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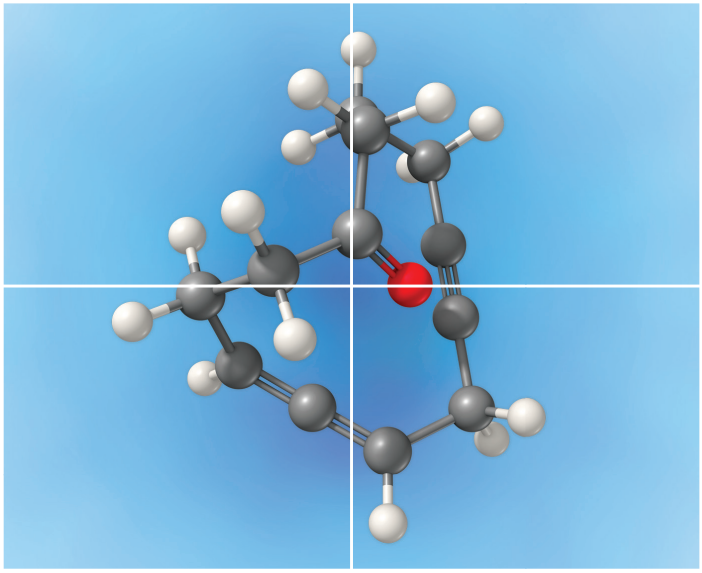

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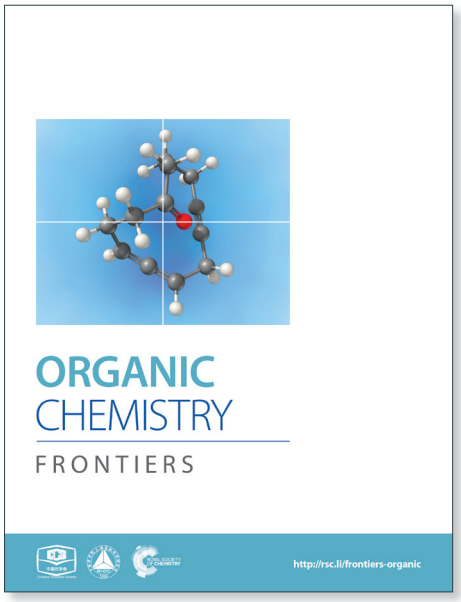

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Organic Chemistry Frontiers

Research Article

Palladium-Catalyzed Alkylation of Unactivated C(sp^3)–H Bonds with Primary Alkyl Iodides at Room Temperature: Facile Synthesis of β-Alkyl α-Amino Acids

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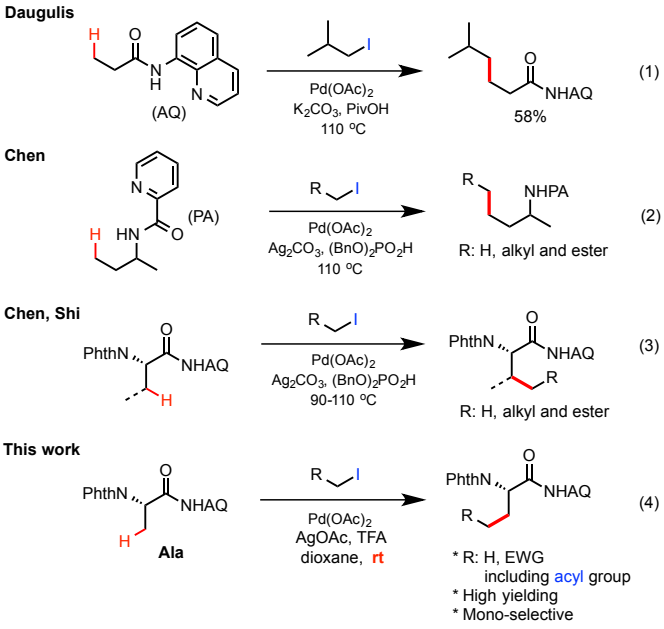
An efficient protocol for the synthesis of β-alkyl α-amino acids via palladium-catalyzed β-C(sp^3)–H alkylation of aminoquinoline-coupled phthaloyl alanine was developed. The new TFA-promoted reaction conditions provide excellent C–H alkylation reactivity with alkyl iodides bearing moderately electron-withdrawing groups at room temperature. A range of β-alkyl α-amino acid products, including some difficult to access by other means, can be quickly prepared from readily available primary alkyl iodide and alanine precursors.

Over the past decade, synthetic methodology for forming C–C bonds via palladium-catalyzed directing group-controlled functionalization of unactivated C(sp^3)–H bonds has been quickly advanced.[1] Despite the realization of various prototypical transformations, Pd-catalyzed C(sp^3)–H functionalization chemistry requires further development to become truly synthetically useful.[2] While C(sp^3)–H arylation chemistry has steadily matured, the development of C(sp^3)–H alkylation reactions is more challenging, paralleling the metal-catalyzed cross-coupling reactions of alkyl groups.[3] Compared with aryl coupling partners, the reactivity of alkyl coupling partners is strongly influenced by their sterics and electronics. The competing side reactions of alkyl coupling partners also often cause problems.

Among the choices of alkyl coupling precursors, alkyl halides are particularly attractive due to their high accessibility and versatility.[4-11] In 2010, Daugulis first reported that the primary β-C(sp^3)–H bonds of 8-aminoquinoline (AQ)-coupled propanamide could be alkylated with isobutyl iodide in moderate yield under palladium catalysis (eq 1, Scheme 1).[6b] In 2012, we discovered that picolinamide-coupled alkylamines can undergo Pd-catalyzed γ-C(sp^3)–H alkylation with primary alkyl halides with high efficiency in the presence of Ag_2CO_3 and dibenzylphosphate additive $(BnO)_2PO_2H$ (eq 2).[7b] Soon after, these phosphate-promoted reaction conditions were successfully applied by the Shi group[8] and



Scheme 1. Pd-catalyzed C(sp^3)–H alkylation with primary alkyl halides

us[7c] in the Pd-catalyzed methylene β-C(sp^3)–H alkylation of AQ-coupled amino acid substrates with primary alkyl halides (eq 3). However, despite these improvements, there are considerable limitations of these Pd-catalyzed AQ-directed C(sp^3)–H alkylation reactions, especially regarding the scope of alkyl halides. While simple primary alkyl halides bearing less interfering substituents such α-haloacetates worked well in previous reaction systems, many other alkyl halides carrying more transformable functional groups such as α-iodomethyl ketones (see **10** in Scheme 2) gave significantly lower yield. Furthermore, alkylation of the β methyl C–H bonds of substrates e.g. AQ-coupled phthaloyl alanine **1** with more reactive alkyl iodides such as MeI[7b, 7c] and α-haloacetates often formed undesired multi-alkylated side products. Herein, we report the development of an improved protocol for Pd-catalyzed β-C(sp^3)–H alkylation of aminoquinoline (AQ)-coupled phthaloyl alanine with a range of primary alkyl iodides bearing moderately

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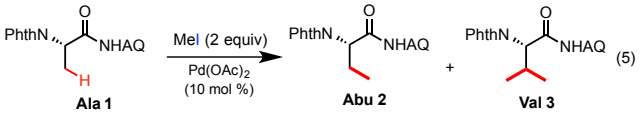
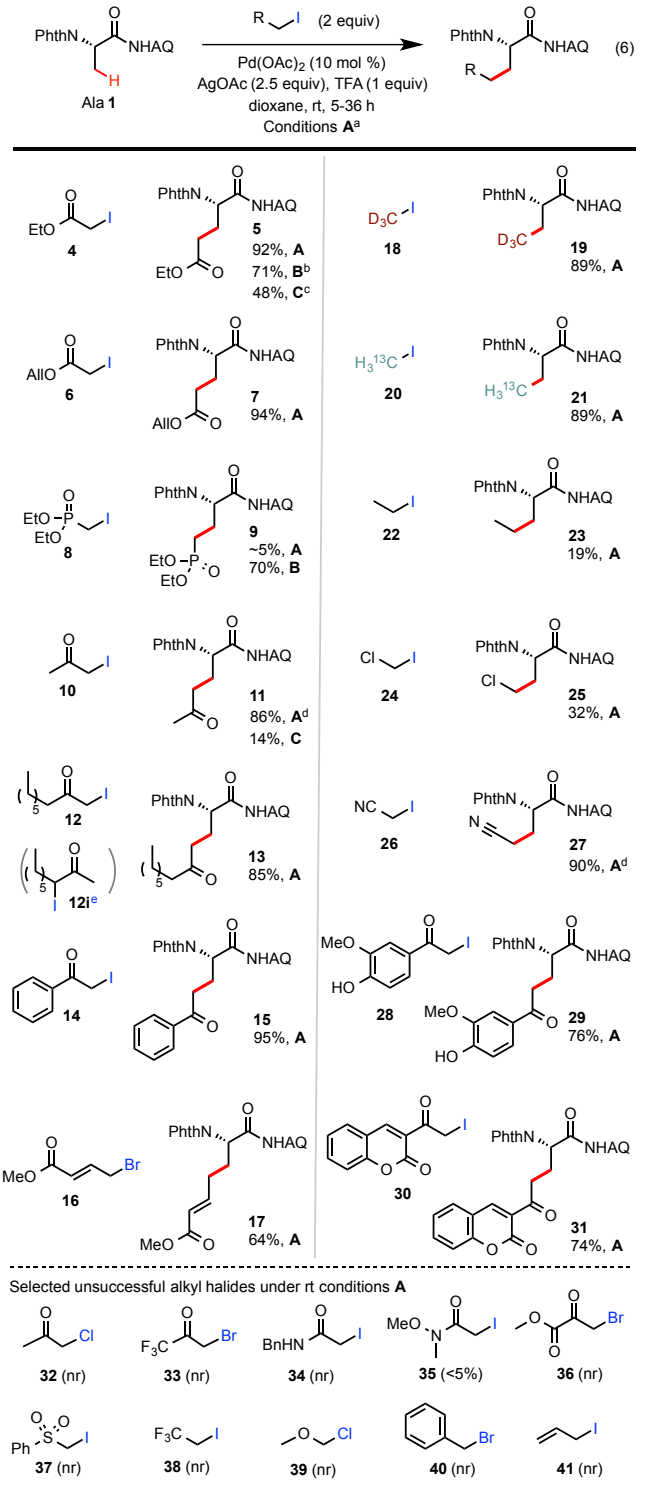
electron withdrawing groups at room temperature. Monoselective methyl C–H alkylation of phthaloyl alanine with readily available alkyl iodides offers a convenient method for the stereoselective synthesis of β-alkyl α-amino acids bearing novel and transformable side chains.



entry	reagents (equiv)	solvents	*t* (°C) / time (h)	yield (%)[a] 2	3
1	Ag_2CO_3 (2) $(BnO)_2PO_2H$ (0.2)[b]	*t*-AmylOH	110 / 24	5	92
2	Ag_2CO_3 (2) $(BnO)_2PO_2H$ (0.2)[c]	*t*-AmylOH	110 / 24	42	15
3	Ag_2CO_3 (2) $(BnO)_2PO_2H$ (0.2)	*t*-AmylOH	60 / 24	51	20
4	Ag_2CO_3 (2)	*t*-AmylOH	110 / 24	7	41
5	Ag_2CO_3 (2)	MeI	rt / 24	9	<2
6	Ag_2CO_3 (2)	dioxane	rt / 24	<2	<2
7	AgOAc (2.5)	dioxane	rt / 24	<2	<2
8	AgTFA (2)	dioxane	rt / 24	10	<2
9	Ag_2CO_3 (2), TFA (1)	dioxane	rt / 24	89	5
10	Ag_2CO_3 (2), TFA (2)	dioxane	rt / 24	69	3
11	Ag_2CO_3 (2), TFA (0.5)	dioxane	rt / 24	86	9
12	Ag_2CO_3 (2), AcOH (1)	dioxane	rt / 24	8	7
13	Ag_2CO_3 (2), TfOH (1)	dioxane	rt / 24	51	10
14	AgOAc (2.5), TFA (1)	dioxane	rt / 24	91(89)[d,e]	5

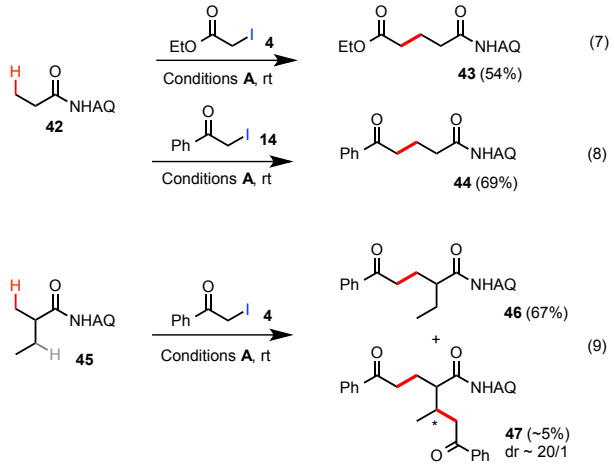
Table 1. AQ-directed β-C(sp^3)–H alkylation of Ala 1 with MeI. a) Yields are based on ^{1}H-NMR analysis on a 0.2 mmol scale, ambient atmosphere. b) 3 equiv of MeI was used. c) 1 equiv of MeI was used. d) Isolated yield on 3 mmol scale (1 gram of Ala 1). e) Product **2** was obtained in 96% ee based on chiral HPLC analysis.

In a previous report, we discovered that AQ-coupled phthaloyl alanine **1** can readily undergo Pd-catalyzed C(sp^3)–H alkylation with MeI at the β-methyl position in the presence of Ag_2CO_3 and $(BnO)_2PO_2H$ at 110 °C (eq 5).[7c] However, the reaction of Ala **1** can not be stopped at the mono-alkylation stage and gave β-dimethylated Val **3** as the major product (entry 1, Table 1). A considerable amount of Val **3** was formed with 1 equiv of MeI at 110 °C or 2 equiv of MeI at 60 °C (entries 2, 3). Interestingly, the reaction can proceed in MeI solvent at rt to give Abu **2** in low yield but high selectivity (entry 5). Recently, we discovered that the combination of silver cation and trifluoroacetate (TFA) served as excellent promoters for Pd-catalyzed β-C(sp^3)–H functionalization of Ala **1** with aryl iodides and vinyl iodides at rt.[12] While the mechanism of the TFA-promoting effect is still unclear, we were delighted to find that the combined use of Ag_2CO_3 or AgOAc and TFA significantly improved the alkylation reactivity of Ala **1** with MeI at rt (entries 6-11). Importantly, mono-alkylated product Abu **2** was obtained with excellent selectivity. Carboxylic acids such AcOH provided little improvement in terms of reactivity or selectivity (entry 12). Finally, the reaction of Ala **1** with 2 equiv of MeI, 2.5 equiv of AgOAc and 1 equiv of TFA in dioxane at rt for 24 h gave Abu **2** in 89% isolated yield at a 1 gram scale (entry 14).

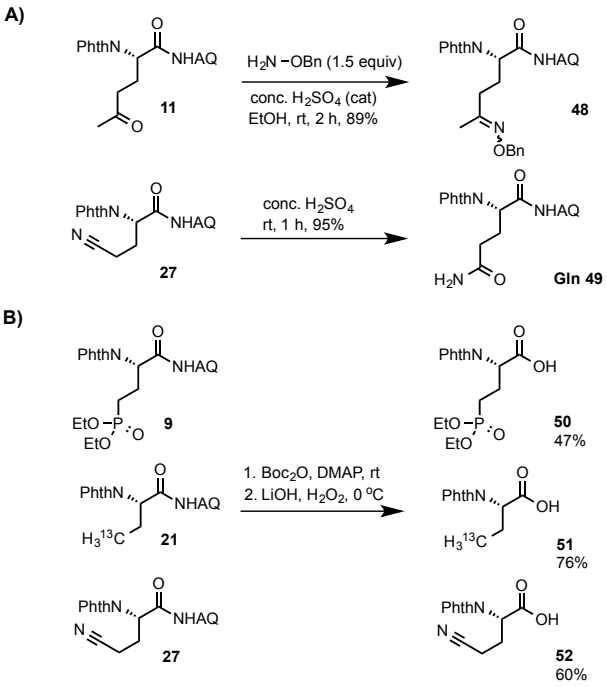


Scheme 2. Scope of alkyl iodides. a) Isolated yields on a 0.2 mmol scale under general conditions A (see entry 14 of Table 1). b) Conditions B: same as A except at 70 °C. c) Conditions C: Ag_2CO_3, $(BnO)_2PO_2H$, *t*-AmylOH, 110 °C, 24 h (see entry 1 of Table 1). d) Isolated yields on a 3 mmol scale (1 gram of Ala 1). e) A 1:1.6 mixture of **12** and **12i** prepared from the methyl ketone precursor was used as starting material; no alkylation product with 12i was formed under the conditions **A**.

Next, we proceeded to evaluate the scope of primary alkyl iodides amenable to β-C–H alkylation of Ala **1** under the general rt reaction conditions **A** (Scheme 2). α-Iodoacetates bearing various ester appendants gave the corresponding glutamate products in excellent yields (>90%) and monoselectivity. The allyl group of Glu **7** was completely conserved. In comparison, the reaction of Ala **1** with ethyl iodoacetate **4** under our previous $(BnO)_2PO_2H$-promoted conditions at 110 °C (conditions **C**) gave Glu **5** in <50% yield along with other unidentified side products. In contrast to α-iodoacetates, α-iodoacetamide **34** show little reactivity probably due to its lower electrophilicity. In addition to α-iodoacetates, we were very pleased to find that reactions of α-iodomethyl ketones e.g. **10**, **12**, **14**, **28**, and **30** proceeded cleanly to give the corresponding δ-ketocarboxamide products in good to excellent yields. It is worth noting that the reactions of these α-iodomethyl ketones under our previous conditions **C** at 110 °C gave only small amount of desired products (see **11**) due to the competing esterification side reactions caused by their high electrophilicity. It also should be noted that secondary alkyl iodide **12i**, a regioisomer of **12**, was completely unreactive under the rt conditions **A**.[13] Compared with MeI, the reactions of Ala **1** with sterically bulkier alkyl iodides such as EtI gave much lower yield at rt (see **23**). Iodoacetonitrile **26** worked very well to give nitrile product **27** in excellent yield. Overall, sterically unhindered primary alkyl iodides bearing moderately electron-withdrawing substituents performed well under the standard rt conditions.[14]

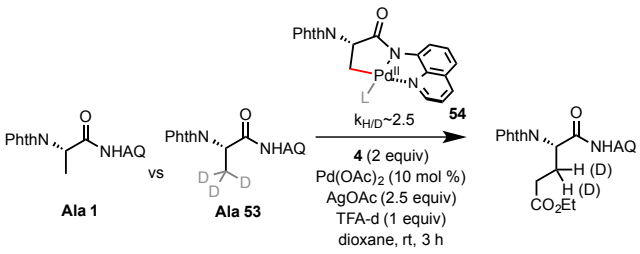


Unsubstituted propanamide **42** was less reactive than Ala **1** under the standard rt C–H alkylation conditions. Alkylation of **42** with α-iodoacetate **4** gave product **43** in 54% yield along with 40% unreacted **42** (eq 7). Alkylation of **42** with α-iodomethylphenylketone **14** proceeded in higher conversion and gave compound **44** in 69% yield (eq 8). As shown in eq 9, compound **45** was selectively alkylated at the β-methyl position to give **46** in 67% yield along with trace amount of dialkylated side product **47**. While the substrate scope and reactivity still need further improvement, these Pd-catalyzed β-C(sp^3)–H alkylation reactions of easily accessible carboxamides with α-iodoacetates or ketones at rt could offer an attractive strategy to construct 5-ketoacid and 1,5-diacid scaffolds, privileged structural motifs in organic synthesis, in an unprecedented fashion.[15]



Scheme 3. Further transformations

As shown in Scheme 3A, compound **11** bearing a ketone group underwent efficient addition reaction with benzyloxyamine to form oxime product **48** in excellent yield at rt.[16] The nitrile group of compound **27** can be cleanly hydrolyzed with conc. H_2SO_4 to give glutamine product **49** at rt. The AQ group of compounds **9**, **21** and **27** can be readily removed to give the corresponding β-alkyl α-amino acids bearing phosphonate,[17] ^{13}C-labeled methyl,[18] and nitrile groups respectively under mild conditions using our previously reported Boc activation and amide cleavage procedure (Scheme 3B).[12a]



Scheme 4. KIE experiments

The alkylation reaction of Ala **1** likely begins with AQ-directed C–H palladation, forming a 5-membered palladacycle intermediate (see **54**, Scheme 4). A primary KIE ($k_{H/D}$ ~2.5 based on parallel experiments) was observed for the C–H alkylation of Ala **1** with α-iodoacetate **4** at rt, suggesting C–H palladation of **1** as the rate-limiting step.[19]

In summary, we have developed an improved protocol for the synthesis of β-alkyl α-amino acids via palladium-catalyzed β-C(sp^3)–H alkylation of aminoquinoline-coupled phthaloyl alanine. Compared with previous methods, TFA-promoted conditions provide excellent reactivity with alkyl iodides bearing moderately electron-withdrawing groups at room temperature. Critically, mild reaction conditions prevent competing esterification reactions of alkyl iodide electrophiles and di-alkylation, providing higher coupling yield and monoselectivity. A range of β-alkyl α-amino acid products, including some difficult to access using the previous conditions or other methods, can be quickly prepared from readily available primary alkyl iodides and alanine precursors.

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‡ We gratefully thank the Pennsylvania State University and NSF (CAREER CHE-1055795) for financial support of this work.

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13 I_2-mediated iodination of the corresponding methylketone precursor provided an inseparable mixture of **12** and **12i**, see Supporting Information for details. No secondary alkyl halides have been successfully applied in a reported Pd-catalyzed C(sp^3)–H alkylation system.

14 Selected unsuccessful alkyl halides in this rt reaction system were listed on the bottom of Scheme 2.

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