

ARTICLE

Received 9 Feb 2014 | Accepted 15 Jul 2014 | Published 20 Aug 2014

DOI: 10.1038/ncomms5707

Silver-catalysed direct amination of unactivated C–H bonds of functionalized molecules

Mingyu Yang¹, Bo Su¹, Yang Wang¹, Kang Chen¹, Xingyu Jiang¹, Yun-Fei Zhang¹, Xi-Sha Zhang¹, Guihua Chen¹, Ye Cheng¹, Zhichao Cao¹, Qing-Yun Guo¹, Lushun Wang² & Zhang-Jie Shi^{1,3,4}

Carbon-nitrogen bond formation from inert C–H bonds is an ideal organic transformation and a highly desirable method for the synthesis of N-containing molecules due to its high efficiency and atom economy. In this report, we develop a general reaction to achieve an unprecedented selective intramolecular amination of unactivated C–H bond in the absence of complex directing groups. Functionalized heterocyclic products are built up from readily available linear amines through simple and reliable silver catalysis, representing a new silver-based C–H functionalization. This method displays preference for primary sp^3 C–H bonds and exhibits distinct chemo- and regioselectivity compared to existing methods of direct amination (Hofmann-Löffler-Freytag reaction and nitrene insertion). The study highlights the manipulation of unfunctionalized groups in organic molecules to furnish complex structural units in the natural and bioactive molecules.

¹Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Green Chemistry Center, Peking University, Beijing 100871, China. ²Shenzhen Graduate School of Peking University, Shenzhen 518055, China. ³State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China. ⁴State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China. Correspondence and requests for materials should be addressed to Z.-J.S. (email: zshi@pku.edu.cn).

Direct functionalization of inert C–H bonds is of great importance with the potential to fundamentally change the strategy of organic synthesis^{1–3}. This chemistry can directly convert simple, cheap and readily available raw materials into highly valuable and useful products by the manipulation of inert unfunctionalized groups^{4–8}. The greatest challenge in this field is therefore to achieve the chemo- and regioselectivity in C–H functionalization among many C–H bonds in organic molecules, while keeping an array of functional groups intact. In addition to the issue of selectivity, there are more challenges toward the direct functionalization of sp³ C–H bonds, including: their high bond dissociation energy, inaccessibility of the independent C–H bonding and antibonding orbitals as well as steric hindrance. In the past decades, great progress has been made in such fields to convert aliphatic sp³ C–H bonds to C–C, C–O and C–B bonds in either stoichiometric or catalytic manner based on transition-metal catalysis^{9–15}. The present article focuses on the direct amination of inert C_{sp³}–H bonds, especially primary C–H bonds to construct aza-heterocycles.

Nitrogen-containing heterocycles, such as pyrrolidines, oxazolidines and tetrahydroquinolines, are dominant both in naturally occurring and man-made compounds, which often exhibit high levels of biological activity. In particular, the pyrrolidine and tetrahydroquinoline derivatives are privileged structural units in natural products and pharmaceuticals as exemplified by the structures of strychnine, folicanthaline and mesembrine and so on (Fig. 1a)^{16–20}. Many chemists have devoted themselves to searching for practical and convenient synthetic methods for accessing such ubiquitous structural units by direct oxidative amination of C–H bonds^{21–38}. In fact, efforts toward such a goal can be traced back to the historical Hofmann–Löffler–Freytag reaction in early 19th century and its advanced versions—the Baldwin and Doll modification and the Suárez modification^{21–29}. Another effective method for approaching direct amination of sp³ C–H bonds is to utilize nitrene insertion via transition-metal catalysis (Fig. 1b)^{30–33}. Amongst these, silver complexes were first founded to promote the nitrene insertion^{34,35}. Recently, Hennessy and Betley³⁶ developed a successful example for carrying out such transformation via Fe catalysis under mild

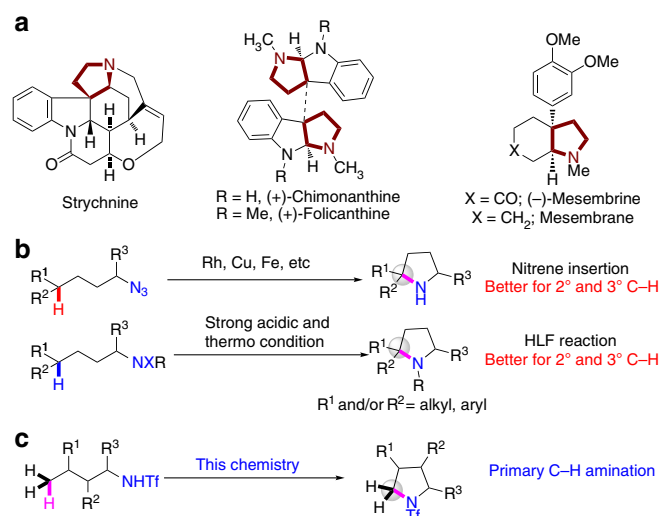


Figure 1 | Pyrroline structural active compounds and synthetic methods.

(a) Diversified structures of alkalines containing semi-unsubstituted pyrroline structural units. (b) Secondary and tertiary aliphatic C–H amination through transition-metal catalyzed nitrene insertion and Hofmann–Löffler–Freytag reaction (HLF reaction). (c) Rational design on direct primary C–H amination via transition-metal catalysis.

conditions. The power of this strategy has also been demonstrated in the synthesis of the natural product tetrodotoxin³⁷.

Notably, the selectivity in these two elegant transformations is highly dependent on the nature of C–H bonds. In general, secondary and tertiary C–H bonds are much more reactive than the primary one for both reactions. Primary C–H bonds could be accessed only in cases of conformational bias^{38,39}. To approach the primary selectivity of direct amination, Chen and Daugulis groups successfully developed a Pd-catalysed cyclization to specific ring systems by using a directing strategy while the manipulation of protecting group by multistep transformations limited its applications^{40–42}.

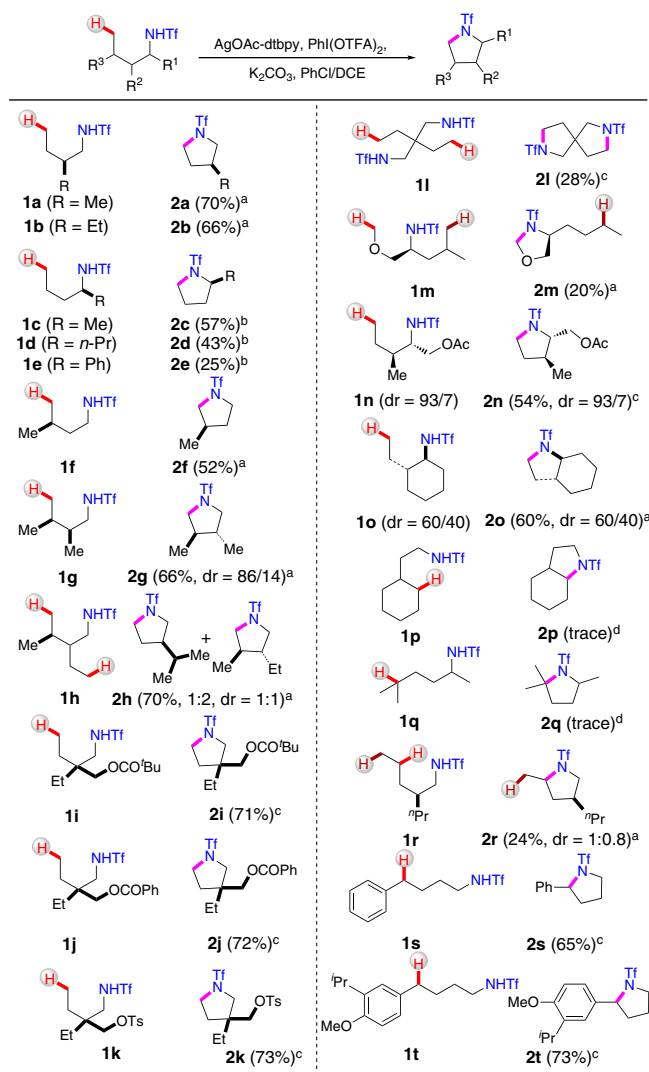


Figure 2 | Direct amination of primary and benzylic C–H bonds. The reaction scheme is shown above the table. ^aUnless otherwise noted, the reaction conditions were as follows: sulphonamide (0.25 mmol), AgOAc (20 mol%), PhI(OTFA)₂ (2.0 equiv), ligand (20 mol%), K₂CO₃ (2.0 equiv), PhCl/dichloroethane (DCE) (1.5 ml/1.5 ml), 120 °C, 12 h. The isolated yield was shown in the parentheses. ^bSulphonamide (0.25 mmol), AgOAc (20 mol%), PhI(OTFA)₂ (2.0 equiv), ligand (20 mol%), K₂CO₃ (4.0 equiv), PhF/Trichloroethane (1.5 ml/1.5 ml), 120 °C, 2 h; then another PhI(OTFA)₂ (2.0 equiv) was added and the reaction was continued for another 2 h. ^cSulphonamide (0.10 mmol), AgOAc (20 mol%), PhI(OTFA)₂ (2.0 equiv), ligand (20 mol%), K₂CO₃ (2.0 equiv), PhCl/DCE (1.0 ml/1.0 ml), 120 °C, 12 h. ^dThe yield was determined by ¹H NMR of the crude reaction mixture.

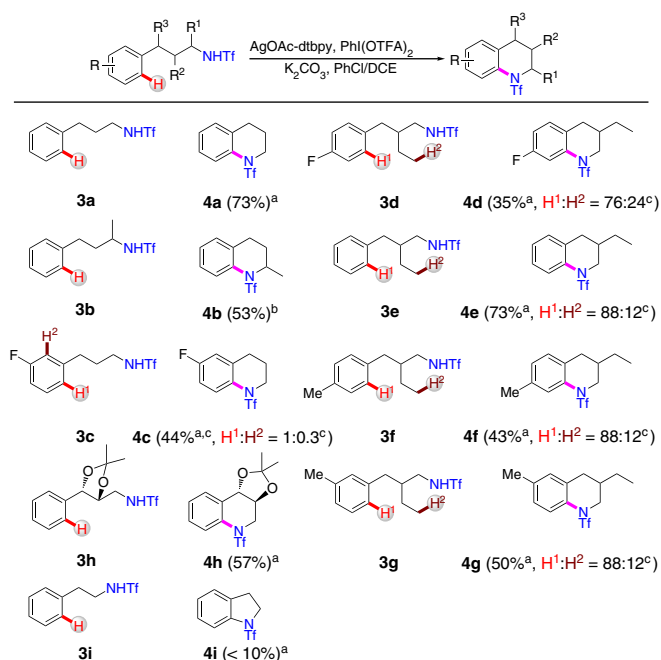


Figure 3 | Direct amination of aromatic C-H bonds. ^aUnless otherwise noted, the reaction conditions were as follows: sulphonamide (0.25 mmol), AgOAc (1.0 equiv), PhI(OTFA)₂ (2.0 equiv), ligand (20 mol%), K₂CO₃ (2.0 equiv), PhCl/dichloroethane (DCE) (1.5 ml/1.5 ml), 120 °C, 12 h. The isolated yield was shown in the parentheses. ^bSulphonamide (0.25 mmol), AgOAc (1.0 equiv), PhI(OTFA)₂ (2.0 equiv), ligand (20 mol%), K₂CO₃ (2.0 equiv), PhCl/DCE (1.0 ml/1.0 ml), 120 °C, 2 h; then another PhI(OTFA)₂ (2.0 equiv) was added and the reaction was continued for 2 h. ^cThe ratio was determined by crude ¹H NMR of the crude reaction mixture.

To achieve the primary selectivity to construct the abundant five-membered heterocyclic products from easily available amine derivatives without the requirement of complicated directing groups, new strategies and new catalytic systems are highly desirable^{43,44}. Notably, the compatibility with an array of the functionalities, the availability of the starting materials and the reliability of the new reaction system are important for potential applications. Herein, we report an unprecedented Ag-catalysed direct amination of primary sp³ C-H, secondary benzylic C-H and aryl C-H bonds from linear triflamide (1,1,1-trifluoromethanesulphonamide) under simple conditions. This represents a powerful approach to access structures widely existing in natural products and druggable molecules.

Results

C-H cyclizations. We chose the sulphonamides as the substrates due to their easy availability and broad application in organic synthesis. After extensive screening of a variety of transition-metal catalysts, oxidants, bases and ligands, we found that the combination of AgOAc, K₂CO₃, 4,4'-di-*t*-butyl-2,2'-bipyridine and PhI(OTFA)₂ gave the best results and the desired pyrrolidines were isolated from linear alkyltriflamide (Supplementary Tables 1-3). This method was successfully applied to a variety of triflamide derivatives, providing the cyclized products in fair to good yields (Fig. 2). Notably, the presence of substituents at the β-position is favourable for the transformation of products and good yields of **2a** and **2b** were obtained. α-Substitution decreased the yields and the examples indicate steric hindrance playing a key role in these annulations (**2c-e**). γ-Substituted linear triflamide afforded the pyrrolidine product in a fair yield (**2f**).

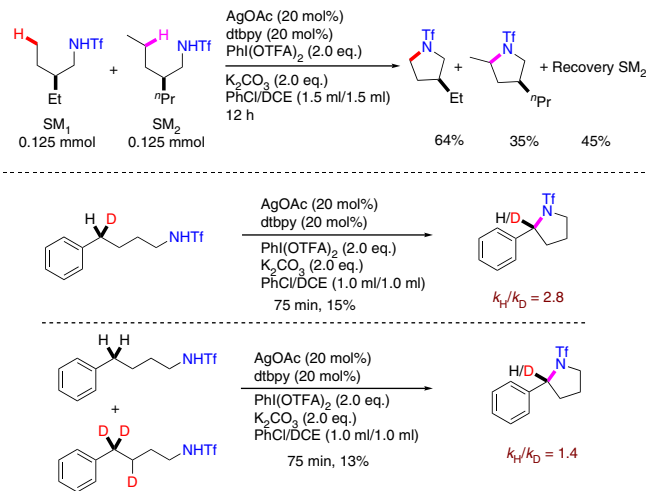


Figure 4 | Competition experiment and kinetic isotope effect. (a) Intermolecular competition experiment. (b) Intra/intermolecular kinetic isotope effect at benzylic position.

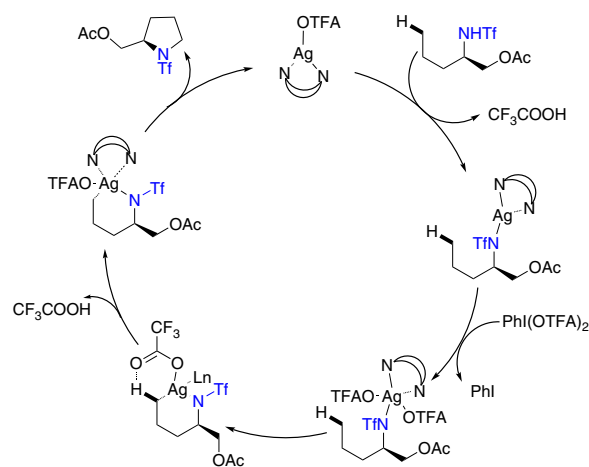


Figure 5 | The proposed catalytic cycle of direct amination via Ag catalysis. A concerted metallation/deprotonation (CMD) process.

Substrate **1g** afforded **2g** in a good yield with the expected preference for the *trans* isomer (86:14).

Substrate scope. We further expanded the substrate scope containing heteroatom functional groups. To our satisfaction, we found that O-containing functional groups are well-tolerated (**2i**, **2j**, **2k**). Remarkably, the excellent leaving group -OTs (4-tolylsulfonyl) was compatible. The spirocyclic **2l** was obtained from substrate **1l** through double cyclization, albeit in relatively low yield. The 1,2-amino alcohol derivative **1m** afforded oxazolidine **2m**, indicating the enhanced reactivity of the C-H bond adjacent to the heteroatom in spite that the reaction leaves much room for the improvement. The protected amino alcohol **1n** well proceeded the cyclization, with the retention of the stereogenic centres, providing an efficient method to produce unnatural proline derivatives. The five-six fused-ring compound **2o** was formed in a satisfactory yield, and the diastereoselectivity was controlled by the starting materials. Compared with primary C-H bonds, secondary or tertiary C-H bonds exhibit poor reactivity, which is distinct from Hofmann-Löffler-Freytag reactions or nitrene insertions, thus probably pointing out the different mechanistic pathway **1p** and **1q** (after 12 h, 59% of **1p** and 51% of **1q** were recovered). Moreover, five-membered ring is

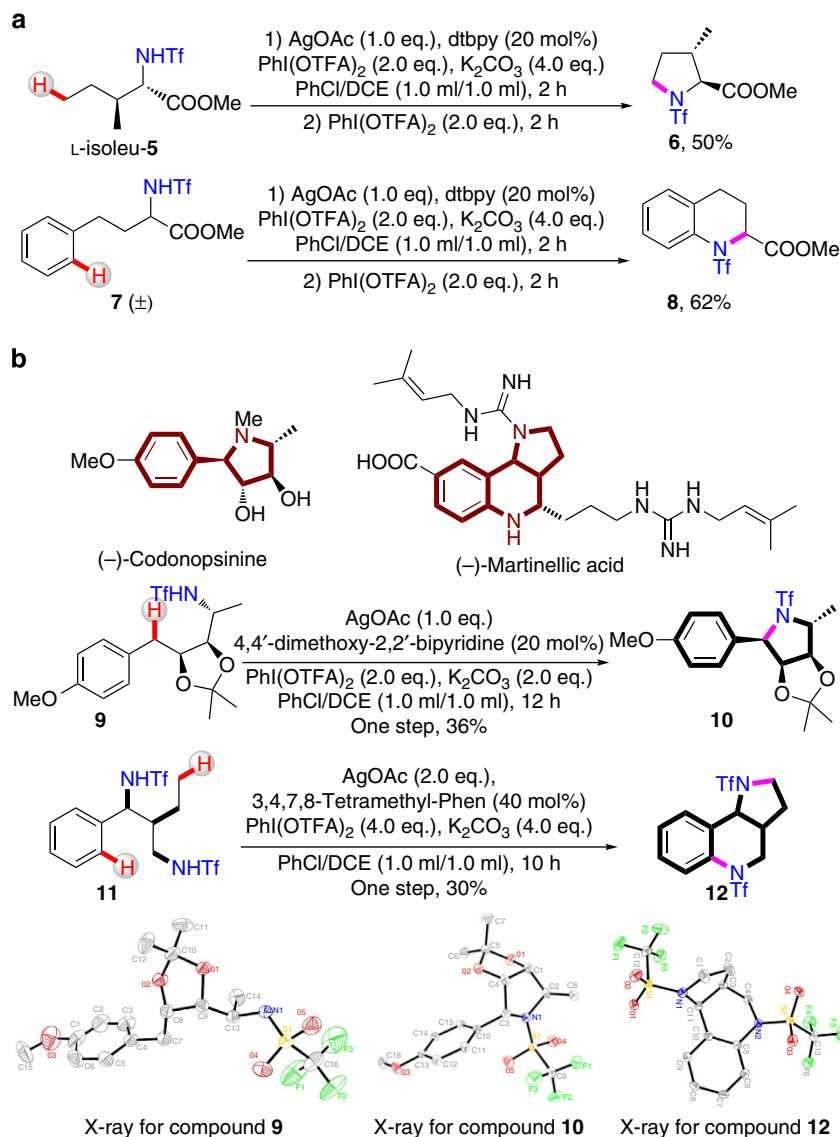


Figure 6 | Direct amination of linear amino acids derivatives. (a) Direct amination to produce substituted proline and tetrahydroquinolyl carboxylic acid derivatives from linear amino acids. (b) Applications to the synthesis of natural structural scaffolds.

much favoured even in the presence of more reactive primary C–H bonds for the formation of six-membered ring (24% of the **1r** was recovered). In contrast, the more reactive benzylic secondary C–H bonds in **1s** and **1t** could be addressed, expanding the scope for further applications.

Due to the distinct proposed pathway of such an amination from previous methods, we envisioned that this chemistry could be applicable for direct amination of aromatic C–H bonds. Thus, we extended this chemistry to build up the structurally important tetrahydroquinoline scaffolds from 3-arylpropyl triflamide **3** (Fig. 3). A series of γ -aryl substituted sulphonamides were examined and it was found that: (1) substituted aliphatic motifs at different positions do not obviously affect the efficiency; (2) electron-rich aromatics react preferentially; (3) compared with the inert primary sp^3 C–H bond, the sp^2 C–H bond on the aromatic ring is more reactive; and (4) notably, functionalized substrate **3h** also exhibited good reactivity, thus indicating great potential for their applications.

Competition experiments. Competition experiment between primary C–H bonds and secondary C–H bonds was carried

out (Supplementary Fig. 1). As predicted, the preference for amination is $C_{Me}-H \gg C_{methylene}-H$ (Fig. 4a). The KIE experiments have been conducted and we found that the intramolecular and intermolecular kinetic isotopic effect values at the benzylic position were 2.8 and 1.4, respectively (Supplementary Figs 2 and 3). On the basis of all these results, we proposed that this transformation was preferred to a proton abstraction pathway. With the assistance of strong σ -donor chelating N-ligands, the silver complex could be oxidized to Ag(III) after the ligand exchange. The hyperelectrophilic Ag(III) centre attacks the less steric hindered primary C–H bonds, followed by electrophilic deprotonation, which probably goes through a concerted metallation/deprotonation process in the presence of TFAO⁻ (1,1,1-trifluoroacetate anion) as a base. Afterwards, the reductive elimination produced the desired product, releasing Ag(I) to fulfil the catalytic cycle (Fig. 5). The steric and electronic outcomes based on different substrates are consistent with this hypothesis. In some cases, a small amount of the desired product is also observed in the absence of the Ag catalyst, indicating the competitive existing radical pathway, which may induce the low KIE in kinetic studies.

Use of amino esters. To show the power of this method, the protected linear amino acid esters **5** and **7** were submitted to the standard condition, and both 3-methylproline **6** and 2-tetrahydroquinonylcarboxylic ester **8** were obtained in satisfying yield. Moreover, more complicated **9** is also converted into tetrasubstituted pyrrolidine **10** as the epimer of natural (–)-codonopsinine with a sole diastereoisomer in a single operation. To our satisfaction, tricyclic scaffold **12**, containing the core structure of the natural product martinellidic acid, can be also constructed via double aminations, in which both primary C_{sp3}–H and aromatic C_{Ar}–H are aminated in a single operation, showing the beauty of this chemistry in organic synthesis.

In conclusion, we first developed an unprecedented site-selective amination of C–H bonds without the requirement of special complicated directing groups. N-heterocyclic products bearing complex functionalities were constructed from simple and easily available linear triflamines via reliable and easily handled Ag catalysis. The method displayed unique chemo- and regioselectivities that differed from the existing methods. This study highlighted the manipulation of unfunctionalized groups in organic molecules to furnish the complex privileged structural units in the synthesis of natural products and bioactive molecules using a new pathway that is broadly applicable in organic synthesis.

Methods

Materials. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. AgOAc and PhI(OTFA)₂ were purchased from J&K Chemical Co., Ltd. 4,4'-Di-tert-butyl-2,2'-dipyridyl was purchased from Sigma-Aldrich. Potassium carbonate, anhydrous (K₂CO₃) was purchased from Alfa Aesar used without any further purification. All the solvents and other reagents were directly used from the purchased without any further purification unless otherwise specified.

General spectroscopic methods. For NMR and X-ray analysis of compounds in this paper, see Supplementary Figs 1–140 and Supplementary Tables 4–6. NMR spectra were recorded on Bruker 400 and 500 M nuclear resonance spectrometers unless otherwise specified. CDCl₃ as solvent and tetramethylsilane (TMS) as the internal standard were employed. Chemical shift values for ¹H NMR and ¹³C NMR are referenced to residual solvent peaks (CHCl₃ in CDCl₃: 7.26 p.p.m. for ¹H, 77.00 p.p.m. for ¹³C). Chemical shifts are reported in δ p.p.m. All coupling constants (*J* values) were reported in Hertz (Hz). Data for ¹H NMR spectra are reported as follows: chemical shift (p.p.m., referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet), coupling constant (Hz) and integration. ¹⁹F NMR data was obtained on Varian 300 M nucleus resonance spectrometers. Column chromatography was performed on silica gel 200–300 mesh. HRMS (high-resolution mass spectra) were recorded on a Bruker Apex IV FTMS mass spectrometer (ESI) in the State-authorized Analytical Center at Peking University. ¹H NMR, ¹³C NMR and ESI spectra are provided for all compounds. See the Supplementary Methods for the characterization data for compounds not listed in this section.

Synthesis of 3-Methyl-1-(trifluoromethyl)sulfonyl-pyrrolidine 2a. Silver acetate (AgOAc, 8.3 mg, 0.05 mmol), 4,4'-Di-tert-butyl-2,2'-dipyridyl (dtbpy, 13.4 mg, 0.05 mmol), [Bis(trifluoroacetoxy)iodo]benzene (PhI(OTFA)₂, 215 mg, 0.5 mmol) and potassium carbonate (K₂CO₃, 69 mg, 0.5 mmol) were placed in a vial under air. Chlorobenzene (PhCl, 1.5 ml), triflamide **1a** (54.8 mg, 0.25 mmol), dichloroethane (1.5 ml) were sequentially added. The mixture was stirred at room temperature for 5 min and then was stirred for 12 h at 120 °C. After the reaction mixture was cooled to room temperature, direct flash silica gel column purification (eluent: 100 ml of PE; then PE/DCM/Et₂O 250/20/5) of the reaction solution provided **2a** (40 mg, 0.17 mmol) in 70% isolated yield. (Because the boiling point of desired product is low, the solvent should be evaporated under low temperature). Colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.63–3.71 (m, 2H), 3.52 (q, *J* = 8.0 Hz, 1H), 3.06 (t, *J* = 8.0 Hz, 1H), 2.40 (octet, *J* = 8.0 Hz, 1H), 2.13 (sext, *J* = 8.0 Hz, 1H), 1.65 (tq, *J* = 8.0, 12.0 Hz, 1H), 1.11 (d, *J* = 4.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 120.44 (q, *J* = 322.0 Hz), 55.32, 48.56, 33.90, 33.57, 17.00. HRMS–ESI (*m/z*): [M + Na]⁺ calcd for C₆H₁₀F₃NNaO₂S, 240.02765; found, 246.02789.

References

- Gutekunst, W. R. & Baran, P. S. C–H functionalization logic in total synthesis. *Chem. Soc. Rev.* **40**, 1976–1991 (2011).
- Cho, S. H., Kim, J. Y., Kwak, J. & Chang, S. Recent advances in the transition metal-catalyzed two fold oxidative C–H bond activation strategy for C–C and C–N bond formation. *Chem. Soc. Rev.* **40**, 5068–5083 (2011).
- Hili, R. & Yudin, A. K. Making carbon–nitrogen bonds in biological and chemical synthesis. *Nat. Chem. Biol.* **2**, 284–287 (2006).
- Godula, K. & Sames, D. C–H bond functionalization in complex organic synthesis. *Science* **312**, 67–72 (2006).
- Bergman, R. G. Organometallic chemistry: C–H activation. *Nature* **446**, 391–393 (2007).
- Lyons, T. W. & Sanford, M. S. Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.* **110**, 1147–1169 (2010).
- Buffat, M. G. P. Synthesis of piperidines. *Tetrahedron* **60**, 1701–1729 (2004).
- Brandi, A., Cicchi, S. & Cordero, F. M. Novel syntheses of azetidines and azetidiones. *Chem. Rev.* **108**, 3988–4035 (2008).
- Liégault, B. & Fagnou, K. Palladium-catalyzed intramolecular coupling of arenes and unactivated alkanes in air. *Organometallics* **27**, 4841–4843 (2008).
- Periana, R. A. *et al.* Platinum catalysts for the high-yield oxidation of methane to a methanol derivative. *Science* **280**, 560–564 (1998).
- Das, S., Incarvito, C. D., Crabtree, R. H. & Brudvig, G. W. Molecular recognition in the selective oxygenation of saturated C–H bonds by a dimanganese catalyst. *Science* **312**, 1941–1943 (2006).
- Michaudel, Q., Thevenet, D. & Baran, P. S. Intermolecular ritter-type C–H amination of unactivated sp³ carbons. *J. Am. Chem. Soc.* **134**, 2547–2550 (2012).
- Simmons, E. M. & Hartwig, J. F. Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol. *Nature* **483**, 70–73 (2012).
- Cho, J.-Y., Tse, M. K., Holmes, D., Maleczka, R. E. & Smith, M. R. Remarkably selective iridium catalysts for the elaboration of aromatic C–H bonds. *Science* **295**, 305–308 (2002).
- Chen, H., Schlecht, S., Semple, T. C. & Hartwig, J. F. Thermal, catalytic, regioselective functionalization of alkanes. *Science* **287**, 1995–1997 (2000).
- Franklin, A. S. & Overman, L. E. Total syntheses of pumiliotoxin A and allopumiliotoxin alkaloids. Interplay of pharmacologically active natural products and new synthetic methods and strategies. *Chem. Rev.* **96**, 505–522 (1996).
- Sridharan, V., Suryavanshi, P. A. & Menéndez, J. C. Advances in the chemistry of tetrahydroquinolines. *Chem. Rev.* **111**, 7157–7259 (2011).
- Knight, S. D., Overman, L. E. & Paireau, G. Asymmetric total syntheses of (–)- and (+)-strychnine and the wieland-gumlich aldehyde. *J. Am. Chem. Soc.* **117**, 5776–5788 (1995).
- Ma, D., Xia, C., Jiang, J. & Zhang, J. First total synthesis of martinellidic acid, a naturally occurring bradykinin receptor antagonist. *Org. Lett.* **3**, 2189–2191 (2001).
- Enamorado, M. F., Ondachi, P. W. & Comins, D. L. A five-step synthesis of (S)-macrostomine from (S)-nicotine. *Org. Lett.* **12**, 4513–4515 (2010).
- Hofmann, A. W. Action of bromine on amines in alkaline solutions. *Ber. Dtsch. Chem. Ges.* **16**, 558–560 (1883).
- Hofmann, A. W. Conhydrine derivatives. *Ber. Dtsch. Chem. Ges.* **18**, 5–23 (1885).
- Löffler, K. & Freytag, C. New method for the formation of N-alkylated pyrrolidines. *Ber. Dtsch. Chem. Ges.* **42**, 3427–3431 (1910).
- Wolff, M. E. Cyclization of N-halogenated amines (The Hofmann-Löffler reaction). *Chem. Rev.* **63**, 55–64 (1963).
- Baldwin, S. W. & Doll, R. J. Synthesis of the 2-aza-7-oxatricyclo[4.3.2.0^{4,8}]undecane nucleus of some gelsemium alkaloids. *Tetrahedron Lett.* **20**, 3275–3278 (1979).
- Carrau, R., Hernandez, R., Suárez, E. & Betancor, C. Intramolecular functionalization of N-cyanamide radicals: synthesis of 1,4- and 1,5-N-cyanopeimine compounds. *J. Chem. Soc. Perkin. Trans. 1*, 937–943 (1987).
- de Armas, P., Francisco, C. G., Hernandez, R., Salazar, J. A. & Suárez, E. Steroidal N-nitroamines. Part 4. Intramolecular functionalization of N-nitroamine radicals: synthesis of 1,4-nitroimine compounds. *J. Chem. Soc. Perkin. Trans. 1*, 3255–3265 (1988).
- Dorta, R. L., Francisco, C. G. & Suárez, E. Hypervalent organoiodine reagents in the transannular functionalisation of medium-sized lactams: synthesis of 1-azabicyclo compounds. *J. Chem. Soc. Chem. Commun.* 1168–1169 (1989).
- Francisco, C. G., Herrera, A. J. & Suárez, E. Intramolecular hydrogen abstraction reaction promoted by N-radicals in carbohydrates. Synthesis of chiral 7-oxa-2-azabicyclo[2.2.1]heptane and 8-oxa-6-azabicyclo[3.2.1]octane ring systems. *J. Org. Chem.* **68**, 1012–1017 (2003).
- Doyle, M. P. in *Comprehensive organometallic chemistry II* (ed. Hegedus, L. S.) (Pergamon Press, New York, 1995).
- Espino, C. G., Wehn, P. M., Chow, J. & Du Bois, J. Synthesis of 1,3-difunctionalized amine derivatives through selective C–H bond oxidation. *J. Am. Chem. Soc.* **123**, 6935–6936 (2001).
- Thu, H.-Y., Yu, W.-Y. & Che, C.-M. Intermolecular amidation of unactivated sp² and sp³ C–H bonds via palladium-catalyzed cascade C–H activation/nitrene insertion. *J. Am. Chem. Soc.* **128**, 9048–9049 (2006).

33. Davies, H. M. L. & Manning, J. R. Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion. *Nature* **451**, 417–424 (2008).
34. Cui, Y. & He, C. A Silver-catalyzed intramolecular amidation of saturated C–H bonds. *Angew. Chem. Int. Ed.* **43**, 4210–4212 (2004).
35. Li, Z., Capretto, D. A., Rahaman, R. & He, C. Silver-catalyzed intermolecular amination of C–H groups. *Angew. Chem. Int. Ed.* **46**, 5184–5186 (2007).
36. Hennessy, E. T. & Betley, T. A. Complex N-heterocycle synthesis via iron-catalyzed, direct C–H bond amination. *Science* **340**, 591–595 (2013).
37. Ahrendt, K. A., Bergman, R. G. & Ellman, J. A. Synthesis of a tricyclic mescaline analogue by catalytic C–H bond activation. *Org. Lett.* **5**, 1301–1303 (2003).
38. Corey, E. J. & Hertler, W. R. A study of the formation of haloamines and cyclic amines by the free radical decomposition of N-haloammonium ions (Hofmann-Löffler Reaction)¹. *J. Am. Chem. Soc.* **82**, 1657–1668 (1960).
39. Huard, K. & Lebel, H. N-tosylloxycarbamates as reagents in rhodium-catalyzed C–H amination reactions. *Chemistry* **14**, 6222–6230 (2008).
40. 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(sp³)–H and C(sp²)–H bonds at γ and δ positions. *J. Am. Chem. Soc.* **134**, 3–6 (2012).
41. Nadres, E. T. & Daugulis, O. Heterocycle synthesis via direct C–H/N–H coupling. *J. Am. Chem. Soc.* **134**, 7–10 (2012).
42. Zhang, S.-Y., He, G., Zhao, Y., Wright, W. A. & Chen, G. Efficient alkyl ether synthesis via palladium-catalyzed, picolinamide-directed alkoxylation of unactivated C(sp³)–H and C(sp²)–H bonds at remote positions. *J. Am. Chem. Soc.* **134**, 7313–7316 (2012).
43. Li, J.-J., Mei, T.-S. & Yu, J.-Q. Synthesis of indolines and tetrahydroisoquinolines from aryethylamines by Pd^{II}-catalyzed C–H activation reactions. *Angew. Chem. Int. Ed.* **47**, 6452–6455 (2008).
44. Mei, T.-S., Wang, X. & Yu, J.-Q. Pd(II)-catalyzed amination of C–H bonds using single-electron or two-electron oxidants. *J. Am. Chem. Soc.* **131**, 10806–10807 (2009).

Acknowledgements

We gratefully acknowledge the financial support by the '973' Project from the MOST of China (2013CB228102, 2009CB825300) and NSFC (Nos 20925207 and 21002001). M.Y. thanks China Postdoctoral science foundation Grant (2013M530465). We thank Professor E.P. Küding for assistance on the manuscript revision.

Author contributions

Z.-J.S. directed the research. M.Y. performed the experiments and analysed the data. B.S. worked on the synthesis of scaffold 12. Y.W. worked on the synthesis of scaffold 10 and some other starting materials. K.C., X.J., Y.-F.Z., X.-S.Z., G.C., Y.C., Z.C., Q.-Y.G. and L.W. worked on product isolation, purification and starting materials preparation. M.Y. and Z.-J.S. wrote the paper. M.Y. wrote the Supplementary Information and contributed other related materials.

Additional information

Accession codes: The X-ray crystallographic structures for 9,10,12 reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 1005416, 1005417,1005418. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Information accompanies this paper at <http://www.nature.com/naturecommunications>

Competing financial 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: Yang, M. *et al.* Silver-catalysed direct amination of unactivated C–H bonds of functionalized molecules. *Nat. Commun.* 5:4707 doi: 10.1038/ncomms5707 (2014).