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Highly Enantioselective Arylation of *N*-Tosylalkylaldimines Catalyzed by Rhodium-Diene Complexes

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Supporting Information

ABSTRACT: A highly enantioselective rhodium-catalyzed arylation of aliphatic *N*-tosylaldimines has been developed. The combination of chiral bicyclo[3.3.0]octadiene ligands, an active rhodium hydroxide complex, and neutral reaction conditions is the key to achieving high yield and enantioselectivity. The application of this method is demonstrated by the enantioselective synthesis of chiral 2-aryl pyrrolidines and piperidines in a one-pot procedure. Furthermore, excellent results are also obtained for the imine substrates with the more readily cleavable *N*-nosyl protecting group.

Chiral α-arylamines are a common structural motif in natural products as well as in pharmaceutical molecules. Some examples are the naturally occurring cytokine modulator (−)-cytoxazone,[1] the third-generation antihistamine levocetirizine,[2] and the selective Kv1.5 blocker BMS-394136.[3] Among the methods to synthesize these structures, asymmetric rhodium-catalyzed arylation of imines represents an attractive approach. Since the first example reported by Tomioka in 2004,[4] significant efforts have been devoted to this rhodium-catalyzed transformation by various research groups.[5−8] In spite of the considerable advancements, the imine substrates are usually limited to aromatic imines. The major challenge in the addition of aliphatic imines is their tendency to undergo imine−enamine tautomerization, decomposition, and self-condensation under common reaction conditions. The only example with aliphatic imines was reported by Ellman and co-workers in 2008, utilizing a chiral bisphosphine ligand.[9] The resulting chiral α-aryl alkylamines were prepared in 68−96% yield with 81−98% ee. Therefore, a more efficient catalytic system is still highly desirable for the preparation of these interesting substructures in higher yield and with improved enantioselectivity.

In 2004, Hayashi reported a rhodium-catalyzed arylation of *N*-tosylarylaldimines with chiral bicyclo[2.2.2]octadiene ligands.[8a] Since then, a wide variety of chiral diene ligands have been successfully applied in this transformation.[7,8] Compared with chiral phosphine ligands, chiral diene ligands have provided higher enantioselectivity in many cases, especially the chiral bicyclo[3.3.0]octadiene ligands, which were first introduced by our group in 2007.[7a] They can readily be prepared in both enantiomeric forms and were found to be superior ligands for enantioselective arylation of *N*-tosyl- or *N*-nosylarylaldimines, providing chiral diaryl amines in extremely high enantioselectivity (98−99% ee). Herein, we report our recent success in the highly efficient arylation of *N*-tosylalkylaldimines with chiral bicyclo[3.3.0]octadiene ligands.[10]

Our investigation commenced with the use of *N*-tosylimine **1a** as a model substrate.[11] Under the standard reaction conditions previously developed for *N*-tosylarylimines, the addition of phenylboronic acid to **1a**, with bicyclo[3.3.0]octadienes **4a**−**4d** as ligands for screening, gave the desired product **3aa** in excellent enantioselectivities (98−99% ee). However, the yields were unsatisfactory (22−40%; Table 1, entries 1−4). Attempts to improve the reaction yield by employing KHF_2 as an additive[7c] (entry 5) or Ellman's reaction conditions proved to be fruitless (entry 6).[9]

We postulated that the low yields were due to the rapid decomposition of *N*-tosylimine **1a**. To verify this speculation, several control experiments were performed. It was found that ∼75% of imine **1a** was destroyed in hot aqueous dioxane (70 °C) in 3.5 h. This process was accelerated in the presence of a given base. For example, no imine **1a** was observed after 3.5 h when K_3PO_4 was added. According to this stability information, there are two possible options to improve the reaction yield: (1) use a more active catalyst to accelerate the imine transforming process or (2) use a base/acid-free reaction condition to slow the decomposition process.

In the following optimization studies, the reaction was carried out with $[RhCl(\mathbf{4a})]_2$ as catalyst without any base additive. Though only 29% yield was obtained, the result was promising, as this arylation could occur under a neutral condition (Table 2, entry 1). When more active $[Rh(OH)(\mathbf{4a})]_2$ was tested,[12] the desired adduct was obtained in almost quantitative yield (99%) with excellent enantioselectivity (>99% ee, entry 2). High enantioselectivities and slightly lower yields were observed when the reactions were conducted at lower temperatures (entries 3 and 4). Dropping the catalyst to 1 mol % did not affect the high selectivity (entry 5). The presence of 4 Å MS was also helpful for achieving high reaction yield (entry 6).

With the optimal reaction conditions in hand (Table 2, entry 2), the reaction scope was examined. Varying the substituent at the 4- or 3-position of the phenyl ring of the boronic acid with either an electron-donating or -withdrawing group gave the product in high yields (91−99%) with excellent enantioselectivities (98 to >99% ee; Table 3, entries 1−7). Slight decreases in the reaction selectivity were observed when the more sterically hindered 2-methoxyphenylboronic acid and 1-napthylboronic acid were used (entries 8 and 9). However, the enantioselectivity could be

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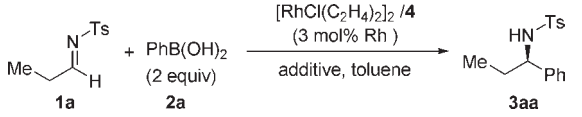
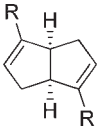
Table 1. Ligand Screening and Initial Optimization of Reaction Conditions[a]



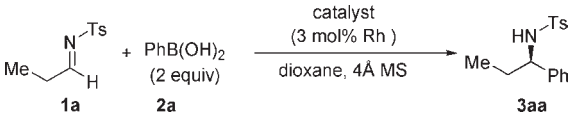
entry	ligand	temp (°C)	additive (equiv)	yield[b] (%)	ee[c] (%)
1	**4a**	55	Et_3N (2.0)	28	99
2	**4b**	55	Et_3N (2.0)	22	99
3	**4c**	55	Et_3N (2.0)	33	98
4	**4d**	55	Et_3N (2.0)	43	98
5[d]	**4a**	55	KHF_2 (4.0)	56	75
6[e]	**4a**	70	K_3PO_4 (0.2)	51	99



4a R = Ph
4b R = 3,5-$(CH_3)_2$Ph
4c R = 2-naphthyl
4d R = benzyl

[a] The reaction was carried out with **1a** (0.25 mmol), phenylboronic acid (0.5 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0038 mmol), and **4** (0.0085 mmol) in toluene (2 mL) at 55 °C, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 4.0 M aqueous KHF_2. [e] Dioxane was used as solvent instead of toluene, and 4 Å MS (300 mg) was added.

Table 2. Further Optimization Studies[a]

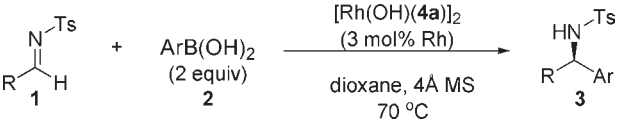


entry	catalyst	temp (°C)	yield[b] (%)	ee[c] (%)
1	$[RhCl(\mathbf{4a})]_2$	70	29	99
2	$[Rh(OH)(\mathbf{4a})]_2$	70	99	>99
3	$[Rh(OH)(\mathbf{4a})]_2$	55	97	99
4	$[Rh(OH)(\mathbf{4a})]_2$	40	79	99
5[d]	$[Rh(OH)(\mathbf{4a})]_2$	70	81	99
6[e]	$[Rh(OH)(\mathbf{4a})]_2$	70	83	99

[a] The reaction was carried out with **1a** (0.25 mmol), phenylboronic acid (0.5 mmol), 4 Å MS (300 mg), and rhodium catalyst (0.0038 mmol) in dioxane (2 mL) at 70 °C, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 1 mol % catalyst loading. [e] Without 4 Å MS.

improved by using $[Rh(OH)(\mathbf{4d})]_2$ as catalyst, in which the hindered phenyl group in the diene ligand was replaced by a flexible benzyl group. A variety of *N*-tosyl alkylaldimines with carbon chains differing in length and branched structure turned to be suitable substrates, providing the corresponding products in high yields (92−95%) and excellent enantioselectivities (>99% ee, entries 10−15). Imines with terminal functional groups such as

Table 3. Asymmetric Rhodium-Catalyzed Arylation of Aliphatic *N*-Tosylimines[a]



entry	R	Ar	3	yield[b] (%)	ee[c,d] (%)
1	Et (**1a**)	C_6H_5 (**2a**)	**3aa**	99	>99
2	Et (**1a**)	4-$MeOC_6H_4$ (**2b**)	**3ab**	99	>99
3	Et (**1a**)	4-MeC_6H_4 (**2c**)	**3ac**	99	99
4	Et (**1a**)	4-$CF_3C_6H_4$ (**2d**)	**3ad**	93	99
5	Et (**1a**)	4-ClC_6H_4 (**2e**)	**3ae**	99	98
6	Et (**1a**)	3-MeC_6H_4 (**2f**)	**3af**	92	99
7	Et (**1a**)	3-$MeOC_6H_4$ (**2g**)	**3ag**	98	99
8[e]	Et (**1a**)	1-naphthyl (**2h**)	**3ah**	99 (97)	91 (93)
9[e]	Et (**1a**)	2-$MeOC_6H_4$ (**2i**)	**3ai**	91 (96)	93 (98)
10	*n*-Pr (**1b**)	C_6H_5 (**2a**)	**3ba**	92	>99
11	*i*-Pr (**1c**)	C_6H_5 (**2a**)	**3ca**	94	>99
12	*n*-Bu(**1d**)	C_6H_5 (**2a**)	**3da**	95	>99
13	*i*-Bu (**1e**)	C_6H_5 (**2a**)	**3ea**	92	>99
14	*c*-Hex (**1f**)	C_6H_5 (**2a**)	**3fa**	93	>99
15	Et_2CH (**1g**)	C_6H_5 (**2a**)	**3ga**	95	>99
16	$PhCH_2CH_2$ (**1h**)	C_6H_5 (**2a**)	**3ha**	99	>99
17	$BnOCH_2CH_2CH_2$ (**1i**)	C_6H_5 (**2a**)	**3ia**	90	>99
18	$ClCH_2CH_2CH_2$ (**1j**)	C_6H_5 (**2a**)	**3ja**	87	>99
19	$ClCH_2(CH_2)_2CH_2$ (**1k**)	C_6H_5 (**2a**)	**3ka**	89	>99

[a] All reactions were performed as described in Table 2 (entry 2) on a 0.25 mmol scale, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configurations of **3aa** and **3ca** were determined to be *R* by comparison with the known optical rotations $[\alpha]_D$ in the literature. The absolute configurations of other compounds were also assigned as *R* by consideration of the stereochemical pathway. [e] The data in parentheses are results obtained with $[Rh(OH)(\mathbf{4d})]_2$ as catalyst.

Ph, BnO, or Cl were also acceptable substrates, affording the desired adducts in 87−99% yield and >99% ee (entries 16−19). This methodology could potentially be used for the synthesis of other interesting nitrogen-containing compounds, such as cyclic amines.

The application of this strategy was next demonstrated by the preparation of chiral 2-aryl pyrrolidines and piperidines. Owing to their wide presence in biologically active compounds, great efforts have been pursued for their asymmetric synthesis.[13,14] Thus, *N*-tosylimines **1j** and **1k** were reacted with representative arylboronic acids, followed by treatment with base in a one-pot procedure, affording several 2-aryl pyrrolidines and piperidines **5** in high yields (73−84%) and excellent enantioselectivities (≥99% ee; Table 4). The tosyl group in each resulting product was removed by reduction with naphthalene/Li. For example, compound **5c** was converted to the chiral amine **6**, an enantiomer of the key unit for BMS-394136, in 77% yield (Scheme 1).[3]

Currently, we are also studying the addition to imines with more readily cleavable protecting groups. Some preliminary results for the *N*-nosylimine substrates are shown in Table 5.[15] Although the reaction yields were slightly decreased compared with those

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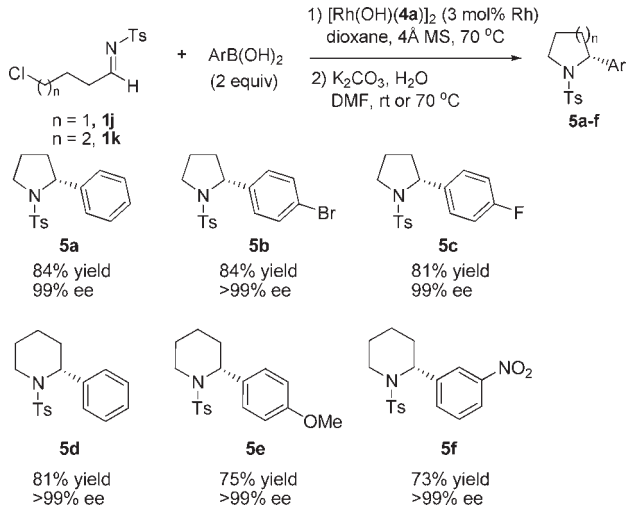
Table 4. One-Pot Synthesis of Chiral 2-Aryl Pyrrolidine and Piperidine Derivatives



[a] All addition reactions were performed as described in Table 2 (entry 2) and followed by a base-promoted cyclization sequence in a one-pot procedure (See Supporting Information for details).

Scheme 1. Removal of Tosyl Protecting Group

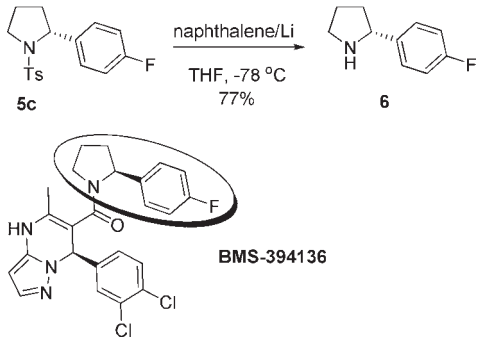
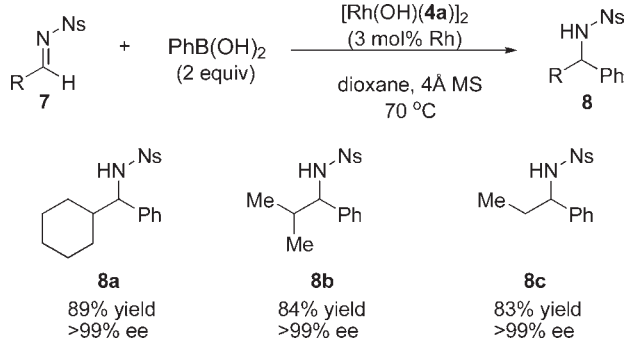


Table 5. Asymmetric Rhodium-Catalyzed Arylation of Aliphatic *N*-Nosylimines[a]



[a] All addition reactions were performed as described in Table 2 (entry 2).

obtained with *N*-tosylimines, excellent enantioselectivities were maintained.

In summary, we have developed a rhodium-catalyzed asymmetric addition of arylboronic acids to aliphatic *N*-tosylimines using chiral rhodium-diene complexes as catalyst.[16] The bicyclo[3.3.0]octadienes proved to be superior ligands for this transformation, providing the resulting products in exceptionally high enantioselectivity (typically ≥99% ee). The combination of an active rhodium hydroxide catalyst and neutral reaction conditions is the key to obtaining high reaction yields. This method was applied to the enantioselective synthesis of chiral 2-aryl pyrrolidines and piperidines in a one-pot procedure. Extension of this methodology to aliphatic *N*-nosylimines is also very successful.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data, ^{1}H and ^{13}C NMR spectra, and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Such addition reactions were unsuccessful for the imine substrates with both *N*-diphenylphosphinoyl [*N*-P(O)Ph_2] and *N*-*tert*-butyloxycarbonyl (*N*-Boc) protecting groups. See Supporting Information for details.

(16) In recent advancements, 1.2 equiv of arylboronic acid is enough to obtain high reaction yield. See Supporting Information for details.