Amino Acids

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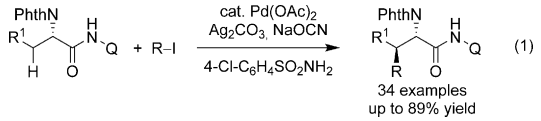
Sulfonamide-Promoted Palladium(II)-Catalyzed Alkylation of Unactivated Methylene C(sp^3)–H Bonds with Alkyl Iodides**

*Kai Chen and Bing-Feng Shi**

Abstract: *The alkylation of unactivated β-methylene C(sp^3)–H bonds of α-amino acid substrates with a broad range of alkyl iodides using $Pd(OAc)_2$ as the catalyst is described. The addition of NaOCN and 4-Cl-$C_6H_4SO_2NH_2$ was found to be crucial for the success of this transformation. The reaction is compatible with a diverse array of functional groups and proceeds with high diastereoselectivity. Furthermore, various β,β-hetero-dialkyl- and β-alkyl-β-aryl-α-amino acids were prepared by sequential C(sp^3)–H functionalization of an alanine-derived substrate, thus providing a versatile strategy for the stereoselective synthesis of unnatural β-disubstituted α-amino acids.*

Over the past several decades, transition-metal-catalyzed C–H alkylation with alkyl halides has emerged as a versatile and highly efficient tool for the synthesis of C–C bonds.[1,2] Compared to the achievements in the area of C(sp^2)–H alkylation,[3,4] catalytic alkylation of unactivated C(sp^3)–H bonds, especially methylene C(sp^3)–H bonds, remains largely undeveloped.[5–10] In 2013, the group of Chen and our group independently reported the only two examples of $(BnO)_2PO_2H$-promoted, 8-aminoquinoline-directed[11,12] alkylation of β-methylene C(sp^3)–H bonds with α-haloacetates and methyl iodide.[9] However, the scope with respect to the coupling partners was limited to these two classes of specific reagents, both of which do not contain β-hydrogen atoms. Direct alkylation proved to be more challenging if the alkyl groups containined β-hydrogen atoms.[2] These limitations encouraged us to develop a protocol for efficient alkylation of unactivated methylene C(sp^3)–H bonds, a protocol which would tolerate a broad range of simple alkyl iodides. In particular, we were drawn to the idea of using this reaction for the stereoselective synthesis of various β-alkylated α-amino acids. The results of this investigation are described herein, and preliminary investigations reveal that the presence of 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN are crucial for the reaction to proceed efficiently [Eq. (1); Phth = phthaloyl, Q = 8-quinolinyl].



(1)

Nonproteinogenic β-alkyl-α-amino acids are considered to be conformationally constrained analogues of α-amino acids. Their incorporation into peptides restrict conformational mobility and increase rigidity, thus leading to enhanced receptor selectivity and metabolic stability.[13] Consequently, there is tremendous interest in the synthesis of nonproteinogenic α-amino acids.[14] As part of our efforts to synthesize biologically important organic molecules by direct C(sp^3)–H functionalization,[15] we envisioned that β-alkyl-α-amino acids could be accessed by the alkylation of the β-methylene C–H bonds of simple α-amino acid derivatives.[16] However, this reaction was rather challenging because of the low reactivity of methylene C(sp^3)–H bonds and the tendency of metal alkyl intermediates to undergo side reactions. Recently, several elegant works have shown that external ligands, such as simple carboxylic acids,[7a,17] amino acids,[18] pyridines, and quinolines,[16a,19] could enhance the reactivity of C(sp^3)–H functionalization reactions. Based on these precedents, we hypothesized that the judicious choice of a ligand or additive might play an important role in tuning the reactivity.

To test this hypothesis, we initiated our investigation with the alkylation of the L-norvaline (Nva) derivative **1a** with *n*-butyliodide (**3a**) as the model system. After extensive optimization, we found that the use of $Pd(OAc)_2$, NaOCN, and Ag_2CO_3 as the halide scavenger in 1,4-dioxane afforded the desired product **4a** in a reasonable yield.[20] As expected, several carboxylic acids, such as PivOH (**L1**), $AdCO_2H$ (**L2**), and Boc-Gly-OH (**L3**) did lead to higher yields, however, the overall efficiency of the reaction remained unsatisfactory (Table 1, entries 1–3). To improve the yield further, we sought to identify a new class of ligands to facilitate this C–H alkylation reaction. Sulfonamides are recognized as versatile ligands in various metal-catalyzed reactions. It has been reported that neutral sulfonamides could serve as labile ligands because of the electron-withdrawing character of the sulfonyl group.[21] Therefore, we reasoned that sulfonamides could reversibly coordinate with palladium to tune reactivity. Consistent with this hypothesis, we found that the addition of 0.3 equivalents of the commercially available sulfonamides **L4** and **L5** to the reaction mixture increased the yield of **4a** to 65 and 72%, respectively (entries 4 and 5). Further examination of different sulfonamides revealed that 4-Cl-

[*] K. Chen, Prof. Dr. B.-F. Shi
Department of Chemistry, Zhejiang University
Hangzhou 310027 (China)
E-mail: bfshi@zju.edu.cn

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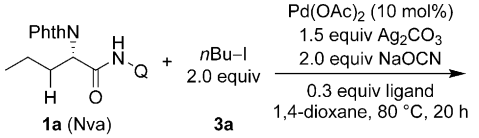
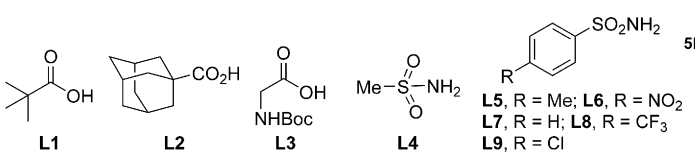
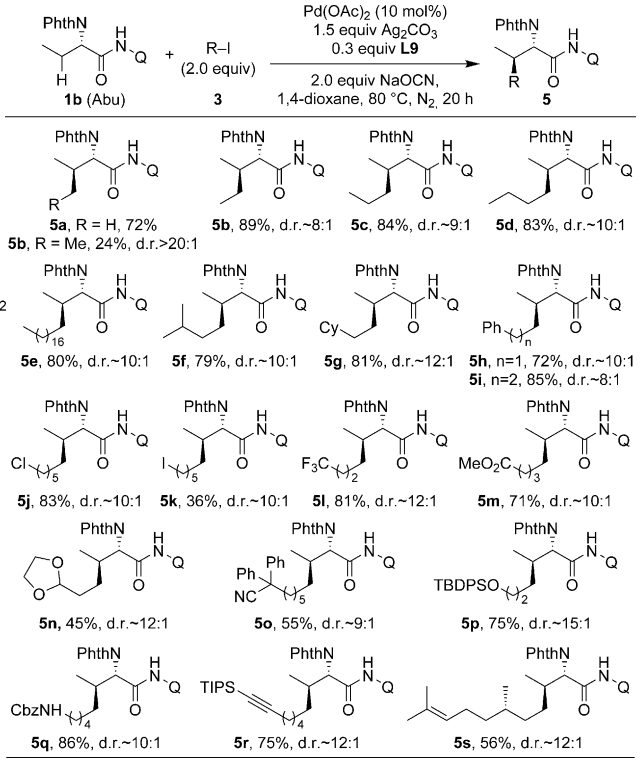
Table 1: Optimization of reaction conditions.[a]



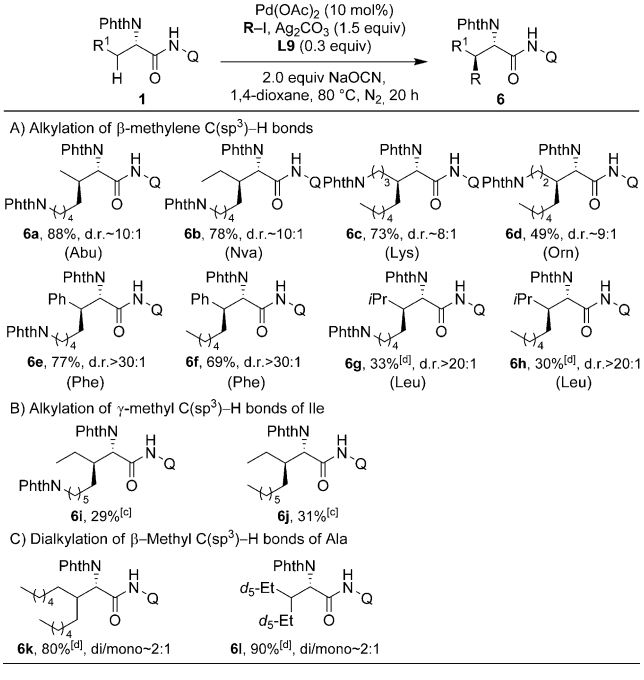


Entry	Ligand	Yield [%][b]	d.r.[c]	**1a** Recovered [%][b]
1	**L1**	59	12:1	25
2	**L2**	63	13:1	18
3	**L3**	61	8:1	24
4	**L4**	65	9:1	22
5	**L5**	72	10:1	15
6	**L6**	61	10:1	22
7	**L7**	71	10:1	13
8	**L8**	72	10:1	12
9	**L9**	76 (75)[d]	10:1	8
10[e]	–	13	9:1	64

[a] Reaction conditions: **1a** (0.15 mmol), **3a** (2.0 equiv), $Pd(OAc)_2$ (0.1 equiv), Ag_2CO_3 (1.5 equiv), NaOCN (2.0 equiv), **L** (0.3 equiv) in 1,4-dioxane (1.5 mL), 80 °C, 20 h. [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR spectroscopy. [d] Yield of isolated product given within parentheses. [e] Conditions reported in Ref. [9b] were used. Boc = *tert*-butoxycarbonyl.



Scheme 1. Alkyl iodide scope. [a] Yield of the isolated product. [b] The diastereomeric ratio was estimated by ^{1}H NMR spectroscopy. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 2. α-Amino acid substrate scope. [a] Yield of the isolated product. [b] The diastereomeric ratio was estimated by ^{1}H NMR spectroscopy. [c] 110 °C. [d] R-I (3.0 equiv) and Ag_2CO_3 (2.0 equiv) were used.

$C_6H_4SO_2NH_2$ (**L9**) was the most effective, thus affording **4a** in 75% yield upon isolation (entry 9, d.r. ≈ 10:1). Furthermore, we compared our optimized reaction with the $(BnO)_2PO_2H$-promoted alkylation process,[9b] and this protocol showed superior reactivity (entry 10).

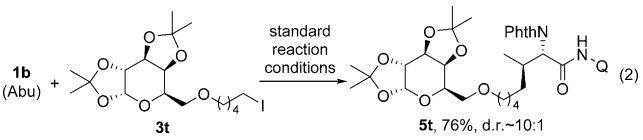
Having optimized the reaction conditions, we next sought to establish the scope of alkyl iodides which were compatible in the reaction. Coupling partners bearing β-hydrogen atoms proceeded smoothly under the optimized reaction conditions (Scheme 1). Generally, linear and branched primary alkyl iodides afforded the desired alkylated products in good yields (**5a–i**). As previously reported, MeI was a superior alkylating reagent, thus giving the β-methylated product **5a** in 72% yield along with β,γ-dimethylated product **5b** in 24% yield. Furthermore, a wide range of functional groups, including chloro (**5j**), iodo (**5k**), trifuoromethyl (**5l**), methoxycarbonyl (**5m**), 1,3-dioxolan-2-yl (**5n**), cyano (**5o**), silyl (**5p**), Cbz-protected amino (**5q**), alkynyl (**5r**), and alkenyl (**5s**) groups were compatible with this protocol. The reduced yields in the cases of **5n**, **5o**, and **5s** may be due to competitive coordination of the palladium catalyst to the Lewis basic functional groups. Notably, a TIPS-protected terminal alkyne remained intact during the reaction (**5r**). Importantly, the alkylated products were consistently obtained with good diastereoselectivity (> 8:1).

With the alkyl iodide coupling partner scope established, we then probed the substrate scope of α-amino acid derivatives (Scheme 2A). Gratifyingly, 2-amino-butyric acid (Abu; **1b**), norvaline (Nva; **1a**), lysine (Lys; **1c**), ornithine

(Orn; **1d**), and phenylalanine (Phe; **1e**) derivatives were all compatible with the alkylation protocol, thus generating the alkylated products **6a–f** in moderate to good yields. Attempts to alkylate a substrate derived from leucine (Leu; **1f**) were lower-yielding (**6g** and **6h**) because of the steric hindrance of the amino acid side chain.

As shown in Scheme 2B, alkylation of the γ-methyl C(sp^3)–H bond of isoleucine (Ile; **1g**) also took place in approximately 30% yield (**6i** and **6j**). When an alanine derivative (Ala; **1h**) was employed as a substrate, homodialkylated products were obtained in good yields (**6k** and **6l**; Scheme 2C). It is worth noting that the alkylation of **1h** with [D_5]EtI gave the deuterated ethylation products in 90% total yield (di/mono = 2:1), thus providing efficient access to isotope-labeled amino acids.

The synthetic utility of this alkylation protocol was further demonstrated in the coupling of **1b** with the sugar-containing alkyl iodide **3t** [Eq. (2)]. The corresponding product **5t** was obtained in 76% yield (d.r. ≈ 10:1). This example showcases

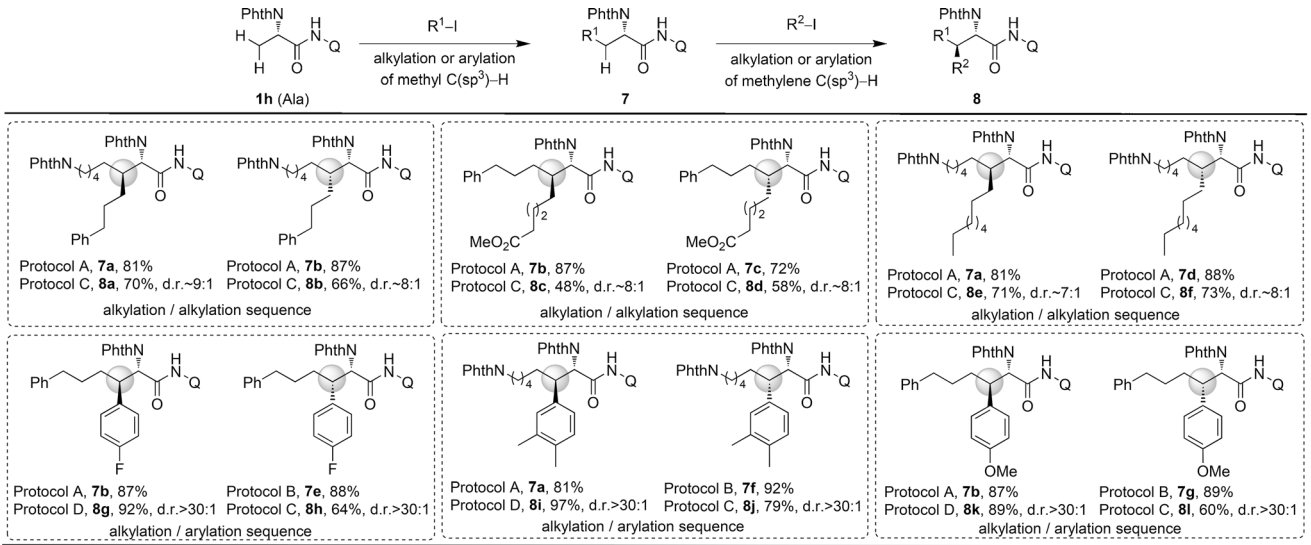


the potential of this reaction for applications in the late-stage modification of complex molecules.

Recently, our group developed palladium-catalyzed monoalkylation and monoarylation reactions for the selective functionalization of methyl C(sp^3)–H bonds.[9b] It was thus envisioned that these transformations[7a,16c] could be used in concert with the current protocol to synthesize various β-branched α-amino acids by sequential C(sp^3)–H functionalization of **1h** (Scheme 3). In this way, a number of β,β-heterodialkylated α-amino acids could be prepared (**8a–f**). Additionally, one of the two alkylation steps could be replaced with an arylation step. Gratifyingly, both alkylation/arylation and arylation/alkylation sequences could be achieved, thus providing a variety of β-alkyl-β-aryl α-amino acids in good yields (**8g–8l**). By simply varying the order in which the two different coupling partners were introduced, both diastereomers of the β,β-disubstituted α-amino acid products could be obtained (**8a** and **8b**, **8c** and **8d**, **8e** and **8f**, **8g** and **8h**, **8i** and **8j**, **8k** and **8l**). These sequential functionalization reactions all proceeded with high diastereoselectivity and in good to excellent yields, thus providing a versatile tool for the stereoselective synthesis of β,β-disubstituted α-amino acids from Ala.

To gain further insight into the reaction mechanism and the origin of the enhanced reactivity under the optimized alkylation conditions, we attempted to isolate and characterize possible palladium-containing intermediates (see Figure S1 in the Supporting Information).[20] The phenylalanine derivative **1e** reacted with 1 equivalent $Pd(OAc)_2$ in MeCN at 35 °C, thus affording the palladium complex **9** in 98% yield. The structure of **9** was confirmed by NMR analysis. The compound **9** was subsequently converted into the corresponding palladacycle **10** by heating the complex in a mixture of DCE/MeCN at 50 °C for 4 hours. The structure of **10** was confirmed by single-crystal X-ray diffraction.[22] Attempts to isolate and characterize a palladium species contianing 4-Cl-$C_6H_4SO_2NH_2$ were unsuccessful. Indeed, Liu and co-workers has previously reported that when a different palladacycle dimer containing two bridging trifluoroacetate anions was reacted with 4-Cl-$C_6H_4SO_2NH_2$, the putative sulfonamide-coordinated palladacycle could not be isolated, likely because of the weak coordination of neutral sulfonamide to palladium.[23]

To elucidate the importance of NaOCN and 4-Cl-$C_6H_4SO_2NH_2$ and probe the catalytic competence of **10**, we conducted a series of stoichiometric and catalytic experiments (see Figure S2 in the Supporting Information).[20] Reaction of



Scheme 3. Synthesis of unnatural α-amino acids by palladium-catalyzed sequential C(sp^3)–H functionalization. Protocol A: Methyl C(sp^3)–H alkylation. Protocol B: Methyl C(sp^3)–H arylation. Protocol C: Methylene C(sp^3)–H alkylation. Protocol D: Methylene C(sp^3)–H arylation. See the Supporting Information for detailed reaction conditions.

10 with *n*-hexyl iodide in the absence of NaOCN or 4-Cl-$C_6H_4SO_2NH_2$ was sluggish and gave the desired product **6 f** in diminished yield. In contrast, alkylation of **10** with *n*-hexyl iodide in the presence of 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN gave **6 f** in 40 % yield (see Figure S2A), thus indicating that both 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN are crucial for the alkylation step. We also found that **10** was catalytically competent for the alkylation reaction in the presence of 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN (see Figure S2B). The moderate yields in both the stoichiometric and catalytic experiments is likely due to the fact that the acetonitrile-coordinated palladacycle is less reactive than the intermediate generated in situ under the optimized reaction conditions.

Considering that the cyclopalladation can occur at mild conditions in the absence of 4-Cl-$C_6H_4SO_2NH_2$, we hypothesize that the lability of sulfonamide as a ligand may contribute to the enhanced reactivity in two other ways: 1) dissociation to provide a vacant coordination site for oxidative addition of the alkyl halide to the Pd^{II} center to generate a new Pd^{IV} species[10a] and 2) subsequent coordination with the Pd^{IV} center to facilitate C(alkyl)–C(alkyl) reductive elimination.[17,24]

In summary, we have developed a palladium(II)-catalyzed alkylation of unactivated β-methylene C(sp^3)–H bonds of α-amino acid substrates using the 8-aminoquinoline (Q) auxiliary. The reaction tolerates a broad range of alkyl iodides and proceeds with high diastereoselectivity. The synthetic utility of this alkylation reaction was demonstrated in the stereoselective synthesis of various β,β-disubstituted α-amino acids through a sequential C(sp^3)–H functionalization approach. A new palladacycle intermediate has been isolated and characterized by single-crystal X-ray diffraction. A series of stoichiometric and catalytic experiments demonstrated that the presence of 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN are crucial for the reaction to proceed efficiently.

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