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Letter

# Synthesis of $CF_3$−Containing Linear Nitriles from α-(Trifluoromethyl)styrenes

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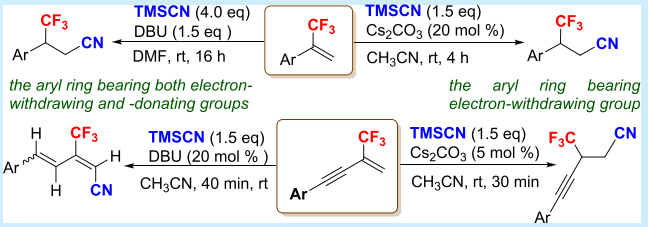
**ABSTRACT:** Four unprecedented base-catalyzed/mediated nucleophilic additions of TMSCN to α-(trifluoromethyl)styrenes and 2-trifluoromethyl enynes were developed. The reaction proceeded smoothly at room temperature under mild and transition-metal-free conditions without affecting the trifluoromethyl group and afforded the corresponding $CF_3$-containing alkyl, alkynyl, and butadienyl nitriles in moderate to excellent yields in a highly regioselective manner, respectively.

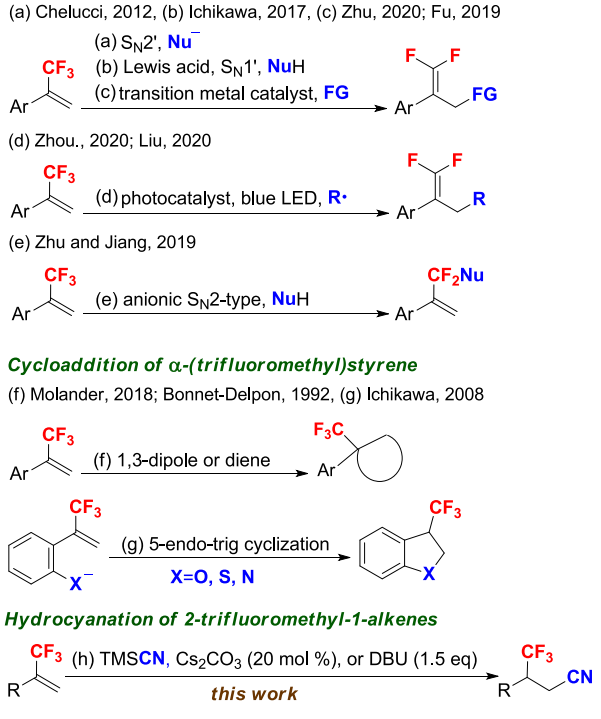





The hydrofunctionalization and difunctionalization of alkenes have received much attention due to their potential applications in organic synthesis.[1] Recently, vicinal trifluoromethyl functionalization of alkenes has become an attractive strategy for the construction of functionalized $CF_3$-containing compounds.[2,3] Among these protocols, cyanotrifluoromethylation of styrenes provides a straightforward access to β-trifluoromethylated nitriles in a single procedure.[4] Although these methods are useful, they still suffer one or more drawbacks, such as the use of expensive Togni's reagents. Furthermore, the scope of these methods limits to the preparation of the $CF_3$-containing branched alkyl nitriles. Therefore, it is highly desirable to develop a general method for the synthesis of $CF_3$-containing linear alkyl nitriles.[5]

Trifluoromethylstyrenes are highly useful $CF_3$-containing building blocks in organic synthesis.[6] The transformation of trifluoromethylstyrenes into other fluorinated or nonfluorinated compounds has become a fascinating field in organic chemistry.[7] However, most research has been focused on the development of efficient methods for the synthesis of the *gem*-difluoroalkenes via cleavage of the C−F bonds in the trifluoromethyl group,[8] which might be ascribed to the fact that trifluoromethylstyrenes are more prone to undergo β-fluoride elimination under various reaction conditions (Scheme 1a−e).[9] The addition reaction of trifluoromethylstyrenes with retaining of three C−F bonds is a great challenge. Considering the importance of the trifluoromethyl group in organic synthesis and the relatively high cost of trifluoromethylated compounds, we envisage that the incorporation of a trifluoromethyl group into organic molecules by utilizing trifluoromethylstyrenes as inexpensive and readily available $CF_3$-containing building blocks without accompanying defluorination of $CF_3$ group is worthy of further exploration. Until now, only a few examples with trifluoromethylstyrenes as dipolarophiles for 1,3-diploar cycloaddition reactions have been reported and several $CF_3$-containing carbocycles and

**Scheme 1. Reactions of α-(Trifluoromethyl)styrenes**

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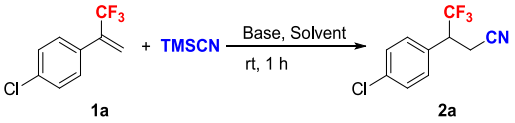
heterocycles have been synthesized, leaving the C−F bond untouched (Scheme 1f).[10] In addition, Ichikawa et al. reported the synthesis of $CF_3$-bearing heterocycles via nucleophilic 5-*endo-trig* cyclization of 2-trifluoromethyl-1-alkenes (Scheme 1g).[11] However, addition of α-(trifluoromethyl)styrenes with nucleophiles without loss of the C−F bond of the $CF_3$ group remains a largely unexplored area.[12] In this paper, we reported an unprecedented base-catalyzed/mediated nucleophilic addition of TMSCN to α-(trifluoromethyl)styrenes and 2-trifluoromethyl enynes under mild reaction conditions, affording the $CF_3$-containing alkyl, alkynyl and butadienyl nitriles in moderate to excellent yields in an anti-Markovnikov manner (Scheme 1h).

Compared to a normal alkene (such as α-methylstyrene), α-(trifluoromethyl)styrene is generally considered as activated olefin due to the σ-electron-withdrawing character of the $CF_3$ group. The trifluoromethyl group attached to a double bond can slightly lower the LUMO energy levels of the olefins, which renders the terminal carbon of α-(trifluoromethyl)-styrene significantly more electrophilic poor than the corresponding α-methylstyrene arene (weak nucleophile).[9g,12b,13] However, in comparison with other standard electrophiles such as α,β-unsaturated ketone, α-(trifluoromethyl)styrene exhibits lower reactivity toward to nucleophiles due to the lack of a strong π-electron-withdrawing group (ketone, nitro, cyano, or ester etc.) which is known to dramatically decrease the LUMO energy level. In consideration of the unique electrophilicity of α-(trifluoromethyl)styrene, we question whether it is capable of undergoing nucleophilic addition if the defluorination reaction is efficiently suppressed.

Based on the above-mentioned considerations, we envisioned that the reaction of nucleophile with α-(trifluoromethyl)styrenes via nucleophilic addition and not via the typical $S_N2'$ type of defluorinative addition−elimination process might be feasible. Initially, the reaction of 1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene with TMSCN were performed in the CuCl/NaO*t*Bu/$CH_3CN$ system. Unfortunately, a mixture of defluorinative product and unreacted starting material was observed. Therefore, effective suppression of the undesired defluorination reaction is a significant problem we should solve. We began our investigation using the nucleophilic addition of **1a** with TMSCN as the model reaction to optimize the reaction conditions without the addition of transition metal catalyst (Table 1). No desired products **2a** was detected and the starting material **1a** was retained in the absence of base (entry 1). Among the various bases tested (entries 2−18), $Cs_2CO_3$ was the most suitable for the reaction, while other bases such as DBN, DBU, and TMG gave lower yields. Screening of different solvents showed that both $CH_3CN$ and DMF were effective for this reaction, whereas the yields were reduced when THF, toluene, $CH_3OH$, NMP, and DMSO were used as solvent (entries 18−24). Decreasing the amount of $Cs_2CO_3$ and TMSCN led to significant decrease in the yields (entries 25 and 26). To our delight, nucleophilic addition product **2a** were detected as the sole product, and no defluorinative product was observed in all cases. Furthermore, the hydrocyanation reactions proceeded in an anti-Markovnikov fashion, and no Markovnikov product was found.

Subsequently, the scope of α-(trifluoromethyl)styrenes was investigated (Scheme 2). The results indicated that the electronic nature of the substituents on the benzene ring played a significant role in the reaction. α-(Trifluoromethyl)-

**Table 1. Optimization of Reaction Conditions**[a]

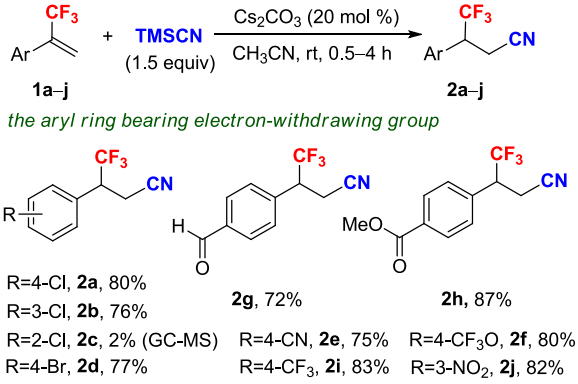



**1a** **2a**

| entry | base (*x* mol %) | TMSCN (*x* equiv) | solvent | **2a** (%)[b] |
|---|---|---|---|---|
| 1 | none | 1.5 | $CH_3CN$ | 0 |
| 2 | $Et_3N$ (20) | 1.5 | $CH_3CN$ | 0 |
| 3 | DABCO (20)[c] | 1.5 | $CH_3CN$ | 0 |
| 4 | TMEDA (20)[c] | 1.5 | $CH_3CN$ | 0 |
| 5 | DMAP (20)[c] | 1.5 | $CH_3CN$ | 0 |
| 6 | DIPEA (20)[c] | 1.5 | $CH_3CN$ | 0 |
| 7 | $Na_2CO_3$ (20) | 1.5 | $CH_3CN$ | 2 |
| 8 | NaOH (20) | 1.5 | $CH_3CN$ | 5 |
| 9 | LiO*t*Bu (20) | 1.5 | $CH_3CN$ | 5 |
| 10 | $K_3PO_4$ (20) | 1.5 | $CH_3CN$ | 6 |
| 11 | $NaOCH_3$ (20) | 1.5 | $CH_3CN$ | 6 |
| 12 | $K_2CO_3$ (20) | 1.5 | $CH_3CN$ | 7 |
| 13 | NaH (20) | 1.5 | $CH_3CN$ | 7 |
| 14 | CsF (20) | 1.5 | $CH_3CN$ | 30 |
| 15 | DBN (20)[c] | 1.5 | $CH_3CN$ | 48 |
| 16 | DBU (20)[c] | 1.5 | $CH_3CN$ | 64 |
| 17 | TMG (20)[c] | 1.5 | $CH_3CN$ | 82 |
| 18 | $Cs_2CO_3$ (20) | 1.5 | $CH_3CN$ | 99 |
| 19 | $Cs_2CO_3$ (20) | 1.5 | THF | 0 |
| 20 | $Cs_2CO_3$ (20) | 1.5 | toluene | 0 |
| 21 | $Cs_2CO_3$ (20) | 1.5 | $CH_3OH$ | 0 |
| 22 | $Cs_2CO_3$ (20) | 1.5 | NMP | 17 |
| 23 | $Cs_2CO_3$ (20) | 1.5 | DMSO | 82 |
| 24 | $Cs_2CO_3$ (20) | 1.5 | DMF | 96 |
| 25 | $Cs_2CO_3$ (15) | 1.5 | $CH_3CN$ | 47 |
| 26 | $Cs_2CO_3$ (20) | 1.2 | $CH_3CN$ | 44 |

[a]Reaction conditions: **1a** (0.1 mmol), solvent (1 mL), rt, 1 h. [b]Yields are determined by GC analysis based on **1a**. [c]For the full names of bases, see the Supporting Information. The reaction vial was sealed with a septum.

**Scheme 2. $Cs_2CO_3$-Catalyzed Hydrocyanation of α-(Trifluoromethyl)styrenes**[a]




[a]Reaction conditions: **1a−j** (0.7 mmol), TMSCN (1.5 equiv, 1.05 mmol), $Cs_2CO_3$ (20 mol %), $CH_3CN$ (7 mL), rt, 0.5−4 h. The reaction vial was sealed with a septum.

styrenes bearing electron-donating groups were unreactive and failed to provide the desired products under the optimal reaction conditions. Only those substrates having electron-withdrawing groups could afford addition products in good yields. A series of functional groups, such as halogen, cyano,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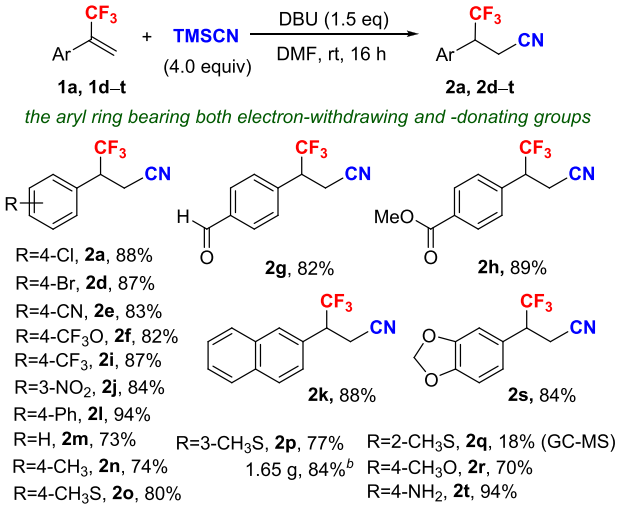
trifluoromethoxy, formyl, ester, trifluoromethyl, and nitro, were well tolerated. α-(Trifluoromethyl)styrenes possessing substituent in the *para*- and *meta*-position on the benzene ring proceeded smoothly (**1a** and **1b**). However, the reaction of *ortho*-substituted styrene did not proceed efficiently and only small amounts of the desired product were observed (**1c**), which might be due to the steric effect of the substituent attached at the *ortho*-position.

Encouraged by the above success, we then turned our attention to the hydrocyanation of α-(trifluoromethyl)styrenes bearing electron-donating groups. With further screening of the reaction conditions, we were delighted to find that the use of strong organic base (DBU) and DMF as solvent could significantly promote the hydrocyanation reaction and afford the cyanation products in good to excellent yields (Scheme 3).

**Scheme 3. DBU-Mediated Hydrocyanation of α-(Trifluoromethyl)styrenes**[a]

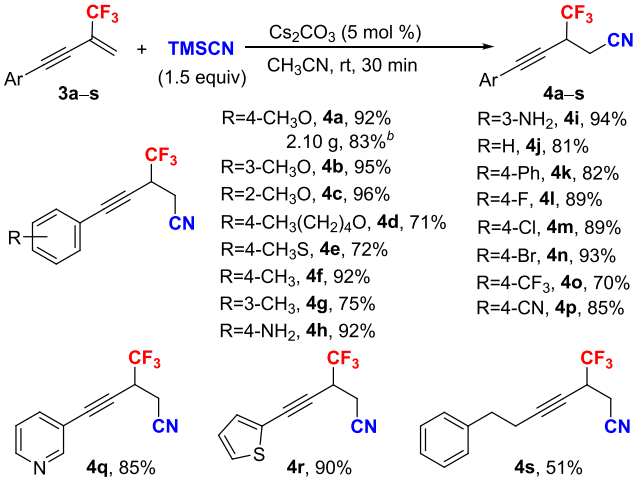



[a]Reaction conditions: **1a**, **1d**–**t** (0.7 mmol), TMSCN (4.0 equiv, 2.8 mmol), DMF (7 mL), rt, 16 h. The reaction vial was sealed with a septum. [b]Performed at 8 mmol scale.

Both substrates bearing strong electron-donating group (OMe, **1r**) and strong electron-withdrawing group ($NO_2$, **1j**) on the benzene ring are compatible with the modified reaction conditions. Substrates that bear a reactive site, such as halogen, cyano, formyl, ester, nitro, and amino groups, remained intact, providing synthetic opportunities for further transformation.

Recently, 2-$CF_3$ enynes have attracted much attention for their potential application in the construction of fluorinated or nonfluorinated heterocycles and $CF_3$-containing compounds.[14] Functionalization of 2-$CF_3$-1,3-enynes is a significant, yet difficult, task because they possess five possible highly reactive sites. In addition, the side reactions relating to fluorine elimination are still a great challenge in these transformations.[12b,15] To further verify the generality of the above-mentioned hydrocyanation reaction, the addition reaction of various 2-$CF_3$ enynes with TMSCN in the presence of 5 mol % $Cs_2CO_3$ was performed, and the results are shown in Scheme 4. In most cases, the reaction proceeded efficiently via a 1,2-addition pattern and provided the 1,2-hydrocyanation products in good to excellent yields with high regioselectivity, irrespective of the nature of the substituent present in the aromatic ring. Changing the aryl ring of the 2-$CF_3$ enynes to pyridine ring (**3q**) or thiophene ring (**3r**) did not make much

**Scheme 4. $Cs_2CO_3$-Catalyzed Hydrocyanation of 2-$CF_3$ Enynes**[a]

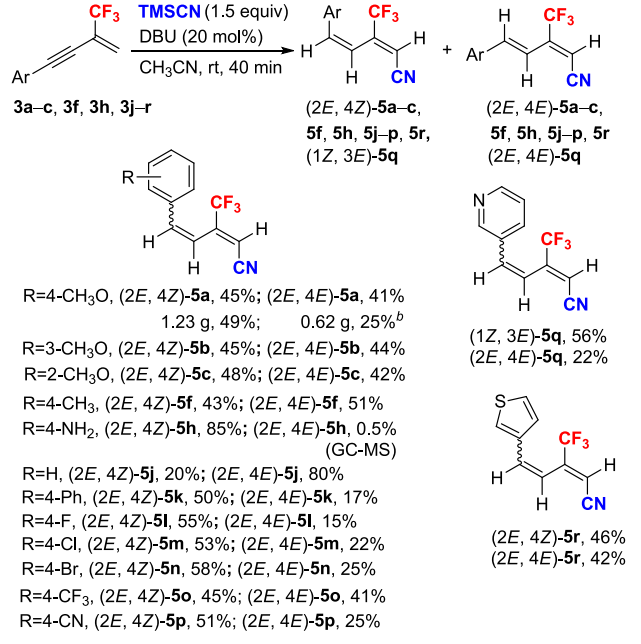



[a]Reaction conditions: **3a**–**s** (0.7 mmol), TMSCN (1.5 equiv, 1.05 mmol), $Cs_2CO_3$ (5 mol %), $CH_3CN$ (7 mL), rt, 0.5 h, Ar. The reaction vial was sealed with a septum. [b]Performed at 10 mmol scale.

difference in the yields of the products. Aliphatic 2-$CF_3$ enyne (**3s**) was also found to be a suitable substrate, and the corresponding addition product was afforded in moderate yield.

When the reaction of 2-$CF_3$ enynes with TMSCN was carried out in the presence of 20 mol % DBU, the reactions also proceeded rapidly within 40 min at room temperature and afforded the unexpected cyanated $CF_3$-substituted 1,3-butadienes in fair to excellent yields (Scheme 5). The reactions

**Scheme 5. DBU-Catalyzed Hydrocyanation of 2-$CF_3$ Enynes**[a]




[a]Reaction conditions: **3a**–**c**, **3f**, **3h**, **3j**–**r** (0.7 mmol), TMSCN (1.5 equiv, 1.05 mmol), DBU (20 mol %), $CH_3CN$ (7 mL), rt, 40 min. The reaction vial was sealed with a septum. [b]Performed at 10 mmol scale.



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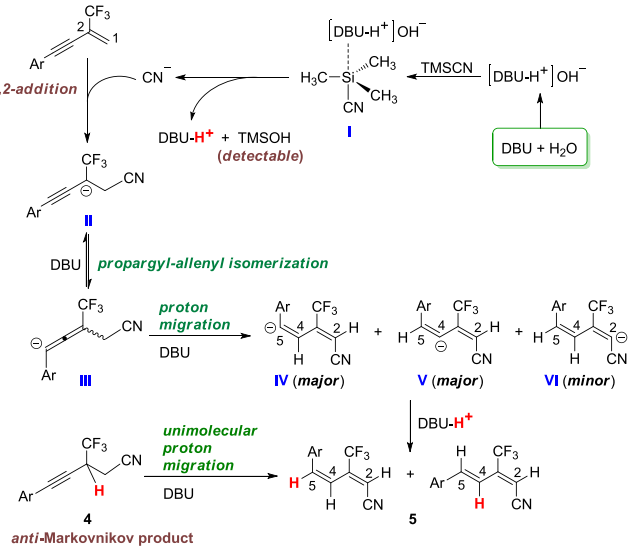
could tolerate various functional groups such as methoxy, amino, halogen, and cyano. A mixture of (2*E*,4*Z*)/(2*E*,4*E*)-1,3-butadienes was formed but with low *E*/*Z*-selectivity. Fortunately, the (2*E*,4*Z*)- and (2*E*,4*E*)-isomers could be isolated by column chromatography. The structures of (2*E*,4*E*)-**5k** and (2*E*,4*Z*)-**5p** were determined by X-ray diffraction (see the Supporting Information).

To demonstrate the practicality of these new developed protocols, three scale-up reactions were performed. Without further optimization, the hydrocyanation of **1p** and **3a** could be scaled up to gram scale; however, the expected products were obtained in slightly lower yields (Scheme 3, **1p**; Scheme 4, **3a**; Scheme 5, **3a**).

To elucidate the source of the hydrogen in the hydrocyanation products, a series of deuterium-labeling and some control experiments were performed (see Schemes S1 and S2). These results indicated that the proton at the 4- and 5-position of **5a** was originated from a trace amount of water in $CH_3CN$ and the methylene group, respectively. The transformation of **4a** to 1,3-butadiene **5a** might proceed via an intramolecular proton migration.

Finally, a plausible reaction mechanism for the DBU-catalyzed hydrocyanation of 2-$CF_3$ enynes is proposed in Scheme 6. First, the reaction is initiated by a catalytic amount

**Scheme 6. Proposed Mechanism of the DBU-Catalyzed Hydrocyanation of 2-Trifluoromethyl Enynes**




of DBU. The reaction of DBU with a trace amount of water in the $CH_3CN$ or reaction system produces the $[DBU\text{-}H]^+$–$OH^-$ complex.[16] This complex coordinates to the silicon atom of TMSCN to activate TMSCN and the reactive hypervalent silicon species **I** is formed. The cleavage of the silicon–CN bond in **I** could afford $CN^-$, DBU-$H^+$, and TMSOH (detectable).[17] Subsequently, nucleophilic 1,2-addition of $CN^-$ to the 1-position of 2-$CF_3$ enyne produces the key propargyl anion **II**. The active trifluoromethylated propargyl anion **II** is unstable due to the strong negative inductive effect of the trifluoromethyl group and it undergoes propargyl-allenyl isomerization with the assistance of DBU to generate the allenyl anion **III**.[18] The allenyl anion **III** could be transformed into butadienyl anions **IV**, **V**, and **VI** through hydride migration.[19] Finally, protonation of the butadienyl anions **IV**, **V**, and **VI** with DBU-$H^+$ furnishes the 1,3-butadienes **5**. The non-nucleophilic, strong tertiary amine base, DBU acts as hydrogen-bonding acceptor, whereas DBU-$H^+$ acts as a proton donor. In addition, on the basis of our labeling experiments (see Schemes S1 and S2), the DBU-catalyzed rearrangement of **4** to the 1,3-butadienes **5** involves the intramolecular migration of two hydrogen atoms, one at the propargyl and the other at the methylene position. Importantly, these reaction conditions suppress the defluorination reaction, and the defluorinative product is not observed.

In summary, we have developed four unprecedented base-catalyzed/mediated nucleophilic additions of TMSCN to α-(trifluoromethyl)styrenes and 2-$CF_3$ enynes. The nucleophilic addition proceeded efficiently at room temperature, and the undesired defluorination reaction was suppressed completely. A variety of $CF_3$-containing alkyl, alkynyl and butadienyl nitriles were obtained in moderate to excellent yields. The results suggested that α-(trifluoromethyl)styrenes could be used as the moderate electrophiles and were sufficiently electrophilic to undergo nucleophilic addition. The mechanism of the DBU-catalyzed hydrocyanation of 2-$CF_3$ enynes involves nucleophilic 1,2-addition, propargyl-allenyl isomerization, intramolecular proton migration, and protonation. We anticipate that this strategy may provide a new method for the synthesis of valuable functionalized $CF_3$-containing compounds from readily available α-trifluoromethylstyrenes.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01988.

Experimental details and spectral data for all new compounds ($^1H$ NMR, $^{13}C$ NMR, and HRMS) (PDF)

### Accession Codes

CCDC 2053222 and 2053257 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Author Contributions

‡S.X. and Y.D. contributed equally.

## Notes

The authors declare no competing financial interest.

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