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Comparative Studies on the Generation and Cyclisation Reactions of Difluoroalkyl Radicals

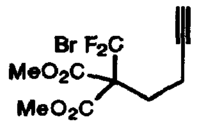
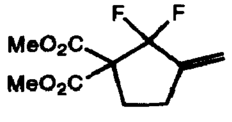
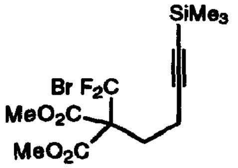
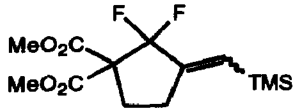
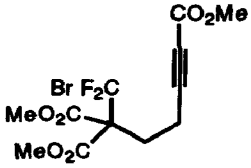
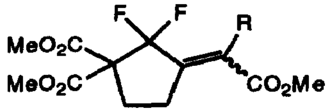
Lisa A. Buttle[a] and William B. Motherwell*[b]

Departments of Chemistry, (a) Imperial College of Science, Technology and Medicine, London, SW7 2AY, UK
(b) Christopher Ingold Laboratories, University College London, 20 Gordon Street, London, WC1H OAJ, UK

Abstract: Treatment of a series of unsaturated bromodifluoromethyl malonate precursors using organotin, samarium, and cobalt reagents as radical triggers leads to the formation of usefully functionalised fluorinated cyclopentanoid products.

Mild and selective methods for the introduction of one or more fluorine atoms into biologically active molecules continue to provide an area of considerable chemical interest and challenge.[1] As part of an ongoing programme designed to highlight the utility of free radical chain reactions for the construction of oxygen atom replacement difluoromethylene analogues of carbohydrates and nucleoside derivatives,[2] we elected to study the behaviour of difluoroalkyl radicals in intramolecular 5-*exo* cyclisation reactions. During the course of our own work, the first reports of such reactions using the ubiquitous organostannane mediated approach have been described.[3] However, to the best of our knowledge, no comparative investigation of the behaviour of other radical triggers has been reported. Furthermore, no systematic study has been carried out to ascertain the relative efficiency of these cyclisations as a function of the electronic nature of the unsaturated radical acceptor in the tethering chain, and hence to glean information on the nucleophilic or electrophilic "character" of the difluoroalkyl radical intermediate. Herein we describe the outcome of these preliminary studies.

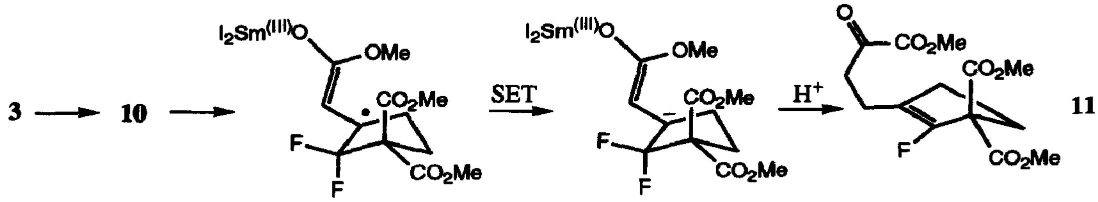
A series of suitable substrates (1)-(7) was readily assembled in good yield by alkylation of the sodium salts of the corresponding monoalkyl malonate derivatives with dibromodifluoromethane using a modification of the conditions reported by Wakselman[4] for the condensation of perhaloalkanes with carbanions. The alkynoate (3) was prepared from (1) by reaction of its derived acetylide anion with methyl chloroformate. In the first instance, we elected to examine the behaviour of the acetylenic series (table 1). Use of the standard tributyltin hydride radical cyclisation protocol[5] led to the formation of difluoromethylene cyclopentanoids (8)-(10) in moderate yield, and in the case of the alkynoate (3) to the isolation of an additional 8% of the *Z*- isomer of the aromatic compound in which the cyclised radical was trapped by benzene solvent.[6] From the stereochemical standpoint, it was of interest to note, as anticipated by the recent observations of Weiler[7] that the selection of tris(trimethylsilyl)silane as reducing agent in conjunction with triethylborane-oxygen as initiator[8] at 0°C led to an improved yield, together with a significant alteration in the *Z*:*E* ratio[6] of vinylsilanes (9) derived from (2).

Substrate	Products	Reagent	*Z* :*E* Ratio	Yield (%)
 **1**	 **8**	A B		42 86
 **2**	 **9**	A B C	3.5 : 1 3.0 : 1 1.4 : 1	45 67 85
 **3**	 **10**	A	R = H R = Ph, *Z* only	49 8

Reagent Conditions:
A: nBu_3SnH (1.1eq), AIBN (10mol.%), benzene, reflux, 12-15h addition
B: SmI_2 (0.1M) in THF), THF : DMPU (9:1), RT
C: $(TMS)_3SiH$ (1.2eq), Et_3B / O_2 (20mol.%), THF, -78°C-0°C

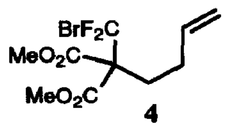
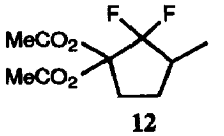
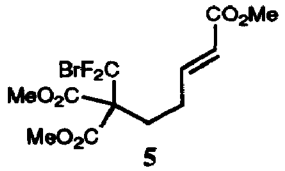
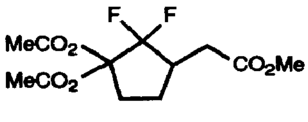
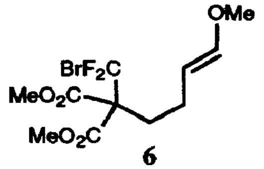
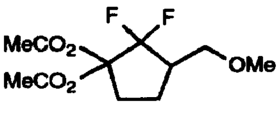
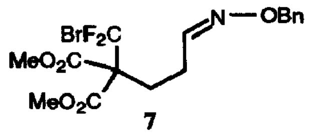
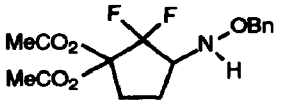
Table 1

The widely successful samarium(II) diiodide/THF/DMPU[9] single electron transfer reagent system also proved superior to the stannane for cyclisation reaction of the parent and silyl substituted alkynes (**1**) and (**2**). To our initial surprise however, the reaction between alkynoate (**3**) and samarium(II) diiodide led to isolation of the monofluorocyclopentene (**11**) in 51% yield. As shown in Scheme 1, we envisage that this product may be formed by further reduction of an initially formed acrylate ester (**10**) (R=H) to a dianionic samarium ester enolate species capable of elimination of fluoride anion.



Scheme 1

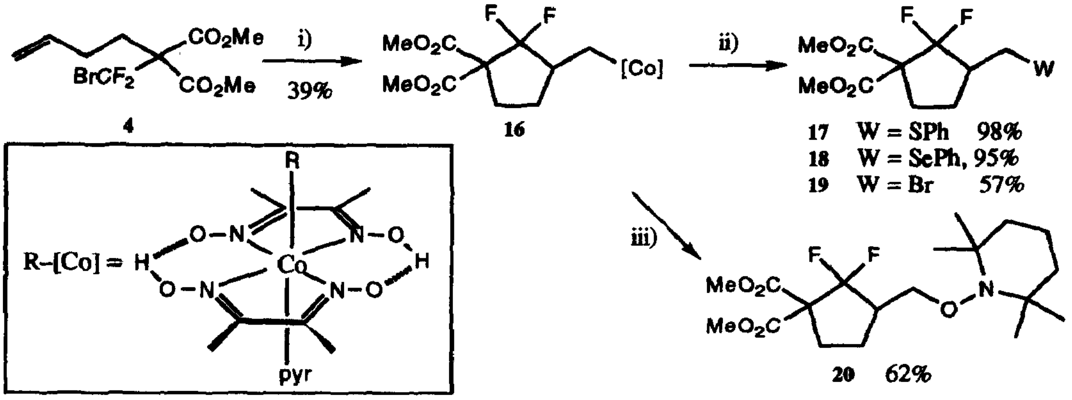
We then directed our attention to the comparative 5-*exo* trigonal reactions of the unsaturated precursors (**4**)-(**7**). Examination of the results shown in table **2** clearly reveals that the most efficient cyclisation reactions are achieved when the difluoroalkyl radical is partnered by a more electron withdrawing substituent at the sp^2 terminus. The relative reluctance of the enol ether (**6**) to undergo cyclisation was made particularly manifest by the isolation, in this sole instance, of the reduced open chain precursor (5%) under tin hydride conditions. Although, at first sight, it might be tempting to speculate that the character of the difluoroalkyl radical should be dominated by the inductive effect of the fluorine atoms, the influence of the neighbouring lone pairs adjacent to the carbon centered radical undoubtedly play a major role, and the SOMO energy of a difluoroalkyl radical is probably similar to that of a simple nucleophilic alkyl radical.[11] In consequence, difluoroalkyl radicals preferentially exhibit nucleophilic character.

Substrate	**Products**	**Reagent**	**Yield (%)**
 **4**	 **12**	**A** **B**	51 53
 **5**	 **13**	**A**	65
 **6**	 **14**	**A** **B**	38* 22
 **7**	 **15**	**B**	71

Reagent Conditions:
A: nBu_3SnH (1.1eq), AIBN (10mol.%), benzene, reflux, 12-15h addition
B: SmI_2 (0.1M in THF), THF : DMPU (9:1), 20°C
* + 5% reduced uncyclised material

Table 2

Finally, in view of the excellent opportunities offered by organocobalt chemistry[10] for further incorporation of useful functionality, we have examined the behaviour of alkene (4) in such systems using the convenient *in situ* borohydride reduction method developed by Branchaud.[11] Interestingly, and in contrast to the case of the parent 6-bromohex-1-ene, this reaction led directly to the cyclised complex (16), which was isolated as an orange crystalline solid (39%), and whose structure was rigorously determined by a single crystal X-ray diffraction study (Scheme 2). As expected, subsequent reaction of (16) with a range of suitable radical trapping agents under photolytic conditions, allowed controlled introduction of oxygen, sulphur, selenium and halogen functionality in good to excellent yield.



Reagent Conditions:
i) dimethylglyoxime (2eq), $CoCl_2.6H_2O$, pyridine, NaOH/$NaBH_4$, MeOH
ii) PhSSPh (1.4eq), or PhSeSePh (1.4eq), or $BrCCl_3$ (1.4eq), benzene, hυ
iii) TEMPO (1.4eq), benzene, hυ

Scheme 2

The foregoing results have hopefully highlighted that a variety of usefully functionalised difluoromethylene cyclopentanoids[12] are accessible using organostannane, samarium and organocobalt mediated radical cyclisations, and that the intermediate difluoroalkyl radicals preferentially exhibit nucleophilic character towards unsaturated acceptors.

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6. Stereochemical assignments were based on the comparative results of nOe experiments. Thus, irradiation of the vinylic proton of the Z-isomer of (9) gave an nOe of +1.5% to the allylic ring protons. In the case of (10) (R=Ph), irradiation of the allylic ring protons led to a +5% enhancement of the aromatic signal. Although compound (10) (R=H) was formed as a single stereoisomer, no definitive assignment can be made.
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12. All compounds listed are fully characterised by ^{1}H, ^{19}F, ^{13}C NMR, and mass spectral analysis.

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