Synthetic Methods

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Silver-Mediated Cycloaddition of Alkynes with CF_3CHN_2: Highly Regioselective Synthesis of 3-Trifluoromethylpyrazoles**

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3-Trifluoromethylpyrazole is the core unit of many drugs, agrochemicals, and related candidates.[1] Among them are Celecoxib and Mavacoxib (antiarthritic), SC-560 (antitumor), AS-136A (antiviral), Razaxaban (anticoagulant), as well as DP-23 (insecticidal activity; Figure 1).[2] As a result of the immense usefulness of 3-trifluoromethylpyrazole derivatives, efficient construction of the 3-trifluoromethylpyrazole framework has become the subject of intensive research in the fields of synthetic and medicinal chemistry.[3] Generally, 3-trifluoromethylpyrazoles can be accessed by cyclocondensations of an appropriate hydrazine with the corresponding 1,3-dicarbonyl compounds.[4] However, these methods often suffer from the formation of regioisomeric mixtures with respect to substituents incorporated at the 3- and 5-positions of the pyrazole ring. Recently, 2,2,2-trifluorodiazoethane has emerged as an attractive synthon in transition-metal-catalyzed/mediated and organocatalytic reactions for the construction of fluorine-containing building blocks.[5–8] In this regard, Morandi, Carreira, and co-workers disclosed a rhodium-catalyzed cyclopropenation of alkynes with CF_3CHN_2 generated in situ from $CF_3CH_2NH_2$·HCl in aqueous media,[6b] and we developed the copper(I)-catalyzed cross-coupling of terminal alkynes and gaseous CF_3CHN_2, thus leading to the formation of C–H insertion products[7] (Scheme 1, top). These reactions are proposed to follow a similar step that involves metal carbene formation. In sharp contrast, the use of 2,2,2-trifluorodiazoethane as a 1,3-dipole for the cycloaddition of alkynes to construct functionalized 3-trifluoromethylpyrazoles has not received much attention. In 1979 Fields and Tomlinson described a dark reaction of terminal alkynes with 2,2,2-trifluorodiazoethane in a sealed tube.[9] Unfortunately, the harsh reaction conditions and long reaction times (over two weeks) render the process impractical and untenable. To address these limitations, we herein report a silver-mediated 1,3-dipolar cycloaddition of various terminal alkynes with 2,2,2-trifluorodiazoethane (Scheme 1, bottom). The notable features of this reaction are its high regioselectivity, operational simplicity, easily accessible starting materials, and mild reaction conditions. Furthermore, the potential application of this cycloaddition reaction was demonstrated as a key step in a new and efficient synthesis of the antiarthritic drug Celecoxib.

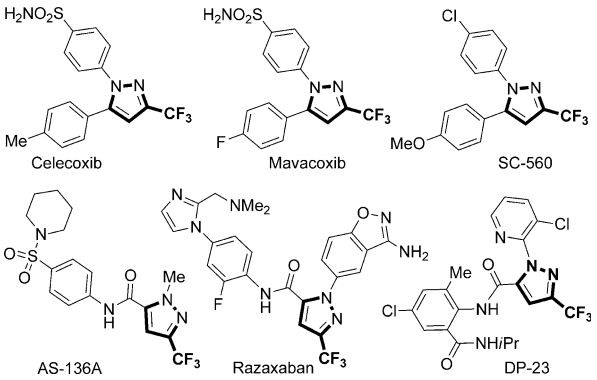
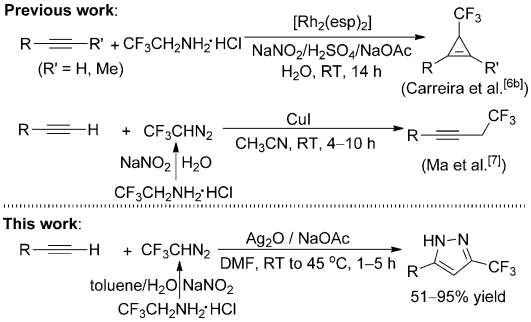


Figure 1. 3-Trifluoromethylpyrazole-based bioactive compounds.



Scheme 1. Different products from the reactions of alkynes with CF_3CHN_2. DMF = *N*,*N*-dimethylformamide.

The intermolecular 1,3-dipolar cycloaddition of electron-deficient diazocarbonyl compounds with alkynes was first disclosed by Li and co-workers,[10a] and additional methods have been reported by the groups of Ready,[10b] Liang,[10c] and Legros.[10d] Considering that CF_3CHN_2 is also an electron-deficient diazo compound, we first examined the model reaction of phenylacetylene (**1a**) with 2,2,2-trifluorodiazoethane under otherwise identical reaction conditions (as reported by the groups of Li, Ready, Liang, and Legros). However, none of the target cycloadduct **2a** was obtained. So the efficient realization of such transformation necessitates the development of new metal systems. Next, a large number of metal salts, which included lithium, magnesium, zinc,

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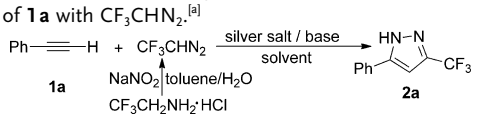
Table 1: Reaction conditions: Optimization for silver-mediated cycloaddition of **1a** with CF_3CHN_2.[a]

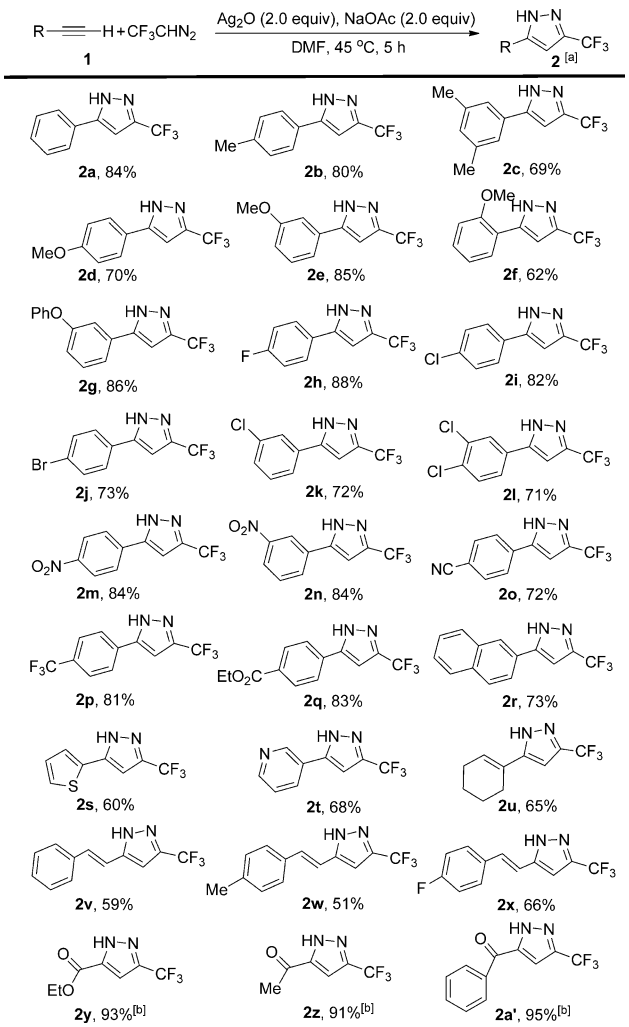


Entry	[Ag]/base	solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	Ag_2O	DMF	25	48	63
2	Ag_2CO_3	DMF	25	48	58
3	$AgNO_3$	DMF	25	48	40
4	AgOAc	DMF	25	48	61
5	Ag_2O/Na_2CO_3	DMF	25	48	65
6	Ag_2O/K_2CO_3	DMF	25	12	69
7	Ag_2O/Cs_2CO_3	DMF	25	12	71
8	Ag_2O/NaOAc	DMF	25	12	78
9	Ag_2O/KOAc	DMF	25	12	78
10[c]	Ag_2O/NaOAc	DMF	25	12	45
11	Ag_2O/NaOAc	DMAC	25	12	76
12	Ag_2O/NaOAc	dioxane	25	12	52
13	Ag_2O/NaOAc	CH_3CN	25	12	53
14	Ag_2O/NaOAc	toluene	25	12	18
15	Ag_2O/NaOAc	THF	25	12	21
16	Ag_2O/NaOAc	CH_2Cl_2	25	12	25
17	Ag_2O/NaOAc	DMF	45	5	84
18	Ag_2O/NaOAc	DMF	60	5	83
19[d]	Ag_2O/NaOAc	DMF	45	5	54
20[e]	Ag_2O/NaOAc	DMF	45	5	86
21[f]	Ag_2O/NaOAc	DMF	45	5	83

[a] General reaction conditions: **1a** (0.22 mmol), Ag salt (2.0 equiv), base (2.0 equiv), solvent (3.0 mL), $CF_3CH_2NH_2$·HCl (4.0 equiv), $NaNO_2$ (5.0 equiv), toluene (0.8 mL) and H_2O (40 μL). [b] Yields of isolated product averaged over two runs. [c] $CF_3CH_2NH_2$·HCl (2.0 equiv). [d] 1.0 equivalent of Ag_2O. [e] 3.0 equivalents of Ag_2O. [f] The use of the regenerated Ag_2O. THF = tetrahydrofuran.

copper, silver, gold, and some of their complexes, were screened for this model reaction. It was found that silver salts were the most promising promoters for the test reaction (Table 1, entries 1–4), whereas all the other metal complexes tested resulted in poor yields (not listed in Table 1; see the Supporting Information). Additionally, cyclopropenation, C–H insertion, or homocoupling of the alkyne was not a detectable side reaction for these silver-mediated processes. These preliminary results encouraged us to further optimize the reaction conditions. The introduction of bases as additives was found to significantly increase the reaction efficiency and yield (Table 1, entries 5–9). After screening several bases, the yield of **2a** was increased to 78% when the reaction was carried out using NaOAc or KOAc (entries 8 and 9). The use of an excess of the $CF_3CH_2NH_2$·HCl reagent was essential for the high efficiency of this cycloaddition. Reducing the loading of $CF_3CH_2NH_2$·HCl to 2.0 equivalents resulted in much lower yield of **2a** (entry 10). Exploration of solvents revealed that besides DMF, its analogue *N*,*N*-dimethylacetamide (DMAC) also promoted this transformation, whereas the use of toluene, THF, or CH_2Cl_2 led to a significantly lower yield (entries 11–16). Notably, a faster conversion was achieved by increasing the reaction temperature (entries 17 and 18). A lesser amount of Ag_2O reduced the reaction yield (entry 19), but 3.0 equivalents of Ag_2O did not improve the yield when compared to that obtained with 2.0 equivalents of Ag_2O (entries 17 and 20). Therefore, the combination of Ag_2O and NaOAc in DMF at 45 °C was found to be the best reaction conditions for this silver-mediated cycloaddition reaction. Although 2.0 equivalents of Ag_2O was employed in the reaction, the excess Ag_2O and the resulting silver species could be recycled conveniently by filtration and treatment with nitric acid and NaOH. The regenerated Ag_2O could still promote this cycloaddition in comparable yield without loss of activity (entry 21).

With the optimized reaction conditions in hand, we next investigated the substrate scope of this silver-mediated cycloaddition of 2,2,2-trifluorodiazoethane with a variety of terminal alkynes, and the results are summarized in Scheme 2. In the case of aryl acetylenes, the cycloaddition

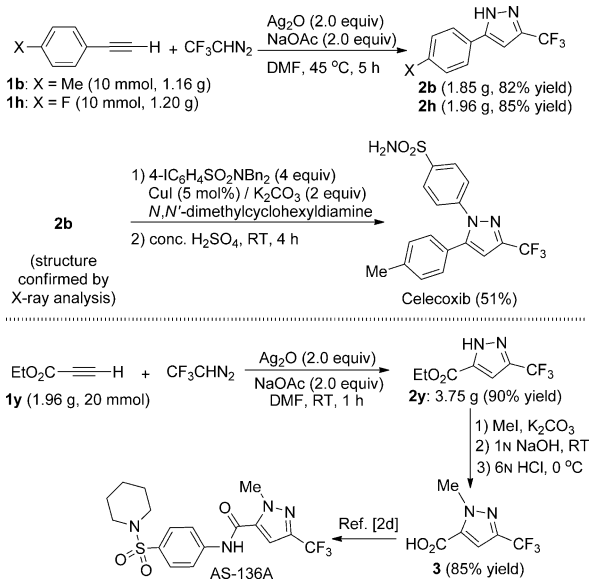


Scheme 2. Scope of the silver-promoted cycloaddition of terminal alkynes with CF_3CHN_2. [a] Yields of isolated products. [b] The reactions were carried out at room temperature for 1 h.

reaction tolerates various substitution patterns and a range of different substituents on the aryl ring. Alkyl-, alkoxy-, halo-, nitro-, cyano-, and alkoxycarbonyl-substituted phenyl acetylenes all undergo the desired reaction to give the cycloadducts **2a**–**q** in good to high yields. The structure of compound **2b** was further confirmed to be 3-trifluoromethyl-5-*p*-tolyl-1*H*-

pyrazole by means of X-ray crystallographic analysis (see the Supporting Information).[11] 2-Naphthyl-, 2-thiophenyl- and 3-pyridyl-substituted aryl acetylenes were also found to be good substrates, thus delivering the products **2r–t** in good yields. Furthermore, several enynes also worked well under the same reaction conditions to afford the corresponding products **2u–x**. It is remarkable that electron-deficient alkynes were found to undergo the desired transformation efficiently, even at room temperature for one hour, thus furnishing the cycloaddition products in excellent yields (**2y**, **2z**, and **2a′**). In all cases, the reaction can be conducted under mild reaction conditions without the need for anhydrous solvents. Finally, we found that alkyl-substituted terminal alkynes cannot be converted using the present protocol, even when the reaction temperature is decreased to 0 °C. We also attempted to optimize the reactions with alkyl-substituted alkynes by increasing the amounts of 2,2,2-trifluorodiazoethane and Ag_2O but still could not obtain any of the desired products.

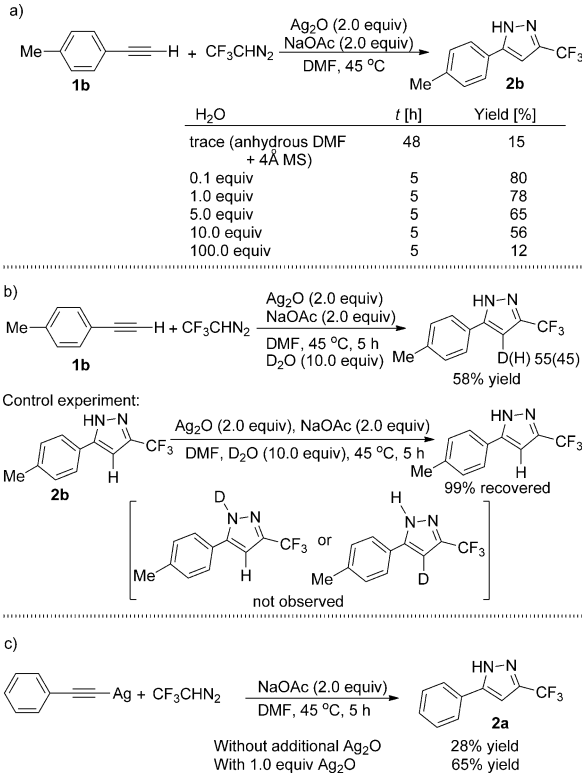
Subsequently, we want to comment on the synthetic utility of this cycloaddition reaction (Scheme 3). As expected, almost the same results were obtained when the cycloaddition



Scheme 3. Scaled-up cycloaddition reaction and further synthetic transformation of the cycloadducts.

reaction of the terminal alkynes **1b**, **1h**, and **1y** with 2,2,2-trifluorodiazoethane was run on a gram scale. These cycloadducts (**2b**, **2h**, and **2y**) are versatile synthetic intermediates, and can be further used in the preparation of relative drugs including Celecoxib, Mavacoxib, AS-136 A, and Razaxaban. For example, copper-catalyzed N arylation of **2b** with *N*,*N*-dibenzyl-4-iodobenzenesulfonamide, and subsequent removal of the benzyl group afforded the antiarthritic drug Celecoxib in the yield of 51%. The melting point and spectral data of Celecoxib are in full agreement with those described in the literature (Scheme 3, top).[2a] Methylation of ethyl 3-trifluoromethyl pyrazole-5-carboxylate (**2y**) with iodomethane in DMF, and subsequent hydrolysis afforded the 3-trifluoromethyl-pyrazole-5-carboxylic acid (**3**) in 85% yield. The acid **3** is a known intermediate in the synthesis of the measles virus inhibitor AS-136A (Scheme 3, bottom).[2d]

It is noteworthy that the amount of water can significantly interfere with this cycloaddition. We found that, in the presence of freshly activated molecular sieve powder (4 Å), the reaction between 4-methylphenylacetylene (**1b**) and 2,2,2-trifluorodiazoethane proceeded very slowly (48 h) to give the cycloadduct **2b** in 15% yield. In contrast, the cycloaddition performed with varying stoichiometric amounts of water led to respectable yields, while excess water was found to inhibit the reaction (Scheme 4a). To gain some

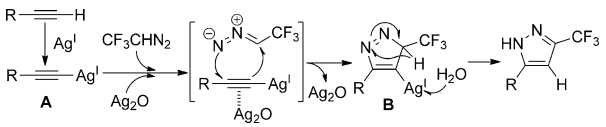


Scheme 4. a) Effect of water on the cycloaddition. b) Isotopic-labeling experiments. 3) reaction of silver phenylacetylide with CF_3CHN_2.

insight into the reaction mechanism and to further identify the role of water in this transformation, we conducted the following experiments under the standard reaction conditions. Reaction **1b** with 2,2,2-trifluorodiazoethane in the presence of D_2O delivered the cycloadduct **2b** in 58% yield upon isolation (Scheme 4b). The deuterated product was detected by ^1H NMR spectroscopy as anticipated. In the control experiment, however, we did not observe any incorporation of the deuterium into the pyrazole ring when D_2O was used as an additive. Therefore, the intermolecular proton exchange between cycloadduct and water is impossible. In addition, we synthesized the silver acetylide,[12] and investigated its reaction with 2,2,2-trifluorodiazoethane (Scheme 4c). Without the additional Ag_2O, the cycloadduct **2a** was obtained in 28% yield. In the presence of additional silver oxide, silver phenylacetylide could react with 2,2,2-

trifluorodiazoethane and afford the product **2a** in good yield. The internal 1,2-diphenylethyne was also tested in the reaction, instead of terminal alkynes, however, no desired product was observed. These results indicate that silver acetylide might be the active species in the reaction, and that the additional silver oxide must be needed to achieve this cycloaddition.

On the basis of these experimental results, we proposed the reaction mechanism as outlined in Scheme 5. Initially, the silver acetylide complex **A** is formed by the reaction of the



Scheme 5. Proposed mechanism.

terminal alkyne **1** with silver(I). Then, through the silver-promoted 1,3-dipolar cycloaddition of **A** with CF_3CHN_2, the crucial intermediate **B** is obtained. The subsequent step is the 1,3-hydrogen shift and hydrolysis of **B**, thus giving rise to the 1*H*-pyrazole product. Further analysis will be necessary to elucidate the nature of this cycloaddition more accurately.

In summary, we have developed a novel silver-mediated cycloaddition reaction of terminal alkynes with CF_3CHN_2 generated from readily available $CF_3CH_2NH_2$·HCl. This protocol represents a direct and efficient way to construct 5-substituted 3-trifluoromethylpyrazoles under mild reaction conditions. The reaction is exceptionally regioselective and the products are of high value for multiple synthetic applications. Meanwhile, the recovery experiment of silver species could dramatically reduce the cost and waste which would allow a large range of applications in the organic synthesis. Efforts are currently underway to elucidate the mechanistic details, and the scope and limitations of this reaction, the results of which will be reported in due course.

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[1] a) C. Lamberth, *Heterocycles* **2007**, *71*, 1467; b) J. Elguero, A. M. S. Silva, A. C. Tomé, *Modern Heterocyclic Chemistry*, 1st ed., Wiley-VCH, Weinheim, **2011**, p. 635.

[2] a) T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Doctor, M. J. Greveto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, S. A. Gregory, C. M. Icoboldt, W. E. Perkus, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347 (Celecoxib); b) S. R. Cox, S. P. Lesman, J. F. Boucher, M. J. Krautmann, B. D. Hummel, M. Savides, S. Marsh, A. Fielder, M. R. Stegemann, *J. Vet. Pharmacol. Ther.* **2010**, *33*, 461 (Mavacoxib); c) E. Lee, M. K. Choi, H. J. Youk, C. H. Kim, I. C. Han, B. C. Yoo, M. K. Lee, S. J. Lim, *J. Cancer Res. Clin. Oncol.* **2006**, *132*, 232 (SC-560); d) A. Sun, N. Chandrakumar, J.-J. Yoon, R. K. Plemper, J. P. Snyder, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5199 (AS-136A); e) J. G. Varnes, D. A. Wacker, D. J. P. Pinto, M. J. Orwat, J. P. Theroff, B. Wells, R. A. Galemo, J. M. Luettgen, R. M. Knabb, S. Bai, K. He, P. Y. S. Lam, R. R. Wexler, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 749 (Razaxaban); f) G. P. Lahm, T. P. Selby, J. H. Freudenberger, T. M. Stevenson, B. J. Myers, G. Seburyamo, B. K. Smith, L. Flexner, C. E. Clark, D. Cordova, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4898 (DP-23).

[3] a) L. Yet, *Comprehensive heterocyclic chemistry III*, 1st ed., Elsevier, Oxford, **2008**, *4*, 1; b) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984.

[4] Selected recent examples, see: a) T. Norris, R. Colon-Cruz, D. H. B. Ripin, *Org. Biomol. Chem.* **2005**, *3*, 1844; b) A. Shavnya, S. M. Sakya, M. L. Munich, B. Rast, K. L. DeMello, B. H. Jaynes, *Tetrahedron Lett.* **2005**, *46*, 6887; c) S. P. Singh, V. Kumar, R. Aggarwal, J. Elguero, *J. Heterocycl. Chem.* **2006**, *43*, 1; d) P. S. Humphries, J. M. Finefield, *Tetrahedron Lett.* **2006**, *47*, 2443; e) Y. Yonetoku, H. Kubota, Y. Okamoto, A. Toyoshima, M. Funatsu, J. Ishikawa, M. Takeuchi, M. Ohta, S.-I. Tsukamoto, *Bioorg. Med. Chem.* **2006**, *14*, 4750; f) V. Montoya, J. Pons, J. García-Antón, X. Solans, M. Font-Bardia, J. Ros, *J. Fluorine Chem.* **2007**, *128*, 1007; g) S. Fustero, R. Román, J. F. Sanz-Cervera, A. Simón-Fuentes, A. C. Cuñat, S. Villanova, M. Murguía, *J. Org. Chem.* **2008**, *73*, 3523; h) H. Dai, Y.-Q. Li, D. Du, X. Qin, X. Zhang, H.-B. Yu, J.-X. Fang, *J. Agric. Food Chem.* **2008**, *56*, 10805; i) X. Yang, S. Shui, X. Chen, H. He, F. Wu, *J. Fluorine Chem.* **2010**, *131*, 426.

[5] a) P. Le Maux, S. Juillard, G. Simmoneaux, *Synthesis* **2006**, 1701; b) P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich, I. V. Komarov, *Synthesis* **2008**, 1757; c) P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich, I. V. Komarov, *Angew. Chem.* **2008**, *120*, 5849; *Angew. Chem. Int. Ed.* **2008**, *47*, 5765; d) O. O. Grygorenko, O. S. Artamonov, I. V. Komarov, P. K. Mykhailiuk, *Tetrahedron* **2011**, *67*, 803.

[6] a) B. Morandi, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 950; *Angew. Chem. Int. Ed.* **2010**, *49*, 938; b) B. Morandi, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 4390; *Angew. Chem. Int. Ed.* **2010**, *49*, 4294; c) B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 1133; *Angew. Chem. Int. Ed.* **2011**, *50*, 1101; d) B. Morandi, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 9251; *Angew. Chem. Int. Ed.* **2011**, *50*, 9085; e) B. Morandi, J. Cheang, E. M. Carreira, *Org. Lett.* **2011**, *13*, 3080.

[7] C.-B. Liu, W. Meng, F. Li, S. Wang, J. Nie, J.-A. Ma, *Angew. Chem.* **2012**, *124*, 6331; *Angew. Chem. Int. Ed.* **2012**, *51*, 6227.

[8] Z. Chai, J.-P. Bouillon, D. Cahard, *Chem. Commun.* **2012**, *48*, 9471.

[9] R. Fields, J. P. Tomlinson, *J. Fluorine Chem.* **1979**, *13*, 147.

[10] a) N. Jiang, C.-J. Li, *Chem. Commun.* **2004**, 394; b) X. Qi, J. M. Ready, *Angew. Chem.* **2007**, *119*, 3306; *Angew. Chem. Int. Ed.* **2007**, *46*, 3242; c) S. He, L. Chen, Y.-N. Niu, L.-Y. Wu, Y.-M. Liang, *Tetrahedron Lett.* **2009**, *50*, 2443; d) D. Vuluga, J. Legros, B. Crousse, D. Bonnet-Delpon, *Green Chem.* **2009**, *11*, 156; e) L. Lin, J. Zhang, R. Wang, *Asian J. Org. Chem.* **2012**, *1*, 222.

[11] CCDC 889113 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] A. Vitérisi, A. Orsini, J.-M. Weibel, P. Pale, *Tetrahedron Lett.* **2006**, *47*, 2779.

