α-amino acids bearing aromatic side chains are important synthetic units in the synthesis of peptides and natural products. Although various β-C-H arylation methodologies for amino acid derivatives involving the assistance of directing groups have been extensively developed, syntheses that directly employ N-protected amino acids as starting materials remain rare. Herein, we report an N-acetylglycine-enabled Pd-catalysed carboxylate-directed β-C(sp³)-H arylation of aliphatic acids. In this way, various non-natural amino acids can be directly prepared from phthaloylalanine in one step in good to excellent yields. Furthermore, a series of aliphatic acids have been shown to be amenable to this transformation, affording β-arylated propionic acid derivatives in moderate to good yields. More importantly, this ligand-enabled direct β-C(sp³)-H arylation could be easily scaled-up to 10 g under reflux conditions, highlighting the potential utility of this synthetic method.
Aliphatic acids are highly important synthetic units, being commonly found in natural products, approved drugs and biologically important molecules.\textsuperscript{1,2} Direct C–H functionalization of C(sp\(^3\))-H bonds in aliphatic acids is highly important and attractive, because it provides a straightforward pathway to afford valuable chemicals with higher atom-economy compared to traditional procedures, for which pre-functionalized substrates are needed.\textsuperscript{3–10} During the last decades, tremendous progress has been made in terms of transition-metal-catalysed functionalization of C–H bonds. Although there have been exciting developments in carboxylate-assisted functionalization of arene C–H bonds,\textsuperscript{11–15} reports of the direct functionalization of aliphatic acids/amino acids are scarce.\textsuperscript{16–18} Thus, the use of various directing groups to achieve regioselective arylation was observed. Therefore, the use of various directing groups to achieve arylation was observed. Thus, the use of various directing groups to achieve regioselective β-C(sp\(^3\))-H bond functionalization of carboxylic acid derivatives has been extensively explored in the past decades (Fig. 1).

In 2005, Yu et al. reported early pioneering work by employing an oxazoline ring as a mono-coordinated directing group.\textsuperscript{19} This work: Ligand-enabled direct C(sp\(^3\))-H arylation of carboxylic acids.

![Diagram](image-url)

**Figure 1 | Directing group strategies for C–H activation.** (a) First example of carboxyl group-assisted β-arylation of an aliphatic acid. (b) General approach for C–H functionalization of aliphatic acid/amino acid. (c) Monodentate directing groups for C–H arylation. (d) Bidentate directing groups for C–H arylation. (e) Our work on ligand-enabled directed C(sp\(^3\))-H arylation of carboxylic acids.
direct β-C(sp³)-H arylation with the assistance of mono-N-protected amino acid ligands (Fig. 1c)⁴⁴–⁴⁷. For example, N-methoxyamide has been used as a directing group for β-C(sp³)-H arylation with a pyridine-type ligand, affording various non-natural amino acids from protected alanine derivatives⁴⁹. These developments have greatly expanded the possible approaches to construct key structures of natural products, pharmaceutical agents and organic materials.

Although the directing group strategy ⁵⁰–⁵³ has been successfully deployed in the past decades, an inevitable drawback is the need for additional synthetic steps for installation and removal of the directing group. Thus, an ideal approach to functionalize an aliphatic acid would directly employ the carboxyl group itself as an auxiliary. However, there is still no efficient general approach for the direct functionalization of aliphatic acids that does not require the installation of a directing group.

α-Amino acids bearing aromatic side chains are important synthetic units in the synthesis of peptides and natural products. To date, various β-C-H arylation protocols for amino acid derivatives involving the assistance of directing groups have been extensively developed⁵⁷,⁴³,⁴⁹,⁵⁴. However, the most straightforward way to synthesize these amino acid derivatives would be to directly employ the N-protected amino acid as the starting material. Inspired by recent developments in ligand-accelerated or ligand-enabled C–H activation reactions ⁵⁴–⁵⁶, we speculated that carboxylate-assisted β-C(sp³)-H activation might be achieved by employing a congruous ligand. Thus, we investigated whether synthetically important phenylalanine derivatives ¹⁴,⁵⁴,⁵⁷–⁶¹ could be directly synthesized from phthaloylalanine through arylation of the β-C(sp³)–H bond with a carboxyl group as a coordination centre and the assistance of a ligand.

Herein, we report our discovery that the carboxyl group itself can act as a coordination centre by combination with a mono-protected amino acid ligand to realize β-C(sp³)-H activation (Fig. 1e). This is the first example of a general, palladium-catalysed, highly site-selective arylation of β-C(sp³)-H bonds of various aliphatic acids. Various aryl iodides are tolerated, directly affording a large number of non-natural amino acids from phthaloylalanine in moderate to excellent yields.

**Figure 2 | Substrate scope of aryl iodides.** Reaction conditions: 1a (0.2 mmol), 2 (0.3 mmol), Pd(OAc)₂ (5 mol%), Ag₂CO₃ (0.2 mmol), K₂CO₃ (0.1 mmol), Ac-Gly-OH (0.06 mmol), HFIP (2 ml), 100 °C, 24 h. Isolated yields. aPd(OAc)₂ (10 mol%). b110 °C.
Selected unsuccessful substrates

**Figure 3 | Substrate scope of carboxylic acids and amino acids.** Reaction conditions: 0.2 mmol scale, Pd(OAc)$_2$ (10 mol%), Ag$_2$CO$_3$ (0.2 mmol), K$_2$CO$_3$ (0.1 mmol), Ac-Gly-OH (0.06 mmol), HFIP (2 ml), 80 °C, 12 h. Isolated yields. a100 °C. b150 °C. cHFIP (4 ml). d60 h. e150 °C.

| Table 1 | Optimization for direct C(sp$^3$)-H bond activation. |
|---|---|---|---|
| entry | ligand | additive 1 | additive 2 | recovery of 1a (%) | yield of 3a (%) |
| 1 | none | Ag$_2$CO$_3$ | (n-BuO)$_2$PO$_2$H | 86 | 8 |
| 2 | PPh$_3$ | Ag$_2$CO$_3$ | (n-BuO)$_2$PO$_2$H | 80 | 10 |
| 3 | dppf | Ag$_2$CO$_3$ | (n-BuO)$_2$PO$_2$H | 93 | Trace |
| 4 | Pyridine | Ag$_2$CO$_3$ | (n-BuO)$_2$PO$_2$H | 96 | 0 |
| 5 | 1,10-phen | Ag$_2$CO$_3$ | (n-BuO)$_2$PO$_2$H | 94 | Trace |
| 6 | Ac-Leu-OH | Ag$_2$CO$_3$ | None | 24 | 65 |
| 7 | Ac-Val-OH | Ag$_2$CO$_3$ | None | 18 | 70 |
| 8 | Ac-isoLeu-OH | Ag$_2$CO$_3$ | None | 40 | 54 |
| 9 | Ac-Gly-OH | Ag$_2$CO$_3$ | None | 5 | 86 |
| 10 | Boc-Gly-OH | Ag$_2$CO$_3$ | None | 89 | 5 |
| 11 | Cbz-Gly-OH | Ag$_2$CO$_3$ | None | 92 | 4 |
| 12 | Ac-Gly-OH | Ag$_2$CO$_3$ | (n-BuO)$_2$PO$_2$H | 48 | 40 |
| 13 | Ac-Gly-OH | Ag$_2$CO$_3$ | 1-AdCO$_2$H | 65 | 26 |
| 14 | Ac-Gly-OH | Cu(OAc)$_2$ | None | 88 | 5 |
| 15 | Ac-Gly-OH | Cu(OAc)$_2$ | None | 90 | Trace |
| 16 | Ac-Gly-OH | Cu(OAc)$_2$ | None | 92 | Trace |

Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), Pd(OAc)$_2$ (5 mol%), additive 1 (0.05 mmol), K$_2$CO$_3$ (0.05 mmol), ligand (0.03 mmol), additive 2 (0.02 mmol), HFIP (1 ml), 100 °C, 24 h. Yields were based on LC-MS analysis using acetyl benzene as an internal standard.
aliphatic acids have also been transformed, highlighting the potential utility of this synthetic method.

**Results**

**Optimization of reaction conditions.** At the beginning of our study, we first treated phthaloylalanine (1a) with 4-iodoanisole in the presence of Pd(OAc)\(_2\) (5 mol%), Ag\(_2\)CO\(_3\) (1 equiv), K\(_2\)CO\(_3\) (0.5 equiv) and (n-BuO)\(_2\)PO\(_2\)H (0.2 equiv) in hexafluoroisopropanol (HFIP) at 100°C for 24 h. Surprisingly, the desired product 3a was obtained in 8% yield along with 86% of recovered 1a (Table 1, entry 1). Encouraged by this result, we screened various additives, ligands and solvents (see Supplementary Information, Supplementary Tables 4–9). The results revealed that the phosphine and N-coordinated ligand could not give the arylated 3a in yields higher than 10%. When we tested some well-known mono-protected amino acid ligands, these displayed effective promoting effects on this arylation of \(\beta\)-C(\(sp^3\))–H bonds (entries 6–11). After screening various mono-protected amino acid ligands, it was found that the simple Ac-Gly-OH afforded the phenylalanine derivative 3a in 86% yield (entry 9). Interestingly, the additives (n-BuO)\(_2\)PO\(_2\)H and 1-AdCO\(_2\)H showed no promoting effect when Ac-Gly-OH was employed as the ligand. Further investigations revealed that Ag\(_2\)CO\(_3\) was indispensable and could not be replaced (entries 14–16).

**Substrate scope of aryl iodides.** With the optimized conditions in hand, phthaloylalanine (1a) was treated with a wide range of aryl iodides to form important non-natural amino acids that are widely applied in the preparation of bioactive peptides. Aryl iodides bearing para or meta substituents afforded the corresponding products in good to excellent yields (see Fig. 2). Various functional groups, such as MeO, Me, \(\tau\)-Bu, F, Cl, Br and CF\(_3\), were well tolerated in this transformation. It is worthy of mention that the functional groups Ac, CO\(_2\)Me, CHO and NO\(_2\) were also compatible with this transformation, and the corresponding

![Figure 4](image-url) | Ten gram scale reaction in one step. Arylation of N-phthaloyl-phenylalanine (1a) on a 10 g scale.

![Figure 5](image-url) | Synthesis of biologically active compounds. (a) Arylation of chiral substrate \(1r\). (b) Remove the protecting groups and further transformations. (c) Synthesis of iopanoic acid.
phenylalanine derivatives were obtained in good yields. An ortho-substituted aryl iodide was also tolerated in this transformation by slightly modifying the conditions (3q). Multiply-substituted aryl iodides performed well, affording the corresponding non-natural amino acids in good yields (3r-x). It is worth mentioning that the bromo functional group in 3h and 3x could be further applied in peptide synthesis under Davis conditions83.

Substrate scope of carboxylic acids and amino acids. To demonstrate the generality of this carboxylate-directed C(sp²)-H arylation reaction, we next investigated its scope in terms of aliphatic acids under the optimal conditions (see Fig. 3). The phthaloyl-protected β-amino acid 1b and 2-cyclohexylopropanoic acid 1c performed well with 4-idoanisole, affording the corresponding arylated products in good yields (4b, 4c). The simple carboxylic acids (1d-g) also performed well when two equivalents thereof were treated with one equivalent of 4-idoanisole at 80 °C for 12 h (4d-g). Benzoyl-protected 2,2-bis(hydroxymethyl)propionic acid was also compatible with this transformation and an acceptable yield of 4i was obtained. Isobutyric acid (1h) and phthaloyl-protected 2-aminoisobutyric acid (1j) both afforded the mono-arylated products in good yields when two equivalents thereof were treated with one equivalent of 4-idoanisole. The diarylation product of 1j could also be obtained by treating it with three equivalents of 4-idoanisole (see Supplementary Information, Supplementary Fig. 47). Direct functionalization of propionic acid is extremely challenging, due to the lack of a steric effect during its cyclopalladation. To our great delight, however, propionic acid also reacted well with 10 mol% palladium acetate at 150 °C for 60 h, affording various β-aryl-propionic acids in synthetically acceptable yields (4k-m). All the results indicated the excellent promoting ability of Ac-Gly-OH in this carboxylic-acid-assisted C(sp²)-H arylation. It is worth mentioning that when 4-idoanisole was treated with six equivalents of pivalic acid in the presence of Pd(OAc)₂ (10 mol%), Ag₂CO₃ (1 equiv), K₂CO₃ (0.5 equiv) and Ac-Gly-OH (0.3 equiv) in HFIP at 80 °C for 12 h, the monoarylated product was obtained in 68% yield and the diarylated product was obtained in less than 5% yield (see Supplementary Fig. 46). However, when carbobenzyloxy-protected alanine (1n) was tested, it failed to give any product and the starting material was recovered. Unfortunately, methylene C(sp²)-H bonds were not tolerated in this ligand-enabled carboxylate-assisted C-H transformation (1o, 1p). Phthaloyl-protected valine (1q) was also treated with 4-idoanisole at 150 °C for 60 h. The desired arylated product was only observed in trace amount, along with near-complete recovery of 1q.

Synthetic potential. Considering the importance of the generated non-natural amino acids, if this newly developed carboxylate-assisted directed C(sp²)-H arylation could be performed on a 10 g scale, it would provide a very attractive and convenient approach for the synthesis of phenylalanine derivatives in the laboratory. To our delight, 10 g scale reactions proceeded well with a range of aryl iodides (Fig. 4, 3a, 10.56 g; 3h, 10.97 g; 3o, 12.88 g) by employing a slightly longer reaction time, even under reflux conditions.

When the chiral substrate 1r was tested under the standard reaction conditions, the product 3y was obtained in 66% yield. There was no significant racemization at the chiral centre, as determined by high-performance liquid chromatography (Fig. 5a). The methoxyl and phthalimide groups were easily removed under the reported conditions49,63, affording L-tyrosine in an overall yield of 84%. The L-tyrosine could be easily transformed into 3,5-diodo-L-tyrosine (10) in 81% yield, which is a key intermediate in the synthesis of L-thyroxine64 (Fig. 5b).

Iopanoic acid, an iodine-containing radiocontrast medium used in cholecystography, could be easily prepared from the simple carboxylic acid 1d in three steps in an overall yield of 47% (ref. 65) (Fig. 5c), highlighting the synthetic importance of the newly developed method66,67.

Discussion

In conclusion, we have developed an efficient route for the palladium-catalysed directed β-C(sp²)-H arylation of carboxylic acids using the carboxyl group itself as a coordination centre. In this way, various non-natural amino acids have been directly prepared from phthaloylalanine in good to excellent yields. A series of aliphatic acids, including the challenging propionic acid and amino acids, have been shown to be compatible with this transformation, highlighting its potential synthetic utility. The important compounds 3,5-dideoxy-1-tyrosine and iopanoic acid have been readily prepared from simple carboxylic acids in good yields. This discovery of ligand-enabled carboxyl-promoted C(sp²)-H bond activation offers a convenient approach for the functionalization of C(sp³)-H bonds in aliphatic acids.

Methods

Typical procedure for Pd-catalysed C-H arylation of aliphatic acids.

To a 15 ml sealed glass vial was added phthaloylalanine (1a, 0.2 mmol, 43.8 mg), 4-idoanisole (0.2 mmol, 70.2 mg), Pd(OAc)₂ (5 mol%, 4.5 mg), Ag₂CO₃ (0.2 mmol, 55.2 mg, 1 equiv), K₂CO₃ (0.1 mmol, 13.8 mg, 0.5 equiv), Ac-Gly-OH (0.06 mmol, 7.0 mg, 0.3 equiv). The tube was then sealed and the reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to provide the desired arylated product 3a as a white solid (54.0 mg; yield 83%).

Data availability. The authors declare that all relevant data supporting the findings of this study are available within the article and its Supplementary Information files.

References

1. Glushakov, A. V., Dennis, D. M. & Martynuk, A. E. Specific inhibition of N-methyl-D-aspartate receptor function in rat hippocampal neurons by L-phenylalanine at concentrations observed during phenylketonuria. Mol. Psychiatr. 7, 359–367 (2002).
2. Hartman, G. D., Egbertson, M. S. & Lynch, J. R. Non-peptide fibrinogen receptor antagonists. 1. Discovery and design of exosite inhibitors. J. Med. Chem. 35, 4660–4662 (1992).
3. Jia, C., Kitamura, T. & Fujisawa, Y. Catalytic functionalization of amines and alkynes via C–H bond activation. Acc. Chem. Res. 34, 633–659 (2001).
4. Godula, K. & Sames, D. C. H-bond functionalization in complex organic synthesis. Science 312, 67–72 (2006).
5. Lyons, T. W. & Sanford, M. S. Palladium-catalyzed ligand-directed C–H functionalization reactions. Chem. Rev. 110, 1147–1169 (2010).
6. Engle, K. M., Mei, T.-S. & Yu, J.-Q. Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. Acc. Chem. Res. 45, 788–802 (2012).
7. McMurray, L., O’Hara, F. & Gaunt, M. J. Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. Chem. Soc. Rev. 40, 1885–1898 (2011).
8. Sun, C.-L., Li, B.-J. & Shi, Z.-J. Recent developments in natural product synthesis using metal-catalysed C–H bond functionalization. Chem. Rev. 111, 1293–1314 (2011).
9. Rouquet, G. & Chatani, N. Catalytic functionalization of C(sp²)-H and C(sp³)-H bonds by using bidentate directing groups. Angew. Chem., Int. Ed. 52, 11726–11743 (2013).
10. Ackermann, L. Carboxylate-assisted ruthenium-catalysed alkylne annihilations by C–H/Het–H bond functionalizations. Acc. Chem. Res. 47, 281–295 (2014).
11. Mei, T.-S., Giri, R. & Yu, J.-Q. Palladium-catalyzed monoselective ortho halogenation of c-h bonds assisted by counter cations: a complementary method to directed ortho lithiation. Angew. Chem., Int. Ed. 47, 5215–5219 (2008).
12. Giri, R. & Yu, J.-Q. Synthesis of 1,2- and 1,3-dicarboxylic acids via Pd(II)-catalysed carboxylation of aryl and vinyl C–H bonds. J. Am. Chem. Soc. 130, 14082–14083 (2008).
13. Chen, X., Engle, K. M. & 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).

ARTICLE NATURE COMMUNICATIONS | DOI: 10.1038/ncomms14904 | www.nature.com/naturecommunications
14. Wang, D.-H., Engle, K. M. & Yu, J.-Q. Ligand-enabled reactivity and selectivity in a synthetically versatile aryl C–H olefination. Science 327, 315–319 (2010).
15. Pickett, C. G. & Goolish, L. J. Carboxylic acids as directing groups for C–H bond functionalization. Chem. Eur. J. 22, 18654–18676 (2016).
16. Giri, R., Maugel, N. & Yu, J.-Q. Palladium-catalyzed methylation and arylation of sp² and sp³ C–H bonds in simple carboxylic acids. J. Am. Chem. Soc. 129, 3510–3511 (2007).
17. Jung, M. E. & Pizzi, G. gem-Diisubstituent effect: theoretical basis and synthetic applications. Chem. Rev. 105, 1735–1766 (2005).
18. Giri, R., Wasa, M. & Yu, J.-Q. Converting gem-dimethyl groups into cyclopropanes via Pd-catalyzed sequential C–H activation and radical cyclization. Org. Lett. 8, 5685–5688 (2006).
19. Giri, R., Chen, X. & Yu, J.-Q. Palladium-catalyzed asymmetric iodoniation of unactivated C–H bonds under mild conditions. Angew. Chem., Int. Ed. 44, 2113–2115 (2005).
20. Zaitsev, V. G. & Daugulis, O. Highly regioselective arylation of sp³ C–H bonds catalyzed by palladium acetate. J. Am. Chem. Soc. 127, 13135–13145 (2005).
21. Shabashov, D. & Daugulis, O. Auxiliary-assisted palladium-catalyzed arylation and alkylation of sp² and sp³ carbon – hydrogen bonds. J. Am. Chem. Soc. 132, 3965–3972 (2010).
22. Wei, Y., Tang, H. & Zeng, X. Pd(II)-catalyzed intermolecular arylation of unactivated C(sp³)-H bonds with alkyl bromides enabled by 8- aminoquinoline auxiliary. Org. Lett. 16, 2248–2251 (2014).
23. Shang, R., Ilije, L., Matsumoto, A. & Nakamura, E. β-arylation of carboxamides via iron-catalyzed C(sp³)-H bond activation. J. Am. Chem. Soc. 135, 6030–6032 (2013).
24. Shang, G., Huang, G. & Yao, P. Palladium-catalyzed unactivated β-methylene C(sp³)-H bond alkenylation of aliphatic alkenes and its application in a sequential C(sp³)-H/C(sp²)-H bond alkenylation. Org. Bio. Chem. 13, 697–701 (2015).
25. Monks, B. M., Fruchey, E. R. & Cook, S. P. Iron-catalyzed C(sp²)H alkylation of carboxamides with primary electrophiles. Angew. Chem., Int. Ed. 53, 11065–11069 (2014).
26. Zhang, S.-Y., Li, Q. & Chen, G. Palladium-catalyzed monoarylation of carboxamides with primary alkyl halides. J. Am. Chem. Soc. 135, 12135–12141 (2013).
27. Aono, Y., Tobisu, M. & Chatani, N. Palladium-catalyzed direct ethynylation of C(sp³)-H bonds in aliphatic carboxylic acid derivatives. J. Am. Chem. Soc. 133, 12380–12383 (2011).
28. Wang, B., Lu, C. & Chen, G. Palladium-catalyzed stereoretentive olefination of unactivated C(sp³)-H bonds with vinyl iodides at room temperature: synthesis of β-vinyl α-α-methylenecarboxylic acids. Org. Lett. 16, 6260–6263 (2014).
29. Han, G., Yang, X. & Yao, R. An efficient palladium-catalyzed C-H alkylation of unactivated methylene and methyl groups with cyclic hypervalent iodine I(3) oxidants. Angew. Chem., Int. Ed. 52, 13606–13610 (2013).
30. He, G., Zhang, S.-Y. & Chen, G. Stereo-differentiation of β-alkylated α-amino acids via palladium-catalyzed alkenylation of unactivated methane C(sp³)-H bonds with primary alkyl halides. J. Am. Chem. Soc. 135, 12135–12141 (2013).
31. Ano, Y., Tobisu, M. & Chatani, N. Palladium-catalyzed direct ethynylation of C(sp³)-H bonds in aliphatic carboxylic acid derivatives. J. Am. Chem. Soc. 133, 12380–12383 (2011).
32. Wang, B., Lu, C. & Chen, G. Palladium-catalyzed stereoretentive olefination of unactivated C(sp³)-H bonds with vinyl iodides at room temperature: synthesis of β-vinyl α-amino acids. Org. Lett. 16, 6260–6263 (2014).
33. Lin, C., Li, D. & Zhang, Y. Direct ortho-thiolation of amines and alkaloids by nickel catalysis. Org. Lett. 17, 1238–1331 (2015).
34. Lin, C., Yu, W. & Zhang, Y. Nickel-catalyzed direct thioetherification of β-(C(sp³)-H) bonds of aliphatic amides. Org. Lett. 17, 1340–1343 (2015).
35. Zhu, Q., J., D. & Xu, Y. Efficient palladium-catalyzed C-H fluorination of C(sp³)-H bonds: synthesis of β-fluorinated carboxylic acids. Org. Lett. 17, 3798–3801 (2015).
36. Zhang, J., Chen, H. & Zhang, Y. Palladium-catalyzed cyclization of aliphatic amides and terminal alkynes with silver-cocatalyst. J. Am. Chem. Soc. 137, 12990–12996 (2015).
37. Tran, L. D. & Daugulis, O. Nonnatural amino acid synthesis by using carbon-hydrogen bond functionalization methodology. Angew. Chem., Int. Ed. 51, 5188–5191 (2012).
38. Zhang, Q., Chen, K. & Shi, B.-F. Stereoselective synthesis of chiral α-ω-lactams through palladium(II)-catalyzed sequential monoarylation/amidation of C(sp³)-H bonds. Angew. Chem., Int. Ed. 52, 13588–13592 (2013).
39. Chen, K., Li, Z.-W. & Shi, Z.-L. Development of modifiable bidentate amino oxazoline directing groups for Pd-catalyzed arylation of secondary C-H bonds. Chem. Eur. J. 21, 7389–7393 (2015).
40. Misal Castro, L. C. & Chatani, N. Palladium(II)-catalyzed ortho C-H arylation/alkylation of N-benzoyl α-amino ester derivatives. Chem. Eur. J. 20, 4548–4553 (2014).
41. Gong, W., Zhang, G. & Yu, J.-Q. Site-selective C(sp³)-H functionalization of di-, tri-, and tetrapeptides at the N-terminus. J. Am. Chem. Soc. 136, 16940–16946 (2014).
42. Toba, T., Hu, Y. & Yu, J.-Q. β-(C(sp³)-H)-arylation of α-hydroxy acid derivatives utilizing amino acid as a directing group. Org. Lett. 17, 5966–5969 (2015).
Acknowledgements
We gratefully acknowledge financial support from the Natural Science Foundation of China (No. 21572149) and Young National Natural Science Foundation of China (No. 21402133, 21403148). The PAPD Project are also gratefully acknowledged.

Author contributions
Y.Z. and Yi.Z. conceived and designed the study. Y.Z. principally performed the experiments. X.C., G.L., C.Y. and J.Z. helped to conduct some experiments and collect data. Yi.Z. provided overall supervision and wrote the manuscript.

Additional information
Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing interests: The authors declare no competing financial interests.

Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/

How to cite this article: Zhu, Y. et al. Pd-catalysed ligand-enabled carboxylate-directed highly regioselective arylation of aliphatic acids. Nat. Commun. 8, 14904 doi: 10.1038/ncomms14904 (2017).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/