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Rhodium(III)-Catalyzed *ortho*-C–H Alkylation of 2-Arylbenzothiazoles and 2-Arylthiazoles with Potassium Alkyltrifluoroborates

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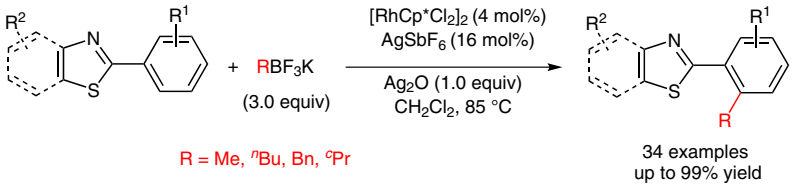

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Abstract A general and efficient Rh(III)-catalyzed *ortho*-C–H alkylation of 2-arylbenzothizazoles and 2-arylthiazoles with potassium alkyltrifluoroborates has been developed. The present method leads to the construction of a library of alkylated 2-arylbenzothiazoles and 2-arylthiazoles with yields up to 99%.

Key words alkylation, alkyltrifluoroborates, 2-arylbenzothiazoles, 2-arylthiazoles, transition metal

Alkyl, especially methyl is one of the most common building blocks in small organic molecules, which is a key structural feature of many biologically active molecules.[1] The introduction of such a simple unit usually can dramatically improve the biological and physical properties of pharmaceuticals, pesticides, and organic functional materials. It is well known that many marketed drugs contain at least one methyl group bound to the core skeleton.[2]

Over the past decade, complementary to traditional Friedel–Crafts alkylation synthesis strategies, transition-metal-catalyzed alkylation reactions have been quickly advanced due to the atom economical and environmental benign properties.[3] Transition-metal-catalyzed directing group assisted alkylation has been extensively reported using various alkylating reagents, such as alkyl halides,[4] alkylzinc halides,[5] alcohols,[6] alkanes,[7] alkenes,[8] allyl acetates,[9] amides,[10] amino acids,[11] ethers,[12] epoxides,[13] nitroalkanes,[14] organotin reagents,[15] peroxides,[16] α-diazoesters,[17] and organboron reagents.[18]

Among these alkyl coupling partners, organboron reagents are particularly attractive due to their commercial availability and synthetic accessibility, low cost, and low toxicity. In 2006, Yu developed pyridine-directed Pd(II)-catalyzed alkylation of sp^2 and sp^3 C–H bonds with methylboroxine and alkylboronic acids.[18a] Recently, Rodríguez and co-workers developed the Mn(III)-mediated direct alkylation of polyaromatic hydrocarbons and benzene with alkylboronic acids.[18b] Zhang[18c] and Gevorgyan,[18d] respectively, reported the amino acid-promoted and Pd(II)-catalyzed pyridyldiisopropylsilyl-directed C–H alkylation using alkylboronic acids as alkyl reagents. In addition, Molander and co-workers reported manganese(III) acetate catalyzed direct alkylation of heteroaryls using potassium alkyl- and alkoxymethyltrifluoroborates.[18e] In 2013, Sanford described Pd(II) and MnF_3 co-promoted direct alkylation of arylpyridines and anilides in the presence of potassium organotrifluoroborates. Yu disclosed the monoprotected amino acid-accelerated and Pd(II)-catalyzed alkylation of phenylacetic and benzoic acids using potassium alkyltrifluoroborated and alkylboronic acids as coupling partners.[18f] In 2015, Li also reported the Rh(III)-catalyzed C–H alkylation of arenes using alkyltrifluoroborates.[18g] Recently, Liu also reported the Rh(III)-catalyzed site-selective C–H alkylation of pyridones using organoboron reagents.[18h]

2-Arylbenzothiazoles are versatile structural motifs in organic medicinal and material chemistry due to their remarkable pharmacological activities[19] and fluorescent properties.[20] Recently, transition-metal-catalyzed C–H bond functionalization of 2-arylbenzothiazoles with various coupling partners has been reported by us[21] and other groups.[17b,22] A series of arylated,[21a] acetoxylated,[21b] halogenated,[21c,d] aminated,[21e] acylated,[21f,g,22b,c] trifluoromethylthiolated,[21h] cyanated,[21i] alkylenated,[22a] alkylated (using α-diazo esters as alkylating reagents),[17b] hydroxylated,[22d,e] and nitrated[22f] 2-arylbenzothiazole derivatives have been prepared. Based on these precedents, we present herein another Rh(III)-catalyzed *ortho*-alkylation of 2-arylbenzothiazoles and 2-arylthiazoles by using alkyltrifluoroborates as the alkyl group source.

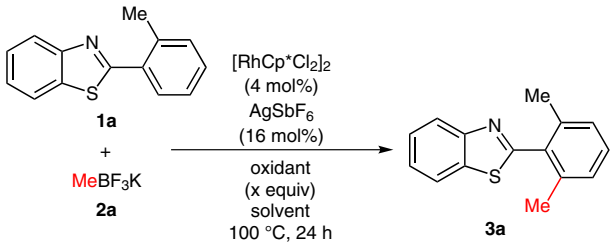
Recent investigations of C–H alkylation of arenes promoted us to use Rh(III)/Ag catalytic system for our designed reaction.[18g,h] Initially, we chose 2-(*o*-tolyl)benzothiazole (**1a**) and potassium methyltrifluoroborate ($MeBF_3K$, **2a**) as model substrates to optimize the coupling reaction conditions, using AgF and Ag_2O as oxidant, respectively (Table 1, entries 1 and 2). To our delight, Ag_2O was found to promote the reaction more efficiently than with AgF in $ClCH_2CH_2Cl$ (DCE). Screening of other solvents revealed that CH_2Cl_2 was the optimal one in this transformation (entries 2–7). Then, a range of other silver oxidants were screened for this coupling reaction in dichloromethane. Ag_2CO_3 and AgOAc were effective to accelerate this reaction with relatively less yields 75% (entries 9 and 10), whereas $AgNO_3$ and $AgBF_4$ were totally ineffective (entries 11 and 12). Fortunately, we were pleased to find that the efficiency was almost maintained even when 1.0 equivalent of oxidant (Ag_2O) was used (entry 14, 84%). In addition, the use of Ag_2O was very important, and no reaction took place in the absence of oxidant. Further investigation indicated that lowering the reaction temperature (85 °C) did not affect the reactivity (entry 17, 84%), while a decrease in the amount of $MeBF_3K$ (2.0 equiv) reduced the yield of the desired product **3a** to 71% (entry 19).

The substrate scope of this benzothiazole-assisted *ortho*-C–H methylation with $MeBF_3K$ (**2a**) was next investigated under the optimal conditions using $[RhCp^*Cl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), and Ag_2O (1.0 equiv). As shown in Scheme 1, moderate to excellent methylation yields were obtained. The reaction of *ortho*-substituted 2-arylbenzothiazoles **1b**,**c** (R^2 = OMe, F) was found to be excellent for this transformation to provide the desired products **3b**,**c** in almost quantitative yields. The reaction was also compatible with 2-(benzothiazol-2-yl)phenol (**1d**; R^2 = OH) to give the corresponding methylated product **3d** in moderate yield (50%). Substrates bearing electron-donating or -withdrawing group (R^1 = Me, F, and Cl) on the phenyl ring of benzothiazole afforded smoothly the desired products **3e–h**,**j–m** in excellent yields (88–99%), apart from 6-fluoro-2-(2-methoxyphenyl)benzothiazole (**1i**), which delivered the desired product **3i** only in 60% yield under optimal reaction conditions. It should be noted that the reaction of *meta*-methyl-substituted substrate **1n** preferentially occurred at the less hindered position to give the monomethylated 2-arylbenzothiazole **3n** in good yield (88%). Subsequently, the methylation reaction of symmetrical substrates **1o–r** (R^2 = 4-*N*,*N*-dimethyl, 4-NH_2, 4-Me, H) was examined under the standard reaction conditions, which delivered mono- and dialkylated products **3o–q**, **1a**, and **3a** in relatively low yields and regioselectivity.

Furthermore, the methylation of 2-arylthiazoles **4** with $MeBF_3K$ (**2a**) under the same conditions (Scheme 2) was studied. Fortunately, 2-(*o*-tolyl)thiazole (**4a**) was transformed perfectly to give the desired product **5a** in 99% yield. In addition, 2-(2-methoxyphenyl)thiazole (**4b**) also underwent the *ortho*-C–H methylation reaction efficiently to afford the desired product **5b** in 87% yield. Interestingly, the *meta*-methyl-substituted 2-(*m*-tolyl)thiazole (**4d**) gave the product **5d** selectively at the less sterically hindered position in good yield (71%).

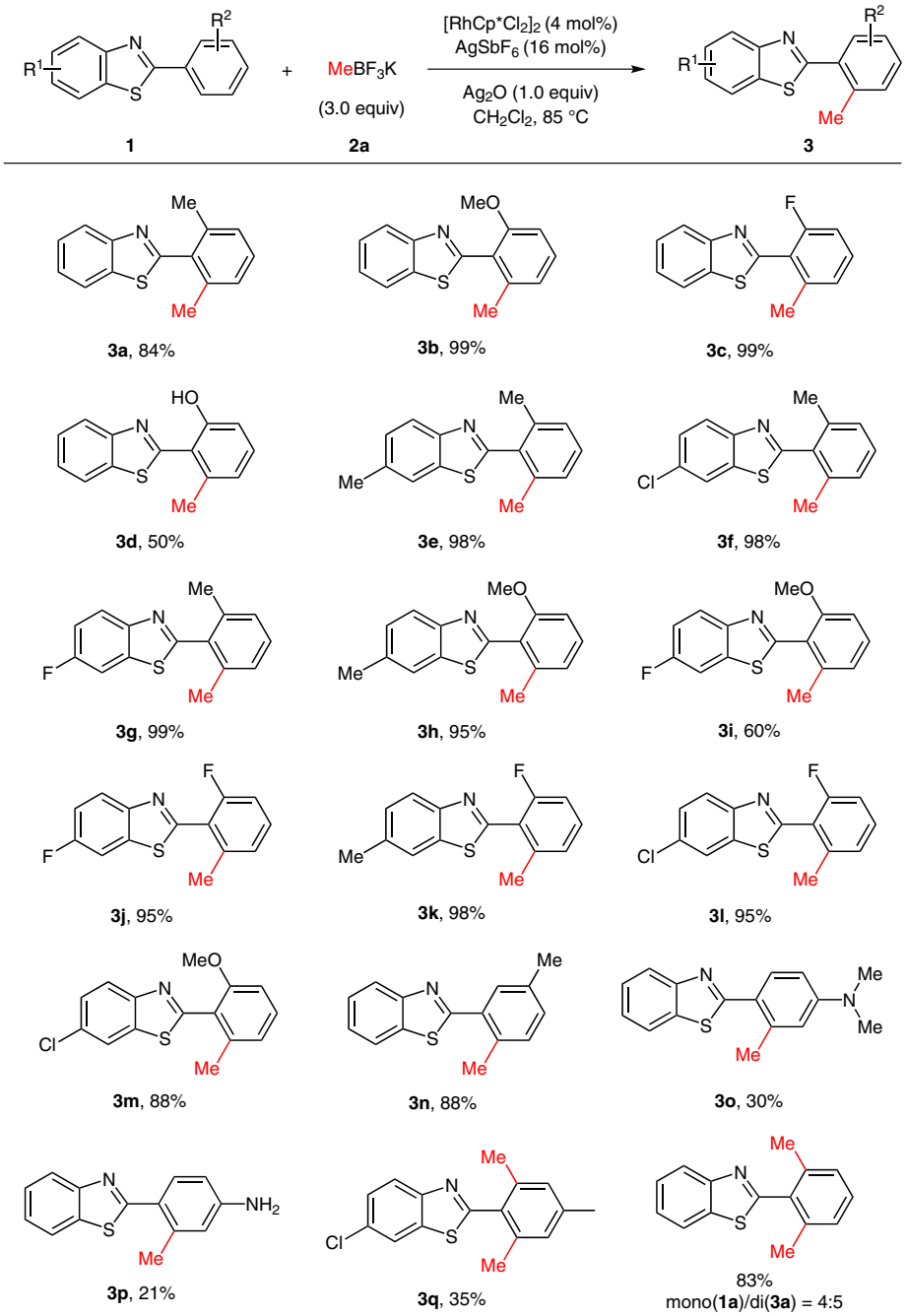
However, 2-(3-fluorophenyl)thiazole (**4e**) with a less hindered fluorine atom at the *meta*-position of 2-phenyl ring gave a mixture of dimethylated product 2-(3-fluoro-2,6-dimethylphenyl)thiazole **5e**(di) in 33% isolated yield and the monomethylated product 2-(5-fluoro-2-methylphenyl)thiazole **5e**(mono) in 33% NMR yield (See Supporting Information). In the case of 2-(naphthalen-2-yl)thiazole (**4f**), mono- and dimethylated products were formed in

Table 1 Optimization of Reaction Conditions[a]



Entry	Oxidant (x equiv)	Solvent	Yield (%)[b]
1	AgF (2.8)	DCE	21
2	Ag_2O (2.8)	DCE	54
3	Ag_2O (2.8)	1,4-dioxane	46
4	Ag_2O (2.8)	toluene	67
5	Ag_2O (2.8)	MeCN	25
6	Ag_2O (2.8)	DMF	42
7	Ag_2O (2.8)	CH_2Cl_2	88
8	AgF (2.8)	CH_2Cl_2	42
9	Ag_2CO_3 (2.8)	CH_2Cl_2	75
10	AgOAc (2.8)	CH_2Cl_2	75
11	$AgNO_3$ (2.8)	CH_2Cl_2	trace
12	$AgBF_4$ (2.8)	CH_2Cl_2	trace
13	Ag_2O (2.0)	CH_2Cl_2	85
14	Ag_2O (1.0)	CH_2Cl_2	84
15	Ag_2O (0.5)	CH_2Cl_2	30
16	–	CH_2Cl_2	trace
17[c]	Ag_2O (1.0)	CH_2Cl_2	84
18[d]	Ag_2O (1.0)	CH_2Cl_2	79
19[e]	Ag_2O (1.0)	CH_2Cl_2	71

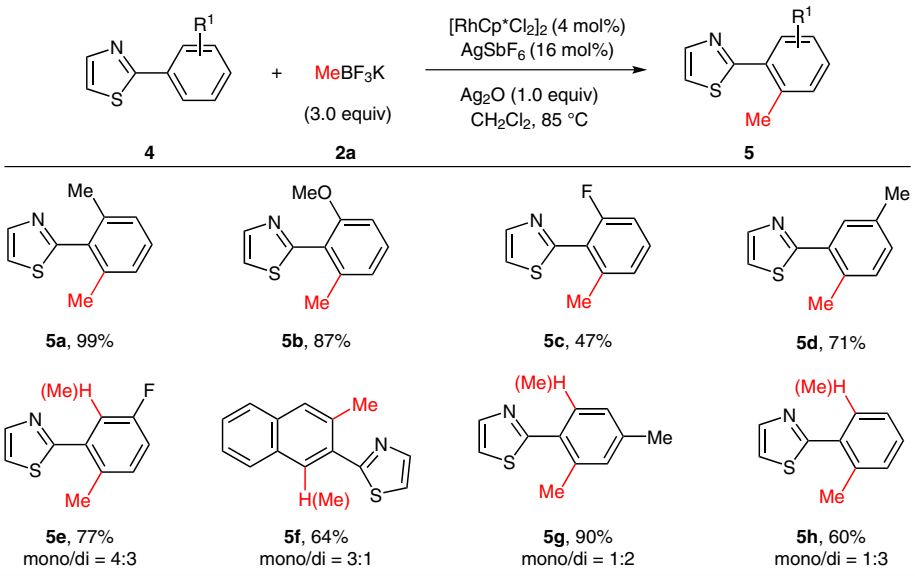
[a] Reaction conditions: 2-(*o*-tolyl)benzothiazole (**1a**; 0.2 mmol), $MeBF_3K$ (**2a**; 0.6 mmol, 3.0 equiv), $[RhCp^*Cl_2]_2$ (4.0 mol%), $AgSbF_6$ (16 mol%), oxidant (x equiv) in a solvent (2.0 mL) at 100 °C for 24 h.
[b] Isolated yield.
[c] Reaction was performed at 85 °C.
[d] Reaction was performed at 70 °C.
[e] Reaction was performed using $MeBF_3K$ (**2a**; 0.4 mmol, 2.0 equiv).



Scheme 1 Rh(III)-catalyzed methylation of 2-arylbenzothiazoles **1** with various substituents

moderate yields with monomethylated at the less hindered position as the major product. Symmetrical substrates like the *para*-methyl-substituted or unsubstituted 2-phenylthiazoles **4g** and **4h** also reacted with **2a** smoothly under the present conditions and led to mixtures of mono- and dimethylated products **5g**/**5g′** and **5h**/**5h′** in good yields with moderate selectivity.

Furthermore, the generality of this selective alkylation of 2-(2-methoxyphenyl)benzothiazole (**1b**) and 2-(2-methoxyphenyl)thiazole (**4b**) was explored with different boron reagent **2** as the alkylating reagent under optimal reaction conditions (Scheme 3). The results revealed that the coupling partners in this catalytic system are not limited only to methyl boron reagent $MeBF_3K$ (**2a**). Long-chain aliphatic boron reagent **2b** efficiently reacted to provide the corre-

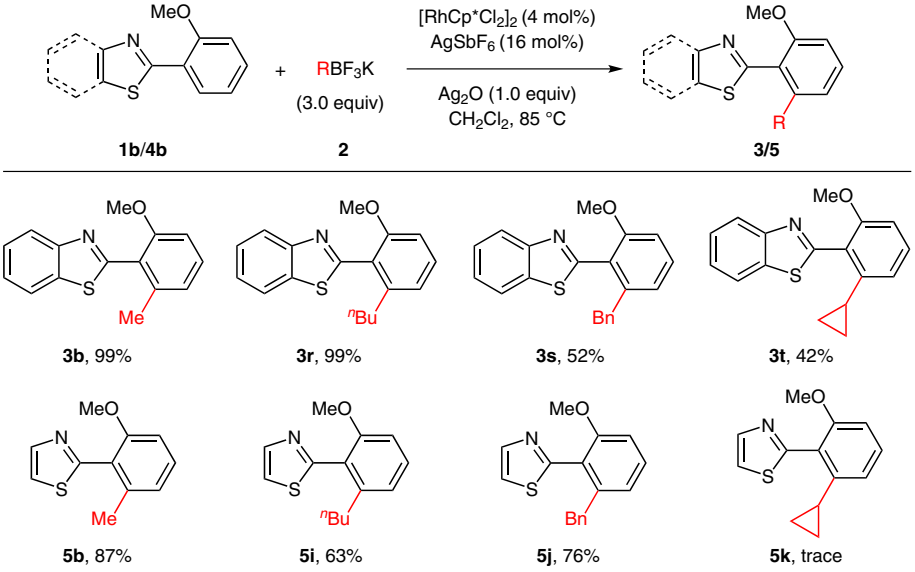


Scheme 2 Rh(III)-catalyzed methylation of 2-arylthiazoles **4**

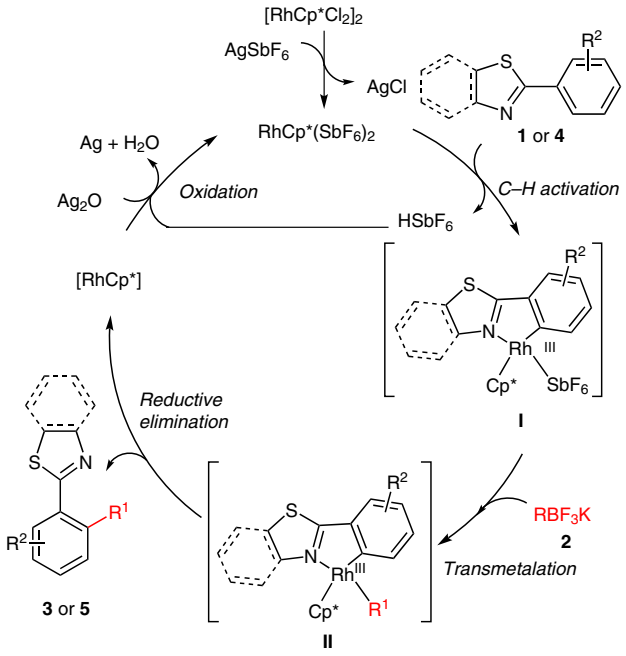
sponding products **3r** and **5i** in 99% and 63% isolated yield, respectively. Boron reagents containing a benzyl **2c** or cyclopropyl group **2d** also gave the corresponding benzylation product **3s** and **5j** and the cycloalkylation product **3t** in moderate to good yields.

Based on recent Rh-catalyzed direct *ortho*-C–H bond functionalization of arenes,[18g,h] a plausible mechanism for the present Rh(III)-catalyzed direct alkylation is shown in Scheme 4. Initially, an active cationic $RhCp^*(SbF_6)_2$ species may generate from the precursor $[RhCp^*Cl_2]_2$ promoted by the addition of $AgSbF_6$. Then, the active Rh(III) species facilitates the formation of a five-membered rhodacycle species **I** via C–H bond activation. Subsequently, the intermediate **II** is formed through transmetalation between the rhodacycle species **I** and boron reagent **2**. Finally, C–C reductive elimination of intermediate **II** will afford the desired alkylated product **3** or **5** along with Rh(I) species, which undergoes reoxidation by oxidant Ag_2O to regenerate the active cationic Rh(III) species for the following catalytic cycle.

In summary, we have successfully developed the rhodium-catalyzed direct *ortho*-C–H bond alkylation of 2-arylbenzothiazoles and 2-arylthiazoles by using alkyltrifluo-



Scheme 3 Scope of alkyl trifluoroborates **2**



Scheme 4 Proposed catalytic pathway

roborates as the alkyl group source. The results show that methyl, long-chain aliphatic group, and benzyl as well as cycloalkyl boron reagents are all compatible with the present alkylation protocol. No β-H elimination was observed in the present catalytic system. The reaction was found to be highly efficient providing a library of alkylated 2-arylbenzothiazoles and 2-arylthiazoles, which are widely present in many pharmaceuticals and biologically active natural products.

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 µm, standard grade). Analytical TLC was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporator at 25–35 °C/~20 Torr. NMR spectra are recorded in parts per million from internal TMS on the δ scale. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants in Hz. High-resolution mass spectrometry (HRMS) was carried out on a micrOTOF II Instrument.

Rhodium(III)-Catalyzed *ortho*-C–H Alkylation of 2-Arylbenzothiazoles and 2-Arylthiazoles with Potassium Alkyltrifluoroborates; General Procedure

A suspension of the respective 2-arylbenzodthiazole **1** (0.2 mmol), alkylboron reagent **2** (0.6 mmol, 3.0 equiv), $[RhCp^*Cl_2]_2$ (4.9 mg, 4 mol%), $AgSbF_6$ (10.9 mg, 16 mol%), and Ag_2O (46.3 mg, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was stirred at 100 °C under air for 24 h. After the completion of the reaction (monitored by TLC), the solvent was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel with PE/EtOAc (30:1–20:1) as the eluent to give the desired product **3**.

2-(2,6-Dimethylphenyl)benzo[*d*]thiazole (3a)[23a]

White solid; yield: 40.0 mg (84%); mp 108.8–110.9 °C; R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 7.8 Hz, 1 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.26 (d, *J* = 8.2 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 2 H), 2.21 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 153.4, 137.3, 136.3, 133.5, 129.5, 127.6, 126.0, 125.1, 123.4, 121.5, 20.1.

2-(2-Methoxy-6-methylphenyl)benzo[*d*]thiazole (3b)

Pale yellow liquid; yield: 50.0 mg (99%); R_f = 0.4 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 3.69 (s, 3 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 157.8, 153.2, 139.5, 136.5, 130.9, 130.6, 125.7, 124.9, 123.4, 122.7, 121.4, 108.5, 55.8, 20.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}NOS^+$: 256.0796; found: 256.0791.

2-(2-Fluoro-6-methylphenyl)benzo[*d*]thiazole (3c)[21c]

White solid; yield: 48.0 mg (99%); mp 37.6–43.8 °C; R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.28–7.23 (m, 1 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 6.95 (t, *J* = 9.0 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 160.6 (d, $^1J_{C,F}$ = 248 Hz), 153.2, 140.3 (d, $^4J_{C,F}$ = 2 Hz), 136.2, 131.0 (d, $^3J_{C,F}$ = 10 Hz), 126.2 (d, $^3J_{C,F}$ = 3 Hz), 126.1, 125.4, 123.6, 121.8 (d, $^2J_{C,F}$ = 14 Hz), 121.4, 113.2 (d, $^2J_{C,F}$ = 22 Hz), 20.3.

2-(Benzo[*d*]thiazol-2-yl)-3-methylphenol (3d)

White solid; yield: 24.0 mg (50%); mp 85.3–86.9 °C; R_f = 0.4 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.91 (s, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 7.8 Hz, 1 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.82 (d, *J* = 7.4 Hz, 1 H), 2.79 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 159.8, 149.3, 137.5, 133.0, 131.7, 126.8, 125.4, 122.6, 121.9, 120.9, 116.7, 116.3, 23.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}NOS^+$: 242.0640; found: 242.0634.

2-(2,6-Dimethylphenyl)-6-methylbenzo[*d*]thiazole (3e)

Faint yellow solid; yield: 49.0 mg (98%); mp 80.9–82.3 °C; R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 1 H), 7.64 (s, 1 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 2 H), 2.43 (s, 3 H), 2.11 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 151.6, 137.4, 136.5, 135.2, 133.7, 129.4, 127.5, 122.9, 121.2, 21.5, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NS^+$: 254.0998; found: 254.0992.

6-Chloro-2-(2,6-dimethylphenyl)benzo[*d*]thiazole (3f)

Pale yellow liquid; yield: 53.0 mg (98%); R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.8 Hz, 1 H), 7.83 (d, *J* = 2.0 Hz, 1 H), 7.40 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 2.11 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 152.0, 137.5, 137.3, 133.1, 131.2, 129.7, 127.7, 126.8, 124.2, 121.1, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}ClNS^+$: 274.0457; found: 274.0456.

2-(2,6-Dimethylphenyl)-6-fluorobenzo[*d*]thiazole (3g)

White solid; yield: 51.0 mg (99%); mp 54.3–55.5 °C; R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 8.8, 4.8 Hz, 1 H), 7.53 (dd, *J* = 8.0, 2.4 Hz, 1 H), 7.23–7.13 (m, 2 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 2.12 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1 (d, $^4J_{C,F}$ = 3 Hz), 160.5 (d, $^1J_{C,F}$ = 244 Hz), 150.1 (d, $^4J_{C,F}$ = 1 Hz), 137.4 (d, $^3J_{C,F}$ = 11 Hz), 137.3, 133.2, 129.7, 127.7, 124.4 (d, $^3J_{C,F}$ = 10 Hz), 114.6 (d, $^2J_{C,F}$ = 25 Hz), 107.7 (d, $^2J_{C,F}$ = 27 Hz), 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}FNS^+$: 258.0753; found: 258.0756.

2-(2-Methoxy-6-methylphenyl)-6-methylbenzo[*d*]thiazole (3h)

White solid; yield: 51.0 mg (95%); mp 74.3–76.5 °C; R_f = 0.3 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1 H), 7.70 (s, 1 H), 7.31 (t, *J* = 8.2 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 3.75 (s, 3 H), 2.50 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 157.9, 151.4, 139.5, 136.7, 135.0, 130.5, 127.2, 123.0, 122.8, 122.7, 121.1, 108.6, 55.8, 21.5, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NOS^+$: 270.0953; found: 270.0947.

6-Fluoro-2-(2-methoxy-6-methylphenyl)benzo[*d*]thiazole (3i)

Pale yellow liquid; yield: 33.0 mg (60%); R_f = 0.4 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 8.8, 4.8 Hz, 1 H), 7.60 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.23 (dt, *J* = 2.4, 8.8 Hz, 1 H), 6.93 (d, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 3.78 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 (d, $^4J_{C,F}$ = 3 Hz), 160.4 (d, $^1J_{C,F}$ = 244 Hz), 157.9, 149.9 (d, $^4J_{C,F}$ = 1 Hz), 139.6, 137.5 (d, $^3J_{C,F}$ = 11 Hz), 130.8, 124.3 (d, $^3J_{C,F}$ = 9 Hz), 122.9, 122.5, 114.3 (d, $^2J_{C,F}$ = 25 Hz), 108.6, 107.4 (d, $^2J_{C,F}$ = 26 Hz), 55.9, 20.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}FNOS^+$: 274.0702; found: 274.0696.

6-Fluoro-2-(2-fluoro-6-methylphenyl)benzo[*d*]thiazole (3j)[21c]

White solid; yield: 50.0 mg (95%); mp 62.0–64.3 °C; R_f = 0.4 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 9.2, 5.2 Hz, 1 H), 7.54 (dd, *J* = 8.0, 2.4 Hz, 1 H), 7.30–7.24 (m, 1 H), 7.18 (dt, *J* = 2.8, 8.8 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 6.96 (t, *J* = 9.0 Hz, 1 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (d, $^4J_{C,F}$ = 3.4 Hz), 160.7 (d, $^1J_{C,F}$ = 245 Hz), 160.6 (d, $^1J_{C,F}$ = 248 Hz), 160.9 (d, $^4J_{C,F}$ = 3.4 Hz), 149.8 (d, $^4J_{C,F}$ = 1.4 Hz), 140.3 (d, $^4J_{C,F}$ = 1.2 Hz), 137.2 (d, $^3J_{C,F}$ = 11.2 Hz), 131.2 (d, $^3J_{C,F}$ = 9.2 Hz), 126.3 (d, $^4J_{C,F}$ = 3.2 Hz), 124.5 (d, $^3J_{C,F}$ = 9.4 Hz), 121.4 (d, $^2J_{C,F}$ = 13.9 Hz), 114.8 (d, $^2J_{C,F}$ = 24.7 Hz), 113.2 (d, $^2J_{C,F}$ = 22 Hz), 107.5 (d, $^2J_{C,F}$ = 26.5 Hz), 20.3 (d, $^4J_{C,F}$ = 2.5 Hz).

2-(2-Fluoro-6-methylphenyl)-6-methylbenzo[*d*]thiazole (3k)

White solid; yield: 50.0 mg (98%); mp 72.3–74.5 °C; R_f = 0.4 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.4 Hz, 1 H), 7.73 (s, 1 H), 7.35–7.30 (m, 2 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.02 (t, *J* = 9.0 Hz, 1 H), 2.51 (s, 3 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6 (d, $^1J_{C,F}$ = 248 Hz), 160.1, 151.4, 140.3 (d, $^4J_{C,F}$ = 1 Hz), 136.4 (d, $^4J_{C,F}$ = 1 Hz), 135.6, 130.9 (d, $^3J_{C,F}$ = 9 Hz), 127.7, 126.2 (d, $^3J_{C,F}$ = 3 Hz), 123.0, 121.9 (d, $^2J_{C,F}$ = 14 Hz), 121.1, 113.1 (d, $^2J_{C,F}$ = 22 Hz), 21.5, 20.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}FNS^+$: 258.0753; found: 258.0753.

6-Chloro-2-(2-fluoro-6-methylphenyl)benzo[*d*]thiazole (3l)[21c]

White solid; yield: 53.0 mg (95%); mp 101.2–102.9 °C; R_f = 0.5 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 2.0 Hz, 1 H), 7.48 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.04 (t, *J* = 9.0 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 160.6 (d, $^1J_{C,F}$ = 249 Hz), 151.7, 140.3 (d, $^4J_{C,F}$ = 1 Hz), 137.4 (d, $^4J_{C,F}$ = 1 Hz), 131.4, 131.2 (d, $^3J_{C,F}$ = 9 Hz), 126.9, 126.4 (d, $^3J_{C,F}$ = 3 Hz), 124.3, 121.3 (d, $^2J_{C,F}$ = 14 Hz), 121.0, 113.3 (d, $^2J_{C,F}$ = 22 Hz), 20.4.

6-Chloro-2-(2-methoxy-6-methylphenyl)benzo[*d*]thiazole (3m)

White liquid; yield: 51.0 mg (88%); R_f = 0.3 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 2.0 Hz, 1 H), 7.44 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 3.78 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 157.9, 151.8, 139.5, 137.7, 130.9, 130.8, 126.5, 124.1, 122.9, 122.3, 120.9, 108.6, 55.8, 20.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}ClNOS^+$: 290.0406; found: 290.0407.

2-(2,5-Dimethylphenyl)benzo[*d*]thiazole (3n)[23b]

White liquid; yield: 42.0 mg (88%); R_f = 0.4 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.58 (s, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.25–7.17 (m, 2 H), 2.61 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 153.8, 138.8, 135.6, 134.1, 132.9, 131.5, 131.0, 130.8, 126.1, 125.0, 123.3, 121.3, 20.8.

4-(Benzo[*d*]thiazol-2-yl)-*N*,*N*,3-trimethylaniline (3o)

Yellow granular solid; yield: 16.0 mg (30%); mp 93.4–96.5 °C; R_f = 0.4 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 6.63 (d, *J* = 2.8 Hz, 1 H), 6.61 (s, 1 H), 3.03 (s, 6 H), 2.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 154.1, 151.3, 138.5, 135.1, 132.0, 125.8, 124.2, 122.6, 121.1, 121.0, 114.4, 109.6, 40.1, 22.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2S^+$: 269.1102; found: 269.1107.

4-(Benzo[*d*]thiazol-2-yl)-3-methylaniline (3p)

Yellow solid; yield: 10.0 mg (21%); mp 92.1–94.3 °C; R_f = 0.2 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 6.61 (s, 1 H), 6.58 (d, *J* = 2.0 Hz, 1 H), 3.91 (s, 2 H), 2.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 154.0, 148.1, 139.0, 132.3, 125.9, 124.5, 123.5, 122.9, 121.1, 117.4, 112.5, 83.2, 21.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2S^+$: 241.0795; found: 241.0794.

6-Chloro-2-mesitylbenzo[*d*]thiazole (3q)

White liquid; yield: 20.0 mg (35%); R_f = 0.5 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 2.0 Hz, 1 H), 7.40 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.88 (s, 2 H), 2.26 (s, 3 H), 2.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 152.1, 139.7, 137.6, 137.1, 131.1, 130.3, 128.5, 126.7, 124.1, 121.1, 21.2, 20.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClNS^+$: 288.0612; found: 288.0608.

2-(2-Butyl-6-methoxyphenyl)benzo[*d*]thiazole (3r)

White liquid; yield: 59.0 mg (99%); R_f = 0.3 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 7.33–7.25 (m, 2 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 3.66 (s, 3 H), 2.49 (t, *J* = 8.0 Hz, 2 H), 1.47–1.39 (m, 2 H), 1.16–1.11 (m, 2 H), 0.69 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 157.9, 153.3, 144.3, 136.6, 130.6, 125.6, 124.9, 123.4, 122.5, 121.8, 121.3, 108.4, 55.8, 33.3, 33.0, 22.4, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NOS^+$: 298.1266; found: 298.1260.

2-(2-Benzyl-6-methoxyphenyl)benzo[*d*]thiazole (3s)

Faint yellow solid; yield: 31.0 mg (47%); mp 76.3–78.4 °C; R_f = 0.2 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.10–7.02 (m, 3 H), 6.93 (d, *J* = 6.4 Hz, 2 H), 6.78 (t, *J* = 6.8 Hz, 2 H), 3.92 (s, 2 H), 3.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 158.0, 153.2, 142.6, 140.4, 136.7, 130.8, 129.0, 128.4, 128.3, 128.2, 125.9, 125.7, 124.9, 123.4, 122.8, 122.6, 121.3, 109.0, 55.9, 39.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}NOS^+$: 332.1102; found: 332.1104.

2-(2-Cyclopropyl-6-methoxyphenyl)benzo[*d*]thiazole (3t)

Faint yellow solid; yield: 20.0 mg (36%); mp 63.3–65.8 °C; R_f = 0.2 (PE/EtOAc, 30:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.25 (t, *J* = 8.2 Hz, 1 H), 7.19–7.17 (m, 1 H), 7.12–7.09 (m, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 6.52 (d, *J* = 7.6 Hz, 1 H), 3.67 (s, 3 H), 1.79–1.72 (m, 1 H), 0.73–0.66 (m, 2 H), 0.62–0.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 157.7, 153.4, 145.0, 136.7, 130.9, 128.36 (d, *J* = 12.2 Hz), 125.9, 125.6, 124.9, 123.4, 121.4, 116.4, 108.2, 55.9, 37.9, 13.2, 9.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NOS^+$: 282.0947; found: 282.0955.

2-(2,6-Dimethylphenyl)thiazole (5a)

Pale yellow liquid; yield: 37.0 mg (99%); R_f = 0.4 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 3.6 Hz, 1 H), 7.46 (d, *J* = 3.4 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 2.13 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 142.8, 137.7, 133.4, 129.1, 127.4, 120.1, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NS^+$: 190.0690; found: 190.0685.

2-(2-Methoxy-6-methylphenyl)thiazole (5b)

Pale yellow liquid; yield: 36 mg (87%); R_f = 0.3 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 3.6 Hz, 1 H), 7.46 (d, *J* = 3.6 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 3.76 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 157.8, 142.3, 139.6, 130.1, 122.8, 122.5, 120.2, 108.4, 55.7, 20.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NOS^+$: 206.0640; found: 206.0634.

2-(2-Fluoro-6-methylphenyl)thiazole (5c)

Transparent liquid; yield: 18.0 mg (47%); R_f = 0.3 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 3.2 Hz, 1 H), 7.53 (d, *J* = 3.6 Hz, 1 H), 7.34–7.27 (m, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.02 (t, *J* = 9.0 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5 (d, $^1J_{C,F}$ = 247 Hz), 160.4, 142.8, 140.3 (d, $^4J_{C,F}$ = 1 Hz), 130.4 (d, $^3J_{C,F}$ = 9 Hz), 126.3 (d, $^3J_{C,F}$ = 3 Hz), 121.5 (d, $^2J_{C,F}$ = 14 Hz), 120.6 (d, $^4J_{C,F}$ = 2 Hz), 113.1 (d, $^2J_{C,F}$ = 22 Hz), 20.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9FNS^+$: 194.0440; found: 194.0434.

2-(2,5-Dimethylphenyl)thiazole (5d)[23c]

White liquid; yield: 27.0 mg (71%); R_f = 0.6 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 3.2 Hz, 1 H), 7.55 (s, 1 H), 7.37 (d, *J* = 3.2 Hz, 1 H), 7.19–7.12 (m, 2 H), 2.54 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 142.8, 135.5, 133.3, 132.7, 131.3, 130.5, 130.1, 119.2, 20.9, 20.8.

2-(3-Fluorophenyl)thiazole (4e)/2-(5-Fluoro-2-methylphenyl)thiazole [5e(mono); 4e/5e(mono): 1:1]

Pale yellow liquid; 43 mg; R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 3.6 Hz, 1 H), 7.88 (d, *J* = 3.2 Hz, 1 H), 7.74–7.69 (m, 2 H), 7.47–7.36 (m, 4 H), 7.27–7.21 (m, 1 H), 7.15–7.09 (m, 2 H), 2.48 (d, *J* = 2.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8 (d, $^4J_{C,F}$ = 3 Hz), 166.6 (d, $^4J_{C,F}$ = 3 Hz), 163.0 (d, $^1J_{C,F}$ = 245 Hz), 161.6 (d, $^1J_{C,F}$ = 243 Hz), 143.9, 143.2, 135.5 (d, $^3J_{C,F}$ = 8 Hz), 135.0 (d, $^3J_{C,F}$ = 5 Hz), 130.5 (d, $^3J_{C,F}$ = 8 Hz), 126.8 (d, $^3J_{C,F}$ = 9 Hz), 125.7 (d, $^4J_{C,F}$ = 2 Hz), 124.1 (d, $^2J_{C,F}$ = 18 Hz), 122.3 (d, $^4J_{C,F}$ = 3 Hz), 119.9, 119.5, 116.8 (d, $^2J_{C,F}$ = 21 Hz), 116.0 (d, $^2J_{C,F}$ = 24 Hz), 113.4 (d, $^2J_{C,F}$ = 23 Hz), 12.0 (d, $^4J_{C,F}$ = 6 Hz).

2-(3-Fluoro-2,6-dimethylphenyl)thiazole [5e(di)]

Pale yellow liquid; yield: 14.0 mg (34%); R_f = 0.4 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 3.6 Hz, 1 H), 7.51 (d, *J* = 3.2 Hz, 1 H), 7.09–7.00 (m, 2 H), 2.09 (s, 3 H), 2.04 (d, *J* = 2.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (d, $^4J_{C,F}$ = 3 Hz), 159.4 (d, $^1J_{C,F}$ = 241 Hz), 143.0, 134.9 (d, $^3J_{C,F}$ = 5 Hz), 133.2 (d, $^4J_{C,F}$ = 3 Hz), 128.2 (d, $^3J_{C,F}$ = 9 Hz), 125.0 (d, $^2J_{C,F}$ = 17 Hz), 120.5, 115.8 (d, $^2J_{C,F}$ = 23 Hz), 19.7, 12.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}FNS^+$: 208.0596; found: 208.0601.

2-(3-Methylnaphthalen-2-yl)thiazole [5f(mono)]

White solid; yield: 20.0 mg (45%); mp 57.8–61.2 °C; R_f = 0.4 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.96 (d, *J* = 3.6 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.74 (s, 1 H), 7.52–7.43 (m, 2 H), 7.42 (d, *J* = 3.2 Hz, 1 H), 2.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 143.2, 133.7, 133.6, 131.8, 131.6, 129.8, 129.4, 128.0, 127.0, 126.9, 125.8, 119.5, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}NS^+$: 226.0690; found: 226.0685.

2-(1,3-Dimethylnaphthalen-2-yl)thiazole [5f(di)]

Faint yellow solid; yield: 9.0 mg (18%); mp 90.3–92.9 °C; R_f = 0.2 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.01 (m, 1 H), 7.98 (d, *J* = 3.4 Hz, 1 H), 7.81–7.79 (m, 1 H), 7.60 (s, 1 H), 7.54–7.48 (m, 3 H), 2.47 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 142.9, 134.6, 134.5, 133.8, 131.7, 131.0, 127.8, 126.5, 126.3, 125.6, 124.5, 120.4, 20.9, 16.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NS^+$: 240.0847; found: 240.0842.

2-(2,4-Dimethylphenyl)thiazole [5g(mono)]

Transparent liquid; yield: 12.0 mg (30%); R_f = 0.5 (PE/EtOAc, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 3.6 Hz, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 3.2 Hz, 1 H), 7.12 (s, 1 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 2.56 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 142.9, 139.4, 136.3, 132.2, 130.2, 130.1, 126.8, 119.0, 21.3, 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NS^+$: 190.0681; found: 190.0685.

2-Mesitylthiazole [5g(di)][23c]

White solid; yield: 24.0 mg (60%); mp 51.2–53.3 °C; R_f = 0.3 (PE/EtOAc, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 3.4 Hz, 1 H), 7.45 (d, *J* = 3.4 Hz, 1 H), 6.93 (s, 2 H), 2.32 (s, 3 H), 2.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 142.8, 139.0, 137.6, 130.5, 128.3, 120.1, 21.1, 20.1.

2-(*o*-Tolyl)thiazole [5h(mono)][23d]

Transparent liquid; yield: 5.0 mg (15%); R_f = 0.5 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 3.2 Hz, 1 H), 7.72 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 3.6 Hz, 1 H), 7.34–7.28 (m, 3 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 143.0, 136.6, 133.0, 131.5, 130.1, 129.4, 126.1, 119.4, 21.4.

2-(2,6-Dimethylphenyl)thiazole [5h(di)]

Transparent liquid; yield: 17.0 mg (45%); R_f = 0.3 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 3.6 Hz, 1 H), 7.48 (d, *J* = 3.6 Hz, 1 H), 7.24 (t, *J* = 7.2 Hz, 1 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 2.14 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 142.9, 137.7, 133.4, 129.2, 127.5, 120.2, 20.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NS^+$: 190.0690; found: 190.0685.

2-(2-Butyl-6-methoxyphenyl)thiazole (5i)

Transparent liquid; yield: 31.0 mg (63%); R_f = 0.4 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 3.2 Hz, 1 H), 7.47 (d, *J* = 3.2 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 3.75 (s, 3 H), 2.51 (t, *J* = 8.0 Hz, 2 H), 1.48–1.39 (m, 2 H), 1.28–1.19 (m, 2 H), 0.80 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 157.9, 144.6, 142.3, 130.2, 122.3, 121.9, 120.2, 108.4, 55.8, 33.3, 33.0, 22.5, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NOS^+$: 248.1104; found: 248.1116.

2-(2-Benzyl-6-methoxyphenyl)thiazole (5j)

Pale yellow liquid; yield: 43.0 mg (76%); R_f = 0.3 (PE/EtOAc, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 3.2 Hz, 1 H), 7.41 (d, *J* = 3.2 Hz, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.17–7.11 (m, 3 H), 6.98 (d, *J* = 6.8 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 3.96 (s, 2 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 157.9, 142.7, 142.2, 140.6, 130.4, 128.9, 128.1, 125.8, 122.7, 122.6, 120.5, 109.0, 55.8, 39.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NOS^+$: 282.0947; found: 282.0946.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588936.

References

(1) For pertinent reviews, see: (a) Schöherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256. (b) Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489. (c) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215.

(2) (a) Vitaku E., Ilardi E. A., Njardarson J. T.; *Top 200 Pharmaceutical Products by US Retail Sales in 2011*; http://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20200%20Pharmaceutical%20Products%20by%20US%20Retail%20Sales%20in%202011_small_0.pdf; accessed February 9, 2017. (b) For the 2008 edition, see: McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.

(3) For reviews, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (c) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (f) Pan, S.; Shibata, T. *ACS Catal.* **2013**, *3*, 704. (g) Yan, G.; Borah, A. J.; Wang, L.; Yang, M. *Adv. Synth. Catal.* **2015**, *357*, 133.

(4) Some selected reports in recent three years: (a) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 2477. (b) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (c) Monks, B. M.; Fruchey, E. R.; Cook, S. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 11065. (d) Chen, K.; Shi, B. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 11950. (e) Zhu, R. Y.; He, J.; Wang, X. C.; Yu, J. Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194. (f) Wu, X.; See, J. W. T.; Xu, K.; Hirao, H.; Roger, J.; Hierso, J.; Zhou, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 13573. (g) Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531. (h) Shen, P. X.; Wang, X. C.; Wang, P.; Zhu, R. Y.; Yu, J. Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574. (i) Li, J.; Warratz, S.; Zell, D.; De Sarkar, S.; Ishikawa, E. E.; Ackermann, L. *J. Am. Chem. Soc.* **2015**, *137*, 13894. (j) Wiest, J. M.; Pothig, A.; Bach, T. *Org. Lett.* **2016**, *18*, 852. (k) Cheng, J.; Deng, X.; Wang, G.; Li, Y.; Cheng, X.; Li, G. *Org. Lett.* **2016**, *18*, 4538. (l) Soni, V.; Jagtap, R. A.; Gonnade, R. G.; Punji, B. *ACS Catal.* **2016**, *6*, 5666. (m) Hu, L.; Liu, X.; Liao, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 9743.

(5) Ilies, L.; Ichikawa, S.; Asako, S.; Matsubara, T.; Nakamura, E. *Adv. Synth. Catal.* **2015**, *357*, 2175.

(6) Some recent reports: (a) Lee, D. H.; Kwon, K. H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (b) Han, S. H.; Choi, M.; Jeong, T.; Sharma, S.; Mishra, N. K.; Park, J.; Oh, J. S.; Kim, W. J.; Lee, J. S.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 11092. (c) Huang, H.; Liu, J.; Liu, X.; Xiao, J.; Zhong, S.; She, X.; Fu, Z.; Yin, D. *Fuel* **2016**, *182*, 373. (d) Zhou, X.; Yu, S.; Qi, Z.; Kong, L.; Li, X. *J. Org. Chem.* **2016**, *81*, 4869. (e) Deibl, N.; Kempe, R. *J. Am. Chem. Soc.* **2016**, *138*, 10786.

(7) Some recent reports: (a) Yonehara, F.; Kido, Y.; Sugimoto, H.; Morita, S.; Yamaguchi, M. *J. Org. Chem.* **2003**, *68*, 6752. (b) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (c) Zhang, X.; Wang, Z.; Fan, X.; Wang, J. *J. Org. Chem.* **2015**, *80*, 10660.

(8) Some recent reports: (a) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 5679. (b) Wang, Z.; Reinus, B. J.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 13954. (c) Oyamada, J.; Hou, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 12828. (d) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474. (e) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876. (f) Tang, S.; Wu, X.; Liao, W.; Liu, K.; Liu, C.; Luo, S.; Lei, A. *Org. Lett.* **2014**, *16*, 3584. (g) Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148. (h) Hu, G.; Xu, J.; Li, P. *Org. Lett.* **2014**, *16*, 6036. (i) Lee, P. S.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 22. (j) Pollice, R.; Dastbaravardeh, N.; Marquise, N.; Mihovilovic, M. D.; Schnurch, M. *ACS Catal.* **2015**, *5*, 587. (k) Shibata, K.; Yamaguchi, T.; Chatani, N. *Org. Lett.* **2015**, *17*, 3584. (l) Dang, Y.; Qu, S.; Tao, Y.; Deng, X.; Wang, Z. X. *J. Am. Chem. Soc.* **2015**, *137*, 6279. (m) Hatano, M.; Ebe, Y.; Nishimura, T.; Yorimitsu, H. *J. Am. Chem. Soc.* **2016**, *138*, 4010. (n) Han, S.; Park, J.; Kim, S.; Lee, S. H.; Sharma, S.; Mishra, N. K.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2016**, *18*, 4666.

(9) Some recent reports: (a) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (b) Howell, J. M.; Liu, W.; Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 5750. (c) Bae, S.; Jang, H. L.; Jung, H.; Joo, J. M. *J. Org. Chem.* **2015**, *80*, 690. (d) Deng, H.; Li, H.; Wang, L. *Org. Lett.* **2015**, *17*, 2450.

(10) Meng, G.; Szostak, M. *Org. Lett.* **2016**, *18*, 796.

(11) Mai, D. N.; Baxter, R. D. *Org. Lett.* **2016**, *18*, 3738.

(12) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932.

(13) (a) Hodgson, D. M.; Charlton, A.; Paton, R. S.; Thompson, A. L. *J. Org. Chem.* **2013**, *78*, 1508. (b) Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 6140. (c) Cheng, G.; Li, T. J.; Yu, J. Q. *J. Am. Chem. Soc.* **2015**, *137*, 10950. (d) Li, D. D.; Niu, L. F.; Ju, Z. Y.; Xu, Z.; Wu, C. *Eur. J. Org. Chem.* **2016**, 3090.

(14) Manna, M. S.; Mukherjee, S. *J. Am. Chem. Soc.* **2015**, *137*, 130.

(15) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

(16) Kubo, T.; Chatani, N. *Org. Lett.* **2016**, *18*, 1698.

(17) (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (b) Choi, M.; Park, J.; Mishra, N. K.; Lee, S.-Y.; Kim, J. H.; Jeong, K. M.; Lee, J.; Jung, Y. H.; Kim, I. S. *Tetrahedron Lett.* **2015**, *56*, 4678.

(18) (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) Castro, S.; Fernández, J. J.; Fañanás, F. J.; Vicente, R.; Rodríguez, F. *Chem. Eur. J.* **2016**, *22*, 9068. (c) Zhang, Y.; Jiang, H.; Chen, D.; Zhang, Y. *Org. Biomol. Chem.* **2016**, *14*, 4585. (d) Sarkar, D.; Gevorgyan, V. *Chem. Eur. J.* **2016**, *22*, 11201. (e) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852. (f) Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 17508. (g) Wang, H.; Yu, S.; Qi, Z.; Li, X. *Org. Lett.* **2015**, *17*, 2812. (h) Peng, P.; Wang, J.; Jiang, H.; Liu, H. *Org. Lett.* **2016**, *18*, 5376.

(19) (a) Benavides, J.; Camelin, J. C.; Mitrani, N.; Flamand, F.; Uzan, A.; Legrand, J. J.; Guérémy, C.; Le Fur, G. *Neuropharmacology* **1985**, *24*, 1085. (b) Malgouris, C.; Bardot, F.; Daniel, M.; Pellis, J.; Rataud, A.; Uzan, A.; Blanchard, J. C.; Laduron, P. M. *J. Neurosci.* **1989**, *9*, 3720. (c) Mortimer, C. G.; Wells, G.; Crochard, J. P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179. (d) Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135.

(20) (a) Katkova, M. A.; Balashova, T. V.; Ilichev, V. A.; Konev, A. N.; Isachenkov, N. A.; Fukin, G. K.; Ketkov, S. U.; Bochkarev, M. N. *Inorg. Chem.* **2010**, *49*, 5094. (b) Wang, R.; Liu, D.; Ren, H.; Zhang, T.; Wang, X.; Li, J. *J. Mater. Chem.* **2011**, *21*, 15494. (c) Santra, M.; Roy, B.; Ahn, K. H. *Org. Lett.* **2011**, *13*, 3422. (d) Woo, H.; Cho, S.; Han, Y.; Chae, W.-S.; Ahn, D.-R.; You, Y.; Nam, W. *J. Am. Chem. Soc.* **2013**, *135*, 4771. (e) Yuan, Y.-J.; Yu, Z.-T.; Gao, H.-L.; Zou, Z.-G.; Zheng, C.; Huang, W. *Chem. Eur. J.* **2013**, *19*, 6340.

(21) (a) Ding, Q.; Ji, H.; Wang, D.; Lin, Y.; Yu, W.; Peng, Y. *J. Organomet. Chem.* **2012**, *711*, 62. (b) Ding, Q.; Ji, H.; Nie, Z.; Yang, Q.; Peng, Y. *J. Organomet. Chem.* **2013**, *739*, 33. (c) Ding, Q.; Ye, C.; Pu, S.; Cao, B. *Tetrahedron* **2014**, *70*, 409. (d) Ding, Q.; Zhou, X.; Pu, S.; Cao, B. *Tetrahedron* **2015**, *71*, 2376. (e) Zhou, X.; Luo, P.; Long, L.; Ouyang, M.; Sang, X.; Ding, Q. *Tetrahedron* **2014**, *70*, 6742. (f) Ding, Q.; Ji, H.; Ye, C.; Wang, J.; Wang, J.; Zhou, L.; Peng, Y. *Tetrahedron* **2013**, *69*, 8661. (g) Wang, J.; Nie, Z.; Li, Y.; Tan, S.; Jiang, J.; Jiang, P.; Ding, Q. *J. Chem. Res.* **2013**, *37*, 263. (h) Luo, P.; Ding, Q.; Ping, Y.; Hu, J. *Org. Biomol. Chem.* **2016**, *14*, 2924. (i) Ping, Y.; Ding, Q.; Chen, Z.; Peng, Y. *J. Organomet. Chem.* **2016**, *815–816*, 59.

(22) (a) Hashimoto, Y.; Ortloff, T.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *Chem. Lett.* **2012**, *41*, 151. (b) Banerjee, A.; Santra, S. K.; Guin, S.; Rout, S. K.; Patel, B. K. *Eur. J. Org. Chem.* **2013**, *7*, 1367. (c) Zheng, Y.; Song, W. B.; Zhang, S. W.; Xuan, L. J. *Tetrahedron* **2015**, *71*, 1574. (d) Banerjee, A.; Bera, A.; Guin, S.; Rout, S. K.; Patel, B. K. *Tetrahedron* **2013**, *69*, 2175. (e) Seth, K.; Nautiyal, M.; Purohit, P.; Parikh, N.; Chakraborti, A. K. *Chem. Commun.* **2015**, *51*, 191. (f) Qiao, H.-J.; Yang, F.; Wang, S.-W.; Leng, Y.-T.; Wu, Y.-J. *Tetrahedron* **2015**, *71*, 9258.

(23) (a) Hartmann, C. E.; Nolan, S. P.; Cazin, C. S. *Organometallics* **2009**, *28*, 2915. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (c) Julliard, M.; Siv, C.; Vernin, G.; Jacques, M. *Helv. Chim. Acta* **1978**, *61*, 2941. (d) Tani, S.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123.