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## Steric Effect of Carboxylate Ligands on Pd-Catalyzed Intramolecular C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H Bond Arylation Reactions

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**Abstract:** A bulky carboxylic acid bearing three cyclohexylmethyl substituents at the  $\alpha$ -position, i.e., tri(cyclohexylmethyl)acetic acid, is demonstrated to act as an efficient ligand source in the Pd-catalyzed intramolecular C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H bond arylation reactions. The reactions proceed smoothly under mild reaction conditions, even at room temperature, taking advantage of the steric bulk of the carboxylate ligands, which accelerates the rate-determining C–H bond activation step in the catalytic cycle.

Carboxylate ligands have proved to be invaluable components in transition metal-catalyzed carbon-hydrogen (C-H) bond activation reactions.<sup>[1]</sup> A pioneering study reported by Fagnou showed that in Pd-catalyzed C-H bond arylation reactions, the pivalate ligand is particularly efficient compared to the conventional acetate ligand.<sup>[2]</sup> The addition of pivalic acid allows realizing milder reaction conditions in various intramolecular C-H arylation reactions<sup>[3]</sup> as well as in the intermolecular C-H arylation of electron-deficient arenes<sup>[4]</sup> and electron-rich heteroarenes.<sup>[5]</sup> Pivalate is a slightly stronger base than acetate (the pKa values<sup>[6]</sup> of pivalic acid and acetic acid are 5.03 and 4.76, respectively), which facilitates the intramolecular deprotonation step.<sup>[7]</sup> In contrast, the steric effect of the carboxylate ligand could be crucial. However, only a few studies have elucidated the specific effect of the steric bulk of carboxylate ligands on the catalytic C-H bond activation reactions.[3e,5g,8] In fact, only known bulky carboxylic acids such as pivalic and 1adamantanecarboxylic acids are currently employed as efficient carboxylate ligand sources.<sup>[2-5]</sup> Recently, Thompson et al. extensively studied the steric effect of carboxylate ligands using 24 different carboxylic acids as additives in the Pd-catalyzed direct arylation polymerization (DArP) at 160 °C.<sup>[9]</sup> The results indicated that the yields of the polymers were not affected by the steric bulk of added carboxylic acids, whereas the smallest one, i.e., cyclopropanecarboxylic acid, provided a polymer with very high molecular weight.

We previously developed various bulky ligands such as pyridines,<sup>[10a]</sup> amines,<sup>[10b]</sup> phosphines,<sup>[10c-e]</sup> and *N*-heterocyclic carbenes<sup>[10f]</sup> bearing substantial steric bulk, which enabled high catalytic activities by suppressing aggregation of catalyst species. We envisioned that carboxylate ligands of appropriate steric bulk, not basicity, would realize highly active catalysts for C–H bond activation reactions. Herein, we describe the design and preparation of carboxylic acids of different steric congestion, and

evaluate them as carboxylate ligands in the Pd-catalyzed intramolecular  $C(sp^2)$ –H and  $C(sp^3)$ –H bond arylation reactions. The steric effect of added carboxylic acids was found to be crucial. Thus, the addition of carboxylic acid of suitable steric bulk remarkably enhanced the catalytic activity and the C–H arylation reactions were shown to occur under milder reaction conditions, even at room temperature.

First, various carboxylic acids were screened as ligand sources for the Pd-catalyzed intramolecular C(sp<sup>2</sup>)-H bond arylation reaction using (2-bromobenzyloxy)benzene (2a)[3e,11] as a substrate. The intramolecular C-H arylation reactions are usually performed at a high reaction temperature (over 100 °C);<sup>[3]</sup> however, herein, the reactions in Table 1 were performed at a low temperature (70 °C) for short reaction time (3 h) to evaluate the efficiency of the added carboxylic acid (1) evidently, employing 30 mol% of **1** in the presence of a catalytic amount (3.0 mol%) of PdCl<sub>2</sub>, and K<sub>2</sub>CO<sub>3</sub> (1.5 equiv) in *N*,*N*-dimethylacetamide (DMA) (conditions A). In the study reported by Fagnou, phosphine ligand was added to the Pd catalytic system.<sup>[2a-b,3,4,5a-d]</sup> However, Hartwig observed that the reactions proceeded in a similar manner without the need for adding phosphines.<sup>[12]</sup> Therefore, for an unambiguous observation of the effect of the carboxylic acid, we performed the reactions without adding any phosphine ligand. As catalyst precursors, PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub> were examined and comparable results were found under the present reaction conditions. Thus, PdCl<sub>2</sub> was selected as a catalyst precursor to eliminate contamination by acetate ligand. Pivalic acid (1a) proved ineffective at 70 °C and product (3a) was obtained in only 14% yield (entry 1, Table 1), whereas the yield increased to 78% at 110 °C and 85% at 125 °C. In the absence of the added carboxylic acid, only a trace amount of 3a was detected in the reactions performed at 70-125 °C. In addition, α-mono- (1b and **1c**) and  $\alpha$ -di- (**1d** and **1e**) substituted carboxylic acids were not effective as ligands (entries 2–5). As for  $\alpha$ -tri-substituted carboxylic acids, 1-adamantanecarboxylic acid (1f) was also inefficient (entry 6). However, other  $\alpha$ -tri-substituted carboxylic acids such as 1g, 1h, 1i, 1j, and 1k afforded 3a in higher or comparable yields compared with **1a** (entries 7–11). Eventually, **11** bearing three cyclohexylmethyl substituents at the  $\alpha$ -position afforded 3a in 93% yield (entry 12). Carboxylic acids containing aromatic rings such as 1m, 1n, 1o, and 1p were ineffective (entries 13-16). Furthermore, at even 25 °C with 11 using 1,3dimethyl-2-imidazolidinone (DMI) as a solvent and Rb<sub>2</sub>CO<sub>3</sub> as a base (conditions B), 3a was obtained in 97% GC yield and 95%

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isolated yield (entry 12). As a Pd catalyst precursor, Pd(OAc)<sub>2</sub> and Pd(NO<sub>3</sub>)<sub>2</sub> in place of PdCl<sub>2</sub> in entry 12 under conditions B also afforded **3a** in 87% and 96% yields, respectively. In contrast, **1a** only provided **3a** in 20% yield under conditions B (entry 1).<sup>[13]</sup> Other  $\alpha$ -mono- (**1b** and **1c**),  $\alpha$ -di- (**1d** and **1e**), and  $\alpha$ -trisubstituted carboxylic acids (**1f**-**k** and **1m**) or aromatic carboxylic acids (**1n**-**p**) proved less effective than **1I** under conditions B (entries 2–11 and 13-16). From these results, it can be concluded that **1I** was the most effective carboxylate ligand source under conditions A and B (entry 12).<sup>[13]</sup>

It is well known that the p*K*a values of carboxylic acids are closely related to the maximum values of their molecular electrostatic potential (max MEP).<sup>[14]</sup> Thus, p*K*a values of **1f–I** were assessed with the max MEP values calculated via DFT method (B3LYP/6-311G++(2d,p)).<sup>[15]</sup> Even with almost similar p*K*a values of **1f–I** (5.27–5.63),<sup>[16]</sup> efficiency of the added **1f–I** differed largely among each other (Table 1). This suggests that steric effects rather than electronic effects (basicity) of **1** are responsible for the efficiency in the C–H arylation reactions.

Table 1. Effect of Carboxylic Acid Additives on the Pd-catalyzed C-H Arylation Reaction of  ${\bf 2a}$ 



[a] Conditions A: **2a** (0.20 mmol), PdCl<sub>2</sub> (0.0060 mmol, 3.0 mol %), carboxylic acid (**1**, 0.060 mmol, 30 mol %), K<sub>2</sub>CO<sub>3</sub> (0.30 mmol, 1.5 equiv) in DMA (1.50 mL) at 70 °C for 3 h. [b] Conditions B: PdCl<sub>2</sub> (0.010 mmol, 5.0 mol %), carboxylic acid (**1**, 0.060 mmol, 30 mol %), Rb<sub>2</sub>CO<sub>3</sub> (0.30 mmol, 1.5 equiv) in DMI (0.50 mL), **2a** (0.20 mmol) at 25 °C for 40 h. [c] Determined by GC analysis using an internal standard method. [d] Yield of isolated product

Next, with the selected carboxylic acid 11 in hand, various substrates (2b-r) were examined (Table 2). A wide variety of fanctionalities were torelated, and products having methoxy (3b), chloro (3c), formyl (3d), methoxycarbonyl (3e), acetyl (3f), cyano (3g), trifluoromethyl (3h) and nitro (3i) substituents were successfully obtained at 25°C in high isolated yields (entries 1-8). Substrates with amine (2j:  $Ms = SO_2CH_3$ ) and amide (2k) tethers also afforded the products (3j and 3k) at 25°C in high isolated yields (entries 9-10), whereas 31 with an ester tether was obtained in 83% yield at 50°C (entry 11). When the reaction of 2I using 1a at higher temperature (100 °C), most of 2I was decomposed and 3I was not obtained at all. The C(sp<sup>2</sup>)-H bond arylation of naphthalene and thiophene rings provided sixmembered rings (3m and 3n) in high yields at 25 °C (entries 12-13). Furthermore, five-membered rings were easily afforded at 25 °C via the C(sp<sup>2</sup>)-H bond arylation of indole ring (3o), whereas 9-fluorenone (3p) and carbazole (3g) skeltons were similarly constructed at 50 °C and at 60 °C, respectively (entries 14-16). In addition, a seven-membered ring product (3r) was smoothly afforded at 70 °C (entry 17).





In general, intramolecular  $C(sp^3)$ –H arylation reactions are known to require high reaction temperatures (~150 °C).<sup>[2b,3c,d]</sup> In contrast, when the reaction of **2s** was performed with **1I** at 90 °C in the presence of a catalytic amount (5.0 mol%) of PdCl<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> (1.5 equiv) in DMA without added phosphine ligands, the corresponding product **3s** was obtained in 84% isolated yield (Scheme 1a). Once again, **3s** was not obtained in the absence of carboxylic acids. In Scheme 1a, **1a** in place of **1I** under otherwise identical conditions afforded **3s** in only 3% yield at 90 °C,<sup>[17]</sup> whereas the yields increased to 48% at 150 °C. When **1b**, **1c**, **1d**, **1e**, **1f**, **1i**, or **1k** was used instead of **1I** in Scheme 1a, **3s** was obtained in only 0%, 2%, 3%, 16%, 12%, 9%, or 32% yields,

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respectively. Thus, again, **1I** was demonstrated to be particularly effective in the C(sp<sup>3</sup>)-H arylation.<sup>[17]</sup> Moreover, upon addition of **1I**, substrates **2t** and **2u** afforded the corresponding products **3t** and **3u** in 84% and 76% isolated yields at 90 °C and 60 °C, respectively (Scheme 1b, c).



[a] Conditions: **2s-u** (0.20 mmol), PdCl<sub>2</sub> (0.010 mmol, 5.0 mol%), **1I** (0.060 mmol, 30 mol%),  $K_2CO_3$  (0.30 mmol, 1.5 equiv) in DMA (2.0 mL) at 90 °C for 16 h. [b] At 60 °C.

Scheme 1. Intramolecular C(sp<sup>3</sup>)–H Arylation Reactions<sup>[a]</sup>

Kinetic isotope effect (KIE) was measured by comparing initial rates of the reactions using **2a** and **2a**- $d_3$  (2-BrC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>-O-(2,4,6- $d_3C_6H_2$ ) under conditions A, affording  $k_H/k_D$  = 4.68.<sup>[15]</sup> Thus, the C–H bond cleavage step must be involved in the rate-determining step.

From the results obtained, the steric effect of the carboxylate ligands can be considered crucial in the present reaction (vide supra). The steric effect of  $\alpha$ -tri-substituted carboxylic acids could be evaluated by analyzing the C1(carbonyl carbon)–C2( $\alpha$ -C)– C3( $\beta$ -C)–C4( $\gamma$ -C) dihedral angle,  $\theta$  (Scheme 2). To this end, single crystals of 11 suitable for X-ray crystallographic analysis were successfully obtained and the corresponding X-ray structure is shown in Figure 1. The dihedral angles  $\theta$  obtained from the X-ray structure are 28.2°, 68.8°, and 178.9° (R = Cy: cyclo-C<sub>6</sub>H<sub>11</sub> in Scheme 2). Further DFT optimization (with B3LYP/6-311G++(2d,p)) with the X-ray structure in Figure 1 as an initial structure afforded the dihedral angles  $\theta$  of 54.5°, 65.9°, and 175.2°. Accordingly, two of the three Cy- substituents would be located in close proximity to the carboxy group causing considerable steric congestion around the coordination site of Pd. In contrast, such steric effect cannot be expected for pivalic acid (R = H in Scheme 2).



Scheme 2. Dihedral Angle for α-tri-Substituted Carboxylic Acid



Figure 1. X-ray Structure of 1I

Cotton et al. examined the X-ray crystal structures of three Pd carboxylates of formula  $[Pd(O_2CR^1)_2]_3$  (R<sup>1</sup> = Et, tBu, 2,4,6-MeC<sub>6</sub>H<sub>2</sub>),<sup>[18a]</sup> finding that all these complexes had analogous trimer structures containing Pd<sub>3</sub> triangles with each pair of Pd atoms bridged by two carboxylate ligands. Notably, these structures are very similar to the trimer structure of the corresponding acetate complex.<sup>[18b,c]</sup> Ozawa et al. reported the structures of  $[PdPh(\mu-O_2CR^2)(PPh_3)]_n$  (R<sup>2</sup> = CH<sub>3</sub> and tBu) complexes<sup>[18d]</sup> relevant to active catalyst species in DArP.<sup>[9,18e]</sup> In this case, they found that acetate and pivalate complexes had almost similar dimer structures:  $[PdPh(\mu-O_2CR^2)(PPh_3)]_2$  (R<sup>2</sup> = CH<sub>3</sub> and tBu). Thus, the structures and nuclearity of these carboxylate complexes did not seem to be affected by the carboxylate ligands. In contrast, 11 introduces a considerable steric bulk around the Pd center as suggested by Figure 1 and Scheme 2 (R = Cy). Therefore, in the present study, the unique steric effect of 1I as a ligand source most likely generates an extremely active mononuclear Pd catalyst species, which could accelerate the rate-determining C-H bond cleavage step even under mild reaction conditions. Further studies on the reaction mechanism are currently in progress.

In summary, we found that a bulky carboxylic acid bearing three cyclohexylmethyl substituents at the  $\alpha$ -position worked as an efficient ligand in the Pd-catalyzed intramolecular C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H bond arylation reactions. The reactions proceed smoothly under very mild conditions, even at room temperature. Studies to extend the scope of **1I** to a variety of C–H activation reactions are currently underway.<sup>[19]</sup>

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**Keywords:** Arylation • Carboxylic Acid • C-H Activation • Palladium

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- [13] Fagnou at al. reported that the use of  $(4-FC_6H_4)_3P$  or PPh<sub>3</sub> with **1a** enhanced the catalytic reactivity in the  $C(sp^2)$ -H arylation reaction.<sup>[3e]</sup> However, the addition of 5 mol% of  $(4-FC_6H_4)_3P$  or PPh<sub>3</sub> to entry 1 in Table 1 under conditions B resulted in the formation of **3a** in only 7% yield in both cases. Furthermore, upon addition of 5 mol% of  $(4-FC_6H_4)_3P$  or PPh<sub>3</sub> to entry 12 in Table 1 (with **1I**) under conditions B, the yield of **3a** decreased considerably from 97% to 14% or 16%, respectively. When the loading of **1I** was reduced to 10 mol% under conditions B, the reaction perfectly proceeded after 72 h.
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- [17] The use of PCy<sub>3</sub>·HBF<sub>4</sub><sup>[2b,3c,d]</sup> (10 mol%) with **1a** under otherwise identical reaction conditions only increased slightly the yield of **3s** from 3% to 5%. Furthermore, the use of PCy<sub>3</sub>·HBF<sub>4</sub> (10 mol%) with **1I** in Scheme 1a afforded a dramatic decrease of the yield of **3s** from 84% to 6%.
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- [19] When the intermolecular C-H arylation reaction of 4-bromotoluene with benzene was carried out, **1I** was not effective (See Supporting Information for details).

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The design and preparation of carboxylic acids of different steric congestion, and evaluation of them as carboxylate ligands in the Pdcatalyzed intramolecular  $C(sp^2)$ –H and  $C(sp^3)$ –H bond arylation reactions. It can be concluded that a bulky carboxylic acid bearing three cyclohexylmethyl substituents at the  $\alpha$ -position, i.e., tri(cyclohexylmethyl)acetic acid was the most effective carboxylate ligand source.