JOC The Journal of Organic Chemistry

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Amination–Oxidation Strategy for the Copper-Catalyzed Synthesis of Monoarylamines

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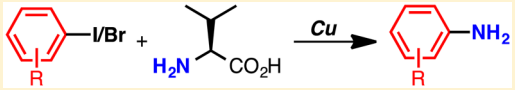
Supporting Information

ABSTRACT: A novel approach for the synthesis of monoarylamines from aryl halides is presented. This method employs an inexpensive, nontoxic metal source (copper) and incorporates a stable ammonia surrogate (α-amino acids), obviating the need for special experimental setup or handling of ammonia reagents. This process, which is proposed to proceed via an amination–oxidation sequence, selectively promotes the transformation of a range of aryl and heteroaryl iodides as well as bromides to the corresponding monoarylamines.



Metal-catalyzed processes have become fundamental to the drug discovery industry.[1] In particular, advancements in palladium-[2] and copper-catalyzed[3] carbon–nitrogen bond formation have substantially impacted the design and identification of drug candidates, with currently >90% of the top-selling pharmaceuticals containing at least one nitrogen atom in their molecular structure.[4] Despite the development of myriad methods for the coupling of alkyl and aryl amines, transformations involving the simplest amine nucleophile (ammonia), yielding the corresponding monoarylamine (aniline) products, are far less common.[5] This scarcity of metal-catalyzed amination processes that employ ammonia has been attributed to several challenges. For example, high concentrations of ammonia can displace supporting ligands from the metal, resulting in catalyst deactivation.[6] An additional complication associated with these cross-coupling processes is the ability of the monoarylamine products to further react with equivalents of the electrophile to form undesired di- and triarylamines byproducts.[7]

Despite these limitations, the importance of anilines to numerous fields (e.g., pharmaceutical industry, material science, and agrochemicals) has led to continued interest in the development of efficient methods that can prepare these structural motifs.[4,8] In particular, a variety of palladium-based catalyst systems (Buchwald,[9] Hartwig,[10] Stradiotto,[11] and Beller[12]) have recently been developed that successfully provide monoarylamine products (Figure 1, eq 1). These reports, which rely on the design and application of phosphine-derived supporting ligands for palladium, established the first methods for the direct coupling of ammonia as well as demonstrated the coupling of typically less reactive electrophiles such as aryl chlorides. Despite these advancements, the processes still maintain several disadvantages including the significant cost and inherent toxicity of palladium.[13] These constraints have consequently led to the investigation of other metals and strategies for the synthesis of monoarylamines.

Copper catalysis has emerged as a promising alternative to palladium-based methods, and protocols for the amination of aryl iodides and bromides with ammonia have been realized (Figure 1, eq 2).[14,15] Although copper cannot broadly transform aryl chlorides to anilines, these systems have several advantages relative to the palladium-based counterparts: (1) catalysts are less prone to deactivation, (2) high selectivity for the monoarylamine product can be obtained when using a large excess of ammonia, (3) copper is less toxic than palladium, and (4) less expensive metal–ligand systems are required. These improvements collectively establish copper-catalyzed methods as an effective option for the synthesis of monoarylamines. However, copper-based systems are also plagued by specific technical challenges, which have unfortunately limited their application. For example, because ammonia is a gas at room temperature, reactions employing anhydrous ammonia often require high-pressure and/or specialized equipment.[16] Liquid ammonia has also been reported as an alternative.[17] However, both of these sources still require special handling and more complex experimental setups. Recent copper-based methods have attempted to obviate these issues through employing aqueous ammonia.[18] However, the concentration of the ammonia solutions is variable, decreasing concentrations of the ammonia over time can complicate industrial applications, and a large excess of amine is typically required to promote monoarylation without formation of byproducts.

To address these limitations, we envisioned the development of a copper-catalyzed process for the efficient synthesis of monoarylamines from aryl halides that employs a stable, easy to handle ammonia surrogate. Although ammonia equivalents (i.e., silylazides,[19] benzophenone imine,[20] benzylamines,[21] and others[22]) have been employed in metal-catalyzed processes, they have yet to find wide application because the surrogates generally require subsequent removal steps, after carbon–nitrogen bond formation, to generate the desired free primary amine. Ideally, to obviate these issues, surrogate moieties would be cleaved post-cross-coupling in the same pot. To this end, we designed a copper-based catalyst system that allowed for carbon–nitrogen bond formation (amination) followed by oxidation of the resulting *N*-arylamine to an *N*-arylimine

Received: October 22, 2015
Published: December 11, 2015

DOI: 10.1021/acs.joc.5b02448
J. Org. Chem. 2016, 81, 330–335

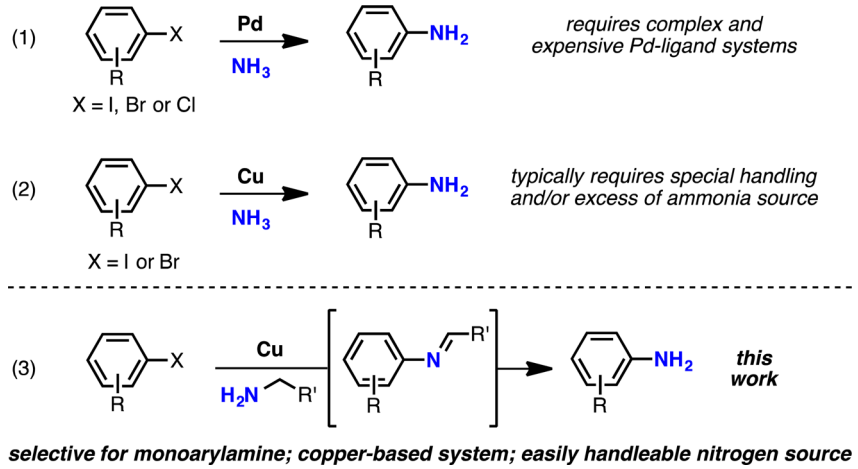


Figure 1. Metal-catalyzed synthesis of monoarylamines.

(Figure 1, eq 3), which is directly hydrolyzed to furnish the desired monoarylamine. Importantly, this method for the selective synthesis of monoarylamines employs an inexpensive, nontoxic metal source (copper) and incorporates a stable ammonia surrogate (valine), which obviates the need for special handling or experimental setup.

In order to determine the optimal components and parameters for the amination−oxidation sequence, we initially examined a variety of copper sources, bases, and solvents for the conversion of 1-iodonaphthalene to the corresponding monoarylamine product, 1-aminonaphthalene (**1**). It was discovered that the nature of the amine source played a crucial role in the efficiency of the catalytic process. For example, when 0.20 equiv of CuI and 1.5 equiv of Cs_2CO_3 in dimethyl sulfoxide (DMSO) were employed, a range of aliphatic and benzyl amines resulted in low conversion of the aryl halide, and no desired product was detected by gas chromatography (Figure 2). However, amino acid based ammonia surrogates were found to be effective for promoting the transformation as employing 1.2 equiv of alanine resulted in a 74% yield of **1** (Figure 2). Valine proved to be ideal as this amine source

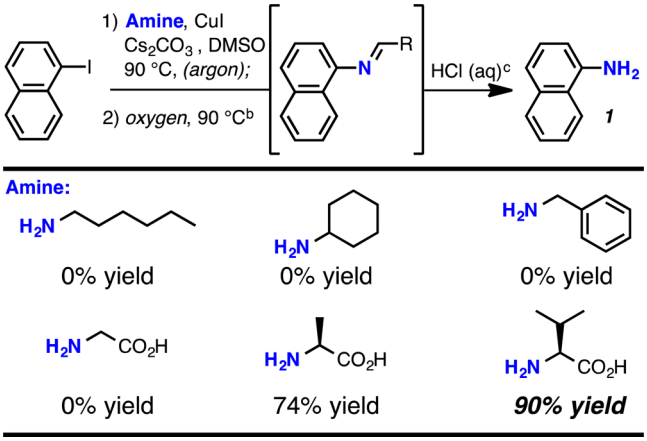


Figure 2. Optimization of amine source. (a) Isolated yield of **1** for each amine source (average of two experiments). (b) Reaction conditions: 0.50 mmol of 1-iodonaphthalene, 0.60 mmol of amine, 0.10 mmol of CuI, and 0.75 mmol of Cs_2CO_3 in 0.50 mL of DMSO under argon atmosphere for 24 h followed by 24 h under oxygen atmosphere. (c) Each reaction was treated with HCl (aqueous) and stirred for 20 min at room temperature prior to isolation.

provided a 100% conversion of the aryl iodide with 90% isolated yield of the desired product (Figure 2). The transformation was selective for the monoarylamine as no di- or triarylamine byproducts were isolated or detected by gas chromatography. Lower catalyst loadings (<0.20 equiv CuI) were also permitted but decreased the overall effectiveness of the transformation as 0.10 or 0.05 equiv of CuI resulted in 65% and 35% yield, respectively, of **1**. We speculate that the success of these α-amino acids in the process was because (1) they can effectively act as a supporting ligand for the metal to prevent catalyst deactivation[23] and (2) they have a greater propensity for oxidation at the tertiary α-carbon.[24] Importantly, valine is a stable, inexpensive, and nontoxic nitrogen source for the transformation that allows the procedure to be conducted without special handling or complex experimental setup.

The substrate scope of the method was examined with a range of aryl iodides, and the optimized conditions proved to be compatible with several functional groups (Figure 3). Specifically, aryl iodides bearing trifluoromethyl groups or ketones (1-iodo-bis(3,5-trifluoromethyl)benzene and 4-iodobenzophenone) successfully furnished the corresponding monoarylamines **4** and **5** in 79% and 44% yield, respectively. In addition, the amination−oxidation sequence was tolerant of aniline-based substrates (i.e., 3-iodoaniline) as the corresponding diamine **6** could be successfully isolated, albeit in lower overall yield. The reaction of 1-chloro-4-iodobenzene was also examined. In agreement with the reactivity trend for oxidative addition of aryl halides, a 45% yield of **3** was obtained without detectable reaction with the aryl chloride; in the examination of a variety of substrates, we have yet to observe the successful amination of an aryl chloride group under our standard conditions.

Although aryl bromides are less reactive than the corresponding iodides in copper-catalyzed cross-coupling processes, they are cheaper and more readily available;[25] therefore, these more challenging electrophiles are of considerable significance in the preparation of monoarylamine-derived biologically active compounds and materials. Importantly, we found that our optimized catalyst system and conditions were efficient in the amination−oxidation reaction of a range of aryl and heteroaryl bromides (Figure 3). For example, this method was applicable to ortho-substituted aryl bromides as the amination of the sterically hindered aryl halide, 1-bromonaphthalene, provided a 55% yield of the correspond-

DOI: 10.1021/acs.joc.5b02448
J. Org. Chem. 2016, 81, 330−335

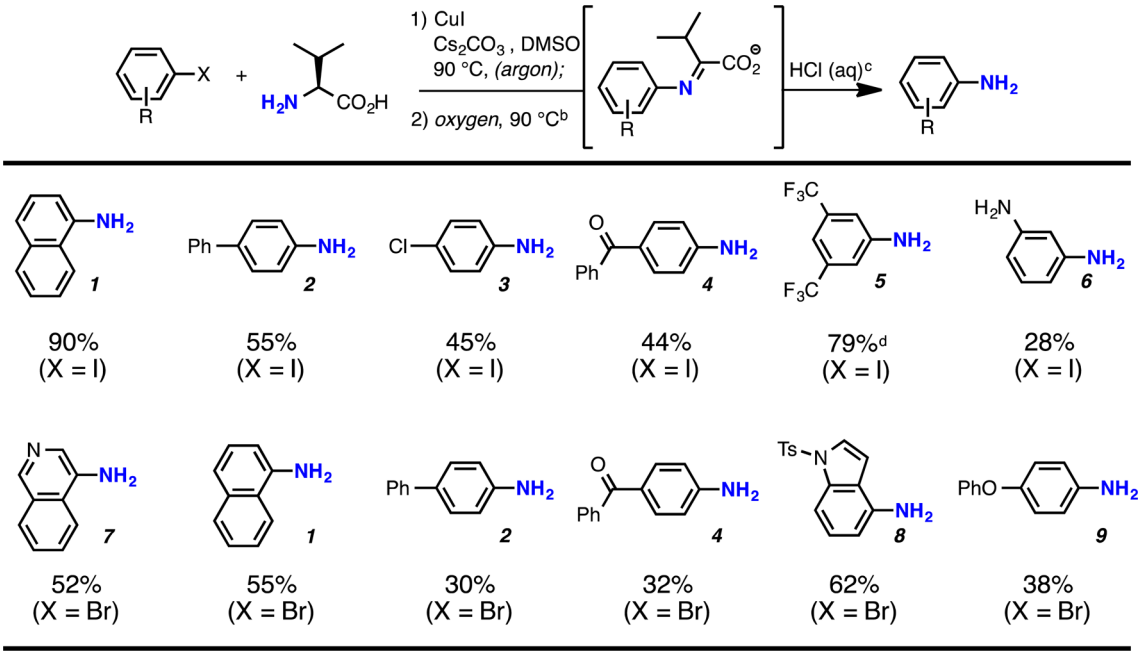


Figure 3. Copper-catalyzed amination−oxidation of (hetero)aryl iodides and bromides with valine. (a) Isolated yield of monoarylamine (average of two experiments). (b) Reaction conditions: 0.50 mmol of aryl or heteroaryl halide, 0.60 mmol of valine, 0.10 mmol of CuI and 0.75 mmol of Cs_2CO_3 in 0.50 mL of DMSO under argon atmosphere for 24 h followed by 24 h under oxygen atmosphere. (c) Each reaction was treated with HCl (aqueous) and stirred for 20 min at room temperature prior to isolation of monoarylamine by column chromatography. (d) Yield based upon NMR of crude product mixture due to volatility of product.

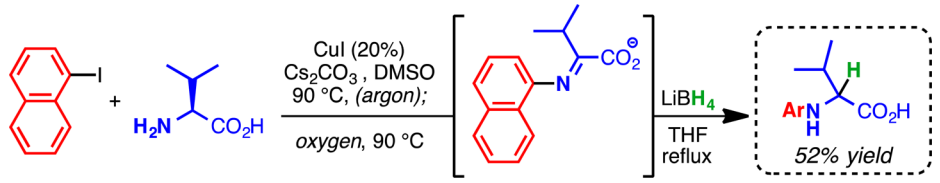


Figure 4. Trapping imine intermediate for the formation of amino acid derivatives.

ing monoarylamine **1**. In addition, although electron-rich aryl halides are known to be more challenging substrates for copper-catalyzed carbon−nitrogen bond-forming processes, 4-bromodiphenyl ether was applicable to this methodology. Further, both electron-neutral (4-bromobiphenyl) and electron-poor (4-bromobenzophenone) compounds were successfully converted to the corresponding monoarylamines **2** and **4** in modest yields (30% and 32%, respectively).

Nitrogen-based heterocycles are ubiquitous in biologically active compounds, but inclusion of these heterocyclic motifs is often found to be detrimental to catalyst activity in other systems.[26] The amination−oxidation reaction of several nitrogen-derived heteroaryl halides was thus examined (Figure 3). The coupling of ortho-substituted 4-bromoisoquinoline was found to be effective, and a 52% yield of **7** was isolated. In addition, we were able to demonstrate that an electron-rich heterocyclic substrate (i.e., 4-bromo-*N*-tosylindole) was applicable to the transformation as a 62% isolated yield of **8** was obtained. These results were consistent with the fact that polycyclic aryl halides, including halonaphthalenes, result in an increased yield of the respective monoarylamine products. This amination−oxidation strategy, which employs a stable and easy to handle amino acid nitrogen source, therefore offers an effective method for the conversion of (hetero)aryl iodides and bromides to monoarylamines.

Under the optimized conditions the carbon−nitrogen bond-forming step must be conducted under an argon atmosphere followed by introduction of oxygen to promote imine formation (Figure 4, entry 1). Interestingly, when argon was employed through the entire process (no oxygen introduced), only a 45% isolated yield of **1** was obtained (Figure 4, entry 2). In addition, if solely oxygen or air atmosphere was utilized for the duration of the reaction, <10% product was observed (Figure 4, entries 3 and 4). Further, when an alternative oxidant to molecular oxygen (i.e., 2,2,6,6-tetramethyl-1-piperidinyl-*N*-oxyl (TEMPO)) was employed in step 2 of the process, only a 22% yield was isolated.

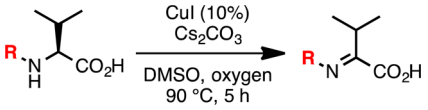
We propose that this transformation proceeds via an *N*-arylimino acid intermediate, which is then hydrolyzed to the desired monoarylamine upon acidic workup. To ascertain whether the process proceeds through an *N*-arylimino acid intermediate, we examined the trapping of the imine intermediate with a nucleophilic hydride reagent. In this event, valine and 1-iodonaphthalene were exposed to the optimized copper-catalyzed amination−oxidation conditions. Then, as opposed to hydrolytic workup, $LiBH_4$ (4.0 equiv) and tetrahydrofuran (THF) were added to the crude reaction, and the mixture was reheated to reflux for 3 h (Figure 4).

This reduction protocol furnished *N*-naphthylvaline in a 52% isolated yield; note that 22% of 1-aminonaphthalene was also isolated. Consistent with our previous observations, only trace

DOI: 10.1021/acs.joc.5b02448
J. Org. Chem. 2016, 81, 330−335

N-naphthylvaline was found when the amination product mixture was exposed directly to hydrolytic conditions. This transformation suggests that an *N*-arylimino acid is formed in situ and the intermediate can be selectively reduced with the appropriate nucleophile.

Copper-catalyzed amine oxidations have been proposed to occur via several mechanisms including (1) single-electron transfer (SET) mechanism via a nitrogen radical cation or (2) initial generation of α-carbon-centered radical intermediate.[27] Since nonenzymatic methods for the oxidation of unprotected α-amino acids to imino acids are rare,[28] we sought to determine whether the *N*-arylamino acid furnished by the amination reaction accelerated the copper-catalyzed oxidation (Figure 5).



Entry	R	Yield (%)
1	H	<1[b]
2	Me	<1[b]
3	4-biphenyl	47[c]

Figure 5. Oxidation of valine derivatives. (a) Reaction conditions: 0.20 mmol of valine derivative, 0.02 mmol of CuI, and 0.30 mmol of Cs_2CO_3 in 0.20 mL of DMSO under oxygen atmosphere for 5 h. (b) No conversion detected by ^{1}H NMR. (c) Final isolated yield of 4-aminobiphenyl reported.

When the rate of oxidation of valine, *N*-methylvaline, and *N*-biphenylvaline under optimized conditions was examined, only *N*-biphenylvaline efficiently provided the desired *N*-arylimino acid product after 5 h, with other derivatives resulting in trace levels of oxidation. This result suggests that the α-aryl amino acid amination products are required to initiate oxidation. The desired oxidation process may further be accelerated through coordination of the *N*-aryl amino acid substrate to the metal. Further studies regarding the mechanism of this reaction and reactivity of the proposed imine intermediate are underway including extending this methodology to the preparation of α-amino acid analogues through use of carbon nucleophiles for imine reduction.

CONCLUSION

In summary, we have designed an amination−oxidation process that successfully converts (hetero)aryl iodides and bromides to the corresponding monoarylamines. This copper-catalyzed method provides a mechanistically novel approach to the synthesis of these important structural motifs. The transformation employs a stable and easily handleable nitrogen source, valine, and obviates the need for the special handling or complex experimental setup. Further, the transformation is selective for the formation of monoarylamine products without significant di- and triarylamine byproducts observed. Lastly, we have demonstrated that substitution at nitrogen using an aryl halide initiator helps facilitate amino acid oxidation.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all reactions were performed under an argon or oxygen atmosphere in oven-dried glassware. Dimethyl sulfoxide (anhydrous), valine (reagent grade), copper(I) iodide (purum, ≥99.5%), and cesium carbonate (99%) were employed. Commercially available aryl iodides and bromides were used without further purification. Reactions were stirred using Teflon-coated magnetic stir bars. Reactions were monitored via gas chromatography and/or thin-layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates with fluorescent indicator. Plates were visualized under UV light without further staining. Products were purified via column chromatography using the solvent system(s) indicated. Silica gel 60, 230−400 mesh, was used for purification.

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and high-resolution mass spectrometry. Known compounds were characterized by ^{1}H NMR and melting points (for solids) and compared to their literature values. NMR spectra were measured on a magnetic resonance spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). ^{1}H chemical shifts are reported relative to the residual solvent peak (chloroform = 7.26 ppm) as follows: chemical shift (δ), (proton ID, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, ddd = doublet of doublet of doublets, dddd = doublet of doublet of..., ddddd = doublet of doublet of... etc., t = triplet, q = quartet, p = pentet), integration, coupling constant(s) in hertz). ^{13}C chemical shifts are reported relative to the residual deuterated solvent ^{13}C signals (chloroform = 77 ppm). Infrared spectra were recorded on a FTIR and are reported in wavenumbers (cm^{-1}). Gas chromatographic analyses were preformed on a gas chromatography instrument with an FID detector using 25 m × 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

Optimization of Reaction Conditions (Figure 2). Each oven-dried reaction tube was equipped with magnetic stir bar and charged with CuI and Cs_2CO_3 (244 mg, 0.75 mmol). The tubes was capped with a septa and then evacuated and backfilled with atmosphere #1 (this sequence was carried out three times). DMSO (0.50 mL) was added via syringe, through the septa, followed by the addition of the 1-iodonaphthalene (127 mg, 73.0 μL, 0.50 mmol) and corresponding amine (0.60 mmol) in a like manner (amines that were solids were added with other reagents before evacuation). Each reaction mixture was heated to 90 °C for 24 h. The reaction mixture was then allowed to cool to room temperature and then evacuated and backfilled with atmosphere #2 (argon, air or oxygen). The reaction mixture was reheated to 90 °C for an additional 24 h. The reaction was cooled to room temperature and dodecane (10 μL) was added to the crude material as an internal standard. The crude mixture for each reaction was then analyzed by gas chromatography in order to determine the conversion of 1-iodonaphthalene. Reactions that resulted in significant conversion of starting material were then purified via flash chromatography on silica gel to obtain the final isolated yield.

General Procedure for Aniline Synthesis with Aryl Halides. An oven-dried reaction tube equipped with magnetic stir bar was charged with CuI (19.0 mg, 0.10 mmol), valine (70.6 mg, 0.60 mmol), and Cs_2CO_3 (244 mg, 0.75 mmol). The tube was capped with a septum and then evacuated and backfilled with argon (this sequence was carried out three times). DMSO (0.50 mL) was added via syringe, through the septum, followed by the addition of the aryl halide (0.50 mmol) in a like manner (aryl halides that were solids were added with other reagents before evacuation). The reaction mixture was heated to 90 °C until aryl halide had been completely consumed, as determined by gas chromatography (24 h). At this point, the reaction mixture was allowed to cool to room temperature and then evacuated and backfilled with oxygen. The reaction mixture was reheated to 90 °C for an additional 24 h. The reaction was cooled to room temperature and partitioned between dichloromethane (1.5 mL) and water (1.5 mL). The solution was acidified to pH = 1 with concd HCl (~5 drops, ~0.25 mL) and allowed to stir for 20 min. Solid sodium bicarbonate was added to neutralize the solution (pH = 7). The aqueous layer was extracted with dichloromethane, and the combined organic layers were concentrated. The crude material so obtained was purified via flash chromatography on silica gel.

1-Aminonaphthalene (1) (Halide/Iodide).[14d] 1-Iodonaphthalene (127 mg, 73.0 μL, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (10/10/80% EtOAc/NEt_3/hexanes) to

DOI: 10.1021/acs.joc.5b02448
J. Org. Chem. 2016, 81, 330−335

provide the title compound in a 90% yield (65 mg) as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70−7.71 (m, 2H), 7.35−7.37 (m, 2H), 7.16−7.20 (m, 2H), 6.65−6.67 (d, J = 8.6 Hz, 1H), 3.62 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 134.6, 128.8, 126.6, 126.0, 125.0, 123.9, 121.0, 119.2, 109.9 ppm.

*4-Aminobiphenyl (**2**) (Halide/Iodide).*[29] 1-Iodobiphenyl (140 mg, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (25/10/65% EtOAc/NEt_3/hexanes) to provide the title compound in a 57% yield (48 mg) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53−7.56 (m, 2H), 7.38−7.44 (m, 4H), 7.26−7.29 (t, J = 7.2 Hz, 1H), 6.75−6.78 (d, J = 8.4 Hz, 2H), 3.70 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 141.6, 131.9, 128.9, 128.3, 126.6, 126.5, 115.6 ppm.

*4-Chloroaniline (**3**) (Halide/Iodide).*[30] 1-Iodo-4-chlorobenzene (119 mg, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (30/70% EtOAc/hexanes) to provide the title compound in a 45% yield (29 mg) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01−7.03 (d, J = 8.8 Hz, 2H), 6.52−6.54 (d, J = 8.8 Hz, 2H), 3.57 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 125.1, 110.3, 104.4 ppm.

*4-Aminobenzophenone (**4**) (Halide/Iodide).*[31] 4-Iodobenzophenone (154 mg, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (40/10/50% EtOAc/NEt_3/hexanes) to provide the title compound in a 44% yield (43 mg) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.65 (m, 4H), 7.44−7.47 (m, 1H), 7.36−7.39 (m, 2H), 6.61−6.59 (d, J = 8.5 Hz, 2H), 4.06 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 150.8, 138.8, 132.8, 131.2, 129.4, 127.9, 127.5, 113.5 ppm.

*3,5-Bis(trifluoromethyl)aniline (**5**) (Halide/Iodide).*[32] 1-Iodo-3,5-bis(trifluoromethyl)benzene (170 mg, 60.1 μL, 0.50 mmol) was employed in the reaction using the standard procedure with the following modification. 1-fluoro-2,4-dinitrobenzene (25 μL) was added to the combined dichloromethane solution. An aliquot of this solution was then subjected to ^{19}F NMR spectroscopic analysis, which indicated that 79% yield of the desired product.

*1,3-Phenylenediamine (**6**) (Halide/Iodide).*[14d] 3-Iodoaniline (110 mg, 88.6 μL, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (30/10/60% EtOAc/NEt_3/Hexanes) to provide the title compound in a 28% yield (15 mg) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (t, J = 2.0 Hz, 1H), 7.69 (d, J = 1.9 Hz, 2H), 7.19 (s, 1H), 4.34 (bs, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 126.1, 110.4, 104.5 ppm.

*1-Aminonaphthalene (**1**) (Halide/Bromide).*[14d] 1-Bromonaphthalene (103.5 mg, 69.9 μL, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (15/85% $EtOAc_3$/hexanes) to provide the title compound in a 55% yield (39 mg) as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69−7.74 (m, 2H), 7.35−7.37 (m, 2H), 7.17−7.24 (m, 2H), 6.69 (d, J = 7.0 Hz, 1H), 3.62 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 134.7, 128.9, 126.5, 126.1, 125.1, 123.9, 121.1, 119.4, 110.0 ppm.

*4-Aminobiphenyl (**2**) (Halide/Bromide).*[29] 1-Bromobiphenyl (116.6 mg, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (20/10/70% EtOAc/NEt_3/hexanes) to provide the title compound in a 36% yield (20 mg) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54−7.58 (m, 2H), 7.41−7.46 (m, 4H), 7.29−7.31 (t, J = 7.2 Hz, 1H), 6.77−6.80 (d, J = 8.4 Hz, 2H), 3.70 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 141.6, 131.9, 128.9, 128.3, 126.6, 126.4, 115.6 ppm.

*4-Aminobenzophenone (**4**) (Halide/Bromide).*[30] 4-Bromobenzophenone (180.6 mg, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (20/10/70% EtOAc/NEt_3/hexanes) to provide the title compound in a 32% yield (32 mg) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72−7.75 (m, 4H), 7.53−7.57 (t, J = 7.0 Hz, 1H), 7.45−7.47 (t, J = 7.5 Hz, 2H), 6.67−6.70 (d, J = 7.9 Hz, 2H), 4.06 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 151.1, 139.2, 133.2, 131.7, 129.7, 128.4, 127.6, 114.0 ppm.

*3-Aminoquinoline (**7**) (Halide/Bromide).*[33] 3-Bromoquinoline (104 mg, 67.9 μL, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (20/10/70% EtOAc/NEt_3/hexanes) to provide the title compound in a 52% yield (38 mg) as an orange-red solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42−8.44 (d, J = 2.8 Hz, 1H) 7.86−7.89 (d, J = 8.2 Hz, 1H), 7.49−7.52 (d, J = 7.6 Hz, 1H), 7.32−7.38 (m, 2H), 7.16 (d, J = 2.7 Hz, 1H), 3.65 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 142.6, 139.6, 129.0, 128.9, 126.9, 125.8, 125.6, 115.1 ppm.

*4-Amino-N-tosylindole (**8**) (Halide/Bromide).*[34] 4-Bromo-*N*-tosylindole (175 mg, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (25% EtOAc/hexanes) to provide the title compound in a 62% yield (89 mg) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74−7.77 (d, J = 8.3 Hz, 2H), 7.47−7.48 (d, J = 3.7 Hz, 1H), 7.40−7.44 (d, J = 8.3 Hz, 1H), 7.19−7.22 (d, J = 8.3 Hz, 2H), 7.08−7.12 (t, J = 8.1 Hz, 1H), 6.56−6.58 (d, J = 3.9 Hz, 1H), 6.48−6.51 (d, J = 7.8 Hz, 1H) 2.32−2.34 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0, 139.6, 136.0, 135.4, 129.8, 126.9, 125.7, 124.5, 119.2, 108.2, 105.1, 104.4, 21.5 ppm.

*4-Aminodiphenyl Ether (**9**) (Halide/Bromide).*[35] 4-Bromodiphenyl ether (125 mg, 87.5 μL, 0.50 mmol) was employed in the reaction using the standard procedure. The crude product was purified via flash column chromatography on silica gel (40/10/50% EtOAc/NEt_3/hexanes) to provide the title compound in a 38% yield (35 mg) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.18−7.121 (m, 2H), 6.90−6.94 (t, J = 7.1 Hz, 1H), 6.83−6.86 (d, J = 8.3 Hz, 2H), 6.78−6.80 (d, J = 8.9 Hz, 2H), 6.58−6.60 (d, J = 8.80 Hz, 2H) ppm. 3.49 (bs, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 142.9, 129.8, 122.3, 121.3, 117.5, 116.5, 27.6 ppm.

Reduction of Imino Acid with $LiBH_4$ (Figure 4). An oven-dried reaction tube equipped with magnetic stir bar was charged with CuI (19.0 mg, 0.10 mmol), valine (70.6 mg, 0.60 mmol), and Cs_2CO_3 (244 mg, 0.75 mmol). The tube was capped with a septum and then evacuated and backfilled with argon (this sequence was carried out three times). DMSO (0.50 mL) was added via syringe, through the septum, followed by the addition of the 1-iodonaphthalene (127 mg, 73.0 μL, 0.50 mmol) in a like manner. The reaction mixture was heated to 90 °C for 24 h. The reaction mixture was allowed to cool to room temperature and then evacuated and backfilled with oxygen. The reaction mixture was reheated to 90 °C for an additional 24 h. The reaction was cooled to room temperature and $LiBH_4$ (43.6 mg, 2.00 mmol) and THF (1.00 mL) were added directly to solution. The reaction was heated to 90 °C for 3 h. The crude product was purified via flash column chromatography on silica gel (25% EtOAc/hexanes) to provide a mixture of 1-naphthylvaline in a 52% yield (63 mg) and 1-aminonapthalene 22% yield (16 mg).

Experimental for Oxidation of Valine Derivatives (Figure 5). An oven-dried reaction tube equipped with magnetic stir bar was charged with CuI (3.8 mg, 0.02 mmol), valine derivative (0.20 mmol), and Cs_2CO_3 (97.7 mg, 0.30 mmol). The tube was capped with a septum and then evacuated and backfilled with oxygen. DMSO-d_6 (0.20 mL) was added via syringe, through the septum. The reaction mixture was heated to 90 °C for 5 h. The reaction mixture was allowed to cool to room temperature and then filtered through a pad of Celite. Each reaction was initially assessed by ^{1}H NMR spectroscopy to determine conversion of valine derivative. Then the solution from the oxidation of *N*-biphenylvaline was partitioned between dichloromethane (1.5 mL) and water (1.5 mL). The solution was acidified to pH = 1 with concd HCl (~5 drops, ~0.25 mL) and allowed to stir for 20 min. Solid sodium bicarbonate was added to neutralize the solution (pH = 7). The aqueous layer was extracted with dichloromethane, and the combined organic layers were concentrated. The crude product was purified via flash column chromatography on silica gel (20/10/

DOI: 10.1021/acs.joc.5b02448
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70% EtOAc/NEt_3/hexanes) to provide *N*-biphenylvaline in a 47% yield (15.9 mg) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54−7.58 (m, 2H), 7.41−7.46 (m, 4H), 7.29−7.31 (t, J = 7.2 Hz, 1H), 6.77−6.80 (d, J = 8.4 Hz, 2H), 3.70 (s, 2H) ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02448.

^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by startup funds granted by the College of Science and Engineering at San Francisco State University.

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DOI: 10.1021/acs.joc.5b02448
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