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Enabling CO Insertion into *o*-Nitrostyrenes beyond Reduction for Selective Access to Indolin-2-one and Dihydroquinolin-2-one Derivatives

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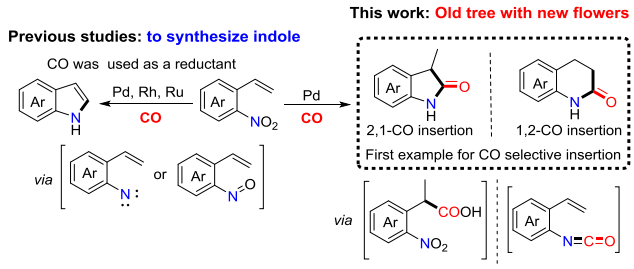
ABSTRACT: The transition metal catalyzed reductive cyclization of *o*-nitrostyrene in the presence of carbon monoxide (CO) has been developed to be a general synthetic route to indole skeleton, in which CO was used as a reductant to deoxidize nitroarene into nitrosoarene and/or nitrene with CO_2 releasing, but the selective insertion of CO into the heterocyclic product with higher atom economy has not yet been realized. Herein, the Pd-catalyzed reduction of *o*-nitrostyrene by CO and its regioselective insertion were efficiently achieved to produce synthetically useful five- and six-membered benzo-fused lactams. Detailed investigations revealed that the chemoselectivity to indole or lactam was sensitive to the nature of the counter anions of Pd^{2+} precursors, while ligands significantly decided the carbonylative regioselectivity by different reaction pathways. Using $PdCl_2/PPh_3/B(OH)_3$ (Condition A), a olefin hydrocarboxylation was primarily initiated, followed by partial reduction of NO_2 moiety and cyclization reaction to give *N*-hydroxyl indolin-2-one, which was further catalytically reduced by CO to afford the indolin-2-one as final product with up to 95% yield. When the reaction was conducted under $Pd(TFA)_2$/BINAP/TsOH·H_2O system (Condition B), the complete deoxygenation and carbonylation of NO_2 group occurred initially to yield the corresponding isocyanate, followed by internal hydrocyclization to generate 3,4-dihydroquinolin-2-one with up to 98 % yield. Importantly, the methodology could be efficiently applied in the synthesis of marketed drug Aripiprazole.

KEYWORDS: *o-nitrostyrene, carbonylation, heterocycle, selectivity, cascade reaction*

1. INTRODUCTION

A Challenge for modern organic synthesis is the creation of efficient catalytic processes that can provide the maximum molecular complexity and diversity with a minimum number of purification steps and chemical waste. Especially appealing are those reactions that involve metal catalyzed construction of heterocyclic skeletons in a selective and atom-economical fashion, and from readily available precursors. It is known that the potentially bioactive indole skeletons can be effectively constructed from widespread *o*-nitrostyrenes using excess reductant such as phosphine reagents,[1] $TiCl_3$ aqueous solution,[2] zinc dust,[3] Grignard reagent,[4] *etc*.[5-7] As a greener alternative, the catalytic synthesis of indole derivatives from *o*-nitrostyrenes was firstly discovered in 1986 by Cenini using metal carbonyl catalysts and carbon monoxide reductant.[8] Over the last three decades, many outstanding catalysts have been successfully developed by Cenini,[9] Driver,[10] Watanabe,[11] Söderberg,[12] Nishiyama[13] and other groups[14] to enhance the catalytic efficiency and broaden the substrate scope (Scheme 1), and all these improvements have enabled this transformation to be a general indole synthesis procedure. Specifically, nitrene and/or nitroso intermediates have been proposed to be involved in the Pd-catalyzed CO reductive cyclization of *o*-nitrostyrene into indole based on the deuterium-labeling experiments,[11a] and CO only served as a deoxygenation agent of nitro group,[8-14] but did not undergo further carbonylation reactions, even though conceivably, the CO can be incorporated into the resultant heterocycles without changing the reaction substrate and atmosphere.



Scheme 1. Metal-Catalyzed Reductive Cyclization of *o*-Nitrostyrenes in the Presence of CO

It can be seen from the structure of *o*-nitrostyrene that it has two possible carbonylation sites, vinyl- and NO_2-group, the former is known to undergo selective 1,2- or 2,1-CO insertion,[15] the latter can be converted to the isocyanate and amide compounds through reductive carbonylation.[16] Therefore, if the CO selective insertion of *o*-nitrostyrenes could be enabled by coupling these two parts in a proper cascade reaction sequence and under a compatible reductive condition, a novel and powerful catalytic methodology can be developed for the

regiodivergent synthesis of two important classes of carbonyl containing heterocycles (Scheme 1), which serve as core structures of numerous natural products and marketed drugs (Figure 1).[17-20] In this work, we report an unprecedented reductive cyclocarbonylation of *o*-nitrostyrenes to selectively offer indolin-2-one and 3,4-dihydroquinolin-2-one by different PdX_2/phosphine catalyst systems in the presence of a proper proton source. Systematical studies were carefully conducted to elucidate the reaction pathways and rationalize the regioselectivity.

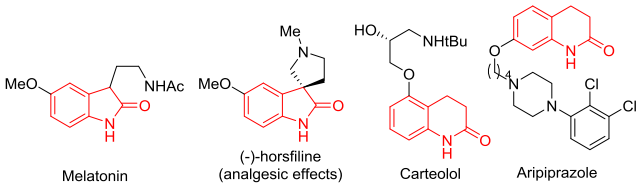
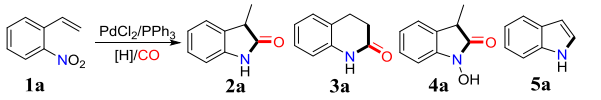
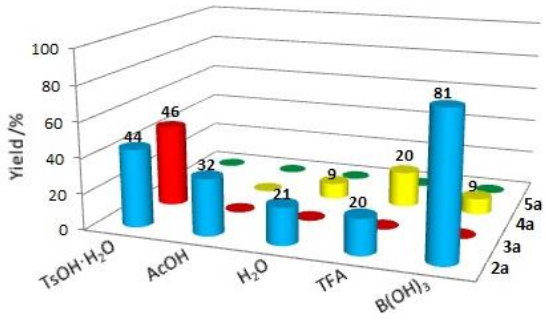


Figure 1. Selected examples bearing the skeleton of indolin-2-one and dihydroquinolin-2-one.

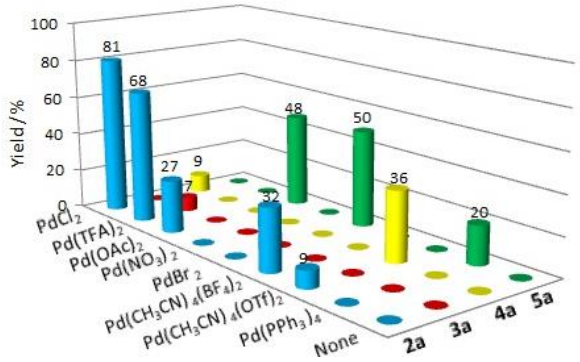
2. RESULTS AND DISCUSSION



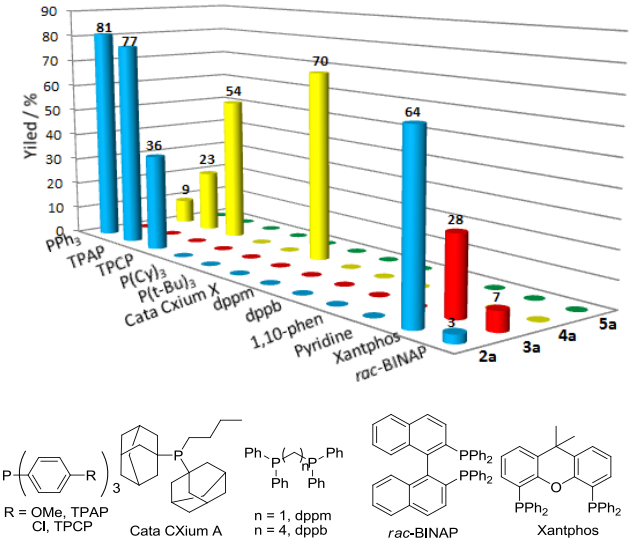


Scheme 2. Influence of Proton Sources for the Reductive Cyclocarbonylation of *o*-Nitrostyrenes.[a] [a]Reaction conditions: **1a** (0.2 mmol), $PdCl_2$ (0.01 mmol), PPh_3 (0.02 mmol), [H] (0.4 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. Isolated yield.

2.1 Reaction condition optimization. It is obvious to see that the carbonylated product, **2a** and **3a,** have two more hydrogens compared with the substrate, so the proton source was expected to be one of the enabling keys for the reaction chemoselectivity. With a simple catalyst system $PdCl_2$/PPh_3 at 80 °C, we initially choose 1-nitro-2-vinylbenzene (**1a**) as a model substrate in the presence of different proton sources to evaluate our proposed strategy (Scheme 2). Surprisingly, with $B(OH)_3$ as the proton source, 81% yield of indolin-2-one (**2a**) by CO 2,1-insertion onto the vinyl group was obtained with excellent chemoselectivity and regioselectivity, and the indole (**5a**) was even not observed, which indicated the expected carbonylation occurred perfectly beyond the well-established reductive cyclization to indole. Acetic acid (AcOH) only gave 32% **2a** yield but with high selectivity, similar and stronger trifluoroacetic acid (TFA) provided lower **2a** yield with the formation of same amount of **4a** that could be possibly further conversed to **2a**, neutral H_2O also afforded lower indolin-2-one yield. Surprisingly, no desired **2a** and only **5a** were obtained in the presence of strong reducing $SnCl_2$ with two crystal H_2O (Supporting Information, Table S1, entry 6). Another aryl bronsted acid, para-toluenesulfonic acid (TsOH·H_2O) gave a 90% yield of carbonylated products with around 50% regioselectivity of **2a** and **3a**, respectively. It could be deduced from these results that the addition of proper proton sources were the key enabling factor for CO insertion, and their acidic property had significant influence on the regio- and chemoselectivity, although there is no strict consistency between catalytic performances and the properties of the tested proton sources.



Scheme 3. Influence of Pd Precursors for the Reductive Cyclocarbonylation of *o*-Nitrostyrenes.[a] [a]Reaction conditions: **1a** (0.2 mmol), [Pd] (0.01 mmol), PPh_3 (0.02 mmol), $B(OH)_3$ (0.4 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. Isolated yield.

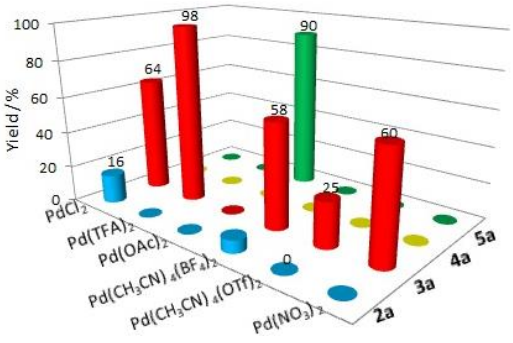


Scheme 4. Ligand Effect for the Pd-Catalyzed Reductive Cyclocarbonylation of *o*-Nitrostyrenes.[a] [a]Reaction conditions: **1a** (0.2 mmol), $PdCl_2$ (0.01 mmol), Ligand (0.02 mmol for monodentate ligand, 0.01 mmol for bidentate ligand), $B(OH)_3$ (0.4 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. Isolated yield.

It is well known that the metal precursor, particularly in terms of its ionic or neutral nature of the counter ion, is one of the most decisive factors in the carbonylative selectivity.[21] Subsequently, we chose $B(OH)_3$ as the necessary and optimized proton source (Scheme 2), simple phosphine (PPh_3) as a standard ligand to investigate the effects of palladium precursor in the reductive cyclocarbonylation synthesis of indolin-2-one (Scheme 3). It was generally found the chemoselectivity to indole or lactams for the conversion of *o*-nitrostyrene in the

presence of CO was sensitive to the nature of the counter anions of Pd^{2+} precursors, $Pd(OAc)_2$ and $PdBr_2$ favored the formation of indole, ionic $Pd(CH_3CN)_4X_2$ (X = BF_4, OTf) provided quite low five-membered 3-methyl indolin-2-one (**2a**) and *N*-hydroxyl-3-methyl indolin-2-one (**4a**), to our delight, $PdCl_2$ gave a 81% yield of **2a** and 9% yield of **4a** with nearly 100% carbonylative selectivity. $Pd(TFA)_2$ gave **2a** in a slightly lower yield of 68%, but a six-membered product 3,4-dihydroquinolin-2(1*H*)-one (**3a**) was also isolated in 7% yield! Interestingly, if you check the structural difference of substrate **1a** with the carbonylated **2a** and **3a**, it seems like they were synthesized via the reductively intramolecular cyclocarbonylation of the nitro group onto the vinyl bond, regioselectively. And other Pd precursors showed no or poor activities for this transformation. These results indicated that $PdCl_2$ was an ideal Pd catalyst precursor for enabling the CO selective insertion for the synthesis of five-membered benzo-fused lactams.

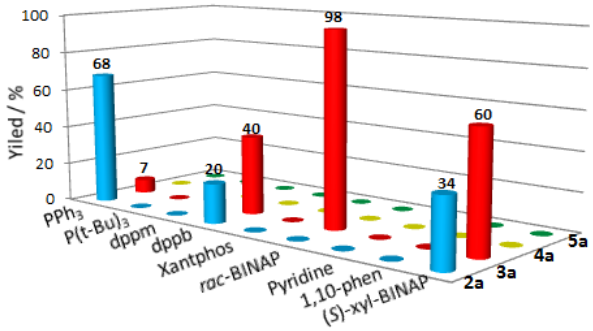
$PdCl_2$ was subsequently selected as the optimal Pd precursor to investigate the ligand effect, another crucial factor to the carbonylative activity and selectivity.[22-25] As displayed in Scheme 4 and Table S2, monodentate PPh_3 and its derivatives (TPAP and TPCP) provided similar and 90% - 100% yields of carbonylated indolin-2-ones (**2a** and **4a**) with different ratios. Bulky and electronic-rich Cata Cxium A afforded 70% yield of **4a** with 100% selectivity under the same reaction conditions. The more electron-donating trialkyl phosphine PCy_3 and $P(t\text{-}Bu)_3$ as well as bidentate alkyl phosphine ligands and the nitrogen-based ligands showed no catalytic activity for the conversion of **1a**. Xantphos, a widely used carbonylation ligand with rigid aryl skeleton, exhibited a good carbonylation activity (total 92% yield) but with moderate regioselectivity with 28% yield of **3a** as a minor product. Interestingly, **3a** could be obtained as the major product when BINAP was used as the complexation ligand, although its catalytic activity was low. These results indicated that mono- and bidentate phosphines led to different regioselectivities for the reductive cyclocarbonylation of *o*-nitrostyrene, and PPh_3, with suitable electronic and steric properties, was selected as the best ligand for the production of **2a** in view of its cost, easy availability and higher selectivity.



Scheme 5. Screen of Pd Catalysts for the Reductive Cyclocarbonylation of *o*-Nitrostyrenes to Dihydroquinolin-2-one.[a] [a]Reaction conditions: **1a** (0.2 mmol), [Pd] (0.01 mmol), *rac*-BINAP(0.01 mmol), $TsOH{\cdot}H_2O$ (0.2 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. Isolated yield.

Since $TsOH{\cdot}H_2O$ led to the production of **3a** (Scheme 2 and S6), and BINAP also preferred to afford **3a** instead of **2a** (Scheme 4), we subsequently chose $TsOH{\cdot}H_2O$ as the proton source and BINAP as the ligand to investigate the effects of the Pd precursor to search for an optimal catalytic system for the synthesis of dihydroquinolin-2-one derivatives (Scheme 5). Counter ions of the neutral and ionic Pd salts again played a crucial role in the catalyst performance. $Pd(OAc)_2$ only gave the indole product, while other tested Pd precursors all showed good selectivity to **3a** in various yields, and $Pd(TFA)_2$ afforded the best result with 98 % yield and 100 % selectivity of **3a**. With $Pd(TFA)_2$/$TsOH{\cdot}H_2O$ as the catalyst system, similarly, monodentate phosphine and nitrogen based ligands showed no or low catalytic activity/selectivity for the formation of **3a**, diphosphine favored to provide **3a** (Scheme 6), particularly, BINAP offered the best result. Thus, the combination of $Pd(TFA)_2$/*rac*-BINAP/$TsOH{\cdot}H_2O$ was the optimized catalyst system for the CO 1,2-insertion onto *o*-nitrostyrenes to produce dihydroquinolin-2-ones.

As illustrated in Figure S1 and Figure S2, even when the CO pressure was reduced to 1 atm, present reductive cyclocarbonylation of *o*-nitrostyrenes did proceed, without indole (**5a**) produced. And 12 % total yield of **2a** and **4a** were obtained under condition A, on the other hand, it was found that the increase of CO pressure was particularly good to the further reductive deoxygenation of **4a** to **2a**.

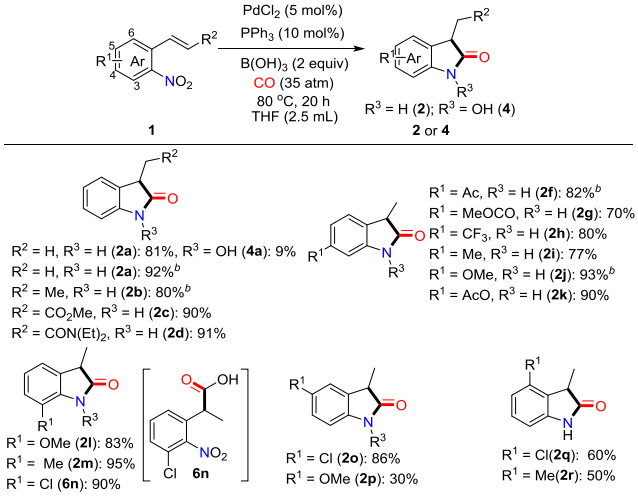


Scheme 6. Ligand Effect for the Pd-Catalyzed Reductive Cyclocarbonylation of *o*-Nitrostyrenes to Dihydroquinolin-2-one.[a] [a]Reaction conditions: **1a** (0.2 mmol), $Pd(TFA)_2$ (0.01 mmol), Ligand (0.02 mmol for monodentate ligand, 0.01 mmol for bidentate ligand), $TsOH{\cdot}H_2O$ (0.2 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. Isolated yield.

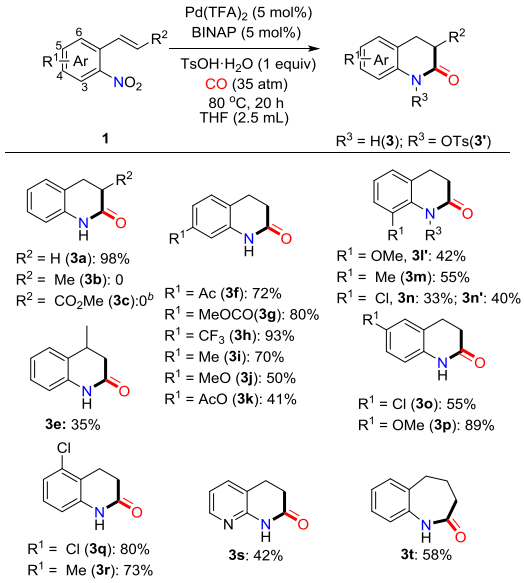
The effects of solvent and temperature were also systematically tested. In the catalytic synthesis of five-membered indolin-2-one, the polarity of solvent showed striking effects on the catalyst efficacy (Table S4), but had little influence on the regioselectivity. Among them, the moderately polar aprotic THF was the best solvent where 81% isolated yield of indolin-2-one could be achieved under standard conditions. The product yields decreased sharply at relatively lower temperatures (Table S5), while the regioselectivity remained similar. An optimal yield of 90% was obtained at 80 °C, which is considered mild as the reductive cyclizations of *o*-nitrostyrenes to indoles were typically carried out at higher temperatures (100 °C to 220 °C).[8-14] The effects of solvent (Table S9) and temperature (Table S10) for the synthesis of six-membered dihydroquinolin-2-one were similar to the indolin-2-one.

2.2 Substrate Scope. With $PdCl_2$/PPh_3/$B(OH)_3$ and $Pd(TFA)_2$/BINAP/ $TsOH{\cdot}H_2O$ as the optimal catalyst for the synthesis of indolin-2-one (**2**) (Scheme 7) and 3,4-dihydroquinolin-2-one (**3**) (Scheme 8), respectively, their substrate scopes were examined. In general, the steric hindrance and electronic effects of substituents were different between

the formations of five- and six-membered benzo-fused lactams. Specifically, increasing steric hindrance of the vinyl group had little effect on the formation of indolin-2-one under condition A (**2a-2d**), while there was almost no corresponding dihydroquinolin-2-one obtained under condition B except in the synthesis of **3c**, wherein 90% yield of the decarboxylated product (**3a**) was surprisingly isolated (**3a-3c**), but the decarbonylation was not observed at all in the production of corresponding **2c**. Electron-withdrawing R^2 substituents gave about 90% yield of desired indolin-2-one (**2c** and **2d**). Similarly, the steric-hindrance effect of 3-position was negligible (**2l** and **2m**), but it was obvious under condition B (**3l'** and **3m**). It could be seen that the electronic effect at 4-substitution was not very pronounced in the synthesis of indolin-2-one (**2f-2k**). On the other hand, electron-withdrawing groups at 4-position could increase the reactivity for the production of dihydroquinolin-2-one in 70-93% yields (**3f-3h**), and electron-donating groups decreased the reactivity of the transformation (**3j** and **3k**). Similar reactivity differences were observed at 3-position. Electron-withdrawing substituents only gave 2-(3-chloro-2-nitrophenyl)propanoic acid under condition A (**6n**) without any ring closed heterocycles observed, suggesting the hydrocarboxylation of the vinyl group may be involved as the initiative step in the synthesis of indolin-2-one, such key point will be investigated and discussed later. On the contrary, the electron-withdrawing substituents at 3-position could promote the synthesis of six-membered dihydroquinolin-2-one under condition B (**3n** and **3n'**). The steric-hindrance effect of 6-position for synthesis of indolin-2-one was very obvious (**2q** and **2r**), but substituent electronic effect at this position was not significant. Both electronic and steric-hindrance effects had little influences on the formation of 3,4-dihydroquinolin-2-one (**3q** and **3r**). Interestingly, the nitrogen-containing substrates also worked smoothly under condition B (**3s**), although nitrogen ligands were unfavorable to the reaction. The reaction even could proceed when the vinyl was replaced with an allyl group under condition B, and a seven-membered benzazepinone was obtained in 58% yield (**3t**), which is the core structure of medicines for treating cardiovascular diseases.[26]



Scheme 7. Substrate Scope for Indolin-2-one Synthesis.[a] [a]Condition A: **1a** (0.2 mmol), $PdCl_2$ (0.01 mmol), PPh_3 (0.02 mmol), $B(OH)_3$ (0.4 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. [b]40 h.



Scheme 8. Substrate Scope for 3,4-Dihydroquinolin-2-one Synthesis.[a] [a]Condition B: **1a** (0.2 mmol), $Pd(TFA)_2$ (0.01 mmol), BINAP (0.01 mmol), $TsOH{\cdot}H_2O$ (0.2 mmol), THF (2.5 mL), CO (35 atm), 80 °C, 20 h. [b]**3a** was obtained in 90% yield.

2.3 Mechanistic insights. The above differences in steric hindrance and electronic effects seem to indicate that the carbonylative regioselectivity was resulted by different reaction pathways. Initially, the kinetic profile of the model reaction of **1a** was conducted under condition A to probe the forming pathway of indolin-2-one (Figure 2). **4a** was generated in the beginning and then gradually increased to approx. 30% before starting to decrease after 400 min, associated with the formation of **2a**, implying that *N*-hydroxyl indolin-2-one was possible the intermediate for the production of N-H indolin-2-one, and the further reduction of **4a** into **2a** was a slower step compared with the formation of **4a** from **1a**. Similar distributions of **4a** and **2a** were observed when varying the CO pressures above 1 atm within the reaction duration of 20 hours (Figure S1).

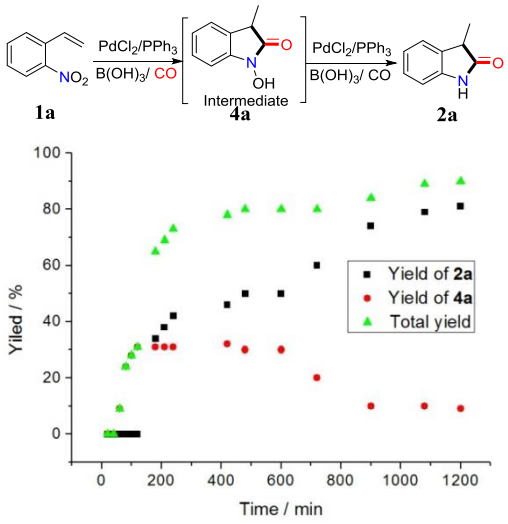
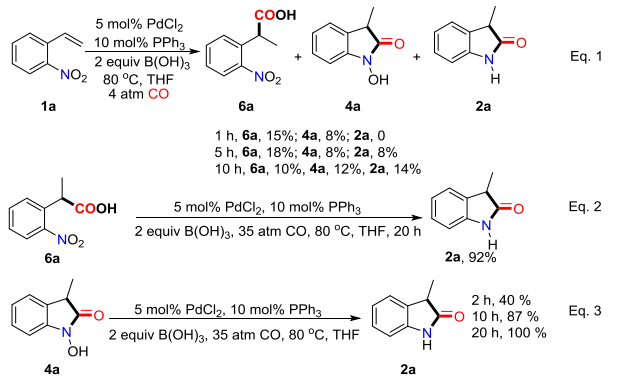


Figure 2. Kinetic profile for the reductive cyclocarbonylation of **1a** to synthesize **2a**.

In the substrate scope test, 2-aryl propionic acid (**6n**) was isolated in nearly 100% selectivity, suggesting that the synthe-

sis of indolin-2-one may be initiated by the hydrocarboxylation at the vinyl group,[15b] followed by the intramolecular ring closing reaction between the carboxylic acid and the half reduced nitroso (N=O) species to yield *N*-hydroxyl indolin-2-one. To further support this hypothesis, the reaction rate was reduced by lowering the CO pressure as indicated above in the model reaction, and indeed, 15% yield of 2-(2-nitrophenyl)propanoic acid (**6a**) and 8% yield of **4a** were obtained after 1 hour without the formation of **2a** at this stage. **2a** was only observed after prolonging the reaction to 5 h and 12 h with various amounts of **6a** and **4a** (Scheme 9, Eq. 1), implying that **6a** may be an intermediate before the formation of **4a** during the production of indolin-2-one. When **6a** and **4a** were used as the starting material, direct conversion to **2a** and dexoygenation to **2a** both proceeded efficiently under the identical reaction conditions for **6a** and **4a**, respectively (Scheme 9, Eq. 2 and Eq. 3). Importantly, these two controlled reactions did not occur without the presence of catalyst or CO (as shown in Supporting Information, Eq. S2-S5). Furthermore, a controlled experiment using $Pd(PPh_3)_4$ as the catalyst without CO was also conducted (Eq. S6), but there was no target product **2a**, which indicated that CO played an important role in the conversion of **4a** into **2a**, this result was also consistent with the deuteration experiment (Eq. S10).



Scheme 9. Controlled Experiments for the Synthesis of Indolin-2-one.

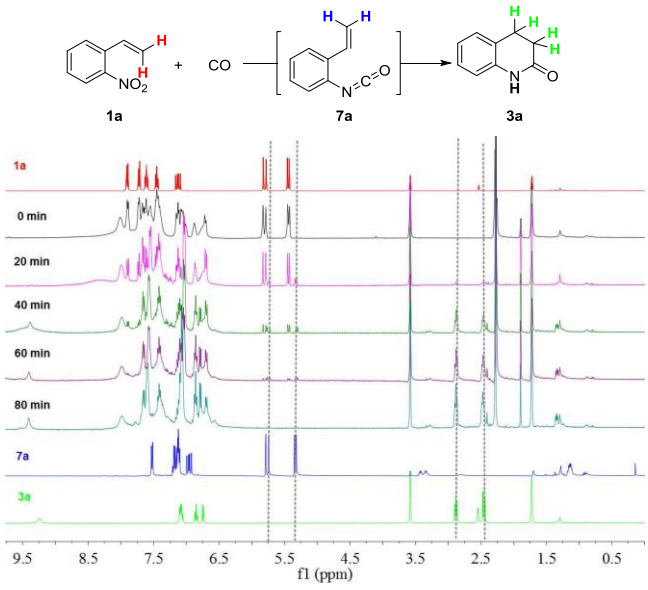
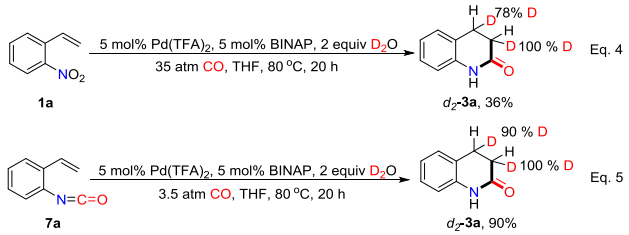


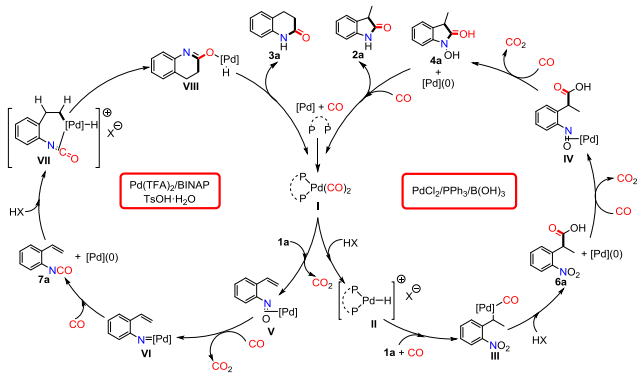
Figure 3. *in situ* ^{1}H NMR investigations in the synthesis of **3a**. Reaction conditions: **1a** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), BINAP (0.02 mmol), $TsOH{\cdot}H_2O$ (0.2 mmol), THF-d_8 (0.5 mL), CO (3 atm), 80 °C.

Given the above detailed studies on the formation of indolin-2-one, we continued to examined whether 2-nitrophenylpropionic acid was also an intermediate for the production of 3,4-dihydroquinolin-2-one. From a controlled experiment under standard condition B (Supporting Information, Eq. S8), however, no reaction occurred. To probe the plausible reaction pathway in the synthesis of 3,4-dihydroquinolin-2-one, *in situ* ^{1}H NMR experiments were conducted using the corresponding optimized $Pd(TFA)_2$/BINAP/$TsOH{\cdot}H_2O$ catalytic system at 80 °C (Figure 3). Under 3 atm of CO for 20 minutes, new ^{1}H NMR signals formed at around 2.5 and 5.3 ppm, which could be assigned to the methylene hydrogen of the desired dihydroquinolin-2-one product and the vinyl hydrogen of a new reaction intermediate, respectively. After 40 minutes, the ^{1}H NMR signals of the intermediates matched well with those of the standard sample of 1-isocyanato-2-vinylbenzene (**7a**) judged by its characteristic peaks of the two terminal C-H of vinyl groups. At the same time, the signals of **3a** also became increasingly intense, particularly for its N-H characteristic peaks at about 9.5 ppm. The concentration of isocyanate intermediate and substrate decreased gradually as the reaction proceeded, and their signals disappeared completely after 80 minutes. These results strongly indicated that **1a** was reductively carbonylated into the 1-isocyanato-2-vinylbenzene at first, followed by the hydrocyclization reaction to afford 3,4-dihydroquinolin-2-one (**3a**). To further confirm whether **7a** was an intermediate of this transformation, a controlled conversion of **7a** was conducted under condition B (Eq. S9), and **3a** was isolated in 90 % yield. In order to study the role of the proton source, **1a** and **7a** were separately treated with two equivalent amount of D_2O under condition B. Intriguingly, 36% and 90% yield of corresponding d_2-**3a** were obtained with no sign of deuteration on the amide N-H (Scheme 10, Eq. 4-5)!



Scheme 10. Deuteration Experiments for the Synthesis of 3,4-Dihydroquinolin-2-one.

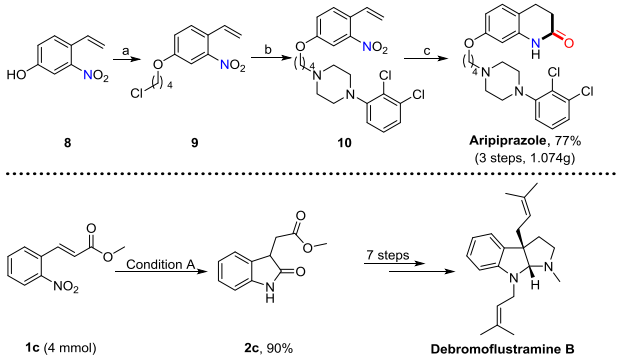
Based on our own investigations and previous reports,[12,15b,27] the catalytic cycles for the formation of indolin-2-one and 3,4-dihydroquinolin-2-one were proposed as shown in Scheme 11. Under condition A, the reductive cyclocarbonylation of *o*-nitrostyrenes was initiated by the hydrocarboxylation of the vinyl group. The insertion of *o*-nitrostyrene (**1a**) to the in-situ formed P_2Pd-H complex (**II**) and the following CO coordination occurred to give the complex **III**,[28a] CO migration and insertion into the alkyl-Pd bond of **III** afforded the isolated intermediate **6a**,[28b] which was reductively catalyzed by the eliminated Pd(0) and CO to provide the Pd-nitrosoarene (**IV**) with release of CO_2,[27] subsequently followed by the cyclization to give the detected 1-hydroxy-3-methylindolin-2-one (**4a**).[29] Finally, the target product indolin-2-one (**2a**) was produced by the deoxygenation of **4a** using CO as the reductant, this step could be reasonably deduced by the controlled experiments (Scheme 9, Eq. 3 and Eq. S4-S6) and deuteration experiment (Eq. S10).



Scheme 11. Different Reaction Mechanisms for the Synthesis of Indolin-2-one and 3,4-Dihydroquinolin-2-one (HX = $B(OH)_3$ or TsOH).

While for the synthesis of dihydroquinolinone, the reductive deoxygenation of nitro moiety of *o*-nitrostyrene was firstly initiated under condition B via Pd-nitrosoarene (**V**) and Pd-nitrene (**VI**) complexes,[27] followed by the insertion of CO into nitrene intermediate (**VI**) to yield the 1-isocyanato-2-vinylbenzene (**7a**) intermediate,[30] which was verified by the *in situ* ^{1}H NMR experiments. Subsequently, the hydropalladation of **7a** with the help of TsOH·H_2O afforded the isocyanate intermediate (**VII**), and then **VII** underwent attack of the nucleophilic alkyl moiety onto the electrophilic carbonyl carbon to give a cyclic imidate (**VIII**),[31] which was finally converted to **3a** through the reductive cleavage and tautomerization.[32] Notably, the origin of two added hydrogen of the resultant **3a** product was supported by the deuteration experiments (Scheme 10, Eq. 4-5).

2.4 Applications. Aripiprazole (brand name Abilify) is a new type of antipsychotic pharmaceutical and primarily used in the treatment of schizophrenia and bipolar disorder, its sales in 2013 ranked the first among all drugs in the United States medicine market.[33] Its conventional synthetic methods generally provided unideal yields due to the formation of isomer which is difficult to remove (Scheme S1),[34] or need excess explosive sodium azide as the nitrogen source and corrosive TFA as a solvent.[35] With **8** as the starting substrate and our methodology as the key catalytic procedure, 77% overall yield of Aripiprazole could be achieved with a shorter synthetic route and under milder reaction conditions (Scheme 12). **2c** and its derivatives have been recognized as the key intermediate in the total synthesis of pyrrolo indole alkaloids,[36-37] such as debromoflustramine B (Scheme 12), which is a selective butyrylcholinesterase inhibitor.[38] With **1c** as the cheap and easily available substrate, **2c** could be synthesized in one-step with 90% yield in 4 mmol scale. These two applications suggest that our convenient and selective catalytic methodologies have great potentials in the synthesis of five- and six- membered benzo-fused lactams.



Scheme 12. Application in the Synthesis of Aripiprazole[a] and Debromoflustramine B.[37b,39] [a]Conditions: (a) 4-bromo-1-chlorobutane (1 equiv), K_2CO_3 (2 equiv), Acetonitrile (0.1 M), 30 °C. (b) 1-(2,3-Dichlorophenyl) piperazine hydrochloride (1.05 equiv), K_2CO_3 (2 equiv), NaI (1.5 equiv), TBAB (0.4 mol %), Acetonitrile (0.1 M), 70 °C. (c) Condition B.

3. CONCLUSIONS

In summary, we have developed a Pd-catalyzed chemo- and regioselective conversion of *o*-nitrostyrenes, beyond the previous deoxygenation reduction of *o*-nitrostyrenes to indole. The chemoselectivity was sensitive to the nature of the counter anions of Pd^{2+} precursors, while ligand controlled the regioselectivity. The kinetic profile and a series of controlled experiments conducted under the optimal $PdCl_2/PPh_3/B(OH)_3$ catalytic system suggest that the catalytic conversion of *o*-nitrostyrene into indolin-2-one is a tandem process involving the hydrocarboxylation of styrene motif to give **6**, the reductive deoxygenation of NO_2 and intramolecular cyclization to afford **4**, and the final deoxygenation of **4** by CO to produce **2**. The *in situ* ^{1}H NMR studies, controlled experiments and deuteration experiments under the optimal $Pd(TFA)_2$/BINAP/TsOH·H_2O catalytic system revealed that substrate **1** underwent NO_2 reduction and carbonylation into the 1-isocyanato-2-vinylbenzene at first, followed by hydrocyclization to afford dihydroquinolin-2-one (**3**). It has been further demonstrated that our novel methodologies could be efficiently applied in the synthesis of antipsychotic pharmaceutical aripiprazole in gram scale with 77% overall yield, and the preparation of the key intermediate (**2c**) for the total synthesis of debromoflustramine B. Further detailed mechanistic studies on the synthesis of indolin-2-one and dihydroquinolin-2-one to elucidate the origin of the regioselectivity are ongoing in our laboratories.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information.

Full experimental details for the syntheses and characterizations of all described compounds, Table S1-S11, Figure S1 and S2, Eq.

S1-S10, Scheme S1-S2, and NMR spectrums. This material is available free of charge via the Internet at http://pubs.acs.org.

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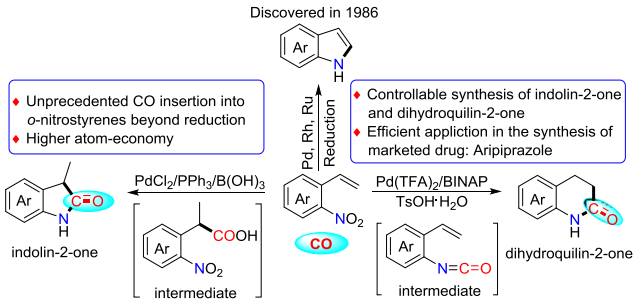
Discovered in 1986
Ar
N
H
Unprecedented CO insertion into o-nitrostyrenes beyond reduction
Higher atom-economy
Pd, Rh, Ru
Reduction
Controllable synthesis of indolin-2-one and dihydroquilin-2-one
Efficient appliction in the synthesis of marketed drug: Aripiprazole
PdCl2/PPh3/B(OH)3
Pd(TFA)2/BINAP
TsOH·H2O
C=O
indolin-2-one
COOH
NO2
intermediate
CO
N=C=O
intermediate
dihydroquilin-2-one