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Direct Access to α-Trifluoromethyl Enones via Efficient Copper-Catalyzed Trifluoromethylation of Meyer–Schuster Rearrangement

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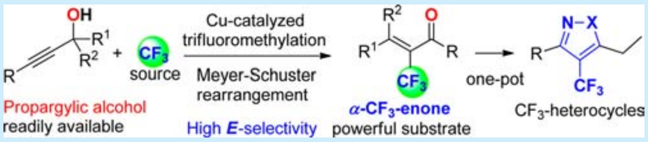
Supporting Information

ABSTRACT: A novel domino copper-catalyzed trifluoromethylated Meyer–Schuster rearrangement reaction with Togni's reagent was developed, leading to α-trifluormethyl (CF_3) enone products with moderate to good yields. Furthermore, α-CF_3 enones can be transformed toward important trifluoromethyl heterocyclic motifs in a one-pot version.



For 2012, three newly approved drugs bearing a trifluoromethyl (CF_3) group (Figure 1) have demonstrated that the introduction of a CF_3 group gives rise to significant changes in the chemical and physical properties of a potential drug candidate owing to displaying excellent solubility and lipophilicity properties.[1] Accordingly, the development of new methods for the construction of a C–CF_3 bond has drawn much attention to synthetic research groups.[2,3] On the other hand, it is well-known that α,β-unsaturated ketones (enones) could be performed as valuable synthetic building blocks due to their flexibility in many reactions,[4] ranging from Michael additions, cycloadditions to hydrogenations, and so on. Therefore, the development of efficient methods for the incorporation of the CF_3 group into the α-position of enone for the formation of complex polysubstituted α-CF_3 enones would be of particular interest as the effect of trifluoromethyl introduction on this motif remains, to the best of our knowledge, thus far widely unexplored (Scheme 1a).[5] In this context, Rasmusson and co-workers[5a] have reported a photocatalyzed reaction of trifluoromethyl iodide with steroidal dienones with ultraviolet light for up to 6 days with only low conversion (32–42%). Chen and co-workers[5b,c] have established an elegant strategy for direct trifluoromethylation of steroidal α-bromo enones with $FO_2SCF_2CO_2Me$ (MFSDA) in the presence of CuI in DMF with good yields. Despite the importance of these methods, they all remain fundamentally limited by the requirement of harsh reaction conditions and toxic or expensive reagents with a very limited substrate scope or low conversion. An additional disadvantage of the reported methods is the required use of prefunctionalized starting materials suffering from tedious procedures. Thus, the development of practical, general, and novel transformations to deliver valuable complex polysubstituted α-CF_3 enone structures from simple starting materials with a broad substrate scope under mild and simple reaction conditions is highly desirable, and its realization would improve the wide usefulness of such compounds in synthetic organic chemistry.

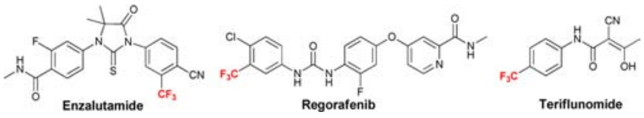
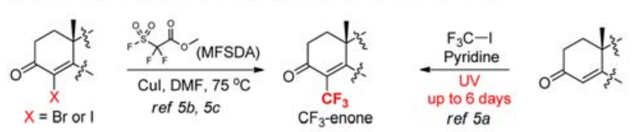


Figure 1. Newly FDA-approved drugs bearing a CF_3 group in 2012.

Scheme 1. General Synthetic Strategies for the Construction of α-CF_3-enones

a. Previous reports on the installation of a CF_3 group into enone derivatives



b. Our synthetic strategies for the construction of CF_3-enones

On the basis of the structural analysis, two synthetic strategies can be envisioned: (1) the direct C–H functionalization with CF_3 source and (2) trapping the allenol intermediate through the Meyer–Schuster reaction with electrophilic CF_3 source (Scheme 1b). Both strategies are full of challenges because of the multireactive centers of enone or propargylic alcohol and the control of selectivity of the active allenol intermediate. It should be noted that the present preliminary investigation suggested the direct C–H functionalization with a CF_3 source needs further powerful effort for a successful result. On the other hand, in our second synthetic proposal, there have been two recent developments that are related to trap the allenol intermediate with other electrophiles.[6,7] First, the Zhang group reported an efficient synthesis of α-halogen enones from propargylic alcohols with NBS or NIS involving cooperative Au/Mo bimetallic catalysis.[6] More recently, Gaunt and co-

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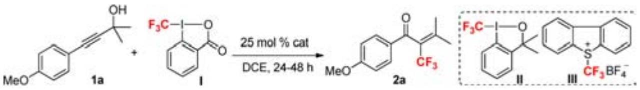
workers developed a new approach to form a broad range of α-aryl enones from propargylic alcohols, employing diaryliodonium salts and copper catalysis.[7] Encouraged by these results and in connection with our continuous efforts devoted to trifluoromethylation,[8] we herein present the first domino trifluoromethylated Meyer–Schuster rearrangement reaction catalyzed by simple copper catalyst with Togni's reagent as CF_3 source. A series of readily accessible substituted propargylic alcohols deliver complicated α-CF_3 enone products mainly as the *E*-isomers with moderate to good yields. Furthermore, the highly functionalized α-CF_3 enone products can be used as versatile synthetic intermediates for the transformation into important heterocyclic motifs in a one-pot version.

In our initial investigation, the reaction of 4-(4-methoxyphenyl)-2-methylbut-3-yn-2-ol (**1a**) in the presence of commercially available Togni's reagent (**I**)[9] with CuI as the catalyst was chosen as a model. The different metal salts CuI or CuBr in the presence of various organic solvents such as CH_3CN or THF all failed to give any desired product. The disappointing results further demonstrated the existence of great challenge and forced us to further optimize the reaction conditions more carefully. It was exciting to find that 25 mol % of CuI could catalyze this reaction in DCE at 65 °C to provide the desired product **2a** with 45% yield (Table 1, entry 1).

Table 1. Screening Results of Reaction Conditions[a]



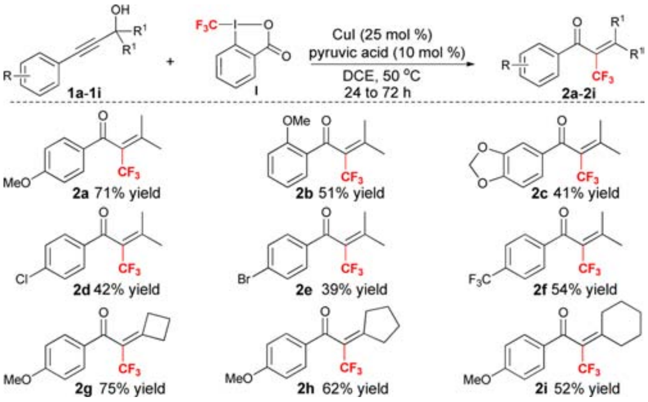
entry	$[CF_3]$	cat.	additive	temp (°C)	yield[b] (%)
1	**I**	CuI	none	65	45
2	**I**	CuI	DTBP	65	58
3[c]	**I**	CuI	DTBP	65	52
4[d]	**I**	CuI	DTBP	65	32
5[e]	**I**	CuI	DTBP	65	56
6[f]	**I**	CuI	DTBP	80	45
7	**I**	CuI	DTBP	80	52
8	**II**	CuI	DTBP	80	22
9	**III**	CuI	DTBP	80	8
10	**I**	CuI	PA	50	71
11	**I**	CuBr	PA	50	47
12	**I**	CuCl	PA	50	trace
13	**I**	CuOAc	PA	50	62
14	**I**	none	PA	50	0

[a] Reaction conditions: (unless otherwise mentioned) **1a** (0.1 mmol), **I** (0.2 mmol), catalyst (0.025 mmol, 25 mol %), DCE (1.0 mL), 24–48 h, under argon (with additive 1.2 equiv of DTBP for entries 2–9 or 0.2 equiv of PA for entries 10–14). [b] Determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c] Dry DCE was used. [d] Dry DCE in the presence of 5 equiv of water was used. [e] 50 mol % of CuI was used. [f] 10 mol % of CuI was used. (DTBP = 2,6-di-*tert*-butylpyridine, PA = pyruvic acid, DCE = 1,2-dichloroethane.)

Encouraged by this result and motivated by Gaunt's optimal conditions,[7] we then tested the domino trifluoromethylated Meyer–Schuster rearrangement process with a base DTBP as an additive. To our delight, the reaction proceeded smoothly with a better yield of 58% (Table 1, entry 2). The presence of a trace amount of water was beneficial to the Meyer–Schuster rearrangement to form the active allenol intermediate, as the yield was slightly lower when anhydrous DCE was used as solvent (Table 1, entry 3). As such, we reasoned that larger amounts of water in the system may improve the results. To our disappointment, negative results were obtained when 5 equiv of water or only water was used as solvent (Table 1, entry 4). Further optimization without any improvements involved the study of catalyst loading and reaction temperature and the change of CF_3 reagent from Togni's reagent **I** to **II** or Umemoto's reagent **III**, probably owing to the coordination of the thio group of reagent **III** with the copper catalyst[3a] (Table 1, entries 5–9). Inspired by the acid-promoted Meyer–Schuster rearrangement,[10] we were delighted to find that the addition of pyruvic acid could improve the yield to 71% (Table 1, entry 10). After evaluating a range of copper(I) and copper(II) catalysts, it became clear that CuI salt led to the best performance (Table 1, entry 10–13). A control experiment revealed that no desired product was observed in the absence of copper catalyst (Table 1, entry 14), unambiguously demonstrating that copper catalyst is essential for this reaction.

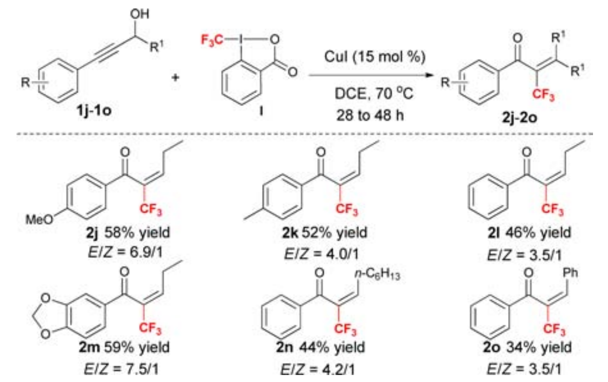
To examine the scope of this transformation, the optimized conditions were applied to the reaction of a variety of propargylic alcohols prepared from ketone with **I**. As shown in Scheme 2, the electronic properties and positions of the aromatic ring substituents had a solid effect on reactivity, giving product yields ranged from 39% to 71%. Interestingly, the substrates started from different cyclic ketones were found to be tolerated under the copper-catalyzed domino process to produce the trifluoromethylated tetrasubstituted enones in good yields.

Scheme 2. Trifluoromethylation of Propargylic Alcohols Prepared from Ketone



To further investigate the scope of this application, we next turned our attention toward expanding the scope of the propargylic alcohols prepared from aldehyde, although we anticipated more challenges associated with *E*/*Z* selectivity during the formation of the double bond.[11] To our delight, after further optimizing the reaction conditions (Supporting Information, Table S1), we recognized the following protocol as optimal conditions: only 15 mol % of CuI without any additive in the presence of 1.7 equiv of **I** with DCE as solvent at 70 °C, and the reaction of 1-(4-methoxyphenyl)pent-1-yn-3-ol (**1j**) gave product **2j** in 58% yield with good *E*-selectivity (*E*/*Z* = 6.9/1).[12] After establishing this new protocol, representative propargylic alcohols were arranged to explore the substrate scope with the displayed results in Scheme 3. Different substitution groups showed some influences on the chemical yields and the double-bond stereoselectivity. For substrates with a strong electron-donating group on the benzene ring, excellent *E*-selectivity was obtained, which may provide an

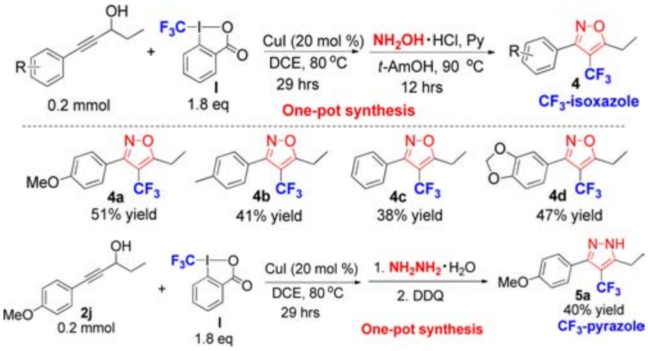
Scheme 3. Trifluoromethylation of Propargylic Alcohols Prepared from Aldehyde



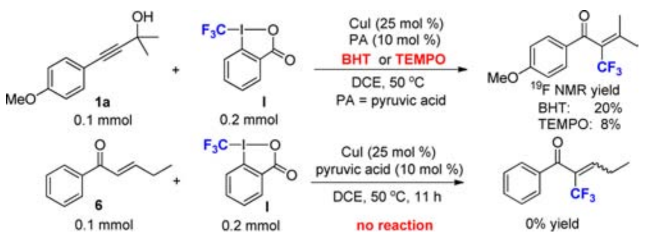
efficient example for the synthesis of kinetically favored α-CF_3 enones.[13a]

The synthetic significance of these CF_3-containing α,β-unsaturated ketones lies in their ability to serve as the precursors for the synthesis of many different classes of organic molecules, including a variety of heterocycles with medicinal and biological applications. As such, we spurred to develop a one-pot process toward the CF_3-isoxazole and CF_3-pyrazole compounds. Subjecting propargylic alcohol **1j** to the standard reaction conditions with Togni's reagent **I** for 29 h, followed by trapping the intermediate with hydroxylamine, provided the desired CF_3-isoxazole **4a** with 51% yield. This one-pot strategy can be extended to other substituted aromatic rings for constructing the desired CF_3-isoxazole products in acceptable results (Scheme 4). Furthermore, CF_3-pyrazole **5a** was also obtained in 40% yield with a subsequent treatment of enone with hydrazine followed by DDQ oxidation (Scheme 4).

Scheme 4. Application of Copper-Catalyzed Trifluoromethylation of Meyer–Schuster Rearrangement

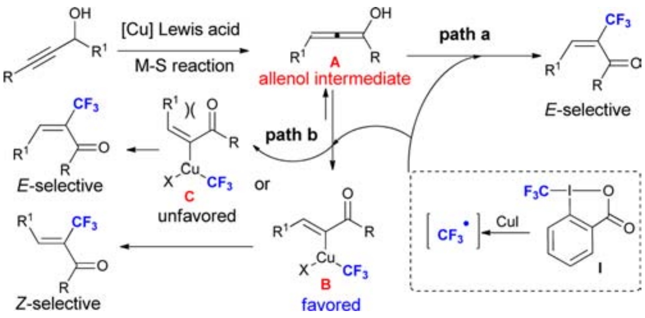


Scheme 5. Control Experiments



In order to gain more insight into the reaction mechanism, several control experiments were performed (Scheme 5). The reaction of **1a** with **I** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions produced the desired products in only marginal yields, while the TEMPO–CF_3 adduct was formed in 45% yield as estimated by ^{19}F NMR analysis (see the Supporting Information). These results indicate that the CF_3 radical may be involved in the transformation. Furthermore, with the hope of finding out whether the C–CF_3 bond formation in this reaction follows a direct C–H activation of enone generated from the exact Meyer–Schuster rearrangement, enone **6** was subjected to the standard conditions, but the reaction provided no anticipated product. The current result revealed that the direct C–H trifluoromethylation of enone can be ruled out.

Scheme 6. Proposed Reaction Mechanism



On the basis of the control experimental results and the previous investigation,[6,14] a reaction mechanism was tentatively proposed (Scheme 6). An initial Cu-catalyzed Meyer–Schuster rearrangement is well documented to form an active allenol intermediate A.[6,7] The resulting intermediate **A** can result in the final α-CF_3 enone products via two possible different pathways: (a) interact directly with active electrophilic CF_3 radical species (path a) or (b) be further activated by the active Cu catalyst to generate Cu-containing intermediate **B** (path b).[13c] Path a would lead to enone with the CF_3 group *trans* to R^1 (*E*-selective isomer) selectively as the active species (CF_3) should approach the more electron-rich enolic C–C double bond from the less hindered face, while the latter (path b) would afford favored intermediate **B** to yield the CF_3 group *cis* to R^1 (*Z*-selective isomer) according to the previous suggested explanation.[13] On the basis of the experimental results with preferred *E*-selectivity, path a may be predominant in our current reaction system. The exact mechanism for the domino process still remains unclear at present and deserves further detailed studies.

In conclusion, a novel approach to transform readily accessible propargylic alcohols into α-CF_3 enones using Togni's reagent and copper catalysis has been achieved. This protocol provided a broad scope of the desired α-CF_3 enone products in moderate to good yields with good *E*-isomeric selectivity. Furthermore, the highly functionalized α-CF_3 enone products can be used as versatile synthetic intermediates for further transformation into important heterocyclic motifs in a one-pot version.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, Table S1, and 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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REFERENCES

(1) For selected reviews, see: (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) For selected reviews on trifluoromethylation of organic compounds, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (d) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (e) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Asian J.* **2012**, *7*, 1744. (f) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (g) Ye, Y.; Sanford, M. S. *Synlett* **2012**, *23*, 2005. (h) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617. (i) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

(3) For selected representative examples on trifluoromethylation via C−H bond activation, see: (a) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (b) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682. (c) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. Trifluoromethylation of arenes through a radical process, see: (d) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (e) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. Trifluoromethylation of simple alkenes, see: (f) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (g) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (h) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1530. (i) Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458. (j) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505. (k) Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955. (l) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480. (m) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (n) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841. (o) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136. (p) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747. Trifluoromethylation of heteroarenes and terminal alkynes, see: (q) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (r) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. For exploration of the CF_3-initiated domino process, see: (s) Chen, Z.-M.; Bai, W.; Wang, S.-H.; Yang, B.-M.; Tu, Y.-Q.; Zhang, F.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9781.

(4) For selected reviews on reactions of enones, see: (a) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.

(5) (a) Rasmusson, G. H.; Brown, R. D.; Arth, G. E. *J. Org. Chem.* **1975**, *40*, 672. (b) Fei, X.-S.; Tian, W.-S.; Chen, Q.-Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1139. (c) Chadalapaka, G.; Jutooru, I.; McAlees, A.; Stefanac, T.; Safe, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2633.

(6) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3112.

(7) Collins, B. S. L.; Suero, M. G.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 5799.

(8) (a) Lin, J.-S.; Xiong, Y.-P.; Ma, C.-L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Chem.—Eur. J.* **2014**, *20*, 1332. (b) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504.

(9) For selected examples on trifluoromethylation with Togni's reagent: (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579. (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (c) Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1059.

(10) (a) Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett.* **1991**, 1413. (b) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159.

(11) (a) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149. (b) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088.

(12) The stereoconfiguration of the products was determined by comparing the NMR spectroscopy of a known compound **2o**; see: Bizet, V.; Pannecoucke, X.; Renaud, J. L.; Cahard, D. *J. Fluorine Chem.* **2013**, *152*, 56.

(13) (a) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147. (b) de Haro, T.; Nevado, C. *Chem. Commun.* **2011**, *47*, 248. (c) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12414.

(14) (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. For an in-depth computational study on similar intermediates, see: (b) Gandon, V.; Lemiere, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7534. (c) Garayalde, D.; Go mez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720.