CATALYTIC METHODS FOR THE DIRECT ASYMMETRIC SYNTHESIS OF β-LACTAMS

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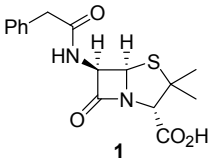
INTRODUCTION

Biological Relevance of β-Lactams

With the discovery of penicillin G **(1)** in 1928, the scientific world became keenly aware of the potent biological activity of compounds containing the β-lactam structural unit. The subsequent development of a number of classes of β-lactam antibiotics has made this family of four-membered ring amides one of the most successful classes of therapeutic agents to date. The penicillins, cephalosporins, cephamycins, carbapenems, monobactams, and monocarbams all contain the β-lactam moiety and also share similar mechanisms of action against bacteria. These compounds function by sequestering the catalytically active serine residue in bacterial transpeptidases and carboxypeptidases via a nucleophilic ring-opening reaction of the β-lactam. The ring-opening of the β-lactam releases approximately 25 kcal/mol of strain energy,[1] and forms a stable, covalently-bound acyl-enzyme adduct, which effectively inhibits these enzymes. Because the transpeptidases and carboxypeptidases are responsible for the cross-linking of peptidoglycan polymers in bacterial cell walls, a biosynthetic process that is crucial for survival of the bacteria, their inhibition by β-lactam antibiotics compromises the integrity of the cell wall, making the cell susceptible to osmotic pressure and eventually leading to cell wall rupture and death.[2,3]



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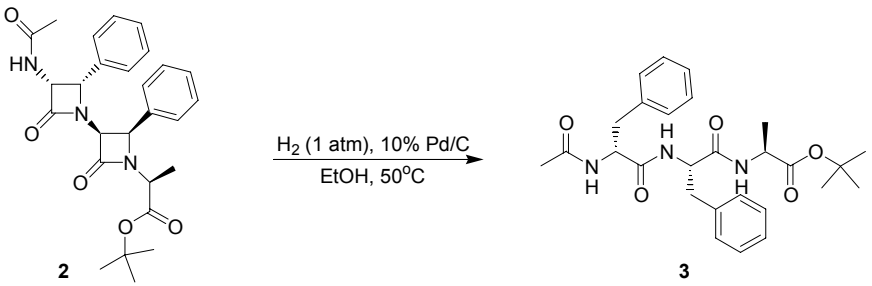
Unfortunately, the effectiveness of the β-lactam antibiotics has declined since their initial development, due to the rapid evolution of β-lactamase enzymes in some bacteria, which effectively catalyze the hydrolytic destruction of β-lactams.[4] While the synthesis of new classes of β-lactam antibiotics and the development of β-lactamase inhibitors, which are often sacrificial β-lactams, will probably prolong the lifetime of β-lactams as effective antibiotics, many scientists have begun to examine new applications of the β-lactam functionality.

One of the most promising non-antibiotic uses of β-lactams is in the inhibition of other serine protease enzymes. Cytomegalovirus protease, [5] prostate specific antigen,[6] thrombin,[7] and elastase,[8] are among the enzymes effectively inhibited by β-lactam compounds. The inhibition of these enzymes holds potential for the control of human cytomegalovirus, prostate and breast cancers, thrombotic episodes, and emphysema, respectively.

β-Lactams as Chiral Synthons

In addition to their diverse current and prospective uses as pharmaceuticals, β-lactams are of interest as synthetic building blocks. These building blocks become increasingly valuable when they are enantiomerically pure. One important application of the β-lactam moiety in synthesis involves the production of natural and non-natural α-amino acids, as well as the corresponding oligopeptides **3**. This methodology takes advantage of the fact that the β-lactam ring **2** can be selectively hydrogenolyzed and opened under mild conditions when an aryl group is α to the ring nitrogen, thus rendering the ring C-N bond benzylic (Scheme 1).[9]

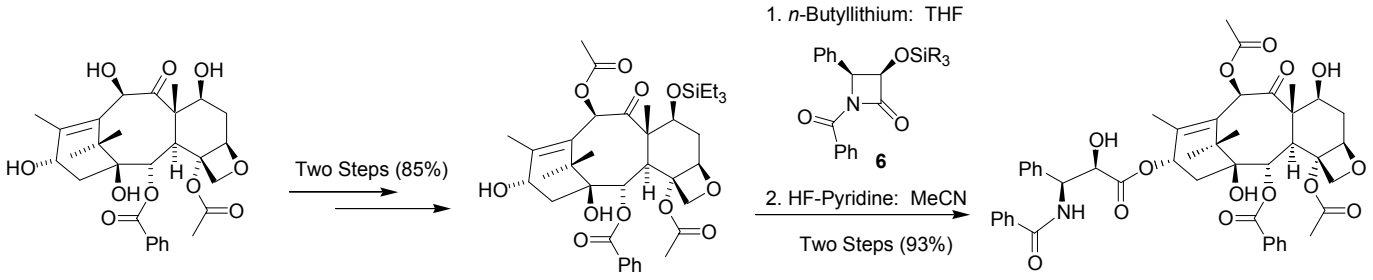
Scheme 1. β-Lactam Synthon Method for Oligopeptide Synthesis



2 **3**

In contrast to hydrogenation of the β-lactam ring, which effectively provides α-amino acid equivalents, nucleophilic attack at the carbonyl of the β-lactam provides β-amino acid products via a ring-opening reaction. One of the most valuable applications of this ring-opening methodology has been in the production of Taxol (**7**), a potent anti-cancer drug. This compound was originally isolated from the bark of the Pacific Yew (*Taxus brevifolia*), but it was quickly realized that sufficient amounts could not be obtained from this source. Fortunately, it was discovered that the needles of the European Yew (*Taxus baccata*) contain a significant amount of 10-deacetyl-baccatin III (**4**), which can be converted to silyl protected baccatin III **5**, a viable precursor for a semisynthetic route to Taxol. This semisynthetic route utilizes chiral β-lactam **6** for the stereospecific installation of a β-amino ester group that proved difficult to install via simple esterification routes. This β-lactam route is used in the commercial production of Taxol, which provided $1.5 billion in sales during 1999 (Scheme 2).[10,11]

Scheme 2. Semisynthesis of Taxol Utilizing β-Lactam Synthon Methodology



4 **5** **6** **7**

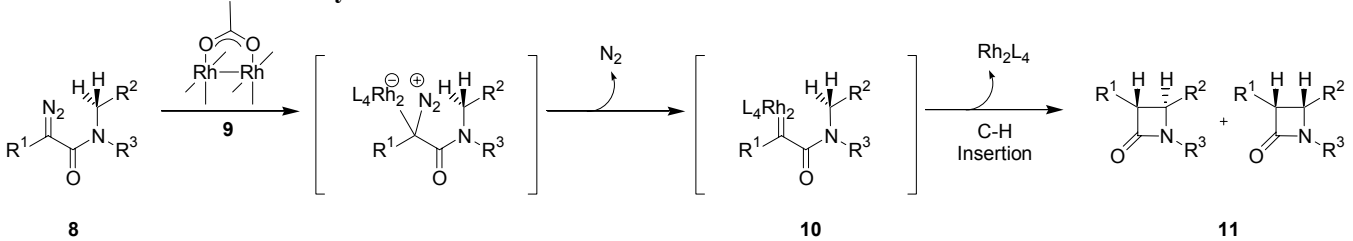
CATALYTIC ASYMMETRIC SYNTHESIS OF β-LACTAMS

The first synthesis of a β-lactam was accomplished in 1907, when Staudinger discovered that ketenes and imines could undergo [2+2] cycloadditions to yield the β-lactam ring.[12] This discovery was made long before the biological activity and therapeutic value of the β-lactam moiety was appreciated. This situation changed with the dawn of the antibiotic age, when the synthesis and especially the enantioselective synthesis, of the β-lactam skeleton became prized. In pursuit of this goal, a number of methods utilizing chiral auxiliaries were developed.[13,14,15,16] While many of these auxiliary-based methods successfully produce enantiomerically enriched β-lactams, they suffer from requiring stoichiometric amounts of chiral starting materials, which are often very expensive. Recently, in an effort to decrease the amount of chiral substance needed for effective enantioselective synthesis, several catalytic asymmetric routes to β-lactams have been developed.[17] In this report, only those methods that allow for isolation of β-lactams directly from the reaction mixture will be discussed.

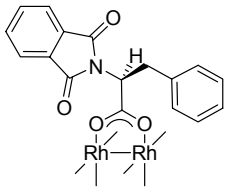
Catalytic Asymmetric C-H Insertion

While it is well known that carbenes can insert readily into C-H bonds, the regio- and enantiocontrol of these reactions is extremely difficult when carbenes, generated thermally and photochemically, are used. By contrast, metal carbenoids offer greater control over the stereochemical outcome of C-H insertions than their free carbene counterparts. Taking advantage of this, Ponsford and Southgate pioneered the synthesis of β-lactams utilizing rhodium-catalyzed carbene insertion into a C-H bond.[18,19] This methodology utilizes an α-diazoacetamide **8**, which in the presence of $Rh_2(OAc)_4$ (**9**) forms a putative rhodium carbenoid **10**. This carbenoid inserts regio- and diastereoselectively into the nearby C-H bond to yield the β-lactam **11** (Scheme 3). In the cases where R^2 is an alkyl group, the possibility exists for the formation of larger rings by C-H insertion at the more remote methylene groups of R^2, and the formation of five-membered rings is typically favored in such carbene ring-forming reactions. However, four-membered rings can be formed in preference to larger rings in the case of α-diazoacetamides, presumably because of conformational influences and/or activation of the methylene group adjacent to the amide nitrogen.[20] While the regio- and diastereocontrol shown by this C-H insertion reaction has made it synthetically useful, it was the simultaneous development of analogous

Scheme 3. Rhodium-Catalyzed C-H Insertion Reaction of α-Diazoacetamides



enantioselective methods, by the research groups of Hashimoto and Doyle, that has helped to realize the full potential of this methodology. To promote an enantioselective reaction, Hashimoto replaced the four acetate ligands on the dirhodium catalyst with four *N*-phthaloyl (*S*)-phenylalinate ligands (**12**), whereas Doyle utilized methyl 2-pyrrolidone-5-carboxylate ligands (**13**). In an effort to force their substrates into conformations that would favor four-membered over five-membered lactam rings, Hashimoto and Doyle utilized different approaches. Hashimoto obtained high yields and moderate enantioselectivities by placing a *tert*-butyl group on the amide nitrogen.[21] Doyle instead utilized amide substrates derived from cyclic secondary amines and obtained excellent yields and enantioselectivities, but only for seven-membered rings.[22] While the preliminary work of both Doyle and Hashimoto showed promise, it was in the synthesis of intermediates **14** for the carbapenem antibiotics (similar products to those made in racemic form by Ponsford and Southgate) that Hashimoto found the most promising substrates for enantioselective C-H insertion. Using a variety of *N*-phthaloyl-(*S*)-amino acid carboxylate ligands, he obtained excellent yields (85-94%) and high enantioselectivities (92:8 to 98:2 er).[23]



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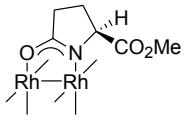

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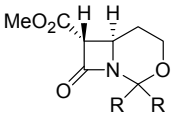

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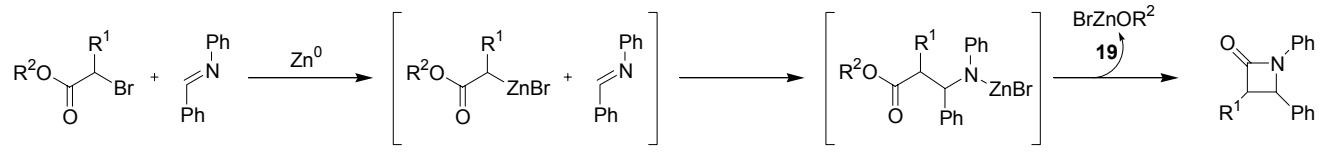
Catalytic Asymmetric Gilman-Speeter Reaction

In 1943, Gilman and Speeter reported the first use of a Reformatsky reaction with an imine.[24] The addition of zinc metal to a mixture of α-bromoester **15** and imine **16** provide β-lactam **20** in 56-85% yield (Scheme 4). The reaction proceeds by formation of the Reformatsky reagent **17**, addition to the imine to form adduct **18**, and ring closure via attack of the β nitrogen at the carbonyl of the ester unit, which displaces the zinc alkoxide **19**. One logical extension of this reaction is the use of lithium ester enolates and lithium thioester enolates.[16,25] These reactions, along with the original Reformatsky approach, are collectively known as the Gilman-Speeter reaction. Many examples of racemic and auxiliary-based enantioselective Gilman-Speeter reactions exist, but it was not until Tomioka and coworkers utilized external chiral ligands, such as **21**, with achiral ester enolates and imines, that the Gilman-Speeter reaction was rendered catalytic and asymmetric.[26] The original method utilizes the assembly of a ternary complex in solution. This ternary complex is composed of a chiral diether ligand **21**, the lithium ester enolate, and one equivalent of lithium amide base. While the specific structure or

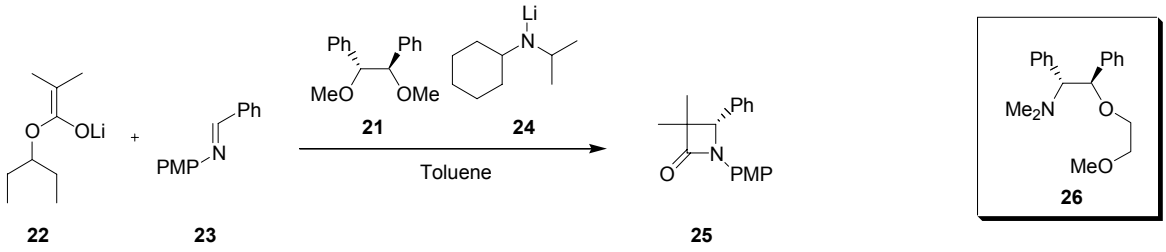
Scheme 4. Gilman-Speeter Reaction



15 **16** **17** **18** **20**

catalytic mechanism of this ternary complex is not well known, it is known that the presence of **21** or lithium amide base increases the rate of reaction between ester enolate and imine, and that the presence of both additives increases the rate even further. The best results have been found using ester enolates that are symmetrically disubstituted at the α position, to eliminate complicating issues of diastereoselectivity. The optimum lithium amide bases were found to be lithium isopropyl cyclohexyl amide (LICA) and lithium dicyclohexyl amide. The reaction of lithium ester enolate **22** with imine **23** in the presence of **21** (0.2 equivalents) and LICA (**24**) provides β-lactam **25** in 85% yield and 94:6 er after 4 hours (Scheme 5). In an effort to eliminate the need for the added lithium amide base, which is capable of causing problems with undesirable deprotonation and side product formation in some systems, Tomioka and coworkers developed a tridentate ligand **26** to replace the bidentate ligand **21**.[27] When **26** is used as a catalyst for the condensation of **22** and **23,** using similar conditions as with ligand **21**, except without amide base, β-lactam **25** is obtained in 99% yield and 95:5 er after 1.5 hours. After recrystallization, the product can be isolated in a 75% yield in optically pure form. While recent attempts utilizing chiral bisoxazoline ligands have seen moderate success, **26** remains the most effective ligand for the asymmetric catalytic Gilman-Speeter reaction.

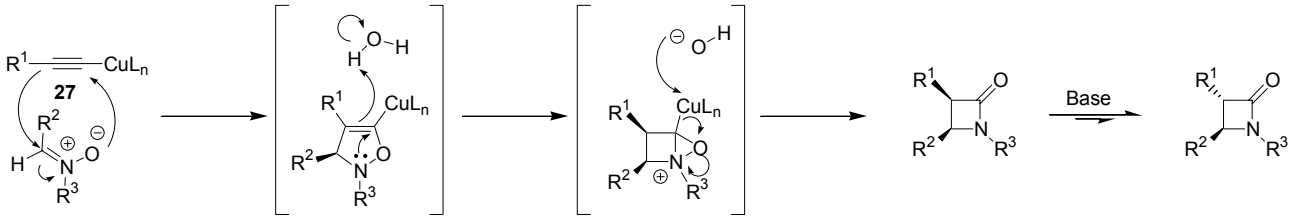
Scheme 5. Catalytic Asymmetric Gilman-Speeter Reaction



Catalytic Asymmetric Kinugasa Reaction

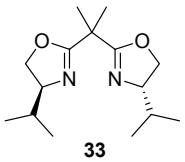
In an effort to investigate the reactions of copper acetylides **27** with nitrones **28**, Kinugasa and coworkers discovered an intriguing transformation that yields *cis*-β-lactams in 50-60% yield.[28] Preliminary mechanistic studies by Ding and Irwin, using D_2O and $H_2{}^{18}O$, showed that the carbonyl oxygen was derived from the oxygen of the nitrone starting material (i.e. no incorporation of ^{18}O in product) and that the proton α to the carbonyl came from solvent (i.e. ^{2}H incorporation observed). Based on this information and the known ability of some alkynes to undergo [3+2] reactions with nitrones, Ding and Irwin proposed a mechanism in which a regioselective [3+2] cycloaddition reaction leads to heterocycle intermediate **29**, which then undergoes rearrangement and protonation on the least sterically hindered face to give *cis* substituted intermediate **30**. Intermediate **30** could then undergo attack of hydroxide ion at copper and rearrangement to observed β-lactam product **31** (Scheme 6).

Scheme 6. Proposed Mechanism for the Kinugasa Reaction



28 29 30 31 32

Ding and Irwin also determined that *cis*-β-lactams, especially those with carbonyl substituents at R^1, can undergo base-catalyzed epimerization at the carbon center α to the lactam carbonyl. While the *cis*-β-lactam **31** is the kinetically favored product of these reactions, the thermodynamically more stable *trans*-β-lactam **32** can become the dominant isomer after epimerization.[29] A significant advance in the utility of the Kinugasa reaction was made by Miura and coworkers, who were able to employ catalytic copper (I) iodide (10 mol%), along with stoichiometric K_2CO_3. In addition to decreasing the amount of copper required for the reaction, Miura and coworkers established the first asymmetric catalytic Kinugasa reaction by employing a catalytic amount of chiral bisoxazoline ligand **33** (20 mol%), but they obtained only moderate asymmetric induction and poor diastereoselectivity.[30] Intrigued by the Kinugasa reaction, Fu and coworkers applied a different C_2-symmetric planar chiral ligand **34** along with a hindered stoichiometric base (Cy_2NMe) and achieved variable yields (42-91%) of *cis*-β-lactam **35** with good enantioselectivity (84:16 to 97:3 er). The best results obtained via this asymmetric catalytic Kinugasa reaction are with substrates containing aromatic substituents at R^3 and electron-withdrawing substituents at R^1.[31]



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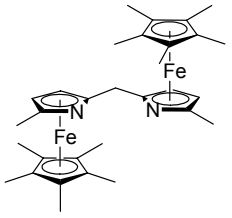

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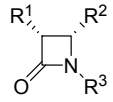

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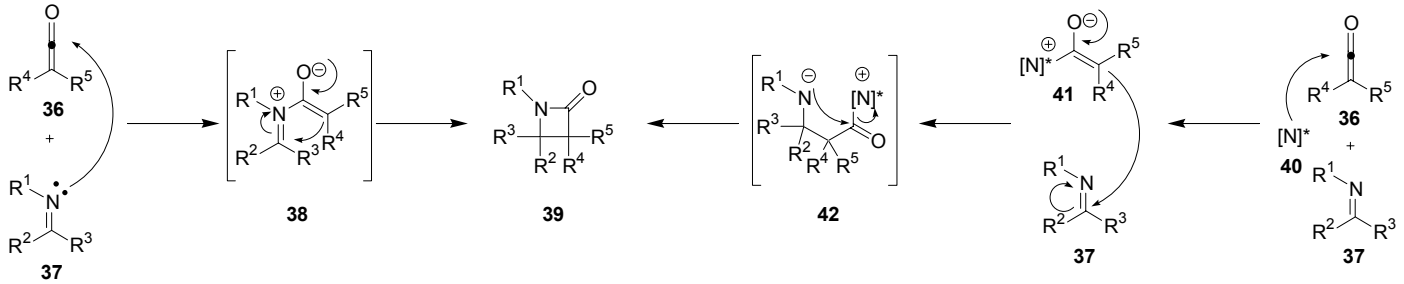
Catalytic Asymmetric Staudinger Reaction

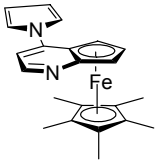
The [2+2] cycloaddition of ketenes and imines, known as the Staudinger reaction, is probably the most widely used method for the asymmetric synthesis of β-lactams.[12] While a number of asymmetric methods utilizing chiral auxiliaries attached to the ketene and/or the imine have been used for many years,[13] it was only recently that Lectka and coworkers developed a catalytic asymmetric method. The accepted mechanism for the Staudinger reaction involves initial attack of the imine **37** nitrogen at the central carbon of the ketene **36** to form intermediate **38**, followed by addition of the terminal ketene carbon to the iminium carbon to provide β-lactam **39**. In their efforts to develop a catalytic asymmetric Staudinger reaction, Lectka and coworkers worked to reverse the order of bond formation between the ketene and imine components, so as to introduce a chiral catalytic element into one of the reaction

partners. To accomplish this goal, an electron withdrawing tosyl group (R^1) was placed on the imine nitrogen **37**, thus decreasing its nucleophilicity. The initial reaction was then between the nucleophile catalyst **40** and the ketene **36**, forming an enolate type intermediate **41**. This enolate then rapidly added into the imine **37**, now acting as an electrophile, to provide intermediate **42**, followed by displacement of the catalyst by the imine nitrogen (Scheme 7). The advantage of the Lectka reaction is that a catalytic amount of chiral nucleophile can provide an enantioselective reaction.

Scheme 7. Typical Staudinger Reaction and Lectka-Staudinger Reaction



In an effort to develop an effective chiral nucleophile catalyst, Lectka explored the use of the cinchona alkaloids benzoylquinine and benzoylquinidine. These "pseudoenantiomeric" nucleophilic catalysts provide enantiomeric *cis*-β-lactams with moderate yields (45-65%) and excellent enantioselectivity (98:2 to 99:1 er). Interestingly, these nucleophilic species can also catalyze the formation of ketenes in situ, from acyl chlorides, when a stoichiometric amount of kinetically inactive but thermodynamically strong base, such as "proton sponge", is used.[32] Using a similar technique to that of Lectka, Fu has utilized a planar chiral nucleophile **43** and obtained good yields (76-93%) and enantioselectivity (90:10 to 97:3 er).[33] In an attempt to improve the practicality of his technology, Lectka has been able to utilize sequential column catalysis to form β-lactams in similar yields and enantioselectivities to those observed using traditional solution phase chemistry.[34] In a very recent development, Lectka has developed a bifunctional catalyst, based on a cinchona alkaloid used in concert with indium triflate, to form a bifunctional nucleophilic/Lewis acidic catalyst. This technique results in improved yields (92-98%), while retaining the excellent enantioselectivity that was observed without the Lewis acid.[35]



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CONCLUSION

Several catalytic asymmetric methods for the synthesis of β-lactams are now available for synthetic applications. As the efficiency and selectivity of these methods improve, their synthetic utility is sure to increase, allowing for the rapid development of biologically valuable β-lactam products.

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