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Synthesis of β-alkynyl α-amino acids via palladium-catalyzed alkynylation of unactivated C(sp^3)–H bonds

Bo Wang, Gang He & Gong Chen*

Department of Chemistry, the Pennsylvania State University, University Park, Pennsylvania 16802, USA

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β-Di-substituted α-amino acids (AAs) contain adjacent carbon stereogenic centers and pose considerable synthetic challenge. Complementary to the conventional synthesis strategies based on the transformation of existing functional groups, we envisioned these molecules could be quickly accessed via selective functionalization of sp^3 hybridized C–H bonds on the side chains of common α-AA precursors. We report a readily applicable method to prepare β-alkynyl α-amino acids via Pd-catalyzed diastereoselective C(sp^3)–H alkynylation of common α-amino acids precursors with acetylene bromide.

α-amino acids, C–H functionalization, palladium

1 Introduction

α-Amino acids (α-AAs) are the basic building blocks for the synthesis of peptides and proteins. Compared with α-AAs bearing simple alkyl side chains, β-di-substituted α-AAs such as valine, isoleucine, and threonine are more effective at modulating the conformation of peptide backbones (Figure 1) [1,2]. In addition to those proteinogenic β-di-substituted α-AAs, nature uses enzyme-catalyzed post-translational modifications such as β-hydroxylation and β-methylation to synthesize various non-proteinogenic β-di-substituted α-AAs, which are critical to the biological activities of many peptide natural products. Besides their widespread occurrence in nature, β-di-substituted α-AAs have also been frequently used as building blocks for the design and synthesis of drug molecules and biochemical probes. These β-di-substituted α-AAs contain adjacent carbon stereogenic centers and pose considerable synthetic challenge [3–8]. While various strategies such as asymmetric hydrogenation and conjugate addition have been successfully

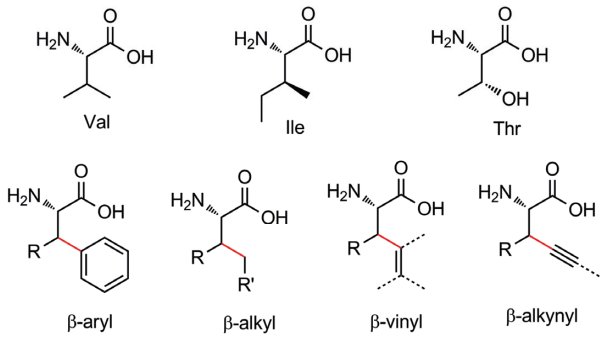


Figure 1 Synthesis of β-di-substituted α-AAs via Pd-catalyzed C(sp^3)–H functionalization.

developed over the past decades, efficient and readily applicable synthesis methods for novel β-di-substituted α-AAs are still in great demand. Complementary to the conventional synthesis strategies based on the transformation of existing functional groups, we envisioned these molecules could be quickly accessed via selective functionalization of sp^3 hybridized C–H bonds on the side chains of common α-AA precursors. Building upon the pioneer work by Daugulis *et al*. [9,10] and Corey *et al*. [11], we and others have developed methods to prepare β-aryl, β-alkyl, and

*Corresponding author (email: guc11@psu.edu)

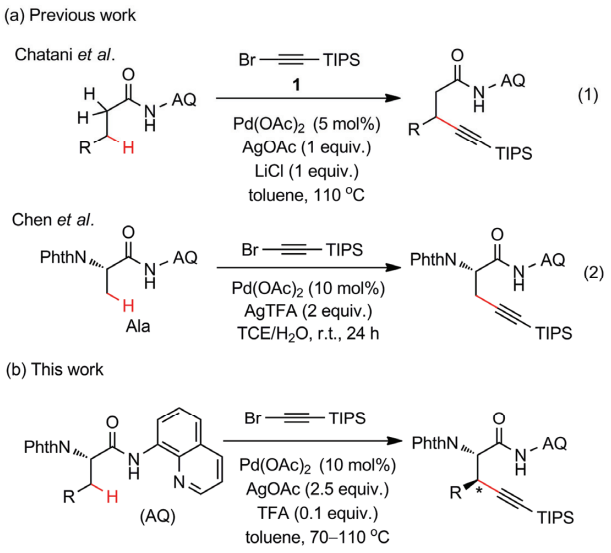
β-vinyl α-AAs via Pd-catalyzed carboxamide-directed C(sp^3)–H functionalization reactions [12–23]. Herein, we report a readily applicable method to prepare β-alkynyl α-amino acids via Pd-catalyzed diastereoselective C(sp^3)–H alkynylation of common α-amino acids precursors with acetylene bromide (Scheme 1).

2 Results and discussion

In 2011, the Chatani group [24–26] reported the first Pd-catalyzed β-C(sp^3)–H alkynylation of aminoquinoline (AQ)-coupled alkylcarboxamides with TIPS-protected acetylene bromide **1** (Scheme 1, Eq. (1)). Interestingly, the alkynylation of normally more challenging methylene C(sp^3)–H bonds proceeded in good yields whereas the alkynylation of β-Me group gave poor results (<10% yield). In 2013, the Yu group [27] reported a similar Pd-catalyzed C(sp^3)–H alkynylation with **1** using a fluroarylamide directing group. More recently, we demonstrated that AQ-coupled phthaloyl alanine (Ala) substrate can undergo C(sp^3)–H alkynylation at the β-Me position with **1** at room temperature (Scheme 1, Eq. (2)) [16]. The use of AgTFA reagent and the lower reaction temperature (r.t.) were critical to achieve the desired mono-selective β-Me alkynylation. Encouraged by these results, we proceeded to investigate whether other α-amino acid substrates can undergo C(sp^3)–H alkynylation at the β-methylene position in a diastereoselective fashion to provide β-di-substituted α-AA products [28].

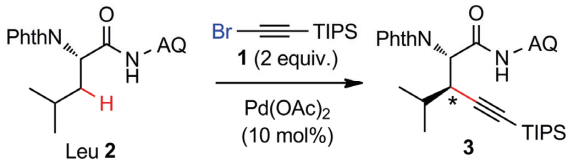
We commenced our study with the reaction of AQ-coupled phthaloyl leucine substrate **2** with 2 equiv. of acetylene bromide **1** under the catalysis of 10 mol% of Pd $(OAc)_2$ (Table 1). Reaction of **2** under our previously reported Ag-free conditions for *ortho* C(sp^2)–H alkynylation of benzylpicolinamides [29] with **1** (Entry 1) and the AgTFA-promoted room temperature conditions for β-Me alkynylation of Ala [16] (Entry 2) gave very low conversion of starting material. The conversion of **2** was significantly improved under the Chatani conditions using the AgOAc/LiCl promoter [25] and 10 mol% of $Pd(OAc)_2$ at 110 °C, affording product **3** in 45% yield and with excellent diastereoselectivity (*dr*>15/1) along with 10% of unidentified side products (Entry 3). Use of 2.5 equiv. of AgOAc alone gave higher yield of **3** (Entry 4). Addition of 1 equiv. of $KHCO_3$ shut down the reaction (Entry 5). In contrast, the addition of $(BnO)_2PO_2H$ [14] or TFA [15] was found beneficial, giving increased yield of **3** and less side products (Entries 6–10). Finally, the optimized conditions using 2.5 equiv. of AgOAc and 0.1 TFA in toluene at 90 °C for 24 h gave product **3** in 68% isolated yield and with excellent diastereoselectivity (*dr*>15:1, Entry 11) [30].

With the optimized conditions in hand, we then tested the scope of α-AA substrates for this β-C(sp^3)–H alkynylation reaction (Scheme 2). Compared with Leu **2** bearing a bulky *i*Pr side chain, alkynylation of α-AAs bearing less bulky side chains, e.g., Abu **5**, Nov **7**, Glu **9**, Lys **11**, and Phe **13**, proceeded in excellent β-regioselectivity but with moderate diastereo-selectivity (4–6:1). Interestingly, the diastereoselectivity of these C–H alkynylation reactions is lower than the corresponding Pd-catalyzed AQ-directed C–H arylation reactions. This may suggest different reactivity of the pal-



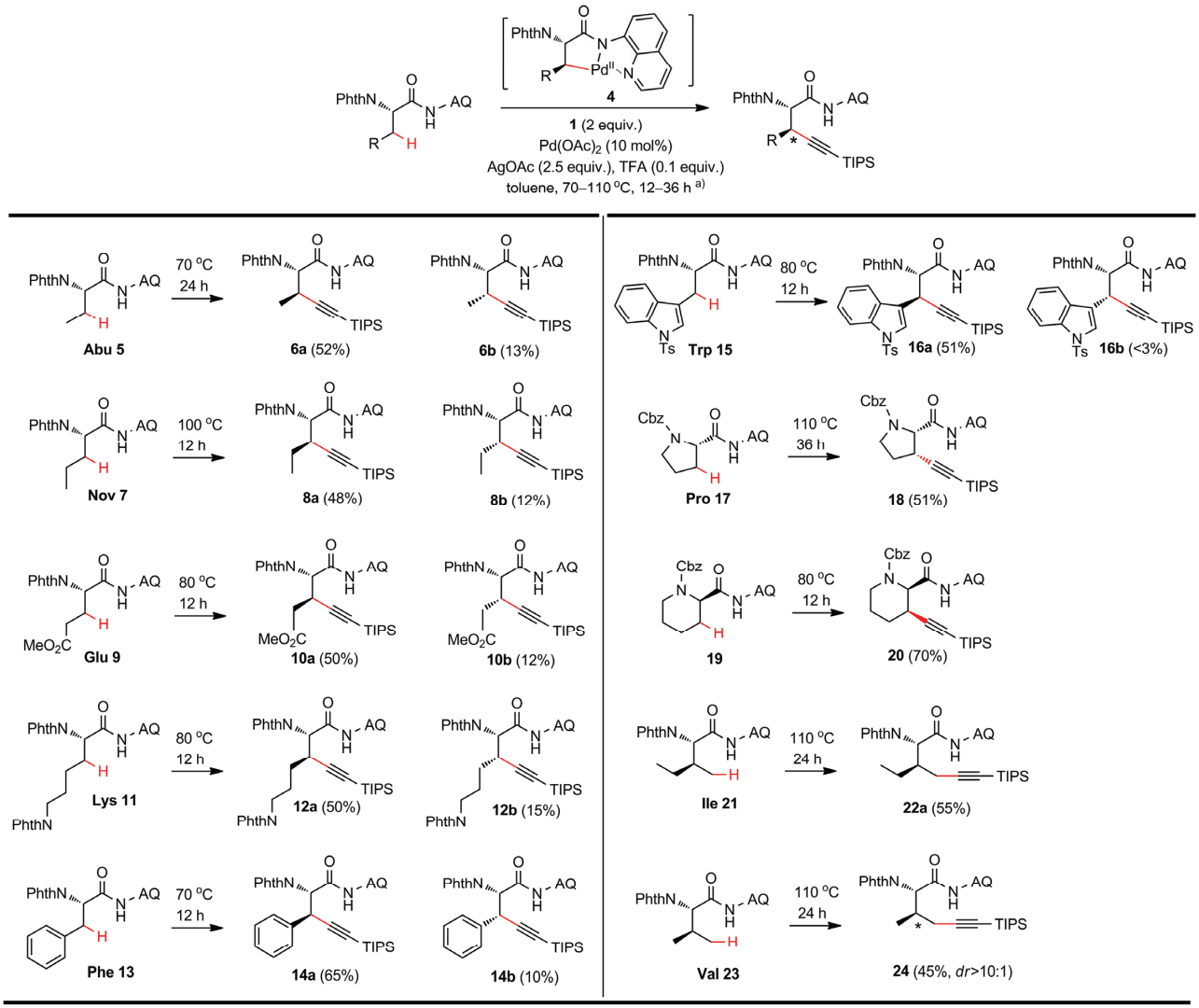
Scheme 1 Pd-catalyzed AQ-directed C(sp^3)–H alkynylation.

Table 1 Pd-catalyzed AQ-directed β-C(sp^3)–H alkynylation of Leu **2** with **1**



Entry	Reagents (equiv.)	Solvents	*T* (°C)/Time (h)	Yield (%) [a]
1	$KHCO_3$ (2), *o*PBA (0.2) [b]	DCE [c]	100/24	6
2	AgTFA (2)	TCE [c]/H_2O (1:1)	r.t./24	<2
3	AgOAc (2.5), LiCl (1.0)	toluene	110/24	45
4	AgOAc (2.5)	toluene	110/24	58
5	AgOAc (2.5), $KHCO_3$ (1.0)	toluene	90/24	<5
6	AgOAc (2.5) $(BnO)_2PO_2H$ (1.0)	toluene	90/24	66
7	AgOAc (2.5) $(BnO)_2PO_2H$ (0.2)	toluene	90/24	52
8	AgOAc (2.5), AcOH (1.0)	toluene	90/24	58
9	AgOAc (2.5), TFA (1.0)	toluene	90/24	60
10	AgOAc (2.5), TFA (0.5)	toluene	90/24	64
11	AgOAc (2.5), TFA (0.1)	toluene	90/24	70 (68) [d]

a) Yields are based on ^{1}H NMR analysis of crude reaction mixture on a 0.2 mmol scale; b) *o*PBA: *ortho*-phenyl benzoic acid; c) DCE: 1,2-dichloroethane, TCE: 1,1,2,2-tetrachloroethane; d) isolated yield, *dr*>15:1.

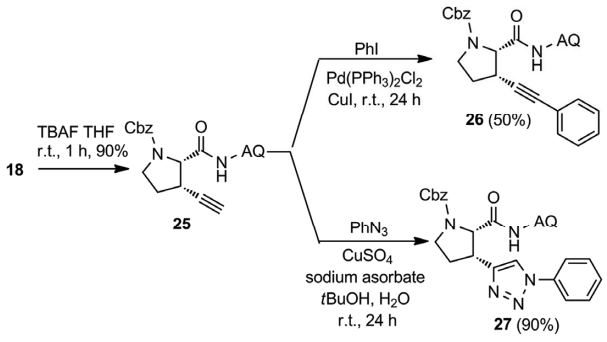


a) Isolated yield on a 0.2 mmol scale.

Scheme 2 Substrate scope of α-amino acids.

ladacycle intermediate (see **4**) with alkynyl bromide **1** and aryl halides in the functionalization step. The two diastereomeric products can be easily separated by silica gel chromatography. Alkylation of Trp **15** gave excellent diastereoselectivity. Alkylation of α-AAs with cyclic side chains e.g., Pro **17** and pipecolic acid **19** gave the β-alkynylated products in exclusive *cis* diastereoselectivity. Similar to the previously reported Pd-catalyzed AQ-directed C(sp^3)–H arylation and alkylation reactions of α-AAs, alkynylation of Ile **21** bearing a 2° β-C–H bond and γ-Me group selectively occurred at the γ-Me position to give product **22** in 52% yield. Val **23** also underwent the γ-Me alkynylation to give product **24** in excellent diastereoselectivity and monoselectivity.

The TIPS-protected alkynyl group installed on the amino acid substrates can be further transformed to other useful functional groups. For instance, the TIPS group of **18** was removed by the treatment of TBAF to give compound **25** (Scheme 3). The terminal alkynyl group can undergo Sonogashira cross-coupling with PhI to give product **26**. The alkynyl group can undergo Click cycloaddition with benzylazide to give triazole compound **27** under Cu-catalyzed condition.



Scheme 3 Further transformations of alkynylated product.

3 Conclusions

In summary, we have developed a readily applicable method to synthesize β-di-substituted α-amino acids carrying an acetylene group on the β position. Under the $Pd(OAc)_2$-catalyzed conditions, a broad range of aminoquinoline-coupled phthaloyl amino acids can be alkynylated with TIPS-protected acetylene bromide at the β methylene position in good yield and diastereoselectivity. The alkynyl-group of these α-amino acid products can serve as a convenient handle for further transformations.

Supporting information

The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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30 It should be noted that alkylation using other alkynyl halide coupling partners gave significantly lower yield.