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Formation of cyclopentanes and cyclopropanes through alkylation of benzylic anions using ethers, thioethers and alcohols as substrates under Grubbs–Stoltz (Et₃SiH/KOtBu) conditions

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Reaction of diarylmethanes with the Grubbs–Stoltz reagent (KOtBu + Et₃SiH) using THF as solvent led to diarylcyclopentanes through an unprecedented double-alkylation reaction, with four of the carbons of the cyclopentane coming from THF. In like manner, reaction of diarylmethanes with the same reagent in 1,4-dioxane as solvent led to double-alkylation to form diarylcyclopropanes, with two of the cyclopropane carbons coming from 1,4-dioxane. Monoalkylated substrates that were likely intermediates on the dialkylation pathway were subjected to the same conditions, leading to cyclisations to form cyclopentanes and cyclopropanes. The cyclisation chemistry also extended to formation of monoarylcyclopropanes from reaction of the corresponding benzylopotassium reagents with ethers, alcohols, sulfides, sulfoxides and sulfones.

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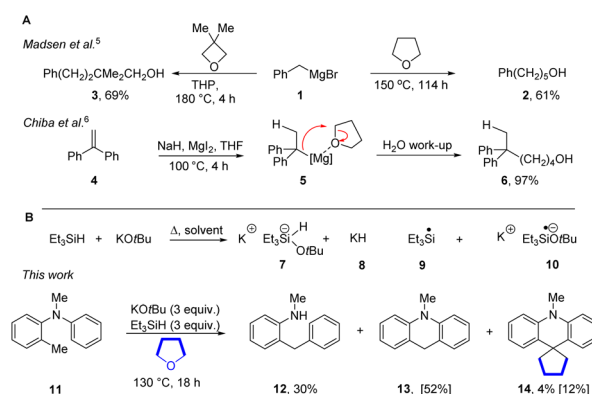
Introduction

Alkylations of carbanions under basic conditions routinely use very reactive electrophiles such as alkyl halides or sulfonate esters. The high reactivity of these reagents makes them convenient to use, but also underpins their ability to alkylate biomolecules, leading to their classification as major safety hazards. Ethers are much less electrophilic – indeed they are usually not recognised as electrophiles in the absence of protic or Lewis acids that activate them to C–O bond cleavage. If ethers could routinely be used as alkylating agents under defined basic conditions, this would be a very useful advance. THF has been deconstructed in many ways in the literature^{1,2} but it has never been subject to a double nucleophilic substitution by carbanions. Substitution of a single C–O bond cleavage has been reported using conventional powerful Lewis acids.^{3,4} Madsen *et al.* showed,⁵ using organomagnesium compounds as both Lewis acids and nucleophiles, that allylic and benzylic Grignard reagents such as **1** open THF and 3,3-dimethyloxetane to form alcohol products *e.g.* **2** and **3** respectively (Scheme 1A). In these cases, the Lewis acidic properties of the magnesium atom are harnessed to assist ring-opening.⁵ Very recently, Chiba *et al.* have generated MgH₂ *in situ* from magnesium halides and

sodium hydride and used it to add to 1,1-diarylethenes (*e.g.* **4**) to generate benzylic organomagnesium intermediates **5** that reacted with cyclic ethers to form alcohol products **6**.⁶ We now report activation of ethers in the presence of benzylic potassium reagents; here, THF and dioxane each act as dual electrophiles in forming cyclopentanes and cyclopropanes respectively.

Results and discussion

The Grubbs–Stoltz reagent, formed by heating a mixture of KOtBu and Et₃SiH,⁷ has been widely investigated since its



Scheme 1 (A) Prior reactions of benzylic organomagnesium reagents; (B) our discovery of cyclopentane formation from THF (NMR yields in brackets).

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introduction in 2013. This reagent is most unusual since it simultaneously generates a number of reactive intermediates, 7–10, that perform hydride transfer, hydrogen atom transfer, deprotonation, radical chemistry, silylation and electron transfer chemistry (Scheme 1B). Simultaneous exposure of substrates to such a variety of reactive entities is very unusual, and has been shown to lead to diverse and novel outcomes.^{7–19} In the course of our studies, we observed the rearrangement of the *N*-methyl-*N*-*o*-tolylaniline **11** to diarylmethane **12** and dihydroacridine **13**; the mechanisms of the formation of **12** and **13** have been investigated and reported.^{16,17} However, in addition to these products, and relevant to this paper, cyclopentane **14** (12%) was also formed (Our reactions were routinely performed in sealed vessels).

The reaction of **11** was repeated with THF-*d*₈ as solvent and led to **14-d**₈ (13%) confirming the origin of the cyclopentane. In a further experiment, this time using a 1 : 1 ratio of THF and THF-*d*₈, the product **14** was a mixture of *d*₈ and *d*₀ isotopologues, with no evidence of H/D exchange. If such exchange had been seen, it would have been evidence of THF-derived radicals playing a part in the reaction. The result instead now focused our thoughts on a double aliphatic nucleophilic substitution of THF.

Our working hypothesis was that dihydroacridine **13** was a likely precursor of **14**. In support of this, when the dihydroacridine **13** was heated with KO*t*Bu and Et₃SiH in THF, the cyclopentane **14** (12%) was again formed (Scheme 2A). In addition, a trace of the dimer **15** was detected by GCMS, indicating a slower background radical chemistry.^{13–17} Abstraction of an H-atom from dihydroacridine **13** *e.g.* by triethylsilyl radicals **9** would form a stabilised acridinyl radical **16**. Such radicals could then dimerise to afford **15**. Interestingly, when 2-methylTHF was used as solvent, the reaction afforded only the dimeric product **15** (64%) and when tetrahydropyran (THP) was used as solvent, no alkylation was detected and product **15** was again seen (20%). The different behaviour of 2-methylTHF was surprising.²⁰ The inertness of THP to this reaction allowed us to use it as solvent in some later reactions.²¹ Before studying

intermediates in this reaction, we tested dihydrobenzofuran **17** and phthalan **18** as substrates (Scheme 2B). We recognised that oxygen-containing heterocycles fused to arene rings can undergo electron transfer from **10** leading to reduction to their arene radical anions, followed by C–O bond cleavage.⁷ Both led to complex mixtures.

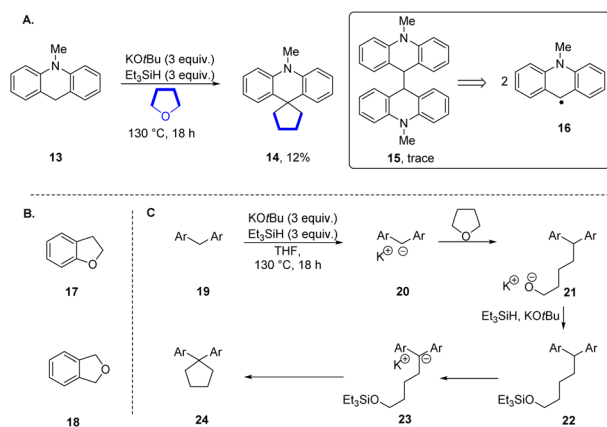
Our proposed mechanism for cyclopentane formation is shown in Scheme 2C. Deprotonation of diarylmethane **19** would afford diarylmethyl potassium **20** which reacts with THF to afford intermediate alkoxide **21**. To proceed to the cyclopentane, this alkoxide would require protection as silyl ether **22**. It is known that when alkoxides are treated with triethylsilane or other silanes, silyl ethers are formed.^{22–24} The silyl alkyl ether component of **22** can then behave as an alkylating agent, reacting intramolecularly in this case with the anion in **23** to form the cyclopentane **24**.

To test this proposal, alcohol **25**, silyl ether **26** and methyl ether **27** were prepared and subjected to the reaction conditions (Table 1, entries 1–3). All three compounds were converted to the cyclopentane **28** (27–77% yields). The formation of cyclopentanes in this way is novel – the cyclisations of silyl ether **24** and methyl ether **27** proceed with very unusual but credible leaving groups.

A byproduct in these reactions was Et₃SiO*t*Bu (Scheme 1B). This compound was tested for its effect on the cyclisation (entry 4). Specifically, this was to probe whether this silyl ether would provide some Lewis acid assistance to the cyclisation. However, this led to a lower yield (17%) for the cyclisation and hence does not facilitate the reaction.

Interestingly, when the silyl ether **26** was subjected to reaction with KO*t*Bu (entry 5), but in the absence of triethylsilane, no cyclisation was observed. This could be due to either or both of two reasons: (i) the silyl ether substrate **26** could be attacked by the excess KO*t*Bu to form Et₃SiO*t*Bu and the diphenylbutoxide anion derived from the substrate. The alkoxide would then not function as an electrophile, and no cyclisation would be seen [This would be consistent with the isolation of **25** (50%) from this reaction]. The alternative possibility was that KO*t*Bu was not a strong enough base to deprotonate **26**, but that when cyclopentanes had successfully formed in previous cases, that this had resulted from the generation of a stronger base, *i.e.* KH, **8**, through interaction of KO*t*Bu with Et₃SiH.^{22–24} It has been shown that LiO*t*Bu reacts with triethylsilane to liberate LiH²⁵ and we have previously shown¹³ that inorganic potassium amides also react with triethylsilane to afford KH; this species would be a much stronger base than KO*t*Bu and should certainly deprotonate **26**.

Accordingly, the role of base was explored with alcohol **25** using NaO*t*Bu, LiO*t*Bu, NaH and KH (entries 6–9 respectively). NaO*t*Bu reacted little, perhaps due to insolubility; LiO*t*Bu converted the alcohol **25** to its silyl ether **26**. The stronger base, NaH, formed a mixture of silyl ether **26** and cyclopentane **28** while KH made a more effective conversion to the cyclopentane product. We have recently observed that potassium salts demonstrate special reactivity relative to their sodium and lithium counterparts in a number of reaction types, and in some



Scheme 2 (A) *N*-Methyldihydroacridine **13** as substrate. (B) Dihydrobenzofuran **17** and phthalan **18**. (C) Mechanistic proposal for formation of cyclopentane **24**.



Table 1 Exploring cyclisation reactions to form diphenylcyclopentane 28

25, R = H
26, R = SiEt₃
27, R = Me

Entry	R	Solvent	Et ₃ SiH	Base	Et ₃ SiOtBu	28 (yield)	26 (yield)
1	H	THF	3 equiv.	KOtBu – 3 equiv.	—	50%	—
2	SiEt ₃	THF	3 equiv.	KOtBu – 3 equiv.	—	77%	—
3	Me	THF	3 equiv.	KOtBu – 3 equiv.	—	27%	—
4	H	THF	3 equiv.	KOtBu – 4 equiv.	3 equiv.	17%	—
5	SiEt ₃	THF	—	KOtBu – 3 equiv.	—	—	36% ^a
6	H	THF	3 equiv.	NaOtBu – 4 equiv.	—	—	3%
7	H	THF	3 equiv.	LiOtBu – 4 equiv.	—	—	76%
8	H	THF	3 equiv.	NaH – 4 equiv.	—	26%	36%
9	H	THF	3 equiv.	KH – 4 equiv.	—	67%	—
10	H	2-MeTHF	3 equiv.	KOtBu – 4 equiv.	—	49%	—

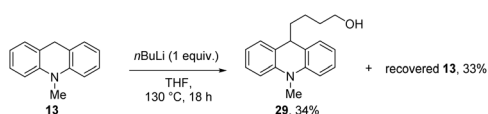
^a From this reaction, alcohol 25 (50%) was also isolated.

cases, we have identified the specific interactions responsible.^{26,27}

Finally, 2-MeTHF was studied (entry 10) as an alternative solvent for the intramolecular alkylation of alcohol 25. Having seen the dramatic differences between THF and 2-methylTHF in the reaction of dihydroacridine 13 above, we were not confident of the outcome. However, in the complex reaction seen with Grubbs–Stoltz conditions, the interplay of kinetics and thermodynamics of the different possible processes, mean that it was valuable to explore this. In effect, the reaction with 25 afforded 28 (49%), similar to the yield seen with THF as solvent (55%, entry 1). So, this shows that THF and 2-MeTHF were equally suitable solvents for reactions that involve intramolecular alkylation.

In our case, K⁺ or an organopotassium species would be a much milder Lewis acid than magnesium ions^{5,6} and our substrates show that magnesium ions are not required for these reactions. Based on these thoughts, a further experiment with base was undertaken. *n*BuLi was examined as base, using *N*-methyl-dihydroacridine 13 as substrate and alcohol 29 (34%) was isolated following workup; here, the reaction was likely assisted by the Lewis acidity of the lithium species (Scheme 3). Further reaction of the alkoxide was not achieved in the absence of silane.

Returning to Grubbs–Stoltz conditions (KOtBu + Et₃SiH), substrates 29 and 30 were then subjected to the cyclisation reaction, leading to the cyclopentanes 14 and 31 in the yields shown in Scheme 4. We did not isolate other products from the

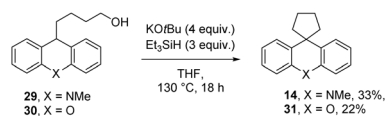


Scheme 3 Action of strong bases on substrates with benzylic C–H.

reaction, but diaryl ethers have previously been shown to undergo cleavage of Ar–O bonds, likely resulting following electron transfer from radical anion 10.⁷ Electron transfer to the oxygen heterocycle of 30 should be easier than to the more electron-rich nitrogen heterocycle of 29, and this could underpin the higher yield of cyclopentane from substrate 29.

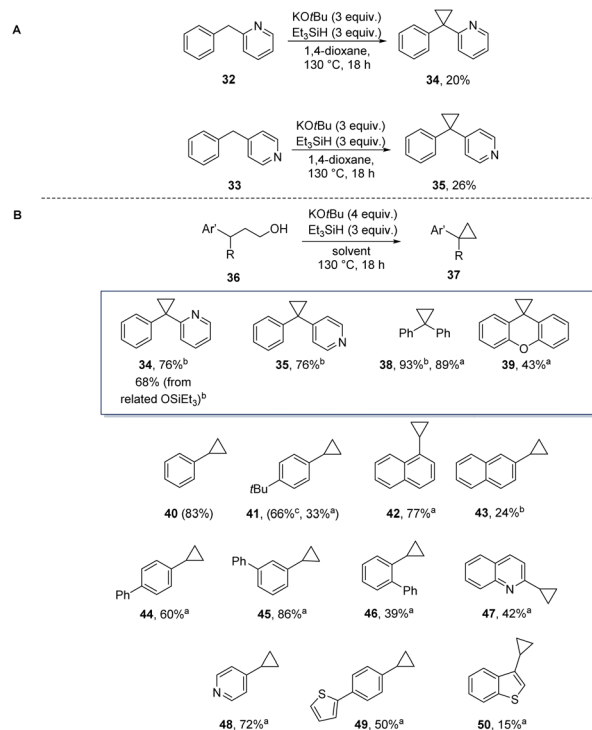
Our first encounter with cyclopropane formation arose when 1,4-dioxane was used as solvent. This converted benzylpyridines 32 and 33 to products 34 and 35 (Scheme 5A). Again, the cyclopropane formation likely arose through sequential substitution reactions on ether C–O bonds. By analogy with the THF case, our proposal was that initial alkylation had afforded a 3,3-diarylpropyl alkyl ether. This led us to select 3,3-diarylpropanols (36, R=Ar') as substrates for cyclopropane formation, leading to 34, 35, 38 and 39 in moderate to excellent yields (Scheme 5B). Clearly, diphenylmethane anions have the right balance of nucleophilicity and basicity to succeed in substitution reactions with the ethers. To extend the scope, simpler benzyl anions were investigated; hydroxypropylbenzenes (36, R=H) were then chosen as substrates, affording arylcyclopropanes 41–50 in a range of yields (15–89% yield) (The simplest substrate (36, Ar = Ph, R=H) cyclised cleanly to 40, giving an NMR yield (83%) but the product was too volatile to get an isolated yield.)

We had previously tested whether cyclopentanations could be achieved by simply using a strong base, KH; this was now investigated for cyclopropanations. Accordingly, substrates 51 (R = Ph, Me, Et) were treated with commercial KH, with THF as



Scheme 4 Alcohols as substrates for cyclopentane formation in the presence of silanes.





Scheme 5 Cyclopropane formation (A) from dioxane solvent and (B) from hydroxypropyl arenes under Grubbs–Stoltz conditions. ^aIn THF as solvent, ^bin dioxane, ^cin THF.

solvent, respectively affording product **38** in 49, 30 and 69% yield (Table 2, entries 1–3). Thus, KH as strong base can achieve these reactions. The yields are lower than when KH acts in conjunction with Et₃SiH, as seen in comparing entries 4 and 5. Although we don't have evidence for the cause of this at this stage, it may relate to aggregation state of KH. Chiba *et al.* have recently shown that the presence of additives can affect both the aggregation state and the reactivity of NaH.²⁹

Table 3 Exploration of scope of silanes

Silane or equivalent	51 (R=H)	38	52
iPr ₃ SiH	—	—	100%
Me ₂ PhSiH	—	76%	—
<i>t</i> BuMe ₂ SiH	—	—	89%
Bu ₃ SnH	89%	—	—

Entries 6–9 examine the effect of temperature on the cyclisation of **51**, R=H. The reaction is clearly more effective at 130 °C than at lower temperatures. Entry 10 shows the outcome of the reaction at 80 °C but for a 3 hour duration (*cf.* entries 6 and 10).

The role of Et₃SiH was next examined in Table 3 (Et₃SiH appeared in Table 2, entry 5, yield 70%). Replacement of Et₃SiH by Me₂PhSi led to a similar outcome (76% yield) in the formation of cyclopropane **38** (R=H). However, more bulky silanes iPr₃SiH and *t*BuMe₂SiH led to silylation of the alcohol as silyl ether **52**, but not to cyclisation, likely due to steric hindrance in the cyclisation step. When tri-*n*-butylstannane was used instead of a silane, then only starting alcohol **51** was isolated.

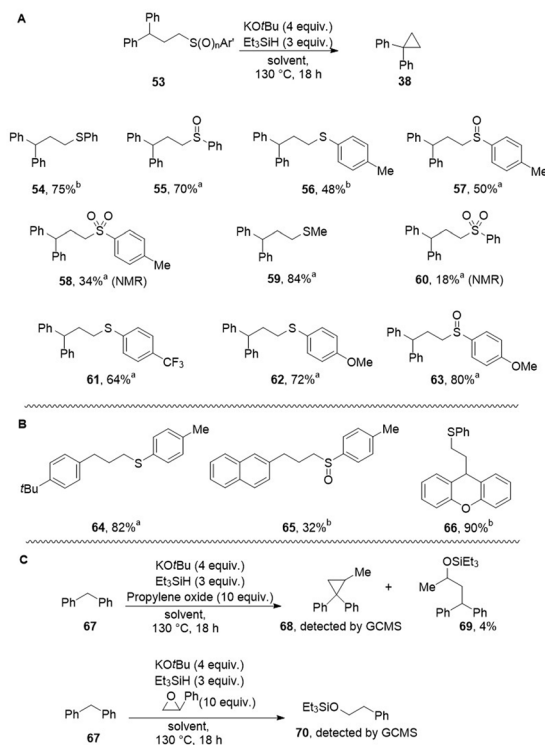
Having seen that ethers behaved favourably, thioethers were next assayed. Scheme 6 shows that cyclopropanes were again formed from sulfides, sulfoxides and sulfones. Thioethers are not viewed as electrophiles in the absence of specific activations. However, conversion of sulfides **53** to cyclopropanes **38** was also achieved. Scheme 6 shows yields (48% to 90%) of cyclopropanes derived from substrates including sulfoxides **55**, **57**, and **63**. Sulfones **58**, **60** also underwent cyclopropane formation on treatment by base in the presence of silane. The sulfones were generally less successful than the corresponding

Table 2 Formation of cyclopropanes

Entry	R	Solvent	Et ₃ SiH	Base	Temp °C	Duration	38 (yield)
1	Me	THF	—	KH – 3 equiv.	130 °C	18 h	49%
2	Et	THF	—	KH – 3 equiv.	130 °C	18 h	30%
3	Ph	THF	—	KH – 3 equiv.	130 °C	18 h	69% ^a
4	SiEt ₃	THF	—	KH – 3 equiv.	130 °C	18 h	34%
5	SiEt ₃	THF	3 equiv.	KH – 3 equiv.	130 °C	18 h	70%
6	H	THF	3 equiv.	KH – 4 equiv.	130 °C	18 h	82%
7	H	THF	3 equiv.	KH – 4 equiv.	100 °C	18 h	67%
8	H	THF	3 equiv.	KH – 4 equiv.	80 °C	18 h	70%
9	H	THF	3 equiv.	KH – 4 equiv.	60 °C	18 h	51%
10	H	THF	3 equiv.	KH – 4 equiv.	80 °C	3 h	42%

^a See ref. 28 for formation of cyclopropanes through displacement of aryloxy leaving groups.





Scheme 6 (A) Substrates **54–63** are converted to cyclopropane **38** in the yields shown; (B) substrates **64–66** are converted into the corresponding cyclopentanes – in view of the importance of these ring systems, we are currently examining the expansion of the scope of this chemistry.

sulfides and sulfoxides, likely due to the relative ease of deprotonation α -to sulfones in competition with deprotonation of the benzylic C–H sites.

Our recent results with the Grubbs–Stoltz reagent have underlined the competition between the different types of processes that can result from intermediates that are generated, notably radical chemistry and electron transfer chemistry. Besides the formation of **15**, mentioned earlier in relation to Scheme 2, the SI file exemplifies some side-reactions that can be attributed to competing processes (see pp. S45–46).

The rates of formations of cycloalkanes of different ring sizes by intramolecular displacement by nucleophiles have been studied for a number of different classes of compounds. In each case, there is a balance between enthalpic and entropic considerations. Accordingly, having witnessed formation of three-membered and five-membered ring originally arising from use of tetrahydrofuran and 1,4-dioxane as solvents, we were interested in exploring possible formation of 4-membered and 6-membered rings. In fact, these efforts led to only traces of cyclisation and the details of products are more fully discussed in the SI file (see page S57 et seq.) In these cases, the appearance of alternative products likely results from slower cyclisation kinetics compared to the 3- and 5-membered rings discussed in this paper.^{30,31} We also examined two epoxides as substrates, namely propylene oxide and styrene oxide, under our Grubbs–Stoltz conditions (Scheme 6C). Propylene oxide afforded a low yield of silyl ether **69** and trace quantities of cyclopropane **68**

were detected by GCMS. With styrene oxide, silyl ether **70** was detected, arising from reductive opening of the styrene oxide. At least with these examples, it thus appears that reactions other than S_N2 attack by benzylic anions occur preferentially.

Conclusions

Initial observations showed diarylcyclopentane formation on treatment of diarylmethanes with the Grubbs–Stoltz reagent (KOtBu + Et₃SiH) when THF was used as solvent. The transformation featured two sequential substitution reactions involving cleavage of C–O bonds, with four of the carbons of the cyclopentane coming from THF. Similar reactivity was shown by 1,4-dioxane as solvent, where double-alkylation led to diarylcyclopropanes, with two of the cyclopropane carbons coming from 1,4-dioxane. In these cases, the intermediate alkoxides react with the silane to form silyl ethers, thereby allowing R₃SiO[−] anions to act as leaving groups in the cyclisation steps. With appropriate substrates, deprotonation of benzylic C–H bonds with potassium bases afforded anions that underwent intramolecular substitution reactions at ethers or silyl ethers to form cyclopentanes and cyclopropanes. The chemistry also extended to formation of cyclopropanes from substitution reactions at sulfides, sulfoxides and sulfones. Our examples show relatively simple cyclopropanes and cyclopentanes – in view of the importance of these ring systems, we are currently examining the expansion of the scope of this chemistry.

Author contributions

AJS, DD, STML, CP, JDB, KMcG, ALK performed the experiments. SF, SMN, SGL and JAM supervised the research. All authors analysed and commented on the results. AJS, DD and STML drafted the manuscript. All authors contributed to the final draft and approved the paper.

Conflicts of interest

CP and DD are now employees of AstraZeneca and may or may not own stock options.

Data availability

Supplementary information: the experimental procedures and spectroscopic data in support of the reported results. See DOI: <https://doi.org/10.1039/d5sc10055k>.

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