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Deaminative Arylation of Amino Acid-derived Pyridinium Salts

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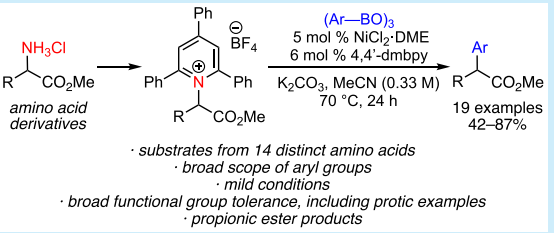
Supporting Information

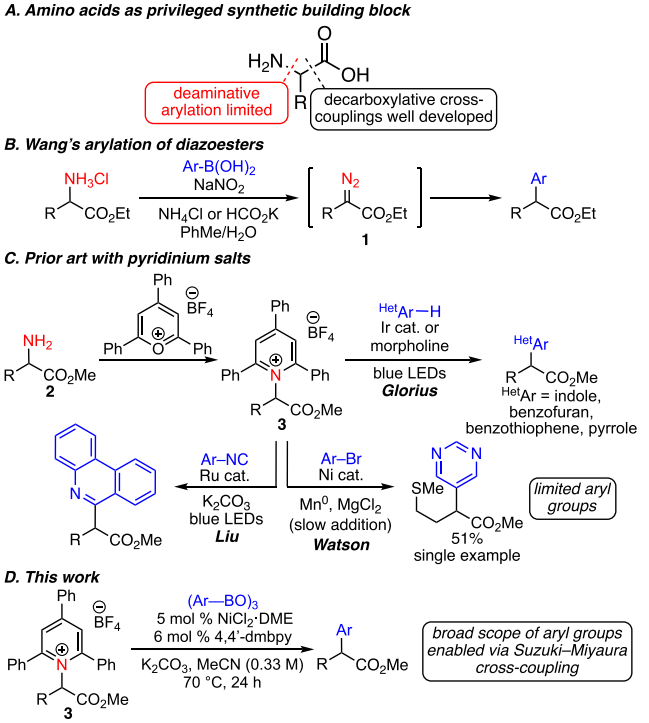
ABSTRACT: A Suzuki−Miyaura cross-coupling of α-pyridinium esters and arylboroxines has been developed. Combined with formation of the pyridinium salts from amino acid derivatives, this method enables amino acid derivatives to be efficiently transformed into α-aryl esters and amides. Under the mild conditions, broad functional group tolerance on both the amino acid derivatives and the arylboroxine are observed, including protic functional groups. Mechanistic studies support an alkyl radical intermediate, similar to other cross-couplings of alkylpyridinium salts.



Amino acids are a privileged class of starting materials for the synthesis of a wide variety of organic molecules, ranging from ligands and organocatalysts to natural products or pharmaceuticals, including both peptides and nonpeptides.[1] In addition to classic synthetic manipulations that allow the carboxy group to undergo esterification, reductions, and substitutions, nickel-catalyzed decarboxylative cross-couplings enable amino acids to be transformed into amines with a range of new groups at the α-carbon (Scheme 1A).[2] However, the chemistry of the amino substituent remains largely limited to classic substitutions on the N atom. Deaminative reactions continue to be underdeveloped, despite the potential to efficiently access valuable products. In particular, deaminative arylations of amino acid derivatives would deliver propionic acids and related compounds, important for their nonsteroidal anti-inflammatory activity.[3,4] An exception is Wang's efficient metal-free reaction of α-diazoesters, generated *in situ*, and arylboronic acids; however, only a single example of a protic functional group (indole) was demonstrated, and the yield was only 36% (Scheme 1B).[5] Based on our work in developing cross-couplings of Katritzky alkylpyridinium salts,[6−8] we envisioned that pyridinium derivatives of amino acids could also be efficient reagents for deaminative arylation. Indeed, Glorius was the first to report an arylation of this class of pyridinium salt, a Minisci-type reaction enabled by photoredox catalysis; however, this method is limited to the installation of electron-rich heteroaryl groups (Scheme 1C).[9] In addition, Liu has developed a photoredox-catalyzed reaction of these pyridinium salts with biphenyl isocyanates to deliver 6-alkyl phenanthridines,[10] and we have reported a single example of a reductive coupling to install a pyrimidine.[11−14] However, beyond these examples of installation of specific heteroaryl groups, arylation of these substrates has not been demonstrated. Specifically, current methods do not allow installation of a broad scope of aryl groups, including electronically varied and functionalized aryl and heteroaryl substituents.

To solve this limitation, we envisioned that a Suzuki−Miyaura cross-coupling of amino acid-derived pyridinium salts with arylboronic reagents would enable the synthesis of a diverse range of α-aryl carboxylates. Suzuki−Miyaura cross-coupling is one of the most well-established methods for the installation of an aryl group, often boasts exceptional scope, and is one of the most useful reactions in medicinal chemistry.[15] Herein, we report the development of this deaminative arylation method, which uses a catalyst from commercially available components,

Scheme 1. Deaminative Arylation of Amino Acid Derivatives



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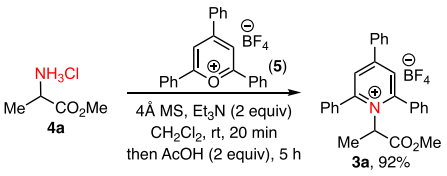
employs mild reaction conditions, and offers wide functional group tolerance (Scheme 1D).

The pyridinium salt substrates were prepared by treating the amino esters with 2,4,6-triphenylpyrilium tetrafluoroborate (**5**) at room temperature in CH_2Cl_2 in the presence of Et_3N and 4 Å MS, followed by acidification with AcOH (Scheme 2). This

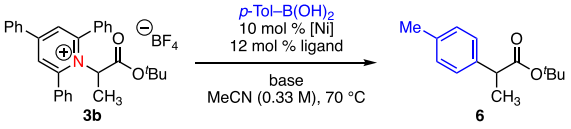
Scheme 2. Optimized Pyridinium Synthesis



method is a modified procedure from that originally reported by Katritzky,[16] and generally gives 20−30% higher yields than heating the amine and 2,4,6-triphenylpyrylium in refluxing EtOH, which is the most common method for pyridinium salt synthesis.[17]

We selected the cross-coupling of pyridinium salt **3b**, derived from alanine, and *p*-tolylboronic acid for optimization. Using $Ni(cod)_2$ and 1,10-phenanthroline as the catalyst system, we observed a dramatic effect of base; although NaOMe and K_3PO_4 resulted in ≤10% yield, the milder K_2CO_3 provided 69% yield of desired product **6** (Table 1, entries 1−3). Notably, the Suzuki−

Table 1. Optimization[a]



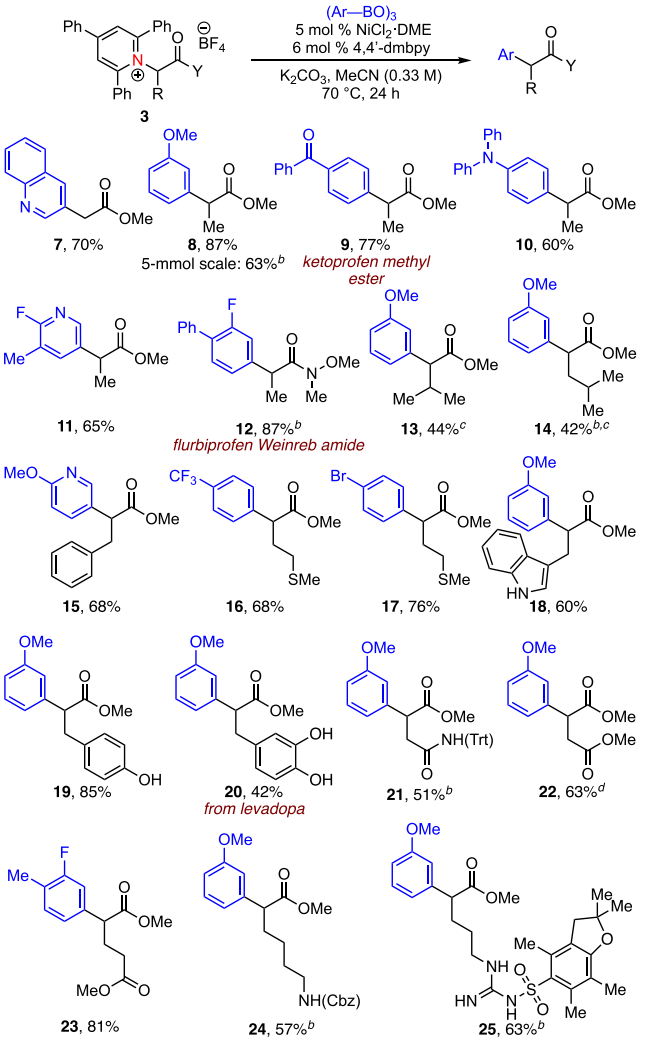
entry	[Ni]	ligand	base	yield (%)[b]
1	$Ni(cod)_2$	1,10-phen	NaOMe	10
2	$Ni(cod)_2$	1,10-phen	K_3PO_4	6
3	$Ni(cod)_2$	1,10-phen	K_2CO_3	69
4[c]	$Ni(cod)_2$	1,10-phen	K_2CO_3	77
5[c]	$NiCl_2$·DME	1,10-phen	K_2CO_3	75
6[c,d,e]	$NiCl_2$·DME	1,10-phen	K_2CO_3	88
7[c,d,e]	$NiCl_2$·DME	4,4′-dmbpy	K_2CO_3	>99
8[d,f]	$NiCl_2$·DME	4,4′-dmbpy	K_2CO_3	>99
9[f,g]	$NiCl_2$·DME	4,4′-dmbpy	K_2CO_3	71
10[d,f,h]	$NiCl_2$·DME	4,4′-dmbpy	K_2CO_3	n.d.[i]
11[f]	none	4,4′-dmbpy	K_2CO_3	n.d.[i]

[a]Conditions: pyridinium salt **3b** (0.10 mmol, 1.0 equiv), [Ni] (10 mol %), ligand (12 mol %), boronic acid (1.5 equiv), base (1.7 equiv), MeCN (0.33 M), 70 °C, 24 h. [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Boronic acid (2.5 equiv), base (2.8 equiv). [d][Ni] (5 mol %), ligand (6 mol %). [e]4 Å MS. [f](*p*-TolBO)$_3$ (0.8 equiv), K_2CO_3 (2.8 equiv). [g][Ni] (2 mol %), ligand (3 mol %). [h]Room temperature. [i]n.d. = not detected.

Miyaura arylation of alkylpyridinium salts with unactivated alkyl groups required a much stronger base (KO^tBu),[7a] potentially indicating that the α-carbonyl facilitates the reaction, consistent with a more stabilized radical intermediate. Increasing the equivalents of boronic acid and base further raised the yield (entry 4). Under these conditions, air-sensitive $Ni(cod)_2$ could be replaced with air-stable $NiCl_2$·DME without a detrimental loss in yield (entry 5). By adding 4 Å MS, the catalyst loading could be lowered to 5 mol % while maintaining high yield (entry 6). Use of the more electron-rich 4,4′-dimethylbipyridine (4,4′-dmbpy) ligand resulted in quantitative yield (entry 7). We hypothesized that the 4 Å MS may be absorbing water from the boronic acid; accordingly, the use of boroxine is also sufficient to achieve high yield (entry 8). We found the use of boroxine more convenient for scope studies (see below), but either protocol can be used (boronic acid and 4 Å MS or boroxine). Control experiments demonstrated that 71% yield can be obtained when the catalyst loading is lowered to 2 mol % (entry 9) and that the reaction requires heating and nickel catalyst (entries 10 and 11).

With these optimized conditions in hand, we examined their generality against the pyridinium salt derivatives of common proteinogenic amino acids (Scheme 3). Of the aliphatic amino acids, pyridinium salts derived from glycine (**7**), alanine (**8**−**12**), and phenylalanine (**15**) esters worked well, including a Weinreb amide (**12**). On 5 mmol scale, the reaction also worked well (**8**). However, more sterically challenging valine (**13**) and leucine (**14**) derivatives reacted in lower yields. Improved yields were achieved by heating the reactions at 80 °C; however, the

Scheme 3. Substrate Scope[a]



[a]Conditions: pyridinium salt **3** (1.0 mmol, 1.0 equiv), [Ni] (5 mol %), ligand (6 mol %), boroxine (0.8 equiv), K_2CO_3 (2.8 equiv), MeCN (0.33 M), 70 °C, 24 h. Average isolated yield of duplicate experiments (±6%), unless noted otherwise. [b]Single experiment. [c]*n*-PrCN, 80 °C. [d]Run on half the normal scale (0.5 mmol **3**).

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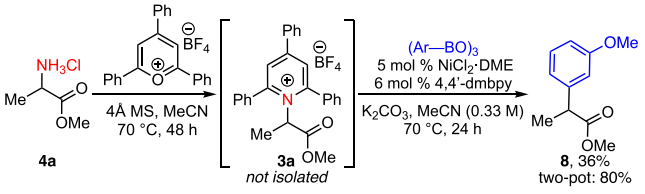
Org. Lett. XXXX, XXX, XXX−XXX

decomposition prevented even higher temperatures.[17] The pyridinium salt derived from methionine also worked well, highlighting that even an often challenging thioether is tolerated (**16**, **17**). Pyridinium salts derived from cysteine and serine methyl esters, with leaving groups in the β-position, could not be formed due to elimination under the pyridinium synthesis conditions.[17] Side chains with protic functional groups were well tolerated, as shown by **18**−**21** and **24**. Even tyrosine (**19**) and levodopa[18] (**20**) derivatives with mildly acidic phenol groups were successful, highlighting the mildness of the reaction conditions. For pyridinium salts derived from asparagine (Trt, **21**), aspartic acid (ester, **22**), glutamic acid (ester, **23**), lysine (Cbz, **24**), and arginine (Pbf, **25**), protecting groups were required. Without these protecting groups, pyridinium salts were formed in low yields and some of the cross-couplings were also poor. For the pyridinium salts derived from histidine and glutamine, even with protection of the side chain, the substrate syntheses were unsuccessful. In total, a wide range of functional groups were tolerated on the pyridinium salts, including esters (**22**, **23**), a Weinreb amide (**12**), thioethers (**16**, **17**), an unprotected indole (**18**), free phenols (**19**, **20**), primary amides (**21**, **24**), and a protected guanidine (**25**).

With respect to the range of arylboroxines amenable to this reaction, we again observed broad functional group tolerance, including ethers (**8**, **13**−**15**, **18**−**22**, **24**−**25**), ketones (**9**), tertiary anilines (**10**), fluoro (**11**, **12**, **23**), trifluoromethyl (**16**), and aryl bromide (**17**). Notably, derivatives of pharmaceuticals, such as ketoprofen (**9**) and flurbiprofen (**12**), can be prepared efficiently.[19] In terms of heteroarylboroxines, quinolinyl (**7**) and 3-pyridyl worked well (**11**, **15**), enabling installation of this prominent heteroaryl. However, electron-rich heteroaryls, such as indole, resulted in low yields, as did arylboroxines with *ortho* substituents.[17]

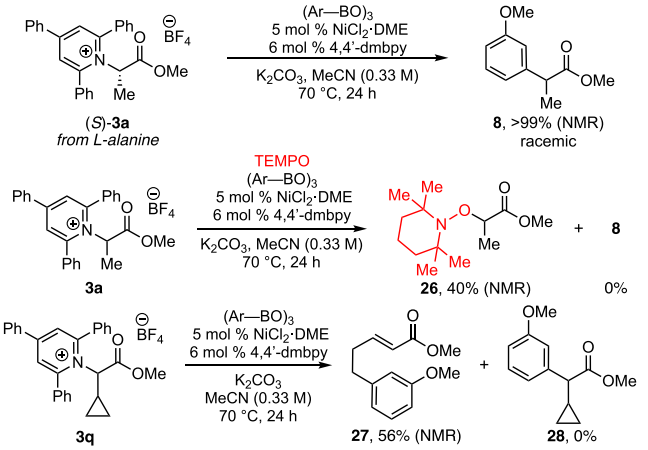
We also attempted to conduct the pyridinium formation and cross-coupling in a single step. Simultaneous addition of the pyrylium tetrafluoroborate and cross-coupling reagents (nickel catalyst, arylboroxine, base) was unsuccessful. However, a one-pot protocol was developed for the transformation of amino ester **4a** to product **8** without isolation of pyridinium **3a** (Scheme 4). Although this protocol resulted in lower yield than when pyridinium **3a** was isolated, such a one-pot protocol may be advantageous in certain cases, such as parallel synthesis.

Scheme 4. One-Pot Transformation of Alanine Methyl Ester



Like previous nickel-catalyzed cross-couplings of alkylpyridinium salts,[7a] we hypothesize that this reaction proceeds via single-electron transfer (SET) from a nickel catalyst to the pyridinium ring to yield a neutral pyridyl radical. C−N bond fragmentation then gives an alkyl radical, which likely combines with a nickel arene intermediate before undergoing reductive elimination to yield the arylated product. In support of an alkyl radical intermediate, we observed racemization in the cross-coupling of enantioenriched **3a**, prepared from L-alanine (Scheme 5, top).[20] Also, the addition of TEMPO to the cross-coupling yielded TEMPO-trapped adduct **26** (Scheme 5, middle). Finally, the cross-coupling of cyclopropane **3q** resulted in formation of ring-opened product **27** (Scheme 5, bottom). Further studies are needed to elucidate the nickel intermediates involved.

Scheme 5. Mechanistic Studies



In summary, we have developed a nickel-catalyzed Suzuki−Miyaura arylation of amino acid-derived pyridinium salts. This reaction harnesses a privileged class of substrates (amino acid derivatives) and delivers α-aryl esters, which can be readily hydrolyzed to carboxylates well-appreciated for their bioactivities. The reaction conditions are mild, enabling a broad range of functional groups to be installed, making this method a useful, complementary reaction for the arylation of amino acid derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02643.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX