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Rhodium-catalyzed Asymmetric Arylation of Nitroalkenes Powered by Simple Chiral Sulfur-Olefin Ligands

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An efficient rhodium-catalyzed enantioselective addition of potassium organotrifluoroborates to nitroalkenes powered by simple chiral sulfur-olefin ligands is reported. This protocol is applicable to a broad range of 2-aryl-, alkyl-, and heteroaryl-substituted nitroalkenes, allowing access to diverse chiral β,β-disubstituted nitroethanes in good to excellent yields with high enantioselectivity under mild conditions.

Keywords: Asymmetric catalysis; Rhodium; Chiral sulfur-olefin ligands; Asymmetric arylation; Nitroalkenes.

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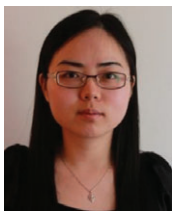

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INTRODUCTION

Rhodium-catalyzed asymmetric conjugate addition of organoboron reagents to electron-deficient olefins has been recognized as one of the most powerful and efficient strategies to construct new C—C bonds and generate diverse chiral β-substituted functional compounds.[1] Among these olefins, α,β-unsaturated carbonyl compounds are the most intensively investigated

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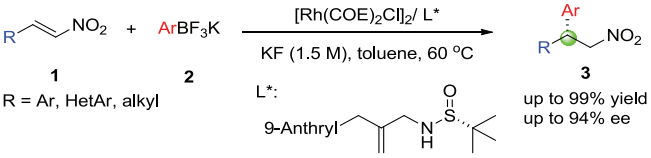
substrates, and remarkable success has been achieved in their highly enantioselective addition with the use of various chiral ligands.[2] Nitroalkenes are another essential type of olefin substrates, as the reaction products bearing a nitro functionality are valuable chiral building blocks.[3] However, unlike the achievements with α,β-unsaturated carbonyl compounds, there have been very few reports of the highly enantioselective addition of nitroalkenes,[4] mainly due to the difficulties encountered in the enantiocontrol of the reaction. In 2000, the Hayashi group successfully accomplished the asymmetric arylation of organoboronic acids to α-substituted nitroalkenes with high enantioselectivity by utilizing Rh/BINAP as catalyst.[5] However, with nitroalkenes that lack α-substitutents, the reaction generally resulted in low levels of enantioselectivity (<50% ee).[4] In 2010, we developed a new reaction system and discovered that high enantiocontrol could be achieved using chiral bicyclo[3.3.0]diene ligands, leading to synthetically useful chiral β,β-disubstituted nitroalkanes with up to 97% ee.[6] Since then, much progress has been made, and chiral sulfoxide-phosphines,[7] sulfoxide-olefins,[8] biaryl phosphites,[9] bridged bicyclo[2.2.1]/[2.2.2] dienes,[10,11] and phosphorous-olefins[12] have been demonstrated to be potential chiral ligands in the rhodium-catalyzed asymmetric arylation of 2-aryl nitroalkenes, affording good to high enantioselectivity. Despite these advances, only scarce examples of the addition of 2-heteroaryl or 2-alkyl nitroalkenes have been reported,[7b,8,12] reflecting the challenges in the use of these substrates. Therefore, the development of versatile catalysts for efficient asymmetric organoboron addition to nitroalkenes with a broader substrate scope is still highly desirable.

In the past few years, our group has been interested in developing olefin-based chiral ligands for transition-metal-catalyzed asymmetric transformations. As a result, a series of structurally interesting chiral olefin ligands including bisolefins,[13] sulfur-olefins,[14] and phosphorous-olefins[15] have been designed and successfully used in asymmetric catalysis. Among them, readily available chiral sulfinamide-olefins ligands (SOLs)[14l] are particularly fascinating because of their extraordinary structural simplicity and excellent catalytic performance in Rh-catalyzed asymmetric additions of organoboron reagents to α-ketoesters,[14d,14e] α-diketones,[14d,14f] imines,[14g–k] and α,β-unsaturated carbonyl compounds.[14a–c] As part of our ongoing exploration of the



Scheme 1. Rh-catalyzed asymmetric arylation of nitroalkenes powered by a branched sulfur-olefin ligand.

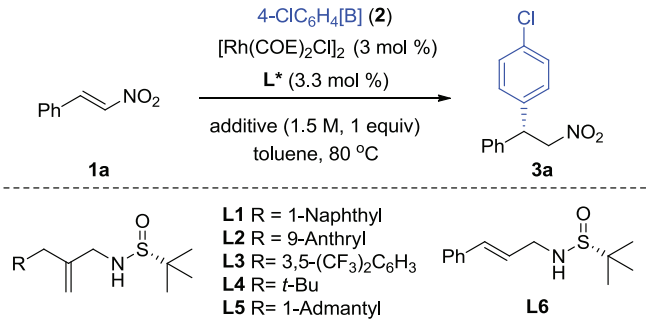
sulfur-olefin chemistry, we conceived that the Rh/SOL catalyst system might also be effective for the asymmetric addition of nitroalkenes. Here we report the enantioselective addition of potassium aryltrifluoroborates to 2-substituted nitroalkenes to provide chiral β,β-disubstituted nitroethanes in good to excellent yield with high enantioselectivity (Scheme 1).

RESULTS AND DISCUSSION

Initially, we conducted the reaction of nitrostyrene **1a** with 4-chlorophenylboronic acid **2a** in the presence of 1.5 mol% of $[Rh(COE)_2Cl]_2$ under aqueous KOH (1.5 M)/toluene at 80°C. With our previously developed branched sulfur-olefin **L1** as the chiral ligand, we were pleased to find that the reaction proceeded to give the desired product **3a** in 64% yield with promising 82% ee (Table 1, entry 1). To investigate the role of additives, K_3PO_4, K_2CO_3, and KF were then screened (entries 2–4), However, no better results were obtained. Changing the solvent from toluene to DCE led to a dramatic decrease of the reaction yield (entry 5), while no reaction was observed in water-miscible solvents like dioxane or THF (entries 6 and 7). Interestingly, switching the organoboron reagent from 4-chlorophenylboronic acid to its corresponding potassium trifluoroborate resulted in some increase in enantioselectivity (entry 8). Further evaluation indicated that the additive had an important effect on the reaction yield (entries 8–11). With KF as the additive, the reaction proceeded very smoothly to give a significantly improved yield (99%) of the corresponding nitroalkane with 86% ee (entry 9). When the reaction temperature was lowered to 60°C, the same yield and enantioselectivity were observed (entry 12).

In an attempt to improve the enantioselectivity, we next turned to the evaluation of different sulfur-olefin ligands. A series of branched SOLs (**L2**–**L5**) with varying R substituents were synthesized and examined under similar reaction conditions. The incorporation of a

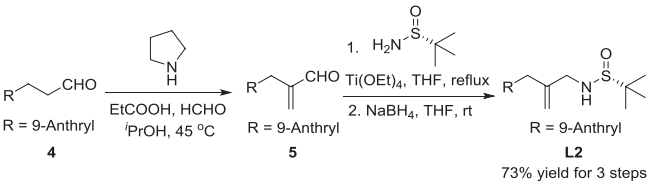
Table 1. Optimization of reaction conditions[a]



Entry	4-ClC_6H_4[B]	L	Additive	Yield (%)[b]	ee (%)[c]
1	4-$ClC_6H_4B(OH)_2$	**L1**	KOH	64	82
2	4-$ClC_6H_4B(OH)_2$	**L1**	K_3PO_4	37	75
3	4-$ClC_6H_4B(OH)_2$	**L1**	K_2CO_3	59	74
4	4-$ClC_6H_4B(OH)_2$	**L1**	KF	24	86
5[d]	4-$ClC_6H_4B(OH)_2$	**L1**	KOH	29	73
6[e]	4-$ClC_6H_4B(OH)_2$	**L1**	KOH	N.R.	N.D.
7[f]	4-$ClC_6H_4B(OH)_2$	**L1**	KOH	N.R.	N.D.
8	4-$ClC_6H_4BF_3K$	**L1**	KOH	61	86
9	4-$ClC_6H_4BF_3K$	**L1**	KF	99	86
10	4-$ClC_6H_4BF_3K$	**L1**	KHF_2	76	86
11	4-$ClC_6H_4BF_3K$	**L1**	K_3PO_4	29	82
12[g]	4-$ClC_6H_4BF_3K$	**L1**	KF	99	87
13[g]	4-$ClC_6H_4BF_3K$	**L2**	KF	99	90
14[g]	4-$ClC_6H_4BF_3K$	**L3**	KF	74	83
15[g]	4-$ClC_6H_4BF_3K$	**L4**	KF	99	82
16[g]	4-$ClC_6H_4BF_3K$	**L5**	KF	99	82
17[g]	4-$ClC_6H_4BF_3K$	**L6**	KF	N.R.	N.D.

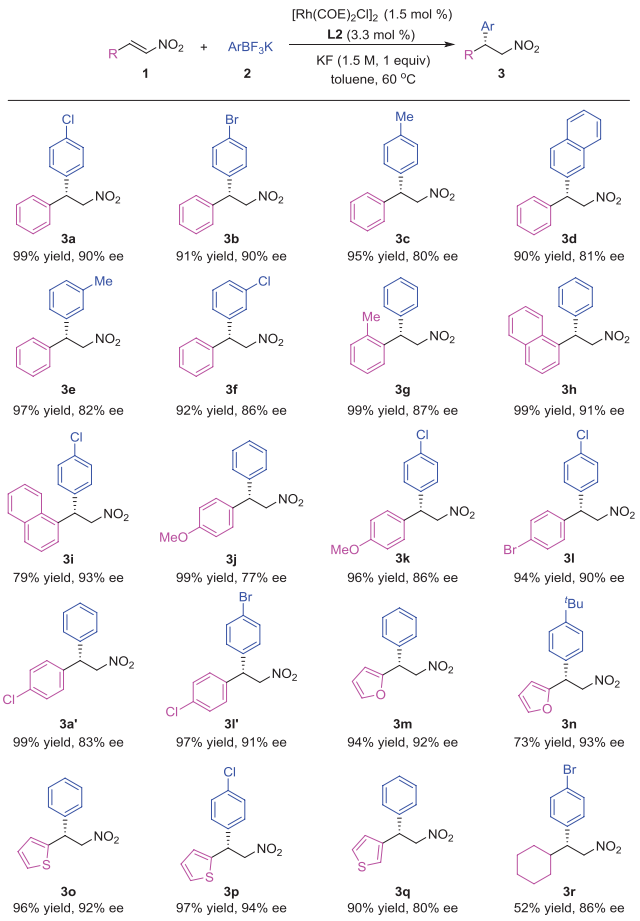
[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol, 2.0 equiv), $[Rh(COE)_2Cl]_2$ (1.5 mol%), ligand (3.3 mol%), and additive (1.5 M, 0.20 mmol, 1.0 equiv) in 2.0 mL of solvent at 80°C for 12 h unless otherwise noted.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] DCE as solvent.
[e] THF as solvent.
[f] Dioxane as solvent.
[g] 60°C.

bulky *t*-Bu group, 1-admantyl group, or the electron-deficient 3,5-bis(trifluoromethyl)phenyl group led to a slight decrease in enantiocontrol (82–83% ee) (entries 14–16), while a closely structurally related analogue of **L1** bearing a 9-anthryl substituent (**L2**) delivered the product in quantitative yield (99%) and improved enantioselectivity (90% ee) (entry 13). Following our previous procedure, this ligand can be easily prepared with the use of 3-(9-anthracenyl)propanal as the starting material via a three-step sequence involving organocatalyzed Mannich reaction, condensation, and reduction (Scheme 2). It is worth noting that the linear SOL **L6** was ineffective in this addition reaction (entry 17), indicating that the ligand structure has a crucial impact on the catalyst activity.



Scheme 2. Synthesis of ligand **L2.**

Table 2. Rh-catalyzed asymmetric arylation of nitroalkenes[a,b,c]



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.20 mmol, 2.0 equiv), $[Rh(COE)_2Cl]_2$ (1.5 mol%), ligand (3.3 mol%), and KOH (1.5 M, 3.0 equiv) in 2.0 mL of toluene at 60°C for 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Under the optimal conditions, we then investigated the substrate scope of the reaction (Table 2). To our delight, a variety of potassium aryltrifluoroborates with diverse electronic and steric properties could be employed. In most cases, the reaction proceeded smoothly to afford the corresponding β,β-diarylnitroethane products in excellent yields with good enantioselectivities. In comparison with the use of electron-rich aryltrifluoroborates and phenyltrifluoroborate, higher enantiomeric excesses were attained with aryltrifluoroborates bearing electron-withdrawing substitutents on the phenyl ring (**3a**,**3b** vs. **3c**, **3f** vs. **3e**, **3i** vs. **3h**, **3k** vs. **3j**, **3l′** vs. **3a′**, **3p** vs. **3o**). It is noteworthy that sterically encumbered nitroalkene substrates possessing bulky aryl groups such as 1-naphthyl and *o*-tolyl performed well in the reaction, yielding the products with high ee values (up to 93%) (**3g**–**3i**). It appears that the electronic nature of the R substitutents of nitroalkenes has little effect on the enantioselectivity of the reaction (**3a** vs. **3l**, **3b** vs. **3l′**, **3k** vs. **3l**). Interestingly, both enantiomers of the product can be readily obtained by simply switching the acceptor and donor aryl substituents under the same catalytic conditions (**3a** vs. **3a′**, **3l** vs. **3l′**). Gratifyingly, the challenging 2-heteroaryl-substituted nitroalkenes were also suitable substrates. For example, a high level of enantiomeric control (92–93% ee) was attained when 2-(2-furyl)nitroethene and 2-(2-thienyl) nitroethene were employed (**3m**–**3p**). To our knowledge, these results are among the best in the asymmetric addition of arylboron reagents to 2-heteroaryl nitroalkenes.[7b,8,9,12] Moreover, 3-thienyl substituted nitroethene could also be applied in this reaction, affording the addition product **3q** in 90% yield with 80% ee. Notably, the catalytic system is compatible with 2-aliphatic substituted nitroalkenes. The reaction could be carried out with 2-nitrovinylcyclohexane to form the corresponding product **3r** with 86% ee, though the yield was somewhat less satisfactory (52%). The stereochemistry of the newly formed carbon stereocenter of product **3a** was determined to be *R* by comparing the $[\alpha]_D$ with known literature data.[6] Accordingly, the absolute configuration of the other products was assigned by assuming an analogous stereochemical pathway.

On the basis of the observed stereochemical outcome of the reaction, we proposed an empirical transition-state model to rationalize the origin of enantioselectivity. As shown in Figure 1, a favored conformation of the arylrhodium species is assumed in which the aryl group coordinated to the rhodium center adopts a trans geometry[16] with the olefin moiety of the ligand, and the *tert*-butyl group is staggered. To avoid

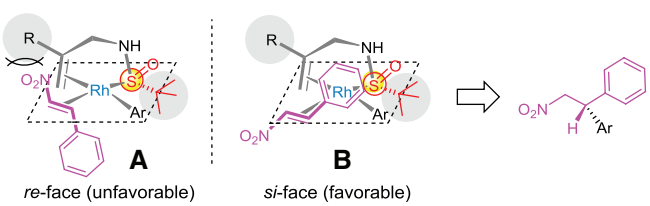


Fig. 1. Proposed transition state model.

unfavorable steric interaction, the nitro group of substrate is oriented away from the bulky R substituent of the olefin ligand. Therefore, the intramolecular transfer of aryl group takes place from the *Si* face of the C=C bond, giving the observed major enantiomer.

CONCLUSIONS

In summary, a new, readily available chiral sulfur-olefin **L2** was discovered to be an effective ligand for rhodium-catalyzed asymmetric addition of aryltrifluoroborates to nitroalkenes. The simple catalytic system tolerates a broad variety of substrates and enables access to a wide range of β,β-diaryl substituted nitroethanes in good to excellent yields with high enantioselectivities under mild reaction conditions. Efforts to expand the applicability of this method for the efficient preparation of related bioactive compounds are currently under way in our laboratory.

EXPERIMENTAL

General

All anaerobic manipulations were carried out with standard Schlenk techniques under argon. Solvents were dried and distilled by standard procedures. NMR spectra were recorded on a Mercury 300 spectrometer (300 MHz for ^{1}H), and a Varian spectrometer (125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.16) for ^{13}C NMR. High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer with an ESI resource or a magnetic sector for EI. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. HPLC was performed on a JASCO 2000 instrument by using Daicel columns with *i*-PrOH/hexane as the eluent.

General procedure for Rh-catalyzed asymmetric conjugate addition to nitroalkenes

Under Ar atmosphere, a solution of nitroalkene **1** (0.20 mmol), $[Rh(COE)_2Cl]_2$ (1.5 mol%, 2.2 mg, 0.006 mmol of Rh), ligand **L2** (2.3 mg, 3.3 mol%, 0.0066 mmol), and potassium aryltrifluoroborates **2** (0.40 mmol) in 2.0 mL of toluene was stirred at 60°C for 30 min. To this mixture was added aqueous KF (0.13 mL, 1.5 M, 0.20 mmol), and then the resulting mixture was stirred at 60°C for 12 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate to afford the corresponding addition product **3**.

ACKNOWLEDGMENTS

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Supporting information

Additional supporting information (experimental procedures, characterization data, and copies of NMR and HPLC spectra) is available in the online version of this article.

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