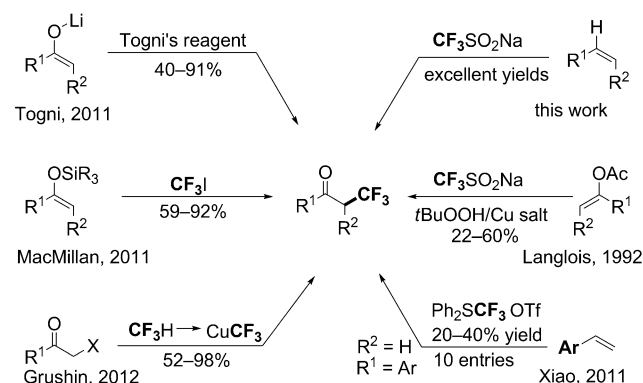


Oxidative Trifluoromethylation of Unactivated Olefins: An Efficient and Practical Synthesis of α -Trifluoromethyl-Substituted Ketones**

Arghya Deb, Srimanta Manna, Atanu Modak, Tuhin Patra, Soham Maity, and Debabrata Maiti*

The incorporation of a CF_3 group in a compound of pharmacological relevance usually results in significant enhancement of its lipophilicity, binding selectivity, and metabolic stability.^[1–5] A number of highly effective methods for the incorporation of a CF_3 moiety into commonly used synthetic scaffolds have been reported.^[2–9] In this context, the synthesis of α - CF_3 -substituted carbonyl compounds^[10–14] has recently drawn significant attention, owing to their importance for both pharmaceutical and synthetic research.

Generally, α - CF_3 -substituted carbonyl compounds are prepared from silyl enol ethers and enolates by using various radical and electrophilic trifluoromethylating agents (Scheme 1).^[6–8] Strong bases, such as lithium diisopropyla-

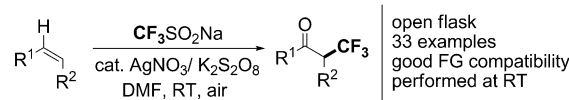


Scheme 1. Synthesis of α - CF_3 -substituted ketones.

ride (LDA), are often employed in the synthesis of these precursors, thus limiting the available methods by extra synthetic steps and precautionary measures. MacMillan and co-workers successfully generated α - CF_3 -substituted carbonyl compounds from aldehydes, ketones, esters, and amides.^[9] Enantiopure α - CF_3 -substituted carbonyl scaffolds were also reported in recent years.^[9b,c,10] In 2012, a nucleophilic trifluor-

omethylation of α -halogenated ketones was developed by Grushin and co-workers, who used fluoroform-derived CuCF_3 and thus circumvented the problem of 1,2 addition of the CF_3 group across the $\text{C}=\text{O}$ bond (Scheme 1).^[11] Despite this significant progress to construct α - CF_3 -substituted carbonyl scaffolds,^[5–9] utilization of widely available olefin feedstock in conjunction with an economic trifluoromethylation source remains elusive. In this context, note that “although styrenes can be used directly in the recently reported^[12] radical trifluoromethylation with costly $[\text{Ph}_2\text{SCF}_3]^+\text{OTf}^-$, the yields of the α - CF_3 -substituted acetophenone products are only 20–40 %.”^[11a]

We have recently reported the stereoselective nitration of olefins through the formation of nitro radicals.^[13] During this study, we envisaged a radical trifluoromethylation of olefins by employing the Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$), because it has been utilized effectively as the source of the CF_3 radical.^[2d,14] Herein, we disclose the oxidative trifluoromethylation of unactivated olefins with inexpensive $\text{CF}_3\text{SO}_2\text{Na}$ as the CF_3 source for the synthesis of α - CF_3 -substituted ketones in excellent yields (Scheme 2). Employing an olefin as the synthetic precursor rather than a preformed substrate



Scheme 2. Oxidative trifluoromethylation of olefins. FG = functional group.

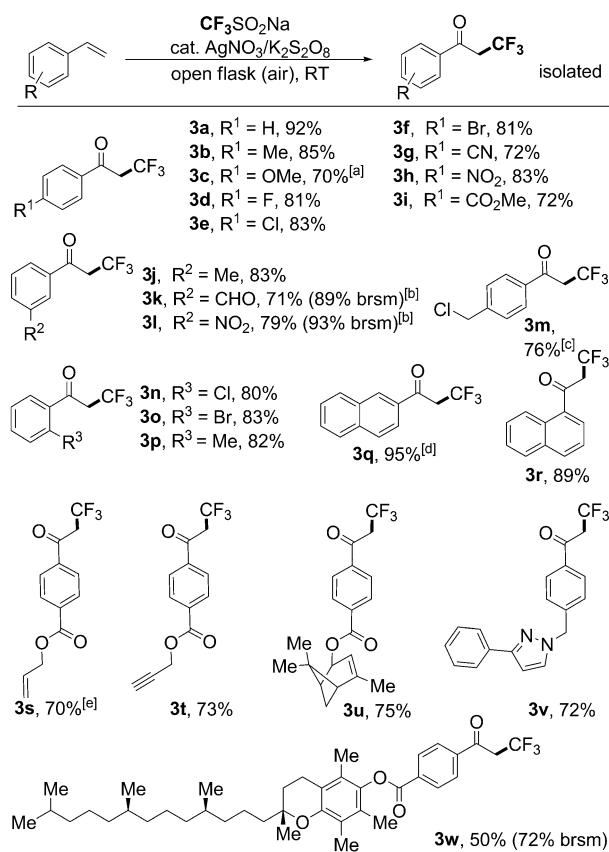
and carrying out the reactions in an open flask at room temperature make this method advantageous.

We began our study with the reaction of 2-vinyl naphthalene and benchtop-stable $\text{CF}_3\text{SO}_2\text{Na}$ in presence of a catalytic amount of $\text{AgNO}_3/\text{K}_2\text{S}_2\text{O}_8$.^[15] Optimized reaction conditions, which include the use of two equivalents of triflinat and 20 mol % of $\text{AgNO}_3/\text{K}_2\text{S}_2\text{O}_8$ in DMF at room temperature, gave the α - CF_3 -substituted ketone in excellent yield. With these operationally simple and optimized reaction conditions established, we evaluated the scope and limitations of the method. We first explored the substrate scope with styrene derivatives (Scheme 3). The reaction with styrene afforded 2-trifluoromethylacetophenone (**3a**) in an excellent yield of 92 %. A wide variety of substituents/functional groups, ranging from NO_2 (**3h** and **3l**), CN (**3g**), CHO (**3k**), to CO_2Me (**3i**), remained intact during the reaction, owing to the exceptionally mild reaction conditions. Consistent with our expectations, halogenated styrenes could also be successfully transformed (**3d–f**). 2-Substituted styrene derivatives reacted

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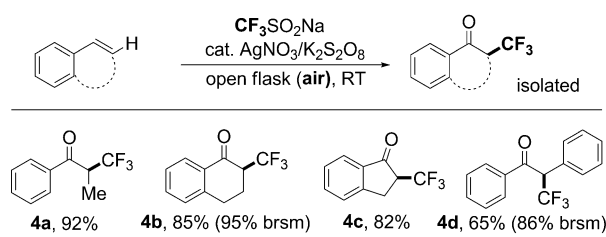


Scheme 3. Synthesis of $\alpha\text{-CF}_3$ -substituted ketones from styrenes. Reaction conditions: olefin (0.25 mmol), $\text{CF}_3\text{SO}_2\text{Na}$ (0.5 mmol), AgNO_3 (20 mol%), $\text{K}_2\text{S}_2\text{O}_8$ (20 mol%), 24 h. [a] $\text{K}_2\text{S}_2\text{O}_8$ (10 mol%). [b] 50 °C. [c] AgNO_3 (10 mol%). [d] 73% yield on a 3 mmol scale. [e] ArCHO isolated, 18%.^[15] brsm = based on recovered starting material.

efficiently to generate $\alpha\text{-CF}_3$ -substituted ketones (**3n–p**). Also, naphthalenes with vinyl groups at positions 1 and 2 gave the desired products in 89% (**3r**) and 95% (**3q**) yields, respectively. The formation of the $\alpha\text{-CF}_3$ -substituted ketone occurred exclusively at the styrene olefin in presence of a terminal aliphatic olefin (**3s**). In case of alkyne-bearing product **3t**, the formation of the $\alpha\text{-CF}_3$ -substituted ketone occurred only at the styrene moiety (**3t**) and the terminal alkyne remained intact during the oxidative trifluoromethylation. Such examples underscore the power of the present strategy to affect the highly selective formation of $\alpha\text{-CF}_3$ -substituted ketones. Styrenes with covalently attached *cis*-verbenol formed $\text{ArCOCH}_2\text{CF}_3$ selectively in 75% yield (**3u**).

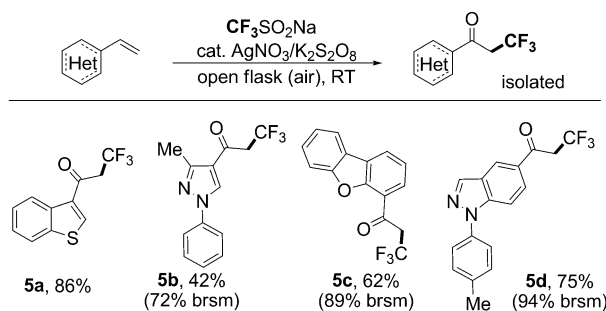
Because of the very mild conditions employed in the present method, a chloromethyl group (**3m**), which can be easily oxidized to the corresponding aldehyde, was also tolerated.^[13] These examples outline the factors that determine the selectivity, and they can be successfully implemented to generate $\alpha\text{-CF}_3$ -substituted ketones in complex molecules.

Products derived from α,β -substituted olefins are ubiquitous in synthetic chemistry and we thought to react these olefins under standard conditions (Scheme 4). Interestingly 1,2-dihydro-naphthalene and 1,2-dihydro-indene were transformed successfully to cyclic ketones containing CF_3 groups



Scheme 4. Synthesis of $\alpha\text{-CF}_3$ -substituted ketones from β -substituted styrenes. Olefin (0.25 mmol), $\text{CF}_3\text{SO}_2\text{Na}$ (0.05 mmol), AgNO_3 (20 mol%), $\text{K}_2\text{S}_2\text{O}_8$ (20 mol%), 24 h.

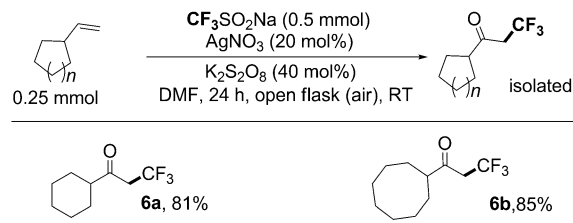
(**4b** and **4c**, respectively). As anticipated, both *cis* and *trans* stilbenes reacted successfully to form the same $\alpha\text{-CF}_3$ -substituted carbonyl compound **4d** under the optimized reaction conditions (around 65% yield). Also, a styrene with a methyl group at the β position (**4a**) reacted as efficiently as the unsubstituted styrene itself (**3a**). The scope of this oxidative trifluoromethylation method was tested on heteroaromatic olefins (Scheme 5). The 3-vinyl benzothio-



Scheme 5. Synthesis of $\alpha\text{-CF}_3$ -substituted ketones from heteroaromatic olefins. For reaction conditions, see Scheme 3.

phene gave the expected $\alpha\text{-CF}_3$ -substituted ketone in 86% yield (**5a**). Olefins with heterocycles that contain nitrogen atoms, such as pyrazole and indazole, were also successfully employed (**5b** and **5d**, respectively).

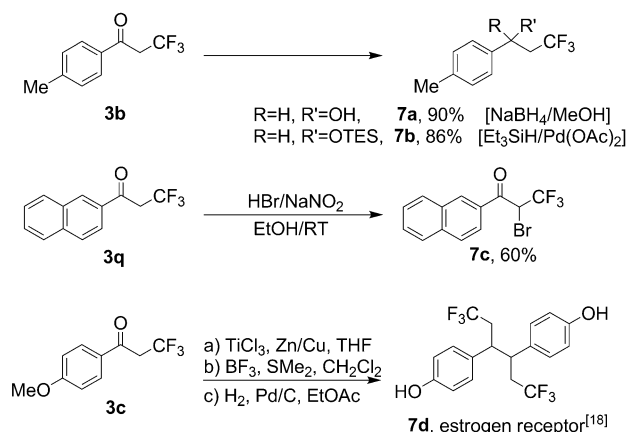
Vinyl cycloalkanes were reacted successfully to produce $\alpha\text{-CF}_3$ -substituted carbonyl compounds in useful yields (Scheme 6, products **6a** and **6b**). Unfortunately, aliphatic olefins with long chains (e.g., dodecene, tetradecene, and 10-bromo-1-decene etc.) gave an inseparable mixture of two uncharacterized products that contain the CF_3 moiety. Further studies are ongoing in our laboratory to synthesize these products in pure form.



Scheme 6. Oxidative trifluoromethylation of vinyl cycloalkanes.

To further confirm the generation of α -CF₃-substituted ketones from the oxidative trifluoromethylation method, characterization (in addition to analytical studies) of **3g** and **5d** were carried out by single-crystal X-ray diffraction studies.^[16]

Compounds that contain an α -CF₃-substituted carbonyl moiety are useful synthetic precursors (Scheme 7).^[5–9,15] The addition of CF₃ and OH groups across an olefin is yet to be

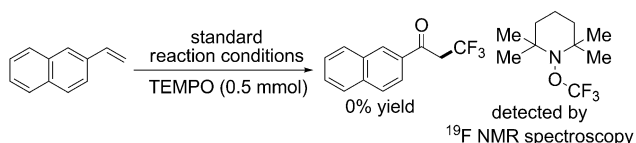


Scheme 7. Synthetic utility of α -CF₃-substituted ketones.

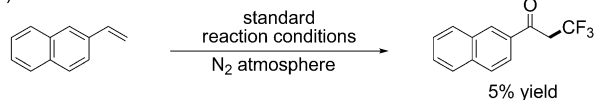
realized in a single step.^[11a,17] But such much desired OH/CF₃-substituted compounds (**7a**) can be prepared easily by reduction of α -CF₃-substituted ketones. Furthermore, the α position of CF₃-substituted ketones can be brominated (**7c**).

A preliminary investigation of the reaction mechanism suggested that the reaction is likely to involve a CF₃ radical. Under the optimized reaction conditions, 2-vinyl naphthalene did not produce an α -CF₃-substituted ketone in the presence of TEMPO (Scheme 8a). Consistent with this observation, TEMPO-CF₃ was detected in the reaction mixture by ¹⁹F NMR spectroscopy. In the absence of air, the formation

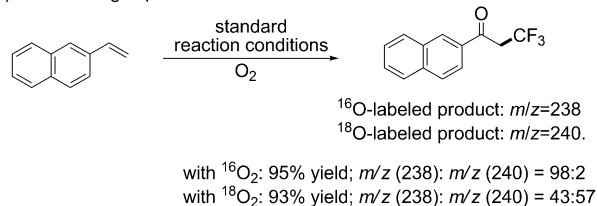
a) evidence in support of a radical pathway:



b) role of air as the oxidant:



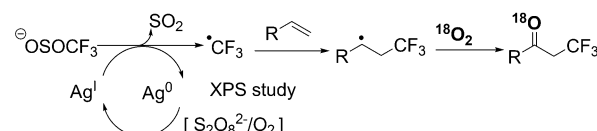
c) ¹⁸O-labeling experiment:



Scheme 8. Preliminary mechanistic investigations.^[15]

of the α -CF₃-substituted ketone was retarded (Scheme 8b). Furthermore, an ¹⁸O-labeling experiment confirmed that both air and K₂S₂O₈ can be the source of the oxygen atom of the ketone (Scheme 8c).

Formation of Ag⁰ in the reaction mixture was confirmed by X-ray photoelectron spectroscopy (XPS).^[15] Based on these studies, a catalytic cycle that involves Ag^I/Ag⁰ has been proposed (Scheme 9). A detailed mechanistic investigation is currently under way in our laboratory.



Scheme 9. Plausible mechanistic pathway.

In conclusion, we have discovered a direct, efficient, and general method to access α -CF₃-substituted ketones.^[17,19] Simple unactivated olefins have been employed as the starting materials. Wide functional-group tolerance, mild reaction conditions, and the use of an inexpensive trifluoromethylating agent are key features of this reaction. Because of its operational simplicity and predictable reactivity pattern in complex settings, we expect this method to find broad application in synthetic, medicinal, and agrochemical research.

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- [1] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; d) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; e) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029; f) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; g) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; h) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305–321; i) X. F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; j) J. P. Bégué, D. Bonnet-Delpon, B. Crousse, J. Legros, *Chem. Soc. Rev.* **2005**, *34*, 562–572.
- [2] a) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228; b) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679–1681; c) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, *0*, 1909–1911; d) J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300–4302; e) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem.* **2011**, *123*, 3877–3882; *Angew. Chem. Int. Ed.* **2011**, *50*, 3793–3798.
- [3] a) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99; b) Y. N. 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*, 14411–14415; c) C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu, J. C. Xiao, *Angew. Chem.* **2011**, *123*, 1936–1940; *Angew. Chem. Int. Ed.* **2011**, *50*, 1896–1900; d) T. Patra, A. Deb, S. Manna, U. Sharma, D. Maiti, *Eur. J. Org. Chem.* **2013**, DOI: 10.1002/ejoc.201300473.
- [4] a) J. B. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478; b) J. A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975–996.
- [5] a) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527; b) P. S. Fier, J. F. Hartwig, *Angew. Chem.* **2013**, *125*, 2146–2149; *Angew. Chem. Int. Ed.* **2013**, *52*, 2092–2095; c) C. P. Zhang, Q. Y. Chen, Y. Guo, J. C. Xiao, Y. C. Gu, *Chem. Soc. Rev.* **2012**, *41*, 4536–4559; d) T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa, T. Yamakawa, *J. Fluorine Chem.* **2010**, *131*, 98–105; e) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li, X. Wu, *Angew. Chem.* **2013**, *125*, 7100–7104; *Angew. Chem. Int. Ed.* **2013**, *52*, 6962–6966.
- [6] a) Y. Itoh, K. Mikami, *Org. Lett.* **2005**, *7*, 649–651; b) Y. Itoh, K. Mikami, *Org. Lett.* **2005**, *7*, 4883–4885; c) Y. Itoh, K. N. Houk, K. Mikami, *J. Org. Chem.* **2006**, *71*, 8918–8925; d) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164; e) Y. Itoh, K. Mikami, *J. Fluorine Chem.* **2006**, *127*, 539–544; f) Y. Tomita, Y. Ichikawa, Y. Itoh, K. Kawada, K. Mikami, *Tetrahedron Lett.* **2007**, *48*, 8922–8925; g) K. Sato, T. Yuki, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *Tetrahedron Lett.* **2008**, *49*, 3558–3561; h) Y. Itoh, K. Mikami, *Tetrahedron* **2006**, *62*, 7199–7203.
- [7] a) K. Sato, T. Yuki, R. Yamaguchi, T. Hamano, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *J. Org. Chem.* **2009**, *74*, 3815–3819; b) K. Mikami, Y. Tomita, Y. Ichikawa, K. Amikura, Y. Itoh, *Org. Lett.* **2006**, *8*, 4671–4673; c) K. Miura, M. Taniguchi, K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 6391–6394; d) N. Kamigata, K. Udodaira, T. Shimizu, *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *129*, 155–168; e) J. C. Blazejewski, M. P. Wilmschurst, M. D. Popkin, C. Wakselman, G. Laurent, D. Nonclercq, A. Cleeren, Y. Ma, H. S. Seo, G. Leclercq, *Bioorg. Med. Chem.* **2003**, *11*, 335–345; f) Y. Tomita, Y. Itoh, K. Mikami, *Chem. Lett.* **2008**, *37*, 1080–1081; g) K. Sato, M. Higashinagata, T. Yuki, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *J. Fluorine Chem.* **2008**, *129*, 51–55.
- [8] a) V. Matousek, A. Togni, V. Bizet, D. Cahard, *Org. Lett.* **2011**, *13*, 5762–5765; b) V. Petrik, D. Cahard, *Tetrahedron Lett.* **2007**, *48*, 3327–3330; c) S. Noritake, N. Shibata, S. Nakamura, T. Toru, M. Shiro, *Eur. J. Org. Chem.* **2008**, 3465–3468.
- [9] a) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem.* **2011**, *123*, 6243–6246; *Angew. Chem. Int. Ed.* **2011**, *50*, 6119–6122; b) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986–4987; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10876.
- [10] a) Q. H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769–10772; b) A. T. Herrmann, L. L. Smith, A. Zakarian, *J. Am. Chem. Soc.* **2012**, *134*, 6976–6979; c) S. Noritake, N. Shibata, Y. Nomura, Y. Y. Huang, A. Matsnev, S. Nakamura, T. Toru, D. Cahard, *Org. Biomol. Chem.* **2009**, *7*, 3599–3604; d) T. Billard, B. R. Langlois, *Eur. J. Org. Chem.* **2007**, 891–897; e) G. Valero, X. Companyo, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018–2037.
- [11] a) P. Novák, A. Lishchynskiy, V. V. Grushin, *J. Am. Chem. Soc.* **2012**, *134*, 16167–16170; b) A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913.
- [12] C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu, J. C. Xiao, *Chem. Commun.* **2011**, 47, 6632–6634.
- [13] S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick, D. Maiti, *J. Am. Chem. Soc.* **2013**, *135*, 3355–3358.
- [14] a) Z. J. Li, Z. L. Cui, Z. Q. Liu, *Org. Lett.* **2013**, *15*, 406–409; b) Y. D. Ye, S. A. Kuenzi, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4979–4981; c) B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525–7528; d) B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1992**, *33*, 1291–1294.
- [15] See the Supporting Information for a detailed description.
- [16] Experimental details of the structure determination can be found in the Supporting Information. CCDC 926149 (entry **3g**) and CCDC 927390 (entry **5d**) contain 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.
- [17] Y. Li, A. Studer, *Angew. Chem.* **2012**, *124*, 8345–8348; *Angew. Chem. Int. Ed.* **2012**, *51*, 8221–8224.
- [18] C. K. Rhee, K. Chae, L. A. Levy, K. S. Korach, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 133.
- [19] A provisional patent on this work has been filed: IPA 1193/Mum/2013.