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Stereoselective Synthesis of β-Alkylated α-Amino Acids via Palladium-Catalyzed Alkylation of Unactivated Methylene C(sp^3)−H Bonds with Primary Alkyl Halides

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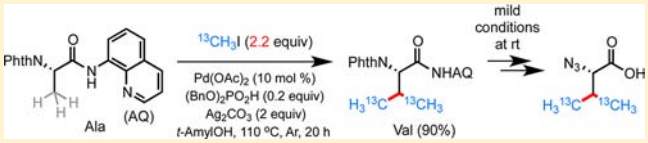
Supporting Information

ABSTRACT: We report a new set of reactions based on the Pd-catalyzed alkylation of methylene C(sp^3)−H bonds of aliphatic quinolyl carboxamides with α-haloacetate and methyl iodide and applications in the stereoselective synthesis of various β-alkylated α-amino acids. These reactions represent the first generally applicable method for the catalytic alkylation of unconstrained and unactivated methylene C−H bonds with high synthetic relevance. When applied with simple isotope-enriched reagents, they also provide a convenient and powerful means to site-selectively incorporate isotopes into the carbon scaffolds of amino acid compounds.



INTRODUCTION

Amino acids are one of nature's most powerful and versatile building blocks for the synthesis of natural products and biomolecules. In addition to the common proteinogenic amino acids, nature uses post-translational modifications (PTMs) to synthesize a myriad of nonproteinogenic amino acids with diverse structures and functions.[1] Among these modifications, alkylation at the β position of α-amino acid residues, e.g. *C*-methyltransferase-mediated methylation, is particularly effective at modulating the conformational and biophysical properties of the parent peptide backbones (Scheme 1).[2−4] These β-alkylated amino acid units contain adjacent carbon stereogenic centers and pose a significant synthetic challenge.[5]

Complementary to conventional synthesis strategies, we envisioned these molecules could be expeditiously accessed via the selective alkylation of sp^3-hybridized C−H bonds on the side chains of simple amino acid precursors.[6] The Corey[7] and Daugulis[8] laboratories have elegantly demonstrated this synthesis concept with Pd-catalyzed auxiliary-directed acetoxylation and arylation of the β-C(sp^3)−H bonds of *N*-Phth-protected amino acids, based on pioneering work from the Daugulis laboratory[9] (eq 1, Scheme 2). However, in contrast with better developed C−H arylation and oxidation reactions, the alkylation of unactivated and nonacidic C(sp^3)−H bonds remains one of the most difficult transformations in organic synthesis.[10] Additionally, despite a few recent successes in the alkylation of primary C(sp^3)−H bonds of methyl groups, alkylation of more prevalent secondary C(sp^3)−H bonds of unactivated methylene groups remains largely undeveloped.[11−15]

In a seminal 2010 paper, the Daugulis laboratory reported that the β-C(sp^3)−H bond of 8-aminoquinoline (AQ)-coupled propionamide **1** could be alkylated with primary alkyl iodides such as **2** under palladium catalysis (eq 2, Scheme 2).[12] Although this alkylation reaction was limited to primary C(sp^3)−H bonds and proceeded in moderate yields, it provided the foundation for our synthesis of β-alkylated amino acids, which relies on Pd-catalyzed AQ-directed C(sp^3)−H alkylation to install β-substituents. The success of our strategy then hinged on the development of new reaction conditions to alkylate less reactive secondary β-C(sp^3)−H bonds in a regio- and stereoselective fashion. In this paper, we report the development of highly efficient palladium-catalyzed alkylations of unactivated methylene C(sp^3)−H bonds of aliphatic 8-aminoquinolyl carboxamides with α-haloacetate and methyl iodide and apply these reactions to the stereoselective synthesis of β-alkylated α-amino acids. When applied with simple isotope-enriched reagents, they provide convenient and powerful means to site-selectively incorporate isotope labels into the carbon scaffolds of amino acid compounds.

RESULTS AND DISCUSSION

We commenced our investigation with simple AQ−butyramide substrate **4** (eq 3, Scheme 2). Our initial trials with *i*BuI (**2**) under the original Pd-catalyzed conditions failed to generate any of the desired product **5**. Our attempts at the intramolecular C(sp^3)−H alkylation of 8-iodooctanamide **6**, despite optimization, provided the cyclized product **7** in poor yield (eq 4, Scheme 2).[16] Given the ease with which β-C−H palladation of **4** occurs in the associated AQ-directed C−H arylation reaction system, we reasoned that the key to this C−H alkylation reaction might be the choice of the alkyl halide electrophile, so as to efficiently intercept the resulting palladacycle intermediate. In addition to promoting the desired alkylation of the palladacycle, side reactions which neutralize alkyl iodides, including esterification with carboxylate ligands

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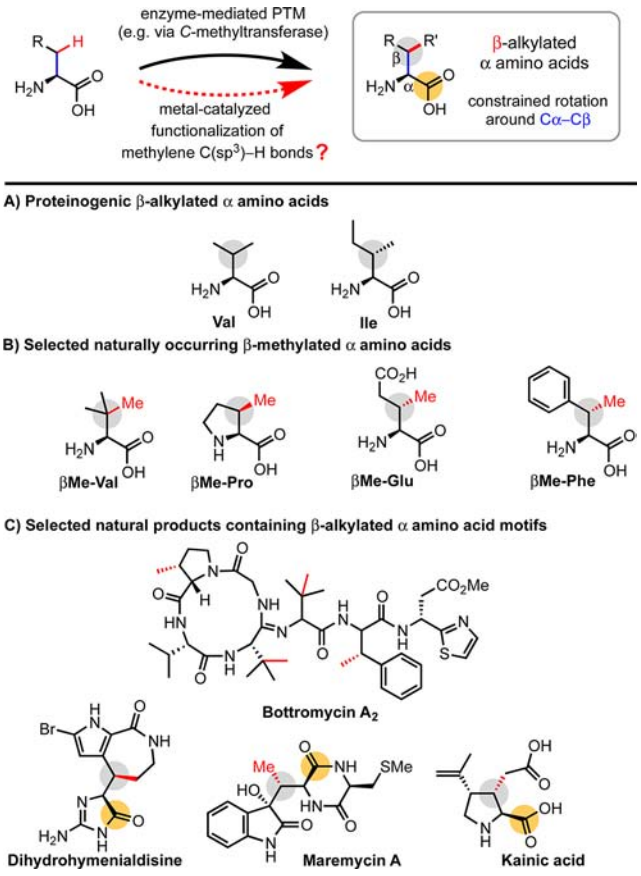
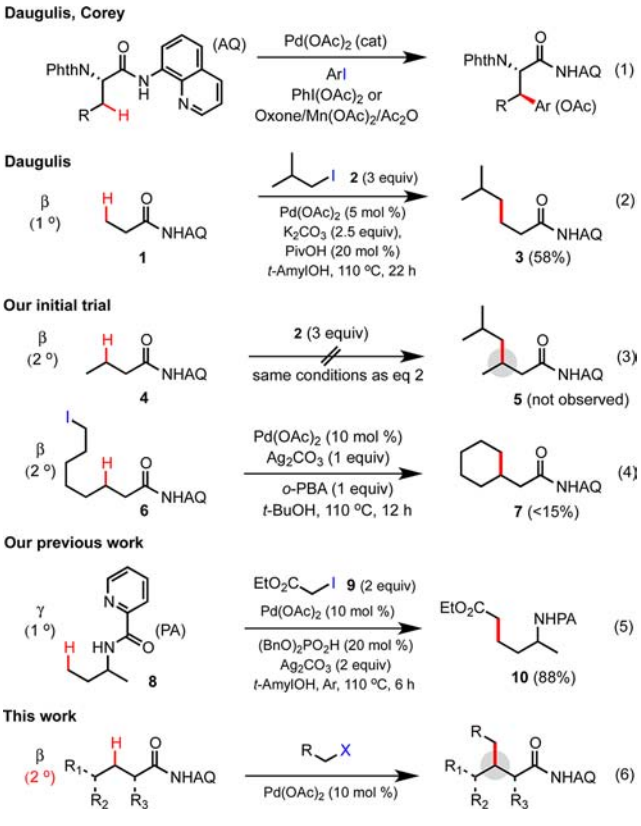
Scheme 1. Occurrence of β-Alkylated α-Amino Acids

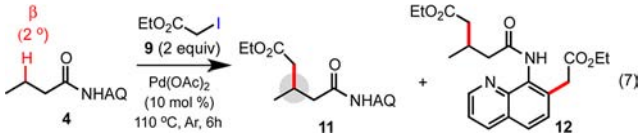


Scheme 2. DG-Mediated Pd-Catalyzed Alkylation of Unactivated C(sp^3)–H Bonds with Primary Alkyl Halides



and decomposition via an E2 pathway, must be effectively suppressed. Our recent success with Pd-catalyzed, picolinamide (PA)-directed alkylation of primary γ-C(sp^3)–H bonds of aliphatic amine substrates prompted us to evaluate the effectiveness of α-iodoacetate **9** and MeI in the AQ-directed alkylation of secondary C(sp^3)–H bonds (eq 5, Scheme 2).[13] To our delight, alkylation of **4** with 2 equiv of **9** and 2 equiv of AgOAc or Ag_2CO_3 at 110 °C in *t*-AmylOH under Ar for 6 h proceeded to give the desired carboxymethylated product **11** in excellent yield (eq 7, entries 4 and 6, Table 1). Application of

Table 1. Optimization of AQ-Directed C(sp^3)–H Alkylation of Simple Aliphatic Carboxamide 4



			yield[b] (%)	
entry	reagents (concn, equiv)	solvent[a]	**11**	**12**
1	K_2CO_3 (2)	A	11	<2
2	K_2CO_3 (2), PivOH (0.2)	A	18	<2
3	PivOH (0.2)	A	<2	<2
4	AgOAc (2)	A	85	3
5	AgOAc (2)	T	46	<2
6	Ag_2CO_3 (2)	A	86	5
7	Ag_2CO_3 (2), PivOH (0.2)	A	75	<3
8	Ag_2CO_3 (2), $(BnO)_2PO_2H$ (0.2)	A	91 (85)[c]	5
9	Ag_2CO_3 (2), $(BnO)_2PO_2H$ (0.2)	T	67	<2
10	Ag_2CO_3 (2), TEMPO (1)	A	82	<2

[a]A = *t*-AmylOH; T = toluene. [b]Yields are based on ^{1}H NMR analysis of the reaction mixture after workup on a 0.2 mmol scale. [c]Isolated yield.

the combination of Ag_2CO_3 (2 equiv) and $(BnO)_2PO_2H$ (20 mol %), originally developed for the PA-directed C–H alkylation reaction, provided a slightly improved alkylation yield (entry 8). Addition of the radical scavenger TEMPO had little effect on the reaction (entry 10). Product **12**, bisalkylated at both the aliphatic β-C(sp^3)–H and at the *ortho*-C(sp^2)–H position of the AQ moiety, was obtained as a minor side product.

We next subjected *N*-Phth-protected amino acid substrate leucine (Leu) **13** to the same carboxymethylation reaction with **9** (eq 8, Table 2). Only a moderate yield of **15a** was obtained under the same Ag_2CO_3-promoted conditions that worked well for simple aliphatic carboxamide **4** (entries 1 and 2). Gratifyingly, application of 2 equiv of Ag_2CO_3 and 20 mol % $(BnO)_2PO_2H$ improved the yield by 40% (entry 5). Additionally, we found α-bromoacetate **14** to be a better electrophile than **9**; application of 2 equiv of **14**, 2 equiv of Ag_2CO_3, and 20 mol % $(BnO)_2PO_2H$ at 110 °C under Ar in *t*-AmylOH for 20 h transformed **13** into **15b** in 70% isolated yield and excellent diastereoselectivity (>15/1) (entry 8). Interestingly, use of 1 equiv of $(BnO)_2PO_2H$ provided a significantly lower yield (entry 9). Chiral HPLC confirmed that the chiral integrity of the α-C of Leu **13** was maintained during the C–H alkylation reaction (>98% ee; see the Supporting Information). The formation of a five-membered palladacycle intermediate with *trans*-Phth-N_α and R_β configurations (see eq 10, Scheme 5) is likely responsible for the stereoselectivity observed in the β-C–H alkylation of α-substituted substrates.

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Table 2. Optimization of AQ-Directed C(sp^3)−H Alkylation of *N*-Phth-Protected Leu 13

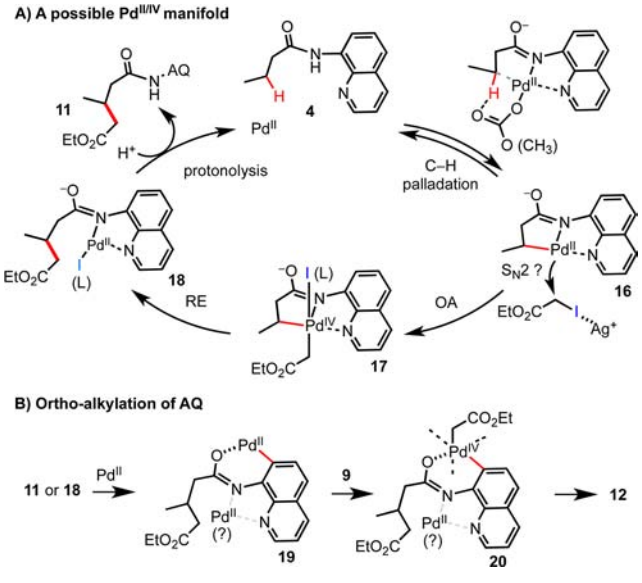
entry	reagents (concn, equiv)	solvent[a]	yield[b] (%) of **15**
1	**9** (2), AgOAc (2)	A	36
2	**9** (2), Ag_2CO_3 (1)	A	31
3	**9** (2), Ag_2CO_3 (1), $(BnO)_2PO_2H$ (0.2)	A	59
4	**9** (2), AgOAc (2), $(BnO)_2PO_2H$ (0.2)	A	45
5	**9** (2), Ag_2CO_3 (2), $(BnO)_2PO_2H$ (0.2)	A	74
6	**9** (2), Ag_2CO_3 (2), BINA-PO_2H[c] (0.2)	A	46
7	**9** (2), Ag_2CO_3 (2), $(PhO)_2PO_2H$ (0.2)	A	59
8	**14** (2), Ag_2CO_3 (2), $(BnO)_2PO_2H$ (0.2)	A	78 (70)[d]
9	**14** (2), Ag_2CO_3 (2), $(BnO)_2PO_2H$ (1)	A	31

[a]A = *t*-AmylOH. [b]Yields are based on ^{1}H NMR analysis of the reaction mixture after workup on a 0.2 mmol scale. [c](*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate. [d]Isolated yield, >98% ee (see the Supporting Information).

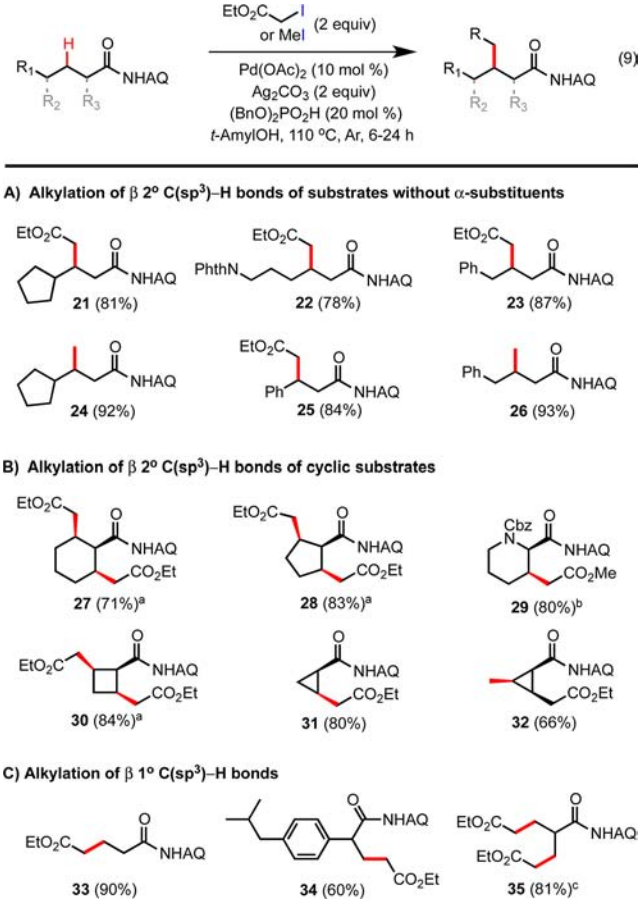
The exact mechanism of this Pd-catalyzed AQ-directed Ag-promoted alkylation has not been clearly established.[12] As shown in Scheme 3A, we postulate that this C−H alkylation reaction proceeds through a C−H palladation/coupling sequence and that a $Pd^{II/IV}$ manifold is operative.[17] Oxidative addition (OA) of **9** onto electron-rich Pd^{II} palladacycle **16** may proceed through an S_N2 pathway, promoted by Ag^+.[13] The Ag^+ ion could also act as a halide scavenger, abstracting the halide ligand from Pd^{IV} intermediate **17** and promoting reductive elimination (RE).[18] Ag^+ could also serve to remove the halide ligand from the Pd^{II} intermediate **18** to promote the regeneration of the more active Pd^{II} catalyst. We can only speculate on the functional role of $(BnO)_2PO_2H$ at the moment.[19] $(BnO)_2PO_2H$ was clearly more effective than all other carboxylic acid additives (e.g., PivOH, entry 7, Table 1) and organic phosphates (e.g., BINA-PO_2H, entry 6, Table 2) tested. $(BnO)_2PO_2H$ could form a soluble complex with Ag_2CO_3 and influence the concentration of otherwise insoluble Ag^+ in the reaction medium. $(BnO)_2PO_2H$ could also act as a ligand (L) for palladium during the OA and RE steps. We also suspect that $(BnO)_2PO_2H$ could help the protonolysis of the Pd-complexed alkylated intermediate **18**, promoting the release of the product **11** and accelerating the turnover of Pd catalyst. As shown in Scheme 3B, the *ortho*-C−H bond of the AQ group of **11** can undergo another alkylation with **9** to form **12**. We suspect that two palladium cations are involved in this second alkylation step. The first Pd cation complexes with alkylated substrate **11** through a strong bidentate interaction; the second Pd is ligated through the *O*-imidate group and effects the *ortho*-palladation and subsequent coupling with **9**, possibly through a $Pd^{II/IV}$ manifold. A similar amide-directed Pd-catalyzed *ortho*-methylation of arenes with MeI was first reported by Tremont et al. in the 1970s.[14a]

We next examined the substrate scope of this AQ-directed C(sp^3)−H alkylation with α-haloacetate **9** and MeI under the general conditions using Ag_2CO_3 (2 equiv)/$(BnO)_2PO_2H$ (20 mol %). As shown in Scheme 4A, excellent alkylation yields were obtained for substrates bearing no α-substituents; functionalizations of these substrates at their methylene C(sp^3)−H bonds is particularly difficult due to their high structural flexibility. Carboxymethylation of a sterically crowded

Scheme 3. Mechanistic Hypothesis



Scheme 4. AQ-Directed C(sp^3)−H Alkylation of Simple Aliphatic Carboxamide Substrates[a]



[a]All yields are based on isolated product on a 0.2 mmol scale. Notes: (a) 3 equiv of **9** was used; (b) 2 equiv of **14** was used; (c) 15 mol % of $Pd(OAc)_2$ and 5 equiv of **9** were used.

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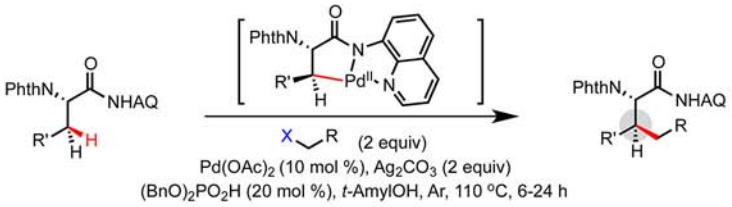
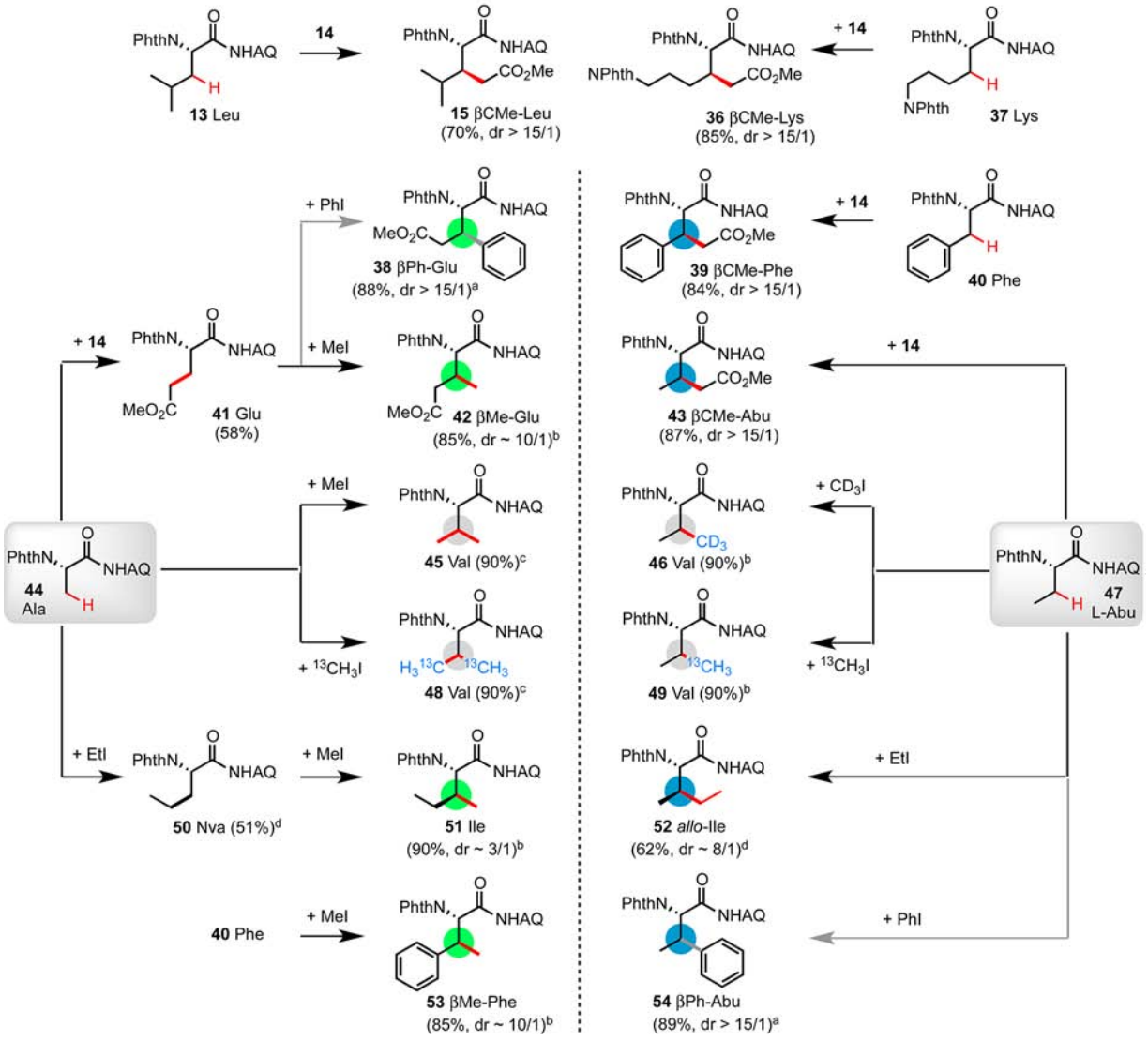
Scheme 5. Pd-Catalyzed AQ-Directed Alkylation of β-C(sp^3)−H Bonds of Amino Acids[a]





[a]All reactions were carried out on a 0.2 mmol scale; yields are based on isolation. Notes: (a) same reaction conditions with 2 equiv of PhI; (b) 1.1 equiv of MeI was used; (c) 2.2 equiv of MeI was used; (d) 3 equiv of EtI and 1 equiv of Ag_2CO_3 were used. See the Supporting Information for experimental details.

cyclopentyl substrate gave **21** in 81% yield. AQ-coupled 3-phenylpropionamide was alkylated at the benzylic position to give **25** in 86% yield. The β-methylene C(sp^3)−H bonds of four- to six-membered cyclic alkane carboxamides were bisalkylated with 3 equiv of **9** in excellent yield and exclusive *cis*-diastereoselectivity (see **27**, **28**, and **30** in Scheme 4B). In contrast, a cyclopropyl carboxamide substrate was preferentially monocarboxymethylated with 2 equiv of **9** to give **31**, which could then be methylated with MeI to give product **32** in moderate yield. Substrates derived from propionic acid, 2-butanoic acid, and ibuprofen were carboxymethylated at the β-Me position to give **33**−**35** under the standard reaction conditions (Scheme 4C). Interestingly, we observed only carboxymethylation of the primary C(sp^3)−H bond, possibly due to the newly installed ester group coordinating to the AQ−Pd complex and inhibiting further functionalization. Compared with MeI and α-haloacetates, other β-H-containing primary alkyl halides gave low to moderate yields under the standard conditions (e.g., EtI for **50**, Scheme 5). The alkylation reaction did not proceed with any secondary alkyl iodides we tested.

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We then applied this Pd-catalyzed C(sp^3)−H alkylation to *N*-Phth-protected amino acid substrates. A range of amino acid substrates bearing either aliphatic or aromatic side chains were alkylated with 2 equiv of **14** or MeI at the β-methylene position in good to excellent yield and diastereoselectivity (Scheme 5).[20] Stereoinduction by the α,β-*trans*-configured five-membered palladacycle intermediate provided us a simple and reliable model to predict the diastereoselectivity of the β-alkylations.[7,8] For instance, lysine (Lys) **37** and phenylalanine (Phe) **40** were cleanly carboxymethylated to give **36** and **39**, respectively. Alanine (Ala) **44** was preferentially monocarboxymethylated at the β-Me position to give a glutamic acid (Glu) product, **41**, similar to the reaction of our propionamide substrate **33**. Glu **41** can be further methylated with MeI at the β position to give βMe-Glu **42**. Glu **41** could also be arylated with PhI under Pd catalysis to give βPh-Glu **38**, a diastereomer of **39**. C−H alkylation of Ala **44** under the standard conditions with 2.2 equiv of MeI gave valine (Val) **45** in 90% yield, which was formed through monomethylated intermediate L-α-amino-butyramide (Abu) **47**. Ala **44** can also be ethylated at the β-methyl position with EtI to give norvaline (Nva) **50** in 50% yield, which could be subsequently methylated at the β position to give isoleucine (Ile) **51** in good yield and moderate diastereoselectivity.

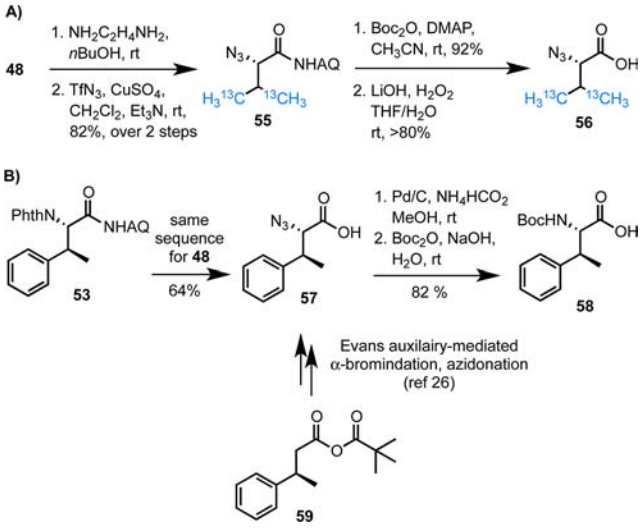
Abu **47** also serves as a versatile precursor for various β-methylated amino acid products bearing inverse stereochemistry at the β position compared to those obtained via AQ-directed C−H methylation. For example, carboxymethylation of Abu **47** gave βCMe-Glu **43**. Analogous to the synthesis of Ile **50**, Abu **47** can also be ethylated with EtI to give *allo*-isoleucine (*allo*-Ile) **52** in moderate yield and diastereoselectivity. Arylation of **47** with PhI gave βPh-Abu **54**, a diastereomer of **53**. *By varying the sequence of C−H alkylation, we can access both diastereomers of a variety of β-alkylated amino acids.* Additionally, C−H methylation of Ala **44** and Abu **47** with $^{13}CH_3I$ or CD_3I under the standard conditions gave isotope-labeled Val products **46**, **48**, and **49** in excellent yield.[21] These reactions offer a unique and simple means for the preparation of various site-selectively isotope-labeled amino acid products, which are of great value in biochemical studies of peptides and proteins.[22]

The amide-linked AQ group of the amino acid products can be removed under mild conditions using our previously reported protocol.[23,24] For example, the *N*-Phth group of ^{13}C-labeled Val **48** can be deprotected with ethylenediamine and converted into an azide group via treatment with TfN_3[25] (Scheme 6A). Activation of the amide group of **55** with Boc_2O and subsequent treatment with $LiOH/H_2O_2$ gave the azido acid product **56** in good yield. β-Me Phe **53** could be converted to the azido acid **57** following the same sequence used for **48** (Scheme 6B). Conventionally, compound **57** can be prepared from an anhydride derivative of enantio-enriched 3-phenylbutyric acid using the Evans auxiliary-mediated bromination and azidonation strategy.[26] The N_3 group of **57** can be reduced to NH_2 by hydrogenation and protected with Boc_2O to give the Boc-protected β-MePhe **58**[27] in good yield.

SUMMARY AND CONCLUSIONS

In summary, we have discovered a new set of reactions based on the Pd-catalyzed alkylation of unactivated methylene C(sp^3)−H bonds of aminoquinolyl aliphatic carboxamides with α-haloacetate and methyl iodide. These reactions are highly efficient and versatile and have broad substrate scope.

Scheme 6. Removal of the AQ Group under Mild Conditions



These reactions represent the first generally applicable method for the catalytic alkylation of unconstrained and unactivated methylene C−H bonds with high synthetic relevance. These reactions enable a streamlined strategy for the synthesis of various natural and unnatural amino acids, particularly β-alkylated α-amino acids, starting from readily available precursors in a diastereoselective manner following a straightforward template. With simple isotope-enriched reagents, they also provide a convenient and powerful solution to site-selectively incorporate isotopes into the carbon scaffolds of amino acid compounds. Applications of this C−H alkylation methodology in the synthesis of complex peptide natural products containing various nonproteinogenic β-alkylated α-amino acids are currently under investigation.

EXPERIMENTAL SECTION

General Procedure for Pd-Catalyzed AQ-Directed C−H Carboxymethylation with α-Haloacetate: Compounds 11 and 12. A mixture of carboxamide **4** (43 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol, 0.1 equiv), Ag_2CO_3 (110 mg, 0.4 mmol, 2 equiv), $(BnO)_2PO_2H$ (11 mg, 0.2 equiv), ICH_2CO_2Et (86 mg, 0.4 mmol, 2 equiv), and *t*-AmylOH (2 mL) in a 10 mL glass vial (purged with Ar, sealed with a PTFE cap) was stirred at 110 °C for 6 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the alkylated product **11** in 85% isolated yield (R_f = 0.5, 25% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 9.83 (s, 1 H), 8.79−8.76 (m, 2 H), 8.16−8.13 (m, 1 H), 7.55−7.24 (m, 3 H), 4.14 (dd, J = 14.1 and 7.2 Hz, 2 H), 2.71−2.62 (m, 2 H), 2.54−2.43 (m, 2 H), 2.36−2.29 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.13 (d, J = 6.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 172.4, 170.3, 148.1, 138.3, 136.3, 134.4, 127.9, 127.3, 121.6, 121.4, 116.4, 60.3, 44.6, 40.9, 28.1, 19.8, 14.2. HRMS: m/z calcd for $C_{17}H_{21}N_2O_3$ [M + H$^+$] 301.1552, found 301.1553. The following are data for compound **12** (R_f = 0.5, 35% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 9.87 (s, 1 H), 8.81−8.71 (m, 2 H), 8.36 (dd, J = 8.7 and 1.2 Hz, 1 H), 7.52−7.43 (m, 2 H), 4.18−4.08 (m, 4 H), 3.98 (s, 2 H), 2.66 (dd, J = 9.6 and 3.6 Hz, 2 H), 2.51−2.46 (m, 2 H), 2.36−2.33 (m, 1 H) 1.28−1.18 (m, 6 H), 1.13 (d, J = 6.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 172.5, 171.3, 170.4, 147.9, 138.6, 134.1, 133.0, 129.1, 127.0, 124.6, 121.6, 116.0, 61.1, 60.4, 44.7, 41.0, 38.4, 28.2, 19.9, 14.3, 14.2. HRMS: m/z calcd for $C_{21}H_{27}N_2O_5$ [M + H$^+$] 387.1920, found 387.1922.

General Procedure for Pd-Catalyzed AQ-Directed C−H Methylation with MeI: Compound 48. A mixture of carboxamide

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44 (69 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol, 0.1 equiv), Ag_2CO_3 (110 mg, 0.4 mmol, 2 equiv), $(BnO)_2PO_2H$ (11 mg, 0.2 equiv), $^{13}CH_3I$ (63 mg, 0.44 mmol, 2.2 equiv), and *t*-AmylOH (2 mL) in a 10 mL glass vial (purged with Ar, sealed with a PTFE cap) was stirred at 110 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the alkylated product **48** in 90% yield (R_f = 0.50, 35% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 10.58 (s, 1 H), 8.86−8.75 (m, 2 H), 8.14−8.12 (m, 1 H), 7.89 (dd, J = 5.7 and 3.3 Hz, 2 H), 7.73 (dd, J = 5.4 and 3.0 Hz, 2 H), 7.51−7.44 (m, 3 H), 4.72−4.67 (m, 1 H), 3.28−3.19 (m, 1 H), 1.44 (t, J = 6.0 Hz, 1.5 H), 1.20 (t, J = 6.0 Hz, 1.5 H), 1.02 (t, J = 6.0 Hz, 1.5 H), 0.78 (t, J = 6.0 Hz, 1.5 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 168.1, 166.8, 148.5, 136.1, 134.2, 131.6, 127.9, 127.2, 123.6, 121,9, 121.6, 117.0, 63.2, 27.3, 20.4 (^{13}C), 19.6 (^{13}C). HRMS: m/z calcd for $C_{20}{}^{13}C_2H_{20}N_3O_3$ [M + H$^+$] 376.1572, found 376.1573.

General Procedure for Removal of the AQ Group: Compound 55. A mixture of compound **48** (75 mg, 0.2 mmol, 1 equiv) and ethylenediamine (120 mg, 2 mmol, 10 equiv) in *n*BuOH (2 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by silica gel flash chromatography (10% MeOH in CH_2Cl_2) to give the free amine intermediate. The amine intermediate was dissolved in CH_2Cl_2 (2 mL). $CuSO_4$ (1 mg, 0.006 mmol, 0.03 equiv), TfN_3[25] (~0.6 M in CH_2Cl_2, ~4 equiv), and Et_3N (0.6 mmol, 3 equiv) were added, and the mixture was stirred at room temperature for 4 h. Water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give compound **55** in 82% yield (two steps, R_f = 0.70, 25% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 10.64 (s, 1 H), 8.91 (dd, J = 4.2 and 1.5 Hz, 1 H), 8.83−8.80 (m, 1 H), 8.20 (dd, J = 8.4 and 1.5 Hz, 1 H), 7.59−7.49 (m, 3 H), 4.10 (dd, J = 7.5 and 4.5 Hz, 1 H), 2.57−2.53 (m, 1 H), 1.42 (dd, J = 6.6 and 5.1 Hz, 1.5 H), 1.28 (dd, J = 6.0 and 5.1 Hz, 1.5 H), 1.00 (dd, J = 6.6 and 5.1 Hz, 1.5 H), 0.86 (dd, J = 6.6 and 5.4 Hz, 1.5 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 167.7, 148.6, 138.7, 136.3, 133.6, 128.0, 127.2, 122.3, 121.7, 116.7 71.5, 32.4, 19.7 (^{13}C), 17.1 (^{13}C). HRMS: m/z calcd for $C_{12}{}^{13}C_2H_{16}N_5O$ [M + H$^+$] 272.1422, found 272.1427.

General Procedure for Removal of the AQ Group: Compound 56. A mixture of compound **55** (44 mg, 0.16 mmol, 1 equiv), Boc_2O (106 mg, 0.48 mmol, 3 equiv), and DMAP (40 mg, 0.32 mmol, 2 equiv) in anhydrous CH_3CN (1 mL) was stirred at room temperature for 6 h. The resulting residue was concentrated in vacuo and then purified by silica gel flash chromatography to give product **55a** in 92% yield (54 mg, R_f = 0.60, 25% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 8.87 (d, J = 3.0 Hz, 1 H), 8.16 (d, J = 8.1 Hz, 1 H), 7.82 (dd, J = 7.5 and 1.5 Hz, 1 H), 7.59−7.51 (m, 2 H), 7.41 (dd, J = 8.4 and 4.2 Hz, 1 H), 5.09 (br, 1 H), 2.52−2.38 (m, 1 H), 1.41 (t, J = 6.0 Hz, 1.5 H), 1.32 (t, J = 6.0 Hz, 1.5 H), 1.21 (s, 9 H). 0.99 (t, J = 6.0 Hz, 1.5 H), 0.90 (t, J = 6.0 Hz, 1.5 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 173.5, 152.5, 150.4, 143.9, 136.3, 135.9, 128.8, 128.6, 128.3, 126.0, 121.6, 83.3, 67.7, 31.4, 27.5, 19.9 (^{13}C), 17.9 (^{13}C). HRMS: m/z calcd for $C_{17}{}^{13}C_2H_{24}N_5O_3$ [M + H$^+$] 372.1946, found 372.1949. Compound **55a** (37 mg, 0.1 mmol, 1 equiv) was dissolved in THF/H_2O (1 mL, 3:1). LiOH·H_2O (8 mg, 0.2 mmol, 2 equiv) and 30% H_2O_2 (0.5 mmol, 5 equiv) were then added at 0 °C. The reaction was stirred at room temperature for 3 h, and Na_2SO_3 (1 mmol, 10 equiv) was added. The reaction mixture was diluted with EtOAc (2 mL), acidified with 0.5 M aqueous HCl, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give compound **56** (14 mg, >80%) (R_f = 0.40, 50% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 3.79 (br, 1 H), 2.29−2.19 (m, 1 H), 1.30−1.21 (m, 3 H), 0.88−0.79 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 176.4, 67.7, 30.9, 19.4 (^{13}C), 17.7 (^{13}C). HRMS m/z calcd for $C_3{}^{13}C_2H_{10}N_3O_2$ [M + H$^+$] 146.0840, found 146.0843.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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