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Pd/Cu-Catalyzed Enantioselective Sequential Heck-Sonogashira Coupling: Asymmetric Synthesis of Oxindoles Containing Trifluoromethylated Quaternary Stereogenic Centers

Xingfeng Bai, Caizhi Wu, Shaozhong Ge* and Yixin Lu*

Dedicated to John F. Hartwig for his 55th birthday

Abstract: An asymmetric palladium and copper co-catalyzed sequential Heck/Sonogashira reaction between *o*-iodoacrylanilides and terminal alkynes to synthesize chiral oxindoles was developed. In particular, a wide range of CF_3-substituted *o*-iodoacrylanilides reacted with terminal alkynes, affording the corresponding chiral oxindoles containing trifluoromethylated quaternary stereogenic centers in high isolated yields with excellent enantioselectivity (94-98% ee). This asymmetric Heck/Sonogashira reaction provides a general approach to access oxindole derivatives containing quaternary stereogenic centers including CF_3-substituted ones.

Organofluorine compounds have found broad applications in medicinal chemistry and agrochemistry because of their stability, reactivity, and unique biological activities.[1] On the other hand, chiral 3,3-disubstituted oxindole cores are important structure motifs that can be frequently found in many bioactive natural products and synthetic analogues.[2] Therefore, it is highly desirable to develop enantioselective protocols to access fluorine-containing 3,3-disubstituted oxindoles because the incorporation of fluorine into these oxindole molecules may endow them new biological properties. Indeed, it has been recently shown that the introduction of a fluorine atom or a trifluoromethyl group to the C3 position of an oxindole molecule enhances its biological activities.[3] While enantioselective approaches to prepare chiral 3-fluorinated oxindoles have been well established,[4] methods to prepare enantio-enriched oxindoles containing CF_3-substituted quaternary stereogenic carbons[5] at the C3-position are rather limited. To the best of our knowledge, asymmetric radical trifluoromethylation of 3-substituted oxindoles is the only known reaction that affords enantio-enriched 3-trifluoromethyloxindoles, which has been recently disclosed by Katayev and co-workers (Figure 1A).[6]

In recent years, enantioselective intramolecular Heck reactions of anilide-tethered haloarene-alkenes have been emerging as effective approaches to prepare chiral oxindole cores.[7] However, only aryl- or alkyl-substituted alkenes have been studied for these asymmetric reactions, and the substrates that contain CF_3-substituted alkenes have not been employed for this Heck-type enantioselective cyclization. In general, Heck reactions of CF_3-substituted alkenes have been much less studied than those of common alkenes, and this is largely due to potential β-fluorine elimination.[8] There was only one example of Pd-catalyzed Heck-type cyclization employing CF_3-substittued alkenes, and CF_3-groups in starting alkenes were converted to CF_2-groups through β-fluorine elimination.[8d] Therefore, it remains elusive to develop Heck-type asymmetric cyclization with CF_3-substituted alkenes to build CF_3-substituted quaternary stereogenic centers.

During our continuous effort in developing enantioselective protocols to make chiral oxindoles,[9] we became interested in the synthesis of chiral oxindoles containing trifluoromethylated quaternary stereocenters at the C3-position. We envisioned that the alkylpalladium species (**I** in Figure 1B) resulting from the carbopalladation step would contain fluorine atoms at the γ-carbon, which suppresses the potential β-fluorine elimination and thus enables the retention of CF_3-substituents in final oxindole products. Herein, we report a highly enantioselective palladium and copper co-catalyzed sequential Heck cyclization/Sonogashira reaction[10] of CF_3-substituted *o*-iodoacrylanilides with alkynes to access chiral 3,3-substituted oxindoles (Figure 1B).[10g] In addition, we also showed that other alkyl- or aryl-substituted *o*-iodocrylanilides underwent this asymmetric reaction to afford propargyl-substituted oxindoles with excellent enantioselectivities.

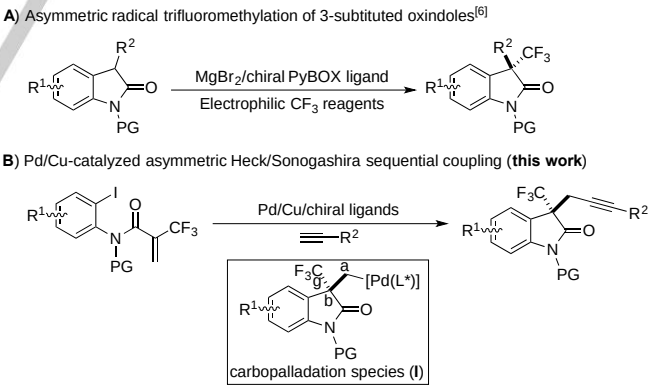

Figure 1. Enantioseletive synthesis of CF_3-substituted oxindoles.

We initiated our study on this sequential asymmetric Heck-Sonogashira coupling reaction by identifying reliable conditions and selective palladium catalysts for the reaction between CF_3-substituted *o*-iodoacrylanilide **1a** and phenylacetylene **2a** with an attempt to synthesize chiral 3-trifluoromethylated oxindole **3a**. The results of selected evaluation experiments are summarized in Table 1. First, we chose a palladium catalyst generated in situ from $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and a Josiphos derivative **L1** to test various copper cocatalysts, bases, solvents, and temperatures for this model reaction (see the Supporting Information for the

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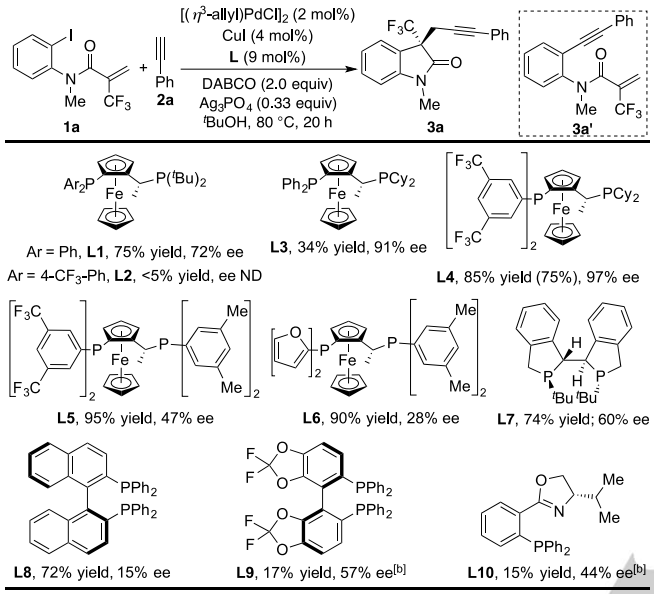
details), and found that the reaction conducted in *tert*-butanol proceeded to offer full conversion of **1a** in 20 h at 80 °C in the presence of CuI as co-catalyst and DABCO/Ag_3PO_4 as bases. This reaction yielded the desired oxindole product **3a** in 75% isolated yield, but with modest enantioselectivity (72% ee).

Table 1. Evaluation of chiral ligands for this Pd-catalyzed asymmetric Heck/Sonogashira reaction of **1a** with phenylacetylene **2a**.[a]

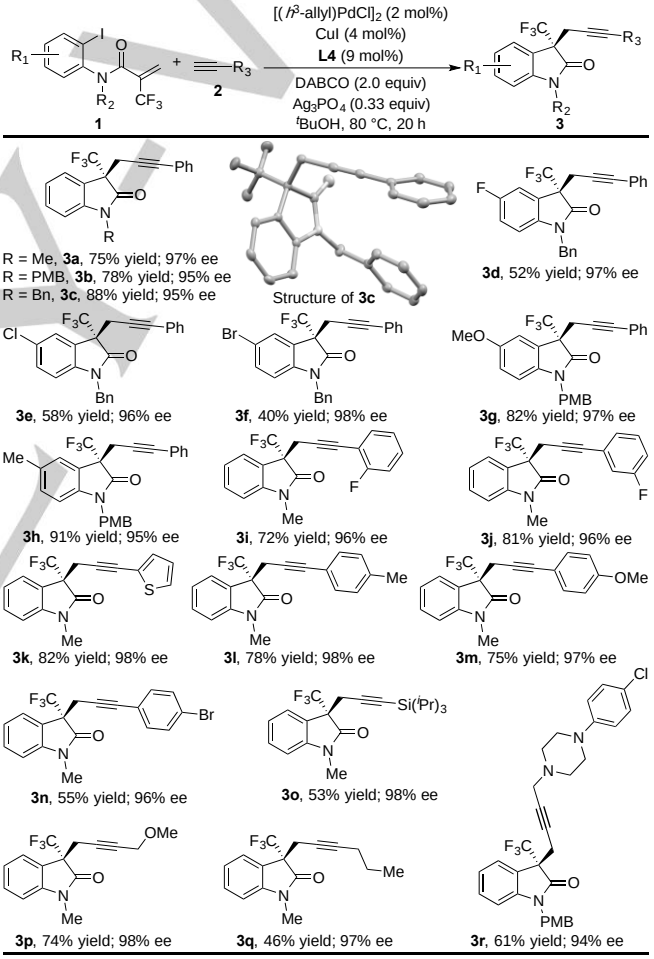


[a] Reaction conditions: **1a** (0.200 mmol), phenylacetylene **2a** (0.300 mmol), [(η^3-C_3H_5)PdCl]$_2$ (8.0 μmol), ligand (18.0 μmol), CuI (8.0 μmol), DABCO (1,4-diazabicyclo[2,2,2]octane, 0.400 mmol), Ag_3PO_4 (0.066 mmol), *t*-BuOH (1 mL), 80 °C, 20 h, yields were determined by NMR analysis with CH_2Br_2 as internal standard; *ee* was determined by chiral HPLC analysis. [b] The other enantiomer of **3a** was obtained. ND: Not Determined.

Subsequently, we evaluated a series of chiral ligands for this reaction under these identified conditions. First, we tested several other chiral ligands of Josiphos family (**L2**–**L6**) for this reaction. The reaction conducted with a palladium catalyst containing **L2** yielded only a trace amount of cyclic product **3a** (<5%) and the major product for this reaction was the uncyclized compound **3a'**, which was formed by direct Sonogashira coupling between **1a** and **2a**. To our delight, the reaction run with **L3**-ligated palladium catalyst afforded **3a** with high enantioselectivity (91%), albeit in low yield (35%). In particular, the reaction employing ligand **L4** proceeded to full conversion of **1a**, furnishing **3a** in 85% yield with excellent enantioselectivity (97% ee). Catalysts generated from **L5** or **L6**, two Josiphos derivative ligands with aryl groups on both phosphine atoms, were less enantioselective for this Pd-catalyzed transformation. In addition, we also tested other chiral ligands, such as (*R*,*R*,*S*,*S*)-duanphos (**L7**), (*S*)-binap (**L8**), (*R*)-difluorphos (**L9**), and (*S*)-^{i}Pr-Phox (**L10**), but these reactions produced the desired oxindole **3a** either in low yields or with modest enantioselectivities.

With the identified catalysts and reliable conditions in hand, we studied the scope of CF_3-substituted *o*-iodoacrylanilides and alkynes for this enantioselective transformation, and the results are summarized in Table 2. *o*-Iodoacrylanilides containing various substituents on the anilide nitrogen atom, such as methyl (**1a**), *para*-methoxyphenyl (PMB, **1b**) and benzyl (**1c**) groups, reacted with phenylacetylene **2a** and afforded chiral CF_3-substituted oxindoles **3a**–**3c** in high yields with high enantioselectivities (>95% ee). The absolute configuration of **3c** was assigned as (*S*) by single crystal X-ray diffraction analysis. In addition, several other CF_3-substituted *o*-iodoacrylanilides containing various substituents, such as fluoro (**1d**), chloro (**1e**), bromo (**1f**), methyl (**1g**) and methoxy (**1h**) groups, on the anilides also reacted with phenylacetylene **1a**, yielding chiral oxindoles **3d**–**3h** with excellent enantioselectivities (96–98% ee). Furthermore, we also showed that a wide range of aryl- and alkyl-substituted terminal alkynes (**2i**–**2p**) reacted with CF_3-substituted *o*-iodoacrylanilide **1a** to produce the corresponding chiral oxindoles (**3i**–**3p**) in good yields (46–82%) and excellent enantioselectivities (96–98% ee).

Table 2. Scope of CF_3-substituted *o*-iodoacrylanilides and alkynes.[a]



[a] Reaction conditions: CF_3-substituted *o*-iodoacrylalinide (0.200 mmol), alkyne (0.300 mmol), **L4** (18.0 μmol), and other conditions are identical to those listed in Table 1.

As asymmetric Pd/Cu-catalyzed sequential Heck/Sonogashira coupling between alkyl- or aryl-substituted *o*-iodoacrylanilides and terminal alkynes to access oxindoles containing quaternary stereogenic centers remains unknown, we subsequently extended our study to non-CF_3-substituted *o*-iodoacrylanilides, and the results are summarized in Table 3. Under the conditions

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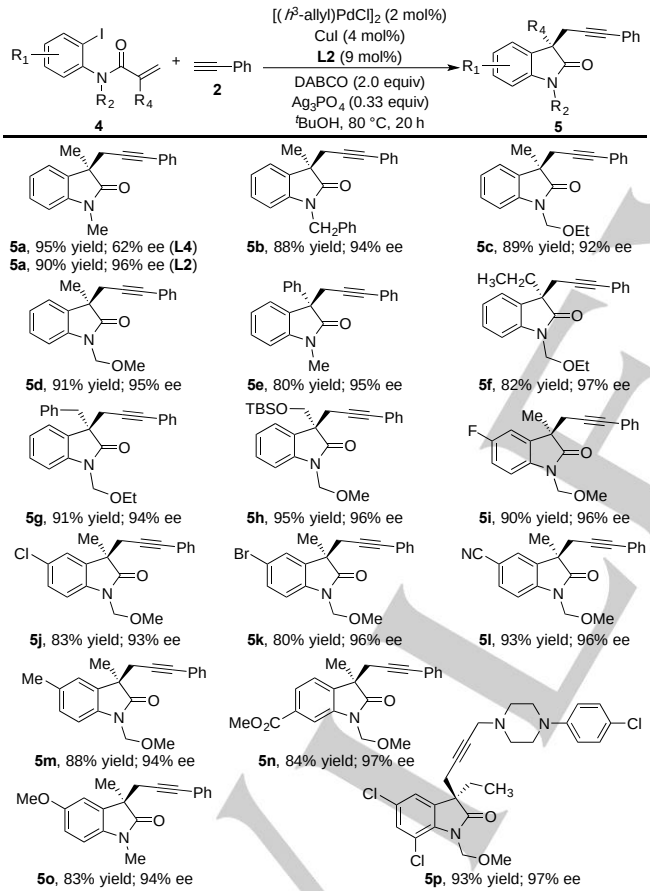
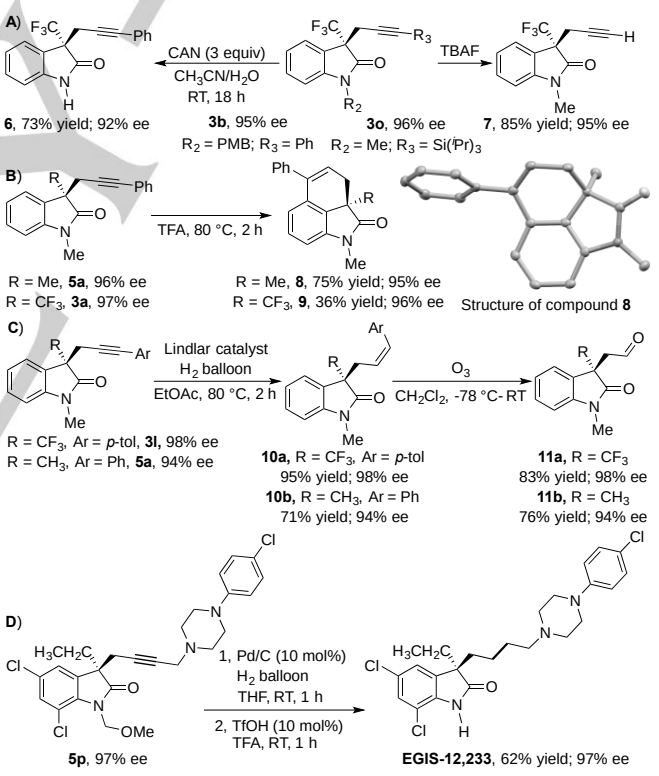
identified for the reaction of CF_3-substituted *o*-iodoacrylanilides, substrate **4a**, the CH_3-congener of *o*-iodoacrylanilide **1a**, reacted with alkyne **2a** to afford oxindole **5a** in high isolated yield (95%), but with only modest enantioselectivity (62% ee). Upon the evaluation of other Josiphos derivative ligands **L1**–**L6** (see Supporting Information for the details), we found that in the presence of **L2**, the reaction between **4a** and **1a** gave oxindole **5a** not only in high isolated yield (90%) but also with excellent enantioselectivity (96% ee). When catalyzed by this ligand/palladium combination, a variety of *o*-iodoacrylanilides containing various substituents on the alkene unit and the anilide nitrogen reacted with alkyne **2a** to produce the corresponding chiral oxindoles in high isolated yields (80–95%) with high enantioselectivities (92–97% ee). This reaction showed good functional group tolerance, and several reactive groups, such as methoxymethyl (**5d**), siloxyether (**5h**), chloro (**5j** and **5p**), bromo (**5k**), cyano (**5l**), and carboxylic ester group (**5n**), could be tolerated under standard reaction conditions.

Table 3. Scope of *o*-iodoacrylanilides and alkynes.[a]



[a] Reaction conditions: *o*-iodoacrylalinide (0.200 mmol), alkyne (0.300 mmol), **L2** (18.0 μmol), and other conditions are identical to those listed in Table 1.

The chiral oxindole products of these enantioselective Pd/Cu-catalyzed Heck/Sonogashira coupling reactions can undergo several enantiospecific organic transformations (Scheme 1). For example, the *p*-methoxyphenyl (PMB) group in oxindole **3b** could be removed with CAN reagent to provide unprotected oxindole **6** in 73% yield while keeping the alkyne functionality intact (Scheme 1, A). The silyl group of **3o** could be also readily removed using TBAF to generate a terminal alkyne product **7** in 85% yield (Scheme 1, A). In addition, the alkyne functionality of **5a** underwent annelation with the phenyl group in the oxindole core to form a tricyclic compound **8** in 75% yield (Scheme 1, B). The structure of **8** obtained by single X-ray crystal diffraction analysis confirmed the absolute configuration of compound **5a**. Similarly, the CF_3-substituted oxindole **3a** also underwent this annelation to afford compound **9**, albeit with a lower yield (Scheme 1, B). The alkyne functionality in CF_3- and CH_3-substituted oxindoles (**3l** and **5a**) could undergo *cis*-semihydrogenation in the presence of Lindlar catalyst to afford *Z*-alkenes **10a** and **10b**, respectively, in high isolated yields with 100% enantiospecificity (Scheme 1, C). Furthermore, ozonolysis of **10a** and **10b** gave chiral aldehyde-containing oxindoles **11a** and **11b** in high yields, respectively (Scheme 1, C). To highlight the synthetic utility of this Pd/Cu-catalyzed Heck/Sonogashira coupling, we showcased an enantioselective synthesis of **EGIS-12,233**,[11] a potent and selective antagonist for 5-$HT_{6/7}$ receptors, by catalytic hydrogenation of chiral oxindole **5p** followed by removal of the methoxymethyl protecting group (Scheme 1, D).



Scheme 1. Further transformations of chiral oxindole products.

In summary, we have developed a highly enantioselective protocol to synthesize chiral oxindoles containing quaternary stereogenic centers, particularly trifluoromethylated ones, by Pd/Cu-catalyzed asymmetric Heck/Sonogashira sequential coupling reaction. In the presence of chiral palladium catalysts containing Joshiphos derivative ligands **L2** or **L4**, a wide range of *o*-iodoacrylanilides reacted with terminal alkynes to afford the

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corresponding chiral oxindoles in high isolated yields with excellent enantioselectivity. The chiral oxindole products can be readily converted to several other oxindole derivatives by standard functional group interconversions. Therefore, this enantioselective Pd/Cu-catalyzed Heck/Sonogashira sequential reaction provides a versatile platform to access a variety of oxindole compounds containing quaternary stereogenic centers.

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Keywords: trifluoromethylated quaternary stereocenters • Heck reaction • Sonogashira reaction • oxindole • asymmetric catalysis

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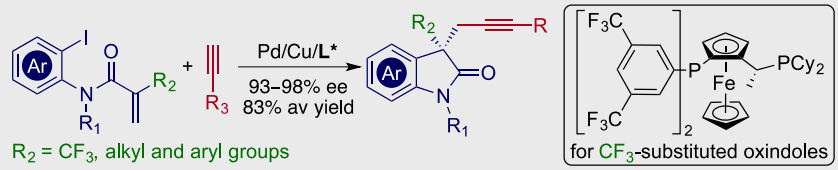

Trifluoromethylated Oxindoles: A highly enantioselective Pd/Cu-catalyzed Heck/Sonogashira sequential coupling reaction was developed to prepare chiral oxindoles containing quaternary stereogenic centers, particularly trifluoromethyated ones. The synthetic utilities of this enantioselective protocol were exemplified through several stereospecific derivatizations and the synthesis of **EGIS-12,233**.

Xingfeng Bai, Caizhi Wu, Shaozhong Ge and Yixin Lu**

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Pd/Cu-Catalyzed Enantioselective Sequential Heck-Sonogashira Coupling: Asymmetric Synthesis of Oxindoles Containing Trifluoromethylated Quaternary Stereogenic Centers

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