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Regio- and Diastereoselective Cu-Mediated Trifluoromethylation of Functionalized Alkenes

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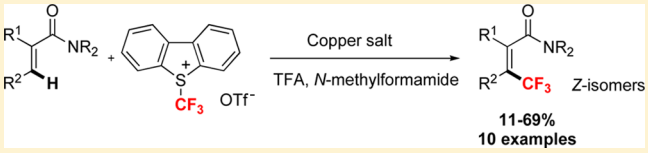
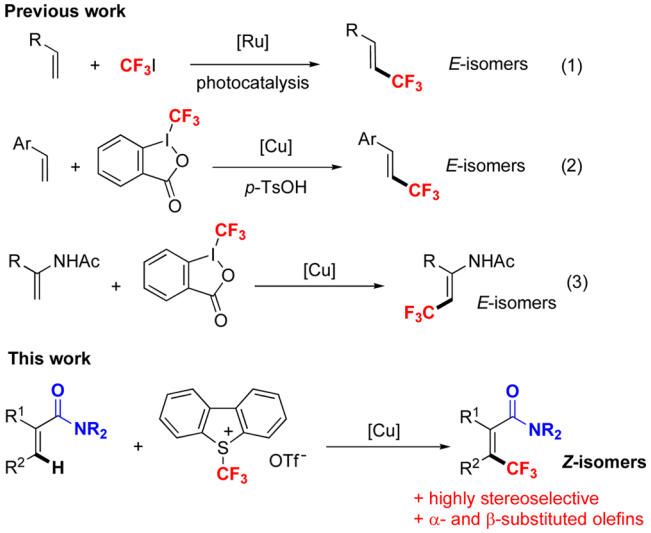
Supporting Information

ABSTRACT: α- and β-substituted *N*,*N*-diethylacrylamides undergo copper-mediated direct β-trifluoromethylation. The amide moiety acts as a directing group for the regio- and the stereo-controlled introduction of the trifluoromethyl group. The reaction is carried out under acidic conditions in the presence of Umemoto's reagent. This method does not require prefunctionalized substrates and delivers excellent stereoselectivity.



The construction of trifluoromethylated molecules keeps the community of organofluorine chemists vibrant by continuously attracting researchers in the quest for new synthetic approaches to and novel applications of these compounds.[1−4] In this context, the trifluoromethyl alkene motif is particularly sought after, for instance, as an amide bond isostere for enhancing the metabolic resistance of peptides.[5,6] Because of its significant importance, the design of innovative routes to access valuable trifluoromethylated olefins has attracted growing interest.[7−11] Of the current methods, several cross-coupling reactions were revealed to be efficient, although the prefunctionalization of alkenes with halogen,[12−21] sulfonates,[22] tin,[23] or boron substituents[24−29] was generally required. α,β-Unsaturated carboxylic acids were also employed as substrates submitted to functional-group interconversion[30] or decarboxylative trifluoromethylation.[31,32] The major advantage of these methods is their regiospecificity. Nevertheless, the stereochemical information (diastereomeric ratio) is sometimes lost, and the prerequisite for functionalized substrates mitigates the development potential of these reactions. In contrast, methods that do not require a prefunctionalization of the alkene are less frequent, although they are more atom-economical. In 2012, Cho and co-workers described the trifluoromethylation of alkenes with CF_3I by visible-light photoredox catalysis (Scheme 1, eq 1).[33] When studying the oxytrifluoromethylation of styrene derivatives, Sodeoka and co-workers noticed that addition of *p*-TsOH to the cationic copper-catalyzed reaction led to the thermodynamically favored *E* isomer of β-trifluoromethylstyrene derivatives (Scheme 1, eq 2).[34] Loh and Feng examined the copper-catalyzed olefinic trifluoromethylation of enamides, leading to *E* isomers of the trifluoromethylated enamides (Scheme 1, eq 3).[35] These three approaches relied on addition−elimination-type mechanisms, affording exclusively the *E* isomers of the products. Surprisingly, the direct C−H bond trifluoromethylation of electron-deficient alkenes giving access to highly substituted olefins has not been explored and still remains an important challenge.

Scheme 1. Examples of Trifluoromethylation Reactions



Our laboratory is interested in the design of new fluorinated alkenes as peptido- and glycomimetics,[36−38] including the development of original methodologies such as palladium- and copper-catalyzed fluoroalkenylation reactions[37] and copper-catalyzed β-difluoroacetylation of dihydropyrans.[38] In this context, we have been investigating new synthetic approaches for the straightforward de novo construction of trifluoromethylated electron-deficient alkenes. By analogy to the strategy reported by Yu and co-workers[39] in the Pd(II)-catalyzed ortho trifluoromethylation of aromatic derivatives using secondary amides as a directing group (DG), we anticipated that a similar approach might be employed for the trifluoromethylation of electron-deficient alkenes, hypothetically leading to synthetically challenging *Z*-trifluoromethylated functionalized alkenes.

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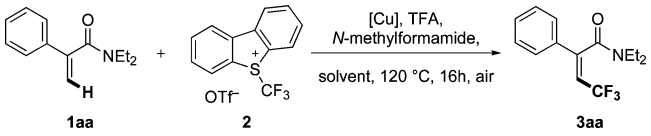
Herein, we report our results on the copper-mediated direct β-trifluoromethylation of α- and β-substituted *N*,*N*-diethylacrylamides in the presence of Umemoto's reagent.[40]

Our investigation started with the study of the trifluoromethylation of phenyl acrylamide **1aa** (Table 1). We were pleased to notice that in presence of CuI, Umemoto's reagent **2**, trifluoroacetic acid (TFA), and *N*-methylformamide at 120 °C in DMF under air, desired product **3aa** was obtained in 17% NMR yield (Table 1, entry 1). Interestingly, **3aa** was obtained as a single *Z* isomer, as ascertained by NMR experiments (NOE, see Supporting Information), clearly indicating the key role of the tertiary amide as a DG in this coupling process. Other solvents were then tested (entries 2−5), leading either to no product formation in chlorobenzene and 1,4-dioxane or to enhanced yield in toluene. Importantly, it turned out that the best reactivity was observed when the reaction was carried out in dichloroethane, affording **3aa** in 70% yield (entry 5). To study the reaction conditions further, different copper sources were tested (entries 5−8), demonstrating that both copper I and copper II species were efficient in the direct trifluoromethylation reaction, yielding **3aa** in the same range of yields (61−70%).[41,42] Therefore, we decided to pursue our optimization with the bench-stable CuI salt. Decreasing the reaction temperature from 120 to 80 °C (entry 9) had a drastic effect as only 7% of **3aa** was detected, indicating that a threshold temperature was required for the transformation to occur. Moreover, control experiments revealed that exclusion of any of the reaction components, including copper salt, TFA,[43] and *N*-methylformamide, afforded no or little of the trifluoromethylated product (entries 10−12). Indeed, we found that TFA was a key additive for the success of the olefinic trifluoromethylation as well as *N*-methylformamide that most likely acted as a ligand for copper.[44] We also evaluated Togni's acid reagent as an alternative source of electrophilic CF_3 donor, but a much lower yield was obtained compared to the use of Umemoto's reagent (entry 13). Furthermore, to minimize the amount of copper salt in the reaction, 10 mol % of copper iodide was used, providing a yield that was 12% lower than that of the reaction run under stoichiometric conditions. Although these results nicely demonstrated the suitability of copper-catalyzed reaction conditions, we decided to pursue our experiments under stoichiometric amounts of copper.

Table 1. Optimization of Reaction Conditions[a]



1aa 2 3aa

entry	copper source	solvent	NMR yield (%)[b]
1	CuI	DMF	17
2	CuI	PhCl	0
3	CuI	1,4-dioxane	traces
4	CuI	toluene	39
5	CuI	DCE	70
6	CuBr	DCE	68
7	Cu(OAc)	DCE	61
8	$Cu(OAc)_2$	DCE	66
9[c]	CuI	DCE	7
10	–	DCE	0
11[d]	CuI	DCE	19
12[e]	CuI	DCE	10
13[f]	CuI	DCE	37

[a]Copper source (1.1 equiv), **1aa** (0.1 mmol), Umemoto's reagent **2** (1.5 equiv), TFA (10 equiv), *N*-methylformamide (15 equiv), [**1aa**] = 0.03 mol L^{-1}, 120 °C, 16 h, air. [b]Yields were determined by ^{19}F NMR of the crude reaction mixture using trifluoroacetophenone as an internal standard. [c]Reaction was carried out at 80 °C. [d]Without TFA. [e]Wihout *N*-methylformamide. [f]Togni's acid reagent was used instead of Umemoto's reagent. DCE, 1,2-dichloroethane; DMF, *N*,*N*-dimethylformamide.

Encouraged by these promising results, the impact of the DG on the reactivity was studied (Figure 1). For this purpose, five substrates bearing a chelating group commonly used in C−H functionalization reactions were examined. The diethyl tertiary amide DG performed better than other typical DGs such as diisopropylamide **1ab** (67 versus 30% yield) or morpholine amide **1ac** (57% of **3ac**). Noteworthy is that the synthetically versatile morpholine amide offers great opportunities for further synthetic transformations, illustrating an additional advantage of this methodology. In contrast, privileged secondary amide DGs such as the pentafluoroarylamide moiety in **1ad** or the bidentate amide prepared from 8-aminoquinoline in **1ae** gave no or little **3ad** and **3ae**, respectively. These results suggested that in our case the acidity of the NH group is not crucial for the reactivity.[39]

With our optimized conditions in hand, the scope of the reaction was then studied using various *N*,*N*-diethylacrylamides. Our methodology was applied to introduce the CF_3 group onto acrylamides featuring different substitution patterns: α- or β-substituted and α,β-disubstituted olefins. Desired trifluoromethylated products **3** were isolated as single *Z* diastereoisomers in up to 69% yield (Scheme 2). First, the functionalization of various α-aryl-substituted acrylamides **3aa**−**3ea** was examined. We were delighted to find that the trifluoromethylation demonstrated good functional-group tolerance. Indeed, electron-donating substituents such as methoxy (**1ba**) and *tert*-butyl (**1ca**) groups or an electron-withdrawing chlorine atom (**1da**) on the aryl moiety allowed the formation of products **3** in good yields, with electron-enriched aryls having a beneficial effect on the reactivity. Notably, a chloride atom on aryl group

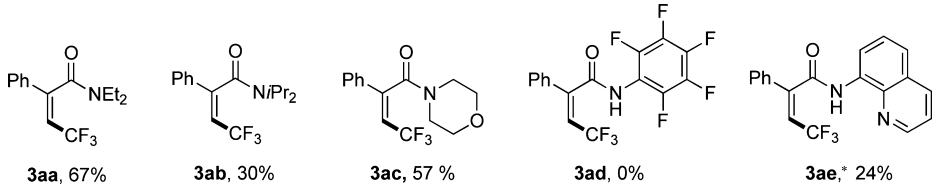


Figure 1. Screening of various directing groups. Reactions were carried out on a 0.3 mmol scale: **1** (0.3 mmol), **2** (1.5 equiv), CuI (1.1 equiv), TFA (10 equiv), *N*-methylformamide (15 equiv), DCE (9 mL), air, 120 °C, 16 h. Isolated yields. *3ae was isolated as an inseparable mixture with **1ae** in a 1:0.65 ratio (**3ae**/**1ae**).

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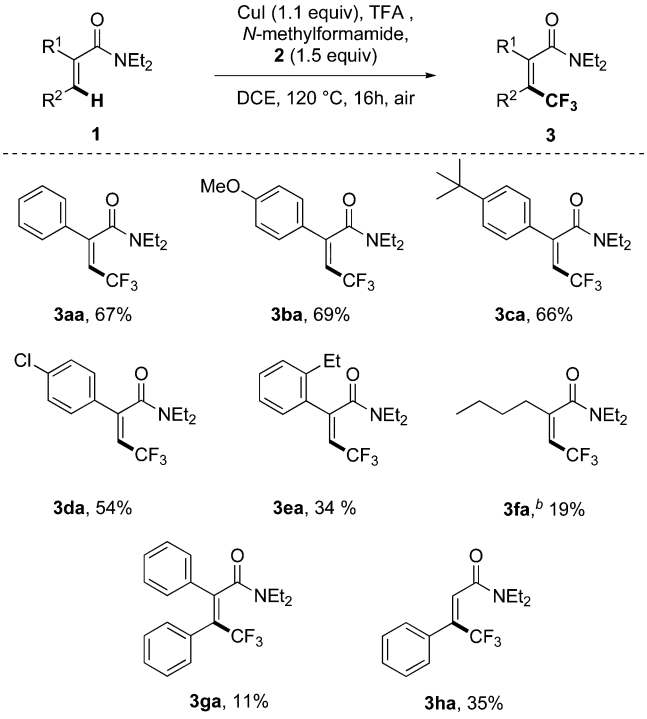
Scheme 2. Scope of the Trifluoromethylation Reaction[a]



[a]Reactions were carried out on a 0.3 mmol scale: **1** (0.3 mmol), **2** (1.5 equiv), CuI (1.1 equiv), TFA (10 equiv), *N*-methylformamide (15 equiv), DCE (9 mL), air, 120 °C, 16 h. Isolated yields. [b]Note that a separate fraction containing 24% of trifluoromethylated allylic product was isolated as an inseparable mixture with unreacted **1fa**.

was tolerated, allowing further functionalization through other cross-coupling reactions. The stereocontrolled trifluoromethylation of these substrates is challenging owing to the presence of two competing C−H positions on the terminal olefin. Not only did a monotrifluoromethylation reaction occurred but also, and most importantly, a single *Z* isomer was formed without detection of the *E* isomer at any stage of the process. Interestingly, acrylamide **1fa** bearing an *n*-butyl chain at the α-position also gave desired product **3fa**, albeit in a lower yield compared to α-aryl derivatives. This was due to the concomitant formation of the trifluoromethylated allylic product resulting from the isomerization of the double bond. To evaluate the scope of the reaction further, the direct trifluoromethylation of the sterically more congested α,β-disubstituted acrylamide **1ga** from (2*E*)-2,3-diphenylacrylic acid led to the formation of desired tetrasubstituted alkene **3ga** in only 11% yield, probably because of the overall steric hindrance. Nevertheless, this example showcased the potential of our method to access fully decorated alkenes. Finally, *E*-configured β-phenyl substrate **1ha** was a suitable substrate, leading to trisubtituted alkene **3ha** in 35% yield. Noteworthy is that products **3ga** and **3ha**, although obtained in moderate yields, are quite exceptional because of their tri- and tetrasubstituted patterns and their obtention as single geometrical isomers by direct C−H functionalization.

In summary, we have developed a new method leading to the regioselective trifluoromethylation of α- or β-substituted and α,β-disubstituted acrylamides in yields ranging from 11 to 69%. This reaction turned out to be valuable for the direct construction of Csp_2-CF_3 bond with a total control of the stereoselectivity toward the otherwise difficult to access *Z* diastereoisomers. This method was not limited to terminal alkenes but was also applied to sterically more hindered, substituted alkenes, offering a straightforward approach for the synthesis of valuable fluorinated building blocks.

EXPERIMENTAL SECTION

General Information. The trifluoromethylation reactions were carried out in dried reaction vessels with Teflon screw caps under air. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. DCE and toluene were distilled over CaH_2 prior to use. Anhydrous DMF and 1,4-dioxane were purchased and used as received. NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts (δ) are quoted in ppm relative to TMS (^1H) and $CFCl_3$ (^{19}F). Coupling constants (J) are quoted in Hz. The following abbreviations were used to show the multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; and m, multiplet. The residual solvent signals were used as references ($CDCl_3$: δ_H = 7.26 ppm and δ_C = 77.00 ppm). High-resolution mass spectrometry was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. The wave numbers (ν) of recorded IR signals (ATR) are quoted in centimeters^{-1}. Note that because of the high volatility of products **3**, evaporation was achieved under a pressure above 60 mbar without heating.

N,N-Diethylacrylamides **1ba**, **1ca**, **1da**, and **1ea** were prepared from the corresponding esters[45] after saponification, formation of acid chloride, and condensation with diethylamine, successively.[46] Note that intermediate acids and acid chlorides were not isolated and were directly engaged in the next step without any purification. *N,N*-Diethylacrylamides **1aa** and **1ga** were obtained by reaction of the commercially available corresponding acids with oxalyl chloride followed by condensation with diethylamine.[46] Other *N,N*-substituted acrylamides **1ab**, **1ac**, **1ad**, and **1ae** were obtained in a similar way from 2-phenylacrylic acid with the aid of diisopropylamine, morpholine, 2,3,4,5,6-pentafluoroaniline, and 8-aminoquinoline, respectively. *N,N*-Diethylacrylamide **1ha** was obtained similarly from the commercially available corresponding acid chloride and diethylamine.[46] *N,N*-Diethylacrylamide **1fa** was obtained by means of Kobayashi's method for the acid synthesis[47] followed by acid chloride formation and condensation with diethylamine.[46] *N,N*-Diethylacrylamides **1aa**,[48] **1ab**,[49] **1ac**,[50] and **1fa**[48] are known compounds. Ester **4e** is a new compound, whereas **4b** (CAS 39729-00-5), **4c** (CAS 1264520-71-9), and **4d** (CAS 101492-44-8) are described in Barluenga and Valdés paper (see the ester structures in the Supporting Information).[45]

Characterization of Acrylamides 1. *N-(Perfluorophenyl)-2-phenylacrylamide (**1ad**).* The product was isolated as a white solid (0.935 g, 60% from the 2-phenylacrylic acid (5 mmol)) using petroleum ether (PE)/EtOAc (90:10) as eluent. R_f (PE/EtOAc = 90:10): 0.31. mp 98−100 °C. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.47−7.32 (m, 5H), 7.26 (s, 1H), 6.20 (s, 1H), 5.76 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.9, 144.6, 143.0, 141.4, 139.3, 135.8, 129.0, 128.9, 128.0, 124.5, 111.6. ATR−FTIR (cm^{-1}): 2977, 2860, 1620, 1458, 1438, 1215, 1108, 916. HRMS (ESI$^+$): *m/z* calcd for $[(C_{15}H_8F_5NO)H]^+$ 314.0599; found, 314.0605.

*2-Phenyl-N-(quinolin-8-yl)acrylamide (**1ae**).* The product was isolated as a yellow oil (0.605 g, 44% from 2-phenylacrylic acid (5 mmol)) using PE/EtOAc (90:10) as eluent. R_f (PE/EtOAc = 90:10): 0.2. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.75 (dd, J = 7.5, 1.5 Hz, 1H), 8.40 (dd, J = 4.2, 1.6 Hz, 1H), 7.84 (dd, J = 8.4, 1.5 Hz, 1H), 7.44−7.18 (m, 7H), 7.12 (dd, J = 8.4, 4.2 Hz, 1H), 6.14 (s, 1H), 5.63 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.5, 148.0, 145.6, 138.3, 136.4, 135.9, 134.1, 128.4, 128.4, 128.1, 127.5, 127.0, 121.9, 121.7, 121.3, 116.3. ATR−FTIR (cm^{-1}): 2976, 2937, 1633, 1444, 1289, 1270, 1114, 765. HRMS (ESI$^+$): *m/z* calcd for $[(C_{18}H_{14}N_2O)H]^+$, 275.1179; found, 275.1190.

*N,N-Diethyl-2-(4-methoxyphenyl)acrylamide (**1ba**).* The product was isolated as a yellow oil (0.105 g, 10% from the ester **4b**) using PE/EtOAc (80:20) as eluent. R_f (PE/EtOAc = 80:20): 0.12. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.28 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz,

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2H), 5.49 (s, 1H), 5.11 (s, 1H), 3.70 (s, 3H), 3.41 (q, J = 7.2 Hz, 2H), 3.14 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.2, 159.6, 144.5, 127.9, 126.6, 113.8, 110.5, 55.0, 42.5, 38.4, 13.8, 12.5. ATR−FTIR (cm^{-1}): 2973, 2937, 1629, 1605, 1510, 1435, 1245, 1180, 1028, 836. HRMS (ESI^+): m/z calcd for $[(C_{14}H_{19}NO_2)H]^+$, 234.1489; found, 234.1489.

*2-(4-tert-Butylphenyl)-N,N-diethylacrylamide (**1ca**).* The product was isolated as a yellow oil (0.328 g, 29% from the ester **4c**) using PE/EtOAc (from 90:10 to 80:20) as eluent. R_f (PE/EtOAc = 80:20): 0.24. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.41−7.31 (broad s, 4H), 5.66 (s, 1H), 5.26 (s, 1H), 3.51 (q, J = 7.2 Hz, 2H), 3.24 (q, J = 6.9 Hz, 2H), 1.31 (s, 9H), 1.23 (t, J = 6.9 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.4, 151.6, 145.0, 132.7, 125.6, 125.2, 112.0, 42.8, 38.7, 34.6, 31.2, 14.0, 12.8. ATR−FTIR (cm^{-1}): 2963, 1632, 1433, 1249, 841. HRMS (ESI^+): m/z calcd for $[(C_{17}H_{25}NO)H]^+$, 260.2014; found, 260.2009.

*2-(4-Chlorophenyl)-N,N-diethylacrylamide (**1da**).* The product was isolated as a white powder (0.364 g, 36% from the ester **4d**) using PE/EtOAc (from 80:20 to 70:30) as eluent. R_f (PE/EtOAc = 70:30): 0.28. mp 58 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.37 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 5.68 (s, 1H), 5.33 (s, 1H), 3.49 (q, J = 6.9 Hz, 2H), 3.21 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.7, 144.3, 134.4, 134.2, 128.9, 126.9, 113.4, 42.7, 38.8, 14.0, 12.7. ATR−FTIR (cm^{-1}): 2982, 2937, 1612, 1435, 1094, 912, 854. HRMS (ESI^+): m/z calcd for $[(C_{13}H_{16}ClNO)H]^+$, 238.0993; found, 238.0995.

*N,N-Diethyl-2-(2-ethylphenyl)acrylamide (**1ea**).* The product was isolated as a yellow oil (0.376 g, 38% from the ester **4e**) using PE/EtOAc (70:30) as eluent. R_f (PE/EtOAc = 70:30): 0.66. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.37−7.11 (m, 4H), 5.72 (s, 1H), 5.46 (s, 1H), 3.42 (q, J = 6.6 Hz, 2H), 3.23 (q, J = 6.9 Hz, 2H), 2.72 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H), 1.17 (t, J = 6.9 Hz, 3H), 0.80 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.5, 146.6, 141.8, 137.3, 129.2, 128.8, 128.2, 126.0, 120.9, 42.6, 39.5, 25.8, 15.3, 13.3, 12.5. ATR−FTIR (cm^{-1}): 2970, 2934, 1629, 1427, 1379, 1218, 1082, 752. HRMS (ESI^+): m/z calcd for $[(C_{15}H_{21}NO)H]^+$, 232.1696; found, 232.1701.

*(E)-N,N-Diethyl-2,3-diphenylacrylamide (**1ga**).* The product was isolated as a white solid (1.52 g, 54% from α-phenylcinnamic acid (10 mmol)) using PE/EtOAc (70:30) as eluent. R_f (PE/EtOAc = 70:30): 0.6. mp 92−94 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.42−7.06 (m, 10H), 6.70 (s, 1H), 3.55−3.26 (m, 4H), 1.32−0.79 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.7, 138.2, 135.2, 129.1, 128.8, 128.8, 128.6, 128.4, 127.9, 127.7, 127.3, 42.7, 38.9, 13.5, 12.5. ATR−FTIR (cm^{-1}): 2996, 1604, 1444, 1429, 1268, 1139, 693. HRMS (ESI^+): m/z calcd for $[(C_{19}H_{21}NO)H]^+$, 280.1696; found, 280.1694.

*N,N-Diethylcinnamamide (**1ha**).* The product was isolated as a colorless oil (0.93 g, 76% from cinnamoyl chloride (6 mmol)) using PE/EtOAc (70:30) as eluent. R_f (PE/EtOAc = 70:30): 0.31. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.71 (d, J = 15.4 Hz, 1H), 7.58−7.28 (m, 5H), 6.82 (d, J = 15.4 Hz, 1H), 3.58−3.41 (m, 4H), 1.34−1.11 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.6, 142.2, 135.4, 129.3, 128.6, 127.6, 117.7, 42.2, 41.0, 15.0, 13.1. ATR−FTIR (cm^{-1}): 3059, 2968, 2932, 1654, 1588, 1431, 1147, 984, 767, 689. HRMS (ESI^+): m/z calcd for $[(C_{13}H_{17}NO)H]^+$, 204.1388; found, 204.1384.

Synthesis of Ethyl 2-(2-Ethylphenyl)acrylate (4e). The product was prepared according to the method described by Barluenga et al.[45] and was isolated as a yellow oil (0.966 g, 86%) using petroleum ether (PE)/EtOAc (8/1) as eluent. R_f (PE/EtOAc = 8:1): 0.46. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.45−7.14 (m, 4H), 6.59 (s, 1H), 5.76 (s, 1H), 4.30 (q, ^3J = 7.2 Hz, 2H), 2.64 (q, ^3J = 7.5 Hz, 2H), 1.33 (t, ^3J = 7.2 Hz, 3H), 1.26 (t, ^3J = 7.5 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.5, 141.7, 136.5, 129.4, 128.0, 127.7, 125.3, 60.7, 26.0, 14.7, 13.9. ATR−FTIR (cm^{-1}): 2969, 2935, 1716, 1304, 1201, 1183, 1083, 1025, 757. HRMS (ESI^+): m/z calcd for $[(C_{13}H_{16}O_2)H]^+$, 205.1229; found, 205.1223.

General Procedure for the Optimization Reaction. Unless otherwise specified, CuI (0.11 mmol, 1.1 equiv), Umemoto's reagent (1.5 equiv), and 3 mL of DCE were united under air in a Schlenk flask (10 mL). Acrylamide derivatives (0.1 mmol scale), TFA (10 equiv), and *N*-methylformamide (15 equiv) were then added, and the reactor was closed and held at 120 °C for 16 h. The reactor was then cooled to rt, and 0.4 g of K_2CO_3 was added. The conversion was then controlled by ^{19}F NMR of the crude mixture, and ^{19}F NMR yields were determined using trifluoroacetophenone as an internal standard. Note that when a catalytic amount of CuI was tested a similar procedure was followed and CuI (0.01 mmol, 10 mol %) was used instead of CuI (0.11 mmol, 1.1 equiv).

General Procedure for the Trifluoromethylation Reaction. Unless otherwise specified, CuI (0.063 g, 0.33 mmol, 1.1 equiv), Umemoto's reagent (0.180 g, 0.45 mmol, 1.5 equiv), and 9 mL of DCE were united under air in a Schlenk flask (50 mL). Acrylamides (0.3 mmol), TFA (10 equiv), and *N*-methylformamide (15 equiv) were then added, and the reactor was closed and held at 120 °C for 16 h. The reactor was then cooled to rt, and the products were directly purified by SiO_2 column chromatography with a K_2CO_3 layer on the top. Note that in the case of solid acrylamides these are added in the Schlenk flask before the solvent.

*(Z)-N,N-Diethyl-4,4,4-trifluoro-2-phenylbut-2-enamide (**3aa**).* The product was isolated as a pale-yellow oil (54.4 mg, 67%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 90:10): 0.35. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.56−7.31 (m, 5H), 5.98 (q, J = 7.9 Hz, 1H), 3.73−3.28 (m, 2H), 3.19−3.03 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −60.35 (d, J = 7.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 146.6 (q, J = 5.5 Hz), 133.6, 130.2, 129.1, 126.4, 122.7 (q, J = 270.3 Hz), 113.5 (q, J = 34.7 Hz), 42.5, 38.4, 13.0, 12.1. ATR−FTIR (cm^{-1}): 2976, 2937, 1633, 1444, 1289, 1270, 1114, 765. HRMS (ESI^+): m/z calcd for $[(C_{14}H_{16}F_3NO)H]^+$, 272.1257; found, 272.1255.

*(Z)-4,4,4-Trifluoro-N,N-diisopropyl-2-phenylbut-2-enamide (**3ab**).* The product was isolated as a pale-yellow oil (26.7 mg, 30%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.56. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.56−7.34 (m, 5H), 5.89 (q, J = 8.1 Hz, 1H), 3.74 (heptuplet, 1H), 3.39 (heptuplet, 1H), 1.56−1.48 (m, 6H), 1.14 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −59.49 (d, J = 8.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.3, 147.4 (q, J = 5.5 Hz), 133.8, 130.1, 129.0, 126.5, 122.8 (q, J = 270.7 Hz), 112.4 (q, J = 34.5 Hz), 50.8, 45.8, 20.0, 19.9, 19.7, 19.6. ATR−FTIR (cm^{-1}): 2972, 2933, 1637, 1444, 1315, 1273, 1128, 1044. HRMS (ESI^+): m/z calcd for $[(C_{16}H_{20}F_3NO)H]^+$, 300.1570; found, 300.1563.

*(Z)-4,4,4-Trifluoro-1-morpholino-2-phenylbut-2-en-1-one (**3ac**).* The product was isolated as a yellow oil (48.8 mg, 57%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. The product, contaminated with residual traces of TFA, was diluted in diethyl ether, washed with an aqueous solution of 5% $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvents were carefully removed under reduced pressure (60 mbar max, no heating). R_f (pentane/Et_2O = 80:20): 0.09. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.55−7.35 (m, 5H), 6.06 (q, J = 7.9 Hz, 1H), 3.86−3.13 (m, 8H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −59.87 (d, J = 7.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.1, 145.4 (q, J = 5.5 Hz), 132.8, 130.6, 129.3, 126.3, 122.4 (q, J = 270.9 Hz), 114.1 (q, J = 34.8 Hz), 66.4, 66.1, 46.6, 41.6. ATR−FTIR (cm^{-1}): 2970, 2859, 1642, 1439, 1274, 1112, 1045. HRMS (ESI^+): m/z calcd for $[(C_{14}H_{14}F_3NO_2)H]^+$, 286.1049; found, 286.1052.

*(Z)-4,4,4-Trifluoro-2-phenyl-N-(quinolin-8-yl)but-2-enamide (**3ae**).* The product was isolated as a pale-yellow oil (40.2 mg, 24% (**3ae**)) as an inseparable mixture with **1ae** (1:0.65 (**3ae**/**1ae**) ratio) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.70. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 10.27 (broad s, 1H, **1ae**), 10.09 (broad s, 1H, **3ae**), 8.95−8.87 (m, 2H), 8.79−8.60 (m, 2H), 8.20−8.08 (m, 2H), 7.68−7.35 (m, 15H), 6.33 (d, J = 0.9 Hz, 1H, **1ae**), 6.21 (q, J = 7.9 Hz, 1H, **3ae**), 5.84 (d, J = 0.9 Hz, 1H, **1ae**). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −58.82 (d, J = 7.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 164.1, 148.4, 148.2, 146.7 (q, J = 5.5 Hz), 145.8, 138.7, 138.3, 138.2, 137.9, 136.7, 136.3, 136.2, 134.4, 133.8, 133.7, 130.4, 129.2, 129.1, 128.7, 128.6, 128.3, 127.9, 127.8, 127.7, 127.3, 127.3, 126.9, 122.5, 122.4 (q, J = 271.1 Hz), 122.3,

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121.9, 121.8, 121.5, 120.6, 117.0, 116.6, 115.7 (q, J = 35.0 Hz). ATR−FTIR (cm^{-1}): 3074, 1666, 1377, 1154, 707. HRMS (ESI^+): m/z calcd for $[(C_{19}H_{13}F_3N_2O)H]^+$, 343.1053; found, 343.1049.

*(Z)-N,N-Diethyl-4,4,4-trifluoro-2-(4-methoxyphenyl)but-2-enamide (**3ba**).* The product was isolated as a pale-yellow oil (62.7 mg, 69%) pentane/Et_2O (from 100:0 to 0:100) as eluent. The product, contaminated with residual traces of TFA, was diluted in diethyl ether, washed with an aqueous solution of 5% $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvents were carefully removed under reduced pressure (60 mbar max, no heating). R_f (pentane/Et_2O = 80:20): 0.08. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.43−7.36 (m, 2H), 6.94−6.84 (m, 2H), 5.88 (q, J = 8.1 Hz, 1H), 3.82 (s, 3H), 3.72−3.26 (m, 2H), 3.24−3.08 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −59.38 (d, J = 8.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.1, 161.2, 145.9 (q, J = 5.6 Hz), 127.9, 125.7, 122.8 (q, J = 270.5 Hz), 114.4, 111.0 (q, J = 35.0 Hz), 55.3, 42.5, 38.3, 13.0, 12.0. ATR−FTIR (cm^{-1}): 2977, 2942, 1634, 1513, 1461, 1244, 1109, 1030, 826. HRMS (ESI^+): m/z calcd for $[(C_{15}H_{18}F_3NO_2)H]^+$, 302.1362; found, 302.1362.

*(Z)-2-(4-tert-Butylphenyl)-N,N-diethyl-4,4,4-trifluorobut-2-enamide (**3ca**).* The product was isolated as a pale-yellow oil (64.5 mg, 66%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.36. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.39 (s, 4H), 5.96 (q, J = 8.1 Hz, 1H), 3.74−3.28 (m, 2H), 3.24 (q, J = 7.2 Hz, 2H), 1.30 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −59.60 (d, J = 8.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.9, 153.7, 146.3 (q, J = 5.5 Hz), 130.6, 126.1, 126.0, 122.8 (q, J = 270.6 Hz), 112.3 (q, J = 34.7 Hz), 42.5, 38.4, 34.7, 31.0, 13.0, 12.1. ATR−FTIR (cm^{-1}): 2967, 1636, 1461, 1291, 1269, 1107, 731. HRMS (ESI^+): m/z calcd for $[(C_{18}H_{24}F_3NO)H]^+$, 328.1888; found, 328.1893.

*(Z)-2-(4-Chlorophenyl)-N,N-diethyl-4,4,4-trifluorobut-2-enamide (**3da**).* The product was isolated as a yellow oil (49.3 mg, 54%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.20. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.48−7.33 (m, 4H), 5.96 (q, J = 7.8 Hz, 1H), 3.78−3.25 (m, 2H), 3.24−3.08 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −59.99 (d, J = 7.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.4, 145.5 (q, J = 5.4 Hz), 136.4, 132.1, 129.4, 127.7, 122.4 (q, J = 271.0 Hz), 113.9 (q, J = 35.2 Hz), 42.5, 38.5, 13.1, 12.0. ATR−FTIR (cm^{-1}): 2982, 2943, 1633, 1493, 1439, 1344, 1287, 1264, 1113, 1095, 821. HRMS (ESI^+): m/z calcd for $[(C_{14}H_{15}ClF_3NO)H]^+$, 306.0867; found, 306.0872.

*(Z)-N,N-Diethyl-2-(2-ethylphenyl)-4,4,4-trifluorobut-2-enamide (**3ea**).* The product was isolated as a pale-yellow oil (30.2 mg, 34%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.42. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.39−7.28 (m, 3H), 7.24−7.13 (m, 1H), 5.68 (q, J = 7.9 Hz, 1H), 3.40 (q, J = 6.9 Hz, 2H), 3.23 (q, J = 6.9 Hz, 2H), 2.83 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −60.27 (d, J = 7.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.0, 147.1 (q, J = 5.6 Hz), 141.9, 134.1, 129.8, 129.3, 128.5, 126.1, 122.2 (q, J = 271.4 Hz), 118.9 (q, J = 34.6 Hz), 42.1, 38.9, 25.5, 15.9, 13.1, 11.9. ATR−FTIR (cm^{-1}): 2975, 2943, 1636, 1433, 1282, 1114, 762. HRMS (ESI^+): m/z calcd for $[(C_{16}H_{20}F_3NO)H]^+$, 300.1570; found, 300.1568.

*(Z)-N,N-Diethyl-2-(2,2,2-trifluoroethylidene)hexanamide (**3fa**).* The product was isolated as a pale-yellow oil (14.1 mg, 19%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.30. ^1H NMR (300.13 MHz, $CDCl_3$): δ 5.45 (qt, J = 7.9, 1.8 Hz, 1H), 3.70−3.16 (m, 4H), 3.41−2.20 (m, 2H), 1.60−1.30 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −60.56 (dt, J = 7.9, 2.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.6, 148.4 (q, J = 5.4 Hz), 122.4 (q, J = 270.8 Hz), 113.4 (q, J = 34.3 Hz), 42.0, 37.8, 34.6, 28.8, 22.2, 13.8, 13.5, 12.0. ATR−FTIR (cm^{-1}): 2946, 1665, 1375, 1148, 704. HRMS (ESI^+): m/z calcd for $[(C_{12}H_{20}F_3NO)H]^+$, 252.1570; found, 252.1574.

*(Z)-N,N-Diethyl-4,4,4-trifluoro-2,3-diphenylbut-2-enamide (**3ga**).* The product was isolated as a yellow oil (11.2 mg, 11%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.55. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.84 (d, J = 7.5 Hz, 1H), 7.63−7.25 (m, 9H), 3.48−2.99 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H), 0.53 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −60.00. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.6, 140.0, 136.6, 135.8, 134.6, 131.9, 130.4, 129.4, 128.9, 128.8, 128.6, 128.4, 128.1, 127.7, 126.2, 124.0 (q, J = 263.0 Hz), 42.4, 38.4, 13.5, 12.2. ATR−FTIR (cm^{-1}): 2977, 1627, 1324, 1167, 1119. HRMS (ESI^+): m/z calcd for $[(C_{20}H_{20}F_3NO)H]^+$, 348.1570; found, 348.1569.

*(Z)-N,N-Diethyl-4,4,4-trifluoro-3-phenylbut-2-enamide (**3ha**).* The product was isolated as a pale-yellow oil (28.3 mg, 35%) using pentane/Et_2O (from 100:0 to 0:100) as eluent. R_f (pentane/Et_2O = 80:20): 0.29. ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.54−7.34 (m, 5H), 5.98 (q, J = 7.9 Hz, 1H), 3.76−3.27 (m, 2H), 3.25−3.11 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282.4 Hz, $CDCl_3$, $CFCl_3$): δ −59.83 (d, J = 7.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 146.6 (q, J = 5.6 Hz), 133.7, 130.3, 129.1, 126.4, 122.6 (q, J = 270.7 Hz), 113.5 (q, J = 34.9 Hz), 42.5, 38.4, 13.1, 12.1. ATR−FTIR (cm^{-1}): 2980, 2939, 1634, 1443, 1289, 1270, 1113, 693. HRMS (ESI^+): m/z calcd for $[(C_{14}H_{16}F_3NO)H]^+$, 272.1257; found, 272.1259.

■ ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C, and ^{19}F NMR spectra. 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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