STUDIES DIRECTED TOWARD THE ENANTIOSELECTIVE ADDITION OF REFORMATSKY REAGENTS TO ALDIMINES

By

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ABSTRACT

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Interest in ß-amino esters and ß-lactams has grown significantly due to their applications in the synthesis of compounds of pharmaceutical interest. Examples include ß-lactam antibiotics such as the penicillin and carbapenem families. Because ß-lactams and ß-amino esters share a common pathway, methods to prepare either are often contaminated and thus complicated by the formation of the other. We have developed convenient and highly controllable method which can afford either product cleanly.

Acknowledgements

In the name of Allah, Most Gracious, Most Merciful. All praise and thanks is due to Him first and foremost. I thank Him for giving me a mind to think with and a heart to believe with.

I am especially grateful to my parents, Ekram and Susan, for their endless love and support. I would also like to thank my brother Omar, my sister Jailan, my brother-in-law Abdul-Majeid, and my beautiful niece Noor. It is their love and support that inspires me to succeed. I owe so much to my friends and family for believing in me and encouraging me throughout my life, and especially through my college years. I am thankful to each and every one of you.

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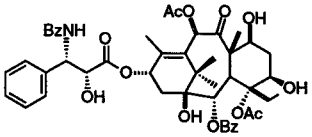
Introduction

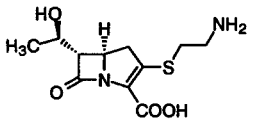
ß-Amino esters and their derivatives are an important class of compounds of pharmaceutical interest. The application of these compounds varies from their use in cancer chemotherapy to antiobiotic drugs.[1] The compound taxol is a pertinent example. It is considered to be one of the most active agents in treating breast cancer.[2] Isolated from the bark of the ewe tree, *Taxus brevifolia*, taxol contains a vital ß-amino ester moiety that is required for its activity (Figure 1).[2]

Figure 1. Taxol



Other important compounds include the ß-lactam antibiotics, examples of which are the penicillin and carbapenem families. Within the carbapenem class, thienamycin is typical. A naturally occurring bicyclic ß-lactam antibiotic[1] (Figure 2), the ß-lactam moiety is required for its antimicrobial activity.

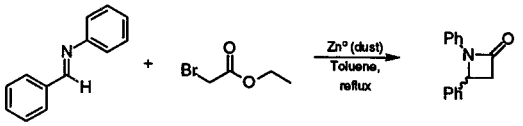
Figure 2. Thienamycin



A convenient method to prepare ß-amino esters and ß-lactams[3] is the Reformatsky reaction with imines. Because they share a common pathway they are often contaminated by the formation of the other. A more controllable method to afford either the ß-lactam or ß-amino ester products cleanly via this simple reaction is needed.

Reformatsky reagents are organozinc reagents similar to the organomagnesium Grignard reagents. Imines are electrophilic species that are susceptible to nucleophilic attack. This was first reported by Gilman and Speeter in 1943.[4] Scheme 1 illustrates their method of generating the Reformatsky reagent *in situ* using zinc dust and ethlyl bromoacetate (**2**), which then reacted with an imine (**1**) in refluxing toluene to generate the ß-lactam (**3**) in 56% yield.

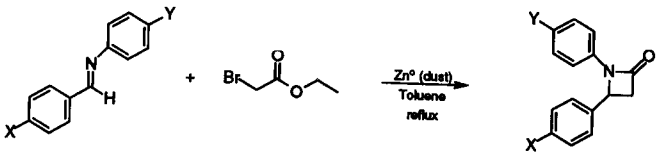
Scheme 1



1 **2** **3**

Mohan and co-workers extended this work by reacting substituted aromatic imines with reformatsky reagents.[5] The Reformatsky reagent, generated *in situ*, was reacted with the various substituted aromatic imines (**4**) to generate ß-lactams (**5**) in 54%- 70% yield (Scheme 2).

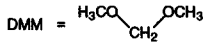
Scheme 2



4 2 5

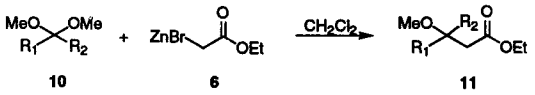
It was observed that having a nitro group substituted on the phenyl ring of the nitrogen (position Y) on the imine inhibited ß-lactam formation, affording only a resinous material. It was concluded generally, that strongly electron withdrawing groups on imine substituent inhibited ß-lactam production. Later, Moreau and co-workers conducted a comprehensive study of the Reformatsky addition to imines.[6] They found that either ß-lactams or ß-amino esters were prepared via the Reformatsky reaction and the result was dependent primarily on reaction temperatures (Scheme 3). At room temperature they obtained a mixture of ß-lactam and ß-amino ester. In refluxing dimethoxymethane, they obtained only the ß-lactam. At -10 °C only the ß-amino ester was formed.

Scheme 3



The role of acetals turns out to be quite salient because these types of compounds can be activated toward Reformatsky reagents under certain conditions. Basile and co-workers have demonstrated that Reformatsky reagents add to acetals in the presence of Lewis acid catalysts to generate ß-methoxy esters.[7] They demonstrated that titanium tetrachloride and borontrifluoroetherate activate dimethyl acetals that would otherwise be inactive. As shown in Scheme 4, once the acetals (**10**) are activated they then react with the Reformatsky reagents (**6**) in methylene chloride to generate the ß-methoxy ester (**11**).

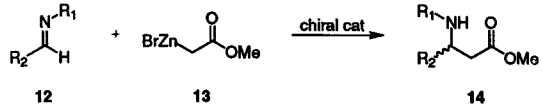
Scheme 4



We wished to develop a method of asymmetrically catalyzing the addition of Reformatsky reagents to aldimines (Scheme 5). This might be done by

reacting the Reformatsky reagent (13) with an aldimine (12) in the presence of a chiral catalyst to generate a chiral ß-amino ester (14).

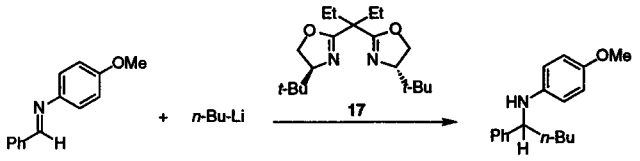
Scheme 5



12 13 14

Catalytic enantioselective additions of organometallic reagents have previously been done to generate chiral compounds.[8] Denmark and co-workers for example, have demonstrated asymmetric addition of organolithium compounds to aldimines in the presence of bisoxazolidines to form chiral amines.[9] Scheme 6 illustrates their synthesis in which they reacted a substituted imine (15) with the nucleophile *n*-butyllithium (16), in the presence of bisoxazolidine (17), a chiral ligand, to the reaction mixture to generate a chiral amine (18).

Scheme 6



15 16 18

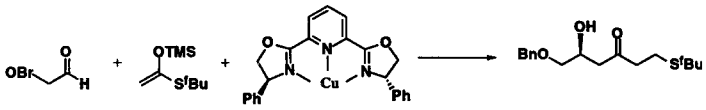
They found that using both stoichiometric and catalytic amounts of the bisoxazolidine generated chiral amines.

What has therefore been studied to a significant extent are the catalytic enantioselective additions of organometallic reagents to aldehydes, but what needs to be studied further are similar catalytic processes with imines.[9] This is exactly what we sought out to do. We knew we could potentially control what product was formed by altering the substituent on the imine. Methylene chloride, a halogenated solvent, could be used in our reactions.[7] Acetals could not be used as the solvent because they are activated by Lewis acids[7] and react with the Reformatsky reagent.

Asymmetric catalysis

Our proposed method of asymmetrically catalyzing the addition of Reformatsky reagents to aldimines involves the use of a chiral metal complex. The use of chiral C_2-symmetric metal complex catalysts for enatioselective additions has received a lot of attention. Evans and co-workers[10] document the use of bis(oxazolinyl) copper(II) complexes as effective enantioselecive catalysts. They found these catalysts are highly effective in activating specific aldehydes through bidentate coordination, thus catalyzing the aldol reaction of (benzyloxy)acetaldehyde with various silylketene acetals (Scheme 7).

Scheme 7

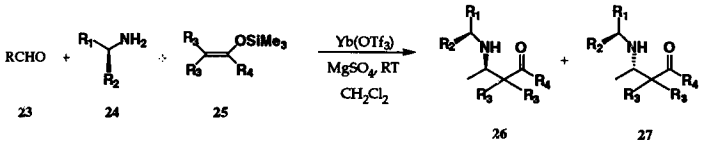


19 20 21 22

The tridentate bis(oxazolinyl)Cu(II) complex (**21**) for catalyzed the reaction of (benzyloxy)acetaldehyde (**19**) and silylketene acetal (**20**) to afford the ß-hydroxy ketone (**22**) with a 99% ee. The chiral tridentate Lewis acid catalysts consistently afforded exceptional levels of enantioselectivity.[10]

Methods using lewis acids to promote reactions between silyl enolates and imines to afford ß-amino esters have appeared recently. In an example, Cozzi and co-workers[11] affected the diastereoselective addition of silyl enolates to chiral imines in the presence of catalytic amounts of ytterbium triflate (Scheme 8).

Scheme 8



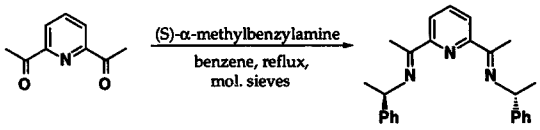
The chiral ß-amino esters that formed (**26**) and (**27**) showed the highest levels of diastereoselectivity when chiral imines derived from (S)-Valine methyl ester were used.

These reactions using Lewis acids have shown to be quite successful and this has lead us to develop them further. The catalyst we sought to develop is similar to the bisoxazoline metal catalyst (**21**) which has been used by Evans and others. Multistep procedures are typical for the synthesis of chiral bis(oxazolinyl) ligands. The preparation of our tridentate ligand, however, consists of only one step.

Synthesis of Ligand

The preparation of our tridentate ligand consists of only one step. This is done by refluxing 2,6-diacetyl pyridine (**28**) and (S)-α-methylbenzylamine in benzene to afford 2,6-bis((S)-*N* -methylbenzyl-acetimidoyl) pyridine (**29**) quantitatively (Scheme 12).

Scheme 12

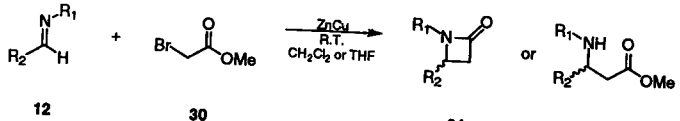


28 **29**

Results

We developed a highly predictable Imine-Reformatsky reaction at room temperature (Scheme 13).

Scheme 13



12 30 31 32

This was done by reacting a zinc-copper couple with an excess of methyl-bromoacetate (30) to generate the Reformatsky reagent. Imines with differing nitrogen substituents (12) then underwent nucleophilic attack by the Reformatsky at room temperture in methylene chloride or tetrahydrofuran. Either the ß-lactam (31) or the ß-amino ester (32) was formed, depending on the nitrogen substituent R_1 (Table 1).

Table 1: Products Formed with Different R_1 and R_2 groups

R_1	R_2	Product Observed
$PhCH_2$	isopropyl	ß-lactam
$PhCH_2$	Ph	ß-lactam
orthomethoxy-phenyl	Ph	ß-amino ester

When R_1 was a benzyl group and R_2 was an isopropyl group, only the ß-lactam was formed in quantitative yield. This can be seen by comparing the ^1H-NMR spectra of the imine starting material (Figure 3) and the ß-lactam product (Figure 4). The signals due to the imine are absent in the spectrum of the product

indicating that only the ß-lactam is present. When R_1 was a benzyl group and R_2 was a phenyl group then a quantitative yield of ß-lactam was obtained. This is evident again in the ^{1}H-NMR spectra of the imine starting material (Figure 5) and the ß-lactam product (Figure 6). Once again the signals due to the imine are absent in the spectrum of the product, therefore only the ß-lactam is present. Changing R_1 to an electron withdrawing group and keeping R_2 as a phenyl group favors the formation of the ß-amino ester. When R_1 is an orthomethoxy-phenyl we obtained a quantitative yield of the ß-amino ester. The ^{1}H-NMR spectrum of the ß-amino ester (Figure 8) does not contain any significant peaks due to the imine starting material (Figure 7).

Figure 3. *N*-isobutylidenebenzylimine

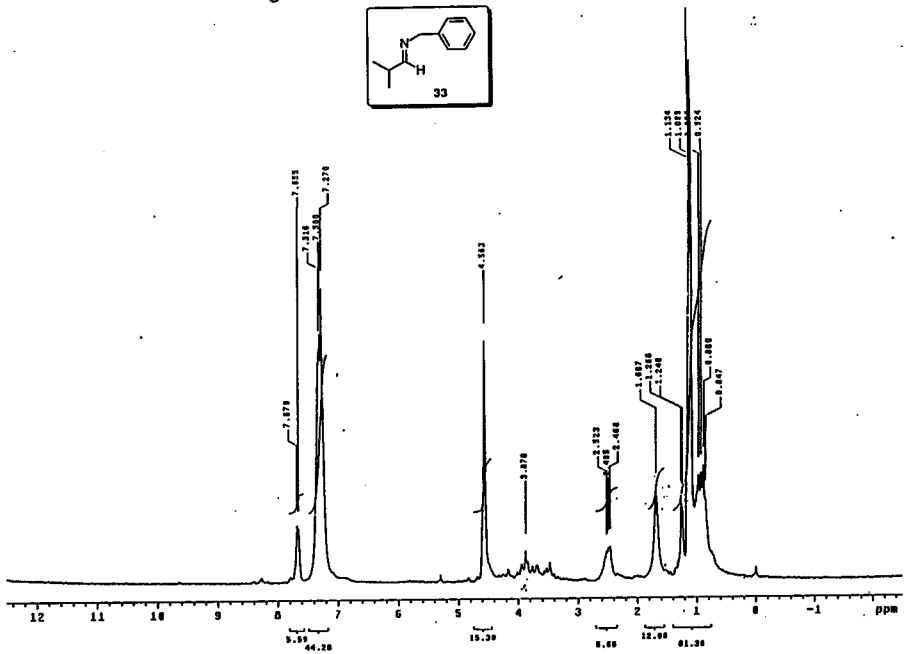
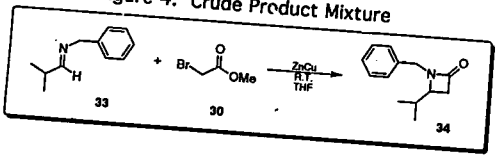


Figure 4. Crude Product Mixture



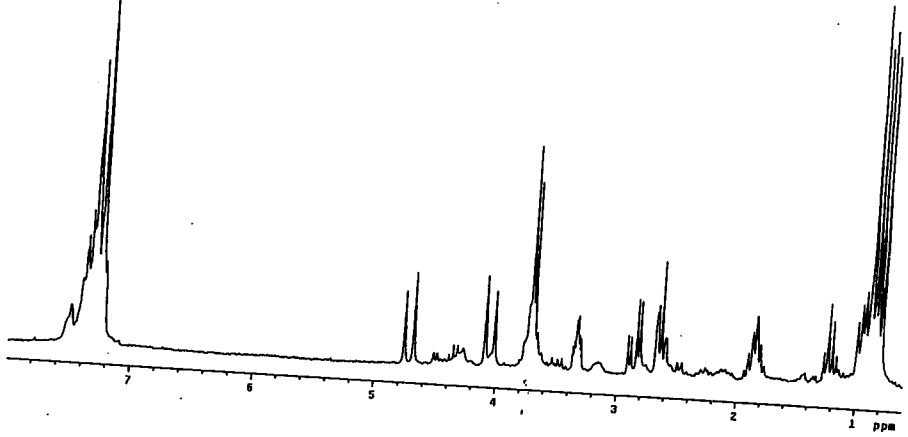


Figure 5. N-benzylidenebenzylimine

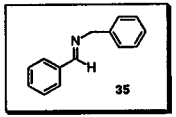


Figure 6. Crude Product Mixture

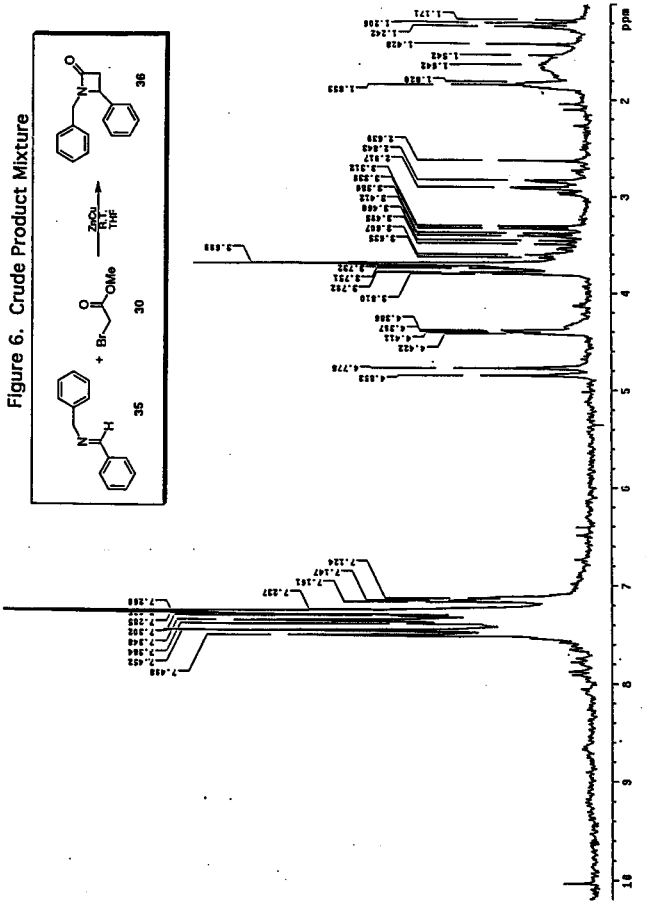


Figure 7. OMe-Imine

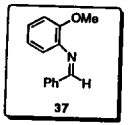
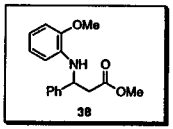


Figure 8. Crude Product Mixture



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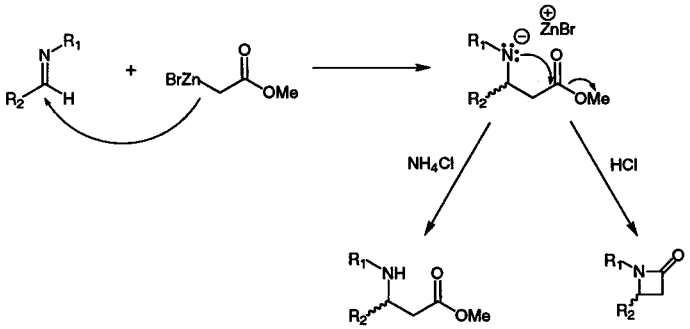
Discussion

A highly predictable imine-Reformatsky reaction at room temperature was developed, based on the nitrogen substituent of the imine. When the nitrogen substituent is an alkyl group, such as benzyl or isopropyl, only the ß-lactam is formed. If the nitrogen subst . is an electron withdrawing group such as ortho-methoxy, then only the ß-amino ester is observed.

These results can be explained by looking at the mechanism behind this reaction (Scheme 9).

Scheme 9

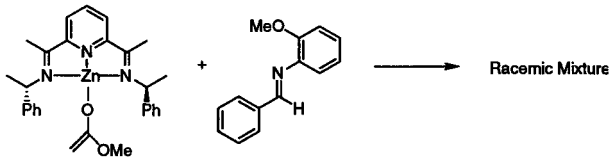


First, the substituted imine undergoes nucleophilic attack by the Reformatsky to generate a zinc amide. If R_1 is an ortho-methoxy group the electronegative oxygen has an inductive effect and decreases the nucleophicity of

the nitrogen anion. This purported reduction in nucleophicity then prevents any cyclization from occurring, thus affording only the ß-amino ester. If the R_1 substituent is an alkyl group there is no electronegative element present to reduce the nucleophicity of the nitrogen. Cyclization then occurs to generate the ß-lactam. An important point here is that the chirality is determined in the initial carbon-carbon bond forming step. That chiral center is maintained in both the ß-amino ester and ß-lactam product.

Two methods were used to attempt asymmetric addition of the Reformatsky reagents using an easily prepared tridentate ligand.[12] In the first, a stoichiometric amount of the ligand (**29**) was added with the zinc-copper couple and methylbromoacetate (**30**) along with the ortho-methoxy substituted imine (**40**) (Scheme 10).

Scheme 10



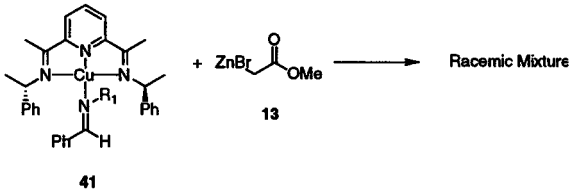
39 **40**

We anticipated that the Reformatsky that would be generated in the reaction would bind to the tridentate ligand and be trapped out as the "chiral" enolate (**39**). This "chiral" enolate complex would then act as the nucleophile to attack

the ortho-methoxyimine (**40**) and generate an enantiomeric excess of the ß-amino ester. What was observed instead was a racemic mixture.

In the second method, the ligand was then used catalytically by forming a chiral Lewis acid comlplex consisting of copper (II) metal bound to the tridentate ligand. The chiral catalyst was then reacted with the ortho-methoxy imine and the Reformatsky, generated again *in situ* (Scheme 11).

Scheme 11



It was expected that the imine would bind to the catalyst and form a complex (**41**) that would undergo nucleophilic attack by the Reformatsky (**13**) to generate the ß-amino ester in enantiomeric excess. However, once again, only a racemic mixture was obtained. An explanation for these observations can be made by examining the reaction pathways (Figure 9).

Figure 9. Mechanistic Pathways

First the imine reacts with the chiral catalyst to generate an activated complex. The activated complex can then react with the Reformatsky reagent to generate the chiral ß-amino ester. There is also a competing, uncatalyzed reaction, where the imine reacts with the Reformatsky reagent that is in low concentration since it is generated *in situ*. This uncatalyzed reaction then generates a racemic mixture.

For enantioselection to occur the catalyzed reaction should be much faster than the uncatalyzed reaction. The observed products were racemic mixtures which suggests either that the uncatalyzed reaction is in fact faster or no activated complex is formed. This later problem may be due to the floppiness of the tridentate ligand which would kinetically inhibit the formation of an activated complex necessary for the ß-amino ester production. It is also possble that the Reformatsky reagent needs to be pre-prepared and then the reactions can be run at lower temperatures.

Future Work

We have been successful in potentially predicting the formation of ß-lactams and ß-amino esters using the imine-Reformatsky reaction. This procedure can be further developed catalytically by the use of a Lewis acid catalyst. The catalyst we synthesized has the advantage of being easily prepared but it seems to be too floppy to be react with an imine to form an activated complex. A more rigid complex might solve this problem and form the activated complex necessary to react with the Reformatsky to form either the ß-lactam or the ß-amino ester. Also, different metals can be bound to the ligand for catalysis such as iron (II), ruthenium (III), or zirconium(IV).

It is also possible that the Reformatsky can be pre-prepared rather than genertaed *in situ*. This will make it possible to run the reactions at lower temperatures.

Experimental

General. Melting points were determined on a Mel-temp II® capillary melting point apparatus and are uncorrected. Low and high resolution mass spectra were performed by the Mass Spectrometry Service of the University of Illinois. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H-NMR spectra were determined at 200 MHz, and ^{13}C-NMR were determined at 50 MHz and were obtained on a Varian Gemini 2200. Spectrometer.

N-benzylidenebenzylamine (35). A solution of 2.50 g (23.6 mmol) of benzaldehyde and 2.53 g (23.6 mmol) of benzylamine in 50 mL of benzene was stirred with mol. Sieves under N_2 at room temperature. After 24 h the reaction was gravity filtered then concentrated *in vacuo* ; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 8.41 (s, 1H), 7.82-7.78 (m, 2H, J= 3Hz), 7.44-7.27 (m, 7H), 4.84 (s, 3H), 1.77 (s, 1H); 50 MHz ^{13}C-NMR ($CDCl_3$) δ 160.6, 129.3, 127.1, 127.0, 126.8, 126.5, 125.5, 63.5; IR (neat) 3056.4, 3015.4, 2830.8, 1697.4, 1641.0, 1600.0, 1579.5, 1492.3, 1446.2, 1374.4, 1307.7, 1071.8 cm^{-1}.

ß-lactam (36). In a 15 mL roundbottom flask fit with magnetic stirring and N_2 was added 0.220 g (1.44 mmol) of methyl-bromoacetate and 0.0975 g of ZnCu in 5 mL THF. To this solution 0.195 g of *N* -benzylidenebenzylimine was added dropwise. After 4 h the reaction was quenched with 1 M HCl and extracted with

2 mL (x2) portions of Et_2O. The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a light yellow oil.

ß-lactam (34). In a 15 mL roundbottom flask fit with magnetic stirring and N_2 was added 0.220 g (1.44 mmol) of methyl-bromoacetate and 0.0975 g of ZnCu in 5 mL THF. To this solution 0.160 g of *N* -isobutylidenebenzylimine was added dropwise. After 4 h the reaction was quenched with 1 M HCl and extracted with 2 mL (x2) portions of Et_2O. The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a light yellow oil.

OMe-Imine (37). Synthesis; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 8.47 (s,1H), 7.93 (q, 2H, J=3.0 Hz), 7.47 (t, 3H, J=3.0 Hz), 7.26-7.16 (m, 1H), 7.00-6.93 (m, 3H), 3.88 (s, 3H). 50 MHz ^{13}C-NMR ($CDCl_3$) δ 159.9, 150.8, 140.4, 134.9, 129.9, 127.4, 127.2, 125.2, 119.6, 118.8, 110.0, 54.3. IR (neat) 3425, 3056, 3005, 2943, 2830, 1815, 1759, 1630, 1584, 1492, 1456, 1364, 1292, 1241, 1174, 1112, 1025, 748.

***N* -isobutylidenebenzylimine (33).** In a 100 mL roundbottom flask fit with magnetic stirring and N_2 was added 2.50 g of isobutyraldehyde and 3.72 g (34.7 mmol) of benzylamine in 50 mL benzene with mol. sieves. After 24 h the reaction mixture was filtered, washing with methylene chloride, and then concentrated *in vacuo* to afford a light yellow oil. The product was purified by Kugelrohr distillation; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.67 (d,1H, J=5.0 Hz), 7.30 (t, 7H, J=4.0 Hz), 2.52-2.46 (m, 1H), 1.68 (s, 2H), 1.27-0.85 (m, 14H). 50 MHz ^{13}C-NMR ($CDCl_3$) δ 169.5, 127.3, 126.9, 126.7, 126.4, 126.3, 125.3, 63.2, 32.5, 17.7. IR (neat) 3312, 3025, 2953, 2871, 2830, 1666, 1533, 1492, 1456, 1364, 1076, 733 cm^{-1}.

2,6-Bis((S)- *N* -methylbenzylacetimidoyl) (29). In a 50 mL roundbottom flask fit wuith magnetic stirring and N_2, 1.63 g (10 mmol) of 2,6-diacetylpyridine was added with 2.42 g (20 mmol) of methylbenzylamine in 10 mL benzene with mol. sieves. After 24 h the reaction was garvity filtered then concentrated *in vacuo* to afford 3.04 g of a brown viscous oil; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 8.24 (d, 2H, J=8.0 Hz), 7.74 (t, 1H, J=8.0 Hz), 7.51-7.20 (m, 10H), 4.93 (q, 2H, J=7.0 Hz), 2.45 (s, 5H), 1.54 (d, 6H, J=7.0 Hz). 50 MHz ^{13}C-NMR ($CDCl_3$) δ 163.5, 154.9, 144.6, 135.5, 135.0,126.9, 125.3, 125.2, 123.1, 120.4, 120.0, 58.9, 58.7, 23.2, 12.1 cm^{-1}.

ß-Amino ester (38). Synthesis; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.43-7.25 (m, 5H), 6.81-6.44 (m, 4H), 5.07 (d, 1H (N-H), J=7.0 Hz), 4.89 (q, 1H, J=7.0 Hz), 3.90 (s, 3H), 3.67 (s, 3H), 2.88 (m, 2H). 50 MHz ^{13}C-NMR ($CDCl_3$) δ 171.3, 146.7, 142.1, 136.4, 128.5, 127.2, 126.0, 120.9, 116.7, 110.9, 109.2, 55.2, 54.4, 51.5, 42.6. IR (neat) 3415, 3025, 2933, 2862, 1733, 1600, 1513, 1456, 1436, 1349, 1251, 1226, 1174, 1123, 1026, 739, 703 cm^{-1}.

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