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Oxazolidine Synthesis by Complementary Stereospecific and Stereoconvergent Methods

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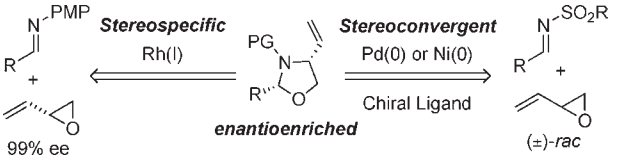
ABSTRACT



Complementary stereospecific and stereoconvergent reactions for enantioselective synthesis of 1,3-oxazolidines are reported. In the presence of a rhodium catalyst, reaction of *enantioenriched* butadiene monoxide with aryl imines is stereospecific (99% ee). Alternatively, the reaction of *racemic* butadiene monoxide, in the presence of a chiral palladium or nickel catalyst, provides an enantioselective synthesis of 1,3-oxazolidines (up to 94% ee). Synthesis of either the *cis*- or *trans*-1,3-oxazolidines is also accomplished under catalyst control.

Oxazolidines are commonly utilized in synthesis as protected amino alcohols and are pharmacophores themselves, embedded within the core of potent antitumor tetrahydroisoquinoline natural products including quinocarcin.[1,2] Catalytic enantioselective synthesis of 1,3-oxazolidines has been reported, often featuring aminohydroxylation of styrenes as a key design element.[3] We report alternative highly enantioselective catalytic strategies for the assembly of oxazolidines. High enantioselectivities are obtained through complementary stereospecific (substrate-controlled) and stereoconvergent (catalyst-controlled) methods, where the stereochemical outcome of the transformation is determined by the rate of isomerization of the requisite allylmetal intermediate. Development of both stereospecific and stereoconvergent methods provides flexibility for synthesis of bioactive compounds.

Formal cycloaddition reactions of vinyl epoxides and electrophiles have been reported and most frequently employ palladium-based catalysts.[4] Inspired by racemic syntheses of 1,3-oxazolidines via formal cycloaddition reactions of imines and vinyl epoxides,[5] we hypothesized that metal complexes known to catalyze allylic substitution reactions could provide enantioselective variants of this transformation. We were attracted to this strategy as allylmetal complexes afford a unique opportunity to catalyze either stereoconvergent or stereospecific reaction pathways by controlling rates of isomerization of allylmetal intermediates. On the basis of the stereochemical outcomes of allylic substitution reactions, we anticipated that nickel and palladium catalysts would provide stereoconvergent transformations, where both enantiomers of vinyl epoxide would be converted to one enantiomer of oxazolidine.[6,7] In contrast, rhodium

(1) A general review of the tetrahydroisoquinoline natural products and analogs: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

(2) (a) The oxazolidine moiety is necessary for antitumor activity of quinocarcin, see: Williams, R. M.; Glinka, T.; Flanagan, M. E.; Gallegos, R.; Coffman, H.; Pei, D. *J. Am. Chem. Soc.* **1992**, *114*, 733. (b) Tomita, F.; Takahashi, K.; Tamaoki, T *J. Antibiot.* **1984**, *37*, 1268.

(3) For Cu(II) catalyzed aminohydroxylation of styrenes with oxaziridines to provide 1,3-oxazolidines, with up to 2.5:1 dr and 89% ee, see: (a) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610. (b) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. *Tetrahedron* **2009**, 5118.

(4) For enantioselective examples, see: (a) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (b) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229. (c) Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907. (d) Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563.

(5) Racemic synthesis of 1,3-oxazolidines from imines and vinyl epoxides: (a) Shim, J.-G.; Yamamoto, Y. *Heterocycles* **2000**, *52*, 885–895. (b) Shim, J.-G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1053.

(6) Ni, Stereoselective: (a) Shintani, R., Hayashi, T. Asymmetric Synthesis. *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Germany, 2005; p 246 and references therein. Stereospecific: (b) Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2007**, *9*, 4603.

(7) Pd: (a) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *96*, 395. (b) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.

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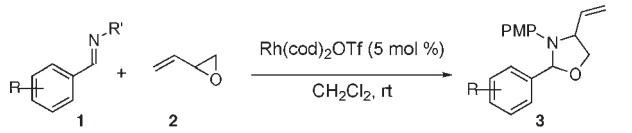
catalysts would produce oxazolidine products in a stereospecific manifold and employ enantioenriched vinyl epoxide.[8,9] In addition to providing facile synthetic access to 1,3-oxazolidines in high optical purity, this investigation contrasts the reactivity of allylrhodium, allylnickel, and allylpalladium complexes.

Table 1. Scope of Rhodium-Catalyzed Oxazolidine Formation[a]



entry	imine	R′	R	epoxide	product	% yield[b]	dr (cis:trans)[c]
1[d]	**1a**	SO_2Tol	H	(±)-**2**	**3a**	≤5	n.d.
2[d]	**1b**	$CH(Ph)_2$	H	(±)-**2**	**3b**	34	n.d.
3	**1c**	PMP	H	(±)-**2**	**3c**	86	6:1
4[e]	**1d**	PMP	4-OCH_3	(±)-**2**	**3d**	60	6:1
5	**1e**	PMP	4-CH_3	(±)-**2**	**3e**	87	3:1
6[e]	**1f**	PMP	4-Cl	(±)-**2**	**3f**	88	5:1
7[e,f]	**1e**	PMP	4-CH_3	(*R*)-**2** (99% ee)	**3e**	81 (99% ee)	6:1
8[e,f]	**1f**	PMP	4-Cl	(*R*)-**2** (99% ee)	**3f**	83 (99% ee)	6:1

[a] Conditions: 1.5 equiv (±)-**2**, [**1**] = 0.20 M. [b] % Isolated yield of **3**. % ee determined by chiral SFC chromatography. [c] *cis*:*trans* ratios determined by ^{1}H NMR. [d] THF used as solvent. [e] Two equivalents of (±)-**2** used. [f] One equivalent by weight of molecular sieves used.

To develop a stereospecific synthesis of 1,3-oxazolidines, we first identified reaction conditions where rhodium catalysts could affect formal cycloaddition of racemic butadiene monoxide (±)-**2** with imines (Table 1). While sulfonyl-protected imines did not provide the desired product, the desired oxazolidine was furnished upon exposure of *p*-methoxyphenyl imines to $Rh(cod)_2OTf$ as catalyst. A series of catalyst precursors, ligands, and solvents were examined.[10] A combination of rhodium(biscyclooctadiene) triflate in dichloromethane as solvent was found to be optimal, generating oxazolidine **3c** in 86% yield with 6:1 diastereoselectivity (entry 3). The more stable *cis*-oxazolidine was formed preferentially in favor of the trans diastereomer.[11] The optimal conditions were observed to be general over a range of aryl imines. Substrates containing electron-donating as well as electron-withdrawing groups were well-tolerated (entries 4−6).

The stereospecificity of the transformation was investigated using enantioenriched vinyl epoxide. Butadiene monoxide (*R*)-**2** was prepared in >99% ee utilizing Jacobsen's hydrolytic kinetic resolution reaction.[12] Under the optimized reaction conditions, employing an achiral rhodium catalyst, enantioenriched vinyl epoxide reacted to produce oxazolidines **3e** and **3f** in 99% ee (Table 1, entries 7 and 8). These results are consistent with our hypothesis that racemization of the putative allylrhodium intermediates is slow relative to heterocycle formation. The reaction was found to provide retention at the stereogenic center derived from the vinyl epoxide, consistent with double inversion. On the basis of the reliable and facile access to either antipode of enantiopure vinyl epoxide, this rhodium-catalyzed stereospecific transformation provides access to either enantiomer of vinyl-substituted 1,3-oxazolidines with the highest levels of enantiomeric excess reported to date.

Palladium and nickel complexes catalyze the dynamic kinetic resolution (DKR) of allylic acetates, via rapid isomerization of the allylpalladium and allylnickel complexes.[7a] Therefore, we anticipated that these catalysts would provide an analogous DKR of racemic vinyl epoxide to provide enantioenriched oxazolidines.[13] As previously mentioned, a palladium-catalyzed synthesis of *racemic* 1,3-oxazolidines from butadiene monoxide and imines was reported;[5] however, no enantioselective variant of the transformation has been described.

We began our investigation of a stereoconvergent transformation by examining catalysts prepared in situ from $Ni(cod)_2$ and chiral phosphines.[14] Upon examining a series of phosphine ligands and reaction conditions, we found that 1,3-oxazolidines could be generated in good yield and excellent diastereoselectivities from tosyl imine **1a** and racemic vinyl epoxide (±)-**2** (Table 2, entry 2). Addition of the Lewis acid cocatalyst such as $Ti(O\textit{i}\text{-}Pr)_4$ or TMSOTf dramatically improved the rate of the reaction, presumably by facilitating oxidative addition.[15] Addition of tetrabutylammonium difluorotriphenylsilicate (TBAT) also significantly improved the rate of the reaction, without impacting enantioselectivity, allowing cooling of the reaction temperature to −20 °C with a marked boost in enantioselectivity (entry 3).[16] Under the optimized reaction conditions,

(8) For rhodium-catalyzed stereospecific addition of alcohols and amines to vinyl epoxides: (a) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. For a complementary stereoselective example using an iridium catalyst: (b) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949.

(9) Examples of rhodium-catalyzed stereospecific allylic substitution: (a) Evans, P. A.; Leahy, D. K. *Chemtracts* **2003**, *16*, 567. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (c) Evans, A. E.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269.

(10) Phosphine ligands (e.g., BINAP, dipamp) inhibit the reaction.

(11) For relative stabilities, see: (a) Beckett, A. H.; Jones, G. R. *Tetrahedron* **1977**, *33*, 3313. (b) Just, G.; Potvin, P.; Uggowitzer, P. *J. Org. Chem.* **1983**, *48*, 2923. For a recent example see: (c) Tremblay, M. R.; Wentworth, P., Jr.; Lee, G. E., Jr.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 698.

(12) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1997**, *277*, 936. (c) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360. (d) White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymm.* **2003**, *14*, 3633.

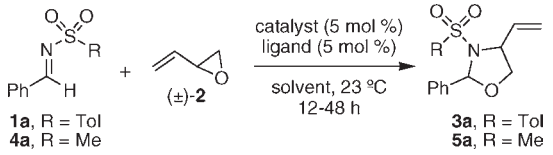
(13) For DKR of **2** with carbodiimides, see ref 4.

(14) Monodentate phosphines provided only crotonaldehyde, resulting from β-hydride elimination. Bidentate ligands with bite angles similar to dppe formed most efficient Ni catalysts for oxazolidine formation.

(15) In the presence of a nickel complex and Lewis acid, crotonaldehyde (a product of β-hydride elimination) is observed by ^{1}H NMR. In the absence of Lewis acid, no reaction is observed.

(16) For select examples of additive effects in reactions involving allylmetal intermediates, see the following. Rh: (a) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. Ir: (b) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917. Pd: (c) References 4c and 9b.

Table 2. Optimization of the Stereoselective 1,3-Oxazolidine Formation



entry	imine	catalyst	ligand	% yield[a]	dr (cis:trans)[b]	% ee[c]
1[d]	**1a**	$Ni(cod)_2$	C_3-Tunephos	20	≥20:1	42
2[d]	**1a**	$Ni(cod)_2$	DIPAMP	87	≥20:1	27
3[d,e]	**4a**	$Ni(cod)_2$	DIPAMP	88	≥20:1	65
4[f]	**4a**	**$Pd_2dba_3 \cdot CHCl_3$**	**C_3-Tunephos**	**92**	**1:3**	**82**
5[f]	**4a**	$Pd_2dba_3 \cdot CHCl_3$	Josiphos-6	80	2:1	89
6[f,g]	**4a**	**$Pd_2dba_3 \cdot CHCl_3$**	**Josiphos-6**	**96**	**2:1**	**91**

[a] % Isolated yield of **3a** or **5a** after column chromatography. [b] *cis*:*trans* determined by ^{1}H NMR spectroscopy. [c] % ee of the major diastereomer determined by chiral SFC chromatography. [d] Conditions: 2.0 equiv (±)-**2**, [imine] = 0.20 M, THF. [e] Additives: 0.30 equiv $Ti(Oi\text{-}Pr)_4$, 1.0 equiv TBAT; −20 °C. [f] Conditions: 1.24 equiv (±)-**2**, THF. [g] Diglyme used as solvent, 6.0 mol % ligand.

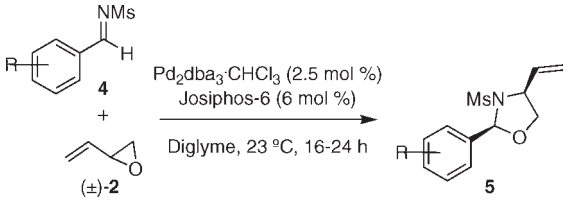
methansulfonyl imine **4a** and vinyl epoxide (±)-**2** could be smoothly converted to produce 1,3-oxazolidine product **5a** in excellent yield, ≥ 95:5 *cis*:*trans* diastereoselectivity, and 65% ee.[17] Upon garnering mechanistic insight into the nickel-catalyzed transformation (vide infra), we concluded that the modest enantioselectivity in this reaction results from inefficient chirality transfer from the catalyst to substrate.

We examined palladium catalysts for the reaction with the objective of identifying a catalyst that would provide higher enantioselectivities and avoid the need for additives to maintain an acceptable reaction rate. Utilizing $Pd_2(dba)_3 \cdot CHCl_3$ as a precatalyst, we examined a variety of bidentate phosphine ligands. Interestingly, we found that diasterocontrol could be achieved through catalyst selection. For example, a palladium-C_3-Tunephos complex provided *trans*-**5a** in excellent yield and good ee (Table 2, entry 4). Notably, this is the less stable diastereomer of the 1,3-disubstituted oxazolidine.[11] Conversely, complexes formed from ferrocenyl ligands, such as the Walphos and Josiphos class of bidentate phosphines produced *cis*-selective reactions (entries 5 and 6). Overall, the palladium-catalyzed reaction proved to be superior in all aspects, except diastereoselectivity, when compared to the nickel-catalyzed system. For the first time 1,3-oxazolidines could be produced in a catalytic enantioselective manner favoring either the *cis*- *or trans*-diastereomer in good to excellent ee.[18]

Aryl imines with a variety of substituent patterns were tolerated in the palladium-catalyzed reaction (Table 3).[19]

For example, *o*-bromobenzaldehyde derived mesyl imine **4e** produced the corresponding oxazolidine **5e** in moderate yield and good ee, demonstrating that oxidative addition of Pd(0) takes place preferentially with vinyl epoxide (±)-**2** over an aryl bromide (entry 5).

Table 3. Enantioselective Synthesis of *cis*-1,3-Oxazolidines[a]



entry	substrate	R	oxazolidine	% yield[b]	dr (cis:trans)[c]	% ee[d]
1	**4a**	H	**5a**	96	2:1	91
2	**4b**	4-Me	**5b**	99	3:1	94
3	**4c**	4-F	**5c**	96	2:1	91
4	**4d**	3,4-OMe	**5d**	97	2:1	89
5	**4e**	2-Br	**5e**	67	2:1	86

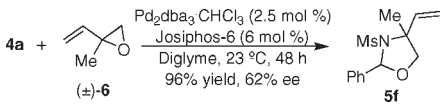
[a] Conditions: 1.24 equiv (±)-**2**. [b] % Isolated yield of **5** after column chromatography. [c] *cis:trans* ratio determined by ^{1}H NMR spectroscopy. [d] % ee of the major diastereomer determined by chiral SFC.

To refine our understanding of the transformation, we undertook mechanistic studies designed to pinpoint the origin of enantioselectivity. In the palladium-catalyzed reaction, a dynamic kinetic resolution clearly occurs to provide enantioenriched product in high yield, based on the mass balance of the reaction. For the nickel-catalyzed reactions, however, two mechanistic scenarios are consistent with the observed results. The first scenario is a dynamic kinetic resolution, such that both enantiomers of the vinyl epoxide are consumed with similar rates ($k_1 \cong k_2$), rapid η^3-η^1-η^3 isomerization occurs to interconvert the diastereomeric allylmetal intermediates ($k_3 > k_4$ and k_5) and

(17) Under the optimized conditions with Ni catalyst a series of aryl imine electrophiles reacted in up to 65% ee See Supporting Information.

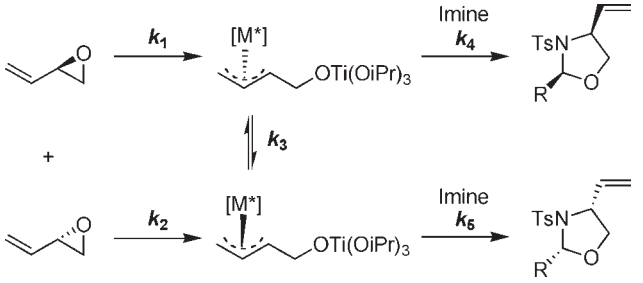
(18) Palladium-catalyzed synthesis of *trans*-1,3-oxazolidines in up to 2.3:1 ratio as a racemic mixture: Chen, D.; Chen, X.; Du, T.; Kong, L.; Zhen, R.; Zhen, S.; Wen, Y.; Zhu, G. *Tetrahedron Lett.* **2010**, *51*, 5131.

(19) Isoprene monoxide provided 98% yield and 62% ee. See Supporting Information for details.



one diastereomer reacts preferentially ($k_4 > k_5$) to provide high ee of the product (Scheme 1). This scenario mirrors the mechanism of the palladium-catalyzed reaction.[20] The alternative scenario is that the asymmetric catalyst performs a kinetic resolution of the vinyl epoxide to preferentially consume one enantiomer of the starting material ($k_1 > k_2$). In the nickel-catalyzed transformations 1.5 equivalents of vinyl epoxide are employed and the product is formed with modest ee (82:18 er), making this mechanism viable.[21]

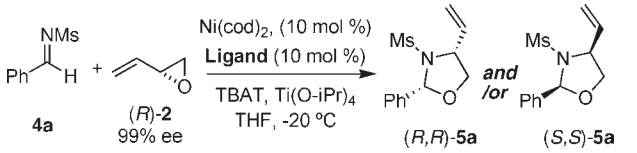
Scheme 1. Possible Mechanistic Scenarios for Asymmetric Induction[a]



[a] Dynamic kinetic resolution: $k_3 > k_4$ and k_5; $k_4 > k_5$. Kinetic resolution: $k_1 > k_2$; $k_4 > k_3$.

To distinguish these two mechanistic scenarios for the nickel-catalyzed reaction we performed experiments utilizing *enantiopure* vinyl epoxide in the presence of an *achiral* bidentate phosphine ligand (dppe), under the standard reaction conditions (Table 4, entry 1). Racemic product was obtained, demonstrating that the allylnickel intermediate indeed undergoes η^3-η^1-η^3 isomerization, which, in the presence of an achiral ligand, results in racemization of the allylnickel intermediate. To determine whether the chiral catalyst used in our enantioselective reaction is able to undergo a similarly rapid isomerization that would result in epimerization of the diastereomeric allylnickel complexes, *enantioenriched* vinyl epoxide was used in conjuction with *chiral* ligand (DIPAMP). The nickel-catalyzed reaction using each enantiomer of DIPAMP provided ees which are similar (Table 4, entries 2 and 3). Most importantly, the opposite enantiomers of ligand provided the opposite enantiomers of product, consistent with a dynamic kinetic resolution wherein isomerization of the diastereomeric allylnickel intermediates is faster than subsequent reaction with imine ($k_3 > k_4$ and k_5). Stereoselectivity is determined during a later step in the transformation.[22]

Table 4. Mechanistic Experiments Support Dynamic Kinetic Resolution of Vinyl Epoxide[a]



entry	ligand	% yield **5a**[b]	% ee (major enantiomer)[c]
1	dppe	65	0
2	(*S*,*S*)-Dipamp	96	58 (*R*,*R*)
3	(*R*,*R*)-Dipamp	78	56 (*S*,*S*)

[a] Conditions: 1.2 equiv (*R*)-**2**, 30 mol % Ti(Oi-Pr), 1.0 equiv TBAT. [b] % Yield of **5a** after purification by column chromatography. [c] % ee of the major diastereomer determined by chiral SFC.

In summary, we demonstrate that both stereoselective and stereospecific syntheses of 1,3-oxazolidines can be accomplished by examining catalysts with differing rates of allylmetal isomerization. Rhodium(I)-catalysis affords stereochemical transfer from enantioenriched vinyl epoxide to 1,3-oxazolidine products in 99% ee and up to 7:1 *cis:trans* diastereoselectivities. In contrast, asymmetric nickel and palladium catalysts effect a dynamic kinetic resolution of the racemic vinyl epoxide to provide enantioenriched 1,3-oxazolidines. Under the conditions developed in this work, we observe efficient DKR with a palladium catalyst system providing excellent yields and enantioselectivities. Taken as a whole, these methods provide mild, complementary catalytic strategies for synthesis of *cis*- or *trans*-oxazolidines.

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Supporting Information Available. Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) (a) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297. (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (c) Also see ref 8a.

(21) Several scenarios that involve a kinetic resolution of the vinyl epoxide are possible. For a detailed discussion of such kinetic resolution reactions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.

(22) Two possibilities are attack of the titanium alkoxide on imine and allylic substitution by the sulfonamide. While we do not have experimental evidence that distinguishes the two, given the high levels of enantioselectivity, we favor reversible attack of the titanium alkoxide on the imine, followed by faster allylic substitution of one diastereomer.