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Construction of Optically Active CF_3-Containing Quaternary Carbon Centers via Stereospecific S_N2' Reaction†

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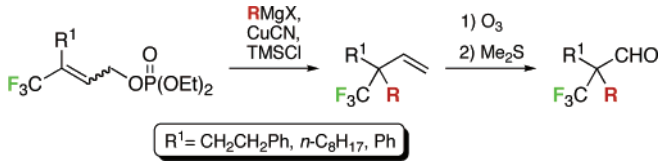
ABSTRACT



Phosphates from 3-substituted 4,4,4-trifluorobut-2-en-1-ols were found to be effective for construction of CF_3-containing quaternary carbon centers by way of Cu(I)-catalyzed Grignard reactions in the presence of catalytic amounts of CuCN and trimethylsilyl chloride (TMSCl) in an anti S_N2' manner.

Since quaternary carbon centers with only carbon atoms were frequently found as the partial structure of various naturally occurring biologically active compounds,[1] synthetic studies of such special units in a stereoselective fashion have been extensively carried out in recent years.[2]

On the other hand, introduction of fluorine atom(s) into organic compounds has been known as one of the major strategies for enhancement or modification of their original biological activities.[3] Thus, from the standpoint of the pharmaceutical utility of fluorinated materials, it would be quite intriguing to substitute a methyl moiety at a quaternary carbon site to a trifluoromethyl (CF_3) group; however, very limited synthetic examples that allowed us to conveniently assemble requisite molecules have been reported.[4] This situation prompted us to further develop new synthetic procedures to access such specific structures.[5]

Recently, we have reported that the CF_3-containing allylic alcohol derivatives such as **1** furnished the substitution products **2** via the clean anti S_N2' mechanism when treated with an appropriate Grignard reagent in the presence of catalytic amounts of CuCN and TMSCl, without any trace

† Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday.

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(2) For a review on the construction of quaternary carbon centers, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105.

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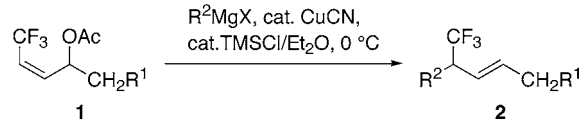
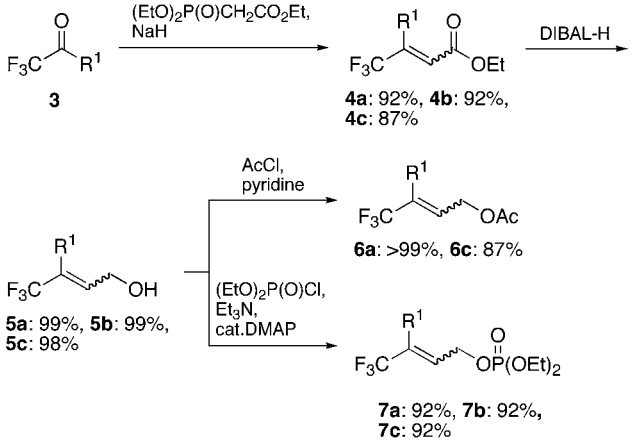
Scheme 1



amount of the corresponding S_N2 products (Scheme 1).[6] Because we have already established enzymatic resolution of the alcoholic part of **1**,[7] construction of chiral **2** was readily attained with high optical purity. In this communication, we would like to report further extension of this S_N2' methodology for formation of materials possessing chiral CF_3-containing quaternary carbon centers.

First of all, we have prepared the requisite substrates for the present purpose, allylic acetates **6** and the corresponding phosphates **7**, by the routine methods as outlined in Scheme 2. The first Horner−Wadsworth−Emmons process afforded

Scheme 2

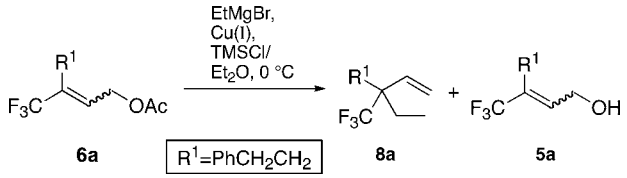


a: R^1= CH_2CH_2Ph (*E*/*Z* = 84/16), **b**: R^1= *n*-C_8H_{17} (*E*/*Z* = 81/19)
c: R^1= Ph (*E*/*Z* = 83/17)

E/*Z* mixtures of **4** in an approximate ratio of 8:2 irrespective of the nature of R^1, which was basically constant until they were derived into **6** and **7**. The previously employed conditions[6] for the construction of CF_3-containing tertiary carbon centers were applied to **6a** to furnish the desired S_N2' compound **8a** in 60% yield along with 28% of deacetylated allylic alcohol **5a**. This side product, not observed at all for **1**,[6] would be formed as the result of increase of steric hindrance around the reaction site. This fact apparently indicated that modulation of the previous conditions was required for nice adjustment to the present system.

It was easily understood that it is only CuCN that was effective in obtaining the desired S_N2' product **8a** (entries

Table 1. Optimization of Reaction Conditions with **6a**



entry	Cu (I) (equiv)	EtMgBr (equiv)	TMSCl (equiv)	isolated yield (%) **8a**	**5a**
1	none	1.2	none	<1	82[a]
2	CuCl (0.2)	1.2	none	<1	76
3	CuI (0.2)	1.2	none	4	74
4	CuCN (0.2)	1.2	none	60	28
5[b]	CuCN (0.2)	1.2	none	51	26
6[c]	CuCN (0.2)	1.2	none	14	13
7	CuCN (0.2)	1.2	0.6	67	20
8	CuCN (0.2)	1.2	1.0	73	22
9	CuCN (0.2)	1.2	1.5	68	26
10	CuCN (0.2)	1.5	1.0	73	23
11	CuCN (0.2)	2.0	1.0	56	37
12	CuCN (0.4)	1.5	1.0	72	19
13	CuCN (0.6)	1.5	1.0	74	20
14	CuCN (1.0)	1.5	1.0	72	16

[a] Also recovered was 11% of **6a**. [b] Stirred at −78 °C for 30 min and then stirred at 0 °C for 30 min. A mixture of **8a**/**9a**/**10a** = 70:11:19 (by ^{19}F NMR) was isolated in 51% yield along with 2% of recovery. [c] In THF/Et_2O (12:1) solvent. A mixture of **8a**/**9a**/**10a** = 2:13:85 (by ^{19}F NMR) was isolated in 14% yield.

1−4), and other Cu(I) catalysts exclusively afforded the deprotected alcohol **5a**. Reaction at lower temperature (−78 °C) allowed us to obtain larger amounts of the S_N2 product and difluorinated diene (vide infra) possibly because of retardation of the reductive elimination rate,[8] facilitating isomerization to the sterically less biased form and β-elimination by intramolecular Cu−F interaction, respectively (entry 5). Similar to the previous case, a quite significant solvent effect gave rise to suppression of the desired pathway in THF (entry 6).[9] The proportion of the S_N2' product **8a** was increased by addition of TMSCl,[10] and 1.0 equiv was found to be the amount of choice (entries 8 and 10); however, its contribution was not as effective as the previous case. Goering reported that although allylic acetates accepted Grignard attack at their carbonyl carbon under the Cu(I)-catalyzed conditions, bulkier pivalate or 2,4,6-trimethylbenzoate were effective in inhibition of such an unfavorable process.[11] We also employed isobutyrate and pivalate, but the yield of the S_N2' product was not remarkably affected (isobutyrate: 72% yield and 11% of **5a**; pivalate: 33% yield and 4% of **5a**). On the other hand, exclusive formation of the S_N2' product was realized in 93% yield by way of the

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corresponding phosphate **7a**. Previously,[6] the usefulness of this leaving group was demonstrated for the cases when an acetoxy moiety did not work properly, but we hesitated to employ it because, from our experience, phosphates sometimes resulted in lower chirality transmission due to their high leaving ability, probably allowing this process to proceed in part via the S_N1 mechanism.

In Table 2, the Grignard-based S_N2' reaction of allylic phosphates **7a**−**c** is summarized. As expected, these substrates showed the complete S_N2' selectivity without yielding the possible regioisomeric S_N2 products **9** when reacted with such primary halide-based reagents as Et- and $PhCH_2CH_2MgBr$. Predominant formation of the S_N2 products **9** was noticed for PhMgBr probably due to the less potent transferability of a phenyl group as a ligand.[12] As the steric bulkiness of the Grignard reagents increased, the S_N2-type reaction and F_2-diene formation became the major pathways along with the desired route to the S_N2' compounds **8**, and the significantly bulky *t*-BuMgCl furnished only sluggish results.

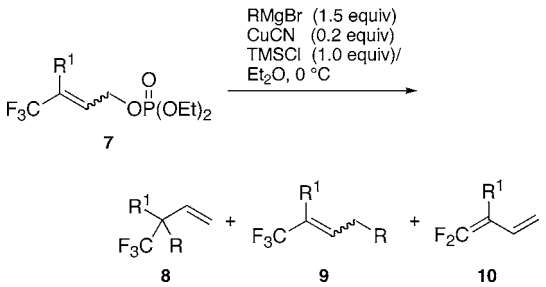
When *n*-C_8H_{17}- and $PhCH_2CH_2MgBr$ were allowed to react with the phosphate **7c** possessing a phenyl group at the γ-position as R^1, a lower level of S_N2' selectivity was obtained because a bulkier phenyl group would cause severe steric and/or electronic repulsive interaction with the incoming nucleophilic species. On the other hand, it was intriguing to note that transformation of the difluorodiene **10** (R^1 = Ph) was not observed for this specific substrate.

The present reaction mechanism was explained as follows (Scheme 3). Similar to the case of our recent work, TMSCl complexation toward cuprates might effectively decrease the activation energy of reductive elimination due to the β-cation stabilizing effect of the Si atom.[13] Thus, when R and R^1 were small enough in size, R migration would relatively readily proceed from **Int-B** to afford the desired products **8**. On the other hand, sterically bulkier alkyl groups rendered this intermediate more congested and less stable, which would increase the likelihood of the Cu−F β-elimination[6,14] or isomerization to sterically more favorable **Int-C**, the latter of which would eventually give the S_N2 products **9**. Steric congestion could also facilitate the attack at the acetate carbonyl group as an alternative route.

Except for limited cases such as entries 2 and 9 in Table 2, the desired CF_3-containing S_N2' products **8** were obtained only as an inseparable mixture with S_N2 and defluorinated products, **9** and **10**, respectively. However, ozonolysis of such mixtures affected the oxidative cleavage at the C=C bond, and addition of Me_2S eventually led to isolation of the corresponding aldehydes **11** with a quaternary center at their α-position without contamination of any other fragments (Table 3).

At the next stage, we extended this process to the chiral allylic alcohol **13** (Scheme 4). We have selected ketone **3a**

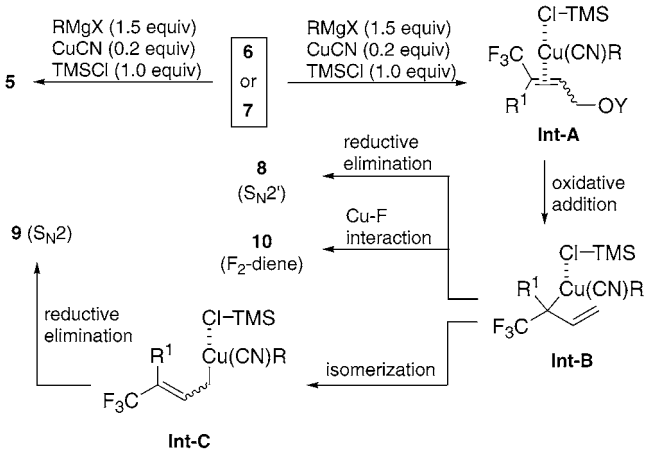
Table 2. S_N2' Reaction of **7** with Various Grignard Reagents



			distribution[b]			
entry	substrate	R[a]	**8**	**9**	**10**	yield (%)[c]
1	**7a**	Me	86	4	10	73
2		Et	>98	<1	<1	93
3		*i*-Pr	39	44	17	81
4		*i*-Bu	86	8	6	94
5		*t*-Bu				d
6		Ph	12	50	38	82
7		$Ph(CH_2)_2$	97	3	<1	>99
8	**7b**	Me	81	8	11	47
9		Et	>98	<1	<1	87
10		*i*-Pr	59	35	6	83
11		*i*-Bu	79	20	1	83
12		*t*-Bu				d
13		Ph	3	70	27	81
14		$Ph(CH_2)_2$	97	3	<1	>99
15	**7c**	*n*-C_8H_{17}	75	25	<1	96
16[e]		*n*-C_8H_{17}	63	37	<1	62
17		*i*-Bu	33	67	<1	48
18		*t*-Bu	8	92	<1	27
19		Ph	<1	>98	<1	61
20		$Ph(CH_2)_2$	68	32	<1	96

[a] In the case of *i*-Pr, *i*-Bu, and *t*-Bu, the corresponding magnesium chloride was used. [b] Product distribution was determined by ^1H NMR and/or ^{19}F NMR. [c] Combined yield. [d] Complex mixture was obtained. [e] **6c** was used as the substrate.

Scheme 3



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(13) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.

(14) Similar type of Cu−F elimination, see: Xu, Y.; Jin, F.; Huang, W. *J. Org. Chem.* **1994**, *59*, 2638.

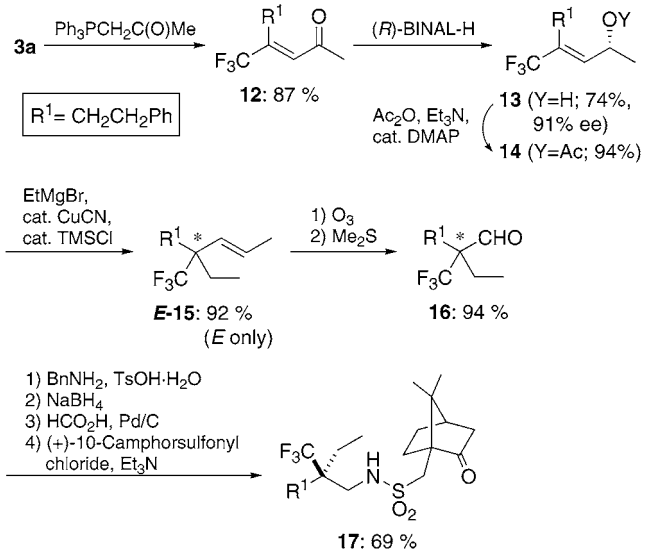
Table 3. Ozonolysis of S_N2' Products

			distribution[a]			
entry	R^1	R	**8**	**9**	**10**	yield of **11**[b] (%)
1	$PhCH_2CH_2$	Et	>98	<1	<1	76
2		*i*-Bu	88	8	4	76
3	*n*-C_8H_{17}	Et	96	4	<1	76
4		*i*-Bu	78	14	8	88
5	Ph	*n*-C_8H_{17}	76	24	<1	82

[a] Material distribution was determined by ^{19}F NMR. [b] Isolated yield based on the S_N2' starting material.

as the starting material, which was converted to α,*β*-unsaturated ketone **12** with exclusive *E*-selectivity by the conventional method. Asymmetric reduction of ***E*-12** in the presence of (*R*)-BINAL-H gave the allylic alcohol **13** in 91% ee, whose absolute configuration was expected to be *R* on the basis of the already proposed *n*-*π*-type electronic repulsion in the transition state between the binaphthoxy oxygen and the unsaturated moiety.[15] Subjection of EtMgBr to an ethereal solution of ***E*-14** in the presence of CuCN and TMSCl realized complete chirality transmission for the formation of ***E*-15**, which was further transformed into the α-chiral aldehyde **16** by ozonolysis. Conversion of **16** to camphorsulfornyl amide **17** was carried out by a four-step sequence, and the single-crystal X-ray diffraction analysis of the latter clarified its absolute configuration as *R*. This stereochemical output is consistently explained as the result of the general organocupper anti S_N2' displacement mechanism starting from (*R*)-allylic alcohol **13**.[16] On the other hand, the corresponding phosphate instead of the acetate **14** gave a mixture of **15** (*E*/*Z* = 90/10) and the corresponding S_N2 product in a ratio of 91:9, and only 63% of chirality transmission was observed for ***E*-15** as was expected.

Scheme 4



In conclusion, the trisubstituted CF_3-containing allylic derivatives were demonstrated to be good candidates for efficient construction of quaternary carbon centers via the S_N2' reaction by treatment with appropriate Grignard reagents in the presence of CuCN and TMSCl. Moreover, this system can be readily extended to the chiral version with the aid of BINAL-H-mediated reduction, which, by way of ozonolysis of the reaction mixture obtained, eventually realized isolation of the optically active aldehyde **16** with the CF_3-substituted quaternary carbon center. The scope and limitation of this method is now under investigation in this laboratory.

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds (**4**−**17**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.