Highly regio- and stereo-selective alkyl substitution with copper reagents for the construction of chiral trifluoromethylated quaternary carbon centres

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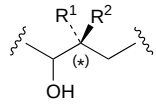
A new route for the asymmetric construction of quaternary carbon centres containing a trifluoromethyl group has been established using a highly regio- and stereo-selective S_N2' reaction of organocopper and organocuprate reagents with allylic mesylates 4 and 8.

Enhancement of biological activity in many natural product classes by the selective introduction of one, two or three fluorine atoms is a proven cornerstone strategy for medicinal and bioorganic chemists.[1] We were intrigued by the stereospecific replacement of either methyl group in the structure **1**, as found

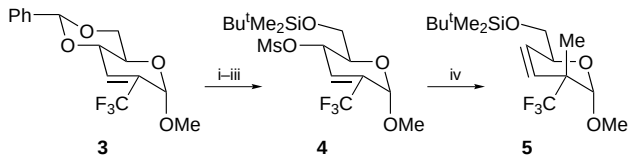


1 $R^1 = R^2 = Me$
2a $R^1 = CF_3$, $R^2 = Me$
2b $R^1 = Me$, $R^2 = CF_3$

in Epothilone A[2] and antitumour active Shikoccidine derivatives,[3] by a trifluoromethyl moiety, which would lead to the sterically as well as electronically modified structures **2a** or **2b** with an additional asymmetric carbon centre. However, as far as we are aware, the Diels–Alder reaction of 2-(trifluoromethyl)acrylate[4] is the only reported procedure to access such a target structure, possibly due to the difficulty of alkyl substitution at a CF_3-attached carbon centre.[5] Although in general the S_N2' reaction and 1,4-addition of cuprates are among the most efficient methods for the synthesis of quaternary centres,[6] such an approach has not yet been attempted in this context.

Recently we reported a novel strategy for the synthesis of optically active compounds with variously fluorinated methyl groups ($CH_{3-n}F_n$: n = 1–3) *via exo*-difluoromethylene compounds synthesised from commercially available D-glucose.[7,8] Utilization of the readily accessible allylic alcohol **3** *via* S_N2' reaction with copper reagents is an attractive way to create diastereoselectively a quaternary centre. An additional synthetic advantage of this approach is the possibility of controlling the alkene stereochemistry as *Z*, an outcome which is not easily obtainable otherwise. Here we describe the regio- and stereoselective alkyl substitution of allylic mesylates **4** and **8** using organocopper and organocuprate chemistry.

At the initial stages of this investigation, we chose the substrate **4** depicted in Scheme 1. To our surprise, reaction of allylic mesylate **4**, easily prepared from **3** in three steps, with

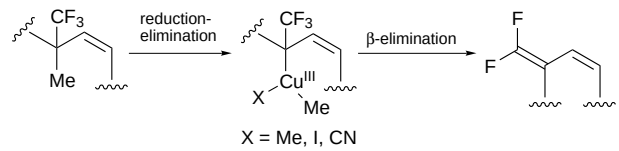


Scheme 1 *Reagents and conditions*: i, TFA, MeOH–H_2O; ii, Bu^tMe_2SiCl, imidazole; iii, MsCl, Et_3N; iv, organocopper and organocuprate reagents

Gilman cuprate Me_2CuLi–LiI in Et_2O gave the unexpected diene **6** in 98% yield, rather than either the S_N2' product or the common S_N2 type byproduct (Table 1, entry 1). Although the desired S_N2' material **5** was furnished in 35% yield after changing the solvent to THF, **6** was still the main product (54% yield, entry 2). Formation of **6** may be rationalized by the preferential Cu–F elimination because of the relatively poor reductive elimination ability of the Me ligand on the intermediary σ-copper(III) adduct (Scheme 2).† One result which supported this assumption was obtained by the addition of the electron-donating bidentate amine tetramethylethylenediamine (TMEDA) to the conditions used in entry 2: TMEDA was considered to make the ground state more stable than the corresponding transition state by analogy with HMPA,‡ and the yield of **6** was significantly increased from 54 to 92% (entry 2 *vs.* 6).

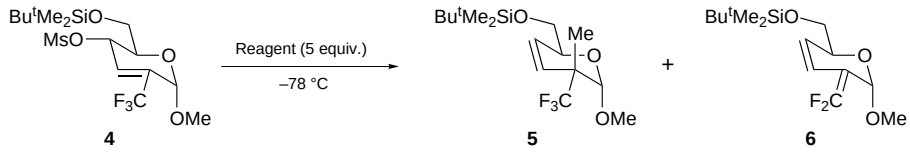
The above unfavourable pathway giving the difluorinated diene **6** was avoided by the use of cyanocuprate, known to undergo a facile reductive elimination,[9,10] resulting in complete S_N2' displacement (entry 5). Moreover, it was also found that addition of BF_3 to the Gilman cuprate Me_2CuLi–LiI effectively suppressed the Cu–F elimination irrespective of the solvent (entries 3 and 4). Treatment of **4** with organocopper reagent, MeCu–LiI, yielded **5** with high stereoselectivity and complete γ-selectivity (entry 7). On the other hand, in sharp contrast to the case of the Gilman reagent, significant retardation of the reaction by BF_3 was observed, and this system furnished the S_N2' product **5** in a disappointing 18% yield (entry 8).

It is well-known that the use of an organocopper reagent in a different solvent and/or in the presence (or absence) of ligands or Lewis acids sometimes leads to the formation of different species or equilibration mixture, and Table 1 collects the proposed reactive species in each specific conditions. Lipshutz *et al.* claimed that in Et_2O solution Me_2CuLi exists in the dimeric form $Me_4Cu_2Li_2$ (entry 1), while further addition of 2 equiv. of BF_3 affords a mixture of $Me_5Cu_3Li_2$ and MeLi–BF_3 (entry 3).[11] In THF, Me_2CuLi forms an equilibrium mixture of MeLi, Me_3Cu_2Li and $Me_4Cu_2Li_2$ (entry 2), which is converted to Me_3Cu_2Li and MeLi–BF_3 when such a solution is treated with BF_3 (entry 4).[12] It should be noted that the dimeric Gilman cuprate $Me_4Cu_2Li_2$ is the reactive species leading to *exo*-difluoromethylene compounds **6** (entries 1 and 2). On the basis of chemical and NMR spectroscopic experiments, Lipshutz also proposed that MeCu–LiI was in an equilibrium with a MeLi–BF_3 complex and I_2CuLi in the presence of BF_3[13] and thus, comparison of entries 7 and 8 suggests only low reactivity of MeLi–BF_3 in this procedure. Consequently, it is concluded that both $Me_5Cu_3Li_2$ and Me_3Cu_2Li should be the 'true' reacting species giving **5** by smooth reductive elimination.



Scheme 2

Table 1 Substitution of allylic mesylate **4** with organocopper and organocuprate reagents



4 **5** **6**

Entry	Reagent[a]	Solvent	Additive	*t*/h	Proposed species	Product (%)[b] **5**	**6**
1	Me_2CuL–LiI	Et_2O	—	0.25	$Me_4Cu_2Li_2$[c]	0	98
2	Me_2CuLi–LiI	THF	—	0.25	MeLi + Me_3Cu_2Li + $Me_4Cu_2Li_2$[c]	35	54
3	Me_2CuLi–LiI	Et_2O	BF_3[d]	0.25	$Me_5Cu_3Li_2$ + MeLi·BF_3[e]	96	0
4[f]	Me_2CuLi–LiI	THF	BF_3[d]	0.25	Me_3Cu_2Li + MeLi·BF_3[e]	95	0
5	$Me_2CuCNLi$	Et_2O	—	2		98	0
6	Me_2CuL–LiI	THF	TMEDA[d]	0.25		5	92
7	MeCu–LiI	Et_2O	—	1.5		95	0
8	MeCu–LiI	Et_2O	BF_3[g]	3	MeLi·BF_3[h]	18[i]	0

[a] 5 quiv. based on **4**. [b] Determined by ^{19}F NMR spectroscopy. [c] Ref. 12. [d] 10 equiv. [e] Ref. 11. [f] BF_3 was added at −60 °C. [g] 5 equiv. [h] Ref. 13. [i] Starting material (76%) was recovered.

Next, we performed the same reaction with a different substrate containing a CF_3 group at the 4-position. The requisite allylic mesylate **8** was prepared as shown in Scheme 3.

As was our expectation, treatment of **8** with cyanocuprate MeCuCNLi, the best reagent with the allylic mesylate **4**, furnished **9** again as a single stereoisomer in 96% yield. For the determination of the stereochemical course of this S_N2' reaction, **9** was subjected to hydrogenation and the C-4 methyl group of thus obtained **11** was concluded to be axially oriented from NOE measurements (Scheme 3). This result is rationalized in terms of the well-accepted *anti* S_N2' mechanism.[14] Deprotection of methyl glucoside **9** with BBr_3 and formation of the dithioacetal allowed us to readily transform **9** into the corresponding acyclic form **10** with complete retention of (*Z*) stereochemistry (11.6 Hz between H-2 and H-3).

In conclusion, a novel pathway for the highly regio- and stereo-selective S_N2' reaction of allylic mesylates **4** and **8** has been realized, which forms a unique strategy for the construction of chiral quaternary carbon centres containing a trifluoromethyl group. Further application of the present reaction to mono- as well as di-fluoromethylated allylic mesylates is currently being pursued in our laboratories.

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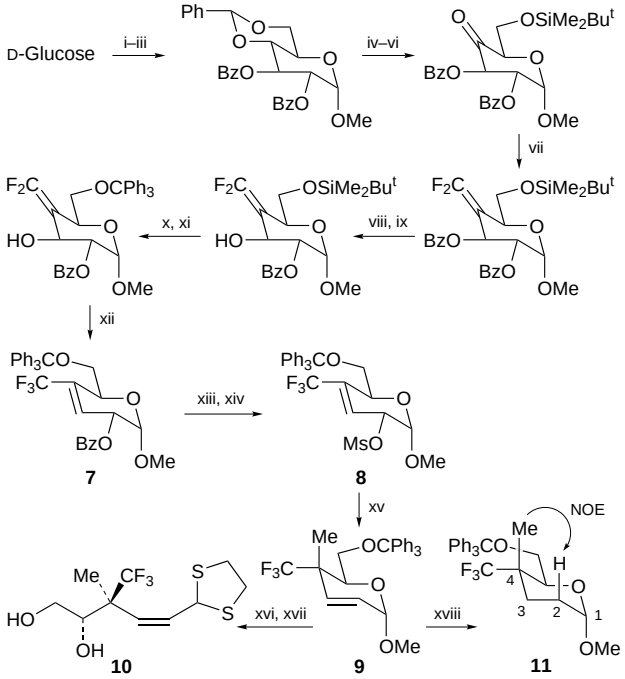

Scheme 3 *Reagents and conditions*: i, MeOH, HCl; ii, PhCH $(OMe)_2$, TsOH (cat.); iii, BzCl, pyridine, room temp.; iv, TsOH (cat.), MeOH; v, Bu^{t}Me$_2$SiCl, imidazole; vi, PDC, Ac_2O; vii, CF_2Br_2–$(Me_2N)_3P$; viii, DIBAL-H; ix, BzCl, pyridine, 0 °C; x, AcOH–H_2O; xi, Ph_3CCl, Et_3N; xii, DAST; xiii, K_2CO_3, MeOH; xiv, MsCl, Et_3N; xv, MeCuCNLi; xvi, BBr_3; xvii, $HS(CH_2)_2SH$, BF_3·Et_2O; xviii, H_2, Pd/C

Footnotes and References

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† This type of elimination was reported in the case of allylic sulfinyl mesylates: see ref. 9.

‡ Strongly electron-donating HMPA was calculated to increase the energy barrier to reductive elimination when added to Me_3Cu: S. H. Bertz, G. Miao, B. E. Rossiter and J. P. Snyder, *J. Am. Chem. Soc.*, 1995, **117**, 11023.

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