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Palladium-catalyzed allylation of 2,2,2-trifluoroethyl phenyl sulfone, a potential 2,2,2-trifluoroethyl pronucleophile

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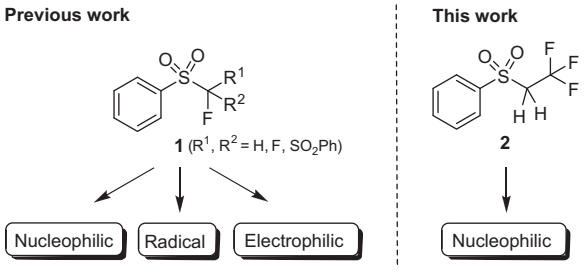
ABSTRACT

A palladium-catalyzed allylation reaction of $PhSO_2CH_2CF_3$ (**2**) with a variety of allyl carbonates has been successfully developed for selective 2,2,2-trifluoroethylation under neutral conditions. With this method, the 1-phenylsulfonyl-2,2,2-trifluoroethyl moiety was efficiently transferred into organic compounds without the competing β-elimination of fluoride, to afford a range of mono-allylated and di-allylated compounds.

Due to the high electronegativity and small size of fluorine, the presence of fluorine atom(s) or fluorinated moieties in organic molecules often modifies the latter's bioactivity by changing the metabolic stability, lipophilicity, and bioavailability.[1,2] Among various fluorinated moieties, the trifluoromethyl group (CF_3) has been the focus of increasing attention owing to its diverse applications.[3] In contrast to the tremendous progress that has been made toward the direct introduction of a trifluoromethyl group into organic compounds,[4,5] the selective transfer of a 2,2,2-trifluoroethyl carbanion ($CF_3CH_2^-$) has remained largely unexplored.[6,7] Although the electron-withdrawing effect of trifluoromethyl group may stabilize the carbanion species, the 2,2,2-trifluoroethyl carbanion is highly unstable and rapidly decomposes to give *gem*-difluoroalkenes by β-elimination of a fluoride ion.[6]

To stabilize the 2,2,2-trifluoroethyl carbanions by charge delocalization, electron-withdrawing groups, such as sulfonyl, carbonyl, or phenyl groups were usually introduced. Therefore, the presence of suitable substituents can make these substrates effective 2,2,2-trifluoroethyl pronucleophiles in the alkylation reactions. In 1983, Ishikawa and Yokozawa reported that the dimethyl(trifluoromethyl)malonate can react with alkyl halide by using CsF as a proton sink, and they found that the Michael addition with dimethyl(trifluoromethyl)malonate was also successful.[8] The alkylations of trifluoroethyl carbanions by using enolates were also developed.[9–11] In 1999, Kitazume demonstrated that palladium-catalyzed allylation of trifluoroethyl ketones proceeded smoothly without β-fluoride elimination.[12] Similar allylation reactions of related trifluoroethyl carbonyl compounds were also reported by the research groups led by Konno et al.,[13] Ando and co-workers,[14] and Shibata and Cahard.[15] Recently, we reported the first palladium-catalyzed trifluoroethylation of organoboronic acids and esters by using the readily available reagent CF_3CH_2I.[7]

Since the phenylsulfonyl group can be regarded as a 'chemical chameleon', during the past decade, we were extensively involved in the nucleophilic, radical, and electrophilic fluoroalkylations using a series of α-fluorinated organosulfur reagents.[16–19] The phenylsulfonyl group can not only stabilize the α-fluorocarbanion (Scheme 1, reagents **1**) by effective charge delocalization,[16–20] it can also stabilize the β-fluorocarbanion (derived from 2,2,2-trifluoroethyl phenyl sulfone, Scheme 1, reagent **2**).[6] Although the



Scheme 1. Different (phenylsulfonyl)fluoroalkylations.

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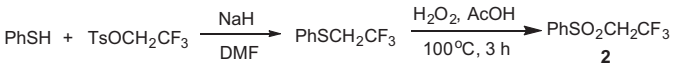


Scheme 2. Preparation of 2,2,2-trifluoroethyl phenyl sulfone.

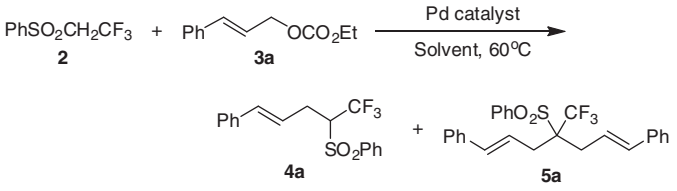
reagent **2** is a simple and easily available compound, which can react with electrophilic reagents such as CH_3I or I_2, the reaction substrates are very limited.[21] To expand our fluorinated organosulfur chemistry and develop the synthetic application of the reagent **2** for 2,2,2-trifluoroethylation, we carried out the palladium-catalyzed allylation reaction of **2** with various allyl carbonates under neutral conditions. We found that the method is very effective for the 2,2,2-trifluoroethylation of a series of 3-aryl-substituted allyl carbonates as well as the parent allyl carbonate. Herein, we want to report our results of this efficient 2,2,2-trifluoroethylation method.[22]

2,2,2-Trifluoroethyl phenyl sulfone ($PhSO_2CH_2CF_3$, **2**) was obtained by the oxidation of $PhSCH_2CF_3$ (using H_2O_2 in AcOH), which in turn was prepared from sodium thiophenolate and 2,2,2-trifluoroethyl *p*-toluenesulfonate (Scheme 2).[23]

With compound **2** in hand, we were able to explore its reactivity with allyl carbonates by using palladium catalysis. As shown in Table 1, initially, we chose cinnamyl ethyl carbonate (**3a**) as a model compound and 10 mol % $Pd(PPh_3)_4$ as a catalyst. Under neutral conditions, the allylation product **4a** was obtained in 38% yield (entry 1). However, the di-allylated product **5a** was also observed in 18% yield (Table 1, entry 1). Then, we focused on the improvement of the selectivity of the reaction by changing various reaction parameters such as the reagent/substrate ratio, temperature, catalysts as well as catalyst loading, and the solvent system. By increasing the amount of compound **2** or changing the solvent to toluene, the amount of di-allylated product **5a** was significantly reduced (entries 3, 4, and 6). Among the catalysts screened, $Pd(PPh_3)_4$ gave better yields than $Pd(dba)_2$ or $Pd(OAc)_2$ (entries 4, 7, and 8) while solvents 1,4-dioxane and DMF were found to be not effective for this reaction (entries 2 and 5). A threefold increase in substrate concentration changed the course of the reaction significantly, resulting in the reversal of the ratio of mono-allylated and di-allylated products from 2:1 to 1:2. (Table 1, entries 1 and 14). Thus, the yield of the di-allylated product increased to 48% yield and the mono-allylated product decreased to 24%. An optimal product yield (76%) of the mono-allylated product **4a** (with only 7% of **5a**) was obtained when the reaction was conducted in THF at 60 °C for 22 h with 4 equiv of reagent **2** and 10 mol % of $Pd(PPh_3)_4$ (entry 13).

Having established the optimized reaction conditions with reagent **2**, we studied the scope of the current 2,2,2-trifluoroethylation protocol by Pd-catalyzed allylation reaction with a range of allylic carbonates. It was found that a variety of structurally diverse

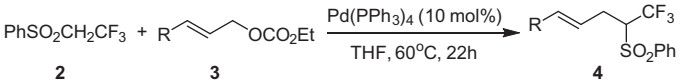
Table 1
Optimization of the reaction conditions for palladium-catalyzed allylation of 2,2,2-trifluoroethyl phenyl sulfone using cinnamyl ethyl carbonate

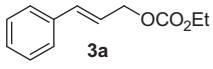
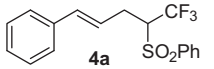
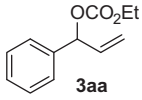
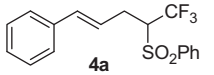
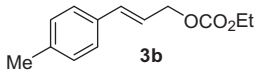
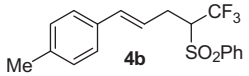
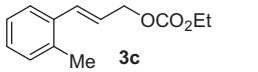
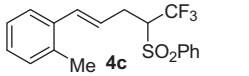
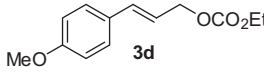
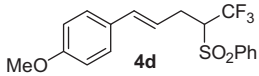
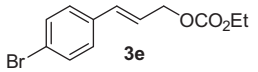
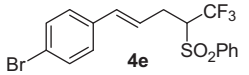
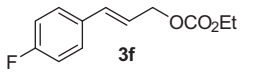
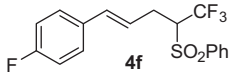
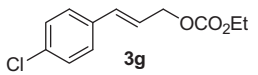
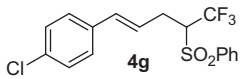
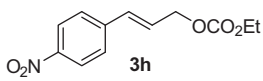
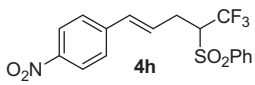
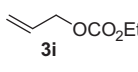
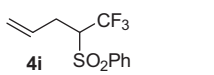


Entry	Ratio 2:3a	Pd catalyst	Pd (mol %)	Solvent	Time (h)	Yield (%) 4a[a]	(5a[a])
1	1:1	$Pd(PPh_3)_4$	10	THF	7	38	(18)
2	1:1	$Pd(PPh_3)_4$	10	Dioxane	7	0	(0)
3	2:1	$Pd(PPh_3)_4$	10	THF	20	39[b]	(3)[b]
4	3:1	$Pd(PPh_3)_4$	10	THF	11	58	(5)
5	3:1	$Pd(PPh_3)_4$	10	DMF	11	30[b]	(2)[b]
6	3:1	$Pd(PPh_3)_4$	10	Toluene	11	47	(1)
7	3:1	$Pd(dba)_2$	10	THF	11	53	(5)[b]
8	3:1	$Pd(OAc)_2$[c]	10	THF	18	14[b]	(0)[b]
9	3:1	$Pd(PPh_3)_4$	20	THF	11	60	(8)
10	3:1	$Pd(PPh_3)_4$	5	THF	22	21	(1)[b]
11	3:1	$Pd(PPh_3)_4$	10	THF	22	70	(9)
12	4:1	$Pd(PPh_3)_4$	10	THF	11	70	(7)
13	**4:1**	**$Pd(PPh_3)_4$**	**10**	**THF**	**22**	**76**	**(7)**[b]
14	1:3	$Pd(PPh_3)_4$	10	THF	22	24[b]	(48)
15	3:1	$Pd(PPh_3)_4$	10	THF/toluene (2:3)	24	52	(1)
16	3:1	$Pd(PPh_3)_4$	10	THF/toluene (5:1)	36	48[b]	(3)[b]
17	3:1	$Pd(PPh_3)_4$	10	THF/toluene (10:1)	29	62[b]	(5)[b]

[a] Isolated yield.
[b] Determined ^{19}F NMR spectroscopy.
[c] PPh_3 (20 mol %) was added.

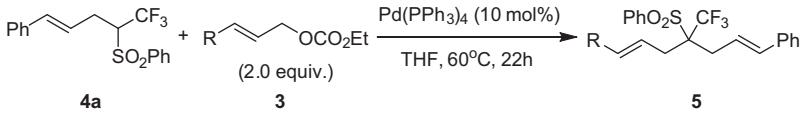
Table 2
Synthesis of allylated trifluoroethyl sulfones using various allyl ethyl carbonates



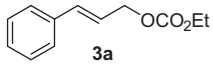
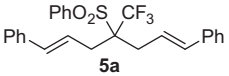
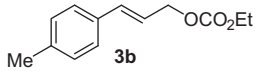
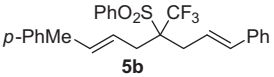
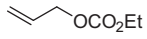
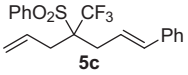
Entry	Substrate	Product	Yield[a] (%)
1	 3a	 4a	76
2	 3aa	 4a	79
3	 3b	 4b	65
4	 3c	 4c	73
5	 3d	 4d	70[b]
6	 3e	 4e	60[c]
7	 3f	 4f	65
8	 3g	 4g	68
9	 3h	 4h	40
10	 3i	 4i	73

[a] Isolated yield.
[b] Determined ^{19}F NMR spectroscopy.
[c] Stirring for 43 h.

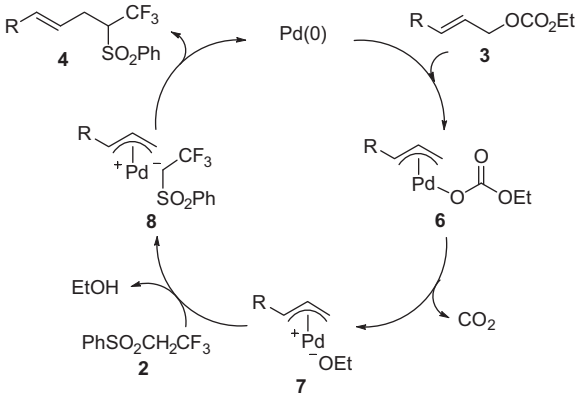
Table 3
Allylation of mono-allylated product **4a** with allylic carbonates



4a **3** **5**

Entry	Substrate	Product	Yield[a] (%)
1	 **3a**	 **5a**	86
2	 **3b**	 **5b**	84
3	 **3i**	 **5c**	85

[a] Isolated yield.



Scheme 3. Proposed reaction mechanism.

allylic carbonates showed good reactivity with reagent **2** under the neutral conditions giving the allyl substituted trifluoroethyl sulfones **4** in moderate to high yields (see Table 2). As shown in entries 1 and 2, the cinnamyl ethyl carbonate **3a** and ethyl 1-phenylallyl carbonate **3aa** gave the same product **4**, clearly manifesting the excellent regioselectivity of the allylic reaction. Reactions of cinnamyl ethyl carbonate bearing electron-donating groups **3b**, **3c**, and **3d** also gave the corresponding products in good yields (Table 2, entries 3–5), while those of allylic carbonate **3h** bearing strong electron-withdrawing group resulted in low yield (entry 9). Furthermore, the product **4i** can be obtained in 73% yield from the simple parent allyl ethyl carbonate **3i** (entry 10).

As mentioned earlier, the Pd-catalyzed allylation reaction could give the di-allylated products (see Table 1). Thus, we decided to investigate the second allylation reaction between mono-allylated product **4a** and other allylic carbonates **3**. It was found, by using 2 equiv of allylic carbonates, the di-allylated products **5a**, **5b**, and **5c** were obtained in 86%, 84%, and 85% yields, respectively (Table 3, entries 1–3). It indicates that, theoretically, it is possible to get a variety of trifluoroethyl compounds with two different allylic groups by choosing the suitable monoallylated product and the allyl ethyl carbonate.

Under the same neutral reaction conditions ($Pd(PPh_3)_4$/THF/60 °C/22 h), neither the trifluoroethyl sulfoxide $PhSOCH_2CF_3$, nor the monofluoroethyl sulfone $PhSO_2CH_2CH_2F$ can react with allylic carbonates. According to the ^{19}F NMR spectroscopy, there is only a peak of reactant of $PhSOCH_2CF_3$ or $PhSO_2CH_2CH_2F$, and this may be due to the weaker acidity of the reagents and weaker charge-stabilization of the carbanions.

The reaction mechanism of the above palladium-catalyzed allylation reaction of $PhSO_2CH_2CF_3$ was proposed as shown in Scheme 3. Under neutral reaction conditions, the π-allyl alkoxy palladium complex **7**, which is derived from the decarboxylation of complex **6**, reacts with the active methylene group in the reagent **2** to give the intermediate **8** and EtOH. Then the mono-allylated compounds **4** are obtained as main products by the reductive elimination of **8**. Meanwhile, the di-allylated product **5** may be produced in the presence of **3** and **4**, through the same reaction mechanism.

In conclusion, the palladium-catalyzed allylation reaction of $PhSO_2CH_2CF_3$ (**2**) with a variety of allyl carbonates has been successfully developed for selective 1-phenylsulfonyl-2,2,2-trifluoroethylation under neutral conditions. With this method, the 1-phenylsulfonyl-2,2,2-trifluoroethyl moiety was efficiently transferred into organic compounds without the competing β-elimination of fluoride, to afford a range of mono-allylated and di-allylated compounds.[24] Further investigations of asymmetric trifluoroethylation chemistry are currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectroscopic data for all isolated new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.094.

References and notes

1. Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*, 2008. Wiley: Hoboken.

2. Prakash, G. K. S.; Chacko, S. *Curr. Opinion Drug. Disc. Dev.* **2008**, *11*, 793.
3. Yamazaki, T.; Taguchi, T.; Ojima, I. Fluorine in Medicinal Chemistry and Chemical Biology In Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009; p 3.
4. (a) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2011**, *112*, 123–131. and the references cited therein; (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4521; (c) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161–2195; (d) Sato, K.; Tarui, A.; Omote, M.; Ando, A.; Kumadaki, I. *Synthesis* **2010**, 1865–1882; (e) Taj, S. A. S. *Chem. Ind. Digest* **2008**, *21*, 92–98.
5. (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146; (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321; (c) Amii, H. *Yuki Gosei Kagaku Kyokaishi* **2011**, *69*, 752–762.
6. Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817–829.
7. Zhao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033–1036.
8. Ishikawa, N.; Yokozawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 724–726.
9. Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3987–3990.
10. Ishihara, T.; Kuroboshi, M.; Yamaguchi, K.; Okada, Y. *J. Org. Chem.* **1990**, *55*, 3107–3114.
11. Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174–13175.
12. Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369–8374.
13. Konno, T.; Kanda, M.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **2005**, *126*, 1517–1523.
14. Sato, K.; Yakifuchi, Y.; Yoshizawa, Y.; Iwase, K.; Shimizu, Y.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Chem. Pharm. Bull.* **2007**, *55*, 1593–1596.
15. Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037–2041.
16. Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930.
17. Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130–1139.
18. Zhang, W.; Ni, C.; Hu, J. *Top. Curr. Chem.* **2012**, *308*, 25–44.
19. Ni, C.; Hu, J. *Synlett* **2011**, 770–782.
20. Prakash, G. K. S.; Wang, F.; Shao, N.; Mathew, T.; Rasul, G.; Haiges, R.; Stewart, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 5358–5362.
21. Uneyama, K.; Momota, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3378–3379.
22. After this manuscript was prepared, we noticed that Shibata and co-workers disclosed the similar results at the 20th International Symposium on Fluorine Chemistry, Kyoto, Japan, July 22–27, 2012. See 20th International Symposium on Fluorine Chemistry 2012, Program & Abstracts, page 205 (Poster-15).
23. Nakai, T.; Tanaka, K.; Setoi, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3069–3070.
24. Although a variety of reaction conditions were scanned, we have not succeeded in the selective desulfonylation of compounds **4** and **5** to give CF_3CH_2-containing products. Further efforts are currently being undertaken to tackle this problem.