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Article

Redox-Neutral Cross-Coupling Amination with Weak *N*-Nucleophiles: Arylation of Anilines, Sulfonamides, Sulfoximines, Carbamates, and Imines via Nickelaelectrocatalysis

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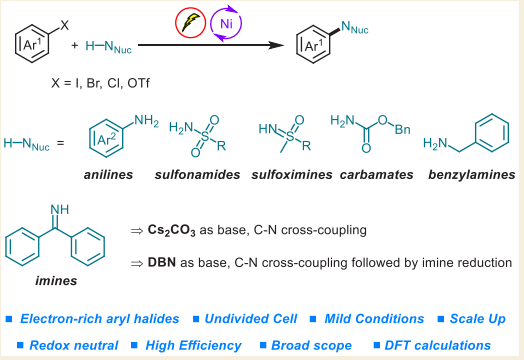
ABSTRACT: A nickel-catalyzed cross-coupling amination with weak nitrogen nucleophiles is described. Aryl halides as well as aryl tosylates can be efficiently coupled with a series of weak *N*-nucleophiles, including anilines, sulfonamides, sulfoximines, carbamates, and imines via concerted paired electrolysis. Notably, electron-deficient anilines and sulfonamides are also suitable substrates. Interestingly, when benzophenone imine is applied in the arylation, the product selectivity toward the formation of amine and imine product can be addressed by a base switch. In addition, the alternating current mode can be successfully applied. DFT calculations support a facilitated reductive elimination pathway.



KEYWORDS: *Nickel, Redox-neutral, Paired electrolysis, C−N bond formation, Aryl halides, DFT calculations, Buchwald−Hartwig amination, Electrochemistry*

Nitrogen-containing molecules belong to one of the most important classes of organic compounds due to their wide application in the fields of synthetic, pharmaceutical, and materials science.[1−3] As such, great efforts have been devoted to the development of general and effective approaches for the construction of C−N bonds.[4−6] In this regard, palladium-,[7−11] copper-,[12−15] or nickel-catalyzed[16−21] aminations of organic halides have had great impact in both academic research as well as industrial applications.[4,22,23] In recent years, the extension to other types of electrophilic coupling partners has been investigated.[24−27] Despite the advances made, many of the protocols still suffer from drawbacks, which may include the use of either air-sensitive or costly metal catalysts, complicated ligand architectures, strong bases, or the need of higher temperature, which results in a narrow application and substrate scope. In order to address these issues, dual catalytic strategies have been developed, which provided the amines under milder reaction conditions.[28] For instance, a photoredox and nickel dual-catalyzed amination reaction of aryl halides with aliphatic amines has been described by MacMillan.[29] Concurrently, Johannes, Oderinde, and co-workers reported a cross-coupling procedure for C−N bond formations by focusing on the cross-coupling of primary arylamines with aryl iodides via a dual-catalyzed methodology.[30] Notably, Johannes and co-workers also realized the amination of aryl halides with aryl azides via a similar strategy.[31] These transformations proceeded under very mild reaction conditions with high efficiency and selectivity in the absence of specialized ligands due to the generation of unstable Ar−Ni^{III}−NR$_1$R$_2$ intermediates resulting in a facile reductive elimination. Recently, organic electrochemistry has attracted the attention of organic chemists due to possible advantages, which may include energy economy, sustainability, mild reaction conditions, adjustability, as well as scalability.[32,33] With the use of renewable electricity and by simply adjusting the current or voltage, various organic transformations could be achieved.[34−43]

In particular, paired electrolysis represents an attractive platform wherein the half-reactions at both the anode and cathode are simultaneously used to generate the desired intermediates or products.[44−47] Importantly, the combination of electrolysis and nickel catalysis led to considerable advances in C−C and C−heteroatom bond formations under mild conditions.[48−58] In this context, the Baran group developed a nickelaelectrocatalyzed amination reaction of aryl halides and triflates with aliphatic amines[48] and extended the scope to amino acid esters, nucleosides, and oligopeptides afterward.[50]

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However, in this leading work, challenging coupling partners such as electron-rich aryl halides as well as weak nucleophilic anilines and sulfonamides remained problematic (Figure 1a).

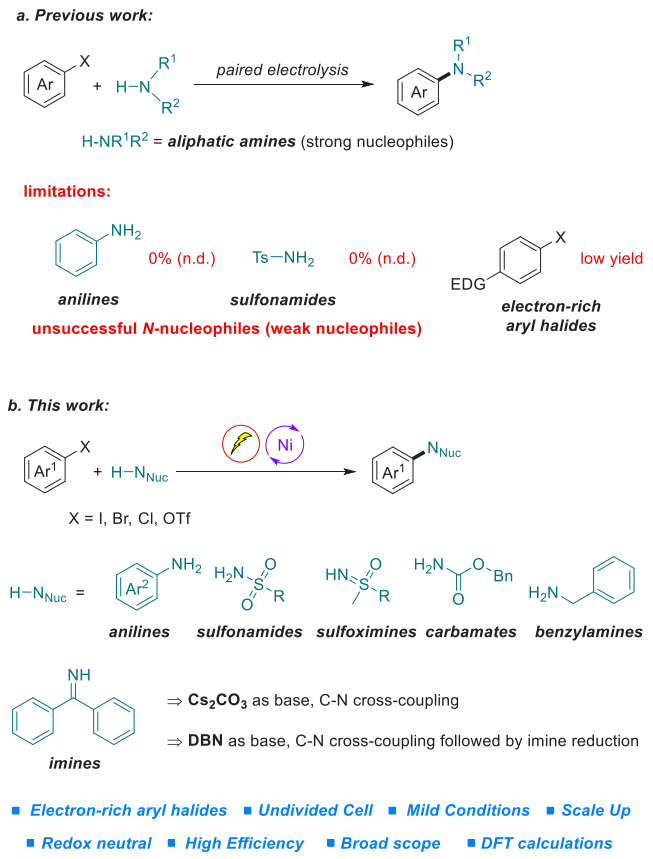
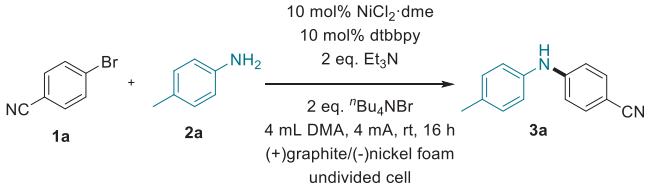


Figure 1. (a) Paired electrolysis for N-arylation reactions with aliphatic amines and limitations. (b) Nickel-catalyzed redox-neutral cross-coupling with weak *N*-nucleophiles including anilines, sulfonamides, sulfoximines, carbamates, benzylamines, and imines via paired electrolysis.

Given our interest in the electrochemical transformations,[59−61] the high importance and demand of amines in chemistry, and the current cross-coupling limitations, we decided to develop a more general amination protocol. Herein, we report a nickelaelectrocatalyzed cross-coupling C−N bond formation of aryl electrophiles with a series of weak nucleophiles including anilines, sulfonamides, sulfoximines,[62] carbamates, benzylamines, and imines via paired electrolysis (Figure 1b).

We started our investigation by evaluating the cross-coupling of 4-bromobenzonitrile **1a** and *p*-toluidine **2a** (Table 1). A series of optimization experiments were conducted, and the best reaction conditions with regard to yield and product selectivity were obtained with $NiCl_2$·dme as the catalyst, dtbbpy as the ligand, Et_3N as the base, $^nBu_4NBr$ as the electrolyte, DMA as the solvent, and with graphite/nickel foam as the electrodes in an undivided cell at room temperature. The evaluation of bases showed that inorganic bases and other organic bases resulted in inferior results when compared to Et_3N (entries 2−6). This may due to the fact that bases such as DBU better coordinate to the Ni intermediate, thus increasing the overall activation energy.[63] The use of other solvents, including DMF and MeCN, provided lower yields (entries 7 and 8). Replacement of the graphite anode and nickel foam cathode with other electrodes such as Cu foam, stainless steel,

Table 1. Optimization of the Reaction Conditions[a]



entry	variables	yield (%)[b]
1	**none**	**76 (72)**
2	DBU as base	NR
3	DIPEA as base	56
4	TMG as base	40
5	BTMG as base	27
6	K_3PO_4 as base	64
7	DMF as solvent	47
8	MeCN as solvent	64
9	Cu foam as cathode	29
10	stainless steel as cathode	8
11	Pt as cathode	9
12	Pt as anode	40
13	bpy as ligand	53
14	d(4-OMe)-bpy as ligand	21
15	2, 6, 8 mA	20, 65, 41
16	4 equiv of LiBr as electrolyte	62
17	$^nBu_4NPF_6$ as electrolyte	53
18	no electricity	NR
19	no nickel	NR
20	no ligand	13
21	no electrolyte	9
22	no base	6

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $NiCl_2$·dme (0.02 mmol), dtbbpy (0.02 mmol), Et_3N (2 equiv), $^nBu_4NBr$ (2 equiv) in 4.0 mL of DMA in an undivided cell at rt under argon for 16 h. I = 4 mA. Anode: graphite, cathode: nickel foam. [b]GC yield using dodecane as an internal standard. Isolated yield in parentheses.

and Pt led to lower yields (entries 8−12). The use of other bipyridine ligands also resulted in lower yields (entries 13 and 14). The adjustment of current indicated that 4 mA provided better yields (entry 15). The use of other electrolytes showed no improvement (entries 16 and 17). The control experiments demonstrated that electricity, nickel, ligand, electrolyte, as well as base are all essential for the success of this nickel-aelectrocatalyzed protocol (entries 18−22). With the optimized reaction conditions in hand, the scope for the cross-coupling of aryl bromides and anilines was examined. As shown in Table 2, a series of electronically and sterically diverse aryl bromides participated in this newly developed nickelaelectrocatalyzed protocol, and the corresponding products were isolated in good yields. The chemoselectivity of the transformation is good as illustrated by the tolerance of functional groups including cyano, ester, ketone, sulfone, trifluoromethyl, trifluoromethoxyl, and trifluoromethylthio moieties (**3a**−**3j**). Importantly, an *ortho* substituent is also compatible with the reaction conditions (**3c**). Furthermore, reactive functional groups such as fluoro- or chloro-substituents or boronic esters are tolerated, providing the possibility for further late-stage functionalization (**3k**−**3m**). Disubstituted aryl bromides also underwent the reaction with good efficiency (**3n** and **3o**). Electron-neutral and electron-rich aryl bromides can also be applied in the amination reaction (**3p** and **3q**). In addition, the reaction also proceeds with good

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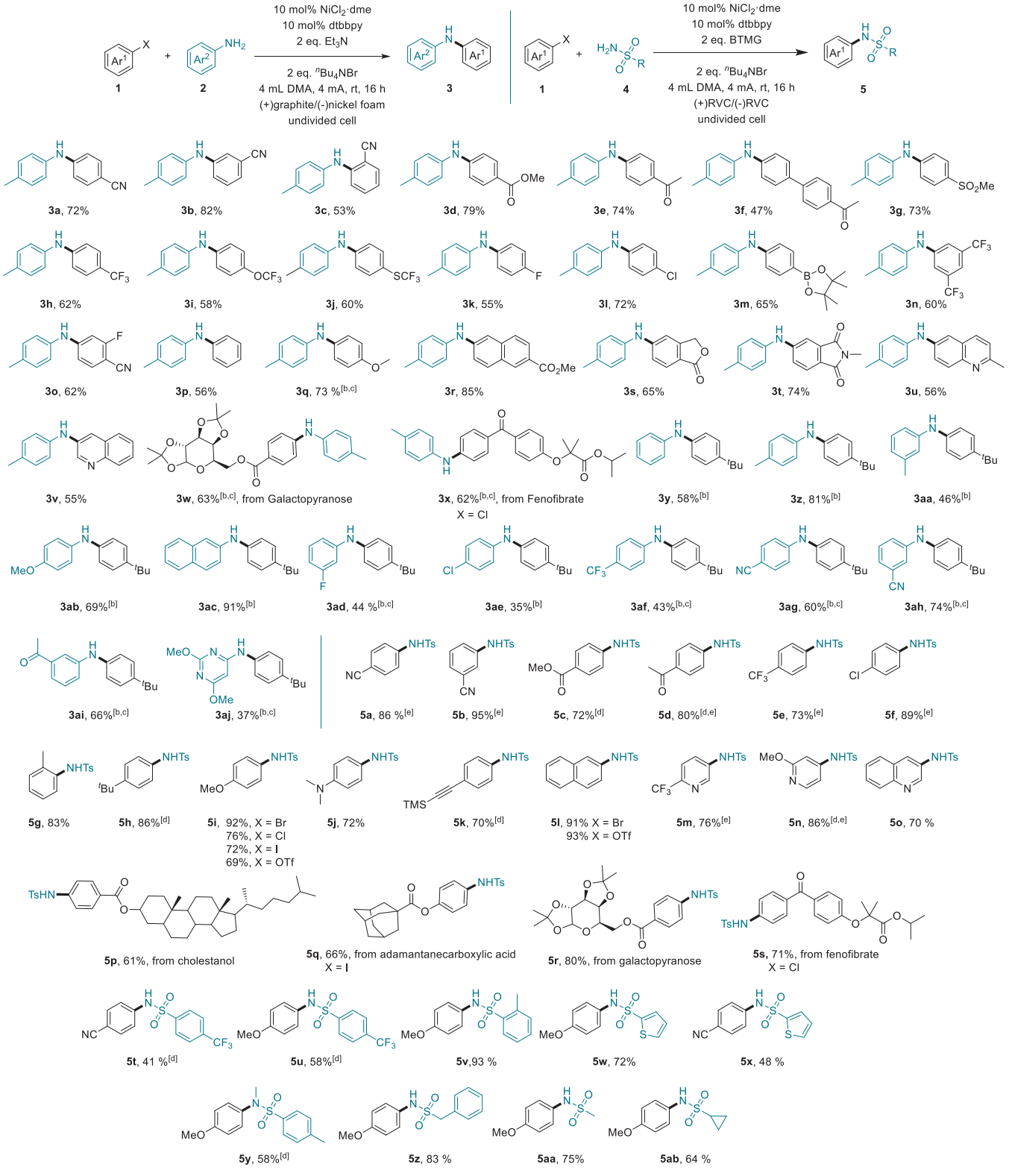
Table 2. Scope of Substrates[a]



[a]General reaction conditions for arylation of anilines: aryl halide **1** (0.2 mmol), anilines **2** (0.4 mmol), $NiCl_2$·dme (0.02 mmol), dtbbpy (ligand, 0.02 mmol), Et_3N (base, 2 equiv), and $^nBu_4NBr$ (electrolyte, 2 equiv) in 4.0 mL of DMA at rt under argon for 16 h. *I* = 4 mA. Anode: graphite, cathode: nickel foam. General reaction conditions for arylation of sulfonamides: aryl halide **1** (0.2 mmol), sulfonamides **2** (0.4 mmol), $NiCl_2$·dme (0.02 mmol), dtbbpy (ligand, 0.02 mmol), BTMG (base, 2 equiv), and $^nBu_4NBr$ (electrolyte, 2 equiv) in 4.0 mL of DMA at rt under argon for 16 h. *I* = 4 mA. Anode: RVC (reticulated vitreous carbon), cathode: RVC. X = Br, except specified. Yields after purification. [b]Anode: RVC, cathode: RVC. [c]TMG (2 equiv) as base. [d]**4** as the limiting reagent (0.2 mmol); 2 equiv of **1** (0.4 mmol) was used. [e]Reaction time 3 h.

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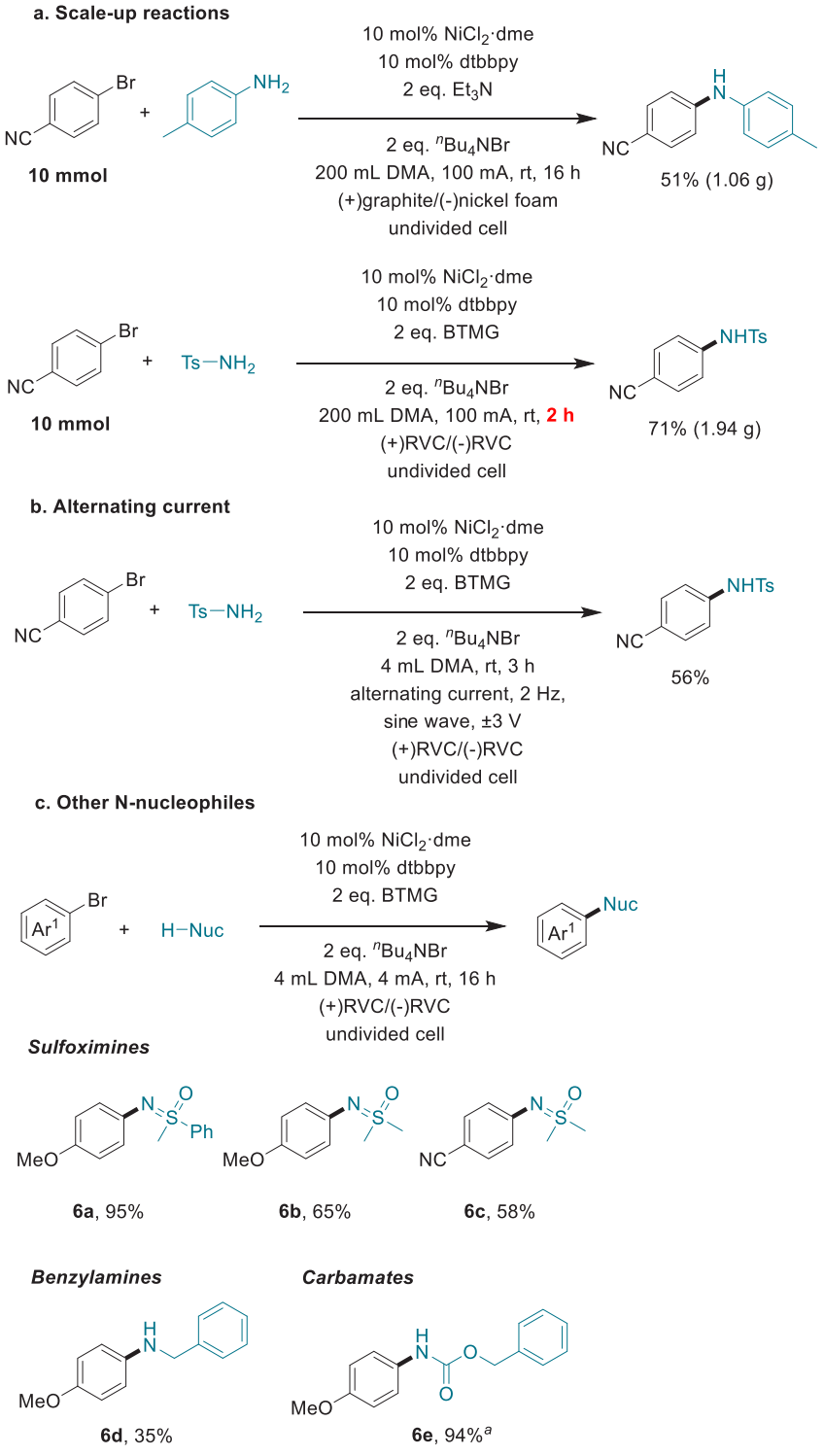

Figure 2. (a) Scale-up reactions. (b) Alternating current reactions. (c) N-Arylation reactions with other *N*-nucleophiles, including sulfoximines, benzylamines, and carbamates. [a]MeCN as solvent.

efficiency with bicyclic substrates containing lactone, imide, and quinoline motifs (**3s**–**3v**). Importantly, galactopyranose-derived aryl bromide and fenofibrate could also be aminated with good efficiency (**3w** and **3x**), showing the potential of this protocol in the functionalization of pharmaceutical-related compounds. Anilines, irrespective of their electronic nature, can be applied in the amination protocol. Whereas the use of electron-neutral and electron-rich anilines provided the products in good yields (**3y**–**3ac**), significantly weaker nucleophiles such as anilines bearing fluoro, chloro, trifluoromethyl, cyano, and acetyl groups also afforded the corresponding products albeit in moderate to good yields (**3ad**–**3ai**). Importantly, heterocyclic pyrimidine amine could also be arylated (**3aj**). Given the good results obtained for the synthesis of diarylamines applying the newly developed nickelaelectrocatalyzed amination protocol of aryl halides with anilines, we decided to also test other *N*-nucleophiles. Sulfonamides are of vital importance in the pharmaceutical

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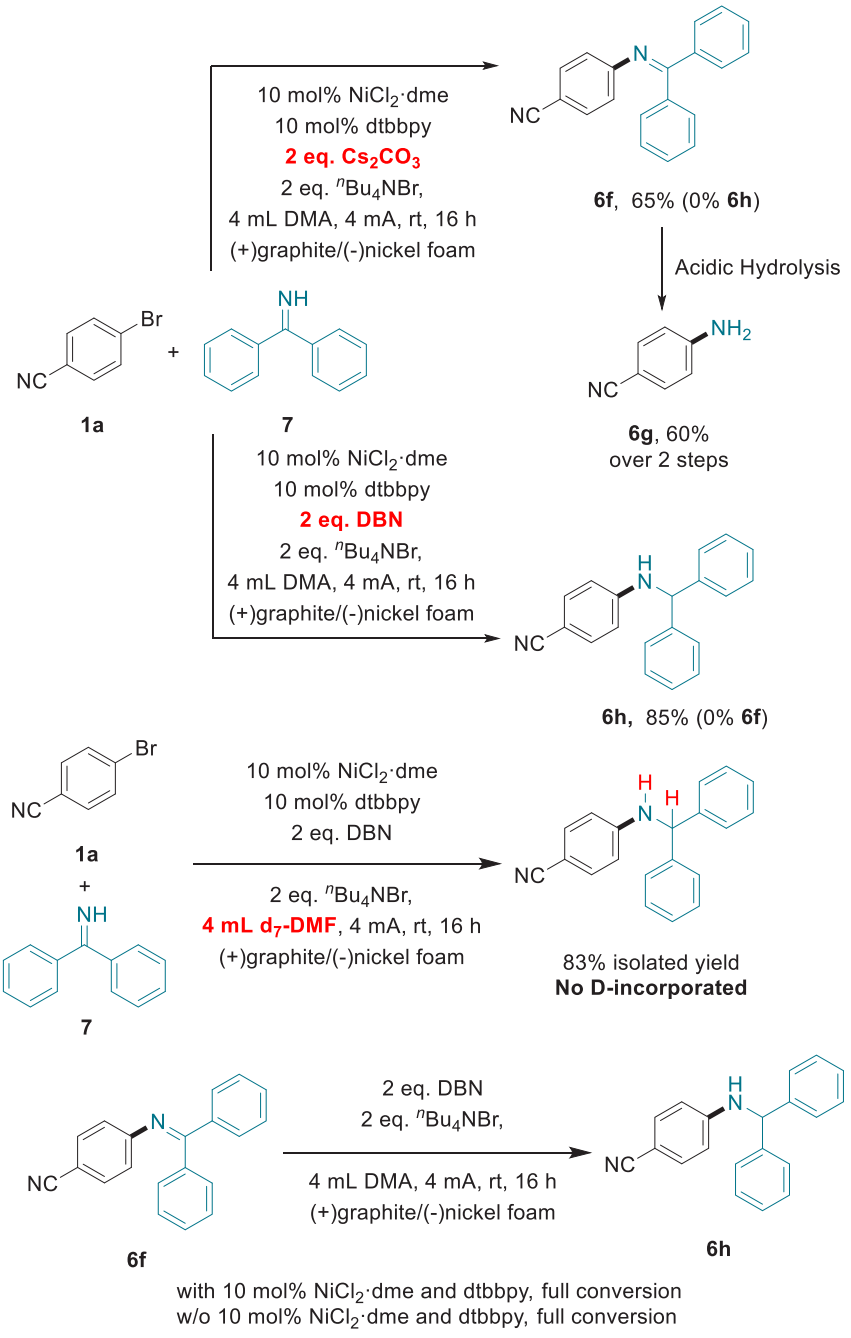

Figure 3. N-Arylation reactions with imines.

industry.[19,64] Gratifyingly, our newly developed protocol can also be applied to the sulfonamidation reaction with little changes in the reaction setup. The scope for the cross-coupling of aryl electrophiles and sulfonamides was investigated with (+)RVC/(−)RVC as the electrodes and BTMG as the base. Similarly, a wide range of electron-rich and electron-poor aryl bromides bearing diverse functional groups can be applied, and the corresponding products can be isolated in good to excellent yields (**5a**−**5i**). Notably, even an alkyne was tolerated in this system (**5k**).

The use of 2-bromotoluene afforded the sulfonamidation product in high yield (**5g**), demonstrating that the steric hindrance has no dramatic influence on the activity of this reaction. Furthermore, aryl bromides, aryl iodides, aryl chlorides, as well as aryl tosylates can all undergo this new nickel-catalyzed sulfonamidation effectively (**5i** and **5l**). Importantly, a series of pharmaceutically relevant heterocyclic substrates containing pyridine, quinolone, and thiazole motifs as well as natural-product-derived complex molecules are all suitable in this reaction, providing access to bioactive compounds (**5m**−**5s**). Electron-poor aryl sulfonamides also showed good reactivity for this transformation (**5t** and **5u**). In addition, the use of an ortho-methyl-substituted aryl sulfonamide provided the product in excellent yield (**5v**). Notably, both thiophene-2-sulfonamide and secondary aryl sulfonamide participated with moderate to good efficiency (**5w**−**5y**). Moreover, benzyl-, methyl-, and cyclopropyl aliphatic sulfonamides all underwent this electrochemical protocol in good yields (**5z**−**5ab**).

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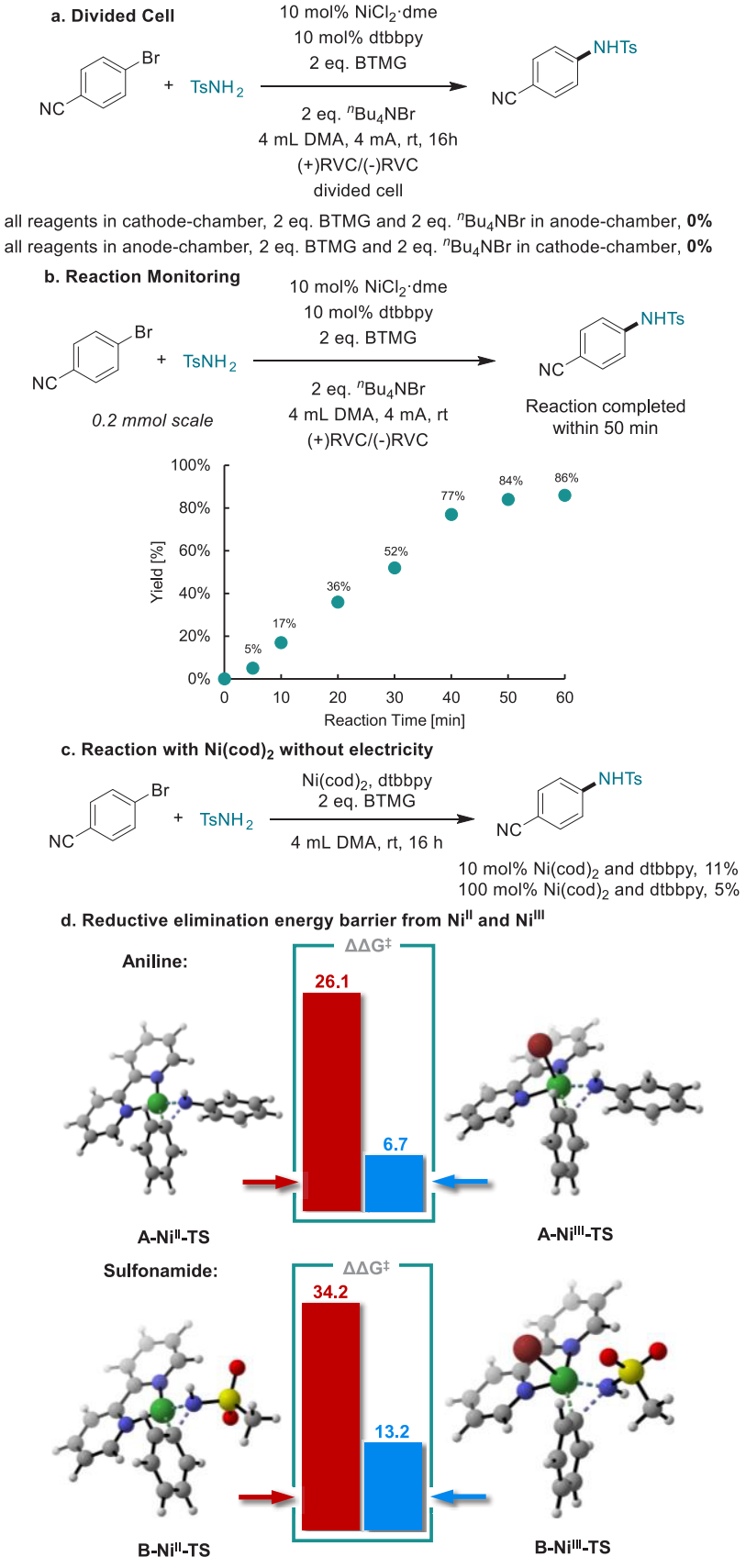

Figure 4. Mechanistic studies. (a) Reactions performed in divided cell. (b) Reaction process monitoring the yield versus the reaction time. (c) Reaction with $Ni(cod)_2$ catalyst without electricity. (d) DFT calculations of the reductive elimination energy barrier from Ni^{II} and Ni^{III} complexes. Free energies in solution (in kcal·mol^{-1}) at the SMD(DMA)-M06/Def2-TZVPP//PBE/Def2-TZVP(Ni)/Def 2-SVP (other atoms) level are displayed.

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Furthermore, the scale-up N-arylations of both aniline and sulfonamide were performed successfully. Notably, the scale-up reaction of sulfonamide was completed within 2 h, showing the high efficiency and practicability of this amination protocol (Figure 2a). In addition, the sulfonamidation reaction proceeded smooothly using alternating current (sine wave, ±3 V, 2 Hz, Figure 2b). In addition, the newly developed nickelaelectrocatalyzed amination protocol could be readily extended to diverse *N*-nucleophiles. Sulfoximines,[65] benzylamines, as well as carbamates can all be employed and gave the corresponding products in good yields (**6a**–**6e**, Figure 2c).

Interestingly, when the reaction was performed with benzophenone imine, either imine or amine product is selectively obtained by simply adjusting the type of base (Figure 3, for optimization details, see SI). When Cs_2CO_3 was used, the electrochemical redox-neutral C−N cross-coupling afforded the imine product, which after hydrolysis provided the valuable primary amine with good efficiency (**6f** and **6g**). However, when the organic base DBN was applied, the cross-coupling was followed by an imine reduction to provide the benzhydryl-protected amine in high yield (**6h**). The control experiment performed in d_7-DMF gave no D-incorporated product, suggesting that the hydrogen source is not from the solvent. Also, imine **6f** could be fully converted to amine **6h** under the electrochemical conditions using DBN as base in the presence or absence of a nickel catalyst and dtbbpy ligand. These results indicate that the amine is formed sequentially to the imine, and the hydrogen source may be the organic base.[66]

The sulfonamidation reaction was also conducted in a divided cell, and no product was observed, showing that this amination process is paired electrolysis, and both the anode and cathode contribute to the formation of the product (Figure 4a).

Monitoring the reaction progress showed that the reaction finished within 50 min (84% GC yield) when 4 mA of current was applied, demonstrating the high efficiency of this protocol. Of note, the current efficiency at 40 min was 154%, which suggests the role of electricity is to suppress the comproportionation of the unstable Ni^{I} and Ni^{III} intermediates (Figure 4b).[61] Furthermore, the reaction of 4-bromobenzonitrile with $TsNH_2$ using $Ni(cod)_2$ without electricity proceeded with very low efficiency, indicating the difficulty of reductive elimination at the Ni^{II} intermediate (Figure 4c), which is further supported by DFT calculations. The calculations show that the reductive elimination energy barrier from Ni^{II} and Ni^{III} complexes in amination reactions are 26.1 and 6.7 kcal/mol, while those for the sulfonamidation reaction are 34.2 and 13.2 kcal/mol, respectively (Figure 4d). These results underpin that Ni^{III} complexes are more prone to undergo reductive elimination in this amination protocol.

In summary, we have developed an efficient and general nickelaelectrocatalyzed protocol for different C−N bond formations. A wide range of weak *N*-nucleophiles (70 examples) including anilines, sulfonamides, and carbamates as well as sulfoximines and imines could be employed with good efficiency under mild electrochemical conditions. The successful application of electron-deficient anilines, pharmaceutical-related heterocycles, and complex molecules demonstrate the effectiveness of this new protocol. Furthermore, a base-controlled selectivity for imine versus amine formation was also realized. The reaction can be scaled up, and the use of alternating current is possible. Moreover, DFT calculations support a facilitated reductive elimination of the generated Ni^{III} intermediate, thus allowing the amination to occur at room temperature. Hence, this amination protocol provides a complementary, widely applicable, and powerful way for the synthesis of diverse N-containing compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.1c00148.

Experimental details, computational details, characterization data, Cartesian coordinates, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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