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Pd-catalyzed intermolecular C–H bond arylation reactions: effect of bulkiness of carboxylate ligands

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A bulky carboxylic acid bearing one 1-adamantylmethyl and two methyl substituents at the α -position is demonstrated to work as an efficient carboxylate ligand source in Pd-catalyzed intermolecular C(sp²)–H bond arylation reactions. The reactions proceeded smoothly under mild conditions, taking advantage of the steric bulk of the carboxylate ligands.

The transition-metal-catalyzed carbon-hydrogen (C–H) bond activation is one of the most straightforward organic transformations.¹ In particular, Pd catalysts are widely utilized in such processes.² Fagnou and Hartwig independently reported that pivalic acid was an effective ligand source in the Pd-catalyzed intermolecular C(sp²)–H arylation reactions.³ Nevertheless, the methods require high reaction temperatures (120 °C and 110 °C, respectively). Intermolecular C(sp²)–H arylation reactions of electron-deficient arenes⁴ and electron-rich heteroarenes reported by other groups⁵ are also carried out at high temperatures (in most cases over 100 °C).

Carboxylates are known as common ligands in transition metal complexes. In catalytic C–H bond activation reactions, carboxylate ligands have proved to play a crucial role in the C–H bond cleavage step via a concerted metalation deprotonation (CMD) pathway.⁶ However, little research is available on the steric effects of carboxylate ligands using transition metal-catalyzed reactions as well as on the development of new carboxylate ligands.⁷ We recently found that a bulky carboxylic acid bearing three cyclohexylmethyl substituents at the α -position, namely tri(cyclohexylmethyl)acetic acid, worked as an efficient ligand source in Pd-catalyzed intramolecular C(sp²)–H and C(sp³)–H arylation reactions under very mild reaction conditions including at room temperature.⁸

Herein, the steric effects of carboxylic acids on Pd-catalyzed intermolecular $C(sp^2)$ –H bond arylation reactions were evaluated. After designing and synthesizing a panel of carboxylic acids exhibiting

different steric congestion, we found the addition of a carboxylic acid with suitable steric bulk remarkably enhanced the catalytic activity and the desired reactions proceeded under milder conditions.

The Pd-catalyzed intermolecular C(sp²)–H bond arylation reaction using 4-bromotoluene (2a) and benzene (3a) was selected as the model reaction.³ In the present study, the reaction demonstrated in Table 1 were performed at a lower temperature (70 °C) compared to previous reports.³ The efficiency of carboxylic acids (1) as the carboxylate ligand source was investigated by employing 30 mol% of 1 in the presence of a catalytic amount (3.0 mol%) of PdCl₂ and Rb₂CO₃ (1.5 equiv) in N,N-dimethylacetamide (DMA). First, various carboxylic acids exhibiting different steric bulk were screened. Conventional pivalic acid (1a) afforded a product 4aa in a low yield of 11% (entry 1). Tri(cyclohexylmethyl)acetic acid (1b), which was the most optimal for intramolecular C(sp²)-H arylation reactions,⁸ was not good in intermolecular reaction (entry 2). When α -mono- (1c and 1d) or α -di-substituted (1e and 1f) carboxylic acids were utilized, 4aa was not obtained at all (entries 3–6). Additionally, α -trisubstituted carboxylic acids such as 1-adamantancarboxylic acid (1g) were less effective than 1a (entry 7). When one of the methyl groups in 1a was replaced by a long alkyl chain (1h), 4aa was obtained in a low yield (entry 8). A carboxylic acid containing a cyclohexylmethyl group at the α -position (**1k**) was more effective than compounds possessing cyclohexyl (1i) or cyclohexylethyl groups (1j) at the same position to afford 4aa in moderate yield (entries 9–11). Thus, we subsequently designed and synthesized modified carboxylic acids based on the structure of 1k. When a cyclohexyl moiety of 1k was replaced with a t-butyl group (11), the yield of 4aa decreased (entry 12). On the other hand, replacing the cyclohexyl group with 1-adamantyl moiety (1m) was effective and afforded 4aa in 72% yield (entry 13). From these results, 1m was determined as the best carboxylate ligand source in the intermolecular reaction. When the loading of 1m was reduced to 10 mol%, the reaction proceeded well (73% yield).⁹ However, the reactions using 7.5 mol% and 5.0 mol% of 1m afforded 4aa in 53% and 47% yields, respectively.

The two key factors, which must be considered when elucidating the role of the carboxylate ligands, are basicity and steric bulk. Considering the basicity aspect, we have previously estimated the pKa values of carboxylic acids using the maximum values of their

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⁺ Footnotes relating to the title and/or authors should appear here.

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molecular electrostatic potential (max MEP)⁹ via a density functional theory (DFT) method (B3LYP/6-311G++(2d,p)).¹⁰ Despite analogous pKa values of α -trisubstituted carboxylic acids **1a**, **1b** and **1g–1m** (5.03–5.50),¹¹ the efficiency of **1a**, **1b** and **1g–1m** considerably differed (**Table S3**)⁹. Thus, it can be concluded that it is the steric effects rather than the electronic effects (basicity) of **1**, which are responsible for the efficiency of the reaction.

Table 1 The effects of carboxylic acids as ligand sources on the Pd-catalyzed C-H arylation reaction using 2a and $3a^a$



 a Conditions: **2a** (0.20 mmol), PdCl₂ (0.010 mmol, 5.0 mol %), carboxylic acid (1, 0.060 mmol, 30 mol %), Rb₂CO₃ (0.30 mmol, 1.5 equiv) in DMA (1.0 mL) and **3a** (1.0 mL) at 70 °C for 40 h. ^{*b*} Determined by GC analysis using an internal standard method.

With the optimal carboxylic acid **1m** in hand, various substrates were applied in the intermolecular $C(sp^2)$ -H bond arylation reactions (Table 2). The reaction using 4-bromotoluene (**2a**) and benzene (**3a**) afforded the corresponding product **4aa** in 62% isolated yield (entry 1). When the sterically crowded 2-bromotoluene (**2b**) was utilized as an aryl halide, the desired reaction proceeded smoothly to afford the desired product (**4ba**) in good yield (entry 2). Subsequently, various arenes (**3b**-**3e**) were evaluated in the intermolecular $C(sp^2)$ -H bond arylation reactions using 2-bromobenzene (**2b**) as the substrate. Applying 1,3-bis(trifluoromethyl)benzene (**3b**) at 55 °C resulted in the formation of **4bb** (entry 3). Both chloro and fluoro substituents were tolerated (**3c** and **3d**), successfully affording **4bc** and **4bd**

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as mixtures of isomers under mild reaction conditions, (entries 4 and 5). Utilizing 1,4-difluorobenzene (3e) as the argument of the product (4be) in a good yield (entry 6).

Next, various aryl halides (2c-2k) and an aryl triflate (2l) were tested in the intermolecular C(sp²)–H bond arylation reactions using 1,4-difluorobenzene (3e) as the aryl source. Pleasingly, a wide variety of functional groups were tolerant, and products having methyl (4ce), trifluoromethyl (4de), methoxy (4ee), and cyano (4fe) substituents at the p-position were successfully obtained at 45 °C in high isolated yields (entries 7–10). Furthermore, formyl and methoxycarbonyl groups at the oposition were also tolerated, and the corresponding products 4ge and 4he were successfully obtained at 45°C in high yields (entries 11 and 12). When these reactions were performed using 1a at a higher temperature (80 °C), the yields of 4ge and 4he were considerably decreased to 53% and 65%, respectively, with full conversion of 2. Introduction of naphthyl moieties using 1- or 2-bromonaphtharenes (2i and 2j) was achieved at 60 °C (entries 13 and 14). An electron-deficient aryl chloride (2k) as well as phenyl triflate (21) were also employed and the corresponding products **4ke** and **4le** were obtained at 60 °C and 50 °C, respectively (entries 15 and 16). When the reactions shown in entries 5 and 12 were carried out using 1b, which was determined as the most optimal carboxylate ligand source in the intramolecular reactions,⁸ the products were obtained in 61 and 49 % yields, respectively. Thus, 1m proved to be the best carboxylate ligand source in the intermolecular reactions in terms of realizing milder reaction condition and wide functional group tolerance.

In order to elucidate reaction mechanisms, the kinetic isotope effect (KIE) was measured by comparing the initial rates of the reactions using benzene (**3a**) and benzene- d_6 at 90 °C (Scheme 1),⁹ affording $k_{\rm H}/k_{\rm D}$ = 5.61, which is in agreement with the value reported in the literature.¹³ Accordingly, the C–H bond cleavage must be involved in the rate-determining step. Our preliminary DFT calculation also revealed that the C–H bond cleavage is the rate-determining step.⁹



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Table 2 Scope of substrates^a

			R ↓ + 2 +	H 3 PdCl ₂ Im (30 Rb ₂ CO DMA / J Temp.,	5.0 mol%) mol%) l ₃ (1.5 equiv) 3 (1:1, v/v) 40 h	R Isolated	d yield		
entry	Ar-X (2)	Ar-H (3)	product (4)	Temperature / Isolated yield	entry	Ar-X (2)	Ar-H (3)	product (4)	Temperature / Isolated yield
1	Br	\bigcirc		70 °C / 62%	9 M	MeO Br	F	MeO	45 °C / 80%
	2a	3a	4aa			2e	3e	4ee	
2	Br			70 °C / 60%	10	NC	F	NC F	45 °C / 89%
	20	3a	4ba			2f	3e	4fe	
3	Br	CF ₃ CF ₃	CF3 CF3	55 °C / 86%	11	CHO Br	F	CHO F	45 °C / 89%
	2b	3b	4bb			2g	3e	4ge	
4	Br	CI	CI	60 °C / 72% ^b	12	Br	Me F		45 °C / 96%
	26	30	4bc			20	зе	4ne	
5	Br	F	F	45 °C / 73%°	13	Br	F	F	60 °C / 95%
	2b	3d	4bd			2 i	3e	4ie	
6	Br	F	F	40 °C / 76%	14	Br	F	F	60 °C / 98%
	2b	3e	4be			2j	3e	4je	
7	Br	F	F	45 °C / 70%	15 (D ₂ N CI	F	O ₂ N F	60 °C / 69%
	2c	3e	4ce			2k	3e	4ke	
8	F ₃ C ^{Br}	F F 3e	3C 4de	45 °C / 89%	16	OTf	F F	F F F	50 °C / 76%
						21	3e	410	

^aConditions: 2 (0.20 mmol), PdCl₂ (0.010 mmol, 5.0 mol %), 1m (0.060 mmol, 30 mol %), Rb₂CO₃ (0.30 mmol, 1.5 equiv) in DMA (1.0 mL) and 3 (1.0 mL) for 40 h. ^bA mixture of three isomers (ortho : meta : para = 33:18:49). ^cA mixture of two isomers (ortho : para = 91:9).

We previously proposed that in intramolecular reactions, the steric effect of the bulky carboxylic acid (1b) used as a ligand source most likely generates active mononuclear Pd species, which accelerates the rate-determining C-H bond cleavage step.8 When carboxylic acids 1a, 1k, 1m and 1b were tested in the intramolecular reactions using 5 in DMA at 70°C, the bulkiest carboxylic acid 1b was the most effective, giving 6 in the highest yield (Scheme 2 (a)). On the other hand, in the intermolecular C(sp²)–H bond arylation reaction, 1b was not effective and carboxylic acid 1m proved to be the most optimal carboxylate ligand source (Scheme 2 (b)). We suspect that as a consequence of its bulkiness, 1b would prevent the access of the

substrate arenes to the Pd center in the intermolecular reactions. Overall, 1m exhibits suitable bulkiness for generating reactive mononuclear Pd species as well as for facilitating access of the substrate to the Pd center.

In summary, we found that a bulky carboxylic acid bearing a 1adamantylmethyl moiety and two methyl groups at the α -position (1m) acted as an efficient carboxylate ligand source in Pd-catalyzed intermolecular C(sp²)-H bond arylation reactions. The desired reactions proceeded smoothly under very mild conditions. Studies to extend the scope of 1m to a variety of C-H activation reactions and

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to elucidate the reaction mechanism as well as the effects of bulky carboxylate ligands are currently underway.

Scheme 2 Comparison of steric effect of carboxylic acids between (a) intramolecular- and (b) intermolecular $C(sp^2)\mbox{--}H$ bond arylation



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Conflicts of interest

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There are no conflicts to declare.

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