Tetrahedron Letters 55 (2014) 5572–5575

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Triflic acid-catalyzed C_{sp^3}—H functionalization of 2-methyl azaarenes with a α-trifluoromethyl imino ester

Mark Blocker, Supriya Immaneni, Abid Shaikh *

Department of Chemistry, Georgia Southern University, 521 College of Education Drive, Statesboro, GA 30460-8064, USA

ARTICLE INFO

Article history:
Received 24 July 2014
Revised 8 August 2014
Accepted 13 August 2014
Available online 19 August 2014

Keywords:
Azaarenes
C–H functionalization
Trifluoromethyl imino ester
Triflic acid
Brønsted acid

ABSTRACT

A Brønsted acid promoted C_{sp^3}—H functionalization of 2-alkyl azaarenes with α-trifluoromethylated imino ester is described. A catalytic amount of triflic acid provided straightforward access to the corresponding trifluoromethylated amino esters via concomitant in situ one step *N*-alkyl deprotection. On further hydrolysis of ester, synthesis of quinoline derived unnatural trifluoromethylated amino acids has been achieved in a short and efficient manner.

Introduction

C_{sp^3}—H functionalization using transition metal catalysts is a valuable tool in C–C bond formation.[1] Recent investigations demonstrated the role of Lewis acid catalysts in C_{sp^3}—H functionalization of 2-methylazaarenes with α,β-unsaturated carbonyls,[2] aldimines,[3] carbonyls,[4] and azodicarboxylates.[5] Our recent investigations revealed the effectiveness of a transition metal-based Lewis acid catalyst $Yb(OTf)_3$ in C–H functionalization of 2-alkylazaarene with α-trifluoromethylated carbonyl compounds under mild reaction conditions.[6] In contrast, Brønsted acid catalyzed C_{sp^3}—H functionalization of 2-methyl azaarenes has not been fully explored and only a few reports are documented in the literature.[7] Thus, the development of Brønsted acid catalyzed synthetic methods for C_{sp^3}—H functionalization is highly desirable. The use of Brønsted acids as catalysts has various advantages, they are inexpensive, readily available and do not involve residual metal contamination as compared to metal-based Lewis acid catalysts.

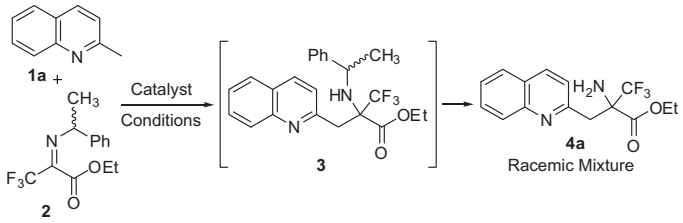
Organofluorine chemistry has received extensive attention especially in the pharmaceutical industry and in materials science due to the unique properties of fluorinated compounds.[8] Trifluoromethylated compounds are of particular interest as the strong electron-withdrawing effect of CF_3 group contributes to a number of biologically important molecular properties.[9] For example, it results in a significant increase in lipophilicity of the molecule, which is a very important feature for drug delivery.[10] The increased lipophilicity, and superior metabolic stability compared to those of the methyl analogues, often account for an improved activity profile.[11] The different medicinal applications of fluorinated organic molecules are widespread. Some of the most well-known drugs are Prozac® (anti-depressant), Diflucan® (anti-fungal agent), Casodex® (anti-cancer agent) and Desflurane (inhalation anesthetic).[12] Recent applications of organofluorine compounds include, potential therapeutics for HIV, cancer and Alzheimer's disease.[13] Accordingly, the synthesis of these molecules is in great demand and the search for new biologically active fluorinated compounds is in the forefront of organic and medicinal chemistry research. Fluorine-containing amino acids in particular, α-trifluoromethyl amino acids are of special interest.[14] Incorporation of a C–F bond on amino acids results in conformationally and proteolytically stable peptides with enhanced lipophilicity.[15] The modified amino acids possess different properties and reactivity resulting from an increase in the electronegativity of the trifluoromethyl group.[16] They can be used as peptidomimetics and therapeutic agents and thus are interesting subjects in current medical investigations.[17]

As a part of our ongoing research in the development of Brønsted acid catalyzed C_{sp^3}—H functionalization of 2-methyl azaarenes that are pre-functionalized with a trifluoromethyl group,[18] herein, we disclose a new efficient approach for the synthesis of a wide variety of quinoline derived α-trifluoromethyl amino esters. Triflic acid (TfOH) promoted the C_{sp^3}—H functionalization of methyl azaarenes with α-trifluoromethyl imino ester to provide the corresponding α-trifluoromethyl amino esters in good yields.

* Corresponding author. Tel.: +1 912 478 0973; fax: +1 912 478 0699.
E-mail address: malnu@georgiasouthern.edu (A. Shaikh).

http://dx.doi.org/10.1016/j.tetlet.2014.08.061
0040-4039/

Table 1
Optimization of reaction conditions using various Lewis acid and Brønsted acid catalysts[a]



Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Time (h)	Conv.[b] (%)
1	AgOTf (10)	THF	80	24	0
2	$Cu(OTf)_2$ (5)	Toluene	110	12	0
3	$Cu(OAc)_2$ (10)	Toluene	110	12	0
4	$Yb(OTf)_3$ (10)	Dioxane	100	12	0
5	$Yb(OTf)_3$ (20)	Dioxane	100	12	0
6	TfOH (10)	Dioxane	100	12	74[c]
7	TfOH (10)	Dioxane	110	24	72[c]
8	TfOH (20)	Dioxane	100	12	85[c]
9	TfOH (20)	Dioxane	80	12	60[c]
10	AcOH (20)	Dioxane	110	12	34[c]
11	TsOH (20)	Toluene	110	12	0
12	TFA (20)	Toluene	110	12	0

[a] Reaction conditions: Ethyl trifluoro imino ester **2** (50 mg, 0.18 mmol), azaarene **1a** (0.36 mmol), catalyst (5–20 mol %).
[b] Determined by ^{19}F NMR using limiting reagent ethyl trifluoro imino ester **2** as a reference.
[c] Exclusively **4a** product formation was observed.

Results and discussion

Continuing with our interest in the development of catalytic direct Mannich reactions, we investigated the Brønsted acid-catalyzed reaction between 2-methyl azaarenes and α-trifluoro-methyl imino ester. Although Lewis acid catalysis could be achieved, the reactions turned out to be sluggish and no product formation was observed. We decided to investigate a strategy based on the activation of both nucleophilic and electrophilic sites via a Brønsted acid utilizing the fact that the equilibrium between 2-methylquinoline and its enamine counterpart bearing an exocyclic double bond can be easily shifted.[19] In order to test the idea, 2-methylquinoline **1a** was initially chosen as an alkyl-azaarene model substrate and imino ester **2** as a reagent. Imino ester **2** was prepared following a literature method[20] from ethyl trifluoropyruvate and α-methyl benzylamine to obtain 94% yield within 4 h of reaction time. Preliminary studies revealed that high temperature (100 °C) and a closed reaction vessel promote the best conditions for this transformation.

Initial trials to activate the C_{sp^3}—H for the new C–C bond formation between **1a** and **2** with Lewis acid catalysts AgOTf and $Cu(OTf)_2$ (Table 1, entries 1 and 2) did not provide the expected product **4a** or the intermediate **3**. $Cu(OAc)_2$ and $Yb(OTf)_3$ also failed to promote the reaction utilizing different solvents and various catalyst stoichiometries (Table 1, entries 3–5). After meeting with no success with Lewis acid catalysts, we began our investigations using Brønsted acid catalyst. The initial trial with triflic acid (TfOH) catalyzed the reaction at 100 °C to provide the product in 74% yield (Table 1, entry 6). Further increasing the temperature to 110 °C did not improve the product yield (Table 1, entry 7). On the other hand, increasing the catalyst concentration from 10 mol % to 20 mol % significantly increased the conversion to 85% at 100 °C (Table 1, entry 8). Trials with other Brønsted acids such as AcOH (20 mol %) also promoted the reaction albeit with lower conversion (Table 1, entry 10). Rather surprisingly, TsOH and CF_3COOH (Table 1, entries 11 and 12) did not provide the desired product. Deprotection of the *N*-benzyl group in the presence of Brønsted acids such as acetic acid and trifluoroacetic acid is reported in the literature[21] that could be complimenting the desired transformation. One-pot deprotection of the *N*-alkyl group provided the amino esters **4a**–**h**. All of the reactions were carried out in a screw-cap pressure tube under argon.

With the optimized conditions in hand, the substrate scope of this reaction was investigated by treating various substituted 2-methyl quinolines **1a**–**h** with α-trifluoromethyl imino ester **2**. The results are summarized in Fig. 1. All the reactions proceeded in good yields ranging from 60% to 80% and no by-product formation was observed. Relatively higher yields were obtained when quinoline bearing electron-donating groups such as methyl **4b** and ethoxy **4d** were used. On the other hand, the presence of an electron-withdrawing group such as halogens proved detrimental and resulted in lower yields of **4c**, **4e**, and **4f**. An important observation worth mentioning is that the reactions with halogenated azaarenes provided the expected products without the loss of halogens. In all cases, the expected *N*-alkyl intermediate was not observed and free amine products were obtained. Reaction of 1-methyl isoquinoline **1h** with ester **2** also proceeded exclusively at the C_{sp^3}—H position; followed by in situ deprotection of the *N*-alkyl group which provided the expected product **4h** in 79% yield. (See Fig. 2)

Based on the excellent results obtained in case of methyl quinolines **1a**–**h**, a similar transformation was tried with 2-alkyl pyridines **5a**–**e** with imino ester **2**. 2-Methyl pyridine **5a** provided the corresponding C_{sp^3}—H functionalization **6a** in 69% yield. 2,3-dimethyl pyridine **5b**, 2,4-diemthyl pyridine **5c**, and 2,6-dimethyl pyridine **5d** provided only C-2 functionalized products **6b**–**d**, respectively. The reactivity of 2-ethyl pyridine with **2** provided the expected product **6e** as a mixture of diastereomers in 55% yield.

In order to extend this approach, the synthesis of unusual fluorine containing amino acid was carried out using the base promoted hydrolysis of ester **4d**. Corresponding trifluoromethyl amino acid **7d** was obtained as a white solid in 88% yield using aq NaOH within 2 h of reaction time. (See Fig. 3)

Mechanistically, Brønsted acid promoted C_{sp^3}—H activation of 2-methyl azaarenes occurs under proton-transfer conditions. 2-Methyl azaarene, the representative example 2-methyl quinoline **1a**, gets protonated at the nitrogen center, which significantly increases the acidity of C_{sp^3}—H bond that triggers the cleavage of

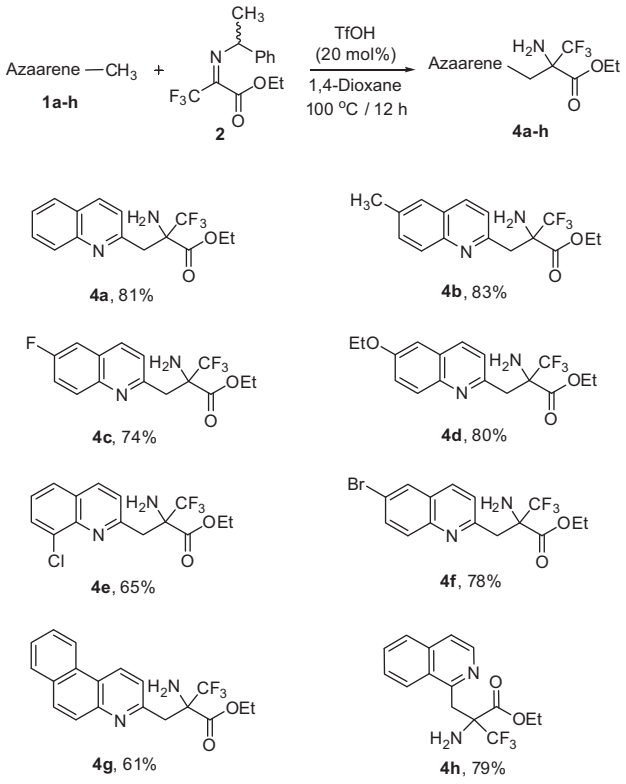


Figure 1. Brønsted acid promoted C_{sp^3}—H functionalization of methyl azaarenes with α-trifluoro imino ester. Reaction conditions: Ethyl trifluoro imino ester **2** (50 mg, 0.18 mmol), azaarene **1a**–**h** (0.36 mmol), TfOH (20 mol %), 1,4-dioxane (2 mL) at 100 °C, 12 h. Isolated yields after flash chromatography.

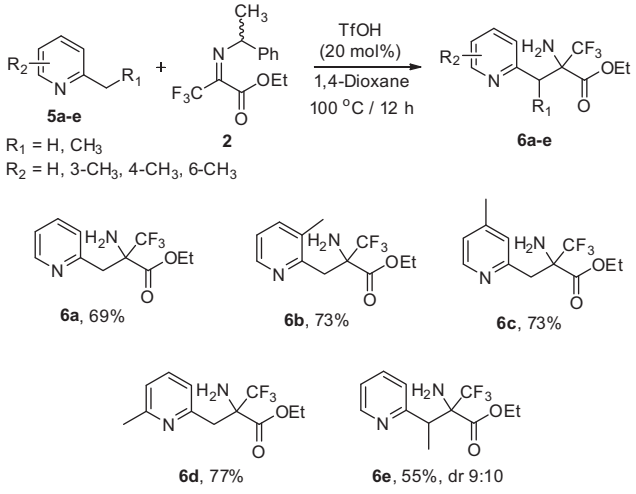


Figure 2. Brønsted acid promoted C_{sp^3}—H functionalization of substituted pyridines with α-trifluoro imino ester. Reaction conditions: Ethyl trifluoro imino ester **2** (50 mg, 0.18 mmol), azaarene **1a**–**h** (0.36 mmol), TfOH (20 mol %), and 1,4-dioxane (2 mL) at 100 °C, 12 h. Isolated yields after flash chromatography.

the C–H bond to generate an enamine species **9**. Subsequent protonation of the imine group of **2** facilitates the nucleophilic addition of azaarene enamine **9** to provide the *N*-alkyl intermediate **3**, which on further cleavage provides the free amine product **4a**. The hypothesis is shown in Fig. 4.

In conclusion, we have developed an efficient and simple protocol for the C_{sp^3}—H functionalization of alkyl azaarenes with α-trifluoromethyl imino ester.[22] Triflic acid catalyzed this reaction

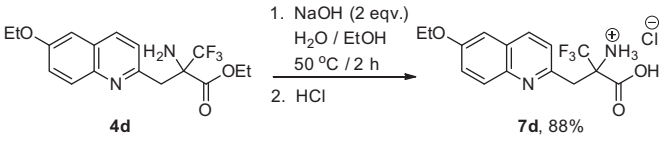


Figure 3. Base promoted hydrolysis of ester **4d** to obtain trifluoromethyl amino acid **7d**.

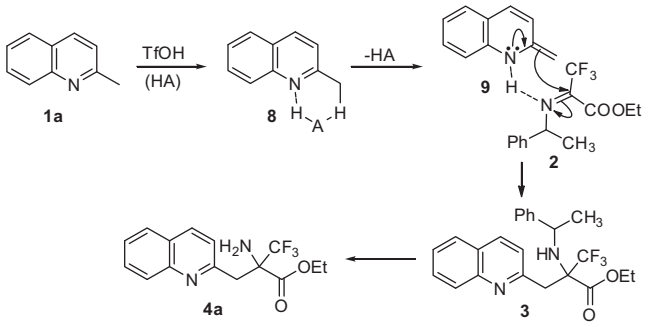


Figure 4. Working hypothesis of Brønsted acid promoted C_{sp^3}—H functionalization of methyl azaarenes with α-trifluoro imino ester.

and also promoted the in situ *N*-alkyl deprotection to provide the corresponding trifluoromethyl amino esters in good yields. In all the cases, exclusively only one product was observed. To broaden the scope of this methodology, amino ester product was converted to the corresponding trifluoromethylated amino acid. In all cases, the products were obtained as a racemic mixture and our current efforts are directed toward developing an enantioselective synthesis for these compounds.

Acknowledgments

Financial support provided by Georgia Southern University, College Office of Undergraduate Research (COUR) award to M.B. and National Science Foundation, USA (DMR 1229292) is gratefully acknowledged.

Supplementary data

Supplementary data (Experimental procedure and full characterization (^{1}H, ^{13}C, ^{19}F NMR and MS data) for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.061.

References and notes

1. (a) Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266; (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155; (c) Haslam, E. *Shikimic Acid Metabolism and Metabolites*; John Wiley & Sons: New York, 1993; (d) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650; (e) Jiang, H.; Chen, H.; Wang, A.; Liu, X. *Chem. Commun.* **2010**, 7259.
2. Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706.
3. (a) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650; (b) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849; (c) Qian, B.; Xie, P.; Xie, Y.; Huang, H. *Org. Lett.* **2011**, *13*, 2580.
4. Niu, R.; Xiao, J.; Liang, T.; Li, X. *Org. Lett.* **2012**, *14*, 676.
5. (a) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304; (b) Liu, J.-Y.; Niu, H.-Y.; Wu, S.; Qu, G.-R.; Gao, H. M. *Chem. Commun.* **2012**, 9723.
6. Graves, V. B.; Shaikh, A. *Tetrahedron Lett.* **2013**, *54*, 695.
7. (a) Niu, R.; Xiao, J.; Liang, T.; Li, X. *Org. Lett.* **2012**, *14*, 676; (b) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195; (c) Rao, N. N.; Meshram, H. M. *Tetrahedron Lett.* **2013**, *54*, 5087; (d) Meshram, H. M.; Rao, N. N.; Rao, L. C.; Kumar, N. S. *Tetrahedron Lett.* **2012**, *53*, 3963.
8. (a) Fried, J.; Sabo, E. T. *J. Am. Chem. Soc.* **1954**, *76*, 1455. (b) Ramachandran, P. V. *Asymmetric Fluoroorganic Chemistry*, ACS Symp. Series, ACS, Washington, DC,

2000. (c) Himaya, T. *Organofluorine Compounds*, Springer-Verlag, 2001. (d) Török, B.; Prakash, G. K. S. *Adv. Synth. Catal.* **2003**, *345*, 165. (e) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, New York, Heidelberg, 2004. (f) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*, American Chemical Society, Washington, DC, 1996.

9. Filler, R. Asymmetric Fluoroorganic Chemistry In Ramachandran, P. V., Ed.; ACS Symp. Series; ACS: Washington, DC, 2000; p 1. Chapter 1.
10. Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119.
11. (a) Pappolla, M.; Bozner, P.; Soto, C.; Shao, H.; Robakis, N. K.; Zagorski, M.; Frangiones, B.; Ghiso, J. *J. Biol. Chem.* **1998**, *273*, 7185; (b) Chyan, Y.-J.; Poeggeller, B.; Omar, R. A.; Chain, D. G.; Frangione, B.; Chiso, J.; Pappolla, M. A. *J. Biol. Chem.* **1999**, *274*, 21937; (c) Poeggeller, B.; Miravalle, L.; Zagorski, M. G.; Wisniewski, T.; Chyan, Y.-J.; Zhang, Y.; Shao, H.; Bryant-Thomas, T.; Vidal, R.; Frangione, B.; Ghiso, J.; Pappolla, M. A. *Biochemistry* **2001**, *40*, 14995.
12. (a) Bendheim, P. E.; Poeggeler, B.; Neria, E.; Ziv, V.; Pappola, M. A.; Chain, D. G. *J. Mol. Neurosci.* **2002**, *19*, 213; (b) Kato, K.; Fujii, S.; Gong, Y. F.; Tanaka, S.; Katayama, M.; Kimoto, H. *J. Fluorine Chem.* **1999**, *99*, 5; (c) Karbwang, J.; White, N. J. *Clin. Pharmacokinet.* **1990**, *19*, 264.
13. (a) Török, M.; Abid, M.; Mhadgut, S. C.; Török, B. *Biochemistry* **2006**, *45*, 5377; (b) Sood, A.; Abid, M.; Hailemichael, S.; Foster, M.; Török, B.; Török, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6931.
14. Enders, D.; Gottfried, K.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 3147.
15. (a) Burger, K.; Mutze, K.; Hollweck, W.; Koksch, B.; Kuhl, P.; Jakubke, H.-D.; Riede, J.; Schier, A. *J. Prakt. Chem.* **1993**, *335*, 321; (b) Sewald, N.; Hollweck, W.; Mutze, K.; Schierlinger, C.; Seymour, L. C.; Gaa, K.; Burger, K.; Koksch, B.; Jakubke, H.-D. *Amino Acids* **1995**, *8*, 187; (c) Koksch, B.; Sewald, N.; Burger, K.; Jakubke, H.-D. *Amino Acids* **1996**, *11*, 425; (d) Koksch, B.; Sewald, N.; Hofmann, H.-J.; Burger, K.; Jakubke, H.-D. *J. Pept. Sci.* **1997**, *3*, 157; (e) Jackel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483; (f) Smits, R.; Koksch, B. *Curr. Top. Med. Chem.* **2006**, *6*, 1483.
16. Kobzev, S. P.; Soloshonok, V. A.; Galushko, S. V.; Yagupolvskii, Y. L.; Kukhar, V. P. *J. Gen. Chem. Russ. (Engl. Transl.)* **1989**, *59*, 801.
17. (a) Bravo, P.; Buch, L.; Pesenti, C.; Viani, F.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2001**, *112*, 153; (b) Margiotta, N.; Papadia, P.; Lazzaro, F.; Crucianelli, M.; De Angelis, F.; Pisano, C.; Vesci, L.; Natile, G. *J. Med. Chem.* **2005**, *48*, 7821.
18. (a) Torok, B.; Abid, M.; London, G.; Esquibel, J.; Torok, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086; (b) Abid, M.; Torok, B. *Adv. Synth. Catal.* **2005**, *347*, 1797; (c) Abid, M.; Savolainen, M.; Landge, S.; Hu, J.; Prakash, G. K. S.; Olah, G. A.; Torok, B. *J. Fluorine Chem.* **2007**, *128*, 587; (d) Abid, M.; Teixeira, L.; Torok, B. *Org. Lett.* **2008**, *10*, 933.
19. Rueping, A.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *13*, 1095.
20. Abid, M.; Teixeira, L.; Torok, B. *Org. Lett.* **2008**, *10*, 933.
21. (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785; (b) Ji, H.; Jing, Q.; Huang, J.; Silverman, R. B. *Tetrahedron* **2012**, *68*, 1359.
22. *General procedure triflic acid-catalyzed* the C_{sp^3}—H *functionalization of 2-methyl azaarenes with α-trifluoromethyl imino ester:* Ethyl trifluoro imino ester **2** (50 mg, 0.18 mmol) and 2-methyl quinoline **1a** (49 μL, 0.36 mol) were placed in a screw-cap pressure tube along with 2 mL 1,4-dioxane. The mixture was flushed with argon and stirred for 2 min at room temperature. Triflic acid (4 μL, 20 mol %) was added with constant stirring. The closed tube was stirred at 100 °C for 12 h. After the reaction was completed, as indicated by TLC and ^{19}F NMR, the resulting reaction mixture was directly subjected to column chromatography (hexane/ethyl acetate 90:10 to 50:50) to obtain a white solid in 81% isolated yield.