Published in final edited form as:

J Am Chem Soc. 2016 February 17; 138(6): 2055–2059. doi:10.1021/jacs.5b13462.

Ligand-Enabled γ -C(sp³)-H Olefination of Amines: En Route to Pyrrolidines

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Abstract

Pd(II)-catalyzed olefination of γ -C(sp³)-H bonds of triflyl (Tf) and 4-nitrobenzenesulfonyl (Ns) protected amines is achieved. Subsequent aza-Wacker oxidative cyclization or conjugate addition of the olefinated intermediates provides a variety of C-2 alkylated pyrrolidines. Three pyridine- and quinoline-based ligands are developed to match different classes of amine substrates, demonstrating a rare example of ligand-enabled C(sp³)-H olefination reaction. The use of Ns protecting group to direct C(sp³)-H activation of alkyl amine is also a significant step towards practical C-H functionalizations of alkyl amines.

1. Introduction

Pd-catalyzed olefination of C(sp²)-H bonds has been extensively developed in the past decade. While the early discovery uses excess amounts of electron-rich arenes as substrates to promote the electrophilic palladation,¹ the recent development exploits directing groups derived from simple functional groups to achieve proximity-driven C-H olefination of a broad range of synthetically useful substrates.² The use of chiral mono-protected amino acid (MPAA) ligands has also led to the development of enantioselective C(sp²)-H olefination.³ In contrast, only a few examples of directed olefination of C(sp³)-H bonds have been reported (Scheme 1, eq 1–2),^{4,5} which reflects the difficulties encountered in Heck coupling of alkyl halides.⁶ Notably, C-H olefination of alkyl amines, a very important class of synthetic substrates, has not been developed to date. The observed significant ligand acceleration in the γ -C(sp³)-H olefination of amides^{4c} prompted us to investigate the feasibility of γ -C(sp³)-H olefination of alkyl amines through the development of new pyridine- and quinoline-based ligands.⁷ Herein we report the development of Pd-catalyzed γ -C(sp³)-H olefination of Tf- and Ns-protected amines. In addition to previously used acrylate coupling partners, styrenes are also shown to be reactive for the first time (Scheme 1, eq 3). The use of pyridine- or quinoline-based ligands is essential for this reaction to proceed. This protocol is compatible with a range of amines includes amino acids and amino alcohols.

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Supporting Information Available. Detailed experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

2. Results and Discussion

Based on the previous finding that mono-protected amino acid (MPAA) ligands promoted γ -C(sp³)-H activation/cross-coupling of Tf-protected alkyl amines with arylborons,⁸ we extensively screened our collection of MPAA ligands for promoting γ -C(sp³)-H olefination of amino acid-derived substrate **1a**. Under various conditions, no desired product could be observed (see the Supporting Information). We then turned to the quinoline-based ligands that have been shown to enable the γ -C(sp³)-H olefination of amides (Table 1).^{4c} We found that the use of 10 mol% Pd(OAc)₂, 20 mol% quinoline-based ligand **L1**, Ag₂CO₃, and NaOAc in DCM afforded pyrrolidine derivative **3a** in 30% yield. Apparently, the initially formed C(sp³)-H olefination product underwent Pd-catalyzed intramolecular aza-Wacker oxidative cyclization⁹ to give **3a**. Since extensive modification of quinoline ligands only led to decrease in yields (for screening of quinoline-based ligands, see Supporting Information), we began to investigate the influence of pyridine-based ligands on this reaction. Among variously alkylated pyridines (**L4**–**L8**), **L7** was most effective affording **3a** in 43% yield. Increasing the electron density of pyridine ligands reduced the yields (**L9**, **L10**). The observed trend guided us to focus on the electron-deficient pyridines. The lack of reactivity of 2-(trifluoromethyl)pyridine (**L11**) is most likely associated with its poor coordinating ability. 3-(Trifluoromethyl)pyridine (**L12**) afforded the desired product in significantly improved yield (65%). 2-Methyl-5-(trifluoromethyl)pyridine (**L13**) and 3-nitropyridine (**L14**) afforded comparable yields (67% and 62% respectively). Ligands containing coordinating electron-withdrawing groups on 3- or 4-positions of the pyridine ring (**L15**–**L17**) were ineffective in this transformation. Gratifyingly, 70% yield was obtained when 3,4-bis(trifluoromethyl)pyridine (**L18**) was used as the ligand. Surprisingly, 3,5-bis(trifluoromethyl)pyridine (**L19**) was significantly less effective. Since computational studies indicate that **L19** is only moderately less electron-deficient than **L18**, we attribute this significant drop in yield to the subtle increase in steric hindrance. Finally, the yield of **3a** was improved to 81% by increasing the equivalent of **L18** from 20 mol% to 30 mol%.

The optimized condition for γ -C(sp³)-H olefination was then applied to various Tf-protected α -amino acid derivatives (Table 2). L-valine and L-*tert*-Leucine derivatives gave **3b** and **3c** in excellent yields. Although only 35% yield of **3d** was obtained from L-isoleucine derivative, L-allo-isoleucine derivative gave **3e** in 77% yield, probably due to the more favorable transition-state of the cyclopalladation in which the 2,3-substituents adopt *anti*-configuration. The desired products **3f** and **3g** were successfully obtained in 45% and 63% yields from TBSO- and *t*-Bu-protected L-threonine. The cyclopropyl C-H bond could also be olefinated to form ring-fused product **3h** in 73% yield. For amino acid derivative **1i** containing both γ -methyl and γ -methylene C(sp³)-H bonds, the methyl C(sp³)-H bond was preferentially olefinated, affording **3i** in 81% yield.

To expand the scope of this C(sp³)-H olefination reaction, we next investigated the reactivity of Tf-protected simple alkyl amines (Table 3). Considering the well-known Thorpe-Ingold effect in the C(sp³)-H cleavage step, 3,3-Dimethylbutan-2-amine derivative **4a** was chosen as the model substrate. Not surprisingly, **4a** was fully recovered from the reaction without ligand. We next examined electron-deficient pyridines **L4**, **L13**, **L14** and **L18** which were

effective for α -amino acid substrate **1a**. Olefination of **4a** with these ligands gave poor yields (27%–35%), suggesting that the less acidic triflamide moiety in **4a** may not match these electron-deficient pyridine ligands in the transition state. We thus began to screen quinoline-based ligands that had also been shown to promote C(sp³)–H activation of amide substrates.⁷ Encouragingly, the use of 30 mol% quinoline (**L20**) improved the yield of the desired product **5a** to 50%. While 2-methylquinoline (**L3**) and 4-methylquinoline (**L21**) did not afford further improvement, 3-methylquinoline (**L22**) gave 55% yield. We therefore tested a number of 3-aryl quinolines (**L23**–**L26**), and found that the use of 3-phenylquinoline (**L24**) gives **5a** in 67% yield. However, other quinoline ligands (**L27**–**L30**) previously developed for C(sp³)–H activation of amide substrates⁷ were not effective for this transformation.

We were pleased to find that this newly identified ligand (**L24**) is capable of promoting γ -C(sp³)–H olefination of a range of Tf-protected alkyl amines including β -amino alcohols and β -amino acids (Table 4). Tf-protected aliphatic amines **4a** and **4b** were olefinated to give **5a** and **5b** in 61% and 39% yields respectively. A number of Tf-protected β -amino alcohol derivatives are also reactive, affording desired products **5c**–**5g** in 41%–77% yields. In addition, olefination of β -amino acid derivatives **4h** and **4i** also gave the desired products **5h** and **5i** in 65% and 53% yields. The unsubstituted simple amines, such as Tf-protected propan-1-amine, are ineffective in this transformation. However, a single substitution at the α -position is sufficient to restore the reactivity to some extent (**5b**, **5e**, **5f**, **5g**, **5i**). The superior reactivity of more substituted amines in table 4 is consistent with the documented Thorpe-Ingold effect in the cyclometalation step (for details of unreactive substrates, see Supporting Information).

A range of α,β -unsaturated olefins and styrenes are shown to be compatible coupling partners (Table 5). Acrylates reacted with **1c** effectively in the presence of **L18** to give **6a**–**6c** in excellent yields. Diethyl vinylphosphonate **2e** afforded the coupling product **6d** in 77% yield. Styrenes are also compatible affording the desired products in 48%–63% yields (**6e**–**6i**). Notably, C(sp³)–H olefination with styrenes has not been demonstrated prior to this finding.

To probe the potential utility of this reaction, we performed the olefination of alkyl amine **4a** at a 2.0 mmol scale and the desired pyrrolidine product **5j** was obtained in 63% yield (Scheme 2, a). Hydrogenation of the double bond gave **5ja**, which underwent a base promoted E1cB elimination followed by hydrogenation to give the Tf-protected elongated alkyl amine **5jb**. The Tf protecting group could also be swapped into a Boc protecting group using a known procedure (**5jc**).⁸ Interestingly, hydrogenation of the pyrrolidine product **6a** gave the Tf-protected alkyl amine **6aa** in one step. Apparently, hydrogenation of the double bond in **6a** triggered E1 or E2 reaction of the saturated pyrrolidine in similar manner to that of the retro-Michael process, and the subsequent hydrogenation of the newly-formed double bond gave the alkyl amine **6aa** (Scheme 2, b).

To improve the practicability of this γ -C(sp³)–H olefination reaction, we also developed conditions to accommodate the use of a common protecting group 4-nitrobenzenesulfonyl (Ns) instead of Tf (Table 6). Extensive screening of our ligand library identified phenanthridine (**L31**) as the most suitable ligand for this practical directing group (see

Supporting Information). Thus, Ns-protected L-*tert*-leucine substrate **7** was olefinated with acrylates and styrenes to give valuable pyrrolidines **8a–8c** in good to excellent yields. With methyl vinyl ketone, 1-phenylprop-2-en-1-one, and acrylonitrile coupling partners, the newly installed double bonds reacted with the Ns-protected amines via diastereoselective conjugate addition to give the saturated pyrrolidines **8d–8f** in 42% to 75% yields. Upon further improvement, this method could find synthetic applications in the preparation of chiral-pyrrolidine-based natural products and bio-active molecules.¹⁰ Finally, deprotection of 4-nitrobenzenesulfonyl group could be readily accomplished using a literature procedure (Scheme 3).¹¹

The overall catalytic cycle is proposed according to the experimental results (Scheme 4). The $X_2Pd^{II}L_n$ catalyst first binds to the sulfonamide under basic conditions and cleaves its $\gamma-C(sp^3)-H$ bonds. The resulting five-membered palladacycle intermediate **9** coordinates with an olefin and undergoes 1,2-migratory insertion to give intermediate **11**. Subsequent β -hydride elimination affords the olefinated intermediate **12** and Pd_0L_n species. Reoxidation of Pd^0L_n by Ag_2CO_3 generates $X_2Pd^{II}L_n$ catalyst to close the catalytic cycle.

On the fate of the olefinated intermediate **12**, two different cyclization pathways could occur to give alkylated or vinylated pyrrolidines respectively. When the newly installed double bonds are conjugated with strong electron-withdrawing groups (i.e. CN, COMe, or CPh), saturated pyrrolidines **8d–8f** will be generated *via* intramolecular conjugate addition (pathway A). Otherwise, the Pd(II)-catalyzed *syn*-addition and β -hydride elimination will take place to give the aza-Wacker product *E*-2-methylene-pyrrolidine **8a–8c** (pathway B).

3. Conclusion

In summary, ligand-enabled olefination of $\gamma-C(sp^3)-H$ bonds of alkyl amines with electron-deficient alkenes and styrenes has been achieved by using pyridine- or quinoline-based ligands. Subsequent aza-Wacker oxidative cyclization or intramolecular conjugate addition of $C(sp^3)-H$ olefinated intermediates provide a variety of pyrrolidine products. For Tf-protected α -amino acid esters, 3,4-bis(trifluoromethyl)pyridine is utilized as a competent ligand and Ag_2CO_3 is used as the sole oxidant. 3-Phenylquinoline is the most effective ligand for Tf-protected aliphatic amines including β -amino alcohols and β -amino acids in the presence of Ag_2CO_3 , $Cu(OAc)_2$, and O_2 . The use of NsNH as directing group is also made possible by using a suitable quinoline-based ligand.

4. Experimental Section

4.1 General Procedure for $\gamma-C(sp^3)-H$ Olefination of Tf-protected α -amino ester **1a**

Substrate **1a** (0.1 mmol, 24.9 mg), benzyl acrylate **2a** (0.4 mmol, 64.8 mg), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), Ag_2CO_3 (0.25 mmol, 68.5 mg), NaOAc (0.4 mmol, 32.8 mg) were weighed in air and placed in a 10.0 mL microwave tube with a magnetic stir bar. DCM (1.0 mL) and **L18** (0.03 mmol, 6.5 mg) were added by syringe under air and then the tube was sealed with a cap. The reaction mixture was stirred at 105 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a short celite tube. The filtrate was concentrated *in vacuo*, and the resulting residue was

purified by preparative thin-layer chromatography using an eluent of toluene/EtOAc to give the desired product.

4.2 General Procedure for γ -C(sp³)-H Olefination of Tf-protected amine **4a**

Substrate **4a** (0.1 mmol, 23.3 mg), benzyl acrylate **2a** (0.4 mmol, 64.8 mg), Pd(OAc)₂ (0.01 mmol, 2.2 mg), **L24** (0.03 mmol, 6.2 mg), Ag₂CO₃ (0.25 mmol, 68.5 mg), Cu(OAc)₂ (0.2 mmol, 36.2 mg), NaOAc (0.4 mmol, 32.8 mg) were weighed in air and placed in a 10.0 mL microwave tube with a magnetic stir bar. The tube was evacuated and backfilled with O₂ for 3 times. DCE (1.0 mL) was added by syringe under O₂ and the tube was then sealed with a cap. The reaction mixture was stirred at 105 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a short celite tube. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by preparative thin-layer chromatography using an eluent of toluene/EtOAc to give the desired product.

4.3 General Procedure for γ -C(sp³)-H Olefination of Ns-protected α -amino ester **7**

Substrate **7** (0.1 mmol, 33.0 mg), tert-butyl acrylate **2c** (0.4 mmol, 51.2 mg), Pd(OAc)₂ (0.01 mmol, 2.2 mg), **L31** (0.03 mmol, 5.4 mg), Ag₂CO₃ (0.25 mmol, 68.5 mg), NaOAc (0.4 mmol, 32.8 mg) were weighed in air and placed in a 10.0 mL microwave tube with a magnetic stir bar. DCE (1.0 mL) was added by syringe under air and then the tube was sealed with a cap. The reaction mixture was stirred at 105 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a short celite tube. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by preparative thin-layer chromatography using an eluent of toluene/EtOAc to give the desired product.

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. We also thank China Scholarship Council (fellowship to H. J., Nanjing University, China).

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Previous work of Pd-catalyzed C(sp³)-H olefination:

This work: Ligand-enabled γ -C(sp³)-H olefination of protected amines:

Scheme 1.
Palladium-Catalyzed C(sp³)-H Olefination

Scheme 2.
Synthetic Application

Scheme 3.
Removal of Protecting Group on **8a**

Scheme 4.
Proposed Catalytic Cycle for γ -C(sp³)-H Olefination/Cyclization

Table 1

Ligand Discovery for C(sp³)-H Olefination of **1a**^{a,b}

— 0%	 L1 , 30%	 L2 , 5%	 L3 , 20%	
 L4 , 40%	 L5 , 21%	 L6 , 25%	 L7 , 43%	
 L8 , 33%	 L9 , trace	 L10 , 28%	 L11 , 0%	
 L12 , 65%	 L13 , 67%	 L14 , 62%	 L15 , 0%	
 L16 , 31%	 L17 , 29%	 L18 , 70% (81%) ^{c,d}	 L19 , 43%	

^a Reaction conditions: substrate **1a** (0.1 mmol), **2a** (4.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol%), Ag₂CO₃ (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h.

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

^c 30 mol% **L18** was used.

^d > 99% ee, determined by chiral HPLC.

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Table 2

Scope of Tf-Protected α -Amino Esters^{a,b}

^aReaction conditions: substrate **1** (0.1 mmol), **2a** (4.0 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol%), **L18** (30 mol%), Ag_2CO_3 (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h.

^bIsolated yields.

^cd. r. = 4.5:1.

^d
d. r. = 1.25:1.

^e
d. r. = 3:1.

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Table 3

Ligand Discovery for C(sp³)-H Olefination of **4a**^{a,b}

— 0%	 L4 , 30%	 L13 , 35%	 L14 , 31%	 L18 , 27%
 L20 , 50%	 L3 , 46%	 L21 , 51%	 L22 , 55%	
 L23 , 59%	 L24 , 67%	 L25 , 60%	 L26 , 62%	
 L27 , 31%	 L28 , 33%	 L29 , 15%	 L30 , 15%	

^a Reaction conditions: substrate **4a** (0.1 mmol), **2a** (4.0 equiv), Pd(OAc)₂ (10 mol%), ligand (30 mol%), Ag₂CO₃ (2.5 equiv), Cu(OAc)₂ (2.0 equiv), NaOAc (4.0 equiv), DCE (1.0 mL), O₂, 105 °C, 20 h.

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

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Table 4

Scope of Tf-Protected Alkyl Amines^{a,b}

^aReaction conditions: substrate 4 (0.1 mmol), 2a (4.0 equiv), Pd(OAc)₂ (10 mol%), L24 (30 mol%), Ag₂CO₃ (2.5 equiv), Cu(OAc)₂ (2.0 equiv), NaOAc (4.0 equiv), DCE (1.0 mL), O₂, 105 °C, 20 h.

^bIsolated yields.

^cd. r. > 20:1.

^dd. r. = 6.5:1.

^e98.7% ee, determined by chiral HPLC.

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Table 5

Scope of Alkenes^{a,b}

^aReaction conditions: substrate **1c** (0.1 mmol), **2** (4.0 equiv), Pd(OAc)₂ (10 mol%), **L18** (30 mol%), Ag₂CO₃ (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h.

^bIsolated yields.

Table 6

Scope of Alkenes for Ns-Protected Amine Ester **7**^{a,b}

^a Reaction conditions: substrate **7** (0.1 mmol), **2** (4.0 equiv), Pd(OAc)₂ (10 mol%), **L31** (30 mol%), Ag₂CO₃ (2.5 equiv), NaOAc (4.0 equiv), DCE (1.0 mL), 105 °C, 20 h.

^b Isolated yields.

^c > 99% ee, determined by chiral HPLC.

^d d. r. = 10:1.

^e d. r. = 12:1.