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β -C(sp³)-H Arylation of α -Hydroxy Acid Derivatives Utilizing Amino Acid as a Directing Group

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Abstract

The Pd(II)-catalyzed intermolecular arylation of unactivated β -C(sp³)-H bonds in α -hydroxy acid derivatives was achieved. A variety of aryl iodides was tolerated giving moderate to good yields.

The feasibility of amino acid auxiliary as a directing group was demonstrated

Graphical abstract

Palladium-catalyzed activation of the inert β -C(sp³)-H bonds of aliphatic carboxylic acid derivatives has met with substantial progress over the past decade utilizing chiral oxazolines,¹ 8-aminoquinoline auxiliary,² 2-(pyridin-2-yl)isopropyl directing group,³ and a variety of weakly coordinating amide directing groups.⁴

Previously, we have reported the synthesis of a variety of unnatural amino acids via the direct β -functionalization of α -amino acids.^{5,6} Our group also demonstrated recently that β -C(sp³)-H bonds of the N-terminal amino acid in dipeptide compounds can be effectively functionalized with the coordination of the C-terminal amino acid.⁷

Despite the progress in α -amino acids, β -C(sp³)-H functionalization of carboxylic acid derivatives bearing oxygen function in its α -position is still rare. Baudoin's group has elegantly utilized silyl ketene acetal for the migrative arylation,⁸ the major drawback of which is the loss of chirality at the α -position. To the best of our knowledge, there has only been one example that utilizes directing-group controlled β -arylation by Douglass' group.⁹

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Supporting Information

Experimental procedures, detailed optimization data and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Herein, we report an intermolecular arylation of unactivated β -C(sp³)-H bonds in α -hydroxy acid derivatives which utilizes an amino acid auxiliary as a directing group.

2-Hydroxy-3-arylpropionic acid is a versatile building block in organic synthesis, and found in several pharmaceuticals and biologically active compounds (Figure 1). β -Arylation of lactic acid derivatives would provide an alternative synthetic route to this target structure.

We have previously disclosed a diverse range of C-H bond activation is enabled or accelerated by mono-N-protected amino acid (MPAA) ligands.¹⁰ Kinetic and computational studies¹¹ suggest that the monomeric Pd(II) complex coordinated by a MPAA in a bidentate manner is highly reactive for cleaving inert C-H bonds. Our report on the β -C(sp³)-H functionalization of di-, tri-, and tetrapeptide compounds⁷ can be rationalized by the intramolecular amino acid constituting the peptide participating as an internal MPAA ligand which coordinates to Pd(II) and promote functionalization of the proximate β -C(sp³)-H bonds in the N-terminus.

Based on above findings, we turned to utilize an amino acid auxiliary as a directing group for the functionalization of *O*-protected α -hydroxy acid derivatives. We selected commercially available *O*-benzyl-D-lactic acid as the starting material for our further experiments.¹² With the initial condition adapted from our previous methods,⁷ subjection of **1a** (R= (*S*)-*i*-Pr) to 10 mol% Pd(OAc)₂, 2 equiv. 4-iodotoluene, 2 equiv. AgOAc and 3 equiv. KF in HFIP gave the arylated product **2a** in 79% NMR yield along with the recovery of 16% of the unreacted **1a** (Scheme 1).

The effect of the directing groups was then investigated. Further screening of the amino acid auxiliary revealed that matching a stereo pair has an influence on the yield, L-valine (**1a**) as a counterpart of D-lactic acid giving higher yield than D-valine (**1b**). The yield for L-isoleucine (**1d**) was comparable to **1a**, while smaller L-alanine (**1c**) or bulkier L-phenylalanine (**1e**) decreased the yield. Achiral glycine (**1g**) gave higher yield than its dimethyl analog (**1f**). The yield for **1g** was comparable to **1a**, but crystalline **1a** as a starting material was easier to handle.

Encouraged by these results, systematic screening was performed using **1a** as a probe compound. Some representative data are shown in Table 1.¹³ Solvent screening led us to discover polar, weakly acidic hexafluoroisopropanol (HFIP) as the solvent of choice. Although salts of other cations were also effective to some extent, potassium was apparently the best cation, for it generally gave higher yields than other salts (Entries 1–6).¹³ The reaction also proceeded in the absence of base, albeit with lower yield (Entry 7). Phosphonate anion apparently had detrimental effect to the yield (Entries 3, 9). Substitution of Cu(OAc)₂ for AgOAc completely suppressed the reaction (Entry 10), showing the necessity of the silver source. It is known that accumulation of iodide anions in reaction mixture leads to catalyst poisoning,¹⁴ and silver salts in combination with aryl iodides can increase the turnover number.¹⁵ Further comprehensive screening data are presented in the Supplementary Information. From the result the best combination of the reagents were found to be Pd(OAc)₂, AgOAc and KF in HFIP.

To further improve the protocol, we then screened reaction time, temperature and chemical equivalents of the reagents. Raising the temperature did not affect the yield (Table 1, Entry 11), and decreasing the reaction time, AgOAc or KF reduced the yield (Entries 12, 13, 15). Excess aryl iodide itself did not improve the yield (Entry 17), but increasing both iodide and AgOAc gave the highest yield (Entry 18). Reducing Pd(OAc)₂ to 5 mol% gave a comparable, but slightly reduced result (Entry 16. See also SI Table S2, Entry 31).

Thus, stirring **1a** with 10 mol% Pd(OAc)₂, 3 equiv. 4-iodotoluene, 3 equiv. AgOAc and 3 equiv. KF in HFIP (0.1 M) at 100 °C for 24 h afforded the β-arylated product **2a** in 77% isolated yield (Scheme 2).

With the optimized conditions in hand, the scope of the coupling partners was then explored (Scheme 2). In general, substrate **1a** was arylated with a wide range of aryl iodides in moderate to good yields. Both electron-donating and electron-withdrawing groups at either para or meta position of the aryl iodide were tolerated. Aryl iodides with ortho substituent gave lower yields presumably due to the steric interference, since ortho-fluorophenyl iodide gave higher yield (**12**). The gram-scale (4.0 mmol) synthesis of **2a** was performed to afford the desired product in 70% isolated yield. Reactions with *p*-bromotoluene failed to give any desired arylation product under the present condition.

Removal of the auxiliary group was accomplished in high yield through N-nitrosylation/hydrolysis sequence (Scheme 3). Thus, **2a** was esterified with TMSCHN₂ to afford **18** in 97%, which was treated with NaNO₂ in AcOH/Ac₂O at 0 °C-rt to yield the acid **19** in 72% (91% based on recovered starting material). Alternatively, **2a** could be heated in conc. HCl/1,4-dioxane to give debenzylated acid **17** in 70% yield. Both acids **17** and **19** showed 99% *ee* determined by HPLC method. These two routes provide orthogonal methods to access differently protected β-aryl-α-hydroxy acid derivatives.

In summary, we have developed an intermolecular arylation of unactivated β-C(sp³)-H bonds in α-hydroxy acid derivatives. The reaction proceeded with a wide range of aryl iodides in moderate to good yields. The auxiliary was removed efficiently, and the feasibility of amino acid auxiliary as a directing group was demonstrated. Further research for expanding the scope of β-C(sp³)-H functionalization is in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Some Examples of Biologically Active β -Aryl- α -Hydroxy Acid Derivatives.

Scheme 1.

Scope of Amino Acid as the Auxiliary ^{a, b}

^a Reaction conditions: Substrate (0.1 mmol), 4-Me-C₆H₄I (2 eq.), Pd(OAc)₂ (10 mol%), AgOAc (2 eq.), KF (3eq.), HFIP (1 mL), 100 °C, 24h. ^b The yields were determined by ¹H NMR analysis of the crude products using CH₂Br₂ as an internal standard.

Scheme 2. Substrate Scope of Pd-Catalyzed β -Arylation of α -Hydroxy Acids ^{a, b}

^a Reaction conditions: Substrate (0.2 mmol), 4-Me-C₆H₄I (3 eq.), Pd(OAc)₂ (10 mol%), AgOAc (3 eq.), KF (3eq.), HFIP (0.1 M), 100 °C, 24h. ^b Isolated yields. ^c The reaction was carried out on a 4.0 mmol scale.

Scheme 3.

Removal of the Auxiliary Group

a) conc. HCl, 1,4-dioxane, 80 °C, 70%; b) TMSCHN₂, toluene, MeOH, rt, 97%; c) NaNO₂, AcOH, Ac₂O, 0 °C-rt, 72% (91% brsm) + **18** (21%)

Table 1

Selected Data From Optimization Study

Entry	[Ag]	[Base]	Yield (%) ^a
1	AgOAc	KF	79
2	AgOAc	KHCO ₃	70
3	AgOAc	K ₂ HPO ₄	21
4	AgOAc	LiF	58
5	AgOAc	NaHCO ₃	51
6	AgOAc	CsF	75
7	AgOAc	(None)	59
8	AgF	KF	76
9	Ag ₃ PO ₄	KF	7
10	Cu(OAc) ₂	KF	0
11 ^b	AgOAc	KF	76
12 ^c	AgOAc	KF	66
13	AgOAc ^d	KF	69
14	AgOAc ^e	KF	69
15	AgOAc	KF ^f	71
16 ^g	AgOAc	KF	77
17 ^h	AgOAc	KF	78
18 ^h	AgOAc ^e	KF	85

^aThe yields were determined by ¹H NMR analysis of the crude products using CH₂Br₂ as an internal standard.

^b120°C

^c16 h

^d1.5 eq

^e3 eq

^f2 eq

^gPd(OAc)₂ 5 mol%

^h4-Me-C₆H₄I(3 eq.)