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Enhancing Substrate-Metal Catalyst Affinity via Hydrogen Bonding: Pd(II)-Catalyzed β -C(sp³)-H Bromination of Free Carboxylic Acids

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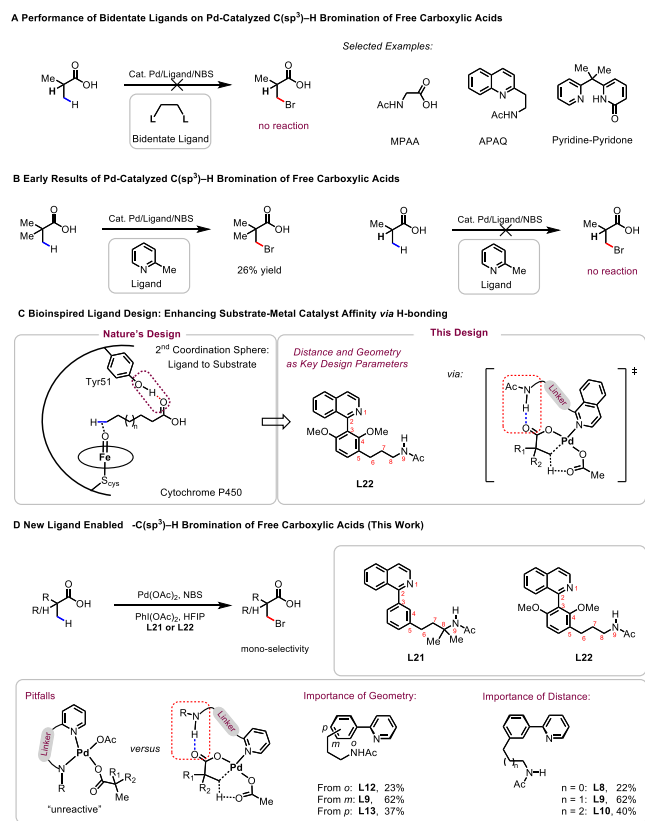
ABSTRACT: Achieving sufficient substrate-metal catalyst affinity is a fundamental challenge for developing synthetically useful C–H activation reactions of weakly coordinating native substrates. While hydrogen bonding has been harnessed to bias site selectivity in existing C(sp²)-H activation reactions, the potential for designing catalysts with hydrogen bond donors (HBDs) to enhance catalyst-substrate affinity, and thereby facilitate otherwise unreactive C(sp³)-H activation, remains to be demonstrated. Herein, we report the discovery of a ligand scaffold containing a remote amide motif that can form a favorable *meta*-macrocyclic hydrogen bonding interaction with the aliphatic acid substrate. The utility of this ligand scaffold is demonstrated through the development of an unprecedented C(sp³)-H bromination of α -tertiary and α -quaternary free carboxylic acids, which proceeds in exceedingly high *mono*-selectivity. The geometric relationship of the NHAc hydrogen bond donor and the coordinating quinoline ligand is crucial for forming the *meta*-macrocyclophane-like hydrogen bonding interaction, providing a guideline for the future design of catalysts employing secondary interactions.

Despite significant developments in transition-metal catalyzed C(sp³)-H functionalization over past decade, performing directed C–H metalation with native functional groups rather than exogenous directing groups (DGs) remains challenging.¹ In this context, the activation of alkyl C–H bonds directed by carboxylic acids based on cation-enabled weak coordination has been the main platform to demonstrate the feasibility of this approach. While innovation in ligand designing has enabled a wide range of free-acid-directed C(sp²)-C and C(sp³)-X bond formations (X = N, O),² bromination of C(sp³)-H still requires the installation of external directing groups.³ Considering the broad utility of alkyl bromides as versatile intermediates in synthetic organic chemistry,⁴ the invention of new methods for *mono*-selective β -C–H bromination of readily available carboxylic acids lags behind the wide range of enzymatic C–H halogenation reactions.⁵

The unique proficiency of bidentate ligands containing internal proton acceptors such as acetamides and pyridones for facilitating a wide range of C–H bond activation reactions of free acid has been demonstrated in numerous previous reports from our lab and others.⁶ However, despite repeated attempts, we have found that bidentate ligands fail to promote the C–H bromination of free carboxylic acids (**Scheme 1A**, *vide infra*). Conversely, we have previously observed that monodentate pyridine-type ligands enable the C(sp³)-H bromination of α -quaternary free carboxylic acid in modest yield.^{3d} Unfortunately, no reactivity was observed with more challenging α -tertiary acids, and efforts to optimize this reactivity through routine screening have proven futile (**Scheme 1B**, *vide infra*). Intriguingly, the latter class of ligands has proven effective when the analogous transformation is directed by a more strongly coordinating electron deficient amide instead of a free carboxylic acid,^{3d} suggesting that the poor reactivity observed with free acids may be the result of insufficient affinity of the catalyst for carboxyl group in the presence of the interfering brominating reagent. In light of these results, we hypothesized that the desired transformation

could be enabled through the design of a new type of monodentate pyridine ligands with an additional function: enhancing the interaction between carboxylic acid substrates and the Pd(II) catalyst.

Scheme 1. Pd(II)-Catalyzed C(sp³)-H Bromination of Free Aliphatic Acids



It is well established that enzymes and metalloproteins can facilitate catalysis through remote hydrogen bonding with their substrates.⁷ For example, in the active site of cytochrome P450-BM3, a fatty acid hydroxylase, hydrogen bond donors interact with the carboxylate group of the acid substrate, thereby directing site-selective C–H bond oxidation (**Scheme 1C**).⁷ Although hydrogen bonding directed catalysis⁸ has been successfully harnessed to bias site selectivity in C(sp²)–H activation,⁹ development of ligands involving hydrogen bonding interaction to promote C(sp³)–H activation of free acid by increasing the binding affinity of the carboxyl group for the metal center remains to be

demonstrated. We were particularly interested in the possibility of using our established *meta*-macrocyclophane geometry¹⁰ to assemble the hydrogen bonding interaction, helping to promote the desired interaction through control over distance and geometry while suppressing undesired chelation of the hydrogen bonding donor motif to the metal center. Herein, we report the development of a β -C(sp³)–H bromination and chlorination of free carboxylic acids enabled by a novel quinoline ligand bearing a pendant NHAc group that forms a hydrogen bonding interaction with the carboxylate in a *meta*-macrocyclophane structure (**Scheme 1D**).

Table 1. Investigation of Ligands for the β -C(sp³)–H Bromination of Free Aliphatic Acids

| | | | | | | |
|------------------|---|------------------|------------------|--|------------------|------------------|
| no ligand | | | | | | |
| N.R. | L1, R = Ph, 11% yield L1', R = Me, 26% yield | L2 14% yield | L3 10% yield | L4 12% yield | L5 17% yield | L6 8% yield |
| | | | | | | |
| L7 17% yield | L8 22% yield | L9 62% yield | L10 40% yield | L11 45% yield | L12 23% yield | L13 37% yield |
| | | | | | | |
| L14 8% yield | L15 62% yield | L16 48% yield | L17 61% yield | L18, R = H, 53% yield L18', R = Me, 21% yield | L19 68% yield | L20 42% yield |
| | | | | | | |
| L21 74% yield | L22 76% yield | L23 63% yield | L24 20% yield | L25 < 5% yield | L26 10% yield | |

Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol%), **ligand** (15 mol%), PhI(OAc)₂ (0.1 mmol), AcOH (0.1 mmol), HFIP (1.0 mL), 100 °C, air, 24 h. ¹H NMR yields, using CH₂Br₂ as an internal standard.

Bearing in mind our earlier effort to achieve β -bromination of pivalic acid using a quinoline ligand only gave 40% yield,^{3d} we began to test various ligands using pivalic acid **1a** as the model substrate (**Table 1**). While no product was observed in the absence of ligand, monodentate pyridine-type ligand **L1'** provided 26% yield of the desired product, which is consistent with our previous report.^{3d} Further screening with this ligand (**L1'**) did not improve the yield (see the Supporting Information for details). Most importantly, **L1'** failed to show any reactivity with α -hydrogen containing acids, highlighting the need for novel ligands. As anticipated, bidentate ligands such as *mono*-acetyl protected aminoalkyl pyridine (MPAPy) ligands (**L2-L3**)

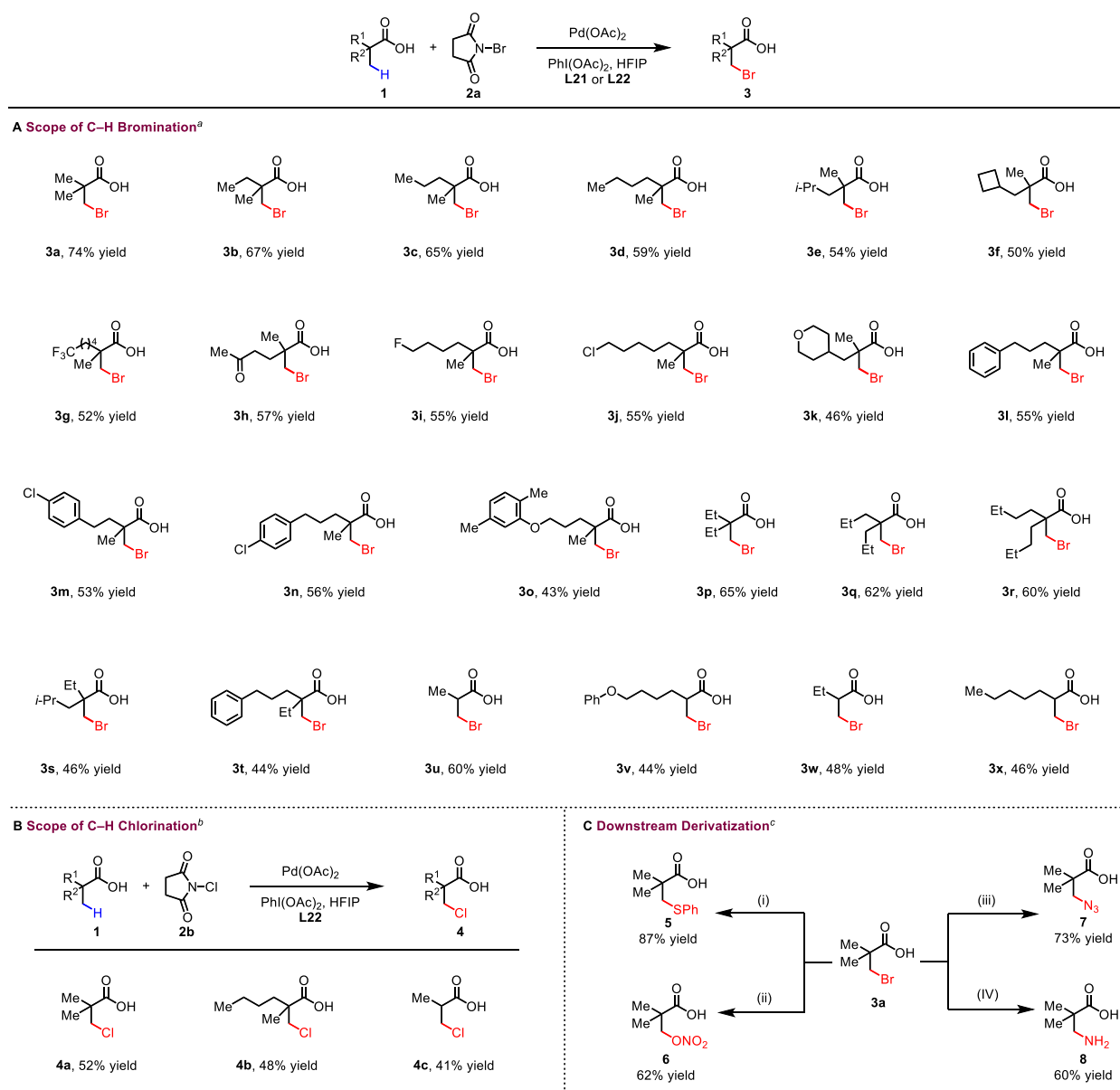
also gave poor yields. We next tried to extend the linker between the pyridine and the NHAc group (**L4-L6**) in the hope of disfavoring bidentate coordination and enabling a macrocyclic hydrogen bonding interactions to enhance the binding affinity of the substrate. Unfortunately, we didn't observe any improvement, which is most likely the result of the highly flexible linker either allowing for undesired chelation by the NHAc moiety or entropically disfavoring the desired H-bonding interaction. Based on our previous understanding of the favorable assembly of *meta*-macrocyclophane transition states in remote C–H activation,¹⁰ we incorporated one phenyl ring bearing the NHAc moiety at the *meta*-position into ligand scaffold and adjusted the

ring size (**L7-L11**) to prevent the potential bidentate coordination. We found **L9** significantly increased the yield to 62%. The poor performance of **L8** (8-membered ring size) or **L10** (10-membered ring size) suggests that the precise ring size of the macrocyclophane hydrogen bonding interaction is crucial for enabling catalysis. The poor yields observed with *ortho*- and *para*-substituted ligands **L12** and **L13** further confirmed the favorable assembly of *meta*-cyclophane structures.

Seeking to optimize ligand **L9**, we observed that further modification of the ligand backbone (**L11-L18**) did not significantly improve the reactivity. Switching from pyridine to isoquinoline (**L19**) resulted in a small increase in yield up to 68%. The comparatively poor performance of one-carbon homologated **L20** further highlighted the importance of the ring size of the macrocyclic H-bonding interactions in this system. To promote angle-compression through the Thorpe–Ingold effect, we introduced a gem-dimethyl in **L21** which gratifyingly led to a

modest improvement in yield. A similar result was also observed with **L22**, which might result from the constrained environment provided by the 2,6-dimethoxy-1,1'-biphenyl moiety. Importantly, the possibility that the active species is a palladacycle formed through isoquinoline-directed intramolecular C–H activation of the ligand was excluded by the high activity observed with *bis-ortho*-substituted **L22**. In support of the crucial role of the proposed hydrogen bond donor, the methylated analogue of **L18** (**L18'**) and phthalimide protected analogue of **L19** (**L24**), both incapable of the proposed hydrogen bonding interaction, gave poor yields similar to the simple mono-dentate pyridine ligand **L1**. Consistent with our hypothesis, **L23** containing a free alcohol as an alternate HBD—remained highly effective, afforded the brominated product in 63% yield. Similarly, the importance of pyridine or isoquinoline motif was highlighted by the failure of thiol-based ligand **L25** and aniline-based ligand **L26** to promote the reaction.

Table 2. β -C(sp³)-H Halogenation of Free Aliphatic Acids



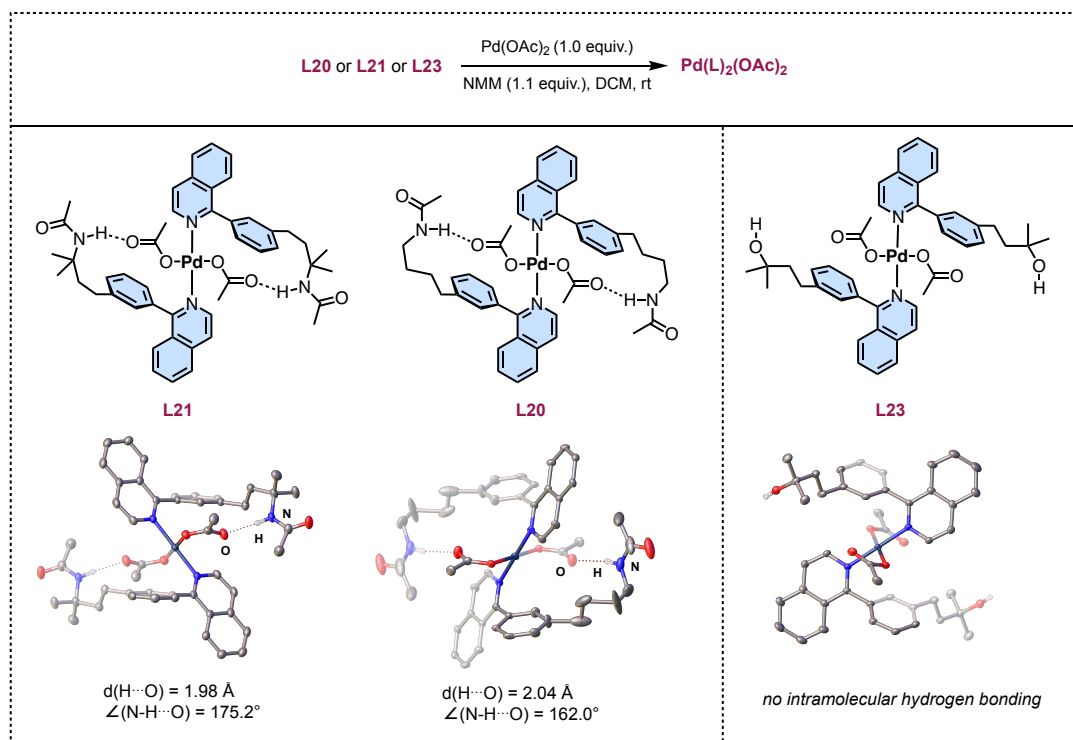
^aConditions: **1** (0.1 mmol), **2a** (2.0 equiv), Pd(OAc)₂ (10 mol%), **ligand** (15 mol%), PhI(OAc)₂ (0.1 mmol), AcOH (0.1 mmol), HFIP (1.0 mL), 100 °C, air, 24 h.
^bConditions: **1** (0.1 mmol), **2b** (2.0 equiv), Pd(OAc)₂ (10 mol%), **ligand** (15 mol%), PhI(OAc)₂ (0.1 mmol), AcOH (0.1 mmol), HFIP (1.0 mL), 100 °C, air, 24 h.
^cConditions for derivatization: (i) PhSH (2.0 equiv), NaOH (2.0 equiv), EtOH, 40 °C, 12 h; (ii) AgNO₃ (2.0 equiv), EtOAc, 80 °C, 24 h; (iii) NaN₃ (4.0 equiv), MeOH, 40 °C, 24 h; (iv) NH₃H₂O (1.0 ml), 80 °C, 12 h.

Having identified highly reactive ligands and reaction conditions, we next sought to examine the scope of bromination reaction (**Table 2A**). α -Gem-dimethyl carboxylic acids with a range of aliphatic chain all proved compatible, affording the β -brominated products in high yields (**3a-3f**). A variety of functional groups, such as fluoro, chloro, trifluoromethyl and ketone were tolerated (**3g-3j**). These functionalities are useful synthetic handles for subsequent derivatization, demonstrating the practicality of this methodology. Notably, in contrast to other β -C(sp³)-H functionalization reactions,^{2a} this protocol displayed exclusive selectivity for mono-functionalization despite the presence of two α -methyl groups. Aliphatic carboxylic acids bearing cyclic rings with four and six-membered rings were tolerated (**3f, 3k**). Phenyl groups were also compatible with these reaction condition (**3l-3n**) and remained intact despite the potential for reactivity of the aryl or benzylic C-H bonds. Even electron-rich phenolic ethers (**3o** and **3v**) were compatible despite the usage of NBS and PIDA oxidants. Gemfibrozil, an oral drug, which is used to decrease lipid levels, could be converted to the corresponding β -brominated product in useful yield (**3o**). In addition, quaternary substrates containing a single α -methyl

group consistently afforded good yields (**3p-3t**). Likewise, α -tertiary aliphatic carboxylic acids afforded the desired mono-bromination products in moderate to good yield (**3u-3x**). These substrates are typically challenging due to the lack of a favorable Thorpe-Ingold effect as well as the potential for side reactions due to the acidic α -C-H bond. In addition, we examined the ability of our novel ligand to promote the Pd(II)-catalyzed β -C(sp³)-H chlorination of free carboxylic acids owing to the bioactivity of alkyl halides in drug discovery (**Table 2B**).¹¹ To our delight, both the quaternary carboxylic acids and α -tertiary acid substrates were chlorinated under this reaction conditions, affording the desired products in 41%-52% yields (**4a-4c**).

The synthetic utility of this C(sp³)-H bromination was demonstrated by converting **3a** to a wide range of β -substituted aliphatic acids via nucleophilic substitutions (**Table 2C**). A diverse array of chemical bonds including C-S, C-O, and C-N bonds were easily forged, providing straightforward access to compounds which might be challenging to access from the free acid using other methods. Notably, this methodology could be applied to the synthesis of valuable β -amino acid (**8**).

Scheme 2. Preparation and Solid-State Structure of Pd-L21 to Pd-L23 Complexes



Conditions: Pd(OAc)₂ (0.11 mmol), **ligand** (0.12 mmol) and N-methylmorpholine (0.12 mmol), DCM (5.0 mL), RT, overnight.

To probe our mechanistic hypothesis experimentally, we first looked at the complexation of **L21**, one of our optimal ligands, with Pd(OAc)₂ (**Scheme 2**). X-ray crystallographic analysis confirmed that this ligand binds to palladium in a monodentate fashion via the quinoline nitrogen and that it engages in a macrocyclic intramolecular hydrogen bonding interaction between the amide and a palladium-bound carboxylate in the solid state.

To highlight the remarkable specificity of this ligand framework, we also examined **L23**, a slightly less reactive ligand bearing an alcohol HBD. In the complex formed from **L23**, we did not observe an intramolecular macrocyclic hydrogen bonding interaction, but the alcohol instead participated in an intermolecular hydrogen bonding interaction with a carboxylate bound to a second equivalent of palladium demonstrating the

electronic viability of the proposed interaction. To gain additional insight into the optimal distance and geometry for the positioning of the NHAc group, we also considered **L20**, which has a longer carbon chain and lacks the gem-dimethyl group present in **L21**. In this case, the same macrocyclic hydrogen bonding interaction was observed as with **L21**, but structural parameters (H–O distance and N–H–O angle) suggested the interaction was weakened, an observation consistent with the

reduced yield observed with **L20** (Table 1). To the best of our knowledge there is no report of similar intramolecular macrocyclic distal hydrogen bonding motifs in transition-metal complexes as demonstrated by a careful search of the Cambridge Crystallographic Data Centre (CCDC). Altogether these data support our hypothesis that a hydrogen bonding interaction between the ligand and the carboxylate directing group can be leveraged to enable increased reactivity.

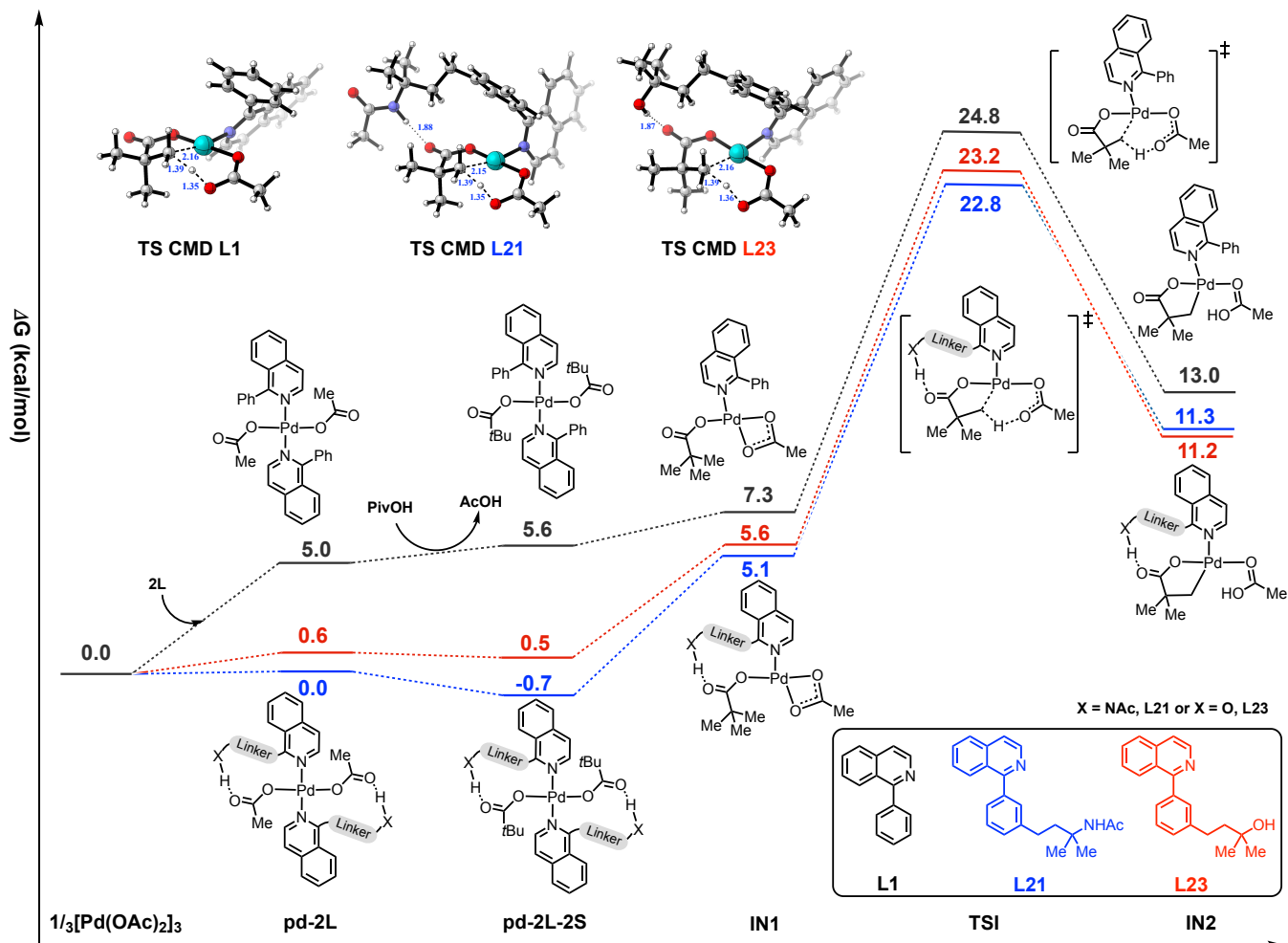


Figure 1. Free energy profiles and optimized TS structures (distances are in Å) with newly designed ligands. Methods: PBE0-D3(BJ)/def2-TZVPP, SMD(Eps=16.7, EpsInf=1.625625) // PBE0-D3(BJ)/SVP, with correction to a solution-phase (0.01mol/L, concentration based on Pd concentration) and with Grimme correction for entropy at 100°C. All energies are in kcal/mol.

In order to further investigate the impact of the proposed hydrogen bonding interaction, we performed density functional theory (DFT) calculations on the C–H activation step and the preceding intermediates at the PBE0-D3(BJ)/def2-TZVPP, SMD(Eps=16.7, EpsInf=1.625625) // PBE0-D3(BJ)/SVP level of theory (C–H activation was determined to be rate determining based on the observation of a primary H/D KIE, see the Supporting Information for details). We first examined a simplified model systems using pyridine ligand **L1** both with and without exogenous hydrogen bond donors (see the Supporting Information for details). As shown in the model system, the hydrogen bonding occurs preferentially at the uncoordinated oxygen of the carboxylate, which also possesses a more negative Hirshfeld charge (Figure S1–S4). However, while exogenous hydrogen bond donors enthalpically stabilized the C–H

cleavage transition state, they were found to be net destabilizing due to the high entropic cost of assembling the higher order complexes (Figure S5, Table S1). We next examined free energy profiles and the optimized structures of the CMD TSs with **L1** and newly designed ligands **L21** and **L23** (Figure 1). As shown in Figure 1, the novel ligands participate in macrocyclic hydrogen bonding interactions with the carboxylate. They stabilize catalyst-substrate complexation in all bound intermediates as well as in the rate-determining C–H activation transition state. Consequently, the free energy barriers for the rate-determining C–H cleavage step are 1.3 kcal/mol (with **L21**) and 1.6 kcal/mol (with **L23**) lower than that with **L1**. These results are consistent with the higher yields obtained in reactions catalyzed by **L21** and **L23** and support a key role for the proposed H–

bonding interaction in increasing catalyst-substrate binding affinity and enabling C–H activation.

In summary, we have discovered a new class of pyridine-based ligands containing a hydrogen bond donor that interacts with carboxyl directing group in substrates, thereby enabling the Pd(II)-catalyzed β -C(sp³)–H bromination and chlorination of free carboxylic acids. The broad substrate scope as well as the ease of valuable downstream transformations of the halogenated products demonstrates the synthetic potentiality of this strategy. Importantly, our bioinspired ligand design employing a secondary coordination sphere hydrogen bonding interaction was the key to the success of this C(sp³)–H halogenation. Based on DFT calculations, the free energy of the reaction pathway using **L21** or **L23**—ligands possessing pendant hydrogen bond donors—is lower than that for **L1**, a ligand incapable of hydrogen bonding. X-ray crystallographic analysis of palladium-ligand complexes provide additional support for the proposed interaction through *meta*-macrocyclephane hydrogen bonding interaction. We expect that this new ligand design concept will be broadly applicable within the field of C–H activation and guide future ligand development efforts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, full characterization of new compounds including ¹H and ¹³C NMR spectra, HRMS data (PDF)

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TOC Graphic

