Efficient preparation of $TMSCCl_2Br$ and its use in dichlorocyclopropanation of electron deficient alkenes

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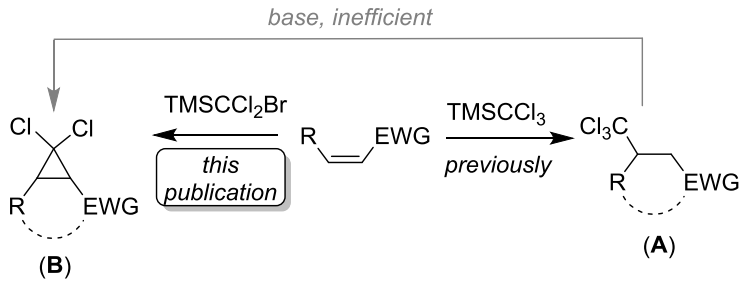
Abstract: The r*eaction of excess TMSCl and $LiCCl_2Br$ at low temperature is a technically simple high yield route to $TMSCCl_2Br$. The latter is a stable source of the dichlorobromomethide carbanion, which undergoes 1,4-addition with cyclic nitroalkenes and (E)-fumarates leading to dichlorocyclopropanes after bromide explusion. For nitrostyrenes the reaction arrests at the 1,4-addition product. Low temperature NMR studies and DFT calculations suggest the formation of an 'ate' species $[(nitronate)SiFMe_3]^-$ which, upon boil off of TMSF at 10 - 20 °C, yields the cyclopropane. DFT calculations also support the experimental differences between fluoride and acetate as promotors.*

Introduction

Dihalocyclopropane motifs are attractive targets frequently associated with biological activity, especially in insects.[1] Additionally, they are potent starting points in their own right for ring modification and expansion chemistry.[2] While electron-rich alkenes react readily with a wide variety of electrophilic $:CCl_2$ sources [e.g. from diazocompounds[3] or via CHX_3 (X = Cl, Br) deprotonations[4]] providing the cyclopropanes directly. Electron deficient alkenes are insufficiently nucleophilic[5] for such strategies. While some difluorocyclopropanes have been attained from electron-poor alkenes, high temperature reactions of $TMSCF_3$ or related analogues[6] were necessary. For the dichloro- and dibromocyclopropanes typically the only generic viable methodology employs stoichiometric quantities of the highly toxic Seyferth reagents $PhHgCX_3$ (X = Cl, Br).[7] Clearly, the latter are also undesirable on environmental grounds. In seeking for a user-friendly approach to dichlorocyclopropanation we had settled on use of $TMSCCl_3$ and recently could demonstrate both its high yield synthesis and its use in the conjugate addition of trichloromethyl units (**A** Scheme 1).[8] However, under the published conditions[8a,c] base-induced closure of **A** to the dichlorocyclopropanes **B** could lead to poor yields or the formation of alternative (elimination) by-products.

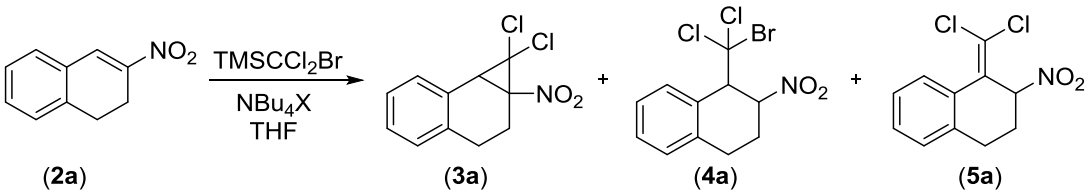


Scheme 1. Approaches to dichlorocyclopropanes based on $TMSCCl_2X$ reagents (X = Cl, Br).

Results and Discussion

A potential route to overcoming the difficulties outlined above would involve the use of $TMSCCl_2Br$[9] (**1**). The greater leaving group ability of bromide (vs. chloride) is expected to facilitate direct closure to the cyclopropane. Existing literature routes to $TMSCCl_2Br$ **1** involving bromination of $TMSCCl_2Li$ with Br_2[9a] are undesirable for preparation of large quantities of reagent. By switching from chloroform to $HCCl_2Br$ we could adapt our previous[8] $TMSCCl_3$ synthesis allowing $TMSCCl_2Br$ **1** to be synthesised in excellent yield (87%) in a simple one-pot reaction from low cost commercially available materials. With $TMSCCl_2Br$ **1** now accessible cleanly and in large quantities, its reactivity and potential as a cyclopropanation reagent was explored. Cyclic nitroolefin (**2a**) was picked as the model alkene for the reaction, as nitroolefins have been reported as potent Michael acceptors for $TMSCCl_3$.[8a,c] Table 1 outlines the effects of different promotors on its cyclopropanation reaction with $TMSCCl_2Br$ **1**. Initial trials were carried out at room temperature and catalytic TBAF (5 mol-%), however, no conversion of **2a** was observed (Table 1, entry 1). When a stoichiometric quantity of TBAF was used poor conversion to mixtures of **3a-5a** also resulted (Table 1, entry 2). It is worth noting that the use of TBAF at room temperature was also accompanied by the formation of a significant quantity of decomposition product which arises from rapid fluoride-promoted activation of $TMSCCl_2Br$ **1**. We believe this is due to the formation of $(CCl_2)_n$ oligomeric species, but the lack of a convenient spectroscopic or other handles has made their characterisation untenable thus far. This behaviour prevents practical use of the high temperature conditions developed by Hu[6] with **1**. Dosing room temperature reactions with extra **1** slightly improves the conversion of **2a**. The milder fluoride source TBAT ($NBu_4[Ph_3SiF_2]$) provided good selectivity in favour of **3a** (Table 1, entry 3); however, removal of Ph_3SiF by-product from **3a** proved difficult so subsequently TBAT was avoided. Using less silylophilic promotors (Cl^- and Br^-, 1.1 equiv.) limited excessive decomposition of the silane reagent **1** (Table 1, entries 4-5); however, with bromide little or no conversion of **2a** was attained and chloride resulted in poor chemoselectivity favouring **5a**. The acetate NBu_4OAc (1.1 equiv.) was found to be an efficient and mild promoter, with no rapid decomposition of **1** observed. In this case starting material **2a** was consumed rapidly (<2 min) at room temperature; however, a mixture of products **3a-5a** was isolated again, with the 1,4-addition product **4a** as the major component (Table 1, entry 6). Using fluoride promoters at lower temperatures avoided the decomposition of **1** and favoured the formation of cyclopropane **3a** (Table 1, entries 7-9). Optimal conditions were found to be dropwise addition of TBAF (1.1 equiv.) at -78 °C with complete consumption of **2a** in <15 min followed by conversion to **3a** exclusively after warming to room temperature (Table 1, entry 9). The analogous reaction with $TMSCCl_3$ led to no cyclopropane formation and only the 1,4-addition product was observed. Interestingly, repeating the optimum conditions with a slow addition of NBu_4OAc at -78 °C favoured the elimination product **5a** and only 11% **3a** was observed (Table 1, entry 10). Cyclopropane formation is favoured in more polar solvents (such as DMF, MeCN, THF), less polar solvents (e.g. toluene, Et_2O) lead to more observed elimination (**5a**) and 1,4-addition (**4a**) products being observed.[10] It is likely that in less polar solvents intermolecular aggregation is favoured leading to more observed **4a** and **5a** (see computational studies later). All cyclopropanes were assigned of the basis of their highly characteristic ^1H NMR spectra: compounds **3a**, **3d** – **3g** give singlets at 3.8 – 4.0 ppm, compounds **3b** – **3c** give double doublets at 2.7 – 3.0, and compounds **3h** – **3j**[11] give singlets at 3.0 – 3.2. Further support for cyclopropane formation arises from the characteristic quaternary CCl_2 at 71 – 79 ppm exhibited by all dihalocyclopropanes in their ^{13}C NMR spectra. Additionally, quaternary C-NO_2 peaks at 62 – 65 ppm are seen for cyclopropanes from nitroalkenes. The presence of the NO_2 groups is also supported by characteristic IR stretches between 1550-1475 and 1360-1290 cm^{-1}. Parent ions were observed in the mass spectra of most of our cyclopropanes but fragile compound **3c** had to be characterised on the first daughter peaks observed. The possibility of alternative connectivity, e.g. 2,3-dichloroprop-1-enes, could be discounted on the basis of our previous work.[8b]

Table 1. Effects of different promoters on the dichlorocyclopropanation reaction.[a]



(**2a**) (**3a**) (**4a**) (**5a**)

Run	NBu_4X (X =)[b]	Loading (equiv.)	Conc. (M)	Temp (°C)	Time (h)	**2a:3a:4a:5a** (%)[c]
1	F	0.05	0.2	RT	16	0:0:0:0
2	F	1.1	0.2	RT	16	92:5:0:3
3	Ph_3SiF_2	1.1	0.2	RT	16	0:80:20:0
4	Br	1.1	0.2	RT	16	0:0:0:0
5	Cl	1.1	0.2	50	16	16:29:12:43
6	OAc	1.1	0.2	RT	<1	0:28:50:22
7	F	1.1	0.1	-40	<1	0:76:0:24
8	F	1.1	0.1	-50	<1	0:89:0:11
9[d]	F	1.1	0.1	-78	<1	0:100:0:0
10	OAc	1.1	0.1	-78	<1	0:11:38:51

[a] Runs 1-6 carried out on: **2a** (0.143 mmol), **1** (1.5 equiv., 0.215 mmol) in THF (0.72 mL, 0.2 M). Runs 7-10 carried out on: **2a** (0.143 mmol), **1** (2 equiv., 0.286 mmol) in THF (1.43 mL, 0.1 M). [b] The TBAF used was a 1 M solution in THF. [c] Yields were determined using ^{1}H NMR spectroscopy. [d] When repeated on 1 mmol scale, 2.2 equiv. TBAF and 2.5 equiv. of $TMSCCl_2Br$ **1** were used to achieve complete conversion to **3a**.

The difference in reactivity between the promoters in Table 1 prompted a mechanistic investigation of the transformation. Multi-nuclear NMR studies of a mixture of $TMSCCl_2Br$ **1** and **2a** (2.5:1) in d_8-toluene were carried out. Toluene was chosen as the NMR solvent as it allows observation of all 3 major reaction products. After **1** was treated with TBAF (2.2 equiv.) at -70 °C, ^{1}H and ^{13}C NMR spectra were recorded as the mixture was raised in 10 °C steps to 20 °C. Initial 1,4-addition began at -70 °C leading to complete consumption of **2a** by -50 °C (30 min). The new species observed (Figure 1) was assigned to the free nitronate anion (**6**) on the basis of its similarity to the previously characterised CCl_3-analogue.[8a] Nitronate **6** was stable to 10 °C (See Supporting Information). However, when the reaction was warmed from 10 to 20 °C, apparent free nitronate **6** was completely consumed and peaks due to the cyclopropane (**3a**), proton quench (**4a**) and elimination product (**5a**) were detected. In fluoride promoted reactions the chemoselectivity to the cyclopropane was always higher than reactions promoted by NBu_4OAc, where the conjugate addition (**4a**) and elimination (**5a**) products were formed in approximately equimolar amounts (Figure 1).

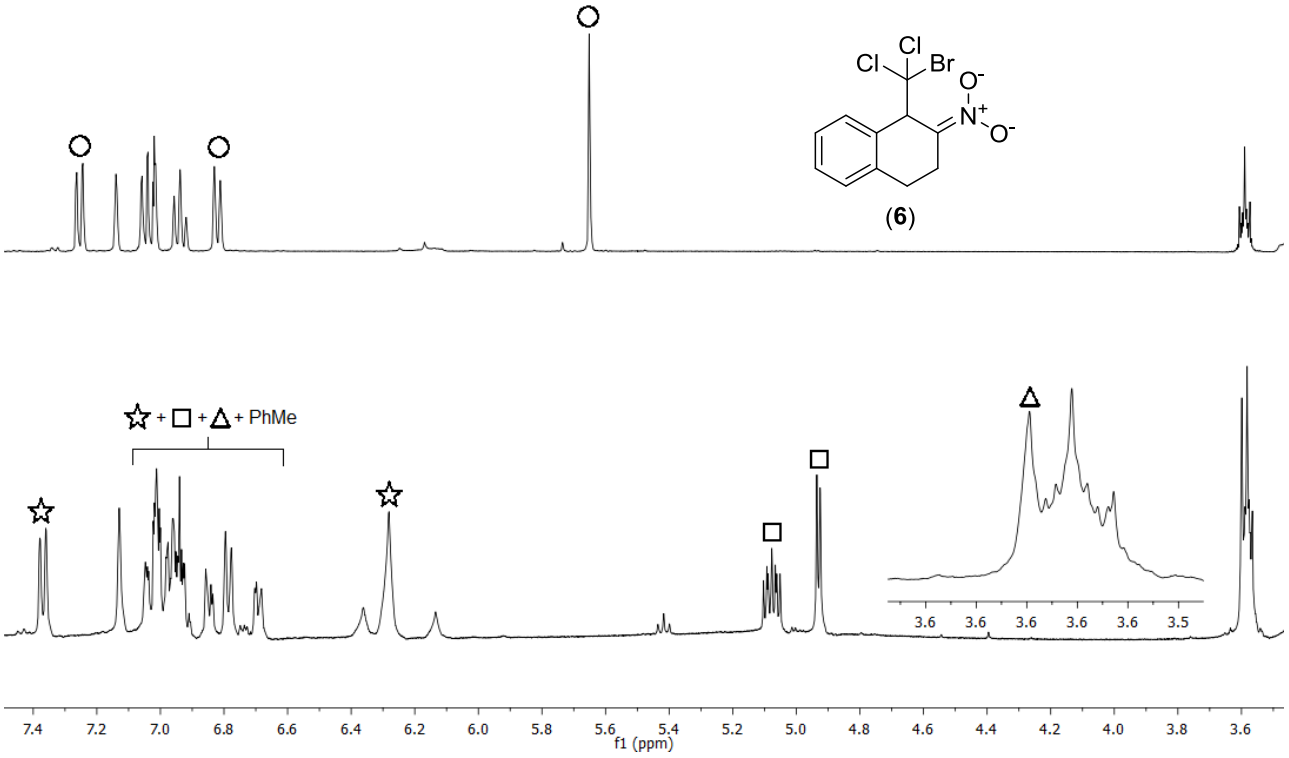


Figure 1. Representative variable temperature partial ^{1}H NMR spectra of the reaction mixture showing the free nitronate **6** *in situ* at 10 °C (top, ○ = **6**). The unlabelled peaks are due to toluene and THF. Decomposition products of **6** at 20 °C are also shown (bottom: cyclopropane △ = **3a**, 1,4-addition □ = **4a**, elimination ☆ = **5a**), these are formed between 10-20 °C.

To support these results DFT computational studies were carried out on the cyclopropane formation (e.g. modelling Table 1, run 9) from TBAF (Chart 1). [All calculations were carried out at the B3LYP/6-31+G(d,p)[12] level of theory using the polarizable continuum model with THF as the solvent, as higher levels of theory proved computationally very time demanding]. In these complex systems we simplified the amine salt to NMe_4F, again to improve computational throughput. The conjugate addition of **1** to **2a** was calculated to proceed over a barrier of 28.4 kcal mol^{-1} via transition state **I** (Chart 1 and Figure 2a). This subsequently forms intermediate **6**, which is 23.5 kcal mol^{-1} lower in energy than the starting structure. From **6**, ring-closure via transition state **II** (Figure 2b) to **3a** is hindered due to induced 3-ring strain and a barrier of 22.3 kcal mol^{-1} was calculated, potentially allowing other reaction pathways to compete.

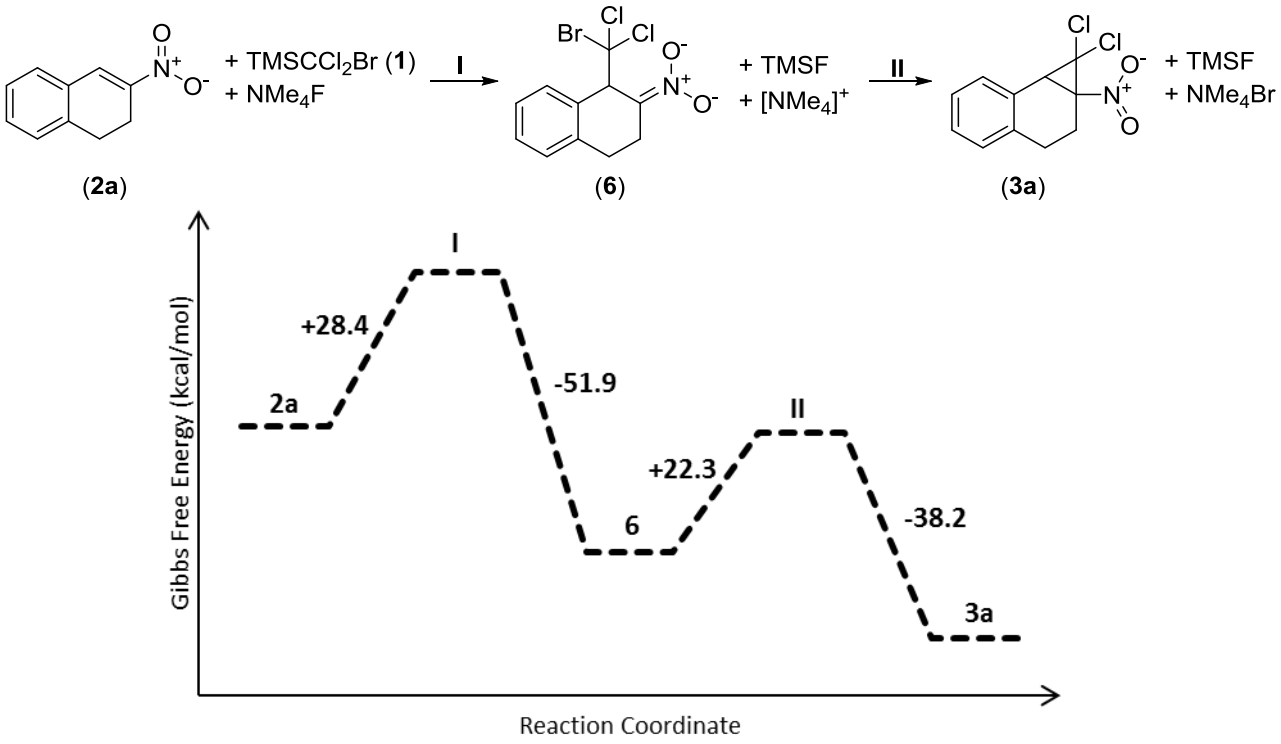


Chart 1. Reaction Pathway of Conjugate addition of $TMSCCl_2Br$ to **2a** and closure of intermediate **6** to **3a**.

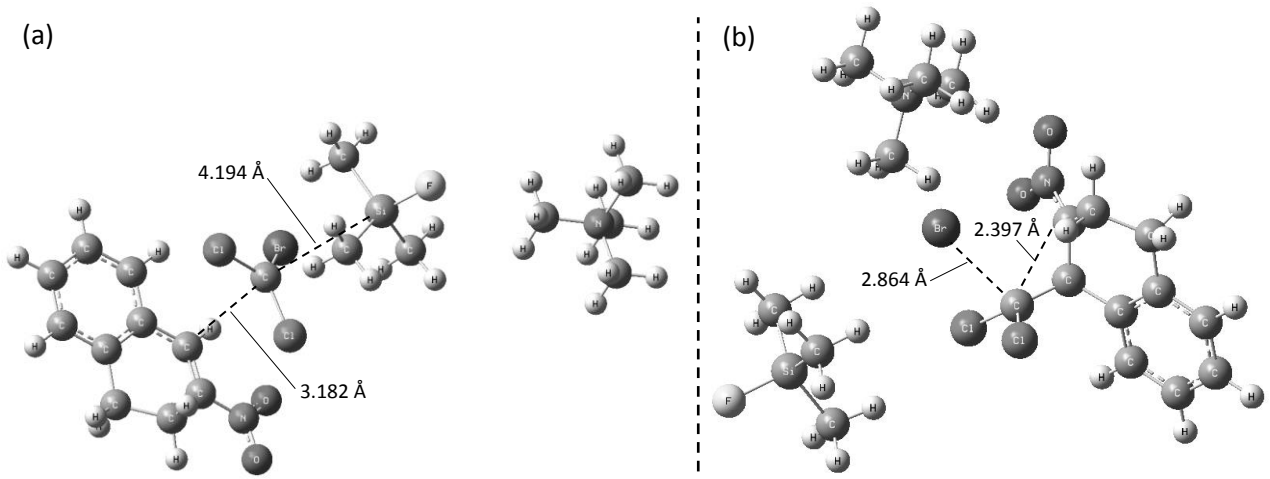


Figure 2. (a) Transition state **I** with highlighted distances; (b) transition state **II** with highlighted distances.

We propose that alkene **5a** is formed by rearrangement of **6** to spectroscopically undetected **7** (Scheme 2). However, computationally at least [with B3LYP/6-31+G(d,p)], unimolecular formation of **7** from **6** was not viable. Using **6'** as a simple model for a second equivalent of nitronate **6** (Chart 2) we were able to obtain a sensible transition state (**III**, Figure 3) that supports viable intermolecular proton transfer between two molecules of nitronate **6**. The validity of this proposal is further supported by the observations from the low temperature NMR experiments described previously (Figure 1): the formation of **5a** is observed with concomitant formation of an equimolar quantity of **4a** without the introduction of an external proton source. The NMR experiment was carried out in toluene-d_8 so increased aggregation compared to THF is expected, favouring bimolecular elimination over cyclopropane formation. In THF we cannot completely

rule out deprotonation by bases other than **6** as in some cases **5a** is observed experimentally in the absence of **4a**.

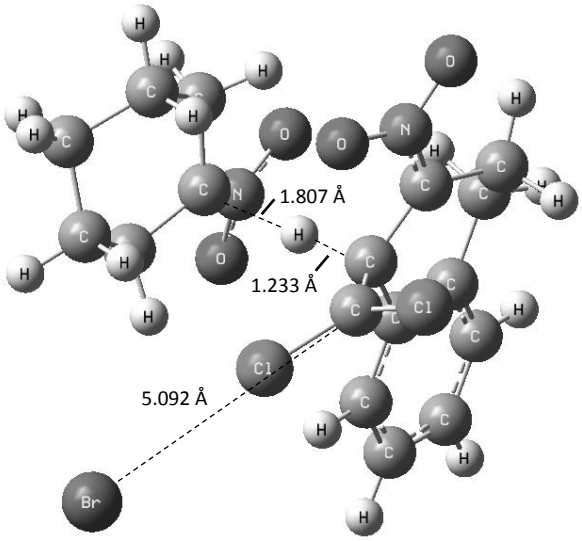
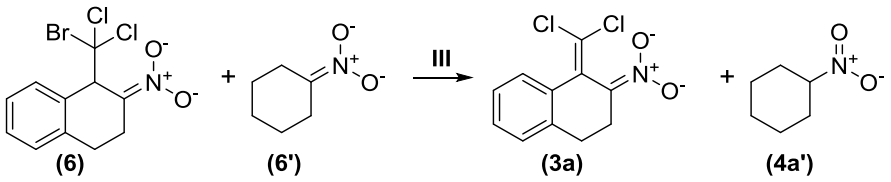


Figure 3. Calculated transition state (**III**) in the formation of **5a**, with the distance between the forming and breaking C-H bond and the breaking C-Br bond highlighted.

If we directly compare the cyclopropane formation (Chart 1) and elimination (Chart 2) pathways, we can see that the ΔE_{act}(calc) for formation of **3a** from **6** (via transition state **II**) is 16.7 kcal mol^{-1} lower than the ΔE_{act}(calc) for the formation of **5a** from **6** (via transition state **III**).



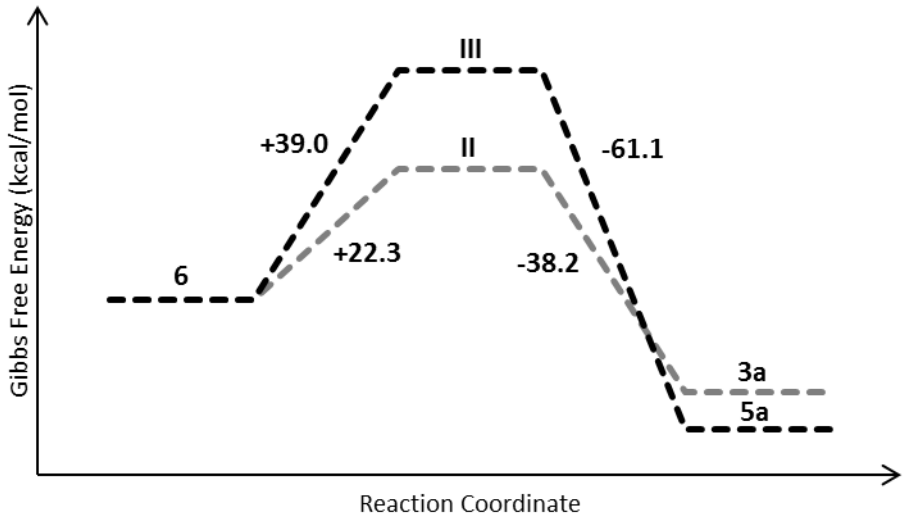
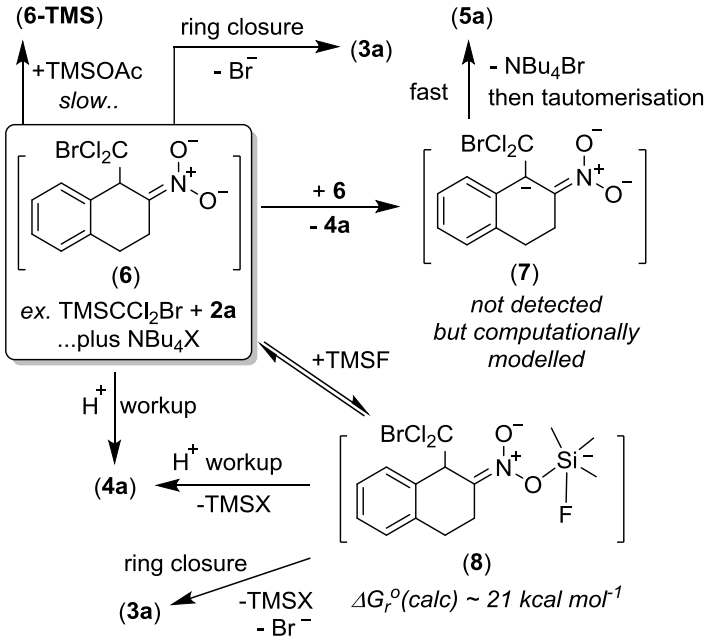


Chart 2. The reaction pathway from intermediate **6** to **5a** versus **6** to **3a**.

The improved chemoselectivity observed for use of TBAF over NBu_4OAc in THF deserves separate mechanistic comment. The by-products from the formation of free **6** in these two cases are TMSF and

TMSOAc respectively; the latter poorly intercepts **6** leading to significant formation of **4a**/**5a** via the routes already discussed (Scheme 2). The TMSF case is more interesting: the strength of the Si-F bond (135 kcal mol^{-1}) precludes formation of a neutral TMS-nitronate ether from **6** + TMSF. The formation of the hypervalent 'ate' species **8** from **6** and TMSF (Scheme 2) appears much more viable ($\Delta G_r°$(calc) = 21.2 kcal mol^{-1}, see Supporting Information). It is likely that **8** acts as a stable reservoir of **6** that is released slowly at ~20 °C due to loss of TMSF (b.p. 16 °C) favouring annulation. Variable temperature ^{19}F and ^{29}Si NMR spectra of the reaction mixture at low temperature (-30 °C to 20 °C) provide some evidence to support this idea. The signals for TMSF in the reaction mixture display a shift that could be interpreted as supporting rapid equilibration with unseen **8**. At 20 °C the TMSF signals become very attenuated supporting 'boil off' of TMSF. In the absence of TMSF, the reactive nitronate **6** is consumed non-selectively via **7**.



Scheme 2. Proposed behaviour for the kinetic nitronate (**6**), derived from the reaction of **2a** with **1** and NBu_4X (X = OAc, F) sources.

Given the proposals of Scheme 2 we sought a computational comparison of the energy barriers of the cyclopropanation that results from the free nitronate (**6b**) versus the TMS-nitronate ether (**6b-TMS**) proposed in the presence of NBu_4OAc (Chart 3). These simple models showed us ΔE_{act}(calc) = 25.5 kcal mol^{-1} for formation of the cyclopropane from the free nitronate and $\Delta G_r°$(calc) = -15.8 kcal mol^{-1} (Chart 3). The ΔE_{act}(calc) for the TMS-nitronate closure was significantly higher at 40.1 kcal mol^{-1} (Chart 3); however, the cyclopropane product from this system is 58.7 kcal mol^{-1} lower in energy than transition state **V** resulting in a similar Gibbs Free Energy of reaction ($\Delta G_r°$(calc) = -18.6 kcal mol^{-1}). The higher energy barrier for cyclopropane closure from the TMS-nitronate indicates that for this system, elimination is likely to be highly competitive with cyclopropane formation. This is backed up by our experimental observations, which show that the NBu_4OAc system [from which our proposed TMS-nitronate (**6-TMS**) may arise] suffers from poor chemoselectivity.

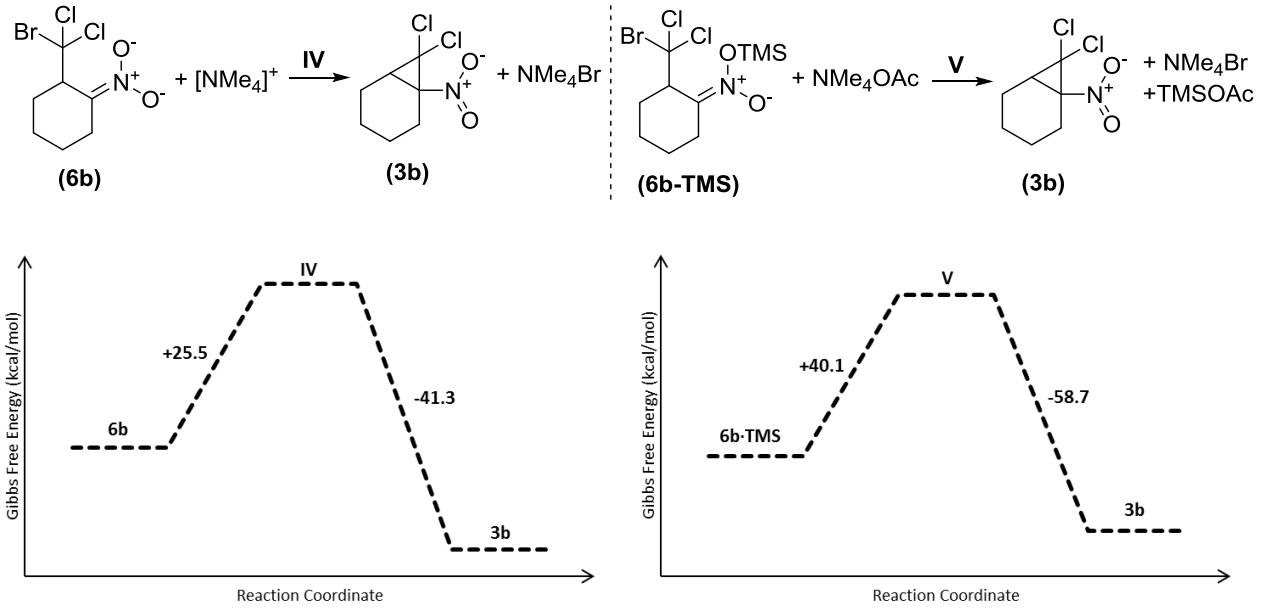


Chart 3. Comparison of cyclopropanation pathways from free nitronate model and TMS-nitronate ether.

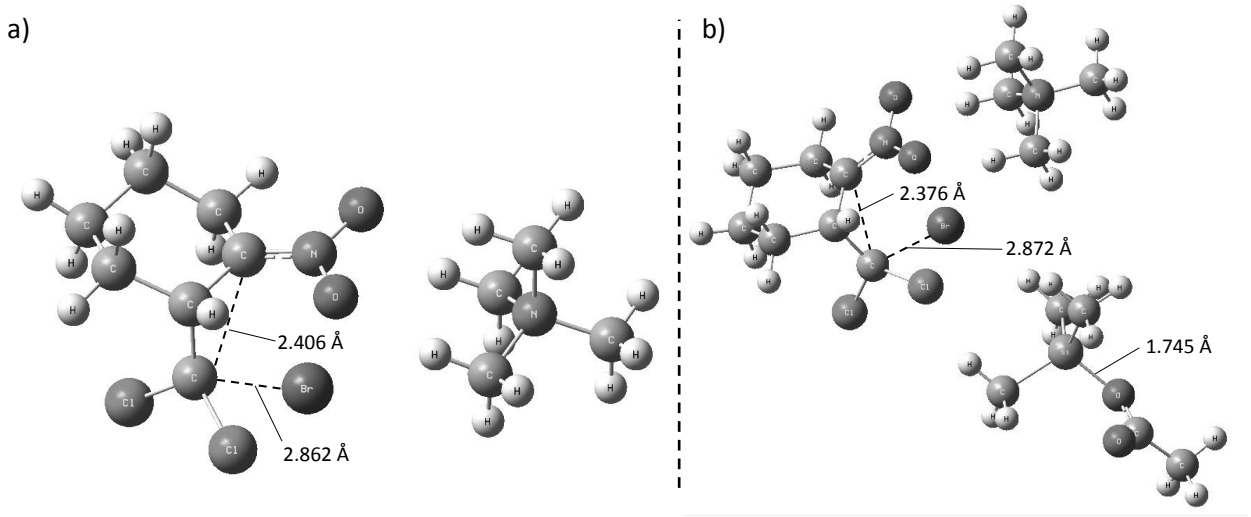
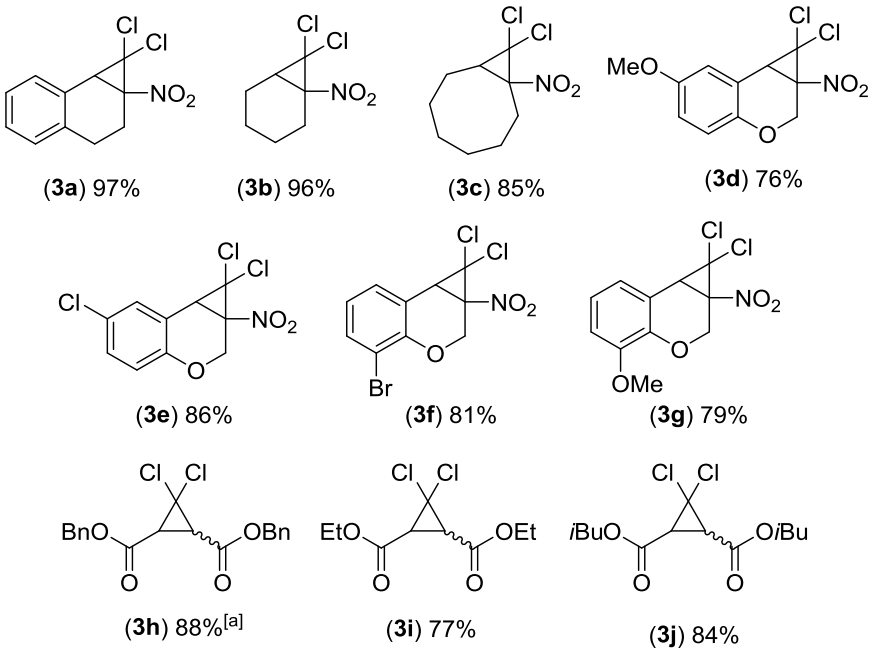


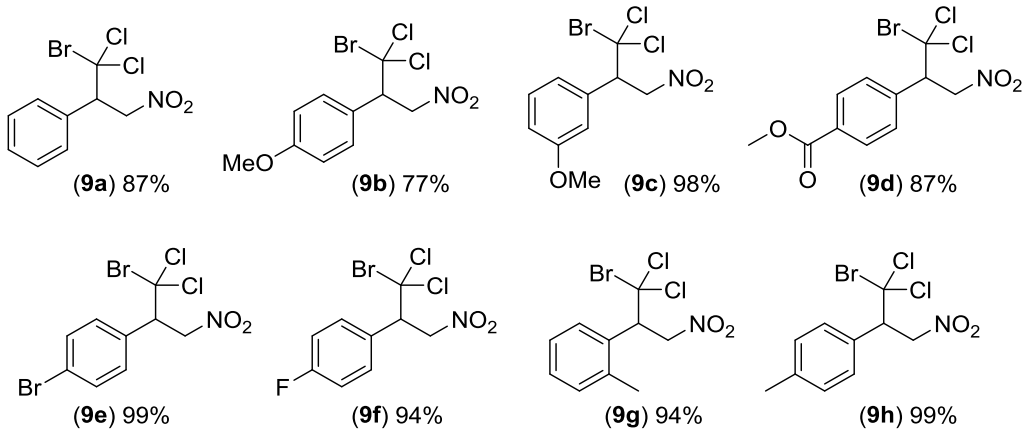
Figure 4. (a) Transition State **IV** showing select distances; (b) transition state **V** showing selected distances.

By applications of the conditions of Table 1, or slight modifications thereof, a range of dichlorocyclopropanes could be isolated (Scheme 3). Fumarates also participated in the reaction yielding the desired cyclopropanes (in this case NBu_4Cl at 50 °C gave cyclopropane exclusively, whereas TBAF at -78 °C gave 1:1 cyclopropane:elimination). Other common Michael acceptors (e.g. enals, chalcones, alkylidene malonates, cyclic enones and acyclic enones) screened favoured 1,2-addition over the thermodynamic 1,4-addition and were not pursued further.[8c] All of the cyclic nitroalkenes we tried formed the corresponding cyclopropanes, however, substrates containing halogens (**3e**-**3f**) were found to require the addition to 20 mol-% TEMPO to provide acceptable yields. This behaviour is attributed to aerobic triggered competing radical reactions, which we have noted before.[8a, 13] Control reactions (absence of anionic promotors and use of other radical traps) indicated that the TEMPO does act as an inhibitor in this case.[14]



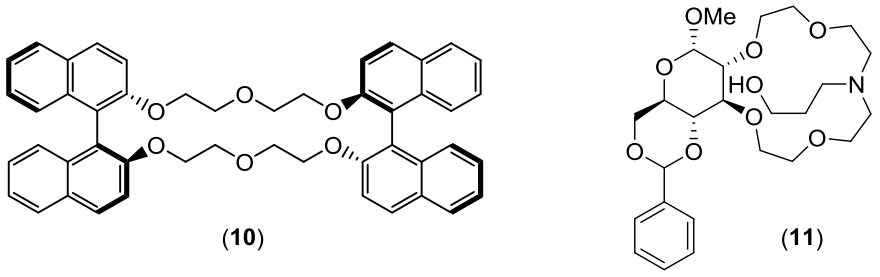
Scheme 3. Dichlorocyclopropanes resulting from the 1,4-addition of $TMSCCl_2Br$. **3a-3h**: Optimal Conditions: Substrate in THF (0.1 M) with$TMSCCl_2Br$ **1** (2.5 equiv.), then addition of TBAF (1 M in THF, 2.2 equiv.) at -78 °C. Monitored by tlc. **3i-3j**: Optimal Conditions: Substrate in THF (0.1 M) with $TMSCCl_2Br$ **1** (1 equiv.) NBu_4Cl added and heated to 50 °C, after 1 h a second portion of **1** was added (1 equiv.) and monitored by tlc until complete. Footnote [a]: **3h** was isolated as an inseparable mixture of cyclopropane: elimination product (1:1).

Acyclic nitroalkenes were also subjected to the conditions of Scheme 3 but favoured the 1,4-addition product exclusively (**9a-h**, Scheme 4). We assume that the 1,4-addition produces a suitable nitronate intermediate, however, this fails to shut to desired cyclopropane due to lack of reactivity and/or induced ring strain. Treatment of the reaction mixtures with halophilic Ag^+, Fe^{3+} or Al^{3+} salts did not aid in the ring closure. Heating the intermediate to 50 °C did lead to consumption of the intermediate nitronate but only undefined polymeric materials were obtained. Clearly cyclisation is not favoured. We note that in his seminal paper Cunico[8d] attained related products and, in only one case (with a nitrostyrene predisposed to close due to the presence of a Thorpe-Ingold effect inducing CR_2 unit) were traces of a cyclopropane observed. We believe similar issues operate in our own system. The motifs **9a-h** are also accessible using our previously reported anionic promotor pool methodology where using 5 mol-% NBu_4OAc typically furnishes the 1,4-addition products in <30 min at room temperature.[8a,c] When NBu_4OAc was used at 5 mol-% with cyclic nitroalkene **2a**, in an attempt to obtain the 1,4-addition product **4a** exclusively, only traces of cyclopropane product **3a** (<10%) were detected by ^1H NMR spectroscopy along with significant degradation.



Scheme 4. 1,4-addition of $TMSCCl_2Br$ to acyclic nitroalkenes. Optimal Conditions: Substrate in THF (0.1 M) with $TMSCCl_2Br$ **1** (1.1 equiv.), then NBu_4OAc (5 mol-%) added at room temp., monitored by tlc.

In the search for a selective catalytic process we found that metal-based salts (i.e. MF, MOAc where M = Na, K, Cs) had potential as stoichiometric promoters for the reactions of Schemes 1-4 as in the absence of suitable catalysts only minimal substrate conversion rates result. Extensive screening of a very wide range of diverse promoters (library of >200 entities) revealed that dibenzo-18-crown-6 (DB18-C-6) resulted in significant ligand accelerated catalysis[15] when in combination with an excess of MF or MOAc. For example, while **2a** is converted to a mixture of **3-5a** by KOAc over 36 h this reaction is complete within 20 minutes in the presence of 5 mol-% DB18-C-6. In these catalytic systems the chemoselectivity to the cyclopropane **3a** was favoured by use of fluoride. However, this also promotes degradation of the $TMSCCl_2Br$ **1** reagent. Potassium acetate was the most active stoichiometric promoter in the presence of catalytic DB18-C-6 (10 mol-%) but these reactions showed poorer chemoselectivity to the cyclopropane (**3a**:**4a**:**5a** ≈ 3:4:18) for the reasons indicated in Scheme 2. Significant attempts were made to extend the catalytic promotion seen for DB18-C-6 to chiral analogues but in all cases (crowns **10**[16]-**11**[17] are representative) negligible enantioselectivity and at best only modest catalysis were observed.



Due to the lack of stereoselectivity in these reactions we sought information on the putative transition states via B3LYP-DFT calculation. To the best of our knowledge no prior attempts have been made to understand the transition state associated with any 1,4-addition of any $TMSCX_3$ species to a Michael acceptor. This step is critical as it defines which stereo face of the acceptor is attacked by a potential asymmetric catalyst. As a simple model we studied the reaction of **2a**, $TMSCCl_2Br$ and NMe_4F *in silico* at the [B3LYP/6-31+G(d,p)] level of theory (Supporting Information). Regardless of where we initialled the reaction coordinate search from, we found that the 1,4-addition step transition state has quite specific requirements with the nitroalkene **2a**, reagent, fluoride and quaternary amine all being co-linear (Figure 5). Based on this simple picture it is clear why attaining efficient chirality transfer is challenging – the triggering promoter (F in NBu_4F) is >9 Å away from the forming stereocenter and the supporting (potentially chiral)

catalytic cation even further away, and with high conformational freedom. While our model uses a simple quaternary amine $[NMe_4]^+$ and a simple promoter (F^-) it is likely that this transition state applies to all the runs with chiral quaternary amines and chiral crown ether complexes, providing some explanation as to why asymmetric induction is so challenging.

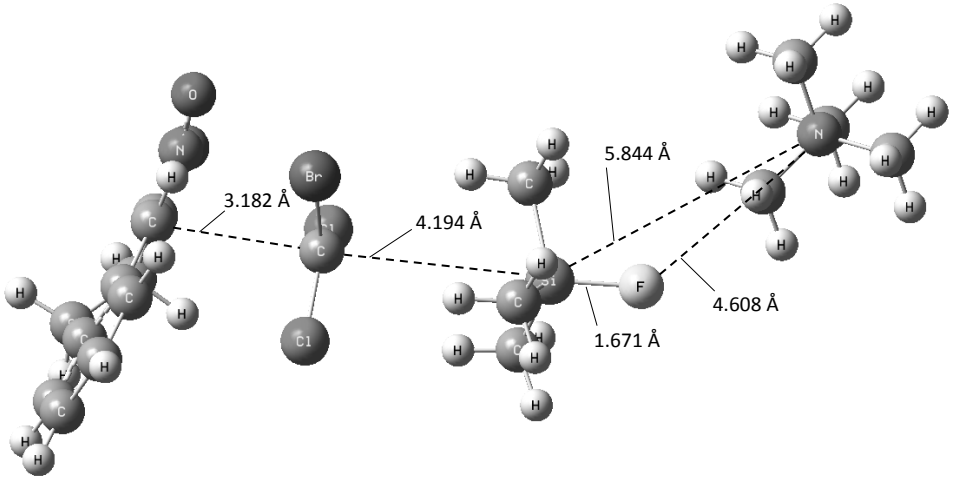


Figure 5. Transition state for the 1,4-addition of $TMSCCl_2Br$ **1** to **2a** in THF, showing the large distance between the substrate, quaternary amine and promoter [B3LYP/6-31+G(d,p)].

Conclusion

By a mixture of synthetic, NMR and basic computational experiments the underlying features of the catalytic cyclopropanation of nitroalkenes have been built up. The kinetic product of the reaction of such alkenes with $TMSCCl_2Br$ is the nitronate **6** which can either close to the cyclopropane, disproportionate to the 1,4-addition and elimination products, or suffer other related events. Conditions controlling the behaviour of **6** were identified by the mechanistic studies and an efficient synthesis of dichlorocyclopropanes from electron deficient alkenes demonstrated. Conditions for the use of largely inert promotors that are activated in the presence of crown ethers have been identified. The reasons for the extreme difficulty in attaining asymmetric dichlorocyclopropanation of electron deficient alkenes have also been identified. It is clear from this study that in order to obtain an efficient enantioselective process the reagent that delivers the haloform anion must be redesigned, allowing two point coordination of both the substrate and the cyclopropanation reagent. Given that and appropriate face-blocking strategies, asymmetric catalysis should be possible given that ligand accelerated catalysis has already been attained.

Experimental

A representative example is given, see supporting information for full details.

To a flame dried Schlenk tube under argon was added the cyclic nitroalkene (50 mg, 0.285 mmol), $TMSCCl_2Br$ (169 mg, 0.714 mmol) and THF (3 mL) [N.B. TEMPO 20 mol-% was added to reactions containing aromatic halogens]. The reaction vessel was cooled to -78 °C in an acetone/dry ice bath and allowed to equilibrate for 15 min. TBAF (0.63 mL, 1 M in THF) was added dropwise to the reaction mixture. The mixture was stirred for 10 min and monitored by TLC. Upon consumption of the starting material the reaction vessel was removed from the cold bath and allowed to warm to room temperature (ca. 20 min). Upon warming, the reaction was examined by TLC and consumption of the intermediate nitronate was monitored. Once the reaction is complete it is quenched immediately with 1 M HCl (2 mL) and extracted with EtOAc (10 mL). After further washing with water (10 mL) the organic fraction was dried over $MgSO_4$,

filtered and the solvent evaporated. The cyclopropanes were isolated by flash chromatography through a small silica plug using 95:5 pentane:EtOAc. Prolonged exposure to silica gel proved detrimental to overall yield and sample quality.

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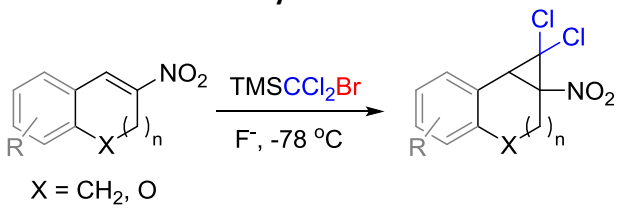
Table of Contents Entry



The efficient synthesis of $TMSCCl_2Br$ provides easy access to an alternative dichlorocyclopropanation reagent. Cyclopropanes from electron deficient alkenes have been synthesised and the mechanism has been probed with NMR and DFT calculations.

Keywords: Dichlorocyclopropane • Michael Addition • Cyclopropanation • Conjugate Addition • Cyclopropane