 Catalytic, asymmetric reactions of ketenes and ketene enolates

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1. Introduction

For over a century, ketenes have intrigued organic chemists with their unusual physical properties and unique spectrum of chemical reactivity; it is not an exaggeration to say that they represent one of the keystone reactive intermediates of physical organic chemistry. Their synthetic potential, originating in part from their high reactivity, has proven to be powerful as well, from the Staudinger synthesis of β-lactams to the photochemical Wolff rearrangement. It is perhaps no surprise that the past several decades have also shown that ketenes are excellent precursors for catalytic asymmetric reactions, creating chiral centers mainly through addition across their C=O bond. Due to their electrophilic nature, ketenes readily react with nucleophiles to form zwiterionic enolates that form the basis for much asymmetric chemistry. Through catalytic, asymmetric methodology, researchers have successfully utilized ketenes in a range of reaction manifolds, including [2+2] and [4+2] cycloadditions, reductive couplings, nucleophilic S_N2 substitutions, as well as both electrophilic and nucleophilic additions. In this review, these reaction pathways are discussed in terms of such diverse reactions as ketene alcoholsysis and aminolysis, α-halogenation, α-amination, α-hydroxylation, and the formation of β-, γ-, and δ-lactones and β- and γ-lactams.

1.1. Ketenes and their properties

In 1905 at the University of Strasbourg, Hermann Staudinger undertook an attempted synthesis of radical species 3 (Eq. 1.1) inspired by the work of Comberg on the triphenylmethyl radical. To his surprise, upon the reaction of α-chlorodiphenylacetyl chloride (1a) with zinc, an entirely unanticipated closed shell compound was formed, one that he eventually identified as diphenylketene (2a, Eq. 1.1). Since this serendipitous discovery, ketenes have been the source of countless scholarly texts and research papers. Due to their unusual properties, ketenes are versatile starting materials for a wide variety of compounds of interest and have been used as precursors for everything from industrially produced acetic acid to antibiotics and more. As can be expected for a ‘marquee’ class of compounds that has been so heavily studied, much research has been done to illuminate ketene reactivity and its dependence on structure and substitution patterns. What follows is meant as an abridged introduction only, as the topic has been thoroughly covered elsewhere, especially in the work of Tidwell.

In light of the wide variability in ketene reactivity and substrate tolerance, it is not surprising that numerous methods of generation have been developed over the years. Thermolysis is a useful method for generating relatively stable substituted ketenes. For example, dimethylketene (2b) can be obtained by thermal cracking of its dimer (Eq. 1.2), and methylphenylketene can be generated by treating methylphenylmalonic acid (4) with trifluoroacetic anhydride (TFAA) followed by pyrolysis (Eq. 1.3). To a lesser extent, photolysis of dimers is also possible, although yields are low due to competing decarbonylation reactions. A more viable light (or heat) based method of ketene generation, one that has seen extensive use in synthetic chemistry, is the Wolff rearrangement. For instance, photolysis of phenylidiazooacetate (5) produces a clean solution of phenyketene (Eq. 1.4). One of the advantages of using the Wolff rearrangement is that it can be used to produce a dilute solution of ketene over an extended period of time; this can be helpful in reducing unwanted side reactions such as ketene dimerization. While these are effective ways to generate ketenes, they are made somewhat less accessible because they involve specialized equipment or unstable starting materials.

1.2. Structure and reactivity of ketenes

Ketenes are characterized by an unusual ‘heteroallenic’ bond structure that is the source of the their distinctive reactivity. The highest occupied molecular orbital (HOMO) of a ketene is located perpendicular to the plane of the ketene while the lowest unoccupied molecular orbital (LUMO) lies in the plane. This orientation places significant negative charge on both the oxygen and the β-carbon, while placing a similarly substantial positive charge on the α-carbon. (Fig. 1.1.) The electropositive nature of the α-carbon in part explains why nucleophiles readily add at this position. The ketene’s substituents play a major role in its reactivity. Electronically, species that are capable of donating electron density into the carbonyl group through σ–p conjugation as well as those that can act as p-acids stabilize the ketene, while electronegative groups and p-donors destabilize the ketene. Similarly, steric bulk on the β-carbon stabilizes

Figure 1.1. Electron density map of diphenylketene; red = electron-rich, blue = electron-deficient.
A more popular method for ketene generation in synthetic chemistry is the dehydrohalogenation of inexpensive acid chlorides with tertiary amines (Eq. 1.5). This method works well for the more stable, distillable disubstituted ketenes. Unfortunately, the more synthetically useful monosubstituted ketenes are generally much more reactive and must therefore be made in situ, where they suffer from contamination with ammonium salt byproducts. Generally, the presence of trialkylammonium byproducts presents no problem; in some cases, these species can potentially erode selectivity in asymmetric reactions by acting either as Brønsted acids or, through equilibrium with the free amine, nucleophilic catalysts. To some extent, these difficulties can be overcome by employing resin-bound bases that leave behind a clean solution of ketene after filtration. For example, Lectka has employed the powerful, resin-bound phosphazene base BEMP for this purpose. Passing a solution of acid chloride through an addition funnel containing at least 1 equiv of BEMP at ~78 °C has been shown to give good results in several systems. While BEMP affords ketene solutions without contaminants, there are disadvantages to this method: BEMP is quite moisture sensitive and can be difficult to handle for larger scale reactions; it is also very expensive when compared to other methods of ketene generation.

In an effort to overcome these challenges, a simple and accessible method of in situ ketene generation known as ‘shuttle deprotonation’ was developed by the Lectka group in 2000. Under these conditions, a catalytic amount of a strong kinetic base (base k) dehydrohalogenates an acid chloride and subsequently transfers the proton to a strong thermodynamic base (base t, Scheme 1.1). By choosing a non-nucleophilic base to sequester the protons and a kinetic base that will act as the chiral catalyst in later steps, namely benzoylquinine (BQ, 6a), the problem of the competitive, achiral nucleophile can be overcome.

Evidence for the preformation of ketene can be obtained from spectroscopic experiments. When BEMP is utilized, ketenes are undoubtedly formed from acid chlorides. On the other hand, the shuttle deprotonation systems that utilize proton sponge, bicarbonate, or Hüning’s base do not require the generation of free ketene for the reaction to proceed as the zwitterionic intermediate enolate is often formed reversibly under these conditions. The situation is more opaque when sodium hydride is used in situ—the presence of catalyst is necessary for the production of phenylketene, but it is not clear whether the BQ catalyst was acting as a nucleophile or a base, or both (Eq. 1.6).

### Scheme 1.1. Shuttle deprotonation.

The shuttle deprotonation reaction can be performed with any number of different thermodynamic bases. In most cases, the mechanism presumably remains the same (Fig. 1.2). Potentially, BQ can generate the ketene through two routes: (1) by direct dehydrohalogenation; or (2) by the generation of an acyl ammonium intermediate that is subsequently deprotonated to give a zwitterionic ketene enolate, which is in equilibrium with free ketene. It is believed that both pathways to enolate formation may operate simultaneously, but which one predominates depends on the properties of the acid chloride.

While proton sponge has been used effectively in many applications, its drawbacks include hydrochloride salt solubility in more polar solvents, and reactivity with potential oxidants, for example, in the conditions for asymmetric α-halogenation (see Section 5). For such applications the use of potassium carbonate, sodium bicarbonate, or sodium hydride has been shown to be effective when paired with catalytic quantities of crown ether and BQ. Additionally, the heterogeneous nature of these reactions has been exploited to allow for nearly pure solutions of ketene to be produced by simple filtration at low temperature following a ketene preformation step. To simplify this procedure, special glassware has been designed (Fig. 1.3). The apparatus consists of two round-bottom flasks linked by a fritted disc; ketene is formed heterogeneously on one side and then filtered through a frit onto the other.

### 1.4. Cinchona alkaloids as catalysts

Cinchona alkaloids are abundant natural products that are one of the more popular chiral organocatalysts and they constitute the most often used catalysts for asymmetric ketene
reactions. They exist as pseudoenantiomeric pairs, for instance quinine (6b) and quinidine (7b) are a complimentary diastereomeric pair that generally provide opposite optical induction. Among their many attributes, cinchona alkaloids are readily derivatized, most often at the chiral alcohol, to provide reactivity and selectivity that is amenable to a wide variety of reaction conditions (Fig. 1.4).

Lectka has employed molecular modeling calculations to account for (and predict) the sense of induction that is consistently observed in cinchona alkaloid catalyzed ketene reactions. For example, molecular mechanics (MM) calculations using a modified MMFF force field on a model BQ–phenylketene complex (1d-Nu) reveal a low energy structure in which the re face is exposed to approach of the electrophile, whereas si-face approach is 2.64 kcal/mol higher in energy (depending on the force field employed, Fig. 1.5).

2.1. Ketene alcoholysis

Despite the promise of Pracejus’s early work, it was not until decades later that researchers sought to adapt and expand upon his methodology. A study by Calmes et al. in 1997 closely examined the effect of the nature of the catalyst in the alcoholysis of in situ generated disubstituted ketenes by chiral alcohols. In the late 1990s Fu et al. re-examined the potential of catalyzed asymmetric ester formation from ketenes, employing their highly selective planar-chiral ferrocene catalysts (9) (Scheme 2.1).

Their early experiments with Pracejus’s substrates gave disappointing results, with ee’s topping out at 55% with 10 mol % catalyst loading. However, careful consideration of their proposed reaction mechanism provided clues to help improve the selectivity (Scheme 2.2). If their proposed mechanism were correct and the abstraction of a proton by complex 2-Nu was the chirality determining step, then the use of an alternate proton source might improve the enantioselectivity of their reactions. Brønsted acid additive screening found that the bulky di-tert-butylpyridinium salt 10 successfully raised the ee to 80%.

2. Asymmetric alcoholysis and aminolysis

In 1960, Pracejus reported one of the earliest catalytic asymmetric reactions of ketenes. He employed chiral trialkylamines to produce chiral ester products from ketenes and alcohols. At –110 °C in toluene, acetylquinine (6c) catalyzes the methanolysis of phenylmethylketene (2c); the α-phenylproionate ester (8a) was obtained in up to 74% ee, representing a tremendous breakthrough in ketene chemistry (Eq. 2.1). He proposed that a complex between the catalyst and ketene had formed and that this was responsible for optical induction during alcoholysis. The complex proposed is what we now refer to as a chiral ammonium zwitterionic ketene enolate, and is the reactive intermediate most often implicated in asymmetric ketene reactions. This pioneering work set the stage for the modern asymmetric reactions of ketenes.
At the same time, the fact that the bulky Brønsted acid additive was able to provide increased enantioselectivity corroborated their working hypothesis. However, it was not until after expanding their methodology to include amide products (see Section 2.2) that an alternate mechanism presented itself, indicating potentially beneficial modification of this system toward high selectivity (Scheme 2.3).21

In this new mechanism, while the abstraction of a proton by an enolate complex is still the chirality determining step, the source of that proton is now the chiral catalyst instead of an achiral acid or alcohol. Such an arrangement could theoretically place the catalyst much closer to the forming chiral center, thus enhancing its effectiveness. Catalyst 9b quantitatively deprotonates phenol in solution, whereas methanol gave no evidence of deprotonation under the same conditions. The use of a bulky phenol instead of methanol allows for much better selectivity, in some cases to above 90% ee (Table 2.1), while both obviating the need for the acid additive and lowering the catalyst loading to 3 mol%.

Table 2.1
A selection of esters synthesized

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Cat</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>9b</td>
<td>77</td>
<td>87</td>
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<tr>
<td>2</td>
<td>Et</td>
<td>Ph</td>
<td>Me</td>
<td>9b</td>
<td>68</td>
<td>92</td>
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<td>3</td>
<td>Me</td>
<td>m-Pho-Ph</td>
<td>Me</td>
<td>9b</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>4-i-Bu-Ph</td>
<td>Me</td>
<td>9b</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Me</td>
<td>2-t-Bu-Ph</td>
<td>9a</td>
<td>79</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>i-Bu</td>
<td>2-t-Bu-Ph</td>
<td>9a</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>o-Anisyl</td>
<td>Me</td>
<td>2-t-Bu-Ph</td>
<td>9a</td>
<td>94</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>p-Cl-Ph</td>
<td>i-Pr</td>
<td>2-t-Bu-Ph</td>
<td>9a</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>3-Thienyl</td>
<td>i-Pr</td>
<td>2-t-Bu-Ph</td>
<td>9a</td>
<td>79</td>
<td>94</td>
</tr>
</tbody>
</table>

Interestingly, Fu expanded this methodology into the realm of enolizable aldehydes (11) in 2005 (Scheme 2.4).22 This alternative method, employing catalyst 9a, produces enol esters in excellent yield and ee up to 98%. As with the simple alcoholysis method above, the authors’ initial mechanistic queries gave results consistent with two mechanisms, analogous to Schemes 2.2 and 2.3, respectively.

### 2.2. Ketene aminolysis

Following their success in the catalytic asymmetric methodology for the synthesis of chiral esters, the Fu research group turned their sights on a logical follow up, chiral amides.23 In theory, by simply employing an amine as the nucleophile instead of an alcohol, the desired products should be readily obtained. Practically, the problem is that amines are too nucleophilic, giving high background rates even at low temperature. It is likely for this reason that Pracejus, who investigated this route to chiral amides concomitant with his early work on chiral esters, chose to focus instead on using chiral amines to impart selectivity in his products.24 Fu et al. sought to render the reaction more manageable by choosing a less reactive amine nucleophile. An initial screen showed pyrrole to be a promising candidate as it gave no background reaction, however, the product of the reaction showed disappointing selectivity. This prompted a further screen of a number of pyrrole derivatives to examine the effect of various substituents on product selectivity (Scheme 2.5).

The screen demonstrated that pyroles possessing electron-withdrawing groups perform better, and 2-cyanopyrrole provided the best enantioselectivity. By combining 2-cyanopyrrole and any of a number of aryl/alkyl ketenes in the presence of catalyst 9a, they were able to produce the desired amide products (13) in excellent yield and with high ee (Table 2.2). These products can be derivatized in a variety of ways, with negligible racemization and in generally high yield. The respective carboxylic acid, ester, or amide can be produced easily, and with the appropriate reducing agent, the corresponding aldehyde or alcohol can be made selectively.

Table 2.2
A selection of amides synthesized

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Ph</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>Ph</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>o-Tolyl</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>o-Anisyl</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>3-(N-methylindolyl)</td>
<td>86</td>
<td>80</td>
</tr>
</tbody>
</table>
Remarkably, in the mechanism of the reaction, the catalyst is believed to act as a Brønsted acid/base (instead of acting as a nucleophile as previously thought). Deprotonation of the pyrrole facilitates its nucleophilic attack on the ketene substrate; then the resulting protonated catalyst acts as a chiral proton source, selectively donating its proton to the pyrrole–ketene enolate (Scheme 2.6).

Fu next sought to expand the utility of the reaction by employing azide as an alternative nucleophile.25 By combining hydrazoic acid with aryl/alkyl disubstituted ketenes in the presence of catalyst 9c, Fu et al. were able to produce acyl azides (13, Scheme 2.7), allowing them to exploit the Curtius rearrangement to produce isocyanates (14) that can then be converted into either chiral amines (15) or carbamates (16) through hydrolysis or alcoholysis, respectively (Scheme 2.7).

Much like the related reactions in this series, this catalytic cycle is believed to proceed through a Brønsted acid/base pathway, analogous to that depicted in Scheme 2.6. The method is fairly robust, working effectively for a variety of disubstituted ketenes, as long as they possess significant steric hindrance (Table 2.3). However, when bulky ketenes are employed, the reaction proceeds smoothly, giving the desired products in excellent yield and very high selectivity. The authors report the production of carbamates from methanol,26 and they show one example of an amine product included (from ethyl o-tolyl ketene, 93% ee, 97% yield). However, the reaction sequence seems capable of efficiently producing a range of chiral amines and their carbamate equivalents.

### Table 2.3 Synthesis of carbamates

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
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<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr</td>
<td>Ph</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>p-MeO-Ph</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>3-Thienyl</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>i-Bu</td>
<td>Ph</td>
<td>76</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>cy</td>
<td>Ph</td>
<td>96</td>
<td>92</td>
</tr>
</tbody>
</table>

### 3. Asymmetric β-lactone synthesis

Interest in the synthesis of β-lactones has a long history, and rightfully so as these compounds possess structures combining the gross atom connectivity of an aldol adduct with bond-strain approaching that of an epoxide. An additional feature that the β-lactone holds over simple aldol products is the ability to be cleaved selectively at the acyl–oxygen or the alkyl–oxygen bond as desired, leading to a myriad of potential products from a single source. Romo’s recent review provides an excellent introduction to the synthetic and medicinal chemistry of β-lactones.27

#### 3.1. Cinchona alkaloid catalyst systems

While β-lactones were investigated by Staudinger soon after his discovery of ketenes,28 it was not until over 70 years later, with the pioneering work of Wynberg, that a catalytic, enantioselective route to their synthesis was found. Wynberg and Staring employed cinchona alkaloids as nucleophilic catalysts to mediate the coupling of unsubstituted ketene with activated ketones and aldehydes.29 In their initial report, they demonstrated the synthesis of both the (R) and the (S) forms of malic acid through the β-lactone intermediate.29c Scheme 3.1 shows the synthetic route for (S)-malic acid (20), obtained by forming the initial β-lactone (18) via quinidine (7b) catalysis. The non-natural (R)-malic acid is obtained by the same means, but employing quinine (6b) as the catalyst.

![Scheme 3.1. A catalytic, asymmetric synthesis of (S)-malic acid.](image)

In their follow-up publication, they expanded upon their β-lactone synthesis, exploring a range of aldehyde reactants (21), and providing a simple and powerful means of directly accessing chiral β-lactones (22).29a As with the initial reaction, employing the
diastereomeric alkaloids quinine and quinidine as catalysts allowed for the synthesis of either enantiomer of a given product as desired, maintaining the flexibility of this method (Table 3.1).

**Table 3.1** Wynberg's β-lactone synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>ee (%)</th>
<th>Yield (%)</th>
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<tbody>
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<td>1</td>
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<td>H</td>
<td>76</td>
<td>89</td>
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<tr>
<td>2</td>
<td>Cl</td>
<td>H</td>
<td>98</td>
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<td>3</td>
<td>H</td>
<td>H</td>
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<td>6</td>
<td>Cl</td>
<td>p-NO2-Ph</td>
<td>89</td>
<td>95</td>
</tr>
</tbody>
</table>

* Runs with catalyst 6b, yields opposite enantiomer.

Wynberg's work forged the way for other researchers, guiding the development of a new and robust range of catalytic methodology for the synthesis of β-lactones (24). As can be expected from a reaction that is so effective within a limited scope, other groups have been inspired to develop the means to make it more general, and thus increase its utility. In a very nice extension, Romo has made use of shuttle deprotonation (see Section 1.3) to generate the unsubstituted ketene substrate in situ from acetyl chloride (1e),

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R1</th>
<th>ee (%)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Cy</td>
<td>94</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>PhOCH3</td>
<td>84</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph(CH2)2</td>
<td>&gt;99</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>p-F-Ph</td>
<td>&gt;99*</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>o-Cl-Ph</td>
<td>&gt;99</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>o-Tol</td>
<td>&gt;99</td>
<td>96</td>
</tr>
</tbody>
</table>
* Runs with catalyst 7d, yields opposite enantiomer.

In his proposal of the reaction mechanism, Nelson suggests that the reactants combine in a six-membered transition state wherein the metal coordinates the catalyst-bound enolate to the aldehyde, both activating the components and generating a tightly stereo-controlled environment for bond formation (Scheme 3.2).

Calter has found that certain metal salt cocatalysts can invert the diastereoselectivity of the reaction, yielding products favoring the trans-diastereomer. By pairing one of their silylated cinchona alkaloid catalysts with 15 mol % Sc(OTf)3 instead of the LiClO4 co-catalyst employed by Nelson, the Calter group has been able to cyclize a number of alkyl-substituted ketene and aromatic aldehyde pairs with excellent diastereo- and enantioselectivity, as well as good yield (Table 3.4).

**3.2. Bifunctional systems**

The Nelson research group has developed a variant of the Wynberg method using shuttle deprotonation for the in situ generation of ketenes. Nelson's optimized reaction employs a silylated cinchona alkaloid catalyst (6d, TMS-Q) and a variable amount of LiClO4 (amount depends on substrate and ranges from 15 to 300 mol %). This effective combination allows for the use of unsubstituted or methyl-substituted ketenes and unactivated aldehydes, greatly enhancing the scope of the reaction while maintaining high enantioselectivity and good yield, as well as producing the disubstituted products (26) with excellent diastereoselectivity (Table 3.3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar ee (%)</th>
<th>Yield (%)</th>
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</tbody>
</table>
In the same communication, Calter reports that lanthanide metal triflates are effective for forming cis-β-lactones when paired with alkoxy-substituted ketenes. In particular Er(OTf)₃ was found to give high diastereoselectivity (Table 3.5). Calter proposes that the change in diastereoselectivity in the reaction is due to a change in transition state prompted by an interaction between the metal cocatalyst and the substrate. He suggests that, initially, each substrate is bound to a separate metal center; the aldehyde is activated by one while the ketene enolate is bound to the other.

Table 3.5  cis-β-Lactone formation with lanthanide cocatalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>ee (%)</th>
<th>dr</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>&gt;99</td>
<td>88:12</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>p-Br-Ph</td>
<td>&gt;99</td>
<td>88:12</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>m-Cl-Ph</td>
<td>&gt;99</td>
<td>92:8</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>p-CN-Ph</td>
<td>&gt;99 ²</td>
<td>87:13</td>
<td>68</td>
</tr>
</tbody>
</table>

² Runs with catalyst 6d yields opposite enantiomer.

The authors believe that when these two complexes associate with each other, one of two things can happen: either one metal fragment is lost and the remaining metal complex helps coordinate to and activates the aldehyde. 

3.3. Lewis acid based catalyst systems

The Miyano group, after an initial report detailing the enantioselective synthesis of β-lactones promoted by a stoichiometric amount of an aluminum–BINOL complex, rapidly published a modified catalyst system (30a) that allows them to produce their products in generally good yield and modest enantioselectivity (up to 74% ee, Scheme 3.3). This method has the advantage of being effective with a range of aldehydes.

Building on Miyano’s research, but working with the more stable silylated ketene (2f), the research groups of Kocienski and Pons employed variants of Miyano’s catalysts (30b) to produce silylated β-lactones in moderate to good yield and enantioselectivity with excellent diastereoselectivity (Scheme 3.4). The authors found that the silylketene reactions require 30% catalyst loading to ensure maximum conversion and selectivity.
on to chiral Lewis acids, employing two different catalyst systems in the pursuit of an efficient asymmetric method (Scheme 3.5). While their TiIV–TADDOL catalyst was effective in this reaction, its performance was generally surpassed by their later developed AlIII–diol catalyst (Scheme 3.6).

Scheme 3.4. The Kocienski and Pons β-lactone synthesis.

Scheme 3.5. The Romo β-lactone synthesis.

Note that the structure of 32 has not definitively been determined, and Romo reports that it may actually exist as a dimeric species. The structure shown in Scheme 3.5 is believed to represent the catalytically active configuration of the Lewis acid. The authors demonstrated the benefit of using catalyst 32 over the TiIV catalyst; in most cases the ee is more than double, and when R = benzyl (25), the previously almost non-selective reaction is improved to 75% ee when 32 is used. The observed dr of the silylated intermediate is also enhanced by the aluminum-based Lewis acid, as is the overall yield of the two-step reaction sequence.

Early work by the Nelson group on β-lactone synthesis focused on the synthesis of racemic products that could then be resolved by the action of an enzyme and an alcohol, leading to a mixture of one enantiomer of the lactone and the alcoholysis product of the other enantiomer. While their early catalyst gave the one enantiomer of the lactone and the alcoholysis product of the efficient processes for converting these racemic products into the corresponding lactone (Scheme 3.5), forming various β-disubstituted lactones in good yield (80% average) and enantioselectivity (83–95% ee, Scheme 3.7), after cleavage of the α-silyl group by KF. The cyclodiaddition is believed to benefit from an orbital interaction between the LUMO of the glyoxylate substrate (activated by the Lewis acid) and the HOMO of the ketene; in essence, Evans regards the ketene as a weak nucleophile in this case.

Evans has reported a similar Lewis acid catalyzed β-lactone forming reaction. This system involves the β-silylketene (2f) and α-keto esters (38). The reaction is catalyzed by a bis(oxaazoline) CuII complex (39), forming various β-disubstituted lactones in good yield (80% average) and enantioselectivity (83–95% ee, Scheme 3.7), after cleavage of the α-silyl group by KF. The cyclodiaddition is believed to benefit from an orbital interaction between the LUMO of the glyoxylate substrate (activated by the Lewis acid) and the HOMO of the ketene; in essence, Evans regards the ketene as a weak nucleophile in this case.

Scheme 3.6. β-Lactone transformations.

Scheme 3.7. Copper(II) catalyzed β-lactone formation.

In an interesting study of his chiral oxazaborolidine catalyst, Corey reported the condensation of ethenone (2e) with several aldehydes (25) to produce the corresponding lactone (29) in good yield and ee (Scheme 3.8). Catalyst optimization studies led them to add tributyltin triflate to catalyst 40 to produce more activated catalyst 41. This second catalyst is proposed to act by insertion of the ketene into the phenoxy–tin bond (42) followed by

Table 3.6 Nelson’s chiral β-lactone synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH2CH2</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>i-Bu</td>
<td>93</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>BnOCH2C≡C</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu-C≡C</td>
<td>85</td>
<td>91</td>
</tr>
</tbody>
</table>
coordination of the aldehyde to the boron and subsequent 'intra-
molecular' cyclization of the ternary complex 43.

### 3.4. Trisubstituted β-lactones

Expanding on his work with disubstituted ketenes, Fu has
developed the synthesis of trisubstituted β-lactones (43),
employing his planar-chiral catalyst (9). This system is capable
of catalyzing the cycloaddition of aromatic aldehydes with alkyl/
alkyl disubstituted ketenes (Table 3.7). In his analysis of the re-
action, Fu suggests that the catalyst in this case acts in analogous
fashion to his ketene methanolysis (see Scheme 2.2), namely by
generating a transient chiral ketene enolate intermediate. He has
also shown that the β-lactone products, despite their increased
bulk, can still undergo the various transformations known for mono- and disubstituted β-lactones in good yield and with re-
tention of ee.

#### Table 3.7
Trisubstituted β-lactone synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Et</td>
<td>Ph</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Et</td>
<td>2-Naphthyl</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>Et</td>
<td>p-CF₃-Ph</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>(CH₂)₆-Pr</td>
<td>Me</td>
<td>Ph</td>
<td>82</td>
</tr>
<tr>
<td>5*</td>
<td>i-Pr</td>
<td>Me</td>
<td>Ph</td>
<td>91</td>
</tr>
</tbody>
</table>

* dr 4:2:1; ee is for the cis diastereomer, yield of both diastereomers.

More recently, Ye et al. reported that chiral N-heterocyclic
carbenes (NHC, 44) are efficient catalysts for the reaction of di-
substituted ketenes with 2-oxoaldehydes (Scheme 3.9). The
NHC catalysts were used putatively to activate disubstituted ke-
tenes in a manner similar to nucleophilic tertiary amines—by
condensing to create a nucleophilic, zwitterionic ketene enolate
as the reactive intermediate (2-Nu). In this way, catalyst 44
provides a variety of trisubstituted lactones from alkyl/aryl dis-
substituted ketenes in good yield (63–99%) with excellent
enantioselectivity (94–99% ee) and good diastereoselectivity as
well. The NHC catalysts are easily prepared in situ by stirring the
Corresponding salt with cesium carbonate, but must be used
immediately.

#### 3.5. Asymmetric ketene dimerization

A perennial difficulty in dealing with ketenes is their tendency
to undergo side reactions that is ironically a consequence of the
reactivity that makes them useful substrates. The most common of
these is dimerization (Eq. 3.1). Whereas the tendency of ketenes to
dimerize can be controlled by factors such as solution concentra-
tion and temperature, it remains an issue in many ketene-based
reactions. However, the structures of ketene dimers reveal both
molecular complexity and chirality, suggesting that this often un-
wanted side reaction can be useful and interesting in itself.

#### 3.5.1. Dimerization of preformed ketenes

The Calter group has sought to exploit the ketene dimerization
reaction by rendering it enantioselective. With an eye toward uti-
lizing the chiral dimers as synthetic intermediates, his early work
focused on the cinchona alkaloid catalyzed dimerization of pregen-
erated methylketene (Scheme 3.10). He screened a number of cin-
chona alkaloid derivatives, finding that quinidine (7b), its silylated
derivative 7d, was most effective, with the two giving the same high
selectivity (98% ee). Quinine (6b) gave only moderate results (70% ee)
but its silylated derivative 6d proved to be effective (99% ee). The drop
in ee observed for quinine was explained by partial O-acylation—
propionylquinine gave only 50% ee when used as the catalyst.

Dimer 46 could not be isolated due to a combination of reactivity
and volatility, requiring its derivatization. As this method was
employed to synthesize polypropionate intermediates, the Calter group moved away from the zinc promoted ketene formation and began to employ a thermolytic ketene generation from propionic anhydride and catalyst 6d or 7d to form dimer 46 at a constant, reproducible rate with high enantioselectivity (Scheme 3.11).52

To generate the desired products, the crude β-lactone mixture was treated with the lithium amide of N,N-dimethylhydroxylamine to open the ring, affording a lithium enolate (47) that reacts directly with a variety of aldehydes giving aldol products with full retention of optical purity and high diastereoselectivity (Table 3.8).

Going a step further, Calter employed (S)-2-methylpentanal to obtain a precursor (48) to the class of natural products known as siphonarienes: siphonarienedione (49), siphonarienolone (50), and siphonarienal (51) (Scheme 3.12).52 The 2-methylpentanal can also be used in its racemic form because the diastereomeric purification is relatively simple.

Ye et al. have also applied their NHC catalyst (52) to the dimerization of disubstituted ketenes.53 Slight catalyst modification from their previous system (44, Scheme 3.9) allowed the authors to obtain the dimers selectively (Scheme 3.13). A variety of alkyl and aryl groups were accommodated by altering reaction time. As before, the NHC catalyst is produced in situ by stirring the corresponding tetrafluoroborate salt with Cs2CO3 immediately prior to the addition of ketene.

3.5.2. Dimerization of in situ generated ketenes

The Calter group later sought to expand upon this synthesis by making use of shuttle deprotonation (see Section 1.3) to generate a selection of ketene substrates in situ.54 By employing a combination of TMS-Q (6d) and Hüning’s base, the desired dimers were produced with high enantioselectivity and in good overall yield (Table 3.9). The authors note that while the reaction is tolerant of...
increasing steric bulk the larger substituents require longer reaction times and higher concentrations to produce the desired products. They also remark that the reaction can be performed with silylated quinidine 7d with similar, or even improved, results to obtain the opposite enantiomer (97% ee and 79% yield for R=Me).

While most of the dimer products formed by this reaction were not isolable, the esterified ketene substrate (entry 6) was purified by rapid filtration through silica gel prior to step two. The authors also undertook a series of mechanistic studies to elucidate the rate limiting and optical induction steps for this reaction. They determined that the rate limiting step in the reaction of propionyl chloride (1g) with catalyst 6d and Hünig’s base was the dehydrohalogenation of propionyl chloride to form methylketene (2g, Eq. 3.2).

For their studies on the stereochemistry determining step of the reaction, they considered two possible pathways to the product (Scheme 3.14). Pathway A could potentially be followed whether or not the ketene was preformed, however, pathway B was only possible if the ketene was formed in situ. A series of experiments followed wherein both preformed and in situ generated ketene were reacted with a variety of catalysts. In all cases, the products were observed to possess identical selectivity (within experimental error) and thus Calter favors a single reaction pathway for both sets of conditions (pathway A, Scheme 3.14).

The Romo research group has also made use of ketene dimerization. Their initial work in this area focused on the epoxidation of racemic dimers to produce unexpectedly stable spiroepoxy β-lactones that can serve as precursors to a variety of useful products.55 During this research, the Romo group discovered that they were able to purify their dimers via flash chromatography. Without purification, the yield and diastereoselectivity in their epoxidation step were low. The resulting disubstituted β-lactones were able to purify their dimers via flash chromatography. Without purification, the yield and diastereoselectivity in their epoxidation step were low. The resulting disubstituted β-lactones were able to purify their dimers via flash chromatography. Without purification, the yield and diastereoselectivity in their epoxidation step were low. The resulting disubstituted β-lactones were able to purify their dimers via flash chromatography.

4. Asymmetric β-lactam synthesis

Intensive research has generated numerous methods of synthesizing the β-lactam skeleton.57 Commonly, the lactam ring is formed through either ketene–imine cyclizations (another ketene application pioneered by Staudinger)58 or ester enolate–imine condensations59 (the Gilman–Speeter reaction). However, other notable methods are sometimes employed, including photoinduced rearrangements60 and radical cyclizations.61 Despite all of these synthetic methods for obtaining achiral or racemic β-lactams, until the last decade asymmetric methodology has remained scarce, largely limited to chiral auxiliary based systems.62 A more general methodology based on asymmetric catalysis for the synthesis of optically enriched β-lactam was desirable.60a

4.1. Organocatalytic methodology

The Lectka group chose to focus their efforts on a catalytic modification of the highly effective Staudinger method, due to the ready availability of substituted imines, and the relative ease of generating ketenes from commercially available acid halides. Many of the new, clinically active β-lactam serine protease inhibitors being studied contain a carboxaldehyde substituent at the β-carbon and could be described as non-natural derivatives of aspartic acid. These could be formed from a Staudinger-type cyclization of ketenes and α-imino esters, which Lectka previously had used fruitfully in the asymmetric synthesis of amino acid derivatives catalyzed by chiral Lewis acids.63

The Staudinger reaction is known as a high background rate process64 normally no catalyst is needed to initiate smooth reaction, even at low temperatures. In order for a catalytic reaction to work, the classical Staudinger pathway (the imine nitrogen acts as a nucleophile toward the electrophilic ketene) must be ‘broken’. Subsequently, the reaction polarity must be reversed (umpolung) so that the imine and ketene switch roles; the imine must become electrophilic and the ketene nucleophilic. Alteration of the imine polarity was accomplished through the addition of an electron-withdrawing group to the imine nitrogen and a carboalkoxy substituent. These could be formed from a Staudinger-type cyclization of ketenes and α-imino esters, which Lectka previously had used fruitfully in the asymmetric synthesis of amino acid derivatives catalyzed by chiral Lewis acids.

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After successful early development of simple diastereoselective amine catalysts,65 the Lectka group was prompted to screen optically active cinchona alkaloid derivatives as potential candidates for enantioselective and diastereoselective catalysts.60 Catalyst development introduced an acyl derivative of quinine, namely benzoylquinine (BQ, 6a). When BQ was applied to the reaction of
diphenylketene with N-tosyl imino ester 53, the corresponding β-lactam was produced with high enantioselectivity (99% ee) albeit in only modest (36%) yield.¹¹ One of the most challenging aspects to this new chemistry, aside from the design of the catalytic system, was the development of techniques for using highly reactive monosubstituted ketenes.⁶⁷ As mentioned previously, these intermediates usually must be formed in situ and at reduced temperatures to prevent unwanted side reactions, most commonly dimerization and polymerization.

While hindered amine bases such as Hüning’s base were often inadequate, the combination of catalytic BQ and the non-nucleophilic amine base proton sponge (PS) as a thermodynamic proton sponge worked well, and the β-lactams were formed with very high enantio- and diastereoselectivity from a variety of acid chloride substrates (Scheme 4.2).⁶⁸ The β-lactam forming reaction is now compatible with a wide variety of ketenes, including aryl, alkyl, alkenyl, halogen, azo, and oxo-substituted (Fig. 4.1).⁶⁹ Of particular note, Lectka was able to synthesize both phthalimido and benzyl-substituted β-lactams that have been identified as precursors to cytomegalovirus protease inhibitors and human leukocyte elastase inhibitors, respectively.⁷⁰

The mechanism of this reaction was examined through a series of kinetics studies. For the reaction of phenylacetyl chloride with imino ester 53 catalyzed by BQ (6a) and using PS as the stoichiometric base, the rate determining step is the reaction between BQ and the acid chloride; this is followed by a series of fast cyclization steps with the imino ester. In some cases, the rate of product formation exceeds that of ketene formation when measured independently. This surprising discovery suggests that enolate generation in these cases occurs directly from the acid chloride; discrete ketene formation is consequently circumvented. This ketene-free mechanistic path is shown as scenario A in Scheme 4.3. On the other hand, acid chlorides with electron-withdrawing substituents tend to follow scenario B when proton sponge is the stoichiometric base, initially forming free ketene. When other stoichiometric bases are used (K₂CO₃, NaH, etc.), discrete ketenes must be synthesized in a ‘preformation’ step to avoid racemization of the product.

Dehydrohalogenation of the acid chloride substrate is accomplished through the shuttle deprotonation mechanism (see Section 1.3). Various bases can be employed, yielding similar results (Scheme 4.4). In these studies, Lectka discovered that with the stronger bases (NaH and K₂CO₃) a ketene preformation step was required, necessitating the use of the double reaction flask (see Fig. 1.3). However, both proton sponge and NaHCO₃, as weaker bases, not only required no preformation step but might, as shown above, bypass ketene formation altogether.

### 4.2. Bifunctional catalytic methodology

#### 4.2.1. cis-β-Lactams

The Lectka group’s interest in the field of bifunctional catalysis arose out of long-standing frustration with the low to moderate yields obtained with previous β-lactam methods (see Section 1.1). While BQ (6a) gives exceptional enantioselectivity,⁶⁶ the authors believe that the desired reaction of the ketene enolate and the tosyl imine (53) was sluggish enough to allow slow side reactions to proceed. Based on previous successes with activated imine alkylations,⁷¹ Lectka reasoned that addition of a Lewis acid cocatalyst would render the imine more electrophilic, thereby increasing the rate of the desired [2 + 2] cycloaddition pathway and suppressing the unwanted secondary reactions.

Initial bifunctional studies tested 10 mol% of the metal complexes that worked best for imine alkylation reactions,⁷² including Rh(PPh₃)₂OTf and Cu(PPh₃)₂ClO₄,⁷³ to the standard reaction conditions to form β-lactams.⁷⁴ Unfortunately, the overall yield decreased in the presence of these cocatalysts. In an attempt to discern the reason that known imine binding complexes were detrimental to the cycloaddition reaction, the authors monitored the Cu¹ reaction by UV–vis spectroscopy and found evidence of metal–BQ binding; this is an example of cocatalyst quenching that must be avoided in bifunctional systems (Scheme 4.5).
On the other hand, Aggarwal et al. found that group III and lanthanide triflates significantly enhanced their DABCO catalyzed Baylis–Hillman reaction, whereas ‘traditional’ Lewis acids lead to diminished yield.75 These findings suggested that harder, less aza-philic metals would minimize the cocatalyst quenching previously observed. A full spectrum of metal salts was screened with this in mind, demonstrating that triflates of Al III, Sc III, Zn II, and In III resulted in increased reaction rates and significantly enhanced chemical yield. Having firmly established In(OTf) 3 as the best overall Lewis acid cocatalyst for this reaction, Lectka applied this system to various substrates to determine the scope of its influence (Fig. 4.2). The yield increases in every case, generally by 1.5- to 2-fold with the In III co-catalyst, and the excellent enantioselectivity remains unaffected.74

4.2.2. Mechanistic inquiry

There are three potential mechanistic scenarios that could account for the observed effect of the Lewis acid. The original postulate was that In III binds to the imino ester and increases its reactivity toward the nucleophilic ketene enolate (A, Fig. 4.3). Another possibility is that the metal binds to the zwitterionic enolate, making it more thermodynamically stable (B, Fig. 4.3). This would have a multifaceted effect: (1) the more stable ketene enolate would be more chemoselective, eliminating undesired side reactions; and (2) assuming equilibrium between the ketene and the enolate, metal binding is expected to increase the relative quantity of the enolate, thereby accounting for the increased rate of reaction. A third scenario involves the simultaneous operation of both alternatives, with the metal organizing a termolecular activated complex (C, Fig. 4.3). Based on substantial mechanistic evidence, the metal–enolate binding scenarios (B and C) were eliminated.74b Notably, several stabilization of the enolate; BQ, MLn

\[
\text{Keq} < 1
\]

Ts
H OEt
Ln
MLn

Ts
H
R

O

BQ

2-Nu

LA-Nu

Lewis acid activation of the imine; consistent with IR and NMR evidence

\[
\text{LA-53}
\]

stabilization of the enolate; without metal \( K_{\text{en}} < 1 \)

\[
\text{2-Nu}
\]

a combination / ternary complex

\[
\text{LA-53} \cdots 2-\text{Nu}
\]

Figure 4.3. Possible roles of the Lewis acid.
seemingly similar bifunctional systems have been reported in which the Lewis acid acts in a different manner: Calter has found that a Lewis acid acts by binding and organizing a chelating version of the ketene enolate instead of activating the imine (see Section 4.2.3).76

The rate determining step (RDS) of the metal-free reaction involves acylation of the catalyst by the acid chloride and/or ketene formation. In the bifunctional system, it was found that the metal cocatalyst does not participate in the RDS but has a substantial effect on the chemoselectivity of a process after the RDS (Scheme 4.6). By using a ‘knock-out’ strategy where the original RDS is circumvented by preformation of the ketene,12b it was determined that In III enhances the rate of the C–C bond forming step. 74b

Lectka also established that metal binding to the imino ester plays a pivotal role in the bifunctional reaction. Coordination and complexion of metals with imino esters are well precedented,77 plays a pivotal role in the bifunctional reaction. Coordination and complexation of metals with imino esters are well precedented,77 and the authors found IR and NMR evidence that In III does bind to the imino ester in this system. However, a more direct (and more elegant) test for productive metal binding was designed, employing a modified imino ester that contains an additional metal binding moiety (55, Scheme 4.7).

In the absence of a metal cocatalyst, 57 reacts slightly faster (1.5 ×) than 55, so the proximity of the methoxy group has the expected effect. However, when In(OTf)3 is added as a cocatalyst, the reactivity is reversed—imino ester 55 reacts four times faster than substrate 57. Both substrates react faster with the metal than without; while imino ester 57 receives only a 3-fold rate increase from the metal cocatalyst, 55 experiences a tremendous 20-fold rate increase. The difference is clearly due to the tridentate nature of 55. The o-methoxy group helps hold the metal in place so it spends relatively more time activating the imine. Combining all of these data allows formulation of a mechanism for the bifunctional reaction of ketenes with imino esters (Scheme 4.8). Acylation of BQ forms the non-metal-coordinated zwitterionic enolate, activation of the imino ester by the InIII cocatalyst facilitates the C–C bond forming addition reaction, and a transacylation then forms the β-lactam and regenerates the catalyst.

4.2.3. α-Phenoxy-β-aryl-β-lactams

The Calter group has recently applied a silylated quinidine catalyst (7d), which they had used successfully in other ketene reactions, to the synthesis of α-phenoxy-β-aryl-β-lactams.76 They found that electron-withdrawing substituents on the nitrogen are essential to promote clean catalysis, settling on a phenylsulfonyl group for their screening after observing little or no yield with substituents such as methoxy and benzyloxy. Metal screening showed that ScIII and YbIII salts provided the highest conversions, and in further diastereoselectivity optimization, Yb(N(TMS)2)3 was a clear ‘winner’. For instance, the ytterbium counterion choice improved the cis/trans dr from 6:1 for triflate to 25:1 for hexa-methyldisilazide. The corresponding ScIII salts gave 2:1 and 18:1 dr. The combination of catalyst 7d and Yb(N(TMS)2)3 gave moderate to good yield and very good enantioselectivity for a variety of imines at loadings of 15 mol % (Table 4.1).

4.3. Trisubstituted β-lactams

4.3.1. Planar-chiral catalysts

Fu has applied his planar-chiral catalyst system to the asymmetric synthesis of trisubstituted β-lactams,78 using pregenerated,
disubstituted ketenes and a selection of imines as substrates. While this system also requires a strong electron-withdrawing group on the imine nitrogen, it is tolerant of a range of cyclic substituents on the α-carbon. His catalyst (9a) provides β-lactam products (62) in good yield and enantioselectivity (Table 4.2). Under the same reaction conditions, and with the same catalyst, Fu was also able to employ unsymmetrical disubstituted ketenes in his reactions, obtaining good cis-diastereoselectivity (8–15:1) with a range of substrates while maintaining high yield and enantioselectivity.

Table 4.2  
Synthesis of trisubstituted cis-β-lactams from disubstituted ketenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Ar</th>
<th>dr</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>-(CH2)5-</td>
<td>–Ph</td>
<td>–Ph</td>
<td>8</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>-(CH2)5-</td>
<td>–1-Furyl</td>
<td>–Ph</td>
<td>92</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-(CH2)5-</td>
<td>–β-Styryl</td>
<td>–Ph</td>
<td>91</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>Ph</td>
<td>Ph</td>
<td>8:1</td>
<td>98</td>
<td>88</td>
</tr>
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<td>Ph</td>
<td>β-Styryl</td>
<td>10:1</td>
<td>98</td>
<td>95</td>
</tr>
</tbody>
</table>

Some years after this initial communication, Fu et al. reported a variation on their reaction system.80 By changing the electron withdrawing substituent on imine nitrogen from tosyl to triflyl, the diastereoselectivity of the reaction favored trans over cis. Both good yield (80% average) and diastereoselectivity (5–50:1) were obtained, along with moderate to good enantioselectivity (63–85% ee, Eq. 4.1).

In an effort to explain this interesting diastereomeric reversal, the Fu group examined the interaction between this new imine substrate and catalyst 9a. For example, NMR studies of a mixture of the tosyl imine (61a) and 9a show no significant interaction between the two components, whereas a mixture of triflylimine 61b and 9a appears to exist almost entirely as a bound, zwitterionic species (61b-Nu). With this evidence in hand, they propose that when N-tosyl imine 61a is employed, the lactam is formed in the now familiar cycle of nucleophilic attack on the ketene by the catalyst followed by attack on the imine by the chiral, zwitterionic, catalyst-bound ketene enolate. The cycle is concluded by closure of the β-lactam ring to produce the product and regenerate the catalyst (scenario A, Scheme 4.9). However, Fu believes that if N-triflyl imine 61b is employed, the catalytic cycle is instead initiated by catalyst attack on the imine, leading to an alternate catalyst-bound, zwitterionic intermediate. The cycle would then complete in an analogous fashion by attack of the intermediate on the ketene followed by ring closure with concomitant catalyst regeneration (scenario B, Scheme 4.9).

4.3.2. N-Heterocyclic carbene based catalysis

β-Lactam formation can also be accomplished by chiral N-heterocyclic carbene (NHC) catalysis, as shown by Ye et al. in 2008.80 In this system, the catalyst is formed in situ from the corresponding tetrafluoroborate salt (44-H) by reaction with cesium carbonate (Scheme 4.10). The resulting chiral NHC then acts similarly to the tertiary amine catalysts we have seen so far, by creating a nucleophilic, zwitterionic ketene enolate from disubstituted ketenes. In this way, the reaction is very similar to their system for producing chiral trisubstituted lactones (see Section 3.4).

Initial catalyst optimization studies were done with N-tosyl aryl imines and disubstituted ketenes, and while yields were excellent, diastereoe- and enantioselectivity suffered. Digging further, they found that their NHC catalyst could react with tosyl substituted imines, potentially following a mechanism similar to Fu’s N-triflyl imines (scenario B, Scheme 4.9). This serendipitous discovery lead Ye to use less activated N-Boc imines for high selectivity, albeit with slightly lower yield (Scheme 4.11). The authors believe that the mechanism follows a stepwise pathway that begins with formation of a zwitterionic enolate (2-Nu).
ketenes was thoroughly screened. Most alkyl/aryl combinations worked well and produced the aza-β-lactam in good to excellent yield (53–90%) and good ee (87% on average, though the products recrystallize to >99% ee with little loss of the major enantiomer). Notably, while the authors believe that the reaction goes through the same mechanism as N-tosyl imine reactions (scenario A, Scheme 4.9), they note that the resulting stereochemistry at the newly generated quaternary center results from the opposite sense of induction.

Figure 4.4. N-Heterocyclic carbene catalysts utilized by smith.

4.4. Aza-β-lactams

The Fu group has expanded their trisubstituted β-lactam methodology to include aza-β-lactams (70). This system is again based on their planar-chiral catalyst 9a in the [2+2] cycloaddition reaction between disubstituted ketenes and azodicarboxylates (Scheme 4.12). Dimethylazodicarboxylate (69) was found to be the best substrate, and its reaction with various alkyl/aryl substituted ketenes was thoroughly screened. Most alkyl/aryl combinations worked well and produced the aza-β-lactam in good to excellent yield (53–90%) and good ee (87% on average, though the products recrystallize to >99% ee with little loss of the major enantiomer). Notably, while the authors believe that the reaction goes through the same mechanism as N-tosyl imine reactions (scenario A, Scheme 4.9), they note that the resulting stereochemistry at the newly generated quaternary center results from the opposite sense of induction.

Figure 4.4. N-Heterocyclic carbene catalysts utilized by smith.

4.5. Oxo-β-lactams

More recently, the Fu group discovered that disubstituted ketenes could react selectively with nitrosoarenes in a [2+2] cycloaddition reaction catalyzed by their planar-chiral catalyst, 9a (Scheme 4.13). The 1,2-oxazetidin-3-one products (72), here dubbed oxo-β-lactams, are produced regioselectively when the nitrosoarene is α-CF3-Ph (71). The cycloadducts are formed generally in high yield (87% average) with good enantioselectivity (78% to >98% ee). The authors also use the oxo-β-lactams to make chiral α-hydroxy acids (73) by a multi-step, high-yielding process.


5. Asymmetric halogenation

Catalytic enantioselective halogenation reactions can result in compounds that serve as useful intermediates in the construction of functionalized molecules. In the case of asymmetric fluorination, the products are medicinally and biochemically valuable in their own right. Halide substituents are amenable to SN2 displacement under a variety of conditions, leading to chiral alcohols, amines, amino acid derivatives, and sulfides. Asymmetric α-halo-lications of carbonyl compounds are particularly appealing, and can be realized with a variety of substrates, catalysts, and halogenating agents. While diatomic halides are known to be highly reactive, they are generally non-selective species and prove to be incompatible with a variety of functional groups within complex molecules, as well as being unsuitable reagents for enantioselective reactions. In order to accomplish asymmetric halogenations of ketenes and derived enolates under suitable conditions, mild sources of electrophilic halogenating agents, tuned precisely to the reactivity of the system, are needed.

In 2001, Lectka became interested in the possibility of catalytic, enantioselective α-halogenation reactions and subsequently published a number of papers on the subject.\(^5\) Historically, stereoselective halogenations have been achieved using either chiral halogenating agents or substrates adorned with chiral auxiliaries.\(^8\) Today, however, much of the focus lies in developing catalytic, asymmetric methods for generating halogenated compounds. Ultimately, the design of a catalytic, enantioselective halogenation reaction would most effectively utilize a very mild source of halogen that could be easily tuned. The first pioneering step in this field was reported by Togni, who developed a halogenation procedure employing a titanium–TADDOL catalyst (Scheme 5.1).\(^5\) This protocol is only effective for the halogenation of α-alkyl-1,3-dicarbonyl compounds that can readily form titanium-based enolates in situ.

### 5.1. α-Chlorination of monosubstituted ketenes

After Togni’s initial report, the catalytic, asymmetric chlorination of acid chlorides was reported by Lectka, who envisioned a process in which cinchona alkaloid derivatized ketene enolates react with a mild electrophilic halogen source in a tandem halogenation/esterification reaction (Scheme 5.1).\(^7\) The electrophilic halogen would add to the α-position of the ketene enolate, producing an acyl ammonium intermediate that subsequently transacylates with the leaving group of the electrophile. This sequence produces a versatile series of α-chloroesters (75) that serve as intermediates for the conversion to optically active amines, amides, ethers, and sulfides. Through the use of a selective halogenating reagent with a nucleophilic leaving group, this process could be adapted to react with ketene enolates enantioselectively.

![Scheme 5.1. Tandem catalytic asymmetric chlorination/esterification.](image)

The most important issue in the early stages concerned the choice of chlorinating agent. Diatomic chlorine was too reactive, whereas most other agents proved to be completely unreactive. Ironically, sources of halogen that are too mild pose the biggest problem, as they are unable to react with the weakly nucleophilic neutral zwitterionic enolate. It was clear that only a very narrow window of reactivity existed in which a desirable chlorinating agent (76) could operate selectively in a catalytic cycle. Nevertheless, Lectka began by screening sources of electrophilic halogen such as N-chlorosuccinimide (NCS), alkylhypochlorites,\(^9\) and various N-chloroamides, in a reaction with in situ generated phenylketene using BQ (6a) as a catalyst. For these tests, phenylacetyl chloride was added to a solution of 10 mol% BQ and 1.1 equiv of proton sponge at −78 °C to generate the ketene. N-Halosuccinimides and N-chloroamides were unsuccessful, as were a bevvy of other candidates such as chlorinated pyridones, iodanes, and sulfonamides. On the other hand, tert-butylihypochlorite was too reactive, chlorinating almost anything in the reaction mixture, including solvent. Attention turned to polyhaloquinone-derived reagents such as 76a,\(^2\) which have a long history as often unanticipated byproducts of aromatic halogenation reactions. Hundreds of them are known in the literature; they are often easy to make (or in certain cases purchase). For example, pentachlorophenol reacts readily with tert-butylihypochlorite to produce quinone 76a in quantitative yield (Eq. 5.2).

![Scheme 5.2. Ketene phenolysis with proton sponge.](image)
In light of these difficulties Lectka decided to focus on pregen-
eration of ketene solutions with the polymer-bound phosphazene
base BEMP. When a solution of phenylacetyl chloride in THF is
passed through an addition funnel containing at least 1 equiv of
BEMP at −78 °C, phenylketene is produced quantitatively. The
ketene solution was allowed to drip slowly into a flask (−78 °C)
containing BQ (76a, 10 mol %) and to this was added a solution of
76a. This process yields pentachlorophenyl α-chlorophenylacetate
in 80% yield and 99% ee (entry 1, Table 5.1). A number of other
acid chlorides were screened using this procedure and those results
are summarized in Table 5.1.

Table 5.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>2-Thiophene</td>
<td>80</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>97</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>1-Np</td>
<td>95</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>2-Np</td>
<td>94</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>PhOCH2</td>
<td>97</td>
<td>57</td>
</tr>
</tbody>
</table>

While this procedure works well, it is somewhat tedious and
BEMP resin is expensive. It was the attempt to overcome the need
for the BEMP system that led to the discovery discussed in Section
1.3, namely that the shuttle deprotonation method can be per-
formed with heterogeneous bases such as NaH. In this case, the
ketene is generated through a system that employs BQ and 15-
crown-5. This process yields pentachlorophenyl α-chlorophenylacetate
in 80% yield and 99% ee (entry 1, Table 5.1). A number of other
acid chlorides were screened using this procedure and those results
are summarized in Table 5.1.

As α-chloro acid derivatives should serve as useful synthetic
precursors to more complex molecules, a general method for the
stereoselective displacement of the halide group is desirable.
D’Angeli et al. have published a report on the stereoselective nu-
cleophilic substitution of 2-bromoamides by amines in the presence
of Ag⁺ or Ag₂O. The authors observed full inversion of configuration
in the presence of AgOTf or powdered Ag₂O as a promoter under soniciation.
Taking their cue, the Lectka group applied a similar procedure to α-chloroamides.
For example, when optically enriched amide 77 is mixed with AgOTf and an amine such as piperidine,
the corresponding α-amino amide is produced in high yield with stereochemical inversion, although about 10% of
optical purity was lost (Eq. 5.5).

5.2. α-Bromination of monosubstituted ketenes

While the α-chlorination method is effective, the synthetic
utility of the product is somewhat limited by the aforementioned
tendency toward racemization in some displacement reactions.
This led to an expansion of the methodology to include alkyl bro-
mides, which are generally believed to be the most synthetically
useful of the halides as they often react through a pure S N2
mechanism and the resulting halides are prone to racemization.
Various differences exist between the chlorination and
bromination reactions. For example, the initial bromination con-
ditions worked well on a small scale, but increasing the scale of the
reaction resulted in exponential loss of yield and enantioselectivity.
As the reaction progressed, the optical purity was lost (Eq. 5.5).

The postulated reaction sequence (Scheme 5.3) matches that for
the α-chlorination reaction, proceeding from the acid chloride
starting material (1) to a zwitterionic enolate (2-Nu) formed by
the action of the nucleophilic catalyst (6e) and a stoichiometric base.
The authors believe that this transient, chiral nucleophile abstracts
electrophilic bromine from the brominating agent (79a), producing
an ion-paired intermediate that undergoes transacylation to pro-
duce the desired product (78) and regenerate the catalyst for an-
other cycle. The resulting optically enriched α-bromoesters are
produced in high ee and moderate to good chemical yield.
The initial bromination conditions were optimized to eliminate problems with loss of selectivity and yield upon scale up. These optimization procedures involved: (1) development, through de novo design, of a more selective catalyst, proQ (6e); (2) using ortho-brominating agent 79a (Scheme 5.3) instead of para-brominating agent 79b (Scheme 5.4); and (3) changing the stoichiometric base from heterogeneous carbonates to homogeneous Hu¨ nig’s base for phenylacetyl chloride (1d) with an 1:1 mixture of 76a and 79b yields products 75a and 78a exclusively at all levels of conversion (Scheme 5.5). In general, the brominating agent (79b) is about 10 times as reactive as the chlorinating agent (76a) in THF at −78 °C. No crossover products that would arise from phenolate/acyl ammonium salt dissociation were observed.

To address the role that ion pairing and/or dissociation plays in racemization, Lectka used another brominating agent derived from 2,6-di-tert-butylphenol, which should provide quick bromination and slow transacylation.16 This would lead to a long-lived ion pair intermediate (Scheme 5.6). However, brominating agent 79c provided little or no desired product (78b) in a standard reaction, but adding 1 equiv of sodium pentachlorophenolate produces a satisfactory yield of product 78c by promoting transacylation and catalyst turnover. This product was virtually racemic; the intervening time between bromination (by 79c) and transacylation is necessarily long compared to reactions that use brominating agent 79b, so racemization does occur in the ion-paired intermediate. Control experiments revealed that sodium pentachlorophenolate neither catalyzes the reaction nor racemizes an optically pure version of the product.17

The displacement of bromine by a variety of nucleophiles provides a distinct advantage as the reaction often proceeds through a pure S_{2}2 mechanism under mild conditions. A practical use for ortho-bromoester products would be the straightforward synthesis of optically active epoxides. Chiral epoxide chemistry has been a topic of intense interest for a generation, and some of the most notable

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**Scheme 5.3.** Optimized catalytic, asymmetric bromination/esterification.

**Scheme 5.4.** The halogenating agent’s effect on intermediate lifetime.

**Scheme 5.5.** Crossover experiments.

**Scheme 5.6.** The effect of a hindered brominating reagent.
advances in asymmetric catalysis have been made in this area.\textsuperscript{98} Several challenges remain; among the most notable is the catalytic, asymmetric synthesis of terminal epoxides, although Jacobsen has addressed the problem from one angle by a catalytic, asymmetric hydrolytic resolution of chiral epoxides.\textsuperscript{99}

The strategy is simple—a reduction of the optically enriched α-bromoester is followed by base-promoted cyclization to the epoxide.\textsuperscript{86} As a proof of principle, this reaction sequence was performed on α-bromoester \textsuperscript{76d}. After conversion to the corresponding alcohol \textsuperscript{80} by NaBH\textsubscript{4}, displacement of bromine, via an intramolecular cyclization to form the chiral epoxide \textsuperscript{81}, was accomplished by treatment of the alcohol with KOH under ambient conditions.\textsuperscript{100} The reaction proceeded in 80\% yield and with full retention of enantioselectivity (Eq. 5.6).

\begin{equation}
\text{Br}_{3}C(OH)Ph + KOH \rightarrow \text{PhO}_{2}C(OH)Br \quad (5.6)
\end{equation}

### 5.3. α-Chlorination of disubstituted ketenes

Recently, Fu et al. published interesting results on the asymmetric halogenations of disubstituted ketenes.\textsuperscript{101} An initial screen showed that many commonly employed chlorinating agents (76) were unsatisfactory, though hexachloroacetone (76c) gave nearly complete conversion with promising enantioselectivity (Scheme 5.7). Reasoning that a conformationally constrained variant of \textsuperscript{76c} might provide improved selectivity, the Fu group turned to 2,2,6,6-tetachlorocyclohexanone (76d) with excellent results. The use of this compound as a halogenating agent produces α-halogenated esters from disubstituted ketenes in good yield and moderate to high enantioselectivity.

\begin{equation}
\text{Ar R} + LG-Cl \rightarrow \text{Ar R} \quad (5.7)
\end{equation}

\begin{center}
\textbf{Scheme 5.7.} Selection of the chlorinating agent.
\end{center}

At this time, the mechanism of this reaction is still unclear. Fu favors two possible scenarios. The first is similar to the catalytic cycle proposed by Lectka (see Scheme 5.1); the reaction is initiated by catalytic attack on the ketene generating a chiral ketene enolate (2-Nu) that abstracts chlorine from the chlorinating agent (76d). The chlorinated intermediate is subsequently converted to the product (75) via catalyst displacement by the enol byproduct of chlorine abstraction from the chlorinating agent, simultaneously regenerating the catalyst for another cycle (scenario A, Scheme 5.8).

The second scenario Fu proposes is analogous to the cycle he has put forth for his catalyzed coupling of disubstituted ketenes with phenols (see Scheme 2.3). In this scenario, the catalyst initiates the reaction by direct attack on the chlorinating agent while the byproduct acylates the ketene, generating the enolate and a catalytic source of chiral, electrophilic chlorine. The enolate then abstracts Cl\textsuperscript{+} from the catalyst complex, simultaneously generating the desired product (75) and regenerating the catalyst for another cycle (scenario B, Scheme 5.8). A key component of the utility of α-haloesters is the flexibility of the ester functionality; the Fu group activates the enol ester with bromine, allowing the conversion to simple alcohols (82) or esters (75c), via a two-step processes in good yield and without loss of ee (Scheme 5.9).

\begin{center}
\textbf{Scheme 5.8.} Possible catalytic cycles for the α-chlorination of disubstituted ketenes.
\end{center}

\begin{center}
\textbf{Scheme 5.9.} Transformations of enol ester products.
\end{center}

### 5.4. α-Fluorination of dually activated ketenes

Ketene enolates have also been found by the Lectka group to react with an electrophilic source of fluorine, N-fluorobenzensulfonylimide (NFSi, 83).\textsuperscript{87a} Fluorinations of any kind have been highly sought after in the last decade, not least because the number of pharmaceutically active compounds or drugs on the market containing fluorine is growing rapidly every year. In addition, only a very small number of currently known natural products contain fluorine; by the year 1999, only about a dozen fluorinated natural products had been isolated 50 years after the discovery of the first.\textsuperscript{102} In the 10 years since, researchers have enthusiastically sought fluorinated natural products because of their medicinal promise, yet only a score more have been characterized; the number of fluorinated drugs on the market now exceeds the
number of known fluorinated natural products by an order of magnitude\cite{103} if a fluorine is desired for a drug candidate, it generally must be installed synthetically. The selective installation of fluorine, particularly at chiral centers, is of crucial importance to medicinal chemistry. Because of the unique properties of the fluorine atom, based on its high electronegativity, small atomic radius, and high C–F bond strength, strategic fluorination can drastically alter the metabolism of a drug, its bioavailability, activity, or a host of other relevant properties.\cite{104} In any case, a general catalytic method for the asymmetric \( \alpha \)-fluorination of carboxylic acid derivatives (85) is highly desirable.

Lectka’s fluorination method is based on a dual-activation strategy where the ketene (generated in situ from acid chlorides) is activated by a chiral catalytic nuclophilic 
ketene anion to form a nucleophilic ketene enolate, the reactivity of which is tuned by an achiral [d\( ^{8} \)] metal complex. This dual-activation strategy was investigated mechanistically in another reaction (see Section 6.1.2),\cite{105} but preliminary evidence suggests that the mechanism of Pd\( ^{II} \) or Ni\( ^{II} \) catalysis is the same in both systems, that is, by formation of a dually activated enolate complex (LA-2-Nu, Scheme 5.10).

In the fluorination system, it seems that the fluorinated acyl ammonium intermediate is resolved by the bis-sulfonimide anion, regenerating the BQd and making the semi-stable intermediate 84. This intermediate was not isolable, but reacted smoothly in situ with any number of mild nucleophiles, serendipitously making this fluorination reaction far more versatile. Acid halides containing aromatic as well as heterocyclic substituents proved to be good substrates, producing products in very high ee and good to excellent yields (Fig. 5.1). Protected aminoketone-substituted acid chlorides also work well, leading to \( \alpha \)-fluorinated \( \beta \)-amino acid derivatives. Other examples, such as the fluorination of an aldol adduct to form 85c shows that the reaction is also compatible with isomerizable carbon–carbon double bonds. A number of acid chloride and quenching nucleophile combinations were screened in this fluorination system, and products were consistently isolated in good yield and excellent ee.

The power of this new method is demonstrated in the broad range of different derivatives that can be synthesized by simple modification of the work up conditions; \( \alpha \)-fluorinated carboxylic acids, amides, esters, and even peptides are all accessible depending on the nucleophile employed to quench the reaction. For example, a water work up affords \( \alpha \)-fluoro carboxylic acids, compounds that potentially are of broad utility as derivatizing agents. Along with an alcohol quench that provides esters, an amine-based work up affords amides; accordingly, thioesters can be readily accessed. In a representative example, work up with l-phenylalanine ethyl ester produces the fluorinated peptide 85d in 68% yield and >99% diastereomeric excess (de). Either enantiomer at the fluorinated carbon can be produced in similarly high ee with the simple selection of BQ or BQd (for instance, 85b was produced by BQ while the rest of the products in Fig. 5.1 were made by BQd catalysis).

One of the best aspects of this method is the ease with which drugs, natural products, and other ‘exotic’ nucleophiles can be functionalized, as the reaction initially provides chiral, \( \alpha \)-fluorinated acylsulfonimides that can be quenched ‘in flask.’ For example, the isoquinoline alkaloid\cite{106} natural product emetine can be used to quench the \( \alpha \)-fluorination reaction of 3-phthalimidopropionyl chloride (1j) (91% yield, >99% de, Eq. 5.7). Given the variety of natural products that can be coupled with the chiral, fluorinated intermediates, large numbers of potentially useful \( \alpha \)-fluorinated derivatives are accessible.

For a complimentary example of the utility of this \( \alpha \)-fluorination method, the Lectka group demonstrated the derivatization of indomethacin (an anti-inflammatory drug, Eq. 5.8). Oxalyl chloride cleanly produces the acyl chloride 86 from indomethacin, which is then subjected to standard reaction conditions (using \( \text{trans-} \) \( \text{PPh}_3 \) \( \text{PdCl}_2 \)) and quenched with the appropriate nucleophile (85f is formed in 85% overall yield and 95% ee when NuH=MeOH). This process should be applicable to a vast array of biologically relevant carboxylic acid derivatives.

6. Asymmetric [4 + 2] cycloaddition reactions

6.1. o-Benzoinonone derivatives

Catalytic, enantioselective cycloaddition reactions of \( \text{p} \)-quinones are well documented.\cite{107} The products of these reactions are potentially very useful in the realm of natural product synthesis; however, until recently, little analogous work has been done on the catalytic, asymmetric reactions of \( \text{o} \)-quinones and derivatives.
o-Quinones have a potentially much richer reactivity spectrum—cycloaddition reactions may involve the ring carbons (as in the well-studied p-quinone isomers), but more interestingly, reactions may proceed through the o-heteroatoms to provide useful bicyclic products (Scheme 6.1).

For example, the o-hydroxy esters obtained from o-quinones have found application as inhibitors of amyloid-β (Aβ) protein production, and thus show promise in the treatment of Alzheimer’s disease.

Chiral o-oxygenated carboxylic acid products can also be derivatized in a variety of useful ways. o-Quinone imides can provide easy access to invaluable, non-natural l-amino acids (both protected and unprotected), which find uses in all areas of biochemical study. Quinone imides also provide access to oxazinones and oxazines, bicyclic products that are useful as antitumor agents, topoisomerase inhibitors, and antibiotics.

o-Benzooxoimino diimides produce quinoxalines and their quinoxaline derivatives, all of which exhibit a wide range of biological activity including antiviral effects, particularly against retroviruses such as HIV.

Lectka has recently discovered that catalytically generated ketene enolates can be used to initiate a cycloaddition reaction with a wide variety of o-benzoquinone derivatives to give [4+2] bicyclic adducts in good to excellent yield and very good to excellent enantiomeric excess (up to >99% ee, Scheme 6.1). While the products of these cycloadditions are interesting and useful as chiral building blocks for organic synthesis, both they and their readily obtained derivatives show even greater utility and promise in a variety of physiological applications. These reactions are discussed in following subsections.

6.1.1. o-Quinone reactions

The redox chemistry of o-quinones has been extensively outlined. Many isolable o-quinones are known in the literature, and many more can be made through straightforward catechol and aminophenol based oxidations. Recently, Pettus et al. have reported a very useful synthesis of o-quinones from phenols using hypervalent iodine oxidants. In many instances o-quinones can be isolated, but they are also frequently used in situ. o-Quinone cycloadditions give rise to several different product classes, depending on the reaction partners. For example, reactions with acetylenes may afford bridged bicyclic adducts, whereas cycloadditions with nucleophilic alkenes, such as enol ethers and enamines, are anecdotally noted to proceed through the quinone oxgens. Since ketene enolates are somewhat similar in structure and reactivity to these substrates, they should react through oxygen atoms as well. The initial screen by Lectka et al. employed o-chloranil (7A), butyryl chloride, and BQd (7B, 10 mol%) in the presence of Hünig’s base (1 equiv) in THF at −78 °C. The yield of the reaction was an excellent 91% with 99% ee (Scheme 6.2). Other o-quinone substrates were also screened, for instance o-bromanil (7Bb) was found to form product 88b in high ee (95%), and 90% yield. 9,10-Phenanthrenequinone (87c) was screened using similar conditions; its reactivity proved to be much lower than o-chloranil. However, when the reaction temperature was raised to 0 °C, reaction occurred sluggishly to afford product (88c) in reasonable yield. On the other hand, 4,5-dimethoxy-o-quinone failed to provide appreciable product under any conditions.

Given the superiority of o-chloranil in the initial tests, the authors decided to investigate its reaction with a variety of acid chlorides. For example, dihydrocinnamoyl chloride performed well, affording cycloadduct 88e (Fig. 6.1) in high ee (99%). Additionally, o-arylacetyl chloride proved to be excellent substrates. For example, phenylacetyl chloride generated product 88d in high yield (90%) and good ee (90%). Using BQd as catalyst, the (R)-enantiomer (assignment based on R priority as if aliphatic) formed preferentially, while the (S)-enantiomer could be obtained in similarly high enantioselectivity when BQ (6a) is used. This sense of induction held for all quinone derivative substrates, as well as all acid chlorides, and is consistent with other asymmetric reactions that have employed these cinchona alkaloid derivatives to catalytically generate ketene enolates.

The o-chloranil-derived cycloadducts can be further modified to produce chiral, o-oxygenated carboxylic acid derivatives (Scheme 6.3). For example, methanalysis of benzodioxinone 88d (Fig. 6.1) followed by ceric ammonium nitrate (CAN) oxidation affords (+)-methyl mandelate (90c, Fig. 6.2) in excellent yield (95%) and ee (90%). For maximum utility, reaction with the nucleophile (H2O, ROH, or RNH2) may occur in the same pot as the cycloaddition. Thus, the quinone can be thought of as a template for chiral, o-oxygenated carboxylic acid and ester synthesis. Several other cycloadducts were likewise converted to optically active o-hydroxy esters (Fig. 6.2). In each case,
the reaction proceeds in high yield and with full retention of optical activity.

**Figure 6.2.** A selection of α-hydroxy esters, from α-chloranil and acid chlorides.

### 6.1.2. Bifunctional catalytic o-quinone reactions

Despite efforts to increase the yields of the α-hydroxy ester products by conventional means, Lectka’s cycloaddition reaction simply proceeds sluggishly, resulting in lower than optimal yields. As he had success in the past with bifunctional catalytic systems, he turned once again to Lewis acid cocatalysis. From the group’s earlier work on a bifunctional β-lactam forming system (see Section 4.2), and two other inverse-electron-demand hetero-Diels–Alder reactions of ketene enolates (discussed in Sections 6.1.3 and 6.1.4), each which favored a similar set of metal cocatalysts, the authors set out to use these bifunctional principals to add a productive metal cocatalyst to the o-quinone cycloaddition reaction (Fig. 6.3). In other words, they sought to increase the electrophilicity of the quinone by coordinating it with a Lewis acid, thereby amplifying its reactivity with the mildly nucleophilic ketene enolate. Unfortunately, this line of screening was met by frustration as oxophilic metal salts were unsuccessful. Surprisingly, it was azaphilic [d8] metal complexes that were able to provide increased rate and yield; bis-triphenylphosphine dichloride salts of nickel, palladium, and platinum each provided increased yields of the cycloaddition reaction (and hence the conversion to α-hydroxy esters) up to a 60% increase caused by trans-[P(Ph3)2PdCl2], along with a corresponding twofold rate increase. Intrigued, Lectka set out to interpret this apparent divergence from the precedent bifunctional catalytic cycloaddition reactions (Scheme 6.3). FTIR and NMR data gave no evidence of coordination between any metal salt and the o-chloranil. It seems that classic Lewis acid action is not the way to understand palladium catalysis in this system, which in turn explains the mechanistic divergence from other analogous cycloaddition reactions.

Using density functional theory (DFT) to calculate the electrostatic charges at the carbonyl carbons for each putative structure of Figure 6.4, we find that ScIII (B) should withdraw electron density from the chloranil relative to bare chloranil (A). This means that if this coordination actually occurred, the ScIII would act as a classical Lewis acid, making the electrophilic quinone more reactive, and should therefore make the cycloaddition reaction faster. Since ScIII actually inhibits the reaction progress, we know that it does not bind in this manner, supporting the binding experiments mentioned earlier. The numbers for the two putative PdII bound structures (C) and (D) are more interesting. They show that if palladium were to bind to the chloranil in either a six- or four-coordinate fashion, it would not be productive; in both cases PdII would decrease the electrophilicity of the quinone.

**Figure 6.4.** DFT (B3LYP/LANL2DZ) calculations of putative o-chloranil (87a) bound metal complexes.

These DFT calculations (along with several other calculations not discussed here, including transition state models) are in line with the spectroscopic data and support the conclusion that the palladium does not act by coordination to the quinone but must play some other role. After controlling for any possibility of Pd0 involvement, it seemed that the most likely remaining scenario involved PdII coordination to the ketene enolate (Eq. 6.1). Intuitively, it seems that this type of coordination would stabilize the ketene enolate rather than making it more nucleophilic. However, as the ketene enolate is only present in solution in equilibrium with free ketene, such stabilization would theoretically increase the concentration of reactive species, thereby increasing the reaction rate. An additional effect could also have to do with the reactivity/selectivity principle, where increased yields could also be explained by higher chemoselectivity—marked by fewer unproductive side reactions.

An experiment designed to shed light on this hypothesis necessitated the use of a more stable ketene; phenylethylketene (PEK,
2k) was chosen because it does not dimerize readily or participate in any other side reactions. In a UV–vis experiment at −78 °C, the amount of ketene enolate was increased by almost 40% when PdII was added to solution of PEK and BQ. With this data, backed by substantial theoretical calculation work, the authors proposed that the way to understand PdII cocatalysis in this cycloaddition reaction is through its binding with the ketene enolate, thereby increasing the reaction rate and chemoselectivity (Scheme 6.4). (After this mechanism was clarified, the Lectka group revisited the reaction rate and chemoselectivity (Scheme 6.4).)87a

With this improved method for the synthesis of α-hydroxy acid derivatives in hand, the authors demonstrated the ability to access a variety of important, biologically relevant classes of compounds in high yield and enantioselectivity, by simply modifying the acid chloride. As an example, by using 4-chlorobutyryl chloride with BQ (6a), γ-lactam (5)-93 can be made in 82% yield (four steps) and >99% ee (Scheme 6.5). This intermediate is the key component in the synthesis of (l)-vasicinone, a drug that serves as a remedy for bronchitis and asthma, and its formation here constitutes a formal total synthesis of (S)-(−)-vasicinone, the most efficient to date.121 γ-Lactams are also known to be potent antibacterial agents,122 HIV protease inhibitors,123 and thrombin inhibitors.124

Analogously, γ-lactones have been employed as novel antibacterial and antitumor agents.125 This structural unit frequently occurs in natural products including classes of alkaloids,126 macrocyclic antibiotics,127 and pheromones.128 This valuable entity can be made by using 4-benzyloxybutyryl chloride to produce γ-lactone 92 in 88% yield (from o-chloranil) and >99% enantiomeric excess (Scheme 6.5).

6.1.3. o-Quinone imide reactions

o-Benzoxquinone imides (94) are intriguing for several reasons; the products of their cycloaddition with ketene enolates are chiral benzoxazines (95) and benzoxazines (97, Scheme 6.6), interesting compounds with biological potential for which few asymmetric syntheses exist. For example, they have been investigated as antitumor agents, as selective inhibitors of drug metabolism and topoisomerase,129 and have been shown to possess promising neuroprotective antioxidant activity.130 Prescription drugs, such as the new generation antibiotic Levaquin (levofloxacin), for example, are also benzoxazines.131 Perhaps most importantly, o-benzoquinone imides can function as a scaffold for the synthesis of optically active non-natural α-amino acid derivatives (98, Scheme 6.6).

Scheme 6.4. Palladium(II) cocatalyzed cycloaddition reaction mechanism.

Scheme 6.5. Synthesis of α-hydroxy γ-lactones and lactams.

Scheme 6.6. Products obtained from reactions of quinone imides.
The isolable o-benzoquinone imides are easily synthesized via 
\( \text{Pb}^{II} \) oxidation of the corresponding 2-aminophenols. In a study 
published in 2001, Nicolaou explored the use of o-benzoquinone 
imides as Diels–Alder dienes, finding that they react through the 
N and O atoms, as desired.\(^{130} \) Importantly, their reactivity can be tuned 
by modifying the substituent on N. For example, an electron-withdrawing 
group (such as an acyl group) on the nitrogen should enhance 
the electrophilicity toward the enolate. Lectka chose to screen 
substituents (derived from the acid chloride), a testament to the flexibility of this method, a wide variety of R- 

derivatives in high chemical yield, and very high enantioselectivity. As 
ao- 

hance the electrophilicity toward the enolate. Lectka chose to screen 
drawing group (such as an acyl group) on the nitrogen should en-
nanpounds rely on metal-based catalysts, for example, asymmetric 
has been a paramount goal of asymmetric catalysis for more than 
catalyzed’ process. \(^{136} \) Another notable advance is represented by 
plex\(^{133} \) leads to the corresponding benzoxazine ( Scheme 6.6 ) in 
zoxazines; a simple reduction with dimethyl sulfide–borane com-
benzoxazinone cycloadducts are also readily converted into ben-
N atoms, as desired.\(^{130} \) Importantly, their reactivity can be tuned 
position are present to block undesired reactivity at the quinone 
ring, as well as to enhance the overall electrophilicity of the system. 

The reaction of various combinations of acid chlorides and 
quinone imides, in the presence of 10 mol % \( \text{BQd} \) \((7a) \) and Hünig’s 
base in THF at \(-78 °C\), forms the desired cycloadducts in fair yield 
and uniformly excellent ee (\(-99% \) ee in all cases, Fig. 6.5).\(^{132} \) The 
benzoxazine cycloadducts are also readily converted into ben-
zoazines; a simple reduction with dimethyl sulfide–borane com-
plex\(^{133} \) leads to the corresponding benzoxazine ( Scheme 6.6 ) in 
good yield and with full retention of ee. 

The efficient synthesis of non-natural \( \alpha \)-amino acid derivatives 
has been a paramount goal of asymmetric catalysis for more than a 
generation. Many approaches to the synthesis of these compounds 
rely on metal-based catalysts, for example, asymmetric 
hydrogenation\(^{134} \) and Lewis acid catalyzed alkylations.\(^{135} \) The 
O’Donnell phase-transfer system is a good example of an ‘organocatalyzed’ process.\(^{136} \) Another notable advance is represented by 
the asymmetric Strecker reaction that can be catalyzed by either 
metal-based or organic systems.\(^{137} \) 

Lectka has developed a complementary approach to the synthesis 
of \( \alpha \)-amino acid derivatives that relies on an asymmetric cycloaddition 
of o-benzoquinone imides with chiral ketene enolates. The 
cycloadducts are derivatized in situ to provide the \( \alpha \)-amino acid 
derivatives in high chemical yield, and very high enantioselectivity. As 
a testament to the flexibility of this method, a wide variety of R-
substituents (derived from the acid chloride), N-acyl groups, and 
carboalkoxy groups can be incorporated into the optically enriched 
products (Figs. 6.6–6.8). The bicyclic products are activated esters and 
react smoothly with alcohols and amines to afford \( \alpha \)-amino esters and 

![Figure 6.5. Benzoxazinone products.](image)

![Figure 6.6. A selection of N-aryl \( \alpha \)-amino acid derivatives.](image)

![Figure 6.7. Highly biologically significant \( \alpha \)-amino acid derivatives.](image)

![Figure 6.8. A selection of \( N \)-protected \( \alpha \)-amino acid derivatives.](image)

![Scheme 6.7. The bifunctional system to form \( \alpha \)-amino acid derivatives.](image)
operates through coordination with the diimide. Zn(OTf)\textsubscript{2} was used on his previous success with activation of imino esters.\textsuperscript{63b} Al\textsuperscript{III} and Lectka screened a number of metal triflates that were chosen based system more electrophilic, thereby increasing the reaction rate; formation of the diimide by coordnation of a Lewis acid should render the byproducts along with the desired cycloaddition product. Activation (GABA)/benzodiazepine receptor complex,\textsuperscript{145} inhibitors of aldose transferase proteins.\textsuperscript{111}

6.1.4. \textit{o}-Quinone diimide reactions

Quinoxalinones (100), products of the Diels–Alder reaction between ketene enolates and \textit{o}-benzoquinone diimides (99), are useful templates for drug development because of their structural relationship to benzodiazepines.\textsuperscript{143} These attractive targets exhibit a wide range of biological activity, including antidiabetic\textsuperscript{144} and antiviral effects,\textsuperscript{112} in particular against retroviruses such as HIV. In addition, they are partial agonists of the \textit{\gamma}-aminobutyric acid (GABA)/benzodiazepine receptor complex,\textsuperscript{145} inhibitors of aldose reductase,\textsuperscript{146} and agonists of the AMPA and antiotensin II receptors.\textsuperscript{147} Related quinoxalines that are easily made from the respective quinoxalinones by a simple reduction also possess biological activity, for example, as inhibitors of cholesteryl ester transferase proteins.\textsuperscript{111}

\textit{o}-Benzoquinone diimides are easily prepared by Pb\textsuperscript{IV} oxidation of the respective 1,2-dianilides, as outlined by Adams and Way.\textsuperscript{148} Initially, the authors screened 4,5-dichloro diimide (99, R\textsubscript{1} = R\textsubscript{2} = Cl, Scheme 6.8) in a reaction with butyryl chloride, Hünig’s base, and BQd at \textdegree \textsuperscript{C} 78 in THF.\textsuperscript{149} The sluggish reaction formed several byproducts along with the desired cycloaddition product. Activation of the diimide by coordination of a Lewis acid should render the system more electrophilic, thereby increasing the reaction rate; Lectka screened a number of metal triflates that were chosen based on his previous success with activation of imino esters.\textsuperscript{53b} Al\textsuperscript{III} and In\textsuperscript{III} provided 64% and 65% yield, respectively, in the standard reaction (a large increase over the metal-free reaction), though Sc\textsuperscript{III} and Zn\textsuperscript{II} were far superior. For example, the initial rate of a standard reaction increased by over 2000% and cycloaddition product was isolated in 82% yield when 10 mol % Zn(OTf)\textsubscript{2} was used as a cocatalyst. An IR experiment confirmed the notion that the Lewis acid operates through coordination with the diimide. Zn(OTf)\textsubscript{2} was used as a cocatalyst in subsequent reactions, providing the bifunctional catalytic system depicted in Scheme 6.8.

\begin{equation}
\text{LA-99} + 2 \text{OTf}^\text{-} \rightarrow \text{BQd} + \text{Zn(OTf)}_2
\end{equation}

Scheme 6.8. A bifunctional catalytic system to produce quinoxalinones.

This bifunctional catalytic methodology was thoroughly tested to determine its scope. A variety of substituted quinoxalinones were produced in good to excellent yield and all products were obtained in >99% ee (Fig. 6.10). In fact, the minor enantiomer was not detected by chiral phase HPLC in any chiral reaction, and for each reaction, only one regiosomer was obtained. The extreme selectivity consistently observed with this method was rationalized by the stepwise mechanism depicted in Scheme 6.9. The bifunctional reaction relies on quinone diimide activation by the Lewis acid (LA-99a) with concurrent nucleophilic activation of the ketene by BQd (2m-Nu). The regioselection comes from nucleophilic attack by the ketene enolate on more electrophilic nitrogen of the activated quinone diimide. Subsequent cyclizations of the stabilized intermediate provide the quinoxalinone product.

\begin{equation}
\text{LA-99a} + 2 \text{OTf}^\text{-} + \text{Zn(OTf)}_2 + \text{BQd} \rightarrow \text{100a}
\end{equation}

Figure 6.10. A sample of quinoxalinone products.
reaction gave the (R)-cycloadduct in >99% ee and moderate yield. Selective deprotection by TFA produces the target quinoxaline (100f) in 94% yield with full retention of ee. A second drug target, a quinoxaline that is known to inhibit cholesteryl ester transfer protein (101, Scheme 6.10), was produced by reduction of the cycloaddition product. Reduction by LiAlH4 cleaves the benzoyl groups and simultaneously reduces the lactam carbonyl, affording the respective quinoxalines (101) in quantitative yield with full retention of ee.

6.2. N-Thioacyl imine reactions

Nelson has successfully applied a bifunctional catalytic system using O-TMS quinine (6d) or quinidine (7d) and cocatalyst LiClO4 to the [4+2] cycloaddition reaction between N-thioacyl imines and ketenes. In this system, both the imine and the ketene are formed in situ by deprotonation of the N-sulfinate mixed acetal and the acid chloride, respectively (Scheme 6.11). Nelson proposes that the Li+ acts to coordinate the transition state complex into a chair-like formation (103), enhancing the rate of reaction by drawing the reactive species together. A variety of cycloadducts (104) were formed, where R1=alkyl and R2=various aryl and alkyl groups, with consistently high ee (>98%) and dr (>97:3), and yields ranging from 51% to 76%.

Ye et al. have recently used chiral N-heterocyclic carbene (NHC) catalysts to effect the reactions of substituted ketenes with a variety of electrophilic substrates (see Schemes 3.9, 3.13, and 4.10). The authors now report that δ-lactones (109) are selectively formed by NHC (44) catalysis of a substituted ketene cyclization reaction with α,β-unsaturated γ-ketoesters (108, Scheme 6.13). Interestingly, the trans-isomer is formed with high dr (16:40:1), but the fully epimerized cis-isomer can be obtained by deprotonation of the product by LDA and kinetically controlled reprotonation by aqueous HCl at ~78 °C, usually in higher ee. There was only one regiosomer formed as well; this can be explained by nucleophilic attack by the catalyst-bound zwitterionic ketene enolate on the slightly more electrophilic carbon. The reaction works well for various aromatic and electron-withdrawn keto substituents (R2, 108) as well as a variety of ketenes. Yields of the cycloaddition are moderate with good enantioselectivity, though excellent ee (95–99%) and dr (pure) were obtained for every product by recrystallization with consistently little or no loss of the desired enantiomer (50–70% overall yield).

6.3. Formation of δ-lactones

The δ-lactone structure occurs in a wide range of natural products and other biologically active compounds. These subunits are found in antiviral and HIV protease inhibitors, antacancer compounds, and antibacterials. In addition, the majority of cholesterol lowering statin drugs like Zocor contain a β-hydroxy-δ-lactone structure, or its open form, for instance, Lipitor. Consequently, general catalytic methods to synthesize chiral δ-lactones are highly valuable. Only recently has catalytic asymmetric ketene chemistry been adapted to the formation of δ-lactones.

6.3.2. Ketene dienolates

Peters and Tiseni have developed a complimentary route to δ-lactones by utilizing ketene dienolates. Their dienolates are made in situ from β-methyl-α,β-unsaturated acid chlorides, purportedly through the unsaturated ketene (2n). Reaction with catalyst O-TMS-quindoline (TMS-Qd, 7d) forms the zwitterionic dienolate (2n-Nu), and the subsequent [4+2] cycloaddition reaction with Lewis acid activated trichloroacetalddehyde most likely takes place in the s-cis conformation of the dienolate (Scheme 6.14). The reaction works well with β-alkyl substituents. Some β-trialkylsilyl substituted acid chlorides also work, improving the utility of the method, but these materials generally require a full equivalent of 7d to give satisfactory yield.

By modification of their system, the authors were able to extend the scope to include a variety of aryl aldehydes (25), as well as lower their catalyst loadings. The modified reaction uses a catalytic chiral vicinal amino alcohol (111) and excess Er(OTf)3 Lewis acid to effect the cycloaddition reaction (Scheme 6.15). In comparison to their previous system, the amino alcohol catalyzed reaction is much better in terms of materials loading and product scope, while raising the enantioselectivity (94% ee average). However, yields varied unpredictably—the 21 reported products were spread fairly evenly through the range of 23–91% yield.
The authors also demonstrate several derivatization schemes for their trichloromethyl \( \delta \)-lactones (110). The trichloromethyl group can be reduced selectively by tetrabutyltin hydride, forming either 110b or 110c by controlling the stoichiometry and temperature (Scheme 6.17). These products can be derivatized in a number of ways; for example, basic hydrolysis of the monochloride 110c to the primary alcohol 10e proceeds without racemization. In addition, LiOH hydrolysis of the trichloride 110a at 60 °C produces the corresponding acid (110d) with only minor loss in optical purity. This reaction proceeds with inversion of stereochemistry; formation of an intermediate dichloroepoxide is implicated in the inverted hydrolysis.\(^{158}\)

7. Olefination of ketenes

Tang et al. have discovered a catalytic, asymmetric way to produce allenes from ketenes and ethyl diazoacetate.\(^{159}\) Their method does rely on a full equivalent of chiral phosphine, but they recover, reduce, and reuse 85% of the phosphine without significant effect on the reaction. In this chiral system, catalytic tetra(\( p \)-chlorophenyl)porphyrin iron chloride (116) activates the diazoacetate (114), forming an Fe\(^{II} \) carbene complex (Scheme 7.1). This activated complex transfers the carbene-type ligand to the chiral phosphine (115) to form the respective ylide, which undergoes a chiral Wittig substitution with the disubstituted ketene. The authors note that this mechanism is supported by the fact that the allene ester products (117) were consistently obtained in high ee (93–98%) when they run the reaction sequentially.

8. Conclusion

Ketenes and their catalytic enolate derivatives have an incredibly rich reactivity spectrum, and many of their products can be obtained with high enantioselectivity. In some cases, enantioselective reactions have been catalyzed by chiral Lewis acids, chiral nucleophiles including NHCs, cinchona alkaloid derivatives, and chiral DMAP derivatives, as well as various bifunctional combinations of organic and metallic catalysts. We have introduced several distinct reaction manifolds, including S$_{N}$2 type substitution reactions (Section 5.4), [2+2] cycloaddition reactions (Sections 3 and 4), pseudo [4+2] pericyclic reaction patterns (Sections 5.1–5.3), and actual [4+2] cycloaddition reactions (Section 6), as well as several different types of bifunctional catalytic reaction activation by Lewis acid/base pairs. In almost all cases, ketene-derived products are synthetically and biologically useful, and usually difficult to synthesize by other means. In summary, harnessing the power of ketenes and ketene enolates has lead to a large (and growing) number of novel and practical catalytic, asymmetric reactions.

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References and notes


3. For a more involved discussion and leading references, see Ref. 2a.


17. Many of the pharmacologically relevant β-lactams are monosubstituted in the 3-position of the azetidin-2-one. One could foresee this moiety arising from the product, but the authors subsequently demonstrated that inversion occurs from phenyl isopropyl ketene, which was obtained in 92% yield and 95% ee, as was reported. For a recent review and leading references, see: Yang, H. W.; Romo, D. Tetrahedron 1995, 55, 6403–6434.


20. In their original publication, the (S)-enantiomer was assigned to the lactone product, but the author’s subsequently demonstrated that inversion occurs during the basic hydrolysis, which proceeds through a dihydroxyperoxide intermediate with full inversion of stereochemistry upon opening. See: Wynberg, H.; Staring, E. G. J. Chem. Soc. Chem. Commun. 1984, 1181–1182.


Biographical sketch

Daniel H. Paull received a B.S. from Rhodes College in 2003. He joined Professor Lectka's research group in 2004, where he investigated asymmetric fluorination reactions and obtained his Ph.D. in the Spring of 2009. He will be a postdoc in the laboratory of Stephen Martin at the University of Texas at Austin from September 2009.

Dr. Anthony Weatherwax was born in Los Angeles, CA and grew up in New York. He holds bachelor's degrees in anthropology (1993, SUNY Albany), art history (1998, University of Arizona), and chemistry (2001, University of Maryland). He joined the Lectka group in the Fall of 2001, received his Ph.D. in 2007, and since then he has been a postdoc in the labs of Andreas Pfaltz in Basel.

Thomas Lectka is a native of Detroit, MI. He obtained his B.A. from Oberlin College and his Ph.D. from Cornell University, where he worked in John McMurry's laboratory. After postdocs at Heidelberg with Rolf Gleiter and Harvard with Dave Evans, he began at Johns Hopkins University in 1994, where he was promoted to Professor in 2002. His research interests broadly span problems in synthetic methods and catalysis.