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Synthesis of γ-Lactams via Pd(II)-Catalyzed C(sp^3)−H Olefination Using a Self-Cleaving Polyfluoroethylsulfinyl Directing Group

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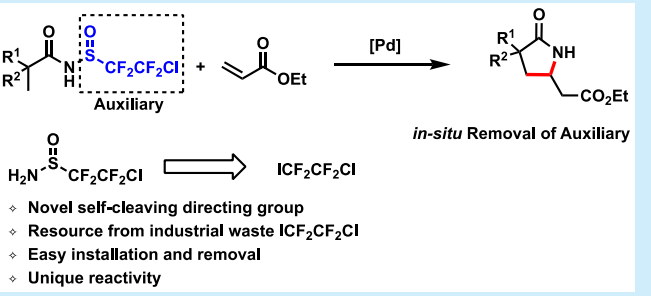
ABSTRACT: A monodentate directing group, 2-chlorotetrafluoroethylsulfinylmide (-NHSOCF$_2$CF$_2$Cl), for inert C(sp^3)−H bond activation is reported. This directing group shows efficient ability in Pd(II)-catalyzed C(sp^3)−H olefination. The desired olefination products undergo subsequent Michael addition and *in situ* expulsion of the auxiliary to provide the free NH γ-lactam products. Preliminary mechanistic studies reveal that the auxiliary group is crucial for C(sp^3)−H activation.



Transition-metal-catalyzed C−H olefination has attracted a tremendous amount of interest, as this family of synthetic methods can enable rapid construction of bioactive molecules.[1] Nevertheless, the activation of aliphatic C(sp^3)−H bonds remains challenging, due to the combination of high pK_a (pK_a > 40) and high bond dissociation energy (BDE > 400 kJ/mol).[2] Moreover, selectively targeting only one C−H bond among many alternative C−H bonds in a similar chemical environment is difficult.[3] In recent years, using a directing group strategy, several C(sp^3)−H olefination precedents have been reported with Pd catalysts. Using heterocyclic directing groups (e.g., pyridine[4a] or pyrazole[4b]) or cyclic aliphatic amines[4c,d] as directing groups, Sanford, Yu, and Gaunt developed straightforward C(sp^3)−H olefinations that afforded open-chain or cyclized products (Figure 1a).[4] A removable directing group strategy has also proven to be successful,[5] as initially reported by Yu in the β-C(sp^3)−H olefination of N-perfluorinated aryl amides.[5a] Similar types of auxiliaries have also facilitated γ-C(sp^3)−H olefination of amine/amide substrates with the aid of pyridine- or quinoline-based ligands, providing lactams or pyrrolidines after subsequent intramolecular cyclization.[5b−d] Maiti achieved γ-C(sp^3)−H olefination to give open-chain products with widely used bidentate 8-aminoquinoline[6] as the directing group (Figure 1b).[5e]

Though these seminal breakthroughs demonstrated the ability to achieve reactivity and selectivity in C(sp^3)−H olefination, the removal of these exogenous auxiliaries is required, which generally involves tedious concession steps and/or harsh conditions.[7] To overcome this problem, Yu reported a free carboxylic acid-directed ligand-enabled β-C(sp^3)−H olefination in 2018. This transformation provided γ-lactones by the subsequent 1,4-addition (Figure 1c),[8] but the synthesis of γ-lactams via facile C(sp^3)−H activation is not compatible. Very recently, Yu reported that native amides are

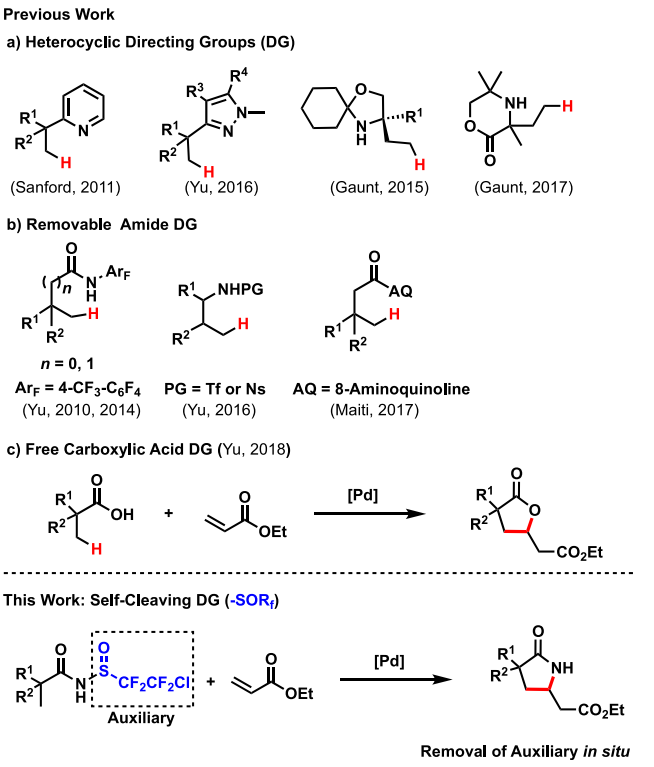


Figure 1. Direct olefination of inert C(sp^3)−H.

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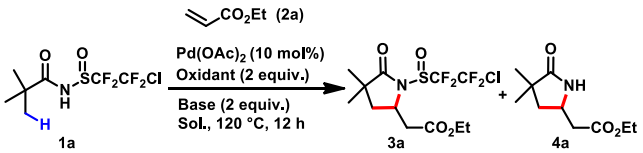
also capable of directing β-C(sp^3)−H olefination to provide open-chain products, but the removal of the directing group is still problematic.[9] The application of a traceless directing group strategy, which is well established in aryl C(sp^2)−H activation,[10] would be highly enabling in C(sp^3)−H functionalization but remains underdeveloped.[11] Herein, we report a self-cleaving amide auxiliary, 2-chlorotetrafluoroethylsulfinyl (SOR_f), and its application in C(sp^3)−H olefination. In this transformation, the auxiliary group (SOR_f) is automatically removed from the desired products during the course of the reaction, thus providing a straightforward protocol for synthesizing free NH γ-lactams, an important bioactive core structure.[12] The *N*-2-chlorotetrafluoroethylsulfinyl ($NHSOR_f$) auxiliary originates from an abundant industrial waste product, ICF_2CF_2Cl, and can thus be easily prepared on a large scale. Liu and Ellman have independently reported elegant uses of this auxiliary in asymmetric nucleophilic addition.[13]

We began the study by examining the reaction of *N*-2-chlorotetrafluoroethanesulfinyl pivalamide (**1a**) and ethyl acrylate (**2a**) (Scheme 1). When using 10 mol % $Pd(OAc)_2$ as the catalyst, 2 equiv of AgOAc as the oxidant, and hexafluoro-2-propanol (HFIP) as the solvent, the desired product **3a**, resulting from C(sp^3)−H olefination and the subsequent Michael addition, was afforded in 14% yield (entry 1). The addition of a base to the reaction mixture significantly increased the yield of **3a**. For example, the use of 2 equiv of NaTFA gave **3a** in 52% yield (entry 2), and the use of CsF afforded **3a** in 72% yield (entry 3). To our delight, we isolated lactam **4a** as a second product in 12% yield, which indicated that the polyfluoroalkylsulfinyl auxiliary (SOR_f) was removed *in situ* under the reaction conditions. Next, we extensively screened various bases, hoping to achieve the convenient synthesis of γ-lactam by using this auxiliary as a self-cleaving directing group in C(sp^3)−H olefination (for details, see the Supporting Information). It turned out that the yield of **4a** could be increased to 81% (78% isolated yield) when using 2 equiv of Na_2CO_3 as the base (entry 4). Other bases, such as K_2CO_3, Cs_2CO_3, and $NaHCO_3$, were found not only to strongly inhibit the formation of **4a** but also to depress alkenylation of **1a** (entries 5−7). We examined various oxidants, only to find that AgOAc was optimal and that other Ag^+ or Cu^{2+} salts were less effective or ineffective for the formation of **3a** or **4a** (entries 8−11). Under these conditions, the reaction was equally effective under either N_2 or O_2 atmospheres (entry 12), indicating that AgOAc is likely playing a key role in reoxidizing the Pd catalyst. Other solvents, such as MeCN, $PhCH_3$, and DCE, gave only **3a** in low yields or did not lead to product formation (entries 13−15, respectively). The decreased reaction temperature resulted in lower yield of **4a** or incomplete conversion of the starting material (entries 16 and 17). On the basis of these findings, we chose entry 4 as the optimal conditions.

Different polyfluoroalkylsulfinyl (SOR_f) auxiliaries were next tested under the optimal conditions (Scheme 2). Pivalamide with a $-CF_3$ auxiliary afforded a 35% yield of **4a**, and the $-C_4F_9$ and $-C_6F_{13}$ auxiliaries provided **4a** in 62% and 56% yields, respectively. All of these auxiliaries were less efficient than $-CF_2CF_2Cl$, demonstrating the unique proprieties of this group.

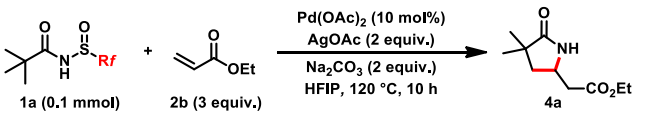
Scheme 1. Optimization of the Reaction Conditions[a]



Entry	Base	Oxidant	Solvent	Yield (%)[b] 3a	Yield (%)[b] 4a
1	None	AgOAc	HFIP	14	n.d.
2	NaTFA	AgOAc	HFIP	52	n.d.
3	CsF	AgOAc	HFIP	72	12
4	Na_2CO_3	AgOAc	HFIP	n.d.	81(78)
5	K_2CO_3	AgOAc	HFIP	n.d.	18
6	Cs_2CO_3	AgOAc	HFIP	n.d.	10
7	$NaHCO_3$	AgOAc	HFIP	5	38
8	Na_2CO_3	Ag_2CO_3	HFIP	n.d.	n.d.
9	Na_2CO_3	Ag_2O	HFIP	n.d.	n.d.
10	Na_2CO_3	AgTFA	HFIP	trace	n.d.
11	Na_2CO_3	$Cu(OAc)_2$	HFIP	n.d.	22
12[c]	Na_2CO_3	AgOAc	HFIP	n.d.	80
13	Na_2CO_3	AgOAc	DCE	20	n.d.
14	Na_2CO_3	AgOAc	MeCN	n.d.	n.d.
15	Na_2CO_3	AgOAc	$PhCH_3$	20	n.d.
16[d]	Na_2CO_3	AgOAc	HFIP	38	28
17[e]	Na_2CO_3	AgOAc	HFIP	30	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2b** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (2 equiv), base (2 equiv), HFIP (2 mL). [b]Yields were determined by ^1H NMR analysis relative to the CH_2Br_2 internal standard. [c]Under a N_2 or an O_2 atmosphere. [d]100 °C. [e]80 °C.

Scheme 2. Efficiencies of Different Auxiliaries



Entry	Rf	NMR Yield of 4a
1	$-CF_3$	35%
2	$-CF_2CF_2Cl$	76%
3	$-C_4F_9$	62%
4	$-C_6F_{13}$	56%

Having optimized the conditions, we evaluated the substrate scope for this transformation. Various α,α-dialkyl-substituted propionic amides bearing the *N*-2-chlorotetrafluoroethylsulfinyl ($NHSOR_f$) auxiliary were examined, and the desired γ-lactams were afforded in moderate to good yields via C(sp^3)−H activation (Scheme 3). The linear substituents on the propionic amides, such as methyl, ethyl, 1-propyl, 2-propyl, and 1-butyl, were compatible with this protocol and afforded the desired γ-lactams in 56−78% yield (**4a**−**4e**). The connectivity of **4a** was confirmed by X-ray diffraction. α,α-Diethyl-substituted propionic amide provided a 50% yield of **4f**. Spirocyclic propionic amide was tolerated under the reaction conditions, and the desired product **4g** was achieved in 51% yield. A substrate bearing a methoxy group was also suitable, offering a 52% yield of the desired product **4h** with a 1.5:1 diastereoselectivity. Phenyl substituents at the β, γ, or δ position of the propionic amides were well tolerated (**4i**−**4n**), and halogen substituents (i.e., -F, -Cl, and -Br) could be readily accommodated on these aryl species (**4i**−**4k** and **4m**). Though

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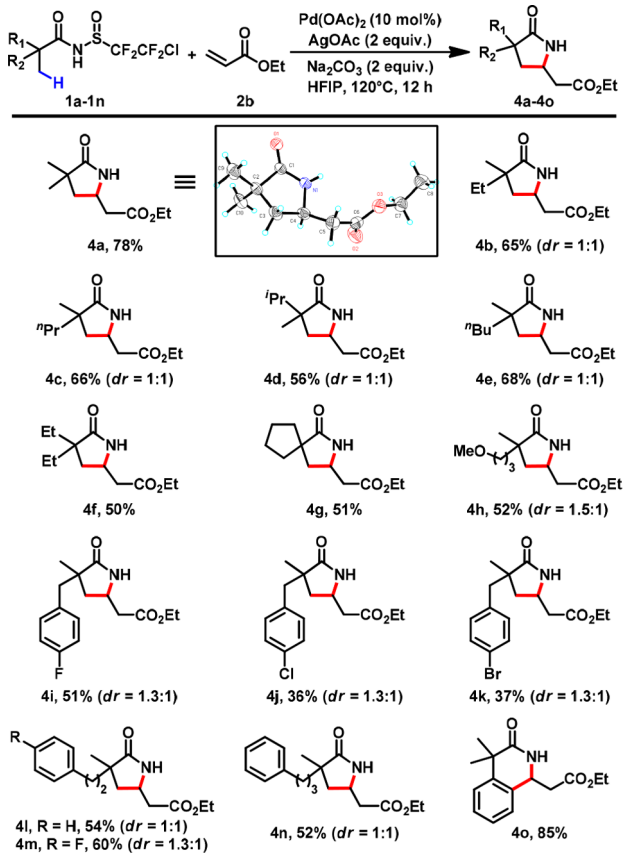
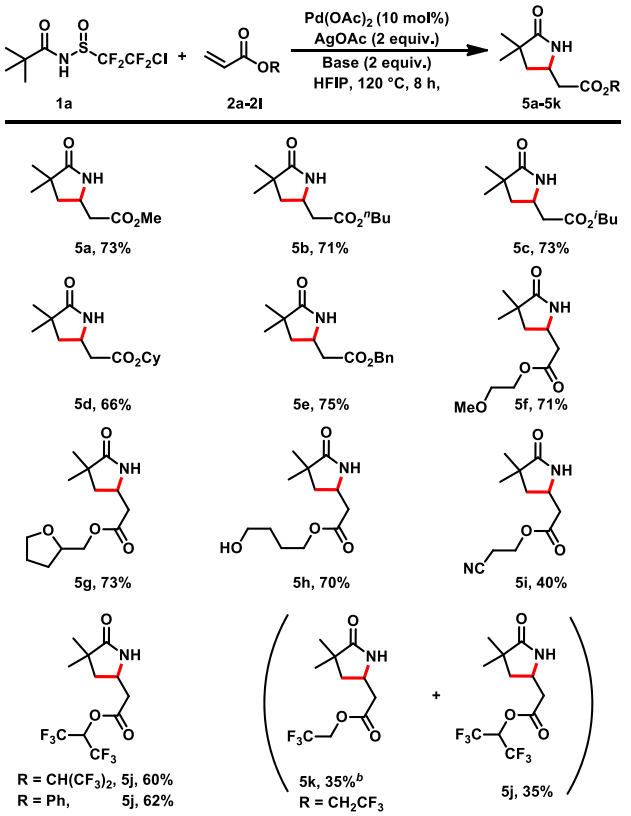
Scheme 3. Substrate Scope for β-C(sp^3)−H Olefination[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2b** (3 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), Na_2CO_3 (2.0 equiv), HFIP (2 mL), 120 °C, 12 h.

Scheme 4. Substrate Scope for Acrylates[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2b** (3 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), Na_2CO_3 (2.0 equiv), HFIP (2 mL), 120 °C, 12 h. [b]2,2,2-Trifluoroethyl acrylate was used, resulting in a mixture of **5k** (35%) and **5j** (35%).

low yields were obtained with β-aryl-substituted substrates, moderate yields were provided when the aromatic rings were instead located at the γ or δ positions, and the desired products were obtained in 52−60% yields (**4l**−**4n**). This *in situ* removable directing group could also be applied to aryl C(sp^2)−H olefination, when α,α-dimethyl-α-phenyl amide was used as the starting material; under the optimal reaction conditions, C−H olefination took place at the aryl C(sp^2)−H bond, providing the corresponding benzo-fused δ-lactam in 85% yield (**4o**).

The scope of the acrylate substrates was next examined with *N*-2-chlorotetrafluoroethanesulfinyl pivalamide (**1a**). Various acrylates were tolerated and provided the corresponding products in moderate to good yields (Scheme 4). For simple acrylates, such as methyl, *tert*-butyl, *iso*-butyl, cyclohexyl, and benzyl acrylate, C(sp^3)−H olefination took place smoothly and provided the desired products in 66−75% yields (**5a**−**5e**, respectively). The reaction also performed well for acrylates that contain various functional groups; for example, methoxyl, 2-furanyl, and hydroxyl groups on the alkoxy fragment of the acrylates were compatible and provided the corresponding γ-lactams in 70−73% yields (**5f**−**5h**). A cyano group on the acrylate was tolerated, albeit in a lower yield (**5i**). Hexafluoro-2-propanyl acrylate afforded the desired coupling product in 60% yield (**5j**). When phenyl acrylate was used as the starting material, the reaction delivered a 62% yield of **5j** as the final product, rather than the expected phenyl ester product, most likely due to the alcoholysis with the HFIP solvent. Similarly, 2,2,2-trifluoroethyl acrylate afforded a mixture of free NH γ-lactam **5j** (35%) and **5k** (35%) under these conditions.

Because self-cleaving directing groups have rarely been reported in C−H functionalization research, several experiments were conducted to shed light on the mechanistic details of this reaction. First, when the reaction was performed in the absence of acrylate, the starting material **1a** was recovered in 81% isolated yield, and a trace amount of pivalamide **6** was detected (eq 1). This result indicates that **1a** is relatively stable under the reaction conditions. Furthermore, when pivalamide **6** was used as the starting material in lieu of **1a** under the standard conditions, **6** was recovered, and no C(sp^3)−H activation products were detected (eq 2). This observation suggests that amide **1a** containing the polyfluoroalkylsulfinyl (SOR_f) auxiliary is the active substrate in C(sp^3)−H activation, rather than pivalamide **6**. On the basis of this insight, we reasoned that the cleavage of the auxiliary group likely takes place after the C(sp^3)−H activation/olefination sequence, though we have never isolated the C(sp^3)−H activation/olefination product(s). Finally, when we used the optically enriched **1a** (94% ee) as the starting material, we obtained the desired γ-lactam product in 47% ee, in 71% isolated yield (eq 3). This result also supports the notion that the auxiliary group is expelled after completion of the C(sp^3)−H olefination/cyclization cascade.

On the basis of these results, we propose a plausible reaction mechanism for this Pd-catalyzed self-cleaving polyfluoroalkylsulfinyl (SOR_f) auxiliary-directed C(sp^3)−H olefination/

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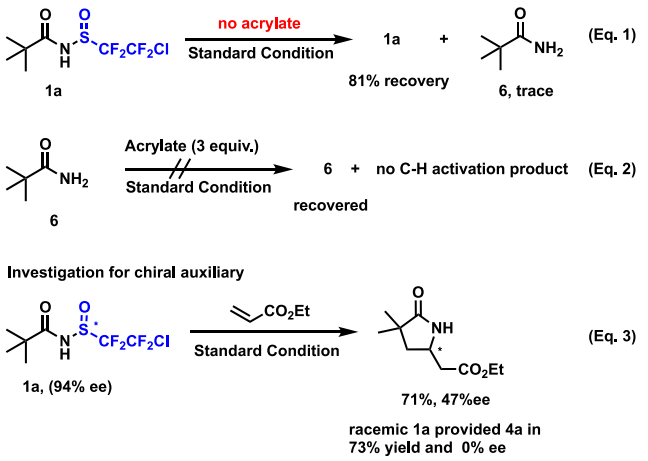
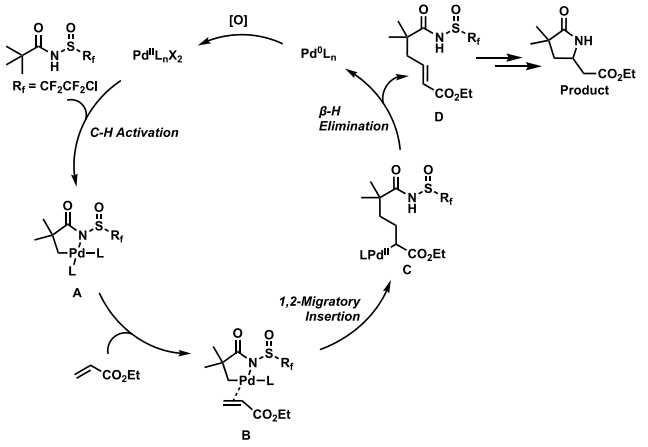


cyclization process (Scheme 5). The Pd^{II} catalyst coordinates to the polyfluoroalkylsulfinylamide and activates the proximal methyl C(sp^3)−H bond to afford a five-membered palladacycle intermediate **A**. The coordination of acrylate and 1,2-migratory insertion of the Pd−C(sp^3) bond into the olefin generate intermediate **C**. Subsequent β-H elimination provides olefinated intermediate **D**; the Pd^{II} catalyst is regenerated by Ag^+ to close the catalytic cycle. Olefinated intermediate **D** undergoes intramolecular Michael addition and *in situ* cleavage of the auxiliary to give the final γ-lactam product.

Scheme 5. Proposed Mechanism



In summary, a new self-cleaving monodentate polyfluoroalkylsulfinyl (SOR_f) auxiliary for Pd(II)-catalyzed aliphatic C(sp^3)−H bond olefination and tandem cyclization has been developed. This transformation provides a practical procedure for synthesizing NH free γ-lactams. Initial mechanistic investigations reveal that the polyfluoroalkylsulfinyl (SOR_f) auxiliary is crucial for C(sp^3)−H activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00326.

^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectra and the experimental procedure (PDF)

Accession Codes

CCDC 1974038 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. C−C Bond Formation via C−H Bond Activation: Synthesis of the Core of Teleocidin B4. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. The Total Synthesis of (+)-Dragmacidin F. *J. Am. Chem. Soc.* **2004**, *126*, 9552. (c) Beck, E. M.; Hatley, R.; Gaunt, M. J. Synthesis of Rhazinicine by a Metal-Catalyzed C−H Bond Functionalization Strategy. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004. (d) Wang, D.-H.; Yu, J.-Q. Highly Convergent Total Synthesis of (+)-Lithospermic Acid via a Late-Stage Intermolecular C−H Olefination. *J. Am. Chem. Soc.* **2011**, *133*, 5767. (e) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. Sequential C_{sp3}−H Arylation and Olefination: Total Synthesis of the Proposed Structure of Pipercyclobutanamide A. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507.

(2) Lu, W.; Zhou, L. *Oxidation of C−H Bonds*; John Wiley & Sons, Ltd., 2003.

(3) For selected reviews of C(sp^3)−H functionalization, see: (a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C−H Bonds. *Chem. Rev.* **2017**, *117*, 8754.

(b) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed C(sp^3)−H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62. (c) Liang, Y.-F.; Jiao, N. Oxygenation via C−H/C−C Bond Activation with Molecular Oxygen. *Acc. Chem. Res.* **2017**, *50*, 1640. (d) Li, B.-J.; Shi, Z.-J. From C(sp^2)−H to C(sp^3)−H: Systematic Studies on Transition Metal-catalyzed Oxidative C−C Formation. *Chem. Soc. Rev.* **2012**, *41*, 5588. (e) He, G.; Wang, B.; Nack, W. A.; Chen, G. Syntheses and Transformations of α-Amino Acids via Palladium-Catalyzed Auxiliary Directed sp^3 C−H Functionalization. *Acc. Chem. Res.* **2016**, *49*, 635. (f) Girard, S. A.; Knauber, T.; Li, C.-J. The Cross-Dehydrogenative Coupling of C_{sp3}−H Bonds: A Versatile Strategy for C−C Bond Formations. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (g) White, M. C.; Zhao, J. Aliphatic C−H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988.

(4) For heterocyclic DGs, see: (a) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. Aerobic Pd-Catalyzed sp^3 C−H Olefination: A Route to Both N-Heterocyclic Scaffolds and Alkenes. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (b) Yang, W.; Ye, S.; Schmidt, Y.; Stamos, D.; Yu, J.-Q. Ligand-Promoted C(sp^3)−H Olefination en Route to Multifunctionalized Pyrazoles. *Chem. - Eur. J.* **2016**, *22*, 7059. (c) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. A Steric Tethering Approach Enables Palladium-catalysed C−H Activation of Primary Amino Alcohols. *Nat. Chem.* **2015**, *7*, 1009. (d) He, C.; Gaunt, M. J. Ligand-assisted Palladium-catalyzed C−H Alkenylation of Aliphatic Amines for the Synthesis of Functionalized Pyrrolidines. *Chem. Sci.* **2017**, *8*, 3586.

(5) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. Pd(II)-Catalyzed Olefination of *sp*^{3} C−H Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. Ligand-Controlled C(sp^3)−H Arylation and Olefination in Synthesis of Unnatural Chiral α−Amino Acids. *Science* **2014**, *343*, 1216. (c) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. Ligand-Enabled γ-C−H Olefination and Carbonylation: Construction of β-Quaternary Carbon Centers. *J. Am. Chem. Soc.* **2014**, *136*, 5267. (d) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. Ligand-Enabled γ-C(sp^3)−H Olefination of Amines: En Route to Pyrrolidines. *J. Am. Chem. Soc.* **2016**, *138*, 2055. (e) Thrimurtulu, N.; Khan, S.; Maity, S.; Volla, C. M. R.; Maiti, D. Palladium Catalyzed Direct Aliphatic γC(sp^3)−H Alkenylation with Alkenes and Alkenyl Iodides. *Chem. Commun.* **2017**, *53*, 12457. For other types of strategies for C(sp^3)−H olefination, using 1,5-HAT with a palladium catalyst, see: (f) Chuentragool, P.; Yadagiri, D.; Morita, T.; Sarkar, S.; Parasram, M.; Wang, Y.; Gevorgyan, V. Aliphatic Radical Relay Heck Reaction at Unactivated C(sp^3)−H Sites of Alcohols. *Angew. Chem., Int. Ed.* **2019**, *58*, 1794. For Pd-catalyzed alkenylation of δ-C(sp^3)−H bonds with alkynes, see: (g) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. Site-Selective Alkenylation of δ-C(sp^3)−H Bonds with Alkynes via a Six-Membered Palladacycle. *J. Am. Chem. Soc.* **2016**, *138*, 10750. For selected example of vinyl iodides as coupling partners, see: (h) He, G.; Chen, G. A Practical Strategy for the Structural Diversification of Aliphatic Scaffolds through the Palladium-Catalyzed Picolinamide-Directed Remote Functionalization of Unactivated C(sp^3)−H Bonds. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (i) Shan, G.; Huang, G.; Rao, Y. Palladium-Catalyzed Unactivated β-Methylene C(sp^3)−H Bond Alkenylation of Aliphatic Amides and Its Application in a Sequential C(sp^3)−H/C(sp^2)−H Bond Alkenylation. *Org. Biomol. Chem.* **2015**, *13*, 697.

(6) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly Regioselective Arylation of sp^3 C−H Bonds Catalyzed by Palladium Acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. Auxiliary-Assisted Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 Carbon−Hydrogen Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(7) (a) Pei, Q.-L.; Che, G.-D.; Zhu, R.-Y.; He, J.; Yu, J.-Q. An Epoxide-Mediated Deprotection Method for Acidic Amide Auxiliary. *Org. Lett.* **2017**, *19*, 5860. Zhang, Z.; Li, X.; Song, M.; Wan, Y.; Zheng, D.; Zhang, G.; Chen, G. Selective Removal of Aminoquinoline Auxiliary by IBX Oxidation. *J. Org. Chem.* **2019**, *84*, 12792.

(8) Zhuang, Z.; Yu, C.-B.; Chen, G.; Wu, Q.-F.; Hsiao, Y.; Joe, C. L.; Qiao, J. X.; Poss, M. A.; Yu, J. Q. Ligand-Enabled β-C(sp^3)−H Olefination of Free Carboxylic Acids. *J. Am. Chem. Soc.* **2018**, *140*, 10363.

(9) Park, H.; Li, Y.; Yu, J.-Q. Utilizing Carbonyl Coordination of Native Amides for Palladium-Catalyzed C(sp^3)−H Olefination. *Angew. Chem., Int. Ed.* **2019**, *58*, 11424.

(10) For selected reviews of a traceless DG strategy for C(sp^2)−H activations, see: (a) Zhang, F.; Spring, D. R. Arene C−H Functionalisation Using a Removable/Modifiable or a Traceless Directing Group Strategy. *Chem. Soc. Rev.* **2014**, *43*, 6906. (b) Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. The Use of Carboxylic Acids as Traceless Directing Groups for Regioselective C−H Bond Functionalization. *Chem. Commun.* **2017**, *53*, 5584. (c) Rej, S.; Chatani, N. Rhodium-Catalyzed C(sp^2)- or C(sp^3)−H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304. For selected examples of traceless DG strategies for C(sp^2)−H activations, see: (d) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. Silanol: A Traceless Directing Group for Pd-Catalyzed *o*-Alkenylation of Phenols. *J. Am. Chem. Soc.* **2011**, *133*, 12406. (e) Lu, Q.; Gressies, S.; Cembellin, S.; Klauck, F. J. R.; Daniliuc, C. G.; Glorius, F. Redox-Neutral Manganese(I)-Catalyzed C−H Activation: Traceless Directing Group Enabled Regioselective Annulation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12778. (f) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. Cobalt-Catalyzed Selective Synthesis of Isoquinolines Using Picolinamide as a Traceless Directing Group. *Org. Lett.* **2017**, *19*, 2102.

(11) For selected examples of halogens as traceless DGs of C(sp^3)−H bonds, see: (a) Baudoin, O. Ring Construction by Palladium(0)-Catalyzed C(sp^3)−H Activation. *Acc. Chem. Res.* **2017**, *50*, 1114. (b) Wu, Z.; Ma, D.; Zhou, B.; Ji, X.; Ma, X.; Wang, X.; Zhang, Y. Palladium-Catalyzed Alkylation with Alkyl Halides by C(sp^3)−H Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12288. For selected examples of traceless silylation of C(sp^3)−H bonds, see: (c) Bunescu, A.; Butcher, T. W.; Hartwig, J. F. Traceless Silylation of β-C(sp^3)−H Bonds of Alcohols via Perfluorinated Acetals. *J. Am. Chem. Soc.* **2018**, *140*, 1502. (d) Su, B.; Lee, T.; Hartwig, J. F. Iridium-Catalyzed, β-Selective C(sp^3)−H Silylation of Aliphatic Amines To Form Silapyrrolidines and 1,2-Amino Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 18032.

(12) For important bioactive molecule moieties containing γ-lactams, see: (a) Kulig, K.; Sapa, J.; Nowaczyk, A.; Filipek, B.; Malawska, B. Synthesis and Pharmacological Evaluation of New 1-[3-(4-phenylpiperazin-1-yl)-propyl]- and 1-[3-(4-phenylpiperidine)-propyl]-3-aryl-3-alkyl-pyrrolidin-2-one Derivatives with Antiarrhythmic and Anti Hypertensive Activity. *Acta Pol. Pharm.* **2009**, *66*, 649. (b) Kulig, K.; Ignasik, M.; Malawska, B. Synthesis of 3,3- and 4,4-Alkyl-phenyl-substituted Pyrrolidin-2-one Derivatives. *Polym. J. Chem.* **2009**, *83*, 1629. (c) Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W.; Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. 3,3-Dialkyl- and 3-Alkyl-3-Benzyl-Substituted 2-Pyrrolidinones: A New Class of Anticonvulsant Agents. *J. Med. Chem.* **1996**, *39*, 1898. For a recent breakthrough routine for γ-lactams with free NH, see: (d) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. Selective formation of γ-lactams via C−H Amidation Enabled by Tailored Iridium Catalysts. *Science* **2018**, *359*, 1016. (e) Conway, J. H.; Rovis, T. Regiodivergent Iridium(III)-Catalyzed Diamination of Alkenyl Amides with Secondary Amines: Complementary Access to γ or δ-Lactams. *J. Am. Chem. Soc.* **2018**, *140*, 135.

(13) For a resource of industrial waste $ClCF_2CF_2I$, see: (a) Petrov, V. A.; Krespan, C. G. Conjugate Electrophilic Iodofluorination of Fluoroolefins. *J. Org. Chem.* **1996**, *61*, 9605. For selected examples of *N*-polyfluoroalkylsulfinyl (SOR_f) as a chiral auxiliary, see: (b) Liu, L.-J.; Chen, L.-J.; Li, P.; Li, X.-B.; Liu, J.-T. Optically Pure Polyfluoroalkanesulfinamides: Synthesis and Application as Promising and Monitorable Chiral Auxiliaries. *J. Org. Chem.* **2011**, *76*, 4675. (c) Liu, L.-J.; Liu, J.-T. 2-Chlorotetrafluoroethanesulfinamide Induced

https://dx.doi.org/10.1021/acs.orglett.0c00326
Org. Lett. XXXX, XXX, XXX−XXX

Asymmetric Vinylogous Mannich Reaction. *Tetrahedron* **2014**, *70*, 1236. (d) Yang, K.; Jiang, M.; Liu, J.-T. Synthesis of Chiral *β*-Aminomalonates from 2-Chlorotetrafluoroethanesulfinyl Aldimines through the Mannich Reaction. *Eur. J. Org. Chem.* **2015**, *2015*, 3109. (e) Wangweerawong, A.; Bergman, R. G.; Ellman, J. A. Asymmetric Synthesis of *α*-Branched Amines via Rh(III)-Catalyzed C−H Bond Functionalization. *J. Am. Chem. Soc.* **2014**, *136*, 8520.

https://dx.doi.org/10.1021/acs.orglett.0c00326
Org. Lett. XXXX, XXX, XXX−XXX