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Authors: Qiang Zhu, Huaanzi Hu, Fan Teng, Jian Liu, Weiming Hu, and Shuang Luo

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Enantioselective Synthesis of 2-Oxindole Spiro-fused Lactone and Lactam via Heck/Carbonylative Cylization: Method Development and Applications

Huaanzi Hu, Fan Teng, Jian Liu, Weiming Hu, Shuang Luo*, and Qiang Zhu*

Abstract: An efficient one-pot assembly of all-carbon spirooxindole compounds from non-oxindole-based materials has been developed through palladium-catalyzed asymmetric tandem Heck/carbonylative lactonization and lactamization. Diversified spirooxindole γ-and δ-lactones/lactams were accessed in high yields with good to excellent enantioselectivity (up to 99% ee) under mild conditions. Natural product coixspirolactam A was conveniently synthesized by applying the current methodology, and thus its absolute configuration was elucidated for the first time. Asymmetric synthesis of an effective CRTH2 receptor antagonist has been demonstrated utilizing this method as a key step.

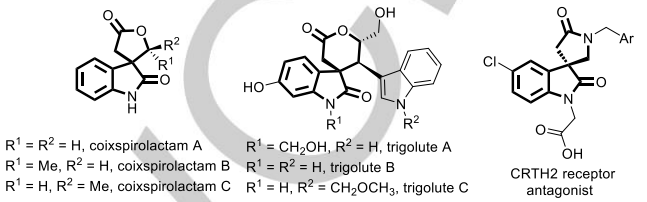
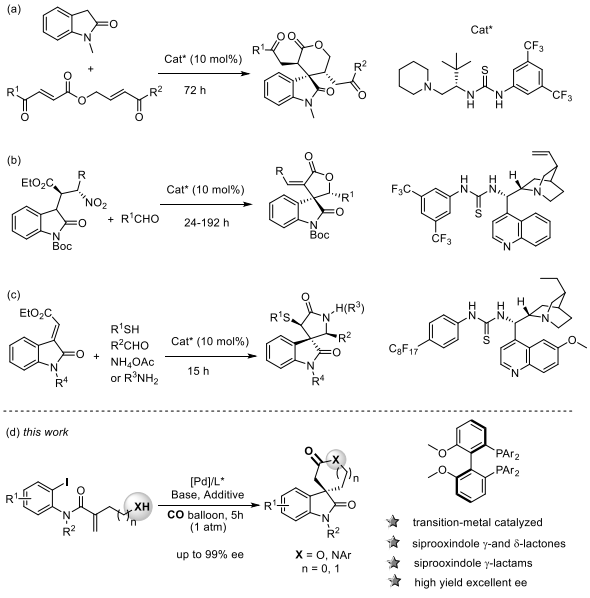


Figure 1. Representative natural products and bioactive molecules containing the spirooxindole lactone or lactam framework.

2-Oxindole spiro-fused with a lactone or lactam moiety is a privileged three-dimensional framework existing across a large family of alkaloid natural products with diverse biological profiles.[1] For example, coixspirolactams A-C, isolated from traditional Chinese medicine adlay bran,[2] exhibit potent anti-proliferative effect on human lung cancer cell A549, human colorectal carcinoma cell HT-29, and COLO 205 (Figure 1).[3] Although their optical rotation was reported, the absolute configuration of the spirocarbon was not elucidated.[3a] Trigolutes A-C are extracted from the twigs of trigonostemonlutescens and show promising activity in the treatment of hemorrhagic fever with renal syndrome.[4] Lactam derivatives of spirooxindole are antagonists on the mouse CRTH2 receptor, which may directly mediate the recruitment of inflammatory cells in allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis.[5] The *S*-enantiomer which is separated by chiral preparative HPLC is about 52 times more active than the *R*-isomer. Therefore, highly enantioselective assembly of these spirooxindole lactones/lactams is of great interest in medicinal chemistry.[6]

Although stereoselective construction of the spirooxindole has been well established,[7] asymmetric synthesis of all-carbon spirooxindoles containing a lactone or lactam moiety has had limited success.[8] In 2014, Liang and Xu developed a novel approach to chiral spirooxindole δ-lactones through bifunctional thiourea catalyzed [5 + 1] annulation of oxindoles with ester-linked bisenones (a, Scheme 1).[8a] An enantioselective synthesis of spirooxindole alkylidene-γ-lactones was successfully developed by Quintavalla through organocatalytic Aldol reaction of C3 alkylated oxindoles with aldehydes (b).[8b] The first asymmetric synthesis of spirooxindoles γ-lactam was accessed by an oxoindolin-3-ylidene involving a four-component reaction promoted by a recyclable fluorous bifunctional cinchona alkaloid/thiourea organocatalyst (c).[8c] Each of these reactions must start from oxindoles or their derivatives to deliver a specific skeleton in normally long reaction time (up to 8 days). Therefore, a general and highly enantioselective approach applicable to all of these spirooxindole γ- and δ-lactones/lactams starting from non-oxindole-based materials under mild conditions is highly desirable.



Scheme 1. Methods to synthesize all-carbon spirooxindole lactones or lactams.

[*] H. Hu, F. Teng, J. Liu, W. Hu, Dr. S. Luo, Prof. Dr. Q. Zhu
State Key Laboratory of Respiratory Disease, Guangzhou Institutes of Biomedicine and Health
Chinese Academy of Sciences
190 Kaiyuan Avenue, Guangzhou 510530, China
E-mail: luo_shuang@gibh.ac.cn; zhu_qiang@gibh.ac.cn

H. Hu, F. Teng, J. Liu, W. Hu, Dr. S. Luo, Prof. Dr. Q. Zhu
University of Chinese Academy of Science
No. 19(A) Yuquan Road, Shijingshan District, Beijing 100049, China

H. Hu, F. Teng, W. Hu, Dr. S. Luo, Prof. Dr. Q. Zhu
Guangzhou Regenerative Medicine and Health Guangdong Laboratory
Guangzhou 510005, China

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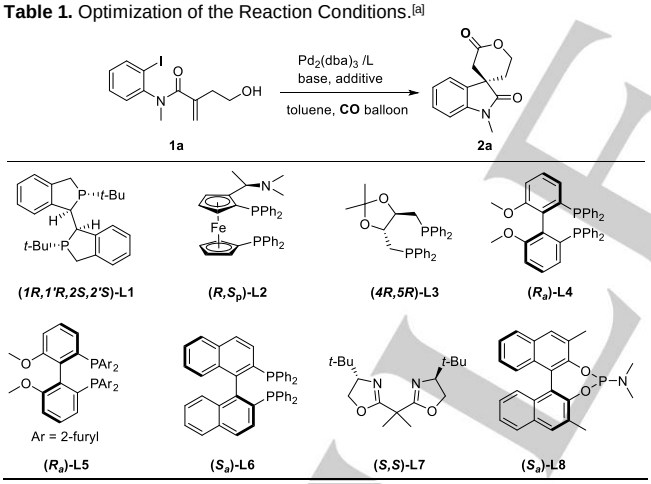
On the other hand, palladium-catalyzed carbonylation offers routine access to carbonyl derivatives including lactones and lactams.[9] Chiral ligand-induced asymmetric carbonylation is occasionally successful mainly in the area of hydroformylation of alkenes[10] together with scattered examples of other reaction types.[11] Meanwhile, carbopalladation initiated transformations in which the formation of Heck products by β-elimination is prohibited or unfavorable can provide efficient approaches to construct all-carbon quaternary stereocenters.[12] The process combining carbopalladation and CO insertion (also known as Heck/carbonylation) is common. [13] However, an enantioselective version of this process to give carbonyl compounds with a quaternary stereocenter is surprisingly scarce.[14] Recently, Correia reported the first successful asymmetric Heck carbonylative Suzuki coupling and esterification reaction enabled by a chiral N,N ligand to deliver ketone or ester substituted quaternary carbon containing dihydrobenzofurans in up to 96% ee.[14b] We envisaged that lactonization or lactamization would take place following Pd-assisted CO insertion when an alkenyl substrate with an embedded oxygen- or nitrogen-based nucleophile is applied (d). The ring size could be modulated by changing the distance between the nucleophilic atom and the alkenyl moiety. Thus, a general method to build spirooxindole γ- and δ-lactones and lactams could be expected as well as in their enantioenriched form. Thus, this method would be expected to find potential application in the synthesis of related natural products and bioactive compounds enantioselectively.

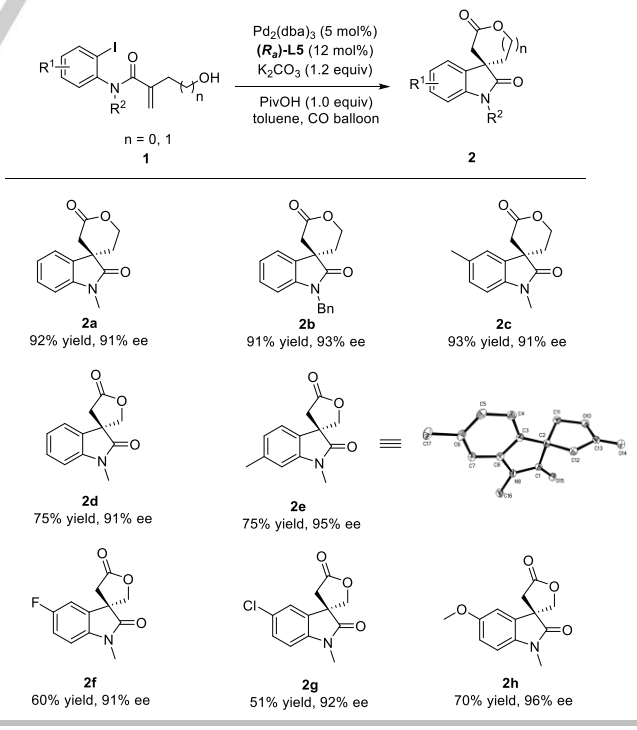
Table 1. Optimization of the Reaction Conditions.[a]



entry	ligand	base	additive	yield (%)[b]	ee (%)[c]
1	PPh_3	DMAP	-	92	-
2	**L1**	DMAP	-	13	-3
3	**L2**	DMAP	-	39	-32
4	**L3**	DMAP	-	20	2
5	**L4**	DMAP	-	12	52
6	**L5**	DMAP	-	17	88
7	**L6**	DMAP	-	9	-15
8	**L7**	DMAP	-	22	7
9	**L8**	DMAP	-	92	11
10	**L5**	DMAP	PivOH	28	91
11	**L5**	Cs_2CO_3	PivOH	53	84
12	**L5**	K_2CO_3	PivOH	92	91
13	**L5**	K_2CO_3	-	46	89

[a] Reaction conditions: **1a** (0.1 mmol), $Pd_2(dba)_3$ (entries 1-10: 4 mol%; entries 11-13: 5 mol%), ligand (entries 2-8: 8 mol%; entries 1 and 9: 16 mol%; entry 10: 10 mol%; entries 11-13: 12 mol%), base (entries 1-11: 1.5 equiv; entry 12-13: 1.2 equiv), PivOH (entry 10: 0.75 equiv; entries 11-13: 1.0 equiv), toluene (1.0 mL), 60 °C, 5 h, CO balloon (1 atm). [b] Isolated yield. [c] Determined by HPLC analysis. DMAP = *N, N*-dimethylpyridin-4-amine.

To test this hypothesis, the *N*-(2-iodophenyl)-*N*-methylacrylamide derivative **1a** bearing a branched homoallylic alcohol was investigated in Pd-catalyzed carbonylation. When PPh_3 was used as a ligand in the presence of balloon pressure of CO, intramolecular carbopalladation followed by carbonylative lactonization occurred to give a racemic spirooxindole δ-lactone **2a** in excellent yield (92%, entry1, Table1). Encouraged by this result, a number of chiral bidentate phosphine ligands were then screened to test their efficiency in asymmetric induction (entries 2-6). To our delight, reaction with **L5** could deliver the product with good enantioselectivity (88% ee) albeit in a low chemical yield (17%, entry 6). Other kinds of ligands, including bisoxazoline **L7** and BINOL-derived phosphoramidite **L8** gave **2a** in poor enantioselectivity. When PivOH was used as an additive, both the yield and enantioselectivity were increased slightly (entry 10). By replacing the organic base DMAP with K_2CO_3, a satisfactory yield of 92% was reached without any loss of ee (entry 12).



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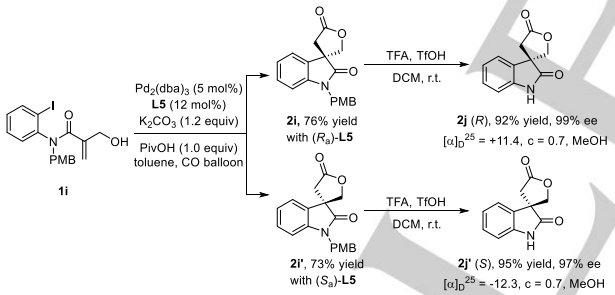
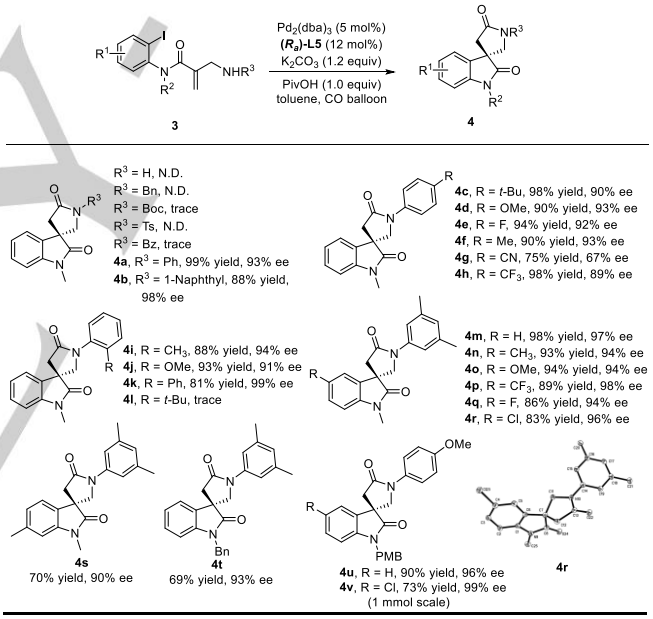
Scheme 2. Scope of lactones. Reaction conditions: **1** (0.1 mmol), $Pd_2(dba)_3$ (5 mol%), **L5** (12 mol%), base (1.2 equiv), PivOH (1.0 equiv), toluene (1.0 mL), 60 °C, 5 h, CO balloon (1 atm).

With the optimal reaction conditions in hand, the substrate scope for the synthesis of spirooxindole δ-lactone was briefly investigated (Scheme 2). When changing the substituent on the nitrogen from methyl to benzyl or adding a methyl group on the aromatic ring, the corresponding products **2b** and **2c** were obtained in excellent yields with 93% and 91% ee, respectively. To synthesize a five-membered spirolactone, substrates in which the alcoholic oxygen was one carbon closer to the alkenyl moiety were synthesized and tested. Under the same reaction conditions, the spirooxindole γ-lactone **2d** was produced in 75% yield with 91% ee. The formation of other substituted γ-lactones **2e**-**2h** was also less efficient (51-75% yield), while the enantioselectivities were maintained or even improved (up to 96% ee for **2h**). Unfortunately, only primary alcohols were able to trap the acyl palladium species. When more sterically hindered secondary alcohol was used as the substrate, the reaction failed to provide the desired product. The stereochemistry of **2e** was confirmed unambiguously as the *R* configuration via X-ray crystallographic analysis (see the Supporting Information (SI) for details). To elucidate the absolute stereochemistry of coixspirolactam A, both enantiomers **2j** and **2j'** were synthesized conveniently through a two-step sequence with 99% and 97% ee, respectively (Scheme 3). By comparing their optical rotations with the reported value ($[\alpha]_D^{25}$ = +9.7, c = 0.70, MeOH),[3a] the structure of coixspirolactam A was confirmed as **2j**.



Scheme 3. Elucidation of the absolute configuration of coixspirolactam A. PMB = 4-methoxybenzyl; TFA = trifluoroacetic acid; TfOH = trifluoromethanesulfonic acid.

In addition to spirooxindole γ- and δ-lactones, their lactam analogues could also be produced starting from similar substrates containing an intramolecular nitrogen-based nucleophile (Scheme 4). Initially, unprotected 2-(aminomethyl)-*N*-(2-iodophenyl)-*N*-methylacrylamide was tested under the same reaction conditions. Unfortunately, the reaction only led to a messy mixture without any separable product. A series of common nitrogen protecting groups such as Bn, Boc, Ts, and Bz were then used but none of these substrates could deliver the desired lactams. Amazingly, phenyl and 1-naphthyl protected substrates could react smoothly delivering **4a** and **4b** in 99% yield (93% ee) and 88% yield (98% ee), respectively. A wide array of substituents (*t*-Bu, OMe, Me, F, and CF_3) at the *para* position of the protecting phenyl group were tolerable to generate the corresponding products **4c-4f** and **4h** in good yields with ee ranging from 89% to 93%. However, substrate **3g** containing a CN group led to **4g** in poor yield and ee probably due to the coordination ability of CN to Pd catalyst. Products **4i**-**4k** containing an *ortho* Me, OMe and Ph were obtained in good yields with excellent enantioselectivity (up to 99% ee), while the formation of *ortho t*-butyl substituted **4l** failed. Excellent result (**4m**) for both isolated yield (98%) and enantioselectivity (97% ee) was identified when applying 3,5-dimethyphenyl as a protecting group. Subsequently, the compatibility of substituents on the iodobenzene ring was then investigated with the optimal nitrogen protecting group fixed. The resulting Heck/carbonylative lactamization proceeded smoothly to deliver **4n-4s** in good to excellent yields and enantioselectivity. It was noted that 1 mmol-scale synthesis of **4v** was also highly stereoselective (99% ee), sacrificing isolated yield to some extent (73% yield). The stereochemistry of **4r** was determined by X-ray crystallographic analysis as *R* configuration similar to the analogous lactones.



Scheme 4. Scope of lactams. Reaction conditions: **3** (0.1 mmol), $Pd_2(dba)_3$ (5 mol%), **L5** (12 mol%), base (1.2 equiv), PivOH (1.0 equiv), toluene (1.0 mL), 60 °C, 5 h, CO balloon (1 atm). Ts = tosyl; Bz = benzoyl.

Although all of the resulting spirooxindole γ-lactams were aryl protected, removal of the aryl protection and further modification on the nitrogen could be realized. For example, the *p*-methoxyphenyl in **4v** was deprotected in 70% yield under oxidative conditions without any influence on the stereogenic center (a, Scheme 5). The resulting NH free lactam **5** could be served as a key intermediate for the synthesis of antagonist on the human CRTH2 receptor.[5] The following four steps of routine transformations including benzylation, deprotection of the PMB, alkylation, and hydrolysis afforded the antagonist **8** enantioselectively (98% ee, a). In addition, the synthesis of enantiomerically pure spirooxindole δ-lactam **10** was accessed by making a detour

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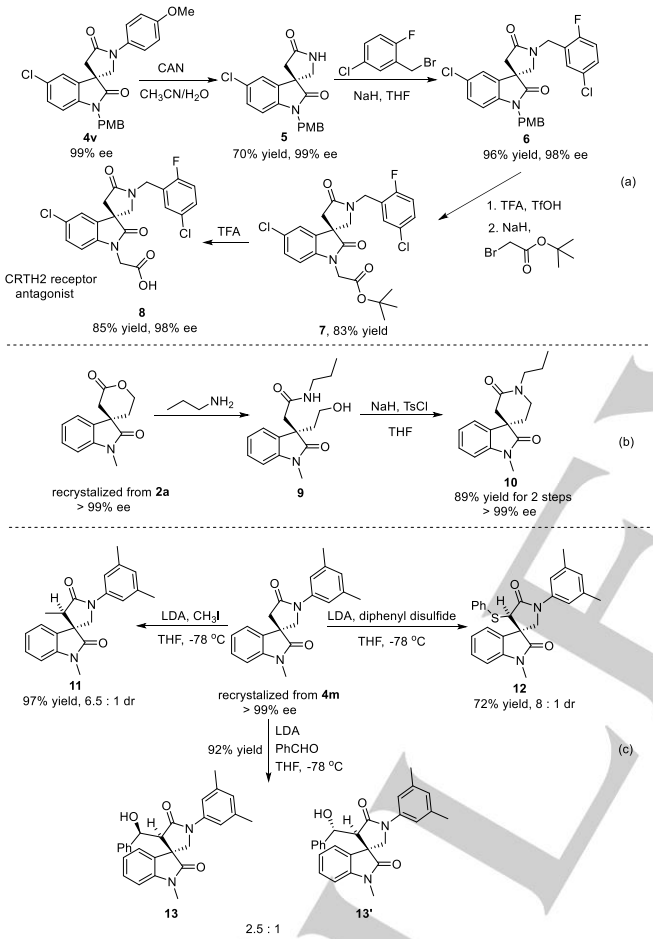
around lactone analog **2a** due to the difficulty in the synthesis of the corresponding homoallylic amino precursor (b). Thus, all of the four oxindole-based scaffolds spiro-fused with a lactone or lactam moiety were accessible enantioselectively. Moreover, the new stereogenic centers introduced around the spiro carbon were accessible (c). For instances, treatment of **4m** with LDA at -78 °C and electrophiles could afford methylated product **11** (97% yield, 6.5:1 dr) and sulfurated derivative **12** (72% yield, 8:1 dr) diastereoselectively. When benzaldehyde was used as an electrophilic reagent, two additional chiral centers were generated simultaneously. Only two diastereoisomers **13** and **13'** were isolated by column chromatography at a ratio of 2.5 : 1.



Scheme 5. Deprotection and further transformation of **4v** (a); synthesis of spirooxindole δ-lactam **10** (b), and derivatization of **4m** (c). PMB = 4-methoxybenzyl; CAN = ceric ammonium nitrate; TsCl = tosyl chloride; LDA = lithium diisopropylamide.

The transition state that determines the asymmetric introduction is proposed in Figure 2. After oxidative addition, the terminal alkene should approach the Pd(II) centre, tightly coordinated with a bidentate phosphine ligand, at an orientation with the side chain stretching to the open area away from ligand (left, Figure 2). Then, migratory insertion of the alkenyl moiety to Ar-Pd(II) forms the quaternary carbon centre stereoselectively, and an alkyl Pd(II) species is ready for CO insertion and nucleophilic cyclization. This favorable approach leads to spirooxindole lactones or lactams in (*R*)-configuration as we observed.

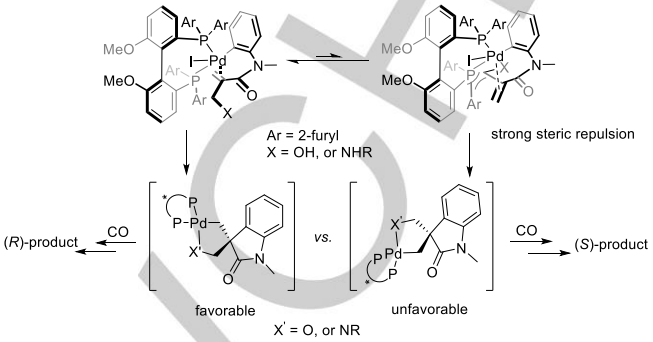


Figure 2. Plausible model for asymmetric introduction.

In conclusion, we developed a general approach to construct enantiomerically pure all-carbon spirooxindole γ- and δ-lactones/lactams through palladium-catalyzed carbonylative Heck cyclization. This is the first case of transition-metal-catalyzed asymmetric synthesis of these valuable skeletons starting from non-oxindole-based materials with good functional group tolerance and excellent enantioselectivity. By utilizing the present methodology as a key step, natural product coixspirolactam A as well as an effective CRTH2 receptor antagonist **8** have been synthesized conveniently. These spirooxindole lactones/lactams could be easily derivatized to introduce more stereogenic cetrers around the chiral quaternary spiro carbon in a diastereoselective manner. The proposed model for asymmetric introduction offers hints for designing new enantioselective Heck/carbonylation reactions.

Accession Codes

CCDC 1889073-1889074 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Keywords: palladium catalyze • asymmetric carbonylation • spirooxindole lactones and lactams

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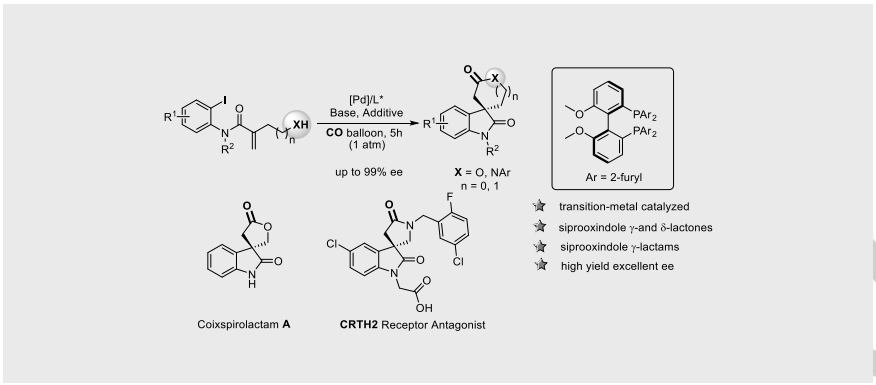

Huaanzi Hu, Fan Teng, Jian Liu, Weiming Hu, Shuang Luo, Qiang Zhu**

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Enantioselective Synthesis of 2-Oxindole Spiro-fused Lactone and Lactam via Heck/Carbonylative Cylization: Method Development and Applications

An efficient one-pot assembly of all-carbon spirooxindole compounds from non-oxindole-based materials has been developed through palladium-catalyzed asymmetric tandem Heck/carbonylative lactonization and lactamization. Diversified spirooxindole γ-and δ-lactones/lactams were accessed in high yields with good to excellent enantioselectivity (up to 99% ee) under mild conditions. Natural product coixspirolactam A was conveniently synthesized by applying the current methodology, and thus its absolute configuration was elucidated for the first time. The asymmetric synthesis of an effective CRTH2 receptor antagonist has been demonstrated utilizing this method as a key step.