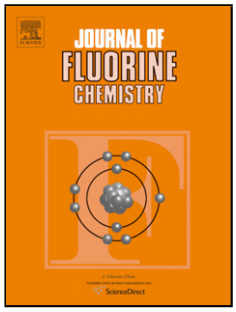

Title: Systematic Study of the Reactivity of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate Towards Different Classes of Nucleophiles

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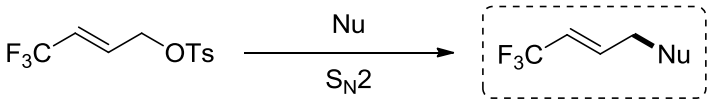
GRAPHICAL ABSTRACT - PICTOGRAM



√ Phenol
× Alcohol
√ Thiols
√ Amines
× Indole
√ Malonates

HIGHLIGHTS

- The reactivity of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate towards different nucleophiles was performed.
- Phenol, amines, thiols, and malonates all provide the substitution product in moderate to excellent yields.
- Benzyl alcohol and indole provide low yield of the desired product.

Systematic Study of the Reactivity of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate Towards Different Classes of Nucleophiles

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ABSTRACT: A systematic study of the reactivity of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate towards different classes of nucleophiles (alcohols, amines, thiols and malonates) was performed. A single set of reaction conditions (with small variations) allowed the isolation of the substitution product in moderate to good yields for all the nucleophiles tested with the exception of benzyl alcohol and indole.

KEYWORDS: trifluoromethyl group, allylic tosylate, substitution reaction, nucleophile, allylic substitution

1. Introduction

A number of aromatic compounds used in medicinal chemistry [1], agrochemistry [2] or in material sciences [3] bear a (*E*)-((4,4,4-trifluorobut-2-en-1-yl)oxy chain. Until recently, these products could only be synthesized through a substitution reaction between a phenol derivative and a suitable electrophilic partner, **1**-**3** (Figure 1) [1,2,3]. This approach is simple and good yields can be generally obtained for various phenols even though the allylic mesylate **2** or the allylic chloride **3** have some volatility and stability issues. Also, the use of other nucleophiles has not been really investigated [4,5].

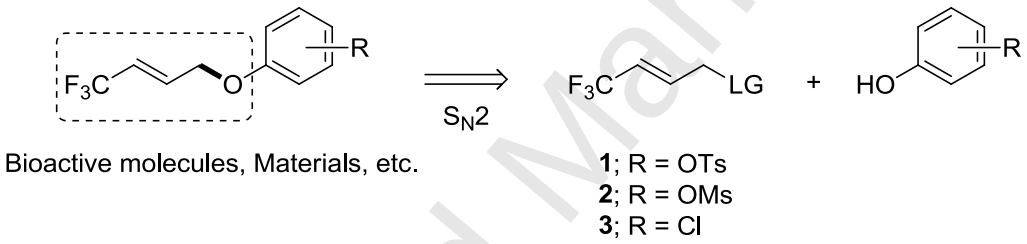
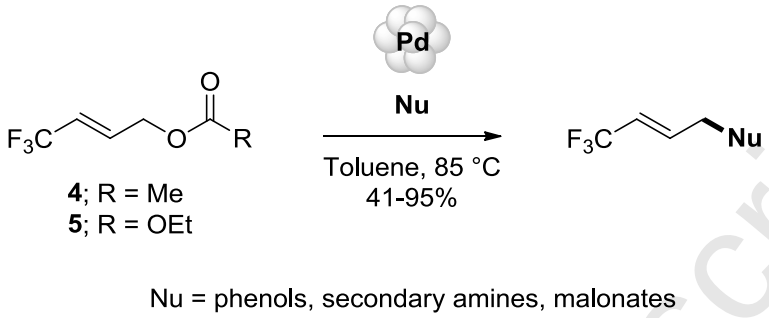


Figure 1. Traditional approach to molecules containing the 4,4,4-trifluorobut-2-ene chain attached to a phenolic oxygen.

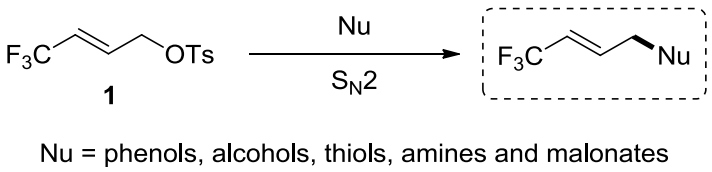
We have recently explored an alternative strategy using a Tsuji-Trost reaction catalyzed by nanoparticles starting from either 4,4,4-trifluorobut-2-en-1-yl acetate (**4**) or ethyl(4,4,4-trifluorobut-2-en-1-yl)-carbonate (**5**) (Scheme 1) [6]. These conditions could be used to attach a 4,4,4-trifluorobut-2-ene chain not only to phenols, but also to secondary amines and malonates for the first time. However, isomerization of the product (up to 20%) was observed in the case of the phenol, and a primary amine and thiols could

not be used as the desired product was observed in low yield along with multiple side-products.



Scheme 1. Regioselective Tsuji−Trost reaction catalyzed by palladium nanoparticles.

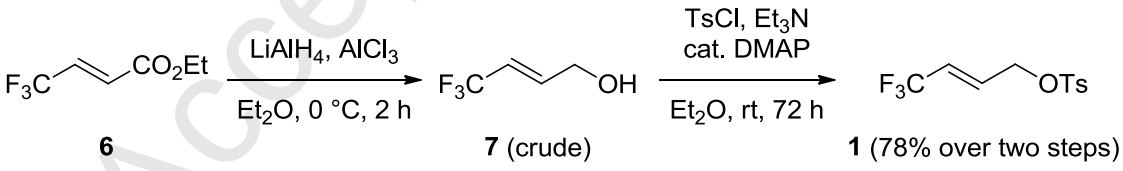
Considering, on one hand, the simplicity of the S_N2 approach, the known practical setbacks of **2** and **3**, and the fact that only phenols has been used as nucleophile, and on the other hand, the limitations observed in our recently developed Tsuji-Trost reaction, we decided to reinvestigate the use of the S_N2 reaction with various nucleophiles, including those who did not behave well in the Tsuji-Trost reaction, using allylic tosylate **1** (Scheme 2). We therefore report herein a systematic study of the reactivity of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (**1**) towards different classes of nucleophiles (alcohols, amines, thiols and malonates). A single set of reaction conditions (with small variations) allowed the isolation of the substitution product in moderate to good yields for all the nucleophiles tested with the exception of benzyl alcohol and indole. For those nucleophiles, the desired products were observed in low yields, suggesting that further optimization may eventually allow their preparation in synthetically useful yields.



Scheme 2. Reactions under study.

2. Results and discussion

The electrophilic partner, (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (**1**) [3b,4], was prepared from ethyl (*E*)-4,4,4-trifluorocrotonate (**6**) in two steps. First, reduction using $LiAlH_4$ in the presence of $AlCl_3$ provided the crude (*E*)-4,4,4-trifluorobut-2-en-1-ol (**7**) [7], which was used without further purification. Installation of the tosylate under standard conditions provided the desired product in 78% for the two steps.

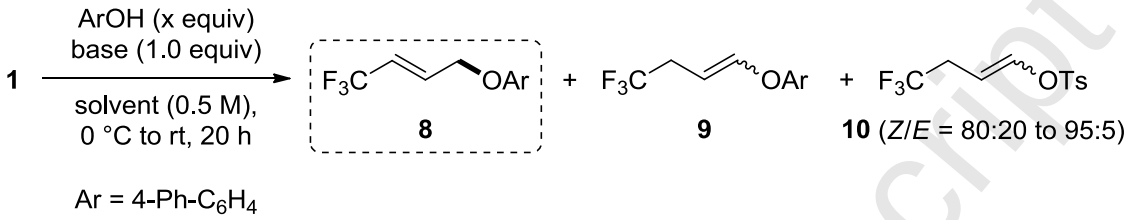


Scheme 3. Synthesis of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (**1**).

We started by investigating the use of phenol, the only nucleophile previous used successfully in this reaction [1,2,3]. We choose 4-phenylphenol as a representative

nucleophile for this class of nucleophile as the product is less volatile than with the unsubstituted phenol and the results are shown in Table 1. Under our initial conditions (entry 1), a conversion of 75% was observed. Analysis of the crude mixture by NMR revealed that the desired product **8**, was the major one (47% yield by NMR). Interestingly, no isomerisation product (i.e., **9**) was observed. This was a significant side-reaction in the palladium-catalyzed transformation [6]. In this case, isomerisation of the starting allylic tosylate was observed instead (**10**; 11% by NMR). The fact that using a larger amount of the base increased its formation (entry 2) suggested that this was a base-mediated process. Changing the solvent from THF to DMF (entry 3) or CH_3CN (entry 4) provided full conversion. As the NMR yield was significantly better with CH_3CN (54% vs 33%), this solvent was chosen for further optimization. Either augmenting the amount of phenol (1.1 equiv instead of 1.0 equiv) or conducting the reaction at higher concentration (0.25 M instead of 0.1 M) provided better yields (entries 5-6). Combining those two factors provide the best NMR yield (75%) under those conditions (entry 7). At this point, we wondered if the use of NaH, a pyrophoric base, was necessary and thus explored the used of K_2CO_3, a safer alternative. Under the optimized conditions (entry 8) but just changing the base, a low conversion of 43% was observed. However, the crude reaction mixture showed a very clean reaction with only 1% of **10** present. Heating the reaction at 60 °C, provided a full conversion with only trace amounts (ca. 3%) of the isomerized product (**9**) and isomerized starting tosylate (**10**) (entry 9). The desired product, **8**, could be isolated in 90% yield. Those conditions would represent the basis of the investigation with the other nucleophiles.

Table 1. Selected optimization results for the synthesis of **8** from **1** using 4-phenylphenol.



Entry	Base	Phenol (x equiv)	Solvent	Conversion (%)[a]	Ratio (**8**/**9**/**10**)[a]	Yield (%)[a]
1	NaH	1.0	THF	75	89:0:11	47
2[b]	NaH	1.0	THF	84	79:0:21	43
3	NaH	1.0	DMF	100	80:7:13	33
4	NaH	1.0	CH_3CN	100	89:3:8	54
5	NaH	1.1	CH_3CN	100	95:trace:5	69
6[c]	NaH	1.0	CH_3CN	100	92:1:7	69
7[c]	NaH	1.1	CH_3CN	96	96:4:trace	75
8[c]	K_2CO_3	1.1	CH_3CN	56	99:0:1	43
9[c,d,e]	**K_2CO_3**	**1.1**	**CH_3CN**	**100**	**97:3:3**	**(90)[f]**

[a] Determined by ^{19}F NMR analysis of the crude mixture using 2-fluoro-4-nitrotoluene as an internal standard.

[b] 1.5 equiv of NaH was used.

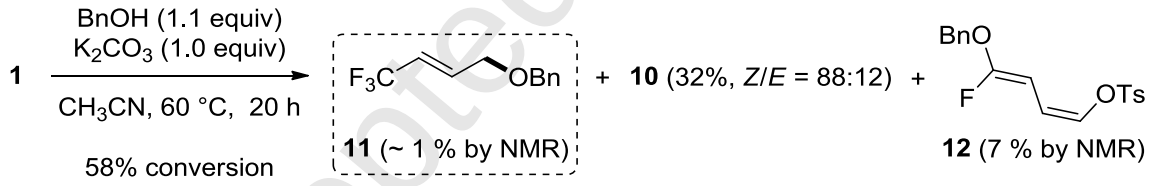
[c] The concentration was 0.25 M.

[d] The temperature was 60 °C.

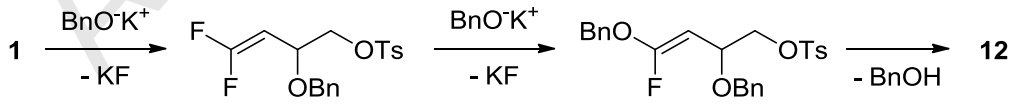
[e] Optimized system highlighted in bold.

[f] Isolated yield after purification by flash chromatography.

We then investigated the use of an aliphatic alcohol, and benzyl alcohol was chosen as a representative nucleophile for this class. Under the optimized conditions (Table 1, entry 9), a moderate conversion of 58% was obtained. Analysis of the crude mixture by NMR spectroscopy revealed the presence of the desired product **11** [8] in trace amounts (ca. 1%). The isomerized tosylate **10** (*Z*/*E* = 87:13) was the major product (32%). Finally, 7% of the product corresponding to the attack of the alcohol at the CF_3 carbon was observed **12**. Formation of a similar product has been previously observed with indole [5] and we proposed that **12** is produced through a similar pathway (Scheme 5).

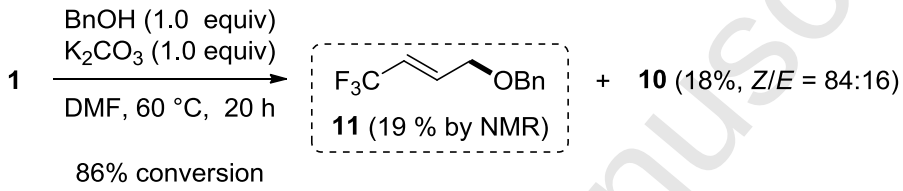


Scheme 4. Initial result using benzyl alcohol as the nucleophile.



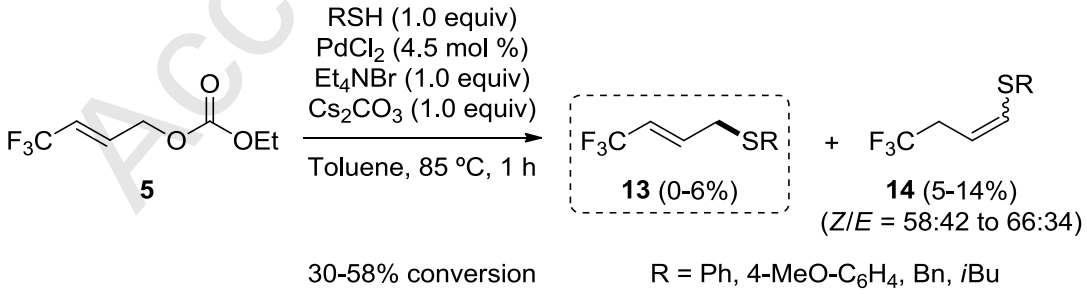
Scheme 5. Proposed pathway for the formation of **12**.

Despite numerous attempts to further optimize the reaction (solvent, reaction temperature, concentration, base, additives, order of addition, etc.), the "best" conditions only provided 19% by NMR of the desired product, **11**, with a similar amount of the isomerized product **10** (Scheme 6). Clearly, this particular transformation will require further investigation.



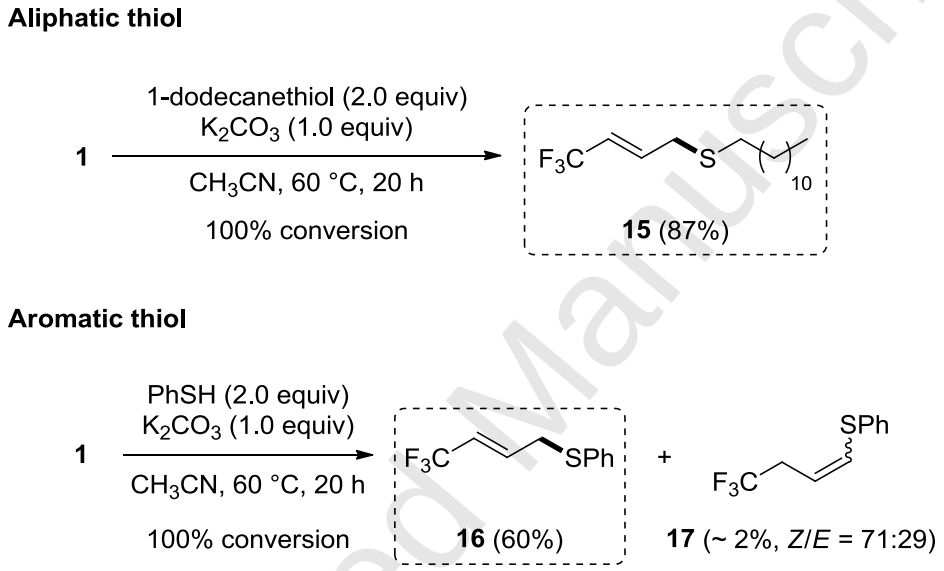
Scheme 6. Promising result obtained for the reaction of **1** with benzyl alcohol.

Thiols have never been used as nucleophile in substitution reactions with reagent **1**-**3**, and they did not behave well in our Tsuji-Trost reaction where they provided only trace amounts (up to 6%) of the desired products (**13**) along with the isomerized product (**14**) and various non-identified fluorinated side-products (7-15%) (Scheme 7) [6].



Scheme 7. Results of the thiols in the Tsuji-Trost reaction of carbonate **5** [6].

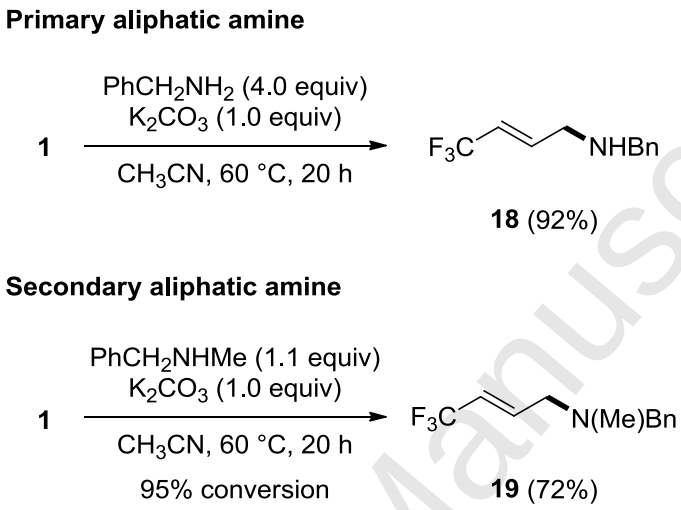
Under slightly modified conditions using either an aliphatic thiol, 1-dodecanethiol, or an aromatic thiol, thiophenol, the desired products (**15** and **16**) were obtained in 87 and 60% yield respectively. While isomerization of the product was not observed for the aliphatic thiol, only a limited amount (ca. 2%) was seen with the aromatic one.



Scheme 8. Thiols: reaction of tosylate **1** with 1-dodecanethiol and thiophenol.

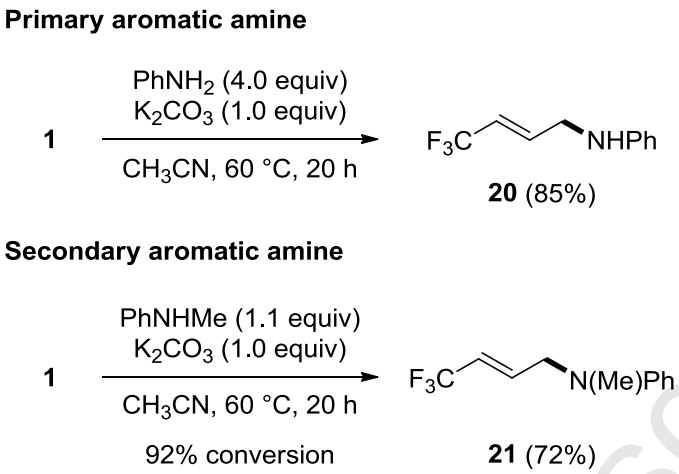
We next investigated the use of amines. As shown in Scheme 9, using a primary aliphatic amine, benzylamine, or a secondary aliphatic amine, *N*-methylbenzylamine, provided excellent yields of the desired products (**18** and **19**). In the case of the primary aliphatic amine, the use of 4.0 equivalents of benzylamine provided better conversions. Notably,

the use of a primary amine was not possible with the Tsuji-Trost system as a complex mixture was obtained [6].



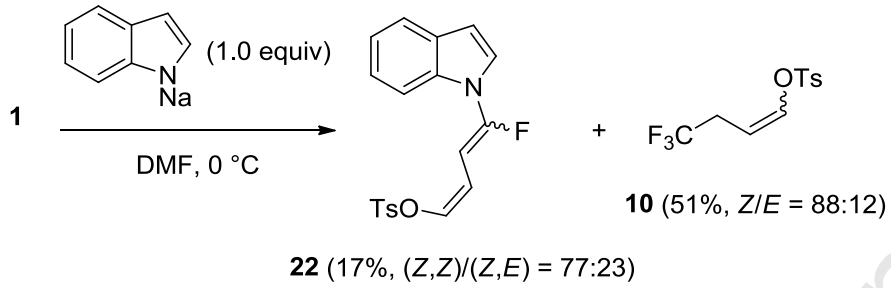
Scheme 9. Aliphatic Amines: reaction of tosylate **1** with benzyl amine and *N*-methylbenzylamine.

We next looked at the use of aromatic amines. Using either a primary aromatic amine, aniline, or a secondary aromatic amine, *N*-methylaniline, the desired products (**20** and **21**) were isolated in good yields (Scheme 10).



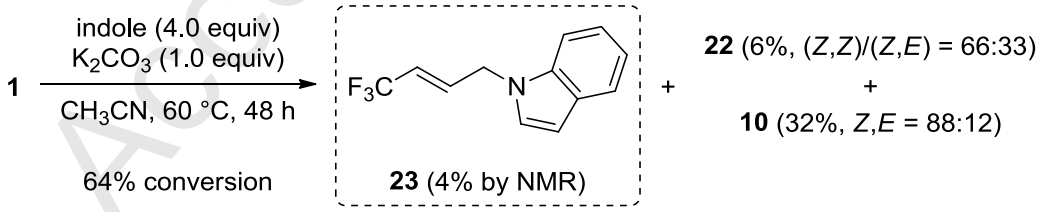
Scheme 10. Aromatic amines: reaction of tosylate **1** with aniline and *N*-methylaniline.

We also investigated the use of indole as its reaction with **1** has been reported to provide, unexpectedly, 4-fluoro-4-(indol-1-yl)buta-1,3-dien-1-yl methanesulfonate (**22**) along with the isomerized starting material, **10**. (Scheme 11) [4,5]. We repeated the reaction under similar conditions (NaH (1.0 equiv), indole (1.1 equiv), CH_3CN, 0 °C to rt) and observe a comparable result (100% conversion, **22** (20%; (*Z*,*Z*)/(*Z*,*E*) = 75:25), **10** (80%, *Z*/*E* = 88:12)).



Scheme 11. Reported reaction of **1** with indole by Marques and coworkers. [4]

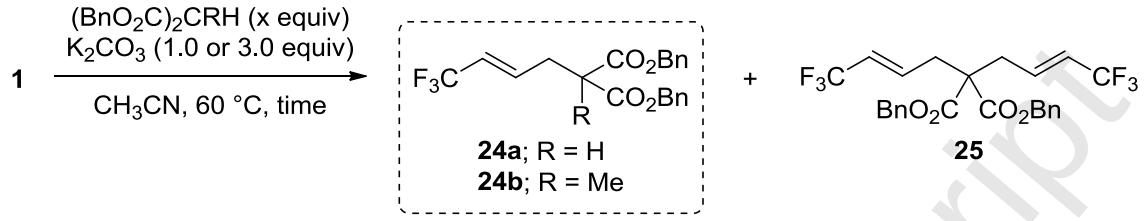
Marques and coworkers, through DFT calculations and experimentations, have shown that various factors, including the base counter-ion and the solvent could influence the reaction outcome (although the desired S_N2 product was never observed). In our case, running the reaction in CH_3CN using K_2CO_3 as the base, a conversion of 64% was observed (Scheme 12). Interestingly, NMR analysis of the crude mixture showed the presence of the desired product, **23**, albeit in low yield (4%). Nonetheless, this result indicates that the desired pathway (i.e., formation of **23**) is possible, even though further optimization will be required to obtain **23** in a useful yield.



Scheme 12. Reaction of **1** with indole under different conditions.

Finally, the use of malonate as the nucleophile was investigated. Specifically, dibenzyl malonate was chosen as the benzyl ester facilitated the purification (since the product is significantly less volatile than the corresponding methyl or ethyl ester). The results are shown in Table 2. Under the standard conditions using 2 equivalent of dibenzyl malonate (R = H), an excellent conversion of 93% was obtained (entry 1). NMR analysis of the crude mixture revealed a mixture of mono (**24a**) and dialkylated (**25**) products in a 71:29 ratio. The yield of the product **24a** was estimated at 49% by NMR. Increasing the number of equivalent of the malonate to 4 provided full conversion in 48 h. A better ratio in favor of **24a** was obtained (83:17) and the desired product could be isolated in 72% yield. This product could not be obtained under the Tsuji-Trost reaction as **25** was the major product [6]. The reaction with dibenzyl methylmalonate proved to be slower and only 70% conversion was obtained after 96 h with 1.1 equivalent of the nucleophile. It this case, the product **24b** could be isolated in 57% yield (entry 3). Using 3.3 equivalent of dibenzyl methyl malonate only slightly improve the conversion. Nonetheless, the desired product could be isolated in 76% yield (entry 4). A slightly lower isolated yield (56%) for the same product was obtained using the Tsuji-Trost reaction using acetate **4** albeit in a shorter reaction time (24 h) [6].

Table 2. Reaction of **1** with dibenzyl malonate and dibenzyl methylmalonate.



Entry[a]	Malonate (x equiv)	Time (h)	Conversion (%)[b]	Ratio (**24**/**25**)[b]	Yield (%)[c]
1	**24a** (2.0)	20	93	71:29	(49)[b]
2	**24a** (4.0)	48	100	83:17	72
3	**24b** (1.1)	96	70	NA	57
4	**24b** (3.3)	96	82	NA	76

[a] For entries 1-3, 1.0 equiv of K_2CO_3 was used while 3 equiv was utilized for entry 4.

[b] Determined by ^{19}F NMR analysis of the crude mixture using 2-fluoro-4-nitrotoluene as an internal standard. NA = not applicable.

[c] Isolated yield after purification by flash chromatography.

3. Conclusion

In conclusion, we have reported a systematic study on the reactivity of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate towards different classes of nucleophiles (alcohols, thiols, amines, and malonates). A single set of reaction conditions (with only small variations) allowed the isolation of the substitution product in moderate to good

yields for all the nucleophiles tested with the exception of benzyl alcohol and indole. For those nucleophiles, the desired products were observed in low yields, suggesting that further optimization may eventually allow their preparation in synthetically useful yields. Overall, this approach complements nicely the Tsuji-Trost reaction catalyzed by nanoparticules developed earlier by our group, and provide altogether convenient approaches for the introduction of a 4,4,4-trifluorobut-2-ene chain into organic molecules.

4. Experimental

4.1. General information

Solvents were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All commercially available compounds were used as received. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Silicyle silica gel 60 Å F254 TLC plates, and visualized under UV or by staining with potassium permanganate. Flash column chromatography was carried out on Silicycle Silica Gel 60 Å, 230-400 mesh. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at ambient temperature using Agilent DD2 500 and Varian Inova 400 spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield of tetramethylsilane and are respectively referenced to tetramethylsilane (δ = 0.00 ppm) and chloroform (δ = 77.16 ppm). For ^{19}F NMR, $CFCl_3$ is used as the external standard. High-resolution mass spectra were obtained on a LC/MS–TOF Agilent 6210 using electrospray ionization (ESI).

Infrared spectra were recorded using a Thermo Scientific Nicolet 380 FT-IR spectrometer.

*4.2. Synthesis of the starting compound (E)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (**1**)*

To a solution of $LiAlH_4$ (1.35 g, 35.5 mmol, 1.5 equiv) in dry Et_2O (13.0 mL) under argon atmosphere was added dropwise a solution of $AlCl_3$ (2.22 g, 16.6 mmol, 0.7 equiv) in dry Et_2O (6.5 mL). After 20 min of stirring at 0 °C, a solution of ethyl (*E*)-4,4,4-trifluorocrotonate (4.00 g, 23.8 mmol, 1.0 equiv) in dry Et_2O was added dropwise. The resulting mixture was allowed to stir at 0 °C for 2 hours. A saturated aqueous solution of Na_2SO_4 was then added (Caution: very exothermic reaction). The mixture was filtrated and the solid was washed several times with Et_2O. The organic layers were combined and washed with brine and dried over $MgSO_4$. Solvent was removed by thorough distillation at atmospheric pressure to afford (*E*)-4,4,4-trifluorobut-2-en-1-ol (**7**) as a colorless oil which was used without any further purification. To a solution of **7** (2.89 g, 22.9 mmol, 1.0 equiv) in dry Et_2O (50 mL) were successively added triethylamine (3.2 mL, 22.9 mmol, 1 equiv), DMAP (280 mg, 2.29 mmol, 0.1 equiv) and TsCl (4.37 g, 22.9 mmol, 1.0 equiv). The resulting mixture was allowed to stir at room temperature for 72 hours. Water was then added to quench the reaction and the mixture was extracted with Et_2O. The organic layers were combined and washed with 3 N aq. HCl then with a saturated aqueous solution of $NaHCO_3$. Organic solvent were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using

hexane/EtOAc (90/10) as the eluent to afford the desired product **1** as a colorless oil (5.2 g, 82 %). IR (ATR, ZnSe) ν (cm^{-1}) = 1363, 1311, 1190, 1175, 1120, 1095, 1052, 943, 813, 757, 696, 661; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (d, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 6.30 (dtq, 1H, *J* = 15.8, 4.4, 2.3 Hz), 5.89 (dqt, 1H, *J* = 15.8, 6.2, 1.9 Hz), 4.68-4.62 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.6, 132.6, 132.0 (q, *J* = 6.6 Hz), 130.2, 128.1, 122.4 (q, *J* = 269.6 Hz), 121.2 (q, *J* = 34.7 Hz), 66.8, 21.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ = -64.9 (m, 3F); HRMS-ESI calcd for $C_{11}H_{11}F_3O_3S$ $[M+H]^+$, 281.0454 found 281.0454.

4.3. Typical procedure for the S_N2 reaction

To a 2-5 mL microwave vial under inert atmosphere were successively charged, the nucleophile (0.27 mmol, 1.1 equiv), K_2CO_3 (0.25 mmol, 1.0 equiv) and dry CH_3CN (0.5 mL). The vial was then sealed with a cap and resulting mixture was heated for 10 min at 60 °C in a preheated oil bath before dropwise addition of (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (0.25 mmol, 1.0 equiv) diluted in dry CH_3CN (0.5 mL). The resulting mixture was heated at 60 °C for 20 h. Water was then added to quench the reaction, and the mixture was extracted three times with EtOAc or Et_2O. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

*4.3.1 (E)-4-((4,4,4-trifluorobut-2-en-1-yl)oxy)-1,1'-biphenyl (**8**)*

Following general procedure: (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), 4-phenylphenol (70 mg, 0.27 mmol, 1.1 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL). The crude product was purified by flash chromatography on silica gel using hexane/EtOAc (98/2) as the eluent to afford **8** as a white solid (62 mg, 90%). Spectral data were in accordance with the literature [6].

*4.3.2 (E)-dodecyl(4,4,4-trifluorobut-2-en-1-yl)sulfane (**15**)*

Following the general procedure using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), 1-dodecanethiol (101 mg, 0.50 mmol, 2.0 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash chromatography on silica gel using pentane (100%) as the eluent to afford **15** as a colorless oil (68 mg, 87%). IR (ATR, ZnSe) ν (cm^{-1}) = 2923, 2853, 1327, 1272, 1184, 1116, 1048, 968; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.36 (dtq, 1H, *J* = 15.6, 4.6, 2.1 Hz), 5.71 (dqt, 1H, *J* = 15.6, 6.3, 1.4 Hz), 3.20-3.17 (m, 2H), 2.45 (m, 2H), 1.58-1.52 (m, 2H), 1.40-1.33 (m, 2H), 1.26 (br s, 16H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.6 (q, *J* = 6.4 Hz), 122.8 (q, *J* = 269.4 Hz), 120.0 (q, *J* = 33.7 Hz), 32.3, 32.1, 31.3, 29.80, 29.78, 29.74, 29.65, 29.5, 29.37, 29.35, 28.9, 22.8, 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ = −63.9 (m, 3F); HRMS-ESI calcd for $C_{16}H_{29}F_3S$ $[M+H]^+$, 311.2015 found 311.2010.

*4.3.3 (E)-dodecyl(4,4,4-trifluorobut-2-en-1-yl)sulfane (**16**)*

Following general procedure using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), thiophenol (51 µL, 0.50 mmol, 2.0 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash chromatography on silica gel using pentane (100%) as the eluent to afford **16** as a colorless oil (33 mg, 60%). IR (ATR, ZnSe) ν (cm^{-1}) = 1326, 1273, 1182, 1110, 1050, 965, 736, 688, 664; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.35 (m, 2H), 7.33-7.29 (m, 2H), 7.27-7.24 (m, 1H), 6.40 (dtq, 1H, *J* = 15.8, 4.8, 2.1 Hz), 5.58 (dqt, 1H, *J* = 15.8, 6.4, 1.4 Hz), 3.57-3.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.5 (q, *J* = 6.5 Hz), 134.1, 113.4, 129.2, 127.9, 122.7 (q, *J* = 269.5 Hz), 120.7 (q, *J* = 33.8 Hz), 35.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ = –64.2 (m, 3F); HRMS-ESI calcd for $C_{10}H_9F_3S$ $[M+H]^+$, 219.0450 found 219.0454.

*4.3.4 (E)-N-benzyl-4,4,4-trifluorobut-2-en-1-amine (**18**)*

Following general procedure with 4.0 equiv of benzylamine using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), benzylamine (0.11 mL, 1.0 mmol, 4.0 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash chromatography on silica gel using hexane/EtOAc (80/20) as the eluent to afford **18** as a colorless oil (49 mg, 92%). Spectral data were in accordance with the literature [6].

*4.3.5 (E)-N-benzyl-4,4,4-trifluoro-N-methylbut-2-en-1-amine (**19**)*

Following general procedure using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), *N*-methylbenzylamine (33 mg, 0.27 mmol, 1.1 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash chromatography on silica gel using pentane/Et_2O (90/10) as the eluent to afford **19** as a colorless oil (41 mg, 72%). Spectral data were in accordance with the literature [6].

4.3.6 (*E*)-*N*-(4,4,4-trifluorobut-2-en-1-yl)aniline (**20**)

Following general procedure with 4.0 equiv of aniline using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), aniline (90 µL, 1.0 mmol, 4.0 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash chromatography on silica gel using hexane/EtOAc (90/10) as the eluent to afford **20** as a colorless oil (43 mg, 85%). Spectral data were in accordance with the literature [6].

*4.3.7 (E)-N-methyl-N-(4,4,4-trifluorobut-2-en-1-yl)aniline (**21**)*

Following general procedure using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (112 mg, 0.4 mmol, 1.0 equiv), *N*-methylaniline (48 µL, 0.44 mmol, 1.1 equiv), K_2CO_3 (55 mg, 0.4 mmol, 1.0 equiv) and CH_3CN (1.6 mL), the obtained crude product was purified by flash chromatography on silica gel using

hexane/EtOAc (96/4) as the eluent to afford **21** as pale yellow oil (62 mg, 72%). Spectral data were in accordance with the literature [6].

*4.3.8 (E)-dibenzyl 2-(4,4,4-trifluorobut-2-en-1-yl)malonate (**24a**)*

Following general procedure with 4.0 equiv of dibenzylmalonate with a reaction time of 48 h using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), dibenzylmalonate (280 mg, 1.0 mmol, 4.0 equiv), K_2CO_3 (35 mg, 0.25 mmol, 1.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash chromatography on silica gel using hexane/Et_2O (90/10) as the eluent to afford **24a** as a colorless oil (69 mg, 70%). IR (ATR, ZnSe) ν (cm^{-1}) = 1731, 1272, 1222, 1115, 969, 732, 695; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.33 (m, 5H), 7.31-7.28 (m, 4H), 6.34 (dtq, 1H, *J* = 15.8, 4.6, 2.1 Hz), 5.68 (dqt, 1H, *J* = 15.8, 6.3, 1.5 Hz), 5.17 (s, 2H), 5.16 (s, 2H), 3.59 (t, 1H, *J* = 7.4 Hz), 2.80-2.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.0, 135.9 (q, *J* = 6.6 Hz), 135.1, 128.7, 128.6, 128.4, 122.6 (q, *J* = 269.5 Hz), 121.5 (q, *J* = 33.7 Hz), 67.6, 50.7 (q, *J* = 0.9 Hz), 30.54; ^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F); HRMS-ESI calcd for $C_{21}H_{19}F_3O_4$ $[M+H]^+$, 393.1308 found 393.1310.

*4.3.9 (E)-dibenzyl 2-methyl-2-(4,4,4-trifluorobut-2-en-1-yl)malonate (**24b**)*

Following general procedure with a reaction time of 96 h using (*E*)-4,4,4-trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (70 mg, 0.25 mmol, 1.0 equiv), dibenzyl 2-methylmalonate (246 mg, 0.825 mmol, 3.3 equiv), K_2CO_3 (104 mg, 0.750 mmol, 3.0 equiv) and CH_3CN (1.0 mL), the obtained crude product was purified by flash

chromatography on silica gel using hexane/Et_2O (90/10) as the eluent to afford **24b** as a colorless oil (77 mg, 76 %). Spectral data were in accordance with the literature [6].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at …

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