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Redox-active benzimidazolium sulfonamides as cationic thiolating reagents for reductive cross-coupling of organic halides†

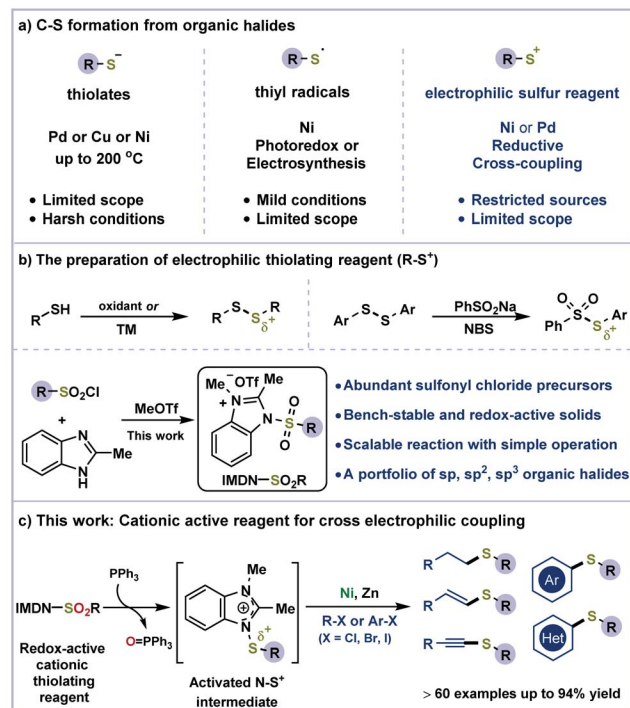
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Redox-active benzimidazolium sulfonamides as thiolating reagents have been developed for reductive C–S bond coupling. The IMDN-SO₂R reagent provides a bench-stable cationic precursor to generate a portfolio of highly active N–S intermediates, which can be successfully applied in cross-electrophilic coupling with various organic halides. The employment of an electrophilic sulfur source solved the problem of catalyst deactivation and avoided odorous thiols, featuring practical conditions, broad substrate scope, and excellent tolerance.

The high frequency of sulfur-containing moieties in natural products,¹ bioactive molecules,² pharmaceuticals,³ organic materials,⁴ fragrances⁵ and asymmetric catalysis as chiral catalysts/ligands⁶ has triggered the best endeavours for the selective construction of C–S bonds. The conventional cross-coupling of thiols with aryl halides generally relies on the conversion of mercaptans to thiolates by means of transition-metal catalysis⁷ (such as Pd,⁸ Cu,⁹ and Ni¹⁰) and other metals,¹¹ although these efforts were plagued by several drawbacks. The strong coordination of thiolates to metals often leads to catalyst deactivation and displays low efficiencies. Therefore, high catalyst loading, specific ligands, excessive heating and strong bases are often required to facilitate this transformation (Scheme 1a, left). Recent development using photochemical¹² and electrochemical¹³ induced thiol radicals as a sulfur source could avoid the problem of catalyst poisoning, although restricted substrate scope was displayed (Scheme 1a, middle). Despite the progress made for C–S bond construction,¹⁴ the longstanding issues that exist in the above-mentioned strategies should not be overlooked.

Compared to classical cross-coupling processes, the nickel-catalyzed reductive cross-coupling of two electrophilic partners has emerged as a powerful tool for the replacement of air- and moisture-sensitive organometallic reagents.¹⁵ The cross electrophilic coupling for the construction of C–S bonds is more challenging due to the lack of sulfur sources and homo-coupling of organic halides (Scheme 1a, right). Several examples

of reductive thiolation¹⁶ have been described using thiol derivatives as S⁺ sources (Scheme 1b). We speculated that readily accessible sulfonyl chloride as an electrophilic sulfur source could avoid the use of highly toxic thiols and significantly the substrate scope.¹⁷ However, the direct reduction of sulfonyl



Scheme 1 Origin of the reaction design. (a) C–S formation from organic halides. (b) The preparation of the electrophilic thiolating reagent ($R-S^+$). (c) This work: cationic active reagent for cross electrophilic coupling.

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chloride inevitably resulted in dimerization to disulfide.^{17b} Putatively, activated by an electron-deficient heterocycle such as imidazole, sulfonyl chloride could be assembled into a bench-stable cationic reagent (Scheme 1b). Benzimidazolium sulfonamides would be better electron acceptors¹⁸ and easily reduced by PPh₃ to generate a highly reactive N-S⁺ species *in situ*. The positive charge of this intermediate is delocalized on both nitrogens of imidazole. Followed by the cleavage of the weak N-S bond (BDE ≈ 70 kcal mol⁻¹),¹⁹ the electrophilic sulfur species can be captured by metal catalysts for cross-coupling. Herein, we have described a redox-active benzimidazolium sulfonamide reagent (IMDN-SO₂R) for Ni-catalyzed reductive coupling of organic halides for a portfolio of C(sp)-S, C(sp²)-S and C(sp³)-S bond formations (Scheme 1c). This strategy avoids the formation of disulfide by-products and the use of organometallic reagents, which facilitates purification and enhances the functionality tolerance.

To determine the suitable conditions for the reductive coupling of the cationic reagent with organic halides, we first studied the reductive thiolation of *p*-iodo-methoxybenzene (**2a**) and **1a** (2 equiv.) with a survey of Ni catalysts in the presence of dtbbpy (20 mol%), PPh₃ (2.5 equiv.), Zn powder (3.0 equiv.) and MgCl₂ (2.0 equiv.) in DMA at 60 °C (Table 1). Ni(OTf)₂ as a catalyst was able to promote the reductive process to afford the desired aryl thioether product **3a** in 92% isolated yield (entry 1). When using Ni(cod)₂, Ni(acac)₂, Ni(OAc)₂·4H₂O and Ni(PCy₃)₂·Cl₂, lower yields were obtained (entries 2–5). Decreasing the **1a** loading to 1.5 equiv., the yield of **3a** reduced to 75% (entry 6). Switching **1a** to a 2-phenyl substituted imidazolium sulfonamide reagent **1b**, similar yields were achieved (entry 7). When

decreasing both Ni(OTf)₂ and dtbbpy loading to 10 mol%, the yield reduced to 75%. In the absence of Ni(OTf)₂ or Zn powder, no desired product was observed (entries 9–10). Switching Zn powder to an organic reductant tetrakis-(dimethylamino) ethylene (TDAE), still a low conversion of the reaction was observed (entry 11). The results demonstrated that no organo-zinc reagents were generated. In the absence of the ligand, MgCl₂ or PPh₃, the reaction resulted in low yields, indicating that these ingredients were essential for this catalytic system (entries 12–14). Thus, the optimized conditions were selected for further investigation of the reaction scope.

The generality of the reductive thiolation was evaluated under the optimized conditions (Scheme 2). A wide range of aryl iodides containing either electron-withdrawing or electron-donating functionality were tolerated, delivering products with methoxy (**3a**, **3c**), trifluoromethoxy (**3b**), methyl (**3d**), acetyl (**3e**), ester (**3f**), boronate (**3g**), and phenyl (**3h**) groups in good to excellent yields (63–94%). 5-Iodobenzo[d][1,3]dioxole and 2-iodofluorene also furnished the corresponding adducts (**3i**, **3j**) in 91% and 82% yields, respectively. Notably, aryl iodides bearing sensitive groups such as amine (**3k**) and hydroxyl (**3l**) were engaged in the cross-coupling to forge the C-S bond in good yields. Aryl bromides (**3a**, **3m**) were also found compatible. The scope of the heteroaryl halide coupling partner was also explored. Various five- and six-membered heterocycles, including thiophene (**3n**), pyrazole (**3o**), quinoline (**3p**), carbazole (**3q**), indole (**3r**), isothiazole (**3s**), benzofuran (**3t**), benzothiophene (**3u**), benzothiazole (**3v**), pyrimidine (**3w**), pyrazine (**3x**), and pyridine (**3y**, **3z**) derived heteroaryl bromides and iodides were treated with **1a** to produce the corresponding sulfides in good yields. In the cases of relatively unreactive organic chlorides, the corresponding coupling products (**3aa**–**3cc**) could be obtained in low yields under the standard conditions. Subsequently, we assessed the scope of aryl sulfonamides. Reagents **1c**–**1k** containing electron-withdrawing and electron-donating substitutions on the benzene ring afforded the desired products in good to excellent yields (**3dd**–**3ll**). Sterically hindered imidazolium sulfonamides 2,4,6-trimethylated **1j** and 2,4,6-triisopropylated **1k** showed good compatibility in this reaction to give the corresponding products **3kk** and **3ll** in high yields.

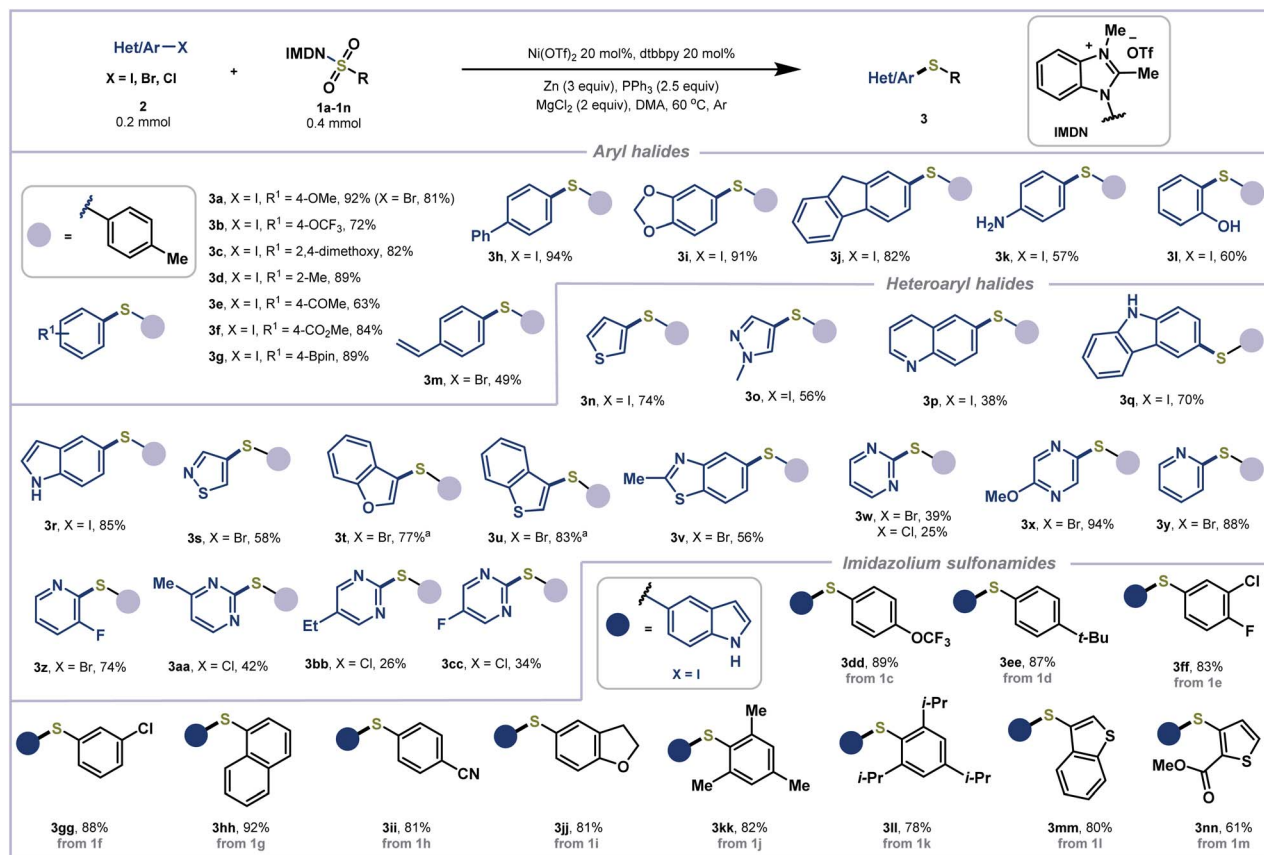
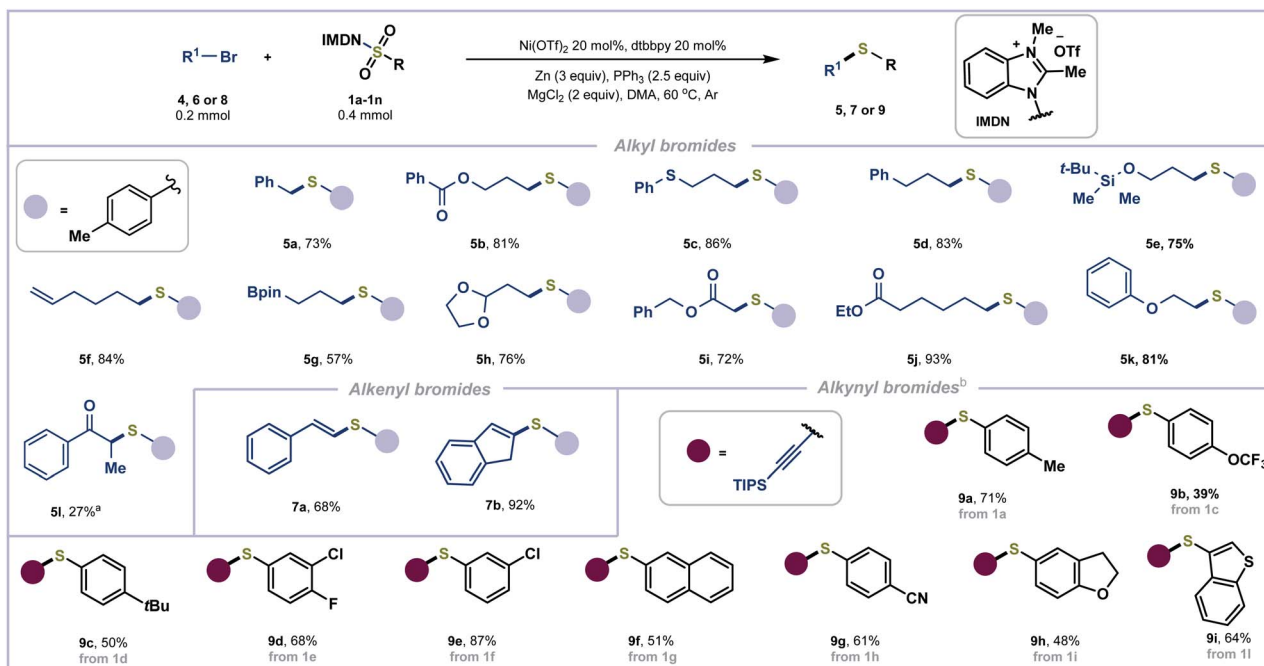
The more challenging aliphatic halides have also been examined with the redox-active reagent **1a** (Scheme 3). Primary and secondary alkyl halides yielded alkyl sulfides (**5a**–**5k** and **5l**) in good to excellent yields. No dimerization side-product was observed. Functionalities including esters (**5b**, **5i**, and **5j**), sulfide (**5c**), alkene (**5f**), acetal (**5h**) and ether (**5k**) are tolerated. Some sensitive functional groups including silyl ether (**5e**) and organoboronate (**5g**) were well tolerated, provided in 75% and 57% yields, respectively. Alkenyl halides were also tolerated to afford **7a** and **7b** in good yields. In addition, alkynyl bromides were employed for reductive thiolation with benzimidazolium sulfonamides **1a** and **1c**–**1i** to afford the corresponding C(sp)-S bond coupling products (**9a**–**9h**) in moderate to good yields.

To demonstrate the synthetic potential of this cross-electrophile coupling, a gram scale reaction was performed with **1a** and *p*-iodo-methoxybenzene **2a** under the standard conditions

Table 1 Optimization of the reaction conditions. Reaction condition: **2a** (0.20 mmol), **1a** (0.40 mmol, 2.0 equiv.), MgCl₂ (2.0 equiv.), PPh₃ (2.5 equiv.), Zn (3.0 equiv.), Ni(OTf)₂ (20 mol%) and dtbbpy (20 mol%) in DMA (2 mL) at 60 °C under Ar. ^aCrude yields determined by ¹H NMR spectroscopy using dibromomethane as an internal standard. ^bIsolated yield. dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. TDAE = tetrakis(dimethylamino)ethylene

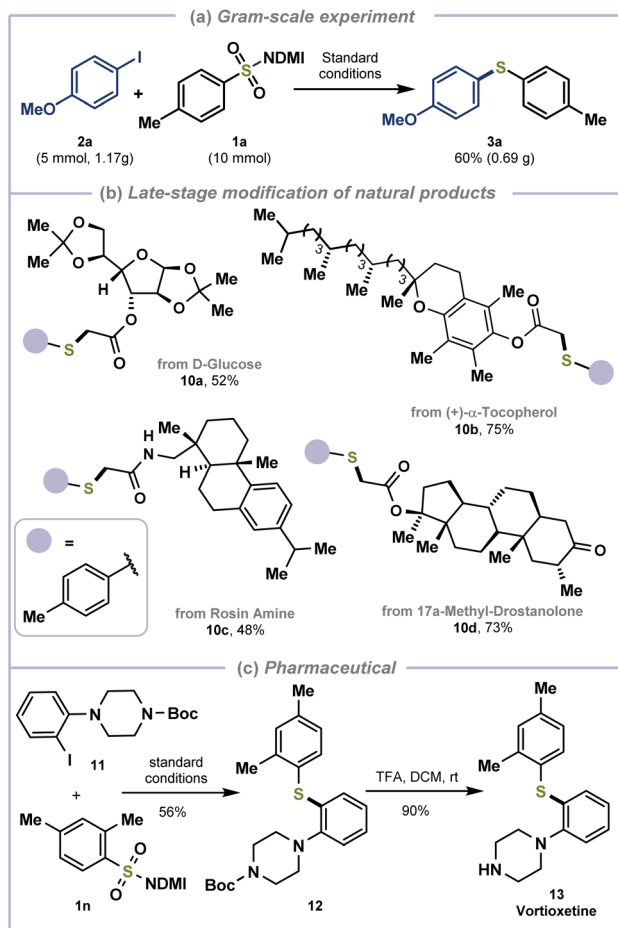
Entry	Variation	Yield ^a /%	Entry	Variation	Yield ^a /%
1	None	96 (92) ^b	8	10 mol% [Ni]	83
2	Ni(acac) ₂	42	9	No Ni(OTf) ₂	nd
3	Ni(cod) ₂	63	10	No Zn	nd
4	Ni(OAc) ₂ ·4H ₂ O	21	11	TDAE for Zn	21
5	Ni(PCy ₃) ₂ Cl ₂	57	12	No dtbbpy	46
6	1.5 equiv. 1a	75	13	No MgCl ₂	39
7	2.0 equiv. 1b	88	14	No PPh ₃	20



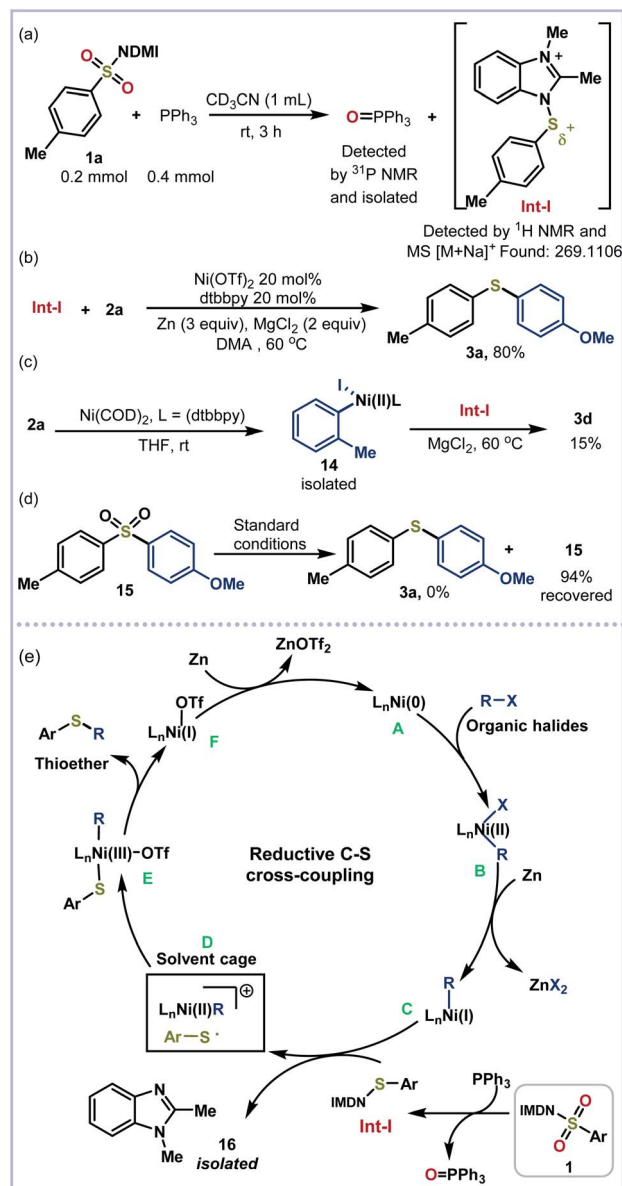
Scheme 2 Substrate scope of (hetero)aryl and benzimidazolium sulfonamides. ^aReaction was performed at 80 °C.Scheme 3 Substrate scope of alkyl, alkenyl and alkynyl bromide. ^aNi(PCy₃)₂Cl₂ instead of Ni(OTf)₂ and without dtbbpy. ^b4-(Trifluoromethyl)pyridine (0.2 mmol) and THF (2 mL) were used instead of dtbbpy and DMA.

(Scheme 4a). The reductive thiolation was also applied in the late-stage modification of biologically active molecules and synthesis of pharmaceutically active molecules. D-Glucose (**10a**), (+)- α -tocopherol (**10b**), rosin amine (**10c**), and 17 α -methyl-drostanolone-derived (**10d**) alkyl halides were compatible to afford thiolated products in good yields (Scheme 4b). Treating benzimidazolium sulfonamide **1n** with piperazine-derived iodobenzene **11** generated the thiolated intermediate **12** and deprotection with TFA afforded anti-depressive vortioxetine **13** (ref. ²⁰) in 50% overall yields (Scheme 4c).

To investigate the mechanism for this reductive thiolation, a series of control experiments have been carried out. First, the treatment of benzimidazolium sulfonamide **1a** with PPh_3 furnished the key N-S⁺ intermediate **Int-I** and $\text{Ph}_3\text{P}=\text{O}$, which were confirmed by ^1H NMR, HRMS data and ^{31}P NMR (Scheme 5a, see the ESI[†]). A mixture of **Int-I** and **2a** was able to afford **3a** in 80% yield under the standard conditions, indicating that the reaction did go through this route (Scheme 5b). Furthermore, the key nickel-complex **14** was prepared and reacted with **Int-I** to furnish thioether **3d** in 15% yield (Scheme 5c). Finally, sulfone **15** was used in the absence of benzimidazolium sulfonamide **1a** and **2a** under standard conditions. No



Scheme 4 Further transformations. (a) Gram-scale experiment. (b) Late-stage modification of natural products. (c) The synthesis of vortioxetine using our protocol.



Scheme 5 Mechanistic studies and proposed mechanism.

reduced product **3a** was detected, which indicates that the PPh_3 reduction occurs before the cross-coupling (Scheme 5d). On the basis of the experimental results and previous reports,^{16c,g} a plausible mechanism for the reductive thiolation of organic halides is proposed (Scheme 5e). Initially, the reduction of the Ni(II) salt by zinc affords the active Ni(0) catalyst **A**, which undergoes oxidative addition into the C-X bond of organic halides to give the intermediate R-Ni(II)X **B**. The following reduction of **B** forms R-Ni(I) intermediate **C**.^{15b,16g} Then **C** and **Int-I** undergo stepwise single-electron transfer with the possibility of radical trapping within a solvent cage to afford intermediate **D** before the generation of R-Ni(III)-SAr **E** and benzimidazole residue **16**. Finally, the reductive elimination of **E** furnishes the desired thioether product and

Ni(I) species **F** which is reduced by zinc to facilitate the next catalytic cycle.

Conclusions

In summary, we have developed a universal reductive thiolation protocol of organic halides with benzimidazolium sulfonamides. This bench-stable crystalline reagent is readily achievable in large quantities from abundant sulfonyl chloride. The key design of this redox-active reagent is the cationic nature. The reduction potential of sulfonyl group can be improved due to the cationic nature and in favor of *in situ* generating electrophilic N-S⁺ reagent by the reduction of triphenylphosphine. This approach features practical conditions, broad substrate scope, and excellent functional group tolerance for the incorporation of sulfur-containing moieties into organic molecules. Further study of the cationic reagent IMDN-SO₂R is underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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