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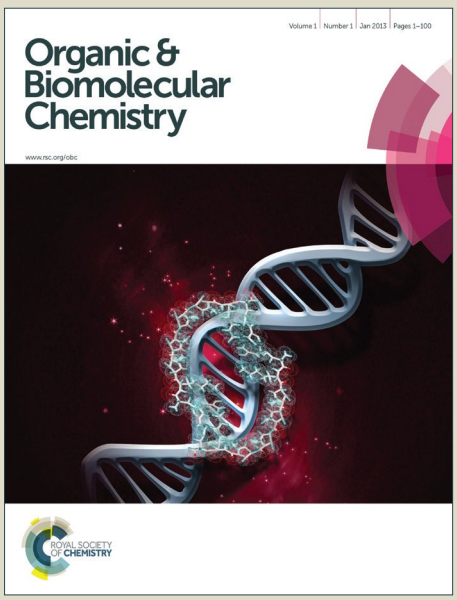

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COMMUNICATION

Amino Acid-Promoted C–H Alkylation with Alkylboronic Acids Using a Removable Directing Group

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Palladium-catalyzed C–H alkylation reaction with alkylboronic acids has successfully been developed using removable pyridyldiisopropylsilyl directing group. The amino acid played a crucial role as a ligand in the reaction. The alkylation protocol is also applicable to the coupling of C(sp^3)–H bonds with alkylboronic acids.

In the past few decades, C–H functionalization has attracted considerable interest and is emerging as a novel and valuable strategy in organic synthesis.[1] While the ubiquility of C–H bonds in organic molecules provides great opportunities for the application of C–H functionalization reactions, it also poses regioselectivity problems for this type of reaction. To develop synthetically applicable C–H functionalization reactions, it is critical to activate desirable C–H bonds selectively. However, C–H bonds often have very similar reactivities, so it is usually challenging to achieve high site-selectivity. Currently, the most common strategy to address this issue relies on the use of directing groups.[2] The directing groups can coordinate to transition-metal catalysts, and as a consequence, only C−H bonds at the appropriate positions can be cleaved through the formation of a cyclic pre-transition state. Although this strategy is efficient and reliable in achieving high selectivity, the directing groups are not needed in products for the majority of the reactions and should be removed. However, many of the directing groups are not easily removable, so it limits the reactions to particular types of substrates bearing directing groups.

Recently, a removable directing group strategy is arousing great attention. For this strategy, the directing groups can be removed after C–H functionalization, so it overcomes the drawbacks of the common directing group strategy. Currently, a variety of removable directing groups have been developed.[3]

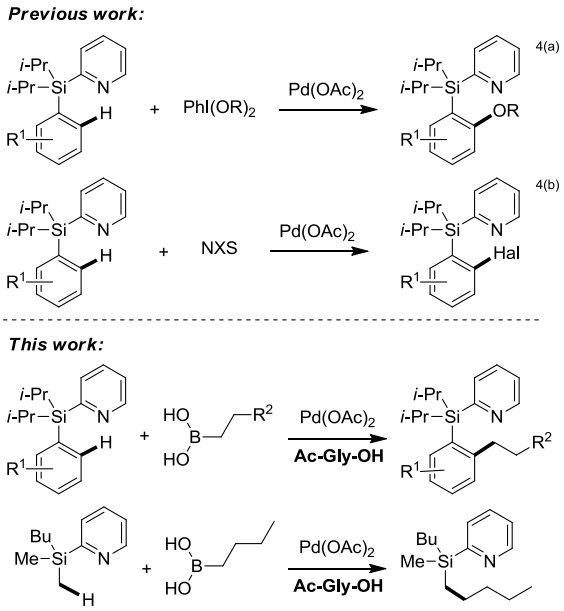

Figure 1. Pyridyldiisopropylsilyl-directed C–H functionalization.

Excellent examples are pyridyldiisopropylsilyl-directed C–H halogenation and acyloxylation reactions developed by the Gevorgyan group (Figure 1).[4] Furthermore, the Gevorgyan[5] and Ge group[6] reported silinol-assisted C–H functionaliztion respectively. Although additional synthetic steps are needed to install the directing group, the synthesis of arylsilanes containing the pyridyldiisopropylsilyl directing group is straightforward.[4a]

Although transition-metal-catalyzed alkylation reactions are usually challenging, owing to its great advantages, C–H alkylation has still been extensively studied. While a number of C–H alkylation reactions using alkyl halides have been reported,[7] the reactions with alkylmetallic reagents remains comparatively underexploited.[8] Attracted by the great advantages of the removable directing group strategy, we set out to investigate its feasibility in C–H alkylation with alkylmetallic reagents. Considering the favorable properties of

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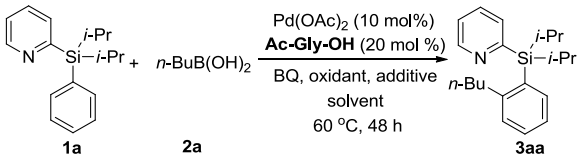
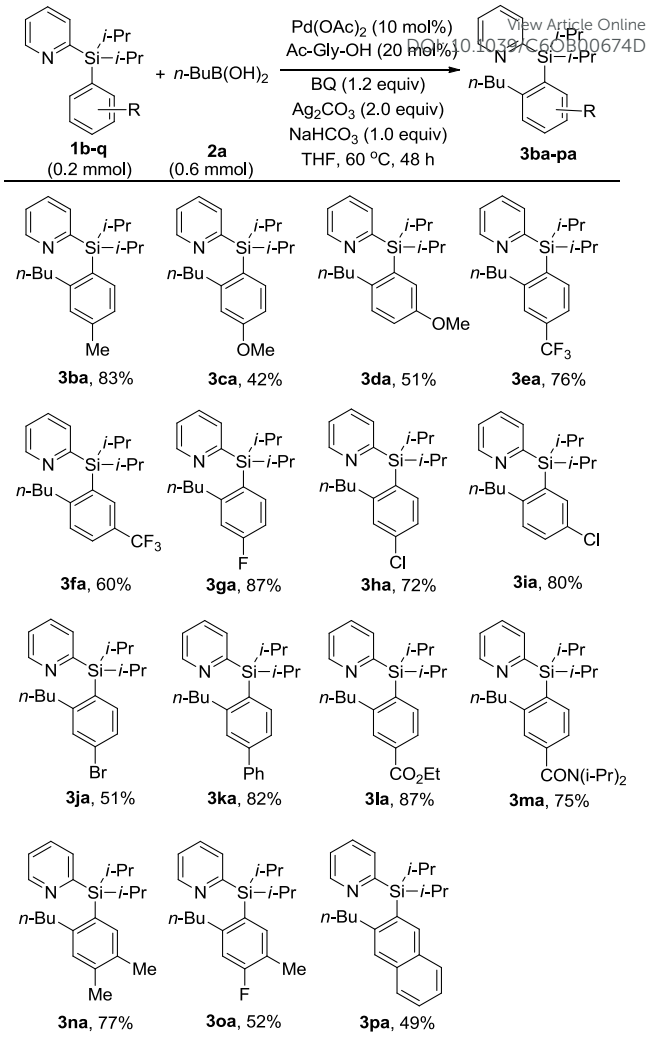
Table 1. Condition Survey for PyrDipSi-Directed C–H Alkylation with Alkylboronic Acid



1a 2a 3aa

entry	BQ (equiv)	oxidant (equiv)	solvent	additive	yield (%)[b]
1	0.5	Ag_2CO_3 (1.0)	*t*-Amyl-OH	/	40
2	0.5	AgOAc (1.0)	*t*-Amyl-OH	/	37
3	0.5	Ag_2O(1.0)	*t*-Amyl-OH	/	39
4	0.5	$Cu(OAc)_2$ (1.0)	*t*-Amyl-OH	/	28
5	1.0	Ag_2CO_3 (1.0)	*t*-Amyl-OH	/	57
6	1.0	Ag_2CO_3 (1.0)	THF	/	72
7	1.0	Ag_2CO_3 (1.0)	Et_2O	/	60
8	1.0	Ag_2CO_3 (1.0)	MeCN	/	trace
9	1.0	Ag_2CO_3 (1.0)	*t*-BuOH	/	55
10	1.0	Ag_2CO_3 (1.0)	dioxane	/	30
11	1.0	Ag_2CO_3 (1.0)	DCE	/	trace
12	1.0	Ag_2CO_3 (1.0)	toluene	/	0
13	1.0	Ag_2CO_3 (1.0)	DMF	/	50
14	1.0	Ag_2CO_3 (1.0)	DMSO	/	0
15	1.2	Ag_2CO_3 (1.0)	THF	/	78
16	1.2	Ag_2CO_3 (2.0)	THF	/	83
17	1.2	Ag_2CO_3 (2.0)	THF	Na_2CO_3	49
18	1.2	Ag_2CO_3 (2.0)	THF	$NaHCO_3$	89 (85[c])
19	1.2	Ag_2CO_3 (2.0)	THF	$KHCO_3$	43
20	1.2	Ag_2CO_3 (2.0)	THF	$NaHCO_3$	21[d]
21	1.2	Ag_2CO_3 (2.0)	THF	$NaHCO_3$	36[e]
22	1.2	Ag_2CO_3 (2.0)	THF	$NaHCO_3$	60[f]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol. 3.0 equiv), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), Ac-Gly-OH (0.04 mmol, 20 mol%), BQ, oxidant, additive (0.2 mmol, 1.0 equiv), solvent (1.0 mL), 60 ℃, 48 h. [b] The yields were determined by ^{1}H NMR analysis of the crude reaction mixtures using $CHCl_2CHCl_2$ as an internal standard. [c] Isolated yield. [d] No Ac-Gly-OH. [e] $Pd(OAc)_2$ (2.5 mol%). [f] $Pd(OAc)_2$ (5.0 mol%)

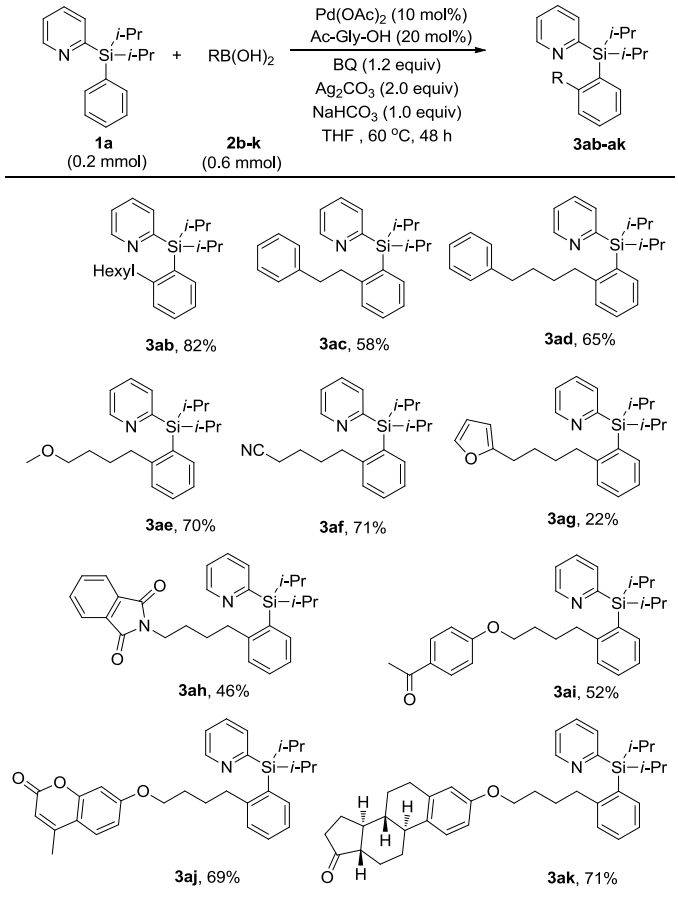


Scheme 1. Substrate Scope with the Respect to 2-(Diisopropyl(phenyl)silyl)pyridine. [g] Isolated yield.

organoboron reagents, we chose alkylboronic acids as the coupling partner. It is noted that some pioneering C–H alkylation reactions with organoboron reagents have been disclosed.[9] However, most of the reactions are limited to methylation, and competing difunctionalizaiton can occur.

Ligands can provide transition-metal-catalysts with novel reactivities and allow for otherwise unfeasible reactions to be realized.[10] In this context, amino acids proved to be extremely versatile and powerful in Pd-catalyzed C–H functionalization, and have enabled a range of reactions to be developed.[9c,11] Amino acids have advantageous properties such as low cost, ready availability, and facile modification, making them desirable ligands. Herein, we report 2-pyridyldiisopropylsilyl (PyrDipSi)-directed C–H alkylation with alkylboronic acids with the aid of an amino acid ligand.

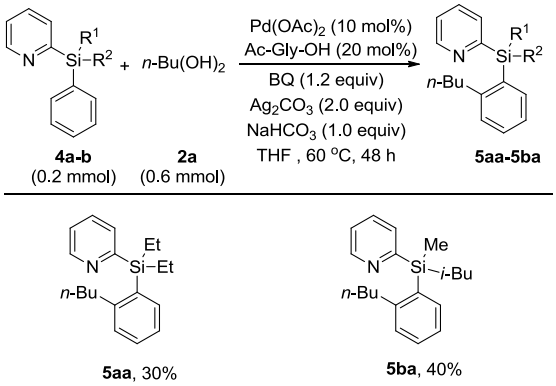
We initiated this research project by investigating the C–H alkylation of 2-(diisopropyl(phenyl)silyl)pyridine (**1a**) with *n*-butylboronic acid (**2a**).After extensive reaction screening, the reaction formed the desired alkylated product (**3aa**) in 40% yield in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% *N*-acetylglycine, 0.5 equiv benzoquinone, and 1.0 equiv Ag_2CO_3 in *tert*-amyl alcohol (Table 1, entry 1). Oxidant survey showed that other silver(I) salt could also promote the reaction (entries 2 and 3) and $Cu(OAc)_2$ was an effective oxidants as well, albeit in a lower yield (entry 4). The yield was improved to 57% when 1.0 equiv Ag_2CO_3 was used in the presence of 1.0 equiv BQ, and was further enhanced to 72% by carrying out the reaction in THF (entry 6). THF proved to be the optimal solvent, since the use of other solvents led to lower yields or even failed to form the alkylated product (entries 7-14). Fine tuning reaction condition enhanced the yield to 83% using 1.2 equiv BQ and 2.0 equiv Ag_2CO_3 (entry 16). To obtain an optimal yield, we examined the impact of inorganic bases on the alkylation reaction. While the reaction gave a lower yield in the presence of Na_2CO_3 or $KHCO_3$ (entries 17 and 19), the yield was optimized to 89% when 1.0 equiv $NaHCO_3$ was added (entry 18). Finally, the absence of *N*-acetylglycine led to a much lower yield, indicating that the amino acid played a critical role in promoting the alkylation reaction (entry 20). To gain some insights into the impact of amino acids on the reaction, a range of other *N*-protected amino acids were examined (See Supporting Information). All the surveyed amino acids gave



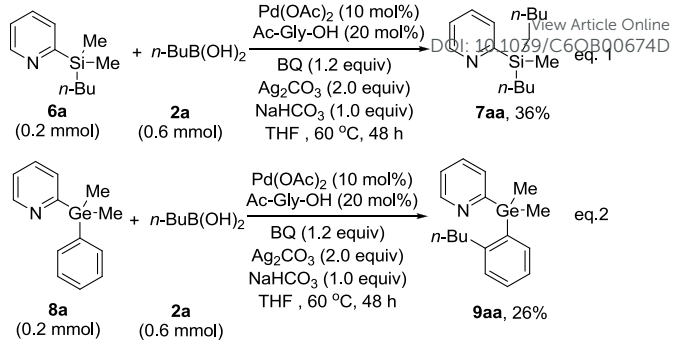
Scheme 2. Substrate Scope with the Respect to Alkylboronic Acids. [a] Isolated yield.

much lower yields. Furthermore, replacing the amino acid with pivalic acid led to 22% yield, which is close to that of the reaction in the absence of an amino acid ligand. Finally, in the presence of 5 or 2.5 mol% $Pd(OAc)_2$, the reaction formed the desired product in 60% and 36% respectively.

With the optimal conditions in hand, we next investigated the substrate scope of this C–H alkylation reaction. We first examined performance of 2-(diisopropyl(phenyl)silyl)pyridine derivatives bearing a variety of substituents on the phenyl group under the optimized conditions. Thus, as shown in Scheme 1, while the substrate containing a *para*-methyl group



Scheme 3. Substrate Scope with the Respect to Directing Groups. [a] Isolated yield.

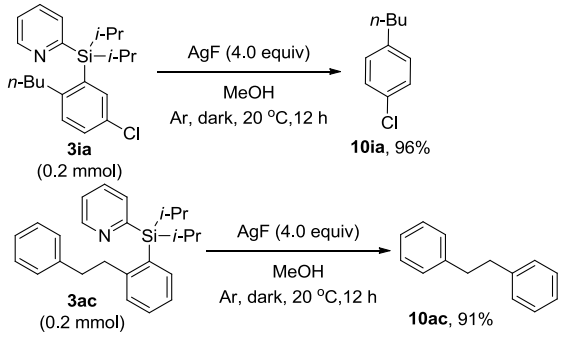


was alkylated in a yield similar to **1a** (**3ba**), the presence of a methoxy group at the *para*- or *meta*-position resulted in much lower yields (**3ca** and **3da**). As a comparison, the substrates with electron-withdrawing trifluoromethyl groups were butylated in medium yields (**3ea** and **3fa**). Notably, the halo groups, including F, Cl, and Br, were well-tolerated in the reaction (**3ga**-**3ja**). The substrates containing other common functional groups, such as phenyl, ester, and amide groups underwent the alkylation reaction in satisfying yield (**3ka**-**3ma**). Finally, the disubstituted benzene rings were successfully alkylated under the reaction conditions (**3na-3pa**).

Subsequently, we investigated the substrate scope with respect to the alkylboronic acid coupling partner. As shown in Scheme 2, linear primary alkylboronic acid containing a variety of functional groups effectively underwent the alkylation reaction under the standard conditions to form the corresponding alkylated products. The phenyl, ether, carbonyl, and cyano groups were tolerated in the reaction (**3ac**-**3af** and **3ai**). The boronic acid bearing furan or isoindoline-1,3-dione moiety at the terminal positions were reactive, albeit in low yields (**3ag** and **3ah**). Notably, a coumarin and estrone derivative could be installed onto the benzene ring of **1a** via the C–H alkylation reaction (**3aj** and **3ak**).

The compatibility of other directing groups was also examined (scheme 3). Although both the diethyl(pyridyl)silyl and isobutyl(methyl)(pyridyl)silyl groups could enable the C–H alkylation to occur, the yields were much lower, primarily due to the decomposition of the directing groups.

Transition-metal-catalyzed $C(sp^3)$–$C(sp^3)$ coupling is one of the most challenging reactions in organometallic chemistry. Although the coupling of $C(sp^3)$–H bonds with with $C(sp^3)$



Scheme 4. Removal of the pyridyldiisopropylsilyl directing group.

boron reagents has been achieved by the Yu group,[9a,12] almost no other reactions involving the coupling of C(sp^3)–H bonds and C(sp^3) organometallic reagents have been reported ever since. Inspired by the success of the alkylation of C(sp^2)-H bonds, we examined the applicability of this protocol for C(sp^3)–H bonds.[13] Therefore, 2-(butyldimethylsilyl)pyridine was subjected to the standard reaction conditions. Gratefully, the methyl group was butylated selectively in 36% (eq. 1).

Interestingly, 2-(dimethyl(phenyl)germyl)pyridine also underwent the alkylation reaction with butylboronic acid and the phenyl group was butylated in 26% yield (eq.2).

The pyridyldiisopropylsilyl directing group can be quantitatively removed using AgF (Scheme 4),[4a] demonstrating the practical utility of this alkylation reaction.

In conclusion, we have successfully developed pyridyldiisopropylsilyl-directed C–H alkylation reaction with alkylboronic acids. The amino acid, Ac-Gly-OH, played a crucial role in the reaction. The pyridyldiisopropylsilyl directing group can be removed or transformed into other functional groups, so the reaction provides an efficient method for the alkylation of arenes. The protocol is also applicable to the coupling of C(sp^3)–H bonds with alkylboronic acid.

Acknowledgements

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