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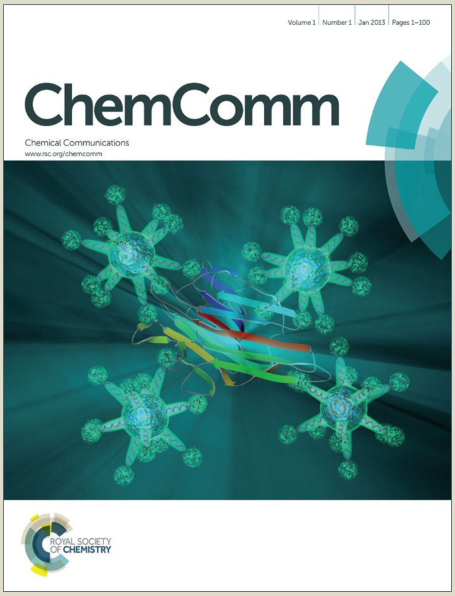

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Palladium-Catalyzed C(sp^3)-C(sp^2) Cross-Coupling of Homoleptic Rare-Earth Metal Trialkyl Complexes with Aryl Bromides: Efficient Synthesis of Functionalized Benzyltrimethylsilanes

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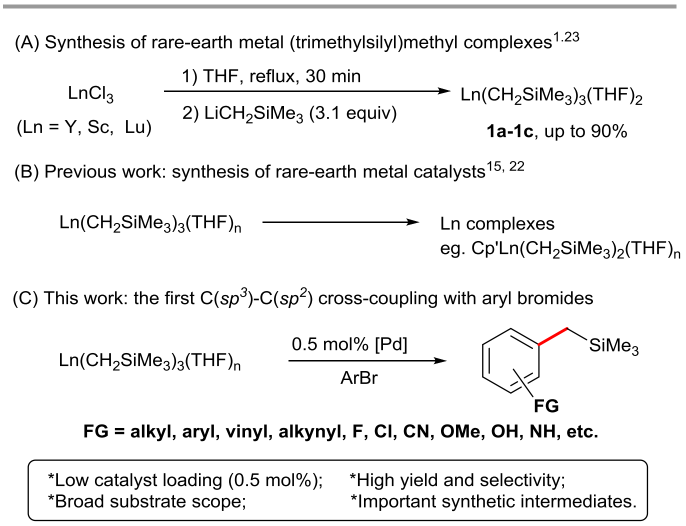
The first C(sp^3)-C(sp^2) cross-coupling of rare-earth metal alkyl complexes with aryl bromides had been developed. This reaction was conducted at low catalyst loading (0.5 mol%) and exhibited broad substrate scope, thus providing a facile method for the synthesis of benzyltrimethylsilanes with diverse functional groups.

As abundant in Earth's crust, rare-earth metals (17 elements, including Sc, Y, and lanthanides) have broad applications in both industry and academic research. In particular, organometallic compounds of rare-earth metals have been extensively studied in the past several decades.[1] Due to the highly polarized M-C bonds and the Lewis acidic metal centers, these compounds exhibit dual properties (electrophilic and nucleophilic or basic and acidic). For example, the cationic complexes with high Lewis acidity could act as competent catalysts in polymerization[2] and organic reactions.[3] On the other side, the neutral complexes often played the role of nucleophiles in many organic transformations[4] including cross-couplings. In 1984, Fujiwara reported the first cross-coupling reaction of rare-earth metal aryl complexes (PhYbI) with organic halides by various transition-metal catalysts.[5] Many years later, Knochel reported a practical method for the synthesis of triaryl-lanthanum reagents (Ar_3La) and demonstrated efficient cross-couplings of these reagents with aryl iodides in the presence of $Pd(PPh_3)_4$.[6] Although lanthanide salts exhibited positive effects in Pd-catalyzed cross-coupling of aryl bromides with triethylaluminium, no unambiguous evidence supported the involvement of *a discrete alkyl lanthanide* as the coupling partner.[7]

Transition-metal catalyzed cross-couplings represent one of the powerful tools to construct carbon-carbon bonds. Versatile synthetic methods utilizing various organometallic reagents (Li,[8] B,[9] Mg,[10] Zn,[11] Si,[12] Sn,[13] In,[14] etc.) have been well developed. To the best of our knowledge, the application of *discrete rare-earth metal alkyl complexes* in transition-metal catalyzed cross-couplings has never been reported. In connection with our interest in organometallic chemistry of rare-earth metals,[15] we examined the cross-coupling of homoleptic rare-earth metal trialkyl complexes with aryl bromides via palladium catalysis and developed a facile method for efficient construction of benzyltrimethylsilanes with diverse functional groups (Scheme 1C).[16-21]

The stability and reactivity of rare-earth metal alkyl complexes are highly dependent on the sizes of the metal cations and the alkyl groups. Particularly, the homoleptic trialkyl complexes are often of low stability at ambient temperature.[22] Due to the steric bulk, the silyl stabilizing effect, and the absence of β-hydrogen and alkyl groups, the rare-earth metal trialkyl complexes $Ln(CH_2SiMe_3)_3(THF)_n$[23] exhibited suitable stability and reactivity, and thus were widely used as the starting materials in organorare-earth metal chemistry (Scheme 1B).[22] Therefore, we synthesized a series of such complexes **1a-1c** in high yield from three rare-earth metal chlorides $LnCl_3$ (Scheme 1A), and tested the cross-coupling of these reagents with 4-bromoanisole **2a**. In the presence of



Scheme 1. Preparation of $Ln(CH_2SiMe_3)_3(THF)_n$ and their application in syntheses

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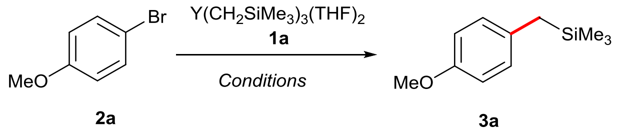
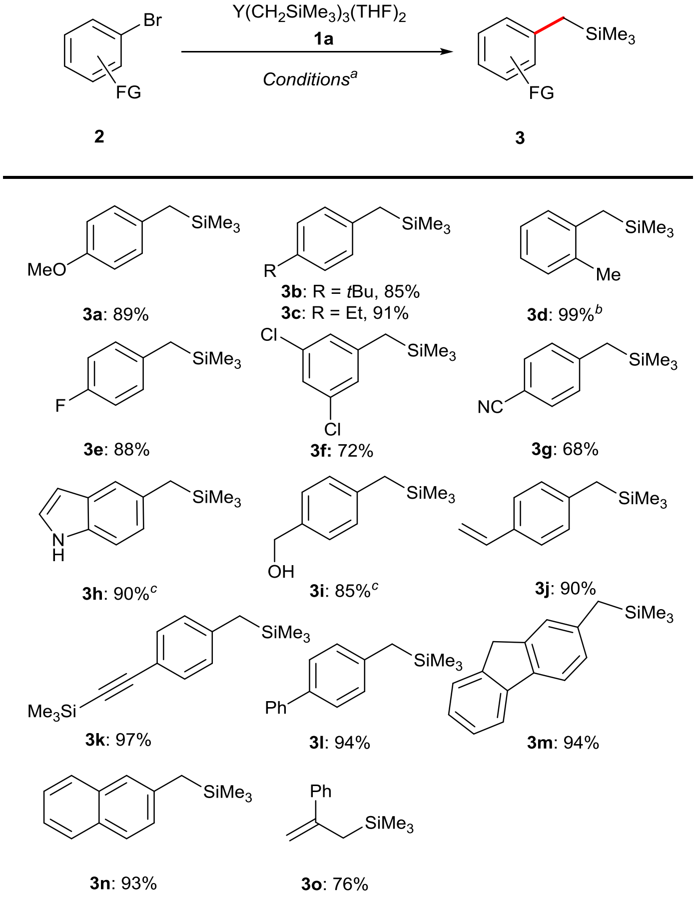
Table 1. Condition optimization for the cross-coupling reaction of 4-bromoanisole **2a** with $Y(CH_2SiMe_3)_3(THF)_2$[a]



Entry	[Pd]/Ligand (mol%)	**1a** (equiv)	Conv. **2a**[b] (%)
1	-/-	0.4	0
2	$Pd_2(dba)_3$ (2.5)/-	0.4	0
3	$Pd_2(dba)_3$ (2.5)/XPhos (10)	0.4	100
4	$Pd_2(dba)_3$ (2.5)/SPhos (10)	0.4	55
5	$Pd(PtBu_3)_2$ (5)/-	0.4	17
6	$Pd_2(dba)_3$ (1)/XPhos (4)	0.33	99
7	$Pd_2(dba)_3$ (0.5)/XPhos (2)	0.33	99 (89)[c]
8	$Pd_2(dba)_3$ (0.25)/XPhos (1)	0.33	85

[a] Conditions: 4-bromoanisole **2a** (1.0 equiv, 0.075 mmol), Pd catalyst, ligand and $Y(CH_2SiMe_3)_3(THF)_2$ **1a** (0.33-0.4 equiv) in toluene-d_8 (1 mL) at room temperature, N_2, 1 h. [b] The conversions of **2a** were determined by ^1H NMR analysis of the reaction mixtures. [c] Isolated yield was provided in the parenthesis.

Table 2. Scope of the reaction of aryl halides with $Y(CH_2SiMe_3)_3(THF)_2$[a]



[a] Conditions: **2** (1.0 equiv, 0.3 mmol), $Pd_2(dba)_3$ (0.5 mol%), XPhos (2 mol%) and $Y(CH_2SiMe_3)_3(THF)_2$ **1a** (0.33 equiv) in toluene (4 mL) at room temperature, N_2, 1 h. [b] 2-iodotoluene was used instead of 2-bromotoluene. [c] 0.66 equiv **1a** was used.

$Pd_2(dba)_3$ (2.5 mol%) and XPhos (10 mol%), all the reactions carried out in toluene at room temperature completed in one hour, and furnished the desired cross-coupling product **3a** in 89-95% yield without homo-coupling product and dehalogenation product detected (See Table S1 in ESI). The full conversion of aryl bromide **2a** in the presence of 0.4 equiv of **1** indicated that all the three alkyl moieties in the complexes were transferred to the product **3a**. It is also worth noting that slow addition of these organometallic reagents over the whole reaction time is not needed.

Further optimization of the reaction conditions using the yttrium complex **1a** and **2a** as the test substrates had been conducted. Key observations leading to the optimum conditions were summarized as follows: (a) Without the palladium catalyst or ligand, no cross-coupling product was observed (entries 1 and 2, Table 1). (b) Among several Pd catalyst/ligand combinations, the $Pd_2(dba)_3$/XPhos was the optimal (entries 3-5, Table 1). Furthermore, the catalyst loading of $Pd_2(dba)_3$/XPhos could be reduced to *0.5 mol%* without the decrease in reaction efficiency and product selectivity for **3a** (entry 7, Table 1). (c) Only 0.33 equiv of trialkylyttrium **1a** was needed for the full conversion of aryl bromide **2a**. This result reflected the high stability and excellent reactivity of the rare-earth metal trialkyl complexes **1** in Pd-catalyzed cross-coupling reaction under ambient conditions. Finally, the optimum conditions were determined as: 4-bromoanisole **2a** (1.0 equiv), $Y(CH_2SiMe_3)_3(THF)_2$ **1a** (0.33 equiv), $Pd_2(dba)_3$ (0.5 mol%), XPhos (2 mol%), and toluene (c_{2a} = 0.075 M) at room temperature under nitrogen atmosphere for 1 h. Under these conditions, the cross-coupling product **3a** was isolated in 89% yield.

With the optimum conditions in hand, the substrate scope of the reaction was next examined (Table 2). Firstly, aryl bromides bearing both electron-donating (OMe, *t*Bu, Et and Me) and electron-withdrawing (fluoro, chloro) groups at *ortho*-, *meta*-, and *para*-positions all coupled with **1a** smoothly and delivered the desired products in good to excellent yields (**3a**, **3b**, **3c**, **3d**, **3e** and **3f**). Although functional groups such as ketone and ester were not compatible to our method due to the fast 1,2-addition reaction, the nitrile-containing substrate (**2g**) was proved to be coupled with only 0.33 equiv **1a** well, giving 4-cyanobenzyltrimethylsilane **3g** in 68% yield. Secondly, functional groups containing active protons (such as OH, NH) were tolerated. Without protection of the OH and NH groups, the reaction of 5-bromoindole **2h** and 4-bromobenzyl alcohol **2i** with 0.66 equiv **1a** gave the corresponding C-C coupling products (**3h** and **3i**) in excellent yields without C-N and C-O coupling products detected. Thirdly, functional groups such as aryl, vinyl and alkynyl were compatible to this reaction very well. The vinyl- and alkynyl-substituted substrates (**2j** and **2k**) reacted with **1a** nicely and furnished the products with vinyl and alkynyl groups. These functionalities in the products provided a handle for further transformations. Finally, this reaction method could not only be applied to aryl and heteroaryl bromides, but also to vinyl bromides. Actually, the reaction of α-bromostyrene **2o** with **1a** afforded the desired allyltrimethylsilane **3o** in 76%.

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In summary, a highly efficient C(sp^3)-C(sp^2) cross-coupling of $Ln(CH_2SiMe_3)_3(THF)_2$ with aryl bromides had been developed for the construction of functionalized benzyltrimethylsilanes. This reaction was conducted at room temperature in the presence of only *0.5 mol%* $Pd_2(dba)_3$/4XPhos and exhibited broad substrate scope. The functionalities in these $ArCH_2SiMe_3$ products provide a handle for further functionalization. Furthermore, these silanes can be transformed into olefins, aldehydes, acylsilanes, alcohols and amines by Peterson olefination,[24] photocatalyzed[25] or gold-catalyzed[26] reactions, and fluoride-mediated addition reactions[27]. The application of this reaction as the key step in total synthesis of natural products is under way.

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