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Palladium/Norbornene-Catalyzed *ortho*-Silylmethylation Reaction: A Practical Protocol for *ortho* Functionalized-one-carbon Homologation of Aryl Iodides†

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A palladium/norbornene-catalyzed *ortho*-silylmethylation reaction by the use of (iodomethyl)cyclohexyloxydimethylsilane as the electrophile was reported. The ((cyclohexyloxy)dimethylsilyl)methyl group was readily oxidized by Fleming–Tamao process or ceric ammonium nitrate to give benzylic alcohol derivatives. This method was successfully applied in a concise synthesis of Schisandrins' biaryl analogue.

One carbon homologation reactions of aromatic compounds are useful transformations in organic synthesis. Introducing one-carbon functional groups into arenes not only increases the complexity of the molecules, but significantly raises the ability for further elaborations. The importance of these transformations was recognized as name reactions, including Vilsmeier-Haack reaction,[1] Gattermann reaction, Gattermann-Koch reaction,[2] Reimer-Tiemann reaction,[3] and so on. Chloromethylation of arenes was realized in the presence of formaldehyde, HCl and $ZnCl_2$.[4] However, these reactions proceeded via Friedel-Crafts-type mechanism or carbene pathway, which generally should be conducted under harsh conditions. Furthermore, the reactivity and regioselectivity were extremely affected by the electronic properties of the substrates. In some case, the reactions gave undesired products via the electronic orientation of (hetero)arenes and their substituents.

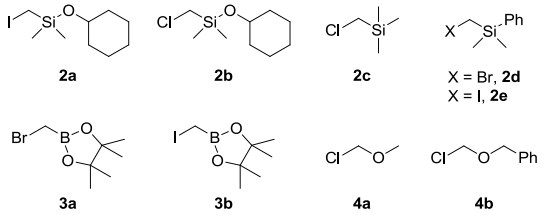
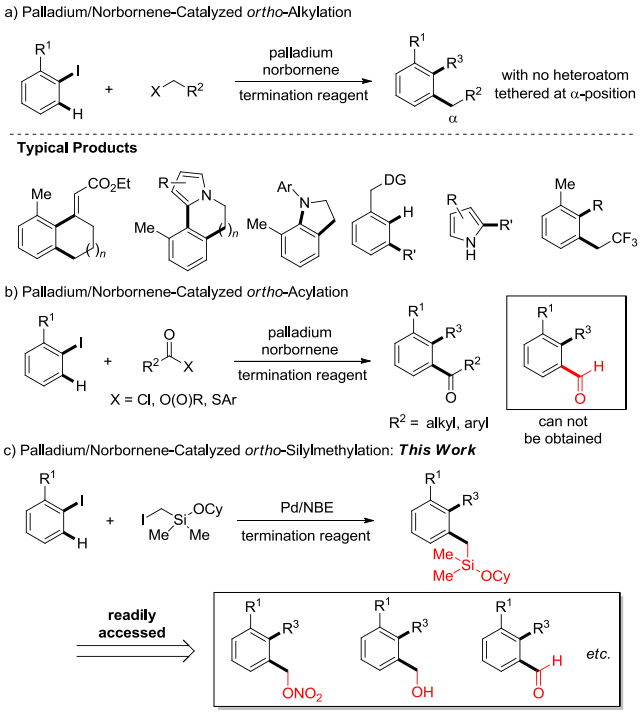


Figure 1 The Screened "One-carbon" Electrophiles



Scheme 1 Catellani *ortho*-C-H Functionalization

Transition metal-catalyzed cyanation, carboxylation and related reactions are also efficient protocols for introducing one-carbon functional groups.[5] In 1997, Catellani and co-workers described a palladium/norbornene-catalyzed reaction of aryl halides and alkyl halides in the presence of acrylates.[6] This powerful transformation, later called Catellani reaction, not only realized an *ipso*-Heck coupling, but successfully introduced alkyl groups at the *ortho* position. The alkyl halides could tether various functional groups, and many interesting

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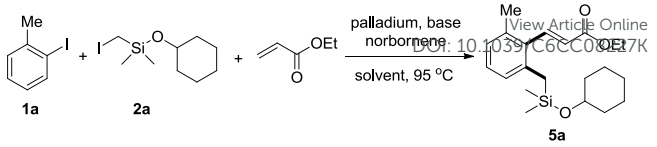
poly-substituted aromatic compounds were synthesized in an efficient and concise manner by the groups of Lautens, Catellani and others (Scheme 1a).[7,8] Furthermore, amino groups could be efficiently introduced to the *ortho* position by the use of *O*-benzoyl hydroxylamines as electrophiles.[9] However, during the early period there was no studies focused on the direct introduction of α-functionalized carbon-chains at the *ortho*-position via Pd/NBE catalysis though the prominence of benzylic amines/alcohols *etc.* is undoubtedly evident from their synthetic utilities and biological activities. Recently acyl groups were introduced at the *ortho*-position of aryl iodides by Liang, Dong and our groups, where acid chlorides, acid (mixed)anhydrides and thiolesters were successfully used as the electrophiles (Scheme 1b).[10] In these reactions aromatic acid chlorides and anhydrides had better performances than the aliphatic acid derivatives. Furthermore, formic acid derived mixed anhydrides failed to give the corresponding aryl aldehydes by this protocol. Given the extreme importance of aryl aldehydes and related benzyl derivatives, herein we report a palladium/norbornene-catalyzed *ortho*-silylmethylation reaction by the use of (iodomethyl)cyclohexyloxydimethylsilane as the electrophilic reagent (Scheme 1c).

Our initial plan was to introduce a functionalized methylene group into *ortho*-position of aryl halides, and the products would be easily converted to benzyl alcohols, benzyl chlorides or benzaldehyde *etc.* With this in mind, we chose halomethylboronates and halomethylsilanes as electrophiles, which were anticipated to be oxidized to give benzylic alcohols. Thus, halomethylsilanes **2a**-**e**, halomethylboronates **3a**-**b** and chloro(alkoxy)methane **4a**-**b** were used to react with **1a** and ethyl acrylate under the catalysis of palladium and norbornene (Figure 1). When **2c-d** were as electrophiles the reaction gave the possible corresponding products (by the analysis of GC-MS), which, however, were contaminated with other unidentified mixtures, and no pure products could be obtained by the column chromatography purification on silica gel. (Cyclohexyloxy)(iodomethyl)dimethylsilane **2a** successfully reacted with **1a** to give **5a** in decent yield (Table 1, entry 1), while the chloride **2b** was totally inert under the identical conditions. The trials by the use of boronates **3a**-**b** and chloro(alkoxy)methane **4a**-**b** as *ortho* alkylation partners failed to deliver the *ortho*-methenylation products. Thus, compound **1a** was chosen as the reagent in all subsequent studies since it showed good reactivity and molecular polarity. Furthermore, the alkoxylsilyl group was ready for further elaborating. Briefly screening indicated that K_2CO_3 was superior over other bases (entry 2). Ligand P(*p*-$MeOC_6H_4$)$_3$ showed better performance than PPh_3 or P(2-furyl)$_3$ (entries 3-4). The reactions under the catalysis of two phosphine based palladium catalysts, $Pd(PPh_3)_4$ or $PdCl_2$/P(2-furyl)$_3$ gave inferior results (entries 5-6). Marginally lower yield was obtained when toluene was used as the solvent (entry 9), while the reactions conducted in DMF or dioxane gave significantly dropped yields (entries 7-8).

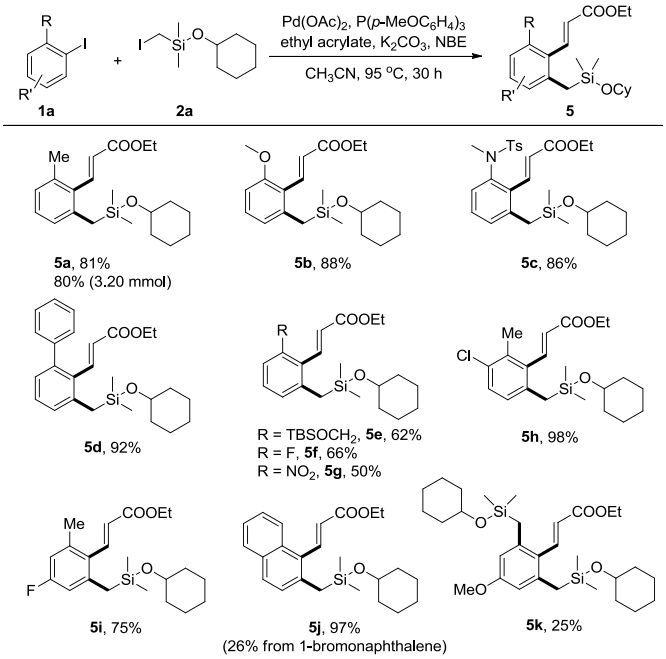
Table 1 Reaction Condition Optimization[a]



entry	Catalyst	base	solvent	Yield of 5a/%[b]
1	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	CH_3CN	45
2	$Pd(OAc)_2/PPh_3$	K_2CO_3	CH_3CN	60
3	$Pd(OAc)_2$/P(furyl)$_3$	K_2CO_3	CH_3CN	66
4	$Pd(OAc)_2$/**L**[c]	K_2CO_3	CH_3CN	81
5	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	68
6	$PdCl_2$/P(furyl)$_3$	K_2CO_3	CH_3CN	45
7	$Pd(OAc)_2$/**L**[c]	K_2CO_3	DMF	67
8	$Pd(OAc)_2$/**L**[c]	K_2CO_3	dioxane	25
9	$Pd(OAc)_2$/**L**[c]	K_2CO_3	toluene	78

[a] The reaction was conducted with **1a** (0.157 mmol), **2a** (2.5 equiv), ethyl acrylate (3.5 equiv), palladium (10 mol %), ligand (20 mol %), base (3.0 equiv), and norbornene (4.0 equiv) at 95 °C for 30 h. [b] Isolated Yields. [c] L = P(p-$MeOC_6H_4$)$_3$

Table 2. With Acrylate as Termination Reagent[a]

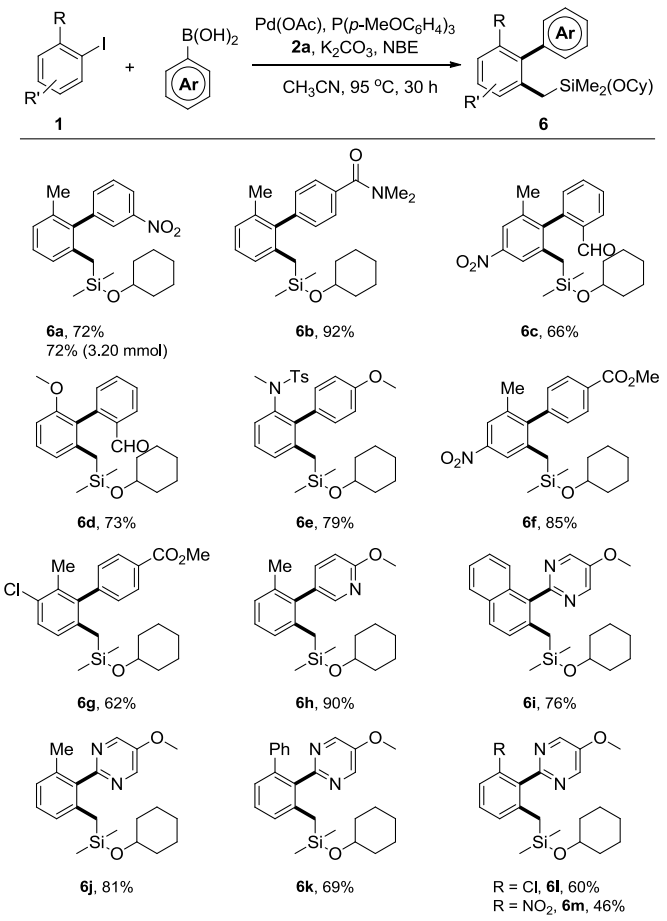


[a] The reaction was conducted with **1** (0.157 mmol), **2a** (2.5 equiv), ethyl acrylate (3.5 equiv), $Pd(OAc)_2$ (10 mol %), P(p-$MeOC_6H_4$)$_3$ (20 mol %), K_2CO_3 (3.0 equiv), and norbornene (4.0 equiv) at 95 °C for 30 h.

With the optimal conditions in hand, we tested the generality of this protocol. Replacing the *o*-methyl group to heteroatom-based groups, such as OMe or NMeTs, did not change the reactivity. For examples, excellent yields of **5b** and **5c** could be achieved. Furthermore, the *ortho* groups could be phenyl (**5d**), $TBSOCH_2$ (**5e**), fluoro (**5f**) and nitro (**5g**) groups, albeit relatively lower yield for electron withdrawing group (**5g**)

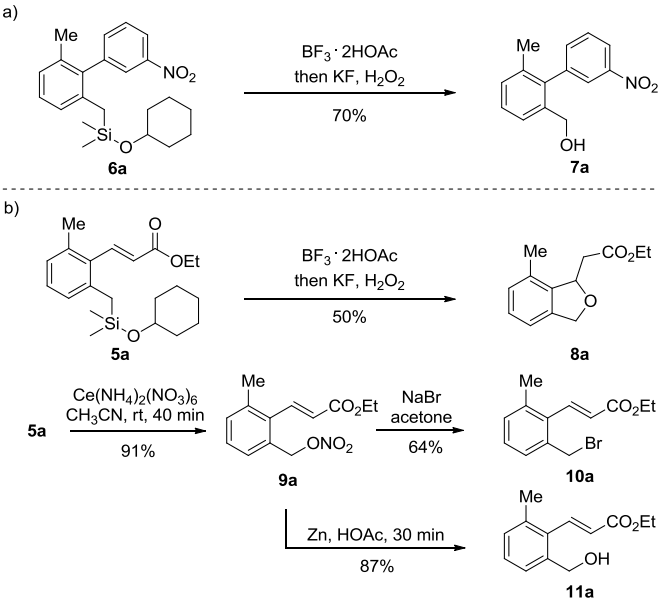
was observed. The reactions with trisubstituted aryl iodides proceeded uneventfully (**5h**-**j**). The reaction with bromoearenes as the substrates proceeded in low efficiency. For example, treatment of 1-bromonaphthalene with 5.0 equiv of **2a** under standard conditions only gave 26% of **5j** and the most of bromoarene was unchanged. Dialkylation of 1-iodo-4-methoxybenzene did give the desired product **5k** albeit in low yield. A reaction with 3.20 mmol (0.698 g) scale of **1a** was performed, and it gave **5a** in 80% yield smoothly.

Table 3 With (Hetero)arylboronates as Termination Reagents

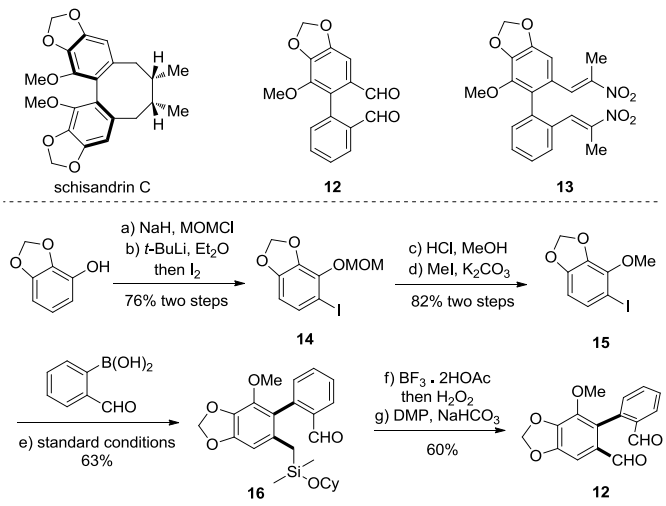


This protocol was also suitable for synthesis biaryl derivatives by applying (hetero)aryl boronic acid as the termination reagents, and the reaction had a fairly broad functional group tolerance (Table 3). The electron-donating groups, such as methoxyl (**6d**), NMeTs (**6e**), and electron-withdrawing groups, such as nitro (**6c**, **6f** and **6m**), chloro (**6g** and **6l**) were compatible functionalities in aryl halide components. Aryl boronic acids could tolerate nitro (**6a**), aldehyde (**6c** and **6d**), ester (**6f** and **6g**), amide (**6b**) and methoxyl groups (**6e**). Moreover, heteroaryl boronic acid, such as (6-methoxypyridin-3-yl)boronic acid (**6h**) and (5-methoxypyrimidin-2-yl)boronic acid (**6i**-**m**) are good coupling partners.

As our hypothesis, the silyl groups were supposed to be converted to other useful functional groups. Pleasingly the biaryl compound **6a** was readily transferred to benzylic alcohol via Fleming–Tamao oxidation (Scheme 2).[11] To our disappointment, treatment of **5a** with $BF_3 \cdot 2HOAc$, then KF, H_2O_2 gave a cyclized product **8a**. Nonetheless, treatment of **5a** with ceric ammonium nitrate (CAN) in CH_3CN at room temperature quickly gave benzyl nitrate **9a** in excellent yield.[12] Subsequently, nitrate **9a** was readily reduced to benzyl alcohol with zinc in acetic acid in good yield. The nitrate **9a** was also smoothly transferred to benzylic bromide, which is suitable for various elaborations.



Scheme 2. Cleavage of the Silyl Groups



Scheme 3. Synthesis of Biaryl Compound **12**

Schisandrins, such as schisandrin C, are isolated from traditional Chinese medicinal plant *Schizandra chinensis* and show promising antitumor effect.[13] Compound **12** is one of biaryl non-dibenzocyclooctene analogous of schisandrins. It showed potent activity against DU145, A549, KB and KB-Vin tumor cell lines (Scheme 3). Diene **13** showed selectivity potential for DU145, A549 against KB and KB-Vin.[14] After masking the free hydroxyl group of benzo[d][1,3]dioxol-4-ol with MOMCl, *ortho*-group-directed lithiation and quenched by

iodine gave compound **14**. Two-step operation of **14**: acidic hydrolysis and methylation would deliver the desired material **15**, which underwent palladium/norbornene-catalyzed *ortho*-silylmethylation reaction under standard conditions to provide **16** uneventfully. Fleming–Tamao oxidation of **16** gave benzyl alcohol, which was oxidized to **12** by Dess-Martin periodinane in decent overall yield.

In conclusion, we developed a palladium/norbornene-catalyzed *ortho*-silylmethylation reaction by the use of (iodomethyl)cyclohexyloxydimethylsilane as the electrophile. The silyl group was readily cleaved either via Fleming–Tamao oxidation or by ceric ammonium nitrate under neutral conditions to give the corresponding alcohol derivatives. Finally biaryl compound **12**, which showed potent anti-tumour activity against DU145, A549, KB and KB-Vin, was synthesized in a concise manner via this newly developed method.

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