# Site-Selective C−H Arylation of Primary Aliphatic Amines Enabled by a Catalytic Transient Directing Group

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**Abstract.** Transition metal-catalyzed direct C−H bond functionalization of aliphatic amines is of great importance in organic and medicinal chemistry research. While several methods have been developed for the direct $sp^3$ C−H functionalization of secondary and tertiary aliphatic amines, site-selective functionalization of primary aliphatic amines remains a challenge. Here we report the direct highly site-selective arylation of primary alkylamines via a palladium-catalyzed C−H bond functionalization process on unactivated $sp^3$ carbons with catalytic glyoxylic acid as a novel, inexpensive, and transient directing group. With this approach, a wide array of γ-arylated primary alkylamines, important structural motifs in organic and medicinal chemistry, were prepared without any protection or deprotection steps.

Aliphatic amines are ubiquitously present in pharmaceuticals with a wide range of biological activities[1,2]. A number of medicines containing aliphatic amine moieties are among the top 100 best-selling drugs in 2013. Due to the extreme popularity and importance of aliphatic amines, development of efficient and straightforward methods for the synthesis and derivatization of these compounds is of great research interest in organic chemistry and medicinal sciences[3,4]. Among various approaches for the modification of aliphatic amines, the transition metal-catalyzed site-selective C−H functionalization[5–15] has attracted considerable attention in the past decades for the avoidance of the prefunctionalization of starting materials, and

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significant progress has been achieved in recent years on secondary and tertiary aliphatic amines. As shown in Fig. 1, α-selective functionalization of secondary and tertiary aliphatic amines has been well established via either an imine or iminium ion intermediate (Fig. 1a)[16–19], or a cyclometalated species with a palladium[20], ruthenium[21] or rhodium catalyst (Fig. 1b)[22]. Furthermore, β-selective functionalization of secondary aliphatic amines has also been demonstrated with a palladium catalyst via an unusual four-membered ring cyclopalladated intermediate (Fig. 1c)[23]. Recently, γ-selective arylation of tertiary alicyclic amines has been developed in Sanford's group with a novel directing group (Fig. 1d)[24]. In addition, an example of γ-selective acetoxylation of a specific cyclic secondary alkylamine was reported by Gaunt and co-workers[23]. In contrast, transition metal-catalyzed site-selective functionalization of primary alkylamines is rare, in part due to the strong binding properties of amines to a metal, and thus the formation of stable bis(amine) metal complexes which disfavors the C−H bond cleavage of an $sp^3$ carbons. To weaken the coordination of amines to a metal, an electron-withdrawing group is often used to attach to the nitrogen atom of an alkylamine (Fig. 1e and 1f) [25–30]. However, the removal of the auxiliary moiety after C−H bond functionalization is often problematic. Very recently, a steric tethering approach was developed in Gaunt's laboratory with a readily removable auxiliary (Fig. 1g)[31]. Furthermore, the palladium-catalyzed β-oxidation of alkylamines was realized with a hydrazone-based bidentate directing group by Dong and co-workers (Fig. 1h)[32]. Despite the elegance of the above approaches, the requirement for the attachment of an auxiliary somewhat reduces their efficiency. From the synthetic stand point, development of novel strategies with preclusion of the initial substrate modification is highly desirable.

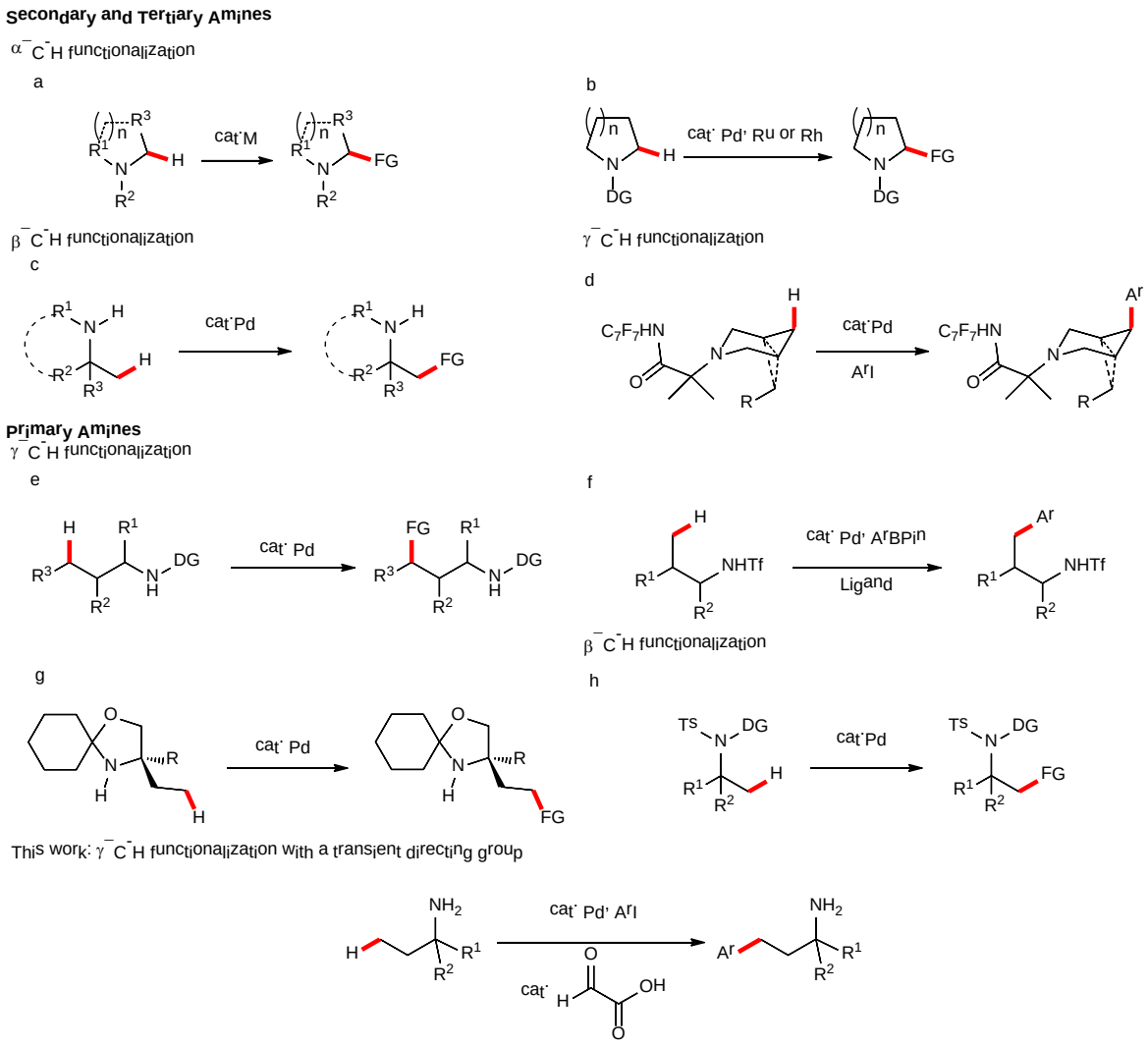



**Figure 1 | Transition metal-catalyzed C−H functionalization of alkylamines.**

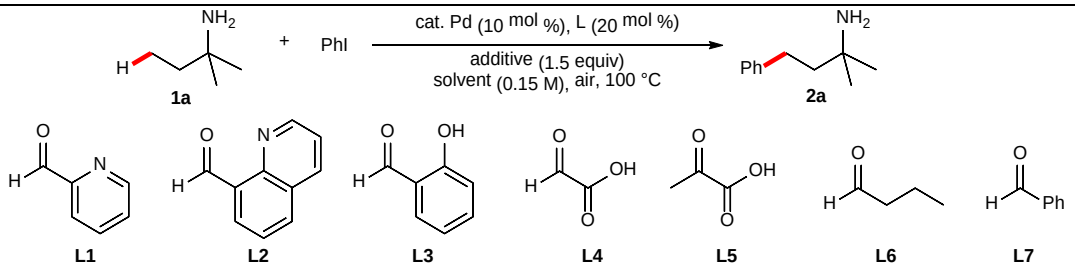
A promising approach for the site-selective C−H functionalization is to introduce a well-designed temporary directing group that binds reversibly to the substrate and the metal centre. Consequently, the desired transformation can be accomplished with a catalytic amount of this transient directing group without changing the function of the substrate. Pioneering studies in this area were conducted by Jun's group, who reported the rhodium-catalyzed functionalization of aldehyde C−H bonds with 2-aminopyridine as an external directing group[33]. In addition, selective C($sp^2$)−H functionalizations of phenols or alcohols have been realized with catalytic amount of phosphinite ligands via reversible transesterification[34,35]. Furthermore, Dong's group showed that the addition of ketone α-C($sp^3$)−H bonds to olefins could be

performed by rhodium(I) catalysis through the reversible formation of enamines[36]. Recently, Yu and co-workers developed the palladium-catalyzed arylation of ketone and aldehyde C($sp^3$)−H bonds with natural amino acids[37]. Inspired by these results, we investiaged the palladium-catalyzed direct γ-arylation of primary amines with catalytic glyoxylic acid as a transient directing group.

## Results

**Reaction condition optimization.** We commenced our investigation of palladium-catalyzed site-selective arylation of *tert*-amylamine (**1a**) with iodobenzene with the initial focus on the ligand screening considering the great importance of an external directing group in this process (Table 1). Although pyridine-based ligands picolinaldehyde (**L1**) and quinoline-8-carbaldehyde (**L2**) and salicylaldehyde (**L3**) were not effective, the reaction could be performed with glyoxylic acid (**L4**) in a good yield with acetic acid as the solvent (entry 4). It was also noticed that the yield was dramatically decreased with 2-oxopropanoic acid (**L5**) (entry 5), showing that the aldehyde moiety is crucial. Furthermore, extremely low yields were obtained with butyraldehyde (**L6**) (entry 6) or benzaldehyde (**L7**) (entry 7) as the ligand, indicating that a bidentate directing group is preferred in this process. Interestingly, the reaction of **1a** could also give the desired product **2a** in 10% NMR yield in the absence of a ligand (entry 8), presumably with amine as a monodentate directing group. With glyoxylic acid (**L4**) as the optimal ligand, a solvent screening was carried out. It turned out that acetic acid is optimal although the reaction could also be performed with hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE) (entries 9 and 10). We then carried out an intensive survey of the palladium catalysts, and $Pd(OAc)_2$ proved to be optimal although several other catalysts could also provide the desired product (entries 12–15). Further screening of the additives showed that AgTFA gave the best result, while several other silver salts could also promote this reaction with moderate to good yields (entries 16–18). It was also noted that there was no reaction occurred in the absence of a silver salt (entry 19). To our delight, the addition of 4 equiv of water further increased the yield of **2a** (entry 20). Additionally, the reaction could be effectively performed under atmospheric $N_2$, indicating that air has no apparent effects on this reaction (entry 21).

**Table 1 | Optimization of Reaction Conditions**[a,b]




| Entry | Pd Source | Ligand | Additive | Solvent | Yield (%) |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | **L1** | AgTFA | HOAc | trace |
| 2 | $Pd(OAc)_2$ | **L2** | AgTFA | HOAc | trace |
| 3 | $Pd(OAc)_2$ | **L3** | AgTFA | HOAc | 5 |
| 4 | $Pd(OAc)_2$ | **L4** | AgTFA | HOAc | 72 |
| 5 | $Pd(OAc)_2$ | **L5** | AgTFA | HOAc | 12 |
| 6 | $Pd(OAc)_2$ | **L6** | AgTFA | HOAc | trace |
| 7 | $Pd(OAc)_2$ | **L7** | AgTFA | HOAc | trace |
| 8 | $Pd(OAc)_2$ | - | AgTFA | HOAc | 10 |
| 9 | $Pd(OAc)_2$ | **L4** | AgTFA | TFE | 5 |
| 10 | $Pd(OAc)_2$ | **L4** | AgTFA | HFIP | 20 |
| 11 | $Pd(OAc)_2$ | **L4** | AgTFA | $^t$BuOH | trace |
| 12 | $Pd(TFA)_2$ | **L4** | AgTFA | HOAc | 70 |
| 13 | $Pd(OPiv)_2$ | **L4** | AgTFA | HOAc | 67 |
| 14 | $Pd(acac)_2$ | **L4** | AgTFA | HOAc | 62 |
| 15 | $PdCl_2$ | **L4** | AgTFA | HOAc | 55 |
| 16 | $Pd(OAc)_2$ | **L4** | AgOAc | HOAc | 46 |
| 17 | $Pd(OAc)_2$ | **L4** | $Ag_2CO_3$ | HOAc | 50 |
| 18 | $Pd(OAc)_2$ | **L4** | $Ag_2O$ | HOAc | 47 |
| 19 | $Pd(OAc)_2$ | **L4** | - | HOAc | 0 |
| 20[c] | $Pd(OAc)_2$ | **L4** | AgTFA | HOAc | 80(74)[d] |
| 21[c,e] | $Pd(OAc)_2$ | **L4** | AgTFA | HOAc | 78 |

[a]Reaction conditions: **1a** (0.30 mmol), iodobenzene (0.45 mmol), Pd source (0.03 mmol), ligand (0.06 mmol), additive (0.45 mmol), solvent (2 mL), 100 °C, air, 15 h. [b]Yields are based on **1a**, determined by $^1$H-NMR using dibromomethane as internal standard. [c]The reaction was performed with $H_2O$ (1.2 mmol). [d]Isolated yield. [e]Under $N_2$.

**Substrate scope of alkylamines.** With the optimized reaction conditions in hand, the scope study of primary aliphatic amines was subsequently carried out (Fig. 2). As we expected, good yields of arylated products were obtained with linear primary amines (**2a**−**e**). Moreover, α-trifluoromethyl, γ-alkoxyl or phenoxyl substituted alkylamines were also effective substrates, providing the corresponding arylated

primary amines in good yields with excellent site-selectivity (**2f**−**i**). Furthermore, the primary amines with a cyclic alkyl group reacted smoothly in this catalytic system (**2j** and **2k**). Although many successful examples for functionalizing unactivated secondary $sp^3$ C−H bonds have been reported with the installation of a mono- or bidentate directing group on the substrates[5-15], direct functionalization of these bonds remains a great challenge with carbonyl compounds using a transient directing group[37] and free aliphatic amines[23,30,31], presumably due to the inherent steric hindrance. In this catalytic system, substrate **1l** with cyclic methylene C−H bonds provided the γ-arylated product **2l** in 23% yield, while arylation of noncyclic secondary C−H bonds was not realized. Thus, selective γ-arylation of the methyl group can be achieved in the presence of multiple γ-C−H bonds (**b**-**d**, **f**-**i**). It was found that 3-decanamine (1m) was not an effective substrate, and only a trace amount of desired product was observed along with unreacted amine (76%) and 3-decanone (14%). Interestingly, the reaction of neopentyl amine, a β-quaternary primary amine, gave arylated products (2n) with moderate reactivity although the products could not be isolated from other unidentified substances. Given these results, the low reactivity of 3-decanamine is possibly attributed to the Thorpe-Ingold effect and α-oxidation of amine as well. It is noteworthy that the reaction showed excellent γ-selectivity and no β- or δ-arylated products were observed for all of the reactive substrates, indicating that the kinetic barrier towards functionalizing the γ-C−H bonds is lower than β- or δ-C−H bonds.

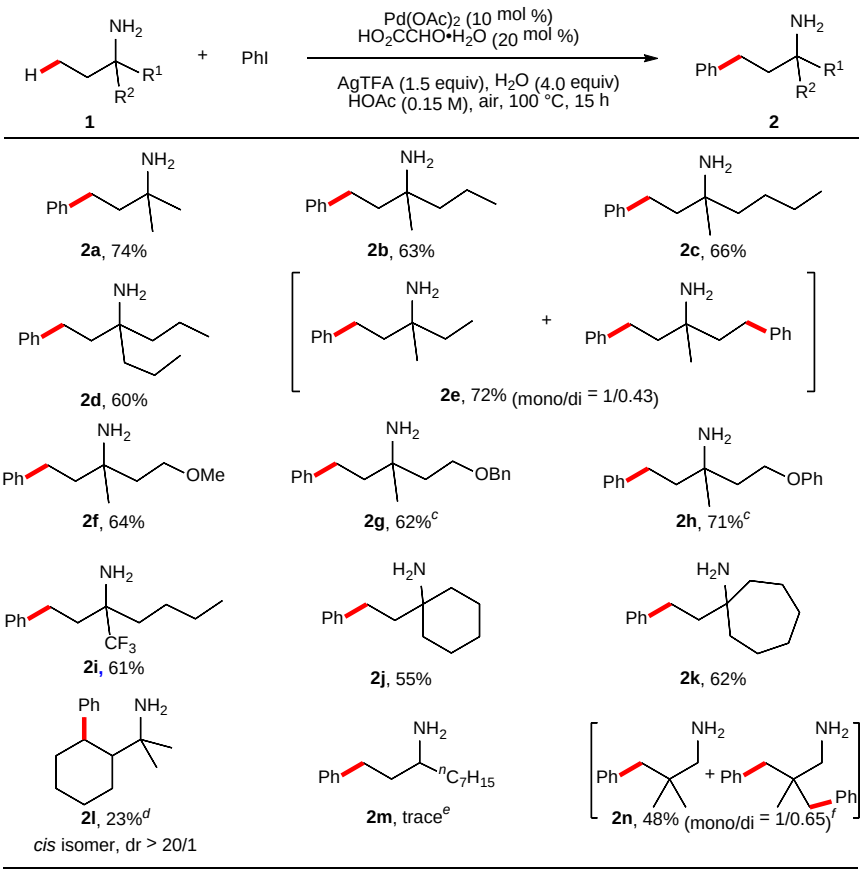



**Figure 2 | Scope of primary alkylamines[a,b].** [a]Reaction conditions: amine **1** (0.30 mmol), iodobenzene (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.06 mmol), AgTFA (0.45 mmol), HOAc (2 mL), 100 °C, air, 15 h. [b]Isolated yields based on **1**. [c]$^1$H-NMR yield of **2** in a mixture with starting material (see Supplementary Information). [d]Unreacted substrate (60%) was determined by crude $^1$H NMR. [e]Unreacted substrate (76%) and 3-decanone (14%) were determined by crude $^1$H NMR. [f]Yield and selectivity were determined by crude $^1$H NMR.

Next, substrate scope of aryl iodides was examined. As shown in Fig. 3, a variety of functional groups including alkoxyl, methyl, alkoxylcarbonyl, nitro, and trifluoromethyl groups were well tolerated in this process, readily furnishing the desired products with excellent site-selectivity (**3a-c, 3g-j** and **3m**). In general, there is no apparent electron effect on the phenyl ring. Furthermore, halogen (fluoro, chloro, or bromo)-substituted phenyl iodides were also found to be viable (**3d-f**, **3k** and **3l**), enabling further manipulation of the γ-arylated products. Unfortunately, *ortho*-iodotoluene was not compatible under current

conditions, presumably due to the steric effect. Considerating important significance of heteroaryl rings in a wide range of biologically active molecules, two representative heteroaryl iodides, 2-(trifluoromethyl)-6-iodopyridine and 6-iodo-1-tosyl-1H-indole, were subjected to the catalytic system, and the desired products **3n** and **3o** were obtained in 72% and 42% yields, respectively.

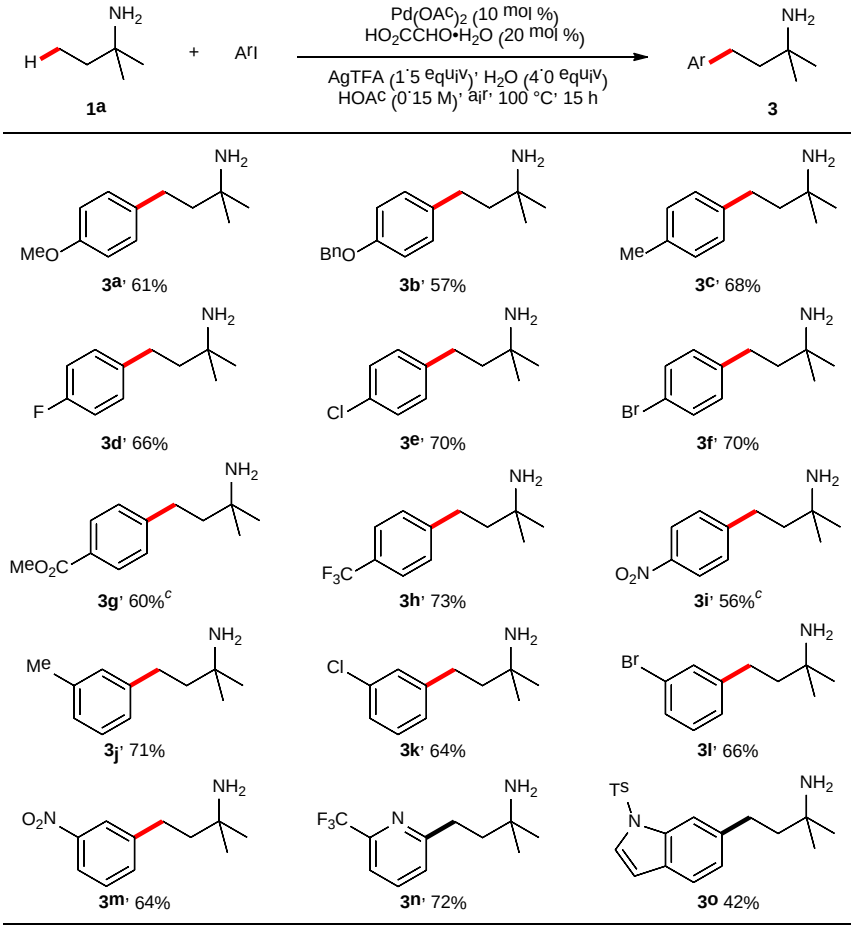



**Figure 3 | Scope of aryl iodides**[a,b]**.** [a]Reaction conditions: amine **1a** (0.30 mmol), ArI (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.06 mmol), AgTFA (0.45 mmol), HOAc (2 mL), 100 °C, air, 15 h. [b]Isolated yields based on **1a**. [c]Without $H_2O$.

To further demonstrate the potential application of this transformation, we carried out the gram-scale reaction of **1a** and iodobenzene. Gratifyingly, the arylated product **2a** was obtained in 77% yield under the slightly modified conditions (Fig. 4).

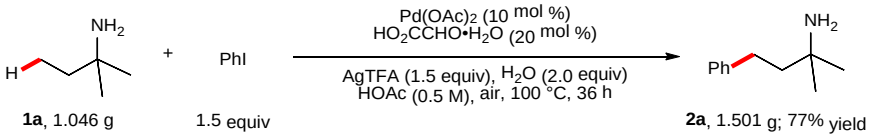



**Figure 4 | Gram scale synthesis of 2-methyl-4-phenylbutan-2-amine (2a).**

Application of this method to the synthesis of molecules related to the pharmaceutical industry was then examined with the initial efforts on the preparation of fingolimod from commercially available starting material **4** (Fig. 5) with this new strategy. Unfortunately, arylation of the silylated amine intermediate with 1-iodo-4-octylbenzene showed only low reactivity, presumably due to the low solubility of this aryl iodide in strongly polar solvent. Fortunately, fingolimod analogues with Me, Br and $CF_3$ groups on the *para*-position of phenyl ring could be straightforward prepared with moderate yields in three steps under the slightly modified conditions without the need of column chromatography purification.

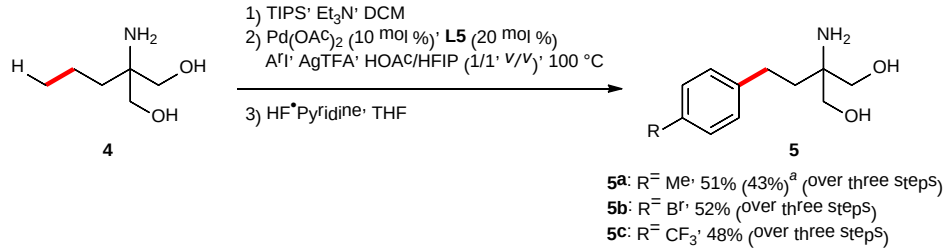



**Figure 5 | Synthetic applications for fingolimod analogues.** [a]Arylation of silylated amine was performed under the standard condtions as Figure **2**.

## Discussion

To provide some insights into the mechanism of this reaction, efforts were made to capture the cyclopalladated intermediate. Delightfully, cyclopalladated complex (**6**) could be obtained from the reaction of glyoxylic acid monohydrate, *tert*-amylamine, and palladium acetate in the presence of stoichiometric amounts of pyridine (Fig. **6a**). The intermediate was then subjected to the arylation conditions, and amine **2a** was isolated in 72% yield (Fig. **6b**).

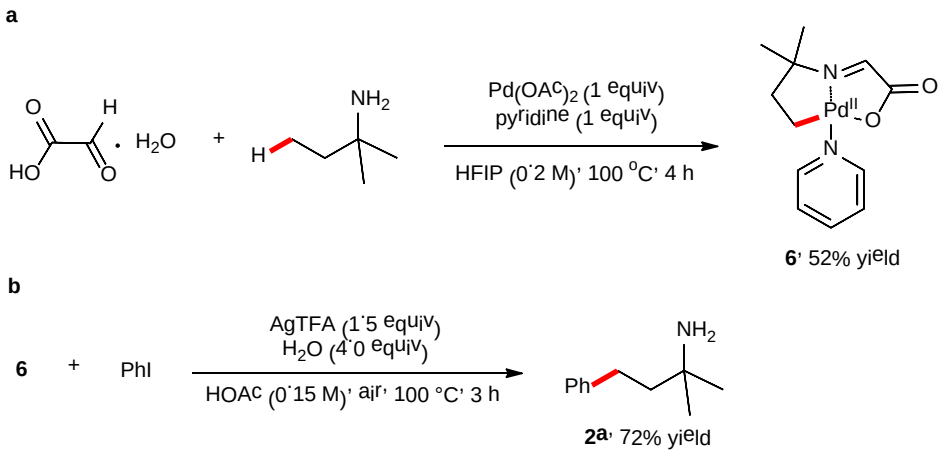



**Figure 6 | Synthesis of cyclopalladated intermediate and arylation of cyclopalladated intermediate.**

On the basis of the above observed results and the previous reports[25,37], a plausible catalytic cycle of this reaction is proposed (Fig. 6). Acid-promoted reversible imine formation from a primary amine with catalytic 2-oxoacetic acid provides the imine intermediate **A**. Coordination of this α-imino acid to a palladium species followed by a ligand exchange process generates the palladium complex **B**. Cyclopalladation of the intermediate **B** gives rise to the five-membered ring intermediate **C** probably through a concerted metallation-deprotonation (CMD) process[38]. Oxidative addition of the intermediate **C** with an aryl iodide produces the palladium (IV) species **D**. Reductive elimination of this palladium complex followed by a ligand dissociation process and iodide abstraction by AgTFA[39,40] provides the α-imino acid **F**, which releases the final product **2** or **3**, and 2-oxoacetic acid, a process facilitated by water. It should be mentioned that the reaction of **1a** failed to provide any of product **2a** in the absence of a silver salt, implying that AgTFA may play other roles besides the iodide abstraction in this catalytic circle.

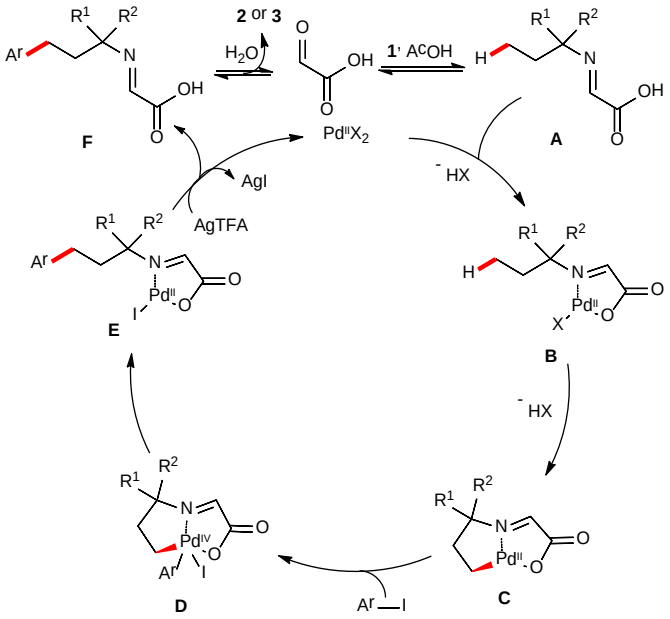



**Figure 6 | Proposed catalytic cycle.**[a] [a]**X =** $^-$OAc, TFA$^-$ or $^-O_2C$-CHO.

In summary, palladium-catalyzed direct arylation of primary aliphatic amines was achieved for the first time via an $sp^3$ C−H bond functionalization process with the assistance of a catalytic directing group[41]. This reaction is featured with high site-selectivity by favoring the γ-C−H bond of the methyl group and good functional group compatibility. This newly developed method using a catalytic transient directing group is inherently superior to previously reported protocols for the direct C−H bond functionalization of primary aliphatic amines due to the avoidance of the pre-installation of a directing group and subsequent removal of this moiety. Considering the prestigious importance of primary aliphatic amines in medicines, the transformation reported here should find broad applications in drug development and discovery processes. Detailed mechanistic studies of this reaction and the substrate scope expansion are currently undergoing in our laboratory.

## Methods

**Typical Procedure for Palladium-Catalyzed C−H Arylation of Primary Aliphatic Amines.** To a 35 mL reaction tube were added $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), glyoxylic acid monohydrate (5.5 mg, 0.06 mmol), AgTFA (99.4 mg, 0.45 mmol), HOAc (2 mL), *tert*-amylamine (**1a**, 26.1 mg, 0.3 mmol),

iodobenzene (91.8 mg, 0.45 mmol) and $H_2O$ (21.6 μL, 1.2 mmol). The tube was then sealed, and the reaction mixture was stirred at room temperature for 15 min before heated to 100 ˚C for 15 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was treated with $Et_2O$ (10 mL) and hydrochloric acid (0.5 M, 8 mL), and then filtered. The aqueous phase was separated from the filtrate and the organic layer was extracted with hydrochloric acid (0.5 M, 3 × 8 mL). The combined aqueous phase was basified (pH > 12) with saturated aqueous NaOH solution and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to provide the desired arylated product 2-methyl-4-phenylbutan-2-amine (**2a**) as a pale yellow oil (36.3 mg, yield: 74%).

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## Author contributions

H. G. conceived and designed the research. Y. L. planned and performed the experiments and analyzed the data. H. G. wrote the manuscript.

## Additional information

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to H. G.

## Competing financial interests

The authors declare no competing financial interests.