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A Trifluoromethylcarbene Source

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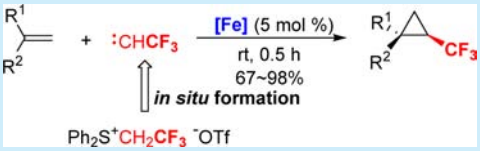
Supporting Information

ABSTRACT: The trifluoromethylcarbene (:$CHCF_3$) was found to be conveniently generated from (2,2,2-trifluoroethyl)diphenyl-sulfonium triflate ($Ph_2S^+CH_2CF_3$ ^-OTf), which was successfully applied in Fe-catalyzed cyclopropanation of olefins, giving the corresponding trifluoromethylated cyclopropanes in high yields.



Trifluoromethylcarbene has proven to be a versatile intermediate for the synthesis of CF_3-containing compounds, which have found widespread application in medicinal and agricultural chemistry due to the unique properties of CF_3-functionality.[1] As a triplet carbene, trifluoromethylcarbene has been applied to a variety of organic transformations,[2] such as trifluoroethylation,[3] cyclopropanation,[4] cyclopropenation,[4f] and aziridination.[5] In spite of these important accomplishments, the safe generation of trifluoromethylcarbene remains a significant challenge. There has been only one known source to produce trifluoromethylcarbene, 2,2,2-trifluorodiazoethane (CF_3CHN_2), which is generated from 2,2,2-trifluoroethyl amine.[2−5] A severe limitation of CF_3CHN_2 is that it is a gas, which is potentially explosive and toxic. As is well-known, carbene could be readily generated from ylides including phosphonium ylides[6] and sulfur ylides.[7] Based on our previous observation that difluorocarbene can be produced from phosphonium ylide[8] and that (2,2,2-trifluoroethyl)diphenylsulfonium triflate ($Ph_2S^+CH_2CF_3$ ^-OTf, **2**) is a mild and general trifluoroethylidenesulfur ylide reagent,[9] we speculated that this sulfur ylide reagent may serve as a trifluoromethylcarbene precursor and have now investigated its application in Fe-catalyzed cyclopropanation of olefins.

We have shown that trifluoroethylidenesulfur ylide is a valuable tool for the cyclopropanation of olefins.[9] However, as is the case for most sulfur ylides, this ylide can only be applied to the conversion of electron-deficient olefins by this approach, not to electron-neutral or -rich olefins. Interestingly, the use of the sulfur ylide as the trifluoromethylcarbene precursor allows for the cyclopropanation of electron-rich, -neutral, and -deficient aryl olefins. The preliminary results are described herein.

Since copper complexes such as cupric sulfate ($CuSO_4$)[10] and cupric acetylacetonate [$Cu(acac)_2$][11] and a rhodium complex[7a] have been found to be able to promote the cyclopropanation with sulfur ylide, we first employed these metal sources as catalysts to examine the conversion of 4-methoxystyrene (**1a**) with **2** in the presence of TBAT, a known nice base for deprotonation of **2** to generate trifluoroethylidenesulfur ylide[9] (Table 1, entries 1−3). Disappointingly, none of them were effective enough for this reaction, prompting us to search for other suitable catalysts. As porphyrin-coordinated transition-metal complexes can efficiently catalyze many transformations,[12] various porphyrin complexes (TPP)M (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine) were then screened (Table 1, entries 4−7). To our delight, a 40% yield was obtained with the use of (TPP)FeCl as the catalyst (Table 1, entry 5). A brief survey of the reaction solvents (Table 1, entries 8−11) revealed that DMA was a suitable solvent, in which the conversion gave the desired product in 88% yield (Table 1, entry 11). Lowering the loading of the catalyst led to a dramatic decrease of the yield (Table 1, entry 12). The examination of the molar ratio of the starting materials (Table 1, entries 13−15) showed that a slight excess of **2** and base could afford the product in high yield (Table 1, entry 14). Other bases were also effective for this reaction (Table 1, entries 15−18). Compared to TBAT, CsF was a better choice due to the cost and the atom-economy issues (Table 1, entry 16). Elevating the temperature did not increase the yield (Table 1, entry 19). Increasing the concentration of starting materials and shortening the reaction time gave comparable yields (Table 1, entries 20−22). The reaction proceeded very fast and could give the product in 85% yield within 0.5 h (Table 1, entry 22).

We then explored the scope of the trifluoromethylcarbene's cyclopropanation under the optimized reaction conditions (Table 1, entry 22). As shown in Scheme 1, the scale was increased by 5-fold to show the practicality and generality of this transformation. Interestingly, **3a** was obtained in a slightly higher yield on the increased scale (^{19}F NMR yield: 91% vs 85%). High diastereoselectivity was observed in all reactions, and the diastereoselectivity determined by ^{19}F NMR was above 98/2 in all cases with the exception of **3p** and **3q**. The *trans*-configuration was assigned by $^1H-^1H$ NOESY analysis of **3a** (see Supporting Information). All of the electron-rich, -neutral, and -deficient aryl olefins could be converted smoothly to the expected products in good to excellent yields (**3a**−**3o**). The conversion of terminal olefins might not be particularly

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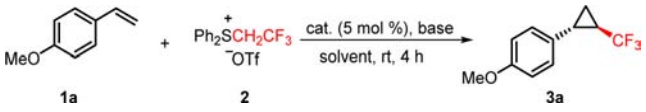
Table 1. Optimization of Reaction Conditions[a]

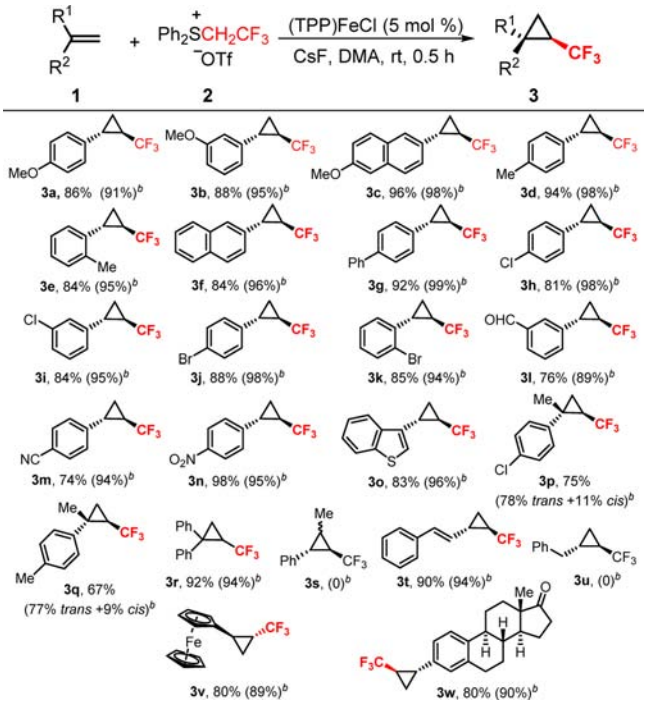


1a 2 3a

entry	solvent	cat.	base	ratio[b]	yield (%)[c]
1	Cy	$CuSO_4$	TBAT	1:2:2	0
2	Cy	$Cu(acac)_2$	TBAT	1:2:2	16
3	Cy	$Rh_2(OAc)_4$	TBAT	1:2:2	0
4	Cy	(TPP)Cu	TBAT	1:2:2	0
5	Cy	(TPP)FeCl	TBAT	1:2:2	40
6	Cy	(TPP)Co	TBAT	1:2:2	3
7	Cy	(TPP)Ni	TBAT	1:2:2	0
8	DCM	(TPP)FeCl	TBAT	1:2:2	10
9	THF	(TPP)FeCl	TBAT	1:2:2	59
10	DMF	(TPP)FeCl	TBAT	1:2:2	74
11	DMA	(TPP)FeCl	TBAT	1:2:2	88
12[d]	DMA	(TPP)FeCl	TBAT	1:2:2	68
13	DMA	(TPP)FeCl	TBAT	2:1:1	83
14	DMA	(TPP)FeCl	TBAT	1:1.1:1.2	86
15	DMA	(TPP)FeCl	TBAT	1.1:1:1.1	81
16	DMA	(TPP)FeCl	CsF	1:1.1:1.2	88
17	DMA	(TPP)FeCl	Cs_2CO_3	1:1.1:1.2	82
18	DMA	(TPP)FeCl	TBAF	1:1.1:1.2	62
19[e]	DMA	(TPP)FeCl	CsF	1:1.1:1.2	85
20[f,g]	DMA	(TPP)FeCl	CsF	1:1.1:1.2	85
21[f,g]	DMA	(TPP)FeCl	CsF	1:1.1:1.2	82
22[f,h]	DMA	(TPP)FeCl	CsF	1:1.1:1.2	85

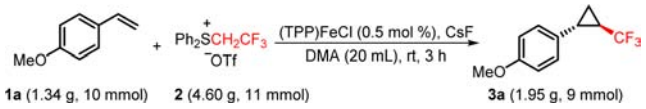
[a]Reaction conditions: **1a** (0.1 mmol), **2** and base in solvent (2 mL); Cy = cyclohexane; TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine. [b]Molar ratio of **1a**:**2**:base. [c]Determined by ^{19}F NMR with the use of trifluoromethylbenzene as an internal standard. [d]2.5 mol % of the catalyst was used. [e]The reaction was performed at 50 °C. [f]1 mL of DMA was used. [g]The reaction time was shortened to 1 h. [h]The reaction time was shortened to 0.5 h.

Scheme 1. Substrate Scope for Cyclopropanation[a]



[a]Isolated yields. [b]Yields were determined by ^{19}F NMR.

Scheme 2. Large-Scale Reaction



sensitive to steric effects, as evidenced by the high yields obtained for products **3p**−**3r**. But the steric effects obviously affect the diastereoselectivity (**3p**−**3q**). In the case of the internal olefin, no desired product was detected by ^{19}F NMR (**3s**). The conversion could be applied well to conjugated aryl 1,3-diene (**3t**). For the reaction of conjugated aliphatic 1,3-diene, a very low yield (<20%) was obtained. Aliphatic olefin cannot be converted at all under these optimal conditions due to its lower reactivity (**3u**). Since Ferrocene derivatives have been widely used as ligands or catalysts,[13] the incorporation of a CF_3-cyclopropyl motif into this scaffold may find new applications in catalytic chemistry (**3v**). The utility of this cyclopropanation reaction was further demonstrated by the development of a convenient route to a CF_3-cyclopropyl estrone derivative (**3w**).

For the small-scale reaction, a 5 mol % of the catalyst loading was required, and the decrease in the catalyst loading would dramatically decrease the yield (Table 1, entry 12 vs 11). However, the use of 0.5 mol % catalyst could afford the desired product in 90% yield (1.95 g) with increase of the scale of the reaction by 100-fold (Scheme 2), demonstrating the synthetic utility of this protocol from a practical point of view.

As the incorporation of the CF_3 group into cyclopropanes represents important structural modifications which can improve the bioactivity of the target molecules,[14] the synthesis of CF_3-cyclopropanes has received a great deal of attention from the synthetic community. Traditional approaches such as intramolecular cyclization of CF_3-substrates suffer from tedious procedures to prepare the starting materials.[4a,15] Recently, Baran found that trifluoromethylcyclopropyl sulfinate salt is a good reagent for a radical reaction to afford CF_3-cyclopropanes.[16] But only one position of the cyclopropyl ring is substituted. Obviously, one of the most straightforward and convenient protocols is the cyclopropanation of olefins with CF_3-containing reagents. As the most commonly used reagent, 2,2,2-trifluorodiazoethane (CF_3CHN_2) has been widely used in the transition-metal-catalyzed cyclopropanation reactions.[4b,d−f] However, CF_3CHN_2 is a gas which is potentially explosive and toxic, thus limiting its application. We have previously reported that **2** is an efficient sulfur ylide reagent for cyclopropanation of olefins, but is only limited to electron-deficient olefins under metal-free conditions.[9] Apparently, the protocol described above is attractive and promising due to the ready availability of salt **2**, a wide substrate scope, and mild reaction conditions.

Trifluoromethylcarbene cannot be directly observed in the reaction system by ^{19}F NMR. Fortunately, we found that salt **2** can react with (TPP)FeCl under the optimal reaction conditions in the absence of olefin substrate to give CF_3-olefins **4**, which was determined by ^{19}F NMR and HRMS (High Resolution Mass Spectroscopy) (Scheme 3, eq 1). The formation of CF_3-olefins suggests that a trifluoromethylcarbene species is formed. If this is the case, **2** should be finally converted to diphenylsulfide (Ph_2S) in the catalytic cyclopropanation reaction. Indeed, Ph_2S was isolated in high yield for cyclopropanation of olefin **3a** (Scheme 3, eq 2). Based on the previous reports that carbene can react with aldehydes in

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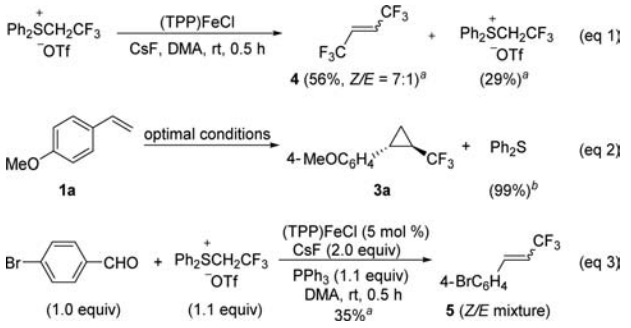
Scheme 3. Experimental Evidence

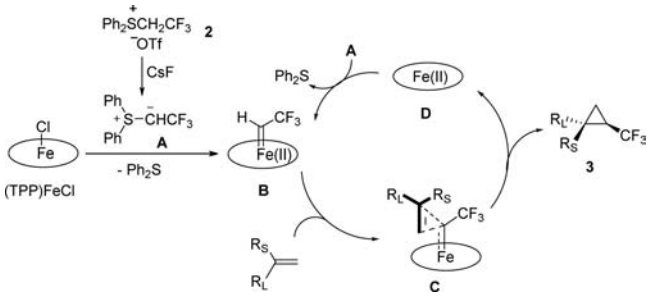


[a]Determined by ^{19}F NMR. [b]Isolated yield based on salt **2**.

the presence of the Ph_3P/Fe-catalyst to give olefins,[17] we examined the conversion of aldehyde 4-BrC_6H_4CHO with the Ph_3P/Fe-catalyst/**2** system to find out if olefin could be produced (Scheme 3, eq 3). Gratifyingly, the aldehyde was successfully transformed into the desired olefin **5**, further supporting the trifluoromethylcarbene hypothesis.

On the basis of the above results, we proposed a reaction mechanism shown in Scheme 4. Sulfur ylides have been

Scheme 4. A Plausible Reaction Mechanism Was Proposed



regarded as substitutes for diazo compounds.[7b] Since ethyl diazoacetate is known to be a mild reducing agent[18] and can reduce porphyrin-coordinated iron(III) to iron(II),[18b] trifluoroethylidenesulfur ylide might also be able to result in the reduction of iron(III) to iron(II). Therefore, the reaction of catalyst (TPP)FeCl with ylide **A** produced from **2** by deprotonation may generate iron(II) carbene species **B**. The olefin substrate approaches the intermediate **B** by the orientation that the substituents R_L and R_S project up and out of the porphyrin plane due to the steric effects (transition state **C**). This orientation explains why internal olefin is inert under these reaction conditions, since the substituent of the internal olefin suffers steric hindrance with the porphyrin ring. The high *trans* selectivity is determined by the steric interaction between the bulky R_L and CF_3 groups.[18b] Cyclopropanation of transition state **C** furnishes the final product **3** and iron(II) complex **D**, which should be the resting state of the catalyst ready for another catalytic turnover.[19]

In conclusion, we found that trifluoromethylcarbene was conveniently converted from the corresponding sulfur ylide. The highly diastereoselective Fe-catalyzed cyclopropanation of olefins was successfully realized to give CF_3-cyclopropanes in high yields. Compared with the widely used trifluoromethylcarbene precursor CF_3CHN_2, a gas which is potentially explosive and toxic, $Ph_2S^+CH_2CF_3$ OTf^- is shelf-stable and easily prepared. This sulfonium salt might be reasonably expected to become an efficient and versatile trifluoromethylcarbene reagent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01042.

Experimental procedures and characterization for new compounds are provided (PDF)

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Notes

The authors declare no competing financial interest.

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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.; Sanchez-Rosello, M.; Acena, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; John Wiley & Sons Ltd.: United Kingdom, 2009.

(2) (a) Molander, G. A.; Ryu, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 14181. (b) Argintaru, O. A.; Ryu, D.; Aron, I.; Molander, G. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13656. (c) Morandi, B.; Carreira, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085. (d) Morandi, B.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 5984. (e) Molander, G. A.; Cavalcanti, L. N. *Org. Lett.* **2013**, *15*, 3166. (f) Cai, A.-J.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2015**, *51*, 8946.

(3) (a) Liu, C. B.; Meng, W.; Li, F.; Wang, S.; Nie, J.; Ma, J. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6227. (b) Luo, H.; Wu, G.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14503. (c) Wu, G.; Deng, Y.; Wu, C.; Wang, X.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4477. (d) Atherton, J. H.; Fields, R. *J. Chem. Soc. C* **1968**, 2276.

(4) For a recent review, please see: (a) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803. For recent examples, please see: (b) Zhu, C.-L.; Yang, L.-J.; Li, S.; Zheng, Y.; Ma, J.-A. *Org. Lett.* **2015**, *17*, 3442. (c) Le Maux, P.; Juillard, S.; Simonneaux, G. *Synthesis* **2006**, *2006*, 1701. (d) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (e) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (f) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938.

(5) (a) Chai, Z.; Bouillon, J.-P.; Cahard, D. *Chem. Commun.* **2012**, *48*, 9471. (b) Kunzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900.

(6) (a) Fedorov, A.; Moret, M. E.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 8880. (b) Van Asselt, A.; Burger, B. J.; Gibson, V. C.; Bercaw, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 5347. (c) Johnson, L. K.; Frey, M.; Ulibarri, T. A.; Virgil, S. C.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8167.

DOI: 10.1021/acs.orglett.6b01042
Org. Lett. 2016, 18, 2471−2474

(7) (a) Muller, P.; Fernandez, D.; Nury, P.; Rossier, J.-C. *Helv. Chim. Acta* **1999**, *82*, 935. (b) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. *Eur. J. Org. Chem.* **2013**, *2013*, 5005.
(8) (a) Deng, X.-Y.; Lin, J.-H.; Xiao, J.-C. *J. Fluorine Chem.* **2015**, *179*, 116. (b) Deng, X. Y.; Lin, J. H.; Zheng, J.; Xiao, J. C. *Chem. Commun.* **2015**, *51*, 8805. (c) Zheng, J.; Cai, J.; Lin, J. H.; Guo, Y.; Xiao, J. C. *Chem. Commun.* **2013**, *49*, 7513. (d) Zheng, J.; Lin, J. H.; Cai, J.; Xiao, J. C. *Chem. - Eur. J.* **2013**, *19*, 15261. (e) Zheng, J.; Lin, J. H.; Deng, X. Y.; Xiao, J. C. *Org. Lett.* **2015**, *17*, 532. (f) Zheng, J.; Lin, J. H.; Yu, L. Y.; Wei, Y.; Zheng, X.; Xiao, J. C. *Org. Lett.* **2015**, *17*, 6150.
(9) Duan, Y.; Zhou, B.; Lin, J. H.; Xiao, J. C. *Chem. Commun.* **2015**, *51*, 13127.
(10) Trost, B. M. *J. Am. Chem. Soc.* **1966**, *88*, 1587.
(11) Cohen, T.; Herman, G.; Chapman, T. M.; Kuhn, D. *J. Am. Chem. Soc.* **1974**, *96*, 5627.
(12) (a) Lemon, C. M.; Dogutan, D. K.; Nocera, D. G. An Overview of Metalloporphyrin-Catalyzed Carbon and Nitrogen Group Transfer Reactions. In *Handbook of Porphyrin Science*; Anding, B. J., Woo, L. K., Eds.; World Scientific: 2010; Vol. *100*, pp 145−319. (b) Zhu, S. F.; Zhou, Q. L. *National Science Review* **2014**, *1*, 580.
(13) (a) Atkinson, R. C.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313. (b) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101. (c) Gomez Arrayas, R.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674.
(14) (a) Kim, J. Y.; Seo, H. J.; Lee, S. H.; Jung, M. E.; Ahn, K.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 142. (b) Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X. H.; Amin, J.; Snodgrass, B.; Hatsis, P. *ACS Med. Chem. Lett.* **2013**, *4*, 514. (c) Abraham, S.; Bhagwat, S.; Campbell, B. T.; Chao, Q.; Faraoni, R.; Holladay, M. W.; Lai, A. G.; Rowbottom, M. W.; Setti, E.; Sprankle, K. G. Quinazoline derivatives as raf kinase modulations and methods of use thereof. WO2009117080, 2009. (d) London, C.; Hoyt, S. B.; Parsons, W. H.; Williams, B. S.; Warren, V. A.; Tschirret-Guth, R.; Smith, M. M.; Priest, B. T.; McGowan, E.; Martin, W. J.; Lyons, K. A.; Li, X.; Karanam, B. V.; Jochnowitz, N.; Garcia, M. L.; Felix, J. P.; Dean, B.; Abbadie, C.; Kaczorowski, G. J.; Duffy, J. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1696. (e) Mori, T.; Ujihara, K.; Matsumoto, O.; Yanagi, K.; Matsuo, N. *J. Fluorine Chem.* **2007**, *128*, 1174. (f) Phillips, D. J.; Davenport, R. J.; Demaude, T. A.; Galleway, F. P.; Jones, M. W.; Knerr, L.; Perry, B. G.; Ratcliffe, A. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4146.
(15) (a) Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett.* **2000**, *2*, 2423. (b) Katagiri, T.; Yamaji, S.; Handa, M.; Irie, M.; Uneyama, K. *Chem. Commun.* **2001**, 2054. (c) Risse, J.; Fernández-Zúmel, M. A.; Cudré, Y.; Severin, K. *Org. Lett.* **2012**, *14*, 3060.
(16) Gianatassio, R.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9851.
(17) (a) Mirafzal, G. A.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 176. (b) Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714. (c) Cheng, G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2003**, *22*, 1468.
(18) (a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300. (b) Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.
(19) Lai, T.-S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, 4845.

DOI: 10.1021/acs.orglett.6b01042
Org. Lett. 2016, 18, 2471−2474