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An unusual silicon mediated transannular cyclopropanation†

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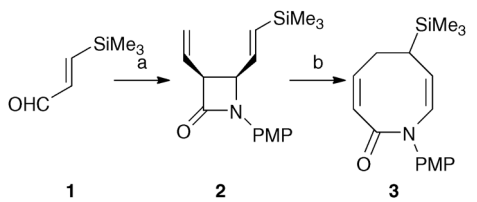
A silicon mediated intramolecular 1,4-conjugate addition of a homoallylic carbon nucleophile leading to cyclopropanation is reported. Specifically, treatment of 6-trimethylsilyl-5,6-dihydroazocinones with fluoride gives 4-azabicyclo(5.1.0)octenones, presenting an unusual extension to the repertoire of silyl group reactivity.

Silyl groups impart versatile reactivity to their compounds.[1] Adapting this useful reactivity to direct common precursors toward varied molecular architectures is attractive,[2,3] not least to provide escape from the 'sameness' perceived to restrict discovery especially in chemical biology.[4] Pursuit of this objective revealed an apparently unique mode of silicon mediated cyclopropanation.

Beta-lactams (azetidin-2-ones) are readily accessible and stable, yet adequately strained to drive skeletal rearrangements.[5] We were intrigued by reports of thermal Cope rearrangement of *cis*-3,4-divinyl-azetin-2-ones (*e.g.* **2**, Scheme 1), leading to 5,6-dihydroazocinones (*e.g.* **3**) in good yield.[6–8] Apart from their unusual shape, the rich functionality displayed by these products is attractive for further transformation. Speculatively, we sought installation of a silyl group within such 5,6-dihydroazocinones with a view to exploring subsequent reactivity for access to novel structures.

(*E*)-3-(Trimethylsilyl)propenal **1**,[9] 4-methoxyaniline and crotonyl chloride were transformed by Staudinger reaction with triethylamine in dichloromethane at room temperature, to produce the corresponding 3,4-divinylazetidin-2-one **2** in acceptable yield (Scheme 1). Subsequent heating of azetindinone **2** to 120 °C in toluene in a sealed tube effected Cope rearrangement to give 5,6-dihydroazocinone **3** in excellent yield. The transformation is accompanied by a characteristic change in the carbonyl stretch in the infrared spectrum from ~1735 cm^{-1} for the azetidinones **2** to ~1657 cm^{-1} for the azocinone **3**. NMR spectroscopy of this compound shows significantly broadened peaks, presumably due to slow conformational exchange as observed for related compounds.[10]

The identity of the 6-trimethylsilyl-5,6-dihydroazocinone **3** was confirmed by X-ray crystallography (Fig. 1).‡ Notably, the 3,4-alkene is twisted out of conjugation by 62° from the amide carbonyl; attempted conjugate addition with external nucleophiles, such as thiophenol and caesium carbonate in THF, returned starting material **3** (not shown).



Scheme 1 Reagents and conditions: (a) 4-methoxyaniline, $MgSO_4$, CH_2Cl_2, rt, 10 min; then *E*-crotonyl chloride, Et_3N, $MgSO_4$, CH_2Cl_2, rt, 16 h, 57%; (b) toluene, 120 °C, sealed tube, 88%.

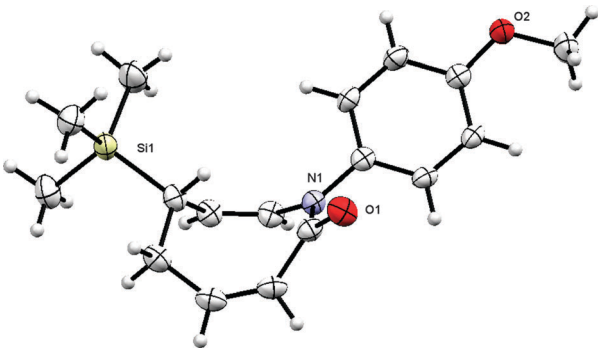


Fig. 1 Crystal structure of 5,6-dihydroazocinone **3**. Ellipsoids are drawn at the 50% probability level.

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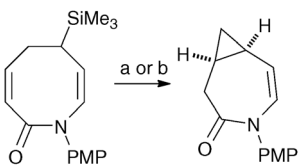
We found that treatment of the 6-trimethylsilyl-dihydroazocinone **3** with TBAF in THF resulted in clean conversion to a single product in 90% yield (Scheme 2). Mass spectrometry confirmed ablation of the trimethylsilyl group, yet the ^{1}H NMR spectrum showed well resolved peaks unrelated to the corresponding azocinone **3**. Upfield peaks at 0.86 and 0.47 ppm in the ^{1}H NMR spectrum and a corresponding methylene peak at 8.1 ppm in the ^{13}C NMR spectrum were suggestive of a cyclopropane.

Ultimately, we obtained a crystal structure that confirmed the identity of the new fused cyclopropane **4** (Fig. 2).‡ The same transformation could be achieved by treating the dihydroazocinone **3** with sodium hydroxide (20% aqueous) in ethanol in 70% yield.

The idea that this was a silicon specific effect was promoted by evaluating the analogous 5,6-dihydroazocinone bearing an ester at the 6-position **6** (Scheme 3). Wittig olefination of 4-oxoazetidine-2-carbaldehyde **5**[11] and Cope rearrangement gave the corresponding 5,6-dihydroazocinone **6** in 70% overall yield.[7] Treatment of this compound with DBU gave tautomer **7**, but no cyclopropanation was observed under these conditions. Alternative means of generating an anion at azocinone the 6-position have not yet been explored however.

An investigation into whether further substituents at the 5- and 6-positions of azocinone precursors were tolerated in this cyclopropanation reaction was carried out (Scheme 4). 3-Methylcrotonoyl chloride and 3-phenylbut-2-enoyl chloride were transformed to azetidin-2-ones **8** (49%)† and **9** (41%)† respectively, then subject to rearrangement to give the corresponding 5,6-dihydroazocinones with 4-methyl **10** (97%), or 4-phenyl **11** (87%). Treatment of either 5,6-dihydroazocinones **10**, **11** with tetrabutylammonium fluoride resulted in transannular cyclopropanation in high yield (**12** R = Me, 93%, **13** R = Ph, 86%).



3 **4**

Scheme 2 Reagents and conditions: (a) 1 M TBAF in THF, CH_2Cl_2, rt, 24 h, 90%; or (b) NaOH (20% aq.), EtOH, rt, 24 h, 70%.

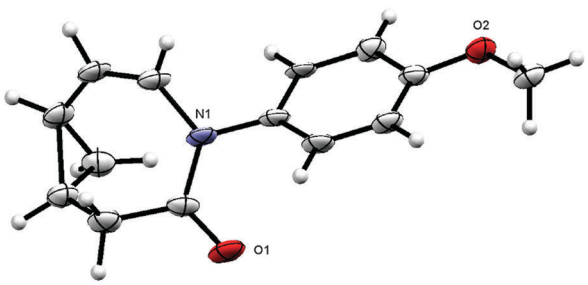
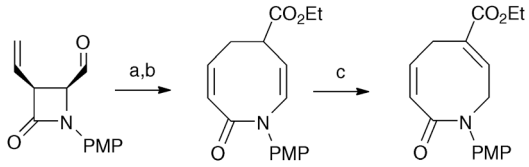


Fig. 2 Crystal structure of 4-azabicyclo(5.1.0)octenone **4**. Ellipsoids are drawn at the 50% probability level.



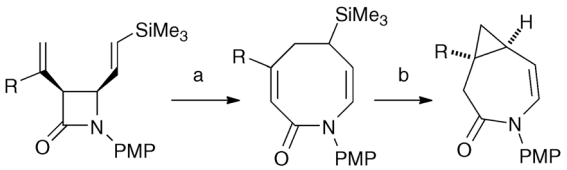
5 **6** **7**

Scheme 3 Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, NaH, THF, rt, 2 h, 77%; (b) toluene, 120 °C, sealed tube, 3 h, 91%; (c) DBU, CH_2Cl_2, rt, 16 h, 92%.

(*E*)-Pent-2-enoyl chloride, was transformed into the corresponding azetidin-2-one **14**, with the 3-propenyl group present as a 1 : 1 mixture of *E* : *Z* isomers (63%). Rearrangement gave 5,6-dihydroazocinone **15** isolated as an approx. 1.5 : 1 mixture of diastereoisomers, as determined by relative integration of the 5-methyl group signals (54%). Reaction of this azocinone **14** with tetrabutylammonium fluoride gave cyclopropane **16** in 91% yield with an approx. 2 : 1 ratio of diastereoisomers as determined by relative integration of the alkene peaks in the ^{1}H NMR spectrum (Scheme 5).

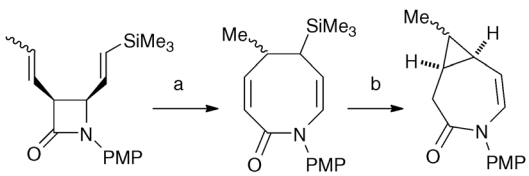
Attempts to introduce additional functional groups adjacent to silicon at the 6-position **20**,† or two substituents at the 5-position **19**,† of the azocinone were not successful since the preceding azetidin-2-ones **17** and **18** respectively did not undergo Cope rearrangement, presumably due to the steric demands of this increased substitution (Scheme 6).

It is likely that the constraint provided by the boat-like conformation of the 5,6-dihydroazocinone helps to guide the observed cyclopropanation, although some conformational rearrangement presumably facilitates the 1,4-conjugate addition. Initial evaluation of an open-chain analogue of this



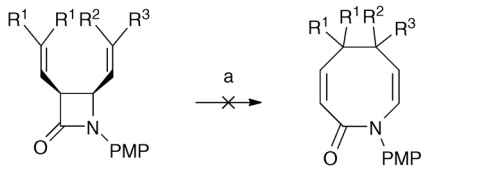
8 R = Me **10** R = Me **12** R = Me
9 R = Ph **11** R = Ph **13** R = Ph

Scheme 4 Reagents and conditions: (a) toluene, 120 °C, sealed tube (**10** – 97%, **11** – 87%); (b) 1 M TBAF in THF, CH_2Cl_2, rt, 24 h, (**12** – 93%, **13** – 86%).



14 **15** **16**

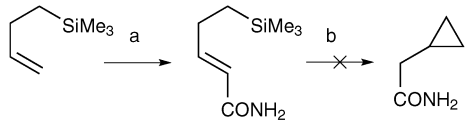
Scheme 5 Reagents and conditions: (a) toluene, 120 °C, sealed tube 54% (b) 1 M TBAF in THF, CH_2Cl_2, rt, 24 h, 90%.



17 R^1 = Me, R^2 = H, R^3 = $SiMe_3$ **19** R^1 = Me, R^2 = H, R^3 = $SiMe_3$

18 R^1 = H, R^2 = $SiEt_3$ R^3 = Me **20** R^1 = H, R^2 = $SiEt_3$ R^3 = Me

Scheme 6 Reagents and conditions: (a) toluene, 120 °C, sealed tube.



21[12] **22** **23**

Scheme 7 Reagents and conditions: (a) Grubbs–Hoveyda 2nd gen. initiator, CH_2Cl_2, reflux, 24 h, 40%, (b) 1 M TBAF in THF, CH_2Cl_2, rt, 24 h.

reaction did not produce cyclopropane **23** (Scheme 7) but more detailed investigations are ongoing.

This reaction could be viewed as a Lewis base promoted,[13] Hosomi–Sakurai reaction,[14] proceeding *via* intramolecular 1,4-conjugate addition.[15,16] There is no precedent for cyclopropanation in this way, however.[17]

The 4-azabicyclo(5.1.0)octenone products of this transannular cyclopropanation are new structures with few close relatives,[18,19] and so offer a new destination for exploration of chemical space. The two step synthesis from accessible *cis*-3,4-divinyl-azetin-2-ones provides expedient access to this scaffold.

In summary, a novel mode of silicon-mediated transannular conjugate addition, leading to a cyclopropane product is reported.

It is likely that the general scope of this reaction will be limited by a requirement for highly organised precursors or reaction intermediates. Nevertheless, it remains tempting to imagine how this reaction might be adapted for construction of other scaffolds featuring cyclopropanes.[20] Further studies to elaborate understanding of this mechanism and develop its application in synthesis are underway.

We thank BBSRC and University of Nottingham for studentships (KH and BY respectively).

Notes and references

‡ Crystal data for **3**. $C_{17}H_{23}NO_2Si$, M = 301.45, monoclinic, a = 15.0245(13), b = 6.5615(6), c = 17.5471(16) Å, U = 1681.5(3) Å^3. T = 150(2) K, space group $P2_1/n$, Z = 4, 14 250 reflections measured, 5415 unique with R = 0.0419 wR_2 = 0.1060. CCDC 906817. Crystal data for **4**. $C_{14}H_{15}NO_2$, M = 229.27, monoclinic, a = 6.0221(8), b = 19.648(4), c = 9.7886(12) Å, U = 1146.0(3) Å^3. T = 90(2) K, space group $P2_1/c$, Z = 4, 3912 reflections measured, 1246 unique with R = 0.1299 wR_2 = 0.3104. CCDC 906818.

1 I. Fleming, A. Barbero and D. Walter, *Chem. Rev.*, 1997, **97**, 2063–2192.
2 Y. K. Wang, M. Jimenez, A. S. Hansen, E. A. Raiber, S. L. Schreiber and D. W. Young, *J. Am. Chem. Soc.*, 2011, **133**, 9196–9199.
3 H. F. Sore, D. T. Blackwell, S. J. F. MacDonald and D. R. Spring, *Org. Lett.*, 2010, **12**, 2806–2809.
4 C. M. Dobson, *Nature*, 2004, **432**, 824–828; R. J. Spandl, A. Bender and D. R. Spring, *Org. Biomol. Chem.*, 2008, **6**, 1149–1158.
5 B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107**, 4437–4492. For a recent example see: R. S. Grainger, M. Betou, L. Male, M. B. Pitak and S. J. Coles, *Org. Lett.*, 2012, **14**, 2234–2237 and references therein.
6 B. Alcaide, C. Rodriguez-Ranera and A. Rodriguez-Vicente, *Tetrahedron Lett.*, 2001, **42**, 3081–3083.
7 P. Almendros, C. Aragoncillo, G. Cabrero, R. Callejo, R. Carrascosa, A. Luna, T. Martínez del Campo, M. C. Pardo, M. T. Quirós, M. C. Redondo, C. Rodríguez-Ranera, A. Rodríguez-Vicente and M. P. Ruiz, *Arkivoc*, 2010, **3**, 74–92.
8 P. Singh, G. Bhargava and M. P. Mahajan, *Tetrahedron*, 2006, **62**, 11267–11273.
9 M. J. Carter, I. Fleming and A. Percival, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2415–2434.
10 S. Derrer, J. E. Davies and A. B. Holmes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2957–2967.
11 B. Alcaide, Y. Martín-Cantalejo, J. Pérez-Castells, J. Rodríguez-López, M. A. Sierra, A. Monge and V. Pérez-García, *J. Org. Chem.*, 1992, **57**, 5921–5931.
12 S. H. Lipponen and J. V. Seppala, *Organometallics*, 2011, **30**, 528–533.
13 S. E. Denmark and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2008, **47**, 1560–1638.
14 A. Hosomi, A. Shirahata and H. Sakurai, *Tetrahedron Lett.*, 1978, **19**, 3043–3046.
15 G. Majetich, R. Desmond and A. M. Casares, *Tetrahedron Lett.*, 1983, **24**, 1913–1916.
16 G. Majetich, K. Hull, J. Defauw and T. Shawe, *Tetrahedron Lett.*, 1985, **26**, 2755–2758.
17 The nearest related example involves intramolecular alkoxide addition to a silyl group driving subsequent 1,2 addition to an aldehyde to give a cyclopropanol: (*a*) I. Fleming and A. K. Mandal, *Chem. Commun.*, 1999, 923–924; (*b*) S. C. Archibald, D. J. Barden, J. F. Y. Bazin, I. Fleming, C. F. Foster, A. K. Mandal, D. Parker, K. Takaki, A. C. Ware, A. R. B. Williams and A. B. Zwicky, *Org. Biomol. Chem.*, 2004, **2**, 1051–1064.
18 A. Mallagaray, G. Domínguez, A. Gradillas and J. Pérez-Castells, *Org. Lett.*, 2008, **10**, 597–600.
19 S. Lochyński, J. Kułdo, B. Frackowiak, J. Holband and G. Wójcik, *Tetrahedron: Asymmetry*, 2000, **11**, 1295–1302.
20 D. Y.-K. Chen, R. H. Pouwer and J.-A. Richard, *Chem. Soc. Rev.*, 2012, **41**, 4631–4642.