Highly strained tertiary sp³ scaffolds: Synthesis of functionalized cubanes and exploration of their reactivity under Pd(II) catalysis

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Supporting Information Placeholder

ABSTRACT: A series of chemically distinct, highly strained, activated cubane scaffolds was synthesized through optimization of the metal-halogen exchange reactions of iodinated cubane derivatives. This included the first reported successful attachment of both boron and phosphorous; key elements in potential transition metal-catalyzed cross coupling reactions; on the cubane scaffold. Additionally, Zn, Sn, Si, S and various C-based systems were also attached in a high-yielding, one-pot reaction from readily available precursors. A comprehensive program investigating the reactivity of these tertiary cubane nucleophiles towards Suzuki-Miyaura, Negishi and Stille cross-coupling methods, never previously reported with the cubane scaffold; is also described, but proved unsuccessful.

INTRODUCTION

The concept of a rigid hydrocarbon cube fascinated chemists for much of the early half of the 20th century.[1,2] Due to its exceptional structure, symmetry and pronounced strain, cubane has been a hallmark in organic chemistry since its discovery by Eaton *et al.* in 1964.[3,4] The extraordinary density of the cubane hydrocarbon together with its incredibly high strain energy has led to significant interest in the fields of high energy fuels and explosives.[5,6]

The search for novel small molecule scaffolds and linking units in organic (and particularly medicinal) chemistry is an ongoing challenge.[7] One of the key requirements for any scaffold system is that the substituents must be arranged in a specific orientation which is precisely known and invariable under target conditions. As such, the majority of such units incorporate conjugating groups such as arenes, aromatic heterocycles, alkenes and alkynes due to the rigidity these enforce on molecules.[8,9] Comparatively little attention has been paid to saturated hydrocarbons, in spite of the many advantages these groups lend in terms of solubility and toxicity.[10] Considering the geometry of cubane, it is noteworthy that the distance across the cube (the body diagonal) is 2.72 Å, which is almost equivalent to the distance across a benzene ring, *i. e.*, 2.79 Å[11,12] which has led to renewed interest in it as an isostere in drug development.[13]

Our interest in the cubane scaffold emerged from a search for rigid linking units which would inhibit electronic communication between bound electron transfer systems.[14] The cubane framework thus stood out but the chemistry of cubane has remained somewhat stagnant for much of the last three decades and, as such, many modern avenues in synthetic chemistry, *e. g.*, transition metal-catalyzed cross-coupling reactions, have not been rigorously applied to the cubane system. The goal of the present work was therefore to develop appropriate cubane building blocks and test their applicability in cross-coupling reactions.

The majority of cubane functionalization reactions incorporate functional group interconversions (FGI) involving the carboxylic groups present after the standard cubane synthesis, which failed to adequately serve our requirements.[1] While *ortho*-lithiation of the cubane framework[15-17] presented an obvious entry-point, the reasonably complex pathways involved led to investigation of potentially more straightforward avenues. Modification of halogen atoms on the cubane periphery presented an attractive approach but comparatively little research on the reactivity of monohalogentaed cubane systems has been performed, most likely due to the interesting and unusual reactions that have been observed when bisiodinated cubane derivatives are exposed to standard lithiating reagents.[18-20] While various individual observations regarding the tendency of monohalogenated cubanes to undergo metal-halogen exchange have been reported,[19-21] no systematic study has been performed.[20,22-24] This led us to expand our initial synthetic program from reactants solely designed for Pd(II)-catalyzed reactions, to incorporate other systems and elements of synthetic interest, namely carbon-based electrophiles or 2nd row elements.

RESULTS AND DISCUSSION

An initial optimization of the metal-halogen exchange conditions was thus performed utilizing both a monoiodo- **1** and monobromocubane **2**. Protected (hydroxymethyl)cubanes were chosen as the basis for this work both to avoid issues relating to isolation of products (as the polarity of Bu-R and cubane-R can be very similar) and to provide a synthetic handle for further substitution reactions. Halogenated (hydroxymethyl)cubanes were prepared by known methodologies[23,25-27] and protected with appropriate groups. While more standard protecting groups proved equally effective, the majority of this work involved protection of the free hydroxyl group as a methyl ether. While this methyl ether could theoretically be deprotected, the reported isomerization of cubylcarbinols[25,28] meant that this was not attempted. Many of the reactions reported herein were also successfully performed with more standard protecting groups (pyran, TIPS) and produced identical results. For simplicity, only the results using **1** are presented.

Reactions of halogenated cubanes **1** and **2** were performed at a constant concentration in THF with an appropriate organolithium reagent. The reactions were allowed to develop for a specific time at varying temperatures (Table 1) before being quenched with MeOH and extracted from a dilute HCl solution. Any lithiated material should therefore be quenched to give the hydrolyzed products **3a/b**. By comparing the ratio

of unreacted starting material to **3** the optimum set of reactants, time and temperature were delineated. A brief summary of the results of this study is shown in Table 1. Iodinated cubanes clearly undergo metal-halogen exchange much easier than brominated analogues. Controlled addition of just two equivalents of *tert*-butyllithium allowed for quantitative metallation and subsequent cleaving when using **1** as substrate.

**Table 1: Optimization of metal-halogen exchange conditions.**

X = I, R^1 = Me, **1**   R^1 = Me, **3a**
X = Br, R^1 = TIPS, **2**   R^1 = TIPS, **3b**
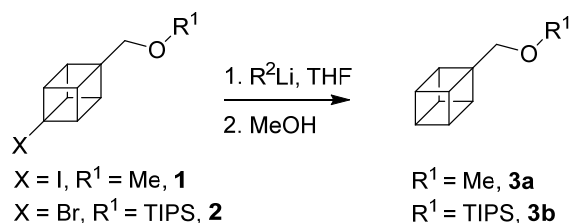
entry	s.m.	R^2 (eq.)	time (min)^a	temp (°C)	result
1	1	*t*-Bu (2)	60	-78	91 % **3a**
2	1	*t*-Bu (2)	30	-78	85 % **3a**
3	1	*n*-Bu (2)	60	-78	83 % **3a**
4	1	*t*-Bu (1.5)	60	-78	74 % **3a**
5	2	*t*-Bu (2)	60	-78	Unreacted **2**
6	2	*t*-Bu (4)	60	0	<20 % **3b**^{b}

Reaction conditions: All reactions were performed at a cubane concentration of 0.16 M in THF under argon. Isolated yields are given except where stated. ^{a} Indicates time between addition of R^{2}Li and quenching with MeOH. ^{b} Estimated from ^{1}H NMR.

Having optimized a set of reaction conditions, attention turned to probing the utility of this methodology towards diverse bond forming reactions. A range of both carbon based electrophiles as well as various metals and non-metals were thus added to a lithiated cubane **4**, prepared from **1** as per Table 1, Entry 1. The results of this study are contained within Table 2. Addition of simple alkyl halides led to hexyl- **5**, tetradecyl- **6** and 4-bromobutyl- **7** substituted cubanes in high yields (Table 2, Entries 1-3). The nature of the leaving group on the alkyl halide appears to play only a minor role with both iodoalkanes and bromoalkanes undergoing near quantitative displacement with **4**. Iodomethane (Entry 4) however, failed to give any product **8**. The recovered material was simply the starting material **1**. Due to the visible generation of a cubyllithium species this is presumably formed from a second metal-halogen transfer reaction with the iodomethane, rather than being unreacted starting material. This indicates the increased stability of the primary methyllithium over **4** and correlates with previous reports.[21]

Table 2: Generation of diverse cubane systems through metal-halogen exchange reactions.
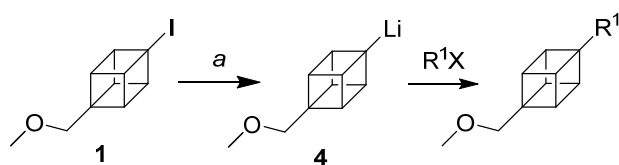
#	R^1	X	time (h)^b	product	yield (%)
1	C$_6$H$_{13}$	I	0.5	**5**	98
2	C$_{14}$H$_{29}$	Br	0.5	**6**	94
3	C$_4$H$_8$Br	Br^c	0.5	**7**	96
4	Me	I^c	0.5	**8**	0^d
5	CHO	NMe$_2$^{c}	4	**9**	<10^e
6	CH$_2$C≡CTMS	Br	1	**10**	n/d^f
7	(pinacol boronate) B	O*i*Pr	1	**11**	84
8	(9-BBN) B	OMe	1	**12**	n/d^g
9	Sn(Bu)$_3$	Cl	1	**13**	78
10	ZnCl	Cl	1	**14**	n/d^g
11	P(Ph)(Ph)	Cl	18	**15b**	79
12	Si(Me)$_3$	Cl	2	**16**	90
13	Si(Cl)	Cl^c	1	**17**	73
14	(S-CH$_2$CH$_2$C(O)O-CH$_2$CH(Bu)Et)	Cl	1	**18**	22

^{a} *Reaction conditions*: All reactions were performed at a cubane concentration of 0.16 M in THF with 2 eq. *t*-BuLi added at -78 °C and **4** allowed to generate for 1 h. Reaction mixtures were warmed to r.t. after addition of 2 eq. of R^{1}X, except where stated. Isolated yields are given where applicable. ^{b} Indicates time between addition of R^{1}X and quenching with dilute HCl. ^{c} 5 eq. R^{1}X employed. ^{d} **1** recovered. ^{e} Estimated from ^{1}H NMR. ^{f} Complex mixture of products. ^{g} Quantitative formation of products observed indirectly.

Attempts to formylate the scaffold by introducing DMF into the reaction vessel proved largely unsuccessful (Entry 5). Some trace amounts of the aldehyde product **9** were observed by ^{1}H NMR but the primary product was hydrolyzed starting material **3a** together with some unreacted **1**. Attempts to isolate **9** or increase the yield to significant levels failed. Using a protected propargyl substrate, 3-bromo-1-TMS-1-propyne (Entry 6), gave a complex mixture of products which could not be separated. Cubane products present in the mix included **3a** and the target **10** but there also appeared to be some brominated cubane, presumably formed by exchange with the propargyl bromide.

In terms of reactive cross-coupling partners the synthesis of cubanylboronic ester **11** and cubanylborane **12** represent the first examples of cubane-boron compounds and were synthesized here in high yields (Table 2, Entries 7/8). Upon standard work-up both **11** and **12** gave NMR spectra consistent with a high degree of purity. During purification **11** was found to decompose on silica, presumably due to its acidic nature, so aluminum

oxide (Al$_2$O$_3$, Alox, Brockmann Grade III) was used to effect its purification. Treatment of **4** with *B*-methoxy-9-BBN at -78 ºC provided access to the BBN-appended cubane **12**. Formation of the target material was observed by TLC analysis and ^{1}H NMR. However, like analogous alkylboranes,[29,30] **12** is susceptible to air and heat so efforts to purify the material proved unsuccessful. The absence of any significant quantity of hydrolyzed material **3a** on work-up, however, indicated that the reaction proceeds at a rate similar to that of **11**, *i. e.* near quantitative. As a result, generation and use of **12** *in situ* provides a reasonable avenue to utilizing it in further reactions.

While cubyl derivatives of tin have been reported previously,[16,22] these involve the more toxic trimethyltin residue. Introduction of the less environmentally toxic tri-*n*-butyltin residue through its chloride adduct provided ready access to stannylated cubane **13**, which was stable in aerobic environments but displayed some decomposition at room temperature. Nevertheless, **13** was easily purified by column chromatography (silica gel) and proved stable indefinitely when stored at 0-4 °C. The addition of Zn was effected through its anhydrous chloride salt and the formation of the reactive cubanylzinc(II) chloride species **14** was observed through several indirect methods (*i. e.* hydrolysis and substitution reactions). Efforts to generate **14** through use of Rieke zinc[31,32] failed completely, indicating a significant energy barrier to oxidative addition among cubane halides.

Together with boron, phosphorous stands out as being one of the few light, reactive, non-metals which are missing in the repertoire of cubane derivatives. Due to the wealth of interesting chemistry organophosphorus compounds possess, phosphanylcubane **15** was targeted as a trial compound, both to probe the reactivity of the cubane scaffold towards P insertion as well as creating a compound which may have many possible uses in the field of catalysis. Treatment of lithiated cubane **4** with chlorodiphenylphosphine (Table 2, Entry 11) produced the P-substituted cubane, which underwent quantitative oxidation under ambient conditions to the phosphine oxide system **15b** (Scheme 1, Figure 1). The reaction time here was extended from the standard one hour, as quenching at this point produced large quantities of **3a**. Stirring at room temperature overnight was sufficient to allow complete conversion of the lithiated cubane to **15**. Compound **15** decomposed on silica gel so direct transfer of the crude reaction product to an Al$_2$O$_3$ (Brockmann Grade III) column was required to effect its purification. Attempts to reduce **15b** to the phosphine complex **15a** failed to yield an appreciable amount of the phosphine system. Further studies to investigate the properties of **15b** are ongoing, as is the synthesis of a library of cubane-phosphorous systems.

Similar to stannylated cubanes, silicon has been successfully introduced onto the cubane scaffold previously.[16,22] However, the most common use of silyl functionality in modern synthetic chemistry, namely in protecting group chemistry remained to be tackled. Two silylated cubanes were prepared. Quenching of lithiocubane **4** with trimethylsilyl chloride gave the TMS-appended cubane **16** in high yield, while addition of an increased excess of dimethyldichlorosilane gave the chlorosilylcubane **17** (Table 2, Entry 12/13). Five equivalents of the dichlorosilane were added in an effort to minimize the formation of any dimeric species. The reactive Si-Cl bond present in **17** raised issues with relation to purification. No aqueous work-up was possible and the acidity of silica gel inhibited its use. Purification by vacuum distillation failed to yield any

product. Column chromatography on Al$_2$O$_3$ proved successful with the compound obtained as a colorless oil in 73 % yield. As an analogue to TBDMS, the use of **17** as a protecting group offers significant potential. Research into the applicability of **17** as a novel protecting group is ongoing.

Scheme 1: Oxidation of 15a to 15b by ambient O$_2$.
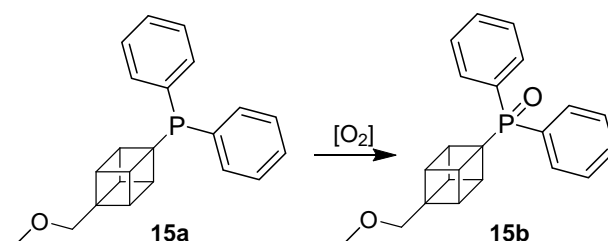
The synthesis of thiocubane is another synthetically interesting example of metal-halogen exchange reported on the cubane scaffold.[24] As a conclusion to the work on lithiated cubanes an alternative and more general method for the introduction of sulfur onto the cubane core in a milder fashion was investigated. Reaction of **4** with a sulfenyl chloride (derived from an odorless thiol which undergoes ready base deprotection to the free thiol[33-35]) was found to give a low yield of the sulfur appended cubane **18** (Table 2, Entry 14). Difficulties involving the dimerization of the sulfenyl chloride species lowered the reaction yield. The successful generation of **18** nevertheless represents an alternative method for sulfur insertion through use of sulfenylchlorides to that previously published. However, further optimization of the reaction must be performed before it can be considered synthetically useful.
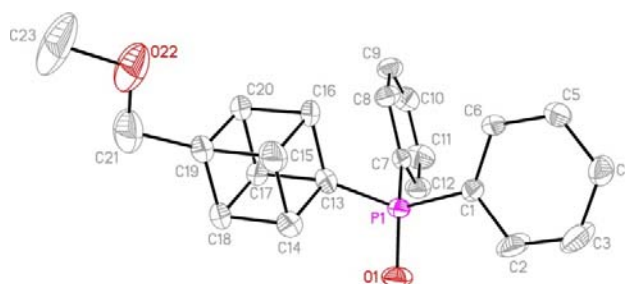

Figure 1: Molecular structure of **15b** (thermal displacement 50%, major component (68%) shown). Hydrogens omitted for clarity.

While tertiary alkanes are characteristically difficult as cross-coupling partners[36] the fact that the external bonds in cubane possess such a significant degree of s-character (approx. 30 %[37]), together with the high energy barrier associated with the β-hydride elimination of cubane[18] from a Pd center, led to the assumption that it may prove an exception to this rule. Additionally, the 90° C-C-C bond angle in cubane causes the adjacent carbon atoms to be somewhat 'tied back' from the reactive center, theoretically decreasing the overall steric demand which has limited the successful couplings of tertiary alkanes. Reported cross-coupling reactions of functionalized adamantane derivatives also proved encouraging.[38,39] A comprehensive program investigating the Pd-catalyzed cross-coupling reactions of **11-14** was thus undertaken. Full details of this study are contained within the Supporting Information.

In brief, the major findings of this study were that while standard cross-coupling conditions allowed for recovery of the cubane system, by moving to more activated conditions; either through use of additives or highly active catalyst systems;

successful transmetallation of the cubane systems to a palladium center was achieved using Suzuki-Miyaura, Negishi and Stille cross-coupling techniques. Unfortunately, successful reductive elimination from this intermediate to form cross-coupled products was not observed in any instance with complete decomposition of the cubane scaffold being observed in all cases. This process appears to be a new, Pd-facilitated, decomposition pattern for the cubane system, distinct from those reported previously,[40,41] and independent of the specific cross-coupling pathway employed. Complete characterization of this product or isolation of the intermediate cubane-Pd complex has not been realized at the present time.

Scheme 2: Palladium catalyzed cross-coupling methodologies attempted with 11-14
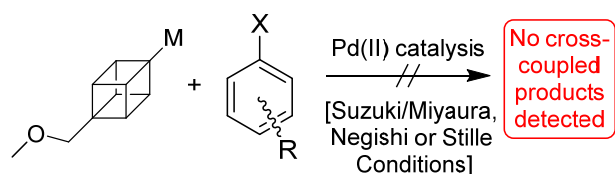
M = Boryl Ester, **11**
M = 9-BBN, **12**
M = Sn(Bu)$_3$, **13**
M = ZnCl$_2$, **14**

(See supporting information for specific details regarding conditions/substrates employed.)

In a sense we rolled the 'dice' and did not hit the jackpot. Still, it is not yet 'rien ne va plus'. While ultimately unsuccessful in the aim of a cross-coupled cubane system, the observed ability of the generated cubane nucleophiles to undergo transmetallation to the palladium center may present a potential avenue for further research. It is possible that, by using a cubane precursor which is less amenable to rearrangement (*e.g.* with a 4-carboxamide substituent), successful reductive elimination and cross-coupling may be achieved. Alternatively, copper or nickel mediated processes may prove more successful by avoiding the Pd-catalyzed transformation. If methods to introduce a cubane scaffold through TM-mediated cross-couplings can be realized, an inexhaustible number of substituted cubane scaffolds may become accessible for use in a multitude of fields.

CONCLUSIONS

In summary, the investigation of metal-halogen exchange on the cubane scaffold resulted in the successful synthesis of a large library of diversely functionalized cubane scaffolds. The retention of functionality at the 4-position of iodocubane presents an alternative to the standard use of iodinated cubanes by enabling further functionalization of the cubane scaffold following modification of the cubane-iodine bond. The optimization of procedures for the metal-halogen exchange reaction on iodinated cubanes facilitated the high yield synthesis of activated cubane nucleophiles (including the first examples of borylated cubanes) for use in Pd-catalyzed reactions. Introduction of phosphorous to the cubane scaffold represents the second completely novel structural archetype attained along this route. Future investigations will focus on the generation of a library of cubane-phosphorous compounds and investigations into their utility as novel ligands in transition metal-catalyzed reactions are planned. Further work is also on-going on improving the synthesis of thiolated cubanes and examining the utility of silylated cubanes in protecting group chemistry.

EXPERIMENTAL SECTION

All commercial chemicals used were supplied by Sigma Aldrich, Frontier Scientific, Inc. and Tokyo Chemical Industry and used without further purification unless otherwise stated. Anhydrous THF was obtained by drying over sodium/benzophenone, followed by distillation. Silica gel 60 (Merck, 230-400 mesh) or aluminium oxide (neutral, activated with 6.5 % H$_2$O, Brockmann Grade III) were used for flash column chromatography. Analytical thin layer chromatography was carried out with silica gel 60 (fluorescence indicator F$_{254}$; Merck) or aluminium oxide 60 (neutral, F$_{254}$; Merck) plates and stained with vanillin or *p*-anisaldehyde solutions where necessary. Melting points are uncorrected and were measured with a Stuart SP-10 melting point apparatus. NMR spectra were recorded using Bruker DPX 400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR), Bruker AV 600 (600.13 MHz for ^{1}H NMR and 150.90 MHz for ^{13}C NMR), Bruker AV 400 (400.13 MHz for ^{1}H NMR, 128.41 MHz for ^{11}B NMR, 162.02 MHz for ^{31}P NMR and 149.24 MHz for ^{119}Sn NMR) or Agilent MR400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR) instruments. Chemical shifts are given in ppm and referenced either to the deuterium peak in the NMR solvent or TMS used as an internal standard. The assignment of the signals was confirmed by 2D spectra (COSY, HMBC, HSQC). ESI mass spectra were acquired in positive and negative modes as required, using a Micromass time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC or a Bruker micrOTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC. APCI experiments were carried out on a Bruker micrOTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe in positive or negative modes. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF) in positive mode at 70eV. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. CHN analyses were performed on an Exeter Analytical CE 440 elemental analyser fitted with a Varian 55B SpectraAA atomic absorption spectrometer and are reported when detected within a 0.4 % error margin.

Dimethyl cubanyl-1,4-dicarboxylate and its precursors were synthesized as per Tsanaktsidis' method.[27] This was converted to methyl 4-iodocubanyl-1-carboxylate and reduced through known procedures.[42] Iodocubane[23] was synthesized by Eaton's procedures from appropriate precursors. Methyl 1-bromocubanyl-4-carboxylate and its precursors were synthesized as described by Klunder and Zwanenburg[26] and converted into **2** through standard methodologies.[43] 1-Bromo-4-iodocubane was synthesized *via* Moriarty's process[44] All compounds and intermediates had analytical data consistent with literature values. (See Supporting Information for further information).

1-Iodo-4-(methoxymethyl)cubane (1): 1-Iodo-4-hydroxymethylcubane[45] (3.5 g, 13.4 mmol) was dissolved in THF (100 mL) at room temperature. Sodium hydride (60 % dispersion in mineral oil, 1.12 g, 26.8 mmol) was added and the solution was stirred for 30 mins before the addition of iodomethane (2.5 mL, 40.2 mmol). The reaction mixture was stirred at room temperature until TLC analyses showed complete consumption of the starting material. Purification by column chromatography (silica gel, *n*-hexane:EtOAc, 7:1, v/v) and removal of solvents followed by recrystallization (CH$_3$OH) gave the title compound as a white solid (3.56 g, 13 mmol, 97 %). R_f = 0.38 (*n*-hexane:EtOAc, 7:1, v/v); M.p.: 59-61 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 3.34 (s, 3H, OCH_3), 3.52 (s, 2H, CCH_2O), 4.02-4.04 (m, 3H, cubanyl-CH), 4.20-4.22 ppm (m, 3H, cubanyl-CH); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 38.9 (q, CI), 48.5 (cubanyl-CH), 54.9 (cubanyl-CH), 57.8 (q), 59.2 (OCH$_3$) and 72.9 ppm (OCH$_2$); IR (neat): $\bar{v}$ = 3360, 3136, 2979, 2822, 1453, 1389, 1299, 1195, 1097, 1029 and 698 cm^{-1}; HRMS (EI) *m/z* calcd. for C$_{10}$H$_{11}$IO [M]$^+$: 273.9855, found 273.9861; Elem. Anal. calcd. for C$_{10}$H$_{11}$IO 43.82 % C, 4.05 % H found 43.62 % C, 3.79 % H.

General Procedure 1 (Lithiation of halogenated cubanes):
The relevant iodinated cubane (0.80 mmol) was dissolved in anhydrous THF (5 mL) in an oven-dried Schlenk flask, under argon, and

cooled to -78 °C. *tert*-Butyl lithium (1.60 mmol) was added dropwise over 10 minutes and the organolithium reagent was allowed to generate at -78 °C for 1 hour. Lithiocubane species **4** was then quenched with the appropriate electrophile (1.60 mmol) and left to warm to room temperature over 1 hour. The reaction was quenched by pouring into dilute HCl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL), dried over $MgSO_4$. The solvents were removed *in vacuo* and the product was purified by column chromatography (silica gel).

(Methoxymethyl)cubane (3a): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using methanol (2 mL, excess) as the electrophile. Purification by column chromatography (silica; *n*-hexane:EtOAc, 9:1, v/v) and removal of solvents gave the title compound as a pale yellow oil (108 mg, 0.73 mmol, 91 %). R_f = 0.28 (*n*-hexane:EtOAc, 6:1, v/v); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 3.36 (s, 3H, OC*H$_3$*), 3.50 (s, 2H, CC*H$_2$*O), 3.88-3.92 (m, 6H, cubanyl-C*H*), 3.99-4.02 ppm (m, 1H, cubanyl-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 44.6 (cubanyl-*C*H), 47.5 (cubanyl-*C*H), 48.4 (cubanyl-*C*H), 57.1 (q, 59.1 (O*C*H$_3$) and 73.6 ppm (O*C*H$_2$); IR (neat): $\bar{v}$ = 2975, 2925, 1726, 1456, 1367, 1150, 1101 and 776 cm^{-1}; LRMS (APCI+) *m/z* calcd. for $C_{10}H_{13}O$ [M+H]$^+$: 149.0961, found 149.0993.

1-Hexyl-4-(methoxymethyl)cubane (5): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using 1-bromohexane (0.22 mL, 1.60 mmol) as the electrophile. Purification by column chromatography (silica; *n*-hexane:EtOAc, 9:1, v/v) and removal of solvents gave the title compound as a colourless oil (182 mg, 0.78 mmol, 98 %). R_f = 0.62 (*n*-hexane:EtOAc, 10:1, v/v); ^{1}H NMR (600 MHz, CDCl$_3$/TMS, 25 °C): δ = 0.91 (t, $^3J_{\text{H-H}}$ = 6.9 Hz, 3H, CH$_2$C*H$_3$*), 1.27-1.33 (m, 8H, hexyl-C*H$_2$*), 1.57-1.59 (m, 2H, hexyl-CC*H$_2$*), 3.40 (s, 3H, OC*H$_3$*), 3.55 (s, 2H, C*H$_2$*O), 3.63-3.64 (m, 3H, cubanyl-C*H*), 3.72-3.74 ppm (m, 3H, cubanyl-C*H*); ^{13}C NMR (150 MHz, CDCl$_3$/TMS, 25 °C): δ = 13.9 (*C*H$_3$), 22.5 (*C*H$_2$), 23.8(*C*H$_2$), 29.4(*C*H$_2$), 31.8 (*C*H$_2$), 32.9 (*C*H$_2$), 43.9 (cubanyl-*C*H), 45.3 (cubanyl-*C*H), 47.4 (q, *C*-hexyl), 57.7 (q, CC*H$_2$*O), 59.0 (O*C*H$_3$) and 73.7 ppm (O*C*H$_2$); IR (neat): $\bar{v}$ = 2958, 2922, 2853, 1725, 1456, 1387, 1115, 1101, 950, 928, 839 and 724 cm^{-1}; HRMS (APCI+) *m/z* calcd. for $C_{16}H_{24}O$ [M]$^+$: 232.1822, found 232.1818.

1-(Methoxymethyl)-4-tetradecylcubane (6): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using 1-bromotetradecane (0.47 mL, 1.60 mmol) as the electrophile. Purification by column chromatography (silica; *n*-hexane:EtOAc, 15:1, v/v) and removal of solvents gave the title compound as a low-melting, waxy, white solid (259 mg, 0.75 mmol, 94 %). M.p.: 32-34 °C; R_f = 0.58 (*n*-hexane:EtOAc, 10:1, v/v); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.86 (t, $^3J_{\text{H-H}}$ = 6.3 Hz, 3H, CH$_2$C*H$_3$*), 1.24 (m, 24H, alkyl-C*H$_2$*), 1.53-1.54 (m, 2H, alkyl-CC*H$_2$*), 3.36 (s, 3H, OC*H$_3$*), 3.51 (s, 2H, CC*H$_2$*O), 3.59-3.60 (m, 3H, cubanyl-C*H*), 3.68-3.69 ppm (app. m, 3H, cubanyl-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.1 (*C*H$_3$), 22.7 (*C*H$_2$), 24.0 (*C*H$_2$), 29.3 (*C*H$_2$), 29.6 (multiple-*C*H$_2$), 29.7 (multiple-*C*H$_2$), 31.9 (*C*H$_2$), 33.0 (*C*H$_2$), 44.0 (cubanyl-*C*H), 45.4 (cubanyl-*C*H), 47.5 (q, *C*-alkyl), 57.8 (q, CC*H$_2$*O), 59.2 (O*C*H$_3$) and 73.8 ppm (O*C*H$_2$); IR (neat): $\bar{v}$ = 2957, 2915, 2897, 1470, 1384, 1323, 1120, 1103, 932, 838 and 720 cm^{-1}; HRMS (APCI+) *m/z* calcd. for $C_{24}H_{41}O$ [M+H]$^+$: 345.3152, found 345.3162.

1-(4-Bromobutyl)-4-(methoxymethyl)cubane (7): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using 1,4-dibromobutane (0.45 mL, 2.40 mmol) as the electrophile. Purification by column chromatography (silica; *n*-hexane:EtOAc, 9:1, v/v) and removal of solvents gave the title compound as a colourless oil (195 mg, 0.69 mmol, 86 %). R_f = 0.38 (*n*-hexane:EtOAc, 10:1, v/v); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.39-1.42 (m, 2H, CC*H$_2$*CH$_2$), 1.58 (t, $^3J_{\text{H-H}}$ = 7.0 Hz, 2H, CC*H$_2$*CH$_2$), 1.82-1.89 (m, 2H, C*H$_2$*CH$_2$Br), 3.36 (s, 3H, OC*H$_3$*), 3.40 (t, $^3J_{\text{H-H}}$ = 6.8 Hz, 2H, C*H$_2$*Br), 3.51 (s, 2H, C*H$_2$*O), 3.60-3.62 (m, 3H, cubanyl-C*H*), 3.69-3.72 ppm (m, 3H, cubanyl-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 22.8 (CC*H$_2$*CH$_2$), 32.1 (CC*H$_2$*CH$_2$), 33.0 (*C*H$_2$CH$_2$Br), 33.9 (*C*H$_2$Br), 44.0 (cubanyl-*C*H),

45.4 (cubanyl-*C*H), 48.5 (q, CC*H$_2$*CH$_2$), 57.9 (q, CC*H$_2$*O), 59.2 (O*C*H$_3$) and 73.7 ppm (O*C*H$_2$); IR (neat): $\bar{v}$ = 2965, 2927, 2831, 1726, 1453, 1387, 1117, 1099, 950, 927, 839 and 733 cm^{-1}; HRMS (APCI+) *m/z* calcd. for $C_{14}H_{20}BrO$ [M+H]$^+$: 283.0692, found 283.0699.

2-(4-(Methoxymethyl)cuban-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.33 mL, 1.60 mmol) as the electrophile. Purification by column chromatography (Al$_2$O$_3$; *n*-hexane:EtOAc, 5:1, v/v) and removal of solvents gave the title compound as a viscous semi-solid (184 mg, 0.67 mmol, 84 %). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.29 (s, 12H, CC*H$_3$*) 3.40 (s, 3H, OC*H$_3$*), 3.55 (s, 2H, CC*H$_2$*O), 3.97 ppm (app. s, 6H, cubanyl-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 24.8 (4 × *C*H$_3$), 44.5 (cubanyl-*C*H), 47.9 (cubanyl-*C*H), 56.7 (q, CC*H$_2$*O), 59.2 (O*C*H$_3$), 60.4 (q, *C*B), 73.6 (O*C*H$_2$) and 83.0 ppm (q, O*C*(CH$_3$)$_2$); ^{11}B NMR (128 MHz, CDCl$_3$, 25 °C): 22.53 ppm; IR (neat): $\bar{v}$ = 3205, 2977, 2261, 1727, 1450, 1371, 1148, 1098, 851 and 710 cm^{-1}; LRMS (APCI+) *m/z* calcd. for $C_{16}H_{24}BO_3$ [M+H]$^+$: 275.1816, found 275.1758.

Tri-*n*-butyl(4-(methoxymethyl)cuban-1-yl)stannane (13): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.60 M solution in hexanes, 1.60 mmol) using tri-*n*-butyltin chloride (0.48 mL, 1.60 mmol) as the electrophile. Purification by column chromatography (silica; *n*-hexane:EtOAc, 19:1, v/v) and removal of solvents gave the title compound as a yellow oil (272 mg, 0.62 mmol, 78 %). R_f = 0.57 (*n*-hexane:EtOAc, 10:1, v/v); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.82-0.88 (m, 15H, SnCH$_2$CH$_2$CH$_2$C*H$_3$*), 1.22-1.31 (m, 6H, CH$_2$C*H$_2$*CH$_2$), 1.47-1.51 (m, 6H, C*H$_2$*CH$_3$), 3.36 (s, 3H, OC*H$_3$*), 3.51 (s, 2H, CC*H$_2$*O), 3.90-3.92 (m, 3H, cubanyl-C*H*), 4.02-4.04 ppm (m, 3H, cubanyl-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 8.6 (Sn*C*H$_2$), 13.7 (*C*H$_2$CH$_3$), 27.2 (*C*H$_2$CH$_3$), 29.3 (*C*H$_2$CH$_2$), 44.6 (q, Sn*C*), 49.0 (cubanyl-*C*H), 50.0 (cubanyl-*C*H), 56.4 (q, CC*H$_2$*), 59.1 (O*C*H$_3$) and 73.5 ppm (O*C*H$_2$); ^{119}Sn NMR (149 MHz, CDCl$_3$, 25 °C): -7.5 ppm; IR (neat): $\bar{v}$ = 2957, 2922, 2871, 2853, 1584, 1484, 1376, 1198, 1103, 947, 877, 841 and 668 cm^{-1}.[46]

(4-(Methoxymethyl)cuban-1-yl)diphenylphosphine(V) oxide (15b): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using chlorodiphenylphosphine (0.29 mL, 1.60 mmol) as the electrophile. Purification by column chromatography (Al$_2$O$_3$; *n*-hexane:EtOAc, 8:1, v/v) and removal of solvents gave the title compound as an off-white solid (210 mg, 0.63 mmol, 79 %). M.p.: 114-116 °C;[47] ^{1}H NMR (600 MHz, CDCl$_3$, 25 °C): δ = 3.38 (s, 3H, OC*H$_3$*), 3.54 (s, 2H, CC*H$_2$*O), 3.99-4.01 (m, 3H, cubanyl-C*H*), 4.24-4.27 (m, 3H, cubanyl-C*H*), 7.47-7.50 (m, 4H, Ph-*m*-C*H*), 7.54-7.56 (m, 2H, Ph-*p*-C*H*), 7.63-7.66 ppm (m, 4H, Ph-*o*-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 44.8 (d, $^3J_{\text{P-C}}$ = 5.5 Hz, cubanyl-*C*H), 46.6 (d, $^2J_{\text{P-C}}$ = 8.1 Hz, cubanyl-*C*H), 53.0 (d, $^1J_{\text{P-C}}$ = 67 Hz, q, *C*P), 57.4 (d, $^4J_{\text{P-C}}$ = 4.3 Hz, q, CC*H$_2$*O), 59.2 (O*C*H$_3$), 72.7 (d, $^5J_{\text{P-C}}$ = 2.3 Hz, O*C*H$_2$), 128.6 (d, $^3J_{\text{P-C}}$ = 11.7 Hz, Ph-*m*-C*H*), 130.9 (d, $^2J_{\text{P-C}}$ = 9.5 Hz, Ph-*o*-C*H*), 131.6 (d, $^1J_{\text{P-C}}$ = 100 Hz, q, Ph) and 131.7 ppm (d, $^4J_{\text{P-C}}$ = 2.7 Hz, Ph-*p*-C*H*); ^{31}P NMR (162 MHz, CDCl$_3$, 25 °C): δ = 25.70 ppm; IR (neat): $\bar{v}$ = 3055, 2981, 2924, 2823, 1437 (P-C deformation band), 1388, , 1175, 1117, 1099, 924, 841, 723 and 695 cm^{-1}; HRMS (APCI+) *m/z* calcd. for $C_{22}H_{22}O_2P$ [M+H]$^+$: 349.1352, found 349.1365.

(4-(Methoxymethyl)cuban-1-yl)trimethylsilane (16): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using chlorotrimethylsilane (0.20 mL, 1.60 mmol) as the electrophile. Purification by column chromatography (silica; *n*-hexane:EtOAc, 8:1, v/v) and removal of solvents gave the title compound as a colourless oil (159 mg, 0.72 mmol, 90 %). R_f = 0.55 (*n*-hexane:EtOAc, 6:1, v/v); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = -0.77 (s, 9H, SiC*H$_3$*), 3.36 (s, 3H, OC*H$_3$*), 3.51 (s, 2H, CC*H$_2$*O), 3.73-3.76 (m, 3H, cubanyl-C*H*), 3.87-3.89 ppm (m, 3H, cubanyl-C*H*); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = -4.9 (Si*C*H$_3$), 43.4 (cubanyl-*C*H), 47.8 (cubanyl-*C*H), 48.4 (q, *C*Si), 57.5 (q, CC*H$_2$*O), 59.1 (O*C*H$_3$) and 73.6 ppm (O*C*H$_2$); IR (neat): $\bar{v}$ = 2954, 2925, 2854, 1727, 1455, 1386, 1247, 1104, 832, 932, 834 and 742 cm^{-}

[1]; HRMS (APCI+) *m/z* calcd. for $C_{13}H_{21}OSi$ [M+H]+: 221.1356, found 221.1344.

Chloro(4-(methoxymethyl)cuban-1-yl)dimethylsilane (17): Following General Procedure 1 with **1** (220 mg, 0.80 mmol) and *t*-BuLi (1.0 mL of 1.6 M solution in hexanes, 1.60 mmol) using dichlorodimethylsilane (0.50 mL, 4.00 mmol) as the electrophile. Purification by column chromatography (Al_2O_3; *n*-hexane:EtOAc, 8:1, v/v) and removal of solvents gave the title compound as a colourless oil (140 mg, 0.58 mmol, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$/TMS, 25 °C): δ = 0.01 (s, 6H, Si*CH₃*), 3.36 (s, 3H, O*CH₃*), 3.51 (s, 2H, CC*H₂*O), 3.77-3.82 (m, 3H, cubanyl-*CH*), 3.87-3.90 ppm (m, 3H, cubanyl-*CH*); ^{13}C NMR (100 MHz, $CDCl_3$/TMS, 25 °C): δ = -3.0 (Si*CH₃*), 43.5 (cubanyl-*CH*), 47.8 (cubanyl-*CH*), 49.4 (q, *C*Si), 57.2 (q, *C*CH₂O), 59.1 (O*CH₃*) and 73.5 ppm (O*CH₂*); IR (neat): $\bar{v}$ = 2959, 2821, 1729, 1451, 1386, 1256, 1083, 1028, 841, 789 and 666 cm⁻¹.[48]

(2-Ethylhexyl 3-((4-(methoxymethyl)cuban-1-yl)thio)propanoate (18): Lithiated cubane **4** was prepared *via* General Procedure 1 with **1** (280 mg, 1.00 mmol) and *t*-BuLi (1.25 mL of 1.6 M soln. in hexanes, 2.00 mmol). In a separate flask freshly recrystallized *N*-chlorosuccinimide (130 mg, 1.00 mmol) was dissolved in anhydrous toluene (1 mL) under argon and shielded from light. 2-Ethylhexyl 3-mercaptopropanoate (0.2 mL, 0.90 mmol) was dissolved in anhydrous toluene (1 mL) and added to the NCS solution over 30 minutes and left to stir at room temperature for another 30 minutes. The sulfenyl chloride solution was then added dropwise to the lithiated cubane **4** at -78 °C and left to warm to room temperature over one hour. Purification by column chromatography (silica; *n*-hexane:EtOAc, 8:1, v/v) and removal of solvents gave the title compound as a colourless oil (72 mg, 0.20 mmol, 22 %). R_f = 0.31 (*n*-hexane:EtOAc, 6:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.90-0.94 (m, 6H, alkyl-C*H₃*), 1.28-1.40 (m, 9H, alkyl-C*H₂*/C*H*), 2.62 (t, $^3J_{H-H}$ = 7.5 Hz, 2H, S*CH₂*CH₂), 2.84 (t, $^3J_{H-H}$ = 7.5 Hz, 2H, SC*H₂*), 3.40 (s, 3H, O*CH₃*), 3.57 (s, 2H, CC*H₂*O), 3.87-3.89 (m, 3H, cubanyl-*CH*), 3.92-3.93 ppm (m, 3H, cubanyl-*CH*), 4.03-4.05 ppm (m, 2H, OC*H₂*); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.0 (alkyl-*CH₃*), 14.1 (alkyl-*CH₃*), 23.0 (alkyl-*CH₂*), 23.8 (alkyl-*CH₂*), 24.6 (S*CH₂*), 28.9 (alkyl-*CH₂*), 30.4 (alkyl-*CH₂*), 35.5 (S*CH₂*CH₂), 38.7 (alkyl-*CH*), 44.7 (cubanyl-*CH*), 48.9 (cubanyl-*CH*), 58.0 (q, *C*CH₂O), 59.3 (O*CH₃*), 60.8 (q, S*C*), 67.2 (*C*O₂CH₂), 73.2 (O*CH₂*) and 172.1 ppm (q, *C*=O); IR (neat): $\bar{v}$ = 2960, 2927, 2859, 1734 (C=O), 1461, 1388, 1348, 1201, 1132, 1101 and 840 cm⁻¹; HRMS (APCI+) *m/z* calcd. for $C_{21}H_{33}O_3S$ [M+H]+: 365.2145, found 365.2141.

ASSOCIATED CONTENT

Supporting Information

Comprehensive details regarding the transition-metal catalyzed reactions attempted with **11-14** together with spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1044128 (**15b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Notes

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REFERENCES

(1) Eaton, P. E. *Angew. Chem., Int. Ed.* **1992**, *31*, 1421-1436.
(2) Griffin, G. W.; Marchand, A. P. *Chem. Rev.* **1989**, *89*, 997-1010.
(3) Eaton, P. E.; Cole, T. W. *J. Am. Chem. Soc.* **1964**, *86*, 962-964.
(4) Eaton, P. E.; Cole, T. W. *J. Am. Chem. Soc.* **1964**, *86*, 3157-3158.
(5) Eaton, P. E.; Zhang, M. X.; Gilardi, R.; Gelber, N.; Iyer, S.; Surapaneni, R. *Propellants Explos. Pyrotech.* **2002**, *27*, 1-6.
(6) Eaton, P. E.; Gilardi, R. L.; Zhang, M. X. *Adv. Mater.* **2000**, *12*, 1143-1148.
(7) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514-5533.
(8) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46-48.
(9) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104-109.
(10) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752-6756.
(11) Fleischer, E. B. *J. Am. Chem. Soc.* **1964**, *86*, 3889-3890.
(12) Hedberg, L.; Hedberg, K.; Eaton, P. E.; Nodari, N.; Robiette, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 1514-1517.
(13) Wlochal, J.; Davies, R. D. M.; Burton, J. *Org. Lett.* **2014**, *16*, 4094-4097.
(14) Ryan, A.; Gehrold, A.; Perusitti, R.; Pintea, M.; Fazekas, M.; Locos, O. B.; Blaikie, F.; Senge, M. O. *Eur. J. Org. Chem.* **2011**, 5817-5844.
(15) Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724-726.
(16) Eaton, P. E.; Higuchi, H.; Millikan, R. *Tetrahedron Lett.* **1987**, *28*, 1055-1058.
(17) Eaton, P. E.; Xiong, Y.; Zhou, J. P. *J. Org. Chem.* **1992**, *57*, 4277-4281.
(18) Eaton, P. E.; Maggini, M. *J. Am. Chem. Soc.* **1988**, *110*, 7230-7232.
(19) Eaton, P. E.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1990**, *112*, 876-878.
(20) Eaton, P. E.; Pramod, K.; Emrick, T.; Gilardi, R. *J. Am. Chem. Soc.* **1999**, *121*, 4111-4123.
(21) Eaton, P. E.; Li, J. C.; Upadhyaya, S. P. *J. Org. Chem.* **1995**, *60*, 966-968.
(22) Della, E. W.; Head, N. J. *J. Org. Chem.* **1995**, *60*, 5303-5313.
(23) Eaton, P. E.; Galoppini, E.; Gilardi, R. *J. Am. Chem. Soc.* **1994**, *116*, 7588-7596.
(24) Priefer, R.; Lee, Y. J.; Barrios, F.; Wosnick, J. H.; Lebuis, A.-M.; Farrell, P. G.; Harpp, D. N.; Sun, A.; Wu, S.; Snyder, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 5626-5627.
(25) Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1975**, *31*, 1419-1426.
(26) Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1972**, *28*, 4131-4138.
(27) Bliese, M.; Tsanaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 189-192.
(28) Della, E. W.; Janowski, W. K. *J. Org. Chem.* **1995**, *60*, 7756-7759.
(29) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544-4568.
(30) Soderquist, J. A.; Justo de Pomar, J. C. *Tetrahedron Lett.* **2000**, *41*, 3537-3539.
(31) Rieke, R. D.; Li, P. T. J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323-4324.
(32) Rieke, R. D. *Science* **1989**, *246*, 1260-1264.
(33) Becht, J.-M.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2003**, *68*, 5758-5761.
(34) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587-4590.
(35) Itoh, T.; Mase, T. *J. Org. Chem.* **2006**, *71*, 2203-2206.
(36) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492.

(37)   Della, E. W.; Hine, P. T.; Patney, H. K. *J. Org. Chem.* **1977**, *42*, 2940-2941.

(38)   Bräse, S.; Waegell, B.; de Meijere, A. *Synthesis* **1998**, 148-152.

(39)   Sämann, C.; Dhayalan, V.; Schreiner, P. R.; Knochel, P. *Org. Lett.* **2014**, *16*, 2418-2421.

(40)   Eaton, P. E.; Cassar, L.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 6366-6368.

(41)   Eaton, P. E.; Stossel, D. *J. Org. Chem.* **1991**, *56*, 5138-5142.

(42)   Griffiths, J. R.; Tsanaktsidis, J.; Savage, G. P.; Priefer, R. *Thermochim. Acta* **2010**, *499*, 15-20.

(43)   Shastin, A. V.; Zakharov, V. V.; Bugaeva, G. P.; Eremenko, L. T.; Romanova, L. B.; Lagodzinskaya, G. V.; Aleksandrov, G. G.; Eremenko, L. L. *Russ. Chem. Bull.* **2006**, *55*, 1304-1306.

(44)   Moriarty, R. M.; Khosrowshahi, J. S.; Dalecki, T. M. *J. Chem. Soc., Chem. Commun.* **1987**, 675-676.

(45)   Priefer, R.; Farrell, P. G.; Harpp, D. N. *Synthesis* **2002**, 2671-2673.

(46)   Compound **13** was not detected via HRMS. Multiple attempts were made but these compounds were unable to be characterized with the machines available.

(47)   Compound **15b** degraded on silica gel TLC plates and Al2O3 plates could not be stained to allow for product visualisation. As such, accurate retention factor could not be obtained.

(48)   Compound **17** was not detected via HRMS. Multiple attempts were made but the compounds could not be characterized with the machines available. The compound also degraded on silica gel so an accurate Rf could not be measured.

Highly strained tertiary sp^3 scaffolds: Synthesis of functionalized cubanes and exploration of their reactivity under Pd(II) catalysis

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Contents

1. Cross-Coupling reactions on cubane systems

This section outlines the investigations performed on the utility of the synthesized cubane systems as cross-coupling partners under palladium-catalyzed conditions. Reactions focused on those techniques which have found most widespread tolerance for alkyl substituents namely, Suzuki-Miyaura, Negishi and Stille cross-coupling reactions. In the case of the Suzuki-Miyaura reaction both halogenated and borylated cubane synthons were employed.

1.1 Halogenated cubanes as Suzuki-Miyaura partners

Testing of halogenated cubanes as Suzuki-Miyaura partners began with methyl 4-bromocubane-1-carboxylate[1] **S1** and phenyl boronic acid **S2**. A variety of conditions were trialled and are shown in Table S1. A range of simple Pd(II) catalysts and Pd(0) precatalysts were used in conjunction with various bases. The only products observed in all cases were homocoupled biphenyl and unreacted starting material **S1**.

*Table S1*: Trial couplings of **S1** as bromide partner in Suzuki-Miyaura cross-coupling.
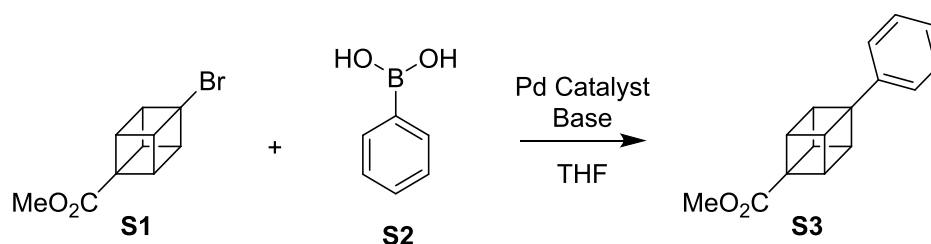
Entry	Catalyst (mol-%)	Base (eq.)	Temp (ºC)	Time (h)	Yield (%)
1	Pd(PPh$_3$)$_4$ (10)	K$_2$CO$_3$ (5)	65	16	0
2	PdCl$_2$(dppf) (10)	K$_2$CO$_3$ (5)	65	16	0
3	PdCl$_2$(dppf) (10)	Cs$_2$CO$_3$ (5)	65	16	0
4	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	65	16	0
5	PdCl$_2$(dppf) (10)	K$_2$CO$_3$ (8)/Ag$_2$O (7)	65	16	0
6	PdCl$_2$(dppf) (10)	25M (aq.) NaOH (10)	65	16	0

Reaction conditions: All reactions were performed at 20 mM cubane concentration using 3 equivalents of **96** under argon.

The absence of any coupled product observed from the reactions of **S1** resulted in attention turning to the more reactive iodocubanes. The initial trial material for these investigations was 1-bromo-4-iodocubane[2] **S4**, obtained *via* iodinative decarboxylation of **S1**. Reactions were performed on test scales with this material and **S2** under a variety of conditions (Table S2, Entries 1-7). While trace product formation was detected by ESI mass spectrometry, this material could not be isolated and identified. Two further (and more readily available) iodocubanes, methyl 4-iodocubane-1-carboxylate[3] **S5** (Table S2, Entries 8-12) and iodocubane[4] **S6** (Table S2, Entries 13-15) were thus utilized under similar conditions. In these cases coupled products could again only be identified in trace amounts; insufficient for characterization; with the major products in all cases being unreacted starting material

and biphenyl. Standard methods of facilitating the coupling of alkyl halides proved ineffective at increasing yields to detectable levels. However, if any trend can be observed, it is that use of PdCl$_2$(dppf) or Ag$_2$O appears more likely to lead to trace product detection. Other criteria seem to play a minimal role in the observed outcomes.

*Table S2*: Suzuki-Miyaura couplings of iodocubanes with **96**.

R^1 = Br, **S4**
R^1 = CO$_2$Me, **S5**
R^1 = H, **S6**

S2

R^1 = Br, **S7**
R^1 = CO$_2$Me, **S3**
R^1 = H, **S8**
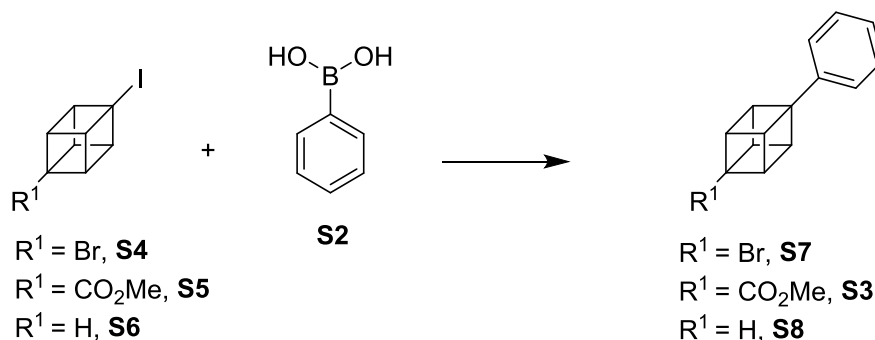
Entry	S.M.	Catalyst (mol-%)	Base (eq.)	Solvent	Time (h)	Temp (ºC)	Result[a]
1	**S4**	PdCl$_2$(dppf) (10)	K$_2$CO$_3$ (8)	THF	72	65	Trace **S7**
2	**S4**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)/ Ag$_2$O (7)	THF	72	65	Trace **S7**
3	**S4**	Pd(PPh$_3$)$_4$ (10)	K$_3$PO$_4$ (8)	THF	16	65	**S7** not detected
4	**S4**	PdCl$_2$(PPh$_3$)$_2$ (10)	K$_3$PO$_4$ (8)	THF	16	65	Trace **S7**
5	**S4**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	THF	16	r.t.	**S7** not detected
6	**S4**	PdCl$_2$(dppf) (10)	Cs$_2$CO$_3$ (4)	THF	16	65	Trace **S7**
7	**S4**	PdCl$_2$(dppf) (5)	Cs$_2$CO$_3$ (4)	THF	16	65	**S7** not detected
8	**S5**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)/ Ag$_2$O (7)	THF	16	65	Trace **S3**
9	**S5**	Pd(PPh$_3$)$_4$ (10)	K$_3$PO$_4$ (8)	THF	48	65	**S3** not detected
10	**S5**	PdCl$_2$(PPh$_3$)$_2$ (10)	K$_3$PO$_4$ (8)	THF	72	65	**S3** not detected
11	**S5**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	THF	72	65	Trace **S3**
12	**S5**	PdCl$_2$(dppf) (10)	K$_2$CO$_3$ (8)	DMF	72	120	Trace **S3**
13	**S6**	PdCl$_2$(PPh$_3$)$_2$ (10)	K$_3$PO$_4$ (8)/ Ag$_2$O (7)	THF	72	65	Trace **S3**
14	**S6**	Pd(PPh$_3$)$_4$ (10)	K$_3$PO$_4$ (8)/ Ag$_2$O (7)	THF	72	65	Trace **S8**
15	**S6**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)/ Ag$_2$O (7)	THF	72	65	Trace **S8**

Reaction conditions: All reactions were performed at 20 mM cubane concentration using 3 equivalents of **S2** under argon. [a] Coupled products detected by EI MS.

1.2 Borylated cubanes in the Suzuki-Miyaura reaction

The first borylated systems to be studied were the class of cubane boronic acid pinacol esters. In the main text the synthesis of **11** (a hydroxymethyl substituted cubane boryl ester) is described. However, this portion of the work was performed prior to the synthesis of **11** and used iodocubane **S6** as the iodinated cubane precursor (Table S3). The borylation reaction of **S6** proceeds exactly as described for **11**, however, complete purification of cubane boronic ester **S9**, proved more complicated than for the disubstituted system (presumably due to enhanced stability and altered solubility profile afforded by the hydroxymethyl group). As a result, **S9** was not isolated but instead typically generated and used *in situ*. Table S3 outlines the various reaction conditions employed to effect the cross-coupling of **S9** with two aryl iodides. The Suzuki-Miyaura couplings of **S9** present two distinct results – either recovery of the majority of the generated **S9** or the complete absence of any cubane product after work-up.

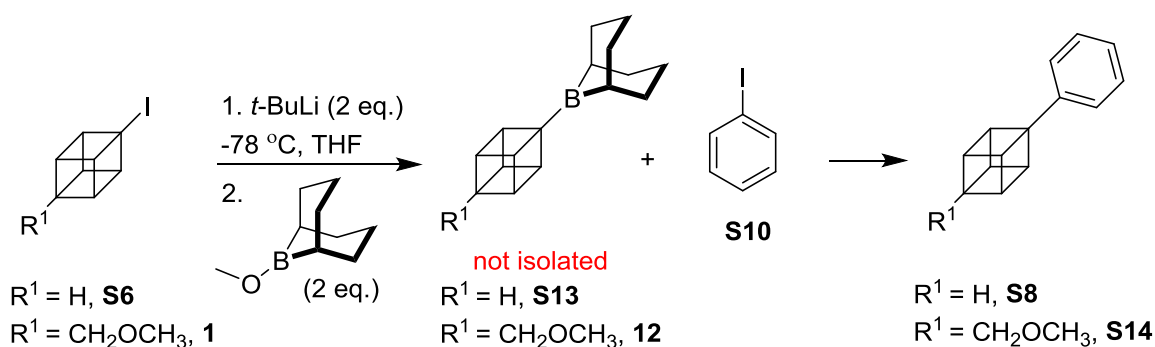*Table S3*: Suzuki-Miyaura couplings of cubane boronic acid pinacol ester.
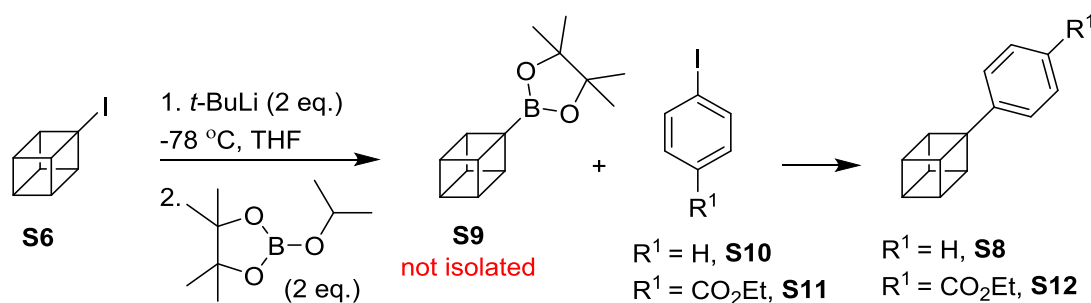
#	ArI	Catalyst (mol-%)	Base (eq.)	Ag$_2$O (5 eq.)	Temp (°C)	Result
1	**S10**	PdCl$_2$(PPh$_3$)$_2$ (10)	K$_3$PO$_4$ (8)	Yes	65	**S9** recovered
2	**S10**	Pd(PPh$_3$)$_4$ (10)	K$_3$PO$_4$ (8)	Yes	65	**S9** recovered
3	**S10**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	Yes	65	No cubane product
4	**S10**	PdCl$_2$(dppf) (10)	10M NaOH (8)	Yes	65	No cubane product
5	**S10**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	No	65	No cubane product
6	**S10**	PdCl$_2$(dppe) (10)	K$_3$PO$_4$ (8)	Yes	65	No cubane product
7	**S10**	Pd$_2$(dba)$_3$ (10)/ AsPh$_3$ (40)	K$_3$PO$_4$ (8)	Yes	65	No cubane product
8	**S11**	PdCl$_2$(PPh$_3$)$_2$ (10)	K$_3$PO$_4$ (8)	Yes	65	No cubane product
9	**S11**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	No	65	No cubane product
10	**S11**	PdCl$_2$(dppf) (10)	Cs$_2$CO$_3$ (4)	No	65	No cubane product
11	**S11**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	No	120[a]	No cubane product
12	**S11**	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	No	20	**S9** recovered
13	**S11**[b]	PdCl$_2$(dppf) (10)	Cs$_2$CO$_3$ (4)	No	65	No cubane product
14	**S11**[b]	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	No	120[a]	No cubane product

Reaction conditions: **S9** was generated *in situ* from the reaction of **S6** with *t*-BuLi in THF at -78 °C. Catalyst, base and aryl iodide were added after generation and heated. All coupling reactions were performed at 20 mM cubane concentration for 16 hours in THF under argon using 1.2 equivalents of aryl iodide unless otherwise stated. [a] THF was removed *in vacuo* after generation of **S9** and DMF added. [b] 0.33 equivalents of **S11** added.

The requirements for the decomposition of the cubane system were thus found to be through use of a bulky, electron-rich ligand at elevated temperatures. There are two explanations that can account for the entirety of these results. Firstly, that, with highly activated conditions, some palladium species is facilitating the decomposition of the cubane scaffold. No indication of any of the reported decomposition pathways of cubane (cyclooctatetraenes,[5] cuneanes[6] or cubenes[7]) was detected by ^{1}H NMR or HRMS analysis after any reaction. From ^{1}H NMR analysis of unpurified reaction mixtures immediately following the removal of the solvent, only aryl halide signals could be identified, with no other identifiable organic signals present. The presence of the aryl halide in all crude mixtures supports the hypothesis that this decomposition is occurring somewhere between transmetallation of the alkylboronic ester and reductive elimination of the coupled product. The other possibility is that the products **S8** and **S12** are being formed but are unstable under the reaction conditions or that homocoupling of **S9** is also occurring and producing a volatile product.

The failure of the boronic esters to produce any clear reaction led to the pursuit of more active substituents, namely cubane-BBN derivatives. The synthesis of hydroxymethyl derivative **12** is detailed in the main text. In a manner akin to that described previously iodocubane **S6** was also used as a precursor for these reactions. In both cases the instability of alkyl-BBN derivatives required the active nucleophiles to be generated and used *in situ*. The results of the couplings of cubane-BBN derivatives **12** and **S13** with iodobenzene are detailed in Table S4. In all cases, using cubane-BBN derivatives in the presence of palladium catalysts led to decomposition of the cubane scaffold. Upon work-up, no identifiable organic signals, with the exception of unreacted iodobenzene **S10**, could be detected in the ^{1}H NMR spectra. This occurred independently of the Pd source used, the presence of silver(I) oxide, the solvent or the base. The failure to recover any of the starting material from any reaction meant that, unlike the previous work with the boronic esters, thermal or aerobic decomposition of **S13** or **12** could not be eliminated as the reason for the absence of any cubane material upon work-up. Several details from later studies (*vide infra*) support the hypothesis that, in an identical manner to that discussed previously, the palladium species, through an unknown pathway, is facilitating decomposition of the cubane scaffold. Unlike in the boronic ester case, however, the higher reactivity of the BBN derivatives towards transmetallation means that this process occurs more favorably and under milder conditions with BBN-appended cubanes.

*Table S4*: Cross-coupling reactions of cubane-BBN derivatives **12** and **S13**.

R^1 = H, **S6**
R^1 = CH$_2$OCH$_3$, **1**

R^1 = H, **S13**
R^1 = CH$_2$OCH$_3$, **12**

S10

R^1 = H, **S8**
R^1 = CH$_2$OCH$_3$, **S14**

#	S.M.	Catalyst (mol-%)	Base (eq.)	Solvent	Temp (ºC)	Result
1	**S13**[a]	PdCl$_2$(dppf) (10)	K$_3$PO$_4$ (8)	THF	65	No cubane
2	**S13**[a]	Pd(PPh$_3$)$_4$ (10)	K$_3$PO$_4$ (8)	THF	65	No cubane
3	**S13**	PdCl$_2$(dppf) (10)	NaOH (3)	THF:H$_2$O (5:1)	65	No cubane
4	**S13**	PdCl$_2$(dppf) (10)	NaOH (3)/ Ag$_2$O (3)	THF:H$_2$O (5:1)	65	No cubane
5	**S13**	PdCl$_2$(dppf) (10)	K$_2$CO$_3$ (8)/ Ag$_2$O (3)	DMF[b]	50	No cubane
6	**12**	PdCl$_2$(dppf) (10)	NaOH (4)	THF:H$_2$O (5:2)	65	No cubane
7	**12**	PdCl$_2$(dppf) (10)	NaOH (4)	THF:H$_2$O (5:2)	r.t.	No cubane
8	**12**	PdCl$_2$(PPh$_3$)$_2$ (10)	NaOH (4)	THF:H$_2$O (5:2)	65	No cubane
9	**12**	Pd(PPh$_3$)$_4$ (5)	NaOH (4)	THF:H$_2$O (5:2)	65	No cubane
10	**12**	PdCl$_2$(dppf) (5)	K$_2$CO$_3$ (8)	DMF[b]	50	No cubane
11	**12**	PdCl$_2$(dppf) (5)	K$_2$CO$_3$ (8)	DMF[b]	r.t.	No cubane

Reaction conditions: Nucleophiles were generated *in situ* from the reaction of iodocubanes with *t*-BuLi in THF at -78 ºC. Catalyst, base and **S10** were added after generation and heated. All coupling reactions were performed at 80 mM cubane concentration for 16 hours under argon using 0.9 equivalents of **S10** unless stated. [a] 0.5 equivalents **S10** added. [b] THF removed after generation and replaced with DMF.

1.3 Negishi reactions of cubylzinc(II) halides

The initial studies into the Negishi cross-coupling of **14** with iodobenzene **S10** are detailed in Table S5. The initial four studies (Entries 1-4) were performed in order to assess the stability of **14** under the reaction conditions by omitting various reagents. Entries 1 and 2 indicate the stability of the cubane scaffold at room temperature in THF. Entry 3 shows that if **14** is heated overnight in THF, in the absence of any other materials, the hydrolyzed product **3a** is obtained after work up and Entry 4 indicates that the same process occurs in the presence of all reagents with the exception of the palladium catalyst. When this hydrolysis is occurring – *i. e*., during the course of the reaction or upon work-up – was not examined as it was deemed unimportant with relation to this study. The iodinated starting material **1** was found to be entirely stable to all conditions employed in Table S5.

*Table S5*: Negishi cross-couplings and stability studies of **14**.
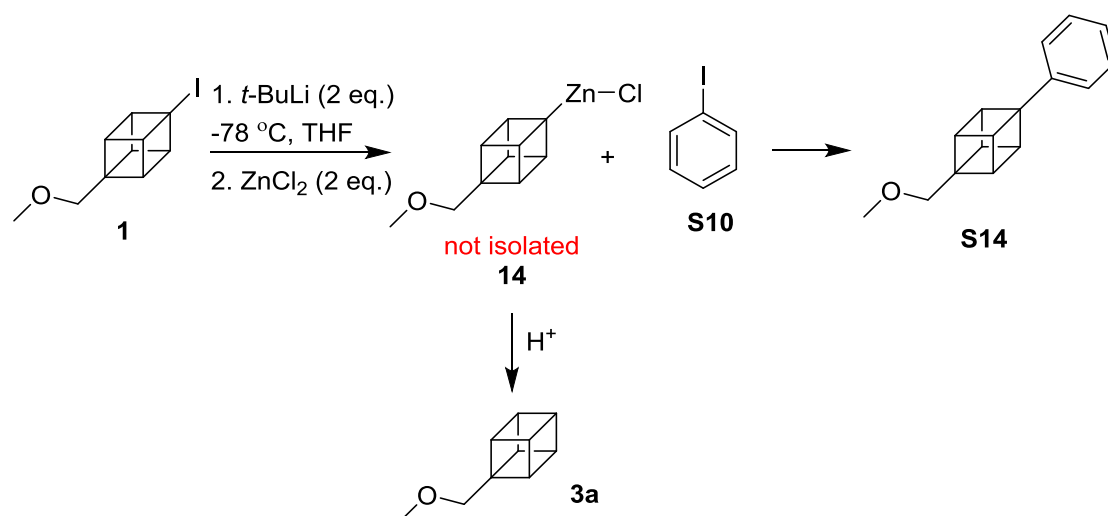
Entry	Catalyst (10 mol-%)	I-Ph (eq.)	NMP (% v/v)	LiCl (eq.)	Temp (ºC)	Time (h)	Observation
1	N/A	0	0	0	r.t.	1	Quantitative **3a**
2	N/A	0	0	0	r.t.	18	Quantitative **3a**
3	N/A	0	0	0	65	18	Quantitative **3a**
4	N/A	1	33	4	65	18	Quantitative **3a**
5	PdCl$_2$(dppf)	2	0	0	65	16	Quantitative **3a**
6	Pd(PPh$_3$)$_4$	2	0	0	65	16	Quantitative **3a**
7	PdCl$_2$(dppf)	2	0	2	65	16	Quantitative **3a**
8	PdCl$_2$(dppf)	1	0	0	65	16	Quantitative **3a**
9	PdCl$_2$(dppf)	1	33	4	65	16	No cubane
10	PdCl$_2$(dppf)	0	33	4	65	16	No cubane
11	PdCl$_2$(dppf)	1	33	4	r.t.	16	Quantitative **3a**
12	PdCl$_2$(dppf)	1	33	4	40	16	Some **3a**
13	Pd$_2$(dba)$_3$/P(Cy)$_3$	1	33	4	65	16	No cubane

Reaction conditions: **14** was generated *in situ* from the reaction of **1** with *t*-BuLi in THF at -78 ºC. Catalyst, salt and **S10** were added after generation and heated. Reactions were quenched with dilute HCl. All reactions were performed at 85 mM cubane concentration under argon.

The process of the Negishi cross-coupling reaction appears remarkably similar to that observed in the Suzuki-Miyaura cross-couplings – *i. e.*, under appropriate conditions the cubane scaffold decomposes with no detectable organic residues remaining. The requirement for some form of palladium species to be present is clear – definitively proving that the process is indeed a Pd-catalyzed one. From Table S5 the conditions that lead to the decomposition of the cubane system under Negishi conditions can be delineated – namely, heating in the presence of palladium in a highly polar NMP/THF solvent system. Absence of any of these three conditions allows for the retrieval of hydrolyzed cubane from the reaction mixture. This result therefore outlines the conditions required to produce transmetallation of the cubane-zinc system.

The outstanding question from Table S5 was that if transmetallation to the Pd center is occurring, then can a more suitable halide coupling partner produce effective cross-coupling? To this end, the

reaction conditions which were shown to lead to decomposition (presumably initially *via* transmetallation) were applied for the cross-coupling of **14** with various aromatic halides as the electrophilic partners (Scheme S1). Both electron withdrawing and donating effects were investigated with this series of electrophiles as well as the nature of the halogen present. In all cases, no cubane product was obtained at the end of the reaction. This lends further proof towards the theory that the palladium-catalyzed route in question is indeed independent of the standard cross-coupling catalytic cycle.
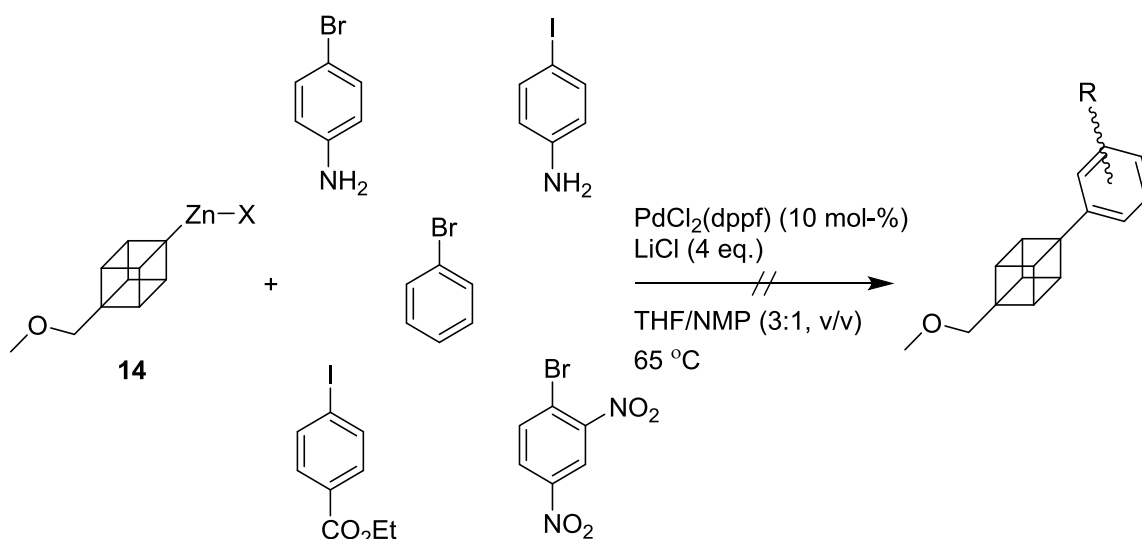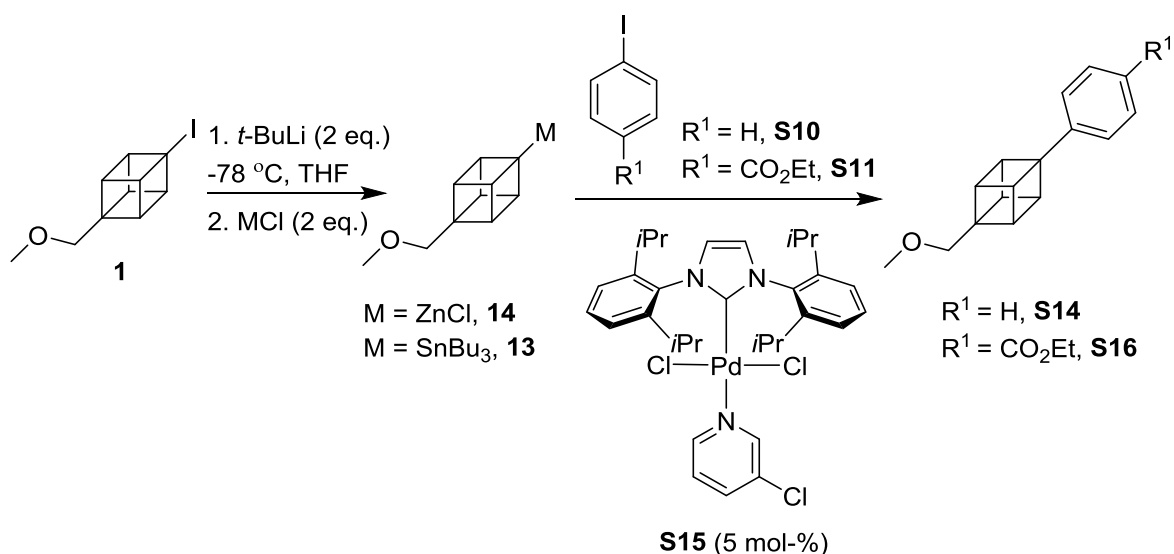

Scheme S1: Attempted Negishi reactions of **14** with various aryl halides.

This work on the Negishi reaction possesses clear parallels to the earlier work on the Suzuki-Miyaura couplings and helps answer some of the outstanding questions from that section. In both cases, a decomposition process of activated cubane systems is occurring in the presence of palladium salts. Similarly, both reactions require highly reactive conditions to effect this process – indicating an energy barrier akin to that existing in transmetallation. Indeed the conditions which, when employed, lead to decomposition, are identical to those reported as being most effective for the transmetallation and subsequent cross-coupling of alkyl substituents.[8]

1.4 Cubane and the Stille reaction

The studies into the effectiveness of Stille cross-coupling conditions were less detailed than those performed previously, in part due to the comparative lack of significant reported modifications and also because the observed initial results were broadly similar to those obtained with the other two methodologies. The results of this investigation are presented in Table S6. One significant advantage the Stille reaction has over the others discussed is the stability of the stannylated cubane component **13**. Unlike the borylated cubanes and cubylzinc(II) halides, these compounds are stable for short periods on silica gel and towards light, heat and air. This eliminates these means of decomposition as plausible avenues, allowing for a more conclusive analysis of results.

The results detailed in Table S6 illustrate an identical pattern of reactivity to that observed previously. Decomposition of the cubane scaffold occurs through use of a bidentate ligand on the Pd complex while heating in a highly polar solvent (Entries 4, 7 and 8). Otherwise, the stannylcubane can be recovered quantitatively from the reaction. The presence of CuI as an activator plays a minimal role in comparison to the other conditions. The stability of **13** indicate that transmetallation of the cubane scaffold must be occurring. Highly activated conditions are required to promote transmetallation of the stannylated cubane scaffold, which may also be required to facilitate the decomposition reaction from the Pd-complex. The close agreement of results indicates that the pathway is largely independent of the specific methodologies employed but rather a general trait of the active Pd-cubane complex.

Table S6: Attempted Stille couplings of **13** with **S10**.

Entry	Catalyst (10 mol-%)	Solvent	Salt (eq.)	Temp (ºC)	Observation
1	Pd(PPh$_3$)$_4$	DMF	LiCl (4)	50	**13** recovered
2	Pd(PPh$_3$)$_4$	DMF	CuI (0.3)	50	**13** recovered
4	PdCl$_2$(dppf)	THF	LiCl (4)	65	**13** recovered
5	PdCl$_2$(dppf)	THF/NMP (3:1)	LiCl (4)	65	No cubane
6	PdCl$_2$(dppf)	THF/NMP (3:1)	CuI (0.3)	65	No cubane
7	PdCl$_2$(dppf)	THF/NMP (3:1)	CuI (0.3)	r.t.	**13** recovered

Reaction conditions: All reactions were performed at 85 mM cubane concentration under argon for 16 hours using 1 eq. **S10**.

1.5 Utilization of highly active catalyst systems

All of the work discussed thus far has focused on the use of standard palladium-phosphine catalyst systems. A representative member of a more highly activated catalyst class, the *N*-heterocyclic carbene Pd-PEPPSI-*i*Pr **S15**, was subsequently utilized in each of the three coupling methodologies discussed. The goal here was to attempt to obtain transmetallation at milder conditions to further probe the catalytic process and test whether the highly activated conditions employed previously are also required for the decomposition process to occur, *i. e.* if transmetallation can be achieved under milder conditions will the desired reductive elimination become possible?. Table S7 outlines the results of this catalyst under Negishi and Stille coupling conditions, whilst Table S8 illustrates the same for the Suzuki-Miyaura protocol.

Table S7: Use of Pd-PEPPSI-*i*Pr as catalyst in Negishi and Stille couplings.

Entry	Cubane ("M")	Ar-I (eq.)	NMP (% v/v)	LiCl (eq.)	Temp (°C)	Time (h)	Observation
1	**14** (ZnCl)	**S11**	33	4	65	18	No cubane
2	**14** (ZnCl)	**S11**	0	4	65	18	No cubane
3	**14** (ZnCl)	**S11**	33	4	r.t.	18	No cubane
4	**14** (ZnCl)	**S11**	0	0	r.t.	18	No cubane
5	**14** (ZnCl)	**S10**	0	0	-55	3	No cubane
6	**14** (ZnCl)	**S10**[a]	0	0	-55	3	Trace **3a**
7	**13** (SnBu₃)	**S11**	33	4	r.t.	18	No cubane
8	**13** (SnBu₃)	**S11**	0	4	r.t.	18	No cubane

Reaction conditions: Metallocubanes were generated *in situ* from the reaction of **1** with *t*-BuLi in THF at -78 °C. Catalyst, salt and Ar-I were added after generation and heated. All coupling reactions were performed at 80 mM cubane concentration under argon using 5 mol-% **S15** and 1 eq. of Ar-I unless stated. [a] 0.33 equivalents **S10** added.

Both tables present distinct reactivities with relation to the previous work. In all cases the PEPPSI catalyst was much more efficient at initiating transmetallation of the activated cubane nucleophiles than standard Pd-phosphine complexes. The product was still not a recognizable cubane system, however, and no organic residues, with the exception of the aryl halide, could be identified in any reaction flask. This led to the conclusion that, in all cases with **S15** as catalyst, the cubane system underwent the same decomposition as was witnessed with the highly activated coupling conditions using Pd-phosphine complexes discussed previously. This decomposition pathway and product(s) are still unidentifiable. Cyclooctatetraene can be confidently ruled out due to the absence of any alkene signals in the ¹H NMR. Cuneane remains a possibility, but the complete absence of any spectral indication of its presence deems it unlikely. The lack of any discernible CH₃-O-CH₂ fragment in the ¹H NMR provides compelling evidence that the products of the catalysis reactions are volatile alkanes and ethers which are too labile for characterization. Removing the THF solvent in as mild a manner as possible failed to allow recovery

of said fragments. Short of isolating the Pd-cubane complex, attempts of which proved unsuccessful, no further method of examining the mechanism could thus be conceived.

Table S8: Suzuki-Miyaura cross-couplings using Pd-PEPPSI-*i*Pr as catalyst.
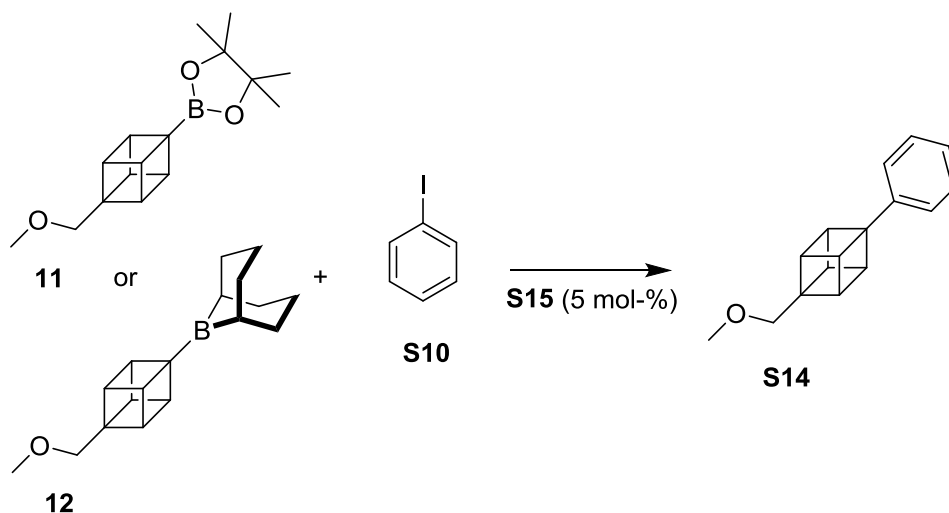
Entry	Cubane	Base (eq.)	T (ºC)	Time (h)	Result
1	**12**	1M NaOH/H$_2$O (4)	r.t.	18	No cubane
2	**12**	1M NaOH/H$_2$O (4)	r.t.	18	No cubane
3	**11**	1M NaOH/H$_2$O (4)	r.t.	18	No cubane
4	**12**	1M NaOH/MeOH (4)	r.t.	18	No cubane
5	**12**	K$_3$PO$_4$ (10)	r.t.	18	No cubane
6	**12**	2M NaOH/MeOH (8)	-55	3	No cubane
7	**11**	2M NaOH/MeOH (8)	-55	3	Trace **11**
8	**12**[a]	2M NaOH/MeOH (8)	-55	3	Trace **12**
9	**11**[a]	2M NaOH/MeOH (8)	-55	3	Trace **11**

Reaction conditions: **11** and **12** was generated *in situ* from the reaction of **1** with *t*-BuLi in THF at -78 ºC. Catalyst, base and **S10** were added after generation and heated. All coupling reactions were performed at 90 mM cubane concentration under argon using 5 mol-% **S15** and 1 equivalent of Ar-I unless stated. [a] 0.33 equivalents **S10** added.

Certain key differences indicating the higher activity of the NHC-catalyst system with relation to the classical systems employed previously were nevertheless observed. Whilst with the standard Pd-phosphine catalysts there appeared to be a significant thermal effect with transmetallation/decomposition typically requiring elevated temperatures; the PdPEPPSI-catalyzed transformation is temperature independent as both Negishi and Suzuki-Miyaura conditions led to decomposition at room temperature as well as when the reaction was performed at -55 °C for just three hours. Similarly, transmetallation and decomposition of the stannylcubane complex proceeded at room temperature. The nature of the additives is also less crucial when utilizing **S15**. The presence of NMP in the Negishi or Stille reaction, which was previously a key component required for the catalytic decomposition, was unnecessary when using **S15** as the catalyst system. The pronounced effect regarding the nature of the boron component in the Suzuki-Miyaura appears to be practically non-

existent when using **S15**. Only when performing the reaction at -55 °C for a short time period was any deviation between the reactivity of **11** and **12** observed.

The decomposition of the cubane systems at -55 °C severely limits further analysis of the process. With the conditions discussed in the previous sections it was theorized that a thermal component may be involved in the decomposition pathway – indicating that if transmetallation could be achieved at lower temperatures reductive elimination and therefore cross-coupling may become competitive. The observed decomposition at low temperatures proves this assumption false, however. While proving that transmetallation can be achieved at much milder conditions it now also appears likely that the decomposition of the Pd-cubane complex is a favorable one both thermodynamically and kinetically and no avenues for trapping or observing this complex appear viable. The conclusion on the basis of the entire study is therefore that, after transmetallation but prior to reductive coupling, the palladium center is catalyzing a sigma-sigma bond migration in an effort to relieve the ring strain of the cubane scaffold. In a departure from such systems which have been previously reported,[5-7] this rearranged intermediate must then be undergoing further decomposition, leading to volatile organic fragments or long chain alkanes and ethers unidentifiable by spectroscopic analysis. The stability of the unactivated, iodinated, cubane scaffold to all of the above conditions has been established and no such decomposition process was observed in the trial couplings of halogenated cubanes previously. The present process must therefore require highly nucleophilic cubane systems. The failure to achieve any cross-coupling reaction with any of the various Pd-catalyzed processes proved a significant disappointment. It does not seem likely that any palladium-catalyzed cross-couplings of cubane scaffolds are viable synthetic pathways. While compelling evidence for the transmetallation of cubane nucleophiles was obtained in all cases, the exact nature of the decomposition products of this complex could not be determined. Ideally, the nature of this Pd-cubane intermediate would be determined, however, no facile way to achieve this could be envisaged and further investigations were deemed beyond the scope of the present synthetic study.

2. General experimental information

All commercial chemicals used were supplied by Sigma Aldrich, Frontier Scientific, Inc. and Tokyo Chemical Industry and used without further purification unless otherwise stated. Anhydrous THF was obtained by drying over sodium/benzophenone, followed by distillation. Silica gel 60 (Merck, 230-400 mesh) or aluminium oxide (neutral, activated with 6.5 % H_2O, Brockmann Grade III) were used for flash column chromatography. Analytical thin layer chromatography was carried out with silica gel 60 (fluorescence indicator F_{254}; Merck) or aluminium oxide 60 (neutral, F_{254}; Merck) plates and stained with vanillin or *p*-anisaldehyde solutions where necessary. Melting points are uncorrected and were measured with a Stuart SP-10 melting point apparatus. NMR spectra were recorded using Bruker DPX 400 (400.13 MHz for ^1H NMR and 100.61 MHz for ^{13}C NMR), Bruker AV 600 (600.13 MHz for ^1H NMR and 150.90 MHz for ^{13}C NMR), Bruker AV 400 (400.13 MHz for ^1H NMR, 128.41 MHz for ^{11}B NMR, 162.02 MHz for ^{31}P NMR and 149.24 MHz for ^{119}Sn NMR) or Agilent MR400 (400.13 MHz for ^1H NMR and 100.61 MHz for ^{13}C NMR) instruments. Chemical shifts are given in ppm and referenced either to the deuterium peak in the NMR solvent or TMS used as an internal standard. The assignment of the signals was confirmed by 2D spectra (COSY, HMBC, HSQC). ESI mass spectra were acquired in positive and negative modes as required, using a Micromass time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC or a Bruker micrOTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC. APCI experiments were carried out on a Bruker micrOTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe in positive or negative modes. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF) in positive mode at 70eV. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. CHN analyses were performed on an Exeter Analytical CE 440 elemental analyser fitted with a Varian 55B SpectraAA atomic absorption spectrometer and are reported when detected within a 0.4 % error margin.

3. Experimental

Dimethyl cubanyl-1,4-dicarboxylate and its precursors were synthesized as per Tsanaktsidis' method.[9] This was converted to methyl 4-iodocubanyl-1-carboxylate **S5** and reduced through known procedures.[3] Iodocubane **S6**[4] was synthesized by Eaton's procedures from appropriate precursors. Methyl 1-bromocubanyl-4-carboxylate **S1** and its precursors were synthesized as described by Klunder and Zwanenburg.[1] 1-Bromo-4-iodocubane **S4** was synthesized *via* Moriarty's process[2] and converted into **2** through standard methodologies.[10] All compounds and intermediates had analytical data consistent with literature values.

4. Copies of NMR spectra for all new compounds

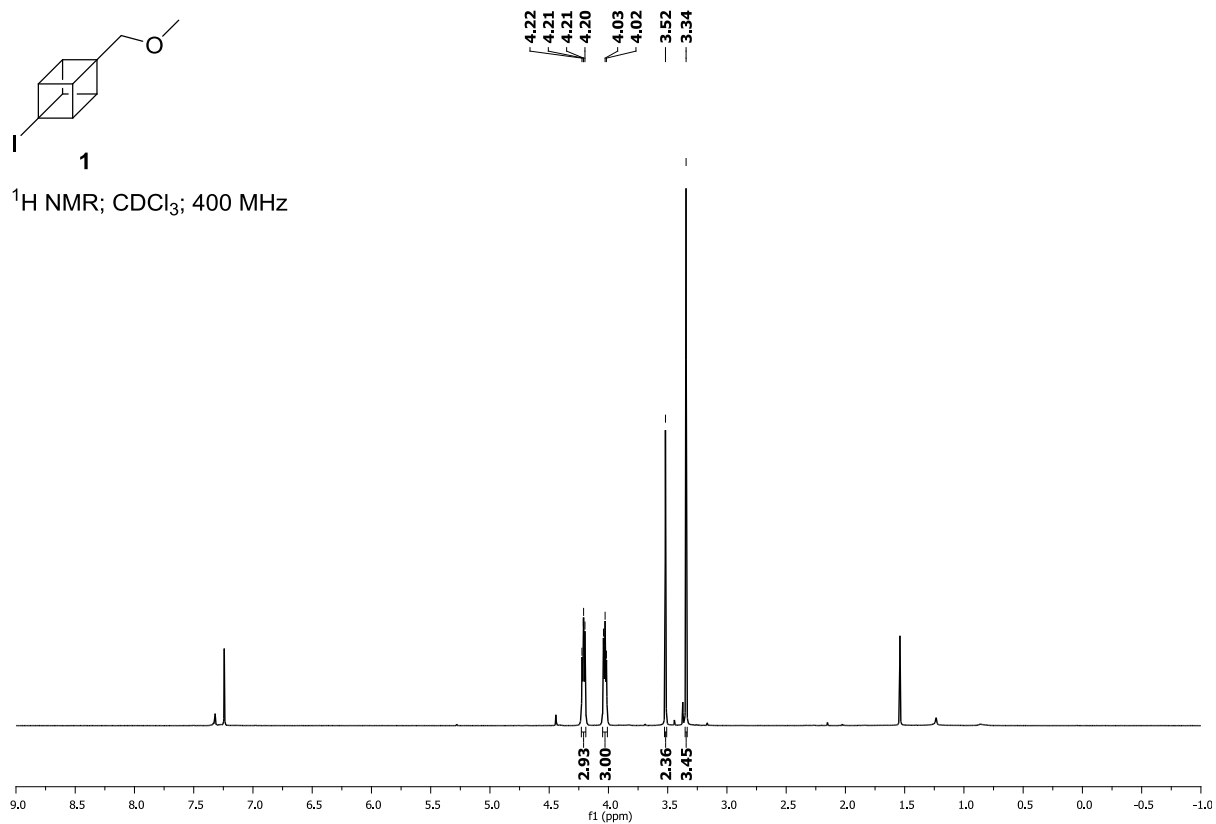**Figure S1:** ^{1}H NMR spectrum of **1** in CDCl$_3$.

^{1}H NMR; CDCl$_3$; 400 MHz

Figure S2: ^{13}C NMR spectrum of **1** in CDCl$_3$.

^{13}C NMR; CDCl$_3$; 100 MHz
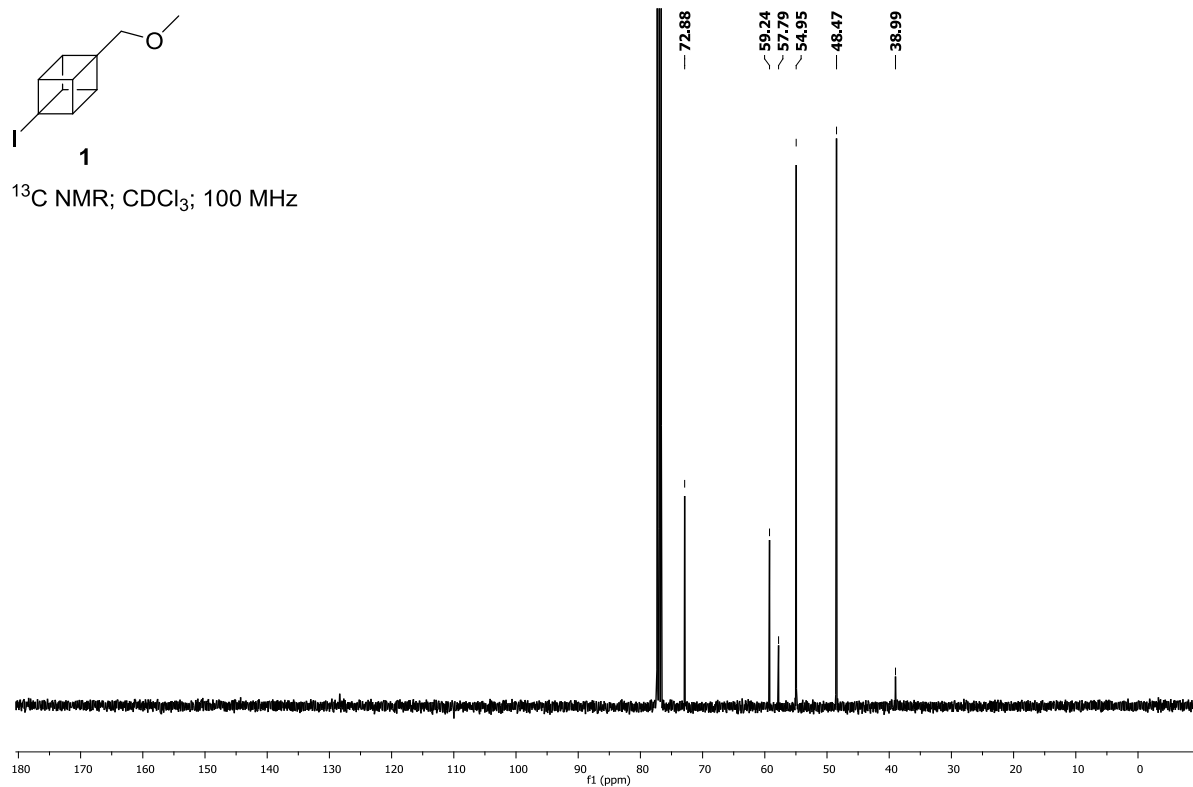
Figure S3: ^{1}H NMR spectrum of **3a** in CDCl$_3$.

3a
^{1}H NMR; CDCl$_3$; 400 MHz

4.01
4.00
3.99
3.98
3.97
3.97
3.96
3.96
3.89
3.88
3.87
3.86
3.85
3.85
3.84
3.48
3.33

0.94
6.00
2.31
3.57

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
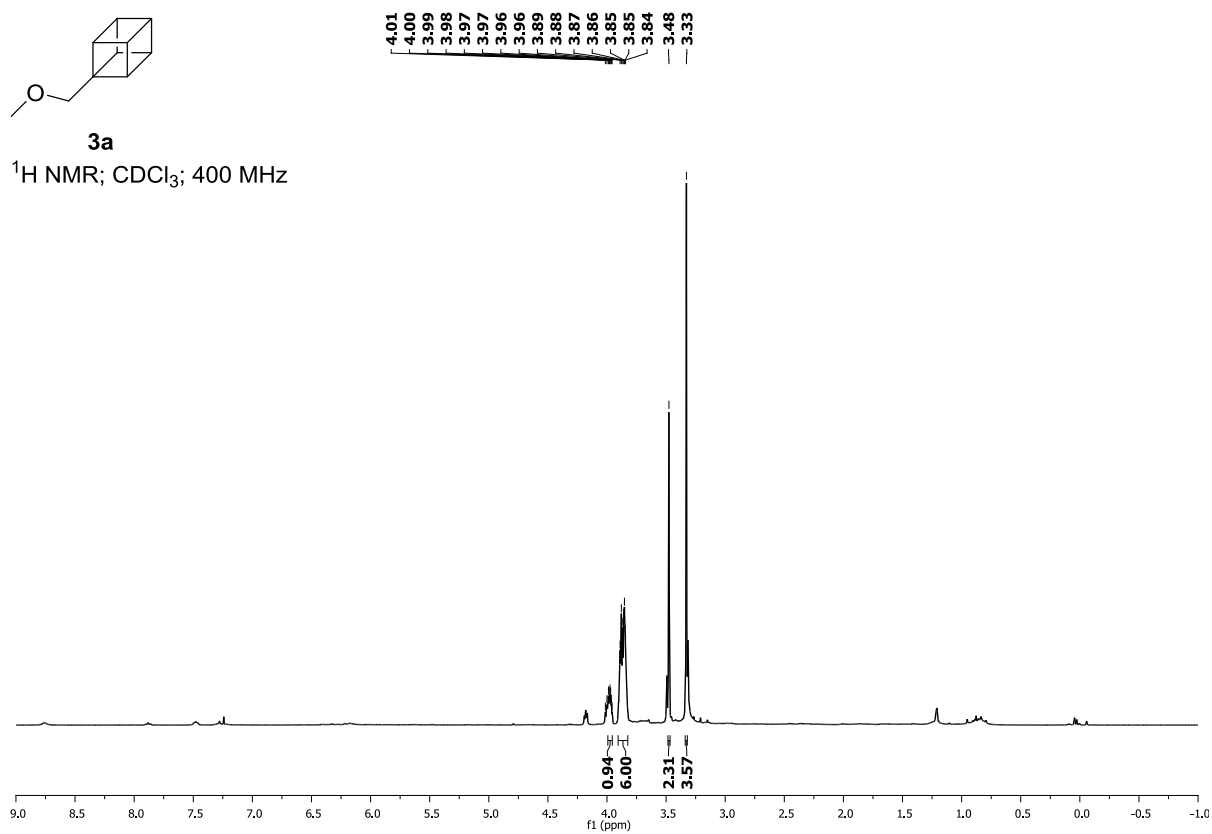
Figure S4: ^{13}C NMR spectrum of **3a** in CDCl$_3$.

3a
^{13}C NMR; CDCl$_3$; 100 MHz

73.6
59.1
57.1
48.4
47.5
44.6

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
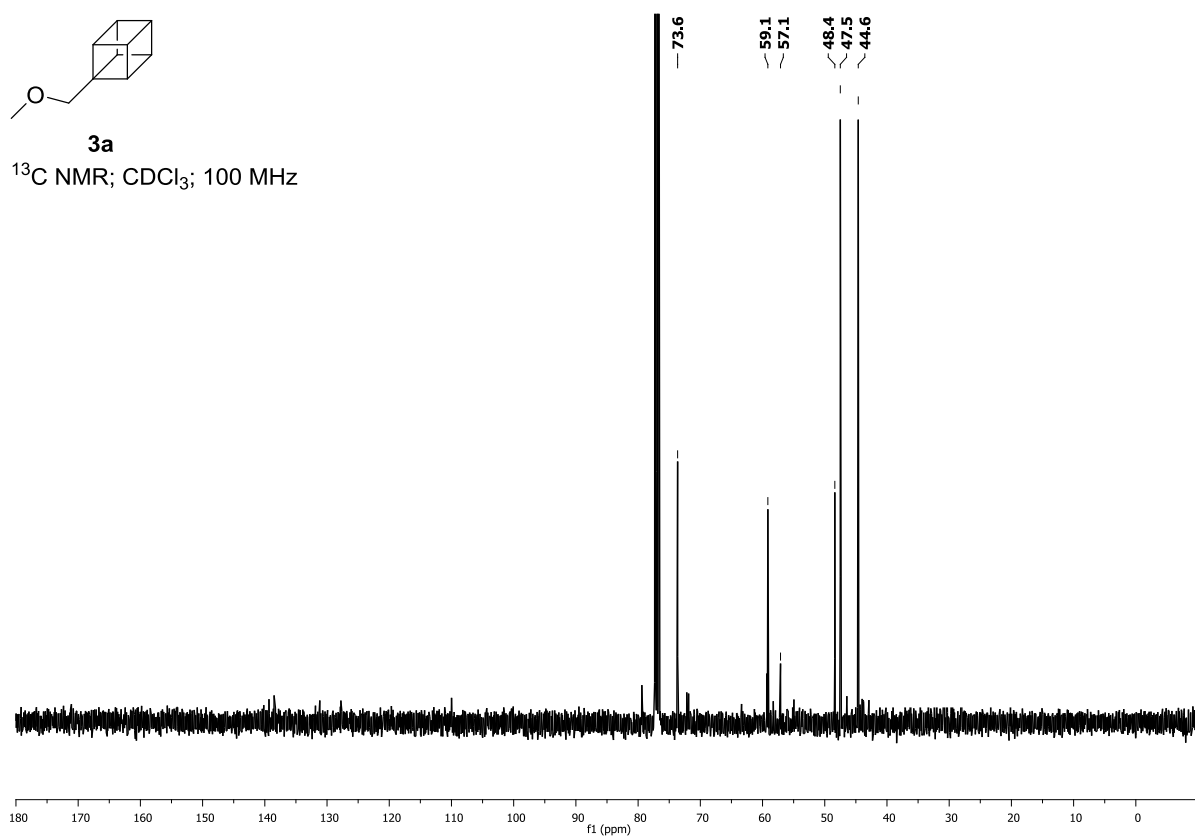
Figure S5: ^{1}H NMR spectrum of **5** in CDCl$_3$.

C$_6$H$_{13}$

5

^{1}H NMR; CDCl$_3$; 600 MHz

3.74
3.73
3.72
3.64
3.63
3.55
3.40

1.59
1.58
1.57
1.28
0.92
0.91
0.90

3.00
3.09
1.97
2.93

2.32
8.81
3.60

f1 (ppm)
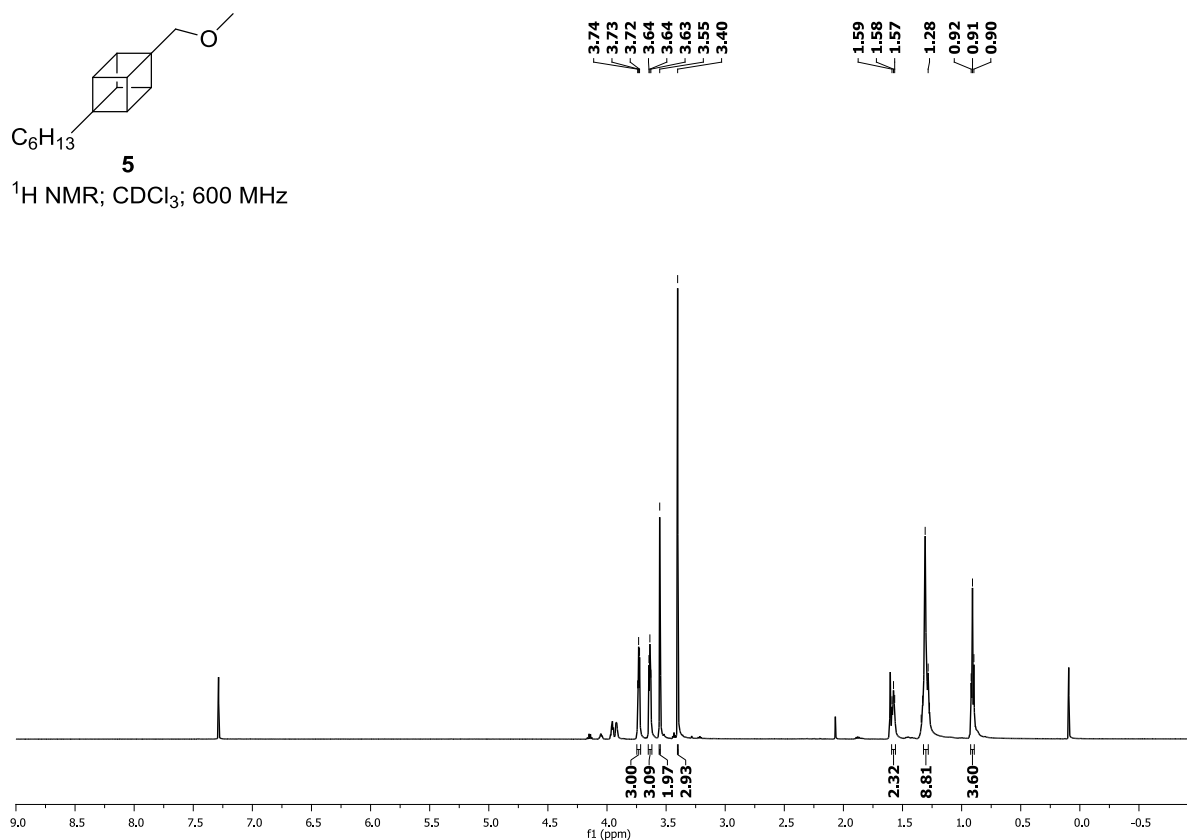
Figure S6: ^{13}C NMR spectrum of **5** in CDCl$_3$.

C$_6$H$_{13}$

5

^{13}C NMR; CDCl$_3$; 150 MHz

73.7

59.0
57.7

47.4
45.3
43.9

32.9
31.8
29.4

23.8
22.5

13.9

f1 (ppm)
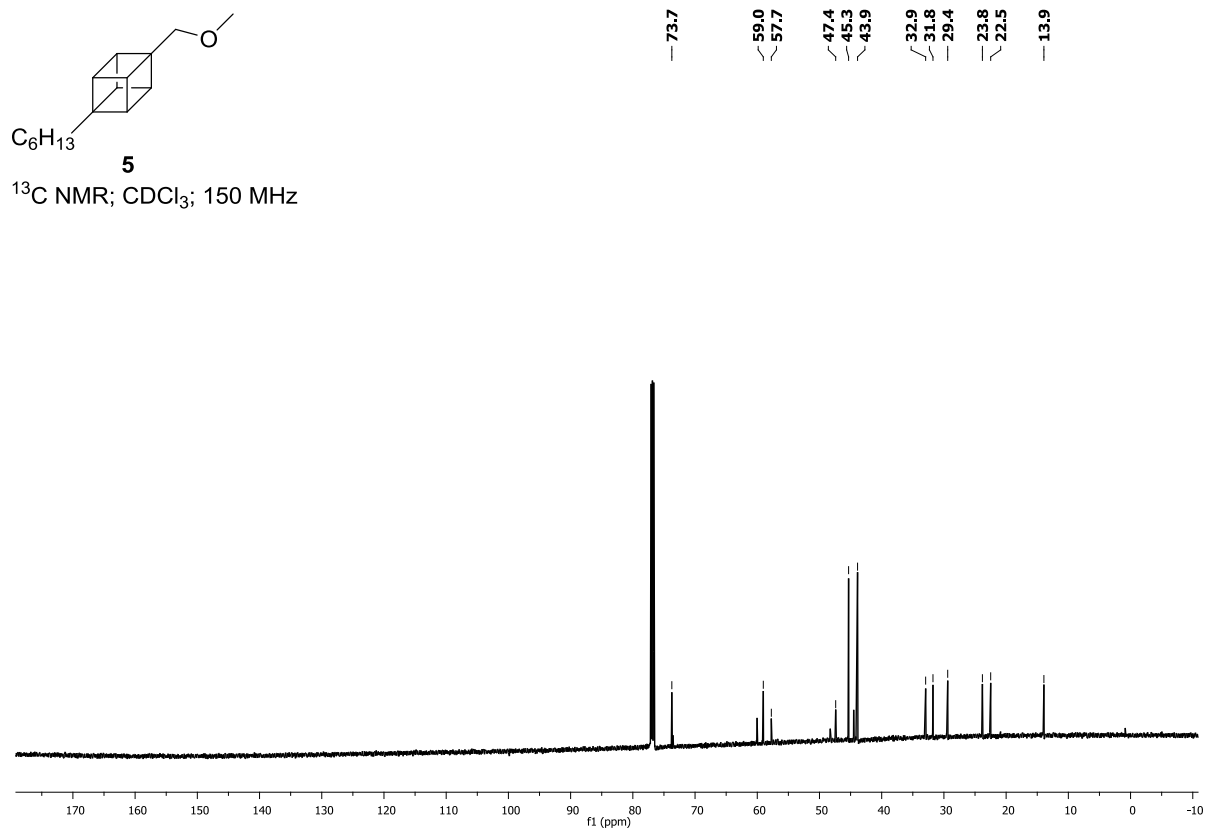
Figure S7: ^{1}H NMR spectrum of **6** in CDCl$_3$.

3.69
3.68
3.60
3.59
3.51
3.36

1.54
1.53

1.24

0.88
0.86
0.84

C$_{14}$H$_{29}$

6

^{1}H NMR; CDCl$_3$; 400 MHz

2.87
3.00
2.05
3.31

2.26

25.21

3.35

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
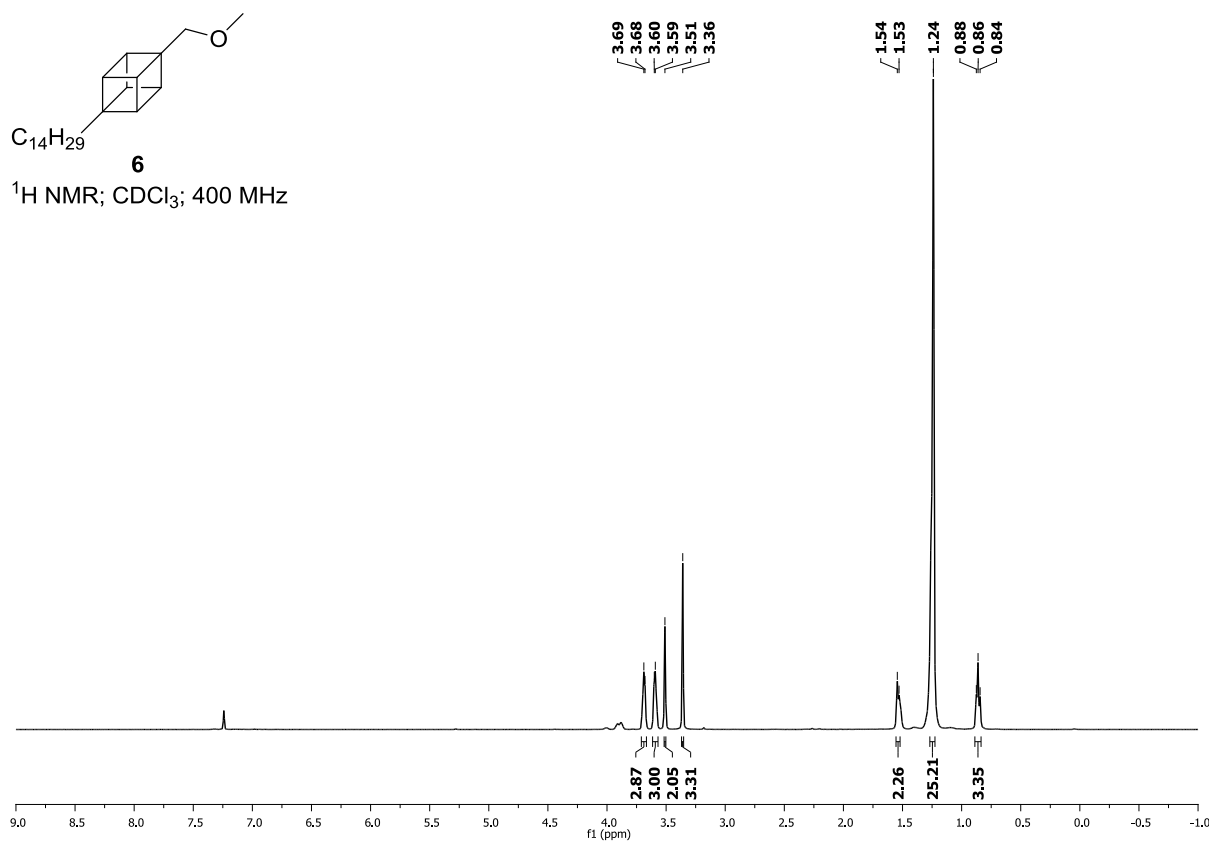
Figure S8: ^{13}C NMR spectrum of **6** in CDCl$_3$.

73.8

59.2
57.8

47.5
45.4
44.0

29.9
29.7
29.6
29.3

24.0
22.7

14.1

C$_{14}$H$_{29}$

6

^{13}C NMR; CDCl$_3$; 100 MHz

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
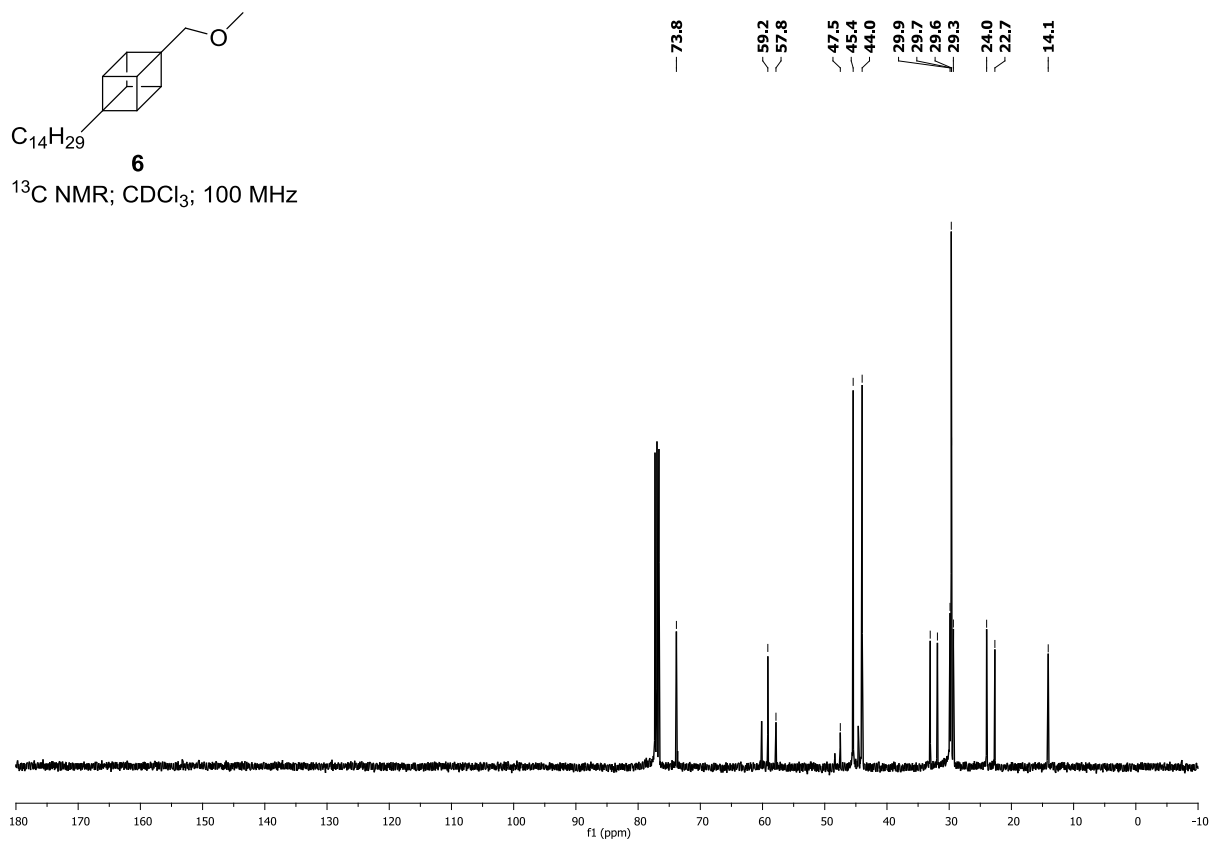
Figure S9: ^{1}H NMR spectrum of **7** in CDCl$_3$.

^{1}H NMR; CDCl$_3$; 400 MHz
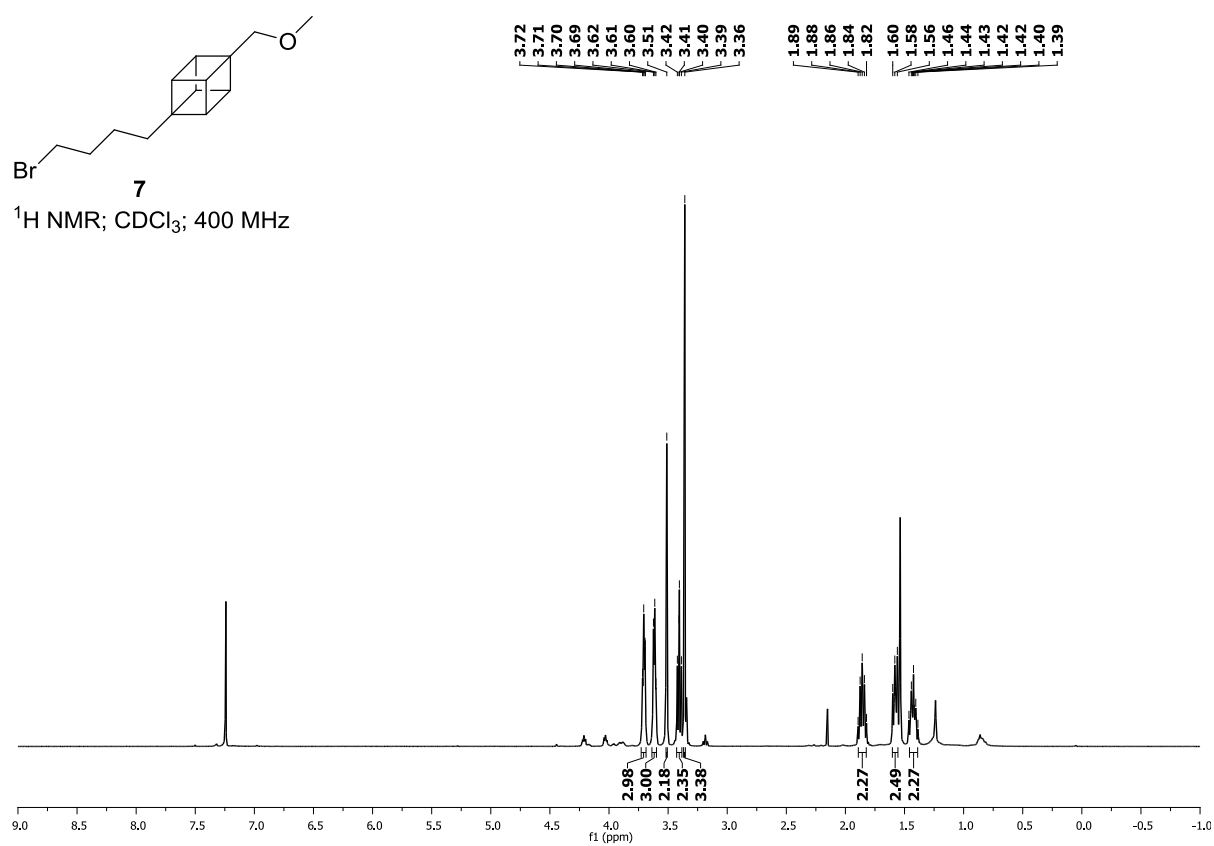
Figure S10: ^{13}C NMR spectrum of **7** in CDCl$_3$.

^{13}C NMR; CDCl$_3$; 100 MHz
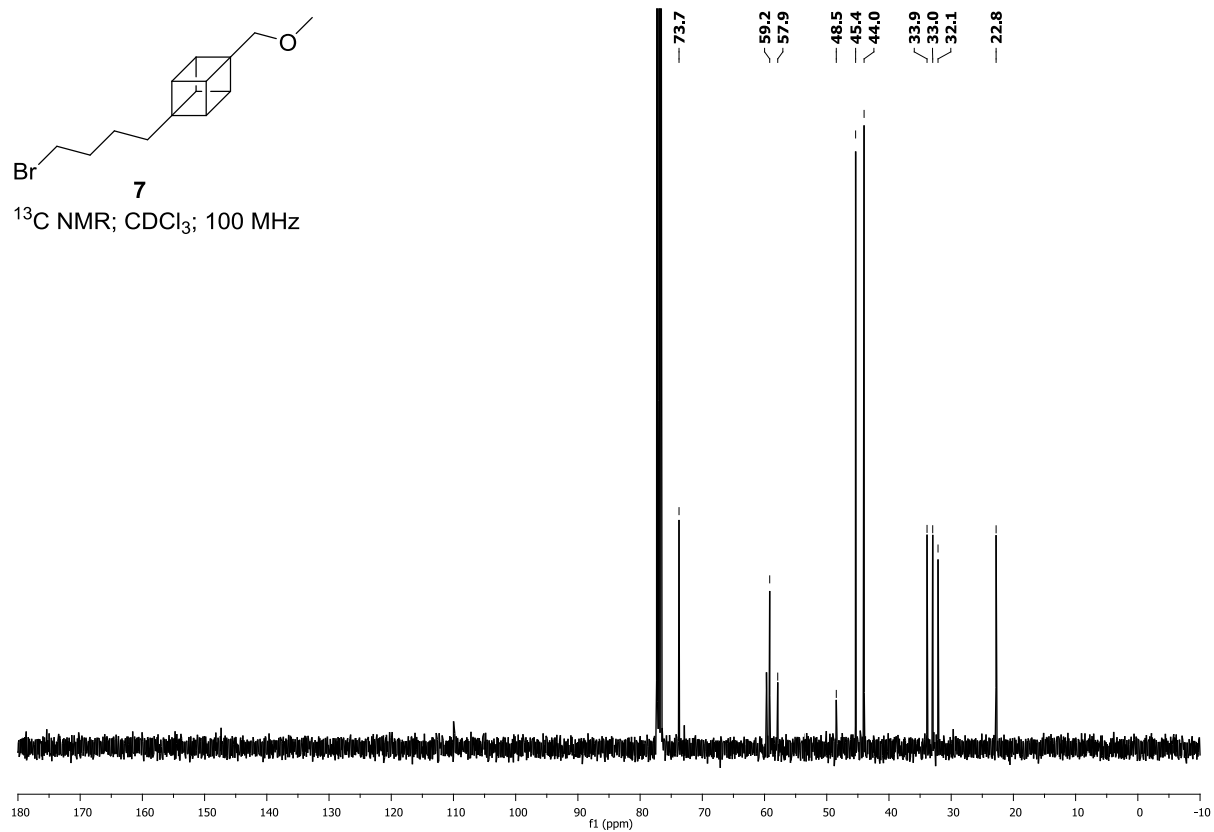
Figure S11: ^1H NMR spectrum of **11** in CDCl$_3$.

^1H NMR; CDCl$_3$; 400 MHz
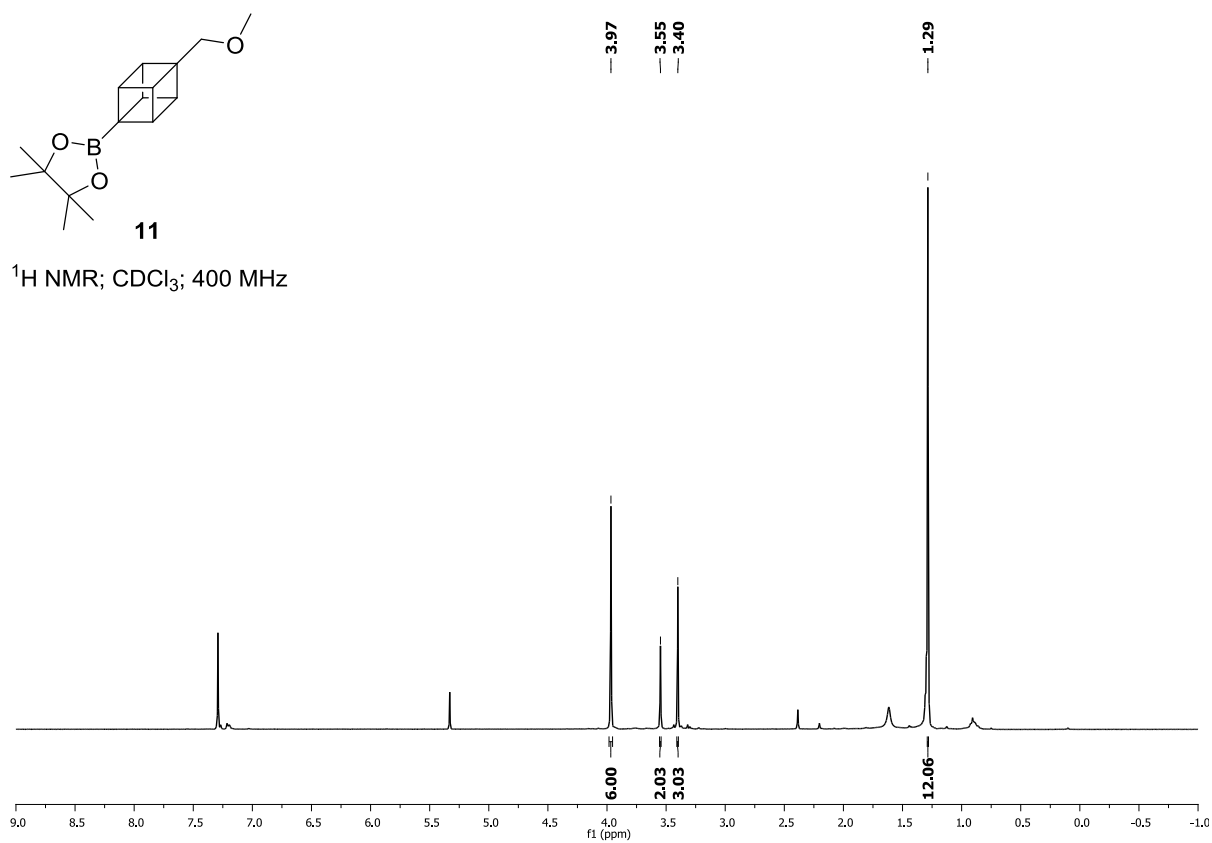
Figure S12: ^{13}C NMR spectrum of **11** in CDCl$_3$.

^{13}C NMR; CDCl$_3$; 100 MHz

S19

Figure S13: ^{11}B NMR spectrum of **11** in CDCl$_3$.

11

^{11}B NMR; CDCl$_3$; 128 MHz

— 22.53

Figure S14: ^{1}H NMR spectrum of **13** in CDCl$_3$.

13

^{1}H NMR; CDCl$_3$; 400 MHz
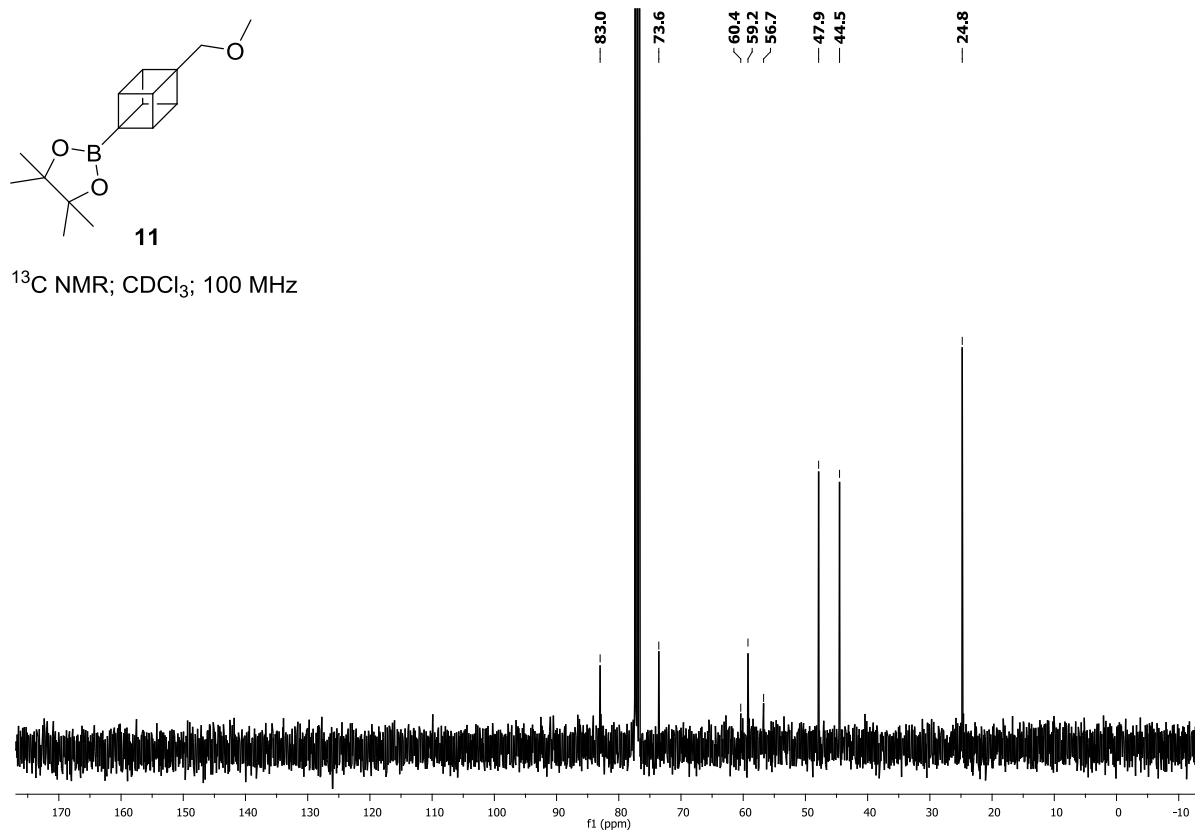
Figure S15: ^{13}C NMR spectrum of **13** in CDCl$_3$.

^{13}C NMR; CDCl$_3$; 100 MHz

13

(C$_4$H$_9$)$_3$Sn

73.5
59.1
56.4
50.0
49.0
44.6
29.3
27.2
13.7
8.6
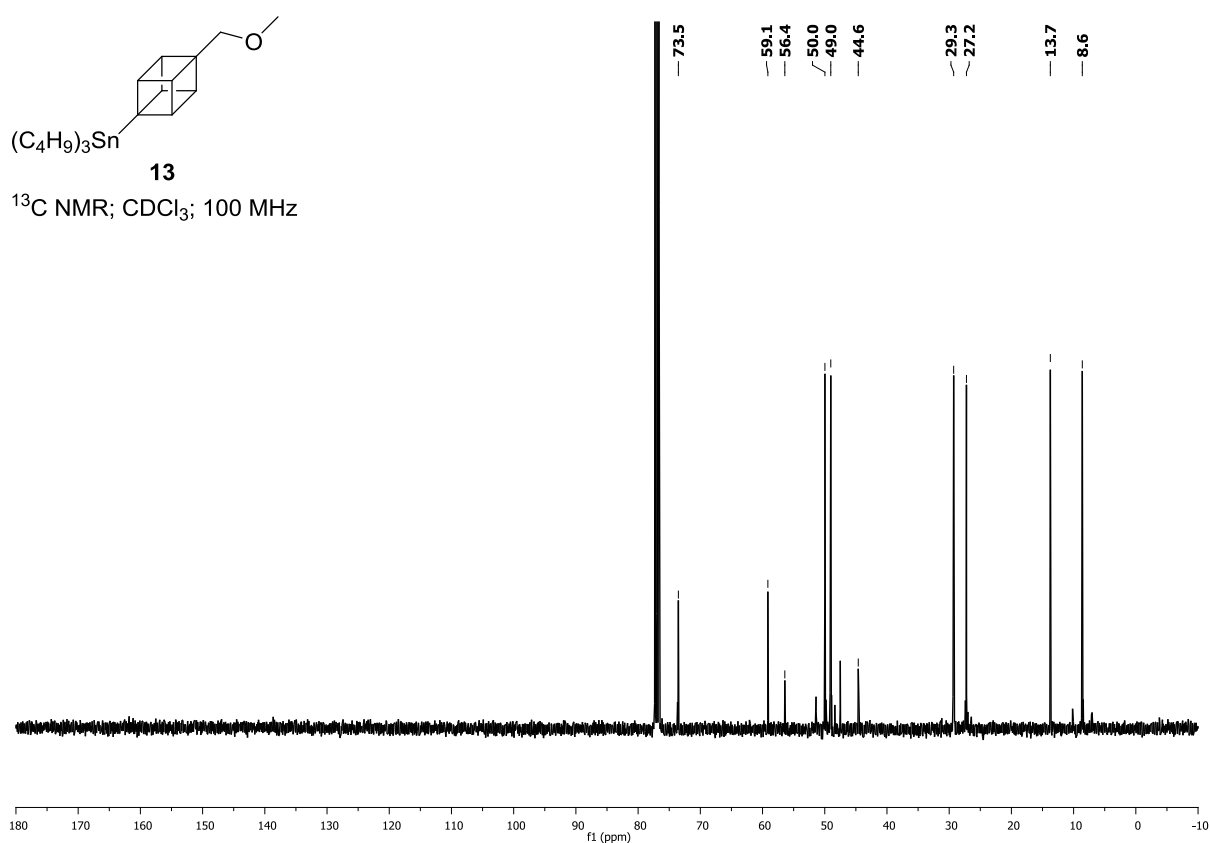
Figure S16: ^{119}Sn NMR spectrum of **13** in CDCl$_3$.

^{119}Sn NMR; CDCl$_3$; 148 MHz

13

(C$_4$H$_9$)$_3$Sn

-7.53
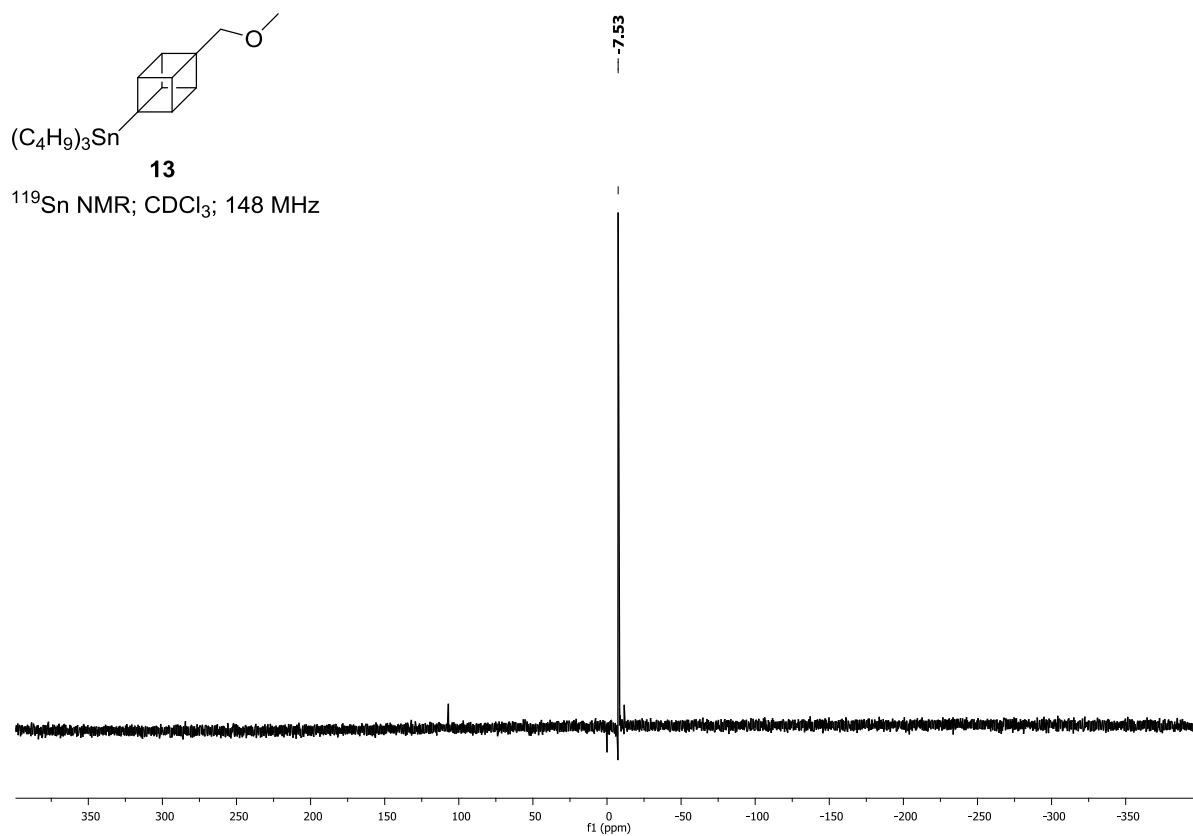
Figure S17: ^{1}H NMR spectrum of **15b** in CDCl$_3$.

7.66
7.65
7.65
7.63
7.56
7.55
7.54
7.50
7.49
7.48
7.48
7.47
7.47

4.27
4.26
4.26
4.25
4.24

4.00
3.99

3.54
3.38

15b
^{1}H NMR; CDCl$_3$; 600 MHz

3.99
2.10
4.17

3.10
3.00

2.01
2.97
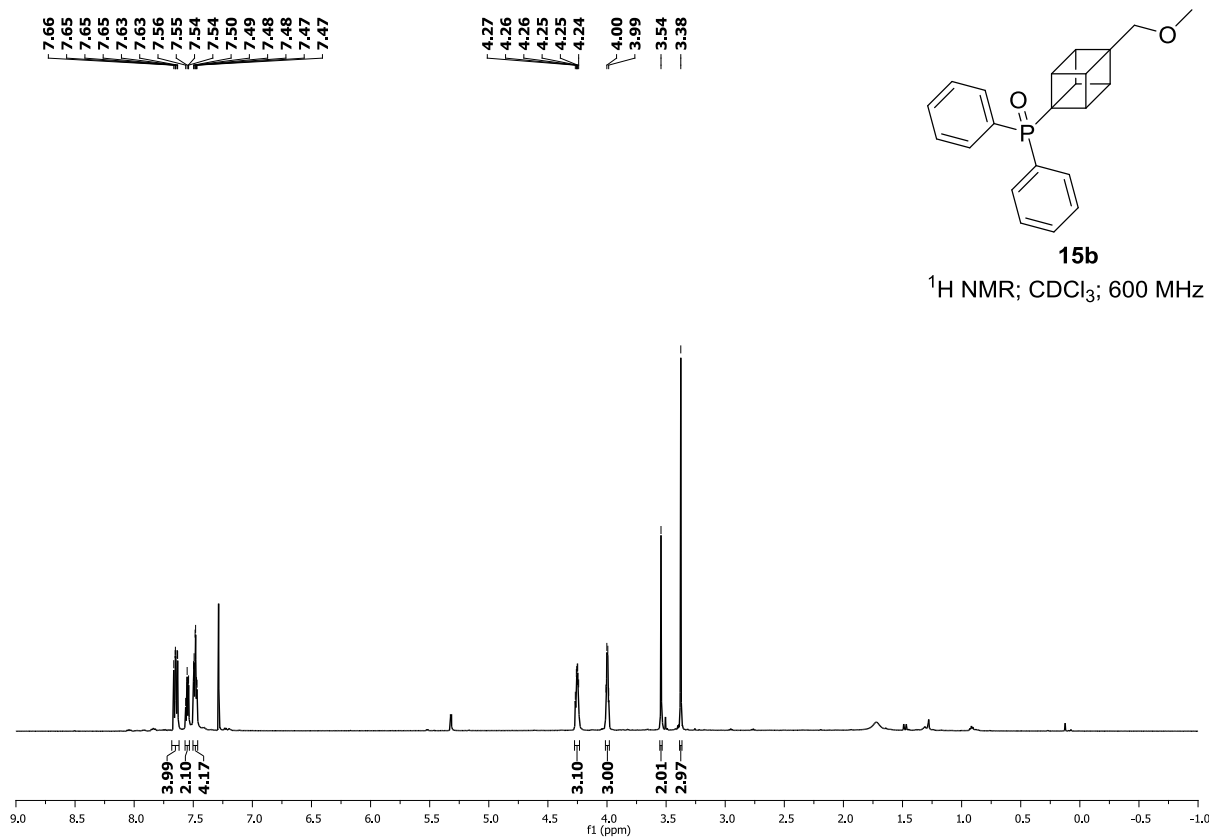
Figure S18: ^{13}C NMR spectrum of **15b** in CDCl$_3$.

132.1
131.7
131.7
131.1
130.9
130.8
128.7
128.5

72.7
72.7

59.2
57.4
57.4

52.7
46.7
46.6
44.8
44.8

15b
^{13}C NMR; CDCl$_3$; 100 MHz
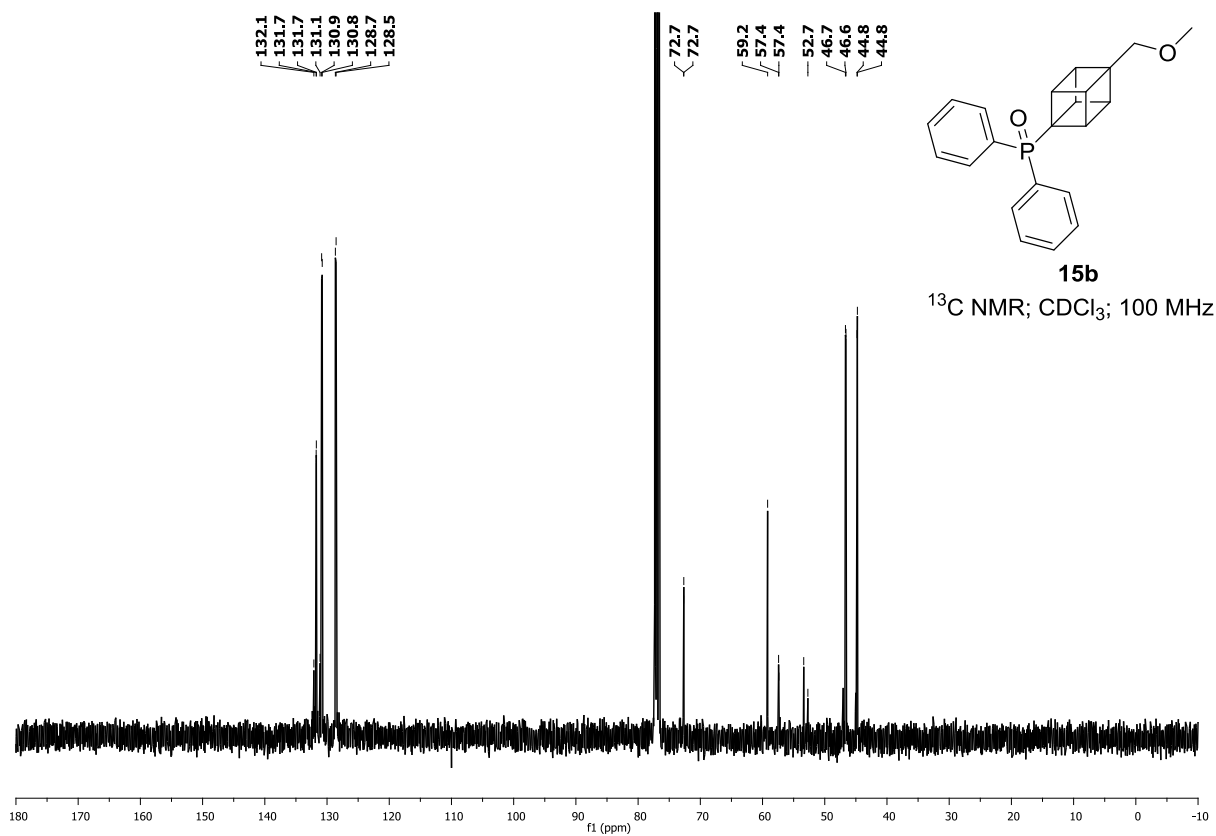
Figure S19: ^{31}P NMR spectrum of **15b** in CDCl$_3$.

15b
^{31}P NMR; CDCl$_3$; 162 MHz

— 25.70

70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15
f1 (ppm)
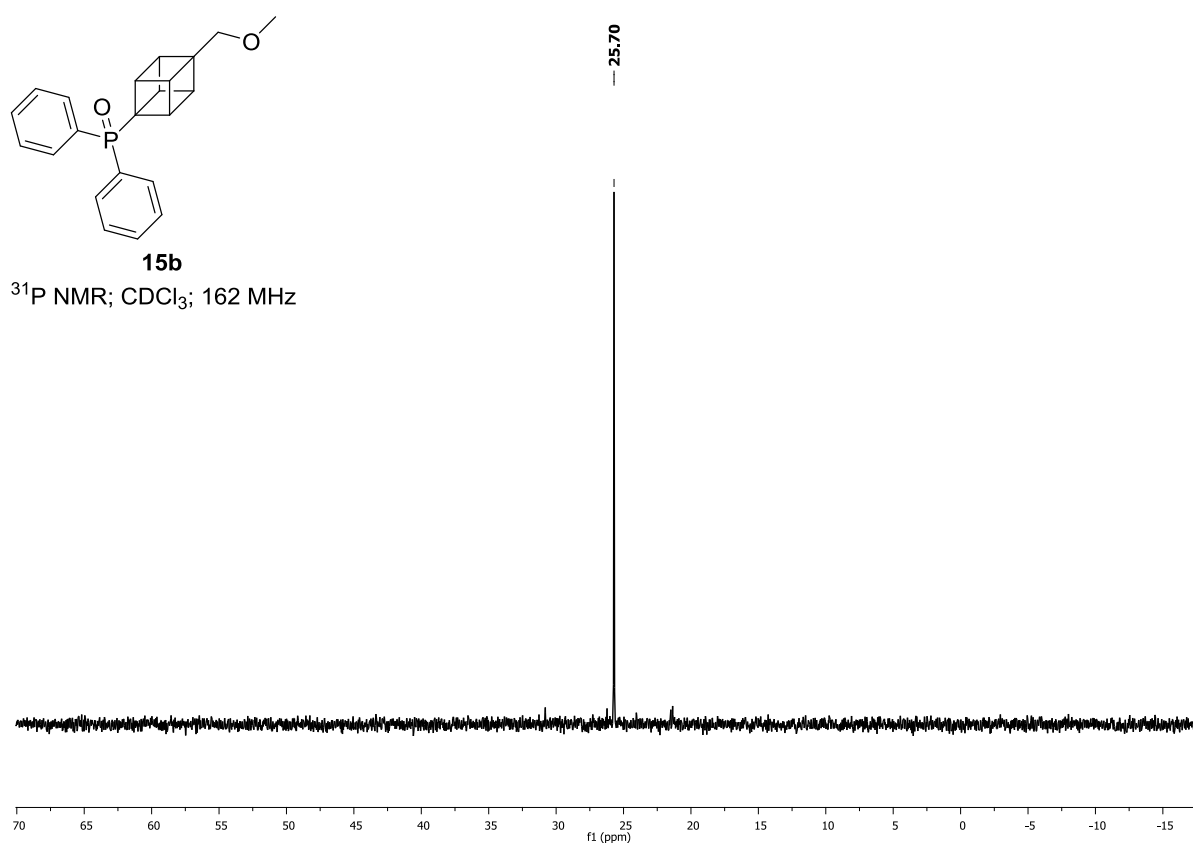
Figure S20: IR spectrum (neat) of **15b**.

%T

3055.80cm-1
2980.82cm-1
2923.80cm-1
2823.24cm-1
1437.02cm-1
1388.17cm-1
1175.50cm-1
1116.83cm-1
1099.77cm-1
924.09cm-1
841.83cm-1
750.32cm-1
722.89cm-1
695.32cm-1

15b
IR spectrum

cm-1
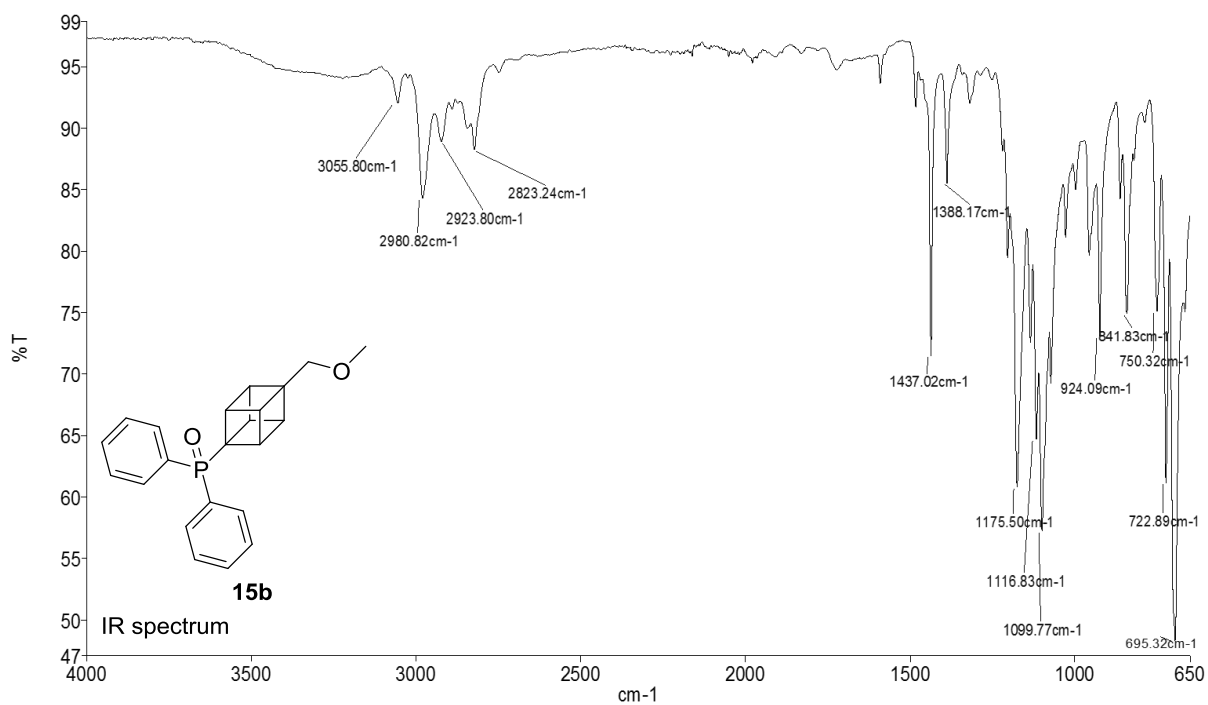
Figure S21: ^{1}H NMR spectrum of **16** in CDCl$_3$.

(H$_3$C)$_3$Si

16

^{1}H NMR; CDCl$_3$; 400 MHz

3.89
3.88
3.87
3.76
3.75
3.73
3.51
3.36
-0.07

3.39
3.00
2.02
3.24
10.39
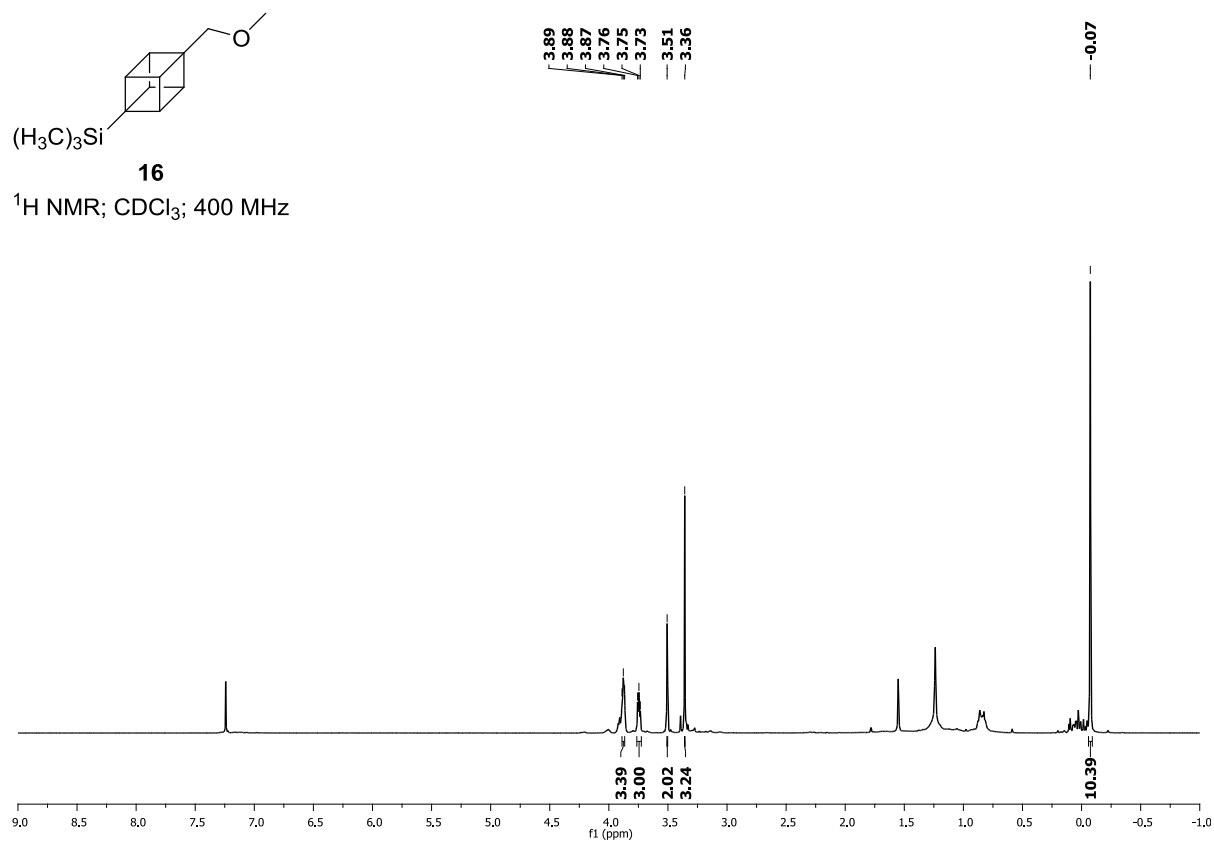
Figure S22: ^{13}C NMR spectrum of **16** in CDCl$_3$.

(H$_3$C)$_3$Si

16

^{13}C NMR; CDCl$_3$; 100 MHz

73.6
59.1
57.5
48.4
47.8
43.4
-4.9
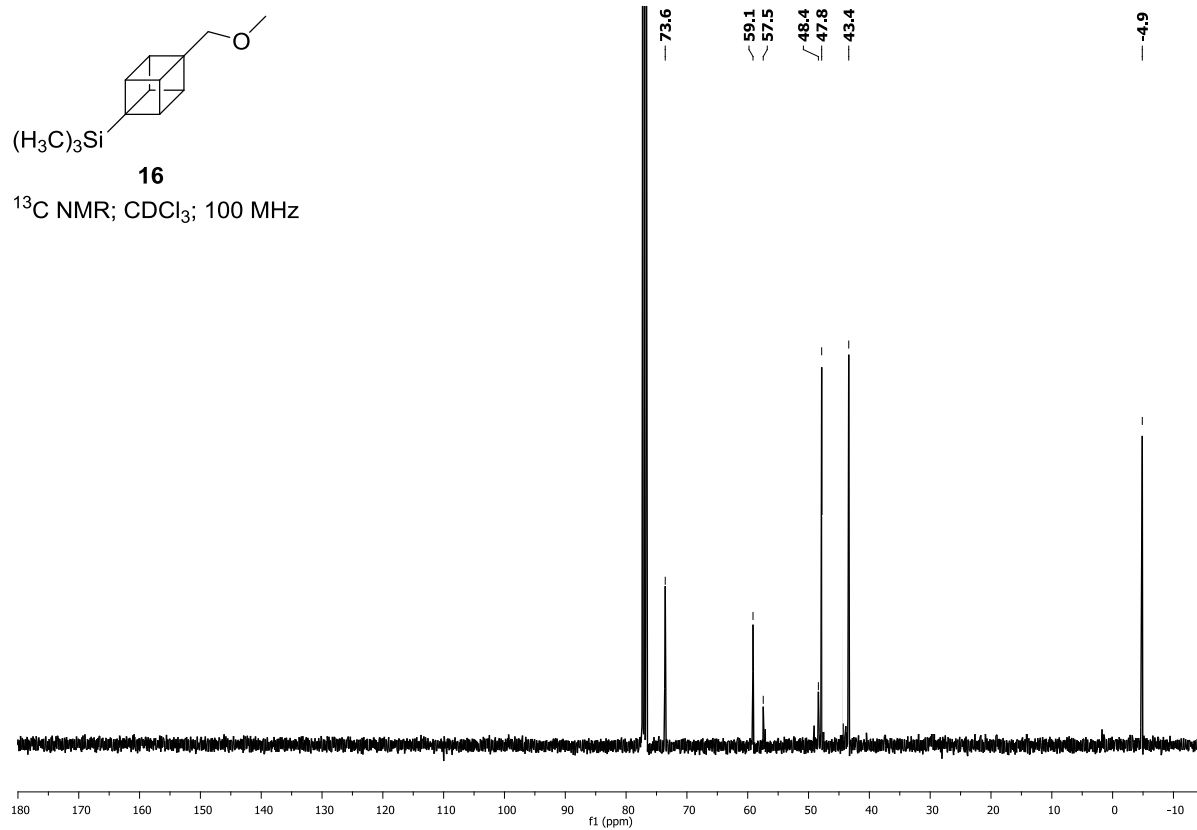
Figure S23: ^{1}H NMR spectrum of **17** in CDCl$_3$.

^{1}H NMR; CDCl$_3$/TMS; 400 MHz
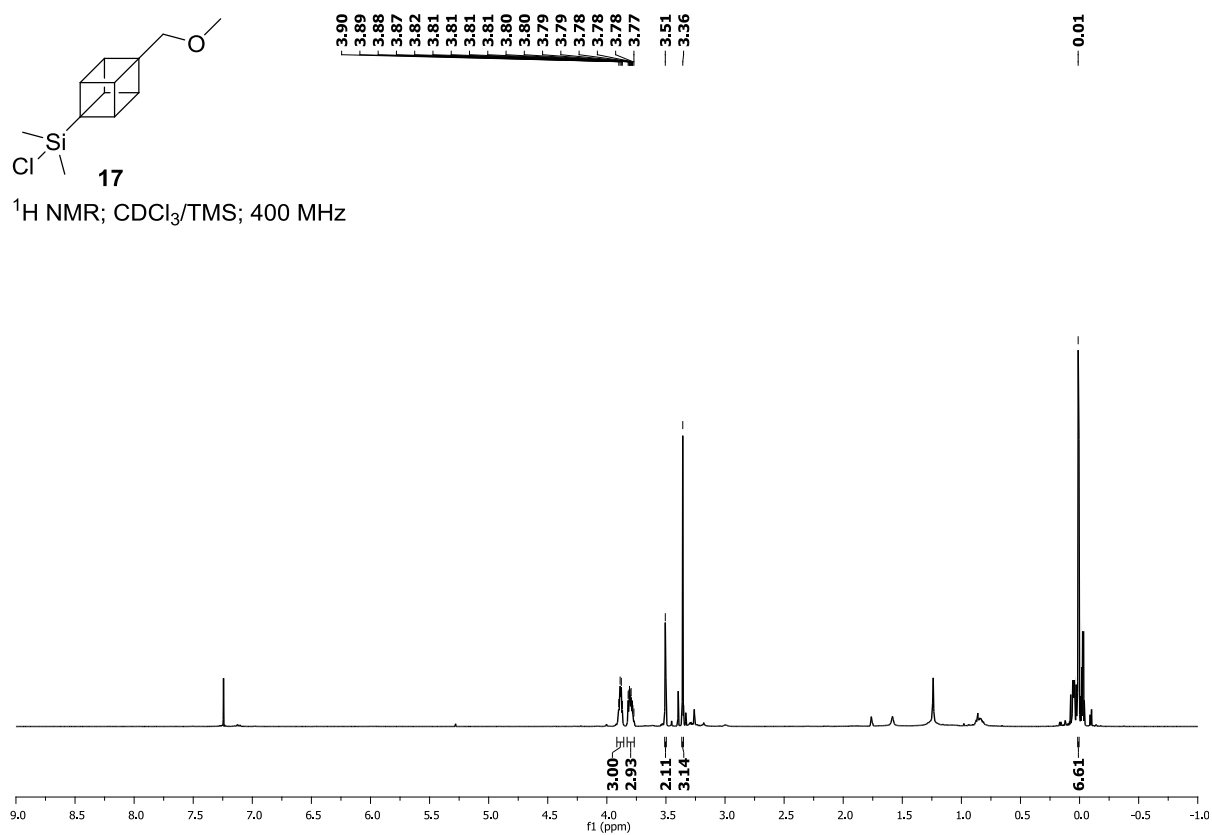
Figure S24: ^{13}C NMR spectrum of **17** in CDCl$_3$.

^{13}C NMR; CDCl$_3$/TMS; 100 MHz
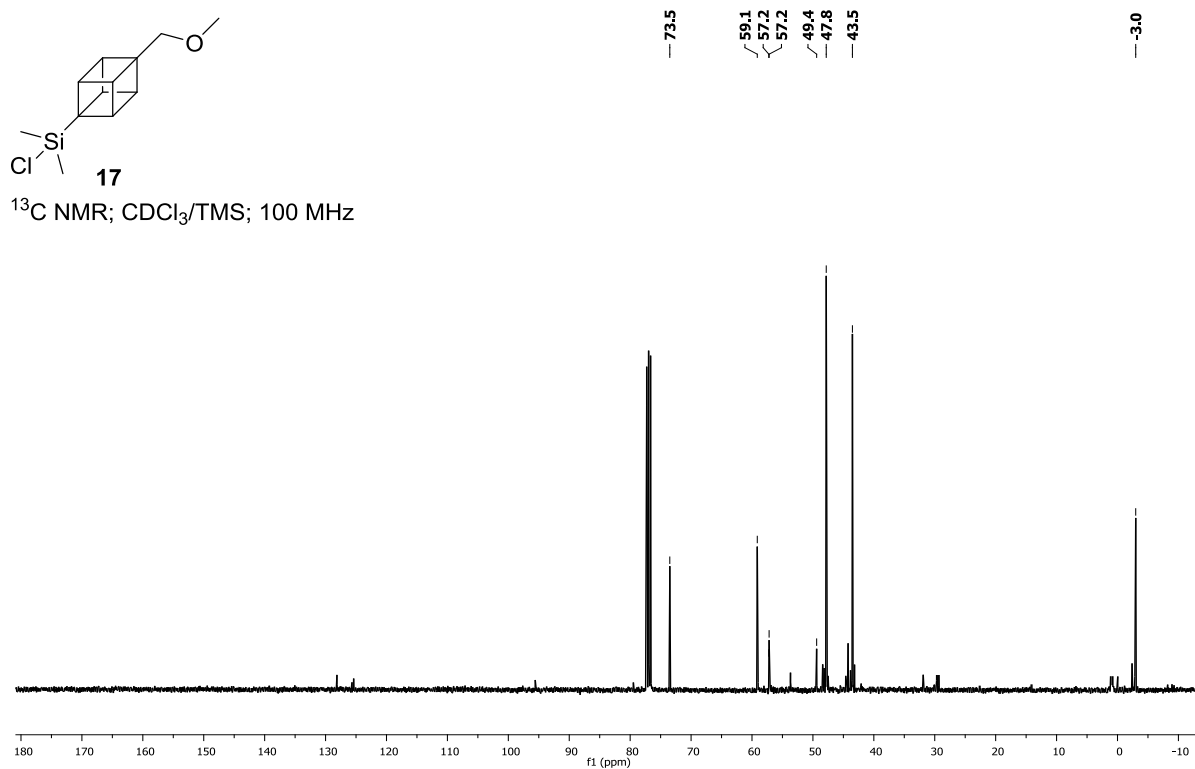
Figure S25: ^{1}H NMR spectrum of **18** in CDCl$_3$.

18

^{1}H NMR; CDCl$_3$; 400 MHz

Figure S26: ^{1}H NMR spectrum of **18** in CDCl$_3$.

18

^{13}C NMR; CDCl$_3$; 100 MHz
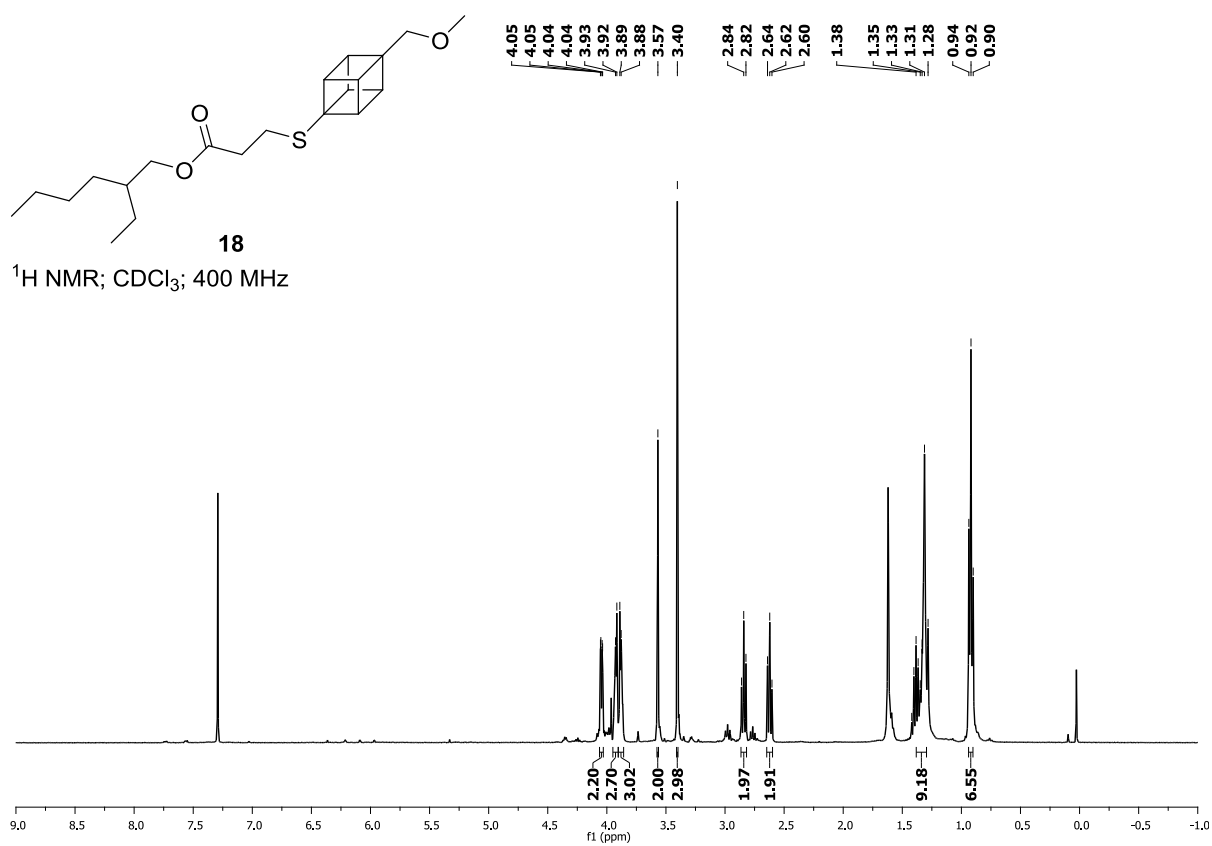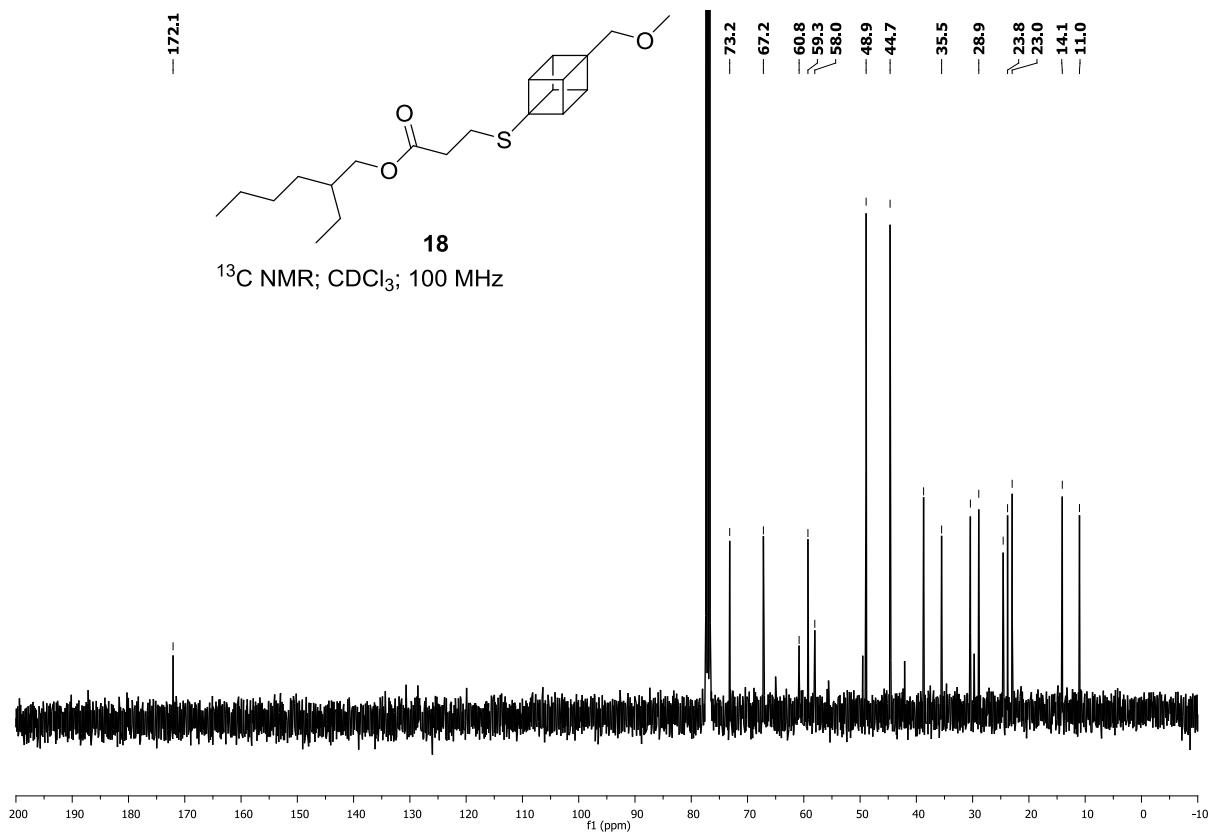
5. Alternate images of crystal structure of 15b
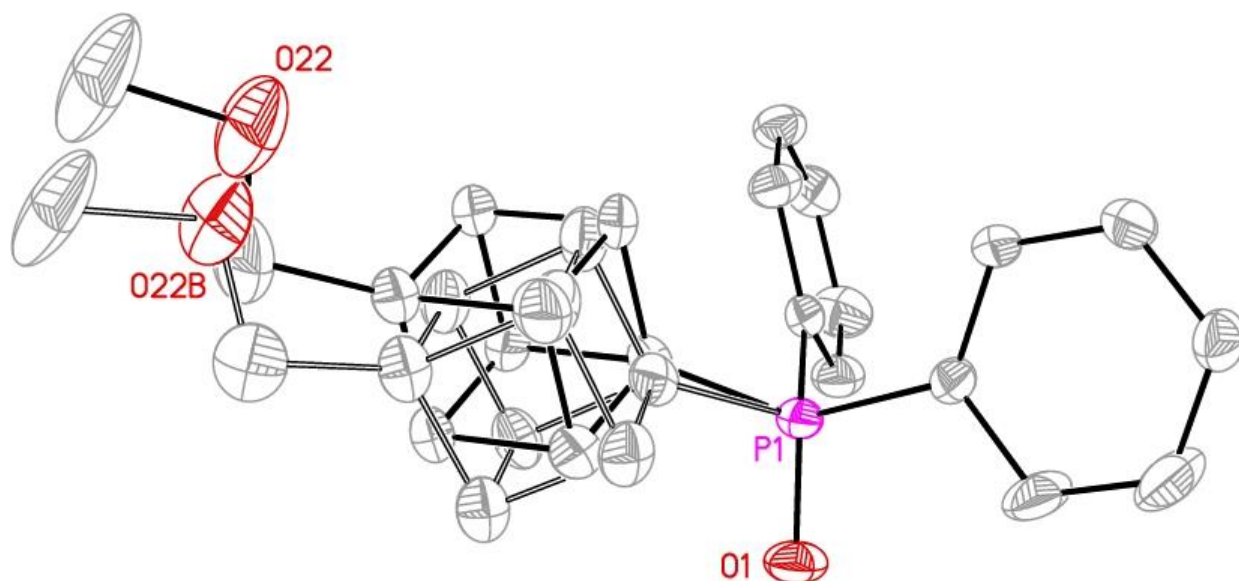
Figure S27: Molecular structure of **15b** (thermal displacement 50%) with both disordered moieties shown (68:32%) Hydrogens omitted for clarity.
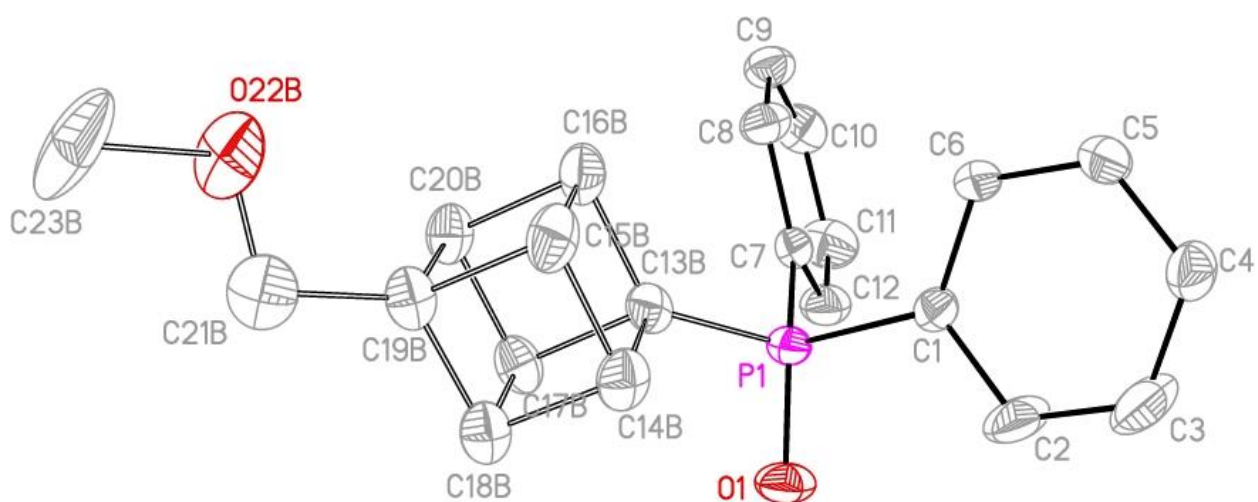

Figure S28: Minor disordered moiety of **15b** (32%). shown with atom labelling. Hydrogens omitted for clarity.
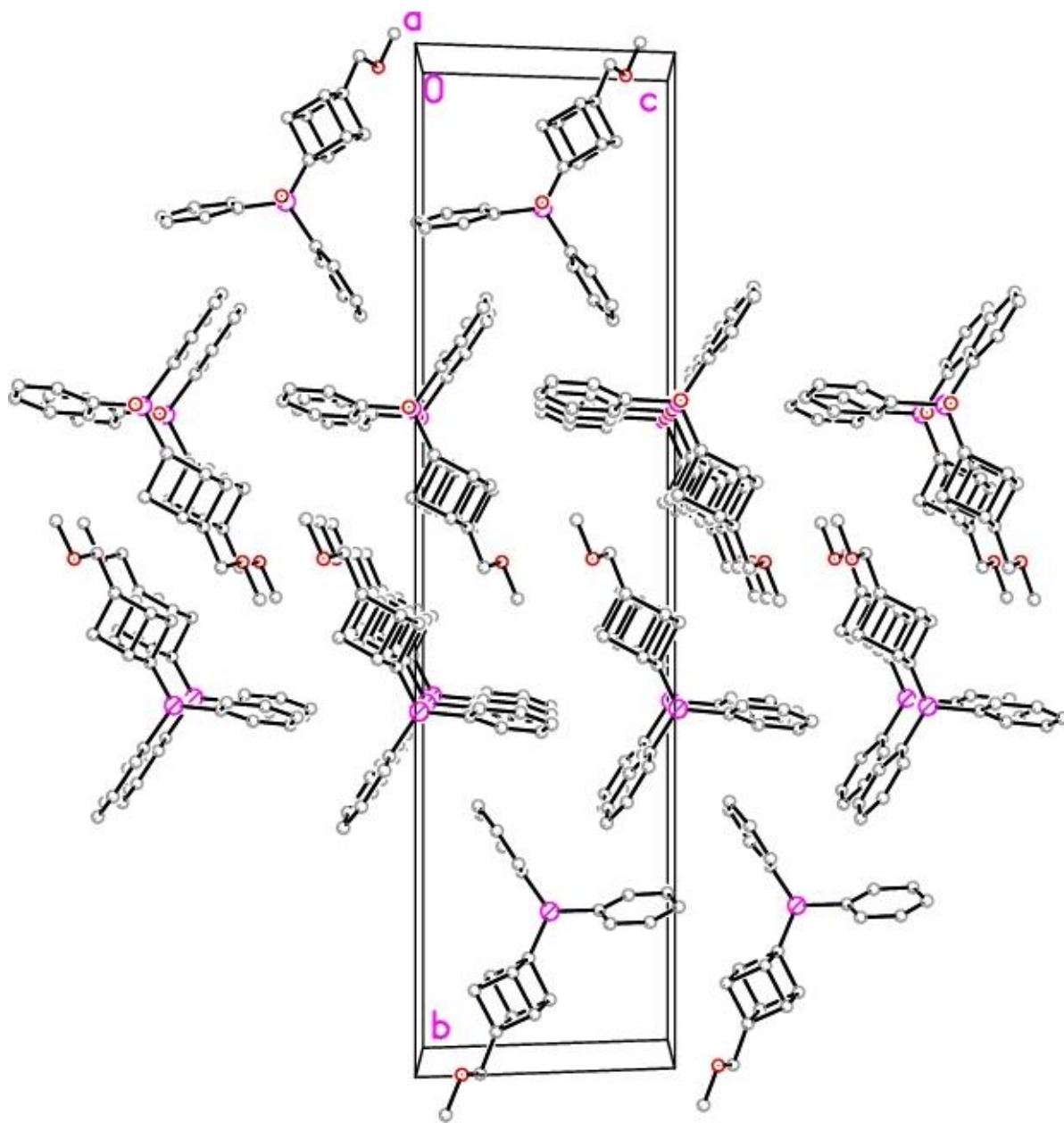
Figure S29: Major disordered moiety packing shown with labels omitted (68%). Hydrogens omitted for clarity.
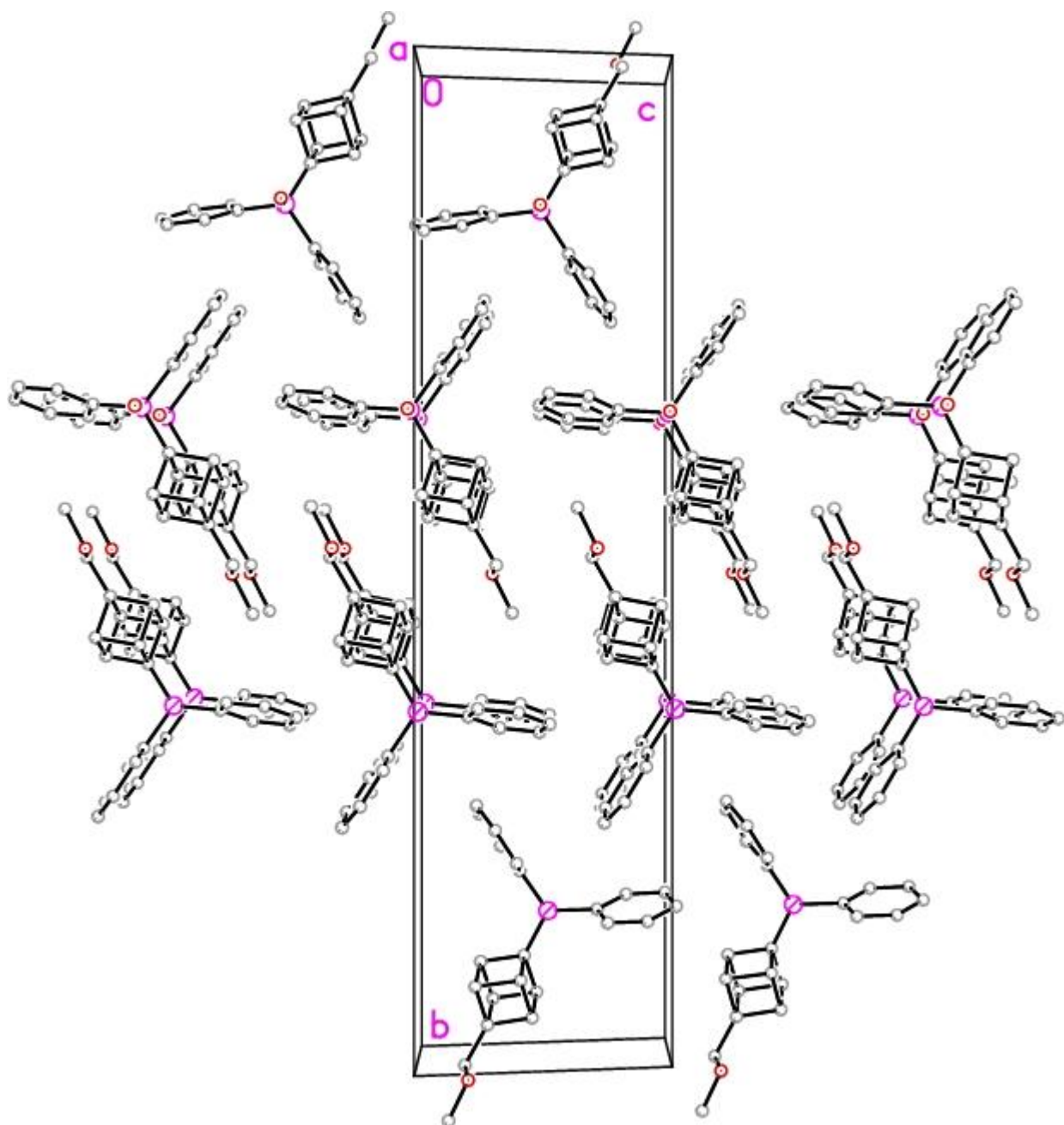
Figure S30: Minor disordered moiety packing shown with labels omitted (32%). Hydrogens omitted for clarity.

6. References

(1) Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1972**, *28*, 4131-4138.
(2) Moriarty, R. M.; Khosrowshahi, J. S.; Dalecki, T. M. *J. Chem. Soc., Chem. Commun.* **1987**, 675-676.
(3) Griffiths, J. R.; Tsanaktsidis, J.; Savage, G. P.; Priefer, R. *Thermochim. Acta* **2010**, *499*, 15-20.
(4) Eaton, P. E.; Galoppini, E.; Gilardi, R. *J. Am. Chem. Soc.* **1994**, *116*, 7588-7596.
(5) Eaton, P. E.; Stossel, D. *J. Org. Chem.* **1991**, *56*, 5138-5142.
(6) Eaton, P. E.; Cassar, L.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 6366-6368.
(7) Eaton, P. E.; Maggini, M. *J. Am. Chem. Soc.* **1988**, *110*, 7230-7232.
(8) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492.
(9) Bliese, M.; Tsanaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 189-192.
(10) Shastin, A. V.; Zakharov, V. V.; Bugaeva, G. P.; Eremenko, L. T.; Romanova, L. B.; Lagodzinskaya, G. V.; Aleksandrov, G. G.; Eremenko, L. L. *Russ. Chem. Bull.* **2006**, *55*, 1304-1306.