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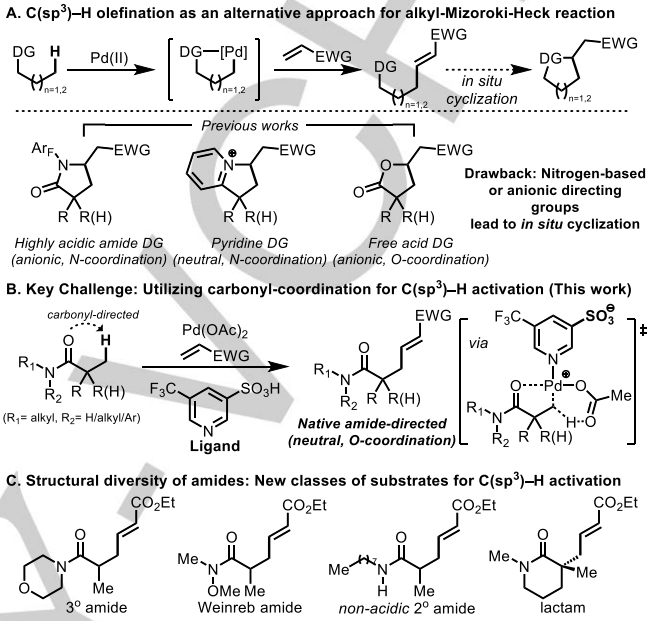
Utilizing Carbonyl-Coordination of Native Amides for Pd–catalyzed C(sp^3)–H Olefination

Hojoon Park,[a] Yang Li,[a] and Jin-Quan Yu*[a]

Abstract: Pd(II)–catalyzed C(sp^3)–H olefination of weakly-coordinating native amides is reported. Three major drawbacks of previous C(sp^3)–H olefination protocols – 1) *in situ* cyclization of products, 2) incompatibility with α-H-containing substrates, and 3) installation of exogenous directing groups – are addressed via harnessing the carbonyl-coordination of amides to direct C(sp^3)–H activation. The method enables direct C(sp^3)–H functionalization of a wide range of native amide substrates, including secondary, tertiary, and cyclic amides, for the first time. The utility of this process is demonstrated by diverse transformations of the olefination products.

The Mizoroki-Heck reaction[1] has proven to be a powerful technology for C–C bond formation.[2] While progress has been made for the alkyl-variant of the Mizoroki-Heck reaction,[3] the well-known challenges of this process[4] – undesired β-hydride elimination[4a] and slow oxidative addition[4b] – still limit its development and application. Recently, alkyl-Mizoroki-Heck reaction operating via alkyl hybrid organometallic-radical intermediates has been shown as a promising strategy.[5] As an alternative approach, our group developed the Pd–catalyzed directed C(sp^3)–H olefination (**Scheme 1A**).[6a] Presumably, the intramolecular coordination of the directing group with the alkyl-Pd intermediate prevents premature β-hydride elimination. Since then, several reports on Pd-catalyzed C(sp^3)–H olefination have been disclosed.[6] However, the resulting olefination products often undergo subsequent cyclization.[6a,6c-e,6h] For example, using the acidic amide directing group gives lactam products which require strongly basic conditions to restore the desired alkenyl moiety.[6a] Even with a weakly-nucleophilic carboxylic acid, the product undergoes a facile cyclization to form a lactone.[6h] While reversibly-cyclizing[6b] and non-cyclizing[6f,6g] C(sp^3)–H olefination reactions have been reported, the directing groups that are used therein are either synthetically limited heterocycles or exogenous auxiliaries, and the substrate scopes are mostly limited to α- or β-quaternary substrates. Overall, C(sp^3)–H olefination still remains largely underdeveloped compared to other extensively studied reactions such as C(sp^3)–H arylation.

In order to develop a broadly useful C(sp^3)–H olefination reaction, the following criteria must be met: 1) the installed alkenyl moiety remains intact without undergoing further reactions, 2) α-H-containing substrates are compatible, and 3) ideally, native functionalities are used as directing groups. To the best of our knowledge, there is no protocol reported that satisfies all three criteria above. The dilemma is that due to the inertness of C(sp^3)–H bonds, directing groups used for C(sp^3)–H activation – either nitrogen-based or anionic directing groups – require a certain degree of Lewis-basicity,[7] which inevitably causes subsequent cyclization via addition to the double bond (**Scheme 1A**). However, utilizing a neutral, oxygen-based functional group that would not cyclize, such as a carbonyl, as a directing group for C(sp^3)–H activation is substantially less effective due to the weakly-coordinating nature.[8]



Scheme 1. Pd-catalyzed C(sp^3)–H Olefination.

Recently, we reported the C(sp^3)–H arylation of Weinreb amides enabled by a pyridine-3-sulfonic acid ligand.[9] Both experimental and computational studies indicated that the non-coordinating anionic sulfonate group of the ligand is crucial in promoting the reaction via preserving the cationic character of the Pd center. While the scope of this method was limited to α-quaternary substrates, we reasoned that this is due to the unfavorable Pd(II)/Pd(IV) catalysis with weak-coordination. On the other hand, C(sp^3)–H olefination involving Pd(II)/Pd(0) catalysis would benefit from weak-coordination and extend the scope to a broader range of native amides through carbonyl coordination (**Scheme 1B**). Amides are undoubtedly one of the most ubiquitous functional groups in organic chemistry,[10] and thus the direct coupling of native amides with olefins through C(sp^3)–H activation would be highly desirable. In terms of C–C bond disconnection strategy, such transformation extends the classical Michael addition disconnection from the α-position of a carbonyl to the β-position. Herein, we report the development of C(sp^3)–H olefination of native amides enabled by 5-(trifluoromethyl)-pyridine-3-sulfonic acid ligand. Another unique advantage of utilizing the carbonyl-coordination, besides the non-cyclizing aspect, is that structurally diverse amides, including non-acidic secondary, tertiary, and cyclic amides, becomes available in the substrate scope (**Scheme 1C**).

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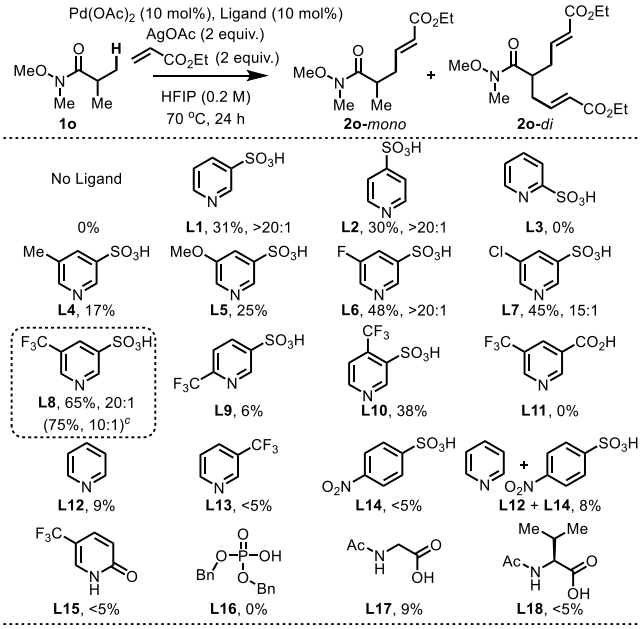
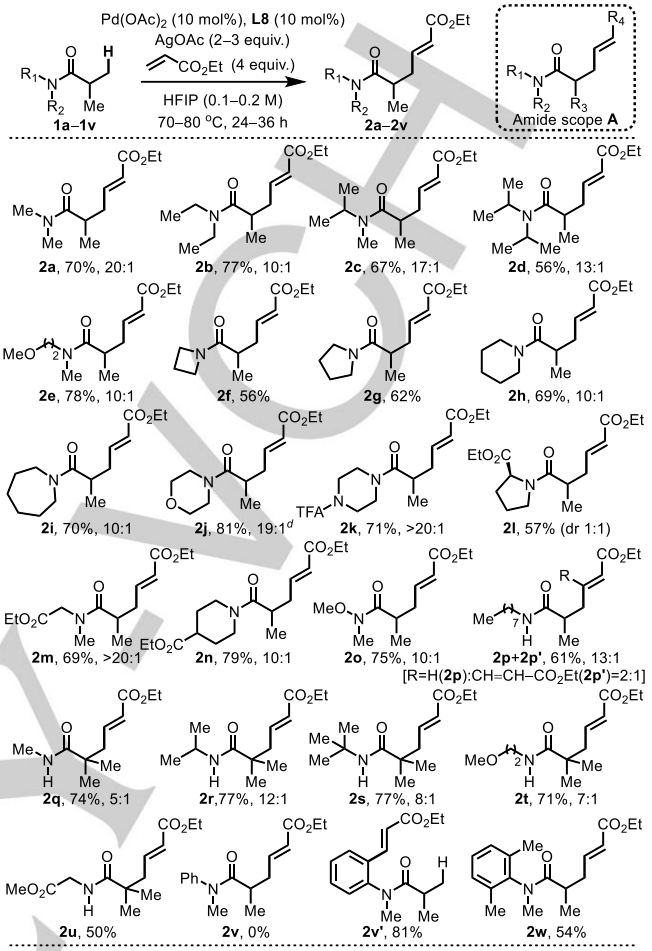
Table 1. Evaluation of Ligands for C(sp^3)–H Olefination[a,b]



[a] Conditions: **1o** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **Ligand** (10 mol%), ethyl acrylate (0.2 mmol), AgOAc (0.2 mmol), HFIP (0.5 mL), 70 °C, 24 h. [b] The yield and *mono*:*di* ratio was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c] ethyl acrylate (0.4 mmol), AgOAc (0.3 mmol), HFIP (1.0 mL), 36 h, isolated yield/*mono*:*di* ratio.

To develop the proposed olefination reaction, we first investigated the ligand effect for the coupling of Weinreb amide **1o** and ethyl acrylate (**Table 1**). While no product was observed in the absence of ligand, using pyridinesulfonic acid ligands **L1** and **L2** enabled the reaction giving 31% and 30% yields of the product, respectively. This is in clear contrast with the previous arylation[9] where α-H-containing substrates were incompatible, implying that unlike Pd(II)/Pd(IV) catalysis, Pd(II)/Pd(0) catalysis can benefit from weakly-coordinating substrates. Pyridine-2-sulfonic acid (**L3**) completely inhibited the reaction, supporting our hypothesis that the charge separation between Pd and ligand is crucial for reactivity. The bidentate binding mode of **L3** would quench the charge separation and lead to catalyst deactivation. Next, substitution effect on the pyridine-3-sulfonic acid ligand was examined. While electron-donating substituents (**L4**, **L5**) decreased the yield, electron-withdrawing substituents (**L6**, **L7**) improved the yield. This trend led us to prepare $-CF_3$-containing pyridine-3-sulfonic acid ligands **L8**–**L10**. To our delight, **L8** was shown to be the superior ligand giving 65% yield, which was further improved to 75% isolated yield with high *mono*-selectivity under slightly modified reaction conditions. Interestingly, only 6% and 38% yields were observed with **L9** and **L10**, respectively, implying that the pyridine-coordination needs to be finely tuned through both sterics and electronics. An analogous carboxylic acid ligand **L11** was ineffective, showing the importance of the non-coordinating property of the sulfonate anion. Simple pyridine ligands (**L12**, **L13**) were ineffective in promoting the reaction. To show that the pyridinesulfonic acid ligands are not serving as simple sulfonic acid additives, 4-nitrobenzenesulfonic acid (**L14**) was tested, and only trace amount of product was observed. Using a combination of ligands **L12** and **L14** were also ineffective.

Table 2. Substrate Scope of Amides - A [a,b,c]



[a] Conditions: **1** (0.1–0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L8** (10 mol%), ethyl acrylate (4 equiv.), AgOAc (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h. See Supporting Information for details. [b] Isolated yield/*mono*:*di* ratio. [c] The isolated *mono*:*di* ratio does not necessarily reflect the *mono*:*di* selectivity of the reaction. [d] 1.0 g (6.37 mmol) scale.

Other X-type ligands (**L15**–**L18**) did not promote the reaction as well. Besides ligand effect, it is important to note that using HFIP as the solvent was also crucial in observing any reactivity.

With the optimal ligand in hand, we evaluated the substrate scope of the olefination. First, isobutyramide substrates bearing diverse amino-groups were tested (**Table 2**). Simple *di*-alkyl amides with varying sterics were compatible (**2a**–**2e**). Amides containing a wide range of cyclic amino-groups were suitable substrates as well (**2f**–**2k**). A gram-scale reaction was conducted to give **2j** in good yield. Substrates derived from amino acids such as proline (**2l**), sarcosine (**2m**), and isonipecotic acid (**2n**) also provided the products in moderate to good yields. It is noteworthy that previous works on peptide/amino acid-directed C–H functionalization[11] cannot utilize these amino acids due to the lack of nitrogen-coordinating site. As described in Table 1, Weinreb amide **1o** also gave good yield. With secondary amide (**1p**), expected primary olefination products and subsequent vinylic olefination products were obtained in 61% total yield (**2p**: **2p' =** 2:1). No cyclization was observed, implying that carbonyl-coordination was utilized instead of nitrogen-coordination. With s-

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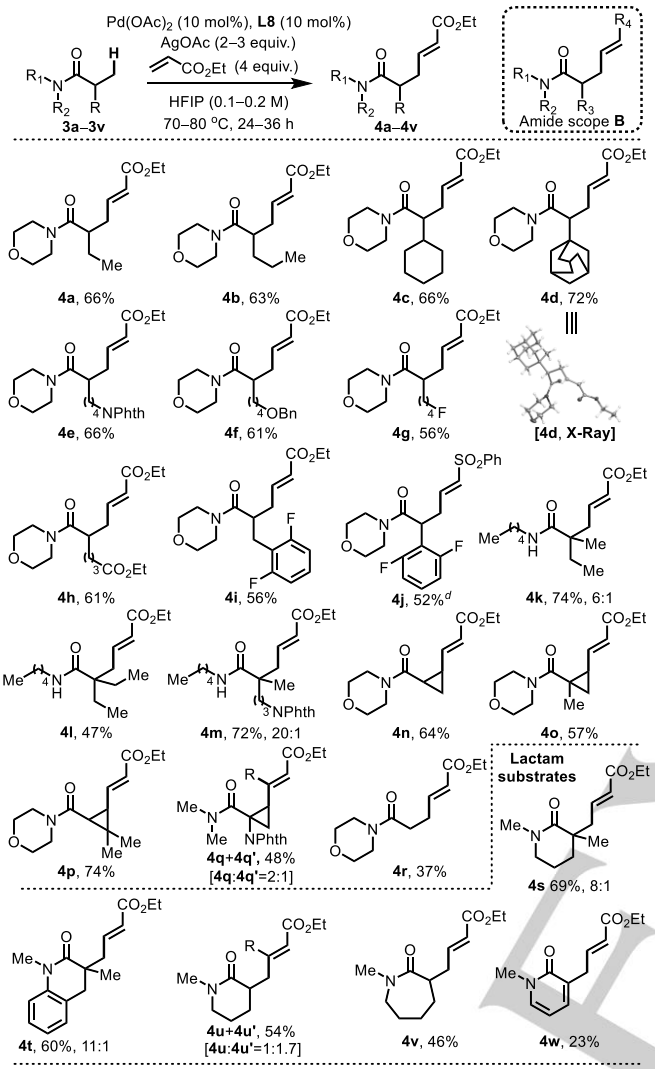
Table 3. Substrate Scope of Amides - B [a,b,c]

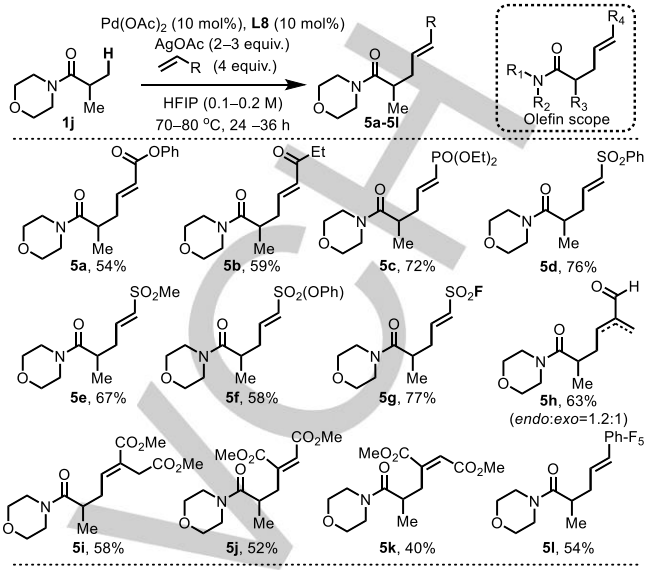


[a] Conditions: **3** (0.1–0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L8** (10 mol%), ethyl acrylate (4 equiv.), AgOAc (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h. See Supporting Information for details. [b] Isolated yield/*mono*:*di* ratio. [c] The isolated *mono*:*di* ratio does not necessarily reflect the *mono*:*di* selectivity of the reaction. [d] Phenyl vinyl sulfone was used for purification purpose.

econdary pivalamides (**1q**–**1u**), the desired olefination products were delivered in moderate to good yields (**2q**–**2u**) with trace amounts of vinylic olefination products. Lastly, we tested whether a coordinating group as weak as an anilide-carbonyl could also serve as a directing group for C(sp^3)–H activation. Anilides have only been used as substrates for C(sp^3)–H activation through nitrogen-coordination via deprotonation of the acidic N–H.[6a,12] With **1v**, only C(sp^2)–H olefination product **2v'** was isolated. To our delight, with the *ortho*-positions of the phenyl ring blocked with methyl groups, **1w** underwent the reaction to give **2w** in 54% yield, demonstrating that Pd/**L8** system can exploit extremely weak coordination for C(sp^3)–H activation.

Next, the scope of the carboxyl component of amides was evaluated (**Table 3**). Various alkyl substituents (**4a**–**4d**), heteroatom-containing functional groups (**4e**–**4h**), and aromatic groups (**4i**–**4j**) on the substrate were tolerated. α-Quaternary amides (**4k**–**4m**) were suitable substrates as well. Cyclopropyl substrates (**4n**–**4q**) also gave moderate to good yields of the products. The formation of **4q** with 1-aminocyclopropane-1-carboxylic acid (ACCA) amide substrate was particularly interesting, as 2-vinyl-ACCA is a motif that is present in numerous drug molecules, especially for the treatment of hepatitis C virus.[13] ACCA-containing dipeptides, however, were incompatible with our olefination conditions. Propionamide substrate delivered **4r** in 37% yield. The lower yield with **4r** is presumably due to the less rigid conformation of the substrate. Lastly, the advantage of utilizing carbonyl-coordination was further demonstrated with the C(sp^3)–H olefination of lactam substrates (**4s**–**4v**). Both 6- (**4s**–**4u**) and 7-membered (**4v**) ring-size, as well as α-tertiary (**4u**–**4v**) and α-quaternary (**4s**–**4t**) structures, were tested and successfully provided the olefination products. Unfortunately, 4- or 5-membered lactams were not reactive, presumably due to the unfavorable geometry between directing group, catalyst, and C–H bond. Albeit low yield, *N*-alkyl pyridone also underwent the reaction to give the product **4w** in 23% yield.

Table 4. Olefin Coupling Partner Scope [a,b]



[a] Conditions: **1j** (0.1–0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L8** (10 mol%), olefin (4 equiv.), AgOAc (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h. See Supporting Information for details. [b] Isolated yield.

Finally, the scope of the olefin coupling partner was investigated (**Table 4**). Commonly used Michael acceptors, including acrylate (**5a**), vinyl ketone (**5b**), vinyl phosphonate (**5c**), vinyl sulfonate (**5d**–**5e**), and vinyl sulfate (**5f**) were installed through C(sp^3)–H olefination in moderate to good yields. Most interestingly, ethenesulfonyl fluoride (ESF)[14] was also reactive and gave **5g** in good yield. ESF has been extensively utilized for the sulfur (VI) fluoride exchange (SuFEx) click reaction.[15] To the best of our knowledge, there is no report of ESF being directly installed at an alkyl carbon center via either C(sp^3)–H olefination[16] or even aliphatic Mizoroki- Heck reaction.[17] We anticipate this protocol to be applied to explore new Fsp^3-rich substrates for SuFEx chemistry. Various di-substituted Michael acceptors were compatible with the reaction to give products **5h**–**5k**. It is noteworthy that fumarate and maleate were successfully employed as coupling partner for C(sp^3)–H olefination for the first

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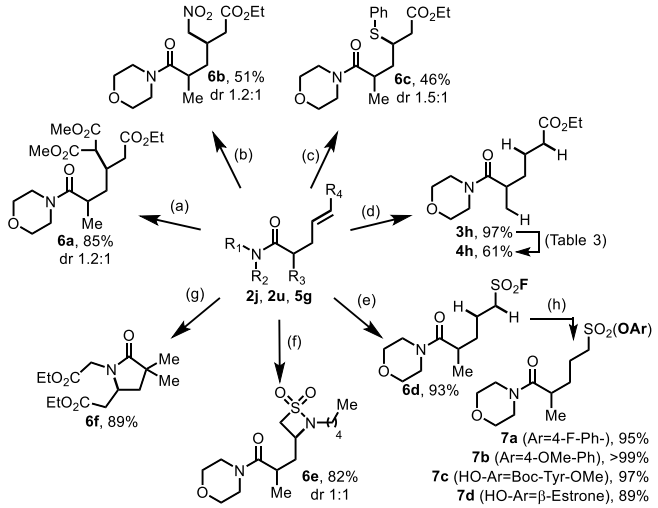

Scheme 2. Diversification of Olefination Products. (a) **2j** (0.1 mmol), dimethyl malonate (2 equiv.), Cs_2CO_3 (1 equiv.), CH_3CN (0.1 M), 70 °C, 32 h. (b) **2j** (0.1 mmol), DBU (1.5 equiv.), CH_3NO_2 (0.5 M), 0 °C, 3 h. (c) **2j** (0.1 mmol), PhSH (2 equiv.), K_2CO_3 (2.2 equiv.), THF (0.1 M), 70 °C, 32 h. (d) **2j** (0.96 mmol), 10% Pd/C (0.07 mmol), EtOAc (0.1 M), H_2 balloon (1 atm), r.t., 24 h. (e) **5g** (0.38 mmol), 10% Pd/C (0.03 mmol), EtOAc (0.1 M), H_2 balloon (1 atm), r.t., 48 h. (f) **5g** (0.1 mmol), *n*-amylamine (4 equiv.), CH_3CN (0.1 M), r.t., 30 min. (g) **2u** (0.49 mmol), DBU (1 equiv.), EtOH (0.25 M), reflux, 1 h. (h) **6d** (0.053 mmol), Ar–OTBS (1.05 equiv.), DBU (10 mol%), CH_3CN (0.1 M), r.t., 16 h.

time (**5j**, **5k**). The formation of these tri-substituted olefins with carboxylate groups in either *E*- or *Z*-configuration could greatly facilitate complex olefin synthesis. Unfortunately, styrenes and aliphatic alkenes were generally not reactive under our reaction conditions. Only pentafluorostyrene successfully delivered the olefinated product **5l** in 54% yield.

The synthetic utility of the Mizoroki-Heck reaction largely comes from the versatile reactivity of an alkenyl group.[2] To emphasize the value of preserving the alkenyl group during C(sp^3)–H olefination, we conducted diverse transformation on the olefination products using the alkenyl group as the functional group handle (**Scheme 2**). Michael addition products were obtained from **2j** with both carbon-based (**6a**–**6b**) and heteroatom-based (**6c**) nucleophiles. Hydrogenation of **2j** and **5g** led to **3h** and **6d** in 97% and 93% yields, respectively. It is noteworthy that **3h** can undergo a 2nd C(sp^3)–H olefination (**Table 3**, **4h**) to install another synthetic handle for further transformation. We also demonstrated that **6d** can lead to sulfonate ester products **7a**–**7d** with various silyl-protected phenols under classical SuFEx conditions. **5g** was treated with *n*-amylamine to form the β-sultam product **6e** in 82% yield, demonstrating the potential "dual warhead" reactivity of vinyl sulfonyl fluorides.[17b,18] With secondary amide **2u**, facile cyclization proceeds with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to form the lactam product **6f** in 89% yield. It is important to note that while previously reported C(sp^3)–H olefination/*in situ* cyclization reactions produce auxiliary-embedded lactams,[6a,6c,6d] our two-step protocol (olefination/DBU-mediated cyclization) can be used to prepare general *N*-alkyl lactams.

In summary, we have developed the Pd(II)–catalyzed C(sp^3)–H olefination of native amides. To utilize the weak carbonyl-coordination, an electron-deficient pyridine-3-sulfonic acid ligand **L8** was designed. Among the known classes of ligands, only pyridinesulfonic acid ligands were effective in promoting the reaction, supporting our hypothesis on the role of the non-coordinating sulfonate group in generating a highly electrophilic catalyst. Using our method, structurally diverse amide substrates, including secondary, tertiary, and cyclic amides, were shown to undergo C(sp^3)–H olefination without the undesired *in situ* cyclization. Finally, olefination products were further diversified using both alkene transformation reactions and SuFEx chemistry. Combining the versatile reactivity of olefins with the combinatorial nature of amides (amine + carboxylic acid) would allow one to rapidly access diverse target compounds.

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Keywords: C–H activation • Palladium catalysis • Ligand design • Amide • Mizoroki-Heck reaction

[1] a) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; b) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320.

[2] For reviews on the synthetic application of the Mizoroki-Heck reaction, see: a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; b) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.

[3] a) L. Firmansjah, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 11340; b) K. S. Bloome, E. J. Alexanian, *J. Am. Chem. Soc.* **2010**, *132*, 12823.

[4] a) F. Ozawa, T. Ito, A. Yamamoto, *J. Am. Chem. Soc.* **1980**, *102*, 6457; b) A. Ariafard, Z. Lin, *Organometallics* **2006**, *25*, 4030; For review on transition metal catalysis with alkyl halides, see: c) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674.

[5] For examples using palladium catalysis, see: a) K. S. Bloome, R. L. McMahen, E. J. Alexanian, *J. Am. Chem. Soc.* **2011**, *133*, 20146; b) C. M. McMahon, E. J. Alexanian, *Angew. Chem. Int. Ed.* **2014**, *53*, 5974; c) D. Kurandina, M. Parasram, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2017**, *56*, 14212; d) G.-Z. Wang, R. Shang, W.-M. Cheng, Y. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 18307; e) D. Kurandina, M. Rivas, M. Radzhabov, V. Gevorgyan, *Org. Lett.* **2018**, *20*, 357; f) P. Chuentragool, D. Yadagiri, T. Morita, S. Sarkar, M. Parasram, Y. Wang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2019**, *58*, 1794; For cobalt catalysis, see: g) Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2002**, *124*, 6514; (h) M. E. Weiss, L. M. Kreis, A. Lauber, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 11125; For review, see: (i) D. Kurandina, P. Chuentragool, V. Gevorgyan, *Synthesis* **2019**, *51*, 985.

[6] a) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680; b) K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541; c) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216; d) S. Li, G. Chen, C.-G. Feng, W. Gong, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 5267; e) H. Jiang, J. He, T. Liu, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 2055; f) W. Yang, S. Ye, Y. Schmidt, D. Stamos, J.-Q. Yu, *Chem. Eur. J.* **2016**, *22*, 7059; g) N. Thrimurtulu, S. Khan, S. Maity, C. M. R. Volla, D. Maiti, *Chem.*

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Commun. **2017**, *53*, 12457; h) Z. Zhuang, C.-B. Yu, G. Chen, Q.-F. Wu, Y. Hsiao, C. L. Joe, J. X. Qiao, M. A. Poss, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 10363.

[7] J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754.

[8] For reviews on C–H activation with weak-coordination, see: a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461.

[9] H. Park, N. Chekshin, P.-X. Shen, J.-Q. Yu, *ACS Catal.* **2018**, *8*, 9292.

[10] A. Greenberg, C. M. Breneman, J. F. Liebman, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Wiley: New York, 2000.

[11] a) W. Gong, G. Zhang, T. Liu, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940; b) T. Liu, J. X. Qiao, M. A. Poss, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10924; c) A. F. M. Noisier, J. García, I. A. Ionuţ, F. Albericio, *Angew. Chem. Int. Ed.* **2017**, *56*, 314; For a recent review, see: d) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700.

[12] a) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886; b) Y. Deng, W. Gong, J. He, J. Q. Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 6692.

[13] T. Sato, K. Izawa, J. L. Aceña, H. Liu, V. A. Soloshonok, *Eur. J. Org. Chem.* **2016**, *2016*, 2757.

[14] a) J. J. Krutak, R. D. Burpitt, W. H. Moore, J. A. Hyatt, *J. Org. Chem.* **1979**, *44*, 3847; b) Q. Chen, P. Mayer, H. Mayr, *Angew. Chem. Int. Ed.* **2016**, *55*, 12664.

[15] J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430.

[16] For examples of C(sp^2)–H fluorosulfonyl vinylation, see: a) C. Li, S.-M. Wang, H.-L. Qin, *Org. Lett.* **2018**, *20*, 4699; b) X.-Y. Chen, Y. Wu, J. Zhou, P. Wang, J.-Q. Yu, *Org. Lett.* **2019**, *21*, 1426; c) G. Ncube, M. P. Huestis, *Organometallics* **2019**, *38*, 76.

[17] For examples of C(sp^2)–X fluorosulfonyl vinylation, see: a) H. L. Qin, Q. Zheng, G. A. L. Bare, P. Wu, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2016**, *55*, 14155; b) P. K. Chinthakindi, K. B. Govender, A. S. Kumar, H. G. Kruger, T. Govender, T. Naicker, P. I. Arvidsson, *Org. Lett.* **2017**, *19*, 480.

[18] A. J. Brouwer, N. Herrero Álvarez, A. Ciaffoni, H. van de Langemheen, R. M. J. Liskamp, *Bioorg. Med. Chem.* **2016**, *24*, 3429.

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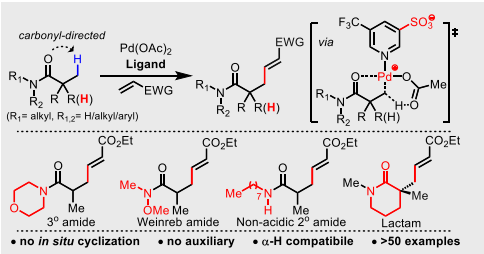
Layout 1:

COMMUNICATION

Pd(II)–catalyzed C(sp^3)–H olefination of native amide substrates was developed. To utilize the extremely weak-coordinating carbonyl-coordination of amides, an electron-deficient pyridinesulfonic acid ligand was designed. Structurally diverse amide substrates, including lactams, underwent olefination without the undesired cyclization. Olefination products were further diversified through synthetic transformations on the alkenyl moiety.



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Utilizing Carbonyl-Coordination of Native Amides for Pd–catalyzed C(sp^3)–H Olefination

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