Preparation of fused polycyclic vinylcyclopropanes *via* radical cascade reactions†

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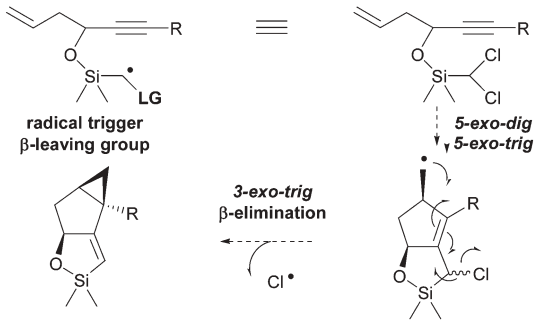
Radical cascades employing (dichloromethyl)dimethylsilyl ethers as both a point of radical initiation and termination, allow efficient entry to fused polycyclic cyclopropanes, and are also suitable for the design of other radical processes terminated by β-elimination of chloride.

Over the past few decades radical chemistry has become a well established approach to efficiently construct complex molecular architectures from simple acyclic starting materials,[1] notably through domino and cascade processes.[2] In large part, the successful evolution of this field is due to an improved understanding of the kinetics of radical reactions[3] which has permitted the rational design of substrates to participate in cascade processes. However, cyclopropanes remain notably absent from the variety of ring systems readily available. This is hardly surprising as the requisite cyclopropylmethyl radicals formed by 3-*exo-trig* cyclization of a 3-butenyl radical are known to rapidly ring-open,[4] and in fact this system comprises one of the most reliably used radical clocks.[5]

Of the scattered reports in the literature,[6] suppression of cyclopropane ring-opening *via* rapid elimination of an atom, or group, at the β-position of a cyclopropylmethyl radical was of significant interest due to our recent success of this approach in other contexts.[7] Through analogy with our extensive experience with bromomethyldimethylsilyl ethers in radical processes,[8] we speculated that the corresponding (dichloromethyl)dimethylsilyl (DCDMS) ethers[9] might play a dual role as both the site of radical initiation and termination through loss of Cl$^{\bullet}$ (Scheme 1).[10]

Appropriately designed starting materials might then allow formation of fused polycyclic cyclopropanes through a radical cascade as illustrated in Scheme 1. The novel application of (dichloromethyl)dimethyl silyl ethers as a radical/β-leaving group equivalent offers a number advantages over previously reported systems.[6] As DCDMSCl is commercially available,[11] a variety of substrates should be readily available through short synthetic sequences, and the expected products contain both a vinylcyclopropane and silacycle suitable for further elaboration. In addition, a number of natural products such as *trans*-sabinol,[12] and precursors to vitamin D or related analogues, are attractive targets for application of this methodology.[13] Finally, the substrates might

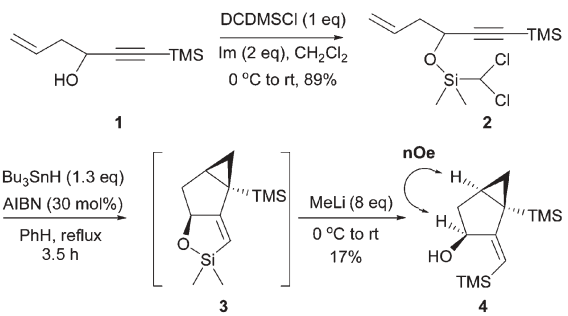


Scheme 1 Approach to fused polycyclic cyclopropanes.

easily be redesigned for other novel radical cascade process (external acceptor, 1,*n*-H transfer) that also incorporate termination by β-elimination (*vide infra*).

Study was initiated on the simple unsaturated alcohol (**1**) which was silylated under standard conditions to yield the moderately acid labile precursor (**2**) for the desired radical cascade (Scheme 2). Pleasingly, subjecting a dilute solution of **2** to classical radical conditions, followed by a MeLi quench of the intermediate silacycle (**3**) to simplify isolation, afforded the desired product (**4**) with high diastereoselectivity (>20 : 1) albeit in rather low yield. The relative stereochemistry was confirmed by NOE experiments and showed a *cis* relationship between the hydroxyl group and the cyclopropane group as predicted from the chair-like transition state typical of these cyclizations.[14]

The reaction conditions were then systematically investigated in an effort to obtain synthetically useful yields. As expected the rate of addition of the radical mediator and initiator was an important factor. Mixing all the reagents together and heating (Bu_3SnH, AIBN, PhH, 80 °C), or *via* photochemical activation (Bu_3SnH, AIBN, $PhCH_3$, 0 °C, *hv*) were ineffective and primarily desilylated



Scheme 2 Initial results.

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starting material was observed. A similar result was obtained with extremely long addition times ($\sim$0.03 mmol h^{-1}); presumably in this case the radical chain was not properly propagated and the initiator unproductively consumed. Intermediate rates (0.21 mmol h^{-1}) of addition of a mixture of Bu_3SnH and AIBN in benzene were found to give the best results.

As the substrate (**2**) and all associated intermediates leading to the formation of, and including, silacycle **3** are likely to be sensitive to acid promoted decomposition pathways, we speculated the addition of an organic base might substantially improve the isolated yields as HCl is presumably formed during the course of the reaction ($Bu_3SnH + {}^{\bullet}Cl \rightarrow Bu_3Sn^{\bullet} + HCl$). Indeed, reaction yields steadily improved as the amount of base was increased (Table 1, entries 1–3; and entries 4–7). Switching from Bu_3SnH to Ph_3SnH provided a further improvement (Table 1, entry 1 *vs.* 4) and may reflect the postulated polar nature of the transition state for reduction of α-chlorosilanes.[15] Triphenyltin hydride, by virtue of the three aromatic rings and significantly different electronics than Bu_3SnH, may be more compatible, and capable of stabilizing the supposed charge separation.[16] Further increases in the amount of triethylamine from 2 to 20 equivalents gave the highest yield of the desired product after MeLi quench with the same level of diastereoselectivity as observed previously (Table 1, entry 7).

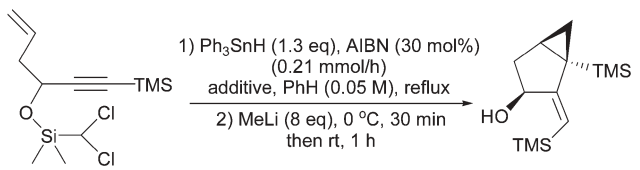
With optimized conditions in hand, a series of homoallylic propargylic DCDMS ethers with a range of substitution patterns at the allylic, alkenyl, and alkynyl positions were prepared to evaluate the scope of the transformation and a selection of the results are displayed in Table 2.

Allylic substitution appears to be well tolerated with both the *gem*-dimethyl (**5**) and *syn*-phenyl (**6**) starting materials affording good yields of the fused cyclopropane products (Table 2). The diastereoselectivity was high for both **4** and **11** (>20 to 1) as indicated by NMR of the crude reaction mixtures. However, this was not the case for the *syn*-phenyl substrate (**6**) where a mixture of two separable diastereomers was observed in a modest ratio of 3.5 to 1. The relative stereochemistry was confirmed by NOE experiments, and further study of the origins of the reduced selectivity are underway.

Attention then focused on the effect of variation of the acetylenic portion of the starting materials (Table 2, substrates **7** and **8**). We were particularly interested in silyl groups that might be easily oxidized following the cyclization event as a handle for further functionalization.[17] Unfortunately, the TBDPS terminated substrate (**4**) displayed both low yield and selectivity under the cyclization conditions. As a viable alternative, the dimethylphenylsilylated alkyne **8** provided much better results affording the desired product (**14**) in reasonable yield and restored selectivity. Other substitution on the alkyne terminus were also investigated (R^1 = CH_2OBn, CH_2OTBS, CO_2Et, phenyl, and cyclopropyl), but under currently employed conditions only traces of the desired products have been observed.

Substrates bearing substituents upon the alkene have also been explored. Introduction of a single methyl group at the internal position of the olefin (**9**) is tolerated, and gave rise to the desired product (**15**) in an isolated yield of 33%. Surprisingly, the

Table 1 Optimization of reaction conditions

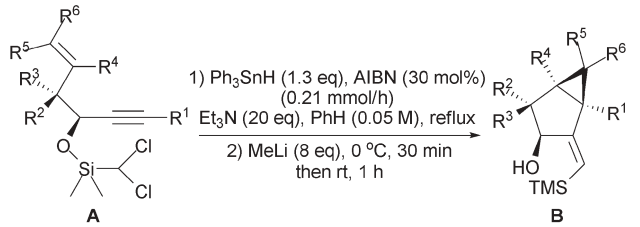


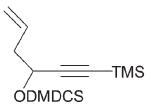
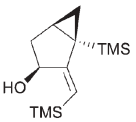
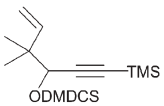
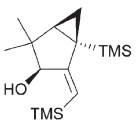
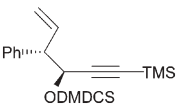
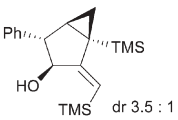
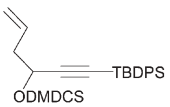
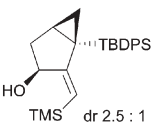
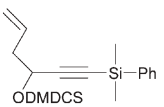
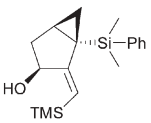
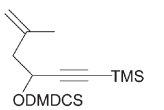
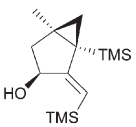
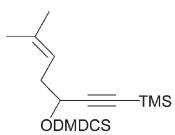
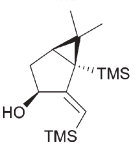
2 **4**

Entry	R_3SnH	Additive (eq.)	Yield[a] (%)
1	Bu_3SnH	—	17
2	Bu_3SnH	Et_3N (1)	45
3	Bu_3SnH	Et_3N (2)	54
4	Ph_3SnH	—	34
5	Ph_3SnH	Et_3N (2)	64
6	Ph_3SnH	Et_3N (5)	73
7	Ph_3SnH	Et_3N (20)	77

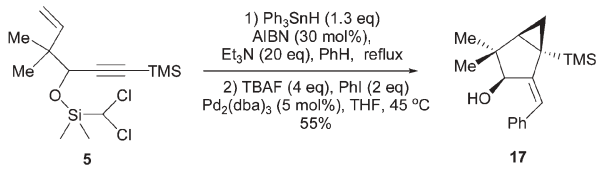
[a] All reactions performed on 0.5 mmol scale, yields refer to isolated material after chromatography.

Table 2 Scope

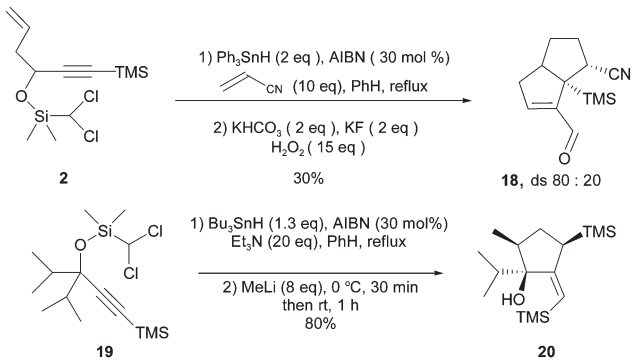


Substrate		Product		Yield[a] (%)
	**2**		**4**	77
	**5**		**11**	71
	**6**		**12**	71
	**7**		**13**	18
	**8**		**14**	47
	**9**		**15**	33
	**10**		**16**	Trace

[a] All reactions performed on 0.5 mmol scale, yields refer to isolated material after chromatography, dr > 20:1 unless otherwise noted.



Scheme 3 Functionalization through Pd mediated cross-coupling.



Scheme 4 Alternative radical cascades.

gem-dimethyl substitution at the olefinic terminus (**10**) returned primarily desilylated starting material, and afforded only a trace of the desired product (**16**).

Although all the products discussed thus far were quenched with MeLi for convenience, it is also possible to perform Pd mediated cross-coupling of the formed silacycles provided, care is taken to avoid exposure to moisture during the solvent exchange (Scheme 3).[18]

Finally, the concept of the DCDMS ether tether as an point of initiation/termination of radical cascades can be extended to other radical sequences. Through addition of an external acceptor it proved possible to interrupt the 3-*exo-trig* cyclization to form the larger five-membered ring carbocycle, in this case isolated after Tamao–Fleming oxidation[17] as a 80 : 20 diastereomeric mixture of enals **18** in 30% yield.[6d,19] Alternatively, substrates such as **19**, capable of undergoing 1,5-H transfer,[20] were found to give the complex carbocycle **20** as a single diastereomer and in excellent yield (Scheme 4).

In summary, (dichloromethyl)dimethylsilyl ethers of homoallylic propargylic alcohols have been shown to be effective radical/β-leaving group equivalents and provide a variety of structurally complex fused polycyclic cyclopropanes in moderate to good yield, and high diastereoselectivity.[21] The silacycles maybe converted to vinylsilanes for ease of isolation, or further functionalized through palladium cross-coupling reactions to provide improved structural diversity. Moreover, the novel concept of employing DCDMS ethers as a readily introduced point of initiation and termination of radical cascades can be extended to a number of other radical sequences with good success. Work is continuing to fully investigate the scope of a number of these interesting reaction cascades and will be reported in due course.

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Notes and references

1 (*a*) *Radicals in Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, vol. 1 & 2; (*b*) W. B. Motherwell and D. Crich, in *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, 1992.
2 (*a*) L. F. Tietze, G. Brasche and K. M. Gericke, in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weiheim, 2006; (*b*) M. Albert, L. Fensterbank, E. Lacôte and M. Malacria, *Top. Curr. Chem.*, 2006, **264**, 1.
3 A. L. J. Beckwith and K. U. Ingold, in *Rearrangements in Ground and Excited States*, ed. P. de Mayo, Academic Press, New York, 1980, vol. 1, pp. 162–310.
4 Rate constants for the allylcarinyl-cyclopropylcarbinyl rearrangement have been found to be 1.0×10^4 s^{-1} for ring closure and 1.3×10^8 s^{-1} for ring opening at 25 °C, see: (*a*) B. Maillard, D. Forrest and K. U. Ingold, *J. Am. Chem. Soc.*, 1976, **98**, 7024; (*b*) T. A. Halgren, J. D. Roberts, J. H. Horner, F. N. Martinez, C. Tronche and M. Newcomb, *J. Am. Chem. Soc.*, 2000, **122**, 2988.
5 (*a*) M. Newcomb, *Tetrahedron*, 1993, **49**, 1151; (*b*) D. C. Nonhebel, *Chem. Soc. Rev.*, 1993, 347.
6 (*a*) C. R. Warner, R. J. Strunk and H. G. Kuivila, *J. Org. Chem.*, 1966, **31**, 3381; (*b*) V. M. Bowry, J. Lusztyk and K. U. Ingold, *J. Chem. Soc., Chem. Commun.*, 1990, 923; (*c*) R. N. Saicic and Z. Cekovic, *Tetrahedron*, 1992, **48**, 8975; (*d*) P. Devin, L. Fensterbank and M. Malacria, *J. Org. Chem.*, 1998, **63**, 6764; (*e*) W.-W. Weng and T.-Y. Luh, *J. Org. Chem.*, 1993, **58**, 5574; (*f*) A. Srikrishna, R. Viswajanani, T. J. Reddy, D. Vijaykumar and P. P. Kumar, *J. Org. Chem.*, 1997, **62**, 5232; (*g*) M. Journet and M. Malacria, *J. Org. Chem.*, 1994, **59**, 718; (*h*) R. Zriba, S. Bezzenine-Laffolée, F. Guibé and M.-G. Guillerez, *Synlett*, 2005, 2362, and references therein.
7 (*a*) B. Delouvrié, L. Fensterbank, E. Lacôte and M. Malacria, *J. Am. Chem. Soc.*, 1999, **121**, 11395; (*b*) D. Leca, K. Song, M. Albert, M. G. Gonçalves, L. Fensterbank, E. Lacôte and M. Malacria, *Synthesis*, 2005, 1405, and references therein.
8 (*a*) L. Fensterbank, M. Malacria and S. M. Sieburth, *Synthesis*, 1997, **8**, 813; (*b*) C. Aïssa, B. Delouvrié, A.-L. Dhimane, L. Fensterbank and M. Malacria, *Pure Appl. Chem.*, 2000, **72**, 1605.
9 K. Tamao, K. Nagata, Y. Ito, K. Maeda and M. Shiro, *Synlett*, 1994, 257. For other radical uses of *gem*-dihalo or -dithio precursors: Y. Nishii, A. Fujiwara, K. Wakasugi, M. Miki, K. Yanagi and Y. Tanabe, *Chem. Lett.*, 2002, 30, and references therein.
10 For previous reports of β-elimination of $Cl^{\bullet}$: (*a*) C. C. Huval and D. A. Singleton, *Tetrahedron Lett.*, 1993, **34**, 3041; (*b*) G. A. Kraus, B. Andersh, Q. Su and J. Shi, *Tetrahedron Lett.*, 1993, **34**, 1741; (*c*) S. Kim, N. Kim, W.-j. Chung and C. H. Cho, *Synlett*, 2001, 937; $Br^{\bullet}$: (*d*) J. M. Tanko and M. Sadeghipour, *Angew. Chem., Int. Ed.*, 1999, **38**, 159.
11 (Dichloromethyl)dimethylchlorosilane is available from Alfa Aesar™ (50 g, $139.00).
12 V. Mamane, T. Gress, H. Krause and A. Fürstner, *J. Am. Chem. Soc.*, 2004, **126**, 8654, and references therein.
13 (*a*) H. E. Paaren, H. F. DeLuca and K. S. Heinrich, *J. Org. Chem.*, 1980, **45**, 3253; (*b*) A. Kutner, K. L. Perlman, A. Lago, R. R. Sicinski, H. K. Schnoes and H. F. DeLuca, *J. Org. Chem.*, 1988, **53**, 3450; (*c*) H. S. Gill, J. M. Londowski, R. A. Corrandino, A. R. Zinsmeister and R. Kumar, *J. Med. Chem.*, 1990, **33**, 480.
14 (*a*) M. Journet and M. Malacria, *J. Org. Chem.*, 1992, **57**, 3085; (*b*) D. P. Curran and N. A. Porter, in *Stereochemistry of Radical Reactions*, Wiley-VCH, Weinheim, 2001, pp. 30–115.
15 J. W. Wilt, F. G. Belmonte and P. A. Zieske, *J. Am. Chem. Soc.*, 1983, **105**, 5665.
16 (*a*) K. W. Krosley, G. J. Gleicher and G. E. Clapp, *J. Org. Chem.*, 1992, **57**, 840; (*b*) D. J. Carlsson and K. U. Ingold, *J. Am. Chem. Soc.*, 1968, **90**, 7047.
17 G. R. Jones and Y. Landais, *Tetrahedron*, 1996, **52**, 7599.
18 S. E. Denmark and S.-M. Yang, *Org. Lett.*, 2001, **3**, 1749.
19 NMR yield based on 60% of conversion.
20 (*a*) S. Bogen, M. Gulea, L. Fensterbank and M. Malacria, *J. Org. Chem.*, 1999, **64**, 4920; (*b*) E. Mainetti, L. Fensterbank and M. Malacria, *Synlett*, 2002, 923.
21 As suggested by a referee, alternative reaction channels are open such as an initial 6-*exo-trig* cyclization, or a 1,5-H transfer from the allylic methylene group. We have not so far isolated products bringing evidence for such pathways. We thank the referee for this suggestion.

