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Ligand-Promoted Alkylation of C(sp^3)−H and C(sp^2)−H Bonds

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Supporting Information

ABSTRACT: 9-Methylacridine was identified as a generally effective ligand to promote a Pd(II)-catalyzed C(sp^3)−H and C(sp^2)−H alkylation of simple amides with various alkyl iodides. This alkylation reaction was applied to the preparation of unnatural amino acids and geometrically controlled tri- and tetrasubstituted acrylic acids.

Transition metal catalyzed C−H alkylation[1] represents a useful alternative tool for C−C bond formation especially when rearrangement, poor selectivity, or functional group tolerance become problematic in traditional alkylation reactions.[2] While alkylation of C(sp^2)−H and C(sp^3)−H bonds via cross-coupling with alkylborons has been demonstrated,[3] alkyl halides have been more widely utilized as the alkylating reagents in Pd-,[4,5] Ni-,[6,7] Ru-,[8] Co-,[9] and Fe[10]-catalyzed C−H alkylation for the past few years. By employing pyridine-based auxiliaries, Daugulis,[4c,5a,e] Ackermann,[6b,8] Chen,[4d,5b,c] and Chatani[6a] have greatly improved the scope of this potentially powerful methodology. Recently, alkylations of aromatic C(sp^2)−H bonds using Co(II) and Fe(III) catalysts have been developed by Nakamura,[9a,10a] Yoshikai,[9b] and Cook.[10b,c] Despite these achievements, the scope and efficiency of transition metal catalyzed C−H alkylation has lagged behind the rapid progress of the Pd(0)-catalyzed cross-coupling of organometallic reagents with alkyl halides.[12] For example, the C(sp^3)−H alkylation is limited to primary alkyl halides, and only a few examples of using alkyl halides containing β-hydrogen have been reported.[4c,5] The stereoselective syntheses of tri- and tetrasubstituted olefins via vinylic C(sp^2)−H alkylation is potentially attractive, and yet only a few pioneering examples are reported using Ru,[11] Ni,[6a] and Fe[10a,c] catalysts. Notably, Pd-catalyzed vinyl C−H alkylation has not been reported to date. Considering the significant role played by ligands in the Pd(0)-catalyzed cross-coupling of organometallic reagents with alkyl halides,[12] we initiated our effort to develop ligands that can promote C−H alkylation reactions.

We have systematically developed the approach of using a weakly coordinating substrate and a ligand to accelerate C−H activation reactions. In this endeavor, the combination of a weakly coordinating amide directing group (CONHAr) and pyridine- or quinoline-based ligands has been shown to be effective for developing a myriad of Pd-catalyzed C(sp^3)−H functionalization transformations including arylation, carbonylation, and olefination.[13] However, we have been unable to achieve the C−H alkylation with alkyl halides using this simple amide directing group due to (1) *N*-alkylation of the acidic amide is a predominant reaction pathway, especially under basic conditions; (2) potential β-hydride elimination of palladium alkyl species or base-promoted eliminations of alkyl halides. We therefore set out to identify a ligand to promote this alkylation while preventing the β-hydride elimination. In addition, we hoped that the ligand may allow us to perform the alkylation under acidic or neutral conditions so that the *N*-alkylation of the acidic amide can be minimized.

Our initial experimental efforts focused on the development of conditions for C−H methylation using methyl iodide, as this would avoid the complication of β-hydride elimination. An extensive survey of Pd sources, silver additives, and solvents was performed using our previously developed quinoline ligand **L1**.[13a] We found that treatment of **1a** with 2.5 equiv of MeI, 10 mol % of Pd(TFA)$_2$, 20 mol % of **L1**, and 2.0 equiv of Ag_2CO_3 in DCE at 80 °C for 20 h gave the desired product in 17% yield (Table 1). The replacement of Ag_2CO_3 by silver pivalate (AgOPiv) dramatically improved the yield to 74%. Notably, the absence of ligand decreased the yield to less than 5%. The significant impact of the ligand on this methylation reaction led us to focus on the screening of various pyridine and quinoline ligands for the β-methylation of amide **1a** (Table 1). Among various pyridine ligands tested (**L2**−**L5**), 2,6-dimethoxypyridine (**L5**) gave the best result. These results suggest that both the steric bulk and electron-donating ability of the pyridine ligands were crucial for higher reactivity. We then turned our attention to the quinoline ligands (**L6**−**L11**). During this screen a similar trend was observed using quinoline ligands (**L1**, **L6**−**L8**) with 2-alkoxyquinoline ligands affording better yields. Further enhancement of the electron-donating ability of the ligand by introducing another methoxy group did not have much impact on the yield (**L9**). Other structural modifications of 2-alkoxyquinoline ligands (**L10**, **L11**) affected the methylation reaction adversely. It was noticed that quinoline ligands were generally better than the corresponding pyridine ligands, which led us to reason that the phenyl motif in the quinoline ligand might play a pivotal role in this reaction. Therefore, we started to screen acridine ligands (**L12**−**L17**). After a systematic survey of acridine ligands, 9-methylacridine was identified as the optimal ligand (**L13**). Pd(TFA)$_2$ and AgOPiv can be reduced to 5 mol % and 1.5 equiv respectively with **L13**, albeit giving slightly lower yields (see Supporting Information).

With the optimal reaction conditions in hand, various amides derived from corresponding carboxylic acids were methylated at the β-position selectively in good yields (Table 2). The unreacted starting materials were mostly recovered. For aliphatic amides (**3a**−**c**), better yields were obtained with the ones having bulkier α-substituents. Substrates containing

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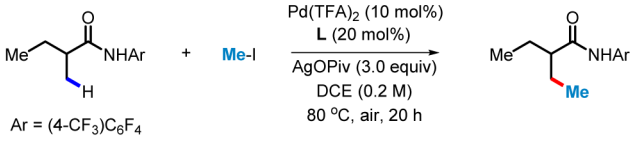
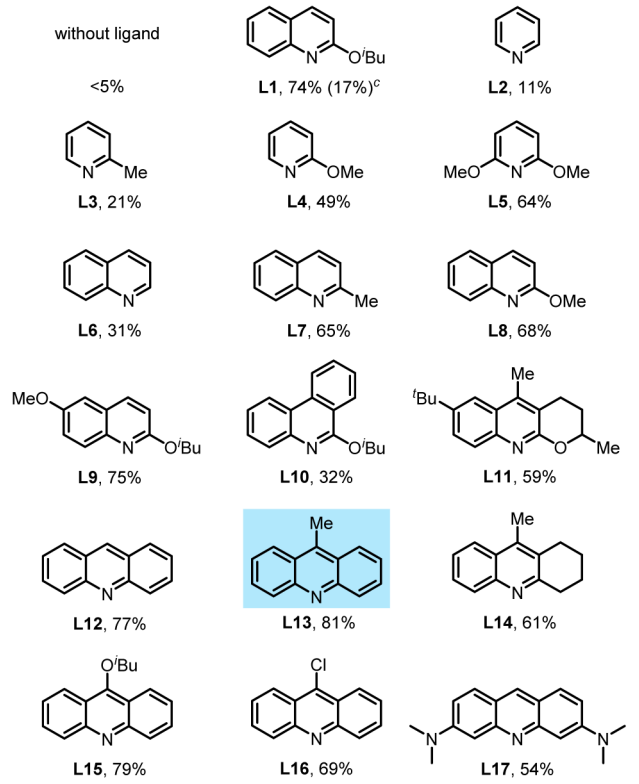
Table 1. Ligand Screening[a,b]

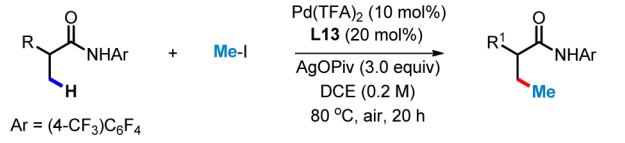


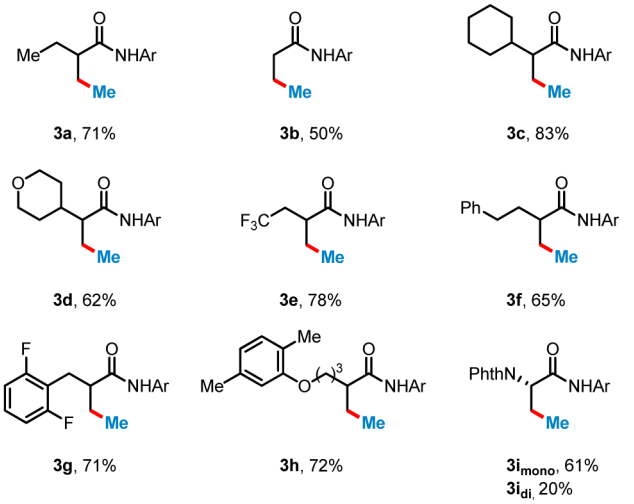


[a]Conditions: 0.1 mmol of **1a**, 2.5 equiv of MeI, 10 mol % of $Pd(TFA)_2$, 20 mol % of ligand, 3.0 equiv of AgOPiv, 0.5 mL of DCE, 80 °C, under air, 20 h. [b]The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. [c]2.0 equiv of Ag_2CO_3 instead of AgOPiv were used.

tetrahydro-2*H*-pyran, trifluoromethyl, aryl, and ether groups were well tolerated (**3d–h**). If the phenyl ring is located at the *β*-position, two *ortho* positions need to be substituted in order to avoid the remote *ortho*-alkylation (**3g**). Importantly, the alanine-derived amide **1i** could be successfully methylated to form the unnatural amino acid derivative (**3i**). The higher reactivity of the methylene C–H bonds in $\mathbf{3i_{mono}}$, presumably due to the Thorpe–Ingold effect, led to the formation of the dimethylated product in 20% yield. Considering the synthetic utility of unnatural amino acids, alanine substrate **1i** was subjected to the alkylation conditions with various alkyl iodides (Table 3). Ethylation of **1i** gave **3j** in 75% yield with complete retention of chirality. The use of sterically hindered isobutyl iodide resulted in a decrease in yield (**3k**). Alkyl iodides containing aryl, chloro, benzyl protected hydroxyl, acetal, ester, and trifluoromethyl functionalities were suitable coupling partners, allowing the introduction of a wide range of functional groups into amino acids (**3l–q**). An alkyl iodide containing a double bond was also used to alkylate **1i** to give **3r** in 43% yield. Notably, the double bond in the alkyl iodide was not preserved in the recently reported Fe-catalyzed C–H alkylation due to a

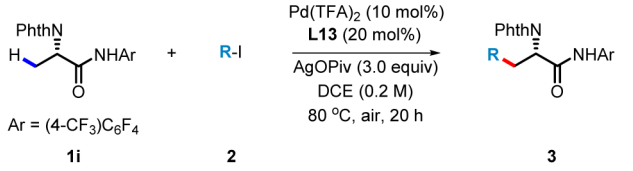
Table 2. C(sp^3)–H Methylation[a,b]

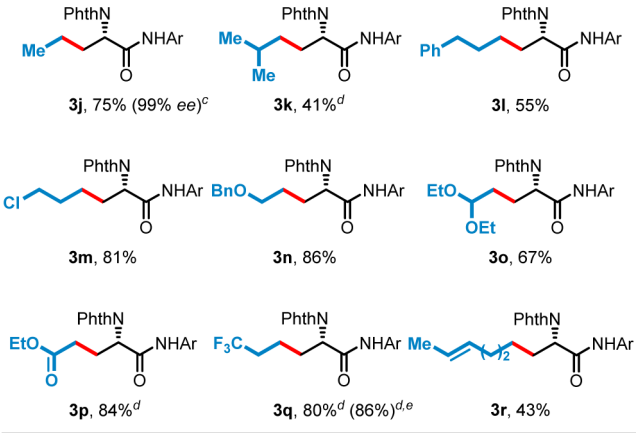




[a]Conditions: 0.1 mmol of **1**, 2.5 equiv of MeI, 10 mol % of $Pd(TFA)_2$, 20 mol % of **L13**, 3.0 equiv of AgOPiv, 0.5 mL of DCE, 80 °C, under air, 20 h. [b]Isolated yields.

Table 3. C(sp^3)–H Alkylation[a,b]





[a]Conditions: 0.1 mmol of **1i**, 2.5 equiv of **2**, 10 mol % of $Pd(TFA)_2$, 20 mol % of **L13**, 3.0 equiv of AgOPiv, 0.5 mL of DCE, 80 °C, under air, 20 h. [b]Isolated yields. [c]The ee value was determined by HPLC analysis on a chiral stationary phase (SI). [d]Using **L1** instead of **L13**. [e]1.0 mmol scale.

presumably radical cyclization process.[10c] This alkylation reaction could be scaled up without a decrease in yield (**3q**). We have also attempted alkylation of **1i** with isopropyl iodide but without success. Interestingly, alkylation of **1i** with ethyl

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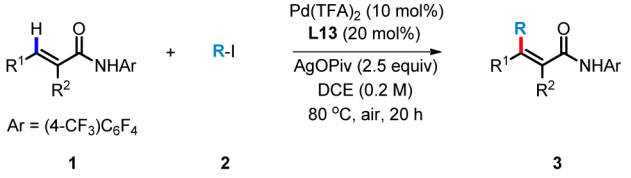
bromide gave the desired product in 36% yield (see Supporting Information).

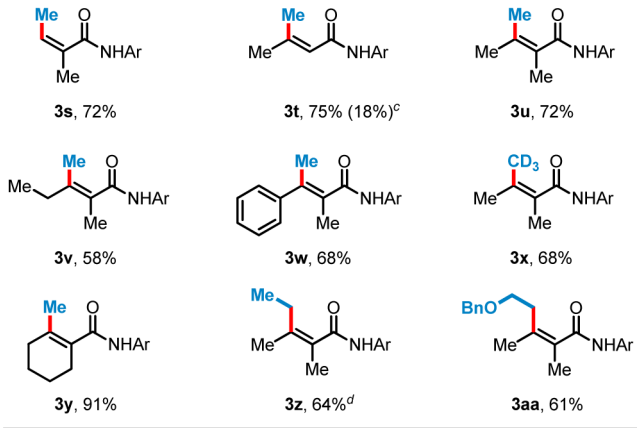
Vinyl C−H alkylation could potentially lead to a fully stereocontrolled alkene synthesis which can be especially difficult for acyclic tri- and tetrasubstituted alkenes. However, Pd-catalyzed vinyl C−H alkylation has not been accomplished to date. We were pleased to find that our ligand-promoted vinyl C−H alkylation proceeded to afford a series of geometrically controlled tri- and tetrasubstituted acrylic amides in good to excellent yields (Table 4). Starting from methacrylic amide, angelic amide was formed via the methylation of the terminal vinylic C−H bond (**3s**). Significantly, the expected facile isomerization of **3s** to the more stable tiglic amide. Amide was not detected by ^{1}H NMR analysis. Di- and trisubstituted crotonic and tiglic amides were also successfully methylated to give the tri- and tetrasubstituted olefins (**3t**−**u**). The retention of stereochemistry in the methylated products **3v** and **3w** is also noteworthy, as these double bonds are prone to isomerization. For example, access to these compounds via Wittig reaction often leads to a mixture of cis- and trans-isomers.[14] The retention of stereochemistry also allowed for the introduction of a D-labeled methyl group to give a single stereoisomer **3x**. A cyclic substrate was also compatible with this alkylation reaction affording the methylated product in high yield (**3y**). Importantly, alkylation with β-hydrogen containing alkyl iodides proceeded to give corresponding alkylated products in synthetically useful yields, thus demonstrating the effectiveness of the ligand (**3z**−**aa**). A control experiment with crotonic amide confirmed that a pyridine type ligand initially developed for C(sp^3)−H activation was also crucial for the alkylation of vinylic C(sp^2)−H bonds (**3t**).

Although Pd-catalyzed alkylation of aromatic C−H bonds using Daugulis' bidentate directing group has been well developed,[4c,d] C−H alkylation directed by weakly coordinating functional groups has been largely unsuccessful except for a single example using dichloroethane as the alkylating reagent.[4b] Thus, we wondered whether ligand **L13** could promote the alkylation of weakly coordinating benzamides. Under the optimized conditions, the alkylation of *ortho*-chlorobenzamide in the absence of ligand gave the desired product **3ab** in 57% yield (Table 5). As we expected, the use of ligand **L13** improved the yield to 80%. The use of pentafluorobenzoic acid (PFBA) was crucial for suppressing the *N*-alkylation of the benzamide. A *meta*-bromoarene and an *ortho*-methylarene were also methylated in good yields (**3ac**, **3ad**). The use of ligand **L11** also allowed for methylation of thiophenes (**3ae**, **3af**). The best results for alkylation with α-iodoacetate, ethyl iodide, and 3-chloropropyl iodide were obtained by using ligand **L1** (**3ag**−**ai**). The ethylation of *ortho*-chlorobenzamide in the absence of ligand proved to be inefficient (**3ah**).

In summary, an acridine ligand is developed to promote alkylation of both C(sp^3)−H and C(sp^2)−H bonds using a simple and weakly coordinating amide directing group. Further optimization of ligand structures to broaden the scope of C−H alkylation is underway in our laboratory.

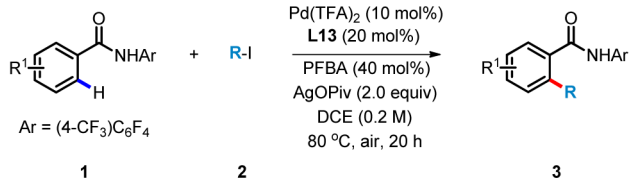
Table 4. Vinylic C(sp^2)−H Alkylation[a,b]

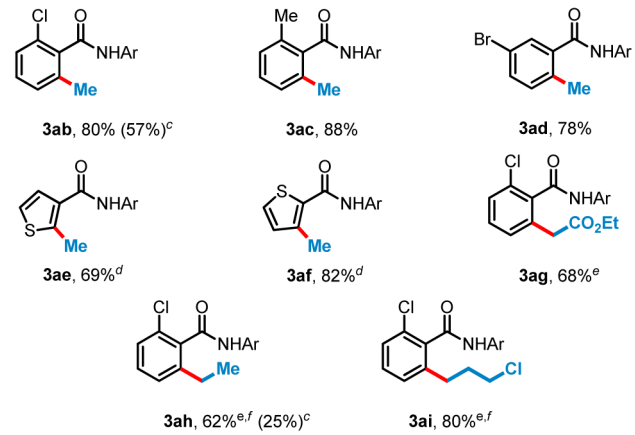




[a]Conditions: 0.1 mmol of **1**, 2.5 equiv of **2**, 10 mol % of Pd(TFA)$_2$, 20 mol % of **L13**, 2.5 equiv of AgOPiv, 0.5 mL of DCE, 80 °C, under air, 20 h. [b]Isolated yields. [c]^{1}H NMR yield without **L13** in parentheses. [d]Using **L1** instead of **L13** and 1.0 equiv of K_2HPO_4.

Table 5. Aromatic C(sp^2)−H Alkylation[a,b]





[a]Condition A: 0.1 mmol of **1**, 2.5 equiv of **2**, 10 mol % of Pd(TFA)$_2$, 20 mol % of **L13**, 2.0 equiv of AgOPiv, 0.5 mL of DCE, 80 °C, under air, 20 h. [b]Isolated yields. [c]^{1}H NMR yield without **L13** in parentheses. [d]Condition B: 0.1 mmol of **1**, 2.5 equiv of **2**, 10 mol % of Pd(OAc)$_2$, 20 mol % of **L11**, 3.0 equiv of AgOAc, 1.5 mL of DCE, 90 °C, under air, 20 h. [e]Condition A, except using **L1** instead of **L13**. [f]Condition A, except using 3.0 equiv of AgOPiv.

■ 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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