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Mechanistic Exploration of the Palladium-catalyzed Process for the Synthesis of Benzoxazoles and Benzothiazoles

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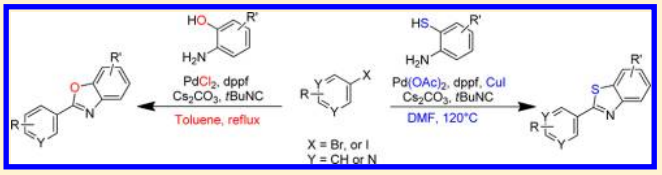
Supporting Information

ABSTRACT: A convenient one-pot palladium-catalyzed cascade process for the preparation of both benzoxazoles and benzothiazoles has been developed. While these reactions proceed to give similar compounds the mechanisms governing the processes are different as are the experimental conditions employed.



INTRODUCTION

Development of new and improved methods, with increasing chemical efficiency, is of great importance in modern synthetic chemistry. The constant evolution of molecular targets[1] means that the reactions required to prepare these compounds of interest have to be constantly evolving.[2] Furthermore, the processes that involve the construction of multiple chemical bonds as part of a single operation[3] offer significant advantages over their multistep equivalents, such as through savings in costs associated with solvents for both reaction and purification. Another advantage is that designing reaction sequences that involve the incorporation of fragments from different starting components allows a high level of complexity and diversity to be built into a molecule as part of a single synthetic operation.

Over the past decades the interest in using transition metal catalysts, particularly palladium, in order to facilitate these complex transformations has greatly increased and has become an increasingly powerful tool in synthetic chemistry and through the development of additional reactions has increased the range of compounds that can be easily prepared.[4,5] Although palladium-catalyzed carbonylation processes[6] have been extensively studied and there have been a number of useful processes reported the use of isocyanides, which are isoelectronic to carbon monoxide and therefore should react in a similar manner, have been substantially less well explored and offer a great deal of opportunity for synthetic chemists to develop new and exciting reactions.

The use of isocyanides offers a number of advantages over carbon monoxide not least because they are nongaseous reagents, making them easier to handle and eliminating the need to use for specialist equipment to carry out the reactions. This is particularly important for the generation of compound screening libraries requires for hit identification purposes in the drug discovery process. Isocyanides have been shown to be efficient in palladium-catalyzed reactions used for the construction of a wide variety of functional groups such as amidines,[7] amides,[8] nitriles[9] and a range of nitrogen-containing heterocycles.[10]

RESULTS AND DISCUSSION

As part of our ongoing efforts to incorporate isocyanides in the palladium catalyzed synthesis of heterocycles we were pleased to find that use of aryl halides **1**−**3** and aminophenols **5**−**7** led to the efficient formation of a range of benzoxazoles (Table 1). This reaction is believed to proceed *via* oxidative addition of the aryl halide to the palladium catalyst followed by insertion of *tert*-butyl isocyanide **4** to give the palladium(II) species **16**. The addition of aminophenol **5** gave **17**, which after cyclization allowed the formation of desired benzoxazole **9** (Scheme 1).

While these conditions worked well for the formation of benzoxazoles, we were disappointed that changing the aminophenol used to aminothiophenol resulted in none of substituted benzothiazole **14** being formed and the only product that could be isolated from the reaction being benzothiazole **20** in a yield of 62%. This result was particularly unexpected, especially when compared to the 95% yield observed for the formation of compound **9** as the only difference between the two molecules is the replacement of oxygen with sulfur.

This raised a fundamental question relating to the respective mechanisms governing these, apparently similar, reactions, that is, is the mechanism different when changing to aminothiophenol **8** from aminophenol **5**? We speculated that the mechanism for the formation of benzothiazole **20** did not require the presence of a palladium catalyst, which was confirmed when aminothiophenol **8** was exposed to *tert*-butyl isocyanide resulting in the formation of the desired product.

Optimization of the reaction conditions, by changing the solvent, raised the yield from 54% (toluene, reflux, 24 h) to 76% (DMF, 120 °C, 24 h). This method has also been applied for the synthesis of alternative benzothiazoles (Table 2), with no additional base being required in cases where the amine used is in the form of a salt (Table 2, entries 2 and 3). However, these conditions cannot be used for the preparation of benzoxazole **23**, further highlighting the difference in the

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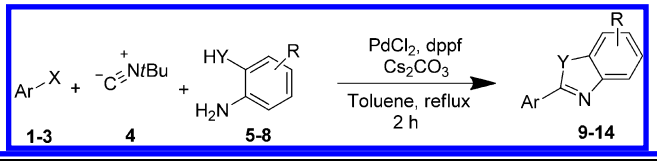
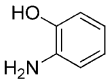
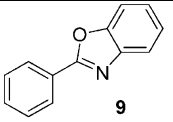
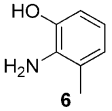
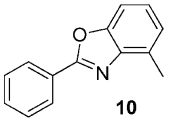
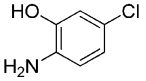
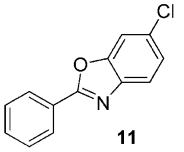
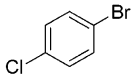
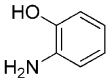
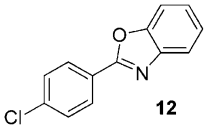
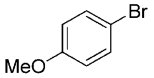
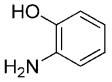
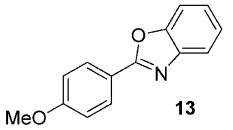
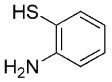
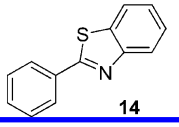
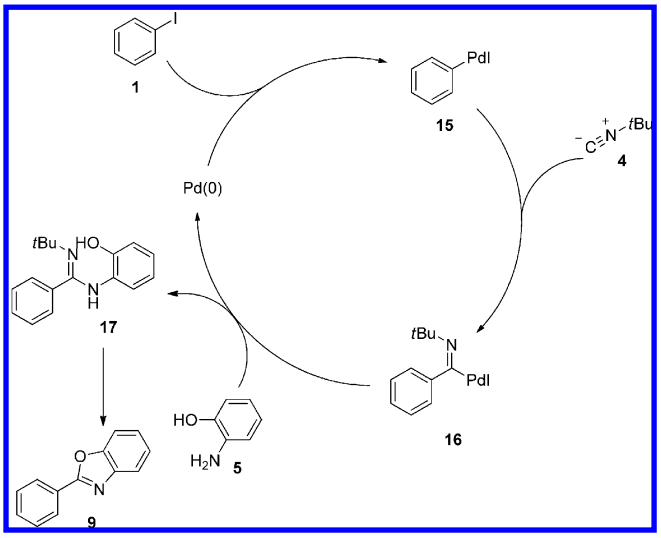
Table 1. Palladium Catalyzed Formation of Benzoxazoles and Attempted Formation of Benzothiazole[a]



Entry	Aryl Halide	Amine	Desired Product	Yield
1	 1	 5	 9	95%
2	 1	 6	 10	96%
3	 1	 7	 11	98%
4	 2	 5	 12	92%
5	 3	 5	 13	99%
6	 1	 8	 14	0%

[a]Conditions: Aryl Halide (1 equiv), tert-Butyl isocyanide (**4**) (1.5 equiv), Amine (5 equiv), Cs_2CO_3 (1.3 equiv), $PdCl_2$ (5 mol %), dppf (5 mol %), Toluene, reflux.

Scheme 1. Proposed Mechanism for the Formation of Benzoxazole 1



reactivity of *tert*-butyl isocyanide with aminophenols when compared to aminothiophenols.

With the current interest in C−H activation processes[11] and studies showing that copper can be added to the carbon at the 2-position of benzothiazole **20** we envisaged that the development of a one-pot procedure that would allow formation of a 2-aryl substituted benzothiazole directly from an aryl halide, *tert*-butyl isocyanide **4** and an aminothiophenol would be particularly useful in synthesis. To this end, a study to ascertain the various parameters required for this transformation was carried out. This study involved the palladium- and copper-catalyzed reaction of iodobenzene **1**, *tert*-butyl isocyanide **4** and aminothiophenol **8** in order to form 2-phenylbenzothiazole **14** varying parameters such as stoichiometry, ligand and base (Table 3).

Pleasingly the addition of copper to the reaction mixture resulted in the formation of desired compound **14**, however an Ullmann-type product **24** was also formed under these conditions. Care had to be taken in selecting the optimum conditions (Table 3, entry 5), so as to suppress the formation of this undesired product. Experimental observations suggest that the desired process proceeds by an initial formation of benzothiazole **20**, which when followed by copper catalyzed C−H activation gives rise to intermediate **26**. Oxidative addition of the iodobenzene to the palladium catalyst facilitated formation of palladium(II) species **15**, which can undergo a transmetalation process to give compound **27** and regenerate the copper cocatalyst. Subsequent reductive elimination allows for formation of 2-phenyl benzothiazole **14** (Scheme 2). The presence of the palladium catalyst is necessary in order to

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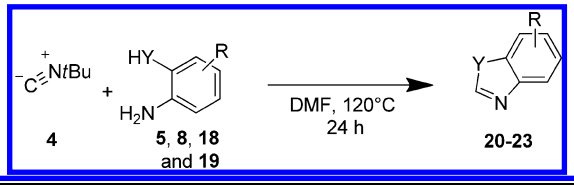
Table 2. Formation of 2-Unsubstituted Compounds[a]

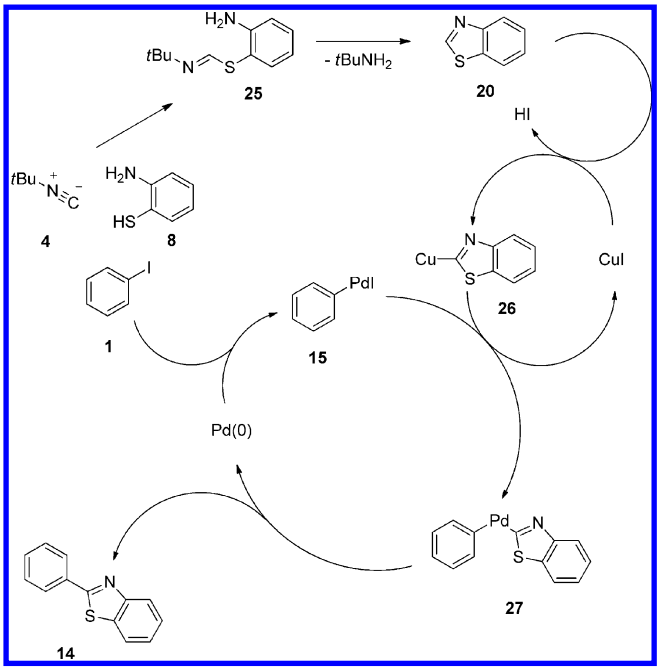


Entry	Amine	Desired Product	Yield
1	8	20	76%
2	18	21	(76%)[b]
3	19	22	(86%)[b]
4	5	23	0%

[a]Conditions: Amine (1 equiv) tert-Butyl isocyanide (**4**) (1.25 equiv), DMF, 120 °C, 24 h. [b]HCl salt of Amine used.

achieve formation of compound **14**. When a control experiment is carried out, where no palladium catalyst is present [Iodobenzene **1** (1 equiv), *tert*-Butyl isocyanide (**4**) (2.5 equiv), Aminothiophenol **8** (2.5 equiv), Cs_2CO_3 (1.3 equiv) and CuI (5 mol %) in DMF at 120 °C], none of compound **14** could be detected with Ullmann-type product **24** being isolated in quantitative yield.

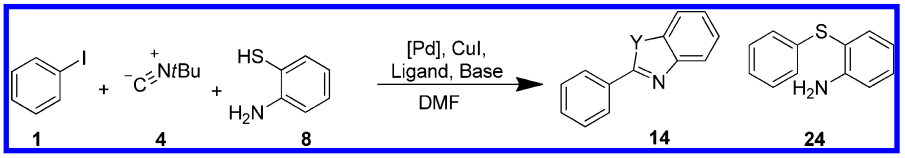
Scheme 2. Proposed Mechanism for the Formation of Benzothiazole 14



This proposed mechanism shows that this desired pathway, leading to the formation of **14**, is a highly atom-economical process with the only byproducts generated as part of the process being *tert*-butylamine and hydrogen iodide. Through careful selection of reaction conditions it is also possible to suppress the undesired process, which leads to formation of Ullmann-type product **24**.

With this in mind, we turned our attention to applying this methodology to the synthesis of a range of 2- substituted arylbenzothiazoles from various aryl halides and amino-

Table 3. Study of Reaction Parameters for One-pot Synthesis of 2-Phenyl Benzothiazole 8[a]



entry	mol % Cu cat.	temp.	base	ligand	Pd cat.	yield of **14**	yield of **24**
1	20%	150 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	19%	35%
2	10%	150 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	22%	64%
3	5%	150 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	42%	9%
4	2%	150 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	41%	23%
5	5%	120 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	61%	10%
6	5%	100 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	37%	31%
7	5%	80 °C	Cs_2CO_3	dppf	$Pd(OAc)_2$	16%	21%
8	5%	120 °C	K_3PO_4	dppf	$Pd(OAc)_2$	40%	12%
9	5%	120 °C	Et_3N	dppf	$Pd(OAc)_2$	43%	33%
10	5%	120 °C	2,6-Lutidine	dppf	$Pd(OAc)_2$	51%	41%
11	5%	120 °C	No Base	dppf	$Pd(OAc)_2$	32%	38%
12	5%	120 °C	Cs_2CO_3	dppp	$Pd(OAc)_2$	27%	56%
13	5%	120 °C	Cs_2CO_3	Xphos[b]	$Pd(OAc)_2$	11%	31%
14	5%	120 °C	Cs_2CO_3	PPh_3[b]	$Pd(OAc)_2$	26%	76%
15	5%	120 °C	Cs_2CO_3	dppf	$PdCl_2$	43%	29%

[a]Conditions: Iodobenzene **1** (1 equiv), *tert*-Butyl isocyanide (**4**) (2.5 equiv), Aminothiophenol **8** (2.5 equiv), base (1.3 equiv), [Pd] (5 mol %), CuI (see table), ligand (6 mol %), DMF. [b]10 mol % of ligand used.

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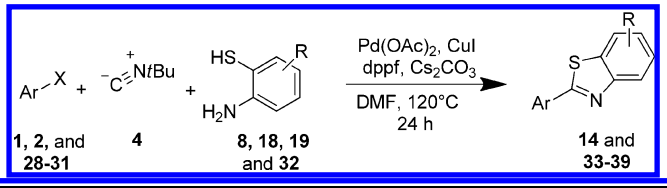
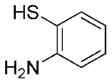
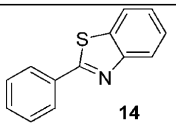
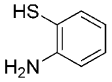
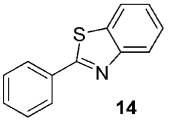
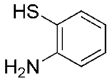
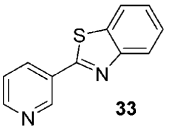
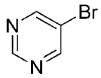
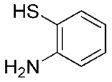
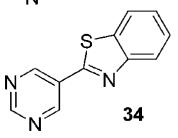
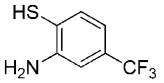
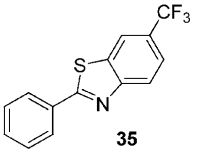
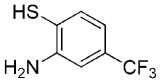
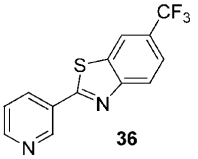
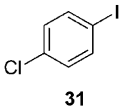
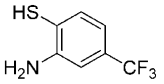
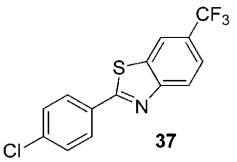
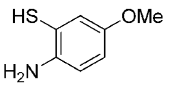
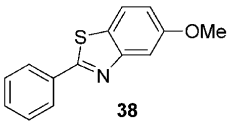
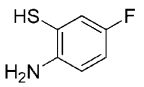
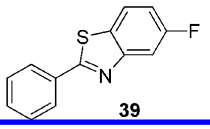
Table 4. Palladium and Copper Co-Catalyzed Formation of Benzothiazoles[a]



Entry	Aryl Halide	Aminothiophenol	Desired Product	Yield
1	 **1**	 **8**	 **14**	61% (99%)[b,c]
2	 **28**	 **8**	 **14**	40%
3	 **29**	 **8**	 **33**	64% (77%)[b,c]
4	 **30**	 **8**	 **34**	29% (61%)[b,c]
5	 **1**	 **18**	 **35**	(92%)[b,c,d]
6	 **29**	 **18**	 **36**	(98%)[b,c,d]
7	 **31**	 **18**	 **37**	(46%)[b,c,d]
8	 **1**	 **19**	 **38**	(77%)[b,c,d]
9	 **1**	 **32**	 **39**	(52%)[b,c,d]

[a]Conditions: Aryl Halide (1 equiv), *tert*-Butyl isocyanide (**4**) (2.5 equiv), Aminothiophenol (2.5 equiv), Cs_2CO_3 (1.3 equiv), $Pd(OAc)_2$ (5 mol %), dppf (6 mol %), DMF, 120 °C, 24 h. [b]Conditions: As before except *tert* -Butyl isocyanide (**4**) (1.8 equiv), Aminothiophenol (1.5 equiv). [c]*tert*-Butyl isocyanide (**4**) and Aminothiophenol heated at 120 °C for 24 h in DMF prior to addition of other reagents. [d]HCl salt of Amine used, Cs_2CO_3 (3 equiv).

thiophenol building blocks (Table 4). While these conditions allowed access to the desired benzothiazoles it was discovered that lowering the quantity of aminothiophenol and *tert*-butyl isocyanide in the reaction and preheating these reagents in DMF prior to the addition of the other the other reagents led to higher yields. The reason for this improvement in yield is that the undesired product **24** arises from direct coupling of the aminothiophenol with the aryl halide before the unsubstituted benzothiazole has been formed in significant quantities. Allowing the unsubstituted benzothiazole intermediate to form before the addition of the other reagents not only increases the quantity of this compound in solution, but also lowers the amount of aminothiophenol remaining and therefore allows more efficient formation of the desired compound.

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CONCLUSION

We have demonstrated the mechanistic differences that occur when changing from the use of an aminophenol to an aminothiophenol in the preparation of benzoxazoles and benzothiazoles. Through gaining a better understanding of the mechanism for the preparation of benzothiazoles it has been shown that the addition of a copper cocatalyst allows efficient preparation of these compounds via an *in situ* formation of the unsubstituted benzothiazole followed by copper-catalyzed C−H activation before this fragment joins the regular palladium catalytic cycle. This procedure has subsequently been applied in order to prepare a range of substituted 2-aryl benzothiazoles.

EXPERIMENTAL SECTION

General Procedure 1. 1,1′-Bis(diphenylphosphino)ferrocene (27.8 mg, 0,05 mmol, 0.05 equiv) and cesium carbonate (423 mg, 1.3 mmol, 1.3 equiv) were suspended in 5 mL of dry and degassed toluene in an oven-dried flask. Aryl halide (1.0 mmol, 1 equiv), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv) and aminophenol (5 mmol, 5 equiv.) were added to the stirring mixture. Palladium chloride (8.9 mg, 0.05 mmol, 0.05 equiv) was added to the mixture, which was heated at reflux for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, eluting with 0−10% ethyl acetate in petroleum ether, to give desired product.

*2-Phenylbenzo[d]oxazole (**9**).*[12] White solid formed using **general procedure 1** (185 mg, 95% yield); mp = 101−102 °C (lit[12] 101−102 °C); υ_{max}(KBr)/cm^{-1} 3060, 1613, 1547, 1445, 1240, 1050, 921, 743, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.29 (2H, d, J = 3.2 Hz), 7.82−7.80 (1H, m), 7.61−7.55 (4H, m), 7.39 (2H, dd, J = 6.2 and 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.6, 150.2, 141.7, 131.0, 128.4, 127.1, 126.7, 124.6, 124.1, 119.5, 110.1; m/z (ESI) 196 (M + H$^+$, 100%), 197 (16%).

*4-Methyl-2-phenylbenzo[d]oxazole (**10**).*[13] Pink/white solid formed using **general procedure 1** (201 mg, 96% yield); mp = 90−92 °C (lit[13] 92−93 °C); υ_{max}(KBr)/cm^{-1} 3049, 1621, 1550, 1484, 1445, 1059, 776, 757, 699, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.31−8.29 (2H, m), 7.56−7.54 (3H, m), 7.43 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 8.0 and 8.0 Hz), 7.17 (1H, d, J = 8.0 Hz), 2.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.8, 150.1, 141.0, 130.8 130.1, 128.3, 127.1, 127.0, 124.6, 124.3, 107.4, 16.1; m/z (ESI) 210 (M + H$^+$, 100%).

*5-Chloro-2-phenylbenzo[d]oxazole (**11**).*[12] White solid formed using **general procedure 1** (224 mg, 98% yield); mp =104−106 °C (lit[12] 107−108 °C); υ_{max} (KBr)/cm^{-1} 3054, 1610, 1552, 1445, 1050, 809, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.26 (2H, dd, J = 7.8 and 1.4 Hz) 7.77 (1H, d, J = 2 Hz), 7.57−7.51 (4H, m), 7.34 (1H, dd, J = 8.8 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.9, 148.9, 142.8, 131.4, 129.5, 128.5, 127.3, 126.2, 124.9, 119.5, 110.8; m/z (ESI) 230 (M + H$^+$, 100%), 232 (33%).

*2-(4-Chlorophenyl)benzo[d]oxazole (**12**).*[12] White solid formed using **general procedure 1** (211 mg, 92% yield); mp =148−150 °C (lit[12] 148−150 °C); υ_{max} 3054 (KBr)/cm^{-1} 1613, 1596, 1481, 1451, 1089, 1056, 381, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (2H, d, J = 8.6 Hz), 7.81−7.77 (1H, m), 7.62−7.60 (1H, m), 7.53 (2H, d, J = 8.6 Hz), 7.40−7.38 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.6, 150.3, 141.6, 137.3, 128.8, 128.4, 125.2, 124.9, 124.3, 119.6, 110.1; m/z (ESI) 230 (M + H$^+$, 100%), 232 (33%).

*2-(4-Methoxyphenyl)benzo[d]oxazole (**13**).*[12] White solid formed using **general procedure 1** (223 mg, 99% yield); mp = 96−98 °C (lit[12] 98 °C); υ_{max} (KBr)/cm^{-1} 1615, 1602, 1503, 1454, 1256, 1242, 1168, 1017, 831, 740, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.23 (2H, d, J = 9.0 Hz), 7.77−7.75 (1H, m), 7.59−7.57 (1H, m), 7.38−7.28 (2H, m), 7.06 (2H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.9, 150.2, 141.8, 128.9, 128.9, 124.1, 123.9, 119.3, 119.1, 113.9, 109.9, 55.0; m/z (ESI) 226 (M + H$^+$, 100%).

General Procedure 2. *tert*-Butylisocyanide (0.28 mL, 2.5 mmol, 1.25 equiv.) and aminothiophenol (2 mmol, 2 equiv) were added in dry and degassed DMF (5 mL) in a flame-dried flask and the reaction mixture was stirred under nitrogen at 120 °C. After 24h, the reaction mixture was left to cool to room temperature. The mixture was then diluted with ethyl acetate (20 mL), washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo* and the residue was purified by column chromatography on silica, eluting with 2−20% ethyl acetate in *n*-hexane, to give desired compound.

*Benzothiazole (**20**).*[14] Pale pink oil formed using **general procedure 2** (204 mg, 76% yield); υ_{max} (ATR)/cm^{-1} 3059, 2924, 1454, 1423, 1315, 1290, 872, 754, 727; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.00 (1H, s), 8.15 (1H, d, J = 7.9 Hz), 7.97 (1H, d, J = 7.9 Hz), 7.53 (1H, ddd, J = 7.9, 7.9, and 1.1 Hz) 7.45 (1H, ddd, J = 7.9, 7.9, and 1.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 153.8, 153.1, 133.6, 126.0, 125.4, 123.5, 121.8; m/z (ESI) 136.1 (M + H$^+$, 100%).

*5-(Trifluoromethyl)benzothiazole (**21**).* Orange solid formed using **general procedure 2** (363 mg, 76% yield); mp =65−66 °C; HRMS (ESI) calcd for $C_8H_5F_3NS$ [M + H]$^+$: 204.0095, found: 204.0089; υ_{max} (ATR)/cm^{-1} 3003, 2970, 1670, 1545, 1331, 1315, 1148, 1119, 1070; ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 9.13 (1H, s), 8.44 (1H, s), 8.10 (1H, d, J = 6.8 Hz), 7.71 (1H, dd, J = 6.8 and 1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz); δ_C 155.8, 152.9, 137.2, 129.0 (q, J = 32.8 Hz), 124.1 (q, J = 272.1 Hz), 122.6, 122.0 (q, J = 3.4 Hz), 120.9 (q, J = 4.1); m/z (ESI) 204.0 (M + H$^+$, 100%).

*6-Methoxybenzothiazole (**22**).*[15] White solid formed using **general procedure 2** (213 mg, 86% yield); mp = 70−71 °C (lit[15] 70−72 °C); υ_{max} (ATR)/cm^{-1} 3061, 2965, 2934, 2833, 1593, 1552, 1474, 1427, 1242; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.82 (1H, s), 8.01 (1H, d, J = 9.2 Hz), 7.39 (1H, d, J = 2.4 Hz), 7.12 (1H, dd, J = 9.2 and 2.4 Hz), 3.88 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 158.0, 151.3, 147.8, 135.1, 123.9, 115.8, 104.0, 55.7; m/z (ESI) 116.1 (M + H$^+$, 100%).

General Procedure 3. 1,1′-Bis(diphenylphosphino)ferrocene (33.4 mg, 0.06 mmol, 0.06 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv) were suspended in dry and degassed DMF (5 mL) in a flame-dried flask. Aryl halide (1 mmol, 1 equiv), *tert*-butylisocyanide (0.28 mL, 2.5 mmol, 2.5 equiv) and 2-aminothiophenol (0.27 mL, 2.5 mmol, 2.5 equiv.) were added in the flask. Palladium acetate (11.2 mg, 0.05 mmol, 0.05 equiv), and copper iodide (9.5 mg, 0.05 mmol, 0.05 equiv) were added and the reaction mixture was stirred under nitrogen at 120 °C. After 24 h, the reaction mixture was left to cool to room temperature then diluted with ethyl acetate (20 mL), washed with a NaOH aqueous solution (2 × 25 mL, 1M), water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica, eluting with 0−40% ethyl acetate in *n*-hexane, to give desired compound.

General Procedure 4. *tert*-Butylisocyanide (0.20 mL, 1.8 mmol, 1.8 equiv) and 2-aminothiophenol (0.16 mL, 1.5 mmol, 1.5 equiv) were suspended in dry and degassed DMF (5 mL) in a flame-dried flask and the reaction mixture was stirred under nitrogen at 120 °C for 24 h. The reaction mixture was left to cool to room temperature. 1,1′-Bis(diphenylphosphino)ferrocene (33.4 mg, 0.06 mmol, 0.06 equiv), Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv), iodobenzene (0.1 mL, 1 mmol, 1 equiv), palladium acetate (11.2 mg, 0.05 mmol, 0.05 equiv), and copper iodide (9.5 mg, 0.05 mmol, 0.05 equiv) were added and the reaction mixture was stirred under nitrogen at 120 °C for 24h. The reaction mixture was left to cool to room temperature then diluted with ethyl acetate (20 mL), washed with a NaOH aqueous solution (2 × 25 mL, 1 M), water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica, 0−50% ethyl acetate in hexane, to give desired compound.

*2-Phenylbenzothiazole (**14**).*[16] White solid formed using **general procedure 3** (128 mg, 61% yield) and using **general procedure 4** (208 mg, 99% yield); mp = 114−115 °C (lit[16] 115−116 °C); υ_{max} (ATR)/cm^{-1} 3065, 1634, 1477, 1433, 1070, 918, 891; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.12−8.08 (3H, m), 7.91 (1H, d, J = 8.4 Hz), 7.51−7.49 (4H, m), 7.39 (1H, ddd J 7.6, 7.6, and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 168.1, 154.0, 135.0, 133.5, 131.0, 129.0, 127.6, 126.4, 125.2, 123.2, 121.6. m/z (ESI) 212.1 (M + H$^+$, 100%).

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*2-(Phenylthio)aniline (**24**).*[17] Yellow oil formed using **general procedure 3** (20 mg, 10% yield); υ_{max} (ATR)/cm^{-1} 3464, 3364, 3059, 3015, 1605, 1580, 1476, 851, 739; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.46 (1H, dd, J = 7.6 and 1.6 Hz), 7.26−7.21 (3H, m), 7.14−7.09 (3H, m), 6.81−6.74 (2H, m), 4.25 (2H, br s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 148.8, 137.4, 136.8, 131.1, 129.0, 126.5, 125.4, 118.7, 115.3, 114.4; m/z (ESI) 202.1 (M + H$^+$, 100%).

*2-(3-Pyridinyl)benzothiazole (**33**).*[11e] Orange solid formed using **general procedure 3** (134 mg, 64% yield) and using **general procedure 4** (163 mg, 77% yield); mp = 127−128 °C (lit[11e] 127 °C); υ_{max} (ATR)/cm^{-1} 3049, 2965, 2926, 2853, 2334, 1584, 1425; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.31 (br., s, 1H), 8.72 (br., s, 1H), 8.35 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.4 Hz), 7.90 (d, 1H, J = 7.6 Hz), 7.50 (t, 1H, J = 8.4 Hz) 7.43−7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 164.5, 153.9, 151.4, 148.4, 134.9, 134.4, 129.7, 126.5, 125.6, 123.8, 123.4, 121.6; m/z (ESI) 213.1 (M + H$^+$, 100%).

*2-(5-Pyrimidinyl)benzothiazole (**34**).*[18] Orange solid formed using **general procedure 3** (62 mg, 29% yield) and using **general procedure 4** (130 mg, 61% yield); mp = 133−134 °C (lit[18] 121−122 °C); HRMS (ESI) calcd for $C_{11}H_8N_3S$ [M + H]$^+$: 214.0439, found: 214.0433; υ_{max} (ATR)/cm^{-1} 3051, 2955, 2920, 2849, 1647, 1593, 1553, 1402; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.40 (2H, br s), 9.33 (1H br s), 8.15 (1H, d, J = 7.8 Hz), 7.98 (1H, d, J = 7.8 Hz), 7.57 (1H, ddd, J = 7.8, 7.8, and 0.8 Hz), 7.48 (1H ddd, J = 7.8, 7.8, and 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 161.0, 159.8, 155.2, 153.9, 134.9, 128.0, 127.0, 126.2, 123.8, 121.9; m/z (ESI) 214.1 (M + H$^+$, 100%).

*2-Phenyl-5-(trifluoromethyl)benzo[d]thiazole (**35**).*[11e] White solid formed using **general procedure 4** (256 mg, 92% yield); mp = 133−134 °C (lit[11e] 132 °C); υ_{max} (ATR)/cm^{-1} 2943, 1510, 1479, 1446, 1330, 1319, 1143; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.35 (1H, s), 8.13−8.10 (2H, m), 8.02 (1H, d, J = 8.4 Hz), 7.63 (1H, dd, J = 8.4 and 1.2 Hz), 7.55−7.53 (3H, m); δ_C 170.1, 143.8, 138.5, 133.1, 131.6, 129.2, 129.0 (q, J = 29.8 Hz), 127.7, 124.2 (q, J = 286.9 Hz), 122.2, 121.5 (q, J = 3.4 Hz), 120.4 (q, J = 4.1 Hz); m/z (ESI) 280.6 (M + H$^+$, 100%).

*2-(3-Pyridinyl)-5-(trifluoromethyl)benzothiazole (**36**).* Light yellow solid formed using **general procedure 4** (275 mg, 92% yield); mp =157−158 °C; HRMS (ESI) calcd for $C_{13}H_8F_3N_2S$ [M + H]$^+$: 281.0360, found: 281.0355; υ_{max} (ATR)/cm^{-1} 3021, 3011, 1572, 1420, 1325, 1317, 1128; ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 9.31 (1H, s), 8.76 (1H, d, J = 4.8 Hz), 8.40 (1H, d, J = 8.0 Hz), 8.38 (1H, s), 8.05 (1H, d, J = 8.5 Hz), 7.67 (1H, d, J = 8.5 Hz), 7.48 (1H, dd, J = 8.0 and 4.8 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C 166.6, 153.5, 152.1, 148.6, 138.3, 134.6, 129.3 (q, J = 32.5 Hz), 125.1, 124.5 (q, J = 172.4 Hz), 123.9, 122.4, 122 (d, J = 3.3 Hz), 120.7 (d, J = 4.2 Hz); m/z (ESI) 281.6 (M + H$^+$, 100%).

*2-(4-Chlorophenyl)-5-(trifluoromethyl)benzothiazole (**37**).* Light yellow solid formed using **general procedure 4** (143 mg, 46% yield); mp =124−125 °C; HRMS (ESI) calcd for $C_{14}H_8ClF_3NS$ [M + H]$^+$: 314.0018, found: 314.0013; υ_{max} (ATR)/cm^{-1} 3049, 2938, 1593, 1477, 1331, 1092; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.34 (1H, s), 8.06−8.02 (3H, m), 7.65 (1H, d, J = 8.4 Hz), 7.52−7.50 (2H, m); ^{13}C NMR ($CDCl_3$, 500 MHz) δ_C 168.7, 153.6, 138.4, 137.8, 131.5, 129.5, 129.3 (q, J = 21.8 Hz), 128.9, 126.5 (q, J = 316.9 Hz) 122.3, 121.7, 120.5 (d, J = 4.3 Hz); m/z (ESI) 314.9 (35) 313.5 (M + H$^+$, 100%).

*6-Methoxy-2-phenylbenzothiazole (**38**).*[19] Light yellow solid formed using **general procedure 4** (186 mg, 77% yield); mp =112−113 °C (lit[19] 112−113 °C); υ_{max} (ATR)/cm^{-1} 3069, 3007, 2965, 2918, 2835, 1601, 1510, 1462, 1435, 1263, 1225; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.07−8.04 (2H m,), 7.97 (1H, d, J = 9.2 Hz), 7.49−7.47 (3H, m), 7.36 (1H, d, J = 2.4 Hz), 7.10 (1H, dd, J = 9.2 and 2.4 Hz), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C 165.5, 157.8, 148.7, 136.4, 133.8, 130.5, 128.9, 127.2, 123.7, 115.6, 104.2, 55.8; m/z (ESI) 242.1 (M + H$^+$, 100%).

*6-Fluoro-2-phenylbenzothiazole (**39**).*[14] Light yellow solid formed using **general procedure 4** (119 mg, 52% yield); mp =134−135 °C; υ_{max} (ATR)/cm^{-1} 3069, 3022, 1607, 1562, 1454, 1443; ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.08−8.06 (2H, m), 8.03 (1H, dd, J = 9.0 and 4.5 Hz), 7.60 (dd, 1H, J = 8.0 Hz, and 2.5 Hz), 7.52−7.51 (m, 3H), 7.24 (1H, ddd, J = 9.0, 9.0, and 2.5 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C 167.4 (d, J = 3.4 Hz), 160.5 (d, J = 245.8 Hz), 150.8, 136.0 (d, J = 11.3 Hz), 133.4, 131.0, 129.0, 127.4, 124.1 (d, J = 9.3 Hz), 114.9 (d, J = 24.7 Hz), 107.8 (d, J = 26.9 Hz); m/z (ESI) 230.1 (M + H$^+$, 100%).

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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