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"Thiol-free synthesized" and sustainable thiolating synthons for nickel-catalyzed reductive assembly of sulfides with high efficiency†

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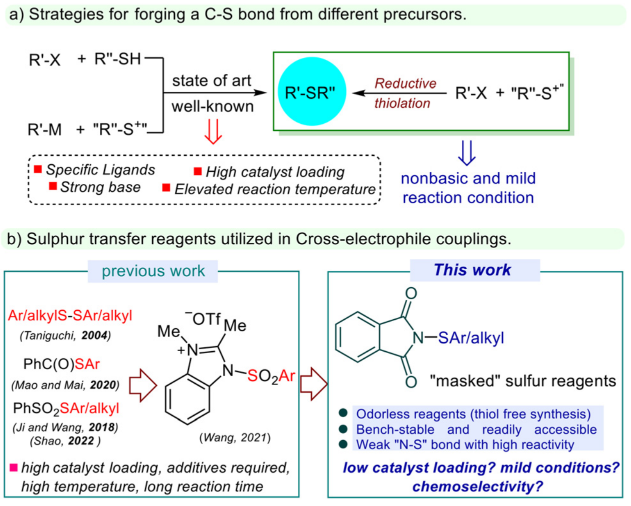
Unsymmetrical sulfides are widely found in the pharmaceutical industry, organic synthesis, and materials science. As a result, it will be of great significance to discover mild and efficient methodologies and electrophilic sulfur transfer reagents, avoiding the general employment of odorous and toxic thiols. Herein, we present a highly efficient nickel-catalyzed cross-electrophile coupling of organic halides with "thiol-free" synthesized *N*-thiophthalimides as direct thiolating surrogates. This practical strategy features extremely low catalyst loading, good functional group tolerance and diverse downstream synthesis, enabling the construction of a broad range of sulfides under "base-free" conditions. Notably, a modified and more efficient reductive thiolation of disulfides was developed by employing our mild reaction conditions.

Introduction

Sulfides, especially unsymmetrical sulfides, are central scaffolds that have found numerous applications in biological chemistry,[1] organic synthesis,[2] and materials science.[3] As a consequence, it will be of great value to forge C–S bonds under mild reaction conditions. Classic nucleophilic substitutions of organic halides by thiols[4] and advanced methods *via* radical pathways promoted by photo[5] or electro-chemistry[6] have already been achieved during the last few decades. However, odorous and toxic thiols, strong bases and/or harsh reaction conditions such as high temperature were the major limitations in the above strategies (Scheme 1a). To overcome the drawbacks of the limited thiols, several powerful electrophilic sulphur transfer reagents have been well developed.[7] However, a majority of them were indeed prepared from the corresponding thiols or disulfides, and step-economy was sacrificed (Scheme 1b). Organolithium and organomagnesium reagents are air and moisture sensitive though they have been well utilized in the transition-metal-catalyzed cross-couplings with electrophilic sulphur synthons.[7a–d]

Nevertheless, electrophilic sulphur reagents could participate in metal-catalyzed cross-electrophile couplings[8] with various carbon atom-centred electrophiles (Scheme 1b).[9] From this viewpoint, thiol-free synthesized cationic thiolating reagents instead of toxic thiols will be a promising alternative in the construction of C–S bonds. Very recently, Wang and coworkers disclosed that shelf-stable benzimidazolium sulfonamides (IMDN-SO_2R) which were prepared from readily accessible sulfonyl chlorides could act as novel cationic thiolating precursors for nickel-catalyzed cross-electrophilic coupling with various organic halides (Scheme 1b, left).[9d]

Selective formation of cross-coupled products has been the long-standing issue existing in cross-electrophile coupling



Scheme 1 Selective strategies and thiolating reagents for C–S bond formation.

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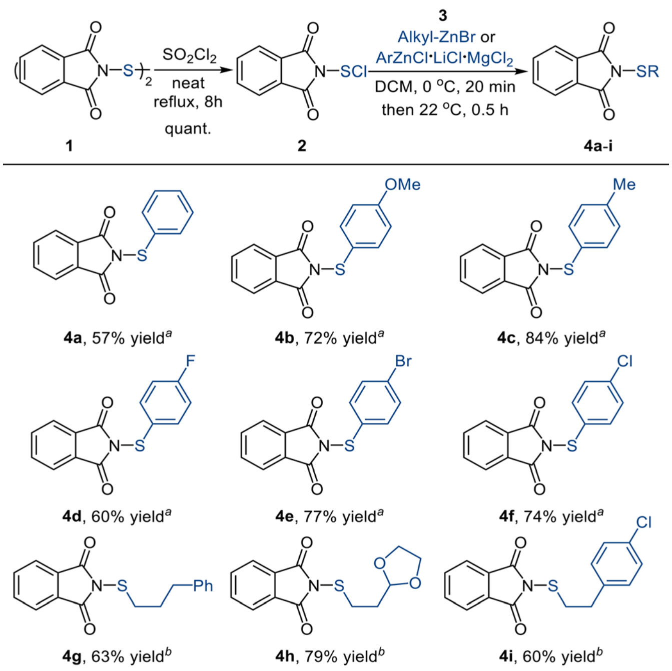
because of the competition of oxidative addition and transmetalation between the two coupling partners.[8a,b] As a result, the disulfides are generated more easily as the major side products and indeed, homo-coupling of the electrophilic sulphur reagents is always observed in many cases. Moreover, a long reaction time and/or elevated reaction temperature were required to achieve good conversions and the scope was limited (Scheme 1b, left).[9b,c]

Based on the significant achievements in the reductive cross-coupling for assembling C–C/C–X (X = Si, Ge, S, Se) bonds[10] with our continuing interest[11] in the development of efficient reagents in synthetic chemistry, we speculate that *N*-thiophthalimides can serve as ideal precursors due to the weak "N–S" bond and easy modification of the reactivity by replacement of substituents on the reagent's skeleton (Scheme 1c). *N*-Thiophthalimides are also air and moisture stable solids and can be further subjected to cross-electrophilic coupling. Thus, this work will provide direct information on "$N–S^+$" type reagents in the reductive thiolation, while the activated "$N–S^+$" intermediate was only confirmed by HRMS in the previous study.[9d] Thus, a facile and "thiol-free" method[12] for preparation of such powerful reagents will directly enable the synthesis of functionalized sulfides under non-basic reaction conditions. More importantly, a sustainable strategy by recycling phthalimide as the original starting material after simple work-up will be developed, providing a good alternative as the electrophile in the C–S bond formation. Herein, we report our efforts on the synthesis of diversified *N*-thiophthalimides especially alkyl substituted ones from organozinc reagents[13] followed by transformation towards the reductive cross-coupling with a variety of organic halides.

Results and discussion

Inspired by the pioneering work of Cornella's group on the synthesis of *N*-arylthiophthalimides,[14] we first tested thiol-free synthesis from easily accessible starting materials. Simply refluxing di(1-phthalimidyl)disulfane **1** in SO_2Cl_2 gave *N*-(chlorosulfenyl)phthalimide **2** in quantitative yield, while continuous bubbling of Cl_2 gas for a long time[15] or an additive such as pyridine[16] were required in previous studies (Table 1). On treatment with freshly-made organozinc reagents for a short time, a number of *N*-arylthiophthalimides containing hydrogen (**4a**), OMe (**4b**), Me (**4c**), F (**4d**), Br (**4e**), and Cl (**4f**) were formed in moderate to high yields after simple silica gel chromatography purification (Table 1). Notably, alkyl organozinc reagents easily generated from the corresponding alkyl bromides in the presence of zinc could react with compound **2** as well, generating challenging *N*-alkylthiophthalimides (**4g–i**) which were rarely explored[14] in moderate yields. Finally, these *N*-thiophthalimides were isolated as shelf-stable solids and could be further stored in a refrigerator for several months without detectable decomposition according to ^1H NMR spectroscopy.

Table 1 Thiol-free synthesis of *N*-thiophthalimides[a]

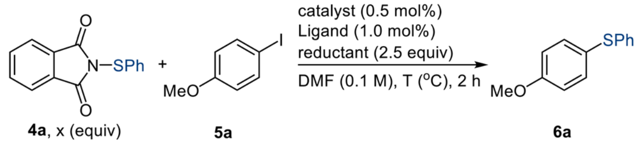


4a, 57% yield[a]
4b, 72% yield[a]
4c, 84% yield[a]
4d, 60% yield[a]
4e, 77% yield[a]
4f, 74% yield[a]
4g, 63% yield[b]
4h, 79% yield[b]
4i, 60% yield[b]

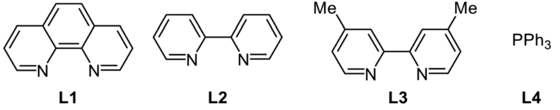
[a] Reaction conditions: **2** (1.67 mmol), organozinc reagent **3a–f** (1.0 equiv.), CH_2Cl_2 (2.5 mL) at 0 °C for 20 min, and then at 22 °C for 0.5 h. [b] Reaction conditions: **2** (1.2 equiv.), organozinc reagent **3g–i** (3.3 mmol), CH_2Cl_2 (2.5 mL) at 0 °C for 20 min, and then at 22 °C for 2.0 h. Isolated yields.

With these readily available reagents in hand, we then investigated the nickel catalyzed reductive thiolation of aryl (hetero) halides with *N*-thiophthalimides we synthesized since the nickel catalyst exhibited a unique ability in such kind of transformations. *N*-Phenylthiophthalimide **4a** and 4-iodoanisole **5a** were chosen as the model substrates for the reaction optimization. Fortunately, the transformation proceeded rather well in the presence of $NiCl_2(PPh_3)_2$ as the catalyst, 1,10-phen **L1** as the ligand, and zinc as the reductant, furnishing thiolated product **6a** in >99% yield (Table 2, entry 1). As a result, it has been one of the most efficient protocols until now in the reductive thiolation. However, other transition-metal salts such as $Cu(OTf)_2$, $CrCl_3$ and $PdCl_2(PPh_3)_2$ were ineffective (Table 2, entries 2–4). Bipyridine type ligands showed better catalytic activity, enabling the formation of sulfide **6a** in high yield while other ligands such as PPh_3 failed to afford the product (Table 2, entries 5–7). To our delight, only 0.5 mol% $NiCl_2(PPh)_2$ and 1.0 mol% 1,10-phen exhibited excellent catalytic activity to give the sulfide **6a** in quantitative yield (Table 2, entry 8). Lower conversion of 4-iodoanisole **1a** was obtained when Mn was employed as the reductant or only 1.0 equiv. of zinc power were used (Table 2, entries 9 and 10). Moreover, no desired product was detected in the absence of zinc with full recovery of the starting materials (Table 2, entry 11). A slightly lower yield of **6a** was achieved when the reaction was conducted in a shorter time (Table 2, entry 12). Switching DMF to less polar solvents such as THF and CH_2Cl_2 led to low

Table 2 Optimization of the reaction conditions for the nickel-catalyzed reductive coupling of **4a** with **5a** [a]



Entry	Catalyst	Ligand	Reductant	Solvent	*x* (equiv.)	*T* (°C)	Yield (%)
1	$NiCl_2(PPh_3)_2$	**L1**	Zn	DMF	2.0	50	>99
2	$Cu(OTf)_2$	**L1**	Zn	DMF	2.0	50	<5
3	$CrCl_3$	**L1**	Zn	DMF	2.0	50	<5
4	$PdCl_2(PPh_3)_2$	**L1**	Zn	DMF	2.0	50	<5
5	$NiCl_2(PPh_3)_2$	**L2**	Zn	DMF	2.0	50	88
6	$NiCl_2(PPh_3)_2$	**L3**	Zn	DMF	2.0	50	92
7	$NiCl_2(PPh_3)_2$	**L4**	Zn	DMF	2.0	50	<5
8	$\mathbf{NiCl_2(PPh_3)_2}$	**L1**	**Zn**	**DMF**	**2.0**	**22**	**>99**
9	$NiCl_2(PPh_3)_2$	**L1**	Mn	DMF	2.0	22	<5
10[b]	$NiCl_2(PPh_3)_2$	**L1**	Zn	DMF	2.0	22	<5
11	$NiCl_2(PPh_3)_2$	**L1**	—	DMF	1.2	22	<5
12[c]	$NiCl_2(PPh_3)_2$	**L1**	Zn	DMF	1.2	22	98
13	$NiCl_2(PPh_3)_2$	**L1**	Zn	THF	1.2	22	<5
14	$NiCl_2(PPh_3)_2$	**L1**	Zn	CH_2Cl_2	1.2	22	<5
15	$NiCl_2(PPh_3)_2$	**L1**	Zn	DMAc	1.2	22	>99
16[d]	$NiCl_2(PPh_3)_2$	**L1**	Zn	DMF	1.2	22	<5



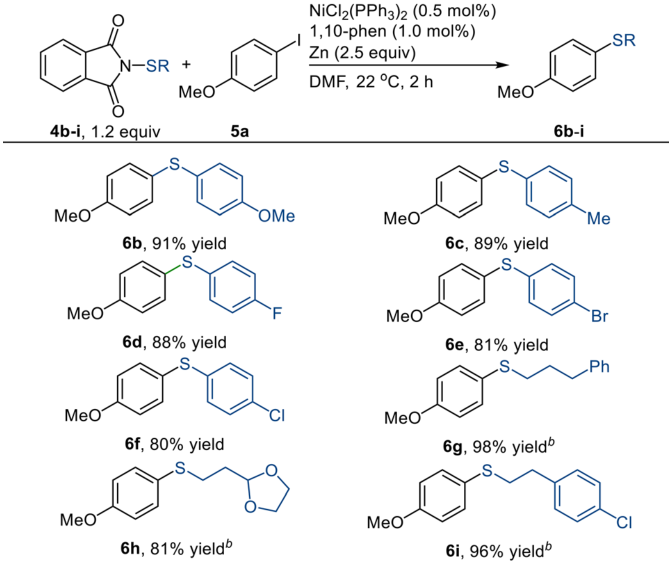
[a] For entries 1–7: catalyst (2.5 mol%), ligand (3.0 mol%); for entries 8–16: $NiCl_2(PPh_3)_2$ (0.5 mol%), ligand **L1** (1.0 mol%). [b] 1.0 equiv. of Zn was used. [c] 1 h. [d] Under air.

conversion, but DMAc, an analogue of DMF, gave the final sulfide **6a** in comparable yield (Table 2, entries 13–15). It was found that the reaction was totally inhibited in the presence of air (Table 2, entry 16).

Under identified conditions, the generality of the current methodology in the reductive thiolation was studied (Table 3). Pleasingly, a variety of functional groups including simple hydrogen (**6a**), methoxyl (**6b**), methyl (**6c**), fluoride (**6d**), bromide (**6e**), and chloride (**6f**) were well tolerated and unsymmetrical sulfides were obtained in moderate to high yields. Moreover, the reaction of alkyl *N*-thiophthalimides (**4g–i**) occurred as well when harsher reaction conditions were employed, affording the alkyl aryl sulfides (**6g–i**) in moderate to good yields.

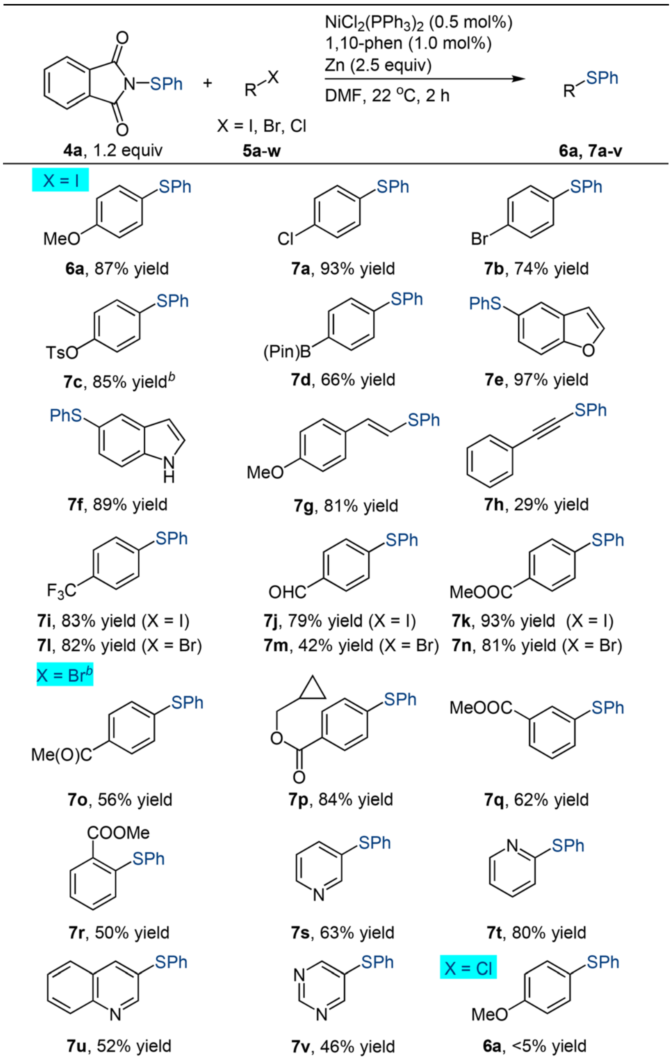
Encouraged by the previously successful attempts, we next explored the versatility of carbon atom-centred electrophiles such as organic halides. It was found that the reaction of aryl (hetero) iodides proceeded smoothly in the presence of only 0.5 mol% $NiCl_2(PPh_3)_2$, 1.0 mol% 1,10-phen **L1**, and 2.5 equiv. of zinc, and the thiolated products were generated in reasonable yields after 2 h at 22 °C. Aryl iodides with functional groups such as methoxyl, chloride, bromide, and trifluoromethyl reacted to deliver the corresponding sulfides **6a**, **7a–b**, and **7i** in high yields (Table 4). Interestingly, substrates bearing the tosyl group **7c** and the boronate group **7d** at the *para*-position of the benzene ring were compatible with the reaction conditions, allowing the downstream synthesis of

Table 3 Scope of the nickel-catalyzed reductive coupling of **4b–i** with **5a** [a]



[a] Reaction conditions: **5a** (0.5 mmol), reagent **4a–f** (1.2 equiv.), $NiCl_2(PPh_3)_2$ (0.5 mol%), 1,10-phen (1.0 mol%), Zn (2.5 equiv.), and DMF (2.5 mL) at 22 °C for 2 h. Isolated yields are reported. [b] Reaction conditions: **5a** (0.5 mmol), reagent **4g–i** (2.0 equiv.), $NiCl_2(PPh_3)_2$ (5.0 mol%), 1,10-phen (10 mol%), Zn (3.0 equiv.), and DMF (0.5 mL) at 120 °C for 4 h. Isolated yields.

Table 4 Scope of the nickel-catalyzed reductive coupling of **4a** with **5a–w**[a]

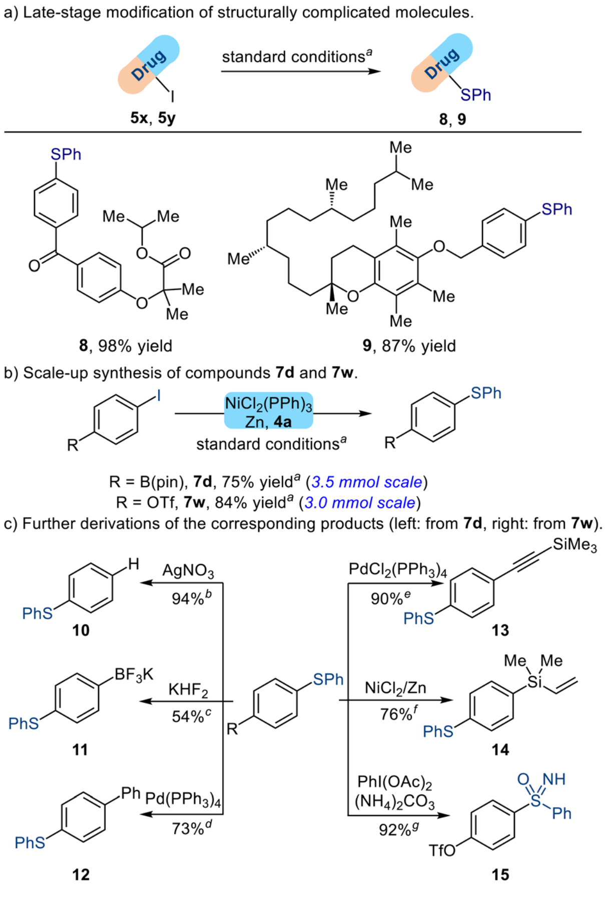


6a, 87% yield
7a, 93% yield
7b, 74% yield
7c, 85% yield[b]
7d, 66% yield
7e, 97% yield
7f, 89% yield
7g, 81% yield
7h, 29% yield
7i, 83% yield (X = I)
7l, 82% yield (X = Br)
7j, 79% yield (X = I)
7m, 42% yield (X = Br)
7k, 93% yield (X = I)
7n, 81% yield (X = Br)
7o, 56% yield
7p, 84% yield
7q, 62% yield
7r, 50% yield
7s, 63% yield
7t, 80% yield
7u, 52% yield
7v, 46% yield
6a, <5% yield

[a] Reaction conditions: **5a–w** (0.5 mmol), reagent **4a** (1.2 equiv.), NiCl$_2$(PPh$_3$)$_2$ (0.5 mol%), 1,10-phen (1.0 mol%), Zn (2.5 equiv.), and DMF (2.5 mL) at 22 °C for 2 h. [b] NiBr$_2$ (2.5 mol%), 1,10-phen (5.0 mol%), NaI (2.0 equiv.), Zn (3.0 equiv.), and DMF (2.5 mL) at 80 °C for 8 h. Isolated yields.

functional derivatives. Heteroaryl iodides including benzofuran **7e** and indole **7f** were engaged in the reductive cross-coupling with electrophilic thiolating reagent **4a** in high yields. Aryl iodides bearing carbonyl groups such as aldehyde **7j** and ester **7k** which were sensitive toward nucleophilic organolithium and organomagnesium reagents reacted facilely to lead to the construction of C–S bonds efficiently. It was discovered that alkenyl and alkynyl iodides **7g–h** could readily convert into the thiolated products, resulting in the formation of the coupled products in acceptable yields. Notably, similar results were also achieved when aryl(hetero) bromides were applied as the coupling partners under the slightly modified reaction conditions. Reactions of aryl bromides containing the ester installed at the different position of the benzene ring as well as strained cyclopropane substituted one led to the coupled products **7l–r** in reasonable yields. Moreover, a series of hetero(aryl) bromides could be successfully transformed into the desired sulfides **7s–v** in moderate to good yields, illustrating the applicability of this mild methodology. Unfortunately, the reaction of 4-choloroanisole **5w** failed to give any coupled product and further optimization of the reaction conditions was needed.

To further show the potential applications of the current protocol, late-stage thiolation of biologically complicated drug molecules and downstream functionalizations were conducted. Drug molecules fenofibrate and vitamin E derived aryl iodides could be successfully incorporated to afford the thiolated analogues **8** and **9** in high yields (Scheme 2a). A scale-up reaction proceeded smoothly, furnishing the coupled sulfides **7d** and


a) Late-stage modification of structurally complicated molecules.

b) Scale-up synthesis of compounds **7d** and **7w**.

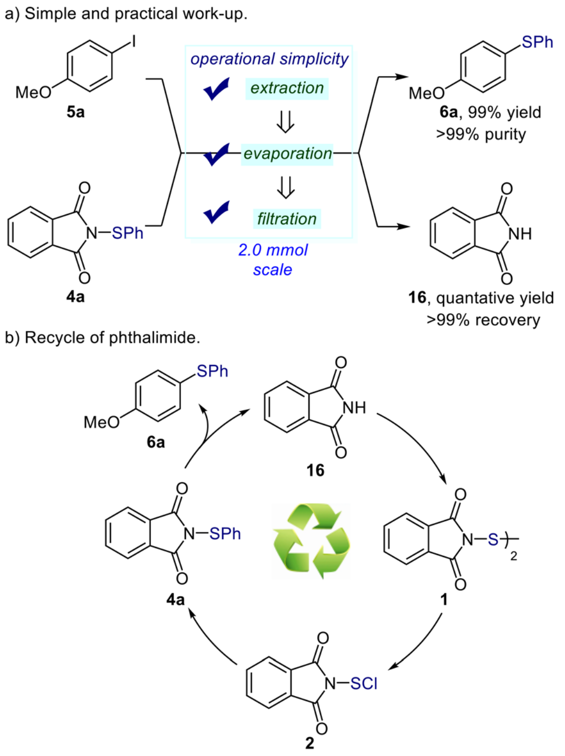
c) Further derivations of the corresponding products (left: from **7d**, right: from **7w**).

Scheme 2 Late-stage modification of complex molecules and synthetic applications. [a] **5x–y** (0.5 mmol) or **5d** and **5z** (0.3 mmol) were used under the optimized conditions for **6a**. [b] **7d** (0.20 mmol), AgNO$_3$ (0.060 equiv.), Et$_3$N (1.0 equiv.), EtOH/H$_2$O at 80 °C for 1 h in air. [c] **7d** (0.20 mmol), KHF$_2$ (5.0 equiv.), MeCN/H$_2$O at 30 °C for 9 h. [d] **7d** (1.2 equiv.), PhI (0.20 mmol), Pd(PPh$_3$)$_4$ (10 mol%), K$_2$CO$_3$ (2.0 equiv.), dioxane at 100 °C for 12 h. [e] **7w** (0.50 mmol), alkyne (1.2 equiv.), PdCl$_2$(PPh$_3$)$_2$ (5.0 mol%), K$_2$CO$_3$ (2.0 equiv.), Et$_3$N/DMF at 100 °C for 12 h. [f] **7w** (0.50 mmol), NiCl$_2$(PPh$_3$)$_2$ (10 mol%), 5,5′-dimethyl-2,2′-bipyridine (20 mol%), Mn (2.5 equiv.), chlorosilane (2.0 equiv.), DMF at 22 °C for 24 h. [g] **7w** (0.50 mmol), PhI(OAc)$_2$ (2.5 equiv.), (NH$_4$)$_2$CO$_3$ (2.0 equiv.), MeOH at 22 °C for 12 h. Isolated yields.

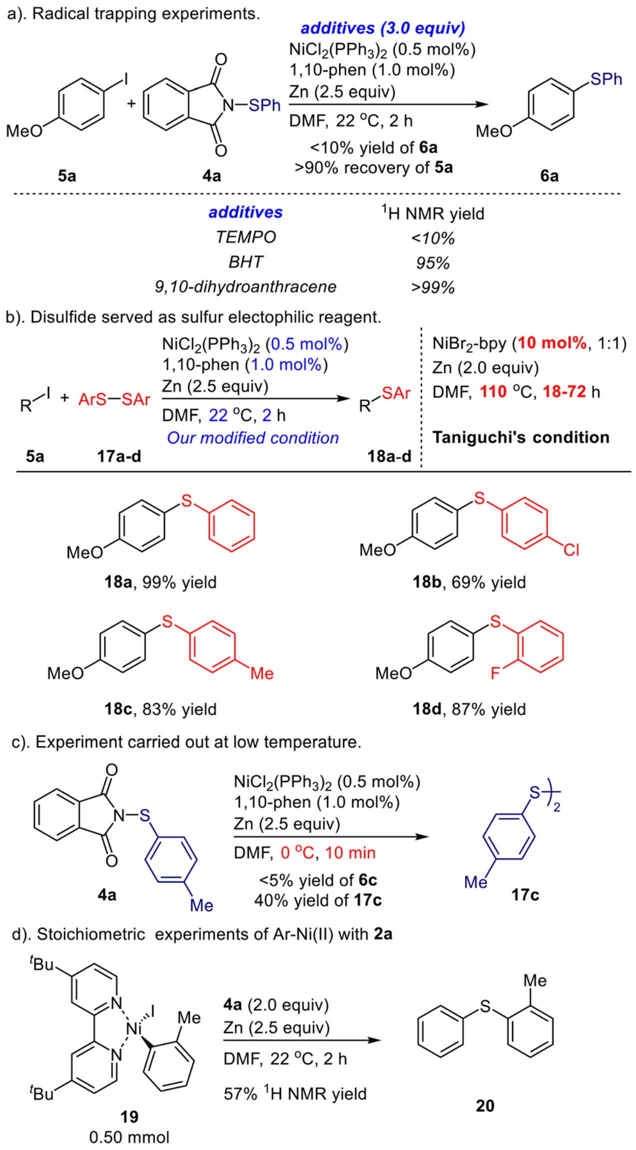
7w with excellent efficiency (Scheme 2b). Further transformations of the products were also explored since both of them were useful building blocks in organic synthesis (Scheme 2c). Thus, the boronic acid ester (R-Bpin) **7d** could readily convert into more stable trifluoroborate potassium salts (R-BF_3K) **11** *via* cleavage of the C–B bond.[17] Suzuki coupling as well as protonation occurred to deliver the corresponding product **12** in moderate to good yields. Likewise, the derivative **7w** could react with the terminal alkyne *via* classic Sonogashira coupling, generating the corresponding product in 90% yield. Based on Shu's pioneering work,[18] compound **7w** underwent a practical cross-electrophile coupling with vinyl chlorosilanes to forge a C(sp^2)–Si bond. Moreover, the same compound could convert into sulfoximine **15** in high yield by treatment of (diacetoxyiodo)benzene and ammonium carbonate.[11a]

This mild method also features sustainable utilization of the original starting material phthalimide **16**, which was isolated in 99% yield with >99% recovery by filtration after evaporation of the extracted solvents (Scheme 3a). Meanwhile, the thiolated product **6a** was obtained directly in 99% yield with >99% purity from the crude mixture after simple work-up on a 2.0 mmol scale (for more details, see the ESI†). *N*-Phenylthiophthalimide **4a**, the coupling partner, could be fully synthesized in three steps from the recycled phthalimide (Scheme 3b). Therefore, it provided a sustainable and practical strategy to construct a series of unsymmetrical sulfides under mild reaction conditions.

To better understand the reaction mechanism of this method, we then carried out the following experiments including radical trapping, a control reaction and a stoichiometric reaction of the ArNi(II)I complex. First of all, no desired product **6a** was detected with >90% recovery of **5a** when TMEPO, a general radical scavenger, was added to the mixture (Scheme 4a). While in the cases of BHT and 9,10-dihydroanthracene, the desired product **5a** could still be obtained in 95% and >99% ^{1}H NMR yield, respectively, indicating that a radical pathway might not be involved. To probe whether disulfides could serve as thiolating surrogates in the reaction, we applied several disulfides to the process under the same reaction conditions employing *N*-thiophthalimides. Surprisingly, the transformation occurred smoothly to afford the corresponding sulfides **18a–d** under much milder reaction conditions (compared to Taniguchi's conditions) with higher efficiency (Scheme 4b). Thus, the disulfides were proved to be quite reactive in the reductive thiolation. Meanwhile, the



Scheme 3 Scale-up reaction and recycling of phthalimide **16**.



Scheme 4 Mechanistic investigations.

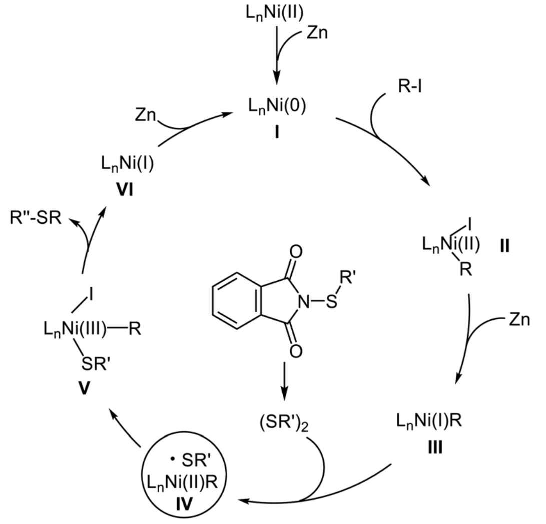


Fig. 1 Plausible mechanism of the current nickel-catalyzed reductive thiolation employing *N*-thiophthalimides.

corresponding disulfide **17c** was obtained in 40% NMR yield with full conversion of *N*-phenylthiophthalimide **4a** in a short time (10 min) when the reaction was conducted in the absence of aryl halides at 0 °C (Scheme 4c). A stoichiometric reaction of the Ar–Ni(II)–I complex **18** with *N*-phenylthiophthalimide **4a** was then examined in the presence or absence of Zn (Scheme 4d) and the thiolated product **20** was generated in 57% ^{1}H NMR yield.

Based on the above experimental results and previous reports,[9d,19] a plausible catalytic cycle for this current nickel-catalyzed reductive thiolation is proposed as illustrated in Fig. 1. Initially, "*in situ*" formed L$_n$Ni(0) **I** undergoes oxidative addition of the C–X bond of aryl halides (R–X) to form the intermediate **II**, and after reduction by Zn, the L$_n$Ni(I)-R **III** was generated. After treatment of disulfides which were formed from the corresponding *N*-thiophthalimides, the L$_n$Ni(I)-R **III** can convert into intermediate **IV** before the formation of the adduct **IV**. Finally, reductive elimination of L$_n$Ni(III)-R **III** occurs to afford the final product and L$_n$Ni(I) **VI**. Upon reduction with Zn(0), catalytically active L$_n$Ni(0) **I** is regenerated and facilitates the next catalytic cycle.

Conclusions

In summary, we successfully developed an efficient, "thiol-free" and sustainable strategy to prepare a series of *N*-thiophthalimides from aryl and alkylzinc reagents. A nickel-catalyzed reductive thiolation of organic halides with bench-stable and readily accessible *N*-thiophthalimides as powerful electrophilic sulphur reagents was also documented. This non-basic process can proceed well under extremely mild reactions promoted by as little as 5.0 mol% loading of nickel catalyst and is further highlighted by late-stage modification of biologically complicated drug molecules, downstream synthesis of related important compounds and sustainable use of the original starting materials. Moreover, direct evidence of the high reactivity of the "N–S" type sulphur transfer reagents in the reductive formation of C–S bonds was explored. Thus, our strategy provided a practical, straightforward and modular platform to assemble a variety of unsymmetrical sulfides in good to excellent yields. Investigation of more challenging substrates such as alkyl halides or unactivated alcohols is under way and the results will be reported in the near future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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