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Communication

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Rh(III)-Catalyzed Asymmetric Synthesis of Axially Chiral Biindolyls by Merging C-H Activation and Nucleophilic Cyclization

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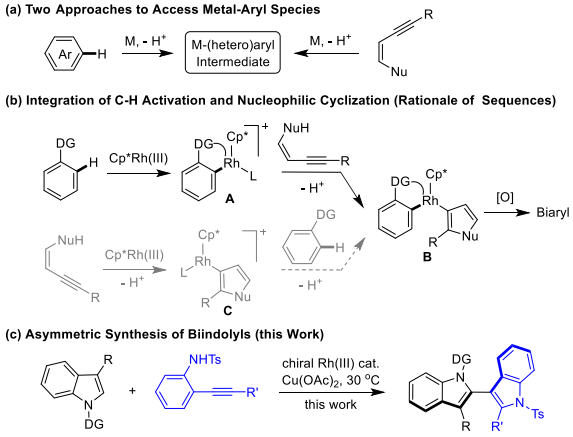
Supporting Information

ABSTRACT: Enantiomeric access to pentatomic biaryls is challenging due to their relatively low rotational barrier. Reported herein is mild and highly enantioselective synthesis of 2,3'-biindolyls via underexplored integration of C-H activation and alkyne cyclization using a unified chiral Rh(III) catalyst. The reaction proceeded *via* initial C-H activation followed by alkyne cyclization. A chiral rhodacyclic intermediate has been isolated from stoichiometric C-H activation, which offers direct mechanistic insight.

Axially chiral biaryls are important structural motifs in natural products and in chiral ligands.[1] Previous studies have been predominantly directed to the construction of chiral hexatomic (six-six) biaryl systems,[2] and asymmetric construction of atropoisomeric biaryls containing pentatomic ring(s) is more challenging and this is largely ascribable to their conformational fluxionality. Two classes of catalytic systems have been developed to access atropisomeric systems containing a pentatomic ring. Tan, Shi, and others have applied organo- or Lewis acid-catalysis toward construction of chiral indole-arene linkages.[3] Besides, metals catalysis have also been employed for asymmetric construction of related five-six biaryls.[4,5] In contrast to these achievements, construction of five-five biaryls severely lags behind and only very few reports are known.[3e,f,5]

On the other hand, C-H bond activation has been established as an increasingly important strategy for construction of complex structures, and various reports on biaryl synthesis have been documented based on twofold C-H activation (CDC reactions).[6] Despite the advances, asymmetric synthesis of biaryls is generally rare, and most studies relied on dynamic kinetic resolution of conformationally labile biaryls,[4,5] as in a notable report by Shi.[5] Besides C-H activation process, metal-aryls can also be accessed via nucleophilic cyclization of alkynes (Scheme 1a).[7] However, this important area almost evolved independently with intermolecular C-H activation.[7a,c]

Scheme 1. Biaryl Synthesis via C-H Activation and Nucleophilic Cyclization

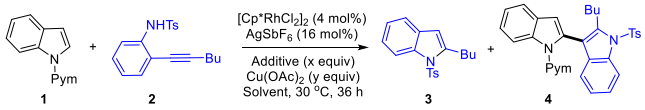


The obstacle to enantioselective synthesis of five-five biaryls via C-H activation likely lies in the indispensably harsh conditions.[6] Our solution then boils down to development of highly active catalytic systems with an activation barrier lower than that of atropisomerism. Given both high activity and Lewis acidity of CpRh(III) catalysts in C-H activation,[8] Rh(III) catalysis may allow merger of C-H activation and nucleophilic cyclization.[9] Since this strategy involves formation of two M-C bonds (Scheme 1b), the sequence of the M-C formation represents a fundamental issue. In the desired pathway, a chelation-assisted arene cyclometalates to give intermediate **A**, followed by alkyne cyclization to give a Rh(III) diaryl **B** that may reductively eliminate the product. The alternative alkyne cyclization-cyclometalation sequence is unfavorable because the cyclized intermediate **C** can be readily (irreversibly) protonolyzed. In fact, intramolecular couplings have been adopted to suppress this simple cyclization.[10] In addition, subsequent cyclometalation of **C** is less feasible because it is coordinatively saturated with respect to a concerted metalation-deprotonation pathway.[11] This calls for judicious design of a catalytic system that orchestrates the reactivity of these two substrates. We now report Rh(III)-catalyzed mild and highly enantioselective synthesis of 2,3'-biindolyls (Scheme 1c).

We applied *N*-directing group-assisted indoles as a reactive arene substrate. The coupling of indole **1** and *o*-alkynylaniline **2**

was explored using $[RhCp^*Cl_2]_2$ as a catalyst (Table 1). Desired oxidative coupling occurred to give product **4** albeit in low yield when $Zn(OAc)_2$ was applied as an additive, together with a significant amount of the cyclization byproduct (**3**). MeCN appears to be the optimal solvent and the yield of product **4** was improved when PivOH was introduced (entries 4-6). By adjusting the ratio of the substrates and the amount of $Cu(OAc)_2$, a good yield was isolated (entry 6). Significantly, formation of indole **3** was retarded when boric acid was used (entries 7, 8), and an excellent yield was secured when the reaction was conducted under air, under which conditions $AgSbF_6$ proved unnecessary (entry 9).

Table 1. Optimization Studies.[a]

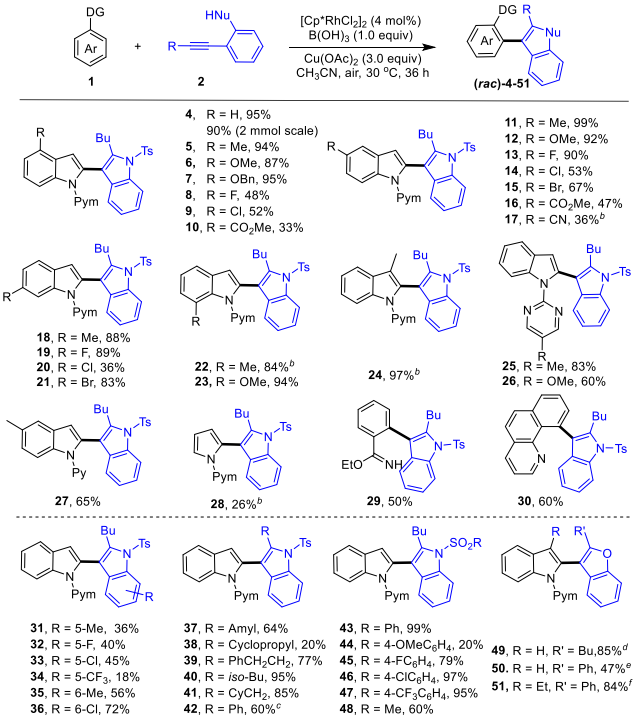


entry	1:2	additive (x equiv)	*y*	solvent	yield (%)	
					3	**4**
1	1:1.5	$Zn(OAc)_2$ (0.5)	2	CH_3CN	65	13
2	1:1.5	$Zn(OAc)_2$ (0.5)	2	MeOH	33	ND
3	1:1.5	$Zn(OAc)_2$ (0.5)	2	Dioxane	15	ND
4	1:1.5	PivOH (2.0)	2	CH_3CN	25	46
5	1:2	PivOH (2.0)	2.5	CH_3CN	23	56
6[b]	1:2	PivOH (2.0)	2.5	CH_3CN	18	76
7	1:1.5	$B(OH)_3$ (1.0)	2.5	CH_3CN	15	68
8[b]	1:2.5	$B(OH)_3$ (1.0)	2.5	CH_3CN	15	88
9[b]	1:2.5	$B(OH)_3$ (1.0)	3	CH_3CN	12	97 (95[c])

[a]Reaction Conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), additive, $Cu(OAc)_2$ (2-3 equiv), Solvent (2 ml) at 30 °C for 36 h under argon, isolated yield; [b]Performed under air. [c]No $AgSbF_6$ was used.

With the optimized conditions in hand, we next examined the scope and generality of this coupling system (Scheme 2). *N*-Pyrimidylindoles bearing various substituents at the 4-, 5-, 6-, and 7- positions coupled smoothly with alkyne **2** in good to excellent yield (**4-23**) although the reaction efficiency tends to be attenuated by electron-withdrawing groups (**10, 16, 17**). Introduction of a 3-Me group is also tolerated under modified conditions (**24**), indicating tolerance of steric effect. Besides a simple pyrimidyl group, several substituted pyrimidyls and a pyridyl ring were also effective directing groups (**25-27**). The C-H substrate was not restricted to indoles. Thus, pyrrole, imidate ester, and benzo[*h*]quinoline were also viable in this coupling system (**28-30**). We next examined the scope of alkynes in the coupling with indole **1**. Various substituents at the 5- and 6-positons of the cyclization-derived indole ring were found to be compatible (**31-36**). The reaction also tolerated different alkyl, cycloalkyl, and aryl groups in the alkyne terminus (**37-42**). Variation of the *N*-sulfonyl group confirmed effectiveness of different types of *N*-sulfonyls activating groups (**43-48**). Significantly, the *ortho*-nucleophile was smoothly extended to phenols. Thus, several indolylbenzofurans were efficiently constructed under modified conditions (**49-51**). In all cases, a small amount of simple cyclization product was detected.

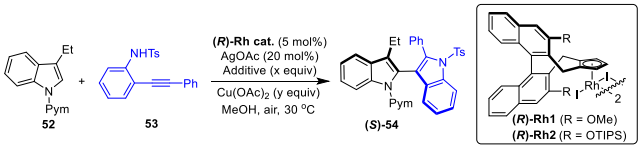
Scheme 2. Scope of Arenes and Alkynes in Biaryl Synthesis.[a]



[a]Reaction Conditions: arene **1** (0.2 mmol), alkyne **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $B(OH)_3$ (0.2 mmol), and $Cu(OAc)_2$ (0.6 mmol) in CH_3CN (2 ml) at 30 °C under air for 36 h, isolated yield. [b]$Cp^*Rh(OAc)_2$ (8 mol%) and $AdCO_2H$ (0.2 mmol) were used. [c]with $AdCO_2H$ (0.2 mmol) in DMF (2 mL) at 60 °C for 12 h. [d]60 °C for 12 h. [e]$AdCO_2H$ (0.2 mmol) in CH_3CN (2 mL) at 60 °C for 12 h. [f]alkyne **2** (0.4 mmol), $Cp^*Rh(OAc)_2$ (8 mol%), and $AdCO_2H$ (0.2 mmol) in MeOH (2 mL) for 24 h.

The mildness of the racemic coupling bolds well development of an asymmetric system. Although Rh(III)-catalyzed asymmetric coupling of arenes has been realized,[12] the C-C coupling is mostly fulfilled via interaction of Rh(III)-aryl species with an unsaturated bond,[13,14] and other types of interactions are limited. The asymmetric coupling of 3-ethylindole **52** and alkyne **53** was evaluated using a chiral $[Cp^xRhI_2]_2$ catalyst (Table 2). The reactions conditions turned out to be drastically different from the racemic ones. The **Rh1** catalyst was active for this coupling in the presence of PivOH and a catalytic amount of AgOAc, affording product (*S*)-**54** in excellent enantioselectivity but in moderate yield (entry 1). Delightfully, excellent yield and enantioselectivity were attained when the amounts of $Cu(OAc)_2$ and PivOH were increased (entries 2-4). Comparably excellent outcomes were also obtained when PivOH was replaced by AdCOOH (entry 6). In contrast, essentially no coupling occurred when **(*R*)-Rh2** was used.

Table 2 Asymmetric Optimization Studies.[a]



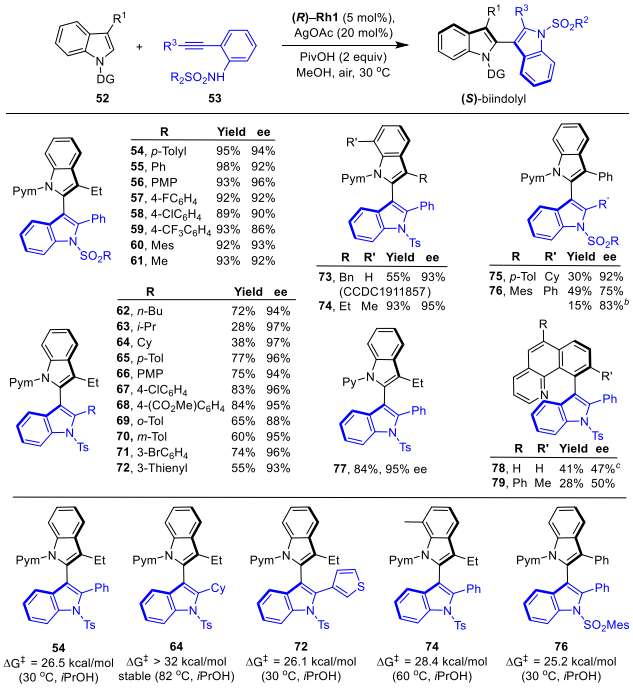
entry	additive (*x* equiv)	*y*	yield (%)	ee (%)[b]
1	PivOH (1)	2.5	58	92
2	PivOH (1)	3	70	96
3[c]	PivOH (1)	3	35	94
4	PivOH (2)	3	93	94
5	H_3BO_3 (1)	3	42	92
6	AdCOOH (1)	3	91	94
7[d]	AdCOOH (1)	3	< 5	ND

[a]Reaction Conditions: indole **52** (0.05 mmol), alkyne **53** (0.125 mmol), additive, (***R***)-**Rh1** cat. (5 mol%), AgOAc (20 mol%) and $Cu(OAc)_2$ (2-3 equiv) in MeOH (1.5 mL) at 30 °C under air for 12 h, isolated yield. [b]Determined by HPLC analysis on a chiral stationary phase. [c]Under Argon. [d]**Rh2** catalyst was used.

We next examined the scope of asymmetric synthesis of axially chiral 2,3'-biindolyls. *o*-Phenylethnylanilines bearing various *N*-sulfonyl activating groups reacted smoothly with a 3-ethylindole, affording the corresponding biindolyls in excellent yields and 86-96% ee (**54**-**61**), regardless of the nature of the sulfonyl group. Impressively, a broad scope of alkynes bearing diverse 1° and 2° alkyls, cycloalkyl, substituted phenyls, and heteroaryl groups has been defined (**62**-**72**, 88-97% ee). The indole substrate was next examined. The 3-substituent of the indole was successfully extended to benzyl (**73**, CCDC1911857) and Ph (**75**-**76**) groups, although lower enantioselectivity (75% ee) was observed for **76** bearing a phenyl substituent in each indole rig, possibly due to lower rotational barrier of this product (*vide infra*). Neither the yield nor enantioselectivity was affected when a 7-Me group was introduced (**74**). The chemical yield and enantioselectivity were consistently high when a pyridyl directing group was adopted (**77**). Besides indoles, benzo[*h*]quinolines only coupled with lower enantioselectivity (**78**, **79**). Unfortunately, only racemic benzofuran[5] products were obtained when different phenol-alkynes were coupled with indole **52** under the standard reaction conditions.

Racemization studies have been carried out to investigate the stereochemical rigidity of representative biindolyls. Product **76** with two phenyl groups showed the lowest rotational barrier, which is correlated to its lower enantioselectivity. Moving to a 3-ethyl substituent resulted in an enhanced rotational barrier (**54**, **64**, **72**, **74**), and the highest barrier among them belongs to indole bearing a 2'-cyclohexyl group (**64**). Overall, the barriers are relatively low for most products, and the efficient control of the enantioselectivity manifested superiority of rhodium(III) catalysis.

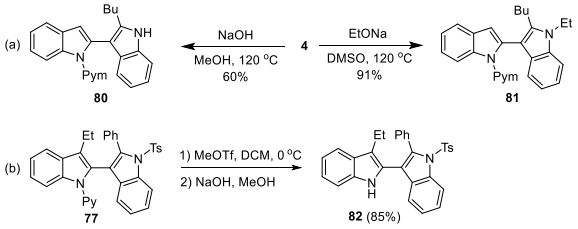
Scheme 3. Enantioselective Synthesis and Rotational Barriers of 2,3'-Biindolyls.[a]



[a]Reaction Conditions: indole (0.1 mmol), alkyne (0.25 mmol), **(*R*)-Rh1** (5 mol%), AgOAc (20 mol%), PivOH (0.2 mmol), and $Cu(OAc)_2$ (0.3 mmol) in MeOH (1.5 mL) under air at 30 °C for 16 h, isolated yield. [b] 6 h. [c] 36 h.

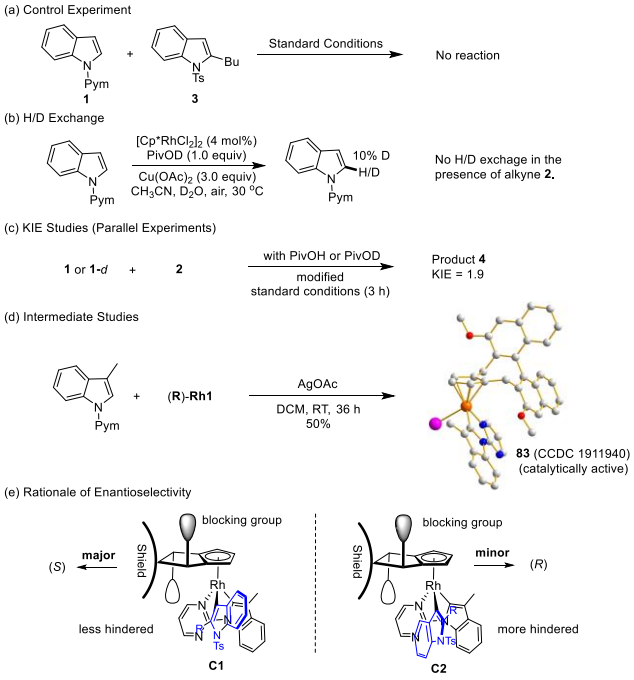
Derivatization reactions haven been briefly implemented to showcase the synthetic utility (Scheme 4). The *N*-Ts activating group in **4** was selectively removed when treated with NaOH/MeOH (**80**). Reaction of **4** and EtONa in DMSO led to conversion of the *N*-Ts group to *N*-Et (**81**). Selective removal of the *N*-directing group afforded conformationally labile indole **82** in high yield.

Scheme 4. Derivatization Reactions.



A series of experiments have been conducted to probe the reaction mechanism (Scheme 5). It was found that no reaction occurred between a simple cyclized indole **3** and different pyrimidylindoles in both racemic (Scheme 5a) and asymmetric (not shown) coupling systems. These findings confirmed that a Rh(III) indolyl instead of the protonolyzed indole is the active species. Next, H/D exchange between indole **1** and PivOD-D_2O revealed slight H/D exchange at the indole C(2) position in the absence of alkyne **2** (Scheme 5b). However, no H/D exchange was observed for either the recovered indole or product **4** when alkyne **2** was present, suggesting irreversibility of the C-H activation. To further explore this C-H activation process, KIE has been measured based on parallel reactions using **1** and **1**-*d* as the individual arene. A value of KIE = 1.9 suggested that C-H activation might be involved in the turnover-limiting process (Scheme 5c).

Scheme 5. Mechanistic Studies.



To delve into the mechanism of asymmetric biindolyl synthesis, a highly enantioenriched rhodacyclic complex **83** was isolated as a single isomer (50% yield) from a stoichiometric reaction of a 2-methylindole and (*R*)-**Rh1** (Scheme 5d, CCDC 1911940).[15] In the crystal structure, the bulky iodide group is disposed distal to the steric shielding group of the Cp^{OMe} ligand. In addition, the directing group plane is nearly parallel to the adjacent naphthalene ring to allow π-π stacking. The orientation of ligands around the Rh(III) center provides direct support to the model proposed by Cramer.[13a,b] This represents the first isolation of enantiomerically pure rhodacycle in asymmetric C-H activation. Designation of **83** as a catalyst precursor (8 mol%) to the coupling of a 3-ethylindole (**52**) and alkyne **53** afforded (*S*)-**54** in yield (83%) and enatioselectivity (94% ee) closely comparable to those of the original catalytic system (see Scheme 3). Collectively, this reaction likely proceeded via initial cyclometallation followed by alkyne cyclization to afford Rh(III) diaryl **C**1 and **C**2 (Scheme 5e). The **C1** is conformationally optimal for C-C reductive elimination due to minimized steric repulsion, leading to formation of the (*S*)-2,3'biindolyl.[16]

In summary, we have realized oxidative coupling of indoles and *o*-alkynylanilines/phenols for mild synthesis of biaryls by merging C-H activation with nucleophilic cyclization. The coupling system has been extended to asymmetric synthesis of highly enantioenriched 2,3'-biindolyls. The synthetic challenges associated with relatively low rotational barriers of pentatomic biaryls were addressed with a highly active Rh(III) system. A chiral rhodacyclic intermediate has been isolated from a stoichiometric reaction, which provided direct insight into rationale of the atropenantioselectivity. Future studies will be directed to the development of other axially chiral biaryl systems under high-valent metal catalysis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of new compounds, NMR spectra, HPLC Chromatograms (PDF), and crystal structures of **73** and **83** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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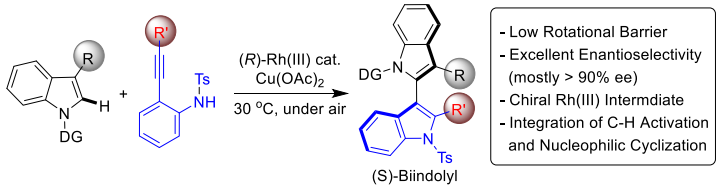
(15) CCDC 1911857 and 1911940 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
(16) An alternative mechanism of alkyne insertion into a Rh-indoyl bond (via C=C isomerization with subsequent C-N coupling) is unlikely because free rotation of indolyl-C(alkenyl) bond of the insertion intermediate should lead to racemic product (see Supporting Information).



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