Diastereoselective Simmons–Smith cyclopropanations of allylic amines and carbamates

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Received (in Cambridge, UK) 25th July 2007, Accepted 14th August 2007
First published as an Advance Article on the web 24th August 2007
DOI: 10.1039/b711358g

Cyclopropanation of 3-(*N*,*N*-dibenzylamino)cyclohexene with either $Zn(CH_2I)_2$ (Wittig–Furukawa reagent) or $CF_3CO_2ZnCH_2I$ (Shi's reagent) gives the corresponding *syn*-cyclopropane as a single diastereoisomer, whilst cyclopropanation of 3-(*N*-*tert*-butoxycarbonylamino)cyclohexene with $CF_3CO_2ZnCH_2I$ gives the corresponding *anti*-cyclopropane exclusively; facile *N*-deprotection gives access to either diastereoisomer of the trifluoroacetic acid salt of 2-aminobicyclo[4.1.0]heptane.

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 nearly 50 years.[1] New classes of highly reactive zinc carbenoids have recently been developed;[2] the efficient cyclopropanation of isolated and electron poor double bonds is now possible and the substrate scope of the reaction is therefore immensely broad.[3] Diastereoselective cyclopropanation relying upon delivery of the incoming methylene group by the binding to zinc of an allylic hydroxyl group has long been exploited[3] although other groups including α,β-unsaturated acetals,[4] amides[5] and boronates[6] 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.[7] The successful Simmons–Smith cyclopropanation of allylic amines has only very recently been achieved[8] by the groups of Aggarwal[9] and Katagiri,[10] who utilised *N*-protecting groups bearing a free hydroxyl to promote cyclopropanation. As part of an ongoing research programme directed towards chemo- and stereoselective functionalisation of allylic amines at the olefin,[11] we became interested in the potential of allylic amines as substrates for the Simmons–Smith reaction and communicate herein the cyclopropanation of a range of *N*-protected 3-aminocyclohexenes which facilitates the stereoselective preparation of either diastereoisomer of the TFA salt of 2-aminobicyclo[4.1.0]heptane.

Initial studies focused on cyclopropanation of 3-(*N*,*N*-dibenzylamino)cyclohexene **1**. Attempted cyclopropanation of **1** with $Zn(CH_2I)_2$ (Wittig–Furukawa reagent)[12] or $Zn(CH_2Cl)_2$ (Denmark's reagent)[13] proceeded with almost complete consumption of starting material,[14] furnishing a low mass return of cyclopropane *syn*-**2**, isolated in only 11 and 33% yield respectively. Cyclopropanation of **1** with $CF_3CO_2ZnCH_2I$ (Shi's reagent),[2a,c] however, proceeded in complete conversion to furnish *syn*-**2** in >98% de[15] (consistent with chelation-directed cyclopropanation) which was isolated in 92% yield (Scheme 1).

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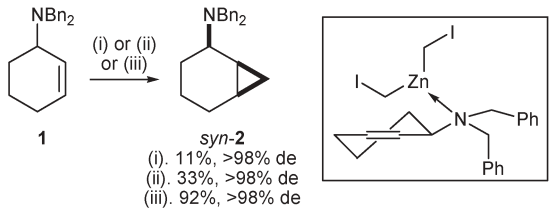
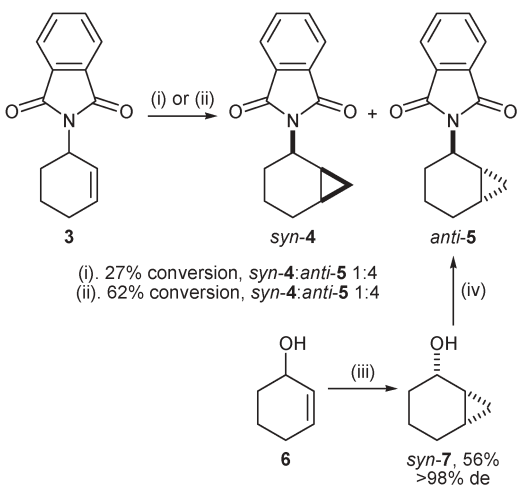


Scheme 1 *Reagents and conditions*: (i) Et_2Zn, CH_2I_2, DCM, rt, 1 h; (ii) Et_2Zn, ICH_2Cl, DCM, rt, 1 h; (iii) Et_2Zn, CH_2I_2, TFA, DCM, rt, 1 h.

The *N*-protecting groups were next varied, in order to probe the possibility of preparing the corresponding *anti*-cyclopropane, with phthalimido and *tert*-butoxycarbonyl groups investigated. Reaction of 3-(*N*-phthalimido)cyclohexene **3** with $Zn(CH_2I)_2$ proceeded to 27% conversion (after 3 hours), giving a 1 : 4 mixture of *syn*-**4** : *anti*-**5**,[16] whereas reaction with $CF_3CO_2ZnCH_2I$ under identical conditions gave 62% conversion to a separable 1 : 4 mixture of *syn*-**4** : *anti*-**5**, from which *syn*-**4** and *anti*-**5** were isolated pure in 8 and 33% yield respectively (Scheme 2). The stereochemistry of the major product *anti*-**5** was proven unambiguously *via* independent chemical synthesis from cyclohex-2-enol **6** and that of the minor product *syn*-**4** by single crystal X-ray crystallographic analysis (Fig. 1).†[17,18] Although the cyclopropanation facial selectivity appears to be predominantly under steric control, competing chelation by the carbonyl group may give rise to the minor product *syn*-**4**.



Scheme 2 *Reagents and conditions*: (i) Et_2Zn, CH_2I_2, DCM, rt, 3 h; (ii) Et_2Zn, CH_2I_2, TFA, DCM, rt, 3 h; (iii) Et_2Zn, ICH_2Cl, DCM, rt, 1 h; (iv) phthalimide, PPh_3, DEAD, THF, rt, 24 h.

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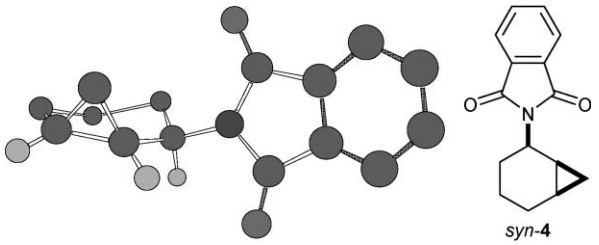
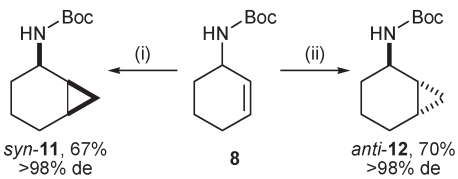


Fig. 1 Chem 3D representation of the X-ray crystal structure of *syn*-**4** (some H atoms removed for clarity). [The compound has crystallographically imposed mirror symmetry and is disordered, with only one conformer being shown].

Cyclopropanation of 3-(*N*-*tert*-butoxycarbonylamino)cyclohexene **8**[19] with $Zn(CH_2I)_2$ gave complete conversion to *syn*-**11** in >98% de,[20] isolated in 67% yield, and cyclopropanation of **8** with $CF_3CO_2ZnCH_2I$ gave *anti*-**12** in >98% de[21] and in 70% yield (Scheme 3). The complementary selectivities of these reactions are postulated to be a result of initial formation of an intermediate zinc complex by deprotonation of the carbamate. In the case of $Zn(CH_2I)_2$, the co-ordinated zinc carbenoid **9** is able to effect rapid, intramolecular, *syn*-cyclopropanation of the double bond to give *syn*-**11**; with $CF_3CO_2ZnCH_2I$, however, a second equivalent of the zinc reagent is required to cyclopropanate the double bond of **10** by approach to the least hindered face, giving *anti*-**12** (Fig. 2).[22] Consistent with this hypothesis, treatment of **8** with 1 equiv. of $Zn(CH_2I)_2$ gave 37% conversion to *syn*-**11** after 1 hour, whereas analogous treatment of **8** with 1 equiv. of $CF_3CO_2ZnCH_2I$ gave no observable cyclopropanation products.

In order to confirm the assigned stereochemistries of the cyclopropane products, and to demonstrate the utility of this protocol for synthesis, cleavage of the *N*-protecting groups was



Scheme 3 *Reagents and conditions*: (i) Et_2Zn, CH_2I_2, DCM, rt, 1 h; (ii) Et_2Zn, CH_2I_2, TFA, DCM, rt, 1 h.

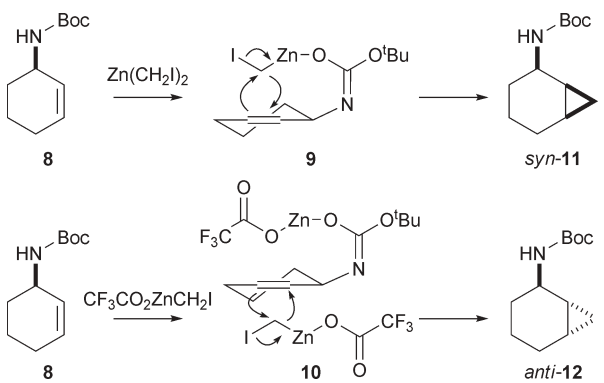
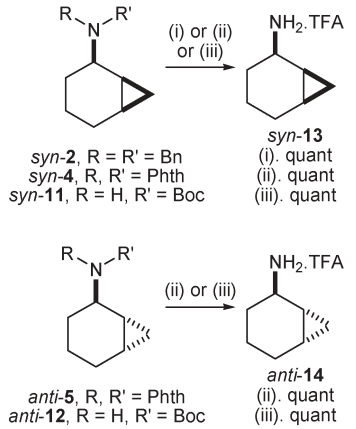


Fig. 2 Proposed mechanistic rationale for the opposite selectivity observed upon cyclopropanation of **8** with $Zn(CH_2I)_2$ and $CF_3CO_2ZnCH_2I$.



Scheme 4 *Reagents and conditions*: (i) H_2 (5 atm), Pd/C (50% w/w), MeOH–H_2O–AcOH (v : v : v 40 : 4 : 1), rt, 12 h, then TFA; (ii) NH_2NH_2, MeOH, reflux, 12 h, then TFA; (iii) TFA, DCM, rt, 1 h.

investigated. Hydrogenolysis of *syn*-**2** and treatment of the crude product with TFA gave *syn*-**13** in quantitative yield. Cleavage of the *N*-Boc protecting group of both pure *syn*-**11** and pure *anti*-**12** was achieved upon treatment with TFA, giving the corresponding trifluoroacetate salts *syn*-**13** and *anti*-**14**, both in quantitative yield. Removal of the *N*-phthaloyl group from *syn*-**4** and *anti*-**5** (of known stereochemistry) was achieved upon treatment with hydrazine, with subsequent treatment with TFA giving the corresponding trifluoroacetic acid salts *syn*-**13** and *anti*-**14** (Scheme 4).

In conclusion, a highly diastereoselective cyclopropanation protocol for allylic tertiary amines and carbamates has been demonstrated, giving, after facile *N*-deprotection, access to either diastereoisomer of the trifluoroacetate salt of 2-aminobicyclo[4.1.0]heptane in good yield. Further investigations to fully delineate the scope of this methodology with application to natural product synthesis are currently ongoing.

Notes and references

† CCDC 644843. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711358g

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17 (*a*) X-ray crystal structure determination for *syn*-**4**: Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 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[18]; (*b*) X-ray crystal structure data for *syn*-**4** [$C_{15}H_{15}NO_2$]: M = 120.64, monoclinic, space group P 1 21/m 1, a = 8.5766(3), b = 7.0349(3), c = 10.6494(5) Å, β = 109.9188(15)°, V = 604.10(4) Å^3, Z = 2, μ = 0.088 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.3 mm^3. A total of 1468 unique reflections were measured for $5 < \theta < 27$ and 1206 reflections were used in the refinement. The final parameters were wR_2 = 0.2057 and R_1 = 0.1044 [$I > 2\sigma(I)$]; (*c*) Due to disorder associated with atoms C(9)–C(15) inclusive, bond stretching restraints and ADP similarity restraints were placed upon them.
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20 Preparation of (1*RS*,2*SR*,3*SR*)-*syn*-2-(*N*-*tert*-butoxycarbonylamino)bicyclo[4.1.0]heptane *syn*-**11** *via* cyclopropanation of 3-(*N*-*tert*-butoxycarbonylamino)cyclohexene **8** with $Zn(CH_2I)_2$: diiodomethane (0.32 mL, 4.0 mmol) was added dropwise to a stirred solution of diethylzinc (1.0 M in hexanes, 2.0 mL, 2.0 mmol) in DCM (2 mL) at −78 °C under an atmosphere of argon, and the mixture allowed to warm to 0 °C. After stirring for 15 min a solution of **8** (197 mg, 1.0 mmol) in DCM (0.5 mL) was added dropwise *via* syringe, the resulting solution allowed to warm to rt, and stirred for a further 1 h at which point sat. aq. Na_2EDTA (25 mL) and sat. aq. $NaHCO_3$ (25 mL) were added. The organic layer was then separated and the aqueous layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica, eluent 30–40 °C petrol–Et_2O, 9 : 1) gave *syn*-**11** as a white crystalline solid (141 mg, 67%, >98% de); mp 41–43 °C; ν_{max} (film) 3343, 2933, 1701; 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(4)H_B, C(5)H_A), 1.42 (9H, br s, CMe_3), 1.69 (1H, app br s, C(3)H_B), 1.84–1.87 (1H, m, C(5)H_B), 3.98 (1H, app br s, C(2)*H*), 4.53 (1H, app br s, N*H*); δ_C (125 MHz, $CDCl_3$) 7.8, 11.6, 15.5, 21.5, 23.0, 27.5, 28.4, 46.5, 78.8, 155.3; *m*/*z* (ESI$^+$) 270 ([M + MeCN + NH_4]$^+$, 100%); HRMS (ESI$^+$) found 234.1465; $C_{12}H_{21}NNaO_2^+$ ([M + Na]$^+$) requires 234.1465.
21 Preparation of (1*RS*,2*RS*,3*SR*)-*anti*-2-(*N*-*tert*-butoxycarbonylamino)-bicyclo[4.1.0]heptane *anti*-**12** *via* cyclopropanation of 3-(*N*-*tert*-butoxycarbonylamino)cyclohexene **8** with $CF_3CO_2ZnCH_2I$: diiodomethane (0.32 mL, 4.0 mmol) was added dropwise to a stirred solution of diethylzinc (1.0 M in hexanes, 2.0 mL, 2.0 mmol) in DCM (2 mL) at −78 °C under an atmosphere of argon, and the mixture allowed to warm to 0 °C. After stirring for 15 min, TFA (0.15 mL, 2.0 mmol) was added dropwise and the solution became homogeneous. After stirring for 15 min a solution of **8** (197 mg, 1.0 mmol) in DCM (0.5 mL) was added dropwise *via* syringe, the resulting solution allowed to warm to rt and stirred for a further 1 h at which point sat. aq. Na_2EDTA (25 mL) and sat. aq. $NaHCO_3$ (25 mL) were added. The organic layer was then separated and the aqueous layer was extracted three times with DCM (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica, eluent 30–40 °C petrol–Et_2O, 9 : 1) gave *anti*-**12** as a white crystalline solid (148 mg, 70%, >98% de); mp 40–42 °C; ν_{max} (film) 3333, 2933, 1703; 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, app br s, C(2)*H*), 4.76 (1H, app br s, N*H*); δ_C (125 MHz, $CDCl_3$) 9.2, 9.7, 16.3, 16.9, 24.8, 28.0, 28.4, 46.4, 78.9, 155.2; *m*/*z* (ESI$^+$) 270 ([M + MeCN + NH_4]$^+$, 100%); HRMS (ESI$^+$) found 234.1465; $C_{12}H_{21}NNaO_2^+$ ([M + Na]$^+$) requires 234.1465.
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