OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Rhodium-Catalyzed Enantioselective Addition of Arylboroxines to Isatin-Derived *N*-Boc Ketimines Using Chiral Phosphite−Olefin Ligands: Asymmetric Synthesis of 3-Aryl-3-amino-2-oxindoles

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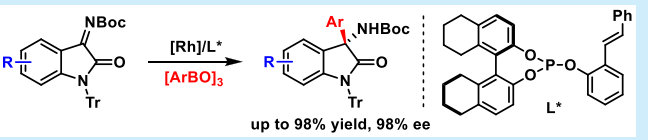
Supporting Information

ABSTRACT: An efficient rhodium-catalyzed enantioselective arylation of isatin-derived *N*-Boc ketimines with arylboroxines has been developed using H_8-BINOL-derived phosphite-olefin as a chiral ligand. This method allows access to a broad variety of valuable tetrasubstituted 3-amino-2-oxindole derivatives in good yields (up to 98%) with excellent enantioselectivities (up to 98% ee).



Oxindoles bearing a tetrasubstituted stereogenic center at the 3-position constitute a privileged class of heterocyclic frameworks, which are present in a wealth of bioactive natural products and pharmaceutically active agents.[1] Among them, 3-aryl-3-amino-2-oxindoles are very important structural motifs found in various drug candidates (Figure 1), including

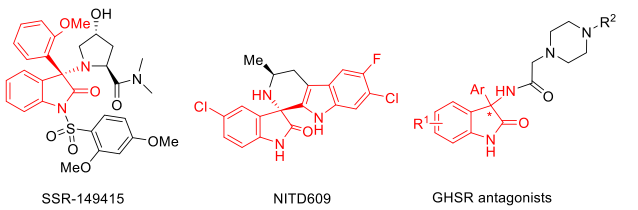


Figure 1. Examples of bioactive 3-aryl-3-amino-2-oxindoles.

SSR-149415, a drug now in clinical trials for treatment of anxiety depression,[2] antimalarial agent NITD609 (also KAE609 or cipargamin),[3] and the ghrelin receptor (GHSR) antagonists.[4] Due to this great importance, the development of catalytic enantioselective methods for their preparation is a subject of particular interest to organic and medicinal chemists. Other than organocatalyzed asymmetric amination of 2-oxindoles[5] and Pd-catalyzed asymmetric intramolecular α-arylation of amides,[6] catalytic asymmetric addition of nucleophiles to isatin-derived ketimines is among the most straightforward and efficient approaches to incorporate the tetrasubstituted carbon stereocenter. However, due to the low reactivity of ketimines and the difficulty in the stereochemical control, only a limited number of processes have been developed.[7,8] A commonly employed strategy relies on the asymmetric aza-Friedel−Crafts reaction, which works well only with electron-rich π-nucleophilic arenes,[7] allowing the sole introduction of indoles, pyrroles, naphthols, or phenols to the 3-position of 2-oxindoles. Alternatively, transition-metal-catalyzed asymmetric addition of readily available arylboron reagents to 3-ketimino-2-oxindoles has been recognized to be a promising method, although only few examples have been reported. In 2011, Ellman achieved the Rh(I)-catalyzed diastereoselective addition of arylboroxines to isatin-derived *N*-*tert*-butanesulfinyl chiral imines with up to 92% de.[8a] In 2016, Zhang and co-workers developed an efficient Pd(II)-catalyzed highly enantioselective addition of arylboronic acids to *N*-*tert*-butylsufonyl-protected ketimines using Pyrox ligands.[8b] In these two reports, the reactions require the use of highly activated sulfinyl or sufonyl imines. The widely used *N*-Boc imines were found fully inactive under the Pd(II)/Pyrox catalysis. Notably, Jiang et al. recently reported their successful development of a new Pd(II)/*N*-tosyl bisimidazoline catalytic system that could enable asymmetric addition of arylboronic acids to isatin-derived *N*-Boc imines with good to excellent enantioselectivities (60−96% ee).[8c] Despite progress, these Pd-catalyzed reactions have not yet proven effective for sterically hindered substrates. On the other hand, reactions involving chiral rhodium complex catalysis remains unexploited. A rhodium(I)-catalyzed enantioselective addition of arylboronic acids to *N*-Boc isatin imines was described by Burke et al.; however, the enantioselectivity was low with only 39% ee when chiral diene ligand was applied.[8d] Therefore, developing new effective catalytic systems for enantioselective arylation of isatin-derived ketimines with a broad scope is still in high demand.

Received: August 7, 2019

DOI: 10.1021/acs.orglett.9b02787
Org. Lett. XXXX, XXX, XXX−XXX

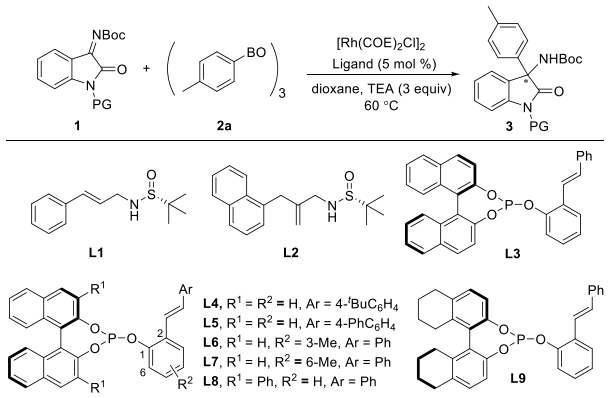
Rh-catalyzed enantioselective addition of organoboron reagents to imines is a particularly useful strategy for constructing chiral amines.[9,10] Previously, we have successfully synthesized various enantioenriched amines bearing α-quaternary stereocenters under this strategy using a new series of chiral sulfur- or phosphorus-based olefin ligands we have developed.[10] On the basis of these successes, we envisioned that these chiral rhodium complexes might also act as effective catalysts for the asymmetric addition of arylborons to isatin-derived ketimines. Herein, we disclose results of our efforts on the development of a new catalytic system for highly enantioselective arylation of isatin-derived *N*-Boc ketimines. The method allows direct access to a variety of 3-aryl-3-amino-2-oxindoles in good yields and excellent enantiomeric excesses.

We began our study by examining the arylation of *N*-Boc imine **1a** derived from *N*-methyl isatin with boroxine **2a** in the presence of 2.5 mol % of $[Rh(COE)_2Cl]_2$ and 5 mol % of chiral hybrid olefins ligands (**L1**, **L2**, **L3**) in TEA/dioxane at 60 °C. The initial results showed that almost no reaction occurred with chiral linear sulfur-olefin **L1** as a ligand (Table 1, entry 1), while branched sulfur-olefin **L2** gave the desired product **3a** in a very low yield and ee (entry 2). To our delight, with simple phosphite-olefin ligand **L3**, the reaction afforded a promising enantioselectivity (57% ee), albeit in an unsatisfactory yield of 16% (entry 3). This result implies that chiral phosphorus-based olefins might be potential ligands for the reaction.[11] Accordingly, the influence of protecting groups on the nitrogen of imine oxindole was investigated (entries 3−5). Interestingly, a significant steric effect of the protecting group was observed. When the sterically bulky trityl was used as the protecting group (ketimine **1c**), the corresponding product **3c** could be formed in 63% yield with 83% ee (entry 5). Notably, the reaction could only generate traces of **3c** in the absence of ligand **L3** (entry 6). Subsequently, the loading ratio of rhodium to ligand was examined. The use of 10 mol % of **L3**, which corresponds to a ligand-to-metal ratio of 2:1 led to a sharp decline in both yield and enantioselectivity (entry 7). Considering the stronger coordinating ability of phosphorus in comparison with olefin, this result suggests the possible formation of a less active rhodium diphosphite complex. To ensure the coordination of rhodium to both the phosphorus atom and olefinic double bond simultaneously, excess rhodium was applied and an optimal result was obtained when 2.75 mol % of $[Rh(COE)_2Cl]_2$ was added in the reaction (entry 8).

On the basis of these findings, a series of structurally diverse phosphite−olefin ligands (**L4**−**9**) were evaluated in the same Rh-catalyzed reaction between **1c** and **2a** (Table 1, entries 10−15). First, the influence of the aromatic moiety attached to the double bond was examined. Introducing a bulky *tert*-butyl substituent onto the *para*-position of phenyl ring was not beneficial for the stereoselectivity (**L4**, entry 10). Ligand **L5** containing a *para*-phenyl substituent exhibited lower catalytic activity (entry 11). Besides, ligand **L6** bearing an *ortho*-methyl and **L7** containing a *meta*-methyl individually to the olefin group showed a slight improvement in the catalytic performance (entries 12−13). In contrast to **L3**, the presence of two phenyl substituents at the 3- and 3′-positions of the binaphthyl moiety led to a clear decrease in yield (50%), albeit with a somewhat higher ee (89%) (**L8**, entry 14). To our delight, with H_8-BINOL-derived **L9** as the ligand, the addition reaction proceeded smoothly, giving product **3c** in both the highest ee (95%) and isolated yield (78%) (entry 15). It appears that the dihedral angle of the two aromatic planes exerts great influence in the reaction transition state for stereocontrol. Given the ease of preparation, superior catalytic activity, and enantioselectivity, **L9** was selected as the preferred ligand for further intensive study.

With the above results in hand, we proceeded to further optimize the reaction parameters. As shown in Table 2, a survey of base additives was performed first. In view of organic base additives examined (TEA, DBU, DABCO, and DIPEA) (entries 1−4), the use of 3 equiv of DIPEA was identified as the best choice, giving the adduct in 82% yield and 96% ee (entry 4). It was found that the *N*-Boc ketimines **1** are very sensitive to water and suffered serious hydrolysis in aqueous base K_3PO_4 and KF, resulting in much lower yields (enteis 5−6). Next, we turned our attention toward investigating the influence of solvent. When the reaction was carried out in THF and DCE, it afforded the desired product in a lower yield while maintaining excellent enantioselectivity (entries 7−8). However, in toluene or Et_2O, a drop in both yield and enantioselectivity was found (entries 9−10). Thus, dioxane was chosen as the best solvent. Additionally, it was found that the presence of 4 Å molecular sieves (MS) in the reaction system would be helpful for suppressing the hydrolysis of imines (entry 11). We also investigated the use of other organoboron reagents instead of arylboroxine. Surprisingly, when phenylboronic acid was employed under the same

Table 1. Initial Screening of Reaction Conditions[a]



entry	1	[Rh] (mol %)	ligand	PG	3	yield[b] (%)	ee[c] (%)
1	1a	5	L1	Me	3a	trace	−
2	1a	5	L2	Me	3a	9	14
3	1a	5	L3	Me	3a	16	57
4	1b	5	L3	Bn	3b	30	77
5	1c	5	L3	Tr	3c	63	83
6	1c	5	−	Tr	3c	trace	−
7[d]	1c	5	L3	Tr	3c	23	63
8	1c	5.5	L3	Tr	3c	63	85
9	1c	6	L3	Tr	3c	64	85
10	1c	5.5	L4	Tr	3c	71	73
11	1c	5.5	L5	Tr	3c	43	87
12	1c	5.5	L6	Tr	3c	68	86
13	1c	5.5	L7	Tr	3c	64	89
14	1c	5.5	L8	Tr	3c	50	89
15	1c	5.5	L9	Tr	3c	78	95

[a]Reaction conditions: 1 (0.2 mmol), $(p\text{-TolBO})_3$ (1 equiv), $[Rh(COE)_2Cl]_2$, ligand (5 mol %), and TEA (3 equiv) in 1.0 mL of dioxane were stirred at 60 °C for 12 h, unless otherwise noted. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]10 mol % of L3

DOI: 10.1021/acs.orglett.9b02787
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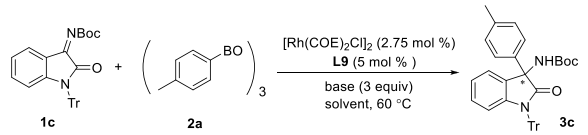
Table 2. Optimization of the Reaction Conditions[a]



entry	solvent	base	yield[b] (%)	ee[c] (%)
1	dioxane	TEA	78	95
2	dioxane	DBU	n.r.	–
3	dioxane	DABCO	trace	–
4	dioxane	DIPEA	82	96
5[d]	dioxane	K_3PO_4 (1.5 M)	50	96
6[d]	dioxane	KF (1.5 M)	44	96
7	THF	DIPEA	63	95
8	DCE	DIPEA	75	96
9	toluene	DIPEA	88	88
10	Et_2O	DIPEA	56	85
11[e]	dioxane	DIPEA	83	97

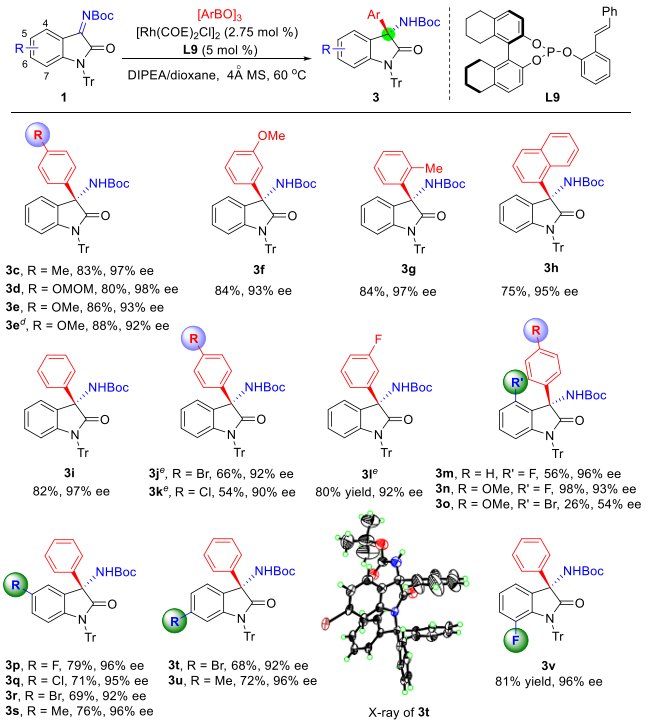
[a]Reaction conditions: **1c** (0.2 mmol), (*p*-TolBO)$_3$ (1 equiv), [Rh(COE)$_2$Cl]$_2$ (2.75 mol %), **L9** (5 mol %), and base (3 equiv) in 1.0 mL of solvent were stirred at 60 °C for 12 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]3 equiv of aqueous base were used. [e]100 mg of 4 Å molecular sieves were added.

conditions, the reaction gave the corresponding product in only 45% yield with 89% ee. With phenylboronate (5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane), no reaction occurred.

Having established the optimal reaction conditions, the scope of the reaction was then explored with diverse substrates. As summarized in Scheme 1, a wide range of arylboroxines and *N*-Boc ketimines bearing different substituents were examined. Gratifyingly, most transformations proceeded smoothly to give a variety of tetrasubstituted 3-aryl-3-aminooxindoles in moderate to good yields with high levels of enantioselectivity (90–98% ee). The overall yield and enantioselectivity are influenced by the nature of the reactants. Electron-rich arylboroxines reacted faster in comparison with phenylboroxine (**3c–g** vs **3i**), while in cases with electron-deficient arylboroxines, the reaction needs to be performed at 80 °C with solid K_3PO_4 as the base additive and displayed a modest decrease in yield and enantiocontrol (**3j–l**, 90–92% ee). Remarkably, *ortho*-substituted arylboroxines are also compatible in this reaction, affording product **3g** and **3h** in good yield and enantioselectivity. It is worth noting that the employment of a sterically hindered arylboron reagent remains problematic under palladium catalysis.[8b,c] Subsequently, various 3-ketimino-2-oxindoles bearing either electron-withdrawing or electron-donating substituents at the C4, C5, C6, or C7 position were found to be tolerated, and in most cases the corresponding products (**3m**, **3n**, **3p–v**) could be obtained in moderate to good yields with high enantioselectivities (92–96% ee). With 4-fluoro-substituted substrate, the yield was slightly reduced when phenylboroxine was employed (**3m**, 56% yield), while electron-rich arylboroxine could give excellent yield (**3n**, 98% yield). However, when bulky bromine was introduced at the C4 position, a sharp decrease in both yield and enantioselectivity was observed due to the difficulty in overcoming the steric encumbrance (**3o**, 26% yield, 54% ee).

Reaction at 1 mmol scale with **1** and tris(4-methoxyphenyl)-boroxin was carried out successfully and gave **3e** in 88% yield and 92% ee. The structure of **3t** was confirmed by X-ray

Scheme 1. Rh-Catalyzed Asymmetric 1,2-Addition of Arylboroxines to Isatin-Derived *N*-Boc Ketimines[a,b,c]

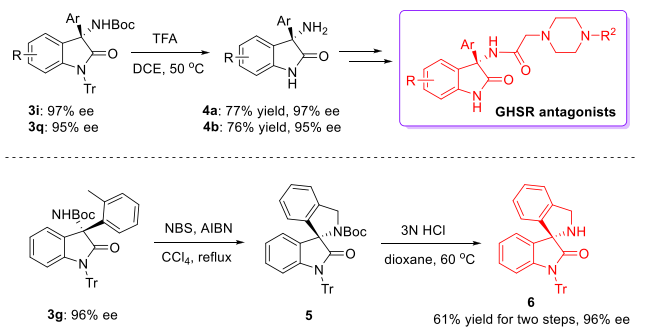


[a]Reaction conditions: imine substrate **1** (0.20 mmol), arylboroxine **3** (1.0 equiv), [Rh(COE)$_2$Cl]$_2$ (2.75 mol %), **L9** (5.0 mol %), and DIPEA (3.0 equiv), 100 mg of 4 Å MS in 1.0 mL of dioxane were stirred at 60 °C for 12 h, unless otherwise noted. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]One mmol scale, stirred for 24 h. [e]The reaction was carried out with 3 equiv of K_3PO_4 at 80 °C.

diffraction analysis (CCDC 1403781), and the stereochemistry of the quaternary carbon center was determined to be *S* (Scheme 1).

We next explored the synthetic utility of the current enantioselective arylation (Scheme 2). The *tert*-butoxycarbonyl

Scheme 2. Transformation of Addition Products



(Boc) and trityl (Tr) group of addition products **3** could be easily removed in one step with trifluoroacetic acid in 1,2-dichloroethane at 50 °C, giving optically active quaternary carbon-containing 3-aryl-3-aminooxindole in good yield without loss of enantiopurity, as exemplified by **4a** and **4b**. Notably, nonprotecting chiral 3-aryl-3-aminooxindoles **4** are critical synthetic intermediates for a series of GHSR antagonists.[4a] In the other case, NBS/AIBN-mediated bromination and cyclization of product **3g** in CCl_4 furnished an interesting

DOI: 10.1021/acs.orglett.9b02787
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spirocyclic compound **5**. The Boc group could be selectively deprotected with 3 N HCl in dioxane at 60 °C to deliver the corresponding (*S*)-spiro[indoline-3,1′-isoindolin]-2-one **6** with no erosion of optical purity. This showcases a unique advantage of our method, as such spirocyclic molecules are otherwise difficult to access particularly in a highly stereoselective manner.

In summary, we have developed an efficient rhodium-catalyzed enantioselective arylation of isatin-derived *N*-Boc ketimines using an exceptionally simple chiral phosphite-olefin as ligand. The method exhibits broad substrate generality and functional group tolerance, enabling ready access to a wide variety of valuable 3-aryl-3-aminooxindoles bearing a stereodefined quaternary carbon center in moderate to good yields (up to 98%) with excellent enantioselectivities (up to 98% ee). Significantly, these versatile products can be conveniently transformed into a range of biologically interesting complex molecules. Further efforts on exploring the application of this practical method in related biological and drug discovery studies are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02787.

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

Accession Codes

CCDC 1403781 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.

■ ACKNOWLEDGMENTS

We thank the National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (2018ZX09711002-006) and the National Natural Science Foundation of China (81521005, 21472205, 21325209) for financial support.

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