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Carbon–Sulfur Bond Formation Catalyzed by [Pd(IPr*^{OMe})(cin)Cl] (cin = cinnamyl)

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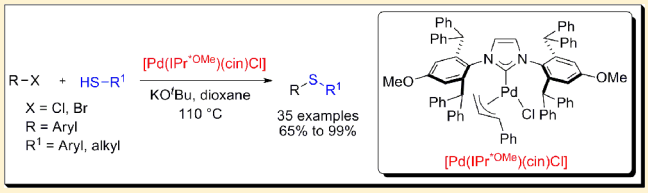
Supporting Information

ABSTRACT: The newly prepared complex [Pd(IPr*^{OMe})(cin)(Cl)] provides high catalytic activity for carbon–sulfur cross-coupling reactions. Nonactivated and deactivated aryl halides were successfully coupled with a large variety of aryl- and alkylthiols using this well-defined palladium *N*-heterocyclic carbene (NHC) complex.



INTRODUCTION

The formation of carbon–sulfur bonds is of significant importance in molecular assembly strategies, as several bioactive compounds with wide ranges of activity contain aryl thioether moieties.[1] Additionally, the opportunity to transform thioethers into other useful functional groups such as sulfoniums, sulfones, or sulfoxides makes them attractive intermediates in organic synthesis.[2]

The synthesis of aryl thioethers and bisaryl thioethers can be achieved in a number of ways.[3] The most common procedures are the nucleophilic substitution of halides by thiolates[4] and the reaction of electrophilic sulfur with strongly nucleophilic organometallic reagents such as Grignard reagents and lithiated derivatives.[5] A major advance in this area has been the emergence of transition metals in coupling catalysis, beginning with the Cu-catalyzed Ullmann reaction.[6] Different metals have been used (e.g., copper, nickel, iron, rhodium, gold, and palladium) for the formation of carbon–sulfur bonds, permitting improved yields and selectivity and requiring milder conditions than the classical methods.[7]

Among these systems, palladium–phosphine-based catalysts have been successfully used in this reaction.[8] In early evolutions of the method, the use of sensitive and expensive phosphine ligands to achieve the coupling, typically with aryl bromides and iodides, remained a major drawback of the methodology. As NHC ligands have been found to be an efficient alternative to phosphines in the Buchwald–Hartwig amination reaction, they were recently studied for carbon–sulfur bond-forming reactions.[9] Indeed, Shi and Organ demonstrated the potential of [Pd(SIPr)(Py)Cl_2][10] and [Pd(IPent)(PEPPSI)Cl_2][11] derivatives, respectively (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation).

The activity of Pd–NHC catalysts is directly linked to the properties of the NHC. Their steric bulk enables stabilization of a low-valent active intermediate and favors reductive elimination, while the strong σ-donor character facilitates the oxidative addition of aryl halides.[12] To study the effects of varying the NHC ligand, we recently described the synthesis of an original NHC ligand, the bulky and electon-rich IPr*^{OMe}·HCl.[13] We present here the use of a well-defined NHC-based catalyst, namely [Pd(IPr*^{OMe})(cin)Cl], and its use in the formation of C–S bonds through a palladium-catalyzed cross-coupling transformation. This catalyst exhibits excellent catalytic performance in carbon–sulfur coupling involving challenging substrates at lower catalyst loadings than are required for other reported catalyst systems for this transformation.

RESULTS AND DISCUSSION

The catalyst [Pd(IPr*^{OMe})(cin)Cl] (**3**) was successfully synthesized by the in situ formation of the free carbene from IPr*^{OMe}·HCl (**1**) with base followed by the addition of the palladium dimer **2** to the THF solution containing the free NHC. The complex is air- and moisture-stable and was obtained in good yield (85%) (Scheme 1).[14]

Optimization of the carbon–sulfur coupling reaction between 4-bromotoluene and thiophenol led us to use KO^{t}Bu as the base and 1,4-dioxane as the solvent at 110 °C. We first studied the reaction of thiophenol with various aryl halides (products **5a–g** in Chart 1). The system showed good to excellent results in all cases. Sterically and/or electronically

Scheme 1. Synthesis of [Pd(IPr*^{OMe})(cin)Cl] (3)

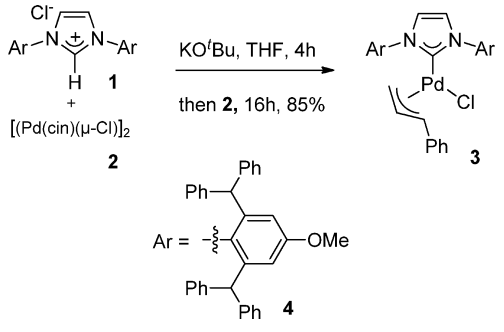


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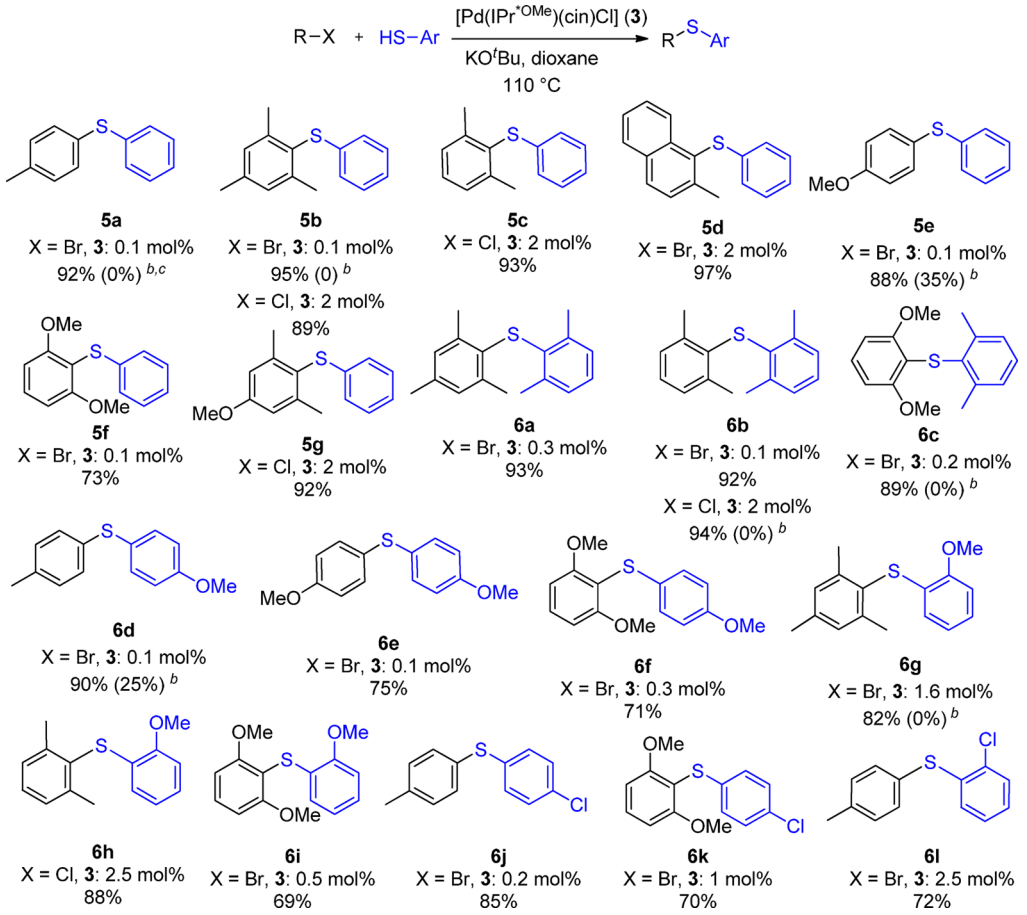
Chart 1. Aryl Halide and Aryl Thiol Cross-Coupling Reaction[a]



[a]Aryl halide (0.50 mmol), thiol (0.6 mmol), Pd precatalyst **3** in 1,4-dioxane (1 mL), KOtBu (0.55 mmol), 110 °C for 12 h. Reaction times were not optimized. Isolated yields after optimal GC conversion followed by chromatography on silica gel (averages of two runs) are shown. [b]The GC yield of the reaction without catalyst is shown in parentheses. [c]Reaction carried out using the aryl chloride.

deactivated halides reacted easily. For complete conversion of the starting materials, aryl bromides required only 0.1 mol % catalyst, whereas aryl chlorides and 2-bromomethylnaphthalene (**5d**) required 2 mol %. As thiophenol showed good reactivity, our attention next focused on the coupling reactions of different aromatic thiols (products **6a–l** in Chart 1). The reaction conditions allowed the condensation of both hindered and deactivated aryl halides. The use of 1,3-dimethylthiophenol led to very hindered products (**6a–c**) using only 0.3 mol % catalyst. In the case of the formation of compound **6b**, it is noteworthy that only 0.1 mol % **3** was used, whereas this coupling reaction is described in the literature as requiring 2 mol % catalyst in the presence of an additive.[11] Nevertheless, the coupling reaction seems to be more sensitive to the thiol moiety (**6a** vs **5b**) because of its chelating and electronic properties. The presence of a methoxy group at the *para* position of the thiol (**6d–f**) did not significantly affect the reaction (**6d** vs **5a**), whereas the presence of the methoxy group at the *ortho* position required higher catalyst loadings (**6g** vs **6i**). The potential chelating property of the methoxy group appears to deactivate the thiol, but catalyst **3** is still efficient. The vigor of the catalyst is more remarkable with the 2- and 4-chlorothiophenol substrates (**6j–l**). Indeed, the effect of the electron-withdrawing group is more significant than the presence of a methoxy group or the steric hindrance brought about by *ortho* substitution. The amount of [Pd(IPr*^{OMe})(cin)Cl)] catalyst used was also optimized (see **6k** vs **6f** and **6l** vs **6j**). In the last examples, no homocoupling reaction was observed, and the selectivity favored the bromine substitution, leaving the chloride intact for eventual further functionalization.

Some of those reactions were studied without catalyst (yields are shown in parentheses), and as expected, it appears that chlorinated substrates cannot react by a nucleophilic aromatic substitution reaction (**5a**). The substitution of bromine by this mechanism failed also with a methyl substituent at the *ortho* position (**6c**); however, when a methoxy group was present at the *para* position, product **5e** was formed, although in poor GC yield. These observations were confirmed by results of experiments carried out with other aryl (**6b**, **6c**, and **6g**) and alkyl (**7e** and **7l**) thiols (Charts 1 and 2), illustrating that the metal-mediated coupling reaction is the best way to synthesize the different thioethers presented here.

Having demonstrated the strength and versatility of the well-defined system in aromatic thiol coupling reactions, we next examined the coupling of alkyl thiols. As nonaromatic thiols are structurally and electronically different from their aromatic congeners, an optimization study could have been necessary. Moreover, these substrates are described in the literature as being particularly challenging.[9−11] However, our previous conditions led to good catalytic performance with alkyl thiols without further optimization.

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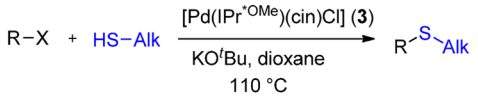
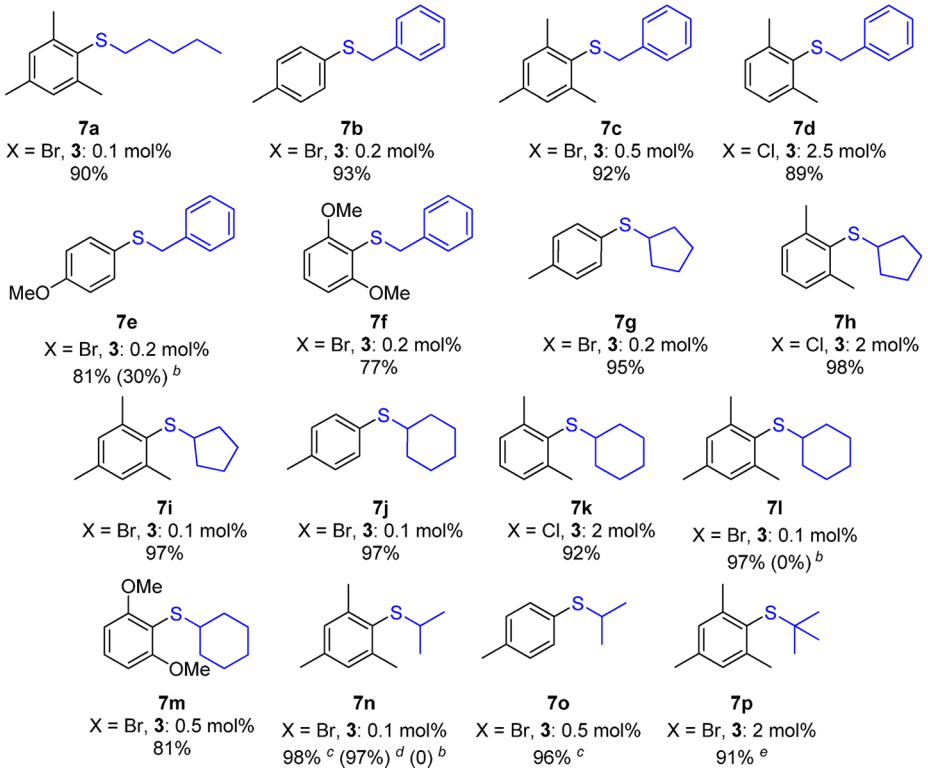
Chart 2. Aryl Halide and Alkyl Thiol Cross-Coupling Reaction[a]

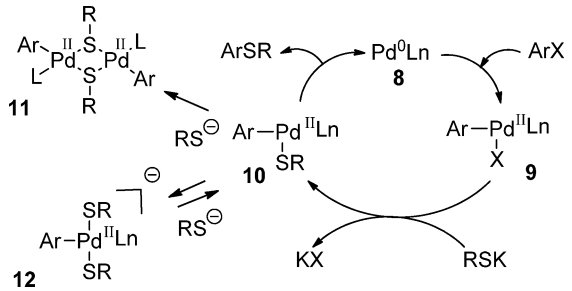




[a]Aryl halide (0.50 mmol), thiol (0.6 mmol), Pd precatalyst **3** in 1,4-dioxane (1 mL), KOtBu (0.55 mmol), 110 °C for 12 h. Reaction times were not optimized. Isolated yields after optimal GC conversion followed by chromatography on silica gel (averages of two runs) are shown. [b]The GC yield of the reaction without catalyst is shown in parentheses. [c]The sodium thiolate was used instead of the thiol under the same conditions. [d]The potassium thiolate was used instead of the thiol under the same conditions. [e]The reaction time was 48 h.

The coupling reactions were efficiently performed on primary (**7a**), benzylic (**7b–f**), secondary (**7g–o**), and tertiary (**7p**) thiols with different aryl halides (Chart 2). The reaction tolerated hindered and deactivated aryl halides, and the tendency of the aryl chlorides to require more catalyst than bromides was again established. Indeed, the catalytic loading was generally 0.2–0.5 mol % for the aryl bromides and around 2 mol % for the aryl chlorides. The benzylic thiol was one of the most challenging substrates (**7c** vs **7a**, **7i**, and **7l**), and its coupling was achieved by increasing the catalyst loading. Not surprisingly, the tertiary thiol was the least reactive of the alkyl thiols. The use of 2 mol % [Pd(IPr*^{OMe})(cin)Cl)] and a reaction time of 48 h were necessary for the formation of **7p**.[15] In the case of the formation of **7n** and **7o**, sodium 2-propanethiolate was used instead of the thiol with 2 equiv of base, and good yields were obtained. The synthesis of **7n** was studied without the KO^{t}Bu and failed. Moreover, a catalytic amount of base (0.02 equiv) gave a yield of only 4%, and 1 equiv afforded a 20% yield of product. As expected, potassium thiolate gave a good yield. These results support the hypothesis that the reactive species is the potassium thiolate and not the sodium thiolate or the thiol. The good results with potassium thiolate are probably due to its low solubility. Indeed, the low accumulation of potassium thiolate in solution prevents the deactivation of complex **10** (Scheme 2).[16]

Scheme 2. Simplified Catalytic Cycle



The mechanism of this reaction is not completely known. However, the standard mechanism for Pd–NHC-catalyzed bond formation is assumed, starting from a palladium (0) species. In this catalytic cycle, oxidative addition of the aryl halide to form complex **9** is facilitated by the electron-donating properties of the NHC. Next, complex **10** is formed by anion exchange between **9** and potassium thiolate (Scheme 2). Two deactivation pathways were established from **10** by the displacement of ligands by thiolates to form the anionic thiolate **12** and the bridging thiolate **11**. Our catalyst appears not to suffer from these poisoning pathways. Indeed, we suppose that ligands facilitate the reductive elimination toward **8** before decomposition of complex **10**. Furthermore, no byproducts are observed.[10,16a]

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CONCLUSION

[Pd(IPr*^{OMe})(cin)Cl] performs well in carbon−sulfur bond formation between aryl bromides or chlorides and aliphatic or aromatic thiols at low catalyst loadings. Moreover, sterically hindered and deactivated compounds are well-tolerated. The reaction can be performed without any additive for a wide range of substrates. The success of the reaction is attributed to the outstanding activity of the new Pd−NHC catalyst [Pd(IPr*^{OMe})(cin)Cl]. Further investigations are currently ongoing in our laboratory to extend its use to other reactions.

EXPERIMENTAL SECTION

Preparation of [Pd(IPr*^{OMe})(cin)Cl] (3). In a glovebox, to a 500 mL round-bottom flask equipped with a magnetic stirring bar were added IPr*^{OMe}HCl (**1**) (2.16 g, 2.2 mmol) and KOtBu (0.28 g, 2.4 mmol) in THF (160 mL). The reaction mixture was stirred at room temperature for 4 h, and then [{Pd(cin)(μ-Cl)}$_2$] (**2**) (0.512 g, 1 mmol) was added. The reaction mixture was then stirred overnight at room temperature. After this time, outside the glovebox, THF was evaporated, and the crude product was dissolved in CH_2Cl_2, filtered on a pad of silica covered with Celite, and eluted with CH_2Cl_2. After evaporation of the solvents, the complex was precipitated in pentane, and the supernatant was removed. After drying under high vacuum, the pure complex was obtained as a beige powder (2.25 g, 85%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.54−7.19 (m, 26H), 7.18−7.07 (m, 12H), 3.90−3.79 (m, 8H), 6.58 (s, 4H), 5.93 (s, 2H), 5.82 (s, 2H), 5.21 (s, 2H), 5.17−5.05 (m, 1H), 4.58 (d, J = 13.1 Hz, 1H), 3.60 (s, 6H), 2.64 (d, J = 6.5 Hz, 1H), 1.27 (d, J = 9.5 Hz, 1H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ: 183.7, 158.9, 144.3, 144.2, 143.5, 143.3, 143.2, 142.9, 137.9, 131.3, 130.4, 129.1, 128.5, 128.3, 128.1, 127.5, 127.1, 126.5, 126.4, 123.4, 114.7, 114.6, 108.9, 90.9, 55.0, 51.6, 47.0. Anal. Calcd for $C_{78}H_{65}ClN_2O_2Pd$: C, 77.79; H, 5.44; N 2.33. Found: C, 77.75; H, 5.51; N, 2.38.

General Procedure for the Preparation of Aryl and Alkyl Thioethers. In a glovebox, to a vial equipped with a stirring bar and sealed with a screw cap fitted with a septum was added KO^{t}Bu (120 mg, 1.0 mmol). Outside the glovebox, under argon, were added the aryl halide (0.5 mmol), the thiol (0.6 mmol), and finally a solution of **3** in dioxane (0.60 mg, 1 mL, 0.1 mol %). The reaction mixture was stirred at 110 °C for 12 h. The solution was then cooled, concentrated under reduced pressure, and quenched with water (2 mL), and the product was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was finally purified by flash chromatography on silica gel with ether/pentane (from 0.5/99.5 to 2/8) as the eluent.

*Phenyl p-Tolyl Sulfide (**5a**).* CAS 3699-01-2. Colorless liquid (92 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46−7.09 (m, 9H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.6, 137.2, 132.3, 131.1, 130.1, 129.8, 129.1, 126.4, 21.2.

*2,4,6-Trimethylphenyl Phenyl Sulfide (**5b**).* CAS 33667-80-0. Colorless liquid (108 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, J = 7.6 Hz, 2H), 7.12−7.05 (m, 1H), 7.04 (s, J = 6.7 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 2.42 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.7, 139.3, 138.4, 129.3, 128.97, 126.9, 125.5, 124.5, 21.7, 21.2.

*1,3-Dimethyl-2-phenylsulfanylbenzene (**5c**).* CAS 54088-93-6. Colorless liquid (99 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28−7.17 (m, 5H), 7.13−7.05 (m, 1H), 6.95 (dd, J = 8.4, 1.2 Hz, 2H), 2.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.9, 138.0, 130.5, 129.3, 128.9, 128.5, 125.6, 124.6, 21.9.

*2-Methyl-1-phenylsulfanylnaphthalene (**5d**).* CAS 93322-81-7. Yellow liquid (121 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60 (d, J = 7.6 Hz, 1H), 7.96−7.84 (m, 2H), 7.59−7.45 (m, 3H), 7.23−7.13 (m, 2H), 7.13−7.05 (m, 1H), 7.02−6.89 (m, 2H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.9, 138.2, 135.7, 132.9, 131.1, 130.0, 129.0, 128.9, 128.3, 127.3, 126.2, 126.0, 125.5, 124.7, 22.3.

*4-Methoxyphenyl Phenyl Sulfide (**5e**).* CAS 5633-57-8. Colorless liquid (95 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52−7.44 (m, 2H), 7.36−7.12 (m, 5H), 7.02−6.89 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.8, 138.6, 135.4, 128.9, 128.2, 125.8, 124.3, 115.0, 55.4.

*1,3-Dimethoxy-2-phenylsulfanylbenzene (**5f**).* CAS 146643-79-0. Yellow solid (90 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (t, J = 8.4 Hz, 1H), 7.24−7.14 (m, 2H), 7.12−7.03 (m, 3H), 6.68 (d, J = 8.4 Hz, 2H), 3.84 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 138.2, 131.7, 128.9, 126.6, 125.0, 107.8, 104.7, 56.7.

*4-Methoxy-2,6-dimethylphenyl Phenyl Sulfide (**5g**).* CAS 108125-21-9. Beige solid (112 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23−7.14 (m, 2H), 7.12−7.02 (m, 1H), 6.97−6.90 (m, 2H), 6.77 (s, 2H), 3.85 (s, 3H), 2.43 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.1, 145.6, 138.8, 128.8, 125.2, 124.4, 121.3, 113.9, 55.2, 22.1.

*2-(2,6-Dimethylphenyl)sulfanyl-1,3,5-trimethylbenzene (**6a**).* White solid (119 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12−6.97 (m, 3H), 6.86 (s, 2H), 2.27 (s, 3H), 2.25 (s, 6H), 2.21 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.4, 140.3, 136.7, 134.6, 130.8, 129.3, 128.4, 126.8, 21.7, 20.8. Anal. Calcd for $C_{17}H_{20}S$: C, 79.63; H, 7.89. Found: C, 79.53; H, 7.81.

*Bis(2,6-dimethylphenyl) Sulfide (**6b**).* CAS 52805-90-0. White solid (111 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.17−6.94 (m, 6H), 2.25 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.5, 134.3, 128.5, 126.9, 21.8.

*2,6-Dimethoxyphenyl 2,6-Dimethylphenyl Sulfide (**6c**).* White solid (122 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18 (t, J = 8.3 Hz, 1H), 7.07−7.00 (m, 3H), 6.53 (d, J = 8.3 Hz, 2H), 3.71 (s, 6H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.4, 142.3, 134.8, 128.9, 128.1, 127.4, 112.5, 108.1, 104.9, 56.4, 22.1. Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 70.15; H, 6.53.

*1-Methoxy-4-(4-methylphenyl)sulfanylbenzene (**6d**).* CAS 6013-47-4. White solid (104 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50−7.34 (m, 2H), 7.21−7.03 (m, 4H), 6.97−6.84 (m, 2H), 3.85 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.5, 136.1, 134.4, 131.1, 129.8, 129.4, 125.6, 114.9, 55.4, 21.0.

*Bis(4-methoxyphenyl) Sulfide (**6e**).* CAS 3393-77-9. White solid (92 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J = 8.9 Hz, 4H), 6.86 (d, J = 8.9 Hz, 4H), 3.81 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 132.8, 127.5, 114.8, 55.4.

*1,3-Dimethoxy-2-(4-methoxyphenyl)sulfanylbenzene (**6f**).* CAS 1314254-20-0. Yellow liquid (98 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (t, J = 8.4 Hz, 1H), 7.21−7.07 (m, 2H), 6.82−6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 2H), 3.85 (s, 6H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.3, 157.8, 130.7, 129.5, 128.4, 114.2, 109.5, 104.4, 56.3, 55.3.

*o-Methoxyphenyl Mesityl Sulfide (**6g**).* CAS 23075-76-5. White solid (106 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14−7.02 (m, 3H), 6.88 (dd, J = 8.1, 1.1 Hz, 1H), 6.75 (td, J = 7.6, 1.2 Hz, 1H), 6.35 (dd, J = 7.8, 1.6 Hz, 1H), 3.98 (s, 3H), 2.41 (s, 6H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.7, 144.6, 139.7, 129.8, 127.0, 126.1, 125.5, 124.8, 121.7, 110.6, 56.3, 22.0, 21.6.

*2,6-Dimethylphenyl 2-Methoxyphenyl Sulfide (**6h**).* White solid (108 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.20 (m, 3H), 7.08 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.74 (t, J = 7.6 Hz, 1H), 6.33 (dt, J = 7.8, 1.9 Hz, 1H), 3.98 (s, 3H), 2.45 (d, J = 1.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8, 144.8, 129.7, 128.9, 126.7, 125.6, 124.9, 121.7, 110.6, 56.3, 22.1. Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found: C, 73.81; H, 6.50.

*2,6-Dimethoxyphenyl 2-Methoxyphenyl Sulfide (**6i**).* Yellow solid (95 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (t, J = 8.4 Hz, 1H), 7.05 (td, J = 7.7, 1.6 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.75−6.61 (m, 3H), 6.50 (dd, J = 7.8, 1.5 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.9, 155.6, 131.3, 126.3, 125.1, 125.0, 120.8, 109.9, 106.2, 104.3, 56.3, 55.7. Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.38; H, 6.11.

*4-Chlorophenyl 4-Methylphenyl Sulfide (**6j**).* CAS 22865-55-0. White solid (100 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45−7.11 (m, 93H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5, 136.4, 132.9, 132.7, 131.2, 131.1, 130.6, 129.6, 21.6.

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*1,3-Dimethoxy-2-(4-chlorophenyl)sulfanylbenzene (**6k**).* CAS 1314254-21-1. Yellow solid (98 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (t, J = 8.4 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 3.86 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.4, 136.5, 131.5, 130.4, 128.6, 127.5, 107.1, 104.4, 56.3.

*2-Chlorophenyl 4-Methylphenyl Sulfide (**6l**).* CAS 92023-43-3. Yellow liquid (85 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46−7.38 (m, 3H), 7.33−7.23 (m, 2H), 7.17−7.07 (m, 2H), 6.94−6.86 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.4, 138.1, 134.7, 132.5, 130.9, 130.0, 129.2, 128.7, 127.5, 127.0, 21.7.

*Mesityl Pentyl Sulfide (**7a**).* Yellow liquid (100 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (s, 2H), 2.68−2.58 (m, 2H), 2.53 (s, 6H), 2.29 (s, 3H), 1.59−1.51 (m, 2H), 1.43−1.26 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.9, 137.8, 130.6, 128.9, 35.6, 31.2, 29.6, 22.4, 22.0, 21.0, 14.0. HRMS (FTMS-APCI): calcd for $C_{14}H_{23}S$, 223.1517; found 223.1515.

*4-Methylphenyl Benzyl Sulfide (**7b**).* CAS 5023-60-9. Colorless liquid (100 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.19 (m, 7H), 7.07 (d, J = 8.0 Hz, 2H), 4.07 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.8, 136.6, 132.4, 130.7, 129.6, 128.8, 128.4, 127.1, 39.8, 21.0.

*Benzyl Mesityl Sulfide (**7c**).* CAS 16928-74-8. Colorless liquid (111 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28−7.20 (m, 3H), 7.10 (dd, J = 7.0, 2.6 Hz, 2H), 6.92 (s, 2H), 3.78 (s, 2H), 2.37 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.4, 138.6, 138.3, 129.5, 128.9, 128.8, 128.3, 126.9, 40.0, 21.7, 21.1. HRMS (FTMS-APCI): calcd for $C_{16}H_{19}S$, 243.1204; found, 243.1202.

*Benzyl 2,6-Dimethylphenyl Sulfide (**7d**).*[8n] Colorless liquid (102 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29−7.21 (m, 3H), 7.17−7.06 (m, 5H), 3.83 (s, 2H), 2.43 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.6, 138.5, 132.8, 128.8, 128.5, 128.3, 128.0, 126.9, 39.9, 21.8. HRMS (FTMS-APCI): calcd for $C_{15}H_{17}S$, 229.1047; found, 229.1045.

*Benzyl 4-Methoxyphenyl Sulfide (**7e**).* CAS 26905-24-8. Beige solid (93 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33−7.17 (m, 7H), 6.81 (d, J = 8.9 Hz, 2H), 3.99 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.2, 138.1, 134.1, 128.9, 128.4, 127.0, 126.1, 114.4, 55.3, 41.3.

*Benzyl 2,6-Dimethoxyphenyl Sulfide (**7f**).* Colorless liquid (100 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37−7.10 (m, 7H), 6.54 (d, J = 8.4 Hz, 2H), 4.00 (s, 2H), 3.81 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.6, 139.1, 130.3, 129.3, 128.4, 127.0, 105.1, 104.5, 56.4, 39.0. HRMS (FTMS-APCI): calcd for $C_{15}H_{17}O_2S$, 261.0945; found, 261.0944.

*Cyclopentyl p-Tolyl Sulfide (**7g**).* CAS 16769-09-8. Colorless liquid (91 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (dt, J = 8.3, 2.0 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 3.53 (dt, J = 13.9, 7.1 Hz, 1H), 2.32 (s, 3H), 2.07−1.94 (m, 2H), 1.84−1.71 (m, 2H), 1.65−1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.1, 133.2, 130.9, 129.5, 46.6, 33.5, 24.7, 21.0.

*2-Cyclopentylsulfanyl-1,3-dimethylbenzene (**7h**).* Colorless liquid (101 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (s, 3H), 3.45−3.29 (m, 1H), 2.59 (s, 6H), 1.97−1.77 (m, 4H), 1.66−1.50 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.2, 134.2, 128.0, 47.6, 33.5, 24.5, 22.3. HRMS (FTMS-APCI): calcd for $C_{13}H_{19}S$, 207.1207; found, 207.1202.

*Cyclopentyl Mesityl Sulfide (**7i**).* Colorless liquid (107 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.97 (s, 2H), 3.41−3.25 (m, 1H), 2.55 (s, 6H), 2.30 (s, 3H), 1.98−1.74 (m, 4H), 1.71−1.49 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.0, 137.8, 130.8, 128.9, 47.7, 33.5, 24.5, 22.2, 21.0. HRMS (FTMS-APCI): calcd for $C_{14}H_{21}S$, 221.1361; found, 221.1358.

*4-Methylphenyl Cyclohexyl Sulfide (**7j**).* CAS 59693-93-5. Colorless liquid (100 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.29 (m, 2H), 7.12 (d, J = 7.9 Hz, 2H), 3.06−3.00 (m, 1H), 2.35 (s, 3H), 2.00−1.97 (m, 2H), 1.83−1.71 (m, 2H), 1.68−1.57 (m, 1H), 1.41−1.19 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.9, 132.8, 131.2, 129.5, 47.1, 33.4, 26.1, 25.8, 21.1.

*2-Cyclohexylsulfanyl-1,3-dimethylbenzene (**7k**).* Colorless liquid (101 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (s, 3H), 2.85 (tt, J = 10.8, 3.7 Hz, 1H), 2.56 (s, 6H), 1.86 (dd, J = 9.6, 4.4 Hz, 2H), 1.76 (dt, J = 6.2, 3.5 Hz, 2H), 1.68−1.58 (m, 1H), 1.39 (dd, J = 18.8, 7.9 Hz, 2H), 1.31−1.20 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.5, 133.1, 127.9, 47.4, 33.7, 26.2, 25.8, 22.4. Anal. Calcd for $C_{14}H_{20}S$: C, 76.30; H, 9.20. Found: C, 76.26; H, 9.04.

*Cyclohexyl Mesityl Sulfide (**7l**).* CAS 1286763-65-2. Colorless liquid (114 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.96 (s, 2H), 2.81 (tt, J = 10.8, 3.7 Hz, 1H), 2.52 (s, 6H), 2.29 (s, 3H), 1.93−1.82 (m, 2H), 1.80−1.70 (m, 2H), 1.68−1.58 (m, 1H), 1.50−1.33 (m, 2H), 1.31−1.16 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.7, 138.1, 130.0, 129.2, 47.9, 34.1, 26.7, 26.3, 22.7, 21.4.

*Cyclohexyl 2,6-Dimethoxyphenyl Sulfide (**7m**).* Yellow oil (102 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (t, J = 8.3 Hz, 1H), 6.59 (d, J = 8.4 Hz, 2H), 3.89 (s, 6H), 3.19 (tt, J = 10.7, 3.6 Hz, 1H), 1.90−1.68 (m, 4H), 1.63−1.56 (m, 1H), 1.45−1.14 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.5, 129.5, 109.6, 104.0, 56.2, 45.5, 33.2, 26.1, 25.9. HRMS (FTMS-APCI): calcd for $C_{14}H_{21}O_2S$, 253.1259; found, 253.1257.

*Isopropyl Mesityl Sulfide (**7n**).* CAS 22740-07-4. Colorless liquid (95 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 (d, J = 0.6 Hz, 2H), 3.11 (hept, J = 6.7 Hz, 1H), 2.52 (s, 6H), 2.29 (s, 3H), 1.23 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.2, 137.8, 130.1, 128.9, 38.8, 23.3, 22.2, 21.0.

*Isopropyl 4-Methylphenyl Sulfide (**7o**).* CAS 14905-81-8. Colorless liquid (80 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.31 (m, 2H), 7.13 (dd, J = 8.4, 0.6 Hz, 2H), 3.32 (hept, J = 6.7 Hz, 1H), 2.36 (s, 3H), 1.29 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.0, 132.8, 131.6, 129.6, 38.7, 23.1, 21.1.

*2,4,6-Trimethylphenyl tert-Butyl Sulfide (**7p**).* CAS 42157-59-5. Colorless liquid (95 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.99 (d, J = 0.5 Hz, 2H), 2.56 (s, 6H), 2.30 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.4, 138.6, 129.3, 129.2, 49.4, 32.0, 23.4, 21.4.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds and general experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For example, see: (a) Thomas, G. L.; Spandl, R. J.; Glansdorp, F. G.; Welch, M.; Bender, A.; Cockfield, J.; Lindsay, J. A.; Bryant, C.; Brown, D. F. J.; Loiseleur, O.; Rudyk, H.; Ladlow, M.; Spring, D. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 2808. (b) Grand, B. L.; Pignier, C.; Letienne, R.; Cuisiat, F.; Rolland, F.; Mas, A.; Vacher, B. *J. Med. Chem.* **2008**, *51*, 3856. (c) Inoue, H.; Konda, M.; Hashiyama, T.; Otsuka, H.; Takahashi, K.; Gaino, M.; Date, T.; Aoe, K.; Takeda, M.; Murata, S.; Narita, H.; Nagao, T. *J. Med. Chem.* **1991**, *34*, 675. (d) Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; Von Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025. (e) Nielsen, S. F.; Nielsen, E. O.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem.* **2000**, *43*, 2217.

(2) (a) Rayner, C. M. *Advances in Sulfur Chemistry*, Vol. 2; JAI Press: Greenwich, CT, 2000. (b) Voss, J.; Solladie, G.; Trost, B. M.; Fleming,

I. In *Comprehensive Organic Synthesis*, Vol. *6*; Pergamon Press: Oxford, U.K., 1991.
(3) (a) Wardell, J. L.; Patai, S. In *The Chemistry of the Thiol Group*; Wiley: Chichester, U.K., 1974. (b) Thuillier, A.; Metzner, P. *Sulfur Reagents in Organic Synthesis*; Academic Press: New York, 1994.
(4) (a) Paradisi, C.; Trost, B. M.; Fleming, I. In *Comprehensive Organic Synthesis*, Vol. *4*; Pergamon Press: Oxford. U.K., 1991. (b) Caruso, A. J.; Colley, A. M.; Bryant, G. L. *J. Org. Chem.* **1991**, *56*, 862.
(5) (a) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236. (b) Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M.-T. *Org. Lett.* **2002**, *4*, 3619.
(6) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211.
(7) For the use of copper, see: (a) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312. (b) Liebeskind, L. S.; Yang, H.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1417. (c) Yu, Y.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2004**, *6*, 2631. (d) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554. For selected reviews, see: (e) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599. (f) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (g) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (h) Bichler, P.; Love, J. A. *Top. Organomet. Chem.* **2010**, *31*, 39−64. (i) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (j) Cheng, J. H.; Ramesh, C.; Kao, H. L.; Wang, Y. J.; Chan, C. C.; Lee, C. F. *J. Org. Chem.* **2012**, *77*, 10369.
(8) (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-i.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (b) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13. (c) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (d) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643. (e) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397. (f) Gao, G.-Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2004**, *69*, 8886. (g) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (h) Cai, L.; Cuevas, J.; Peng, Y.-Y.; Pike, V. W. *Tetrahedron Lett.* **2006**, *47*, 4449. (i) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133. (j) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069. (k) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937. (l) Fernández-Rodríguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (m) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.—Eur. J.* **2006**, *12*, 7782. (n) Eichman, C. C.; Stambuli, J. P. *J. Org. Chem.* **2009**, *74*, 4005. For selected reviews, see: (o) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (p) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314 and references cited therein. (q) Wang, L.; Zhou, W.-Y.; Chen, S.-C.; He, M.-Y.; Chen, Q. *Adv. Synth. Catal.* **2012**, *354*, 839.
(9) Fu, C.-F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Tetrahedron* **2010**, *66*, 2119.
(10) Shi, Y.; Cai, Z.; Guan, P.; Pang, G. *Synlett* **2011**, 2090.
(11) Sayah, M.; Organ, M. G. *Chem.—Eur. J.* **2011**, *17*, 11719.
(12) For selected reviews, see: (a) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (b) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122. (c) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151. (d) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.
(13) Meiries, S.; Speck, K.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2013**, *32*, 330.
(14) (a) Song, Y.-J.; Jung, I. G.; Lee, H.; Lee, Y. T.; Chung, Y. K.; Jang, H.-Y. *Tetrahedron Lett.* **2007**, *48*, 6142. (b) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. *Chem.—Eur. J.* **2012**, *18*, 4517.
(15) Generally, the catalyst loading can be decreased by increasing the reaction time.
(16) (a) Sayah, M.; Lough, A. J.; Organ, M. G. *Chem.—Eur. J.* **2013**, *19*, 2749. (b) Soria-Castro, S. M.; Peñéñory, A. B. *Beilstein J. Org. Chem.* **2013**, *9*, 467.