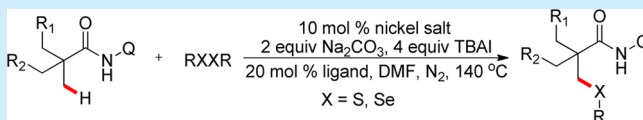


Nickel-Catalyzed Direct Thioetherification of  $\beta$ -C(sp<sup>3</sup>)-H Bonds of Aliphatic AmidesCong Lin,<sup>†</sup> Wenlong Yu,<sup>†</sup> Jinzhong Yao,<sup>†</sup> Bingjie Wang,<sup>†</sup> Zhanxiang Liu,<sup>†</sup> and Yuhong Zhang<sup>\*,†,‡</sup><sup>†</sup>Department of Chemistry, Zhejiang University, Hangzhou 310027, China<sup>‡</sup>State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

## S Supporting Information

**ABSTRACT:** The nickel-catalyzed  $\beta$ -thioetherification of unactivated C(sp<sup>3</sup>)-H bond of propionamides is established with the assistance of 8-aminoquinoline auxiliary, leading to the  $\beta$ -thio carboxylic acid derivatives. A broad range of functional groups is compatible with this thioetherification reaction. The process represents the first successful example of metal-catalyzed C-S bond formation from unactivated C(sp<sup>3</sup>)-H bonds.



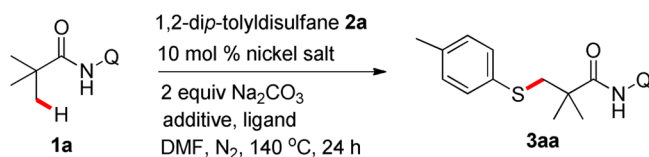
Development of applicable methods for the catalytic functionalization of unactivated  $\text{sp}^3$  C-H bonds remains a pressing task in current organometallic and synthetic organic chemistry.<sup>1</sup> Over the past decades, significant advances have been made in the formation of new C-C or C-X bonds through the metal-catalyzed activation of C(sp<sup>3</sup>)-H bonds of arenes.<sup>2,3</sup> However, the functionalization of unactivated C(sp<sup>3</sup>)-H bonds is still a particularly difficult challenge owing to its inertness. The pioneering work by Sanford<sup>4</sup> and Yu<sup>5</sup> has demonstrated that the direct functionalization of  $\text{sp}^3$  C-H bonds could be achieved by the use of the directing groups. More recently, a number of elegant transformations of  $\text{sp}^3$  C-H bonds have been established<sup>6-9</sup> by employing the bidentate directing group since a seminal report by Daugulis in 2005.<sup>10</sup> Despite this remarkable progress, most of the examples of the  $\text{sp}^3$  C-H bond functionalization are focused on the formation of C-C, C-O and C-N bonds. The selective construction of C-S bonds from inert C(sp<sup>3</sup>)-H is completely undeveloped.

The prevalence of sulfur atom in myriad molecules of biological interest and functional materials motivates the development of methods to streamline the introduction of sulfur atoms into organic molecules. Catalytic methods for C-S bond formation represent a fundamentally important transformation and occupies a prominent position in modern synthetic organic chemistry.<sup>11,12</sup> The development of a new, general, catalytic system for C-S bond construction from  $\text{sp}^3$  C-H bonds would be quite appealing. However, it is well-accepted that the strong binding of sulfur species, in particular by thiols and disulfides (RSH and R<sub>2</sub>S<sub>2</sub>), to transition metals may result in the deactivation of metal catalysts. Furthermore, the most presently used method for  $\text{sp}^3$  C-H activation by Pd(II)/Pd(IV) catalysis requires oxidants such as PhI(OAc)<sub>2</sub>, which might damage the sulfur substrates.<sup>13</sup> To address these problems, the development of new catalytic systems is highly desired. Since a Ni(II)/Ni(IV) catalysis works very well for the arylation of  $\text{sp}^3$  C-H bonds in the absence of oxidant,<sup>14</sup> and since the prevalence of nickel catalysis, we envisioned that nickel catalysts should not be inherently

inferior to the palladium species. Herein, we report a new approach to  $\beta$ -thio carboxylic acid derivatives by direct thioetherification of  $\beta$ - $\text{sp}^3$  C-H bonds of propionamides with disulfides, in which the 8-aminoquinoline auxiliary plays the crucial role. The eco-friendly and cheap nickel exhibited the unprecedented catalytic power for the construction of C-S bond from unactivated  $\text{sp}^3$  C-H bond.

Very recently, nickel has been demonstrated to possess the intrinsic catalytic potential for unactivated  $\text{sp}^3$  C-H bonds by Chatani's and Ge's groups.<sup>14a,b</sup> In light of these excellent achievements, we explored the thioetherification of  $\beta$ -C(sp<sup>3</sup>)-H bonds of aliphatic amides with disulfides by using nickel as the catalyst. We initially selected a variety of commercially available nickel salts at 10 mol % loading to examine the thioetherification reaction of amide **1a** and disulfide **2a** of 2 equiv of Na<sub>2</sub>CO<sub>3</sub> at 140 °C for 24 h (Table 1). Various nickel salts, including NiBr<sub>2</sub>, NiCl<sub>2</sub>, and NiI<sub>2</sub>, catalyzed this reaction to give thioether **3a** in acceptable conversion (Table 1, entries 1–3), but Ni(OTf)<sub>2</sub> exhibited obviously higher reactivity, furnishing **3a** in 68% yield (entry 4). Ni(OAc)<sub>2</sub> showed higher reactivity, but the dithioetherification product was generated to give the 57% monothioetherification product as well as 14% dithioetherification product (Table 1, entry 5). Ni(acac)<sub>2</sub> was found to be less effective for this transformation, and Ni(COD)<sub>2</sub> was almost inactive (entries 6 and 7). As an activating reagent, the addition of TBAI promoted the reaction, and an obvious loss of reactivity was observed in the absence of TBAI (Table 1, entry 8). Replacing the additive of TBAI with TBAB or NaI led to a lower conversion (Table 1, entries 9 and 10), while CsI and CuI almost halted the reaction (Table 1, entries 11 and 12). The efficiency of the reaction was also significantly affected by the ligands. The commonly used nitrogen and phosphine ligands, such as phenanthroline (1,10-phen), PPh<sub>3</sub>, dppe, Xantphos, showed little effect on the reaction (Table 1, entries 13–17). The significant function of the amino

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Table 1. Optimization of Reaction Conditions<sup>a</sup>

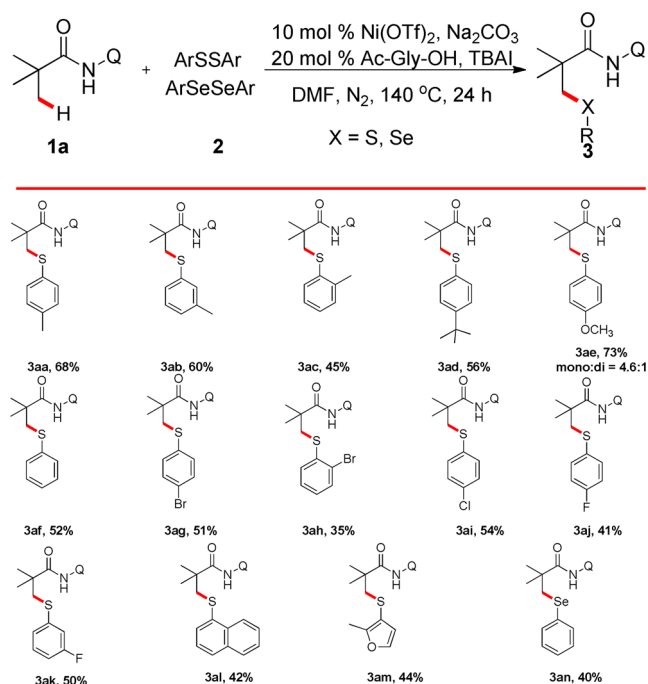
entry	catalyst	additive	ligand	yield <sup>b</sup> (%)
1	NiBr <sub>2</sub>	TBAI	Ac-Gly-OH	63
2	NiCl <sub>2</sub>	TBAI	Ac-Gly-OH	65
3	NiI <sub>2</sub>	TBAI	Ac-Gly-OH	64
4	Ni(OTf) <sub>2</sub>	TBAI	Ac-Gly-OH	68
5	Ni(OAc) <sub>2</sub>	TBAI	Ac-Gly-OH	71 (4:1) <sup>c</sup>
6	Ni(acac) <sub>2</sub>	TBAI	Ac-Gly-OH	36
7	Ni(COD) <sub>2</sub>	TBAI	Ac-Gly-OH	<5
8	Ni(OTf) <sub>2</sub>		Ac-Gly-OH	40
9	Ni(OTf) <sub>2</sub>	TBAB	Ac-Gly-OH	46
10	Ni(OTf) <sub>2</sub>	NaI	Ac-Gly-OH	63
11	Ni(OTf) <sub>2</sub>	CsI	Ac-Gly-OH	27
12	Ni(OTf) <sub>2</sub>	CuI	Ac-Gly-OH	trace
13	Ni(OTf) <sub>2</sub>	TBAI		56
14	Ni(OTf) <sub>2</sub>	TBAI	1,10-Phen	58
15	Ni(OTf) <sub>2</sub>	TBAI	PPh <sub>3</sub>	50
16	Ni(OTf) <sub>2</sub>	TBAI	dppe	40
17	Ni(OTf) <sub>2</sub>	TBAI	Xantphos	trace
18	Ni(OTf) <sub>2</sub>	TBAI	PhCO <sub>2</sub> H	48
19	Ni(OAc) <sub>2</sub>	TBAI	<i>o</i> -NBA <sup>d</sup>	79 (2.5:1) <sup>c,e</sup>
20	Ni(OTf) <sub>2</sub>	TBAI	Ac-Gly-OH	trace <sup>f</sup>

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), 1,2-di-*p*-tolylidysulfane **2a** (0.4 mmol), Ni salt (0.02 mmol), Na<sub>2</sub>CO<sub>3</sub> (2 equiv), ligand (0.04 mmol), and additive (4 equiv), DMF (0.6 mL) in N<sub>2</sub> at 140 °C for 24 h.

<sup>b</sup>Isolated yield, Q = 8-quinoliny. <sup>c</sup>The ratio of mono- and dithioetherification products was presented in parentheses. <sup>d</sup>*o*-NBA = *o*-nitrobenzoic acid. <sup>e</sup>1,2-Bis(4-methoxyphenyl)disulfane **2e** was used. <sup>f</sup>In the presence of 2 equiv of zinc powder.

acid ligands on the transformation was observed, and the use of 20 mol % Ac-Gly-OH could improve the efficiency of the reaction to increase the yield from 56% to 68% (Table 1, entries 4 and 13). Among the carboxylic acid ligands screened (Table 1, entries 4, 18, and 19), *o*-nitrobenzoic acid exhibited an unexpected effect on the reaction, although the products were a mixture of 56% mono- and 23% dithioetherification. In the presence of 2 equiv of zinc powder, the reaction was entirely inhibited (Table 1, entry 20).

With the optimal reaction conditions in hand, we next examined the scope of the disulfides in this new thioetherification protocol (Scheme 1). In general, the disulfides reacted with both steric and electronic variations on the aryl ring under these reaction conditions. It was found that the disulfides with an electron-rich aryl group showed higher reactivity and gave slightly higher yields than the substrates with an electron-deficient aryl group. When 1,2-bis(4-methoxyphenyl)disulfane was used as the substrate, the dithioetherification product **3ae'** was isolated in 14% yield besides the 59% monothioetherification product **3ae**. The steric hindrance significantly influenced the transformation. For instance, in the case of *o*-methylphenyl disulfide, a significant amount of amide **1a** was recovered, and the thioether **3ac** was only isolated in 45% yield. The aryl-halogen bonds were tolerated under the reaction conditions: products **3ag–ak** were obtained efficiently without any thioetherification products of C–X bonds.  $\beta$ -Naphthalene disulfide participated in the reaction smoothly to give the products **3al** in a 42% yield. Remarkably, 2-methylfuran-3-disulfide was a viable substrate to afford the

Scheme 1. Substrate Scope of Disulfide<sup>a,b</sup>

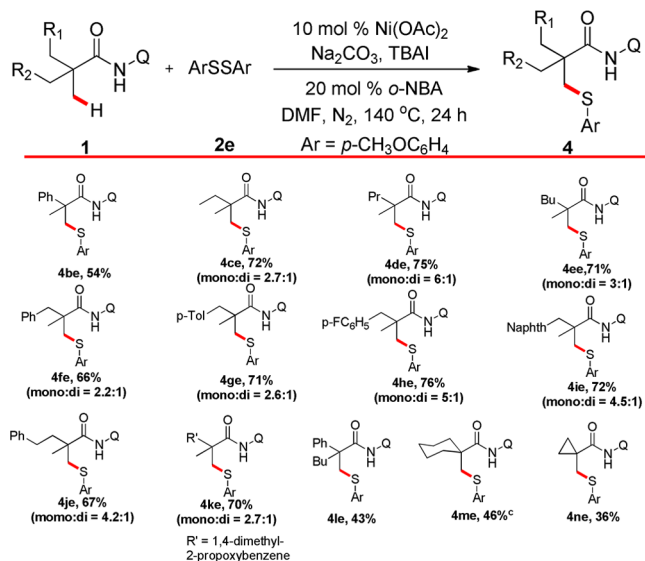
<sup>a</sup>Reactions were carried out by using **1a** (0.2 mmol), **2** (0.6 mmol), Ni(OTf)<sub>2</sub> (0.02 mmol), Na<sub>2</sub>CO<sub>3</sub> (2 equiv), TBAI (4 equiv), Ac-Gly-OH (0.04 mmol), DMF (0.6 mL), N<sub>2</sub>, 140 °C, 24 h. <sup>b</sup>Isolated yield by flash column chromatography.

corresponding thioetherification product **3am**. An effort to use aliphatic disulfides as the substrates failed. By an extension of this reaction, the analogous 1,2-diphenyl diselenide was found to react with **1a** under the reaction conditions to yield 40% of the corresponding selenide **3an**.

This thioetherification reaction was compatible with a variety of the amide substrates as shown in Scheme 2. The amide substrates bearing  $\beta$ -methyl groups with three  $\alpha$ -substituents participated in the thioetherification reaction to provide the corresponding  $\beta$ -thio amides including mono- and dithioetherification in moderate yields (Scheme 2, **4be–ke**). The regioselectivity of the reaction was always such that the  $\beta$ -methyl group is preferred over the  $\beta$ -methylene and  $\gamma$ -methyl groups (Scheme 2, **4be–ke**). The amide substrates without a  $\beta$ -methyl group were inactive under the reaction conditions. In addition, a tertiary  $\alpha$ -carbon atom in the amide substrates was required for the success of the thioetherification. The substrates with one  $\beta$ -methyl group delivered the monothioetherification products (Scheme 2, **4le–ne**).

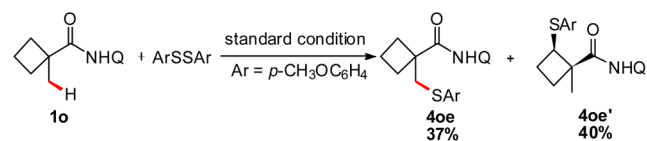
In the case of 1-methyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide **1o**, the monothioetherification product **4oe** was obtained in 37% yield, and the *ortho*-thioetherification of cyclobutanecarboxamide occurred to give the corresponding *ortho*-functionalized cyclobutanecarboxamide product **4oe'** in 40% yield (Scheme 3). The results of NOESY experiments demonstrated the correlation of  $\beta$ -methyl group with the hydrogen of the thioether carbon in the cyclobutane ring (see the Supporting Information), illustrating the *cis* configuration of the thioether with the amide directing group.

The primary mechanistic study revealed that the addition of radical scavenging reagents such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) had a poor impact on the reaction (Scheme 4, eq 1). This

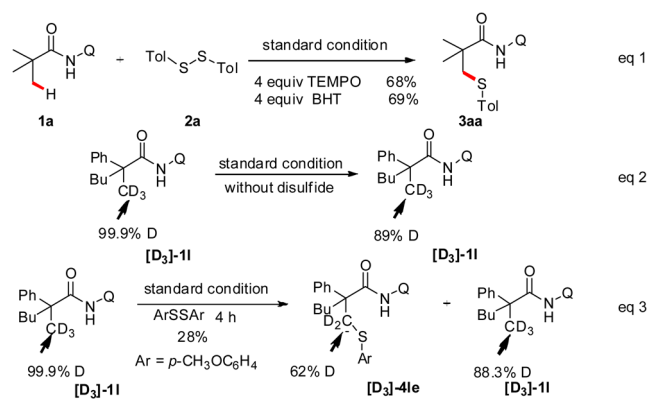
Scheme 2. Substrate Scope of Aliphatic Amides<sup>a,b</sup>

<sup>a</sup>Reactions were carried out by using **1** (0.2 mmol), **2e** (0.6 mmol), Ni(OAc)<sub>2</sub> (0.02 mmol), Na<sub>2</sub>CO<sub>3</sub> (2 equiv), TBAI (4 equiv), *o*-nitrobenzoic acid (0.04 mmol), DMF (0.6 mL), N<sub>2</sub>, 140 °C, 24 h.  
<sup>b</sup>Isolated combined yield of mono- and disubstituted products.  
<sup>c</sup>Purified by GPC.

## Scheme 3. Thioetherification of Cyclobutanecarboxamide



## Scheme 4. Control Experiment and Deuterium-Labeling Result

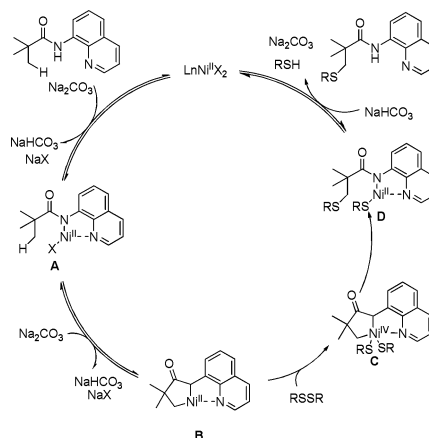


result is incompatible with a Ni(I)/Ni(III) pathway that might involve the single-electron-transfer process.<sup>14b,15</sup> On the other hand, the reaction became very sluggish when 10 mol % Ni(COD)<sub>2</sub> or the combination of 10 mol % Ni(OAc)<sub>2</sub> and 2 equiv of zinc powder was used (Table 1, entries 7 and 20), indicating that Ni(0) is quite difficult to initiate the reaction.

It was found that the D content in the amide **D<sub>3</sub>-11** after 4 h decreased from >99% to 89% in the absence of disulfide under the standard reaction conditions (Scheme 4, eq 2). This result illustrates that the C–H cleavage step occurs and is reversible. To gain further evidence for H/D exchange, the deuterium-labeling experiment of disulfide was carried out. The occurrence of the H/

D exchange in the  $\beta$ -methyl group for the deuterium-labeled starting amide **D<sub>3</sub>-11** was observed again (Scheme 4, eq 3), implicating that the cyclometalation step from intermediate **A** to intermediate **B** is reversible (Scheme 5). Based on these results

## Scheme 5. Proposed Reaction Mechanism



and previous reports,<sup>14a,16</sup> a plausible reaction pathway of Ni(II)/Ni(IV) is proposed as shown in Scheme 5. First, the Ni(II) center coordinates with the nitrogen in 8-aminoquinoline auxiliary followed by a ligand exchange under basic condition to form the intermediate **A**. The cyclometalation of intermediate **A** gives intermediate **B**, which undergoes the oxidative addition with disulfide to generate the intermediate **C**. The reductive elimination of the intermediate **C** forms the intermediate **D**, which liberates the product and regenerates the Ni(II) species through the exchange of anions and protonation to fulfill the cycle.

In summary, we have developed a new method for the 8-aminoquinolinyl-assisted thioetherification of the  $\beta$ -sp<sup>3</sup> C–H bond of propioamides with good functional group tolerance. For the first time, abundant and low cost nickel is applied as the catalyst for the successful construction of C–S bonds by the direct coupling of disulfide with C(sp<sup>3</sup>)–H bonds. The reaction shows high regioselectivity for a preferential thioetherification of C(sp<sup>3</sup>)–H bonds of methyl groups over the methylene C(sp<sup>3</sup>)–H bonds. Further investigations to extend the reaction scope and elucidate mechanism are in progress.

## ■ ASSOCIATED CONTENT

## S Supporting Information

General procedures, analytical data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Notes

The authors declare no competing financial interest.

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