Letter

Transient Directing Group Enabled Pd-catalyzed #-C(sp3)–H Oxygenation of Alkyl Amines

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Transient Directing Group Enabled Pd-catalyzed γ-C(sp³)–H Oxygenation of Alkyl Amines

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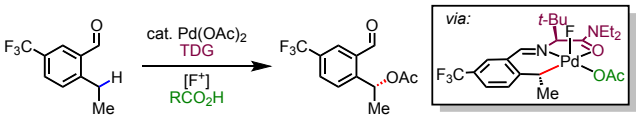
ABSTRACT: We report a general protocol for γ-C(sp³)–H acyloxylation and alkoxylation of free amines using 2-hydroxynicotinaldehyde as the transient directing group. In the presence of an electrophilic fluorinating bystanding oxidant and acetic acid, a wide range of aliphatic amines could be oxygenated selectively at the γ-methyl positions. A vast variety of aryl, heteroaryl, and aliphatic acids could also be successfully coupled under this C–O bond formation reaction to afford amine containing esters. Switching the nucleophile from acids to alcohols enables alkoxylation of free amines. Importantly, natural products and drug molecules such as ibuprofen, isozepac, fenbufen, and lithocholic acid are all compatible coupling partners. Notably, synthesis of these mono-protected amino alcohols from free amino alcohols using conventional selective protection are not always feasible.

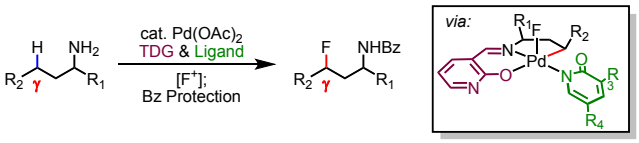
KEYWORDS: Transient Directing Group, C(sp³)–H Activation, Palladium, C(sp³)–H Oxygenation, Bystanding Oxidant, Amine

One of the major challenges in directed C−H activation is to enable the use of native substrates without covalently installing external directing groups. While the combination of weak coordination from substrates and ligand acceleration has been successful in enabling a wide range of C−H activation reactions of free carboxylic acids and Weinreb amides,[1] the development of catalytic transient directing groups (TDGs) for aliphatic aldehydes, ketones, and free amines has emerged as a complementary approach.[2-5] While most of these reactions are limited to (hetero)arylations,[3-5] efforts to develop other C−X, and C−O bond forming reactions have recently afforded new advances.[6] Using an electrophilic [F⁺] reagent as either the bystanding oxidant or the fluorinating agent, we have recently developed selective C−O and C−F bond formation reactions of 2-alkylbenzaldehydes via a novel amino amide transient directing group (**Scheme 1**).[6a] Inspired by this development, we have subsequently developed the first example of TDG enabled γ-C(sp³)–H fluorination of free amines using similar [F⁺] reagents (**Scheme 2**).[6b] Based on this particular investigation and our previous studies of using [F⁺] as bystanding oxidant for making C–C, C–N or C–O bonds,[7] we decided to explore the possibility of γ-oxidation of free amines using transient directing groups.

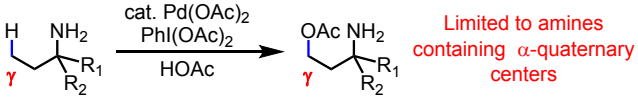
Considering the synthetic utility, we began to develop γ-acyloxylation with carboxylic acids and γ-etherification with alcohols which could afford of mono-protected amino alcohols that are not trivial to make. Although γ-C(sp³)–H acetoxylation of amines have been reported before, most of these reactions require the installation of exogenous directing groups.[8-9] A single example of free amine directed γ-C(sp³)–H acetoxylation is limited to amines containing α-quaternary centers (**Scheme 3**).[10] Herein, we report a transient directing group strategy for γ-C(sp³)–H oxygenation of broad range of free amines using N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the bystanding oxidant (**Scheme 4**). Advantageous to traditional γ-amino alcohol derivative synthesis which requires protection and deprotection of the amino group, our protocol features a one-step coupling between a wide range of aliphatic amines and a vast variety of acids and alcohols via selective C–O bond formation at the unactivated γ positions.



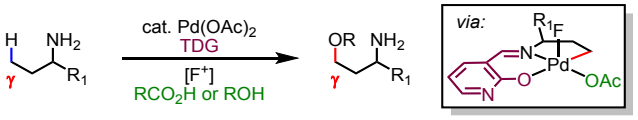
Scheme 1. TDG Enabled Acetoxylation of 2-Alkylbenzaldehydes



Scheme 2. Pyridone Assisted γ-C(sp³)–H Fluorination of Free Amines

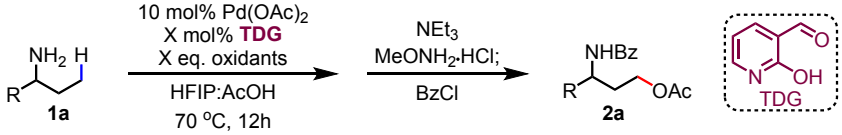


Scheme 3. Free Amine Directed γ-C(sp³)–H Acetoxylation



Scheme 4. This Work: TDG Enabled γ-C(sp³)–H Acylocylation and Alkoxylation of Free Amines

Table 1. Initial Studies and Reaction Optimization of γ-C(sp³)–H Acetoxylation of Amines[a,b]



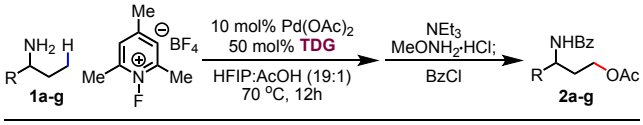
Entry	Oxidants	Reaction Conditions	Yield (%)
1	1.50 eq. N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	20 mol% TDG, HFIP:AcOH (19:1)	68 (63[c])
2	1.50 eq. N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	No TDG, HFIP:AcOH (19:1)	<10
3	1.50 eq. $PhI(OAc)_2$	20 mol% TDG, HFIP:AcOH (19:1)	17
4	1.50 eq. H_2O_2	20 mol% TDG, HFIP:AcOH (19:1)	15
5	1.50 eq. AcOOtBu	20 mol% TDG, HFIP:AcOH (19:1)	21
6	1.50 eq. TBHP (5M in decane)	20 mol% TDG, HFIP:AcOH (19:1)	53
7	1.50 eq. $K_2S_2O_8$	20 mol% TDG, HFIP:AcOH (19:1)	36
8	2.0 eq. TBHP (5M in decane)	50 mol% TDG, HFIP:AcOH (19:1)	68 (67)[c]
9	2.0 eq. $K_2S_2O_8$ + 10 mol% $(n\text{Bu})_4NOAc$	30 mol% TDG, HFIP:AcOH (2:1)	66
10	2.0 eq. N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	30 mol% TDG, HFIP:AcOH (19:1)	89
11	2.0 eq. N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	30 mol% TDG, HFIP:AcOH (2:1)	89
12	2.0 eq. N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	50 mol% TDG, HFIP:AcOH (19:1)	**94 (91)[c]**

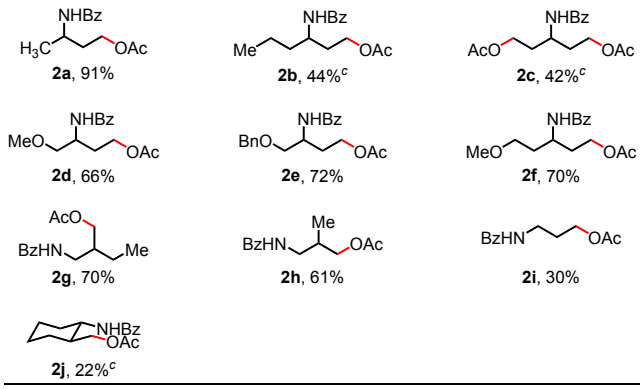
[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), **TDG**, oxidants, HFIP:AcOH (0.5 mL), 70 °C, 12 h. [b]Yields were determined by ^1H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yields.

We began our experimental efforts by testing γ-acetoxylation of *sec*-butylamine (**Table 1**). Under similar reaction conditions as our previous γ-methyl fluorination conditions in a 19:1 mixture HFIP and AcOH,[6b] we were pleased to find the desired acetoxylated product in 68% NMR yield when N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate was used as the [F⁺] bystanding oxidant and 2-hydroxylnicotinaldehyde as the TDG (**Table 1**, entry 1). Only less than 10% of the product was detected in the absence of TDG, thus demonstrating the importance of TDG in this acetoxylation reaction. (entry 2). Since we had already established moderate reactivity with pyridinium salt, we wondered whether other cheaper and more accessible oxidants could also promote this reaction. When we changed the oxidant to $PhI(OAc)_2$ the yield lowered to only 17% (entry 3). Upon evaluation of various peroxide-based oxidants, we discovered that although H_2O_2 and AcO*t*Bu gave inferior yields of the product in 15% and 21% respectively (entry 4-5), TBHP was an effective oxidant for this reaction, providing the product in 53% yield (entry 6). $K_2S_2O_8$ was also identified as another potentially effective oxidant for this reaction (entry 7). Unfortunately, despite extensive reaction optimization, the reaction could only be improved to around 70% yield using TBHP or $K_2S_2O_8$ as the oxidant (entry 8-9). Gratifyingly, the reaction could be further optimized to above 90% isolated yield by increasing the loading of the TDG with 2.0 eq. of N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (entry 10-12).

With the optimized conditions in hand, we next investigated the amine scope of this acetoxylation reaction (**Table 2**). For ease of analysis and separation, the acetoxylated products were isolated in the form of the Bz-protected amines. While *sec*-butylamine could be acetoxylated in 91% isolated yield (**2a**), the yield lowered to 44% when 3-aminohexane was employed as the substrate (**2b**). For 3-aminopentane, the di-acetoxylated product was obtained as the sole product in 42% yield (**2c**). Various oxygen containing substrates could also be acetoxylated in moderate yields (**2d-f**). Simple aliphatic amines without α-alkyl substituents such as 2-methylbutylamine, isobutylamine and even propylamine were also compatible substrates for this reaction, affording the corresponding products in 30–70% yields (**2g-i**). Acetoxylation of *trans*-2-methyl-cyclohexylamine could afford the product in 22% yield, whereas the *cis* isomer was completely unreactive (**2j**). Since AcOH was a good oxygen source for this protocol, we wondered whether other acids could also be coupled similarly for this reaction. We were pleased to find that γ-C(sp³)–H oxygenation of **1a** with a vast variety of aryl acids proceeded smoothly with good to excellent yields (**Table 3**). Notably, no acetoxylation product was observed in the presence of a different carboxylic acid without AcOH in pure HFIP. Various benzoic acids containing *para* and *meta* substituents, including methyl, methoxy, trifluoromethyl, nitro, cyano, and halogens, were well tolerated regardless of their electronic properties (**2a$_{1-9}$**). *Ortho*-substituted benzoic acids containing iodo or phenyl groups provided the corresponding products in good to excellent yields (**2a$_{10-12}$**). Sterically demand-

Table 2. Scope of Alkyl Amines for γ-C(sp³)–H Acetoxylation[a,b]

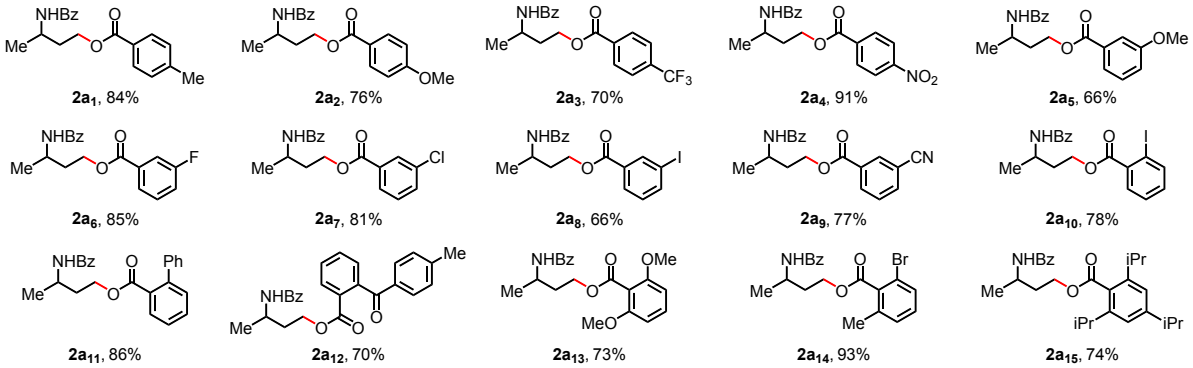




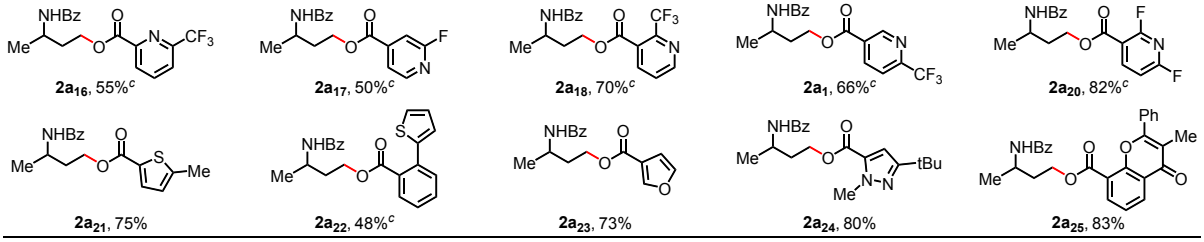
[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), **TDG** (0.05 mmol), N-fluoro 2,4,6-methylpyridinium tetrafluoroborate (0.20 mmol), HFIP:AcOH (19:1) (0.5 mL), 70 °C, 16 h. [b]Isolated yields. [c]Reaction performed with 0.75 eq of **TDG**.

Table 3. Scope of Aromatic Acids for γ-C(sp^3)–H Acyloxylation of Free Amines[a,b]

ArCO$_2$H

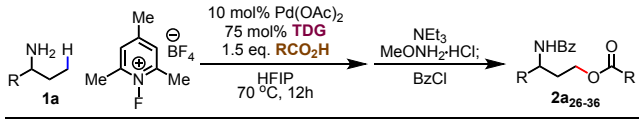


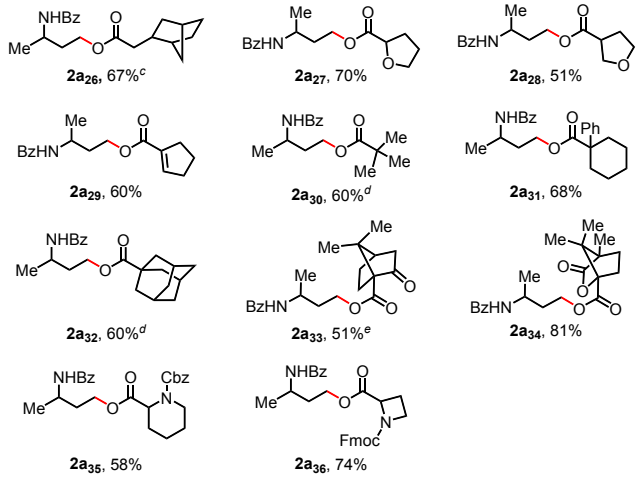
HetArCO$_2$H



[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), **TDG** (0.05 mmol), N-fluoro 2,4,6-methylpyridinium tetrafluoroborate (0.20 mmol), HFIP (0.5 mL), 70 °C, 16 h. [b]Isolated yields. [c]Reaction performed with 0.75 eq of **TDG**.

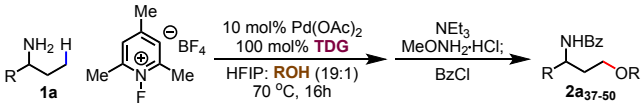
Table 4. Scope of Aliphatic Acids for γ-C(sp^3)–H Acyloxylation of Free Amines[a,b]



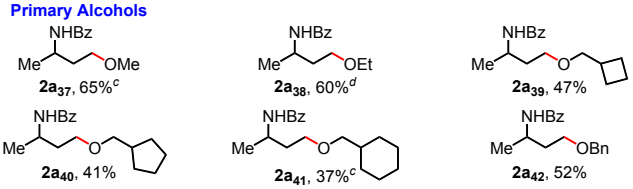


[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), **TDG** (0.075 mmol), N-fluoro 2,4,6-methylpyridinium tetrafluoroborate (0.20 mmol), HFIP (0.5 mL), 70 °C, 16 h. [b]Isolated yields. [c]Reaction performed with 0.5 eq of **TDG**. [d]Reaction performed with 2.0 eq of acid. [e]Reaction performed with 1.0 eq of **TDG**.

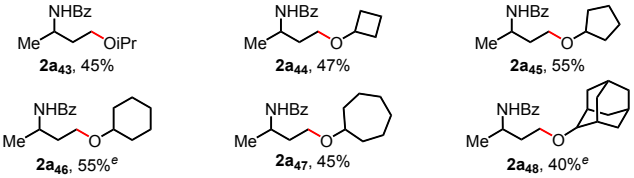
Table 5. Scope of Aliphatic Alcohols for γ-C(sp^3)–H Alkoxylation of Free Amines[a,b]



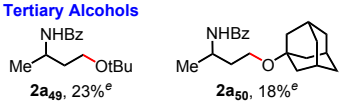
Primary Alcohols



Secondary Alcohols



Tertiary Alcohols



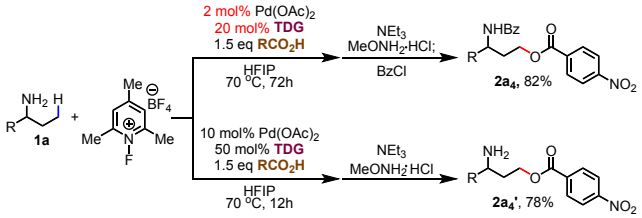
[a]Experiments were performed with substrate **1a** (0.10 mmol), Pd(OAc) (0.01 mmol), **TDG** (0.1 mmol), N-fluoro 2,4,6-methylpyridinium tetrafluoroborate (0.20 mmol), HFIP:ROH (19:1) (0.5 mL), 70 °C, 16 h. [b]Isolated yields. [c]Reaction performed with 0.75 eq **TDG** (0.075 mmol) and 0.5 eq of 5-chloro-3-nitropyridin-2-ol as the pyridone ligand. [d]Reaction

performed with 0.5 eq of **TDG**. [e]Reaction performed with 1.0 eq **TDG** (0.1 mmol) and 0.5 eq of 5-chloro-3-nitropyridin-2-ol as the pyridone ligand.

ing substrates such as 2,6-dimethoxy, 2-bromo-6-methyl, and even2,4,6-triisopropyl benzoic acids were also well tolerated (**2a**$_{13\text{-}15}$). Importantly, heteroaryl acids containing pyridines with different substitutions such as fluoro- and trifluoromethyl groups are all compatible coupling partners, providing 50–82% yields (**2a**$_{16\text{-}20}$). Coupling with other heteroaryl acids containing thiophene, furan, chromene, and even pyrazole groups were successfully accomplished with this protocol (**2a**$_{21\text{-}25}$). Notably, higher TDG loadings are used for certain heteroaryl acids presumably to prevent catalyst poisoning by the heteroaryl acids.

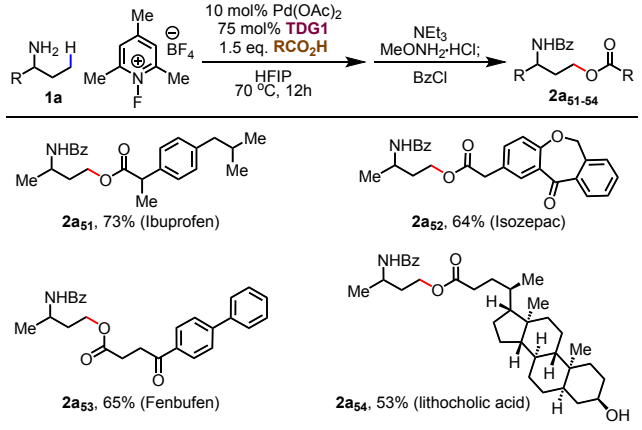
The scope of various aliphatic acids was investigated next (**Table 4**). Primary aliphatic acid such as 2-norbornaneacetic acid afforded the corresponding ester product in 67% isolated yield (**2a**$_{26}$). Secondary aliphatic acids containing oxygenated functionalities and unsaturation were also tolerated in moderate yields (**2a**$_{27\text{-}29}$). Sterically demanding tertiary acids containing tert-butyl, phenyl, and adamantyl groups were all coupled successfully in 60–68% islolated yields (**2a**$_{30\text{-}32}$). Aliphatic acids from natural products such as ketopinic acid and camphanic acid afforded the corresponding products in 51% and 81% respectively (**2a**$_{33\text{-}34}$). Lastly, N-protected amino acids could also be coupled under this protocol in good efficiencies (**2a**$_{35\text{-}36}$).

Since the reaction was compatible with a vast range of different carboxylic acids, we next wondered whether other oxygen containing nucleophiles such as alcohols could also serve as effective coupling partners for this reaction. We were pleased to find that γ-C(sp^3)–H oxygenation of **1a** with a range of aliphatic alcohols could also be accomplished, albeit in lower efficiencies (**Table 5**). Primary alcohols such as methanol, ethanol, cyclobutylmethanol, cyclopentylmethanol, cyclohexylmethanol, and benzyl alcohol all underwent the desired alkoxylation reaction in 37–65% yields (**2a**$_{37\text{-}42}$). Secondary alcohols such as isopropanol, cyclobutanol, cyclopentanol, cyclohexanol, cycloheptanol, and even 2-adamantanol were also effective nucleophiles, affording the hindered ethers in 40–55% isolated yields (**2a**$_{43\text{-}48}$). Remarkably, even tertiary alcohols such as *t*BuOH, and 1-adamantanol were competent nucleophiles to afford the highly hindered ethers in 23% and 18% isolated yields respectively with the aid of an electron-deficient pyridone ligand (**2a**$_{49\text{-}50}$). The ability to perform C–H oxygenation with secondary and tertiary alcohols provides a straight-forward method for the synthesis of hindered aminoethers, which is difficult to achieve via conventional approaches. Furthermore, we have also evaluated other less reactive amines (**1c-d**, **1g-h**, **1i**) with methanol as the coupling partner. The NMR yields of **1c** and **1d** were similar to that of the model substrate **1a**. Roughly 40% NMR yield of the alkoxylated product was detected for **1g** and **1h**. Simple propylamine (**1i**) with methanol only gave 10-15% NMR yields.



Scheme 5. Catalyst Loading and Synthetic Applications

Table 6. Scope of Drug Derivatives[a,b]



[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), **TDG** (0.075 mmol), N-fluoro 2,4,6-methylpyridinium tetrafluoroborate (0.20 mmol), HFIP (0.5 mL), 70 °C, 16 h. [b]Isolated yields.

To demonstrate the synthetic utility of this γ-C(sp^3)–H oxygenation reaction, we were pleased to find that the catalyst and TDG loading could be lowered to 2 mol% and 20 mol% respectively, thus rendering our protocol highly efficient (**Scheme 5**). In addition, the C–H oxygenated free amine product could also be isolated in 78% yield. More importantly, natural products and drug molecules such as ibuprofen, isozepac, fenbufen, and lithocholic acid were all well tolerated (**Table 6**), thus demonstrating this protocol's potential to perform late-stage functionalization and provide facile access to amine containing drug analogs.

In summary, we have developed a general method for γ-C(sp^3)–H oxygenation of free aliphatic amines using 2-hydroxynicotinaldehyde as the transient directing group and N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the [F$^+$] bystanding oxidant. This reaction features a wide amine scope with good functional group tolerance. A vast range of aryl, heteroaryl, and aliphatic acids, as well as primary, secondary, and even tertiary alcohols are all compatible nucleophiles in this γ-C(sp^3)–H oxygenation reaction. Compared to traditional γ-amino alcohol derivative synthesis which require protection and deprotection of the amino group, our reaction provides facile access to these compounds and even hindered ethers in a single step. More importantly, natural products and drug molecules are also competent coupling partners, thus demonstrating this protocol's potential for late-stage functionalization to access amine containing drug analogs. Efforts in designing new TDG and ligands to enable coupling of other nucleophiles are currently underway in light of these developments.

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Supporting Information. Experimental procedures and spectral data for all new compounds and full computational data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunder, L. B.; Yu, J.-Q. Palladium-Catalyzed Methylation and Arylation of sp^2 and sp^3 C–H Bonds in Simple Carboxylic Acids. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. b) Chen, G.; Zhuang, Z.; Li, G.-C.; Saint-Denis, T. G.; Xiao, Y.; Joe, C. L.; Yu, J.-Q. Ligand-Enabled β-C–H Arylation of α-Amino Acids Without Installing Exogenous Directing Groups. *Angew. Chem., Int. Ed.* **2017**, *56*, 1506–1509. c) Zhu, Y.; Chen, X.; Yuan, C.; Li, G.; Zhang, J.; Zhao, Y. Pd-catalysed ligand-enabled carboxylate-directed highly regioselective arylation of aliphatic acids. *Nat. Commun.* **2017**, *8*, 14904. d) Ghosh, K. K.; van Gemmeren, M. Pd-Catalyzed β-C(sp^3)–H Arylation of Propionic Acid and Related Aliphatic Acids. *Chem. Eur. J.* **2017**, *23*, 17697–17700. e) Zhuang, Z.; Yu, C.; Chen, G.; Wu, Q.; 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*, 10363–10367. f) Uttry, A.; Gemmeren, M. Van. The Direct Pd-Catalyzed β-C(sp^3)−H Activation of Carboxylic Acids. *Synlett.* **2018**, *29*, 1937–1943. g) Park, H.; Chekshin, N.; Shen, P.; Yu, J.-Q. Ligand-Enabled, Palladium-Catalyzed β-C(sp^3)–H Arylation of Weinreb Amides. *ACS Catal.* **2018**, *8*, 9292–9297. h) Ghosh, K. K.; Uttry, A.; Koldemir, A.; Ong, M.; Gemmeren, M. Van. Direct β-C(sp^3)–H Acetoxylation of Aliphatic Carboxylic Acids. *Org. Lett.* **2019**, *21*, 7154–7157. i) Dolui, P.; Das, J.; Chandrashekar, H. B.; Anjana, S. S.; Maiti, D. Ligand-Enabled Pd^{II}-Catalyzed Iterative γ-C(sp^3)–H Arylation of Free Aliphatic Acid. *Angew. Chem. Int. Ed.* **2019**, *58*, 13773–13777. j) Liu, L.; Liu, Y.; Shi, B. Synthesis of Amino Acids and Peptides with Bulky Side Chains via Ligand-Enabled Carboxylate-Directed γ-C(sp^3)–H Arylation. *Chem. Sci.* **2020**, *11*, 290–294. k) Zhuang, Z.; Yu, J.-Q. Lactonization as a General Route to β-C(sp^3)–H Functionalization. *Nature* **2020**, *577*, 656–659.

(2) For selected reviews on transient directing groups: a) Zhao, Q.; Poisson, T.; Pannecoucke, X.; Basset, T. The Transient Directing Group Strategy: A New Trend in Transition-Metal-Catalyzed C–H Bond Functionalization. *Synthesis.* **2017**, 49, 4808−4826. b) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem.* **2018**, 4, 199−222. c) St John-Campbell, S.; Bull, J. A. Transient imines as 'next generation' directing groups for the catalytic functionalisation of C–H bonds in a single operation. *Org. Biomol. Chem.* **2018**, 16, 4582−4595. d) Rasheed, O. K.; Sun, B. Advances in Development of C–H Activation/Functionalization Using a Catalytic Directing Group. *ChemistrySelect*. **2018**, *3*, 5689−5708. e) Niu, B.; Yang, K.; Lawrence, B.; Ge, H. Transient Ligand-Enabled Transition Metal-Catalyzed C-H Functionalization. *ChemSusChem.* **2019**, *12*, 2955−2969.

(3) For examples on TDG enabled C(sp^3)–H (hetero)arylations on Aldehydes: a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C(sp^3)–H bonds using a transient directing group. *Science.* **2016**, *351*, 252−256. b) Yang, K.; Li, Q.; Liu, Y.; Li, G.; Ge, H. Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand. *J. Am. Chem. Soc.* **2016**, *138*, 12775−12778. c) Ma, F.; Lei, M.; Hu, L. Acetohydrazone: A Transient Directing Group for Arylation of Unactivated C(sp^3)–H Bonds. *Org. Lett.* **2016**, *18*, 2708−2711. d) St, J.-C. S.; White, A. J. P.; Bull, J. A. Single operation palladium catalysed C(sp^3)–H functionalisation of tertiary aldehydes: investigations into transient imine directing groups. *Chem. Sci.* **2017**, *8*, 4840−4847. e) Gou, B.; Liu, H.; Chen, J.; Zhou, L. Palladium-Catalyzed Site-Selective C(sp^3)–H Arylation of Phenylacetaldehydes. *Org. Lett.* **2019**, *21*, 7084−7088. f) Li, B.; Lawrence, B.; Li, G.; Ge, H. Ligand-Controlled Direct γ-C-H Arylation of Aldehydes. *Angew. Chem. Int. Ed.* **2020**, 59, 3078−3082. g) Wen, F.; Li, Z. Semicarbazide : A Transient Directing Group for C(sp^3)–H Arylation of 2-Methylbenzaldehydes. *Adv. Synth. Catal.* **2020**, *362*, 133−138.

(4) For examples on TDG enabled C(sp^3)–H (hetero)arylations on Ketones: a) Hong, K.; Park, H.; Yu, J.-Q. Methylene C(sp^3)–H Arylation of Aliphatic Ketones Using a Transient Directing Group. *ACS Catal.* **2017**, *7*, 6938−6941. b) Wang, J.; Dong, C.; Wu, L.; Xu, M.; Lin, J.; Wei, K. Palladium-Catalyzed β-C−H Arylation of Ketones Using Amino Amide as a Transient Directing Group: Applications to Synthesis of Phenanthridinone Alkaloids. *Adv. Synth. Catal.* **2018**, *360*, 3709−3715. c) Dong, C.; Wu, L.; Yao, J.; Wei, K. Palladium-Catalyzed β-C–H Arylation of Aliphatic Aldehydes and Ketones Using Amino Amide as a Transient Directing Group. *Org. Lett.* **2019**, *21*, 2085−2089.

(5) For examples on TDG enabled C(sp^3)–H (hetero)arylations on Amines: a) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. Pd-Catalyzed γ-C(sp^3)–H Arylation of Free Amines Using a Transient Directing Group. *J. Am. Chem. Soc.* **2016**, *138*, 14554−14557. b) δ-C(sp^3)−H arylation of 2-tert-butylaniline was demonstrated: Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. Catalytic C(sp^3)−H Arylation of Free Primary Amines with an exo Directing Group Generated In Situ. *Angew. Chem. Int. Ed.* **2016**, *55*, 9084−9087. c) Liu, Y.; Ge, H. Site-selective C–H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017**, *9*, 26−32. d) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. Buttressing Salicylaldehydes: A Multipurpose Directing Group for C(sp^3)−H Bond Activation. *Angew. Chem. Int. Ed.* **2017**, *56*, 1073−1076. e) St John-Campbell, S.; Ou, A. K.; Bull, J. A. Palladium-Catalyzed C(sp^3)−H Arylation of Primary Amines Using a Catalytic Alkyl Acetal to Form a Transient Directing Group. *Chem. Eur. J.* **2018**, *24*, 17838−17843. f) Lin, H.; Wang, C.; Bannister, T. D.; Kamenecka, T. M. Site-Selective γ-C(sp^3)−H and γ-C(sp^2)−H Arylation of Free Amino Esters Promoted by a Catalytic Transient Directing Group. *Chem. Eur. J.* **2018**, *24*, 9535−9541. g) Kapoor, M.; Liu, D.; Young, M. C. Carbon Dioxide-Mediated C(sp^3)-H Arylation of Amine Substrates. *J. Am. Chem. Soc.* **2018**, *140*, 6818−6822.

(6) a) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. Controlling Pd(IV) Reductive Elimination Pathways Enables Pd(II)-Catalysed Enantioselective C(sp3)-H Fluorination. *Nat. Chem.* **2018**, *10*, 755−762. b) Chen, Y-Q.; Singh, S.; Wu, Y.; Wang, Z.; Qiao, J.; Sunoj, R.; Yu, J-Q. Pd-catalyzed γ-C(sp^3)–H Fluorination of Free Amines. *J. Am. Chem. Soc.* **2020**, under revision.

(7) a) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. Bystanding F^+ Oxidants Enable Selective Reductive Elimination from High-Valent Metal Centers in Catalysis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1478–1491. b) Mei, T.; Wang, X.; Yu, J.-Q. Pd (II)-Catalyzed Amination of C-H Bonds Using Single-Electron or Two-Electron Oxidants. *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807. c) Wang, X.; Lu, Y.; Dai, H.; Yu, J.-Q. Pd(II)-Catalyzed Hydroxyl-Directed C-H Activation / C-O Cyclization : Expedient Construction of

Dihydrobenzofurans. *J. Am. Chem. Soc.* **2010**, *132*, 12203–12205. d) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C − H Activation/C − O Bond Formation: Synthesis of Chiral Benzofuranones. *J. Am. Chem. Soc.* **2013**, *135*, 1236−1239.

(8) a) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. 1,2,3-Triazoles as Versatile Directing Group for Selective sp^2 and sp^3 C–H Activation: Cyclization vs Substitution. *Chem. Sci.* **2013**, *9*, 3712−3716. b) Cheng, T.; Yin, W.; Zhang, Y.; Zhang, Y.; Huang, Y. Palladium Catalyzed Acetoxylation of Benzylic C–H Bonds Using a Bidentate Picolinamide Directing Group. *Org. Biomol. Chem.* **2014**, *12*, 1405−1411. c) Li, Q.; Zhang, S.; He, G.; Nack, W. A.; Chen, G. Palladium-Catalyzed Picolinamide-Directed Acetoxylation of Unactivated γ-C(sp^3)-H Bonds of Alkylamines. *Adv. Synth. Catal.* **2014**, *356*, 1544−1548. d) Liu, P.; Han, J.; Chen, C. P.; Shi, D. Q.; Zhao, Y. S. Palladium-Catalyzed Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds under the Assistance of Oxalyl Amide. *RSC Adv.* **2015**, *5*, 28430−28434. e) Pasunooti, K. K.; Yang, R.; Banerjee, B.; Yap, T.; Liu, C. 5-Methylisoxazole-3-Carboxamide-Directed Palladium-Catalyzed γ-C(sp^3)−H Acetoxylation and Application to the Synthesis of γ-Mercapto Amino Acids for Native Chemical Ligation. *Org. Lett.* **2016**, *18*, 2696−2699. f) Zheng, Y.; Song, W.; Zhu, Y.; Wei, B.; Xuan, L. Pd-Catalyzed Acetoxylation of γ-C(sp^3)−H Bonds of Amines Directed by a Removable Bts-Protecting Group. *J. Org. Chem.* **2018**, *83*, 2448−2454. g) Jia, W.; Fernández-Ibáñez, M. Á. Ligand-Enabled γ-C(sp^3)–H Acetoxylation of Triflyl-Protected Amines. *Eur. J. Org. Chem.* **2018**, 6088−6091.

(9) a) 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*, 1009−1061. b) Buettner, C. S.; Willcox, D.; Chappell, B. G. N.; Gaunt, M. J. Mechanistic Investigation into the C(sp^3)–H Acetoxylation of Morpholinones. *Chem. Sci.* **2019**, *10*, 83−89.

(10) Chen, K.; Wang, D.; Li, Z.-W.; Liu, Z.; Pan, F.; Zhang, Y.-F.; Shi, Z.-J. Palladium Catalyzed C(sp^3)–H Acetoxylation of Aliphatic Primary Amines to γ-amino Alcohol Derivatives *Org. Chem. Front.* **2017**, 4, 2097−2101.

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