Organic LETTERS

Letter

pubs.acs.org/OrgLett

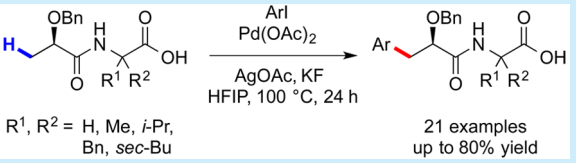
β-C(sp^3)–H Arylation of α-Hydroxy Acid Derivatives Utilizing Amino Acid as a Directing Group

Tetsuya Toba,[†,‡] Yi Hu,[§,‡] Anh T. Tran, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: The Pd(II)-catalyzed arylation of unactivated β-C(sp^3)–H bonds in α-hydroxy aliphatic acid with a variety of aryl iodides was developed utilizing an amino acid auxiliary as a directing group. This protocol provides access to biologically active β-arylated-α-hydroxy acid derivatives.



Palladium-catalyzed activation of the inert β-C(sp^3)–H bonds of aliphatic carboxylic acid derivatives has met with substantial progress over the past decade with the development of a number of directing groups such as chiral oxazolines,[1] 8-aminoquinoline,[2] and 2-(pyridin-2-yl)isopropyl[3] as well as a variety of weakly coordinating fluorinated 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 employing the weakly coordinating perfluorinated aryl amides[5] and *N*-methoxyamide directing groups.[6] Recently, our group also demonstrated that *C*-terminal amino acids, by coordination with Pd(II), can activate proximal β-C(sp^3)–H bonds of *N*-terminal amino acids in dipeptides.[7] A similar approach has been elegantly adopted by Hong and co-workers utilizing *C*-terminal amino acid amides to achieve asymmetric β-C(sp^3)–H functionalization of cyclopropane carboxylic acid derivatives.[8]

Although there are numerous reports describing the β-C(sp^3)–H functionalization of carboxylic acid derivatives employing bidentate directing groups[2,3,9] or weakly coordinating auxiliaries such as perfluorinated arylamides,[4b] examples of β-functionalization of α-hydroxy carboxylic acids are limited. In 2010, Shabashov and Daugulis reported a single example of β-arylation of benzyl protected lactic acid employing a 2-methylthioaniline auxiliary.[10] More recently, Baudoin's group has elegantly utilized silyl ketene acetals for the migrative arylation to deliver β-arylated α-hydroxy carboxylic esters, albeit with loss of chirality at the α-position.[11] Herein, we report the arylation of unactivated β-C(sp^3)–H bonds in α-hydroxy acid derivatives that utilizes an amino acid auxiliary as a directing group to deliver various 2-hydroxy-3-arylpropionic acids with high stereochemical integrity. We envisaged that this protocol would facilitate access to a variety of 2-hydroxy-3-arylpropionic acids, which are frequently found building blocks in several pharmaceuticals and biologically active compounds (Figure 1), from readily available lactic acid feedstock.

We have previously disclosed a diverse range of C–H bond activation reactions that are either enabled or accelerated by

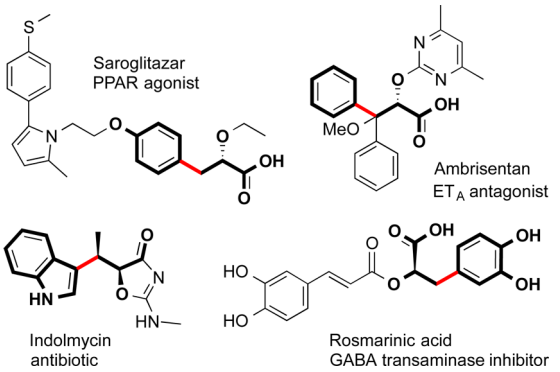


Figure 1. Some examples of biologically active β-aryl-α-hydroxy acid derivatives.

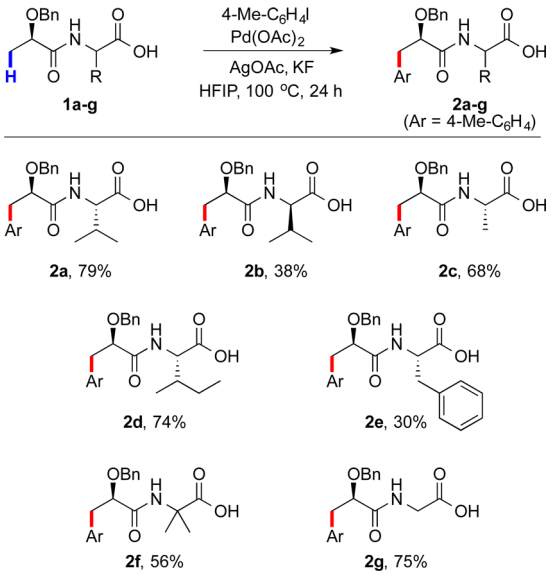
mono-*N*-protected amino acid (MPAA) ligands.[12] Kinetic[13] and computational studies[14] suggest that the monomeric Pd(II) complex coordinated by a MPAA in a bidentate manner is highly reactive for cleaving inert C–H bonds. Our report on the β-C(sp^3)–H functionalization of di-, tri-, and tetrapeptide compounds[7] can be rationalized by the intramolecular amino acid constituting the peptide participating as an internal MPAA ligand, which coordinates to Pd(II), and promotes functionalization of the proximal β-C(sp^3)–H bonds at the *N*-terminus.

Based on the above findings, we turned to utilize an amino acid auxiliary as a directing group for the functionalization of *O*-protected α-hydroxy aliphatic acid derivatives. We selected commercially available *O*-benzyl-D-lactic acid as the starting material for further investigation.[15] Using our previously reported conditions for β-C(sp^3)–H functionalization of di-, tri-, and tetrapeptide compounds,[7] arylation of **1a** [R= (*S*)-*i*-Pr] with 4-iodotoluene in HFIP afforded the desired product **2a** in a promising 79% yield along with unreacted starting material (Scheme 1). This result is particularly encouraging considering that the perfluorinated aryl amide auxiliary only

Received: October 6, 2015

DOI: 10.1021/acs.orglett.5b02900
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Scope of Amino Acids as the Auxiliaries[a,b]



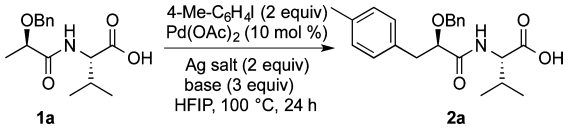
[a]Reaction conditions: substrate (0.1 mmol), 4-Me-C_6H_4I (2 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), KF (3 equiv), HFIP (1 mL), 100 °C, 24 h. [b]The yields were determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.

gave the desired arylation product in 50% yield despite extensive optimization. As a control experiment, the corresponding amino ester was not reactive.

The effect of the directing groups was then investigated. Further screening of the amino acid auxiliary revealed match/mismatch effects. Specifically, in the arylation of D-lactic acid with 4-iodotoluene, the L-valine auxiliary (**1a**) afforded a higher yield of the desired product (**2a**: 79%, Scheme 1) than the D-valine counterpart (**2b**: 38%, Scheme 1). The yield for L-isoleucine (**1d**) was comparable to **1a**, while the smaller L-alanine (**1c**) or bulkier L-phenylalanine (**1e**) decreased the yield. Achiral glycine (**1g**) gave a higher yield than its *gem*-dimethyl analogue (**1f**).

Encouraged by these results, systematic screening was performed using **1a** as model substrate. Representative screening results are shown in Table 1 (see the Supporting Information for comprehensive screening tables). 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).[16] The reaction also proceeded in the absence of base, albeit with lower yield (entry 7). Counteranions also played an important role with fluoride being the best anion (entry 1) while phosphate anion was shown to have a detrimental effect on yield (entries 3, 9). Substitution of $Cu(OAc)_2$ for AgOAc completely suppressed the reaction (entry 10), demonstrating the necessity of the silver source. It has been postulated in the literature that silver salts play dual roles. First, the reaction of the alkylpalladium(II) with ArI is often promoted by Ag(I) salts. Second, Ag(I) can act as iodide scavengers, thereby preventing catalyst poisoning resulting from accumulation of iodide anions in the reaction mixture[17] and resulting in an increase in turnover number.[18] From the screening results, the best combination of the reagents were found to be $Pd(OAc)_2$, AgOAc, and KF in HFIP.

Table 1. Selected Data from Optimization Study



entry	[Ag]	[base]	yield[a] (%)
1	AgOAc	KF	79
2	AgOAc	$KHCO_3$	70
3	AgOAc	K_2HPO_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_3PO_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**

[a]The yields were determined by ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard. [b]120 °C. [c]16 h. [d]1.5 equiv. [e]3 equiv. [f]2 equiv. [g]$Pd(OAc)_2$ (5 mol %). [h]4-Me-C_6H_4I (3 equiv)

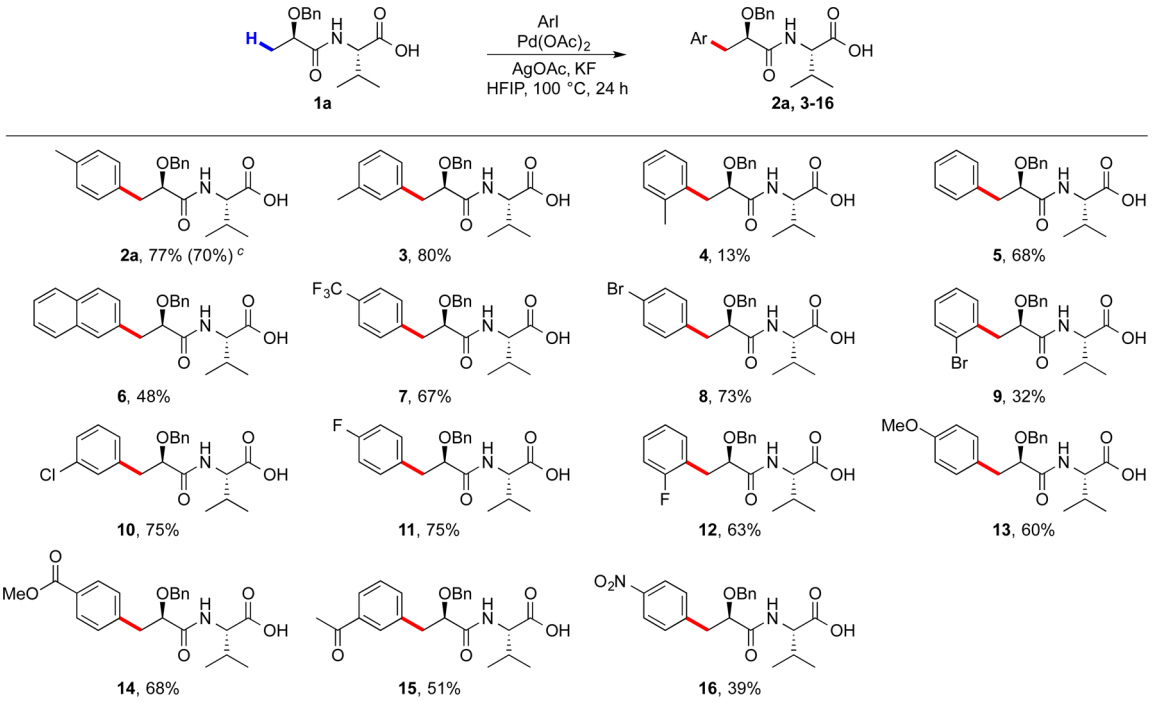
To improve the protocol further, we evaluated the effects of temperature, reaction time, and chemical equivalents of the reagents on the efficiency of the arylation reaction. Raising the temperature did not affect the yield (Table 1, entry 11), while decreasing the reaction time, AgOAc, or KF reduced the yield (entries 12, 13, and 15, respectively). It was also found that while excess aryl iodide alone did not improve the yield (entry 17), a simultaneous increase of both iodide and AgOAc gave rise to the highest yield (entry 18). It was also possible to lower the $Pd(OAc)_2$ loading to 5 mol %, albeit with a small reduction in yield (entry 16). For further information, see Table S2, entry 31, in the Supporting Information).

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 the *meta* or *para* positions of the aryl iodides were tolerated. Aryl iodides with *ortho* substituents gave lower yields, presumably due to the steric hindrance, since a small *o*-F substituent on the aryl iodide was well tolerated (**12**). Under the present reaction conditions, *p*-bromotoluene was not reactive. To demonstrate the scalability of this protocol, a gram-scale synthesis (4.0 mmol) of **2a** was performed. We were pleased to find that the desired product could be obtained in 70% isolated yield.

Removal of the auxiliary group was accomplished in high yield through an *N*-nitrosylation/hydrolysis sequence (Scheme 3). Thus, **2a** was esterified with $TMSCHN_2$ to afford **18** in 97% yield, which was treated with $NaNO_2$ in $AcOH/Ac_2O$ to give the acid **19** in 72% yield (91% based on recovered starting material). Alternatively, **2a** could be heated in concentrated HCl/1,4-dioxane to give free α-hydroxy acid **17** in 70% yield. These two routes provide orthogonal

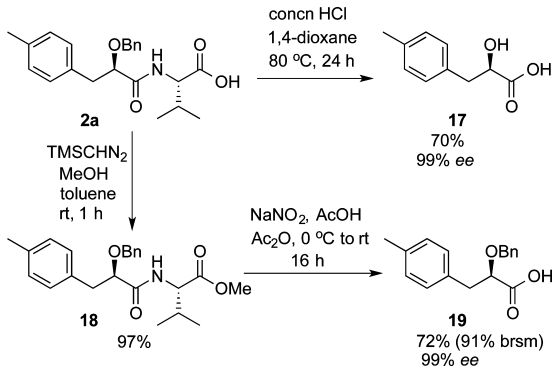
DOI: 10.1021/acs.orglett.5b02900
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of Coupling Partners for Pd-Catalyzed β-Arylation of α-Hydroxy Acids[a,b]



[a]Reaction conditions: substrate (0.2 mmol), ArI (3 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (3 equiv), KF (3 equiv), HFIP (0.1 M), 100 °C, 24 h. [b]Isolated yields. [c]The reaction was carried out on a 4.0 mmol scale.

Scheme 3. Removal of the Amino Acid Auxiliary



methods to access differently protected β-aryl-α-hydroxy acid derivatives without erosion in the stereochemistry with acids **17** and **19** being obtained in 99% ee as determined by analytical chiral HPLC.

In summary, we have developed an arylation procedure for unactivated β-C(sp^3)−H bonds in α-hydroxy acid derivatives directed by a commercially available amino acid auxiliary. The reaction proceeded with a wide range of aryl iodides to deliver biologically important β-aryl-α-hydroxy acids in moderate to good yields with high stereochemical integrity. The amino acid auxiliary demonstrated superior reactivity to the perfluorinated aryl amide counterpart while also allowing for efficient removal using two complementary methods to afford differentially protected β-aryl-α-hydroxy acids. Further research for expanding the scope of this β-C(sp^3)−H functionalization protocol is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02900.

Experimental procedures, detailed optimization data, and characterization of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yu200@scripps.edu.

Present Addresses

†(T.T.) Medicinal Chemistry Function, Asubio Pharma Co., Ltd.

§(Y.H.) College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University.

Author Contributions

‡T.T. and Y.H. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support. We thank Asubio Pharma Co., Ltd. for financial support to T.T., Nanjing Tech University and Jiangsu Provincial Department of Education for the visiting scholar fellowship to Y.H., and The University of Sydney for postdoctoral funding to A.T.T.

DOI: 10.1021/acs.orglett.5b02900
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112−2115.

(2) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984−12986. (c) Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Chem. Sci.* **2014**, *5*, 3952−3957.

(3) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588−13592.

(4) (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676−17677. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886−9887.

(5) (a) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216−1220. (b) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194−13197.

(6) Chen, G.; Shigenari, T.; Jain, P.; Zhang, Z.; Jin, Z.; He, J.; Li, S.; Mapelli, C.; Miller, M. M.; Poss, M. A.; Scola, P. M.; Yeung, K.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 3338−3351.

(7) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940−16946.

(8) Kim, J.; Sim, M.; Kim, N.; Hong, S. *Chem. Sci.* **2015**, *6*, 3611−3616.

(9) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868−3871.

(10) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965−3972.

(11) Aspin, S.; López-Suárez, L.; Larini, P.; Goutierre, A.-S.; Jazzar, R.; Baudoin, O. *Org. Lett.* **2013**, *15*, 5056−5059.

(12) (a) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137−14151. (b) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315−319. (c) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518−522. (d) Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 17508−17513. (e) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344−16347. (f) Wan, L.; Dastbaravardeh, N.; Li, G.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 18056−18059. (g) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146−150. (h) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215−220. (i) Deng, Y.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 888−891. (j) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042−2046.

(13) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 4600−4606.

(14) (a) Musaev, D. G.; Kaledin, A.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 1690−1698. (b) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894−897.

(15) In our preliminary campaign utilizing the perfluoroanilide auxiliary groups (data not shown), the benzyl group was shown to be one of the best protecting groups for the hydroxyl group.

(16) For further details, see the Supporting Information.

(17) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581−590.

(18) Tremont, S. J.; Hayat ur Rahman. *J. Am. Chem. Soc.* **1984**, *106*, 5759−5760.

DOI: 10.1021/acs.orglett.5b02900
Org. Lett. XXXX, XXX, XXX−XXX