

# Synthesis of Enantiopure Unnatural Amino Acids by Metallaphotoredox Catalysis

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**ABSTRACT:** We describe herein a two-step process for the conversion of serine to a wide array of optically pure unnatural amino acids. This method utilizes a photocatalytic cross-electrophile coupling between a bromoalkyl intermediate and a diverse set of aryl halides to produce artificial analogues of phenylalanine, tryptophan, and histidine. The reaction is tolerant of a broad range of functionalities and can be leveraged toward the scalable synthesis of valuable pharmaceutical scaffolds via flow technology.

**KEYWORDS:** *unnatural amino acids, photoredox catalysis, heterocycles, nickel catalysis, flow chemistry*

## INTRODUCTION

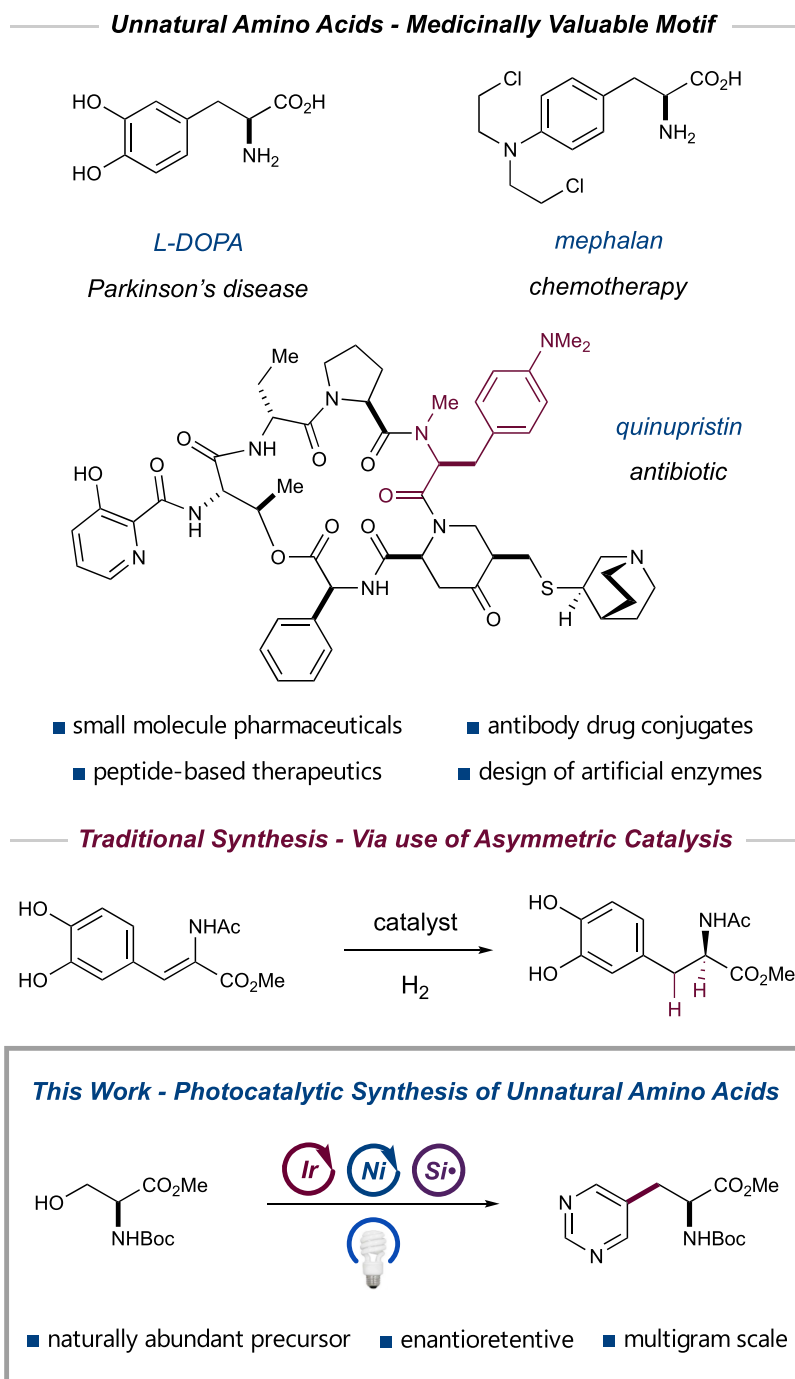
The amino acid motif is of paramount importance in biochemistry, constituting the basic building block of peptides and proteins and playing a crucial role in nearly every biological process.<sup>1</sup> As such, novel analogues of the amino acids produced by nature have found broad application in chemical biology, biochemistry, and medicine.<sup>2</sup> The versatility of these unnatural amino acids stems from their utility as chiral frameworks and their ability to confer increased potency and atypical conformations on peptide-based pharmaceuticals.<sup>3</sup> Unnatural amino acids are an important feature of many antibody drug conjugates, as they provide bioconjugation sites orthogonal to native functional groups, thereby allowing the controlled production of homogeneous, site-specific adducts.<sup>4</sup> In the enzymatic context, the incorporation of unnatural amino acids into novel biocatalysts can allow for tuning of a native enzyme's activity or incorporation of unnatural metallic cofactors.<sup>5</sup> Given the biomedical import of these motifs, there is a strong impetus to invent new methods that permit facile access to diverse collections of unnatural amino acids (Figure 1).

The chemical synthesis of amino acids is a challenge of longstanding interest to the field of organic chemistry. Since the publication of the Strecker reaction in the mid-nineteenth century,<sup>6</sup> a wide variety of catalytic technologies and elegant asymmetric catalyst designs have been developed for the synthesis of enantiopure unnatural amino acids.<sup>7</sup> Notable examples include the pioneering asymmetric hydrogenation used in the synthesis of L-DOPA,<sup>8</sup> asymmetric variants of the venerable Strecker reaction, and<sup>9</sup> photocatalytic Michael additions of aryl radicals into dehydroalanine,<sup>10</sup> among many others.<sup>11</sup> Unnatural amino acids can also be accessed via derivatization of natural amino acids, although this strategy remains relatively undeveloped. Notably, in recent years, the Yu group has pioneered the use of palladium-catalyzed C–H activation to derivatize alanine into a number of unnatural analogues.<sup>12</sup> A derivatization approach offers a clear benefit: by

harnessing the resident stereocenter of the natural amino acid, it should be possible to gain access to a diverse array of structurally complex, enantiopure unnatural amino acids without the need to develop novel asymmetric catalytic platforms. The successful realization of this objective would require the development of a protocol that is sufficiently mild to avoid racemization and tolerant of a broad range of functionalities. With these considerations in mind, we sought to design a reaction platform that would allow the facile synthesis of unnatural amino acids bearing complex structural motifs of interest to the synthetic and biomedical community.

Metallaphotoredox catalysis is a powerful new platform for bond construction that involves the synergistic merger of photochemical activation with transition metal catalysis. Our laboratory and others have exploited this reactivity manifold to develop a host of novel methodologies for carbon–carbon and carbon–heteroatom bond formation.<sup>13</sup> Notably, these photocatalytic reactions are conducted under mild conditions, with radical mechanisms proceeding at ambient temperature without the need for harsh reagents, such as strong bases or organometallic nucleophiles. We hypothesized that metallaphotoredox catalysis could be brought to bear on the challenge of synthesizing unnatural amino acids directly from natural amino acid precursors. Specifically, photochemical cross-electrophile coupling is characterized by high efficiency, mild conditions, and extraordinary substrate scope and could thus offer a means to achieve the conversion of abundant, naturally occurring amino acids to their arylated analogues.<sup>14</sup> Herein, we report a mild and enantioselective protocol for the conversion of serine to a range of amino acids bearing aromatic

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**Figure 1.** Applications and synthesis of unnatural amino acids.

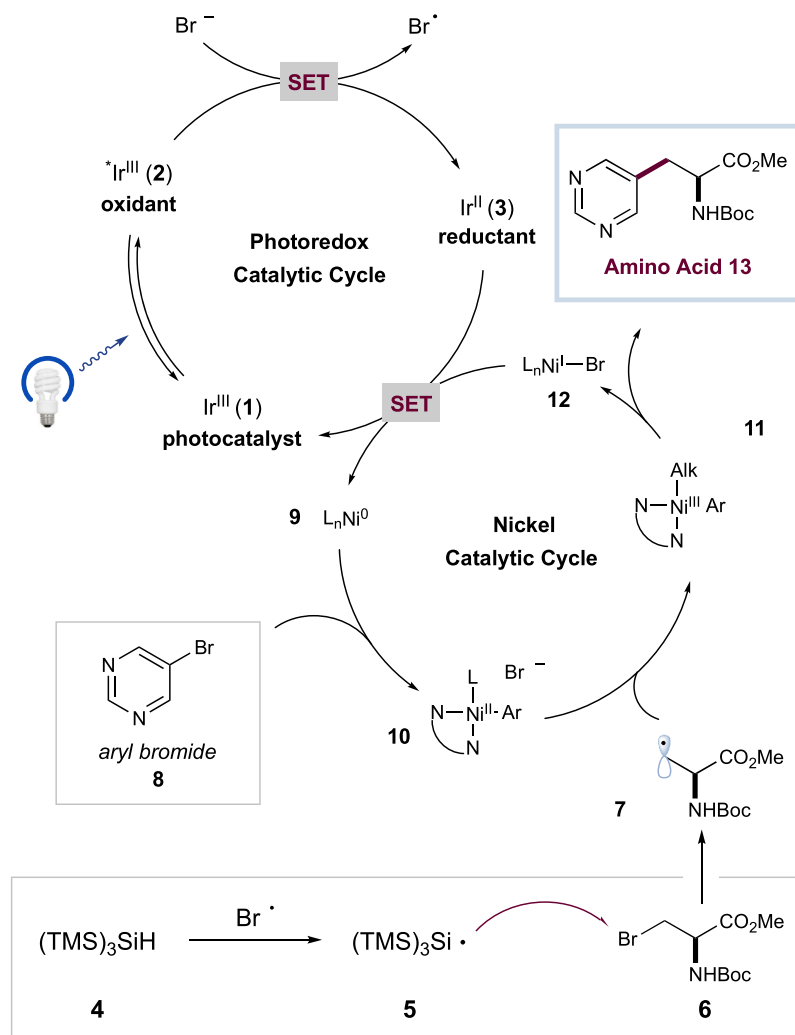
side chains via the intermediacy of a  $\beta$ -bromoalanine intermediate. This protocol provides ready access to a wide variety of arylated amino acid derivatives, including both carbo- and heterocyclic frameworks.

## RESULTS AND DISCUSSION

Serine was selected as a starting point for amino acid derivatization due its biomass abundance and readily derivatized hydroxyl group side chain. The  $\beta$ -bromoalanine (6) derivative can be easily produced via an Appel reaction on scales of greater than 450 mmol. The proposed mechanism for the metallaphotoredox-catalyzed amino acid synthesis is illustrated in Scheme 1. Initial visible light excitation of the

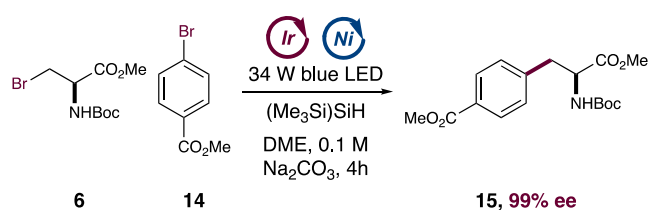
iridium(III) photocatalyst  $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  ( $\text{dF}(\text{CF}_3)\text{ppy}$  = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine,  $\text{dtbbpy}$  = 4,4'-di-*tert*-butyl-2,2'-bipyridine) (1) generates the long-lived ( $\tau$  = 2.3  $\mu\text{s}$ ) excited-state  $^*\text{Ir}(\text{III})$  complex 2. This highly oxidizing species ( $E_{1/2}^{\text{red}} [^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21$  V versus saturated calomel electrode (SCE) in  $\text{CH}_3\text{CN}$ )<sup>15</sup> can favorably undergo single-electron transfer (SET) with the bromide anion ( $E_{1/2}^{\text{red}} [\text{Br}^\bullet/\text{Br}^-] = +0.80$  V vs SCE in DME) to produce reduced Ir complex 3 along with an electrophilic bromine radical that can subsequently abstract a hydrogen atom from  $(\text{TMS})_3\text{SiH}$  (4, super silane) to yield silyl radical 5. Halogen atom abstraction by radical 5 from  $\beta$ -bromoalanine (6) affords the alkyl radical (7) and  $(\text{TMS})_3\text{Si-}$

## Scheme 1. Proposed Mechanism for Cross-Electrophile Coupling



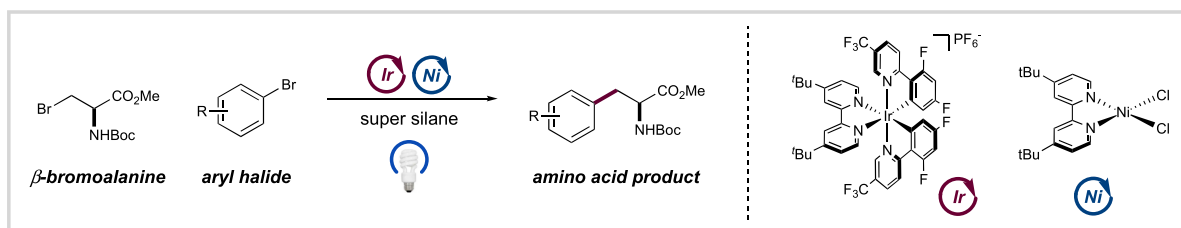
Br as a byproduct. Concurrently, a Ni<sup>0</sup> species **9** undergoes facile oxidative addition into an aryl bromide coupling partner (**8**) to generate the Ni<sup>II</sup> intermediate **10**. Trapping of the alkyl radical **7** by nickel species **10** affords the putative Ni<sup>III</sup> complex **11**, which, upon reductive elimination, yields target amino acid **13** and a Ni<sup>I</sup> intermediate (**12**). Finally, SET from strongly reducing iridium species **3** ( $E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V vs SCE}$  in CH<sub>3</sub>CN) to **12** serves to regenerate catalytically active **9** and simultaneously close the photoredox cycle.

The proposed cross-electrophile coupling was explored using aryl bromide **14** as the coupling partner. As shown in Table 1, in the presence of the iridium photocatalyst [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)] (mol %), NiCl<sub>2</sub>·dtbbpy (0.5 mol %), super silane (1 equiv), and sodium carbonate (2 equiv), the aryl bromide (**14**) and β-bromoalanine (**6**) underwent efficient cross-coupling to generate the desired amino acid **15** in 85% yield (entry 1). As anticipated, no reaction was observed when the photocatalyst, nickel catalyst, light, or silane was excluded from the reaction mixture (entries 2–5). The choice of silane proved important. As shown in entries 6 and 7, the use of silanes bearing strong Si–H bonds, compared to (TMS)<sub>3</sub>SiH, resulted in decreased reaction efficiency. These findings are consistent with those of the proposed mechanism of silyl radical formation via Si–H abstraction. Interestingly, addition of Hantzsch ester as an alternate reductant afforded

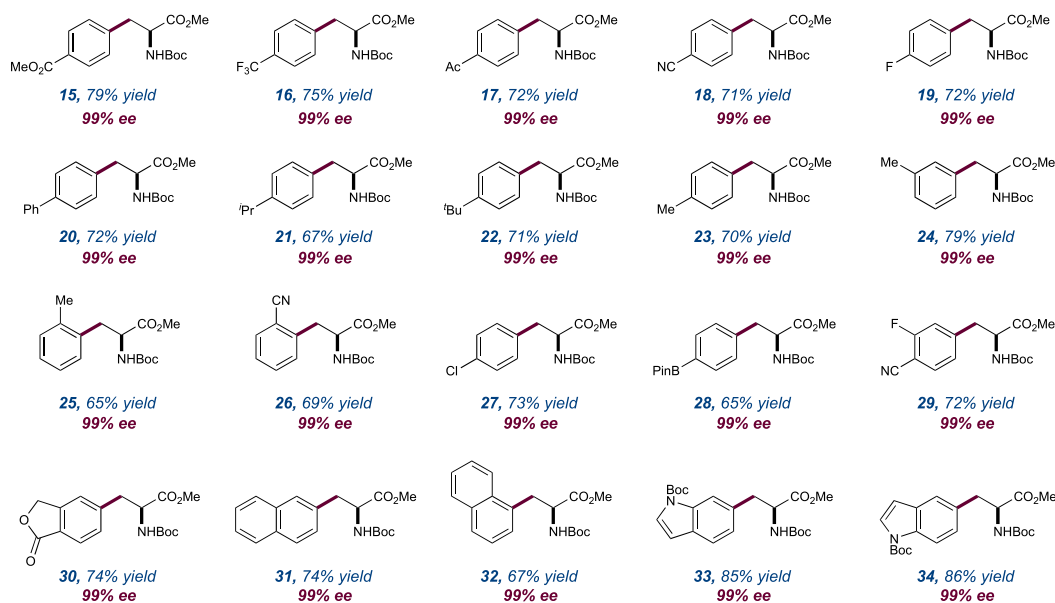
Table 1. Cross-Electrophile Coupling Control Experiments<sup>a</sup>

entry	conditions	yield <b>15</b> <sup>b</sup> (%)
1	as shown above	85
2	no photocatalyst	0
3	no nickel	0
4	no light	0
5	no silane	0
6	Ph <sub>3</sub> SiH as the silane source	34
7	Et <sub>3</sub> SiH as the silane source	0
8	Hantzsch ethyl ester instead of silane	36
9	serine tosylate in place of alkyl bromide <sup>c</sup>	80

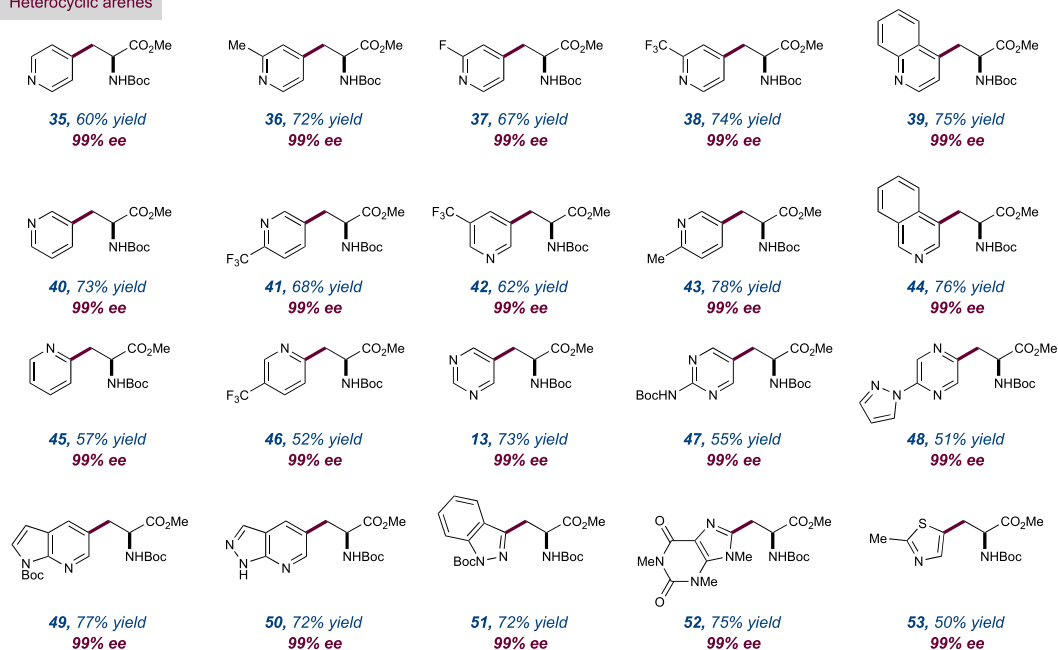
<sup>a</sup>Performed with 1 mol % photocatalyst [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]·PF<sub>6</sub>, NiCl<sub>2</sub>·dtbbpy (0.5 mol %), (TMS)<sub>3</sub>SiH (1 equiv), alkyl halide (1 equiv, 0.1 mmol), and aryl halide (1.5 equiv) in DME for 4 h. <sup>b</sup>NMR yields using mesitylene as an internal standard. <sup>c</sup>Performed under identical conditions with (*n*-Bu)<sub>4</sub>NBr (2 equiv). No product observed without (*n*-Bu)<sub>4</sub>NBr added.

Table 2. Scope of Unnatural Amino Acids from Serine Derived from the  $\beta$ -bromoalanine Starting Material<sup>4a</sup>

## Carbocyclic arenes



## Heterocyclic arenes



<sup>4a</sup>Reactions performed on the 1 mmol scale; all yields are of isolated products unless otherwise indicated. See the Supporting Information for experimental details.

**15** in 36% yield (Table 1 entry 8), indicating that a mechanism involving sequential oxidative additions into the aryl and alkyl bromides, with silane acting as a reductant, cannot be ruled

out. This mechanism may be occurring in tandem with the silyl radical-mediated pathway. Finally, we examined whether the  $\beta$ -bromoalanine (**6**) could be formed *in situ* from a serine

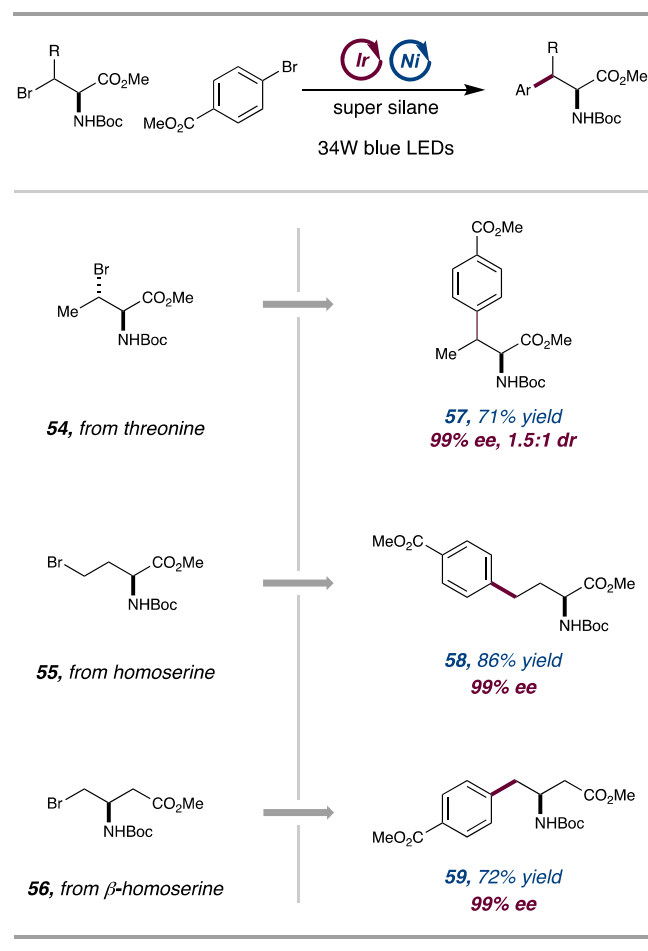
tosylate precursor. As shown in entry 9, in the presence of serine tosylate and tetrabutylammonium bromide, the reaction proceeded efficiently, to provide adduct **15** in 80% yield. This reaction presumably proceeds via the  $\beta$ -bromoalanine intermediate, as no product is observed without the addition of tetrabutylammonium bromide. Importantly, both electrophiles led to product formation in >99% ee without any detectable erosion of the enantiopurity of the starting material.

With optimized conditions in hand, we next investigated the scope of the reaction with respect to the aryl bromide coupling partner. We first turned our attention to carbocyclic aryl bromide frameworks incorporating a variety of electronic and steric motifs. As shown in Table 2, electron-deficient aryl bromides bearing ester, trifluoromethyl, acetyl, and nitrile functionalities proceed in excellent efficiency (**15–18**, 71–79% yields). Notable among these is *p*-acetophenylalanine (**17**), an unnatural amino acid commonly used in antibody–drug conjugates.<sup>16</sup> Electron-rich and electron-neutral motifs, including fluoro-, aryl-, and alkyl-arenes, reacted with similar efficiency (**19–25**, 65–79% yields). Ring substitution at the ortho-, meta-, and para-positions was well-tolerated (**23–26**, 69–79% yields), although ortho-substituted aryl halides required a higher loading of the nickel catalyst (5 mol %), presumably owing to more sluggish oxidative addition. We were also able to incorporate motifs, such as chlorides and boronate esters, that allow for further modification to the arene framework of the amino acid (**27** and **28**, 73 and 65% yield, respectively). In these cases, exclusive functionalization was observed at the bromide-bearing position. Bifunctionalized aryl bromides reacted efficiently to give unnatural amino acids such as **29**. In addition, bicyclic arenes such as naphthalenes, lactones, and indoles were readily converted to the corresponding amino acids (**30–34**, 67–86% yield). Perhaps most noteworthy among these are the indole-derived amino acids, **33** and **34**, which correspond to unnatural 5- and 6-substituted isomers of tryptophan, respectively.

Having explored the scope of carbocyclic arene coupling partners, we turned our attention to medically relevant heterocyclic motifs.<sup>17</sup> Indeed, this new reaction protocol was found to be readily applied to a broad range of heterocyclic arenes. In comparison to carbocyclic aryl bromide substrates, higher loadings of the nickel catalyst (>3 mol %) were generally required to achieve good efficiency with heterocyclic substrates. Electronically varied 2-, 3-, and 4-bromopyridines were well tolerated (Table 2, **35–46**, 52–78% yield). In the case of 2-pyridines, the silanol reagent (TMS)<sub>3</sub>Si–OH gave superior yields compared to the standard super silane. This could be attributed to slower generation of the alkyl radical species, which, coupled with an increase in nickel loading (5 mol %), aligns the rate of the photocatalytic and nickel cycles. Diazines, such as pyrimidines and pyrazines, were effectively converted to the aryl amino acid products (**13**, **47**, and **48**, 51–73% yields). Bicyclic heteroaromatic rings, such as quinolines, were well tolerated as were bi-heteroaryl systems, which give rise to a wide range of artificial tryptophan derivatives (**39**, **44**, **49**, and **50**, 72–77% yields). Importantly, five-membered heterocyclic arenes, traditionally challenging partners in cross-coupling reactions, could be converted into unnatural tryptophan (**51**, 72% yield) and histidine analogues (**52** and **53**, 75 and 50% yield, respectively). All of these reactions proceeded with complete retention of enantiopurity of the bi-derived starting material.<sup>18</sup>

We next sought to examine whether other naturally occurring amino acids might be employed in the cross-coupling reaction to provide access to distinct classes of unnatural amino acids. Along these lines, we targeted three biologically important amino acid precursors: threonine, homoserine, and  $\beta$ -homoserine. These structural motifs are of particular interest because derivatives of homophenylalanine and  $\beta$ -homophenylalanine are present in many pharmaceutical molecules and have been found to play a role in modulating the peptide function.<sup>19</sup> As shown in Scheme 2, the bromo-

**Scheme 2. Scope of Naturally Derived Amino Acid Bromides**



derivatives of these amino acids (**54–56**) underwent efficient electrophilic cross-coupling to generate adducts **57–59** in good yields and with complete enantioretention. In order to be widely adopted by practitioners of synthetic chemistry, this novel protocol must be capable of providing material on a multigram scale. Flow technology is a valuable technique in process chemistry and manufacturing, enabling the scaling of reactions that cannot easily be conducted on a large scale under batch conditions.<sup>20</sup> We thus set out to identify optimized flow conditions for electrophilic cross-coupling of  $\beta$ -bromoalanine and aryl bromides. Initial studies, using methyl 4-bromobenzoate as the arene component, indicated that concentrations of up to 0.5 M could be accommodated, leading to an excellent 85% yield of the desired product within a residence time of 20 min. This result represents a considerable increase in throughput compared to batch

conditions. In the flow reaction, a lutidine base was used in place of sodium bicarbonate because of its enhanced solubility in DME. Under these conditions, homogeneous conditions are achieved at the outset of the reaction. Previous studies in our laboratory have demonstrated that reactions performed with high-intensity light sources are more efficient with a homogeneous base due to more rapid neutralization of the HBr byproduct.<sup>21</sup>

In order to demonstrate the applicability of this chemistry to valuable pharmaceutical motifs, we sought to synthesize multigram quantities of a representative, medically valuable scaffold. We subjected an aryl bromide analogue of Celebrex, a non-steroidal anti-inflammatory drug, to our optimized flow conditions and obtained the amino acid–Celebrex derivative **60** in 55% yield within 20 min residence time, with substantial quantities of aryl bromide remaining (Table 3, entry 1). We aimed to improve the efficiency of the reaction by increasing the loading of the nickel catalyst and modulating the LED

wavelength. As shown in Table 3, a clear correlation was observed between wavelength and reaction efficiency. The lower wavelength light (385 nm), which better matches the absorption maximum of the photocatalyst, was found to substantially accelerate the reaction compared with higher wavelength sources (Table 3, entries 2–4). Under the optimal conditions shown in entry 5, the use of 1 mol % nickel catalyst and a 385 nm lamp produced **60** in 90% yield within 20 min. Using these conditions, we conducted the reaction on the 1.5 mmol scale and obtained 700 mg of product (80% yield) in a total reaction time of 30 min.

Attempts to conduct larger scale flow reactions for extended time periods were impeded by accumulation of a precipitate, lutidinium bromide, which is formed when lutidine neutralizes the HBr byproduct. In an effort to tailor the reaction conditions for homogeneity, we made a series of modifications to the original conditions: (a) DMA was used as the solvent in place of DME; (b) the reaction was run at more dilute concentrations (0.2 M); (c) the base loading was decreased to 1 equivalent; (d) the reaction temperature was increased from 30 to 40 °C; and (e) the residence time was increased to 45 min. These changes collectively served to increase the solubility of the lutidinium bromide salt, providing the desired adduct in a synthetically useful yield of 60%. We subsequently performed this reaction on scales of up to 20 mmol, obtaining 6 g of the Celebrex-derived amino acid **60** in 60% yield. We thus have developed flow conditions that allow rapid access to pharmaceutical products on a medium scale and homogeneous conditions that can afford multigram quantities of product when run continuously over extended time periods.

In summary, we have developed a mild and enantioselective protocol for the conversion of serine to a wide range of unnatural amino acids via a  $\beta$ -bromoalanine intermediate. This protocol provides ready access to a vast range of arylated amino acid derivatives, including a wide variety of phenylalanine, tryptophan, and histidine derivatives. We have further demonstrated that methylphenylalanine derivatives can be prepared via arylation of threonine and that  $\beta$ -amino acids may be accessed via  $\beta$ -homoserine. The synthesis of multigram quantities of valuable amino acid derivatives of pharmaceutical agents has been demonstrated. We anticipate that this methodology will see wide adoption in industrial laboratories due to its broad scope, scalability, and ease of operation.

## EXPERIMENTAL SECTION

### Procedure for Cross-Electrophile Coupling Reaction.

To an oven-dried 8 mL vial was added the photocatalyst Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy) (0.6 mg, 0.5  $\mu$ mol, 1 mol %), aryl bromide (0.05 mmol, 1.5 equiv), methyl 3-bromo-2-((*tert*-butoxycarbonyl)amino)propanoate (21 mg, 0.075 mmol, 1 equiv), and anhydrous sodium carbonate (11 mg, 0.1 mmol, 2 equiv). The vial was sealed and placed under nitrogen, and tris(trimethylsilyl)silane (23  $\mu$ L, 0.075 mmol, 1.5 equiv) was added via a syringe. To a separate vial was added NiCl<sub>2</sub>·glyme (2.8 mg, 12.5  $\mu$ mol, 0.25 equiv) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (3.4 mg, 12.5  $\mu$ mol, 0.25 equiv). The catalyst vial was sealed and purged with nitrogen, and then, to it was added 2.5 mL of DME. The precatalyst solution was sonicated for 10 min, after which, 0.5 mL of the solution (5 mol % catalyst, 2.5  $\mu$ mol, 0.05 equiv) was syringed into the reaction vessel (0.1 M). The solution was degassed by sparging with nitrogen for 10 min before sealing with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp with fan cooling at

**Table 3. Development of Flow Conditions for Multigram Synthesis**

Entry	Nickel loading (mol%)	LED wavelength	Yield <b>60</b> <sup>b</sup>
1	0.5 mol%	420 nm	55%
2	5 mol%	420 nm	74%
3	5 mol%	385 nm	85%
4	5 mol%	450 nm	34%
5	1 mol%	385 nm	90%

Celebrex		Amino acid analogue <b>60</b>	
Celebrex		Amino acid analogue <b>60</b>	
<b>Heterogeneous conditions</b>		<b>Homogeneous conditions</b>	
DME, 0.5 M, 2 equiv lutidine		DMA, 0.2 M, 1 equiv lutidine	
1.5 mmol scale, $\tau$ = 20 min		18 mmol scale, $\tau$ = 45 min	
30 min total reaction time		8 hours total reaction time	
<b>80% yield, 700 mg isolated</b>		<b>60% yield, 6 g isolated</b>	

<sup>a</sup>Flow reactions performed on a Vapourtec E-series flow reactor with aryl halide (1 equiv), alkyl halide (1.5 equiv), 1 mol % photocatalyst [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub>, (TMS)<sub>3</sub>SiH (1.5 equiv), and Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O; see the Supporting Information for more details.

<sup>b</sup>NMR yields using mesitylene as an internal standard.

30 °C for 6 h. The reaction was quenched by exposure to air, and the solvent was removed *in vacuo*. Purification via flash column chromatography (C18) yielded the cross-coupled product.

**Heterogeneous Flow Conditions.** A reaction solution was prepared using methyl-(*R*)-4-bromo-3-((*tert*-butoxycarbonyl)amino)butanoate (635 g, 2.25 mmol, 1.5 equiv), Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy) (17 mg, 0.015 mmol, 1 mol %), 4-(5-(4-bromophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (669 g, 1.5 mmol, 1 equiv), lutidine (0.35 mL, 3 mmol, 2 equiv), tris(trimethylsilyl)silane (0.7 mL, 2.25 mmol, 1.5 equiv), Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (3.7 mg, 0.015 mmol, 0.01 equiv), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mg, 0.015 mmol, 0.01 equiv). The reaction components were dissolved in DME (3 mL, 0.5 M), sonicated until homogeneous, and degassed via nitrogen sparging for 20 min. The reaction mixture was pumped through a 2 mL reactor coil (internal diameter 2.0 mm) for 30 min (0.1 mL/min, 20 min residence time) at 30 °C under irradiation from an 18 W 385 nm LED lamp. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried with sodium sulfate and filtered, and the solvent was removed *in vacuo*. Purification via column chromatography yielded the pure product as a white solid (700 mg, 80% yield).

**Homogeneous Flow Conditions.** A reaction solution was prepared using methyl-(*R*)-4-bromo-3-((*tert*-butoxycarbonyl)amino)butanoate (7.62 g, 27 mmol, 1.5 equiv), Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy) (202 mg, 0.18 mmol, 1 mol %), 4-(5-(4-bromophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (8 g, 18 mmol, 1 equiv), lutidine (4.2 mL, 36 mmol, 2 equiv), tris(trimethylsilyl)silane (8.33 mL, 27 mmol, 1.5 equiv), Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (45 mg, 0.18 mmol, 0.01 equiv), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (48 mg, 0.18 mmol, 0.01 equiv). The reaction components were dissolved in DMA (90 mL, 0.2 M), sonicated until homogeneous, and degassed via nitrogen sparging for 20 min. The reaction mixture was pumped through a 10 mL reactor coil (internal diameter 2.0 mm) for 8 h (0.225 mL/min, 45 min residence time) at 40 °C under irradiation from an 18 W 385 nm LED lamp. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried with sodium sulfate and filtered, and the solvent removed *in vacuo*. Purification via column chromatography yielded the pure product as a white solid (6 g, 60% yield).

Methyl-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(1-(4-sulfamoylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)phenyl)propanoate (**60**): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.94–7.87 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.15 (s, 4H), 6.76 (s, 1H), 5.03 (d, *J* = 8.4 Hz, 1H), 4.90 (d, *J* = 20.5 Hz, 2H), 4.60 (d, *J* = 7.3 Hz, 1H), 3.72 (d, *J* = 4.9 Hz, 3H), 3.10 (ddd, *J* = 69.8, 13.8, 6.0 Hz, 2H), 1.42 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 172.17, 155.14, 144.93, 142.49, 141.65, 138.21, 130.14, 129.11, 127.65, 125.62, 106.62, 80.35, 60.57, 54.43, 52.58, 38.45, 28.42, 21.21, 14.33. HRMS (ESI-TOF) *m/z* calcd for C<sub>25</sub>H<sub>27</sub>F<sub>3</sub>SN<sub>4</sub>NaO<sub>6</sub> ([M + Na]<sup>+</sup>), 591.1501; found, 591.1486. IR (film): λ<sub>(max)</sub> 2980, 1700, 1500, 1368, 1238, 1163, 976, 739 cm<sup>-1</sup>. Chiral HPLC OJ column, 20% IPA/hexanes, 1.0 mL/min, >99% ee, *t*<sub>R</sub>(minor) = 9.22 min, *t*<sub>R</sub>(major) = 24.74 min.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.1c00208>.

Experimental methods, characterization data and spectra of all isolated compounds, and optimization details of flow reactions (PDF)

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### Notes

The authors declare no competing financial interest.

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