C–H Functionalization

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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**

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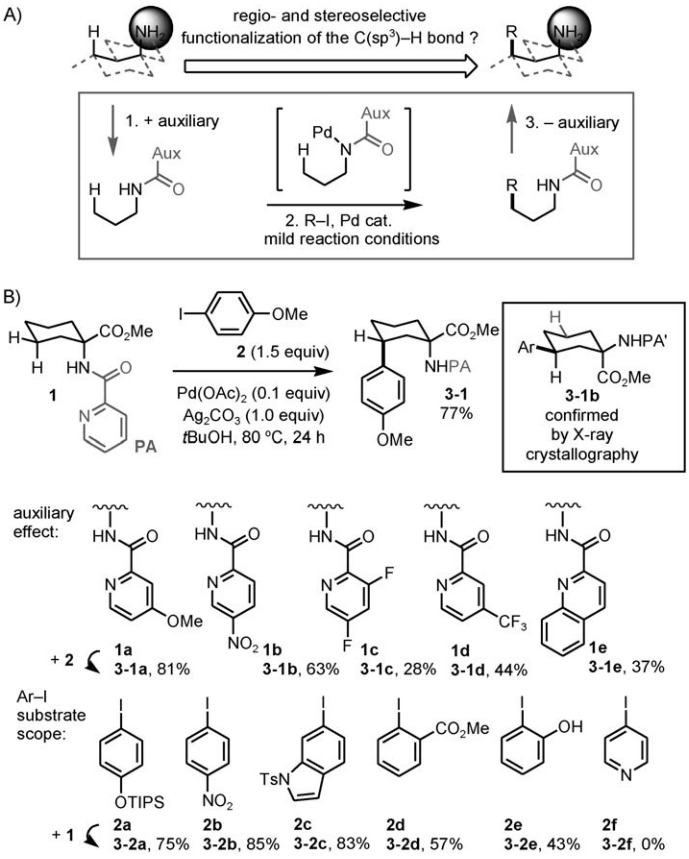
Powerful synthetic methods based on the regioselective functionalization of C(sp^2)–H bonds of arenes and heteroarenes are becoming readily available.[1] In keeping with this trend, the selective functionalization of C(sp^3)–H bonds to construct stereogenic centers and create complex structures would be an important and useful advance.[2] As well as providing straightforward and operationally economical solutions for target-oriented synthesis, C(sp^3)–H functionalization could also significantly expand current strategies for diversity-oriented synthesis in medicinal-chemistry research.[3] Readily accessible aliphatic substrates could be tailored by the selective replacement of C(sp^3)–H bonds with other structural motifs. Such a method would offer advantages over conventional de novo synthesis.[4]

Catalytic processes for the functionalization of non-activated C(sp^3)–H bonds are less developed than reactions which involve aryl or vinyl C–H bonds. In comparison with radical-, carbene-, and nitrene-mediated processes,[5,6] the palladium-catalyzed functionalization of C(sp^3)–H bonds through an innersphere mechanism offers the advantage of more versatile bond transformations via palladacycle intermediates.[7] Although a number of ligand directing strategies have been successfully developed for such transformations, truly practical methods are still lacking.[8] Interestingly, the research groups of Daugulis[9] and Yu[10] have demonstrated that amide groups possess a superior ability to direct palladium-catalyzed regioselective functionalizations of C-(sp^3)–H bonds. If generally applicable, we envisioned that this amide directing strategy might find great utility in the synthesis of many nitrogen-containing pharmaceutical agents and natural products. Herein, we report a practical synthetic strategy based on the picolinamide-directed palladium-catalyzed arylation and alkenylation of the remote C(sp^3)–H bonds of a variety of aliphatic substrates under mild conditions and the application of this transformation to the formal synthesis of (+)-obafluorin.

We envisioned a general three-step sequence to introduce different R groups at remote C–H bonds through the direction of an amide-linked auxiliary (Scheme 1 A).[11] For this strategy to be synthetically useful, the auxiliary should be easy to introduce and should promote the highly regio- and even stereoselective functionalization of a specific C(sp^3)–H bond. Furthermore, the C–H functionalization must be sufficiently mild to be compatible with sensitive functional groups and stereogenic centers in complex substrates. Finally, the removal of the auxiliary to reveal the amine should be facile. The discovery of a picolinamide-directed C–H arylation by Daugulis and co-workers provided a key blueprint for our initial study.[9a] The original study demonstrated that a picolinamide (PA) moiety facilitates the palladium-catalyzed arylation of the γ C(sp^3)–H bonds of aliphatic substrates with aryl iodides as the arene source. However, rather forcing



Scheme 1. Initial screening of picolinamide auxiliaries and aryl iodide substrates in the proposed reaction. Air and moisture were not strictly excluded. The yield of the isolated product is given in all cases. TIPS = triisopropylsilyl, Ts = *p*-toluenesulfonyl.

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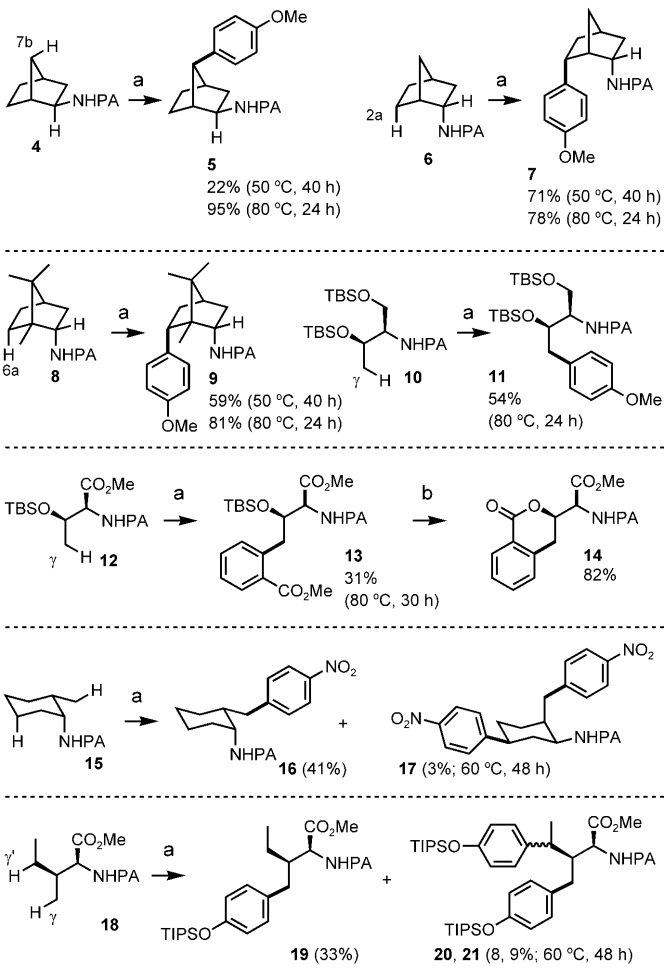
reaction conditions ($Pd(OAc)_2$ (0.05 equiv), AgOAc (1.0 equiv), ArI (4 equiv), 130–150 °C, no solvent) were required for this transformation.[12] Nonetheless, intrigued by the unique remote directing ability of the PA moiety, we screened various PA-based auxiliaries systematically in an attempt to develop milder reaction conditions (Scheme 1 B). Thus, we carried out the arylation of the cyclohexylamino acid substrates **1** and **1a–e** with 4-iodoanisole (**2**; 1.5 equiv) at 80 °C with different combinations of Pd^{II} and Ag^{I} salts. Initial screening revealed the optimal reaction conditions: the use of $Pd(OAc)_2$ (0.1 equiv) and Ag_2CO_3 (1.0 equiv) with *t*BuOH or trifluoroethanol as the solvent. Stereoselectively monoarylated cyclohexane derivatives were obtained as the major product in all cases. Interestingly, no products bisarylated at both the γ and γ′ positions were observed. The structure of **3-1b** (*p*-NO_2-PA) was confirmed by X-ray crystallography.[13] The electronic properties of the substituents on the pyridine ring of the PA had a clear effect on the arylation reaction: the presence of electron-withdrawing substituents, as in **1b**, **1c**, and **1d**, led to a decrease in the arylation yield, whereas the presence of an electron-donating substituent, as in substrate **1a**, led to an increase in the yield. Owing to the advantages of low cost and high performance, the unmodified PA was employed for further exploratory studies.

A broad range of aryl iodides were used successfully in the arylation of substrate **1** (Scheme 1 B). *O*-TIPS, NO_2, tosyl amide, and CO_2Me groups were tolerated well under the reaction conditions. Even a free phenol, **2e**, was incorporated in moderate yield. However, the pyridine substrate **2f** failed to give any arylated product. Although the arylation of **1** with iodides **2** was complete within 24 h at 80 °C, the reaction also proceeded smoothly at 60 °C in 48 h. Some **3-1** (ca. 15 %) was generated even at 40 °C with extended reaction times (5 days).

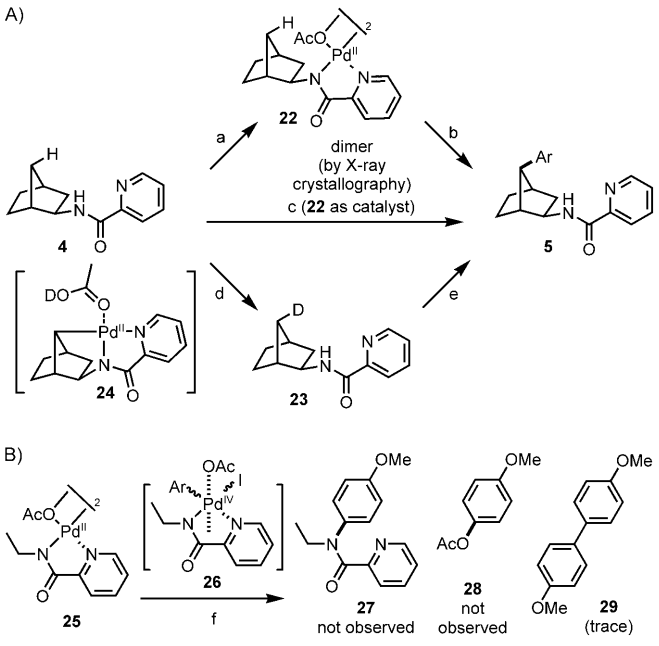
Encouraged by the excellent performance of substrate **1** in this C–H arylation system, we examined a variety of other aliphatic amine scaffolds. Gratifyingly, excellent yields and selectivities were observed for most substrates under mild conditions (Scheme 2). For example, the *exo*-2-aminonorbornane **4** gave the product **5** of arylation exclusively at the C7–H_b position, whereas the *endo*-2-aminonorbornane **6** gave the product **7** of arylation exclusively at the C2–H_a position. The *endo* bornylamine substrate **8** was selectively arylated at the C6–H_a position: the 1-CH_3 group remained untouched. To our surprise, acyclic substrates also reacted well under the same arylation conditions. Threoninol **10** was arylated cleanly. The threonine methyl ester **12** even underwent arylation with *ortho*-substituted methyl 2-iodobenzoate at the γ-CH_3 position to give **13** in moderate yield with complete chiral integrity. Upon the heating of **13** with *p*-TsOH in toluene, benzolactone **14** was obtained in excellent yield. The *cis*-2-methylcyclohexylamine-derived substrate **15** was arylated preferentially at the CH_3 group to provide the monoarylated product **16** along with bisarylated **17** as a minor product at 60 °C. The isoleucine-derived substrate **18** was arylated preferentially at the γ-CH_3 position to give the monoarylated product **19** (33 %) and the bisarylated diastereomers **20** and **21** (17 % combined yield) at 60 °C. No significant amount of *gem*-diarylated products (< 3 %) was observed in any of these



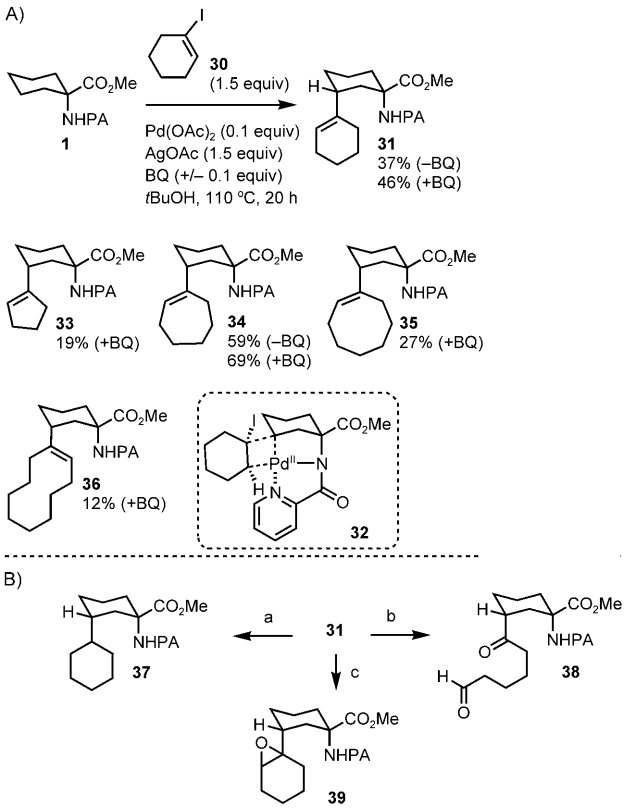
Scheme 2. Substrate scope of the palladium-catalyzed picolinamide-directed C(sp^3)–H arylation. Reaction conditions: a) amide substrate (1.0 equiv), ArI (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), Ag_2CO_3 (1.0 equiv), *t*BuOH or trifluoroethanol, 0.2 M (air and moisture were not strictly excluded; yields refer to the isolated product); b) *p*-TsOH·H_2O (1.0 equiv), toluene, 82 %. TBS = *tert*-butyldimethylsilyl, TsOH = *p*-toluenesulfonic acid.

reactions, presumably because of steric factors. Whereas the γ regioselectivity was controlled by the five-membered palladacycle intermediate, the relative conformation of the C–H bond and the Pd center had a strong influence on the regio- and stereoselectivity of the arylation reaction.

At the outset of our studies, the mechanism of this pallladium-catalyzed PA-directed C–H arylation was not well understood. The original report suggested that the process proceeded through a Pd^{II}/Pd^{IV} pathway.[9a,14] However, the order of the C–H activation and ArI-coupling steps remained elusive. To address this question, we conducted some preliminary mechanistic studies with substrate **4** (Scheme 3 A). The dimeric Pd complex **22** was formed cleanly within 30 min upon the mixing of **4** with $Pd(OAc)_2$ (1.0 equiv) in *t*BuOH at 80 °C (as confirmed by X-ray crystallography: see the Supporting Information). Complex **22** reacted with **2** to give the arylated product **5** in excellent yield in the absence of Ag_2CO_3. Furthermore, **22** acted as a competent catalyst for the arylation of **4** with **2**. Isolation of the speculative



Scheme 3. Preliminary mechanistic studies. Reaction conditions: a) $Pd(OAc)_2$ (1.0 equiv), *t*BuOH, 80 °C, 30 min, quantitative; b) **2** (1.1 equiv), *t*BuOH, 80 °C, 24 h, without Ag^+, 81 %; c) **22** (0.1 equiv), **2** (1.5 equiv), Ag_2CO_3 (1.0 equiv), *t*BuOH, 80 °C, 24 h, 90 %; d) $Pd(OAc)_2$ (0.1 equiv), CH_3CO_2D (10 equiv), *t*BuOD (solvent), 80 °C, 48 h, 76 %; e) **23** (or **4**) (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), **2** (1.5 equiv), Ag_2CO_3 (1.0 equiv), 80 °C, 1–7 h, primary $k_{H/D} \approx 4$ (**4**/**23**); f) **25** (1.0 equiv), **2** (1.1 equiv), *t*BuOH, 80 °C, 24 h.



Scheme 4. Picolinamide-directed $C(sp^3)$–H alkenylation with cyclic vinyl iodides. Reagents and conditions: a) NH_4HCO_2, Pd/C, MeOH, reflux, 73 %; b) 1. O_3, CH_2Cl_2; 2. PPh_3, −78 °C→RT, 55 %; c) *m*CPBA, CH_2Cl_2, 0 °C, 76 %. *m*CPBA = 3-chloroperoxybenzoic acid.

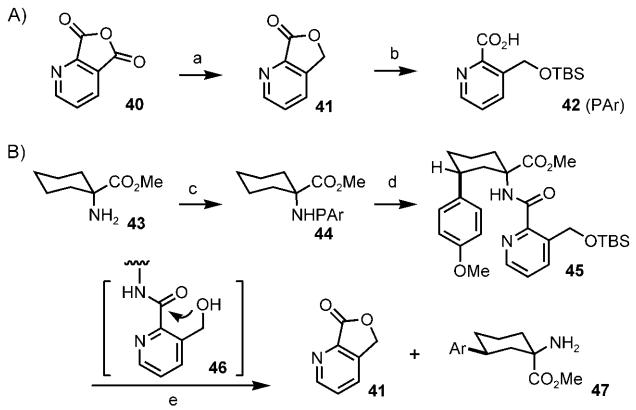
palladacycle intermediate has not been successful so far. However, the C–H bond at the 7b-position of **4** was completely deuterated to give **23** under the catalysis of $Pd(OAc)_2$ (0.1 equiv) and AcOD (10 equiv) in *t*BuOD at 80 °C. This experiment indicates that C–H activation can take place under the reaction conditions without the involvement of the ArI substrate and that the palladation process is reversible. A primary kinetic isotope effect was observed on the basis of the arylation of substrates **4** and **23** with **2** (see the Supporting Information). Finally, ethyl picolinamide **25**, which lacks a γ C–H bond, was prepared as a control substrate and examined under the arylation conditions used for **22** (Scheme 3B). According to the alternative ArI oxidative addition/C–H activation pathway, either **27**[15] or **28**[16] could be formed through reductive elimination from the hypothetical Pd^{IV} complex **26**. However, treatment of the palladium complex **25** with **2** in *t*BuOH at 80 °C provided neither **27** nor **28**; only a trace amount of the biphenyl side product **29** (ca. 5 %) was obtained. Although not conclusive, our experiments strongly favor a sequential C–H activation/ArI-coupling pathway for this C–H arylation reaction.

Encouraged by the success of the PA-directed C–H arylation with aryl iodides, we decided to test the feasibility of the direct functionalization of $C(sp^3)$–H bonds with alkenyl iodides (Scheme 4). Precedent for the catalytic alkenylation of $C(sp^3)$–H bonds is scarce; in most examples, simple acrylate or monosubstituted vinyl halides have been used.[17] We were pleased to find that the alkenylation of **1** with various disubstituted cyclic vinyl iodides provided the desired alkenylated product in moderate to good yields at slightly elevated temperatures (vinyl iodide (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), and AgOAc (1.5 equiv) in *t*BuOH at 110 °C). Interestingly, the ring size of the cyclic vinyl iodide had a strong influence on the reaction yield; the seven-membered iodide gave the highest yield (69 % yield of the isolated product **34**). Furthermore, the addition of benzoquinone (0.1 equiv) led to a slight increase in the reaction yield.[18] The mechanism of the alkenylation process remains elusive. Although a Pd^{II}/Pd^{IV} pathway similar to the C–H arylation process is possible, insertion of the vinyl iodide into the Pd–C bond to form the intermediate **32**, followed by a *trans* β-halogen elimination, could also lead to formation of the alkenylated product (Scheme 4A).[19]

Multisubstituted alkenes are valuable precursors for many synthetic operations (Scheme 4B). For example, **31** was reduced by Pd/C-catalyzed transfer hydrogenation to provide a formally alkylated product **37**. The double bond of **31** was cleaved selectively by ozonolysis to provide a formally acylated product **38**. Expoxide **39** was also obtained in good yield upon the treatment of **31** with *m*CPBA.

For this PA-directed C–H functionalization method to be synthetically useful, the PA auxiliary must be readily removable under mild conditions. However, cleavage of the picolinamide linkage turned out to be a challenging problem. A variety of conventional methods, including activation of the amide with a *tert*-butoxycarbonyl (Boc) group or by nitro-

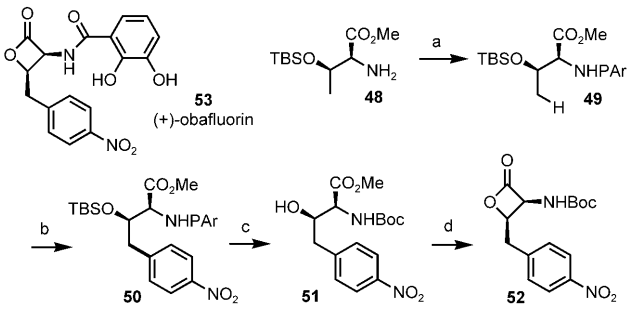
sation, failed to provide satisfactory results. Taking a lesson from peptide chemistry, we hoped that a methylene hydroxy group installed at the *ortho* position of PA might facilitate amide cleavage through intramolecular acyl transfer under acidic conditions (Scheme 5B).[20] Accordingly, a modified



Scheme 5. Removable picolinic acid auxiliary (PAr) for C(sp^3)–H arylation. Reagents and conditions: a) 1. MeOH, 90 °C, 84%; 2. CDI, THF, room temperature, then $NaBH_4$ in MeOH/H_2O, room temperature, 65% (2 steps); b) 1. NaOH, THF/H_2O, room temperature; 2. benzyl bromide, DMF, 34% (2 steps); 3. TBSCl, imidazole, DMF, room temperature, 92%; 4. Pd/C, H_2, EtOAc, room temperature, quantitative; c) HATU, DIPEA, DMF, room temperature, 89%; d) Pd(OAc)$_2$ (0.1 equiv), Ag_2CO_3 (1.0 equiv), *t*BuOH, 80 °C, 69%; e) aqueous HCl (1 M, 10 equiv), MeOH, 80 °C, 4 h, **47** (70%), **41** (60% recovery). CDI = 1,1′-carbonyldiimidazole, DIPEA = *N*,*N*-diisopropylethylamine, DMF = dimethylformamide, HATU = 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

picolinic acid (PAr) was prepared from the commercially available anhydride **40** in a short reaction sequence (Scheme 5A).[21] PAr **42** can be installed on the amino substrate by standard amide coupling. PAr functioned well as a directing group for the palladium-catalyzed C–H arylation of **44** under our typical reaction conditions. Finally, upon treatment of the arylated product **45** with aqueous HCl (1M, 10 equiv) in MeOH at 80 °C, the desired amine product **47** was generated cleanly. The auxiliary precursor **41** could also be recovered in good yield.

To further demonstrate the synthetic utility of this new, readily removable auxiliary, we carried out a formal synthesis of the natural product (+)-obafluorin **53**. Whereas the original synthesis of (+)-obafluorin was based on an aldol route with a chiral glycine synthon,[22] our topologically straightforward synthetic strategy was based on a γ C–H arylation of a threonine-derived substrate (Scheme 6). Compound **49** was easily prepared from the readily accessible threonine derivative **48**. The arylation of **49** with *p*-nitrophenyl iodide under our optimized conditions (Pd(OAc)$_2$: 0.15 equiv) gave the desired product **50** in 60% yield. The PAr group of **50** was readily removed upon treatment with acid, and Boc protection then provided **51** in 81% yield over two steps. The saponification and lactonization of **51** gave compound **52**, which successfully intercepts the Vederas synthesis.[22]



Scheme 6. Formal synthesis of (+)-obafluorin by PAr-directed C(sp^3)–H arylation. Reagents and conditions: a) **42**, HATU, DIPEA, DMF, room temperature, 80%; b) 4-iodonitrobenzene (1.5 equiv), Pd(OAc)$_2$ (0.15 equiv), Ag_2CO_3 (1.0 equiv), *t*BuOH, 70 °C, 40 h, 60%; c) 1. aqueous HCl (1 M, 10 equiv), MeOH, 80 °C, 2 h; 2. Boc_2O, TEA, < CH_2Cl_2, room temperature, 81% (2 steps); d) 1. LiOH, MeOH, H_2O, room temperature; 2. BOP, DIPEA, CH_2Cl_2, room temperature, 12 h, 55%. BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, TEA = triethylamine.

In summary, we have developed a highly effective protocol for the structural diversification of aliphatic scaffolds through a palladium-catalyzed picolinamide-directed functionalization of unactivated C(sp^3)–H bonds under mild reaction conditions. High levels of regio- and stereoselectivity have been demonstrated with a broad range of amine substrates and both aryl and vinyl iodide coupling partners. A new removable auxiliary has been developed and applied in a concise formal synthesis of the natural product (+)-obafluorin.

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