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Enantioselective Rhodium-Catalyzed Alkenylation of Aliphatic Imines

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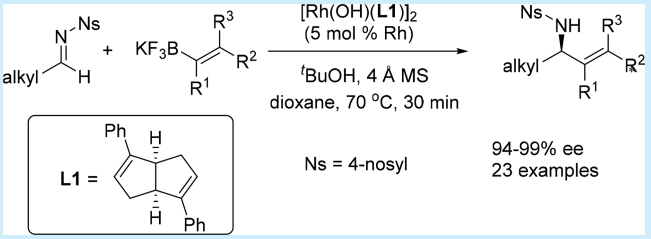
S *Supporting Information*

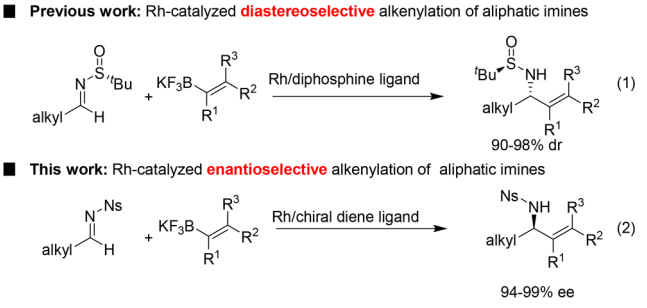
ABSTRACT: An efficient, enantioselective rhodium-catalyzed addition of potassium alkenyltrifluoroborates to *N*-nosyl aliphatic imines has been realized. Good reaction yields and excellent enantioselectivities (94−99% ee) were obtained for a variety of aliphatic imines and nucleophilic alkenyltrifluoroborates. An active rhodium-diene catalyst and the precise reaction condition control proved to be pivotal for success.



Chiral, α-branched amines are commonly found in many biologically active molecules and natural products.[1] The rhodium-catalyzed, asymmetric addition of organoboron reagents to imines serves as a powerful strategy to access these interesting compounds.[2] Since the first example was reported by Tomioka's group in 2004,[3a] in which rhodium-catalyzed, enantioselective addition of arylboronic acids to arylimines was realized, significant effort has been devoted to expanding the substrate scope of this transformation.[3−7] The utilization of aliphatic imines and alkenylboron reagents represents two important leaps toward this goal. Due to the relatively lower stability of aliphatic imines, the study of their addition reaction lagged far behind the aromatic imines. In 2009, Ellman and co-workers first reported the addition of arylboronic acids to aliphatic imines using a rhodium/bisphosphine catalyst.[4a] Later, this reaction was greatly improved by our group with the discovery of an efficient catalytic system based on an active rhodium/diene catalyst.[4b] Recently, Yamamoto and co-workers reported a rhodium/bis(phosphoramidite) catalytic system for this reaction.[4c] On the other hand, despite the obvious advantages brought by the introduction of the alkenyl moiety, examples with alkenylboron reagents were rather scarce. In 2001, Shintani, Hayashi, and co-workers provided a single example, in which an alkenylboron reagent was first used in the rhodium-catalyzed, enantioselective imine addition.[5a] Soon, a systematic research with cyclic aromatic imines was described by Lam and co-workers.[5b] For the alkenylation of less active acyclic imines, the Wu group[5c] and our group[5d] independently achieved this enantioselective addition in 2014.

The addition of alkenylboron reagents to aliphatic imines would provide not only chiral alkylalkenylamines but also chiral dialkylamines by a further simple hydrogenation step. However, only rhodium-catalyzed, diastereoselective reactions using chiral aliphatic *N*-*tert*-butanesulfinyl imines have been reported by Ellman and co-workers (Scheme 1).[8] To the best of our knowledge, rhodium-catalyzed enantioselective alkenylation of aliphatic imines has not been realized yet.

Scheme 1. Rhodium-Catalyzed Asymmetric Alkenylation of Aliphatic Imines



Encouraged by our previous success in asymmetric addition reactions with rhodium/chiral bicyclo[3.3.0]octadiene complexes,[9,10] we sought to explore these catalysts further in the addition reactions with more challenging substrates. Herein, we describe our development of an elegant catalytic system for the highly enantioselective addition of potassium alkenyltrifluoroborates to aliphatic imines (Scheme 2).

In the initial attempts, the addition of (*E*)-styrylboronic acid to *N*-4-nosyl-protected alkylimine **1a** was carried out under the previous successful reaction conditions for arylboronic acids.[4b] Unfortunately, a significantly lower reaction yield and enantioselectivity were obtained in contrast to the excellent results with phenylboronic acid, which may be partly attributed

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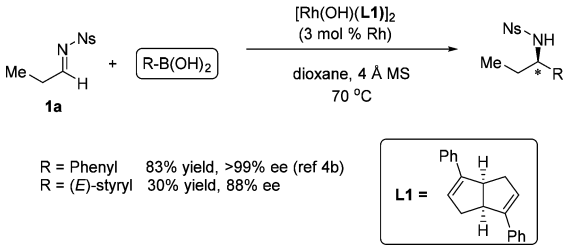
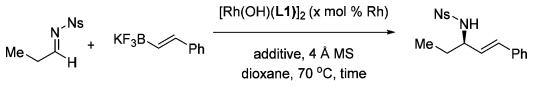
Scheme 2. Preliminary Results in the Rhodium-Catalyzed Asymmetric Alkenylation of Aliphatic Imines



to the lower stability of alkenylboronic acids under the reaction conditions.[11,12]

Accordingly, the boronic acids were replaced by the more stable trifluoroborates[13] in the following screening process, and some representative results were summarized in Table 1. In the

Table 1. Optimization of Reaction Conditions[a]



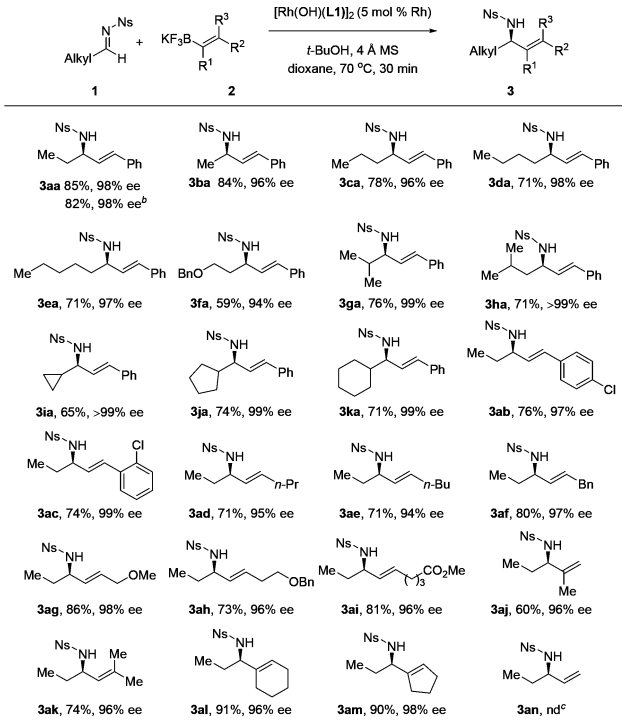
entry	rhodium loading (mol %)	temp (°C)	additive (equiv)	time (h)	yield[b] (%)	ee[c] (%)
1	3	70	MeOH (5)	6	42	97
2	3	80	MeOH (5)	6	30	97
3	3	60	MeOH (5)	6	22	97
4	3	70	MeOH (3)	6	67	97
5	3	70	MeOH (2)	6	66	96
6	3	70	EtOH (3)	6	66	94
7	3	70	^{i}PrOH (3)	6	44	95
8	3	70	^{t}BuOH (3)	6	80	97
9	3	70	H_2O (3)	6	59	91
10	3	70	^{t}BuOH (3)	0.5	81	97
11	3	70	^{t}BuOH (3)	0.17	80	97
12	5	70	^{t}BuOH (3)	0.5	89	98
13	10	70	^{t}BuOH (3)	0.5	88	97
14[d]	5	70	^{t}BuOH (3)	0.5	27	96

[a]Unless otherwise noted, reactions were carried out with **1a** (0.20 mmol), **2a** (0.40 mmol), 4 Å molecular sieves (150 mg) in dioxane (2 mL). [b]Yields were determined by ^{1}H NMR spectroscopy using CBr_2H_2 as an internal standard. [c]Determined by chiral HPLC analysis. [d]Without 4 Å molecular sieves.

presence of the active rhodium−diene complex ([Rh(OH)-(**L1**)]$_2$), molecular sieves, and proton source, the addition of (*E*)-styryltrifluoroborate **2a** to alkylimine **1a** proceeded at 70 °C to give the desired product in 42% yield with excellent enantioselectivity (entry 1). Either increasing or decreasing the reaction temperature resulted in lower reaction yield (entries 2 and 3). The proton source and its quantity can affect both the reaction yield and enantioselectivity, and 3 equiv of *t*-BuOH proved to be optimal (entries 4−9). A careful examination of reaction time indicated that the reaction could actually go to completion within 10 min (entry 11), and we chose to run the reaction for 30 min to ensure the full conversion of starting material in the following study (entries 10). The reaction yield can be further improved to 89% by increasing the catalyst loading to 5 mol % (entry 12). Interestingly, we noticed a profound impact of molecular sieves on the reaction yield, and only 27% yield was obtained without this additive (entry 14).[14]

Using the optimized conditions, the scope of alkylimine was explored (Scheme 3). Good reaction yield and enantioselectivity

Scheme 3. Rhodium-Catalyzed Asymmetric Alkenylation of Aliphatic Imines[a]



[a]Reactions conditions: **1** (0.20 mmol), **2** (0.40 mmol), [Rh(OH)-(**L1**)]$_2$ (0.005 mmol), and 4 Å molecular sieves (150 mg) in dioxane (2 mL) at 70 °C for 30 min. Yields refer to isolated product. Enantiomeric excesses were determined by chiral HPLC analysis. [b]Reaction was run in 1 mmol scale. [c]Not detected.

were observed when acetaldehyde-derivatized imine with a shorter chain length was used (**3ba**). However, alkylimines with longer chain length gave decreased reaction yields, accompanied by a slight variation in enantioselectivity (**3ca**−**3ea**). An imine bearing a terminal BnO group was also a competent substrate, albeit with reduced reaction yield and enantioselectivity (**3fa**). Improved enantioselectivities were achieved with *α*- or *β*-branched alkylimines, which could be attributed to the beneficial effect of the increased steric hindrance in the substrates (**3ga** and **3ha**). The same trend was also observed when cyclic alkylimines bearing three-, five-, or six-membered rings were examined (**3ia**−**3ka**).[15]

Next, the scope of alkenyltrifluoroborates was examined in the addition to imine **1a**. Introduction of chlorine substituent to different positions of the phenyl ring of (*E*)-styryltrifluoroborate **2a** resulted in a slight loss in reaction yield, albeit with almost equally high enantioselectivities (**3ab** and **3ac**). In contrast, a slight loss in enantioselectivity was observed when the phenyl ring was replaced by a flexible linear alkyl chain (**3ad** and **3ae**). Methyloxy (**3ag**), benzyloxy (**3ah**) and CO_2Me (**3ai**) groups were well tolerated, providing the desired products in high yields with excellent enantioselectivities. While the reaction of *α*-branched or trisubstituted trifluoroborate also proceeded well, notably in higher reaction yields with cyclic alkenylboronates (**3aj**−**3am**), the unsubstituted vinyltrifluoroborate failed to give any observable product (**3an**).[16]

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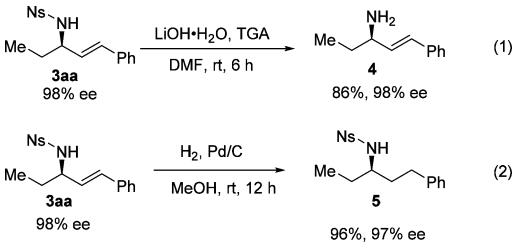
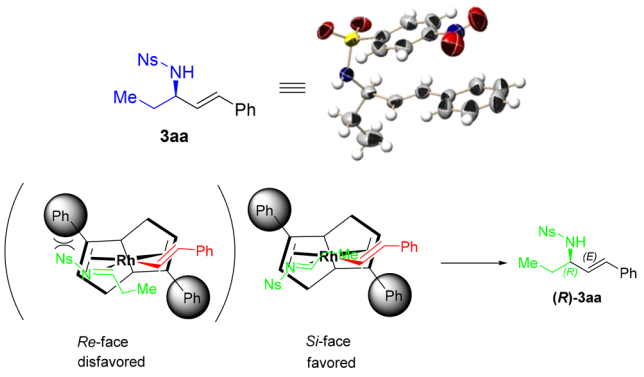
The *N*-nosylamide **3aa** can easily be transformed to the corresponding free amine **4** by treatment with classic 2-thioglycolic acid (TGA)/LiOH at room temperature (eq 1).[5d] In addition, **3aa** can be hydrogenated under benign reaction conditions, providing a *N*-nosyl-protected chiral dialkylamine **5** (eq 2).



The absolute configuration of **3aa** was determined unambiguously to be *R* by X-ray crystallographic structure analysis. This stereoselectivity could be explained by the model depicted in Scheme 4, which originates from Hayashi's model for the arylation of arylimine catalyzed by the rhodium−diene catalyst.[3b]

Scheme 4. X-ray Crystallographic Structure of 3aa and Proposed Stereochemical Defining Model



In conclusion, we discovered an efficient rhodium catalytic system for the highly enantioselective alkenylation of aliphatic imines. Various alkenyltrifluoroborates with different branch structures and functional groups could successfully react with a variety of aliphatic imines, providing the desired products in good yields and excellent enantioselectivities. The key to the success is the utilization of an active diene−rhodium catalyst as well as the precise control of reaction conditions. Our developed transformation provides a modular synthetic approach, not only for chiral alkylalkenylamines but also for chiral dialkylamines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02737.

Experimental procedures, compound characterization data (PDF)

X-ray data for **compound 3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) Several other chiral bicyclo[3.3.0]octadiene ligands were evaluated but did not afford better results than the used diene **L1**. See the Supporting Information for details.
(15) Cyclohexanecarboxaldehyde-derived imines with *N*-Boc or *N*-diphenylphosphinoyl protecting group were also tested but failed to afford desired products.
(16) The (*Z*)-styryltrifluoroborate was tested to afford the addition product in <10% yield and as an inseparable *Z*/*E* mixture (*Z*/*E* = 2:1).

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