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Ligand-Enabled Cross-Coupling of C(sp³)–H Bonds with Arylsilanes

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Abstract

Pd(II)-catalyzed cross-coupling of C(sp³)–H bonds with organosilicon coupling partners has been achieved for the first time. The use of a newly developed quinoline-based ligand is essential for the cross-coupling reactions to proceed.

Graphical abstract

Inspired by the Pd(0)-catalyzed cross-coupling reactions,¹ we embarked on the development of Pd(II)-catalyzed cross-coupling of C–H bonds with organometallic reagents. A Pd(II)/Pd(0) catalytic cycle has been established for the cross-coupling of C(sp²)–H bonds with organotin² and organoboron reagents³ with limited substrate scopes. Subsequently, C–H cross-coupling with readily available organoboron reagents are expanded to broadly useful substrates including benzoic acids and phenyl acetic acids.^{4,5} In contrast, analogous cross-coupling of C(sp³)–H bonds with organometallic reagents has met with limited success.⁶ Although pyridine-directed C(sp³)–H cross-coupling with alkyl boronic acids is successful,³ extending this methodology to aliphatic acid substrates affords poor yields (<30%) (Eq 1).⁴ The development of an efficient *N*-methoxyamide directing group allowed for a rare cross-coupling of β -C(sp³)–H bonds with boronic acids (Eq 2).⁷ Unfortunately, this protocol is incompatible with the substrates containing α -hydrogen atoms. These limitations call for further development of new protocols for C(sp³)–H cross-coupling. Herein, we report the first example of β -C(sp³)–H cross-coupling of carboxylic acids with arylsilanes using perfluorinated *N*-arylamide auxiliary (Eq 3).⁸ The discovery of a new quinoline-based ligand is crucial for the development of this cross-coupling of C(sp³)–H bonds with arylsilanes.

A wide range of organosilicon reagents have been successfully used as coupling partners in the Hiyama cross-coupling reactions of aryl halides.^{1f,9} Important advances have also been made in the cross-coupling of alkyl halides with arylsilanes.¹⁰ Despite significant progress of Pd-,^{11,12} Rh-,¹³ and Ni-catalyzed¹⁴ C(sp²)-H cross-coupling with arylsilanes, cross-coupling of inert C(sp³)-H bonds with organosilicon reagents remains to be reported. Encouraged by our recent observation that pyridine- and quinoline-based ligands promote C(sp³)-H olefination via a Pd(II)/Pd(0) catalytic cycle,¹⁵ we launched our efforts to develop new ligands that could promote β -C(sp³)-H cross-coupling of carboxylic acid derivatives with organosilicon reagents.

Our experiments commenced by investigating the coupling of an alanine-derived amide **1** with various organosilicon reagents (see supporting information). We examined various oxidants and solvents, as well as those additives previously proven to be beneficial to the Hiyama cross-coupling. We found the reaction of amide **1** with 2 equiv. of triethoxyphenylsilane (**2a**) in the presence of 10 mol% of Pd(OAc)₂, 20 mol% of 2-picoline (**L1**), and 3 equiv. of AgF in 1,4-dioxane at 110 °C afforded the desired product **3a** in 40% yield. AgF proves to be the only effective additive which has dual functions in this transformation: 1) silver salts are one of the most efficient and commonly used oxidants to reoxidize Pd(0) to Pd(II) in Pd(II)/Pd(0) catalytic cycles;¹⁶ 2) fluoride sources are known to activate organosilicon coupling partners, promoting transmetalation of aryl groups to Pd(II).¹⁷ Analysis of the reaction mixture showed that a substantial amount of organosilicon reagents were homo-coupled to give the biaryl side product. In the absence of ligands, the desired coupling reaction did not proceed, indicating a significant ligand effect. We therefore began to examine a variety of substituted pyridine and quinoline ligands that could potentially accelerate the C(sp³)-H cross-coupling further in order to outcompete the homo-coupling process (Table 1). 2,6-Lutidine (**L2**) and 2,6-dimethoxypyridine (**L3**) gave the desired product in lower yields (28% and 13% respectively), demonstrating that the increase of steric bulk and electron-donating ability of pyridine-based ligands has negative impact on the reaction. However, replacement of 2-picoline (**L1**) with electron-deficient 2-trifluoromethylpyridine (**L4**) resulted in a complete loss of reactivity.

These failed attempts to optimize pyridine ligands directed our attention to quinoline-based ligands (**L5–L18**). The tricyclic quinoline ligands (**L5**, **L6**) were initially chosen because they were previously used to promote Pd-catalyzed C(sp³)-H olefination reactions via Pd(II)/Pd(0) catalysis.¹⁵ We found that the use of **L6** increased the yield of **3a** to 48%. Based on this finding, we systematically surveyed different types of quinoline-based ligands. Gratifyingly, the simple quinoline (**L7**) further improved the reactivity, giving **3a** in 56% yield. While the substituent at the 6-position of quinoline **L8** did not affect the yield, installation of a methyl group at the 8-position (**L9**) drastically decreased the reaction efficiency. Any substitution at the 2-positions of quinoline-based ligands (**L10**, **L11**) was detrimental to the cross-coupling reactions. These investigations showed that this Hiyama-type cross-coupling is very sensitive to the steric effect of quinoline-based ligands. In terms of electronic effects, electron-donating groups at the 3- or 4-positions of quinolines (**L12–L14**) gave moderate yields from 48% to 52% whereas electron-deficient 4-chloroquinoline (**L15**) afforded only 34% yield. Given that quinolines containing fused carbocyclic rings

could have distinct steric and electronic properties, we introduced 5-, 6-, and 7-membered rings to the ligands (**L16–L18**), and found **L18** provided the highest yield of 70%. The yield was further increased to 93% when a second batch of **2a** and AgF was added after 8 hours.

Cross-coupling reactions of alanine-derived amide **1** with a broad range of electron-rich and electron-poor triethoxyarylsilanes were carried out under the standard conditions (Table 2). Triethoxyarylsilanes containing methyl and methoxy groups on the aryl ring afforded desired products in excellent yields (**3b**, **3c**). *para*-Fluoro, chloro, bromo, and trifluoromethyl groups are well tolerated, furnishing phenylalanine derivatives in yields from 75% to 82% (**3d–3g**). This reaction is also compatible with *meta*- and *ortho*-substituted triethoxyarylsilanes (**3h**, **3i**). Furthermore, the cyclobutyl C(sp³)–H bond in amide substrate **4** derived from 1-aminocyclobutane-1-carboxylic acid was successfully functionalized to afford the corresponding β -alkyl- β -aryl- α -amino acid derivatives in 72% yield with high levels of diastereoselectivity (Scheme 2). The cross-coupling reaction was also carried out on a gram scale without a noticeable decrease in yield (**3e**). Importantly, complete retention of α -chirality (**3b**) was observed in the β -C(sp³)–H cross-coupling using amide **1** (99% ee) as the substrate.

To investigate the compatibility of this protocol with other aliphatic acids, amide **6a** derived from 2-methylpentanoic acid was subjected to standard conditions to afford the arylated product **7a** in 45% yield. Extensive optimization including changing ligands and bases (see SI) improved the yield to 67% (Table 3). Under these new conditions, a variety of amides derived from aliphatic acids were arylated in good yields (**7b–7d**). The cross-coupling of amide **6e** containing a trifluoromethyl group afforded the desired product **7e** in 80% yield. A number of aryl groups on the β - and γ -positions of amide substrates are tolerated (**7e–7i**). The reaction is also tolerant of different types of ether groups including a benzyl protected β -hydroxyl group (**7j–7l**).

While the β - and γ -aryls did not interfere with the β -C(sp³)–H activation, the α -aryl group in the ibuprofen-derived substrate was preferentially *ortho*-arylated under these conditions (Scheme 3). To achieve the site-selective β -C–H arylation of **8**, we turned to our previously developed arylation protocol with aryl iodides and successfully obtained the β -arylated product **10** in 83% yield.^{15a} We anticipate the ability to achieve these orthogonal site-selectivity using two different protocols will be highly useful in synthesis.

In conclusion, ligand-enabled cross-coupling of β -C(sp³)–H bonds in carboxylic acid derivatives with arylsilanes has been achieved using a new quinoline-based ligand. The development of this coupling reaction further demonstrates the potential utility of quinoline-based ligands in Pd-catalyzed C–H activation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Previous work:

Ligand-enabled cross-coupling:

Scheme 1.

Palladium-Catalyzed C(sp³)-H Activation/Cross-Coupling Reactions of Carboxylic Acid Derivatives

Scheme 2.
Cross-Coupling of Cyclobutyl C(sp³)-H Bonds

Scheme 3.
C–H Functionalizations of an Ibuprofen-Derived Amide

Table 1

Screening of Ligand for C(sp³)-H Cross-Coupling with Arylsilanes^{a,b}

—				
0%	40%	28%	13%	0%
42%	48%	56%	54%	
6%	23%	47%	48%	52%
50%	34%	63%	67%	70% (93%) ^c

^a Reaction conditions: substrate **1** (0.1 mmol), **2a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), ligand (20 mol%), AgF (3.0 equiv.), 1,4-dioxane (1.0 mL), 110 °C, 12 h.

^b The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

^c After 8 h, the second batch of **2a** (2.0 equiv.) and AgF (3.0 equiv.) was added, and the reaction proceeded for another 10 h.

Table 2

Synthesis of Phenylalanine Derivatives using Ligand-Enabled C(sp³)–H Cross-Coupling with Arylsilanes^{a,b}

^a Reaction conditions: substrate **1** (0.1 mmol), **2** (2.0 equiv.), Pd(OAc)₂ (10 mol%), **L18** (20 mol%), AgF (3.0 equiv.), 1,4-dioxane (1.0 mL), 110 °C. The second batch of **2** (2.0 equiv.) and AgF (3.0 equiv.) was added at 8 h. The reactions were run for 18 h total.

^b Isolated yields.

^c The ee value was determined by chiral HPLC.

^d Isolated yield of a gram-scale reaction in the parenthesis.

Table 3

 β -C(sp³)-H Cross-Coupling of Carboxylic Acid Derivatives with Arylsilanes^{a,b}

^a Reaction conditions: substrate **6** (0.1 mmol), **2a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), **L6** (20 mol%), KHCO₃ (2.0 equiv.), AgF (3.0 equiv.), 1,4-dioxane (1.0 mL), 110 °C. The second batch of **2a** (2.0 equiv.) and AgF (3.0 equiv.) was added at 8 h. The reactions were run for 18 h total.

^b Isolated yields.