ChemPubSoc Europe

DOI: 10.1002/chem.201600377

CHEMISTRY
A European Journal
Communication

Synthetic Methods

Trichloromethylthiolation of N-Heterocycles: Practical and Completely Regioselective

Johannes B. Ernst, Andreas Rühling, Birgit Wibbeling, and Frank Glorius*[a]

Dedicated to the late Prof. Peter Hofmann

Abstract: The first trichloromethylthiolation of a broad range of indoles and pyrroles is reported employing bench-stable *N*-trichloromethylthiosaccharin as reagent. This methodology is highly regioselective, exhibits high functional group tolerance, and provides access to two previously unknown classes of potentially bioactive compounds.

N-Heteroarenes represent, without doubt, one of the most important structural motifs in the fields of bioactive compounds.[1] In particular, indole- and pyrrole-based compounds are greatly present in a vast variety of natural products, pharmaceuticals, and agrochemicals.[2] Therefore, the development of efficient and selective methods for the C–H-functionalization of N-heterocycles is highly desirable not only within academia, but also for industry.[3]

The introduction of the trifluoromethylthio group (CF_3S) has received considerable interest in the last years due to its unique biological properties.[4] However, the introduction of other trihalomethylthio groups into heterocycles is limited to methods for thiophenes[5] and pyridines;[6] hence, the effect of other trihalomethylthio groups on the properties of potentially bioactive heterocyclic compounds could not be thoroughly investigated so far. Of particular importance is the trichloromethylthio group (Cl_3CS), because its ability to induce lipophilicity and membrane permeability is superior to commonly applied fluorine-containing functional groups (Hansch constants 1.65 versus 1.44 for SCF_3 and 0.88 for CF_3).[7] The trichloromethylthio-containing fungicides Folpet and Captan are produced on industrial scale for the application in viticulture and fruit growing because they possess high activity against fungi and bacteria (Figure 1).[8,9] Additionally, trichloromethylthiolated compounds exhibit herbicidal and insecticidal activity.[8] It is important to note that the biological activity is not a property of only the nitrogen-bonded $SCCl_3$ groups and that numerous other trichloromethylthio-containing compounds display biological activity.[8,10]

Inspired by the state of the art reagents applied in the trifluoromethylthiolation of various N-heterocycles,[11] we focused on the development of a method employing a bench-stable reagent for the trichloromethylthiolation of N-heterocycles. The reagent of choice for the trichloromethylthiolation of 6-fluoroindole was **1b** (Scheme 1). To our delight, we were able to

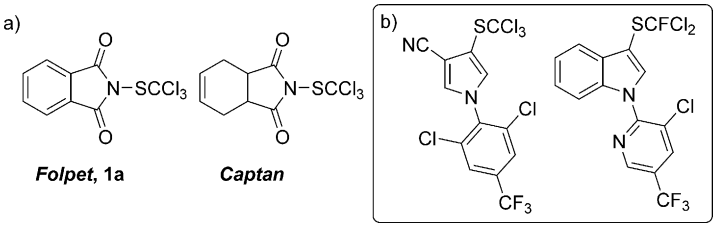
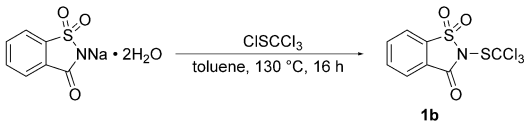


Figure 1. a) Examples of industrially produced trichloromethylthio-containing fungicides. b) Trichloro- and dichlorofluoromethylthio-containing pesticides.



Scheme 1. Synthesis of trichloromethylthiolating reagent **1b**.

observe the desired trichloromethylthiolated product in a moderate yield and with excellent regioselectivity using **1b** (Table 1). After optimizing the reaction conditions, we could isolate the desired product in high yield and as a single regioisomer. A slight excess of reagent **1b** (1.5 equiv) was needed for full conversion of the starting materials, and the addition of trimethylsilyl chloride (1.5 equiv) as a Lewis-acidic activator proved, especially for electron-deficient substrates, to be beneficial.[12] Surprisingly, when we utilized known **1a** instead of **1b**, we were neither able to observe product formation nor conversion of **1a** under the optimized reaction conditions.

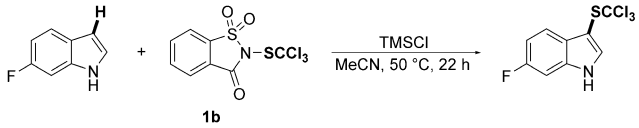
With the optimized conditions in hand, we decided to investigate the substrate scope of the trichloromethylthiolation of a variety of substituted indoles (Table 2). A broad range of indoles could be successfully trichloromethylthiolated under the

[a] J. B. Ernst, A. Rühling, B. Wibbeling, Prof. Dr. F. Glorius
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/chem.201600377.

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. Optimization of reaction conditions.[a]

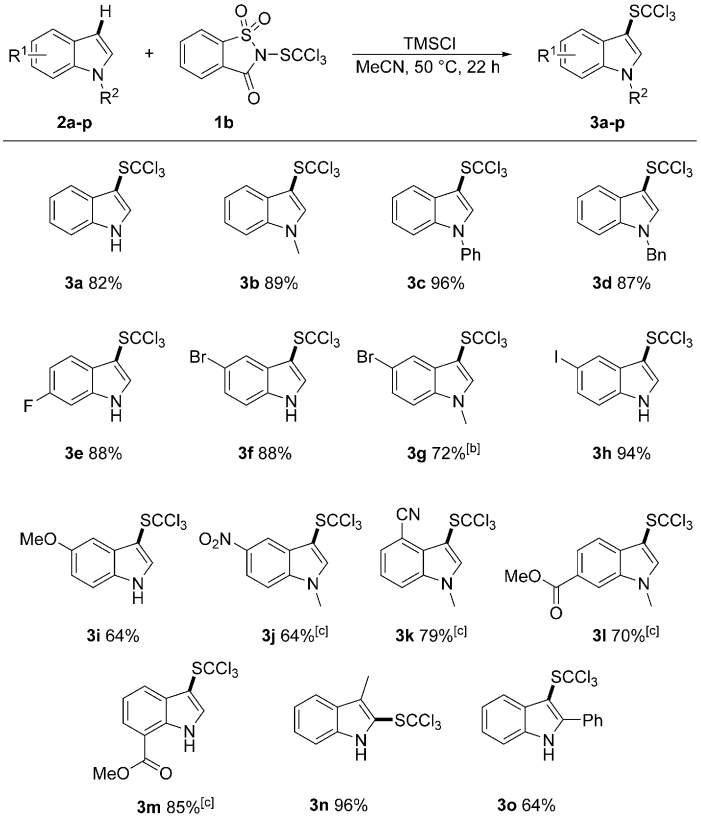


1b

Entry	Solvent	Reagent	Yield [%][b]
1	DCE	**1b**	45
2	toluene	**1b**	82
3	DMF	**1b**	0
4	DMSO	**1b**	0
5	1,4-dioxane	**1b**	27
6	MeCN	**1b**	99 (88)
7	MeCN	**1a**	0

[a] Reactions were performed on a 0.1 mmol scale with TMSCl (1.5 equiv) and reagent (1.5 equiv). [b] Yields determined by ^{19}F NMR spectroscopic analysis with 1-fluoronaphthalene as internal standard. Isolated yields in parentheses.

Table 2. Trichloromethylthiolation of indoles.[a]



[a] Reactions were performed on a 0.5 mmol scale. Isolated yields of products are reported. [b] Reaction was performed on a 2.5 mmol scale. [c] Reaction was run at 100 °C.

reaction conditions, impressively with complete C3-regioselectivity. In addition to the unprotected indole, various substituents on the nitrogen were tolerated in good to excellent yields (**3a–d**). Electron-deficient substituents on the nitrogen, for example, acetyl or *tert*-butyloxycarbonyl, did not lead to the product formation, even at elevated temperatures. Modifying the substitution pattern of the benzene ring did not affect the generality of our method. Halides (**3e–h**) as well as an ether (**3i**), as functional groups that represent a possible handle for further diversification of the structural motif, were tolerated well. Strongly electron-deficient substituents required elevated temperatures for the product formation. Indoles containing ester, nitro, and cyano substituents were isolated in good yields (**3j–m**). Finally, substituting either the 2- or 3-position of indole provided the desired trichloromethylthiolated products (**3n** and **3o**) in good to excellent yields that should allow for the trichloromethylthiolation of various naturally abundant indole alkaloids.[3e] The obtained regioselectivity was unequivocally validated by single-crystal X-ray analysis of **3b** (Figure 2).[13]

To further demonstrate the generality, we performed the trichloromethylthiolation of more sensitive pyrroles under the optimized reaction conditions (Table 3). In all cases, the reaction exclusively provided the single regioisomer shown. Pleasingly, alkyl and aryl substituents on the nitrogen were tolerated in moderate to good yields (**5a–c**) that is of high importance because N-substituted pyrroles are core structures for various bioactive compounds.[3c] Additionally, several substitution patterns at the pyrrole core provided the desired products; ketone-, ester-, and aryl-substituted pyrroles could be isolated in moderate to good yields (**5d–f**). Substituting the reactive 2- and 5-position of the pyrrole core did not inhibit the reaction, with the trichloromethylthiolation at the 3-position occurred in moderate yield (**5g**).

With the trichloromethylthiolated products in hand, we wanted to explore possible diversifications of the $SCCl_3$ group (Scheme 2). Subjecting product **3c** to meta-chloroperbenzoic acid (*m*CPBA) afforded sulfonyl **6a** in a moderate yield, giving access to previously inaccessible trichloromethylsulfonyl-substituted indole derivatives. Additionally, we were able to selectively perform the chlorine/fluorine exchange employing triethylamine trihydrofluoride as fluoride source in good yield and perfect selectivity. The trichloromethylthiolated products could, therefore, act as precursors for ^{18}F-radiolabelled compounds, which cannot be synthesized from the corresponding trifluoromethylthiolated compounds. Furthermore, dichlorofluoromethylthiolated indoles possess biological activity against acarids and insects.[14]

After determining the scope of the reaction, we wanted to explore the robustness of our developed method. Therefore, we decided to also apply an additive-based robustness screen to our reaction (Table 4).[15] Using this screen, it is possible to identify which functional groups are tolerated under the reaction conditions and by the reaction. To our delight, a broad range of different additives bearing a variety of functional groups were tolerated under the reaction conditions. In addition to halides

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

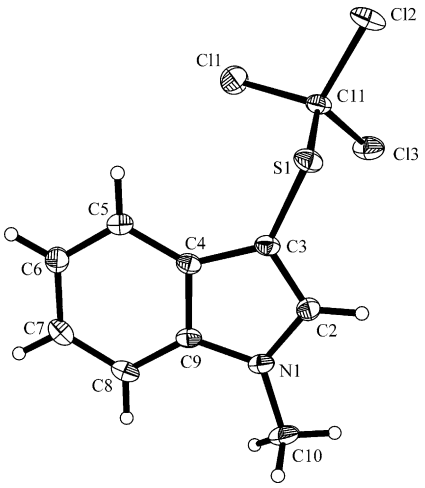
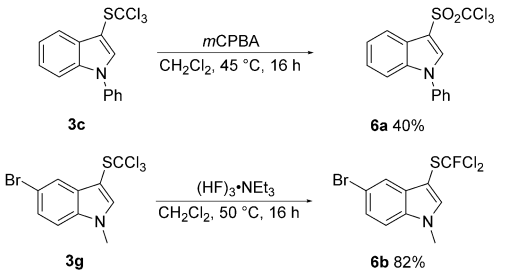
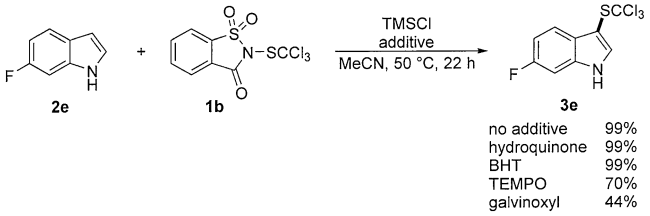


Figure 2. X-ray analysis of product **3b**.



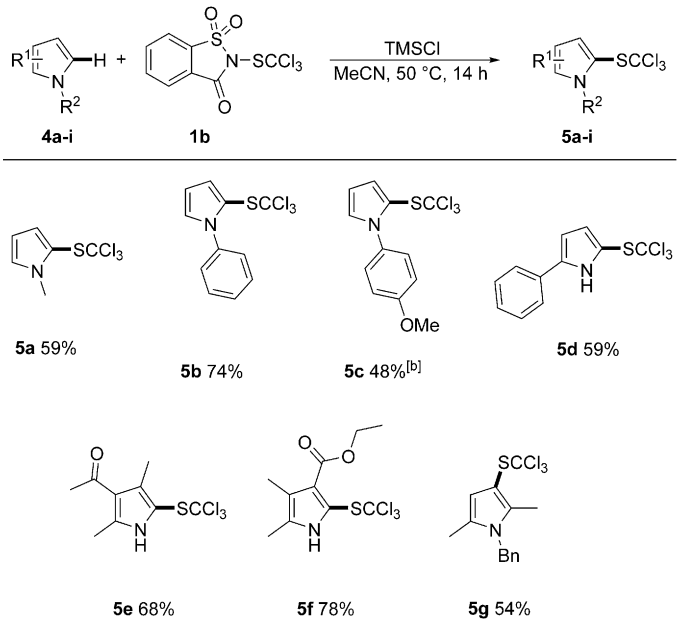
Scheme 2. Further product diversifications. Reactions were performed on a 0.2 mmol scale. Isolated yields of products are reported.



Scheme 3. Radical inhibition experiments. Reactions were performed on a 0.1 mmol scale with 0.05 mmol additive. Yields determined by ^{19}F NMR spectroscopic analysis with 1-fluoronaphthalene as internal standard.

(entries 2 and 10), nitrile (entry 4), unsaturated hydrocarbons (entries 5 and 8), ester (entry 6), and amide (entry 9) were also well tolerated. Under the reaction conditions, different heterocycle-containing additives were found to be moderately (entries 12 and 13) to excellently tolerated (entries 11 and 14–17). The stability of these additives under the reaction conditions was in a range from complete decomposition (entries 12 and 13) to excellent stability (entries 14–17). Additives with a low tolerance are compounds containing nucleophilic functional groups (entries 3, 7, and 9). This is due to side reactions with the electrophilic reagent **1b** leading to a decreased product yield and a high decomposition of the additive. However, it is important to note that none of the applied additives inhibits the reaction completely or affects the regioselectivity. These results imply that the reaction is very robust against a variety of functional groups and therefore, combined with the knowledge about the substrate scope, could find applications in the trichloromethylthiolation of complex indole- and pyrrole-based target molecules.

Table 3. Trichloromethylthiolation of pyrroles.[a]

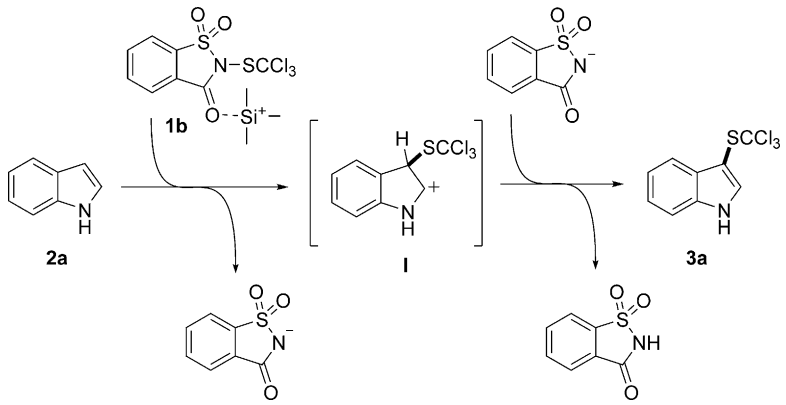


[a] Reactions were performed on a 0.5 mmol scale. Isolated yields of products are reported. [b] Reaction was performed on a 0.3 mmol scale.

To gain insight into the reaction mechanism, we carried out a number of studies. Specifically we wanted to elucidate whether a radical process was occurring. Therefore, we performed the reaction in the presence of different radical inhibitors and free radicals, and analyzed the reaction regarding yield and possible radical coupling products. With the radical inhibitors, hydroquinone and 2,4-di-*tert*-butyl-4-methylphenol (BHT), neither a significant depletion in the yield nor the regioselectivity of the reaction was observed. In the case of the free radicals 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and galvinoxyl, diminished yields were observed though no radical coupling products could be detected. These observations and the observed C3-regioselectivity, indicate that the reaction mechanism is likely not to be radical in nature (Scheme 3).

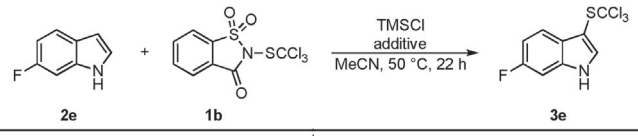
According to the results of the radical inhibition experiments, the electrophilic nature of **1b**, and the fact that electron-deficient substrates require elevated temperatures, we propose the following mechanism, which follows an electrophilic aromatic substitution pathway (Scheme 4). Attack of the enamine moiety of indole **2a** onto the reagent **1b**, followed by deprotonation of the formed Wheland intermediate **I** by saccharinide results in the desired product

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

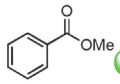
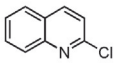


Scheme 4. Proposed mechanism for the trichloromethylthiolation of indoles.

Table 4. Robustness screen for the trichloromethylthiolation of 6-fluoroindole.[a]



2e 1b 3e

Entry		Yield of 3e %[b]	Additive remaining %[c]
1	none	99	
2		92	>95
3		28	7
4		74	79
5		89	79
6		91	80
7		66	10
8		94	82
9		95	>95
10		94	>95
11		75	42
12		66	<5
13		64	<5
14		85	>95
15		78	89
16		78	>95
17		99	>95

[a] Reactions were performed on a 0.1 mmol scale with additive (0.1 mmol). [b] Yields determined by ^{19}F NMR spectroscopic analysis with 1-fluoronaphthalene as internal standard. [c] Additive consumption determined by GC-FID analysis.

3a and saccharine as side product, which could be observed in the reaction mixture. In this mechanism, it is likely that trimethylsilyl chloride acts as an activator by coordination to the carbonyl oxygen atom of the reagent **1b** that results in an increased electrophilicity of **1b**, compensating the reduced electrophilicity especially of indoles containing electron-withdrawing substituents. This behavior is in accordance to the literature for the application of *N*-trifluoromethylthiosaccharin as an electrophilic trifluoromethylthiolating reagent.[11b]

In conclusion, we have developed the first trichloromethylthiolation of indoles and pyrroles giving access to two new classes of potentially bioactive compounds. The method exhibits an outstanding level of regioselectivity, generally C3-selective for indoles and C2-selective for pyrroles, and the robustness screen showed a high tolerance towards many different functional groups. Furthermore, it is a mild and operationally simple method, which can also be carried out on unprotected N-heteroarenes.

Experimental Section

Unless otherwise noted, N-heterocycle (if solid, 0.5 mmol, 1.0 equiv) and $SCCl_3$-reagent **1b** (249 mg, 0.75 mmol, 1.5 equiv) were added to a flame-dried Schlenk-tube. MeCN (2.5 mL), TMSCl (95 μL, 0.75 mmol, 1.5 equiv) and N-heterocycle (if liquid, 0.5 mmol, 1.0 equiv) were added and the reaction mixture was stirred for 14–22 h at the given temperature. The reaction mixture was allowed to cool down to room temperature and adsorbed on silica. The desired product was obtained after purification by silica-gel column chromatography.

Acknowledgements

Generous financial support by the Fonds der Chemischen Industrie (J.B.E.) and the Deutsche Forschungsgemeinschaft (Leibniz Award and SFB 858) are gratefully acknowledged. We thank Dr. L. Candish, M. Fleige, R. Honeker, D. Janssen-Müller, A. Lerchen, and L. Rakers for fruitful discussions.

Keywords: bioactive compounds · electrophilic substitution · heterocycles · organic chemistry · trichloromethylthiolation

[1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.
[2] a) L. D. Quin, J. A. Tyrell, *Fundamentals of Heterocyclic Chemistry*, Wiley, Hoboken, **2010**; b) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620; c) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442;

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

d) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265; e) K. Higuchi, T. Kawasaki, *Nat. Prod. Rep.* **2007**, *24*, 843; f) I. S. Young, P. D. Thornton, A. Thompson, *Nat. Prod. Rep.* **2010**, *27*, 1801; g) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma, *RSC Adv.* **2015**, *5*, 15233.

[3] For selected references on trifluoromethylation of indoles: a) M. Wiehn, E. Vinogradova, A. Togni, *J. Fluorine Chem.* **2010**, *131*, 951; b) R. Shimizu, H. Egami, T. Nagi, J. Chae, Y. Hamashima, M. Sodeoka, *Tetrahedron Lett.* **2010**, *51*, 5947; c) X. Mu, S. Chen, X. Zhen, G. Liu, *Chem. Eur. J.* **2011**, *17*, 6039; d) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298; e) R. Rey-Rodriguez, P. Retailleau, P. Bonnet, I. Gillaizeau, *Chem. Eur. J.* **2015**, *21*, 3572.

[4] For reviews on electrophilic trifluoromethylthiolation: a) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415; b) X. Shao, C. Xu, L. Lu, Q. Shen, *Acc. Chem. Res.* **2015**, *48*, 1227; c) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731.

[5] A. Hass, V. Hellwig, *Chem. Ber.* **1976**, *109*, 2475.

[6] A. Haas, U. Niemann, *J. Fluorine Chem.* **1978**, *11*, 509.

[7] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207.

[8] G. Sosnovsky, *Chem. Rev.* **1958**, *58*, 509.

[9] A. R. Kittleson, *Science* **1952**, *115*, 84.

[10] G. Sosnovsky, *J. Chem. Soc.* **1956**, 3139.

[11] For references employing electrophlic reagents in the trifluoromethylthiolation of N-heterocycles: a) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650; *Angew. Chem.* **2014**, *126*, 1676; b) C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316; *Angew. Chem.* **2014**, *126*, 9470; c) Q. Wang, Z. Qi, F. Xie, X. Li, *Adv. Synth. Catal.* **2015**, *357*, 355; d) R. Honeker, J. B. Ernst, F. Glorius, *Chem. Eur. J.* **2015**, *21*, 8047; e) A. Ferry, T. Billard, E. Bacqué, B. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160; f) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782; g) B. Ma, X. Shao, Q. Shen, *J. Fluorine Chem.* **2015**, *171*, 73; h) S. Alazet, T. Billard, *Synlett* **2015**, 76; i) Z. Huang, Y.-D. Yang, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 1094; j) X. Shao, C. Xu, L. Lu, Q. Shen, *J. Org. Chem.* **2015**, *80*, 3012; k) L. Jiang, J. Qian, W. Yi, G. Lu, C. Cai, W. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14965; *Angew. Chem.* **2015**, *127*, 15178.

[12] No product formation could be observed in the absence of TMSCl for electron-deficient indoles at 50 °C and 100 °C.

[13] CCDC 1438516 (**3b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[14] For references on bioactive dichlorofluoromethylthiolated indoles: a) H. Hotta, S. Kawada, A. Masui, T. Watabe, S. Kodama (Nippon Kayaku Co., Ltd.), JP 06092935, **1994**; b) T. Tanabe, H. Hotta, T. Totani, K. Hosoda (Nippon Kayaku Co., Ltd.), JP 2003146809, **2003**.

[15] a) K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597; b) K. D. Collins, F. Glorius, *Tetrahedron* **2013**, *69*, 7817; c) K. D. Collins, A. Rühling, F. Glorius, *Nat. Protoc.* **2014**, *9*, 1348; d) K. D. Collins, A. Rühling, F. Lied, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3800; e) K. D. Collins, F. Glorius, *Acc. Chem. Res.* **2015**, *48*, 619.

Received: January 27, 2016
Published online on February 16, 2016

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim