δ-C(sp^3)–H Activation of Free Alcohols Enabled by Rationally Designed H-Bond-Acceptor Ligands

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Abstract: The ability to employ a wide range of native substrates is essential for the broad application of transition-metal-catalyzed C–H activation. Recent advances have made native carboxylic acids, ketones, and amines amenable to C(sp^3)–H activation, but alcohols, perhaps the most common functionality in organic chemistry, have remained intractable due to their low affinity for late-transition-metal catalysts. Herein we describe the rational development of ligands to overcome this challenge and enable alcohol-directed δ-C(sp^3)–H arylation reactions. Our ligand design strategy employs charge balance and a secondary-coordination-sphere H-bonding interaction—evidenced by SAR studies, computational modelling, and crystallographic data—to stabilize L-type hydroxyl coordination to palladium, thereby facilitating the assembly of the key C–H cleavage transition state. In contrast to prior studies in C–H activation, where secondary interactions were used to control selectivity in the context of established reactivity, this

report demonstrates the feasibility of employing secondary interactions to enable challenging novel reactivity by enhancing substrate-catalyst affinity.

Main Text: Directed C–H activation has the potential to transform the synthesis of organic molecules by circumventing the often-lengthy sequences of pre-activation and functionalization typical of classical methods[1,2]. To harness the full potential of this approach, it is crucial to develop catalysts capable of site-selective C–H activation promoted by reversible binding to common native functionality, such as alcohols, carboxylic acids, amides, aldehydes, ketones, and amines (Fig. 1A). Over the past decade, dramatic advances have been made in C–H activation directed by most of these functional groups[3,4]. In particular, the development of bifunctional ligands has enabled a wide range of carboxylate[5-7] and amide[6-8] directed transformations, while the use of imine-based transient directing groups[9] has provided a practical solution for many classes of amines, aldehydes, and ketones. However, alcohols—by far the most common functional group in nature[10]—have proven significantly more challenging. Although alcohols are the archetypal DG in classical organic reactions including epoxidations, cyclopropanations, hydrogenations, and hydrometallations[11], few free-alcohol-directed C–H activation reactions have been reported, and all are limited to easier C(sp^2)–H bond cleavage[12-22].

The key obstacles hindering the use of alcohol DGs in C–H activation is their low binding affinity for Pd(II) as neutral ligands[12,15,23] (see also Note S1) and their increased conformational flexibility relative to more commonly used native directing groups (Fig. 1B). Although cation-enhanced weak coordination has proven to be a powerful approach for

facilitating the functionalization of palladacyclic intermediates[24], this strategy still relies on sufficient DG coordination to enable the C–H cleavage step. The low affinity of the hydroxyl lone pair for Pd(II) strongly disfavors substrate coordination to the catalyst, preventing directed C–H activation. Moreover, the fully sp^3 character of alcohols makes them more flexible than commonly used native directing groups such as carboxylates, reducing the ability of hydroxyl DGs to organize the pre-transition-state agostic complex. An additional challenge arises from the neutral charge of alcohols. The majority of recently developed ligands for Pd-catalyzed C–H activation are monoanionic L,X chelates designed for anionic directing groups[6,7]. If used with neutral DGs, the resulting agostic complex would be destabilized due to the lack of charge balance at the metal center. Although deprotonation of alcohols can increase their affinity for late transition metals[25] and would provide charge balance with L,X ligands, Pd-alkoxides are prone to undesired side reactions such as μ-alkoxo-bridged dimer formation[26], oxidation[27], and fragmentation[13,14], and they have previously been shown to be inferior to neutral alcohols in directed C(sp^2)–H activation reactions[15]. As a result of these challenges, ligands that are effective for C(sp^3)–H activation with other native DGs provide little or no reactivity in hydroxyl-directed reactions (*vide infra*). To date, reported methods for "hydroxyl directed" C(sp^3)–H activation have relied on derivatization of the alcohol to install more strongly coordinating DGs[12]. Because of the synthetic value of alcohol-directed reactivity, numerous such methods have been developed[5,12,28-30], but their practicality is often limited by the necessity for DG synthesis, installation, and removal (see also Note S2).

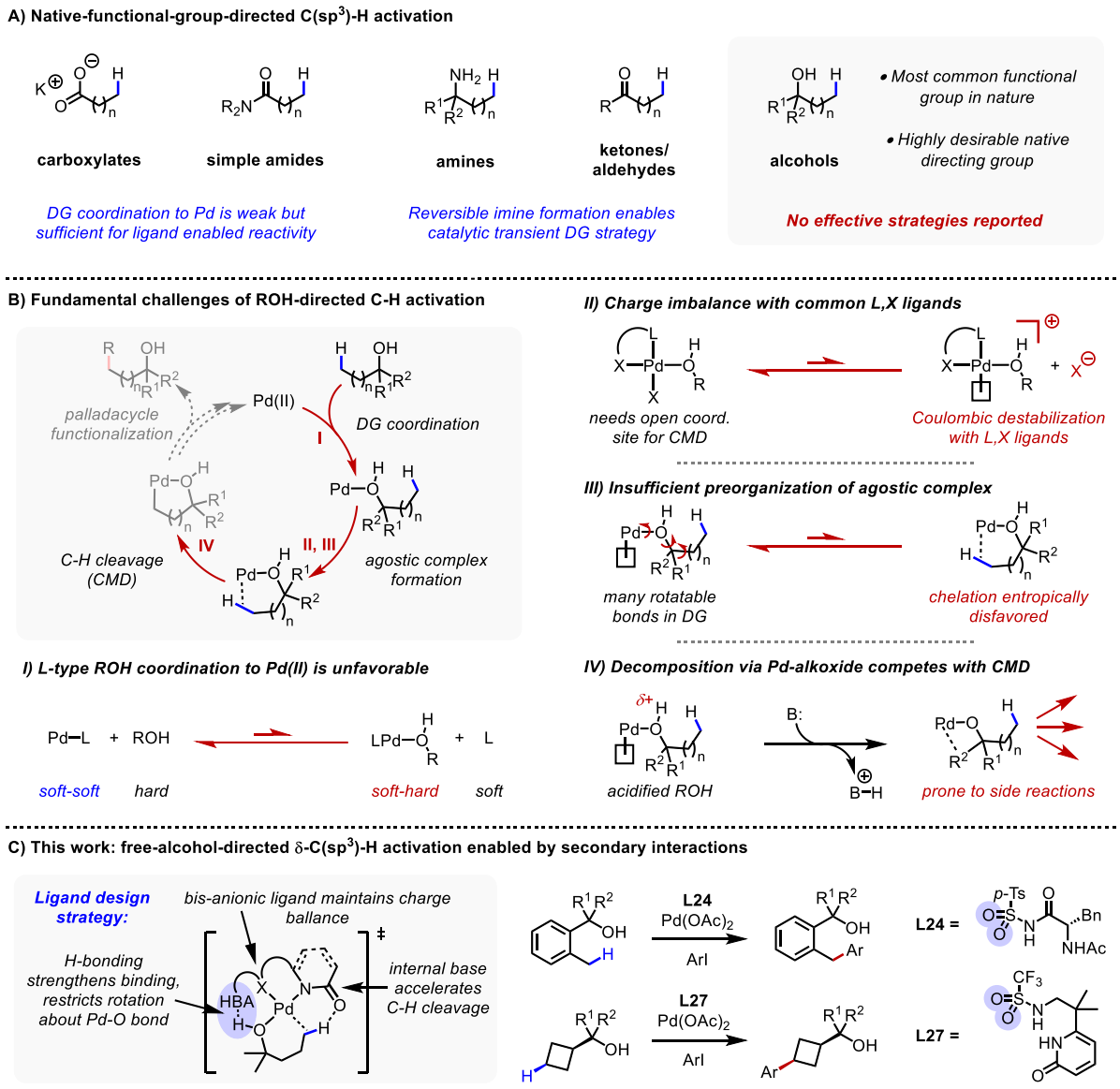

Fig. 1: Free-alcohol-directed C(sp^3)–H activation: value, challenges, and ligand design strategy. A) Native functional group directed C–H activation enhances synthetic efficiency. Alcohol-directed C(sp^3)–H activation is a significant unmet challenge. **B)** The weak coordination of alcohols to Pd and their lack of rigidity disfavor formation of the agostic complex and CMD. With commonly used L,X chelating ligands, alcohol coordination is further destabilized by charge separation. Pd(II)-alkoxides readily undergo undesired side reactions such as oxidation and fragmentation. **C)** (This work) Rationally designed bis-anionic ligands containing an H-bond acceptor and a CMD-active base enable free-alcohol-directed δ-C(sp^3)–H arylations.

We hypothesized that ligands designed to selectively strengthen and rigidify hydroxyl coordination to Pd(II) could enable free-alcohol-directed C(sp^3)–H activation. Our ligand design strategy relied on two key principles: charge balance to Coulombically favor the coordination of neutral alcohol DGs and the incorporation of a secondary coordination sphere H-bonding interaction to stabilize the substrate-catalyst complex and help organize the agostic complex by restricting rotation about the Pd–O bond (Fig. 1C). Herein we report the successful execution of this strategy through the development of free-alcohol-directed δ-C(sp^3)–H arylations of two distinct classes of substrates. Structure-activity-relationship (SAR) studies indicate that X,X-chelating ligands containing both an appropriately positioned CMD-active base and an H-bond acceptor (HBA) are critical for achieving high reactivity, and control experiments, computational modelling, and crystallographic data support a key role for the proposed secondary-coordination-sphere H-bonding interaction.

Given the absence of published reports on alcohol-directed C(sp^3)–H activation, we first sought to identify a simple model system. We were particularly interested in examining δ-functionalizations because Pd-catalyzed reactions of hydroxyl derivatives are almost exclusively limited to β- and γ-C–H activation due to the binding mode of their DGs (see Note S3 for details). We hypothesized that free-alcohol-directed reactivity would be better suited for engaging remote positions, as direct coordination of the hydroxyl group to Pd would allow for δ-functionalization through a 6-membered palladacycle. Accordingly, we selected benzylic alcohol **1a** as a model substrate, which was found to undergo measurable C(sp^3)–H arylation in the presence of $Pd(OAc)_2$ to afford **2a** in 4% NMR yield (Fig. 2A). Routine additive and condition screening revealed that the addition of bases or the replacement of AgOAc with more

basic silver salts decreased the yield of **2a** (see also Figs. S2-3 and S11), mirroring observations from C(sp^2)–H activation reactions reported to involve L-type hydroxyl coordination[12,15]. Based on these results and the catalyst SAR data, crystallographic evidence, and computational modelling reported below, we propose that alcohols coordinate as neutral directing groups in the reactions described here.

We next sought to increase reactivity by employing bidentate ligands containing CMD-active amide or pyridone bases[6]. A suite of CMD-active L,X ligands have been developed for carboxylate-directed C–H activation[6,7], but we anticipated that these would perform poorly with neutral alcohol directing groups due to Coulombic destabilization of the resulting cationic agostic complex and CMD transition state[8]. Indeed, representative members of each major class of L,X ligands (**L1-L6**) inhibited the $Pd(OAc)_2$-catalyzed reaction of **1a**, in all cases providing **2a** in <1% yield (Fig. 2B). In contrast, a series of X,X-ligands (**L7-L11**) afforded **2a** in 2-6% yields (Fig. 2C, see also Fig. S1), confirming the importance of employing bis-anionic ligands and providing support for the proposed L-type coordination of the hydroxyl.

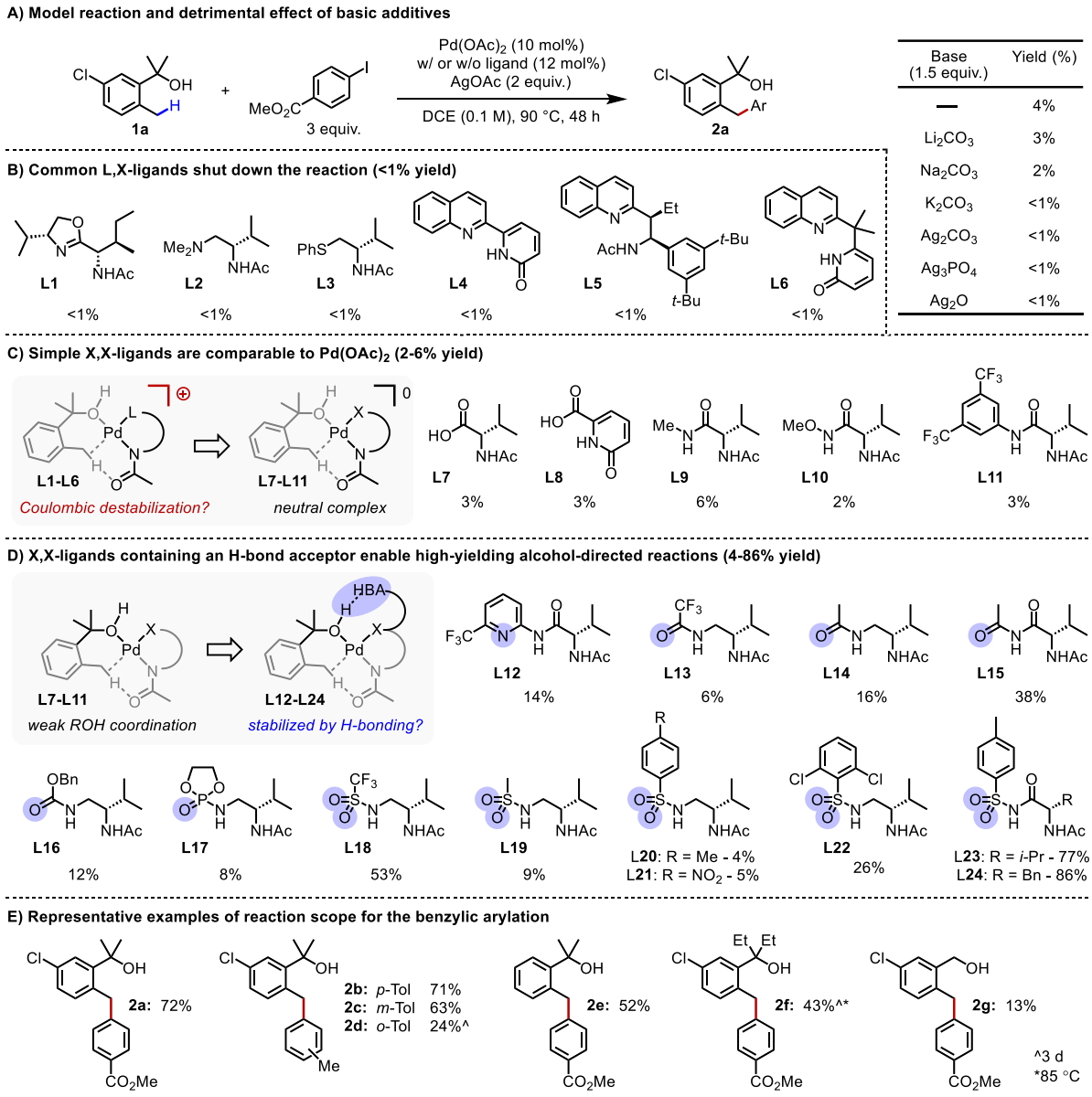

Fig. 2: Model system and ligand design. A) Trace reactivity is observed with $Pd(OAc)_2$, but is suppressed by added base. **B)** L,X ligand shut down ROH-directed reactivity. **C)** Simple X,X ligands provide similar reactivity to $Pd(OAc)_2$. **D)** X,X-HBA ligands allow for high-yielding alcohol-directed C(sp^3)–H activation. Yields in Fig. 2 A-D are determined by NMR relative to CH_2Br_2 as an internal standard. **E)** Representative scope examples with isolated yields. For detailed information on reaction setup, see General Procedure A in the Supporting Information.

The poor reactivity of **1a** in the presence of a range of established ligands suggested that an alternate approach would be necessary to compensate for the excessively weak coordination of hydroxyl DGs to palladium. Thus, we decided to explore the possibility of using non-covalent interactions in the secondary coordination sphere to stabilize alcohol coordination to the catalyst[31]. In particular, we recognized that the hydroxyl directing group would be acidified upon coordination to Pd(II), increasing its ability to serve as an H-bond donor (HBD)[32-34] (see also Note S4). We hypothesized that an HBA installed on the ligand could form an intramolecular H-bond with the Pd-bound alcohol (Fig. 2D), strengthening and rigidifying its coordination to the metal[35]. To examine this hypothesis, we synthesized **L12**, which contains a pyridine moiety with the pyridyl nitrogen available to form a 6-membered cyclic H-bond with the Pd-bound hydroxyl. This ligand provided greater reactivity than any previously tested, increasing the yield of **2a** to 14%. Notably, **L12** provided more than 4 times the yield of **2a** than did **L11**, which is structurally similar, but lacks an HBA. Based on this result, we evaluated a series of N-acetyl-*L*-valine derivatives bearing potential HBAs. While these data lack clear trends with respect to HBA identity, the HBA-containing ligands consistently outperformed **L1**-**L11** (see Note S5 for additional discussion). Acyl-sulfonamides[36] proved particularly effective, with **L23** providing **2a** in 77% yield. Routine screening within this ligand class (Fig. S8) resulted in the identification of phenylalanine derivate **L24** as the optimal ligand.

A brief examination of the reaction scope (Fig. 2E, see Fig. S9 for complete scope) revealed that the reaction shows little sensitivity to the electronic properties of the aryl iodide (**2a**, **2b**) or the presence of a *meta*-substituent (**2c**), though substitution of the *ortho*-position

(**2d**) resulted in reduced yield. Removal of the 5-substituent, which helps shield the *ortho* position of the substrate from C–H activation, led to reduced yield due to competing C(sp^2)–H arylation, but **2e** remained the major product, indicating that **L24** is selective for sp^3 over sp^2 arylation (contrasting the selectivity observed with $Pd(OAc)_2$ alone, see Fig. S1). Variation of the α-alkyl substituents on tertiary alcohols is also tolerated (**2f,**). Despite competing oxidation, arylated primary alcohol **2g** could also be obtained in low yield, offering a promising starting point for the future development of primary- and secondary-alcohol-directed reactions.

Having identified ligands capable of promoting our model benzylic C–H activation reaction, we questioned whether this strategy could be extended to more challenging substrates. We were particularly interested in the possibility of achieving δ-functionalizations of cyclobutyl alcohols to access *cis*-1,3-disubstitued cyclobutanes, a motif which is gaining attention in medicinal chemistry for its ability to serve as a rigidified alternative to ethyl and propyl linkers or as a replacement for larger cycloalkanes or arenes[37]. Moreover, the angle and positioning of the 1- and 3-subsituents almost exactly mimic those in *meta*-substituted arenes (Fig. S10), offering the potential for *cis*-1,3-disubstituted cyclobutanes to serve as simple, saturated bioisosteres of this common motif, complementing the rigid bicyclo[3.1.1]heptanes recently disclosed by Anderson and co-workers[38]. While $Pd(OAc)_2$—either alone or with any of **L1**-**L11**—failed to catalyze the reaction of cyclobutyl alcohol **3a** (Fig. S18), we were encouraged to find that **L24** enables the formation of **4a** in a modest 37% yield with exclusive selectivity for arylation of the δ-position (Fig. 3A). Recent studies have demonstrated that pyridone-containing ligands are particularly effective for the activation of methylene C–H bonds[39], so we hypothesized that reactivity could be improved by replacing the acetamide

internal base with a pyridone. While 5-membered chelate **L25** proved ineffective, the corresponding 6-membered chelate (**L26**) afforded **4a** in 12% yield, suggesting that increased linker flexibility is required to compensate for the rigidity of the pyridone moiety. To further increase flexibility, the acyl-tosylamide moiety of **L26** was replaced with an alkyl triflamide. The resulting pyridone-triflamide ligand, **L27**, proved optimal for the reaction of **3a**, providing **4a** in 67% NMR yield while maintaining exclusive selectivity for arylation of the δ-position (for complete ligand optimization data, see Fig. S18-S21).

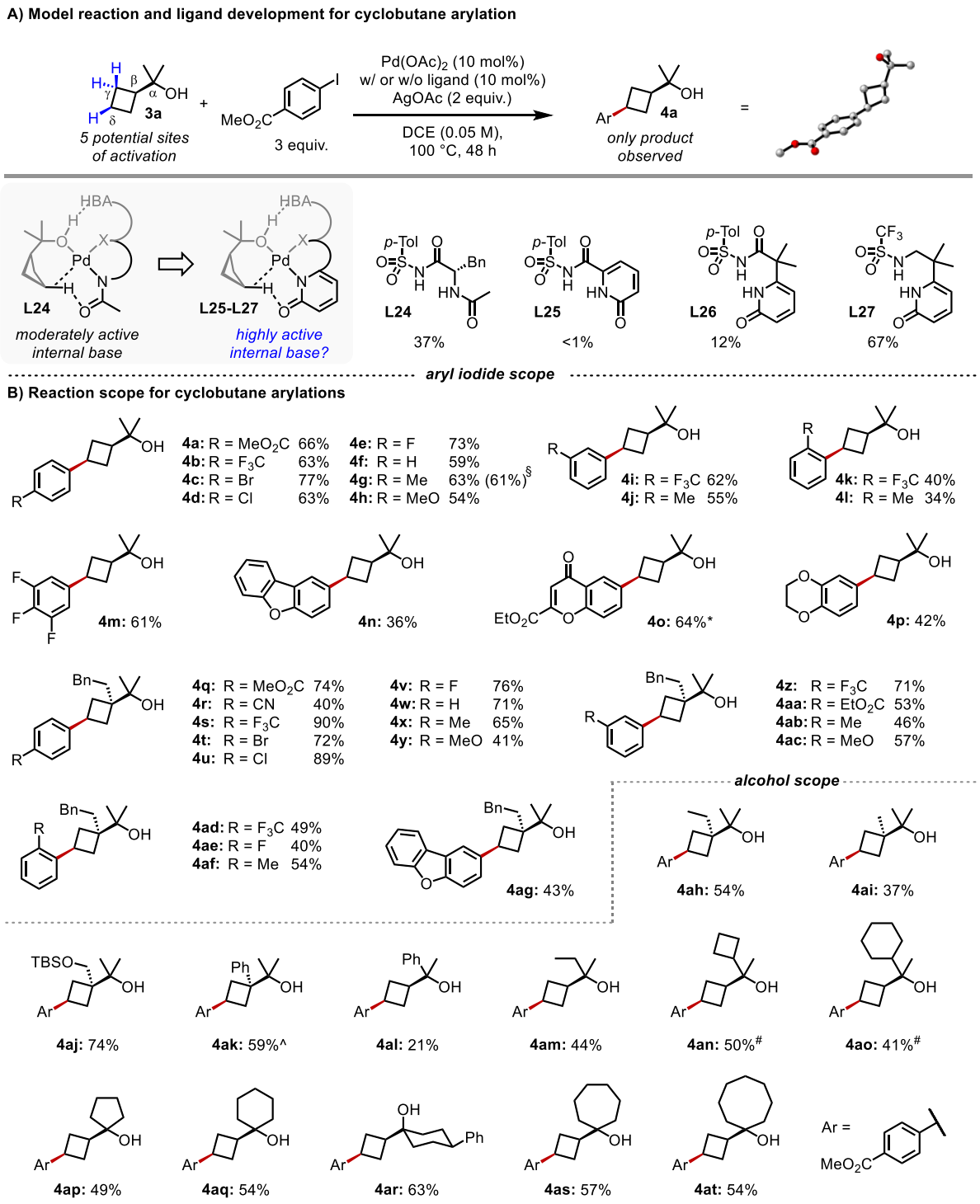

Fig. 3: Ligand design and scope for alcohol-directed δ-arylations of cyclobutanes. A) Model reaction for δ-arylations of cyclobutane alcohols and design of pyridone-triflamide ligand **L27 B)** Scope studies with isolated yields. For detailed information on reactions setup, see Supporting Information General Procedure B. §Reaction performed on 1 mmol scale at 105 °C. *****1.2 equiv. of Ar–I used. ^24-hour reaction time. #**L24** used instead of **L27.**

Examination of the scope of the reaction revealed that **3a** undergoes δ-arylation in synthetically useful yields with a wide range of electronically varied *para*- and *meta*-substituted aryl iodides (Fig. 3B, **4a-4j**). Yield proved insensitive to reaction scale, with product **4g** being obtained in nearly identical yields in 0.1 mmol and 1 mmol scale reactions. The introduction of an *ortho*-substituent resulted in decreased reactivity, but the corresponding products (**4k-4l**) were still obtained in moderate yields. Poly-substituted and heterocyclic aryl iodides also reacted in moderate to high yields (**4m-4p**). We next investigated the reactivity of β-quaternized substrates, employing phenethyl derivative **3q** as a model substrate to screen coupling partners. Despite the presence of four additional C–H bonds as competing reaction sites, the desired arylated products (**4q**-**4ag)** were obtained in moderate to high yields with reactivity trends similar to those observed with **3a**. Moderate to high yields were also obtained with quaternized alcohol substrates bearing a range of other β-substituents (**4ah-4ak**), with only methyl substituted **4ai** showing significantly decreased yield. The reaction proved to be somewhat more sensitive to variation of the α-substituents. Although primary and secondary alcohols failed to form product (see Fig. S22 for poorly performing substrates) and α-phenyl-substituted-**3al** was poorly reactive, moderate yields were obtained with α-ethyl, α-cyclobutyl, and α-cyclohexyl substrates (**4am**-**4ao, L24** was optimal for **4an** and **4ao**). Moreover, reactions with cyclic alcohols—a particularly notable substrate class since the products would be difficult to access from cyclobutane acid, aldehyde, or ketone derivatives—resulted in δ-arylation of the cyclobutane fragment in synthetically useful yields across a variety of rings sizes (**4ap-4at**).

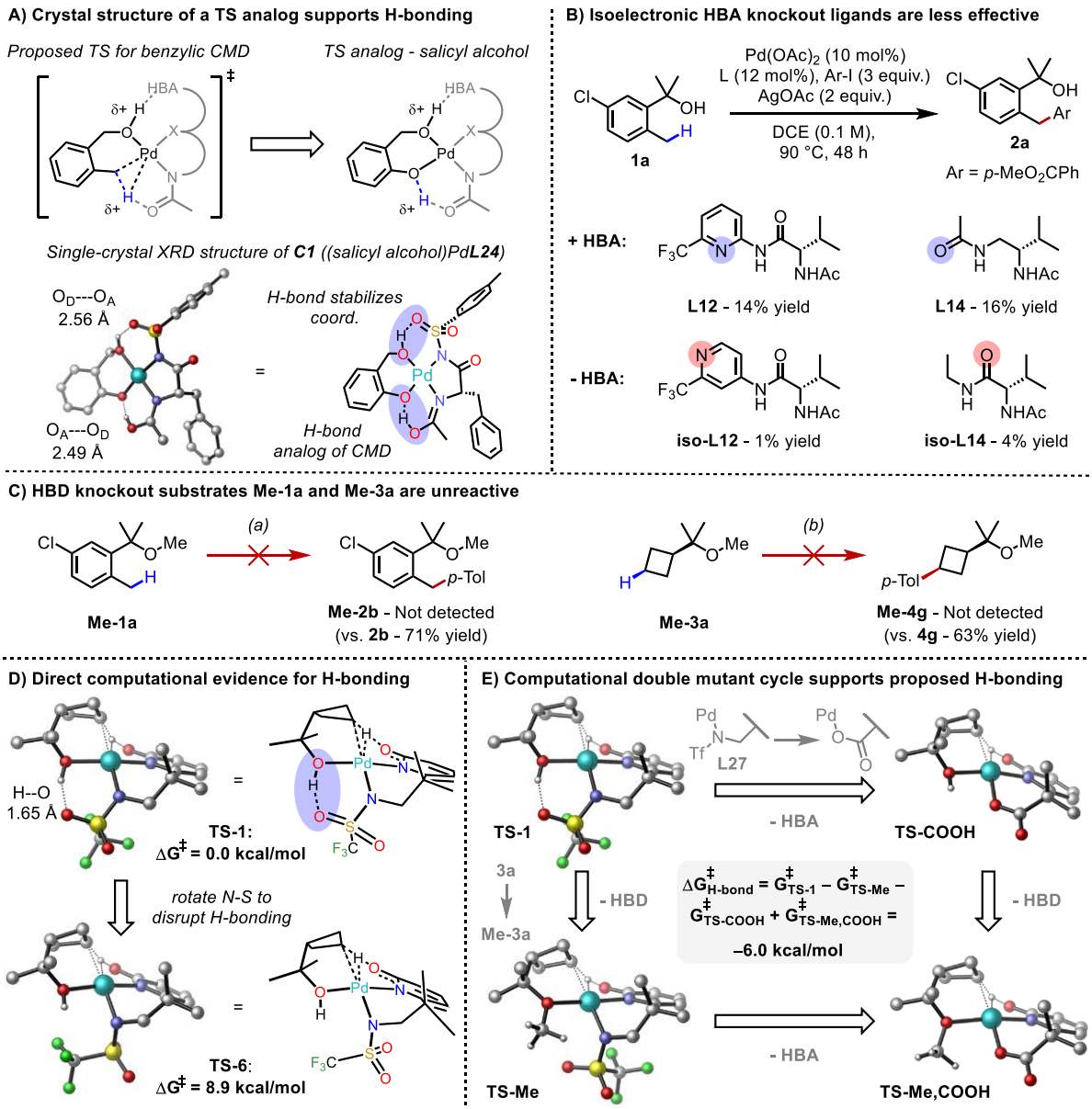

Fig. 4: Evidence for H-bonding. A) Crystal structure of a Pd(II)-**L24** complex bound to a transition state analog showing the proposed H-bonding interaction. **B)** Isoelectronic "HBA-knockout" variants of **L12** and **L14** are ineffective. **C)** Methyl ether "HBD-knockout" substrates are unreactive. (*a*) $Pd(OAc)_2$ (10 mol%), **L24** (12 mol%), *p*-Tol-I (3 equiv.), AgOAc (2 equiv.), DCE (0.1 M), 90 ºC, 48 h; (*b*) $Pd(OAc)_2$ (10 mol%), **L27** (10 mol%), *p*-Tol-I (3 equiv.), AgOAc (2 equiv.), DCE (0.05 M), 100 ºC, 48 h. **D)** H-bonding stabilizes the lowest energy transition structure for δ-C–H cleavage with substrate **3a** (**TS-1**). **E)** A computational double mutant cycle provides further evidence that the H-bonding interaction contributes significant stabilization to **TS-1**. See the Supporting Information for computational details.

In order to build a foundation for the further extension of alcohol-directed C(sp^3)–H activation chemistry, we next sought to examine the validity of the H-bonding interaction at the heart of our ligand design strategy. The structure of a Pd(II)-**L24** complex bound to 2-hydroxybenzyl alcohol—a transition state analog for the C–H activation of substrate **1** wherein H-bonding between the phenolate and the protonated amide mimics proton transfer during CMD—was obtained by X-ray diffraction (Fig. 4A). The crystal structure of **C1** supports the proposed hydrogen bonding interaction between the alcohol directing group and the tosylamide moiety on the ligand, with an O_D--O_A distance of 2.56 Å (for details and crystal structures of additional **L24** and **L27** complexes, see the Supporting Information). To probe the effect of the H-bonding interaction on reactivity, we synthesized isoelectronic variants of **L12** (**iso-L12**) and **L14** (**iso-L14**) and examined their ability to promote arylation of **1a** (Fig. 4B). Although **L12** and **L14** only provided **2a** in modest 14-16% yields, they easily outperformed **iso-L12** and **iso-L14**. We next sought to perturb the proposed interaction through methylation of the alcohol DG (Fig. 4C). Neither **Me-1a** nor **Me-3a** underwent arylation, indicating that the presence of a free hydroxyl is essential for reactivity. Lastly, we turned to computational modelling to investigate the H-bond using density functional theory (DFT, see the Supporting Information for computational details and computational modelling of the acyl-sulfonamide promoted reaction of substrate **1e**, which produced qualitatively similar results to those in Fig. 4). In **TS-1**, the lowest energy transition state identified for δ-C–H activation of **3a** (δ-C–H activation was determined to be irreversible based on deuterium incorporation studies of both the **L24**-promoted arylation of **1a** and the **L27** promoted arylation of **3ak**. See Fig. S23-S31 for details and discussion), the hydroxyl proton was found to be 1.65 Å from a sulfonamide oxygen with

an O–H–O angle of 156º, a distance and geometry consistent with the proposed H-bonding interaction (Fig. 4D). Moreover, disruption of the H-bond by rotating the sulfonamide oxygens away from the directing group (**TS-6**) resulted in nearly 9 kcal/mol of destabilization. A double mutant cycle was devised as an alternate method for interrogating the strength of the H-bond in the DFT model (Fig. 4E, see Fig. S40 for detailed discussion and Figs. S41-S50 for additional double mutant cycles that produced qualitatively similar results). This analysis suggested that H-bonding contributes approximately 6.0 kcal/mol of stabilization in the DFT model. Taken together, the crystallographic studies, extensive catalyst and substrate SAR data, computational modelling, evidence from solvent screening data (see Figs. S4 and S12), and literature precedent for stabilizing intramolecular H-bonding to sulfonamides in Ni(II)-aquo complexes[40] strongly support a key role for the proposed H-bonding interaction in enabling alcohol-directed C(sp^3)–H activation.

The utilization of stabilizing non-covalent interactions in organic methodology has grown from pioneering studies in the field of organocatalysis[41] to become a standard tool for catalyst design[31,35,42,43]. Despite tantalizing evidence that these interactions can provide pronounced rate acceleration and significantly improve catalytic efficiency[35,41], to date, most research efforts in synthetic methodology have focused on employing stabilizing secondary interactions primarily to control the *selectivity* of organic transformations (including notable examples in C–H activation[44-46]). In principle, the ability of these interactions to stabilize transition states could be an equally powerful tool for enabling novel and otherwise inaccessible *reactivity*[47] (see also Note S6). We propose that this strategy, demonstrated here as a solution to the longstanding challenge of free-alcohol-directed C(sp^3)–H activation, is

particularly well suited to transformations involving weakly coordinating directing groups. In reactions where substrate coordination to the catalyst is thermodynamically disfavored, non-covalent interactions that stabilize substrate-catalyst binding are likely to selectively stabilize transition states involving the catalyst-substrate complex throughout the catalytic cycle, providing a rational and potentially generalizable foundation for the design of ligands that will accelerate key elementary steps such as C–H cleavage. We anticipate that this ligand design strategy will be broadly applicable for enabling a wide range of challenging substrate-directed organometallic transformations.

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Author contributions: D. A. S. conceived of the project and developed the arylation of benzylic C–H bonds. D. A. S. and C.-Y. C. developed the arylation of cyclobutyl substrates, and C.-Y. C. performed scope studies for the cyclobutyl system. H.-S. P. developed the pyridone-sulfonamide ligands and performed scope studies on the benzylic arylation. J. P.

developed the acyl-sulfonamide ligands. D.A.S. performed the computational studies. D. A. S. and J.-Q. Y. prepared the manuscript. J.-Q. Y. directed the project.

Competing interests: The authors declare no competing interests.

Supplementary Information is available in the online version of the paper.

Data availability: The data supporting the findings of this study are available within the article and its Supplementary Information files.

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