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RESEARCH ARTICLE

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# Palladium-Catalyzed Enantioselective Heck Carbonylation with a Monodentate Phosphoramidite Ligand: Asymmetric Synthesis of (+)-Physostigmine, (+)-Physovenine, and (+)-Folicanthine

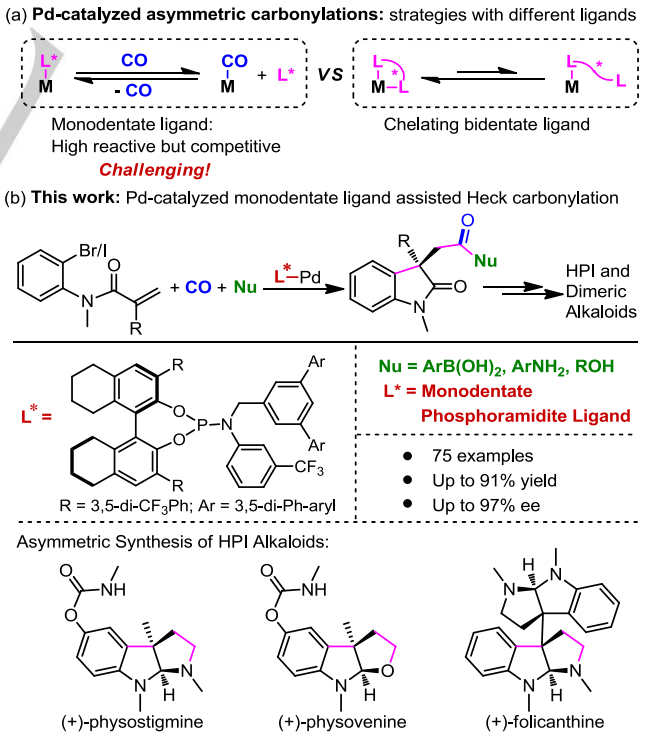
Ming Chen, Xucai Wang, Pengfei Yang, Xun Kou, Zhi-Hui Ren, and Zheng-Hui Guan*

**Abstract:** We report herein the development of the first monodentate ligand assisted Pd-catalyzed enantioselective domino Heck carbonylation reaction with CO. The highly enantioselective domino Heck carbonylation of *N*-aryl acrylamides and various nucleophiles including arylboronic acids, anilines and alcohols, in the presence of CO was achieved. A novel monodentate phosphoramidite ligand Xida-Phos has been developed for this reaction that displays excellent reactivity and enantioselectivity. The reaction employs readily available starting materials, tolerates a wide range of functional groups, and provides straightforward access to a diverse array of enantioenriched oxindoles having *β*-carbonyl substituted all-carbon quaternary stereocenters, thus providing a facile and complementary method for the asymmetric synthesis of bioactive hexahydropyrroloindole and its dimeric alkaloids.

## Introduction

Carbonylation reaction with CO represents a fundamental and promising approach for the synthesis of diverse carbonyl compounds.[1,2] One of the most important aspects in this area is how to develop enantioselective carbonylations for the synthesis of carbonyl compounds bearing an α- or β-stereocenter.[3] However, it represents a daunting challenge due to the critical competitive coordination between CO and chiral ligands to transition metal catalysts.[4] An effective strategy for improving the enantiocontrol of carbonylation is to use the chiral chelating bidentate ligands.[5,6] Indeed, Pd-catalyzed asymmetric carbonylations assisted by chelating bisphosphine or bisoxazole ligands have been ingeniously developed toward the synthesis of enantioenriched carbonyl compounds.[3a,b,7,8] In this context, due to no “chelate effect”, the monodentate ligands assisted enantioselective carbonylations with CO is rather limited (Scheme 1a). The sharp lack of effective monodentate ligands for Pd-catalyzed enantioselective carbonylations hampers to a large extent the diversification of the reactions.[9]

Recently, palladium-catalyzed asymmetric domino Heck reaction has received particular attention in organic synthesis.[10] Incorporation of the significance of Heck-type domino reactions in construction of complex molecules,[10-13] the development of enantioselective domino Heck carbonylation reaction would offer a straightforward approach to the enantioenriched *β*-carbonyl substituted all-carbon quaternary stereocenters, that was significant for complex natural products synthesis.[9a] The Pd-catalyzed BINAP assisted domino Heck carbonylation of acrylamides with 28% ee has emerged in 1998 by Overman and coworkers.[9a] Nevertheless, less progress had been made along this direction over the past two decades. Recently, Pd-catalyzed highly enantioselective Heck-Matsuda carbonylation of aryldiazonium salts and Heck-carbonylative spirocyclization have been developed by the groups of Correia, Luo and Zhu by using bidentate bisoxazole or bisphosphine ligand.[14] Notwithstanding the progress, the use of either aryldiazonium salts or intramolecular nucleophiles is mandatory. Since the high reactivity of monodentate ligands in the non-asymmetric Pd-catalyzed Heck reactions,[4a,15] and as exemplified by recent enantioselective dearomative Heck reactions,[16] the development of monodentate ligand assisted Pd-catalyzed enantioselective domino Heck carbonylations, although extremely challenging, is highly desirable.




**Scheme 1.** Pd-catalyzed enantioselective domino Heck carbonylation and HPI alkaloides synthesis.

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Based on our interest in carbonylation reactions,[17] we present herein the development of the first monodentate ligand assisted Pd-catalyzed highly enantioselective domino Heck carbonylation reaction (Scheme 1b). An effective monodentate phosphoramidite ligand Xida-Phos (**L18**) has been developed, thus making a board scope of coupling partners including arylboronic acids, anilines, and alcohols were compatible with the reaction. Importantly, the reaction provided an approach to effective asymmetric synthesis of bioactive hexahydropyrroloindole (HPI) and its dimeric alkaloids including (+)-physostigmine, (+)-physovenine, and (+)-folicanthine.

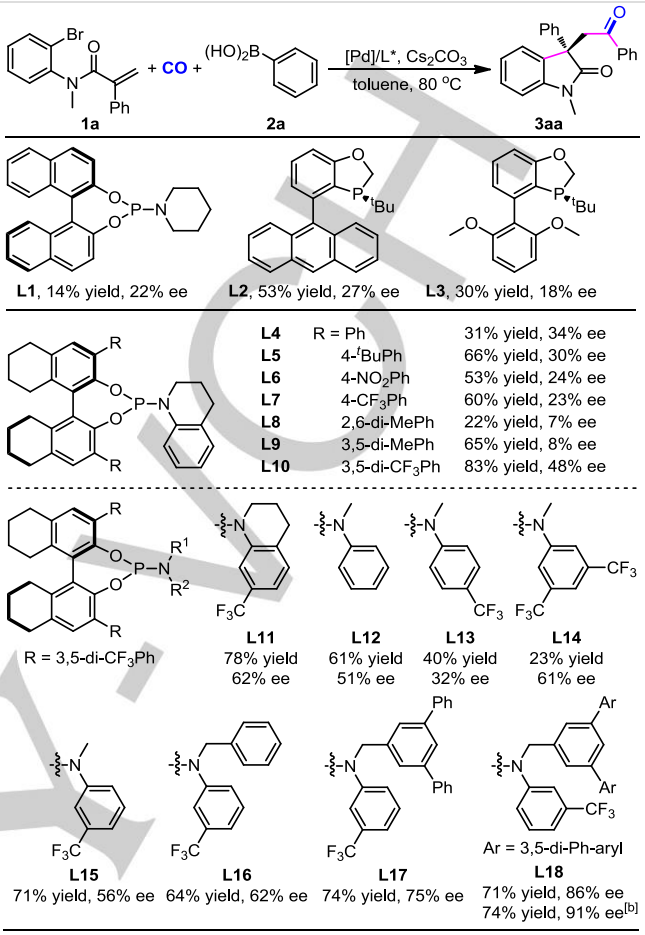
## Results and Discussion

**Development of A Monodentate Phosphoramidite Ligand for Pd-Catalyzed Enantioselective Domino Heck Carbonylative Suzuki Reaction.** Owing to its low toxicity and commercial availability, arylboronic acids are amongst the most important carbon nucleophiles in Pd-catalyzed cross-coupling reactions.[18] Thus, Pd-catalyzed domino Heck carbonylative Suzuki reaction of the *N*-aryl acrylamide **1a** and phenylboronic acid **2a** in the presence CO was initially studied. The reactions were carried out in toluene with $Cs_2CO_3$ as the base in the presence of $Pd_2(dba)_3$ (2.5 mol%) and a ligand in 80 °C (Table 1). Firstly, a number of commonly used ligands in Pd-catalyzed asymmetric carbonylations, including BINAP, DIOP, MeO-BIPHEP, SegPhos, BinaPhos, *i*Pr-Phox, Ph-Pymox, and Box, were screened; nevertheless, no reaction was observed under many attempts (Table S1 in SI). These results revealed the limitation of the bidentate ligands and the challenge associated with accomplishing this domino carbonylation reaction.

The transmetalation of arylboronic acid to Pd atom generally takes place on a coordinatively unsaturated Pd−O−B intermediate.[19] As such, a monodentate ligand can be expected to facilitate the transmetalation step of this reaction. Thus, further screening of the various monodentate ligands, we found that the use of monodentate phosphoramidite ligand **L1** can lead to 14% yield of desired product **3aa** with 22% ee (Table 1).[20] And 53% yield of **3aa** with 27% ee was obtained by using AntPhos **L2** as the ligand.[21] On the basis of these primary results, we devoted our efforts to develop an effective monodentate ligand for this carbonylative reaction.

In this context, various phosphoramidite ligands with a range of steric and electronic variation on the 3,3'-positions of $H_8$-BINOL-framework was screened (**L4**-**L10**). It was found that 3,5-di-$CF_3$-aryl on the 3,3'-positions of $H_8$-BINOL can importantly improve the reactivity and enantioselectivity of the reaction (**L10**: 83% yield, 48% ee). After several attempts in modification of the tetrahydroquinoline moiety (**L11**), we then paid attention to fine-tuning the amino moiety by employing acyclic *N*-alkyl anilines as the structural motif (**L12**-**L18**). Further attempts suggested the *N*-alkyl 3-$CF_3$-anilines were privileged based on the reactivity and enantioselectivity. On this occasion, the enantioselectivity were strongly responsive to the expanse of the substitutions of the alkyl moiety on *N*-alkyl 3-$CF_3$-anilines (**L15**-**L18**), with the sterically bulky ligand **L18** (Xida-Phos) being optimal (71% yield, 86% ee). Finally, the optimal conditions were obtained by screening of other reaction parameters including catalyst precursors, solvents, bases and temperatures (74% yield, 91% ee) (Table S2 in SI).

**Table 1.** Optimization the reaction conditions.[a]



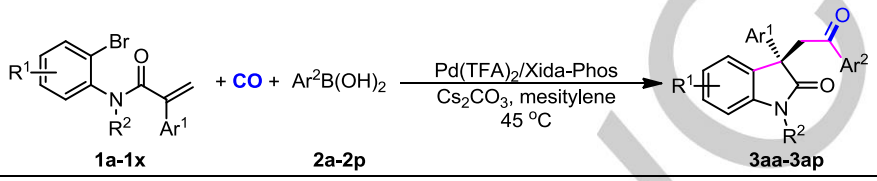

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv), CO:Ar = 1:6 (1 atm), $Pd_2(dba)_3$ (2.5 mol%), **L1**-**L18** (15 mol%), $Cs_2CO_3$ (2.0 equiv), toluene (1.6 mL), 80 °C, 48 h, GC analysis of the crude product using n-hexadecane as an internal standard, and ee were determined by chiral HPLC analysis. [b] $Pd(TFA)_2$ (3 mol%), mesitylene (1.6 mL), 45 °C, isolated yield.

**Reaction Scope of Pd-Catalyzed Enantioselective Domino Heck Carbonylative Suzuki Reaction.** With the optimal conditions in hand, we have investigated the reaction scope (Table 2). Firstly, different substituents at the nitrogen atom on *N*-aryl acrylamides **1a-1c** were investigated. The ethyl and benzyl groups showed similar enantioselectivity and slightly higher reactivity in comparison with methyl (**3aa**-**3ca**). Studying of the functional group tolerance on the aniline moiety suggested that a range of groups including methyl, methoxyl, sterically bulky isopropyl and *t*-butyl, were well compatible with the conditions to produce the corresponding oxindoles bearing *β*-ketone substituted all-carbon quaternary stereocenters **3da**-**3ja** with 96%-97% ee in 63%-80% yields. *N*-Aryl acrylamides bearing a 5- or 4,5-disubstituents on the *ortho*-Br-aniline moiety gave rise to **3ka-3na** with 92%-96% ee in 71%-88% yields. Specifically, the halide substituents, including F, Cl, and even Br were compatible with the conditions to form the corresponding **3oa**-**3ra** with 90%-94% ee in 68%-79% yields. In addition, electron-withdrawing group such as $CF_3$, was tolerated in the reaction to afford **3sa** with 94% ee in 84% yield. Furthermore, 2-aryl acrylamides bearing different substituents on the acryl moiety such as methyl, methoxyl, F, Cl and $CF_3$, were

compatible in the reaction to afford **3ta**-**3xa** with 90%-94% ee in good to high yields.

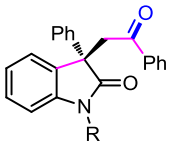
The substrate scope with respect to arylboronic acids was investigated. All of the *para*-, *meta*-, and *ortho*-tolylboronic acids gave the corresponding oxindoles **3ab-3ad** in high yields and ee, thus indicating that the reaction was insensitive to the steric hindrance of arylboronic acids. We were delighted to observe that various arylboronic acids were well compatible with the conditions to form the *β*-ketone substituted oxindoles **3ae-3aj** with 92%-94% ee in 72%-85% yields. Notably, arylboronic acids with a halide substituent such as F, Cl and Br, are tolerated in the reaction (**3ak-3am**). In addition, polycyclic arylboronic acids, including 1-naphthyl, 2-naphthyl, and 9-phenanthryl boronic acid underwent the reaction smoothly to produce the oxindoles **3an-3ap** with high ee in high yields.

**Table 2** Scope of enantioselective domino Heck carbonylative Suzuki reaction.[a]

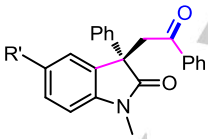



**1a-1x** **2a-2p** **3aa-3ap**

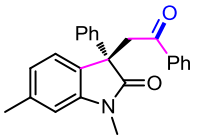
Scope of *N*-Aryl Acrylamides:



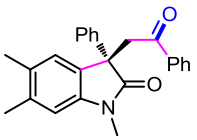
R = Me **3aa**, 74% yield, 91% ee
R = Et **3ba**, 82% yield, 91% ee
R = Bn **3ca**, 86% yield, 90% ee



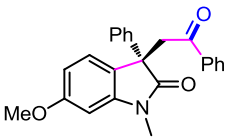
R' = Me **3da**, 66% yield, 96% ee
R' = Et **3ea**, 69% yield, 96% ee
R' = $^{i}$Pr **3fa**, 72% yield, 97% ee
R' = $^{n}$Bu **3ga**, 63% yield, 96% ee
R' = $^{t}$Bu **3ha**, 69% yield, 97% ee
R' = OMe **3ia**, 70% yield, 96% ee
R' = OEt **3ja**, 80% yield, 97% ee



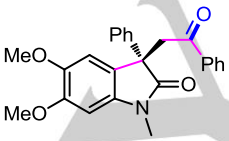
**3ka**, 71% yield, 92% ee



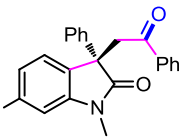
**3la**, 75% yield, 96% ee



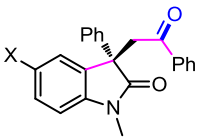
**3ma**, 71% yield, 94% ee



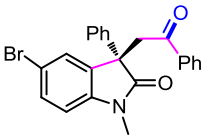
**3na**, 88% yield, 94% ee



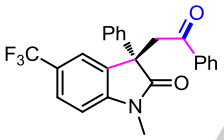
**3oa**, 79% yield, 91% ee



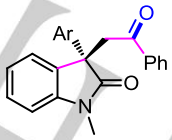
X=F, **3pa**, 68% yield, 90% ee
X=Cl,**3qa**, 74% yield, 94% ee



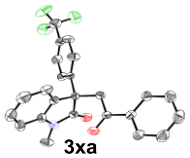
**3ra**, 68% yield, 93% ee



**3sa**, 84% yield, 94% ee

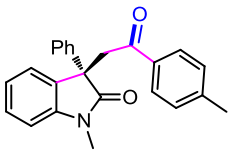


Ar = 4-MePh **3ta**, 75% yield, 90% ee
Ar = 4-MeOPh **3ua**, 55% yield, 91% ee
Ar = 4-FPh **3va**, 77% yield, 92% ee
Ar = 4-ClPh **3wa**, 81% yield, 94% ee
Ar = 4-$CF_3$Ph **3xa**, 91% yield, 91% ee

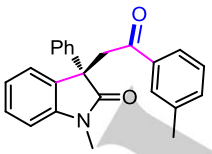


**3xa**

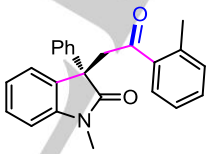
Scope of Arylboronic Acids:



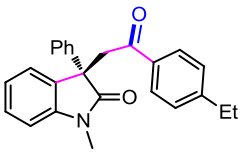
**3ab**, 78% yield, 91% ee



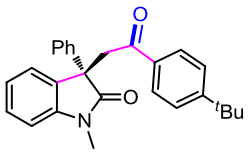
**3ac**, 80% yield, 90% ee[b]



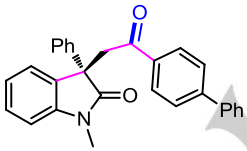
**3ad**, 81% yield, 92% ee[b]



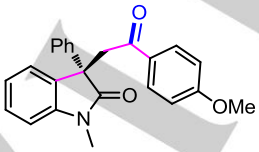
**3ae**, 85% yield, 92% ee



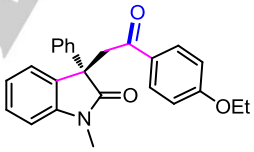
**3af**, 81% yield, 92% ee



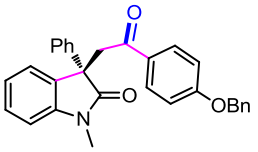
**3ag**, 72% yield, 92% ee



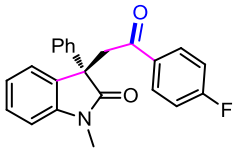
**3ah**, 77% yield, 94% ee



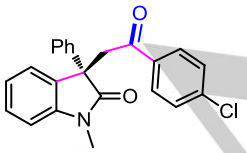
**3ai**, 81% yield, 92% ee



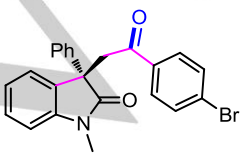
**3aj**, 79% yield, 94% ee



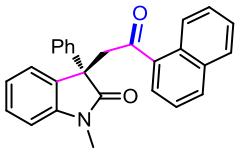
**3ak**, 79% yield, 93% ee[b]



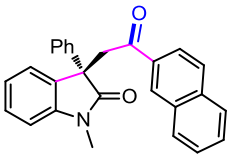
**3al**, 86% yield, 89% ee[b]



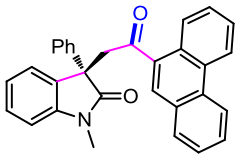
**3am**, 84% yield, 85% ee



**3an**, 83% yield, 91% ee



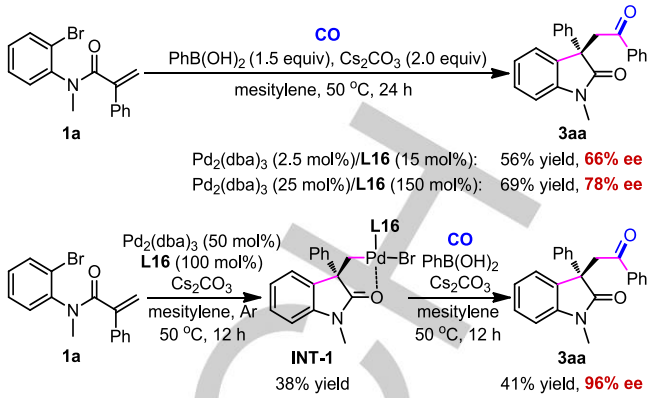
**3ao**, 80% yield, 90% ee[b]



**3ap**, 82% yield, 85% ee[b]

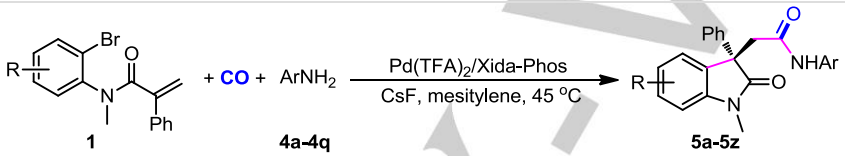
[a] Conditions: **1a**-**1x** (0.1 mmol), **2a**-**2p** (1.5 equiv), CO:Ar = 1:6 (1 atm), $Pd(TFA)_2$ (3 mol%), Xida-Phos (15 mol%), $Cs_2CO_3$ (2.0 equiv), mesitylene (1.6 mL), 45 °C, 48 h. [b] CsF (3.0 equiv) was used as the base.

**Mechanistic Investigation.** To gain mechanistic insight into the reaction, control experiments have been performed (Scheme 2). Whereas only 66% ee was obtained in the presence of $Pd_2(dba)_3$ (2.5 mol%) and **L16** (15 mol%), an improved 78% ee was observed when $Pd_2(dba)_3$ (25 mol%) and **L16** (150 mol%) were employed. This improvement is probably because the increased concentration ratio of Pd/**L16** to CO in the solvent. Namely, the competitive coordination between CO and **L16** to Pd atom is presumably thought to erode the enantioselectivity. To verify this speculation, the stoichiometric reaction was conducted. Delightedly, an important complex **INT-1** was obtained in 38% yield.[22] Treating the **INT-1** with CO and $PhB(OH)_2$, a 41% yield of **3aa** with 96% ee was obtained. This experiment not only suggests that the palladium complex **INT-1** was a key intermediate in the reaction but also reveals the challenge associated with the reaction: CO eroded the enantioselectivity.[4] On the other hand, the effectiveness of our optimal ligand **L18** (Xida-Phos) was illustrated.

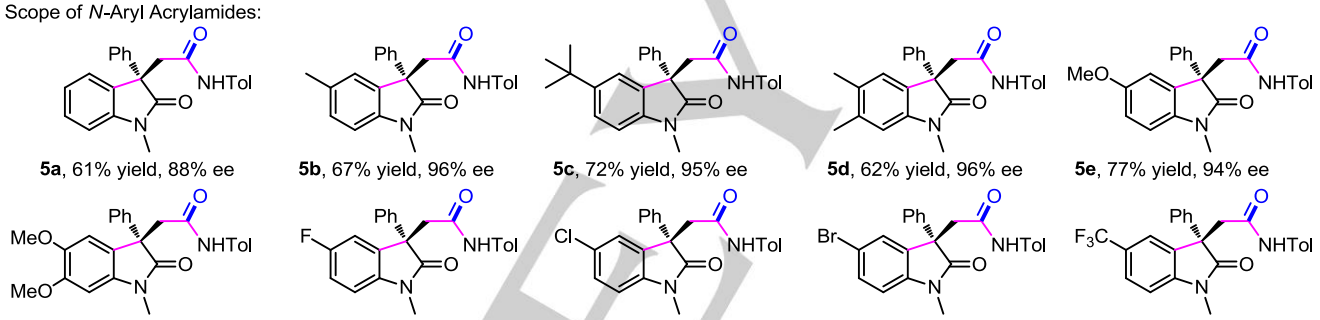



**Scheme 2.** Mechanistic investigation.

**Table 3** Scope of enantioselective domino Heck carbonylative amidation reaction.[a]




Scope of *N*-Aryl Acrylamides:

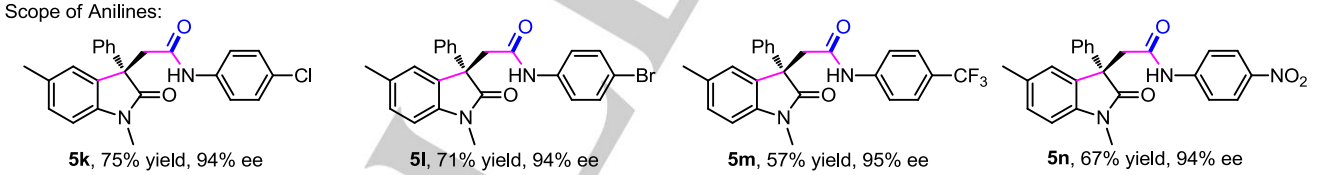


**5a**, 61% yield, 88% ee; **5b**, 67% yield, 96% ee; **5c**, 72% yield, 95% ee; **5d**, 62% yield, 96% ee; **5e**, 77% yield, 94% ee

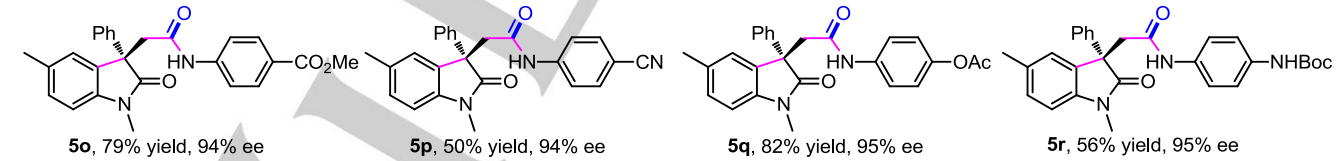


**5f**, 71% yield, 97% ee; **5g**, 68% yield, 88% ee; **5h**, 73% yield, 93% ee; **5i**, 81% yield, 91% ee; **5j**, 79% yield, 93% ee

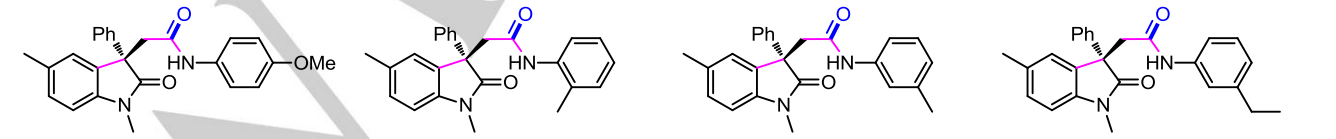
Scope of Anilines:



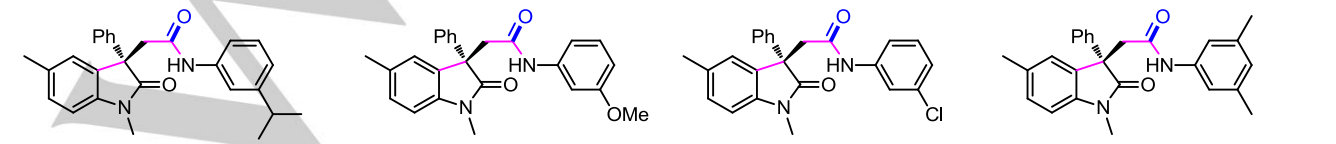
**5k**, 75% yield, 94% ee; **5l**, 71% yield, 94% ee; **5m**, 57% yield, 95% ee; **5n**, 67% yield, 94% ee



**5o**, 79% yield, 94% ee; **5p**, 50% yield, 94% ee; **5q**, 82% yield, 95% ee; **5r**, 56% yield, 95% ee



**5s**, 75% yield, 95% ee; **5t**, 55% yield, 94% ee; **5u**, 74% yield, 96% ee; **5v**, 72% yield, 94% ee



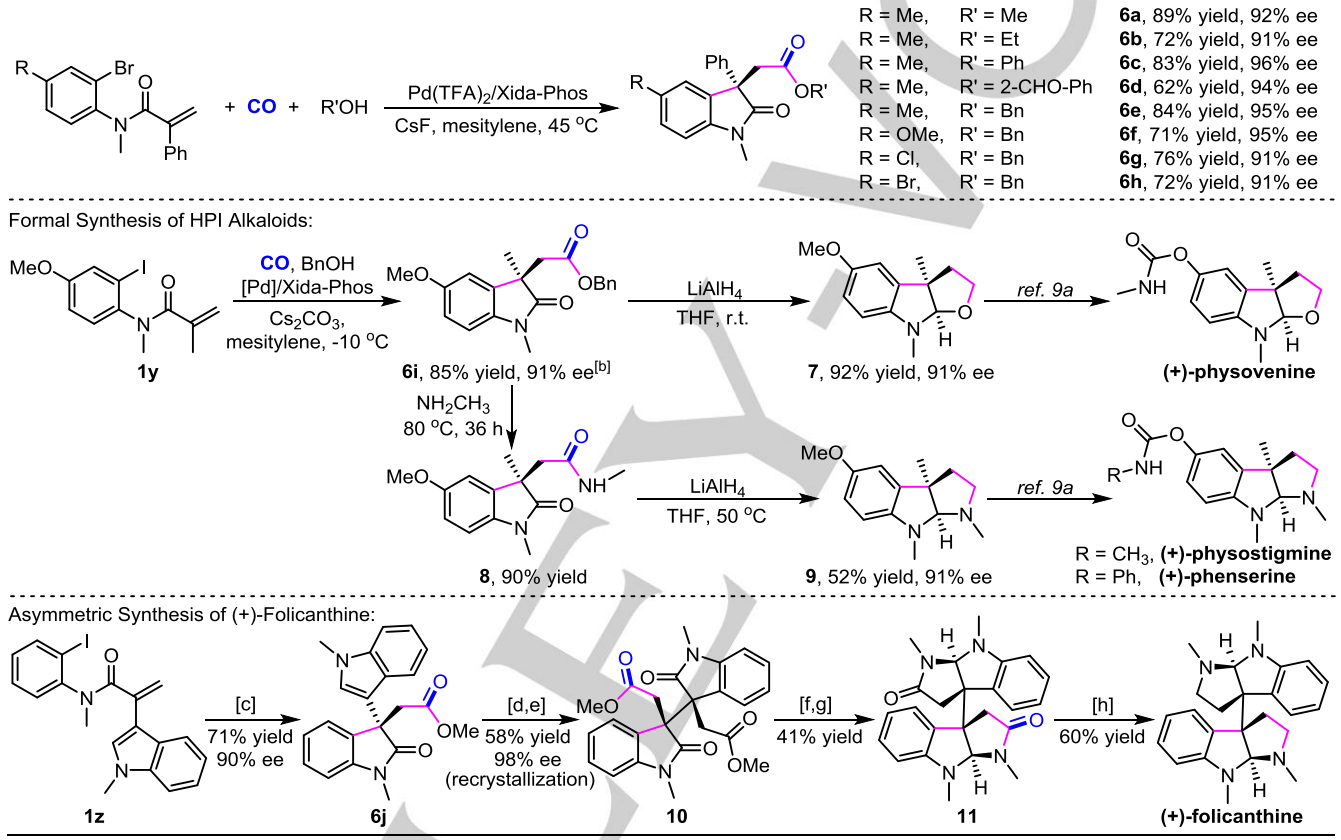
**5w**, 83% yield, 94% ee; **5x**, 73% yield, 92% ee; **5y**, 63% yield, 94% ee; **5z**, 70% yield, 94% ee

[a] Conditions: **1** (0.1 mmol), **4a**-**4q** (2 equiv), CO:Ar = 1:6 (1 atm), $Pd(TFA)_2$ (6 mol%), Xida-Phos (15 mol%), CsF (3 equiv), mesitylene (1.6 mL), 45 °C, 48 h.

**Reaction Scope of Pd-Catalyzed Enantioselective Domino Heck Carbonylative Amidation Reaction.** Encouraged by the success of the Heck carbonylative Suzuki reaction, we have studied the Heck carbonylative amidation with anilines. With CsF as the base, various *N*-aryl acrylamides and a broad scope of anilines were screened (Table 3). Like the functional group compatibility noted above, functional groups including methyl, bulky *tert*-butyl, methoxy, F, Cl, Br, and $CF_3$, on the *N*-aryl acrylamides were well tolerated in the reaction. And the electronic properties of these substituents have little influence on the reaction. Thus, the oxindoles bearing *β*-amide all-carbon quaternary stereocenters **5a**-**5j** were obtained in 61%-81% yields with 88%-97% ee.

Similarly, the ability of the reaction to tolerate functional groups in the aniline component is remarkable. Anilines with an electron-withdrawing group, such as Cl, Br, $CF_3$, $CO_2Me$, strong $NO_2$ and coordinative CN, were well compatible with the conditions to afford **5k**-**5p** and **5y** with 94%-95% ee in 50%-79% yields. Anilines with an electron-donating group including alkyl, OAc, coordinative NHBoc and methoxy, were also tolerated in the reaction to give the **5q**-**5x**, and **5z** with 92%-96% ee in high yields.

**Table 4** Scope of enantioselective domino Heck esterification reaction.[a]




[a] Conditions: **1a** (0.1 mmol), MeOH or EtOH (5.0 equiv), PhOH and BnOH (1.5 equiv), CO:Ar = 1:6 (1 atm), $Pd(TFA)_2$ (6 mol%), Xida-Phos (15 mol%), CsF (3.0 equiv), mesitylene (1.6 mL), 45 °C, 48 h. [b] **1y** (0.5 mmol), BnOH (2.0 equiv), $Pd(TFA)_2$ (3 mol%), Xida-Phos (15 mol%), $Cs_2CO_3$ (2.0 equiv), mesitylene (16 mL), -10 °C, 24 h. [c] **1z** (0.2 mmol), MeOH (40 μL), $Pd(TFA)_2$ (4 mol%), Xida-Phos (15 mol%), $Cs_2CO_3$ (2.0 equiv), mesitylene (3.2 mL), -10 °C, 24 h, 71% yield, 90% ee. [d] DMSO (180 μL), HCl (1.2 mL), HOAc (10 mL), r.t., 12 h. [e] $BrCH_2CO_2Me$ (2.0 equiv), $Bu_4NHSO_4$ (20 mol%), NaOH (20 equiv, 50% in water), toluene (7 mL), r.t., 1 h, 77% yield and 90% ee from **6j**; further recrystallization to give **10** with 98% ee (dr > 20:1) in 75% yield. [f] $MeNH_2$ in MeOH (33% wt., 5 mL), 80 °C, 48 h, 90% yield. [g] LDA (2.5 equiv), DIBAL-H (10 equiv), THF (70 mL), -10 to -30 °C to r.t., 36 h, 45% yield. [h] red-Al (20 equiv, 70% in toluene), toluene (10 mL), r.t., 60% yield.

**Reaction Scope of Pd-Catalyzed Enantioselective Domino Heck Esterification Reaction and Asymmetric Synthesis of HPI Alkaloids.** Owing to the utility of the esterification in the synthesis of natural HPI alkaloids, we continued to investigate the Pd-catalyzed enantioselective domino Heck esterification reaction (Table 4). Delightedly, the Heck esterification reaction proceeded smoothly with a range of *N*-aryl acrylamides and alcohols, thus providing an effective approach for the synthesis of oxindoles bearing *β*-ester substituted all-carbon quaternary stereocenters **6a**-**6h** in high yield and ee. In particular, salicylaldehyde produced the desired product **6d** with 94% ee in 62% yield. Notably, *N*-aryl acrylamide iodides show higher reactivity than bromides. The Heck esterification of *N*-(*p*-MeO)-aryl acrylamide iodide **1y** proceeded smoothly under -10 °C. Therefore, a high valuable *β*-ester substituted oxindole **6i** was obtained in 85% yield and 91% ee. With this key compound **6i** in hand, the HPI alkaloids (+)-physostigmine, (+)-physovenine and (+)-phenserine can be easily synthesized via simple transformations.[9a,23]

The unique and intricate structure and important bioactivity of dimeric HPI alkaloids made them attractive targets for total synthesis.[24] Whereas genius synthetic strategies have been developed, including Overman's intramolecular double Heck and dialkylation strategies,[25] Movassaghi's reductive dimerization

and assembly of cyclotryptamines strategies,[26] Gong's nucleophilic substitution of 3-hydroxyoxindole,[27] Kanai and Matsunaga's double Michael reaction of bisoxindole,[28] and Tu's recent organo-cation catalyzed dialkylation of bisoxindole strategy,[29] a novel and effective strategy toward HPI alkaloids family is still highly desirable. In this regard, the Pd-catalyzed Heck esterification incorporation of oxidation and alkylation could provide a complementary protocol for the asymmetric synthesis of dimeric HPI alkaloids. For example, the Heck esterification of **1z** produced the indole-3-yl oxindole **6j** in 71% yield and 90% ee, which could be readily converted into the key intermediate **10** by oxidation and alkylation in 77% yield and 90% ee. And the enantiopurity of **10** could be further improved to 98% ee (dr > 20:1) by recrystallization. Ester-amide exchange reaction of **10** followed by reductive amidation and amide reduction[27] of **11** affords the (+)-folicanthine in 10.1 % overall yield in total 6 steps from *N*-aryl acrylamide.

## Conclusion

In summary, we have developed a novel monodentate phosphoramidite assisted Pd-catalyzed enantioselective domino Heck carbonylation reaction of *N*-aryl acrylamides and various nucleophiles in the presence of CO. A monodentate ligand exhibited first time as an effective ligand in Pd-catalyzed enantioselective carbonylations. Various nucleophiles including arylboronic acids, anilines and alcohols were tolerated in the reaction, thus providing a straightforward method for the synthesis of oxindoles bearing *β*-carbonyl substituted all-carbon quaternary stereocenters in high yields and enantioselectivities. And the reaction provided a complementary approach to facile asymmetric synthesis of bioactive hexahydropyrroloindole and its dimeric alkaloids.

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**Keywords:** asymmetric catalysis • palladium • carbonylation • domino Heck reaction • monodentate ligand

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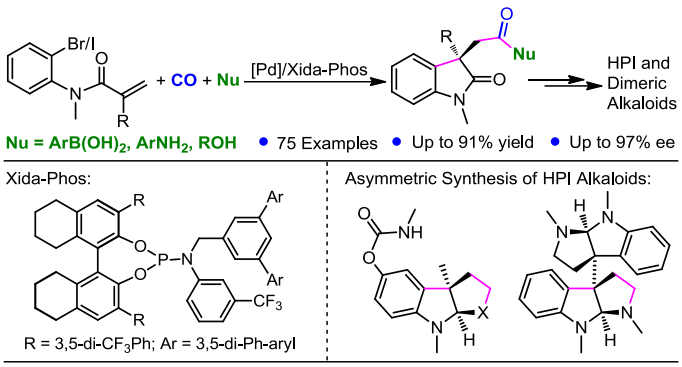


A new monodentate phosphoramidite ligand Xida-Phos assisted Pd-catalyzed enantioselective domino Heck carbonylative reaction for the synthesis of oxindoles having *β*-carbonyl substituted all-carbon quaternary centres has been developed.