nature chemistry

ARTICLES

PUBLISHED ONLINE: 12 SEPTEMBER 2016 | DOI: 10.1038/NCHEM.2606

Site-selective C–H arylation of primary aliphatic amines enabled by a catalytic transient directing group

Yongbing Liu and Haibo Ge*

Transition-metal-catalysed direct C–H bond functionalization of aliphatic amines is of great importance in organic and medicinal chemistry research. Several methods have been developed for the direct sp^3 C–H functionalization of secondary and tertiary aliphatic amines, but site-selective functionalization of primary aliphatic amines in remote positions remains a challenge. Here, we report the direct, highly site-selective γ-arylation of primary alkylamines via a palladium-catalysed C–H bond functionalization process on unactivated sp^3 carbons. Using glyoxylic acid as an inexpensive, catalytic and transient directing group, a wide array of γ-arylated primary alkylamines were prepared without any protection or deprotection steps. This approach provides straightforward access to important structural motifs in organic and medicinal chemistry without the need for pre-functionalized substrates or stoichiometric directing groups and is demonstrated here in the synthesis of analogues of the immunomodulatory drug fingolimod directly from commercially available 2-amino-2-propylpropane-1,3-diol.

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[3]. Due to the extreme popularity and importance of aliphatic amines, the 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[4,5]. Among various approaches for the modification of aliphatic amines, transition-metal-catalysed site-selective C–H functionalization[6–16] has attracted considerable attention in recent decades to avoid the pre-functionalization of starting materials, and significant progress has been made in the use of secondary and tertiary aliphatic amines as substrates. As shown in Fig. 1, α-selective functionalization of secondary and tertiary aliphatic amines has been well established, via either an imine or an iminium intermediate (Fig. 1a,i)[17–20] or a cyclometalated species with a palladium[21], ruthenium[22] or rhodium[23] catalyst (Fig. 1a,ii). The β-selective functionalization of free secondary aliphatic amines has also been demonstrated with a palladium catalyst via an unusual four-membered ring cyclopalladated intermediate (Fig. 1b)[24]. Recently, γ-selective arylation of secondary alicyclic amines has been developed in Sanford's group with a novel directing group (Fig. 1c)[25]. In addition, an example of γ-selective acetoxylation of a specific cyclic secondary alkylamine has been reported by Gaunt and co-workers[24]. In contrast, transition-metal-catalysed site-selective functionalization of free 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 disfavours the C–H bond cleavage of an sp^3 carbon. An electron-withdrawing group is often affixed to the nitrogen atom of an alkylamine to weaken the coordination of amines to a metal (Fig. 1d,i,ii)[26–31]. However, the removal of such an 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. 1d,iii)[32]. Furthermore, the palladium-catalysed β-oxidation of alkylamines has been realized with a hydrazone-based bidentate directing group by Dong and co-workers (Fig. 1e)[33]. Despite the elegance of the above approaches, the requirement for the attachment of an auxiliary somewhat reduces their efficiency. From a synthetic standpoint, the development of novel strategies without initial substrate modification is highly desirable.

A promising approach for site-selective C–H functionalization is to introduce a well-designed temporary directing group that binds reversibly to the substrate and the metal centre. The desired transformation can thus be accomplished with a catalytic amount of this transient directing group, without changing the function of the substrate. Pioneering studies in this area have been conducted by Jun's group, who reported the rhodium-catalysed functionalization of aldehyde C–H bonds with 2-aminopyridine as an external directing group[34]. In addition, selective C(sp^2)–H functionalizations of phenols or alcohols have been realized with catalytic amounts of phosphinite ligands via reversible transesterification[35,36]. Dong's group have also shown 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[37]. Recently, Yu and co-workers developed the palladium-catalysed arylation of ketone and aldehyde C(sp^3)–H bonds with natural amino acids[38]. Here, we report the palladium-catalysed direct γ-arylation of primary amines with catalytic glyoxylic acid as a transient directing group (Fig. 1f).

Results

Reaction condition optimization. Considering the great importance of an external directing group in this process, we commenced our investigation of palladium-catalysed site-selective arylation of *tert*-amylamine (**1a**) with iodobenzene with an initial focus on ligand screening (Table 1). Although pyridine-based ligands picolinaldehyde (**L1**, entry 1) and quinoline-8-carbaldehyde (**L2**, entry 2) and salicylaldehyde (**L3**, entry 2) were not effective, the reaction could be performed with glyoxylic acid (**L4**) in good yield with acetic acid as the solvent (entry 4). It was

Department of Chemistry and Chemical Biology, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana 46202, USA.
*e-mail: geh@iupui.edu

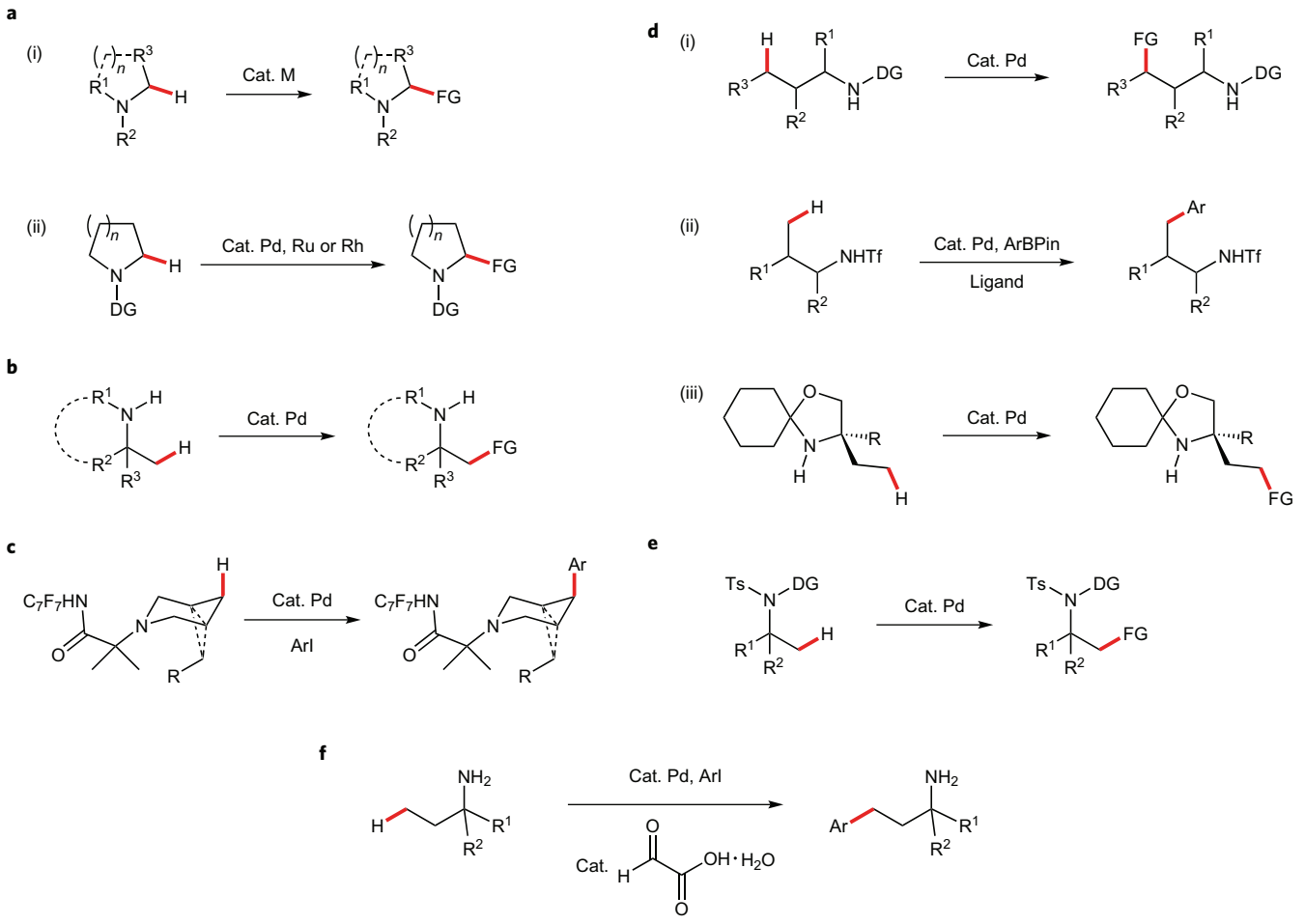
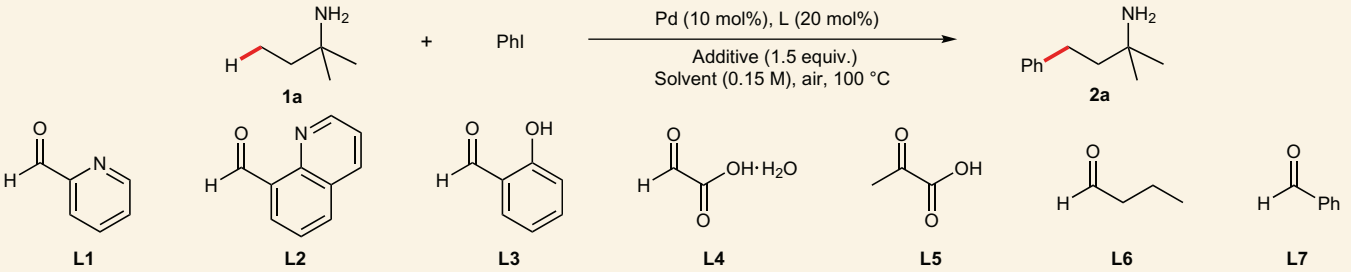


Figure 1 | Transition-metal-catalysed C–H functionalization of alkylamines. a, α-C–H functionalization of secondary and tertiary amines. **b**, β-C–H functionalization of secondary amines. An unusual four-membered ring cyclopalladated intermediate was disclosured. **c**, γ-C–H functionalization of secondary amines with a directing group. A transannular approach was used to selectively functionalize C–H bonds of alicyclic amines at sites remote to nitrogen. **d**, γ-C–H functionalization of primary amines with a removable auxiliary. **e**, β-C–H functionalization of primary amines with a directing group. **f**, γ-C–H functionalization of primary amines with a transient directing group (this work). FG, functional group; DG, directing group; C_7F_7, *p*-$CF_3C_6F_4$; Ar, aryl; Tf, trifluoromethanesulfonyl; Ts, tosyl.

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 trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) (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, although several other silver salts could also promote this reaction with moderate to good yields (entries 16–18). It was also noted that 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).

Substrate scope of alkylamines. With the optimized reaction conditions in hand, the scope study of primary aliphatic amines was subsequently carried out (Table 2). As expected, good yields of arylated products were obtained with linear primary amines (**2a–e**). Moreover, γ-alkoxyl, phenoxyl or α-trifluoromethyl 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[6–16], direct functionalization of these bonds remains a great challenge with carbonyl compounds using a transient directing group[38] and free aliphatic amines[24,32], 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 non-cyclic 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 (**2b–d**, **2f–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

Table 1 | Optimization of reaction conditions.



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*	$Pd(OAc)_2$	L4	AgTFA	HOAc	80(74)†
21*,‡	$Pd(OAc)_2$	L4	AgTFA	HOAc	78

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. Yields are based on 1a, determined by ^{1}H-NMR using dibromomethane as internal standard. *Reaction performed with H_2O (1.2 mmol); †Isolated yield; ‡Reaction carried out under N_2; Ph, phenyl; Ac, acetyl; TFA, trifluoroacetate; Piv, pivaloy; acac, acetylacetonate; TFE, 2,2,2-trifluoroethanol; HFIP, hexafluoroisopropanol; ^{t}Bu, *tert*-butyl.

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 as well as α-oxidation of the amine. 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 for β- or δ-C–H bonds.

The substrate scope of the aryl iodides was examined next. As shown in Table 3, a variety of functional groups, including alkoxyl, methyl, alkoxylcarbonyl, trifluoromethyl and nitro 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 electronic 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 the current conditions, presumably due to the steric effect. Considering the importance 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.

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

Application of this method to the synthesis of molecules related to the pharmaceutical industry was then examined, with initial efforts on the preparation of fingolimod from commercially available starting material **4** (Fig. 2b) using this new strategy. Unfortunately, arylation of the silylated amine intermediate with

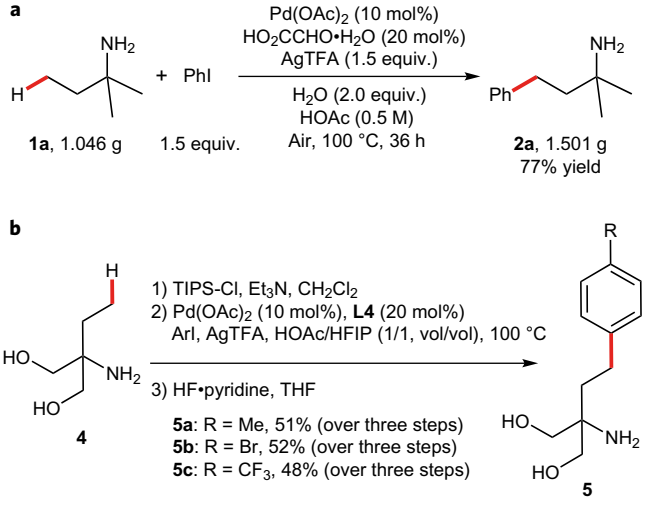
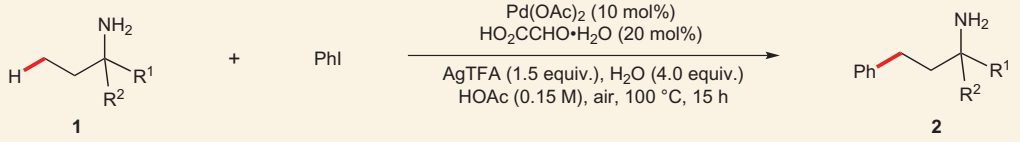
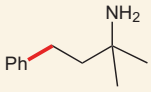


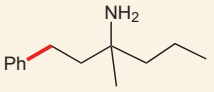
Figure 2 | Synthetic applications of palladium-catalysed arylation of alkylamines. a, Gram-scale synthesis of 2-methyl-4-phenylbutan-2-amine (**2a**). **b**, Synthesis of fingolimod analogues. The synthesis of analogues to fingolimod, a drug for treating multiple sclerosis, can be achieved in three steps from commercial reagents. TIPS, triisopropylsilyl; Et, ethyl.

Table 2 | Scope of primary alkylamines.

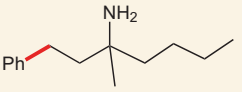




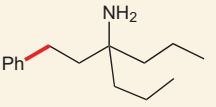
2a, 74%



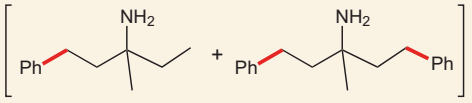
2b, 63%



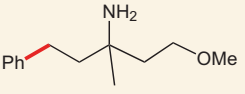
2c, 66%



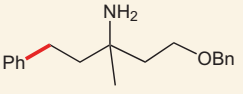
2d, 60%



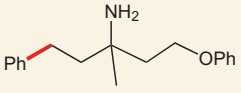
2e, 72% (mono: **2e1**, di: **2e2**, **2e1**/**2e2** = 1/0.43)



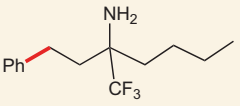
2f, 64%



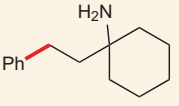
2g, 62%*



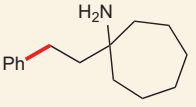
2h, 71%*



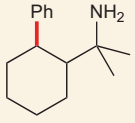
2i, 61%



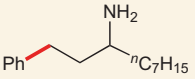
2j, 55%



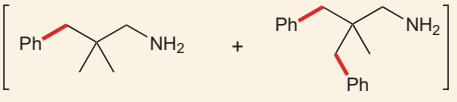
2k, 62%



2l, 23%†
cis isomer, d.r. > 20/1



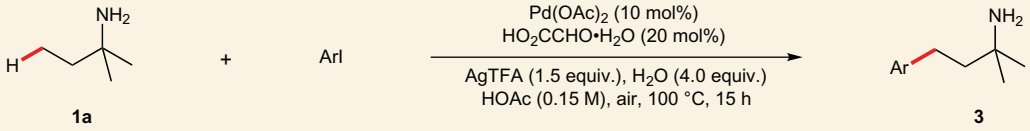
2m, trace‡

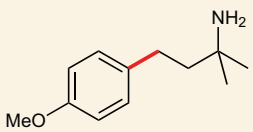


2n, 48% (mono: **2n1**, di: **2n2**, **2n1**/**2n2** = 1/0.65)§

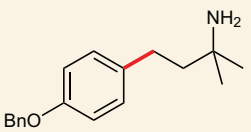
Reaction conditions: amine **1** (0.30 mmol), iodobenzene (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.06 mmol), AgTFA (0.45 mmol), HOAc (2 ml), 100 °C, air, 15 h. Isolated yields based on **1**; *^{1}H-NMR yield of **2** in a mixture with starting material (see Supplementary section 'Analytical data of products'); †Unreacted substrate (60%) was determined by crude ^{1}H-NMR; ‡Unreacted substrate (76%) and 3-decanone (14%) were determined by crude ^{1}H-NMR; §Yield and selectivity were determined by crude ^{1}H-NMR. Bn, benzyl; ^{n}C_7H_{15}, heptyl.

Table 3 | Scope of aryl iodides.

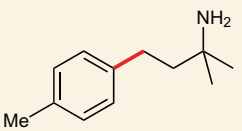




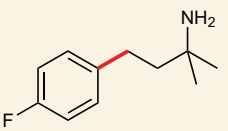
3a, 61%



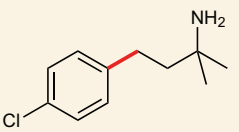
3b, 57%



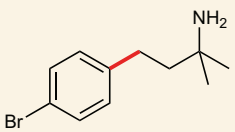
3c, 68%



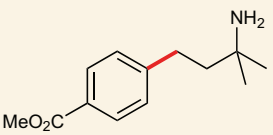
3d, 66%



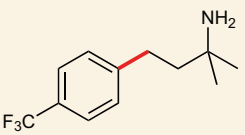
3e, 70%



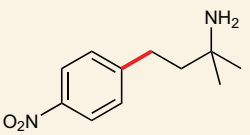
3f, 70%



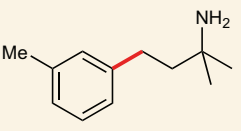
3g, 60%*



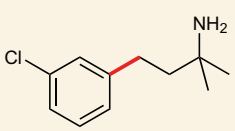
3h, 73%



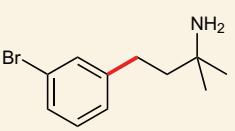
3i, 56%*



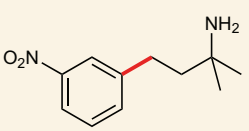
3j, 71%



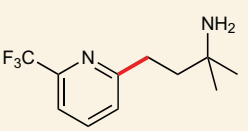
3k, 64%



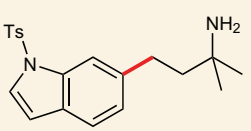
3l, 66%



3m, 64%



3n, 72%



3o, 42%

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. Isolated yields based on **1a**. *Reaction carried out without H_2O.

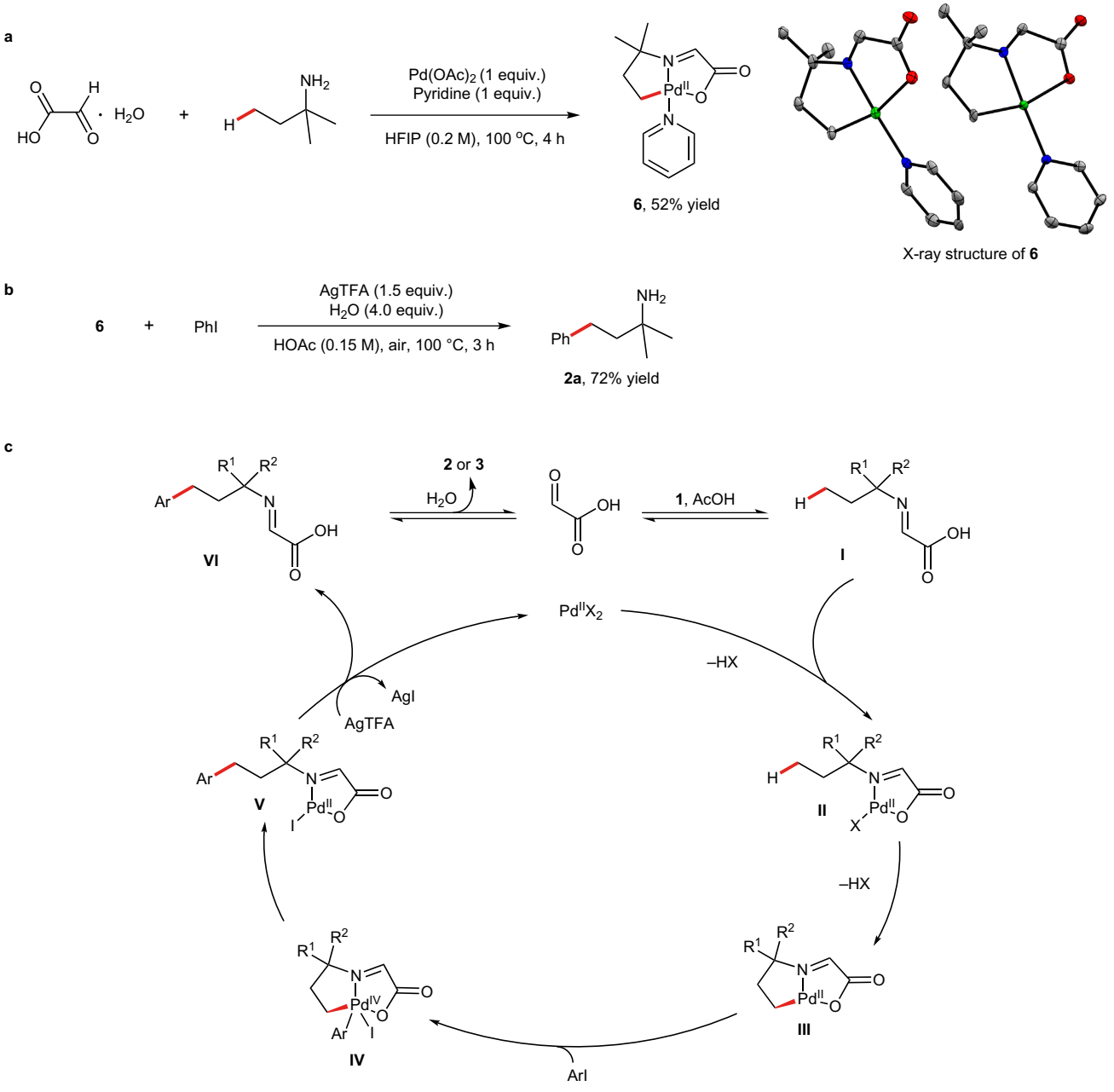


Figure 3 | Insights into the reaction mechanism of palladium-catalysed arylation of alkylamines. a, Synthesis of cyclopalladated intermediate. Crystals of **6** were grown by diffusion of hexane into a dichloromethane solution of **6**. Hydrogen atoms have been omitted for clarity. Two molecules of **6** were found per asymmetric unit. Selected bond lengths (Å) and angles (deg) on the palladacycles: Pd–C 2.014(5) and 2.013(5); C–Pd–N 84.6(2) and 84.9(2), N–Pd–O 79.0(1) and 79.2(1). **b**, Arylation of cyclopalladated intermediate. **c**, Proposed catalytic cycle, in which the ligand on palladium has been omitted for clarity. **X** = AcO^-, TFA^- or $OHC\text{-}CO_2^-$.

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 at the *para*-position of the phenyl ring could be prepared in a straightforward manner with moderate yields in three steps under slightly modified conditions, without the need for purification by column chromatography.

Discussion

To provide some insights into the mechanism of this reaction, efforts were made to capture the cyclopalladated intermediate. Pleasingly, 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. 3a). The intermediate was then subjected to arylation conditions and amine **2a** was isolated in 72% yield (Fig. 3b).

On the basis of the above observed results and previous reports[26,38], a plausible catalytic cycle is proposed for this reaction (Fig. 3c). Acid-promoted reversible imine formation from a primary amine with catalytic 2-oxoacetic acid provides the imine intermediate **I**. Coordination of this α-imino acid to a palladium species followed by a ligand exchange process generates palladium complex **II**. Cyclopalladation of intermediate **II** gives rise to the five-membered ring intermediate **III**, probably through a concerted metallation–deprotonation (CMD) process[39]. Oxidative addition of intermediate **III** with an aryl iodide produces the palladium(IV) species **IV**. Reductive elimination of this palladium complex followed by a ligand dissociation process and iodide abstraction

by AgTFA (refs 40,41) provides the α-imino acid **VI**, which releases 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 iodide abstraction in this catalytic circle.

During the review of this manuscript, a related work on C(sp^3)–H arylation of free primary amines was reported by Dong and colleagues[42].

Conclusions

In summary, palladium-catalysed direct arylation of primary aliphatic amines was achieved via an sp^3 C–H bond functionalization process with the assistance of a catalytic directing group. This reaction demonstrates high site selectivity by favouring the γ-C–H bond of the methyl group, as well as good functional group compatibility. This newly developed method using a catalytic transient directing group is inherently superior to previously reported protocols for the site-selective C–H bond functionalization of primary aliphatic amines due to the avoidance of the pre-installation and subsequent removal of a directing group. Considering the 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 expansion of the substrate scope are currently ongoing in our laboratory.

Methods

Typical procedure for palladium-catalysed 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 being 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%).

Data availability. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as CCDC 1491489 (**6** at 100 K) and can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/getstructures.

Received 12 April 2016; accepted 1 August 2016; published online 12 September 2016

References

1. Kittakoop, P., Mahidol, C. & Ruchirawat, S. Alkaloids as important scaffolds in therapeutic drugs for the treatments of cancer, tuberculosis, and smoking cessation. *Curr. Top. Med. Chem.* **14,** 239–252 (2014).
2. Cushnie, T. P. T., Cushnie, B. & Lamb, A. J. Alkaloids: an overview of their antibacterial, antibiotic-enhancing and antivirulence activities. *Int. J. Antimicrob. Agents* **44,** 377–386 (2014).
3. McGrath, N. A., Brichacek, M. & Njardarson, J. T. A graphical journey of innovative organic architectures that have improved our lives. *J. Chem. Educ.* **87,** 1348–1349 (2010).
4. Salvatore, R. N., Yoon, C. H. & Jung, K. W. Synthesis of secondary amines. *Tetrahedron* **57,** 7785–7811 (2001).
5. Hager, A., Vrielink, N., Hager, D., Lefranc, J. & Trauner, D. Synthetic approaches towards alkaloids bearing α-tertiary amines. *Nat. Prod. Rep.* **33,** 491–522 (2016).
6. Chen, X., Engle, K. M., Wang, D.-H. & Yu, J.-Q. Palladium(II)-catalyzed C–H activation/C–C cross-coupling reactions: versatility and practicality. *Angew. Chem. Int. Ed.* **48,** 5094–5115 (2009).
7. Baudoin, O. Transition metal-catalyzed arylation of unactivated C(sp^3)–H bonds. *Chem. Soc. Rev.* **40,** 4902–4911 (2011).
8. Li, H., Li, B.-J. & Shi, Z.-J. Challenge and progress: palladium-catalyzed sp^3 C–H activation. *Catal. Sci. Technol.* **1,** 191–206 (2011).
9. White, M. C. Adding aliphatic C–H bond oxidations to synthesis. *Science* **335,** 807–809 (2012).
10. Yamaguchi, J., Yamaguchi, A. D. & Itami, K. C–H bond functionalization emerging synthetic tools for natural products and pharmaceuticals. *Angew. Chem. Int. Ed.* **51,** 8960–9009 (2012).
11. Colby, D. A., Bergman, R. G. & Ellman, J. A. Rhodium-catalyzed C–C bond formation via heteroatom-directed C–H bond activation. *Chem. Rev.* **110,** 624–655 (2010).
12. Daugulis, O., Roane, J. & Tran, L. D. Bidentate, monoanionic auxiliary-directed functionalization of carbon–hydrogen bonds. *Acc. Chem. Res.* **48,** 1053–1064 (2015).
13. Lyons, T. W. & Sanford, M. S. Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.* **110,** 1147–1169 (2010).
14. Rouquet, G. & Chatani, N. Catalytic functionalization of C(sp^2)–H and C(sp^3)–H bonds by using bidentate directing groups. *Angew. Chem. Int. Ed.* **52,** 11726–11743 (2013).
15. Chen, Z. *et al.* Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2,** 1107–1295 (2015).
16. 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.* **49,** 635–645 (2016).
17. Yoo, W.-J. & Li, C.-J. Cross-dehydrogenative coupling reactions of sp^3-hybridized C–H bonds. *Top. Curr. Chem.* **292,** 281–302 (2010).
18. Yeung, C. S. & Dong, V. M. Catalytic dehydrogenative cross-coupling: forming carbon–carbon bonds by oxidizing two carbon–hydrogen bonds. *Chem. Rev.* **111,** 1215–1292 (2011).
19. Zhang, C., Tang, C. & Jiao, N. Recent advances in copper-catalyzed dehydrogenative functionalization via single electron transfer (SET) process. *Chem. Soc. Rev.* **41,** 3464–3484 (2012).
20. Girard, S. A., Knauber, T. & Li, C.-J. The cross-dehydrogenative coupling of Csp^3–H bonds: a versatile strategy for C–C bond formations. *Angew. Chem. Int. Ed.* **53,** 74–100 (2014).
21. Spangler, J. E., Kobayashi, Y., Verma, P., Wang, D.-H. & Yu, J.-Q. α-Arylation of saturated azacycles and *N*-methylamines via palladium(II)-catalyzed C(sp^3)–H coupling. *J. Am. Chem. Soc.* **137,** 11876–11879 (2015).
22. Pastine, S. J., Gribkov, D. V. & Sames, D. sp^3 C–H bond arylation directed by amidine protecting group: α-arylation of pyrrolidines and piperidines. *J. Am. Chem. Soc.* **128,** 14220–14221 (2006).
23. Chatani, N. *et al.* Carbonylation at sp^3 C–H bonds adjacent to a nitrogen atom in alkylamines catalyzed by rhodium complexes. *J. Am. Chem. Soc.* **122,** 12882–12883 (2000).
24. McNally, A., Haffemayer, B., Collins, B. S. L. & Gaunt, M. J. Palladium-catalysed C–H activation of aliphatic amines to give strained nitrogen heterocycles. *Nature* **510,** 129–133 (2014).
25. Topczewski, J. J., Cabrera, P. J., Saper, N. I. & Sanford, M. S. Palladium-catalysed transannular C–H functionalization of alicyclic amines. *Nature* **531,** 220–224 (2016).
26. Zaitsev, V. G., Shabashov, D. & Daugulis, O. Highly regioselective arylation of sp^3 C–H bonds catalyzed by palladium acetate. *J. Am. Chem. Soc.* **127,** 13154–13155 (2005).
27. He, G., Zhao, Y., Zhang, S., Lu, C. & Chen, G. Highly efficient syntheses of azetidines, pyrrolidines and indolines via palladium-catalyzed intramolecular amination of C(sp^3) and C(sp^2)–H bonds at γ and δ positions. *J. Am. Chem. Soc.* **134,** 3–6 (2012).
28. Zhang, S.-Y. *et al.* Efficient alkyl ether synthesis via palladium-catalyzed, picolinamide-directed alkoxylation of unactivated C(sp^3)–H and C(sp^2)–H bonds at remote positions. *J. Am. Chem. Soc.* **134,** 7313–7316 (2012).
29. Zhang, S.-Y. *et al.* Palladium-catalyzed picolinamide-directed alkylation of unactivated C(sp^3)–H bonds with alkyl iodides. *J. Am. Chem. Soc.* **135,** 2124–2127 (2013).
30. Rodríguez, N., Romero-Revilla, J. A., Fernández-Ibáñez, M. Á. & Carretero, J. C. Palladium-catalyzed *N*-(2-pyridyl)sulfonyl-directed C(sp^3)–H γ-arylation of amino acid derivatives. *Chem. Sci.* **4,** 175–179 (2013).
31. Chan, K. S. L. *et al.* Ligand-enabled cross-coupling of C(sp^3)–H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis. *Nat. Chem.* **6,** 146–150 (2014).
32. Calleja, J. *et al.* A steric tethering approach enables palladium-catalysed C–H activation of primary amino alcohols. *Nat. Chem.* **7,** 1009–1016 (2015).
33. Huang, Z., Wang, C. & Dong, G. A hydrazone-based *exo*-directing group strategy for β-C–H oxidation of aliphatic amines. *Angew. Chem. Int. Ed.* **55,** 5299–5303 (2016).
34. Jun, C.-H., Lee, H. & Hong, J.-B. Chelation-assisted intermolecular hydroacylation: direct synthesis of ketone from aldehyde and 1-alkene. *J. Org. Chem.* **62,** 1200–1201 (1997).
35. Rousseau, G. & Breit, B. Removable directing groups in organic synthesis and catalysis. *Angew. Chem. Int. Ed.* **50,** 2450–2494 (2011).
36. Dydio, P. & Reek, J. N. H. Supramolecular control of selectivity in transition-metal catalysis through substrate preorganization. *Chem. Sci.* **5,** 2135–2145 (2014).
37. Mo, F. & Dong, G. Regioselective ketone α-alkylation with simple olefins via dual activation. *Science* **345,** 68–72 (2014).
38. 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* **351,** 252–256 (2016).
39. Lapointe, D. & Fagnou, K. Overview of the mechanistic work on the concerted metallationdeprotonation pathway. *Chem. Lett.* **39,** 1118–1126 (2010).

40. Arroniz, C., Denis, J. G., Ironmonger, A., Rassias, G. & Larrosa, I. An organic cation as a silver(I) analogue for the arylation of sp^2 and sp^3 C–H bonds with iodoarenes. *Chem. Sci.* **5,** 3509–3514 (2014).
41. Weibel, J.-M., Blanc, A. & Pale, P. Ag-mediated reactions: coupling and heterocyclization reactions. *Chem. Rev.* **108,** 3149–3173 (2008).
42. 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.* **55,** 9084–9087 (2016).

Acknowledgements

The authors acknowledge Indiana University–Purdue University Indianapolis and NSF CHE-1350541 for financial support. The authors thank J. Miao and K. Yang for discussions on this project.

Author contributions

Y.L. and H.G. conceived and designed the experiments. Y.L. performed the experiments. Y.L. and H.G. analysed the data. H.G. wrote the manuscript.

Additional information

Supplementary information and chemical compound information are 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.