ORGANIC LETTERS

2012
Vol. 14, No. 20
5366–5369

# Decarboxylative Allylation of Trifluoroethyl Sulfones and Approach to Difluoromethyl Compounds

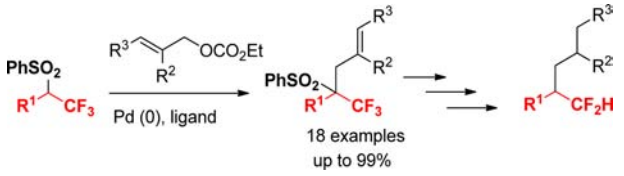
**Norio Shibata,*,† Kazunobu Fukushi,† Tatsuya Furukawa,† Satoru Suzuki,† Etsuko Tokunaga,† and Dominique Cahard‡**

*Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan, and UMR 6014 CNRS COBRA, Université et INSA de Rouen, 76821 Mont-Saint-Aignan, France*

*nozshiba@nitech.ac.jp*

**Received September 20, 2012**

## ABSTRACT




**Allyl carbonates undergo palladium-catalyzed decarboxylative allylation of trifluoroethyl phenyl sulfones. The success of the allylation, which is not efficient under typical strong base-mediated conditions, is the result of mild conditions thanks to a progressive delivery of ethoxide. Indeed, ethyl allyl carbonates act as a latent source of ethoxide for generation of the trifluoroethyl carbanion that reacts with the $\pi$-allylpalladium complex. The utility of the method is illustrated in a new approach to difluoromethyl compounds.**

Within the ever-growing field of organofluorine chemistry, finding novel applications for simple and easily available fluorinated building blocks is of prime interest and highly challenging. In this context, new reactions that allow the introduction of fluoroalkyl moieties into organic molecules are eagerly sought after.[1] Among the variety of synthetically important fluoroalkyl groups, fluoromethyl groups represented by $CF_3$, $CF_2H$, and $CFH_2$ are the smallest units that are known to play important roles in a wide field of science, especially in medicinal chemistry.[2] Therefore, development of efficient methods for the synthesis of fluoromethylated compounds is in great demand. Trifluoromethyl trimethylsilane, $Me_3Si-CF_3$, called the Ruppert–Prakash reagent, is one of the most successful trifluoromethyl anion sources to obtain trifluoromethylated compounds.[3] A difluoromethyl variant of this reagent, $Me_3Si-CF_2H$, has also been investigated.[4] Unlike the huge amount of information reported in the chemistry of fluoromethyl anions, the potential of the trifluoroethyl carbanion $CF_3CH_2^-$ has been scarcely explored essentially because of the feared defluorination reaction.[5] Undeniably, the alkylation of carbanions bearing a trifluoromethyl

† Nagoya Institute of Technology.
‡ Université et INSA de Rouen.

(1) (a) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (b) Ni, C.; Hu, J. *Synlett* **2011**, 770. (c) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, No.65. (d) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (e) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (f) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallowb, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Bégué, J. P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, Germany, 2008. (d) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.

(3) (a) Prakash, S. G. K.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633.

(4) (a) Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524.

(5) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817.

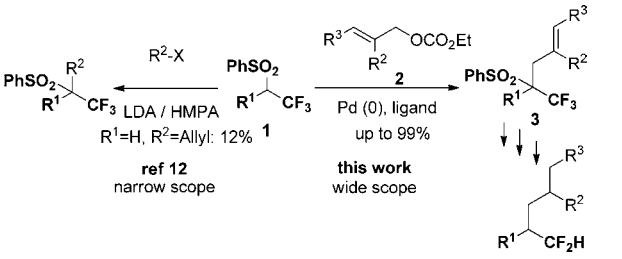
(6) (a) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369. (b) Sato, K.; Takiguchi, Y.; Yoshizawa, Y.; Iwase, K.; Shimizu, Y.; Tarui, A.; Omoto, M.; Kumadaki, I.; Ando, A. *Chem. Pharm. Bull.* **2007**, *55*, 1593. (c) Yamauchi, Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, *4*, 173. (d) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276. (e) Ishikawa, N.; Yokozawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 724. (f) Yokozawa, T.; Nakai, T.; Ishikawa, M. *Tetrahedron Lett.* **1984**, *25*, 3987. (g) Yokozawa, T.; Nakai, T.; Ishikawa, M. *Tetrahedron Lett.* **1984**, *25*, 3991. (h) Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 7043. (i) Fujita, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4377. (j) Grellepois, F.; Kikelj, V.; Coia, N.; Portella, C. *Eur. J. Org. Chem.* **2012**, 509.

10.1021/ol302589w 
**Published on Web 10/10/2012**

group is one of the most difficult tasks in carbanion chemistry. Although some reactions of such carbanions have been reported,[6] practical alkylation of trifluoroethyl carbanions and their synthetic application remain important synthetic challenges. Since our research group has recently focused on the synthetic utility of monofluoromethylated phenylsulfone derivatives such as FBSM[7,8] and FBDT,[9] we next became interested in 2,2,2-trifluoroethyl phenylsulfones, $CF_3CHRSO_2Ph$ **1**,[10−12]as precursors of trifluoroethyl carbanions $CF_3CRH^-$. In addition to the utility of the phenylsulfonyl group in synthetic organic chemistry, the trifluoroethyl phenylsulfonyl moiety itself is of great importance as a key component in biologically active compounds, for example, stromelysin-1, a potent inhibitor of MMP-3.[13]

An early study by Uneyama and Momota in 1989 revealed that alkylation of the phenylsulfonyl 2,2,2-trifluoroethyl carbanion is problematic.[12] After careful investigation, 3 equiv of LDA and tetraethylammonium chloride in THF-HMPA plus 10 equiv of methyl iodide provided the methylation product in 80% yield. However, allyl iodide gave the allylated 2,2,2-trifluoroethyl phenylsulfone in only 12% yield and other alkylating agents (ethyl iodide, benzyl bromide) failed to react. In 2011, we reported a new approach toward α-carbonyl $CF_3$-bearing quaternary centers based on a palladium-catalyzed intramolecular decarboxylative allylation.[14] We surmised that failures encountered in allylation of the trifluoroethyl carbanion in the studies by Uneyama would be solved under the neutral reaction conditions of an intermolecular palladium-catalyzed decarboxylative allylation. The generated trifluoroethyl carbanions $CF_3CRH^-$ should be dually stabilized by the electron-withdrawing phenylsulfonyl group and the cationic allyl palladium ligand.[15,16] Herein, we report efficient conditions for allylation of 2,2,2-trifluoroethyl phenylsulfones **1** through a palladium-catalyzed decarboxylative allylation with allyl carbonates **2** to provide allylated sulfone derivatives **3** that feature a tertiary or a quaternary trifluoromethylated carbon center. The products obtained are of great interest not only as components of biologically active compounds but also as precursors of difluoromethylated compounds after three successive reductive treatments (Scheme 1).

**Scheme 1.** Strategies for Allylation of Trifluoroethyl Sulfones **1**




Our investigations started with the reaction conditions for the decarboxylative allylation of α-trifluoromethyl β-keto esters:[14] 2.5 mol % tris(dibenzylideneacetone) dipalladium [$Pd_2(dba)_3$] and 1,2-bis(diphenylphosphino) ethane (dppe) in THF. Under these conditions in the presence of ethyl allyl carbonate **2a**, the allylation of phenyl trifluoroethyl phenylsulfone **1a** takes place within 1 h at 40 °C to provide the desired allylated phenyl trifluoroethyl phenylsulfone **3a** in 92% yield (Table 1, entry 1). Further optimization of the reaction conditions using a variety of palladium(II) sources, ligands including mono- and bidentate phosphines, solvents, and various ligand-to-palladium ratios did not improve the yields (see Table S1 in the Supporting Information).

We next examined the substrate scope for the decarboxylative allylation under the best reaction conditions. Trifluoroethyl phenylsulfones **1b**−**g** having a variety of aromatic groups at the reaction center were effectively allylated to provide the desired products **3b**−**g** that feature a quaternary trifluoromethylated carbon center in 91 to 99% yields (entries 2−7). Substitution of the benzene ring as well as group position did not affect yield and reactivity. Alkyl, allyl, cinnamyl, and chloro substituted substrates **1h**−**l** were also efficiently transformed into the corresponding allylated trifluoroethyl phenylsulfones **3h**−**l** in over 90% yields. The reaction of nonsubstituted trifluoroethyl phenylsulfone **1m** with allyl ethyl carbonate (**2a**) or cinnamyl ethyl carbonate (**2b**) provided the desired allylation products **1j, k** having a tertiary stereocenter, although the yields were low due to competitive bis-allylation (entries 13−14). Fortunately, changing the ligand from dppe to 1,1'-bis(diphenylphosphino)ferrocene (dppf) improved the yields of monoallylation significantly (entries 15 and 16), while bis-allylation was selectively observed in a high yield of 97% when 2 equiv of allyl carbonate were used in the presence of dppe (entry 17). Evaluation of ethyl methallyl carbonate (**2c**) in this decarboxylative process required adjustment of the reaction conditions: rac-BINAP was used as a diphosphine ligand in toluene at 110 °C. With this appropriate protocol, products **3m**−**o** were obtained in

(7) FBSM: fluorobis(phenylsulfonyl)methane. (a) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Yasui, H.; Nakamura, S.; Toru, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4973. (b) Furukawa, T.; Kawazoe, J.; Zhang, W.; Nishimine, T.; Tokunaga, E.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 9684. (c) Ogasawara, M.; Murakami, H.; Furukawa, T.; Takahashi, T.; Shibata, N. *Chem. Commun.* **2009**, 7366.

(8) Ni, C.; Li, Y.; Hu, J. *J. Org. Chem.* **2006**, *71*, 6829.

(9) FBDT: 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide. Furukawa, T.; Goto, Y.; Kawazoe, J.; Tokunaga, E.; Nakamura, S.; Yang, Y.; Du, H.; Kakehi, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1642.

(10) A series of 2,2,2-trifluoroethyl phenylsulfones $CF_3CHRSO_2Ph$ **1** are readily synthesized from $CF_3CHRSPh$ (ref 11) by oxidation or another method (ref 12). See Supporting Information for details.

(11) (a) Nakai, T.; Tanaka, K.; Setoi, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3069. (b) Uneyama, K.; Momota, M. *Tetrahedron Lett.* **1989**, *30*, 2265.

(12) Uneyama, K.; Momota, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3378.

(13) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Adv. Synth. Catal.* **2012**, *354*, 1141.

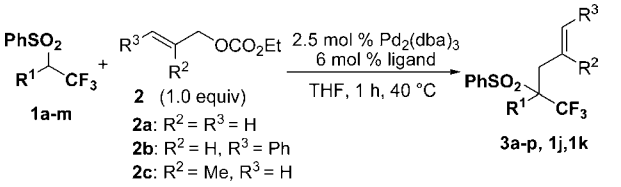
(14) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037.

(15) For an example of intramolecular decarboxylative allylation, see: (a) Weaver, J. D.; Tunge, J. A. *Org. Lett.* **2008**, *10*, 4657. (b) Weaver, J. D.; Ka, B. J.; Morris, D. K.; Thompson, W.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12179.

(16) (a) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Crawley, M. *Chem. Rev.* **2003**, *103*, 2921.

77 to 98% yields (entries 18−20). The reaction of **1k** with **2b** proceeded in the presence of dppf to give symmetrical **3p** in 96% yield (entry 21).

**Table 1.** Substrate Scope




| entry | 1 | $R^1$ | 2 | ligand | 3 | yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | **2a** | dppe | **3a** | 92 |
| 2 | **1b** | 4-$MeC_6H_4$ | **2a** | dppe | **3b** | 91 |
| 3 | **1c** | 4-$MeOC_6H_4$ | **2a** | dppe | **3c** | 98 |
| 4 | **1d** | 3,4-$Me_2C_6H_3$ | **2a** | dppe | **3d** | 97 |
| 5[b] | **1e** | 3,4-$MeO_2C_6H_3$ | **2a** | dppe | **3e** | 93 |
| 6 | **1f** | 4-$^i$Pr$C_6H_4$ | **2a** | dppe | **3f** | 91 |
| 7 | **1g** | 4-$^t$Bu$C_6H_4$ | **2a** | dppe | **3g** | 99 |
| 8 | **1h** | Me | **2a** | dppe | **3h** | 91 |
| 9 | **1i** | $CH_2CH_2CH_2Ph$ | **2a** | dppe | **3i** | 93 |
| 10 | **1j** | $CH_2CH{=}CH_2$ | **2a** | dppe | **3j** | 90 |
| 11 | **1k** | $CH_2CH{=}CHPh$ | **2a** | dppe | **3k** | 97 |
| 12 | **1l** | Cl | **2a** | dppe | **3l** | 95 |
| 13 | **1m** | H | **2a** | dppe | **1j** | 20 |
| 14 | **1m** | H | **2b** | dppe | **1k** | 29 |
| 15[c] | **1m** | H | **2a** | dppf | **1j** | 58 |
| 16[d] | **1m** | H | **2b** | dppf | **1k** | 52 |
| 17[e] | **1m** | H | **2a** | dppe | **3j** | 97 |
| 18[f] | **1b** | Me | **2c** | BINAP | **3m** | 95 |
| 19[f] | **1j** | $CH_2CH{=}CH_2$ | **2c** | BINAP | **3n** | 77 |
| 20[f] | **1k** | $CH_2CH{=}CHPh$ | **2c** | BINAP | **3o** | 98 |
| 21[c,d,g] | **1k** | $CH_2CH{=}CHPh$ | **2b** | dppf | **3p** | 96 |

[a] Isolated yield. [b] Reaction time was 2 h. [c] Reaction time was 8 h. [d] Reaction was carried out at 60 °C. [e] 2 equiv of **2a** were used. [f] Reaction conditions: **1** (0.1 mmol), [$Pd_2(dba)_3$] (2.5 mol %), rac-BINAP (6 mol %), toluene, reflux, 8 h. [g] 2 equiv of **2b** were used.

The reaction proceeds via an oxidative addition of the allyl carbonate to the Pd(0)−phosphine complex to form a cationic $\pi$-allyl Pd complex with an ethoxide counteranion and concomitant elimination of $CO_2$. Substrate **1** is deprotonated by the ethoxide anion and reacts with the $\pi$-allyl Pd complex leading to the product **3** and regeneration of the Pd(0) catalyst in a reductive elimination step (Figure 1).

To further demonstrate the utility of the products, two examples of functional group transformation were performed. The symmetric bis-allyl compound **3j** was converted to a synthetically attractive cyclopentene derivative **4** under Grubbs' olefin metathesis conditions[6j] in 95% yield (Scheme 2). The unsymmetric bis-allyl compound **3k** and symmetrical **3p** were submitted to three successive reductions, which include a reductive desulfonylation step

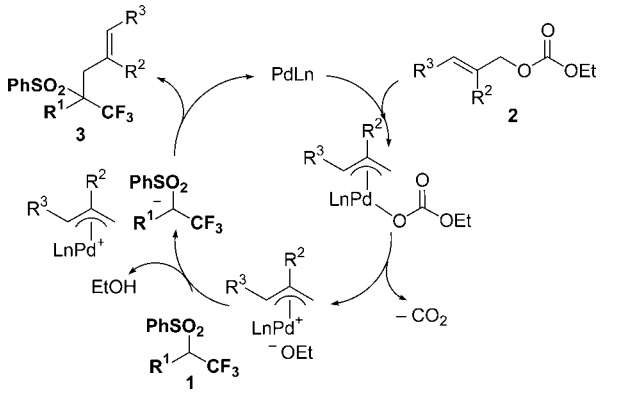
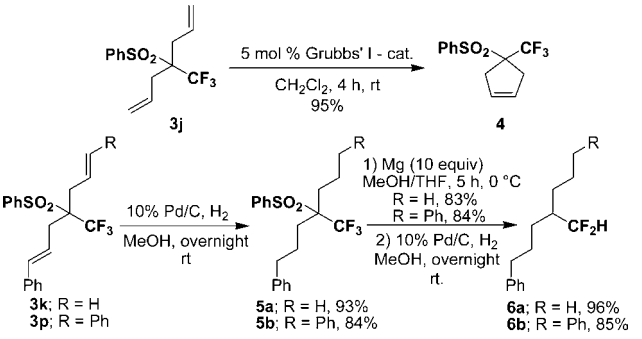



**Figure 1.** Putative mechanism of decarboxylative allylation.

**Scheme 2.** Examples of Utility of **3j**, **3k**, and **3p**




to afford compounds **6a**,**b** that possess a difluoromethyl group at a nonactivated position; such compounds are otherwise difficult to obtain by other methods.[17]

In summary, we have developed a practical intermolecular decarboxylative allylation of trifluoroethyl phenylsulfones **1** that provide medicinally attractive building blocks **3**.[18] The decarboxylative allylation is remarkable for its high yields and provides compounds that are not accessible under conventional base-mediated allylations. The products can be converted to difluoromethyl compounds after removal of the traceless phenyl sulfonyl group. This methodology introduces a novel approach to difluoromethyl compounds.[17] Further utility of trifluoroethyl phenylsulfones $CF_3CHRSO_2Ph$ **1** as precursors of the trifluoroethyl carbanions $CF_3CRH^-$ are under investigation.

**Acknowledgment.** The authors thank the JSPS in Japan and CNRS in France for financial support of this work through a Joint Research Project. This study was financially

(17) (a) Prakask, S. G. K.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. (b) Huang, W.; Ni, C.; Zhao, Y.; Zhang, W.; Dilman, A. D.; Hu, J. *Tetrahedron* **2012**, *68*, 5137. (c) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494.

(18) We noticed that Mathew, Hu and co-workers reported similar results at the international conference. See 20th International Symposium on Fluorine Chemistry 2012, Program & Abstracts, page 195 (Poster-5). It appeared after submission of this manuscript. Zhang, W.; Zhao, Y.; Ni, C.; Mathew, T.; Hu, J. *Tetrahedron Lett.* **2012**, *53*, in press, DOI: http://dx.doi.org/10.1016/j.tetlet.2012.09.094.

supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (Project name: Advanced Molecular Transformation by Organocatalysts) (Project name: Platform for Drug Discovery, Informatics and Structural Life Science). We also thank the Asahi Glass Foundation.

**Supporting Information Available.** Experimental details and copies of $^{1}H$, $^{13}C$, and $^{19}F$ spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

---

The authors declare no competing financial interest.