Catalytic Benzolactamization through Isonitrile Insertion Enabled 1,4-Palladium Shift

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Isoindolinone is a class of versatile *N*-heterocycles embedded in many bioactive molecules and natural products. The invention of new methods to synthesize these heterocyclic compounds with easily accessible chemicals is always attractive. Herein, a conceptually novel approach to access this bicyclic system via isonitrile insertion enabled 1,4-pallaidum shift is described. Compared with conventional isonitrile participated C-H bond activation, both carbon and nitrogen atoms in isonitrile moiety are engaged in new bond formation. Notably, two different isoindolinones can be obtained selectively by switching the bases employed. Mechanistic studies including DFT calculations have shed lights on the reaction mechanism and

explained the selectivity led to different products. Moreover, the power of current benzolactamization is further demonstrated by providing concise routes to key intermediates of indoprofen, indobufen, aristolactams, lennoxamine and falipamil.

Introduction

Because of the high economy and overall efficiency, reactions involving transition metal-catalyzed direct C-H bond functionalization have become important achievements in modern organic synthesis.[1-4] Among them, transformation via "through space" 1,4-metal shift represents an extraordinary reaction mode to achieve selective C-H bond activation.[6-7] Seminal works done by Larock and others demonstrated that a palladium(II) intermediate obtained through oxidative addition might migrate.[8-14] Although the C-H bond activation can proceed in high site-selectivity, one major drawback is that the preparation of a multifunctionalized reactant could be non-trivial (Fig. 1a). An ideal solution is to develop an intermolecular reaction of readily available reactants to build the requisite intermediate that suitable for migration.[15] This conceptually novel approach has proved to be highly useful to prepare value-added chemicals from feedstock chemicals. For example, reaction of aryl haides with alkynes could give 9-alkylidene-9H-fluorenes,[16] where palladium migration took place after the insertion of alkyne (Fig. 1b). We recently described methods for the synthesis of isocoumarins, medium cyclic lactones and lactams based on 1,4-palladium shift enabled by carbene migratory insertion (Fig. 1c).[17-22] In spite of these significant progress, intermolecular reactions enabled palladium migration is still in its infancy, and the reported reactions are limited in scope, mainly focusing on alkynes or diazo type substrates. Thus, further development of novel intermolecular reaction enabled palladium migration is still of great significance.

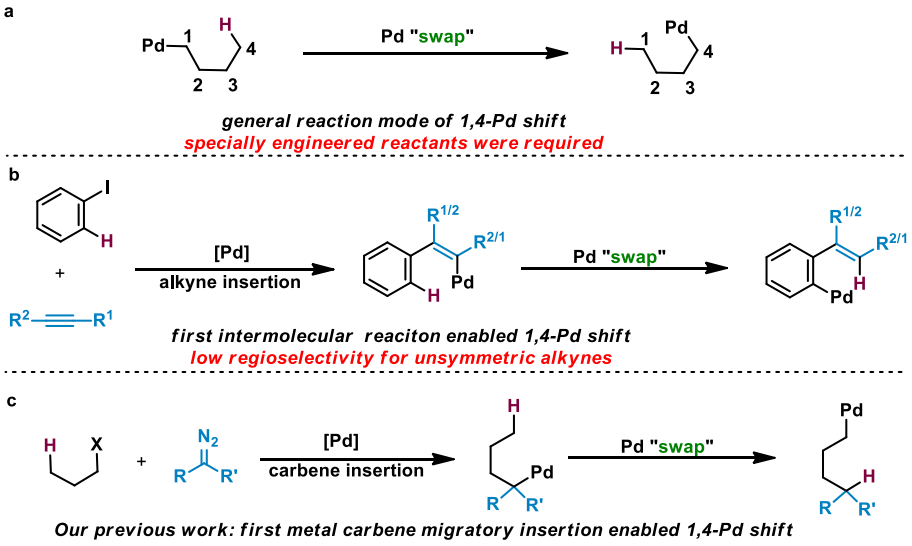


Fig. 1. C-H bond activation through 1,4-palladium migration. a. General reaction mode for 1,4-Pd shift. **b.** Alkyne insertion enabled 1,4-Pd shift. **c.** Metal carbene migratory insertion enabled 1,4-Pd shift.

Compounds bearing isoindolinone motif are ubiquitous. Many of them not only possess interesting biologoical activity, and also serve as key intermediates to prepare nature products and pharmaceutical molecules (Fig. 2a).[23-29] 3-Unsubstituted isoindolinone is structrually simple, wherein two protons sitting at the benzylic position offer ample opportunities for futher synthetic manipulations.[30-33] It is notwithstanding that the development of selective and practical approach to construct this seemingly simple heterocyclic system is not always trivial.[34-38] In view of the readily accessible characters of starting materials and step economy, direct C-H bond carbonylation of benzylic amines[39-42] and monoreduction of phthalimide analogues[43,44] have been developed, but nonnegligible limitations are still remained. For examples, the former procedures involving C-H bond activation, besides the selectivity and directing group issues, often require stoicheometric amounts of metal oxidants to cycle the metal catalysts (Fig. 2b). On the other hand, although the

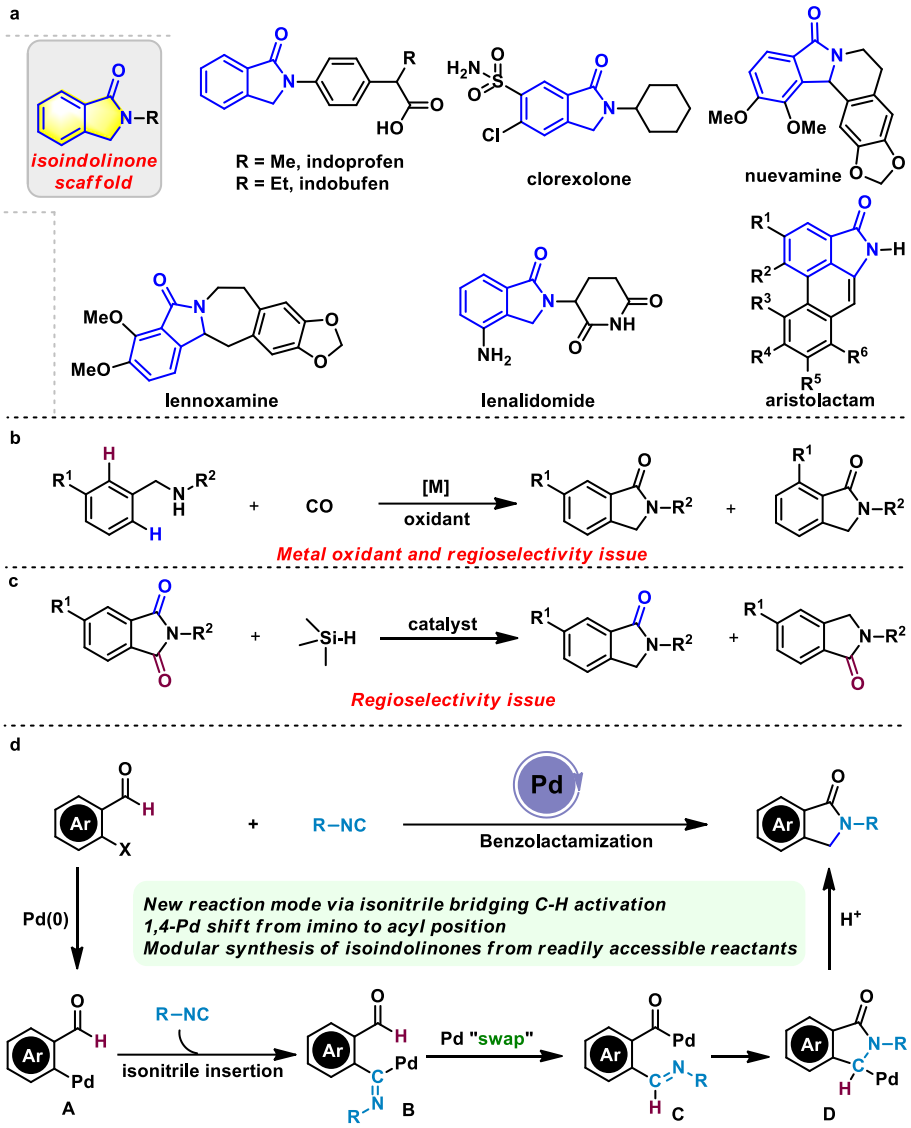


Fig. 2. Compounds containing isoindolinone scaffold and their preparation. a. Selected bio-active molecules containing isoindolinone scaffolds. **b.** Isoindolinone synthesis through carbonylation of benzylic amine derivatives. **c.** Isoindolinone synthesis through monoreduction of phthalimide analogues. **d.** Rational design on isoindolinone preparation through isonitrile insertion enabled 1,4-Pd shift.

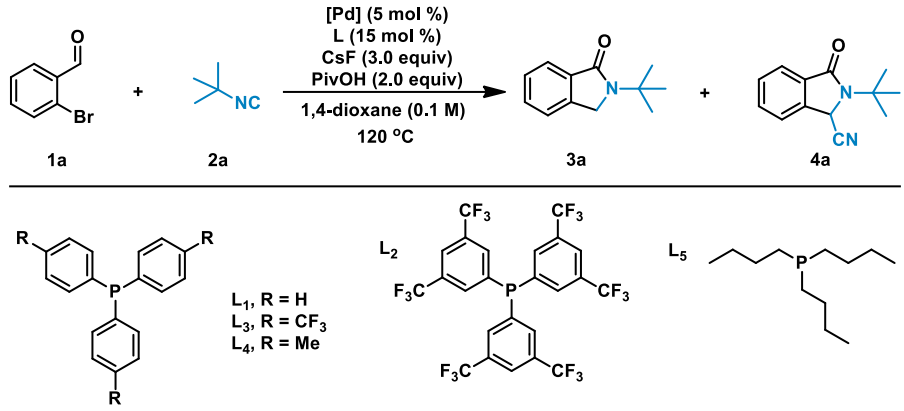
reductive approaches reported by Beller and others do not require the participation of any metal catalysts, when unsymmetric substituted phthalimides were employed as reactants, the reactions would lose the regioselective control, and result in a mixture of regio isomeric products (Fig. 2c). Ever since the discovery of Passerini and Ugi reactions,[45] isonitriles have been widely employed as ambivalent reagents to prepare

nitrogen-containing products.[46-51] Inspired by our recent achievements on carbene bridging C-H activation (CBA),[17-22] we envisioned that a palladium-catalyed formal [2+3] annulation of isonitriles with *ortho*-bromobenzaldehydes would give 3-unsubstituted isoindolinones in a rapid manner (Fig. 2d). Mechanistically, oxidative addition of a proper low valent palladium catalyst to *ortho*-(psudo)halobenzaldehyde would generate a palladium(II) intermediate **A**. Homologation of **A** via isonitrile insertion would produce intermediate **B**, which possesses an adequate geometry to undergo 1,4-palladium migration from imino carbon to tethered aldehyde carbon atom to furnish an acyl palladium(II) species **C**. Migratory insertion of the C-N double bond could build up the bicyclic framework **D**. Protodepalladation of **D** could eventually give expected 3-unsubstituted isoindolinones. To the best of our knowledge, an isonitrile insertion enabled 1,4-palladium shift has never been reported. Moreover, despite isonitrile has been entensively employed in C-H bond functionalization reactions,[49] the nitrogen atom in isonitrile moiety has rarely been involved in new C-N bond formation.[52] To this end, the successul execution of this assumption would not only unveil a modular approach to prepare isoindolinones, but also pave a conceptually new way for C-H bond functionalization.

Results

Reaction development. In accordance with abovementioned assumption, our study commenced with palladium-catalyzed reaction of *o*-bromobenzaldehyde **1a** with isonitrile **2a**. Pleasingly, after extensive evaluation of the reaction parameters, we found that isoindolinones **3a** and **4a** were produced in 80% and 12% NMR yields, (Table 1, entry 1). The formation of **4a** indicates a dual function of **2a**, which not only serves as a two-atom coupling partner for the ring formation and also as cyano source

Table 1. Evaluation of reaction conditions.



entry[a]	[Pd]	L	**3a** (%)	**4a** (%)
1	$Pd(OAc)_2$	-	80(77)	12
2	$[Pd_2(dba)_3]•CHCl_3$	-	78(73)	15
3	$[Pd_2(dba)_3]•CHCl_3$	L_1	77(71)	13
4	$[Pd_2(dba)_3]•CHCl_3$	L_2	71	11
5	$[Pd_2(dba)_3]•CHCl_3$	L_3	73	16
6	$[Pd_2(dba)_3]•CHCl_3$	L_4	77	14
7	$[Pd_2(dba)_3]•CHCl_3$	L_5	70	16
8	$PdCl_2$	-	55	6
9[b]	$Pd(OAc)_2$	-	45	-
10[c]	$[Pd_2(dba)_3]•CHCl_3$	-	20	64
11[c]	$[Pd_2(dba)_3]•CHCl_3$	L_1	31	57
12[c,d]	$[Pd_2(dba)_3]•CHCl_3$	L_1	11	66
13[c,d,e]	$[Pd_2(dba)_3]•CHCl_3$	L_1	4	73(70)
14[f]	$Pd(OAc)_2$	-	75	12

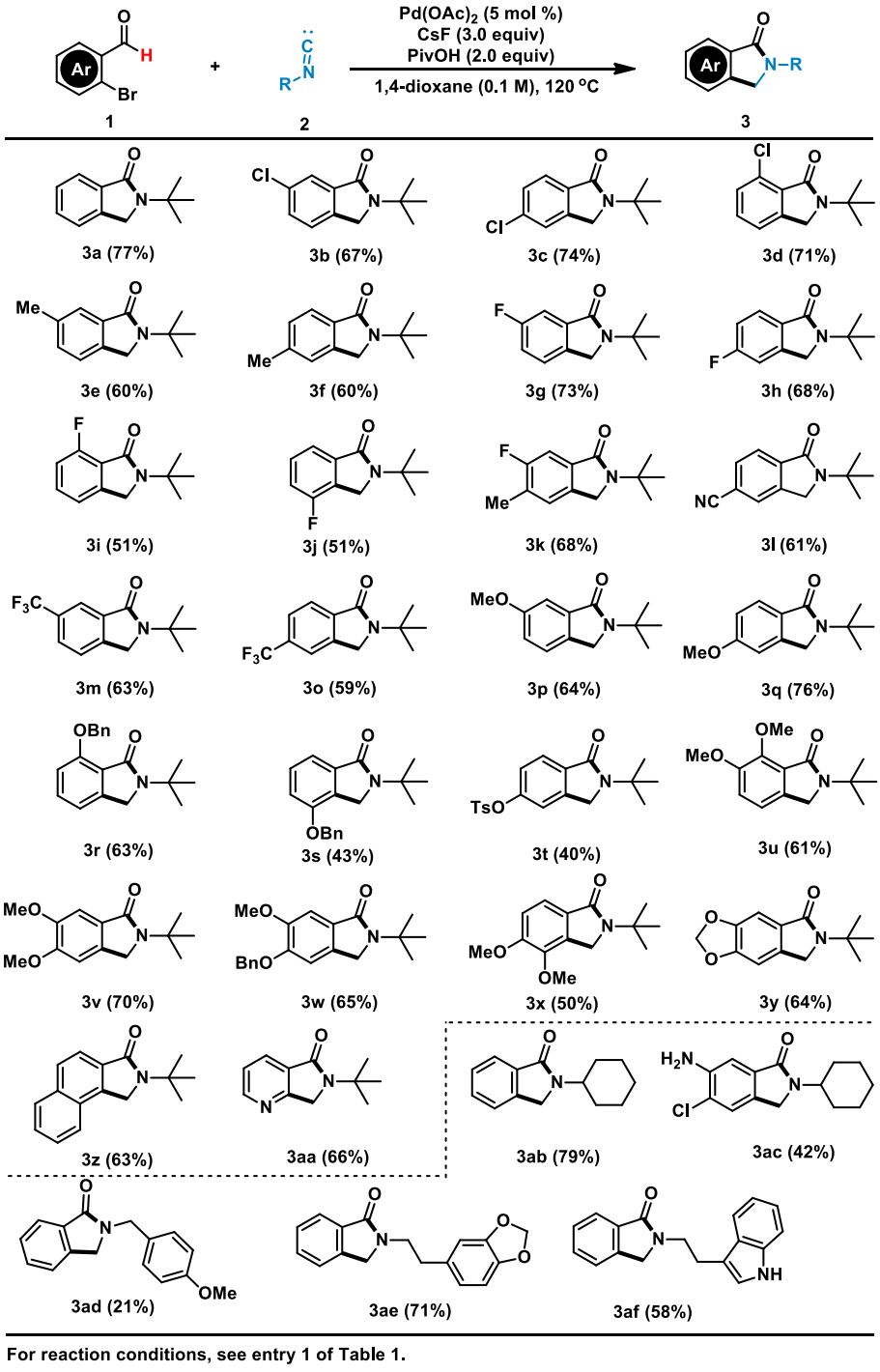
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), [Pd] (5 mol %), L_1 (15 mol %), CsF (0.6 mmol), PivOH (0.4 mmol), solvent (2.0 mL), stirring under an argon atmosphere at 120 °C, and yields were determined by ^1H NMR using 4-(N,N-dimethyl)benzaldehyde as internal standard. Numbers in parentheses are referred to isolated yields. [b]$PhCO_2H$ (0.4 mmol) was added instead of PivOH. [c]Cs_2CO_3 (0.4 mmol) was added instead of CsF. [d]The reaction was run in EA (CH_3CO_2Et, 2.0 mL). [e]The reaction was carried out at 130 °C. [f]CsOPiv (0.6 mmol) was employed.

for additional cyanation. The structure of **4a** was unambiguously confirmed by the X-ray crystallographic analysis. Similar reaction outcomes were observed when $[Pd_2(dba)_3]•CHCl_3$ was employed as the palladium source (Table 1, entry 2). Addition of external phosphine ligand led to no positive effects on enhancement of the

chemoselectivity (Table 1, entries 3-7). Replacement of $Pd(OAc)_2$ with $PdCl_2$ resulted in lower yields of **3a** and **4a**, probably because of the lower solubility of the palladium salt (Table 1, entry 8). Interestingly, when Cs_2CO_3 was used as base instead of CsF, the chemoselectivity was switched, favoring the formation of cyano substituted isoindolinone **4a**, with 64% NMR yield (Table 1, entry 10). By adding Ph_3P as ligand and switching the reaction media to ethyl acetate (EA), the yield of **4a** could be increased to 66% (Table 1, entries 11 and 12). Elevating the reaction temperature to 130 ^oC further increased the selectivity, giving **4a** in 70% isolated yield (Table 1, entry 13). Additional control experiment revealed that **3a** could be obtained 75% NMR yield when CsOPiv was employed as base (Table 1, entry 14).

Substrate scope. Having established optimal conditions for the synthesis isoindolinone derivatives, we first explored the generality and limitation for the synthesis of **3** by using $Pd(OAc)_2$ as catalyst, CsF as base (Table 2). In general, with respect to aldehydes **1**, substituents at the *ortho*-, *meta*-, and *para*-positions of the phenyl ring were all tolerated, regardless of their electronic nature. Aldehydes bearing functional groups like chloride, nitrile and tosylate substituents could react with isonitrile **2a**, to give the corresponding isoindolineones (**3b**-**3d**, **3l** and **3t**) in moderate to high yields. The tolerance of multiple donating groups (**3u**-**3y**) has offered alternative useful means to prepare intriguing target molecules (*vide infra*). Aldehydes containing napthalenyl and pyridinyl rings could participate in current isonitrile bridging C-H activation as well, and gave corresponding isoindolinones **3z** and **3aa** in 63% and 66% isolated yields, respectively.

Table 2. Substrate scope for 3-unsubstituted isoindolinone **3**.

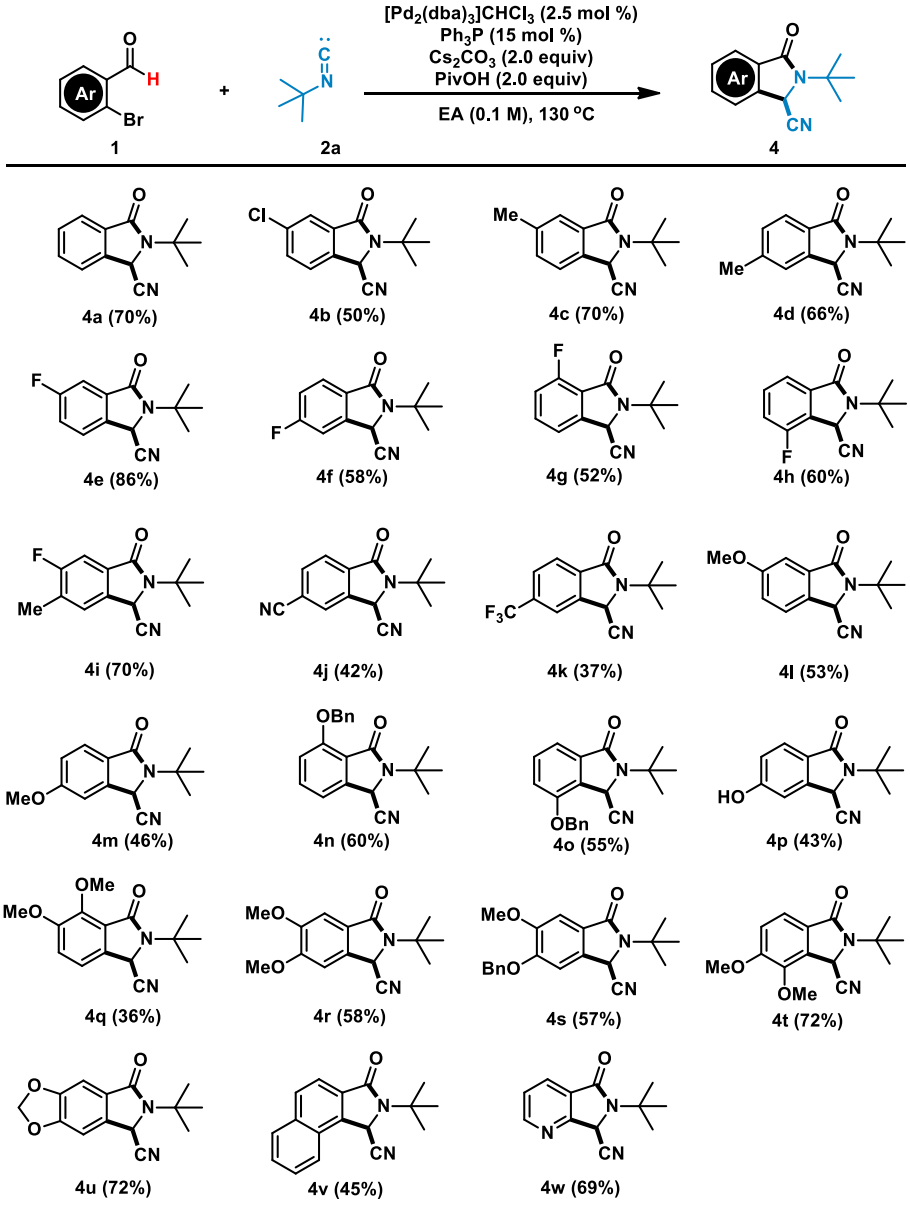


For reaction conditions, see entry 1 of Table 1.

Besides **2a**, other isonitriles derived from cyclohexylamine, benzylamine, 2-(1,3-benzodioxol-5-yl)ethanamine and tryptamine were all viable substrates for current isonitrile bridging C-H activation, and gave corresponding isoindolinones **3ab** to **3af** in 21-79% isolated yields. The tolerance of free amine group is noteworthy, the

product **3ac** obtained could be considered as an analogue of sulfonamide diuretic clorexolone.

Table 3. Substrate scope for 3-cyano-substituted isoindolinone **4**.



For reaction conditions, see entry 13 of Table 1.

Subsequently, the scope for the benzolactamization and cyanation leading to the formation of **4** was briefly examined. As summarized in Table 3, a wide range of *ortho*-bromo arylaldehydes with electron-donating and electron-withdrawing groups, such as Cl, Me, CN, F and CF_3, regardless of the position on the phenyl ring, could

readily react with isonitrile **2a** to afford the desired cyano substituted isoindolinone products **4b**-**4k** in 37%-86% yields. Furthermore, aldehydes with MeO-, BnO- were viable substrates for current isonitrile bridging C-H activation reactions, giving corresponding isolindolinones **4l**-**4o** and **4q**-**4s** in 36-60% isolated yields. 6-Bromopiperonal reacted well with **2a**, and the corresponding functionalized isolindolinone **4t** was obtained in 72% yield upon isolation after column chromatography. *Ortho*-bromobenzaldehyde bearing OTs group was compatible with this bridging C-H activation as well, the corresponding formal cycloadduct **4p** with in situ removal of Ts group was isolated in 43% yield. An aldehyde bearing a naphthyl moeity was also suitable for this cascade reaction, giving product **4v** in moderate yield. It is worthwhile to mention that aldehyde bearing a pyridinyl ring could also react with **2a** smoothly, affording fused *N*-heterocyclic product **4w** in 69% yield.

Mechanistic investigation. To gain better understanding of the mechanisms and chemoselectivities of the reactions, we carried out experiments and DFT calculations to study the reactions of **1a** and **2a** (entries 3 and 13 in Table 1). The computational protocol is detailed in Supplementary Information.

Experimentally, **3a** and **4a** could not interconvert to each other under standard conditions. To identify plausible reactive intermediates, we performed the stoichiometric reactions of palladium(II) complex **5** with **2a**. **3a** and **4a** were obtained in 53% and 70% isolated yields, respectively (Fig. 3a). The experimental results indicate that the reactions involve oxidative addition to access **5**. In addition, we carried out the reactions at room temperature (Fig. 3b). Although attempts to isolate palladium complexes were unsuccessful, two species were detected with high-resolution mass spectrometry (HRMS-(ESIpos) (*m/z*): $[M+H]^+$ 981.1824 and 271.1803). When the reaction mixture was further heated to 130 ^oC, **4a** could be

isolated in 56% yield. When the reaction mixture was treated with toluene-4-sulfonic acid, amide **8** was obtained in 49% yield upon isolation.

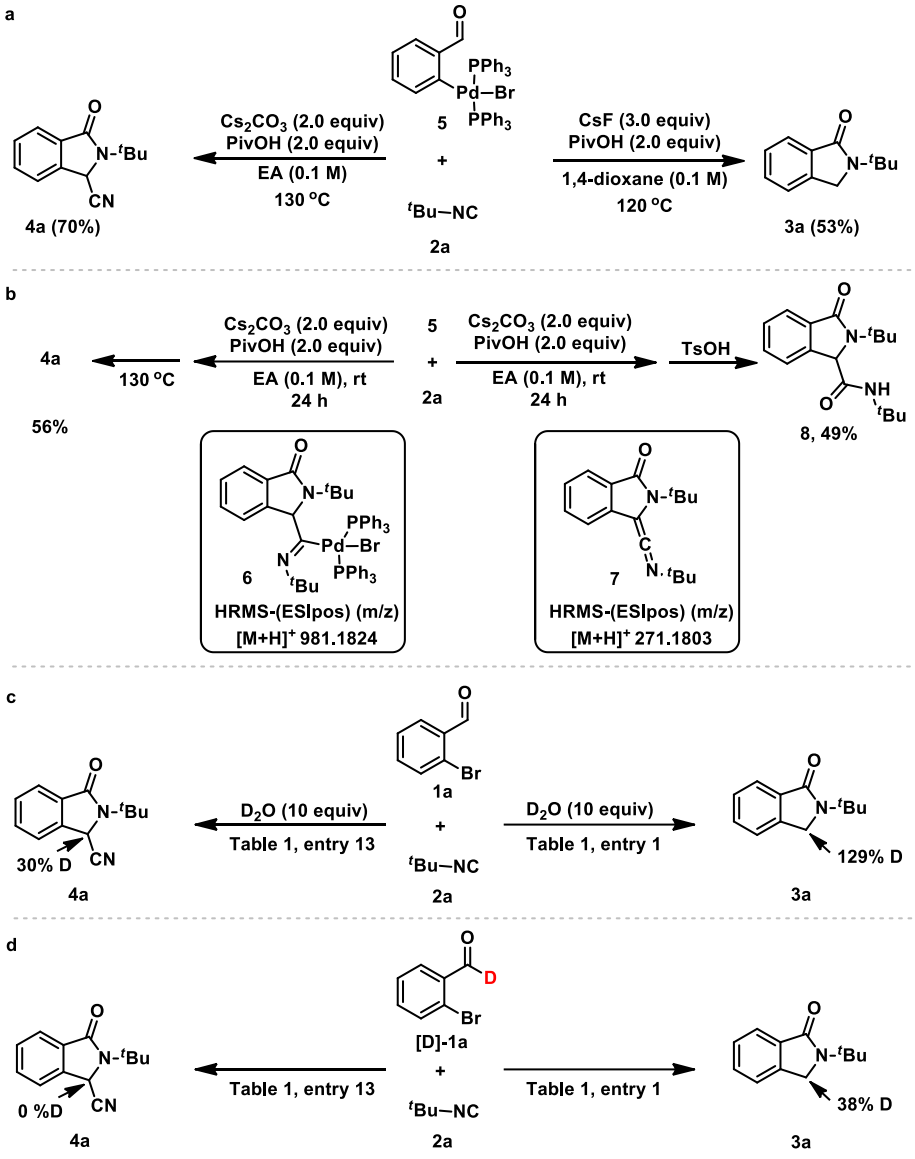


Fig. 3. Mechanistic studies. a. Reaction of palladium complex **5** with **2a** under standard conditions. **b.** Attempt to identify reactive intermediates by the reaction of palladium complex **5** with **2a** at room temperature. **c.** Reaction of **1a** with **2a** in presence of 10 equiv. of D_2O under standard conditions. **d.** Reaction of **[D]-1a** with **2a** under standard conditions.

These experimental results suggest that the reactions might pass through a palladium complex **6** and ketene imine **7**. To probe the process for aldehyde C-H bond activation, several deuterium labeling experiments were carried out. As depicted in Fig. 3c, under

otherwise identical conditions, aldehyde **1a** reacted with **2a** in the presence of 10 equiv. of D_2O, **3a** (129% D) and **4a** (30% D) were obtained in significant amount of deuterium atom incorporation at the benzylic position. The reaction of **[D]-1a** with **2a** under standard conditions gave **4a** without any deuterium incorporation, while 38% deuterium incorporation was observed in **3a** under similar conditions (Fig. 3d).

DFT calculations. Aided by these experimental results, we further elaborated the mechanisms with DFT calculations. Fig. 4 shows our computed energy profile for the reaction of **1a** and **2a** with Cs_2CO_3 (modeled by CO_3^{2-}) and PivOH as the additives. Beginning with $Pd(PPh_3)_3$ generated from the palladium source through ligand exchange, **1a** undergoes oxidative addition via **TS1** to form **IM2**. One of the PPh_3 ligands in **IM2** can be replaced with **2a** to give **IM3** or **IM3'**. Although **IM3** is less stable than **IM3'**, the isonitrile ligand in **IM3** can undergo migratory insertion via **TS2**, moving the reaction forward to reach **IM4**. Substitution of a PPh_3 ligand with **2a** in **IM4** gives **IM5**. Relative to **IM4**, the substitution is uphill slightly, but the resultant **IM5** can be stabilized by CO_3^{2-}, giving **IM6**. The aldehyde C-H bond is then activated by intramolecular deprotonation with base via **TS3**, which simultaneously enables palladation to form palladacycle **IM7**. Compared to the C-H bond activation via deprotonation with **TS3**, the activation mode via oxidative addition of aldehyde C-H bond to **IM5** with **TS3'** could be excluded. Protodepalladation of **IM7** with PivOH via **TS4** gives **IM8**, which allows intramolecular C=N bond migratory insertion via **TS5**, giving **IM9**. The much higher **TS4**' than **TS4** excludes the direct C-N bond formation via **TS4'**. After the ligation of **2a** to **IM9** giving **IM10**, two pathways are possible to continue the reaction, including migratory insertion of ^{t}BuNC through **TS6a** (Path-a) and protonation with PivOH via **TS6b** (Path-b). Note that **TS6a** and **TS6b** are the lowest transition states among those we located for these two processes,

respectively (see Figure S1 in Supplementary Information). In the following, we first show that Path-a leads to **4a**. To begin with, **IM11a** associates with CO_3^{2-} to give **IM12a**. Intermolecular deprotonation via **TS7a** converts **IM12a** to **IM13a** which can be represented by the two resonance structures **IM13a** and **IM13a'**. Considering **IM13a'**, it can undergo ligand exchange with PPh_3 to furnish **7**. Considering **IM13a**, CO_3^{2-} replaces Br^- to give **IM14a**. The substitution of Br^- with CO_3^{2-} not only drives the reaction down to **IM14a** but also enables the C-H bond cleavage of ^{t}Bu group via **TS8a** to give **IM15a**. It was confirmed that **IM12a** cannot undergo a similar C-H bond cleavage, as evidenced by much higher **TS7a'** than **TS7a**, because a methyl C-H bond is more difficult to be activated than a tertiary C-H bond. Subsequent to the C-H bond cleavage, the product **4a** can be easily generated via cleavage of the isonitrile C-N bond via **TS9a**, followed by protonation through **TS10a.**

Subsequent to the protodepalladation of **IM10** to give **3a** and a Pd(II) species **IM11b**, Fig. 4 (bottom) describes the energy profile for Path-b to recover the Pd(0) species from **IM11b**. The simultaneous substitutions of Br^- with $PivO^-$ and **2a** result in **IM12b**, followed by ^{t}BuNC migratory insertion into Pd-O bond via **TS7b** to afford **IM13b**. After releasing **2a** ligand from **IM13b**, 1,3-migration of the -C(O)-^{t}Bu acyl group in **IM14b** takes place via **TS8b**. The migration drives the reaction down to **IM15b**, which can further undergo C-O reductive elimination via **TS9b** to give **IM16b**. As a by-product, **9** could be released from **IM16b**, but it is not stable and can undergo decarboxylation from **IM16b** to **IM18b**. With PivOH as proton source, protodepalladation takes place via **TS12b**, giving amide by-product **10** and **IM20b**. Finally, reductive elimination via **TS13b**, followed by ligand exchange, recovers the Pd(0) species $Pd(PPh_3)_3$ and releases anhydride by-product PivOPiv. With similar

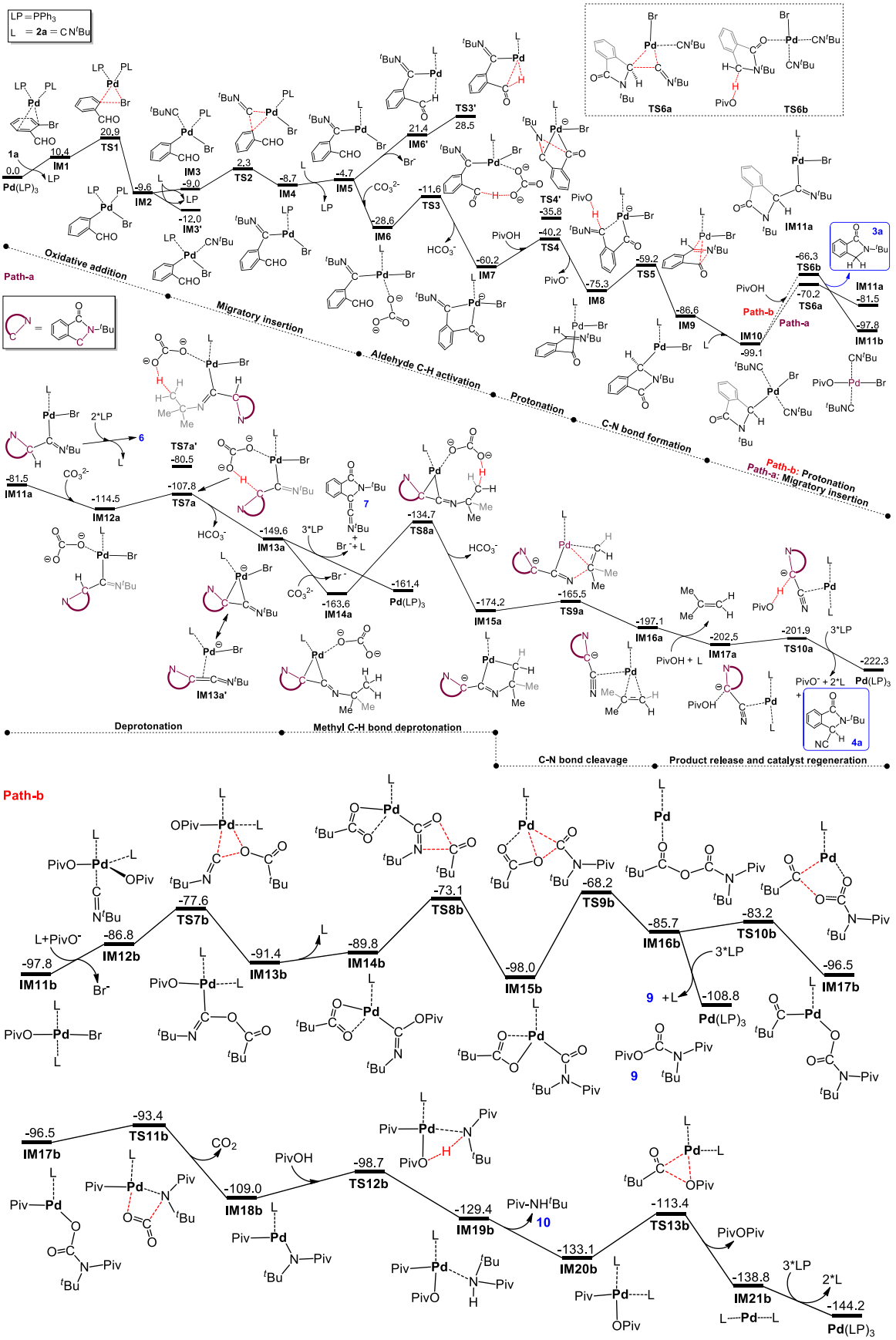


Fig. 4. Energy profiles for the reaction of 1a and 2a with Cs_2CO_3 and PivOH as additives. Values are relative free energies in kcal/mol.

mechanism, water can also serve as the proton source to convert Pd(II) species **IM18b** to Pd(0) species (see Figure S2 in Supplementary Information).

Comparing the two pathways bifurcated at **IM10**, Path-a leading to **4a** is 3.9 kcal/mol more favourable than Path-b giving **3a**. The kinetic preference is in reasonable agreement with our experimental observation of **4a** as the major product.

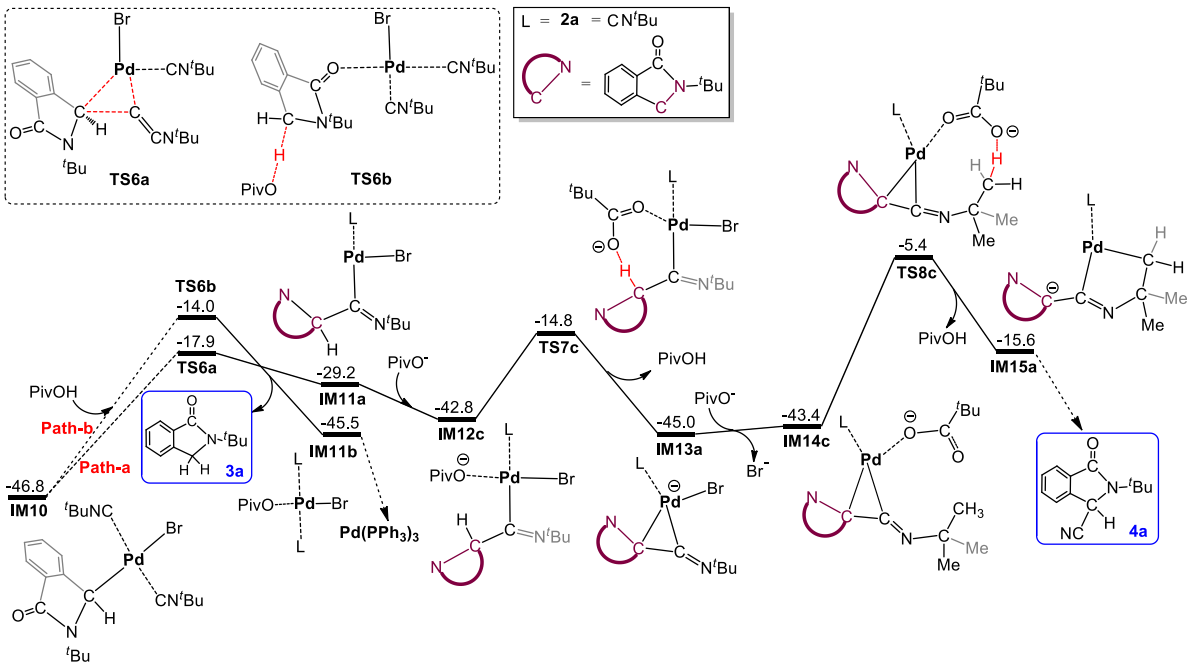


Fig. 5. Free energy profiles for IM10 to undergo migratory Insertion (Path-a) and protodepalladation (Path-b) with PivO$^-$ as base. Values are relative free energies in kcal/mol.

On the basis of the mechanism discussed above, we next understand how the switch of the additives from Cs_2CO_3/PivOH to CsF/PivOH affords **3a** as the major product. As CsF is not basic strongly enough to activate aldehyde bond, CsOPiv could promote the production of **3a** in comparable yield (Table 1, entry 14). Thus, we conceived that CsOPiv (modeled by PivO$^-$) could play the role and used it as the base to calculate the pathway. Similar to CO_3^{2-}, PivO$^-$ also promotes the reaction of **1a** and **2a** to generate **IM10** (see Figure S3 in Supporting Information). Fig. 5 describes the energy profiles for **IM10** to undergo migratory insertion (Path-a) and protodepalladation (Path-b) with PivO$^-$ as the base. Given that Path-b in Fig. 4 only involves PivO$^-$ base, the Path-

b in Fig. 5 is the same as that in Fig. 4, leading to **3a**. For Path-a, because $PivO^-$ (pKa(PivOH)=5.03) is a much weaker base than CO_3^{2-}(pKa(HCO_3^-)=10.3), it is much harder for $PivO^-$ than CO_3^{2-} to activate a methyl C-H bond of ^{t}Bu, thus **TS8c** is much higher than **TS6b**. As a result, in spite of the lower **TS6a** than **TS6b**, the reaction would prefer Path-b to afford **3a**, which is consistent with our experimental observation of **3a** as the major product.

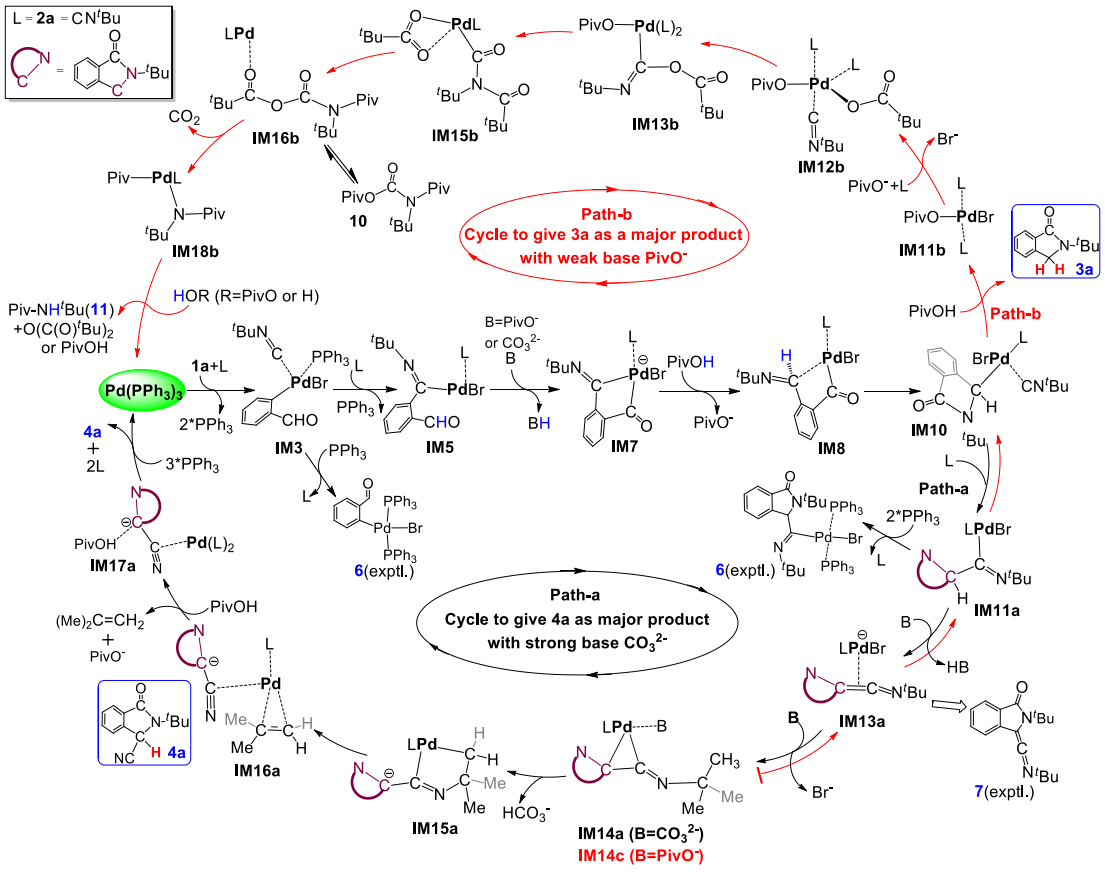


Fig. 6. Overall catalytic cycles.

On the basis the discussions above, Fig. 6 summarizes the catalytic cycles for the two reactions. Starting with $Pd(PPh_3)_3$, no matter which (CO_3^{2-} or $PivO^-$) base is presented, the reactions first generate. The events to generate **IM10** include ^{t}BuNC-bridging from **IM3** to **IM5**, 1,4-palladium migration from **IM5** to **IM8**, and C-N bond formation from **IM8** to **IM10**. The intermediate **IM10** can undergo either isonitrile

migratory insertion or protonation with PivOH. With a strong base CO_3^{2-}, the reaction goes through the Path-a catalytic cycle in which a methyl C-H bond and C-N bond in isonitrile are cleaved, finally affording **4a**. With a weak base $PivO^-$, because the base is not strong enough to break the methyl C-H bond in ^{t}Bu group, the reaction bounces back from **IM14c** to undergo the Path-b cycle to afford **3a**.

Given that simplified CO_3^{2-} and $PivO^-$ were used to model the elusive structures/effects of Cs_2CO_3 and CsOPiv salts, the mechanisms qualitatively agree with the experimental results from the stoichiometric reactions (Fig. 3b), observing the species **5**~**8**, which can be accessed from **IM3**, **IM11a** and **IM13a**, respectively. The release of isobutene from Path-a is precedented in the cyanation with isonitrile as cyanide source. In our study, besides **3a**, we also observed the formation of *N*-(*tert*-butyl)pivalamide **10** (60% GC yield).

The mechanisms also explain the deuterium-labeling experiments. According to the mechanism, the benzylic hydrogen atoms (colored in red) in **3a** and **4a** originate from proton source PivOH (see the processes, **IM7→IM8**, **IM10→IM11b**, and **IM16a**→$Pd(PPh_3)_3$). In the experiment of Fig. 3c, because PivOH can exchange with D_2O to form PivOD, both **3a** and **4a** exhibit H/D scrambling. The aldehyde C-D bond is activated by CO_3^{2-} or $PivO^-$ (see **IM5→IM7**). If the base is CO_3^{2-}, the (C-)D atom of aldehyde goes into DCO_3^- which as a proton donor is too weak to reenter the catalytic cycle. Thus, no D-incorporated **4a** could be observed. However, if the base is $PivO^-$, the activation of aldehyde C-D bond gives PivOD which can reenter the catalytic cycle to result in **3a** with H/D scrambling.

Synthetic manipulation. The synthetic utility of our method is briefly demonstrated in Fig. 7. As illustrated, the cyano group in **4a** has offered a versatile handle for

downstream transformation. For example, hydrogenolysis of **4a** could give **11** bearing primary amine functionality. Treatment of **4a** with NaOH could furnish 4H-isoquinoline-1,3-dione analogue **12** in 78% yield. The t-butyl group in **3** could be easily removed in presence of TFA. Following the reported procedures, a range of bio-active molecules including indoprofen,[53] indobufen,[54] (+)-lennoxamine,[31] aristolactam BII[34,36,38] and falipamil[42] could be facilely prepared.

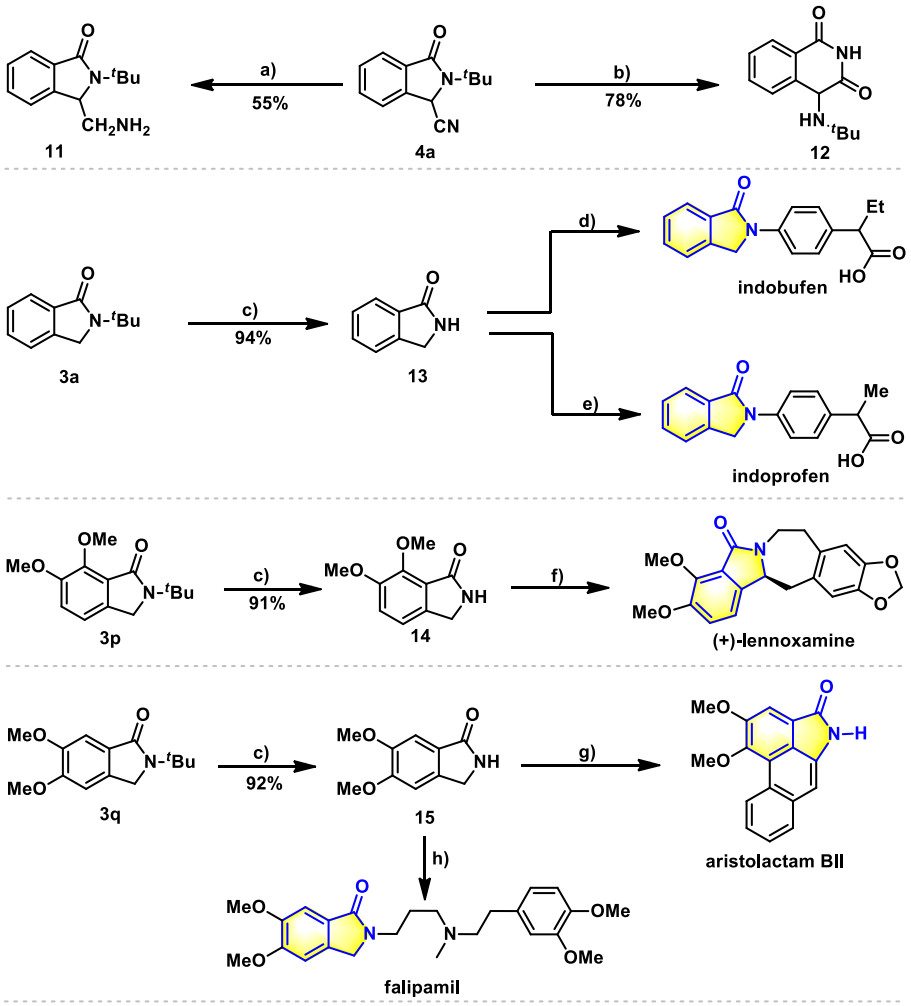


Fig. 4. Synthetic manipulations. Reagents and conditions: Reaction conditions: a) **4a**, Pd/C (10%w/w), H_2 balloon, MeOH, rt, 24 h. b) NaOH, H_2O, 90 °C, 24 h. c) TFA, 85 °C. d) ref 54. e) ref 53. f) ref 31. g) ref 34. h) ref 42.

Discussion

In conclusion, we have developed a palladium-catalyzed isonitrile insertion enabled 1,4-Pd shift, which provides a divergent approach to access valuable isoindolinone derivatives. Both carbon and nitrogen atoms in isonitrile moiety were engaged in new bonds formation and *N*-heterocyclic ring construction. Mechanistic studies including stoichiometric experiments, deuterium labeling reactions and DFT calculations have shed light on possible reaction intermediates, energy profile and explained how bases controlled the chemoselectivity. We believe that such a reaction mode on isonitrile bridging C-H activation can serve as a new approach to prepare valuable *N*-heterocyclic compounds.

Methods

General procedure for the synthesis of 3. To an oven-dried reaction tube containing a stirring bar was added $Pd(OAc)_2$ (5 mol%), CsF (3.0 equiv), PivOH (2.0 equiv) and aryl bromide (if solid). The tube was evacuated and refilled with dry argon for three times. 1,4-dioxane (0.1 M), aryl bromide (if liquid) (0.2 mmol) and isonitrile (2.5 equiv) were added via syringe. The mixture was stirred at 120 °C. When reaction was completed (monitored by thin-layer-chromatography), the crude mixture was cooled room temperature and then filtered through a short pad of celite. The resulting solution was concentrated by rotary evaporation. The residual was purified by column chromatography on silica gel to give the desired product **3**.

General procedure for the synthesis of 4. To an oven-dried reaction tube containing a stirring bar was added $[Pd_2(dba)_3]$•$CHCl_3$ (5 mol%), Cs_2CO_3 (2.0 equiv), PivOH (2.0 equiv), PPh_3 (15 mol%) and aryl bromide (if solid). The tube was evacuated and refilled with dry argon for three times. Ethyl acetate (0.1 M), aryl bromide (if liquid) (0.2 mmol) and tert-butyl isocyanide (2.5 equiv) were added via syringe. The mixture

was stirred at 130 °C. When reaction was completed (monitored by thin-layer-chromatography), the crude mixture was cooled room temperature and then filtered through a short pad of celite. The resulting solution was concentrated by rotary evaporation. The residual was purified by column chromatography on silica gel to give the desired product **4.**

Data availability: The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its Supplementary Information files, or from the corresponding author upon request. X-ray structural data of compound **4a** and **8** are available free of charge from the Cambridge Crystallographic Data Centre under the deposition numbers CCDC 2061298 and 2061299. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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