ARTICLES
PUBLISHED ONLINE: 5 JANUARY 2014 | DOI: 10.1038/NCHEM.1836
nature chemistry

Ligand-enabled cross-coupling of C(sp^3)–H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis

Kelvin S. L. Chan, Masayuki Wasa, Ling Chu, Brian N. Laforteza, Masanori Miura and Jin-Quan Yu*

There have been numerous developments in C–H activation reactions in the past decade. Attracted by the ability to functionalize molecules directly at ostensibly unreactive C–H bonds, chemists have discovered reaction conditions that enable reactions of C(sp^2)–H and C(sp^3)–H bonds with a variety of coupling partners. Despite these advances, the development of suitable ligands that enable catalytic C(sp^3)–H bond functionalization remains a significant challenge. Herein we report the discovery of a mono-*N*-protected amino acid ligand that enables Pd(II)-catalysed coupling of γ-C(sp^3)–H bonds in triflyl-protected amines with arylboron reagents. Remarkably, no background reaction was observed in the absence of ligand. A variety of amine substrates and arylboron reagents were cross-coupled using this method. Arylation of optically active substrates derived from amino acids also provides a potential route for preparing non-proteinogenic amino acids.

Transition-metal-catalysed C–H activation directed by heteroatom directing groups has rapidly emerged as a fertile field for developing a diverse range of catalytic carbon–carbon and carbon–heteroatom bond-forming reactions[1–10]. During our efforts towards the development of Pd(II)-catalysed C–H activation reactions using a broad range of synthetically useful substrates, it became evident that controlling the reactivity and selectivity of catalysts through the use of external ligands, such as amino acids[11–16], pyridines and quinolines[17,18], is crucial to realizing their full potential as useful tools for synthesis. Previously, we demonstrated that weak coordinating functional groups, such as –COOH, –OH, –CN and –OMe, can cooperate with a mono-*N*-protected amino acid (MPAA) ligand on the Pd(II) centre to lower the transition-state energy and drastically accelerate the aromatic C(sp^2)–H activation step[12–16]. On the contrary, typically C(sp^3)–H activation reactions are promoted by a strong coordinating directing group without ligand assistance[19–24], except for a rare example of moderate rate enhancement by MPAA ligands in the lactonization of benzylic C(sp^3)–H bonds[25]. Therefore we embarked on the development of a ligand scaffold that can promote C(sp^3)–H activation of amine derivatives, a major class of synthetically useful compounds. Although a number of examples of arylation of γ-C(sp^3)–H bonds in amines using strong coordinating auxiliaries have been reported (Fig. 1a)[26–30], ligand-enabled activation of γ-C(sp^3)–H bonds in amines remains to be established. Herein we report the first example of Pd-catalysed cross-coupling of γ-C(sp^3)–H bonds of triflyl-protected amines (R–NHTf) with arylboron reagents through the use of a MPAA ligand. Remarkably, no background reaction is observed in the absence of the MPAA ligand (Fig. 1b), which thus implies the feasibility of using MPAA as a ligand to control the regioselectivity and enantioselectivity in the activation of C(sp^3)–H bonds. This reaction also allows for rapid generation of novel amino acids and amino alcohols that are broadly useful in syntheses of bioactive molecules and chiral compounds[31].

Results and discussion

Recently, the use of inert C–H bonds as coupling partners for Suzuki coupling with organoboron reagents has been made possible using Pd(II)/Pd(0) catalysis[19,32,33]. Although this new catalytic reaction provides a variety of new disconnections for carbon–carbon bond formation, cross-coupling of C(sp^3)–H bonds with organoboron reagents is generally limited to substrates derived from carboxylic acids[14,19,34,35]. The synthetic importance of amines guided us to focus on the development of cross-coupling of C(sp^3)–H bonds in alkylamines with arylboron reagents. In particular, we envisioned that rapid generation of a library of non-proteinogenic amino esters could be achieved via γ-C(sp^3)–H functionalization of substrates derived from amino acids such as **1**. Encouraged by our previous studies on triflamide-directed C(sp^2)–H olefination,

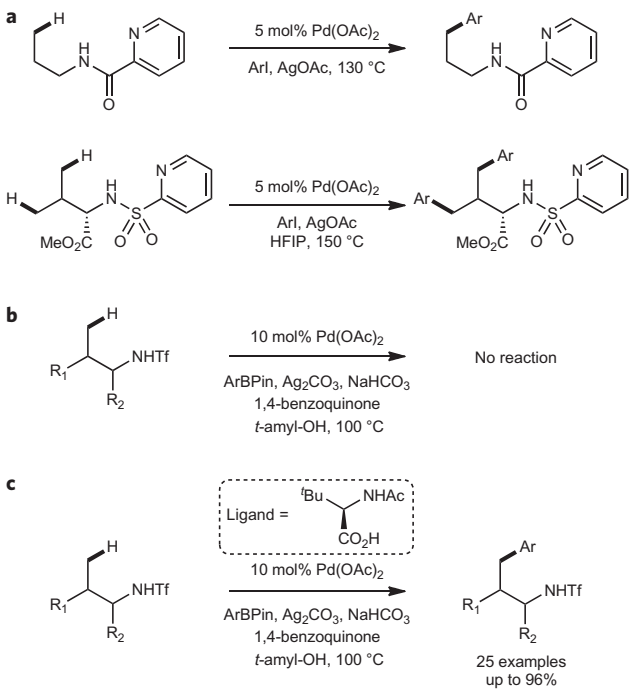
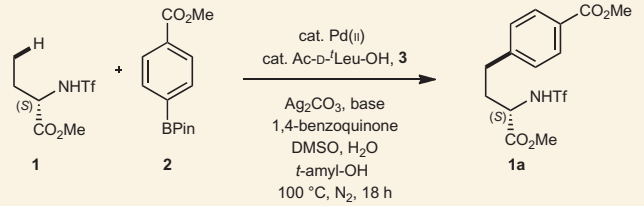


Figure 1 | Ligand-enabled C(sp^3)–H activation. a, C–H activation of aliphatic amines directed by strong σ chelation. **b**, Unreactive amine substrates in the absence of strong σ chelation. **c**, Ligand-enabled γ-C(sp^3)–H arylation of amines. HFIP, hexafluoroisopropanol.

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA. *e-mail: yu200@scripps.edu

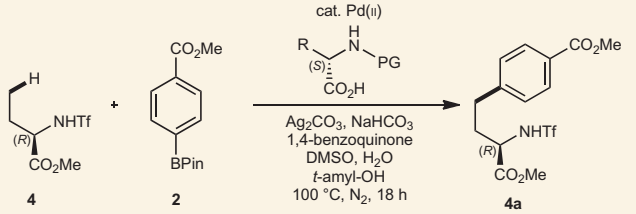
Table 1 | Optimization of reaction conditions.

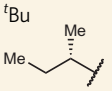


Entry	Ligand	Pd(II) catalyst	Base	Yield* (%)
1	Ac-L-Val-OH	$Pd(OAc)_2$	Na_2CO_3 (2.0 equiv.)	42
2	Ac-L-^{t}Leu-OH	$Pd(OAc)_2$	Na_2CO_3 (2.0 equiv.)	46
3	Ac-D-Val-OH	$Pd(OAc)_2$	Na_2CO_3 (2.0 equiv.)	57
4	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	Na_2CO_3 (2.0 equiv.)	65
5	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	None	0
6	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	Na_2HPO_4 (2.0 equiv.)	72
7	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	K_2HPO_4 (2.0 equiv.)	41
8	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	K_2CO_3 (2.0 equiv.)	41
9	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	Li_2CO_3 (2.0 equiv.)	69
10	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	$KHCO_3$ (4.0 equiv.)	63
11	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	$NaHCO_3$ (4.0 equiv.)	70
12	Ac-D-^{t}Leu-OH	$Pd(OAc)_2$	$NaHCO_3$ (6.0 equiv.)	74
13	Ac-D-^{t}Leu-OH	$Pd(TFA)_2$	$NaHCO_3$ (6.0 equiv.)	73
14	Ac-D-^{t}Leu-OH	$Pd(OTf)_2(MeCN)_4$	$NaHCO_3$ (6.0 equiv.)	82
15	Ac-D-^{t}Leu-OH	$Pd(OTf)_2(MeCN)_4$	$NaHCO_3$ (6.0 equiv.)	46†
16	Ac-D-^{t}Leu-OH	None	$NaHCO_3$ (6.0 equiv.)	0

Experiments were performed with 1 (0.2 mmol), 2 (0.4 mmol), Pd(II) catalyst (0.02 mmol), 3 (0.04 mmol), base, Ag_2CO_3 (0.4 mmol), 1,4-benzoquinone (0.1 mmol), DMSO (0.08 mmol), H_2O (1.1 mmol) in *t*-amyl-OH (1 ml) for 18 hours at 100 °C under N_2 atmosphere. *Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. †Performed with $Pd(OTf)_2(MeCN)_4$ (0.01 mmol) and 3 (0.02 mmol). BPin, boronic acid pinacol ester.

Table 2 | Screening of ligand for the C(sp^3)–H cross-coupling reaction.



Entry	Ligand		Yield* (%)
	R	PG	
1	^{i}Pr	Me	0
2	^{i}Pr	Formyl	18
3	^{i}Pr	Ac	68
4	^{i}Pr	Boc	12
5	^{i}Pr	Fmoc	15
6	^{i}Pr	Cbz	9
7	^{i}Pr	Troc	0
8	H	Ac	31
9	Me	Ac	50
10	^{n}Pr	Ac	68
11	^{i}Bu	Ac	57
12	^{t}Bu	Ac	75
13		Ac	82

Experiments were performed with 4 (0.2 mmol), 2 (0.4 mmol), $Pd(OTf)_2(MeCN)_4$ (0.02 mmol), ligand (0.04 mmol), $NaHCO_3$ (1.2 mmol), Ag_2CO_3 (0.4 mmol), 1,4-benzoquinone (0.1 mmol), DMSO (0.08 mmol), H_2O (1.1 mmol) in *t*-amyl-OH (1 ml) for 18 hours at 100 °C under N_2 atmosphere. *Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

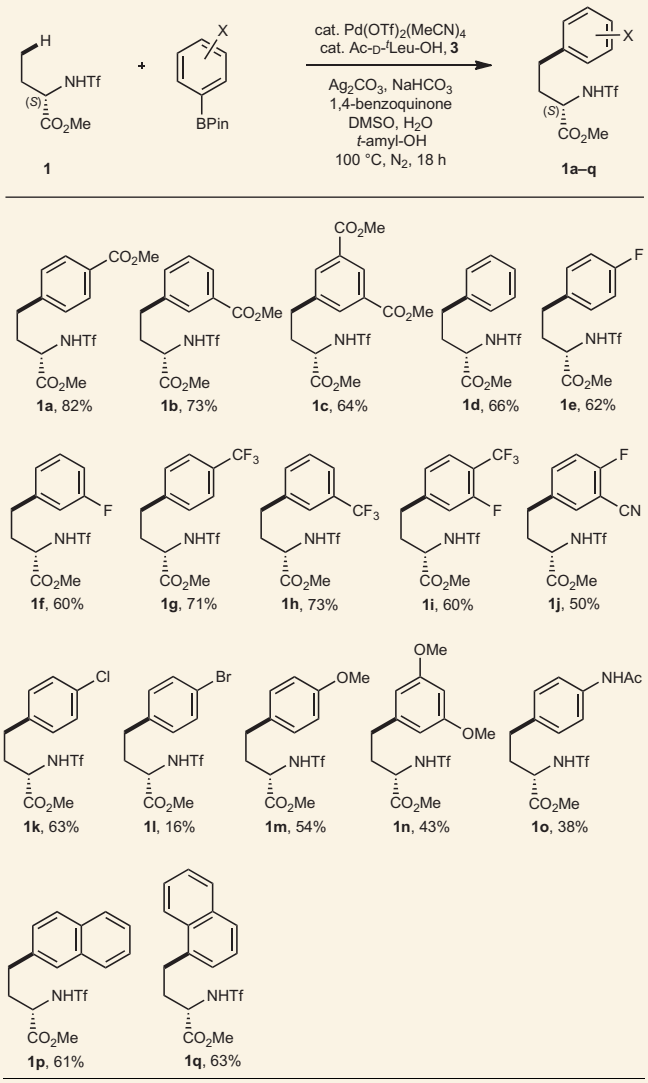
iodination and fluorination reactions[36–38], we attempted to cross-couple substrate 1 with 4-methoxycarbonylphenylboronic acid pinacol ester (2) under various previously established conditions. However, this failed to give any desired arylation product (Fig. 1b).

Analogous to the decisive role played by phosphine ligands in Suzuki coupling[39–41], we postulated that further development of this important transformation in C–H activation reactions would critically depend on the introduction and development of ligands. The ligands would alter the steric and electronic properties of the active catalyst, and could drastically accelerate C(sp^3)–H activation and subsequent coupling reactions (Fig. 1c). Previously, we demonstrated that a combination of weak σ coordination from the heteroatom-directing group of the substrate and bidentate coordination from a MPAA ligand on the Pd(II) centre could accelerate C(sp^2)–H activation[16]. We hypothesized that the triflamide could form an imidate-like moiety as a weak coordinating σ donor when deprotonated under basic conditions. We therefore began screening of conditions in the presence of MPAA ligands to achieve the cross-coupling of 1 with arylboron reagent 2.

To our delight, when we introduced *N*-acetyl-L-valine (Ac-L-Val-OH) into the reaction mixture, we obtained the desired γ-arylation product in 42% yield (Table 1, entry 1). Further screening of MPAA ligands revealed that L-amino ester 1 gave a higher yield when D-enantiomers of the MPAA ligands were used (Table 1, entries 1–4). For example, the L-enantiomer of *N*-acetyl-*tert*-leucine (Ac-^{t}Leu-OH) gave a yield of only 46%, but the D-enantiomer improved the yields to 65%. This provides evidence for the spatial (steric) impact of MPAA ligands on the reactivity of the catalytic system. Encouraged by these results, we proceeded to optimize the reaction conditions using Ac-L-^{t}Leu-OH, and found that the use of mild bases, such as $NaHCO_3$, was crucial to the reactivity. In general, sodium salts performed better than their corresponding potassium counterparts (Table 1, entries 6 and 7). Among the bases screened, carbonates and bicarbonates were found to be optimal, with 6.0 equiv. sodium bicarbonate affording the highest yield of 74% (Table 1, entries 8–12). To further improve the protocol, we also screened a variety of Pd(II) catalysts (Table 1, entries 13 and 14), and found that $Pd(OTf)_2(MeCN)_4$ (OTf = OSO_2CF_3) gave the highest yield of 82%. The use of 5 mol% Pd catalyst dropped the yield to 46% (Table 1, entry 15). The control experiment carried out in the absence of a Pd(II) catalyst gave no product (Table 1, entry 16). Further comprehensive screening data are presented in the Supplementary Information.

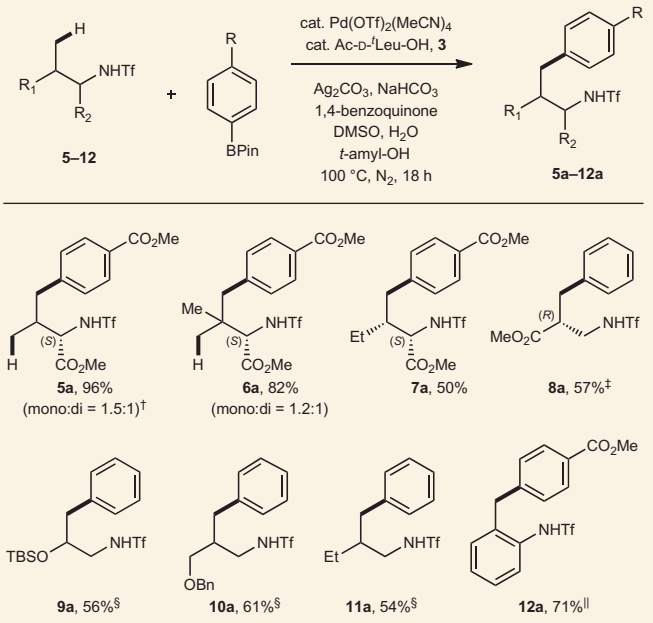
With preliminary conditions for the cross-coupling in hand, we proceeded to re-examine systematically the MPAA ligand in an effort to develop a high-yielding protocol (Table 2). As described in Table 1, there was an observed increase in yield when the L-enantiomer of the substrate reacted in the presence of the D-enantiomer of the MPAA ligand. To screen a variety of MPAA ligands,

Table 3 | Scope of arylboron reagents for the C(sp^3)–H cross-coupling reaction.



Experiments were performed with **1** (0.2 mmol), ArBPin (0.4 mmol), $Pd(OTf)_2(MeCN)_4$ (0.02 mmol), **3** (0.04 mmol), $NaHCO_3$ (1.2 mmol), Ag_2CO_3 (0.4 mmol), 1,4-benzoquinone (0.1 mmol), DMSO (0.08 mmol), H_2O (1.1 mmol) in *t*-amyl-OH (1 ml) for 18 hours at 100 °C under N_2 atmosphere. *Isolated yields.

Table 4 | Substrate scope for the C(sp^3)–H cross-coupling reaction.



Experiments were performed with substrate (0.2 mmol), ArBPin (0.4 mmol), $Pd(OTf)_2(MeCN)_4$ (0.02 mmol), **3** (0.04 mmol), $NaHCO_3$ (1.2 mmol), Ag_2CO_3 (0.4 mmol), 1,4-benzoquinone (0.1 mmol), DMSO (0.08 mmol), H_2O (1.1 mmol) in *t*-amyl-OH (1 ml) for 18 hours at 100 °C under N_2 atmosphere. *Isolated yields. †Diastereomeric ratio 4.7:1. ‡Performed with PhBPin (2.0 equiv.) and Ac-L-tLeu-OH (0.04 mmol). §Performed with PhBPin (2.0 equiv.) and Na_2CO_3 (2.0 equiv.). ‖Performed with $Pd(OTf)_2(MeCN)_4$ (0.01 mmol), **3** (0.02 mmol) and at 80 °C for eight hours.

we opted to perform the ligand screening on the more abundant L-enantiomer of the amino acids, and the D-enantiomer of the triflamide substrate (**4**). Our initial ligand screening focused on identifying the optimal *N*-protecting group by screening a variety of L-valine derivatives. We discovered that *N*-methyl-L-valine (Me-L-Val-OH, Table 2, entry 1) gave no product, but *N*-formyl-L-valine (For-L-Val-OH, Table 2, entry 2) afforded only 18% yield. Among the protecting groups screened, Ac-L-Val-OH (Table 2, entry 3) afforded the highest yield of 68%, but *N*-carbamates (Table 2, entries 4–7) performed poorly. Having identified the acetyl moiety as the best *N*-protecting group, we proceeded to identify the optimal side chain. *N*-acetyl-glycine (Ac-Gly-OH) and *N*-acetyl-L-alanine (Ac-L-Ala-OH) gave modest yields of 31% and 50%, respectively (Table 2, entries 8 and 9). Side chains that were more sterically hindered improved the yields, and among the protected amino acids screened, *N*-acetyl L-isoleucine (Ac-L-Ile-OH) afforded the highest yield of 82% (Table 2, entries 10–13).

Although we identified Ac-L-Ile-OH (Table 2, entry 13) as the most-effective MPAA ligand for the D-enantiomer of the substrate, we needed a D-enantiomer of the MPAA ligand to arylate the natural L-amino acid substrate. As Ac-D-Ile-OH is difficult to access, we decided to use the more economical Ac-D-*t*Leu-OH (**3**) as the ligand, which gave a comparable yield (Table 2, entry 12). With the optimized reaction conditions in hand, we cross-coupled L-amino ester **1** with a wide variety of arylboronic acid pinacol esters (ArBPins) in the presence of ligand **3** (Table 3). Ester groups at the *meta*- and *para*-positions of the phenyl ring gave yields from 64 to 82% (**1a**–**1c**), and the unsubstituted phenyl ring afforded a moderate yield of 66% (**1d**). There was no significant racemization at the chiral centre, as determined by high-performance liquid chromatography. The reaction conditions were amenable to a variety of fluorinated and trifluoromethyl-substituted aryls (**1e**–**1j**), which yielded from 60 to 73%, although the presence of a cyano group in **1j** lowered the yield to 50%. 4-Chlorophenylboronic acid pinacol ester reacted to give **1k** in a respectable yield of 63%, but bromo substitution in the coupling partner decreased the yield to only 16% (**1l**). The coupling partners that contained electron-donating methoxy and acetamide groups provided moderate yields from 38 to 54% (**1m**–**1o**). 1-Napthyl- and 2-napthylboronic acid pinacol esters, however, performed better and gave yields up to 63% (**1p** and **1q**). Heteroarylboronates that contained pyridine-, pyrazole- or furan-type motives were unreactive under these conditions (see Supplementary Information). In all cases, unreacted substrate was recovered fully and the methylene C(sp^3)–H bonds present did not react under these reaction conditions. Finally, we found that aryl iodides can replace the ArBPins as coupling partners, which suggests that the MPAA ligands also promote C(sp^3)–H arylation through a Pd(II)/Pd(IV) catalytic manifold (see Supplementary Information).

We then explored the amine substrate scope of the ligand-enabled cross-coupling protocol (Table 4). Gratifyingly, we were able to functionalize valine and *t*-leucine derivatives (**5** and **6**) to give a mixture of mono- and diarylated products in 96%

and 82% yield, respectively, with the monoarylated product **5a** obtained with a diastereomeric ratio of 4.7:1. We anticipate further optimization of ligands could improve the monoselectivity and diastereoselectivity. Arylation of isoleucine derivative **7** gave the corresponding product **7a** in 50% yield. The β-amino acid derivative **8** could also be arylated to give **8a** in 57% yield. We were also delighted to be able to functionalize *O*-TBS-protected 1,2-amino alcohol **9** (TBS = *t*-butyldimethylsilyl) and *O*-Bn-protected 1,3-amino alcohol **10** to give **9a** and **10a** in 56% and 61% yields, respectively. Aliphatic amine **11** could also undergo cross-coupling to give **11a** in 54% yield. We also found that the benzylic C(sp^3)–H bond in aniline **12** could be arylated with this method with lower catalyst and ligand loading, lower reaction temperature and a reduced reaction time (5 mol% Pd and 10 mol% ligand, 80 °C and eight hours).

Conclusion

In summary, we have developed Pd(II)-catalysed cross-coupling of γ-C(sp^3)–H bonds in R–NHTf with arylboron reagents using a MPAA ligand. γ-C(sp^3)–H bonds in a variety of alkyl amines, including 1,2- and 1,3-amino alcohols and amino acids, can be coupled with a diverse range of arylboron reagents. The demonstration of the ligand-enabled C(sp^3)–H bond activation provides guidance for further development of more-effective catalysts. The complete absence of background reaction without ligands bodes well for developing enantioselective C(sp^3)–H bond activation reactions.

Methods

In a 50 ml Schlenk tube, starting material **1** (49.8 mg, 0.2 mmol), 4-methoxy carbonylphenylboronic acid pinacol ester (**2**) (104.8 mg, 0.4 mmol), $Pd(OTf)_2(MeCN)_4$ (11.4 mg, 0.02 mmol), Ac-D-^{t}Leu-OH (**3**) (6.9 mg, 0.04 mmol), $NaHCO_3$ (100.8 mg, 1.2 mmol), Ag_2CO_3 (110.3 mg, 0.4 mmol) and 1,4-benzo quinone (10.8 mg, 0.1 mmol) were combined. The flask was evacuated and backfilled with N_2 three times, before a solution of dimethylsulfoxide (DMSO, 6.0 mg, 0.076 mmol), water (20 mg, 1.1 mmol) and *t*-amyl-OH (1 ml, 0.2 M) was added. The reaction mixture was then stirred at 100 °C for 18 hours. After being allowed to cool to room temperature, the mixture was diluted with a 1:1 mixture of hexanes:ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the resulting residue purified by column chromatography using an eluent of hexanes:ethyl acetate. The product, **1b**, was obtained as a light-yellow liquid (62.9 mg, 82%).

The above procedure to prepare **1b** is generally representative for all the products shown in Tables 3 and 4. Any deviations from this protocol are specified in the footnotes of the tables.

Received 23 August 2013; accepted 25 November 2013; published online 5 January 2014

References

1. Engle, K. M., Mei, T-S., Wasa, M. & Yu, J-Q. Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. *Acc. Chem. Res.* **45,** 788–802 (2012).
2. Lyons, T. W. & Sanford, M. S. Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.* **110,** 1147–1169 (2010).
3. Daugulis, O., Do, H-Q. & Shabashov, D. Palladium- and copper-catalyzed arylation of carbon–hydrogen bonds. *Acc. Chem. Res.* **42,** 1074–1086 (2009).
4. Wencel-Delord, J., Dröge, T., Liu, F. & Glorius, F. Towards mild metal-catalyzed C–H bond activation. *Chem. Soc. Rev.* **40,** 4740–4761 (2011).
5. Satoh, T. & Miura, M. Oxidative coupling of aromatic substrates with alkynes and alkenes under rhodium catalysis. *Chem. Eur. J.* **16,** 11212–11222 (2010).
6. Kakiuchi, F. *et al.* Catalytic addition of aromatic carbon–hydrogen bonds to olefins with the aid of ruthenium complexes. *Bull. Chem. Soc. Jpn* **68,** 62–83 (1995).
7. 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).
8. Guimond, N., Gorelsky, S. I. & Fagnou, K. Rhodium(III)-catalyzed heterocycle synthesis using an internal oxidant: improved reactivity and mechanistic studies. *J. Am. Chem. Soc.* **133,** 6449–6457 (2011).
9. Park, S. H., Kim, J. Y. & Chang, S. Rhodium-catalyzed selective olefination of arene esters via C–H bond activation. *Org. Lett.* **13,** 2372–2375 (2011).
10. Ackermann, L. & Pospech, J. Ruthenium-catalyzed oxidative C–H bond alkenylations in water: expedient synthesis of annulated lactones. *Org. Lett.* **13,** 4153–4155 (2011).
11. Shi, B-F., Maugel, N., Zhang, Y-H. & Yu, J-Q. Pd^{II}-catalyzed enantioselective activation of C(sp^2)–H and C(sp^3)–H bonds using monoprotected amino acids as chiral ligands. *Angew. Chem. Int. Ed.* **47,** 4882–4886 (2008).
12. Wang, D-H., Engle, K. M., Shi, B-F. & Yu, J-Q. Ligand-enabled reactivity and selectivity in a synthetically versatile aryl C–H olefination. *Science* **327,** 315–319 (2010).
13. Engle, K. M., Wang, D-H. & Yu, J-Q. Ligand-accelerated C–H activation reactions: evidence for a switch of mechanism. *J. Am. Chem. Soc.* **132,** 14137–14151 (2010).
14. Wasa, M., Engle, K. M., Lin, D. W., Yoo, E. J. & Yu, J-Q. Pd(II)-catalyzed enantioselective C–H activation of cyclopropanes. *J. Am. Chem. Soc.* **133,** 19598–19601 (2011).
15. Engle, K. M., Thuy-Boun, P. S., Dang, M. & Yu, J-Q. Ligand-accelerated cross-coupling of C(sp^2)–H bonds with arylboron reagents. *J. Am. Chem. Soc.* **133,** 18183–18193 (2011).
16. Baxter, R. D., Sale, D., Engle, K. M., Yu, J-Q. & Blackmond, D. G. Mechanistic rationalization of unusual kinetics in Pd-catalyzed C–H olefination, *J. Am. Chem. Soc.* **134,** 4600–4606 (2012).
17. Wasa, M. *et al.* Ligand-enabled methylene C(sp^3)–H bond activation with a Pd(II) catalyst. *J. Am. Chem. Soc.* **134,** 18570–18572 (2012).
18. Kubota, A., Emmert, M. H. & Sanford, M. S. Pyridine ligands as promoters in $Pd^{II/0}$-catalyzed C–H olefination reactions. *Org. Lett.* **14,** 1760–1763 (2012).
19. Chen, X., Goodhue, C. E. & Yu, J-Q. Palladium-catalyzed alkylation of sp^2 and sp^3 C–H bonds with methylboroxine and alkylboronic acids: two distinct C–H activation pathways. *J. Am. Chem. Soc.* **128,** 12634–12635 (2006).
20. Baudoin, O. Transition metal-catalyzed arylation of unactivated C(sp^3)–H bonds. *Chem. Soc. Rev.* **40,** 4902–4911 (2011).
21. Ano, Y., Tobisu, M. & Chatani, N. Palladium-catalyzed direct ethynylation of C(sp^3)–H bonds in aliphatic carboxylic acid derivatives. *J. Am. Chem. Soc.* **133,** 12984–12986 (2011).
22. Chen, K., Hu, F., Zhang, S-Q. & Shi, B-F. Pd(II)-catalyzed alkylation of unactivated C(sp^3)–H bonds: efficient synthesis of optically active unnatural α-amino acids. *Chem. Sci.* **4,** 3906–3911 (2013).
23. Shang, R., Ilies, L., Matsumoto, A. & Nakamura, E. β-Arylation of carboxamides via iron-catalyzed C(sp^3)−H bond activation. *J. Am. Chem. Soc.* **135,** 6030–6032 (2013).
24. He, G. & Chen, G. A practical strategy for the structural diversification of aliphatic scaffolds through the palladium-catalyzed picolinamide-directed remote functionalization of unactivated C(sp^3)–H bonds. *Angew. Chem. Int. Ed.* **50,** 5192–5196 (2011).
25. Novak, P., Correa, A., Gallardo-Donaire, J. & Martin, R. Synergistic palladium-catalyzed C(sp^3)–H activation/C(sp^3)–O bond formation: a direct, step-economical route to benzolactones. *Angew. Chem. Int. Ed.* **50,** 12236–12239 (2011).
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. Reddy, B. V. S., Reddy, L. R. & Corey, E. J. Novel acetoxylation and C–C coupling reactions at unactivated positions in α-amino acid derivatives. *Org. Lett.* **8,** 3391–3394 (2006).
28. 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)–H and C(sp^2)–H bonds at γ and δ positions. *J. Am. Chem. Soc.* **134,** 3–6 (2012).
29. 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).
30. Chen, G. *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).
31. Liu, C. C. & Schultz, P. G. Adding new chemistries to the genetic code. *Annu. Rev. Biochem.* **79,** 413–444 (2010).
32. 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).
33. Yamaguchi, K., Kondo, H., Yamaguchi, J. & Itami, K. Aromatic C–H coupling with hindered arylboronic acids by Pd/Fe dual catalysts. *Chem. Sci.* **4,** 3753–3757 (2013).
34. Giri, R. *et al.* Palladium-catalyzed methylation and arylation of sp^2 and sp^3 C–H bonds in simple carboxylic acids. *J. Am. Chem. Soc.* **129,** 3510–3511 (2007).

35. Wang, D-H., Wasa, M., Giri, R. & Yu, J-Q. Pd(II)-catalyzed cross-coupling of sp^3 C–H bonds with $sp^2$and sp^3 boronic acids using air as the oxidant. *J. Am. Chem. Soc.* **130,** 7190–7191 (2008).
36. Li, J-J., Mei, T-S. & Yu, J-Q. Synthesis of indolines and tetrahydroisoquinolines from arylethylamines by Pd^{II}-catalyzed C–H activation reactions. *Angew. Chem. Int. Ed.* **47,** 6452–6455 (2008).
37. 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).
38. Wang, X., Mei, T-S. & Yu, J-Q. Versatile $Pd(OTf)_2{\cdot}2H_2O$-catalyzed *ortho*-fluorination using NMP as a promoter. *J. Am. Chem. Soc.* **131,** 7520–7521 (2009).
39. Chemler, S. R., Trauner, D. & Danishefsky, S. J. The *B*-alkyl Suzuki–Miyaura cross-coupling reaction: development, mechanistic study, and applications in natural product synthesis. *Angew. Chem. Int. Ed.* **40,** 4544–4568 (2001).
40. Doucet, H. Suzuki–Miyaura cross-coupling reactions of alkylboronic acid derivatives or alkyltrifluoroborates with aryl, alkenyl or alkyl halides and triflates. *Eur. J. Org. Chem.* 2013–2030 (2008).
41. Molander, G. & Canturk, B. Organotrifluoroborates and monocoordinated palladium complexes as catalysts – a perfect combination for Suzuki–Miyaura coupling. *Angew. Chem. Int. Ed.* **48,** 9240–9261 (2009).

Acknowledgements

This work was supported by The Scripps Research Institute and the National Institutes of Health (NIGMS, 2R01GM084019). K.S.L.C. thanks the Agency for Science, Technology and Research (A*STAR) Singapore for a predoctoral fellowship. M.W. thanks Bristol Myers Squibb for a predoctoral fellowship. M.M. thanks Astellas Pharma Inc. for a postdoctoral fellowship. This is The Scripps Research Institute (TSRI) manuscript no. 25049.

Author contributions

K.S.L.C. conceived the study, principally performed the experiments and wrote the manuscript, M.W. helped with conceiving the study and preparing the manuscript, L.C. and B.N.L. performed experiments on coupling-partner scope, M.M. helped with identifying the deprotection strategy and J-Q.Y. provided overall supervision. All the authors discussed the results and commented on 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 sed to J-Q.Y.

Competing financial interests

The authors declare no competing financial interests.