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Ligand-Enabled Cross-Coupling of C(sp³)–H Bonds with Arylboron Reagents via Pd(II)/Pd(0) Catalysis

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Abstract

There have been numerous developments in C–H activation reactions in the past decade. Attracted by the ability to directly functionalize molecules at ostensibly unreactive C–H bonds, chemists have discovered reaction conditions that enable reaction 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. Here, we report the discovery of a mono-*N*-protected amino acid (MPAA) ligand that enables Pd(II)-catalyzed coupling of γ-C(sp^3)–H bonds in triflyl-protected amines (R–NHTf) 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 amino acid-derived substrates also provides a potential route for preparing non-protenogenic amino acids.

Transition metal-catalyzed 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)-catalyzed C–H activation reactions using a broad range of synthetically useful substrates, it has become 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 for realizing their full potential as useful tools for synthesis. We have previously demonstrated that weak coordinating functional groups such as -COOH, -OH, -CN, and -OMe can cooperate with a mono-*N*-protected amino acid

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Supplementary information and chemical compound information are available in the online version of the paper.

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. J.-Q. Y. provided overall supervision. All the authors discussed the results and commented on the manuscript.

Competing Financial Interests

The authors declare no competing financial interests.

(MPAA) ligand on the Pd(II) center to lower the transition state energy and drastically accelerate the aromatic C(sp^2)–H activation step[11–16]. On the contrary, C(sp^3)–H activation reactions are typically promoted by a strong coordinating directing group without ligand acceleration[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]. We therefore 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 of γ-C(sp^3)–H bonds in amines using strongly coordinating auxiliaries have been reported (Figure 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-catalyzed cross-coupling of γ-C(sp^3)–H bonds of triflyl-protected amines with arylboron reagents through the use of a mono-protected amino acid ligand (MPAA). Remarkably, no background reaction is observed in the absence of the MPAA ligand (Figure 1b), thus implying 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 diverse libraries of novel amino acids and amino alcohols that are broadly useful in syntheses of bioactive molecules and chiral compounds.[31]

Results and Discussion

The use of inert C–H bonds as coupling partners for Suzuki coupling with organoboron reagents has recently been made possible using Pd(II)/Pd(0) catalysis[19, 32, 33]. While 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 currently limited to carboxylic acid-derived substrates[14, 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-protenogenic amino esters could be achieved via γ-C(sp^3)–H functionalization of amino acid-derived substrates such as **1**. Encouraged by our previous studies on triflamide-directed C(sp^2)–H olefination, 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, it failed to give any desired arylation product (Figure 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 (Figure 1c). We have previously 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) center 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 extensive 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 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** gives a higher yield when D-enantiomers of the MPAA ligands were used (Table 1, entries 1–4). For example, the L-enantiomer of Ac-^{t}Leu-OH gave only 46% yield, while the D-enantiomer improved the yields to 65%. This provided 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 for 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 equivalents of 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 $Pd(OTf)_2(MeCN)_4$ 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 is presented in the Supplementary Information.

With preliminary conditions for the cross-coupling in hand, we proceeded to systematically reexamine 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 was reacted in the presence of the D-enantiomer of the MPAA ligand. In order to screen a variety of MPAA ligands, 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 Me-Val-OH (Table 2, entry 1) gave no product, while For-Val-OH (Table 2, entry 2) afforded only 18% yield. Among the protecting groups screened, Ac-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 then proceeded to identify the optimal side chain. Ac-Gly-OH and Ac-Ala-OH gave modest yields of 31% and 50%, respectively (Table 2, entries 8 and 9). More sterically hindered side chains improved the yields, and among the protected amino acids screened, Ac-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 in order to arylate the natural L-amino acid substrate. Since 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 in the presence of ligand **3** (Table 3). Ester groups at the *meta*- and *para*-positions of the phenyl ring gave yields from 64–82% (**1a**–**1c**), and the unsubstituted phenyl ring afforded a moderate yield of 66% (**1d**). There was no significant racemization at the chiral center as determined by HPLC. The reaction conditions were amenable to a variety of fluorinated and

trifluoromethyl-substituted aryls (**1e**–**1j**), yielding from 60–73%, 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 containing electron-donating methoxy and acetamide groups provided moderate yields from 38–54% (**1m–1o**). 1-napthyl- and 2-napthylboronic acid pinacol esters, however, performed better and gave yields up to 63% (**1p** and **1q**). Heteroarylboronates containing pyridine, pyrazole or furan-type motives were unreactive under these conditions (see Supplementary Information). In all cases, unreacted substrate is fully recovered and the methylene C(sp^3)–H bonds present are not reacted under these reaction conditions. Finally, we found that aryl iodides can replace the arylboronic acid pinacol esters as coupling partners suggesting 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 di-arylated products in 96% and 82% yield respectively, with the mono-arylated product **5a** obtained with a diastereomeric ratio of 4.7:1. We anticipate further optimization of ligands could improve the mono-selectivity 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**, 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. Notably, we also found that the benzylic C(sp^3)–H bond in aniline **12** could also be arylated with this method using a lowered catalyst and ligand loading, and reaction temperature, as well as reduced reaction time (5 mol% Pd and 10 mol% ligand, 80 °C and 8 h).

Conclusion

In summary, we have developed Pd(II)-catalyzed cross-coupling of γ-C(sp^3)–H bonds in triflyl-protected amines (R–NHTf) with arylboron reagents using a mono-*N*-protected amino acid (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-methoxycarbonylphenylboronic 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-benzoquinone

(10.8 mg, 0.1 mmol) were combined. The flask was evacuated and backfilled with N_2 three times, before a solution of dimethylsulfoxide (6.0 mg, 0.076 mmol), water (20 mg, 1.1 mmol), and ^{t}AmylOH (1 mL, 0.2 M) was added. The reaction mixture was then stirred at 100 °C for 18 h. 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 legend of the tables.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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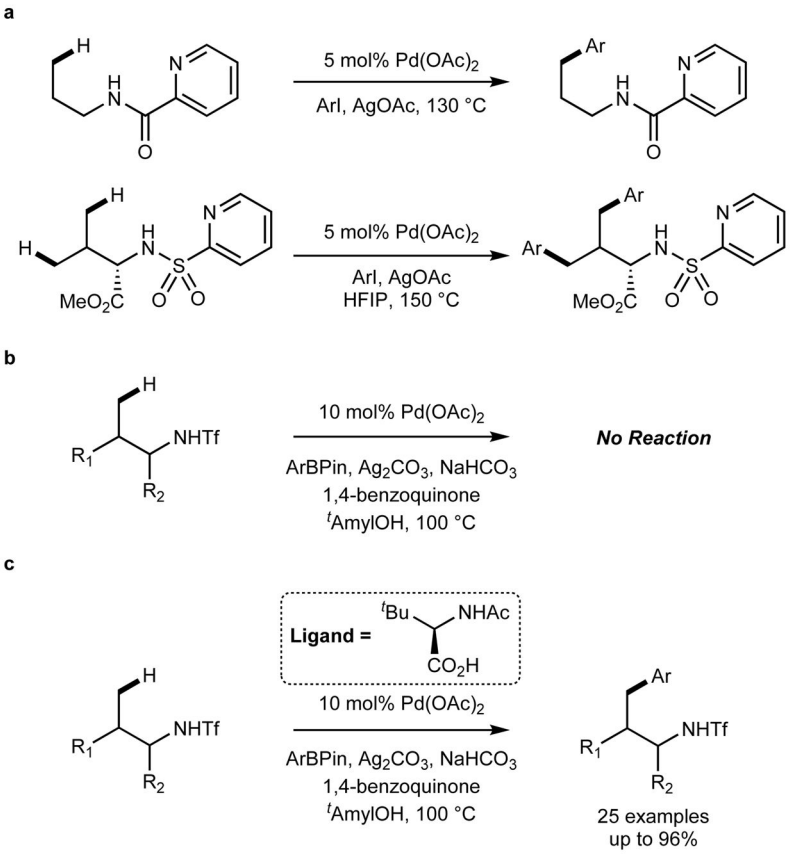


Figure 1. Ligand-enabled C(sp^3)–H activation

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. ArBPin = arylboronic acid pinacol ester.

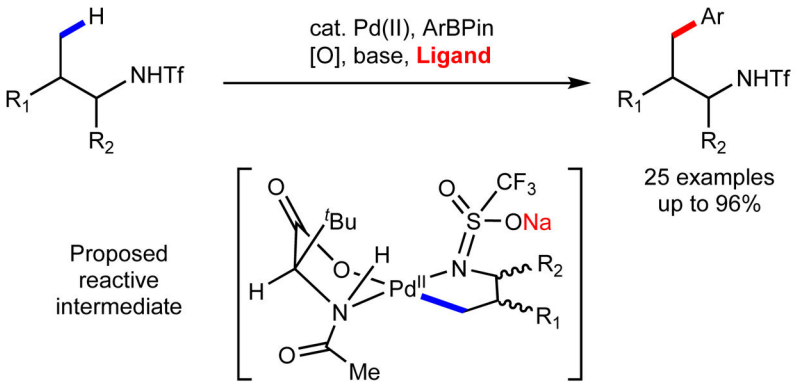
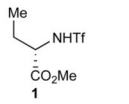


Figure 2.

Ligand-Enabled Cross-Coupling of C(sp3)–H Bonds with Arylboron Reagents via Pd(II)/Pd(0) Catalysis, and proposed reactive intermediate.



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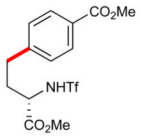

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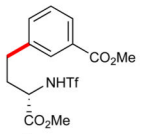

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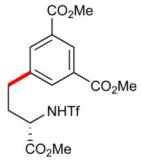

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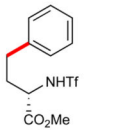

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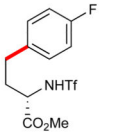

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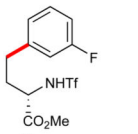

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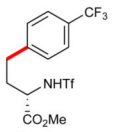
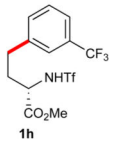
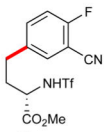


1g (*S*)-methyl 4-(4-(trifluoromethyl)phenyl)-2-(trifluoromethylsulfonamido)butanoate

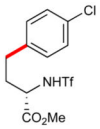


1h (*S*)-methyl 4-(3-(trifluoromethyl)phenyl)-2-(trifluoromethylsulfonamido)butanoate

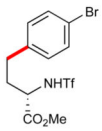
1i (*S*)-methyl 4-(3-fluoro-4-(trifluoromethyl)phenyl)-2-(trifluoromethylsulfonamido)butanoate



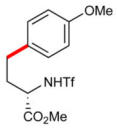
1j (*S*)-methyl 4-(3-cyano-4-fluorophenyl)-2-(trifluoromethylsulfonamido)butanoate



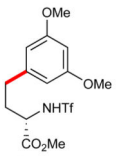
1k (*S*)-methyl 4-(4-chlorophenyl)-2-(trifluoromethylsulfonamido)butanoate



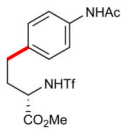
1l (*S*)-methyl 4-(4-bromophenyl)-2-(trifluoromethylsulfonamido)butanoate



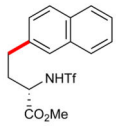
1m (*S*)-methyl 4-(4-methoxyphenyl)-2-(trifluoromethylsulfonamido)butanoate



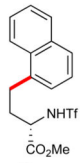
1n (*S*)-methyl 4-(3,5-dimethoxyphenyl)-2-(trifluoromethylsulfonamido)butanoate



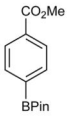
1o (*S*)-methyl 4-(4-acetamidophenyl)-2-(trifluoromethylsulfonamido)butanoate



1p (*S*)-methyl 4-(naphthalen-2-yl)-2-(trifluoromethylsulfonamido)butanoate



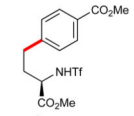
1q (*S*)-methyl 4-(naphthalen-1-yl)-2-(trifluoromethylsulfonamido)butanoate



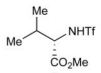
2 methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

3 (*R*)-2-acetamido-3,3-dimethylbutanoic acid

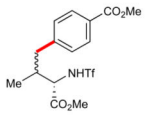
4 (*R*)-methyl 2-(trifluoromethylsulfonamido)butanoate



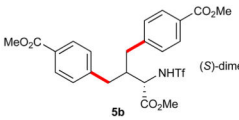
4a (*R*)-methyl 4-(4-methoxy-4-oxo-3-(trifluoromethylsulfonamido)butyl)benzoate



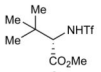
5 (*S*)-methyl 3-methyl-2-(trifluoromethylsulfonamido)butanoate



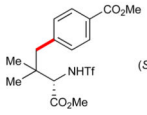
5a methyl 4-((3*S*)-4-methoxy-2-methyl-4-oxo-3-(trifluoromethylsulfonamido)butyl)benzoate



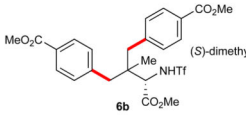
5b (*S*)-dimethyl 4,4'-(2-(2-methoxy-2-oxo-1-(trifluoromethylsulfonamido)ethyl)propane-1,3-diyl)dibenzoate



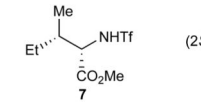
6 (*S*)-methyl 3,3-dimethyl-2-(trifluoromethylsulfonamido)butanoate



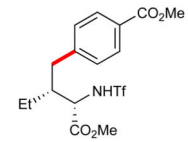
6a (*S*)-methyl 4-(4-methoxy-2,2-dimethyl-4-oxo-3-(trifluoromethylsulfonamido)butyl)benzoate



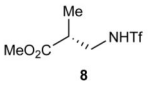
6b (*S*)-dimethyl 4,4'-(2-(2-methoxy-2-oxo-1-(trifluoromethylsulfonamido)ethyl)-2-methylpropane-1,3-diyl)dibenzoate



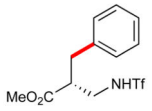
7 (2*S*,3*S*)-methyl 3-methyl-2-(trifluoromethylsulfonamido)pentanoate



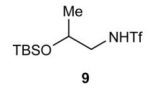
7a methyl 4-((2*R*,3*S*)-2-ethyl-4-methoxy-4-oxo-3-(trifluoromethylsulfonamido)butyl)benzoate



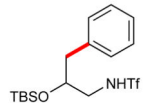
8 (*R*)-methyl 2-methyl-3-(trifluoromethylsulfonamido)propanoate



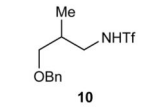
8a (*R*)-methyl 2-benzyl-3-(trifluoromethylsulfonamido)propanoate



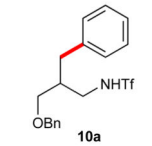
9 *N*-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-1,1,1-trifluoromethanesulfonamide



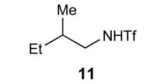
9a *N*-(2-((*tert*-butyldimethylsilyl)oxy)-3-phenylpropyl)-1,1,1-trifluoromethanesulfonamide



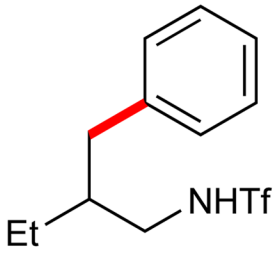
10 *N*-(3-(benzyloxy)-2-methylpropyl)-1,1,1-trifluoromethanesulfonamide



10a *N*-(2-benzyl-3-(benzyloxy)propyl)-1,1,1-trifluoromethanesulfonamide

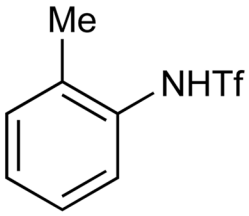


11 1,1,1-trifluoro-*N*-(2-methylbutyl)methanesulfonamide



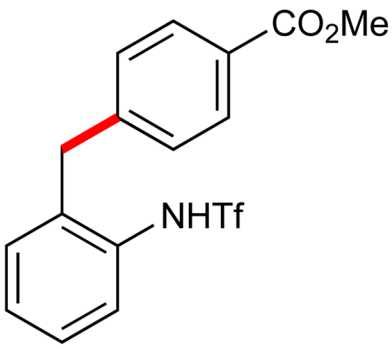
11a

N-(2-benzylbutyl)-1,1,1-trifluoromethanesulfonamide



12

1,1,1-trifluoro-*N*-(*o*-tolyl)methanesulfonamide



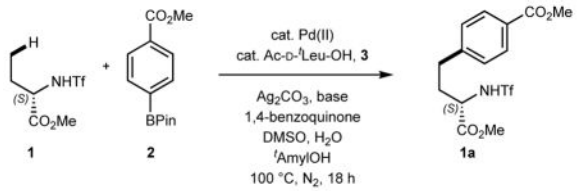
12a

methyl 4-(2-(trifluoromethylsulfonamido)benzyl)benzoate

Figure 3.
Substrates and products of C-H activation reaction.

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

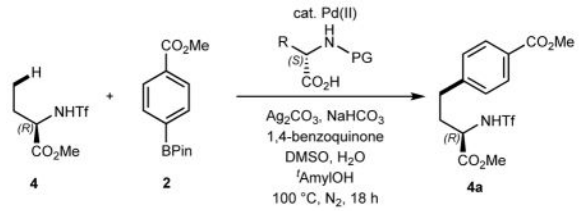
Experiments were performed with **1** (0.2 mmol), **2** (0.4 mmol), Pd(II) catalyst (0.02 mmol), **3** (0.04 mmol), base, Ag_2CO_3 (0.4 mmol), 1,4-benzoquinone (0.1 mmol), DMSO (0.08 mmol), H_2O (1.1 mmol) in ^{t}AmylOH (1 mL) for 18 h at 100 °C under N_2 atmosphere.

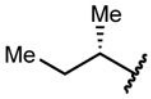
*Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

§Performed with $Pd(OTf)_2(MeCN)_4$ (0.01 mmol) and **3** (0.02 mmol).

Table 2

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



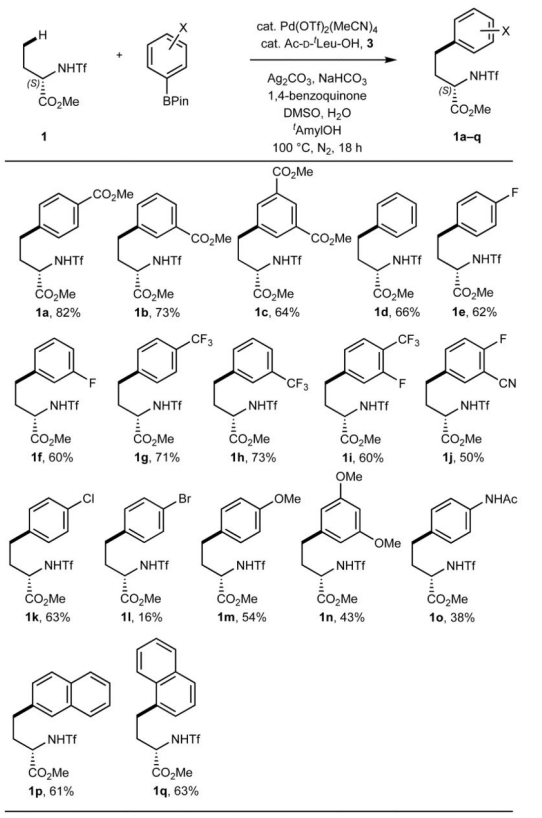
Entry	Ligand		Yield* (%)
	R	PG	
1	^{i}Pr	Me	0
2	^{i}Pr	Formyl	18
3	^{i}Pr	Ac	68
4	^{i}Pr	Boc	12
5	^{i}Pr	Fmoc	15
6	^{i}Pr	Cbz	9
7	^{i}Pr	Troc	0
8	H	Ac	31
9	Me	Ac	50
10	^{n}Pr	Ac	68
11	^{i}Bu	Ac	57
12	^{t}Bu	Ac	75
13		Ac	82

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}AmylOH (1 mL) for 18 h at 100 °C under N_2 atmosphere.

*Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Table 3

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

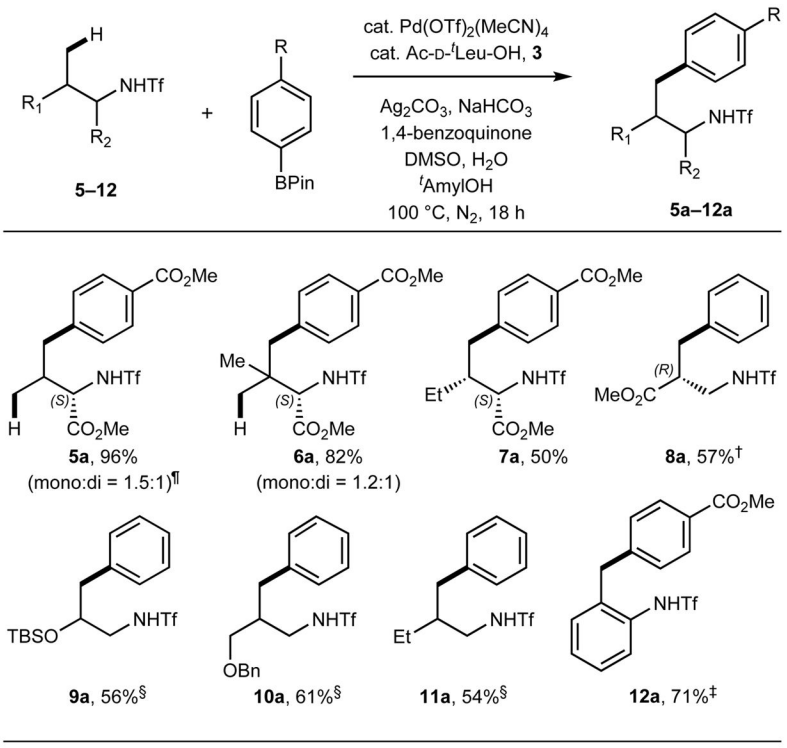


Experiments were performed with **1** (0.2 mmol), arylboronic acid pinacol ester (0.4 mmol), $Pd(OTf)_2(MeCN)_4$ (0.02 mmol), **3** (0.04 mmol), $NaHCO_3$ (1.2 mmol), Ag_2CO_3 (0.4 mmol), 1,4-benzoquinone (0.1 mmol), DMSO (0.08 mmol), H_2O (1.1 mmol) in ^{t}AmylOH (1 mL) for 18 h at 100 °C under N_2 atmosphere.

*Isolated yields.

Table 4

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



Experiments were performed with substrate (0.2 mmol), arylboronic acid pinacol ester (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}AmylOH (1 mL) for 18 h at 100 °C under N_2 atmosphere.

*Isolated yields.

¶Diastereomeric ratio 4.7:1.

†Performed with PhBPin (2.0 equiv.) and Ac-L-^{t}Leu-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 8 h.