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Weak, bidentate chelating group assisted cross-coupling of C(sp^3)–H bonds in aliphatic acid derivatives with aryltrifluoroborates†

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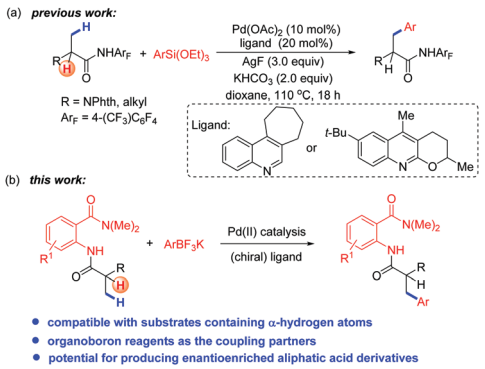
A protocol of Pd(II)-catalyzed, weak bidentate directing group assisted β-C(sp^3)–H activation/cross-coupling with organoboron reagents has been achieved, affording arylation of aliphatic acid derivatives that contain α-hydrogen atoms in moderate to good yields. The potential of this method for an asymmetric β-C(sp^3)–H arylation *via* desymmetrization was also presented.

In the past two decades, despite a range of success in transition-metal-catalyzed C(sp^2)–H bond functionalizations with organometallic reagents,[1–3] considerable limitations still exist in this type of reaction at C(sp^3)–H bonds.[2d,f,4–7] In the arylation and alkylation of β-C(sp^3)–H bonds of aliphatic acids or their derivatives with organometallic reagents such as organoboron, organosilicon and organozinc reagents, the substrates are mostly restricted to those without α-hydrogen atoms, *i.e.* those possessing quaternary centers at the α-position.[2f,4,5] The only exception is the protocol of Pd(II)-catalyzed cross-coupling of C(sp^3)–H bonds in aliphatic amides containing α-hydrogen atoms by using arylsilanes as the coupling partners *via* a Pd(II)/Pd(0) catalytic cycle (Scheme 1a).[6] To date, no report has been disclosed on transition-metal-catalyzed cross-coupling of β-C(sp^3)–H bonds in aliphatic acids or their derivatives that contain α-hydrogen atoms with other organometallic reagents such as organoboron reagents.[1c–e,8] The fundamental explanation of this incompatibility can be that the resulting metallacycle (*e.g.* palladacycle) after the C–H activation can undergo β-hydride elimination with the α-hydrogen atom, which out-competes the desired transmetallation step.[1a] Another reason might be that the rate of C–H cleavage of the substrates containing α-hydrogen atoms is slower than those without α-hydrogen atoms due to a favourable Thorpe–Ingold effect in the latter substrates. And due to the slower rate, metal-mediated homocoupling of the organometallic reagents can outpace the C–H cleavage step.



Scheme 1 Pd(II)-Catalyzed C(sp^3)–H cross-coupling of aliphatic acid derivatives containing α-H atoms with organometallic reagents.

To overcome the challenging substrate scope limitation and encouraged by the pioneering works on Pd(II)-catalyzed cross-coupling of C(sp^3)–H bonds in aliphatic acids or their derivatives with organoboron reagents,[2f,4] we envisioned to develop a weak, bidentate directing group, which might be capable of increasing the rate of C–H cleavage of aliphatic acid derivatives without the Thorpe–Ingold effect and facilitating the transmetallation in the catalytic cycle due to its weak coordination (Scheme 1b).[9] Herein we report a cross-coupling of C(sp^3)–H bonds in aliphatic acid derivatives bearing α-hydrogen atoms with aryltrifluoroborates through a Pd(II)/Pd(0) catalytic cycle. Importantly, this method also holds the potential to produce enantioenriched aliphatic acid derivatives.[10]

To start our study on developing a suitable weak and bidentate directing group,[9] we engineered amide **1a** from isobutyric acid and examined its reaction with potassium 4-methylphenyltrifluoroborate **2a** (Table 1). After extensive reaction condition screening, the reaction was found to proceed to afford the mono- and di-arylated products in 31% combined yield in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% of *N*-Ac-Ile-OH, 2.0 equivalents of Ag_2CO_3, 10 mol% of 1,4-benzoquinone and 1.5 equivalents of

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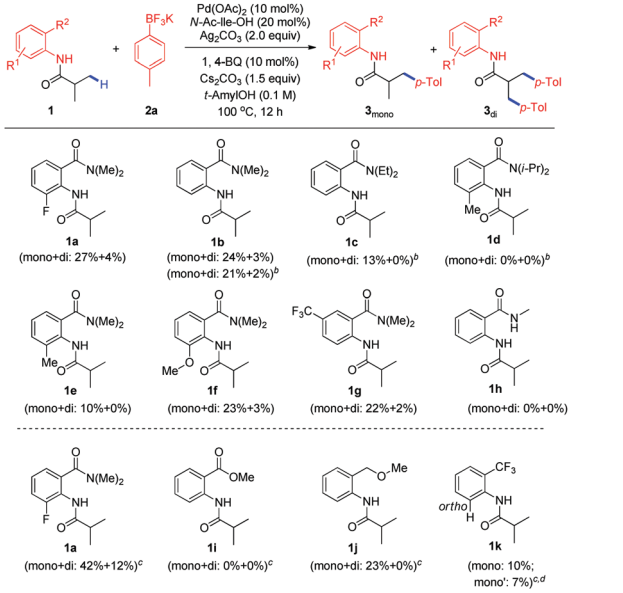
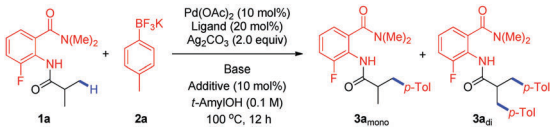
Table 1 Directing group optimization[a]

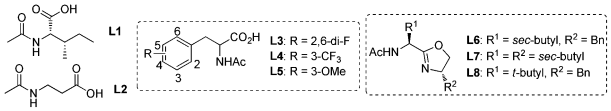


[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), *N*-Ac-Ile-OH (0.02 mmol), Ag_2CO_3 (0.2 mmol), Cs_2CO_3 (0.15 mmol), 1,4-BQ (0.01 mmol), *t*-AmylOH (1 mL, 0.1 M), 12 h, 100 °C. The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard. [b] 120 °C. [c] Cs_2CO_3 (0.5 equiv.), *t*-AmylOH (0.2 M). [d] Mono' was the product of arylation of *ortho*-C(sp^2)–H bond. 1,4-BQ: 1,4-benzoquinone.

Table 2 Optimization of reaction conditions[a]



Entry	Ligand	Base (equiv.)	Additive	Yield (%) ($3a_{mono}/3a_{di}$)[b]
1	**L1**	Cs_2CO_3 (0.5)	BQ-1	48 (3.8 : 1)
2[c]	**L1**	Cs_2CO_3 (0.5)	BQ-1	49 (3.5 : 1)
3[c,d]	**L1**	Cs_2CO_3 (0.5)	BQ-1	47 (4.2 : 1)
4	**L1**	Cs_2CO_3 (0.5)	BQ-2	43 (5.1 : 1)
5	**L1**	Cs_2CO_3 (0.5)	BQ-3	4 (1 : 0)
6	**L1**	Cs_2CO_3 (0.5)	—	5 (1 : 0)
7	—	Cs_2CO_3 (0.5)	BQ-1	4 (1 : 0)
8[e]	**L1**	Cs_2CO_3 (0.5)	BQ-1	54 (3.5 : 1)
9[f]	**L1**	Cs_2CO_3 (0.5)	BQ-1	51 (4.1 : 1)
10[g]	**L1**	Cs_2CO_3 (0.5)	BQ-1	35 (6 : 1)
11[e]	**L1**	K_2CO_3 (0.5)	BQ-1	44 (4.5 : 1)
12[e]	**L1**	K_2CO_3 (2.0)	BQ-1	58 (2.6 : 1)
13[e]	**L2**	K_2CO_3 (2.0)	BQ-1	39 (3.9 : 1)
14[e]	**L3**	K_2CO_3 (2.0)	BQ-1	59 (2.5 : 1)
15[e]	**L4**	K_2CO_3 (2.0)	BQ-1	55 (2.7 : 1)
16[e]	**L5**	K_2CO_3 (2.0)	BQ-1	42 (4.2 : 1)
17[e]	**L6**	K_2CO_3 (2.0)	BQ-1	52 (3.3 : 1)
18[e]	**L7**	K_2CO_3 (2.0)	BQ-1	54 (2.8 : 1)
19[e]	**L8**	K_2CO_3 (2.0)	BQ-1	61 (2.2 : 1)
20[c,e,h]	**L8**	K_2CO_3 (2.0)	BQ-1	65 (2.1 : 1)



[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.02 mmol), Ag_2CO_3 (0.2 mmol), base, additive (0.01 mmol), *t*-AmylOH (1 mL, 0.1 M), 12 h, 100 °C. [b] The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard. [c] 24 h. [d] After 12 h, a second batch of **2a** (0.2 mmol) and Ag_2CO_3 (0.2 mmol) was added, and the reaction was continued for another 12 h. [e] 0.2 M. [f] 0.4 M. [g] 0.05 M. [h] 28% of **1a** was recovered. BQ-1 = 1,4-benzoquinone (1,4-BQ); BQ-2 = 2-methylcyclohexa-2,5-diene-1,4-dione; BQ-3 = 2,3,5,6-tetramethylcyclohexa-2,5-diene-1,4-dione.

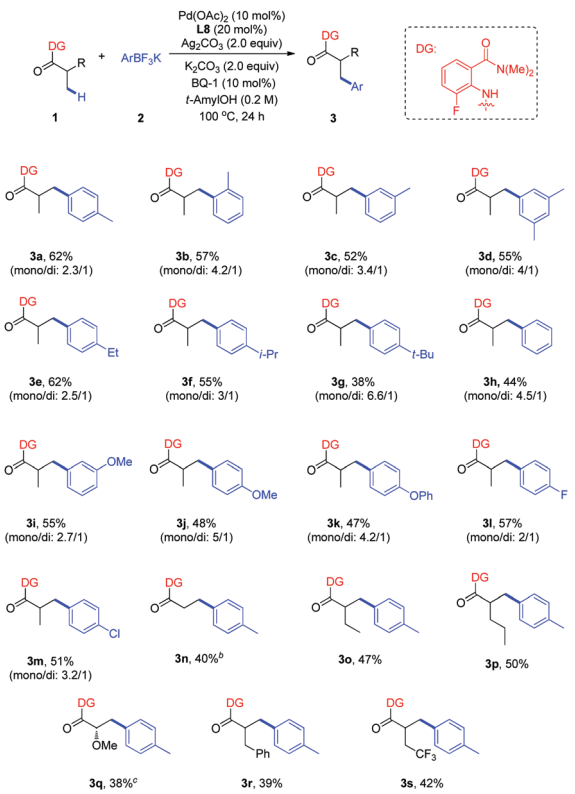
Cs_2CO_3 in *t*-AmylOH at 100 °C for 12 h. Notably, the directing group in **1b** without a fluoro-substituent also led to comparable yields of products, and no arylation was detected on the aromatic ring of **1b**. This result implied that the *ortho*-fluoro group of **1a** might weaken the coordinating ability of the directing group by reducing the electronic density of the coordinating atoms, rather than acting as a blocking group to avoid arylation of the aromatic ring. Subsequently, extensive fine tuning of the directing groups (**1c–1h**) was carried out in order to examine the influence of electronic properties and steric hindrance on the reactivity of the substrates (see also the ESI† for the evaluation of more substrates, including hydroxamic acids and Weinreb amide). Ultimately, substrate **1a** proved to be the best one with the highest reactivity. Directing groups with even weaker bidentate coordination (**1i** and **1j**) were then tested, leading to no or lower yield of the desired products, which implied that bidentate coordination was important in promoting the reaction. It should be noted that the yield was also increased with substrate **1a** using 0.5 equivalent of Cs_2CO_3. Finally, arylation of the C(sp^2)–H bond on the aromatic ring of the directing group occurred if the directing group was monodentate (**1k**), which further proved the existence of bidentate coordination in the directing group of **1a**.

With the model substrate **1a** in hand, extensive reaction condition optimization was conducted to obtain the optimal result (Table 2). Firstly, the yield increased to 48% when reducing the loading of Cs_2CO_3 to 0.5 equivalent (entry 1). Only a slight increase in the yield was obtained when extending the reaction time to 24 hours (entry 2). More **2a** and Ag_2CO_3 added in batches had no positive effect (entry 3). Other benzoquinone derivatives were also examined but led to no better results (entries 4 and 5). It was also proved both the 1,4-BQ and the ligand were essential for the reaction (entries 6 and 7). The concentration of the reaction was also important (entries 8–10). And a higher reaction concentration (0.2 M) could further increase the yield to 54%. Other bases such as K_2CO_3 were also evaluated and the best choice was 2.0 equivalents of K_2CO_3 (entries 11 and 12). Other ligands, including *N*-mono protected amino acid (**L2–L5**) ligands and acetyl-protected aminomethyl oxazoline (**L6–L8**) ligands, were also investigated,[7i,10a,e] and **L8** was found to be the optimal ligand for this reaction (entries 13–19). Finally, the best combined yield was achieved with **L8** in 24 hours, together with the recovery of 28% of **1a** (entry 20). Extensive efforts were also made to fully convert the substrate to the desired products, but all of these efforts, including extending the reaction time, failed (see the ESI† for more screening tests).

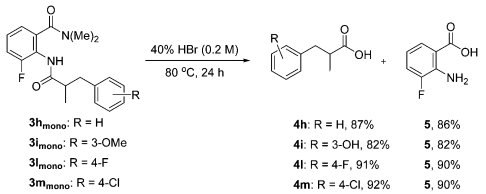
With the optimal reaction conditions in hand, a series of potassium aryltrifluoroborates were used in the reaction (Table 3). Methyl and other alkyl substituents on the phenyl ring of the organoboron reagents were well tolerated to afford

the desired products (**3a–3g**). Subsequently, simple phenyltrifluoroborate (**3h**) and several electron-rich (**3i–3k**) as well as electron-poor (**3l** and **3m**) aryltrifluoroborates were also compatible with this method to afford moderate yields of the desired products. Other aliphatic acid amides were then evaluated with reagent **2a** under the standard conditions. Notably, the reaction with a simple propionamide could still afford the desired product (**3n**) in a shorter reaction time, albeit in a modest yield. Amides with an ethyl or *n*-propyl group at the α-position were also capable of producing the desired arylated products (**3o** and **3p**). However, much to our surprise, only very low yield was obtained with the amide prepared from pivalic acid, which contains no α-hydrogen atom. It is worth mentioning that the amide derived from L-(+)-lactic acid was also compatible with this protocol utilizing ligand **L3** to generate the desired product **3q**, albeit in a lower yield. The process could also be successfully extended to amides containing a benzyl or trifluoroethyl group at the α-position (**3r** and **3s**). It should be noted that efforts to convert the unreacted substrates to the desired products were not successful. However, most of the unreacted substrates could be recovered, although minor decomposition of these substrates also occurred. Finally, the directing group could be readily removed to afford 2-methyl-3-phenylpropanoic acid **4** in 87% yield, and the auxiliary **5** was recycled in 86% yield *via* treatment with $\mathbf{3h}_{mono}$ in 40% aqueous HBr solution at 80 °C for 24 h (Scheme 2). Products with functional groups could also be hydrolyzed under the above conditions ($\mathbf{3i}_{mono}$, $\mathbf{3l}_{mono}$, and $\mathbf{3m}_{mono}$), although the methoxyl group was converted into a hydroxyl group under the acidic conditions ($\mathbf{3i}_{mono}$).

Table 3 Scope of the cross-coupling of C(sp^3)–H bonds of aliphatic acids with aryltrifluoroborates[a]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), **L8** (0.02 mmol), Ag_2CO_3 (0.2 mmol), K_2CO_3 (0.2 mmol), BQ-1 (0.01 mmol), *t*-AmylOH (0.5 mL), 24 h, 100 °C; isolated yield. [b] 12 h. [c] **L3** was used instead of **L8**.



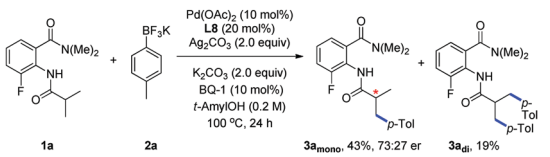
Scheme 2 Removal of the directing auxiliary.

Since substrate **1a** possesses a prochiral center, we were particularly interested in obtaining a hint of developing an asymmetric β-C(sp^3)–H arylation *via* desymmetrization (Scheme 3).[10]

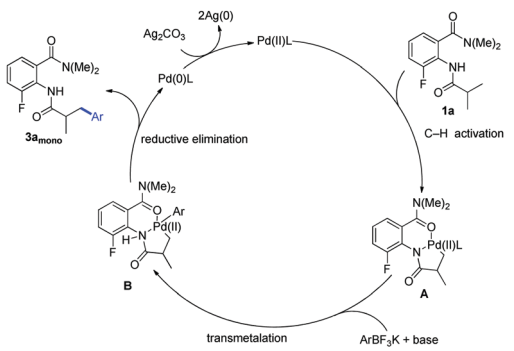
With the chiral ligand **L8** that had been used for asymmetric β-C(sp^3)–H arylation with aryl iodide,[10e] we were pleased to find a promising enantiomeric ratio (er) of 73 : 27. This important observation paved the way for our subsequent investigation into this desymmetrization reaction.

A plausible catalytic cycle was proposed for this β-C(sp^3)–H arylation (Scheme 4). Initially, intermediate **A** is generated from **1a** *via* C(sp^3)–H bond activation assisted by the bidentate auxiliary with one of the coordination sites being the lone electron pair of the oxygen atom of the *N*,*N*-dimethylbenzamide group. Subsequently, transmetallation of the aryltrifluoroborate reagents with intermediate **A** gives intermediate **B** which undergoes reductive elimination to release the cross-coupling product and Pd(0). The Pd(0) species is re-oxidized to regenerate the active Pd(II) species to re-enter the catalytic cycle.

In summary, we developed a Pd(II)-catalyzed cross-coupling of C(sp^3)–H bonds in aliphatic acid derivatives that contain



Scheme 3 Asymmetric β-C(sp^3)–H arylation *via* desymmetrization.



Scheme 4 Tentative catalytic cycle.

α-hydrogen atoms with aryltrifluoroborates, which was assisted by a novel weak bidentate directing group. An asymmetric β-C(sp^3)–H arylation *via* desymmetrization was also presented by the use of a chiral ligand, offering a promising technique for producing enantioenriched molecules. This asymmetric version of the method is under investigation in our laboratory and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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