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The Rational Design and Synthesis of Water-Soluble Thiourea Ligands for Recoverable Pd-Catalyzed Aerobic Aqueous Suzuki–Miyaura Reactions at Room Temperature

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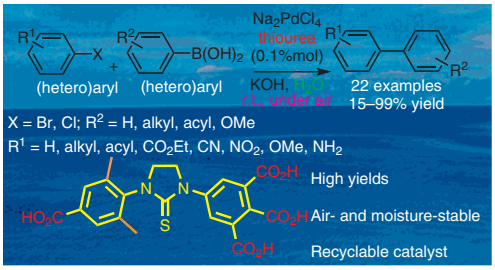

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Abstract Eight precatalysts containing carboxylic-functionalized thiourea ligands are prepared and their activities and recyclability are evaluated in aerobic aqueous Suzuki–Miyaura reactions. A bulky monothiourea–Pd complex, functionalized with four carboxylic groups, shows the best activity and recyclability in the coupling of aryl bromides with arylboronic acids. The catalyst can be reused at least five times without any significant reduction in its catalytic activity. TEM analysis and the confirmed catalytic activity of the observed black precipitate reveal that Pd nanoparticles are formed during the reactions and are stabilized by the carboxylic-functionalized thiourea ligands.

Key words water-soluble, thiourea, ligands, palladium-catalyzed, Suzuki–Miyaura reactions

The palladium-catalyzed cross-coupling reaction is one of the most powerful tools for forming carbon–carbon bonds.[1] A substantial challenge is the development of environmentally friendly, safe and energy/resources-saving protocols, which allow the cross-coupling reactions to be performed in aqueous solution.[2] With the increasing importance of green chemistry, the development of water-soluble Pd complexes as recyclable catalysts for cross-coupling reactions in aqueous solution has become a current focus.[3] Various water-soluble phosphine ligands have been applied in phosphine–palladium catalysts,[4] however, the air-sensitivity of phosphine ligands significantly limits the catalyst recycling and their synthetic applications.[5] Accordingly, current work is focused on the search for new catalytic systems overcoming the limitations of recyclability and stability. The Suzuki–Miyaura reaction is a widely used and versatile tool in organic synthesis.[1b,6] Although a variety of water-soluble palladium complexes of N-heterocyclic carbenes (NHCs) for Suzuki–Miyaura reactions in aqueous solution have been frequently studied,[4g,7] it is relatively difficult to conduct this reaction at room temperature.[8] Notably, toxicity examinations of NHC ligands are extremely rare.[7r] Therefore, the development of more stable, easy to recycle and less toxic ligands is desirable. In continuation of our studies on air- and moisture-stable cyclic bulky monothiourea and bis(thiourea) ligands,[9a–c] we were interested in the area of undeveloped water-soluble and reusable thiourea–palladium complexes. Inspired by the toxicity examinations of thioureas,[10] we envisaged that the preparation of water-soluble thiourea–palladium complexes as less toxic and recyclable catalysts would be possible. In this work, we report the rational design and synthesis of carboxylic-functionalized thiourea ligands, and evaluate their performance as precatalysts in Suzuki–Miyaura reactions in water. Furthermore, transmission electron microscopy (TEM) analysis revealed that Pd nanoparticles (PdNPs) were formed during the reactions. The water-soluble thiourea ligands serve as stabilizers of these nanoparticles.

It is a common strategy to make hydrophobic ligands water-soluble by introduction of a carboxylate moiety.[7l,11] Yang et al.[12] and our group[9] have also demonstrated that cyclic bulky monothiourea, N,N-disubstituted acyclic and cyclic bis(thiourea) ligands are active catalysts for Heck and Suzuki reactions. Thus, the water-soluble and recyclable carboxylic-functionalized thiourea ligand is designed to meet the needs of activity and recyclability by introducing two methyls and four carboxylates into the thiourea skeleton (Figure 1).

Since the structure of each thiourea ligand has a significant influence on the catalytic efficacy of its palladium complex,[9,12] eight carboxylic-functionalized thiourea ligands (**1a–c** and **1e–i**) with different thiourea skeletons

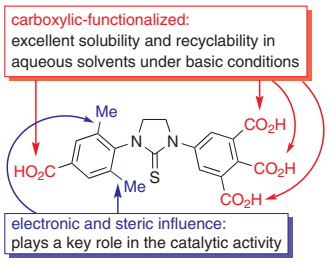
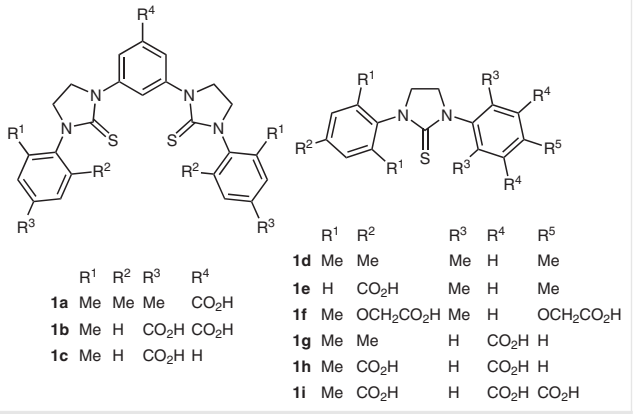


Figure 1 Rational design of a water-soluble thiourea ligand

were prepared (Figure 2). The synthetic pathways toward the carboxylic-functionalized thiourea ligands **1a–c**, **1e** and **1g–i** are summarized in Scheme 1 and Scheme 2. Amides **3** were easily prepared in yields of 57–88% via nucleophilic substitution of 2-bromo-*N*-arylacetamides[13] with the corresponding arylamine. The resulting amides **3** were smoothly converted into the corresponding amines by borane reduction, and the crude products were subsequently treated with thiophosgene without purification to give the corresponding thioureas **2a–c**, **2e** and **2h–i** in 31–69% yield (two steps). Subsequent basic hydrolysis of thioureas **2** with NaOH in THF and H_2O, followed by acidification to pH 1 with concentrated HCl solution gave rise to thiourea ligands **1a–c**, **1e** and **1h–i** in good yields ranging from 65–92%.



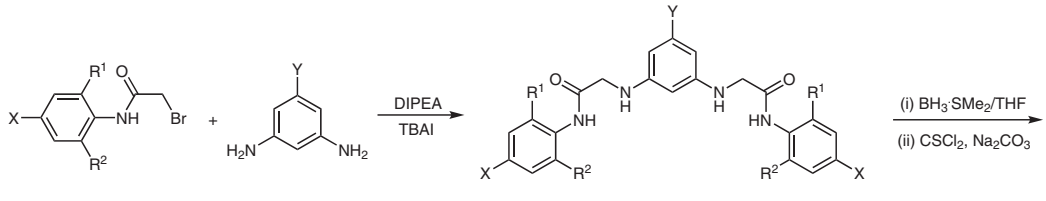
	R^1	R^2	R^3	R^4
1a	Me	Me	Me	CO_2H
1b	Me	H	CO_2H	CO_2H
1c	Me	H	CO_2H	H

	R^1	R^2	R^3	R^4	R^5
1d	Me	Me	Me	H	Me
1e	H	CO_2H	Me	H	Me
1f	Me	OCH_2CO_2H	Me	H	OCH_2CO_2H
1g	Me	Me	H	CO_2H	H
1h	Me	CO_2H	H	CO_2H	H
1i	Me	CO_2H	H	CO_2H	CO_2H

Figure 2 Structures of the thiourea ligands

The carboxylic-functionalized thiourea ligand **1f** was prepared in a facile three-step synthesis (Scheme 3). Compound **4f** was easily prepared in 77% yield via nucleophilic substitution of ethyl 2-bromoacetate with 4-[2-(4-hydroxy-2,6-dimethylphenylamino)ethylamino]-3,5-dimethylphenol.[14] The diester **4f** was subsequently treated with thiophosgene to give the thiourea **2f** in 57% yield. Subsequent basic hydrolysis of thiourea **2f** with NaOH in THF and H_2O, followed by acidification to pH 1 with concentrated HCl solution gave rise to thiourea ligand **1f** in 96% yield. Carboxylic-functionalized thiourea ligands **1a–c** and **1e–i** were characterized by IR and NMR spectroscopy and mass spectrometry, and demonstrated good solubility in water under basic conditions.

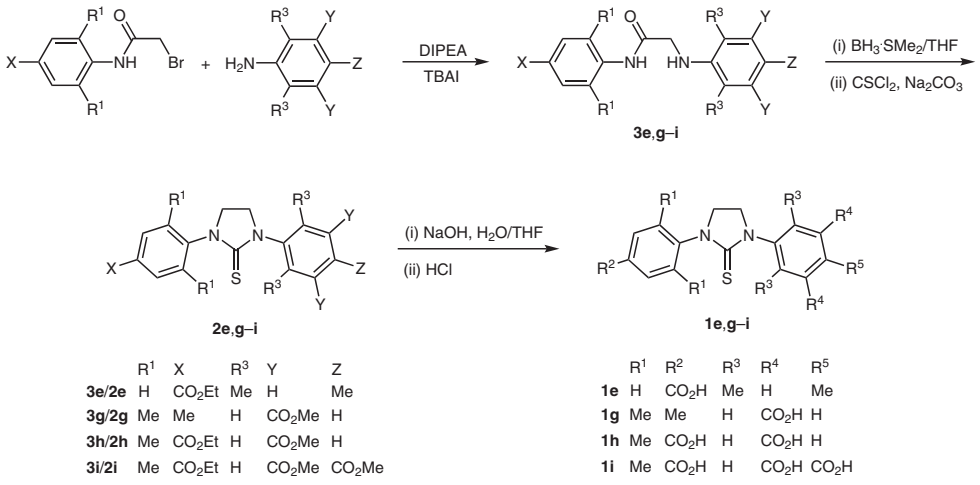
With the different thiourea ligands **1a–i** in hand, the catalytic activity of the thiourea–Pd complexes was screened in aqueous Suzuki–Miyaura reactions between 4-bromoanisole and phenylboronic acid in pure water at 100 °C, employing NaOH as the base (Table 1). The reactions were conducted in air and all the reagents were used directly as received. Initial studies[9] showed that a 1:1 ratio of bis(thiourea) or a 2:1 ratio of monothiourea to Pd was cru-



	R^1	R^2	X	Y
3a/2a	Me	Me	Me	CO_2Et
3b/2b	Me	H	CO_2Me	CO_2Et
3c/2c	Me	H	CO_2Me	H

	R^1	R^2	R^3	R^4
1a	Me	Me	Me	CO_2H
1b	Me	H	CO_2H	CO_2H
1c	Me	H	CO_2H	H

Scheme 1 Synthesis of carboxylic-functionalized thiourea ligands **1a–c**



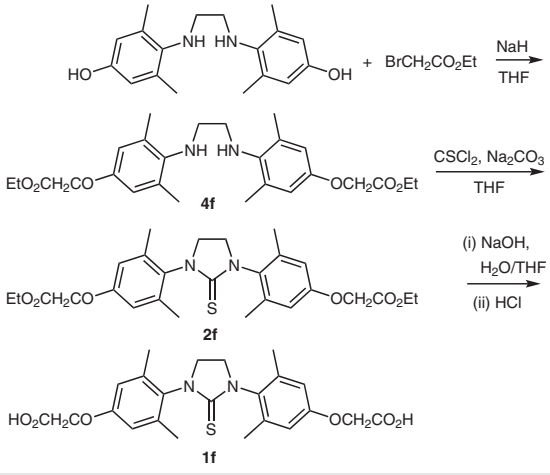
	R1	X	R3	Y	Z
3e/2e	H	CO_2Et	Me	H	Me
3g/2g	Me	Me	H	CO_2Me	H
3h/2h	Me	CO_2Et	H	CO_2Me	H
3i/2i	Me	CO_2Et	H	CO_2Me	CO_2Me

	R1	R2	R3	R4	R5
1e	H	CO_2H	Me	H	Me
1g	Me	Me	H	CO_2H	H
1h	Me	CO_2H	H	CO_2H	H
1i	Me	CO_2H	H	CO_2H	CO_2H

Scheme 2 Synthesis of carboxylic-functionalized thiourea ligands **1e** and **1g–1i**

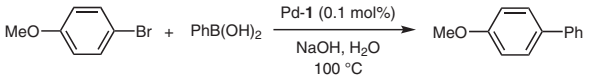
cial to achieve high catalytic activity; an excess of thiourea ligand tended to dramatically decrease the conversion rate. As shown in Table 1, thiourea ligands **1a**, **1d**,[9d] and **1e–i** displayed high catalytic activity, giving good to excellent yields of coupled products within 20 hours in the first run (entries 2, 3 and 8–19). The other two thiourea ligands (**1b** and **1c**) gave only traces to low yields within 24 hours in the first runs (entries 4–7). Moreover, $Pd(dba)_2$, $PdCl_2(MeCN)_2$ and Na_2PdCl_4 were screened with thiourea ligands **1a–1i**. $PdCl_2(MeCN)_2$ and Na_2PdCl_4 exhibited better reactivity and recyclability than $Pd(dba)_2$ in the thiourea-ligand-assisted aqueous Suzuki–Miyaura reaction (cf. entries 2, 3, 10, 11, 18 and 19 vs entries 1 and 9).

According to our previous studies,[9a–c] it is further enforced that the different catalytic activities of thiourea ligands **1a–i** are attributed to the electronic and steric effects of the thiourea moieties of the Pd complexes. In general, the



Scheme 3 Synthesis of carboxylic-functionalized thiourea ligand **1f**

Table 1 Comparison of Thiourea Ligands **1a–i** in Aqueous Suzuki–Miyaura Reactions[a]



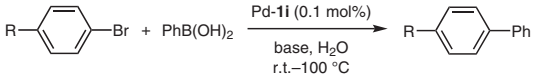
Entry	Ligand	Pd	Time (h)	Yield (%)[b]
1	**1a**	$Pd(dba)_2$	8	trace
2	**1a**	$PdCl_2(MeCN)_2$	20 (20[c])	84 (trace[c])
3	**1a**	Na_2PdCl_4	20 (20[c])	90 (trace[c])
4	**1b**	$Pd(dba)_2$	8	trace
5	**1b**	$PdCl_2(MeCN)_2$	24	trace
6	**1b**	Na_2PdCl_4	24	40
7	**1c**	$Pd(dba)_2$	8	trace
8	**1d**	$Pd(dba)_2$	8 (12[c])	95 (trace[c])
9	**1e**	$Pd(dba)_2$	8 (12[c])	92 (trace[c])
10	**1e**	$PdCl_2(MeCN)_2$	8 (12[c])	99 (trace[c])
11	**1e**	Na_2PdCl_4	8 (12[c])	99 (trace[c])
12	**1f**	$PdCl_2(MeCN)_2$	8 (24[c])	79 (trace[c])
13	**1f**	Na_2PdCl_4	8 (24[c])	90 (trace[c])
14	**1g**	$PdCl_2(MeCN)_2$	8 (12[c])	97 (31[c])
15	**1g**	Na_2PdCl_4	8 (12[c])	94 (trace[c])
16	**1h**	$PdCl_2(MeCN)_2$	8 (12[c])	95 (46[c])
17	**1h**	Na_2PdCl_4	8 (12[c])	90 (41[c])
18	**1i**	$PdCl_2(MeCN)_2$	8 (12[c])	90 (67[c])
19	**1i**	Na_2PdCl_4	8 (12[c])	91 (74[c])

[a] Reactions were conducted under aerobic conditions. Unless indicated otherwise, the reactions were conducted with 5 mmol of aryl halide, 7.5 mmol of phenylboronic acid, 10 mmol of NaOH and 5 mL of H_2O, Pd/bis-thiourea = 1:1, Pd/monothiourea = 1:2.
[b] Yield of isolated product.
[c] Second run.

palladium complexes formed with relatively bulky thiourea ligands (**1a**, **1d–i**) exhibit higher catalytic activities. The relatively poor activities of **1b** and **1c** may be associated with the substituents of low steric hindrance (cf. entries 4–7 vs entries 2 and 3). Moreover, monothiourea ligands **1d–i** displayed higher catalytic activity than the bis(thiourea) ligand **1a** (cf. entries 8–19 vs entries 1–3). As shown in Table 1, monothiourea ligand **1i** displayed the best catalytic activity and recyclability, giving good yields even in the second run (entries 18 and 19). This result supports the hypothesis of the number of carboxylic groups having an important influence on the recyclability (cf. entries 18 and 19 vs entries 8–17). Since the electronic and steric properties of the ligands **1g**, **1h** and **1i** are quite similar, it is reasonable to deduce that the solubility influence introduced by the four carboxylic groups of ligand **1i** played a key role in its high recyclability (74% yield obtained in the second run) under basic conditions (cf. entry 19 vs entries 14–17).

With the superior ligand **1i** in hand, the aqueous Suzuki–Miyaura reaction conditions were further optimized (Table 2). Firstly, we screened the commonly used water-soluble base K_2CO_3 for the model reaction of 4-bromoanisole and phenylboronic acid with 0.1 mol% of Pd-**1i** at 100 °C (entries 1 and 2). A high yield (82%) was still observed within 12 hours in the fourth run using Na_2PdCl_4 as the Pd source (entry 2). These results were significantly better than the 74% yield obtained in the second run catalyzed by Na_2PdCl_4-**1i** in the presence of NaOH (see Table 1, entry 19). It is known that the addition of tetra-*n*-butylammonium bromide (TBAB) can accelerate the rate of aqueous Suzuki–Miyaura reactions due to the formation of $Bu_4NPhB(OH)_3$.[1e,7,15] The addition of TBAB (1 equiv) to the coupling of 4-bromoanisole with phenylboronic acid increased the conversion from 54% (0.4 equiv TBAB) to 90% within 24 hours at room temperature (entries 4 vs 6). To our surprise, excellent yields were also obtained even in the second run catalyzed by Na_2PdCl_4-**1i**, using KOH as the base and within 24 hours at room temperature when 1 equivalent of TBAB was used as the additive (entry 8). The recyclability of the Na_2PdCl_4-**1i** catalyst was further investigated using 4′-bromoacetophenone and 4-bromoanisole in aqueous Suzuki–Miyaura couplings with phenylboronic acid (entries 9–11). It is notable that the increment of temperature to 100 °C led

Table 2 Screening of Recoverable Reaction Conditions in Aqueous Suzuki–Miyaura Reactions Assisted by Ligand **1i**[a]



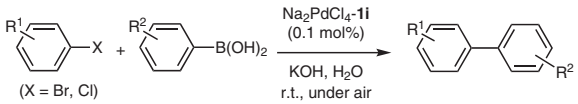
Entry	R	Base	Pd	Time (h)	Yield (%)[b]
1[c]	OMe	K_2CO_3	$PdCl_2(MeCN)_2$	8 (12[d]/12[e]/12[f])	99 (99[d]/99[e]/76[f])
2[c]	OMe	K_2CO_3	Na_2PdCl_4	8 (12[d]/12[e]/12[f])	99 (99[d]/99[e]/82[f])
3[g,h]	OMe	K_2CO_3	$PdCl_2(MeCN)_2$	24	64
4[g,h]	OMe	K_2CO_3	Na_2PdCl_4	24	54
5[g,i]	OMe	K_2CO_3	$PdCl_2(MeCN)_2$	24	92
6[g,i]	OMe	K_2CO_3	Na_2PdCl_4	24	90
7[g,i]	OMe	KOH	$PdCl_2(MeCN)_2$	24 (24[d])	97 (40[d])
8[g,i]	OMe	KOH	Na_2PdCl_4	24 (24[d])	99 (90[d])
9[c,i]	OMe	KOH	$PdCl_2(MeCN)_2$	1 (1[d]/1[e]/1[f])	99 (99[d]/99[e]/92[f])
10[c,i]	OMe	KOH	Na_2PdCl_4	1 (1[d]/1[e]/1[f])	99 (99[d]/99[e]/90[f])
11[c,i]	Ac	KOH	Na_2PdCl_4	0.5 (0.5[d]/1[e]/1.5[f])	99 (99[d]/99[e]/99[f])
12[g,i,j]	OMe	KOH	Na_2PdCl_4	24 (24[d])	95 (23[d])
13[g,i,j]	OMe	KOH	Na_2PdCl_4	1 (1[d]/1[e])	>99 (73[d]/32[e])

[a] Reactions were conducted under aerobic conditions. Unless indicated otherwise, the reactions were conducted with 5 mmol of aryl halide, 7.5 mmol of phenylboronic acid, 10 mmol of base and 5 mL of H_2O, Pd/**1i** = 1:2.
[b] Yield of isolated product.
[c] At 100 °C.
[d] Second run.
[e] Third run.
[f] Fourth run.
[g] At 25 °C.
[h] With the addition of TBAB (2 mmol).
[i] With the addition of TBAB (5 mmol).
[j] In the absence of thiourea ligand.

to excellent conversion into the desired products within 1.5 hours with 0.1 mol% of Na_2PdCl_4-**1i** loading, even in the fourth run (entries 10 and 11).

Having established the optimum conditions, the scope and limitations of the aqueous Suzuki–Miyaura reactions was explored with various aryl halides and arylboronic acids at room temperature. As revealed in Table 3, fifteen different (hetero)aryl bromides were used and treated with ten (hetero)arylboronic acids (entries 1–33). As a result, both electron-deficient and electron-rich arylboronic acids and aryl bromides gave the corresponding coupling products in excellent yields with 0.1 mol% of Na_2PdCl_4-**1i** loading at room temperature (entries 1–11). For deactivated bromides or hindered arylboronic acids, almost quantitative yields were achieved within 12 hours in the presence of 0.1 mol% Pd at 100 °C (entries 12–17). We also conducted the Suzuki–Miyaura reaction at a decreased catalyst loading (0.01 mol%), and a quantitative yield was obtained for deactivated 4-bromoanisole at 100 °C within 4 hours (entry 18). For a hindered aryl bromide (entry 19), activation of 2-bromo-1,3,5-trimethylbenzene with phenylboronic acid at 100 °C proved to be difficult and only traces of the desired biaryl formed. For bulky substrates, the arylboronic acid (entries 12–14) showed much higher reactivity compared with the aryl halide (entry 19). It is known that the oxidative addition is the rate-determining step of the catalytic cycle in most cases.[16a] The concerted and SN_2 mechanisms are used to describe the oxidative addition process during cross-coupling reactions, and both mechanisms consider palladium(0) as a nucleophile and the organohalide as an electrophile. The concerted mechanism requires a three-centered transition state. On the other hand, if an SN_2 mechanism is operative then the process generally involves several steps. The reaction is initiated via nucleophilic attack by the metal center at the less electronegative atom in the substrate, leading to cleavage of the R–X bond to give a $[Pd–R]^+$ intermediate, which is followed by rapid coordination of the anion to the cationic metal center.[16b,c] For the transmetalation in the Suzuki–Miyaura process, calculations show that the activation barrier is very high in the absence of a base, while transmetalation occurs easily in the presence of a base.[16c,d] These theoretical results are in agreement with the experimental observations in our work. Moreover, as the concerted and SN_2 mechanisms in oxidative addition are both sensitive to steric hindrance, we speculate that the coupling reactivity is mainly reliant on the barrier to the oxidative addition reaction of the aryl halide to L_nPd. On the other hand, steric hindrance in transmetalation (due to a bulky arylboronic acid) may have a minor influence on the coupling reactivity. This may explain why the bulky arylboronic acid (in reactions with low steric hindrance aryl halides, entries 12–14) showed much higher reactivity than a bulky aryl halide (entry 19). Only a low yield (28%) was obtained after 96 hours when activated

Table 3 Substrate Scope of Na_2PdCl_4-**1i** in Catalytic Aqueous Suzuki–Miyaura Reactions[a]



Entry	R^1 (X)	R^2	Time (h)	Yield (%)[b]
1	4-Ac (Br)	H	24	>99
2	4-MeO (Br)	2-Me	24	>99
3	4-MeO (Br)	3-Ac	24	>99
4	4-MeO (Br)	4-F_3C	24	>99
5	3-O_2N (Br)	H	24	>99
6	4-OHC (Br)	H	24	>99
7	4-Me (Br)	H	24	>99
8	4-$EtCO_2$ (Br)	2-Me	24	97
9	3-Me (Br)	2-Me	24	>99
10	2-NC (Br)	2-Me	48	>99
11	4-F_3C (Br)	2-Me	24	>99
12[c]	3-Me (Br)	2,6-$(Me)_2$	12	93
13[c]	4-Ac (Br)	2,6-$(Me)_2$	1	>99
14[c]	4-MeO (Br)	2,6-$(Me)_2$	5	95
15[c]	4-MeO (Br)	2-Me	2	>99
16[c]	4-MeO (Br)	3-Ac	1	>99
17[c]	4-MeO (Br)	4-F_3C	1	>99
18[c,d]	4-MeO (Br)	H	4	>99
19[c]	2,4,6-$(Me)_3$ (Br)	H	12	trace
20	4-O_2N (Cl)	4-MeO	96	28
21[c]	4-O_2N (Cl)	4-MeO	10	>99
22[c]	4-O_2N (Cl)	H	10	92
23[c]	4-O_2N (Cl)	2-Me	12	>99
24[c]	4-O_2N (Cl)	4-F_3C	12	>99
25[c]	4-O_2N (Cl)	2,6-$(Me)_2$	18	trace
26[c]	4-Ac (Cl)	H	18	40
27[c]	4-H_2N (Br)	4-MeO	1	>99
28[c]	4-MeO (Br)	3-thiopheneboronic acid	3	93
29[c]	2-bromopyridine	H	16	45
30[c]	3-bromothiophene	4-MeO	4	15
31[c]	3-bromopyridine	4-Ac	2	trace
32[c]	4-Ac (Br)	3-pyridylboronic acid	2	trace
33[c]	4-Ac (Br)	2-furanboronic acid	2	trace

[a] Reactions were conducted under aerobic conditions. Unless indicated otherwise, the reactions were conducted with 5 mmol of (hetero)aryl halide, 7.5 mmol of (hetero)arylboronic acid, 10 mmol of KOH, 5 mmol of TBAB and 5 mL of H_2O, Pd/**1i** = 1:2.
[b] Yield of isolated product.
[c] At 100 °C.
[d] Na_2PdCl_4-**1i** (0.01 mol%) was added.

4-nitrochlorobenzene was applied at room temperature (entry 20). However, almost quantitative yields could be achieved within 12 hours by increasing the reaction temperature to 100 °C (entries 21–24). Attempts to couple activated 4-nitrochlorobenzene with hindered arylboronic acids such as 2,6-dimethylphenylboronic acid failed (entry 25). On the other hand, a moderate yield (40%) was observed within 18 hours when activated 4′-chloroacetophenone and phenylboronic acid were applied at 100 °C (entry 26). Moreover, the optimum conditions could be applied for an aryl halide bearing an active proton; an excellent yield was obtained within 1 hour when 4-bromoaniline was coupled with 4-methoxyphenylboronic acid at 100 °C (entry 27). These results reveal that Na_2PdCl_4-**1i** tolerates functional groups on aryl bromides and arylboronic acids at room temperature and is effective for coupling several deactivated substrates in moderate to good yields at 100 °C. With respect to heteroaryl substrates such as (hetero)aryl bromides or (hetero)arylboronic acids (entries 28–33), coupling of (hetero)aryl bromides with (hetero)arylboronic acids at 100 °C proved to be difficult, and only a trace or low yields (15–45%) of the desired products were formed (entries 29–33). However, a good yield of 93% was obtained within 3 hours when 4-bromoanisole was coupled with 3-thiopheneboronic acid at 100 °C (entry 28).

Since the formation of a black precipitate is observed during the coupling reactions, more experiments were designed to investigate the nature of the water-soluble thiourea–Pd complexes in water. A black precipitate due to Pd nanoparticles (PdNPs) can be visually observed during the coupling reactions in the absence of TBAB (Table 2, entries 1 and 2). After the coupling reactions, moderate to good yields (76–82%) were still observed within 12 hours in the fourth run using Na_2PdCl_4 as the Pd source in the absence of TBAB (Table 2, entries 1 and 2). On the other hand, the black precipitate was not obtained from the Pd catalyst and thiourea ligands under the reaction conditions without both the halide and the boronic acid. A clear solution was still obtained when Na_2PdCl_4 was treated with water-soluble thiourea ligands at 100 °C over a period of 2 hours in the absence of both the halide and boronic acid. Moreover, when 4-bromoanisole and phenylboronic acid were treated with Na_2PdCl_4 and TBAB under the reaction conditions in the absence of the thiourea ligand (Table 2, entries 12 and 13), an obvious decrease in the activity was observed after two (at r.t., Table 2, entry 12) or three (at 100 °C, Table 2, entry 13) consecutive cycles. These results further confirm that PdNPs are formed from the stabilization of thiourea ligands.

After the aqueous coupling reactions of 4′-bromoacetophenone and phenylboronic acid, the black solid (obtained from 0.1 mol% of Na_2PdCl_4-**1i**) was isolated by centrifugation. The resulting supernatant solution was directly applied in the catalytic coupling of 4′-bromoacetophenone and phenylboronic acid in water at 100 °C over a period of 2 hours. However, a low yield (27%) was observed. Furthermore, the isolated black solid (obtained from 0.1 mol% of Na_2PdCl_4-**1i**) was directly applied in the catalytic coupling of 4′-bromoacetophenone and phenylboronic acid in water at 100 °C over a period of 2 hours, and a quantitative yield of the coupling product was obtained in the second run. Moreover, no obvious loss of catalytic activity was observed even after the black solid had been used five times. It is known that active Pd nanoparticles are usually involved in palladium-catalyzed cross-coupling reactions.[3c,7l,8a,17] Therefore, TEM analysis was performed after the first and the fifth runs of the coupling reactions between 4′-bromoacetophenone and phenylboronic acid. Following the coupling reactions, the black precipitate was isolated by centrifugation and was washed with methanol (5 × 3 mL) and water (5 × 3 mL). The black precipitate was again centrifuged and dispersed in ethanol for TEM analysis.[7l,8a] The TEM images in Figure 3 clearly reveal the presence of PdNPs both after the first run and the fifth run (Figures 3a,b and 3c,d). The water-soluble thiourea ligand **1i** acts as a stabilizer of the nanoparticles in water. Furthermore, no obvious aggregation of Pd nanoparticles was visually observed after five consecutive cycles (Figure 3, c and d). We report here characterization using TEM analysis for the size and distri-

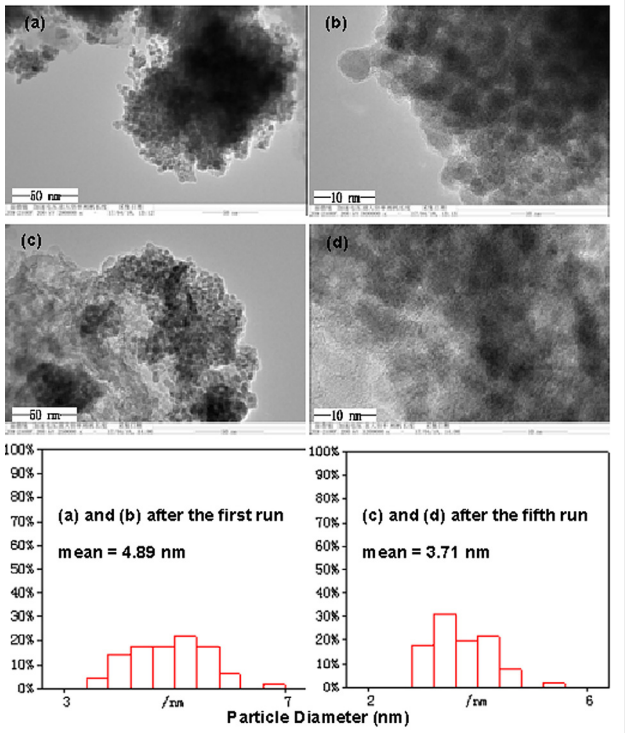


Figure 3 TEM images of PdNPs generated from the Na_2PdCl_4-**1i** complex: (a) and (b) after the first run of the coupling reaction of 4′-bromoacetophenone and phenylboronic acid; (c) and (d) after the fifth run of the coupling reaction of 4′-bromoacetophenone and phenylboronic acid. In all, >100 particles were counted in each case using 'Nano Measurer' software.

bution of Pd nanoparticles. Both sets of nanoparticles formed in consecutive coupling reactions were observed to have an estimated average size of 4 ± 1 nm (Figure 3, a,b and c,d). These results further confirm the hypothesis that the coupling reaction is catalyzed by Pd nanoparticles.

In summary, a series of eight precatalysts of carboxylic-functionalized thiourea ligands has been synthesized in a straightforward manner. Complex Na_2PdCl_4-**1i**, functionalized with four carboxylic groups, displayed the best catalytic activity and recyclability. Moreover, the coupling of aryl bromides and phenylboronic acids can even be conducted at room temperature while the catalyst can be recycled in at least five consecutive runs. TEM analysis shows that Pd nanoparticles form during the reactions. These novel water-soluble thiourea ligands are air- and moisture-stable, and the resulting Pd nanoparticles can be readily recycled in water under air. Work is in progress in our laboratory to extend the applications of water-soluble thiourea ligands in palladium- and other transition-metal-catalyzed reactions.

All reagents were used as supplied from commercial sources without further purification. TLC was performed on Yucheng chemical glass-backed silica plates. Column chromatography was performed using Yucheng chemical silica gel (200–300 mesh) eluting with EtOAc and petroleum ether (PE). Melting points were obtained using a X-4A digital micro melting point apparatus (made by Gongyi City Kerui Instrument Co., Ltd.). IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR. ^{1}H NMR spectra were recorded at 600 or 400 MHz, and ^{13}C NMR spectra were recorded at 150 or 100 MHz using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform, δ 7.26; DMSO, δ 2.50), carbon (chloroform, δ 77.0; DMSO, δ 39.5). Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), br s (broad singlet). Coupling constants are reported in hertz (Hz). High-resolution mass spectrometry (ESI) was performed with a Finnigan LCQ^{DECA} ion-trap mass spectrometer. Transmission electron microscopy (TEM) was performed on a JEOL JEM-2100F electron microscope operating at 200 kV. The TEM samples were prepared by pipetting a drop of an EtOH solution of the PdNPs on copper grids covered with a Quantifoil Multi A holey carbon film with a 2-nm carbon film on top.

Amides 3a–c,e,g–3i; General Procedures

Two methods were used for the synthesis of amides **3**.

Method A: Amides 3g–i

A mixture of the arylamine (12 mmol), 2-bromo-*N*-arylacetamide[13] (13.2 mmol), TBAI (222 mg, 0.6 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (1.86 g, 14.4 mmol) was stirred at 130 °C for 2 h, then after cooling to 80 °C, EtOH (60 mL) and H_2O (60 mL) were added. The mixture was then stirred at r.t. for 2 h. The resulting precipitate was collected by filtration and washed with EtOH (3 × 15 mL). The pure amide **3** was obtained as a white or pale-yellow solid through flash chromatography (PE/EtOAc, 3:1 to 1:1).

Dimethyl 5-{[2-(Mesitylamino)-2-oxoethyl]amino}isophthalate (3g)

Yield: 4.06 g (88%); white solid; mp 209–210 °C.

IR (KBr): 3259, 2952, 1728, 1668, 1609, 1529, 1439, 1359, 1241, 1134, 1000, 756 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.86 (s, 1 H), 7.56 (d, *J* = 1.2 Hz, 2 H), 6.84 (s, 2 H), 4.99 (t, *J* = 4.8 Hz, 1 H), 4.03 (d, *J* = 5.3 Hz, 2 H), 3.91 (s, 6 H), 2.22 (s, 3 H), 2.11 (s, 6 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.4, 166.3, 147.3, 137.2, 135.0, 131.6, 130.3, 128.9, 121.1, 118.0, 52.3, 48.3, 20.9, 18.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_5$: 385.1758; found: 385.1737.

Dimethyl 5-[(2-{[4-(Ethoxycarbonyl)-2,6-dimethylphenyl]amino}-2-oxoethyl)amino]isophthalate (3h)

Yield: 3.77 g (71%); white solid; mp 220–221 °C.

IR (KBr): 3249, 2962, 1720, 1671, 1527, 1419, 1258, 1114, 1009, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (t, *J* = 1.3 Hz, 1 H), 7.96 (s, 1 H), 7.74 (s, 2 H), 7.60 (d, *J* = 1.3 Hz, 2 H), 4.81 (t, *J* = 5.4 Hz, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.10 (d, *J* = 5.5 Hz, 2 H), 3.93 (s, 6 H), 2.22 (s, 6 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 166.4, 166.3, 147.2, 137.5, 135.5, 132.0, 129.6, 129.4, 121.8, 118.3, 61.1, 52.6, 48.7, 18.7, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_7$: 443.1818; found: 443.1806.

Trimethyl 5-[(2-{[4-(Ethoxycarbonyl)-2,6-dimethylphenyl]amino}-2-oxoethyl)amino]benzene-1,2,3-tricarboxylate (3i)

Yield: 3.42 g (57%); white solid; mp 148–149 °C.

IR (KBr): 3315, 2952, 1735, 1602, 1436, 1254, 1205, 1136, 1031, 800, 773, 704 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 8.26 (s, 2 H), 7.69 (s, 2 H), 4.57 (br s, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 3.98 (s, 3 H), 3.90 (s, 2 H), 3.88 (s, 6 H), 2.35 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.7, 169.3, 166.8, 164.7, 149.8, 138.4, 131.8, 130.7, 129.0, 127.6, 124.1, 123.4, 60.6, 53.0, 52.8, 51.5, 18.7, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{29}N_2O_9$: 501.1868; found: 501.1858.

Method B: Amides 3a–c,e

A mixture of the arylamine (12 mmol), 2-bromo-*N*-arylacetamide[13] (for amides **3a–c**: 26.4 mmol; for amide **3e**: 13.2 mmol), TBAI (222 mg, 0.6 mmol), MeCN (60 mL) and *N*,*N*-diisopropylethylamine (DIPEA) (for amides **3a–c**: 3.72 g, 28.8 mmol; for amide **3e**: 1.86 g, 14.4 mmol) was refluxed for 12–24 h. Upon completion, the MeCN was removed and H_2O (50 mL) was added. The mixture was then extracted with EtOAc (3 × 50 mL) and washed with brine, dried (Na_2SO_4), and concentrated. The pure amide **3** was obtained as a white or pale-yellow solid through flash chromatography (PE/EtOAc, 5:1 to 1:1).

Ethyl 3,5-Bis{[2-(mesitylamino)-2-oxoethyl]amino}benzoate (3a)

Yield: 5.48 g (86%); white solid; mp 119–120 °C.

IR (KBr): 2976, 2859, 1664, 1610, 1509, 1239, 1108, 1032, 851, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 2 H), 6.87 (d, *J* = 1.5 Hz, 2 H), 6.82 (s, 4 H), 6.24 (s, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 3.92 (s, 4 H), 2.22 (s, 6 H), 2.09 (s, 12 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 166.8, 148.3, 137.3, 135.1, 132.8, 130.6, 129.1, 105.4, 102.5, 61.2, 48.6, 21.0, 18.5, 14.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{39}N_4O_4$: 531.2971; found: 531.2971.

Dimethyl 4,4'-[(2,2′-{[5-(Ethoxycarbonyl)-1,3-phenylene]-bis(azanediyl)}bis(acetyl))bis(azanediyl)]bis(3-methylbenzoate) (3b)

Yield: 5.74 g (81%); pale-yellow solid; mp 104–105 °C.

IR (KBr): 2952, 1716, 1610, 1526, 1438, 1276, 1124, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 2 H), 8.17 (d, *J* = 8.5 Hz, 2 H), 7.86 (d, *J* = 8.5 Hz, 2 H), 7.77 (s, 2 H), 6.91 (s, 2 H), 6.16 (s, 1 H), 4.44–4.22 (m, 4 H), 3.96 (d, *J* = 5.2 Hz, 4 H), 3.88 (s, 6 H), 2.04 (s, 6 H), 1.35 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 166.8, 166.4, 148.3, 139.5, 133.3, 131.9, 128.8, 127.1, 126.2, 120.6, 106.3, 102.0, 61.4, 52.1, 49.6, 17.3, 14.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{35}N_4O_8$: 591.2455; found: 591.2440.

Methyl 4-(2-{[3-({2-[(4-Acetoxy-2-methylphenyl)amino]-2-oxo-ethyl}amino)phenyl]amino}acetamido)-3-methylbenzoate (3c)

Yield: 4.67 g (75%); pale-yellow solid; mp 184–185 °C.

IR (KBr): 2962, 1609, 1523, 1256, 1120, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 2 H), 8.24 (d, *J* = 8.5 Hz, 2 H), 7.88 (dd, *J* = 8.5, 1.9 Hz, 2 H), 7.78 (d, *J* = 1.4 Hz, 2 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 6.23 (dd, *J* = 8.1, 2.2 Hz, 2 H), 6.03 (t, *J* = 2.1 Hz, 1 H), 4.46 (t, *J* = 5.4 Hz, 2 H), 3.93 (d, *J* = 5.5 Hz, 4 H), 3.89 (s, 6 H), 2.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 166.8, 148.2, 139.6, 131.8, 131.1, 128.9, 126.7, 125.9, 120.2, 105.6, 98.8, 52.2, 49.9, 17.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{31}N_4O_6$: 519.2244; found: 519.2229.

Ethyl 4-[2-(Mesitylamino)acetamido]benzoate (3e)

Yield: 3.11 g (76%); white solid; mp 75–76 °C.

IR (KBr): 3241, 2978, 1703, 1677, 1523, 1486, 1409, 1277, 1178, 1109, 1028, 853, 770 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 8.04 (d, *J* = 8.7 Hz, 2 H), 7.70 (d, *J* = 8.7 Hz, 2 H), 6.87 (s, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.73 (s, 2 H), 3.10 (br s, 1 H), 2.29 (s, 6 H), 2.25 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8, 166.3, 141.9, 141.6, 133.3, 131.0, 130.1, 130.0, 126.3, 118.7, 61.0, 52.8, 20.7, 18.4, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1861.

Thioureas 2a–c,e,g–i; General Procedure

To a solution of amide **3** (3 mmol) in THF (30 mL) was added BH_3·SMe_2 (2 M in THF, for bisthioureas **2a–c**: 12 mL, 24 mmol, 8 equiv; for monothioureas **2e**,**g–i**: 6 mL, 12 mmol, 4 equiv) at 0 °C. The solution was refluxed for 6 h then, after cooling to r.t., MeOH (15 mL) was added dropwise in order to destroy the excess BH_3. The solvent was removed, and the resulting amine was used directly in the next step.

To a stirred mixture of the amine obtained above and Na_2CO_3 (for bis-thioureas **2a–c**: 763 mg, 7.2 mmol, 2.4 equiv; for monothioureas **2e**,**g–i**: 382 mg, 3.6 mmol, 1.2 equiv) in dry THF (20 mL) was added a dilute solution of thiophosgene (for bisthioureas **2a–c**: 828 mg, 7.2 mmol, 2.4 equiv; for monothioureas **2e**,**g–i**: 414 mg, 3.6 mmol, 1.2 equiv) in THF (10 mL) over about 12 h. After stirring at r.t. overnight, THF was removed under vacuum, and H_2O (30 mL) and EtOAc (30 mL) were added. The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The pure thiourea **2** was obtained as a white or pale-yellow solid through flash chromatography (PE/EtOAc, 5:1 to 1:1) and recrystallization from methanol.

Ethyl 3,5-Bis(3-mesityl-2-thioxoimidazolidin-1-yl)benzoate (2a)

Yield: 915 mg (52%, two steps); white solid; mp >240 °C.

IR (KBr): 2972, 2915, 1713, 1602, 1476, 1421, 1273, 1247, 1110, 1026, 856, 771, 695 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.62 (t, *J* = 2.0 Hz, 1 H), 8.09 (d, *J* = 2.0 Hz, 2 H), 6.97 (s, 4 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 4.36–4.27 (m, 4 H), 3.97–3.87 (m, 4 H), 2.31 (s, 6 H), 2.28 (s, 12 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.8, 165.9, 141.1, 138.6, 136.4, 134.6, 131.4, 129.6, 125.0, 121.7, 61.5, 49.3, 47.3, 21.2, 18.0, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{39}N_4O_2S_2$: 587.2514; found: 587.2527.

Dimethyl 4,4′-{[5-(Ethoxycarbonyl)-1,3-phenylene]bis(2-thioxo-imidazolidine-3,1-diyl)}bis(3-methylbenzoate) (2b)

Yield: 893 mg (46%, two steps); pale-yellow solid; mp 123–124 °C.

IR (KBr): 2950, 2892, 1719, 1602, 1474, 1425, 1305, 1109, 770, 718, 678 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.58–8.51 (m, 1 H), 8.10 (d, *J* = 1.8 Hz, 2 H), 8.01 (s, 2 H), 7.96 (d, *J* = 8.1 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.36–4.26 (m, 4 H), 4.01 (t, *J* = 8.7 Hz, 4 H), 3.92 (s, 6 H), 2.39 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 181.3, 166.6, 165.7, 143.4, 140.9, 137.3, 132.8, 131.6, 130.3, 128.7, 128.3, 125.6, 122.3, 61.6, 52.4, 49.5, 49.1, 18.2, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{35}N_4O_6S_2$: 647.1998; found: 647.1990.

Dimethyl 4,4′-[1,3-Phenylenebis(2-thioxoimidazolidine-3,1-diyl)]bis(3-methylbenzoate) (2c)

Yield: 534 mg (31%, two steps); pale-yellow solid; mp >230 °C.

IR (KBr): 2950, 1714, 1604, 1478, 1426, 1277, 1200, 1110, 772 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13 (t, *J* = 1.9 Hz, 1 H), 8.01 (s, 2 H), 7.96 (dd, *J* = 8.2, 1.5 Hz, 2 H), 7.55–7.48 (m, 2 H), 7.45 (dd, *J* = 9.1, 6.7 Hz, 1 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 4.28 (t, *J* = 8.4 Hz, 4 H), 3.99 (t, *J* = 8.8 Hz, 4 H), 3.92 (s, 6 H), 2.40 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 181.3, 166.6, 143.5, 140.8, 137.3, 132.8, 130.2, 129.0, 128.7, 128.3, 121.9, 121.1, 52.4, 49.8, 49.1, 18.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{31}N_4O_4S_2$: 575.1787; found: 575.1798.

Ethyl 4-(3-Mesityl-2-thioxoimidazolidin-1-yl)benzoate (2e)

Yield: 685 mg (62%, two steps); pale-yellow solid; mp 165–166 °C.

IR (KBr): 2971, 1706, 1605, 1421, 1264, 1106, 765 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.8 Hz, 2 H), 6.97 (s, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 4.32–4.25 (m, 2 H), 3.94–3.87 (m, 2 H), 2.31 (s, 3 H), 2.26 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.2, 166.2, 144.8, 138.6, 136.2, 134.5, 130.1, 129.6, 126.6, 122.2, 60.9, 48.8, 47.0, 21.2, 17.9, 14.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_2S$: 369.1637; found: 369.1614.

Dimethyl 5-(3-Mesityl-2-thioxoimidazolidin-1-yl)isophthalate (2g)

Yield: 854 mg (69%, two steps); white solid; mp 176–177 °C.

IR (KBr): 2950, 1729, 1605, 1455, 1356, 1311, 1239, 1129 1076, 996, 754 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 1.4 Hz, 2 H), 8.53 (t, *J* = 1.4 Hz, 1 H), 6.98 (s, 2 H), 4.36–4.29 (m, 2 H), 3.99–3.92 (m, 8 H), 2.31 (s, 3 H), 2.28 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 180.7, 165.9, 141.4, 138.6, 136.2, 134.3, 130.9, 129.5, 128.8, 127.5, 52.5, 48.9, 47.1, 21.1, 17.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{24}N_2O_4SNa$: 435.1349; found: 435.1317.

Dimethyl 5-{3-[4-(Ethoxycarbonyl)-2,6-dimethylphenyl]-2-thioxoimidazolidin-1-yl}isophthalate (2h)

Yield: 734 mg (52%, two steps); pale-yellow solid; mp 197–198 °C.

IR (KBr): 2917, 1734, 1594, 1435, 1318, 1247, 1121, 1025, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 1.5 Hz, 2 H), 8.54 (t, *J* = 1.5 Hz, 1 H), 7.85 (s, 2 H), 4.45–4.31 (m, 4 H), 4.02–3.88 (m, 8 H), 2.37 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 166.2, 165.9, 141.2, 141.1, 137.3, 131.2, 130.7, 130.1, 129.0, 127.8, 61.2, 52.7, 49.2, 46.9, 18.2, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_6S$: 471.1590; found: 471.1582.

Trimethyl 5-{3-[4-(Ethoxycarbonyl)-2,6-dimethylphenyl]-2-thioxoimidazolidin-1-yl}benzene-1,2,3-tricarboxylate (2i)

Yield: 777 mg (49%, two steps); pale-yellow solid; mp 222–223 °C.

IR (KBr): 2952, 1742, 1604, 1480, 1434, 1241, 1136, 1009, 798, 773 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.62 (s, 2 H), 7.86 (s, 2 H), 4.41–4.36 (m, 4 H), 3.99 (s, 3 H), 3.99–3.95 (m, 2 H), 3.93 (s, 6 H), 2.36 (s, 6 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.9, 168.5, 166.1, 164.9, 141.2, 140.8, 137.1, 133.3, 130.7, 130.0, 129.0, 128.2, 61.1, 53.0, 52.9, 48.7, 46.6, 18.1, 14.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{29}N_2O_8S$: 529.1639; found: 529.1628.

Diethyl 2,2′-({[Ethane-1,2-diylbis(azanediyl)]bis(3,5-dimethyl-4,1-phenylene)}bis[oxy])diacetate (4f)

To a suspension of NaH (60% dispersion in mineral oil, 120 mg, 3 mmol) in dry THF (10 mL) at 0 °C was added 4-[2-(4-hydroxy-2,6-dimethylphenylamino)ethylamino]-3,5-dimethylphenol[14] (300.4 mg, 1 mmol) in THF (10 mL). After 10 min, ethyl 2-bromoacetate (334 mg, 2 mmol) was added and the mixture was stirred at r.t. for 4 h. Upon completion, the reaction solution was diluted with EtOAc (30 mL) and then slowly quenched with H_2O (30 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified via recrystallization from petroleum ether.

Yield: 364 mg (77%); pale-yellow solid; mp 112–113 °C.

IR (KBr): 3369, 2936, 1751, 1600, 1482, 1209, 1155, 1091, 1024, 857, 829, 714 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.60 (s, 4 H), 4.55 (s, 4 H), 4.27 (q, *J* = 7.1 Hz, 4 H), 3.09 (s, 4 H), 2.29 (s, 12 H), 1.30 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4, 153.2, 139.9, 132.0, 115.0, 65.9, 61.4, 49.4, 18.8, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{37}N_2O_6$: 473.2652; found: 473.2646.

Diethyl 2,2′-{[(2-Thioxoimidazolidine-1,3-diyl)bis(3,5-dimethyl-4,1-phenylene)]bis(oxy)}diacetate (2f)

To a stirred mixture of amine **4f** (1.42 g, 3 mmol) and Na_2CO_3 (382 mg, 3.6 mmol, 1.2 equiv) in dry THF (20 mL) was added a dilute solution of thiophosgene (414 mg, 3.6 mmol, 1.2 equiv) in THF (10 mL) over about 12 h. After stirring at r.t. overnight, the THF was removed under vacuum, and H_2O (30 mL) and EtOAc (30 mL) were added. The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified through flash chromatography (PE/EtOAc, 3:1 to 1:1) and recrystallization from EtOH.

Yield: 293 mg (57%); pale-yellow solid; mp 176–177 °C.

IR (KBr): 2986, 2956, 1752, 1595, 1489, 1316, 1272, 1217, 1159, 1094, 1011, 850 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.68 (s, 4 H), 4.59 (s, 4 H), 4.28 (q, *J* = 7.1 Hz, 4 H), 3.96 (s, 4 H), 2.30 (s, 12 H), 1.32 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 181.4, 169.0, 157.2, 138.4, 131.1, 114.6, 65.4, 61.4, 47.7, 18.2, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{35}N_2O_6S$: 515.2210; found: 515.2185.

Thioureas 1a–c,e–i; General Procedure

Thiourea **2** (1 mmol), excess NaOH (600 mg, 15 mmol), H_2O (20 mL) and THF (20 mL) were stirred at r.t. for 24 h. The solution was then diluted with Et_2O (20 mL) and the organic phase was washed with H_2O (5 mL). The aqueous layer was collected and slowly acidified with concentrated HCl solution to pH = 1. The resulting precipitate was collected by filtration and washed with H_2O (5 mL). The pure thiourea **1** was obtained as a white or pale-yellow solid through flash chromatography (CH_2Cl_2/MeOH, 10:1 to 1:1) or by recrystallization from EtOAc.

3,5-Bis(3-mesityl-2-thioxoimidazolidin-1-yl)benzoic Acid (1a)

Yield: 369 mg (66%); pale-yellow solid; mp >240 °C.

IR (KBr): 2916, 1713, 1688, 1600, 1476, 1423, 1307, 1271, 1075, 1032, 854, 775, 693 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 13.12 (s, 1 H), 8.29 (s, 1 H), 8.23 (s, 2 H), 6.97 (s, 4 H), 4.36 (t, *J* = 8.7 Hz, 4 H), 3.92 (t, *J* = 8.6 Hz, 4 H), 2.27 (s, 6 H), 2.20 (s, 12 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.3, 166.8, 141.2, 137.3, 136.1, 134.9, 130.5, 128.9, 122.1, 121.0, 48.8, 46.8, 20.6, 17.4.

HRMS (ESI negative ion): *m*/*z* [M – H]$^+$ calcd for $C_{31}H_{33}N_4O_2S_2$: 557.2045; found: 557.2035.

4,4′-[(5-Carboxy-1,3-phenylene)bis(2-thioxoimidazolidine-3,1-diyl)]bis(3-methylbenzoic Acid) (1b)

Yield: 484 mg (82%); pale-yellow solid; mp >240 °C.

IR (KBr): 2961, 1710, 1605, 1476, 1419, 1306, 1278, 775, 681 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.93 (br s, 3 H), 8.29 (t, *J* = 2.0 Hz, 1 H), 8.22 (d, *J* = 2.0 Hz, 2 H), 7.92 (s, 2 H), 7.86 (dd, *J* = 8.2, 1.7 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 4.35 (dd, *J* = 18.6, 9.8 Hz, 4 H), 4.05 (dd, *J* = 15.3, 7.9 Hz, 4 H), 2.35 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.7, 166.9, 166.7, 143.5, 141.0, 137.1, 131.8, 130.8, 130.4, 128.5, 128.0, 122.0, 121.7, 49.1, 48.8, 17.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{27}N_4O_6S_2$: 591.1372; found: 591.1367.

4,4′-[1,3-Phenylenebis(2-thioxoimidazolidine-3,1-diyl)]bis(3-methylbenzoic Acid) (1c)

Yield: 377 mg (69%); pale-yellow solid; mp 218–219 °C.

IR (KBr): 2923, 1697, 1606, 1423, 1280, 775 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 12.72 (br s, 2 H), 8.08 (s, 1 H), 7.91 (s, 2 H), 7.85 (d, *J* = 7.7 Hz, 2 H), 7.61 (d, *J* = 7.9 Hz, 2 H), 7.52–7.37 (m, 3 H), 4.43–4.20 (m, 4 H), 4.10–3.97 (m, 4 H), 2.34 (s, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 180.2, 167.4, 144.1, 141.3, 137.6, 132.2, 130.7, 128.9, 128.6, 128.4, 121.5, 119.8, 49.8, 49.2, 18.2.

HRMS (ESI negative ion): *m*/*z* [M – H]$^+$ calcd for $C_{28}H_{25}N_4O_4S_2$: 545.1317; found: 545.1319.

4-(3-Mesityl-2-thioxoimidazolidin-1-yl)benzoic Acid (1e)

Yield: 310 mg (91%); white solid; mp >240 °C.

IR (KBr): 2978, 1701, 1606, 1422, 1273, 1131, 776 cm^{-1}.

^{1}HNMR (600 MHz, DMSO-d_6): δ = 12.85 (br s, 1 H), 8.00 (s, 4 H), 6.99 (s, 2 H), 4.37 (d, *J* = 8.1 Hz, 2 H), 3.93 (t, *J* = 8.4 Hz, 2 H), 2.29 (s, 3 H), 2.20 (s, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.2, 167.4, 145.2, 137.9, 136.4, 135.3, 129.9, 129.4, 126.7, 122.4, 48.9, 47.1, 21.1, 17.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_2S$: 341.1324; found: 341.1313.

2,2′-{[(2-Thioxoimidazolidine-1,3-diyl)bis(3,5-dimethyl-4,1-phenylene)]bis(oxy)}diacetic Acid (1f)

Yield: 440 mg (96%); white solid; mp >230 °C.

IR (KBr): 2923, 1736, 1493, 1314, 1279, 1166, 1093, 848, 695 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 6.68 (s, 4 H), 4.66 (s, 4 H), 3.94 (s, 4 H), 2.20 (s, 12 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 180.6, 170.7, 157.2, 138.4, 131.4, 114.2, 64.8, 47.8, 18.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_6S$: 459.1590; found: 459.1584.

5-(3-Mesityl-2-thioxoimidazolidin-1-yl)isophthalic Acid (1g)

Yield: 354 mg (92%); white solid; mp >230 °C.

IR (KBr): 2956, 1735, 1600, 1436, 1306, 1279, 1214, 760, 669 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 8.52 (d, *J* = 1.5 Hz, 2 H), 8.29 (t, *J* = 1.5 Hz, 1 H), 6.95 (s, 2 H), 4.43–4.37 (m, 2 H), 3.93–3.87 (m, 2 H), 2.25 (s, 3 H), 2.18 (s, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.7, 166.8, 142.0, 137.9, 136.5, 135.3, 131.8, 129.4, 128.5, 126.5, 48.9, 47.3, 21.1, 17.9.

HRMS (ESI negative ion): *m*/*z* [M – H]$^+$ calcd for $C_{20}H_{19}N_2O_4S$: 383.1071; found: 383.1073.

5-[3-(4-Carboxy-2,6-dimethylphenyl)-2-thioxoimidazolidin-1-yl]isophthalic Acid (1h)

Yield: 269 mg (65%); white solid; mp >230 °C.

IR (KBr): 2966, 1714, 1602, 1453, 1311, 1237, 901, 761, 678 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 8.52 (s, 2 H), 8.30 (s, 1 H), 7.74 (s, 2 H), 4.45 (t, *J* = 8.8 Hz, 2 H), 4.02–3.90 (m, 2 H), 2.29 (s, 6 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 179.2, 167.2, 166.6, 141.5, 137.5, 137.4, 131.8, 130.7, 129.5, 128.4, 126.6, 49.0, 46.7, 17.7.

HRMS (ESI negative ion): *m*/*z* [M – H]$^+$ calcd for $C_{20}H_{17}N_2O_6S$: 413.0813; found: 413.0816.

5-[3-(4-Carboxy-2,6-dimethylphenyl)-2-thioxoimidazolidin-1-yl]benzene-1,2,3-tricarboxylic Acid (1i)

Yield: 344 mg (75%); pale-yellow solid; mp 239–241 °C.

IR (KBr): 2980, 1702, 1604, 1430, 1245, 896, 776, 671 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 8.40 (s, 2 H), 7.74 (s, 2 H), 4.49–4.40 (m, 2 H), 3.99–3.92 (m, 2 H), 2.29 (s, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.0, 168.7, 167.2, 166.8, 141.4, 141.0, 137.5, 133.1, 130.7, 130.6, 129.6, 127.4, 48.8, 46.8, 17.8.

HRMS (ESI negative ion): *m*/*z* [M – H]$^+$ calcd for $C_{21}H_{17}N_2O_8S$: 457.0706; found: 457.0708.

Suzuki Reactions of Aryl Halides with Boronic Acids; General Procedure

The aryl halide (5.0 mmol), arylboronic acid (7.5 mmol), base (10.0 mmol), the calculated amount of thiourea, Pd and H_2O (5 mL) were added to a flask containing a magnetic stir bar under air. The flask was sealed with a rubber septum and the contents were stirred at the specified temperature for the appropriate period of time. Upon completion, the reaction mixture was extracted using Et_2O (3 × 10 mL). The solvent was removed on a rotary evaporator and the residue was purified by flash chromatography on silica gel to afford the desired product. The coupling products were characterized by ^1H NMR and ^{13}C NMR spectroscopy (see the Supporting Information). The identities of the products were confirmed by comparison with literature spectroscopic data.[18]

Recycling of Catalyst 1i-Na_2PdCl_4 in Aqueous Suzuki–Miyaura Reactions

The catalyst **1i** (1 mol%, 4.6 mg), Na_2PdCl_4 (0.5 mol%, 1.5 mg), phenylboronic acid (914.5 mg, 7.5 mmol), KOH (561 mg, 10.0 mmol), TBAB (5 mmol, 1.61 g) and the aryl halide (5.0 mmol) were added to a flask containing a magnetic stir bar. H_2O (5 mL) was added and the mixture was stirred at 25 °C or 100 °C for the appropriate period of time. Upon completion, the mixture was extracted with Et_2O (3 × 10 mL). The organic solvent was collected by centrifugation and removed on a rotary evaporator. The residue was purified by flash chromatography on silica gel to give the product. The aqueous phase from the centrifugation was evaporated under reduced pressure to remove any residual Et_2O. The aqueous catalytic system was recharged with the same substrates and base for the next run.

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Supporting Information

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