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Ligand-Enabled Cross-Coupling of C(sp^3)–H Bonds with Arylsilanes

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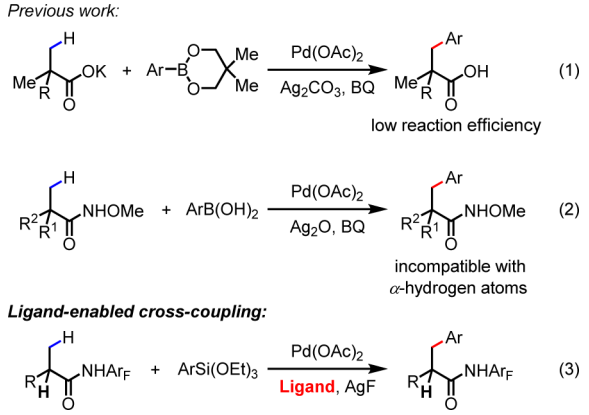
Supporting Information

ABSTRACT: Pd(II)-catalyzed cross-coupling of C(sp^3)–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.

Inspired by 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 was established for the cross-coupling of C(sp^2)–H bonds with organotin[2] and organoboron reagents[3] with limited substrate scopes. Subsequently, C–H cross-coupling with readily available organoboron reagents has been expanded to broadly useful substrates including benzoic acids and phenylacetic acids.[4,5] In contrast, analogous cross-coupling of C(sp^3)–H bonds with organometallic reagents has met with limited success.[6] Although pyridine-directed C(sp^3)–H cross-coupling with alkylboronic acids has been successfully achieved,[3] extending this methodology to aliphatic acid substrates affords poor yields (<30%) (Scheme 1, eq 1).[4]

Scheme 1. Palladium-Catalyzed C(sp^3)–H Activation/Cross-Coupling Reactions of Carboxylic Acid Derivatives



The development of an efficient *N*-methoxyamide directing group allowed for a rare cross-coupling of β-C(sp^3)–H bonds with boronic acids (eq 2).[7] Unfortunately, this protocol is incompatible with substrates containing α-hydrogen atoms. Although β-C(sp^3)–H arylation with aryl halides via Pd(II)/Pd(IV) catalysis has been developed to accommodate a broader range of substrates,[8] the C(sp^3)–H cross-coupling reaction involving a Pd(II)/Pd(0) catalytic cycle offers a distinct platform for ligand development that will lead to improved catalysis and selectivity. Herein we report the first example of β-C(sp^3)–H cross-coupling of carboxylic acids with arylsilanes using a perfluorinated *N*-arylamide auxiliary (eq 3).[9] The discovery of a new quinoline-based ligand is crucial for the development of this cross-coupling of C(sp^3)–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,10] Important advances have also been made in the cross-coupling of alkyl halides with arylsilanes.[11] Despite significant progress in Pd-,[12,13] Rh-,[14] and Ni-catalyzed[15] C(sp^2)–H cross-coupling with arylsilanes, cross-coupling of inert C(sp^3)–H bonds with organosilicon reagents remains to be reported. Encouraged by our recent observation that pyridine- and quinoline-based ligands promote C(sp^3)–H olefination via a Pd(II)/Pd(0) catalytic cycle,[16] we launched our efforts to develop new ligands that could promote β-C(sp^3)–H cross-coupling of carboxylic acid derivatives with organosilicon reagents.

Our experiments commenced with an investigation of the coupling of alanine-derived amide **1** with various organosilicon reagents (see the 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 % $Pd(OAc)_2$, 20 mol % 2-picoline (**L1**), and 3 equiv of AgF in 1,4-dioxane at 110 °C afforded the desired product **3a** in 40% yield. AgF proved to be the only effective additive, which has dual functions in this transformation: (1) silver salts are among the most efficient and commonly used oxidants to reoxidize Pd(0) to Pd(II) in Pd(II)/Pd(0) catalytic cycles,[17] and (2) fluoride sources are known to activate organosilicon coupling partners, promoting transmetalation of aryl groups to Pd(II).[18] Analysis of the reaction mixture showed that a substantial amount of organosilicon reagents were homocoupled 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 ligands that could potentially accelerate the C(sp^3)–H cross-coupling further in order to outcompete the homocoupling 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 increasing the steric bulk and electron-donating ability of pyridine-based ligands has a negative impact on the reaction. However, replacement of **L1** with electron-deficient 2-

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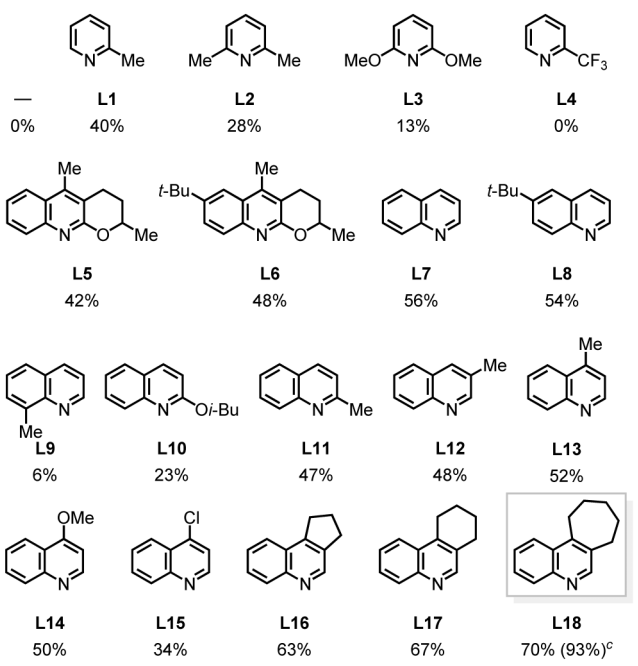
Table 1. Screening of Ligands for C(sp^3)−H Cross-Coupling with Arylsilanes[a,b]



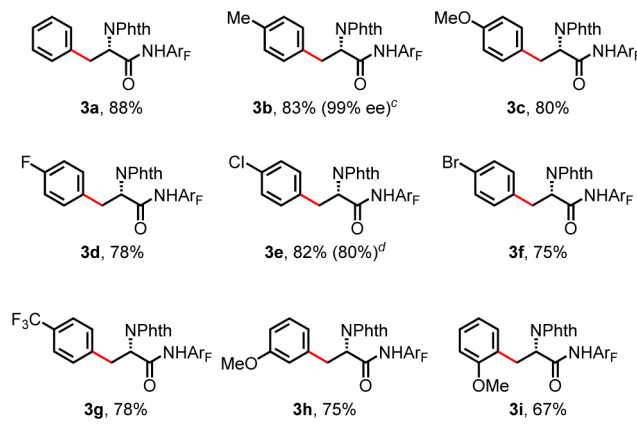
[a]Reaction conditions: substrate **1** (0.1 mmol), **2a** (2.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), AgF (3.0 equiv), 1,4-dioxane (1.0 mL), 110 °C, 12 h. [b]The yields were determined by ^{1}H NMR analysis of the crude products using CH_2Br_2 as the internal standard. [c]After 8 h, a second batch of **2a** (2.0 equiv) and AgF (3.0 equiv) was added, and the reaction proceeded for another 10 h.

trifluoromethylpyridine (**L4**) resulted in a complete loss of reactivity.

While these pyridine ligands have been previously shown to promote arylation of C(sp^3)−H bonds with aryl iodides,[19] the failed attempts to improve the reaction suggested that the transmetalation and reductive elimination at the Pd(II) center require a different type of ligands. The tricyclic quinoline ligands **L5** and **L6** were therefore chosen because they were previously used to promote Pd-catalyzed C(sp^3)−H olefination reactions via Pd(II)/Pd(0) catalysis.[16] We found that the use of **L6** increased the yield of **3a** to 48%. On the basis of 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-position of quinoline-based ligands (**L10**, **L11**) was detrimental to the cross-coupling reaction. 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 the quinoline (**L12**−**L14**) gave moderate yields from 48% to 52%, whereas electron-deficient 4-chloroquinoline (**L15**) afforded only 34% yield. Given that quinolines containing fused carbocylic rings can have distinct steric and electronic properties, we introduced five-, six-, and seven-membered rings into the ligands (**L16**−**L18**) and found that **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 h.

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

Table 2. Synthesis of Phenylalanine Derivatives using Ligand-Enabled C(sp^3)−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. A 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 are shown. [c]The ee value was determined by chiral HPLC. [d]The isolated yield of a gram-scale reaction is shown in parentheses.

on the aryl ring afforded desired products in excellent yields (**3b**, **3c**). *p*-Fluoro, -chloro, -bromo, and -trifluoromethyl groups were well-tolerated, furnishing phenylalanine derivatives in yields from 75% to 82% (**3d**−**g**). This reaction is also compatible with meta- and ortho-substituted triethoxyarylsilanes (**3h** and **3i**, respectively). Furthermore, the cyclobutyl C(sp^3)−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, in the absence of external inorganic bases, complete retention of *α*-chirality (**3b**) was observed in the *β*-C(sp^3)−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 the standard conditions and afforded the arylated product **7a** in 45% yield. Extensive optimization

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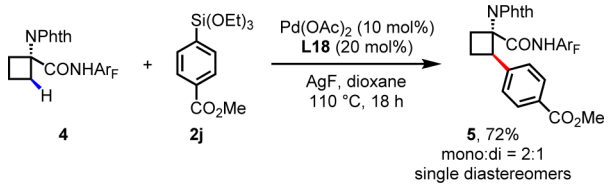
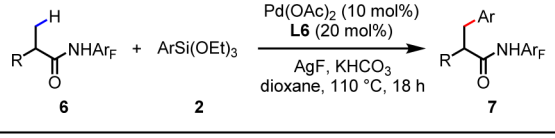
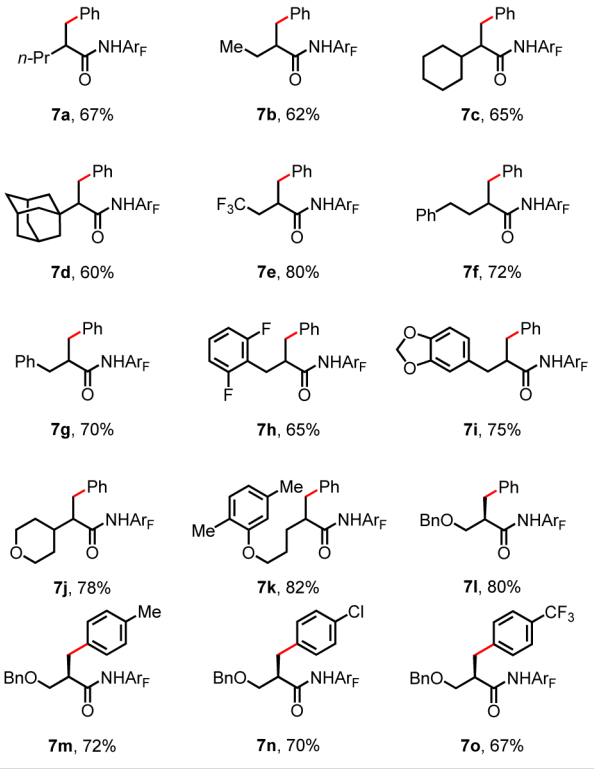
Scheme 2. Cross-Coupling of Cyclobutyl C(sp^3)−H Bonds



including changing the ligand and the base (see the Supporting Information) 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**−**d**). The cross-coupling of amide **6e** containing a trifluoromethyl group afforded the desired product **7e** in 80% yield. A number of aryl groups at the β- and γ-positions of the amide substrates were tolerated (**7e**−**i**). The reaction was also tolerant of different types of ether groups, including a benzyl-protected β-hydroxyl group (**7j**−**l**). Various triethoxyarylsilane partners containing methyl, chloro, and trifluoromethyl groups were coupled with substrate **6l** to give the desired products in good yields (**7m**−**o**). It should be noted that arylation of alanine-derived amide **1** also proceeds under these conditions but leads to substantial racemization of the product.

Table 3. β-C(sp^3)−H Cross-Coupling of Carboxylic Acid Derivatives with Arylsilanes[a,b]

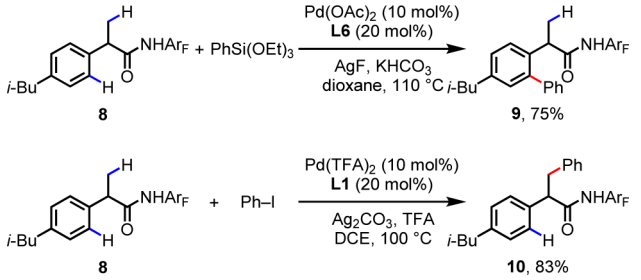




[a]Reaction conditions: substrate **6** (0.1 mmol), **2** (2.0 equiv), Pd(OAc)$_2$ (10 mol %), **L6** (20 mol %), KHCO$_3$ (2.0 equiv), AgF (3.0 equiv), 1,4-dioxane (1.0 mL), 110 °C. A second batch of **2a** (2.0 equiv) and AgF (3.0 equiv) was added at 8 h. The reactions were run for 18 h total. [b]Isolated yields are shown.

While the β- and γ-aryl substituents did not interfere with the β-C(sp^3)−H activation, the α-aryl group in the ibuprofen-derived substrate **8** 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.[16] The observed opposite site selectivity with Pd(II)/Pd(IV)[16] and Pd(II)/Pd(0) catalysis speaks to the importance of developing different catalytic cycles for C−H activation reactions. We anticipate that the ability to arylate C−H bonds at different positions using two different protocols will be highly useful in synthesis.

Scheme 3. C−H Functionalizations of Ibuprofen-Derived Amide 8



In conclusion, ligand-enabled cross-coupling of β-C(sp^3)−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.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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