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Palladium-Catalyzed Stereoretentive Olefination of Unactivated C(sp^3)−H Bonds with Vinyl Iodides at Room Temperature: Synthesis of β-Vinyl α-Amino Acids

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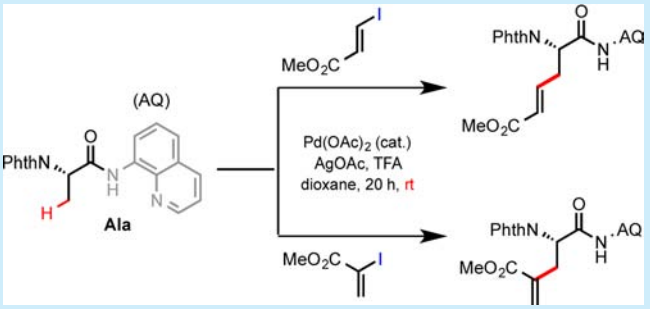
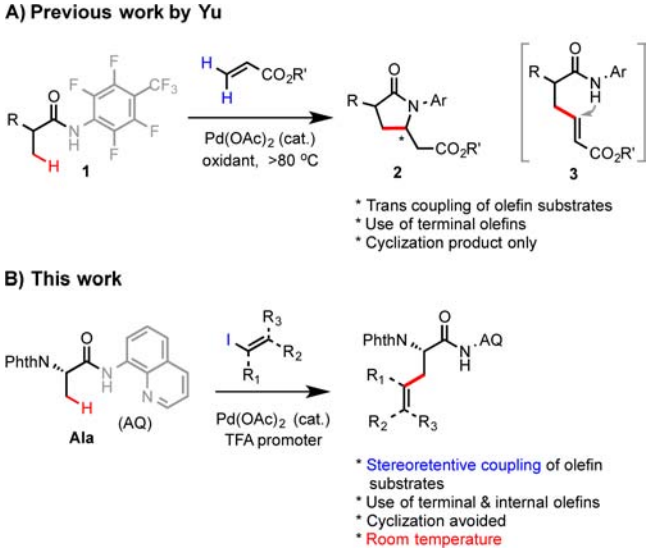
Supporting Information

ABSTRACT: A method is reported for palladium-catalyzed *N*-quinolyl carboxamide-directed olefination of the unactivated C(sp^3)−H bonds of phthaloyl alanine with a broad range of vinyl iodides at room temperature. This reaction represents the first example of the stereoretentive installation of multisubstituted terminal and internal olefins onto unactivated C(sp^3)−H bonds. These methods enable access to a wide range of challenging β-vinyl α-amino acid products in a streamlined and controllable fashion, beginning from simple precursors.



Over the past decade, metal-catalyzed C−H functionalization has emerged as a powerful strategy for the formation of C−C bonds in organic synthesis.[1] In contrast to C−H arylation[2] methods, methods for the functionalization of C−H bonds with nonaromatic coupling partners have been less developed.[3] In particular, the development of olefination reactions of unactivated C(sp^3)−H bonds, providing multisubstituted olefins, has lagged far behind.[4−12] Compared with aryl and alkyl groups, vinyl groups can readily undergo further transformations, providing unique flexibility and versatility in synthesis planning. However, unlike C−H arylation and alkylation reactions, the inherent reactivity and metal-binding properties of the olefin products can interfere with and even inhibit metal-catalyzed C−H functionalization processes.[5] In 2010, Yu reported Pd-catalyzed fluoroarylcarboxamide-directed functionalization of primary C(sp^3)−H bonds with terminal olefins bearing electron withdrawing substituents (e.g., acrylates) (Scheme 1A).[6,7] However, the expected *trans* C−H olefination products (e.g., **3**) cannot be isolated, as they immediately undergo intramolecular Michael addition to give diastereomeric N-aryl substituted γ-lactams in this reaction system. Unlike olefinated products, the resulting saturated lactams should not interfere with the reaction. Complementary to Yu's approach using terminal olefins under oxidative conditions, C−H olefination can also be achieved with vinyl halide reagents in the absence of external oxidants, analogous to the use of aryl halides in many metal-catalyzed C−H arylations.[9,10] Sporadic examples from Baran and our own laboratory have demonstrated the feasibility of such a Pd-catalyzed C(sp^3)−H olefination, albeit with limited scope.[11] Herein, we report an efficient method for the palladium-catalyzed *N*-quinolyl carboxamide-directed olefination of the β-C(sp^3)−H bonds of alanine with vinyl iodides at room temperature. For the first time, the stereoretentive installation of multisubstituted olefin precursors in either a *cis* or *trans* configuration onto unactivated C(sp^3)−H bonds has been achieved. This method enables the synthesis of a wide range of challenging β-vinyl α-amino acid products from simple precursors in a streamlined and controllable fashion.

Scheme 1. Pd-Catalyzed Olefination of Unactivated C(sp^3)−H Bonds of Alkyl Carboxamides



Our research in C−H functionalization chemistry stems from an interest in synthetic and biological studies of peptide compounds. Building upon earlier work by Daugulis[13] and

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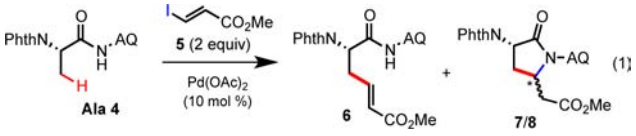
Corey,[14] we have developed methods to prepare complex β- and γ-substituted α-amino acids (AAs) through carboxamide-directed Pd-catalyzed C−H arylation, alkylation, amidation, and alkoxylation of simple α-AA precursors.[15−17] To further expand this synthetic strategy, we proceeded to investigate C−H olefination to provide α-AAs bearing various vinyl side groups, which are valuable and difficult-to-access building blocks for natural product and complex molecule synthesis.[18,19]

We commenced our study with the reaction of aminoquinoline (AQ) carboxamide-coupled phthaloyl alanine substrate **4** with methyl *trans*-3-iodoacrylate **5** (2 equiv) under the catalysis of $Pd(OAc)_2$ (eq 1, Table 1).[9] Reaction of **4** under our

Table 1. AQ-Directed β C(sp^3)−H Olefination of Ala with 5



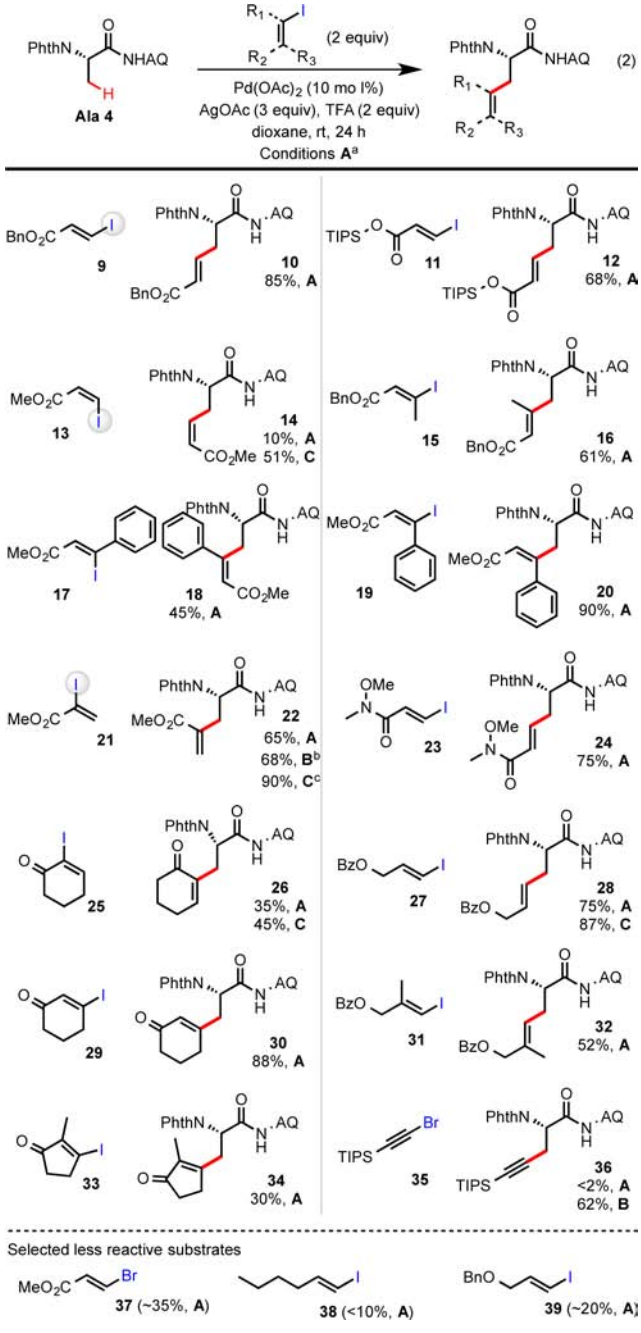
entry	reagents (equiv)	solvents	t (°C)/ time (h)	yield (%)[a] 6	7/8
1	AgOAc (3)	DCE	100/24	<2	<2
2	$KHCO_3$ (2), *o*PBA (0.2)	DCE	100/24	<2	<2
3	AgTFA (2.5)[b]	DCE	100/24	~5	~5
4	AgTFA (2.5)	DCE	65/24	~5	24
5	AgTFA (2.5)	TCE	rt/24	48	<2
6	AgTFA (2.5), TFA (2)	TCE	rt/24	19	<2
7	AgOAc (3), TFA (2)	dioxane	rt/24	71(68)[c]	<2
8	AgOAc (3), TFA (2)	THF	rt/24	62	<2
9	AgOAc (3), TFA (2)	dioxane/H_2O (9:1)	65/24	59	28
10	AgOAc (3), AcOH (3)	dioxane	rt/24	<2	<2
11	AgTFA (2)	TCE/H_2O (1:1)	rt/24	51	<2
12	AgTFA (2)	TCE/H_2O (1:1)	65/24	80	<2
13	AgTFA (2.5)[d]	TCE/H_2O (1:1)	65/24	53	<2

[a]Yields are based on ^{1}H NMR analysis on a 0.2 mmol scale, ambient atmosphere. [b]Complete consumption of **4**; complex product mixture formed. [c]Isolated yield. [d]10 mol % of $Pd(TFA)_2$ was used as catalyst.

previously developed conditions for the *ortho*- C(sp^2)−H olefination of benzylpicolinamides with vinyl iodides (*ortho*-phenylbenzoic acid (*o*PBA) additive and $KHCO_3$ base in 1,2-dichloroethane (DCE) at 100 °C) gave little conversion (entry 2).[10c] Interestingly, use of silver trifluoroacetate (AgTFA) considerably improved the conversion of Ala **4**, but gave a very complex mixture of products including γ-lactam Michael cyclization products **7** and **8** (entry 3). To our delight, the reaction of **4** at room temperature (rt) with AgTFA in 1,1,2,2-tetrachloroethane (TCE) gave a much cleaner transformation, forming only small amounts of cyclized side products (entry 5).[20] The combination of 3 equiv of AgOAc and 2 equiv of TFA in dioxane at rt gave further improved olefination results, affording a 68% isolated yield of **6** with excellent retention of chiral integrity at Cα (>98% ee, entry 7).[21] Moisture and air are well tolerated. A biphasic solvent system of TCE/H_2O (1:1) also gave good results (entries 11 and 12).

Under the room temperature conditions **A** with AgOAc/TFA in dioxane (entry 7, Table 1), we proceeded to evaluate the scope of vinyl iodides amenable to β-C(sp^3)−H olefination of Ala **4** (Scheme 2).[22] *trans*-3-Iodoacrylates bearing various ester or amide appendants (e.g., **9**, **11**, and **23**) gave the corresponding *trans* olefin products in good to excellent yields with exclusive *trans*-specificity. While less reactive than the *trans* isomer **5**, methyl *cis*-3-iodoacrylate **13** afforded *cis*-olefin **14** in 10% yield with exclusive *cis*-specificity. A 51% yield of **14** was obtained at 65 °C under biphasic conditions **C** (AgTFA, TCE/

Scheme 2. Scope of Vinyl Iodides[a]



[a](a) Conditions A: 0.2 mmol scale, isolated yields, ambient atmosphere. (b) Conditions B: AgTFA, TCE/H_2O, rt, 24 h; see entry 11 of Table 1. (c) Conditions C: same as B except at 65 °C; see entry 12 of Table 1.

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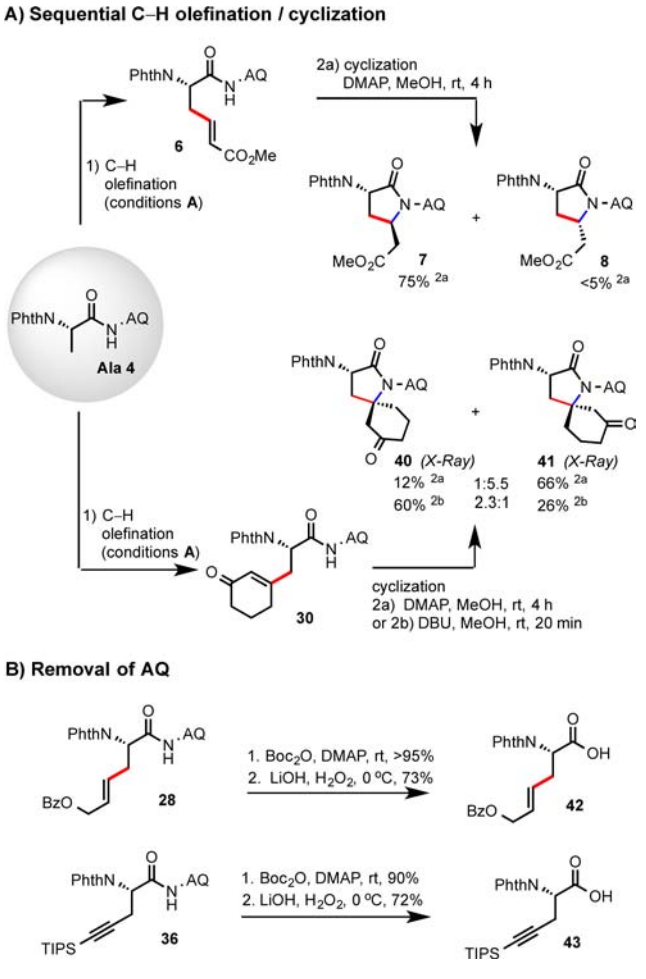
H_2O; see entry 12 of Table 1). Methyl 2-iodoacrylate **21** gave terminal olefin **22** in good yield and with complete stereoretention under room temperature conditions **A**. More densely substituted vinyl iodides, either cyclic or acyclic, e.g. **17**, **19**, **25**, **29**, and **33**, gave tri- and even tetrasubstituted olefins with complete stereoretention. It is worth noting that this level of stereochemical control is not seen in Fujiwara-type oxidative C−H olefination using terminal olefins, which forms the thermodynamically favored *trans* olefin product.[8] As exemplified by **5**, **13**, and **21**, the use of vinyl halide coupling partners in this reaction system allows us to regio- and stereospecifically construct complex olefins of any desired substitution pattern. In general, vinyl iodides bearing moderately electron-withdrawing substituents performed well under rt conditions **A**; vinyl bromides, e.g. methyl *trans*-3-bromoacrylate **37**, and electron-rich vinyl iodides, e.g. **38**, are considerably less reactive under the rt conditions.[23] For instance, while *trans*-3-iodoallyl benzoate **27** gave product **28** in 75% yield, the corresponding more electron-rich benzyl ether analogue **39** gave a much lower yield (~20%) at rt. C−H alkynylation of Ala **4** with TIPS-protected acetylene bromide **35** proceeded smoothly under the biphasic conditions **B** at rt to give product **36** in good yield.[24]

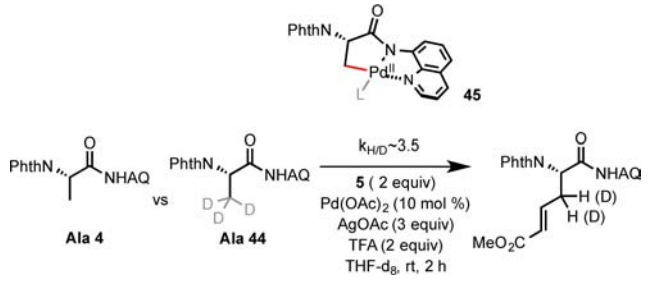
As shown in Scheme 3A, olefination product **6** can cleanly undergo intramolecular Michael addition to form γ-lactam **7** in excellent yield and diastereoselectivity (>15/1) upon treatment with 1.2 equiv of 4-dimethylaminopyridine (DMAP) in MeOH at rt for 4 h. Similarly, compound **30** cyclized following treatment with DMAP, providing spirolactams **40** and **41** as separable diastereomers in excellent yield and 1/5.5 diastereoselectivity. Interestingly, a reversed diastereoselectivity (2.3/1) was obtained following treatment of **30** with 1.2 equiv of 1,8-diazabicycloundec-7-ene (DBU) at rt. The AQ group of the olefinated or alkynylated products can be removed to give the corresponding carboxylic acid under mild conditions using our previously reported Boc activation and amide cleavage procedure (Scheme 3B).[15d]

The olefination reaction of Ala **4** likely starts with AQ-directed C−H palladation, forming a 5-membered palladacycle intermediate (see **50**, Scheme 4).[25] A primary KIE ($k_{H/D}$ ~3.5) was observed for the rt C−H olefination of Ala **4** with vinyl iodide **5**.[26]

Scheme 3. Further Transformations



Scheme 4. KIE Experiments



In summary, we have developed a new set of synthetic methods which provide β-olefinated α-amino acids via the palladium-catalyzed olefination of the β C(sp^3)−H bonds of aminoquinoline-coupled phthaloyl alanine. For the first time, a broad range of vinyl iodides bearing various substitution patterns can be incorporated in a stereoretentive fashion under mild conditions at room temperature. Notably, our protocol allows the isolation of olefinated products, enabling further useful transformations. A wide range of challenging β-olefinated α-amino acid products can be prepared from simple precursors in a streamlined and controllable fashion.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic analysis, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(20) In a recent study, we found that a TFA anion was necessary to achieve high reactivity in the Pd-catalyzed β-C−H arylation of Ala**4** with aryl iodides at rt (ref 15d).
(21) See Supporting Information for an improved preparation of enantiopure Ala **4**.
(22) Many other AQ-coupled carboxylic acid substrates, e.g. unsubstituted propanamide and O-Bn lactamide, gave a much lower C−H olefination yield (<10%) under the standard rt conditions **A**.
(23) Use of biphasic conditions **C** at an elevated temperature (110 °C) gave much improved olefination yields for the less reactive vinyl halides, and these results will be reported in a separate account. Overall, these C−H olefination reactions only form small amounts of undesired side products (<10%); unreacted Ala **4** and vinyl iodide can be recovered from most low-conversion reactions.
(24) Pd-catalyzed AQ-directed β-C(sp^3)−H alkynylation using **35** was first reported by Chatani; see: Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. Interestingly, these C−H alkynylation reactions were limited to methylene C−H bonds. In our own experiments, only a trace amount of β methyl alkynylation product **36** was formed under the original conditions.
(25) The functional role of the TFA anion is unclear at the moment. Control experiments indicate that TFA is a competent ligand for the C−H palladation step (entry 13 of Table 1).
(26) In comparison, a small secondary KIE (∼1.2) was observed for our recently reported TFA-promoted AQ-directed C(sp^3)−H arylation of Ala **4** with aryl iodides at rt (ref 15d). While a $Pd^{II/IV}$ mechanism could be operative for the functionalization of **45** with vinyl iodides, an alternative $Pd^{II/II}$ mechanism involving migratory insertion and β-halogen elimination cannot be completely ruled out.

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