ChemPubSoc Europe
DOI: 10.1002/chem.201503524
CHEMISTRY
A European Journal
Communication

Synthetic Methods |Hot Paper|

Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper

Christian Matheis, Victoria Wagner, and Lukas J. Goossen*[a]

Abstract: Aromatic and heteroaromatic diazonium salts were efficiently converted into the corresponding trifluoromethylthio- or selenoethers by reaction with Me_4NSCF_3 or Me_4NSeCF_3, respectively, in the presence of catalytic amounts of copper thiocyanate. These Sandmeyer-type reactions proceed within one hour at room temperature, are applicable to a wide range of functionalized molecules, and can optionally be combined with the diazotizations into one-pot protocols.

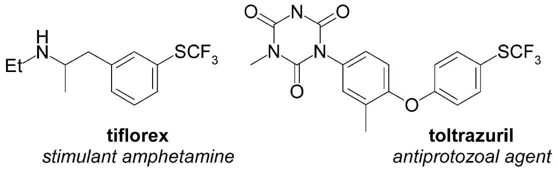


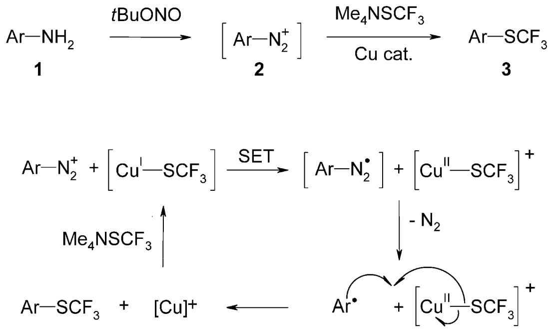
Figure 1. Biologically active trifluoromethyl thioethers.

Fluorine-containing residues are key functionalities in bioactive compounds and present in up to 40% of currently marketed agrochemicals and 25% of pharmaceuticals.[1] Thus, the systematic introduction of fluorinated groups, so called “fluorine scans”, has become standard procedure in drug discovery. Hence, new methods for the late-stage introduction of fluorinated moieties into functionalized molecules are highly sought-after. In the last decade, a particular focus was set on CF_3 groups, and various powerful trifluoromethylation methods have been developed.[2] The attention has recently shifted towards trifluoromethyl thioethers, because the SCF_3 group induces an even higher lipophilicity (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3) and membrane permeability.[3] Trifluoromethylthio groups are key functionalities in several pharmaceutical and agrochemical products, including tiflorex and toltrazuril (Figure 1).

Traditional strategies for the introduction of SCF_3 groups include the halogen/fluorine exchange of trihalomethyl thioethers with HF or SbF_3,[4] and the trifluoromethylation of sulfur-containing precursors, for example, thiols, disulfides, and thiocyanates.[5,6] However, these methods are limited by substrate availability and/or functional group tolerance. Contemporary trifluoromethylthiolation reactions are based on electrophilic,[7] nucleophilic,[8] radical,[9] or oxidative processes,[10] usually starting from arylboronic acids or aryl halides, or proceed via C–H activation.[9,11]

Sandmeyer-type trifluoromethylthiolations are advantageous alternatives, because they start from inexpensive and broadly available anilines, use inexpensive copper mediators, and are usually orthogonal to halide-based cross-coupling reactions.

In the course of our research on Sandmeyer-type fluoroalkylations,[12] we have developed a trifluoromethyl thioether synthesis via Sandmeyer thiocyanation followed by Langlois-type nucleophilic CN/CF_3 substitution.[13] Due to its low cost, this two-step approach, in which the sulfur and the CF_3 groups originate from different reagents, is advantageous particularly for large-scale applications. However, on laboratory scale, a Sandmeyer-type trifluoromethylthiolation based on a preformed SCF_3 reagent would be a welcome alternative (Scheme 1). In this context, Me_4NSCF_3 appeared to be the reagent of choice, because it is readily available on preparative scales from tetramethylammonium fluoride, elemental sulfur, and $TMSCF_3$, and can easily be stored and handled. It was first synthesized by Röschenthaler[14] and Yagupolskii and coworker[15] and has successfully been employed in trifluorome-



Scheme 1. Sandmeyer trifluoromethylthiolation of aromatic amines.

---

[a] C. Matheis, V. Wagner, Prof. Dr. L. J. Goossen
FB Chemie-Organische Chemie
Technische Universität Kaiserslautern
Erwin-Schrödinger-Strasse, Geb. 54
67663 Kaiserslautern (Germany)
E-mail: goossen@chemie.uni-kl.de
Homepage: http://www.chemie.uni-kl.de/goossen

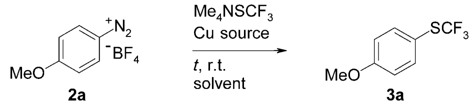
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503524.

thylthiolations of vinyl iodides,[16] boronic acids,[10c] and aryl halides[8b,17] catalyzed by Cu, Ni, and Pd complexes.

The feasibility of such a Sandmeyer-type trifluoromethylation with catalytic amounts of copper was unclear, since Clark and co-workers had found that the reaction of arenediazonium salts with stoichiometric amounts of $CuSCF_3$ gives only moderate yields and has a narrow substrate spectrum.[18] Moreover, our two-step trifluoromethylthiolation had been shown to proceed via Cu−SCN rather than $Cu-SCF_3$ intermediates.

To probe the viability of the approach sketched in Scheme 1, we investigated the reaction of 4-methoxybenzenediazonium tetrafluoroborate (**2a**) with Me_4NSCF_3 in the presence of several copper salts under various conditions (Table 1).[12a] In the presence of a stoichiometric amount of CuSCN, a promising yield of 64% was obtained at room temperature in acetonitrile (Table 1, entry 1). Other solvents were less effective (Table 1, entries 2 and 3). Of the copper sources tested, CuSCN gave the best yields (entries 4–6). Further investigations revealed that at least 1.8 equivalents of Me_4NSCF_3 are required to push the reaction to completion (Table 1, entries 7–8). The reaction gave near-quantitative yields within one hour at room temperature even when reducing the amount of CuSCN to 10 mol% (Table 1, entries 9–11). This is remarkable, because most Sandmeyer protocols call for much higher copper loadings. Control experiments confirmed that the reaction does not proceed without copper (Table 1, entry 12).

Table 1. Optimization of the reaction conditions.[a]



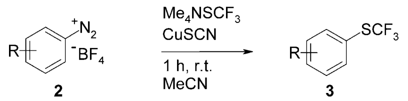
Entry	Solvent	Cu source	Me_4NSCF_3 [equiv]	Yield **4** [%]
1	MeCN	CuSCN	1.2	64
2	DMF	"	"	22
3	THF	"	"	0
4	MeCN	Cu	"	54
5	"	CuOAc	"	56
6	"	CuI	"	18
7	"	CuSCN	1.5	85
8	"	"	1.8	99
9[b]	"	"	"	99
10[c]	"	"	"	72
11[d]	"	"	"	99
12	"	–	"	0
13[e]	"	CuSCN	"	95

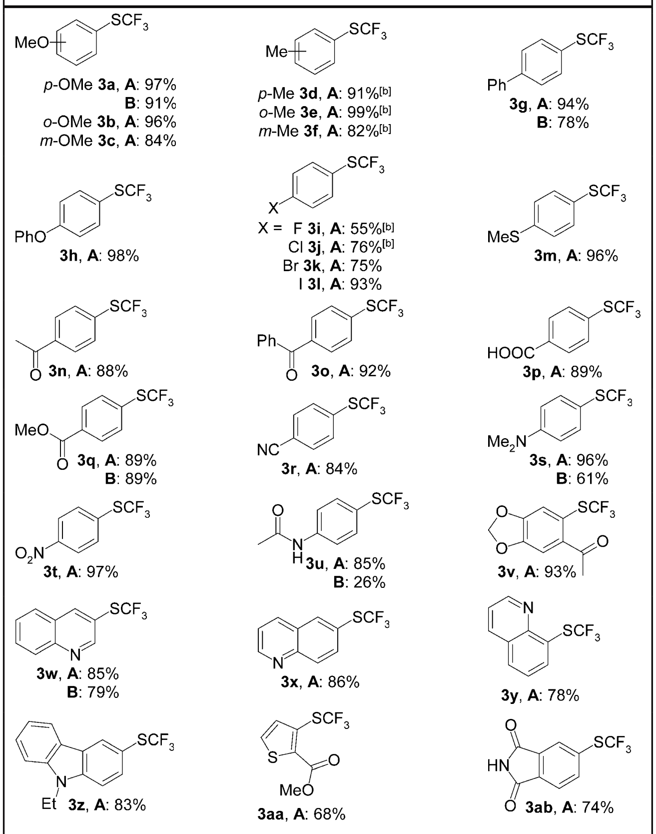
[a] Reaction conditions: dropwise addition of 0.5 mmol diazonium salt **2a** in 1 mL solvent to Me_4NSCF_3 and 0.5 mmol copper source in 1 mL solvent, 15 h at room temperature. Yields were determined by ^{19}F NMR analysis using trifluoroethanol as an internal standard. [b] Cu source (10 mol%). [c] Cu source (5 mol%). [d] 1 h reaction time. [e] **2a** was generated in situ.

The diazonium salt can optionally be generated in situ from the corresponding anilines. When 4-methoxyaniline (**1a**) was treated with *p*-toluenesulfonic acid and *tert*-butyl nitrite; and the resulting mixture was added to a solution of 10 mol% CuSCN and 1.8 equivalents of Me_4NSCF_3 in acetonitrile, **3a** was formed in 95% yield (Table 1, entry 13).

Having thus identified an effective and convenient protocol for a Sandmeyer-type trifluoromethylthiolation, we next investigated its scope. Diversely substituted aryl trifluoromethyl thioethers were synthesized in high yields from the corresponding arenediazonium tetrafluoroborates (Table 2, Method A). Both electron-withdrawing and electron-donating substrates gave similarly high yields. Various common functionalities are tolerated, such as ether, ester, thio, keto, cyano, amino, nitro, amido, and acetal groups. The reaction is applicable even to halides and carboxylic acids, which opens up opportunities for further derivatization. Heteroarenediazonium salts, including quinoline, carbazole, thiophene, and phthalimide derivatives, were also successfully converted. The scalability of this reaction variant was demonstrated by the synthesis of **3a** in 93% on a gram scale.

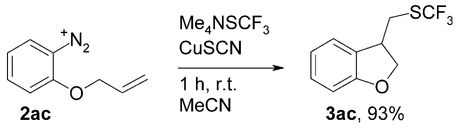
Table 2. Scope of the Sandmeyer trifluoromethylthiolation.[a]




p-OMe **3a**, **A**: 97%
B: 91%
o-OMe **3b**, **A**: 96%
m-OMe **3c**, **A**: 84%
p-Me **3d**, **A**: 91%[b]
o-Me **3e**, **A**: 99%[b]
m-Me **3f**, **A**: 82%[b]
3g, **A**: 94%
B: 78%
3h, **A**: 98%
X = F **3i**, **A**: 55%[b]
Cl **3j**, **A**: 76%[b]
Br **3k**, **A**: 75%
I **3l**, **A**: 93%
3m, **A**: 96%
3n, **A**: 88%
3o, **A**: 92%
3p, **A**: 89%
3q, **A**: 89%
B: 89%
3r, **A**: 84%
3s, **A**: 96%
B: 61%
3t, **A**: 97%
3u, **A**: 85%
B: 26%
3v, **A**: 93%
3w, **A**: 85%
B: 79%
3x, **A**: 86%
3y, **A**: 78%
3z, **A**: 83%
3aa, **A**: 68%
3ab, **A**: 74%

[a] Method A: dropwise addition of 1.0 mmol diazonium salt (**2**) in 2 mL MeCN to 1.8 mmol Me_4NSCF_3 and 0.1 mmol CuSCN in 2 mL MeCN, 1 h at RT. Method B: **2** was generated in situ from 1.0 mmol aromatic amine, 1.0 mmol *tert*-butyl nitrite and 1.5 mmol *p*-TSA in 2 mL MeCN. Yields of isolated products. [b] Yields were determined by ^{19}F NMR analysis using trifluoroethanol as standard.

The scope of the one-pot diazotization/trifluoromethylthiolation protocol was also investigated with functionalized aromatic and heteroaromatic amines (Table 2, Method B). It was found to be broadly applicable, but the yields were somewhat lower than for the two-step process. A series of experiments was performed to shed some light on the reaction mechanism. The addition of radical quenchers, such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone, suppressed the reaction, and with 2-(allyloxy)diazonium tetrafluoroborate (**2 ac**) as the substrate, the cyclized product **3 ac** was formed exclusively (Scheme 2). A signal at $\delta = -28.0$ ppm in the ^{19}F NMR spectrum of a mixture of Me_4NSCF_3 and CuSCN suggests the formation of $CuSCF_3$.[14] Together, these findings support a classical Sandmeyer-type single-electron transfer (SET) mechanism involving aryl radicals (Scheme 1).



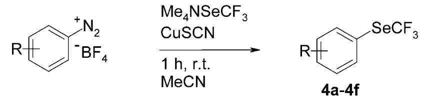
Scheme 2. Radical-capture experiment.

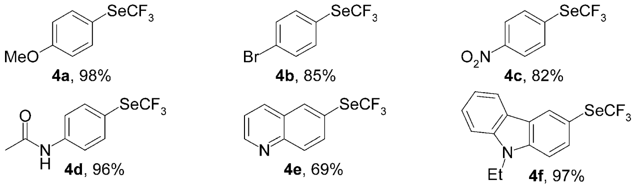
Next, we probed whether this reaction concept can also be utilized for the synthesis of trifluoromethyl selenoethers. The $SeCF_3$ moiety imparts similar properties to the SCF_3 group,[19] but its introduction can be cumbersome.[6d,20] Schoenebeck and co-workers recently disclosed an effective Pd-catalyzed trifluoromethylselenolation, which is, however, based on expensive aryl iodides.[19a]

We were pleased to find that by simply replacing Me_4NSCF_3 with Me_4NSeCF_3, our Sandmeyer protocol can be turned into an efficient synthesis of trifluoromethyl selenoethers. The scope of this reaction variant is demonstrated by the examples given in Table 3, which include diversely functionalized arenes and heteroarenes.

In conclusion, the Sandmeyer-type processes reported herein open up convenient entries to trifluoromethyl thio- and selenoethers from easily available aromatic amines. The key advantages of this set of methods are their mild reaction conditions (neutral, 1 h at room temperature), the use of an inexpensive copper catalyst, and the exceptional functional group tolerance. As a result, they are well suited for the late-stage introduction of trifluoromethylthio or -seleno groups into drug-like molecules.

Table 3. Scope of the Sandmeyer trifluoromethylselenolation.[a]





[a] Reaction conditions: 1.0 mmol diazonium salt in 2 mL MeCN was added dropwise to a mixture of 1.8 mmol Me_4NSeCF_3 and 0.1 mmol CuSCN in 2 mL MeCN. The reaction mixture was stirred for 1 h at room temperature. Yields of isolated products are given.

Experimental Section

An oven-dried crimp-cap vessel (20 mL) with stirrer bar was charged with CuSCN (12 mg, 0.10 mmol), Me_4NSCF_3 (315 mg, 1.80 mmol), and MeCN (2 mL). Then, the diazonium salt **2 a**–**ac** (1 mmol) in MeCN (2 mL) was added dropwise, and the reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with diethyl ether (20 mL), then washed with water (2×10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the aryl trifluoromethyl thioethers **3 a**–**ac**. The yields of particularly volatile compounds were determined by ^{19}F NMR spectroscopy, and their identity by MS.

Acknowledgements

We thank Kévin Jouvin for helpful discussions and Nanokat for financial support.

Keywords: copper · fluorine · fluoroalkylthiolation · Sandmeyer reaction · synthetic methods

[1] a) *Fluorine in Medicinal Chemistry and Chemical Biology* (Eds.: I. Ojima), Wiley, Chichester, **2009**; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; c) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369.

[2] a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; d) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679–6687; e) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; *Angew. Chem.* **2013**, *125*, 8372–8423; f) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730; g) C. Alonso, E. Martínez de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847–1935.

[3] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207–1216.

[4] a) E. A. Nodiff, S. Lipschutz, P. N. Craig, M. Gorden, *J. Org. Chem.* **1960**, *25*, 60–65; b) A. E. Feiring, *J. Org. Chem.* **1979**, *44*, 2907–2910.

[5] C. Wakselman, M. Tordeux, *J. Org. Chem.* **1985**, *50*, 4047–4051.

[6] a) C. Wakselman, M. Tordeux, J.-L. Clavel, B. Langlois, *J. Chem. Soc. Chem. Commun.* **1991**, 993–994; b) B. Quiclet-Sire, R. N. Saicic, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 9057–9058; c) T. Billard, B. R. Langlois, *Tetrahedron Lett.* **1996**, *37*, 6865–6868; d) T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65–68; e) N. Roques, *J. Fluorine Chem.* **2001**, *107*, 311–314; f) G. Blond, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2001**, *42*, 2473–2475; g) C. Pooput, M. Medebielle, W. R. Dolbier, *Org. Lett.* **2004**, *6*, 301–303; h) C. Pooput, W. R. Dolbier, M. Médebielle, *J. Org. Chem.* **2006**, *71*, 3564–3568; i) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, *46*, 754–757; *Angew. Chem.* **2007**, *119*, 768–771; j) A. Harsányi, É. Dorkó, Á. Csapó, T. Bakó, C. Peltz, J. Rábai, *J. Fluorine Chem.* **2011**, *132*, 1241–1246; k) S. Potash, S. Rozen, *J. Fluorine Chem.* **2014**, *168*, 173–176.

[7] a) F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382–10385; *Angew. Chem.* **2012**, *124*, 10528–10531; b) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460; *Angew. Chem.* **2013**, *125*, 3541–3544; c) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782–8785; d) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650–1653; *Angew. Chem.* **2014**, *126*, 1676–1679; e) C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316–9320; *Angew. Chem.* **2014**, *126*, 9470–9474.

[8] a) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312–7314; *Angew. Chem.* **2011**, *123*, 7450–7452; b) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185; c) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548–1552; *Angew. Chem.* **2013**, *125*, 1588–1592.

[9] L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237–18240.

[10] a) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495; *Angew. Chem.* **2012**, *124*, 2542–2545; b) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454–12457; c) C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756–1758; d) S.-Q. Zhu, X.-H. Xu, F.-L. Qing, *Eur. J. Org. Chem.* **2014**, 4453–4456.

[11] a) C. Xu, Q. Shen, *Org. Lett.* **2014**, *16*, 2046–2049; b) W. Yin, Z. Wang, Y. Huang, *Adv. Synth. Catal.* **2014**, *356*, 2998–3006; c) H.-Y. Xiong, T. Besset, D. Cahard, X. Pannecoucke, *J. Org. Chem.* **2015**, *80*, 4204–4212; d) S. Guo, X. Zhang, P. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4065–4069; *Angew. Chem.* **2015**, *127*, 4137–4141; e) H. Wu, Z. Xiao, J. Wu, Y. Guo, J.-C. Xiao, C. Liu, Q.-Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 4070–4074; *Angew. Chem.* **2015**, *127*, 4142–4146.

[12] a) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 7972–7975; *Angew. Chem.* **2013**, *125*, 8130–8133; b) B. Bayarmagnai, C. Matheis, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343–2348; c) C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984–5987.

[13] a) G. Danoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312–1316; b) C. Matheis, M. Wang, T. Krause, L. Goossen, *Synlett* **2015**, *26*, 1628–1632; c) B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753–5756; *Angew. Chem.* **2015**, *127*, 5845–5848; d) K. Jouvin, C. Matheis, L. J. Goossen, *Chem. Eur. J.* **2015**, *21*, 14324–14327.

[14] P. Kirsch, G. V. Roeschenthaler, B. Bissky, A. Kolomeitsev (Merck GmbH), DE-A1 10254597, **2003**.

[15] W. Tyrra, D. Naumann, B. Hoge, Y. L. Yagupolskii, *J. Fluorine Chem.* **2003**, *119*, 101–107.

[16] M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. Eur. J.* **2013**, *19*, 14043–14046.

[17] a) G. Yin, I. Kalvet, U. Englert, F. Schoenebeck, *J. Am. Chem. Soc.* **2015**, *137*, 4164–4172; b) G. Yin, I. Kalvet, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 6809–6813; *Angew. Chem.* **2015**, *127*, 6913–6917.

[18] D. J. Adams, A. Goddard, J. H. Clark, D. J. Macquarrie, *Chem. Commun.* **2000**, 987–988.

[19] a) M. Aufiero, T. Sperger, A. S.-K. Tsang, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 10322–10326; *Angew. Chem.* **2015**, *127*, 10462–10466; b) A. Leo, P. Y. C. Jow, C. Silipo, C. Hansch, *J. Med. Chem.* **1975**, *18*, 865–868; c) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[20] a) T. Billard, N. Roques, B. R. Langlois, *J. Org. Chem.* **1999**, *64*, 3813–3820; b) N. Kondratenko, A. Kolomeytsev, V. Popov, L. Yagupolskii, *Synthesis* **1985**, 667–669; c) C. Chen, L. Ouyang, Q. Lin, Y. Liu, C. Hou, Y. Yuan, Z. Weng, *Chem. Eur. J.* **2014**, *20*, 657–661; d) C. Chen, C. Hou, Y. Wang, T. S. A. Hor, Z. Weng, *Org. Lett.* **2014**, *16*, 524–527; e) S. Potash, S. Rozen, *J. Org. Chem.* **2014**, *79*, 11205–11208.

Received: September 3, 2015