Synthesis of Billard-Langlois Reagents and their Derivatives by Copper-Catalyzed N - Trifluoromethylthiolation of Arylamines with a Trifluoromethanesulfonyl Hypervalent Iodonium Yli...

ARTICLE *in* ASIAN JOURNAL OF ORGANIC CHEMISTRY · MARCH 2015

Impact Factor: 3.32 · DOI: 10.1002/ajoc.201500067

4 AUTHORS, INCLUDING:

Zhongyan Huang

Nagoya Institute of Technology

8 PUBLICATIONS **18** CITATIONS

SEE PROFILE

Norio Shibata

Nagoya Institute of Technology

408 PUBLICATIONS **7,991** CITATIONS

SEE PROFILE

ACES

DOI: 10.1002/ajoc.201500067

ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

Synthetic Methods

Synthesis of Billard–Langlois Reagents and their Derivatives by Copper-Catalyzed *N*-Trifluoromethylthiolation of Arylamines with a Trifluoromethanesulfonyl Hypervalent Iodonium Ylide

Zhongyan Huang, Yu-Dong Yang, Etsuko Tokunaga, and Norio Shibata*[a]

Abstract: A one-step synthesis of Billard–Langlois reagents and their derivatives, trifluoromethanesulfenamides, is reported. A series of primary and secondly arylamines were directly N–H trifluoromethylthiolated by a trifluoromethanesulfonyl hypervalent iodonium ylide under mild, copper-catalyzed reaction conditions in high yields. Heteroaromatic amines were also successfully trifluoromethylthiolated under the same reaction conditions. An arylamine with an NH-pyrrole moiety was chemoselectively N-trifluoromethylthiolated.

As is generally recognized in modern pharmaceutical research, fluoro-functionalization such as fluorination and trifluoromethylation of organic compounds is one of the most rational strategies designing biologically active molecules with rather high probability.[1] In this context, the use of fluoro-functionalization reagents and their reactions are key for the successful synthesis of target molecules.[2] Among them, the development of trifluoromethylthiolation has now come into full bloom in this research area in recent years.[2e,g] The trifluoromethylthio (trifluoromethanesulfenyl, or trifluoromethanesulfanyl) group (SCF_3) is of great interest because of its remarkable hydrophobicity (Hansch parameter $\pi_R = 1.44$), and electronegativity, which permeates cell membranes well.[1a]

Several methods for the introduction of this group into organic substrates have been developed, and the use of gaseous CF_3SCl, CF_3SH, and CF_3SSCF_3 served as synthetic approaches in the early days.[3] Due to the toxic nature of these classical reagents, shelf-stable and easy-to-handle reagents have emerged as proposed alternatives,[4,5] in particular, electrophilic trifluoromethylthiolation reagents[5] in recent years (Figure 1) such as *N*-(trifluoromethylthio)phthalimide **1** by Munavalli et al.,[5a] trifluoromethanesulfenamides **2** by Billard and Langlois,[5b,c] *O*-trifluoromethylthio-ether **3** by Lu, Shen, and co-workers[5d,e,i] *N*-(trifluoromethylthio)saccharin **4** by Shen and co-workers,[5j] and a few more examples of $NSCF_3$-type reagents.[5k–m] In 2013, we developed a reagent, a trifluoromethanesulfonyl hypervalent iodonium ylide **5**, for the trifluoromethylthiolation reaction of enamines, indoles, and β-keto esters.[6a] Reagent **5** is easily synthesized from ubiquitous trifluoromethanesulfonyl (SO_2CF_3) compounds and is now commercially available as the Shibata reagent II.[6b] The utility of reagent **5** was expanded to the functionalization of pyrroles,[6c] allylsilanes, and silyl enol ethers[6d] in recent years.

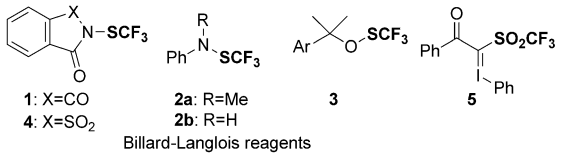
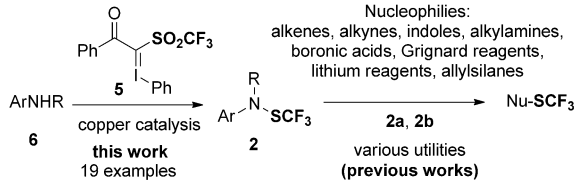


Figure 1. Shelf-stable reagents for electrophilic trifluoromethylthiolation.

Although these reagents are equally useful for the trifluoromethylthiolation of a wide variety of nucleophiles, Billard–Langlois reagents,[5b,c,7] trifluoromethanesulfenamides ($ArNRSCF_3$ **2a** and **2b**) are a very attractive subset among these. Many kinds of functionalization have been achieved with **2a** and **2b** including of alkenes, alkynes, indoles, alkylamines, boronic acids, Grignard reagents, lithium reagents, allylsilanes, and more.[7] The Billard–Langlois reagents **2a** and **2b** are accessed in steps starting from diethylaminosulfur trifluoride, the Ruppert-Prakash reagent (CF_3SiMe_3), and arylamines.[8,9] Because of the wide utility of **2a** and **2b** for trifluoromethylthiolation and the potential bioactivity of general aryl $NSCF_3$ compounds **2**, which is directed by the high Hansch's hydrophobicity parameter of $NSCF_3$ ($\pi_R = 1.50$),[7h,10] we herein explored the one-step synthesis of Billard–Langlois reagents and their derivatives **2** by trifluoromethylthiolation of arylamines with trifluoromethanesulfonyl hypervalent iodonium ylide **5** under copper catalysis (Scheme 1). Heteroaromatic amines are also successfully tri-



Scheme 1. Trifluoromethanesulfenamides **2**: Synthesis of **2** with trifluoromethanesulfonyl hypervalent iodonium ylide **5** (this work) and the utility of **2a** and **2b** for various trifluoromethylthiolation reactions (previous works).

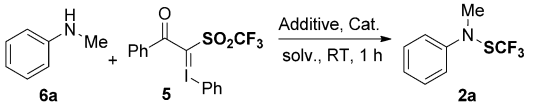
[a] *Z. Huang, Dr. Y.-D. Yang, E. Tokunaga, N. Shibata*
Department of Nanopharmaceutical Sciences
Nagoya Institute of Technology
Gokiso, Showa, Nagoya, 466-8555 (Japan)
E-mail: nozshiba@nitech.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ajoc.201500067.

fluoromethylthiolated under the same reaction conditions. Interestingly, an arylamine with an NH-pyrrole moiety was chemoselectively N-trifluoromethylthiolated.

The direct preparation of Billard–Langlois reagent **2a** from *N*-methyl aniline (**6a**) using **5** was first optimized (Table 1). The

Table 1. Screening for optimal conditions for the trifluoromethylation of amine **6a** with reagent **5**.[a]



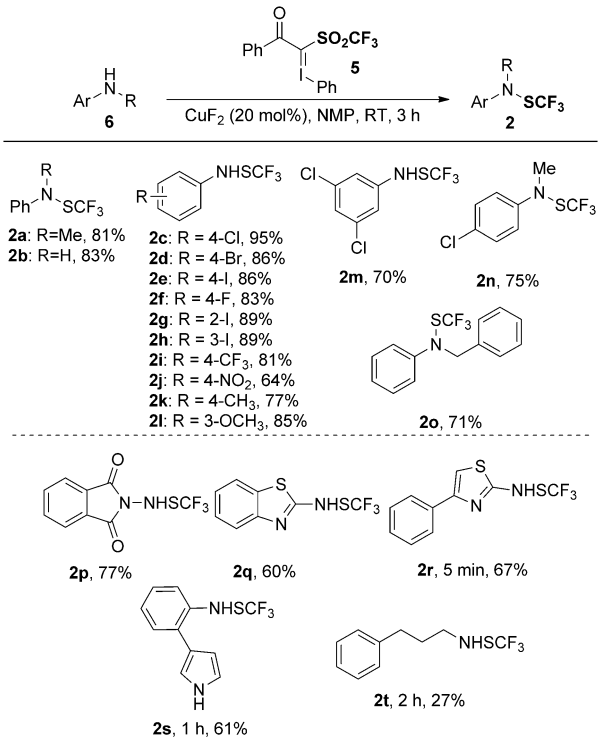
6a **5** **2a**

Entry	Equiv. of **5**	Cat. (mol%)	Additive	Solvent (time)	Yield [%][b]
1	2	CuCl (20)	–	1,4-dioxane	33
2	2	CuCl (20)	–	THF	19
3	2	CuCl (20)	–	DMF	7
4	2	CuCl (10)	–	1,4-dioxane	8
5	2	CuCl (50)	–	1,4-dioxane	31
6	2	CuCl (20)	Et_3N (1.0 equiv)	1,4-dioxane	26
7	2	CuCl (20)	$PhNMe_2$ (0.2 equiv)	1,4-dioxane	7
8	2	CuCl (20)	AcOH (1.0 equiv)	1,4-dioxane	11
9	2	CuCl (20)	PhOH (1.0 equiv)	1,4-dioxane	0
10	2	CuCl (20)	–	THF	19
11	2	CuCl (20)	–	DMF	7
13	2	CuF_2 (20)	–	DMF	60
14	2	CuF_2 (20)	–	THF	trace
15	2	CuF_2 (20)	–	DMA	81
16	2	CuF_2 (20)	–	NMP (3 h)	90
17	1.5	CuF_2 (20)	–	NMP (3 h)	90
18	1.2	CuF_2 (20)	–	NMP (3 h)	76

[a] Reaction conditions: **6a** (0.1 mmol), **5** (0.2 mmol), and solvent (0.5 mL) under a N_2 atmosphere. [b] Yield was determined by ^{19}F NMR spectroscopy of the crude mixture with trifluorotoluene as the internal standard.

trifluoromethylthiolation of **6a** with **5** under the standard conditions described in a previous paper,[6a] CuCl (20 mol%) in 1,4-dioxane under a nitrogen atmosphere at room temperature, produced **2a** in 33% yield (entry 1). In THF or *N*,*N*-dimethylformamide (DMF), **2a** was produced in even lower yields (entries 2 and 3). A lower catalyst loading sharply decreased the yield of **2a** while higher catalyst loading did not improve the yield (entries 4 and 5). Lower yields were detected independent of whether base or acid were added (entries 6–9). Reaction catalyzed by $Cu(OAc)_2$ and CuF_2 also afforded low yields in 1,4-dioxane (entries 10 and 11). To our surprise, when the reaction was conducted in the presence of CuF_2 in DMF, product **2a** was produced in 60% yield, whereas a trace of **2a** was detected when the reaction was run in THF (entries 13 and 14). Encouraged by this result (entry 13), we changed the solvent to *N*,*N*-dimethylacetamide (DMA), which offered a high yield of 81% of **2a** (entry 15). 1-Methyl-2-pyrrolidinone (NMP) was also suitable for this transformation, producing **2a** in 90% (entry 16). The high yield of **2a** was sustained with the use of 1.5 equivalents of **5** but decreased with 1.2 equivalents of **5** (entries 17 and 18). These results indicate that the reaction proceeded successfully in NMP with CuF_2 as the catalyst at room temperature to produce an excellent yield of **2a**.

Under the optimal conditions, a broad set of arylamines **6** were very nicely trifluoromethylated with **5** in high to excellent yields independent of the electron-donating or electron-withdrawing character of the aryl group (Scheme 2, **2a**–**o**). First,



Scheme 2. Trifluoromethylthiolation of amine **6** with reagent **5**. Reaction conditions: **6** (0.2 mmol), **5** (0.3 mmol), CuF_2 (20 mol%), NMP (1.5 mL), stirred at RT. For **2q** CuF_2 (15 mol%)/CuCl (5 mol%) were used. For **2r** **5** (0.4 mmol) and CuCl (20 mol%) in 1,4-dioxane (1.5 mL) were used. For **2s** **6s** (0.2 mmol), **5** (0.4 mmol), and CuF_2 (20 mol%), in NMP (1.5 mL) were used. For **2t**: reaction conditions: **6** (0.2 mmol), **5** (0.4 mmol), MgO (0.2 mmol), CuF_2 (20 mol%), DMF (1.5 mL), stirred at RT; the yield was determined by ^{19}F NMR spectroscopy of the crude mixture with trifluorotoluene as the internal standard.

Billard–Langlois reagents **2a** and **2b** were nicely prepared by this method in 83% and 81% isolated yield, respectively. As can be seen in Scheme 2, various functional groups, including halo, nitro, methoxy, and trifluoromethyl, were well tolerated under the reaction conditions to furnish **2c**–**n**. Notably, the halo and nitro groups are valuable for further transformation. The position of the functional group at *o*, *m*, or *p* did not significantly influence the yield of **2**. N-aliphatic-substituted anilines **6n** and **6o** were also converted into the corresponding $NSCF_3$ products **2n** and **2o** in high yields. Even *N*-aminophthalimide (**6p**) was trifluoromethylthiolated under the same conditions to give **2p** in 77% yield. Heteroaromatic amines **6q** and **6r** were also suitable for this method with moderate yields of **2q** and **2r** of 60–67%. The reaction of substrate **6s**, containing two reactive NH moieties, aniline and pyrrole, led to chemoselective trifluoromethylthiolation on the aniline's amine group to provide **2s** in 61% yield. Aliphatic amine **6t** could not be transformed under the standard conditions, however, the de-

sired $NSCF_3$ product **2t** was produced in the presence of MgO (1 equiv.) and CuF_2 in DMF in 27% yield (see the details for the optimization of reaction conditions in the Supporting Information).

In summary, we have developed a copper-catalyzed trifluoromethylthiolation of arylamines with trifluoromethanesulfonyl hypervalent iodonium ylide **5**. A broad range of arylamines were transformed into the corresponding products in good to excellent yields at room temperature. Billard–Langlois reagents, **2a** and **2b** were directly prepared by this method from commerically available anilines. Other trifluoromethanesulfenarylamides **2** that were prepared are attractive not only as electrophilic trifluoromethylthiolation reagents, but also as potential bioactive fragments for drug discovery.

Experimental Section

General Procedure for the Synthesis of Arylamines

To a mixture of arylamine **6** (0.2 mmol) and reagent **5** (0.3 mmol) in NMP (1.5 mL), was added CuF_2 (0.04 mmol). The reaction was stirred at room temperature and monitored by TLC. After the reaction was complete, the reaction mixture was extracted with Et_2O, washed with water and brine, and dried over Na_2SO_4. Column chromatography on silica gel, using *n*-hexane and AcOEt as eluents, was used to purify the desired product.

Acknowledgements

This research was financially supported in part by the Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT Japan, the Advanced Catalytic Transformation (ACT-C) from the Japan Science and Technology (JST) Agency, a JSPS Grand-in-Aid Scientific Research (B) (25288045), a JSPS Grand-in-Aid for Exploratory Research (25670055), the Hoansha Foundation, and the Kobayashi International Scholarship Foundation.

Keywords: arylamines · copper · hypervalent iodine · trifluoromethanesulfenamides · trifluoromethylthiolation

[1] a) R. E. Banks, B. E. Smart, J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, **1994**; b) T. Hiyama, *Organofluorine Compounds: Chemistry and Properties*, Springer, Berlin, **2000**; c) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, Germany, **2004**; d) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, U.K., **2006**; e) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319; f) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432 – 2506.

[2] For selected reviews, see: a) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880 – 921; b) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors, F. R. Leroux, *Beilstein J. Org. Chem.* **2013**, *9*, 2476 – 2536; c) A. Tlili, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 6818 – 6819; *Angew. Chem.* **2013**, *125*, 6952 – 6954; d) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214 – 8264; *Angew. Chem.* **2013**, *125*, 8372 – 8423; e) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415 – 2428; f) W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Acena, K. Izawa, H. Liu, V. A. Soloshonok, *J. Fluorine Chem.* **2014**, *167*, 37 – 54; g) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731 – 764.

[3] a) O. Scherer, *Angew. Chem.* **1939**, *52*, 457 – 459; b) E. H. Man, D. D. Coffman, E. L. Muetterties, *J. Am. Chem. Soc.* **1959**, *81*, 3575 – 3577; c) E. A. Nodiff, S. Lipschutz, P. N. Craig, M. Gordon, *J. Org. Chem.* **1960**, *25*, 60 – 65; d) S. Andreades, J. F. Harris, Jr., W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 898 – 900; e) M. Hanack, A. Kühnle, *Tetrahedron Lett.* **1981**, *22*, 3047 – 3048; f) C. Wakselman, M. Tordeux, *J. Chem. Soc. Chem. Commun.* **1984**, 793 – 794; g) A. Kolasa, *J. Fluorine Chem.* **1987**, *36*, 29 – 40; h) V. I. Popov, A. Haas, M. Lieb, *J. Fluorine Chem.* **1990**, *47*, 131 – 136; i) V. Soloshonok, V. Kukhar, Y. Pustovit, V. Nazaretian, *Synlett* **1992**, 657 – 658; j) D. J. Adams, J. H. Clark, *J. Org. Chem.* **2000**, *65*, 1456 – 1460; k) D. J. Adams, A. Goddard, J. H. Clark, D. J. Macquarrie, *Chem. Commun.* **2000**, 987 – 988; l) J. M. Kremsner, M. Rack, C. Pilger, C. O. Kappe, *Tetrahedron Lett.* **2009**, *50*, 3665 – 3668.

[4] 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. Vivic, *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.

[5] For selected examples, see: a) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Commun.* **2000**, *30*, 2847 – 2854; b) F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382 – 10385; *Angew. Chem.* **2012**, *124*, 10528 – 10531; c) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814 – 10817; *Angew. Chem.* **2013**, *125*, 11014 – 11017; d) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457 – 3460; *Angew. Chem.* **2013**, *125*, 3541 – 3544; e) X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 12860 – 12864; *Angew. Chem.* **2013**, *125*, 13098 – 13102; f) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856 – 12859; *Angew. Chem.* **2013**, *125*, 13093 – 13097; g) M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. Eur. J.* **2013**, *19*, 14043 – 14046; h) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650 – 1653; *Angew. Chem.* **2014**, *126*, 1676 – 1679; i) F. Hu, X. Shao, D. Zhu, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 6105 – 6109; *Angew. Chem.* **2014**, *126*, 6219 – 6223; j) C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316 – 9320; *Angew. Chem.* **2014**, *126*, 9470 – 9474; k) C. Xu, Q. Shen, *Org. Lett.* **2014**, *16*, 2046 – 2049; l) K. Kang, C. Xu, Q. Shen, *Org. Chem. Front.* **2014**, *1*, 294 – 297; m) S. Alazet, L. Zimmer, T. Billard, *Chem. Eur. J.* **2014**, *20*, 8589 – 8593.

[6] a) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782 – 8785; b) TCI America, http://www.tcichemicals.com/en/us/product/tci-topics/ArticleHighlights_20141201.html (Checked, 2015/03/11); http://www.synquestlabs.com/product/id/98242.html; SynQuest Laboratories, http://www.synquestlabs.com/product/id/98242.html (Checked, 2015/03/11); c) Z. Huang, Y.-D. Yang, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 1094 – 1097; d) A. Arimori, M. Takada, N. Shibata, *Org. Lett.* **2015**, *17*, 1063 – 1065.

[7] a) A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551 – 8555; *Angew. Chem.* **2009**, *121*, 8703 – 8707; b) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160 – 163; c) Q. Xiao, J. Sheng, Z. Chen, J. Wu, *Chem. Commun.* **2013**, *49*, 8647 – 8649; d) S. Alazet, K. Ollivier, T. Billard, *Beilstein J. Org. Chem.* **2013**, *9*, 2354 – 2357; e) J. Sheng, S. Li, J. Wu, *Chem. Commun.* **2014**, *50*, 578 – 580; f) J. Liu, L. Chu, F.-L. Qing, *Org. Lett.* **2013**, *15*, 894 – 897.

[8] A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *J. Org. Chem.* **2008**, *73*, 9362 – 9365.

[9] Billard–Langlois reagents can also be synthesized from **4**. See Ref. [5j].

[10] A. Ferry, New Reactivity of DAST and its Analogs: Synthesis and Applications of Fluorinated Sulfinamidines and Sulfanylamines. Ph.D. Thesis, University of Lyon, Lyon, France, **2007**.

Received: February 17, 2015
Published online on ■■ ▮▮, 0000

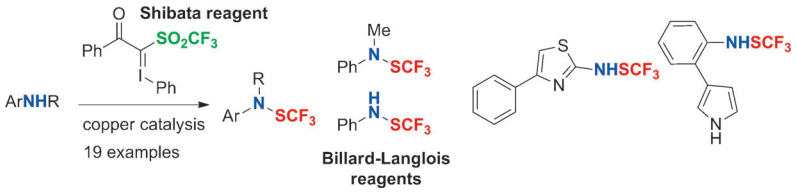
COMMUNICATION

Synthetic Methods

*Zhongyan Huang, Yu-Dong Yang, Etsuko Tokunaga, Norio Shibata**

■■ – ■■

Synthesis of Billard–Langlois Reagents and their Derivatives by Copper-Catalyzed *N*-Trifluoromethylthiolation of Arylamines with a Trifluoromethanesulfonyl Hypervalent Iodonium Ylide



Billard–Langlois reagents from Shibata reagent: A one-step synthesis of Billard–Langlois reagents and their derivatives, trifluoromethanesulfenamides, is reported. A series of primary and secondly arylamines were directly N–H trifluoromethylthiolated by a trifluoromethanesulfonyl hypervalent iodonium ylide, the Shibata reagent, under mild, copper-catalyzed reaction conditions in high yields.