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Nickel-Catalyzed C–H Chalcogenation of Anilines

Thomas Müller[a] and Lutz Ackermann[a]*

Abstract: The C–H thiolation of aniline derivatives was accomplished with a versatile nickel(II) catalyst under ligand-free conditions. The robust nature of the nickel catalysis regime was reflected by C–H thiolation with good functional group tolerance and ample scope, employing anilines possessing removable directing groups. The widely applicable nickel catalyst also allowed for aniline C–H selenylations, while mechanistic studies provided strong support for rate-determining C–H activation.

2-Aminothiophenols and their selena-analogs are integral structural motifs of various bioactive compounds, and represent powerful intermediates in the synthesis of valuable heterocycles of interest to medicinal chemistry, material sciences and pharmaceutical industries.[1] For instance, 2-aminothiophenols provide expedient access to among others substituted phenothiazines, dibenzothiazepines, and benzothiazoles, which constitute key scaffolds of various antipsychotic, antidepressant and immunosuppressive agents (Figure 1).[2] The traditional syntheses of 2-aminothiophenols are largely based on the interconversion of prefunctionalized starting materials, leading to lengthy synthetic operations, along with undesired by-product formation. During the past decade step-economical C–H functionalizations have emerged as a transformative platform, avoiding the use of prefunctionalized substrates.[3] In this context, C–H chalcogenations have gained considerable momentum, predominantly relying on the use of precious 4d transition metals.[4] In light of the economic benefits associated with 3d transition metal complexes, recent focus has however shifted towards the use of earth-abundant base metal catalysis,[5] with considerable advances being realized in nickel-catalyzed C–H activations.[6] Despite the undisputable progress in nickel-catalyzed C–H thiolation,[7] the previously established methods were largely restricted to electron-deficient benzamide derivatives bearing bidentate[8] directing groups. Within our program on nickel-catalyzed C–H transformations,[9] we have now developed unprecedented nickel-catalyzed C–H chalcogenations of aniline derivatives, on which we report herein. Notable features of our findings include (i) the use of a monodentate pyrimidyl group, (ii) expedient C–H thiolations and selenylations of electron-rich anilines, (iii) ligand-free, user-friendly nickel(II) catalysis, and (iv) a removable[10] directing group approach.

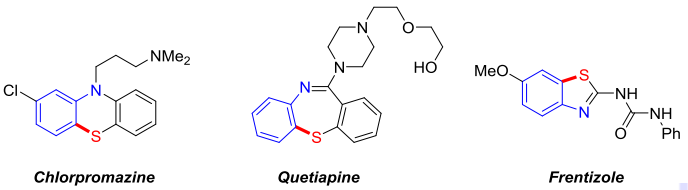
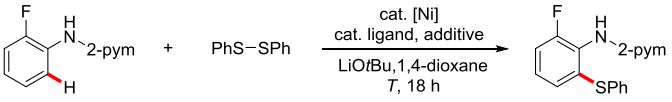


Figure 1. Bioactive drugs derived from 2-aminothiophenes.

Our study was initiated by probing various reaction conditions for the envisioned C–H thiolation of pyrimidyl aniline **1a** (Table 1 and Table S-1 in the Supporting Information).[11] Orienting optimization studies indicated that previously employed nitrogen and phosphorus ligands proved ineffective in the nickel-catalyzed aniline C–H thiolation regime (Table 1, entries 1–5). Thus, among a set of representative nickel precursors, [(DME)$NiCl_2$] and $Ni(OTf)_2$ provided the best performance. In stark contrast to our previous studies,[9a,b] additives exerted a significantly more pronounced effect than did ligands (entry 6–12), with optimal results being accomplished with MnO_2 (entry 13–15). Control experiments confirmed that a nickel catalyst was essential for the C–H thiolation catalysis (entry 13).

Table 1. Establishing the nickel-catalyzed C–H thiolation of aniline **1**.[a]



1a **2a** **3aa**

entry	[Ni]	ligand	additive	yield (%)
1	$NiCl_2$	D*t*BEDA	–	24
2	$Ni(acac)_2$	D*t*BEDA	–	14
3	[(DME)$NiCl_2$]	D*t*BEDA	–	31
4	[(DME)$NiCl_2$]	PPh_3	–	26
5	$Ni(OTf)_2$	D*t*BEDA	–	31
6	$Ni(OTf)_2$	D*t*BEDA	$Zn(OTf)_2$	50[b]
7	$Ni(OTf)_2$	PPh_3	$Zn(OTf)_2$	35[b]
8	$Ni(OTf)_2$	PPh_3	V_2O_5	24[b]
9	$Ni(OTf)_2$	PPh_3	$FeCl_3$	18[b]
10	$Ni(OTf)_2$	PPh_3	MnO_2	73[b]
11	$Ni(OTf)_2$	PPh_3	MnO_2	91
12	$Ni(OTf)_2$	PCy_3	MnO_2	68
13	–	–	MnO_2	–
14	**$Ni(OTf)_2$**	**–**	**MnO_2**	**96**
15	$Ni(OTf)_2$	–	MnO_2	89[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 equiv), [Ni] (10 mol %), ligand (20 mol %), LiO*t*Bu (2.0 equiv), additive (1.0 equiv) 1,4-dioxane (1.5 mL), 120 °C, 18 h; yields of isolated products. [b] 0.5 equiv additive. [c] $Ni(OTf)_2$ (2.5 mol %). D*t*BEDA = di-*tert*-

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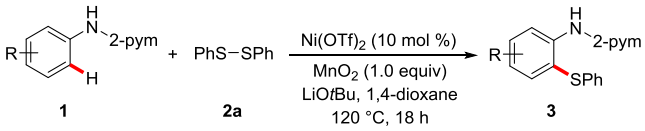
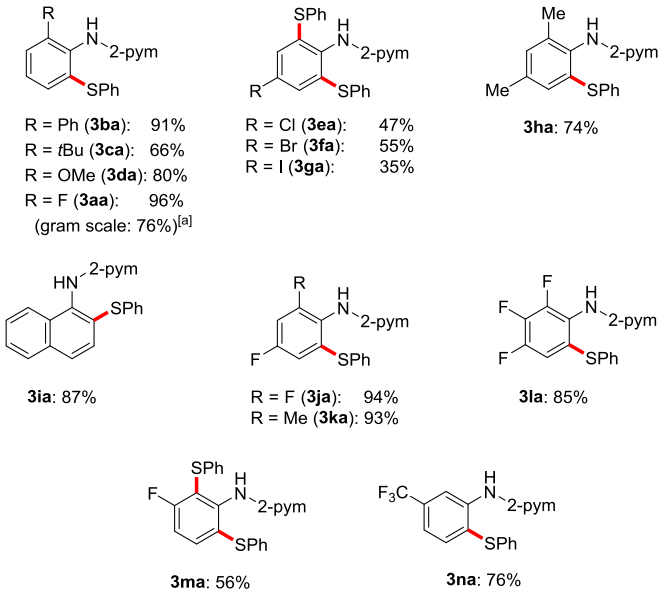
butylethylenediamine

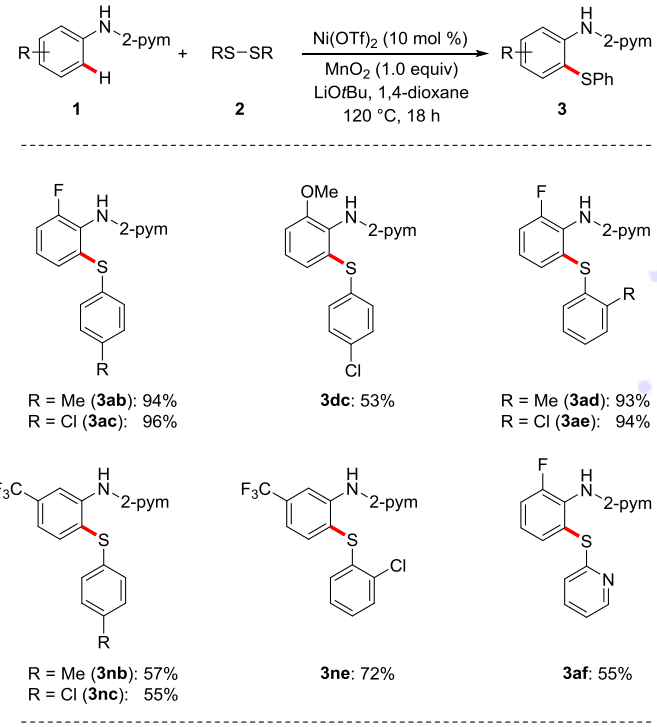
Encouraged by these results, we next explored the catalyst's versatility in the C–H thiolation process (Scheme 1). The optimized protocol was characterized by high levels of positional selectivities, thereby solely delivering the *ortho*-thiolated products **3aa**–**3na**.[12] The C–H functionalization with naphthalene derivative **1i** occurred site-selectively at the β-position, while the peri-C–H bond remained unchanged. The conversion of *ortho*-fluoro-substituted anilines **1a**, **1j** and **1l** chemo-selectively occurred by C–H functionalization, while products stemming from C–F[13] functionalization were not observed. C–H thiolations on *meta*-decorated arenes **1m** and **1n** proceeded preferentially at the less congested C–H bond. The robustness of the optimized nickel catalyst was reflected by tolerating valuable electrophilic functional groups, such as chloro, bromo and iodo substituents, thus providing a handle for further diversification. Moreover, the gram-scale synthesis of product **3aa** was accomplished in high yields at a significantly reduced catalyst loading.





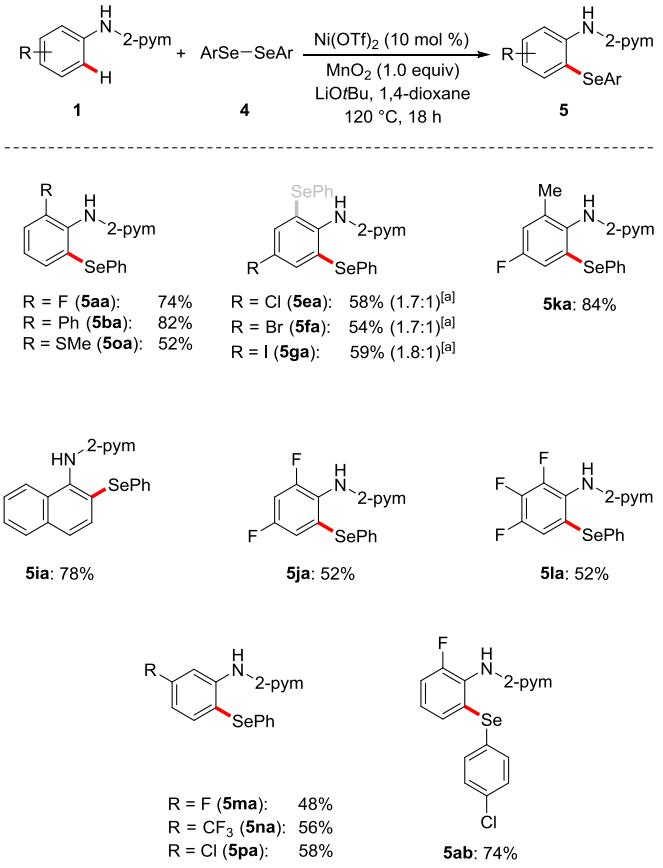
Scheme 1. Scope of the nickel-catalyzed C–H thiolation of anilines **1**, yields of isolated products. [a] $Ni(OTf)_2$ (2.5 mol %).

Subsequently, the scope of viable disulfides **2** was explored (Scheme 2). Indeed, substituents in the *para*- and the more sterically congested *ortho*-position were well accepted by the optimized nickel catalyst. Interestingly, the challenging pyridyl disulfide **2f** was identified as a viable substrate likewise, despite of its remarkable bidentate coordination ability.



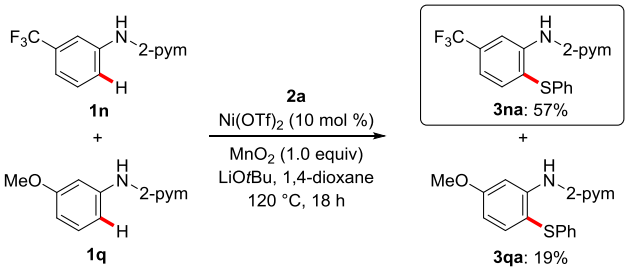
Scheme 2. Nickel-catalyzed C–H thiolation with disulfides **2**.

The versatility of the optimized nickel catalyst was further illustrated by allowing for the aniline C–H selenylation under otherwise identical reaction conditions. Thus, a variety of aniline derivatives **1** and diselenides **4** were efficiently converted to the desired 2-aminoselenophenols **5** (Scheme 3). The C–H selenylation proceeded with high positional selectivity and good tolerance of valuable functional groups.



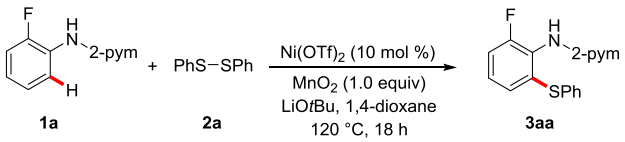
Scheme 3. C–H Selenation of anilines **1** with diselenide **4**, all yields of isolated products. [a] mono/di selectivity in parenthesis.

In consideration of the unique features of the nickel-catalyzed aniline C–H chalcogenation, we became attracted to delineating its mode of action. To this end, we performed intermolecular competition experiments that highlighted electron-poor anilines to react preferentially (Scheme 4), thereby rendering an electrophilic mode of action unlikely to be operative.



Scheme 4. Intermolecular competition experiment.

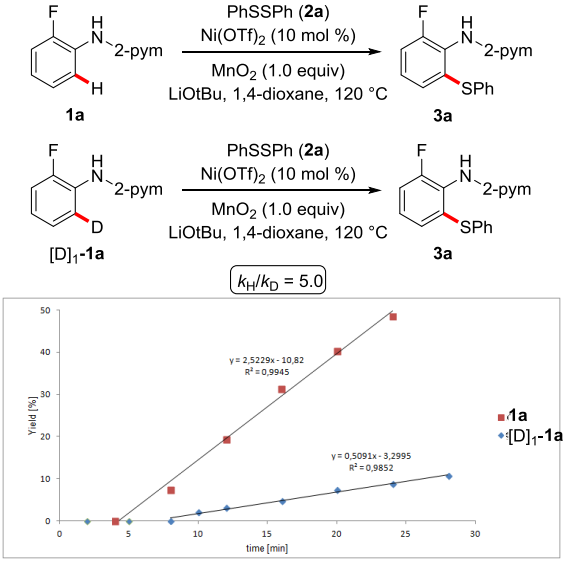
The nickel-catalyzed C–H functionalization was inhibited by the addition of representative radical scavengers (Scheme 5). These findings can be rationalized in terms of SET-type processes being of key relevance.



additive (2.0 equiv)	Yield
TEMPO	6%
BHT	---
galvinoxyl	---

Scheme 5. Influence of radical scavengers.

Subsequently, we studied the kinetics of the C–H thiolation process. Hence, independent experiments with the substrate **1a** and its isotopically labeled [D]$_1$-**1a** revealed a kinetic isotope effect (KIE) of $k_H/k_D \approx 5$ (Scheme 6), indicating a rate-determining C–H activation.



Scheme 6. KIE by independent experiments.

Based on our mechanistic findings, we propose a catalytic cycle to commence by rate-determining C–H nickelation (Scheme 7). Then, oxidation by a sulfenyl radical generates a nickel(III) species that subsequently undergoes reductive elimination. The active nickel(II) catalyst is proposed to be regenerated by the action of the disulfide **2**, which itself is formed by the action of the oxidant MnO_2.[14]

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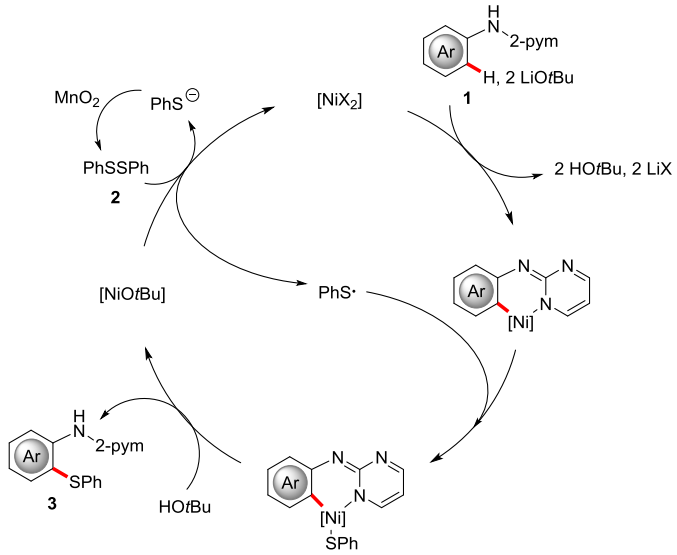
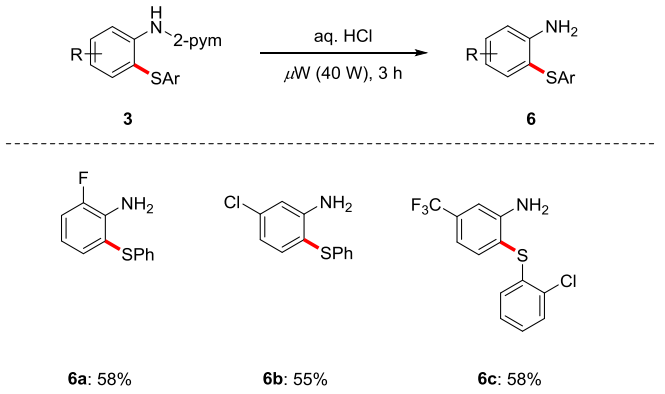


Scheme 7. Plausible catalytic cycle.

The practical utility of the nickel-catalyzed C–H chalcogenation strategy was illustrated by the facile removal of the pyrimidyl group in a traceless fashion, thereby deliberating the desired 2-amino thiophenols **6** (Scheme 8).



Scheme 8. Pyrimidyl removal in a traceless fashion.

In summary, we have reported on the first nickel-catalyzed C–H chalcogenation of aniline derivatives. Thus, a ligand-free $Ni(OTf)_2$ catalyst enabled expedient C–H thiolation with high levels of positional control and good chemo-selectivity. The robustness of the catalyst was reflected by tolerating valuable functional groups as well as by enabling first nickel-catalyzed aniline C–H selenylations. Mechanistic studies provided evidence for SET-type processes and a rate-limiting C–H activation. The traceless removal of the pyrimidyl group set the stage for an efficient access to synthetically meaningful 2-amino thiophenols.

Acknowledgements

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Keywords: C–H activation • mechanism • nickel • selenylation • sulfenylation

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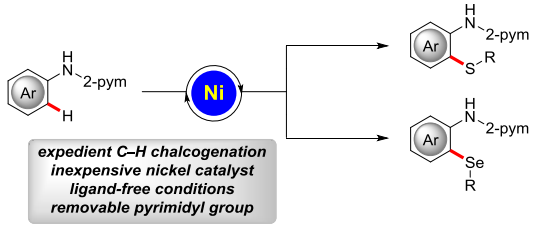

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Nickel-Catalyzed C–H Chalcogenation of Anilines

Expedient nickel-catalyzed C–H thiolations were achieved under ligand-free reaction conditions, which also enabled site-selective C–H selenylation with ample scope through a removal directing group strategy.