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Palladium-Catalyzed C−H Silylation of Aliphatic Ketones Using an Aminooxyamide Auxiliary

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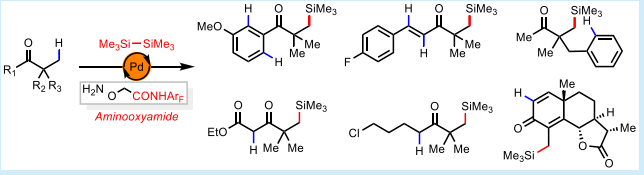
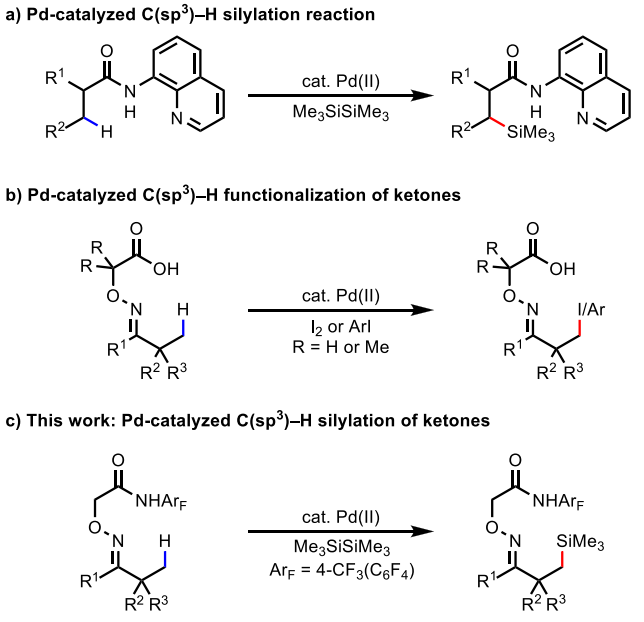
ABSTRACT: A palladium-catalyzed β-C(sp^3)−H silylation of aliphatic ketones with disilanes to afford β-silyl ketones is reported. The aminooxyamide auxiliary is critical for the C−H activation and silylation. The reaction tolerates a number of functional groups and shows good selectivity in silylating β-C(sp^3)−H bonds in the company of C(sp^2)−H bonds and acidic α-C(sp^3)−H bonds. The reaction is scalable, and the aminooxyamide auxiliary is readily removed to give β-silyl ketones, which could serve as useful building blocks for organic synthesis. Late-stage diversification using this protocol is demonstrated in the silylation of santonin with good yield.



Organosilicon compounds have distinct chemical and physical character that endows them an important role in organic synthesis,[1] material science,[2] and medicinal chemistry.[3] Transition-metal-catalyzed direct and selective aliphatic C(sp^3)−H silylation is of great value in accordance with atom and step economy. Thus, plenty of efforts have been devoted to develop new methodologies in this respect during the past decades. Significant advances have been made in transition-metal-catalyzed reactions using Ru, Rh, Ir, and Pt as catalysts.[4] Compared with the reported palladium-catalyzed C(sp^2)−H silylation,[5] palladium-catalyzed direct silylation of aliphatic C(sp^3)−H bonds remains a great challenge.[6] The strategy employing directing-group assistance was proved to be crucial for the intermolecular silylation of unactivated aliphatic C−H bonds. Since the pioneering work by the Kanai group,[7] an 8-aminoquinoline auxiliary was successfully employed in the palladium-catalyzed β-C(sp^3)−H silylation of aliphatic carboxylic acids and amino acids[8,9] (Scheme 1a) and later in the γ-C(sp^3)−H silylation of aliphatic carboxylic acids.[10] Moreover, oxalyl amide assisted benzylic silylation of amine derivatives[11] and picolinamide assisted γ-C(sp^3)−H silylation of peptides were also developed.[12] As far as we know, direct silylation of distal C(sp^3)−H bonds of aliphatic ketones has never been reported.

The direct functionalization of unactivated C−H bonds of ketones will expand their synthetic applications and provide new synthetic disconnections, as ketones are widely present in bulk chemicals, synthetic building blocks, and natural products. Oxime-directed β-C(sp^3)−H acetoxylation, arylation and amination of ketones,[13] β-C(sp^3)−H arylation of ketones or aldehydes using a transient directing group,[14] as well as β-C(sp^3)−H iodination and arylation of ketones using a practical aminooxyacetic acid auxiliary (Scheme 1b)[15] have been reported. However, the direct C(sp^3)−H functionalization of ketones[16] has been highly limited in both the types of transformations and the scope of substrates. Inspired by Yu's recent work using the L, X-type aminooxyacetic acid auxiliary[15] to facilitate catalytic C−H functionalizations of aliphatic

Scheme 1. Palladium-Catalyzed C(sp^3)−H Silylation and C(sp^3)−H Functionalization of Ketones



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ketones, we have developed the palladium-catalyzed direct β-C(sp^3)−H silylation of aliphatic ketones. The resulting β-silyl ketones would serve as useful building blocks for organic synthesis.

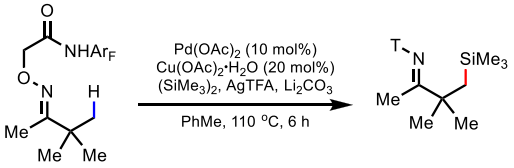
Pinacolone was chosen as the model substrate in our study, and an oxime auxiliary was installed (Table 1). To our delight, after extensive screening of various reaction parameters, the desired silylated product **2a** was obtained in 73% yield (72% isolated yield) using $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), hexamethyldisilane (2.5 equiv), AgTFA (3.0 equiv), and Li_2CO_3 (2.0 equiv) in toluene (2 mL) at 110 °C for 6 h with the aminooxyamide auxiliary $\mathbf{DG_1}$ (entry 1). Other types of carboxylic acid auxiliaries such as $\mathbf{DG_2}$ and $\mathbf{DG_3}$, which were employed in the C(sp^3)−H iodination and arylation of ketones,[15] or amide auxiliary $\mathbf{DG_4}$, all gave poor yields (entries 2−4). Using other inorganic bases than Li_2CO_3, the yield of silylated products decreased (entries 5−7). The reaction became less efficient without $Cu(OAc)_2{\cdot}H_2O$ and with other copper salts (entries 8−10). The yield decreased at other temperatures (entries 11−13).

With the optimal auxiliary and reaction conditions discovered, we explored the scope of ketones using hexamethyldisilane as the silylation partner. We continued the studies with various methyl (**2a**−**2i**) and alkyl (**2j**−**2l**) ketones (Table 2). Alkyl substituted ketones were β-silylated in good to excellent yields (**2a**, **2i**, **2k**). Aromatic moieties *trans* to the aminooxyamide moiety were compatible under the silylation conditions, and no C(sp^2)−H silylation was observed (**2b**−**2e**). Ketone derived from Gemfibrozil was silylated at the β-methyl group with 72% yield (**2e**). A variety of functional groups, including ester, chlorine, and alkene substituents, were well tolerated (**2f**−**2h**, **2j**, **2l**). No α-silylation happened with the acidic α-hydrogen; only β-C(sp^3)−H silylation products were isolated (**2j**). For alkenyl ketone, β-C(sp^3)−H silylation product was obtained in 57% yield (**2h**) with an inseparable minor C(sp^2)−H silylation product in 14% yield (**2h′**). Notably, cyclobutyl substituted ketone was β-silylated at the methylene C−H bond in 62% yield (**2i**).

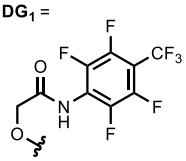
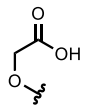
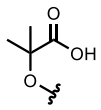
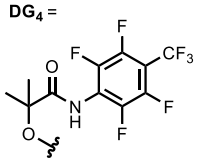
The scopes of aryl (**2m**−**2s**), heteroaryl (**2t**), and styrenyl (**2u**−**2y**) ketones were also investigated (Table 3). Aryl ketones with electron-donating groups, including methoxyl, methyl, and *tert*-butyl groups, or halogen groups, including fluorine and chlorine, were compatible under the silylation conditions (**2m**−**2s**). Heteroaryl ketone containing thiophene was tolerated (**2t**). Styrenyl ketones with electron-withdrawing groups, such as cyano and nitro groups, or fluorine, were tolerated (**2u**−**2y**). Notably, no C(sp^2)−H silylation was observed in these ketones containing phenyl or alkenyl C(sp^2)−H bonds.

Removal of the aminooxyamide auxiliary was achieved by reacting the silylation products with 4 M HCl in 1,4-dioxane and water at 80 °C, delivering β-silylated ketone (**3d**) in 73% yield (Scheme 2a). To further demonstrate the synthetic value

Table 1. Optimization Studies[a,b]

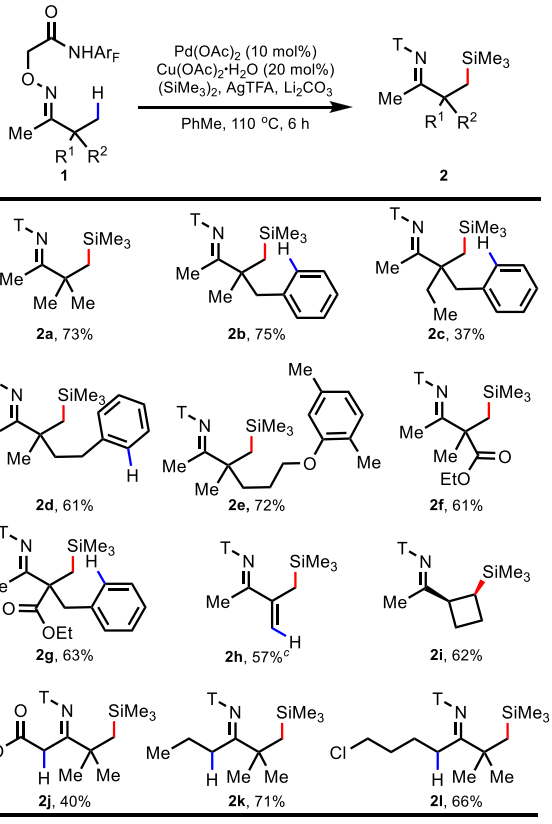


entry	deviation from conditions	yield (%)
1	None	73 (72)
2	$\mathbf{DG_2}$ instead of $\mathbf{DG_1}$	33
3	$\mathbf{DG_3}$ instead of $\mathbf{DG_1}$	6
4	$\mathbf{DG_4}$ instead of $\mathbf{DG_1}$	11
5	K_2CO_3 instead of Li_2CO_3	29
6	LiF instead of Li_2CO_3	37
7	NaOAc instead of Li_2CO_3	43
8	No $Cu(OAc)_2{\cdot}H_2O$	15
9	$Cu(TFA)_2$ instead of $Cu(OAc)_2{\cdot}H_2O$	60
10	$CuBr_2$ instead of $Cu(OAc)_2{\cdot}H_2O$	43
11	100 °C instead of 110 °C	45
12	120 °C instead of 110 °C	69
13	130 °C instead of 110 °C	60

$\mathbf{DG_1}$ =  $\mathbf{DG_2}$ =  $\mathbf{DG_3}$ =  $\mathbf{DG_4}$ = 

[a]Conditions: **1a** (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), $(SiMe_3)_2$ (2.5 equiv), AgTFA (3.0 equiv), Li_2CO_3 (2.0 equiv), toluene (2.0 mL), 110 °C, under air, 6 h. [b]Yield determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as the internal standard. The yield in parentheses is the isolated yield.

Table 2. Scope of Methyl and Alkyl Ketones[a,b]



[a]Conditions: substrate (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (10 mol %), $(SiMe_3)_2$ (2.5 equiv), AgTFA (3.0 equiv), Li_2CO_3 (2.0 equiv), toluene (2.0 mL), under air, at 110 °C for 6 h. [b]Isolated yields. [c]The C(sp^2)−H silylation product (**2h′**) was observed in 14% yield.

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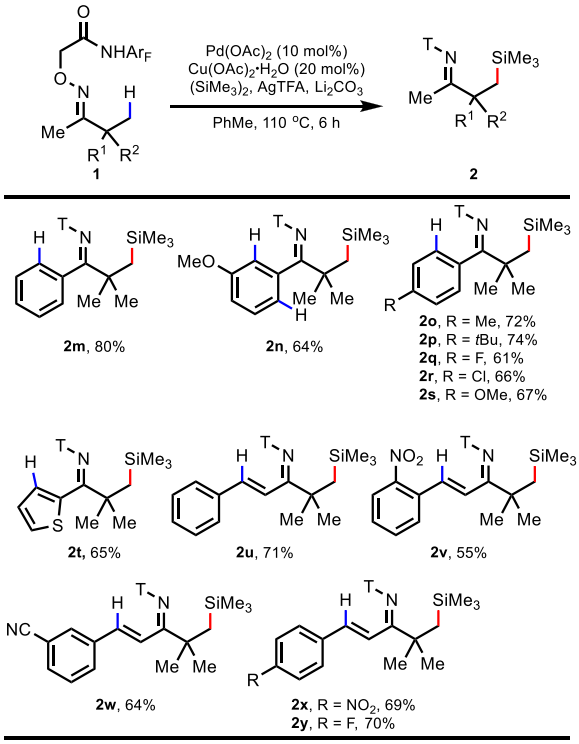
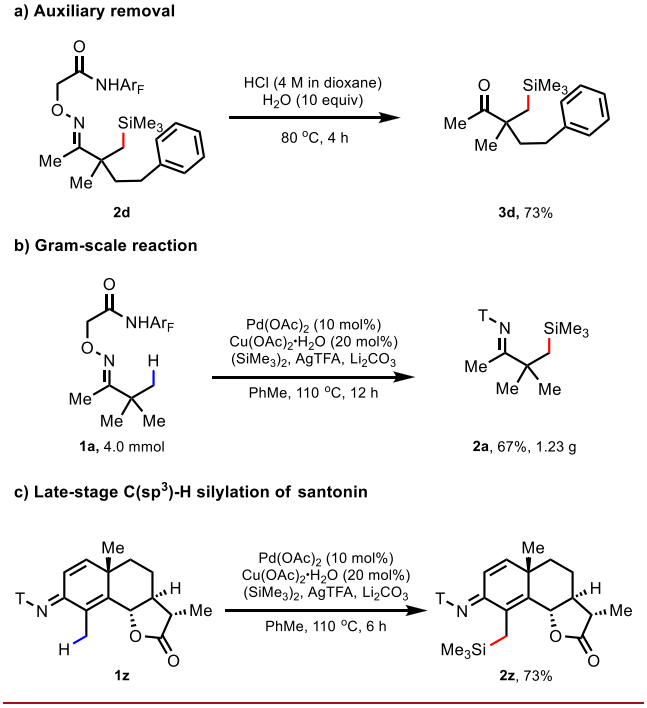
Table 3. Scope of Aryl, Heteroaryl, and Styrenyl Ketones[a,b]



[a]Conditions: substrate (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2·H_2O$ (10 mol %), $(SiMe_3)_2$ (2.5 equiv), AgTFA (3.0 equiv), Li_2CO_3 (2.0 equiv), toluene (2.0 mL), under air, at 110 °C for 6 h. [b]Isolated yields.

Scheme 2. Auxiliary Removal, Gram-Scale Reaction, and Late-Stage C(sp³)−H Silylation of Santonin



of this method, silylation of **1a** was carried out on a 4.0 mmol scale and the desired silylation product was obtained in gram scale in 67% yield (Scheme 2b). The abundant existence of an aliphatic ketone motif in a big portion of natural products and bioactive molecules makes the silylation a practical method for late-stage diversification. Thus, direct C(sp³)−H silylation of santonin was performed to provide its potentially useful silylated analogue **2z** in 73% yield (Scheme 2c).

In summary, C(sp³)−H silylation of aliphatic ketones was developed using an aminooxyamide auxiliary. Broad substrate scope and selectivity for aliphatic ketones and the application for late-stage C(sp³)−H functionalizations have been revealed. This reaction also features facile installation and removal of the auxiliary. Further studies of silylation of other challenging C−H bonds in aliphatic ketones, such as γ-methyl or methylene C−H bonds, are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01678.

Additional screening tables, detailed experimental procedures, compound characterization data, and NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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