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Highly active nickel catalysts for enantioselective reductive alkenylation of N-sulfonyl aldimines

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Abstract

Chiral nickel complexes of bis(oxazoline)s serve as highly active catalysts for an enantioselective reductive alkenylation of *N*-sulfonyl and *N*-sulfamoyl aldimines, using readily available alkenyl bromides and triflates as reagents. The new method is readily scalable with low loadings of nickel catalysts, as low as 0.2 mol%. The reaction condition is almost neutral and tolerated polar groups of esters, thioethers, carbamates, heterocyclic pyridine and quinoline, and weakly acidic alcohols. Mechanistically, density functional theory (DFT) calculations reveal that alkenyl transfer to *N*-sulfonyl imines occurs on nickel catalysts via a classical 1,2-migratory insertion.

Keywords: Asymmetric catalysis, aldimine, alkenylation, nickel catalysis, reductive addition, chiral alkylamines

1. Introduction

Aliphatic amines are important motifs in small-molecule medicines[1]. For example, chiral benzylic amines are present in cinacalcet, rivastigmine, and ontazolast. Thus, efficient stereoselective methods to prepare these chiral amines have been a longstanding quest among synthetic chemists[2]. Copper-catalyzed asymmetric imine addition of alkenyl metal reagents of Mg, Zn, Al, and Zr is often practiced, but the method is often limited by poor compatibility with sensitive functional groups[3]. Another family of benchtop-stable nucleophiles, *alkenyl* boronic acids and boronates, can add to various imines when promoted by chiral rhodium complexes[4]. Recently, cobalt- and nickel-catalysts were also reported for enantioselective addition of alkenyl boronic acids to cyclic *N*-sulfonyl imines[5].

In recent years, researchers have reported cobalt-[6] and nickel-catalyzed[7] enantioselective reductive addition of aryl and alkenyl halides to imines. These reductive methods directly use readily accessible *alkenyl* halides, sulphonates, and acetates, and avoid the preparation and use of organometallic reagents and organoboron reagents. For example, Shi *et al*. reported a cobalt-catalyzed asymmetric addition of *aryl* halides to a special type of activated cyclic aldimines, benzo[*d*]isothiazole 1,1-dioxides (Figure 1a), which are conformationally locked in (*Z*)-geometry[8]. Chen and coworkers have reported a cobalt-catalyzed asymmetric addition of *alkenyl* iodides to α-iminoesters for the formation of unnatural amino acids, and the iminoesters chelated on chiral cobalt complexes for asymmetric alkenyl transfer from the metal center (Figure 1b)[9]. Recently, Tao and coworkers disclosed that a chiral dinickel complex can selectively activate β-arylvinyl chlorides in asymmetric addition to *N*-tosyl aldimines (Figure 1c), but alkenyl halides having other substituents gave no products[10]. Very recently, Liu and coworkers reported that nickel complexes of bis(dihydroimidazole) promoted efficient asymmetric addition of aryl iodides to *N*-sulfonyl imines, but the addition of alkenyl iodides led to low-to-moderate yields and < 90% ees (Figure 1d)[11].

In 2023, we disclosed a nickel-catalyzed asymmetric addition of *aryl* halides to *N*-picolyl aldimines in excellent ees[12]. Recently, we successfully extended the asymmetric addition of alkenyl halides and triflates, having various substitution patterns, to *N*-picolyl

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imines (Figure 1e)[13]. These reactions proceed via a mechanism of elementary 1,4-addition on nickel catalysts. We also reported catalytic reductive addition of aryl and alkenyl halides to *N*-Boc aldimines lately[14].

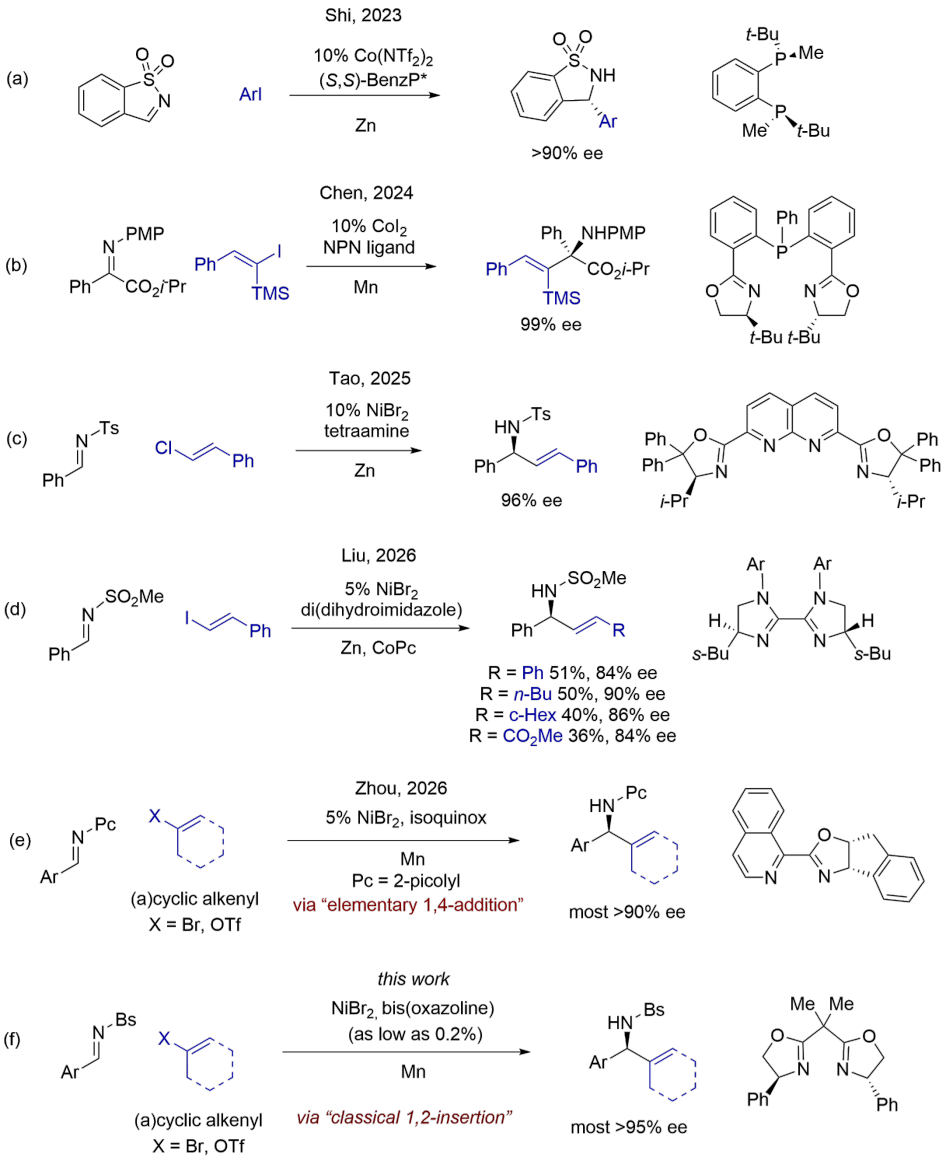


Figure 1. Nickel-catalyzed reductive addition of alkenyl halides and sulfonates to *N*-sulfonyl and sulfamoyl aldimines.

We report here new catalytic methods for enantioselective alkenylation of aldimines having *N*-sulfonyl and sulfamoyl groups (Figure 1f)[15]. The mild conditions allow tolerance of various polar groups, azacycles, and weakly acidic alcohols. The method can be scaled up using low loadings of nickel catalysts, as low as 0.2 mol%. The use of alkenyl halides and triflates having various substituents also introduces these alkenyl fragments into chiral benzylamines, which are difficult to access from other catalytic reactions. For example, catalytic reductive couplings of aldimines and alkynes are mostly limited to terminal alkynes, which become 1,2-disubstituted alkenyl fragments in the chiral alkylamine[16]. Moreover, olefinic units in products are readily converted to functionalized aliphatic groups via hydrogenation, hydrofluorination, hydroamination, for example, which expands chemical space of chiral alkylamines accessible from this key reaction.

2. Experimental Section

A general procedure for catalytic alkenylation: in an argon-filled glove box, $NiBr_2$(DME) (1.5 mg, 0.005 mmol, 5 mol%), (4*R*,4′*R*)-bis(oxazoline) **L7** (2.0 mg, 0.006 mmol, 6 mol%), *N*-sulfonyl imine **1a** (0.1 mmol) and dry 1,4-dioxane (0.3 mL) were added to a dry 10-mL Schlenk tube. After stirring at rt for 20 min, Mn powder (16.5 mg, 0.3 mmol, from Alfa Aesar), dry hexafluoroisopropanol (HFIP) (33.6 mg, 0.2 mmol), Ti(O*i*-Pr)$_4$ (56.8 mg, 0.2 mmol), 1-bromocyclohexene (32 mg, 0.2 mmol) and gas chromatography (GC) standard *n*-$C_{12}H_{26}$ (20 μL) were added sequentially. The mixture was vigorously stirred at rt for 12 hours. At the end, the reaction

mixture was diluted and filtered through a pad of silica gel with washings of 4:1 petroleum ether/ethyl acetate. The filtrate was concentrated, and the crude product was purified by flash chromatography on silica gel to provide analytically pure alkylamines. The enantiomeric excess was determined by chiral high-performance liquid chromatography (HPLC) analysis. The racemic samples were prepared via a similar procedure using an achiral ligand, bipy. The *N*-sulfonyl imines can also be prepared by condensation of sulfonamides and aldehydes (1:1 molar ratio) in refluxing dry toluene in the presence of dry $MgSO_4$, filtered in the glove box and concentrated under reduced pressure to remove solvents.

3. Results and Discussion

3.1 Condition optimization

In a study of catalytic reductive alkenylation of aldimines having electron-withdrawing *N*-sulfonyl groups, we selected *N*-benzenesulfonyl aldimine **1a** and 1-cyclohexenyl bromide for a benchmark reaction (Figure 2).

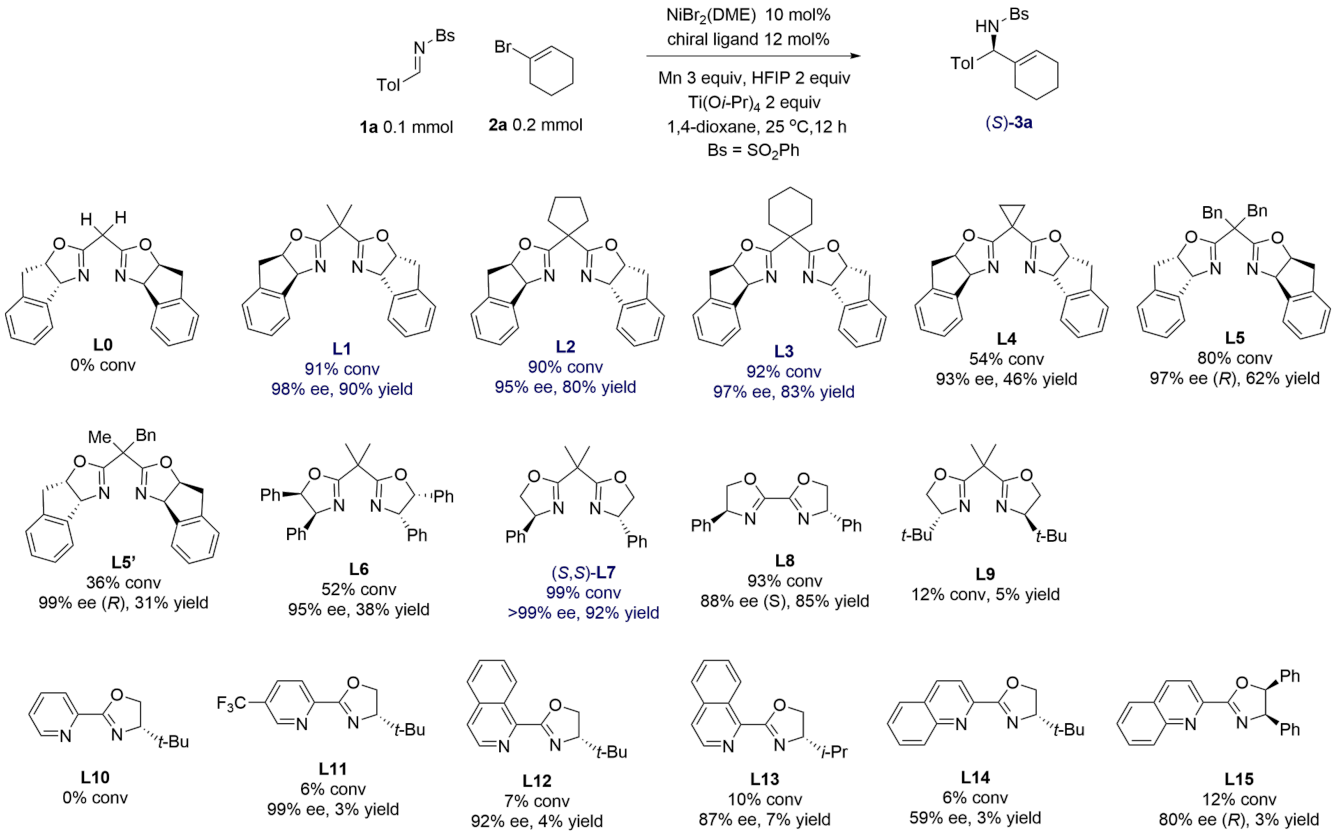


Figure 2. Optimization of ancillary ligands for a model alkenylation of aldimine **1a** giving product **3a**. Calibrated GC yields (Tol = 4-tolyl). GC: gas chromatography.

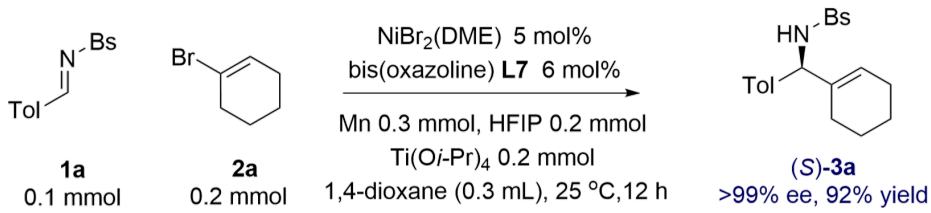
Among a series of chiral ligands, bis(oxazoline)s **L1**-**L3**, which featured two rigid indane-fused oxazoline rings and 1,1'-allkylene linkers, provided amine **3a** in very high ees. For instance, the nickel complex of **L1** yielded amine **3a** in 98% ee and 90% yield. However, an analogous ligand **L0** has a simple methylene linker showed no catalytic activity, which may be caused by a lower binding constant to nickel. Nickel complexes of di(oxazoline) **L7** afforded the product in almost perfect enantiopurity (> 99% ee) and 92% yield, so it was chosen for the study of substrate scope. A di(oxazoline) ligand **L8** with a conjugated p-system also showed high catalytic activity and gave 88% ee in the model reaction. However, a more hindered *t*-butyl-substituted ligand **L9** did not form an active nickel catalyst. The absolute configuration of amine **3a** was determined to be (*S*) by X-ray crystallography.

Previously, we reported that nickel complexes of chiral pyrox and (iso)quinox types having extensive p-conjugation gave excellent reactivity and > 90% ees in nickel-catalyzed reductive addition of aryl and alkenyl halides to conjugated enones[17], *N*-pyridyl aldimines[12,18], and *N*-Boc aldimines[14]. However, these ligands **L10**-**L15** showed very low catalytic activity. Common chiral diphosphines BINAP, Segphos, Difluorphos, and *t*-butyl-substituted (diphenylphosphino)oxazoline (*t*-Bu-PHOX) failed to produce active nickel catalysts for the model reaction.

Titanium isopropoxide was an indispensable additive, and its absence led to complete failure of the reaction (Table 1, entry 1). The reaction proceeded well in several ethereal solvents, among which the best results of 92% yield and > 99% ee were obtained in 1,4-dioxane (entry 2). In tetrahydrofuran (THF), the reaction provided 88% yield and 95% ee (entry 3). In 1,2-dimethoxyethane (DME)

and dichloromethane (DCM), moderate 60-70% yields with 90-93% ee were obtained (entries 5-6). Notably, in highly polar solvents such as *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), no product was formed (entries 7-8). The use of additive HFIP proved critical; no conversion occurred using other alcohols or water as an additive (entries 9-12). Ti(O*i*-Pr)$_4$ reacts rapidly with HFIP to give Lewis-acidic mixed titanium alkoxides, as we monitored the reaction by ^{19}F NMR spectroscopy[19]. The mixed titanium alkoxides may accelerate the reduction of oxidative addition complexes (L)Ni(Ar)Br$_2$ and (L)Ni(Ar)Br to active species (L)Ni(Ar), by capturing the halide before the reduction[20] or after reduction on the Mn surface. Manganese powder served as the terminal reductant for the catalytic reaction.

Table 1. Optimization of conditions for model alkenylation of aldimine **1a** (calibrated GC yields).



1a 0.1 mmol | **2a** 0.2 mmol | (*S*)-**3a** >99% ee, 92% yield

Entry	Change of conditions	Conv of **1a** (%)	Yield of **3a** (%)	Ee (%)
1	no Ti(O*i*-Pr)$_4$	32	0	-
2	1,4-dioxane (standard)	99	**92**	>99
3	THF	90	**88**	95
4	2-MeTHF	91	**86**	93
5	DME	84	60	93
6	DCM	80	71	90
7	DMF	38	0	-
8	DMSO	40	0	-
9	HFIP 0 equiv	0	0	-
10	CF3CH2OH 2 equiv	3	0	-
11	*t*-BuOH 1.5 equiv	2	0	-
12	H2O 1.5 equiv	2	0	-

GC: gas chromatography; THF: tetrahydrofuran; DME: 1,2-dimethoxyethane; DCM: dichloromethane; DMF: *N*,*N*-dimethylformamide; DMSO: dimethyl sulfoxide; HFIP: hexafluoroisopropanol.

In the model reaction under the condition using 5 mol% nickel catalyst of bis(oxazoline) **L7** and Ti(OR)$_4$, a long induction period of hours was detected before initiating the catalytic process, and it was difficult to reduce the loading of the nickel catalyst. We found that another set of conditions without titanium alkoxide allowed the reactions to scale up with low loadings of nickel (Figure 3a). In the model reaction of **1a** in THF, a 5 mol% nickel catalyst of **L7** gave 68% conversion of **1a** and amine **3a** in 44% yield and 84% ee. Switching the chiral ligand to di(oxazoline) **L8** improved the result to 85% yield and 90% ee. This new procedure was easily scaled up to 1 mmol using 0.2 mol% nickel catalyst of **L8**. Thus, 1 mmol of imine **1a** provided amine **3a** in 72% yield and 91% ee, while a methoxypyridyl imine gave amine **3k** in 54% yield and 80% ee (Figure 3b,c). However, the ees of these two products were slightly lower than those obtained under the conditions using titanium alkoxide.

3.2 The reaction scope

The crude *N*-sulfonyl aldimines were easily prepared via heating aldehydes and sulfonamides with MgSO$_4$ in toluene in a sealed tube at 140 °C (external temperature in an oil bath). Crude aldimines were obtained after filtration and concentration, and they were used directly in reductive alkenylation without further purification. The results are summarized in Figure 4. Various substituents can be present on the *N*-sulfonyl groups of aldimines (**3a**-**3f**), including anisyl, naphthyl, thienyl, cyclopropyl, methyl, and *t*-butyl. Among them, the *t*-butylsulfonyl group in benzylic amine **3g** is easily removable by the treatment of HCl, while the *N*-2-thiophenesulfonyl group is susceptible to reductive cleavage by magnesium dust in methanol. An *N*-carbamoyl aldimine reacted to provide amine **3h** in 82% yield and 95% ee. The *N*-carbamate group is removable by acids[21].

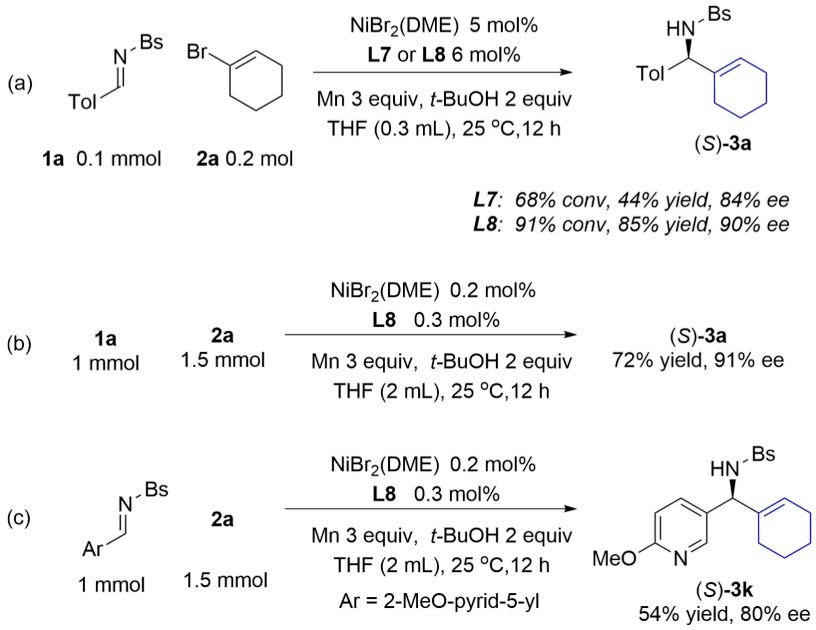


Figure 3. Catalytic alkenylation of aldimine **1a** under conditions without titanium isopropoxide: (a) A reaction on a 0.1 mmol scale using 5% nickel catalyst; (b-c) Reactions on a 1 mmol scale using 0.2% nickel catalyst. DME: 1,2-dimethoxyethane; THF: tetrahydrofuran.

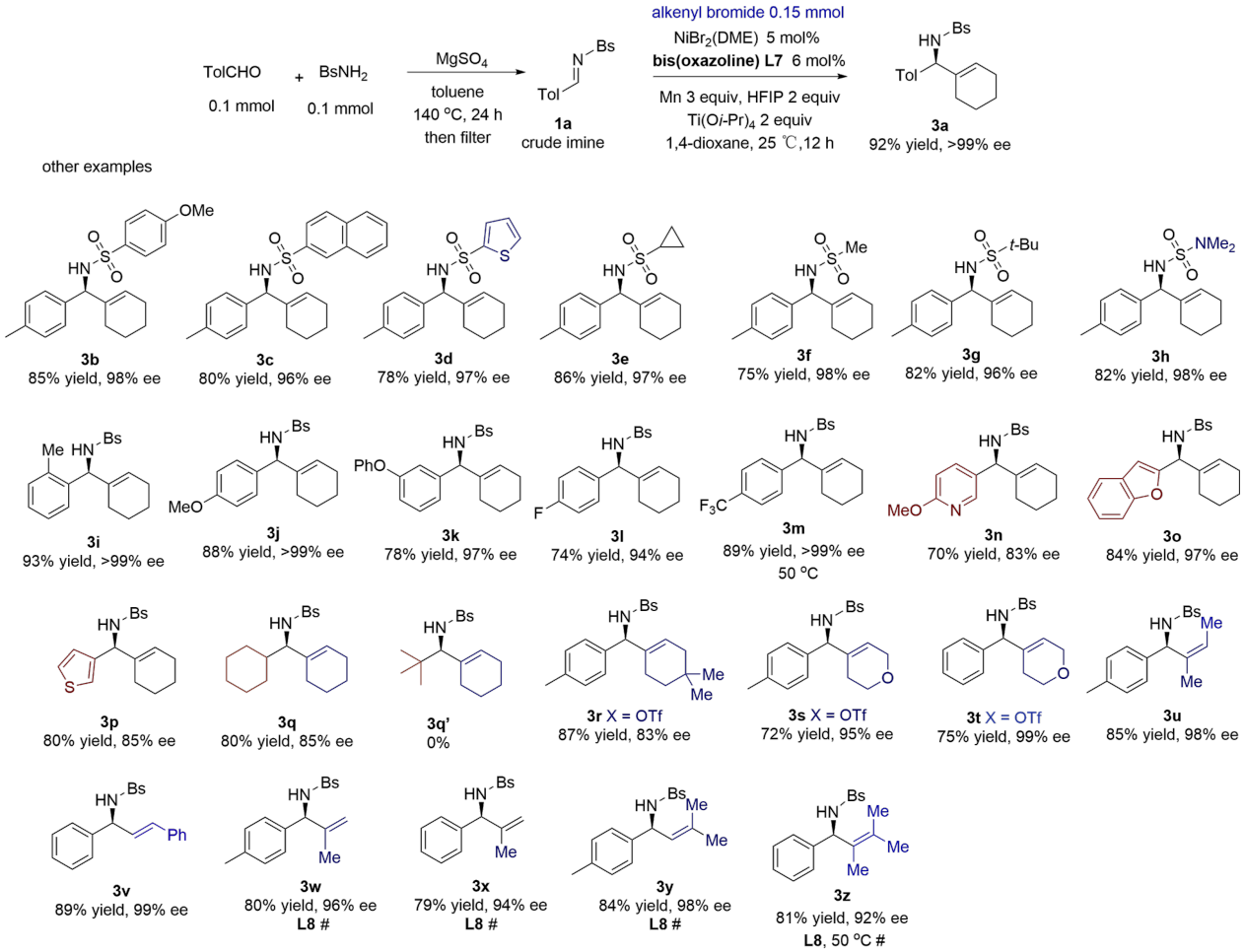


Figure 4. One-pot synthesis and alkenylation of *N*-sulfonyl aldimines using alkenyl bromides and triflates. Isolated yields from reactions of 0.2 mmol of aldehydes and 0.2 mmol of heterocyclic amines unless described otherwise. # conditions: 3 equiv Mn, 2 equiv *t*-BuOH, THF (0.4 mL), 25 °C,12 h; THF: tetrahydrofuran.

$MgSO_4$ efficiently promoted the condensation of $BsNH_2$ with various aldehydes. The resulting crude imines were directly used in catalytic alkenylation, producing chiral benzylic amines in high yields and excellent ees. A range of aromatic imines having *ortho*-methyl (**3i**), electron-donating OMe and OPh groups (**3j** and **3k**) and electron-withdrawing F and CF_3 groups (**3l** and **3m**) reacted successfully. Heteroaryl imines derived from aldehydes of 2-methoxypyridine, benzofuran, and thiophene reacted in good yields and 83-97% ees (**3n**-**3q**). For example, 6-methoxypyridine-3-carboxaldehyde gave amine **3k** in 70% yield and 83% ee.

N-Bs-cyclohexylimine was converted to amine **3q** in 80% yield and 85% ee. However, *N*-Bs-*t*-butyl aldimine completely failed to give amine **3q'** due to severe steric effects. The condensation of primary aliphatic aldehydes with Bs-amine failed to give clean samples of *N*-Bs-aldimines in the presence of $MgSO_4$, $Ti(Oi\text{-}Pr)_4$, or 4Å molecular sieve, owing to side reactions from the aldol reaction. The catalytic alkenylation failed completely when applied to the *N*-sulfonyl ketimine of acetophenone.

A diverse set of alkenyl bromides and triflates possessing different steric and electronic properties participated in reductive alkenylation in excellent ees under the standard conditions. The examples of triflates included 1-cyclohexenyl bromide having 4-gem-dimethyl substituents (**3r**) and a 4-oxa-derivative (**3s** and **3t**). (*Z*)-2-butenyl bromide gave amine **3u** in 85% yield and 98% ee, while (*E*)-Styrenyl bromide gave amine **3v** in 89% yield and 99% ee. (*E*)-Styrenyl iodide failed due to fast reductive coupling forming a 1,3-diene.

Ligand re-optimization was often required to achieve high levels of ees for asymmetric transfer of other alkenyls having other α- or cis-β-substituents. Thus, under the conditions using ligand **L8** without titanium isopropoxide, several acyclic alkenyl bromides gave good yields and excellent 92-98% ees, including 2-propenyl bromide (**3w** and **3x**), 1-isobutenyl bromide (**3y**) and trimethylvinyl bromide (**3z**). For example, hindered trimethylvinyl bromide provided amine **3z** in 81% yield and 92% ee under the condition without titanium isopropoxide at 50 °C. The standard conditions using the titanium alkoxide gave low yields, in comparison. Cyclohexenyl chloride did not react, while *trans*-β-styrenyl iodide gave a low yield of the amine due to fast homocoupling.

3.3 Synthetic applications

The alkenyl groups in the chiral amines are easily converted to aliphatic groups. These alkylated compounds may not be easily prepared from catalytic asymmetric alkylation reactions otherwise (Figure 5). For example, Pd/C-catalyzed hydrogenation with additive Et_3N[22] efficiently hydrogenated the cyclohexenyl ring in **3a**, affording chiral benzylic amine **4a** in almost qualitative yield. Notably, the *N*-benzenesulfonyl group of **3a** was reductively cleaved by SmI_2 to provide unprotected benzylic amine **4b** in 80% yield[23]. Additionally, we conducted iron-mediated olefin hydrofluorination, giving **4c** under our modified Boger's condition[24] using $Fe(NO_3)_3{\times}9H_2O$[25]. No erosion of ees was detected in these transformations described above. Chiral benzylic amines substituted with functionalized alkyl groups are common core motifs in many drugs[26].

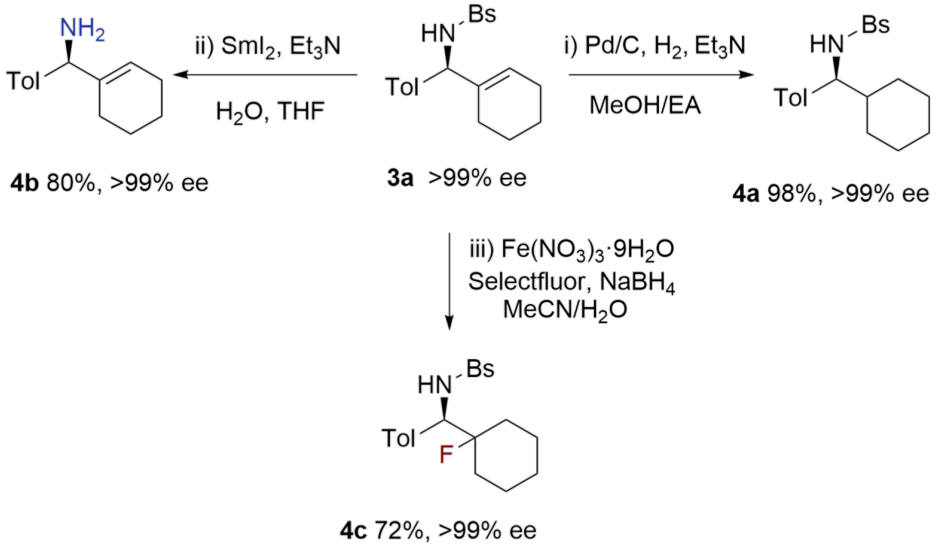


Figure 5. Product derivatization of amine **3a**.

We envisioned that catalytic hydrogenation of olefins and arenes in these products would allow access to *chiral methylamines* having two aliphatic substituents, which are difficult to prepare otherwise[27]. Thus, *N*-Bs-amine **3u** was converted to *N*-Cbz-amine **4d** after SmI_2 deprotection, full hydrogenation of the olefin and arene by Adom's catalyst[28] and *N*-Cbz protection (Figure 6a). Similarly, amines **3a** and **3q** were saturated by Adom's catalyst, affording *N*-Cbz-amines **4e** (dr 1.4:1) and **4f** in good yields (Figure 6b,c). The *N*-desulfonylation and full hydrogenation of **3v** gave unprotected primary alkylamine **4g** (Figure 6d). No erosion of ee values was detected in these transformations. These chiral alkylamines are difficult to obtain in high ees from other catalytic methods.

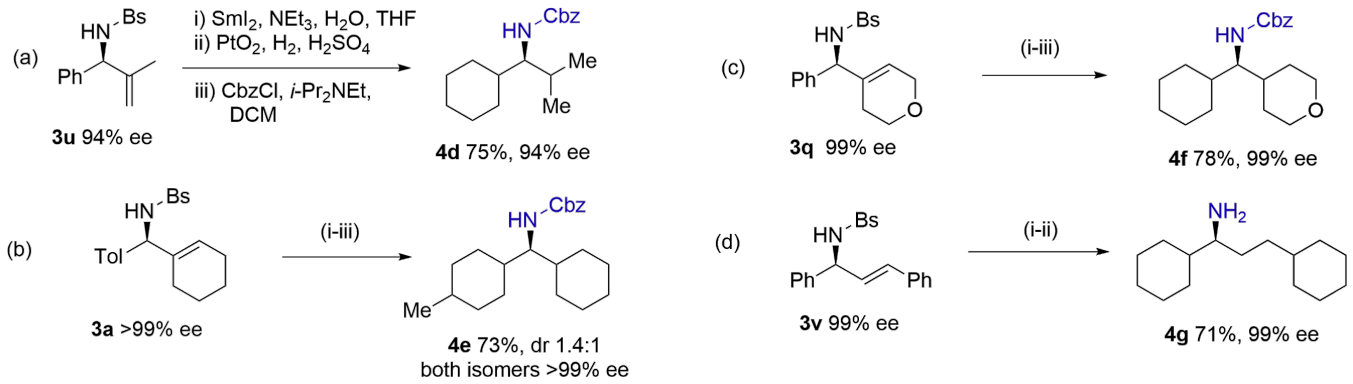


Figure 6. Catalytic hydrogenation of olefins and arenes to access methylamines having α,α-dialkyl substituents in high ees.

3.4 Computational mechanistic studies

For the alkenyl insertion of the neutral complex (1-cyclohexenyl)nickel of ligand **L7** into (*E*)-*N*-Bs-imine **1a**, we have identified 12 ground-state conformers and 12 transition states (see the Supplementary materials). Importantly, the C_2-symmetric ligand bis(oxazoline) **L7**, upon chelation to nickel, forms an *unsymmetrical* puckered ring. It is evident that one central methyl group of **L7** points up vertically while the other points back in the coordination plane, as shown in Figure 7. Consequently, the two phenyl substituents of **L7** are dispositioned in different orientations in space, the right phenyl ring is pointing downward vertically while the left phenyl is tilted close off the coordination plane.

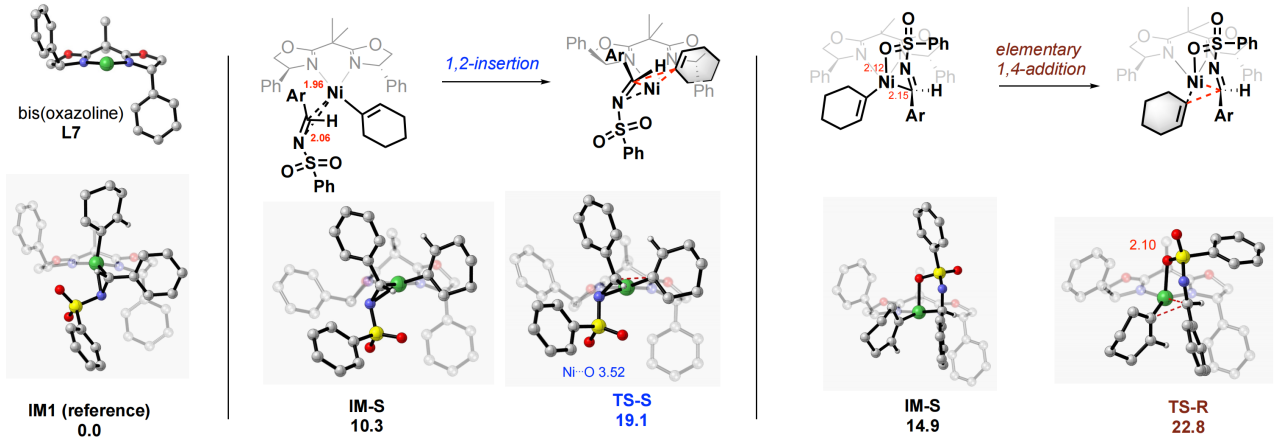


Figure 7. Calculated ground states and corresponding transition structures of the lowest-energies for asymmetric alkenyl addition of neutral complex of **L7** (cyclohexenyl)nickel to (*E*)-*N*-benzenesulfonyl imine **1a**.

We chose to use the lowest-energy ground state **IM1** having an h^2-imine coordination as the reference structure, for comparison of energies of different transition states. The two lowest-energy TSs leading to the major (*S*)-isomer and minor (*R*)-isomer are shown in Figure 7. The Gibbs free energy of **TS-S** is 19.1 kcalmol^{-1}, which is 3.7 kcalmol^{-1} lower than that of **TS-R**. It is consistent with the almost perfect enantioinduction observed experimentally using the nickel catalyst. Notably, the insertion *barrier* of **TS-S** from its own ground-state **IM-S** is only 8.8 kcalmol^{-1}. The 4-membered core structure of **TS-S** is close to a planar classical 1,2-insertion. The nickel(I) ion is 3.52 Å away from the closest sulfonyl oxygen, way beyond the sum of the van der Waas radii of the two atom/ion. A closer examination of structure **TS-R** leading to the minor isomer, however, reveals a nonplanar 6-membered cyclic TS featuring a short Ni-O bond distance of 2.10 Å, which is reminiscent of a mechanism of "elementary 1,4-addition". Other insertion structures can be found in the SI.

4. Conclusion

We report here nickel-catalyzed asymmetric reductive alkenylations of aromatic aldimines featuring various *N*-sulfonyl and sulfamoyl groups. The reactions produce chiral benzylic amines in excellent stereoselectivity, with most examples having > 95% ees. These reactions offer several practical advantages over existing catalytic alkenylations using organometallic reagents and alkenyl boronic acids: nearly neutral conditions, excellent compatibility with polar groups and heterocycles such as pyridine, thiophene, and benzofuran. A broad scope of both cyclic and acyclic alkenyl bromides and sulfonates are suitable electrophiles with different

substituents. One procedure was scalable with low loadings of nickel catalysts (as low as 0.2 mol%). Moreover, olefinic groups in products can be readily converted to other aliphatic groups via Pd/C hydrogenation and iron-catalyzed radical hydrofluorination, for example, offering access to other types of chiral benzylic amines. Additionally, complete hydrogenation of arenes and olefins using Adom's catalyst provided chiral methylamines carrying two different aliphatic groups with exceptionally high ees. They are challenging to prepare by other efficient methods. Importantly, density functional theory (DFT) calculations revealed that in the reactions of *N*-sulfonyl imines, the major pathway proceeds through classical 1,2-migratory insertion of alkenyl nickel species via planar four-membered-ring transition states.

Supplementary materials

The supplementary material for this article is available at: Supplementary materials.

Declarations

Authors contribution

Zhou JS: Conceptualization, supervision, writing-original draft, writing-review & editing.
Zhao M: Methodology, investigation, data curation.
Sun L: Investigation, data curation.
Xiao B: Investigation, data curation.

Conflicts of interest

Jianrong Steve Zhou is an Advisory Editor of *Chiral Chemistry*. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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