Silylation

Deutsche Ausgabe: DOI: 10.1002/ange.201607766
Internationale Ausgabe: DOI: 10.1002/anie.201607766

Divergent and Stereoselective Synthesis of β-Silyl-α-Amino Acids through Palladium-Catalyzed Intermolecular Silylation of Unactivated Primary and Secondary C–H Bonds

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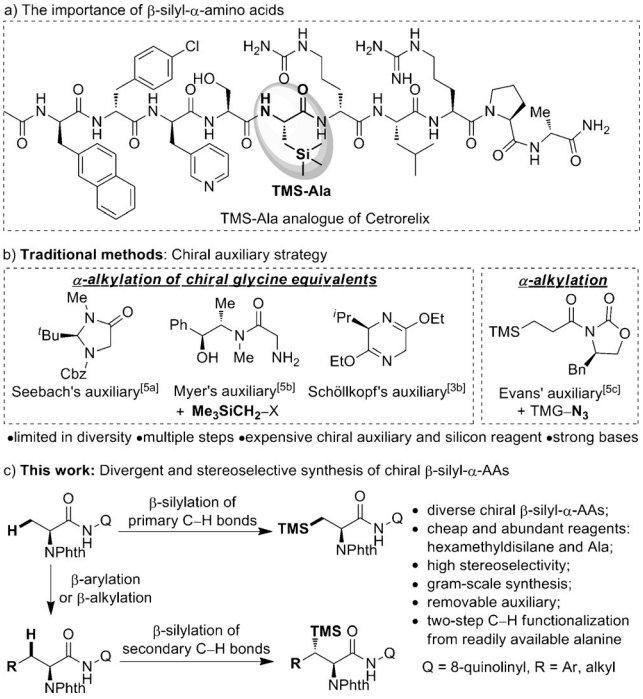
Abstract: *A general and practical Pd^{II}-catalyzed intermolecular silylation of primary and secondary C–H bonds of α-amino acids and simple aliphatic acids is reported. This method provides divergent and stereoselective access to a variety of optical pure β-silyl-α-amino acids, which are useful for genetic technologies and proteomics. It can also be readily performed on a gram scale and the auxiliary can be easily removed with retention of configuration. The synthetic importance of this method is further demonstrated by the late-stage functionalization of biological small molecules, such as (−)-santonin and β-cholic acid. Moreover, several key palladacycles were successfully isolated and characterized to elucidate the mechanism of this β–C(sp^3)-H silylation process.*

Amino acids, specifically α-amino acids (α-AAs), are the building blocks of bioactive peptides, peptidomimetics, and proteins.[1] The incorporation of silicon into α-amino acids can have a dramatic influence on the stability, solubility, lipophilicity, and pharmacokinetic properties.[2] For example, β-trimethylsilyl alanine (TMS-Ala) plays an important role in peptidomimetic strategies as a bioisostere for phenylalanine.[3] Cetrorelix is a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity. Its silicon analogue, in which the tyrosine in position 5 is replaced with TMS-Ala, was found to lower both testosterone and luteinizing hormone levels longer than the carbon analogue (Scheme 1 a).[3b] Since the first preparation of racemic β-silyl-α-AAs by Birkofer and Ritter through classical α-alkylation of a glycine anion equivalent,[4] the exploration of efficient methods for the chemical synthesis of chiral β-silyl-α-AAs has received much attention.[5] Asymmetric α-alkylation of chiral glycine equivalents and amination of β-silyl propionic acid derivatives induced by chiral auxiliaries have been investigated (Scheme 1 b).[5] A series of chiral auxiliaries, such as Seebach's auxiliary,[5a] Myer's auxiliary,[5b] Schöllkopf's auxiliary[3b] and Evans' auxiliary,[5c] have been employed for this purpose. Although these elegant methods have been successfully applied in the synthesis of certain β-silyl-α-AAs, there are still some limitations, such as narrow substrate scope with limited diversity, the requirement for multiple steps, the use of expensive chiral auxiliaries and silicon reagents, and harsh reaction conditions with strong bases. Therefore, new methods to prepare chiral β-silyl-α-AAs that are efficient, practical, and divergent are in high demand.



Scheme 1. The importance of β-silyl-α-amino acids and their asymmetric synthesis.

Recently, transition-metal-catalyzed C–H silylation has emerged as a promising strategy for broadening the diversity of silicon-containing compounds.[6] However, catalytic silylation of aliphatic C(sp^3)–H bonds is rather rare, mostly due to the fact that bulky silyl groups are reluctant to transfer to catalytic metal centers.[7–11] So far, most of the established methods for C(sp^3)–H silylation have been limited to intramolecular examples [8] or those involving activated C(sp^3)–H bonds.[9,10] The intermolecular silylation of unactivated C(sp^3)–H bonds is even more challenging.[10a,11] Ir-[10a] and Ru-catalyzed[11a] silylation of unactivated primary C–H bonds assisted by a nonremovable pyridine auxiliary has been reported. The pioneering work of Kanai and co-workers demonstrated that Pd-catalyzed silylation of purely aliphatic C–H bonds can be achieved with the assistance of bidentate

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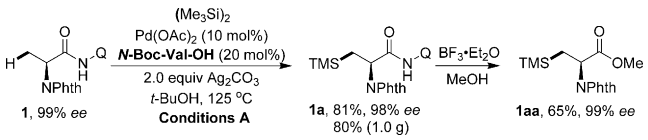
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607766.

auxiliary. However, the reaction proceeded with low efficiency (17–39% yield) and narrow scope.[11b] Herein, we report a Pd-catalyzed stereoselective synthesis of chiral β-silyl-α-AAs through intermolecular silylation of unactivated primary and secondary C–H bonds with the assistance of an 8-aminoquinoline (AQ) auxiliary (Scheme 1b).[12,13] This method enables the divergent and gram-scale synthesis of various chiral β-silyl-α-AAs with excellent diastereoselectivity and complete retention of configuration. The late-stage silylation of natural products such as (−)-santonin and β-cholic acid further showcases the importance of this method.

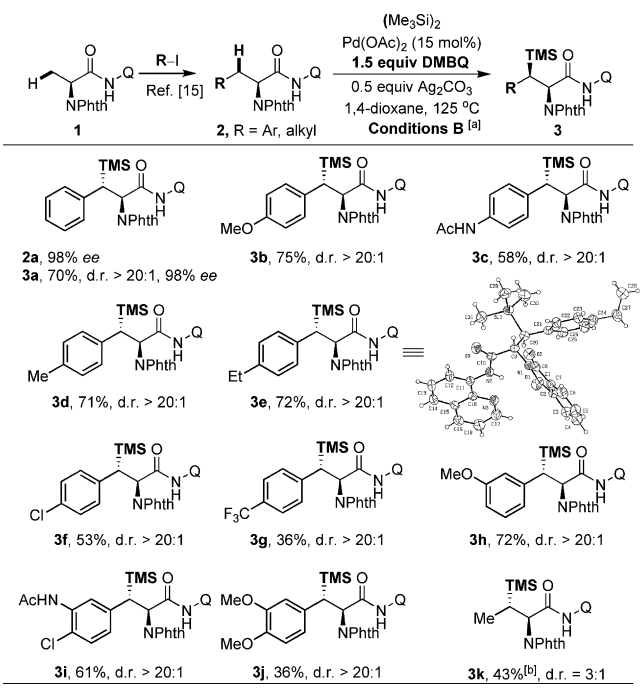
Given the applicability of chiral TMS-Ala, we began this study by examining the feasibility of Pd-catalyzed silylation of alanine derivative **1**, which bears an AQ auxiliary. This auxiliary was first introduced by Daugulis[12,13] and has been proven to be highly efficient in the Pd-catalyzed C–H functionalization of α-AAs.[14–16] After extensive screening of the reaction conditions (see Tables S1, S2 in the Supporting Information for details), we were delighted to find that TMS-Ala **1a** could be obtained in 81% yield without racemization (98% *ee*) under the following conditions (Conditions A): $Pd(OAc)_2$ (10 mol%), *N*-Boc-Val-OH (20 mol%), hexamethyldisilane (5.0 equiv), and Ag_2CO_3 (2.0 equiv) in *t*BuOH under air at 125 °C for 12 h. The use of *N*-Boc-Val-OH was found to be crucial for the efficiency of the reaction.[17] Additionally, the reaction could be scaled up to 3 mmol, and chiral TMS-Ala derivative **1a** was prepared in 80% yield (1.0 gram, Scheme 2). Notably, the auxiliary could be removed by treatment with $BF_3{\cdot}Et_2O$ in MeOH, leading to β-L-TMS-alanine methyl ester **1aa** in 65% yield without racemization (99% *ee*).[14b,15]



Scheme 2. Gram-scale synthesis of chiral TMS-Ala through Pd-catalyzed primary C–H silyation, and removal of theauxiliary.

Encouraged by this promising result, we next focused on the exploration of direct silylation of secondary C–H bonds to prepare an array of more complicated chiral β-silyl-α-AAs. *N*-Phthaloyl phenylalanine derivative **2a**, which was obtained through a Pd-catalyzed monoarylation of alanine **1** established by our group,[15a] was chosen as the model substrate. After screening various additives that are commonly used in promoting C–H functionalization (Table S3),[18] we found that β-Silylated product **3a** could be obtained in 71% yield under the optimized conditions (Conditions B): $Pd(OAc)_2$ (15 mol%), hexamethyldisilane (5.0 equiv), Ag_2CO_3 (0.5 equiv), DMBQ (1.5 equiv) in *t*BuOH under air at 125 °C for 12 h. Importantly, the chiral β-TMS-phenylalanine product **3a** was obtained with excellent diastereoselectivity (d.r. > 20:1) without racemization (Scheme 3, 98% *ee*).

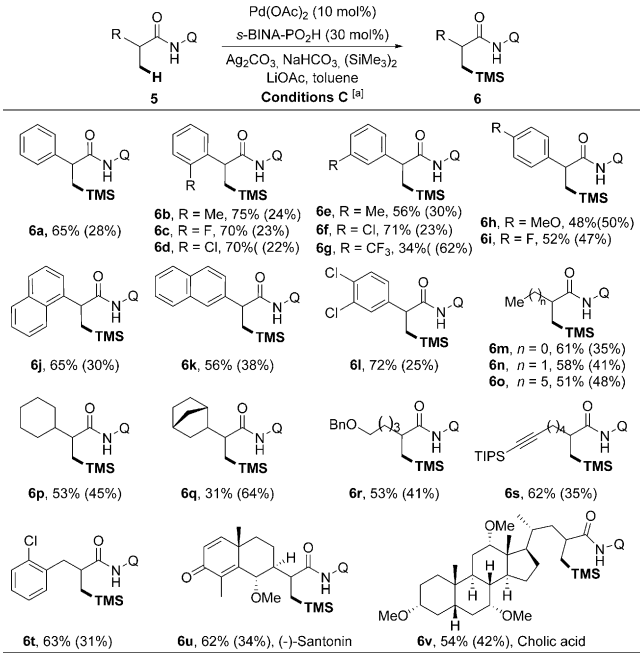
With the reliable silylation procedure in hand, a series of L-arylalanine derivatives (**2a**–**2j**) that were synthesized through monoarylation of L-alanine derivative **1** were subjected to Conditions B (Scheme 3, **3a**–**3j**). A wide variety of functional groups, including methoxy (**3b, 3h** and **3j**), acetamino (**3c** and **3i**), chloro (**3f**), and trifluoromethyl (**3g**) groups, were well tolerated. It is worth noting that the silylation of arylalanine derivatives proceeded with uniformly high stereoselectivity (**3a**–**3j**, d.r. > 20:1), regardless of the electronic properties on the phenyl ring. The relative and absolute stereochemistry of **3e** was unambiguously determined by X-ray analysis.[19] The *trans* orientation of the newly introduced trimethylsilyl and the N-phthaloyl group was consistent with previous reports and isolated palladacycles (Scheme S2, **Int-B**).[14,15c] Importantly, the silylation method also worked with an aliphatic secondary C–H bond, albeit in a modest yield (**3k**, 43%) and with relatively low diastereoselectivity (d.r. = 3:1). This is likely a result of the reduced degree of steric repulsion between the methyl group and the N-phthaloyl group in the palladacycle intermediate. Notably, the α-amino butyric acid derivative **2k** was prepared through β-methylation of alanine **1** by using our established method.[15b] Therefore, this method also showcases the preparation of chiral β-silyl-α-AAs through a two-step C–H functionalization sequence.



Scheme 3. Pd-catalyzed silylation of secondary C–H bonds. [a] Conditions B: **2** (0.1 mmol), $Pd(OAc)_2$ (15 mol%), hexamethyldisiliane (5.0 equiv), Ag_2CO_3 (0.5 equiv), DMBQ (1.5 equiv) in 1.0 mL 1,4-dioxane at 125 °C under air for 12 h. Yields of isolated product are shown. isolated yield. [b] 140 °C. DMBQ = 2,6-dimethoxy-1,4-benzoquinone.

2-Aryl propionic acids (2-APAs) are common motifs in drug molecules, including ibuprofen, naproxen, flurbiprofen. Direct C–H silylation could provide a potentially useful modification of this class of biologically useful molecules. We thus tested a number of 2-APA derivatives with modified conditions (Conditions C): $Pd(OAc)_2$ (10 mol%), *s*-BINA-PO_2H (30 mol%), hexamethyldisilane (5.0 equiv), $NaHCO_3$ (2.0 equiv), LiOAc (0.5 equiv) and Ag_2CO_3 (2.0 equiv) in

toluene under air at 125 °C for 12 h (Tables S4–S8) and discovered that the silylation selectively occurred at the β-methyl C(sp^3)–H bonds (Scheme 4). Substrates bearing both electron-donating and electron-withdrawing substituents at different positions reacted smoothly, providing the silylated products in moderate to good yields (**6b–6l**).



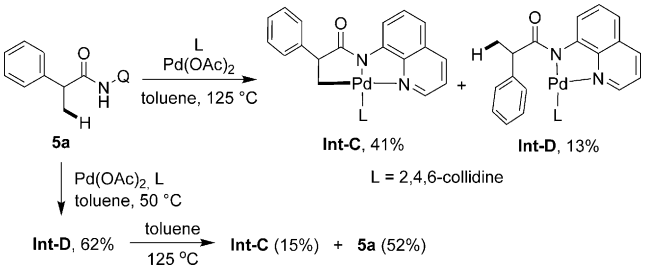
Scheme 4. Pd-catalyzed silylation of primary C–H bonds. [a] Conditions C: **5** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), hexamethyldisiliane (5.0 equiv), *s*-BINA-PO_2H (30 mol%), Ag2CO3 (2.0 equiv), $NaHCO_3$ (2.0 equiv), LiOAc (0.5 equiv) in 1.0 mL toluene at 125 °C under air for 12 h. Yields of isolated product are shown; the yields in parentheses are for recovered carboxamides **5**.

The compatibility of this method with 2-alkylpropanamides was investigated next (Scheme 4, **6m–6v**). Generally, amides derived from aliphatic carboxylic acids gave the desired β-silylation products in moderate to good yields. The potential of this C(sp^3)–H silylation was further demonstrated by the late-stage modification of amides **5u** and **5v**, which are derived from (−)-santonin and β-cholic acid respectively.

Finally, β-TMS-Phe **3a** was easily transformed into its methyl ester **4a** in 62 % yield with retention of configuration (Scheme S1a, 97 % *ee*).[14b,15] The auxiliary in **6a** can be removed in good yield through a two-step sequence (Scheme S1b).[14d]

To understand the process of formation of the β-silyl-α-amino acids, palladacycles **Int-A**[19] and **Int-B**[15c] were prepared, and the structure of **Int-A** was unambiguously confirmed by X-ray analysis (Scheme S2).[19] We found that both **Int-A** and **Int-B** react with hexamethyldisilane stoichiometrically to give the silylation products **1a** and **3a**, respectively. Catalytic reactions also suggested that these palladacycles are viable intermediates for primary and secondary C–H silylation (Scheme S2).

Based on the unusual observation that silylation of **5a** exclusively takes place at β-C(sp^3)–H bonds rather than γ-C(sp^2)–H bonds in the same molecule, we were eager to gain further insight into the origin of the site selectivity (Scheme 5). We anticipated that palladacycle intermediates, if attainable, could directly offer evidence for the site selectivity. Unfortunately, the reaction of **5a** with stoichiometric $Pd(OAc)_2$ under the standard reaction conditions failed to give any isolable intermediates. We postulated that the introduction of a strong neutral ligand might stabilize the resulting palladacycle.[20] Consistent with this hypothesis, we found that the reaction of **5a** with 1 equivalent of $Pd(OAc)_2$ in the presence of 2 equivalents of 2,4,6-collidine in toluene at 50 °C afforded the six-membered palladacycle **Int-D** in 62 % yield through γ-C(sp^2)–H bond activation (Scheme 5). When the reaction was performed at 125 °C, the five-membered palladacycle **Int-C** was isolated in 41 % yield, together with 13 % of **Int-D**. Interestingly, when a solution of **Int-D** in toluene was heated at 125 °C, it was transformed into **Int-C** in 15 % yield, with 52 % recovered **5a** (Scheme 5).



Scheme 5. Experimental investigations of the origin of the site selectivity in the C–H silylation of 2-APA.

To further understand the reaction mechanism, we sought to ascertain whether **Int-C** or **Int-D** is the active intermediate in the silylation reaction. Stoichiometric reactions of **Int-C** and **Int-D** with hexamethyldisilane under Conditions C were conducted. **Int-C** successfully gave product **6a** in 46 % yield. However, **Int-D** failed to afford γ-C(sp^2)–H silylation product **6ab** and solely gave **6a** in 51 % yield (Scheme S3). According to these experimental results, we are able to draw the following conclusions: 1) the formation of six-membered palladacycle **Int-D** is kinetically favored, while **Int-C** is thermodynamically more stable; 2) the C(sp^2)–H activation step is reversible; 3) the β-C(sp^3)–H silylation is favored over the γ-C(sp^2)–H silylation, which can be explained by Curtin–Hammett principle.

In summary, we have developed a general and practical Pd^{II}-catalyzed intermolecular silylation of primary and secondary C–H bonds of α-amino acids and aliphatic acids by employing an 8-aminoquinoline auxiliary. This method allows stereoselective access to a series of chiral β-silyl-α-AAs. Moreover, this method can be scaled up to the gram scale and used for the late-stage functionalization of biological small molecules. Several key intermediates have been successfully isolated to elucidate the mechanism of this β-C(sp^3)–H silylation process. We anticipate that this method may offer an opportunity to access various silicon-containing molecules for medicinal and biological applications.

Acknowledgements

Financial support from the National Basic Research Program of China (2015CB856600) and the NSFC (21572201, 21422206) is gratefully acknowledged.

Keywords: amino acids · asymmetric transformations · chiral auxiliaries · C–H activation · silylation

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 13859–13862
Angew. Chem. **2016**, *128*, 14063–14066

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Received: August 11, 2016
Revised: September 10, 2016
Published online: September 28, 2016

