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Ni-catalyzed reductive cross-couplings of diaryl disulfides with aryl bromides for biaryl synthesis through C–S bond cleavage†

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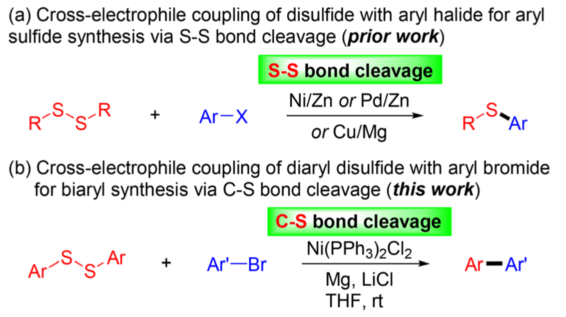
In previous reports, the cross-couplings of diaryl disulfides with aryl halides in the presence of transition metal catalysts (*e.g.*, Ni and Cu) and metal mediators (*e.g.*, Mg and Zn) usually led to the corresponding aryl sulfides *via* old S–S bond cleavage and new C–S bond formation. In the present study, we found that the reductive cross-couplings of diaryl disulfides with aryl bromides proceeded *via* unusual C–S bond cleavage in the presence of a nickel catalyst, magnesium, and lithium chloride in THF at room temperature, leading to a variety of biaryls in modest to good yields. In addition, the reaction could be scaled up with ease. Mechanistic studies showed that the reaction possibly proceeds *via* the *in situ* production of an arylmagnesium compound as a reaction intermediate *via* LiCl-facilitated Mg insertion into aryl bromide. Most importantly, the combinatory use of the Ni(II) catalyst and Mg mediator is key to the unusual cleavage of the C–S bond in diaryl disulfide to form the corresponding arylnickel(II) species, which serves as another important intermediate in the present desulfurative cross-coupling reaction.

Introduction

In the past two decades, transition metal-catalyzed cross-electrophile couplings[1] involving the direct utilization of two distinct electrophiles have attracted extensive attention from researchers, because the cross-electrophile couplings bypass the use of scarcely available, comparatively expensive, and sensitive organometallic compounds,[2] which are usually widely employed in traditional redox-neutral coupling reactions. As a result, cross-electrophile couplings, which are characterized by operational simplicity, step-economy, and cost-effectiveness, serve as a powerful and straightforward synthetic tool for facilely accessing a wide diversity of organic molecules, as the coupling electrophiles are not only broadly abundant in chemical feedstocks[1,3] but also relatively more stable and easier to handle when compared to commercial or pre-generated organometallics, which should be operated with extreme caution.

Among the various cross-electrophile couplings reported to date, the transition metal-catalyzed direct cross-couplings of disulfides with aryl halides under reductive conditions in the presence of a reducing metal *via* old S–S bond cleavage and new C–S bond formation have been proven to be efficient methods for the synthesis of aryl sulfides.[4–9] For example, it has been disclosed that aryl sulfides could be readily prepared *via* the direct cross-couplings of aryl iodides or bromides with disulfides under reducing conditions with the use of either a Ni(II)/Zn,[4] Pd/Zn,[5] or Cu(I)/Mg[6] catalytic system (Scheme 1a). Besides, the cross-electrophile couplings of disulfides with



Scheme 1 Cross-electrophile couplings of disulfides with aryl halides.

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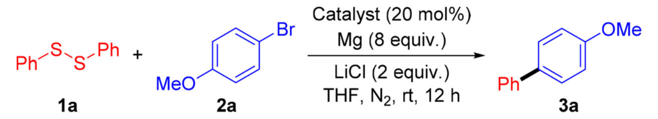
other organohalide variants (*e.g.*, NHPI esters and dialkyl carbonates) for aryl sulfide assembly under reductive conditions have also been described by the groups of Wang and others.[7] Although the reductive cross-couplings of disulfides with other aryl halides (or equivalents) have made considerable advancements, all these precedents proceeded *via* the cleavage of the relatively reactive S–S bond. In contrast, the activation of the comparatively less reactive C–S bond in disulfides in a reductive environment has remained unexplored thus far. As a continued endeavor of our group in developing effective reductive cross-couplings of two different electrophilic reagents,[10] we herein describe an efficient reductive cross-coupling of diaryl disulfide with aryl bromide with the assistance of nickel as the catalyst, magnesium as the reducing mediator, and lithium chloride as the additive. The reactions proceeded smoothly at room temperature in THF *via* unusual C–S bond activation to afford diverse biaryls instead of aryl sulfides in moderate to good yields (Scheme 1b). Noteworthily, biaryls are important structural moieties that are widely present in naturally occurring products,[11] chiral ligands,[12] bioactive compounds,[13] and functionalized materials.[14]

Results and discussion

To begin with, diphenyl disulfide **1a** (1 equiv.) and 1-bromo-4-methoxybenzene (**2a**, 8 equiv.) were selected as substrates to optimize the reaction conditions by using magnesium (8 equiv.) as the reducing metal and lithium chloride (2 equiv.) as the additive in THF at room temperature for 12 h in the presence of various metallic catalysts (Table 1). It was gratifying to find that, among the different transition metal catalysts examined (entries 1–6), including $FeCl_3$, $CuCl_2$, $CrCl_3$, $Co(PPh_3)_2Cl_2$, $Pd(OAc)_2$, and $Ni(PPh_3)_2Cl_2$, the use of $Ni(PPh_3)_2Cl_2$ as the catalyst could deliver the desired cross-coupled product **3a** in 80% NMR yield (entry 6). However, a subsequent survey of other nickel catalysts did not improve the reaction performance further (entries 7–16). In addition, investigation of other solvents (*e.g.*, DME, 1,4-dioxane, 2-MeTHF, ^{t}BuOMe, ^{i}Pr$_2$O, tetrahydropyran, DMF, and DMA) and metal promoters (such as Fe, Mn, Al, Pb, Bi, and In) showed that THF and Mg are still the solvent and metal of choice for the present cross-coupling reaction (see Tables S1 and S2 in the ESI† for details). Evaluation of other reaction parameters by decreasing the amount of both **2a** and Mg from 8 equiv. to 6 equiv., reducing the loading of $Ni(PPh_3)_2Cl_2$ from 20 mol% to 10 mol%, or conducting the reaction at other temperatures (60 °C or 0 °C) all resulted in eroded product yields (entries 17–20). Moreover, control experiments indicated that the reaction could not take place in the absence of either the Ni catalyst or Mg turnings (entries 21 and 22), and the product yield decreased considerably when LiCl[15] was removed from the reaction system (entry 23). It should be mentioned that the product yield was calculated based on the transfer of both phenyl groups in substrate **1a** to the final product **3a**. As a result, a large excess of **2a** and Mg (8 equiv.) should be utilized in the transformation in order to obtain a satisfactory product yield (entry 6). Furthermore, the use of aryl bromide (**2a**) as the coupling partner is necessary for the efficient progress of the present cross-electrophile coupling, as the employment of less reactive 1-chloro-4-methoxybenzene as a substrate failed to produce any desired product **3a** and the utilization of relatively reactive 1-iodo-4-methoxybenzene as a substrate only produced the desired product **3a** in 13% NMR yield (mainly gave the homo-coupling product derived from 1-iodo-4-methoxybenzene as the major byproduct).

Table 1 Optimization of reaction conditions by using various catalysts[a]



Entry	Catalyst	Yield[b] (%)
1	$FeCl_3$	34
2	$CuCl_2$	8
3	$CrCl_3$	<5
4	$Co(PPh_3)_2Cl_2$	24
5	$Pd(OAc)_2$	61[c]
6	**$Ni(PPh_3)_2Cl_2$**	**80 (77)**[d]
7	$NiCl_2$	27
8	$NiBr_2$	41
9	NiI_2	45
10	$Ni(acac)_2$	42
11	$Ni(PCy_3)_2Cl_2$	70
12	$Ni(Py)_4Cl_2$	39
13	$NiCl_2·DME$	26
14	$Ni(dppe)Cl_2$	62
15	$Ni(dppf)Cl_2$	55
16	$Ni(OTf)_2$	67
17	$Ni(PPh_3)_2Cl_2$	52[d,e]
18	$Ni(PPh_3)_2Cl_2$	62[f]
19	$Ni(PPh_3)_2Cl_2$	56[g]
20	$Ni(PPh_3)_2Cl_2$	26[h]
21	$Ni(PPh_3)_2Cl_2$	0[i]
22	—	0
23	$Ni(PPh_3)_2Cl_2$	34[j]

[a] The reactions were performed at room temperature for 12 h under a nitrogen atmosphere by using **1a** (0.5 mmol, 1 equiv.), **2a** (4 mmol), catalyst (20 mol%, 0.1 mmol), magnesium turnings (4 mmol), and LiCl (1 mmol) in anhydrous THF (2 mL). [b] Yields were determined by NMR analysis of the crude reaction mixture after work-up by using 1,4-dimethoxybenzene as an internal standard. [c] Using 5 mol% $Pd(OAc)_2$. [d] Isolated yield. [e] Using 6 equiv. of both **2a** and Mg. [f] Using 10 mol% $Ni(PPh_3)_2Cl_2$. [g] At 60 °C instead of rt. [h] At 0 °C instead of rt. [i] Without Mg. [j] Without LiCl.

With the optimal reaction conditions in hand, we proceeded to examine the scope of the desulfurative cross-coupling reactions with respect to aryl bromides **2**. As shown in Table 2, the reductive cross-couplings of disulfides **1a** or **1j** with aryl bromides **2b–d** containing electron-withdrawing trifluoromethyl, trifluoromethoxy, and fluoro groups in the aryl ring proceeded well under optimized conditions to give the corresponding products **3b–d** in 49–57% yields. Likewise, aryl bromides **2e–o** derived from electron-rich aryl rings bearing electron-donating groups (*e.g.*, MeO, Me, MeS, OTBS, OCH_2O, OCH_2CH_2O, NMe_2, and NPh_2) worked equally well under the

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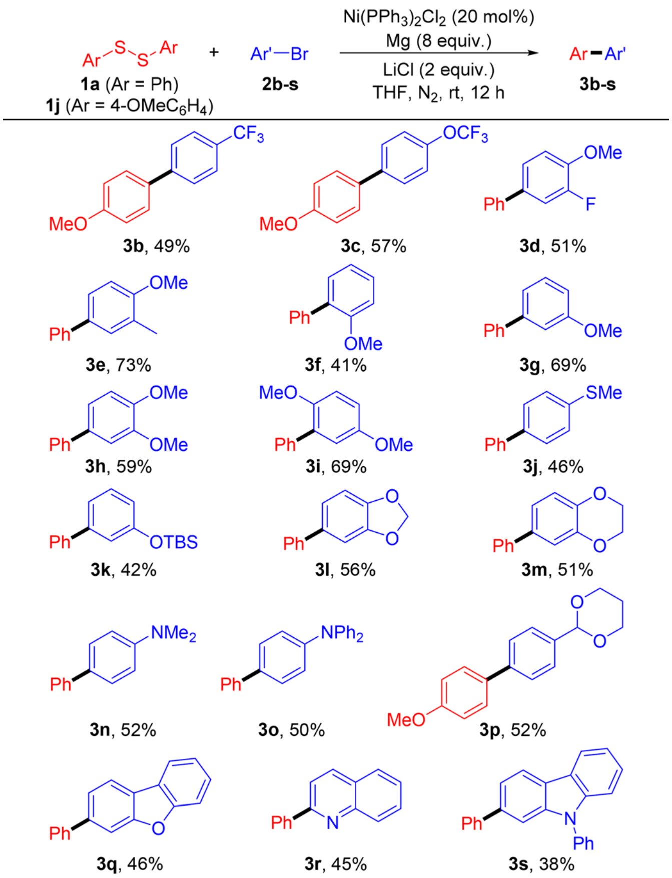
Table 2 Substrate scope study by using various aryl bromides[a,b]



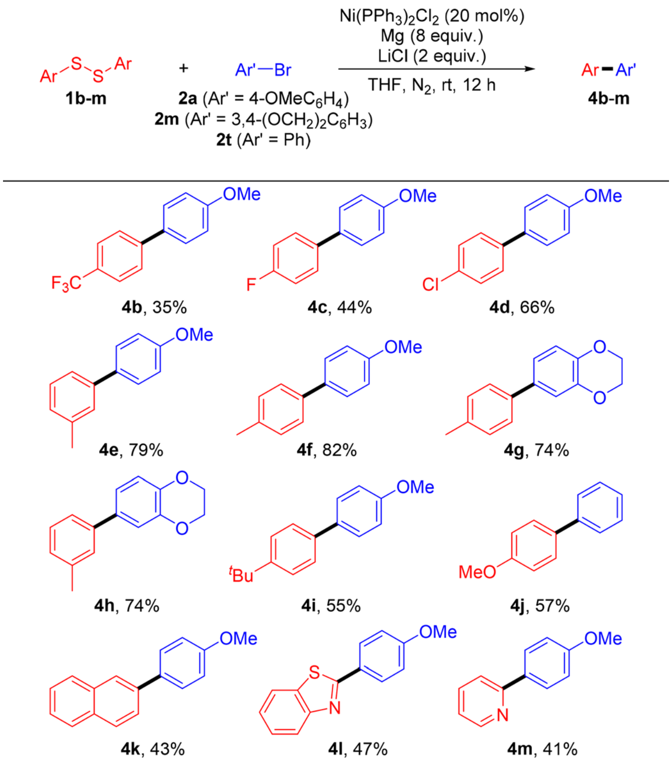
[a] The reactions were performed at room temperature for 12 h under a nitrogen atmosphere by using **1a** or **1j** (0.5 mmol), **2b–s** (4 mmol), Ni$(PPh_3)_2Cl_2$ (20 mol%, 0.1 mmol), magnesium turnings (4 mmol), and LiCl (1 mmol) in anhydrous THF (2 mL). [b] Isolated yield.

established conditions to afford the desired products **3e–o** in moderate to good yields. Notably, aryl bromides **2f** and **2i** possessing a methoxy group at the *ortho* position of the benzene ring could be amenable to the reaction, irrespective of steric hindrance. Acetal-containing aryl bromide **2p** as a masked aryl aldehyde could be employed as well, which reacted with disulfide **1j** to give the expected product **3p** in 52% yield. Pleasingly, heteroaromatic bromides **2q–s** possessing dibenzofuran, quinoline, and carbazole moieties were demonstrated to be suitable starting materials for the present transformations, leading to the target products **3q–s** in acceptable yields. Remarkably, functional groups or substituents, including CF_3, OCF_3, F, OMe, Me, MeS, OTBS, OCH_2O, OCH_2CH_2O, NMe_2, NPh_2, and acetal, could be well tolerated under the reaction conditions. However, aryl bromides containing electron-withdrawing groups (*e.g.*, CN, NO_2, and COOEt) could not take part in the current protocol, presumably because of their poor compatibility with the reactive magnesium metal and/or the possibly *in situ* generated arylmagnesium intermediate in the reaction. In addition, replacing the aryl bromide with an alkyl bromide or iodide as the coupling partner also failed to give the corresponding cross-coupled product.

Next, we continued to evaluate the substrate generality of the present cross-electrophile couplings by utilizing a spectrum of diaryl disulfides **1** as starting materials. As outlined in Table 3, not only disulfides **1b–d** with electron-withdrawing groups (*e.g.*, CF_3, F, and Cl) could be successfully utilized in the cross-couplings with aryl bromide **2a** but also disulfides **1e–j** possessing electron-donating methyl, *tert*-butyl, and methoxy substituents were proven to be appropriate substrates for the reactions to provide the corresponding products **4e–j** in 55–82% yields. In addition, naphthyl-derived disulfide **1k** reacted in the same manner, leading to the desired product **4k** in a moderate yield. Heteroaryl-based disulfides **1l** and **1m** derived from benzo[*d*]thiazole and pyridine proved to be good reactants as well, and the anticipated cross-coupled products **4l** and **4m** were obtained in 47% and 41% yields, respectively. However, the reaction with the use of dialkyl disulfide (*e.g.*, dipropyl disulfide) as the substrate could not produce any desired coupling product, presumably because of the poorer reactivity of dialkyl disulfide as compared with diaryl disulfide.

Subsequently, we proceeded to investigate the scalability of the reaction as well as the reaction mechanism. It was observed that the scale-up synthesis of biaryl **3a** on a 5 mmol

Table 3 Substrate scope study by using various diaryl disulfides[a,b]



[a] The reactions were performed at room temperature for 12 h under a nitrogen atmosphere by using **1b–m** (0.5 mmol), **2a** or **2m** or **2t** (4 mmol), Ni$(PPh_3)_2Cl_2$ (20 mol%, 0.1 mmol), magnesium turnings (4 mmol), and LiCl (1 mmol) in THF (2 mL). [b] Isolated yield.

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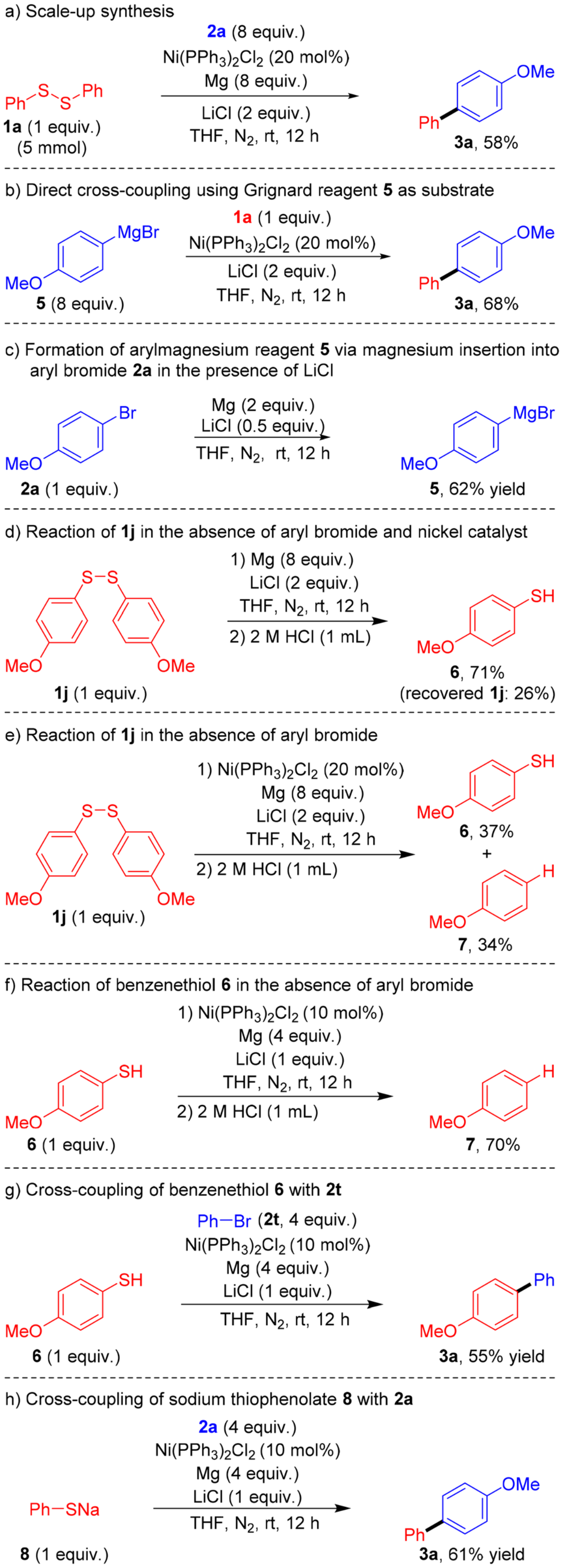
scale could also work well under the well-established conditions to generate the target product **3a** in 58% yield (Scheme 2a). In addition, the direct nickel-catalyzed cross-coupling of arylmagnesium reagent **5** with disulfide **1a** could also proceed well to furnish the cross-coupled product **3a** in 68% yield, indicating that the arylmagnesium reagent, which is possibly generated from the *in situ* insertion of Mg into aryl bromide, might be the pivotal intermediate of the present protocol (Scheme 2b). We also performed the insertion reaction of Mg into aryl bromide **2a** in the presence of LiCl, which provided the corresponding aryl Grignard reagent **5** in 62% yield, thereby confirming the *in situ* formation of the arylmagnesium reagent in the present coupling reaction (Scheme 2c). Moreover, treatment of disulfide **1j** with Mg and LiCl (in the absence of aryl bromide and the nickel catalyst) followed by acid hydrolysis could deliver the corresponding benzenethiol **6** in 71% yield along with the recovery of the unreacted substrate **1j** in 26% yield (Scheme 2d), implying that Mg might induce the cleavage of the S–S bond to afford the corresponding ArS^- species. Interestingly, when the same reaction was performed in the presence of $Ni(PPh_3)_2Cl_2$, benzenethiol **6** was furnished in 37% yield, along with the production of the desulfurated product **7** in 34% yield (Scheme 2e). This result revealed that a Ni(0) species formed *in situ* through the Mg-mediated reduction of Ni(II) possibly serves as a robust transition metal catalyst which is capable of undergoing oxidative addition into the C–S bond in the *in situ* generated ArS^- species to produce the corresponding reactive ArNi(II) intermediate; after acidic workup, the eventual product **7** could be delivered. We also applied the Ni(II)/Mg system directly to benzenethiol **6**, and the desulfurated product **7** could also be obtained in 70% yield (Scheme 2f), which further confirmed the feasibility of the *in situ* production of the reactive arylnickel(II) species by means of Ni(0) insertion into the C–S bond during the course of the reaction. Furthermore, we also directly utilized benzenethiol **6** and sodium thiophenolate **8** as substrates to cross-couple with aryl bromides **2t** and **2a**, respectively (Scheme 2g and h). As expected, the coupling reactions also worked to give the corresponding products **3a** in 55% and 61% yields, respectively. These results further demonstrated the possibility of the *in situ* formation of the ArNi(II) intermediate *via* the oxidative addition of Ni(0) into the C–S bond of ArS^- species.

On the basis of the above mechanistic study and previous reports,[1,10] a plausible reaction mechanism similar to the Kumada reaction is proposed (Fig. 1). In the beginning, an ArS^- species (possibly in the form of $(ArS)_2Mg$ or $ArSMg_{1/2}$) is generated from the reduction of diaryl disulfide by Mg.[7b,8i,16] Next, an $L_nNi(0)$ complex **A**, which is also produced *via* the reduction of $Ni(PPh_3)_2Cl_2$ by magnesium, readily inserts into the C–S bond of the ArS^- species to form an ArNi(II) intermediate **B**. Subsequently, an arylmagnesium compound **2′**, which is formed through LiCl-facilitated insertion of Mg into aryl bromide **2**,[15] undergoes transmetallation with organonickel(II) **B** to give a diarylnickel(II) intermediate **C**. After subsequent reductive elimination, **C** is transformed into biaryl **3** or **4**, accompanied by the regeneration of the robust $L_nNi(0)$



Scheme 2 Scale-up synthesis and mechanistic studies.

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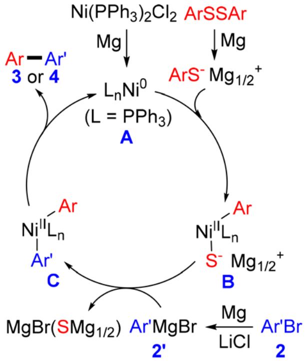
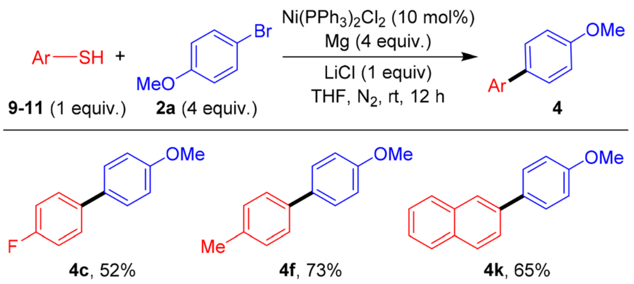


Fig. 1 Tentatively proposed mechanism.



Scheme 3 Cross-coupling of aryl thiols **9–11** with **2a**.

complex **A**. It should be mentioned that other possibilities could not be excluded at the present stage.

Finally, we also examined the cross-electrophile couplings of aryl thiols **9–11** with aryl bromide **2a** under nickel catalysis. Gratifyingly, the reactions also proceeded effectively in the presence of the Ni catalyst and Mg/LiCl to provide the corresponding biaryls **4c**, **4f**, and **4k** in reasonable yields (Scheme 3).

Conclusion

In summary, an efficient reductive cross-coupling of diaryl disulfide with aryl bromide, which proceeded *via* an unusual C–S bond cleavage with the aid of nickel as a transition metal catalyst and magnesium as a reducing mediator, was successfully accomplished. The reactions proceeded efficiently in the presence of LiCl in THF at ambient temperature, enabling facile access to a range of structurally varied biaryls in moderate to good yields. The reaction could be subjected to scale-up synthesis. Mechanistic investigations revealed that the *in situ* generated arylmagnesium reagent and arylnickel(II) species, derived from the oxidative addition of Mg into aryl bromide in the presence of LiCl and the insertion of *in situ* produced robust Ni(0) (generated by Mg-promoted reduction of Ni(II)) into the C–S bond of diaryl disulfide, respectively, might function as the two pivotal intermediates of the present coupling reaction. Currently, the applications of the Ni/Mg system in C–S bond activation and other reductive cross-coupling reactions are ongoing in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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