

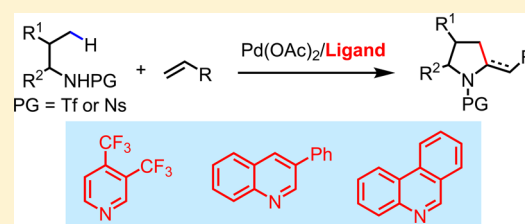
Ligand-Enabled γ -C(sp³)-H Olefination of Amines: En Route to Pyrrolidines

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S Supporting Information

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 reactions. The use of Ns protecting group to direct C(sp³)-H activation of alkyl amines is also a significant step toward practical C-H functionalizations of alkyl amines.



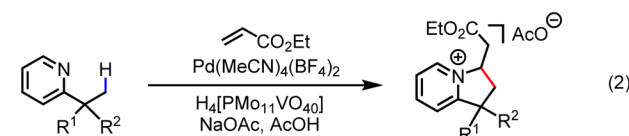
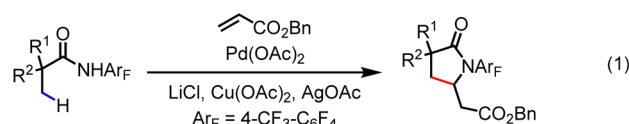
1. INTRODUCTION

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 monoprotected 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, eqs 1 and 2),^{4,5} which reflects the difficulties encountered in Heck coupling of alkyl halides.⁶ Notably, C-H olefination of alkyl

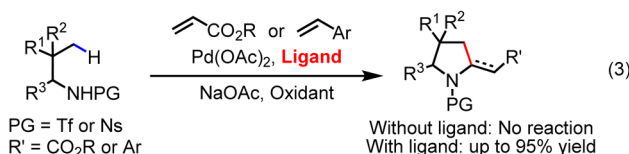
amines, a very important class of synthetic substrates, has not been developed to date. The observed significant ligand acceleration in the γ -C(sp³)-H olefination of amides^{4c} prompted us to investigate the feasibility of γ -C(sp³)-H olefination of alkyl amines through the development of new pyridine- 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.

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

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



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

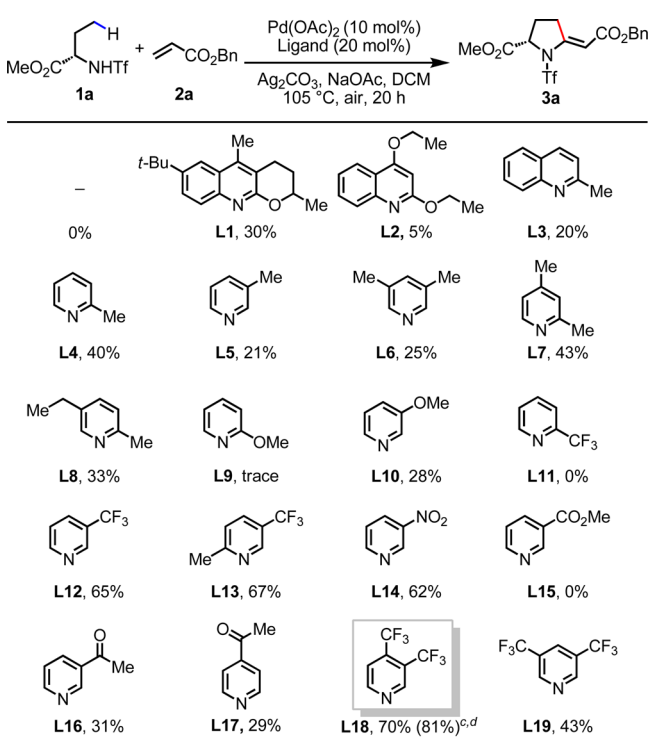


2. RESULTS AND DISCUSSION

Based on the previous finding that monoprotected 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

Received: December 24, 2015

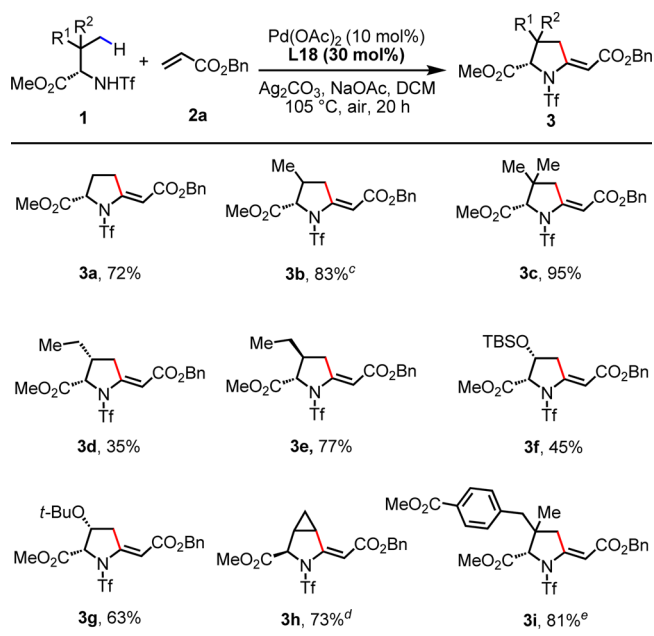
Published: January 21, 2016

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

^aReaction 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. ^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. ^c30 mol % **L18** was used. ^d>99% ee, determined by chiral HPLC.

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

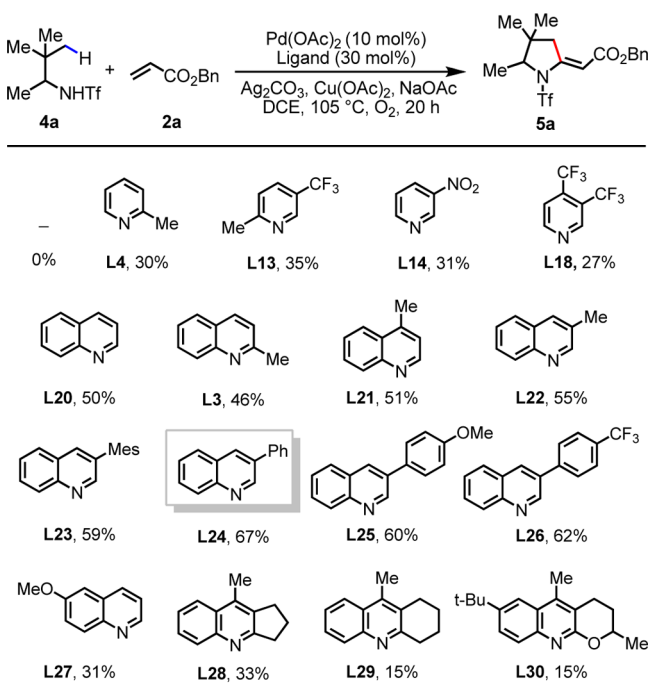
Table 2. Scope of Tf-Protected α -Amino Esters^{a,b}

^aReaction conditions: substrate **1** (0.1 mmol), **2a** (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. ^cd.r. = 4.5:1. ^dd.r. = 1.25:1. ^ed.r. = 3:1.

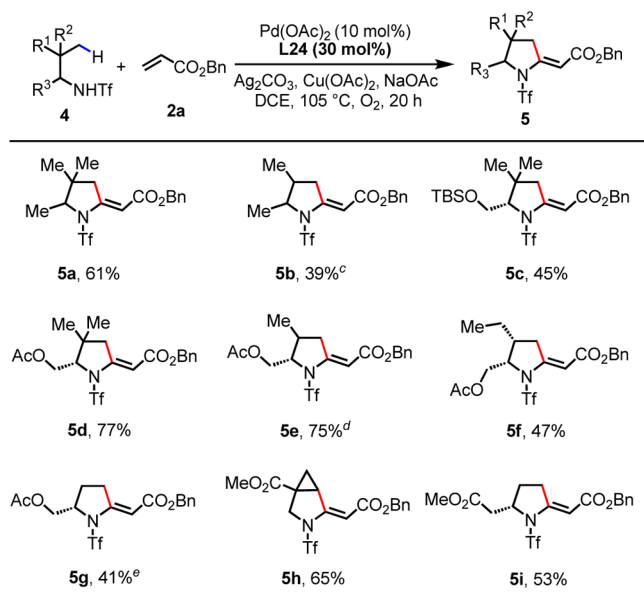
successfully obtained in 45% and 63% yields from TBSO- and *t*-Bu-protected L-threonine. The cyclopropyl C-H bond could also be olefinated to form ring-fused product **3h** in 73% yield. For amino acid derivative **1i** containing both γ -methyl and γ -methylene C(sp³)-H bonds, the methyl C(sp³)-H bond 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**) gave **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

Table 3. Ligand Discovery for C(sp³)-H Olefination of 4a^{a,b}

^aReaction 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.

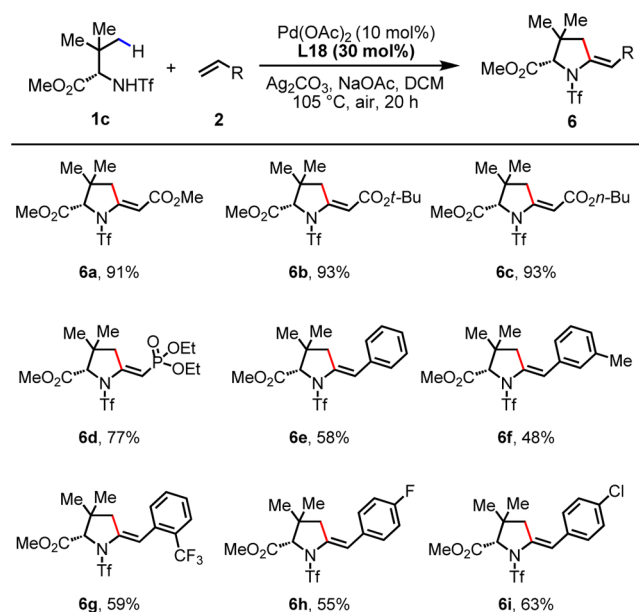
Table 4. Scope of Tf-Protected Alkyl Amines^{a,b}

^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.

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

Table 5. Scope of Alkenes^{a,b}

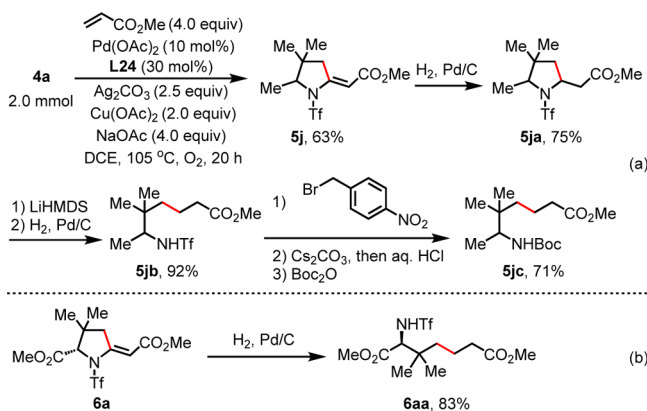
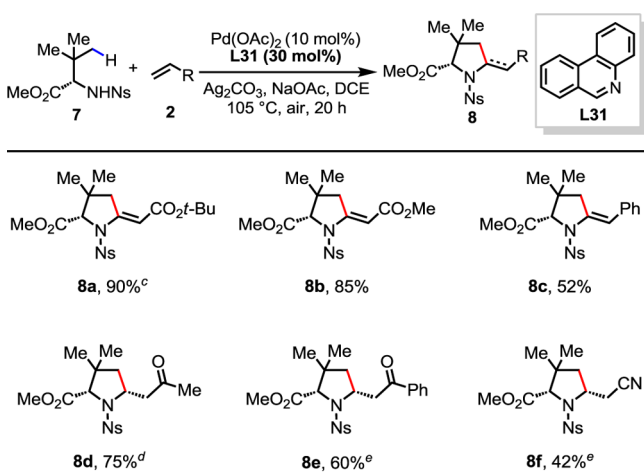
^aReaction conditions: substrate 1c (0.1 mmol), 2 (4.0 equiv), Pd(OAc)₂ (10 mol %), L18 (30 mol %), Ag₂CO₃ (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h. ^bIsolated yields.

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

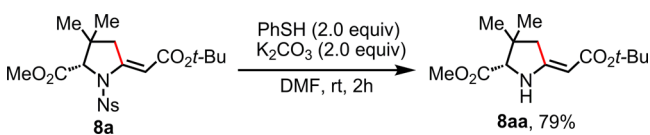
Scheme 2. Synthetic Application

Table 6. Scope of Alkenes for Ns-Protected Amine Ester **7**^{a,b}

^aReaction 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. ^bIsolated yields. ^c>99% ee, determined by chiral HPLC. ^dd.r. = 10:1. ^ed.r. = 12:1.

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 bioactive 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 X₂Pd^{II}L_n catalyst first

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

binds to the sulfonamide under basic conditions and cleaves its γ -C(sp³)-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 Pd⁰L_n species. Reoxidation of Pd⁰L_n by Ag₂CO₃ generates X₂Pd^{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 vinylylated 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

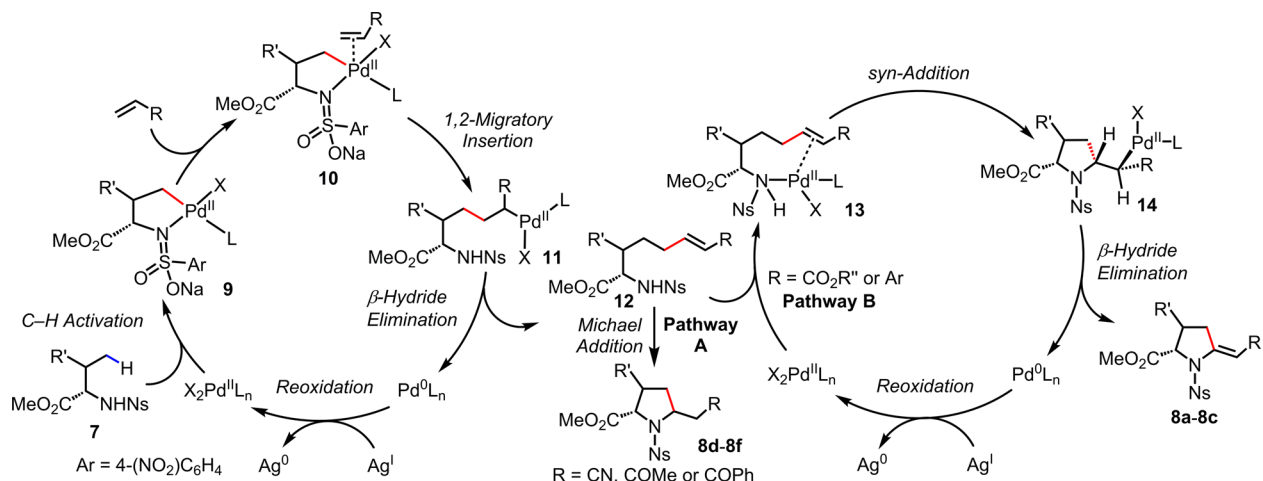
In summary, ligand-enabled olefination of γ -C(sp³)-H bonds of alkyl amines with electron-deficient alkenes and styrenes has been achieved by using pyridine- or quinoline-based ligands. Subsequent aza-Wacker oxidative cyclization or intramolecular conjugate addition of C(sp³)-H olefinated intermediates provides a variety of pyrrolidine products. For Tf-protected α -amino acid esters, 3,4-bis(trifluoromethyl)pyridine is utilized as a competent ligand and Ag₂CO₃ 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 Ag₂CO₃, Cu(OAc)₂, and O₂. 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 γ -C(sp³)-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), Ag₂CO₃ (0.25 mmol, 68.5 mg), and 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 h. 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), and 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 h. 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), and 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

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

by syringe under air and then the tube was sealed with a cap. The reaction mixture was stirred at 105 °C for 20 h. 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13462.

Detailed experimental procedures; characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ 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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