Asymmetric Hydroamination

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A Highly Enantioselective Zirconium Catalyst for Intramolecular Alkene Hydroamination: Significant Isotope Effects on Rate and Stereoselectivity**

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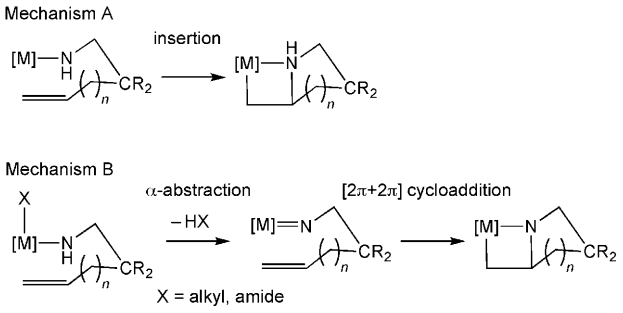
In memory of Victor S.-Y. Lin

Asymmetric olefin hydroamination/cyclization is a promising method for the synthesis of optically active cyclic amines.[1] To date, the most selective catalysts are C_2-symmetric rare earth and zirconium complexes.[2,3] These C_2-symmetric catalysts contrast with seminal C_1-symmetric *ansa*-lanthanidocenes that epimerize under catalytic conditions.[4] Despite advances, current asymmetric hydroamination/cyclization catalysts are highly sensitive to substrate substitution patterns.

Two distinct pathways have been proposed for C–N bond formation in zirconium-catalyzed processes:[1b] olefin insertion into a M–NR_2 bond (Scheme 1, Mechanism A)[5] and α-abstraction followed by $[2\pi+2\pi]$ cycloaddition (Mechanism B).[3,6] These two pathways can be difficult to distinguish because of conflicting observations, including large deuterium isotope effects and first- or second-order rate laws.

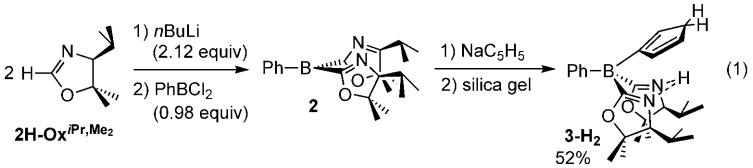
Our research group has recently described an achiral catalyst $[\{PhB(C_5H_4)(Ox^{Me_2})_2\}Zr(NMe_2)_2]$ (**1**; Ox^{Me_2} = 4,4-dimethyl-2-oxazolinyl) that cyclizes aminoalkene compounds at room temperature.[7]



Scheme 1. Mechanism A: olefin insertion into a M–N bond; Mechanism B: α-abstraction and $[2\pi+2\pi]$ cycloaddition.

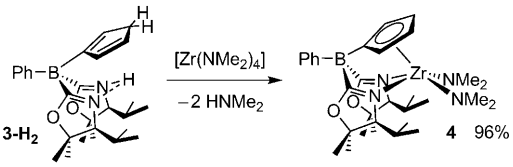
This unusually high activity motivated the preparation of optically active oxazolinylborate analogues that might provide highly reactive, robust, and non-epimerizable complexes. Herein, we report a chiral catalyst that provides pyrrolidine derivatives with excellent enantiopurity. Our data, including a unique deuterium isotope effect on enantioselectivity, unambiguously rules out both pathways of Scheme 1.

Precatalyst preparation is outlined in Equations (1) and (2).[8] Deprotonation of the oxazoline substrate **2H-Ox^{iPr,Me_2}** by *n*BuLi and subsequent treatment with 0.5 equivalents of $PhBCl_2$ provided chiral borane **2**.[9] A crude sample of **2** was then treated with NaC_5H_5 in THF and gave **3-H$_2$** as a mixture of C_5H_5 isomers; one isomer is shown in Equation (1).



(1)

Reaction of $[Zr(NMe_2)_4]$ and **3-H$_2$** afforded **4** in excellent yield of isolated product [Eq. (2)]. One $\tilde{\nu}_{CN}$ band at 1565 cm^{-1} in the IR spectrum of **4** suggests that both oxazoline units are coordinated to zirconium (for comparison, **2H-Ox^{iPr,Me_2}**: $\tilde{\nu}_{CN}$ = 1632 cm^{-1}).



(2)

A catalytic amount of **4** (2–10 mol%) and primary aminoalkenes **5a–9a** rapidly yielded pyrrolidines **5b–9b** with enantiomeric excesses ranging from 89% to 98% (see Table 1). Although the reaction rate is sensitive to catalyst and substrate concentration, the enantioselectivity is not. The catalyst can be recycled once without loss of activity or enantioselectivity. The secondary aminoalkene **5a-NMe** was not cyclized by **4**, even upon heating for 12 hours at 80, 120, 140, or 170°C. However, upon addition of $nPrNH_2$, 20% conversion into **5b** was observed at room temperature.

Significantly, the *ee* values obtained with **4** as the catalyst are the highest to date for unprotected pyrrolidines **5b**, **6b**,

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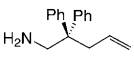
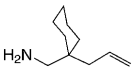
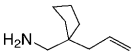
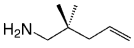
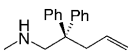
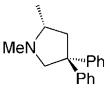
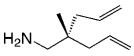
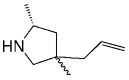
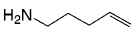
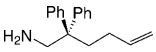
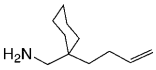
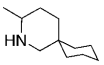
Table 1: Cyclization of aminoalkenes catalyzed by **4**.

Substrate	Product[a]	Solvent	*t* [h]	Conversion [%]	*ee* [%][b]
					
5a	**5b**	C_6D_6	1.25	>95, 93[c]	93
5a[d]	**5b**	C_6D_6	6	96	93
5a	**5b**	CD_2Cl_2	5	>95	94
5a	**5b**	[D_8]THF	5	>95	95
5a[e]	**5b**	[D_8]THF	12	>95	96[g]
5a[f]	**5b**	[D_8]THF	5 days	>95	98[g]
					
6a	**6b**	C_6D_6	1.25	>95, 88[c]	90
6a[d]	**6b**	C_7D_8	6.5	>95	90
6a[e]	**6b**	[D_8]THF	11	93	94
					
		C_6D_6	4	88	92
					
		C_6D_6	7	89	89
					
5a-NMe[h]	**5b-NMe**	C_6D_6	24	0	n.d.
5a-NMe	**5b-NMe**	C_6D_6 + *n*PrNH$_2$[i]	1	20	n.d.
					
9a	**9b**	C_6D_6	0.5	>95, d.r. = 1.1:1	93, 92
					
10a[j]	**10b**	C_6D_6	5	24	n.d.
					
11a	**11b**	C_6D_6	30	65	46
					
12a	**12b**	C_6D_6	40	48	31[g]

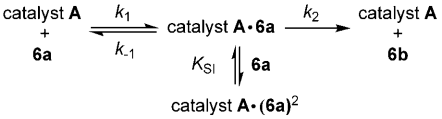
[a] Reaction conditions: 10 mol% of **4** and room temperature unless otherwise noted. [b] The *ee* values (±0.5%) were determined by ^{1}H and/or ^{19}F NMR spectroscopy of Mosher amide derivatives. Assignments of absolute configuration were based on literature reports.[2,3,8] [c] Yield of isolated product. [d] 2 mol% of **4**. [e] 0°C. [f] −30°C. [g] The *ee* values were determined by HPLC on a chiral stationary phase. [h] 170°C. [i] 10–30 mol%. [j] 110°C. n.d. = not determined.

7b, and **9b**.[10] Catalytic species derived from **1** and **4** are uncommonly active below room temperature compared to reported zirconium(IV) catalysts, including related [(CGC)Zr(Me)Cl] (CGC = $Me_2Si(C_5Me_4)(NtBu)$),[5c] [(dpm)Zr(NMe_2)$_2$] (dpm = 5,5-dimethyldipyrrolylmethane),[5d] and [Cp*(salicyloxazolinato)Zr(NMe_2)$_2$] (Cp* = pentamethylcyclopentadienyl) complexes.[6d] C_1-symmetric **4** produces pyrrolidines at 0°C and even at the low temperature of −30°C with improved *ee* values of up to 98%.

Cyclization occurs upon addition of aminoalkenes to **4** without a detectable induction period; $HNMe_2$ and **5b–9b** are observed within approximately two minutes. ln[**6a**] varies linearly with time for about two half-lives to provide k_{obs}. A linear relationship between k_{obs} and [**4**] provides the empirical rate law $-d[\mathbf{6a}]/dt = k'_{obs}[\mathbf{4}][\mathbf{6a}]$, which is consistent with reversible substrate–catalyst association preceding the turnover limiting step (TLS). To test this hypothesis, initial cyclization rates were measured over a 9.8–154 mM concentration range with respect to **6a** ([**4**] = 5.4 mM, 23°C). Indeed, the rate increases with [**6a**] until saturation is observed (Figure 1). At higher concentrations of **6a**, the rate decreases slightly as a result of inhibitory association of another equivalent of substrate. The plot also contains a nonzero x-intercept that coincides with [**4**]. A nonlinear least-squares regression analysis of the data provides good correlation with Equation (3), corresponding to the reaction mechanism shown in Equation (4) that describes the initial stage of the reaction.[11]

$$\frac{-d[\mathbf{6a}]}{dt} = \frac{k_2([\mathbf{6a}]-[\mathbf{4}])[\text{catalyst }\mathbf{A}]}{K' + ([\mathbf{6a}]-[\mathbf{4}]) + ([\mathbf{6a}]-[\mathbf{4}])^2 K_{SI}} \quad (3)$$

The three parameters obtained from the fit are k_2 ($1.7 \pm 0.3 \times 10^{-2}\,\text{M}^{-1}\text{s}^{-1}$), K' ($2.8 \pm 0.7 \times 10^{-2}$ M; $(k_{-1}+k_2)/k_1$), and K_{SI} ($5 \pm 2\,\text{M}^{-1}$; [catalyst·**6a**^{2}]/[**6a**][catalyst·**6a**]; substrate inhibition). The curve does not pass through the origin because one equivalent of substrate is required to form the active catalyst, thus giving the terms ([**6a**]–[**4**]; i.e., corrected substrate concentration). This analysis separates the TLS (k_2) from the substrate binding constant



(4)

(K'), thus allowing the measurement of the isotope effect (k_H/k_D) for k_2. A nonlinear least-squares fit ($R = 0.99$) of

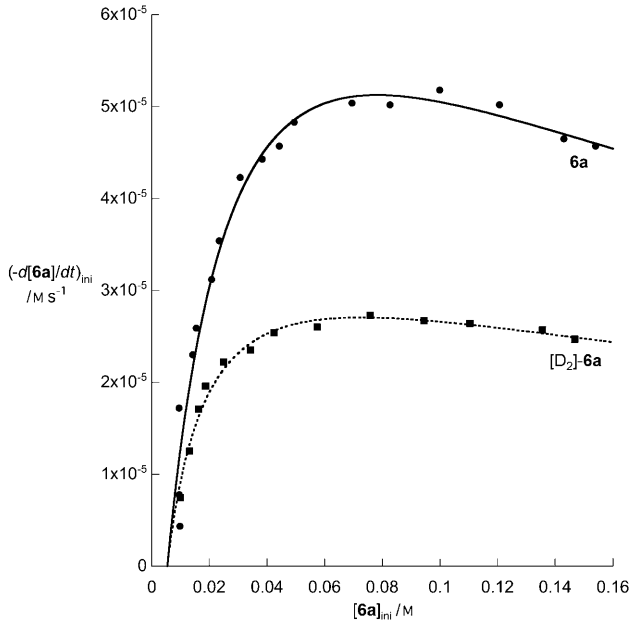
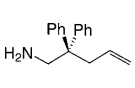
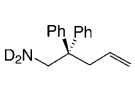
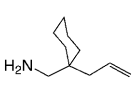
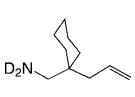
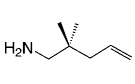
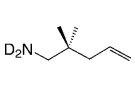


Figure 1. Plot of initial cyclization rate $(-d[\mathbf{6a}]/dt)_{ini}$ versus $[substrate]_{ini}$ for **6a** (●) and $[D_2]$-**6a** (■), measured in $[D_8]$toluene at 23 °C. The curves represent nonlinear least-squares fits [Eq. (3)].

Table 2: The *ee* values for proteo- and deutero-pyrrolidines obtained by cyclization of aminoalkenes catalyzed by **4**.[a]

Substrate	Product	*ee* [%][b]
5a		93
$[D_2]$-**5a**		95
6a		90
$[D_2]$-**6a**		97, 98[c]
8a		89
$[D_2]$-**8a**		92

[a] Reaction conditions: 23 °C, C_6D_6, 1.25–12 h, quantitative yield. [b] The *ee* values were determined by HPLC on a chiral stationary phase. [c] −30 °C in THF.

$(-d[[D_2]\text{-}\mathbf{6a}]/dt)_{ini}$ vs. $[[D_2]\text{-}\mathbf{6a}]_{ini}$ provides a curve with the values: $k_2^{(D)} = 7.2 \pm 0.5 \times 10^{-3}\,M^{-1}s^{-1}$, $K'^{(D)} = 1.5 \pm 0.2 \times 10^{-2}\,M$, and $K_{SI}^{(D)} = 3.2 \pm 0.9\,M^{-1}$.

The composition of the catalytic species can be partly assessed from this kinetic analysis. First, interaction of **6a** and **4** in a 1:1 ratio provides the active catalyst **A** that is likely [(**3**)Zr(NHR)(NMe_2)] (catalyst initiation; NHR = amidoalkene). The equilibrium step (k_1/k_{-1}) involves reversible interaction of catalyst **A** with **6a** to give [(**3**)Zr$(NHR)_2$] and $HNMe_2$. A secondary amide ligand (i.e. NMe_2 or pyrrolide) is not a sufficient coligand for cyclization of an amidoalkene. The kinetic isotope effects (KIE) from initial rate plots $k_2^{(H)}/k_2^{(D)}$ (2.3 ± 0.5) and from second-order rate constants, $k'_{obs}{}^{(H)}/k'_{obs}{}^{(D)} = 3.5$ indicate that an N–H bond is broken during the TLS. These isotope effects are inconsistent with 1,2-olefin insertion into the Zr–N bond. A KIE in olefin hydroamination/cyclization was noted by Marks and co-workers for the [Cp^*_2LnR] (Ln = lanthanoid) and [(CGC)U$(NMe_2)_2$] systems—in those cases a proton-assisted insertion is proposed.[5c,12]

Importantly, the *ee* values for deuteron-pyrrolidines ($[D_2]$-**5b**, $[D_2]$-**6b**, and $[D_2]$-**8b**) are systematically and significantly higher than the values for the corresponding proteo-pyrrolidines (Table 2). In the most dramatic example, the *ee* value for cyclization increases from 90% ($\Delta\Delta G^{\ddagger} = 1.7$ kcal mol^{-1}) for **6b** to more than 97% ($\Delta\Delta G^{\ddagger} = 2.5$ kcal mol^{-1}) for $[D_2]$-**6b**. By using the rate constants $k_2^{(H)}$ and $k_2^{(D)}$ and the ratio of enantiomers, the KIE for formation of each stereoisomer is calculated: major *R* enantiomer: $k_H{}^R/k_D{}^R = 2.2 \pm 0.5$; minor *S* enantiomer: $k_H{}^S/k_D{}^S = 7.7 \pm 0.1$.

The H (or D) atom from the amine is central to the step that determines stereochemistry, thus ruling out intramolecular $[2\pi + 2\pi]$ cycloaddition of a {Zr=$NCH_2CR_2CH_2HC$=CH_2} species because an NH group is not present in the imido moiety. Thus, the accumulated data including the rate law, the KIE, isotopic perturbation of enantioselectivity, and the KIE for the two enantiotopic pathways eliminate olefin insertion and $[2\pi + 2\pi]$ cycloaddition as possible mechanisms for C–N bond formation.

C–N bond formation establishes the configuration of the new stereocenter, whereas the new C–H bond is not attached to the stereogenic carbon atom. However, the stereochemical relationship between the N–H and the C–N bond suggests that C–N and C–H bond formation and cleavage of the N–H bond occur in a concerted fashion during the cyclization step. Given that an N–H bond is broken during the TLS and the catalytic intermediate contains two NHR ligands, we propose a six-center transition state in which N–H transfer from one amide group to the terminal methylene unit of the other amidoalkene is concerted with intraligand C–N bond formation (Figure 2). The two participating ligands are proposed to be two amido groups because kinetics indicate that two substrates interact with the catalyst in the turnover limiting step, and the addition of a third substrate, presumably as a coordinated amine, inhibits the cyclization. Finally, this mechanism is consistent with the observation that secondary aminoalkenes are cyclized only in the presence of a primary amine. Presumably, a primary amido ligand is formed that transfers a proton to the cyclizable amidoalkene ligand.

Some of the observations reported here have been previously observed in zirconium(IV)-, rare-earth-, and organoactinide-mediated hydroamination reactions; including a second-order rate law,[13] substantial KIE,[2,5c,6d,12,13c] and isotope effects on diastereoselectivity.[12] Here, saturation kinetics provide a mechanistic connection between zero-order and first-order substrate dependence, as illustrated by

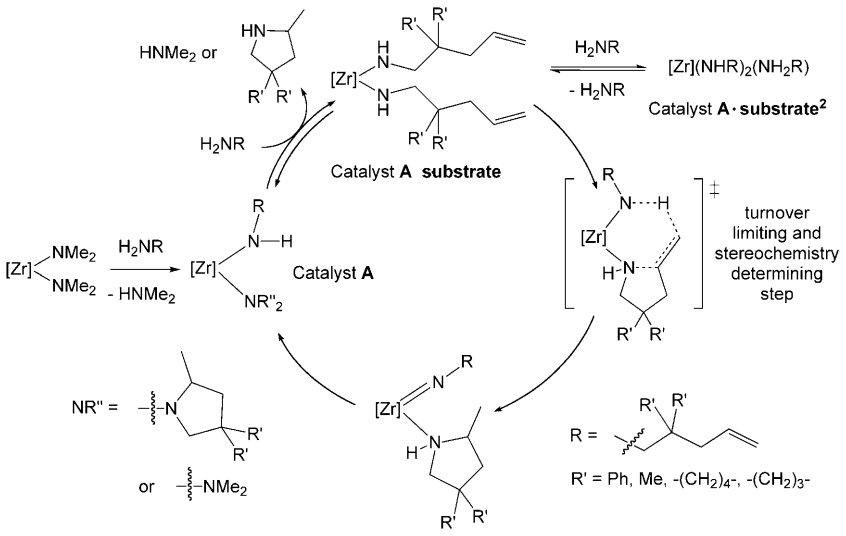


Figure 2. Proposed new catalytic cycle for hydroamination of aminoalkenes as catalyzed by **4**.

our observations on an oxazolinylborate magnesium hydroamination system.[14] Still, the involvement of the mechanism proposed here in other early transition metal catalyzed hydroamination reactions requires further experiments, as considerable evidence supports the insertion mechanism for many olefin hydroaminations, including those catalyzed by $[Cp_2ZrMe]^+$ (Cp = cyclopentadienyl), [(CGC)Zr(Me)Cl], and $[(dpm)Zr(NMe_2)_2]$.[5a,c,d] Furthermore, computational studies have provided support for olefin insertion into La–N bonds as well as neutral {Zr=NR/alkene} $[2\pi + 2\pi]$ cycloaddition reactions in other systems.[15] The unusually high reactivity and enantioselectivity available with **4** as a precatalyst in hydroaminations may relate to the ability of the {**3**}Zr moiety to stabilize the proposed six-center transition state. Studies are currently underway that will test our proposed mechanism and develop a model that rationalizes the observed enantioselectivity through variation of the ancillary ligands.

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Keywords: enantioselectivity · hydroamination · isotope effects · oxazolines · pyrrolidines

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