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Nickel-Catalyzed Directed Sulfenylation of sp[2] and sp[3] C-H Bonds

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Directed sulfenylation of both sp[2] and sp[3] C-H bonds was achieved through nickel catalyzed directed C-S bond formation, giving the desired product in good to excellent yield (up to 90%). Other metal cations, including Cu, Fe, Pd, Rh, Ru and Co, gave almost no reaction under identical conditions, which highlighted the unique reactivity of this Ni system.

During the last decade, transition metal catalysed C-H functionalization has been applied as an efficient approach for complex molecule synthesis.[1] Among all reported methods, the chelation assisted directing group strategy has gained rising attention for site-selective C-H activation.[2] Generally, ,the chelating effect enhances the metal reactivity, especially towards less reactive sp[3] C-H bonds.[3] Due to the significance of the organosulfur compounds in chemical and biological research, selective C-H sulfenylation received more and more attentions. Transition metal catalyzed C-S bond formation is a challenging task, due to the coordination ability of sulfur atom towards various metal cations (potential poisoning of the catalyst). Thus, new approaches that can efficiently construct C-S bonds are always highly desirable.

Previously, the cross coupling approach between aryl-halide and thiol/disulfide has been achieved for the sp[2] C-S bond construction under special conditions (solvents, catalyst and ligand) with limited reaction scope.[4] Directed C-H sulfenylation offers high efficiency and better atom economy (by avoiding the usage of aryl halides), though challenges still arise. These issues are manifested by the strong coordination between metal and sulfur, potentially inhibiting C-H activation and or catalyst turnover.[5] Very recently, Daugulis and co-workers reported a successful example of sp[2] C-H sulfenylation using 8-aminoquioline (Q) moiety as the chelate directing group with Cu(OAc)$_2$ as catalyst (up to 50% loading).[6] However, under their optimal conditions, sp[3] C-H sulfenylation did not occur (< 15% yield) when using 1 equiv. of Cu(OAc)$_2$ (**Scheme 1B**). Moreover, disulfides were required as the sulfur source/oxidant, decreasing atom economy with limited scope. Herein, we report the successful C-H sulfenylation of both sp[3] and sp[2] C-H bonds using a Ni-based catalyst and thiols as the sulfur source. Additionally, directed sp[3] C-H sulfenylation could be

performed using a broad substrate scope with good yields observed (Scheme 1C).[7]
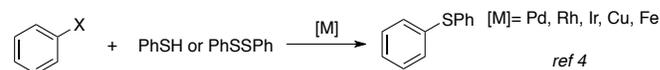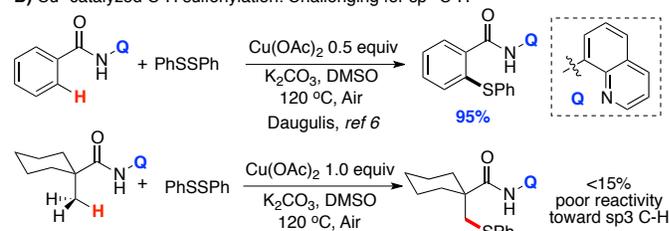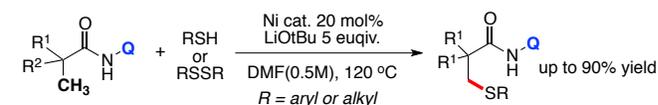
Scheme 1. Catalytic C-H sulfenylation

To explore the possibility of sp[3] C-H sulfenylation, we turned our attention to nickel complexes. Nickel catalysis is known for its versatile reactivity including rapid single electron transfer (SET).[8] During the past several years, nickel catalysis has received increasing attentions due to the promising reactivity toward directed sp[3] C-H functionalization. This is evidenced through several examples reported in literature for C-C and C-N formation.[9] To explore the feasibility of directed C-H sulfenylation, we prepared various amide **1** (containing different directing groups) and charged them with nickel catalyst precursor under different conditions. The results are summarized in Figure 1.
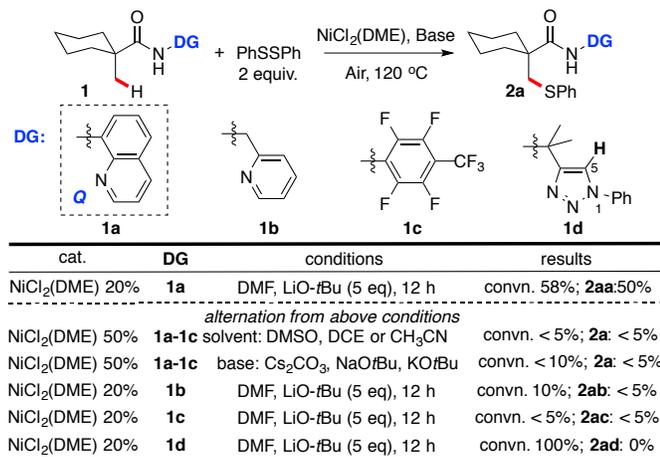
Figure 1. Ni-catalyzed sp³ C-H sulfenylation

As shown in **Figure 1**, substrates with various literature-reported directing groups were prepared, including quinoline (**1a**), pyridine (**1b**),[10] Yu-Wasa auxiliary (**1c**)[11] and 1,2,3-triazole (**1d**).[12] In Daugulis' previous report, DMSO was revealed to be the optimal solvent for sp² C-H sulfenylation. One plausible reason was the inherent redox-stabilization ability of DMSO towards thiol-disulfide interconversion.[13] However, with nickel catalyst, no sp³ C-H activation was observed using DMSO as solvent under various conditions. Interestingly, the only condition giving the desired sp³ C-H sulfenylation was the reaction of the quinoline directing group modified substrate **1a** in DMF with LiO*t*Bu as the base (50% yield, 58% conversion). Notably, both the choice of solvent and base are crucial: using other solvents (DMSO, DCE or MeCN) with LiO*t*Bu or using other bases (Cs₂CO₃, KO*t*Bu or NaO*t*Bu) in DMF gave significantly lower reactivity. Moreover, the quinoline substrate **1a** gave significantly better result than other directing groups.[14] Based on these preliminary results, we conducted detailed condition screening. As shown in Table 1, under the optimal conditions with Ni(OTf)₂ as catalyst precursor, LiOtBu as base, DMF as solvent and with argon protection, the desired sp³ C-H sulfenylation product **2a** was obtained in 86% isolated yields.

Table 1. Selected conditions on Ni catalyzed sp³ C-H sulfenylation.[a]

entry	Variations from the "standard" conditions	yield (convn.)
1	**none**	**88% (100%)**
2	Other catalysts (100%), including Cu(OAc)₂, CuI, Pd(OAc)₂, [Rh(COD)Cl]₂, RuCl₃, Fe(OTf)₃ et al.	<5% (<10%)
3	Other solvents, including DMSO, CH₃CN, DMA	<20% (<30%)
4	NaOtBu as base	<5% (<5%)
5	KOtBu as base	9% (15%)
6	NiCl₂(DME) 20 % as cat.	84% (95%)
7	Ni(acac)₂ 20 % as cat.	82% (91%)
8	Under air, no argon	75% (82%)
9	Air, Ni(OTf)₂ + dppbz	70% (82%)
10	Air, Ni(OTf)₂ + MesCOOH	78% (88%)
11	1.5 equiv PhSSPh	56% (67%)
12	10% Ni(OTf)₂	52% (50%)
13	PhSH 2.5 equiv.	15% (20%)
14	PhSH under Air	50% (56%)[b]
15	**o-FPhSH, under Air**	**83% (100%)[b]**

[a] Reaction conditions: **1a** (0.2 mmol), PhSSPh (2.5 equiv.), Ni(OTf)₂ (20 mol%), Base (5 equiv.) and additive (if applicable) in dry DMF (0.4 mL), Ar; [b] ArSH (4 equiv.), LiOtBu (7 equiv.) was used; [c] The yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

Interestingly, reaction parameters in the optimal conditions seemed crucial. First, under the identical conditions, other tested metal complexes, including Cu(OAc)₂, CuI, Pd(OAc)₂, [Rh(COD)Cl]₂, RuCl₃, Fe(OTf)₃, gave little reactivity with <10% C-H sulfenylation product obtained (entry 2). Similarly, DMF and LiOtBu were both critical for the reaction performance (entries 3-5); Ni(OTf)₂ gave the best results when compared with other nickel salts (entries 6-7). The reaction could not reach a total completion without argon protection (entry 8), suggesting the decomposition of nickel catalysts under air atmosphere over time. Finally, the addition of previously reported assisting ligands (dppbz and MesCOOH, entries 9 and 10) did not show improvement. Considering the strict reliance on DMF as the optimal solvent and lithium base, it suggested the formation of Ni-DMF complexes under the reaction conditions, which served as the actual catalyst in promoting the reaction. Decreasing nickel catalyst loading or reducing the amount of disulfide caused lower yields due to uncompleted reaction over time (entries 11-12). Interestingly, thiophenol also gave 15% yield under optimal conditions, suggesting the importance of oxidant involved in the catalytic cycle. Inspired by this result, coupling with thiophenol was explored. As shown in entry 14, reaction of thiophenol could not reach a full conversion (56%) under air and significant product decomposition was observed. To our delight, electron-deficient benzenethiol exhibits better performance with 83% yield (100% conversion). To the best of our knowledge, this is the first example that successfully achieved sp³ C-H sulfenylation with disulfide or thiol in excellent yields. With this optimal condition in hand, we embarked on the evaluation of the reaction substrate scope.

Table 2. Reaction scope of Ni catalyzed sp³ C-H sulfenylation.[a,b]
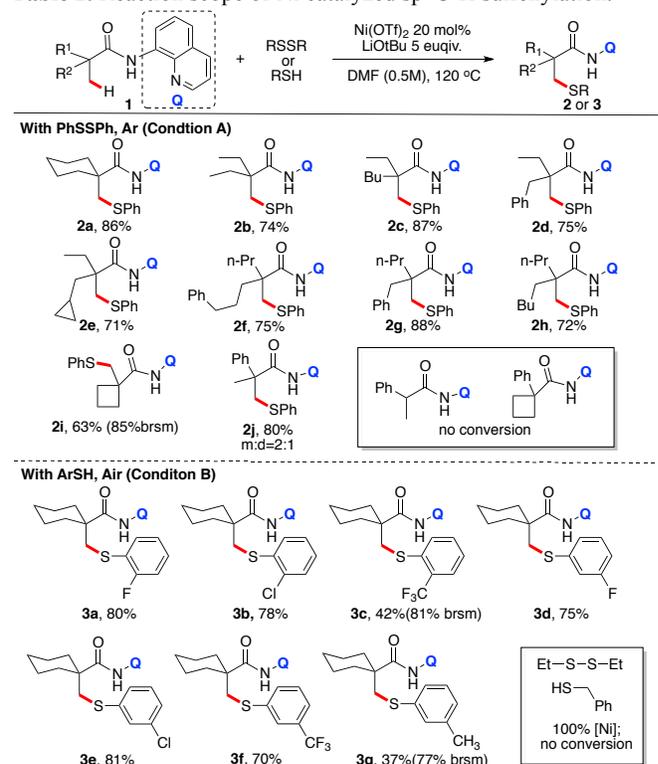
[a] Reaction conditions: **Condition A**: **1a** (0.3 equiv.), PhSSPh (2.5 equiv.), Ni(OTf)₂ (20 mol%), LiO*t*Bu (5 equiv.) in dry DMF (0.6 mL), Ar, 120 °C. **Condition B**: **1a** (0.3 mmol), Ni(OTf)₂ (20 mol%), ArSH (4 equiv.), LiO*t*Bu (7 equiv.) in dry DMF (0.6 mL), Air, 120 °C; [b] Isolated yield.

As shown in Table 2, the quinoline directing group effectively promoted sp^3 C-H bond activation and furnished the sulfenylation products in good yields. In general, the reaction targeted on methyl C-H (CH$_3$) over methylene (CH$_2$), even with the presence of benzylic CH$_2$ (**2d**). Similarly, 1-methyl-cyclobutane derivatives gave the desired sulfenylation product with **2i** without C-H sulfenylation on the ring. Notably, substrates with cyclopropane on the side chain could also tolerate this transformation (**2e**). Modest selectivity was observed when two methyl groups were present (formation of mixture of mono and disulfenylation, **2j**).

Considering the obvious practical advantages, we explored various thiols (instead of disulfides) as the sulfur source. Most EWG substituted thiolphenols gave good yields (**3a**, **3b**, **3d-3f**). Lower yields were observed with electron rich thiolphenols (**3g**) and ortho-CF$_3$ thiolphenols (**3c**). Reactions with alkyl thiol or disulfide did not proceed under this condition, even with 100% nickel catalyst precursor loading. Nevertheless, even with some limitation, this method provides the first successful example to achieve sp^3 C-H sulfenylation.

Table 3. Reaction scope for sp^2 C-H sulfenylation.^{a,f}
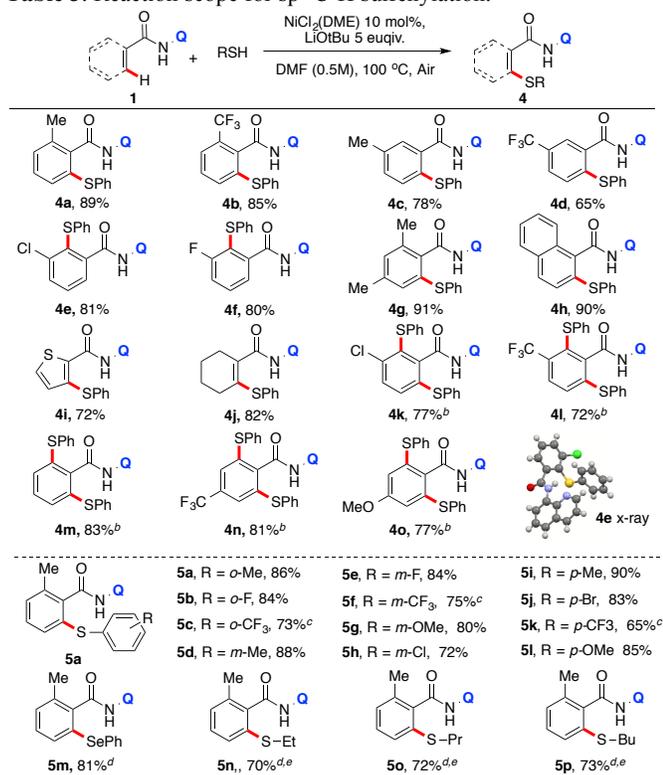
^{a} Reaction conditions: **1a** (0.3 mmol), ArSH (2.2 equiv.), NiCl$_2$(DME) (10 mol%), LiOtBu (5 equiv.) in dry DMF (0.6 mL), Air, 100 °C; ^{b} ArSH (4.0 equiv.), NiCl$_2$(DME) (15 mol%), LiOtBu (7 equiv.) was used, 110 °C; ^{c} 120 °C; ^{d} Disulfide 1.5 equiv. was used; ^{e} 50 mol% NiCl$_2$(DME) was used; ^{f} Isolated yield.

Although the exact reason for significantly better results using the combination of DMF and LiOtBu is unclear, this new condition could presumably be extended to the sp^2 C-H sulfenylation. Furthermore, the application of thiophenol as the sulfur source greatly extended the reaction scope. After a brief screening, a general condition was revealed with air-stable NiCl$_2$(DME) as catalyst precursor (10 mol%) at 100 °C under ambient pressure (open flask). Under these mild conditions, good to excellent yield of sp^2 C-H sulfenylation was achieved. The substrate scope is summarized in Table 3.

First, both EWG and EDG substituted benzenes were suitable for this reaction. Good regioselectivity was observed for the *meta*-substituted benzenes (**4c** and **4d**) with sulfenylation occurring on the less hindered C-H bond. Interestingly, a reversed regioselectivity was obtained with *m*-Cl and *m*-F substituted benzene (**4e** and **4f**), giving the C-S bond formation at the adjacent C-H bond (confirmed by X-ray crystallography). The exact reason of this unusual regioselectivity is currently under investigation. The selectivity between mono- and di-sulfenylation was poor as other reported cases. In those cases, the di-sulfenylation products were achieved with good yields (**4m-4o**) with increasing amount of thiophenol/LiOtBu. Notably, this strategy was also suitable for di-sulfenylation for *meta*-substituted benzene (**4k** and **4l**) though with the presence of steric hindrance. Thiophene was also suitable for this reaction with C-S products formed in good yield (**4i**). The scope of thiols was also evaluated. Besides thiophenol, both electron-rich and electron-deficient benzenethiol were tolerated, giving promising yields. Notably, with halides present on the benzene ring, the C-S bond formation occurred over oxidative addition (**5h**, **5j**). Diphenylselenium (**5m**) were examined and gave the desired products in good yields. A gram-scale synthesis was carried out as shown in Scheme 2, which showcased the robust nature of this new method. The challenging aliphatic thiols showed almost no reactivity under standard condition. Remarkably, using aliphatic disulfide and 50% NiCl$_2$(DME), the reactions proceeded well and the desired products (**5n-5p**) were produced in good yields. These results clearly highlighted the significantly improved reactivity of this newly discovered catalytic system in C-H sulfenylation.
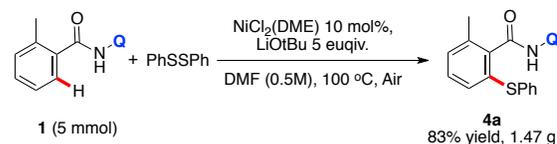
Scheme 2 Gram-scale syntheses.

To understand the reaction mechanism, we first performed the radical trapping experiment (Scheme 3A). TEMPO (3 eq.) did not influence the reaction efficiency. This result suggested a single electron transfer (SET) process was likely not involved. Mercury poisoning at the starting pointing (t=0) and/or at the reaction point (t=25 min) showed no quenching of reactions (See SI), indicating a homogenous nickel catalytic process. The competition experiment between different arenes gave exclusively sulfenylation on electron-deficient aromatic ring (Scheme 3B). This result strongly suggests that C-H bond cleavage might be dependent on acidity.
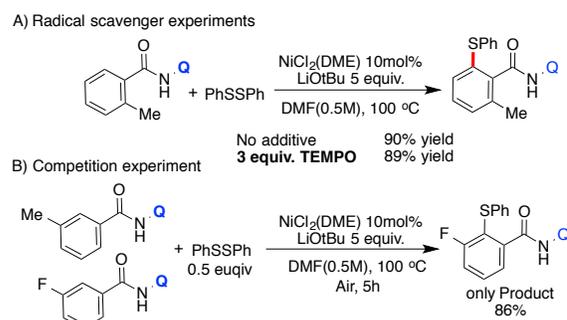
Scheme 3. Mechanism investigations

Presumably, the disulfide performed as a true oxidant in promoting either Ni(I)/Ni(III) or Ni(II)/Ni(IV) catalytic cycle under disulfide/Ar condition.[15] However, the thiol/air system gave faster reaction kinetic than disulfide reactions. Thus, it is clear that these transformations likely proceed through different mechanism under these two different conditions. Detailed mechanistic investigations are currently undergoing in our lab.

Conclusions

In summary, we have developed a general synthesis of substituted sulfide carboxylic acid derivatives from directed C-H sulfenylation. The efficient C-S bond formation was enabled through homogenous nickel catalysis with C-H bond activation on both sp2 and sp3 carbon atoms. Furthermore, this study revealed a new efficient and economic approach towards sulfur containing product formation (using thiol directly), highlighting the potential application of the former in biological and pharmaceutical sciences. Such investigation is currently underway in our laboratory.

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15. For the plausible reaction mechanism, see SI.