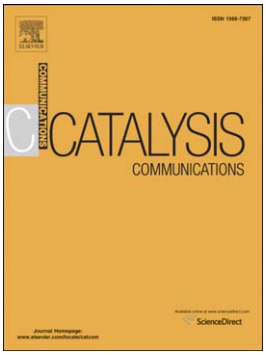

Steric effect of carboxylic acid ligands on Pd-catalyzed C–H activation reactions

Tetsuaki Fujihara, Atsushi Yoshida, Motoi Satou, Yutaka Tanji, Jun Terao, Yasushi Tsuji

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Catalysis Communications

Steric effect of carboxylic acid ligands on Pd-catalyzed C–H activation reactions

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Abstract

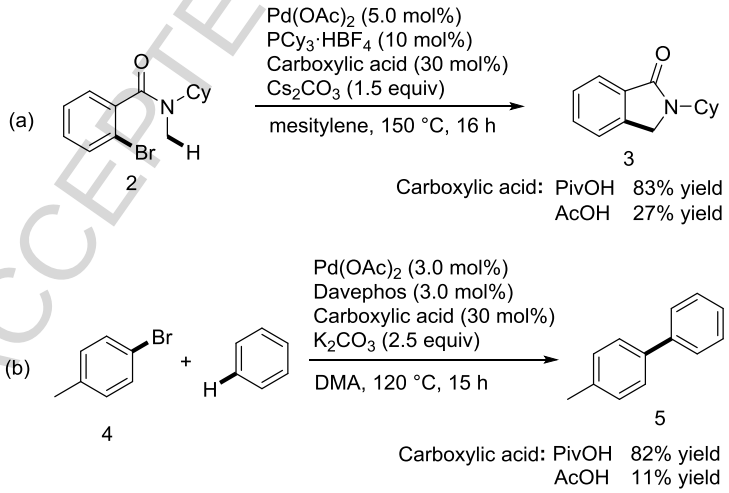
Various carboxylic acids with different substitution patterns were used as ligands in intra- and intermolecular Pd-catalyzed C–H activation reactions to investigate steric effect of the ligands. Bulky carboxylic acids suppress deactivation of Pd catalysts.

Key Word

Carboxylic Acid, C–H Activation, Homogeneous Catalysis, Palladium

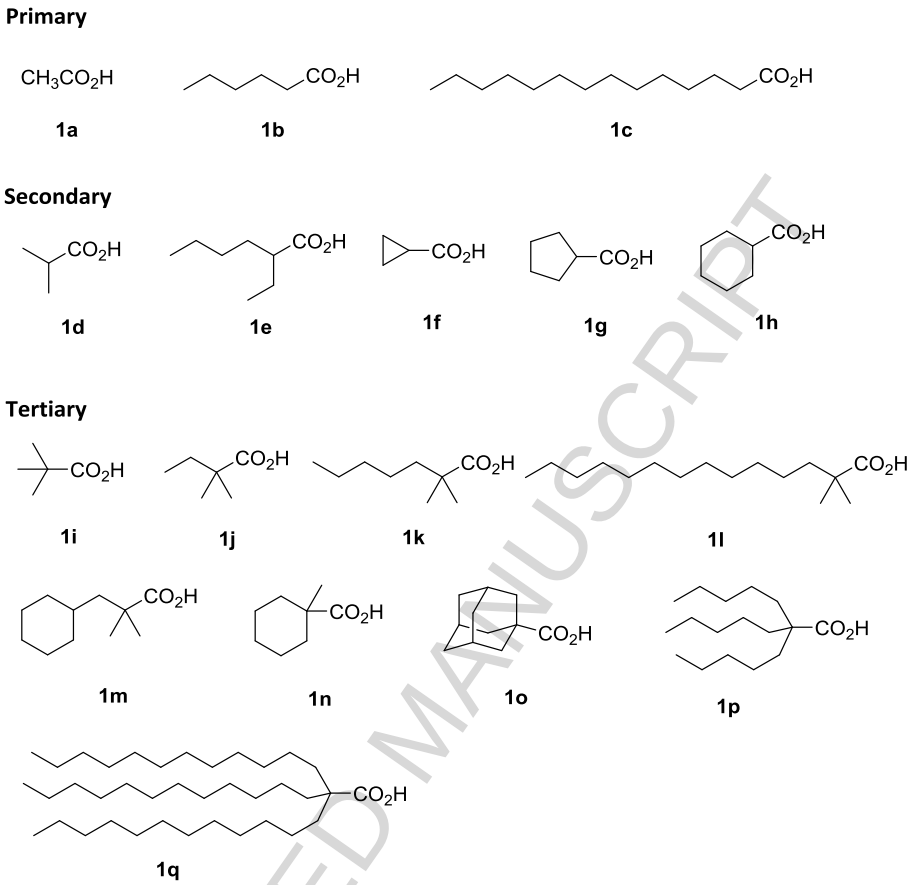
1. Introduction

Transition-metal-catalyzed carbon-hydrogen (C–H) bond activation reaction is one of the most straightforward methods in organic transformations [1-7]. Among them, Pd catalysis is widely utilized [8-14]. In these cases, carboxylic acids, typically pivalic acid, play an important role as the ligand in C–H bond activation step via concerted metalation deprotonation (CMD) mechanism [15-17]. Fagnou reported that the Pd-catalyzed intramolecular C(sp^3)–H bond arylation reactions proceeded efficiently with pivalic acid as the ligand (Scheme 1a) [18]. In the reaction, acetic acid was not so effective. Fagnou also reported that pivalic acid was more effective ligand than acetic acid in the Pd-catalyzed intermolecular C(sp^2)–H arylation with aryl bromides (Scheme 1b) [19]. Therefore, it is interesting to see how steric effect of the carboxylic acids (carboxylates) influences the C-H bond activation reactions. Recently, Thompson investigated the effect of various carboxylic acids on the Pd-catalyzed direct arylation polymerization with 3-hexylthiophene [20]. However, it is still unclear how the nature of carboxylic acid ligands affects the C–H bond activation reactions.



Scheme 1. Pd-catalyzed C–H bond activations: (a) Intramolecular C(sp^3)–H arylation. (b) Intermolecular C(sp^2)–H arylation.

In the present study, a series of primary (**1a**–**c**), secondary (**1d**–**1h**), and tertiary (**1i**–**1o**) α-substituted carboxylic acids (Scheme 2) were evaluated as a ligand in the Pd-catalyzed intra- and intermolecular C–H bond activation reactions shown in Schemes 1a and 1b.



Scheme 2. Primary, secondary, and tertiary α-substituted carboxylic acids used in this study.

2. Experimental

2.1 General procedure

All the manipulations were performed under argon atmosphere using standard Schlenk-type glasswares and a dual-manifold Schlenk line. THF and toluene were dried and purified before use by usual methods [21]. Mesitylene, *N*,*N*-dimethylacetoamide (DMA), *p*-bromobenzene, and benzene were purified by distillation under reduced pressure and stored under Ar atmosphere [22]. Unless otherwise noted, materials obtained from commercial suppliers were used as received. ^{1}H NMR spectra were measured with a Bruker AVANCE-500 spectrometer or a JEOL ECX-400P spectrometer. The ^{1}H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm). The GC analysis was carried out using a Shimadzu GC-17A instrument equipped with a capillary column (CBP-5, 0.25 mm i.d. × 25 m). The column chromatography was carried out using silica gel (Kanto N60, spherical, neutral, 63-210 μm). The TLC analyses were performed using commercial glass plates containing a 0.25-mm layer of Merck Silica gel 60F254. Carboxylic acids **1a**–**j, 1n** and **1o**

were purchased and used as received. Carboxylic acids **1k**–**m** and **1p** were prepared according to a modified literature method [23,24]. **1q** was a new compound and prepared as shown below.

2.2 Synthesis of **1q**

A freshly prepared lithium diisopropyl amide (LDA) solution (11 mmol) in THF was added to a solution of acetonitrile (0.52 mL, 10 mmol) in THF (5.0 mL) at 0 °C and stirred for 25 min. Then, 1-bromododecane (2.4 mL, 10 mmol) was slowly added and the reaction mixture was stirred at room temperature for 40 min. Then, the sequential addition of the LDA solution (11 mmol) and 1-bromododecane (2.4 mL, 10 mmol) was repeated for three times. The resulting reaction mixture was stirred at room temperature for 16 h. The reaction was quenched by adding 1 M HCl aq., and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by silica gel column chromatography (EtOAc / hexane = 1 / 40, R_f = 0.19), affording 2,2-didodecyltetradecanenitrile (3.7 g, 6.8 mmol) in 68% yield. The nitrile was added to 75% sulfuric acid (15 mL), and the reaction mixture was stirred at 100 °C for 23 h. After cooling to room temperature, $NaNO_2$ (1.9 mg, 27 mmol) was added and the reaction mixture was stirred for 20 min. The mixture was diluted with water (30 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (EtOAc / hexane = 1 / 15, R_f = 0.10), giving **1q** (3.0 g, 5.2 mmol) in 77 % yield as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.00 (brs, 1H), 1.56–1.40 (m, 6H), 1.38–1.08 (m, 60H), 0.88 (t, J = 6.8 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.38, 48.80, 34.33, 31.93, 30.14, 29.70, 29.66, 29.49, 29.37, 23.83, 22.70, 14.11 (two peaks were overlapped). IR (neat): 2918.3, 2848.9, 1699.3, 1465.9, 723.3 cm^{-1}. ESI-HRMS: Calcd. for $C_{38}H_{75}O_2$ ([M–H]$^-$), 563.5773. Found, 563.5776.

2.3 Catalytic reaction

2.3.1 Pd-catalyzed intramolecular C(sp^3)–H arylation reaction

To a 10-mL Schlenk flask equipped with a reflux condenser was added Rb_2CO_3 (0.20 g, 0.87 mmol) and dried with a heating-gun under vacuum. The flask was backfilled with argon. Then, $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 5.0 mol%), $PCy_3 \cdot HBF_4$ (21 mg, 0.058 mmol, 10 mol%), carboxylic acid (**1**, added here if it is a solid, 0.17 mmol, 30 mol%), and 2-bromo-*N*-cyclohexyl-*N*-methylbenzamide (**2**, 0.17 g, 0.58 mmol) were added to the flask. The flask was evacuated and backfilled with argon three times. Then, mesitylene (2.9 mL) and

carboxylic acid (**1**, added here if it is a liquid , 0.17 mmol, 30 mol%) was added to the flask. The resulting reaction mixture was stirred at 150 °C for 16 h. After cooling to room temperature, the reaction mixture was analyzed by GC, and the yield of 2-cyclohexylisoindolin-1-one **3** was determined using tetradecane (50 μL) as an internal standard.

2.3.2 Pd-catalyzed intermolecular C(sp^2)–H arylation reaction

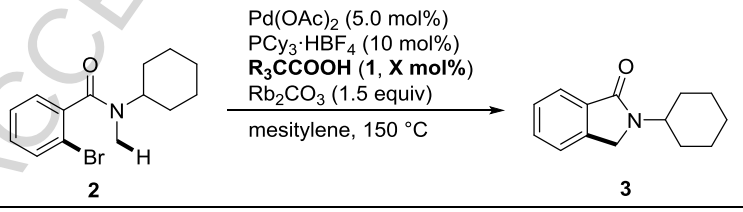
To a 10-mL Schlenk flask equipped with a reflux condenser was added Rb_2CO_3 (0.20 g, 0.87 mmol) and carboxylic acid (**1**, added here if it is a solid, 0.060 mmol, 30 mol%), and dried with a heating-gun under vacuum. The flask was backfilled with argon three times. Then, $Pd(OAc)_2$ (0.0060 mmol, 3.0 mol% as a stock solution in DMA, 1.2 mL) and carboxylic acid (**1**, added here if it is a liquid, 0.060 mmol, 30 mol%) was added. The mixture was stirred at room temperature for 30 min. Then, 4-bromotoluene (**4**, 25 μL, 0.20 mmol) and benzene (1.0 mL) were added to the mixture, and the resulting reaction mixture was stirred at 90 °C for 20 h. After cooling to room temperature, the reaction mixture was analyzed by GC, and the yield of compound **5** was determined using tetradecane (50 μL) as an internal standard.

3. Results and Discussion

First, we carried out the intramolecular Pd-catalyzed C–H activation shown in Scheme 1a as a model reaction. Thus, the reaction of 2-bromo-*N*-cyclohexyl-*N*-methylbenzamide (**2**) to 2-cyclohexylisoindolin-1-one (**3**) was carried out using 30 mol% of carboxylic acid **1** in the presence of a catalytic amount (5.0 mol%) of $Pd(OAc)_2/PCy_3{\cdot}HBF_4$ in mesitylene at 150 °C (Table 1). When acetic acid (**1a**) was used as the ligand, **3** was obtained in only 26% yield (entry 1), as reported in the original report [4]. Other primary α-substituted carboxylic acids afforded **3** in moderate yields (entries 2 and 3). The use of secondary α-substituted carboxylic acids such as 2-methylpropionic acid (**1d**) and 2-ethylhexanoic acid (**1e**) improved the yields of **3** to 80% and 79%, respectively (entries 4 and 5), whereas **1f**, **1g**, and **1h** with a cyclopropyl, cyclopentyl, and cyclohexyl group, respectively, were not efficient (entries 6–8). Pivalic acid (**1i**), which was the best carboxylic acid ligand in the previous report [4], was more effective, producing **3** in 74% yield (entry 9). Gratifyingly, the yield of **3** significantly increased by elongating one of the methyl substituents of **1i** to ethyl (**1j**: 80%), *n*-pentyl (**1k**: 88%) and *n*-dodecyl (**1l**: 91%) groups, respectively (entries 10–12). However, the use of **1m** bearing a cyclohexylmethyl substituent decreased the yield of **3** to 55% (entry 13). Other carboxylic acids (**1n** and **1o**) bearing alicyclic systems showed good catalytic activity (entries

14 and 15). Thus, the bulkiness of the carboxylic acid ligands (**1**) affected the yield of **3** and the ligands with longer primary alkyl chains showed high catalytic activity.

Because the carboxylic acid bearing a longer *n*-alkyl chain (**1l**) was a promising ligand (entry 12, Table 1), carboxylic acid ligands bearing three *n*-pentyl (**1p**) and *n*-dodecyl chains (**1q**) were synthesized (Scheme 2). When **1i**, **1p** and **1q** were used as the carboxylate ligand under the same reaction conditions as shown in Table 1 (reaction time: 16 h), **3** was obtained in 74% (entry 9, Table 1), 52%, and 59% yields, respectively. When the reaction time was prolonged to 40 h, the yields of **3** increased to 88% and 88% with **1p** and **1q**, respectively, whereas **1i** afforded the same yield (Scheme 3). Importantly, upon reducing the amount of the carboxylic acid from 30 mol% to 10 mol%, **1i** was inefficient, affording **3** in only 8% yield after 40 h. In the reaction, Pd black was generated in the reaction mixture after 16 h, indicating the catalyst decomposed under the reaction conditions. In sharp contrast, with **1p** and **1q**, the catalytic activity was maintained even under the low carboxylic acid loadings and the product was obtained in 88% and 92% yields, respectively. When the reaction was carried out using 10 mol% of **1l**, the product was also obtained in 87% yield. Thus, the longer alkyl chains prevent the aggregation of Pd species because of their bulkiness. We have already reported the suppression of Pd black formation using bulky pyridine ligands [25,26].



2 **3**

	1i R = CH_3	**1p** R = *n*-C_5H_{11}	**1q** R = *n*-$C_{12}H_{25}$
30 mol%, 16 h	74%	52%	59%
30 mol%, 40 h	74%	88%	88%
10 mol%, 40 h	8%	88%	92%

Scheme 3. Pd-catalyzed intramolecular C(sp^3)–H bond arylation of **2** under low carboxylic acid loading.

Next, the Pd-catalyzed C(sp^2)–H arylation of benzene with 4-bromotoluene (**4**) was carried out. In the original report [19], Fagnou used both pivalic acid (**1i**) and basic phosphine

as ligands in DMA at 120 °C. Later, Hartwig reported that the reaction proceeded with only **1i** as the ligand (without any phosphine) at 110 °C [27]. Therefore, in the present study, the catalytic reaction was performed without phosphines. The reaction was carried out employing various carboxylic acids (**1a**–**o**) as carboxylate ligands in the presence of a catalytic amount of $Pd(OAc)_2$ in a mixture of benzene and DMA at a lower temperature (90 °C) than the Hartwig's conditions [27]. The results are shown in Table 2. Using primary and secondary α-substituted carboxylic acids (**1a**–**1h**) as the ligands, the reactions virtually did not proceed (entries 1–8). When pivalic acid (**1i**) was used [19,27], 4-phenyltoluene (**5)** was obtained in 47% yield (entry 9). By replacing one of the methyl groups of **1i** to an ethyl group (**1j**), the reaction smoothly proceeded affording **5** in 71% yield (entry 10). Similarly, *n*-pentyl (**1k**) and *n*-dodecyl (**1l**) substituted carboxylic acids furnished **5** in 63% and 52%, respectively (entries 10–12). Furthermore, **1m** bearing cyclohexylmethyl and two methyl substituents at the α-position was most effective ligand in this particular reaction and provided **5** in 72% yield (entry 13). All the other more bulky carboxylic acid ligands (**1n**, **1o**, **1p**, and **1q**) were inefficient and the yields of **5** were quite low. Thus, the bulkiness of these carboxylic acid ligands significantly affects the catalytic activity. Regarding carboxylato palladium complexes, a palladium trimer was afforded with **1a** as the ligand [28]. A bulky **1i** also afforded a similar palladium trimer [29]. In contrast, more bulky carboxylic acid ligands may suppress the aggregation of the Pd center and maintain an active Pd catalyst species by steric effect.

4. Conclusion

Various carboxylic acids were evaluated in the intra- and intermolecular Pd-catalyzed C–H activation reactions. In the intramolecular reaction of 2-bromo-*N*-cyclohexyl-*N*-methylbenzamide, a bulky carboxylic acid bearing three long alkyl chains at the α-position suppressed the deactivation of Pd catalysts. In the intermolecular direct C–H arylation of an aryl bromide with benzene, the reaction proceeded smoothly when a bulky carboxylic acid bearing a cyclohexylmethyl group at the α-position was used. Further studies on mechanism and substrate scope are underway.

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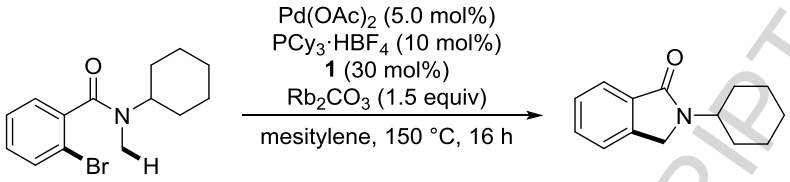
Table 1.

Effect of carboxylic acids on the Pd-catalyzed intramolecular C(sp^3)–H bond arylation of **2**.[a]



2 **3**

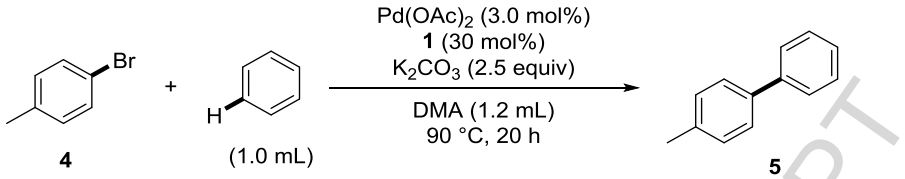
Entry	Carboxylic acid (**1**)	Yield of **3** (%)[b]
1	**1a**	26
2	**1b**	57
3	**1c**	59
4	**1d**	80
5	**1e**	79
6	**1f**	23
7	**1g**	58
8	**1h**	39
9	**1i**	74
10	**1j**	80
11	**1k**	88
12	**1l**	91
13	**1m**	55
14	**1n**	82
15	**1o**	65

[a] Reaction conditions: 2-bromo-*N*-cyclohexyl-*N*-methylbenzamide (**2**, 0.58 mmol), $Pd(OAc)_2$ (0.029 mmol, 5.0 mol%), $PCy_3{\cdot}HBF_4$ (0.058 mmol, 10 mol%), carboxylic acid (**1**, 0.17 mmol, 30 mol%), Rb_2CO_3 (0.87 mmol, 1.5 equiv) in mesitylene (2.9 mL) at 150 °C for 16 h.

[b] Determined by GC analysis using an internal standard method.

Table 2.

Effect of carboxylic acids on the Pd-catalyzed C(sp^2)–H bond arylation with **4**.[a]

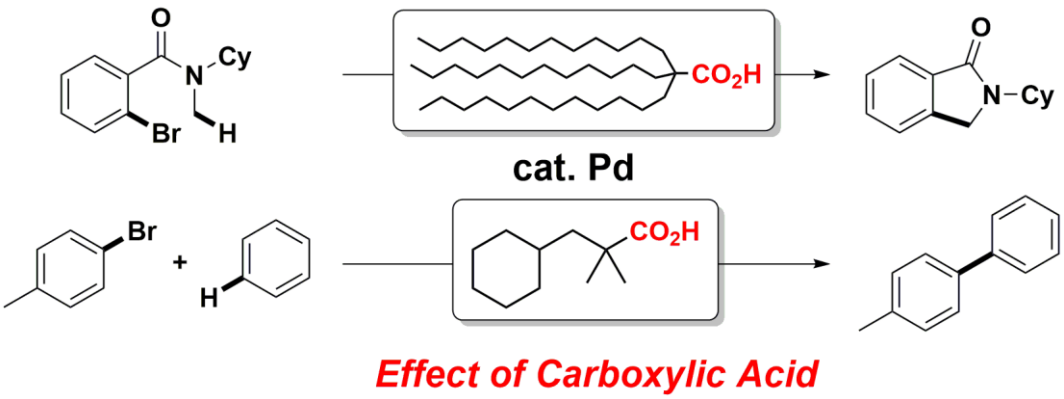


4 **5**

Entry	Carboxylic acid (**1**)	Yield of **5** (%)[b]
1	**1a**	0
2	**1b**	0
3	**1c**	0
4	**1d**	0
5	**1e**	1
6	**1f**	0
7	**1g**	2
8	**1h**	1
9	**1i**	47
10	**1j**	71
11	**1k**	63
12	**1l**	52
13	**1m**	72
14	**1n**	0
15	**1o**	5
16	**1p**	11
17	**1q**	4

[a] Reaction conditions: 4-bromotoluene (**4**, 0.20 mmol), $Pd(OAc)_2$ (0.0060 mmol, 3.0 mol%), carboxylic acid (**1**, 0.060 mmol, 30 mol%), K_2CO_3 (0.50 mmol, 2.5 equiv) in DMA (1.2 mL) and benzene (1.0 mL) at 90 °C for 20 h.

[b] Determined by GC analysis using an internal standard method.



Graphical abstract

Reserach Highlights

Steric effect of carboxylic acid ligands on Pd-catalyzed C–H activation reactions

Tetsuaki Fujihara,* Atsushi Yoshida, Motoi Satou, Yutaka Tanji, Jun Terao, and Yasushi Tsuji*

Various carboxylic acids were used as ligands Pd-catalyzed C–H activation reactions.

A carboxylic acid bearing three long alkyl chains suppress the deactivation.

A carboxylic acid bearing a cyclohexylmethyl group was efficient in C-H arylation.