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Construction of Atropisomeric 3-Arylindoles via Enantioselective Cacchi Reaction

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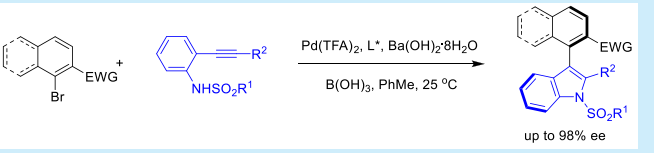
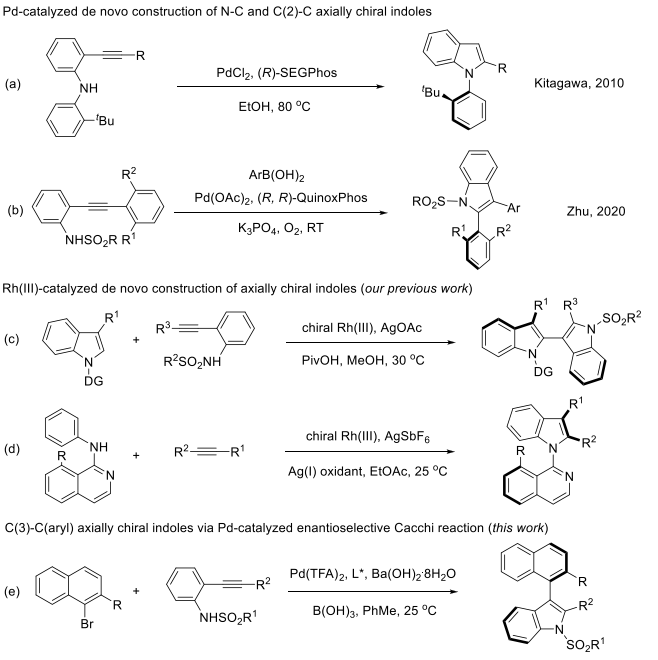
ABSTRACT: The *de novo* construction of axially chiral 3-arylindoles bearing a C(3)−C(aryl) chiral axis has been realized by Pd-catalyzed enantioselective Cacchi reaction between aryl bromides and *o*-alkynylanilines. The reaction proceeded under mild conditions in high yields and excellent enantioselectivities.



Indoles make up an important class of heteroaromatics featured in a wide range of natural products, pharmaceuticals, agrochemicals, and organic materials.[1] In particular, axially chiral arylindoles widely exist in the nature and have also been used as ligands in asymmetric catalysis.[2] Although great effort has been devoted to the construction of C−C and C−N axially chiral arylindoles via organocatalysis[3] or metal catalysis,[4] the asymmetric synthesis of atropisomeric indoles remains underexplored partially due to their relatively low barrier of racemization.[3,4]

In terms of metal catalysis, direct functionalization of an existing indole ring is a common method for the synthesis of axially chiral indoles.[5] It is worth noting that the Cacchi reaction, developed by Cacchi and co-workers in 1992,[6] has become a convenient and important approach for constructing substituted indoles.[7] In 2010, Kitagawa described a palladium-catalyzed cyclization of 2-alkynylaniline derivatives for the synthesis of C−N axially chiral 1-arylindoles (Scheme 1a).[8] Zhu and co-workers recently developed a palladium-catalyzed enantioselective oxidative Cacchi reaction of sterically hindered alkynes for the synthesis of indoles bearing a chiral C(2)−aryl axis with arylboronic acids as arylating reagents (Scheme 1b).[9] Our group realized Rh(III)-catalyzed oxidative coupling of indoles and *o*-alkynylanilines for the asymmetric synthesis of 2,3′-biindolyls by merging C−H activation and nucleophilic cyclization (Scheme 1c).[10] Very recently, we reported the Rh(III)-catalyzed C−H activation of anilines bearing an *N*-isoquinolyl directing group for oxidative [3+2] annulation with internal alkynes, affording C−N axially chiral indoles (Scheme 1d).[11] Encouraged by these discoveries and as a continuation of our interest in nucleophilic cyclization[10] toward construction of axially chiral biaryls,[12] we now report construction of indoles bearing a C(3)−C(aryl) chiral axis via Pd-catalyzed enantioselective Cacchi reaction between sterically hindered aryl bromides and *o*-alkynylanilines (Scheme 1e). Although indoles with a chiral C(2)−C(aryl) axis have been accessed via oxidative Cacchi reactions using arylboronic acids,[9] the redox-neutral version, which is the original definition of the Cacchi reaction, offers indoles with a complementary C(3)−C chiral axis.

Scheme 1. Metal-Catalyzed *De Novo* Construction of Axially Chiral Indoles



Prior to the development of the asymmetric system, the racemic version of Pd-catalyzed Cacchi reaction of methyl 1-bromo-2-naphthoate (**1a**) and *o*-alkynylaniline (**2a**) was

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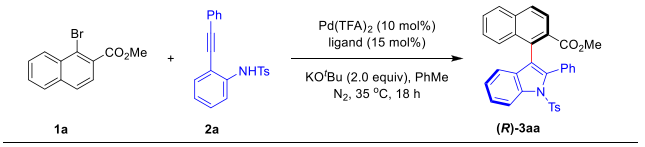
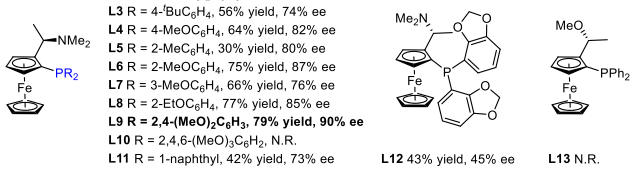
examined (see Table S1). The desired racemic product was obtained in 75% yield when the reaction was conducted with $Pd(OAc)_2$ as the catalyst, 1,2-bis(diphenylphosphenyl)benzene (dppbz) as the ligand, and Cs_2CO_3 as the base in toluene at 100 °C. Subsequently, various chiral ligands were investigated under these initially optimized conditions except at a lower reaction temperature (see Table S2). An enantioselectivity of 65% ee was achieved when ferrocene-based N,P-ligand **SL18** was employed at 70 °C. After an additional series of experiments had been performed to optimize the solvents, bases, temperatures, and palladium sources (see Table S3), the reaction afforded product **3aa** in moderate yield with 81% ee when using $Pd(TFA)_2$ as the catalyst and KO^{t}Bu as the base in toluene at 35 °C. Inspired by these initial results, we further applied modified ferrocene-based N,P-ligands for optimization studies. Thus, ferrocene-based N,P-ligands **L1**−**12** and O,P-ligand **L13** were investigated (Scheme 2). Among all of these ligands, ligand **L9** gave product **3aa** in 79% yield with 90% ee.

Scheme 2. Optimization of Chiral Ligands[a]





L1 R = Cy, 35% yield, 51% ee[b]
L2 R = 3,5-$(CF_3)_2C_6H_3$, 23% yield, 55% ee[c]
L3 R = 4-^{t}BuC_6H_4, 56% yield, 74% ee
L4 R = 4-MeOC_6H_4, 64% yield, 82% ee
L5 R = 2-MeC_6H_4, 30% yield, 80% ee
L6 R = 2-MeOC_6H_4, 75% yield, 87% ee
L7 R = 3-MeOC_6H_4, 66% yield, 76% ee
L8 R = 2-EtOC_6H_4, 77% yield, 85% ee
L9 R = 2,4-$(MeO)_2C_6H_3$, 79% yield, 90% ee
L10 R = 2,4,6-$(MeO)_3C_6H_2$, N.R.
L11 R = 1-naphthyl, 42% yield, 73% ee

L12 43% yield, 45% ee

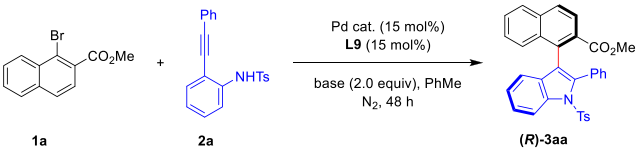
L13 N.R.

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), $Pd(TFA)_2$ (10 mol %), ligand (15 mol %), and KO^{t}Bu (2.0 equiv) in toluene (0.5 mL) under N_2 at 35 °C for 18 h. The enantiomeric excess values were determined by HPLC analysis on a chiral stationary phase. [b]At 60 °C. [c]At 50 °C.

Further optimization studies have been carried out by adjusting other reaction parameters (Table 1). The ee value of **3aa** was increased to 92%, but the yield was slightly lower when the reaction was conducted at 25 °C (Table 1, entry 2). Then, the bases were further explored, and product **3aa** was obtained in 87% yield with 92% ee when $Ba(OH)_2{\cdot}8H_2O$ was employed as a base (Table 1, entry 5). The yield of **3aa** was improved to 94% by adding $B(OH)_3$ (Table 1, entry 6),[10] which effectively suppressed the formation of the corresponding 3-unfunctionalized indole. No improvement was made by changing palladium salts (entries 7−10), and no better results could be realized by adjusting the loading of palladium catalysts or the ratio of the substrates (see Table S5). Finally, the following conditions were eventually established for subsequent studies: $Pd(TFA)_2$ (15 mol %) as the catalyst, **L9** (15 mol %) as the ligand, $Ba(OH)_2{\cdot}8H_2O$ (2.0 equiv) as the base, and $B(OH)_3$ (1.0 equiv) as the additive in toluene at 25 °C for 48 h.

With the optimized reaction conditions in hand, we next examined the scope of *o*-alkynylaniline **2** with 1-naphthyl bromide **1a** as the arylating reagent (Scheme 3). *o*-Alkynylanilines bearing various substituents at positions 4 and 5 reacted smoothly with **1a** in good to excellent yields and 91−94% ee (**3aa**−**ah**). The absolute configuration of **3ah** was determined

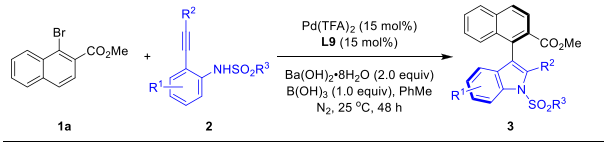
Table 1. Optimization of Reaction Conditions[a]

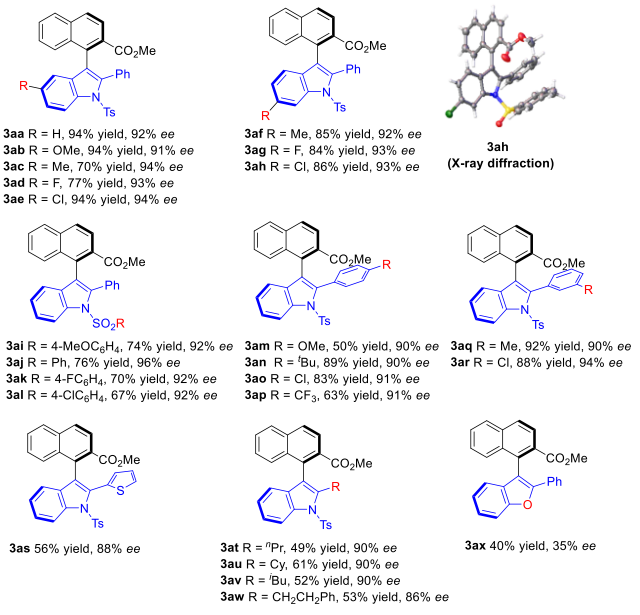


entry	[Pd]	base	yield (%)	ee (%)
1[b]	$Pd(TFA)_2$	KO^{t}Bu	79	90
2	$Pd(TFA)_2$	KO^{t}Bu	75	92
3	$Pd(TFA)_2$	K_2CO_3	52	92
4	$Pd(TFA)_2$	K_3PO_4	57	92
5	$Pd(TFA)_2$	$Ba(OH)_2{\cdot}8H_2O$	87	92
6[c]	**$Pd(TFA)_2$**	**$Ba(OH)_2{\cdot}8H_2O$**	**94**	**92**
7[c]	$Pd(acac)_2$	$Ba(OH)_2{\cdot}8H_2O$	70	92
8[c]	$Pd(hfac)_2$	$Ba(OH)_2{\cdot}8H_2O$	83	92
9[c]	$Pd(OAc)_2$	$Ba(OH)_2{\cdot}8H_2O$	85	92
10[c]	$[Pd(allyl)Cl]_2$	$Ba(OH)_2{\cdot}8H_2O$	78	89

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Pd] (15 mol %), ligand (15 mol %), and base (2.0 equiv) in toluene (1.0 mL) under N_2 at 25 °C for 48 h. Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase. [b]At 35 °C. [c]$B(OH)_3$ (1.0 equiv) was added.

Scheme 3. Scope of 2-Alkynylanilines[a]





[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(TFA)_2$ (15 mol %), **L9** (15 mol %), $Ba(OH)_2{\cdot}8H_2O$ (2.0 equiv), and $B(OH)_3$ (1.0 equiv) in toluene (1.0 mL) under N_2 at 25 °C for 48 h. Isolated yields.

by X-ray crystallographic analysis (CCDC 2089667), and those of other products were assigned by analogy. The introduction of different *N*-sulfonyl groups gave products **3ai**−**al** in good yields with ee values ranging from 92% to 96%. Alkynes bearing diverse substituted phenyls furnished **3am**−**ar** in moderate to excellent yields with 90−94% ee values.

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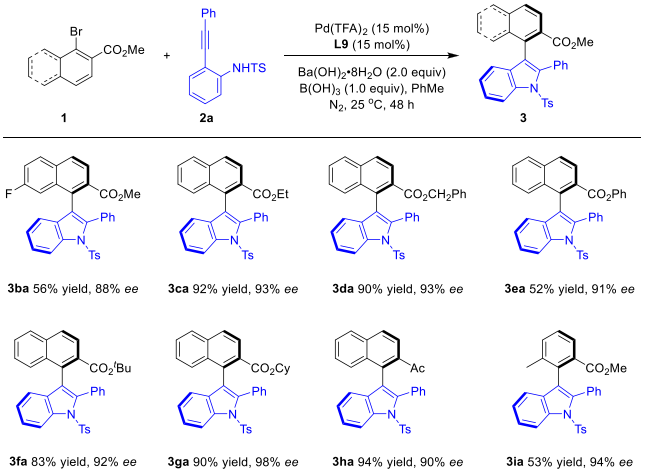
Impressively, alkynes bearing a heteroaryl, a primary and secondary alkyl, and cycloalkyl terminus were also amenable to the reaction conditions, and the corresponding products (**3as**–**aw**) were obtained in moderate yields with 86–94% ee. In addition, the *ortho* nucleophile was extended to a phenol, affording an axially chiral naphthylbenzofuran **3ax**, albeit with a lower yield and a lower enantioselectivity. Moreover, a larger-scale (1 mmol) synthesis of **3aa** resulted in a 82% yield with a 91% ee. Racemization studies were also carried out to investigate the stereochemical stability of **3aa** (see the Supporting Information for more details). Product **3aa** proved to be essentially atropomerically stable, and no decay of ee was detected at 80 °C (DMF). It was found that **3aa** has a barrier of enantiomerization of 34.96 kcal/mol at 120 °C in DMF.

To further demonstrate the generality of this method, the scope of aryl bromide was investigated with *o*-alkynylaniline **2a** as the coupling partner (Scheme 4). 7-Fluoro-functionalized

Scheme 4. Scope of Aryl Bromide Substrates[a]

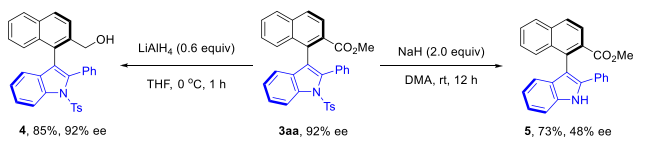


[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(TFA)_2$ (15 mol %), **L9** (15 mol %), $Ba(OH)_2{\cdot}8H_2O$ (2.0 equiv), and $B(OH)_3$ (1.0 equiv) in toluene (1.0 mL) under N_2 at 25 °C for 48 h. Isolated yields.

aryl bromide **1b** reacted to afford the corresponding product **3ba** in high enantioselectivity. Various 1-bromo-2-naphthoic esters were fully compatible, providing **3ca**–**ga** in moderate to excellent yields with 91–98% ee values. The substrate was not limited to 1-bromo-2-naphthoic esters. Employing 1-bromo-2-acetonaphthone (**2h**) and methyl 2-bromo-3-methylbenzoate (**2i**) allowed smooth isolation of products **3ha** and **3ia** in 94% and 53% yields, respectively, and incomparably excellent enantioselectivities.

To demonstrate the synthetic utility of this coupling system, derivatization reactions have been briefly carried out for a representative product (Scheme 5). Treatment of **3aa** with $LiAlH_4$ in THF afforded product **4** in good yield without erosion of the enantiopurity. Removal of the N-protecting

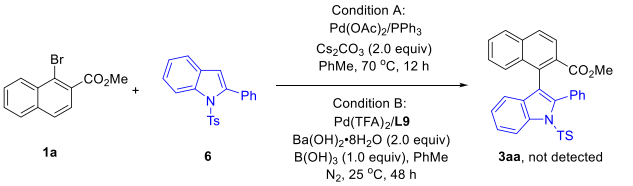
Scheme 5. Derivatization of Product 3aa



group of **3aa** upon treatment with NaH provided the corresponding indole **5** in a significantly lower ee, likely due to a lower barrier of racemization as a result of the electronic effect of the protic indole.

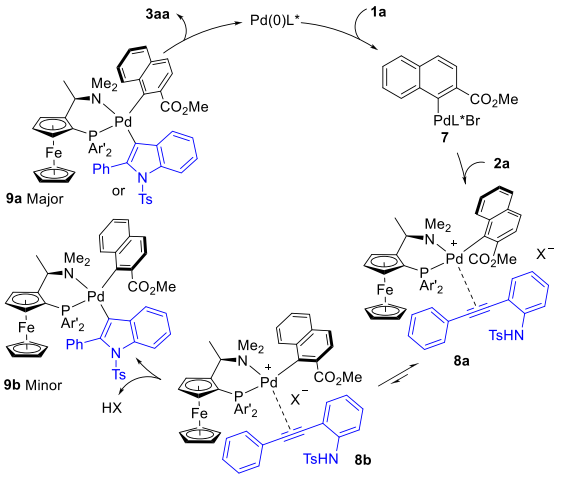
Control experiments have been briefly conducted to probe the reaction mechanism. Thus, two reactions between **1a** and cyclization-derived indole **6** under both racemic and asymmetric reaction conditions were conducted. No desired product was detected in either case (Scheme 6), indicating that the cyclization-derived Pd–C bond acts as the active organopalladium species in the catalytic cycle.

Scheme 6. Mechanism studies



On the basis of these results and literature precedent,[13] we propose a plausible catalytic cycle for this reaction (Scheme 7).

Scheme 7. Proposed Mechanism



The reaction starts with a Pd(0) active catalyst. Oxidative addition of **1a** leads to an arylpalladium(II) species **7**. Then, coordination of **7** to the triple bond of **2a** gives intermediates **8a** and **8b**. Complex **8a** is expected to be more stable than **8b** due to less steric interactions. Subsequently, the metal-activated alkyne undergoes nucleophilic attack of the nitrogen atom and provides the major intermediate **9a** and minor intermediate **9b**, which would undergo reductive elimination to produce the major product enantiomeric **3aa** and simultaneously regenerates the catalysts for the next catalytic cycle.

In conclusion, we have realized efficient and atropisomeric construction of 2,3-disubstituted indoles by palladium-catalyzed enantioselective Cacchi reaction between aryl bromides and *o*-alkynylanilines. The reaction proceeded under mild reaction conditions in high yields and excellent enantioselectivities. This reaction provides a *de novo* approach to catalytically access C(3)–C(aryl) axially chiral indoles.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02012.

Experimental details, characterization data, and HPLC data (PDF)

Accession Codes

CCDC 2089667 contains 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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