

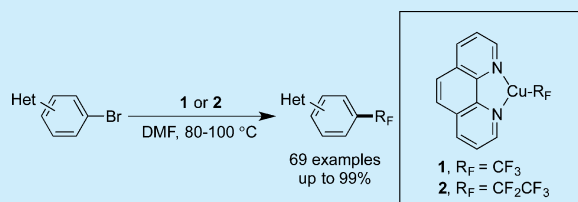
Copper-Mediated Perfluoroalkylation of Heteroaryl Bromides with (phen)CuR_F

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Supporting Information

ABSTRACT: The attachment of perfluoroalkyl groups onto organic compounds has been a major synthetic goal over the past several decades. Previously, our group reported phenanthroline-ligated perfluoroalkyl copper reagents, (phen)CuR_F, which react with aryl iodides and aryl boronates to form the corresponding benzo-trifluorides. Herein the perfluoroalkylation of a series of heteroaryl bromides with (phen)CuCF₃ and (phen)CuCF₂CF₃ is reported. The mild reaction conditions allow the process to tolerate many common functional groups. Perfluoroethylation with (phen)CuCF₂CF₃ occurs in somewhat higher yields than trifluoromethylation with (phen)CuCF₃, creating a method to generate fluoroalkyl heteroarenes that are less accessible from trifluoroacetic acid derivatives.



The trifluoromethyl group is present in numerous pharmaceuticals, agrochemicals, and materials. As a result, there has been considerable interest in developing practical reactions to incorporate perfluoroalkyl groups into organic compounds under mild conditions. In medicinal and agrochemistry, the introduction of a trifluoromethyl group can lead to increases in activity and stability.¹ The top selling drugs fluoxetine (Prozac) and mefloquine (Lariam) and the leading agrochemical fluazinam contain CF₃ groups (Figure 1).

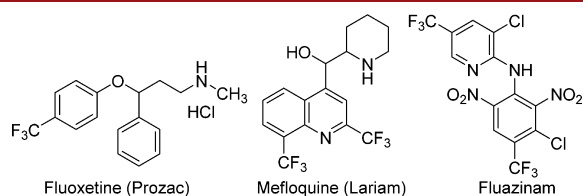


Figure 1. Bioactive compounds containing CF₃ groups.

The Swarts reaction, which involves the treatment of benzotrichlorides with HF or SbF₅, remains the most prevalent method for the industrial-scale synthesis of trifluoromethyl arenes and certain heteroarenes.^{2a} Although this method is effective in the bulk production of simple benzotrifluorides, its utility on the laboratory scale for the synthesis of complex molecules and late-stage functionalization is limited by the low functional group compatibility and toxic reagents. Furthermore, the Swarts reaction cannot be applied to the synthesis of longer-chain perfluoroalkyl moieties, such as the C₂F₅ group.

Although there has been considerable progress in copper-mediated perfluoroalkylation reactions in recent years, these reactions are mostly limited to aryl iodide and arylboron substrates.² Perfluoroalkylation reactions of aryl bromides, which are more commercially and synthetically available than aryl iodides, have been limited to substrates containing

electron-withdrawing groups. A single report for the trifluoromethylation of aryl chlorides with Pd has been reported.³ However, these reactions require an expensive palladium precatalyst, ligand, and CF₃ source. Most relevant to our current work, the majority of the current methods have not been demonstrated to be applicable to the synthesis of fluoroalkyl heteroarenes with significant scope. This limitation is important because of the prevalence of heteroarenes in medicinal and agrochemistry.

The difference in availability of aryl iodides and bromides is even greater for heteroaryl halides. There are only about one-fifth as many commercially available iodopyridines compared to bromopyridines, and the price of 2-iodopyridine is nearly 40 times higher than that of 2-bromopyridine per mole.⁴ A Reaxys search shows that there are also twice as many procedures to synthesize any bromopyridine isomer compared to procedures to synthesize the corresponding iodopyridines.

Grushin has recently reported the perfluoroalkylation of heteroaryl bromides with CuCF₃ formed by the direct cupration of HCF₃.^{5a,b} Although the functional group tolerance and yields of this method are high, the CuCF₃ reagent cannot be stored.^{5c} Thus, each reaction must be initiated by generation of CuCF₃ from gaseous HCF₃, and such a transformation is challenging to conduct in common laboratory settings.

Methods for the radical trifluoromethylation of heteroarenes have also been reported recently.⁶ While these methods do not require prefunctionalized substrates, the yields and regioselectivities of these reactions are often modest, and limited functional group compatibility has been demonstrated. Thus, methods for the synthesis of fluoroalkylheteroarenes from heteroaryl bromides with easily handled reagents that occur with broad scope and complete site selectivity are desirable.

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Our group recently reported the trifluoromethylation of aryl iodides with a phenanthroline–CuCF₃ complex, (phen)CuCF₃ (**1**) (Figure 2B).^{7a} This thermally stable, commercially available solid reacts with a variety of aryl iodides and electron-deficient aryl bromides under mild conditions. We also showed that aryl bromides can be converted to trifluoromethylarenes indirectly by initial conversion to arylboronate esters, followed by a reaction of the boronate with **1** in air.^{7b}

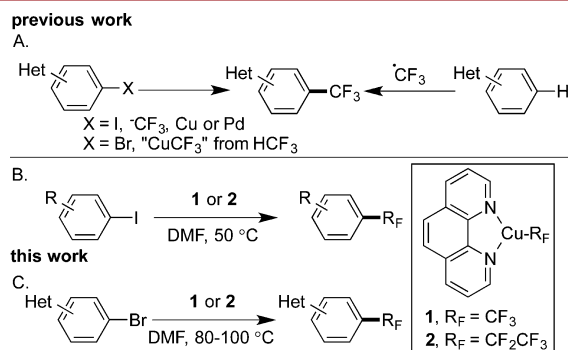


Figure 2. Synthesis of perfluoroalkyl heteroarenes.

Because **1** was shown to react with electron-deficient aryl bromides, we considered that **1** would react similarly with heteroaryl bromides that are inherently more electron-deficient than the corresponding arenes, such as pyridines and diazines. However, reactions of CuCF₃ reagents with bromopyridines could be challenging because pyridines can bind to the metal center and alter the inherent reactivity. Moreover, bromopyridines are less reactive toward oxidative addition than iodopyridines, and the oxidative addition step is likely the rate-limiting step for reactions with copper centers containing electron-withdrawing perfluoroalkyl groups.⁹ We hypothesized that the chelating phen ligand in preformed **1** would minimize bonding of the pyridine to the copper center, in addition to rendering the copper complex isolable and easy to handle. Herein, we report that copper complexes **1** and **2** react with a range of heteroaryl bromides to form perfluoroalkylheteroarenes in good yields. The reactivity and functional group compatibility for the reaction of bromopyridines with **1** is higher than those of prior methods for the fluoroalkylation of heteroarenes.

Table 1 shows a comparison of the yield for the trifluoromethylation of methyl 6-bromopicolinate, a represen-

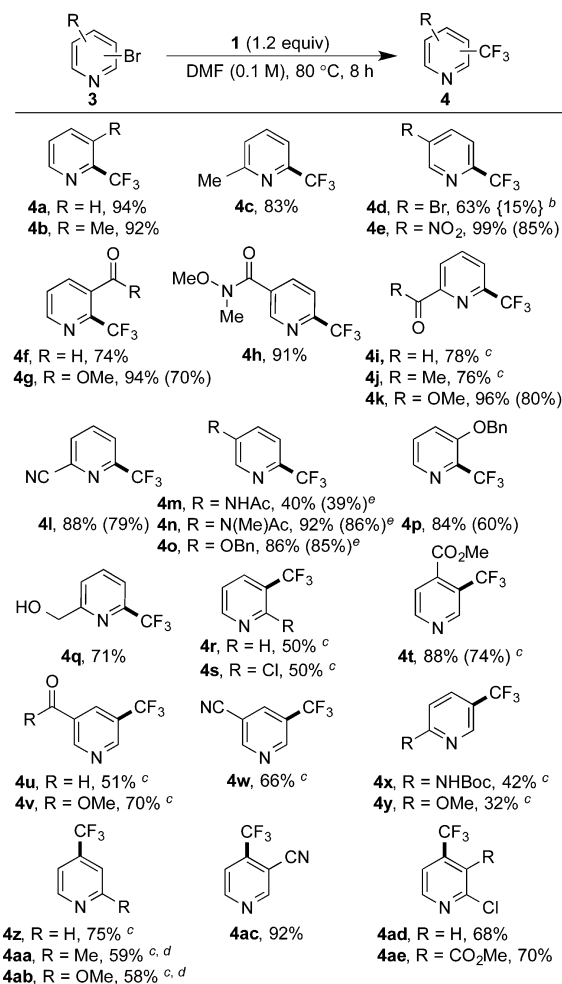
Table 1. Comparison of Copper-Mediated Trifluoromethylations of a Functionalized Bromopyridine^a

conditions	yield
(phen)CuCF ₃ , DMF, 80 °C	96%
(PPh ₃) ₃ CuCF ₃ (1.0 equiv), 'Bu-bpy, PhMe, 80 °C	56% ^b
K[(MeO) ₃ BCF ₃], CuI (20 mol %), phen (20 mol %), DMSO, 60 °C	17% ^c
TESCF ₃ , KF, CuI (10 mol %), phen (10 mol %), DMF/NMP, 60 °C	20% ^d
MeO ₂ CCF ₃ , CsF, CuI (10 mol %), DMF, 160 °C	24% ^e
TESCF ₃ , KF, CuI (1.5 equiv), DMF/NMP, 80 °C	<5% ^f

^aYields were determined by ¹⁹F NMR spectroscopy. ^bReference 8a. ^cReference 8b. ^dReference 8c. ^eReference 8d. ^fReference 8e.

tative bromopyridine containing a potentially reactive ester. Although the 2-position is activated, the prior methods reported for trifluoromethylation generate the 2-trifluoromethylpyridine in low to modest yield. In contrast, the reaction of this bromopyridine with **1** occurs in essentially quantitative yield.

Scheme 1. Trifluoromethylation of Bromopyridines with (phen)CuCF₃ (**1**)^a



^aReaction conditions: bromopyridine (**3**, 0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ¹⁹F NMR spectroscopy. Yields in parentheses are isolated yields. ^bYield of bis-trifluoromethylated product. ^cReaction was run at 100 °C. ^d1.5 equiv of **1** was used. ^eIsolated product contains trace (2–3%) perfluoroethyl product.

The scope of the trifluoromethylation reaction of various 2-, 3-, and 4-bromopyridines with complex **1** is shown in Scheme 1. 2-Bromopyridines containing both electron-donating and electron-withdrawing substituents at each position of the ring afforded the products in excellent yields within 8 h. Substrates bearing aldehyde, ketone, ester, and the Weinreb amide functionality (**3f–k**) reacted in good yields; side products resulting from nucleophilic addition of CF₃ to the carbonyl group were not observed. Competitive addition to a carbonyl group is commonly observed in systems involving nucleophilic CF₃ reagents.⁸ In addition, substrates containing nitro and cyano groups (**4e** and **4l**) reacted in high yields. Ortho-substituted 2-bromopyridines formed products **4b**, **4f**, **4g**, and

4p in 74–94% yield. Protic X–H bonds of alcohols, amides, and carbamates were tolerated under the reaction conditions. However, a lower yield (**4m**, 40%) was observed from the reaction of a substrate containing a secondary amide compared to that from a substrate containing a tertiary amide (**4n**, 92%).

For certain compounds (**4m–o**), the isolated product was found to contain trace (2–3%) perfluoroethyl product resulting from difluorocarbene insertion into the CuCF_3 reagent.^{5c} The reaction of 2,5-dibromopyridine (**3d**) occurred preferentially at the 2-position over the 5-position, but the product from trifluoromethylation at both the 2- and 5-position formed in 15% yield. No product was observed corresponding to trifluoromethylation at the 5-position alone. 2-Chloropyridines and pyrimidines were also investigated for their reactivity toward **1**. However, low yields (5–20%) of the trifluoromethylated products were obtained from the heteroaryl chlorides.

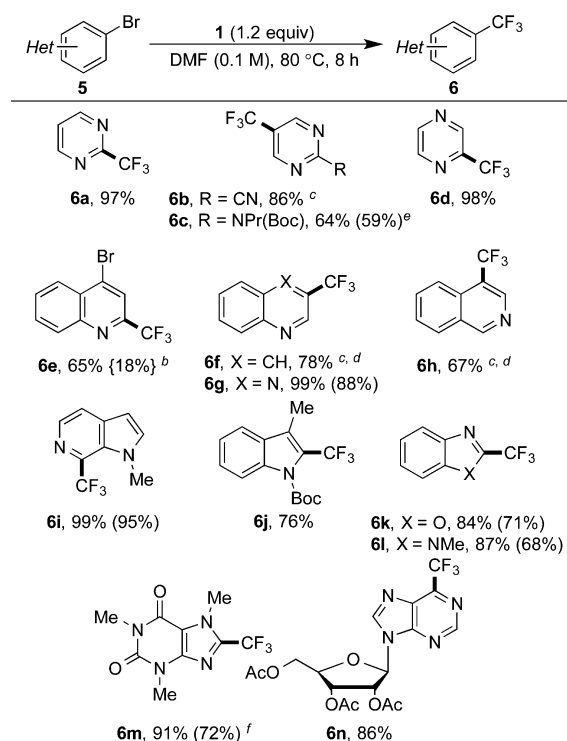
Pyridines containing bromine at the 4-position were less reactive than those containing bromine at the 2-position. High yields were observed when the bromoheteroarene contained electron-withdrawing groups (**3ac–ae**). The product of trifluoromethylation was obtained in modest yield from 4-bromopyridines bearing electron-donating groups (**4aa**, **4ab**).

3-Bromopyridines were less reactive toward this process than 2- and 4-bromopyridines, but synthetically useful amounts of the 3-trifluoromethylpyridines did form. We presume the lower reactivity is due to the greater electron density at the 3-position of pyridines than at the 2- and 4-positions, making them more akin to bromoarenes and less prone to undergo oxidative addition to the Cu(I) reagent. Consistent with this assertion, the reactions of 3-bromopyridines required heating at a higher temperature (100 °C) than the reactions with 2-bromopyridines (80 °C). The trifluoromethylation of 3-bromopyridines containing electron-donating substituents (**3x**, **3y**) afforded products in modest yields. However, the trifluoromethylation of 3-bromopyridines containing electron-withdrawing substituents (**3s–w**) formed the products in good yields. Thus, this simple reaction provides a method to form a range of 3-trifluoromethylpyridine derivatives.

To enhance the reactivity of 3-bromopyridines toward **1**, we tested several changes to the reaction conditions (see Table S1 in the Supporting Information). However, changes to the temperature, equivalents of **1**, reaction time, concentration, ligand, and solvent had little effect on the yield. Catalytic quantities of Lewis acids to bind to pyridine and decrease electron density at the 3-position led to no reaction. Reactions of the corresponding pyridine-*N*-oxide and *N*-(TBS)pyridinium triflate formed the trifluoromethylpyridine derivatives in trace quantities. We are continuing to investigate methods to increase the reactivity of electron-rich 3-bromopyridines toward **1**.

The scope of the trifluoromethylation reaction with **1** encompassed reactions with other brominated nitrogen heterocycles (Scheme 2). For example, 2- and 5-bromopyrimidines reacted with **1** to form the corresponding trifluoromethylpyrimidines in good yield (**6a–c**). Complex **1** also reacted with a range of bromopyrazines (**5d**), quinolines (**5e**, **5f**), quinoxolines (**5g**), isoquinolines (**5h**), and aza-indoles (**5i**) when bromine was located adjacent to nitrogen. The reaction with 2,4-dibromoquinoline occurred selectively at the 2-position; only 18% of the bis-trifluoromethylated side product (**6e**) formed.

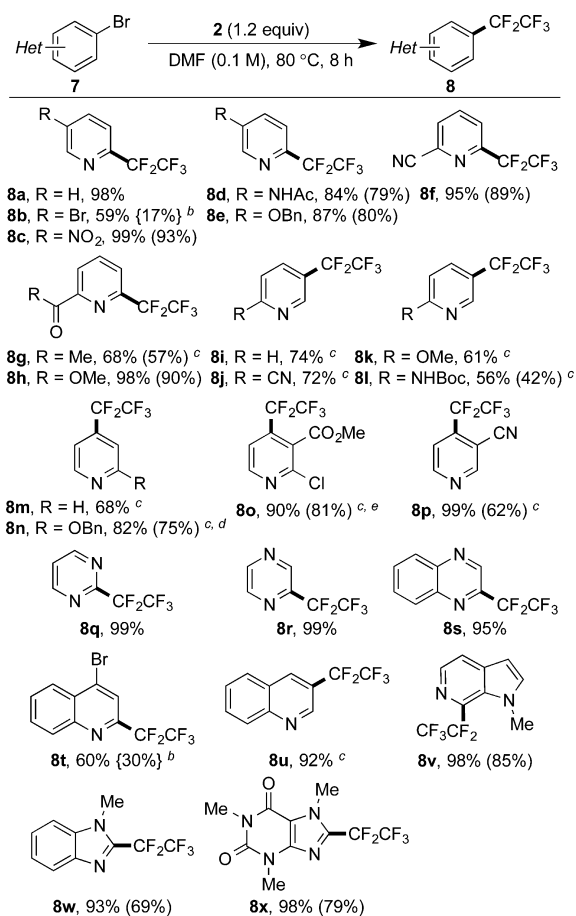
Scheme 2. Trifluoromethylation of Heteroaryl Bromides with (phen)CuCF₃ (**1**)^a



^aReaction conditions: bromoheteroarene (**5**, 0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ¹⁹F NMR spectroscopy. Yields in parentheses are isolated yields. ^bYield of bis-trifluoromethylated product. ^cReaction was run at 100 °C. ^d1.5 equiv of **1** was used. ^eIsolated product contains 20% perfluoroethyl product. ^fIsolated on a 4.8 mmol scale.

The electron-rich property of five-membered heterocycles might lead one to expect that these systems would not react readily with **1**. However, complex **1** does react with certain five-membered heterocycles containing bromine in the 2-position. The reactions of **1** with 2-bromo indole (**5j**), benzimidazole (**5l**), and benzoxazole (**5k**) formed the trifluoromethylated products in good to high yield. Brominated caffeine was also transformed to the trifluoromethylated product and isolated on gram scale in high yield (**6m**), demonstrating the applicability of this method for the large-scale trifluoromethylation of complex heterocyclic substrates. Finally, the nucleoside derivative **5n** underwent trifluoromethylation in high yield. Reactions of 2-bromofurans and 2-bromothiophenes also were explored, but only low yields of the trifluoromethylation product were obtained. Furthermore, unprotected N–H derivatives of **5i** and **5l** did not react with **1** to form trifluoromethylated products.

Given the limited synthetic procedures for the incorporation of longer chain perfluoroalkyl groups, we investigated the extension of this reaction to the perfluoroethylation of bromoheteroarenes with (phen)CuCF₂CF₃ (**2**) (Scheme 3). In fact, the perfluoroethyl heteroarene products were generated in higher yield than the trifluoromethyl analogues. This higher yield was observed for 2-, 3-, and 4-bromopyridines. For example, 3-bromopyridine reacted with **2** to form 3-pentafluoroethylpyridine in 74% yield, and 2-methoxy-3-bromopyridine reacted with **2** to form the –C₂F₅ product in 65% yield. We propose the increased yields with **2** result, in part,

Scheme 3. Perfluoroethylation of Heteroaryl Bromides with (phen)CuCF₂CF₃ (2)^a


^aReaction conditions: bromoheteroarene (**5**, 0.10 mmol) and **2** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ¹⁹F NMR spectroscopy. Yields in parentheses are isolated yields. ^bYield of bis-perfluoroethylated product. ^cReaction was run at 100 °C. ^dIsolated product contains 7% of **7n**. ^eIsolated product contains 4% bis-perfluoroethylated product.

from the greater thermal stability of **2** compared to that of **1**. Heating complexes **1** and **2** separately in DMF at 80 °C caused 80% of **1** to decompose, compared to only 6% of **2** after 24 h.

The reactions of bromopyridines with **2** occurred with similar functional group compatibility as was observed for the reactions of **1** (Scheme 3). Although the yields were high in almost all cases, bromopyridines bearing electron-withdrawing substituents generally reacted in higher yields than those bearing electron-donating substituents. Various diazines also underwent the perfluoroethylation reaction.

In summary, we developed a simple synthetic procedure for the generation of perfluoroalkyl heteroarenes from reactions of stable CuCF₃ and CuC₂F₅ complexes **1** and **2** with heteroaryl bromides. These reactions are an improvement over current perfluoroalkylation reactions of heteroaryl iodides because heteroaryl bromides are significantly less expensive and more readily available than heteroaryl iodides. The high reactivity of complexes **1** and **2**, as well as the mild reaction conditions, allowed for the perfluoroalkylation of heteroaryl bromides containing both electron-donating and -withdrawing groups as well as electrophilic and protic functional groups. We anticipate that this process will enable the synthesis of perfluoroalkyl

derivatives of a wide range of heteroarenes as part of studies on structure–reactivity relationships.

■ ASSOCIATED CONTENT
Supporting Information

Experimental procedures, details on reaction development, and characterization of reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare the following competing financial interest(s): A provisional patent application has been filed by the University of California. J.F.H. is a founder of Catylix; he and the company may benefit financially from the expected results of the PHS-funded research conducted in his laboratory.

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■ REFERENCES

- (1) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
- (2) For reviews on perfluoroalkylation reactions, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.
- (3) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.
- (4) Sigma-Aldrich prices.
- (5) (a) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901. (b) Lishchynskiy, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. *J. Org. Chem.* **2013**, *78*, 11126. (c) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832.
- (6) For examples of radical trifluoromethylation reactions, see: (a) Ji, Y.; Bruecki, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (b) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.
- (7) (a) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793. (b) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 563.
- (8) (a) Tomashenko, O. A.; Escudero-Adán, E. C.; Belmonte, M. M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 7655. (b) Knauber, T.; Arian, F.; Röshenthaler, G.-V.; Gooßen, L. J. *Chem.—Eur. J.* **2011**, *17*, 2689. (c) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909. (d) Schareina, T.; Wu, X.-F.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Top. Catal.* **2012**, *55*, 426. (e) Urata, H.; Fuchikami, H. *Tetrahedron Lett.* **1991**, *32*, 91.
- (9) Kieltch, I.; Dubinina, G. G.; Hamacher, C.; Kaiser, A.; Torres-Nieto, J.; Hutchison, J. M.; Klein, A.; Budnikova, Y.; Vicic, D. A. *Organometallics* **2010**, *29*, 1451.