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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(sp^3)–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(sp^3)–H olefination reaction. The use of Ns protecting group to direct C(sp^3)–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(sp^2)–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(sp^2)–H olefination.[3] In contrast, only a few examples of directed olefination of C(sp^3)–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(sp^3)–H olefination of amides[4c] prompted us to investigate the feasibility of γ-C(sp^3)–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(sp^3)–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(sp^3)–H activation/cross-coupling of Tf-protected alkyl amines with arylborons,[8] we extensively screened our collection of MPAA ligands for promoting γ-C(sp^3)–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(sp^3)–H olefination of amides (Table 1).[4c] We found that the use of 10 mol% $Pd(OAc)_2$, 20 mol% quinoline-based ligand **L1**, Ag_2CO_3, and NaOAc in DCM afforded pyrrolidine derivative **3a** in 30% yield. Apparently, the initially formed C(sp^3)–H olefination product underwent Pd-catalyzed intramolecular aza-Wacker oxidative cyclization[9] 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(sp^3)–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-substitutents 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(sp^3)–H bonds, the methyl C(sp^3)–H bond was preferentially olefinated, affording **3i** in 81% yield.

To expand the scope of this C(sp^3)–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(sp^3)–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(sp^3)–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(sp^3)–H activation of amide substrates[7] were not effective for this transformation.

We were pleased to find that this newly identified ligand (**L24**) is capable of promoting γ-C(sp^3)–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(sp^3)–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(sp^3)–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 sulfonaimine under basic conditions and cleaves its γ-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 COPh), 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(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 γ-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(sp^3)–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), Ag_2CO_3 (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 O_2 for 3 times. DCE (1.0 mL) was added by syringe under O_2 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(sp^3)–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), 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. 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

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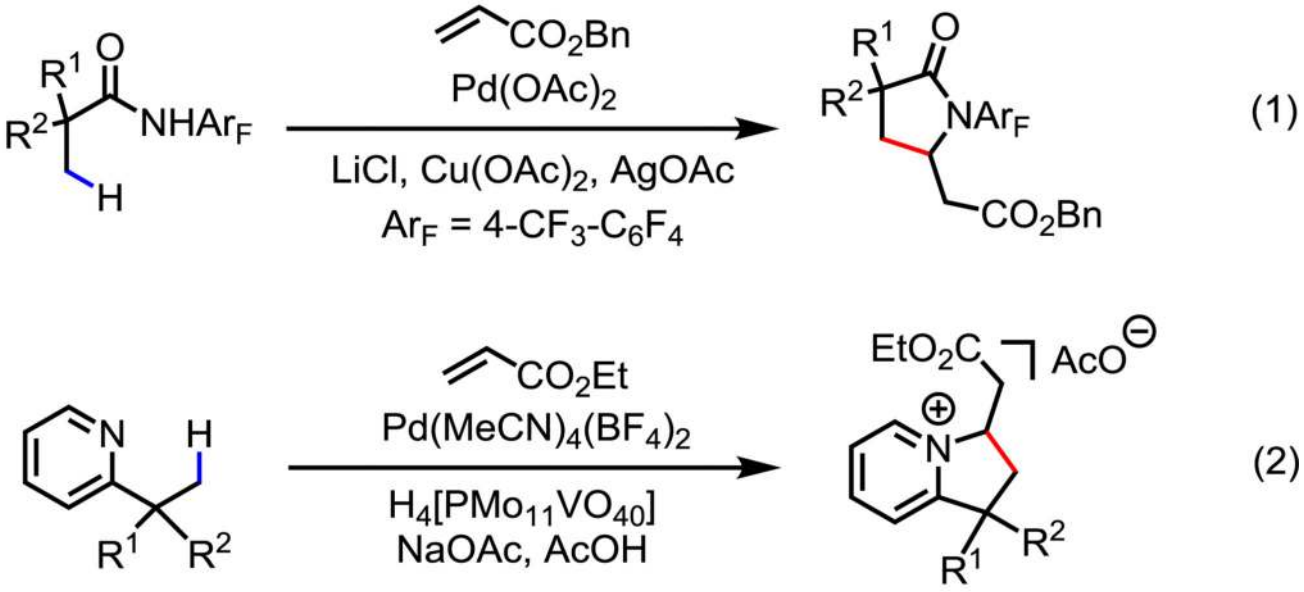
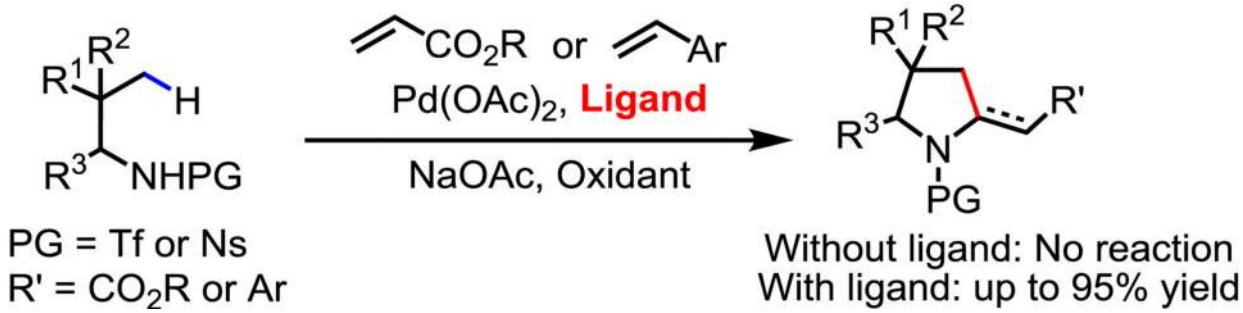
Previous work of Pd-catalyzed C(sp^3)–H olefination:



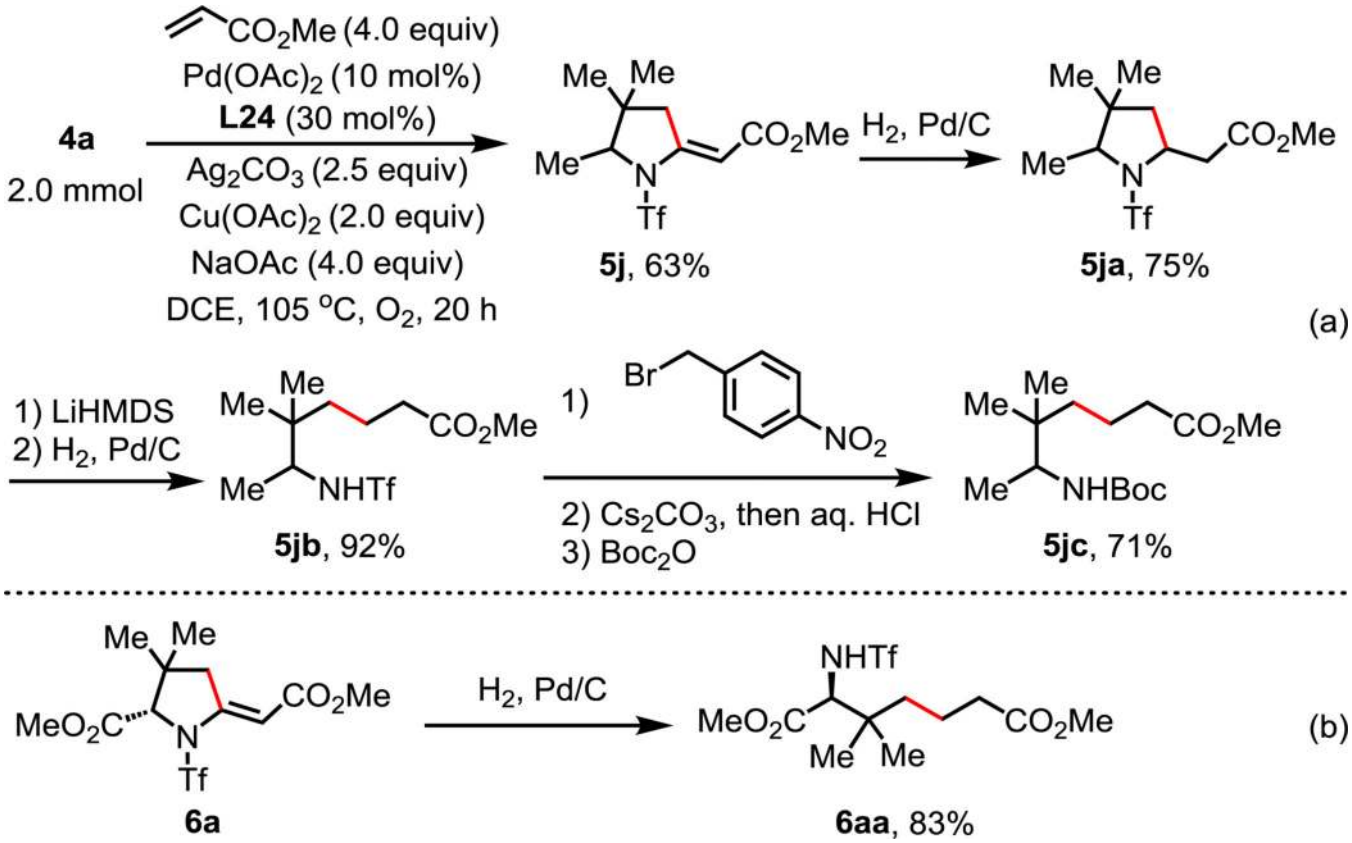
This work: Ligand-enabled γ-C(sp^3)–H olefination of protected amines:



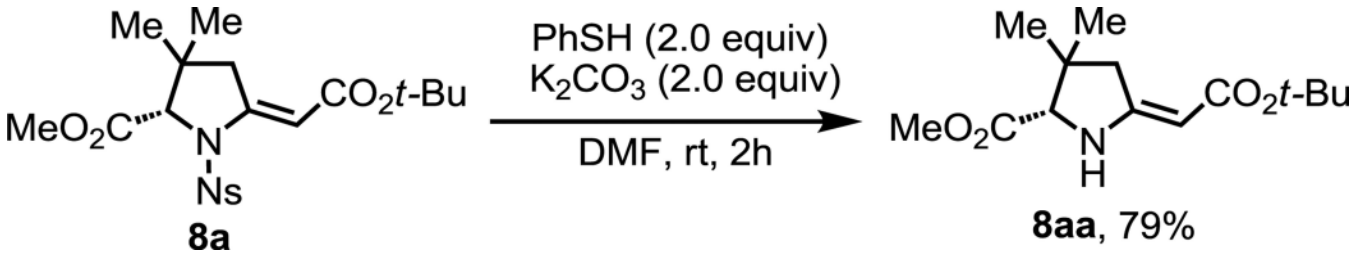
PG = Tf or Ns
R' = CO_2R or Ar

Without ligand: No reaction
With ligand: up to 95% yield

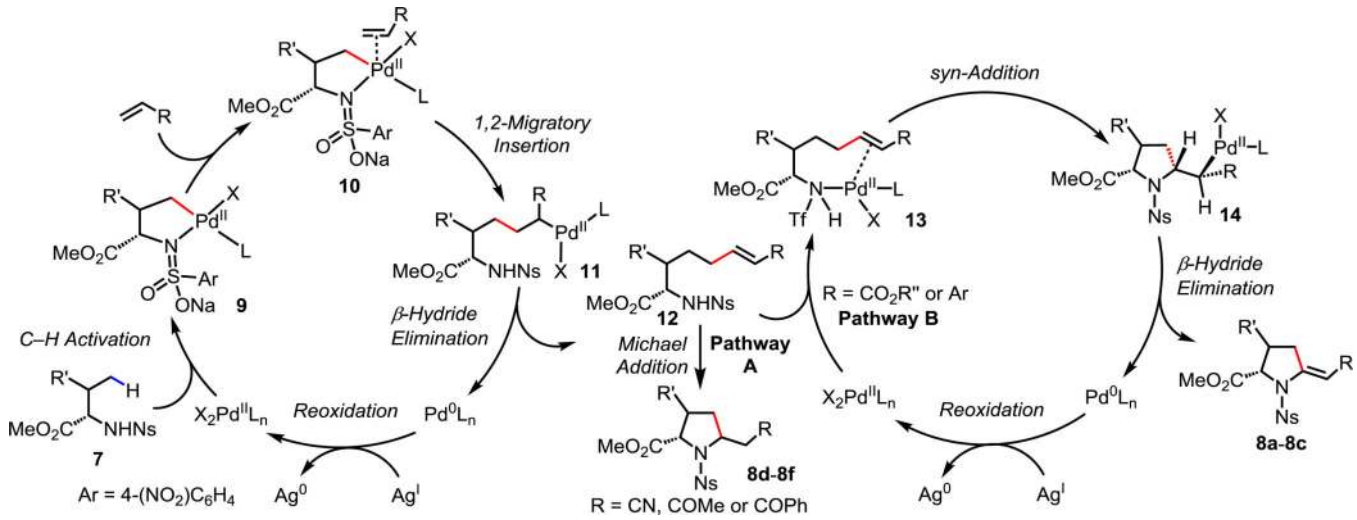
Scheme 1.
Palladium-Catalyzed C(sp^3)–H Olefination



Scheme 2.
Synthetic Application



Scheme 3.
Removal of Protecting Group on 8a

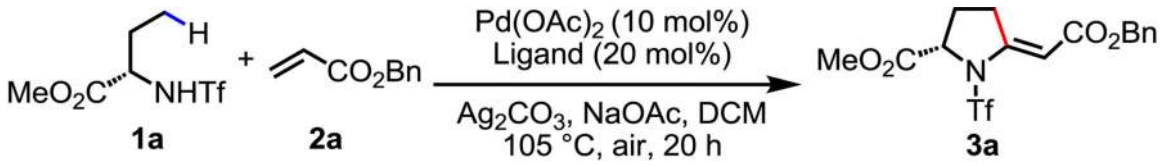


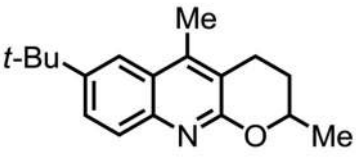
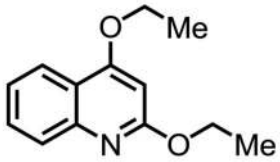
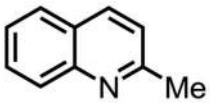
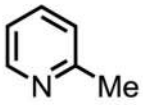
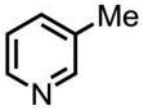
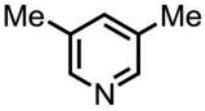
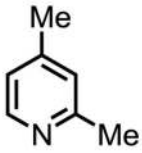
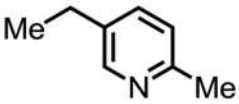
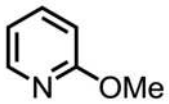
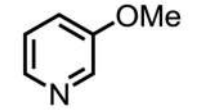
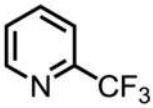
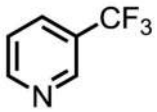
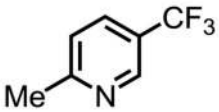
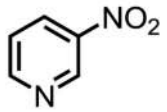
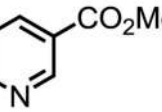
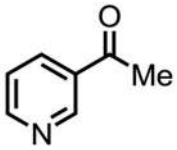
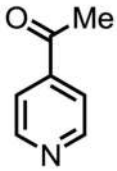
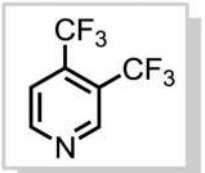
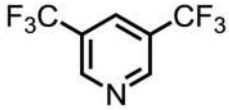
Scheme 4.

Proposed Catalytic Cycle for γ-C(sp^3)–H Olefination/Cyclization

Table 1

Ligand Discovery for C(sp^3)–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%), Ag_2CO_3 (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h.

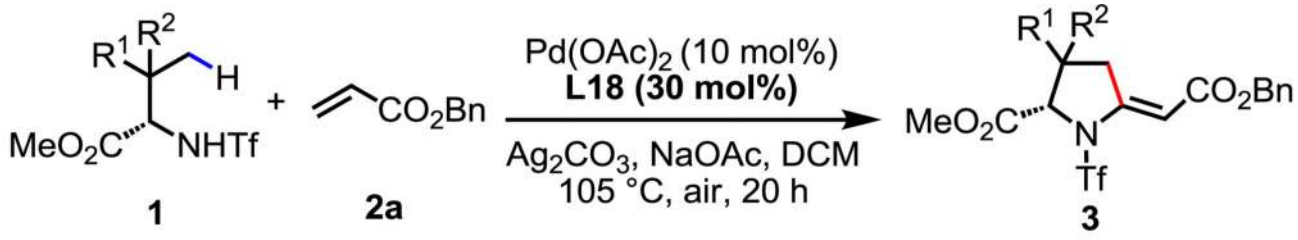
[b]The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

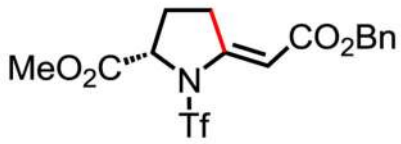
[c] 30 mol% **L18** was used.

[d] > 99% ee, determined by chiral HPLC.

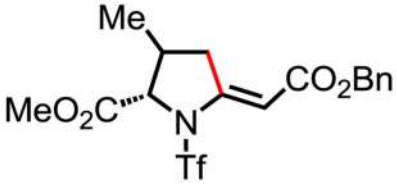
Table 2

Scope of Tf-Protected α-Amino Esters[a,b]

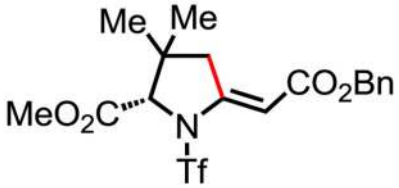




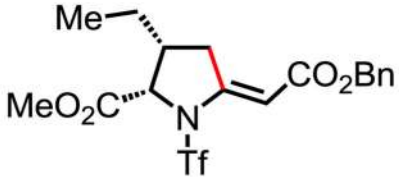
3a, 72%



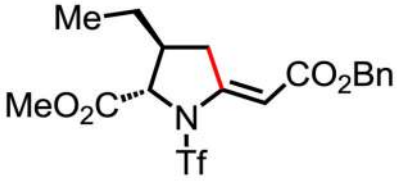
3b, 83%[c]



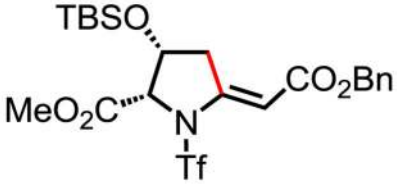
3c, 95%



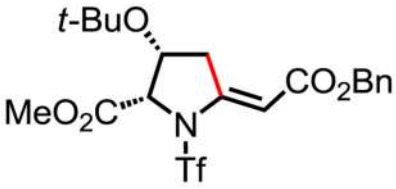
3d, 35%



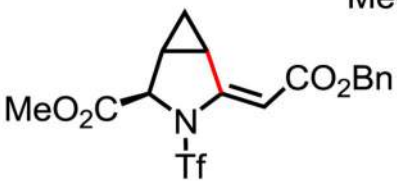
3e, 77%



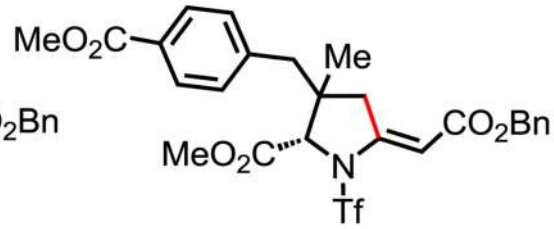
3f, 45%



3g, 63%



3h, 73%[d]



3i, 81%[e]

[a]Reaction conditions: substrate **1** (0.1 mmol), **2a** (4.0 equiv), $Pd(OAc)_2$ (10 mol%), **L18** (30 mol%), Ag_2CO_3 (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h.

[b]Isolated yields.

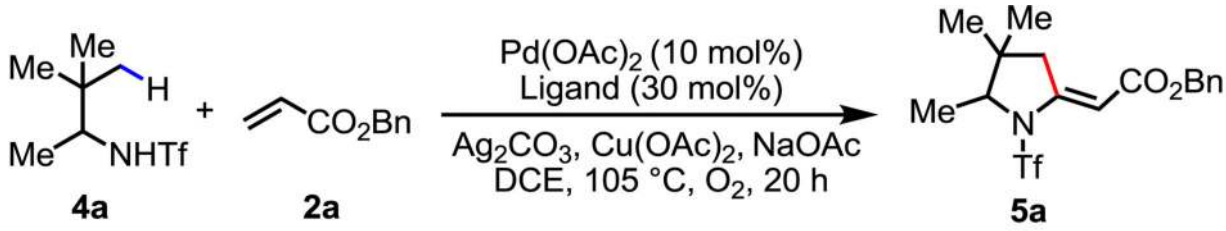
[c]d. r. = 4.5:1.

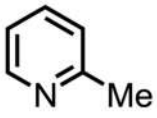
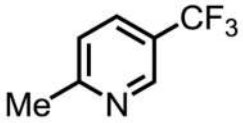
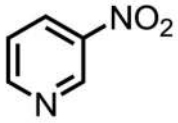
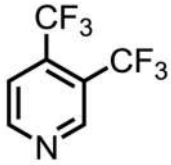
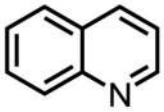
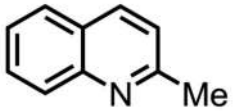
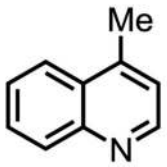
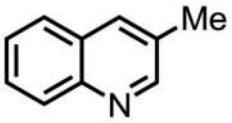
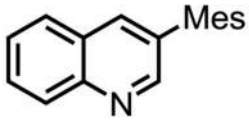
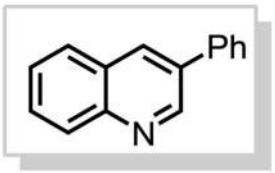
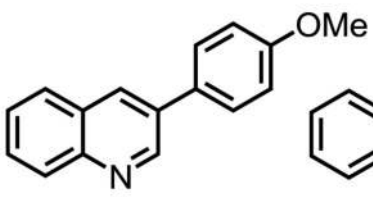
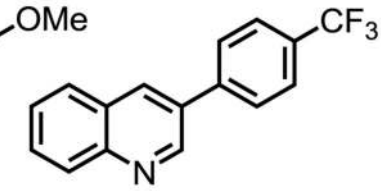
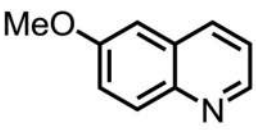
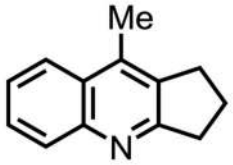
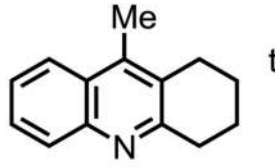
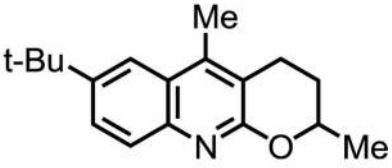
[d] d. r. = 1.25:1.

[e] d. r. = 3:1.

Table 3

Ligand Discovery for C(sp^3)–H Olefination of 4a[a,b]



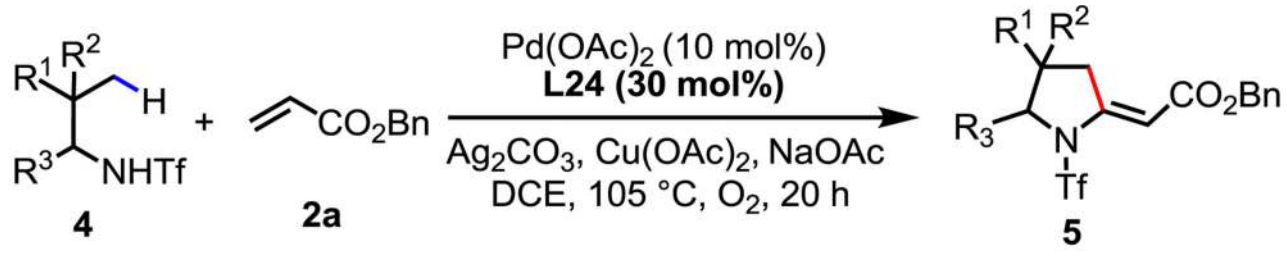
–				
0%	**L4**, 30%	**L13**, 35%	**L14**, 31%	**L18,** 27%
				
L20, 50%	**L3**, 46%	**L21**, 51%	**L22**, 55%	
				
L23, 59%	**L24**, 67%	**L25**, 60%	**L26**, 62%	
				
L27, 31%	**L28**, 33%	**L29**, 15%		**L30**, 15%

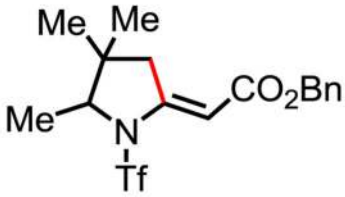
[a]Reaction conditions: substrate **4a** (0.1 mmol), **2a** (4.0 equiv), $Pd(OAc)_2$ (10 mol%), ligand (30 mol%), Ag_2CO_3 (2.5 equiv), $Cu(OAc)_2$ (2.0 equiv), NaOAc (4.0 equiv), DCE (1.0 mL), O_2, 105 °C, 20 h.

[b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

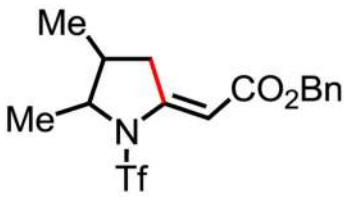
Table 4

Scope of Tf-Protected Alkyl Amines[a,b]

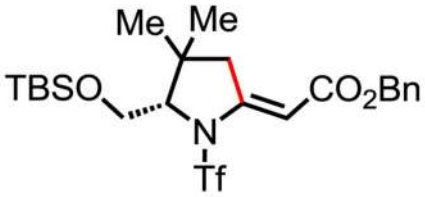




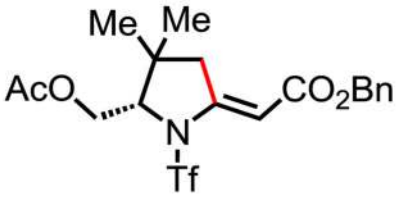
5a, 61%



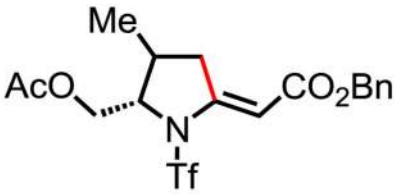
5b, 39%[c]



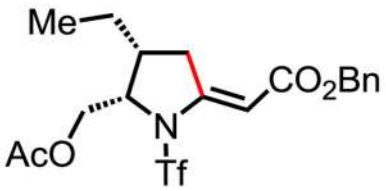
5c, 45%



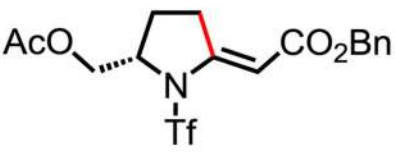
5d, 77%



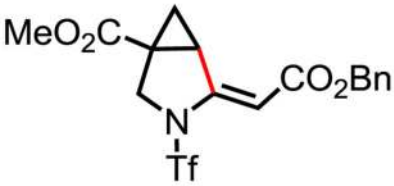
5e, 75%[d]



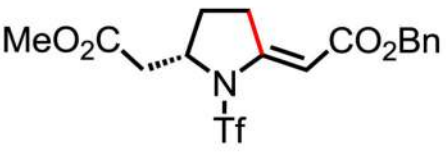
5f, 47%



5g, 41%[e]



5h, 65%



5i, 53%

[a]Reaction conditions: substrate **4** (0.1 mmol), **2a** (4.0 equiv), $Pd(OAc)_2$ (10 mol%), **L24** (30 mol%), Ag_2CO_3 (2.5 equiv), $Cu(OAc)_2$ (2.0 equiv), NaOAc (4.0 equiv), DCE (1.0 mL), O_2, 105 °C, 20 h.

[b]Isolated yields.

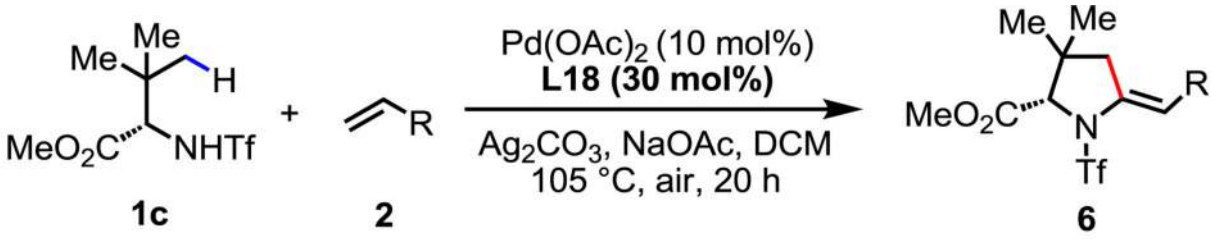
[c]d. r. > 20:1.

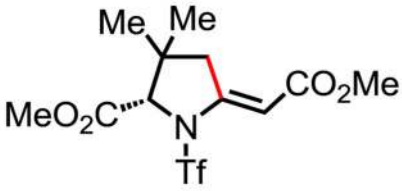
[d]d. r. = 6.5:1.

[e] 98.7% ee, determined by chiral HPLC.

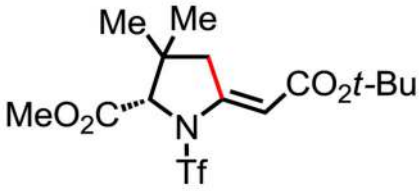
Table 5

Scope of Alkenes[a,b]

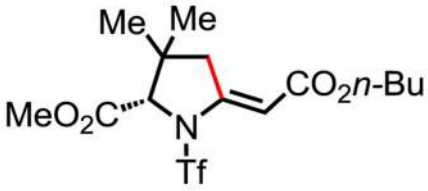




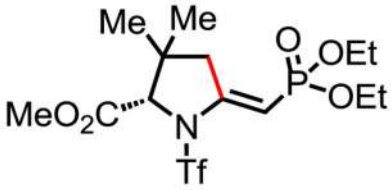
6a, 91%



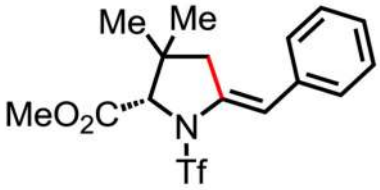
6b, 93%



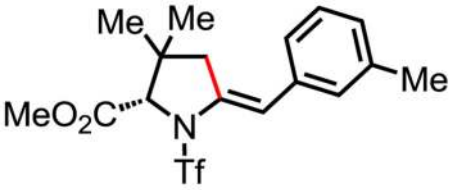
6c, 93%



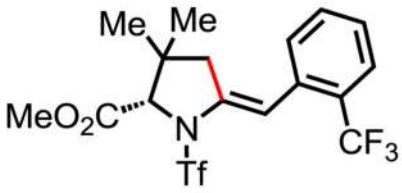
6d, 77%



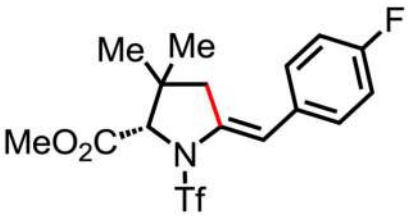
6e, 58%



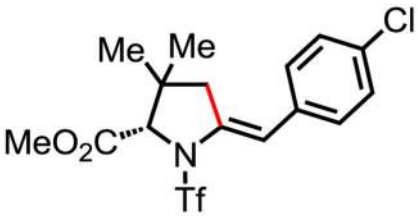
6f, 48%



6g, 59%



6h, 55%



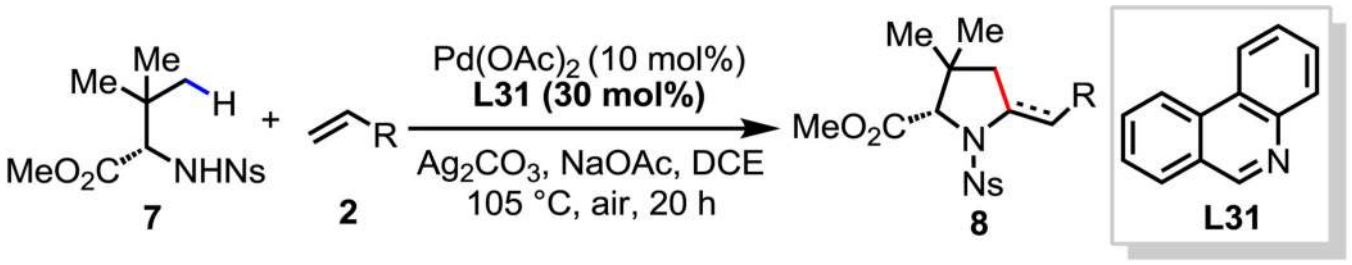
6i, 63%

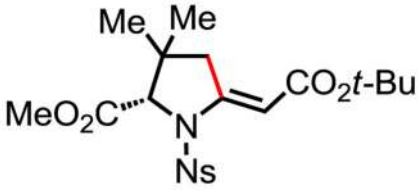
[a]Reaction conditions: substrate **1c** (0.1 mmol), **2** (4.0 equiv), $Pd(OAc)_2$ (10 mol%), **L18** (30 mol%), Ag_2CO_3 (2.5 equiv), NaOAc (4.0 equiv), DCM (1.0 mL), 105 °C, 20 h.

[b]Isolated yields.

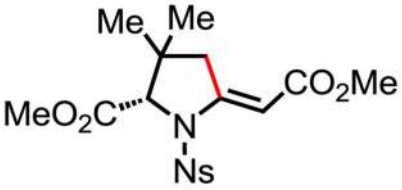
Table 6

Scope of Alkenes for Ns-Protected Amine Ester 7[a,b]

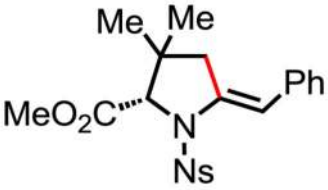




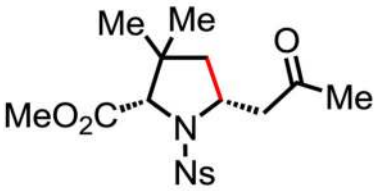
8a, 90%[c]



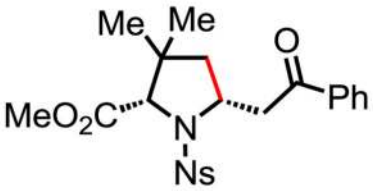
8b, 85%



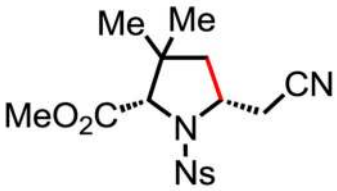
8c, 52%



8d, 75%[d]



8e, 60%[e]



8f, 42%[e]

[a]Reaction conditions: substrate **7** (0.1 mmol), **2** (4.0 equiv), $Pd(OAc)_2$ (10 mol%), **L31** (30 mol%), Ag_2CO_3 (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.