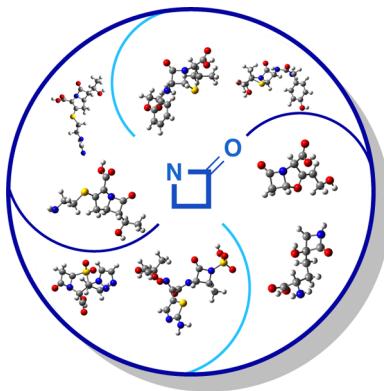


Chemical Synthesis of β -Lactams: Asymmetric Catalysis and Other Recent Advances

Cody Ross Pitts and Thomas Lectka*

Department of Chemistry, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, United States



CONTENTS

1. Introduction	7930
2. The β -Lactam Ring	7930
3. Catalytic, Asymmetric Synthesis of β -Lactams	7931
3.1. Carbonylative Ring-Opening of Aziridines	7931
3.2. Intramolecular C–H Insertion Reactions	7932
3.3. Kinugasa Reaction	7934
3.4. Enolate–Imine Condensation	7937
3.5. Umpolung Staudinger Approach	7938
3.6. Annulation-Lactamization	7941
4. Other Recent Advances in β -Lactam Synthesis (2008–2013)	7941
4.1. Staudinger Reaction	7941
4.2. Enolate–Imine Condensation	7944
4.3. Kinugasa Reaction	7945
4.4. Intramolecular Cyclization Reaction	7946
4.5. Carbonylation Reaction	7948
4.6. Multicomponent Reaction	7949
4.7. Ring Contraction	7950
5. Concluding Remarks	7950
Author Information	7950
Corresponding Author	7950
Notes	7950
Biographies	7951
References	7951

1. INTRODUCTION

The history of the β -lactam (2-azetidinone) ring, arguably one of the most acclaimed heterocycles studied over the last century, tells a tale rich in curiosity, serendipity, and gravity spanning the fields of chemistry, biology, and medicine. Its fame is attributed to the enormous influence of β -lactam antibiotics on global health since Sir Alexander Fleming's discovery of penicillin and its ability to annihilate pathogenic bacteria in 1928¹ and Dorothy Crowfoot-Hodgkin's confirmation

of its structure by X-ray crystallography in 1945.² Additionally, studying the formation and destruction of the β -lactam ring has provided remarkable insight to chemical reactivity and biochemical mechanisms. From the chemist's perspective, both the synthesis of the β -lactam scaffold and the understanding of its reactivity as a synthetic building block (a synthon) to other non- β -lactam structures are pivotal in illuminating *in vivo* structure–activity relationships (SAR), accessing/studying novel compounds, and allotting new possibilities for drug discovery. Considering encyclopedias are more appropriate for a truly comprehensive gaze at the chronicles of the β -lactam in any given field, this Review only examines recent significant developments from the viewpoint of a synthetic chemist and serves as a liaison to some additional review articles and books that may also be of interest to the reader.

The purpose of this Review is 2-fold: (1) to compile and discuss catalytic, asymmetric chemical syntheses of β -lactams and (2) to gather other recently published synthetic methods spanning from 2008 to 2013, as an extension of the *Chemical Reviews* article by Brandi, Cicchi, and Cordero.³ The scope of this Review is limited to novel synthetic assembly of the β -lactam (2-azetidinone) ring; for information on the synthesis and biological activity of monocyclic β -lactams⁴ and carbapenems,⁵ the synthesis and biological activity of cephalosporins, oxacephems, penams, and sulbactam,⁶ the use of β -lactams in the synthesis of non- β -lactam products,⁷ mechanisms and applications of β -lactam biosynthesis,⁸ combinatorial approaches to the synthesis of β -lactams,⁹ classic modification or total synthesis of β -lactam antibiotics,¹⁰ or books on either synthetic approaches to¹¹ or a physical organic discussion of¹² β -lactams, see attached references. Additionally, some other pertinent reviews are attached to the subtitles in section 3.

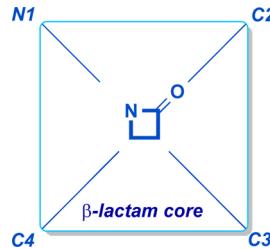


Figure 1. The β -lactam (2-azetidinone) ring.

Special Issue: 2014 Small Heterocycles in Synthesis

Received: October 7, 2013

Published: February 20, 2014



2. THE β -LACTAM RING

Despite the ubiquitous nature of both cyclic and acyclic amides in chemistry and biology, the β -lactam ring (Figure 1) stands apart. The rotational barrier of an acyclic amide C–N bond is approximately 16–22 kcal/mol, as determined by gas-phase¹³ and dynamic NMR experiments,¹⁴ due to a strong degree of resonance between the nitrogen atom lone pair and the π -system of the carbonyl. The angle strain in the four-membered β -lactam scaffold disrupts this harmonious resonance so much as to alter the reactivity of the notoriously stable amide carbonyl to that of an acid chloride in the extreme case,¹⁵ but obviously most β -lactams are stable enough to be isolated from natural sources. Unlike the famously low carbonyl absorption signals of acyclic amides around 1660 cm^{−1}, the infrared spectrum of a β -lactam typically shows a distinct stretch between 1730 and 1815 cm^{−1}, with higher frequency shifts being characteristic of fused rings and lower shifts of monocyclic β -lactams. The diastereotopic C3 and C4 protons of disubstituted β -lactams also show distinct ¹H NMR coupling constants based on relative stereochemistry (i.e., generally cis = 5–8 Hz; trans = 0–2 Hz),¹⁶ which has been confirmed by X-ray crystallography.

The unique characteristics and in vivo reactivity of the β -lactam make it a coveted pharmacophore to assemble and a valuable synthetic building block to transform. It can be chemically constructed through cyclization reactions, cyclo-addition reactions, organometallic-mediated reactions, and other miscellaneous approaches such as ring contraction and radical processes. Note that *cis* β -lactams can often be readily converted to the more thermodynamically stable *trans* isomers by a straightforward base-catalyzed isomerization.¹⁷ Also, given the attenuated strength of the amide bond, β -lactams have been used extensively as building blocks for other types of compounds, whose destruction allows access to heterocycles of various sizes, amino(hydroxyl) acid derivatives, β -amino ketones, γ -amino alcohols, and other compounds.⁷ Regardless of the application, the chemical synthesis of the β -lactam core structure has been, is, and will continue to be a very significant and desirable field to cultivate.

3. CATALYTIC, ASYMMETRIC SYNTHESIS OF β -LACTAMS

Synthetic methods that construct the β -lactam ring have been developing exorbitantly over the last century from almost every imaginable set of synthons. Yet, there is still a necessity for innovation and improvement in the field, even within each category of well-established reactions. Fortunately, a better understanding of reaction mechanisms has allowed chemists to think critically about the initial phenomenal discoveries, then optimize and build upon them in an expansive relay race to pragmatism. Although practicality comes in many forms in synthetic chemistry,¹⁸ in the world of medicinal chemistry, access to effective syntheses of optically pure compounds is often paramount, as enantiomers can have drastically different effects in vivo. Accordingly, stereoselective variants of established synthetic methods may be globally considered the most “practical” and necessary advancements in forming β -lactam rings, the core structures of the majority of antibiotics.

In stereoselective synthesis, optical purity is bestowed upon a parent molecule through asymmetric induction, either from an inherently asymmetric molecule (achievable for achiral molecules by installing chiral auxiliaries) or from an external

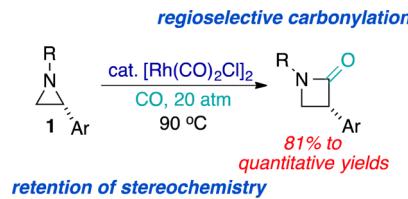
chiral reagent. Stereoselective synthetic methods often rely on chiral auxiliaries, which are effective, but stoichiometric quantities of the chiral auxiliaries are required as are extra steps in the synthesis (adding/removing the auxiliary). Considering chirality comes with a cost, the use of a substoichiometric or catalytic amount of an external chiral reagent, when possible, is very appealing. The same goes for certain transition metals or other organometallic reagents, as these, too, can be very expensive in large quantities. Therefore, the goal of this section is to take a fairly comprehensive look at the progress of mutually inclusive catalytic, asymmetric syntheses of the β -lactam ring.¹⁹

3.1. Carbonylative Ring-Opening of Aziridines¹⁹

Following some of the first examples of catalytic carbonylative ring-opening reactions of heterocycles in the 1950s,²⁰ metal-catalyzed carbonylation reactions used to make β -lactam rings by inserting carbon monoxide into a C–N bond have been recorded since 1981 by Alper and co-workers with the carbonylation of azirines.²¹

The first metal-catalyzed carbonylation of aziridines to make β -lactams was communicated by the same group in 1983,²² and expanded upon in 1989.²³ Using a rhodium(I) catalyst in 5 mol % under CO pressure (20 atm) at 90 °C, the authors were able

Scheme 1



to achieve regiospecific and enantiospecific carbonylation of aryl-substituted aziridines **1**, that is, exclusive insertion of carbon monoxide into the aryl-substituted C–N bond²⁴ of an aziridine ring with complete retention of stereochemistry (Scheme 1). These findings, in accordance with high to quantitative yields, inspired the authors to examine an asymmetric synthesis through kinetic resolution, that is, conditions (e.g., using a chiral additive) whereby one enantiomer in a racemic mixture is more reactive than the other, allowing formation of an enantio-enriched product (Figure 2). In the presence of chlorodicarbonylrhodium(I) dimer (5 mol %) and chiral additive *l*-menthol **2** (5 mol %), for example, the (*S*)- β -lactam **3** was formed in 25% optical yield from racemic 1-*tert*-butyl-2-phenyl-aziridine **4** (R = *t*-Bu). Beyond this initial result, more success was found when increasing the amount of *l*-menthol to 3.0 equiv (48% optical yield) and then by using a chloro(1,5-cyclooctadiene)rhodium(I) dimer as the catalyst instead (>99.5% optical yield). Other examples were reported under their optimized conditions to give optical yields of 96% or greater. After 24 h, β -lactam products were isolated in only 21–25% yield (keep in mind that the maximum yield via kinetic resolution is 50%), and the authors also note that isolated yields increase over time at the expense of optical purity.

Although this methodology marked one of the first asymmetric syntheses of β -lactams in conjunction with “catalysis,” it is ostensibly less practical than the types of approaches that would follow it in the years to come. As was also pointed out in a review by Jacobsen and co-workers on

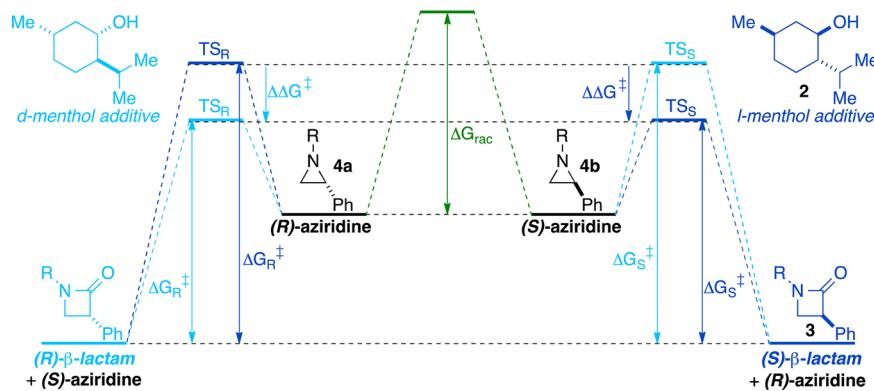


Figure 2. Kinetic resolution concept for carbonylative ring-opening of aziridines.

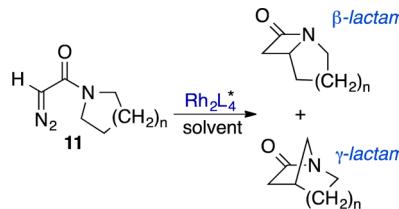
kinetic resolution reactions,²⁵ enantio-enriched aziridines (and the corresponding β -lactams) are arguably better generated from enantio-enriched epoxide retrosynthetic precursors, which can be kinetically resolved by other protocols.²⁶ However, the concept and application of this asymmetric carbonylation reaction was a significant advancement in terms of its efficacy and simplicity in achieving high optical yield with an inexpensive, commercially available chiral additive.

3.2. Intramolecular C–H Insertion Reactions²⁷

Diazo compounds, through formation of a carbene (or carbenoid) intermediate, can effectively undergo an intra-

reactions of diazoacetamides in 1992 using a dirhodium(II) catalyst (1 mol %) and either chiral pyrrolidone **5a** or oxazolidinone **5b,c** ligands.³¹ In this report, moderate enantioselectivity was achieved (20–80% ee), but the β -lactam **6** product yields (Scheme 2, path B) suffered greatly as they were in competition with the typically more favorable γ -lactam **7** and **8** formation (Scheme 2, paths A and C); that is, a typical isolated β -lactam yield, maintaining moderate enantioselectivity, does not surpass 19%. The distribution of γ - and β -lactams was dependent on the substitution at the 2-position of the N-alkyl chain of the *N*-alkyl-*N*-(*tert*-butyl)diazoacetamides **9** screened and the chiral carboxamide ligand employed. In one stand-alone example reported the same year using a BINAP-based dirhodium catalyst **10** instead, a *trans* β -lactam was formed exclusively in 93% yield, but in only 26% ee.³²

Scheme 3



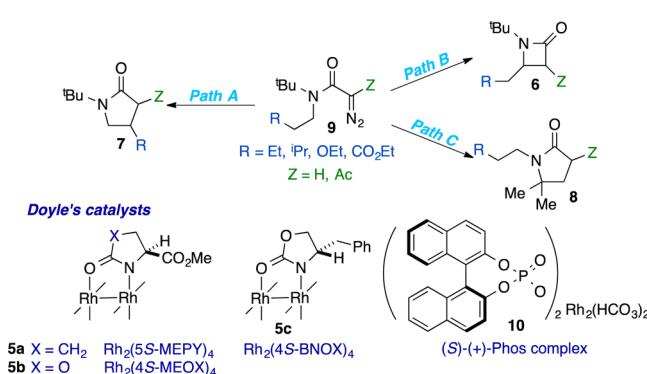
<i>n</i>	catalyst	$\beta:\gamma$	% ee ($\beta:\gamma$)
3	$\text{Rh}_2(5\text{S-MEPY})_4$	>99:1	97 ^a
4		67:33	30:96
4	$\text{Rh}_2(4\text{S-MEOX})_4$	49:51	8:96
4	$\text{Rh}_2(4\text{S-MACIM})_4$	39:61	66:96

^a % ee for γ -lactam not determined.

molecular C–H bond insertion reaction to furnish β -lactams. The first report of a β -lactam synthesis by this strategy was in 1965 by Corey and Felix,²⁸ and started to develop slowly thereafter.²⁹ Aspects of the studied reaction mechanism prove this system amenable to asymmetric catalysis (Figure 3).³⁰

Doyle and co-workers appear to provide the first evidence of an enantioselective β -lactam synthesis by C–H insertion

Scheme 2



Considering γ -lactam formation was favored in the *N*-alkyl-*N*-(*tert*-butyl)diazoacetamides **9** originally under scrutiny, Doyle and co-workers later looked at more conformationally constrained “diazoacetylazacycloalkanes” **11** to push β -lactam formation with their chiral dirhodium(II) carboxamate catalysts (Scheme 3).³³ While the authors report no success with the diazoacetamides of pyrrolidine, piperidine, or morpholine-based systems, the azacycloheptane and 3-azabicyclo[3.2.2]-nonane analogues displayed excellent regioselectivity with >99:1 $\beta:\gamma$ lactam formation, moderate to good yields (67–81%), and very high enantioselectivity (92–97% ee) with either $\text{Rh}_2(4\text{S-MEOX})_4$ or $\text{Rh}_2(5\text{S-MEPY})_4$ in 2 mol %. The azacyclooctane analogue, however, is flexible enough for

competitive γ -lactam formation under most conditions. The authors also report an interesting instance with the Rh-carbenoid derived from the diazoacetamide of *cis*-2,6-dimethylpiperidine **12** where β -lactam formation is preferred over insertion into the methyl C–H bond (89:11 $\beta:\gamma$) in 78%

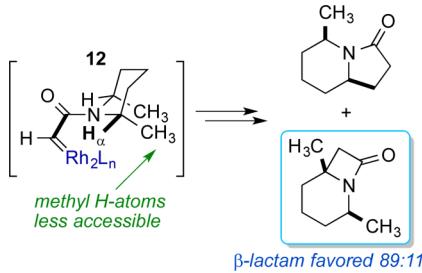


Figure 4. Rationale for α -C–H preference.

yield and 86% ee using $\text{Rh}_2(5S\text{-MEPY})_4$ in DCM. The preference for α -C–H insertion in this example is rationalized by a planar *N*-acyl chair conformation where the methyl groups sit in axial positions (distal to the acetyl substituent to minimize steric interactions), leaving the α -C–H bonds more accessible (Figure 4).³⁴

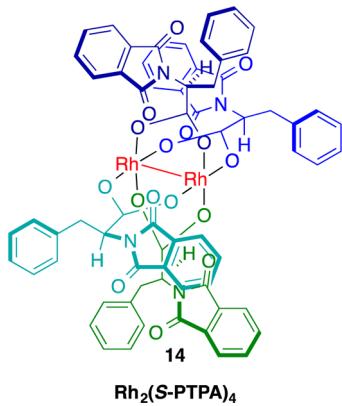


Figure 5. *N*-Phthaloyl-(S)-phenylalaninate dirhodium(II) catalyst.

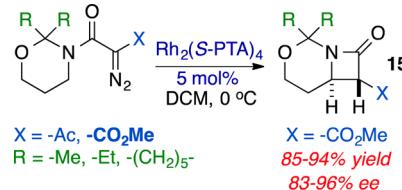
After Doyle's initial reports exhibiting the possibility of a catalytic, asymmetric variant, Hashimoto and co-workers examined the C–H insertion reactions of *N*-alkyl-*N*-(*tert*-butyl)- α -methoxycarbonyl- α -diazoacetamides **13**, electronically geared toward β -lactam formation, with a chiral dirhodium(II) catalyst **14** in 2 mol % derived from *N*-phthaloyl-(S)-phenylalaninate (Figure 5).³⁵ A preliminary study with two α -acetyl- α -diazoacetamides gave *trans* β -lactams in 64% and 69% yields with 50% ee and 38% ee, respectively, but higher yields (94–98%) and enantioselectivities (56–74% ee) were achieved using α -methoxycarbonyl- α -diazoacetamides. Interestingly,

Scheme 4



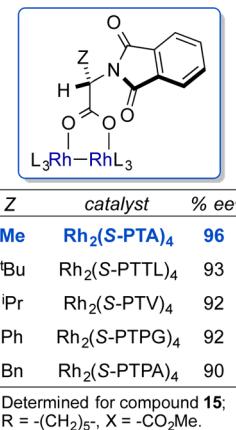
these α -methoxycarbonyl compounds provided exclusively *cis* stereochemistry, leading the authors to suggest that *cis*–*trans*

Scheme 5



isomerization occurs during the reaction of the α -acetyl compounds (Scheme 4).³⁶

One extension of this work in 1998 explored other *N*-phthaloyl-amino acid-based chiral dirhodium(II) catalysts for an optimized synthesis of 3-oxa-1-azabicyclo[4.2.0]octanes **15** (Scheme 5).³⁷ These compounds are of general interest as synthetic precursors to carbapenem antibiotics. Similar to their

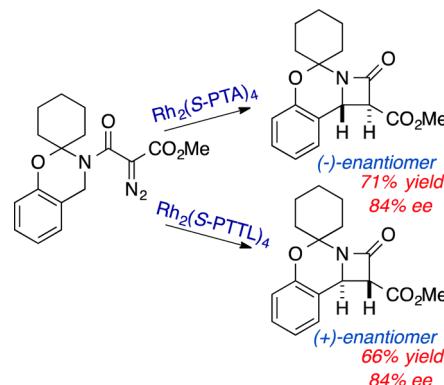


^a Determined for compound **15**; R = $-(\text{CH}_2)_5-$, X = $-\text{CO}_2\text{Me}$.

Figure 6. Catalyst abbreviations.

previous account, the α -acetyl compounds gave inferior results, forming completely racemic *trans* β -lactams, while the α -methoxycarbonyl compounds provided products in 85–94% yield and 83–96% ee. Yields and enantioselectivity varied with *N,O*-acetal substitution and chiral amino acid ligands used. Note the best results were obtained from the *N*-phthaloyl-(S)-alanine-based catalyst ($\text{Rh}_2(\text{S-PTA})_4$) in 5 mol % (Figure 6). The authors demonstrated the value of this method by synthesizing enantio-enriched known intermediates for the

Scheme 6



synthesis of 1-unsubstituted and 1 β -methyl-substituted carbapenems.

During the same year, Hashimoto and co-workers also used a variation of this protocol en route to making known synthetic intermediates to trinem antibiotics (Scheme 6).³⁸ Both the (+)- and the (-)-enantiomers of the *trans* β -lactams of interest were accessed using dirhodium(II) catalysts derived from *N*-phthaloyl-(S)-*tert*-leucine ($Rh_2(S\text{-PTTL})_4$) and *N*-phthaloyl-(S)-alanine ($Rh_2(S\text{-PTA})_4$), respectively. The (+)-enantiomer was obtained in 66% yield and 84% ee, and the (-)-enantiomer was obtained in 71% yield and 84% ee.

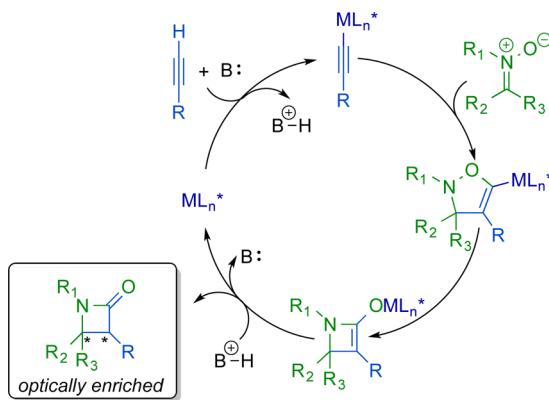


Figure 7. Concept for catalytic, asymmetric Kinugasa reaction.

3.3. Kinugasa Reaction³⁹

In 1972, Kinugasa and Hashimoto reported a β -lactam synthesis from a reaction between copper(I) phenylacetylidyde and nitrones.⁴⁰ The original reaction mechanism was reported by Ding and Irwin in 1976 using a stoichiometric amount of copper, which is currently still accepted.⁴¹ It was later proven amenable to catalysis (Figure 7).

The first catalytic modification of the Kinugasa reaction was described by Miura and co-workers in 1993,⁴² and their work was later extended to incorporate chiral ligands.^{17a} The reaction between nitrones and terminal alkynes proceeds with a catalytic amount of CuI, a ligand, and K_2CO_3 , with product distribution (i.e., β -lactams, azaenynes, imines, and carboxylic acids) and yields being heavily dependent on the amount/type of ligand used. Particularly, excess pyridine in DMF proved amenable in forming β -lactams preferentially. Their additional success in β -lactam formation using a catalytic amount of 1,10-phenanthroline implored them to consider chiral nitrogen-containing ligands of the bis(oxazoline) moiety. Although a reaction using 10 mol % CuI and 20 mol % diisopropyl-substituted bis(oxazoline) ligand **16** did not proceed well due to precipitation of copper(I) phenylacetylidyde, a reaction using a stoichiometric amount of chiral ligand gave a β -lactam product in 45% yield and a diastereomeric ratio of 65:35 (cis:trans). For this same example, a chiral lanthanide shift reagent⁴³ was used to determine an enantiomeric excess of 40% for each of the cis and trans isomers. Also note that treatment of the products with K_2CO_3 at 80 °C gave the trans isomer quantitatively with 40% ee. A modification in the procedure where the alkyne is slowly added and allowed the use of 10 mol % CuI and 20 mol % ligand gave a *trans* β -lactam in 50% yield and 57% ee, after treatment with K_2CO_3 (Scheme 7). Higher enantiomeric excess was achieved with a stoichiometric amount of CuI and ligand

Scheme 7

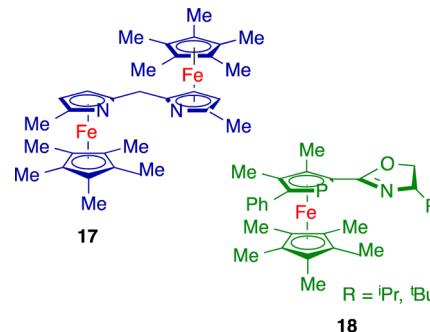
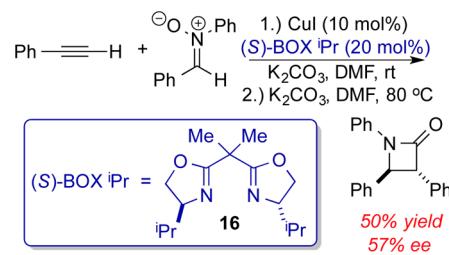
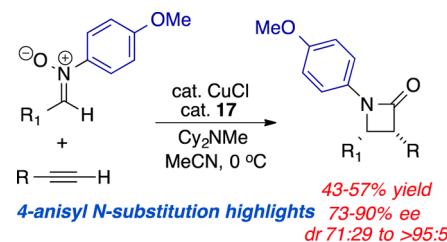


Figure 8. Fu's planar-chiral ligands.

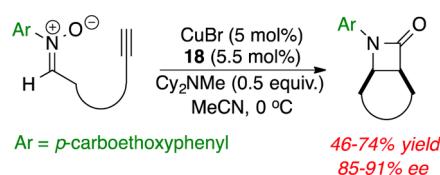
Scheme 8



(up to 68% ee), but this methodology showed that a catalytic, asymmetric Kinugasa reaction was plausible.

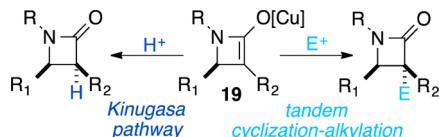
The first diastereo- and enantioselective catalytic variant was reported by Fu and Lo in 2002.⁴⁴ In this methodology, a variety of nitrones and terminal alkynes were coupled to make *cis* β -lactams selectively using 1–2.5 mol % of CuCl and a C_2 -symmetric planar-chiral bis(azaferrocene) ligand **17** (Figure 8) in the presence of dicyclohexylmethylamine (Scheme 8). They reported success with a broad scope of *N*-aryl and C-alkyl, -acyl, and -aryl nitrones, as well as alkyl, alkenyl, and aryl substituted alkynes. Considering the use of 4-anisyl as a protecting group for nitrogen in β -lactam chemistry, the authors particularly emphasize the high enantioselectivity (72–93% ee) achieved with 4-anisyl-substituted nitrones. Overall, products are given in typically very high diastereoselectivity ($\geq 90:1$ cis:trans, with one exception being 71:29), good enantioselectivity (67–93% ee), and modest isolated yields (42–79%, with one outlier at 91%).

Scheme 9



Fu and Shintani extended this work in 2003 by developing the first intramolecular catalytic enantioselective Kinugasa reaction (Scheme 9).⁴⁵ In light of the recalcitrance of their bis(azaferrocene) ligand **17** (giving poor yields and almost no enantioselectivity), another short ligand screening was conducted to find that a planar-chiral phosphaferrocene-oxazoline ligand **18** (5.5 mol %), with CuBr (5 mol %) and dicyclohexylmethylamine (0.5 equiv), performed suitably for this reaction. The authors report a number of tricyclic β -lactams in high enantioselectivity (85–91% ee) and modest yields (46–74%), forming both six- and seven-membered rings alongside the β -lactam ring. These substrates are particularly interesting,

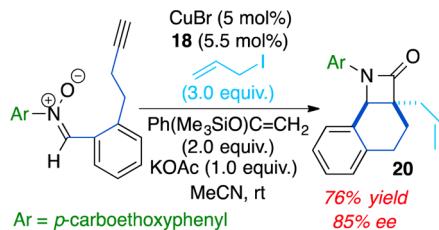
Scheme 10



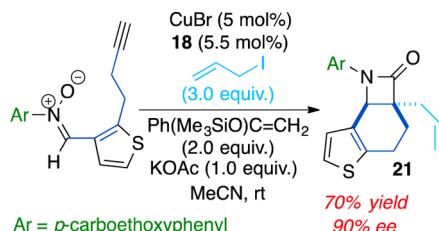
as other methods in the literature have placed little to no emphasis on catalytic, asymmetric syntheses of bicyclic or polycyclic β -lactam skeletons directly thus far.

Furthermore, Fu and Shintani recognized the formation of the conjugate base of a β -lactam (enolate **19**) during the proposed mechanistic pathway as an opportunity to provide additional functionalization at the α -carbon with a proper electrophile (Scheme 10). A particularly appealing goal was to

Scheme 11



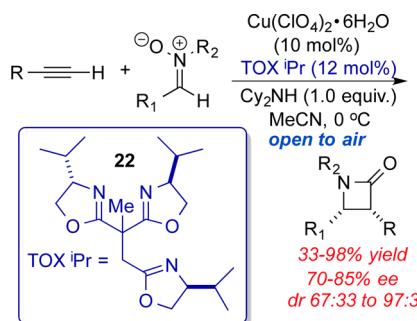
Scheme 12



create a quaternary stereocenter in a tandem cyclization-alkylation reaction. In fact, the authors were able to achieve this with allyl iodide under another set of conditions: 5 mol % CuBr, 5.5 mol % ligand, 3.0 equiv of allyl iodide, 2.0 equiv of a silyl enol ether, and 1.0 equiv of KOAc as a base. Two examples **20** and **21** were reported in high enantioselectivity (85% and 90% ee) and good yields (76% and 70%, respectively) for such a nontrivial reaction (Schemes 11 and 12).

Also in 2003, Tang and co-workers communicated the first method to use a copper(II) catalyst in place of the more air-sensitive copper(I) salts previously implemented (Scheme 13).⁴⁶ This gives the added advantage of being able to conduct the reaction open to air, as opposed to the nitrogen atmosphere

Scheme 13



necessary for the other catalytic, asymmetric methods. They coupled a variety of *C,N*-diaryl-substituted nitrones with aryl and alkenyl-substituted alkynes using catalytic $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (10 mol %), a pseudo C_3 -symmetric tris(oxazoline) ligand **22** (12 mol %), and a base (1.0 equiv) to make *cis* β -lactams. These products were typically formed in very high diastereoselectivity (most examples $\geq 91:9$ *cis:trans*), good enantioselectivity (70–85% ee), and modest yields (33–75%, with one outlier in 98%). The authors also stress that the type of organic base used greatly impacted product yields and selectivity. Although most amine bases promote the reaction, primary amines performed miserably overall, tertiary amines gave high diastereoselectivity but only modest yields and enantioselectivity, and secondary amines, particularly dicyclohexylamine, seemed to provide the best results overall.

Tang and co-workers published the full paper on their tris(oxazoline)/copper(II)-catalyzed Kinugasa method in 2006, expanding greatly upon the scope and limitations of the reaction.⁴⁷ A few mechanistic observations were also made (Figure 9): (1) Copper(II) is proposed to be reduced to copper(I) *in situ* by phenylacetylene, making copper(I) the active catalyst.⁴⁸ Isolation of a small amount of the coupling product, diphenylbutadiyne, under their reaction conditions (except under nitrogen atmosphere) may support this notion.⁴⁹ (2) The dynamic coordination equilibrium of the copper/tris(oxazoline) was studied via ^{13}C NMR and led them to propose a stereochemical model to rationalize selectivity (consistent with the work of Gade and co-workers).⁵⁰ (3) An alternate mechanistic pathway is also proposed involving a ketene intermediate, but no such intermediate was trapped, and confirmation requires further study.

Determined to optimize the system further, Tang and co-workers revisited this methodology in 2012 with a larger screen of copper reagents, ligands, alkynes, and nitrones.⁵¹ Despite the advertised practicality of their copper(II) catalyst being used under air atmosphere, they reported better isolated yields (34–98%) and selectivity (typically 88–99% ee; 86:14 to 97:3 *cis:trans*) using copper(I) triflate (10 mol %) and another tris(oxazoline) ligand **23** derived from Inda-bis(oxazoline) (12 mol %) under nitrogen (Scheme 14). The extended substrate scope includes a plethora of aryl, alkenyl, and alkyl-substituted alkynes, as well as *C,N*-diaryl-substituted nitrones. The authors highlight the use of *N*-PMP protected nitrones and the high functional group tolerance on aryl groups (e.g., trifluoromethyl, nitro, halide, ester, etc.) with no correlative dramatic effect on yield or selectivity.

Following the independent works of Fu and Tang published in 2003, Guiry and co-workers applied a class of *P,N*-ligands, viz., HETPHOX ligands, to an intermolecular catalytic,

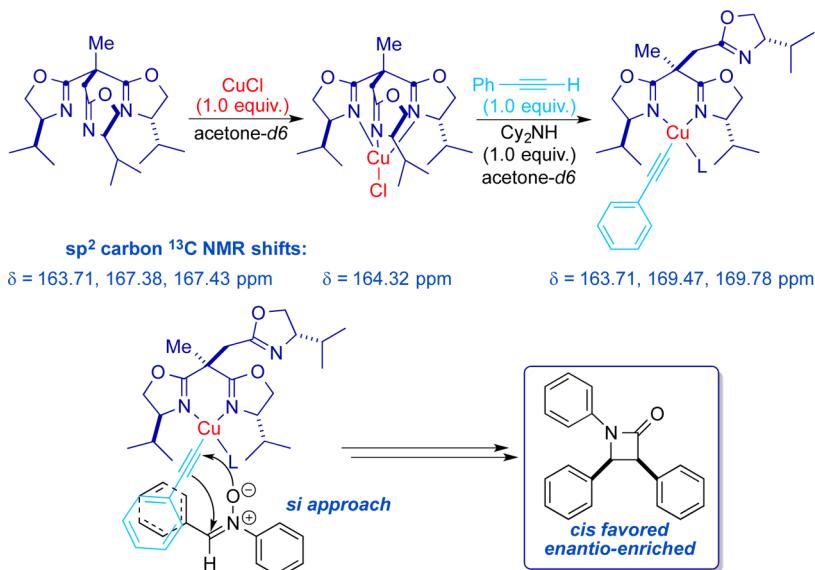


Figure 9. Dynamic coordination equilibrium and stereochemical model.

Scheme 14

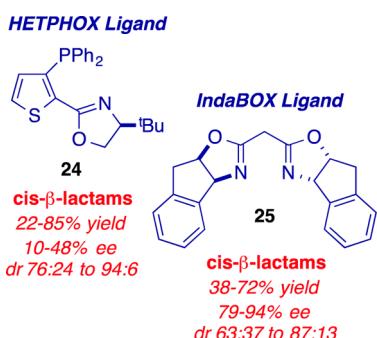
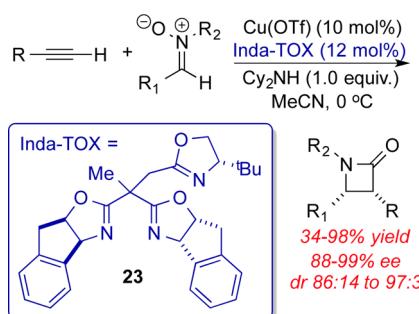


Figure 10. Examples of ligands used in catalytic, asymmetric Kinugasa reactions.

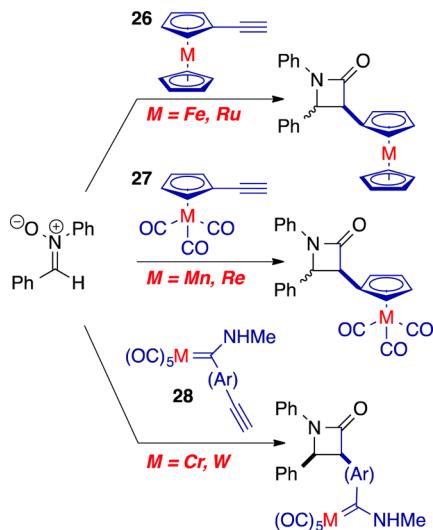
asymmetric Kinugasa reaction in 2004.⁵² Their best results were attained from the use of cuprous chloride (10 mol %) and a *tert*-butyl substituted HETPHOX ligand 24 (12 mol %) under nitrogen atmosphere at 15 °C (Figure 10). Primarily *cis* β-lactams were reported in moderate conversions (22–85%)⁵³ and good diastereoselectivity (76:24 to 94:6 *cis*:*trans*), but fairly poor enantioselectivity (10–48% ee). The authors found a particularly interesting dependence of diastereoselectivity on the electronics of the alkyne substituted in an extreme case: 3,5-bis(trifluoromethyl)phenylacetylene, under normal reaction conditions with diphenyl nitrone, effected a switch in preference for the *trans* isomer (64% conversion; 53% ee; 8:92 *cis*:*trans*). In this instance, the additional withdrawing

effect of two trifluoromethyl substituents may be increasing the acidity of the proton in the C3 position so much as to foster base-promoted isomerization *in situ*, while maintaining a high degree of enantioselectivity. Also, consistent with previously reported findings, electron-donating and electron-withdrawing substituents had a minimal influence on yield and selectivity, but the 1- and 2-naphthyl-substituted nitrones did have a small (presumably) steric influence on conversion and selectivity in juxtaposition with the phenyl-substituted prototype.

In 2009, Saito, Otani, and co-workers published another method highlighting the use of a copper(II) catalyst for the Kinugasa reaction.⁵⁴ After the traditional screening, the authors report their best results using cupric triflate (20 mol %), a *C*₂-symmetric Inda-bis(oxazoline) ligand 25 (22 mol %), and di-*sec*-butyl amine (1.5 equiv) in isopropyl acetate at 5 °C (Figure 10). Reaction conditions hold up for coupling a variety of *C,N*-diaryl-substituted nitrones and aryl, alkenyl, and ester-substituted alkynes to make *cis* β-lactams with overall moderate yields (38–72%), good enantioselectivity (79–94% ee), and good diastereoselectivity (63:37 to 87:13 *cis*:*trans*). Note that electron-withdrawing substituents on the alkyne are also seen to have an effect on diastereoselectivity, beginning to favor the *trans* adduct instead. In the instance of an ester-substituted alkyne, solely the *trans* β-lactam was formed in 54% yield and 32% ee in a fraction of the amount of time reported for the reaction to occur in several other instances (0.1 h vs 48 h, for example).

A general approach to 3-metal-substituted β-lactams was published by Casarrubios, Sierra, and Baeza in 2013 using the Kinugasa strategy (Scheme 15).⁵⁵ Using familiar conditions, this reaction couples a variety of metal complexes with an alkyne moiety to nitrones with cuprous chloride (2.5 mol %), Inda-bis(oxazoline) ligand 25 (2.75 mol %), and dicyclohexylmethylamine (0.5 equiv) at room temperature. Applying alkynes substituted with sandwich 26 (M = Fe, Ru), half-sandwich 27 (M = Mn, Re), and arene-tethered Fischer carbene complexes 28 (M = Cr, W) afforded metalla-β-lactam products in overall moderate to good yields (48–78%), but little to no enantioselectivity (with an achiral nitrone, <15% ee for alkynes proximal to a metal center and 21–35% ee for those distal) or diastereoselectivity (in the case of sandwich and half-

Scheme 15



sandwich complexes). However, the use of a chiral acetal-substituted nitrone provided β -lactams in a 1:1 cis:trans ratio, but with only a single enantiomer of each. Also, in the instance of the Fischer carbenes, where the metal is placed farther away from the alkyne, only the cis products are formed, albeit in low enantioselectivity (21–35% ee). Regarding diastereoselectivity, the authors ran a control experiment to rule out base-mediated epimerization by dicyclohexylmethylamine during the course of the reaction and otherwise conclude that the chiral ligand is not an influence, but the bulkiness of the arene-tethered Fischer carbenes is. Last, they note that, although the chiral nitrone helped overcome the issue of poor enantioselectivity, the origin of their poor enantioselectivity is still under scrutiny.

3.4. Enolate-Imine Condensation⁵⁶

A report from Gilman and Speeter in 1943, a Reformatsky reaction with benzalaniline, was the first example of a β -lactam

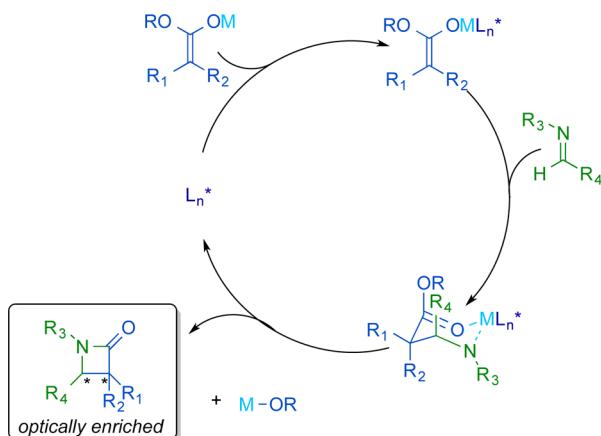


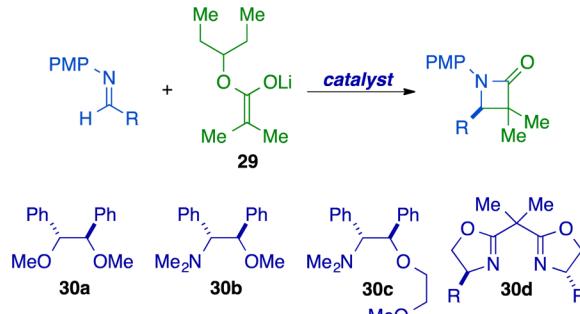
Figure 11. Concept for catalytic, asymmetric enolate-imine condensation.

synthesis using enolate chemistry.⁵⁷ In 1977, Ojima and co-workers used ketene silyl acetals as isolable enolate derivatives to react with imines in the presence of titanium tetrachloride to form the β -lactam core.⁵⁸ In 1980, Newcomb, Bergbreiter, and co-workers expanded on this to effect a β -lactamization using

lithium ester enolates.⁵⁹ Using a chiral ligand, one can envision an opportunity for asymmetric catalysis (Figure 11).

After many years of evolution, a catalytic, asymmetric variant was first produced by Tomioka and co-workers in 1997.⁶⁰ Evidence for a catalytic method was discovered while studying a stoichiometric asymmetric method for coupling lithium ester enolates with imines based on a ternary complex (a lithium

Scheme 16



ester enolate, a lithium amide, and a chiral ether ligand). The group reported that the lithium amide and the chiral ligand must both be present to increase the reactivity of the lithium ester enolate at low temperatures, leading them to test a reaction at -78°C between the lithium ester enolate generated from 3-pentyl isobutyrate 29 and a *p*-methoxyphenyl (PMP) protected imine with their chiral ether ligand in only 10 mol % (Scheme 16). To their satisfaction, the corresponding *cis* β -lactam was produced in 75% yield and 82% ee. They reported one more example in modest yield and enantioselectivity in this paper, as well, but most importantly revealed a possible strategy for asymmetric catalysis in enolate-imine condensation reactions to form β -lactams.

The Tomioka group published an extension of this method in 1999.⁶¹ Chiral ligands 30 were screened in search of increased selectivity and a way to circumvent the use of excess lithium amide (Scheme 16).⁶² The best result, a tridentate amino diether ligand 30c in 20 mol % used to produce a putative binary complex, gave *cis* products in excellent yields (90–99%) but still only modest enantioselectivity (65–90% ee). In 2000, Tomioka and co-workers reported the examination of chiral bis(oxazoline) (Box) ligands 30d for lithium ester enolate-imine condensation.⁶³ They studied an interesting dependence of enantioselectivity on the equivalency of the chiral Box ligand, noting that higher enantiomeric excess was actually achieved using a catalytic amount over a stoichiometric, but enantioselectivity still remained modest at best (70% ee with 20 mol % ligand).

Another effort surfaced in 2004 looking at the catalytic enhancement of a reaction between an imine and methyl alkanoates (incorporating a chiral auxiliary) using either a diether or an amino diether chiral ligand.⁶⁴ Dramatic increases in yield and enantioselectivity were typically observed with the properly matched chiral auxiliary and external chiral ligand catalyst (in 5 mol %) as compared to the sole application of the chiral auxiliary under their conditions. Yields remained high for this method and there was more improvement in enantioselectivity, with one example reported in 94% ee.

Lectka and co-workers later developed a diastereoselective *trans* β -lactam synthesis in 2009 from silyl ketene acetals and a PMP-protected α -imino ester using a phosphonium fluoride

precatalyst.⁶⁵ Although the initial precatalyst studied was a chiral BINAP-derived phosphonium fluoride, similar results were achieved with an achiral tetraphenylphosphonium fluoride catalyst. High yields (up to 95%) and diastereomeric ratios (up to 1:88 cis:trans) were obtained, but this method left enantioselectivity as only an alluring goal.

3.5. Umpolung Staudinger Approach⁶⁶

The concept for the most effective catalytic, asymmetric syntheses of β -lactams to date hails from the first reported synthesis of the β -lactam ring by Hermann Staudinger in 1907 (a cycloaddition reaction of ketenes and imines).⁶⁷ Mechanistically, it is broadly accepted that the [2 + 2] cycloaddition takes place in two steps (nucleophilic addition of the imine nitrogen to the ketene, then conrotatory electrocyclization),

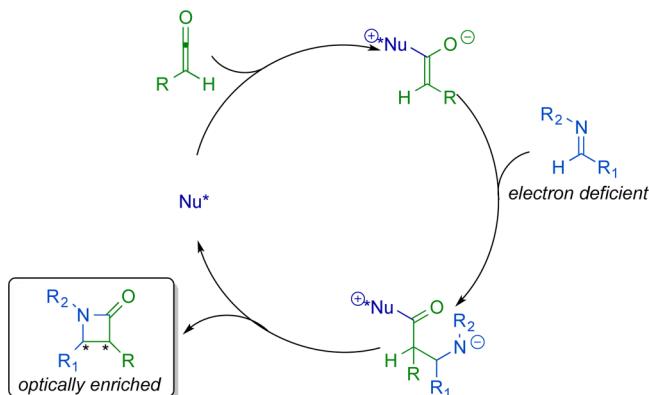
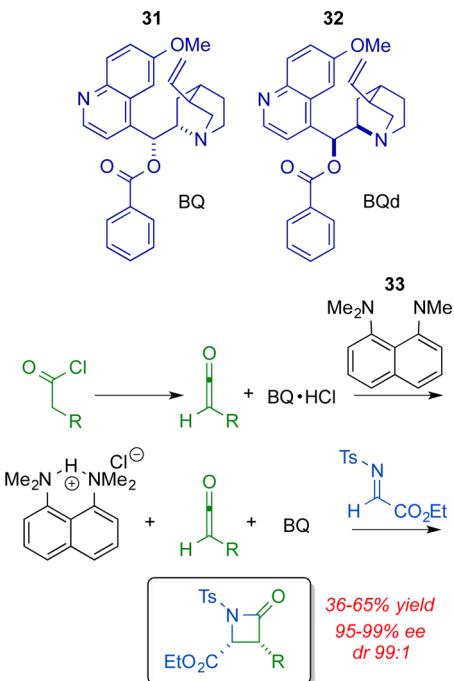


Figure 12. Concept for catalytic, asymmetric umpolung Staudinger reaction.

although some aspects of the reaction are still under scrutiny.⁶⁸ Prima facie this reaction appears to be an unlikely candidate for asymmetric catalysis. However, an umpolung version of the Staudinger reaction, initiated by nucleophilic addition of a ketene-enolate to an imine as opposed to nucleophilic addition of an imine to a ketene, has actually proven to be an excellent venue over the past decade (Figure 12).

Lectka and co-workers pioneered this work in 2000 by employing chiral nucleophilic amine catalysts, viz., cinchona alkaloid derivatives benzoylquinine 31 (BQ) and benzoylquinalidine 32 (BQd) in 10 mol %, to the condensation of electron-deficient imines (α -imino esters⁶⁹) and ketenes (Scheme 17).⁷⁰ The reactive nature of the majority of the desired monosubstituted ketenes required in situ formation from the corresponding acid chlorides and a (typically amine) base;⁷¹ however, to successfully avoid excess base catalyzing the reaction in a racemic fashion (via forming an undesirable ketene-enolate), a non-nucleophilic deprotonating agent was examined, proton sponge 33. Despite proton sponge not being able to form the ketene independently,⁷² the group found that the more kinetically active BQ and BQd can effectively dehydrohalogenate the acid chloride and shuttle the proton to the thermodynamic sink that is proton sponge, which precipitates in toluene as the hydrochloride salt. After proton sponge liberates BQ and BQd, they are free to form ketene-enolates that react favorably with tosyl α -imino esters⁷³ in effecting a catalytic *cis* β -lactam synthesis. This initial communication reports products in excellent enantioselectivity (95–99% ee) and diastereoselectivity (99:1 cis:trans), and in

Scheme 17



modest yields (36–65%). Note that more cost-effective bases were subsequently examined (i.e., bicarbonate salts⁷⁴ and

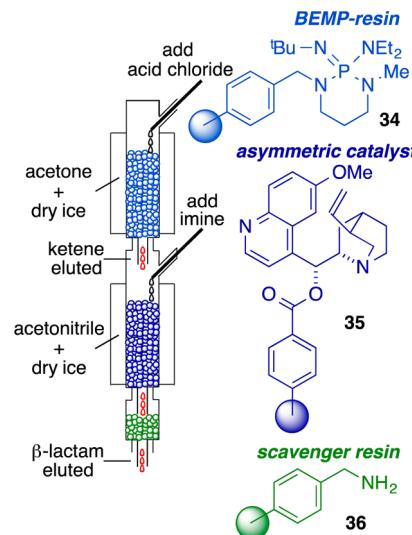


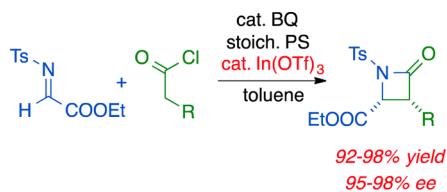
Figure 13. Column asymmetric catalysis.

sodium hydride/crown ether⁷⁵), but proton sponge appears to be the superior base for optimal results.

An immediate extension of this work explored the possibility of combining asymmetric catalysis with solid-phase chemistry for β -lactam synthesis in what was referred to as column asymmetric catalysis (Figure 13).⁷⁶ The reaction was envisioned to take place on sequentially linked columns packed with a solid-supported dehydrohalogenation reagent (top), a solid-supported chiral nucleophile catalyst (middle), and then an optional scavenger resin, used to remove unreacted starting materials (bottom). Procedurally, an acid chloride dissolved in THF can be loaded onto the top column, held at -78°C by a jacket of dry ice/acetone, where it is transformed to the ketene

upon percolation through a basic resin (a BEMP resin 34 proved suitable for ketene formation). As the ketene elutes to the middle column, held at -43°C by a jacket of dry ice/acetonitrile, the imine is introduced through a port, and the two cyclize upon reaction with solid-supported BQ 35 or BQd. After the sample passes through the scavenger resin 36, the columns are washed with THF, and a crude β -lactam is obtained upon concentration in high ee (91% ee in their prototypical example). After recrystallization, that same

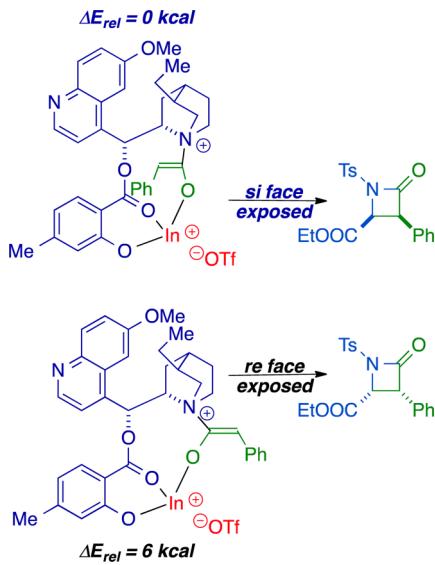
Scheme 18



prototypical example was reported in 65% yield, both optically and analytically pure. They also reported regenerating and reusing the columns up to 20 times without sacrificing yield (62%) or enantioselectivity (90% ee before recrystallization).

In an effort to increase product yields, this system (acid chloride, imine, proton sponge, cinchona alkaloid catalyst) was revisited with a bifunctional catalytic approach (Scheme 18).⁷⁷ Lectka and co-workers reasoned that the additional activation of the imine by an achiral Lewis acid could promote the desired reaction pathway over divergent reactions involving the zwitterionic ketene-enolate; however, this system would then demand cooperation of a Lewis acid with a Lewis base catalyst. Although potential cocatalysts such as $\text{Mg}(\text{OTf})_2$, $\text{CuClO}_4 \cdot (\text{MeCN})_4$, and YbCl_3 proved deleterious to product yields under standard reaction conditions (quenching some of the

Scheme 19



chiral amine catalyst), the group discovered that $\text{Al}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, $\text{Zn}(\text{OTf})_2$, and especially $\text{In}(\text{OTf})_3$ effectively increased yields by 1.5–2 times from the original system. For example, the addition of 10 mol % $\text{In}(\text{OTf})_3$ to the reaction involving phenylacetyl chloride and tosyl imino ester increased the yield from 65% to 95%, with 98% ee and a dr (cis:trans) of

60:1 (high enantioselectivity rationalized⁷⁸ in Scheme 19). Note that an isolated example was also reported with a bulkier Lewis acid, a putative bis(cyclophanyl diol) aluminum triflate complex, showing the possibility of optimizing the diastereo-

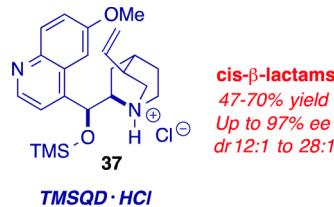
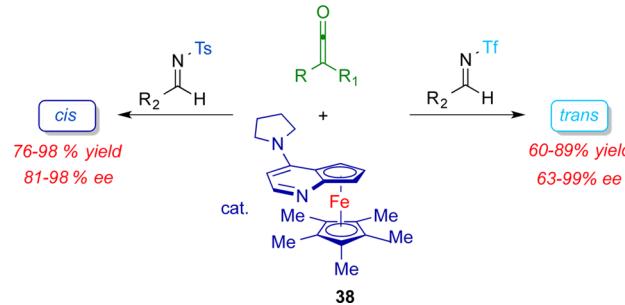


Figure 14. Calter's cinchona alkaloid catalyst.

meric ratio (99:1 cis:trans) while maintaining high yield and excellent enantioselectivity.⁷⁹ Thus, the evolution of the original system to a bifunctional asymmetric catalytic approach made for a practical and mechanistically interesting optimized system for the synthesis of *cis* β -lactams.

The Calter group reported a similar system in 2007 using a silylated variant of a cinchona alkaloid catalyst 37 (Figure 14) in 15 mol %, a Lewis acid in 15 mol %, and 2.2 equiv of Hünig's base to condense phenoxyketene (generated *in situ*) and aryl-substituted sulfonyl imines into *cis* β -lactams.⁸⁰ This reaction extends the substrate scope to α -phenoxy- β -aryl- β -lactams and

Scheme 20



typically provides modest product yields (47–70%), good diastereomeric ratios (from 12:1 to 28:1), and fairly high enantioselectivity (up to 97%).

Fu and co-workers expanded on Lectka's original strategy in 2002 by applying planar-chiral nucleophile catalyst 38 derived from 4-(pyrrolidino)pyridine (PPY) in 10 mol % (Scheme 20).⁸¹ Where the Lectka methodology focused on the condensation of monosubstituted ketenes with almost exclusively the tosyl imino ethyl ester, Fu's first communication focused on the condensation of more stable disubstituted ketenes with an expanded tosyl imine scope (derived from aliphatic, aromatic, and α,β -unsaturated aldehydes). In the instance of symmetrical ketenes, very good product yields and enantioselectivity were demonstrated (up to 93% yield and 94% ee). Where diastereoselectivity is relevant, in the instance of unsymmetrical disubstituted ketenes, good diastereomeric ratios were achieved up to 15:1 (cis:trans) in addition to high yields and enantioselectivity (here, up to 98% yield and 98% ee). Mechanistically, this system is believed to operate in a manner similar to the Lectka methodology, but requires preformation of the ketene.

Considering Fu's major contribution to this umpolung Staudinger concept was centered on considerably expanding

substrate scope with his PPY system, one logical advance from varying substituents on the imine carbon atom would be to vary substituents on the imine nitrogen atom. In fact, Fu and co-workers followed up on their work and published a very interesting result with *N*-triflyl-substituted imines that also exhibited an unforeseen reversal in diastereoselectivity, now favoring the trans adduct (Scheme 20).⁸² This variation allows a switch in selectivity using the Fu methodology by simply changing substituents on the nitrogen atom (i.e., tosyl favors cis, triflyl favors trans). The trans method is a little less well behaved; products are formed in typically moderate to good yields from 60% to 89%, moderate enantiomeric excess with a few exceptions (63–99% ee), and diastereomeric ratios ranging from 20:80 to 2:98 (cis:trans). Note that their mechanistic

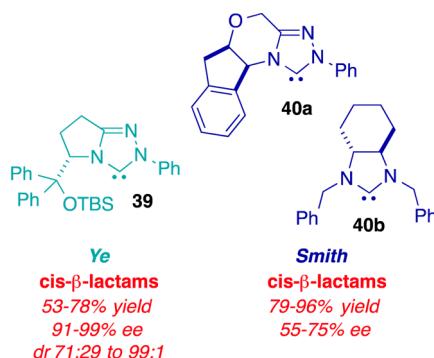


Figure 15. NHC catalysts.

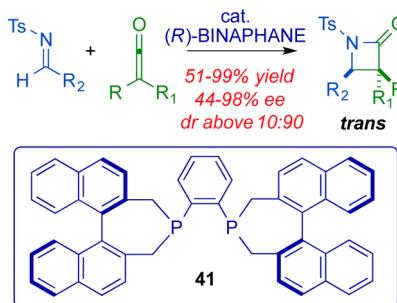
explanation for this trans stereochemistry is purely speculative, but they suggest their PPY catalyst reacts with the imine first, rather than initial formation of the ketene-enolate, based on the added electrophilicity of the imine induced by the triflyl group.

The Ye group revisited the same umpolung Staudinger concept in 2008 utilizing another type of chiral nucleophile: an *N*-heterocyclic carbene (Figure 15).⁸³ A triazolium salt with a diphenyl(trialkylsiloxy)methyl substituent in 10 mol % serves as the precursor for NHC **39**,⁸⁴ which reportedly catalyzes reactions between disubstituted ketenes and *N*-*tert*-butoxycarbonyl (Boc)-substituted imines to form *cis* β-lactams in moderate yields (53–78%), very good enantiomeric excess (91–99% ee), and diastereomeric ratios ranging from 71:29 to 99:1 (cis:trans). In addition to introducing another type of effective catalyst and another nitrogen substitution to the repertoire of the umpolung Staudinger catalytic, asymmetric methods, Ye and co-workers also reported an interesting result with an *N*-tosyl imine and phenylethylketene using a stable achiral NHC (*N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), that is, a reversal in diastereoselectivity favoring trans stereochemistry 24:76 (cis:trans). Similarly to the switch in diastereoselectivity noted by Fu, the Ye group considers a reaction of the NHC with the imine first instead of the ketene, but has no substantial mechanistic confirmation apart from one experiment that a preformed NHC–tosyl imine complex reacts with phenylethylketene to form the product in yield and dr similar to that of the catalytic counterpart. Interestingly, this topic has been investigated further in recent years, and both computational and mechanistic experiments seem to be more in favor of the “ketene first” mechanism.⁸⁵

Independently, the Smith group also reported an asymmetric synthesis with NHC catalysts in 2008 (Figure 15).⁸⁶ Their method examined the reaction of diphenylketene with a variety

of *N*-tosyl imines in the presence of two different chiral NHC catalysts **40** in 10 mol % (and KHMDs in 9 mol %). Although yields were typically very good, ranging from 79% to 96%, enantiomeric excess was only modest (55–75% ee), relying on recrystallization to achieve more desirable percentages of 92–99% ee. Diastereoselectivity was irrelevant, given their sole usage of a symmetrical disubstituted ketene, but this was an

Scheme 21

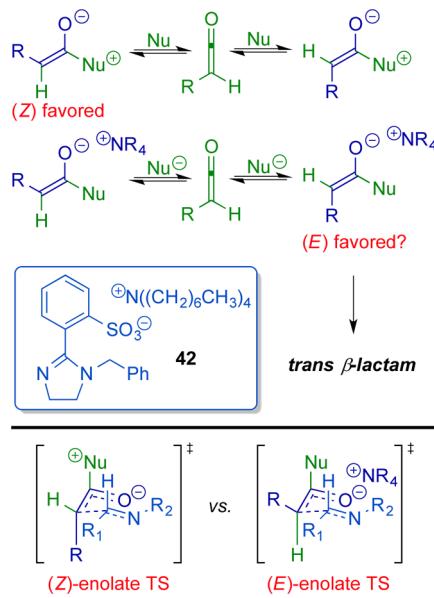


alternative approach for an enantioselective umpolung Staudinger reaction with an NHC catalyst.

Most recently, in 2012, the Kerrigan group published a methodology favoring *trans* β-lactam formation using disubstituted ketenes, *N*-tosyl arylimines, and 10–15 mol % of a phosphine nucleophilic catalyst, viz., BINAPHANE **41** (Scheme 21).⁸⁷ This method emphasizes the use of less expensive *N*-tosyl imines over the *N*-triflyl imines required for trans selectivity in the Fu method. Products are formed in a wide variety of yields and enantioselectivity (51–99% yield and 44–98% ee) and typically high diastereomeric ratios, with several examples greater than 10:90 (cis:trans). Kerrigan and co-workers also briefly examined the “imine first” mechanism proposed by Fu seeking explanation for their observed trans stereochemistry, but apart from ³¹P NMR evidence for interaction between the phosphine and an *N*-tosyl imine, their ³¹P NMR spectroscopic studies could not conclusively rule out the formation of a phosphine-enolate *in situ*.

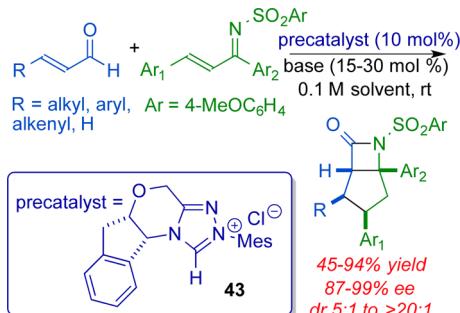
An important subject to ponder is the origin of diastereoselectivity in these reactions. Intuitively, the stereochemistry is installed upon attack of the imine by the zwitterionic ketene-enolate species (or, if Fu’s mechanistic supposition is correct for his *N*-triflyl system, the attack of the zwitterionic imine on the ketene). The thermodynamic preferences in geometry, in these instances, the (*Z*)-ketene-enolate and the (*E*)-imine, reliably install *cis* selectivity. It can be argued that a simple change in geometry of either species should alter the preference from *cis* to *trans* (Scheme 22). In fact, Lectka and co-workers tested this idea in 2005 by designing an anionic nucleophilic catalyst that would putatively place a bulky tetraalkylammonium counterion next to the enolate oxygen, altering the preference in geometry to an (*E*)-enolate.⁸⁸ Condensation of a variety of aryl-substituted acid chlorides (ketene precursors) with the notorious *N*-tosyl imino ester using 10 mol % of 2-aryl-2-imidazoline catalyst **42** containing an anionic sulfonate group and proton sponge afforded *trans* β-lactams in moderate yields (35–70%) and diastereoselectivity ranging from 1:5 to 1:50 (cis:trans). Although the *trans* adducts are formed preferentially, the Lectka group does not unequivocally attribute this to a flip in enolate geometry; another possible explanation is that the (*Z*)-enolate geometry is retained, but the negative charge on this

Scheme 22



species alters the approach of the imine (presenting the opposite diastereoface).⁸⁹ Regardless, this offers a good way to approach diastereoselective control in the umpolung Staudinger reaction and will be even more appealing if/when the system evolves to incorporate enantioselective control, as well.

Scheme 23



3.6. Annulation-Lactamization

A unique NHC-catalyzed asymmetric annulation reaction surfaced in 2008 by He and Bode that directly forms cyclopentyl-fused *cis* β -lactams from enals and *N*-sulfonyl ketimines (Scheme 23).⁹⁰ This reaction, coupling a variety of 3-alkyl- or 3-aryl-substituted enals with 1,3-aryl-substituted *N*-sulfonyl ketimines (chalcone-imine derivatives), establishes up to four new stereocenters concurrently on a bicyclic β -lactam framework in good yields (45–94%), good diastereoselectivity (5:1 to >20:1 *cis:trans*), and excellent enantioselectivity (87–99% ee, or greater). The authors used chiral triazolium-based precatalyst 43 in 10 mol % and an amine base, noting success with DBU in ethyl acetate (15 mol %) and DMAP in acetonitrile (30 mol %), the latter of which resulted in better diastereoselectivity at the expense of velocity. The DMAP modification is also notably amenable to both electron-rich and electron-deficient starting materials.

Although the authors do not report a full mechanistic study, they propose a catalytic cycle inferring intermediates that would explain the stereochemical outcome of the reaction (Figure 16).

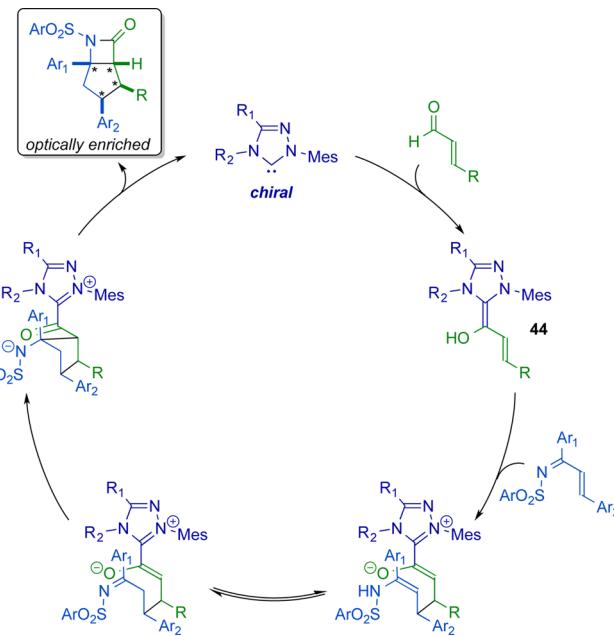


Figure 16. Concept for catalytic, asymmetric annulation-lactamization reaction.

They suggest that the NHC undergoes a nucleophilic addition to the enal to form an adduct 44 that is poised to react with the imine in an aza-benzoin/oxy-Cope fashion⁹¹ via a boat transition state (to rationalize the *cis* configuration on the cyclopentane ring).⁹² Subsequent tautomerization followed by a reversible intramolecular Mannich reaction would establish the cyclopentane ring (in 45), and then lactamization would liberate the catalyst, conceivably with one viable stereochemical outcome. They also recognize a potential competing mechanistic pathway favoring *trans* stereochemistry about the cyclopentane ring involving homoenolate anion formation, based on observations by Nair and co-workers.⁹³

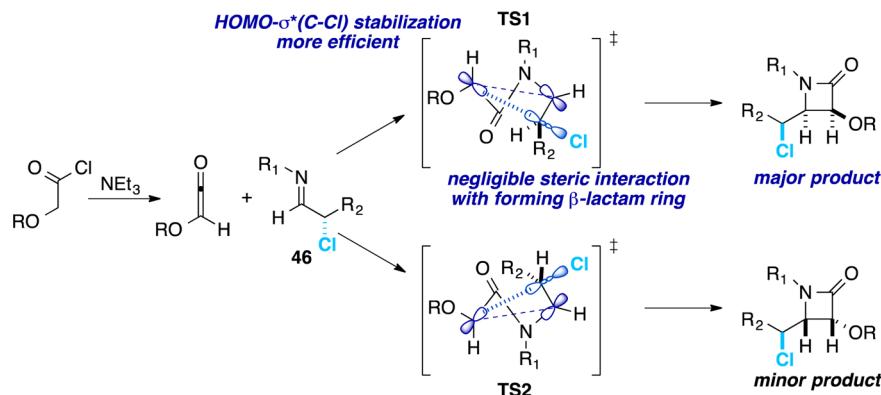
4. OTHER RECENT ADVANCES IN β -LACTAM SYNTHESIS (2008–2013)

Although the primary objective of this Review is to comprehensively discuss the development of chemical syntheses of β -lactams with respect to asymmetric catalysis, there have been other noteworthy methods published since the last *Chemical Reviews* article that do not explicitly fall under this category. Such methods illustrate tactics to expand the substrate scope of known reactions, approach stereoselectivity from innovative angles, access novel β -lactam compounds, and incorporate contemporary synthetic techniques, among other things. As we feel these advances should also be tabulated in this Review, this section receives the torch from Brandi and co-workers, who extensively covered the literature from 2000 to 2008,³ and discusses chemical syntheses of the β -lactam ring from 2008 to 2013 to the best of our knowledge. It is important to note that any recent advances that fall under the category of asymmetric catalysis are only discussed in the section above, and reactions that are either asymmetric, catalytic, or neither may appear under each subcategory in section 4, pertinent to recent developments.

4.1. Staudinger Reaction

De Kimpe and co-workers explored an alternative to stereoselective β -lactam synthesis based on steric interactions; that is,

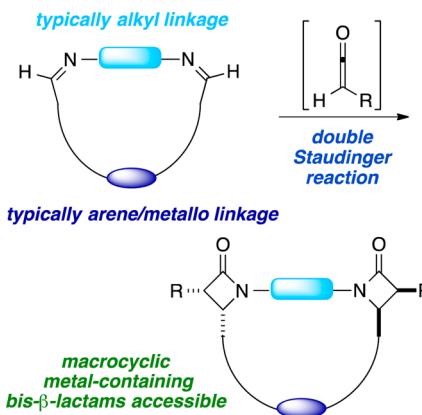
Scheme 24



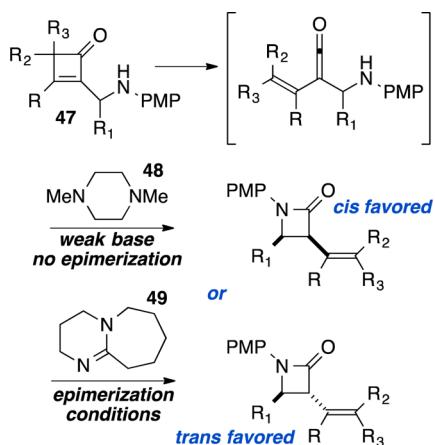
they reported the use of chiral α -chloro imines **46** as asymmetric inducers in a standard Staudinger mechanism, relying on stereoelectronic interactions (Scheme 24).⁹⁴ This concept was envisioned from (1) the reportedly favored HOMO- $\sigma^*(C-X)$ (X = electronegative atom) stabilization of transition state **TS1** over **TS2** during the final cyclization step by AM1 calculations⁹⁵ and (2) the significant increase in $\sigma^*(C-X)$ acceptor ability using halogens over oxygen and nitrogen.⁹⁶ As an initial investigation, racemic α -chloro imines were reacted with acid chlorides (ketene precursors) under basic conditions to give *cis* β -lactams in consistently good yields (70–80%) and excellent diastereoselectivity (96% to >99% de). This prompted examination of optically enriched α -chloro imines and their effect on enantioselectivity. Because of volatility/isolability issues, the chiral α -chloro imines were synthesized from chiral 2-chloro-1-propanol and reacted with the ketene in three consecutive reactions done in one pot. Despite overall low isolated yields (6–43%), high diastereomeric excess was retained (80–89% de) and good enantiomeric excess was achieved (~90% ee), as determined using the Mosher ester technique.⁹⁷ The resistance of the α -chloro

of substituted aminocyclobutenones can be accessed retrosynthetically by chemoselective reduction of iminocyclobutenones, which are formed by a conjugate addition of ketene silyl acetals to alkynyl imines (both reactions giving good product yields, 67–95%). Heating aminocyclobutenones in octane at 110 °C for 24–48 h to access a putative ketene intermediate gave primarily *cis* β -lactams in good yields (51–89%) and good diastereoselectivity (up to 80:20 *cis*:*trans*). The authors sequentially screened amine “proton transfer” additives in attempt to improve *cis* selectivity, and found that 1,4-dimethylpiperazine **48** in 2.0 equiv gave *cis* β -lactams in higher yields (77–99%) and diastereoselectivity (82:18 to 98:2 *cis*:*trans*). On the other hand, a stronger base, viz., DBU **49** (1.0 equiv), provided the corresponding *trans* β -lactams (59–80% yield; 3:97 to 2:98 *cis*:*trans*) under the same reaction

Scheme 26



Scheme 25



imines to epimerization under reaction conditions is also noteworthy.

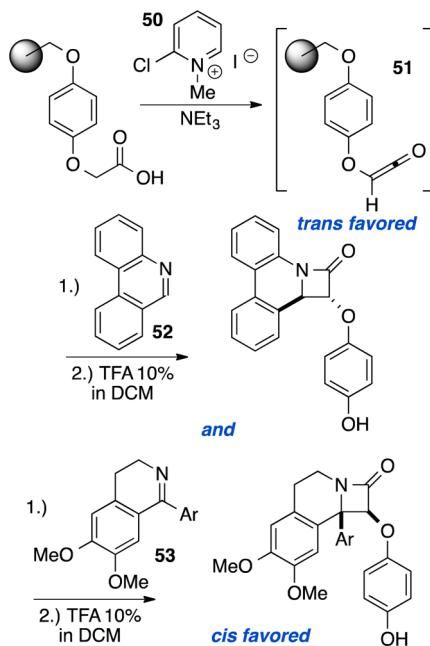
In 2009, Shimizu and co-workers reported a thermal rearrangement reaction of aminocyclobutenones **47** to form disubstituted β -lactams with diastereoselective control dictated simply by choice of amine base (Scheme 25).⁹⁸ A good variety

conditions, likely due to isomerization of the kinetically formed *cis* analogues.

In a series of papers, Sierra and co-workers have applied a double [2 + 2] cycloaddition reaction to two imine sites on a molecule in one pot toward the syntheses of macrocyclic bis- or tetra- β -lactams (Scheme 26).⁹⁹ Either before or after the double Staudinger reaction, a metal complex is introduced into the macrocycle, providing β -lactams that contain ferrocene and square planar platinum and palladium complexes. The lactamization step in these papers is accomplished under standard Staudinger conditions, that is, with *in situ* ketene formation from an acid chloride and triethylamine. Although this type of cycloaddition reaction is well established, it is interesting to note how these reaction conditions hold up to

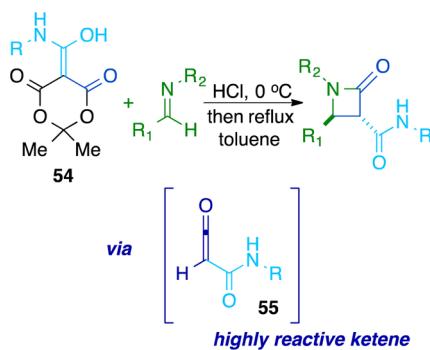
the syntheses of novel macrocyclic bio-organometallic compounds, with anywhere from 26% to 98% yield of the double lactamization step.

Scheme 27



Aiming to acquire polycyclic carbacepham derivatives through solid-phase synthesis, Mata and co-workers used the Mukaiyama reagent **50** to access the ketene **51** of Wang resin-bound 4-hydroxyphenoxyacetic acid and explored its Staudinger cycloaddition reaction with a variety of cyclic imines (Scheme 27).¹⁰⁰ The initial screening with phenantridine **52** gave a tetracyclic *trans* β -lactam in 57% overall yield, after being liberated from the resin by stirring with 10% trifluoroacetic acid in DCM for 1 h at room temperature. Subsequently, 3,4-dihydroisoquinoline derivatives **53** were explored. The reaction with 3,4-dihydroisoquinoline evidently displayed a β -lactam product by gel-phase ^{13}C NMR, but it was not easily removed from the resin. On the other hand, 6,7-dimethoxy-1-aryl-3,4-dihydroisoquinoline derivatives (available via Bishler–Napieralski reaction¹⁰¹) provided β -lactams in 44–77% overall yields. By ^1H NMR NOE analysis, these products were obtained with *cis* stereochemistry. The same group has reported recently the synthesis of other resin-bound β -lactams, for example, those

Scheme 28

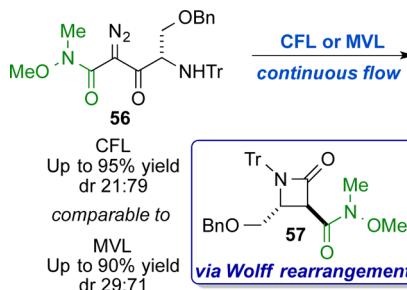


attached to the support by multidetectable linkers, using the Mukaiyama reagent.¹⁰²

Makowiec and co-workers produced a method in 2010 to make β -lactams with retro-amide side chains by coupling imines with Meldrum's acid derivatives **54**, prepared by stirring Meldrum's acid and isocyanates in the presence of triethylamine (Scheme 28).¹⁰³ These Meldrum's acid derivatives thermally decompose to carbamoylketenes **55**, which were believed to undergo a classic Staudinger cycloaddition in the presence of aldimines. Low and behold, for a variety of *N*-aryl-substituted Meldrum's acid derivatives and alkyl- and aryl-substituted imines, β -lactams were formed in moderate yields (41–72%). The β -lactam formation was unsuccessful when attempted with two *N*-alkyl-substituted Meldrum's acid derivatives. On the basis of ^1H NMR analysis of coupling constants (H3 and H4 from 1.9 to 2.4 Hz in all cases), the authors conclude that solely the *trans* isomers are being formed.

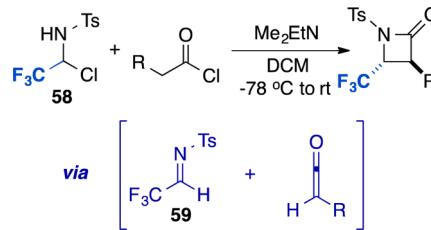
Another established method of accessing ketenes is by the Wolff rearrangement;¹⁰⁴ Konopelski and co-workers expanded on this technique in developing an intramolecular Wolff rearrangement/ β -lactamization method using a continuous

Scheme 29



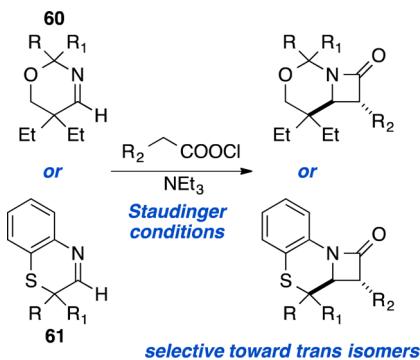
flow photochemical reactor, which was constructed from common laboratory materials.¹⁰⁵ The authors found that a 100 W compact fluorescent light (CFL) could be used in place of a medium-pressure mercury vapor lamp (MVL) for photolyzing α -diazo-*N*-methoxy-*N*-methyl β -ketoamides **56** derived from amino acids to produce β -lactams **57** with a C3-Weinreb amide substitution in 81–95% yield (Scheme 29), offering a safer and cheaper alternative. This Weinreb amide substitution is highlighted as a good substituent for divergent functionalization of the accessible β -lactams, and the *N*-trityl protecting group utilized in their syntheses is notably robust enough to help the β -lactam core remain stalwart in the presence of organolithium reagents or other strong bases. Although varying mixtures of *cis* and *trans* β -lactams were obtained by this method, note that simple thermolysis in the absence of base provided efficient epimerization of C3 to favor the *trans* moiety.

Scheme 30



Petrik and co-workers showed access to *trans*-3-trifluoromethyl-substituted β -lactams from α -chloroamines **58** and acid chlorides (Scheme 30).¹⁰⁶ Circumventing the high moisture sensitivity of a preformed electron-deficient trifluoromethyl-substituted imine **59**, the imine is generated *in situ*, as is the ketene, in the presence of 3.0 equiv of dimethylethylamine. Conveniently, these α -chloroamine “imine precursors” can be prepared in two steps from readily available fluoral hemiacetals. Trifluoromethylated- β -lactams are reported from various aliphatic acid chlorides in 63–80% yield and with excellent diastereoselectivity (6:94 to 1:99 *cis:trans*). The authors are unclear as to what the origin of the *trans* selectivity is, but claim that it is likely derived from reagent’s approach (suggested by results of a dynamic ^{19}F NMR spectroscopic

Scheme 31



analysis). Complete epimerization to the *trans* isomer can be obtained by letting a 20:80 *cis:trans* mixture stir in the presence of triethylamine at room temperature for 15 h.

Martens and co-workers recently applied the classical Staudinger cycloaddition reaction to β -lactam formation from two specific heterocyclic imines: 5,6-dihydro-2*H*-[1,3]oxazines **60** and 2*H*-1,4-benzothiazines **61** (Scheme 31).¹⁰⁷ Alkyl and aryl-substituted imines (at R and/or R₁ in Scheme 31) were coupled with a few ether and phthalimido-substituted acid chlorides (ketene precursors) in the presence of triethylamine to yield selectively *trans* β -lactams in isolated yields ranging from 18% to 82%. With two exceptions, diastereomeric ratios are all 5:95 *cis:trans* or better. The authors show the availability of several unique polycyclic β -lactams through these heterocyclic imines.

Jarrahpour and Zarei (independently and as co-authors) and co-workers have also reported a large number of methods in the last 5 years (and prior) analogous to the Staudinger cycloaddition, focused on *in situ* generation of the ketene by converting carboxylic acids into activated esters under basic conditions. They have synthesized a large quantity of β -lactams by presumed ketene formation through activated ester intermediates **62–67** accessed by reagents such as DMF-dimethyl sulfate **62a**,¹⁰⁸ the Vilsmeier reagent **62b**,¹⁰⁹ methoxy-methylene-N,N-dimethyliminium salt **62c**,¹¹⁰ cyanuric chloride-DMF **62d**,¹¹¹ diethyl chlorophosphate **63**,¹¹² DMF-benzoyl chloride **62d**,¹¹³ 2-fluoro-1-methylpyridinium *p*-toluenesulfonate **64**,¹¹⁴ thiocarbonyldiimidazole **65**,¹¹⁵ cyanuric fluoride **66**,¹¹⁶ and phosphonitrilic chloride **67** (Figure 17).¹¹⁷ These systems operate in a manner similar to one of the original reports using this tactic by Mukaiyama and co-workers,¹¹⁸ but show much versatility in achieving the “activated ester” intermediary. Additionally, the authors reported applications

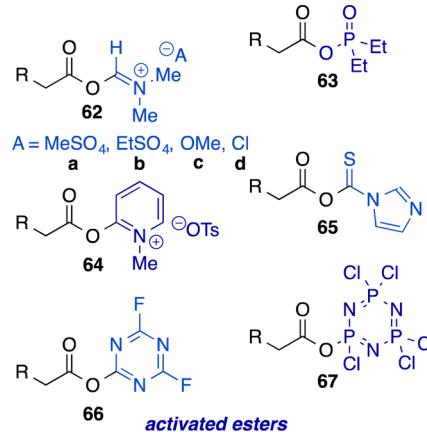
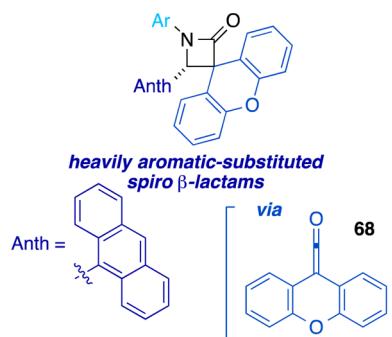


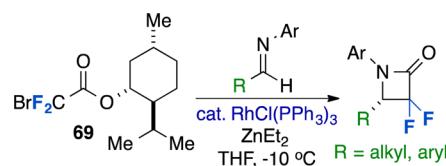
Figure 17. Examples of activated ester ketene precursors.

of the Staudinger reaction to make solid-supported β -lactams on Merrifield resin¹¹⁹ and carbon nanotubes¹²⁰ using their methods and traditional methods of accessing the ketene via an activated ester.

Figure 18. Spiro- β -lactams accessible.

Jarrahpour and co-workers have also explored the potential of the Staudinger reaction for accessing polycyclic mono- and bis-spiro- β -lactams (another example of a double Staudinger reaction from a diimine) from anthranyl-substituted imines and ketene **68** derived from 9*H*-xanthene-9-carboxylic acid (Figure

Scheme 32



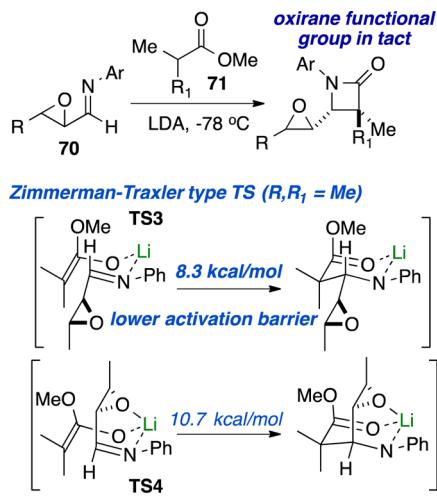
18).¹²¹ The heavily aromatic-substituted compounds reported can be obtained in typically moderate to good yields (25–96%) for such congested scaffolds.

4.2. Enolate-Imine Condensation

Recognizing the attractiveness of fluorinated pharmaceuticals, Ando and co-workers developed an asymmetric synthesis of difluoro- β -lactams by way of a Reformatsky-type reaction (Scheme 32).¹²² Chiral bromodifluoroacetates **69** and both alkyl- and aryl-substituted imines were coupled using catalytic tris(triphenylphosphine)rhodium(I) chloride and diethylzinc in

THF at -10°C in modest yields (41–71%) and good enantioselectivity (80–94% ee). The enantioselectivity of the reaction is channeled by an inexpensive (−)- or (+)-menthol chiral auxiliary constituent of bromodifluoroacetate (easily synthesized from bromodifluoro ethyl acetate) that is spontaneously expelled (and accordingly can be recovered) upon the final lactamization step. It is noted that electron-withdrawing groups on the C-substituted aryl rings on the imine are deleterious to selectivity.¹²² Additionally, although the cyclohexyl C-substituted imine gave 80% ee, the isopropyl variant gave a purely racemic mixture in lower yield. Further in-depth study of this phenomenon was stunted by reported difficulty in synthesizing imines of various linear and tertiary

Scheme 33



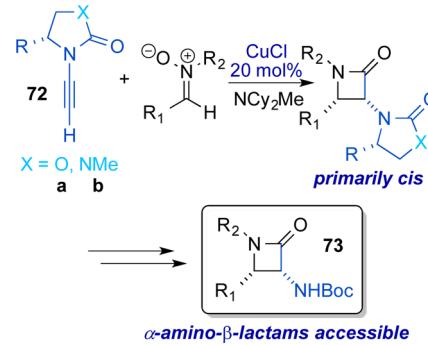
side chains. The authors attribute the high reactivity and chemoselectivity of lactamization over addition to the imine to the rhodium catalyst, which is likely assisting the initial formation of the zinc enolate.¹²³

Würthwein and co-workers synthesized an array of oxiranyl-substituted β -lactams chemoselectively from a reaction between oxiranecarbaldimines **70** (synthesized in two steps from α,β -unsaturated aldehydes)¹²⁴ and lithium enolates derived from methyl esters **71** (Scheme 33).¹²⁵ For a number of alkyl- and aryl-substituted oxiranecarbaldimines and alkyl-substituted lithium ester enolates, *trans* β -lactams were greatly favored in reported diastereoselectivities of >95% to 99% de and yields ranging from 12% to 92%. Quantum mechanical calculations revealed that a Zimmerman–Traxler type transition state¹²⁶ involving equatorial positioning (TS3) of the epoxide ring is actually 2.4 kcal/mol more favorable than an axial epoxide (TS4) poised for coordination of its oxygen atom to lithium, which affords selectivity consistent with experimental results. The authors also stress that enantio-enriched β -lactams can be accessed by this methodology, as the stereochemistry of enantio-enriched oxiranecarbaldimines is preserved. Additionally, they show some examples of complex dioxiranyl-substituted di- β -lactams being synthesized from naphthalene diimines (7–57% yield).

4.3. Kinugasa Reaction

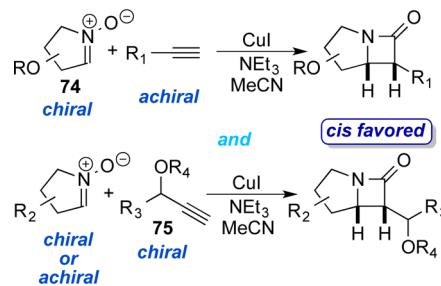
In 2008, Hsung and co-workers applied the Kinugasa strategy to the coupling of nitrones with chiral ynamides **72** en route to optically enriched α -amino- β -lactams **73** (Scheme 34).¹²⁷ Alkyl, alkenyl, and aryl C- and N-substituted nitrones were coupled

Scheme 34



with chiral oxazolidinone **72a** or diazolidinone **72b** based ynamides using cuprous chloride (20 mol %) and dicyclohexylmethylamine (4.0 equiv) in acetonitrile. Primarily *cis* β -lactams were obtained in typically moderate yields (26–80%) and great diastereoselectivity (82:18 to 95:5 *cis*:*trans*, or greater). The authors mention that cuprous iodide can be used in place of cuprous chloride as a catalyst for some examples.

Scheme 35



Synthetic routes for obtaining the corresponding α -amino- β -lactams beyond the initial lactamization are also exhibited. Last, their conclusions about the stereoselectivity model for the reaction (as drawn from computational evidence) are consistent with the notion that both the cycloaddition and the protonation steps occur in a stereoselective fashion.

Chmielewski and co-workers used the Kinugasa tactic with acetylenes and 5-membered cyclic nitrones to directly form β -lactams of the extended carbapenam skeleton (Scheme 35).¹²⁸ The initial report revealed an influence of chiral cyclic nitrones **74** (derived from S-malic acid¹²⁹ and L-tartaric acid¹³⁰) on the diastereoselectivity of the reaction, which greatly favors *cis* stereochemistry under optimized conditions (i.e., using equimolar cuprous iodide and triethylamine in acetonitrile, running the nitrone in 2-fold excess of the acetylene). Given the high diastereoselectivity (74:26 *cis*:*trans* to quantitatively *cis*) and fair to moderate yields (10–80%), the authors

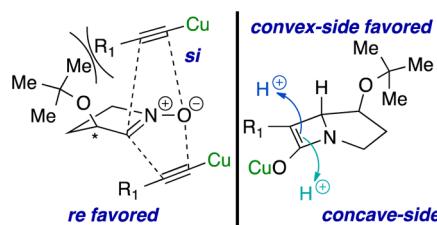
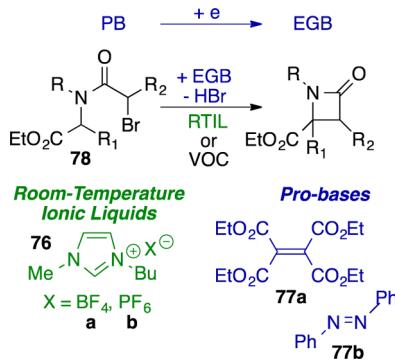


Figure 19. Model for origin of selectivity.

subjected this method to further investigation, with added emphasis on the origin of the stereoselectivity. Extending the substrate scope to include chiral acetylenes **75** allowed them to study the effects of double asymmetric induction using “matched” and “mismatched” pairs of nonracemic starting materials. Results led them to propose that (1) the copper acetylidyne approaches exclusively anti to the chiral nitrone in the 1,3-dipolar cycloaddition step (Figure 19), (2) the chiral acetylene will only dictate the stereochemistry in the first step if an achiral nitrone is used, and (3) the customary cis stereochemistry can be explained by a convex-side (anti-Felkin–Anh¹³¹) protonation during the enolate step (Figure 19). In the instance of matched pairs by their stereochemical analysis, there is an evident increase in each yield (up to 94%),

Scheme 36

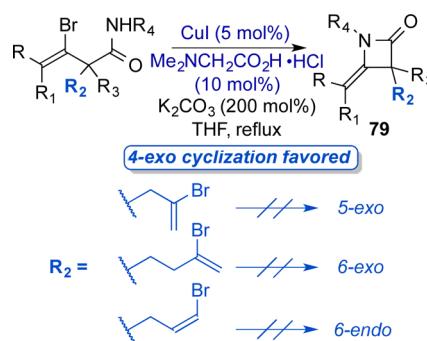


diastereoselectivity (most examples >95:5 cis:trans), and reaction rate, feasibly for the desired pathway over other side reactions.

4.4. Intramolecular Cyclization Reaction

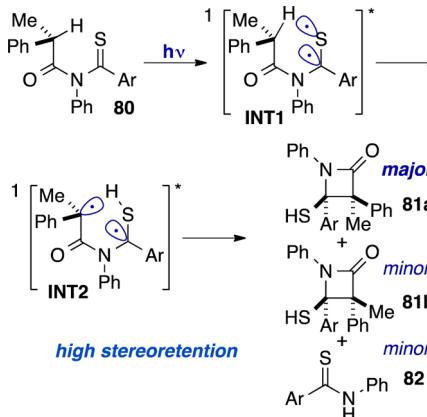
Taking an electrochemical approach, Sotgiu and co-workers devised a system that utilizes an electrogenerated base (EGB) to deprotonate an acidic C4 (β -lactam numbering) C–H bond and cyclize upon nucleophilic displacement of a C3 C–Br bond (Scheme 36).¹³² The real appeal of this methodology comes from the ability to conduct the reaction in room-temperature ionic liquids (RTILs) **76**, which are emphasized as being much “greener” than volatile organic solvents. For a number of bromoamides, using two different pro-bases (PB) **77a** and **77b**,¹³³ β -lactams are produced via a constant potential electrolysis experiment in generally rather good yields (32–99%) in imidazolium-based RTILs that proved competitive with or better than the corresponding reaction in MeCN, EtCN, DMF, or DMSO with an added electrolyte. Regarding stereoselectivity, the cis isomer dominates in every case (73:27 cis:trans to quantitatively cis). The authors extended their study to ascertain the role of the imidazolium RTILs, considering the corresponding NHCs are easily accessible making the solvent potentially non innocent.¹³⁴ One control experiment adding benzaldehyde to the RTIL provided the NHC–benzaldehyde adduct in 22% yield, showing that the carbene is being produced. Another set of experiments looked at the reaction in the absence of a pro-base, and showed that the electrogenerated NHCs are strong enough to deprotonate a malonyl ester proton ($R_1 = CO_2Et$ in **78**) to accomplish the reaction in good yields (77% and 91%), but the pro-bases are required to deprotonate the less acidic protons in CH_2CO_2Et derivatives ($R_1 = H$ in **78**), and thus are not obsolete.

Scheme 37



Li and Zhao developed an intramolecular copper(I)-catalyzed C–N coupling reaction that allows facile access to various 4-alkylidene- β -lactams **79** (Scheme 37).¹³⁵ Using cuprous iodide (5 mol %), *N,N*-dimethylglycine hydrochloride (10 mol %), and potassium carbonate (200 mol %), intramolecular coupling of secondary amides and vinyl bromides was achieved, giving β -lactams in excellent yields (92–99%, with one lower exception) with retention of configuration of the C=C bond when appropriate. Furthermore, the authors studied the preference for 4-exo ring closure over other modes of cyclization, viz., 5-exo, 6-exo, and 6-endo, and found that the β -lactams are formed nearly quantitatively in

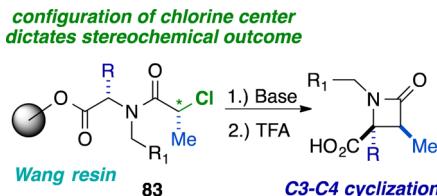
Scheme 38



their cleverly devised intramolecular “competition” experiments. They report no definitive mechanistic explanation as to why this 4-exo cyclization is so favorable though. Last, they report that this method can be extended to the synthesis of larger sized (eight- and nine-membered) lactams in a tandem C–N bond-forming reaction.

Sakamoto and co-workers developed an enantioselective β -lactam synthesis exhibiting a chiral-memory effect that is initiated by photochemical excitation of a thioimide (Scheme 38).¹³⁶ They suggest that irradiation of these carefully crafted thioimides **80** (obtained from (*S*)-arylpropanoyl chlorides and thioaroylanilides) accesses a singlet excited state of the thiocarbonyl (INT1) that is poised to effect a γ -hydrogen atom abstraction, and that the resultant 1,4-biradical intermediate (INT2) then undergoes a rapid intramolecular cyclization to form the β -lactam ring. Stereochemistry was predicted to be preserved at the site of γ -hydrogen abstraction, considering the expected rates of biradical cyclization versus the rates of bond rotation (racemization), and this was observed

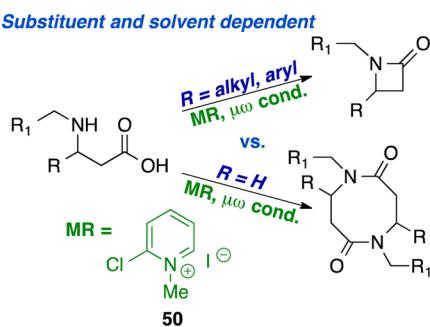
Scheme 39



experimentally. Two 4-mercaptop- β -lactams **81** were obtained from each reaction, in addition to a benzothioanilide **82** byproduct, in fairly high enantioselectivities (85–96% ee), with the favored isomers in 50–59% yield.

González-Muñiz and co-workers reported a stereoselective C3–C4 cyclization reaction of 2-(S)-chloropropionyl amino acid derivatives **83** anchored on solid support (Wang resin) using enolate chemistry (Scheme 39).¹³⁷ Computational modeling supports the idea that the configuration of the chlorine-containing chiral center dictates the stereochemical outcome of the reaction, independent of the amino acid configuration, which is a more facile way to impart stereoselectivity without the need for a chiral auxiliary.¹³⁸ For a large

Scheme 40

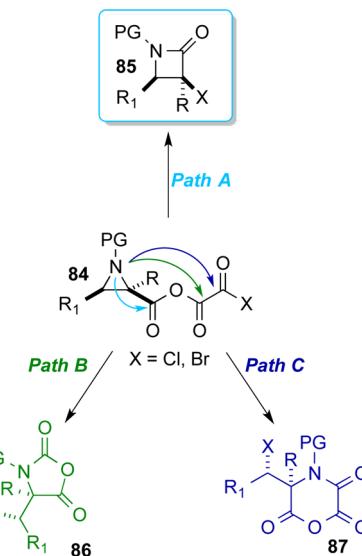


number of examples with varying N-substitution and amino acid side chains, *cis* β -lactams were obtained in isolated yields of 11–61%. The enantioselectivity and ease of derivatization with this method make it an appealing strategy to obtain libraries of tetra-substituted β -lactams from amino acids using solid-phase synthesis.

Escalante and co-workers studied the behavior of β -amino acids activated by either phenyl-phosphonic dichloride or the Mukaiyama reagent **50** under microwave conditions (Scheme 40).¹³⁹ Depending on the substrate and conditions used, β -lactam formation was potentially in competition with cyclo- β -dipeptide formation. For instance, 3-substituted (alkyl and aryl) β -amino acids produced β -lactam products selectively using phenyl-phosphonic dichloride (50–90% yield, with one low exception), whereas the non-3-substituted β -amino acids favored cyclo- β -dipeptide products, albeit in low yield (only up to 37%). Solvent also had an effect on chemoselectivity; that is, using the Mukaiyama reagent, the reaction in benzene affords a noticeable degree of cyclo- β -dipeptides, while the reaction in acetonitrile affords solely β -lactams under their specified conditions.

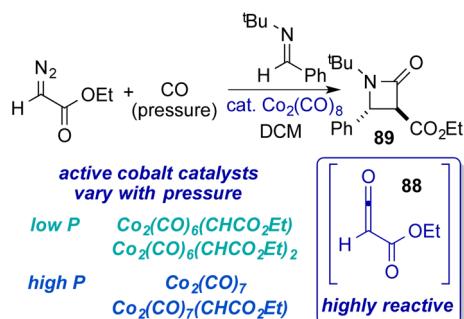
Wulff and co-workers pursued a ring-expansion reaction of optically enriched 2-aziridine carboxylic acids **84** to form either β -lactams **85**, morpholin-2,3,5-triones **86**, or cyclic *N*-carboxyanhydrides **87**, depending on the substrate and reaction conditions (Scheme 41).¹⁴⁰ Substitution on the aziridine ring

Scheme 41



heavily dictated the selection of the major expansion product: 2,3-disubstituted aziridine carboxylic acids favored morpholin-2,3,5-trione formation when subjected to oxalyl chloride, while 2,2,3-trisubstituted aziridine carboxylic acids favored either β -lactam or *N*-carboxyanhydride formation depending on the substituent in the 3-position (i.e., alkyl produced a β -lactam, aryl produced an *N*-carboxyanhydride). These 3-alkyl-substituted aziridines, with oxalyl chloride or bromide, were converted to 3-halo-substituted β -lactams in typically good yields, ranging from 38% to quantitative. The reaction is stereospecific, *cis* and *trans* aziridines translate to their corresponding *cis* and *trans* β -lactams, and most *cis* examples using oxalyl chloride do not build up any appreciable amount of the epimerized *trans* β -lactam product. On the other hand, when oxalyl bromide is used, epimerization is significant (different conditions giving 9:1 to 1:2 *cis:trans*, in the most extreme case). The authors also note that in the case of 3-aryl-substituted aziridines: (1) the product preference switches from morpholin-2,3,5-triones to β -lactams using oxalyl chloride with an increasing amount of DMF and (2) β -lactams are accessible

Scheme 42

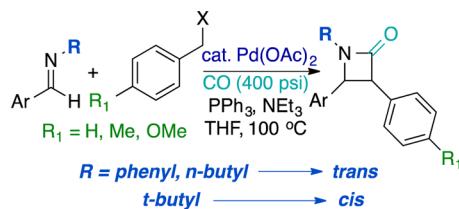


using the Vilsmeier reagent (22–85% yield). Both of these conditions are passing through the presumed intermediacy of an acid chloride in the 2-position of the aziridine ring. Last, the authors highlight that the 3-halo-substituted β -lactams can be easily functionalized to a number of other optically enriched compounds.

4.5. Carbonylation Reaction

The synthesis of β -lactams derived from the highly reactive ethoxycarbonyl ketene **88** was reported by Ungváry and co-workers using a cobalt catalyst (Scheme 42).¹⁴¹ From ethyl diazoacetate and *N*-*tert*-butylbenzaldimine, *N*-*tert*-butyl-*trans*- α -ethoxycarbonyl- β -phenyl- β -lactam **89** was prepared in 95% yield using a catalytic amount of octacarbonyldicobalt in a carbon monoxide atmosphere under pressure (75 bar) at room temperature. The authors also report successful scavenging of the ethoxycarbonyl ketene with *N*-methyl and *N*-benzyl-substituted imines to form *trans* β -lactams, but unexcitingly with respective isolated yields of 11% and 13%. Among other mechanistic findings, the authors determined that the reaction proceeds through different catalytic cycles at low versus high pressure; that is, at high pressure the likely active catalytic species are $\text{Co}_2(\text{CO})_7$ and $\text{Co}_2(\text{CO})_7(\text{CHCO}_2\text{Et})$ and at low pressure $\text{Co}_2(\text{CO})_6(\text{CHCO}_2\text{Et})$ and $\text{Co}_2(\text{CO})_6(\text{CHCO}_2\text{Et})_2$. They also report theoretical studies that suggest (1) the lactamization is proceeding through the generally accepted two-step mechanism for the Staudinger cycloaddition, (2) in accordance with experiment, *trans* stereochemistry predominates as the thermodynamic and kinetic preference computationally, and (3) the intermediate can be said to have more

Scheme 43

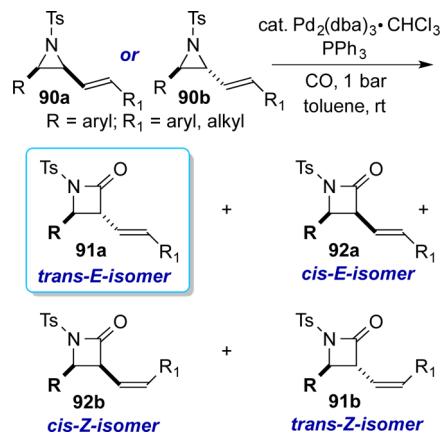


"covalent" character than zwitterionic by natural population analysis.

Troisi and co-workers published a palladium-catalyzed cyclocarbonylation of benzyl halides and imines¹⁴² to synthesize 3,4-diaryl β -lactams that is an extension of work by Torii and co-workers in 1993 (using allyl phosphates).¹⁴³ Benzyl bromides and chlorides were reacted with alkyl- and aryl-substituted imines with catalytic palladium(II) acetate, triphenylphosphine, and triethylamine in a CO atmosphere (400 psi) at 100 °C for 60–90 h to generally give either *cis* or *trans* β -lactams in good diastereoselectivity, contingent upon the nature of the substituents (Scheme 43). For instance, a phenyl or *n*-butyl substituent on the imine nitrogen atom guides selectivity toward *trans* products (12:88 to 1:99 *cis*:*trans*, or greater), while a *tert*-butyl group ushers the reaction toward products with *cis* stereochemistry (16:84 *cis*:*trans* to quantitatively *cis*). Product yields were usually good, ranging from 58% to 97%. Subjecting an enantiomerically pure imine ((*R*)-benzylidene-*N*-phenylethylamine) and benzylbromide to these reaction conditions yielded solely the *trans* diastereomers in a ratio of 5:3 (3*R*,4*S*,1*R*):(3*S*,4*R*,1*R*), as well as a small amount of an acyclic amide byproduct.

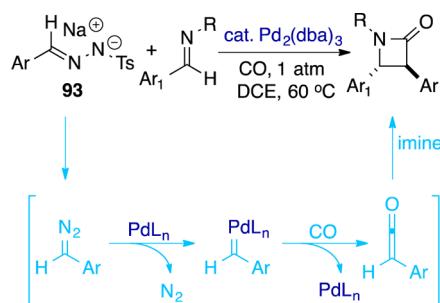
Inspired by initial reports of Ohfune and co-workers¹⁴⁴ and Tanner and Somfai¹⁴⁵ in the early 1990s, Aggarwal and co-workers studied the palladium-catalyzed carbonylation of vinyl aziridines **90** to better understand the reaction and control it to access a larger scope of β -lactams.¹⁴⁶ In an effort to extend the

Scheme 44



reaction scope from previously reported unsubstituted vinyl aziridines to include aryl-substituted vinyl aziridines in the β -lactamization reaction (avoiding the dichotomous pathway to δ -lactam products), the authors found that tris-(dibenzylideneacetone)dipalladium(0), or $\text{Pd}_2(\text{dba})_3$, in 5 mol % and triphenylphosphine (0.6 equiv) under CO atmosphere (1 bar) in toluene offer suitable conditions for the formation of *trans* 4-aryl-3-vinyl- β -lactams (Scheme 44). Remarkably, whether the starting aziridines were diastereomerically enriched (*cis* or *trans*) or mixed, the *trans*-*E*-isomers **91a** of the vinyl-substituted β -lactams were formed preferentially over *trans*-*Z*-isomer **91b** and *cis* isomers **92** in high diastereoselectivity (90:10 to 100:0 *trans*-*E*-isomer:other products, with two lower exceptions) and in moderate yields (59–79%). For one

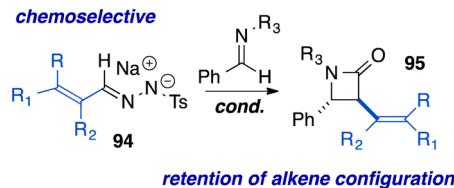
Scheme 45



enantio-enriched *trans* vinyl aziridine example, enantiomeric excess was carried over to the β -lactam product. In another special case, when increasing the pressure to 50 bar, diastereoselectivity switched in favor of the *trans*-*Z*-isomer **91b**. Other observations included switches in diastereoselectivity based on solvent, temperature, catalyst loading, and alkene substituents (noting potential switches in chemoselectivity, as well).

Wang and co-workers proposed a β -lactamization reaction resulting from in situ ketene formation via a palladium-catalyzed carbonylation of a carbene in the presence of an imine in 2011 (Scheme 45).¹⁴⁷ The ketene is generated from *N*-tosylhydrazone salts **93** in the presence of $\text{Pd}_2(\text{dba})_3$ (2.5 mol %) and carbon monoxide (atmospheric pressure) at 60 °C, and subsequently reacts with the imine to form primarily *trans* β -lactams (two instances favored *cis* stereochemistry). For diaryl-substituted β -lactams, diastereoselectivity is typically high (eight examples with dr of 5:95 *cis*:*trans*, or greater), and yields range

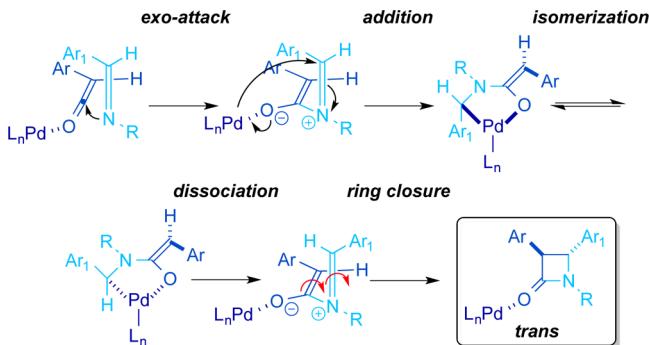
Scheme 46



from modest to excellent (22–98% yield, erring on higher end). The authors also explored the reaction of α,β -unsaturated N-tosylhydrazone salts 94 with imines and found efficient C3-alkenyl-substituted β -lactam 95 formation (Scheme 46) in high diastereoselectivity (16:84 to 5:95 cis:trans, or greater) and good isolated yields (73–93%). Note that the authors also report access to a variety of other amide and ester species from the ketene intermediate generated from either diazo compounds or N-tosylhydrazone salts, often in good yields, as well.

Computational studies were also conducted in attempt to explain primarily the involvement of palladium beyond ketene formation and the preference for trans stereochemistry. Wang and co-workers first studied the formation of the palladium–ketene complex and advocate that (1) a palladium–CO complex is the effective catalyst, (2) palladium prefers initially coordination to the terminal nitrogen of the diazo compound (formed in situ from the N-tosylhydrazone salt), (3) dinitrogen is expelled leaving the Pd–C bond, after which CO migratory insertion occurs, and that subsequently (4) there is a putative equilibrium between η^2 -(C,C) and η^2 -(C,O) palladium–ketene complexes or the palladium could be coordinated to the ketene

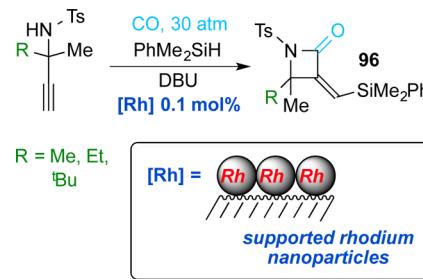
Scheme 47



oxygen atom; free energy calculations determined that an η^1 -(O) palladium–ketene complex is actually the most stable (so this was used for the metal–ketene–imine complex in studying the lactamization).¹⁴⁷ Regarding the mechanism of β -lactam formation, the authors determined that the *exo*-attack (of the imine) transition state is more favorable by 4.5 kcal/mol and that, most importantly, palladium can assist the isomerization of the C=N bond in this newly formed zwitterionic intermediate prior to the conrotatory ring closure, explaining the preference for trans stereochemistry (Scheme 47). Otherwise, the metal has only a minimal effect on both the initial nucleophilic attack of the imine and the ring closure step.

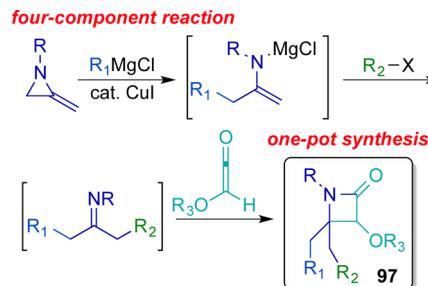
The Aronica laboratory published an atypical methodology to synthesize α -methylene- β -lactams 96 in 2012 with nanoparticles, prepared via the metal vapor synthesis (MVS) technique, of rhodium solvated metal atom (SMA) derived species (Scheme 48).¹⁴⁸ Inspired by the work of Matsuda and

Scheme 48



co-workers invoking a homogeneous rhodium catalyst,¹⁴⁹ the authors sought to effect a silylcyclization of propargyl amines (and alcohols to make β -lactones) with a heterogeneous catalyst that would allow a more facile workup and catalyst recovery. Out of the studied Rh/C (MVS), Rh/Fe₂O₃ (MVS), and Rh/ γ -Al₂O₃ (MVS) supported species, 0.1 mol % Rh/C (MVS) performed most suitably with very chemoselective conversions to β -lactams of 75–98% after 4 h with 10 mol % DBU in DCM at 100 °C under CO at 30 atm. However, leaching experiments suggest that the active catalytic species is not the heterogeneous matrix, but is, in fact, the rhodium nanoparticles that have leached into solution. Thus, their MVS catalysts are more accurately depositories for highly active homogeneous rhodium catalysts that are cast into solution under the aforementioned reaction conditions. They also suggest that some of their less effective catalysts behaved as such due to stronger metal–atom bonds, effectively decreasing the degree of leaching.

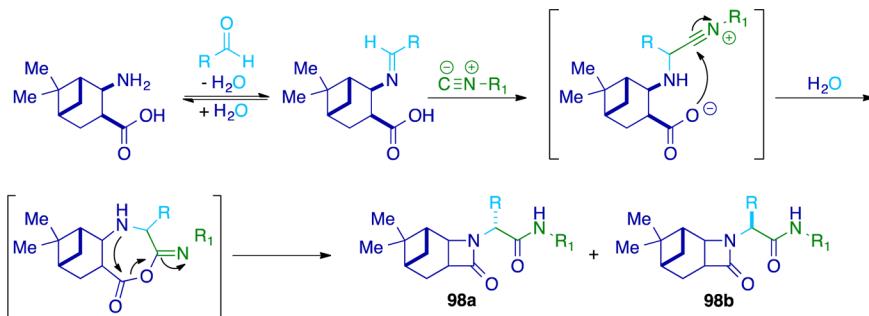
Scheme 49



4.6. Multicomponent Reaction

Exploiting the appeal of multicomponent reactions, Shipman and co-workers developed a four-component synthesis of tetra-substituted β -lactams 97 starting from 2-methyleneaziridines.¹⁵⁰ This is achieved via three consecutive reactions that are completed in one pot: (1) nucleophilic addition of a Grignard reagent to the aziridine ring, opening the ring and forming a metalloenamine; (2) introduction of an alkyl halide as a suitable electrophile for attack by the enamine, forming an imine and another new C–C bond; and (3) generation of a ketene in situ from an acid chloride and a base, which undergoes a standard Staudinger reaction with the newly formed imine from the previous step (Scheme 49). Under their optimized conditions, the system appears to endure changes in all four components (Grignard reagent, methyleneaziridine, primary or secondary alkyl halide, and acid chloride) in consistently moderate overall isolated yields of 46–63%, averaging 77–86% yield per each

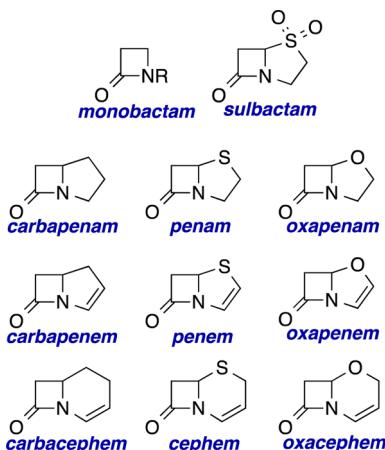
Scheme 50



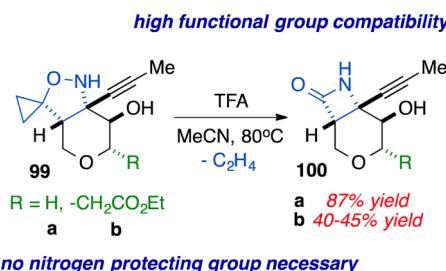
"step". The isolated yields indicate the total amount of β -lactam products formed, which is typically a 1:1 mixture of diastereomers as the system lends itself to little diastereosecontrol.

Fülöp and co-workers accessed conformationally constrained tricyclic apopinane-based β -lactams 98 through Ugi four-center three-component reactions (Scheme 50).¹⁵¹ An apopinane-based β -amino acid was coupled with an aldehyde (benzaldehyde, propanal, or 2,2-dimethylpropanal) and an isocyanide (benzyl or *tert*-butyl) in each methanol, water, and solvent-free conditions to give the corresponding tricyclic product in moderate yields (44–82%, with one low exception) and generally high diastereoselectivity (67:33 to 100:0 Z-isomer:*E*-isomer). Running the reaction in water or with no solvent at all is a much greener approach, but is even more practical here as reaction times are greatly reduced from when methanol is used. However, this is only advantageous for their reactions with propanal and 2,2-dimethylpropanal, as they give mostly comparable product yields, but not for reactions with

molecules are heavily garnished with alcohol, alkene, alkyne, ether, and/or ester moieties.

Figure 20. Common β -lactam antibiotic core structures.

Scheme 51



benzaldehyde, which give little to no products (in water, likely due to solubility issues of the putative imine intermediate).

4.7. Ring Contraction

The acidic fragmentation of spirocyclopropane oxazolidines was highlighted in the review by Brandi et al. as another viable route for the synthesis of N-substituted mono- and polycyclic β -lactam derivatives.³ In 2013, Carreira and Diethelm notably extended the scope of this reaction in a total synthesis application.¹⁵² En route to the synthesis of gelsemoxonine, the authors demonstrated the ability of two N-unsubstituted spirocyclopropane oxazolidines 99 to hold up to standard reaction conditions (trifluoroacetic acid in acetonitrile at elevated temperature) and form β -lactams 100a and 100b in 87% and 40–45% yield, respectively (Scheme 51). These examples (and one N-substituted example in 81% yield provided by the authors) also showcase the broad functional group tolerance of this ring contraction reaction, as the starting

5. CONCLUDING REMARKS

The eclectic collection of recent synthetic methods for constructing the β -lactam ring, either in the realm of asymmetric catalysis or otherwise, is a testament to the current livelihood of the field. By expanding upon known reactivity and actively seeking fundamentally new chemistry, several laboratories are helping β -lactam chemistry continue to flourish. This is both comforting and necessary, as bacterial resistance likely has emerged proelium ad infinitum for the human race.¹⁵³ Greater accessibility of novel and enantiopure β -lactam compounds is a logical goal for future methods, perhaps with an emphasis on catalytic, asymmetric strategies to directly construct bicyclic compounds of the common antibiotics core structures (Figure 20). Protein engineering is also a promising inchoate field that will be exciting to watch evolve as an alternative strategy to synthesize various β -lactam structures with powerful stereocontrol by not mimicking, but manipulating, the enzymes.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lectka@jhu.edu.

Notes

The authors declare no competing financial interest.

Biographies



Cody Ross Pitts is a native of Waterbury, Connecticut who graduated from the Monmouth University Honors School in 2010 with a B.S. in chemistry and minors in both physics and musical theatre. His graduate career at Johns Hopkins began in 2011 with an Ernest M. Marks Fellowship when he joined the research group of Professor Tom Lectka. Cody's Ph.D. research currently focuses on the development and mechanistic investigation of direct, mild C–H fluorination methods.



Thomas Lectka is a native of Detroit and a graduate of Oberlin College who worked in John McMurry's laboratory at Cornell University, obtaining his Ph.D. in 1990. After an Alexander von Humboldt Fellowship to study at Heidelberg in 1991, he joined Dave Evans's laboratory at Harvard University with an NIH Postdoctoral Fellowship. In 1994 he began his tenure at Johns Hopkins University, where he was promoted to full Professor in 2002; at the present he is the Jean and Norman Scowe Professor of Chemistry. His research interests have included catalytic, asymmetric reactions of imines, amides, and ketenes, asymmetric halogenation reactions, "switchable" mechanisms in synthesis, solid-phase synthesis, nonnatural product synthesis, symmetrical fluoronium ions in solution, catalyzed fluorination reactions, and synthetic rotamase catalysts.

REFERENCES

- (1) Fleming, A. *Rev. Infect. Dis.* **1980**, *2*, 129.
- (2) Crowfoot, D.; Bunn, C. W.; Rogers-Low, B. W.; Turner-Jones, A. In *Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton University Press: Princeton, NJ, 1949.
- (3) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.
- (4) Galletti, P.; Giacomini, D. *Curr. Med. Chem.* **2011**, *18*, 4265.
- (5) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 69.
- (6) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 93.
- (7) (a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.
- (8) Hamed, R. B.; Gomez-Castellanos, J. R.; Henry, L.; Ducho, C.; McDonough, M. A.; Schofield, C. J. *Nat. Prod. Rep.* **2013**, *30*, 21.
- (9) (a) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144. (b) Laborde, M. A.; Mata, E. G. *Mini-Rev. Med. Chem.* **2006**, *6*, 109.
- (10) (a) Sammes, P. G. *Chem. Rev.* **1976**, *76*, 113. (b) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
- (11) (a) Banik, B. K. *Topics in Heterocyclic Chemistry*; Springer: Berlin; New York, 2013. (b) Georg, G. I. *The Organic Chemistry of β -Lactams*; VCH Publishers: New York, 1993.
- (12) Greenberg, A.; Breneman, C. M.; Lieberman, J. F. *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*; Wiley-Interscience: New York, 2000.
- (13) (a) Drakenberg, T.; Dahlqvist, K. I.; Forsen, S. *J. Phys. Chem.* **1972**, *76*, 2178. (b) Ross, B. D.; True, N. S. *J. Am. Chem. Soc.* **1984**, *106*, 2451. (c) Ross, B. D.; True, N. S.; Matson, G. B. *J. Phys. Chem.* **1984**, *88*, 2675. (d) Taha, A. N.; Crawford, S. M. N.; True, N. S. *J. Am. Chem. Soc.* **1998**, *120*, 1934.
- (14) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH Publishers, Inc.: Deerfield Beach, FL, 1985.
- (15) Johnson, J. R.; Woodward, R. B.; Robinson, R. In *The Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton University Press: Princeton, NJ, 1949.
- (16) Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1965**, 3325.
- (17) (a) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999. (b) Fujisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307. (c) Shimizu, M.; Kume, K.; Fujisawa, T. *Chem. Lett.* **1996**, 545.
- (18) Reaction time, scope, ease of workup, commercial availability of starting materials/reagents, cost, yield, amount of waste, safety, scalability, recoverability of reagents/catalysts, etc.
- (19) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414.
- (20) (a) Reppe, W.; Kroper, H.; Pistor, J.; Weissbarth, O. *Justus Liebigs Ann. Chem.* **1953**, *582*, 87. (b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816.
- (21) Alper, H.; Perera, C. P.; Ahmed, F. R. *J. Am. Chem. Soc.* **1981**, *103*, 1289.
- (22) Alper, H.; Urso, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737.
- (23) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931.
- (24) Ardura, D.; Lopez, R.; Sordo, T. L. *J. Org. Chem.* **2006**, *71*, 7315.
- (25) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.
- (26) (a) Schurig, V.; Betschinger, F. *Bull. Soc. Chim. Fr.* **1994**, *131*, 555. (b) Archer, I. V. J. *Tetrahedron* **1997**, *53*, 15617. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (d) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.
- (27) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.
- (28) Corey, E. J.; Felix, A. M. *J. Am. Chem. Soc.* **1965**, *87*, 2518.
- (29) (a) Brunwin, D. M.; Lowe, G.; Parker, J. *J. Chem. Soc. C* **1971**, 3756. (b) Brunwin, D. M.; Lowe, G.; Parker, J. *J. Chem. Soc. D* **1971**, 865. (c) Lowe, G.; Parker, J. *J. Chem. Soc. D* **1971**, 577. (d) Franich, R. A.; Parker, J.; Lowe, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2034. (e) Lowe, G.; Ramsay, M. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 479. (f) Tomioka, H.; Kitagawa, H.; Izawa, Y. *J. Org. Chem.* **1979**, *44*, 3072. (g) Tomioka, H.; Kondo, M.; Izawa, Y. *J. Org. Chem.* **1981**, *46*, 1090. (h) Ponsford, R. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 846.
- (30) (a) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (b) Pirrung, M. C.; Morehead, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 8162.
- (31) Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819.
- (32) McCarthy, N.; Mckervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983.
- (33) Doyle, M. P.; Kalinin, A. V. *Synlett* **1995**, 1075.

- (34) (a) Lunazzi, L.; Macciantelli, D.; Tassi, D.; Dondoni, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 717. (b) Schnur, D. M.; Yuh, Y. H.; Dalton, D. R. *J. Org. Chem.* **1989**, 54, 3779.
- (35) Watanabe, N.; Anada, M.; Hashimoto, S.; Ikegami, S. *Synlett* **1994**, 1031.
- (36) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, 30, 5397.
- (37) Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun.* **1998**, 1517.
- (38) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, 39, 9063.
- (39) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, 43, 2198.
- (40) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.
- (41) Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382.
- (42) Okuro, K.; Enna, M.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1107.
- (43) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, 73, 553.
- (44) Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, 124, 4572.
- (45) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, 42, 4082.
- (46) Ye, M. C.; Zhou, J.; Huang, Z. Z.; Tang, Y. *Chem. Commun.* **2003**, 2554.
- (47) Ye, M. C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, 71, 3576.
- (48) Knopfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, 125, 6054.
- (49) (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, 2. (b) Eglinton, G.; Galbraith, A. R. *Chem. Ind.* **1956**, 737.
- (50) Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadeohl, H.; Gade, L. H. *Chem. Commun.* **2005**, 5115.
- (51) Chen, J. H.; Liao, S. H.; Sun, X. L.; Shen, Q.; Tang, Y. *Tetrahedron* **2012**, 68, 5042.
- (52) Coyne, A. G.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, 18, 199.
- (53) Determined by ^1H NMR.
- (54) Saito, T.; Kikuchi, T.; Tanabe, H.; Yahiro, J.; Otani, T. *Tetrahedron Lett.* **2009**, 50, 4969.
- (55) Baeza, B.; Casarrubios, L.; Sierra, M. A. *Chem.—Eur. J.* **2013**, 19, 11536.
- (56) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, 89, 1447.
- (57) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, 65, 2255.
- (58) Ojima, I.; Inaba, S. I.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643.
- (59) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. J. *Org. Chem.* **1980**, 45, 3413.
- (60) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, 119, 2060.
- (61) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715.
- (62) An excess of strong lithium amide reagents may effect, for instance, undesirable deprotonation or nucleophilic addition reactions.
- (63) Kambara, T.; Tomioka, K. *Chem. Pharm. Bull.* **2000**, 48, 1577.
- (64) Hata, S.; Iwasawa, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *Synthesis* **2004**, 1471.
- (65) Abraham, C. J.; Paull, D. H.; Dogo-Isonagie, C.; Lectka, T. *Synlett* **2009**, 1651.
- (66) (a) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, 37, 592. (b) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, 64, 10465. (c) Tuba, R. *Org. Biomol. Chem.* **2013**, 11, 5976.
- (67) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, 356, 51.
- (68) Cossio, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, 41, 925.
- (69) (a) Drury, W. J.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, 120, 11006. (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *Abstr. Pap. Am. Chem. Soc.* **1998**, 216, U488. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, 120, 4548.
- (70) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, 122, 7831.
- (71) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. H. *J. Am. Chem. Soc.* **1999**, 121, 9742. (b) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.
- (72) (a) Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* **1990**, 26, 255. (b) Alder, R. W. *Chem. Rev.* **1989**, 89, 1215.
- (73) (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, 36, 10. (b) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, 49, 5058.
- (74) Shah, M. H.; France, S.; Lectka, T. *Synlett* **2003**, 1937.
- (75) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, 4, 627.
- (76) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, 2, 3963.
- (77) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, 4, 1603.
- (78) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, 127, 1206.
- (79) Wack, H.; France, S.; Hafez, A. M.; Drury, W. J.; Weatherwax, A.; Lectka, T. *J. Org. Chem.* **2004**, 69, 4531.
- (80) Huang, Y. Z.; Calter, M. A. *Tetrahedron Lett.* **2007**, 48, 1657.
- (81) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, 124, 1578.
- (82) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 127, 11586.
- (83) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, 10, 277.
- (84) The NHC is formed in situ in the presence of Cs_2CO_3 .
- (85) (a) Tang, K.; Wang, J. H.; Cheng, X. L.; Hou, Q. Q.; Liu, Y. J. *Eur. J. Org. Chem.* **2010**, 6249. (b) Tang, K.; Wang, J. H.; Hou, Q. Q.; Cheng, X. L.; Liu, Y. J. *Tetrahedron: Asymmetry* **2011**, 22, 942. (c) Hans, M.; Wouters, J.; Demonceau, A.; Delaude, L. *Chem.—Eur. J.* **2013**, 19, 9668.
- (86) Duguet, N.; Campbell, C. D.; Slawin, A. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, 6, 1108.
- (87) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, 14, 1784.
- (88) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, 7, 3461.
- (89) A third mechanistic scenario, epimerization of an original cis product to trans, was discounted by control experiments.
- (90) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, 130, 418.
- (91) Chiang, P. C.; Kaeobamrungr, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, 129, 3520.
- (92) (a) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5770. (b) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, 102, 774. (c) Paquette, L. A. *Tetrahedron* **1997**, 53, 13971.
- (93) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, 128, 8736.
- (94) D'hooghe, M.; Van Brabandt, W.; Dekeukeleire, S.; Dejaegher, Y.; De Kimpe, N. *Chem.—Eur. J.* **2008**, 14, 6336.
- (95) Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martinezripoll, M. *J. Am. Chem. Soc.* **1992**, 114, 9360.
- (96) Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, 124, 3175.
- (97) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, 34, 2543.
- (98) Hachiya, I.; Yoshitomi, T.; Yamaguchi, Y.; Shimizu, M. *Org. Lett.* **2009**, 11, 3266.
- (99) (a) Sierra, M. A.; Rodriguez-Fernandez, M.; Casarrubios, L.; Gomez-Gallego, M.; Allen, C. P.; Mancheno, M. *J. Dalton Trans.* **2009**, 8399. (b) Pellico, D.; Gomez-Gallego, M.; Ramirez-Lopez, P.; Mancheno, M. J.; Sierra, M. A.; Torres, M. R. *Chem.—Eur. J.* **2009**, 15, 6940. (c) Pellico, D.; Gomez-Gallego, M.; Ramirez-Lopez, P.; Mancheno, M. J.; Sierra, M. A.; Torres, M. R. *Chem.—Eur. J.* **2010**, 16, 1592.
- (100) Mendez, L.; Mata, E. G. *J. Comb. Chem.* **2010**, 12, 810.
- (101) Zhao, B. X.; Yu, Y.; Eguchi, S. *Org. Prep. Proced. Int.* **1997**, 29, 185.
- (102) Poeylaut-Palena, A. A.; Mata, E. G. *J. Comb. Chem.* **2009**, 11, 791.

- (103) Janikowska, K.; Pawelska, N.; Makowiec, S. *Synthesis* **2011**, 1, 69.
- (104) (a) Wolff, L.; Bock, P.; Lorentz, G.; Trappe, P. *Justus Liebigs Ann. Chem.* **1902**, 325, 134. (b) Meier, H.; Zeller, K. P. *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 32. (c) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.
- (105) Vaske, Y. S. M.; Mahoney, M. E.; Konopelski, J. P.; Rogow, D. L.; McDonald, W. J. *J. Am. Chem. Soc.* **2010**, 132, 11379.
- (106) Petrik, V.; Roschenthaler, G. V.; Cahard, D. *Tetrahedron* **2011**, 67, 3254.
- (107) Stalling, T.; Johannes, K.; Polina, S.; Martens, J. *J. Heterocycl. Chem.* **2013**, 50, 654.
- (108) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2009**, 50, 1568.
- (109) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2009**, 65, 2927.
- (110) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2010**, 66, 5017.
- (111) Zarei, M.; Jarrahpour, A. *Synlett* **2011**, 2572.
- (112) Zarei, M. *J. Chem. Res.* **2012**, 118.
- (113) Zarei, M. *Bull. Chem. Soc. Jpn.* **2012**, 85, 360.
- (114) Zarei, M. *Monatsh. Chem.* **2013**, 144, 1021.
- (115) Zarei, M.; Karimi-Jaber, Z.; Movahedi, A. *Synth. Commun.* **2013**, 43, 728.
- (116) Zarei, M. *J. Chem. Res.* **2013**, 25.
- (117) Zarei, M. *Tetrahedron* **2013**, 69, 6620.
- (118) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465.
- (119) Jarrahpour, A.; Fadavi, A.; Zarei, M. *Bull. Chem. Soc. Jpn.* **2011**, 84, 320.
- (120) Jarrahpour, A.; Doroodmand, M. M.; Ebrahimi, E. *Tetrahedron Lett.* **2012**, 53, 2797.
- (121) Jarrahpour, A.; Ebrahimi, E. *Molecules* **2010**, 15, 515.
- (122) Tarui, A.; Ozaki, D.; Nakajima, N.; Yokota, Y.; Sokeirik, Y. S.; Sato, K.; Orriote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2008**, 49, 3839.
- (123) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, 2, 2549.
- (124) Bilke, J. L.; Dzuganova, M.; Frohlich, R.; Wurthwein, E. U. *Org. Lett.* **2005**, 7, 3267.
- (125) Michel, K.; Frohlich, R.; Wurthwein, E. U. *Eur. J. Org. Chem.* **2009**, 5653.
- (126) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, 79, 1920. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, 113, 2177.
- (127) Zhang, X. J.; Hsung, R. P.; Li, H. Y.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Org. Lett.* **2008**, 10, 3477.
- (128) (a) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2008**, 73, 7402. (b) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2009**, 74, 3094. (c) Maciejko, M.; Stecko, S.; Staszewska-Krajewska, O.; Jurczak, M.; Furman, B.; Chmielewski, M. *Synthesis* **2012**, 44, 2825.
- (129) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, 60, 4743.
- (130) Cicchi, S.; Hold, I.; Brandi, A. *J. Org. Chem.* **1993**, 58, 5274.
- (131) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 99, 1191.
- (132) Sotgiu, G.; Chiarotto, I.; Feroci, M.; Orsini, M.; Rossi, L.; Inesi, A. *Electrochim. Acta* **2008**, 53, 7852.
- (133) The term “pro-base” is designated to a compound that can effectively act as a base upon accepting an electron, in this instance, by electrochemical means.
- (134) (a) Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, 107, 2615. (b) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, 63, 2363.
- (135) Zhao, Q. W.; Li, C. Z. *Org. Lett.* **2008**, 10, 4037.
- (136) Sakamoto, M.; Kawanishi, H.; Mino, T.; Fujita, T. *Chem. Commun.* **2008**, 2132.
- (137) Perez-Faginas, P.; Aranda, M. T.; Coady, L.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. *Adv. Synth. Catal.* **2008**, 350, 2279.
- (138) Perez-Faginas, P.; Garcia-Lopez, I. A. M. T.; Gonzalez-Muniz, R. *Tetrahedron Lett.* **2008**, 49, 215.
- (139) Hernandez-Vazquez, L. G.; Leyva, M. A.; Metta-Magana, A. J.; Escalante, J. *Helv. Chim. Acta* **2012**, 95, 2218.
- (140) Huang, L.; Zhao, W. J.; Staples, R. J.; Wulff, W. D. *Chem. Sci.* **2013**, 4, 622.
- (141) Fordos, E.; Tuba, R.; Parkanyi, L.; Kegl, T.; Ungvary, F. *Eur. J. Org. Chem.* **2009**, 1994.
- (142) Troisi, L.; Pindinelli, E.; Strusi, V.; Trinchera, P. *Tetrahedron: Asymmetry* **2009**, 20, 368.
- (143) Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A. K. M. A.; Tanaka, H. *Tetrahedron Lett.* **1993**, 34, 6553.
- (144) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91.
- (145) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, 3, 2415.
- (146) Fontana, F.; Tron, G. C.; Barbero, N.; Ferrini, S.; Thomas, S. P.; Aggarwal, V. K. *Chem. Commun.* **2010**, 46, 267.
- (147) Zhang, Z. H.; Liu, Y. Y.; Ling, L.; Li, Y. X.; Dong, Y.; Gong, M. X.; Zhao, X. K.; Zhang, Y.; Wang, J. B. *J. Am. Chem. Soc.* **2011**, 133, 4330.
- (148) Aronica, L. A.; Caporosso, A. M.; Evangelisti, C.; Botavina, M.; Alberto, G.; Martra, G. *J. Organomet. Chem.* **2012**, 700, 20.
- (149) Matsuda, I.; Sakakibara, J.; Nagashima, H. *Tetrahedron Lett.* **1991**, 32, 7431.
- (150) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, 73, 9762.
- (151) Szakonyi, Z.; Sillanpaa, R.; Fulop, F. *Mol. Diversity* **2010**, 14, 59.
- (152) Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, 135, 8500–8503.
- (153) McKenna, M. *Nature* **2013**, 499, 394.