Published in final edited form as:

J Am Chem Soc. 2018 March 14; 140(10): 3564–3568. doi:10.1021/jacs.8b01359.

Ligand-Enabled γ -C(sp³)-H Activation of Ketones

Ru-Yi Zhu[†], Zi-Qi Li[†], Han Seul Park[†], Chris H. Senanayake[‡], and Jin-Quan Yu[†]

[†]Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States

[‡]Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States

Abstract

We report the first example of Pd(II)-catalyzed γ -C(sp³)-H activation of ketones directed by a practical 2,2-dimethyl aminoxyacetic acid auxiliary. 2-Pyridone ligands are identified to enable C(sp³)-H activation for the first time. A rare six-membered palladacycle intermediate was isolated and characterized to elucidate the reaction mechanism. Both (hetero)arylation and vinylation of γ -C(sp³)-H bonds are demonstrated. Sequential β - and γ -C(sp³)-H (hetero)arylation of muscone showcases the utility of this method for late-stage diversification. A convenient Mn(II)-catalyzed auxiliary removal is also developed to further underscore the practicality of this transformation.

Graphical abstract

Transition metal-catalyzed β -C(sp³)-H functionalization *via* a thermodynamically favored five-membered metallacycle have been extensively developed in the past decade.¹ Efforts to develop γ -C(sp³)-H functionalization, however, have met with limited success due to the formation of a less favorable six-membered metallacycle. A handful examples of γ -C(sp³)-H functionalizations reported thus far are limited to carboxylic acid derived substrates containing β -quaternary carbon centers.² To date, only a single example of γ -C(sp³)-H arylation of methyl neopentyl ketone containing a β -quaternary carbon center has been reported.³ We have recently developed a versatile aminoxyacetic acid auxiliary for β -C(sp³)-H iodination and (hetero)arylation of ketones.^{4,5} Despite the high reactivity of this new auxiliary, γ -C(sp³)-H functionalization has not been successful using this protocol. Herein, we report the discovery that an electron-deficient 2-pyridone ligand enables γ -

Correspondence to: Jin-Quan Yu.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

C(sp³)-H (hetero)arylation of ketones including substrates without a β -quaternary center. This finding also establishes, for the first time, the significant enhancing effect of an optimized X-type 2-pyridone ligand for C(sp³)-H activation.

Based on our previous β -methylene C-H arylation,^{4b} we began our study by conducting γ -C(sp³)-H arylation of 4-methyl-2-nonanone derived substrate **1a** in the presence of Pd(OAc)₂ (10 mol%), methyl 4-iodobenzoate (2.0 equiv), and AgTFA (2.0 equiv) in HFIP at 120 °C (Table 1). We were pleased to observe that arylation using 2,2-dimethyl aminoxyacetic acid auxiliary afforded the desired arylated product **2a** in 6% yield. However, extensive screening of conditions and other directing groups failed to improve the yield. Analysis of the proposed transition state involving this auxiliary and Pd(OAc)₂ led us to search for an X-type ligand that can displace the OAc and accelerate the C-H activation step.^{4a} We first tried PivOH and phosphoric acid as both have been used to promote C-H activation.¹ However, neither showed noticeable increase in yields presumably due to (A) both behaved similarly with OAc/OTFA; and/or (B) both failed to replace OAc/OTFA and coordinate the palladium catalyst (**L1**, **L2**). Therefore, we aimed at seeking for stronger binding X-type ligands. Guided by our recent finding that 2-pyridone ligand can accelerate C(sp²)-H activation,⁶ we set out to screen this type of ligands. Encouragingly, the yield increased to 24% with a simple 2-pyridone ligand (**L3**). Quinolone (**L4**) or isoquinolone (**L5**) did not enable efficient catalysis. Next, we systematically varied the substituents at the 5-position of 2-pyridone (**L6–11**). 5-Methyl-2-pyridone (**L6**) provided a similar yield to **L3**. The yields were improved to 30–35% with 5-halogen substituted 2-pyridone ligands (**L7–9**). The yield was further increased to 40% by installing a trifluoromethyl group (CF₃) at the 5-position (**L10**). A more electron-withdrawing nitro group at the 5-position drastically improved the yield to 70% (**L11**). Decreasing the loading of **L11** to 20 and 10 mol% resulted in lower yields (56% and 40% respectively). This trend loosely correlates to enhancing the acidity of the 2-pyridone ligand, indicating that the ability to tune the pK_a of this ligand is valuable when developing new C-H functionalizations. After identifying the optimal nitro substituent, we began to test 4-nitro- and 3-nitro-2-pyridones. However, only lower yields (45% and 49% respectively) were obtained. Further structural variation of ligand **L11** was also carried out. The introduction of various electron-withdrawing groups at the 3-position all gave inferior reactivity (**L14–17**). Sterically hindered **L18** gave a significantly lower yield, presumably due to ineffective binding with the palladium catalyst. Protection of the hydroxyl in the ligand resulted in a complete loss of ligand effect (**L19**), indicating the importance of X-type ligand for accelerating C-H activation with this directing group (DG).

With the optimal ligand and reaction conditions established, we explored the scope of ketones (Table 2). Installation of DG for all ketones is simple and chromatography free. Methyl alkyl ketones **1a–h** were functionalized at the γ -position in good yields (**2a–h**). This demonstrates that this reaction does not require the substrate to have β -quaternary centers, a feature that has been previously observed in other γ -C(sp³)-H functionalizations. Notably, mono-arylation could be achieved for methyl isobutyl ketone by shortening the reaction time (**2b**). An array of functional groups, such as aryl, amino, hydroxyl, ether, and ester groups were well tolerated (**2e–h**, **2k**, **2l**). Ketones possessing β -quaternary centers were also

successfully arylated at γ -position (**2i–m**). The γ -C(sp³)-H arylation of methyl neopentyl ketone gave mono- and di-arylated products in 80% combined yield (**2i**). Arylation of **1l** was mono-selective, albeit in moderate yield (**2l**). Besides methyl alkyl ketones, symmetrical and unsymmetrical alkyl alkyl ketones were also compatible substrates (**2m–o**). 2-*tert*-Butylcyclohexanone was arylated to afford mono- and di-arylation products in good yield (**2m**). The reaction of di-isobutyl ketone afforded mono- and di-arylated products in 82% combined yield. Interestingly, the second arylation occurred at the other side of imine moiety in high selectivity (**2n**). **2o** was obtained through selective β -methylene C(sp³)-H arylation of *n*-butyl isobutyl ketone followed by subsequent γ -C(sp³)-H arylation in a stepwise manner. This sequential C-H arylation reaction showcases the utility of using two sets of catalysts to control site selectivity by differentiating β -methylene and γ -primary C-H bonds. It is worth pointing out that β -methylene C-H bonds are more reactive than γ -primary C-H bonds as observed with substrate **1o**. Finally, arylation of **1a** in 1.0 mmol scale was also performed to give similar yield (see SI for details).

Next, we examined the scope of aryl and heteroaryl iodides (Table 3). The reaction of **1b** with a plethora of aryl iodides furnished mono-arylated products in good yields, exhibiting great functional group compatibility (**3a–j**). Various electron-donating/withdrawing groups and coordinative cyano and nitro were well tolerated. 2-Naphthyl iodide was coupled with **1b** to give **3i** in 62% yield. *Ortho*-fluorine substituted aryl iodide showed comparable reactivity (**3j**). More importantly, diverse heterocycles were installed at γ -position through γ -C(sp³)-H activation for the first time (**3k–x**). We started with a diverse range of iodopyridines (**3k–t**). Heteroarylation of **1i** with 2-substituted 4-iodopyridines proceeded smoothly in good yields (**3k–m**), except that 4-iodopyridine gave lower yield (40%) due to stronger binding of 4-iodopyridine (**3n**). 3-Iodopyridines were demonstrated as competent coupling partners (**3o**, **3p**). Less coordinative 6-Br and 6-CF₃ substituted 2-iodopyridines were employed to provide heteroarylated products in 72% and 75% yields, respectively (**3q**, **3r**). Moderate yields were obtained for 2-iodopyridines without a 6-substituent due to their increasing coordinating ability (**3s**, **3t**). In addition to pyridines, other heterocycles including quinoline, pyrimidine, imidazopyridine, and pyrrole were successfully installed at γ -position of **1g** (**3u–x**). It is worth noting that the heteroarylation with coordinative heteroaryl iodides is highly mono-selective presumably due to that the intramolecular competitive coordination of heterocycles that inhibits the second C-H activation. Unfortunately, (hetero)aryl bromides or chlorides are not reactive under current conditions.

The ligand effect was also further demonstrated by a preliminary investigation of γ -C(sp³)-H vinylation using 3-iodocyclopent-2-enone (Scheme 2). The desired vinylated product **4** was formed in 75% yield. We also envision the different reactivity of the ligandless catalyst and the 2-pyridone supported catalyst offers a useful method for late-stage functionalization of bioactive natural products at multiple sites. Hence, (*R*)-muscone, an ingredient in both perfumery and medicine was selected to test this approach (Scheme 3). Selective β -methylene C-H arylation of muscone was conducted without ligand, affording β -arylated muscone **5** in 71% yield. Subsequently, γ -C(sp³)-H heteroarylation of **5** was performed with **L11** to give heteroarylated product **6** in 55% yield, thus providing an avenue to access diverse range of muscone derivatives.

To further improve the practicality of this DG, we also embarked on the development of more efficient method for its removal. Decarboxylation of this DG under single electron transfer (SET) oxidative conditions⁷ or photo irradiation⁸ to generate an iminyl radical is known. Based on this radical decarboxylation pathway, we screened various metal catalysts as a single-electron oxidant (see SI for details). Mn(OAc)₂ was identified as the optimal catalyst, giving γ -C(sp³)-H arylated ketone **7** in 92% yield under mild conditions and without chromatography (Scheme 4). A plausible mechanism was described in Scheme 4, where Mn(OAc)₂ oxidizes **2a** to release CO₂ and acetone, affording iminyl radical **9** which is then reduced by Mn^I. The DG removal reaction proceeded smoothly under N₂, which rules out the possibility that Mn^I is oxidized by air to regenerate Mn^{II}. The recovery of the DG can also be achieved by using previously developed method.^{4b}

In order to gain insight on the mechanism of this reaction and the role of the 2-pyridone ligand, we embarked on the isolation and characterization of the elusive six-membered cyclopalladation intermediate. Based on our proposed mechanism, the anionic 2-pyridone ligand will dissociate from the Pd(II) center following the C-H insertion step to give **12**. We therefore used PPh₃ to stabilize **12** and isolated a rare six-membered palladacycle **14** (see SI for details, Scheme 5). The structure of this complex is determined by X-ray crystallography. To further probe the ligand effect, we have lowered the ligand quantity to 10 and 20 mol% and found ligand effect remains significant (40 and 56% yields, respectively. See Table 1). The yield can be improved to 70% with 50 mol% **L11**, presumably because high concentration of this anionic ligand helps the displacement of the OAc/OTFA on Pd(II) to form the reactive precursor **11**.

In summary, we have developed the first example of γ -C(sp³)-H (hetero)arylation of diverse ketones. 5-Nitro-2-pyridone was identified as the optimal X-type ligand for enabling this reaction. A rare six-membered palladacycle intermediate was isolated and characterized to elucidate the reaction mechanism. Broad substrate scope for ketones and (hetero)aryl iodides as well as the capability for late-stage C(sp³)-H functionalizations have been demonstrated. Finally, a mild radical-based Mn(II)-catalyzed DG removal was developed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support. R.-Y. Zhu is supported by the Boehringer Ingelheim Fellowship. H.S.P thanks the Korea Foundation for Advanced Studies for a predoctoral fellowship. We thank Arnie Rheingold and Milan Gembicki for X-ray crystallography.

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Previous work: *limited to β -quaternary carboxylic acids*

This work: *2-pyridone-enabled γ -C(sp³)-H (hetero)arylation of ketones*

Scheme 1.
Pd(II)-Catalyzed γ -C(sp³)-H Arylation

Scheme 2.

γ -C(sp³)-H Vinylation with Vinyl Iodide^{a,b}

^a Conditions: **1i** (0.1 mmol, 1.0 equiv), 3-iodocyclopent-2-enone (1.5 equiv), Pd(OAc)₂ (10 mol%), **L11** (50 mol%), AgTFA (2.0 equiv), HFIP (1.0 mL), 120 °C, under air, 20 h. See SI for workup procedures. ^b Isolated yield; product isolated as *E/Z* mixture.

Scheme 3. Sequential C(sp³)-H (Hetero)Arylation of Muscone ^{a,b,c}

^a Conditions: **1p** (0.3 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)₂ (10 mol%), AgTFA (2.0 equiv), HFIP (3.0 mL), 100 °C, under air, 20 h. See SI for workup procedures. ^b Conditions: **5** (0.1 mmol, 1.0 equiv), 2-chloro-4-iodopyridine (1.5 equiv), Pd(OAc)₂ (10 mol%), **L11** (50 mol%), AgTFA (2.0 equiv), HFIP (1.0 mL), 100 °C, under air, 20 h. See SI for workup procedures. ^c Isolated yields; product isolated as *E/Z* mixture.

Scheme 4. Mn(II)-Catalyzed Auxiliary Removal^{a,b}

^a Conditions: **2a** (0.1 mmol, 1.0 equiv), $\text{Mn}(\text{OAc})_2$ (20 mol%), HFIP (1.0 mL), 80 °C, under air, 20 h. See SI for workup procedures. ^b Isolated yield.

Scheme 5.
A Plausible Mechanism

Table 1

Ligand Evaluation for γ -C(sp³)-H Arylation ^{a,b,c}

Without ligand 6%	 L1, 7%	 L2, 6%	 L3, 24%	 L4, 6%
 L5, 8%	 L6, 22%	 L7, 32%	 L8, 35%	 L9, 30%
 L10, 40%	 L11, 70% ^d	 L12, 45%	 L13, 49%	 L14, 37%
 L15, 58%	 L16, 60%	 L17, 63%	 L18, 5%	 L19, 8%

^a Conditions: **1a** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)₂ (10 mol%), ligand (50 mol%), AgTFA (2.0 equiv), HFIP (1.0 mL), 120 °C, under air, 20 h.

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

^cProduct observed as *E/Z* mixture.

^d20 mol% **L11**, 56% yield; 10 mol% **L11**, 40% yield.

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Table 2

Scope of Ketones ^{a,b}

^aConditions: **1** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)₂ (10 mol%), **L11** (50 mol%), AgTFA (2.0 equiv), HFIP (1.0 mL), 120 °C, under air, 20 h. T' means no further methyl esterification; acid form was isolated. See SI for workup procedures.

^bIsolated yields; products isolated as *E/Z* mixture.

^cReaction time 4 h.

^dAgOAc instead of AgTFA.

^eNumbers in parentheses indicate the ratio of mono:di.

^f_{dr} for diarylated product 1:1.

^g_{dr} 1:1.

Table 3

Scope of (Hetero)Aryl Iodides^{a,b,c}

^a Conditions: **1b** (0.1 mmol, 1.0 equiv), aryl iodide (2.0 equiv), Pd(OAc)₂ (10 mol%), **L11** (50 mol%), AgTFA (2.0 equiv), HFIP (1.0 mL), 120 °C, under air, 4 h. See SI for workup procedures.

^b Conditions: **1b** (0.1 mmol, 1.0 equiv), heteroaryl iodide (1.5 equiv), Pd(OAc)₂ (10 mol%), **L11** (50 mol%), AgTFA (2.0 equiv), HFIP (1.0 mL), 120 °C, under air, 20 h. T⁺ means no further methyl esterification; acid form was isolated. See SI for workup procedures.

^c Isolated yields; products isolated as *E/Z* mixture.

^d Numbers in parentheses indicate the ratio of mono:di.

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