Origin of Stereochemistry in the α-Amino Acid Esters and Amides Generated from Optically Active Zirconaaziridine Complexes[1]

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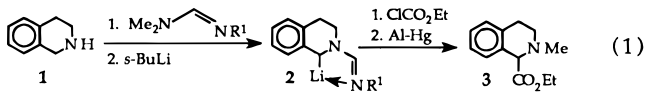
Abstract: Methane elimination from ethylenebis(tetrahydroindenyl)(methyl)zirconium amides (R = alkyl or aryl, R′ = aryl) (*S*,*S*)-**26** gives a mixture of epimeric zirconaaziridines **25** and **30**. When zirconaaziridines with R = alkyl are trapped with ethylene carbonate as they are formed, methyl α-amino acid esters **16** are obtained in poor ee (+14% to −56%); the ee's of **16** reflect the kinetic ratio of **25** to **30**. When epimeric zirconaaziridines with R = aryl are allowed to equilibrate before ethylene carbonate is added, the esters **16** are obtained in >96% ee. When epimeric zirconaaziridines with R = alkyl are allowed to equilibrate before ethylene carbonate is added, **16** is obtained in 21−97% ee. When isocyanates are added to the zirconaaziridine epimers **25** and **30**, phenylglycinamides are obtained in 80−99% ee. The ee's of the esters and amides are better when R′ is *o*-anisyl than when R′ is Ph. A *Curtin*−*Hammett*−*Winstein*−*Holness* analysis explains the stereochemistry in the esters and amides. When an equilibrated mixture of epimers (R = CH_2Ph, R′ = *o*-anisyl) **25g** and **30g** is treated with increasing ethylene carbonate concentrations, the ee of the ester **16g** increases from 53% to 89%. The ee of **16g** at saturation with ethylene carbonate implies that K_{eq} (k_{25g}/k_{30g}) is 17.2 for the **30g** ⇌ **25g** equilibrium. A similar result (19.0) is obtained from the de of the insertion product *rac*-**38** when **30g** ⇌ **25g** is treated with an excess of *t*-BuNCO.

Introduction

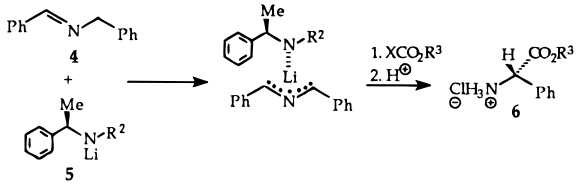
The carboxylation of long-chain amines is an attractive route for the synthesis of α-amino acids.[2] Meyers and co-workers have used formamidines to attach CO_2 synthons at the α-carbon of amines,[3] e.g., the carboethoxylation of tetrahydroisoquinoline (**1**) in eq 1.[3a] Treatment of the metalated formamidine **2** with ethyl chloroformate gave the racemic ethyl α-amino acid ester **3**.



(1)

Duhamel and co-workers have employed the optically active base **5** to effect the asymmetric carboxylation of the imine **4**.[4] Acidic removal of the benzylidene fragment gave the phenylglycine esters **6** in 0−41% enantiomeric excess (ee) (eq 2).

In an approach similar to the one in eq 2, Beak and co-workers have used (−)-sparteine to effect the asymmetric deprotonation of 7 to give the optically active adduct **8** and, after electrophilic addition of CO_2, (*R*)-**9** in 88% ee (eq 3).[5]



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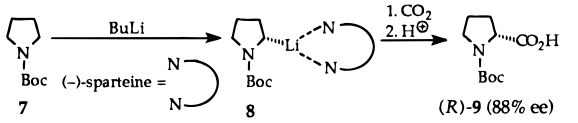
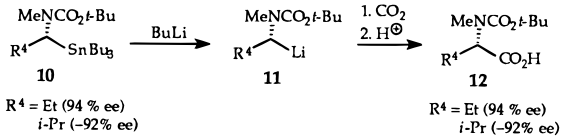


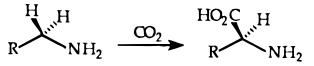
(3)

Chong and Park have generated configurationally stable α-aminoorganolithiums **11** from optically active α-aminoorganostannanes **10**. Treatment of **11** with CO_2 gave the *N*-Boc-protected *N*-methyl-α-amino acids **12** with excellent retention of stereochemistry (eq 4).[6]



(4)

We have been exploring the use of zirconaaziridines[7] **13** to effect reactions like eq 5. We recently reported the regioselective



(5)

insertion of CO_2 into the Zr−C bond of **13b**[8] to give the

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(1) Because organozirconocenes of this type behave with electrophiles as if they have a Zr−C *σ* bond, we prefer to call them zirconaaziridines rather than zirconium imines.

(2) Williams has said that "asymmetric carboxylation [at the α position of an amine] is a surprisingly rarely studied approach [and] ... a future area of investigation". Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989; Vol. 7.

(3) (a) Meyers, A. I.; Hellring, S.; Hoeve, W. T. *Tetrahedron Lett*. **1981**, *22*, 5115. (b) Bolster, J. M.; Hoeve, W. T.; Vaalburg, W.; Van Dijk, T. H.; Zijlstra, J. B.; Paans, A. M. J.; Wynberg, H.; Woldring, M. G. *Int. J. Appl. Radiat. Isot*. **1985**, *36*, 339.

(4) Duhamel, L.; Duhamel, P.; Fouquay, S.; Eddine, J. J.; Peschard, O.; Plaquevent, J.-C.; Ravard, A.; Solliard, R.; Valnot, J.-Y.; Vincens, H. *Tetrahedron* **1988**, *44*, 5495.

(5) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc*. **1994**, *116*, 3231.

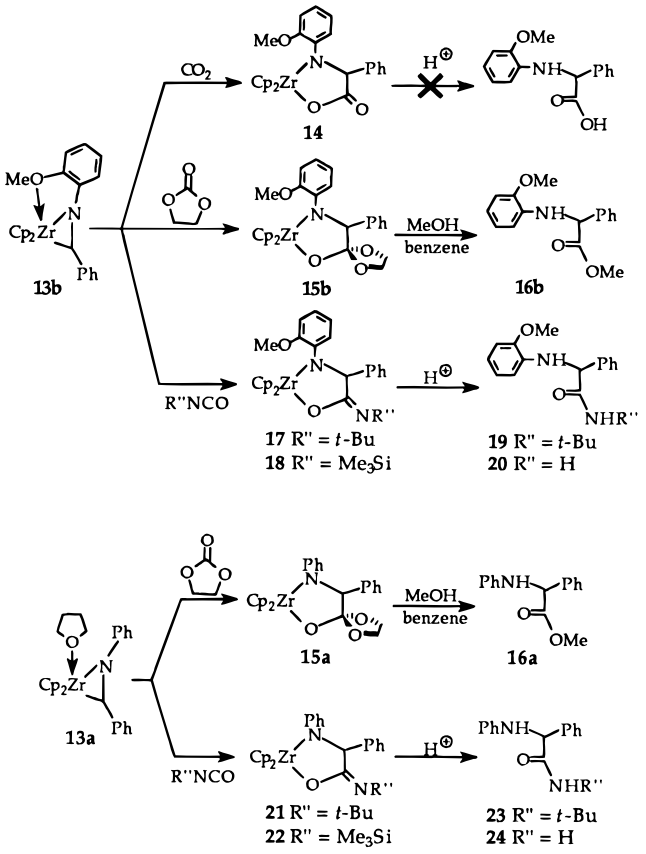
(6) Chong, J. M.; Park, S. B. *J. Org. Chem*. **1992**, *57*, 2220.

(7) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc*. **1989**, *111*, 4486.

(8) X-ray analysis of **13b** (R = Ph, R′ = *o*-anisyl) shows the oxygen of the *o*-anisyl substituent bound to Zr: Gately, D. A.; Norton, J. R.; Goodson, P. A. Unpublished results.

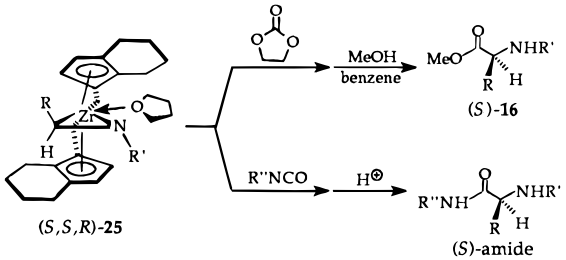
0002-7863/96/1518-3479$12.00/0

Scheme 1



zirconocene α-aminocarboxylate **14**.[9] Because we could not obtain the desired α-amino acid from **14**, we treated **13a,b** with ethylene carbonate (a CO_2 synthon) to give **15a,b** and, after methanolysis in benzene, the racemic methyl α-amino acid esters **16a,b**. Treatment of **13a,b** with isocyanates (*t*-BuNCO and Me_3-SiNCO) gave the metallacycles **17**, **18**, **21**, and **22** and, after methanolysis, the racemic phenylglycinamides **19**, **20**, **23**, and **24** (Scheme 1).

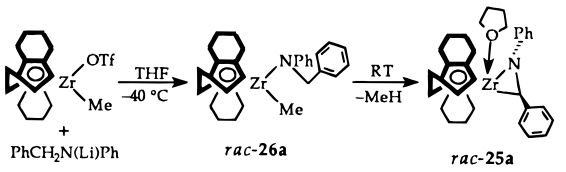
Grossman, Davis, and Buchwald[10] used the C_2-symmetric ethylenebis(tetrahydroindenyl) (EBTHI) ligand[11] to prepare allylic amines in high ee from zirconaaziridines in noncoordinating solvents,[12] and concluded that the ligand orients the aziridine substituent R away from the six-membered ring. We have therefore investigated the stereochemistry of ethylene carbonate (and isocyanate) insertion reactions with optically active zirconaaziridines such as (*S,S,R*)-**25**; if stereoselective, such insertions should lead to enantiomerically enriched (*S*)-**16** (or (*S*)-amide) (eq 6).



(6)

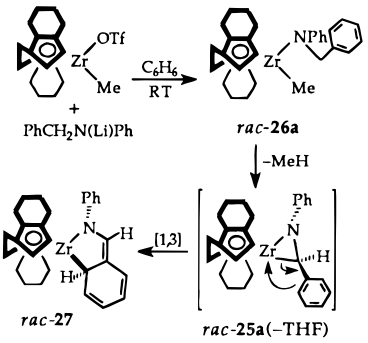
Results and Discussion

Asymmetric Carbomethoxylation of RCH_2NHR' When R Is Aromatic. One would expect elimination of methane from the racemic zirconium amide *rac*-**26a**, generated from $PhCH_2N$-(Li)Ph and *rac*-[EBTHI]ZrMe(OTf), in THF (eq 7), to give the



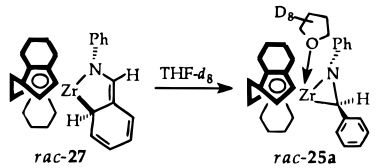
(7)

single diastereomer *rac*-**25a** drawn in eqs 6 and 7. When *rac*-**26a** was prepared at −40 °C *in THF* and warmed to room temperature, **25a** was indeed formed; only one diastereomer was detectable by ^1H NMR. However, as reported by Grossman and Buchwald,[10] *rac*-**26a** at room temperature *in benzene* gave instead the zirconaisoindole *rac*-**27** (eq 8).



(8)

Separate signals (like those we had seen[9] with the unsubstituted cyclopentadienyl analog **13a**) could not be seen for free and coordinated THF in a solution of **25a**. However, other experiments imply that the THF is coordinated to the Zr in **25a** (as in **13a**). Dissolving *rac*-**27** in THF-d_8 at room temperature converts it to *rac*-**25a** (eq 9).



(9)

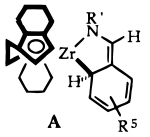
Treatment of (*S,S,R*)-**25a**−**c** with ethylenecarbonate should produce the spirocyclic complexes (*S,S,S*)-**28a**−**c**, and methanolysis of (*S,S,S*)-**28a**−**c** should give the *S*-α-amino acid esters **16a**−**c** (Scheme 2). When (*S,S,R*)-**25a**−**c** was treated with ethylene carbonate, methanolysis, carried out in the presence of added Cp_2ZrMe_2,[13] gave the methyl α-amino acid esters (+)-**16a**−**c** in 53−67% overall yield and >96% ee (Table 1, Scheme 2).

(9) Gately, D. A.; Norton, J. R.; Goodson, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 986.

(10) (a) Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321. (b) Grossman, R. B. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1991.

(11) Wild, F. R. W. P.; Wasiucionek, M.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1985**, *288*, 63.

(12) When they attempted to prepare the EBTHI analog of **13a** in benzene, Grossman and Buchwald obtained the zirconaisoindole **A** below. Analogous species were formed in all cases when R = aryl and no coordinating atoms were present (see ref 10b).



(13) With the EBTHI ligand we found Zr-promoted transesterification[9] (like that of **29**) to be extremely slow unless Cp_2ZrMe_2 was added.

Scheme 2

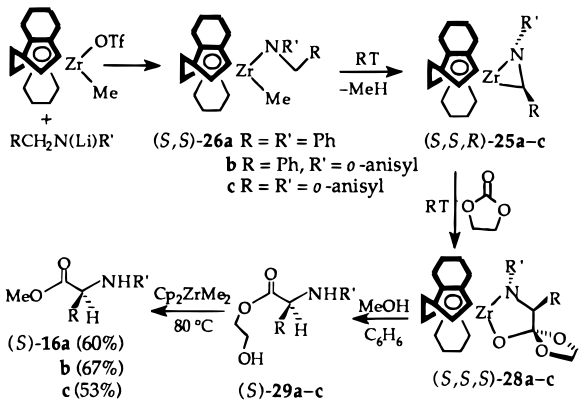
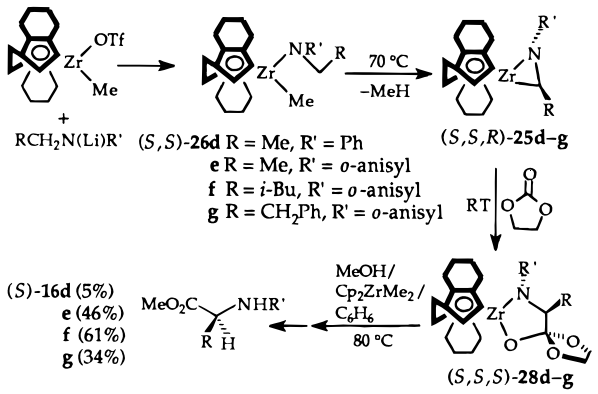


Table 1. Product Yields, Configurations, and ee's of (*S*)-**16a**−**c** from the Reaction of Ethylene Carbonate with (*S,S,R*)-**25a**−**c**[a] (Scheme 2)

product	R	R′	yield of $MeO_2CCH(R)NHR'$ (**16**)[b] (%)	configuration/ (optical sign)	ee[c] (%)
16a	Ph	Ph	60	*S*/(+)	>98
16b[d]	Ph	Ar	67	*S*/(−)	96
16c	Ar	Ar	53	*S*/(−)	98

[a] (*S,S,R*)-**25a**−**c** was prepared at room temperature. [b] Isolated yields, >98% pure by HPLC and ^{1}H NMR. [c] Obtained from stationary phase chiral HPLC. [d] Ar = *o*-anisyl.

Scheme 3



The absolute stereochemistry of (+)-**16a** has been assigned by comparing the sign of its rotation to that of its enantiomer (−)-**16a**.[14] The absolute configuration of (−)-**16a** is known to be *R*, so the absolute configuration of (+)-**16a** must therefore be *S*. A product (**16**) of the same configuration (*S*) is predicted if ethylene carbonate inserts into the Zr−C bond of (*S,S,R*)-**25** with retention of stereochemistry. The absolute stereochemistry of the other products (**16b,c**) (R = aromatic) formed by the same procedure (Scheme 2) is also presumed to be *S*.

Asymmetric Carbomethoxylation of RCH_2NHR' When R Is Alkyl. For R = alkyl (**26d**−**g**) elimination of methane and formation of **25d**−**g** occurred during several h at 70 °C (Scheme 3). When the mixture containing (*S,S,R*)-**25d**−**g** was cooled to room temperature and treated with ethylene carbonate, methanolysis gave **16d**−**g** in 5−61% yield and 21−97% ee (Table 2). The absolute stereochemistry of (−)-**16d** has been assigned by comparing the sign of its rotation to that of its enantiomer (+)-**16d**.[15] The absolute configuration of (+)-**16d** is known to be *R*, so the absolute configuration of (−)-**16d** must be *S*. The absolute stereochemistry of the other products (**16e**−**g**) (R = alkyl) formed by the same procedure (Scheme 3) is also presumed to be *S*.

Table 2. Product Yields, Configurations, and ee's of (*S*)-**16d**−**g** from the Reaction of Ethylene Carbonate with (*S,S,R*)-**25d**−**g**[a] (Scheme 3)

product	R	R′	yield of $MeO_2CCH(R)NHR'$ (**16**)[b] (%)	configuration/ (optical sign)	ee[c] (%)
16d	Me	Ph	5	*S*/(−)	21
16e[d]	Me	Ar	46	*S*/(−)	97
16f	*i*-Bu	Ar	61	*S*/(−)	54
16g	CH_2Ph	Ar	34	*S*/(+)	53

[a] (*S,S,R*)-**25d**−**f** was prepared at 70 °C and then allowed to cool to room temperature before addition of ethylene carbonate. [b] Isolated yields, >98% pure by HPLC and ^{1}H NMR. [c] Obtained from stationary phase chiral HPLC. [d] Ar = *o*-anisyl.

Table 3. Product Yields, Configurations, and ee's of **16a,c**−**f** Obtained from Trapping **25a,c**−**f**[a] with Ethylene Carbonate (Schemes 4 and 5)

product	R	R′	yield of $MeO_2CCH(R)NHR'$ (**16**)[b] (%)	configuration/ (optical sign)	*T* (°C)	ee[c] (%)
16a	Ph	Ph	trace	*S*/(+)	−40	
16c[d]	Ar	Ar	43	*S*/(−)	−40	>99
16d	Me	Ph	68	*S*/(−)	70	22
16e	Me	Ar	58	*R*/(+)	70	56
16f	*i*-Bu	Ar	51	*S*/(−)	70	14
16g	CH_2Ph	Ar	49	*R*/(−)	70	52

[a] **25a,c** were prepared from **26a,c** at −40 °C; **25d**−**f** were prepared at 70 °C. [b] Isolated yields, >98% pure by HPLC and ^{1}H NMR. [c] Obtained from stationary phase chiral HPLC. [d] Ar = *o*-anisyl.

In Situ Trapping of 25d−g with Ethylene Carbonate at 70 °C. It seemed possible that the yields of the insertion products (*S,S,S*)-**28d**−**g** and the methanolysis products (*S*)-**16d**−**g** would improve if ethylene carbonate were present as (*S,S,R*)-**25d**−**g** formed. (Buchwald and Grossman had obtained good yields and high ee's of allylic amines by generating zirconaaziridines in the presence of alkynes.[10,12])

If methane elimination from (*S,S*)-**26d**−**g** gave (*S,S,R*)-**25d**−**g**, trapping with ethylene carbonate (and retention of stereochemistry in the insertion step) would give (*S,S,S*)-**28d**−**g**. Methanolysis of (*S,S,S*)-**28d**−**g** should give (*S*)-**16d**−**g**. In fact we obtained (*S*)-(−)-**16d** in 68% yield (improved from 5% in Scheme 3) and (*S*)-(−)-**16f** in 51% yield, although in poor ee (22% for (*S*)-(−)-**16d** and 14% for (*S*)-(−)-**16f**) (Table 3, Scheme 4).

To our surprise, the products (*R*)-(+)-**16e** (from (*S,S*)-**26e**) and (*R*)-(−)-**16g** (from (*S,S*)-**26g**) had *R* configurations, *opposite* that (*S*) predicted by Scheme 3! If the insertion occurred with retention, the *R* configuration must have come from (*S,S,S*)-**30e,g** via (*S,S,R*)-**31e,g** (Scheme 4).[16]

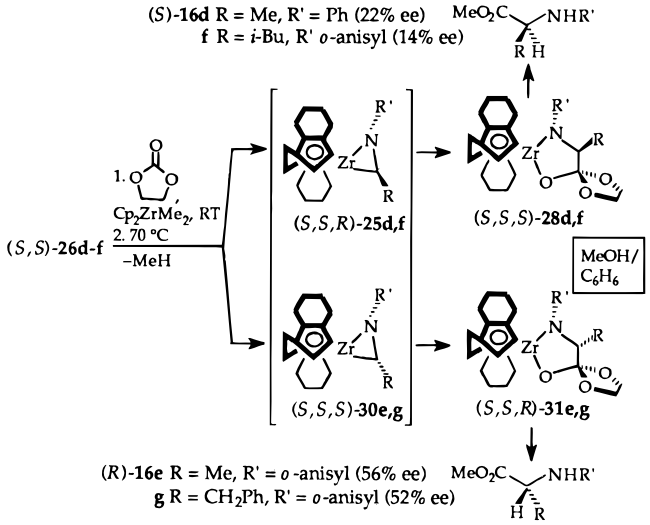
In Situ Trapping of 25a,c with Ethylene Carbonate below Room Temperature. We then examined the effect of trapping **25a,c** with ethylene carbonate as it was formed. A THF solution containing (*S,S*)-**26c** (prepared as in Scheme 2) was treated with ethylene carbonate and Cp_2ZrMe_2 at −40 °C. (Solutions of **25a**−**c** are red in the absence of ethylene carbonate; a persistent yellow color suggested that (*S,S,R*)-**25c** was short-lived.) Methanolysis gave (*S*)-(−)-**16c** in 43% yield and >99% ee (Scheme 5, Table 3). However, similar treatment of (*S,S*)-**26a** (R = R′ = Ph) gave only trace amounts of (*S*)-(+)-**16a** (Table 3).

(14) Christoskova, St.; Berova, B.; Simova, E.; Spassov, St.; Kurtev, B.; Snatzke, G. *Proceedings of the F.E.C.S. International Conference on Circular Dichroism*; VCH: Weinheim, 1987; pp 315−21.

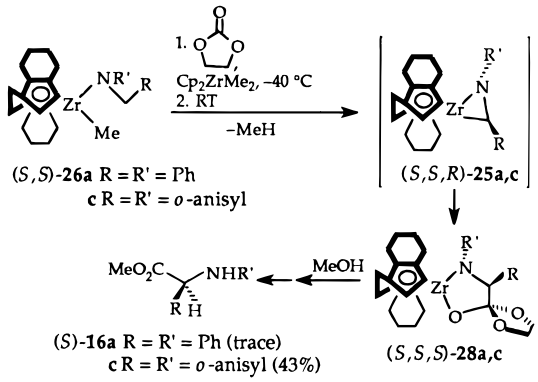
(15) Paradisi, M. P.; Romeo, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 596.

(16) C−H epimerization of the esters **16** (or amides) was not detected (via loss of optical rotation) under the conditions used in the workup procedure.

Scheme 4



Scheme 5



***N*-Ph vs *N*-*o*-Anisyl.** In Scheme 2, good yields and excellent ee's were obtained for (*S*)-**16a**−**c** regardless of whether R′ was Ph or *o*-anisyl. However, in Schemes 4 and 5, when (*S*,*S*,*R*)-**25** was trapped by ethylene carbonate as it was formed, the nature of R′ had a dramatic effect on the ee and yield of (*S*)-**16**. (In Table 3, compare the ee's and yields of **16a** (R′ = Ph) vs those of **16c** (R′ = *o*-anisyl), and those of **16d** (R′ = Ph) vs those of **16e**−**g** (R′ = *o*-anisyl).)

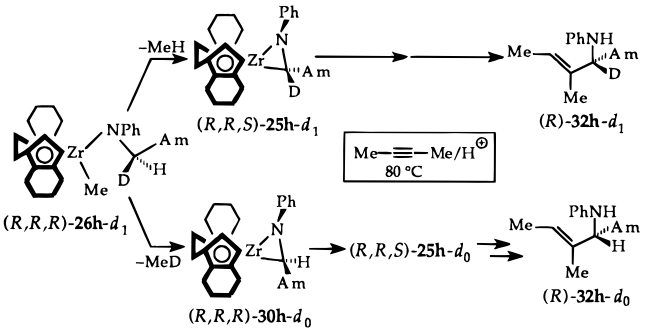
Whether ethylene carbonate was added *after* (Scheme 3) or *before* (Scheme 4) (*S*,*S*,*R*)-**25d** was formed, the ee of **16d** (R′ = Ph) was not affected. (Compare the 21% ee of **16d** in Scheme 3 vs 22% in Scheme 4.) In contrast, the ee's of **16e**−**g** (R′ = *o*-anisyl) declined, and in some cases reversed, between the conditions used in Scheme 3 and those used in Scheme 4. (Compare the 53−97% ee of **16e**−**g** in Scheme 3 vs the ee's (14% *S* to 56% *R*) in Scheme 4.)

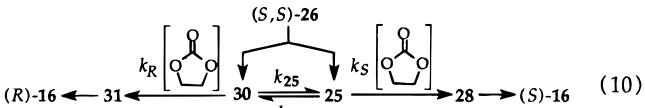
Origin of Stereochemistry in the Methyl α-Amino Acid Esters 16. In an effort to understand how R′ and different reaction conditions affect the stereochemistry in **16**, we have investigated the mechanisms of the key steps in Schemes 2−5.

Stereochemistry of Zirconaaziridine Intermediates. An explanation for the poor ee's of **16d**−**g** in Scheme 4 can be deduced from an elaborate deuterium labeling study performed by Grossman.[10b] The ratio of MeH to MeD loss in Scheme 6 (and related experiments) reflects not only the isotope effect but the stereoselectivity. Because an infinitely large (or small) **32h**-d_1/d_0 isotope ratio did not result from this experiment, Grossman concluded that the C−H activation step **26h** → **25h**/**30h** was not very diastereoselective.

The fact that (1) Grossman and Buchwald obtained the *S* configuration of allylic amines **32** in high ee[17] and (2) we obtained the *S* configuration of the methyl α-amino acid esters **16** in Schemes 2, 3, and 5 suggests that the zirconaaziridine in both cases is largely (*S*,*S*,*R*)-**25**. However, if interconversion of **25** and **30** is facile, the insertion reactions can be described by eq 10 and analyzed by the *Curtin*−*Hammett*−*Winstein*−*Holness* principle.[18]

Scheme 6





(10)

Curtin−Hammett−Winstein−Holness Principle. If the enantiomeric purity of **16** in Schemes 2 and 3 is governed by eq 10, it should depend on the first-order rate constants k_{25} and k_{30} in the **30** ⇌ **25** equilibrium and the competing k_R[ethylene carbonate] and k_S[ethylene carbonate], where k_R and k_S are second-order rate constants.

Boundary Condition I.[18a] In reference to eq 10, if k_{25} and $k_{30} \gg k_R$[ethylene carbonate] and k_S[ethylene carbonate], the (*S*)-**16**/(*R*)-**16** product ratio is given by eq 11 where $K_{eq} = k_{25}/k_{30}$. The (*S*)-**16**/(*R*)-**16** product ratio in eq 11 depends on both the first-order (k_{25}, k_{30}) and second-order (k_R, k_S) rate constants in eq 10.

$$\frac{(S)\text{-}\mathbf{16}}{(R)\text{-}\mathbf{16}} = \frac{(S,S,S)\text{-}\mathbf{28}}{(S,S,R)\text{-}\mathbf{31}} = K_{eq}\frac{k_S}{k_R} \qquad (11)$$

Boundary Condition II.[18a] Alternatively, if k_{25} and $k_{30} \ll k_R$[ethylene carbonate] and k_S[ethylene carbonate], the (*S*)-**16**/(*R*)-**16** product ratio is given by eq 12. The (*S*)-**16**/(*R*)-**16** product ratio in eq 12 reflects the equilibrium ratio **30** ⇌ **25** in eq 10 and depends only on the first-order rate constants k_{25} and k_{30} there.

$$\frac{(S)\text{-}\mathbf{16}}{(R)\text{-}\mathbf{16}} = \frac{(S,S,S)\text{-}\mathbf{28}}{(S,S,R)\text{-}\mathbf{31}} = K_{eq} \qquad (12)$$

A simple way of seeing if the ee in **16** reflects the operation of eq 10 is to measure the (*S*)-**16**/(*R*)-**16** ratio (ee) as the concentration of added ethylene carbonate increases or decreases. An increase or decrease in the ee of **16** should occur as we move from boundary condition I to boundary condition II.

(17) The only exception was the ee (18%) of (*S*)-**32a** (R = R′ = Ph). However, Grossman reported that the de of its precursor ((*S*,*S*,*S*)-**41a**) varied "with the temperature and other conditions" (refs 10b and 12).

(18) (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 648−655. (c) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York, 1990; pp 215−216.

Table 4. Product Yields, Configurations, and ee's of $MeO_2CCH(R)NHR'$ (**16a,c,f,g**) from Addition of Various Concentrations of Ethylene Carbonate to **25a,c,f,g**[a]

entry	product	R	R′	yield[b] (%)	configuration/(optical sign)	ee[c] (%)	amount of ethylene carbonate (mmol) in a volume of approximately 20 mL
1	**16a**	Ph	Ph	60	*S*/(+)	>98	0.64
2	**16a**	Ph	Ph	24	*S*/(+)	>98	6.4
3[d]	**16c**	Ar	Ar	53	*S*/(−)	98	0.64
4	**16c**	Ar	Ar	35	*S*/(−)	92	6.4
5	**16f**	*i*-Bu	Ar	61	*S*/(−)	54	0.64
6	**16f**	*i*-Bu	Ar	24	*S*/(−)	79	6.4
7	**16g**	CH_2Ph	Ar	34	*S*/(+)	53	0.64
8	**16g**	CH_2Ph	Ar	31	*S*/(+)	77	1.6
9	**16g**	CH_2Ph	Ar	27	*S*/(+)	85	6.4
10	**16g**	CH_2Ph	Ar	14	*S*/(+)	89	19.2
11	**16g**	CH_2Ph	Ar	49	R/(−)	52	0.64
12	**16g**	CH_2Ph	Ar	35	*R*/(−)	54	6.4

[a] [**25a,c,f,g**] = 0.32 mmol, ca. 8 mM. In entries 1−4, **25a,c** were prepared at room temperature, followed by addition of ethylene carbonate in benzene or THF at room temperature. In entries 5−10, **25f,g** were prepared at 70 °C, followed by addition of ethylene carbonate at room temperature. In entries 11−12, **25f,g** were prepared at 70 °C in the presence of ethylene carbonate. [b] Isolated yields, >98% pure by HPLC and ^{1}H NMR. [c] Obtained from stationary phase chiral HPLC. [d] Ar = *o*-anisyl.

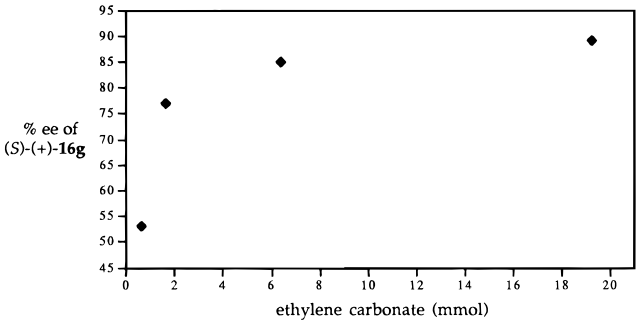


Figure 1. Percent ee of (*S*)-(+)-**16g** vs amount of ethylene carbonate (mmol) in a volume of approximately 20 mL. Data points were taken from entries 7−10 in Table 4. (*S,S,R*)-**25g** (0.32 mmol) was prepared at room temperature and then treated with ethylene carbonate.

Ethylene Carbonate Concentration vs the ee of 16. Indeed, when **25g** (0.32 mmol) was treated with increasing ethylene carbonate concentrations (from 0.64 to 19.2 mmol, in a volume of approximately 20 mL, entries 7−10 in Table 4), the ee of (*S*)-(+)-**16g** increased from 53% to 89% (Figure 1) and then leveled off. The ee (89%) of (*S*)-(+)-**16g** at saturation (Figure 1) therefore reflects the equilibrium ratio **30g** ⇌ **25g**; K_{eq} = 17.2 from eq 12. Similar results were obtained when **25f** (0.32 mmol) was treated with increasing ethylene carbonate concentrations (from 0.64 to 6.4 mmol, in a volume of approximately 20 mL, entries 5 and 6 in Table 4); the ee of (*S*)-(+)-**16f** increased from 54% to 79%.

The opposite trend was observed when **25c** (0.32 mmol) was treated with increasing ethylene carbonate concentrations (from 0.64 to 6.4 mmol, in a volume of approximately 20 mL, entries 3 and 4 in Table 4); the ee of (*S*)-(−)-**16c** decreased from 98% to 92%. The latter may reflect the equilibrium ratio **30c** ⇌ **25c**.

However, when **25a** (0.32 mmol) was treated with increasing ethylene carbonate concentrations (0.64 → 6.4 mmol, in a volume of approximately 20 mL, entries 1 and 2 in Table 4), the ee of (*S*)-(+)-**16a** did not change. This result suggested that boundary condition II was applicable even when only 0.64 mmol of ethylene carbonate was added. The **30a** ⇌ **25a** equilibrium therefore lies far to the right; $K_{eq} \approx 99$ from eq 12.

Ratio of k_S to k_R for Various Zirconaaziridines (eq 11). Because K_{eq} (17.2) is known for the **30g** ⇌ **25g** equilibrium in the upper limit (entry 10, Table 4) of ethylene carbonate concentration, we can calculate what k_S/k_R would be if entry 7 (Table 4) represents the lower limit (boundary condition I). The ee of 53% implies that $k_S/k_R < 0.19$ (eq 11). The k_R[ethylene carbonate] step in eq 10 is at least five times faster with the minor diastereomer **30g** than the k_S[ethylene carbonate] step is with the major diastereomer **25g**.

In contrast, if the ee (92%) of (*S*)-(−)-**16c** reflects the equilibrium ratio **30c** ⇌ **25c** in the upper limit (entry 4, Table 4) of ethylene carbonate concentration, then $K_{eq} \approx 24.0$ from eq 12. The ee (98%) of (*S*)-(−)-**16c** at the lowest feasible ethylene carbonate concentration (entry 3, Table 4) combined with K_{eq} (24.0) gives $k_S/k_R > 4.1$ from eq 11 for **25c** and **30c**. The k_S[ethylene carbonate] step in eq 10 is at least 4 times faster with the major diastereomer **25c** than the k_R[ethylene carbonate] step is with the minor diastereomer **30c**.

Curtin−Hammett−Winstein−Holness Conditions Are Not Achieved in Scheme 4. A Curtin−Hammett−Winstein−Holness situation requires that a mixture of **30** ⇌ **25** be initially equilibrated. Because the **25**/**30** ratio in Scheme 4 is kinetically controlled, i.e., **25** and **30** have not been equilibrated, the product ratio should be insensitive to the concentration of ethylene carbonate. Indeed, when (*S,S*)-**26g** (R = CH_2Ph, R′ = *o*-anisyl; 0.32 mmol) was heated to 70 °C in the presence of increasing ethylene carbonate concentrations (from 0.64 to 6.4 mmol, in a volume of approximately 20 mL, entries 11 and 12 in Table 4), the ee of (*R*)-(−)-**16g** increased negligibly from 52% to 54%.

Direct Measurement of K_{eq} in Eq 10? We then attempted to measure the equilibrium ratio **30** ⇌ **25** directly by ^{1}H NMR. The required zirconaaziridine *rac*-**25g** was obtained by adding $Ph(CH_2)_2NLi$(*o*-anisyl) to *rac*-[EBTHI]ZrMe(OTf) and heating the solution in benzene to 70 °C overnight; during this time methane was eliminated from *rac*-**26g** to give *rac*-**25g** in quantitative yield. Unfortunately, direct ^{1}H NMR observation of the product mixture containing *rac*-**25g** in C_6D_6 at room temperature (or at −105 °C in THF-d_8 or −95 °C in toluene-d_8) showed only one compound and offered no evidence for the equilibrium mixture *rac*-**30g** ⇌ *rac*-**25g**.

Ethylene Carbonate Concentration vs Insertion Product Ratio (28/31). When *rac*-**25g** (ca. 19.6 μmol) was treated with ~26 μmol of ethylene carbonate in a volume of approximately 0.5 mL for 1 h, an 84/16 *rac*-**28g**/*rac*-**31g** product ratio resulted ($t_{1/2} \approx 12$ min). When the concentration of ethylene carbonate was increased to ~190 μmol, in a volume of approximately 0.5 mL, a 94/6 *rac*-**28g**/*rac*-**31g** product ratio resulted after about 10 min ($t_{1/2} \approx 2$ min) (Scheme 7). The diastereomeric excess (de) of *rac*-**28g** increased from 68% to 88% (recall that a similar change in ethylene carbonate concentration increased the ee of its methanolysis product (*S*)-(+)-**16g** from 53% to 89%). This result implied that the minor diastereomer *rac*-**30g** must have

Scheme 7

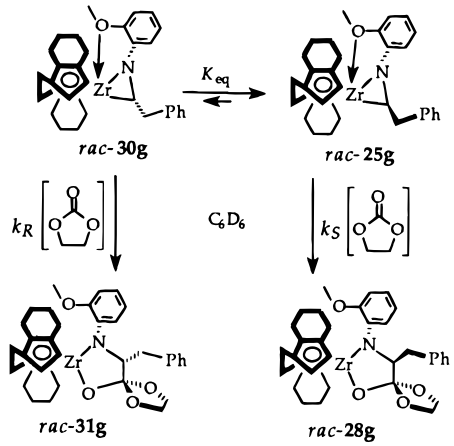
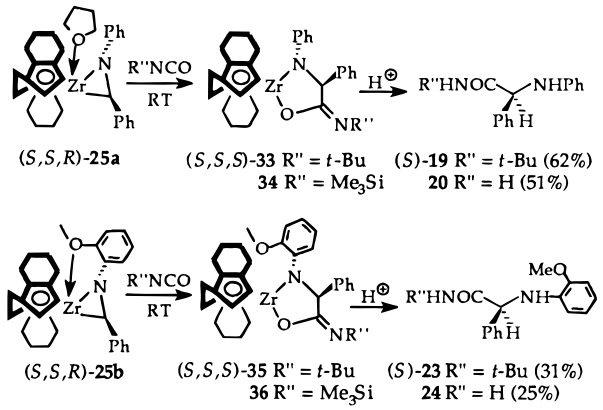


Table 5. Product Yields, Configurations, and ee's of Amides **19**, **20**, **23**, and **24** from the Reaction of R″NCO with (*S*,*S*,*R*)-**25a** and (*S*,*S*,*R*)-**25b**[a] (Scheme 8)

product	R′	R″	configuration/ (optical sign)	yield of amide R″NHCOCH(Ph)NHR′ [b] (%)	ee[c] (%)
19	Ph	*t*-Bu	*S*/(+)	62	92
20	Ph	H	*S*/(+)	51	80
23[d]	Ar	*t*-Bu	*S*/(−)	31	>99
24	Ar	H	*S*/(−)	25	98

[a] (*S*,*S*,*R*)-**25a,b** were prepared at room temperature. [b] Isolated yields, >98% pure by HPLC and ^{1}H NMR. [c] Obtained from stationary phase chiral HPLC. [d] Ar = *o*-anisyl.

Scheme 8

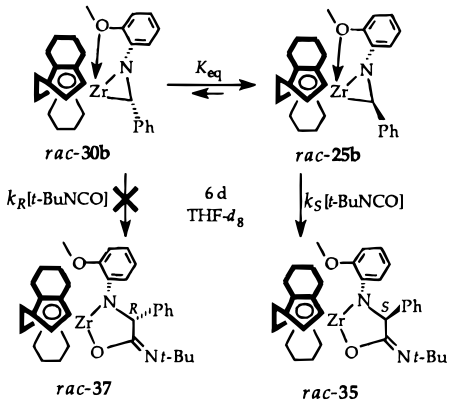


been present in equilibrium with *rac*-**25g**. (The absence of the minor diastereomer *rac*-**30g** in the previous ^{1}H NMR experiment suggests that the *rac*-**30g** ⇌ *rac*-**25g** interconversion is fast relative to the NMR time scale.)

Asymmetric Carboamidation of 25a. We then examined the stereoselectivity of the isocyanate insertion reactions of **25**. Treatment of (*S*,*S*,*R*)-**25a** (prepared as in Scheme 2) with *t*-BuNCO should give the metallacycle (*S*,*S*,*S*)-**33** and, after protonolysis, amide (*S*)-**19**. In fact, we obtained (*S*)-(+)-**19** in high ee (92%). Similar treatment of (*S*,*S*,*R*)-**25a** with Me_3-SiNCO gave, after protonolysis, (*S*)-(+)-**20** in good ee (80%) (Table 5, Scheme 8). The absolute configurations of (+)-**19** and (+)-**20** were assumed to be *S*, because they were from the same (*S*,*S*,*R*)-**25a** that had given (*S*)-**16a** (see Table 1 and accompanying discussion).

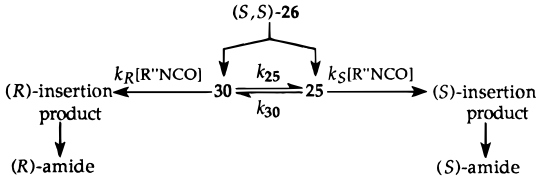
Asymmetric Carboamidation of 25b. In contrast, treatment of (*S*,*S*,*R*)-**25b** with *t*-BuNCO gave, after protonolysis, (*S*)-(−)-**23** in excellent ee (>99%) but low yield. Similar treatment of (*S*,*S*,*R*)-**25b** with Me_3SiNCO gave, after protonolysis, (*S*)-(−)-**24** (98% ee), also in low yield (Table 5, Scheme 8). The absolute stereochemistry of (−)-**23** and (−)-**24** formed by the same procedure (Scheme 8) was also presumed to be *S*.

Scheme 9



Zr ← O Chelation in 25b Slows Insertion Reactions. The low yields of (*S*)-(−)-**23** and (*S*)-(−)-**24** reflect the slow insertion reaction of R″NCO with (*S*,*S*,*R*)-**25b**, presumably because of the Zr ← O interaction from the *N*-*o*-anisyl fragment in (*S*,*S*,*R*)-**25b**. When *rac*-**25b** was treated with about 4.1 equiv of *t*-BuNCO in THF-d_8, 6 days ($t_{1/2} \approx 29$ h) was required to obtain the metallacycle *rac*-**35** in quantitative yield (Scheme 9) (the minor diastereomer *rac*-**37** was not detected by ^{1}H NMR). Overall, inserting reagents react much faster when R′ is Ph in **25** (or when R′ is Ph in **13**) than they do when R′ is *o*-anisyl.

Origin of Stereochemistry in the Amides 19, 20, 23, and 24. As with the esters (*S*)-**16** in eqs 10−12, the enantiomeric purity of the amides **19**, **20**, **23**, and **24** from Scheme 8 should reflect the operation of the Curtin−Hammett−Winstein−Holness equations (eqs 13−15).



(13)

(Boundary Condition I, $k_{25}, k_{30} >> k_R$[R″NCO], k_S[R″NCO])

$$\frac{(S)\text{-amide}}{(R)\text{-amide}} = \frac{(S)\text{-insertion product}}{(R)\text{-insertion product}} = K_{eq}\frac{k_S}{k_R} \quad (14)$$

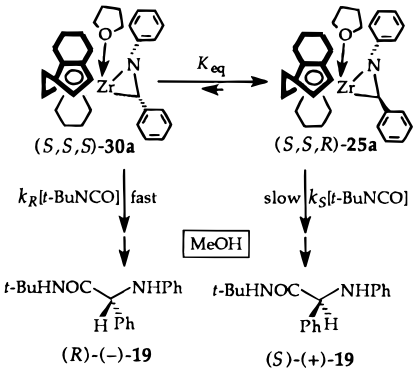
(Boundary Condition II, $k_{25}, k_{30} << k_R$[R″NCO], k_S[R″NCO])

$$\frac{(S)\text{-amide}}{(R)\text{-amide}} = \frac{(S)\text{-insertion product}}{(R)\text{-insertion product}} = K_{eq} \quad (15)$$

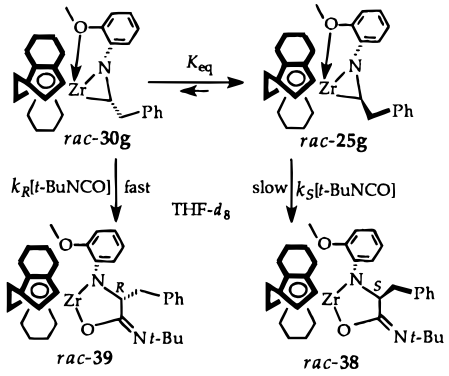
Effect of *t*-BuNCO Concentration on the Stereochemistry of the Amides. The addition of a dilute[19] solution of *t*-BuNCO to excess (*S*,*S*,*R*)-**25a** gave a significant decrease in the ee of (*S*)-(+)-**19** from the one (92% ee) found above (Scheme 8, Table 5). When (*S*,*S*,*R*)-**25a** (0.320 mmol) was treated with *t*-BuNCO (32 mM, 0.256 mmol), the ee of (*S*)-(+)-**19** decreased to 36% (Scheme 10).

(19) Low concentrations of isocyanates must be used to effect a significant change in the ee's of the phenyl-substituted amides **19** and **20**; the isocyanate must be added as a dilute solution so that mixing is complete before the insertion reaction occurs. In contrast, because the *o*-anisyl-substituted zirconaaziridines react more slowly, the concentrations of isocyanate low enough to effect a change in the ee's of the *o*-anisyl-substituted amides **23** and **24** can be added neat to **25b**.

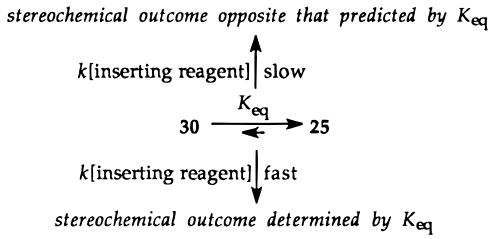
Scheme 10



Scheme 11



Scheme 12

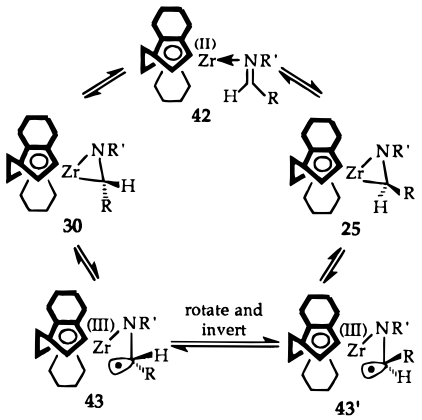


Ratio of k_S to k_R for the Zirconaaziridines in Scheme 10. The ee (36%) of (*S*)-(+)-**19** in the limit of low *t*-BuNCO concentration implies that $k_S/k_R < 0.02$ from eq 14. Thus, the k_R[*t*-BuNCO] step with the minor diastereomer **30a** in Scheme 10 is at least 50 times faster than the k_S[*t*-BuNCO] step with the major diastereomer **25a**.

***K*eq Is Independent of Inserting Reagent.** K_{eq} for the **30** ⇌ **25** equilibrium is independent of the nature of the inserting reagent (ethylene carbonate or *t*-BuNCO). Thus, the product ratio in eq 15 should be the same as that in eq 12. In fact, when *rac*-**25g** (ca. 20.1 μmol) was treated with excess *t*-BuNCO (ca. 454 μmol, in a volume of approximately 0.5 mL), a 95/5 *rac*-**38**/*rac*-**39** ratio was obtained in the ^{1}H NMR (Scheme 11). This result gives $K_{eq} = 19.0$ from eq 15 for the **30g** ⇌ **25g** equilibrium mixture, similar to the one ($K_{eq} = 17.2$) found (see discussion below eq 12) from the addition of excess ethylene carbonate to the equilibrium mixture **30g** ⇌ **25g**.

Influence of the Rate of Insertion on Stereoselectivity. Two reagents that insert at different rates may give different stereochemical results with the same zirconaaziridine. Equations 10 and 13 predict that the stereochemistry of the insertion product should depend on the rate at which inserting reagents add to the equilibrium mixture **30** ⇌ **25**. If an inserting reagent adds to the **30** ⇌ **25** equilibrium mixture in a fast step (k[inserting reagent] ≫ $k_{forward}$ or k_{back} of the equilibrium) and K_{eq} is large, the stereochemical outcome of the insertion product

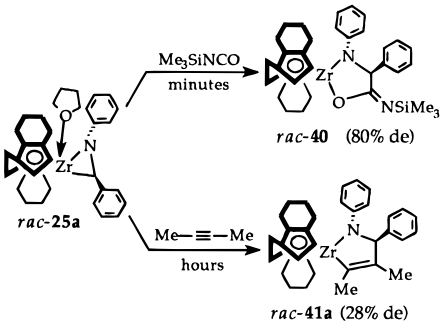
Scheme 13



should reflect K_{eq} (Scheme 12); the ee of the hydrolysis product should therefore be high. The opposite effect is predicted when an inserting reagent adds in a slow step (k[inserting reagent] ≪ $k_{forward}$ or k_{back} of the equilibrium).

The validity of Scheme 12 is evident when the rates and stereoselectivities of the ethylene carbonate insertions of **25** are compared with those of the isocyanate ones. Ethylene carbonate reacts about 3 times more rapidly with **25g** than does *t*-BuNCO: when *rac*-**25g** (ca. 17.6 μmol) was treated at room temperature with ca. 22.2 μmol of either reagent in a volume of approximately 0.5 mL, the ethylene carbonate reaction (Scheme 7) took only 1 h ($t_{1/2} \approx 12$ min) whereas the *t*-BuNCO reaction (Scheme 11) took 3 h ($t_{1/2} \approx 36$ min). As predicted by Scheme 12, the de was considerably higher (68% vs 28%) with ethylene carbonate.

Reagents less reactive than isocyanates put us closer to boundary condition I and give results even further removed from K_{eq}. Treatment of *rac*-**25a** (∼20 μmol) with 2-butyne (ca. 83.0 μmol, in a volume of approximately 0.5 mL) gave *rac*-**41a** in 28% de (eq 16), whereas treatment of Me_3SiNCO (ca. 24.0



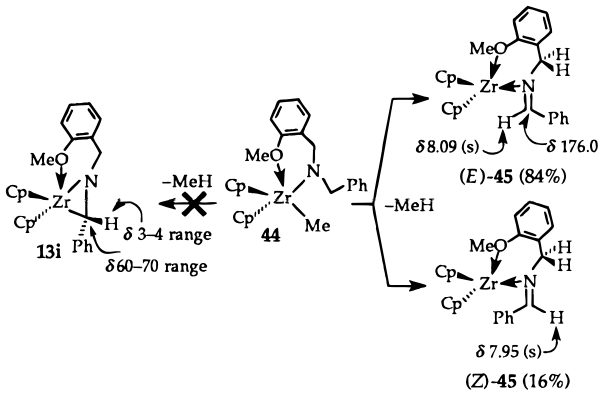
(16)

μmol, in a volume of approximately 0.5 mL) gave *rac*-**40** in 80% de. However, sufficiently high concentrations of even a relatively unreactive reagent such as 2-butyne move us back toward the bottom of Scheme 12 (boundary condition II). Increasing the concentration of 2-butyne from 0.03 to 12.8 mM increased the de of *rac*-**41a** from 24% to 99%!

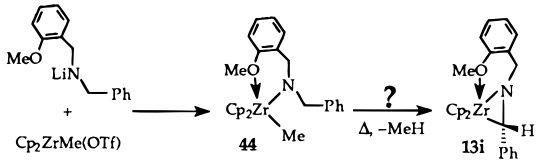
Mechanism of 30 ⇌ 25 Epimerization? In order for the **30** ⇌ **25** epimerization to occur, the Zr−C bond must cleave from **30** to give either a Zr(II)−imine complex such as **42** or a Zr(III) complex such as **43** with a carbon radical.[20] After rotation of the (Ph)CH−N bond and inversion of configuration of the carbon (**43′**), recombination of the Zr−C bond in **43′** would give **25**. With **42**, recombination of its Zr−C bond is all that is required to give **25** (Scheme 13).

(20) Grossman suggested that the **30** ⇌ **25** epimerization involved the **43** ⇌ **43′** equilibrium in Scheme 13 (see ref 10b).

Scheme 14

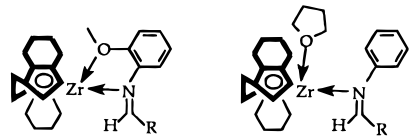


In an unrelated study we found evidence of a Zr(II)−imine complex like the one shown (**42**) in Scheme 13. We expected treatment of the lithium amide (*o*-anisyl)CH_2N(Li)CH_2Ph with Cp_2ZrMe(OTf) to give the (methyl-)zirconium amide **44** and,after regioselective C−H activation and loss of methane, the zirconaaziridine **13i** in eq 17.



The (methyl-)zirconium amide **44** was easily isolated. However, to our surprise, we obtained (*E*)-**45** (84%) and (*Z*)-**45** (16%) instead of **13i** (Scheme 14)! The NMR of **45** shows a ^{1}H methine singlet resonance (δ 8.09, δ 7.95) and a ^{13}C methine carbon resonance (δ 176.0), indicative of the CH═N imine fragment in **45**; these ^{1}H and ^{13}C resonances are well downfield of the ^{1}H methine proton resonance (δ 3−4 ppm) and ^{13}C methine carbon resonance (δ 60−70 ppm) expected in the zirconaaziridine **13i**. Moreover, the ^{1}H resonance of the Cp's for (*E*)-**45** (δ 5.71) and (*Z*)-**45** (δ 5.85) and the ^{1}H resonance of the methylene signals for (*E*)-**45** (δ 4.52) and (*Z*)-**45** (δ 4.46) were all singlets, indicative of a plane of symmetry bisecting the CpZrCp and HCH planes.[21]

Possible intermediates in the **30** ⇌ **25** interconversion are thus **46** when R′ = *o*-anisyl and **47** when R′ = Ph.



Experimental Section

Materials. All air-sensitive compounds were prepared and handled under a nitrogen atmosphere, using standard Schlenk and inert-atmosphere-box techniques. Most of the solvents used were distilled under N_2 from sodium−benzophenone ketyl; hexanes were stirred over H_2SO_4 and distilled from sodium−benzophenone ketyl in the presence of tetraglyme. Trifluoromethanesulfonic acid (TfOH) was degassed by three freeze/pump/thaw cycles at −196 °C, and finally transferred into a flame-dried vacuum bulb. Isocyanates were stirred over P_4O_{10} for 24 h and transferred by high vacuum into a flame-dried vacuum bulb. All other reagents employed were used without further purification. Cp_2ZrMe_2,[22] *rac*-[EBTHI]$ZrMe_2$,[23] (*S*,*S*)-[EBTHI]$ZrMe_2$,[10b] and (*S*,*S*)-[EBTHI]ZrMe(OTf)[10b] were prepared by standard procedures. Cp_2ZrCl_2 was generously supplied by Boulder Scientific. Anilines were prepared by reduction of the carboxamide with BH_3·SMe_2/BF_3·Et_2O as described by Brown and co-workers.[24]

^{1}H NMR data were collected on a Bruker WNX 300-MHz FT spectrometer; residual solvent proton shifts were used as internal standards. Elemental analyses of air- and moisture-sensitive compounds were performed by Analytische Laboratorien, Gummersbach, Germany; those of all other compounds were performed by Midwest Laboratories, Indianapolis, IN.

Chiral stationary phase HPLC data were collected on a Varian 9050 Star Detector. Compounds **16c**, **19**, **20**, **23**, and **24** were separated on a Bakerbond OD chiralcel column; all others were separated on a Bakerbond OJ chiralcel column. All compounds were detected at 254 nm. The presence of enantiomerically enriched esters **16** and amides **19**, **20**, **23**, and **24** was confirmed by spiking the HPLC samples with authentic (±)-**16** and (±)-**19**, -**20**, -**23**, and -**24**. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III. The optical rotations ($[\alpha]_{measured}$) for **16** and **18** were obtained at 26 °C. Specific rotations ($[\alpha]_D$) are reported in deg/dm, and the concentration (*c*) is given in g/100 mL (THF). The ee (>99%) of (*S*,*S*)-[EBTHI]$ZrMe_2$ was determined by treatment with excess (*R*)-(−)-*O*-acetylmandelic acid in C_6D_6; the ratio of the resulting diastereomers was determined by ^{1}H NMR from the sp^2 C*H* indenyl resonances.[10b]

General Procedure for the Preparation of (±)-16b,c (MeO_2CCH(R)NHR′). The following procedure is modified from the one described earlier.[9] A solution containing Cp_2ZrMe_2 (378 mg, 1.5 mmol) and THF (10 mL) was cooled to −78 °C and treated with TfOH (127 μL, 1.44 mmol). The pale yellow solution was warmed to room temperature, stirred for 1 h, and again cooled to −78 °C. In a separate flask BuLi (1.6 M, 900 μL, 1.44 mmol) was added to a cold (0 °C) ether (10 mL) solution containing RCH_2NHR' (1.44 mmol), and the solution stirred for 5 min. The $RCH_2N(Li)R'$ was transferred by cannula to the Cp_2-ZrMe(OTf) and stirred for 0.5 h at −78 °C; the solution was warmed to room temperature and stirred overnight. The solvent was removed and replaced with benzene (20 mL) containing ethylene carbonate (136 mg, 1.54 mmol). After stirring overnight, the solution was treated with MeOH (1 mL) and stirred for an additional 8 h at 80 °C. The solvent was removed, and the residue was treated with CH_2Cl_2 (20 mL) and filtered. The residue from the filtrate was spotted on a Chromatotron plate eluted with hexanes/ethyl acetate (25/1); further purification was not needed.

(±)-16b (MeO_2CCH(Ph)NH(*o*-anisyl)). Yield: 252 mg (64%). ^{1}H and ^{13}C NMR data for (±)-**16b** prepared by a different procedure were reported earlier.[9]

(±)-16c (MeO_2CCH(*o*-anisyl)NH(*o*-anisyl)). Yield: 247 mg (52%). ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 1 H), 7.32 (t, 1 H), 6.98 (t, 2 H), 6.88−6.69 (m, 3 H), 6.58 (d, 1 H), 5.65 (s, 1 H), 5.47 (v br s, 1 H), 3.97 (s, 3 H), 3.88 (s, 3 H), 3.77 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 172.7, 157.0, 147.0, 136.2, 129.2, 127.8, 126.3, 121.0, 117.1, 111.0, 110.3, 109.5, 55.7, 55.3, 54.0, 52.4. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.89; H, 6.38; N, 4.71.

General Procedure for the Preparation of (±)-16d−g (MeO_2-CCH(R)NHR′). The procedure was the same as that described above for (±)-**16b,c**, but with the following modifications. After addition of the $RCH_2N(Li)R'$ to $Cp_2ZrMe(OTf)$, the solution was warmed to room temperature. The solvent was removed and replaced with benzene (20 mL) containing ethylene carbonate (136 mg, 1.54 mmol); the solution was transferred to a vacuum bulb, and the bulb was sealed and then heated to 70 °C overnight.

(±)-16d (MeO_2CCH(Me)NHPh). Yield: 124 mg (48%). ^{1}H NMR ($CDCl_3$): δ 7.17 (t, 2 H), 6.74 (t, 1 H), 6.62 (d, 2 H), 4.18 (C*H* q overlapped with N*H* br s, 2 H), 3.76 (d, 3 H). ^{13}C NMR ($CDCl_3$): δ 175.1, 146.5, 129.3, 118.3, 113.8, 52.2, 51.9, 19.0. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.29; H, 7.31; N, 7.78.

(21) Complex **45** failed to give crystals suitable for X-ray analysis; it was unaffected by ethylene carbonate at room temperature or at 80 °C in C_6D_6. Moreover, (*o*-anisyl)N═CH(Ph) did not displace the imine fragment in **45** to give the known complex **13b**.

(22) (a) Samuel, E.; Rausch, M. D. *J. Am. Chem. Soc.* **1973**, *95*, 6263. (b) References 7 and 9.

(23) Waymouth, R. M.; Bangerter, F.; Pino, P. *Inorg. Chem.* **1988**, *27*, 758.

(24) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

(±)-16e ($MeO_2CCH(Me)NH(o$-anisyl)). Yield: 198 mg (66%). ^{1}H NMR ($CDCl_3$): δ 6.88−6.67 (m, 3 H), 6.54 (d, 1 H), 4.73 (v br s, 1 H), 4.17 (q, 1 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 1.52 (d, 3 H). ^{13}C NMR ($CDCl_3$): δ 174.9, 146.8, 136.3, 121.0, 117.3, 110.0, 109.6, 55.2, 52.0, 51.5, 18.8. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.00; H, 7.27; N, 6.73.

(±)-16f ($MeO_2CCH(i$-Bu)NH(o-anisyl)). Yield: 195 mg (54%). ^{1}H NMR ($CDCl_3$): δ 6.89−6.63 (m, 3 H), 6.56 (d, 2 H), 4.58 (br d, 1 H), 4.12 (q, 1 H), 3.87 (s, 3 H), 3.71 (s, 3 H), 1.83 (m, 1 H), 1.71 (t, 2 H), 1.04 (d, 3 H), 0.97 (d, 3 H). ^{13}C NMR ($CDCl_3$): δ 175.1, 147.0, 136.9, 121.1, 117.3, 110.1, 109.7, 55.4, 54.7, 51.9, 42.3, 24.9, 22.7, 22.1. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.80; H, 8.39; N, 5.67.

(±)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)). Yield: 191 mg (46%). ^{1}H NMR ($CDCl_3$): δ 7.33−7.18 (m, 5 H), 6.87−6.68 (m, 3 H), 6.55 (d, 1 H), 4.79 (br s, 1 H), 4.36 (t, 1 H), 3.82 (s, 3 H), 3.65 (s, 3 H), 3.16 (d, 2 H). ^{13}C NMR ($CDCl_3$): δ 173.5, 147.0, 136.4, 136.2, 129.1, 128.3, 126.7, 121.0, 117.4, 110.3, 109.7, 57.6, 55.3, 51.8, 38.7. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.35; H, 6.65; N, 4.89.

Preparation of Methyl α-Amino Acid Esters by Scheme 2. A Schlenk flask containing RCH_2NHR' (0.323 mmol) in cold (0 °C) ether (5 mL) was treated with BuLi (1.6 M, 200 μL, 0.320 mmol) and stirred for 5 min. The $RCH_2N(Li)R'$ was transferred by cannula to a cold (−40 °C) THF (5 mL) solution containing (*S*,*S*)-[EBTHI]ZrMe(OTf) (169 mg, 0.325 mmol). After 5 min at −40 °C and 2 h at room temperature, the red (or orange) solution was evaporated to dryness and the residue was treated with benzene (20 mL). A separate solution containing ethylene carbonate (56 mg, 0.640 mmol), Cp_2ZrMe_2 (202 mg, 1.28 mmol), and benzene (20 mL) was transferred by cannula to the solution containing **25**. After stirring overnight, the pale yellow solution was treated with MeOH (300 μL) and heated to 80 °C for 4 h or until the β-hydroxyethyl ester **29** was consumed (as detected by TLC). The solvent was filtered and evaporated to dryness. The residue was spotted on a Chromatotron plate and eluted with hexanes/ethyl acetate (25/1). RCH_2NHR' ($R_f \approx 0.6$) was separated (typically 15−30%) from the band that contained (*S*)-(+)- or (*S*)-(−)-**16a**−**c** ($R_f \approx 0.3$). (*S*)-(+)- or (*S*)-(−)-**16a**−**c** were >98% pure by ^{1}H NMR.

(*S*)-(+)-16a ($MeO_2CCH(Ph)NHPh$) was prepared by the general Scheme 2 procedure, but with the following modifications. After 5 min at −40 °C and 2 h at room temperature, the orange solution changed immediately to cherry red upon addition of ethylene carbonate (56 mg, 0.640 mmol) and Cp_2ZrMe_2 (201 mg, 0.800 mmol) in THF (10 mL). After stirring overnight, the solvent was evaporated and the residue was treated with benzene (20 mL) (yield 46 mg (60%), >98% ee, hexane/ethanol (95/5), flow rate 0.85 mL/min, retention time (min) 42.4 and 47.5, $[\alpha]_D = +68.3°$ ($c = 0.315$)).

(*S*)-(+)-16a ($MeO_2CCH(Ph)NHPh$) (entry 2, Table 4) was prepared by the general Scheme 2 procedure, except that 20 equiv (6.4 mmol) of ethylene carbonate was used (yield 18 mg (23%), >98% ee (determined by $[\alpha]_{measured}$ in THF), $[\alpha]_D = +70.3°$ ($c = 0.175$)).

Data for (*S*)-(−)-16b ($MeO_2CCH(Ph)NH(o$-anisyl)): yield 58 mg (67%), 96% ee, hexane/ethanol (100/0) for 45 min, flow rate 1.0 mL/min and then changed to hexane/ethanol (95/5), flow rate 0.85 mL/min, retention time (min) 60.3 and 63.9, $[\alpha]_D = -35.7°$ ($c = 0.070$).

Data for (*S*)-(−)-16c ($MeO_2CCH(o$-anisyl)$NH(o$-anisyl)): yield 51 mg (53%), 98% ee, hexane/ethanol (95/5), flow rate 1.0 mL/min, retention time (min) 11.6 and 25.4, $[\alpha]_D = -52.1°$ ($c = 0.165$).

(*S*)-(−)-16c ($MeO_2CCH(o$-anisyl)$NH(o$-anisyl)) (entry 4, Table 4) was prepared by the Scheme 2 procedure, except that 20 equiv (6.4 mmol) of ethylene carbonate was used (yield 34 mg (35%, 92% ee), $[\alpha]_D = -52.3°$ ($c = 0.065$)).

Preparation of Methyl α-Amino Acid Esters by Scheme 3. After addition of the $RCH_2N(Li)R'$ to (*S*,*S*)-[EBTHI]ZrMe(OTf) (Scheme 2 procedure), the solution was warmed to room temperature. The solvent was removed, and the residue containing (*S*,*S*)-**26** was treated with benzene (20 mL). The solution was transferred to a vacuum bulb and heated to 70 °C overnight. The solution was cooled to room temperature (1 h) and treated with ethylene carbonate (56 mg, 0.640 mmol) and Cp_2ZrMe_2 (202 mg, 1.28 mmol) in benzene (20 mL); the bulb was sealed, and the solution was stirred at room temperature overnight. (*S*)-(+)- or (*S*)-(−)-**16d**−**g** was >98% pure by ^{1}H NMR with the exception of (*S*)-(−)-**16d** (95% pure by ^{1}H NMR).

Data for (*S*)-(−)-16d ($MeO_2CCH(Me)NHPh$): yield ∼3 mg (5%), 21% ee, hexane/ethanol (95/5), flow rate 0.85 mL/min, retention time (min) 24.4 and 37.3, $[\alpha]_D = -85°$ ($c = 0.040$).

Data for (*S*)-(−)-16e ($MeO_2CCH(Me)NH(o$-anisyl)): yield 39 mg (58%), 97% ee, hexane/ethanol (95/5), flow rate 0.9 mL/min, retention time (min) 17.0 and 21.3, $[\alpha]_D = -42.8°$ ($c = 0.150$).

Data for (*S*)-(−)-16f ($MeO_2CCH(i$-Bu)$NH(o$-anisyl)): yield 49 mg (61%), 54% ee, hexane/ethanol (99/1), flow rate 0.9 mL/min, retention time (min) 12.4 and 16.5, $[\alpha]_D = -70.9°$ ($c = 0.170$).

(*S*)-(−)-16f ($MeO_2CCH(i$-Bu)$NH(o$-anisyl)) (entry 6, Table 4) was prepared by the general Scheme 3 procedure, except that 20 equiv (6.4 mmol) of ethylene carbonate was used (yield 19 mg (24%, 79% ee), $[\alpha]_D = -69.2°$ ($c = 0.105$)).

Data for (*S*)-(+)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)): yield 31 mg (34%), 53% ee, hexane/ethanol (80/20), flow rate 0.85 mL/min, retention time (min) 16.3 and 30.5, $[\alpha]_D = +9.6°$ ($c = 0.650$).

(*S*)-(+)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)) (entry 8, Table 4) was prepared by the general Scheme 3 procedure, except that 5 equiv (1.6 mmol) of ethylene carbonate was used (yield 28 mg (31%, 77% ee), $[\alpha]_D = +10.6°$ ($c = 0.360$)).

(*S*)-(+)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)) (entry 9, Table 4) was prepared by the general Scheme 3 procedure, except that 20 equiv (6.4 mmol) of ethylene carbonate was used (yield 25 mg (27%, 85% ee), $[\alpha]_D = +10.4°$ ($c = 0.590$)).

(*S*)-(+)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)) (entry 10, Table 4) was prepared by the general Scheme 3 procedure, except that 60 equiv (19.2 mmol) of ethylene carbonate was used (yield 13 mg (14%, 89% ee), $[\alpha]_D = +10.1°$ ($c = 0.310$)).

Preparation of Methyl α-Amino Acid Esters in Scheme 4. After addition of the $RCH_2N(Li)R'$ to (*S*,*S*)-[EBTHI]ZrMe(OTf) (Scheme 2 procedure), the solution was warmed to room temperature. The solvent was removed, and the residue containing (*S*,*S*)-**26** was treated with benzene (20 mL). The solution was transferred to a vacuum bulb containing ethylene carbonate (56 mg, 0.640 mmol) and Cp_2ZrMe_2 (202 mg, 1.28 mmol) in benzene (20 mL); the bulb was sealed and the solution heated to 70 °C overnight. (*S*)-(−)-**16d,f** and (*R*)-(+)- or (*R*)-(−)-**16e,g** were >98% pure by ^{1}H NMR.

Data for (*S*)-(−)-16d ($MeO_2CCH(Me)NHPh$): yield 39 mg (68%, 22% ee), $[\alpha]_D = -92.8°$ ($c = 0.118$).

Data for (*R*)-(+)-16e ($MeO_2CCH(Me)NH(o$-anisyl)): yield 39 mg (58%, 56% ee), $[\alpha]_D = +38.1°$ ($c = 0.150$).

Data for (*S*)-(−)-16f ($MeO_2CCH(i$-Bu)$NH(o$-anisyl)): yield 41 mg (51%, 14% ee), $[\alpha]_D = -72.7°$ ($c = 0.138$).

Data for (*R*)-(−)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)): yield 45 mg (49%, 52% ee), $[\alpha]_D = -11.7°$ ($c = 0.770$).

(*R*)-(−)-16g ($MeO_2CCH(CH_2Ph)NH(o$-anisyl)) (entry 12, Table 4) was prepared by the general Scheme 4 procedure, except that 20 equiv (6.4 mmol) of ethylene carbonate was used (yield 31 mg (34%, 54% ee), $[\alpha]_D = -11.9°$ ($c = 0.530$)).

Preparation of Methyl α-Amino Acid Esters by Scheme 5. After addition of the $RCH_2N(Li)R'$ to (*S*,*S*)-[EBTHI]ZrMe(OTf) (Scheme 2 procedure), the solution was stirred at −40 °C for 1 h. In a separate flask, a cold (−40 °C) THF (20 mL) solution containing ethylene carbonate (56 mg, 0.640 mmol) and Cp_2ZrMe_2 (202 mg, 1.28 mmol) was transferred by cannula to the flask containing (*S*,*S*)-**26**; the solution was stirred for 15 min at −40 °C before warming to room temperature and stirring overnight. The solvent was removed, and the residue was treated with benzene (20 mL) and MeOH (900 μL). (*S*)-(−)-**16c** was >98% pure by ^{1}H NMR.

Data for (*S*)-(−)-16c ($MeO_2CCH(o$-anisyl)$NH(o$-anisyl)): yield 41 mg (43%, >99% ee), $[\alpha]_D = -57.6°$ ($c = 0.085$).

Preparation of *rac*-25g. A solution containing *rac*-[EBTHI]$ZrMe_2$ (318 mg, 0.820 mmol) and THF (10 mL) was cooled to −78 °C and treated with TfOH (73 μL, 0.820 mmol). The pale yellow solution was warmed to room temperature and stirred for 1 h, followed by recooling to −78 °C. In a separate flask BuLi (1.6 M, 513 μL, 0.820 mmol) was added to a cold (0 °C) Et_2O (5 mL) solution containing $Ph(CH_2)_2NH(o$-anisyl) (189 mg, 0.820 mmol), and the solution was stirred for 5 min. The $Ph(CH_2)_2NLi(o$-anisyl) was transferred by cannula to the *rac*-[EBTHI]ZrMe(OTf); the yellow solution was stirred

for 0.5 h at −40 °C before warming to room temperature. The solvent was evaporated, and the residue was dissolved in benzene and heated to 70 °C overnight. The solution was filtered by cannula with benzene washes (2 × 5 mL), and the filtrate was evaporated to yield an orange solid. ^{1}H NMR of the product mixture showed only one diastereomer. Yield: 434 mg (90% pure by ^{1}H NMR). An analytically pure sample was obtained from benzene/THF/hexanes (5/1/100). ^{1}H NMR (C_6D_6): δ 7.52 (d, 2 H), 7.31 (t, 2 H), 7.18 (t overlapped with residual C_6H_6, 1 H), 6.71 (t, 1 H), 6.32 (t, 1 H), 6.26 (d, 1 H), 6.13 (d, J = 2.99 Hz, 1 H), 5.93 (d, 1 H), 5.30 (d, J = 3.01 Hz, 1 H), 5.18 (d, J = 2.77 Hz, 1 H), 4.42 (d, J = 2.74 Hz, 1 H), 3.59−3.31 (m, 2 H), 3.20 (s, 3 H), 2.72−2.07 (m, 14 H), 1.99−1.78 (m, 2 H), 1.69−1.26 (m, 5 H). Anal. Calcd for $C_{35}H_{39}NOZr$: C, 72.37; H, 6.77; N, 2.41. Found: C, 72.14; H, 6.61; N, 2.47.

^{1}H NMR of *rac*-28g and *rac*-31g (Scheme 7). A 5 mm NMR tube was charged with *rac*-**25g** (11.4 mg, 0.0196 mmol) and ∼0.5 mL of C_6D_6. After complete dissolution of *rac*-**25g**, 1.3 equiv of ethylene carbonate (2.3 mg, 0.0263 mmol) was added to the orange solution. In <1 h, *rac*-**25g** was consumed and a pale yellow solution containing *rac*-**28g**/*rac*-**31g** (84/16, 68% de) was obtained as shown by its ^{1}H NMR. Selected ^{1}H NMR resonances of *rac*-**31g** (C_6D_6): δ 6.63 (aromatic d, J = 7.93 Hz, 1 H), 5.82 (C*H* indenyl d, J = 2.44 Hz, 1 H), 5.13 (C*H* indenyl d, J = 2.38 Hz, 1 H), 4.91 (C*H* methine d, J = 8.05 Hz, 1 H). Similar treatment of *rac*-**25g** (11.7 mg, 0.0201 mmol) with 9.3 equiv of ethylene carbonate (16.4 mg, 0.186 mmol) gave, after <10 min, a 94/6 (88% de) *rac*-**28g**/*rac*-**31g** ratio. ^{1}H NMR of *rac*-**28g** (C_6D_6): δ 7.54 (d, 2 H), 7.24 (t, 2 H), 7.15 (aromatic m overlapped with C*H* indenyl resonance and residual C_6H_6, 2 H), 6.96 (t, 1 H), 6.70 (d, J = 7.74 Hz, 1 H), 6.57 (d, J = 6.75 Hz, 1 H), 6.47 (t, 1 H), 5.55 (d, J = 2.47 Hz, 1 H), 5.44 (d, J = 2.94 Hz, 1 H), 5.13 (d, J = 2.56 Hz, 1 H), 5.03 (C*H* methine dd, J = 11.3 Hz, 1 H), 3.90−3.72 (m, 2 H), 3.53 (OCH_3 s overlapped with m, 3 H), 3.48−3.04 (m overlapped with ethylene carbonate resonance, 4 H), 2.94−2.56 (m, 8 H), 2.47−2.06 (m, 9 H), 1.60−1.09 (m, 6 H).

(±)-23 (*t*-BuNHCOCH(Ph)NH(*o*-anisyl)). A 100 mL Schlenk flask was charged with **13b** (217 mg, 0.5 mmol), benzene (20 mL), and *t*-BuNCO (69 μL, 0.6 mmol). After stirring overnight, the solution was treated with MeOH (1 mL) and stirred for 4 h. The solvent was removed, and the residue was treated with CH_2Cl_2 (20 mL) and filtered. The residue from the filtrate was spotted on a Chromatotron plate and eluted with ethyl acetate/hexanes (2/1); evaporation of solvent afforded a white solid that was washed with hexanes. Yield: 78 mg (52%). ^{1}H NMR ($CDCl_3$): δ 7.48−7.31 (m, 5 H), 6.89−6.76 (m, 3 H), 6.73 (br s, 1 H), 6.58 (d, 1 H), 5.01 (v br s, 1 H), 4.54 (s, 1 H), 3.82 (3 H, s), 1.31 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 170.3, 147.0, 139.1, 136.6, 128.9, 128.1, 127.2, 121.0, 118.4, 111.5, 109.2, 65.1, 55.2, 50.9, 28.4. Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.69; H, 7.80; N, 8.97.

(±)-24 (H_2NCOCH(Ph)NH(*o*-anisyl)). Preparation of (±)-**24** was carried out as described above for (±)-**23**, except that Me_3SiNCO (160 μL, 1.0 mmol) replaced *t*-BuNCO. The residue from the filtrate was spotted on a Chromatotron plate and eluted with ethyl acetate/hexanes (7/1); evaporation of solvent afforded a white solid that was washed with hexanes. Yield: 54 mg (42%). ^{1}H NMR ($CDCl_3$): δ 7.53−7.36 (m, 5 H), 6.89−6.66 (m, 3 H), 6.61 (br s, 1 H), 6.58 (d, 1 H), 5.53 (br s, 1 H), 4.71 (s, 1 H), 3.82 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 174.1, 147.1, 138.5, 136.3, 129.2, 128.6, 127.4, 121.2, 118.7, 111.3, 109.5, 64.1, 53.4. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.24; H, 6.29; N, 10.87.

(*S*)-(+)-19 (*t*-BuNHCOCH(Ph)NHPh) (Scheme 8). A solution containing (*S*,*S*)-[EBTHI]ZrMe_2 (579 mg, 1.5 mmol) and THF (10 mL) was cooled to −78 °C and treated with TfOH (133 μL, 1.5 mmol). The pale yellow solution was warmed to room temperature and stirred for 1 h followed by recooling to −78 °C. In a separate flask BuLi (2.0 M, 750 μL, 1.5 mmol) was added to a cold (0 °C) Et_2O (5 mL) solution containing $PhCH_2NHPh$ (275 mg, 1.5 mmol), and the solution was stirred for 5 min. The $PhCH_2NLi(Ph)$ was transferred by cannula to the (*S*,*S*)-[EBTHI]ZrMe(OTf), and the solution was stirred for 0.5 h at −78 °C and then warmed to room temperature and stirred overnight. Neat *t*-BuNCO (177 μL, 1.5 mmol) was added, and the resulting red solution was stirred for 1 h and then treated with MeOH (1 mL). The solvent was removed, the residue was treated with CH_2Cl_2 (20 mL), and the solution was filtered. The residue from the filtrate was spotted on a Chromatotron plate and eluted with ethyl acetate/hexanes (7/1); evaporation of solvent afforded a white solid that was washed with hexanes (yield 264 mg (62%), 92% ee, hexane/2-propanol (90/10), flow rate 0.6 mL/min, retention time (min) 14.1 and 21.8, $[\alpha]_D$ = +76.5° (c = 0.780)). ^{1}H and ^{13}C NMR data for (±)-**19** were reported earlier;[9] (*S*)-(+)-**19** was >98% pure by ^{1}H NMR.

(*S*)-(+)-20 (H_2NCOCH(Ph)NHPh) (Scheme 8) was prepared like (*S*)-(+)-**19**, except that neat Me_3SiNCO (262 μL, 1.5 mmol) replaced *t*-BuNCO. The residue was spotted on a Chromatotron plate and eluted with hexanes/ethyl acetate (2/1); after evaporation, the white solid was washed with hexanes (yield 173 mg (51%), 80% ee, hexane/2-propanol (85/15), flow rate 0.6 mL/min, retention time (min) 37.6 and 48.2, $[\alpha]_D$ = 146.9° (c = 0.770)). ^{1}H and ^{13}C NMR data for (±)-**20** were reported earlier;[9] (*S*)-(+)-**20** was >98% pure by ^{1}H NMR.

(*S*)-(−)-23 (*t*-BuNHCOCH(Ph)NH(*o*-anisyl)) (Scheme 8) was prepared like (*S*)-(+)-**19b**, but with the following modifications. A solution containing $PhCH_2NH$(*o*-anisyl) (69 mg, 0.323 mmol) and Et_2O (5 mL) was cooled to 0 °C and treated with BuLi (1.6 M, 200 μL, 0.320 mmol), and the solution was stirred for 5 min. The $PhCH_2NLi$-(*o*-anisyl) was transferred by cannula to a cold (−40 °C) solution containing (*S*,*S*)-[EBTHI]ZrMe(OTf) (169 mg, 0.325 mmol) in THF (5 mL); the flask that contained $PhCH_2NLi$(*o*-anisyl) was rinsed with Et_2O (2 mL). After 5 min at −40 °C and overnight at room temperature, the orange-red solution was treated with neat *t*-BuNCO (46 μL, 0.400 mmol) and stirred overnight. The pale yellow solution was treated with MeOH (1 mL) and stirred for 4 h (yield 30 mg (31%), >99% ee, hexane/ethanol (95/5), flow rate 0.9 mL/min, retention time (min) 8.0 and 10.4, $[\alpha]_D$ = −40.0 (c = 0.123)). (*S*)−(−)-**23** was >98% pure by ^{1}H NMR.

(*S*)-(−)-24 (H_2NCOCH(Ph)NH(*o*-anisyl)) (Scheme 8) was prepared in the same way as (*S*)-(−)-**23**, except that neat Me_3SiNCO (54 μL, 0.400 mmol) replaced *t*-BuNCO (yield 22 mg (25%), 98% ee, hexane/ethanol (80/20), flow rate 0.8 mL/min, retention time (min) 16.6 and 19.5, $[\alpha]_D$ = −100.9° (c = 0.095)). (*S*)-(−)-**24** was >98% pure by ^{1}H NMR.

Compound *rac*-25b was prepared like *rac*-**25g**, but with the following modifications. $PhCH_2NH$(*o*-anisyl) (175 mg, 0.820 mmol) replaced $Ph(CH_2)_2NH$(*o*-anisyl). After the $PhCH_2NLi$(*o*-anisyl) was transferred by cannula to the *rac*-[EBTHI]ZrMe(OTf), the resulting yellow solution was warmed to room temperature and the solution turned red. After 1 h, the solvent was evaporated and the orange red solid was dissolved in benzene (25 mL); the solution was filtered by cannula, the solid was washed with benzene (2 × 5 mL), and the filtrate was evaporated to yield crude *rac*-**25b**. ^{1}H NMR of the product mixture showed only one diasteromer. Yield: 440 mg (85% pure by ^{1}H NMR). An analytically pure sample was obtained from benzene/THF/hexanes (5/1/100). ^{1}H NMR (C_6D_6): δ 7.48 (d, 2 H), 7.39 (t, 2 H), 7.07 (t, 1 H), 6.98 (t, 1 H), 6.68 (d, 1 H), 6.53 (t, 1 H), 6.48 (d, 1 H), 5.41 (d, J = 3.07 Hz, 1 H), 5.18 (d, J = 2.80 Hz, 1 H), 4.84 (d, J = 3.09 Hz, 1 H), 4.70 (d, J = 2.76 Hz, 1 H), 3.78 (s, 1 H), 3.27 (s, 3 H), 2.67−1.94 (m, 15 H), 1.69−1.18 (m, 5 H).

Compound *rac*-25a was prepared like *rac*-**25b**, but with the following modifications. $PhCH_2NHPh$ (59 mg, 0.320 mmol) replaced $PhCH_2NH$(*o*-anisyl). After the $PhCH_2NLiPh$ was transferred by cannula to the *rac*-[EBTHI]ZrMe(OTf), the yellow solution turned red as it warmed to room temperature. After 1 h, the solvent was evaporated to yield an orange solid. Compound *rac*-**25a** was ∼38% pure (the remaining 62% was a mixture of LiOTf, THF, and ca. 10−15% $PhNHCH_2Ph$) and was used without further purification. Selected ^{1}H NMR resonances of *rac*-**25a** (THF-d_8): δ 6.28 (aromatic t, 1 H), 5.51 (C*H* indenyl d, J = 2.49 Hz, 1 H), 5.40 (C*H* indenyl d, J = 2.55 Hz, 1 H), 5.26 (C*H* indenyl d, J = 2.61 Hz, 1 H), 4.28 (C*H* indenyl d, J = 2.61 Hz, 1 H), 3.55 (C*H* methine s, 1 H).

^{1}H NMR of *rac*-35 (Scheme 9). A 5 mm NMR tube was charged with *rac*-**25b** (12.0 mg, 0.0210 mmol), THF-d_8 (∼0.5 mL), and 4.1 equiv of neat *t*-BuNCO (6.2 mg, 0.0625 mmol); after 6 days, *rac*-**25b** was consumed. Selected ^{1}H NMR resonances of *rac*-**35** (THF-d_8): δ 7.47 (aromatic d, 2 H), 6.53 (aromatic t, 1 H), 6.28 (aromatic d, 1 H), 5.98 (aromatic d, 1 H), 5.88 (C*H* indenyl d, J = 2.61 Hz, 1 H), 5.84 (C*H* indenyl d, J = 2.58 Hz, 1 H), 5.80 (C*H* indenyl d, J = 2.65 Hz, 1 H), 5.61 (C*H* indenyl d, J = 2.70 Hz, 1 H), 5.26 (C*H* methine s, 1

H), 4.33 (OCH_3 s, 3 H), 1.19 (*t*-Bu s, 9 H). The minor diastereomer *rac*-**37** was not detected by ^{1}H NMR.

(*S*)-(+)-19 (*t*-BuNHCOCH(Ph)NHPh) (Scheme 10) was prepared like (*S*)-(+)-**19**, but with the following modifications. The solution that contained (*S*,*S*,*R*)-**25a** (0.320 mmol, 20 mM) was treated with a dilute benzene solution of *t*-BuNCO (0.256 mmol, 32 mM); methanolysis and workup gave (*S*)-(+)-**19** in 45% yield (36% ee, hexane/2-propanol (92/8), flow rate 0.85 mL/min, retention time (min) 11.8 and 20.3).

^{1}H NMR of *rac*-38 and *rac*-39 (Scheme 11). A 5 mm NMR tube was charged with *rac*-**25g** (11.7 mg, 0.0201 mmol) and THF-d_8 (∼0.5 mL). After complete dissolution of *rac*-**25g**, 26 equiv of neat *t*-BuNCO (45 mg, 0.454 mmol) was added to the orange solution. In <5 min, the *rac*-**25g** was consumed and a 95/5 (90% de) *rac*-**38**/*rac*-**39** product ratio was shown by ^{1}H NMR. Selected ^{1}H NMR resonances of *rac*-**38** (THF-d_8): δ 7.47 (d, J = 7.14 Hz, 2 H), 7.12 (t, 2 H), 7.03 (t, 1 H), 6.94 (d, 1 H), 6.75 (d, 1 H), 6.38 (t, 1 H), 6.17 (d, 1 H), 5.69 (apparent q, two overlapping d from C*H* indenyl resonances, J = 2.71 Hz, and J = 2.71 Hz, 2 H), 5.57 (d, J = 2.72 Hz, 1 H), 5.45 (d, J = 2.70 Hz, 1 H), 4.44 (C*H* methine dd, J = 7.68 Hz, 1 H), 4.23 (OCH_3 s, 3 H), 3.46−3.40 (dd, 1 H), 1.41 (t-Bu s, 9 H). Similar treatment of *rac*-**25g** (10.2 mg, 0.0176 mmol) with 1.3 equiv of *t*-BuNCO (2.2 mg, 0.0222 mmol) in THF-d_8 gave, after 3 h, a 64/36 (28% de) *rac*-**38**/*rac*-**39** product ratio. Selected ^{1}H NMR resonances of *rac*-**39** (THF-d_8): δ 7.51 (aromatic d overlapped with *rac*-**38** d, J = 7.36 Hz, 2 H), 5.92 (C*H* indenyl *d*, J = 2.86 Hz, 1 H), 5.79 (C*H* indenyl d, J = 2.50 Hz, 1 H), 5.46 (C*H* indenyl d, J = 2.71 Hz, 1 H), 4.34 (OCH_3 s, 3 H), 1.27 (*t*-Bu s, 9 H).

^{1}H NMR of *rac*-40 (Reaction 16). A 5 mm NMR tube was charged with *rac*-**25a** (∼11 mg, 0.02 mmol), THF-d_8 (∼0.5 mL), and neat Me_3SiNCO (2.8 mg, 0.024 mmol). After 5 min, the ^{1}H NMR showed *rac*-**40** (ca. 90% de). Selected ^{1}H NMR resonances of *rac*-**40** (THF-d_8): δ 7.47 (aromatic d, 2 H), 6.13 (C*H* indenyl d, 1 H), 5.93 (C*H* indenyl d, 1 H), 5.88 (aromatic d, 2 H), 5.56 (C*H* indenyl resonance overlapped with C*H* methine s, 2 H), 5.24 (C*H* indenyl d, 1 H), 0.02 (s, 9 H).

^{1}H NMR of *rac*-41a (Reaction 16). A 5 mm NMR tube was charged with *rac*-**25a** (∼11 mg, 0.02 mmol) and ∼0.5 mL of THF-d_8. After complete dissolution of *rac*-**25a**, 4.2 equiv of 2-butyne (4.5 mg, 0.083 mmol) was added to the orange-red solution. After 24 h, 2-butyne was consumed and the red solution showed *rac*-**41a** in 24% de.

In a similar fashion, a 5 mm NMR tube was charged with *rac*-**25a** (∼11 mg, 0.02 mmol) and neat 2-butyne (∼0.5 mL, 6.4 mmol). After standing overnight, the excess 2-butyne was evaporated and the orange residue was dissolved in THF-d_8. The ^{1}H NMR showed *rac*-**41a** in >99% de. Selected ^{1}H NMR resonances of *rac*-**41a** (THF-d_8): δ 6.79 (C*H* indenyl d, 1 H), 5.92 (C*H* indenyl d, 1 H), 5.78 (aromatic d, 2 H), 5.34 (C*H* indenyl d, 1 H), 5.05 (C*H* indenyl d, 1 H), 4.89 (C*H* methine br s, 1 H), 1.92 (CH_3 s overlapped with indenyl resonances), 1.24 (CH_3 s overlapped with indenyl resonances).

Similar treatment of *rac*-**25a** (0.02 mmol) with *n* equiv of 2-butyne (mg, mmol) gave the following de's of *rac*-**41a**: 4.2 equiv (4.5 mg, 0.083 mmol), 28% de; 13 equiv (14 mg, 0.26 mmol), 46% de; 32 equiv (35 mg, 0.64 mmol), 60% de.

Preparation of 44. A solution containing Cp_2ZrMe_2 (3.02 g, 12 mmol) and THF (40 mL) was cooled to −78 °C and treated with TfOH (1.06 mL, 12 mmol). The pale yellow solution was warmed to room temperature, stirred for 1 h, and again cooled to −78 °C. In a separate flask BuLi (2.0 M, 6 mL) was added to a cold (0 °C) Et_2O (40 mL) solution containing (*o*-anisyl)CH_2NHCH_2Ph (2.73 g, 12 mmol); the solution was stirred for 5 min. The pink solution containing (*o*-anisyl)-CH_2N(Li)CH_2Ph was transferred by cannula to the Cp_2ZrMe(OTf), stirred for 0.5 h at −78 °C, and warmed to room temperature. The solvent was evaporated from the red solution, the residue was treated with benzene (75 mL), the solution was filtered by cannula, and the residue was washed with benzene (25 mL). The filtrate was evaporated, and the residue was treated with hexanes (100 mL) to give a tan precipitate. The solid was filtered by cannula, washed with hexanes (2 × 30 mL), and dried overnight under vacuum. Yield: 3.43 g (62%). ^{1}H NMR (C_6D_6): δ 7.39 (d, 1 H), 7.31−7.09 (m, 7 H), 6.59 (d, 1 H), 5.75 (Cp s, 10 H), 4.53 (CH_2 s, 2 H), 4.35 (CH_2 s, 2 H), 3.25 (OCH_3 s, 3 H), 0.32 (ZrCH_3 s, 3 H). ^{13}C NMR (C_6D_6): δ 158.1, 142.4, 129.5, 128.6, 128.4 (DEPT), 128.0 (DEPT), 127.4 (DEPT), 126.5, 120.4, 110.2, 110.0 (Cp), 59.5 (*C*H_2, DEPT), 54.5 (O*C*H_3, DEPT), 54.0 (*C*H_2, DEPT), 20.9 (Zr*C*H_3, DEPT). Anal. Calcd for $C_{26}H_{29}NOZr$: C, 67.49; H, 6.32; N, 3.03. Found: C, 67.20; H, 6.14; N, 2.99.

^{1}H and ^{13}C NMR of 45 (Scheme 14). A 5 mm NMR tube was charged with **44** (50 mg, 0.108 mmol) and C_6D_6 (∼0.5 mL). The sample was sealed, and the tan solution was heated to 80 °C for 1 h to give a deep red solution. ^{1}H NMR showed the major (*E*)-**45** (84%) and minor (*Z*)-**45** (16%) isomers. ^{1}H NMR of (*E*)-**45** (C_6D_6): δ 8.09 (C*H*═N s, 1 H), 7.43 (d, 1 H), 7.23−7.07 (aromatic m overlapped with aromatic resonances of (*Z*)-**45**), 5.71 (Cp s, 10 H), 4.56 (CH_2 s, 2 H), 3.69 (OCH_3 s, 3 H). Selected ^{1}H NMR of (*Z*)-**45** (C_6D_6): δ 7.95 (C*H*═N s, 1 H), 5.85 (Cp s, 10 H), 4.52 (CH_2 s, 2 H), 3.79 (OCH_3 s, 3 H). ^{13}C NMR of (*E*)-**45** (C_6D_6): δ 176.0 (CH═N, DEPT), 142.5, 141.7, 140.3, 129.5, 128.8, 128.2 (DEPT), 128.1 (DEPT), 127.7, 127.1, 123.2, 111.0 (Cp of (*Z*)-**45**), 109.9 (Cp of (*E*)-**45**), 61.6 (*C*H_2, DEPT), 59.2 (O*C*H_3, DEPT).

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