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Paired Electrolysis

Nickel-Catalyzed *N*-Arylation of *NH*-Sulfoximines with Aryl Halides via Paired Electrolysis

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Abstract: *A novel strategy for the N-arylation of NH-sulfoximines has been developed by merging nickel catalysis and electrochemistry (in an undivided cell), thereby providing a practical method for the construction of sulfoximine derivatives. Paired electrolysis is employed in this protocol, so a sacrificial anode is not required. Owing to the mild reaction conditions, excellent functional group tolerance and yield are achieved. A preliminary mechanistic study indicates that the anodic oxidation of a Ni^{II} species is crucial to promote the reductive elimination of a C–N bond from the resulting Ni^{III} species at room temperature.*

Transition-metal-catalyzed *N*-arylation of sulfoximines has received significant attention[1] since *N*-arylated sulfoximines are essential structural units in chiral auxiliaries,[2] ligands for various catalytic asymmetric reactions,[3] building blocks in pseudopeptides,[4] and bioactive molecules (Figure 1 a).[5] For instance, in 1998 Bolm and Hildebrand reported an elegant example of Pd-catalyzed *N*-arylation of sulfoximines with aryl bromides at 110 °C for 48 h using BINAP as the ligand.[6] Inspired by this seminal work, various protocols for Pd-catalyzed *N*-arylation of sulfoximines using different arene sources have been developed.[7] Additionally, Cu-catalyzed *N*-arylation of sulfoximines with aryl iodides, aryl bromides, aryl boronic acids, and diaryliodonium salts has been developed by Bolm and others, although the coupling with aryl chlorides has not been disclosed.[8] In contrast, *N*-arylation of sulfoximines with aryl halides using nickel catalysis is less explored, although nickel catalysts are inexpensive and exhibit high reactivities toward less reactive electrophiles such as aryl chlorides in cross-coupling reactions between aryl halides and amines.[9,10] Bolm and co-workers reported the sole example, specifically using $Ni(COD)_2$ with BINAP to catalyze the *N*-arylation of sulfoximines with aryl tosylates, although elevated temperatures was required, only two substrate examples were shown, and yields were modest (Figure 1 b).[11] Common drawbacks to these catalytic *N*-arylations of sulfoximines with aryl halides include the need for high temperatures, restricted substrate scope, and the reliance on alkoxide bases. To address the aforementioned issues, König and Wimmer recently developed *N*-arylation of sulfoximines with aryl bromides at room temperature, by merging Ni catalysis with Ir photocatalysis.[12] Subsequently, Hande and co-workers reported a similar transformation with aryl iodides.[13] Unfortunately, expensive Ir catalysts are needed for these protocols, and *N*-arylation of *NH*-sulfoximines using readily available aryl chlorides has not been reported.

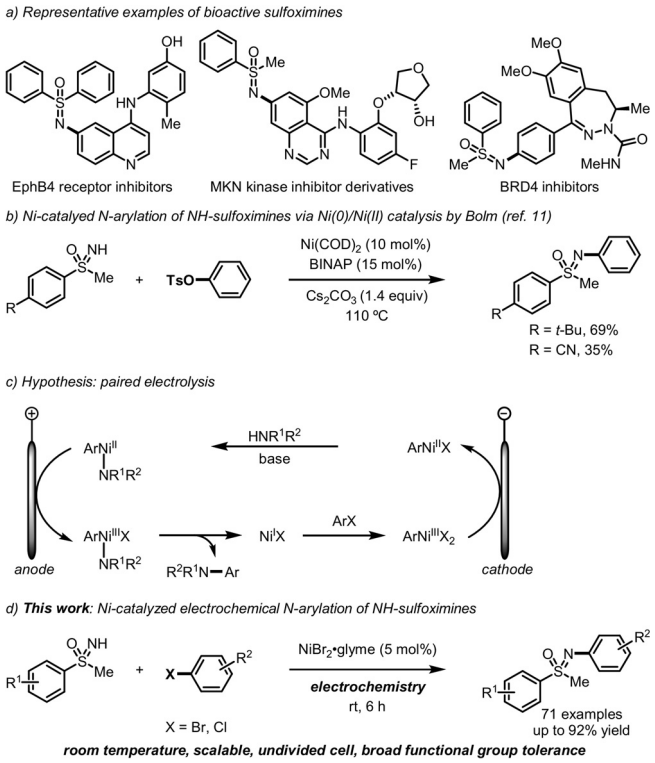

Figure 1. a) Representative examples of bioactive sulfoximines. b) Conventional transition-metal-catalyzed *N*-arylation of *NH*-sulfoximines. c) Our hypothetical nickel-catalyzed electrochemical approach. d) This work.

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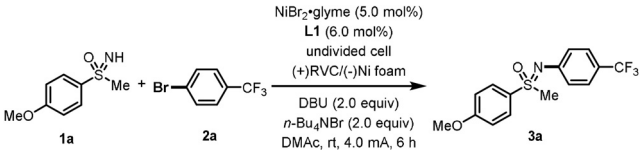
chemical oxidants or reductants and also provides alternative reactivity and selectivity modes.[14] In particular, the merger of nickel catalysis and electrochemistry has emerged as a useful strategy for cross-coupling reactions.[15] For instance, Baran and co-workers reported Ni-catalyzed amination of aryl halides under mild reaction conditions,[16] whereby more than two oxidation states of nickel can be accessed in the same pot.[17] Our group has a long-standing interest in Ni-catalyzed electrochemical couplings with aryl halides.[18] We hypothesized that Ni-catalyzed electrochemical *N*-arylation of *NH*-sulfoximines with aryl halides could take place under mild reaction conditions via paired electrolysis,[19] wherein anodic oxidation could generate a Ni^{III} species to promote C-N reductive elimination while cathodic reduction could produce a Ni^{I} species from a Ni^{II} precatalyst. The resulting Ni^{I} species could oxidatively add to an aryl halide to give $ArNi^{III}X_2$, which could readily undergo cathodic reduction to produce a $ArNi^{II}X$ intermediate (Figure 1c). Herein, we establish that Ni-catalyzed *N*-arylation of *NH*-sulfoximines using aryl bromides and chlorides can be executed efficiently at room temperature (Figure 1d). A preliminary mechanistic study indicates that the anodic oxidation of a Ni^{II} species is crucial to promote the C–N bond reductive elimination from the resulting Ni^{III} species.

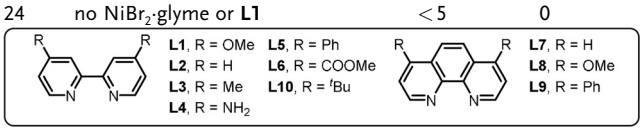
Initially, we employed *NH*-sulfoximine **1a** and bromoarene **2a** as model reactants and probed various reaction conditions in an undivided cell for the envisioned electrochemical *N*-arylation (Table 1; see Tables S1 and S2 in the Supporting Information for additional details). After extensive optimization, we found that 90% isolated yield of the desired *N*-arylated sulfoximine **3a** could be obtained under constant-current electrolysis at 4.0 mA in the presence of 5.0 mol% of $NiBr_2$·glyme, 6.0 mol% 4,4′-dimethoxy-2,2′-bipyridine **L1**, two equivalents of DBU, and two equivalents of *n*-Bu_4NBr in DMAc at room temperature after 6 h (Table 1, entry 1). The reactivity diminished significantly when an electrode such as carbon or platinum was used (entries 2–5). Other Ni catalysts such as $NiBr_2$, $NiCl_2$·glyme, and NiI_2 resulted in lower yields (entries 6–8). Additionally, other bases such as DBN, DABCO, and Et_3N proved ineffective. Finally, evaluating different bipyridine ligands and phenanthroline ligands revealed that **L1** is optimal (entries 12–20). 76% isolated yield is obtained when the reaction is carried out with IKA ElectraSyn 2.0 at room temperature (entry 21). Control experiments indicated that the Ni catalyst, electric current, and ligand are all required for this reaction (entries 23–24, Table 1).

With optimized reaction conditions in hand, the substrate scope was investigated to probe the generality and to identify limitations of this Ni-catalyzed electrochemical *N*-arylation of *NH*-sulfoximines. As shown in Table 2, the catalytic system exhibits excellent functional group tolerance. In general, both electron-deficient and electron-rich aryl bromides afford good yields under the standard conditions (**3b**–**3i**). A variety of functional groups are readily accommodated, including ester (**3b**), cyano (**3c**), sulfone (**3d** and **3e**), amino (**3f**, **3g**, and **3x**), ethers (**3h**, **3i**, **3l**, **3m**), thioethers (**3j** and **3k**), fluoro (**3n**), chloro (**3o**), boronic acid pinacol ester (**3p**), alcohol (**3q**), aryl (**3r** and **3s**), and alkyl (**3t**–**3v**) groups. The presence

Table 1: Reaction optimization and control studies.[a]



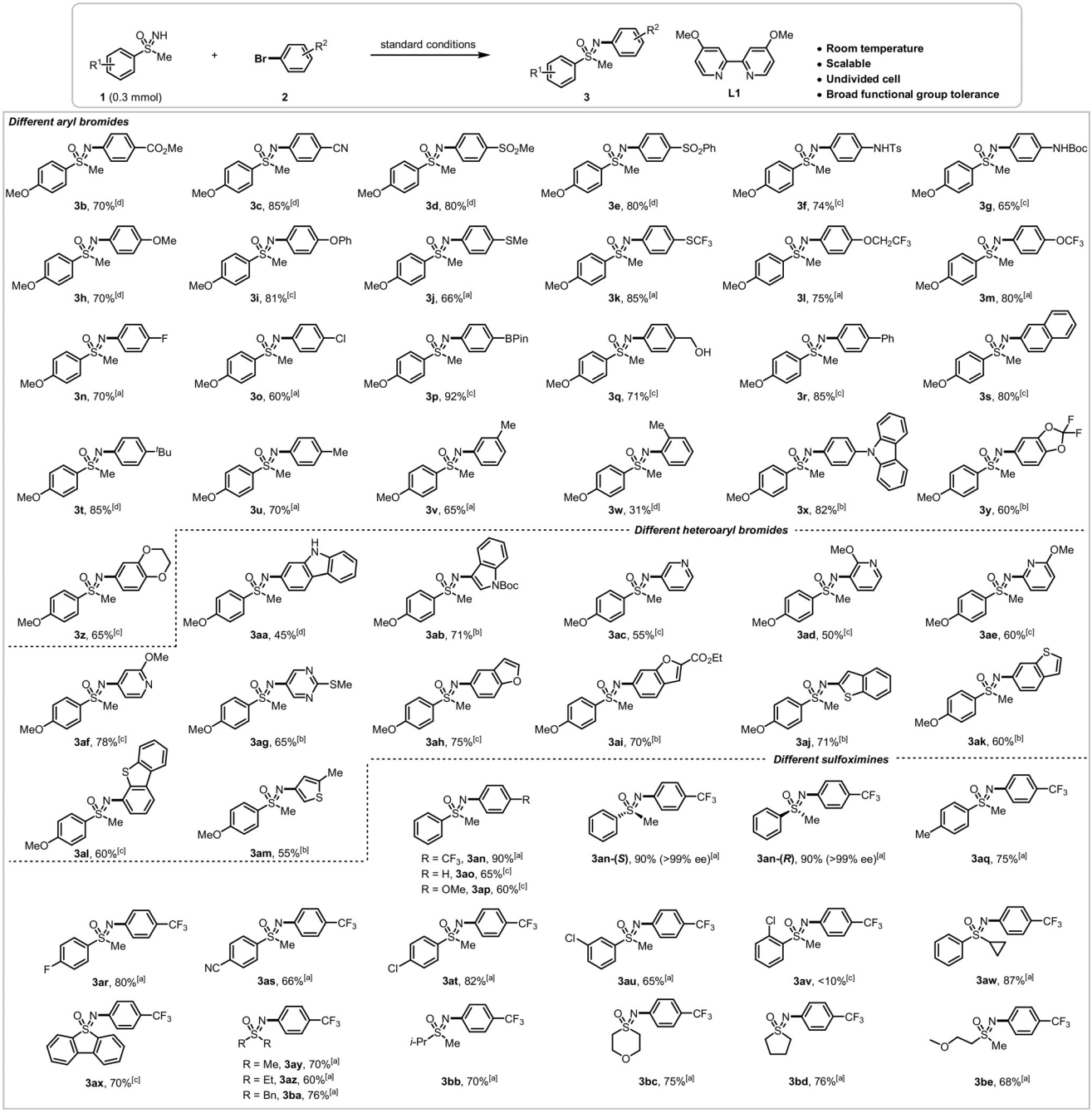
Entry	Deviation from standard conditions	Conv. [%][b]	Yield [%][b]
1	none	100	91 (90)[c]
2	C in lieu of RVC	35	20
3	Pt in lieu of RVC	28	15
4	C in lieu of Ni foam	10	NR
5	Pt in lieu of Ni foam	5	NR
6	$NiBr_2$ in lieu of $NiBr_2$·glyme	85	80
7	$NiCl_2$·glyme in lieu of $NiBr_2$·glyme	56	55
8	NiI_2 in lieu of $NiBr_2$·glyme	80	78
9	DBN in lieu of DBU	71	60
10	DABCO in lieu of DBU	14	11
11	Et_3N in lieu of DBU	10	5
12	**L2** in lieu of **L1**	70	55
13	**L3** in lieu of **L1**	74	70
14	**L4** in lieu of **L1**	31	30
15	**L5** in lieu of **L1**	60	55
16	**L6** in lieu of **L1**	22	20
17	**L7** in lieu of **L1**	58	50
18	**L8** in lieu of **L1**	30	15
19	**L9** in lieu of **L1**	85	53
20	**L10** in lieu of **L1**	100	80
21	IKA ElectraSyn 2.0	90	76[c]
22	gram scale	100	85[d]
23	no electric current	< 5	0
24	no $NiBr_2$·glyme or **L1**	< 5	0



[a] Standard reaction conditions: **1a** (1.5 equiv), **2a** (0.2 mmol) $NiBr_2$·glyme (5.0 mol%), **L1** (6.0 mol%), DBU (2.0 equiv), *n*-Bu_4NBr (2.0 equiv), and DMAc (2.0 mL) at rt, in an undivided cell subject to 4.0 mA of current for 6 h using RVC ($1.2\times1.2\times0.3$ cm^3) and Ni foam (2.0×3.0 cm^2) electrodes, argon, 4.97 $F mol^{-1}$. [b] Determined by ^{19}F NMR analysis using 1-fluoronaphthalene as an internal standard. [c] Isolated yield in parentheses. [d] Gram Scale (5.0 mmol of **2a**), see the Supporting Information for details. RVC = reticulated vitreous carbon, DMAc = *N*,*N*-dimethylacetamide, DBN = 1,5-diazabicyclo-[4.3.0]non-5-ene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

of a methyl group in the *ortho* position reduced reactivity (**3w**), presumably because of increased steric encumbrance. Heterocycles such as carbazole (**3x**), benzodioxine (**3y**), and benzodioxole (**3z**) are well tolerated. Additionally, various heteroaryl bromides are also competent coupling partners, including carbazole (**3aa**), indole (**3ab**), pyridine (**3ac**–**3af**), pyrimidine (**3ag**), benzofuran (**3ah**–**3ai**) benzothiophene (**3aj**–**3al**), and thiophene (**3am**), affording the corresponding arylated sulfoximines in good yields. Encouraged by the above results, the scope of *NH*-sulfoximine was examined using 4-bromobenzotrifluoride **2a** as a mode aryl halide as shown in Table 2. Electron-neutral (**3an**), electron-rich (**3aq**), and electron-deficient (**3ar**–**3av**) sulfoximines were tested, and the corresponding products were furnished in good to excellent yields. Notably, sulfoximines bearing cyclopropyl

Table 2: Evaluation of substrate scope.[a]



[a] Yield of isolated products unless otherwise indicated. The reaction was carried out in an undivided cell with $NiBr_2$·glyme (5.0 mol%), **L1** (6.0 mol%), DMAc (0.1 M), *n*-Bu_4NBr (2.0 equiv), DBU (2.0 equiv), RVC anode (1.2×1.2×0.3 cm^3), Ni foam cathode (2.0×3.0 cm^2), constant current (I = 4.0 mA, 6.0 h for 0.2 mmol scale), RT. [b] $NiBr_2$·glyme (5.0 mol%), **L1** (15.0 mol%). [c] $NiBr_2$·glyme (10.0 mol%), **L1** (12.0 mol%). [d] $NiBr_2$·glyme (10.0 mol%), **L1** (30.0 mol%).

(**3aw**), diaryl (**3ax**), and dialkyl (**3ay**–**3be**) groups are well tolerated and afford the respective products in good to excellent yields. To further demonstrate the utility of our method, we reacted enantiopure *NH*-methylphenylsulfoximine with 4-bromobenzotrifluoride **2a** and no racemization was observed (**3an-*R***, **3an-*S***).

Ni-catalyzed *N*-arylation of *NH*-sulfoximines with aryl chlorides is unknown, although aryl chlorides are more readily available than aryl bromides or aryl iodides. To our delight, the developed protocol could be applied to the diversification of medicinally relevant compounds containing aryl chlorides (**4a**–**4f**), showcasing the utility of this chemistry (**5a**–**5l**). In contrast, Cu-catalyzed reactions with aryl chlorides[8j] lead to low yields as shown in Figure 2a.

To gain insight into the mechanism of this electrochemical *N*-arylation of *NH* sulfoximines, we first treated 2-bromo-

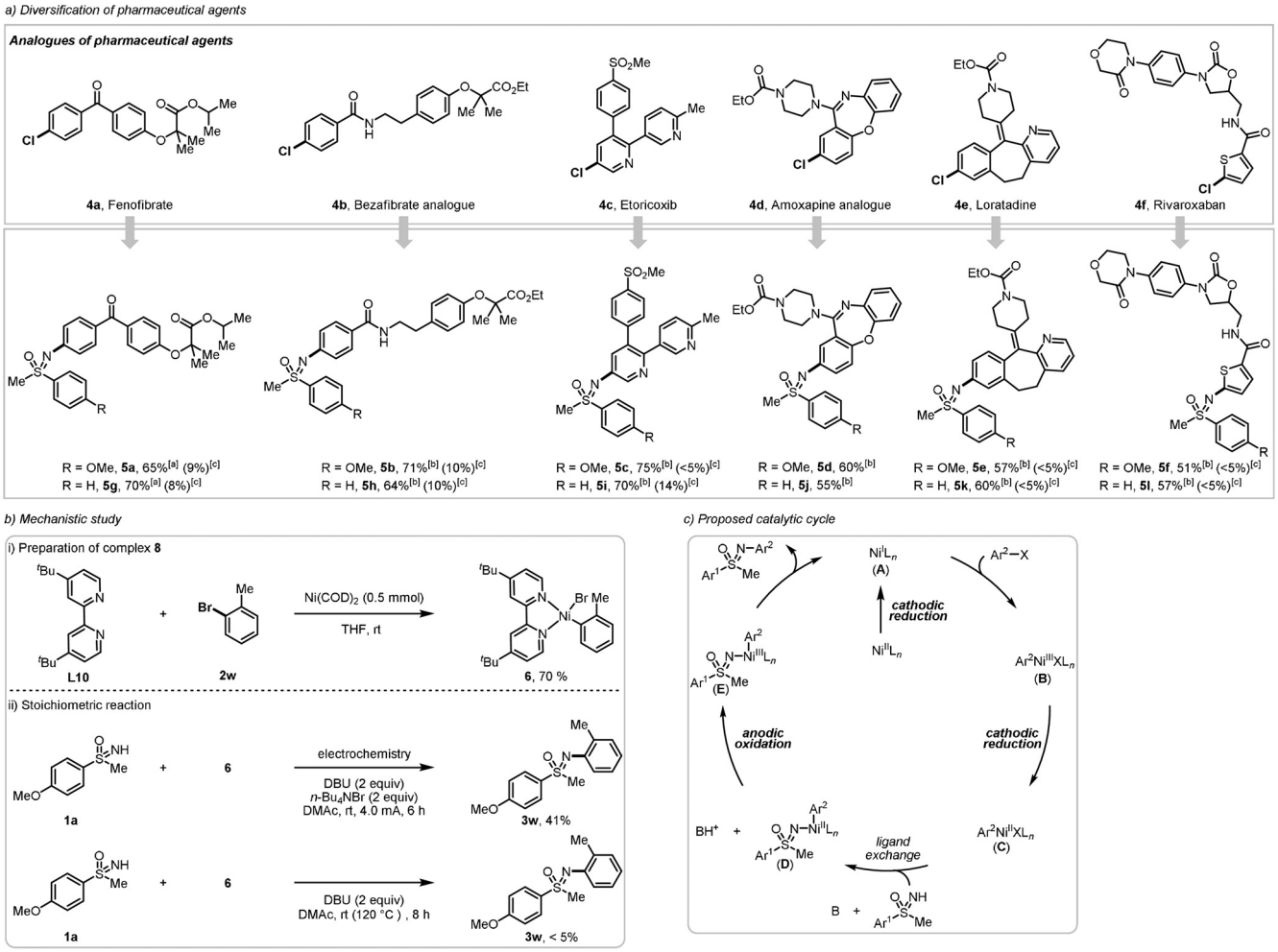


Figure 2. Diversification of pharmaceutical agents, mechanistic study, and proposed catalytic cycle. [a] $NiBr_2$·glyme (10.0 mol%), **L1** (30.0 mol%). [b] $NiBr_2$·glyme (15.0 mol%), **L1** (30.0 mol%), 8.0 h. [c] aryl chloride (2.0 equiv), CuI (10.0 mol%), DMEDA (20.0 mol%), NaI (4.0 equiv), dioxane, 110°C, 20 h, then addition of sulfoximine(1.0 equiv), Cs_2CO_3 (2.5 equiv) followed by further stirring at 110°C for 20 h. DMEDA stands for *N*,*N*-dimethylethylene diamines.

toluene **2w** with 4,4′-*tert*-butyl-2,2′-bipyridine **L10** in the presence of one equivalent of $Ni(COD)_2$ at room temperature for four hours, affording Ni^{II} complex **6** in 70% yield. Treatment of **6** with sulfoximine **1a** at room temperature, 120°C did not give significant amounts of product **3w**. However, when **6** and **1a** were subjected to electric current, **3w** was formed in 41% yield, indicating that anodic oxidation of $ArNi^{II}$ species to form $ArNi^{III}$ is crucial for the product formation (Figure 2b).

Based on literature support[17] and our own cyclic voltammetric studies (see Figures S1–S4 in the Supporting Information for details), we propose a plausible catalytic cycle as shown in Figure 2c. First, the Ni^{II} catalyst is reduced to Ni^{I} species (**A**) by cathodic reduction. Then, after the oxidative addition, an $ArNi^{III}$ intermediate (**B**) is generated. Upon cathodic reduction of **B**, the resulting $ArNi^{II}$ species can undergo ligand exchange with a *NH*-sulfoximine in the presence of a base, affording the corresponding $ArNi^{II}$ species (**D**). After anodic oxidation of the resulting **D**, the $ArNi^{III}$ species (**E**) is formed, which undergoes reductive elimination to give the arylated product **3** or **5** and regenerate the Ni^{I} species. However, we cannot rule out other possible pathways at this stage, in which a $Ni^{0}/Ni^{II}/Ni^{III}/Ni^{I}$ catalysis sequence is involved[20] instead of the aforementioned $Ni^{I}/Ni^{III}/Ni^{II}/Ni^{I}$ sequence.

In summary, we have demonstrated the first example of Ni-catalyzed electrochemical *N*-arylation of *NH* sulfoximines with aryl bromides and chlorides in an undivided cell at room temperature, affording sulfoximidoyl derivatives with good to excellent yields. The protocol is operationally simple and robust. Owing to the mild reaction conditions, excellent functional group tolerance is achieved and the developed protocol is amenable to the diversification of medicinally relevant compounds. Further research to explore the mechanism and to develop metal-catalyzed electrochemical cross-couplings is currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arylation · Ni catalysis · organic electrochemistry · paired electrolysis · sulfoximines

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