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Chemo-Controlled Cross-Coupling of Di(hetero)aryl Disulfides with Grignard Reagents: C−C *vs.* C−S Bond Formation

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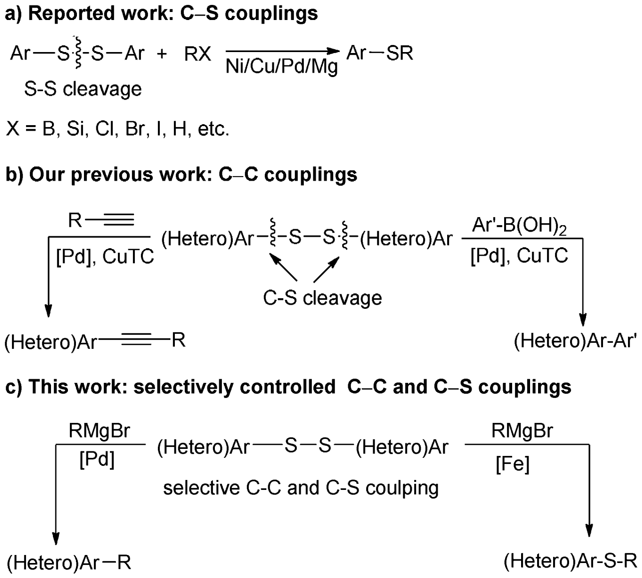
Abstract: A general protocol for the chemoselectivity-controlled C−C and C−S coupling reactions of di(hetero)aryl disulfides with Grignard reagents catalyzed by ferrocene and palladium acetate has been developed. Ferrocene favored the formation of C−S coupled products at low temperature, whereas C−C bond couplings were favored when palladium acetate was used. All the reactions proceeded with excellent chemoselectivity and in good yields under mild conditions, and a library of molecules with pyridine and pyrimidine scaffolds was produced.

Keywords: catalysis; cross-coupling; C−S bond cleavage; di(hetero)aryl disulfides; Grignard reagents

Transition metal-catalyzed C−C and C−heteroatom cross-coupling reactions, as versatile and effective methods in organic synthesis,[1,2] play a significant role in materials chemistry and medicinal chemistry. Generally, such procedures involve the coupling of an activated electrophilic substrate with a nucleophile through a transition metal-mediated cross-coupling reaction. In the past decades, great efforts have been devoted to extending this reaction to different electrophiles. However, in most cases, the electrophiles were confined to aryl and alkenyl halides due to their higher reactivity towards transition metal catalysis.[3] Therefore, the development of new types of electrophiles is still in high demand.[3a]

Currently, organosulfur compounds, present in many biologically active compounds, are widely used as building blocks in organic synthesis and receive considerable attention. Some methods for the construction of C−S bonds have been developed using a variety of aromatic moieties and sulfur-containing reagents.[4,5] Several papers dealing with the reactions of alkenyl, vinyl, and aryl sulfides with Grignard reagents, mediated by Ni or Pd catalysts, and leading to alkenes and biaryl compounds, have been published.[5f,6] Since the pioneering work of Liebeskind, in which Pd/Cu(I) carboxylate was employed as a catalyst to achieve copper-mediated desulfurative coupling of organosulfur compounds, these compounds have attracted considerable interest as alternative candidates for organohalide reagents among synthetic organic chemists in the past decade.[7] Recently, some examples of Rh- or Pd-catalyzed cross-coupling reactions of aryl methyl sulfides with organoboron or organozinc compounds were reported. In these elegant methods, the cross-coupling reaction was rationalized by a C−S cleavage pathway to construct the new C−C bond.[8,9]

It is well known that disulfides (R_2S_2) are an important class of organosulfur reagents for the construction of C−S bonds, and various nucleophilic reagents have been employed to react with disulfides to construct C−S bonds through S−S bond cleavage (Scheme 1, path a).[10–15] However, examples of the coupling between disulfides and Grignard reagents remain limited. In 1997, Rieke reported one example of a cross-coupling between 3-thienylmagnesium iodide and alkyl disulfides, affording 3-alkylthiothiophenes in moderate yield.[11a] Then, Glass and coworkers used *meta*-terphenyl Grignard reagents to react with $MeSSO_2Me$ or PhSSPh, synthesizing unsymmetrical diaryl sulfides.[11b] There are no reports on the utilization of an iron-catalyzed reaction of disulfides with Grignard reagents to realize the construction of a C−C bond, although one paper from Itami et al. described the C−C cross-coupling reaction of alkenyl sulfides with Grignard reagents using $Fe(acac)_3$ as a catalyst.[16] Our group recently devel-



Scheme 1. Strategy for the construction of C–C and C–S bonds through the coupling of disulfides.

oped the palladium- and copper-catalyzed desulfurative cross-coupling reactions of amines, arylboronic acids and alkynes with disulfides as electrophiles to generate C–C and C–N bonds (Scheme 1, path b).[17] It was logical to question whether disulfides could also serve as electrophilic partners in reactions with Grignard reagents to achieve the selective formation of C–C and C–S bonds.

Herein, we report our work on the reaction of di(hetero)aryl disulfides with Grignard reagents, which has resulted in the construction of C–S and C–C bonds under Fe- and Pd-catalyzed conditions, respectively.

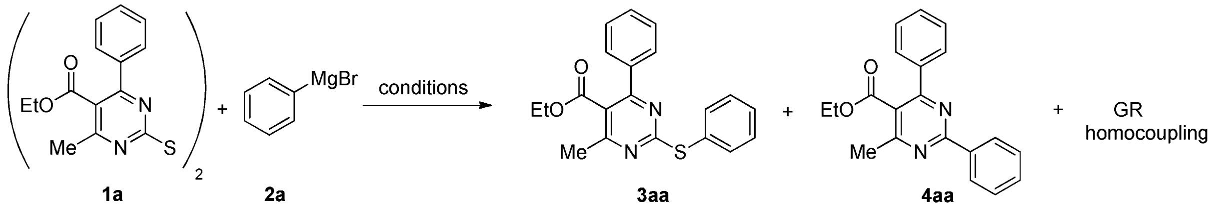
Interestingly, the reaction catalyzed by an Fe catalyst readily gives the C–S bond formation product, whereas the Pd catalyst favors C–C bond formation (Scheme 1, path c). Such a catalyst-based control of the chemoselectivity would provide a highly selective entry into different products from the same substrates. Control of selectivity – the same substrates are applied for different products – remains one of the most important challenges in organic chemistry.[18] Among the methods that have been employed, control of selectivity by catalysts has been proven to be very beneficial.[19]

Initially, our studies were focused on the selectivity of C–C and C–S couplings. The reaction of **1a** with an excess amount of PhMgBr (**2a**) was used as a model reaction to test the possibility of selective C–C and C–S coupling. First, Fe catalysts were applied, and the use of $Fe(acac)_3$ resulted in both C–C and C–S coupling products **4aa** and **3aa** in 8% and 48% yield, respectively (entry 1), while $FeCl_3$ gave **3aa** as the sole product in 42% yield with formation of the homocoupling product of the Grignard reagent (GR homocoupling) (entry 2). Similar to $Fe(acac)_3$, ferrocene gave both **3aa** and **4aa**, and higher temperatures and longer times improved the yield of the C–C coupling product (entries 3–5). It was discovered that ferrocene at a lower temperature (–20 °C) produced the most promising results, providing **3aa** in 74% yield in a shorter time (entries 6 and 7). Lowering the temperature (entry 8) or raising the equivalents of **2a** (**1a**:**2a** = 1:4.8) (entry 9) did not provide better results. Use of an excess of Grignard reagent decreased the selectivity, resulting in a slightly lower yield of the C–S coupling product (entry 9 compared with entry 7). With respect to its outstanding performance and lower price, ferrocene was chosen as a better catalyst for the C–S coupling reaction (entry 7), although $Pd(OAc)_2$ was also an efficient catalyst favoring **3aa** (entry 10).

With the best reaction conditions for C–S bond formation established, C–C bond formation was considered. From the results in Table 1, higher temperatures favored C–C bond formation, but the yield was poor (Table 1, entry 5). To reverse the selectivity, with the purpose of highly selective formation of the C–C coupling product **4aa**, different Pd catalysts were then screened. The use of $PdCl_2$ with a molar ratio of **1a:2a** = 1:2.4 gave the C–S coupled **3aa** as the major product (entry 11). However, an alteration of the molar ratio to 1:4.8 resulted in the formation of **4aa** in 57% yield with 79:21 selectivity (entry 12). When $Pd(OAc)_2$, $Pd(PPh_3)_4$, or $PdCl_2(dppf)_2$ was employed as the catalyst (entries 13–16), the selectivity was reversed. A good yield (73%) and selectivity (97:3) were obtained at 0 °C to room temperature for 2 h (entry 13). The yield of **4aa** decreased at higher temperatures, with the formation of the homocoupled product of **2a** (entry 17). Then, solvent screening was performed, and 1,4-dioxane was better than THF (entry 18). Finally, a trial of the reaction in the absence of a catalyst and ligand was performed, and **3aa** was obtained as the only product in 35% yield (entry 19).

Then, the generality of this C–S cross-coupling was investigated under the optimized Fe-catalyzed conditions (Table 1, entry 7). In general, a variety of di(hetero)aryl disulfides smoothly reacted with different Grignard reagents (RMgBr), leading to the C–S cross-coupling products (Scheme 2). Both electron-rich magnesium bromides, such as methyl and 2-methoxyphenyl, and electron-poor magnesium bromides, such as 4-chlorophenyl, underwent C–S cross-couplings to deliver the products **3ab–3ah** in good yields. Thienyl and 1-naphthyl groups could also be tolerated in this reaction. Similarly, a series of diheteroaryl disulfides (**1**) with various Grignard reagents (**2**), including ethyl-, butyl-, hexyl-, heptyl-, and nonylmagnesium bromides, selectively generated C–S coupled products **3ai–3am** in 71–79% yield. The use of

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst/Ligand	**1a:2a**[c]	Temp. [°C]	Time	Yield [%][b]		Selectivity
					3aa	**4aa**	**3aa:4aa**
1	$\mathrm{Fe(acac)_3}$/–	1:4.8	0–r.t.	4 h	4	8	86:14
2	$\mathrm{FeCl_3}$/–	1:4.8	0–r.t.	4 h	42	<2	95:5
3	ferrocene/–	1:4.8	0–r.t.	4 h	55	12	82:18
4	ferrocene/–	1:4.8	0–r.t.	24 h	51	16	76:24
5	ferrocene/–	1:4.8	0–65	24 h	48	24	67:33
6	$\mathrm{fe(acac)_3}$/–	1:2.4	−20	2 h	63	<5	93:7
7	**ferrocene/–**	**1:2.4**	**−20**	**0.5 h**	**74**	**<2**	**97:3**
8	ferrocene/–	1:2.4	−40	0.5 h	65	<2	97:3
9	ferrocene/–	1:4.8	−20	0.5 h	70	10	88:12
10	$\mathrm{Pd(OAc)_2}$/DPE-Phos	1:2.4	0–r.t.	0.5 h	71	8	89:11
11	$\mathrm{PdCl_2/PPh_3}$	1:2.4	0–r.t.	4 h	66	7	90:10
12	$\mathrm{PdCl_2/PPh_3}$	1:4.8	0–r.t.	4 h	15	57	21:79
13	$\mathrm{Pd(OAc)_2}$/DPE-Phos	1:4.8	0–r.t.	4 h	<2	73	3:97
14	$\mathrm{Pd(OAc)_2}$/DPE-Phos	1:4.8	0–r.t.	2 h	<2	73	3:97
15	$\mathrm{Pd(PPh_3)_4}$	1:4.8	0–r.t.	2 h	5	62	7:93
16	$\mathrm{PdCl_2(dppf)_2}$	1:4.8	0–r.t.	2 h	<5	65	7:93
17	$\mathrm{Pd(OAc)_2}$/DPE-Phos	1:4.8	65	4 h	<2	41	5:95
18[d]	**$\mathrm{Pd(OAc)_2}$/DPE-Phos**	**1:4.8**	**0–r.t.**	**2 h**	**<2**	**78**	**2:98**
19	–	1:2.4	r.t.	2 h	35	–	–

[a] *Conditions:* 0.2 mmol **1a**, **2a** (1.0 M in THF), catalyst (5 mol%), in 3 mL THF, under N_2 atmosphere, unless otherwise noted.

[b] Isolated yield based on disulfide **1a** (2 mmol).

[c] Molar ratio of **1a** to **2a**.

[d] The reaction was carried out in 2 mL THF and 1 mL 1,4-dioxane.

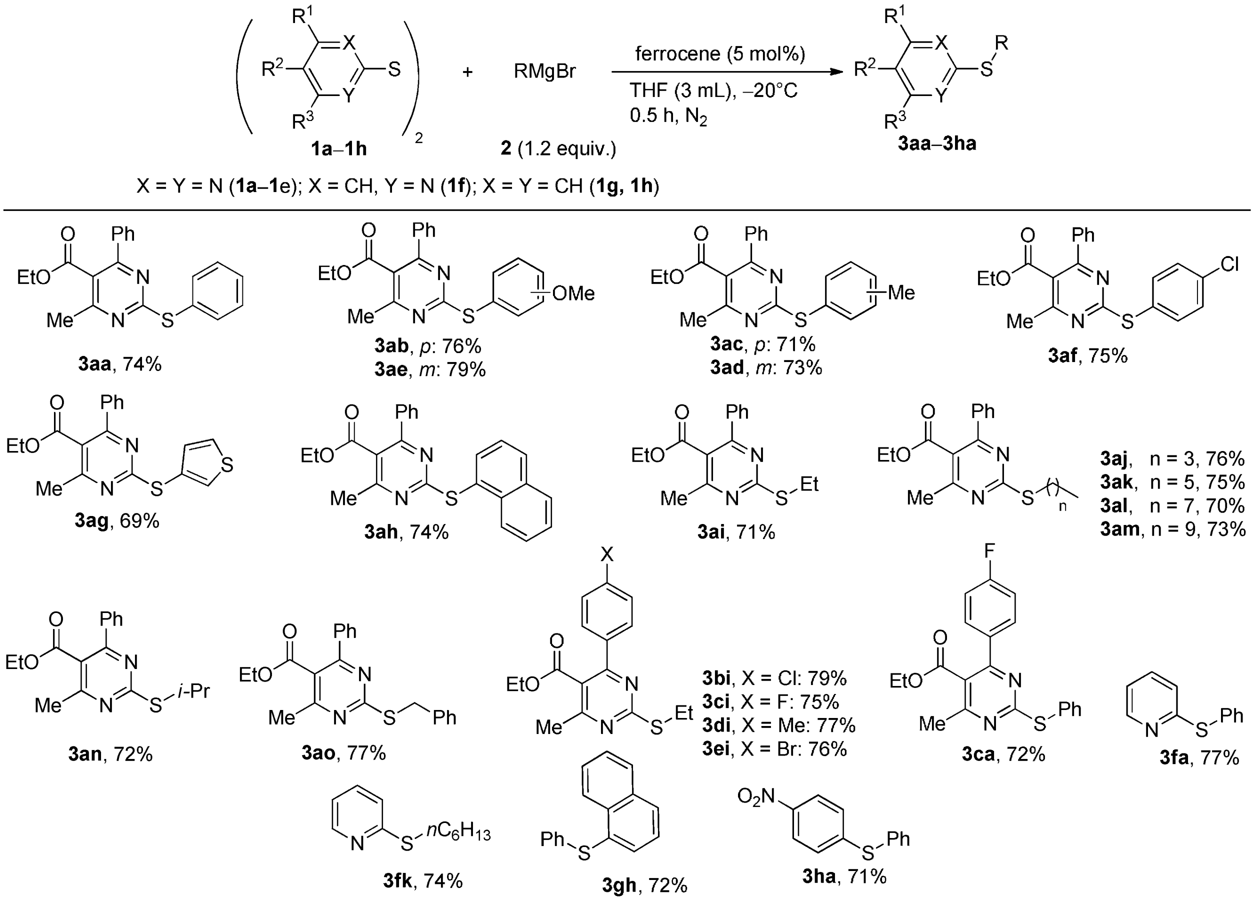
branched isopropylmagnesium bromide and the more reactive benzylmagnesium bromide did not decrease the efficiency of the reaction, giving the desired **3an–3ao** in good yields. Notably, 1,2-di(pyridin-2-yl) disulfide and aryl disulfides also resulted in 71–77% yields of **3fa–3ha**.

Next, the optimized Pd-catalyzed conditions were explored to test the generality of the C–C coupling (Scheme 3). Different diheteroaryl disulfides (**1**) could be well tolerated in this process, leading to the desired products **4**. Different Grignard reagents with both aromatic and aliphatic groups gave the expected products **4aa–4ca** in good yields, whereas the 1,2-di(pyridin-2-yl) disulfide reacted with phenyl- and hexylmagnesium bromide smoothly at 65 °C for 6 h, yielding the desired products **4fa** and **4fk** in lower yields. Compared with the tested nitrogen-containing diheteroaryl disulfides, aryl disulfides showed much lower reactivity. For example, the reaction of 1,2-diphenyl disulfide and 1,2-bis(4-nitrophenyl) disulfide with arylmagnesium bromides did not result in any C–C coupled product under similar reaction conditions, but the C–S coupled products **3gh** and **3ha** were obtained as unique products, showing a lower activity in this process. This reactivity of disulfides was also observed in a previous study.[17b]

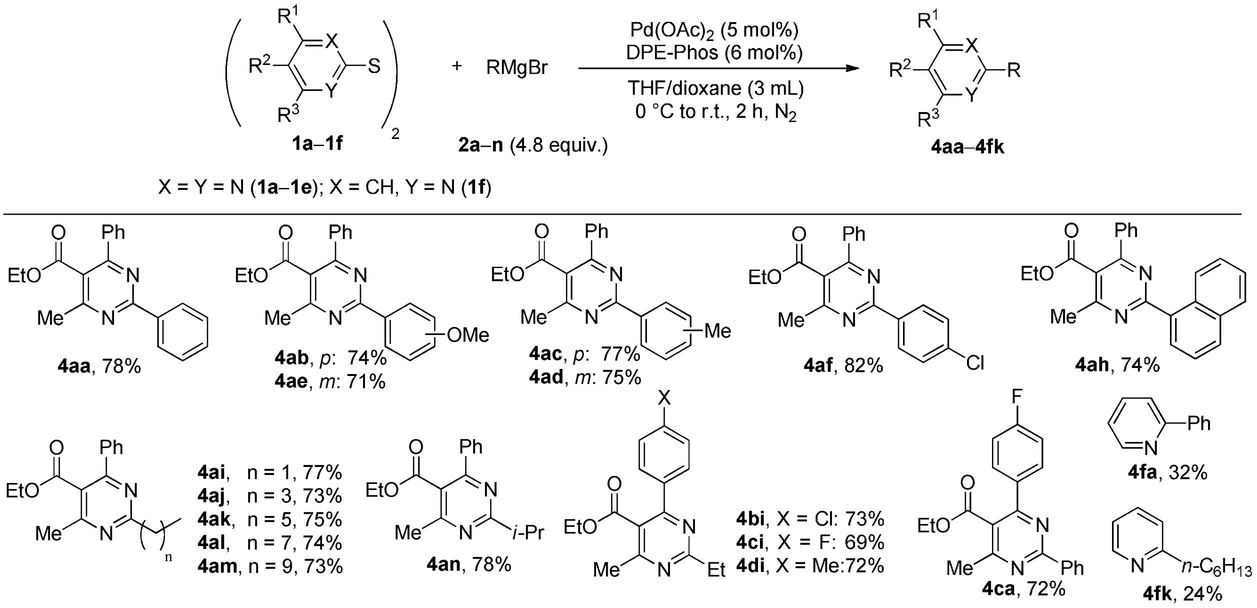
After the tests with symmetrical diheteroaryl disulfides, an unsymmetrical disulfide (**1i**) substrate was examined. When the reaction of **1i** with **2a** was performed under the C–C coupling conditions, a mixture of **4aa** (70%), **4fa** (8%), and the C–S coupling product **3fa** (48%) was obtained (Scheme 4).

In addition to the disulfide employed, the C–S coupled product **3aa** can further react with **2a** under the standard C–C coupling conditions. The C–C coupling product **4aa** was isolated in 71% yield together with the homocoupling product **2a** (Scheme 5). This result implied that the C–S coupled product **3** might be an important intermediate for the C–C coupling product.

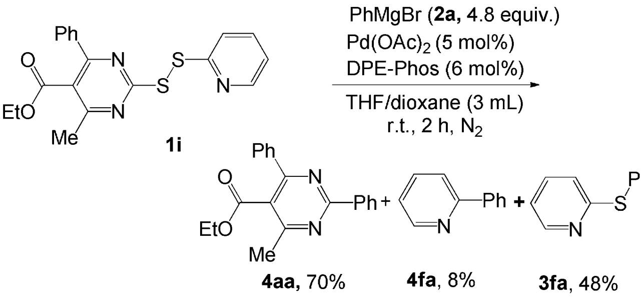
The control experiments used iodobenzene instead of the Grignard reagent to compare the reactivity of a Grignard reagent with a halogen substituent (Scheme 6). The reaction of disulfide **1a** with iodobenzene was performed under the C–S (Path a) and



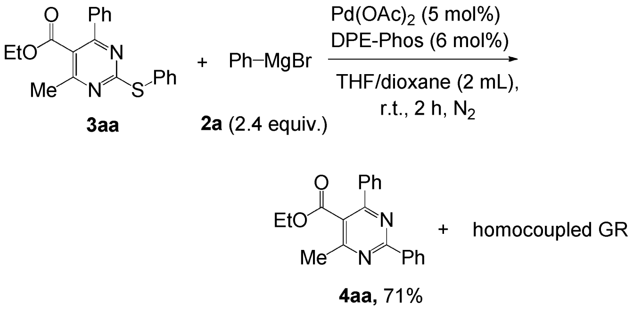
Scheme 2. Scope of the ferrocene-catalyzed C–S cross-coupling of di(hetero)aryl disulfides and Grignard reagents.



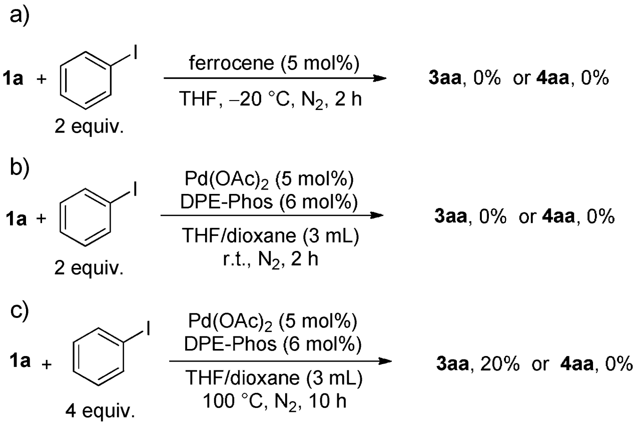
Scheme 3. Scope of the Pd-catalyzed C–C cross-coupling reaction between diheteroaryl disulfides **1a–1f** and Grignard reagents **2**.



Scheme 4. Selective cross-coupling of unsymmetrical disulfide **1i**.



Scheme 5. Identifying the components of the cross-coupling reaction.



Scheme 6. Reactivity of iodobenzene in the cross-coupling with disulfide **1a**.

C–C (Path b) coupling conditions. Unfortunately, no desired product **3aa** was obtained, and the starting materials were recovered. When the reaction that was catalyzed by $Pd(OAc)_2$ in the presence of DPE-Phos was heated at 100 °C for 10 h, only a 20% yield of C–S coupled product **3aa** was obtained without forming the C–C coupled product **4aa** (Path c). These results revealed that disulfides are favored over aryl halides in the C–C/C–S cross-coupling reactions.

Generally, the mechanism of iron(III or II)-catalyzed cross-coupling of aryl halides with Grignard reagents has been studied thoroughly. Low-valent iron species (low-valent iron complexes) have been characterized and it has been proven that they are the most active catalysts for the cross-coupling. However, it remains largely unknown if and how low-valent organoiron species react with Grignard reagents in solution.[20] Alternatively, a mechanism based on addition/elimination was also proposed.[16] Recently, Neto proposed that the cation $[Fe(C_5H_5)]^+$ ($m/z = 121$), formed as a consequence of ferrocene decomposition, might be a stronger Lewis acid and capable of catalyzing the Biginelli reaction.[21] However, the cation $[Fe(C_5H_5)]^+$ ($m/z = 121$) was not detected by ESI-MS in the reaction of **1a** with **2a** at room temperature. We surmised that a similar addition/elimination mechanism might be possible in the ferrocene-catalyzed C–S coupling reaction. Finally, we have to stress that the exact mechanism is yet to be established with more experimental and theoretical studies.

In conclusion, we have developed simple and efficient ferrocene- and $Pd(OAc)_2$-catalyzed cross-couplings of di(hetero)aryl disulfides with Grignard reagents, providing C–S and C–C bonds with excellent chemoselectivity under mild conditions. Unlike the previous reports, Grignard regents were used as nucleophiles, giving a high selectivity between C–C and C–S bond formation and producing a library of molecules with pyrimidine and pyridine scaffolds in good isolated yields. The selectivity with different metal catalysts may be worthy of investigation. Further studies, including synthetic applications of this reaction and the effects of the catalyst on the selectivity, are being carried out in this group.

Experimental Section

General Procedure for the Synthesis of Thioethers 3 (3aa–3gh)

Under a nitrogen atmosphere, **1** (0.2 mmol, 109 mg) and ferrocene (5 mol%, 1.9 mg) were added to a Schlenk tube. The tube was stoppered and degassed with nitrogen three times. Distilled THF (3 mL) was added by syringe and the mixture was stirred for 15 min. Then, the Grignard reagent **2** (0.48 mmol, 2.4 equiv., 1.0 M solution in THF) was added under nitrogen using a syringe. The reaction mixture was allowed to stir for approximately 0.5 h at –20 °C and the reaction was monitored by TLC analysis. Then, 2 mL water were added to the mixture to quench the reaction, the organic components were extracted with ethyl acetate and the resulting extract was evaporated under vacuum and further purified by column chromatography on silica gel with petroleum ether/ethanol (30:1) to give the corresponding products **3**.

General Procedure for the Desulfurative Coupling Process (4aa–4fk)

Under a nitrogen atmosphere, **1** (0.2 mmol, 109 mg), $Pd(OAc)_2$ (5 mol%, 2.4 mg), and DPE-Phos (6 mol%, 6.6 mg) were added to a Schlenk tube. The tube was stoppered and degassed with nitrogen three times. Then, **2** (1 mmol) and the solvent (THF/dioxane, 3 mL) were added by syringe, and the mixture was stirred for 15 min. Next, the mixture was cooled to 0 °C and the Grignard reagent **2** (0.96 mmol, 4.8 equiv., 1.0 M solution in THF) was added under nitrogen using a syringe at a low flow rate. Then, the reaction mixture was allowed to stir for approximately 2 h at room temperature, and the reaction was monitored by TLC analysis. Then, 2 mL of water were added to the mixture to quench the reaction, the organic components were extracted with ethyl acetate, the resulting extract was evaporated under vacuum and the residue further purified by column chromatography on silica gel with petroleum ether/ethanol (45:1) to give the corresponding C–C coupling products.

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