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Activation of diverse carbon–heteroatom and carbon–carbon bonds *via* palladium(II)-catalyzed β-X elimination

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Abstract

Chemists' ability to synthesize structurally complex, high-value organic molecules from simple starting materials is limited by a paucity of methods to selectively activate and functionalize strong covalent bonds. Recent activity in this field has focused on the activation of abundant C–O, C–N, and C–C bonds *via* a mechanistic paradigm of oxidative addition of a low-valent, electron-rich transition metal. This approach typically employs nickel(0), rhodium(I), ruthenium(0), and iron(I) catalysts under conditions that are finely tuned for specific, electronically activated substrates, sometimes assisted by chelating functional groups or ring strain. For instance, in the context of C–O oxidative addition, common substrates include esters or aryl, benzyl, or allyl ethers. By adopting a distinct strategy involving palladium(II)-catalyzed C–H activation followed by β-heteroatom/carbon elimination, we describe a novel catalytic method to activate alkyl C(sp^3)–oxygen, nitrogen, carbon, fluorine, and sulfur bonds. Directed hydrofunctionalization of the resultant palladium(II)-bound alkene intermediate leads to a formal functional group metathesis. The method is applied toward amino acid upconversion with complete regioselectivity and moderate to high retention of enantiomeric excess. Low-strain five- and six-membered heterocycles undergo strong bond activation and substitution to give ring-opened products. High selectivity is obtained with substrates containing multiple potentially reactive C–heteroatom bonds by virtue of the high site-selectivity of the directed C–H activation step.

The selective activation of strong covalent bonds *via* transition metal catalysis allows functionalization of traditionally inert starting materials and enables novel retrosynthetic disconnections. In recent years, immense effort has focused on the use of transition metals for activating C–O, C–N, and C–C bonds *via* an oxidative addition pathway using mainly nickel(0), rhodium(I), ruthenium(0), and iron(I) catalysts, allowing the respective starting materials to serve as electrophiles in catalytic transformations, such as cross-coupling (Figure 1a–c).[1–20] Oxidative addition to a C–heteroatom or C–C bond requires an appropriately electron-rich metal center, a directing group proximal to the bond of interest, an activated bond (*e.g.*, a strained ring or a system that contains an adjacent heteroatom), or a combination of these features. Consequently, the substrate scope and synthetic utility are limited. In regards to catalytic C–O bond activation *via* oxidative addition, for instance,

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substrates are limited to aryl, vinyl, benzyl, or allyl C–O bonds[1, 2, 5–7] or strained-ring systems, such as epoxides[4]. Successful cases of oxidative addition to an *unactivated* alkyl C–O bond generally involve stoichiometric transition metal species and reactions that are driven by the high stability of the resulting well-defined organometallic complexes.[21–27] These limitations are largely a consequence of an oxidative addition approach to strong covalent bond activation, pointing to the need for alternative catalytic approaches to C–heteroatom and C–C cleavage that would complement the selectivity and reactivity patterns of existing methods. To this end, we envisioned a strategy that would take advantage of β-heteroatom/carbon (β-X) elimination from an alkylpalladium(II) intermediate[28–35] generated from an initial C(sp^3)–H activation step (Figure 1d). This approach takes inspiration from non-classical C–F and C–O bond activation by stoichiometric iridium pincer complexes[36–38] and iron catalysts[39]. To ensure selectivity, we chose to access this intermediate from a well-established C–H activation step enabled by Daugulis's bidentate 8-aminoquinoline (AQ) directing group.[40] Though the fundamental β-X elimination step has been previously documented[28–35], examples of its application toward small molecule synthesis are rare, with the Catellani reaction being a notable exception[30].

To initiate the study, we examined a series of butanoic acid substrates bearing the AQ group and various leaving groups at the γ-position. With the AQ group, we sought to access an alkyl palladium species through well-precedented C–H activation at the β-position,[40] leading to β-X elimination and thus selective activation of the γ C–X bond. In the presence of a suitable nucleophile, the putative alkene intermediate would undergo hydrofunctionalization[41–43] to effect net functional group metathesis and render the process catalytic. We optimized the reaction using phthalimide as the leaving group (see SI), as it had intermediate reactivity compared to other leaving groups, and identified optimal conditions with $Pd(OAc)_2$ (10 mol%) as catalyst, 1-adamantane carboxylic acid (1-Ada-CO_2H) (50 mol%) as promoter, and MeCN as solvent at 120 °C for 16 h. Notably, other inexpensive carboxylic acid promoters, such as acetic acid, functioned nearly as well. We then proceeded to survey an array of oxygen-, nitrogen-, carbon-, fluorine-, and sulfur-based leaving groups with *N*-methylindole as the nucleophile (Figure 2). Surprisingly, reaction efficiency under optimized conditions does not closely follow classical leaving group ability trends. Comparison of substrates **1e** (acetate) and **1f** (methoxide) demonstrates this point, as the respective leaving group conjugate acids have pK_a values that are greater than 10 log units apart, yet perform similarly in the reaction. At the time, these trends cannot be easily explained. We found oxygen-based leaving groups to be most efficient with nearly quantitative yields for phenol leaving groups (**1a–c**). Groups on which S_N2 reactions are untenable such as benzyloxide (**1d**), methoxide (**1f**), and siloxide (**1h**) functioned well under our conditions. Additionally, C–O bond activation in these cases were selective for the γ-position regardless of classic oxidative addition trends. For example, an oxidative addition approach would be unselective if possible in the case of **1f** (a dialkyl ether) and selective for the undesired benzylic position in the case of **1d**. For C–N bond activation, yields were slightly lower. Interestingly, the nitro leaving group in **1q** was operative in our reaction. Carbon-based leaving groups[42] were significantly lower yielding, with **1s** proving the highest yielding at 32%. However, substrates **1s–v** demonstrate that activation of sterically encumbered C–C bonds without assistance of ring strain is possible in our system.

Furthermore, alkyl C–F and C–S bond activation were also demonstrated in moderate yields *via* β-fluoride[44–45] and β-sulfur elimination with sulfoxide, sulfone, and sulfide containing substrates (**1x–z**).

To assess different nucleophiles, we chose **1a** as our standard substrate due to its excellent performance with *N*-methylindole as nucleophile. Various nucleophiles our laboratory previously employed in alkene hydrofunctionalization gave good to excellent yields with electron-rich arenes and 1,3-dicarbonyl-type (pro)nucleophiles (Figure 3a).[42] Moderate to excellent yields were also obtained with nitrogen nucleophiles.[41, 43] This method of interchanging C–O or other C–X bonds with C–C or C–N bonds is synthetically enabling where the saturated starting material with a leaving group is more readily available than the corresponding alkene (Figure 4a). The stability and ubiquity of the compatible leaving groups enable orthogonal reactivity and fewer protecting group interconversions.

Inspired by the power of the Fries and Claisen rearrangements of phenol derivatives, we next sought to leverage the fact that some of our leaving groups can also double as nucleophiles (**1g**, **1i**). By reengaging with the putative alkene through a different nucleophilic site, we hypothesized that a formal [1,3]-rearrangement could be achieved (Figure 3b). In the event, when **1g** and **1i** were subjected to the reaction conditions without exogenous nucleophile for 48 h, we isolated 25% and 39% of the formal [1,3]-rearrangement products **2e** and **1j**, respectively.

Most substrates with nitrogen leaving groups can be easily synthesized from GABA (γ-aminobutyric acid). We reasoned that this strong bond activation reaction could thus be expanded to chiral pool α-amino acids with γ-heteroatom substitution to generate an array of enantioenriched unnatural amino acids that would be difficult to access otherwise (Figure 4a).[46] By comparison, enantiopure vinyl glycine is expensive from commercial suppliers or must be prepared in several synthetic steps.[47] To explore this “amino acid upconversion,” we started with a DAB (2,4-diaminobutyric acid) derivative, bearing phthalimide (-NPhth) groups at the α- and γ-positions. At the outset, we were concerned that either of the two C–N bonds could be activated; however, upon subjection of **3c** to the reaction conditions, we observed not only regioselective substitution of exclusively the γ-phthalimide but almost complete preservation of the α-stereocenter, demonstrating high selectivity (Figure 5). In hopes of using more abundant natural amino acid starting materials, we synthesized the γ-methylsulfoxide variant of **3c** (**3a**) from methionine and found it to work efficiently in our reaction. The corresponding γ-methylsulfide (**3d**) and γ-methylsulfone (**S7**) were also synthesized but did not perform nearly as well. Lastly, our method is also compatible with a homoserine derivative (**3b**). Suitable nucleophiles include *N*-methylindole, 2-naphthol, acetylacetone, and carbazole, albeit with moderate epimerization of the α-stereocenter.

Furthermore, this β-elimination pathway was applied towards nucleophilic opening of unstrained rings. In previous reports of catalytic ring opening from alkyl-palladium intermediates, success has been limited to strained systems, such as oxonorbornadienes.[48] With focus on catalytic opening of unstrained heterocycles, we subjected a pyran motif **5a** to our conditions and observed the unexpected product of *in situ* lactonization with the intermediate pendant alcohol following ring opening. Sequestration of the resulting free AQ

group by a stoichiometric copper(II) additive and solvent optimization provided conditions for nucleophilic ring opening of unstrained six-membered and five-membered rings with oxygen- (**5a–c**) and nitrogen- (**5d–h**) based leaving groups (Figure 4b). Again, the method is selective only for the C–O or C–N bond at the γ-position without requirement for a symmetric five-membered ring, as is the case for an oxidative addition approach (Figure 5). With six-membered rings and nucleophilic leaving groups, lactonization/lactamization is observed (**6a**, **6d**, **6e**). In the case of **5h**, the resulting tosylamide is presumably too weak of a nucleophile to displace the AQ group. However, the tosylamide intermediate is not observed due to a rapid second β-elimination event, leading to a bis-indole substituted product **6h**. Lastly, **6b** is isolated after Fischer esterification with the solvent.

Though a detailed mechanistic investigation is outside of the scope of the present work, we performed several preliminary experiments (Figure 6). Three limiting scenarios could be envisioned: (I) Pd(II) serves as a hard Lewis acid to activate the leaving group for S_N2-type displacement, (II) following C–H activation to form an alkylpalladium(II) intermediate, the nucleophile displaces the leaving group in an S_N2 fashion, possibly facilitated by Pd(II) coordination, (III) after C–H activation, β-X elimination leads to a Pd(II)-π-alkene complex, and hydrofunctionalization occurs as previously described. The β-elimination step could take place with (III.A) *syn* (inner sphere) or (III.B) *anti* (outer sphere) geometry with respect to the metal center (See SI).

To examine these pathways, we prepared substrate **7a**, which we expected would not undergo C–H activation. When we exposed **7a** to the reaction conditions, no product formation was observed by ^{1}H-NMR. This is inconsistent with pathway (I). Next, we prepared enantiopure *trans* (**7b**) and *cis* (**7c**) versions of a cyclopentane substrate **7** and subjected them to the reaction conditions with *N*-methylindole as nucleophile. With **7b** (*trans*), we observed a moderately high yield of **8b** and determined its relative stereochemistry to be *trans*. With **7c** (*cis*), we again observed the same product **8b** with *trans* stereochemistry, but with significantly lower yield. In both cases, the enantiopurity was largely preserved, ruling out epimerization that would convolute the analysis (see SI). The fact that *trans* **7b** is converted to *trans* **8b** is inconsistent with pathways (I) and (II). Collectively, the data support a mechanistic model in which β-X elimination proceeds in a predominantly *anti* fashion but the *syn*-pathway is also energetically accessible in cases where *anti* elimination is geometrically forbidden (**7c**). The *trans* stereochemistry of the final product **8b** regardless of the starting material stereochemistry (*cis* or *trans*) is consistent with anti-nucleopalladation from a common Pd(II)-bound alkene intermediate, as characterized previously.[41–43] In attempts to isolate the proposed alkene intermediate, we subjected **1a** to the reaction conditions without addition of nucleophile, but only observed quantitative amounts of starting material (See SI). This could potentially be due to nucleophile assistance in the C–H activation or β-X elimination steps or due to rapid reinsertion into the intermediate alkene. We observed deuterium exchange at the β-position of substrate **1m** (see SI) and obtained a crystal structure of the proposed C–H activated intermediate without added nucleophile. Additionally, the results from Fig. 3b indicate that the overall reaction can take place in the absence of exogenous nucleophile. Thus, we believe that nucleophile is not necessary for the C–H activation or β-X elimination steps and that rapid reinsertion into

the proposed alkene is the main reason behind our inability to observe this intermediate. Independently prepared alkene was found to be a competent starting material in accessing **2a** under these reaction conditions (see SI). These preliminary mechanistic experiments are consistent with the catalytic cycle shown in Figure 1.

In conclusion, we have designed a palladium(II)-catalyzed reaction system that allows for activation of strong alkyl C(sp^3)–O, N, C, F, and S bonds by strategic application of a rarely used elementary step in catalysis, β-X elimination. Following activation of the strong covalent bond, non-classical nucleophilic substitution can be achieved with a range of carbon and nitrogen nucleophiles. Specifically, this C–H activation/β-X elimination/ hydrofunctionalization cascade enabled novel [1,3]-rearrangements, diversification of abundant amino acids, and nucleophilic ring opening of unstrained heterocycles. Each of these reactions serves as a specific example of how a new approach toward strong covalent bond activation through β-X elimination can be strategically employed in catalytic reaction development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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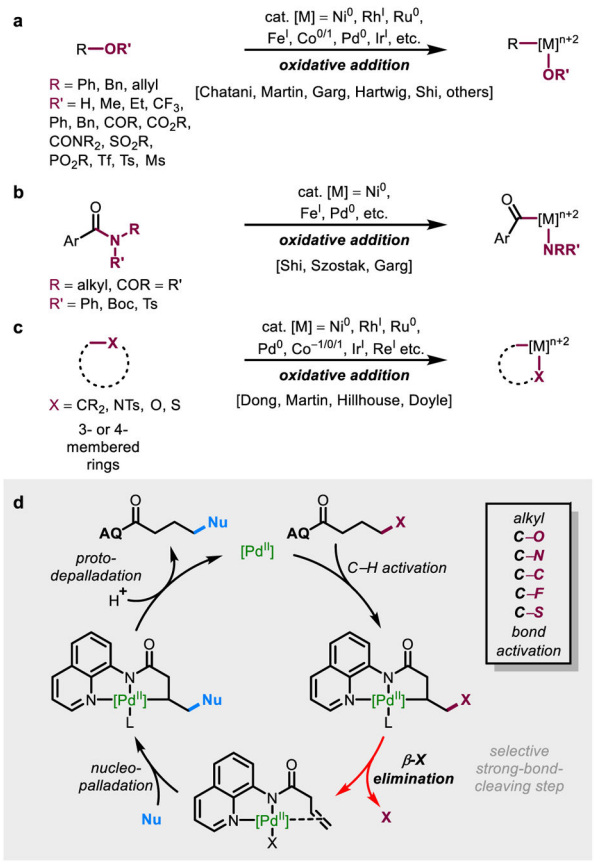

Figure 1. Common approaches to activate strong bonds *via* oxidative addition and this new strategy for activating alkyl C–O, N, C, F, and S bonds

A brief overview of well-known methods to activate strong bonds **a**, oxidative addition into aryl, benzyl, or allyl C–O bonds, **b**, oxidative addition into protected amide C–N bonds, **c**, oxidative addition facilitated by ring strain release. **d**, This work, a different approach through C–H activation followed by β-elimination to break strong bonds selectively.

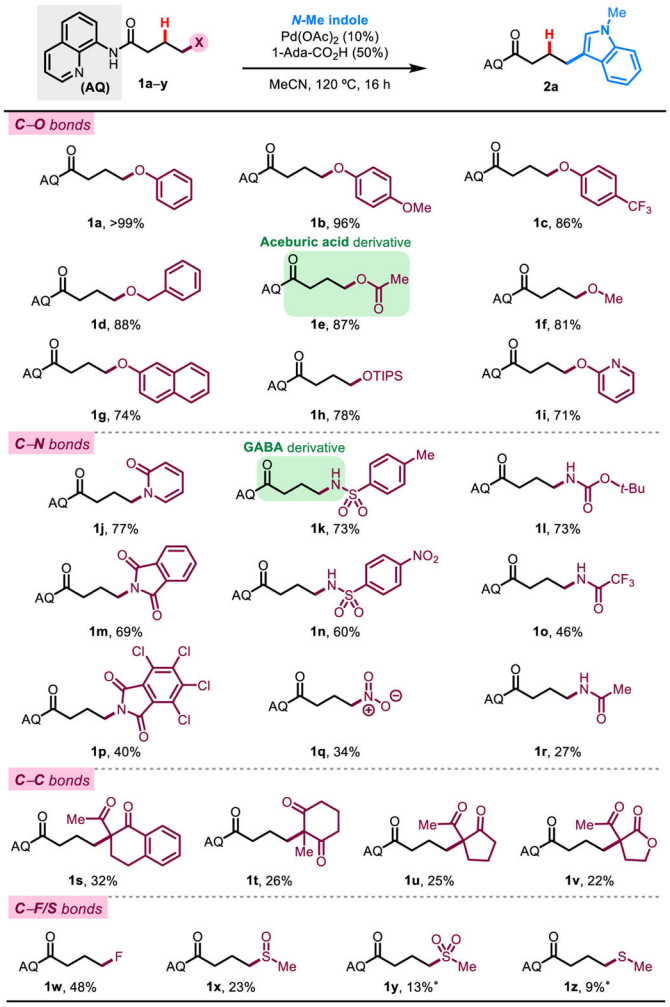

Figure 2. Leaving group scope

An array of alkyl C–O, C–N, C–C, C–F, and C–S bonds that can be activated using β-elimination. *Yields determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as internal standard.

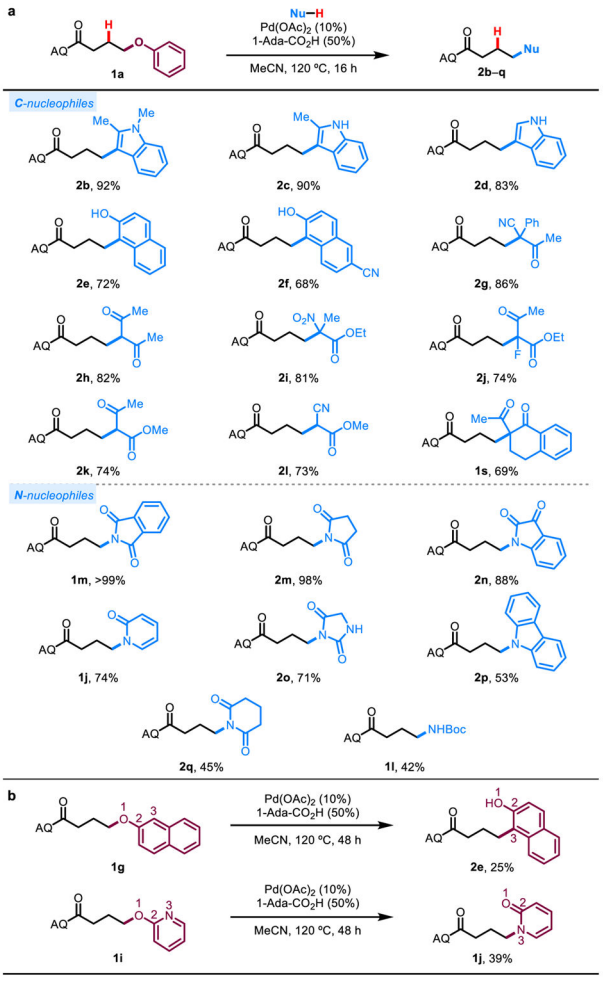

Figure 3. Nucleophile scope

a, Various operative carbon and nitrogen nucleophiles. **b**, Examples of formal [1,3]-rearrangments following C–O bond activation.

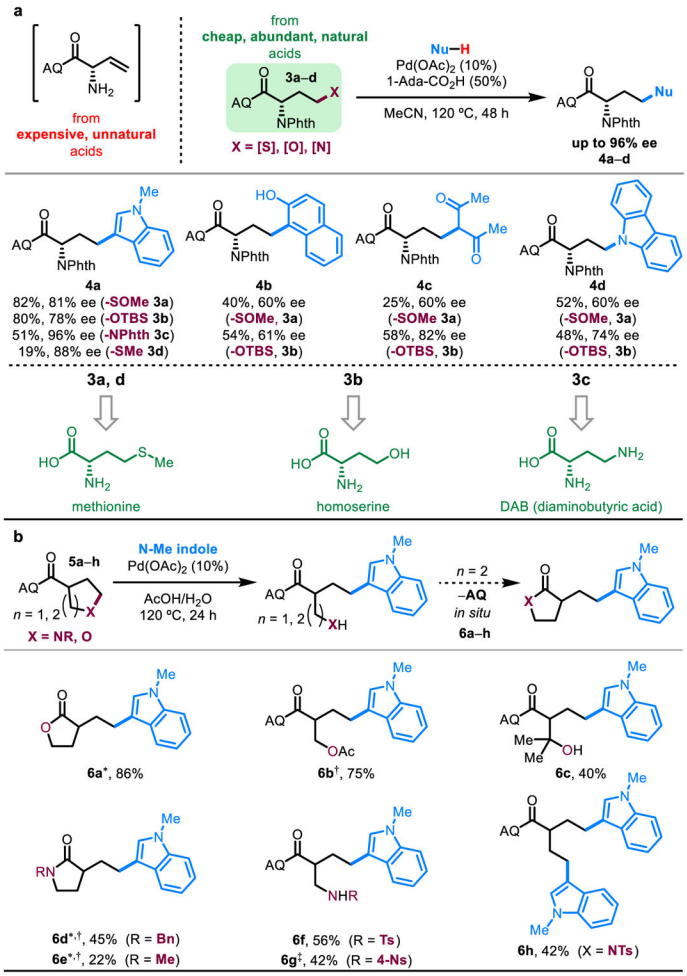

Figure 4. Applications toward small molecule synthesis

a, Amino acid upconversion through selective C–S, C–O, and C–N activation. **b**, Ring opening and substitution of unstrained rings through selective C–O and C–N activation. *1 equiv $CuSO_4$•$5H_2O$. †AcOH as solvent. ‡50% AcOH, HFIP as solvent.

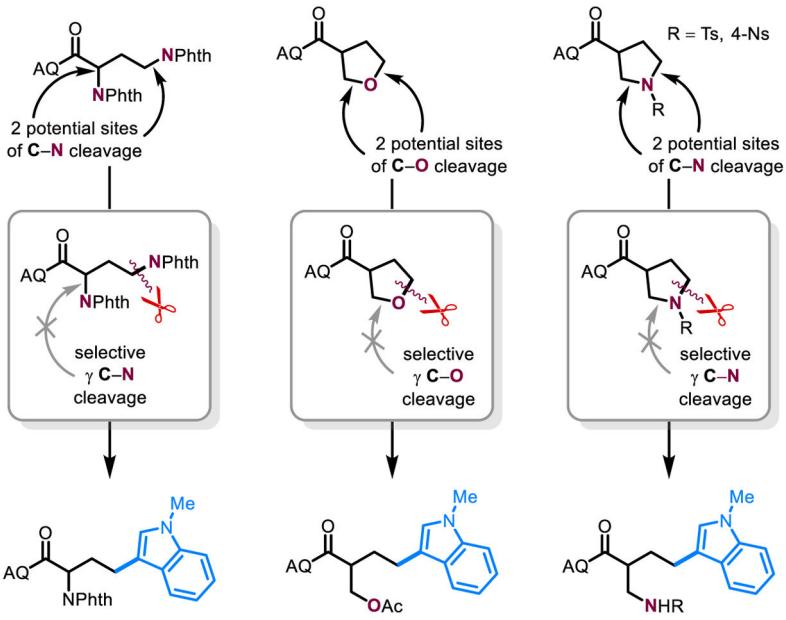

Figure 5. Exceptional selectivity

Regioselective strong bond activation of alkyl C–O and C–N bonds exclusively at the γ-position.

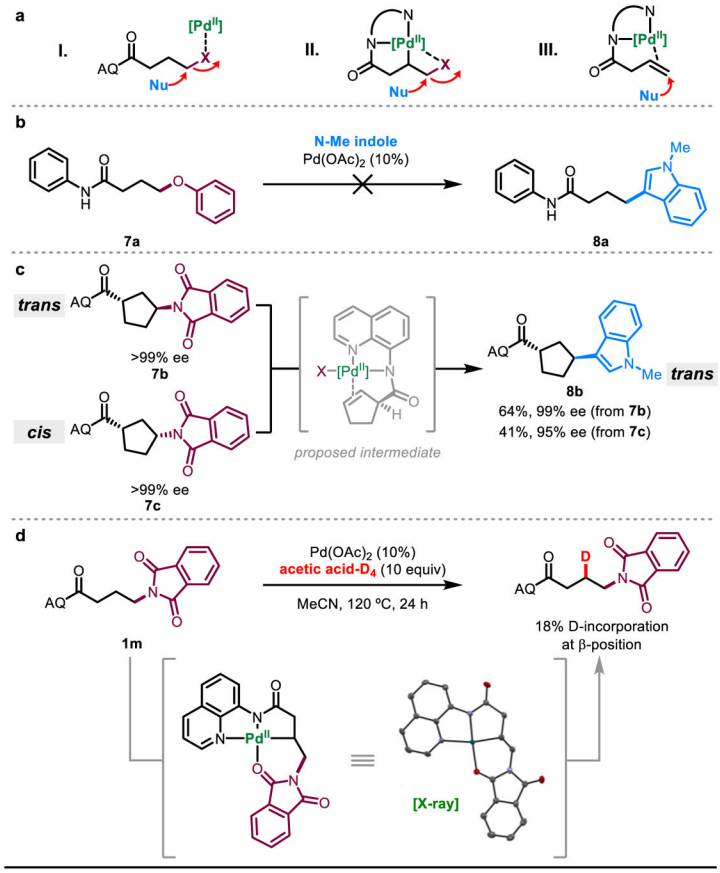

Figure 6. Mechanistic experiments

a, Three proposed mechanistic scenarios, **b**, Directing group control. **c**, Testing possibilities of *anti* and *syn* β-elimination. **d**, Demonstrating feasibility of C–H activation step.