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An exploratory study of ring closures of aryl radicals onto cyclopropyl- and oxiranyl-isocyanate acceptors

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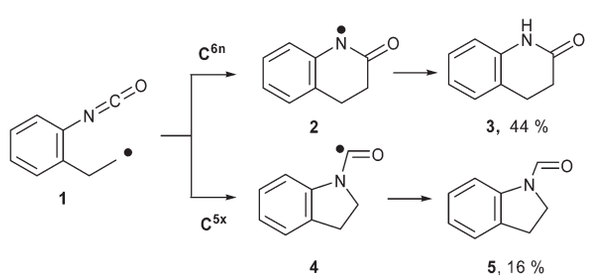
The idea that ring closures of C-centred radicals onto isocyanates could be made permanent by designing the cyclised radical to undergo a rapid onward β-scission, was investigated for the 2-(2-isocyanato)cyclopropylphenyl and 2-(2-isocyanato)oxiranylphenyl radicals. The radical precursors, *trans*- and *cis*-1-bromo-(2-isocyanatocyclopropyl)benzene and (2-bromophenyl)-3-isocyanatooxirane, were prepared from the corresponding bromophenylcyclopropane and bromophenyloxirane carboxylic acids *via* Curtius rearrangements of the derived azides. The structure of the *trans*-2-(2-isocyanato)cyclopropylphenyl radical prevents cyclization, however, it was shown that isomerisation to the analogous *cis*-radical occurred, probably by scission of the disubstituted cyclopropane bond followed by internal rotation of the resulting resonance stabilised diradical. It was found, however, that the main product from homolytic reactions of both *trans*- and *cis*-isocyanatocyclopropyl compounds, with tributyltin hydride and tris(trimethylsilyl)silane, was the direct reduction product, *trans*-(2-isocyanatocyclopropyl)benzene. Only traces of cyclised products, that were probably 4,5-dihydrobenzo[*c*]azepin-1-one from the cyclopropane precursor and 5*H*-6-oxa-8-azabenzocyclohepten-9-one from the oxirane precursor, were detected. We conclude, therefore, that the rate of cyclization onto isocyanate acceptor groups must be slower in these systems than hex-5-enyl cyclization or that the reverse ring-opening process must be faster than for analogous radicals.

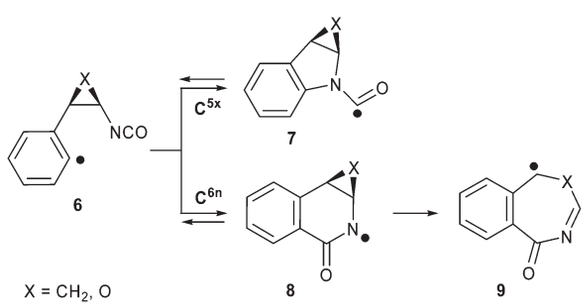
Introduction

Scarcely any preparations of *N*-heterocycles *via* cyclizations of ω-isocyanato-C-centered radicals have been reported. The reason for this neglect can be traced to the rapid reverse ring opening process which counteracts the cyclisation. For example, the 2-(isocyanatocarbonyl)ethyl radical cyclised rapidly to the succinimidyl radical but the rate of ring opening was almost as fast.[1,2] Similarly, the 3-(isocyanatocarbonyl)propyl radical afforded the glutarimidyl radical; but this 6-*endo*-type process was reversible.[2] We showed recently that the 2-(2-isocyanatophenyl)ethyl radical (**1**) underwent ring closure at the central C-atom, in the *endo* mode, to afford acylaminyl radical **2** and, to a minor extent, at the N-terminus to produce aminoacyl radical **4** (Scheme 1).[3] The resonance stabilisation of radical **2** reinforced the ring closure and inhibited the reverse ring opening so that substantial amounts of cyclised products could be isolated (Scheme 1).



Scheme 1 Cyclisation of the 2-(2-isocyanatophenyl)ethyl radical.

Another potential way of avoiding reversal of ring closure onto –NCO groups might be to offer the cyclised species an alternative, more rapid, onward process. For example, if the radical centre in the cyclised species was created adjacent to a three-membered ring, opening of the strained ring should supervene, thus preserving the initial cyclised structure. The system shown in Scheme 2 was designed to test out this idea. The 2-(2-isocyanato) cyclopropylphenyl radical **6** might ring close to afford carbamoyl radical **7a**. However, literature precedents[1,3] indicated that the main cyclisation mode would be 6-*endo* (**C**^{6n}) to generate the dihydroisoquinolinonyl radical **8a**. Aryl radical **6** will be electronically neutral, unlike the nucleophilic alkyl radicals. Ring closure onto the electrophilic C-atom of NCO should also be favoured because amidyl radical **8a** is more thermodynamically stabilised. Radical **8a** contains a cyclopropylaminyl structural unit that is expected to ring open very rapidly by β-scission of its inter-ring bond to afford the dihydrobenzoazepinonyl radical **9a**. Radical **9a** is a resonance stabilised benzyl type radical and therefore its formation will be favoured over that of the alternative six-membered ring dihydroisoquinolinonylmethyl radical that would result from scission of the outer cyclopropane bond.[4,5] It was anticipated that the rapid formation of **9** would ensure that formation of dihydrobenzoazepinones would supersede the reverse **C**^{6n} step.



Scheme 2 Domino cyclisation and ring opening of 2-(2-isocyanato)-cyclopropylphenyl radicals.

To test the practicality of this idea we prepared 1-bromo-(2-isocyanatocyclopropyl)benzene **13** and (2-bromophenyl)-3-isocyanatooxirane **26** as radical precursors and examined their reactions with several radical generating reagents.

Results and discussion

Trans-bromophenylpropenoate **10** was made by palladium-catalysed coupling of methyl acrylate with 2-bromoiodobenzene under phase transfer conditions with tetra-*n*-butyl ammonium chloride.[6] Cyclopropanation of **10** with diazomethane in the presence of 0.005 equivalents of palladium(II) acetate afforded the *trans*-ester **11** in high yield after purification on a silica column (Scheme 3). The first attempt at this cyclopropanation gave a mixture of *trans*-**11** together with some *cis*-isomer. However, the reaction was subsequently repeated many times and gave solely *trans*-**11**. The observation of some *cis*-isomer was probably due

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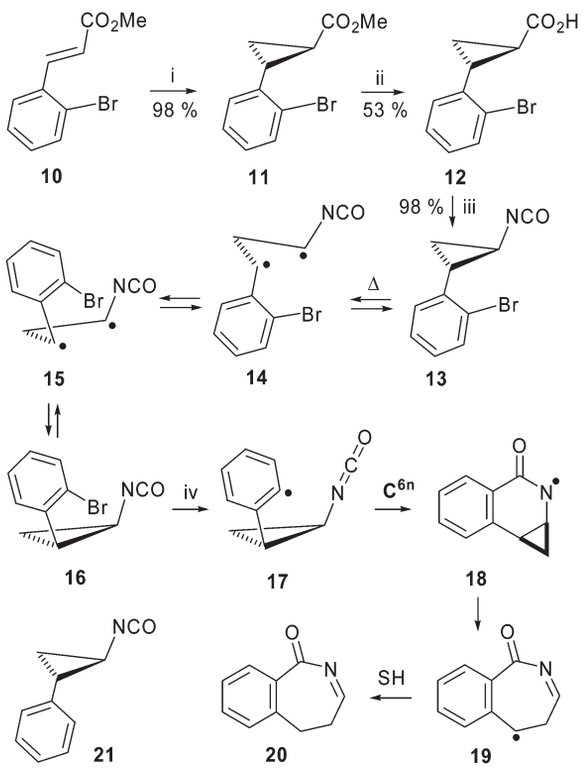


i CH_2N_2, $Pd(OAc)_2$; ii NaOH, MeOH; iii Et_3N, $ClCO_2Et$, NaN_3
iv R_3MH, AIBN

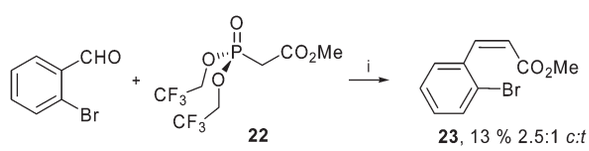
Scheme 3 Preparation and homolytic reactions of 1-bromo-(2-isocyanatocyclopropyl)benzene.

to thermal isomerisation (see below). Alkaline hydrolysis of **11** provided acid **12** which was treated with sodium azide and ethyl chloroformate under anhydrous conditions to produce *trans*-isocyanate **13** *via* a Curtius rearrangement. The easily degraded isocyanate was used without purification for the radical reactions.

Trans-bromo-isocyanate **13** and azobisisobutyronitrile (AIBN) were photolysed with tributyltin hydride in toluene at ambient temperature (*ca.* 40 °C). The sole product obtained under these conditions was the direct reduction product *trans*-(2-isocyanatocyclopropyl)benzene (**21**). No other products were observed when the reaction was carried out at 70 °C or when hexamethylditin was used in place of tributyltin hydride. A reaction was also carried out in which the Bu_3SnH was added with a syringe pump over 3 hours during continuous photolysis. The main product under these circumstances was again **21**. However, GC-MS analysis of the product mixture showed a minor amount of a product having $M^+ = 159$ [$C_{10}H_9NO$]. The fragmentation pattern was in better agreement with the 4,5-dihydrobenzo[*c*]azepin-1-one structure **20** for this product rather than 4-methyl-4*H*-isoquinolin-1-one; which is the main alternative. Reactions were also carried out with tris(trimethylsilyl)silane (TTMSS) and 1,1′-azobiscyclohexanecarbonitrile in benzene at 70 °C and also gave **21** as the only significant product. A reaction initiated with ethyl piperidine hypophosphite (EPHP)[7] at 70 °C in benzene yielded only a complex intractable mixture none of whose components could be identified.

The lack of ring closure could result from the *trans* structure of compound **13** (and that of its derived *trans*-aryl radical **6a**). The distance between the radical centre and the isocyanate moiety will be large and the structure will be quite rigid so that the stereoelectronically favoured transition state geometry cannot be attained. However, we expected that *trans*-**13** would readily interconvert with the *cis*-isomer **16** *via* a stabilised diradical intermediate **14** (Scheme 3). Heating **13** should lead to rupture of the weak disubstituted cyclopropane bond with production of diradical **14** which is stabilised by resonance delocalisation of both unpaired electrons. Analogous cyclopropane isomerisations are well documented[8–10] and can occur rapidly when the intermediates are thermodynamically stabilised. Internal rotation about one of the CH_2–$CH^{\cdot}$ bonds will convert **14** to the *cis*-diradical **15**, ring closure of which will provide the *cis*-precursor **16**. A similar thermal interconversion is feasible for the *trans*- and *cis*-radicals **6a** and **17**. 6-*endo*-ring closure, and/or 5-*exo*-ring closure, of *cis*-radical **17** would then be favourable. The interconversion process might lead to thermodynamic control of the cyclization. To encourage this isomerization, a photolysis was carried out using **13** in neat *n*-Bu_3SnH at 150 °C. At this temperature the main product was again **21** from simple reduction. However, the GC-MS analysis showed that the residual **13** had isomerised to a mixture of *trans*- and *cis*-isomers, *i.e.* that the cyclopropane rearrangement of Scheme 3 had occurred to some extent. The product analysis also showed a minor amount of 2-phenylcyclopropylamine which suggested that some hydrolysis of **21** occurred under these forcing conditions.

The presence of residual *cis*-**16** in this experiment suggested that the cyclization step did not compete effectively with hydrogen atom transfer from the tin hydride. To examine this conclusion more thoroughly we set out to prepare the *cis*-cyclopropyl-isocyanate **16** directly. *cis*-Bromophenylpropenoate **23** was prepared in low yield by reaction of trifluoroethylphosphonoester **22**[11] with 2-bromobenzaldehyde using the optimal base system $KN(TMS)_2$/18-crown-6-acetonitrile (Scheme 4).[12] The *cis*/*trans* mixture was converted to the corresponding cyclopropylisocyanate, following the same procedure as for the *trans*-isomer, and a 2.5 : 1 mixture of *cis* : *trans* cyclopropanes was obtained. The radical cyclization of this *cis*/*trans* mixture was attempted with *n*-Bu_3SnH but showed no cyclised products. Reaction with TTMSS and 1,1′-azobiscyclohexanecarbonitrile was carried out at 103 °C. The GC showed **21** as the main product together with residual starting bromide. During this reaction the *cis*/*trans* ratio of **13** : **16** changed from 2.5 : 1 to 1 : 5, *i.e.* isomerization took place to favour the thermodynamically more stable *trans*-isomer. Probably cyclization could not compete with rapid isomerization and H-atom transfer reactions.



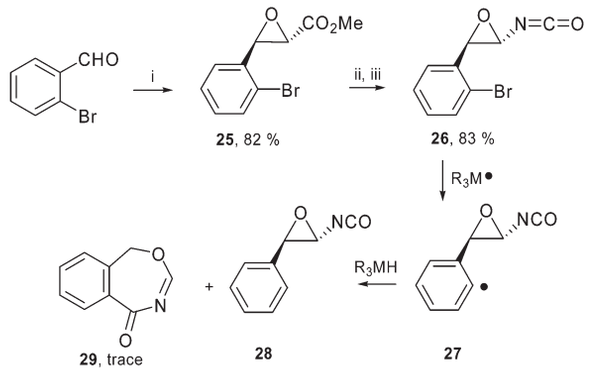
i, $KN(TMS)_2$, 18-crown-6-acetonitrile complex, THF, -78°

Scheme 4 Preparation of methyl *cis*-bromophenylpropenate.

Replacement of the cyclopropane ring with an oxiranyl ring was also investigated. Methyl 3-(2-bromophenyl)-2-oxirane carboxylate **25** was made in 24% yield by treating alkenyl ester **10** with *m*-chloroperbenzoic acid following a literature procedure.[13] Because of the poor yield, the method of Wunsch,[14] involving reaction of 2-bromobenzaldehyde with methyl chloroacetate mediated by NaOMe was carried out and afforded **25** in a much improved yield of 82% (Scheme 5). Oxirane ester **25** was then converted to the corresponding *trans*-isocyanate **26** using the same method as for the corresponding cyclopropane derivative. Treatment of **26** with *n*-Bu_3SnH gave a mixture of products. The main component of which, 2-bromophenyl-3-aminooxirane, was probably formed by hydrolysis of the isocyanate. TTMSS was also employed, with 1,1′-azobiscyclohexanecarbonitrile as initiator, in reactions at 83 °C and at 103 °C. Analysis by ^{1}H NMR and GC-MS showed much unreacted **26** at both temperatures together with (2-bromophenyl)-3-aminooxirane (from hydrolysis) and the reduced compound, 2-isocyanato-3-phenyloxirane. The GC-MS showed the presence of a minor product having $M^+ = 161$ [$C_9H_7NO_2$]. Attempts to isolate and characterise this were unsuccessful but it was probably due to traces of the cyclised product 5*H*-6-oxa-8-azabenzocyclohepten-9-one, **29**.

Conclusions

Analysis of the residual 1-bromo-(2-isocyanatocyclopropyl)-benzene showed that isomerization of **16** to **13** occurred rapidly at 150 °C (and likely also at lower temperatures) probably by the



i; $ClCH_2CO_2Me$, Na/MeOH. ii; KOH, EtOH; iii; Et_3N, $ClCO_2Et$, NaN_3

Scheme 5 Preparation and reaction of an oxiranyl-isocyanate.

mechanism outlined in Scheme 3. The analogous *cis*- and *trans*-aryl radicals are σ-radicals with localised radical centres. They are therefore structurally very similar to their parent bromides and probably equilibrate *via* a similar rearrangement. Cyclization of the *trans*-radical is structurally forbidden. However, the *cis*-radical **17** appears capable of ring closure preferably in the 6-*endo* mode onto the C-atom of the isocyanate moiety. Although **17**, and the analogous oxiranyl radical **27**, were generated under a variety of experimental conditions, only traces of cyclised products were detected. Previous work with ω-isocyanato-C-centered radicals has shown that they cyclise with rate constants comparable to that of the archetype hex-5-enyl radical.[1,3] However, it appears that for **17** (and *cis*-**27**) the cyclization cannot compete with H-atom transfer from *n*-Bu_3SnH (or TTMSS) and/or the reverse ring opening reaction. Cyclizations of other hex-5-enyl type radicals can compete with H-atom transfer from both metal hydrides under similar experimental conditions. We conclude, therefore, that the rate of cyclization of **17** (and *cis*-**27**) must be slower than hex-5-enyl cyclization or that the reverse ring-opening process must be faster than for analogous radicals. The presence of the cyclopropane ring (or oxirane ring) and near-linear NCO group in the chain of **17** (and *cis*-**27**) affects their conformational preferences significantly in comparison with hex-5-enyl. The chains are likely to be stiffer and much less flexible so that approach from above the π-system of the isocyanate group in either the 5-*exo* or 6-*endo*-modes may be more difficult. This may explain their reluctance to cyclise.

Experimental

^1H, and ^{13}C, NMR spectra were obtained using Bruker AM300, Bruker Avance 300 and Varian Gemini 2000 spectrometers. All samples were dissolved in deuterated chloroform, unless otherwise stated, using Me_4Si as an internal standard. Chemical shifts are given in ppm. IR spectra were obtained using a Perkin-Elmer 1710 Infrared FT spectrometer. Frequencies are given in cm^{-1}. Mass spectra and GC-MS spectra were obtained using a Finnigan Incos 50 quadrupole instrument coupled to a Hewlett Packard HP 5890 chromatograph fitted with a 25 m HP 17 capillary column (50% phenyl methyl silicone). All melting points were determined in open capillary tubes and are reported uncorrected. TLC was performed on pre-coated plates of silica gel G-60 F-254 (Merck). Elemental analyses were recorded with an Agilent 7500 Series ICP-MS spectrometer that had built in laser ablation capability or on a Carlo Erba CHNS analyser. Column chromatography was performed using BDH silica gel (40–63 μm) eluting with the given solvent mixture.

Methyl *trans*-2-(2-bromophenyl)propenoate 10[6]

A mixture of 2-bromoiodobenzene (7.0 g, 24.7 mmol), methyl acrylate (2.8 cm^3, 31.9 mmol), palladium acetate (0.1 g, 0.5 mmol), tetrabutylammonium chloride (6.9 g, 24.7 mmol), and finely ground potassium carbonate (8.6 g, 62.0 mmol) in DMF (26 cm^3) was stirred at 50 °C for 19 h. Petroleum ether (150 cm^3) and brine (40 cm^3) were added and the mixture was filtered under suction. The filtrate was collected, and the aqueous layer was extracted with petroleum ether (3 × 30 cm^3). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was purified on a silica column (ether/hexane, 1 : 3) to afford pure **10** as a clear yellow oil (4.9 g, 81%). δ_H 3.85 (3H, s, Me), 6.43 (1H, d, CHCOOR, *J* 16.0), 7.25–7.40 (2H, m, ArH), 7.65–7.75 (2H, m, ArH), 8.83 (1H, d, =CHAr, *J* 16.0); δ_C 51.8, 120.6, 125.2, 127.6, 127.7, 131.1, 133.3, 134.4, 143.1, 166.7.

Methyl *trans*-2-(2-bromophenyl)cyclopropanecarboxylate 11[6]

A solution of *p*-tolylsulfonylmethylnitrosamide in ether (12 g in 70 cm^3) was added over 30 min to a solution of potassium hydroxide (3 g) in water (5 cm^3), monoethyl ether of diethylene glycol (13 cm^3) and ether (5 cm^3) at 75–80 °C. As soon as all the nitrosamide solution had been added, additional ether (60 cm^3) was added at the previous rate until the distillate was colourless. The resulting ether solution of diazomethane was continuously distilled into a stirred, cooled (−10 °C) solution of methyl *trans*-3-(2-bromophenyl)propenoate (1.0 g, 5.6 mmol) and palladium acetate (0.006 g, 0.003 mmol) in dichloromethane/ether (1 : 2, 75 cm^3). The reaction was quenched by addition of 2 cm^3 of acetic acid after 2 h. The resulting mixture was washed with saturated aqueous sodium hydrogen carbonate (3 × 5 cm^3), dried over magnesium sulfate, filtered, and concentrated. The crude product was purified on a silica column eluted with ether/hexane (1 : 1) to afford pure **11** (2.0 g, 98%); δ_H 1.35–1.40 (1H, m, CH), 1.60–1.70 (1H, m, CH), 1.80–1.70 (1H, m, CH), 2.70–2.80 (1H, m, CH), 3.80 (3H, s, Me), 7.00–7.20 (2H, m, ArH), 7.25–7.35 (1H, m, ArH), 7.60–7.65 (1H, m, ArH); δ_C 15.8, 22.9, 27.0, 51.9, 126.2, 127.4, 127.5, 128.2, 132.6, 138.9, 173.7.

trans-2-(2-Bromophenyl)cyclopropane carboxylic acid 12[6]

Ester **11** (1 g, 5.2 mmol) was dissolved in methanol (10 cm^3), and 2 M aqueous sodium hydroxide (5 cm^3) was added. The solution was stirred at room temperature for 2 h. The methanol was evaporated, and the remaining solution was diluted with water (15 cm^3), washed with ether (20 cm^3), acidified with 5 M aqueous hydrochloric acid, and extracted with ether (3 × 30 cm^3). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford pure **12** (0.5 g, 53%); δ_H 1.25–1.40 (1H, m, CH), 1.50–1.65 (1H, m, CH), 1.65–1.80 (1H, m, CH), 2.60–2.80 (1H, m, CH), 6.90–7.10 (2H, m, ArH), 7.15–7.20 (1H, m, ArH), 7.40–7.60 (1H, m, ArH).

trans-1-Bromo-(2-isocyanatocyclopropyl)benzene 13

A mixture of *trans*-3-(2-bromophenyl)cyclopropanecarboxylic acid **12** (0.5 g, 2.1 mmol), triethylamine (0.3 g, 2.9 mmol), and ethyl chloroformate (0.3 g, 3.1 mmol) in dry acetone (20 cm^3) was stirred at −10 °C. A solution of sodium azide (0.2 g, 3.6 mmol) in H_2O (10 cm^3) was added after 2.5 h. The stirring was discontinued after an additional 30 min. The resulting suspension was poured into cold H_2O (22 cm^3) and was extracted with toluene. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to about 50% of the volume to remove remaining traces of H_2O. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased, and the solution was concentrated to give the resulting isocyanate as an oil. The NMR spectra showed that the isocyanate has been obtained as a mixture of the *trans* and *cis* isomers; δ_H 1.20–1.38 (4H, m, *cis* + *trans*), 1.40–1.58 (0.5H, m, *cis*), 1.65–1.80 (0.5H, m, *cis*), 2.30–2.40 (1H, m, *trans*), 2.80–2.90 (2H, m, *cis* + *trans*), 6.90–7.10 (4H, m, ArH, *cis* + *trans*), 7.15–7.20 (2H, m, ArH, *cis* + *trans*), 7.40–7.60 (2H, m, ArH, *cis* + *trans*). ^1H NMR (*trans*-isomer); δ_H 1.20–1.38 (2H, m), 2.30–2.40 (1H, m), 2.80–2.90 (1H, m), 6.95 (1H, d, ArH, *J* 8.8), 7.10 (1H, t, ArH, *J* 8.1), 7.20 (1H, t, ArH, *J* 8.1), 7.55 (2H, d, ArH, *J* 8.8); δ_C (*trans*-isomer) 17.5, 26.0, 29.4, 126.5, 127.6, 127.9, 128.8, 132.9, 138.4, 179.5; ν_{NCO} = 2273 cm^{-1}; *m*/*z* (%), 238/236 (M^+ 2), 208/210 (8), 182/184 (6), 158 (100), 130 (28), 115 (29), 103 (23), 89 (7), 77 (7), 63 (8), 51 (16). (Found: C, 50.35; H, 3.36; N, 5.78. $C_{10}H_8BrNO$ requires C, 50.45; H, 3.39; N 5.88%).

Reaction of *trans*-1-bromo-(2-isocyanatocyclopropyl)benzene (13) with tributyltin hydride

Procedure 1. *trans*-1-Bromo-(2-isocyanatocyclopropyl)benzene **13** (10 mg, 0.04 mmol) and tributyltin hydride (11 mg, 0.04 mmol) in solution in toluene (5 cm^3) were photolysed for 4.5 h in the presence of 10% of AIBN. GC-MS: major product; *peak 198*, *trans*-(2-isocyanatocyclopropyl)benzene (**21**, library fit 95%), *m*/*z* (%) 159 (M^+ 13), 115 (2), 91 (100), 65 (11), 51 (3). Several additional minor components were present on the chromatogram.

Procedure 2. Tributyltin hydride (11 mg, 0.04 mmol) was added slowly into a solution of **13** (10 mg, 0.04 mmol) in toluene (5 cm^3) in the presence of 10% of AIBN. The solution was photolysed for 3 h. GC-MS: *peak 215*; *trans*-(2-isocyanatocyclopropyl)benzene **21**, *peak 238*; *trans*-1-bromo-(2-isocyanatocyclopropyl)benzene. Several additional minor components were present on the chromatogram.

Procedure 3. A quartz tube was heated in an oil bath at 150 °C then **13** (100 mg, 0.42 mmol) was added and, after 5 min, tributyltin hydride (147 mg, 0.50 mmol). The mixture was photolysed and monitored by GC-MS. After 30 min the product mixture was subjected to column chromatography (hexane/EtOAc, 1 : 3). *Fraction 3*, *trans*-(2-isocyanatocyclopropyl)benzene **21**, *fraction 4* contained *trans*- + *cis*-2-phenyl-cyclopropylamine (library fit 96%), *m*/*z* (%) M^+ 132 (M^+ 100), 115 (40), 104 (14), 91 (20), 77 (18), 63 (8), 56 (39), together with residual **13** and **16**.

Reactions of *trans*-1-bromo-(2-isocyanatocyclopropyl)benzene (13) with hexamethylditin and with EPHP

Trans-isocyanate **13** (10 mg, 0.04 mmol) and hexamethylditin (12.4 mg, 0.04 mmol) in solution in toluene (5 cm^3) were photolysed for 3 h in presence of 10% of AIBN. GC-MS analysis showed a complex mixture, but no trace of cyclised products.

Trans-isocyanate **13** (0.50 g, 2 mmol) and EPHP (10 eq.) in solution in benzene (30 cm^3) were heated for 1 h under a nitrogen atmosphere at 70 °C. AIBN (0.04 eq.) was added in two portions over 30 min and reflux was continued for 3 days. On cooling, the reaction was diluted with petroleum ether and washed successively with sodium hydrogen carbonate, aqueous hydrochloric acid (2 M), sodium hydrogen carbonate and brine. The organic layer was then dried over magnesium sulfate, filtered and concentrated *in vacuo*. GC-MS showed only a complex mixture of unidentified components.

Reaction of *trans*-1-bromo-(2-isocyanatocyclopropyl)benzene (13) with TTMSS

trans-Isocyanate **13** (60 mg, 0.25 mmol) and tris(trimethylsilyl)-silane (75 mg, 0.30 mmol) in solution in C_6D_6 (1 cm^3) were heated for 2 h at 103 °C in the presence of 10% of 1,1′-azodicyclohexanecarbonitrile (0.006 g). The ^1H NMR spectrum, showed mainly starting material plus several resonances due to minor unidentified components. GC-MS showed *trans*-(2-isocyanatocyclopropyl)benzene **21** and unreacted **13**. Reaction at 83 °C gave a similar result.

Methyl *cis*-2-(2-bromophenyl)propenoate 23

A solution of bis(trifluoroethyl)phosphonoacetate[11] (1.92 g, 7 mmol) and 18-crown-6-acetonitrile complex[12] (11.62 g, 5 eq.) in anhydrous THF (15 cm^3) was cooled to −78 °C under nitrogen and treated with $KN(TMS)_2$ (1.34 g, 1 eq., 0.6 M in toluene). 2-Bromobenzaldehyde (1.24 g, 7 mmol) was then added and the resulting mixture was stirred for 30 min at −78 °C. Saturated NH_4Cl was added and the product was extracted into ether (3 × 30 cm^3). The organic phases were dried over magnesium sulfate and evaporated. Flash chromatography was performed (7 : 3 EtOAc : petroleum ether) and the product was eluted at the same time as the aldehyde. The solution was treated with sodium bisulfite to remove the bromobenzaldehyde and a second column was then run using the same conditions to afford **23** (0.2 g, 13%); δ_H 3.23 (1H, s, CH), 3.75 (3H, s, Me), 3.94 (1H, s, CH), 6.05 (1H, d, *J* 13.2), 6.13 (1H, d, *J* 13.2), 7.2–8.0 (4H, m). The *trans*-isomer was also observed in the NMR spectrum in a 1.0 : 2.5 ratio (*trans* : *cis*).

***cis*-2-(2-Bromophenyl)cyclopropane carboxylic acid**

An ether solution of diazomethane from *p*-tolylsulfonylmethyl-nitrosamide (7.2 g) was continuously distilled into a stirred, cooled (−10 °C) solution of methyl *cis*-3-(2-bromophenyl)propenoate (200 mg 0.8 mmol) and palladium acetate (0.089 g) in dichloromethane/ether (1 : 2, 75 cm^3). The reaction was quenched by addition of 1 cm^3 of acetic acid after 2 h. The resulting mixture was washed with saturated aqueous sodium hydrogen carbonate (3 × 5 cm^3), dried over magnesium sulfate, filtered, and concentrated to afford 0.2 g of crude product. The product was purified on a silica column eluted with ether/hexane (2 : 1) to afford the *cis*- plus *trans*-esters as a yellow oil (0.06 g, 30%); δ_H 1.35–1.40 (1H, m, CH), 1.60–1.70 (1H, m, CH), 1.80–1.70 (1H, m, CH), 2.70–2.80 (1H, m, CH), 3.80 (3H, s, Me), 7.00–7.20 (2H, m, ArH), 7.25–7.35 (1H, m, ArH), 7.60–7.65 (1H, m, ArH).

The methyl 3-(2-bromophenyl)cyclopropenoate isomer mixture (0.06 g, 0.24 mmol) was dissolved in ethanol (10 cm^3), and 2 M aqueous potassium hydroxide (5 cm^3) was added. The solution was stirred at room temperature for 2 h. The ethanol was evaporated, and the remaining solution was diluted with water (5 cm^3), washed with ether (20 cm^3), acidified with 5 M aqueous hydrochloric acid, and extracted with ether (3 × 10 cm^3). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the *cis*- and *trans*-3-(2-bromophenyl)cyclopropane carboxylic acids (0.057 g, 98%). ^1H NMR (acetone) *cis* + *trans*: δ_H 1.07–1.12 (2H, m, CH), 1.40–1.55 (2H, m, CH), 1.75–1.81 (1H, m, CH), 2.03–2.07 (1H, m, CH), 7.09–7.86 (8H, m, ArH).

***cis*-1-Bromo-(2-isocyanatocyclopropyl)benzene 16**

The mixture of *cis*- and *trans*-3-(2-bromophenyl)-cyclopropane carboxylic acids (0.55 g, 0.24 mmol), triethylamine (0.03 g, 1.4 eq.), and ethyl chloroformate (0.04 g, 1.5 eq.) in dry acetone (10 cm^3) was stirred at −10 °C and a solution of sodium azide (0.03 g, 1.7 eq.) in H_2O (0.1 cm^3) was added after 2.5 h. The stirring was discontinued after an additional 30 min. The resulting suspension was poured into cold H_2O (5 cm^3) and was extracted with toluene. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to about 50% of the volume to remove remaining traces of H_2O. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased, and the solution was concentrated to give a mixture of **13** and **16** (ratio 1.0 : 2.5) (0.055 g, 98%). ν_{NCO} 2272 cm^{-1}; ^1H NMR (benzene) *cis*-isomer: δ_H 1.20–1.40 (2H, m, CH), 1.50–1.65 (0.5H, m, CH), 1.65–1.80 (0.5H, m, CH), 2.60–2.80 (1H, m, CH), 6.90–7.10 (2H, m, ArH), 7.15–7.20 (1H, m, ArH), 7.40–7.60 (1H, m, ArH).

Reaction of *cis*-1-bromo-(2-isocyanatocyclopropyl)benzene (16) with TTMSS

The mixture of **13** and **16** (20 mg, 0.08 mmol) and tris(trimethylsilyl)silane (25 mg, 0.10 mmol) in solution in C_6D_6 (1 cm^3) was heated at 103 °C for 2 h in the presence of 10% of 1,1′-azodicyclohexanecarbonitrile (0.002 g). Analysis by ^1H NMR and GC-MS showed: *peak* t_R *12.89*, *trans*-(2-isocyanatocyclopropyl)-benzene (**21**); *peak* t_R *15.50*, *cis*-**16** and, *peak* t_R *15.65*, *trans*-**13** (*cis* : *trans* ratio: 1 : 5). Traces of several unidentified components were also observed.

Methyl 3-(2-bromophenyl)-2-oxiranecarboxylate 25[14,15]

Method 1. A solution of methyl *cis*-2-(2-bromophenyl)-propenoate (2.5 g, 10.4 mmol) in dichloromethane was treated with *m*-CPBA (2.15 g, 12.5 mmol) and refluxed for 48 h. The reaction mixture was cooled with ice, filtered, and the filtrate was extracted with saturated $NaHSO_3$, aq $NaHCO_3$ and brine. The resulting

organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The product was purified by column chromatography to afford **25** (24%).

Method 2[14]**.** 2-Bromobenzaldehyde (9.25 g, 50 mmol) and methyl chloroacetate (6.6 cm^3, 75 mmol) were added dropwise at the same time to Na (1.8 g, 78.5 mmol) in dry methanol (75 cm^3). The solution was stirred for 1 h at −10 °C, then for 16 h at rt. HCl (60 cm^3 of 0.3 M) was added and the solution was extracted with dichloromethane. The organic phases were then dried over magnesium sulfate and the solvent evaporated under reduced pressure. The product was purified by fractional distillation (bp 112–120 °C) to afford epoxide **25** as a clear oil which crystallised on standing (10.5 g, 82%); δ_H 3.29 (1H, s, CH), 3.76 (3H, s, CH_3), 4.27 (1H, s, CH), 7.08–7.24 (3H, m, ArH), 7.41–7.43 (1H, m, ArH); *m*/*z* (%) 257/249 (M^+ 43), 225 (20), 199 (100), 169 (29), 89 (9). (Found: C, 46.26; H, 3.59. $C_{10}H_9BrO_3$ requires: C, 46.72; H, 3.53%).

(2-Bromophenyl)-2-oxirane carboxylic acid[14]

Methyl-3-(2-bromophenyl)-2-oxiranecarboxylate (2.1 g, 8.2 mmol) was dissolved in ethanol (20 cm^3), and 2 M aqueous potassium hydroxide (15 cm^3) was added. The solution was stirred at room temperature for 2 h. The methanol was evaporated, and the remaining solution was diluted with water (15 cm^3), washed with ether (20 cm^3), acidified with 5 M aqueous hydrochloric acid, and extracted with ether (3 × 30 cm^3). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford pure (2-bromophenyl)-2-oxirane carboxylic acid (1.96 g, 98%), mp 108 °C; δ_H 3.42 (1H, s, CH), 4.45 (1H, s, CH), 5.45 (1H, br, OH), 7.21–7.41 (3H, m, ArH), 7.56–7.65 (1H, m, ArH); δ_C 55.9, 58.5, 123.1, 126.7, 128.2, 130.6, 132.9, 134.7, 173.1; *m*/*z* (%) 243/245(M^+, 76), 227 (31), 199 (100), 185 (140), 168 (28), 119 (7), 57 (20). (Found: C, 44.48; H, 2.68. $C_9H_7BrO_3$ requires: C, 44.47; H, 2.90%).

trans-2-(2-Bromophenyl)-3-isocyanatooxirane 26

A mixture of (2-bromophenyl)-2-oxirane carboxylic acid (1.0 g, 4.0 mmol), triethylamine (0.5 g, 5.0 mmol), and ethyl chloroformate (0.6 g, 5.5 mmol) in dry acetone (30 cm^3) was stirred at −10 °C. A solution of sodium azide (0.45 g, 6.9 mmol) in H_2O (2 cm^3) was added after 2.5 h. The stirring was discontinued after an additional 30 min. The resulting suspension was poured into cold H_2O (12 cm^3) and was extracted with toluene. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to about 50% of the volume to remove remaining traces of H_2O. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased, and the solution was concentrated to give **26** as a clear oil (83%); δ_H 3.08 (1H, s, CH), 4.46 (1H, s, CH), 6.60–6.83 (1H, m, ArH), 7.01–7.29 (2H, m, ArH), 7.71–7.77 (1H, m, ArH); ν_{NCO} 2260 cm^{-1}; *m*/*z* (%) 239/241 (M^+ 100), 195/197 (3), 183/185 (60), 153/155 (18), 132 (15), 115 (20), 89 (25), 75 (20), 50 (15).

Reaction of 26 with tributyltin hydride

Oxirane **26** (50 mg, 0.21 mmol) and tributyltin hydride (60 mg, 0.21 mmol) in solution in C_6D_6 (0.5 cm^3) were photolysed at 40 °C for 3 h. The GC-MS showed no trace of the cyclised product. Only the product of reduction was identified. Several traces of unidentified components were observed. GC-MS, *peak 373*, 3-phenyloxiranylamine, *m*/*z* (%) 135 (M^+ 100), 118 (17), 107 (68), 91 (67), 79 (49), 65 (16), 51 (14).

Reaction of 26 with TTMSS

Oxirane **26** (40 mg, 0.17 mmol) and TTMSS (50 mg, 0.20 mmol) in solution in C_6D_6 (1 cm^3) were heated for 2 h at 103 °C in the presence of 1,1′-azodicyclohexanecarbonitrile (0.004 g). The same procedure was repeated at 83 °C for 7 h. The results were essentially identical. The ^{1}H NMR spectrum showed mainly the unreacted starting materials. GC-MS: *peak* t_R *18.4*: *m*/*z* (%) 161 (M^+ 100), 144 (3), 117 (15), 105 (70), 91 (4), 77 (36), 51 (13) [$C_9H_7NO_2$, probably 5*H*-6-oxa-8-azabenzocyclohepten-9-one, **29**], together with residual **26** and several minor unidentified components.

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