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Enantioselective Alkenylation of Aldimines Catalyzed by a Rhodium–Diene Complex

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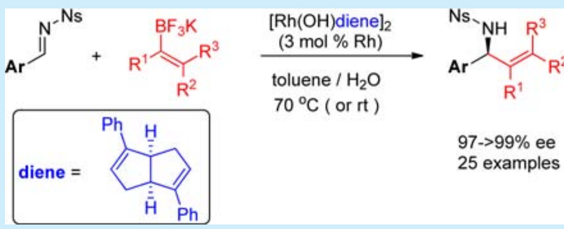
Supporting Information

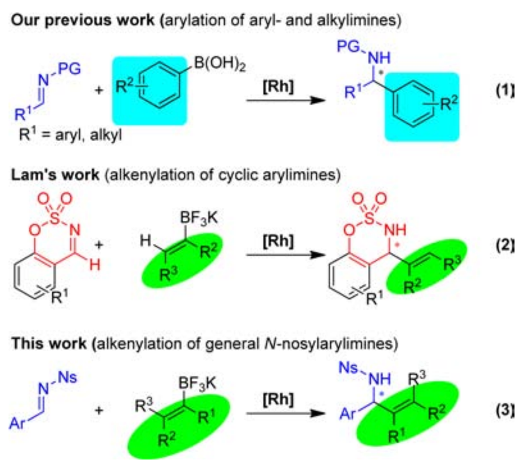
ABSTRACT: An efficient rhodium-catalyzed asymmetric addition reaction of potassium alkenyltrifluoroborates to *N*-nosylaldimines has been developed. Under optimal conditions, the reactions proceeded with good to excellent yields and excellent enantioselectivities (97 → 99% ee). The utility of this method is demonstrated by the formal synthesis of (−)-aurantioclavine.



Chiral α-branched allylic amines are an important structural motif because of their versatile synthetic utilities as chiral building blocks as well as their wide existence in natural products.[1] Over the past decades, many catalytic asymmetric methods have been developed for their synthesis, including the rearrangement of allylic imidates,[2] the metal-catalyzed allylic amination,[3] the hydroamination of alkynes or allenes,[4] and the nucleophilic additions to imines.[5−8] Among all of the strategies, rhodium-catalyzed enantioselective 1,2-addition of alkenylboron reagents to imines is an attractive transformation due to a variety of practical advantages, such as the flexibility of its modular synthesis, the benign reaction conditions, and the easy accessibility of alkenylboron reagents and imines. However, compared with the extensive research on rhodium-catalyzed enantioselective 1,2-addition of arylboronates to imines,[7,8] the application of alkenylboronates is underappreciated and far less studied,[9] particularly in the context of general acyclic imines.

The comparatively slow development of the addition with alkenylboronates is partially associated with the relatively lower stability of the alkenylboron reagents.[10] Recently, Lam and co-workers reported an enantioselective addition of alkenyltrifluoroborates to active cyclic imines derived from α-hydroxyl aromatic aldehydes (eq 2).[11] The only single successful example with acyclic imines was reported by Shintani, Hayashi, and co-workers in their research focusing on the application of aryltrifluoroborates.[12] Despite these seminal works, the application of this useful transformation is hindered by the lack of a general method that can use common acyclic imine substrates and functionalized alkenylborates. As part of our continuous interest in the exploration of new asymmetric rhodium-catalyzed addition reactions of imines with chiral diene ligands,[13,8c,e] we herein report a highly enantioselective addition of potassium alkenyltrifluoroborates[14] to arylaldimines with rhodium complexes as catalysts.

We started our investigation with the evaluation of several chiral ligands in the addition reaction of potassium



(*E*)-1-pentenyl-trifluoroborate **2a** to *N*-nosyl aldimine **1a** using our previous reaction conditions (Table 1).[8e] Bicyclo[3.3.0]-octadiene based chiral diene **L1** gave the desired product **3a** in 32% yield with 98% ee (entry 1), while only a trace amount of racemic product was generated by using diene **L2**[8d] as the ligand (entry 2). Low enantioselectivity was observed when phosphine–olefin hybrid ligand **L3**[15] was applied, albeit with a slightly improved reaction yield of 56% (entry 3). Some commonly used phosphine ligands, such as (*R*)-BINAP (**L4**), (*R*)-SEGPHOS (**L5**), and (*R*)-Monophos (**L6**), were also examined, furnishing the product **3a** in ≤10% yield and with 9−58% ee (entries 4−6). With chiral diene **L1** as the optimal ligand, a higher reaction yield of 50% was achieved by switching the catalyst to its rhodium chloride complex $[RhCl(\mathbf{L1})]_2$ (entry 7). Delightfully, the more reactive rhodium hydroxide complex $[Rh(OH)(\mathbf{L1})]_2$ proved to be the best catalyst,

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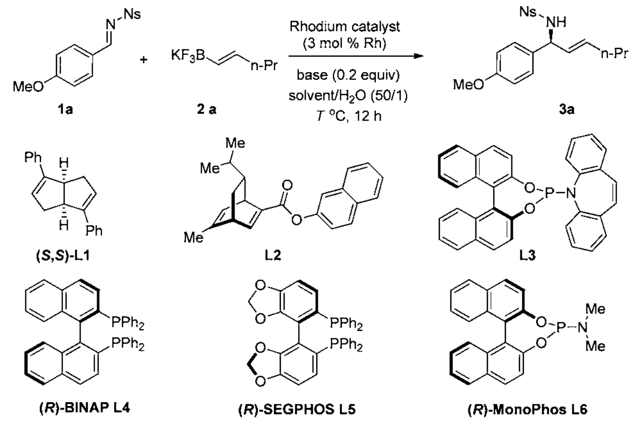
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	$[RhCl(C_2H_4)_2]_2$/ **L1**	K_3PO_4	toluene	70	32	98
2	$[RhCl(C_2H_4)_2]_2$/ **L2**	K_3PO_4	toluene	70	3	0
3	$[RhCl(C_2H_4)_2]_2$/ **L3**	K_3PO_4	toluene	70	56	37
4	$[RhCl(C_2H_4)_2]_2$/ **L4**	K_3PO_4	toluene	70	4	10
5	$[RhCl(C_2H_4)_2]_2$/ **L5**	K_3PO_4	toluene	70	8	58
6	$[RhCl(C_2H_4)_2]_2$/ **L6**	K_3PO_4	toluene	70	5	9
7	[RhCl(**L1**)]$_2$	K_3PO_4	toluene	70	50	97
8	[Rh(OH)(**L1**)]$_2$	K_3PO_4	toluene	70	92	99
9	[Rh(OH)(**L1**)]$_2$	K_3PO_4	toluene	rt	24	98
10	[Rh(OH)(**L1**)]$_2$	K_3PO_4	dioxane	70	59	95
11	[Rh(OH)(**L1**)]$_2$	K_3PO_4	THF	70	39	98
12	[Rh(OH)(**L1**)]$_2$	KF	toluene	70	15	98
13	[Rh(OH)(**L1**)]$_2$	KOH	toluene	70	60	96

[a]Reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), and base (0.2 equiv). [b]Isolated yield. [c]Determined by chiral HPLC analysis.

providing the product **3a** in 92% yield and with 99% ee (entry 8).[16] Further efforts to improve the reaction yield by tuning the effect of temperature, solvent, and base turned out to be unhelpful (entries 9−13).

With optimal reaction conditions identified, the scope of the method was then investigated by additions of different alkenyltrifluoroborates to various *N*-nosyl arylaldimines (Figure 1). Alkenyltrifluoroborates with di- or trimethyl substitutions at the double bond gave the addition products in 85−99% yields with ≥99% ee (**3b**−**d**). Reaction with a less sterically congested *α*-methyl-substituted trifluoroborate resulted in slight loss of reaction yield (**3e**), however, keeping the same high enantioselectivity. A similar trend was also observed when other substitutions were introduced onto the double bond. The more hindered potassium cyclohexenyltrifluoroborate (**3f**) afforded a higher reaction yield than *β*-benzyl-substituted trifluoroborate (**3g**), while excellent enantioselectivities of 99% ee were obtained in both cases. In addition, both benzyloxy and ester groups were well tolerated, providing the addition products in high yields with excellent enantioselectivities (**3h** and **3i**). The reactions with different combinations of imines and alkenyl trifluoroborates proceeded smoothly in very high yields and excellent enantioselectivities. For example, the imines with electron-withdrawing 3-Cl or

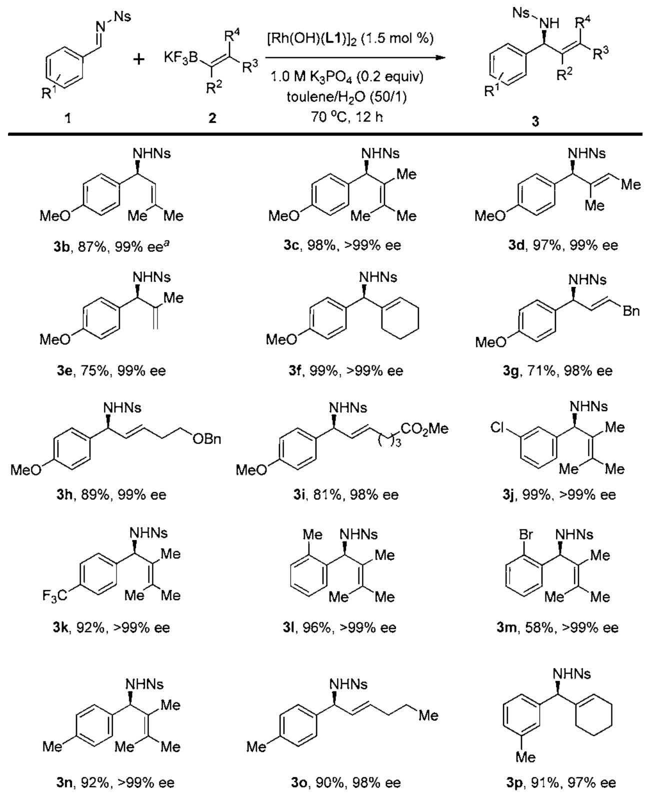


Figure 1. Rhodium-catalyzed asymmetric alkenylation with alkyl-substituted alkenyltrifluoroborates. Yields refer to isolated product. Enantiomeric excesses were determined by chiral HPLC analysis. (a) Used dioxane as the solvent.

4-CF_3 groups at the phenyl ring were also excellent substrates for this addition reaction (**3j** and **3k**). The *ortho*-substitution at the phenyl ring, such as 2-Me or 2-Br, did not affect the enantioselectivity of this addition process although a decreased reaction yield was obtained for the 2-Br-substituted imine (**3m** and **3n**).

Next, some *β*-aryl-substituted vinyltrifluoroborates were also examined. However, lower reaction yields were observed under the current reaction conditions. We reason that these alkenyltrifluoroborates may be highly reactive and easily undergo hydrolysis at high reaction temperature.[10] As we expected, lowering the reaction temperature to room temperature and replacing the base K_3PO_4 with KF significantly improved the reaction yields. A variety of *β*-aryl-substituted vinyltrifluoroborates were successfully added to different imines, giving the desired products in 90−98% yields and as high as ≥99% ee (Figure 2). It is worthy to note that the 2-thiophenecarboxaldehyde-derived imine also worked well to afford the desired product in 90% yield and 99% ee (**5i**). The stereochemistry of product **5f** was assigned as *S* by comparing its optical rotation with the known value in the literature, which is also in agreement with the stereochemical model proposed by Hayashi for the arylation of imines.[17]

As our method provides an applicable synthesis of protected chiral amines, facile deprotection of the product and the potential for scale-up are also very appealing. The nosyl group in **5g** was easily removed by treatment with 2-thioglycolic acid (TGA) and LiOH·H_2O at room temperature to produce free allylic amine **6** in 93% yield (eq 4). Furthermore, a gram-scale reaction was performed to generate the product **5g** in 95% yield and 99% ee, although the reaction time was prolonged to ensure the full conversion of imine **1g** (eq 5).

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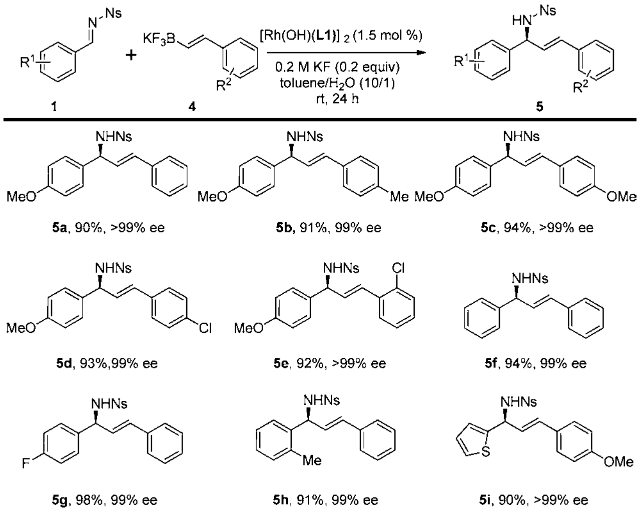
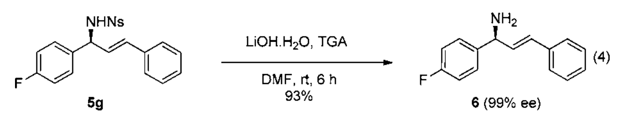
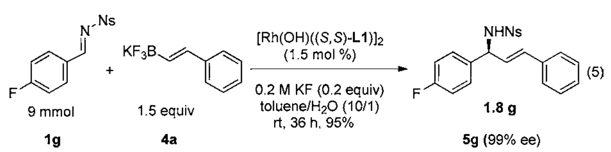
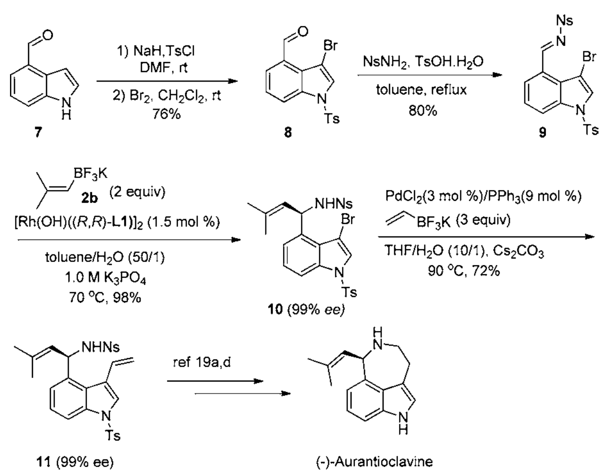


Figure 2. Rhodium-catalyzed asymmetric alkenylation with β-aryl-substituted vinyltrifluoroborates. Yields refer to isolated product. Enantiomeric excesses were determined by chiral HPLC analysis.





Scheme 1. Formal Synthesis of (−)-Aurantioclavine



To demonstrate further the utility of our method, we conducted the synthesis of (−)-aurantioclavine,[18,19] a natural product first isolated from *Penicillium aurantiovirens* in 1981,[20] which aroused considerable interest due to its proposed role as an intermediate in the biosynthesis of communesin family.[21,22] Our synthesis started from N-Ts protection of indole **7**, which underwent bromination at the C-3 position of the indole core and subsequent condensation with $NsNH_2$ to afford *N*-nosyl imine **9**. The key step, rhodium-catalyzed asymmetric addition of trifluoroborate **2b** to imine **9**, produced the desired adduct **10** in 98% yield with 99% ee. It should be mentioned that diene ligand (*R*,*R*)-**L1** was used in this reaction to achieve the correct stereochemistry in the synthesis of (−)-aurantioclavine.[19d] Suzuki coupling of **10** with vinyltrifluoroborate introduced a vinyl group at the 3-position of indole, generating a properly decorated indole **11**, a key intermediate in Stoltz's total synthesis.[19a,d] Our approach provided a formal synthesis of (−)-aurantioclavine (Scheme 1).

In summary, an asymmetric rhodium-catalyzed addition reaction of potassium alkenyltrifluoroborates to acyclic aldimines was developed, providing a simple, reliable, and scalable method for the modular synthesis of chiral α-branched allylic amines. The reaction displays a broad scope with respect to both imine and alkenylborate partners. The utility of this method is demonstrated by the concise formal synthesis of (−)-aurantioclavine.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure and characterization of all new compounds. 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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