Asymmetric Formation of α-Amino Acid Esters through Dynamic Kinetic Resolution: A Cyclic Carbonate as an Optically Active CO_2 Synthon

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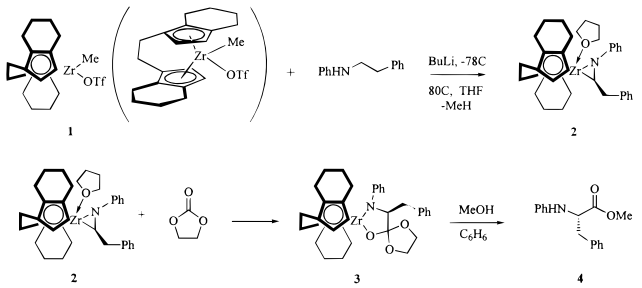
We have reported the conversion of *N*-aryl benzyl and phenethylamines into α-amino acid esters utilizing ethylene carbonate as a CO_2 equivalent.[1,2] Use of the optically active ethylenebis(tetrahydroindenyl) (EBTHI) zirconium complex **1** resulted in product formation in >98% ee (Scheme 1). These experiments revealed that the ring carbons of zirconaaziridines[3] such as **2** are configurationally labile; thus, the optical purity of the products depended on the concentration of ethylene carbonate.[1b,c]

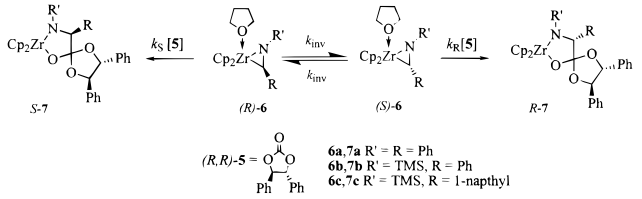
The utility of the transformation in Scheme 1 is limited by the stoichiometric use of the optically active EBTHI complex. We now report that asymmetric induction is achieved when an enantiopure carbonate is allowed to react with a racemic zirconaaziridine derived from the inexpensive Cp_2ZrCl_2. Cyclic carbonates with C_2 symmetry[4] are attractive as optically active CO_2 synthons because the required vicinal diols are available in high yield and optical purity from the Sharpless dihydroxylation.[5] For our initial investigation we have used 1,2-diphenylethylene carbonate (**5**), because both enantiomers of the corresponding diol are easily prepared on a kilogram scale[5b] and are commercially available.

The stereochemical outcome of Scheme 2 will be determined by Curtin−Hammett kinetic considerations similar to those previously applied[1b] to Scheme 1. The kinetic system in Scheme 2 displays two well-defined boundaries. If (a) the two enantiomers *(R)*-**6** and *(S)*-**6** are not converting on the time scale of the insertion (i.e., $k_S[\mathbf{5}]$, $k_R[\mathbf{5}] \gg k_{inv}$), the reaction can be run as a kinetic resolution. However, the yield of optically pure product is limited to 50%, and the enantiomeric purity of the product is greatly affected by the extent of conversion. If (b) the enantiomers are rapidly interconverting relative to insertion (i.e., $k_S[\mathbf{5}]$, $k_R[\mathbf{5}] \ll k_{inv}$), the reaction can be run to 100% conversion, and the product ratio will equal the relative rates of insertion. The latter extreme (condition b) is termed a dynamic kinetic resolution (DKR)[6] and avoids limitations on yield and conversion.

Scheme 1



Scheme 2



We have determined the configurational lability, necessary for DKR, of the ring carbons in zirconaaziridines derived from Cp_2ZrCl_2. To obtain a diastereoexcess from treatment of a racemic mixture with a stoichiometric amount of an optically active reagent, the enantiomers of the racemate must not only interconvert but also react at different rates.[7] The insertion of **5** into the racemic zirconaaziridines **6** is such a case. Addition of 1.2 equiv of **5** to **6a** in C_6D_6 at room temperature resulted in a 24% de. Repeating this experiment with **6b** gave **7b** in 25% de, indicating that epimerization was competitive with insertion.

A Curtin−Hammett kinetic analysis[8] shows that, at low conversion, the product ratio *R*-**7**/*S*-**7** will be equal to k_R/k_S. This ratio, termed the selectivity factor *s*, can be more accurately determined with the use of a test developed by Hoffmann.[7] When a racemic zirconaaziridine is treated with a racemic C_2 symmetric carbonate, the ratio of diastereomeric products is equal to k_R/k_S (Scheme 3). Thus, when **6a** is allowed to react with racemic **5**, the de is 76%, indicating an *s* of 7.3. When **6b** is treated in the same manner, the de is 90%, indicating a rate constant ratio *s* of 19. The data in Table 1 show that the diastereodifferentiation is good for zirconaaziridines with aromatic substituents. Importantly, this test is independent of the rate of epimerization of the zirconaaziridine.

In order for DKR to be possible, inversion at the ring carbon must be much faster than insertion. Unfortunately, when **5** is added all at once to **6** at room temperature the maximum selectivity is not realized. For example, rapid addition of **5** to **6b** provides the product metallacycle in only 22% de.

However, insertion can be kept much slower than epimerization if **5** is added to **6** slowly via syringe pump. Thus, syringe pump addition of a solution of **5** to **6b** over the period of 4 h forms the product metallacycle **7b** in 90% de at 100% conversion. The same experiment repeated with **6a** results in a 76% de. As Table 2

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Scheme 3

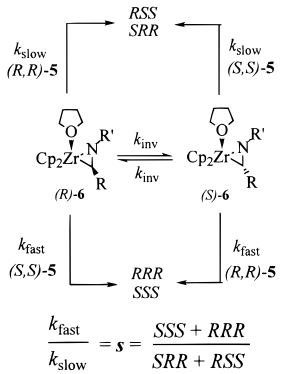


Table 1. Selectivity Factors *s* Determined from the Reaction of Complexes **6** and **9** with (*rac*)-5 at Room Temperature (Scheme 3)

complex	de[a] (%)	*s*	complex	de[a] (%)	*s*
6a	76	7.3	**9e**	82	10.1
6b	90	19	**9f**	21	1.5
6c[b]	>95	>39	**9g**	45	2.6
9d	74	6.7			

[a] Determined by integration of the ^{1}H NMR Cp resonances. [b] Determined by the generation of **6c** in the presence of (*rac*)-**5**.

Table 2. Results of Syringe Pump Addition[a] of (*R,R*)-**5** to **6** and **9**

complex	de (obs)[b] (%)	de (predicted) (%)	complex	de (obs)[b] (%)	de (predicted) (%)
6a	76	76	**9e**	77	82
6b	90	90	**9f**	18	21
9d	71	74			

[a] 0.6 M (*R,R*)-**5** in C_6H_6 added to 0.3 M zirconium complex in C_6H_6 via syringe pump over the period of 4−4.5 h at room temperature. [b] Determined by integration of the ^{1}H NMR Cp resonances.

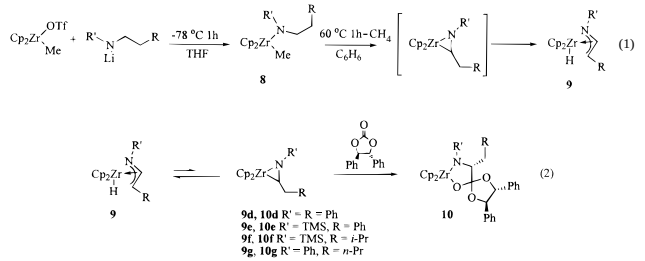
Table 3. Yields and ee's of Amino Acid Methyl Esters Prepared by Hydrolysis and Transesterification of Complexes **7** and **10** (eq 3)

α-amino ester	ee (%)[a]	yield[b]	α-amino ester	ee (%)[a]	yield[b]
12a	98.6	57	**12d**	99.1	47
12b	96	69	**12e**	>95	30

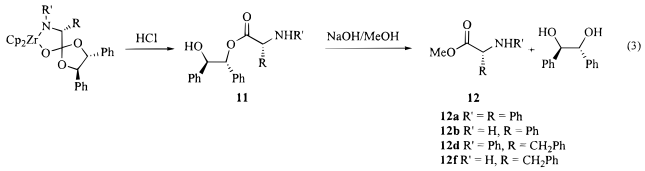
[a] Determined by ^{1}H NMR analysis of the (+)-MTPA[13a,14] amides except for **12a** and **12d** which were determined by HPLC separation on a Bakerbond OD chiralcel column. [b] Yields correspond to overall yields based on (*R,R*)-**5**. Configurations of **12a,b,e** were verified by comparison of ^{1}H NMR spectra of (+)-MTPA amides or HPLC retention times with those of authentic samples.

shows, these values are in good agreement with those predicted by the Hoffmann test, showing that dynamic kinetic resolution conditions have been reached.

Attempting to generate zirconaaziridines containing β-hydrogens leads instead to η^3-1-azaallyl zirconocene hydride complexes of the type **9** (eq 1). A similar result has been observed by Whitby and co-workers, who noted that the azaallyl complex reacted to give products expected from a zirconaaziridine.[9,10] Our complexes **9** also react like zirconaaziridines to give the expected metallacycles, implicating an equilibrium between the azaallyl form and the zirconaaziridine (eq 2). The Hoffmann test results for **9e** indicate a maximum de of 82% for the reaction of **9e** with *(R,R)*-**5**. Syringe pump addition of carbonate *(R,R)*-**5** to a solution of **9e** results in a product having 77% de (Table 2), showing that the DKR limit is nearly reached. Similarly, syringe pump addition of *(R,R)*-**5** to **9d** produces the product **7d** with a 71% de, approaching the maximum value predicted by the Hoffmann test.



Protonolysis of the metallacycles formed in the above reactions gives 2-hydroxyethyl esters **11** (eq 3). These compounds can be obtained in >95% de by recrystallization or by chromatography. The 2-hydroxy group facilitates hydrolysis,[11] so that the esters can be transesterified to the methyl esters under mild conditions. Treatment with catalytic amounts of NaOH in MeOH provides the methyl esters in quantitative yield after 15 min at room temperature.[12] Likewise, NaOH/H_2O treatment gives the optically active α-amino acids. The transesterification occurs without significant racemization[13] (Table 3), and the optically active diol is recovered.



The reactions we report here permit the direct asymmetric carboalkoxylation of the α position of an amine with an optically active CO_2 equivalent. Future experiments will attempt to determine the rates and mechanism of the interconversion (k_{inv}) of enantiomeric zirconaaziridines.

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Supporting Information Available: Spectroscopic and analytical data for complexes **6**−**10** and amino acid esters **11** and **12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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