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Thioesters as Bifunctional Reagents for 2-Naphthylamine Sulfuracylation

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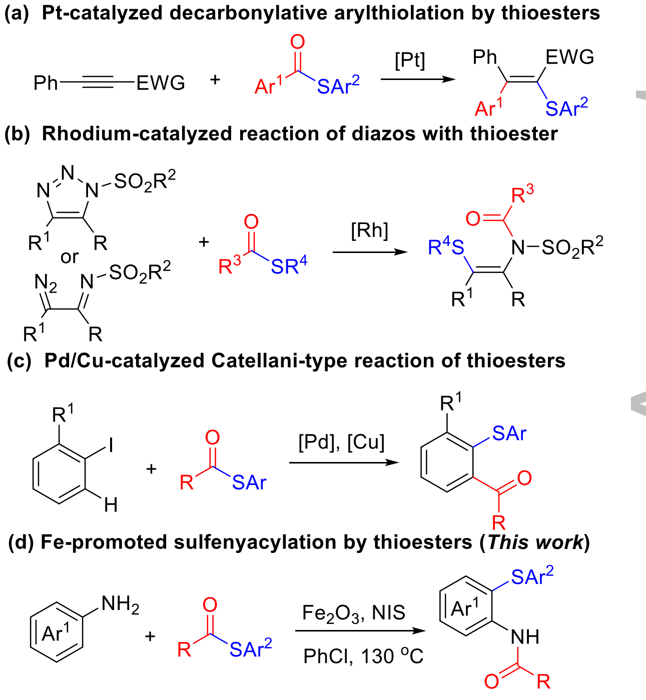
Abstract: An efficient and convenient strategy for the preparation of diaryl sulfides *via* a Fe-promoted direct sulfuracylation of 2-naphthylamine using thioesters as bifunctional reagents is described. This synthetic strategy features high chemoselectivity, good substrate scope and functional group tolerance.

Keywords: Thioesters; bifunctional; sulfuracylation; diaryl sulfides.

Sulfur-containing functional groups are widely presented in numerous natural products and bioactive compounds.[1] In particular, organosulfur compounds have been more and more important in organic synthesis since they can be used as the efficient coupling partners or building blocks. Hence, highly selective activation, cleavage, and transformation of C-S bonds are a more attractive and challenging area in organic chemistry.[2] Over the past few decades, numerous synthetic strategies have been developed for C–S bond transformations with transition-metal-catalysis including cross-couplings of thioethers,[3] thioesters,[4] ketene dithioacetals,[5] sulfonyl chlorides,[6] and other diverse organosulfur compounds.[7] However, most methodologies use only one of the fragments from C-S bond cleavage for coupling reaction. As a consequence, the discovery of new fragment assembling strategy for selective activation and functionalization of the C–S bond deserves to be explored.

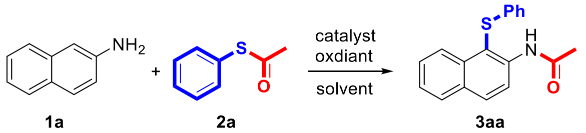
Thioesters are extremely important in pharmaceuticals and bioactive products, such as thioesters of coenzyme A (CoA), polyketide synthases (PKSs) and nonribosomal polypeptide synthetases (NRPKs).[8] Furthermore, thioesters are versatile synthetic building blocks in cross-couplings, reductions, decarbonylation, cleavage and photoredox catalysis reactions. For example, in 2000, Liebeskind and Srogl reported Pd-catalyzed, Cu-mediated cross-coupling of thiolesters with boronic acids to get ketone products (so-called "Liebeskind-Srogl cross coupling").[9] Since then, employing thioesters as coupling partner to synthesize ketones, thioethers or amides has attracted considerable attention.[10] With the development of green chemistry, more and more attention has been paid to efficient atom-economic reactions. Thioester as a bifunctional reagent could better embody the characteristic of atomic economy in green chemistry. In 2008, Kambe reported the Pt-catalyzed decarbonylative fragmentation of thioesters with internal alkynes to provide vinyl sulfides.[11] Miura and Wang reported Rh-catalyzed


(a) Pt-catalyzed decarbonylative arylthiolation by thioesters
(b) Rhodium-catalyzed reaction of diazos with thioester
(c) Pd/Cu-catalyzed Catellani-type reaction of thioesters
(d) Fe-promoted sulfenyacylation by thioesters (*This work*)

Scheme 1 New strategy for synthesis of diaryl sulfides.

C–S/C–N coupling reaction of diazos with thioester.[12] Recently, Gu and co-workers developed Pd/Cu-catalyzed ortho C−H acylation and ipso thiolation of aryl halides with thioesters.[13] Despite of significant advances, these protocols largely rely on precious 4d transition metals. In sharp contrast, the use of less toxic 3d transition metals as catalyst for C-S bond cleavage and recombination is rare.[14] Inspired by these elegant works and as our interest in C−H sulfuration, herein, we supposed a simple and efficient functionalization approach of 2-naphthylamine using thioesters as bifunctional reagents. The advantages of this reaction system include the first iron catalysis, high chemoselectivity and good substrate scope.

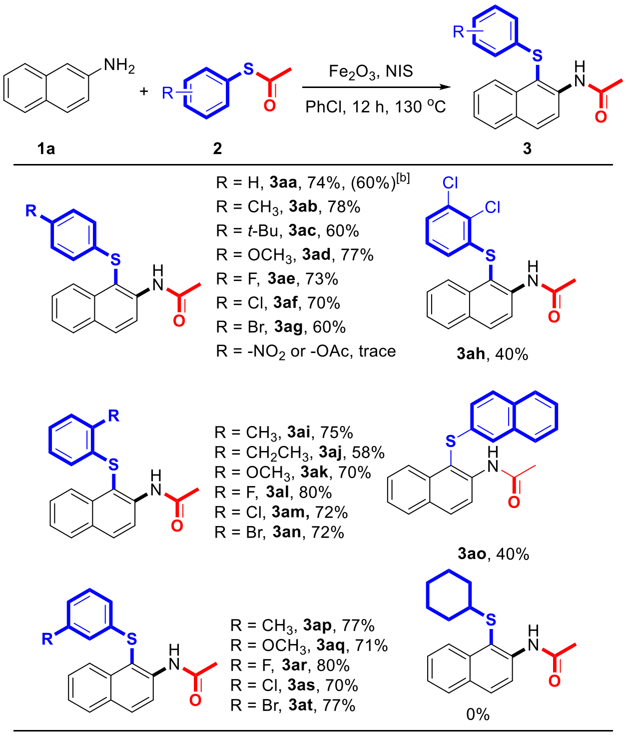
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b]
1	$FeCl_3$	NIS	PhCl	50
2	Fe	NIS	PhCl	47
3	$Fe(acac)_3$	NIS	PhCl	29
4	Ferrocene	NIS	PhCl	18
5	$Fe_2(SO_4)_3$	NIS	PhCl	56
6	Fe_2O_3	NIS	PhCl	82
7	Fe_2O_3	TBHP	PhCl	0
8	Fe_2O_3	$K_2S_2O_8$	PhCl	0
9	Fe_2O_3	NCS	PhCl	0
10	Fe_2O_3	NBS	PhCl	0
11	Fe_2O_3	$PhI(OAc)_2$	PhCl	35
12	Fe_2O_3	ICl	PhCl	40
13	Fe_2O_3	I_2 (1 eq.)	PhCl	48
14	Fe_2O_3	NIS	DMSO	trace
15	Fe_2O_3	NIS	*p*-xylene	68
16	Fe_2O_3	NIS	*o*-DCB	57
17	Fe_2O_3	NIS	$PhCH_3$	35
18	Fe_2O_3	NIS	1,4-dioxane	26
19	Fe_2O_3		PhCl	0
20		NIS	PhCl	20
21[c]	Fe_2O_3	NIS	PhCl	58
22[d]	Fe_2O_3	NIS	PhCl	60

[a] Conditions : **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), oxidant (2 equiv), solvent (1 mL), 130 °C, 12 h, air.
[b] GC yield.
[c] NIS (1 equiv).
[d] 120 °C.

Table 2. Scope of *S*-phenyl benzothioate.[a]

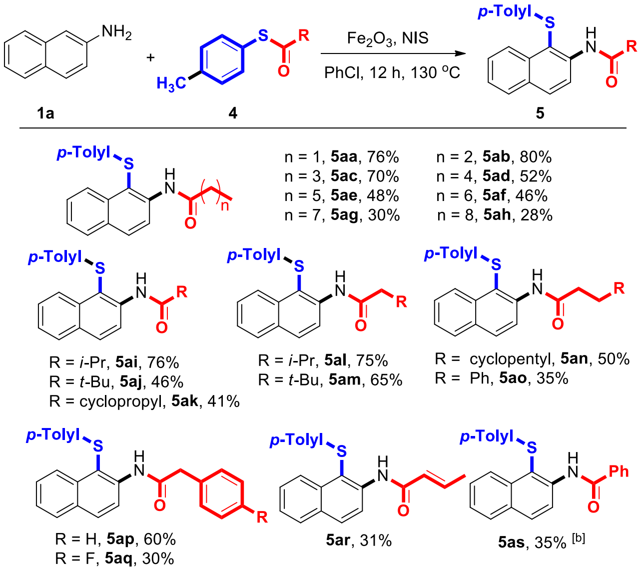


[a] Conditions : **1a** (0.2 mmol), **2a** (0.4 mmol), Fe_2O_3 (5 mol%,≥ 99.9%), NIS (2 equiv), PhCl (1 mL), 130 °C, 12 h, air. [b] 6 mmol.

Our initial investigation began with 2-naphthylamine (**1a**) and *S*-phenyl benzothioate (**2a**) in the presence of $FeCl_3$ and *N*-iodosuccinimide (NIS) in chlorobenzene. To our delight, the desired product **3aa** was obtained in 50% yield (Table 1, entry 1). Encouraged by this result, we screened various other iron catalysts including iron powder, $Fe(acac)_3$, ferrocene, $Fe_2(SO_4)_3$, and Fe_2O_3 (entries 2-6). Among them, Fe_2O_3 was proved to be the most effective catalyst for the coupling reaction, giving the desired product in 82% yield (entry 6), whereas ferrocene gave a lower yield (entry 4). The desired product was not observed when other oxidants such as *tert*-butyl hydroperoxide (TBHP), $K_2S_2O_8$, NCS, and NBS were used (entries 7-10). The use of $PhI(OAc)_2$, ICl and molecular iodine did not show better efficiency, in contast lower yields were obtained (entries 11-13). Further investigation of solvents revealed that PhCl demonstrated the best performance, while DMSO, *p*-xylene, 1,2-dichlorobenzene (*o*-DCB), toluene and 1,4-dioxane were proved to be unsuitable reaction media (entries 14-18). As a control experiments, no reaction was occurred in the absence of any iodide-containing additives (entry 19). The product **3aa** was obtained in only 20% yield when the reaction was carried out without iron catalyst (entry 20). We speculated that the addition of catalytic amount of Fe_2O_3 would facilitate the C-S bond cleavage of thioesters. Decreasing the amount of NIS or the reaction temperature both led to decrease the product yields (entries 21-22).

With this concurrent functionalization procedure in hand, the substrate scope toward this novel 2-naphthylamine sulfuration was then investigated, and the results are listed in Table 1. First, we examined the influence of substituent on the phenyl sulfide ring. The desired product **3aa** was isolated in 74% yield when the model reaction of **1a** and **2a** was carried out under established conditions. Substrates with electron-donating groups (-CH_3, and -OCH_3) at the *para* position of the phenyl sulfide ring (**3ab**–**3ad**) had similar yields except for **3ac** in lower yield. Halogen substituents on the phenyl sulfide ring were also amenable for this sulfuracylation (**3ae**–**3ag**). Interestingly, the steric hindrance effect of the substituent was not apparent, whether the substituents were at *ortho* or *meta* position. For example, when the methoxy was located in *para* (**2d**), *ortho* (**2k**) or *meta* (**2q**) position on the phenyl sulfide ring, the corresponding products **3ad**, **3ak** and **3aq** were obtained in 77%, 70% and 71% yields, respectively. However, the yield was dramatically decreased when the chloro was located at both *ortho* and *meta* position (**3ah**). When *S*-(naphthalen-2-yl) ethanethioate (**2o**) was used, the desired product **3ao** was observed albeit in 40% yield. Unfortunately, no corresponding product was obtained when the thioester was changed from *S*-aryl ethanethioate to *S*-alkyl ethanethioate.

Table 3. Scope of the thioester.[a]

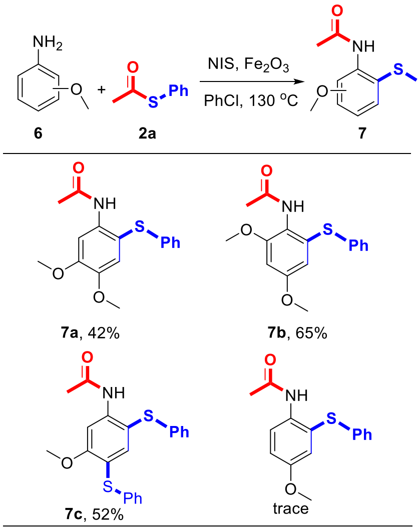


[a] Conditions : **1a** (0.2 mmol), **4** (0.4 mmol), Fe_2O_3 (5 mol%, ≥ 99.9%), NIS (2 equiv), PhCl (1 mL), 130 °C, 12 h, air. [b] 30 mol% of Fe_2O_3 was used.

Furthermore, to further expand the scope of this methodology, the acyl component was also examined (Table 3). The results show that the desired product yields were significantly affected by the alkyl chain length of acyl. Good yields were achieved when the length of acyl chain contains 3 to 5 carbons (**5aa-5ac**). And the yields were decreased with the increasing of chain length (**5ad-5ah**). Moderate to good yields of the target products were generally obtained when other acyl substrates with branched chains were used (**5ai-5ao**). Phenyl acetyl substrates produced the corresponding products (**5ap** and **5aq**) with a big gap in the yields. In addition, crotonoyl and benzoyl thioesters can also work with **1a** to afford the corresponding products **5ar** and **5as** in 31% and 35% yield, respectively.

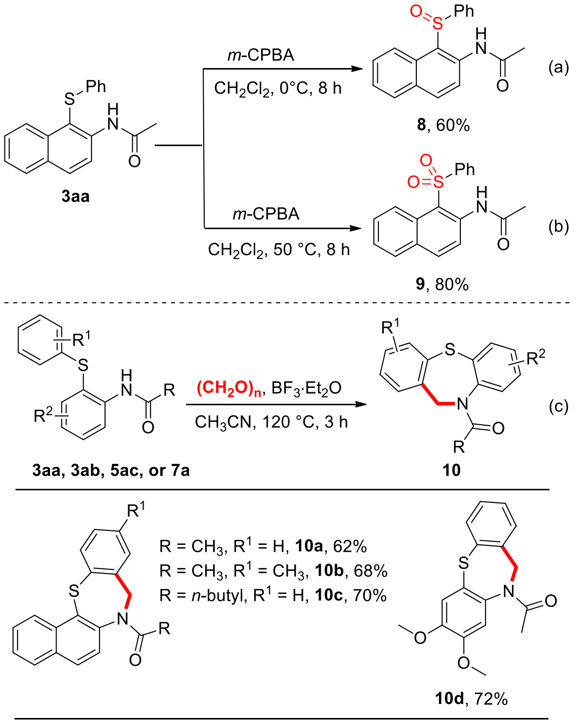
Apart from 2-naphthylamine (**1a**), other methoxy substituted anilines such as 3,4-dimethoxyaniline (**6a**), 2,4-dimethoxyaniline (**6b**), and 3-methoxyaniline (**6c**) could also be applied in this reaction system to provide the corresponding products in moderate yields. It is noteworthy that the disulfuracylation product **7c** was obtained when using 3-methoxyaniline (**6c**) as the substrate (Table 4).

Table 4. Scope of anilines.[a]

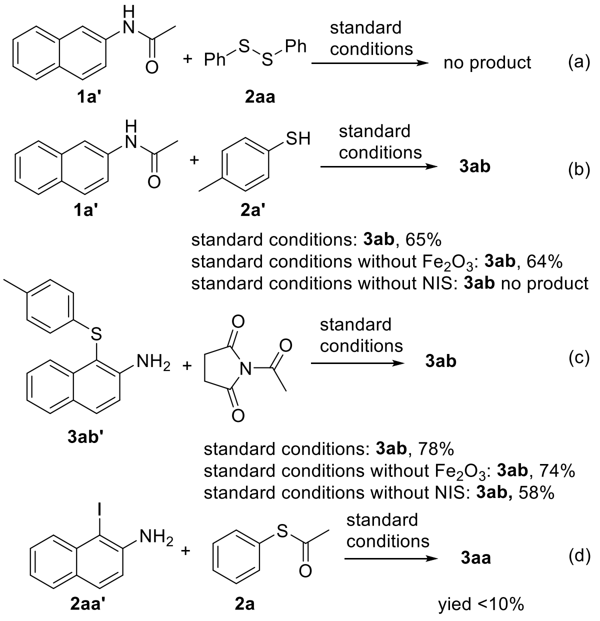


[a] Conditions : **6** (0.2 mmol), **2a** (0.4 mmol), Fe_2O_3 (5 mol%, ≥ 99.9%), NIS (2 equiv), PhCl (1 mL), 130 °C, 12 h, air.

Further examples of the synthetic applications of this method are shown in scheme 2. When **3aa** was treated with *m*-CPBA in dichloromethane at 0 °C, the oxidation product sulfoxide **8** was obtained in 60% yield (Scheme 2, a). Furthermore, the sulfone product **9** can be obtained in 80% when the temperature was raised to 50 °C (Scheme 2, b). Cyclization of the diaryl sulfides were exemplified using paraformaldehyde as the carbon source promoted by $BF_3{\cdot}Et_2O$, which afforded the seven-membered ring products in good yields (Scheme 2, c). The product **10a** was obtained in 62% yield when **3aa** was used as substrate. The yields of cyclization products **10b** and **10c** were slightly increased when **3ab** and **5ac** were used as substrates. When *N*-(4,5-dimethoxy-2-(phenylthio)phenyl)acetamide (**7a**) was used, the seven-membered ring product **10d** was observed in 72% yield. This reaction was initiated by the formation of an imide ion and then electrophilic addition with the benzene ring to form a 7-membered ring (Pictet–Spengler Reaction).[15]

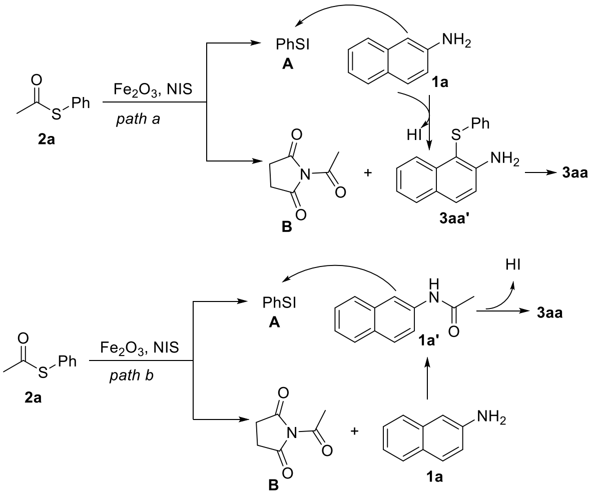


Scheme 2. Application of products.



Scheme 3. Control experiments.

In order to elucidate the reaction mechanism, more control experiments were carried out. The reaction of *N*-(naphthalen-2-yl)acetamide **1a'** (detected by GC-MS) with 1,2-diphenyldisulfane **2aa** did not produce the corresponding product (Scheme 3, a). While 4-methylbenzenethiol can react with *N*-(naphthalen-2-yl)acetamide **1a'** to produce the corresponding product **3ab** in 65% yield. The similar yield of **3ab** was obtained without Fe_2O_3. But no desired product was obtained in absence of NIS (Scheme 3, b). The 1-(*p*-tolylthio)naphthalen-2-amine **3ab'** (detected by GC-MS) can be acylated by 1-acetylpyrrolidine-2,5-dione to form corresponding amides **3ab** in 78% yield. And this reaction can be carried out smoothly without iron or NIS (Scheme 3, c). Trace yield of desired product **3aa** was obtained when 1-iodonaphthalen-2-amine **2aa**' was used as a substrate with *S*-phenyl ethanethioate under standard conditions (Scheme 3, d). This result indicates the products are not generated *via* sequential transformation involving *ortho*-iodination, acylation with the thioesters. The time-dependent change of the contained products (**3aa**, **3aa**' and **1a**') during the reaction has been analyzed (see SI, Table S1). These results indicate this reaction probably involves two pathways. In the first way, naphthylamine is thioetherified to form 2-aminodiaryl sulfide,[16] which can be acylated to synthesize the corresponding products (Scheme 4, path a). In the second way, naphthylamine was acylated to form amides and then sulfided to synthesize the corresponding products (Scheme 4, path b). Unfortunately, the exact reaction mechanism of Fe_2O_3 facilitate the C-S bond cleavage of thioesters is still not clear at this stage.



Scheme 4. Plausible mechanism.

In summary, we have reported an efficient sulfuracylation reaction of 2-naphthylamine with thioesters. In this strategy, thioesters were used as bifunctional reagents, and C-S/C-N bonds were formed with high chemoselectivity. Moreover, the broad functional group tolerance makes this method attractive for the synthesis of highly functionalized diaryl sulfides.

Experimental Section

General procedure

A 10 mL oven-dried reaction vessel was charged with Fe_2O_3 (1.6 mg, 0.01 mmol), NIS (90 mg, 0.4 mmol), 2-naphthylamine (**1a**, 28.6 mg, 0.2 mmol), *S*-phenyl ethanethioate (**2a**, 54 μL, 0.4 mmol), and PhCl (1 mL) under air. The sealed reaction vessel was stirred at 130 ºC for 12 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (5 mL). The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to yield the desired product **3aa** as white solid (43.3 mg, 74% yield), mp = 129-131 °C. R_f = 0.45 (10:1 = petroleum ether/EtOAc).

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References

[1] a) *Sulfur Compounds: Advances in Research and Application*; A. Acton, Q. Ed, Scholarly Editions: Atlanta, GA, **2012**; b) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev*. **2014**, *114*, 8807; c) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev*. **2011**, *111*, 1596; d) M. Mellah, A. Voituriez, E. Schulz, *Chem. Rev*. **2007**, *107*, 5133; e) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev*. **2014**, *114*, 8807; f) C. F. Lee, Y. C. Liu, S. S. Badsara, *Chem. Asian J.* **2014**, *9*, 706; g) C. F. Lee, Y. C. Liu, S. S. Badsara, *Topics in Current Chemistry*. **2018**, *25*, 376.

[2] For selected reviews, see: a) F. Pan, Z.-J. Shi, *ACS Catal*. **2014**, *4*, 280; b) L. Wang, W. He, Z. Yu, *Chem. Soc. Rev*. **2013**, *42*, 599; c) K. Gao, S. Otsuka, A. Baralle, K. Nogi, H. Yorimitsu, A. Osuka, *J. Synth. Org. Chem. Japn*. **2016**, *74*, 1119; d) F. Dénès, C. H. Schiesser, P. Renaud, *Chem. Soc. Rev*. **2013**, *42*, 7900.

[3] For selected examples, see: a) J. Li, Y. An, J. Li, S. Yang, W. Wu, H. Jiang, *Org. Chem. Front*. **2017**, *4*, 1590; b) F. Zhu, Z.-X. Wang, *Org. Lett.* **2015**, *17*, 1601; c) A. Baralle, H. Yorimitsu, A. Osuka, *Chem. Eur. J*. **2016**, *22*, 10768; d) L. Gao, B. Chang, W. Qiu, L. Wang, X. Fu, R. Yuan, *Adv. Synth. Ca*tal. **2016**, *358*, 1202; e) K. Gao, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* **2016**, *55*, 4573; f) H.-M. Guo, Q.-Q. Zhou, X. Jiang, D.-Q. Shi, W.-J. Xiao, *Adv. Synth. Catal.* **2017**, *359*, 4141; g) H. Zang, J.-G. Sun, X. Dong, P. Li, B. Zhang, *Adv. Synth. Catal*. **2016**, *358*, 1746.

[4] For selected examples, see: a) M. Arisawa, T. Tazawa, S. Tanii, K. Horiuchi, M. Yamaguchi, *Org. Chem*. **2017**, *82*, 804; b) B. Kang, S. H. Hong, *Chem. Sci*. **2017**, *8*, 6613; c) N. Ichiishi, C. A. Malapit, Ł. Woźniak, M. S. Sanford, *Org. Lett*. **2018**, *20*, 44; d) C. Liu, M. Szostak, *Chem. Commun*. **2018**, *54*, 2130.

[5] For selected examples, see: a) K. Murakami, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed*. **2014**, *53*, 7510; b) Q. Wang, X. Yang, P. Wu, Z. Yu, *Org. Lett*. **2017**, *19*, 6248; c) Y. Dong, B. Liu, P. Chen, Q. Liu, M. Wang, *Angew. Chem. Int. Ed*. **2014**, *53*, 3442; d) B. Li, G. Zheng, X. Liu, C. Xu, J. Liu, M. Wang, *Chem. Commun*. **2013**, *49*, 2201.

[6] For selected examples, see: a) S. R. Dubbaka, P. Vogel, *J. Am. Chem. Soc*. **2003**, *125*, 15292; b) C. M. R. Volla, P. Vogel, *Angew. Chem. Int. Ed*. **2008**, *47*, 1305; c) G.-B. Deng, Z.-Q. Wang, J.-D. Xia, P.-C. Qian, R.-J. Song, M. Hu, L-B. Gong, J.-H. Li, *Angew. Chem. Int. Ed*. **2013**, *52*, 1535; d) S. K. Pagire, A. Hossain, O. Reiser, *Org. Lett*. **2018**, *20*, 648.

[7] For selected examples, see: a) X. Zhou, J. Luo, J. Liu, S. Peng, G. J. Deng, *Org. Lett*. **2011**, *13*, 1432; b) G. Wang, T. Miao, *Chem. Eur. J*. **2011**, *17*, 5787; c) F.-L. Yang, X.-T. Ma, S.-K. Tian, *Chem. Eur. J*. **2012**, *18*, 1582; d) B. Liu, J. Li, F. Song, J. You, *Chem. Eur. J*. **2012**, *18*, 10830; e) L. Huang, J. Qi, X. Wu, W. Wu, H. Jiang, *Chem. Eur. J*. **2013**, *19*, 15462; f) L.-W. Qian, M. Sun, J. Dong, Q. Xu, Y. Zhou, S.-F. J. Yin, *Org. Chem*. **2017**, *82*, 6764.

[8] a) V. Hirschbeck, P. H. Gehrtz, I. Fleischer, *Chem. Eur. J.* **2018**, *24*, 7092; b) F. Pietrocola, L. Galluzzi, J. M. Bravo-San Pedro, F. Madeo, G. Kroemer, *Cell Metab.* **2015**, *21*, 805; c) M. B. Austin, J. P. Noel, *Nat. Prod. Rep*. **2003**, *20*, 79; d) C. L. Yi, Y. T. Huang, C. F. Lee, *Green Chem.* **2013**, *15*, 2476; e**)** J. W. Zeng, Y. C. Liu, P. A. Hsieh, Y. T. Huang, C. L. Yi, S. S. Badsara, C. F Lee, *Green Chem.* **2014**, *16*, 2644; f**)** Y. T. Huang, S. Y. Lu, C. L. Yi, C. F. Lee, *J. Org. Chem*. **2014**, *79*, 4561.

[9] L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc*. **2000**, *122*, 11260.

[10] For selected examples, see: a) G. K. Min, D. Hernández, A. T. Lindhardt, T. Skrydstrup, *Org. Lett.* **2010**, *12*, 4716; b) H. Ochiai, Y. Uetake, T. Niwa, T. Hosoya, *Angew. Chem. Int. Ed.* **2017**, *56*, 2482; c) M. Arisawa, M. Kuwajima, F. Toriyama, G. Li, M. Yamaguchi, *Org. Lett.* **2012**, *14*, 3804; d) C. L. Joe, A. G. Doyle, *Angew. Chem. Int. Ed.* **2016**, *55*, 4040.

[11] F. Yamashita, H. Kuniyasu, J. Terao, N. Kambe, *Org. Lett.* **2008**, *10*, 101.

[12] a) T. Miura, Y. Fujimoto, Y. Funakoshi, M. Murakami, *Angew. Chem. Int. Ed.* **2015**, *54*, 9967; b) F. Ma, J. Qian, P. Lu, Y. Wang, *Org. Biomol. Chem.* **2018**, *16*, 439.

[13] F. Sun, M. Li, C. He, B. Wang, B. Li, X. Sui, Z. Gu, *J. Am. Chem. Soc.* **2016**, *138*, 7456.

[14] P. H. Gehrtz, V. Geiger, T. Schmidt, L. Srsan, I. Fleischer, *Org. Lett.* **2019**, *21*, 50.

[15] X. Wang, X. Zheng, R. Liu, J. Reiner, J. Chang, *Tetrahedron*, **2007**, *63*, 3389.

[16] a) D. Yang, K. Yan, W. Wei, J. Zhao, M. Zhang, X. Sheng, G. Li, S. Lu, H. Wang, *J. Org. Chem.* **2015**, *80*, 6083; b) H. Tian, H. Yang, C. Zhu, H. Fu, *Adv. Synth. Catal.* **2015**, *357*, 481; c) F. Xiao, S. Chen, J. Tian, H. Huang, Y. Liu, G.-J. Deng, *Green Chem.* **2016**, *18*, 1538.

COMMUNICATION

Thioesters as Bifunctional Reagents for 2-Naphthylamine Sulfuracylation

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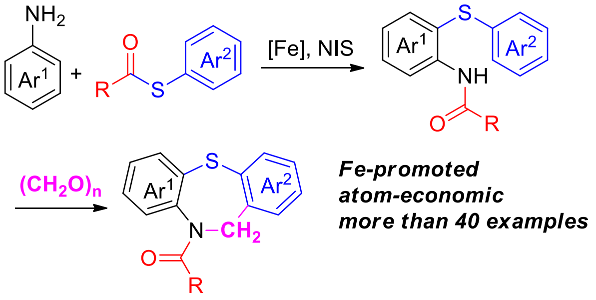

Fe-promoted
atom-economic
more than 40 examples