

# Copper-Catalyzed Substitution of $\alpha$ -Triflyloxy Nitriles and Esters with Silicon Nucleophiles under Inversion of the Configuration

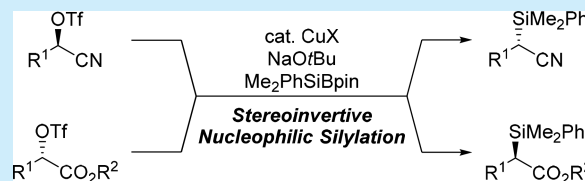
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**S** Supporting Information

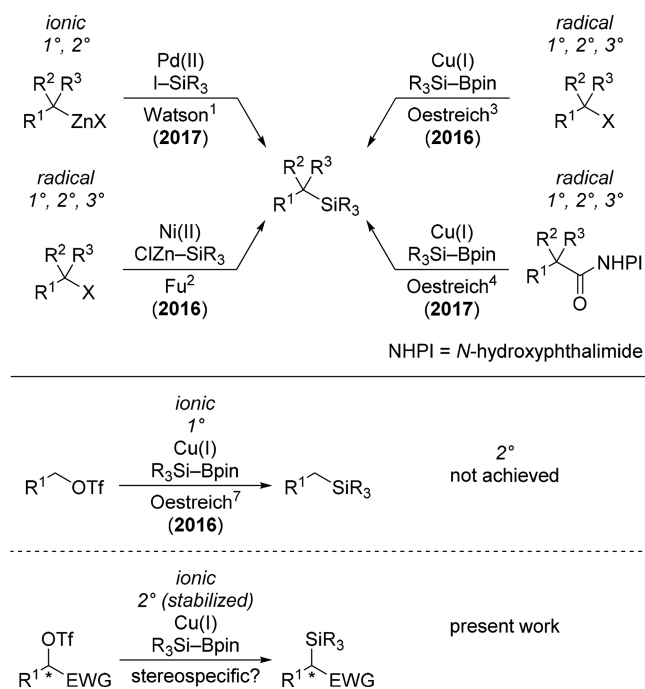
**ABSTRACT:** A copper-catalyzed nucleophilic displacement of  $\alpha$ -triflyloxy nitriles and esters with silicon nucleophiles allows for the stereospecific generation of highly enantioenriched  $\alpha$ -silylated carboxyl compounds. The enantioselective synthesis of  $\alpha$ -silylated nitriles is unprecedented. The catalytic system exhibits good functional group tolerance. The stereochemical course of the substitution is shown to proceed with inversion of the configuration.

The new reaction is an addition to the still limited number of methods for catalytic  $C(sp^3)$ –Si cross-coupling.



Catalytic cross-coupling reactions to form carbon–silicon bonds at saturated carbon atoms have long been elusive. Three solutions to this problem were recently disclosed (Scheme 1, top). Watson and co-workers accomplished the cross-coupling of zinc-based carbon nucleophiles and silicon electrophiles, essentially a silicon version of the Negishi reaction.<sup>1</sup> A distinctly different approach was chosen by Fu and co-workers<sup>2</sup> as well as our laboratory<sup>3</sup> where unactivated carbon electrophiles are coupled with zinc- and boron-based silicon nucleophiles, respectively. These cross-couplings pro-

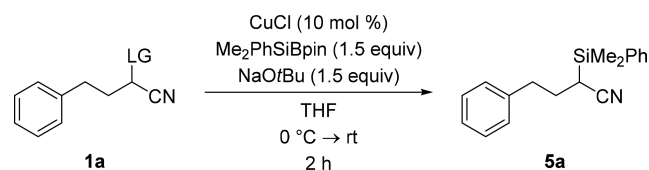
**Scheme 1.** Catalytic  $C(sp^3)$ –Si Bond-Forming Reactions (X = Br and I)



ceed through radical intermediates and are mechanistically related to a decarboxylative method to achieve the same carbon–silicon bond formation.<sup>4</sup> Our catalytic setup makes use of copper(I) salts and Si–B reagents<sup>5,6</sup> as silicon pronucleophiles.<sup>3,4</sup> That combination also enabled the nucleophilic displacement of the triflate leaving group but this was strictly limited to primary carbon atoms as secondary electrophiles were prone to  $\beta$ -elimination (Scheme 1, bottom).<sup>7</sup> We assume an ionic mechanism in this case and asked ourselves whether “stabilized” secondary triflates would participate in this nucleophilic substitution, even retaining stereochemical information if asymmetrically substituted at the electrophilic carbon center. We report here the enantiospecific silylation of  $\alpha$ -triflyloxy nitriles<sup>8,9</sup> and esters<sup>10</sup> derived from readily available enantioenriched cyanohydrins<sup>11</sup> and  $\alpha$ -hydroxy esters.<sup>12</sup>

Our study commenced with an optimization of the catalytic system in the racemic series by using nitriles **1a–4a** with different leaving groups in the  $\alpha$  position (Table 1). A systematic screening of catalytic systems for the  $\alpha$ -triflyloxy-substituted substrate and  $\text{Me}_2\text{PhSiBpin}$  as the silicon pronucleophile led to  $\text{CuCl}/\text{NaOtBu}$  in THF (**1a**  $\rightarrow$  **5a**, entry 1; for the full set of tested reaction conditions see the Supporting Information). Substrates **2a–4a** with other common leaving groups<sup>2,3</sup> did not afford any **5a** (entries 2–4). The reaction time was crucial as prolonged exposure to the basic reaction medium resulted in complete decomposition (entry 5). No product formation was seen in the absence of the copper salt and the base, respectively (entries 6 and 7).  $\text{MePh}_2\text{SiBpin}$  instead of  $\text{Me}_2\text{PhSiBpin}$  participated in lower yield (entry 8) whereas heteroatom-substituted  $\text{Me}_2\text{PhSiBpin}$  ( $\text{NiPr}_2$ )<sub>2</sub> yielded just trace amounts (entry 9). Interestingly, zinc-based nucleophile  $(\text{Me}_2\text{PhSi})_2\text{Zn}$ <sup>13</sup> furnished **5a** in substantial quantities (entry 10) while only low yields had been obtained in the radical cross-coupling with this reagent.<sup>3</sup>

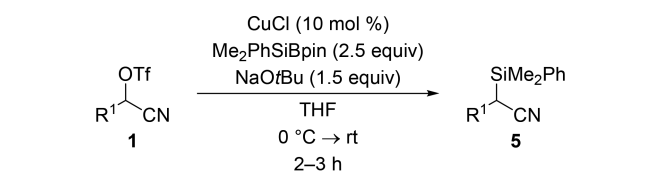
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**Table 1. Selected Examples of the Reaction Optimization (LG = Leaving Group)<sup>a</sup>**

entry	LG	variation	yield <sup>b</sup> (%)
1	OTf (1a)		94 (68 <sup>c</sup> )
2	Cl (2a)		<i>d</i>
3	Br (3a)		<i>e</i>
4	OTs (4a)		<i>d</i>
5	OTf (1a)	16 h instead of 2 h	<i>e</i>
6	OTf (1a)	w/o CuCl	<i>e</i>
7	OTf (1a)	w/o NaOtBu	<i>e</i>
8	OTf (1a)	w/MePh <sub>2</sub> SiBpin	57 <sup>f</sup>
9	OTf (1a)	w/Me <sub>2</sub> PhSiB(NiPr <sub>2</sub> ) <sub>2</sub>	trace
10	OTf (1a)	w/(Me <sub>2</sub> PhSi) <sub>2</sub> Zn	32 <sup>f</sup>

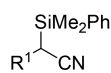
<sup>a</sup>All reactions were performed on a 0.20 mmol scale. <sup>b</sup>Determined by GLC analysis with tetracosane as an internal standard. <sup>c</sup>Isolated yield after purification by flash chromatography on silica gel. <sup>d</sup>Little or no conversion of the starting material was observed. <sup>e</sup>Decomposition. <sup>f</sup>Determined by <sup>1</sup>H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

With the optimized setup in hand, we tested the scope of the nucleophilic substitution of  $\alpha$ -triflyloxy nitriles (Scheme 2). The model substrate and its electronically modified derivatives afforded yields around 50% or higher (1a–d  $\rightarrow$  5a–d). It must

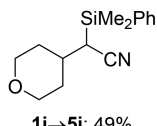
**Scheme 2. Copper-Catalyzed Nucleophilic Substitution of  $\alpha$ -Triflyloxy Nitriles**

1a  $\rightarrow$  5a (X = H): 68%  
 1b  $\rightarrow$  5b (X = OMe): 77%  
 1c  $\rightarrow$  5c (X = Cl): 48%  
 1d  $\rightarrow$  5d (X = Br): 53%

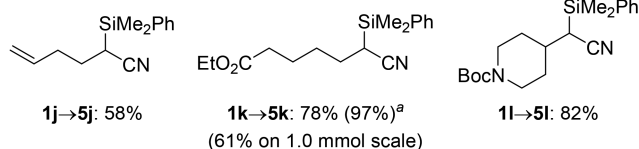
1e  $\rightarrow$  5e: 59%



1f  $\rightarrow$  5f (R<sup>1</sup> = *n*Pr): 74%  
 1g  $\rightarrow$  5g (R<sup>1</sup> = *t*Bu): 57%  
 1h  $\rightarrow$  5h (R<sup>1</sup> = *t*Bu): 30%



1i  $\rightarrow$  5i: 49%



1j  $\rightarrow$  5j: 58%

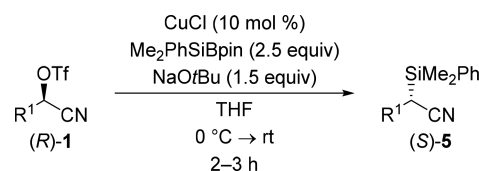
1k  $\rightarrow$  5k: 78% (97%)<sup>a</sup>  
 (61% on 1.0 mmol scale)

1l  $\rightarrow$  5l: 82%

<sup>a</sup>Determined by <sup>1</sup>H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

be noted that partial hydrodebromination was found for 1d  $\rightarrow$  5d, forming 5d along with 10% of 5a.<sup>14</sup> A comparison of cyclohexyl- and isomeric alkyl-substituted 1e–h showed that branching in the  $\beta$ - and  $\gamma$ -positions is tolerated with the yield decreasing with increasing steric hindrance. For example, *tert*-butyl-substituted 1h converted into 5h in 30% yield while linear 1f afforded 5f in 74% yield. Similar to our earlier results for primary alkyl triflates,<sup>7</sup> several representative functional groups were compatible with this transformation. Substrates containing various Lewis-basic groups as well as an  $\alpha$ -olefin reacted in moderate to good yields (1i–l  $\rightarrow$  5i–l).<sup>15</sup> Generally, yields are eroded by competing base-mediated desilylation of 5 (cf. Table 1, entry 5).

We then investigated the stereospecificity of this nucleophilic displacement (Table 2). To our delight, selected enantioen-

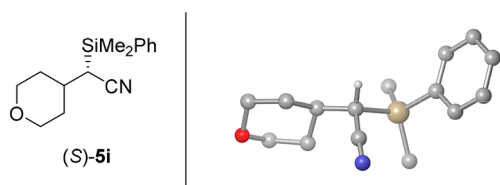
**Table 2. Stereospecific Copper-Catalyzed Nucleophilic Substitution of Enantioenriched  $\alpha$ -Triflyloxy Nitriles with Inversion of the Configuration**

entry	substrate (R)-1 <sup>a</sup>	product (S)-5		
		yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	es <sup>d</sup> (%)
1	(R)-1a (99% ee)	73	97	98
2	(R)-1c (95% ee)	43	89	93
3	(R)-1e (68% ee) <sup>e</sup>	62	67	99
4	(R)-1g (94% ee)	51	87	92
5	(R)-1i (96% ee)	40	95	99

<sup>a</sup>The enantiomeric excess was determined at the stage of the corresponding cyanohydrin or  $\alpha$ -triflyloxy nitrile. The absolute configuration was assigned as *R* based on the work of Hertzberg and Moberg where enantioselective cyanoacylation of aldehydes promoted by a dimeric titanium–salen catalyst and subsequent enzymatic kinetic resolution of the resulting  $\alpha$ -bromoacyl cyanides consistently led to the *R* configuration.<sup>11c</sup> <sup>b</sup>Isolated yield after purification by flash chromatography on silica gel. <sup>c</sup>Determined by HPLC analysis on chiral stationary phases. <sup>d</sup>es = enantiospecificity. <sup>e</sup>Erosion of the enantiomeric purity occurred during the triflation of the corresponding cyanohydrin.

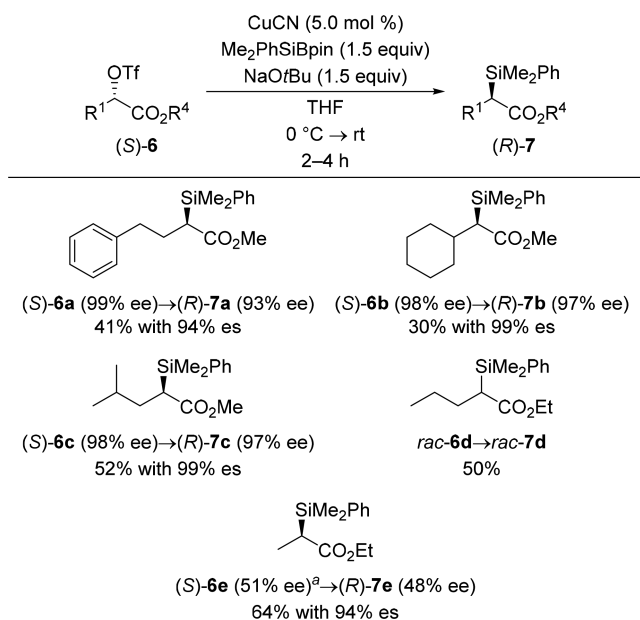
riched  $\alpha$ -triflyloxy nitriles (R)-1 transformed into the desired  $\alpha$ -silylated nitriles (S)-5 with essentially no loss of enantiomeric purity. (S)-5 is therefore configurationally stable under the reaction conditions but, as mentioned before, decomposes at longer reaction times. The stereochemical course of the reaction was established by X-ray analysis of (S)-5i (Figure 1) and comparison of the optical rotations of known cyanohydrins.<sup>16</sup> These reactions proceed with inversion of the configuration, thus supporting the postulated S<sub>N</sub>2 mechanism.

To expand the scope, we moved from cyano to carboxyl as the electron-withdrawing group. Breit and co-workers had already developed a broadly applicable enantiospecific substitution with carbon nucleophiles starting from those  $\alpha$ -triflyloxy esters.<sup>10</sup> For these substrates, our original procedure for primary alkyl triflates emerged as superior to the above setup (cf. Table 1, entry 1).<sup>7</sup> CuCl instead of CuCN caused more desilylation, and more Si–B reagent did not improve the yield. The results are summarized in Scheme 3. Chemical yields for 6  $\rightarrow$  7 were generally lower than those for  $\alpha$ -triflyloxy



**Figure 1.** Assignment of absolute configuration: molecular structure of compound (S)-5i.

### Scheme 3. Stereospecific Copper-Catalyzed Nucleophilic Substitution of Enantioenriched $\alpha$ -Triflyloxy Esters with Inversion of the Configuration



<sup>a</sup>Erosion of the enantiomeric purity occurred during the triflation of the corresponding  $\alpha$ -hydroxy ester.

nitriles (cf. **1** → **5**, Scheme 2 and Table 2). However, the enantiospecificity was again excellent throughout, thus providing a convenient and practical access to this class of compounds.<sup>17,18</sup> The low enantiomeric excess of  $\alpha$ -triflyloxy ester **6e** is due to racemization during triflation of the sterically unhindered  $\alpha$ -hydroxy ester. The absolute configuration of the  $\alpha$ -silylated esters (R)-7 was secured by comparison with the literature-known optical rotation of (R)-7e.<sup>17a</sup>

We have shown here that a range of  $\alpha$ -triflyloxy nitriles and esters undergo copper-catalyzed C(sp<sup>3</sup>)-Si cross-coupling with inversion of the configuration. The resulting enantioenriched  $\alpha$ -silylated nitriles had not been accessible before while the present formation of  $\alpha$ -silylated esters complements the existing approach by enantioselective carbenoid insertion into Si-H bonds.<sup>17,19</sup>

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03279.

General procedures, experimental details, and characterization/spectral data for all new compounds (PDF)

## Accession Codes

CCDC 1580335 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

- Cinderella, A. P.; Vulovic, B.; Watson, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 7741–7744.
- Chu, C. K.; Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2016**, *138*, 6404–6407.
- Xue, W.; Qu, Z.-W.; Grimme, S.; Oestreich, M. *J. Am. Chem. Soc.* **2016**, *138*, 14222–14225.
- Xue, W.; Oestreich, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 11649–11652.
- For recent reviews of Si–B chemistry, see: (a) Delvos, L. B.; Oestreich, M. In *Science of Synthesis Knowledge Updates 2017/1*; Oestreich, M., Ed.; Thieme: Stuttgart, Germany, 2017; pp 65–176. (b) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402–441.
- For the preparation of the Si–B reagents, see: Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647–4649.
- Secondary alkyl triflates without a geminal electron-withdrawing group were not stable, even at temperatures below 0 °C: Scharfbier, J.; Oestreich, M. *Synlett* **2016**, *27*, 1274–1276.
- For the catalytic generation of racemic  $\alpha$ -silylated nitriles by hydrosilylation see: (a) Ojima, I.; Kumagai, M.; Nagai, Y. *J. Organomet. Chem.* **1976**, *111*, 43–60. (b) Dong, H.; Jiang, Y.; Berke, H. *J. Organomet. Chem.* **2014**, *750*, 17–22. (c) Komine, N.; Abe, M.; Suda, R.; Hirano, M. *Organometallics* **2015**, *34*, 432–437. For the synthesis of  $\alpha$ -silylated nitriles by a cuprate addition–migration sequence, see: (d) Kondo, J.; Ito, Y.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 106–108. (e) Kondo, J.; Inoue, A.; Ito, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2005**, *61*, 3361–3369.
- Stereospecific Suzuki–Miyaura cross-coupling of  $\alpha$ -triflyloxy nitriles: (a) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524–2525. Stereoconvergent Negishi coupling of racemic  $\alpha$ -bromo nitriles: (b) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105. Enantioselective reductive coupling of racemic  $\alpha$ -chloro nitriles and heteroaryl iodides: (c) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480–10483.
- Breit and co-workers developed a methodology based on stereospecific zinc-catalyzed nucleophilic substitution of  $\alpha$ -triflyloxy esters with Grignard reagents: (a) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451–5455. (b) Brand, G. J.; Studte, C.; Breit, B.

*Org. Lett.* **2009**, *11*, 4668–4670. (c) Schmidt, Y.; Lehr, K.; Breuninger, U.; Brand, G.; Reiss, T.; Breit, B. *J. Org. Chem.* **2010**, *75*, 4424–4433. Asymmetric Kumada coupling of racemic  $\alpha$ -bromo esters: (d) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 17662–17668.

(11) For an overview of methods for the generation of enantiomerically enriched cyanohydrins, see: (a) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146–5226. For the generation of cyanohydrins by asymmetric cyanosilylation, see: (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106–8107. For the generation of highly enantioenriched  $\alpha$ -bromoacylated cyanohydrins by minor enantiomer recycling, see: (c) Hertzberg, R.; Moberg, C. *J. Org. Chem.* **2013**, *78*, 9174–9180.

(12) Highly enantioenriched  $\alpha$ -hydroxy esters are readily available from the corresponding  $\alpha$ -hydroxy acids by acid-catalyzed esterification.

(13) Weickgenannt, A.; Oestreich, M. *Chem. - Eur. J.* **2010**, *16*, 402–412.

(14) We do not think that the hydrodebromination is indicative of the involvement of radicals. This defunctionalization is related to Ito's alkoxide-mediated Si–B chemistry and was found to be a side reaction: Yamamoto, E.; Ukigai, S.; Ito, H. *Chem. Sci.* **2015**, *6*, 2943–2951.

(15) Full conversion of the starting material was observed for all examples.

(16) Reported optical rotations of the corresponding cyanohydrins: (a) Zeng, Z.; Zhao, G.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, 1615–1618 (for **1a**). (b) Kurono, N.; Arai, K.; Uemura, M.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6643–6646 (for **1e**). (c) Niedermeyer, U.; Kragl, U.; Kula, M. R.; Wandrey, C.; Makryaleas, K.; Drauz, K. Enzymic Preparation of Optically Active Cyanohydrins. DE 38 23 864 A1, 1989 (for **1g**).

(17) (a) Zhang, Y.-Z.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8496–8498. (b) Sambasivan, R.; Ball, Z. T. *J. Am. Chem. Soc.* **2010**, *132*, 9289–9291. (c) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010**, *12*, 2112–2115. (d) Yasutomi, Y.; Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 4510–4511. (e) Chen, D.; Zhu, D.-X.; Xu, M.-H. *J. Am. Chem. Soc.* **2016**, *138*, 1498–1501. (f) Kan, S. B. J.; Lewis, R. D.; Chen, K.; Arnold, F. H. *Science* **2016**, *354*, 1048–105.

(18) For an overview of the chemistry of  $\alpha$ -silylated carboxyl and carbonyl compounds, see: (a) Larson, G. L. *Pure Appl. Chem.* **1990**, *62*, 2021–2026. For an approach in the racemic series by C-silylation of ester enolates, see: (b) Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 2418–2419.

(19) For a recent catalyst-controlled approach to enantioenriched  $\alpha$ -silylated ketones starting from  $\alpha$ -silylated diazoalkanes and aldehydes, see: Kim, J. Y.; Kang, B. C.; Ryu, D. H. *Org. Lett.* **2017**, *19*, 5936–5939.