Carbonylation of heterocycles by homogeneous catalysts

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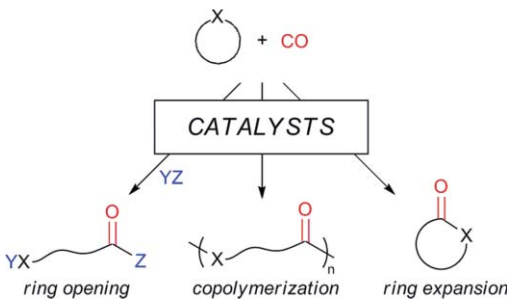
This article summarizes the recent developments (particularly the uses of homogeneous organometallic catalysts) in ring-opening carbonylations, ring-opening carbonylative polymerizations and ring-expansion carbonylations of heterocycles such as epoxides, aziridines, lactones and oxazolines.

1 Introduction

The incorporation of carbonyl functionality into organic molecules through the transition-metal-mediated insertion of carbon monoxide (CO) is among the most important and synthetically useful catalytic transformations.[1] Such carbonylations are highly atom-economical and result in one or more new C–C bonds. Metal-catalyzed carbonylations can elaborate diverse functional groups; the most commonly examined groups are alkyl halides, alkenes and alkynes. Recently, considerable research efforts have focused on one subset of this powerful class of reactions—the carbonylation of heterocycles.[2] In this article, we aim to provide an overview of catalytic heterocycle carbonylation chemistry, focusing on reactions that have been studied in the past decade.

Broadly speaking, catalytic heterocycle carbonylation may be further divided into three types: ring-opening carbonylation, ring-opening carbonylative polymerization, and ring-expansion carbonylation (Scheme 1). The diverse and desirable products of these reactions include β-hydroxyesters, β-hydroxyamides, β-hydroxyaldehydes, γ-hydroxyaldehydes, poly(β-hydroxyalkanoate)s, poly(β-peptoid)s, β-lactones, β-lactams, γ-lactones, succinic anhydrides and oxazinones.



Scheme 1 Reaction categories for the carbonylation of heterocycles.

Though catalyst development in this field is grounded in discoveries some 50 years old, contemporary advances have made this field a burgeoning one. The advent of well-defined catalysts promises to bring heterocycle carbonylation, a process rife with synthetic utility, to more sophisticated problems. This article focuses on modern catalysts for this reaction, both well and poorly defined, and discusses their impact on synthesis.

Heck's cobalt-carbonyl-mediated heterocycle carbonylation is among the most influential early publications in this field.[3] His pioneering work established that epoxides and oxetanes, when exposed to the cobalt tetracarbonyl anion $[Co(CO)_4]^-$,

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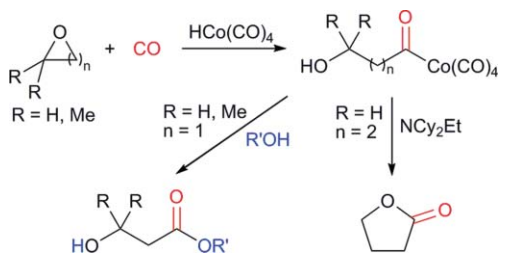
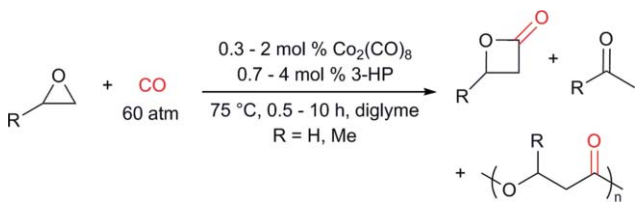
Geoffrey W. Coates obtained a BA degree in chemistry from Wabash College in 1989 and a PhD from Stanford University in 1994, working with Robert Waymouth. He was an NSF Postdoctoral Fellow with Robert H. Grubbs at the California Institute of Technology. In 1997 he joined the faculty of Cornell University as an Assistant Professor of Chemistry. He was promoted to Associate Professor in 2001, and to Professor in 2002. He became Associate Chair of Chemistry in 2004. His research focuses on the development of catalysts for organic and polymer synthesis.

can be ring opened to form a cobalt–acyl species (Scheme 2). The products of these stoichiometric reactions are β-hydroxyesters or γ-lactones, depending on the specific substrate used and reagents added.



Scheme 2 Heck's carbonylation of epoxides and oxetanes to β-hydroxyesters and γ-butyrolactones, respectively.

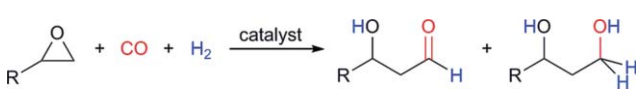
The past twelve years have seen a resurgence of interest in heterocycle carbonylation, much of it stimulated by one patent.[4] Drent and Kragtwijk claimed the catalytic production of β-lactones from epoxides and carbon monoxide, although the generation of side products was also acknowledged (Scheme 3). The catalytic system was composed of a cobalt source and a hydroxy-substituted pyridine, preferably dicobalt octacarbonyl, $Co_2(CO)_8$ and 3-hydroxypyridine (3-HP), respectively. The patent states that a number of epoxides were carbonylated to form the corresponding β-lactones, and also notes that upon standing, or if the reaction was run at high temperatures or for long times, polymer was formed. Subsequent investigations by other researchers have found a variety of outcomes when attempting to reproduce this work,[5–7] and this has renewed interest in the development of new heterocycle carbonylation catalysts, as well as their application to new systems. In the following sections, we will highlight the recent developments in each of the three aforementioned subsets of heterocycle carbonylation.



Scheme 3 Drent's carbonylation of epoxides to give β-lactones, oligo(β-hydroxyalkanoate) and ketone. 3-HP = 3-hydroxypyridine.

2 Advances in ring-opening carbonylations

The most studied ring-opening carbonylations of epoxides are hydroformylations, the net additions of CO and H_2. Hydroformylations of epoxides yield mixtures of 1,3-diols and β-hydroxyaldehydes, with the ratio of products depending on reaction conditions (Scheme 4). Reports of this reaction

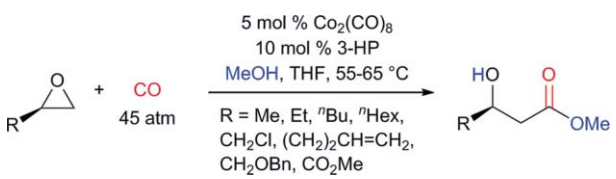


Scheme 4 The catalytic hydroformylation of epoxides.

have appeared almost exclusively in the patent literature,[8] though a few journal articles exist.[9] Of particular recent importance is the hydroformylation of ethylene oxide to 1,3-propanediol. Research in the past 15 years has transformed this reaction from one which is uneconomical on the industrial scale[10] to a commercially viable process.[11] The sheer volume of patents discussing epoxide hydroformylation places it beyond the scope of this review, but the importance of the reaction should not be understated.

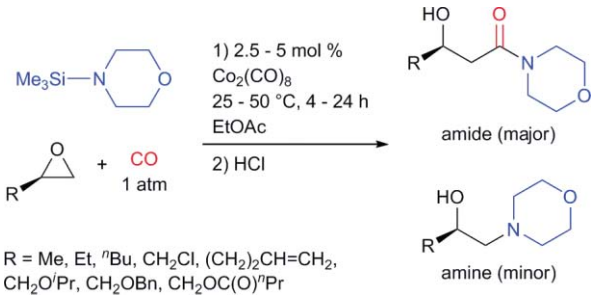
Much significant work in other ring-opening carbonylations has occurred in recent years.[12] The methoxycarbonylation of epoxide using methanol and CO was first reported by Eisenmann *et al.*,[3c] who used $Co_2(CO)_8$ to catalyze the reaction. The analogous reaction has been examined with isopropanol,[13] and the methoxycarbonylation procedure of Eisenmann has been modified to work with epichlorohydrin.[14]

In 1999, Hinterding and Jacobsen extended the scope of epoxide alkoxycarbonylation significantly by using Drent's 2 : 1 mixture of 3-HP and $Co_2(CO)_8$ to catalyze the alkoxycarbonylation of a variety of enantiomerically pure epoxides (Scheme 5).[15] The reaction was completely selective for the linear product shown, except when R = Me, in which case 2% branched product was reported.[16] The isolated yields were all >90%, except when R = benzyloxymethyl (86% yield). Absolute configuration and enantiomeric purity were retained in all cases.[17] Notable exceptions to the well-behaved nature of this system occurred with 1,2-epoxy-3-butene and styrene oxide. In these cases, a 1 : 1 mixture of linear and branched products was obtained, in only 10 to 15% yield. Jacobsen's method has been adapted by Törös and co-workers for the ring-opening carbonylation of epoxy-steroids.[18] More recently, Liu *et al.* have shown that additives, particularly 3-HP, allow $Co_2(CO)_8$ to methoxycarbonylate propylene oxide (PO) under reduced CO pressures, and to higher yield and selectivity.[19] Further, Lewis acids have been shown to accelerate the methoxycarbonylation of ethylene oxide.[20]



Scheme 5 Jacobsen's alkoxycarbonylation of epoxides.

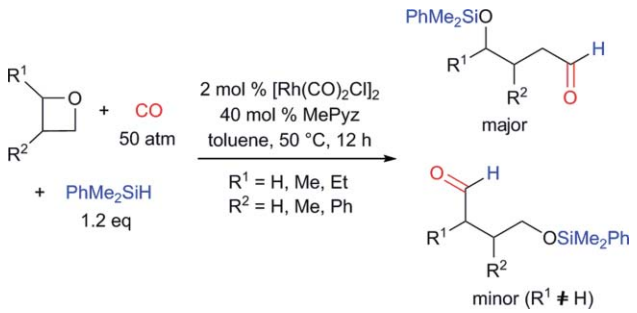
Goodman and Jacobsen have also reported increased rates and yields for silylaminocarbonylation,[21] a reaction originally reported by Watanabe *et al.*[22] In Watanabe's communication, a collection of epoxides were reacted with *N*-(trimethylsilyl)-benzylamine and $Co_2(CO)_8$ using 1 atm CO at room temperature for 24–50 h. Isolated yields of the β-silyloxyamide products ranged from 60 to 84%, and the reactions were completely regioselective. Jacobsen substituted the benzylamine derivative with *N*-(trimethylsilyl)morpholine and focused on the carbonylation of enantiopure epoxides to generate synthetically useful morpholine amides (Scheme 6).[21] Enantiomeric purity was maintained for the variety of epoxides examined, though a mixture of carbonylated (amide) and non-carbonylated (amine) products were produced in all



Scheme 6 Jacobsen's silylaminocarbonylation of epoxides by $Co_2(CO)_8$.

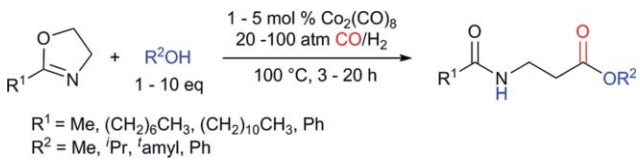
cases. Amide-to-amine ratios varied from 80 : 20 to 92 : 8, and the desired amide was isolated in 67 to 85% yield. Despite the mixture of products obtained, the shorter reaction times (4–12 h) and good yields of enantiopure products represent significant contributions to this area.

Murai has reported the silylformylation of oxetanes, catalyzed by $[Rh(CO)_2Cl]_2$ and *N*-methylpyrazole (Scheme 7), to give γ-silyloxyaldehydes.[23] The catalyst system exhibited excellent regiocontrol of carbonyl insertion; the major isomer was obtained as ⩾95% of the product, though yields ranged from 42 to 83%. An exception to the consistency of regiocontrol was the silylformylation of 3,3-dimethyloxetane, which gave only 42% conversion to the γ-silyloxyaldehyde, and also returned a tetrahydrofuran derivative (3%), a doubly carbonylated linear product (17%), and unreacted starting material.



Scheme 7 Murai's silylhydroformylation of epoxides. MePyz = *N*-methylpyrazole.

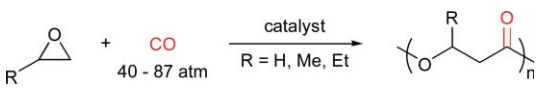
In a 1984 patent,[24] Garapon *et al.* reported the $Co_2(CO)_8$-catalyzed carbonylation of oxazolines in the presence of an alcohol to give *N*-acyl-β-amino esters (Scheme 8). Isolated yields of the products (16–69%) were dependent upon the identity of the alcohol and the substituent in the 2 position of the oxazoline ring. There was little effect of CO pressure on conversion.



Scheme 8 Alkoxycarbonylation of 2-oxazolines.

3 Advances in ring-opening carbonylative polymerizations

The ring-opening copolymerization of propylene oxide (PO) and carbon monoxide (R = Me, Scheme 9) was first reported by Furukawa *et al.* in 1965,[25] but saw few subsequent developments until recently. The product of this reaction is poly(β-hydroxybutyrate) (PHB), a representative example of a class of biodegradable polymers called poly(β-hydroxyalkanoate)s (PHAs).[26] The physical and mechanical properties of some PHAs are similar to those of isotactic polypropylene, and this has generated more interest in the field. There have been a number of reports on epoxide/CO copolymerization, primarily from the groups of Osakada,[27] Rieger,[28] and Alper.[29] All three groups used a cobalt-based catalyst and an additive, most commonly $Co_2(CO)_8$ and a pyridine derivative, respectively. Osakada varied the additive from amine bases to alcohols in the copolymerization of PO and CO and obtained polymer molecular weights (M_n) ranging from 0.8 to 2.6 kg mol^{-1}, with molecular weight distributions (M_w/M_ns) ranging from 1.1 to 2.5. The use of a $Co_2(CO)_8/Ru_3(CO)_{12}$/additive catalyst system gave good control of polymer regiochemistry, though M_n values were still very low (less than 3.0 kg mol^{-1}).



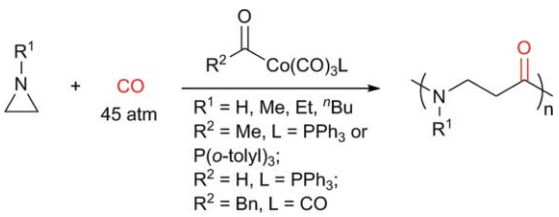
Scheme 9 Copolymerization of epoxides and CO to poly(β-hydroxyalkanoate)s.

Rieger and co-workers have examined the use of different catalytic species and precursors.[6,28] For the copolymerization of PO and CO, polyester was obtained with M_n values in the range of 1.0–6.7 kg mol^{-1} and M_w/M_n values between 1.1 and 2.0. While these M_n values are an improvement on previous reports, they are still substantially lower than those required for typical applications. Another important contribution from this group is the copolymerization of (*R*)-PO or (*S*)-PO with CO to give isotactic PHB.[28c] Typical copolymerizations behave similarly to those using racemic monomer; however, methanol-insoluble polymers are isolated. The isotacticity of these polymers is supported by their optical rotations. For example, the polyester resulting from the copolymerization of (*R*)-PO and CO exhibits an optical rotation identical to that of (*R*)-PHB obtained from natural sources. Additionally, when racemic PO is introduced in the monomer feed, the polymers exhibit a decrease in T_m, consistent with a loss of tacticity *via* incorporation of both enantiomers.

In 2004, Lee and Alper examined the use of $Co_2(CO)_8$, bipyridine derivatives, and electrophiles (*p*-TsOH, CH_3I or $PhCH_2Br$) to copolymerize PO and CO.[29] The combination of $Co_2(CO)_8$, a 1,10-phenanthroline derivative, and benzyl bromide afforded polyester with the highest reported M_n value (19.4 kg mol^{-1}, M_w/M_n = 1.41) for an epoxide/CO copolymer. In addition to PO, 1,2-epoxybutane was also successfully copolymerized with CO to yield the corresponding poly(β-hydroxypentanoate) with an M_n value of 16.7 kg mol^{-1} and a M_w/M_n of 1.28. Though a mechanism was proposed, the role of benzyl bromide is unclear.

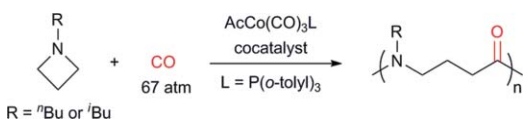
Through the use of *in situ* IR spectroscopy, Rieger and co-workers rigorously demonstrated that polymerization proceeds through direct epoxide enchainment, rather than by the production and subsequent ring opening of β-lactone,[6] and the same behavior was later observed by Alper in a modified system.[29] A variety of mechanisms for epoxide enchainment have been proposed;[6,27,28*a–d*,*h*,29] most are based upon the theme of epoxide reacting directly with an acyl cobalt species and a nucleophile (either a nitrogenous base or $[Co(CO)_4]^-$) in an ill-defined transition state. While these proposed mechanisms indicate concerted epoxide enchainment, there remain questions regarding the manner of propagation.

Ring-opening carbonylative heterocycle polymerization was extended to aziridines by Jia *et al.*, who synthesized poly(β-peptoid)s using a variety of cobalt catalysts (Scheme 10).[30] Polymer M_n values were as high as 27.5 kg mol^{-1} and typical M_w/M_n values varied from 1.11 to 1.64. Using *in situ* IR spectroscopy, Jia, Darensbourg and co-workers ascertained the rate-determining step for their system to be aziridine ring opening;[30*d*] they have also proposed a catalytic cycle for the copolymerization. Catalyst development has led to a system that readily polymerizes *N*-alkylaziridines, epoxides, and CO to give diblock poly(amide-*block*-ester)s. Molecular weights are typically 7.4–9.1 kg mol^{-1} with M_w/M_n values of 1.25–1.40.[30*e*]



Scheme 10 Aziridine/CO copolymerization using acylcobalt catalysts.

In a recent report, Jia has extended the catalyst capability to azetidines and CO (Scheme 11).[31] The acyl–cobalt catalyst, when combined with the appropriate cocatalyst, exhibits >99 : 1 selectivity for polymer over cyclics, and is capable of producing polyamides with M_n values up to 14.9 kg mol^{-1} and M_w/M_n values as low as 1.23.



Scheme 11 The catalytic copolymerization of azetidines with CO.

4 Advances in epoxide ring-expansion carbonylations

4.1 Introduction

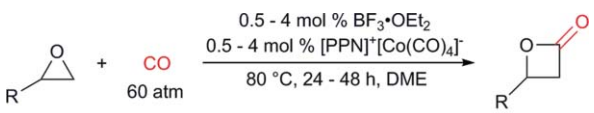
The vast majority of recent research in ring-expansion carbonylation has focused on two substrates: epoxides and aziridines. We will therefore devote the bulk of this review to reactions involving these substrates. Relative to aziridines, epoxides are both more commercially available, and more easily synthesized.[32] Advances in enantioselective catalysis have also made a broad range of enantiopure epoxides accessible.[33] Furthermore, the products of epoxide-expansion carbonylation, β-lactones, are highly attractive synthetic targets due to their versatility in organic synthesis[34,35] and presence in biologically active natural and synthetic products.[36,37] They are also appealing monomers for the synthesis of biodegradable PHAs.[38,39] Preparation of β-lactones, particularly in enantiomerically pure form, has thus been a longstanding goal,[40–42] and advances in epoxide-expansion carbonylation therefore have the potential to significantly impact chemical synthesis. However, this can only occur using catalysts which are tolerant of diverse functionality, have high productivities, are easy to synthesize, and can be used in equipment readily available in most synthetic laboratories.

4.2 Development of the catalytic reaction

Though hints at the ring-expansion carbonylation of vinyl-substituted epoxides were present in the literature half a century ago,[3] the field developed slowly until recently. Prior to 1994, epoxide-expansion carbonylation was restricted to a few substrates, and was catalyzed by complexes of expensive metals such as Rh and Pd.[43] For example, Ohta and co-workers carbonylated styrene oxide, and to a much lesser extent propylene oxide, to α-substituted-β-lactones using $RhCl(CO)(PPh_3)_2$ as a catalyst,[44] and possible pathways for this process have been discussed.[2*a*,44] Shimizu, Yamamoto and co-workers have reported α-substituted-β-lactone as a byproduct in the $Pd_2(\eta^3\text{-}C_4H_7)_2Cl_2$-catalyzed carbonylation of alkenyl-substituted epoxides.[45] The carbonylation of α,β-unsaturated epoxides has also been catalyzed by $[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene), though this reaction yields β,γ-unsaturated δ-lactones.[46]

Contemporary work in epoxide-expansion carbonylation was spurred by Drent and Kragtwijk's 1994 patent, which described the carbonylation of epoxides to β-lactones and polyesters using $Co_2(CO)_8$/3-HP.[4] While an undeniably major and motivating advance, Drent and Kragtwijk's system required high pressure and long reaction times, utilized a mixture of compounds for the catalyst, had significant side reactions, and was demonstrated for only a few substrates.

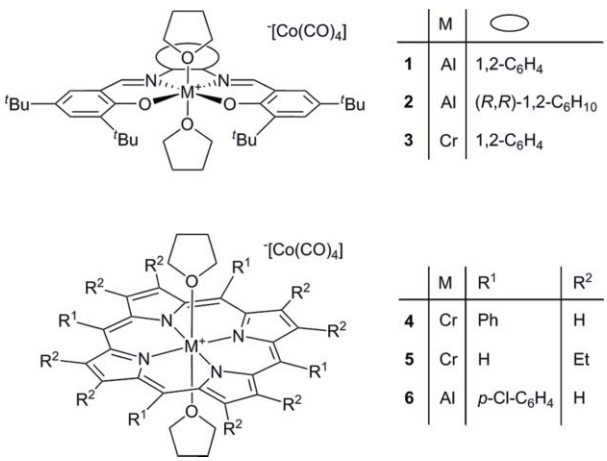
In 2001, Alper and co-workers reported that mixtures of neutral Lewis acids (such as $BF_3{\cdot}OEt_2$) with $[PPN]^+[Co(CO)_4]^-$ ($[PPN]^+$ = bis(triphenylphosphine)iminium) catalyzed the ring-expansion carbonylation of a range of epoxides (Scheme 12).[7] They demonstrated the system to be inactive without a Lewis acid, thus clarifying the necessity of both a Lewis acid and a nucleophilic metal carbonyl. Although this system required long reaction times (typically 24–48 h), it produced several β-lactones in good yields. For most



Scheme 12 Alper's carbonylation of epoxides to β-lactones.

substrates, the yield was 60–90%, though unsubstituted and 1,2-disubstituted epoxides were somewhat less successful. When published, this catalyst system was the fastest and most selective for the carbonylation of epoxides to β-lactones.

In 2002, we described the complex $[(salph)Al(THF)_2]^+[Co(CO)_4]^-$ (**1**, Scheme 13, salph = *N*,*N*′-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran), also an active catalyst for epoxide-expansion carbonylation.[5] This compound combines a Lewis acidic cation and a nucleophilic metal-carbonyl anion into a single, well-defined complex that selectively carbonylates epoxides to β-lactones more quickly and under milder conditions than previous systems. We also attempted the carbonylation of PO using $[Co(CO)_4]^-$ salts with several non Lewis acidic counterions, but no β-butyrolactone (β-BL) was formed. Thus a Lewis acid appears to be a requisite component of cobalt-carbonyl-based catalyst systems for epoxide-expansion carbonylation. In the course of mechanistic investigations (see Section 4.5), researchers collaborating at BASF and the University of Ulm[28,47] have examined the use of various Lewis acids and cobalt-carbonyl sources on the carbonylation of PO to β-BL and PHB, and have also found the reaction to demand a Lewis acid. We have proposed that,[5] in the Drent system of $Co_2(CO)_8$/3-HP, a Lewis acidic cobalt (I) cation is accessible through the ligand-induced disproportionation of $Co_2(CO)_8$ (eqn (1)),[48] with 3-HP, the solvent (diglyme), or the substrate serving as ligand.



	M	
1	Al	1,2-C_6H_4
2	Al	(*R*,*R*)-1,2-C_6H_{10}
3	Cr	1,2-C_6H_4

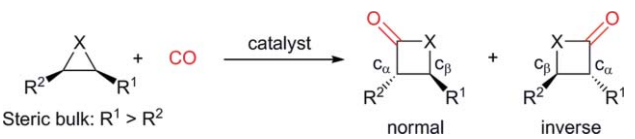
	M	R^1	R^2
4	Cr	Ph	H
5	Cr	H	Et
6	Al	*p*-Cl-C_6H_4	H

Scheme 13 Well-defined [Lewis acid]$^+$[Co(CO)$_4$]$^-$ catalysts for the carbonylation of epoxides to β-lactones.

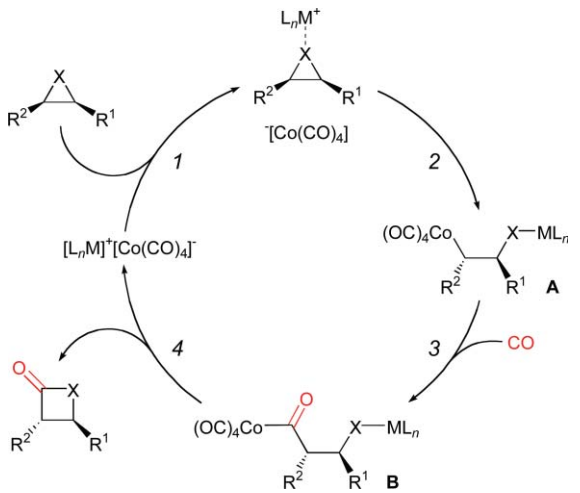
The well-defined nature of catalyst **1** has permitted us to design a number of related catalysts for epoxide-expansion carbonylation (Scheme 13).[49–55] We have also found that the compound $[Cp_2Ti(THF)_2]^+[Co(CO)_4]^-$,[56] **7**, is an active catalyst for this reaction, though it finds greater utility in aziridine carbonylation (see section 6.2).[57] Each of these catalysts features a metal cation to which two THF ligands are bound in the solid state, substantiating its Lewis acidity. In the case of the aluminium-based catalysts **1**, **2** and **6**, which are easily characterized by ^{1}H NMR spectroscopy, we have confirmed that the THF ligands remain bound in benzene-d_6 solution, but that they exchange extremely rapidly with added THF at room temperature. Due to the lability of aluminium, the THF ligands do not prevent the metal from interacting with epoxide. Our chromium(III)-based carbonylation catalysts **3–5** are paramagnetic and therefore have not been characterized by ^{1}H NMR spectroscopy. Though all [Lewis acid]$^+$[M(CO)$_n$]$^-$ compounds that, to date, have shown activity for the carbonylation of strained heterocycles feature $[Co(CO)_4]^-$, we have proposed[5] and continue to believe that other nucleophilic metal carbonyls, in conjunction with the proper Lewis acids, will prove effective as well.

$$Co_2(CO)_8 + 2L \underset{+CO}{\overset{-CO}{\rightleftharpoons}} [L_2Co(CO)_3]^+[Co(CO)_4]^- \qquad (1)$$

In addition to the necessity of a Lewis acid and a nucleophilic metal carbonyl, two notable trends among the β-lactone products unite the epoxide-expansion carbonylations reported by Drent, Alper and our group (Scheme 14). Both of these trends are also observed in the carbonylation of aziridines to β-lactams. First, carbonyl insertion generally occurs between the heteroatom and the least hindered carbon. Second, in the case of 1,2-disubstituted epoxides, carbonylation proceeds with interconversion of *cis*/*trans* configuration. Though these trends are not without exceptions (*vide infra*),[58] they have allowed the construction of catalytic cycles for the carbonylation of three-membered heterocycles by Lewis acid/cobalt-carbonyl catalysts. Alper first proposed a catalytic cycle for the expansion carbonylation of aziridines by $[Co(CO)_4]^-$,[59,60] and we have proposed a similar cycle for epoxide carbonylation by Lewis acid/cobalt-carbonyl catalysts (Scheme 15), taking into account the Lewis acidic cation.[5,57] It consists of four steps: (1) the activation of substrate by



Scheme 14 Trends in the catalytic carbonylation of three-membered heterocycles. X = O, NR.

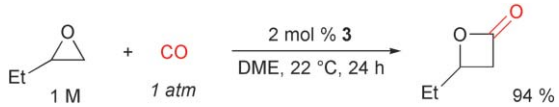


Scheme 15 Proposed catalytic cycle for the carbonylation of three-membered heterocycles. X = O, NR; L_nM^+ = Lewis acid.

coordination to a Lewis acid; (2) the S_N2 attack on the substrate by $[Co(CO)_4]^-$; (3) the insertion of CO into the new cobalt-carbon bond, and the subsequent uptake of CO; and (4) ring closing with extrusion of product and regeneration of the catalytic species. This reaction sequence accounts for the observed results of heterocycle carbonylation, in that (a) the attack of $[Co(CO)_4]^-$ on the activated epoxide occurs at the least substituted carbon of the epoxide, resulting in CO insertion adjacent to this center; and (b) the attack proceeds *via* an S_N2 pathway, resulting in inversion of stereochemistry at the α carbon and the concomitant reversal of *cis*/*trans* stereochemistry. In further support of this mechanism, we have demonstrated that (*R*)-PO is carbonylated by **1** with complete retention of stereochemistry at the lactone β-carbon, yielding (*R*)-β-BL.[5]

In addition to providing validation for the catalytic cycle shown in Scheme 15, the stereospecificity of epoxide-expansion carbonylation is vital to its application in organic synthesis. Catalyst **1** carbonylates optically active epoxide to β-lactone without compromise of the enantiopurity, and we have also aimed to develop a catalyst capable of the kinetic resolution of epoxides during carbonylation. Based on the success of **1**, which features $[(salph)Al(THF)_2]^+$ as the Lewis acidic cation, we synthesized the analogous compound, $[(R,R\text{-salcy})Al(THF)_2]^+[Co(CO)_4]^-$ (**2**, Scheme 13; salcy = *N*,*N*′-1,2-cyclohexenebis(3,5-di-*tert*-butylsalicylideneimine).[52] This catalyst had a molecular structure very similar to that of **1** (based on X-ray diffraction), and it carbonylated epoxides at comparable rates. Further, in the carbonylation of (*rac*)-*trans*-2,3-epoxybutane, it produced the β-lactone, *cis*-3,4-dimethyl-oxetan-2-one, in 44% ee (for T_{rxn} = 30 °C, 49% conversion; a k_{rel} of 3.8).[61] Though this catalyst did not display synthetically useful enantioselectivity, it remains the only enantioselective catalyst for epoxide-expansion carbonylation to date, and is a step toward the goal of combining this reaction with kinetic resolution.

Finally, a recently reported catalyst has greatly increased the accessibility of epoxide carbonylation, and bears mention here. Most catalyst systems for the conversion of epoxides to β-lactones require the use of elevated CO pressures (>7 atm) to suppress parallel ketone formation. The isomerization of epoxides to ketones occurs in the absence of CO with $[Lewis\ acid]^+/[Co(CO)_4]^-$ mixtures,[62] possibly through β-hydride elimination by a cobalt–alkyl intermediate such as **A** (Scheme 15).[63] As higher CO pressure limits this side reaction, epoxide carbonylations are generally performed in high-pressure, stainless steel reactors. Recently, however, we reported that $[(salph)Cr(THF)_2]^+[Co(CO)_4]^-$ (**3**) selectively carbonylated a range of epoxides using only balloon pressures of carbon monoxide, even on the multigram scale.[49] As **3** allows β-lactones to be generated from epoxides using standard laboratory glassware, it makes the reaction available to most synthetic chemistry laboratories (eqn (2)).



(2)

4.3 Substrate scope

In their 1994 patent, Drent and Kragtwijk describe the carbonylation of ethylene oxide, propylene oxide and isobutylene oxide; no examples are given for epoxides with substituents other than methyl groups.[4] Using their $[PPN]^+[Co(CO)_4]^-/BF_3{\cdot}OEt_2$ system, Alper and co-workers significantly extended the substrate scope of the reaction, carbonylating epoxides with pendant alkyls, alkenes, ethers, alcohols and chloroalkyls.[7] Our first carbonylation catalyst, **1**, also carbonylated several epoxides to β-lactones in high yields, and in stereospecific fashion (*vide supra*).[5]

Though **1** and $[PPN]^+[Co(CO)_4]^-$/Lewis acid are active and selective catalysts for β-lactone formation, their substrate scope is still limited. However, exploration of new Lewis acidic cations for this system led us to discover that the compounds $[(TPP)Cr(THF)_2]^+[Co(CO)_4]^-$ (**4**, Scheme 13; TPP = *meso*-tetraphenylporphyrinato) and $[(OEP)Cr(THF)_2]^+[Co(CO)_4]^-$ (**5**, OEP = 2,3,7,8,12,13,17,18-octaethylporphyrinato) carbonylate epoxides with very high activity.[50,51] In addition to carbonylating substrates for which **1** is inactive or very slow, **4** and **5** carbonylated several disubstituted and large-ring-alicyclic epoxides (Chart 1) at lower pressures and catalyst loadings than were possible with previous catalysts.[53,57] Catalyst **5** is more active than **4**, carbonylating long-chain-alkyl-substituted epoxides an order of magnitude faster. It also allows the clean carbonylation of glycidyl ethers with additional functionality, Scheme 16. As some of the functional groups examined can serve as protecting groups for alcohols,[64] **5** allows access to hydroxymethyl-substituted β-lactones, which are generally not the product of glycidol carbonylation (see Section 4.4.3).

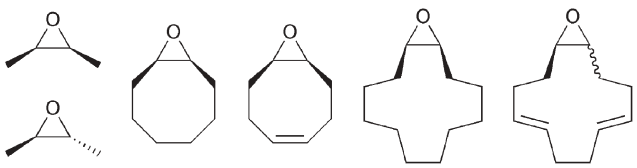
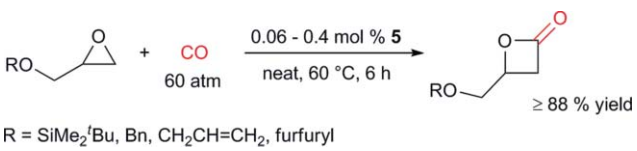
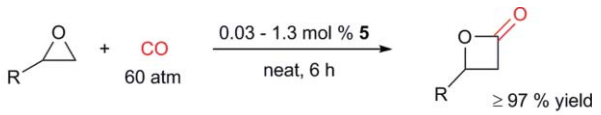


Chart 1 Disubstituted and large-ring-alicyclic epoxides carbonylated rapidly by **4** and **5**.



Scheme 16 Carbonylation of functionalized glycidyl ethers by **5**.

The development of **5** has also permitted the ring-expansion carbonylation of epoxides with pendant ester and even secondary amide groups (Scheme 17).[50] Epoxides with remote (*i.e.*, separated by more than one methylene unit) esters and dialkylamides are cleanly carbonylated to β-lactones (neat epoxide, 60 atm CO, 60 °C, 6 h). Glycidyl esters undergo a rearrangement reaction under these conditions (see Section 4.4.3); however, they form β-lactones at 40 °C in the same time



at 60 °C: R = $(CH_2)_xOC(O)^nPr$ (x = 2,3), $(CH_2)_2CO_2{}^nPr$, $(CH_2)_8C(O)NMe_2$
at 40 °C: R = CH_2OAc, $CH_2OC(O)^nPr$, $CH_2OC(O)Ph$

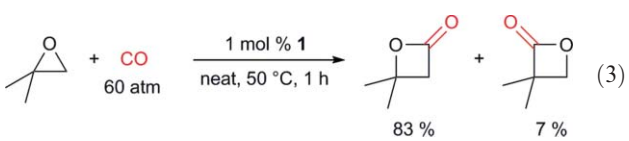
Scheme 17 The epoxide-expansion carbonylation of substrates with pendant esters and amides, catalyzed by **5**.

frame, albeit using higher catalyst loadings than are necessary for remote esters.

Despite the recent advances in the scope of epoxide-expansion carbonylation, a few substrates remain inaccessible to the reaction. Consistent with the atypical reactivity observed by Jacobsen for the alkoxycarbonylation of styrene oxide (Section 2), Alper found that this epoxide could not be carbonylated by $[PPN]^+[Co(CO)_4]^-/BF_3{\cdot}OEt_2$.[7] To date, there are no published reports of the carbonylation of styrene oxide or 1,2-epoxy-3-butene to β-lactone by Lewis acid/cobalt-carbonyl catalysts.

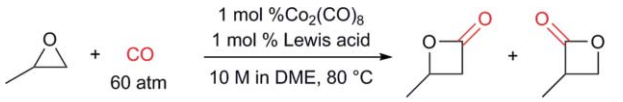
4.4 Unusual products in epoxide-expansion carbonylations

4.4.1 Regiochemistry. Though most catalytic ring-expansion carbonylations of monosubstituted or 2,2-disubstituted epoxides yield β-lactones substituted at the β position, there are a few exceptions. We have already mentioned the formation of α-substituted-β-lactones from the carbonylation of vinyl-substituted epoxides (*vide supra*) by late-transition-metal-based catalysts. In the case of the recently developed Lewis acid/cobalt carbonyl catalysts, the significant formation of α-substituted β-lactones occurs only with select substrates or catalysts. For instance, the geminally disubstituted isobutylene oxide produces only the normal, β,β-disubstituted β-lactone upon carbonylation with $Co_2(CO)_8$/3-HP.[4] This is also the major product upon carbonylation using **1**, but some α,α-disubstituted β-lactone is also formed (eqn (3)).[5] We propose that when isobutylene oxide coordinates to $[(salph)Al(THF)_x]^+$, positive charge accumulates at its tertiary carbon. The more substituted center is thus activated toward attack by $[Co(CO)_4]^-$,[65] resulting in the formation of α,α-dimethyl-β-propiolactone. As this proves to be a minor product, steric accessibility, rather than electrophilicity, is the dominant factor in determining the site of $[Co(CO)_4]^-$ attack in this case.



(3)

With proper choice of Lewis acid, even the monosubstituted PO can be carbonylated by $[Lewis\ acid]^+[Co(CO)_4]^-$ to yield both β- and α-methyl-β-propiolactone. Alper and co-workers observed the normal product, and only a trace of regioisomer, when this substrate was carbonylated with $Co_2(CO)_8$/$BF_3{\cdot}OEt_2$, but noted significant regioisomer formation when the reaction was catalyzed by $Co_2(CO)_8/B(C_6F_5)_3$ (Scheme 18).[7] Though no rationale for this reactivity is given, it is possible that the strongly electron-withdrawing



Lewis acid	t (h)	Yield (%)	
$BF_3{\cdot}OEt_2$	24	77	trace
$B(C_6F_5)_3$	7	68	17

Scheme 18 The formation of regioisomers from the carbonylation of propylene oxide catalyzed by $Co_2(CO)_8$ and Lewis acids.

nature of $B(C_6F_5)_3$ results in the buildup of positive charge on the bound epoxide, leading to the formation of the α-substituted-β-lactone.

4.4.2 Stereochemistry. The sole 2,3-disubstituted epoxide that is carbonylated to β-lactone with retention of *cis*/*trans* stereochemistry is cyclopentene oxide, CPO. Though the ring-opening carbonylation of CPO has been reported,[66–68] only recently was its ring-expansion carbonylation accomplished. Catalyst **5** cleanly and quantitatively converts CPO to the *cis*-ring-fused lactone product, *cis*-**8** (Fig. 1).[50] That CPO is not carbonylated to the *trans* lactone is predictable, as the *trans* ring fusion of a four- and a five-membered ring would be energetically prohibitive.[69] However, from the reaction cycle shown in Scheme 15, it is not clear how *cis*-**8** is formed. We have proposed that this carbonylation could proceed *via* coordination of CPO to $[(OEP)Cr(THF)_x]^+$ and subsequent opening of the epoxide ring to form a secondary carbocation;[50] a better understanding of the process awaits further investigation.

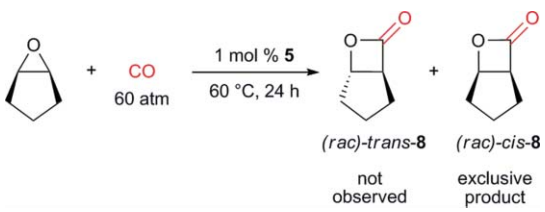
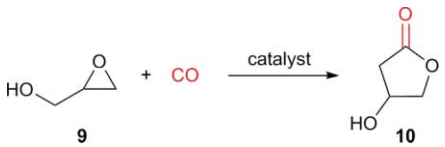


Fig. 1 Unusual stereochemical outcome in the **5**-catalyzed carbonylation of cyclopentene oxide: *cis* configuration is retained.

4.4.3 γ-Lactone formation. In view of the broad spectrum of functional groups that can be present in substrates for catalytic epoxide-expansion carbonylation, it is perhaps unsurprising that additional reactions can occur during, or after, carbonylation. A number of epoxides, when subjected to Lewis acid/metal-carbonyl catalysts under the appropriate conditions, yield products that are isomeric to the expected β-lactones.

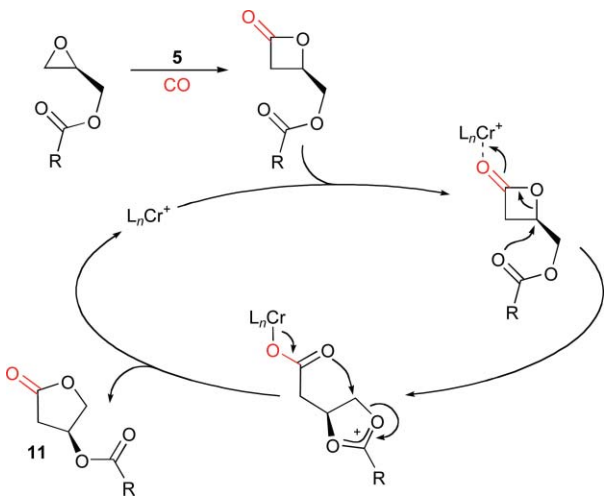
Glycidol (**9**) undergoes carbonylative rearrangement by Lewis acid/metal-carbonyls (eqn (4)). Glycidol carbonylation was first reported by Brima,[70] who used metal carbonyls such as $Co_4(CO)_{12}$ or $HCo(CO)_4$ to catalyze the reaction between glycidol and CO, and formed β-hydroxy-γ-butyrolactone (**10**, eqn (4)). Under different reaction conditions, Alper reported that glycidol could be carbonylated without rearrangement, to yield β-hydroxymethyl-β-butyrolactone.[7] We have repeated the carbonylation of glycidol under the conditions of Alper,[71] and have found **10** to be the only product. Further,

carbonylation of glycidol by catalyst **1** also yields **10**.[71] The formation of **10** during glycidol carbonylation can be rationalized by examining intermediate **B** in Scheme 15. For most substrates, the metal alkoxide of **B** attacks the cobalt-acyl group, forming the four-membered lactone ring. In the case of glycidol (R^1 = CH_2OH and R^2 = H), the oxygen atom of R^1 can also attack the cobalt acyl. This attack forms a more stable five-membered ring, and yields **10**.



9 **10** (4)

At 40 °C, **5** carbonylates glycidyl esters to β-lactones having pendant esters (see Scheme 17). However, if these reactions are performed at 60 °C, the product is not a β-lactone. Rather, a β-acyloxy-γ-butyrolactone is formed selectively and quantitatively (**11**, Scheme 19).[50] Contrary to the one observed with glycidol, this rearrangement is unlikely to occur from intermediate **B** (Scheme 15); direct attack of a glycidyl ester (R^1 = $CH_2OC(O)R$, R^2 = H) on the cobalt acyl would not form the observed product. Instead, we believe that the normal β-lactone product is produced in the carbonylation reaction, and is then rearranged to the product γ-lactone *via* the Lewis acid catalyzed pathway shown in Scheme 19.[50] We propose that this rearrangement occurs as a nucleophilic substitution with anchimeric assistance from the pendant ester group,[72] similar to a mechanism proposed for the anomerization of *O*-acetylated glycosides.[73] In support of this mechanism, we found that rearrangements of β-acyloxymethyl-β-propiolactones to β-acyloxy-γ-butyrolactones do not require catalyst **5**, but occur readily in the presence of the Lewis acid $MgBr_2{\cdot}OEt_2$. Further, (*R*)-glycidyl butyrate was carbonylated to (*R*)-β-butyroxymethyl-β-propiolactone at 40 °C, but to (*S*)-β-butyroxy-γ-butyrolactone at 60 °C. That the normal carbonylation occurs with retention at the stereocenter, but the carbonylative rearrangement occurs with inversion, is consistent with the mechanism in Scheme 19.



Scheme 19 Proposed mechanism for the production of β-acyloxy-γ-butyrolactone in the **5**-catalyzed carbonylation of glycidyl esters. L_nCr^+ = $[(OEP)Cr(THF)_x]^+$, where x = 0, 1 or 2.

4.5 Mechanism

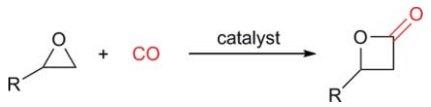
The mechanism of catalytic epoxide-expansion carbonylation has been the subject of several investigations. Because catalytic β-lactone formation from epoxides generates a new carbonyl compound, it is easily monitored by *in situ* IR spectroscopy, and this strategy has been utilized by us[74] and others.[28b,d,h,47] The related copolymerizations of CO with epoxides[6,28a,c,d] and with aziridines[30d] have also been examined using this technique. In addition, kinetic and reactivity studies,[74] as well as theoretical calculations (using the DFT[47] and metadynamics[75] methods), have been used to probe the mechanism of epoxide-expansion carbonylation. For detailed descriptions of these investigations, the reader is referred to the individual publications. Here, we will use the results of these studies to direct a discussion of the factors that affect the rate, scope, and selectivity of epoxide-expansion carbonylation catalyzed by Lewis acid/cobalt-carbonyl compounds or mixtures.

4.5.1 Lewis acidity. As the presence of a Lewis acid is mandatory for carbonylation of epoxides to β-lactones in cobalt-carbonyl-based systems, it is reasonable to expect that the particular Lewis acid chosen will impact the reaction. The effect of Lewis acid strength is a facet of this reaction that awaits systematic experimental study, though a computational study of some simple Lewis acids is available.[47] The absence of an experimental study is likely due, at least in part, to the dearth of practical methods for quantifying Lewis acidity.[76,77]

Even in the absence of systematic experimental data on Lewis acid strength and its effect on epoxide carbonylation, considerable insight into the latter subject can be gleaned from existing studies. Examining Scheme 15, we see that the charge density about the Lewis acid changes significantly at two points in the catalytic cycle. First, as the epoxide ring is opened by attack of $[Co(CO)_4]^-$, it is transformed from a neutral donor into an anionic ligand. At this stage, a strong Lewis acid will benefit the reaction by stabilizing the charge on the alkoxide. Conversely, as the lactone ring is closed, the anionic alkoxide group is released, forming a less basic, neutral β-lactone donor. Here, a weaker Lewis acid is advantageous. Therefore, the overall carbonylation of epoxide to β-lactone will be fastest when either: (1) a careful balance in Lewis acidity is achieved, or (2) the strength of the Lewis acid can be adjusted *in situ*.

To date, the fastest epoxide carbonylation catalysts reported feature strong, cationic Lewis acids (Table 1).[28d,47,49–51] It is clear how these catalysts benefit the epoxide-ring-opening step; we need therefore consider how they effect rapid lactone ring closing. Based on the results of DFT calculations, Molnar *et al.* have attributed the epoxide-carbonylation ability of $[AlMe_2{\cdot}diglyme]^+/[Co(CO)_4]^-$ to the availability of a stabilizing interaction between the Co and an H atom of the β-lactone in the ring-closing transition state.[47] In separate systems, we have found experimentally that moderately Lewis basic solvents (such as THF or glyme solvents) greatly accelerate the carbonylation of 1,2-epoxybutane by **1** (Table 2),[74] and **6**,[54] which also feature cationic Lewis acids. We have proposed that Lewis basic solvents bind to the aluminium center, *trans* to the alkoxide group, and serve to stabilize the aluminium

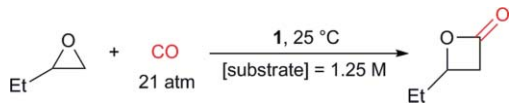
Table 1 Highly active catalysts for the carbonylation of epoxides



Entry	Catalyst	R	Solvent	*P*/ atm	*T*/ °C	*t*/ h	[Epoxide]/ [Catalyst]	TOF[a]
1	$Co_2(CO)_8/AlMe_3$[b]	Me	Diglyme	59	75	2	160	30
2	$Co_2(CO)_8/AlMe_3$[b]	Me	Diglyme	59	75	5	160	74
3	**3**[c]	Et	DME[d]	1.0	22	6	50	8.1
4	**4**[e]	Et	Neat	61	60	6	300	50
5	**5**[f]	Et	Neat	61	60	6	3500	583

[a] TOF = Turnover frequency = moles of lactone produced per mole of catalyst per hour. [b] $[Co_2(CO)_8]$: $[AlMe_3]$ = 1 : 4; proposed to form $[Me_2Al(diglyme)]^+[Co(CO)_4]^-$ *in situ*. See ref. 28*d*. [c] From ref. 49. [d] DME = 1,2-Dimethoxyethane. [e] From ref. 51. [f] From ref. 50.

Table 2 Effect of solvent on the carbonylation of 1,2-epoxybutane (EB) by **1**[a]



Entry	Solvent	[**1**]/mM	Time to completion/min
1	Tetrahydrofuran	11.6	90
2	Diglyme	11.6	180
3	1,2-Dimethoxyethane	11.6	230
4	2-Methyltetrahydrofuran	11.6	725
5	2,5-Dimethyltetrahydrofuran	5.8	>1500

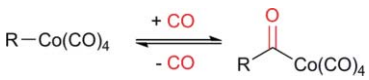
[a] The reaction rate is independent of [EB].

cation that is formed upon closing of the β-lactone ring.[74] This interaction does not prevent epoxide binding or ring opening, however, due to the rapidity of substitution at the aluminium center. Though the studies on $[AlMe_2{\cdot}diglyme]^+/[Co(CO)_4]^-$, **1**, and **6** constitute only three examples, the results obtained suggest that modulation of the catalyst's Lewis acidity over the course of the catalytic cycle may play a significant role in enabling highly active catalysis.

Additionally, Stirling *et al.* have recently calculated a reaction pathway for epoxide ring closing that, while it is very high in energy for the hard Lewis acid BF_3, is actually quite reasonable for the softer $B(CH_3)_3$.[75] Though this result has yet to be examined experimentally, it suggests that the polarizability of a Lewis acid, in addition to its strength, may influence its ability to catalyze the carbonylation of epoxide to β-lactone.

Finally, as noted in Section 4.4.1, the choice of Lewis acid can affect the ratio of regioisomers formed during the carbonylation of epoxides. Thus, the choice of Lewis acid can determine not only the rate, but also the regioselectivity, of carbonylation.

4.5.2 Pressure of carbon monoxide. Of the reaction steps shown in Scheme 15, the insertion of CO into a tetracarbonylcobalt–alkyl bond and subsequent uptake of CO (Scheme 15, step *3*) has certainly been the best studied. A constituent of several catalytic processes (notably the industrially practised hydroformylation reaction), this reaction has been examined at length, and its mechanism is well-established.[78,79] Under CO pressures typical of epoxide-expansion carbonylation (14–60 atm in most cases), this reaction is rapid.[79d] Further, though tetracarbonylcobalt alkyl ($RCo(CO)_4$) and tetracarbonylcobalt acyl ($RC(O)Co(CO)_4$) species exist in equilibrium, the equilibrium lies far to the side of the acyl complex under these conditions (eqn (5)).[78b,c,79a] Accordingly, we have found that the pressure of carbon monoxide does not affect the rate of epoxide carbonylation by **1** or **6** over this range; the incorporation of CO is rapid relative to the overall reaction.[54,74] At pressures of CO below ~7 atm, the rate and/or selectivity of epoxide-expansion carbonylation by most catalysts suffers, as ketone is formed.[49,74] To our knowledge, complex **3** is the only carbonylation catalyst capable of selectively converting epoxides to β-lactones under only an atmosphere of CO.[49,80] The reasons for this unusual selectivity are not currently clear.

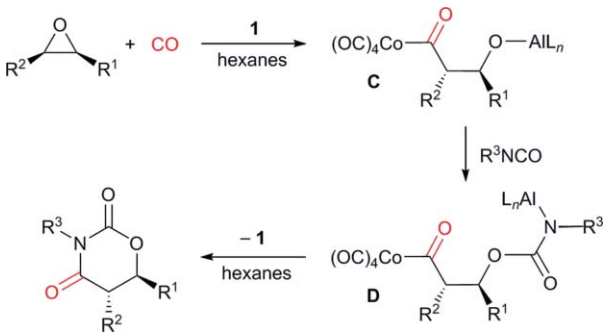


(5)

4.5.3 Solvent. The carbonylation of epoxides by catalysts **1–6** can be performed in a number of solvents, or in the absence of solvent. The particular solvent employed for a carbonylation reaction impacts its outcome, and therefore merits discussion here.

In our study of the mechanism of epoxide carbonylation to β-lactone by **1**,[74] we found that solvent had a profound effect on the rate of carbonylation, and the same behavior has recently been observed for epoxide carbonylation by **6**.[54] The solvent's donor ability is the dominant factor in regulating this effect,[74] so interaction between catalyst and solvent can clearly contribute to the reaction rate. Although moderate electron donors, particularly ethers, accelerated carbonylation by **1** (Table 2), very strong donors, such as acetonitrile, slowed it. In this case, it is likely that the acetonitrile bound the (salph)Al cation quite strongly, and inhibited epoxide binding. Similarly, Eisenmann noted that the $Co_2(CO)_8$-catalyzed rearrangement of propylene oxide occurred to a much greater degree in methanol than in pyridine,[62] despite the fact that both solvents are capable of inducing the disproportionation of $Co_2(CO)_8$ (eqn (1)). The strongly donating character of pyridine was proposed to inhibit epoxide binding to cobalt in that system.

Recent studies on the effect of solvent on the rate of β-lactone formation by **1** have allowed us to extend its synthetic capability to a new type of reaction. We have found the resting state for epoxide carbonylation by this catalyst to be the aluminium–alkoxide/cobalt–acyl species **C** (Scheme 20, *cf.* **B**, Scheme 15, where L_nM = (salph)Al).[74] In solvents in which β-lactone formation is slow, **C** is sufficiently long-lived to be trapped by isocyanates. This reaction produces 1,3-oxazinane-2,4-diones (ODs), presumably through an aluminium carbamate such as **D**. With hexanes as solvent, we have used catalyst **1** to produce ODs with a variety of substituents in high yield.[81]



Scheme 20 Reaction of the cobalt–acyl/metal–alkoxide intermediate **C**, generated from the reaction of **1** with epoxide, and an isocyanate yields a 1,3-oxazinane-2,4-dione.

Thus the synthetic chemist, in choosing a solvent for epoxide carbonylation, has several factors to consider. In many cases, it is economical to run the reaction in the absence of solvent. It is sometimes necessary to employ solvent in order to obtain the desired product in good yield;[50] in still other instances, solvent is not required but accelerates the reaction. Even a 'poor' solvent for carbonylation can prove constructive by permitting other reactions to forestall β-lactone formation, therefore allowing the synthesis of different heterocycles.

5 Ring-expansion carbonylation of 4-membered oxa- and thiacycles

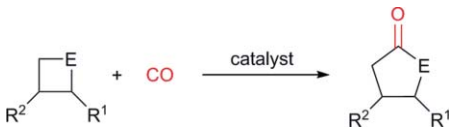
5.1 Oxetanes and thietanes

Thiiranes, the sulfur analogues of epoxides, have not been catalytically carbonylated to β-thiolactones.[82] However, recent advances in the catalytic ring-expansion carbonylation of four-membered oxygen and sulfur heterocycles, oxetanes and thietanes, have been made.[83] The catalytic carbonylation of oxetane to γ-butyrolactone was first described by Nienburg and Elschnigg in 1959.[84] The utility of their method, which used cobalt acetate as a catalyst, was limited by the high pressures (250 atm) and temperatures (200 °C) required. Nevertheless it remained the sole example of this reaction for 30 years. In 1989, Alper and co-workers reported that $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ were competent in catalyzing the ring-expansion carbonylation of oxetane and thietane, and that an equimolar mixture of the two catalysts was significantly better (Table 3, entries 1 and 3).[85] Using substituted heterocycles, Alper and co-workers found that CO insertion occurred preferentially into the less substituted carbon–heteroatom bond (entries 6 and 8), as is the case in epoxide carbonylation. Contrary to the epoxide case, however, they found that oxetane-expansion carbonylation occurred with retention of all substituent stereochemistry, indicating that a different mechanism is operative for this system.

We have recently demonstrated that catalyst **1** is capable of oxetane carbonylation (Table 3, entry 2).[86] Using lower temperature and catalyst loading than the previous report, **1** quantitatively converted oxetane to γ-butyrolactone.

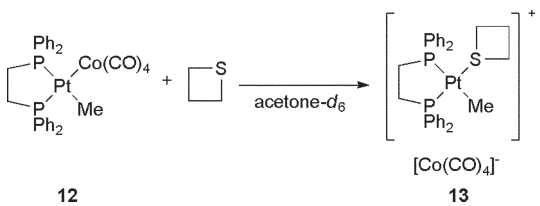
In 2003, the carbonylation of thietanes was elaborated by Komiya and co-workers, who demonstrated that the heterobimetallic complex (dppe)MePt–$Co(CO)_4$ (**12**, dppe = 1,2-(diphenylphosphino)ethane) effectively catalyzed the reaction (Table 3, entry 4).[87] Notably, several related compounds (for example, (dppe)MePt–$Mn(CO)_5$, entry 5) were found to be inactive or only weakly active for thietane-expansion carbonylation. Under relatively low CO pressures, catalyst **12** carbonylated thietane and 2-methylthietane (entry 7) in very good yields, producing γ-thiobutyrolactone and γ-thiovalerolactone, respectively. Insight into the mechanism of thietane carbonylation was gleaned from the stoichiometric reaction of **12** with thietane to form the ion pair **13** in acetone-d_6 solution (eqn (6)). When treated with CO at room temperature, compound **13** formed γ-thiobutyrolactone in 91% yield and regenerated catalyst **12**.[88] Based on these experiments, and on the observation that carbonylation of 2-methylthietane occurs at the least substituted C–S bond, Komiya and co-workers[87] proposed a catalytic cycle, analogous to the one shown in Scheme 15, for thietane carbonylation by **12**.

Table 3 Carbonylation of oxetanes and thietanes



Entry	Catalyst	mol%	E	R^1	R^2	*P*/ atm	*T*/ °C	Yield (%)
1	$Co_2(CO)_8/Ru_3(CO)_{12}$[a]	10–20	O	H	H	60	190	70
2	**1**[b]	0.5	O	H	H	14	80	>99
3	$Co_2(CO)_8/Ru_3(CO)_{12}$[a]	10–20	S	H	H	60	125	100
4	(dppe)(Me)Pt–$Co(CO)_4$[c]	2	S	H	H	10	100	99
5	(dppe)(Me)Pt–$Mn(CO)_5$[c]	5	S	H	H	10	100	0
6	$Co_2(CO)_8/Ru_3(CO)_{12}$[a]	10–20	S	Me	H	60	120	95
7	(dppe)(Me)Pt–$Co(CO)_4$[c]	2	S	Me	H	10	100	89
8	$Co_2(CO)_8/Ru_3(CO)_{12}$[a]	10–20	S	H	OMe	60	145	87

[a] From ref. 85. [b] From ref. 86. [c] From ref. 87. dppe = 1,2-bis(diphenylphosphino)ethane.



(6)

12 **13**

5.2 β-Lactones

Given the increase in β-lactone accessibility that has occurred over the past two decades,[40-42] it is perhaps not surprising that the carbonylation of these compounds to succinic anhydrides[89] has also been explored. The reaction was originally described by Mori and Tsuji,[90] who reported in 1969 that β-propiolactone was carbonylated by $Co_2(CO)_8$ at high temperature and pressure to give mixtures of succinic anhydride and acrylic acid. When the carbonylation was run in the presence of H_2, the products were succinic acid and γ-butyrolactone. In this case, the authors proposed that succinic acid was formed by hydrolysis of succinic anhydride, with the required H_2O having been produced during the formation of γ-butyrolactone. Similarly, Jenner and co-workers have reported that reaction of β-propiolactone, β-butyrolactone, or γ-butyrolactone with

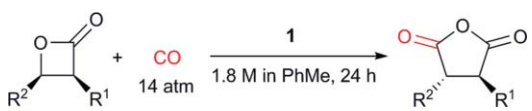
H_2 and CO in the presence of a Rh-based catalyst yields the homologated α,ω-diacid.[91] After this report, however, it was close to two decades before the carbonylation of β-lactones to succinic anhydrides was further elaborated.

During the course of developing the carbonylation of epoxides to β-lactones by **1**, we found that a small amounts of succinic anhydrides could also be formed in the reaction.[86] We suspected that this was the result of ring-expansion carbonylation of β-lactone, and we confirmed this by carbonylating β-butyrolactone to methylsuccinic anhydride using **1**. Based on the wealth of β-lactones available from epoxide carbonylation and other methods,[40–42] we considered this a practical route to succinic anhydrides, and therefore pursued the catalytic carbonylation of β-lactones.

The carbonylation of β-lactones was successful with substrates bearing alkyl, alkenyl, and ether substituents, as well as with the unsubstituted β-propiolactone. Under the reaction conditions employed (Table 4), all of these substrates can be converted to succinic anhydrides in ⩾90% yield, using catalyst loadings of 0.5–5 mol%. Using the enantiomerically pure (*R*)-β-BL, we demonstrated that the reaction occurred with inversion of configuration at the β position of the starting lactone.[92] Carbonylation of the disubstituted *cis*-3,4-dimethyloxetan-2-one occurred with interconversion of *cis*/*trans* stereochemistry, indicating that the configuration at the α carbon of the β-lactone was retained. We therefore proposed that β-lactone carbonylation proceeded by a reaction sequence analogous to those for epoxides and aziridines (Scheme 21). The β-lactone is activated through binding to the Lewis acid center (*1*), and attacked in an S_N2 fashion by $[Co(CO)_4]^-$ (*2*). Nucleophilic attack in this system occurs adjacent to the ring oxygen, with the lactone carboxylate functionality serving as a leaving group. Following the insertion of CO into the cobalt–alkyl bond (*3*), the carboxylate group can attack the cobalt acyl to form the five-membered anhydride ring, and regenerate the catalytic species (*4*).

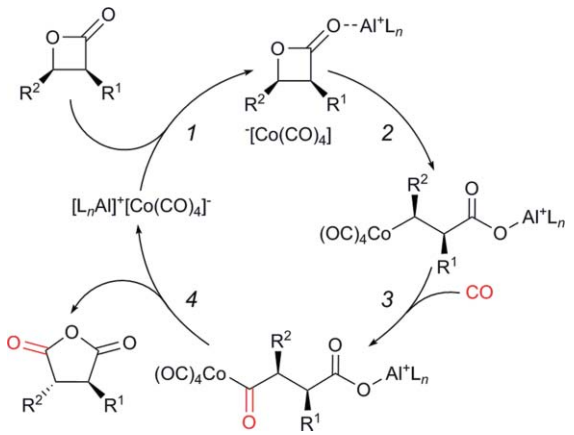
Though β-lactone carbonylation is a high-yielding and selective route to succinic anhydrides, the one-pot, tandem carbonylation of epoxides directly to succinic anhydrides is more desirable. Prior to our serendipitous discovery of β-lactone carbonylation, double carbonylation from epoxide

Table 4 The carbonylation of β-lactones to succinic anhydrides by **1**



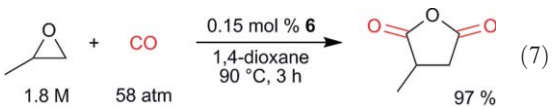
R^1	R^2	*T*/°C	[lactone]/[**1**]	Yield (%)
H	Me	80	220	95
H	(*R*)-Me	55	110	94[a]
Me	*cis*-Me	50	50	96[b]
H	Et	80	120	93
H	$(CH_2)_9CH_3$	80	50	>99
H	CH_2O^nBu	80	50	90
H	$CH_2OSiMe_2{}^tBu$	80	20	97
H	$(CH_2)_2CH{=}CH_2$	80	20	90
H	H	24	300	98

[a] Product was (*S*)-methylsuccinic anhydride. [b] Product was *trans*-2,3-dimethylsuccinic anhydride.



Scheme 21 Proposed mechanism for the **1**-catalyzed carbonylation of β-lactones to succinic anhydrides.

to succinic anhydride was unknown, although styrene oxide and aryl epoxyalcohols have been doubly[93] and triply carbonylated,[94] respectively, to other products. Unfortunately, in the case of **1**, the single-pot tandem carbonylation reaction is impractical, as conditions that accelerate the first carbonylation impede the second, and *vice versa*. However, we have recently discovered that under appropriate conditions, catalyst **6** is capable of rapidly and efficiently carbonylating epoxides to succinic anhydrides, without isolation of the β-lactone intermediate.[54] The carbonylations of epoxide and β-lactone by **6** were found to occur separately and sequentially, with β-lactone carbonylation occurring only after all of the epoxide had been carbonylated. Epoxide carbonylation by **6** follows the same mechanism as by **1**, and β-lactone carbonylation by **6** follows the analogous sequence of steps depicted in Scheme 21. Further investigation of β-lactone carbonylation by **6** revealed it to be governed by pre-rate-determining coordination of β-lactone to the aluminium cation, followed by rate-determining β-lactone ring opening. β-Lactone carbonylation was slow in polar or donor solvents. As epoxide and β-lactone carbonylation have opposing solvent dependences, the success of **6** in catalyzing both carbonylation reactions in a single pot depends critically upon the choice of solvent. The best solvent for the one-pot, tandem carbonylation, 1,4-dioxane, is sufficiently donating to accelerate epoxide carbonylation, but is only weakly polar, allowing rapid β-lactone carbonylation (eqn (7)).



(7)

6 Aziridine expansion carbonylation

6.1 Overview

β-Lactam synthesis includes a diverse array of synthetic methods,[95] among which aziridine carbonylation is becoming increasingly important. Aziridine carbonylation has long been a major focal point of ring-expansion carbonylation, and significant advances continue to be made. Although the demonstration of principle was a significant contribution to

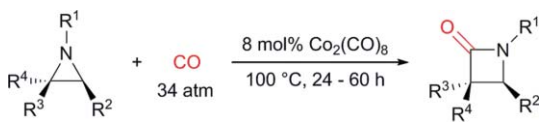
this area, improvement of catalytic efficiency and expansion of the substrate scope remain overarching goals. Important contributions in aziridine carbonylation have been reported by Alper, as well as by his collaborators, Davoli and Prati.[59,60,96] Both groups have worked to expand the substrate scope of aziridine-expansion carbonylation, and Davoli and Prati have also applied the methodology to the synthesis of specific target molecules and key intermediates.[96a,d]

6.2 Expansion of substrate scope

Contrary to the case of epoxides, there is not a wide range of commercially available aziridines; this has limited carbonylation of the latter to select compounds. The aziridines for which carbonylation has recently been reported can be divided into four groups: (1) those that undergo normal insertion of CO (or are symmetrically substituted),[59,96b] (2) those that are 2-phenyl substituted,[59,96b,d] (3) those that yield a mixture of regioisomers,[59,60,96a,b] and (4) those that are not reactive under the tested conditions.[60,96b]

The recent literature contains many examples of the normal carbonylation of aziridines, which places the more sterically encumbered carbon at the β position of the product lactam (Table 5).[59,96b] Reactions were reported to run between 14 and 24 h, and typically achieved isolated yields of >90%. Bicyclic aziridines (R^2–R^3 = –$(CH_2)_4$–) have also been carbonylated successfully, although yields varied significantly (28–80%) and longer reaction times (60 h) were required. These highly strained *trans*-β-lactams were formed more quickly with bulkier N-substitutents such as *tert*-butyl, cyclohexyl, and 1-adamantyl.[97] Additionally, there was a strict temperature dependence of the reaction: $T_{rxn} < 100$ °C resulted in slow carbonylation, while $T_{rxn} > 105$ °C led to the decomposition of product. All of these reactions occurred with inversion of configuration at the site of carbonyl insertion.

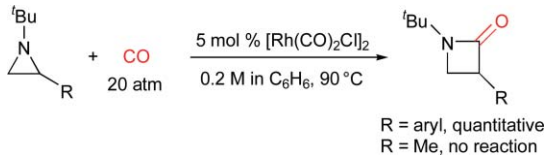
Table 5 The 'normal' carbonylation of aziridines to yield β-lactams (10 other examples have been reported)



Entry	R^1	R^2	R^3	R^4	Yield[a] (%)
1	*p*-$MeOC_6H_4$	^{t}Bu	H	H	50
2	$(CH_2)_2Ph$	Me	H	Me	95
3	$(CH_2)_2Ph$	–$(CH_2)_4$–		H	44
4	Bn	$CH_2OSi^tBuMe_2$	H	H	40
5	Bn	CH_2OH	Me	H	84

[a] Isolated yield of β-lactam product.

Aziridines having phenyl substituents on carbon are carbonylated with distinct regioselectivity – the phenyl group is exclusively on the α carbon of the product lactam, regardless of other substitution. In 1983, Alper *et al.* used $[Rh(CO)_2Cl]_2$ to quantitatively carbonylate 2-arylaziridines to 3-aryl-2-azetidinones (Scheme 22).[98] The reaction was completely regio- and stereoselective, with CO insertion occurring adjacent to the aryl-substituted carbon and with retention of



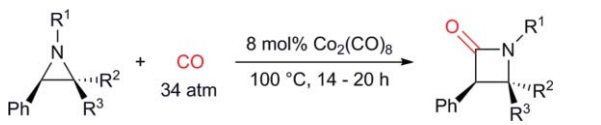
Scheme 22 Carbonylation of 2-arylaziridines to β-lactams by $[Rh(CO)_2Cl]_2$.

stereochemistry.[99] Further, the 2-aryl substituent was key to the success of the reaction; *N-tert*-butyl-2-methylaziridine was not carbonylated under the reaction conditions (Scheme 22).[99] Based on these observations, Alper suggested that coordination of the arene ring to rhodium may precede carbonylation,[99] or that the aryl group may direct the reaction *via* a π-benzyl intermediate.[2a] Recently, Sordo and co-workers have addressed these selectivity issues quantitatively using DFT calculations.[100] They found that coordination of a monomeric $[Rh(CO)_2Cl]$ fragment to the aziridine nitrogen, rather than to the arene ring, initiated the reaction. The conformation adopted by the rhodium-bound aziridine permitted interactions with the arene ring to significantly weaken the N–C(Ph) bond, resulting in the observed regiochemistry.[101] In the case of the aliphatic substrate *N-tert*-butyl-2-methylaziridine, Sordo and co-workers reported that a more stable metal-aziridine complex, combined with a less stable transition state for aziridine ring opening, created a much higher barrier to carbonylation; this accounts for the inability of $[Rh(CO)_2Cl]_2$ to carbonylate 2-alkyl-substituted aziridines.

$Co_2(CO)_8$-catalyzed ring-expansion carbonylation of phenyl-substituted aziridines also produces solely α-phenyl-substituted lactams (Table 6).[59,96b,d] For cobalt-carbonyl-based systems, yields are generally high (≥80%), with the lowest yields (~40%) observed for *trans*-2,3-disubstituted aziridines or simply *N*-isopropyl 2-phenylaziridine. Reduced reactivity towards carbonylation of *trans*-2,3-disubstituted substrates is common to both aziridines and epoxides. Consistent with the cobalt-catalyzed carbonylation of other substrates, stereochemistry is inverted at the site of carbonyl insertion.

A recent note by Davoli *et al.*[96d] reported the carbonylation of *N*-allyl 2-alkenyl-3-phenylaziridines using their standard reaction conditions (21–66% yield), followed by ring-closing

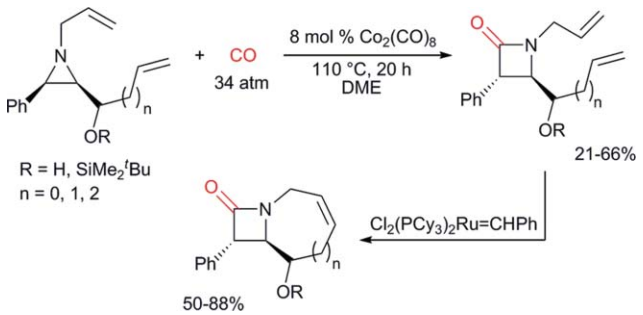
Table 6 The carbonylation of 2-phenylaziridines by $Co_2(CO)_8$ (nine other examples have been reported)



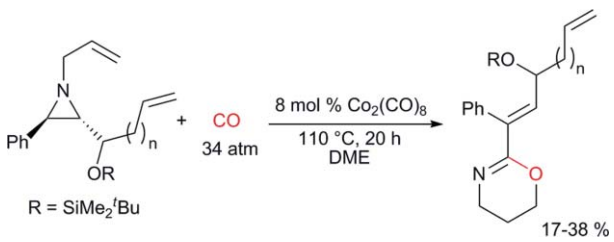
Entry	R^1	R^2	R^3	Yield[a] (%)
1	Bn	$CH_2OSi^tBuMe_2$	H	40
2	Bn	H	CH_2NH_2	68
3	CH_2CO_2Et	H	$CH_2OSi^tBuMe_2$	63
4	^{i}Pr	H	Me	94
5	$CH_2CH{=}CH_2$	H	$CH(OH)CH_2CH{=}CH_2$	42

[a] Isolated yield of β-lactam product.

alkene metathesis (50–88% yield) to generate N-bridgehead-fused bicyclic β-lactams (Scheme 23). These 2,3-fused bicyclic β-lactams constitute the framework for many β-lactam antibiotics.[102] The extension of aziridine carbonylation to these particular *cis*-2,3-disubstituted substrates, in conjunction with the subsequent alkene metathesis, form a useful synthetic strategy. The *trans* isomers, under analogous conditions, were subject to a rearrangement yielding 5,6-dihydro-1,3-oxazines (Scheme 24).



Scheme 23 The sequential carbonylation/ring-closing metathesis of *N*-allyl-*cis*-2-alkenyl-3-phenylaziridines to yield bicyclic β-lactams.



Scheme 24 Carbonylation and rearrangement of *N*-allyl-*trans*-2-alkenyl-3-phenylaziridines to yield 5,6-dihydro-1,3-oxazines.

There is a single example of a non-phenyl-substituted aziridine that is carbonylated adjacent to the bulkier substituent.[103] Aggarwal and co-workers reported that *cis*-1,3-di-*n*-butyl-2-trimethylsilylaziridine is carbonylated by $Co_2(CO)_8$ to yield exclusively *trans*-1,4-di-*n*-butyl-3-trimethylsilylazetidin-2-one (Fig. 2). The authors use the carbonylation procedure of Piotti and Alper,[59] though they add a small amount of ether to the reaction. The reasons for the unusual regiochemical preference observed in this case are not discussed.

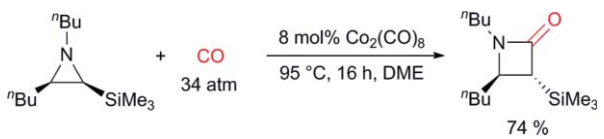


Fig. 2 Carbonylation of a 2-silyl-3-alkylaziridine. The carbonylation occurs adjacent to the more hindered carbon atom.

A number of 2,3-disubstituted aziridines yield a mixture of regioisomers when carbonylated (Table 7), although carbonyl insertion at the less hindered site is still preferred.[59,60,96a,b] All of these substrates are *N*-Bn and 2-CH_2OR or 2-CH_2OSiR_3 substituted, but this should not be taken as a causal factor; the lack of substrate diversity prohibits direct comparison of substrates across publications. Reactions with *cis*-disubstituted aziridines are generally faster, higher yielding, and proceed with better regiocontrol than those with the corresponding *trans* isomers. Though catalyst loading and CO pressure are identical across these reports, variation of reaction time and temperature make absolute comparisons difficult. Consistent with other substrates, stereochemistry is inverted at the site of carbonyl insertion.

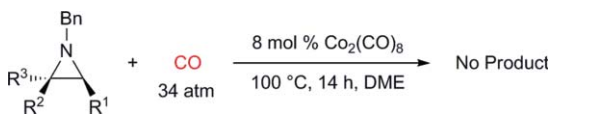
Table 7 Carbonylation of aziridines to give regioisomeric β-lactams

Entry	R^1	R^2	R^3	Yield[a] (%)	N : I[b]
1	$CH_2OSi^tBuMe_2$	Me	H	>99	92 : 8
2	$CH_2OSi^tBuMe_2$	H	Me	63	88 : 12
3	$CH_2OSi^tBuMe_2$	Et	H	98	83 : 17
4	$CH_2OSi^tBuMe_2$	H	Et	60	73 : 27
5	CH_2OAc	Me	H	82	88 : 12

[a] Total isolated yield of β-lactam. [b] Ratio of normal to inverse carbonylation.

Aziridines that give no isolated yield of β-lactam[60,96b] are typically *cis* disubstituted with electron-withdrawing substituents adjacent to the ring, though there is one exception (R^1 = CH_2OH, R^2 = H, R^3 = Ph) (Table 8). Interestingly, these unreactive aziridines are almost all 2-phenyl derivatives, which are typically more reactive than 2-alkylaziridines.[2a]

Table 8 Aziridines for which ring-expansion carbonylation has not been successful



Entry	R^1	R^2	R^3
1	$CH_2OSi^tBuMe_2$	H	CF_3
2	CO_2CH_3	Ph	H
3	$COCH_3$	Ph	H
4	CHO	Ph	Et
5	CH_2OH	H	Ph

6.3 Modified catalytic systems

Two modified systems, both based on Alper's $[Rh(CO)_2Cl]_2$ catalyst (*vide supra*), also possess notable properties. Using $[Rh(CO)_2Cl]_2$, or more effectively the related complex $[Rh(COD)Cl]_2$, with enantiopure menthol as an additive, Alper and co-workers achieved the enantioselective carbonylation of *N*-*tert*-butyl- and *N*-adamantyl-2-arylaziridines,[99] producing the corresponding *N*-alkyl-3-phenylazetidin-2-ones in up to 99.5% optical yield (isolated yield = 25%).[104] Following the carbonylation, both the starting aziridine and the product β-lactam were isolated in excellent optical yield.

This reaction can therefore be used as a kinetic resolution of aziridines, as well as an enantioselective synthesis of β-lactam.

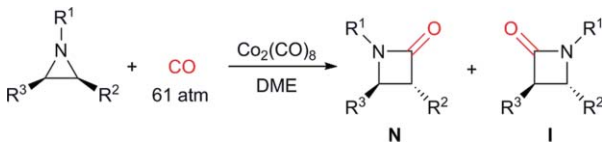
In a recent note, Lu and Alper reported that rhodium-complexed dendrimers, immobilized on a resin, were active for the ring-expansion carbonylation of 2-arylaziridines.[96c] Though this catalyst required several steps to prepare,[105] it was easily separated from the reaction products by filtration, and reused multiple times with only a slight loss of efficiency. These authors have also applied this catalyst to olefin hydroformylation,[105] and have applied a related palladium-containing catalyst to carbonylative ring-forming reactions.[106]

6.4 [Lewis Acid]$^+$[Co(CO)$_4$]$^-$ catalysts

Despite the functional diversity of aziridines that have shown reactivity for carbonylation, the overall efficiency of the catalyst, $Co_2(CO)_8$, had not been improved. Given the importance of β-lactams in medicinal,[107] organic,[108] and polymer chemistry,[109] we have focused on improving the efficiency of aziridine carbonylation through the use of well-defined catalysts. As we have not worked extensively with aziridines, coverage here will be brief.

Following our discovery of **1**, we hypothesized that complexes of the general form [Lewis acid]$^+$[M(CO)$_x$]$^-$ would be active catalysts for heterocycle carbonylations. In the structure of **1**, the THF molecules bound to the aluminium center herald its Lewis acidity; thus we considered that complexes sharing this trait might also be active catalysts for heterocycle carbonylation. A survey conducted of the Cambridge Structural Database for such compounds revealed [Cp$_2$Ti(THF)$_2$]$^+$[Co(CO)$_4$]$^-$, **7**, an easily synthesized complex.[56] This compound was active for epoxide carbonylation, though less robust and efficient than **1**. However, **7** proved to be a very active catalyst for aziridine carbonylation, producing several β-lactams in good or excellent yield. The results of aziridine carbonylations using **1** and **7**, as well as using $Co_2(CO)_8$ (the most common aziridine-carbonylation catalyst) for comparison, are shown in Table 9. The well-defined [Lewis acid]$^+$[Co(CO)$_4$]$^-$ catalysts produced β-lactams in high yields after shorter reaction times than $Co_2(CO)_8$. We attempted the carbonylation of *N*-substituted 2-methylaziridine derivatives (entries 1, 2, 6 and 7) in addition to previously examined substrates (entries 3, 4 and 8). While stoichiometric Ni(CO)$_4$ has been used to carbonylate *N*-benzyl 2-methylaziridine,[110] the toxicity of this metal carbonyl reagent makes its use prohibitive. Though catalyst **7** converts only 35% of the *N*-toluenesulfonyl 2-methylaziridine, **1** gives complete conversion to β-lactam under the same reaction conditions. This is a particularly promising result due to the accessibility of enantiomerically pure *N*-toluenesulfonyl aziridines.[111]

Table 9 Carbonylation of aziridines to β-lactams using [Cp$_2$Ti(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (**7**) and [(salph)Al(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (**1**)[a]



Entry	R^1	R^2	R^3	Catalyst	mol%	*T*/ °C	*t*/ h	N (%)	I (%)
1[b]	Bn	H	Me	**7**	5	60	6	90	[c]
2[b]	Bn	H	Me	**1**	5	60	6	50	[c]
3[b]	Bn	–(CH$_2$)$_4$–		**7**	5	80	18	80	[c]
4[b]	Bn	–(CH$_2$)$_4$–		**1**	5	80	18	<5	[c]
5[d]	Bn	–(CH$_2$)$_4$–		$Co_2(CO)_8$	8	100	48	28	[c]
6[b]	Ts	H	Me	**7**	5	90	6	35	[c]
7[b]	Ts	H	Me	**1**	5	90	6	99	[c]
8[b]	Bn	Me	CH$_2$OSi^{t}BuMe$_2$	**7**	5	60	5	90	5
9[e]	Bn	Me	CH$_2$OSi^{t}BuMe$_2$	$Co_2(CO)_8$	8	100	16	92	8

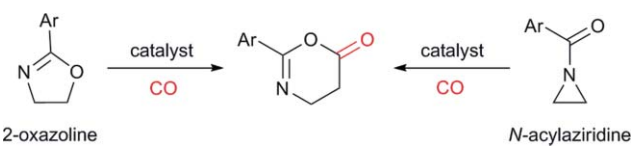
[a] [Substrate] = 0.2 M in DME. [b] From ref. 57. [c] None detected. [d] From ref. 59. [e] From ref. 60.

6.5 Other three- and four-membered azacycles

In reports that predate the scope of this review, catalytic carbonylations of azirines,[112] α-lactams,[113] diaziridines,[114] and azetidines[115] have been described. Recently, the stoichiometric carbonylation of diaziridinones has also been accomplished.[116]

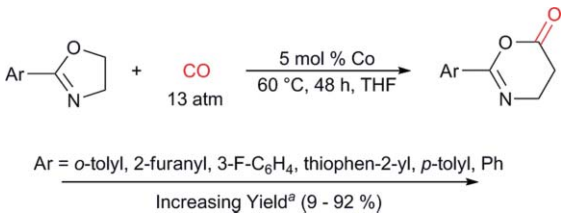
7 Oxazoline expansion carbonylation

There are many reports of carbonylations of three-membered and four-membered heterocycles; these reactions are feasible due to the inherent ring strain of the substrates. The carbonylation of five-membered rings, however, has received significantly less attention.[2a] Of the five-membered rings for which carbonylation has been reported,[43,117] 2-oxazolines have received the greatest recent attention, and form perhaps the most useful products. As discussed in Section 2, Garapon and co-workers have studied the ring-opening carbonylation of oxazolines.[24] Xu and Jia have investigated the ring-expansion carbonylation of 2-oxazolines to give 2-oxazin-6-ones,[118] which we have reported[53] *via* the carbonylation of *N*-acylaziridines (Scheme 25). Jia's initial report used PhCH$_2$Co(CO)$_4$, which under standard reaction conditions (60 °C, 13 atm) exists in an equilibrium with the acyl–cobalt species, PhCH$_2$C(O)Co(CO)$_4$ (R = CH$_2$Ph, eqn (5)). The carbonylation of 2-phenyl-2-oxazoline proceeded smoothly, yielding 95% of the corresponding oxazinone in 48 h. $Co_2(CO)_8$ was far less active (4% conversion); though when mixed with radical initiator azo-bis-isobutyronitrile, it generated a viable catalytic species, and achieved 85% conversion to product under the same reaction conditions.



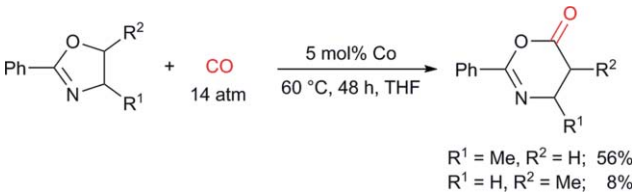
Scheme 25 2-Oxazin-6-ones from 2-oxazolines[118] or *N*-benzoyl aziridines[53] *via* ring-expansion carbonylation.

The effect of the aryl group in the 2 position of the oxazoline ring was examined using different aromatic heterocycles and substituted phenyl rings (Scheme 26). In general, isolated yields ranged from 9 to 92%, following a trend of increasing yield with electron-donating character of the aromatic ring. There was one exception; an *o*-tolyl group reduced oxazinone yield to 30%, while the presence of a *p*-tolyl group increased conversion to >98%. The carbonylation of the 4-methyl- and



Scheme 26 Ring-expansion carbonylation of a series of 2-aryl 2-oxazolines. [a]Isolated yield of 2-oxazin-6-one product.

5-methyl-2-phenyl-2-oxazolines gave 56% and 8% conversion, respectively, indicating a pronounced steric effect of these positions (Scheme 27). The carbonylation of the 5-phenyl derivative proceeded to 52% conversion under standard reaction conditions, with PhC(O)NHCH=CHPh as the major byproduct. Improved conversion (83%) and reduced byproduct formation were possible using higher CO pressure (67 atm). The proposed mechanism for oxazoline carbonylation by this catalyst is based upon the generation of a 17-electron $\cdot Co(CO)_4$ species.



Scheme 27 Carbonylation of 4-methyl and 5-methyl 2-phenyl-2-oxazoline.

Subsequent studies by Jia and co-workers involved ^{1}H NMR spectroscopic analysis of the reaction stereospecificity.[119] The results of these experiments indicated that inversion of stereochemistry occurs at the site of attack (5-position), similar to the carbonylation of both epoxides and aziridines (*vide supra*). This is consistent with an S_N2-type mechanism for oxazoline ring opening.

8 Outlook and conclusions

Heterocycles are a class of compounds pervasive throughout chemistry. Their construction and modification through simple atom-economic transformations is therefore of substantial value to the scientific community. Metal-catalyzed carbonylation is a class of such reactions, and there have been significant recent advances in its application to heterocycles. There remain, however, important challenges in this area, such as the synthesis of high-molecular-weight PHAs and poly(β-peptoid)s, enantioselective carbonylation catalysts, ring-expansion carbonylation of less reactive heterocycles, and catalysts with higher functional-group tolerance. We believe that well-defined catalysts will be instrumental in future developments; the synergy between mechanistic studies and new reaction types will continue to drive progress in this field.

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