*(3)), 50.8 (NCH_2Ph), 51.8 (*C*(2)), 126.8, 128.2, 128.4 (*o*,*m*,*p*-*Ph*), 141.0 (*i*-*Ph*); *m*/*z* (ESI$^+$) 202 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{20}N^+$ ([M+H]$^+$) requires 202.1590, found 202.1588.

4.49. (1*RS*,2*SR*,3*RS*)-Bicyclo[4.1.0]heptan-2-amine trifluoroacetate 74



Method A: Pd/C (50 mg, 10% wt) was added to a degassed solution of **9** (100 mg, 0.34 mmol) in MeOH/H_2O/AcOH (40:4:1, 0.6 mL). The vessel was charged with H_2 (5 atm) and the reaction mixture was stirred rapidly at rt for 16 h, after which time the solution was filtered through a pad of Celite (eluent MeOH) and TFA (1.0 mL) was added. The resultant mixture was concentrated in vacuo to give **74** as a pale yellow oil (77 mg, quant, >99:1 dr); ν_{max} (film) 3425 (N–H), 2935 (C–H), 1680, 1205, 1140; δ_H (400 MHz, $CDCl_3$) 0.38 (1H, app q, *J* 5.0, C(7)H_A), 0.66–0.71 (1H, m, C(7)H_B), 1.05–1.10 (1H, m, C(3)H_A), 1.15–1.26 (3H, m, C(1)*H*, C(6)*H*, C(4)H_A), 1.35–1.43 (1H, m, C(5)H_A), 1.47–1.52 (1H, m, C(4)H_B), 1.74–1.79 (1H, m, C(3)H_B), 1.92–1.97 (1H, m, C(5)H_B), 3.70–3.80 (1H, m, C(2)*H*), 7.62 (3H, br s, NH_3); δ_C (100 MHz, $CDCl_3$) 8.1 (*C*(7)), 12.1 (*C*(1)), 13.0 (*C*(6)), 20.8 (*C*(4)), 22.1 (*C*(5)), 24.7 (*C*(3)), 49.0 (*C*(2)); *m*/*z* (FI$^+$) 112 ([M+H]$^+$,

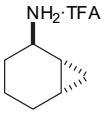
100%); HRMS (FI^+) $C_7H_{14}N^+$ ($[M+H]^+$) requires 112.1126, found 112.1124.

Method B: $N_2H_4\cdot H_2O$ (8 μL, 0.16 mmol) was added to a stirred solution of **50** (34 mg, 0.15 mmol) in MeOH (2 mL) at rt and the resultant suspension was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt, filtered and concentrated in vacuo. The residue was triturated with $CHCl_3$ (3×10 mL) and the organic washings were acidified to pH 2 with TFA (1 mL) then concentrated in vacuo to give **74** as a pale yellow oil (32 mg, quant, >99:1 dr).

Method C: Pd/C (4 mg, 10% wt) was added to a degassed solution of **65** (12 mg, 0.05 mmol) in MeOH/EtOAc (4:1, 0.5 mL) and the resultant mixture was stirred under H_2 (1 atm) for 1 h. The reaction mixture was then filtered through Celite (eluent EtOAc), TFA (50 μL) was added to the filtrate and the resultant mixture was concentrated in vacuo to give **74** as a yellow oil (10 mg, quant, >99:1 dr).

Method D: TFA (30 μL, 0.43 mmol) was added to a stirred solution of **53** (30 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 3 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo to give **74** as a yellow oil (32 mg, quant, >99:1 dr).

4.50. (1*RS*,2*RS*,3*SR*)-Bicyclo[4.1.0]heptan-2-amine trifluoroacetate 75

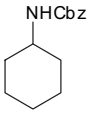


Method A: $N_2H_4\cdot H_2O$ (11 μL, 0.23 mmol) was added to a stirred solution of **51** (50 mg, 0.21 mmol) in MeOH (2 mL) at rt and the resultant suspension was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt, filtered and concentrated in vacuo. The residue was triturated with $CHCl_3$ (3×10 mL) and the organic washings were acidified to pH2 with TFA (~1 mL) then concentrated in vacuo to give **75** as a pale yellow oil (47 mg, quant, >99:1 dr); ν_{max} (film) 3440 (N–H), 1680 (C=O), 1440, 1205, 1140; δ_H (400 MHz, $CDCl_3$) 0.13 (1H, app d, *J* 4.6, C(7)H_A), 0.72–0.77 (1H, m, C(7)H_B), 0.87–0.91 (1H, m, C(1)*H*), 1.06–1.12 (2H, m, C(6)*H*, C(4)H_A), 1.28–1.37 (1H, m, C(3)H_A), 1.44–1.49 (1H, m, C(4)H_B), 1.65–1.71 (2H, m, C(5)H_A, C(3)H_B), 1.80–1.88 (1H, m, C(5)H_B), 3.44–3.48 (1H, m, C(2)*H*), 7.89 (3H, br s, NH_3); δ_C (100 MHz, $CDCl_3$) 9.0 (*C*(7)), 10.1 (*C*(6)), 12.9 (*C*(1)), 15.7 (*C*(4)), 21.9 (*C*(5)), 26.3 (*C*(3)), 48.2 (*C*(2)); *m*/*z* (FI^+) 112 ($[M+H]^+$, 100%); HRMS (FI^+) $C_7H_{15}N^+$ ($[M+H]^+$) requires 111.1126, found 111.1124.

Method B: Pd/C (10% wt, 30% w/w, 12 mg) was added to a degassed solution of **69** (39 mg, 0.16 mmol) in MeOH/EtOAc (4:1, 2.0 mL) and the resultant mixture was stirred under H_2 (1 atm) for 1 h. The reaction mixture was then filtered through Celite (eluent EtOAc), TFA (159 μL) was added to the filtrate and the resultant mixture was concentrated in vacuo to give **75** as a yellow oil (33 mg, quant, >99:1 dr).

Method C: TFA (30 μL, 0.43 mmol) was added to a stirred solution of **54** (30 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 3 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo to give **75** as a yellow oil (32 mg, quant, >99:1 dr);

4.51. Benzyl (*RS*)-cyclohexylcarbamate 77



NEt_3 (1.53 mL, 11.0 mmol) and benzyl chloroformate (1.57 mL, 11.0 mmol) were sequentially added to a stirred solution of cyclohexylamine (1.14 mL, 10.0 mmol) in THF (100 mL) at 0 °C. The resultant mixture was stirred for 16 h at rt then washed with brine (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic extracts were dried and concentrated in vacuo to give **77** as a white solid (2.32 g, 99%);[76] mp 82–84 °C (lit.[76] mp 79–80 °C); δ_H (400 MHz, $CDCl_3$) 1.08–1.22 (3H, m, 3×CH_2), 1.31–1.40 (2H, m, 2×CH_2), 1.56–1.64 (1H, m, 1×CH_2), 1.66–1.74 (2H, m, 2×CH_2), 1.93–1.96 (2H, m, 2×CH_2), 3.51–3.53 (1H, m, C*H*N), 4.66 (1H, br s, N*H*), 5.09 (2H, br s, OCH_2Ph), 7.30–7.40 (5H, m, *Ph*).

4.52. (*RS*,*RS*)-1-Phenylbicyclo[4.1.0]heptane 79

Following General procedure 1, **76** (154 mg, 0.50 mmol), $ZnEt_2$ (0.5 mL, 0.5 mmol) and CH_2I_2 (81 μL, 1.0 mmol) in CH_2Cl_2 (0.5 mL) were reacted for 1 h to give **79** as a colourless oil (160 mg, 60%, >99:1 dr);[13c] δ_H (400 MHz, $CDCl_3$) 0.64 (1H, dd, *J* 5.6, 4.3, C(7)H_A), 0.95 (1H, dd, *J* 9.4, 4.5, C(7)H_B), 1.21–1.42 (4H, m, 3×CH_2, C(6)*H*), 1.45–1.52 (1H, m, 1×CH_2), 1.92–1.99 (1H, m, 1×CH_2), 2.03–2.12 (2H, m, 2×CH_2), 7.14–7.18 (1H, m, *Ph*), 7.27–7.29 (4H, m, *Ph*).

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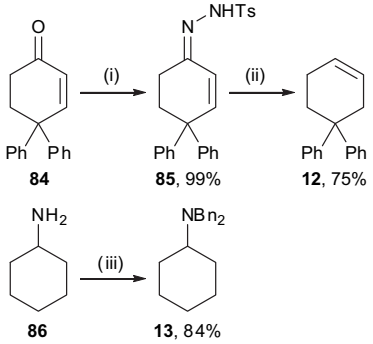
28. Attempts at N-methylation of **9** with either MeI or MeOTf were not successful, even at elevated temperatures.
29. Alternative (iodomethyl)zinc acetate reagents were also screened, although it was found that the yield of *syn*-**9** increased with the reactivity of the carbenoid used [$CH_3CO_2ZnCH_2I$, <10%; $CH_2ClCO_2ZnCH_2I$, 62%; $CHCl_2CO_2ZnCH_2I$, 89%; $CCl_3CO_2ZnCH_2I$, 66%; $CF_3CO_2ZnCH_2I$, 92%].
30. Extended reaction times led to lower yields of the desired cyclopropane product *syn*-**9** [1 h, 92%; 6 h, 71%; 12 h, 64%].
31. 4,4-Diphenylcyclohex-1-ene **12** was synthesised in two steps from commercially available enone **84** in 74% overall yield. *N*,*N*-Dibenzyl cyclohexylamine **13** was synthesised by benzylation of cyclohexylamine **86** to give **13** in 84% yield, according to the procedure detailed in: Ju, Y.; Varma, R. S. *Green Chem.* **2004**, *6*, 219.



Reagents and conditions: (i) $TsNHNH_2$, MeOH/PhMe (2:1), rt, 16 h; (ii) catechol borane, $CHCl_3$, 0 °C to rt, 2 h then $NaOAc·H_2O$, 60 °C, 1 h; (iii) BnBr, NaOH (0.5 M aq), 80 °C, 30 min.

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56. Carbamate **77** was readily synthesised from cyclohexylamine **86** in 99% yield by reaction with benzyl chloroformate.
57. The relative configuration within *syn*-**80** was established by single crystal X-ray analysis. Crystallographic data (excluding structure factors) have been

deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 779449; see also Ref. 21b.
58. The observation that the total conversion is greater than 100% may indicate that the deprotonation step does not proceed to 100% conversion. This would allow a proportion of the $Zn(CH_2I)_2$ to transfer more than 1.0 equiv of carbene.
59. Aliquots were taken every 5 min from the reaction of either **76** or **78** with 2.0 equiv of $Zn(CH_2I)_2$ and the product distributions were analysed by ^1H NMR spectroscopic analysis.
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