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Asymmetric Synthesis of 2*H*-Azirines with a Tetrasubstituted Stereocenter by Enantioselective Ring Contraction of Isoxazoles

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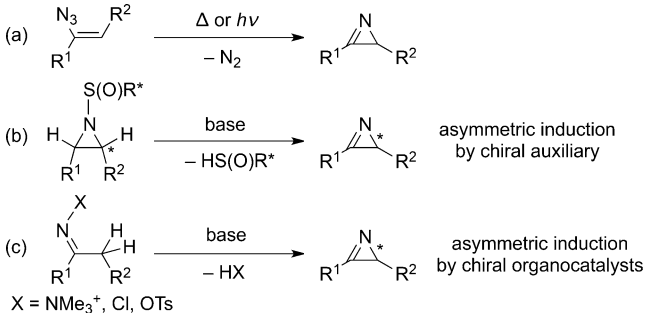
Abstract: *Highly strained 2H-azirines with a tetrasubstituted stereocenter were synthesized by the enantioselective isomerization of isoxazoles with a chiral diene–rhodium catalyst system. The effect of ligands and the coordination behavior support the proposed catalytic cycle in which the coordination site is fixed in favor of efficient enantiodiscrimination by a bulky substituent of the ligand. In silico studies also support the existence of a rhodium–imido complex as a key intermediate for enantiodiscrimination.*

Nitrogen-containing small-membered heterocyclic compounds are recognized as an important class of compounds often found in biologically active molecules, such as antitumor aziridines and antibiotic β-lactams.[1] Of such compounds, 2*H*-azirines, the most highly strained class of N-heterocycles with C=N bonds, are useful building blocks for the construction of various nitrogen-containing molecules by means of strain release.[2,3] Antibiotic natural products containing chiral 2*H*-azirines are also known, such as azirinomycin and dysidazirine.[4]

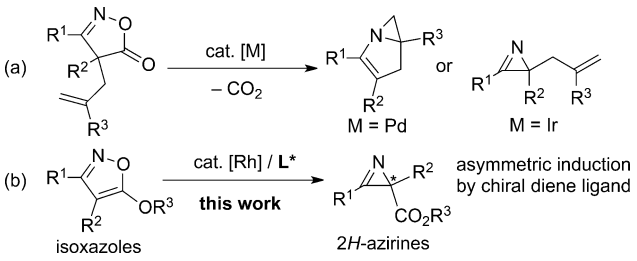
Synthetic methods for 2*H*-azirines are classified mainly into three types (Scheme 1). The thermal or photochemical denitrogenative cyclization of vinyl azides is the simplest way to access achiral 2*H*-azirines without generating waste, although the starting azides are generally unstable and potentially explosive (Scheme 1a).[5] For the enantioselective synthesis of 2*H*-azirines, base-mediated elimination reactions from aziridines with stoichiometric chiral auxiliaries, such as sulfoxide moieties, have been reported (Scheme 1b).[6] Neber-type reactions involving base-catalyzed elimination from oxime or hydrazonium derivatives are also representative methods for the synthesis of 2*H*-azirines (Scheme 1c). Successful examples of the catalytic asymmetric synthesis of 2*H*-azirines are limited to only a few studies, in which enantiomerically enriched 2*H*-azirines were generated by Neber-type reactions of oxime sulfonates with chiral organocatalysts, such as a quinine, a chiral phase-transfer catalyst, or a chiral thiourea catalyst.[7,8] The enantioselective synthesis of 2*H*-azirines with tetrasubstituted stereocenters has never been achieved before.



Scheme 1. Classification of synthetic methods for 2*H*-azirines. Ts = *p*-toluenesulfonyl.

We have developed a series of transition-metal-catalyzed decarboxylative reactions of isoxazol-5(4*H*)-ones that afford various nitrogen-containing products depending on the transition metal.[9,10] Small N-heterocycles, such as bicyclic aziridines[9a] and 2*H*-azirines,[9d,f] were synthesized selectively (Scheme 2a). In our previous studies, catalytic asymmetric reactions to afford three-membered molecules by using chiral ligands were not successful, probably because the starting compounds already had chirality on the isoxazolone ring. Therefore, we decided to employ another strategy towards the 2*H*-azirine ring: a [1,3] sigmatropic rearrangement of isoxazoles.[11,12] We envisioned that an enantioselective transformation would be possible by using a combination of a chiral transition-metal catalyst and isoxazoles[13] with both an achiral planar ring and a metal-coordination site. We herein report a rhodium-catalyzed asymmetric ring contraction of isoxazoles as a novel enantioselective method for the synthesis of 2*H*-azirines with tetrasubstituted stereocenters (Scheme 2b).

Initially, we examined the effect of achiral and chiral ligands by using the bis(ethylene)rhodium chloro-bridged dimer $[RhCl(C_2H_4)_2]_2$ (5 mol% Rh) as the catalyst precursor



Scheme 2. Transition-metal-catalyzed transformation of isoxazole derivatives.

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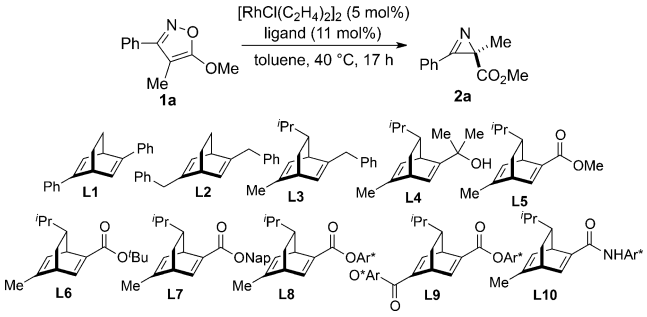
in the isomerization of isoxazole **1a**. The reaction proceeded without any supporting ligand to afford racemic **2a** (Table 1, entry 1). Chiral bisphosphine and monophosphine ligands resulted in poor conversion and enantioselectivity (entries 2–6). The cyclooctadiene-coordinates complex $[RhCl(cod)]_2$ effectively catalyzed the reaction to afford racemic **2a** in good yield (entry 7). Encouraged by this result, we then utilized chiral diene ligands, which are known to as efficient ligands for rhodium-catalyzed conjugate addition reactions.[14] Simple C_2-symmetric chiral diene ligands, such as Ph-bod (**L1**) and Bn-bod (**L2**), afforded the products, but with low enantioselectivity (3% *ee* with **L1** and 30% *ee* with **L2**; entries 8 and 9). To further vary the substituents on the ligands, we then employed a series of chiral diene ligands **L3**–**L10** readily prepared from commercially available α-phellandrene.[15] The dialkyl-substituted diene **L3** resulted in almost the same *ee* value as observed with **L2** (entry 10). The hydroxyalkyl-substituted diene **L4** and methoxycarbonyl-substituted diene **L5** gave moderate enantioselectivity (58 and 59% *ee*; entries 11 and 12). Use of the more hindered *tert*-butoxycarbonyl-substituted diene ligand **L6** improved the enantioselectivity (67% *ee*; entry 13). 2-Naphthyl ester substituted **L7** also provided moderate enantioselectivity (69% *ee*; entry 14). Finally, with ligand **L8**, bearing a bulky aromatic ester moiety, and DCE as the solvent, the catalyst loading could be decreased to 5 mol% Rh, and the product was obtained in 86% yield with 94% *ee* (Table 1, entry 18). An iridium catalyst with ligand **L8** exhibited higher catalytic activity and comparable enantioselectivity (the reaction reached completion even at 0°C; 91% yield, 92% *ee*; entry 19). The presence of two ester moieties on ligand **L9** did not improve the *ee* value of the product further (84% *ee*; entry 20),[16] and the use of amide-substituted ligand **L10** resulted in lower enantioselectivity (53% *ee*; entry 21).

Table 1: Rhodium-catalyzed enantioselective isomerization of isoxazole **1a** to give 2*H*-azirine **2a**.[a]

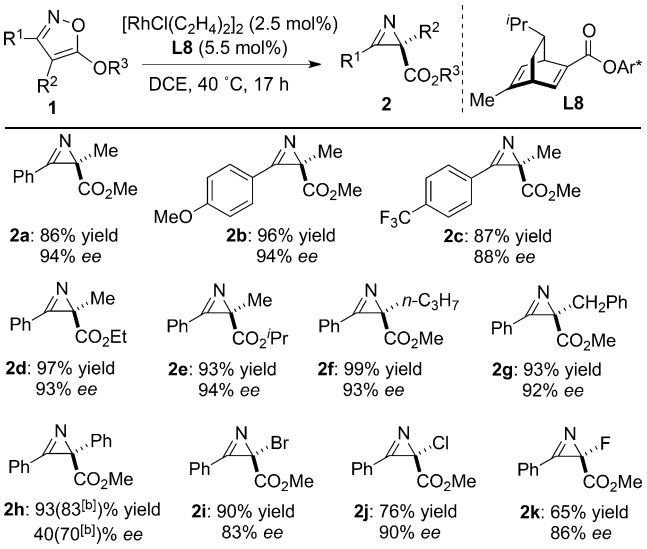


Entry	Ligand	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	none	86	75	–
2	(*R*)-binap	22	9	8
3	(*R*)-segphos	10	(9)	nd
4	(*R*)-phanephos	33	(14)	nd
5	(*R*)-mop	31	(21)	nd
6	(*R*)-monophos	0	(0)	nd
7[e]	cod	100	68	–
8	**L1**	71	50	3
9	**L2**	94	79	30
10	**L3**	98	77	31
11	**L4**	100	85	58
12	**L5**	76	38	59
13	**L6**	83	64	67
14	**L7**	89	51	69
15	**L8**	99	89	88
16[f]	**L8**	100	82	53
17[g]	**L8**	98	84	85
18[g,h]	**L8**	100	86	94
19[i]	**L8**	100	91	92
20	**L9**	100	91	84
21	**L10**	93	83	53

[a] The reaction was carried out with isoxazole **1a** (0.20 mmol), $[RhCl(C_2H_4)_2]_2$ (5 mol%), and a ligand (10 mol%) in toluene (1.5 mL). [b] Conversion was determined by ^{1}H NMR spectroscopy of the crude product. [c] Yield of the isolated product. Yields in parentheses were determined by ^{1}H NMR spectroscopy. [d] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [e] $[RhCl(cod)]_2$ (5 mol%) was used as the catalyst. [f] The reaction was carried out at 80°C. [g] The reaction was carried out with 2.5 mol% of $[RhCl(C_2H_4)_2]_2$ and 5.5 mol% of the ligand. [h] 1,2-Dichloroethane (DCE) was used instead of toluene. [i] $[IrCl(C_2H_4)_2]_2$ was used at 0°C instead of $[RhCl(C_2H_4)_2]_2$. Ar* = 2,6-diisopropylphenyl, cod = 1,5-cyclooctadiene.

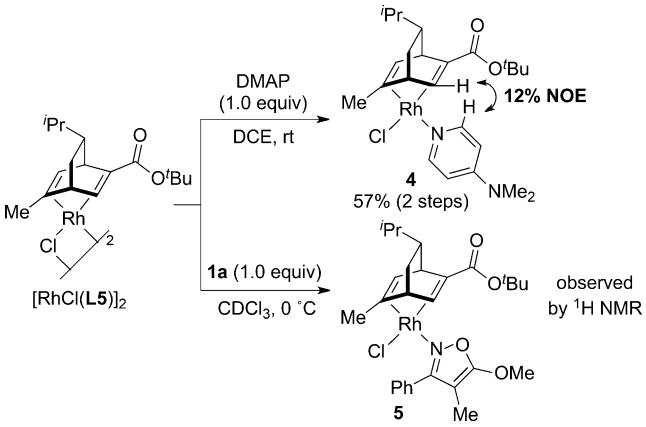
The present asymmetric isomerization method was applied to the reaction of various 5-alkoxy isoxazoles **1** and afforded the corresponding azirine-2-carboxylates **2** in good yields with high enantioselectivity (Table 2). *p*-Methoxy- and *p*-trifluoromethylphenyl groups were suitable as the R^1 substituent (products **2b**,**c**). 5-Ethoxy and 5-isopropoxy isoxazoles also reacted to form ethyl ester **2d** and isopropyl ester **2e** with high *ee* values. *n*-Propyl and benzyl groups were suitable as the R^2 substituent (products **2f**,**g**). Azirine **2h**, with a phenyl group as the R^2 substituent, was obtained with low enantioselectivity (40% *ee*), probably owing to a steric effect of the phenyl group. In this case, the use of the corresponding iridium catalyst in the reaction at 0°C improved the *ee* value to 70%. 2*H*-Azirines with halogen substituents at the R^2 position were obtained with high *ee* values (**2i**–**k**).

Table 2: Scope of the enantioselective synthesis of 2*H*-azirines **2**.[a]



[a] The reaction was performed with isoxazoles **1** (0.10 mmol), $[RhCl(C_2H_4)_2]_2$ (2.5 mol%), and **L8** (5.5 mol%) in DCE (1.0 mL) at 40°C for 17 h. Yields are for the isolated product. HPLC analysis on a chiral stationary phase was used to determine *ee* values. [b] $[IrCl(C_2H_4)_2]_2$ was used instead of $[RhCl(C_2H_4)_2]_2$. The reaction temperature was 0°C.

To gain insight into the reaction mechanism and the origin of enantioselectivity, we carried out some stoichiometric experiments with chiral diene–rhodium complexes. First, a mixture of $[RhCl(C_2H_4)_2]_2$ and chiral diene ligand **L6** was stirred in DCE at room temperature for 12 h, and then *N*,*N*-dimethylaminopyridine (DMAP) was added to the mixture (Scheme 3).[17] Characterization of the resulting DMAP



Scheme 3. Coordination experiments with the rhodium-**L6** complex.

complex **4** by ^{1}H NMR spectroscopy including NOE analysis revealed the site selectivity of DMAP coordination. The DMAP ligand in complex **4** coordinates at the site *cis* to the alkene substituted with the *tert*-butoxycarbonyl group, which indicates that the coordination site of heteroaromatic molecules containing a coordinating nitrogen atom is definitive owing to the non-C_2-symmetric coordination sphere.[18] The actual substrate **1a** similarly coordinated to the chiral diene–rhodium complex to form isoxazole complex **5** as a single isomer, which also exhibited a similar spectral change (see the Supporting Information). Isoxazole **1a** is also considered to occupy the site *cis* to the electron-deficient alkene.

On the basis of the above results and discussion, we propose the following catalytic cycle (Figure 1):[19] First, chiral-diene–rhodium dinuclear species **A**, which is not predominant in the whole reaction,[20] undergoes coordination with isoxazole **1** to form isoxazole complex **B**. The coordination site of isoxazole **1** in complex **B** is fixed by analogy with the observed complex **5**. Complex **B** then undergoes N–O bond cleavage to form imido complex **C** as a possible

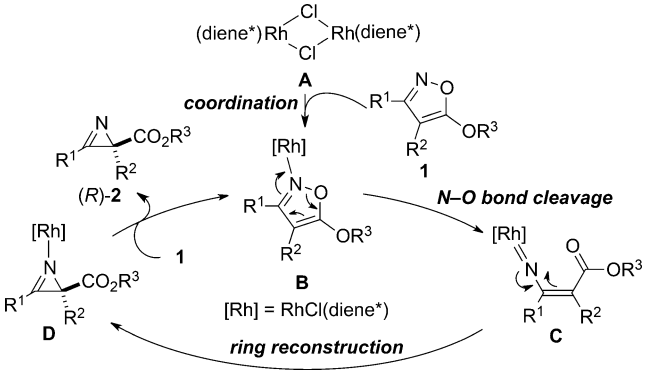


Figure 1. Proposed catalytic cycle for the rhodium-catalyzed asymmetric isomerization of isoxazoles.

intermediate. Complex **C** causes the C–N bond-forming ring reconstruction to form azirine complex **D**. Finally, azirine **2** is released in exchange for the coordination of isoxazole **1**, which regenerates complex **B**.

In silico studies were performed with a simplified model for the rhodium-catalyzed 2*H*-azirine formation (Figure 2). The starting isoxazole complex **B** undergoes the N–O bond cleavage to give imido complex **C** as an intermediate via transition state **TS1** ($\Delta G^{\ddagger} = 17.6$ kcal mol^{-1}). In imido complex **C**, the substrate moiety has an planar structure and is almost in the plane of the coordination square plane. The ester moiety on the substrate then moves to avoid the steric repulsion from the ester moiety on the chiral diene ligand. Transition state **TS2** lies at the highest free energy level ($\Delta G^{\ddagger} = 19.0$ kcal mol^{-1}), but such a low activation barrier can be overcome at the reaction temperature of 40 °C. Although further calculation studies are required to reveal the origin of the high enantioselectivity, the present insight supports the existence of the rhodium–imido complex as the key intermediate.[21]

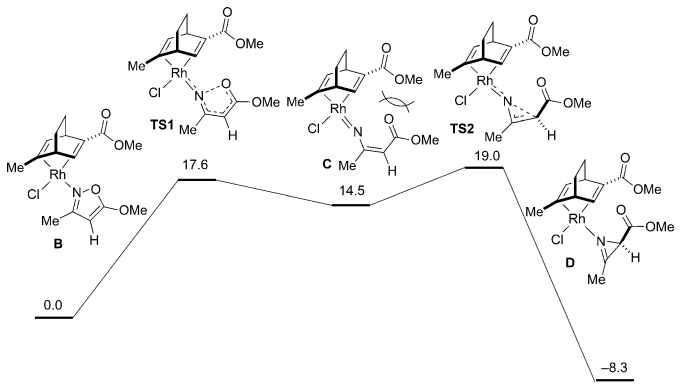
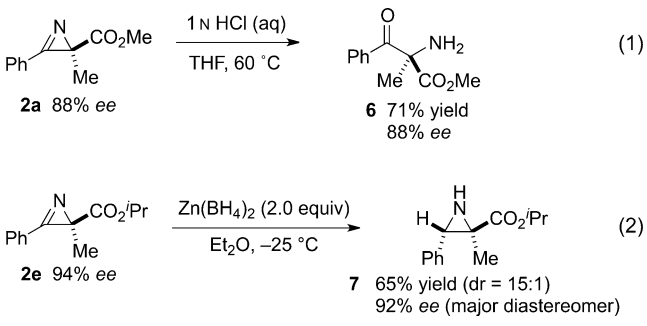


Figure 2. Reaction coordinate calculated with density functional methods (DFT) at the B3LYP/6–311 + G(d,p) level. Free-energy differences [kcal mol^{-1}] from isoxazole complex **B** are shown.

The product azirine-2-carboxylic esters could readily be transformed into various nitrogen-containing chiral molecules by simple reactions. Azirine **2a** was hydrolyzed by treatment with dilute aqueous HCl to give ketoamino acid ester **6** without any loss of optical purity [Eq. (1)]. Treatment with $Zn(BH_4)_2$ caused diastereoselective hydride reduction by chelation control to afford N–H aziridine **7** with 15:1 dr [Eq. (2)].[22] The *ee* value of the major diastereomer was maintained from that of the starting azirine.[23]



In conclusion, we have developed a novel asymmetric synthesis of 2*H*-azirines with a tetrasubstituted stereocenter based on rhodium-catalyzed asymmetric ring contraction of isoxazoles. 2-Alkoxycarbonyl 2*H*-azirines with various substituents, including halogen groups, were obtained with high enantioselectivity by employing non-C_2-symmetric electron-deficient chiral diene ligands. Mechanistic investigations provided insight into the coordination behavior of isoxazoles to the rhodium center. The site selectivity of the coordination can enable efficient enantiodiscrimination by the bulky ester moieties of the ligand. The catalytic cycle supported by DFT calculations includes a rhodium–imido complex as the most probable intermediate for the present reaction. Further theoretical and experimental studies that support the mechanistic aspects of the reaction are under way.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 2*H*-azirines · chiral diene ligands · isoxazoles · nitrogen heterocycles · rhodium catalysis

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[21] We tried to calculate the mechanism of concerted [1,3] sigmatropic rearrangement from isoxazole complex **B** directly to azirine complex **D**, but failed to find transition states with a sufficiently low activation barrier.

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