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# Pd-Catalyzed Diamination of 1,2,4-Triazinyl Complexant Scaffolds

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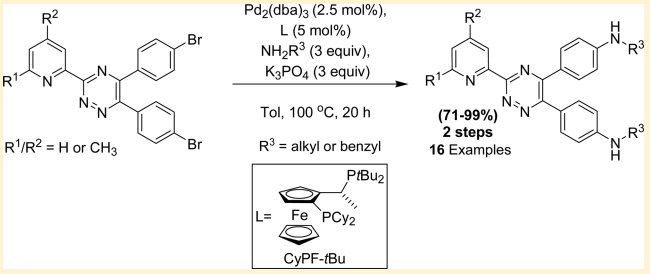
Supporting Information

**ABSTRACT:** As part of ongoing efforts in this laboratory to design and synthesize multidentate soft-N-donors as effective complexants for chemoselective minor actinide extraction from used nuclear fuel, a series of aminated mono-1,2,4-triazinylpyridines were required. This study focuses on streamlining convergent access to a diverse array of functionalized N-donors using Pd-catalysis from a common synthon affording access to pyridinyl triazines as the 4,4′-amino derivatives which are commercially limited and unsuccessful in traditional condensation chemistry. A general Pd-catalyzed method for the double amination of functionalized pyridinyl-1,2,4-triazines with low catalyst/ligand loadings enabling the formation of 16 novel complexants is presented.




## INTRODUCTION

Used nuclear fuel is composed of a variety of materials derived from the actinides and lanthanides. Various separation methods have been developed to address the challenges of selective speciation.[1] Selective removal of the neutron-absorbing minor actinide $Am^{3+}$ is critical for partitioning and transmutation toward fuel for advanced reactors. The aforementioned material is present in extremely low concentration as the result of the normal fuel cycle but possess high levels of radiotoxicity and contributes a high heat load, rendering its removal essential. The minor actinides and lanthanides possess similar charge radii and similar complexation properties, rendering chemoselective separation challenging. As part of ongoing research in this laboratory to synthesize soft-N-donor complexants with favorable solubility performance in process-relevant, nonpolar solvent systems for study as chemoselective complexants of trivalent minor actinides from the lanthanides a series of pyridinyl-1,2,4-triazines were required. Heterocycles bearing a 1,2,4-triazine are common in the development of pharmaceuticals,[2] luminescent materials,[3] materials for forensic science,[4] and complexants utilized in liquid−liquid extraction.[5] Synthesis of pyridinyl-1,2,4-triazines from the requisite carbonitrile and an appropriate 1,2-dicarbonyl was demonstrated by Case in 1965.[6]

Monotriazinylpyridine (MTP) **1**, bis-triazinylpyridine (BTP) **2**, bis-triazinyl-bipyridine (BTBP) **3**, and bis-triazinylphenanthroline (BT-Phen) **4** complexant scaffolds are frequently utilized in chemoselective minor actinide extraction processes (Figure 1). The utility of the BTP[7] and BTPhen[8] scaffolds as complexants in this area are well documented, and several materials (**3**) are in process development in Europe and the U.S.[9] The soft-Lewis basic nature of the aforementioned scaffolds facilitate dative coordination of various metals. The central N atom in these species frequently exhibits electron-donating ability, as opposed to the triazinyl N atom which often must accept electron density.[10]

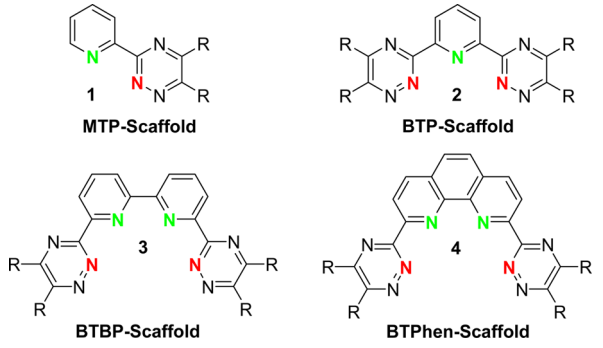



**Figure 1.** Common soft-N-donor 1,2,4-triazinyl scaffolds.

Currently, limited structural diversity of 1,2-dicarbonyls is accessible at reasonable cost from commercial suppliers. Often synthetic access to functionalized dicarbonyls can involve multiple steps.[11] The most significant limitation of current synthetic methods for the preparation of MTP, BTP, and BTPhen 1,2,4-triazines for separations processes is ease of modular diversity to vary ligand solubility toward achieving high complexant loadings, minimizing the need for solubility modifiers, and preventing third-phase formation in high concentrations of nitric acid. Contemporary strategies are dependent upon the commercial availability or rapid preparation of 1,2-dicarbonyl moieties for condensation chemistry. Frequently, substituent effects on the 1,2-dicarbonyl can play a significant role in the favorable outcome in the formation of 1,2,4-triazines. Previous efforts to access ligand scaffolds with amphiphilic amino functionality on MTP, BTP,[12] and

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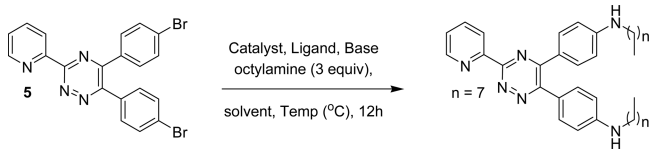
**Table 1. Condition Screening for Pd-Mediated Diamination**




| entry | catalyst | ligand | base | solvent | temp (°C) | result |
|---|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ (10 mol %) | BINAP (20 mol %) | NaO*t*Bu (5 equiv) | Tol (0.5 M) | 100 | **5** |
| 2 | $Pd(PPh_3)_4$ (10 mol %) | – | $K_3PO_4$ (2 equiv) | DMA (0.8 M) | 100 | **5** |
| 3 | Pd(dppf)$Cl_2$ (5 mol %) | – | NaO*t*Bu (3 equiv) | DME (0.5 M) | 80 | **5** |
| 4 | Pd(dppf)$Cl_2$ (5 mol %) | – | $K_3PO_4$ (3 equiv) | DME (0.5 M) | 80 | **5** |
| 5 | CuI (10 mol %) | *N*,*N*-diethylsalicylamide (40 mol %) | $K_3PO_4$ (2 equiv) | DMF (0.5 M) | 100 | **5** |
| 6 | CuI (10 mol %) | *N*,*N*-diethylsalicylamide (20 mol %) | $K_3PO_4$ (2 equiv) | – | 100 | 10% |
| 7 | $Pd_2(dba)_3$ (5 mol %) | *t*BuX-Phos (10 mol %) | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | **5** |
| 8 | $Pd_2(dba)_3$ (5 mol %) | *t*BuX-Phos (10 mol %) | NaO*t*Bu (3 equiv) | Tol (0.5 M) | 100 | decomp |
| 9 | $Pd_2(dba)_3$ (5 mol %) | *t*BuX-Phos (10 mol %) | LiHMDS (3 equiv) | Tol (0.5 M) | 100 | **5** |
| 10 | *t*BuBrettPhos precatalyst (5 mol %) | *t*BuBrettPhos (10 mol %) | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | **5** |
| 11 | RuPhos precatalyst (5 mol %) | RuPhos (10 mol %) | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | **5** |
| 12 | RockPhos precatalyst (5 mol %) | RockPhos (10 mol %) | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | **5** |
| 13 | $Pd(MeCN)_2Cl_2$ (5 mol %) | CyPF-*t*Bu (10 mol %) | NaO*t*Bu (3 equiv) | DME (0.5 M) | 100 | 50% |
| 14 | $Pd_2(dba)_3$ (5 mol %) | CyPF-*t*Bu (10 mol %) | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | 99% |
| 15 | $Pd_2(dba)_3$ (5 mol %) | CyPF-*t*Bu (10 mol %) | NaO*t*Bu (3 equiv) | Tol (0.5 M) | 100 | 90% |
| 16 | $Pd_2(dba)_3$ (5 mol %) | CyPF-*t*Bu (10 mol %) | LiHMDs (3 equiv) | Tol (0.5 M) | 100 | decomp |
| 17 | – | CyPF-*t*Bu (10 mol %) | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | **5** |
| 18 | $Pd_2(dba)_3$ (5 mol %) | – | $K_3PO_4$ (3 equiv) | Tol (0.5 M) | 100 | **5** |

BTPhen[13] scaffolds leveraging condensation chemistry were all unsuccessful, leading us to postulate that strongly electron-donating functionality in the 4,4′-positions of the benzil significantly impacted the electrophilicity of the carbonyl moiety during the condensation event.

## RESULTS AND DISCUSSION

While current research suggests that substituents on the aromatic moiety of a 1,2,4-triazinyl complexant play a limited electronic role in the material's efficacy toward chemoselective minor actinide extraction,[14] such functionality could play a decisive role in enhanced performance. While amination of aryl and heteroaryl halides has been extensively investigated, metal-catalyzed methods for the double amination of complexant scaffold **5** have not been previously communicated. Given the tremendous opportunity amination of such a scaffold would present in the context of potential complexant solubility in process-relevant solvents, we set out to develop an efficacious method for the Pd-mediated diamination of functionalized heteroaryl-1,2,4-triazines. The described substrate presents several unique challenges for method development including the substrate for the reaction serving as a potentially competitive bidentate dative ligand for Pd, the need for diamination, a significant stoichiometric excess of required amine relative to catalyst loading, and the poor ambient temperature solubility of the required substrates in solvents common for amination such as *tert*-butyl alcohol, 1,4-dioxane, THF, or toluene.[15] Several additional unknowns prior to project initiation included the potential for substrate oligomers and C−Br bond reduction via reductive elimination. Relying on previously described methods for Pd-catalyzed amination developed in the Buchwald,[16] Hartwig,[17] and other laboratories[18] as an initial guide, a series of screening experiments were performed, leading to the results listed in Table 1.

The use of BINAP as a ligand for $Pd^0$ has been extensively investigated and was employed in this context according to the method described by Organ[19] (entry 1) without success. Additional methods including palladium tetrakis[20] and palladium diphosphinoferrocene dichloride[21] with potassium phosphate and sodium *tert*-butoxide (entries 2−4) did not afford conversion of **5**. Subsequent evaluation of a copper(I)-mediated method described by Buchwald[22] in DMF (entry 5) led to no conversion, but X < 10% conversion was observed when the reaction was performed neat (entry 6). Palladium-catalyzed methods incorporating alkylbiaryl phosphine ligands developed in the Buchwald laboratories were also screened without success. Initial examples focused on the use of $Pd_2(dba)_3$ with *t*BuX-Phos[23] (entries 7−9) with increasing base strength. In the case of potassium phosphate (entry 7) and LiHMDS (entry 9) no conversion was observed. Decomposition of starting material was observed with the use of sodium *tert*-butoxide as base (entry 8). Initially concerned that potential interference from the dibenzylidene acetone ligand competing for coordination sites on the metal with the dialkylbiaryl phosphine ligand could be contributing to the observed results, a series of experiments were performed utilizing *t*BuBrettPhos,[24] RuPhos,[25] and RockPhos[26] as ligands with the commercially available methanesulfonic acid matched Pd(II) precatalysts (entries 10−12). All of the aforementioned failed to afford any conversion of the starting material leading to a revised hypothesis that the substrate may be shutting down the requisite catalytic cycle.

Hartwig has published results on a highly active $Pd^{(II)}$/CyPF-*t*Bu catalyst/ligand system for the Pd-catalyzed amination of a variety of hetero aryl halides with extremely low loadings.[27] This system was screened with catalyst formation in situ (entry 13) but did not afford complete conversion. Entries 14−16 evaluated a modified catalytic system of the CyPF-*t*Bu ligand paired with $Pd_2(dba)_3$ in concert with a base screen. Gratifyingly, entry 14 with 5 mol % catalyst and 10 mol % ligand loading with potassium phosphate as base led to complete diamination of the starting material after 12 h at 100



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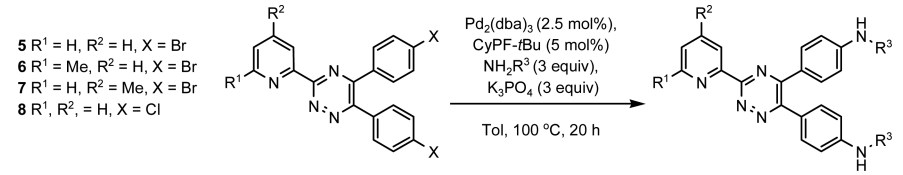
**Table 2. Pd-Catalyzed Diamination Substrate Scope**




| Entry | Substrate | Amine | Product | Yield[b] |
|---|---|---|---|---|
| 1<br>2<br>3 | **5** | $H_2N(CH_2)_nCH_3$<br>n = 7, 9, or 13 | **9** n = 7<br>**10** n = 9<br>**11** n = 13 | **9** (99)<br>**10** (99)<br>**11** (99) |
| 4[a]<br>5[a] | **6**<br>**7** | $H_2N(CH_2)_7CH_3$<br>$H_2N(CH_2)_5CH_3$ | **12** $R^1$ = H, $R_2$ = $CH_3$, n = 5<br>**13** $R^1$ = $CH_3$, $R_2$ = H, n = 7 | **12** (90)<br>**13** (97) |
| 6 | **5** | $H_2N$ | | **14** (73) |
| 7[a] | **5** | $H_2N$ | | **15** (95) |
| 8[a]<br>9[a]<br>10[a]<br>11[a] | **5** | $H_2N$ R<br>R = H, $CH_3$, $C(CH_3)_3$ or $OCH_3$ | **16** R = H<br>**17** R = $CH_3$<br>**18** R = $C(CH_3)_3$<br>**19** R = $OCH_3$ | **16** (78)<br>**17** (81)<br>**18** (72)<br>**19** (71) |
| 12[a] | **7** | $H_2N$ | | **20** (94) |
| 13[a] | **5** | $H_2N$ | | **21** (99) |
| 14 | **7** | $H_2N$ O | | **22** (95) |
| 15 | **5** | $H_2N$ | | 0[c] |
| 16<br>17 | **5** | $H_2N$ OH<br>n = 0, or 2 | n = 0<br>n = 2 | 0[c]<br>0[c] |
| 18<br>19 | **5**<br>**6** | $H_2N$ OMe<br>n = 2 | **23** $R^1$ = H<br>**24** $R^1$ = $CH_3$ | (94)<br>(84) |
| 20<br>21 | **5** | $H_2N$ R OH O<br>R = H, or Arg | R = H<br>R = Arg | 0[c]<br>0[c] |
| 22 | **5** | $NH_2Ph$ | | 0[c] |
| 23 | **8** | $H_2N(CH_2)_nCH_3$<br>n = 7 | n = 7 | 0[c] |

[a]5.0% catalyst, 10% ligand, 2.0 equiv of amine utilized. [b]Isolated, purified yield over two synthetic steps. [c]Starting material was recovered.

°C. To the best of our knowledge at the time of publication, this represents the first time this catalyst ligand-system has been employed in the context of a diamination sequence of aryl bromides. Conversion was also realized in the case of entry 15 which incorporated sodium *tert*-butoxide as base, but the presence of unidentified impurities led to further evaluation of entry 14 as the candidate system. Control experiments were also performed. As postulated, no conversion of the starting material to the desired product was observed in the absence of ligand, or catalyst (entries 17 and 18).

After a potential method for the construction of the desired diamination product was established, a catalyst and ligand loading study was attempted to evaluate the limits of the catalyst complex performance. It was observed that complete conversion of the starting material could be obtained with 2.5 mol % of $Pd_2(dba)_3$ and 5 mol % of CyPF-*t*Bu, or a modest 1.25 mol % and 2.5 mol % of catalyst and ligand, respectively, per aryl bromide. When catalyst loading was performed at 1 mol %, approximately 10% conversion was observed. Attempts to lower catalyst loading to 0.1 or 0.01 mol % resulted in no conversion (starting material recovered in these cases). It was also observed during the course of the substrate scope study that the impurity profile of certain reactions could be improved with 5 mol % catalyst and 10 mol % ligand loadings.



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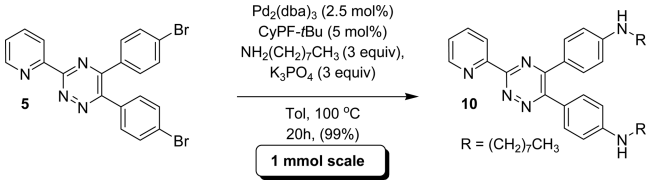
After high conversion of **5** with low catalyst/ligand loadings using optimized conditions was observed, a subsequent study to evaluate the percent conversion of starting material as a function of time was undertaken. In an effort to ascertain an exact time when starting material conversion and the impurity profile of the reaction were balanced, a series of experiments to test starting material conversion as a function of time were executed. Experimentation with 2.5 mol % of catalyst, 5 mol % of ligand, and 3 equiv of amine on the model system revealed complete conversion of the starting material after 12 h ($^1$H NMR). With a viable system established, the focus of the investigation turned to amine screening experiments to evaluate the limits of the method (Table 2).

Preparation of the requisite substrates for this work (**5**–**8**) were accomplished using prior methods developed in this laboratory. A variety of primary alkyl and aryl amines were evaluated in the context of the developed procedure (Table 1). Diamination of all substrates with primary alkyl amines (entries 1–5, 7), with the exception of hexylamine (product decomposition) for substrate **5**, exhibited excellent performance, with complete conversion of the starting material and the desired products isolated in high yield. Diamination with $\gamma$-branched primary amines (entry 6) was also successful. Benzyl amine (entry 8) as well as derivatives with inductively or resonance-donating substituents (alkyl or methoxy) also proceeded with favorable conversion and purified yields (entries 9–12), although a slight increase in catalyst/ligand loading was required to improve the impurity profile. Phenethylamine was similarly amenable to the developed conditions (entry 13). Furfuryl amine was also a suitable amine (entry 14). As expected, methylpyridine congeners (entries 4–5, 12, 18) performed comparably to **5**. Ethanolamine and a homologous derivative failed to afford the desired coupling products, presumably due to catalyst poisoning. The methoxy variant (entries 17 and 18) was possible with scaffolds **5** and **6**, suggesting that the free OH group does play an inhibitory role in the productive catalytic cycle. Several amino functionalities were not successful in the described work including hindered primary and secondary amines, amino acids, or anilines. Steric hindrance was reasoned to be the main issue with hindered primary and secondary amines, which can be common with Josiphos type ligands, while diminished nucleophilicity of the nitrogen atom contained in the amino acids and aniline screened were postulated. Assessment of the aryl chloride (**8**), entry 22, was unsuccessful even at higher catalyst/ligand loadings. Ongoing work continues to satisfactorily address current limitations. To validate the utility of the developed method on a larger scale appropriate to the production of significant quantities of material for complexation studies, a 500 mg, 1 mmol experiment, which represented a 10-fold increase in scale relative to development work, was executed. The described experiment performed comparably to the general method with respect to preparation and purification, affording the desired diaminated heterocycle **10** in 99% isolated yield (Scheme 1).

Figure 2 below represents a proposed catalytic cycle for the described transformation according to a traditional Buchwald–Hartwig amination process that occurs twice to afford the previously described complexants. Precomplexation of the $Pd_2(dba)_3$ with the CyPF-*t*Bu ligand affords the proposed catalytically active species. Oxidative addition of the Pd catalyst into the aryl bromine bond affords a Pd(II) intermediate which could diverge through two different pathways to afford the

**Scheme 1. Pd-Catalyzed Amination Scale-Up Experiment**



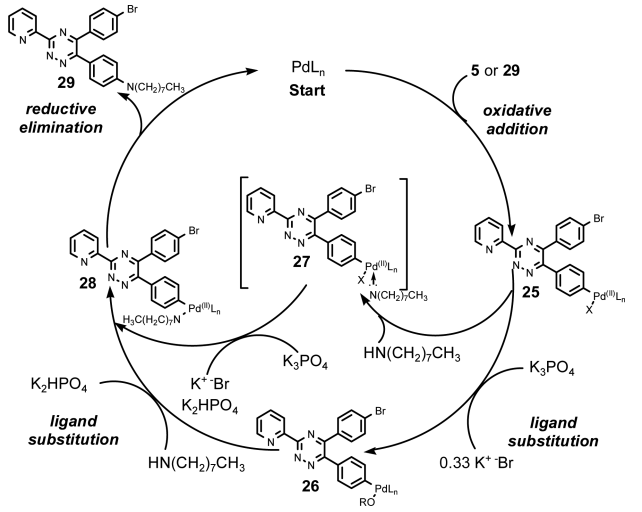




**Figure 2.** Proposed catalytic cycle for palladium-catalyzed diamination.

ligand-substituted intermediate **28** requisite for reductive elimination, affording the new C–N bond and regenerating the catalytically active species for additional turnovers. The monoaminated moiety would undergo a subsequent amination via an analogous catalytic cycle to afford the listed diaminated complexants. It should be noted that detailed mechanistic studies were not undertaken during the described work and an alternatively plausible catalytic cycle could potentially involve simultaneous amination via two discrete Pd catalyst complexes. It is postulated that the rate of ligand association of the electron-rich CyPF-*t*Bu, which promotes concomitant dissociation of the dibenzylidene acetone ligand, precludes catalyst poisoning via bidentate dative chelation, with the pyridinyl and triazinyl nitrogens forming a five-membered unproductive Pd-complex. Control experiments support the aforementioned, as product formation was not observed with the described conditions in the absence of CyPF-*t*Bu (Table 1, entry 18).

## ■ CONCLUSION

In summary, we have demonstrated a Pd-catalyzed diamination protocol for heteroaryl-1,2,4-triazines with primary alkyl, benzyl, and more functionalized amines using $Pd_2(dba)_3$ and the CyPF-*t*Bu ligand as a highly active system, leading to the formation of 16 novel materials. This protocol enables access to pyridinyl triazines as the 4,4′-amino derivatives which are commercially limited, unsuccessful in traditional condensation chemistry, and allows the opportunity for modular diversity toward the development of complexants that could negate the need for additional solubility modifiers. Future work will focus on separation assays with the described materials, adaptation of this method to BTP and BTPhen scaffolds, and amino moieties not currently viable.



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## EXPERIMENTAL SECTION

**General.** All reagents were purchased from U.S. chemical suppliers, stored according to published protocols, and used as received unless indicated otherwise. All experiments were performed in oven- or flame-dried glassware under an inert atmosphere of Ar except where indicated. Reaction progress was monitored using thin-layer chromatography on glass-backed silica gel plates and/or $^1$H NMR analysis of crude reaction mixtures. $R_f$ values for compounds that resulted in a concentrically observed spot on normal phase silica gel are reported using the conditions listed. All reported yields listed are for pure compounds and corrected for residual solvent, if applicable, from $^1$H NMR spectroscopy unless otherwise indicated. Infrared spectral data was acquired from the (form) listed. All $^1$H and $^{13}$C NMR chemical shifts are reported using the $\delta$ scale and are referenced to the residual solvent signal: $CDCl_3$ ($\delta$ 7.26) or DMSO-$d_6$ ($\delta$ 2.50) for $^1$H NMR and chloroform ($\delta$ 77.0), DMSO-$d_6$ ($\delta$ 39.52) for $^{13}$C NMR. Splittings are reported as follows: (s) = singlet, (d) = doublet, (t) = triplet, (dd) = doublet of doublets, (dt) = doublet of triplets, (br) = broad, and (m) = multiplet. High resolution mass spectrometry (HRMS) data were obtained utilizing electron impact ionization (EI) with a magnetic sector (EBE trisector), double focusing-geometry mass analyzer unless indicated otherwise.

Preparations of **5** and **8** have been reported previously.[12]

**5,6-Bis(4-bromophenyl)-3-(6-methylpyridin-2-yl)-[1,2,4]-triazine (6).** To a 15 mL round-bottom flask equipped with magnetic stirring bar under at ambient temperature was charged 6-methylpyridine-2-carbonitrile (500 mg, 4.23 mmol, 1.00 equiv) in anhydrous EtOH (1.25 mL, 2.5 vol). The resulting suspension was cooled to 0 °C and treated dropwise with hydrazine hydrate, 64% hydrazine (0.50 mL, 10.58 mmol, 2.50 equiv). The ice bath was removed, and the heterogeneous mixture was continued toward ambient temperature for 1 h followed by heating to 40 °C for 16 h. The heterogeneous mixture was filtered under reduced pressure, and the cake was conditioned with a minimal amount of cold hexanes to afford the hydrazonamide as a yellow crystalline solid (602 mg, 94.8%). Conversion of the starting material was complete as observed from $^1$H NMR, and the compound was telescoped directly to the formation of **6** without further purification, HRMS (EI) $m/z$ calculated for $C_7H_{10}N_4$ = 150.0905; found: 150.0905. To a 25 mL round-bottom flask equipped with a magnetic stirring bar at ambient temperature was charged the hydrazonamide (636 mg, 4.20 mmol, 1.00 equiv) in anhydrous THF (4.00 mL, 2.4 vol) followed by addition of dibromobenzil (1.635 g, 4.44 mmol, 1.05 equiv). The heterogeneous mixture was heated to 66 °C for 16 h upon which time the reaction was cooled to ambient temperature. The resulting solids were isolated by vacuum filtration, and the cake was conditioned with a minimal amount of 0 °C EtOH. The solids were dried under reduced pressure at ambient temperature to constant mass to afford the title compound **6** as a fine orange-yellow solid (1.387 g, 65%) which was used without further purification, mp 215−220 °C. $R_f$ = 0.70, 10% MeOH:DCM; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 8.35 (d, $J$ = 10.0 Hz, 1H), 7.97 (t, $J$ = 10.0 Hz, 1H), 7.70 (d, $J$ = 5.0 Hz, 2H), 7.68 (d, $J$ = 5.0 Hz, 2H), 7.57−7.53 (m, 4H), 7.51 (d, $J$ = 5.0 Hz, 1H), 2.63 (s, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 161.2, 159.2, 155.8, 155.6, 152.3, 138.1, 135.1, 134.9, 132.3, 132.14, 132.09, 132.01, 125.8, 125.1, 124.0, 121.8; IR ($CDCl_3$): $\nu_{max}$ = 3304, 3051, 2919, 1606, 1530, 1490, 1473, 1371, 1183, 828, 733 cm$^{-1}$; HRMS (EI): $m/z$ calculated for $C_{21}H_{14}Br_2N_4$: 479.9585; found: 479.9585.

**4-Methylpyridinyl-2-hydrazonamide (25).** To an 8 mL reaction vial equipped with magnetic stirring bar at ambient temperature was charged 4-methylpyridine-2-carbonitrile (100 mg, 0.846 mmol, 1.00 equiv) in anhydrous EtOH (0.1 mL, 10 vol). The resulting suspension was cooled to 0 °C and treated dropwise with hydrazine hydrate, 64% hydrazine (1.23 mL, 5.08 mmol, 6.00 equiv). The ice bath was removed, and the heterogeneous mixture was continued toward ambient temperature followed by heating to 40 °C for 23 h. The mixture was concentrated under reduced pressure at ambient temperature, suspended in THF (1 mL), and filtered under reduced pressure. The orange solids were conditioned with a minimal amount of cold hexanes to afford the title compound **25** as an orange-crystalline solid (99.7 mg, 78.4%). Conversion of the starting material was complete as observed from $^1$H NMR, and the compound was telescoped directly to the formation of **7** without further purification, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.34 (d, $J$ = 6.0 Hz, 1H), 7.81 (s, 1H), 7.05 (d, $J$ = 6.0 Hz, 1H), 5.30 (br-s, 2H), 4.33 (br-s, 2H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 152.1, 147.9, 147.2, 143.6, 124.4, 119.9, 21.1, IR ($CDCl_3$): $\nu_{max}$ = 3447, 3274, 3056, 1625, 1602, 1554, 1469 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_7H_{10}N_4$: 150.0905; found: 150.0911.

**5,6-Bis(4-bromophenyl)-3-(4-methylpyridin-2-yl)-[1,2,4]-triazine (7).** To a 25 mL round-bottom flask equipped with a magnetic stirring bar at ambient temperature was charged **25** (634 mg, 4.232 mmol, 1.05 equiv) in anhydrous THF (3.00 mL, 5 vol) followed by addition of dibromobenzil (1.635 g, 4.44 mmol, 1.05 equiv). The resulting heterogeneous mixture was heated to 66 °C and continued for 12 h upon which time the mixture was cooled to ambient temperature to afford a yellow-crystalline solid that was isolated under reduced pressure. The cake was conditioned with a minimal amount of 0 °C EtOH and dried to constant mass to afford the title compound **7** as a fine-yellow solid (1.464 g, 68.9%). Conversion of **25** was complete as observed from $^1$H NMR, and the compound was used directly in the described Pd-catalyzed amination procedures without further purification, mp = 207−212 °C, $R_f$ = 0.90, 10% MeOH:DCM; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.77 (d, $J$ = 5.0 Hz, 1H), 8.52 (s, 1H), 7.57−7.50 (m, 8H), 7.31 (dd, $J$ = 5.0, 1.0 Hz, 1H), 2.51 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 161.2, 155.4, 155.2, 152.5, 150.5, 148.6, 134.4, 134.1, 132.3, (132.*X*, overlaps with 132.3), 131.6, 131.2, 126.7, 126.0, 125.3, 124.9, 21.4; IR ($CDCl_3$): $\nu_{max}$ = 3059, 2963, 2921, 1586, 1485, 1370, 821 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{21}H_{14}Br_2N_4$: 479.9585; found: 479.9600.

**General Procedure for Pd-Catalyzed Diamination.** To an 8 mL reaction vial equipped with a magnetic stir bar at ambient temperature were charged $Pd_2(dba)_3$, CyPF-*t*Bu, $K_3PO_4$ (3 equiv), the required substrate (0.11 mmol), and toluene (0.3 M). The resulting reddish-brown mixture was allowed to precomplex for 30 min upon which time the necessary amine was added. The resulting dark-brown heterogeneous mixture was heated to 100 °C for 16−20 h upon which time complete conversion of the starting material was observed. Concentration of the crude reaction mixtures under reduced pressure at ambient temperature followed by purification on normal phase silica gel using automated flash-column chromatography with EtOAc:hexanes or MeOH:DCM gradient mobile phases to afford the compounds described in the listed yields.

**5,6-Bis(4-octylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (9).** Prepared according to the general procedure discussed above with substrate **5**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.61, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0593 g, 99%; brown gum; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.88 (d, $J$ = 5.0 Hz, 1H), 8.64 (d, $J$ = 10.0 Hz, 1H), 7.88 (dt, $J$ = 10.0, 5.0 Hz, 1H), 7.71 (d, $J$ = 10.0 Hz, 2H), 7.57 (d, $J$ = 10.0 Hz, 2H), 7.41 (ddd, $J$ = 10.0, 5.0, 1.0 Hz, 1H), 6.58 (d, $J$ = 10.0 Hz, 2H), 6.51 (d, $J$ = 10.0 Hz, 2H), 3.15−3.11 (m, 4H), 1.66−1.58 (m, 4H), 1.40−1.28 (m, 24H), 0.90−0.87 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.5, 155.6, 155.2, 153.8, 150.8, 150.3, 149.8, 136.9, 131.7, 130.7, 124.9, 124.6, 124.0, 123.9, 112.5, 112.1, 43.8, 43.6, 31.9, 29.6, 29.53, 29.51, 29.4, (29.*X* × 2, overlaps with 29.4), 27.29, 27.24, 22.9, 22.*X* (overlaps with 22.9), 14.2, 14.*X* (overlaps with 14.2); IR ($CDCl_3$): $\nu_{max}$ = 3313, 3057, 2926, 2854, 1606, 1532, 1468, 1338, 826 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{36}H_{48}N_6$ = 564.3940; found: 564.3956.

**5,6-Bis(4-decylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (10).** Prepared according to the general procedure discussed above with substrate **5**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.64, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0502 g, 99%; brown gum; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.89 (d, $J$ = 5.0 Hz, 1H), 8.65 (d, $J$ = 5.0 Hz, 1H), 7.88 (dt, $J$ = 5.0, 1.0 Hz, 1H), 7.71 (d, $J$ = 10.0 Hz, 2H), 7.58 (d, $J$ = 10.0 Hz, 2H), 7.42 (dd, $J$ = 5.0, 5.0 Hz, 1H), 6.59 (d, $J$ = 10.0 Hz, 2H), 6.51 (d, $J$ = 10.0 Hz, 2H), 3.16−3.12 (m, 4H), 1.66−1.58 (m, 4H), 1.45−1.23 (m, 22H), 0.88 (t, $J$ = 5.0 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.4, 155.6,



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155.2, 153.8, 150.8, 150.3, 149.7, 137.0, 131.8, 130.7, 124.9, 124.6, 124.0, 123.9, 112.5, 112.1, 43.9, 43.7, 32.0, 32.*X* (overlaps with 32.0), 29.7, 29.64, 29.56, 29.45 (8 other carbons overlap in this region), 27.3, 27.2, 22.8, 22.*X* (overlaps with 22.8), 14.3, 14.*X* (overlaps with 14.3); IR ($CDCl_3$): $\nu_{max}$ = 3309, 3055, 2922, 2852, 1604, 1530, 1467, 1366, 825, 788 $cm^{-1}$, HRMS (EI) *m*/*z* calculated for $C_{40}H_{56}N_6$ = 620.4566; found: 620.4569.

**5,6-Bis(4-tetradecylaminophenyl)-3-pyridin-2-yl-[1,2,4]-triazine (11).** Prepared according to the general procedure discussed above with substrate **5**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.66, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0556 g, 99%; brown gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.92 (d, *J* = 6.0 Hz, 1H), 8.68 (dd, *J* = 0.5, 6.0 Hz, 1H), 7.92 (t, *J* = 6.0 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 7.48−7.44 (m, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 9.0 Hz, 2H), 3.17−3.11 (m, 4H), 1.68−1.57 (m, 4H), 1.50−1.15 (m, 44H), 0.88 (t, *J* = 6.0 Hz, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.7, 155.0, 153.9, 153.1, 151.5, 150.2, 149.8, 137.3, 131.0, 129.9, 125.2, 123.4, 122.4, 121.3, 111.5, 111.1, 42.5, 42.3, 31.3, 31.*X* (overlaps with 31.3), 29.1, (11 other carbon resonances overlap with 29.1), 28.9, 28.8, 28.7, 28.*X* (overlaps with 28.7), 28.6, 28.5, 26.6, 26.7, 22.1, 22.*X* (overlaps with 22.1), 13.9, 13.*X* (overlaps with 13.9); IR ($CDCl_3$): $\nu_{max}$ = 3309, 3056, 2925, 2853, 1607, 1532, 1468, 1337, 827 $cm^{-1}$; HRMS (EI) *m*/*z* calculated for $C_{48}H_{72}N_6$ = 732.5818; found: 732.5789.

**5,6-Bis(4-octylaminophenyl)-3-(6-methylpyridin-2-yl)-[1,2,4]triazine (12).** Prepared according to the general procedure discussed above with substrate **6**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.65, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0540 g, 90%; brown gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.41 (d, *J* = 9.0 Hz, 1H), 7.75 (t, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 1H), 6.54 (d, *J* = 9.0 Hz, 2H), 6.50 (d, *J* = 9.0 Hz, 2H), 3.14−3.09 (m, 4H), 2.73 (s, 3H), 1.66−1.54 (m, 4H, 1.45−1.15 (br-m, 20H), 0.89−0.85 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.1, 159.0, 155.3, 154.9, 152.7, 150.6, 150.6*X* (overlaps with 150.6), 137.43, 131.71, 130.55, 124.92, 123.84, 123.8*X* (overlaps with 123.84), 121.08, 112.87, 112.08, 44.14, 43.61, 31.81, 31.8*X* (overlaps with 31.81), 29.38, 29.25, 29.05, 28.94, [28.9*X* × 2] (overlaps with 28.94), 27.14, 27.11, 24.66, 24.6*X* (overlaps with 24.66), 22.66, 14.11, 14.*X* (overlaps with 14.1); IR ($CDCl_3$): $\nu_{max}$ = 3307, 3057, 2923, 2853, 1604, 1575, 1531, 1472, 1360, 1180, 826, 796 $cm^{-1}$, HRMS (EI) *m*/*z* calculated for $C_{37}H_{50}N_6$ = 578.4097; found: 578.4078.

**5,6-Bis(4-hexylaminophenyl)-3-(4-methylpyridin-2-yl)-[1,2,4]triazine (13).** Prepared according to the general procedure discussed above with substrate **7**: (5% catalyst, 10% ligand), $R_f$ = 0.50, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0507 g, 97%; dark brown gum; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 8.65 (d, *J* = 5.0 Hz, 1H), 8.31 (s, 1H), 7.55 (d, *J* = 10.0 Hz, 2H), 7.42−7.41 (m, 1H), 7.40 (d, *J* = 10.0 Hz, 2H), 6.59 (d, *J* = 10.0 Hz, 2H), 6.53 (d, *J* = 10.0 Hz, 2H), 6.38 (t, *J* = 5.0 Hz, 1H), 6.08 (t, *J* = 5.0 Hz, 1H), 3.06−3.02 (m, 4H), 2.46 (s, 3H), 1.59−1.50 (m, 4H), 1.42−1.25 (m, 12H), 0.89−0.85 (m, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.9, 154.9, 153.8, 153.1, 151.5, 150.2, 149.6, 147.8, 131.0, 129.8, 125.9, 124.1, 122.4, 121.4, 111.5, 111.1, 42.5, 42.3, 31.1, 31.1, 28.6, 28.5, 26.4, 26.3, 22.1, 22.*X* (overlaps with 22.1), 20.7, 13.9, 13.*X* (overlaps with 13.9); IR ($CDCl_3$): $\nu_{max}$ = 3310, 2954, 2928, 2856, 1606, 1533, 1489, 1469, 1363, 829 $cm^{-1}$, HRMS (EI) *m*/*z* calculated for $C_{33}H_{42}N_6$ = 522.3471; found: 522.3452.

**5,6-Bis(4-isoamylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (14).** Prepared according to the general procedure discussed above with substrate **5**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.70, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0387 g, 73%; brown gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.90−8.88 (m, 1H), 8.65 (dd, *J* = 3.0, 6.0 Hz, 1H), 7.89 (dt, *J* = 3.0, 6.0 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.45−7.41 (m, 1H), 6.59 (d, *J* = 9.0 Hz, 2H), 6.51 (d, *J* = 9.0 Hz, 2H), 3.18−3.12 (m, 4H), 1.77−1.66 (m, 2H), 1.57−1.47 (m, 4H), 0.97−0.94 (m, 12H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.8, 155.0, 153.9, 153.2, 151.5, 150.2, 149.9, 137.2, 131.0, 129.9, 125.2, 123.4, 122.41, 121.40, 111.5, 111.1, 40.7, 40.5, 37.6, 37.5, 25.37, 25.31, 22.5, 22.*X* (overlaps with 22.5), 22.45, 22.*X* (overlaps with 22.45); IR ($CDCl_3$): $\nu_{max}$ = 3311, 3055, 2954, 2870, 1607, 1532, 1469, 1367, 828 $cm^{-1}$; HRMS (EI) *m*/*z* calculated for $C_{30}H_{36}N_6$ = 480.3001; found: 480.2995.

**5,6-Bis(4-methylenecyclohexylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (15).** Prepared according to the general procedure discussed above with substrate **5**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.70, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0544 g, 95%; reddish-brown gum; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.88 (d, *J* = 5.0 Hz, 1H), 8.64 (d, *J* = 10.0 Hz, 1H), 7.88 (dt, *J* = 10.0, 5.0 Hz, 1H), 7.71 (d, *J* = 10.0 Hz, 2H), 7.57 (d, *J* = 10.0 Hz), 7.42 (ddd, *J* = 10.0, 5.0, 1.0 Hz, 1H), 6.58 (d, *J* = 10.0 Hz, 2H), 6.51 (d, *J* = 10.0 Hz, 2H), 3.00−2.98 (m, 4H), 1.83−1.68 (m, 8H), 1.62−1.54 (m, 2H), 1.28−1.16 (m, 8H), 1.03−0.95 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.4, 155.6, 155.1, 153.8, 151.0, 150.3, 149.9, 137.0, 131.7, 130.7, 124.9, 123.9, [123.*X* × 2] (overlaps with 123.9), 112.5, 112.1, 50.4, 50.2, 37.8, 37.*X* (overlaps with 37.8), 31.42, 31.36, 26.7, 26.6, 26.1, 26.06; IR ($CDCl_3$) $\nu_{max}$ = 3326, 3058, 2923, 2850, 1607, 1531, 1469, 826 $cm^{-1}$; HRMS (EI) *m*/*z* calculated for $C_{34}H_{40}N_6$ = 532.3312; found: 532.3324.

**5,6-Bis(4-benzylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (16).** Prepared according to the general procedure discussed above with substrate **5**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.64, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0435 g, 78%; orange-brown gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.92−8.89 (m, 1H), 8.67 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.92 (dt, *J* = 6.0, 3.0 Hz, 1H), 7.73 (d, *J* = 6.0 Hz, 2H), 7.59 (d, *J* = 6.0 Hz, 2H), 7.48−7.44 (m, 1H), 7.38−7.27 (m, 10H), 6.64 (d, *J* = 6.0 Hz, 2H), 6.58 (d, *J* = 6.0 Hz, 2H), 4.38 (s, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 158.8, 155.0, 153.9, 153.1, 151.1, 149.9, 139.7, 139.4, 137.2, 130.9, 129.8, 128.3, 128.*X* (overlaps with 128.3), 127.3, 126.8, 125.2, 123.4, 122.9, [122.*X* × 3] (overlaps with 122.9), 112.0, 111.6, 46.2, 46.0; IR ($CDCl_3$): $\nu_{max}$ = 3316, 3061, 3029, 2924, 2853, 1606, 1489, 1470, 1372, 1183, 789, 732, 698 $cm^{-1}$, HRMS (EI) *m*/*z* calculated for $C_{34}H_{28}N_6$ = 520.2375; found: 520.2384.

**5,6-Bis(4-(4′-methyl)benzylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (17).** Prepared according to the general procedure discussed above with substrate **5**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.61, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0472 g, 81%; orange-brown gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.89−8.87 (m, 1H), 8.64 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.92−7.86 (m, 1H), 7.69 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.45−7.40 (m, 1H), 7.28−7.14 (m, 8H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 9.0 Hz, 2H), 4.32 (br-s, 4H), 2.34 (br-s, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.8, 155.0, 153.9, 153.1, 151.2, 149.9, 137.2, 136.6, 136.3, 135.9, 135.8, 130.9, 129.8, 128.9, 127.3, 125.2, 123.4, 122.8, 121.9, 112.0, 111.6, 46.0, 45.7, 20.7, 20.*X* (overlaps with 20.7); IR ($CDCl_3$): $\nu_{max}$ = 3026, 2923, 2854, 1606, 1487, 1470, 1371, 828 $cm^{-1}$; HRMS (EI) *m*/*z* calculated for $C_{36}H_{32}N_6$ = 548.2688; found: 548.2683.

**5,6-Bis(4-(4′-*tert*-butyl)benzylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (18).** Prepared according to the general procedure discussed above with substrate **5**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.61, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0489 g, 72%; orange-brown gum; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.91 (d, *J* = 5.0 Hz, 1H), 8.67 (d, *J* = 10.0 Hz, 1H), 7.92 (dt, *J* = 10.0, 5.0 Hz, 1H), 7.95 (d, *J* = 10.0 Hz, 2H), 7.59 (d, *J* = 10.0 Hz, 2H), 7.45 (dd, *J* = 10.0, 5.0 Hz, 1H), 7.39−7.36 (m, 4H), 7.31 (d, *J* = 10.0 Hz, 2H), 7.27 (d, *J* = 10.0 Hz, 2H), 6.65 (d, *J* = 5.0 Hz, 2H), 6.58 (d, *J* = 5.0 Hz, 2H), 4.33 (s, 4H), 1.33 (s, 9H), 1.32 (s, 9H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.8, 155.0, 153.9, 153.1, 151.2, 149.9, 149.*X* (overlaps with 149.9), 149.24, 149.17, 137.2, 136.6, 136.3, 130.9, 129.9, 127.2, 125.1, 123.4, 122.8, 122.*X* (overlaps with 122.8), 121.9, 111.9, 111.5, 45.9, 45.7, 34.2, 34.*X* (overlaps with 34.2), 31.2, 31.*X* (overlaps with 31.2); IR ($CDCl_3$): $\nu_{max}$ = 3313, 3053, 2959, 2866, 1606, 1486, 1469, 1392, 1371, 825 $cm^{-1}$, HRMS (EI) *m*/*z* calculated for $C_{42}H_{44}N_6$ = 632.3627; found: 632.3618.

**5,6-Bis(4-(4′-methoxy)benzylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (19).** Prepared according to the general procedure discussed above with substrate **5**: (5.0% catalyst, 10.0% ligand), $R_f$ =



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0.63, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0442 g, 71%; orange-brown gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.89−8.87 (m, 1H), 8.66−8.62 (m, 1H), 7.88 (dt, $J$ = 9.0, 3.0 Hz, 1H), 7.73−7.66 (m, 2H), 7.61−7.54 (m, 2H), 7.42 (ddd, $J$ = 9.0, 4.00, 3.0 Hz, 1H), 7.30−7.25 (m, 4H), 6.91−6.85 (m, 4H), 6.65−6.61 (m, 2H), 6.57−6.54 (m, 2H), 4.28 (s, 4H), 3.80 (s, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.8, 158.2, 155.0, 153.9, 153.2, 151.2, 151.$X$ (overlaps with 151.2), 149.9, 149.$X$ (overlaps with 149.9), 137.2, 131.5, 131.2, 130.9, 129.8, 128.6, 128.$X$ (overlaps with 128.6), 125.2, 123.4, 122.8, 121.9, 113.8, 113.$X$ (overlaps with 113.8), 55.0, 55.$X$ (overlaps with 55.0), 45.7, 45.5; IR ($CDCl_3$): $\nu_{max}$ = 3311, 2918, 2851, 1606, 1488, 1469, 1372, 1182, 822 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{36}H_{32}N_6O_2$ = 580.2587; found: 580.2584.

**5,6-Bis(4-(4′-methyl)benzylaminophenyl)-3-(4-methylpyridin-2-yl)-[1,2,4]triazine (20).** Prepared according to the general procedure discussed above with substrate **7**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.49, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0559 g, 94%; orange solid; mp 97−102 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 8.64 (d, $J$ = 5.0 Hz, 1H), 8.29 (s, 1H), 7.51 (d, $J$ = 10.0 Hz, 2H), 7.51 (d, $J$ = 10.0 Hz, 2H), 7.40 (d, $J$ = 5.0 Hz, 1H), 7.36 (d, $J$ = 10.0 Hz, 2H), 7.27−7.23 (m, 4H), 7.15−7.12 (m, 4H), 6.94 (t, $J$ = 5.0 Hz, 1H), 6.67 (t, $J$ = 5.0 Hz, 1H), 6.62 (d, $J$ = 10.0 Hz, 2H), 6.57 (d, $J$ = 10.0 Hz, 2H), 4.27 (s, 2H), 4.26 (s, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.9, 154.9, 153.9, 153.0, 151.1, 149.8, 149.6, 147.9, 136.33, 136.30, 135.9, 135.8, 130.9, 129.8, 128.9, 128.$X$ (overlaps with 128.9), 127.3, 127.$X$ (overlaps with 127.3), 125.9, 124.1, 122.8, 121.9, 112.0, 111.6, 45.9, 45.7, 20.7, 20.$X$ (overlaps with 20.7); IR ($CDCl_3$): $\nu_{max}$ = 3309, 3027, 2921, 2852, 1606, 1530, 1489, 1372, 1181, 826, 809 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{37}H_{34}N_6$ = 562.2845; found: 562.2843.

**5,6-Bis(4-phenethylaminophenyl)-3-pyridin-2-yl-[1,2,4]-triazine (21).** Prepared according to the general procedure discussed above with substrate **5**: (5.0% catalyst, 10.0% ligand), $R_f$ = 0.67, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0586 g, 99%; orange-brown gum; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.89 (d, $J$ = 5.0 Hz, 1H), 8.65 (d, $J$ = 5.0 Hz, 1H), 7.91−7.87 (m, 1H), 7.71 (d, $J$ = 10.0 Hz, 2H), 7.58 (d, $J$ = 10.0 Hz, 2H), 7.44−7.42 (m, 1H), 7.33−7.31 (br-m, 4H), 7.24−7.20 (br-m, 4H), 6.60 (d, $J$ = 10.0 Hz, 2H), 6.53 (d, $J$ = 10.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.6, 155.7, 155.2, 153.7, 150.4, 149.3, 149.$X$ (overlaps with 149.3), 139.1, 139.0, 137.0, 131.8, 130.8, 128.9, 128.$X$ (overlaps with 128.9), 128.8, 128.$X$ (overlaps with 128.8), 126.73, 126.70, 125.0, 124.9, 124.5, 123.9, 112.8, 112.4, 44.8, 44.6, 35.6, 35.5; IR ($CDCl_3$): $\nu_{max}$ = 3309, 3060, 2929, 2860, 1606, 1530, 1489, 1470, 1369, 827 cm$^{-1}$, HRMS (EI) $m/z$ calculated for $C_{36}H_{32}N_6$ = 548.2688; found: 548.2704.

**5,6-Bis(4-furfurylaminophenyl)-3-(4-methylpyridin-2-yl)-[1,2,4]triazine (22).** Prepared according to the general procedure discussed above with substrate **7**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.56, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0489 g, 95%; dark-orange gum; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.72 (d, $J$ = 3.0 Hz, 1H), 8.49 (s, 1H), 7.70 (d, $J$ = 6.0 Hz, 2H), 7.57 (d, $J$ = 6.0 Hz, 2H), 7.39−7.37 (m, 3H), 6.67 (d, $J$ = 9.0 Hz, 2H), 6.60 (d, $J$ = 9.0 Hz, 2H), 6.35−6.32 (m, 2H), 6.27−6.24 (m, 2H), 4.36 (br-s, 4H), 2.49 (s, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 159.5, 155.5, 154.4, 153.5, 153.3, 153.0, 151.3, 150.1, 150.0, 148.4, 142.7, 142.6, 131.4, 130.3, 126.4, 124.6, 123.7, 122.7, 112.5, 112.1, 110.9, 107.8, 107.7, 60.2, 60.$X$ (overlaps with 60.2), 21.1; IR ($CDCl_3$): $\nu_{max}$ = 3304, 1606, 1530, 1489, 1473, 1371, 1183, 828 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{31}H_{26}N_6O_2$ = 514.2117; found 514.2103. Scaffolds **5** and **6** were also successful in terms of the amination method, but purification to publication standards was not realized.

**5,6-Bis(4-methoxypropylaminophenyl)-3-pyridin-2-yl-[1,2,4]triazine (23).** Prepared according to the general procedure discussed above with substrate **5**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.45, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0518 g, 94%; orange-brown gum; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.88 (d, $J$ = 5.0 Hz, 1H), 8.64 (d, $J$ = 10.0 Hz, 1H), 7.88 (dt, $J$ = 5.0, 1.0 Hz, 1H), 7.70 (d, $J$ = 10.0 Hz, 2H), 7.57 (d, $J$ = 10.0 Hz, 2H), 7.42 (dd, $J$ = 5.0, 5.0 Hz, 1H), 6.59 (d, $J$ = 10.0 Hz, 2H), 6.52 (d, $J$ = 10.0 Hz, 2H), 3.52 (t, $J$ = 5.0 Hz, 2H), 3.51 (t, $J$ = 5.0 Hz, 2H), 3.36 (s, 3H), 3.35 (s, 3H), 1.93−1.86 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.5, 155.7, 155.2, 153.8, 150.8, 150.3, 149.7, 137.0, 131.8, 130.7, 124.9, 123.9, [123.$X$ × 2] (overlaps with 123.9), 112.5, 112.1, 71.4, 71.3, 58.9, 58.$X$ (overlaps with 58.9), 41.8, 41.6, 29.4, 29.3; IR ($CDCl_3$): $\nu_{max}$ = 3335, 2920, 2851, 1607, 1470, 1371, 1185, 828 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{28}H_{32}N_6O_2$ = 484.2587; found: 484.2576.

**5,6-Bis(4-methoxypropylaminophenyl)-3-(6-methylpyridin-2-yl)-[1,2,4]triazine (24).** Prepared according to the general procedure discussed above with substrate **6**: (2.5% catalyst, 5.0% ligand), $R_f$ = 0.84, 10% MeOH:DCM; eluent, EtOAc/hexanes (gradient); isolated yield 0.0434 g, 84%; reddish-brown gum; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 8.25 (d, $J$ = 10.0 Hz, 1H), 7.91 (t, $J$ = 10.0 Hz, 1H), 7.55 (d, $J$ = 10.0 Hz, 2H), 7.44 (d, $J$ = 10.0 Hz, 1H), 7.40 (d, $J$ = 10.0 Hz, 2H), 6.60 (d, $J$ = 10.0 Hz, 2H), 6.54 (d, $J$ = 10.0 Hz, 2H), 6.39 (t, $J$ = 5.0 Hz, 1H), 6.11 (d, $J$ = 5.0 Hz, 1H), 3.43 (t, $J$ = 5.0 Hz, 2H), 3.40 (t, $J$ = 5.0 Hz, 2H), 3.25 (s, 3H), 3.24 (s, 3H), 3.13−3.09 (m, 4H), 2.61 (s, 3H), 1.82−1.74 (m, 4H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 158.9, 158.3, 154.9, 153.8, 152.7, 151.4, 150.1, 137.3, 131.0, 129.9, 124.5, 122.5, 121.6, 120.7, 115.5, 111.1, 69.7 (69.$X$ overlaps with 69.7), 57.9, 57.$X$ (overlaps with 57.9), (two additional resonances overlap with DMSO-$d_6$), 28.7, 28.$X$ (overlaps with 28.7), 24.2; IR ($CDCl_3$): $\nu_{max}$ = 3318, 3055, 2924, 2871, 1606, 1475, 1382, 1182, 827, 797 cm$^{-1}$; HRMS (EI) $m/z$ calculated for $C_{29}H_{34}N_6O_2$ = 498.2743; found: 498.2735.

## ■ ASSOCIATED CONTENT

### Supporting Information

Catalyst loading and time studies, and copies of $^1$H and $^{13}$C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00710.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) (a) Lantham, W. B.; Runion, T. C. *PUREX Process for Plutonium and Uranium Recovery*; USAEC report ORNL-479; Oak Ridge National Laboratory: Oak Ridge, TN, 1949. (b) Warf, J. C. *J. Am. Chem. Soc.* **1949**, *71*, 3257. (c) Schulz, W. W.; Navratil, J. D. *Science and Technology of Tributyl Phosphate*; CRC Press: Boca Raton, FL, 1990; Vol. *III*. (d) Hill, C. In *Ion Exchange and Solvent Extraction*; Moyer, B. A., Ed.; CRC Press: Boca Raton, 2010; Vol. *19*.

(2) (a) Downward, A. M.; Jane, R. T.; Polson, M. I. J.; Moore, E. G.; Hartshorn, R. M. *Dalton Trans.* **2012**, *41*, 14425−14432. (b) Downward, A. M.; Moore, E. G.; Hartshorn, R. M. *Chem. Commun.* **2011**, *47*,




DOI: 10.1021/acs.joc.5b00710
J. Org. Chem. 2015, 80, 6275−6282

7692−7694. (c) Xian-Lan, H.; Li, H.; Peng, C.-H. *J. Mol. Struct.* **2011**, *990*, 197−203.
(3) (a) Katsagounos, G.; Stathatos, E.; Arabatzis, N. B.; Keramidas, A. D.; Lianos, P. *J. Lumin.* **2011**, *131*, 1776−1781. (b) Miguirditchian, M.; Guillaneux, D.; Francois, N.; Airvault, S.; Ducros, S.; Thauvin, D.; Madic, C.; Illemassene, M.; Lagarde, G.; Krupa, J.-C. *Nucl. Sci. Eng.* **2006**, *153*, 223−232.
(4) Szumera, J.; Welniak, M.; Olejniczak, A.; Lukaszewicz, J. P. *J. Foren. Sci.* **2010**, *55*, 944−952.
(5) (a) For a recent review see: Panak, P. J.; Geist, A. *Chem. Rev.* **2013**, *113*, 1199−1236. (b) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Distler, P.; John, J.; Stamberg, K.; Núñez, A.; Galán, H.; Espartero, A. *Eur. J. Org. Chem.* **2012**, 1509−1519. (c) Laventine, D. M.; Afsar, A.; Hudson, M. J.; Harwood, L. M. *Heterocycles* **2012**, *86*, 1419−1429. (d) Afsar, A.; Laventine, D. M.; Harwood, L. M.; Hudson, M. J.; Geist, A. *Chem. Commun.* **2013**, *49*, 8534−8536. (e) Hudson, M. J.; Harwood, L. M.; Laventine, D. M.; Lewis, F. W. *Inorg. Chem.* **2013**, *52*, 3413−3428. (f) Hudson, M. J.; Boucher, C. E.; Braekers, D.; Desreux, J. F.; Drew, M. G. B.; St. J. Foreman, M. R.; Harwood, L. M.; Hill, C.; Madic, C.; Marken, F.; Youngs, T. G. A. *New J. Chem.* **2006**, *30*, 1171−1183. (g) Guillet, G. L.; Dempsey-Hyatt, I. F.; Hillesheim, P. C.; Abboud, K. A.; Scott, M. J. *New J. Chem.* **2013**, *37*, 119−131. (h) Drew, M. G. B.; Hudson, M. J.; Youngs, T. G. A. *J. Alloys Compd.* **2004**, *374*, 408−415.
(6) (a) Case, F. H. *J. Heterocycl. Chem.* **1971**, *8*, 1043−1046. (b) Kolarik, Z.; Müllich, U.; Gassner, F. *Solvent Extr. Ion Exch.* **1999**, *17*, 23−32. (c) Kolarik, Z.; Müllich, U.; Gassner, F. *Solvent Extr. Ion Exch.* **1999**, *17*, 1155−1170. (d) Lewis, F. W.; Hudson, M. J.; Harwood, L. M. *Synlett.* **2011**, 2609−2632.
(7) (a) Case, F. H. *J. Heterocycl. Chem.* **1971**, *8*, 1043−1046. (b) Kolarik, Z.; Müllich, U.; Gassner, F. *Solvent Extr. Ion Exch.* **1999**, *17*, 23−32. (c) Lewis, F. W.; Hudson, M. J.; Harwood, L. M. *Synlett.* **2011**, 2609−2632.
(8) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Drew, M. G. B.; Desreux, J. F.; Vidick, G.; Bouslimani, N.; Modolo, G.; Wilden, A.; Sypula, M.; Vu, T.-H.; Simonin, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 13093−13102.
(9) Wilden, A.; Schreinemachers, C.; Sypula, M.; Modolo, G. *Solvent. Extr. Ion Exch.* **2011**, *29*, 190−212.
(10) Kolarik, Z.; Müllich, U.; Gassner, F. *Solvent Extr. Ion Exch.* **1999**, *17*, 1155−1170.
(11) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Drew, M. G. B.; Desreux, J. F.; Vidick, G.; Bouslimani, N.; Modolo, G.; Wilden, A.; Sypula, M.; Vu, T.-H.; Simonin, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 13093−13102.
(12) Tai, S.; Marchi, S. V.; Carrick, J. D. *J. Heterocycl. Chem.* **2015**.
(13) Tai, S.; Williams, N. J.; Carrick, J. D. *J. Heterocycl. Chem.* **2015** (early view). DOI: 10.1002/jhet.2295.
(14) Adam, C.; Kaden, P.; Beele, B. B.; Müllich, U.; Trumm, S.; Geist, A.; Panak, P. J.; Denecke, M. A. *Dalton Trans.* **2013**, *42*, 14068−14074.
(15) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766−5768.
(16) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361. (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27−50. (c) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57−68.
(17) (a) For a recent review see: Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (b) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586−6596. (c) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848−13849. (d) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944−6945. (e) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848−13849.
(18) (a) Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P.; Kirsch, G. *Eur. J. Org. Chem.* **2007**, *10*, 1678−1682. (b) Abel, A. S.; Averin, A. d.; Maloshitskaya, O. A.; Savelyev, E. N.; Orlinson, B. S.; Novakov, I. A.; Beletskaya, I. P. *Molecules* **2013**, *18*, 2096−2109.
(19) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 1991−1994.
(20) Stauffer, S. R.; Steinbeiser, M. A. *Tetrahedron Lett.* **2005**, *46*, 2571−2575.
(21) Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109−4112.
(22) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796.
(23) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem. Int., Ed.* **2006**, *45*, 6523−6527.
(24) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552−13554.
(25) Charles, M. D.; Schutlz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965−3968.
(26) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9943−9947.
(27) (a) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int., Ed.* **2005**, *44*, 1371−1375. (b) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109−4112.


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