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Ruthenium-Catalyzed Intermolecular Direct Silylation of Unreactive C(sp^3)−H Bonds

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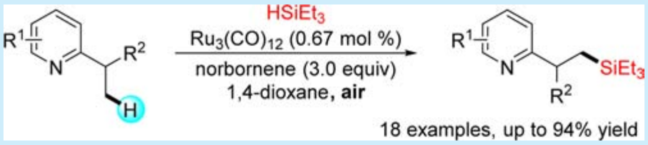
Supporting Information

ABSTRACT: A Ru-catalyzed intermolecular silylation of unreactive, aliphatic C(sp^3)−H bonds has been described for the first time. This protocol features low catalyst loading, a relatively broad substrate spectrum, good functional group tolerance, and no sensitivity to air, which provides a convenient and practical pathway for the construction of C−Si bonds.

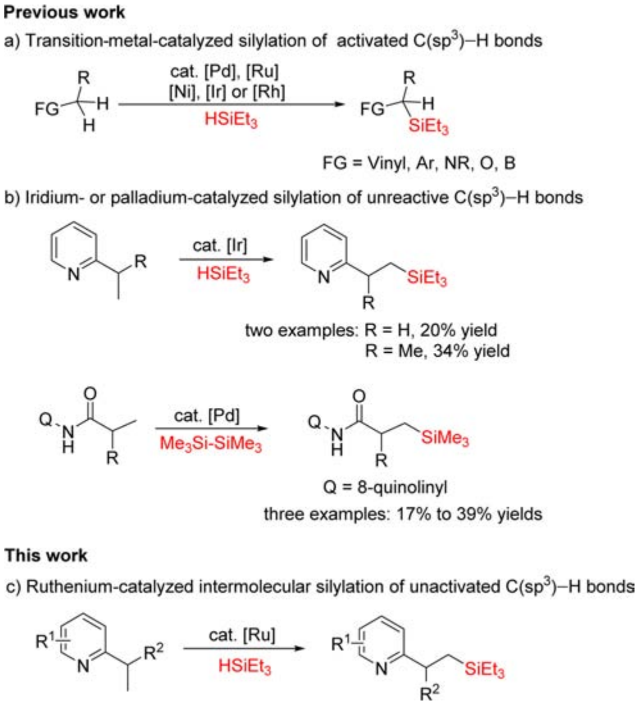


Organosilane compounds are not only valuable synthetic intermediates that can be converted into various useful molecules[1] but also important structural units existing in pharmaceuticals and materials.[2] Thus, it is of great importance to install the silyl groups into an organic compound in synthetic chemistry. Since transition-metal-catalyzed C−H bond activation and subsequent functionalization have been one of the most significant strategies for the synthesis of various organic molecules,[3] more attention has been paid to catalytic silylation to construct C−Si bonds via direct C−H activation.[4]

Recently, a wide variety of catalytic methods have been established in the area of aromatic and vinylic C−H bond silylation.[5] Meanwhile, a few examples of transition-metal-catalyzed silylation of activated α-C(sp^3)−H bonds, such as allylic[6] and benzylic,[7] and C(sp^3)−H adjacent to a heteroatom[8] have also been reported (Scheme 1a). However, the intermolecular silylation of unreactive, aliphatic C(sp^3)−H bonds remains under-developed.[8b,9,10] Although both Ir[8b] and Pd[10] complexes catalyze the intermolecular silylation of unreactive C(sp^3)−H bonds with the aid of chelate directing groups (Scheme 1b), quite low efficiency, poor selectivity, and a narrow substrate scope limit the synthetic utility of these methods. Consequently, it is highly valuable and desirable to develop a new method to achieve an efficient and practical silylation of unreactive C(sp^3)−H bonds. Following our continued interest in C(sp^3)−H bond activation,[11] we herein disclose the first Ru-catalyzed, chelation-assisted intermolecular silylation of unactivated C(sp^3)−H bonds (Scheme 1c).[12] In particular, we showcase the catalytic potential of low-valent $Ru_3(CO)_{12}$ in unreactive C(sp^3)−H bond functionalization because the evolution of stoichiometric C(sp^3)−H activation reactions by a low-valent transition metal to catalytic versions has proven significantly more challenging.[12,13]

Initially, 2-ethylpyridine **1a** and triethylsilane were chosen as starting materials to explore the reaction conditions (Table 1). The product **2a** was successfully obtained in 75% yield in the presence of Ru(cod)Cl_2 (5 mol %) and norbornene (3.0 equiv) in dioxane at 150 °C under an air atmosphere (Table 1, entry 1).

Scheme 1. Transition-Metal-Catalyzed Intermolecular Silylation of C(sp^3)−H Bonds



The yield of **2a** decreased to 15% in the absence of norbornene, indicating that norbornene might play an important role as a hydrogen acceptor (Table 1, entry 2). Next, other additives such as styrene and cyclohexene were investigated. It is found that styrene and cyclohexene afforded **2a** in 57% and trace yields, respectively (Table 1, entries 3 and 4). Among the various solvents examined, 1,4-dioxane proved to be superior to

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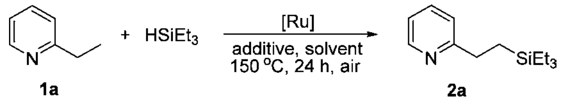
Table 1. Optimization of Ruthenium-Catalyzed Unactivated $C(sp^3)$−H Silylation of 2-Ethylpyridine[a]



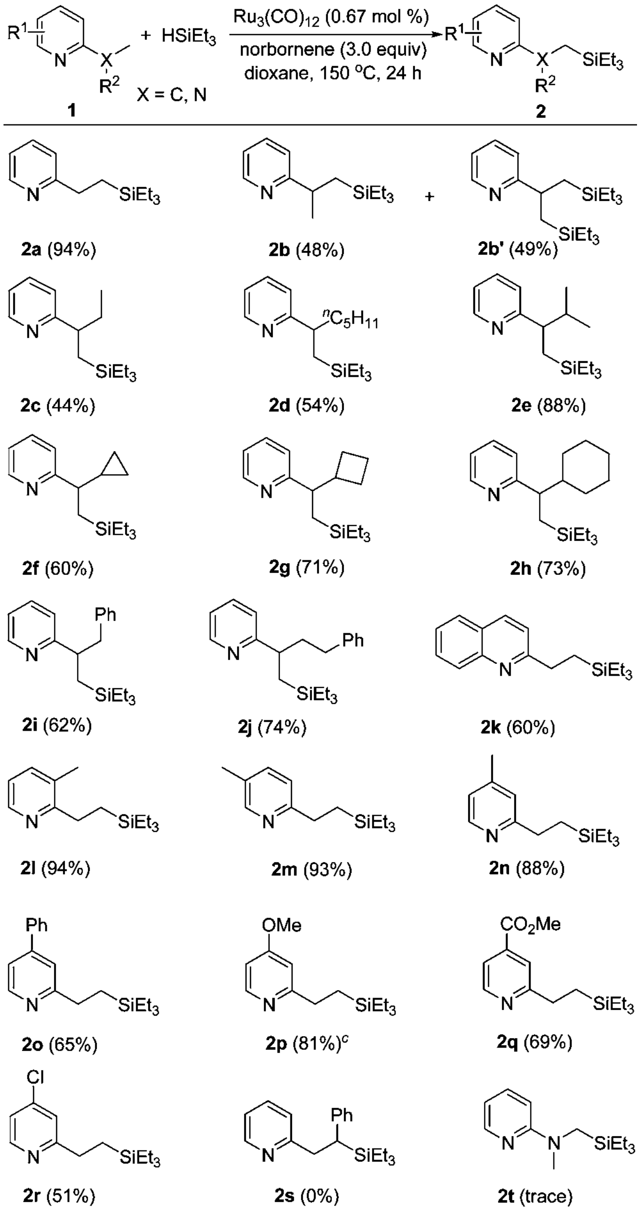
entry	catalyst (mol %)	additive	solvent	yield (%)[b]
1	$Ru(cod)Cl_2$ (5.0)	norbornene	1,4-dioxane	75
2	$Ru(cod)Cl_2$ (5.0)	–	1,4-dioxane	15
3	$Ru(cod)Cl_2$ (5.0)	styrene	1,4-dioxane	57
4	$Ru(cod)Cl_2$ (5.0)	cyclohexene	1,4-dioxane	trace
5	$Ru(cod)Cl_2$ (5.0)	norbornene	THF	71
6	$Ru(cod)Cl_2$ (5.0)	norbornene	toluene	5
7	$Ru(cod)Cl_2$ (5.0)	norbornene	DCE	0
8	$Ru(cod)Cl_2$ (5.0)	norbornene	CH_3CN	0
9	$Ru(cod)Cl_2$ (5.0)	norbornene	MeOH	0
10	$Ru(PPh_3)_3Cl_2$ (5.0)	norbornene	1,4-dioxane	34
11	$[Ru(cymene)Cl_2]_2$ (2.5)	norbornene	1,4-dioxane	69
12	$RuCl_3{\cdot}nH_2O$ (5.0)	norbornene	1,4-dioxane	22
13	$Ru_3(CO)_{12}$ (1.7)	norbornene	1,4-dioxane	90
14	**$Ru_3(CO)_{12}$ (0.67)**	**norbornene**	**1,4-dioxane**	**94**
15[c]	$Ru_3(CO)_{12}$ (0.67)	norbornene	1,4-dioxane	92

[a]Reaction conditions: 2-ethylpyridine **1a** (0.5 mmol), triethylsilane (2.5 mmol), catalyst, additive (3.0 equiv), and solvent (2.0 mL) at 150 °C for 24 h under an air atmosphere. [b]Isolated yields. [c]The reaction was performed under an Ar atmosphere.

tetrahydrofuran (THF), toluene, 1,2-dichloroethane (DCE), acetonitrile, and methanol (Table 1, entries 1 and 5−9). We further screened other ruthenium precursors (Table 1, entries 1 and 10−13). As a result, $Ru_3(CO)_{12}$ showed the highest catalytic activity, and the desired product **2a** was obtained in 90% yield. We were pleased to find that a slightly better yield (94%) was gained when the loading of $Ru_3(CO)_{12}$ was reduced to 0.67% (Table 1, entry 14). An Ar atmosphere instead of air gave a comparative yield of **2a** (Table 1, entry 15). Finally, the optimized reaction conditions consist of 0.67 mol % of $Ru_3(CO)_{12}$ as a catalyst and 3.0 equiv of norbornene as a hydrogen acceptor in 1,4-dioxane at 150 °C for 24 h under an air atmosphere.

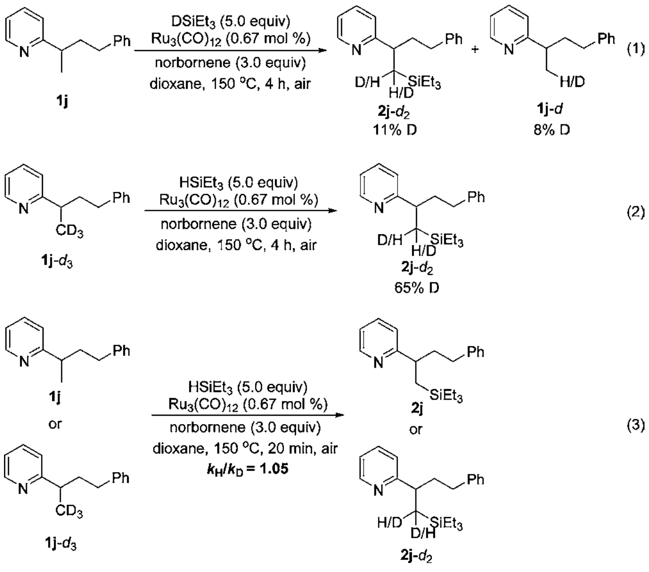
With the optimized reaction conditions in hand, the scope of 2-ethylpyridine derivatives was investigated (Scheme 2). Substrates with various alkyl groups on the benzylic position of 2-ethylpyridine reacted with triethylsilane to afford the corresponding silylated products in moderate to excellent yields, and the silylation selectively occurred at the primary $C(sp^3)$−H site at the pyridine *β* position (**2b**−**2j**). When using 2-isopropylpyridine as the substrate, monosilylated product **2b** and bis-silylated product **2b**′ were obtained in 48% and 49% yields, respectively. In comparison with straight-chain alkyl, branched chain alkyl and cycloalkyl on the benzylic position of 2-ethylpyridine led to higher yields (**2c**−**2h**). Moreover, 2-ethylquinoline could also be applicable to the catalytic system, and the silylated product was obtained in 60% yield (**2k**). Moreover, both electron-donating substituents such as Me, Ph, and MeO and electron-withdrawing groups such as CO_2Me and Cl on the pyridine ring were compatible with this reaction, giving the desired products in moderate to excellent yields (**2l**−**2r**). The silylation of the secondary $C(sp^3)$−H bond did not proceed under the standard conditions (**2s**). When the reaction of more reactive *N*,*N*-dimethylpyridin-2-amine was performed, only a trace amount of **2t** was obtained. We assumed that the catalyst could be poisoned by the coordination of dimethylamino to the Ru. In addition, we also investigated $HSiMe_2Ph$ under the standard conditions, but no product was detected.

Scheme 2. Ruthenium-Catalyzed Intermolecular Silylation of $C(sp^3)$−H Bonds[a,b]



[a]Reaction conditions: **1** (0.5 mmol), triethylsilane (2.5 mmol), $Ru_3(CO)_{12}$ (0.67 mol %), norbornene (3.0 equiv), dioxane (2.0 mL) at 150 °C for 24 h under an air atmosphere. [b]Isolated yields. [c]2.0 mol % of $Ru(cod)Cl_2$ was used.

To gain some preliminary insights into the silylation mechanism, hydrogen−deuterium exchange experiments were performed. When treatment of 2-(4-phenylbutan-2-yl)pyridine **1j** with $DSiEt_3$ under the standard conditions occurred, 8% of the methyl hydrogen in **1j** was deuterated and the product **2j**-d_2 containing 11% D at the position adjacent to the silicon atom was obtained (eq 1). On the other hand, when **1j**-d_3 reacted with triethylsilane, the product **2j**-d_2 that contains 65% D at the position adjacent to the silicon atom was obtained (eq 2). These results indicated that cleavage of the C−H bond is reversible. Then the primary kinetic isotopic effect (KIE) experiments were



carried out with two parallel competition reactions (eq 3). The value of KIE was observed to be 1.05, suggesting that the C(sp^3)−H cleavage is not the rate-determining step in the catalytic process.[14]

In conclusion, we have described the first example of the Ru-catalyzed intermolecular silylation of unreactive, aliphatic C(sp^3)−H bonds. This protocol features a low catalyst loading, relatively broad substrate spectrum, good functional group tolerance, and no sensitivity to air, which offers an efficient and practical method to construct C−Si bonds via unreactive C(sp^3)−H bond activation. Further studies to clarify the reaction mechanism and to develop the transformations of silylated products are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03593.

Experimental procedures, characterization data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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