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Communication

Enhancing Substrate–Metal Catalyst Affinity via Hydrogen Bonding: Pd(II)-Catalyzed β-C(sp^3)–H Bromination of Free Carboxylic Acids

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ABSTRACT: The achievement of sufficient substrate–metal catalyst affinity is a fundamental challenge for the development of synthetically useful C–H activation reactions of weakly coordinating native substrates. While hydrogen bonding has been harnessed to bias site selectivity in existing C(sp^2)–H activation reactions, the potential for designing catalysts with hydrogen bond donors (HBDs) to enhance catalyst–substrate affinity and, thereby, facilitate otherwise unreactive C(sp^3)–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(sp^3)–H bromination of α-tertiary and α-quaternary free carboxylic acids, which proceeds in exceedingly high *mono*-selectivity. The geometric relationship between the NHAc hydrogen bond donor and the coordinating quinoline ligand is crucial for forming the *meta*-macrocyclophane-like hydrogen bonding interaction, which provides a guideline for the future design of catalysts employing secondary interactions.

Despite significant developments in transition-metal-catalyzed C(sp^3)–H functionalization over the 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 on the basis of weak cation coordination has been the main platform to demonstrate the feasibility of this approach. While innovation in ligand design has enabled a wide range of free-acid-directed C(sp^2)–C and C(sp^3)–X bond formations (X = N, O),[2] the bromination of C(sp^3)–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 the facilitation of 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(sp^3)–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 proved futile (Scheme 1B, vide infra). Intriguingly, the latter class of ligands has proved effective when the analogous transformation is directed by a more strongly coordinating electron-deficient amide instead of a free carboxylic acid,[3d] which suggests that the poor reactivity observed with free acids may be the result of insufficient affinity of the catalyst for a carboxyl group in the presence of the interfering brominating reagent.[7] In light of these results, we hypothesized that the desired transformation could be enabled through the design of a new type of monodentate pyridine ligand with an additional function: enhancement of the interaction between carboxylic acid substrates and the Pd(II) catalyst.

It is well established that enzymes and metalloproteins can facilitate catalysis through remote hydrogen bonding with their substrates.[8] 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).[8] Although hydrogen-bonding-directed catalysis[9] has been successfully harnessed to bias site selectivity in C–H activation,[10] the development of ligands involving a hydrogen-bonding interaction to promote the C(sp^3)–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

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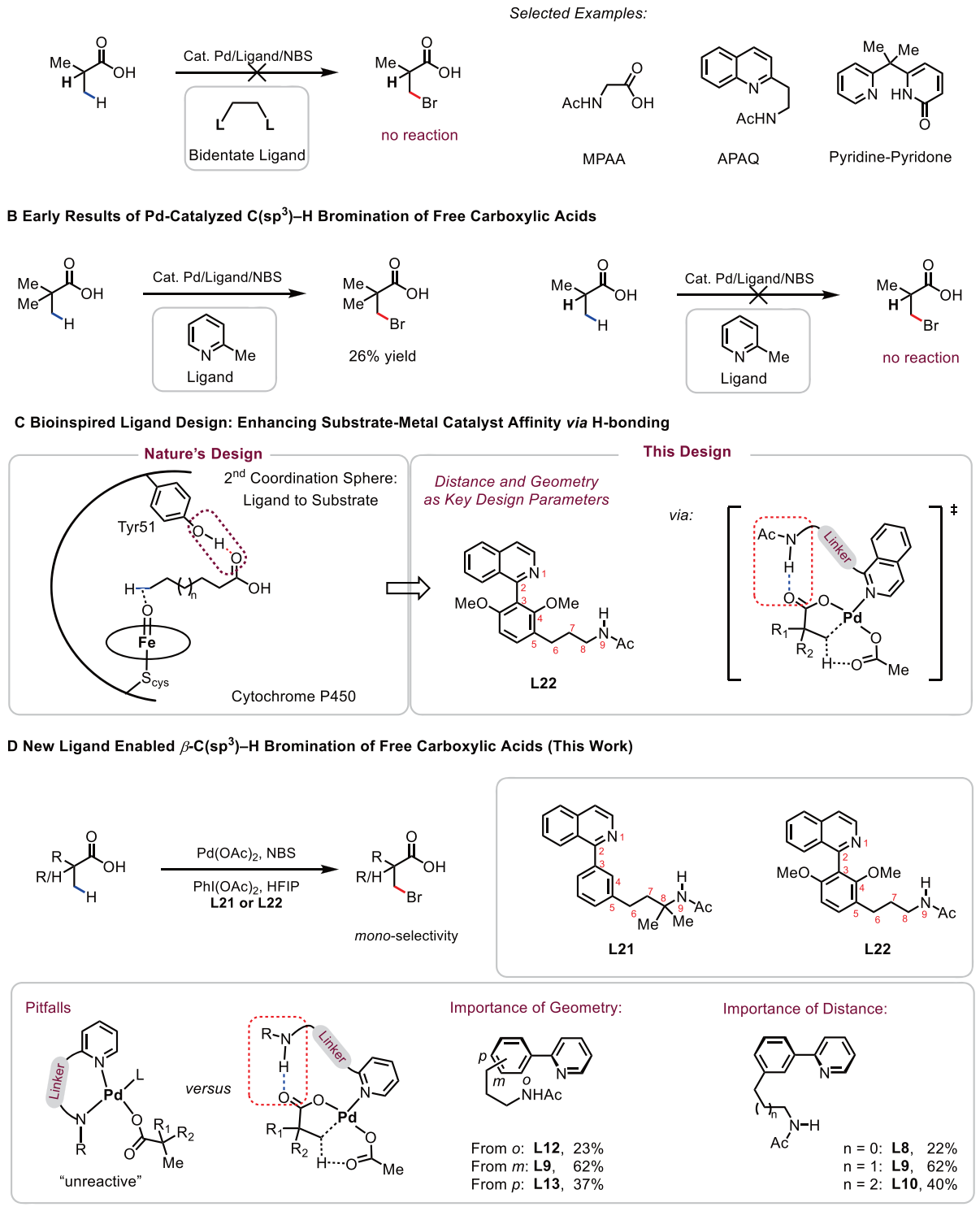
Scheme 1. Pd(II)-Catalyzed C(sp^3)–H Bromination of Free Aliphatic Acids



established *meta*-macrocyclophane geometry[11] to assemble the hydrogen bonding interaction and help 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(sp^3)–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).

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

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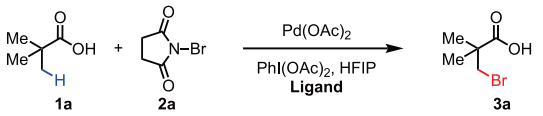
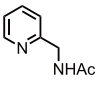
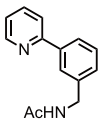
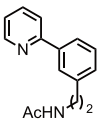
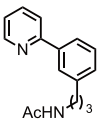
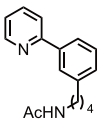
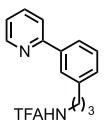
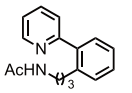
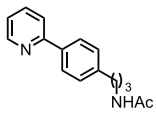
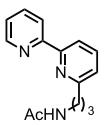
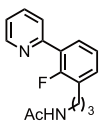
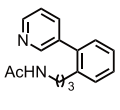
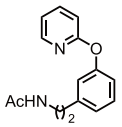
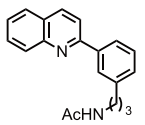
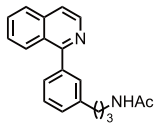
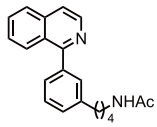
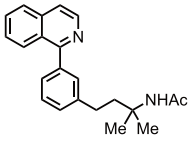
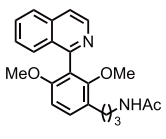
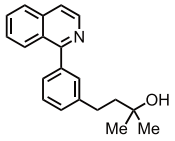
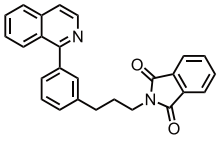
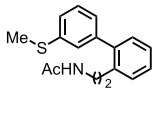
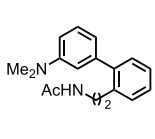
Table 1. Investigation of Ligands for the β-C(sp^3)−H Bromination of Free Aliphatic Acids[a]



no ligand						
N.R.	**L1**, R = Ph, 11% yield **L1'**, 2,6-Lutidine, 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** 53% 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	

[a]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), hexafluoroisopropanol (HFIP) (1.0 mL), 100 °C, air, 24 h. ^1H NMR yields obtained using CH_2Br_2 as an internal standard.

with our previous report.[3d] Further screening with this ligand (**L1′**) did not improve the yield. Most importantly, **L1′** failed to show any reactivity with α-hydrogen-containing acids, thereby highlighting the need for novel ligands. As anticipated, bidentate ligands such as *mono*-acetyl-protected aminoalkylpyridine (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 macrocyclic hydrogen-bonding interactions to enhance the binding affinity of the substrate. Unfortunately, we did not 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. On the basis of our previous understanding of the favorable assembly of *meta*-macrocyclophane transition states in remote C−H activation,[11] we incorporated one phenyl ring bearing the NHAc moiety at the *meta*-position into the ligand scaffold and adjusted the ring size (**L7**−**L11**) to prevent the potential bidentate coordination. We found that **L9** significantly increased the yield to 62%. The poor performance of **L8** (eight-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 the *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 of 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

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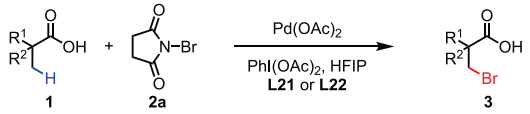
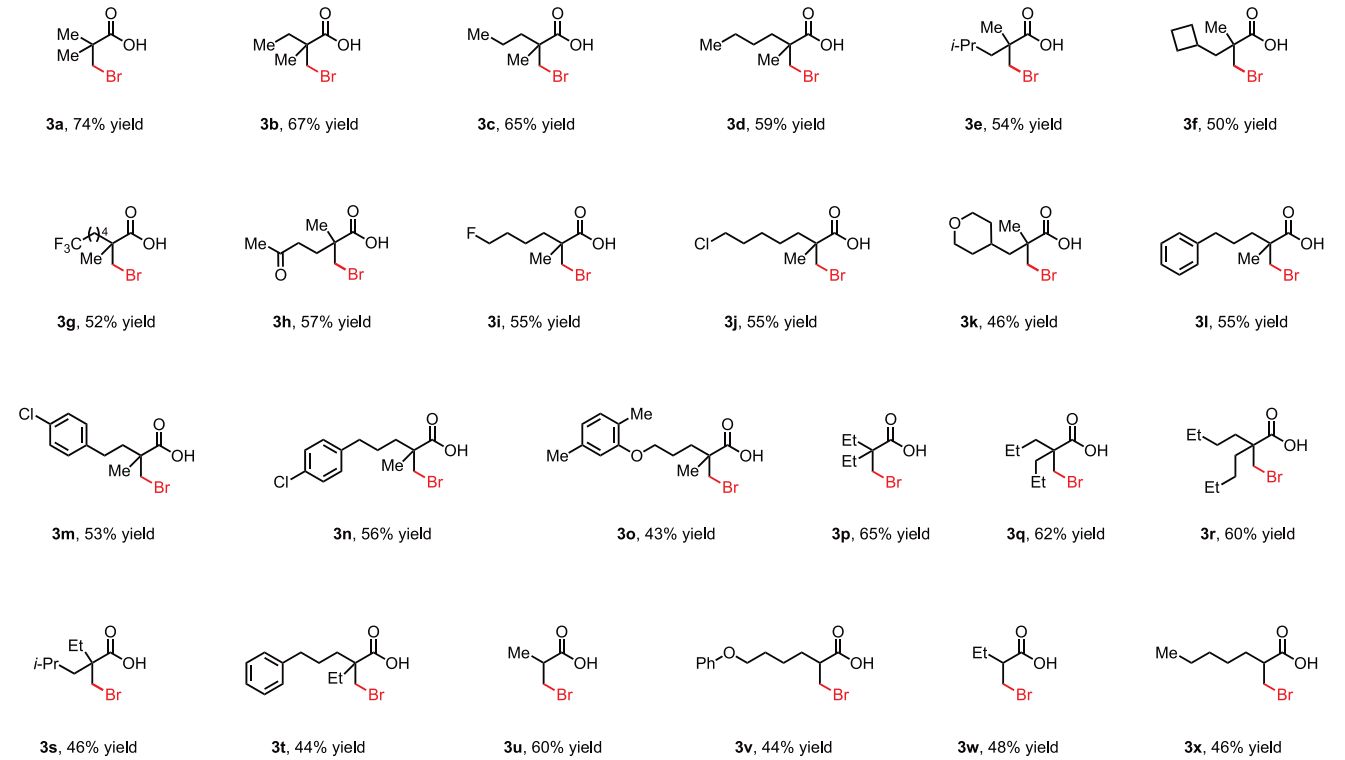
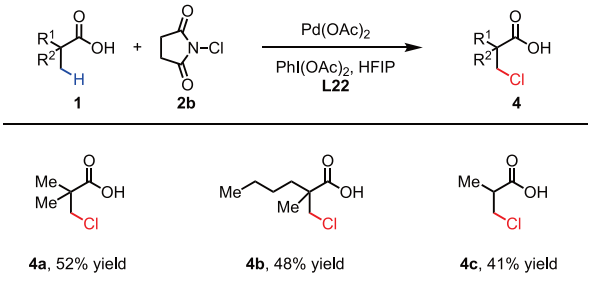
Table 2. β-C(sp^3)−H Halogenation of Free Aliphatic Acids[a]



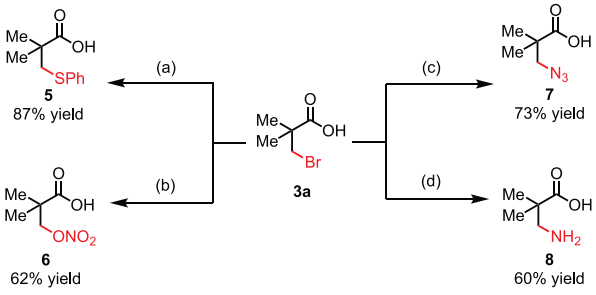
A Scope of C–H Bromination[b]



B Scope of C–H Chlorination[c]



C Downstream Derivatization[d]



[a]**L22** was applied to **3a**, **3g**−**3k**, and **3u**−**3x**. [b]Conditions: **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. [c]Conditions: **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. [d]Conditions for derivatization: (i) PhSH (2.0 equiv), NaOH (2.0 equiv), EtOH, 40 °C, 12 h; (ii) $AgNO_3$ (2.0 equiv), EtOAc, 80 °C, 24 h; (iii) NaN_3 (4.0 equiv), MeOH, 40 °C, 24 h; (iv) NH_3H_2O (1.0 mL), 80 °C, 12 h.

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 monodentate pyridine ligand **L1**. Consistent with our hypothesis, **L23** containing a free alcohol as an alternate hydrogen bond donor (HBD) remained highly effective, thereby affording the brominated product in 63% yield. Similarly, the importance of the pyridine or isoquinoline motif was highlighted by the failure of thiol-based ligand **L25** and aniline-based ligand **L26** to promote the reaction.

Having identified highly reactive ligands and reaction conditions, we next sought to examine the scope of the bromination reaction (Table 2A). *α-gem*-Dimethyl carboxylic acids with a range of aliphatic chains all proved compatible and afforded 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

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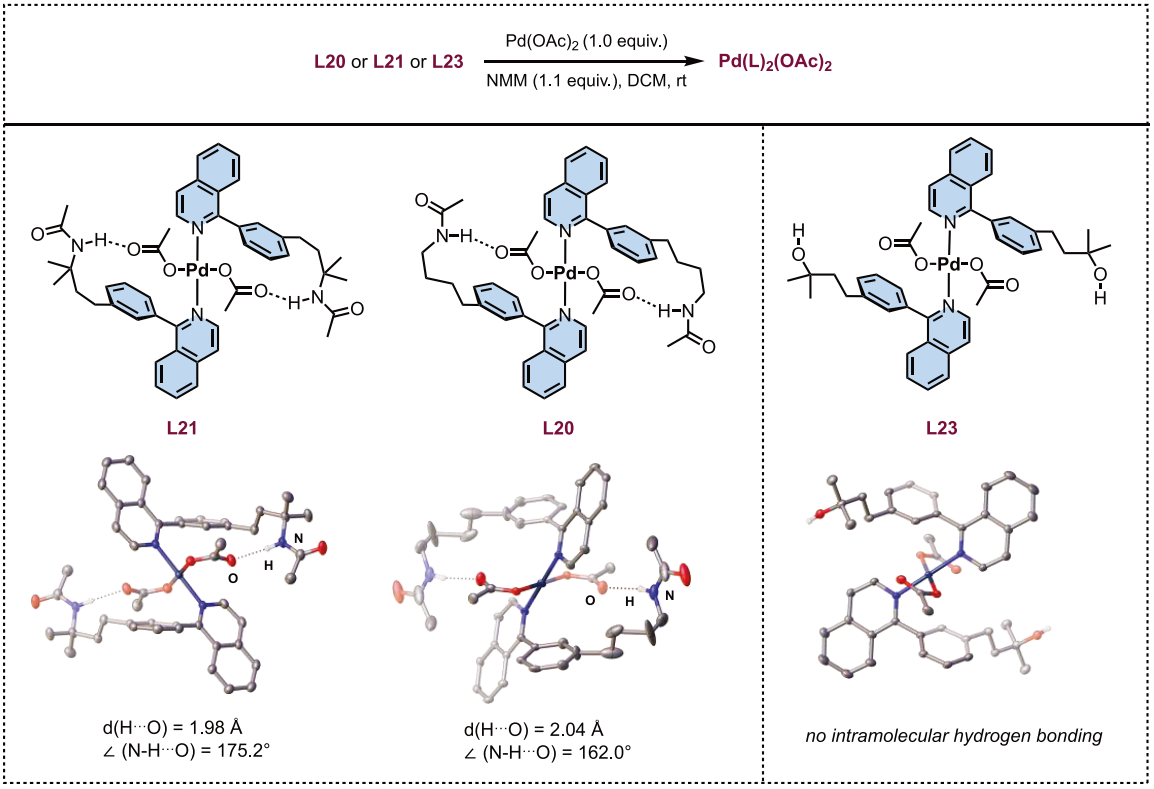
Scheme 2. Preparation and Solid-State Structure of Pd-L20, Pd-L21, and Pd-L23 Complexes[a]



[a]Conditions: $Pd(OAc)_2$ (0.11 mmol), **ligand** (0.12 mmol), and *N*-methylmorpholine (0.12 mmol), DCM (5.0 mL), rt, overnight.

derivatization, thereby demonstrating the practicality of this methodology. Notably, in contrast with other β-C(sp^3)−H functionalization reactions,[2a] this protocol displayed exclusive selectivity for monofunctionalization despite the presence of two α-methyl groups (see the Supporting Information for more discussion). Aliphatic carboxylic acids bearing cyclic rings with four- and six-membered rings were tolerated (**3f**, **3k**). Phenyl groups were also compatible with these reaction conditions (**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 use of NBS and phenyliodine(III) diacetate (PIDA) oxidants. Gemfibrozil, an oral drug that 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 monobromination products in moderate to good yield (**3u**−**3x**). These substrates are typically challenging because of 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(sp^3)−H chlorination of free carboxylic acids because of the bioactivity of alkyl halides in drug discovery (Table 2B).[12] To our delight, both the quaternary carboxylic acids and α-tertiary acid substrates were chlorinated under these reaction conditions to afford the desired products in 41%−52% yields (**4a**−**4c**).

The synthetic utility of this C(sp^3)−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, thereby providing straightforward access to compounds that 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**).

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 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, which demonstrated 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 that 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

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by a careful search of the Cambridge Crystallographic Data Centre (CCDC). These observations and additional comparative DFT studies (detailed in the Supporting Information) support our hypothesis that a hydrogen-bonding interaction between the ligand and the carboxylate directing group can be leveraged to enable increased reactivity.

In summary, we have discovered a new class of pyridine-based ligands containing a hydrogen bond donor that interacts with a carboxyl directing group in substrates, thereby enabling the Pd(II)-catalyzed β-C(sp^3)−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(sp^3)−H halogenation. On the basis of 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 provides additional support for the proposed interaction through *meta*-macrocyclophane 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 at https://pubs.acs.org/doi/10.1021/jacs.3c04223.

Experimental details and full characterization of new compounds, including ^{1}H and ^{13}C NMR spectra and HRMS data (PDF)

Accession Codes

CCDC 2261815−2261816 and 2270324 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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