

Pd-Catalyzed α -Arylation of α,α -Difluoroketones with Aryl Bromides and Chlorides. A Route to Difluoromethylarenes

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S Supporting Information

ABSTRACT: We report the Pd-catalyzed α -arylation of α,α -difluoroketones with aryl and heteroaryl bromides and chlorides catalyzed by an air- and moisture-stable palladacyclic complex containing P(*t*-Bu)₂Cy₂ as ligand. The combination of this Pd-catalyzed arylation and base-induced cleavage of the acyl-aryl C–C bond within the α -aryl- α,α -difluoroketone constitutes a one-pot, two-step procedure to synthesize difluoromethylarenes from aryl halides. A broad range of electronically varied aryl and heteroaryl bromides and chlorides underwent these two transformations, providing α -aryl- α,α -difluoroketones, difluoromethylarenes, and difluoromethylheteroarenes in high yields.

Aromatic compounds containing a fluorine atom or a trifluoromethyl group on an aromatic ring are now widespread in medicinal chemistry.¹ It is well established that fluorine and trifluoromethyl substituents modulate the lipophilicity and metabolic stability of organic compounds; they also alter the non-covalent interactions of the aryl group, providing a method to affect binding affinities and selectivities.² However, compounds containing more complex alkyl groups with fluorine atoms at the benzylic position are less studied because they are challenging to prepare. Reliable methods to form a carbon–carbon bond between an aryl electrophile and a difluoroalkyl nucleophile have not been developed.³

This limitation on the coupling of aryl electrophiles with fluoroalkyl nucleophiles arises from several properties of fluoroalkyl groups. First, a majority of coupling reactions mediated by transition metal complexes form the aryl–alkyl bond by reductive elimination from an arylmetal alkyl intermediate,⁴ and this reductive elimination is slow when the alkyl group contains fluorine on the α carbon. Second, there are few methods to prepare α,α -difluoroalkylmetal reagents;⁵ therefore, transition-metal complexes containing an α,α -difluoroalkyl group are rare.

The carbonyl functionality is one of the cornerstones of organic chemistry because it can be transformed into a wide range of functional groups, including alcohols, amines, alkyl groups, and esters. Considering the versatile chemistry of the carbonyl functionality, we considered that an approach to prepare a variety of alkylarenes containing fluorine on the benzylic carbon atom would result from the coupling of aryl halides with fluorinated enolates. This coupling and subsequent derivatization could afford a variety of α -aryl- α,α -difluoro-carbonyl compounds. However, the couplings of fluorinated

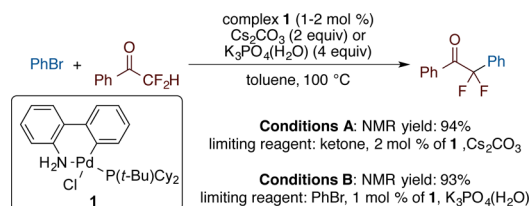
enolates with aryl electrophiles are limited to reactions that require stoichiometric amounts of copper, high temperatures, or both.⁶ Because of the severity of these reaction conditions, the scope of these coupling reactions is narrow and does not encompass haloarenes containing many of the common functional groups of medicinally important compounds.

We report the synthesis of a wide range of α -aryl- and α -heteroaryl- α,α -difluoroketones by palladium-catalyzed coupling of aryl and heteroaryl halides with difluoroacetophenones. We show that the products of these reactions can be converted, in addition to alcohols and amines by standard functional group interconversions, to the corresponding difluoromethylarenes by C–C bond cleavage. The reactions occur with an air-stable palladium catalyst and aryl halide as limiting reagent, thereby constituting a practical method to create a large family of difluoroalkylarene and heteroarene derivatives.

We initiated our studies by seeking to develop a mild, high-yielding Pd-catalyzed α -arylation of α,α -difluoroacetophenones. Prior studies on this reaction required an excess of toxic tributyltin fluoride,⁷ impractically high catalyst loadings (10 mol % Pd and 20 mol % ligand), and temperatures (130–160 °C) that were high enough to limit the tolerance of the process to auxiliary functionality and to lead to product mixtures that contained several materials resulting from P–C bond cleavage of the phosphine.^{6b}

We chose the direct arylation of α,α -difluoroacetophenone with bromobenzene shown in Scheme 1 as a model reaction to

Scheme 1. α -Arylation of α,α -Difluoroacetophenone with PhBr Catalyzed by Complex 1



identify an active Pd catalyst and reaction components to conduct this transformation under relatively mild conditions. We tested this reaction with Pd catalysts generated from 5 mol % of Pd(dba)₂ and a range of bisphosphines (BINAP, BIPHEP, DPPF, and DCPF) and monophosphines (PCy₃, P(*t*-Bu)₂Cy₂, P(*t*-Bu)₂Cy, P(*t*-Bu)₃, P(*t*-Bu)₂Ph, P(*t*-Bu)Ph₂,

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Table 1. α -Arylation of α,α -Difluoroacetophenone with Aryl Bromides and Aryl Chlorides Catalyzed by Complex 1^a

$$\text{ArX} + \text{Ph-CO-CF}_2\text{H} \xrightarrow[\text{toluene, 100 }^\circ\text{C for ArBr; 110 }^\circ\text{C for ArCl}]{\text{complex 1 (2 mol \% for conditions A; 1 mol \% for conditions B), Cs}_2\text{CO}_3 \text{ (2 equiv) for conditions A; K}_3\text{PO}_4(\text{H}_2\text{O}) \text{ (4 equiv) for conditions B}}$$

$$\text{Ar-CO-CF}_2\text{Ph} \quad \text{2a-2z, 3a-3e}$$

 2a X = Br, Conditions A: 89% Conditions B: 92% ^b X = Cl, Conditions B: 84% ^b	 2b X = Br, Conditions A: 72% Conditions B: 74% ^b	 2c X = Br, Conditions A: 92% ^c Conditions B: 85% X = Cl, Conditions B: 92%	 2d X = Br, Conditions A: 62% Conditions B: 91%	 2e X = Br, Conditions A: 93% Conditions B: 91% X = Cl, Conditions B: 88%	 2f X = Br, Conditions A: 91% Conditions B: 88% ^b X = Cl, Conditions B: 85% ^b	 2g X = Br, Conditions A: 84% Conditions B: 89% X = Cl, Conditions B: 81%
 2h X = Br, Conditions A: 87% Conditions B: 86% X = Cl, Conditions B: 84%	 2i X = Br, Conditions A: 86% Conditions B: 90% X = Cl, Conditions B: 89%	 2j X = Br, Conditions A: 88% Conditions B: 85% X = Cl, Conditions B: 83%	 2k X = Br, Conditions A: 92% Conditions B: 89%	 2l X = Br, Conditions A: 85% Conditions B: 88% X = Cl, Conditions B: 85%	 2m X = Br, Conditions A: 80% Conditions B: 87%	
 2n X = Br, Conditions A: 85% Conditions B: 81%	 2o X = Br, Conditions A: 91% Conditions B: 90% X = Cl, Conditions B: 93%	 2p X = Br, Conditions A: 90% Conditions B: 91%	 2q X = Br, Conditions A: 80% Conditions B: 77%	 2r X = Br, Conditions A: 82% Conditions B: 86%	 2s X = Br, Conditions A: 75% Conditions B: 72%	
 2t X = Br, Conditions A: 84% Conditions B: 81%	 2u X = Br, Conditions A: 86% Conditions B: 77%	 2v X = Br, Conditions A: 84% Conditions B: 88%	 2w X = Br, Conditions A: 72% ^{c,d}	 2x X = Br, Conditions A: 80% Conditions B: 81% X = Cl, Conditions B: 80%	 2y X = Br, Conditions A: 75% ^c Conditions B: 69%	
 2z X = Br, Conditions A: 72% ^c Conditions B: 65% X = Cl, Conditions B: 68%	 3a X = Cl, Condition B: 90% ^e	 3b X = Cl, Condition B: 92% ^e	 3c X = Cl, Condition B: 84% ^e	 3d X = Cl, Condition B: 88% ^e	 3e X = Cl, Condition B: 88% ^e	

^aConditions A: α,α -difluoroacetophenone (0.400 mmol), aryl bromide (0.800 mmol), Cs_2CO_3 (0.800 mmol), complex 1 (8.0 μmol), toluene (1 mL), 100 $^\circ\text{C}$, 24 h. Conditions B: aryl bromide or aryl chloride (0.200 mmol), α,α -difluoroacetophenone (0.400 mmol), $\text{K}_3\text{PO}_4(\text{H}_2\text{O})$ (0.800 mmol), complex 1 (2 μmol), toluene (1 mL), 100 $^\circ\text{C}$ for aryl bromide and 110 $^\circ\text{C}$ for aryl chloride, 30 h. ^bYields were determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as internal standard. ^cComplex 1 (20 μmol , 5 mol %). ^d120 $^\circ\text{C}$. ^eComplex 1 (4 μmol , 2 mol %).

PCy_2Ph , $\text{PAd}_2(n\text{-Bu})$, SPhos, and Q-Phos) in the presence of relatively weak base Cs_2CO_3 at 80 $^\circ\text{C}$ (see Table S1 in the Supporting Information). We found that the reaction catalyzed by the combination of $\text{Pd}(\text{dba})_2$ (5 mol %) and the rarely utilized phosphine $\text{P}(t\text{-Bu})\text{Cy}_2$ or $\text{PAd}_2(n\text{-Bu})$ (6 mol %) afforded the coupled product in 84% yield; the same reaction with $\text{P}(t\text{-Bu})\text{Cy}_2$ as ligand at 100 $^\circ\text{C}$ afforded the coupled product in 95% yield.

To render the catalyst convenient to use, we prepared a single-component palladacyclic complex 1 containing $\text{P}(t\text{-Bu})\text{Cy}_2$ as the dative ligand. Similar palladacyclic precursors have been used for C–C and C–N cross-coupling reactions.⁸ The model reaction occurred in high yields in the presence of 1–2 mol % of complex 1 as catalyst and Cs_2CO_3 as base with ketone as the limiting reagent (conditions A) or in the presence of $\text{K}_3\text{PO}_4(\text{H}_2\text{O})$ as base with bromobenzene as the limiting reagent (conditions B) in toluene at 100 $^\circ\text{C}$ (Scheme 1).

Selected results of our studies on the reaction scope are summarized in Table 1. These reactions were conducted under the two sets of conditions having ketone or haloarene as the limiting reagent (conditions A and B, as in Scheme 1). In general, a wide range of electronically varied aryl bromides and

aryl chlorides underwent this cross-coupling process with α,α -difluoroacetophenone in high yields. Reactions of aryl chlorides afforded the coupled products in yields that were comparable to those of reactions of the corresponding aryl bromides under conditions B (2a, 2c, 2e–2j, 2l, 2h, 2x, and 2z).

These arylation reactions tolerate a range of functionalities, including nitro (2d), ether (2g, 2i, and 2l), thioether (2h), ester (2q and 2u), non-enolizable ketone (2s), and carbamate (2v) moieties. Reactions of substrates bearing both bromo and chloro substituents occurred selectively at the bromide (2n), leaving the C–Cl bond intact and accessible for further functionalization. Free hydroxyl, aniline, amine, cyano, enolizable ketone, or aldehyde functionalities are not compatible with the reaction conditions. However, aryl bromides containing a dimethylamino (2o) or dimethylaminomethyl (2p) group, protected alcohol (2q), protected aldehyde (2r), or protected enolizable ketone (2t) coupled with α,α -difluoroacetophenone in high yields. The scope of the reaction also encompassed α,α -difluoroacetophenones containing a variety of electronically varied aryl groups.⁹ The reactions of these ketones with 4-chloroanisole were conducted under conditions B with 2 mol % of complex 1, and the coupled

products (**3a–3e** in Table 1) were isolated in high yields (84–92%).

The coupling of difluoroacetophenone also occurred with brominated nitrogen-containing heterocycles, such as bromopyridine, quinolines, and isoquinoline (**2w–2z**). For these reactions a higher catalyst loading (5 mol %) (**2w**, **2y**, and **2z** with conditions A) and temperature (120 °C) (**2w**) were used to obtain good yields of the coupled products.

These coupling reactions can be conducted without a drybox and on a larger scale. The coupling of α,α -difluoroacetophenone with 2-(3-bromophenyl)-1,3-dioxolane conducted outside a drybox on a 2 mmol scale catalyzed by only 0.5 mol % of complex **1** occurred in a high yield (89%) similar to that of the reaction conducted inside a drybox on a smaller scale (**2r**, Table 1). Thus, these reactions should be practical for a number of applications in medicinal chemistry.

The α -aryl- α,α -difluoroacetophenone products of the coupling process undergo reactions characteristic of typical carbonyl functionality. For example, they undergo nucleophilic addition of Grignard reagents to form tertiary alcohols, and they are reduced by NaBH₄ to afford primary alcohols (see the Supporting Information for details). Of particular interest, the C–C bond adjacent to the carbonyl group in these ketones can be readily cleaved to afford difluoromethylarenes (ArCF₂H).

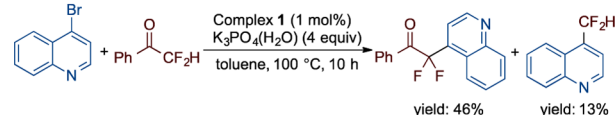
Aromatic compounds containing a difluoromethyl (CF₂H) group are valuable for medicinal chemistry because the difluoromethyl group can act as a bio-isostere of alcohols and thiols and as a lipophilic hydrogen bond donor.¹⁰ However, methods for the introduction of the difluoromethyl group onto arenes are limited, and each method has significant limitations.

The most common method to access these difluoromethylarenes is the deoxofluorination of benzaldehydes with sulfur tetrafluoride and *N,N*-diethylaminosulfur trifluoride derivatives.¹¹ However, these fluorinating reagents are highly sensitive toward moisture and can undergo explosive decomposition upon heating. Amii's group reported a three-step sequential reaction sequence comprising copper-mediated cross-coupling of aryl iodides with α -silyldifluoroacetates, hydrolysis of the α -aryldifluoroacetates, and decarboxylation of the resulting α -aryldifluoroacetic acids.^{6a,12} However, these sequential reactions occurred in overall modest yields, required 200 °C for the decarboxylation of α -aryl-difluoroesters containing electron-neutral aryl groups, and did not occur with those containing electron-rich aryl groups. Baran and co-workers reported a direct introduction of the difluoromethyl group onto heteroarenes with zinc difluoromethanesulfinate.¹³ However, reactions with arenes have not been reported thus far, and the regioselectivity for reactions of heteroarenes is distinct from that of halogenated heteroarenes. Finally, our group and Prakash's group recently reported copper-mediated difluoromethylation of aryl iodides with Me₃SiCF₂H and *n*-Bu₃SnCF₂H, respectively, but the scope of these reactions is limited to aryl iodides.¹⁴

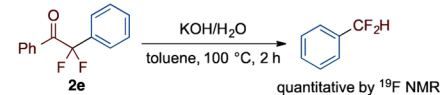
Our investigation of the base-induced cleavage of the α -aryl- α,α -difluoroacetophenone products to form difluoromethylarene was spurred by the observation of small but significant amounts of 4-difluoromethylquinoline (13%) from the coupling of α,α -difluoroacetophenone with 4-bromoquinoline (Scheme 2A). We found that the analogous base-induced C–C cleavage of isolated α -phenyl- α,α -difluoroacetophenone (**2e**) occurred in the presence of KOH and H₂O in toluene at 100 °C (Scheme 2B) to afford (difluoromethyl)benzene in quantitative yield in 2 h, as determined by ¹⁹F NMR spectroscopy.

Scheme 2. Base-Induced C–C Cleavage of α -Aryl- α,α -difluoroacetophenones

A. Formation of 4-difluoromethylquinoline during the coupling of 4-bromoquinoline with α,α -difluoroacetophenone

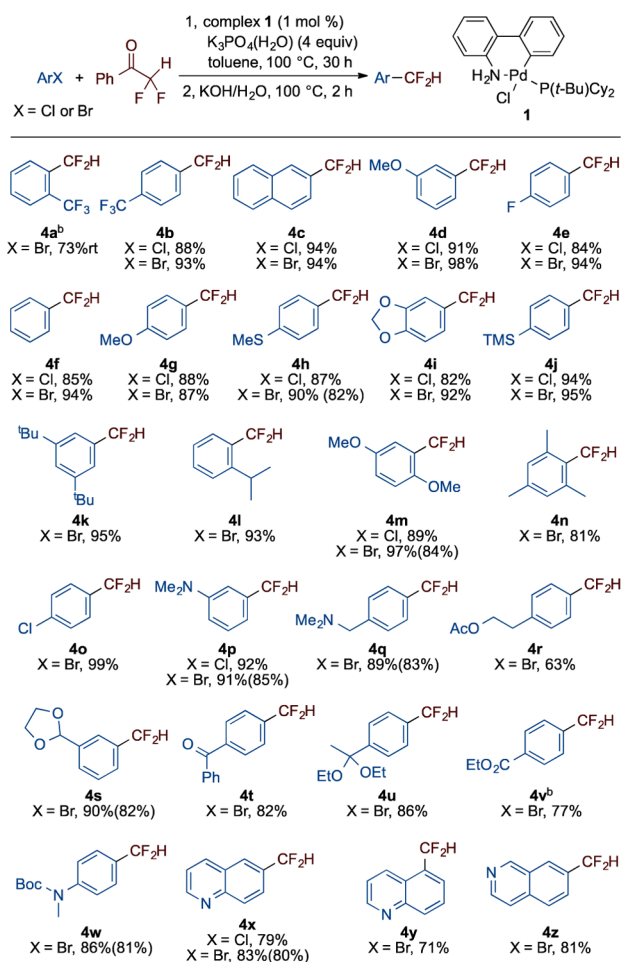


B. Haller-Bauer reaction of α -phenyl- α,α -difluoroacetophenone (**2e**)



Having demonstrated the α -arylation and the C–C bond cleavage as individual steps, we developed a one-pot procedure for the synthesis of difluoromethylarenes. The scope of aryl bromides and aryl chlorides that undergo the combination of α -arylation and the base-induced C–C bond cleavage is summarized in Table 2. In many cases, the resulting

Table 2. One-Pot Synthesis of Difluoromethylarenes^a



^aConditions: step 1, aryl bromide or aryl chloride (0.200 mmol), α,α -difluoroacetophenone (0.400 mmol), K₃PO₄(H₂O) (0.800 mmol), complex **1** (2 μ mol), toluene (1 mL), 100 °C for aryl bromide and 110 °C for aryl chloride, 30 h; step 2, KOH (100 mg), H₂O (50 μ L), 100 °C, 2 h. Yields are determined by ¹⁹F NMR spectroscopy with 1-bromo-4-fluorobenzene as internal standard. Isolated yields are shown in parentheses for products with high boiling points. ^bStep 2 was conducted at room temperature.

difluoromethylarenes are volatile, and the yields of these reactions were determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard. Isolated yields were obtained for the reactions affording the difluoromethylarenes with high boiling points.

The scope of aryl bromides and aryl chlorides that undergo this transformation mirrors the scope of aryl bromides and aryl chlorides that undergo Pd-catalyzed α -arylation of α,α -difluoroacetophenone described in Table 1. In general, a wide range of electronically varied aryl bromides and aryl chlorides underwent this reaction sequence to afford the corresponding difluoromethylarenes in high yields. Reactions of aryl chlorides afforded the desired products in yields comparable to those of the reactions of aryl bromides (**4b–4j**, **4m**, **4p**, and **4x**). Like the single-step coupling reaction, the sequential reactions tolerate a range of functionalities, including ether (**4d**, **4g**, and **4i**), thioether (**4h**), ester (**4r** and **4v**), non-enolizable ketone (**4t**), and carbamate (**4w**) moieties. Reactions of 1-bromo-4-chlorobenzene occurred selectively at the bromide (**4o**), and aryl bromides containing *N,N*-dimethylamino (**4p**), dimethylaminomethyl (**4q**), protected alcohol (**4r**), protected aldehyde (**4s**), and protected enolizable ketone (**4u**) functionality reacted to form the corresponding difluoromethylarenes in high yields. Brominated nitrogen-containing heterocycles, such as quinolines (**4x** and **4y**) and isoquinoline (**4z**), also gave the difluoromethyl heteroarenes in good yields.

In summary, we have developed a convenient and efficient protocol for the coupling of α,α -difluoroketones with aryl and heteroaryl bromides and chlorides catalyzed by a single-component, moisture- and air-stable palladacyclic precatalyst **1**. The mechanism of this reaction likely comprises oxidative addition of the aryl halide, generation of an arylpalladium fluoroenolate complex, and reductive elimination of the α -aryl- α,α -difluoroketone product from the arylpalladium fluoroenolate complex. Reductive elimination reactions from perfluoroalkyl complexes have been limited to those from complexes of bisphosphines that bind with large bite angles or from complexes of phosphines containing extremely hindered substituents.¹⁵ The catalyst used for the difluoroenolate coupling reported here contains a ligand that has rarely been used for catalysis but contains standard alkyl substituents. Studies to understand the relationship between reductive elimination from perfluoroalkyl complexes and fluorinated enolate complexes will be the subject of future work.

■ ASSOCIATED CONTENT

📄 Supporting Information

Detailed experimental procedure, characterization of all compounds, and ^1H and ^{13}C NMR spectra of all compounds. 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) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
- (2) (a) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Compounds: Principles and Commercial Applications*; Plenum: New York, 2000. (b) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2013.
- (3) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669.
- (4) Enchavarren, A. M.; Cárdenas, D. J. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008; Vol. 1, p 1.
- (5) Zemtsov, A. A.; Kondratyev, N. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2013**, *79*, 818.
- (6) (a) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560. (b) Guo, C.; Wang, R.-W.; Qing, F.-L. *J. Fluorine Chem.* **2012**, *143*, 135.
- (7) Guo, Y.; Shreeve, J. n. M. *Chem. Commun.* **2007**, 3583.
- (8) (a) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876. (c) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916.
- (9) Reactions of aliphatic ketones $\text{RCH}_2\text{C}(\text{O})\text{CF}_2\text{H}$ so far occur at the non-fluorinated methylene position.
- (10) (a) Araújo, R.; Anhalt, E.; René, L.; Badet-Denisot, M.-A.; Courvalin, P.; Badet, B. *Biochemistry* **2000**, *39*, 15971. (b) Hope, H. R. *J. Lipid Res.* **2000**, *41*, 1604.
- (11) (a) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787. (b) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (c) Dolbier, W. R.; Xie, P.; Zhang, L.; Xu, W.; Chang, Y.; Abboud, K. A. *J. Org. Chem.* **2008**, *73*, 2469.
- (12) Fujikawa, K.; Kobayashi, A.; Amii, H. *Synthesis* **2012**, *44*, 3015.
- (13) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494.
- (14) (a) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (b) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swaback, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090.
- (15) (a) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644. (b) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.