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Introduction of the 4,4,4-Trifluorobut-2-ene Chain Exploiting a Regioselective Tsuji–Trost Reaction Catalyzed by Palladium Nanoparticles

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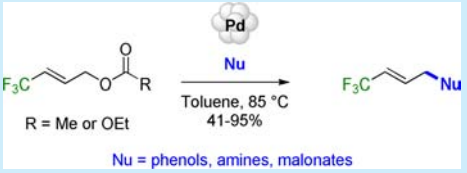
Supporting Information

ABSTRACT: A palladium-nanoparticle-catalyzed Tsuji–Trost reaction of 4,4,4-trifluorobut-2-en-1-yl acetate and ethyl(4,4,4-trifluorobut-2-en-1-yl)carbonate was accomplished with various nucleophiles including phenols, amines, and malonates. In the case of the phenols, isomerization of the double bond in the product (up to 20%) was observed as a side reaction. Further synthetic transformations including hydrogenation, the Diels–Alder reaction, and asymmetric dihydroxylation of a product were also examined.



A 4,4,4-trifluorobut-2-ene chain attached to a phenolic oxygen has been shown over the years to be a useful fluorinated substituent in medicinal chemistry,[1] agrochemistry,[2] and material sciences.[3] Illustrative examples are shown in Figure 1.

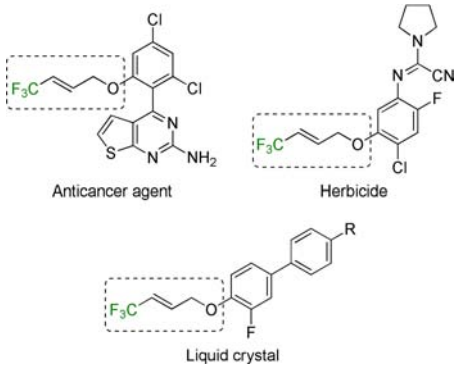


Figure 1. Molecules containing the 4,4,4-trifluorobut-2-ene chain.

The main synthetic strategy used to produce such compounds, **3**, is the reaction between the oxygen-based nucleophile with a suitable electrophilic partner, **2**,[4] using a S_N2 reaction (Figure 1).[1−3,5] While this approach is simple and good yields can be generally obtained, the electrophilic partner bearing a chlorine or a mesylate (**2**; R = Cl or OMs) has setbacks (e.g., volatility, stability). Finally, no examples using other nucleophiles have been reported.[6]

With these limitations in mind, we became interested in investigating an alternative strategy. Herein, we report the first use of a regioselective Tsuji–Trost reaction[7] catalyzed by palladium nanoparticles for the introduction of the 4,4,4-trifluorobut-2-ene chain.[8] Notably, nucleophiles other than phenol can be employed, including amines (both aliphatic and aromatic) and malonates. Molecules bearing this fluorinated chain on a nitrogen atom (**4**)[5c,9] or the β-carbon of malonates have not been reported. Finally, in this approach, the fluorinated chain is introduced in the form of the 4,4,4-trifluorobut-2-en-1-yl acetate (**2a**) and/or the ethyl(4,4,4-trifluorobut-2-en-1-yl)-carbonate (**2b**), both prepared from ethyl 4,4,4-trifluorocrotonate (**1**), a cheap and readily available CF_3-containing building block (Figure 2).[10] Overall, this novel approach is versatile and provides facile access to an important class of fluorinated compounds.

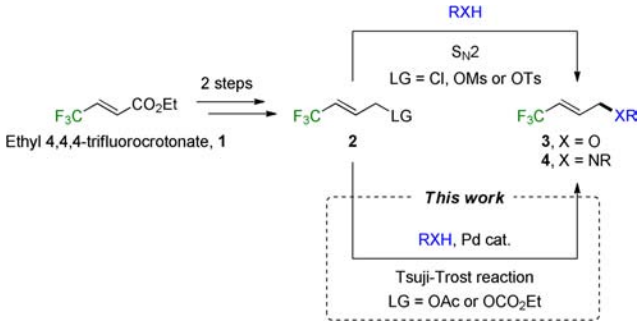


Figure 2. Building block approach using ethyl 4,4,4-trifluorocrotonate for the introduction of a 4,4,4-trifluorobut-2-ene chain.

The initial work aimed at identifying a suitable catalytic system. Out of the few ones tested, the use of in situ generated palladium nanoparticles[11] looked promising (Scheme 1). Indeed, under slightly modified reaction conditions, a moderate conversion (~58%) of the allyl acetate **2a** was observed after 24 h and provided the desired product **3a** in low yield (22%). NMR analysis of the crude mixture revealed the presence of the isomerized product **5a** as the major component. We later

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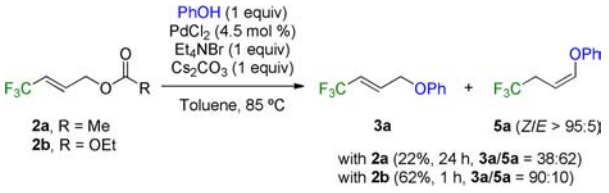
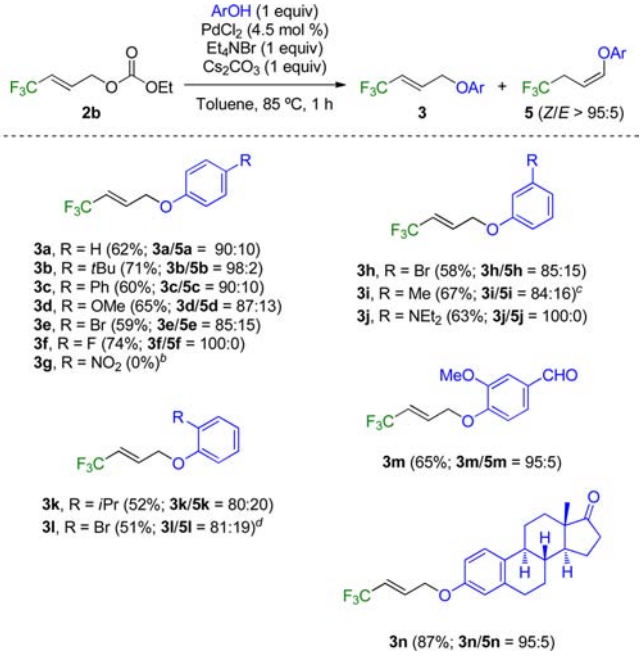
Scheme 1. Initial Results



confirmed through NMR experiments that **3a** slowly isomerized to **5a** under the reaction conditions.[12,13] Hoping to reduce the reaction time and thus the isomerization process, we then switched to the more reactive carbonate **2b**. We were pleased to find that a complete conversion could be achieved in only 1 h, which allowed the isolation of **3a** in 62% yield. In this case, the crude mixture showed a 90:10 ratio of **3a**/**5a**.

Using carbonate **2b**, the scope of phenols was next investigated (Scheme 2). The phenol could be substituted at the para position

Scheme 2. Scope Using Phenols as Nucleophiles[a]

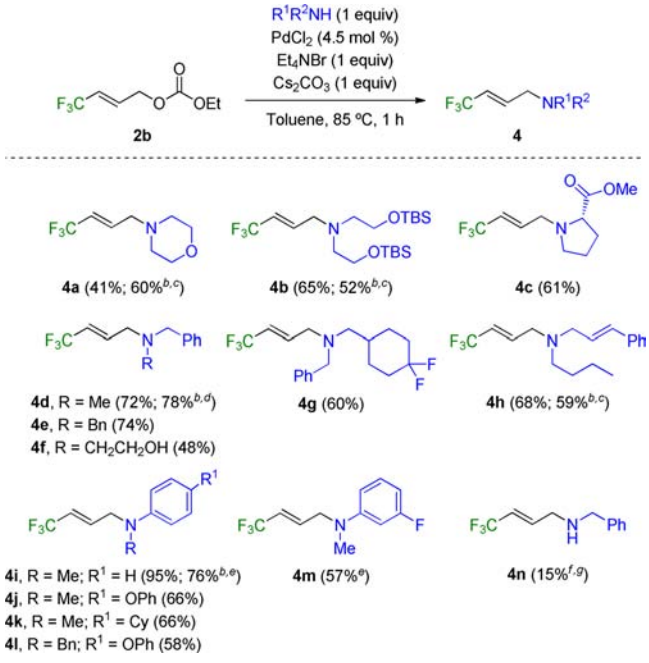


[a]Isolated yield of **3**. [b]No conversion of **2b** was observed. [c]*Z*/*E* for **5i** is 90:10. [d]*Z*/*E* for **5l** is 43:57.

with both electron-donating and electron-withdrawing substituents (with the exception of a nitro group), and the corresponding products **3a**−**f** were obtained in moderate to good yields. Substitution at the meta position had limited effect on the reaction, whereas slightly lower yields (and selectivities) were observed for a phenol substituted in ortho position. Notably, a bromine atom is well-tolerated at every position (cf. **3e**, **3h**, **3l**), opening the door for further metal-catalyzed transformations. Finally, vanillin and estrone, more complex phenols, reacted smoothly to provide the desired products **3m** and **3i** in 65 and 87% yield, respectively, with excellent selectivities.

We then examined the use of amines as nucleophiles, and the results are shown in Scheme 3. Interestingly, little or no isomerized products were detected with either the acetate **2a** or the carbonate **2b**.[14] When we focused on the use of the latter, a wide range of secondary amines was tolerated, including

Scheme 3. Scope Using Amines as Nucleophiles[a]

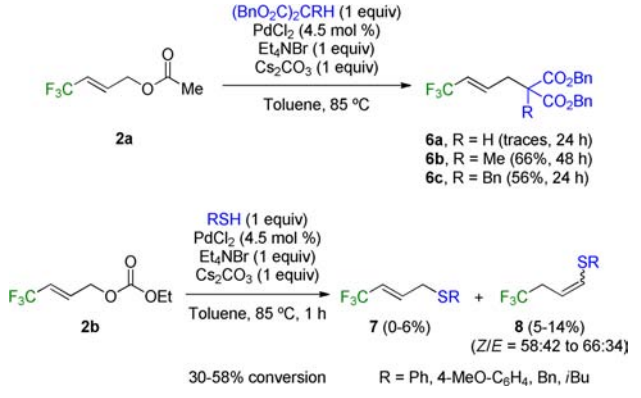


[a]Isolated yield of **4**. [b]Isolated yield of **4** using acetate **2a**. [c]Reaction time was 48 h. [d]Reaction time was 18 h. [e]Reaction time was 24 h. [f]Yield of **4n** estimated by NMR analysis. [g]Complex mixture.

aliphatic, benzylic, and aromatic amines, and the resulting products were isolated in moderate to excellent yields. In cases where both the acetate **2a** and the carbonate **2b** were tested, similar results were generally obtained. Practically, the reactions with the acetate were slower but provided cleaner crude mixtures. Unfortunately, the use of benzylamine, a primary amine, provided a complex mixture from which the desired product (~15% by NMR) could not be extracted.

To complete this study, we investigated the use of other nucleophiles (Scheme 4). When using dibenzyl malonate,[15] the

Scheme 4. Reaction with Malonates and Thiols



presence of an acidic hydrogen in the product was problematic as the dialkylated product (not shown) was the major product observed, with trace amounts of monoalkylated **6a** also present along with other inseparable side products. Replacing the hydrogen with either a methyl group or a benzyl group solved the problem, and the corresponding products **6b** and **6c** could be isolated in good yields. In general, for the malonates, the use of acetate provided cleaner reactions, which facilitated the

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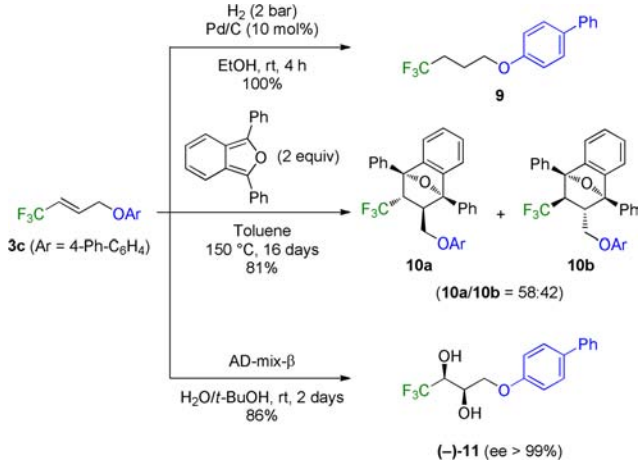
purification step. When using various thiols with carbonate **2b**, low to moderate conversions (30−58%) were observed. NMR analysis of the crude mixtures unfortunately revealed that the major component was the isomerized products **8** along with other unidentified fluorinated side products (7−15%).[16] The desired allylic thioethers **7** were only observed in low yield (2−6%) when R = Ph or Bn. Further NMR experiments confirmed the rapid isomerization of **7** to **8** under the reaction conditions. We believe that, in this case, the isomerization process is facilitated due to the increased acidity of the allylic proton located α to the sulfur atom. This observation would also support a base-mediated process for the isomerization.[12,17] The lower conversions observed may result from poisoning of the palladium catalyst.

Finally, we investigated the possibility to further functionalize the product obtained using **3c** as a model compound, and the results are shown in Scheme 5. For instance, hydrogenation

Scheme 5. Further Functionalization of 3c



under standard conditions provided the saturated compounds **9** in quantitative yield.[18] Even though the number of known Diels−Alder reactions of trifluoromethylalkenes is limited,[19] a Diels−Alder reaction using 1,3-diphenylisobenzofuran was realized, thus representing a new access to monotrifluoromethyl-substituted saturated cycles.[20] Indeed, a combined isolated yield of 81% was obtained because the crude mixture of diastereoisomers (58:42) could be separated by flash chromatography. Finally, asymmetric Sharpless dihydroxylation could also be performed, and diol (−)-**11** was obtained in good yield and excellent enantioselectivity (>99% ee).[21,22]

In conclusion, we have reported the use of a regioselective Tsuji−Trost reaction catalyzed by palladium nanoparticles for the introduction of the 4,4,4-trifluorobut-2-ene chain using various nucleophiles. Notably, molecules bearing this fluorinated chain on a nitrogen atom or the β-carbon of malonates have not been reported. The requisite precursors (acetate or carbonate) are easily prepared from ethyl 4,4,4-trifluorocrotonate, a cheap and readily available CF_3-containing building block. In addition, the palladium nanoparticles are generated using one of the most economical sources of palladium, $PdCl_2$. Furthermore, the products are amenable to additional synthetic transformations. Overall, this method provides a new and alternative approach to useful fluorinated molecules.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Isomerization was only significantly observed (∼15%) in the case of **4f** starting from **2b**.

(15) The benzyl ester was used to facilitate purification because the product is less volatile than the corresponding ethyl ester.

(16) See Supporting Information for details.

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(22) The same transformation performed with AD-mix α instead over 7 days provided diol (+)-**11** in 68% yield and >99% ee. See Supporting Information for details.

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