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Solid-State Radical C–H Trifluoromethylation Reactions Using Ball Milling and Piezoelectric Materials

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Abstract: The first application of piezoelectricity for the generation of trifluoromethyl (CF_3) radicals is reported together with the development of a method for the mechanochemical C–H trifluoromethylation of aromatic compounds. Compared to conventional solution-based approaches, this mechanoredox C–H trifluoromethylation enables cleaner and more sustainable access to a wide range of trifluoromethylated *N*-heterocycles and peptides, which are important structural motifs in modern drug discovery. This study thus represents an important milestone for future applications of mechanoredox systems to medicinal and pharmaceutical science.

During the last few years, mechanochemical synthesis using ball milling has become a practical and sustainable technique that enables solvent-free organic transformations.^[1–3] The advantages of mechanochemical approaches, i.e., the avoidance of potentially harmful organic solvents, shorter reaction times, and operational simplicity, have created a significant demand for their application to pharmaceutical synthesis.^[4] Fluorinated compounds continue to be of major interest for the design of new pharmaceuticals.^[5] In this context, the trifluoromethyl (CF_3) group plays a crucial role in the realm of medicinal chemistry given that its incorporation into drug molecules can dramatically improve the metabolic stability and other pharmacokinetic properties of drug molecules.^[5] Therefore, the development of new mechanochemical methods for the efficient and selective introduction of a CF_3 group into a diverse array of skeletons could provide medicinal chemical solutions that are both cleaner and safer than those currently available.^[4,5] Despite the recent progress of mechanochemical transformations, there have been no reports in the literature pertaining to trifluoromethylation reactions under solid-state mechanochemical conditions.^[1,2,6,7]

We have recently discovered a conceptually new redox system, in which electrons are transferred from distorted piezoelectric materials in the solid-state to trigger organic transformations.^[8] In these reactions, the agitation of BaTiO_3 via ball milling generates particles that are temporarily highly polarized and can thus act as charge-transfer catalysts^[9] to reduce aryl diazonium salts to generate aryl radicals (Scheme 1A). This mechanoredox system represents a unique solid-state approach that can be applied to arylation and borylation reactions in a manner analogous to photoredox catalysts.^[10] Prior to the development of our solid-state ball milling approach, pioneering

studies revealed that ultrasonic agitation of BaTiO_3 in solution can also be used in water splitting,^[11a] the piezocatalytic degradation of model pollutants such as rhodamine B,^[11b] and via the reduction of a Cu(II) catalyst precursor to an active Cu(I) compound, in controlled atom transfer radical polymerizations.^[11c,d] Shortly after our report on the first BaTiO_3 /ball milling system,^[8] Bolm and Hernández reported a mechanochemical radical cyclization based on the reduction of a Cu(II) salt via a similar ball milling reaction with BaTiO_3 .^[12] Although the use of piezoelectric materials as charge-transfer catalysts offers great potential in organic chemistry, its application to the synthesis of small organic molecules still remains very limited.^[8,12]

Scheme 1. Radical C–H Trifluoromethylation of Aromatic Compounds Using Ball Milling and Piezoelectric Materials.

In this study, we envisioned that the piezoelectric reduction of electrophilic trifluoromethylation reagents via a single electron transfer (SET) pathway could produce a CF_3 radical. This could potentially enable, via the use of ball milling, the development of a solid-state radical C–H trifluoromethylation of aromatic compounds **1** (Scheme 1B). To this end, we selected easily available Umemoto reagents **2** as the CF_3 radical source.^[13] This choice was motivated by the strong electron-accepting character of these reagents. For example, Umemoto reagent **2a** has a reduction potential of -0.26 V (versus SCE; Figure S3)^[12c] which

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would, when subjected to ball milling, undergo piezoelectric reduction to generate a CF_3 radical (Scheme 1C).^[13b,14] Subsequent radical addition to aromatic **1** would provide trifluoromethylated intermediate **A**, which would then be oxidized by the hole in the agitated BaTiO_3 (**B**). A subsequent deprotonation would give the trifluoromethylated product **3** (Scheme 1C).^[7]

We initially conducted a study to optimize the mechanoredox C–H trifluoromethylation reaction conditions using 3-methyl indole (**1a**) and various electrophilic trifluoromethylation reagents in the presence of commercially available piezoelectric materials (Table 1). All reactions were carried out in a Retch MM400 mixer mill (1.5 mL stainless-steel milling jar using a 5 mm diameter stainless-steel ball; Table 1). Unfortunately, the reaction with Umemoto reagent **2a** in the presence of piezoelectric tetragonal BaTiO_3 (particle size: $<3\ \mu\text{m}$ at 30 Hz for 90 minutes did not generate the desired product **3a** (entry 1). However, trace amounts of **3a** were obtained when the reaction was performed with the difluorinated Umemoto reagent **2b**. This reagent is a more electrophilic trifluoromethylation reagent than **2a**^[13b] (reduction potential: $-0.23\ \text{V}$ versus SCE; Figure S3) (entry 2). Next, we attempted liquid-assisted grinding (LAG), which uses a substoichiometric liquid additive to improve the reactivity (entries 3–6).^[15] In the LAG reactions, we used $0.20\ \mu\text{L}$ of liquid per mg of solid reactant. To our delight, polar solvents such as *N,N*-dimethylformamide (DMF), acetonitrile (MeCN), or acetone improved the reactivity and provided **3a** in good yield (58%, 58%, and 62% NMR yield, respectively). Conversely, in hexane, the reaction did not proceed (1%). The use of cubic BaTiO_3 (particle size: $<75\ \mu\text{m}$), which is highly symmetric and generates less polarized particles in response to mechanical impact, significantly decreased the yield of **3a** (8%; entry 7).^[8,11] Using other piezoelectric materials, such as LiNbO_3 (particle size: $<70\ \mu\text{m}$) or ZnO (particle size: $<10\ \mu\text{m}$), also afforded **3a**, albeit in lower yield (43% and 18%, respectively; entries 8 and 9). When the reaction was carried out in the absence of BaTiO_3 , only a very small amount of **3a** was obtained (2%; entry 10). Reactions using non-piezoelectric ceramic materials, such as TiO_2 (particle size: $<2\ \mu\text{m}$), BaCO_3 (particle size: $<5\ \mu\text{m}$), or Al_2O_3 (particle size: $<1\ \mu\text{m}$) only yielded trace amounts of **3a** (entries 11–13). These results suggest that piezoelectric materials are essential for the success of this C–H trifluoromethylation reaction. When the reaction was performed in acetone (0.3 M) with a stirring bar at room temperature for 24 h, the formation of **3a** was not observed (entry 14). This result indicates that mechanical agitation by ball milling is essential for the generation of a piezoelectric potential that is sufficient to reduce **2b**. In addition, the reaction that was carried out with ultrasonic sonication in acetone provided trace amounts of **3a** (entry 15). This suggests that the use of ball milling to generate a piezoelectric potential may have a different reactivity profile compared to a solution-based approach using ultrasonic agitation.^[8,9,11,12] Next we investigated other types of Umemoto reagents such as **2c** (reduction potential: $-0.13\ \text{V}$ versus SCE; Figure S3) (entry 16).^[13b] However, the yield did not improve (61%). The use of **4**, which is a widely employed CF_3 radical precursor in solution-based photoredox-catalyzed reactions,^[16] did not provide **3a** under mechanoredox conditions (entry 17).

Table 1. Initial Optimization Study.^[a]

Entry	CF_3 reagent	Piezoelectric material (Particle size)	Liquid	Yield (%) ^[b]
1	2a	BaTiO_3 ($<3\ \mu\text{m}$)	none	<1
2	2b	BaTiO_3 ($<3\ \mu\text{m}$)	none	1
3	2b	BaTiO_3 ($<3\ \mu\text{m}$)	DMF	58
4	2b	BaTiO_3 ($<3\ \mu\text{m}$)	MeCN	58
5	2b	BaTiO_3 ($<3\ \mu\text{m}$)	hexane	1
6	2b	BaTiO_3 ($<3\ \mu\text{m}$)	acetone	62
7 ^[c]	2b	BaTiO_3 ($<75\ \mu\text{m}$)	acetone	8
8	2b	LiNbO_3 ($<70\ \mu\text{m}$)	acetone	43
9	2b	ZnO ($<10\ \mu\text{m}$)	acetone	18
10	2b	none	acetone	2
11	2b	TiO_2 ($<2\ \mu\text{m}$)	acetone	<1
12	2b	BaCO_3 ($<5\ \mu\text{m}$)	acetone	1
13	2b	Al_2O_3 ($<1\ \mu\text{m}$)	acetone	<1
14 ^[d]	2b	BaTiO_3 ($<3\ \mu\text{m}$)	acetone	<1
15 ^[e]	2b	BaTiO_3 ($<3\ \mu\text{m}$)	acetone	1
16	2c	BaTiO_3 ($<3\ \mu\text{m}$)	acetone	61
17	4	BaTiO_3 ($<3\ \mu\text{m}$)	acetone	<1

[a] Conditions: **1a** (0.6 mmol), trifluoromethylation reagent (0.3 mmol), piezocatalyst (1.5 mmol), and liquid additive ($0.20\ \mu\text{L}/\text{mg}$) in a stainless-steel milling jar (1.5 mL) with a stainless-steel ball (5 mm). [b] Determined by ^{19}F NMR analysis of the crude reaction mixture using an internal standard. [c] Cubic BaTiO_3 (particle size: $<75\ \mu\text{m}$) was used instead of tetragonal BaTiO_3 (particle size: $<3\ \mu\text{m}$). [d] The reaction was carried out in acetone (0.3 M) with a stirring bar at room temperature for 24 h. [e] The reaction was carried out in acetone (0.3 M) under ultrasonic agitation at room temperature for 1.5 h.

To improve the reaction further, we investigated the effect of different mechanochemical parameters on this mechanoredox C–H trifluoromethylation (Table 2). We found that conducting the reaction with a smaller ball (3 mm diameter) or at a lower ball-milling frequency (25 Hz and 20 Hz), which subjects BaTiO_3 to lower-impact mechanical collisions than under the standard conditions, substantially decreased the yield of **3a** (4%, 19%, and 2%, respectively; entries 1–4). These results are consistent with our hypothesis that the piezoelectric potential required for a successful reaction is generated by the mechanical force induced by the ball milling. The use of a larger ball and a larger jar improves the yield of **3a** (73%, entry 5). Finally, we found that prolonging the reaction time and increasing the number of balls used provided the desired product **3a** in high yield (80%; entry 6).

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Table 2. Investigation of the Effect of Varying the Mechanochemical Parameters.^[a]

Entry	Jar size (mL)	Ball size (mm)	Frequency (Hz)	Time (h)	Yield (%) ^[b]
1	1.5	5	30	1.5	62
2	1.5	3	30	1.5	4
3	1.5	5	25	1.5	19
4	1.5	5	20	1.5	2
5	5	7.5	30	1.5	73
6 ^[c]	5	7.5	30	3	80 (76)

[a] Conditions: **1a** (0.6 mmol), **2b** (0.3 mmol), tetragonal BaTiO₃ (<3 μm) (1.5 mmol), and acetone (0.20 μL/mg) in a stainless-steel milling jar with a stainless-steel ball. [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture using an internal standard. Isolated yields are shown in parenthesis. [c] Two balls were used.

With the optimal reaction conditions in hand (Table 2, entry 6), a series of indole and pyrrole derivatives were tested to

investigate the substrate scope of this mechanoredox C–H trifluoromethylation reaction (Table 3). The reactions proceeded efficiently to furnish the corresponding CF₃-substituted products in moderate to good yield. *N*-Methyl-, *N*-ethyl-, and *N*-benzyl-substituted indoles (**1b–1d**) reacted with **2b** to afford the corresponding C–H trifluoromethylation products (**3b–3d**) in good yield. Additionally, the C–H trifluoromethylation proceeded at the 3-position of 2-substituted indole **1e** to provide **3e** in moderate yield. Next, we turned our attention to the substrate scope with respect to the pyrrole derivatives. Pyrrole **1f**, which bears a linear alkyl-chain on the nitrogen atom, provided **3f** in a good yield. It is noteworthy that the use of trifluoromethylation reagent **2c**, which has a lower reduction potential than **2b**,^[13b] is crucial for successful reactions involving pyrroles that bear electron-withdrawing groups on the five-membered ring (**1g–1j**). When **2c** was used, **3g–3j** were produced in good yield. Substrates that contain a ring-fused structure (**1k**) or a chlorine group (**1l**) did not hamper the reaction. Pleasingly, the desired CF₃-substituted Melatonin **3m** was also obtained in good yield. Despite the fact that solution-based photoredox systems can be applied to other substrate classes, other heteroaromatic derivatives such as furan and thiophene did not provide the desired products under the applied mechanoredox conditions (for details, see the Supporting Information).^[7,16]

Table 3. Mechanoredox Radical C–H Trifluoromethylation Reactions of Aromatic Compounds in the Solid State.^[a]

N-Heterocycles Electron-rich arenes Peptides

1 2 3

N-Heterocycles

3b
 with **2b**: 67% (79%)

3c
 with **2b**: 60% (74%)

3d
 with **2b**: 46% (60%)

3e
 with **2b**: 35% (47%)

3f
 with **2b**: 63% (75%)

3g
 with **2b**: (1%)
 with **2c**: 48% (57%)

3h
 with **2b**: (28%)
 with **2c**: 57% (61%)

3i
 with **2b**: (18%)
 with **2c**: 45% (48%)

3j
 with **2b**: (31%)
 with **2c**: 43% (48%)

3k
 with **2b**: 51% (59%)

3l
 with **2b**: 52% (73%)

3m
 with **2b**: 65%
CF₃-substituted Melatonin

Electron-rich arenes

3n
 with **2b**: 83% (89%)

3o
 with **2b**: 57% (60%)

3p
 with **2b**: (5%)
 with **2c**: (20%)

Tryptophan-containing peptides

3q
 Ac-Trp-OEt
 with **2b**: 49% (55%)

3r
 Boc-Trp-Gly-OEt
 with **2b**: 46% (50%)

3s
 Fmoc-Asp(OtBu)-Trp-OMe
 with **2b**: 29%

3t
 Boc-Trp-Phe-OMe
 with **2b**: 40%

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[a] Conditions: **1** (0.6 mmol), **2** (0.3 mmol), tetragonal BaTiO₃ (<3 μ m) (1.5 mmol), and acetone (0.20 μ L/mg) in a stainless-steel milling jar (5 mL) with two stainless-steel balls. Isolated yields are shown. ¹⁹F NMR yields are shown in parenthesis.

We found that this method is also applicable to electron-rich arenes (Table 3). The reaction of benzene molecules that bear three methoxy groups, such as **1n** and **1o**, proceeded efficiently to give the corresponding products (**3n** and **3o**) in high yield. However, when 1,4-dimethoxy-substituted benzene **1p** was used as the substrate, the yield of **3p** decreased dramatically. When substrates that do not bear electron-donating groups on the aromatic ring were employed in this mechanoredox C–H trifluoromethylation, the reaction did not proceed (for details, see the Supporting Information).

Tryptophan (Trp) is an ideal platform to test post-synthetic transformations of peptide-based bioactive compounds.^[17] To demonstrate the applicability of the newly developed method for the post-functionalization of peptides, tryptophan-containing peptides were tested under the previously established standard reaction conditions (Table 3). Pleasingly, both protected tryptophan and several dipeptides (**1q–1t**) reacted smoothly to afford the corresponding 2-CF₃-substituted tryptophan-containing peptides in a site-selective manner.^[18]

Given that the mechanoredox system shows significantly higher reactivity toward the C–H trifluoromethylation of indoles and pyrroles than other classes of substrates, we envisioned that the present method could be used for the site-selective C–H trifluoromethylation of aromatic compounds that contain multiple reactive C–H bonds. To this end, we investigated the C–H trifluoromethylation of substrate **1u**, which contains pyrrole and furan rings that are both potentially reactive (Scheme 2). Under the applied mechanoredox conditions, we observed excellent site-selectivity for the C–H trifluoromethylation of the pyrrole moiety in **1u**. In contrast, a mixture of products (**3u–3w**) was obtained when the photoredox catalyst *fac*-Ir(ppy)₃ was used under conventional solution-based photoredox conditions.^[19] The observed site-selectivity under mechanoredox conditions may be due to the poor reactivity of the gaseous CF₃ radical,^[20] generated in the solid-state reaction mixture, which can only react with the highly nucleophilic pyrrole ring.^[11] These results suggest that this mechanoredox system has great potential for the selective installation of CF₃ groups that are otherwise difficult to install via conventional solution-based photoredox reactions, into complex molecules in the solid state.

To demonstrate the practical utility of this protocol, we investigated the recycling of BaTiO₃ (Scheme 3). After separation from the crude reaction mixture and washing, BaTiO₃ could be re-used for the mechanoredox C–H trifluoromethylation of **1n** under the same reaction conditions at least three times without declining the yield of **3n**. However, the recovery loss of BaTiO₃ would limit the recycling times (for details, see the Supporting Information).

Scheme 2. Site-selective Mechanoredox C–H Trifluoromethylation of **1u**.^[a,b]

[a] Conditions for the mechanoredox C–H trifluoromethylation: **1u** (0.3 mmol), **2b** (0.36 mmol), tetragonal BaTiO₃ (<3 μ m) (1.5 mmol), and DMF (0.20 μ L/mg) in a stainless-steel milling jar (5 mL) with a stainless-steel ball at 30 Hz for 3 h. [b] Conditions for the photoredox C–H trifluoromethylation: **1u** (0.2 mmol), **2b** (0.24 mmol), *fac*-Ir(ppy)₃ (2 mol %) in MeCN under irradiation from blue LEDs for 3 h.

Scheme 3. Exploration of BaTiO₃ Recycling.^[a]

[a] For experimental details, see the Supporting Information.

We believe that the mechanoredox C–H trifluoromethylation reaction involves two SET events, in which a CF₃ radical is generated via piezoelectric reduction (Scheme 1). This hypothesis is supported by the results of our preliminary mechanistic investigations (Scheme 4). When the reaction of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, **5**) with the trifluoromethylation reagent **2b** was conducted in the absence of 3-methyl indole (**1a**), the TEMPO-trapped intermediate **6** was obtained in 25% NMR yield (Scheme 4A). Furthermore, the addition of **5** to the mechanoredox C–H trifluoromethylation of **1a** terminated the reaction and yielded the same TEMPO-trapped intermediate **6** (Scheme 4B). In their entirety, these results suggest that the mechanoredox C–H trifluoromethylation with BaTiO₃ most likely proceeds via the piezoelectric reduction of **2** to generate a CF₃ radical.

To identify the role of ball milling in this transformation, we conducted the reaction using an alternative form of mechanical impact (Scheme 4C). First, the reaction mixture was prepared by gently grinding the components in a mortar. The mixture was then wrapped in a piece of weighing paper and placed in cotton before

being struck with a hammer over 250 times. Even under these conditions, the mechanoredox C–H trifluoromethylation product **3a** was obtained in 14% yield. This suggests that the role of ball milling is not only to mix the reactants, but also to provide sufficient mechanical impact to activate the BaTiO₃.^[8]

Scheme 4. Results of the Preliminary Mechanistic Study.^[a]

[a] For experimental details, see the Supporting Information.

In conclusion, we have described the first application of piezoelectricity for the generation of CF₃ radicals, which has enabled the development of a radical C–H trifluoromethylation reaction under mechanochemical conditions. This solid-state mechanoredox C–H trifluoromethylation can be carried out in air without the use of large amounts of dry and degassed organic solvents and does not require specific handling techniques. This operational simplicity suggests that the present strategy may complement existing solution-based approaches to provide rapid and sustainable access to a wide range of trifluoromethylated molecules, privileged structural motifs in modern drug discovery. This study thus illustrates the outstanding potential of mechanoredox systems for advancing medicinal mechanochemistry.^[4]

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Conflict of interest

The authors declare no conflict of interests.

Keywords: Mechanochemistry • C–H Trifluoromethylation • Solid-state reaction • Radical reaction • Synthetic method

- For selected reviews on reaction development using mechanochemistry, see: a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, 41, 413–447; b) G.-W. Wang, *Chem. Soc. Rev.* **2013**, 42, 7668–7700; c) J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, 3, 13–19; d) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, 82, 4007–4019; e) T.-X. Métro, J. Martinez, F. Lamaty, *ACS Sustainable Chem. Eng.* **2017**, 5, 9599–9602; f) T. K. Achar, A. Bose, P. Mal, *Beilstein J. Org. Chem.* **2017**, 13, 1907–1931; g) O. Eguagie, J. S. Vyle, P. F. Conlon, M. A. Gilea, Y. Liang, *Beilstein J. Org. Chem.* **2018**, 14, 955–970; h) J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, 9, 3080–3094; i) J. Andersen, J. Mack, *Green Chem.* **2018**, 20, 1435–1443; j) C. Bolm, J. G. Hernández, *Angew. Chem., Int. Ed.* **2019**, 58, 3285–3299; *Angew. Chem.* **2019**, 131, 3320–3335; k) T. Friščić, C. Mottillo, H. M. Titi, *Angew. Chem., Int. Ed.* **2020**, 59, 1018–1029; *Angew. Chem.* **2020**, 132, 1030–1041.
- For selected examples on reaction development using mechanochemistry, see: a) P. J. Nichols, C. L. Raston, J. W. Steed, *Chem. Commun.* **2001**, 1062–1063; b) D. A. Fulmer, W. C. Shearouse, S. T. Medonza, J. Mack, *Green Chem.* **2009**, 11, 1821–1825; c) D. Crawford, J. Casaban, R. Haydon, N. Giri, T. McNally, S. L. James, *Chem. Sci.* **2015**, 6, 1645–1649; d) J.-L. Do, C. Mottillo, D. Tan, V. Štrukil, T. Friščić, *J. Am. Chem. Soc.* **2015**, 137, 2476–2479; e) N. Pétry, H. Benakki, E. Clot, P. Retailleau, F. Guenoun, F. Asserer, C. Sekkat, T.-X. Métro, J. Martinez, F. Lamaty, *Beilstein J. Org. Chem.* **2017**, 13, 2169–2178; f) A. A. L. Michalchuk, I. A. Tumanov, S. Konar, S. A. J. Kimber, C. R. Pulham, E. V. Boldyreva, *Adv. Sci.* **2017**, 4, 1700132; g) J. L. Howard, M. C. Brand, D. L. Browne, *Angew. Chem., Int. Ed.* **2018**, 57, 16104–16108; *Angew. Chem.* **2018**, 130, 16336–16340; h) C. Bolm, R. Mocchi, C. Schumacher, M. Turberg, F. Puccetti, J. G. Hernández, *Angew. Chem., Int. Ed.* **2018**, 57, 2423–2426; *Angew. Chem.* **2018**, 130, 2447–2450; i) R. F. Koby, T. P. Hanusa, N. D. Schley, *J. Am. Chem. Soc.* **2018**, 140, 15934–15942; j) E. O. Pentsak, V. P. Ananikov, *Eur. J. Org. Chem.* **2019**, 4239–4247; k) C. G. Vogt, S. Grätz, S. Lukin, I. Halasz, M. Etter, J. D. Evans, L. Borchardt, *Angew. Chem., Int. Ed.* **2019**, 58, 18942–18947; *Angew. Chem.* **2019**, 131, 19118–19123; l) A. Hosseini, P. R. Schreiner, *Eur. J. Org. Chem.* **2020**, Early View. DOI: 10.1002/ejoc.202000612.
- For selected examples of mechanochemical organic transformations from our group, see: a) K. Kubota, T. Seo, K. Koide, Y. Hasegawa, H. Ito, *Nat. Commun.* **2019**, 10, 111–122; b) Y. Pang, T. Ishiyama, K. Kubota, H. Ito, *Chem. – Eur. J.* **2019**, 25, 4654–4659; c) K. Kubota, R. Takahashi, H. Ito, *Chem. Sci.* **2019**, 10, 5837–5842; d) T. Seo, T. Ishiyama, K. Kubota, H. Ito, *Chem. Sci.* **2019**, 10, 8202–8210; e) R. Takahashi, K. Kubota, H. Ito, *Chem. Commun.* **2020**, 56, 407–410; f) T. Seo, K. Kubota, H. Ito, *J. Am. Chem. Soc.* **2020**, 142, 9884–9889.
- D. Tan, L. Loots, T. Friščić, *Chem. Commun.* **2016**, 52, 7760–7781.
- a) P. Kirsch, *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004; b) K. Uneyama, *Organofluorine Chemistry*; Blackwell Publishing:

- Oxford, 2006; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; d) T. Furuya, A. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; e) A. Studer, *Angew. Chem., Int. Ed.* **2012**, *51*, 8950–8958; *Angew. Chem.* **2012**, *124*, 9082–9090; f) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826–870; g) J.-W. Lee, M. T. Oliveira, H. B. Jang, S. Lee, D. Y. Chi, D. W. Kim, C. E. Song, *Chem. Soc. Rev.* **2016**, *45*, 4638–4650; h) S. V. Kohlhepp, T. Gulder, *Chem. Soc. Rev.* **2016**, *45*, 6270–6288; i) J. Miró, C. Pozo, *Chem. Rev.* **2016**, *116*, 11924–11966; j) M. G. Holl, C. R. Pitts, T. Lectka, *Angew. Chem., Int. Ed.* **2018**, *57*, 2758–2766; *Angew. Chem.* **2018**, *130*, 2806–2815; k) S. Fustero, D. M. Sedgwick, R. Román, P. Barrio, *Chem. Commun.* **2018**, *54*, 9706–9725; l) D. D. Bume, S. A. Harry, T. Lectka, C. R. Pitts, *J. Org. Chem.* **2018**, *83*, 8803–8814; m) J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes, B. Koksche, *Chem. Rev.* **2019**, *119*, 10718–10801; n) Y. Ogiwara, N. Sakai, *Angew. Chem., Int. Ed.* **2020**, *59*, 574–594; *Angew. Chem.* **2020**, *132*, 584–605.
- [6] For selected examples of trifluoromethylation by means of cross-coupling reactions mediated or catalyzed by transition metals in solution, see: a) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga, N. Shibata, *Org. Lett.* **2011**, *13*, 3596–3599; b) J.-B. Liu, C. Chen, L. Chu, Z.-H. Chen, X.-H. Xu, F.-L. Qing, *Angew. Chem., Int. Ed.* **2015**, *54*, 11839–11842; *Angew. Chem.* **2015**, *127*, 12005–12008; c) N. Früh, A. Togni, *Angew. Chem., Int. Ed.* **2014**, *53*, 10813–10816; *Angew. Chem.* **2014**, *126*, 10989–10992; d) Q. Wang, C. Ni, M. Hu, Q. Xie, Q. Liu, S. Pan, J. Hu, *Angew. Chem., Int. Ed.* **2020**, *59*, 8507–8511; *Angew. Chem.* **2020**, *132*, 8585–8589; e) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Angew. Chem., Int. Ed.* **2011**, *50*, 1896–1900; *Angew. Chem.* **2011**, *123*, 1936–1940; f) P. Novák, A. Lishchynskiy, V. V. Grushin, *J. Am. Chem. Soc.* **2012**, *134*, 16167–16170; g) X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330–10333; h) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679–1681; i) H. Shen, Z. Liu, P. Zhang, X. Tan, Z. Zhang, C. Li, *J. Am. Chem. Soc.* **2017**, *139*, 9843–9846; j) D. J. P. Kornfilt, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2019**, *141*, 6853–6858; k) M. S. Winston, W. J. Wolf, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 7777–7782; l) N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 2878–2879.
- [7] For selected examples of C–H trifluoromethylation reactions in solution that proceed via radical mechanisms, see: a) B. Yang, D. Yu, X.-H. Xu, F.-L. Qing, *ACS Catal.* **2018**, *8*, 2839–2843; b) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357–9360; c) R. Tomita, Y. Yasu, T. Koike, M. Akita, *Angew. Chem., Int. Ed.* **2014**, *53*, 7144–7148; *Angew. Chem.* **2014**, *126*, 7272–7276; d) R. Zhu, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2013**, *52*, 12655–12658; *Angew. Chem.* **2013**, *125*, 12887–12890; e) H. Xiao, H. Shen, L. Zhu, C. Li, *J. Am. Chem. Soc.* **2019**, *141*, 11440–11445; f) P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y.-H. Lam, E. C. Sherer, D. W. C. MacMillan, *Nat. Chem.* **2020**, *12*, 459–467; g) F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot, T. Ritter, *Angew. Chem., Int. Ed.* **2019**, *58*, 14615–14619; *Angew. Chem.* **2019**, *131*, 14757–14761; h) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14411–14415; i) E. A. Meucci, S. N. Nguyen, N. M. Camasso, E. Chong, A. Ariafard, A. J. Canty, M. S. Sanford, *J. Am. Chem. Soc.* **2019**, *141*, 12872–12879.
- [8] K. Kubota, Y. Pang, A. Miura, H. Ito, *Science* **2019**, *366*, 1500–1504.
- [9] For recent reviews on the use of piezoelectric materials for catalytic applications in solution, see: a) M. Wang, B. Wang, F. Huang, Z. Lin, *Angew. Chem., Int. Ed.* **2019**, *58*, 7526–7536; *Angew. Chem.* **2019**, *131*, 7606–7616; b) S. Li, Z. Zhao, J. Zhao, Z. Zhang, X. Li, J. Zhang, *ACS Appl. Nano Mater.* **2020**, *3*, 1063–1079.
- [10] a) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961; b) J. Yu, L. Zhang, G. Yan, *Adv. Synth. Catal.* **2012**, *354*, 2625–2628.
- [11] For selected examples of the use of BaTiO₃ with ultrasonic agitation to produce an electrochemical potential, see: a) K.-S. Hong, H. Xu, H. Konishi, X. Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997–1002; b) X. Xu, Z. Wu, L. Xiao, Y. Jia, J. Ma, F. Wang, L. Wang, M. Wang, H. Huang, *J. Alloy. Comp.* **2018**, *762*, 915–921; c) H. Mohapatra, M. Kleiman, A. P. Esser-Kahn, *Nat. Chem.* **2017**, *9*, 135–139; d) Z. Wang, X. Pan, J. Yan, S. Dadashi-Silab, G. Xie, J. Zhang, Z. Wang, H. Xia, K. Matyjaszewski, *ACS Macro Lett.* **2017**, *6*, 546–549.
- [12] C. Schumacher, J. G. Hernández, C. Bolm, *Angew. Chem., Int. Ed.* **2020**, Early View. DOI: 10.1002/anie.202003565.
- [13] a) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164; b) T. Umemoto, B. Zhang, T. Zhu, X. Zhou, P. Zhang, S. Hu, Y. Li, *J. Org. Chem.* **2017**, *82*, 7708–7719; c) S.-M. Wang, J.-B. Han, C.-P. Zhang, H.-L. Qin, J.-C. Xiao, *Tetrahedron* **2015**, *71*, 7949–7976.
- [14] (a) N. Noto, Y. Tanaka, T. Koike, M. Akita, *ACS Catal.* **2018**, *8*, 9408–9419; b) M. Li, X.-S. Xue, J.-P. Cheng, *Acc. Chem. Res.* **2020**, *53*, 182–197.
- [15] T. Friščić, S. L. Childs, S. A. A. Rizvi, W. Jones, *CrystEngComm* **2009**, *11*, 418–426.
- [16] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228.
- [17] For selected examples of postsynthetic transformations of tryptophan-containing peptides, see: a) J. M. Antos, M. B. Francis, *J. Am. Chem. Soc.* **2004**, *126*, 10256–10257; b) B. V. Popp, Z. Ball, *J. Am. Chem. Soc.* **2010**, *132*, 6660–6662; c) K. L. Seim, A. C. Obermeyer, M. B. Francis, *J. Am. Chem. Soc.* **2011**, *133*, 16970–16976; d) L. Mendive-Tapia, S. Preciado, J. García, R. Ramón, N. Kielland, F. Albericio, R. Lavilla, *Nat. Commun.* **2015**, *6*, 7160–7168; e) Y. Seki, T. Ishiyama, D. Sasaki, J. Abe, Y. Sohma, K. Oisaki, M. Kanai, *J. Am. Chem. Soc.* **2016**, *138*, 10798–10801; f) A. Schischko, H. Ren, N. Kaplaneris, L. Ackermann, *Angew. Chem., Int. Ed.* **2017**, *56*, 1576–1580; *Angew. Chem.* **2017**, *129*, 1598–1602; g) Y. Yu, L.-K. Zhang, A. V. Buevich, G. Li, H. Tang, P. Vachal, S. L. Colletti, Z.-C. Shi, *J. Am. Chem. Soc.* **2018**, *140*, 6797–6800; h) M. J. Terry, A. Holmes, C. C. Perry, W. B. Cross, *Org. Lett.* **2019**, *21*, 7902–7907.
- [18] For selected examples of solution-based radical C–H trifluoromethylation of tryptophan-containing peptides, see: a) P. Liu, W. Liu, C.-J. Li, *J. Am. Chem. Soc.* **2017**, *139*, 14315–14321; b) N. Ichiishi, J. P. Caldwell, M. Lin, W. Zhong, X. Zhu, E. Streckfuss, H.-Y. Kim, C. A. Parish, S. W. Krska, *Chem. Sci.* **2018**, *9*, 4168–4175; c) M. Imiolek, G. Karunanithy, W.-L. Ng, A. J. Baldwin, V. Gouverneur, B. G. Davis, *J. Am. Chem. Soc.* **2018**, *140*, 1568–1571; d) B. Ding, Y. Weng, Y. Liu, C. Song, L. Yin, J. Yuan, Y. Ren, A. Lei, C.-W. Chiang, *Eur. J. Org. Chem.* **2019**, 7596–7605; e) C. W. Kee, O. Tack, F. Guibbal, T. C. Wilson, P. G. Isenegger, M. Imiolek, S. Verhoog, M. Tilby, G. Boscutti, S. Ashworth, J. Chupin, R. Kashani, A. W. J. Poh, J. K. Sosabowski, S. Macholl, C. Plisson, B. Cornelissen, M. C. Villis, J. Passchier, B. G. Davis, V. Gouverneur, *J. Am. Chem. Soc.* **2020**, *142*, 1180–1185; f) I. Guerrero, A. Correa, *Org. Lett.* **2020**, *22*, 1754–1759.
- [19] a) Y. Yasu, T. Koike, M. Akita, *Angew. Chem., Int. Ed.* **2012**, *51*, 9567–9571; *Angew. Chem.* **2012**, *124*, 9705–9709; b) T. Koike, M. Akita, *Acc. Chem. Res.* **2016**, *49*, 1937–1945.
- [20] a) O. S. Herrera, J. D. Nieto, S. I. Lane, E. V. Oexler, *Can. J. Chem.* **2003**, *81*, 1477–1481; b) K. Maruyama, A. Sakai, T. Goto, *J. Phys. D: Appl. Phys.* **1993**, *26*, 199–202; c) K. Maruyama, K. Ohkouchi, Y. Ohtsu, T. Goto, *Jpn. J. Appl. Phys.* **1994**, *33*, 4298–4302.

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