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Copper-Catalyzed Direct Propargylation of Polyfluoroarenes with Secondary Propargyl Phosphates

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Supporting Information

ABSTRACT: A copper-catalyzed direct propargylation of polyfluoroarenes with secondary propargyl phosphates has been developed. The reaction proceeds under mild reaction conditions with high efficiency and regioselectivity and provides a concise and straightforward method for the synthesis of polyfluoroarylated derivatives of interest in both life and materials science.

Propargylation of arenes is a fundamental transformation in organic synthesis, allowing access to various useful molecules.[1] A classical technique used to prepare propargylated compounds relies on the Nicholas reaction.[2] However, the requirement of a stoichiometric amount of $Co_2(CO)_8$ in a multistep procedure restricts its widespread applications in organic synthesis. In this regard, transition-metal-catalyzed cross-couplings or Lewis acid promoted direct C−H propargylations of arenes have emerged as efficient and straightforward alternatives.[3,4] However, such Friedel−Crafts type reactions are generally limited to electron-rich arenes. To the best of our knowledge, the direct C−H propargylation of electron-deficient arenes has not been reported thus far, and it remains a synthetic challenge due to the poor reactivities of electron-deficient arenes. Inspired by our recent work on palladium-catalyzed direct allylation of polyfluoroarenes,[5] we envisioned that the transition-metal-catalyzed C−H propargylation of higly electron-deficient polyfluoroarenes with propargylic electrophiles would be possible and would provide a facile access to propargylated, electron-deficient arenes.

Over the past few years, significant progress has been made in the direct C−H functionalization of polyfluoroarenes.[6] However, most of them mainly focus on the construction of a $C(sp^2)-C(sp^2)$ bond. To date, only limited examples of direct C−H functionalization of polyfluoroarenes with formation of a $C(sp^2)-C(sp^3)$ bond have been reported.[7] In particular, the introduction of a secondary alkyl group, such as a secondary propargyl group, onto polyfluoroarenes remains challenging, although the secondary allylation[7a,b] and benzylation[7f] of polyfluoroarenes have been developed. Recently, a copper-catalyzed cross-coupling between electron-deficient polyfluoroarenes and propargylic alcohol derivatives has been reported, but only allenic polyfluoroarenes were provided.[8] Herein, we report a copper-catalyzed, direct propargylation of polyfluoroarenes with secondary propargyl phosphates. This method provides facile access to branched, propargylated polyfluoroarenes with high regioselectivity, which can serve as versatile building blocks in the synthesis of various useful polyfluoroarene derivatives of interest in both life and materials science.

Initially, according to our previous work,[5a,b] we set out to investigate the feasibility of palladium-catalyzed reactions between pentafluorobenzene **1a** and a series of propargyl electrophiles. However, we immediately found that it is difficult to obtain propargylated pentafluorobenzene with this strategy because of the decomposition of propargyl electrophiles at high reaction temperature (120−140 °C). Considering that the acidity of pentafluorobenzene **1a** can enable the strong base, such as *t*-BuOLi, to react with **1a** and copper under mild reaction conditions to generate a pentafluorophenylcopper (C_6F_5Cu) species,[9] we then turned our attention to the copper-catalyzed propargylation of polyfluoroarenes.

We began this study by choosing secondary propargyl phosphate **2a** as a model substrate (Table 1), which can be easily prepared from the reaction of ethynyltriisopropylsilane with an aliphatic aldehyde. Furthermore, the deprotected, terminal alkyne can serve as a versatile functional group for further transformations. However, no product **3a** was formed when the reaction was carried out with **1a** (2.0 equiv), **2a** (1.0 equiv), and *t*-BuOLi in the presence of CuCl (20 mol %) and 1,10-phenanthroline (phen) in THF at 50 °C (entry 1). Switching the ligand from phen to bipyridine (bpy) also failed to provide **3a** (entry 2). When PPh_3 was used as a ligand, a 20% yield of **3a** was afforded without observation of an allenic side product (entry 3). Encouraged by this result, a survey of the phosphine ligands and copper catalysts were conducted (entries 4 and 5; for details, see the Supporting Information). It was found that the absence of ligand with CuOAc as a catalyst can dramatically improve the yield of **3a** to 45% (entry 6). Increasing the reaction temperature to 80 °C benefited the reaction efficiency and provided **3a** in a 68% yield (entry 7). Other bases, such as *t*-BuONa and *t*-BuOK, or alternative

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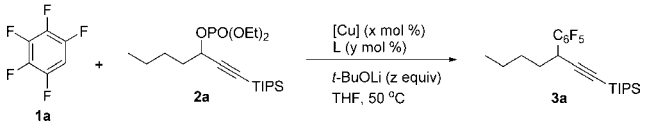
Table 1. Representative Results for Optimization of Cu-Catalyzed Cross-Coupling of Pentafluorobenzene 1a with Secondary Propargyl Phosphate 2a[a]



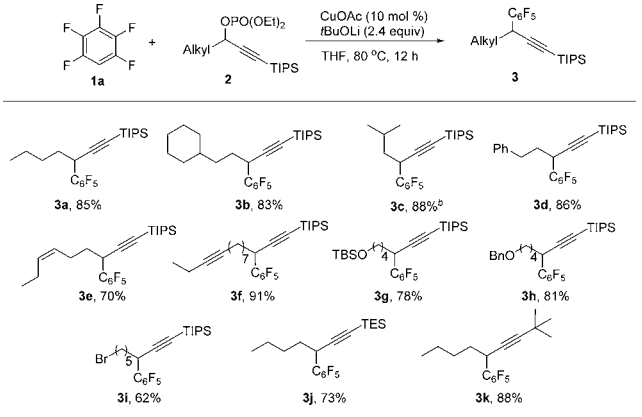
entry	[Cu] (x)	ligand (y)	t-BuOLi (equiv)	yield (%)[b]
1	CuCl (20)	phen (20)	(1.2)	ND
2	CuCl (20)	bpy (20)	(1.2)	ND
3	CuCl (20)	PPh_3 (40)	(1.2)	20
4	CuI (20)	PPh_3 (40)	(1.2)	21
5	CuOAc (20)	PPh_3 (40)	(1.2)	30
6	CuOAc (20)	–	(1.2)	45
7	CuOAc (20)	–	(1.2)	68[c]
8	CuOAc (20)	–	(2.4)	75[d]
9	CuOAc (10)	–	(2.4)	90 (85)[e]
10	–	–	(2.4)	ND

[a]Reaction conditions (unless otherwise specified): **1a** (0.6 mmol), **2a** (0.3 mmol, 1.0 equiv), 50 °C, THF (1 mL), 8 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard and number in parentheses is isolated yield. [c]Reaction run at 80 °C. [d]**1a** (2.0 equiv), **2a** (0.3 mmol, 1.0 equiv), 80 °C, 12 h. [e]**1a** (3.0 equiv), **2a** (0.6 mmol, 1.0 equiv), THF (2 mL), 80 °C, 12 h.

solvents led to lower yields or no product (see the Supporting Information). Finally, the optimized reaction conditions were identified by reducing the loading amount of CuOAc to 10 mol % using **1a** (3.0 equiv), **2a** (1.0 equiv), and t-BuOLi (2.4 equiv) at 80 °C for 12 h, providing **3a** in an 85% yield upon isolation (entry 9). Yet, no product **3a** was formed without a copper catalyst (entry 10), thus clearly demonstrating the essential role of copper in the promotion of the reaction.

To ascertain the substrate scope of this transformation, a variety of secondary propargylated phosphates were examined and provided the corresponding products **3** with high yields (Scheme 1). Substrates bearing an alkenyl or another alkynyl group did not interfere with the reaction (**3e** and **3f**); even a high yield of **3f** (91%) was afforded. Protected hydroxy groups, such as a silyl ether and a benzyloxy moiety, underwent the

Scheme 1. Cu-Catalyzed Secondary Propargylation of Pentafluorobenzene 1a with Various Propargyl Phosphates[a]

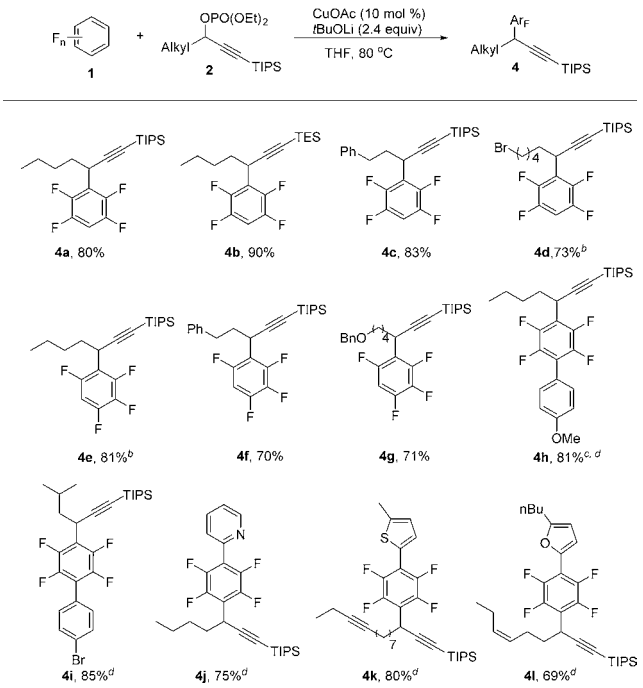


[a]Reaction conditions (unless otherwise specified): **2** (0.6 mmol, 1.0 equiv), **1a** (1.8 mmol, 3.0 equiv), THF (2 mL). Yields of isolated products are given. [b]20 mol % of CuOAc was used.

reaction smoothly (**3g** and **3h**). Remarkably, an alkyl bromide tolerated the reaction well with high efficiency (**3i**), thus highlighting the good chemo- and regioselectivity of the current process. Furthermore, the reaction can also be extended to triethylsilyl and *tert*-buyl substituted alkynes with good yields (**3j** and **3k**).

In addition to demonstrating the substrate scope of this reaction, couplings of tetrafluorobenzene bearing more than one reaction site were investigated (Scheme 2). Good to high

Scheme 2. Cu-Catalyzed Propargylation of Polyfluorobenzene 1 with Propargyl Phosphates[a]



[a]Reaction conditions (unless otherwise specified): **2** (0.6 mmol, 1.0 equiv), **1** (2.4 mmol, 4.0 equiv), THF (2.0 mL). Yields of isolated products are given. [b]20 mol % of CuOAc was used. [c]Reaction run at 100 °C. [d]3.0 equiv of fluoroarenes were used.

yields of monopropargylated products were still observed (**4a**–**4g**). Moreover, aryl substituted tetrafluorobenzenes were applicable to the reaction with high efficiency (**4h**–**4i**). Importantly, no fluoroarylation of aryl bromide was observed when 4′-bromo-2,3,5,6-tetrafluoro-1,1′-biphenyl **1e** was examined (**4i**). Heterocycles, such as pyridyl, thienyl, and furanyl groups, containing tetrafluoroarenes also underwent the reaction smoothly (**4j**–**4l**). In view of the importance of polyfluoroarene-thiophenes, -furans, and -azines (e.g., pyridine, quinolone) structures in photoelectronic materials, this transformation is highly relevant to materials science.

The importance of this protocol can also be featured by the rapid access of highly functionalized polyfluoroarenes via iterative transition-metal-catalyzed C–H bond functionalization. As depicted in Scheme 3, after selective gram-scale synthesis of secondary propargylated polyfluoroarene **4a** through the current process, compound **4a** was directly allylated[5b] or benzylated[5e] to furnish the highly functionalized polyfluoroarenes with high efficiency.

To demonstrate the utility of this reaction further, transformations of building block **9**, which was derived from the deprotection of compound **3d**, were performed. As shown in

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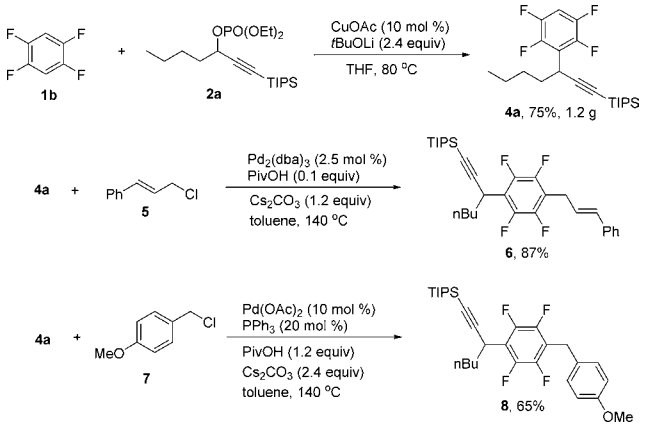
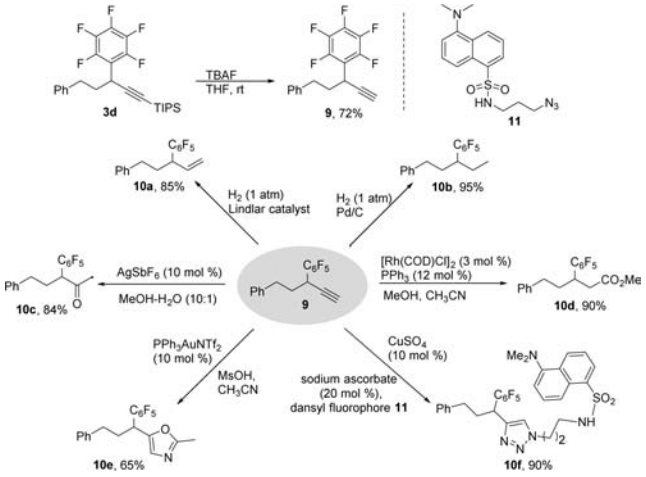
Scheme 3. Iterative C−H Bond Functionalization of Polyfluoroarene



Scheme 4, diverse secondary alkylated polyfluoroarenes can be rapidly accessed from compound **9**.

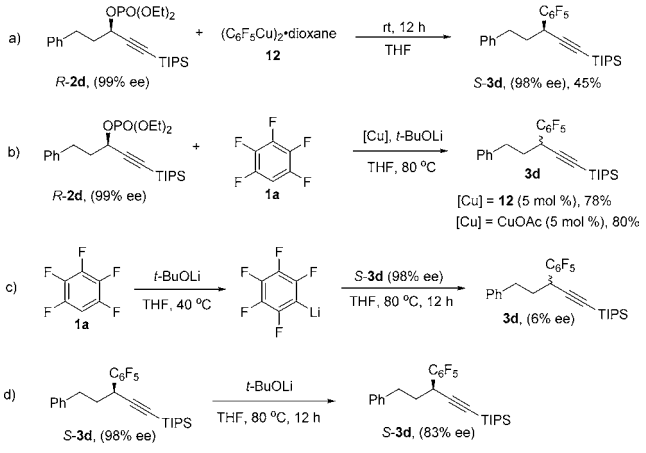
Scheme 4. Transformations of Terminal Alkyne 9



Selective hydrogenation of **9** led to secondary allylated or alkylated polyfluoroarene **10a** and **10b** with high efficiency. Hydration of the alkyne with $AgSbF_6$ proceeded smoothly and afforded ketone **10c** in a high yield (84%).[10] Compound **9** was also applicable to the rhodium-catalyzed oxygenative addition to terminal alkyne and produced methyl ester **10d** in 90% yield.[11] These results are noteworthy, as compounds **10c** and **10d** are difficult to prepare through conventional methods otherwise. In addition, heteroaromatics, such as oxazole, can be easily constructed from compound **9** through gold-catalyzed intermolecular [2 + 2 + 1] annulation,[12] thus highlighting the validity of the current process further. Finally, the successful click reaction of **9** with the dansyl fluorophore **11** also features the advantages of this protocol in light of the importance of polyfluoroarenes in life science.[13]

To gain some mechanistic insights into this reaction, a pentafluorophenyl copper complex $C_6F_5Cu\cdot$(dioxane) **12**[14] and an optically pure *R*-**2d** (99% ee)[15] were prepared. It was found that when *R*-**2d** was treated with **12** at room temperature, a configuration retained product *S*-**3d** was produced in 45% yield with high enantioselectivity (98% ee) (Scheme 5a). This result clearly suggests that the S_N1 or S_N2 pathway is not involved in the reaction. Surprisingly, treatment of *R*-**2d** with **1a** in the

Scheme 5. Mechanistic Studies

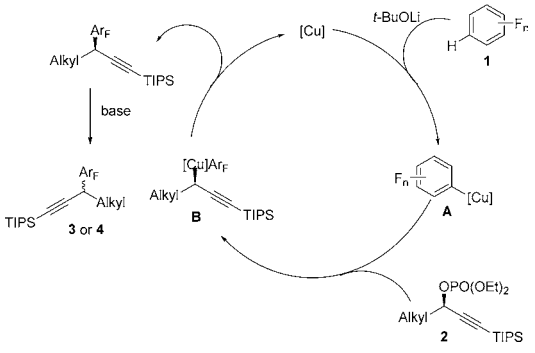


presence of **12** or CuOAc (5 mol %) under standard reaction conditions led to a racemized **3d** (Scheme 5b). Even with the reaction run at room temperature, a racemized product **3d** was still observed in 15% yield (for details, see the Supporting Information).

We envisioned that these results probably arose from the excess strong base *t*-BuOLi or the resulting pentafluorophenyllithium generated from the reaction of *t*-BuOLi with **1a**, which may racemize the starting material *R*-**2d** or the newly formed product *S*-**3d**. Accordingly, pentafluorophenyllithium was prepared by the reaction of **1a** with *t*-BuOLi in THF at 40 °C for 2 h, which was then reacted with *R*-**2d** or *S*-**3d** in THF at 80 °C. It was found that *S*-**3d** can be easily racemized by the pentafluorophenyllithium (Scheme 5c), but *R*-**2d** was not (see Scheme S3b in the Supporting Information). In addition, when *S*-**3d** was treated with *t*BuOLi, a decreased ee value (83%) of *S*-**3d** was also observed (Scheme 5d). However, no erosion of the enantioselectivity of *R*-**2d** was observed under the same reaction conditions (see Scheme S4a in the Supporting Information). Thus, these results demonstrate that a strong base can racemize the newly formed propargylated polyfluoroarenes (for details, see the Supporting Information).

On the basis of these results and previous reports,[7e] a plausible reaction mechanism is proposed (Scheme 6). The reaction begins with the *t*-BuOLi-assisted direct cupration of polyfluoroarene **1** to produce polyfluoroarylcopper complex **A**. **A** subsequently undergoes oxidative addition with propargyl phosphate **2** to generate a configuration retained intermediate propargyl Cu(III) species **B**. Finally, reductive elimination of **B** delivers the propargylated polyfluoroarene with retention of

Scheme 6. Proposed Reaction Mechanism



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configuration, which can be easily racemized by the excess polyfluoroaryllithium or *t*-BuOLi under current reaction conditions to give a racemic mixture.

In conclusion, we have developed the first example of direct propargylation of polyfluoroarenes. The current copper-based simple catalytic system proceeds smoothly under mild reaction conditions and provides facile access to secondary propargylated ploy fluoroarenes. Importantly, all of the target molecules are previously unknown and can serve as versatile and useful building blocks in organic synthesis and functional materials science. Preliminary mechanistic studies reveal that a polyfluoroarylcopper complex is involved in the reaction, which can lead to progarylated polyfluoroarenes. Further studies to uncover the detailed reaction mechanism and to develop derivative reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01642.

Detailed experimental procedures, and characterization data for new compounds PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews related to propargylations, see: (a) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, *2009*, 6263−6276. (b) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914−1937. For selected reviews related to transformations of alkynes, see: (c) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937−2980. (d) Trost, B. M.; Li, C. J. *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Wiley: Weinheim, 2014.

(2) (a) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163−4165. (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214.

(3) For ruthenium-catalyzed propargylation of arenes, see: (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846−11847. (b) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495−1498. (c) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488−6491. (d) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561−5564. For Lewis acids catalyzed propargylation of arenes, see: (e) Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325−1327. (f) Li, C.; Wang, J. *J. Org. Chem.* **2007**, *72*, 7431. (g) McCubbin, J. A.; Nassar, C.; Krokhin, O. V. *Synthesis* **2011**, *2011*, 3152−3160.

(4) For transition-metal-catalyzed cross-coupling between propargylated electrophiles and arylmetals, see: (a) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645−12647. (b) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966. (c) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588−16593.

(5) (a) Fan, S.; Chen, F.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918−5928. (b) Yu, Y.-B.; Fan, S.; Zhang, X. *Chem. - Eur. J.* **2012**, *18*, 14643−14648. For our contributions to other types of transition-metal-catalyzed direct functionalization of polyfluoroarenes, see: (c) He, C. Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850−12852. (d) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.- X. *J. Am. Chem. Soc.* **2010**, *132*, 4506−4507. (e) Fan, S.; He, C. Y.; Zhang, X. *Chem. Commun.* **2010**, *46*, 4926−4928.

(6) For selected examples of transition-metal-catalyzed C−H functionalization of polyfluoroarenes, see: Arylation: (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128−1129. (c) Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377−16379. Alkenylation: (d) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170−16171. Alkynylation: (g) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522−2523 and ref 5.

(7) For allylation of polyfluoroarenes, see: (a) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2990−2994. (b) Makida, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4122−4127. (c) Jiang, H.; Yang, W.; Chen, H.; Li, J.; Wu, W. *Chem. Commun.* **2014**, *50*, 7202−7204. (d) Wang, G.-W.; Zhou, A.-X.; Li, S.-X.; Yang, S.-D. *Org. Lett.* **2014**, *16*, 3118−3121. (e) Xie, W.; Kim, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 1876−1880 and ref 5a, b. Benzylation: (f) Xu, S.; Wu, G.; Ye, F.; Wang, X.; Li, H.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4669−4672 and ref 5e. Alkylation: (g) Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. *J. Am. Chem. Soc.* **2010**, *132*, 6935−6937.

(8) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2012**, *14*, 2586−2589.

(9) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185−15192.

(10) Thuong, M. B. T.; Mann, A.; Wagner, A. *Chem. Commun.* **2012**, *48*, 434−436.

(11) Kim, I.; Lee, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 10023−10026.

(12) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482−8485.

(13) (a) Woll, M. G.; Hadley, E. B.; Mecozzi, S.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 15932−15933. (b) Zheng, H.; Comeforo, K.; Gao, J. *J. Am. Chem. Soc.* **2009**, *131*, 18−19.

(14) Cairncross, A.; Sheppard, W. A.; Wonchoba, E.; Guildford, W. J.; House, C. B.; Coates, R. M. *Org. Synth.* **1980**, *59*, 122.

(15) For the detailed synthesis of enantiopure *R*-**2d**, see the Supporting Information.

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