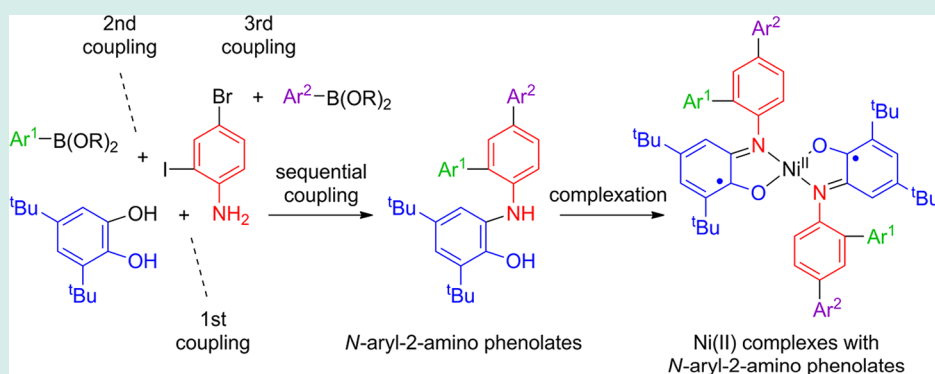


Sequential Coupling Approach to the Synthesis of Nickel(II) Complexes with *N*-aryl-2-amino Phenolates

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Supporting Information



ABSTRACT: A sequential multicomponent coupling approach is a powerful method for the construction of combinatorial libraries because structurally complex and diverse molecules can be synthesized from simple materials in short steps. In this paper, an efficient synthesis of nickel(II) complexes with *N*-aryl-2-amino phenols via a sequential three-step coupling approach is described, for potential use in nonlinear optical materials, bioinspired catalytic systems, and near-infrared absorbing filters. Seventeen *N*-aryl-2-amino phenolates were successfully synthesized in high yields based on the coupling of 3,5-di-*tert*-butylbenzene-1,2-diol with a pivotal aromatic scaffold, 4-bromo-2-iodo-aniline, followed by sequential Suzuki–Miyaura coupling with aryl boronates. A total of 16 analytically pure nickel(II) complexes with *N*-aryl-2-amino phenolates were obtained from 17 complexation trials. The procedure allowed us to assemble 4 components in high yields without protection, deprotection, oxidation or reduction steps. Various building blocks that included electron-donating, electron-withdrawing, and basic were used, and readily available, nontoxic and environmentally benign substrates and reagents were employed with no generation of toxic compounds. No strict anhydrous or degassed conditions were required. Absorption spectroscopic measurement of the synthesized nickel(II) complexes revealed that the *ortho*-substituent Ar^1 exerted more influence on the absorption wavelength of the complexes than the *para*-substituent Ar^2 . On the other hand, both substituents Ar^1 and Ar^2 influenced the molar absorptivity values. These observations should be useful for the design of new and useful nickel(II) complexes as near-infrared chromophores.

KEYWORDS: sequential multicomponent coupling, combinatorial libraries, Suzuki–Miyaura coupling, nickel(II) complex, *N*-aryl-2-amino phenol, near IR absorption

INTRODUCTION

Multicomponent coupling approaches to functional molecules should meet the following criteria: (1) that multiple components be sequentially coupled without extra steps such as protection, deprotection, oxidation and reduction; (2) that each of the coupling steps be compatible with a variety of functional groups; (3) that good yields are obtained without the inconvenience of strictly anhydrous and/or degassed conditions; and, (4) that readily available, nontoxic, and environmentally benign substrates and reagents be employed with no generation of toxic compounds. From this point of view, sequential Suzuki–Miyaura coupling reactions based on aromatic scaffolds containing iodo- and bromo-groups are useful. Because the iodo-group can be chemoselectively activated without affecting the bromo-group, such molecules engage and give sequential coupling reactions with good control of regioselectivity, high yields, and high functional group compatibility.

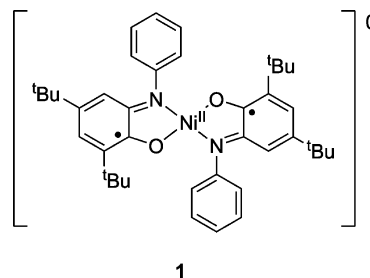
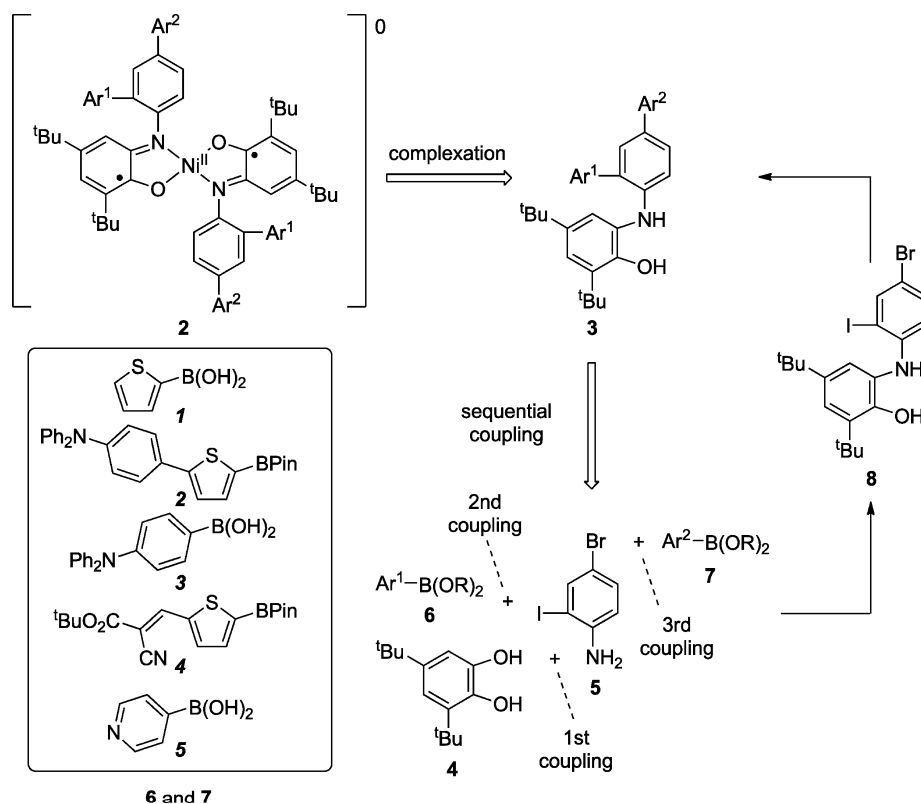
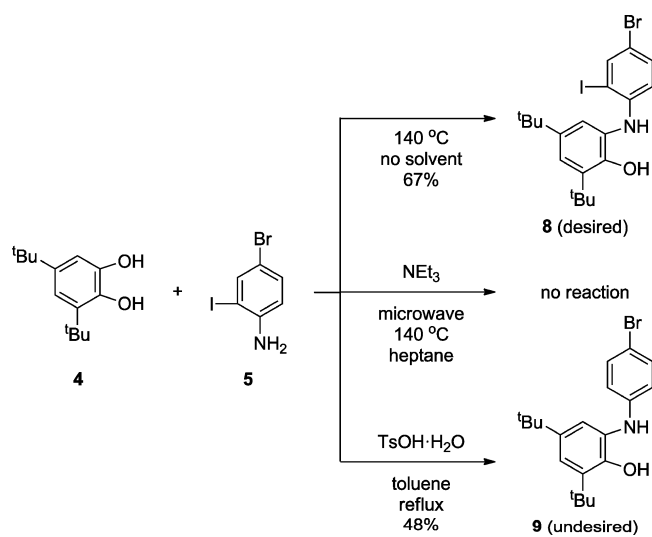


Figure 1. Structure of a nickel(II) complex with *N*-aryl-2-amino phenolates.

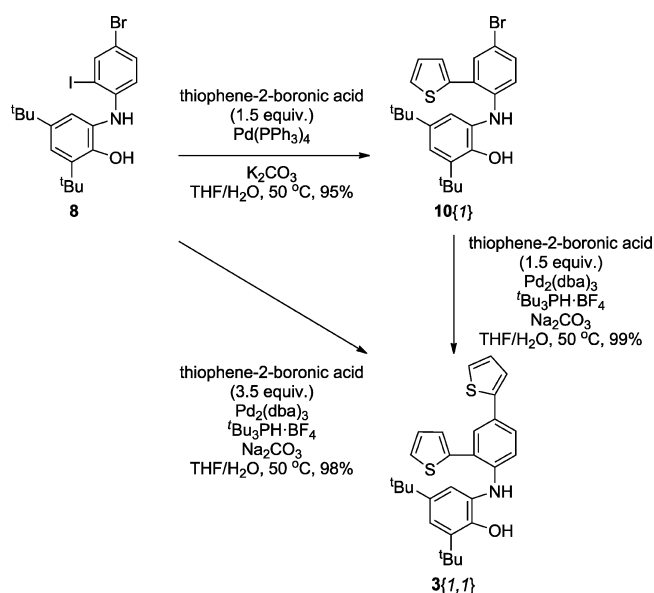
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Scheme 1. Combinatorial Synthesis of Nickel(II) Complexes with *N*-aryl-2-amino PhenolatesScheme 2. First Coupling Reaction of the Aromatic Scaffold, 4-Bromo-2-iodo-aniline (5) with 3,5-Di-*tert*-butylbenzene-1,2-diol (4)

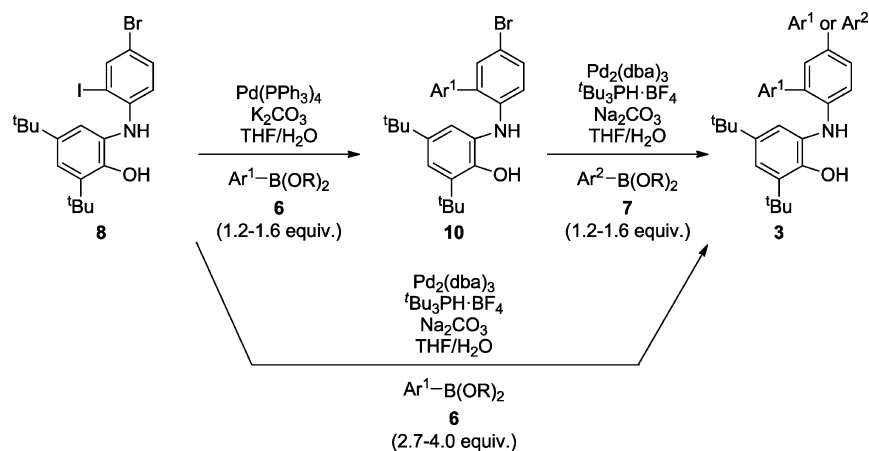
Scheme 3. Sequential Suzuki–Miyaura Coupling Reaction Based on the Aromatic Scaffold 8



In addition, Suzuki–Miyaura coupling^{1,2} requires neither anhydrous conditions nor a toxic substrate, and generates no toxic compounds. Several excellent syntheses employing the sequential Suzuki–Miyaura coupling reaction based on the aromatic scaffolds containing iodo- and bromo-groups have been reported.^{3–8}

In 2001, Wieghardt and co-workers first reported a square-planar, neutral, nickel(II) complex with *N*-aryl-2-amino-phenolate 1 and revealed its unique singlet diradical character by theoretical calculation, chemical synthesis, and spectroscopic

analysis (Figure 1).^{9–11} Recently, a nickel(II) complex with *N*-aryl-2-amino-phenolate has garnered attention because of its potential use for nonlinear optical materials,¹² bioinspired catalytic systems,¹³ and near-infrared absorbing filter.¹⁴ The development of a divergent, protection/deprotection-free, short, synthetic route for the construction of nickel(II) complexes with 2-amino-phenolates would encourage further applications of these structures.

Scheme 4. Synthesis of 17 *N*-aryl-2-amino Phenols Using Our Developed ProcedureTable 1. Synthesis of 17 *N*-aryl-2-amino Phenols Using Our Developed Procedure

entry	building block	product	yield ^a		
			first coupling	second coupling	
1	6{1}	3{1,1}		98%	
2	6{2}	3{2,2}		quant.	
3	6{3}	3{3,3}		71%	
4	6{4}	3{4,4}		97%	
5	6{5}	3{5,5}		30%	
6	6{1}	7{2}	3{1,2}	95%	93%
7	6{1}	7{3}	3{1,3}	95%	99%
8	6{1}	7{4}	3{1,4}	95%	quant.
9	6{1}	7{5}	3{1,5}	95%	90%
10	6{2}	7{1}	3{2,1}	83%	77%
11	6{2}	7{3}	3{2,3}	83%	69%
12	6{3}	7{1}	3{3,1}	81%	78%
13	6{3}	7{2}	3{3,2}	81%	68%
14	6{4}	7{1}	3{4,1}	71%	89%
15	6{4}	7{5}	3{4,5}	71%	56%
16	6{5}	7{1}	3{5,1}	30% (2 steps) ^b	
17	6{5}	7{4}	3{5,4}	36% (2 steps) ^b	

^aIsolated yield. ^bThe first coupling products could not be purified because of their poor solubilities; therefore, the obtained products were used for the second coupling reaction without isolation.

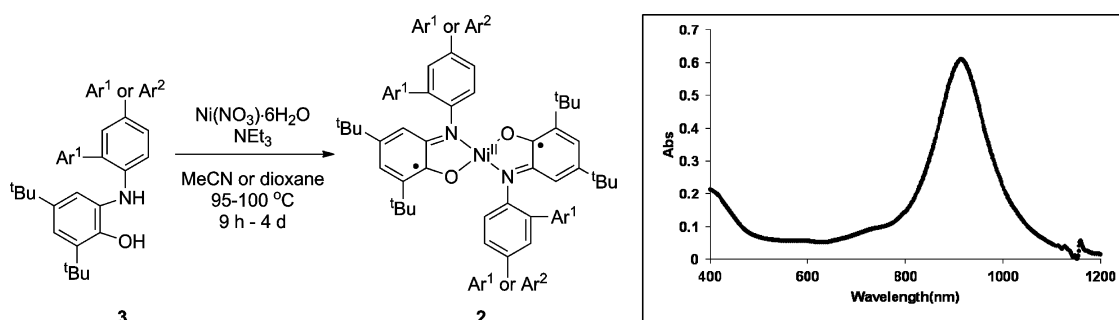
We have developed a multicomponent coupling approach for the synthesis of bioactive compounds and functional materials in solution and in a solid phase for decades.^{15–21} Recently, we

Table 2. Nickel(II) Complexes of the Prepared *N*-aryl-2-amino Phenols 3

entry	substrate	product	yield ^a	λ_{\max}^b (nm)	ϵ^c (M ⁻¹ ·cm ⁻¹)
1	3{1,1}	2{1,1}	22%	914	7.0 × 10 ³
2	3{2,2}	2{2,2}	42%	925	1.6 × 10 ⁴
3	3{3,3}	2{3,3}	57%	909	3.0 × 10 ⁴
4	3{4,4}	2{4,4}	47%	923	2.1 × 10 ⁴
5	3{5,5}	2{5,5}			
6	3{1,2}	2{1,2}	65%	917	1.6 × 10 ⁴
7	3{1,3}	2{1,3}	13%	917	2.3 × 10 ⁴
8	3{1,4}	2{1,4}	44%	916	1.2 × 10 ⁴
9	3{1,5}	2{1,5}	67%	917	1.8 × 10 ⁴
10	3{2,1}	2{2,1}	70%	920	1.2 × 10 ⁴
11	3{2,3}	2{2,3}	17%	917	2.7 × 10 ⁴
12	3{3,1}	2{3,1}	66%	909	2.1 × 10 ⁴
13	3{3,2}	2{3,2}	71%	912	3.1 × 10 ⁴
14	3{4,1}	2{4,1}	53%	922	2.3 × 10 ⁴
15	3{4,5}	2{4,5}	61%	920	1.6 × 10 ⁴
16	3{5,1}	2{5,1}	20%	905	7.1 × 10 ³
17	3{5,4}	2{5,4}	16%	911	1.0 × 10 ⁴

^aIsolated yield. ^bAbsorption maxima in dichloromethane. ^cMolar absorption coefficients in dichloromethane.

reported a sequential palladium-catalyzed cross-coupling approach to the synthesis of rod-like liquid crystals¹⁶ and resorcylic acid lactones^{19,20} based on aromatic scaffolds that would retain multiple reactive sites. Here, we wish to report the development of a highly efficient sequential coupling

Scheme 5. Complexation of *N*-aryl-2-amino Phenol 3 with Nickel(II), and the Absorption Spectrum of the Nickel(II) Complex 2{1,1} in Dichloromethane

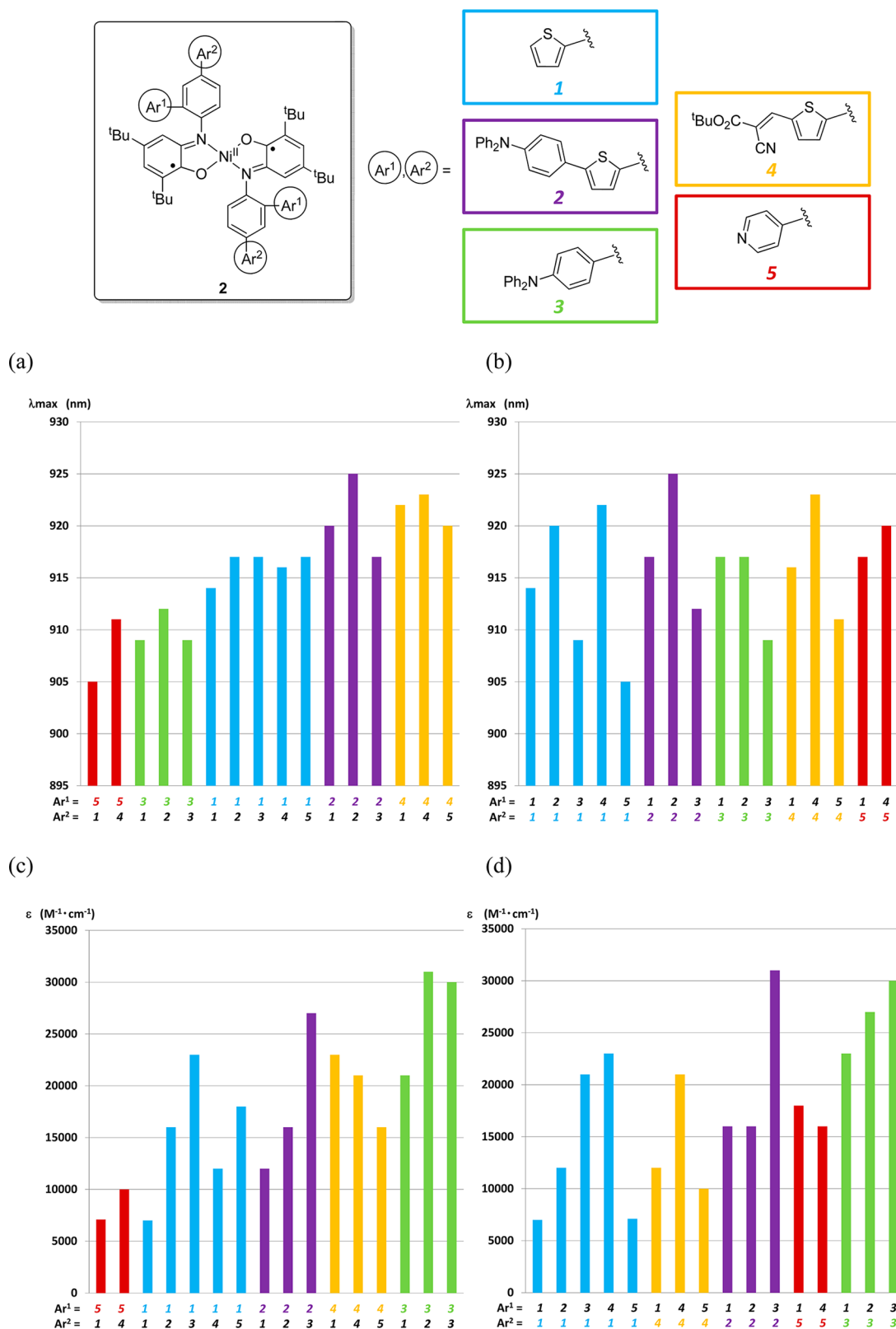


Figure 2. (a) λ_{\max} (nm) of the nickel complexes **2**. $\text{Ar}^1 = 1$ (blue), 2 (purple), 3 (green), 4 (yellow), 5 (red). (b) λ_{\max} (nm) of **2**. $\text{Ar}^2 = 1$ (blue), 2 (purple), 3 (green), 4 (yellow), 5 (red). (c) ϵ values ($\text{M}^{-1}\cdot\text{cm}^{-1}$) of **2**. $\text{Ar}^1 = 1$ (blue), 2 (purple), 3 (green), 4 (yellow), 5 (red). (d) ϵ values ($\text{M}^{-1}\cdot\text{cm}^{-1}$) of **2**. $\text{Ar}^2 = 1$ (blue), 2 (purple), 3 (green), 4 (yellow), 5 (red).

approach based on the aromatic scaffold retention of 3 reactive sites, that is, amino-, bromo-, and iodo-groups in the synthesis of nickel(II) complexes with *N*-aryl-2-amino phenolates.

RESULTS AND DISCUSSION

The synthetic plan for the construction of a library of nickel(II) complexes with *N*-aryl-2-amino phenolates is shown in Scheme 1.

Structurally diverse nickel complexes **2** with various aryl groups, Ar¹ and Ar², would be synthesized by the complexation of *N*-aryl-2-amino phenols **3** with nickel(II).⁹ The essence of our synthetic route was sequential coupling reactions of the commercially available 4-bromo-2-iodoaniline (**5**) at amino-, iodo- and bromo-groups with components **4**, **6**, and **7**. In the first coupling reaction, the amino group of scaffold **5** was required to react with 3,5-di-*tert*-butylbenzene-1,2-diol (**4**) without affecting the bromo- and iodo-groups. While the analogous coupling reaction of 4-bromo-aniline with **4** was previously reported,²² the bulky and reactive iodo group adjacent to the amino group caused some concern regarding amine reactivity and elimination of the iodo group. The second step, a Suzuki–Miyaura coupling reaction requiring activation of the carbon–iodine bond of **8** without affecting the bromo group, is well-known for simple aromatic scaffolds.⁸ In our case, the task was to achieve such chemoselectivity with an adjacent bulky and electron-rich arylamino group. After introducing the building block **6** in the second coupling reaction, the remaining carbon–bromine bond would be targeted for a third coupling reaction with building block **7**. This strategy would allow us to introduce the same or different building blocks into the key aromatic scaffold **5**. The arylboronate building blocks chosen included a simple thiophene {**1**}, a thiophene containing an electron-donating triarylamine substituent {**2**}, an electron-rich triarylamine building block {**3**}, an electron-deficient thiophene bearing *tert*-butyl cyanoacrylate {**4**}, and a *para*-pyridyl unit {**5**}.

The reaction of **4** and **5** was tested under different conditions (Scheme 2). Heating at 140 °C in the presence of NEt₃ as previously reported²² gave no reaction and recovered starting materials, whereas heating under acidic conditions afforded the undesired deiodinated product **9**. In contrast, the desired coupling product **8** was obtained in a good yield after heating without additional reagents or solvent.²³

The key Suzuki–Miyaura coupling reaction of **8** (Scheme 3) with a simple thiophene-2-boronic acid was found to proceed smoothly to give **10**{**1**} (95% yield) under mild reaction conditions (Pd(PPh₃)₄, K₂CO₃ in THF/H₂O) in spite of the presence of the adjacent bulky arylamino group. A subsequent Suzuki–Miyaura coupling of the aryl bromide **10**{**1**} with thiophene-2-boronic acid using the more active monophosphine-palladium complex of tris(*tert*-butyl)phosphine similarly gave the desired product, **10**{**1**,**1**}, in excellent yield (99%). It was possible to perform both steps simultaneously with the second catalyst with an excellent yield (98%). None of these steps required strict anhydrous or degassed conditions.

The above conditions were applied to the synthesis of 17 *N*-aryl-2-amino phenols (Scheme 4 and Table 1). All the products were adequately characterized using ¹H NMR, ¹³C NMR, IR, and HRMS. Although slightly decreased yields were observed with the use of a building block containing pyridine (entries 5, 15, 16, and 17), other combinations afforded the desired products in good to excellent yields regardless of the electronic factor presented by building blocks **6** and **7**. Thus, structurally diverse *N*-aryl-2-amino phenols, some of which can be expected to retain antiviral²² and antioxidative²⁴ activities, can be synthesized in only three steps from commercially available 4-bromo-2-iodoaniline (**5**).

The complexation of *N*-aryl-2-amino phenols **3** with nickel(II) was examined (Scheme 5 and Table 2) using a standard reaction procedure at 95 °C, in acetonitrile solvent containing triethylamine. After cooling to 0 °C, the desired products were isolated as precipitates and purified by recrystallization (CH₂Cl₂-MeOH).

With one exception, the desired nickel(II) complexes **2** were all obtained in varying yields as a dark solids. A noticeable feature of their IR spectra was the absence of the bands at 3446 cm⁻¹ attributable to ν(OH) and ν(NH) of corresponding *N*-aryl-2-amino phenols **3**.¹³ The ¹H NMR spectra of complexes **2** were quite similar to those of the corresponding *N*-aryl-2-amino phenols **3**. Complexation of **3**{**5**,**5**} gave an insoluble black precipitate instead of the expected compound **2**{**5**,**5**}, presumably because of coordination polymerization involving the pyridine groups. The near IR absorption peak (905–925 nm) of all examples of **2** (Table 2), and the ¹H NMR spectra supported the assignment of the desired nickel(II) complex structure. All complexes **2** were stable in air at room temperature.

Relationships between structure and photophysical properties of UV-near-IR absorbing compounds have been previously investigated.^{25,26} Absorption maxima (λ_{max}) and molar absorption coefficients (ε) of the prepared nickel complexes **2** are shown in panels (a)–(d) in Figure 2. Interestingly, the *ortho*-substituent Ar¹ exerted more influence on λ_{max} of the complexes than the *para*-substituent Ar², as shown in panels (a) and (b). The wavelength of the maximum absorption became longer in the following order Ar¹ = 5 < 3 < 1 < 2 < 4. On the other hand, both substituents Ar¹ and Ar² influenced the ε values, as shown in panels (c) and (d). The ε values increased in the following order Ar¹ = 5 < 1 < 2 < 4 < 3, Ar² = 1 = 4 < 2 < 5 < 3. The use of building block **3** increased the ε values of the complexes irrespective of the substituent position. The influence of the other substituents varied by position. For instance, building block **5** decreased the ε values of the complexes when it was employed as Ar¹, whereas the same substituent increased the ε values when employed as Ar².

CONCLUSION

The solution-phase combinatorial synthesis of 17 *N*-aryl-2-amino phenolates, and their complexation with nickel(II) was successfully demonstrated. The key for the synthesis was a highly efficient three-step coupling procedure involving the sequential engagement of aromatic amino, iodo, and bromo substituents without extra steps such as protection, deprotection, oxidation, and reduction. A total of 16 analytically pure nickel(II) complexes with *N*-aryl-2-amino phenolates were obtained from 17 complexation trials. Various building blocks including electron-donating, electron-withdrawing, and basic components were used, and readily available, non toxic, and environmentally benign substrates and reagents were employed with no generation of toxic compounds. In addition, the developed procedure required no strict anhydrous or degassed conditions. Absorption spectra of the synthesized nickel(II) complexes revealed that the *ortho*-substituent (Ar¹) exerted more influence on the near-IR absorption wavelength than the *para*-substituent (Ar²), whereas both substituents influenced molar absorptivity. These observations should be useful for the further design of nickel(II)-based near-infrared dyes.

ASSOCIATED CONTENT

Supporting Information

Analytical data (¹H, ¹³C NMR, and absorption spectra) for the compounds are provided. 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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