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Synthesis of Diverse *o*-Arylthio-Substituted Diaryl Ethers by Direct Oxythiolation of Arynes with Diaryl Sulfoxides Involving Migratory *O*-Arylation

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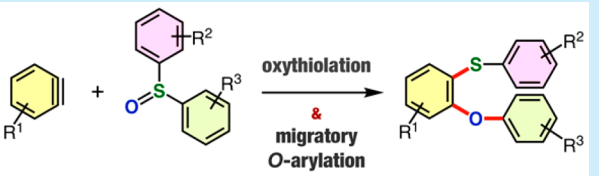
Supporting Information

ABSTRACT: A diverse range of *o*-arylthio-substituted diaryl ethers has been synthesized by direct oxythiolation of arynes with diaryl sulfoxides that involves the formation of the C−O and C−S bonds followed by migratory *O*-arylation.



Diaryl ethers are used in a wide range of fields, including medicinal chemistry and materials science.[1,2] In particular, diaryl ethers bearing an arylthio group have been gaining much attention because they play versatile roles such as synthetic intermediates, ligands for transition-metal catalysts, and organic light-emitting materials.[3] These thiolated diaryl ethers have been synthesized from phenols by nucleophilic aromatic substitution with electron-deficient haloarenes or cross-coupling reactions with haloarenes.[4] However, synthesizable compounds by the conventional methods are limited and a novel approach that can expand the scope of available compounds is eagerly anticipated. Here we describe a facile method for the synthesis of diverse diaryl ethers bearing an *o*-arylthio group by the direct oxythiolation of arynes[5,6] with diaryl sulfoxides.

Recently, we have reported methods for the synthesis of diverse aniline derivatives by the direct thioamination of arynes with sulfilimines or sulfoximines (Figure 1A).[7] Mechanistic studies suggested that these reactions proceeded through C−N and C−S bond formations and subsequent migratory *N*-arylation. We assumed that using diaryl sulfoxides instead of sulfilimines or sulfoximines in the reaction with arynes would directly provide *o*-arylthio-substituted diaryl ethers through a similar reaction pathway. In this context, several transformations involving formal [2 + 2] reactions of arynes with sulfoxides have been recently reported.[8−10] Except for the synthesis of *o*-sulfinylaryl vinyl ethers by the direct reaction between arynes and vinyl sulfoxides bearing an electron-withdrawing substituent that was reported by Studer and co-worker (Figure 1B),[9] most of these transformations are three-component coupling reactions. This is because these reactions were either conducted in the presence of an electrophile, such as α-bromoketone, or performed by generating excess amounts of aryne, to trap the alkoxide intermediate **I** formed by the reaction of an aryne with a sulfoxide (Figure 1C).[8,10] These studies indicated the difficulty of achieving the direct oxythiolation between arynes and diaryl sulfoxides.

Indeed, an initial attempt to achieve the direct oxythiolation by generating 3-methoxybenzyne from *o*-silylaryl triflate **1a** in the presence of di(*p*-tolyl) sulfoxide (**2a**) under optimal conditions for the direct thioamination (KF, 18-crown-6, THF, 60 °C) was unfruitful (Figure 1D). Although the reaction proceeded in a regioselective manner, the major product was triarylsulfonium salt **4a**,[9,10] and the desired diaryl ether **3a** was obtained in quite a low yield. To facilitate the intramolecular *O*-arylation and to prevent the formation of the sulfonium salt via the intermolecular arylation of intermediate **I** with another aryne, we examined the reaction by using *p*-bromophenyl *p*-tolyl sulfoxide (**2b**) and *o*-bromophenyl *p*-tolyl sulfoxide (**2c**), bearing an electron-deficient *p*-bromo- and *o*-bromophenyl group, respectively. Thus, although the reaction using **2b** afforded diaryl ether **3b** in a slightly higher yield, the reaction using **2c** afforded **3c** in a considerably high yield as a sole isolable product, in which the *o*-bromophenyl group selectively migrated.

Optimization of the reaction conditions largely improved the yields of diaryl ethers **3a**−**c** (Table 1). For the synthesis of **3c** from 3-methoxybenzyne precursor **1a** and **2c**, various activators such as cesium fluoride, tetrabutylammonium difluorotriphenylsilicate, and cesium carbonate with 18-crown-6 in the absence of fluoride[6c] were exploitable, although tetrabutylammonium fluoride was not useful (entries 1−4). Using acetonitrile as a solvent instead of THF significantly lowered the yield of **3c** (entry 5). The reaction temperature was a considerably important factor. Although the reaction became sluggish at room temperature (entry 6), desired product **3c** was obtained in a higher yield when the reaction was conducted at 80 °C in 1,4-dioxane (entry 7). This modification improved the yield of **3a** that is obtained from the reaction of **1a** with the less reactive **2a** (entry 8). Moreover, by conducting the reaction at a higher temperature (110 °C) using increased amounts of reagents, **3a**

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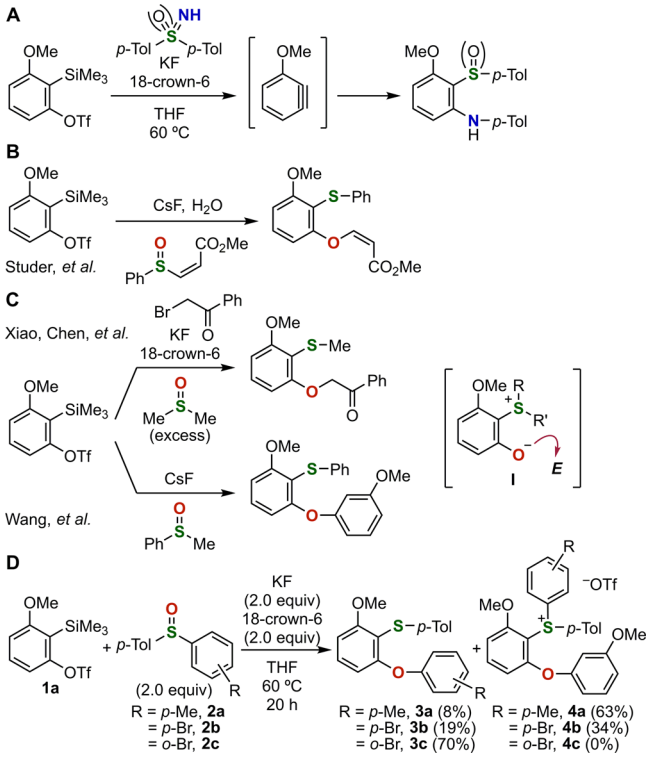
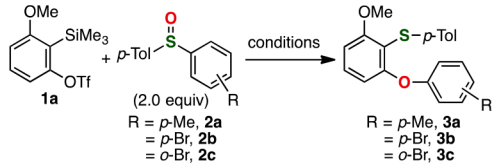


Figure 1. (A) Our previous study; direct thioamination of arynes with sulfilimines or sulfoximines. (B) Reported direct oxythiolation of arynes with vinyl sulfoxides bearing an electron-withdrawing substituent. (C) Reported three-component coupling reactions between arynes and sulfoxides in the presence of an electrophile (***E***). (D) Initially attempted reactions between 3-methoxybenzyne and diaryl sulfoxides.

Table 1. Optimization of the Reaction Conditions



entry	2	conditions[a]	3	yield (%)[b]
1	**2c**	CsF, THF, 60 °C, 20 h	**3c**	67
2	**2c**	*n*-$Bu_4N[Ph_3SiF_2]$, THF, 60 °C, 13 h	**3c**	50
3	**2c**	Cs_2CO_3, 18-crown-6, THF, 60 °C, 13 h	**3c**	48
4	**2c**	*n*-Bu_4NF, THF, 60 °C, 13 h	**3c**	trace
5	**2c**	KF, 18-crown-6, CH_3CN, 60 °C, 14 h	**3c**	25
6	**2c**	KF, 18-crown-6, THF, rt, 14 h	**3c**	19
7	**2c**	KF, 18-crown-6, 1,4-dioxane, 80 °C, 40 h	**3c**	80[c] (82)[d]
8	**2a**	KF, 18-crown-6, 1,4-dioxane, 80 °C, 48 h	**3a**	38
9	**2a**	KF,[e] 18-crown-6,[e] 1,4-dioxane, 110 °C, 30 h	**3a**	71[c]
10	**2b**	KF, 18-crown-6, 1,4-dioxane, 110 °C, 48 h	**3b**	78[c]

[a]Unless otherwise noted, 0.10 mmol of **1a** and 2.0 equiv of reagents were used. [b]Yields based on ^{1}H NMR analysis, unless otherwise noted. [c]Isolated yields. [d]Isolated yield using 1.0 mmol of **1a** in parentheses. [e]Using 3.0 equiv of reagents.

was afforded in a satisfactory yield (entry 9). Similarly, diaryl ether **3b** was prepared efficiently from **2b** (entry 10).

A broad range of arynes that were generated from the corresponding *o*-silylaryl triflates **1** under the optimized conditions (Table 1, entry 7) participated in the direct oxythiolation (Figure 2). For example, unsubstituted benzyne,

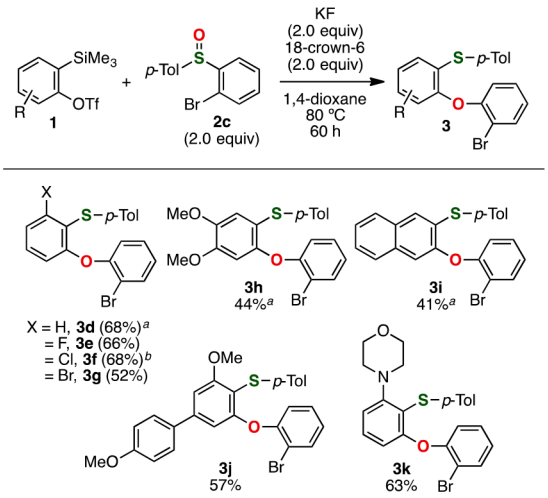


Figure 2. Reactions of various arynes with sulfoxide **2c**. [a]The reactions were performed at 110 °C. [b]The reaction was performed for 18 h.

3-fluoro-, 3-chloro-, and 3-bromobenzyne smoothly reacted with sulfoxide **2c** to afford the products **3d**–**g**, leaving the halogeno groups untouched. Oxythiolations of 4,5-dimethoxybenzyne, 2,3-naphthalyne, and 5-(4-anisyl)-3-methoxybenzyne[6d,e] with **2c** also afforded diaryl ethers **3h**–**j**. Moreover, 3-morpholinobenzyne, which was generated from the precursor that was easily prepared by our recently reported method,[6m] reacted with sulfoxide **2c** to afford highly functionalized diaryl ether **3k**.

Various diaryl sulfoxides were applicable to the oxythiolation as demonstrated in the reaction with 3-methoxybenzyne (Figure 3). The reactions of unsymmetrical diaryl sulfoxides afforded the products such as **3l**–**z**, wherein migratory *O*-arylation at the more electron-deficient aryl groups proceeded selectively. Notably, the migration of the 2-benzofuranyl group over-rode that of the 2-bromophenyl group to afford **3r** in high yield. This is probably because the formation of the Meisenheimer complex at the 2-benzofuranyl group from the intermediate in the S_NAr-type rearrangement was favored rather than that at the 2-bromophenyl group (vide infra). The reactions using *o*-bromophenyl *p*-bromophenyl sulfoxide and *o*-bromophenyl *p*-chlorophenyl sulfoxide afforded *o*-bromophenyl-migrated products **3u** and **3v** preferentially, although a small amount of isomers **3u′** and **3v′** were also obtained in these cases. Conducting the reaction at a higher temperature (110 °C) facilitated the reactions of substrates with more electron-rich aryl groups such as diphenyl, di(*p*-chlorophenyl), di(*p*-methoxyphenyl), and ferrocenyl *p*-tolyl sulfoxides, which afforded **3w**–**z**, respectively. Notably, by using dibenzothiophene *S*-oxide **5**, a unique eight-membered tribenzoxathiocine **6** was obtained in good yield via selective ring expansion (eq 1). From the reaction of *o*-fluorophenyl *p*-tolyl sulfoxide (**2d**), the phenoxathiinium derivative **7** was obtained instead of an anticipated *O*-*o*-fluorophenylated product **3aa** (eq 2), thus indicating that the defluorinative S_NAr reaction was favored rather than that via the C–S bond cleavage. In addition, the reaction with methyl *p*-tolyl sulfoxide (**2e**) also afforded the oxythiolated product **3ab**, which was formed via the selective migration of the methyl group (eq 3).

To gain insight into the reaction mechanism, we conducted several control experiments in the reaction with 3-methoxybenzyne (Figure 4). For example, a crossover experiment using a mixture of sulfoxides **2a** and **2f** resulted in the formation of **3a** as a major product and **3x** as a minor product, and the crossover

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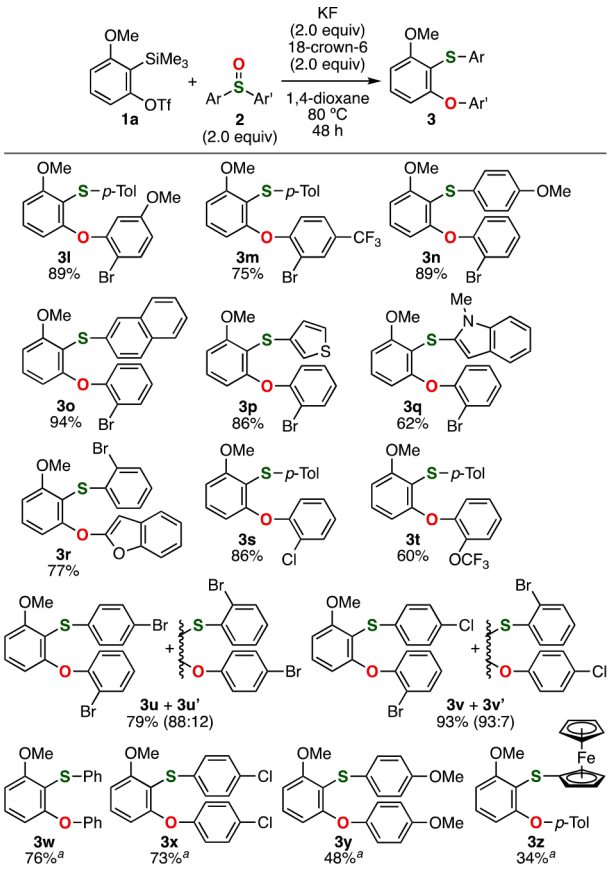
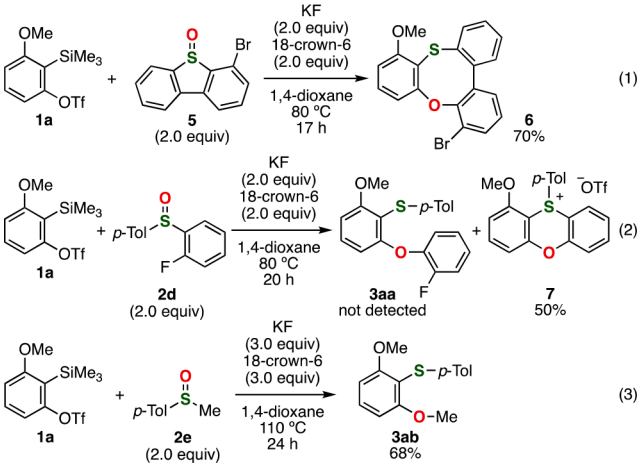


Figure 3. Reactions of 3-methoxybenzyne with various diaryl sulfoxides. [a]The reactions were performed at 110 °C.



products **3ac** and **3ad** were not detected (Figure 4A). From an experiment generating 3-methoxybenzyne in the presence of a mixture of sulfoxide **2g** and sulfilimine **8**, the thioaminated product **9** was obtained exclusively (Figure 4B). On the basis of these results, we consider that the reaction proceeds via the mechanism that is similar to that of the thioamination of arynes with sulfilimines. This involves the addition of sulfoxide **2c** with aryne **II**, followed by a four-membered ring formation (**III** to **IV**), cleavage of the S−O bond (**IV** to **V**), and S_NAr-type rearrangement of *o*-bromophenyl group via Meisenheimer complex **VI** to afford the product **3c** (Figure 4C).[7] The higher temperature required for oxythiolation with sulfoxides than thioamination with sulfilimines was possibly due to the poor

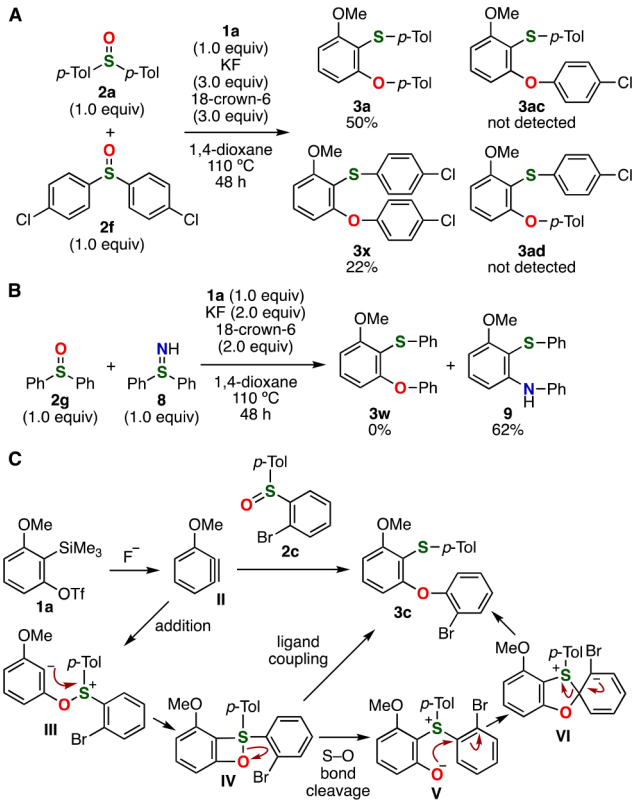


Figure 4. Mechanistic studies: (A) crossover experiment; (B) competition experiment; (C) plausible reaction pathways.

nucleophilicity of the oxygen as compared to nitrogen for the intermolecular *O*-arylation of sulfoxide **2c** with aryne **II** and the intramolecular migratory *O*-arylation of **V**. Nevertheless, the possibility of a pathway involving direct ligand coupling on the sulfur of **IV** cannot be excluded.[12]

The broad functional group tolerance of oxythiolation of arynes enabled the synthesis of diverse *o*-arylthio-substituted diaryl ethers bearing a functional group that was available for further derivatizations (Figure 5). For example, palladium-catalyzed intramolecular cyclization[11] by means of the bromo groups in **3c** and **3ae** afforded disubstituted dibenzofuran **10** and dibenzothiophene **11**, respectively (Figure 5A,B). Moreover, the oxidation of the oxythiolated product **3f** and the use of the resulting sulfoxide as an arynophile for the oxythiolation of another aryne such as 3-morpholinobenzyne afforded highly functionalized aromatic tri(thio)ether **3af** (Figure 5C).

In summary, an efficient synthetic method for *o*-arylthio-substituted diaryl ethers involving the reaction between arynes and diaryl sulfoxides has been developed. By conducting the reaction at high temperature (80−110 °C), the direct oxythiolation of arynes with diaryl sulfoxides and subsequent migratory *O*-arylation for substrates bearing electron-donating, -neutral, or -withdrawing substituents could be facilitated. The method enables the synthesis of various diaryl ethers, including those fused with heteroaromatic rings, which are difficult to synthesize by conventional methods. In concert with recently reported approaches to diaryl sulfides[13] that render a wide range of diaryl sulfoxides easily synthesizable, this method allows the facile preparation of a diverse range of compounds via a modular synthesis.[5c] Further studies on synthetic applications of this method and theoretical studies involving the reaction mechanism are currently underway.

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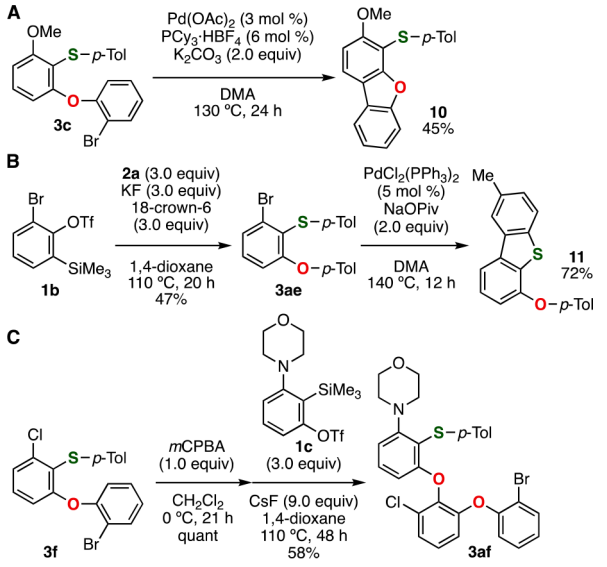

Figure 5. Transformations of oxythiolated products: (A) benzofuran synthesis; (B) benzothiophene synthesis; (C) further oxythiolation using a sulfoxide prepared from an oxythiolated product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02599.

Experimental procedures, characterization for new compounds including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Pitsinos, E. N.; Vidali, V. P.; Couladouros, E. A. *Eur. J. Org. Chem.* **2011**, 1207.

(2) (a) Hiraoka, M. *Crown Ethers and Analogous Compounds*; Elsevier Science: Amsterdam, 1992. (b) Im, Y.; Lee, J. Y. *Dyes Pigm.* **2015**, *113*, 743.

(3) (a) Bocquet, A.; Sablayrolles, S.; Vacher, B.; Le Grand, B. *Br. J. Pharmacol.* **2010**, *161*, 405. (b) Khairutdinov, B.; Ermakova, E.; Sitnitsky, A.; Stoikov, I.; Zuev, Y. *J. Mol. Struct.* **2014**, *1074*, 126. (c) Han, B.; Sun, D.; Li, X.; Gao, C.; Zhang, S. *J. Appl. Polym. Sci.* **2016**, *133*, 43892.

(4) (a) Cristau, P.; Vors, J.-P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Crowley, B. M.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2885. (d) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876. (e) Takise, R.; Isshiki, R.; Muto, K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139*, 3340.

(5) For some recent reviews on arynes, see: (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (b) Goetz, A. E.; Shah, T. K.; Garg, N. K. *Chem. Commun.* **2015**, *51*, 34. (c) Yoshida, H. Aryne-Based Multicomponent Reactions. In *Multicomponent Reactions in Organic Synthesis*; Zhu, J., Wang, Q., Wang, M., Ed.; Wiley-VCH: Weinheim, 2015; pp 39–71. (d) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1450. (e) García-López, J.-A.; Greaney, M. F. *Chem. Soc. Rev.* **2016**, *45*, 6766. (f) Bhojgude, S. S.; Bhunia, A.; Biju, A. T. *Acc. Chem. Res.* **2016**, *49*, 1658. (g) Shi, J.; Li, Y.; Li, Y. *Chem. Soc. Rev.* **2017**, *46*, 1707.

(6) For selected recent reports on arynes, see: (a) Shi, J.; Qiu, D.; Wang, J.; Xu, H.; Li, Y. *J. Am. Chem. Soc.* **2015**, *137*, 5670. (b) Yoshida, S.; Uchida, K.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 691. (c) Yoshida, S.; Hazama, Y.; Sumida, Y.; Yano, T.; Hosoya, T. *Molecules* **2015**, *20*, 10131. (d) Yoshida, S.; Shimomori, K.; Nonaka, T.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1324. (e) Demory, E.; Devaraj, K.; Orthaber, A.; Gates, P. J.; Pilarski, L. T. *Angew. Chem., Int. Ed.* **2015**, *54*, 11765. (f) Holden, C. M.; Sohel, S. M. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 2450. (g) Sundalam, S. K.; Nilova, A.; Seidl, T. L.; Stuart, D. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 8431. (h) Ikawa, T.; Masuda, S.; Takagi, A.; Akai, S. *Chem. Sci.* **2016**, *7*, 5206. (i) Fine Nathel, N. F.; Morrill, L. A.; Mayr, H.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 10402. (j) Pérez-Gómez, M.; García-López, J.-A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14389. (k) Li, Y.; Mück-Lichtenfeld, C.; Studer, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14435. (l) Sumida, Y.; Sumida, T.; Hashizume, D.; Hosoya, T. *Org. Lett.* **2016**, *18*, 5600. (m) Yoshida, S.; Nakamura, Y.; Uchida, K.; Hazama, Y.; Hosoya, T. *Org. Lett.* **2016**, *18*, 6212. (n) Umezu, S.; dos Passos Gomes, G.; Yoshinaga, T.; Sakae, M.; Matsumoto, K.; Iwata, T.; Alabugin, I.; Shindo, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 1298. (o) Shi, J.; Xu, H.; Qiu, D.; He, J.; Li, Y. *J. Am. Chem. Soc.* **2017**, *139*, 623. (p) Uchida, K.; Yoshida, S.; Hosoya, T. *Org. Lett.* **2017**, *19*, 1184. (q) Yoshida, S.; Nagai, A.; Uchida, K.; Hosoya, T. *Chem. Lett.* **2017**, *46*, 733. (r) Ross, S. P.; Hoye, T. R. *Nat. Chem.* **2017**, *9*, 523. (s) Xu, F.; Xiao, X.; Hoye, T. R. *J. Am. Chem. Soc.* **2017**, *139*, 8400. (t) Kitamura, T.; Gondo, K.; Oyamada, J. *J. Am. Chem. Soc.* **2017**, *139*, 8416. (u) Lin, J. B.; Shah, T. K.; Goetz, A. E.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139*, 10447.

(7) (a) Yoshida, S.; Yano, T.; Misawa, Y.; Sugimura, Y.; Igawa, K.; Shimizu, S.; Tomooka, K.; Hosoya, T. *J. Am. Chem. Soc.* **2015**, *137*, 14071. (b) Yoshida, S.; Nakajima, H.; Uchida, K.; Yano, T.; Kondo, M.; Matsushita, T.; Hosoya, T. *Chem. Lett.* **2017**, *46*, 77.

(8) (a) Liu, F.-L.; Chen, J.-R.; Zou, Y.-Q.; Wei, Q.; Xiao, W.-J. *Org. Lett.* **2014**, *16*, 3768. (b) Li, H.-Y.; Xing, L.-J.; Lou, M.-M.; Wang, H.; Liu, R.-H.; Wang, B. *Org. Lett.* **2015**, *17*, 1098. (c) Li, Y.; Qiu, D.; Gu, R.; Wang, J.; Shi, J.; Li, Y. *J. Am. Chem. Soc.* **2016**, *138*, 10814.

(9) Li, Y.; Studer, A. *Org. Lett.* **2017**, *19*, 666.

(10) Li, X.; Sun, Y.; Huang, X.; Zhang, L.; Kong, L.; Peng, B. *Org. Lett.* **2017**, *19*, 838.

(11) (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Saravanan, P.; Anbarasan, P. *Org. Lett.* **2014**, *16*, 848.

(12) Finet, J. P. *Ligand Coupling Reactions with Heteroatomic Compounds*; Elsevier Sciences: Oxford, 1998.

(13) (a) Yoshida, S.; Sugimura, Y.; Hazama, Y.; Nishiyama, Y.; Yano, T.; Shimizu, S.; Hosoya, T. *Chem. Commun.* **2015**, *51*, 16613. (b) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760. (c) Kawashima, H.; Yanagi, T.; Wu, C.-C.; Nogi, K.; Yorimitsu, H. *Org. Lett.* **2017**, *19*, 4552. (d) Kanemoto, K.; Sugimura, Y.; Shimizu, S.; Yoshida, S.; Hosoya, T. *Chem. Commun.* **2017**, *53*, 10640.

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