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Construction of Chiral Tricyclic Indoles through a Rhodium-Catalyzed Asymmetric Arylation Protocol

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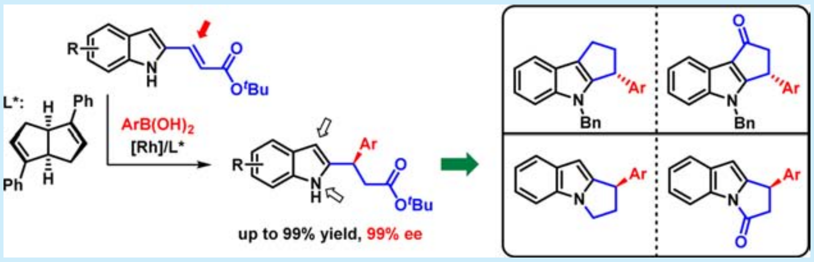
Supporting Information



ABSTRACT: A rhodium/diene complex catalyzed asymmetric 1,4-addition of arylboronic acids to indole-derived *α*,*β*-unsaturated esters to access highly enantioenriched 3-(1*H*-indol-2-yl)-3-arylpropanoates has been developed. By taking advantage of the nucleophilic character of indole at C3 and N1 positions, construction of a series of valuable chiral tricyclic indole frameworks such as 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles and cyclopenta[*b*]indoles can be efficiently achieved.

Polycyclic indoles constitute an important and unique class of fused heterocycles that are widely found in diverse biologically active natural products and pharmaceutical compounds.[1] Among them, 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles and -cyclopenta[*b*]indoles are especially attractive due to their vital roles in medicinal chemistry and organic synthesis. For example, flinderole C (**1**) was identified as having selective antimalarial activity;[1a] yuremamine (**2**) was isolated from *Mimosa hostilis* and was found to have hallucinogenic and psychoactive effects;[1b] isatisine A (**3**) bearing a 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole skeleton exhibits strong antiviral activity;[1c] compound **4** displays effects for treatment of cardiovascular and renal disorders and recently has also been tested as a psychotropic drug;[1d] yeuhchukene (**5**) displays potent anti-implantation activity;[1e] and MK-0524[1f] is a selective prostaglandin D_2 receptor antagonist used for the prevention of niacin-induced flushing (Figure 1).

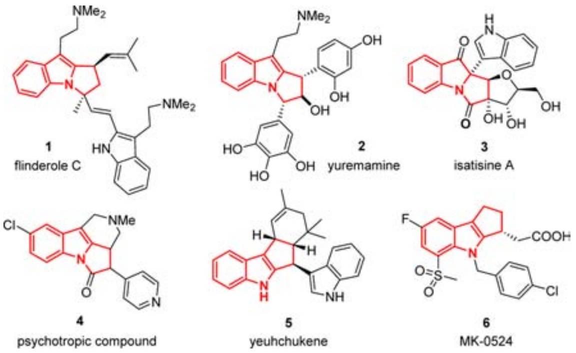


Figure 1. Examples of polycyclic indole-based bioactive compounds.

Because of this great importance, development of efficient methods for the highly stereoselective synthesis of various chiral polycyclic indoles from readily available materials is in particular demand. In the past few years, a number of valuable studies was conducted for the construction of chiral 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles[2] and -cyclopenta[*b*]indoles[3] by use of a chiral auxiliary or asymmetric catalysis approach to incorporate the stereogenic center(s). The key ring-closing strategy mainly involves Friedel−Crafts alkylation,[3b−e] *N*-alkylation/acylation/hemiacetalization,[2b−f] and C−H activation.[2a,j,3a] In general, most of these methodologies rely on the use of rationally designed indole substrates with C3 and/or N1 position(s) blocked or prefunctionalized. While these methods are efficient, they generally could only lead to the formation of either pyrrolo[1,2-*a*]indoles or cyclopenta[*b*]indoles. To the best of our knowledge, there are no reports describing a versatile asymmetric approach capable of the convenient construction of both structural motifs. We therefore devised a viable strategy that would be flexible enough to allow rapid assembly of both chiral pyrrolo[1,2-*a*]indoles and cyclopenta[*b*]indoles in a highly stereoselective manner.

Rhodium-catalyzed asymmetric 1,4-addition of arylboron reagents to electron-deficient olefins represents one of the most practical methods to obtain enantioenriched compounds.[4] Over the past two decades, significant advances have been made

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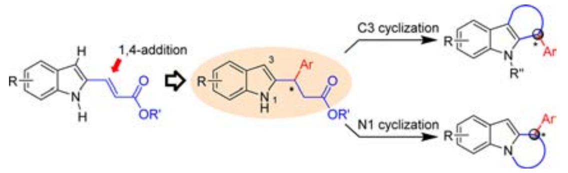
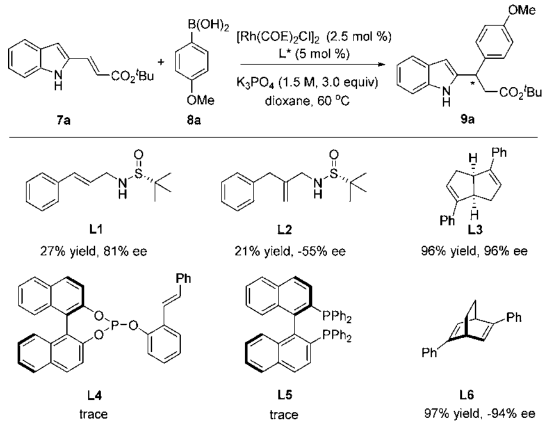
in the development of highly effective catalyst systems.[5] We have also demonstrated that a series of simple chiral olefins including hybrid sulfur–olefins and phosphorus–olefins as well as dienes are superior ligands for the Rh-catalyzed reactions over a broad variety of substrates.[6] Inspired by the success of these achievements, we reasoned that the proper combination of indole and *α*,*β*-unsaturated ester elements might allow us to design a new type of potential substrates, 2-indolyl acrylates, for rhodium-catalyzed enantioselective 1,4-addition (Scheme 1). By taking advantage of the inherent nucleophilic character of indole at nonsubstituted N1/C3 positions and the ester functionality, the resulting products could be expected to undergo site-selective cyclization for flexible construction of chiral 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles and cyclopenta[*b*]indoles. Herein, we present our successful development of a highly efficient approach for the synthesis of chiral tricyclic indoles through Rh/diene-catalyzed asymmetric 1,4-addition.

Scheme 1. Synthetic Strategies to Chiral Tricyclic Indoles



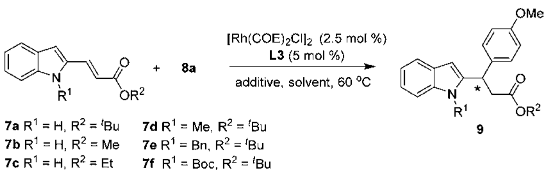
The 2-indolyl acrylate substrates could be readily prepared from indole-2-carboxylic acid through reduction and Witting olefination.[7] We began our work by studying the reaction between *tert*-butyl free-(NH)-2-indolyl acrylate **7a** and *p*-methoxyphenylboronic acid **8a** in K_3PO_4 (1.5 M)/dioxane at 60 °C in the presence of 2.5 mol % of $[Rh(COE)_2Cl]_2$ and 5 mol % of various chiral ligands (**L1**–**L6**) that are available in our laboratory. As shown in Scheme 2, reactions with our typical sulfinamide–olefin ligands[6e,g] **L1** and **L2** produced the desired product **9a** in low yields with modest enantioselectivities (81% and 55% ee), while almost no reaction was observed with phosphite–olefin ligand[6h] **L4** and BINAP (**L5**). Gratifyingly, the two chiral diene ligands **L3** and **L6** both exhibited great catalytic reactivity and enantioselectivity, providing **9a** with excellent yields and enantiomeric excesses. Among them, our previously developed [3.3.0]diene[6a,b] **L3** gave the highest ee (96%).

Scheme 2. Ligand Screening



We next investigated the structural influence of substrate under the above identified reaction conditions. Changing the ester group from bulky *tert*-butyl to sterically less hindered methyl or ethyl resulted in a significant decrease of enantioselectivity (Table 1, entries 1–3). Interestingly, when *N*-substituted indoles **7d**–**f** were subjected to the reaction, no better ee's were obtained, and with *N*-Boc substrate **7f**, surprisingly, even lower yield and ee were afforded (entry 6). These results suggested that the *N*-protection of the indole is dispensable. Further investigation on reaction parameters such as additive, solvent, and catalyst loading was also conducted. Among the various additives screened (entries 7–11), K_3PO_4 was found to be the best. Varying the solvent did not furnish better results (entries 12 and 13). In addition, lowering the catalyst loading would lead to somewhat diminished yield while still maintaining the enantioselectivity (entry 14).

Table 1. Substrate Evaluation and Conditions Optimization[a]



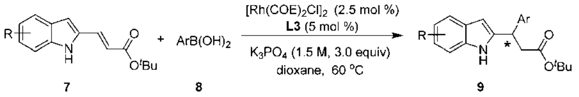
entry	7	solvent	additive[b]	yield[c] (%)	ee[d] (%)
1	**7a**	dioxane	K_3PO_4	96	96
2	**7b**	dioxane	K_3PO_4	59	76
3	**7c**	dioxane	K_3PO_4	76	81
4	**7d**	dioxane	K_3PO_4	98	94
5	**7e**	dioxane	K_3PO_4	94	96
6	**7f**	dioxane	K_3PO_4	50	77
7	**7a**	dioxane	KOH	trace	-
8	**7a**	dioxane	K_2HPO_4	84	96
9	**7a**	dioxane	KF	92	96
10	**7a**	dioxane	KHF_2	75	96
11	**7a**	dioxane	NEt_3	22	89
12	**7a**	toluene	K_3PO_4	85	88
13	**7a**	DCE	K_3PO_4	94	95
14[e]	**7a**	dioxane	K_3PO_4	86	96

[a] The reaction was carried out with 0.2 mmol of unsaturated indole esters 7, 2.0 equiv of *p*-methoxyphenylboronic acid **8a** in the presence of 5.0 mol % of [Rh], 5.0 mol % of **L3**, and K_3PO_4 (1.5 M, 3.0 equiv) in 2.0 mL of solvent at 60 °C for 15 h. [b] Unless noted, 3.0 equiv of additive (1.5 M) was used. [c] Isolated yield. [d] Determined by Chiral HPLC. [e] 3 mol % of [Rh] and **L3** was employed.

With the optimized conditions in hand, the substrate scope of the reaction was explored (Table 2). We were pleased to find that the catalyst system applies to various arylboronic acids with either electron-donating or -withdrawing group(s) on the phenyl ring at different positions. In all cases, good to excellent enantioselectivities (92–99% ee) could be obtained. Notably, methyl substitution at the ortho-position could give the product with extremely high enantioselectivity (99% ee); however, the yield dropped significantly due to obvious steric reasons. Accordingly, reactions with other sterically less bulky or unencumbered arylboronic acids generally proceeded well. Moreover, 2-indolyl acrylates having substituents on the indole phenyl ring were found to be equally suitable substrates, furnishing products **9q**–**v** in 93–97% ee. Unfortunately, the reaction failed to give product with more challenging alkenylboronic acids such as styrylboronic acid.

The absolute configuration of the newly formed chiral center was unequivocally determined to be *R* by X-ray crystallographic

Table 2. Asymmetric Arylation of 2-Indolylacrylate[a]



entry	R	Ar	9	yield[b] (%)	ee[c] (%)
1	H	4-MeOC$_6$H$_4$	**9a**	96	96
2	H	Ph	**9b**	99	96
3	H	4-MeC$_6$H$_4$	**9c**	95	96
4	H	4-FC$_6$H$_4$	**9d**	92	97
5	H	4-ClC$_6$H$_4$	**9e**	96	97
6	H	4-BrC$_6$H$_4$	**9f**	78	97
7	H	3-MeOC$_6$H$_4$	**9g**	96	95
8	H	3-MeC$_6$H$_4$	**9h**	98	96
9	H	3-FC$_6$H$_4$	**9i**	92	98
10	H	2-MeC$_6$H$_4$	**9j**	36	99
11	H	2-naphthyl	**9k**	98	92
12	H	4-PhC$_6$H$_4$	**9l**	98	95
13	H	4-^{t}BuC$_6$H$_4$	**9m**	95	95
14	H	4-MOMOC$_6$H$_4$	**9n**	90	96
15	H	3,5-(Me)$_2$C$_6$H$_3$	**9o**	94	94
16	H	3,4-O$_2$CH$_2$C$_6$H$_3$	**9p**	91	96
17	5-F	Ph	**9q**	94	95
18	5-MeO	Ph	**9r**	97	95
19	5-F	4-MeOC$_6$H$_4$	**9s**	98	97
20	5-MeO	4-MeOC$_6$H$_4$	**9t**	89	95
21	6-Cl	Ph	**9u**	94	94
22	6-Me	Ph	**9v**	96	94

[a]The reaction was carried out with 0.2 mmol of unsaturated indole esters **7**, 2.0 equiv of arylboronic acid **8** in the presence of 5.0 mol % of [Rh], 5.0 mol % of ligand **L3**, and K$_3$PO$_4$ (1.5 M, 3.0 equiv) in 2.0 mL of dioxane at 60 °C for 15 h. [b]Isolated yield. [c]Determined by Chiral HPLC.

analysis of the adduct **9f** (Figure 2). Assuming an analogous reaction mechanism, the same absolute configurations of the obtained products could be assigned.

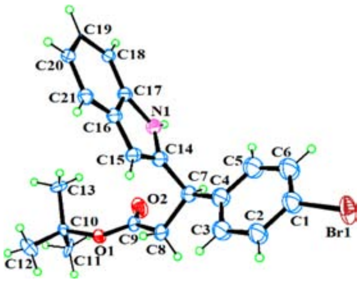
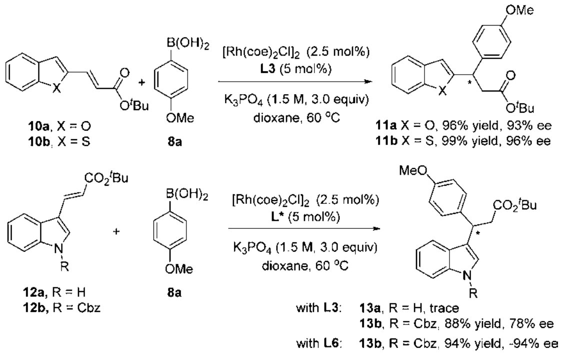


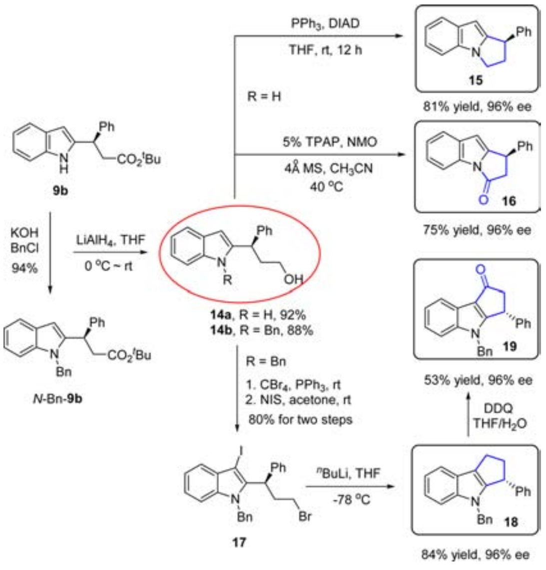
Figure 2. X-ray structure of (*R*)-**9f**.

Scheme 3. Asymmetric Arylation of Other Structurally Similar Acrylates



Encouraged by the above success, we explored the utility of this catalyst system in asymmetric arylation of other structurally analogous *α*,*β*-unsaturated esters. To our delight, under the standard conditions, benzofuran- and benzothiophene-derived acrylates **10a** and **10b** could also serve as appropriate Michael acceptors to form the addition products **11a** and **11b** in high yields (96% and 99%) and with excellent enantioselectivities (93% and 96% ee) (Scheme 3). Surprisingly, unlike *tert*-butyl free-(NH)-2-indolyl acrylate, *tert*-butyl free-(NH)-3-indolyl acrylate **12a** could not undergo efficient 1,4-addition. Nevertheless, it is interesting to note that the reaction using *N*-Cbz-protected acrylate **12b** was smooth,[8] affording the desired arylation product in 88% yield with 78% ee. In this case, Hayashi diene **L6** was found to be more effective, delivering **13b** in high yield (94%) with largely improved enantioselectivity (94% ee) under the same conditions. These results indicate that the current method showcases a broad-scope application potential in asymmetric synthesis.

Scheme 4. Construction of Chiral Polycyclic Indoles



Following the original plan, we next turned our attention to the feasibility of the site-selective cyclization for construction of chiral pyrrolo[1,2-*a*]indole and cyclopenta[*b*]indole frameworks. As represented by **9b** in Scheme 4, the synthesis of a series of chiral tricyclic indole-based heterocycles was carried out. LAH reduction of the *tert*-butyl ester **9b** and *N*-Bn-**9b** gave alcohol intermediates **14a** and **14b**. Exposure of **14a** under Mitsunobu reaction conditions smoothly provided the *N*-cyclized product **15** in 81% yield without loss of enantiopurity. In the other case, treatment of **14a** with the oxidant TPAP and NMO[9] at 40 °C furnished the corresponding tricyclic ketone product **16**. In considering the different cyclization from the indole C3 site, we initially attempted to carry out a direct intramolecular Friedel–Crafts alkylation or acylation. However, we found that the benzylic carbon stereocenter was quite sensitive to the acidic conditions, and the attempts were not successful. Fortunately, bromination and iodination of the alcohol **14b**, followed by ^{n}BuLi-mediated intramolecular substitution,[10] afforded the expected cyclic product 4-benzyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole **18** in good yield over three steps. Oxidative dehydrogenation of the resulting **18** with DDQ in THF/H_2O successfully provided its tricyclic ketone **19** in moderate yield. It should be noted that no ee erosion was observed in all these transformations. Thus, as anticipated, we were able to flexibly construct all four interesting types of indole-based tricyclic chiral heterocycle structures in a highly enantioenriched manner through simple site-selective cyclization of the aforementioned arylation products **9**. Importantly, these heterocycles might be further elaborated to access more functionalized or complicated polycyclic molecules that are useful in medicinal chemistry.

In summary, we have developed a highly effective rhodium/diene catalytic system for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated N1/C3-free 2-indolyl acrylates to afford the corresponding arylation products in high yields with excellent enantioselectivities (92−99% ee). The method is applicable to α,β-unsaturated benzofuran- and benzothiophene-derived acrylates as well as *N*-protected 3-indolyl acrylates. By taking advantage of the nucleophilic character of indole at N1/C3 positions and the ester functionality, the synthetic utility of the arylation products in the flexible and facile construction of four different types of indole-based tricyclic structural motifs through site-selective intramolecular cyclization was demonstrated. Given the unique presence of polycyclic indoles in a wide variety of natural products and biologically active compounds, we believe that this protocol should find an attractive application in related biological and drug discovery studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03585.

Experimental procedures and spectroscopic data of all new compounds (PDF)

X-ray crystal structure data for (*R*)-**9f** (CIF)

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Notes

The authors declare no competing financial interest.

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