Cross-Coupling

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α-Arylation/Heteroarylation of Chiral α-Aminomethyltrifluoroborates by 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. New $C(sp^3)$–$C(sp^2)$ bonds are forged starting from abundant and inexpensive natural amino acids.*

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 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]

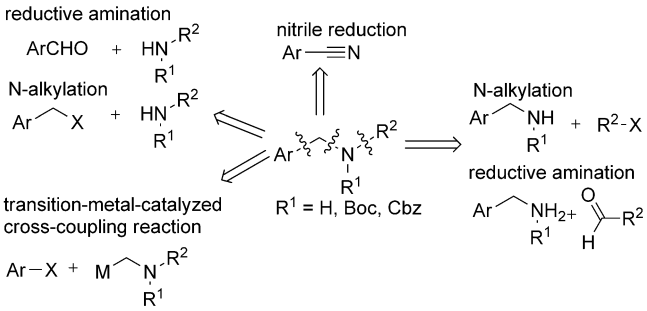

Figure 1. Synthetic approaches toward benzylic amines. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

may not be readily applicable. Additionally, these approaches suffer from limitations because of their intolerability toward reducible functional groups or the limited commercial availability of benzylic halides, benzylic amines, aryl nitriles, and aryl aldehydes (compared to aryl halides).[14–16]

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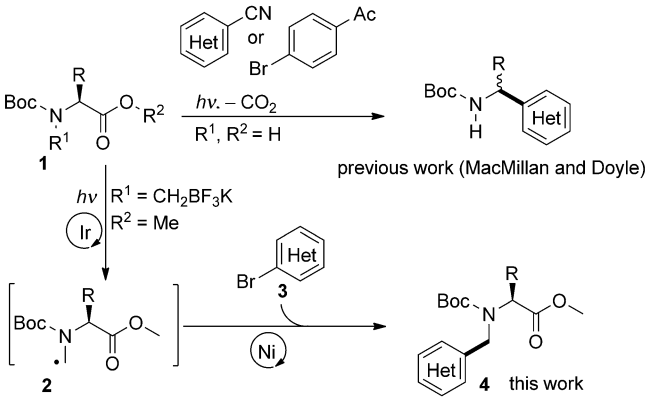
Our group has established an interest in the development of complementary aminomethylating[7,14–18] and related[19,20] cross-coupling procedures that take advantage of the vast number of commercially available aryl halides by using air- and moisture-stable *N*-trifluoroboratomethyl derivatives in cross-coupling 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 palladium-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]

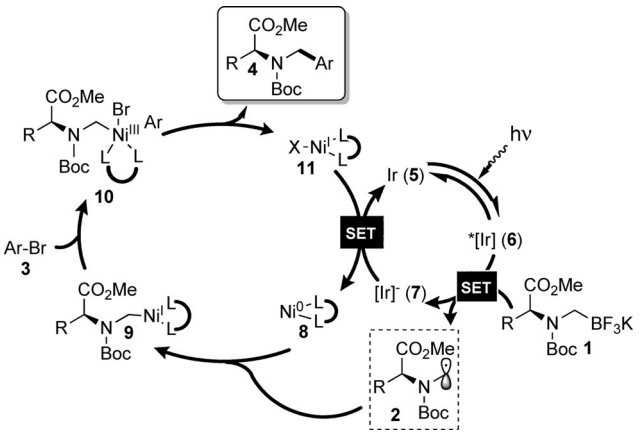
A recent focus of research in our laboratory has been the exploration of cross-coupling through $C(sp^3)$-centered radicals formed by a single-electron oxidation/transmetalation of organotrifluoroborate precursors, a process that allows access to $C(sp^3)$–$C(sp^2)$ cross-coupling products.[22–26] Organotrifluoroborate 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 CO_2H[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, thus 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



Scheme 1. Photoredox-generated α-amino radicals utilized in α-arylation/heteroarylation cross-coupling.



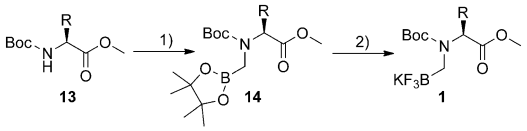
Scheme 2. Proposed mechanism toward enantioenriched aminomethylarenes.

founded on established evidence that visible-light irradiation (26 W compact fluorescent lamp, CFL) of $[Ir(dFCF_3ppy)_2(bpy)]PF_6$ [$dFCF_3ppy$ = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, depicted as **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 acids (**1**; e.g., Boc-*N*-CH_2BF_3K-L-Val-OMe, $E_{1/2}^{red}$ = +1.01 V vs. SCE in MeCN), thus forming the desired reactive C(sp^3)-centered α-amino radicals **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 the Ni^0 species **8** to generate Ni^I species **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 **10**[26] would facilitate the cross-coupling, thus 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 species **11** is reduced to **8** at the same time the iridium photocatalyst is reoxidized by 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 the Boc-protected amino acids **13** with iodomethylpinacolboronate in the presence of KHMDS afforded the corresponding pinacol esters **14**. Addition of KHF_2 generated the desired *N*-trifluoroboratomethyl amino acids **1** required to test the mechanistic hypotheses.

An investigation of the cross-coupling process was examined by exposing Boc-*N*-CH_2BF_3K-Gly-OMe (**1a**) to *p*-bromobenzonitrile (**3a**) under reaction 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 $Ni(NO_3)_2{\cdot}6H_2O$ and the ligand **L1** in a variety of solvents (entries 1, 2, and 5–7) 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**–**L4**; entries 2, and 6–10; data for **L5**–**L11** are in the Supporting Information) was performed. The bioxazole ligand **L4** (entry 10) was determined to provide the optimal yield in this ligand screen. An examination of various substituted bioxazole ligands (see 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, dicyclo-

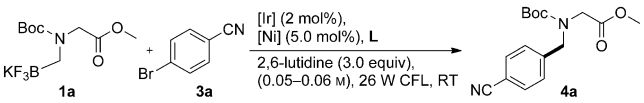
Table 1: Preparation of *N*-methyltrifluoroborate-derived amino-acid starting materials.[a]

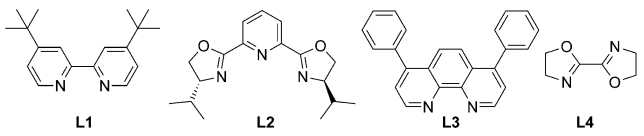


Entry	Amino acid	Yield [%]	
		14	**1**
1	Boc-Gly-OMe	49	92
2	Boc-L-Ala-OMe	68	94
3	Boc-D-Ala-OMe	61	94
4	Boc-L-Phe-OMe	55	85
5	Boc-L-Tyr(OMe)-OMe	65	91
6	Boc-L-Val-OMe	–[b]	93
7	Boc-L-Ile-OMe	–[b]	95

[a] Reagents and conditions: 1) ICH_2Bpin (1.0 equiv), KHMDS (0.9 equiv), THF (0.35 M), −78 °C to RT, 5 h; 2) KHF_2 (5.0 equiv, 4.5 M), K_2CO_3 (1.0 equiv), MeCN (0.3 M), 0 °C to RT, 1–3 h. [b] The intermediate **14** was directly converted into **1** without isolation and characterization. KHMDS = potassium hexamethyldisilazide, THF = tetrahydrofuran.

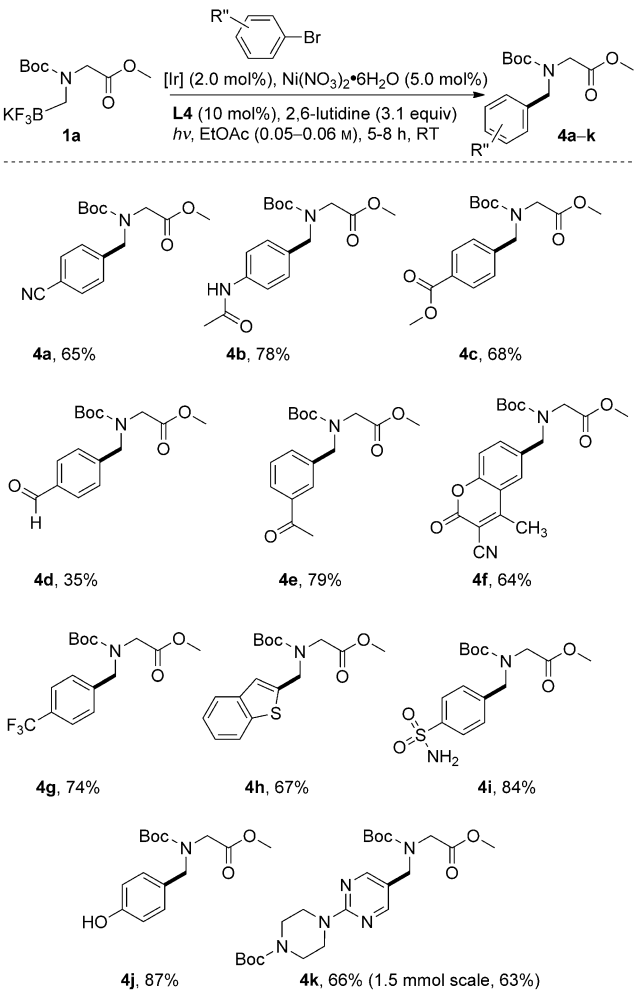
Table 2: Optimization of reaction conditions with Boc-*N*-trifluoroboratomethyl glycine methyl ester and *p*-bromobenzonitrile.





Entry	Ligand (mol%)	Solvent	Catalyst	Yield [%][a]
1	**L1** (5)	THF	$Ni(NO_3)_2{\cdot}6H_2O$	n.r.
2	**L1** (5)	EtOAc	$Ni(NO_3)_2{\cdot}6H_2O$	10
3	**L1** (5)	EtOAc	$[Ni(cod)_2]$	2
4	**L1** (5)	EtOAc	$NiCl_2{\cdot}$dme	n.r.
5	**L1** (5)	*i*PrOAc	$Ni(NO_3)_2{\cdot}6H_2O$	n.r.
6	**L1** (5)	MeCN	$Ni(NO_3)_2{\cdot}6H_2O$	n.r
7	**L1** (5)	acetone	$Ni(NO_3)_2{\cdot}6H_2O$	n.r.
8	**L2** (5)	EtOAc	$Ni(NO_3)_2{\cdot}6H_2O$	20
9	**L3** (5)	EtOAc	$Ni(NO_3)_2{\cdot}6H_2O$	12
10	**L4** (5)	EtOAc	$Ni(NO_3)_2{\cdot}6H_2O$	45
11[b]	**L4** (10)	EtOAc	$Ni(NO_3)_3{\cdot}6H_2O$	65
12	**L4** (15)	EtOAc	$Ni(NO_3)_2{\cdot}6H_2O$	62

[a] Yields are based on isolated **4a**. [b] **1a** (1 equiv) and **3a** (1 equiv) were used for the optimized reaction conditions. cod = 1,5-cyclooctadiene, dme = 1,2-dimethoxyethane, n.r. = no reaction.



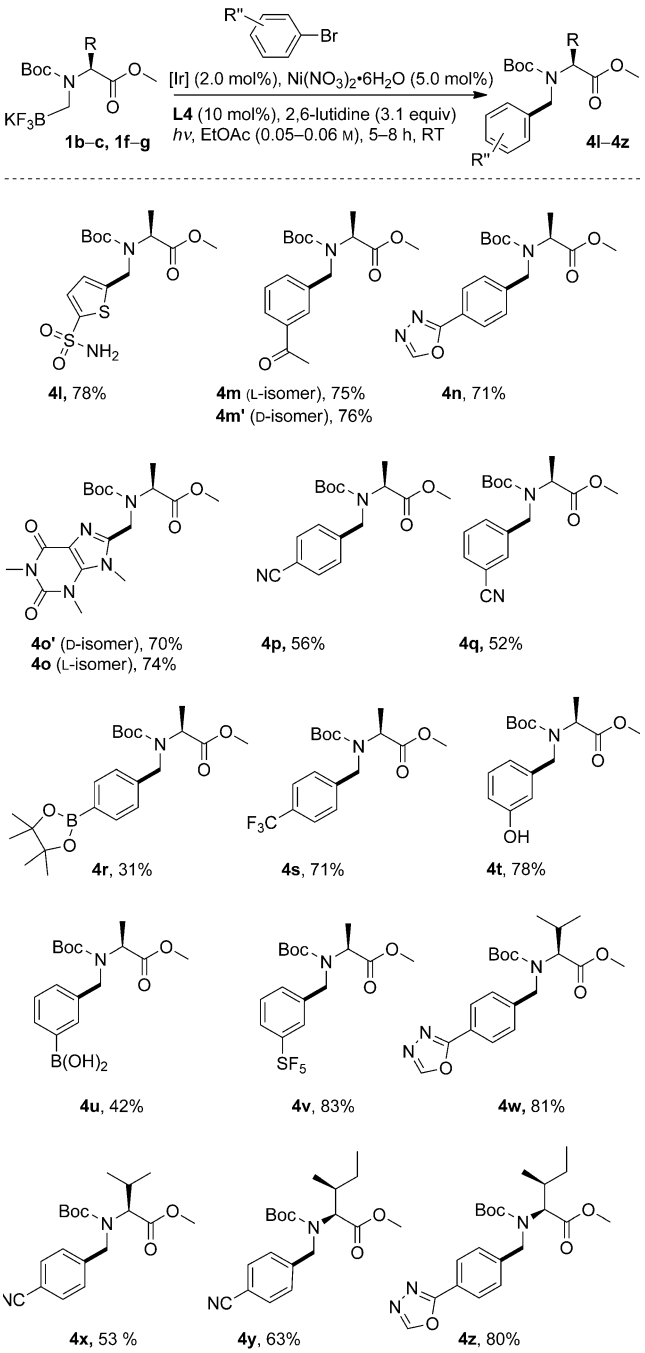
Scheme 3. Substrate scope with respect to the Boc-protected aminoglycine methylarenes.

hexylamine, Cs_2CO_3, or a combination of bases was deemed ineffective. An assessment of Ir/Ni/**L4** loadings (entries 10–12 and see the Supporting Information) revealed that a ratio of 2:5:10 mol% provided the best yield (65%) of the isolated product for this reaction, thus affording **4a** as a mixture of rotamers as confirmed by NMR analysis. Finally, the required participation of the iridium and nickel complexes, **L4**, base, light, and inert conditions (argon atmosphere) were verified by control experiments (see Table S1). 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 hours, thus 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 the Supporting Information). Although the heterogeneity of the reactions and resulting light scattering introduced uncertainty into these measurements, the photochemical quantum yield (Φ) (λ_{ex} = 406 nm) was measured to be $\Phi = 0.45$, thus indicating that chain-radical mechanisms do not appear to be the major reaction pathway.

Under the reaction conditions developed, the scope of aryl- and heteroaryl bromides was first examined using **1a** (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, thus affording products containing coumarin (**4f**) and benzothiophene (**4h**), as well as 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.

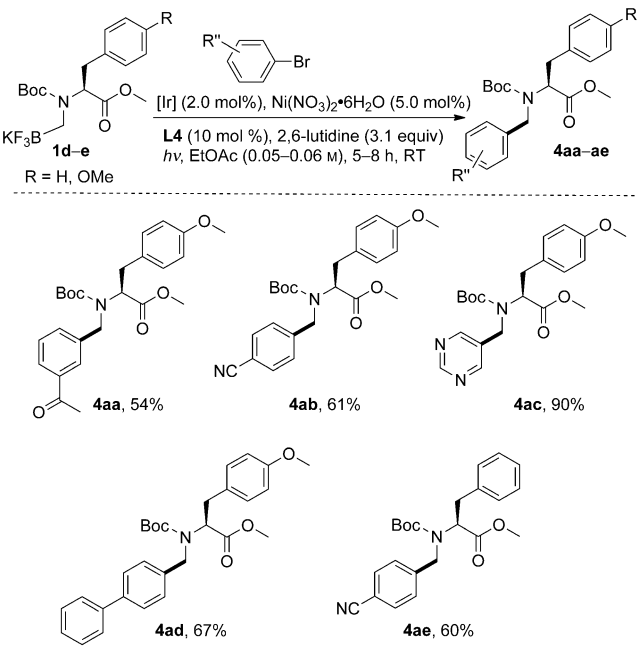
Modification of the amino-acid component, incorporating chiral alkyl side chains (L-Ala, D-Ala, L-Val, and L-Ile), was then examined with various aryl- and heteroaryl bromides (Scheme 4) and proved successful, thus affording interesting enantiopure benzylic amines in good to excellent yields. Remarkably and most notable is the use of complex aryl- and heteroaryl bromides, including motifs such as caffeine (**4o**), the SF_5 functional group (**4v**), thienyl sulfonamides (**4l**), ketones (**4m** and **4m′**), and 4-oxadiazolylphenyl (**4n**, **4w** and **4z**). Moreover, the 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, thus validating further the ambient conditions required to obtain such complex, chiral benzylic amines.



Scheme 4. Substrate scope with respect to the enantiopure aliphatic Boc-protected aminomethylarenes.

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 connection and complements previously



Scheme 5. Substrate scope with respect to the chiral aromatic Boc-protected aminomethylarenes.

reported methods in providing access to novel, enantiopure amino-acid derivatives through a process which begins with stable, storable reagents, and transpires at room temperature under exceedingly mild reaction conditions.

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