C(sp³)–H Activation Hot Paper

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Palladium-Catalyzed C(sp³)–H Activation: A Facile Method for the Synthesis of 3,4-Dihydroquinolinone Derivatives**

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Abstract: *3,4-Dihydroquinolinones were synthesized by the palladium-catalyzed, oxidative-addition-initiated activation and arylation of inert C(sp³)–H bonds. $Pd(OAc)_2$ and $P(o\text{-}tol)_3$ were used as the catalyst and ligand, respectively, to improve the efficiency of the reaction. A further advantage of this reaction is that it could be performed in air. A relatively rare seven-membered palladacycle was proposed as a key intermediate of the catalytic cycle.*

In bioactive molecules, pharmaceutics, natural products, and industrial materials, C–H bonds are ubiquitous. For years, chemists have been considering the direct functionalization of C–H bonds for the synthesis of important molecules to avoid tedious and sluggish synthetic procedures.[1] In recent years, C–H bond activation reactions have experienced great developments, and among all of these progresses, palladium-catalyzed C–H bond activation has shown its great advantages.[2] However, most of the current research mainly focuses on the activation of C(sp²)–H bonds,[2e,h–j] as such transformations benefit substantially from the interactions between the catalyst and the π electrons,[2a,e] which enables catalyst–substrate binding and C(sp²)–H bond cleavage through electrophilic metalation,[3] a concerted metalation–deprotonation (CMD) process,[4] or other pathways.[5] The aforementioned methods could also be applied to some C(sp³)–H bond activation reactions. For example, several beautiful examples of the activation of benzylic C(sp³)–H bonds and allylic C(sp³)–H bonds have been described.[6] However, the activation of common C(sp³)–H bonds has remained more challenging[7] because of a lack of π electrons and high steric hindrance. Fortunately, chemists have developed another strategy as an alternative method to the direct activation of C(sp³)–H bonds that is initiated by the oxidative addition of organohalides to Pd^0 precatalysts. In fact, both intramolecular[8] and intermolecular[9] activation reactions have been reported and have thus been confirmed to be efficient processes. Notably, for intramolecular C(sp³)–H activation reactions, the formation of either four-membered[8a,c–e] or five-membered[8f–i] rings has been particularly successful, whereas the synthesis of six-membered or larger rings has still rarely been reported (Figure 1).[10] Obviously,

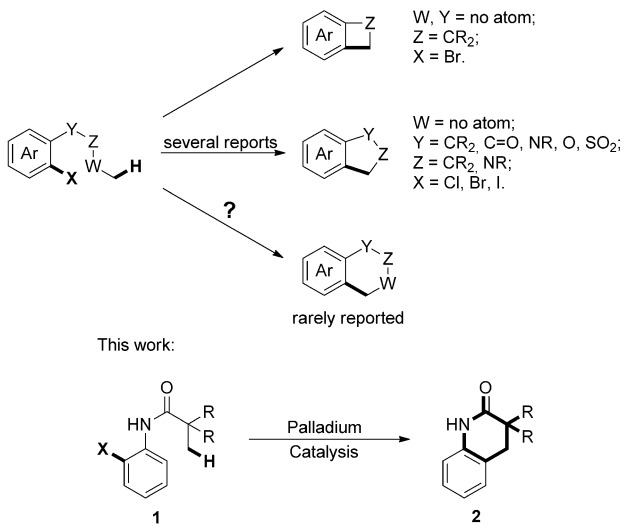

Figure 1. C(sp³)–H activation reactions that are initiated by oxidative addition.

the formation of seven-membered or even larger palladacycle intermediates during the catalytic process is more difficult than that of five- or six-membered palladacycles.[4f,10] Herein, we reported a successful method to synthesize 3,3-disubstituted 3,4-dihydroquinolinone derivatives by an oxidative-addition-initiated strategy that features seven-membered palladacycles as key intermediates through direct C(sp³)–H bond activation.

Inspired by the pioneering works from the groups of Cramer,[4f,10b] Baudoin,[8d,e] Kündig,[8j,k] Martin,[11a,b] Su[11c,d] and others,[8a,b,h] we initially chose amide **1a** as a standard substrate to test the feasibility of intramolecular C(sp³)–H bond activation to form six-membered rings. The blocked α-position of the carbonyl group, the nine chemically equal hydrogen atoms, and the *gem*-dimethyl structure of this molecule should support the desired C–H bond activation and cyclopalladation process.[12,13] Fortunately, the desired product was obtained in 30% yield (as determined by ^{1}H NMR spectroscopy) in the presence of $Pd(OAc)_2$ as the catalyst, PCy_3 as the ligand, and PivOH as an additive

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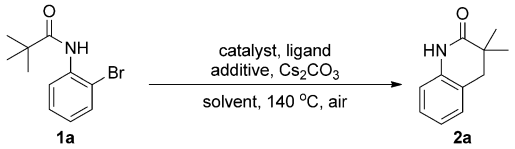
Table 1: Optimization of the intramolecular C(sp^3)–H activation of **1a**.

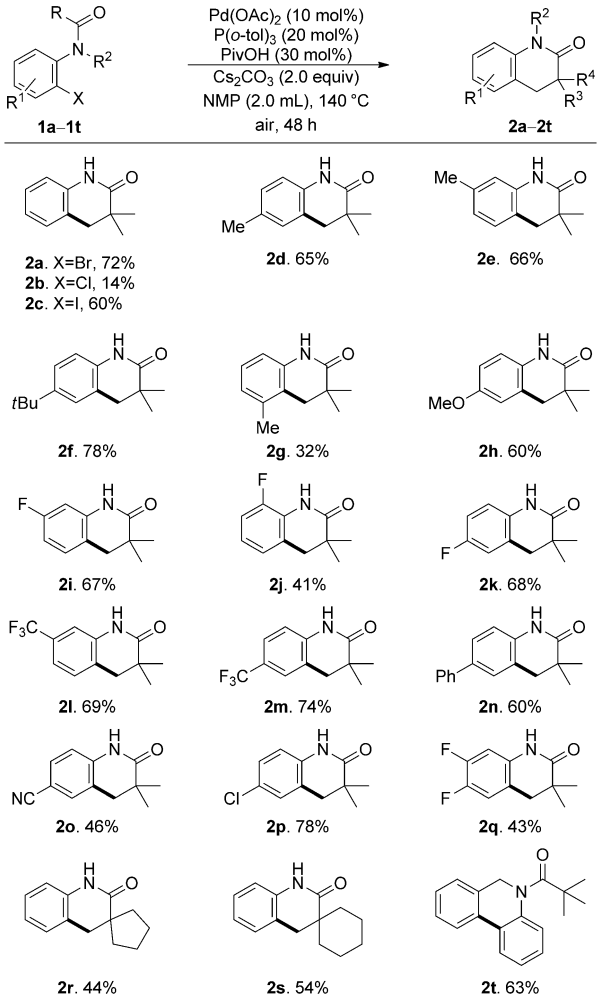


Entry[a]	Catalyst	Ligand	Additive	Solvent	Yield[b] [%]
1	$Pd(OAc)_2$	PCy_3	PivOH	DMF	30
2	$Pd(OAc)_2$	$PtBu_3{\cdot}HBF_4$	PivOH	DMF	25
3	$Pd(OAc)_2$	$P(o\text{-tol})_3$	PivOH	DMF	43
4	$Pd(OAc)_2$	XPhos	PivOH	DMF	40
5	$Pd(OAc)_2$	$P(4\text{-}FC_6H_4)_3$	PivOH	DMF	21
6	$Pd(OTFA)_2$	$P(o\text{-tol})_3$	PivOH	DMF	27
7	$Pd(dba)_2$	$P(o\text{-tol})_3$	PivOH	DMF	28
8	$Pd(OAc)_2$	$P(o\text{-tol})_3$	PivOH	mesitylene	<5
9	$Pd(OAc)_2$	$P(o\text{-tol})_3$	PivOH	toluene	<5
10	$Pd(OAc)_2$	$P(o\text{-tol})_3$	PivOH	NMP	(63)
11	$Pd(OAc)_2$	$P(o\text{-tol})_3$	PivOH	DMAc	21
12[c]	$Pd(OAc)_2$	$P(o\text{-tol})_3$	PivOH	NMP	(72)
13[c]	$Pd(OAc)_2$	$P(o\text{-tol})_3$	–	NMP	(64)
14[c]	–	$P(o\text{-tol})_3$	PivOH	NMP	–[d]

[a] General reaction conditions: Substrate **1a** (0.2 mmol) in the solvent (2.0 mL) at 140°C for 24 h in air; 10 mol% of the catalyst, 20 mol% of the ligand, 30 mol% of the additive, and 2.0 equiv of Cs_2CO_3 were used. [b] Determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. Yields of isolated products are given in parentheses. [c] 48 h. [d] not determined. Cy = cyclohexyl, DMAc = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, NMP = *N*-methyl-2-pyrrolidinone, OTFA = trifluoroacetate, Piv = pivaloyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

(Table 1, entry 1). Further explorations showed that electron-rich phosphine ligands gave similar results (entries 2–4), whereas the use of electron-deficient phosphine ligands resulted in much lower yields (entry 5). In comparison, phosphine ligands with substantial steric hindrance enhanced the efficiency, and $P(o\text{-tol})_3$ seemed to work best (entries 3 and 4).[8c] $P(o\text{-tol})_3$ might give the best results as this bulky phosphine ligand easily dissociates from the palladium center to form coordinatively unsaturated palladium centers, which are crucial for the C(sp^3)–H bond activation process. The catalytic ability of the palladium species was also examined. Among all of the common Pd^{II} and Pd^0 species, $Pd(OAc)_2$ gave the best results (entries 3, 6, and 7). Next, different solvents were screened to enhance the efficiency of this reaction. In previous reports, similar reactions were mainly carried out in two kinds of solvents, namely polar aprotic solvents[8a–c,e] or non-polar solvents with π-conjugated systems.[8f–i] Some representative solvents were chosen for our studies, and it was confirmed that polar solvents are a better choice for this transformation (entries 3, 10, and 11). Only a trace amount of the desired product could be obtained in non-polar solvents (entries 8 and 9). Among all of the tested polar solvents, NMP gave the best results, and the desired product **2a** could be isolated in 63% yield (entry 10). When the reaction time was extended to 48 hours, the desired product was obtained in 72% yield (entry 12). In the absence of the additive PivOH, which has been shown to have significant effects on many C–H activation reactions,[8f–i,14] the product was isolated in a reduced, but still reasonable yield (entry 13), which indicates that PivOH does not greatly enhance the efficiency of this transformation. As expected, when the palladium catalyst is not included in the reaction system, the desired product was not detected (entry 14). This observation revealed the crucial role of $Pd(OAc)_2$ for this reaction.

With the optimized reaction conditions in hand, the substrate scope of this reaction was studied (Scheme 1). First,



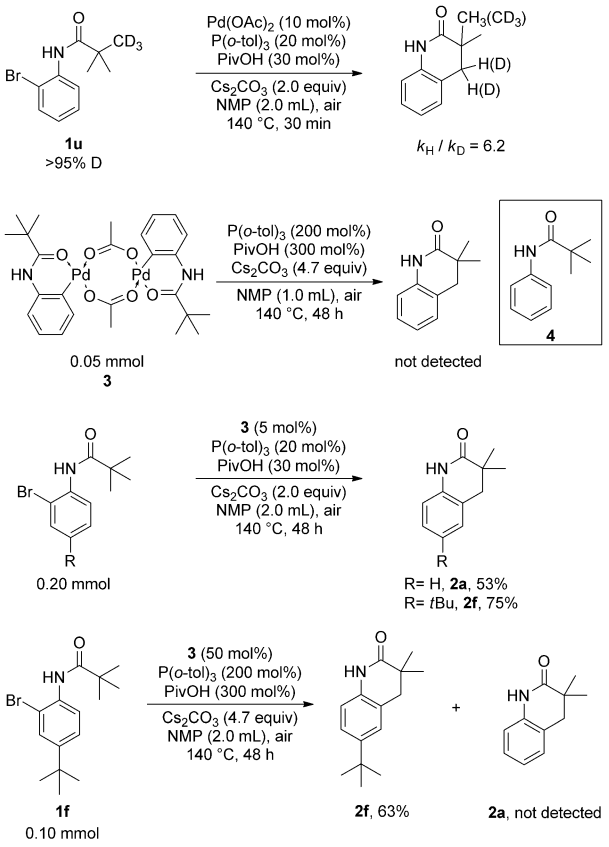
Scheme 1. Substrate scope of the intramolecular C(sp^3)–H bond activation of amides **1**. Reaction conditions: **1a–t** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), $P(o\text{-tol})_3$ (0.04 mmol), PivOH (0.06 mmol), Cs_2CO_3 (0.40 mmol) in NMP (2.0 mL), air atmosphere, 140°C, 48 h. If not otherwise noted, X = Br.

the reactivity of different C–X bonds was investigated. The 2-chloro-substituted substrate **1b** showed a low reactivity, which possibly arises from the lower reactivity of the carbon–chlorine bond. 2-Iodo-substituted compound **1c** also gave a lower yield than the 2-bromo-substituted compound **1a**. In this reaction, we observed that more protonated side product was produced. Moreover, different bromo-substituted amides were used to test whether different functional groups are tolerated under the reaction conditions. When the amide

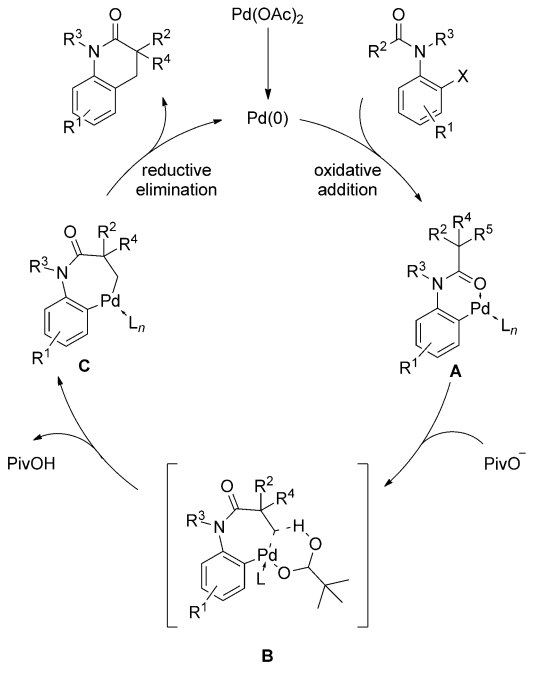
contains alkyl substituents on the 4- or 5-position, the reaction proceeded well and offered the desired products in good yields (**2d–f**). The 4-phenyl-substituted substrate **1n** and a substrate containing a methoxy group (**1h**) also gave the corresponding products in moderate yields. Fluoro, trifluoromethyl, and cyano groups were tolerated under the reaction conditions, and the corresponding products could be isolated in good yields (**2i**, **2k–m**, **2o**), indicating the compatibility of this transformation with electron-deficient substituents. However, when there are substituents at the 3- or 6-position, the cyclized products were obtained in low yields (**2g**, **2j**), which indicates that steric hindrance plays a key role in influencing the efficiency of this reaction. Notably, the 4-chloro-substituted substrate **1p** could give the 4-chloro-substituted product **2p** in good yield, which provides another opportunity for further transformations through orthogonal cross-couplings. Unfortunately, a substrate with several fluoro substituents gave a much worse result (**2q**), and the amount of protonated side product substantially increased. Furthermore, some sensitive functional groups, such as nitro, ester, and acyl groups, were not tolerated. When changing the acyl group from the pivaloyl group to a 1-methylcyclopentanecarbonyl or a 1-methylcyclohexanecarbonyl group, the corresponding products could also be obtained in a moderate yield (**2r** and **2s**), which indicates that this reaction could also be applied to the syntheses of polycyclic compounds with spiro centers. However, in the presence of a $C(sp^2)$–H bond that is located at a suitable position for intramolecular C–H activation, the desired product of $C(sp^3)$–H activation could not be observed (**2t**). It was thus confirmed that $C(sp^2)$–H bonds of aromatic rings are easier to activate than inert $C(sp^3)$–H bonds.

To gain insight into the mechanistic pathway of this transformation, we conducted mechanistic studies to determine the kinetic isotope effect (KIE) of this $C(sp^3)$–H activation process (Scheme 2).[15] The results obtained further supported our initial hypothesis, and the intramolecular KIE value of $k_H/k_D = 6.2$ indicates that the $C(sp^3)$–H bond activation step is involved in the rate-determining step of the catalytic cycle. We then tried to isolate the possible active intermediate. To our delight, complex **3**,[16] which contains a six-membered palladacycle, could be synthesized and used as the reactant in a stoichiometric reaction under the standard conditions. Unfortunately, the desired product could not be detected, and only the protonated product **4** was observed. However, when **3** was submitted to the standard conditions as the catalyst instead of $Pd(OAc)_2$, the desired product **2a** and product **2f**, which bears a *tert*-butyl group in the 4-position, were isolated in 53% and 75% yield, respectively. Notably, when **1f** and **3** were mixed in a ratio of 2:1, product **2f** was obtained in 63% yield, whereas product **2a** could not be observed.

Based on these preliminary results and the mechanisms previously proposed by other groups,[8f,g,10a] we propose a plausible mechanism (Scheme 3). First, the Pd^0 species is generated by the in situ reduction of the Pd^{II} species. Then, oxidative addition of the carbon–halogen bond to the Pd^0 species affords intermediate **A**. Subsequently, intermediate **A** is transformed into intermediate **B** with the assistance of pivalic acid.[17] Intermediate **B** undergoes concerted metalation–deprotonation (CMD) to give intermediate **C**, which features a seven-membered palladacycle. According to our



Scheme 2. Mechanistic studies for the intramolecular $C(sp^3)$–H bond activation.



Scheme 3. Plausible reaction mechanism.

prediction, this step is the key rate-determining step of the whole reaction. Finally, reductive elimination of intermediate **C** could give the desired product and regenerate the Pd^0 species.

In conclusion, we have achieved the activation of an inert $C(sp^3)$–H bond and developed a facile method for the synthesis of 3,3-disubstituted 3,4-dihydroquinolinone derivatives from easily available *ortho*-halogenated acetilide derivatives under mild conditions. A relatively rare seven-membered palladacycle was proposed as a key intermediate of the catalytic cycle. Further investigations for a clearer understanding of the reaction pathway and to explore similar activation reactions of other inert $C(sp^3)$–H bonds are under way in our laboratory.

Experimental Section

$Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $P(o\text{-tol})_3$ (12.2 mg, 0.04 mmol), Cs_2CO_3 (130.3 mg, 0.40 mmol), and amides **1a**–**t** (0.20 mmol; **1g**–**i** and **1r** were added by syringe) were added to a Schlenk tube (25 mL). Then, PivOH (6.1 mg, 0.06 mmol, ca. 6.7 μL) was added to the tube with a microinjector. NMP (2.0 mL) was added by syringe, and the reaction was performed on a parallel reactor for 48 hours in air and at 140 °C. After the reaction was finished, the reaction mixture was cooled to room temperature and filtered through a celite pad using EtOAc as the eluent. The reaction mixture was concentrated under reduced pressure, and the resulting mixture was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1) as the eluent.

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