Letter

NHC Ligand-Enabled, Palladium-Catalyzed Non-Directed C(sp3)–H Carbonylation to Access Indanone Cores

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NHC Ligand-Enabled, Palladium-Catalyzed Non-Directed C(sp³)–H Carbonylation to Access Indanone Cores

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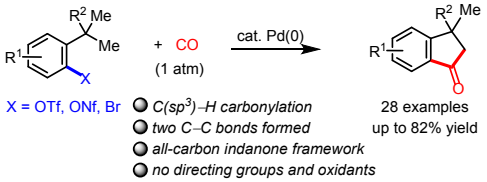
Supporting Information Placeholder

ABSTRACT: A palladium-catalyzed C(sp³)–H carbonylation of alkylated aryl triflates or bromides under 1 atm of CO has been developed, in which no directing group or oxidant were required. The essence of this reaction is the combination of appropriate NHC ligands with palladium to facilitate the formation of five-membered cyclopalladium intermediate. Mechanism studies suggest that the insertion of carbon monoxide into two five-membered cyclopalladium species generated via palladium migration might be the crucial step of this transformation. This method offers an efficient solution for expedient construction of indanone cores, which are valuable synthons and pharmacophores ubiquitously found in numerous natural products.



KEYWORDS: *palladium, C–H activation, carbonylation, indanone, NHC ligand*

Transition-metal-catalyzed C−H bond functionalization has emerged as a straightforward and efficient strategy for the synthesis of complex natural products and functional molecules, due to its step- and atom-economical manner induced by the direct transformation from ubiquitous C−H bonds.[1] As one of the most important and readily available carbonylating sources, the insertion of carbon monoxide (CO) into organic molecules via direct C−H bond functionalization has been developed as an efficient method for incorporation of carbonyl group.[2] While a variety of transition-metal-catalyzed carbonylations of C(sp²)–H bonds have been established, only few examples have been demonstrated on the C(sp³)–H carbonylation due to its high stability. Since Fujiwara's pioneering work in 1989,[3] direct carbonylation reactions of simple alkanes and toluenes have been established via Pd, Cu, or Rh-catalyzed alkyl and benzylic C−H activation (Scheme 1a).[4] However, such methods normally required high pressure of CO (10-50 atm), a large excess of substrates, and/or lack of regioselectivity, thus clearly hampering their application in organic synthesis.

To solve the perennial problems of low reactivity and poor site selectivity in non-directed C(sp³)–H carbonylation, directing group strategy has been employed. The Yu group and the Chatani group have reported Pd and Ru-catalyzed *β*-carbonylation of alkyl amides for synthesis of succinimides, respectively.[5] Inspired by these results, a series of directing groups, including 8-aminoquinoline, oxalyl amide, secondary aliphatic amine and others, have been exploited by many research groups to facilitate the carbonylation of C(sp³)–H (Scheme 1b).[6] However, these reactions require N-containing directing groups, which are also used as building blocks, fur-

Scheme 1. Transition-Metal-Catalyzed Carbonylation of C(sp³)−H Bonds

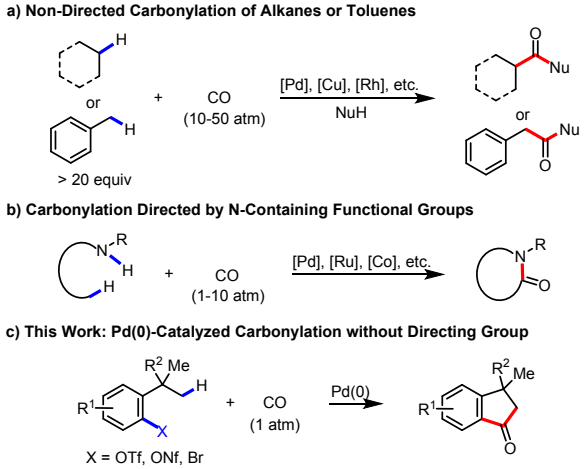


Chart 1. Samples of Natural Products Containing Indanone Cores

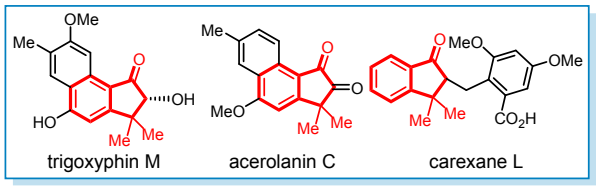
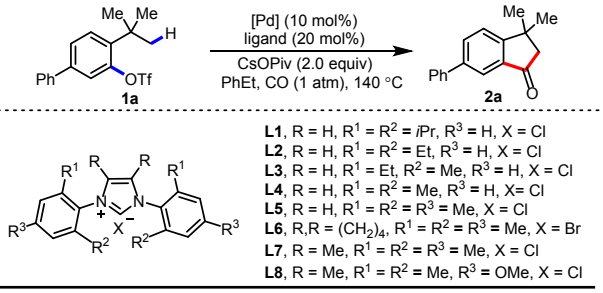


Table 1. Pd-Catalyzed C(sp^3)–H Carbonylation: Optimization of Conditions[a]



L1, R = H, R^1 = R^2 = *i*Pr, R^3 = H, X = Cl
L2, R = H, R^1 = R^2 = Et, R^3 = H, X = Cl
L3, R = H, R^1 = Et, R^2 = Me, R^3 = H, X = Cl
L4, R = H, R^1 = R^2 = Me, R^3 = H, X= Cl
L5, R = H, R^1 = R^2 = R^3 = Me, X = Cl
L6, R,R = $(CH_2)_4$, R^1 = R^2 = R^3 = Me, X = Br
L7, R = Me, R^1 = R^2 = R^3 = Me, X = Cl
L8, R = Me, R^1 = R^2 = Me, R^3 = OMe, X = Cl

Entry	[Pd]	Ligand	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	0
2	$Pd(OAc)_2$	P(*o*-tol)$_3$	0
3	$Pd(OAc)_2$	PCy_3	trace
4	$Pd(OAc)_2$	(^{t}Bu$_3$PH)BF$_4$	0
5	$Pd(OAc)_2$	**L1**	5
6	$Pd(OAc)_2$	**L2**	23
7	$Pd(OAc)_2$	**L3**	41
8	$Pd(OAc)_2$	**L4**	43
9	$Pd(OAc)_2$	**L5**	49
10	$Pd(acac)_2$	**L5**	62
11	$PdCl_2$	**L5**	52
12	$Pd(OPiv)_2$	**L5**	66
13	$Pd(TFA)_2$	**L5**	69
14	$Pd(TFA)_2$	**L6**	74
15	$Pd(TFA)_2$	**L7**	76
16	$Pd(TFA)_2$	**L8**	70
17[c]	$Pd(TFA)_2$	**L7**	82 (72)

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), [Pd] (10 mol%), ligand (20 mol%), CsOPiv (2.0 equiv), PhEt (1.5 mL), CO (1 atm), 140 °C, 24 h. [b]Yields were determined by GC using dodecane as an internal standard; number in parentheses was isolated yield. [c][Pd] (15 mol%), ligand (30 mol%), 48 h.

nishing only cyclic amides or their derivatives. Besides, the addition of extra oxidants goes against the the atom-economy of such C–H functionalizations. As one part of our continuous efforts to develop novel methods via C–H activation,[7, 6c] we envision that Pd(0)-catalyzed C–H activation, also known as a redox-neutral process with high selectivity, could handle those problems. Our strategy relies on the use of oxidative addition of a carbon-leaving group bond to Pd(0) species to induce intramolecular C(sp^3)–H activation[8-9] and the subsequent insertion of CO into the *in situ*-formed cyclopalladium intermediate.

Herein, we described a palladium-catalyzed C(sp^3)–H carbonylation of alkylated aryl triflates or halides under 1 atm of CO, in which no directing group or oxidant were required. The essence of this reaction is the combination of appropriate NHC ligands with palladium to facilitate the formation of five-membered cyclopalladium intermediate. This method offers an efficient solution for the expedient synthesis of indanone cores, which can be use as valuable synthons and pharmacophores ubiquitously found in numerous natural products (Chart 1).[10]

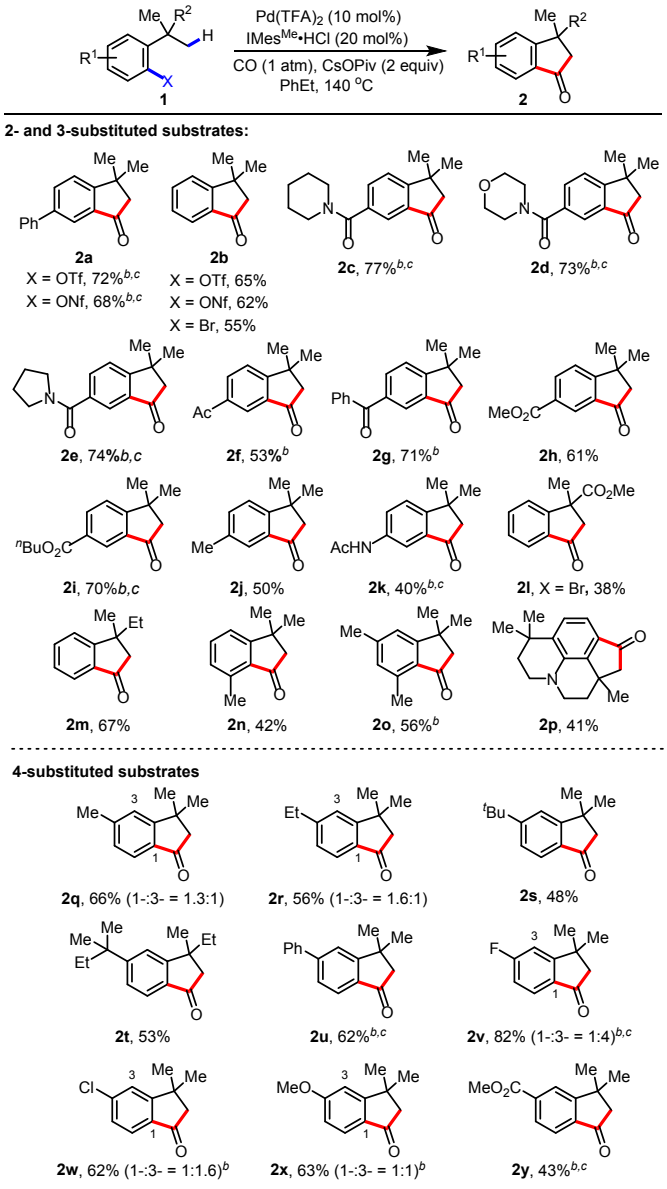
Our study commenced with *t*-butyl biphenyl triflate **1a** as the pilot substrate in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol%) in ethylbenzene under 1 atm of CO at 140 °C (Table 1). A variety of phosphine ligands, which facilitated the formation of five-membered cyclopalladium,[9] failed to promote this transformation (entries 1-4). To our delight, NHC ligand **L1** enabled the desired C(sp^3)–H carbonylation to furnish **2a** successfully, albeit with a pretty low yield (5%, entry 5). Stimulated by this result, a number of NHC ligands were synthesized and investigated in this reaction. With the decreasing of the steric hindrance of the NHC ligands (**L2**-**L4**), interestingly, the yield was gradually promoted to 43% (entries 6-8). Additionally, compared with **L4**, IMes•HCl (**L5**) was a more suitable ligand to facilitate this reaction (entry 9). Next, after careful screening of palladium sources (entries 10-13), $Pd(TFA)_2$ was indicated as the optimal choice with 69% GC yield. To further improve the yield, further modifications of NHC ligands on the imidazole ring and aryl ring were next performed (entries 14-16). To our satisfaction, the examination showed that NHC ligand with dimethyl groups on the 4,5-position of imidazole ring (IMes^{Me}•HCl, **L7**) gave the best result (76%, entry 15). However, the yields of **2a** decreased when a more electron-rich ligand (**L8**) was investigated, suggesting that a critical demand of both steric and electronic effects of the NHC ligand was required in this system (entry 16). Finally, by increasing the catalyst loading to 15 mol% and prolonging reaction time to 48 h, the isolated yield of **2a** was improved to 72% (entry 17).

With the optimized reaction conditions in hand, we next explored the scope of this C(sp^3)–H carbonylation reaction. As shown in Table 2, a large number of aryl substrates were carbonylated smoothly, furnishing the corresponding indanone products **2** in medium to good yields. Notably, aryl triflates, nonaflates as well as bromides were all compatible with this catalytic reaction (**2a**, **2b**). Impressively, aryl triflates installed with electron-withdrawing groups at the *meta*-position of aryl rings, including amides (**2c**-**2e**), ketones (**2f**, **2g**), and esters (**2h**, **2i**), showed high reactivity for this transformation. In contrast, aryl triflates with electron-donating groups gave relatively lower yields (**2j**, **2k**), which was consistent with the proposal that the cleavage of C(sp^3)–H bond underwent through the concerted metalation-deprotonation (CMD) mechanism.[11] Moreover, the subjection of aryl triflate **1m** into the reaction system furnished indanone **2m** as the sole product, indicating that the cleavage of methyl C(sp^3)–H was more favorable over the methylene C(sp^3)–H and the formation of a five-membered cyclopalladium was prefered over a six-membered ring. Yet intriguingly, 2-*t*-butyl-6-methylphenyl triflate (**1n**) was carbonylated only at the most steric hindered position of the aryl ring without any migration product (vide infra). More interestingly, julolidine derivate **1p** was also well tolerated in this reaction, affording tetracyclic indanone **2p** in an acceptable yield.

To further investigate the scope of aryl triflates in this carbonylation system, *para*-substituted aryl triflates were next examined. As expected, the desired indanones were isolated as mixtures of regioisomers for the carbonylation occurred at either 1- or 3-positions of the aryl rings, which clearly

indicated a palladium migration was involved via a ring-opening C(sp^2)–H activation of the cyclopalladium intermediate. To

Table 2. Pd-Catalyzed C(sp^3)–H Carbonylation[a]

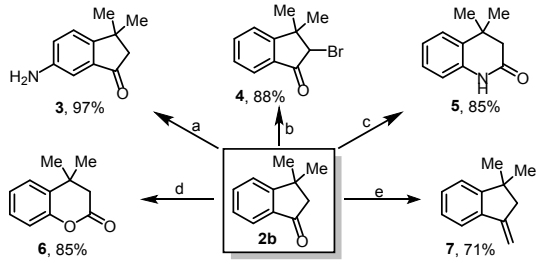


[a]Reaction Conditions: **1** (0.2 mmol, 1.0 equiv), Pd(TFA)$_2$ (10 mol%), IMes^{Me}•HCl (20 mol%), CsOPiv (2.0 equiv), PhEt (1.5 mL), CO (1 atm), 140 °C, 24 h; unless otherwise noted, X = OTf. [b]Pd(TFA)$_2$ (15 mol%), IMes^{Me}•HCl (30 mol%). [c]48 h.

our interest, as shown in Table 2, both steric and electronic effects had subtle influence on our catalytic system. For example, while indanone **2q** was afforded in 66% yield as a mixture of two regioisomers in 1.3:1 ratio, **2r** was obtained at a slightly higher ratio of 1.6:1in the reaction of **1r**. From the collective results above, they indicated that a bulkier *para*-substituent on the aryl rings might suppress the palladium migration of cyclopalladium intermediate. To verify this speculation, aryl triflates installed with large steric hindrance groups at the *para*-position were tested in this catalytic reaction, which gave the less steric hindered products as the only products (**2s** and **2t**). Meanwhile, the isolation of **2u** as the sole product showed phenyl ring was also bulky enough to control the regioselectivity. Gratifyingly, halogen substituents such as fluoro (**1v**) and chloro (**1w**) were also well tolerated, while furnishing the migration products in majority. Importantly, while aryl triflate installed with electron-donating group such as methoxy (**1x**) gave two regioisomers in a ratio of 1:1, triflate with electron-withdrawing substituent afforded indanone **2y** as as the single regioisomer. These results indicated that the electronic effect also played a key role in controlling in controlling the regioselectivity of this transformation as well.

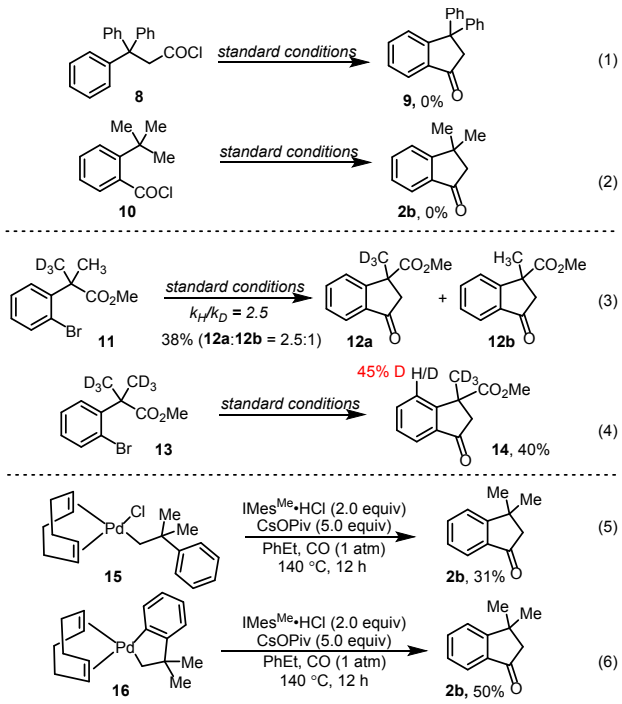
To demonstrate the synthetic potential of this novel method, further transformations of the produced indanone were next elucidated (Scheme 2). According to the literatures,[12] the nitration of **2b** with fresh prepared nitric acid followed by Pd-catalyzed hydrogenation could afford aniline **3** in 97% yield (Scheme 2a). Meanwhile, indanone **2b** could be brominated at the α-carbon of carbonyl group using N(n-Bu)$_4$Br$_3$ as a mild brominating reagent (**4**, Scheme 2b). Next, after oximation of **2b** with hydroxylamine, a Beckmann rearrangement of the corresponding ketoxime was performed to afford lactam **5** in 85% yield. Additionally, a classical Baeyer-Villiger oxidation of ketone **2b** by *m*-CPBA at room temperature could furnish lactone **6** in 85% yield. Finally, a Wittig reaction of **2b** also afford exocyclic alkene **7** in 71% yield.

Scheme 2. Synthetic Transformations of Indonane 2b

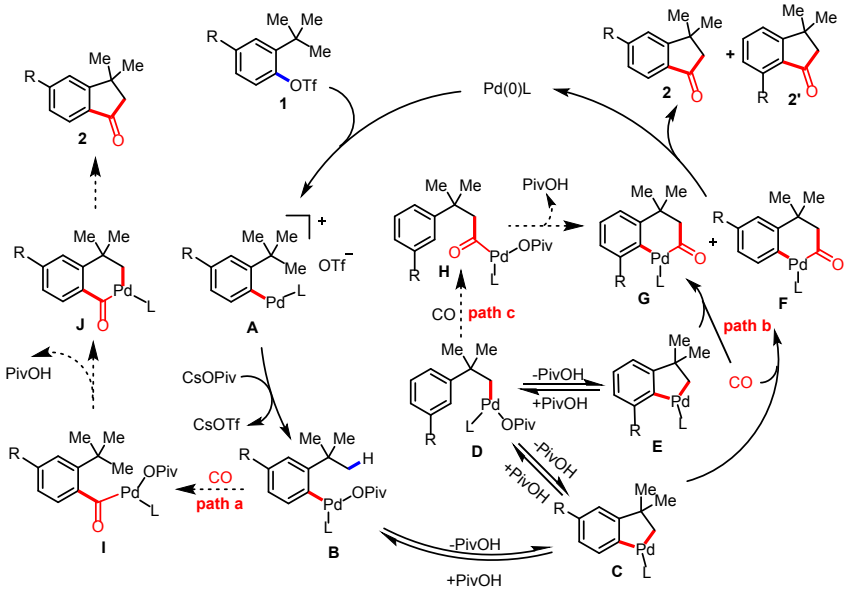


a) KNO_3, H_2SO_4, -5 °C; Pd/C, H_2, MeOH; b) (n-Bu)$_4$NBr$_3$, $CHCl_3$, 0 °C; c) NH_2OH•HCl, NaOAc, EtOH, reflux; CBr_4, PPh_3, toluene, 80 °C; d) *m*-CPBA, CH_2Cl_2, rt; e) PPh_3PCH_3Br, ^{t}BuOK, THF, rt.

Scheme 3. Mechanistic Experiments



Scheme 4. Proposed Mechanism



To gain some insights into the mechanism of this reaction, a series of control experiments were next carried out. Firstly, the subjection of acid chloride **8** or **10** into the standard conditions gave none of the desired product, which indicated that the carbonylation step might happen after the C−H activation step (Eq. 1-2, Scheme 3).[13] Next, the reaction of partially deuterated aryltriflate **11** under the optimized conditions allowed the determination of a primary intramolecular isotope effect of 2.5 (Eq. 3, Scheme 3), which indicated that the cleavage of C–H bond might be the rate-determining step. Furthermore, the *ortho*-deuterated product **14** was isolated when **13** was used as the deuterated substrate, which demonstrated a palladium migration might be involved in the catalytic cycle (Eq. 4, Scheme 3). Finally, the reaction of the putative palladium species **15** and its cyclopalladium intermediate **16** under the standard conditions could furnished the target indanone **2b** in 31% yield and 50% yield, respectively (Eq. 5-6, Scheme 3).[14] Both results suggested that the five-membered cyclopalladium was generated via C–H bond cleavage before the insertion of carbon monoxide.

On the basis of collective results and previous reports,[9] a plausible mechanism of Pd-catalyzed C(sp^3)–H activation/CO insertion was described as Scheme 4. Initially, oxidative addition of aryl triflate **1** to Pd(0) forms cationic aryl palladium complex **A**, which transformed to palladium complex **B** quickly via ligand exchange. The palladium complex **B** might be inserted by CO, followed by C(sp^3)–H bond activation to give product **2** (path a). However, the

detection of migration products (**2q**, **2r**, **2v-x,** Table 2) could exclude this assumption. On the contrary, intramolecular C(sp^3)−H activation of Pd(II) species **B** will generate cyclopalladium **C** before the insertion of CO. While cyclopalladium **C** might coexist in equilibrium with **E** via the formation of the alkyl palladium intermediate **D**, The carbonyl palladium complexes **F** and **G** were then afforded by the subsequent insertion of CO (path b).[15] The final reductive elimination from **F** and **G** furnishes the indanone products **2** and **2'**, and regenerates Pd(0) catalyst. On the other hand, the proposal described in path c that alkyl palladium intermediate **D** might be inserted by CO could also be excluded by our control experiment (eq. 1, Scheme 3).

In conclusion, we have developed a novel palladium-catalyzed C(sp^3)–H carbonylation of alkylated aryl triflates or bromides under 1 atm of CO. The combination of appropriate NHC ligands with palladium facilitates this transformation successfully. Mechanism studies suggest that the insertion of carbon monoxide into two five-membered cyclopalladium species, which are generated via palladium migration, is the crucial step of this transformation. This method offers a solution for construction of all carbon indanones, and paves an efficient way for synthesizing bioactive compounds containing such valuable synthons and pharmacophores. Further exploration of the detailed mechanism and application of this strategy to synthesize bioactive molecules are still ongoing in our laboratory.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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