

# Spatial Anion Control on Palladium for Mild C–H Arylation of Arenes

Jyoti Dhankhar, Elisa González-Fernández, Chao-Chen Dong, Tufan K. Mukhopadhyay, Anthony Linden, and Ilija Čorić\*



Cite This: <https://dx.doi.org/10.1021/jacs.0c09611>



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Supporting Information

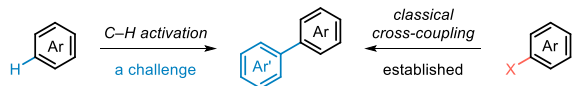
**ABSTRACT:** C–H arylation of arenes without the use of directing groups is a challenge, even for simple molecules, such as benzene. We describe spatial anion control as a concept for the design of catalytic sites for C–H bond activation, thereby enabling nondirected C–H arylation of arenes at ambient temperature. The mild conditions enable late-stage structural diversification of biologically relevant small molecules, and site-selectivity complementary to that obtained with other methods of arene functionalization can be achieved. These results reveal the potential of spatial anion control in transition-metal catalysis for the functionalization of C–H bonds under mild conditions.

Catalytic activation of C–H bonds with transition metals offers a transformative methodology for organic synthesis, enabling more sustainable and resource-efficient processes.<sup>1–5</sup> In particular, the direct arylation of C–H bonds in arenes represents a streamlined alternative to common C(sp<sup>2</sup>)–C(sp<sup>2</sup>) cross-coupling reactions, which require prefunctionalized substrates (Figure 1a).<sup>6</sup> Palladium

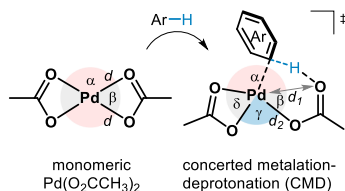
direct arylation process remains a challenge,<sup>19</sup> even for simple substrates.

Experimental and theoretical studies of palladium-based catalytic C–H activation reactions often support a concerted metalation–deprotonation (CMD)<sup>31</sup> mechanism, where the metal and the coordinated anion cooperatively cleave the C–H bond through a six-membered cyclic transition state (Figure 1b).<sup>22,32–40</sup> Although palladium(II) acetate is a common precatalyst for C–H functionalizations and computational studies suggest that simple mononuclear palladium(II) carboxylates could promote facile C–H activation,<sup>34,36</sup> the reactions without additives are inefficient, in part due to the coordination behavior of the carboxylate groups. Carboxylates can block potential substrate coordination sites through  $\kappa^2$ -coordination and behave as bridging ligands to form species of higher nuclearity.<sup>41,42</sup> Nondirected, palladium-catalyzed C–H activation reactions, where the arene is the limiting reactant, are accelerated by using various neutral and anionic ligands.<sup>7,8,14,18,26</sup> For example, 2-pyridone and combined amino acid–pyridine systems were recently utilized for direct C–H olefination and cyanation reactions.<sup>7–10,12</sup> However, the development of new concepts for nondirected C–H activation could further facilitate rational catalyst design, thereby enabling reduced ligand loadings, mild reaction conditions, and challenging late-stage functionalizations and impact the development of ligand-controlled regioselectivity. With these goals in mind, we describe here a general strategy for the design of palladium(II) sites for C–H activation and demonstrate nondirected C–H arylation of arenes as limiting

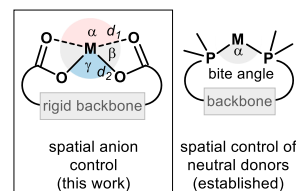
a) Increase of molecular scaffold complexity by direct C–H arylation



b) Relevance of anion coordination geometry for C–H activation



c) Spatial control in metal catalysis



**Figure 1.** Spatial anion control concept for C–H activation.

shows promise for versatile, nondirected transformations of C–H to C–C bonds,<sup>7–14</sup> although the catalytic activity, regioselectivity, application to complex molecules, and reactions such as C–H arylation remain challenging.<sup>15–19</sup> Arylation of arenes without the use of directing groups requires excess arene, high temperatures, and acidic, basic, or transition-metal additives and is limited to certain classes of substrates.<sup>18–30</sup> C–H arylation of simple dialkyl arenes as limiting reactants was recently enabled by a palladium-catalyzed, norbornene derivative-mediated functionalization process, but in the case of benzene, an excess of the substrate was required.<sup>18</sup> A nondirected C–H activation followed by a

Received: September 7, 2020



reactants at ambient temperature. The method utilizes rationally designed bis(carboxylate) anions, palladium(II) precatalysts, and iodine(III) arylation reagents and avoids additives such as silver(I) salts.<sup>43–48</sup>

The geometric parameters of the carboxylate coordination on palladium, namely, the O–Pd–O angles and Pd–O distances, change significantly in the CMD transition state (Figure 1b). We envisioned that the controlled spatial arrangement of constrained bis(anions) could modulate the coordination parameters, as exemplified in Figure 1c, left. The spatial anion control could lead to stabilization of the geometry required for the CMD transition state over, for example,  $\kappa^2$ -coordination in the palladium-bis(carboxylate) catalyst, thus lowering the barrier for C–H activation. This approach can be compared with the well-established spatial control of neutral donors in transition-metal catalysis where parameters, such as the bite angle, are influenced by the geometric requirements of the ligand backbone (Figure 1c, right).<sup>49</sup>

Our anion design for spatial anion control on palladium, as shown in Figure 2a, utilizes two 1-naphthyl carboxylic acid-derived side-arms, which are structurally constrained by a central aromatic spacer group. The size and geometry of the spacer modulates the relative spatial arrangement of the four carboxylate oxygen atoms, while sterically demanding mesityl groups prevent the carboxylate groups from coordinating in a

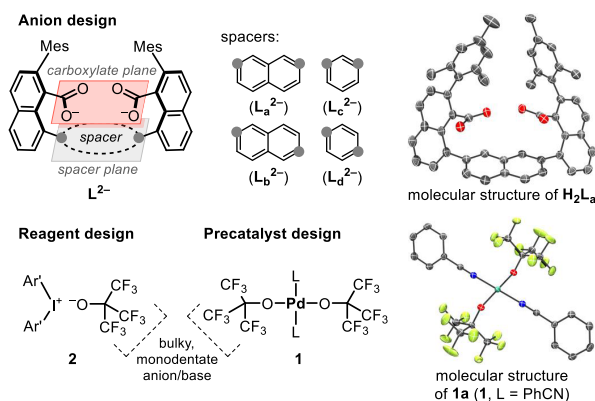
bridging mode. The crystal structure of the constrained bis(carboxylic) acid  $H_2L_a$  (spacer = 2,7-naphthyl) confirms that the carboxylate groups are arranged approximately in a plane, which is parallel to that of the central arene spacer. Palladium precatalysts **1** and arylation reagents **2**, which contain nonafluoro-*tert*-butoxide anions, were designed with the goal of avoiding the use of silver(I) compounds and any other potentially interfering additives or anions (Figure 2a). The bulky monodentate  $(CF_3)_3CO^-$ , which does not participate in the six-membered CMD process, can be displaced from palladium by  $H_2L_a$  (see Supporting Information) and act as a mild base<sup>50</sup> to remove  $H^+$  after the C–H activation step, as demonstrated by the Larossa group.<sup>51–54</sup>

The potential of the proposed spatial anion control to address challenging C–H functionalization reactions with palladium was examined by performing the nondirected arylation of arenes as limiting reactants. The constrained bis(carboxylic) acid  $H_2L_a$  and palladium precatalyst **1a** enabled catalytic C–H arylation of arene **3a** with diaryl iodonium reagent **2a** at ambient temperature, yielding **4a** in 39% yield (Figure 2b, Figure S2). In contrast,  $H_2L_b$  and  $H_2L_c$  afforded **4a** in 17% and 1% yield, respectively, whereas with  $H_2L_d$  and simpler carboxylates,<sup>22,55–57</sup> no product was observed (Figure 2c, see Figure S1 for additional screening and control experiments), which attests to the relevance of the relative spatial positioning of the two carboxylate groups for the catalytic reactivity. Furthermore, a derivative of  $H_2L_a$ , which lacks the shielding mesityl groups, exhibited no reactivity (Figure S1b). Diaryl iodonium salts with  $BF_4^-$  and  $CF_3SO_3^-$  anions have been used previously for the nondirected functionalization of arenes, but high temperature, an acid cosolvent, and an excess of arene were required.<sup>24,27</sup> In our system, the common diaryl iodonium salts were unsuitable, while other palladium precatalysts proved to be inferior to **1a**, thereby demonstrating the importance of the  $(CF_3)_3CO^-$  anion (Figure 2c).

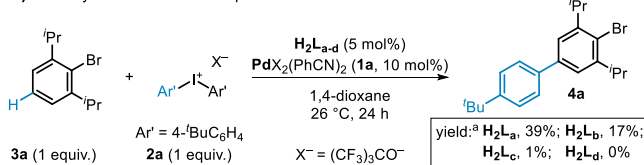
The constrained anion-enabled catalytic C–H arylation is applicable to a wide range of arenes **3** at 26 °C (Scheme 1). C–H arylation of substrate **3a** with increased precatalyst loading provided biaryl product **4a** in 55% isolated yield, while C–H functionalization of benzene using 5 mol % of  $H_2L_a$  and 10 mol % of **1a** afforded monoarylation and bis-arylation products in a combined yield of 58% after 1 day (**4b**). Arenes with strongly activating groups undergo efficient arylation at the sterically exposed electron-rich C–H site (**4c**, **4d**). Aryl and bulky alkyl substituents effectively suppress ortho C–H activation (**4e–g**), although arylation next to smaller alkyl groups, such as methyl, is possible unless an additional meta substituent is present (**4h**). Halogen-substituted arenes are similarly functionalized at the meta and para positions to the halogen group (**4i–n**). Iodoarenes and aryl triflates can be used as substrates, demonstrating complementary reactivity of the current system to common Pd-catalyzed carbon–carbon bond-forming processes (**4l–o**).<sup>6</sup> Fused (hetero)arenes are suitable substrates, and yields of up to 86% could be obtained with naphthalene derivatives (**4p–s**). In cases where two equivalent C–H bonds are present, bis-functionalization is observed (**4p**, **4q**, **4s**), which further demonstrates the potential for polyarylation reactions (**4p-bis**).

The direct C–H arylation is compatible with electrophilic functional groups, such as activated ketones and epoxides (**4t**, **4u**), and is suitable for late-stage functionalization of functionally rich molecules, as demonstrated with tryptophan

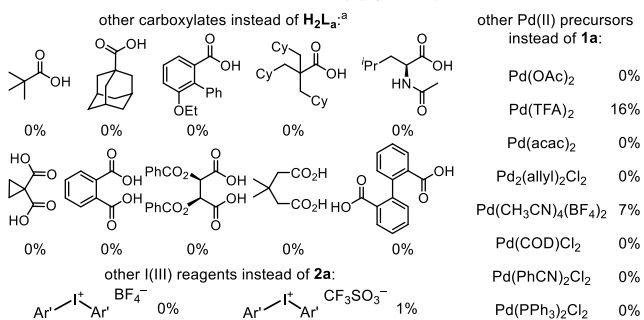
### a) Design of the catalytic system



### b) C–H arylation at ambient temperature

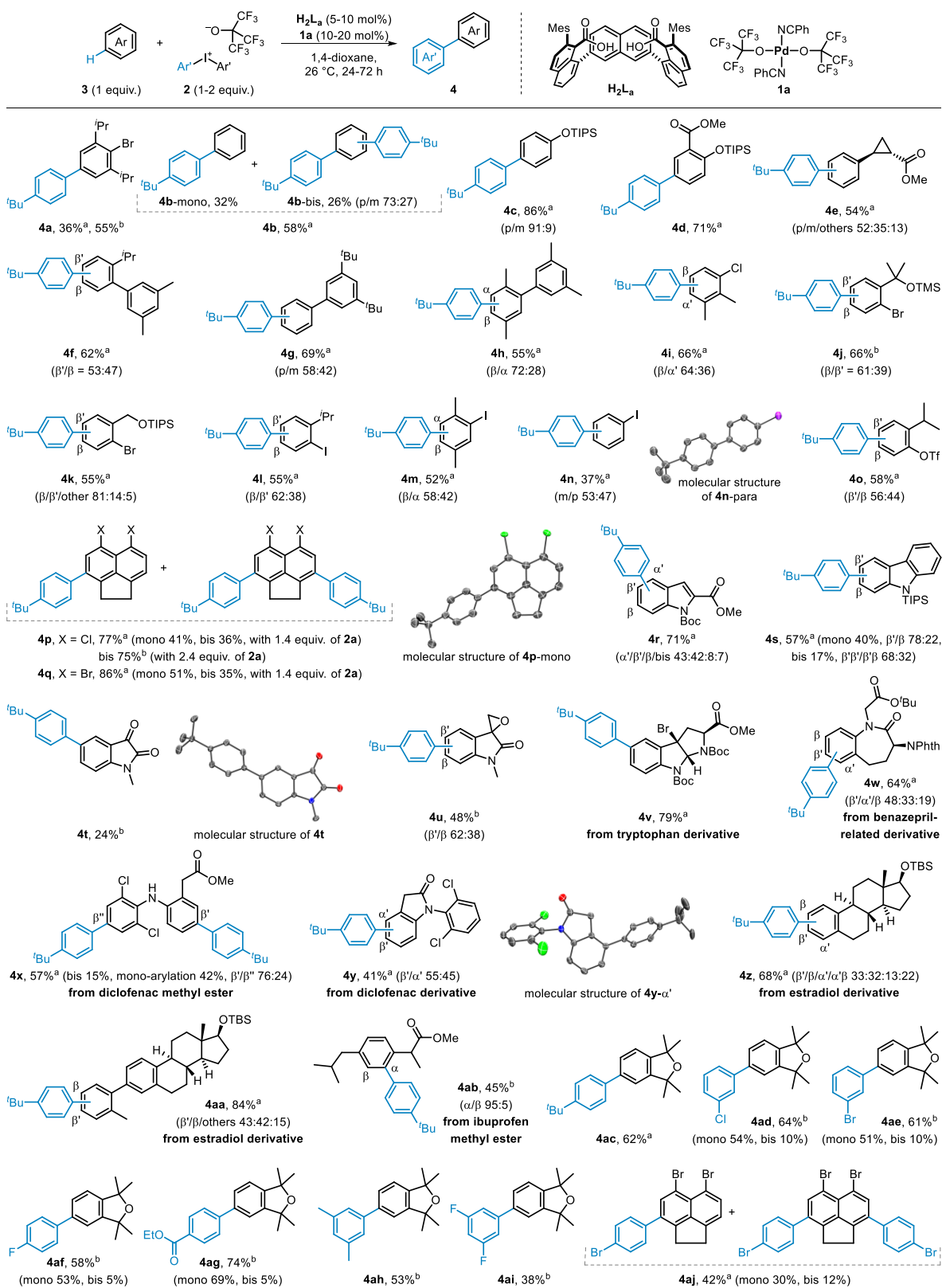


### c) Variations from optimal reaction components ( $H_2L_a$ , **1a**, **2a**)<sup>a</sup>



**Figure 2.** Development of a catalytic system for mild C–H arylation.  
<sup>a</sup>For details, see Supporting Information.

## Scheme 1. C–H Arylation Reactions at Ambient Temperature



<sup>a</sup> $H_2L_a$  (5 mol %), **1a** (10 mol %), 24–72 h. <sup>b</sup> $H_2L_a$  (10 mol %), **1a** (20 mol %), 48–72 h. Combined yields of isolated products are given.

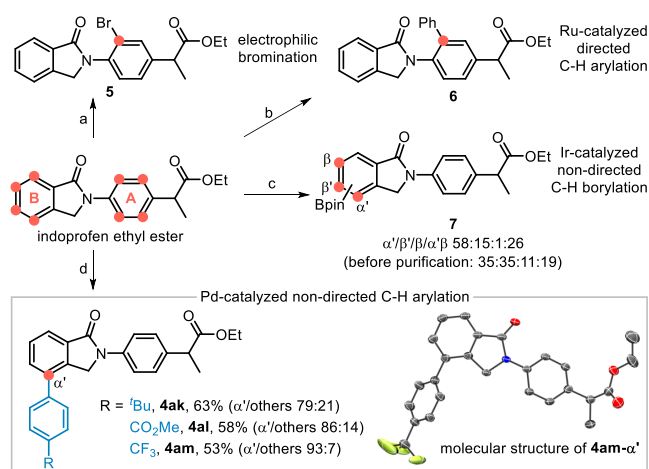
derivative **3v** and 1-benzazepine-derived compound **3w** (**4v**, **4w**). Interestingly, while the C–H bond para to the electron-donating nitrogen substituent in **3v** was strongly favored, the electronically related arene in **3w** showed comparable reactivity

for two other C–H bonds. The influence of the substrate structure on the regioselectivity is further exemplified by the arylation of diclofenac and estradiol derivatives. The regioselectivity obtained with diclofenac methyl ester **3x** is

directed by the electron-donating free amine group to the para positions of both arenes, while in the cyclic amide derivative **3y**, the  $\alpha'$  and  $\beta'$  sites are arylated (**4x**, **4y**). For the estradiol derivatives, significant arylation is observed ortho to the methylene group in **4z**, in comparison with the methyl group in **4aa**. In the absence of more sterically accessible sites, the reaction can take place ortho to larger aliphatic groups, as demonstrated by the highly regioselective C–H arylation of ibuprofen methyl ester (**4ab**). The catalytic C–H arylation enables the introduction of different aromatic groups, which possess electron-withdrawing or -donating substituents in meta or para positions (**4ac–4ai**). The subsequent C–H arylation of the product at the newly introduced aryl group becomes significant when sterically exposed C–H bonds are present (**4ad**, **4ae**). Polybrominated polyaromatic hydrocarbons can be accessed when halogen substituents are present in both reaction substrates (**4aj**).

Next, the regioselectivity of the C–H arylation reaction was compared with other common methods for arene functionalization by using indoprofen ethyl ester as the substrate (Scheme 2; for additional studies about the regioselectivity, see

### Scheme 2. Site-Selectivity in Comparison with Other Methods for Arene Functionalization<sup>a</sup>



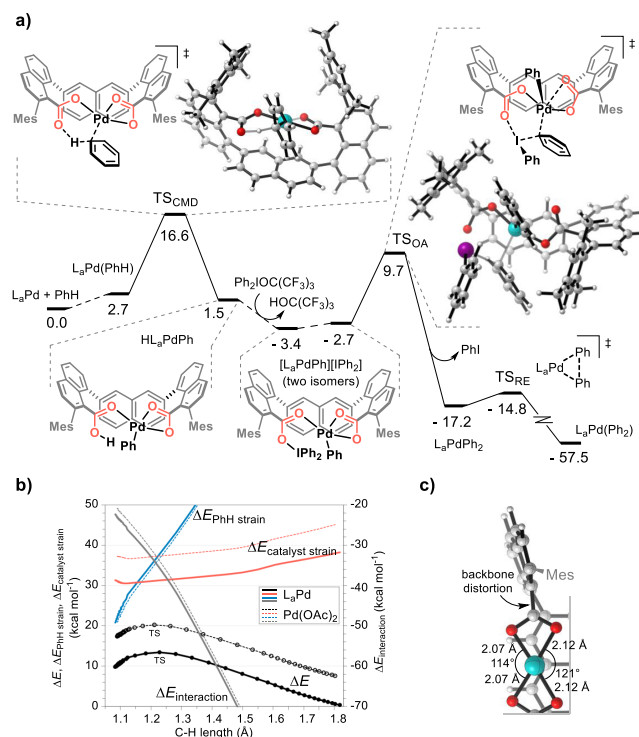
• = C(sp<sup>2</sup>)-H sites in the reactant and the main functionalization sites in the products

<sup>a</sup>Conditions: (a) Br<sub>2</sub>, DMF, rt, 20 h, 46%; (b) PhB(OH)<sub>2</sub> (2.5 equiv), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol %), AgSbF<sub>6</sub> (20 mol %), Ag<sub>2</sub>O (1 equiv), Cu(OTf)<sub>2</sub> (20 mol %), THF, 90 °C, 20 h, 85% (from ref 58); (c) B<sub>2</sub>pin<sub>2</sub> (0.72 equiv), [Ir(COD)OMe]<sub>2</sub> (1 mol %), dtbbpy (2 mol %), THF, 50 °C, 2 h, 30%; (d) **2a**, **2i**, or **2j** (1.2 equiv), H<sub>2</sub>L<sub>a</sub> (10 mol %), **1a** (20 mol %), 1,4-dioxane, 26 °C, 72 h.

Supporting Information). Direct bromination with Br<sub>2</sub> and the reported amide-directed ruthenium-catalyzed C–H arylation<sup>58</sup> result in the functionalization of the more electron-rich arene A. Conversely, iridium-catalyzed C–H borylation<sup>5</sup> functionalizes the  $\alpha'$ ,  $\beta'$ , and  $\beta$  positions on the more sterically accessible arene B (for the regioselectivity under different conditions, see Supporting Information). Despite the presence of more exposed C–H bonds, our reaction proceeds at the  $\alpha'$  position with good regioselectivity, thereby enabling direct C–H functionalization of indoprofen ethyl ester with aryl groups, which possess electron-rich (**4ak**), electron-poor (**4al**), and fluorinated substituents (**4am**).

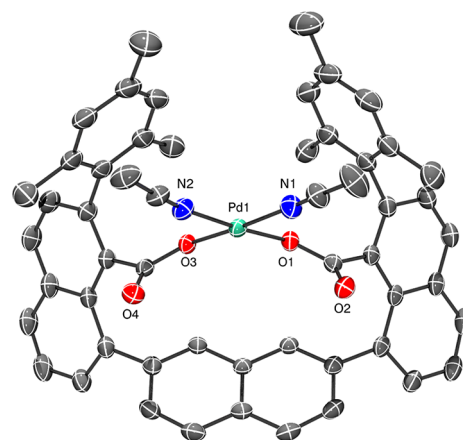
The proposed mechanism of the C–H arylation reaction, which is supported by DFT calculations using benzene and

Ph<sub>2</sub>IOC(CF<sub>3</sub>)<sub>3</sub> as model substrates and L<sub>a</sub>Pd as the active catalytic species, is shown in Figure 3a (for details, see Tables



**Figure 3.** Role of the constrained bis(carboxylate). (a) Calculated free energy profile (kcal mol<sup>-1</sup>) for the proposed mechanism. (b) Activation strain analysis of the CMD transition states with L<sub>a</sub>Pd and mononuclear Pd(O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub> with respect to separated PhH and the catalysts. (c) Backbone-induced distortion in the computed structure of L<sub>a</sub>Pd.

S1 and S2). The calculations reveal a potential Pd(II)/Pd(IV) catalytic cycle<sup>59</sup> with the C–H activation as the rate-limiting step ( $\Delta G^{\ddagger}_{\text{CMD}} = 16.6$  kcal/mol). Experimentally, the rate-limiting C–H activation on a L<sub>a</sub>2<sup>-</sup>-bound palladium(II) species is supported by the arylation reactivity of the isolated complex L<sub>a</sub>Pd(CH<sub>3</sub>CN)<sub>2</sub> (Figure 4, Figure S1a), faster reaction of C<sub>6</sub>H<sub>6</sub> compared with C<sub>6</sub>D<sub>6</sub>, a large kinetic isotope effect in a competition experiment (8 ± 1), and the observed C–H functionalization of benzene with methyl acrylate and **1a**



**Figure 4.** Molecular structure of isolated L<sub>a</sub>Pd(CH<sub>3</sub>CN)<sub>2</sub>.

as reagents in the presence of catalytic  $H_2L_a$  (see Supporting Information).<sup>7,8</sup> In the calculated pathway, the deprotonation of  $HL_aPdPh$ , formed in the CMD step, by the  $(CF_3)_3CO^-$  anion of the arylation reagent is followed by the oxidative addition of  $Ph_2I^+$  to a Pd(II) site through a carboxylate-bridged, six-membered cyclic transition state ( $\Delta G_{OA}^\ddagger - \Delta G_{[LaPdPh][Ph_2I]} = 13.1$  kcal/mol, Figure 3a). The spatial anion control and the absence of alternative counter-cations in our system could favor the formation of the ion pair  $[LaPdPh]^- [Ph_2I]^+$ , which contains an electron-rich anionic palladium(II) center,<sup>60–62</sup> thus facilitating the oxidative addition.<sup>63</sup> At this point, we cannot exclude alternative functionalization mechanisms (see Supporting Information), although dimeric Pd(II) species are less likely with the bulky anion  $L_a^{2-}$  and the current system does not require light.<sup>64,65</sup> The More O'Ferrall–Jencks plot shows that the Pd–C bond formation is more advanced than the C–H bond cleavage in the C–H activation transition state (Figure S6), which is consistent with the BIES and the eCMD mechanistic classifications by Ackermann and Carrow, respectively.<sup>66,67</sup>

The role of the constrained anion in the key CMD step was investigated by using activation strain analysis,<sup>68</sup> which revealed that the lower catalyst strain in the transition state, relative to the geometrically relaxed catalyst ( $\Delta E_{\text{catalyst strain}}$ ), is the main contributing factor to the reduced overall electronic energy ( $\Delta E$ ) when  $L_aPd$  is used, compared with that of mononuclear palladium(II) acetate (Figure 3b). Structural factors resulting from the bent spatial orientation of the two constrained carboxylates, such as distortion of the bis(anion) backbone and deviation from optimal coordination bond lengths and angles, could contribute to the strain in the ground state of  $L_aPd$ , which is relieved in the CMD transition state (Figure 3c). The spatial anion control imposed by  $L_a^{2-}$  is further supported by the uncommon coordination of the two  $\kappa^1$ -carboxylates and two nitriles in  $L_aPd(CH_3CN)_2$  (Figure 4, Table S2),<sup>69</sup> with the geometrical parameters, O3–Pd1–O4, 44.55(4)°, Pd1–O3, 1.9801(10) Å, and Pd1–O4, 3.1839(14) Å, being similar to those in  $TS_{CMD}$ , 45.9°, 2.06 Å, and 3.12 Å, respectively (Figure 3a).

Our results demonstrate that structurally constrained carboxylates, combined with precatalysts and reagents that avoid the use of interfering anions or additives, can enable nondirected C–H arylation of arenes as limiting reactants at ambient temperature. The mild reaction conditions compare favorably, even against traditional cross-coupling reactions with prefunctionalized arenes, and enable late-stage structural diversification of functionally rich molecules. The DFT studies show that spatially controlled carboxylates are powerful cooperative ligands for C–H activation on Pd(II) and could facilitate functionalization through Pd(IV) intermediates. The spatial anion control offers a general concept for the refinement of catalytic cycles and might find broad use in transition-metal catalysis and coordination chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c09611>.

Experimental details, characterization spectra, single-crystal data, and computational details (PDF)

Crystallographic data (CIF)

## ■ AUTHOR INFORMATION

### Corresponding Author

Ilija Ćorić – Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland; [orcid.org/0000-0002-0435-1313](https://orcid.org/0000-0002-0435-1313); Email: [ilija.coric@chem.uzh.ch](mailto:ilija.coric@chem.uzh.ch)

### Authors

Jyoti Dhankhar – Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland; [orcid.org/0000-0002-7088-6201](https://orcid.org/0000-0002-7088-6201)

Elisa González-Fernández – Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland; [orcid.org/0000-0002-2027-4063](https://orcid.org/0000-0002-2027-4063)

Chao-Chen Dong – Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland; [orcid.org/0000-0003-4106-4847](https://orcid.org/0000-0003-4106-4847)

Tufan K. Mukhopadhyay – Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland; [orcid.org/0000-0001-8888-5373](https://orcid.org/0000-0001-8888-5373)

Anthony Linden – Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland; [orcid.org/0000-0002-9343-9180](https://orcid.org/0000-0002-9343-9180)

Complete contact information is available at: <https://pubs.acs.org/10.1021/jacs.0c09611>

### Notes

The authors declare the following competing financial interest(s): The authors are pursuing the protection of intellectual property in relation to this work.

## ■ ACKNOWLEDGMENTS

This work was supported by the Department of Chemistry, University of Zurich (UZH), UZH Alumni - FAN (Fonds zur Förderung des Akademischen Nachwuchses) (fellowship to I.Ć.), Dr. Helmut Legerlotz-Stiftung, Prof. Dr. Hans E. Schmid-Stiftung, Foundation for Research in Science and the Humanities at the UZH, Alfred Werner-Legat, and Holcim Stiftung. E.G.-F. acknowledges the support from a Forschungskredit Postdoc UZH, and C.-C.D. is grateful for support by the China Scholarship Council. This work made use of infrastructure services provided by S3IT ([www.s3it.uzh.ch](http://www.s3it.uzh.ch)), the Service and Support for Science IT team at UZH, as well as an X-ray diffractometer funded by the Swiss National Science Foundation (R'Equip grant no. 206021\_164018) and UZH. We thank K. Gademann and C. Nevado for research support, and K. Rehm and U. Stalder for assistance with MS measurements.

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