Palladium Nanoparticles Immobilized on Nanosilica Triazine Dendritic Polymer (Pd_{np}-nSTDP) as Catalyst in the Synthesis of Mono-, Di-, and Trisulfides through C–S Cross-Coupling Reactions

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Abstract: A wide variety of diaryl sulfides has been synthesized in excellent yields via C–S cross-couplings of aryl/heteroaryl halides with aromatic/heteroaromatic thiols in the presence of palladium nanoparticles immobilized on nanosilica triazine dendritic polymer (Pd_{np}-nSTDP) as a reusable catalyst under thermal conditions and microwave irradiation. Pd_{np}-nSTDP also showed excellent catalytic activity for the preparation of a series of di- and trisulfides with benzene, pyridine, pyrimidine, and/or 1,3,5-triazine as the central cores by one-pot multi C–S cross-coupling reactions.

Key words: supported catalysis, palladium, cross-coupling, dendrimers, thiols

The synthesis of diaryl sulfides via C–S cross-coupling reaction is of great significance due to their abundance in many natural products as well as their widespread applications in biology and pharmacology.[1] A great number of compounds containing diaryl sulfide moieties has been employed as effective drugs for the treatment of inflammation,[2] cancer,[3] immunodeficiency virus (HIV),[4] and Alzheimer's and Parkinson's diseases.[5] Due to their importance and useful properties, various methods for the synthesis of diaryl sulfides have been reported. Generally, the C–S cross-coupling reactions leading to diaryl sulfides are catalyzed by palladium-,[6] copper-,[7] nickel-,[8] cobalt-,[9] indium-,[10] rhodium-,[11] platinum-,[12] and iron-[13]based catalysts. However, some of these synthetic methods suffer from disadvantages such as high temperature, long reaction times, high loading of catalysts, low yields, and the use of nonreusable catalysts. Accordingly, the development of an efficient and convenient method employing a reusable catalyst for the synthesis of diaryl sulfides is still desirable.

In the course of the last two decades, dendritic polymers have attracted a great interest because of their wide range of applications in macromolecular chemistry,[14] nanosci-

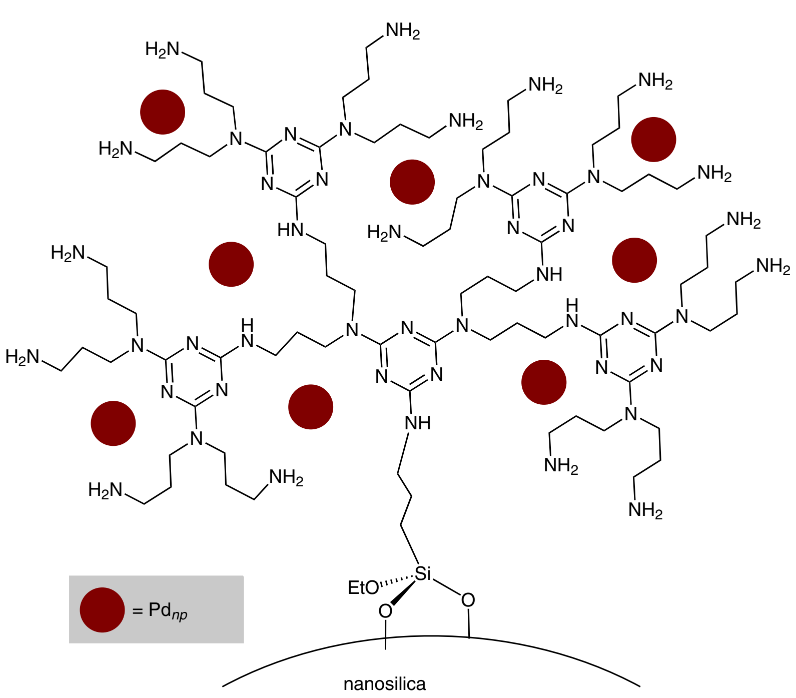

Figure 1 Palladium nanoparticles immobilized on nanosilica triazine dendritic polymer (Pd_{np}-nSTDP) catalyst

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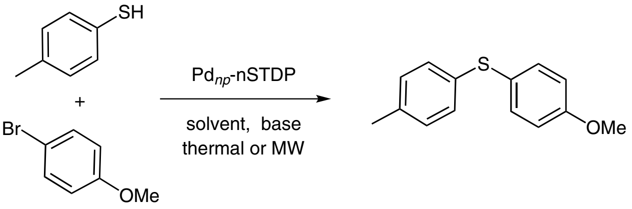
ence,[15] gene therapy,[16] drug delivery,[17] and medicinal chemistry.[18] Dendritic polymers, due to their highly branched and three-dimensional structures, have also been used as molecular boxes for encapsulation of a variety of ions and molecules. One of the main applications of these metal encapsulated-dendritic polymers is in the field of catalysis.[19] Moreover, immobilization of these metal-containing dendrimer catalysts on various insoluble supports, especially porous materials with high surface areas, is of great interest from economical and environmental points of view, as they can be easily recovered and reused without significant loss of activity.[15d,20]

Recently, we reported palladium nanoparticles immobilized on nanosilica triazine dendritic polymer (Pd_{np}-nSTDP) as an efficient and reusable catalyst for Suzuki–Miyaura cross-coupling and Heck reactions.[21] In continuation of our interest in exploring the use of Pd_{np}-nSTDP catalytic system in organic synthesis, we herein report an efficient and convenient method for the preparation of mono-, di-, and trisulfides using Pd_{np}-nSTDP (Figure 1) as a recyclable catalyst under thermal conditions and microwave irradiation (Scheme 1). To the best of our knowledge, this is the first report on the use of a palladium-nanoparticle-based dendritic catalyst for the synthesis of mono-, di-, and trisulfides through C–S cross-coupling reactions.

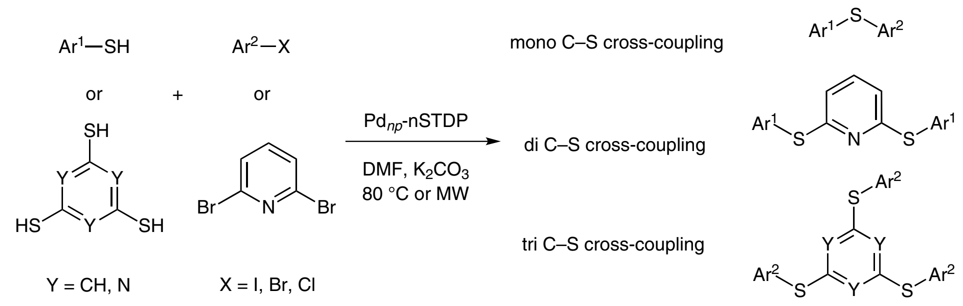
At the outset, the coupling reaction of 4-bromoanisole (1 mmol) with 4-methylthiophenol (1 mmol) in the presence of Pd_{np}-nSTDP catalyst was employed to screen the reaction parameters including the type of base and solvent, temperature, catalyst loading, and microwave power (Table 1). Various bases, such as triethylamine (Et_3N), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), piperidine, sodium hydroxide (NaOH), potassium *tert*-butoxide (KO*t*-Bu), sodium carbonate (Na_2CO_3), and potassium carbonate

Table 1 Optimization of the C–S Cross-Coupling of 4-Bromoanisole with 4-Methylthiophenol Catalyzed by Pd_{np}-nSTDP



Entry	Base[a]	Catalyst (mol% Pd)	Solvent[a]	Method	Time	Yield (%)[b]
1	Et_3N	0.05	DMF	thermal (80 °C)	24 h	20
2	DBU	0.05	DMF	thermal (80 °C)	24 h	39
3	piperidine	0.05	DMF	thermal (80 °C)	24 h	25
4	NaOH	0.05	DMF	thermal (80 °C)	24 h	42
5	KO*t*-Bu	0.05	DMF	thermal (80 °C)	24 h	37
6	Na_2CO_3	0.05	DMF	thermal (80 °C)	16 h	61
7	K_2CO_3	0.05	DMF	thermal (80 °C)	10 h	95
8	K_2CO_3	0.05	toluene	thermal (80 °C)	24 h	46
9	K_2CO_3	0.05	EtOH	thermal (80 °C)	24 h	40
10	K_2CO_3	0.05	H_2O	thermal (80 °C)	24 h	66
11	K_2CO_3	0.05	DMF	thermal (100 °C)	10 h	95
12	K_2CO_3	0.07	DMF	thermal (80 °C)	10 h	95
13	K_2CO_3	0.05	DMF	thermal (70 °C)	10 h	70
14	K_2CO_3	0.03	DMF	thermal (80 °C)	10 h	57
15	K_2CO_3	0.05	DMF	MW (230 W, 80 °C)	20 min	96
16	K_2CO_3	0.07	DMF	MW (230 W, 80 °C)	20 min	96
17	K_2CO_3	0.03	DMF	MW (200 W, 70 °C)	20 min	75
18	K_2CO_3	0.05	DMF	MW (250 W, 90 °C)	20 min	96
19	K_2CO_3	0.05	DMF	MW (150 W, 50 °C)	30 min	60

[a] Reaction was performed using 1.5 mmol of base and 2 mL of solvent.
[b] Isolated yield.

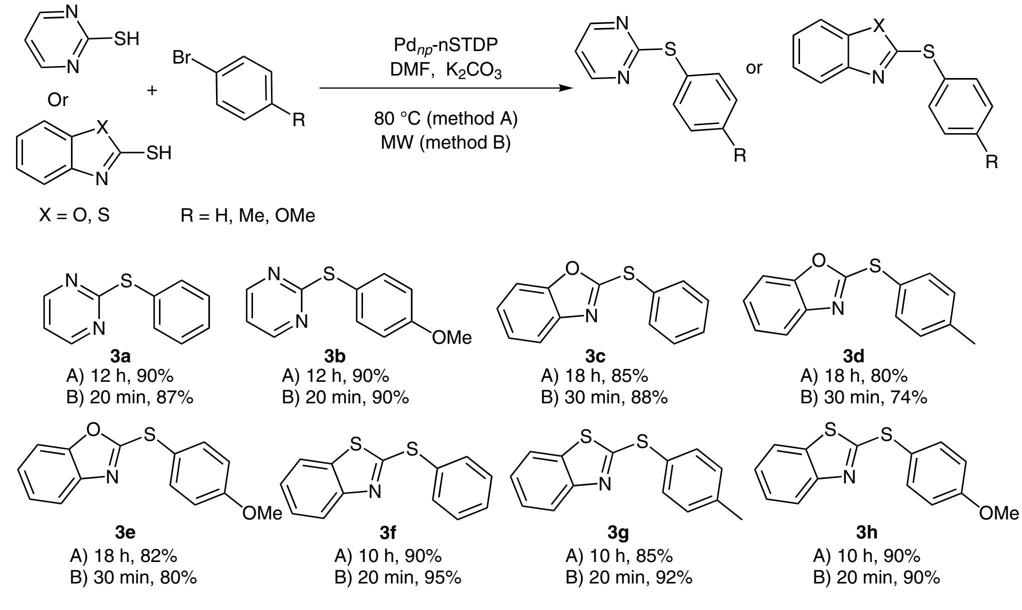


Scheme 1 C–S Cross-coupling catalyzed by Pd$_{np}$-nSTDP

(K_2CO_3) were examined (Table 1, entries 1–7); with K_2CO_3 giving the highest conversion (Table 1, entry 7). Different solvents such as toluene, ethanol (EtOH), water (H_2O), and *N*,*N*-dimethylformamide (DMF) were tested in this coupling reaction (Table 1, entries 7–10). Among the solvents investigated, DMF was found to be the most effective reaction medium (Table 1, entry 7). The effects of temperature and amount of the catalyst were also investigated; the best yield being obtained using 0.05 mol% of palladium catalyst at 80 °C. On increasing the temperature or the amount of the catalyst, the yield of the desired product did not increase further (Table 1, entries 11 and 12), but the yield decreased on lowering these parameters, (Table 1, entries 13 and 14). Based on the above results, K_2CO_3 as the base, DMF as the solvent, together with 0.05 mol% of palladium catalyst at 80 °C were selected as the optimized reaction conditions (Table 1, entry 7). Under microwave irradiation,[22] using the above-mentioned conditions, the best result was obtained with an applied power of 230 W at 80 °C (Table 1, entry 15).

To clarify the generality and efficiency of the procedure, a range of halides and aromatic thiols was examined under the optimized conditions. The results are listed in Table 2.[23] A wide range of structurally diverse aryl iodides and bromides was reacted with various aromatic thiols in the presence of Pd$_{np}$-nSTDP catalyst at 80 °C, leading to the corresponding diaryl sulfides in excellent yields (Table 2, entries 1–12). It is noteworthy that under Pd$_{np}$-nSTDP catalysis, aryl chlorides (both activated and nonactivated) underwent coupling reactions to produce the desired diaryl sulfides in high yields (Table 2, entries 13–16).

Moreover, the chemoselectivity of the present method is remarkable, since the C–S cross-coupling was performed in the presence of the NH_2 group with excellent selectivity (Table 2, entry 7). The C–S cross-coupling reactions were also examined under microwave irradiation. As shown in Table 2, a variety of aryl iodides, bromides, and chlorides as reacted with aromatic thiols in the presence of Pd$_{np}$-nSTDP under the optimized microwave irradiation to afford the desired cross-coupling products in 77–96% yields within 15–45 minutes. The results indicate that microwave irradiation has the evident advantage of short reaction times over the classical heating mode. The reactions were generally clean and no side products such as symmetrical disulfides were produced; in all cases, diaryl sulfides were obtained as the sole products.



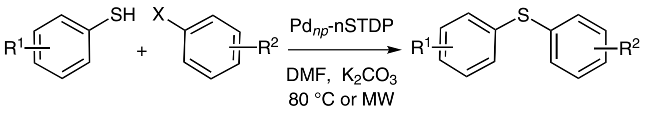
Scheme 2 C–S Cross-coupling of aryl bromides and heteroaromatic thiols catalyzed by Pd$_{np}$-nSTDP. *Reagents and conditions*: aryl halide (1 mmol), thiol (1 mmol), K_2CO_3 (1.5 mmol), Pd$_{np}$-nSTDP (0.05 mol% Pd), DMF (2 mL), 80 °C or MW (230 W, 80 °C); isolated yields are given.

In order to expand the scope of the reaction substrates, various heteroaromatic thiols were also examined. As revealed in Scheme 2, heteroaromatic thiols such as 2-mercaptopyrimidine, 2-mercaptobenzoxazole, and 2-mercaptobenzothiazole were coupled smoothly with aryl bromides under thermal conditions and microwave irradiation to produce the corresponding heteroaryl sulfides in high yields.

In a further study, the activity of the Pd_{np}-nSDTP catalyst was evaluated in reactions involving heteroaryl halides. As shown in Scheme 3, the reaction of 2-bromopyridine with 4-methylthiophenol and/or 2-mercaptobenzothiazole proceeded efficiently under thermal conditions and microwave irradiation to generate excellent yields of the desired cross-coupling products.

After successful generation of diaryl sulfides via Pd_{np}-nSTDP-catalyzed cross-coupling of aryl/heteroaryl halides with aromatic/heteroaromatic thiols, we decided to explore the potential of this catalytic system to one-pot multi C–S cross-couplings to produce di- and trisulfides.[24,25] The results are summarized in Table 3. 2,6-Dibromopyridine underwent twofold C–S cross-coupling reaction with 4-methylthiophenol, 2-mercaptobenzoxazole, or 2- mercaptobenzothiazole in the presence of Pd_{np}-

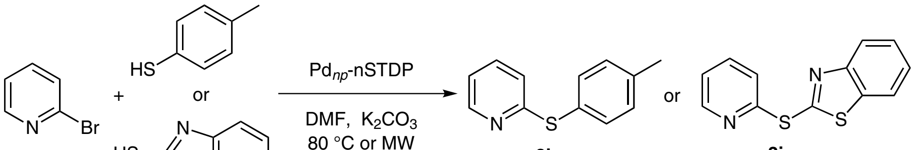
Table 2 C–S Cross-Coupling of Aryl Halides with Aromatic Thiols Catalyzed by Pd_{np}-nSTDP[a]



Entry	R1	X	R2	Thermal conditions		Microwave irradiation	
				Time (h)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	4-Me	I	H	6	92	15	95
2	4-Me	I	4-Me	6	90	15	95
3	4-MeO	I	4-Me	5	95	15	93
4	4-Me	I	4-Ac	5	95	15	95
5	H	I	4-Me	6	95	15	95
6	4-Me	Br	4-Ac	8	93	15	92
7	2-H_2N	Br	4-MeO	12	92	25	94
8	4-Me	Br	H	10	94	20	95
9	H	Br	4-Me	10	91	20	95
10	4-MeO	Br	3-MeO	10	93	20	95
11	4-Me	Br	4-MeO	10	95	20	96
12	4-Me	Br	4-HOC	8	93	20	90
13	4-Me	Cl	2-Me	24	81	45	77
14	4-Me	Cl	4-OHC	18	90	30	88
15	4-Me	Cl	4-Ac	18	90	30	90
16	4-Me	Cl	H	24	85	45	82

[a] Reaction conditions: aryl halide (1 mmol), thiol (1 mmol), K_2CO_3 (1.5 mmol), Pd_{np}-nSTDP (0.05 mol% Pd), DMF (2 mL), 80 °C or MW (230 W, 80 °C).

[b] Isolated yield.



3i 3j

thermal: 8 h, 93% 7 h, 95%

MW: 20 min, 92% 20 min, 95%

Scheme 3 C–S Cross-coupling of 2-bromopyridine with aromatic/heteroaromatic thiols catalyzed by Pd_{np}-nSTDP

nSTDP catalyst under thermal conditions and microwave irradiation to provide the corresponding disulfides in excellent yields (Table 3, 4a–c). Moreover, a series of trisulfides was produced in high yields by threefold C–S cross-coupling reaction of benzene-1,3,5-trithiol, pyrimidine-2,4,6-trithiol or 1,3,5-triazine-2,4,6-trithiol with aryl bromides under thermal conditions and microwave irradiation (Table 3, 4d–j). The structures of the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis. Furthermore, the structure of **4h** was confirmed by X-ray crystallographic analysis (Figure 2; CCDC 948049).

Table 3 Synthesis of Di- and Trisulfides via One-Pot Multifold C–S Cross-Coupling Catalyzed by Pd$_{np}$-nSTDP

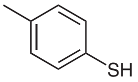
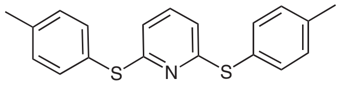
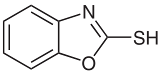
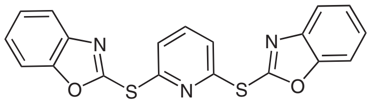
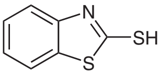
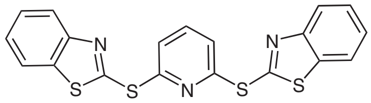
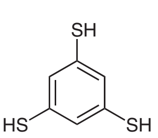
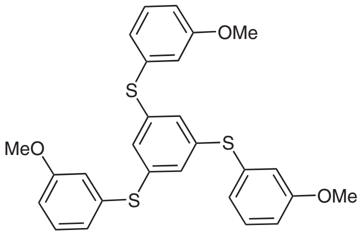
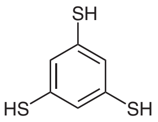
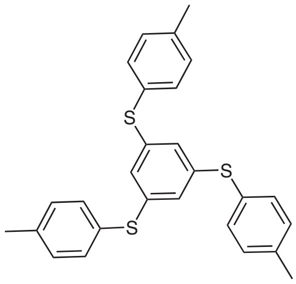
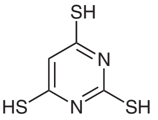
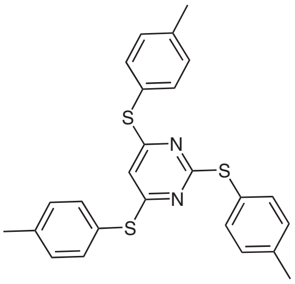
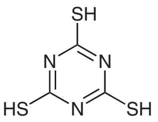
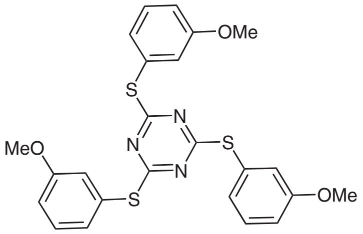
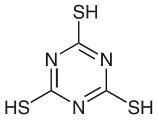
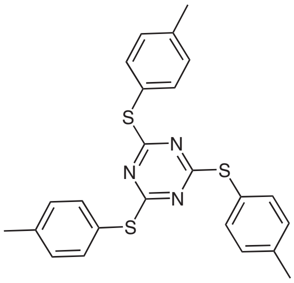
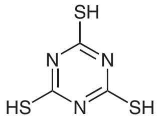
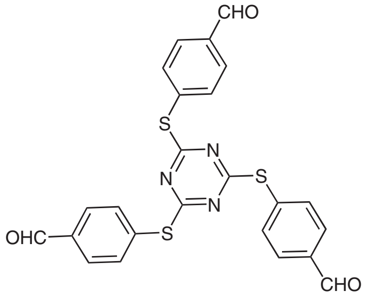
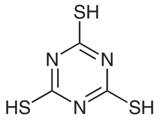
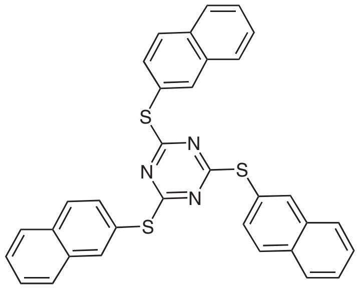
Thiol	Product		Thermal conditions		Microwave irradiation	
			Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
		**4a**[b]	14	90	30	86
		**4b**[b]	24	86	45	90
		**4c**[b]	14	90	30	90
		**4d**[c]	16	88	30	92
		**4e**[c]	14	82	30	85
		**4f**[c]	16	85	30	84
		**4g**[c]	16	88	30	92

Table 3 Synthesis of Di- and Trisulfides via One-Pot Multifold C–S Cross-Coupling Catalyzed by Pd_{np}-nSTDP (continued)

Thiol	Product		Thermal conditions		Microwave irradiation	
			Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
		**4h**[c]	16	86	30	85
		**4i**[c]	16	81	30	89
		**4j**[c]	16	85	30	85

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[a] Isolated yield.

[b] Reaction conditions: 2,6-dibromopyridine (1 mmol), thiol (2 mmol), K_2CO_3 (2.5 mmol), Pd_{np}-nSTDP (0.05 mol% Pd), DMF (3 mL), 80 °C or MW (230 W, 80 °C).

[c] Reaction conditions: aryl bromide (3 mmol), thiol (1 mmol), K_2CO_3 (2.5 mmol), Pd_{np}-nSTDP (0.05 mol% Pd), DMF (3 mL), 80 °C or MW (230 W, 80 °C).

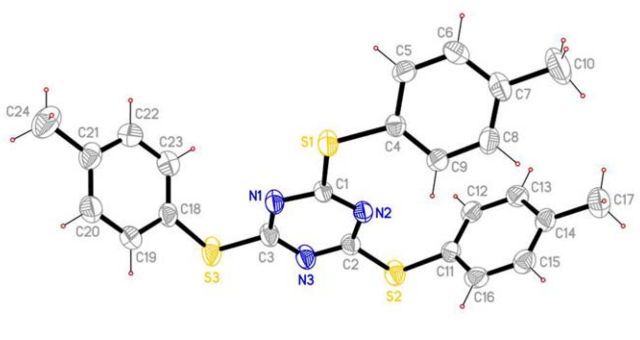

Figure 2 X-ray crystal structure of **4h**

The recovery and reusability of the catalyst, which are very important from commercial and economical points of view, were examined in the coupling of 4-bromoanisole with 4-methylthiophenol. After completion of the reaction, the mixture was cooled to room temperature and diethyl ether (15 mL) was added. The catalyst was separated by centrifugation, dried, and reused for subsequent reactions. As shown in Table 4, the catalyst could be recycled and reused at least six times without any detectable loss of its activity. The analysis of palladium leaching from Pd_{np}-nSTDP catalyst by inductively coupled plasma (ICP) indicated that only a trace amount of palladium (less than 2%) had been leached in the first run.

In conclusion, a highly efficient protocol for the preparation of a wide variety of diaryl sulfides by C–S cross-coupling between aryl/heteroaryl halides and aromatic/heteroaromatic thiols catalyzed by Pd_{np}-nSTDP under thermal conditions and microwave irradiation is described. Furthermore, one-pot multi C–S cross-coupling reactions were successfully performed in the presence of this catalyst affording the corresponding di- and trisulfides in high yields. The high performance as well as recyclability of the catalyst make this method a valuable contribution to the existing methodologies.

Table 4 The Recycling of Pd_{np}-nSTDP in the C–S Cross-Coupling of 4-Bromoanisole with 4-Methylthiophenol[a]

Cycle	Yield (%),[b] thermal conditions	Yield (%),[b] MW irradiation
1	95	96
2	93	96
3	94	95
4	94	93
5	92	94
6	94	91
7	90	92

[a] Reaction conditions: 4-bromoanisole (1 mmol), 4-methylthiophenol (1 mmol), K_2CO_3 (1.5 mmol), Pd_{np}-nSTDP (0.05 mol% Pd), DMF (2 mL), 80 °C or MW (230 W, 80 °C).

[b] Isolated yield.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(22) The microwave system used in these experiments includes the following items: Micro-SYNTH Labstation, equipped with a glass door, a dual magnetron system with pyramid shaped diffuser, 1000 W delivered power, exhaust system, magnetic stirrer, ‘quality pressure’ sensor for flammable organic solvents, and a ATCFO fiber optic system for automatic temperature control.

(23) **General Procedure for the Synthesis of Diaryl Sulfides via C–S Cross-Coupling Catalyzed by Pd_{np}-nSTDP**
In a round-bottom flask equipped with a condenser and a magnetic stirrer, a mixture of aryl halide (1 mmol), aromatic/heteroaromatic thiol (1 mmol), K_2CO_3 (1.5 mmol), and Pd_{np}-nSTDP (0.05 mol% Pd) in DMF (2 mL) was stirred at 80 °C or irradiated with MW (230 W, 80 °C) for the desired time according to Table 2 and Scheme 2. The progress of the reaction was monitored by TLC (eluent: Et_2O–EtOAc, 5:1). After completion of the reaction, the mixture was cooled to r.t., Et_2O (15 mL) was added, and the catalyst was separated by centrifugation. The organic layer was washed with H_2O (2 × 10 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent and purification of the crude product by recrystallization from Et_2O–EtOAc (5:1) afforded the pure product.

(24) **General Procedure for the Synthesis of Disulfides via Twofold C–S Cross-Coupling Catalyzed by Pd_{np}-nSTDP**
A mixture of 2,6-dibromopyridine (1 mmol), aromatic/heteroaromatic thiol (2 mmol), K_2CO_3 (2.5 mmol), and Pd_{np}-nSTDP (0.05 mol% Pd) in DMF (3 mL) was stirred at 80 °C or exposed to MW irradiation (230 W, 80 °C) for the appropriate time as mentioned in Table 3. The reaction progress was monitored by TLC (eluent: Et_2O–EtOAc, 3:1). After completion of the reaction, the mixture was cooled to r.t., EtOAc (10 mL) was added, and the catalyst was separated by centrifugation. The organic phase was washed with H_2O (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting crude product was purified by recrystallization from EtOAc to give the pure product.

(25) **General Procedure for the Synthesis of Trisulfides via Threefold C–S Cross-Coupling Catalyzed by Pd_{np}-nSTDP**
A mixture of aromatic trithiol (1 mmol), aryl bromide (3 mmol), K_2CO_3 (2.5 mmol), and Pd_{np}-nSTDP (0.05 mol% Pd) in DMF (3 mL) was stirred at 80 °C or subjected to MW irradiation (230 W, 80 °C) for the appropriate time according to Table 3. The workup was performed as mentioned for the synthesis of disulfides, and the pure trisulfide was obtained by recrystallization of the crude product from EtOAc.