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α -Arylation/Heteroarylation of Chiral α -Aminomethyltrifluoroborates *via* Synergistic Iridium Photoredox/Nickel Cross-Coupling Catalysis

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Abstract

Direct access to complex, enantiopure benzylamine architectures using a synergistic iridium photoredox/nickel cross-coupling dual catalysis strategy has been developed, where Csp³-Csp² bonds are forged, starting from abundant and inexpensive natural amino acids.

Graphical Abstract

A novel dual catalytic route to enantiopure benzylic amines is outlined that takes advantage of photoredox catalysis in conjunction with nickel-catalyzed cross-coupling. Starting materials are robust organotrifluoroborates, which can engage with an expanded range of densely functionalized aryl- and heteroaryl halides in the title reaction.

Keywords

photoredox; dual catalysis; nickel; amino acid; chiral benzylic amines

The impetus to discover novel chemical transformations for the construction of biologically active compounds is of continuing interest in the pharmaceutical and agrochemical industries.^[1–3] Among nitrogen-containing molecules, aminomethylated arenes are

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privileged substructures that are found in many bioactive materials, exhibiting activity against a wide array of diseases.^[4–7]

Despite their importance, access to enantioenriched benzylic amines is not general, and traditional routes to aminomethylated arenes, including reductive amination,^[8] CN reduction,^[9,10] or *N*-alkylation methods (Figure 1)^[11–13] may not be readily applicable. Additionally, these approaches suffer from limitations because of their intolerance toward reducible functional groups or the limited commercial availability of benzylic halides, benzylic amines, aryl nitriles, or aryl aldehydes, respectively (compared to aryl halides).^[14–16]

Our group has established an interest in the development of complementary aminomethylating^[7,14–18] and related^[19,20] cross-coupling procedures that take advantage of the vast number of commercially available aryl halides by using air- and moisture stable *N*-trifluoroboratomethyl derivatives in cross-coupling reactions. Based on this strategy, a preparation of enantiopure aminomethylarenes was sought. However, all efforts in our group to utilize *N*-trifluoroboratomethyl salts derived from naturally occurring amino acids to cross-couple with aryl halides failed under traditional Pd-catalyzed Suzuki-Miyaura conditions. This failure can be attributed to the slow rate of transmetalation of the alkylboron species and the high temperatures and basic conditions required, an inherent problem related to the two-electron nature of the process.^[21,22]

A recent focus of research in our laboratory has been the exploration of cross-coupling through Csp³-centered radicals formed via a single-electron oxidation/transmetalation of organotrifluoroborate precursors, a process that allows access to Csp³-Csp² cross-coupling products.^[22–26] Organotrifluoroborate derivatives are excellent radical precursors because of their high stability, low toxicity, and functional group tolerability. In the current context, efforts were thus directed toward the generation of α -amino radicals starting from chiral *N*-trifluoroboratomethyl salts. These versatile α -amino radicals^[6,27–35] were envisioned to allow the assembly of enantioenriched building blocks of potential value.^[6,28]

The intermediacy of α -amino radicals to elaborate aryl- and heteroaryl substructures has recently been demonstrated in photoredox catalysis^[6,25,28,36] from both unfunctionalized amines (toward the preparation of JAK2 inhibitor LY2784544),^[6] and those with the TMS^[35,37,38] and CO₂H^[2,39] activating groups (Scheme 1).

Herein, the first report of complementary, photoredox-generated, enantiopure α -amino radicals from chiral *N*-trifluoroboratomethyl amino acids and their subsequent α -arylation/heteroarylation is described, exploiting iridium photoredox-nickel cross-coupling dual catalysis to generate complex enantiopure benzylic amines (Scheme 1). This process represents an efficient and general transformation that has not previously been accomplished, and importantly, *both the carboxylate functional group and the stereogenic centers of the amino acid starting materials remain intact in the cross-coupling*. An overarching goal of this work was to establish the precedent that amino acids^[8,40,41] with an *N*-trifluoroboratomethyl moiety can be efficiently oxidized to generate versatile and unique enantiopure α -amino radicals under photoredox conditions.

The process envisioned for α -arylation/heteroarylation of *N*-trifluoroboratomethyl amino acids (Scheme 2) was founded on established evidence that visible-light irradiation (26 W compact fluorescent lamp, CFL) of Ir[dFCF₃ppy]₂(bpy)PF₆ [dFCF₃ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, depicted as Ir (**5**) in Scheme 2] generates the excited state [Ir]* species **6**, a strong oxidant ($E_{1/2}$ [Ir*^{III/II}] = +1.21 vs. SCE in MeCN),^{22,32,34,35,38,41–43} which was anticipated to undergo single electron transfer (SET) oxidation of *N*-trifluoroboratomethyl amino acid **1** (e.g., Boc-N-CH₂BF₃K-L-Val-OMe, $E_{1/2}^{\text{red}}$ = +1.01 V vs. SCE in MeCN), forming the desired reactive Csp³-centered α -amino radical **2**. Based on the developed rationale,³⁴ the process was expected to be an autoregulated release because the radical does not accumulate, but rather is captured by the second catalytic cycle mediated by the nickel species. The predominant pathway was expected^[26] to involve capture of the α -amino radical by Ni⁰ **8** to generate Ni^I **9**, which would then undergo oxidative addition^[26] with the aryl/heteroaryl bromide **3** to afford the Ni^{III} intermediate **10**. The low energy of activation expected in the formation of Ni^{III} **10**^[26] would facilitate the cross-coupling, overcoming the slow C-C bond formation step that would otherwise be necessary in such systems to afford the desired chiral benzylic amine **4**. The dual catalytic cycles need to be synchronized, whereby the generated Ni^I **11** is reduced to Ni⁰ **8** at the same time the Ir photocatalyst is reoxidized via a SET process. The entire process was expected to occur without a strong exogenous base or high temperature.^[23,25,39,42–44]

The requisite Boc-protected *N*-trifluoroboratomethyl amino acids **1** were prepared starting from inexpensive and naturally-abundant amino acids (Table 1).^{15–18} *N*-Alkylation of Boc-protected amino acids **13** with iodomethylpinacolboronate in the presence of KHMDS afforded the corresponding pinacol esters **14**. Addition of KHF₂ generated the desired *N*-trifluoroboratomethyl amino acids **1** (Table 1) required to test the mechanistic hypotheses.

An investigation of the cross-coupling process was examined by exposing Boc-N-CH₂BF₃K-Gly-OMe **1a** to *p*-bromobenzonitrile **3a** under conditions previously successful for benzylic trifluoroborates (Table 2).^[23] Although the result was promising, showing that the proposed mechanism was feasible, the observed reaction efficacy was very poor, with a yield of 5% of the desired product. A deeper investigation of the reaction conditions was undertaken, and a variety of solvents, nickel catalysts, ligands and bases were screened (comprehensive results and all screenings employed are shown in Table S1 of the Supporting Information). Based on the initial screenings, the first study using Ni(NO₃)₆•6H₂O and ligand **L1** against a variety of solvents (entries 1,2,5–7; THF, EtOAc, *i*-PrOAc, MeCN, acetone) was deemed ineffective, with EtOAc giving the highest yield of 10%. The role of the ligand was recognized to be critical, and thus an evaluation of a variety of structurally and electronically different ligands (**L1–4** entries 2, 6–10, Table 2 and **L5–11** in Supporting Information) was performed. Ligand bioxazole **L4** (entry 10, Table 2) was determined to provide the optimal yield in this ligand screen. An examination of various substituted-bioxazole ligands (Table S1 in the Supporting Information) did not improve the yield of the reaction. 2,6-Lutidine afforded the best results among the bases tested, while the use of pyridine, dicyclohexylamine, Cs₂CO₃ or a combination of bases was deemed ineffective. An assessment of Ir/Ni/**L4** loadings (entries 10–12, Table 2 and Supporting Information)

revealed that the ratio of Ir/Ni/**L4** (2:5:10 mol %) provided the best isolated yield (65%) for this reaction, affording **4a** as a mixture of rotamers as confirmed by NMR analysis. Finally, the required participation of Ir and Ni complexes, ligand **L4**, base, light and inert [Ar(g)] conditions were verified via control experiments (Table S1 in the Supporting Information). An important observation was that the starting aryl bromide is not fully consumed in the reaction. The conversion is not improved by the addition of a second batch of catalyst after 12 h, suggesting that trifluoroborate decomposition rather than catalyst decomposition is responsible for this phenomenon.

As a test of the mechanistic hypothesis, the quantum yield of the reaction was measured (see Supporting Information). Although the heterogeneity of the reactions and resulting light scattering introduced uncertainty into these measurements, the measured quantum yield (Φ) of the reaction under blue LED light (406 nm) was $\Phi = 0.45$, while that taken under a 26 W CFL was $\Phi = 1.97$, indicating that chain radical mechanisms do not appear to be the major reaction pathway.

Under the conditions developed, the scope of aryl- and heteroaryl bromides was first examined against Boc-*N*-methyl-Gly-OMe (Scheme 3). The mild reaction conditions readily accommodated a range of electron-withdrawing and electron-donating functional groups, including nitrile, amide, ester, aldehyde, phenol, ketone, sulfonamide and trifluoromethyl groups. Complex architectures were tolerated, affording products containing coumarin (**4f**), benzothiophene (**4h**) as well as the piperazin-1-yl-pyrimidine (**4k**, performed on a 1.5 mmol scale) cores. In general, the use of para- and meta-substituents afforded the desired products. However, ortho substituents inhibited the reaction.

Modification of the amino acid component, incorporating chiral alkyl side chains (L-Ala, D-Ala, L-Val, and L-Ile), was then examined against various aryl- and heteroaryl bromides (Scheme 4) and proved successful, affording interesting enantiopure benzylic amines in good to excellent yields. Remarkably and most notable is the use of complex aryl- and heteroaryl bromides, including motifs such as caffeine (**4o**), the SF₅ functional group (**4v**), thienyl sulfonamides (**4l**), ketones (**4m** and **4m'**) and 4-oxadiazolylphenyl (**4n**, **4w** and **4z**). Moreover, products **4r** and **4u** demonstrate the possibility of orthogonal cross-coupling, because the Bpin and boronic acid moieties are not affected under the reaction conditions. Also notable is the fact that in those cases where the stereochemical integrity of the process was rigorously tested (**4m/4m'**, **4o/4o'**, **4q/4q'**, **4y** and **4z**), no epimerization of the stereogenic center could be detected, validating further the ambient conditions required to obtain such complex, chiral benzylic amines.

Finally, the use of aromatic side chains on the amino acid moiety was studied (Scheme 5). From these, enantioenriched benzylic amines were afforded using L-Tyr and L-Phe amino acids containing the ketone (**4aa**), nitrile (**4ab** and **4ae**), pyrimidine (**4ac**) and biphenyl (**4ad**) components in good to excellent yields. Importantly, these target structures possess both aminomethylated arenes as well as phenethylamines within their cores, both units of which are important in many pharmacologically active materials.

The method described herein represents an approach to a novel bond connect that complements previously reported methods in providing access to novel, enantiopure amino acid derivatives through a process that begins with stable, storable reagents and transpires at room temperature under exceedingly mild reaction conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Synthetic Approaches toward Benzylic Amines.

Scheme 1.
Photoredox Generated α -Amino Radicals Utilized in α -Arylation/Heteroarylation Cross-Coupling.

Scheme 2.
Proposed Mechanism toward Enantioenriched Aminomethylarenes.

Scheme 3.

Substrate Scope of Boc-Protected Aminoglycine-Methylarenes.

Scheme 4.

Substrate Scope of Enantiopure Aliphatic Boc-Protected Aminomethylarenes.

Scheme 5.
Substrate Scope of Chiral Aromatic Boc-Protected Aminomethylarenes.

Table 1Preparation of *N*-Methyltrifluoroborate-derived Amino Acid Starting Materials.^a

entry	amino acid	14, yield (%)	1, yield (%)
1	Boc-Gly-OMe	49	92
2	Boc-L-Ala-OMe	68	94
3	Boc-D-Ala-OMe	61	94
4	Boc-L-Phe-OMe	55	85
5	Boc-L-Tyr(OMe)-OMe	65	91
6	Boc-L-Val-OMe	<i>_b</i>	93
7	Boc-L-Ile-OMe	<i>_b</i>	95

^aReagents and conditions: (i) ICH₂Bpin (1.0 equiv), KHMDS (0.9 equiv), THF (0.35 M), -78 °C to rt, 5 h; (ii) KHF₂ (5.0 equiv, 4.5 M), K₂CO₃ (1.0 equiv), MeCN (0.3 M), 0 °C to rt, 1–3 h.

^bIntermediate **14** was directly converted to **1** without isolation and characterization.

Table 2

Optimization of Reaction Conditions with Boc-*N*-Trifluoroboratomethyl Glycine Methyl Ester and *p*-Bromobenzonitrile.

entry	ligand (mol %)	solvent	Ni catalyst	4a, yield (%) ^a
1	L1 (5)	THF	NiNO ₃ •6H ₂ O	n.r.
2	L1 (5)	EtOAc	NiNO ₃ •6H ₂ O	10
3	L1 (5)	EtOAc	Ni(COD) ₂	2
4	L1 (5)	EtOAc	NiCl ₂ •dme	n.r.
5	L1 (5)	<i>i</i> -PrOAc	NiNO ₃ •6H ₂ O	n.r.
6	L1 (5)	MeCN	NiNO ₃ •6H ₂ O	n.r.
7	L1 (5)	acetone	NiNO ₃ •6H ₂ O	n.r.
8	L2 (5)	EtOAc	NiNO ₃ •6H ₂ O	20
9	L3 (5)	EtOAc	NiNO ₃ •6H ₂ O	12
10	L4 (5)	EtOAc	NiNO ₃ •6H ₂ O	45
11 ^b	L4 (10)	EtOAc	NiNO ₃ •6H ₂ O	65
12	L4 (15)	EtOAc	NiNO ₃ •6H ₂ O	62

^a Yields are based on isolated **4a**; n.r. = no reaction.

^b **1a** (1 equiv) and **3a** (1 equiv) were used for the optimized reaction condition.