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A General Synthesis of α-Trifluoromethylstyrenes through Palladium-Catalyzed Cross-Couplings with 1,1,1-Trifluoroacetone Tosylhydrazone

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Abstract: 1,1,1-Trifluoroacetone tosylhydrazone is presented as a very convenient substrate for the palladium-catalyzed cross-coupling with aryl halides. Under the proper reaction conditions, 3,3,3-trifluoromethylstyrenes – very valuable trifluoromethylated synthetic intermediates – are obtained with high yields. The reaction features a very wide scope, as the presence of most functional groups is tolerated. Moreover, the reaction has been extended to substituted trifluoromethylstyrenes by employing substituted tosylhydrazones derived from other trifluoromethyl ketones.

Keywords: cross-coupling; diazo compounds; palladium; tosylhydrazones; trifluoromethyl substituents

Introduction

The presence of trifluoromethyl groups in organic molecules has a strong influence on their physical, chemical and biological properties.[1] Indeed, a large number of agrochemicals and pharmaceuticals currently marketed bear fluorinated substituents (F, CF_3, CHF_2), that affect their stability, lipophilicy and bioavailability.[2] Moreover, fluoropolymers also feature unique properties, and find application in several technological areas.[3] For these reasons, over the last years, a growing interest has emerged in the development of efficient methodologies for the introduction of fluorinated one-carbon units (CF_3 and CHF_2) in organic molecules. Indeed, the development of methodologies for the trifluoromethylation of diverse types of organic molecules has attracted the attention of a large number of research group and, in turn, remarkable advances have been achieved.[4–8] On the other hand, the incorporation of small fragments containing fluorinated one-carbon units may represent an attractive alternative for the generation of trifluoromethylated organic moieties. The employ of *in situ* generated (trifluoromethyl)diazomethane constitutes one nice example of this approach.[9]

In particular, α-trifluoromethylstyrenes are very versatile intermediates for the preparation of more complex fluorinated molecules. The reaction with nucleophiles through the highly electrophilic β-carbon gives rise to 1,1-difluoroalkenes *via* an S_N2' reaction.[10] Very interestingly, the intramolecular version of this reaction with *ortho*-substituted α-trifluoromethylstyrenes has enabled the synthesis of a wide variety of heterocycles bearing di- and trifluorinated one-carbon units through nucleophilic cyclizations, depending on the reaction conditions,[11] and even monofluorinated heterocycles.[12] Moreover, α-trifluoromethylstyrenes can also participate as dienophiles and dipolarophiles in cycloaddition reactions,[13] and serve as an entry into the biologically relevant 2,2,2-trifluoroisopropyl group. Finally, α-trifluoromethylstyrenes can be employed as monomers for novel fluorinated polymers.[14]

Nevertheless, in spite of the growing synthetic usefulness of α-trifluoromethylstyrenes, the methods available for their preparation are far from ideal. The Suzuki cross-coupling stands as the most popular methodology (Scheme 1, a). However, the coupling between boronic acids and 2-bromo-3,3,3-trifluoropropene,[14–16] requires the employment of a large excess of this expensive and highly volatile bromoalkene. The complementary approach, the coupling of 2-(3,3,3-trifluoropropenyl)boronic acid with aryl halides (Scheme 1, b), which would be more desirable due to the easier availability of aryl halides, is ham-

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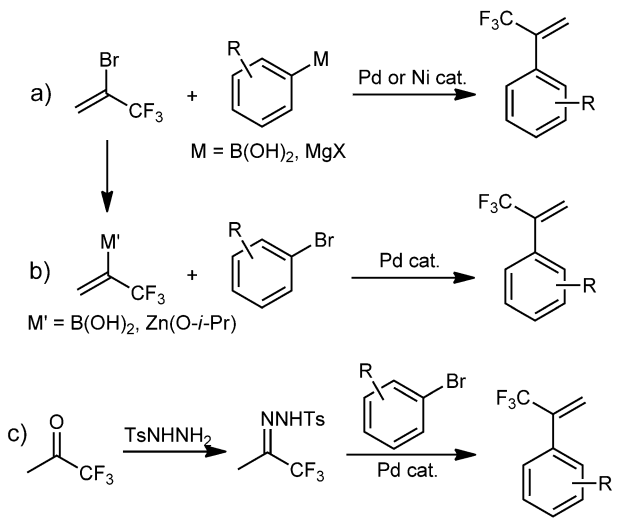


Scheme 1. General strategies for the synthesis of α-trifluoromethylstyrenes through cross-coupling reactions (a, b) *vs.* this work (c).

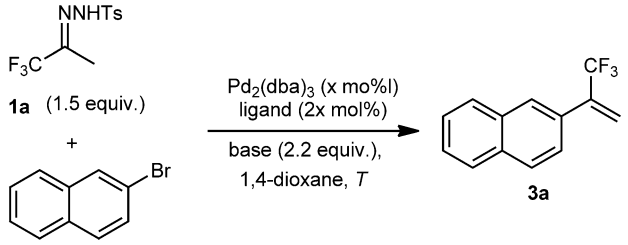
pered by the difficult preparation of the boronic derivative, again from 2-bromo-3,3,3-trifluoropropene.[17] Alternative methodologies, involving also the employment of 2-bromo-3,3,3-trifluoropropene, include the Pd-catalyzed coupling of aryl bromides with the *in situ* generated 2-(3,3,3-trifluoropropenyl)zinc bromide,[18] and the Pd- or Ni-catalyzed cross-coupling with Grignard reagents, although these latter methods feature very limited scope.[19,20] Another possible approach, the direct Csp^2–CF_3 bond formation, widely employed in CF_3 aromatic trifluoromethylation,[5] and in the synthesis of β-trifluoromethylstyrenes,[6a–h,21] to the best of our knowledge has not been effectively applied to the preparation of α-trifluoromethylstyrenes.[6g]

The Pd-catalyzed cross-coupling of tosylhydrazones with aryl halides and sulfonates, first reported in 2007,[22a] has been established since then as a very efficient methodology for the synthesis of polysubstituted alkenes.[22,23] Moreover, since the tosylhydrazones are readily prepared from the corresponding carbonyl compounds, from a synthetic point of view, the carbonyl can be regarded as the nucleophilic component in the cross-coupling reaction. Continuing with our interest in this reaction, we envisioned that the employment of readily available trifluoromethyl ketones as tosylhydrazone precursors might represent a new entry into the interesting α-trifluoromethylstyrenes.[24] Indeed, we have been able to devise proper reaction conditions for this transformation (Scheme 1, c), that has led to a very efficient and general method for the preparation of α-trifluoromethylstyrenes from trifluoroacetone, a readily available and affordable source of trifluoromethylated subunits. We report our results herein.

Results and Discussion

The reaction between tosylhydrazone **1a**[23] and 2-bromonaphthalene **2a** was selected to develop proper conditions for the cross-coupling. Preliminary experiments under the standard conditions for tosylhydrazone cross-couplings[22] (Table 1, entry 1) failed completely, and the desired α-trifluoromethylstyrene **3a** was not even detected. For this reason, a detailed investigation of the reaction conditions was conducted. Selected results are presented in Table 1.

Table 1. Selected data on the influence of the reaction parameters in the cross-coupling reaction between tosylhydrazone **1a** and **2a**.[a]



Entry	Pd [mol%]	Ligand[b,f]	Base	*T* [°C]	**2a**:**3a**[c]
1	4	Xphos	LiO-*t*-Bu	110	100:0
2	4	Xphos	LiO-*t*-Bu	140	100:0
3	4	Davephos	LiO-*t*-Bu	140	100:0
4	4	Davephos	NaO-*t*-Bu	140	100:0
5	4	Davephos	Cs_2CO_3	140	90:10
6	4	Davephos	K_2CO_3	140	80:20
7	4	Davephos	Na_2CO_3	140	15:85
8	–	–	Na_2CO_3	140	100:0
9	1	Davephos	Na_2CO_3	140	93:7
10	2	Davephos	Na_2CO_3	140	65:35
11	5	Davephos	Na_2CO_3	140	0:82[d]
12	4	Davephos	Na_2CO_3	90	87:13
13	4	Davephos	Na_2CO_3	110	40:60
14	4	Davephos	Na_2CO_3	130	35:65
15	4	Sphos	Na_2CO_3	140	89:11
16	4	Xantphos	Na_2CO_3	140	100:0
17	4	Xphos	Na_2CO_3	140	20:80
18	4	Xphos	Na_2CO_3	150	5:95 (91)[e]

[a] *Reaction conditions:* **1a** (0.75 mmol, 1.5 equiv.), **2a** (0.5 mmol), base (2.2 equiv.), 1,4-dioxane 1.5 mL, *T*, 2 h, sealed tube.
[b] A 2:1 ligand:Pd ratio is employed.
[c] Determined by GC-MS.
[d] Naphthalene (18%) was detected in the reaction mixture.
[e] Isolated yield of **3a** is indicated in brackets.
[f] Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; Davephos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; Sphos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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A set of experiments oriented to investigate the effect of the base was carried out in a sealed tube, in the presence of 1.5 equiv. of tosylhydrazone **1a**, 1 equiv. of bromonaphthalene **2a**, $Pd_2(dba)_3$ (2 mol%) and Davephos (8 mol%), and employing 1,4-dioxane as solvent (entries 3–7). No trifluoromethylstyrene **3a** formation was observed with alkoxide bases (NaO-*t*-Bu and LiO-*t*-Bu) (entries 3 and 4). However, the employment of alkaline carbonates Cs_2CO_3 (entry 5) and K_2CO_3 (entry 6) provided the desired product, although in low conversions, even after extended reaction times. Delightfully, it was found that Na_2CO_3 was a better base for this reaction providing the desired product with 85% conversion (entry 7).

Continuing with the optimization studies, attempts to reduce the catalyst loading were not successful (entries 9 and 10). Nevertheless, catalyst loadings above 5% mol of Pd(0) did not improve the result, due to the partial debromination of **2a** leading to substantial amounts of naphthalene (entry 11). As a control experiment, the model reaction was conducted in the absence of catalyst, and complete recovery of the starting material **2a** was observed (entry 8). The reaction also proceeded at lower temperatures, but with a notable decrease in the conversion (entries 12, 13 and 14). In further screening studies, different phosphine ligands were tested. Catalysts based on bidentate phosphine ligands such as Xanthphos were not effective (entry 16) and only a few monodentate ligands afforded the desired product. The employ of Sphos resulted in poor conversion (entry 15), whereas both Davephos and Xphos led to high conversions under the optimal conditions (entries 7 and 17). Finally, the best result was obtained with a slight increase in the temperature. Thus, when the reaction was carried out with Xphos at 150 °C (entry 18) a 95% conversion was observed, with a 91% isolated yield of **3a**.

The influence of the base in the results presented in Table 1 is worth mentioning, and could be rationalized considering the mechanism proposed for the cross-coupling reaction, which is presented in Figure 1.[22a] The base-promoted thermal decomposition of the tosylhydrazone **1a** leads to the formation of the diazo compound **A**. In the presence of the Pd catalyst, formation of a Pd-carbene **C** may occur by reaction of the arylpalladium complex **B** with the diazo compound. Then, migratory insertion gives rise to alkylpalladium complex **D**. Finally, β-hydride elimination furnishes the coupling product **3**. However, the diazo compound can also undergo uncatalyzed decomposition, most likely to give 3,3,3-trifluoropropene **4**, (a highly volatile compound that could not be detected in our experimental setting), through the Bamford–Stevens reaction.

For the cross-coupling reaction to be successful, the rate of the catalytic reaction must be *much faster* than the uncatalyzed decomposition of the diazo compound **A**. Our observations tend to indicate that the presence of the trifluoromethyl group confers the tosylhydrazone a higher tendency to undergo uncatalyzed decomposition. Strong bases such as alkoxides, which are the bases of choice for Pd-catalyzed cross-couplings with most *N*-tosylhydrazones,[22] build a high concentration of the diazo compound **A**, which apparently decomposes at much higher rate than the catalytic cycle. However, in the presence of less soluble and weaker bases such as the alkaline carbonates, the diazo compound must be formed at a much slower rate that, in turn, can be properly synchronized with the catalytic cycle turnover, avoiding its uncatalyzed decomposition.

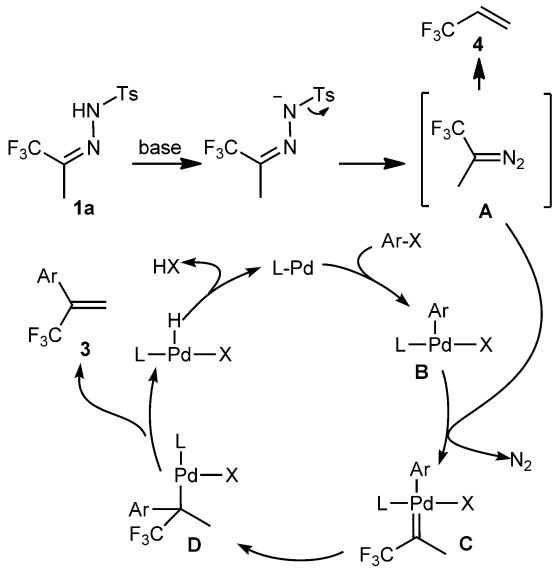

Figure 1. Possible reaction pathways for the tosylhydrazone **1a** under the conditions of the Pd-catalyzed reaction.

The scope of the reaction was studied under the optimized conditions, using a set of aromatic and heteroaromatic bromides **2**. The examples presented in Table 2 demonstrate the remarkable generality of the reaction. The cross-coupling proceeded successfully with electron-rich (**3b**, **3c**) and electron-poor (**3d–j**) aromatic derivatives with different substitution patterns, and features high functional group tolerance, such as the presence of both enolizable and non-enolizable ketones (**3d**, **3e**), esters (**3f**), nitriles (**3g**, **3j**) and even unprotected aldehydes (**3h**). Moreover, under the reaction conditions, the coupling can be conducted in the presence of chloro substituents (**3i**). The reaction was also applied successfully to diverse heterocycles, allowing for the introduction of the trifluoromethylvinyl unit in different heteroaromatic rings including pyridine (**3n**), quinoline (**3k**), benzofuran (**3l**) and benzothiophene (**3m**).

At this point it is very important to emphasize the convenience of *N*-tosylhydrazone **1a** as a source of tri-

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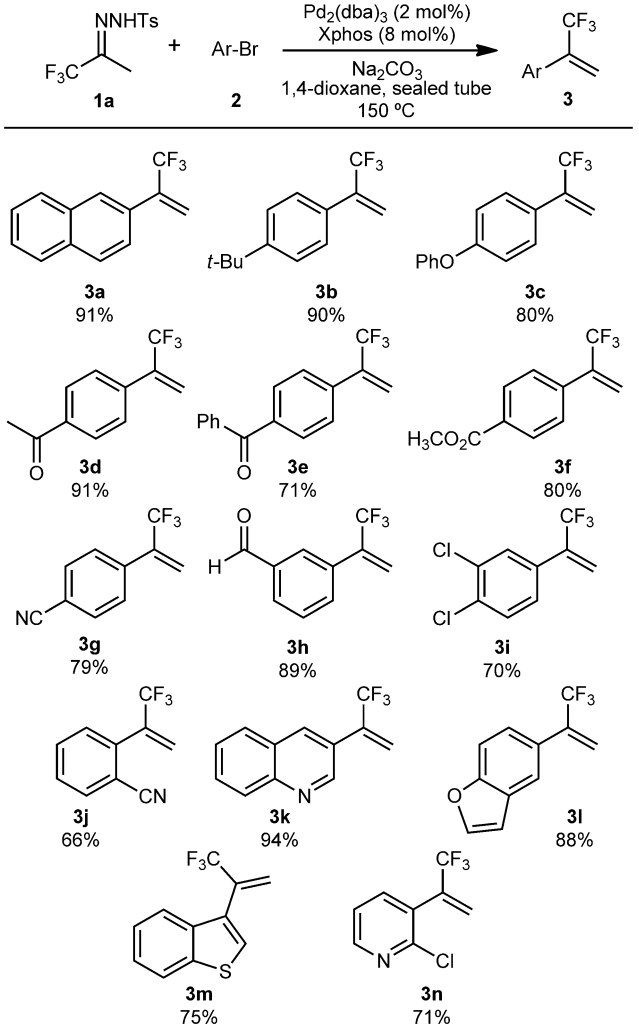
Table 2. Trifluoromethylstyrenes **3** prepared by cross-coupling of tosylhydrazone **1a** and aryl bromides **2**.[a,b]

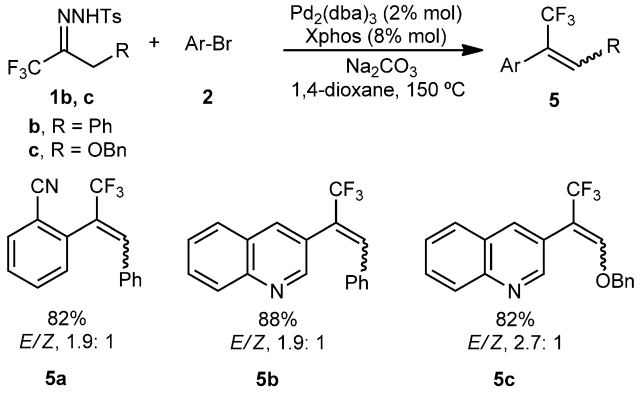


[a] *Reaction conditions:* **1a** (0.75 mmol, 1.5 equiv.), **2a** (0.5 mmol, 1 equiv.), Na_2CO_3 (2.2 equiv.), 1,4-dioxane 1.5 mL, 150 °C, 2 h, sealed tube.

[b] Isolated yields after column chromatography.

fluoromethyl substituents. Tosylhydrazone **1a** is an air and bench stable white solid that can be very easily prepared on a large scale by dissolving trifluoromethyl acetone (1 equiv.) and tosyl hydrazide (1.1 equiv.) in ethanol and stirring the mixture at 70 °C for 3 h (see the Supporting Information for details). In fact, we have prepared 36 g of **1a** in a single run with an 81% yield.

On the other hand, the reaction has also been successfully expanded to other trifluoromethyl tosylhydrazones **1b**, **c**, under the same reaction conditions, affording trifluoromethylalkenes **5** with very high yields, as a mixture of *Z* and *E* isomers. Although the reaction features poor stereoselectivity, it is still a very interesting transformation considering that the synthesis



Scheme 2. Synthesis of trifluoromethylalkenes **5** from trifluoromethyl tosylhydrazones **1b** and **1c**.

of α-trifluoromethyl-β-substituted styrenes is not well resolved at present,[6f,25] and that the potential of these products for further synthetic transformations is very high. The examples presented involve some challenging aryl bromides, including *ortho*-functionalized aromatic systems (**5a**) and heteroaromatics (**5b**, **5c**) (Scheme 2).

Conclusions

We have presented a novel entry into α-trifluoromethylstyrenes, which are a very versatile source of fluorinated one-carbon units, from 1,1,1-trifluoromethylacetone tosylhydrazone, through Pd-catalyzed cross-couplings with aryl bromides. It has been observed that trifluoromethyl-substituted *N*-tosylhydrazones display much higher tendency to undergo base-promoted thermal decomposition than other *N*-tosylhydrazones, and thus, completely different reaction conditions had to be developed for the cross-coupling. Nevertheless, under the optimized conditions, the coupling reaction exhibits wide scope and functional group tolerance, and provides generally high yields. Moreover, the reaction can be also applied to substituted trifluoromethyl tosylhydrazones, leading to substituted trifluoromethylstyrenes. Considering the high affordability and ease of use of 1,1,1-trifluoromethylacetone tosylhydrazone when compared with other sources of trifluoromethyl moieties, we believe that this methodology will be advantageous in many synthetic scenarios, and therefore will find ample application in organic synthesis. Additionally, this contribution opens the door for the development of other valuable transition metal-catalyzed or uncatalyzed transformations employing trifluoromethyl tosylhydrazones. Research in this regard is ongoing in our laboratories.

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Experimental Section

General Procedure for the Synthesis of *N*-Tosylhydrazones 1a–c

In a round-bottom flask provided with a reflux condenser a 0.5 M solution of the corresponding trifluoromethyl ketone **1** in ethanol was prepared. Then the tosylhydrazide was added and the mixture heated at 70 °C for 3 h. The solvent was evaporated to give the desired crude product as a white or pale yellow solid. Recrystalization from EtOH afforded the desired product in crystalline form.

General Procedure for the Synthesis of α-Trifluoromethylstyrenes 3 and 5

A 20-mL microwave glass vial from Biotage (ref. 355632) was charged with $Pd_2(dba)_3$ (2 mol%, 9.2 mg), Xphos (8 mol%, 19 mg), Na_2CO_3 (2.2 equiv., 117 mg), *N*-tosylhydrazone **1** (0.75 mmol, 1.5 equiv.), 1,4-dioxane (1.5 mL) and the corresponding aryl or heteroaryl bromide **2** (0.5 mmol). The vial was sealed and the mixture was conventionally heated at 150 °C in a DRYSYN ϕ 28 mm plate for 2 h. The reaction mixture was cooled to room temperature, opened, and then diluted with heptane, filtered through celite and concentrated under reduced pressure. The residue thus obtained was purified by automated flash chromatography on silica gel. The desired fractions were collected and concentrated under reduced pressure to afford the corresponding products as colorless oils.

CAUTION: A reaction in a closed vessel at high temperature develops considerable pressure, and therefore the proper equipment must be employed. By using the vials described above, we have not observed any safety problem during the development of this work.

Supporting Information

Detalied experimental data, characterization and copies of the spectra of compounds **1**, **3** and **5**. are available in the Supporting Information.

Note Added in Proof

After submission of the revised version of this manuscript, the following closely related article appeared: X. Wang, Y. Xu, Y. Deng, Y. Zhou, J. Feng, G. Yi, Y. Zhang, J. Wang, *Chem. Eur. J.* **2014**, *20*, 961.

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References

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; b) *Organofluorine Compounds: Chemistry and Applications*, (Ed.: T. Hiyama), Springer, New York, **2000**; c) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**; d) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218; *Angew. Chem. Int. Ed.* **2005**, *44*, 214.

[2] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881.

[3] a) J. Scheirs, *Modern Fluoropolymers*, Wiley, New York, **1997**; b) G. Hougham, T. Davidson, P. Cassidy, K. Johns, *Fluoropolymers*, Kluvert, New York, **1999**; c) B. Ameduri, B. Boutevin, *Well Architectured Fluoropolymers: Synthesis Properties and Applications*, Elsevier, Amsterdam, **2004**.

[4] For reviews, see: a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744; b) A. Studer, *Angew. Chem.* **2012**, *124*, 9082; *Angew. Chem. Int. Ed.* **2012**, *51*, 8950; c) T. Besset, C. Schneider, D. Cahard, *Angew. Chem.* **2012**, *124*, 5134; *Angew. Chem. Int. Ed.* **2012**, *51*, 5048; d) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.

[5] For some recent reviews on aromatic trifluoromethylation. see: a) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161; b) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475. For some selected recent examples of aromatic trifluoromethylation, see: c) P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem.* **2012**, *124*, 7887; *Angew. Chem. Int. Ed.* **2012**, *51*, 7767; d) T. Liu, X. Shao, Y. Wu, Q. Shen, *Angew. Chem.* **2012**, *124*, 555; *Angew. Chem. Int. Ed.* **2012**, *51*, 540; e) Y. Ye, S. A. Künzi, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4979; f) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 551; *Angew. Chem. Int. Ed.* **2012**, *51*, 536; g) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679; 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. USA* **2011**, *108*, 14411; i) O. A. Tomashenko, E. C. Escudero-Adán, M. Martínez Belmonte, V. V. Grushin, *Angew. Chem.* **2011**, *123*, 7797; *Angew. Chem. Int. Ed.* **2011**, *50*, 7655; j) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224.

[6] For recent examples of alkene trifluoromethylation, see: a) E. J. Cho, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 6552; b) A. T. Parsons, T. D. Senecal, S. L. Buchwald, *Angew. Chem.* **2012**, *124*, 3001; *Angew. Chem. Int. Ed.* **2012**, *51*, 2947; c) N. Iqbal, S. Choi, E. Kim, E. J. Cho, *J. Org. Chem.* **2012**, *77*, 11383; d) Y. Yasu, T. Koike, M. Akita, *Chem. Commun.* **2013**, *49*, 2037; e) H. Lin, X. Dong, Y. Li, Q. Shen, L. Lu, *Eur. J. Org. Chem.* **2012**, *77*, 4675; f) A. Hafner, S. Braese, *Adv. Synth. Catal.* **2011**, *353*, 3044; g) Z. Li, Z. Cui, Z.-Q. Liu, *Org. Lett.* **2013**, *15*, 406; h) Y. Li, L. Wu, H. Neumann, M. Beller, *Chem. Commun.* **2013**, *49*, 2628; i) L. Chu, F.-L. Qing, *Org. Lett.* **2012**, *14*, 2106; j) C. Feng, T.-P. Loh, *Chem. Sci.* **2012**, *3*, 3458; k) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 6632; l) A. T. Parsons, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 9286; *Angew. Chem. Int. Ed.* **2011**, *50*, 9120; m) H. Egami, R. Shimizu, S.

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Kawamura, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4000.
[7] Selected miscellaneous trifluoromethylations, see: a) ketones: Q.-H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769; b) haloketones: P. Novák, A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2012**, *134*, 16167; c) alkylboronic acids: J. Xu, B. Xiao, C.-Q. Xie, D.-F. Luo, L. Liu, Y. Fu, *Angew. Chem.* **2012**, *124*, 12719; *Angew. Chem. Int. Ed.* **2012**, *51*, 12551; d) diazo esters: M. Hu, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 15257; e) alkynes: L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2010**, *132*, 7262; f) X. Jiang, L. Chu, F.-L. Quing, *J. Org. Chem.* **2012**, *77*, 1251; g) allyl halides: Y. Miyake, S.-i. Ota, Y. Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 13255; h) allylsilanes: R. Shimizu, H. Egami, Y. Hamashima, M. Sodeoka, *Angew. Chem.* **2012**, *124*, 4655; *Angew. Chem. Int. Ed.* **2012**, *51*, 4577; i) trifluoromethylations with fluoroform of C, Si, S, and B centers: G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324.
[8] For some recent examples of difluoromethylation, see: a) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494; b) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524.
[9] a) B. Morandi, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 950; *Angew. Chem. Int. Ed.* **2010**, *49*, 938; b) B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 1133; *Angew. Chem. Int. Ed.* **2011**, *50*, 1101; c) S. A. Kunzi, B. Morandi, E. M. Carreira, *Org. Lett.* **2012**, *14*, 1900; d) G. A. Molander, L. N. Cavalcanti, *Org. Lett.* **2013**, *15*, 3166.
[10] a) J.-P- Bégué, D. Bonnet-Delpon, M. H. Rock, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1409; b) J. Ichikawa, H. Fukui, Y. Ishibashi, *J. Org. Chem.* **2003**, *68*, 7800.
[11] a) T. Mori, J. Ichikawa, *Chem. Lett.* **2004**, *33*, 1206; b) J. Ichikawa, T. Mori, Y. Iwai, *Chem. Lett.* **2004**, *33*, 1354; c) T. Mori, Y. Iwai, J. Ichikawa, *Chem. Lett.* **2005**, *34*, 778; d) J. Ichikawa, Y. Iwai, R. Nadano, T. Mori, M. Ikeda, *Chem. Asian J.* **2008**, *3*, 393; e) J. Ichikawa, M. Ikeda, M. Hattori, *Heterocycles* **2009**, *77*, 1285.
[12] K. Fuchibe, M. Takahashi, J. Ichikawa, *Angew. Chem.* **2012**, *124*, 12225; *Angew. Chem. Int. Ed.* **2012**, *51*, 12059.
[13] D. Bonnet-Delpon, J.-P. Begue, T. Lequeux, M. Ourevitch, *Tetrahedron* **1996**, *52*, 59.
[14] J. Walkowiak, d. C. T. Martinez, B. Ameduri, V. Gouverneur, *Synthesis* **2010**, 1883.
[15] a) Z.-K. Wan, E. Chenail, H.-Q. Li, C. Kendall, Y. Wang, S. P. Gingras, J. Xiang, W. W. Massefski, T. S. Mansour, E. Saiah, *J. Org. Chem.* **2011**, *76*, 7048; b) A. P. Truong, G. Toth, G. D. Probst, J. M. Sealy, S. Bowers, D. W. G. Wone, D. Dressen, R. K. Hom, A. W. Konradi, H. L. Sham, J. Wu, B. T. Peterson, L. Ruslim, M. P. Bova, D. Kholodenko, R. N. Motter, F. Bard, P. Santiago, H. Ni, D. Chian, F. Soriano, T. Cole, E. F. Brigham, K. Wong, W. Zmolek, E. Goldbach, B. Samant, L. Chen, H. Zhang, D. F. Nakamura, K. P. Quinn, T. A. Yednock, J.-M. Sauer, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6231; c) R.-q. Pan, X.-x. Liu, M-z. Deng, *J. Fluorine Chem.* **1999**, *95*, 167.
[16] A Scifinder reaction search gave over 15 different patents which include this particular transformation in the 2007–2012 period.
[17] B. Jiang, Q. F. Wang, C. G. Yang, M. Xu, *Tetrahedron Lett.* **2001**, *42*, 4083.
[18] a) B. Jiang, Y. Xu, *J. Org. Chem.* **1991**, *56*, 7336; b) G.-q. Shi, X.-H. Huang, F. Hong, *J. Org. Chem.* **1996**, *61*, 3200.
[19] a) O. Kobayashi, D. Uraguchi, T. Yamakawa, *J. Fluorine Chem.* **2009**, *130*, 591.
[20] For the synthesis of some α-trifluoromethylstyrenes through olefination of aryl trifluoromethyl ketones, see: B. S. Nader, J. A. Cordova, K. E. Reese, C. L. Powell, *J. Org. Chem.* **1994**, *59*, 2898.
[21] For some other approaches to β-trifluoromethylstyrenes, see: a) G. K. S. Prakash, H. S. Krishnan, P. V. Jog, A. P. Iyer, G. A. Olah, *Org. Lett.* **2012**, *14*, 1146; b) M. Omote, M. Tanaka, A. Ikeda, S. Nomura, A. Tarui, K. Sato, A. Ando, *Org. Lett.* **2012**, *14*, 2286.
[22] a) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587; b) J. Barluenga, M. Tomás-Gamasa, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2008**, *14*, 4792; c) J. Barluenga, M. Escribano, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2009**, *15*, 13291; d) J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem.* **2010**, *122*, 7008; *Angew. Chem. Int. Ed.* **2010**, *49*, 6856; e) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Chem. Eur. J.* **2010**, *16*, 12801; f) Q. Xiao, J. Ma, Y. Yang, Y. Zhang, J. Wang, *Org. Lett.* **2009**, *11*, 4732; g) E. Brachet, A. Hamze, J.-F. Peyrat, J.-D. Brion, M. Alami, *Org. Lett.* **2010**, *12*, 4042; h) Z. Zhang, Y. Liu, M. Gong, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem.* **2010**, *122*, 1157; *Angew. Chem. Int. Ed.* **2010**, *49*, 1139; i) J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2011**, *13*, 510; j) E. Rasolofonjatovo, B. Tréguier, O. Provot, A. Hamze, J.-D. Brion, M. Alami, *Eur. J. Org. Chem.* **2012**, *77*, 1603.
[23] For some reviews, see: a) J. Barluenga, C. Valdés, *Angew. Chem.* **2011**, *123*, 7626; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560; c) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236.
[24] The reaction of 1,1,1-trifluoroacetophenone tosylhydrazones with organolithium compounds has been recently reported and gives rise to terminal 1,1-difluorostyrenes: M. Kang, S.-A. Lee, N. Kang, B. Moon, *Bull. Korean Chem. Soc.* **2011**, *32*, 3022.
[25] a) P. A. Byrne, K. V. Rajendran, J. Muldoon, D. G. Gilheany, *Org. Biomol. Chem.* **2012**, *10*, 3531; b) Y. Uchiyama, N. Kano, T. Kawashima, *J. Org. Chem.* **2006**, *71*, 659.

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