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Rhodium-Catalyzed Asymmetric Arylation of *N*-Tosyl Ketimines

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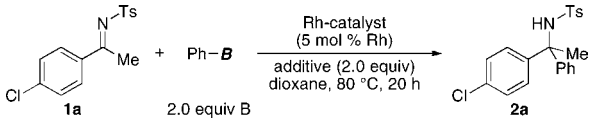
Abstract: A rhodium-catalyzed addition of sodium tetraarylborates to *N*-tosyl ketimines is described. Highly efficient asymmetric catalysis has been achieved by employing a chiral diene ligand, constructing chiral amine derivatives possessing α-tetrasubstituted carbon stereocenters with high enantioselectivity.

Catalytic asymmetric addition of carbon-based nucleophiles to ketimines provides straightforward access to enantioenriched chiral amines possessing an α-tetrasubstituted carbon stereocenter.[1] Strecker-[2] and Mannich-type[3] reactions are most widely used in the literature, but the use of organometallic reagents as the nucleophile has been much less studied. In fact, to the best of our knowledge, only an allylboronate[4] and dialkylzincs[5] have been employed under copper catalysis to effect allylation and methylation/ethylation, respectively. In this context, herein we describe the development of a rhodium-catalyzed arylation of *N*-tosyl ketimines by using air-stable sodium tetraarylborates as effective nucleophiles to give α,α-disubstituted arylmethylamine derivatives, including its highly enantioselective variant by the use of a chiral diene ligand.[6,7]

Initially, we chose *N*-tosyl imine of 4′-chloroacetophenone (**1a**) as a model substrate[8] and attempted an addition of phenylboronic acid (2.0 equiv) under the catalysis of $[Rh(OH)(cod)]_2$ (5 mol % Rh) in aqueous dioxane at 80 °C (Table 1, entry 1).[9] Although phenylboronic acid was completely consumed under these conditions, addition product **2a** was obtained only in 16% yield, and no significant improvement was observed by the use of phenylboroxine or phenylboronic acid neopentylglycol ester as the nucleophile in anhydrous dioxane (22−24% yield, entries 2 and 3). In contrast, somewhat higher yield of **2a** was realized by using triphenylborane in methanolic dioxane (42% yield, entry 4). Similar reactivity was also observed with potassium phenyltrifluoroborate[10] in the presence of $[RhCl(cod)]_2$ (5 mol % Rh) (45% yield, entry 5), and the use of sodium tetraphenylborate[11] as the nucleophile led to the formation of **2a** in as high as 91% yield (entry 6). In comparison, $[RhCl(binap)]_2$,[12] a rhodium/bisphosphine complex, did not catalyze the addition of sodium tetraphenylborate to **1a** (entry 7).

Table 1. Rhodium-Catalyzed Addition of Phenylboron Reagents to **1a**: Effect of Catalyst and Nucleophile

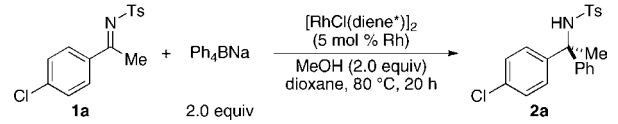


entry	Rh catalyst	Ph−B	additive	yield (%)[a]
1	$[Rh(OH)(cod)]_2$	$PhB(OH)_2$	H_2O	16
2	$[Rh(OH)(cod)]_2$	$(PhBO)_3$	none	22
3	$[Rh(OH)(cod)]_2$	$PhB(OR)_2$[b]	none	24
4	$[Rh(OH)(cod)]_2$	Ph_3B	MeOH	42
5	$[RhCl(cod)]_2$	$PhBF_3K$	MeOH	45
6	$[RhCl(cod)]_2$	Ph_4BNa	MeOH	91[c]
7	$[RhCl(binap)]_2$	Ph_4BNa	MeOH	0

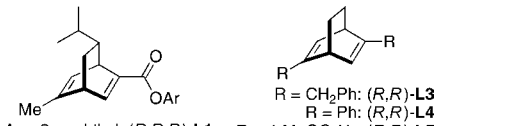
[a] Determined by ^1H NMR analysis against an internal standard. [b] $(OR)_2 = OCH_2CMe_2CH_2O$. [c] Isolated yield.

On the basis of the results in Table 1, we examined chiral diene ligands[13−15] for the development of its asymmetric variant and found that the reaction of **1a** with sodium tetraphenylborate smoothly proceeded in the presence of ester-attached C_1-symmetric dienes (*R*,*R*,*R*)-**L1**[11d,16] and (*R*,*R*,*R*)-**L2**[16] to give **2a** with 82% and 78% ee, respectively (Table 2, entries 1 and 2). The use of C_2-symmetric diene (*R*,*R*)-**L3**[17] with benzyl groups on the olefins turned out to be somewhat more effective (87% ee, entry 3), and changing its substitutents to phenyl groups ((*R*,*R*)-**L4**)[17] led to the formation of **2a** with 90% ee (entry 4). Although electron-rich 4-methoxyphenyl-substituted diene (*R*,*R*)-**L5** did not show further improvement on the enantioselectivity (90% ee, entry 5), modification of the ligand substituents to electron-deficient 4-trifluoromethylphenyl groups ((*R*,*R*)-**L6**)[17b] enhanced the enantioselectivity to 95% ee (entry 6). The best yield and ee were achieved by lowering the reaction temperature to 60 °C (83% yield, 97% ee, entry 7), and the absolute configuration of the product was determined to be *S* by X-ray crystallographic analysis.[18]

Table 2. Rhodium-Catalyzed Asymmetric Addition of Sodium Tetraphenylborate to **1a**: Effect of Ligand



entry	diene	yield (%)[a]	ee (%)[b]
1	(*R*,*R*,*R*)-**L1**	77	82 (*S*)
2	(*R*,*R*,*R*)-**L2**	70	78 (*S*)
3	(*R*,*R*)-**L3**	83	87 (*S*)
4	(*R*,*R*)-**L4**	68	90 (*S*)
5	(*R*,*R*)-**L5**	76	90 (*S*)
6	(*R*,*R*)-**L6**	73	95 (*S*)
7[c]	(*R*,*R*)-**L6**	83	97 (*S*)



[a] Isolated yield. [b] Determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol = 95/5. [c] The reaction was run at 60 °C.

Under the conditions using $[RhCl((R,R)\text{-}\mathbf{L6})]_2$ as the catalyst, several aryl methyl ketone-derived imines **1a**−**d** effectively undergo phenylation to give the corresponding 1,1-diarylethylsulfonamides (**2a**−**d**) in high yield with excellent enantioselectivity (94−97% ee; Table 3, entries 1−4).[19] In addition, indanone- and tetralone-derived imines (**1e**,**f**) as well as a dialkyl ketimine (**1g**) can be employed as suitable substrates for the present catalysis (≥98% ee, entries 5−7). With regard

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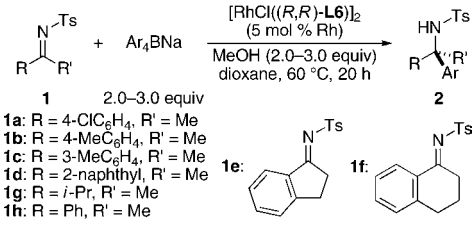
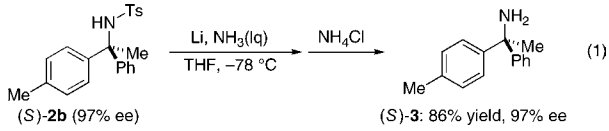
to the nucleophilic component, several other aryl groups can be effectively added to the *N*-tosyl imine of acetophenone (**1h**) with high enantiomeric excesses (95−98% ee, entries 8−12). Highly enantioselective preparation of 1,1-diarylethylsulfonamides having substituents on both of the aryl groups is also possible, as exemplified in entry 13. The tosyl group on the nitrogen atom of (*S*)-**2b** can be easily removed to give 1,1-diarylethylamine (*S*)-**3** in 86% yield, retaining its enantiomeric purity (eq 1).

Table 3. Rhodium-Catalyzed Asymmetric Addition of Sodium Tetraarylborates to **1**: Scope

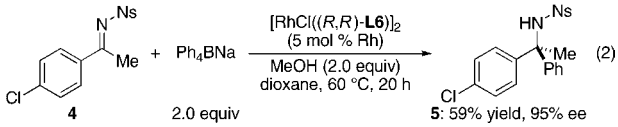


entry	1	Ar	product	yield (%)[a]	ee (%)[b]
1	**1a**	Ph	(*S*)-**2a**	83	97
2	**1b**	Ph	(*S*)-**2b**	78	97
3	**1c**	Ph	(*S*)-**2c**	82	94
4	**1d**	Ph	(*S*)-**2d**	82	94
5	**1e**	Ph	(*S*)-**2e**	97	>99.5
6[c]	**1f**	Ph	(*S*)-**2f**	53	98
7[c]	**1g**	Ph	(*R*)-**2g**	64	98
8[d]	**1h**	4-ClC_6H_4	(*R*)-**2a**	86	98
9[e]	**1h**	4-MeC_6H_4	(*R*)-**2b**	92	98
10[e]	**1h**	4-$MeOC_6H_4$	(*R*)-**2h**	91	98
11[f]	**1h**	3-FC_6H_4	(*R*)-**2i**	63	95
12[d]	**1h**	3-MeC_6H_4	(*R*)-**2c**	95	98
13[e]	**1a**	4-MeC_6H_4	(*S*)-**2j**	75	96

[a] Isolated yield. [b] Determined by chiral HPLC. [c] The reaction was run for 48 h with 10 mol % of catalyst. [d] The reaction was run at 80 °C. [e] The reaction was run in THF. [f] The reaction was run at 90 °C.



In addition to *N*-tosyl ketimines, the present catalysis has also been applied to the reaction with *N*-nosyl ketimines. For example, a reaction of the *N*-nosyl imine of 4′-chloroacetophenone (**4**) with sodium tetraphenylborate gave addition product **5** in 59% yield with 95% ee (eq 2).



In summary, we have disclosed that rhodium/diene complexes can effectively catalyze the addition of sodium tetraarylborates to *N*-tosyl ketimines. A highly efficient asymmetric variant has also been described to provide chiral amine derivatives possessing an α-tetrasubstituted carbon stereocenter by employing chiral diene (*R*,*R*)-**L6** as the ligand.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF) and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) See Supporting Information for details.
(19) *N*-Tosyl imines of 2′-methylacetophenone and 4′-chloropropiophenone do not undergo phenylation effectively under the present conditions.

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