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Highly Enantioselective Rh-Catalyzed Alkenylation of Imines: Synthesis of Chiral Allylic Amines via Asymmetric Addition of Potassium Alkenyltrifluoroborates to *N*-Tosyl Imines

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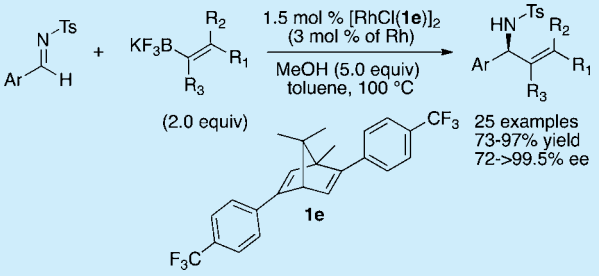
Supporting Information

ABSTRACT: For the first time, simple *N*-tosyl aryl aldimines, prepared from the condensation of tosyl amide and aromatic aldehydes, can be used as substrates in the rhodium catalyzed 1,2-addition reaction using alkenylboron nucleophiles. In the presence of 1.5 mol % of [RhCl(**1e**)]$_2$, enantioselective addition of various potassium alkenyltrifluoroborates to aryl aldimines furnished the corresponding chiral allylic amines in 73−96% yield and 72−>99.5% ee. Notably, this method efficiently provides the di-, tri-, and tetrasubstituted allylic *N*-tosyl amines with high asymmetric induction.



Owing to the ubiquitous existence of the chiral allylic amine moiety in biologically and pharmacologically active molecules, tremendous effort has been focused toward the development of efficient methodologies for their synthesis.[1] Herein, we report the first asymmetric addition of potassium alkenyltrifluoroborates to prochiral *N*-tosyl aryl and heteroaryl aldimines, providing chiral allylic *N*-tosyl amines with high enantioselectivities in the presence of a rhodium/chiral diene catalyst.

Asymmetric transformations catalyzed by transition-metal complexes offer reliable access to optically active allylic amines. Palladium- and iridium-catalyzed enantioselective substitution of allylic electrophiles with amine-based nucleophiles is probably the most widely used method for the synthesis of enantioenriched allylic amines.[2] Additionally, the enantioselective rearrangement of allylic imidates has been demonstrated to efficiently afford chiral allylic amines with high ee.[3] In principle, the asymmetric addition of vinyl nucleophiles to imines is a reasonably straightforward approach to chiral allylic amines.[4−7] The rhodium-catalyzed enantioselective addition of nucleophiles to imines has been increasingly used in recent times for the synthesis of chiral amines. While the use of arylboron nucleophiles is well documented in this transformation owing to their ready availability and their generally high stability,[8] reports of the utilization of the corresponding alkenylboron species is scarce.[9,10] Ellman et al. have reported a highly diastereoselective Rh(I)-catalyzed addition of various alkenylboron reagents to chiral *N*-*tert*-butanesulfinyl aldimines using an achiral Rh(I) catalyst,[11] but this methodology relies on the stoichiometric amount of the chiral auxiliary to induce asymmetry during the addition reaction. With respect to the enantioselective version of this addition reaction, although only one single example of the use of an *alkenyl*trifluoroborate nucleophile was described by Hayashi et al. in their study of asymmetric addition of potassium *aryl*trifluoroborates to *N*-sulfonyl ketimines,[12a] and a subsequent report from Lam et al. has demonstrated the Rh-catalyzed highly enantioselective addition of potassium alkenyltrifluoroborates to cyclic imines,[12b] to the best of our knowledge there is no report of Rh-catalyzed enantioselective addition of alkenylboron reagents to *N*-tosyl aldimines.

Previously we reported the development and application of a series of novel and stable chiral bicyclo[2.2.1] dienes[13] that serve as effective chiral ligands for the Rh-catalyzed asymmetric 1,4-addition of various arylboronic acids to fumarates,[13b] cyclic[13c] and acyclic α,β-unsaturated carbonyl compounds,[13d] and nitroolefins,[13e] yielding the desired adducts with high optical purities. As compared to other diene ligands, these ligands provide more active catalysts when combined with rhodium(I) for 1,4-addition reaction of arylboronic acids while using low catalyst loadings (TON up to 2000). Additionally, this catalytic system has been applied to the synthesis of highly enantioenriched chiral diarylmethylamines from the asymmetric addition of various arylboronic acids to *N*-tosyl aldimines at room temperature (eq 1; see Table 1 for ligand structure[14]).

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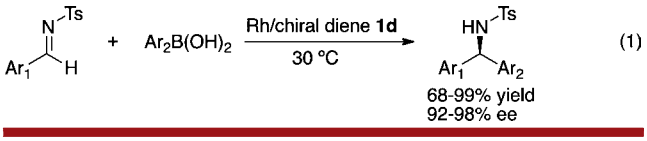
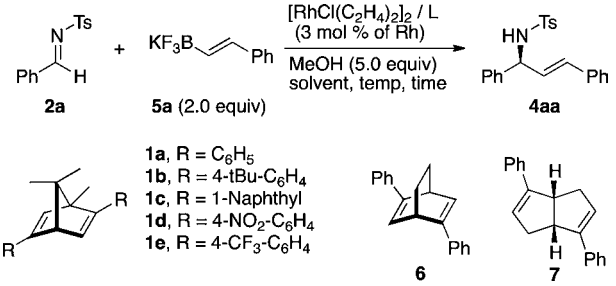


Table 1. Rh-Catalyzed Asymmetric Addition of Potassium *trans*-Styryltrifluoroborate (5a) to *N*-Tosyl Aldimine 2a[a]



entry	L	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	dioxane	80	20	66	83
2	**6**	dioxane	80	20	31	−85
3	**7**	dioxane	80	20	22	−87
4	**1b**	dioxane	80	20	93	80
5	**1c**	dioxane	80	20	93	87
6	**1d**	dioxane	80	20	95	90
7	**1e**	dioxane	80	20	99	92
8[d]	**1e**	dioxane	100	15	83	94
9[d]	**1e**	toluene	100	15	92	94

[a]Reaction conditions: **2a** (0.125 mmol), **5a** (0.250 mmol), $[RhCl(C_2H_4)_2]_2$, (1.87 μmol, 1.5 mol %), **L** (4.50 μmol, 3.6 mol %), MeOH (0.625 mmol), and dioxane (2 mL). [b]Isolated yield. [c]Determined by chiral HPLC on an OD-H column. [d]$[RhCl(\mathbf{1e})]_2$ was used.

In the context of ongoing studies of these catalysts and their asymmetric addition reactions, it seemed natural to extend their use to alkenylboronic acids as nucleophiles. In a preliminary test of this concept using 3 mol % of the rhodium catalyst, generated *in situ* from the reaction of $[RhCl(C_2H_4)_2]_2$ and chiral diene ligand **1a**, the model addition reaction of (*E*)-2-phenylethenylboronic acid (**3**) with imine **2a** in MeOH and NEt_3 (2.4 equiv) proceeded at 60 °C for 20 h to furnish the desired optically active allylic amine **4aa** in 37% yield with 82% ee (eq 2). This promising finding immediately prompted us to

instead test the potassium trifluoroborate derivative of compound **3**, which was found to be a reactive alkenylboron nucleophile in the studies of Ellman et al.,[11] Hayashi et al.,[12a] and Lam et al.[12b]

The enantioselective addition of potassium (*E*)-2-phenylethenyltrifluoroborate (**5a**), in the presence of 3 mol % of Rh/**1a** catalyst, proceeded at an elevated temperature (80 °C) to provide the desired adduct **4aa** with an appreciably improved chemical yield (66%) but similar selectivity (83% ee) (Table 1, entry 1). For a direct comparison, commercially available chiral diene ligands bearing bicyclo[2.2.2] and bicyclo[3.3.0] skeletons (**6** and **7**) were also tested in this transformation, giving the desired product in comparatively low chemical yields with comparable enantioselectivities under the same reaction conditions (entries 2 and 3). Subsequently, our own variously substituted diene ligands (**1b**−**1e**) were investigated in the parent vinylation reaction. While the use of ligand **1b** with bulky *para*-substituents on the benzene rings exhibited a much improved chemical yield (93%, entry 4), both improved yields and asymmetric induction were observed upon the employment of ligands **1c** and **1d**, which bear 1-naphthyl substituents (entry 5) or electron-withdrawing nitro groups at the *para*-position of benzene rings (entry 6), respectively. Chiral diene ligand **1e**, with 4-CF_3-phenyl substituents, displayed better catalytic activity and enantioselectivity, yielding adduct **4aa** in 99% yield and 92% ee (entry 7). While the use of preformed $[RhCl(\mathbf{1e})]_2$ offered adduct **4aa** in a disappointing 83% yield when using dioxane as a solvent (entry 8), a significantly improved 92% yield with the same level of enantiomeric induction (94% ee) was witnessed when the reaction was conducted in toluene (entry 9). With dioxane being a highly undesirable solvent in the manufacture of pharmaceuticals due to its relatively high toxicity,[15] identification of comparatively less toxic toluene as a solvent was pleasing. All subsequent tests were conducted with this industrially acceptable solvent. The absolute configuration of **4aa** was unambiguously determined to be (*S*) by X-ray crystallography (Figure 1).

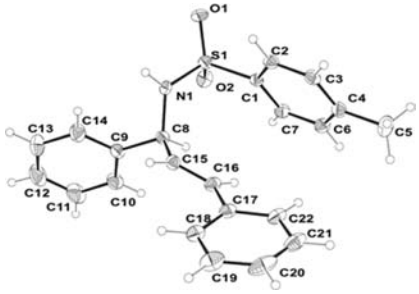


Figure 1. ORTEP illustration of chiral allylic amine **4aa** with thermal ellipsoid drawn at 30% probability level.

Using the preferred conditions (Table 1, entry 9) identified during the preliminary screening studies, the asymmetric alkenylation of a variety of *N*-Ts-aldimines (**2a**−**n**) with various potassium alkenyltrifluoroborates (**5a**−**j**) was examined (Table 2). Formation of (*E*)-1,3-disubstituted chiral allylic amines (**4aa**−**4la**) with high ee (78−97%) was obtained from the asymmetric addition of compound **5a** to aryl aldimines substituted with both electron-donating and -withdrawing groups (entries 1−12). A negligible effect on the reaction outcome was observed when substituted aryl alkenyltrifluoroborates (**5b**, R_1 = 4-F-C_6H_4; **5c**, R_1 = 4-Me-C_6H_4) were tested, offering adducts **4ab** and **4ac** in good chemical yields with 95% and 87% ee, respectively (entries 13 and 14). Asymmetric addition of the nonaromatic nucleophile (*E*)-1-octenyltrifluoroborate (**5d**, R_1 = *n*-hexyl, R_2 = H, R_3 = H) to imine **2a** furnished the desired product **4ad** in 82% yield, however, with diminished asymmetric induction (72% ee) (entry 15). Trisubstituted nonaromatic potassium (2*Z*)-2-buten-2-yltrifluoroborate (**5e**, R_1 = R_3 = Me, R_2 = H) was also a good nucleophile for addition to aldimines **2a**, **2b**, **2m**, and **2n** derived from benzaldehyde, *p*-tolualdehyde, 2-furaldehyde, and 2-thiophenecarboxaldehyde, respectively, yielding the corresponding chiral (*E*)-1,2,3-trisubstituted allylic amines (**4ae**, **4be**, **4me**, and **4ne**) in good yields (89−94%). In these examples of nonaromatic nucleophiles, however, much higher enantioin-

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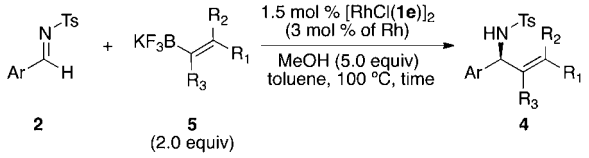
Table 2. Rh-Catalyzed Asymmetric Alkenylation of Various *N*-Tosyl Aldimines[a]



2 5 (2.0 equiv) 4

5a : R1 = C_6H_5, R_2 = R_3 = H
5b : R1 = 4-F-C_6H_4, R_2 = R_3 = H
5c : R1 = 4-Me-C_6H_4, R_2 = R_3 = H
5d : R_1 = *n*-Hex, R_2 = R_3 = H
5e : R_1 = R_3 = Me, R_2 = H
5f : R_1-R_3 = $(CH_2)_4$, R_2 = H
5g : R_1 = CO_2Me, R_2 = Me, R_3 = H
5h : R_1 = R_2 = H, R_3 = Me
5i : R_1 = R_3 = H, R_2 = Me
5j : R_1 = R_2 = R_3 = Me

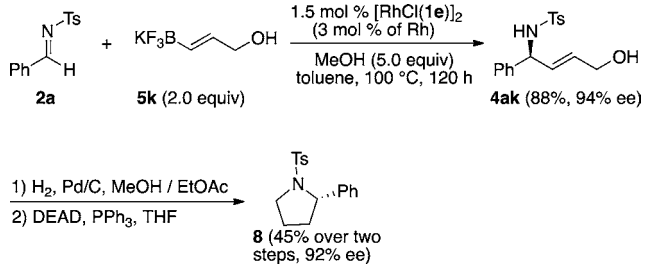
entry	Ar	5	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5 (**2a**)	**5a**	15	92 (**4aa**)	94
2	4-Me-C_6H_4 (**2b**)	**5a**	48	85 (**4ba**)	94
3	3-Me-C_6H_4 (**2c**)	**5a**	62	85 (**4ca**)	93
4	2-Me-C_6H_4 (**2d**)	**5a**	50	95 (**4da**)	93
5	4-MeO-C_6H_4 (**2e**)	**5a**	48	85 (**4ea**)	97
6	4-F-C_6H_4 (**2f**)	**5a**	36	96 (**4fa**)	93
7	2-F-C_6H_4 (**2g**)	**5a**	40	90 (**4ga**)	88
8[d]	2-Cl-C_6H_4 (**2h**)	**5a**	55	90(82) (**4ha**)	78(93)
9	2,4-Cl_2-C_6H_3 (**2i**)	**5a**	34	80 (**4ia**)	88
10[d]	3,4-Cl_2-C_6H_3 (**2j**)	**5a**	60	82(72) (**4ja**)	84(96)
11[d]	1-naphthyl (**2k**)	**5a**	36	87(80) (**4ka**)	83(95)
12[d]	2-naphthyl (**2l**)	**5a**	54	65(60) (**4la**)	84(94)
13	C_6H_5 (**2a**)	**5b**	96	73 (**4ab**)	95
14	C_6H_5 (**2a**)	**5c**	72	89 (**4ac**)	87
15	C_6H_5 (**2a**)	**5d**	15	82 (**4ad**)	72
16	C_6H_5 (**2a**)	**5e**	62	89 (**4ae**)	91
17	4-Me-C_6H_4 (**2b**)	**5e**	38	97 (**4be**)	93
18	2-furyl (**2m**)	**5e**	30	91 (**4me**)	90
19	2-thienyl (**2n**)	**5e**	16	94 (**4ne**)	96
20	C_6H_5 (**2a**)	**5f**	60	82 (**4af**)	98
21	C_6H_5 (**2a**)	**5g**	144	93 (**4ag**)	>99.5
22	C_6H_5 (**2a**)	**5h**	20	90 (**4ah**)	98
23	C_6H_5 (**2a**)	**5i**	20	93 (**4ai**)	91
24	C_6H_5 (**2a**)	**5j**	20	97 (**4aj**)	98

[a]General reaction conditions: *N*-tosyl aldimines **2** (0.125 mmol), **5** (0.250 mmol), [RhCl(**1e**)]$_2$ (1.87 μmol, 1.5 mol %), MeOH (0.625 mmol) in toluene (2 mL). [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase. [d]The value in the parentheses was obtained after recrystallization.

duction (90−96% ee) was achieved and no isomerization of the double bond was observed (entries 16−19). Six-membered endocyclic alkenyltrifluoroborate **5f** provided the trisubstituted (*E*)-allylic amine (**4af**) bearing a cyclohexenyl group in high selectivity (98% ee; entry 20). Notably, when benzaldimine **2a** was treated with the (*E*)-β-substituted trifluoroborate derivative of methyl 1-methyl-acrylate (**5g**) that harbors two β-substituents (R_1 = CO_2Me, R_2 = Me), the desired (*E*)-1,3,3-trisubstituted allylic amine (**4ag**) was produced with exceptional ee (>99.5%), albeit slowly due to the lower nucleophilicity resulting from the electron-withdrawing ester group (entry 21). The addition of potassium trifluoroborate **5h** (R_1 = R_2 = H, R_3 = Me) to aldimine **2a** gave the corresponding gem-disubstituted allylic amine (**4ah**) in 90% yield with 98% ee (entry 22). Chiral (*Z*)-allylic amine **4ai** was synthesized by employing the reaction of potassium *cis*-1-propenyltrifluoroborate (**5i**) and aldimine **2a** in 93% yield with 91% ee, notably without isomerization of the *cis*-geometry of the double bond (entry 23). Even the tetrasubstituted potassium trifluoroborate **5j** (R_1 = R_2 = R_3 = Me) underwent addition to imine **2a** in a highly selective manner (98% ee) and high yield (97%) to offer **4aj** (entry 24).

A facile synthesis of an enantioenriched 2-arylpyrrolidine derivative, which is from a structural family found in numerous natural products and biologically active compounds,[16] was also examined. Enantioselective addition of potassium trifluoroborate **5k**, under the optimized conditions, to aldimine **2a** furnished allylic aminoalcohol **4ak** in 88% yield and 94% ee, notably without recourse to protection of the hydroxyl group, which following hydrogenation and cyclization under Mitsunobu conditions[17] offered *N*-tosyl-2-phenyl pyrrolidine (**8**) with 92% ee in 45% yield over two steps (Scheme 1).

Scheme 1. Synthesis of *N*-Tosyl-2-phenyl Pyrrolidine (8)



Shown in Figure 2 is a proposed transition structure comprising a coordination complex of *N*-tosyl imine **2a** and

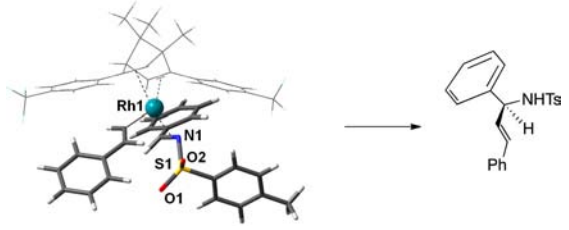


Figure 2. A transition structure for the asymmetric addition reaction to imine **2a**.

the Rh-**1e**-styryl species as identified using DFT calculations employing the 6-31G+ (d) method for C, N, O, S, F and the 6-31G+ (d, p) method[18] for H of the ligand structure and the effective core potentials (def2-TZVP)[19] for the Rh atom. The steric repulsion between the 4-CF_3-phenyl groups on the diene skeleton and the imine renders the initial coordination of the Rh-atom to the *Si*-face of the imino group more favorable, leading to the formation of (*S*)-**4aa**.

In conclusion, we have described the first preparation of chiral allylic *N*-tosyl amines *via* the asymmetric 1,2-addition of potassium alkenyltrifluoroborates to *N*-tosyl arylaldimines catalyzed by a novel rhodium/chiral diene complex. Generally, the enantioselective alkenylation reaction proceeded smoothly in a highly enantioselective manner to provide optically active allylic *N*-tosyl amines in good yields. The reaction was tolerant of unprotected alcohol and ester functionality in the nucleophile as well as various substituted aryl and heteroaryl aldimines. The geometries of the olefins were preserved, and the methodology worked well for a tetrasubstituted alkenyl nucleophile. This method provides products that can be readily further functionalized to provide more complex and useful structures as successfully demonstrated by the synthesis of chiral *N*-tosyl-2-phenyl pyrrolidine (**8**).

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and complete characterizations of the 1,2-addition products (NMR spectra, HPLC chromatograms of racemic and enantioenriched compounds, IR, HRMS and melting points). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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