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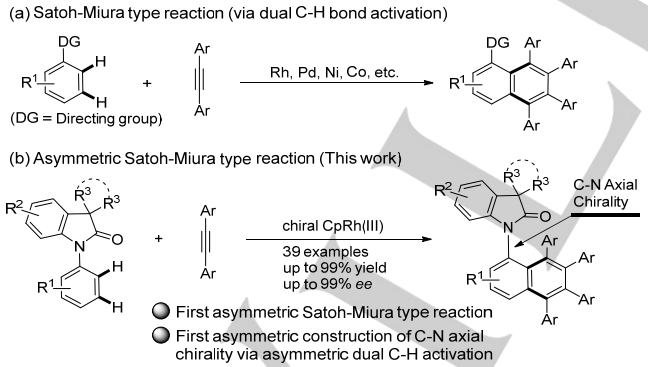
Enantioselective Synthesis of C–N Axially Chiral *N*-Aryloxindoles by Asymmetric Rhodium-Catalyzed Dual C-H Activation

Honghe Li,[‡] Xiaoqiang Yan,[‡] Jitan Zhang, Weicong Guo, Jijun Jiang, and Jun Wang*

Dedicated to Professor Xiaoming Feng on the occasion of his 55th birthday

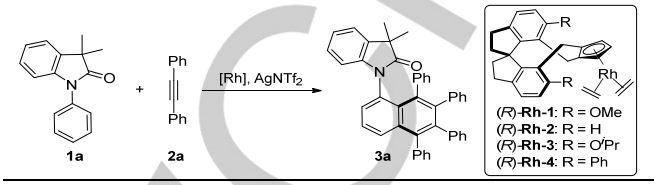
Abstract: *The first enantioselective Satoh-Miura type reaction is reported. A variety of C–N axially chiral N-aryloxindoles have been enantioselectively synthesized by an asymmetric rhodium-catalyzed dual C-H activation reaction of N-aryloxindoles and alkynes. High yields and enantioselectivities were obtained (up to 99% yield and up to 99% ee). To the best of our knowledge, it is also the first example of asymmetric synthesis of C-N axially chiral compounds by transition-metal catalyzed asymmetric dual C-H activation strategy.*

Axially chiral compounds are prevalent in natural products,[1] medicinal chemistry[2] and chiral ligand pool[3]. Their asymmetric syntheses have attracted much attention of chemists.[4] But the C-N axial chirality is less studied than the C-C axial chirality. The ways to obtain C-N axially chiral compounds include asymmetric C-N forming reaction,[4d, 5] asymmetric *N*-functionalization of anilides[6], and others[7]. In this study, we present an alternative way to construct C-N axial chirality by the strategy of asymmetric dual C-H activation.[8] In 2008, Satoh and Miura disclosed a Rh^{III}-catalyzed aromatic homologation reaction by a chelation-assisted successive double C-H activation[9] (Scheme 1a, DG = pyrazoyl group).[10] Same reactions could also occur with other directing groups[11] or even without any directing groups.[12] However, since its discovery, the Satoh-Miura type reaction has never been achieved enantioselectively. Herein, we describe a Rh^{III}-catalyzed asymmetric Satoh-Miura type reaction, by which a variety of C–N axially chiral *N*-aryloxindoles have been synthesized in up to 99% yield with up to 99% ee (Scheme 1b).



Scheme 1. Asymmetric Satoh-Miura Type Reaction

Table 1. Optimization of Reaction Conditions[a]



entry	[Rh] (mol %)	additive (equiv)	yield[b] (%)	ee[c] (%)
1	**Rh-1**	AgOAc (2.2)	73	83
2	**Rh-1**	$^{i}PrCO_2Ag$ (2.2)	90	90
3	**Rh-1**	Ag_2O (1.1)	36	92
4	**Rh-1**	$^{i}PrCO_2H$ (2.2) + Ag_2O (1.1)	75	93
5	**Rh-2**	$^{i}PrCO_2H$ (2.2) + Ag_2O (1.1)	70	82
6	**Rh-3**	$^{i}PrCO_2H$ (2.2) + Ag_2O (1.1)	64	89
7	**Rh-4**	$^{i}PrCO_2H$ (2.2) + Ag_2O (1.1)	8	62
8[d]	**Rh-1**	$^{i}PrCO_2H$ (2.2) + Ag_2O (1.1)	94 (92)[e]	93

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (2.2 equiv), [Rh] (5 mol %), $AgNTf_2$ (10 mol %), additive, DCE (0.5 mL) at 70 ℃ under N_2 for 24 h. [b]Determined by ^1H NMR analysis of crude reaction mixture with methoxybenzene as the internal standard. [c]Determined by HPLC. [d]$AgNTf_2$ (20 mol %), 36 h. [e]Isolated yield.

This research started from our discovery of a new Satoh-Miura type reaction. Namely, in the presence of Cp^*Rh^{III}, the *N*-phenyloxindole **1a** reacted with diphenylacetylene **2a** to afford *N*-naphthyloxindole **3a** that was axially chiral around C-N bond. Driven by our continuous interests in the asymmetric C-H activation reactions[13] and inspired by the aforementioned literature surveys, we decided to head directly towards the study of the corresponding enantioselective reaction, which is much more challenging. Intensive studies of reaction conditions indicated that the chiral spiro CpRh catalyst developed by You's group[8i] was the most effective. And the product **3a** was obtained in 73% yield and 83% ee with (*R*)**-Rh-1** (5 mol %) as the precatalyst and AgOAc (2.2 equiv) as the additive (Table 1, entry 1). To our delight, when $^{i}PrCO_2Ag$ was used instead of AgOAc, **3a** was formed in 90% yield and 90% ee (entry 2). It was assumed that the C-H activation should proceed via carboxylate-assisted concerted metalation-deprotonation (CMD) mechanism and the sterically bulkier isobutyrate could lead to better differentiation of the two enantiotopic C-H bonds of **1a**. When Ag_2O was used, the enantioselectivity increased to 92% ee, but the yield decreased dramatically to 36% (entry 3). Interestingly, when $^{i}PrCO_2H$ (2.2 equiv) and Ag_2O (1.1 equiv) were employed together in order to in situ generate $^{i}PrCO_2Ag$, the desired product **3a** was obtained in better enantioselectivity (93% ee) albeit in decreased yield (75% yield) (entry 4). Screening of chiral rhodium catalysts indicated (*R*)**-Rh-1** worked best (entries 5-7). Finally, increasing the amount of $AgNTf_2$ to 20 mol % and extending the reaction time to 36 hours led to the optimal reaction conditions, under which the product **3a** was obtained in 92% yield and 93% ee (entry 8). For more details

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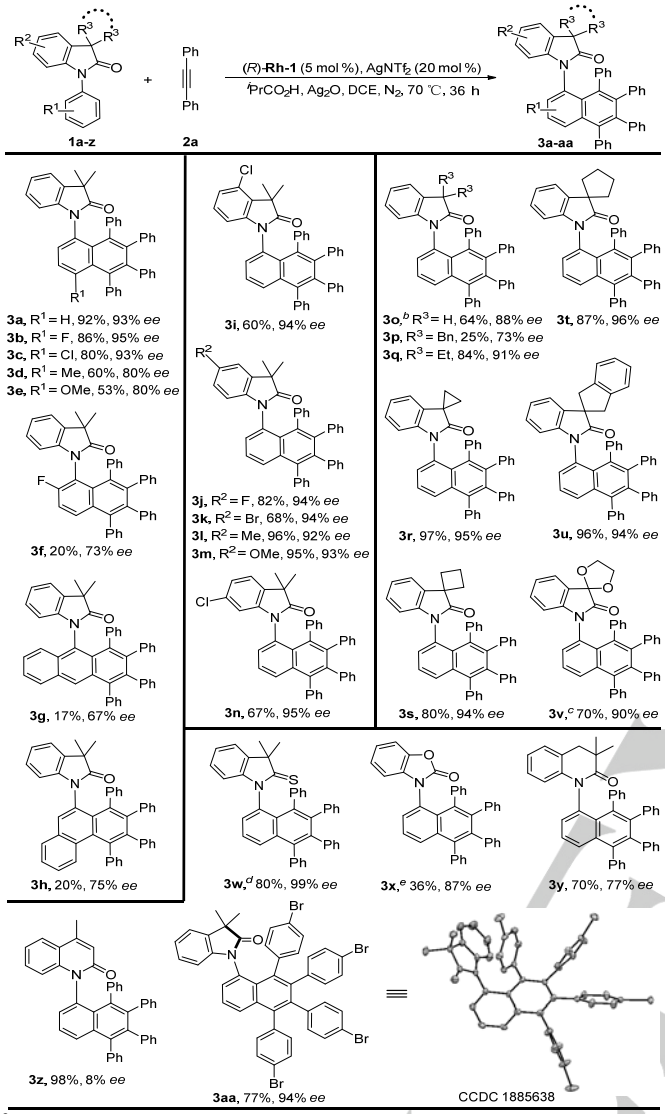
about optimization of reaction conditions, please refer to Supporting Information.

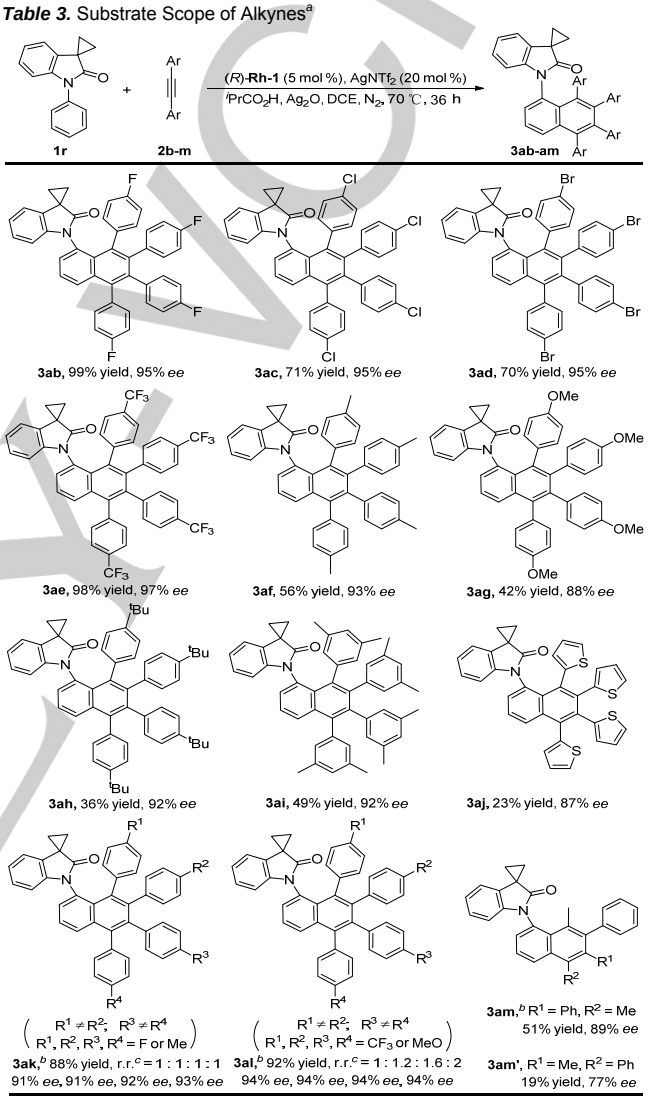
Table 2. Substrate Scope of *N*-phenyloxindoles[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (2.2 equiv), (*R*)-**Rh-1** (5 mol %), $AgNTf_2$ (20 mol %), $^iPrCO_2H$ (2.2 equiv), Ag_2O (1.1 equiv), DCE (1 mL) at 70 ℃ under N_2 for 36 h. Isolated yields are reported. [b](*R*)-**Rh-1** (10 mol %), 80 ℃, 48 h. [c](*R*)-**Rh-1** (10 mol %), 70 ℃, 60 h. [d]AgOAc (2.2 equiv) was used. [e]80 ℃, 48 h.

With optimized reaction conditions in hands, various *N*-aryloxindole **1** were allowed to react with diphenylacetylene **2a** (Table 2). The substrates bearing either an electron-withdrawing or an electron-donating group (R^1 = F, Cl, Me, OMe) at the *N*-phenyl ring are tolerable, giving the desired products in 53−92% yields and 80−95% ee (**3a–e**). However, *N*-2-FC_6H_4 and naphthyl oxindoles only gave moderate results (**3f–h**). Substitution with electron-withdrawing or electron-donating group (e.g., F, Cl, Me, OMe) at the oxindole aromatic moiety has little impact on the reaction. The corresponding products were obtained in good to high yields (60-96%) with high enantioselectivities (92-95% ee). Then, a series of 1-phenylindolinones with different 3,3-disubstituents were examined. Delightedly, good to high yields (up to 97%) and high enantioselectivities (up to 96% ee) were achieved for nonsubstituted (**3o**), open-chained dialkylsubstituted (**3p–q**), and biologically relevant spiro oxindoles (**3r–v**)[14]. Besides, indoline-2-thione (**1w**), oxazolone (**1x**), and quinolinones (**1y–z**) were also investigated as substrates, affording the desired products in moderate to high yields and enantioselectivities. In addition, the tetrabromo product **3aa** was prepared in purpose of growing single-crystals. Its structure was confirmed and the absolute configuration was determined to be *R* configuration by single-crystal X-ray diffraction.[15]

Table 3. Substrate Scope of Alkynes[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (2.2 equiv), (*R*)-**Rh-1** (5 mol %), $AgNTf_2$ (20 mol %), $^iPrCO_2H$ (2.2 equiv), Ag_2O (1.1 equiv), DCE (1 mL) at 70 ℃ under N_2 for 36 h. Isolated yields are reported. [b]48 h. [c]Regioselectivity; determined by ^1H NMR analysis.

Subsequently, various alkynes were investigated by reacting with *N*-phenyloxindoles (**1r**) (Table 3). For symmetric diaryl alkynes, both electron-withdrawing and electron-donating substituents were tolerated by the reaction, providing good to excellent yields (42−99%) and enantioselectivities (88−97% ee) (**3ab–ag**). Greater steric demanding substituents were also compatible (**3ah–3ai**). Moreover, when the heteroaromatic alkyne **2j** was used, the product **3aj** was obtained with good

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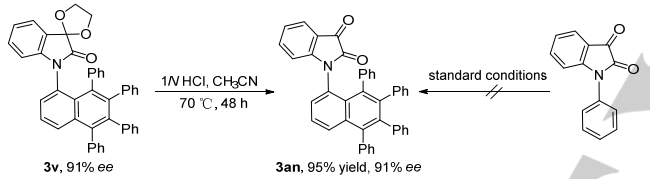
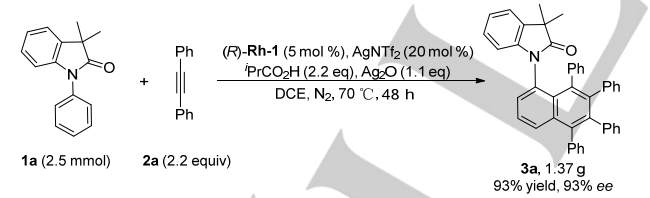
enantioselectivity (87% ee) albeit in moderate yield (23% yield), which was probably due to the toxic effect of sulfur on the rhodium catalyst. Besides symmetric diaryl alkynes, some asymmetric diaryl alkynes were also investigated. When (4-fluorophenyl)(4-methylphenyl)ethyne was subjected to the reaction conditions, four regiomers of **3ak** were generated in equal amount and in high overall yields. The ee values for each regiomers were comparable and high. Similar situation also happened to the electronically biased asymmetric alkyne 1-(4-methoxyphenyl)-2-[4-(trifluoromethyl)phenyl]acetylene, affording four regiomers of **3al** in high overall yields, high enantioselectivities, but unsatisfying regioselectivity. When phenyl methyl acetylene was employed, only two regiomers were obtained (**3am** : **3am'** = 2.7 : 1). The major regiomer **3am** was obtained in 51% yield and 89% ee. Its structure was identified by single-crystal X-ray diffraction.[15] In addition, no desired reaction occurred when phenylacetylene or the aliphatic alkyne hex-3-yne was applied.

Notably, the product **3v** can be facilely transformed to the corresponding *N*-phenylisatin **3an** by 1 *N* HCl without any loss of enantiopurity (Scheme 2). It should be mentioned that isatins are commonly found in natural compounds, pharmaceuticals and synthetic intermediates.[16] Interestingly, if *N*-phenylisatin was employed as substrate, no reaction took place, which was probably due to strong chelation effect of the two adjacent carbonyl groups with the rhodium catalyst.



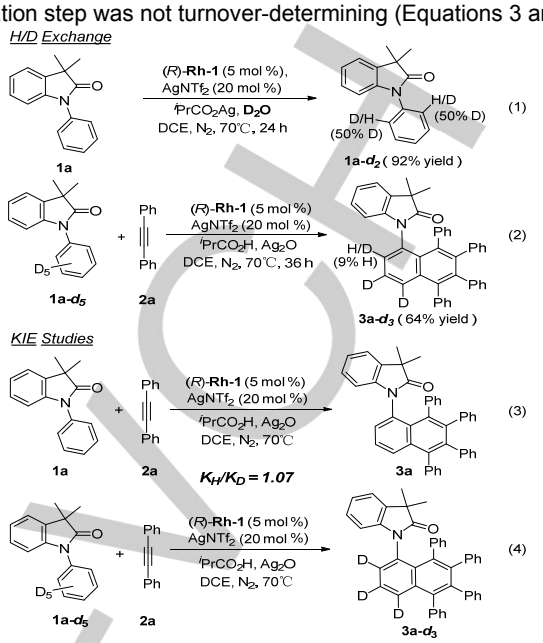
Scheme 2. Transformation of the Product **3v** to Isatin **3an**

To demonstrate the reliability of this methodology, the reaction of **1a** with **2a** was attempted in a large scale of 2.5 mmol. The desired product **3a** was obtained in 93% yield (1.37 g) with 93% ee (Scheme 3). Moreover, the barrier of the N-Ar bond rotation for the product **3a** was measured to be 151 kJ/mol in hexane at 170 ℃. The barrier of this magnitude is sufficiently high to preclude racemization at reaction temperature of 70 ℃.

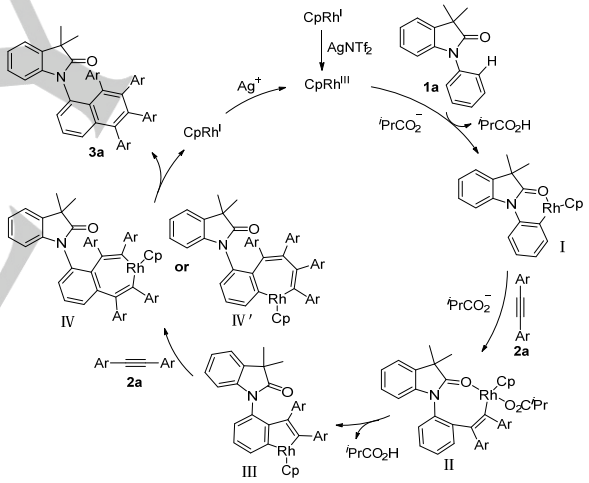


Scheme 3. Gram-scale Synthesis of the *N*-Naphthyloxindole **3a**

Preliminary studies of reaction mechanism were carried out. Firstly, when the oxindole **1a** was subjected to the reaction conditions in the presence of D_2O, considerable H/D exchange at the *ortho* position was observed, indicating the C-H bond activation process is reversible (Scheme 4, Equation 1). Secondly, when the oxindole **1a-*d*$_5$** was allowed to react with the alkyne **2a**, the product **3a-*d*$_3$** was obtained in 64% yield with merely 9% of contamination of **3a-*d*$_2$**, suggesting that the reverse reaction of C-H activation was much slower than the step succeeding the C-H activation (Equation 2). Thirdly, a kinetic isotope effect (KIE) of 1.07 was observed from parallel reactions using **1a** and **1a-*d*$_5$**, respectively, indicating the C-H activation step was not turnover-determining (Equations 3 and 4).



Scheme 4. Mechanistic Studies



Scheme 5. Proposed Reaction Mechanism

According to above mechanistic studies and previous studies[10-11], a plausible reaction mechanism is proposed (Scheme 5). First, the chiral $CpRh^{I}$ is oxidized to $CpRh^{III}$ by $AgNTf_2$. Then, coordination of the oxygen atom of *N*-phenyloxindole **1a** to the Rh^{III} catalyst assists the first C-H bond cleavage possibly via CMD mechanism to afford the six-membered rhodacyclic intermediate Ⅰ. Subsequently, insertion of the alkyne **2a** generates the intermediate Ⅱ. Then, activation of the second C-H bond occurs to generate the intermediate Ⅲ. Insertion of a second molecule of alkyne **2a** forms the intermediate Ⅳ or Ⅳ', which undergoes reductive elimination to give the product **3a** and the $CpRh^{I}$ species. Finally, $CpRh^{I}$ was reoxidized to $CpRh^{III}$ by Ag^{+} to close the catalytic cycle.

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In summary, we present the first example of asymmetric Satoh-Miura type reaction, which also constitutes the first example of asymmetric construction of C–N axial chirality by the strategy of asymmetric dual C–H activation. Specifically, a variety of C–N axially chiral *N*-aryloxindoles have been enantioselectively synthesized from *N*-aryloxindoles and alkynes in up to 99% yield and with up to 99% ee with a chiral rhodium catalyst. Preliminary mechanistic studies were performed and a plausible catalytic cycle was proposed.

Acknowledgements

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Keywords: Satoh-Miura type reaction • C-N axial chirality • dual C-H activation • alkyne • *N*-aryloxindole

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[15] CCDC 1885638 and 1902396 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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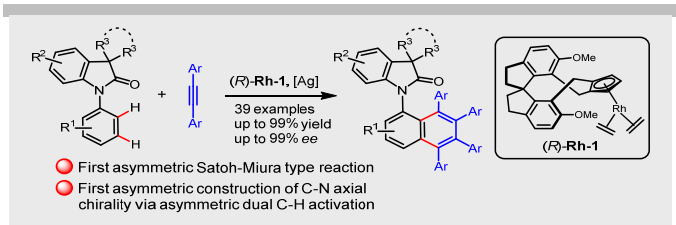

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