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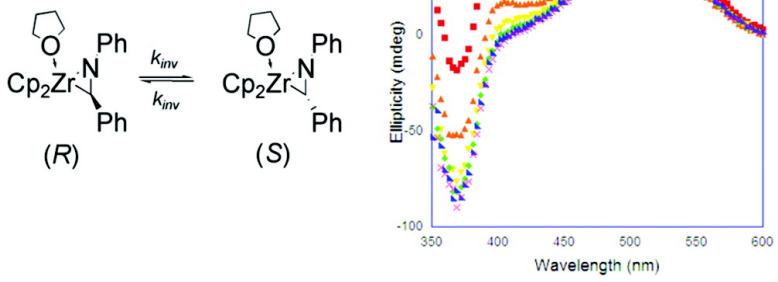

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Direct Measurement of the Rate of Interconversion of Zirconaaziridine Enantiomers

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Abstract: The insertion of enantiopure C_2-symmetric diphenylethylene carbonate into the Zr−C bonds of zirconaaziridines leads to the asymmetric synthesis of amino acid methyl esters. Because the zirconaaziridine enantiomers interconvert, the reaction is a dynamic kinetic resolution (DKR). The efficiency of the DKR (the ratio of the two diastereomeric products) is determined by the balance between the rate of enantiomer interconversion and the rate of insertion; slow addition of the inserting enantiopure carbonate is often required to maximize the stereoselectivity. For a case when enantiomer interconversion is fast, its rate constant k_{inv} has been determined by NMR line broadening; for a case when interconversion is slow, k_{inv} has been determined by computer simulation of the formation of the diastereomeric products as a function of time; for several intermediate cases, k_{inv} has been determined by making the zirconaaziridine enantioenriched and monitoring its racemization by CD spectroscopy. The observed k_{inv} is independent of [THF], implying that interconversion occurs with THF coordinated. Interconversion presumably occurs via an achiral intermediate, either a rapidly inverting (via an η^1-N structure) η^3-azaallyl hydride or an η^1-imine. As addition of THF slows insertion without affecting enantiomer interconversion, it produces a more efficient DKR without slow addition of the enantiopure carbonate.

Introduction

We have employed (*R*,*R*)-diphenylethylenecarbonate ((*R*,*R*)-DPEC), a readily available and enantiopure synthon for CO_2, in the asymmetric synthesis of amino acid methyl esters[1,2] from racemic zirconaaziridines[3,4b,5] (an example is shown in Scheme 1). The reaction is a "dynamic kinetic asymmetric transformation" or a "dynamic kinetic resolution" (DKR).[6]

The stereochemistry of the new chiral center in **2** (and of the α carbon in the methyl ester **3**) is determined by competition between the first-order rate of interconversion of the zirconaaziridine enantiomers and the second-order rate of insertion of the carbonate (Scheme 2). If we start with racemic zirconaaziridine **1**, with the enantiomer ratio (er) (*S*)-**1**/(*R*)-**1** initially 1:1, the ratio of the diastereomers of **2** that we obtain can be predicted from Curtin−Hammett kinetic considerations.[7] A fast quench ($k_{inv} \ll k_R$[(*R*,*R*)-DPEC], k_S[(*R*,*R*)-DPEC]) will result in no selectivity (eq 1). The maximum diastereoselectivity (and thus the maximum ratio of the enantiomers of the amino acid ester product) will be obtained when insertion is slow relative to the rate of enantiomer interconversion ($k_{inv} \gg k_R$[(*R*,*R*)-DPEC], k_S[(*R*,*R*)-DPEC]). The product ratio (eq 2) will then be k_R/k_S, also known as the selectivity factor *s*.

$$\frac{[R,R,R-\mathbf{2}]}{[R,R,S-\mathbf{2}]} = K_{eq} = \frac{[S-\mathbf{1}]}{[R-\mathbf{1}]} = 1$$

Boundary Condition II:

$$k_{inv} \ll k_R[(R,R)\text{-DPEC}],\ k_S[(R,R)\text{-DPEC}] \quad (1)$$

$$\frac{[R,R,R-\mathbf{2}]}{[R,R,S-\mathbf{2}]} = K_{eq}\frac{k_R}{k_S} = \frac{k_R}{k_S} = s$$

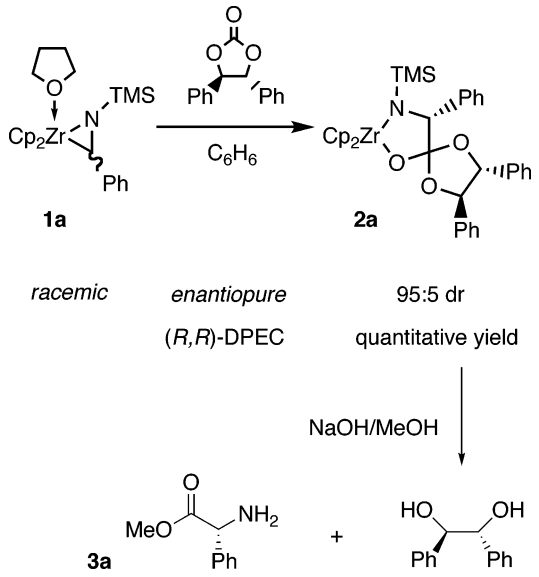
Boundary Condition I:

$$k_{inv} \gg k_R[(R,R)\text{-DPEC}],\ k_S[(R,R)\text{-DPEC}] \quad (2)$$

The factor *s* can be determined by measuring the ratio of the diastereomers of **2** when the insertion is carried out with racemic carbonate.[8] Getting the diastereomer ratio up to *s* with the enantiopure carbonate often requires slow addition of the carbonate to the zirconaaziridine via syringe pump.[1] This procedure maintains a low [(*R*,*R*)-DPEC] and keeps k_R[(*R*,*R*)-DPEC] and k_S[(*R*,*R*)-DPEC] ≪ k_{inv}. Such a procedure is potentially useful with *any* enantioselective reagent, but to plan

(1) Tunge, J. A.; Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 4520−4521.
(2) Chen, J-X.; Tunge, J. A.; Norton, J. R. *J. Org. Chem.* **2002**, *67*, 4366.
(3) Cummings, S. A.; Tunge, J. A.; Norton, J. R. *Top. Organomet. Chem.* **2005**, *10*, 1−39. Some of the results in the present manuscript were mentioned in this review as "unpublished results" without experimental details.
(4) (a) Gately, D. A.; Norton, J. R.; Goodson, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 986−996. (b) Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 3479−3489.
(5) (a) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486−4494. (b) Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776−777. (c) Davis, J. M.; Whitby, R. J.; Jaxachamiec, A. *Tetrahedron Lett.* **1992**, *33*, 5655−5658. (d) Coles, N.; Whitby, R. J.; Blagg, J. *Synlett* **1992**, *2*, 143−145. (e) Harris, M. C. J.; Whitby, R. J.; Blagg, J. *Tetrahedron Lett.* **1994**, *35*, 2431−2434. (f) Harris, M. C. J.; Whitby, R. J. *Tetrahedron Lett.* **1995**, *36*, 4287−4290. (g) Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495−4496. (h) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469−4472. (i) Honda, T.; Satoh, S.; Mori, M. *Organometallics* **1995**, *14*, 1548−1550. (j) Scott, M. J.; Lippard, S. J. *Organometallics* **1997**, *16*, 5857−5868. (k) Gianni, L.; Caselli, A.; Solari, E.; Floriani, C.; ChiesiVilla, A.; Rizzoli, C.; Re, N.; Sgamellotti, A. *J. Am. Chem. Soc.* **1997**, *119*, 9709−9719. (l) Barluenga, J.; Sanz, R.; Fananas, J. *J. Org. Chem.* **1997**, *62*, 5953−5958.

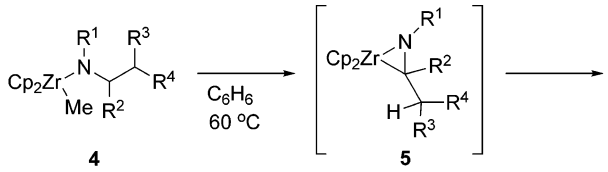
Scheme 1



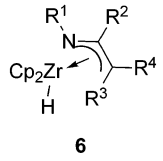
its application, we must know the rate constant for inversion, k_{inv}, of various zirconaaziridines. We report herein the preparation of zirconaaziridines that undergo unusually rapid enantiomer interconversion, and the development of several methods by which k_{inv} can be determined.

Results and Discussion

Attempted Preparation of Zirconaaziridines with Primary Alkyl Substituents on Carbon: Dynamics of η^3-1-Azaallyl Zirconocene Hydrides. In 1994, an attempt by Whitby and co-workers to prepare the zirconaaziridine **5a** from the methyl amide **4a** led instead to the formation of the η^3-1-azaallyl zirconocene hydride **6a** (eq 3).[9] We have found this reaction to be general when we attempt to prepare zirconaaziridines with substituents such as Me, Bn, and *n*-Pr that bear hydrogens on their α carbons (eq 3).[10,11] The observation of diastereotopic Cp resonances at low temperatures is only consistent with η^3 coordination of the azaallyl, and the chemical shifts of the azaallyl hydrogens (δ 4.5−3 NCH=C*H*Ph) distinguish η^3 from η^1 coordination (we would expect a shift of about δ 4.8 for uncoordinated NCH=C*H*Ph).[12] For compounds **6b**,[1] **6c**,[1] and **6d**,[1] N−C*H*=C*H* coupling constants of 12 Hz imply a *syn* geometry for the azaallyl ligands.



a R^1 = Ph; R^2 = Me; R^3 = R^4 = H
b R^1 = Ph; R^2 = R^3 = H; R^4 = Et

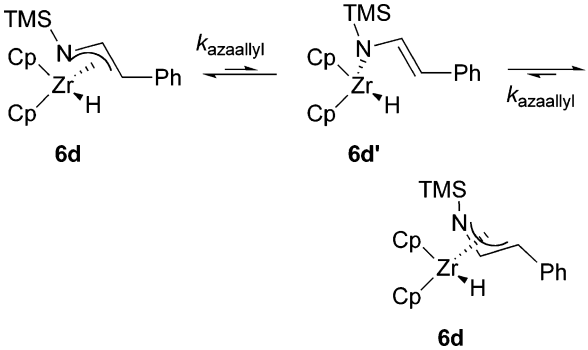


(3)

c R^1 = R^4 = Ph; R^2 = R^3 = H
d R^1 = TMS; R^2 = R^3 = H; R^4 = Ph

These azaallyl zirconocene hydrides are stable for months in toluene solution but decompose in a few hours/days in THF (with concomitant THF polymerization). They can be isolated as solids from cold pentane but form oils or gummy solids at room temperature; thus, we have generated them without isolation for the NMR experiments that follow.

All the azaallyl zirconocene hydrides **6** show a single cyclopentadienyl resonance in their room temperature ^{1}H and ^{13}C NMR spectra, indicating a dynamic process that produces a plane of symmetry.[1] The obvious possibility is an η^3 to η^1-N conversion, as drawn for **6d** in eq 4; one rotamer of that η^1 species (**6d′** in eq 4) will have a plane of symmetry. This process is analogous to the well-documented π-σ-π allyl isomerization.[13] The dissociation of olefin is usually rate determining, so the π-σ-π isomerization of allyl ligands has been used to estimate the binding energies of olefins to d^0 metals.[14]



(4)

When a toluene solution of **6d** was cooled to 185 K, its ^{1}H NMR spectrum showed two separate Cp resonances. As the solution was warmed, they broadened and eventually coalesced at 208 K. Analysis of the line widths as a function of

(6) The first step in Scheme 1 surely qualifies as a "dynamic kinetic asymmetric transformation", or DYKAT,[a] as it transforms a racemic starting material into a diastereoenriched product.[b] It can also be described as a dynamic kinetic resolution, or DKR, if we focus our attention on the enantiomeric composition of the unreacted starting material.[c] Mislow has remarked that "asymmetric syntheses and kinetic resolutions are often different sides of the same coin, that is, inseparable if distinct aspects of the same phenomenon".[d,e] (a) Trost, B. M.; Patterson, D. E.; Hembre, E. J. *Chem.−Eur. J.* **2001**, *7*, 3768−3775. (b) The conversion with an enantiopure reagent of freely interconverting enantiomers of a chiral substrate into unequal amounts of two diastereomers can also be termed, simply, an "asymmetric transformation". McNaught, A. D.; Wilkinson, A. *IUPAC Compendium of Chemical Terminology*, 2nd ed.; Royal Society of Chemistry: Cambridge, U.K., 1997. (c) A kinetic resolution starts with a racemic mixture. See Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall: Englewood Cliffs, NJ, 1971; pp 30−35. (d) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 396. (e) Mislow, K. *Introduction to Stereochemistry*; W. A. Benjamin, Inc.: Menlo Park, CA, 1965; p 139.

(7) (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 648−655. (c) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed; Plenum: New York, 2000; pp 215−216. (d) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715−727.

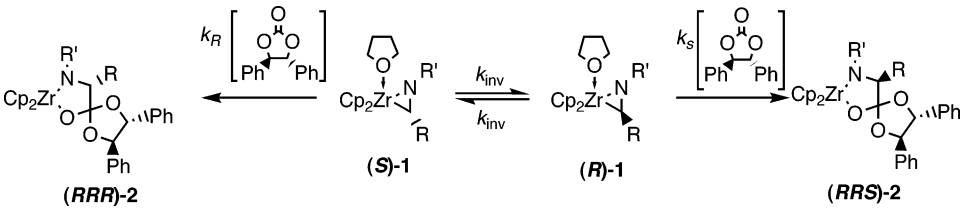
(8) (a) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975−982. (b) Hoffmann, R. W.;Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721−1726. (c) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1409−1411.

(9) Coles, N.; Harris, M. C. J.; Whitby, R. J.; Blagg, J. *Organometallics* **1994**, *13*, 190−199.

(10) For other examples of η^3-1-azaallyl zirconium complexes, see: (a) Hitchcock, P. B.; Lappert, M. F.; Liu, D.-S. *J. Chem. Soc., Chem. Commun.* **1994**, 2637−2638. (b) Bonomo, L.; Toraman, G.; Solari, E.; Scopelliti, R.; Floriani, C. *Organometallics* **1999**, *18*, 5198−5200. (c) Guram, A. S.; Swenson, A. S.; Jordan, R. F. *J. Am. Chem. Soc.* **1992**, *114*, 8991−8996.

(11) The η^3-azaallyl zirconium hydrides undergo insertion reactions via the isomeric zirconaaziridines, as can be inferred from refs 1 and 9.

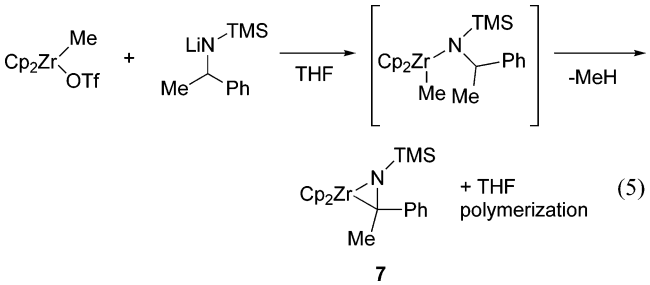
Scheme 2



temperature[15] gave $\Delta H^{\ddagger} = 10.2(1)$ kcal/mol and $\Delta S^{\ddagger} = 1.9(8)$ eu, which imply that, at 25 °C, the rate constant for azaallyl inversion, $k_{azaallyl}$, is $5.6(7) \times 10^5$ s^{-1} (the Eyring plot is shown in Figure S2, Supporting Information). (The observed $k_{azaallyl}$ at coalescence fell on a line generated by the line width data.)

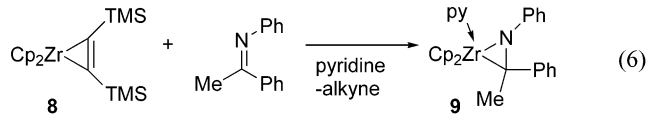
Repeating this analysis with **6c** between 204 and 228 K (the Eyring plot is shown in Figure S3, Supporting Information) gave $\Delta H^{\ddagger} = 12.9(1)$ kcal/mol and $\Delta S^{\ddagger} = 7.9(4)$ eu, corresponding to a $k_{azaallyl}$ of $1.1(1) \times 10^5$ s^{-1} at 25 °C. Thus, the rate of inversion for the *N*-phenyl azaallyl complex is ca. 5 times slower than that of the *N*-TMS azaallyl complex. This may reflect the fact that the TMS−N is a better electron donor, which should facilitate olefin dissociation to form the electron-deficient intermediate **6d′** that is necessary for inversion.

Preparation of a Stable Ligand-Free Zirconaaziridine. In an effort to generalize the preparation of **6a**, we treated Cp_2-Zr(Me)OTf[16] with the lithium amide of *N*-TMS-α-methylbenzylamine in THF (eq 5). To our surprise, the reaction gave a zirconaaziridine rather than an azaallyl hydride. Moreover, the ligand-free **7** (previously prepared in solution by Whitby[5d]) is formed rather than the more common THF adduct. The azaallyl hydride structure is probably destablized by the steric effect of the 2-phenyl substituent, and the space around the Zr in the zirconaaziridine structure is made sufficiently congested by the two substituents on C that THF coordination becomes unfavorable. To our knowledge, **7** is the first isolated ligand-free zirconaaziridine.

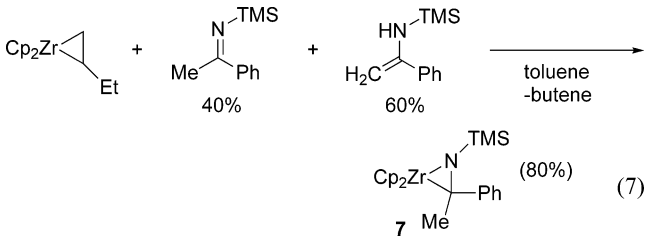


(5)

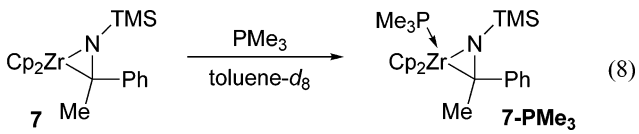
The reaction in eq 5 was problematic in that it resulted in some polymerization of the THF solvent, and the product **7** was impure. The reported preparation of the closely related **9** from the "Cp_2Zr" precursor **8** (eq 6)[17] suggested an alternative. The use of Negishi's reagent (also a "Cp_2Zr" precursor)[18] in toluene with an imine/enamine mixture gave **7** in higher yield and greater purity (eq 7). Whereas THF does not coordinate well to **7**, better donors such as pyridine or PMe_3 (eq 8) form adducts that are stable enough to be isolated.



(6)

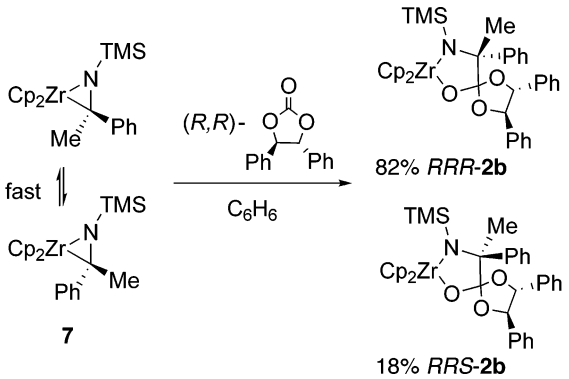


(7)



(8)

Treating the disubstituted zirconaaziridine **7** with 1 equiv of racemic DPEC gave a diastereomer ratio of 82:18, implying that *s* for the reaction of **7** with (*R*,*R*)-DPEC is 4.6 and that the maximum dr for this reaction is 82:18. Interestingly, treatment of racemic **7** with (*R*,*R*)-DPEC *gave that maximum dr even if the carbonate was added without a syringe pump* (eq 9), implying that the enantiomers of **7** interconvert rapidly at room temperature. (The rapid racemization of **7** was implied by an observation of Whitby: forming **7** from an enantiopure amine, and treating it with 4-octyne, led to a racemic allyl amine.[5d])



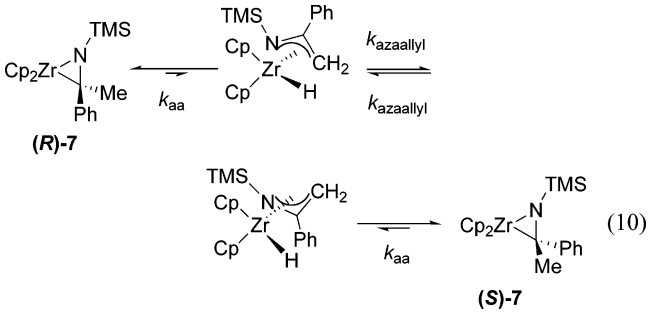
(9)

Measurement of k_{inv} in a Case Where Enantiomer Interconversion Is Fast. Fast interconversion was confirmed by examining the ^{1}H NMR of **7** as a function of temperature. The

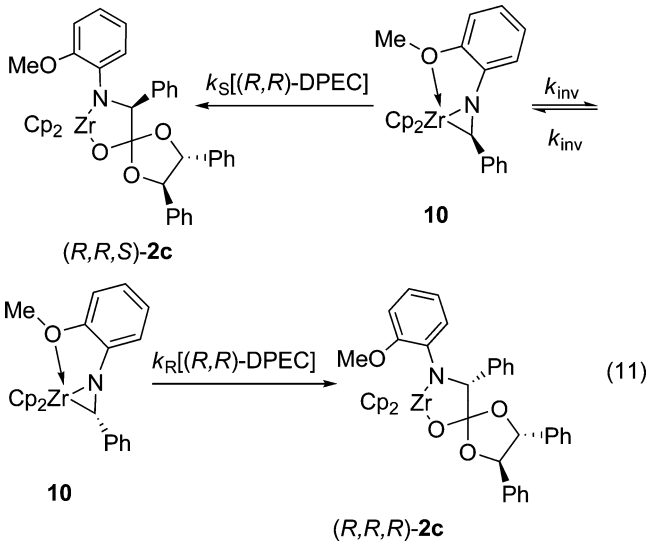
(12) For η^1-1-azaallyl zirconium complexes see: (a) Beshouri, S. M.; Chebi, D. E.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1990**, *9*, 2375−2385. (b) Fulton, J. R.; Hanna, T. A.; Bergman, R. G. *Organometallics* **2000**, *19*, 602−614. (c) Deelman, B-J.; Hitchcock, P. B.; Lappert, M. F.; Leung, W-P.; Lee, H-K.; Mak, T. C. W. *Organometallics* **1999**, *18*, 1444−1452. (d) Hitchcock, P. B.; Hu, J.; Lappert, M. F. *Chem. Commun.* **1998**, *1*, 143−144.
(13) Bercaw, J. E.; Moss, J. R. *Organometallics* **1992**, *11*, 639−645.
(14) Abrams, M. B.; Yoder, J. C.; Loeber, C.; Day, M. W.; Bercaw, J. E. *Organometallics* **1999**, *18*, 1389−1401.
(15) (a) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982. (b) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995
(16) (a) Luinstra, G. A. *J. Organomet. Chem.* **1996**, *517*, 209−215. (b) Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321−2322.

cyclopentadienyl rings of **7** are diastereotopic but exchange upon enantiomer interconversion.[19] The Cp signals of **7** were sharp at 250 K but broad at room temperature and coalesced at 354 K. Values of k_{inv} for **7** were obtained by observing the broadening of its Cp signals between 287 and 323 K (14 and 50 °C). The data in Figure S4 (Supporting Information) gave activation parameters $\Delta H^{\ddagger} = 10.1(6)$ kcal/mol, $\Delta S^{\ddagger} = -20(2)$ eu, and $\Delta G^{\ddagger} = 16.08(3)$ kcal/mol at 298 K, indicating that k_{inv} is about 10 s^{-1} at that temperature.

Presumably the azaallyl hydride structure is still available as an intermediate in enantiomer interconversion (eq 10). Comparison of $k_{azaallyl}$ for **6c** and **6d** with k_{inv} for **7** indicates that azaallyl inversion is about 10^4 faster than interconversion of the enantiomers of **7**, so the rate-determining step from (*R*)-**7** to (*S*)-**7** must be isomerization to the azaallyl hydride, that is, $k_{inv} = k_{aa}$.[20,21]



Determination of k_{inv} in a Case Where Enantiomer Interconversion Is Slow. The enantiomers of most zirconaaziridines interconvert too slowly to allow direct measurement of the inversion rate by NMR line shape analysis. For example, the Cp signals of the chelated zirconaaziridine **10**[4a] do not broaden below 80 °C and the stereochemical outcome of its reaction with (*R*,*R*)-DPEC (eq 11) implies that enantiomer interconversion is as slow as insertion (hours).



When we treated a solution of **10** with racemic DPEC, the diastereomer ratio, and therefore the $s = k_R/k_S$ value, was about 6. When we used (*R*,*R*)-DPEC, the (*R*,*R*,*R*)/(*R*,*R*,*S*) ratio varied with time, eroding from 85:15 dr ($\approx s$[22]) at low conversion to 75:25 dr at 4.7 h and 70:30 dr at full conversion (12 h); apparently, enantiomer interconversion was competitive with, but not much faster than, insertion. A computer simulation of the formation of (*R*)-**2c** and (*S*)-**2c** (Kintecus,[23] eqs 12−15, Figure 1), with k_R/k_S held constant at 6 and k_S and k_{inv} varied, converged with k_S as $1.195(1) \times 10^{-3}$ $M^{-1}s^{-1}$, k_R as $7.176(6) \times 10^{-3}$ $M^{-1}s^{-1}$, and k_{inv} as $5.3(7) \times 10^{-6}$ s^{-1}.[24]

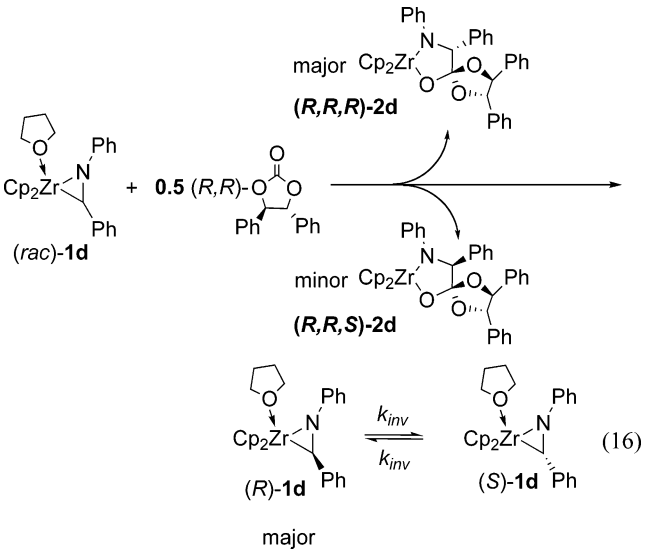
$$(R)\text{-}\mathbf{10} + (R,R) - \text{DPEC} \xrightarrow{k_S} (R,R,S)\text{-}\mathbf{2c} \qquad (12)$$

$$(S)\text{-}\mathbf{10} + (R,R) - \text{DPEC} \xrightarrow{k_R} (R,R,R)\text{-}\mathbf{2c} \qquad (13)$$

$$(R)\text{-}\mathbf{10} \xrightarrow{k_{inv}} (S)\text{-}\mathbf{10} \qquad (14)$$

$$(S)\text{-}\mathbf{10} \xrightarrow{k_{inv}} (R)\text{-}\mathbf{10} \qquad (15)$$

Circular Dichroism of DPEC Insertion Reactions. Although kinetic simulation provides some insight into the rate of racemization of zirconaaziridines, it is obviously preferable to determine k_{inv} *directly*, which can be accomplished by monitoring the racemization of an unequal mixture of zirconaaziridine enantiomers. Such a mixture can be created by kinetic resolution of a racemic zirconaaziridine with less than 1 equiv of enantiopure carbonate—as long as insertion is *faster* than inversion. We can maximize the rate of insertion by keeping [(*R*,*R*)-DPEC] as high as possible, making k_R[(*R*,*R*)-DPEC] and k_S[(*R*,*R*)-DPEC] $\gg k_{inv}$. Thus, we add our (*R*,*R*)-DPEC (typically 0.5 equiv) to a zirconaaziridine such as **1d**[4] as rapidly as possible, generating the two diastereomers of the insertion product **2d** in a ratio approximating k_R/k_S and leaving the 0.5 equiv of unreacted zirconaaziridine enriched in one enantiomer (eq 16).[25]



As any chiral, nonracemic substance exhibits circular dichroism (CD) in the region of an accompanying electronic absorption

(17) (a) Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burkalov, V. V.; Rosenthal, U. *Synlett* **1996**, 111−118. (b) Kempe, R.; Spannenberg, A.; Lefeber, C.; Zippel, T.; Rosenthal, U. *Z. Kristallogr. New Crystal Structures* **1998**, *213*, 791−792.

(18) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829−2832.

(19) A reviewer has pointed out that the Cp ligands of **7** would also be exchanged by rotation of the η^2 imine about the axis linking it to the Zr. We think such "imine rotation" unlikely with an early transition metal, where the complex is better described as a metallaaziridine.

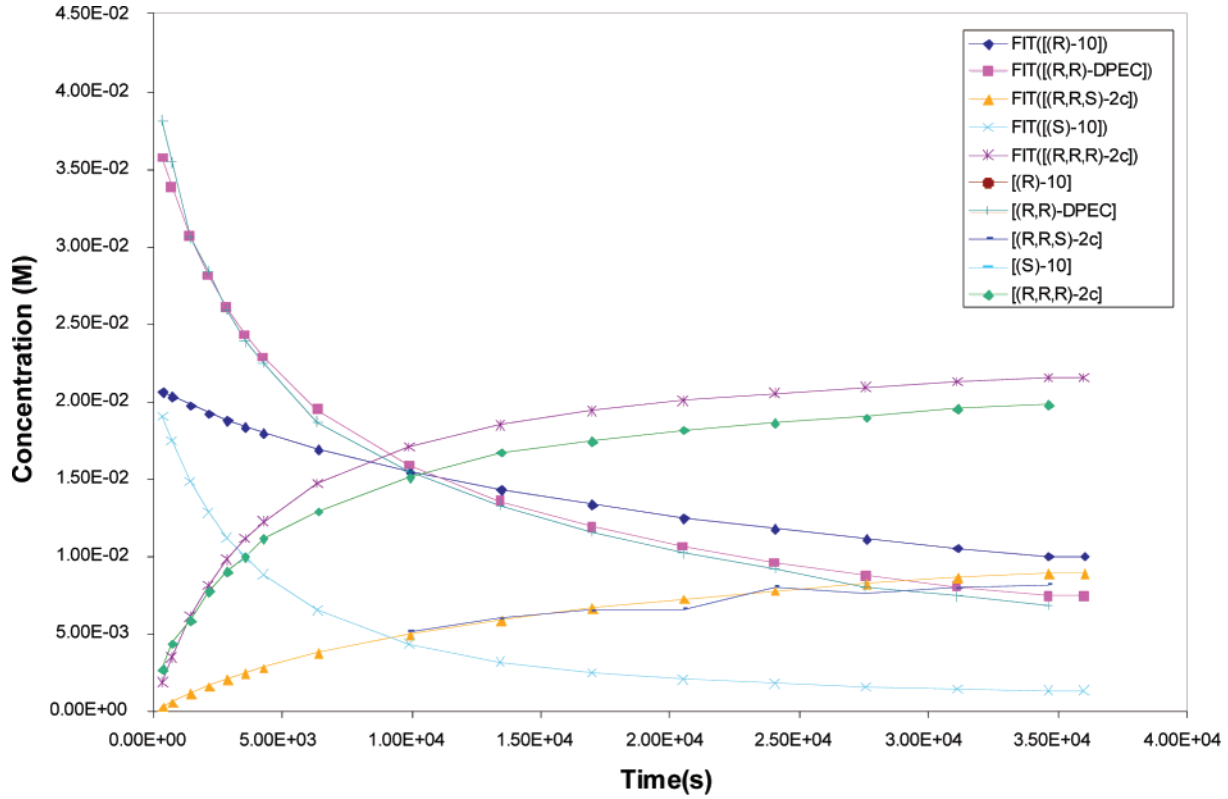


Figure 1. Simulation of the reaction of 0.04 M **10** with 0.04 M (*R*,*R*)-DPEC in C_6D_6, with $k_S = 1.195(1) \times 10^{-3}$ $M^{-1}s^{-1}$; $k_R = 7.176(6) \times 10^{-3}$ $M^{-1}s^{-1}$; $k_{inv} = 5.3(7) \times 10^{-6}$ s^{-1}.

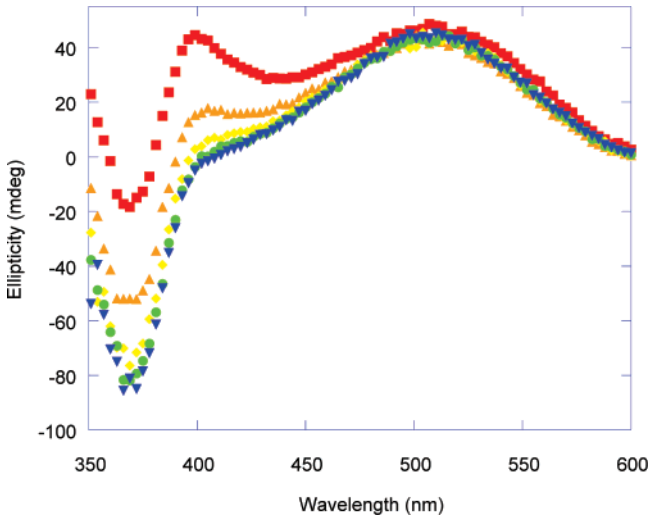


Figure 2. CD observation of **1d** racemization. A solution of **1d** (4 mL, 0.00303 M in benzene) was mixed with a solution of 0.5 equiv of (*R*,*R*)-DPEC (73 μL, 0.0882 M in benzene) immediately before the first scan. A point was taken every 3 nm with 0.1 s between points; each scan from 600 to 350 nm took ~1.5 min.

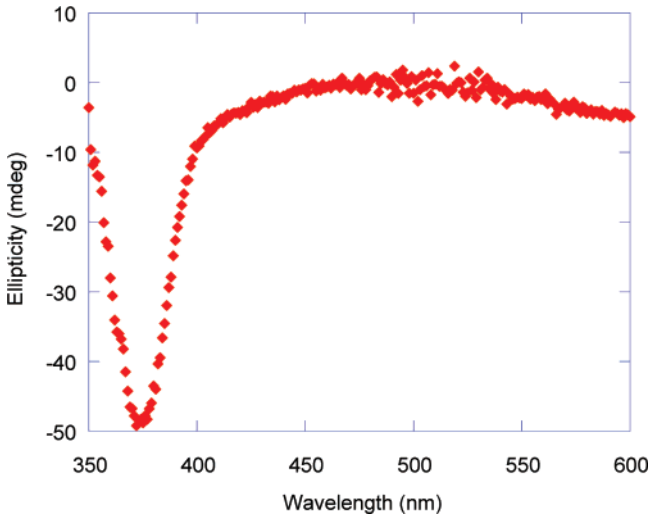


Figure 3. Rapid addition of 1 equiv of DPEC to **1d** results in a kinetic quench and ~1:1 mix of *RRR* and *RRS* insertion products **2d**. A solution of **1d** (4 mL, 0.00303 M in benzene) was mixed with 1 equiv of (*R*,*R*)-DPEC (146 μL, 0.0882 M in benzene) before measurement.

band,[26] it should to monitor the racemization of the unreacted zirconaaziridine by time-dependent CD spectroscopy. (Note that the rate constant for racemization, k_{rac}, is $2k_{inv}$.) An unequal mixture be possible of the enantiomers of **1d** was prepared in an airfree cuvette (by eq 16) and placed in the CD spectrometer immediately after mixing, and a 350−600 nm CD spectrum was recorded every 1.5 min (Figure 2).

(20) It is barely possible, although we think it unlikely, that $\eta^2 \rightarrow \eta^1$ isomerization (Path C under **Mechanism**), accelerated by the steric demands of the Me and Ph substituents, affects enantiomer interconversion even for **7**.
(21) (a) Alibrandi, G.; Scolaro, L. M.; Minniti, D.; Romeo, R. *Inorg. Chem.* **1990**, *29*, 3467. (b) Bryndza, H. E. *J. Chem. Soc., Chem. Commun.* **1985**, 1696. (c) Evans, J.; Schwartz, J.; Urquhart, P. W. *J. Organomet. Chem.* **1974**, *81*, C37.
(22) At the beginning of such a reaction, with the enantiomers of **10** present in equal amounts, the product ratio (*R*,*R*,*R*)/(*R*,*R*,*S*) will equal k_R/k_S.
(23) Ianni, J. *Kintecus* V3.8.
(24) The uncertainties in the k_R and k_S values for **2c** (obtained by kinetic simulation) are reported as the standard deviation of each rate constant for two data sets.
(25) We know, from ref 1, that kinetic resolution leaves zirconaaziridine enriched in the *R* enantiomer for **1a** and **1d** and assumes that the configuration is the same in the other cases.
(26) Drago, R. *Physical Methods for Chemists*, 2nd ed.; Surfside: Gainesville, FL, 1992; pp 137−141.

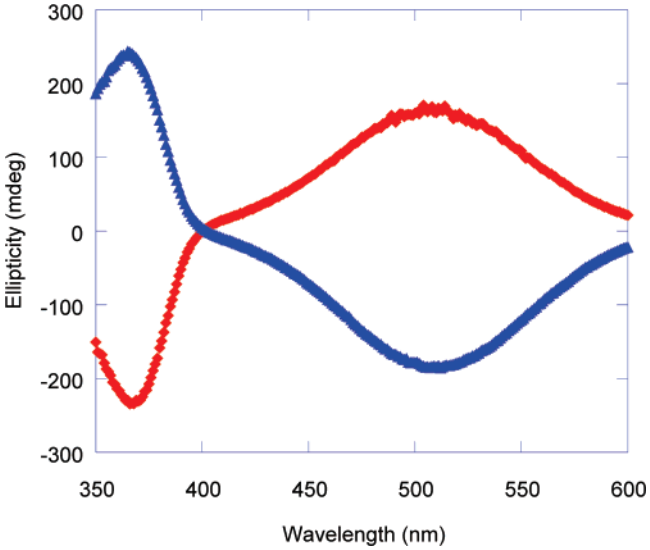


Figure 4. Comparison of the CD spectra of the DPEC insertion product **2d** enriched in the *RRR* diastereomer (red, generated by adding in small portions 1 equiv of (*R*,*R*)-DPEC (146 μL, 0.0882 M in benzene) to zirconaaziridine **1d** (4 mL, 0.00303 M in benzene) and the DPEC insertion product **2d** enriched in the *SSS* diastereomer (blue, generated by portionwise addition of 1 equiv of (*S*,*S*)-DPEC (146 μL, 0.0882 M in benzene) to zirconaaziridine **1d** (4 mL, 0.00303 M in benzene).

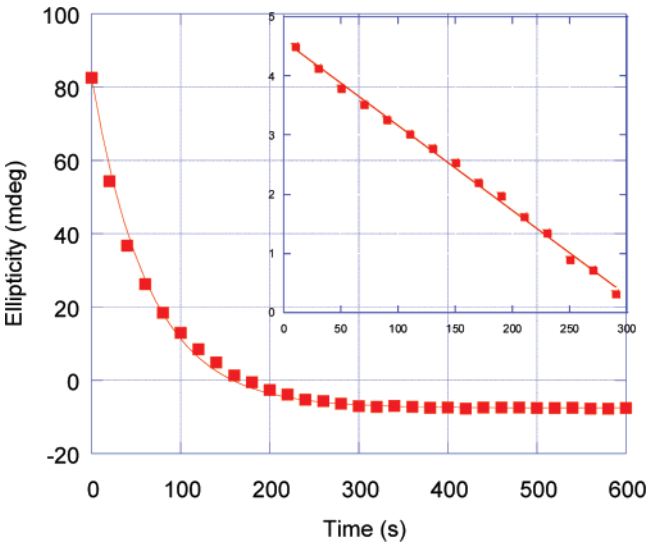


Figure 5. CD observation of **1d** racemization at a single wavelength (403 nm) gives a first-order exponential and linear plot for ln(CD) vs time (inset graph). A solution of **1d** (4 mL, 0.00303 M in benzene) was mixed with 0.5 equiv of (*R*,*R*)-DPEC (73 μL, 0.0882 M in benzene) before measurement.

Repeated UV−vis scans (Figure S5, Supporting Information) showed no change in the 400−600 nm electronic spectrum after the time it took to mix the reactants and to place the reaction mixture in the spectrometer. Thus, insertion is complete before the first scan in Figure 2, no net chemistry (i.e., no change in atom connectivity) is occurring as the scans continue, and the differences between the CD traces must be attributed to the racemization process. Presumably, the time-invariant portions of the CD spectra (Figure 2) arise from the insertion product **2d**, whereas the portions of the CD spectra that change reflect the racemization of the enantio-enriched **1d**.

The assignment of the time-invariant CD band at 505 nm to the insertion product **2d** is supported by the observation

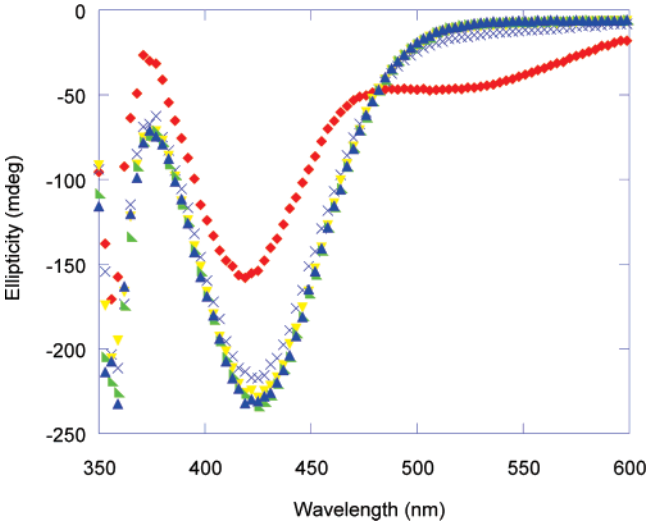


Figure 6. CD observation of racemization of **1a**. A solution of **1a** (4 mL, 0.00308 M in benzene) was mixed with 0.5 equiv of (*R*,*R*)-DPEC (70 μL, 0.0882 M in benzene) before measurement. A point was taken every 3 nm with 0.1 s between points; each scan from 600 to 350 nm took ~1.5 min.

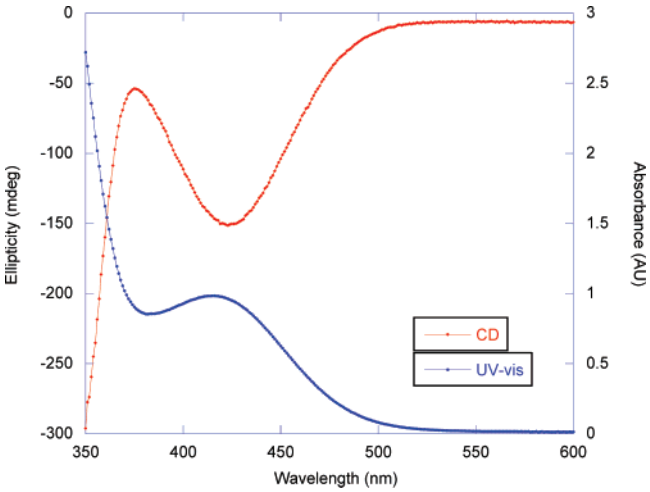
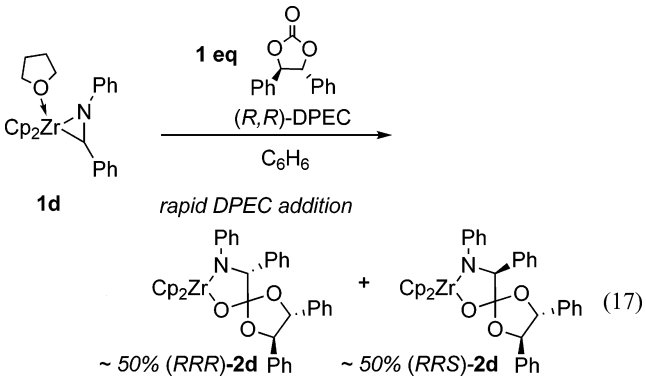


Figure 7. CD (red) and UV−vis (blue) spectra of **2a**, formed by the rapid addition of 1 equiv of (*R*,*R*)-DPEC to **1a**. A solution of **1a** (4 mL, 0.00308 M in benzene) was mixed with one of (*R*,*R*)-DPEC (70 μL, 0.0882 M in benzene) before measurement.

of an electronic transition for **2d** in that region (Figure S5, Supporting Information) and the absence of an electronic transition for **1d** in that region (Figure S6, Supporting Information). Furthermore, the magnitude and sign of the 505 nm CD band show the behavior expected for a band due to **2d**.

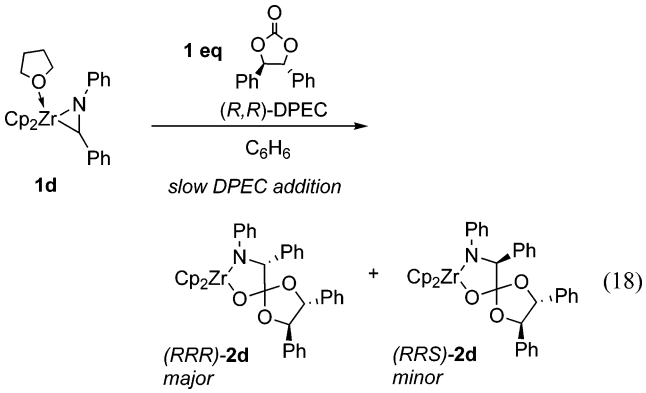
The 505 nm band disappeared when the *RRR* and *RRS* diastereomers of **2d** were generated in equal amounts. The rapid addition of 1 equiv of (*R*,*R*)-DPEC to **1d** (eq 17) should quench the equal populations of (*R*)-**1d** and (*S*)-**1d** present in racemic **1d** and give approximately a 1:1 mix of the *RRR* and *RRS* diastereomers of **2d**; integration of the ^{1}H NMR Cp resonances confirmed this prediction. The CD spectrum of such a 1:1 *RRR*:*RRS* mixture contained a band at 370 nm but none at 505 nm (Figure 3). Thus, the 370 nm band must arise from the stereochemically constant part of **2d**. Insertion of the C═O bond surely occurs with retention of the stereochemistry of the (*R*,*R*)-DPEC backbone carbons, so the

configuration of those two carbons will remain *R* in both diastereomers.



(17)

The 505 nm band thus arises from the chiral center in the zirconaoxazolidine ring of **2d**, an assignment that has been further confirmed by examining the CD spectrum of chemically pure **2d** enriched in the *RRR* diastereomer. Such **2d** was prepared by the *slow* addition of 1 equiv of (*R*,*R*)-DPEC to the zirconaaziridine **1d** (eq 18). As Figure 4 shows, this *RRR*-enriched **2d** gave a positive CD signal in the 505 nm region. Since the metal is formally Zr(IV) and d^0, the electronic transition responsible (the UV−vis spectrum of **2d** is Figure S5, Supporting Information) is likely a ligand-to-metal charge-transfer band.



(18)

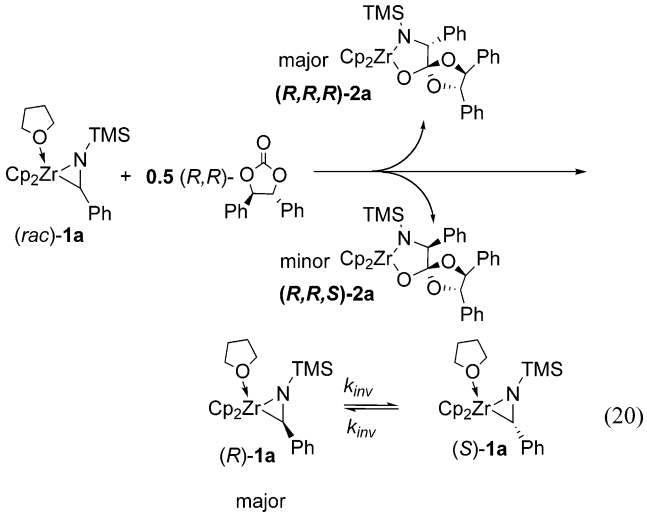
A sample of **2d** enriched in the *SSS* diastereomer can be prepared by slow addition of 1 equiv of (*S*,*S*)-DPEC into zirconaaziridine **1d**. The CD spectrum of this (*S*,*S*,*S*)-enriched **2d** is—as we would expect for a pair of enantiomers—the mirror image of that of the (*R*,*R*,*R*)-enriched **2d** above. Both traces are compared in Figure 4.

A General Method for the Determination of k_{inv}. It is clear from the above experiments, and in particular from Figure 2, that CD spectroscopy can be used to monitor changes in the configuration at carbon of a zirconaaziridine. The rate constant for inversion, k_{inv}, can be determined from the time dependence of the CD at a given wavelength. It can be seen from eq 19[26] that the molar circular dichroism, $\epsilon_L - \epsilon_R$, is a linear function of the extent of inversion, where *k* is the absorption coefficient, *I* and I_0 are the intensities of the incident and resultant light (respectively), $I = I_0 10^{-kcl}$, *l* is the path length (cm), and *c* is the concentration (g cm^{-3}).

$$\epsilon_L - \epsilon_R = \frac{k_l - k_r}{c} \tag{19}$$

Fitting the 403 nm CD data from Figure 2 to a first-order exponential (Figure 5) gives the rate constant for racemization; the rate constant for inversion ($k_{rac}/2$), k_{inv}, of **1d** is $7(2) \times 10^{-3}$ s^{-1} (25 °C). Thus, the half-life for inversion is 90 s, and the half-life for racemization is 45 s. The change in CD at a different wavelength—370 nm—gives a rate constant of $7.2(3) \times 10^{-3}$ s^{-1}, within experimental error of the 403 nm rate constant; the agreement confirms that the same first-order process is being monitored at both wavelengths.

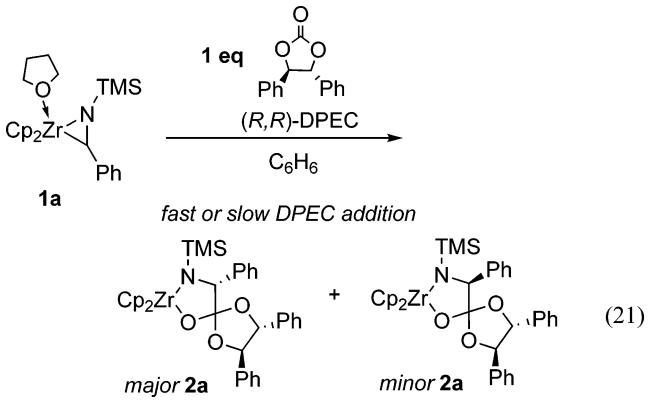
Similar time-dependent CD measurements have been carried out on zirconaaziridine **1a**,[5a] a bright-yellow solid which appears orange-yellow in benzene solution. The UV−vis spectrum of **1a** showed λ_{max} at 440 nm, whereas its yellow insertion product **2a** showed λ_{max} in the visible (420 nm) and in the near UV (<370 nm) (Figure 7).



(20)

An unequal mixture of the enantiomers **1a** was prepared by the procedure in eq 20. The solution was placed in the CD immediately after mixing, and the CD in the 350−600 nm range was monitored for 10 min. The traces (Figure 6) showed obvious changes at 350, 423, and 520 nm. In contrast to the situation with **1d**, the CD peaks in Figure 6 could not be assigned exclusively to the zirconaaziridine **1a** or to the insertion product **2a**; both apparently absorb in the same region.

To determine the contributions of the insertion product **2a** to the CD traces in Figure 6, we prepared samples of **2a** that were chemically pure but diastereomerically enriched. Sample A was prepared by adding 1 equiv of (*R*,*R*)-DPEC rapidly to the zirconaaziridine **1a**; sample B was prepared by adding 1 equiv of (*R*,*R*)-DPEC in several portions to the zirconaaziridine **1a** (eq 21). The CD spectra of both A and B (Figures 7 and S7, Supporting Information) showed bands at 350 and 423 nm. However, the magnitude of the CD band at 423 is greater for sample B, implying that the diastereomer ratio is also greater. By analogy with **2d**, the band at 350 nm must arise from the stereochemically constant part of **2a**, whereas the 423 nm band must arise from the chiral center in the zirconaoxazolidine ring of **2a**.

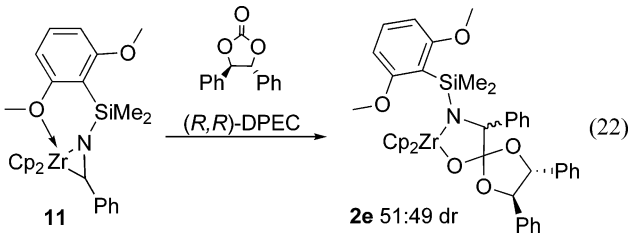


(21)

However, the CD band at 423 nm in Figure 7 becomes more negative with time, so it must contain a contribution from the zirconaaziridine **1a** as well as a contribution from **2a**. Moreover, the CD from **1a** must be positive in this region, opposing the negative CD from **2a**.

The fact that Sample A (rapid addition of (*R*,*R*)-DPEC to **1a**) showed a CD signal at 420 nm in Figure 7 implies that some interconversion of the enantiomers of **1a** occurred during that addition. Qualitatively, comparison of this result (Figure 7) with that for **1d** (Figure 3) suggests that k_{inv} is faster for **1a** (*N*-TMS) than for **1d** (*N*-Ph). Indeed, the change of the CD in Figure 7 at 423 nm—or at 520 nm—with time (Figure 8) gives k_{inv} for **1a** as 9.1(1) $\times$ 10^{-3} s^{-1} (25 °C). The half-life for inversion is 69 s for **1a**; its half-life for racemization is 35 s.

Next, we became curious as to the effect of chelation on the rate of racemization of zirconaaziridines. Indirect evidence implied that k_{inv} for chelate complex **11** was very slow. Neither its diastereotopic cyclopentadienyls nor its diastereotopic Si methyls showed signs of exchange at an accessible temperature. The stereochemical outcome of reaction with enantiopure DPEC confirmed this conclusion. The insertion of racemic DPEC into the Zr−C bond of racemic **11** gave a dr of 84:16 for **2e**, implying an $s = k_R/k_S$ of about 5. However, the insertion of 1 equiv of (*R*,*R*)-DPEC gave a dr of only 51:49 at room temperature (eq 22); use of a syringe pump over 8 h did not raise the dr appreciably.



(22)

The fact that DPEC insertion into the Zr−C bond of **11** is rapid (insertion occurs within minutes) made it easy to create an enantiomerically enriched sample of that zirconaaziridine by the method of eq 17 (rapid addition of half an equiv of (*R*,*R*)-DPEC). The racemization of **11** was then monitored by CD at 440 nm (Figure 9). The increasingly negative ellipticity at 440 nm is probably the result (as with **1a**) of overlap between a negative contribution from **2e** and a decreasing positive contribution from **11**.

The change in the CD at 440 nm as a function of time gave (Figure 10) k_{inv} as 9.31(5) $\times$ 10^{-4} s^{-1} (25 °C). As expected, k_{inv} is ca. 10 times slower for **11** than for **1a** and **1d**.

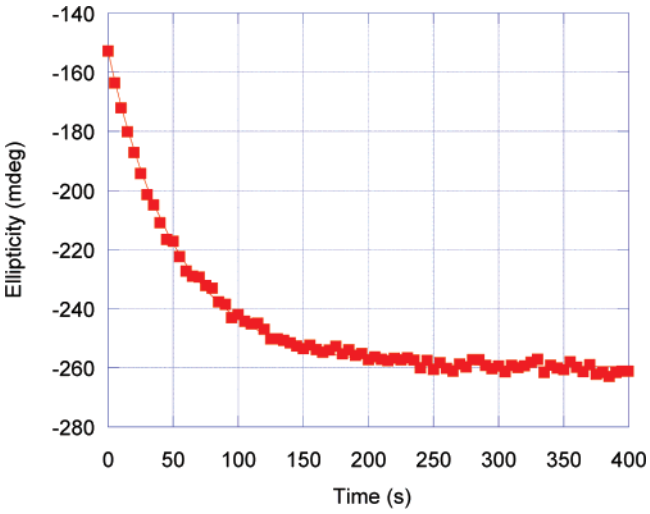


Figure 8. CD observation of **1a** racemization at a single wavelength (423 nm) gives first-order exponential decay at 423 nm. A solution of **1a** (4 mL, 0.00303 M in benzene) was mixed with 0.5 equiv of (*R*,*R*)-DPEC (73 μL, 0.0882 M in benzene) before measurement.

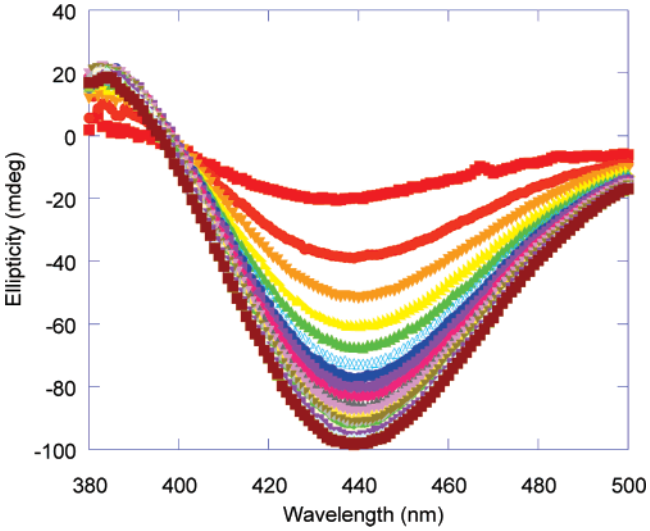


Figure 9. CD observation of **11** racemization. A solution of **11** (4 mL, 0.00303 M in benzene) was mixed with 0.5 equiv of (*R*,*R*)-DPEC (73 μL, 0.0882 M in benzene) before measurement.

Comparison of Measured k_{inv} Values with Synthetic Experience. Knowing k_{inv} allows us to determine the rate at which (*R*,*R*)-DPEC must be added to a zirconaaziridine to effect the best possible DKR. To obtain the maximum diastereomer ratio *s* (= k_R/k_S), we must add (*R*,*R*)-DPEC slowly enough to keep k_R[(*R*,*R*)-DPEC], k_S[(*R*,*R*)-DPEC] $\ll$ k_{inv}. For the zirconaaziridines **1a**, **1d**, **7**, and **11**, our k_{inv} values agree well (Table 1) with our empirical observations in the laboratory. With **7**, there are no negative consequences of adding the carbonate quickly; with **1a**, the maximum dr can be achieved at ambient temperature by syringe pump addition of the carbonate over a 4 h period; with **1d**, the maximum dr can be achieved by syringe pump addition over <4 h. With **11**, however, enantiomer interconversion is so slow that even syringe pump addition of (*R*,*R*)-DPEC overnight (>8 h) is not slow enough to achieve the maximum possible selectivity.

Mechanism of Enantiomer Interconversion. The rapid racemization of **7** is plainly due to its ability to access an azaallyl

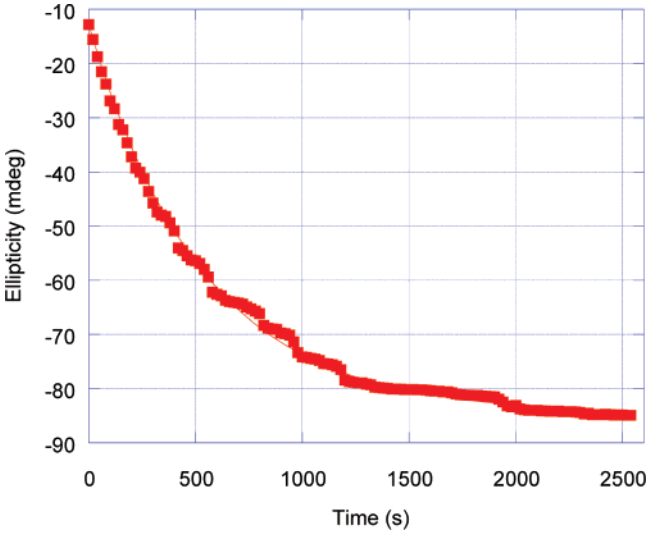
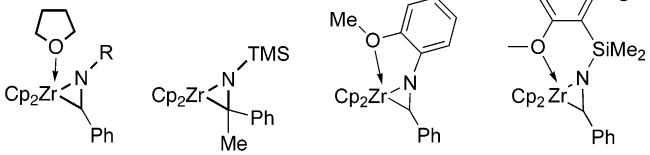
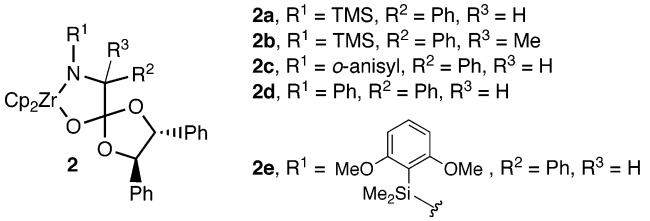


Figure 10. CD observation of **11** racemization at a single wavelength. A solution of **11** (4 mL, 0.00303 M in benzene) was mixed with 0.5 equiv of (*R*,*R*)-DPEC (73 μL, 0.0882 M in benzene) before measurement.

Table 1. Measured k_{inv} Agree with Time Required for Addition of (*R*,*R*)-DPEC for the Best Possible DKR





zirconaaziridine	insertion product	k_{inv} (s^{-1})	predicted dr ($=k_R/k_S$)	addition time required to obtain maximum dr
7	**2b**	10	4.6	fast addition OK
10	**2c**	$5.3(7) \times 10^{-6}$	6	>8 h
1a	**2a**	$9.1(1) \times 10^{-3}$	19	<4 h
1d	**2d**	$7(2) \times 10^{-3}$	7.3	4 h
11	**2e**	$9.31(5) \times 10^{-4}$	5.3	>8 h

hydride structure. A similar β-hydrogen elimination mechanism has been established by the Bergman group for the rapid racemization of alkyl-substituted azazirconacyclobutenes **12** (R = *n*-Pr, *i*-Pr, and *c*-Hex).[27] It seems safe to predict that *any zirconaaziridine with a β hydrogen will racemize rapidly* or, like **5a**−**d**, will isomerize to an azaallyl hydride that will racemize rapidly (eq 3).

Both azazirconacyclobutenes **12** and our zirconaaziridines racemize more slowly when they bear aryl substituents,[27] and a different mechanism must be involved. Bergman and

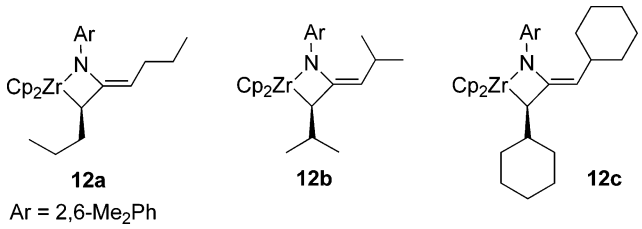
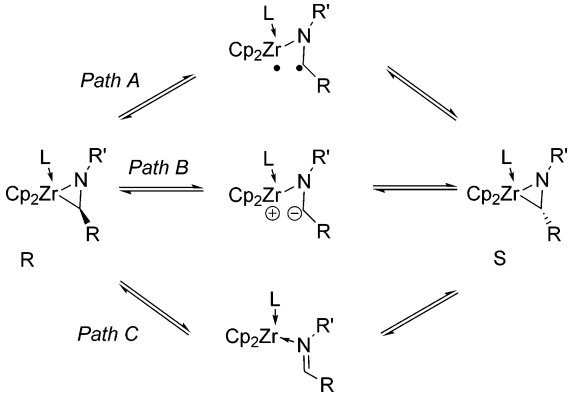
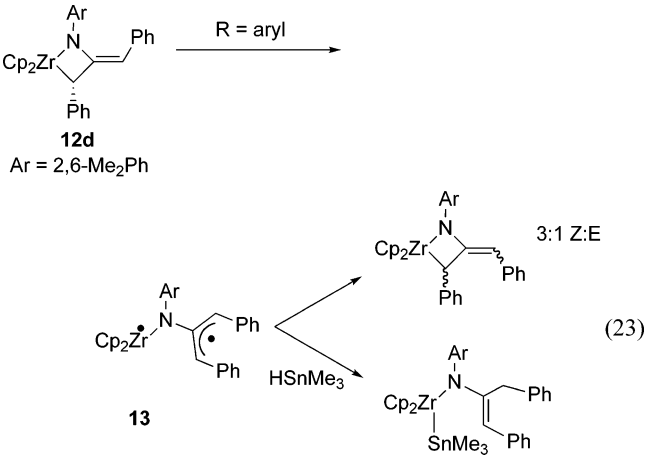


Figure 11. Alkyl-substituted azazirconacyclobutenes, prepared by Bergman and co-workers,[27] have accessible β-H's which allow them to undergo a facile racemization.

Scheme 3



co-workers have offered convincing evidence that homolytic cleavage of the Zr−C bond is responsible for the racemization of aryl-substituted azazirconacyclobutenes. Mild oxidants, such as benzophenone, disulfides, and ferricenium, catalyze both the racemization and *E*/*Z* isomerization of **12**. Addition of trimethyltin hydride or a disulfide gives products that appear to result from trapping of an intermediate diradical (eq 23).[27]



(23)

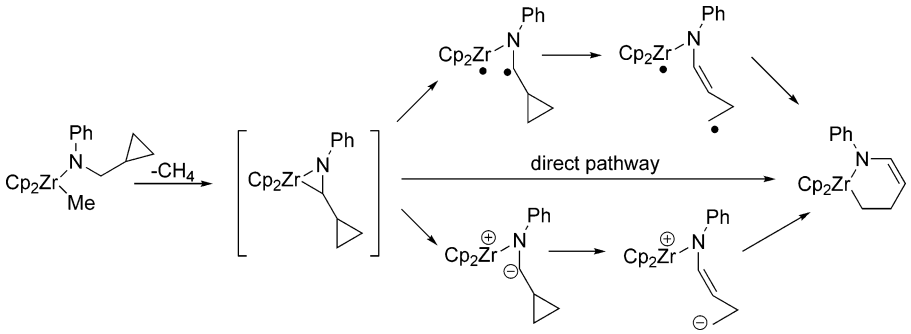
Of the possibilities in Scheme 3 (homolytic cleavage of the Zr−C bond (A), heterolytic cleavage of the Zr−C bond (B), or isomerization to a planar η^1 complex (C)), we favor C, an option not available to azazirconacyclobutenes.

Path C, with an η^1-imine complex as an intermediate for enantiomer interconversion, is favored over Path A and Path B by DFT calculations using a continuum solvation model.[28] Such η^1-complexes ("σ complexes") are known to interconvert

(27) Michael, F. E.; Duncan, A. P.; Sweeney, Z. K.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 1752−1764.

(28) Baik, M.-H.; Frost, B. J.; Norton, J. R.; Friesner, R. A. Unpublished work, quoted in ref 3.

Scheme 4

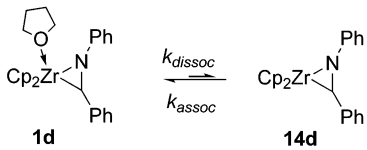


enantiomers of Re aromatic aldehyde complexes.[29] Furthermore, equilibration between η^1 and η^2-W complexes of thioaldehydes and selenoaldehydes has been observed.[30] Last, two Cp_2Zr(II) η^1-imine complexes have been reported, although neither structure has been confirmed by X-ray crystallography.[4b,31]

An argument for either a homolytic (A) or heterolytic (B) pathway for enantiomer interconversion in zirconaaziridines comes from Whitby's observation of a ring-opened product (Scheme 4) when he attempted to generate a zirconaaziridine with a cyclopropyl substituent.[32] This observation does not distinguish between Paths A and B because both cyclopropylmethyl radicals[33] and anions[34] ring open rapidly. The mechanism that carries out the transformation in Scheme 4 may be unique to cyclopropyl-substituted zirconaaziridines. The formation of an azaallyl hydride is not practical, but the "direct pathway" in Scheme 4 is possible; there are several precedents for β-alkyl eliminations onto Zr.[35]

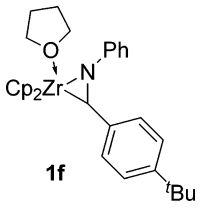
Role of THF in Enantiomer Interconversion. The relatively slow enantiomer interconversions (Table 1) of the chelated zirconaaziridines **10** and **11** suggested that ligand dissociation might be necessary for racemization. We therefore studied the [THF] dependence of k_{inv}.

Data on exchange between the coordinated THF in **1d** and free THF were available from earlier studies of Gately and Norton.[4a] They concluded that the exchange was dissociative (eq 24), and reported rate constants k_{dissoc} that extrapolate to 325 s^{-1} at 25 °C. Thus, k_{dissoc} is much larger than k_{inv} for **1d**, and the equilibrium (eq 25) for loss of THF to form the coordinatively unsaturated **14d** is rapidly maintained on the time scale of k_{inv}. The equilibrium for THF dissociation lies far to the left for the closely related zirconaaziridine **1f**; the coordinatively unsaturated **14f** is not observed in the low temperature "stopped exchange" ^{1}H NMR spectrum of an 0.03 M solution of **1f** in toluene, implying that $K < 8 \times 10^{-5}$ M.[36]

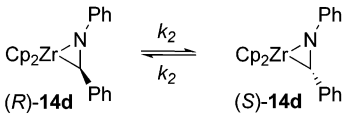


(24)

$$K = \frac{[\mathbf{14d}][\mathrm{THF}]}{[\mathbf{1d}]} \tag{25}$$



If we take both sides of eq 24 (**1d** and **14d**) together as *T*, and assume that only the coordinatively unsaturated **14d** can undergo enantiomer interconversion (rate constant k_2 in eq 26), we obtain the rate law in eq 27 for the conversion of **(***R***)-*T*** to (*S*)-*T*, with k_{inv} given by eq 28.



(26)

$$\frac{-\mathrm{d}[(R)\text{-}T]}{\mathrm{d}t} = \frac{\mathrm{d}[(S)\text{-}T]}{\mathrm{d}t} = \frac{Kk_2[(R)\text{-}T]}{K + [\mathrm{THF}]} = k_{inv}[(R)\text{-}T] \tag{27}$$

where $[(R)\text{-}T] = [(R)\text{-}\mathbf{1d}] + [(R)\text{-}\mathbf{14d}]$ and

$$k_{inv} = \frac{Kk_2}{K + [THF]} \tag{28}$$

With $K < 8 \times 10^{-5}$ M, eq 28 simplifies to eq 29 at significant concentrations of THF. If THF dissociation is *not* required before rate-determining enantiomer interconversion, k_{inv} will of course be independent of [THF].

$$k_{inv} = \frac{Kk_2}{[THF]} \tag{29}$$

Determining k_{inv} for **1d** in the presence of excess THF has been

(29) Gladysz, J. A.; Boone, B. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 551−583. Huang, Y.-H.; Gladysz, J. A. *J. Chem. Ed.* **1988**, *65*, 298−303.
(30) (a) Fischer, H.; Zeuner, S.; Gerbing, U.; Riede, J.; Kreiter, C. G. *J. Organomet. Chem.* **1989**, *377*, 105−122. (b) Fischer, H.; Zeuner, S. *Z. Naturforsch., B: Chem. Sci.* **1985**, *40B*, 954−960. (c) Fischer, H.; Zeuner, S.; Riede, J. *Angew. Chem.* **1984**, *96*, 707−708.
(31) Cadierno, V.; Žablocka, M.; Donnadieu, B.; Igau, A.; Majoral, J.-P.; Skowronska, A. *J. Am. Chem. Soc.* **1999**, *121*, 11086−11092. However, a referee of the present manuscript has pointed out that the two inequivalent Cp signals observed for their ostensible "η^1 imine complexes" are inconsistent with the structures they propose, and we have been unable to find examples of late-transition-metal η^1/η^2 equilibria in the reference they cite (their ref 18).
(32) Dimmock, P. W.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2323−2324.
(33) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. Rappaport, Z. *The Chemistry of the Cyclopropyl Group*; Wiley: New York, 1987.
(34) Charette, A. B.; Naud, J. *Tetrahedron Lett.* **1998**, *39*, 7259−7262 and references therein.
(35) For recent examples with Zr, see: (a) Chirik, P. J.; Dalleska, N. F.; Henling, L. M.; Bercaw, J. E. *Organometallics* **2005**, *24*, 2789. (b) Yang, P.; Baird, M. C. *Organometallics* **2005**, *24*, 6005−6012.
(36) Tunge, J. A.; Czerwinski, C. J.; Gately, D. A.; Norton, J. R. *Organometallics* **2001**, *20*, 254−260.

complicated by the effect of THF on the rate of insertion.[36] Kinetic resolution of racemic **1d** with enantiopure carbonate requires that insertion be *faster* than inversion, and it is difficult to meet that requirement in excess [THF], which slows down insertion. To avoid this problem, we have added the THF *after* the kinetic resolution of **1d** with (*R*,*R*)-DPEC but *before* significant racemization has occurred.

The data in Figure S8 show that [THF] has no effect on the rate of interconversion of the enantiomers of **1d** (at least at low [THF]). Thus, the THF ligand remains coordinated to Zr during racemization, as we expect if $\eta^2 \rightarrow \eta^1$ isomerization of the coordinated imine is involved.

This result has important practical consequences. Increasing the [THF] will slow the insertion rate, but not the enantiomer interconversion rate, thus decreasing k_R[(*R*,*R*)-DPEC] and k_S-[(*R*,*R*)-DPEC] relative to k_{inv}. Therefore, conducting the insertion in THF should allow us to approach the maximum diastereomer ratio of *s* without slow addition of the carbonate. Indeed, when an equivalent of (*R*,*R*)-DPEC is added *all at once* to **1d** *in THF*, insertion is slow, occurring over a period of several h (as evidenced by the change in color from yellow to red), but **2d** is formed in a dr of 78:22, close to the maximum dr of 88:12 obtained by syringe pump addition over 4 h in benzene,[1] and more selective than the dr of 62:38 obtained by rapid addition of (*R*,*R*)-DPEC to **2d** in benzene.[1]

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Supporting Information Available: All experimental and kinetic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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