

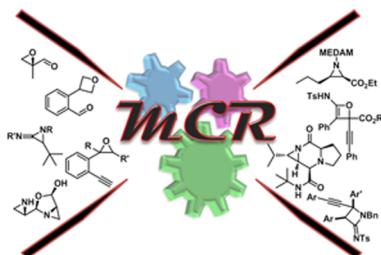
## Small Heterocycles in Multicomponent Reactions

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### 1. INTRODUCTION

Small-ring heterocycles have found many applications both as useful starting materials in the synthesis of more elaborate structures and as valuable targets of synthesis. Our review summarizes progress made in multicomponent reactions (MCRs) that either produce small heterocycles or employ them as starting materials. For the purposes of this paper, we have considered heterocycles consisting of three and four atoms as “small”. By definition, MCRs simultaneously engage three or more components, resulting in products that incorporate the elements of all starting materials in their frameworks. This integrative nature of MCRs is attractive when a rapid increase in molecular diversity is desired. Using a combinatorial approach, sets of components (such as amines, carboxylic acids, alcohols, etc.) can be systematically distributed in arrays of reactions to generate iterations on a common MCR-product scaffold.

Given the central role of strained rings in synthesis, we felt compelled to evaluate their involvement in MCRs. The most well recognized function of small heterocycles is their propensity to undergo ring-opening reactions by cleavage of a carbon–heteroatom bond and formation of a new bond with an incoming nucleophile. This process can lead to subsequent bond formation, whereby a small heterocycle effectively links two other reactants that may not otherwise react with one another. The analogous process leading to small-ring formation operating on the same principles is also true in MCRs. By building up an electrophilic center at a selected atom, an appropriately placed heteroatom may be compelled into ring formation by carbon–heteroatom bond formation.

In the section titled “Multicomponent Reactions with Heterocyclic Substrates”, the reader will find a discussion of examples of MCRs in which a reactant features a small heterocycle. In most of these cases, a heterocycle is engaged as an electrophile and undergoes ring opening or ring expansion. In other cases, the heterocycle survives the transformation and acts as nucleophile or a directing group for nearby stereo-selective MCRs. The many ways in which small rings are deployed in synthesis and MCRs is illustrative of their versatility. On one hand, small ring heterocycles can provide new ways of designing the thermodynamic driving forces of

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MCRs, through strain-releasing ring-opening or ring-expansion processes. Many of these MCRs succeed by managing the release of strain through a number of bond-forming steps, amounting to “strain relay”. On the other hand, it is equally interesting to consider MCRs that bypass the involvement of strained rings in bond-forming steps, yet rely on them as auxiliary elements. Given the relatively harsh nature of some of the oxidants that are used to make aziridines and epoxides (e.g., by olefin oxidation), there are significant benefits to reactions that take on strained starting materials and modify them with high selectivity without prematurely engaging their strained fragments. The following section, “Multicomponent Reactions Producing Heterocycles”, focuses on MCRs that generate small heterocycles. While in many of these examples a small ring is an isolable product, in others the rings are consumed in situ, leading to downstream products. We note that our coverage does not take into account reactions where small heterocycles serve as mere bystanders and do not influence MCR selectivity.

An important theme that is apparent when considering the reactions discussed throughout the review is that the observed reactivity is contingent on careful positioning of the reactive centers to favor the desired transformations. It will be shown that this strategy can be applied in several forms for different purposes. In some cases, the reaction environment must be designed to favor one reaction pathway over alternatives in order to temper inherent reactivity. Consider, for example, complexation of an epoxide to a sterically shielding Lewis acid to prevent premature ring opening (section 2.4). The selection of a noncoordinating solvent to reduce the electron density on a metal catalyst center allows interception of a synthetically useful intermediate (section 2.7). In another instance, the use of chiral Brønsted acid catalysts enables synthesis of enantioenriched aziridines (section 3.5). In each of these examples, the reactants under less optimized conditions lead to premature bond formation or nonselective reactions. Whether or not this selectivity has its origins in catalyst or substrate control, it is evident that many of the MCRs discussed in this review are products of vigilant reactivity tuning of steric and electronic environments.

Conversely, the reaction environment is often curated to promote bond formation from less reactive molecular arrangements. The intercepted Ugi reactions (section 2.3) succeed by virtue of an aziridine being positioned relative to a well-established MCR intermediate (a mixed anhydride) to open up an alternative mechanistic pathway. Similarly, anion-relay chemistry relies on epoxide ring-opening setting the stage for a 1,3-Brook rearrangement (section 2.6), and Brønsted acid catalysis promotes epoxide ring opening (section 2.5). The many examples of the Ugi reaction being applied for  $\beta$ -lactam preparation (section 3.2) are also evidence of the utility of careful positioning of reactive sites to take advantage of small heterocycle chemistry. It is helpful to treat these MCRs as manifestations on the theme of scaffold-driven reactivity to control the relative rates of many possible mechanistic avenues.

There are also a number of examples discussed within this review which have been the subject of extensive optimization to overcome selectivity challenges to develop a so-called “true” MCR (in which multiple reactive components are present simultaneously in the reaction media). It is evident from section 3.6 that a truly multicomponent aza-Darzens reaction was a goal for many research groups working in this area until it was definitively achieved in 2011. In other cases, MCRs were developed and it was only later that the reactivity they relied

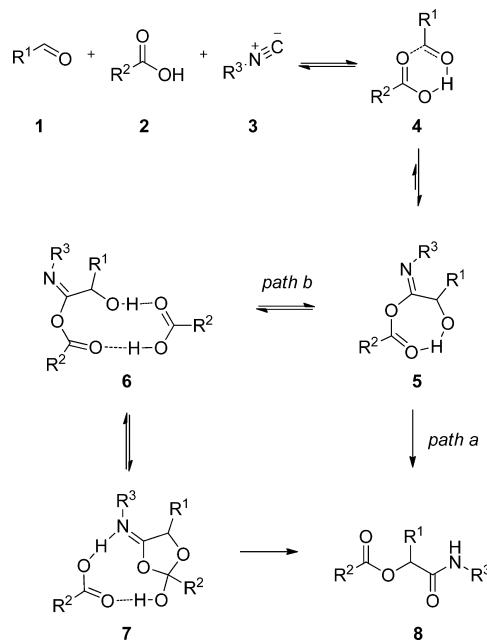
upon was fully understood. Such insights have led to MCRs being harnessed to develop new transformations that serve the same broad purposes of direct access to complex molecular scaffolds from simpler starting materials. Even if these new transformations do not conform to the strict definitions of MCRs, it is clear that they share the same aims, obey many of the same principles, and in some way are also the products of MCRs.

## 2. MULTICOMPONENT REACTIONS WITH HETEROCYCLIC SUBSTRATES

### 2.1. Passerini Reactions

Among multicomponent reactions (MCRs), those based upon the reactivity of isocyanides hold a distinction for their capacity to provide complex products from simple reactants, such as aldehydes or ketones (oxo compounds), carboxylic acids and their analogues, and amines. Isocyanide-based MCRs are made possible by the 1,1-amphoteric nature of the isocyanide functional group. Passerini and Ugi reactions are the two most well-known isocyanide-based MCRs. The Passerini process is a three-component reaction (3CR) linking oxo compounds (**1**), carboxylic acids (**2**), and isocyanides (**3**) to produce  $\alpha$ -acyloxycarboxamides (**8**).<sup>1</sup> Mechanistically, a hydrogen-bonded cluster of the aldehyde and carboxylic acid (**4**) has been suggested to activate addition of the isocyanide (Scheme 1). It is not known if a discrete isonitrilium ion is formed or if

**Scheme 1. Proposed Mechanisms of the Passerini Reaction As Described by Maeda et al.<sup>2</sup>**

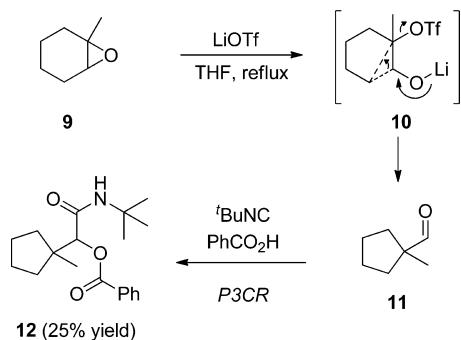


the  $\alpha$ -addition is a concerted process. Computational studies have suggested multiple pathways, and it is likely that a number of them are operative, depending on the reaction conditions (Scheme 1).<sup>2</sup> The  $\alpha$ -addition is likely irreversible, and transacylative collapse of a mixed anhydride is the thermodynamic driving force.

One strategy to extend MCR reactivity is to substitute one component of a known MCR with a small heterocycle. As an adaptation of the Passerini reaction, Kern and Motherwell developed a novel isocyanide-based 3CR in which an epoxide

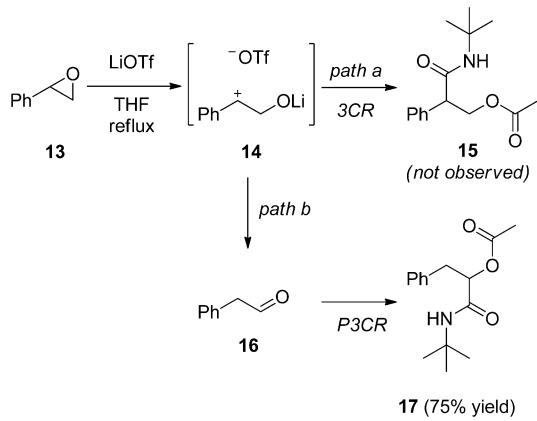
was used as the initiation electrophile in place of an aldehyde.<sup>3</sup> In the presence of a metal triflate catalyst, an MCR occurred between an epoxide, a carboxylic acid, and an isocyanide. In one example, 1-methylcyclohexene oxide (9) underwent a skeletal rearrangement<sup>4</sup> to 1-methylcyclopentane-1-carboxaldehyde (11) before engaging the isocyanide and carboxylic acid in a traditional Passerini reaction (Scheme 2).

**Scheme 2. Rearrangement of 1-Methylcyclohexene Oxide (9) to 1-Methylcyclopentane-1-carboxaldehyde (11) Prior to P3CR**



The authors suggested that benzylic and allylic epoxides would lead to formation of stabilized carbocations that could react with an isocyanide molecule directly and initially assigned products of such reactions as  $\beta$ -acyloxy carboxamides, or “homo-Passerini” products, such as 15 (Scheme 3). Analogous

**Scheme 3. 3CR with Styrene Oxide (13), Acetic Acid, and *tert*-Butyl Isocyanide Proceeds through a Benzylic Cation (14)<sup>a</sup>**



<sup>a</sup>Although initially proposed to proceed through direct attack of the isocyanide on the cation (path a), a rearrangement proceeds preferentially (path b) to give P3CR product 17.

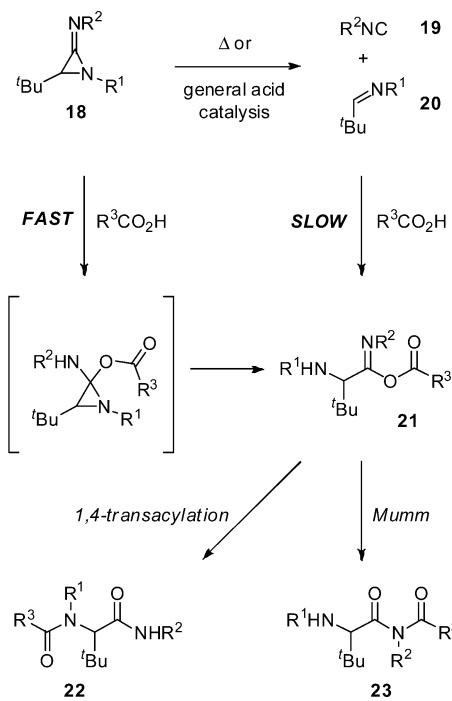
transformations using aziridines were also reported, producing  $\beta$ -dipeptide motifs. Later it was clarified that even carbocations derived from benzylic and allylic epoxides underwent a rearrangement to the aldehyde, followed by classical Passerini-type reactivity.<sup>5</sup> Thus, strained rings have the capacity to release carbocations that can engage in MCRs. The possibility of more elaborate carbocation rearrangements should enable access to skeletally diverse products using this method.

## 2.2. Ugi Reactions

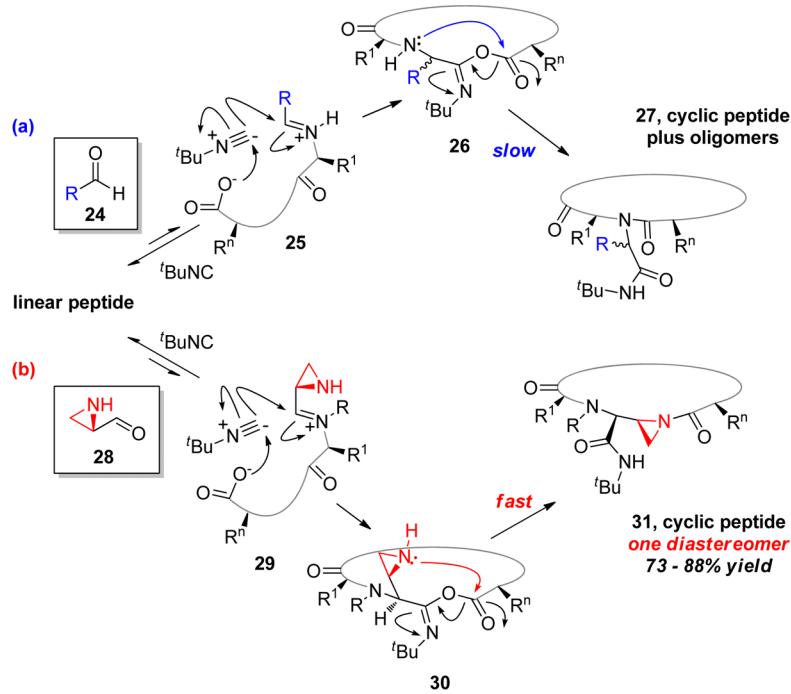
The Ugi reaction is a 4CR that expands upon the Passerini reaction with the addition of ammonia or a primary or secondary amine.<sup>6</sup> Condensation of the amine and oxo components gives rise to an electrophilic iminium ion that reacts with the isocyanide and carboxylate with high selectivity over the possible competing P3CR. The resulting mixed anhydride intermediate is prone to transacylative decomposition to give, in this case,  $\alpha$ -acylamino amide products. Computational studies aimed at elucidating the mechanisms at play in the Ugi reaction have been carried out and suggested that subtle differences in the elementary steps result from changes in the nature of the solvent.<sup>7</sup> In contrast to the P3CR, protic solvents are the norm for the U4CR (Ugi four-component reaction),<sup>8</sup> and an isonitrilium intermediate was identified in theoretical studies that used a methanol solvent model. In all solvents, the reaction of the isocyanide is believed to be rate-determining. The formation of amides serves as the thermodynamic driving force.

Similar to how epoxides can be employed in the Passerini reaction in place of the oxo component, iminoaziridines (18) can be used as synthetic precursors for three components of the U4CR. Under thermal activation or general acid catalysis, 18 fragments to form isocyanide 19 and imine 20. Subsequently, the U4CR reaction proceeds in the presence of a carboxylic acid. Alternatively, direct addition of a carboxylic acid to 18 at low temperature leads to the same mixed anhydride intermediate (21) and the corresponding rearrangement products (Scheme 4).<sup>9</sup> Unlike the U4CR, where formation of 21 is rate-limiting, the highly reactive iminoaziridines allowed for characterization of 21 in solution by <sup>1</sup>H and <sup>13</sup>C NMR when sterically hindered carboxylic acids, such as di-*tert*-butylacetic acid, were used. Several insights were gained from this study. When nonracemic iminoaziridines (18) were employed, little to no racemization was detected in the

**Scheme 4. Iminoaziridines (18) Provide an Alternative Approach to the U4CR**



Scheme 5. Comparison of Multicomponent Ugi Reactions with (a) Conventional Aldehydes and (b) Aziridine Aldehydes



products. This suggests that the reaction does not proceed through a retro-[2 + 1] cycloaddition with intermediates **19** and **20**. Rather, the sterically encumbered carboxylic acids (e.g., *tert*-butylacetic acid) rapidly add to **18** and lead to synthetically valuable nonracemic Ugi products (**22**). When the aziridinyl *N*-substituent was large (i.e., R<sup>1</sup> = <sup>t</sup>Bu, Scheme 4), formation of **22** by 1,4-transacylation was disfavored relative to the 1,3-Mumm rearrangement, which produced imide **23**. Heating or excess carboxylic acid reversed this selectivity to favor **22** but still did not compromise the stereochemistry of the reaction. This is especially important, given the historical challenges of developing asymmetric Ugi reactions.<sup>10</sup>

### 2.3. Intercepted Ugi Reactions

The multicomponent nature of the Ugi condensation makes it an advantageous method for amide bond formation due to the capacity to link four components. Application of the Ugi MCR for macrocyclization of peptides would confer similar synthetic advantages as well as bridge the ends of the peptide in a single step. However, this approach is plagued by competing oligomerization and epimerization processes. As a result, this method has failed to gain traction for the preparation of cyclic peptides.<sup>11</sup> Götz and co-workers attempted to use an Ugi four-center–three-component reaction (U4C–3CR) in the synthesis of cyclic peptides from linear peptides and simple aldehydes (**24**) such as isobutyraldehyde. In the absence of auxiliary nucleophilic functionality in the aldehyde, a cyclo-dimer was formed (Scheme 5a).<sup>12</sup> By increasing the length of the linear peptide, the reaction produced the monomeric 18-membered cyclic peptide from (Gly)<sub>6</sub>, albeit in low yields.

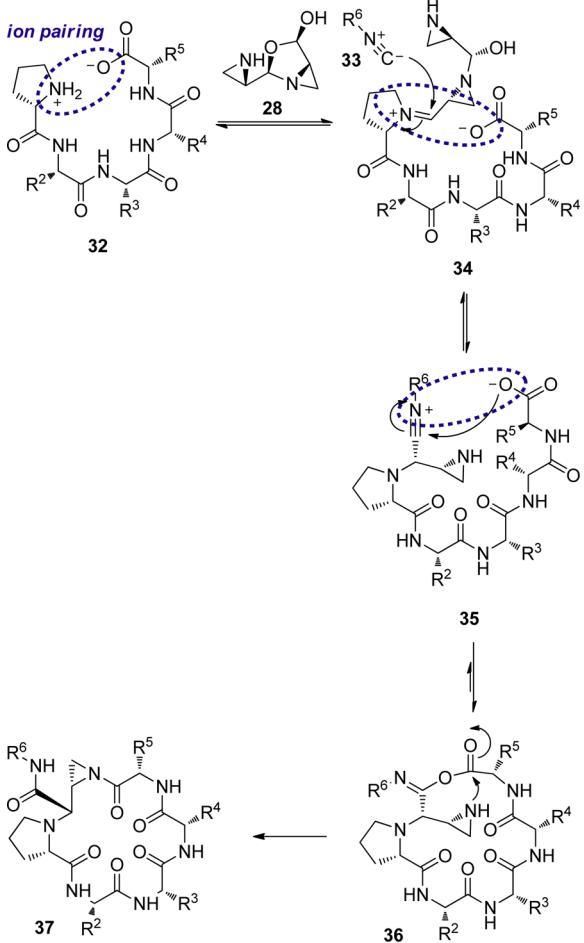
In 2010, the Yudin group reported a peptide macrocyclization protocol with a rerouted version of the U4C–3CR.<sup>13</sup> As in the classical U4CR, the four functional groups involved were made up of an isocyanide, an aldehyde, an amine, and a carboxylic acid. In this case, however, an amphoteric aziridine aldehyde (**28**) was employed in lieu of conventional aldehydes with a single reactive site. Aziridine aldehydes such as

**28** allowed the MCR to proceed through iminium formation (**29**) followed by attack of isocyanide and carboxylic acid to generate a mixed anhydride (**30**). Through the use of **28**, transannular attack of the newly formed secondary amine on the mixed anhydride (e.g., **26** → **27**, Scheme 5a) is superseded by attack of the nucleophilic aziridine, which is positioned exocyclic to the electrophilic mixed anhydride (**30** → **31**, Scheme 5b). Accordingly, aziridine aldehyde-mediated cyclization has allowed the formation of challenging rings. An added benefit to this strategy is the presence of an aziridine within the peptide backbone of the final product (**31**), which serves as a handle to bring in further functionality through nucleophilic ring opening of the aziridine moiety.

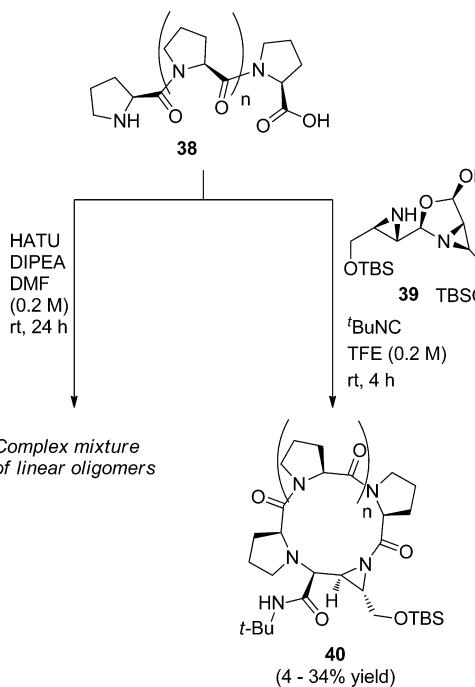
A question arises as to the origin of high selectivity for the monocyclic product in aziridine aldehyde mediated macrocyclization of peptides. In contrast to the activated ester strategy often used in peptide cyclization,<sup>11</sup> ion-pairing between the termini is enforced throughout the mechanism (**32**, **34**, **35**) until a ring is constructed by the attack of carboxylate onto the proposed isonitrilium intermediate (**35**, Scheme 6). The cooperativity between Coulombic interactions and hydrogen bonds is now the subject of intense investigations in our laboratories and in those of other groups.<sup>15</sup>

The electrostatic attraction that is maintained between the peptide termini over the course of the cyclization has allowed the Yudin group to address the long-standing challenge of oligoproline cyclization (Scheme 7).<sup>16</sup> Oligoproline stretches (**38**), ranging in size from 2 to 12 repeating residues in length, were cyclized without the need for specific cyclization-conducive diastereomers.<sup>17</sup> Computational modeling with Monte Carlo multiple minima simulations supported the zwitterionic hypothesis and in all cases isonitrilium intermediates were found and featured the peptide termini in close proximity (3.2–5.8 Å). This work demonstrated the ability of the aziridine aldehyde-mediated macrocyclization to override the extreme rigidity present in homochiral oligoprolines.<sup>18</sup>

**Scheme 6. Zwitterionic Control in Aziridine Aldehyde-Driven Macrocyclization**

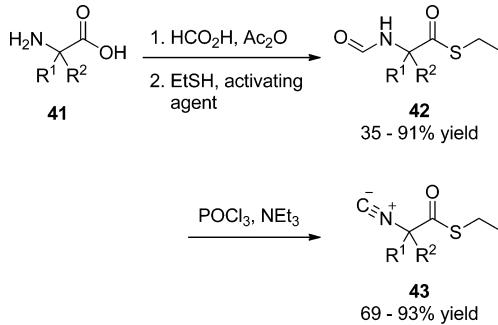


**Scheme 7. Aziridine Aldehyde-Mediated Macrocyllization Affords Cyclic Oligoproline Molecules ( $n = 0-2, 4, 6, 8, 10$ )**



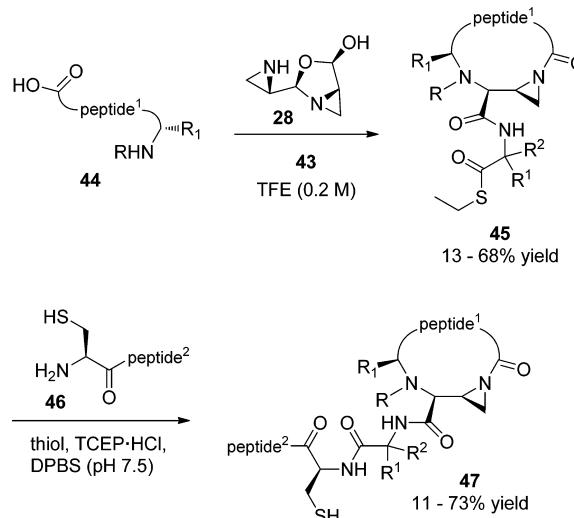
To enable further diversification of macrocyclic peptides prepared using aziridine aldehyde-enabled cyclization, the Yudin group developed a set of novel thioester isocyanides (43, Scheme 8),<sup>19</sup> to provide a handle for downstream native

**Scheme 8. Synthesis of Thioester Isocyanides (43) from Amino Acids**



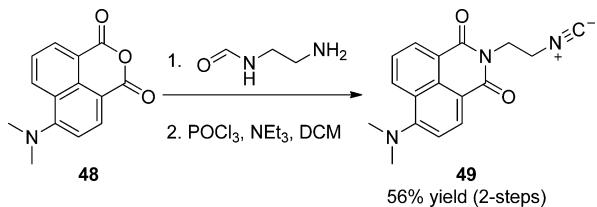
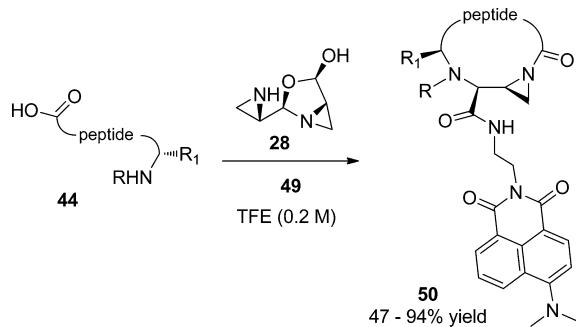
chemical ligation<sup>20</sup> applications. The synthesis proceeded by the formylation of an amino acid (41) and coupling of ethanethiol and subsequent dehydration by POCl<sub>3</sub>. After macrocyclization, the resultant peptide macrocycles with thioester side chains (45) were ligated to cysteine N-terminated peptides (46) to furnish synthetic cycle-tail peptides (47), a privileged scaffold for antimicrobial compounds (Scheme 9).<sup>21</sup>

**Scheme 9. Use of Thioester Isocyanides for Chemical Ligation to Linear Peptides**

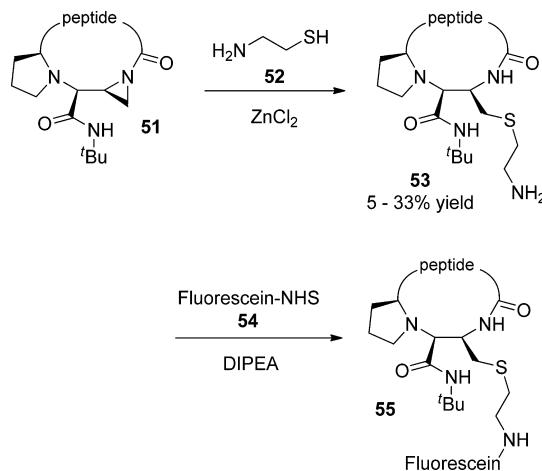


A similar approach was applied in the investigation of fluorescent isocyanides as site-specific tags for peptide labeling in MCRs. Dehydration of the formamide derived from 48 yielded the fluorescent isocyanide 49 (Scheme 10). The isocyanide was then used in the aziridine aldehyde-mediated macrocyclization to afford labeled piperazinones (67–93% yield) and peptides (50, 47–94% yield, Scheme 11).<sup>22</sup> Using the solvatochromic naphthalimide-derived isocyanide, organelle-selective macrocycles were designed by the cyclization of previously reported mitochondria-penetrating peptides.<sup>23</sup>

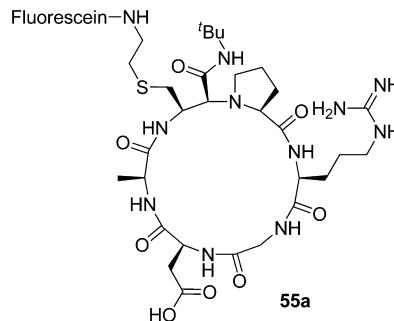
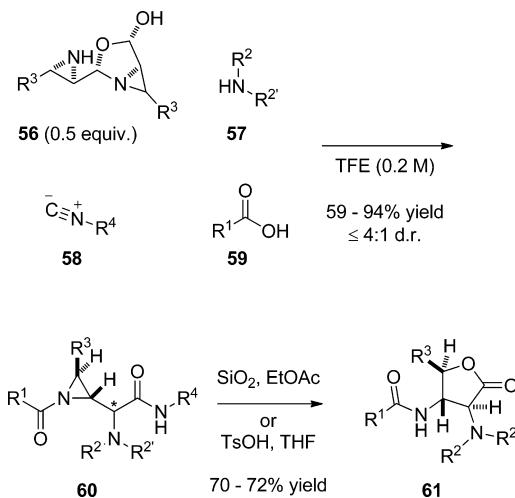
An alternative route to appending functionally useful moieties to peptide macrocycles is afforded by aziridine ring opening with nucleophiles. A protocol with step-by-step

**Scheme 10. Synthesis of Solvatochromic Isocyanide 49****Scheme 11. Use of Fluorescent Isocyanide for Preparation of Solvatochromic Macroyclic Peptide Probes**

instructions for the ring-opening of aziridines embedded within peptide macrocycles has been published.<sup>24</sup> This approach has been used by the Zheng and Yudin groups toward the formation of isoform-specific integrin probes.<sup>25</sup> The macrocyclic probes were rendered fluorescent by aziridine ring opening with cysteamine (52) and subsequent coupling to a fluorescein N-hydroxysuccinimide ester (54, Scheme 12). Eighteen-membered rings (55a) derived from the protected PRGDA parent peptide were found to be micromolar inhibitors (IC<sub>50</sub>) in a cell adhesion assay (Figure 1).

**Scheme 12. Aziridine Ring Opening with Cysteamine Affords a Handle for Further Downstream Functionalization with Fluorescent Molecules**

In the same way that the NH group of aziridine aldehydes can be used as a kinetic trap for embedded cyclic mixed anhydrides, linear mixed anhydrides can also be trapped by a proximal aziridine. The Yudin group demonstrated this with a variety of acid, amine, isocyanide, and aziridine aldehyde components in a homo-Ugi four-component–five-center reaction (Scheme 13).<sup>26</sup> Limited diastereoselectivity (up to

**Figure 1. Example of an RGD-based selective macrocyclic probe for the  $\alpha/\beta_3$  integrin receptor.****Scheme 13. Aziridine-2-carboxaldehyde Dimers (56) Participate in Ugi Four-Component–Five-Centered Reactions<sup>a</sup>**

<sup>a</sup>The “homo-Ugi” products (60) undergo acid-catalyzed rearrangement of acyl aziridines to lactones 61.

4:1) for the isocyanide addition was observed in contrast to the cyclization methodology. Under the acidic conditions of silica gel purification, the aziridine amide 60 rearranged, by way of intramolecular attack of the neighboring amide, into lactone 61 (Scheme 13).

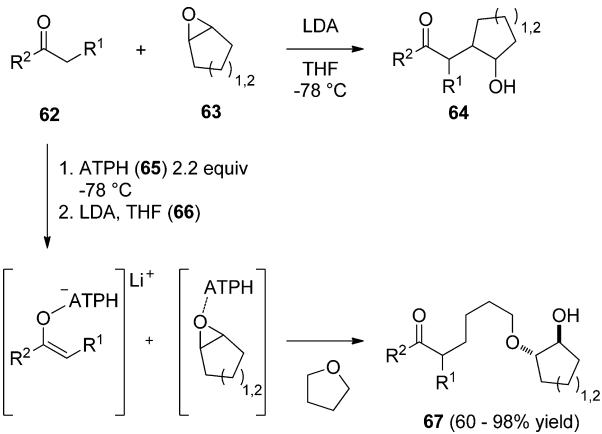
#### 2.4. Epoxide Ring Openings

Ring-opening reactions of epoxides are well-regarded as efficient methods for carbon–carbon or carbon–heteroatom bond formation.<sup>27</sup> Under basic or neutral conditions, chiral or prochiral epoxides are likely to be opened via S<sub>N</sub>2 anti-attack of the nucleophile and serve as an effective means of setting vicinal relative stereochemistry. Under acidic conditions, epoxides can give rise to carbocations and can be employed for bond formation with poorly nucleophilic species. As a result of this versatile reactivity, epoxide ring opening has been explored as an elementary step in many MCRs.

Upon exposure to lithium diisopropyl amide (LDA), an enolizable ketone (62) reacted with an epoxide (63) to form a single carbon–carbon bond and  $\gamma$ -hydroxy ketone 64. Yamamoto and co-workers hypothesized that this reactivity could be attenuated by complexation of the reaction partners to a sterically shielding Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH, 65).<sup>28</sup> Any potential coupling would then need to be mediated by a third reactant partner and

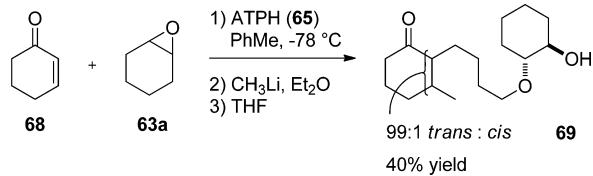
concomitant formation of multiple covalent bonds. When cyclohexanone (**62a**) and cyclohexene oxide (**63a**) were each precomplexed with ATPH in THF (**66**) prior to addition of LDA, enolization of **62** led to alkylation by sequential ring opening of THF and **63** to give good yield of *trans*-**67** (Scheme 14).<sup>29</sup> The scope included several cyclic and acyclic aliphatic

**Scheme 14.** Three-Component Coupling of Ketone (**62**), Epoxide (**63**), and THF (**66**) in the Presence of ATPH (**65**)



ketones. A similar four-component reaction was also reported in which methylolithium was added to a solution of ATPH-complexed  $\alpha,\beta$ -unsaturated ketone (**68**) and ATPH-**63a**, followed by addition of THF. The product (**69**) was isolated in 40% yield with high *trans*-selectivity at both pairs of vicinal stereocenters (Scheme 15).

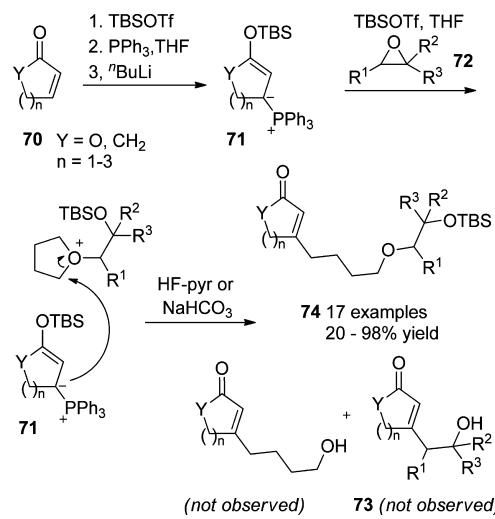
**Scheme 15.** Four-Component Reaction Including Methylolithium,  $\alpha,\beta$ -Unsaturated Ketone **68**, Cyclohexene Oxide (**63a**) and THF, Mediated by Sterically Encumbered Lewis Acid ATPH (**65**)



While THF may seem to be an unexpected reactant in MCRs, another example of it participating in epoxide ring opening has been reported. Starting off with the goal of using phosphonium ylides (**70**) as carbon nucleophiles in the ring-opening of epoxides (**72**), Kim and Jung noted that the products of the reaction did not correspond to direct attack at the epoxide (i.e., **73**, Scheme 16).<sup>30</sup> Rather, THF had intervened in the intended coupling to produce ether **74**. The authors proposed that the three-component reaction takes place by Lewis acid-assisted attack of THF onto the epoxide to facilitate the terminal electrophile for the ylide. The authors observed diminished reactivity when acyclic  $\alpha,\beta$ -unsaturated carbonyls were used, and no products were reported. This work highlights how strained ring systems can unlock reactivity from even mild nucleophiles such as cyclic ethers in the context of multicomponent reactions.

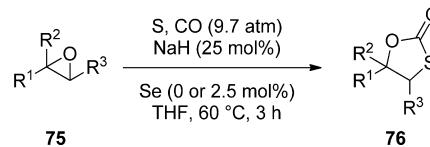
In addition to oxygen-based nucleophiles, sulfur- and carbon-based nucleophiles have also been employed in epoxide ring opening MCRs. Epoxides (**75**) underwent ring expansion to

**Scheme 16.** Coupling between Phosphonium Ylide **70** and Epoxide **72** Is Mediated by THF



1,3-oxathiolan-2-ones (**76**) by reaction with sulfur and carbon monoxide (Scheme 17).<sup>31</sup> Sodium hydride and high pressures

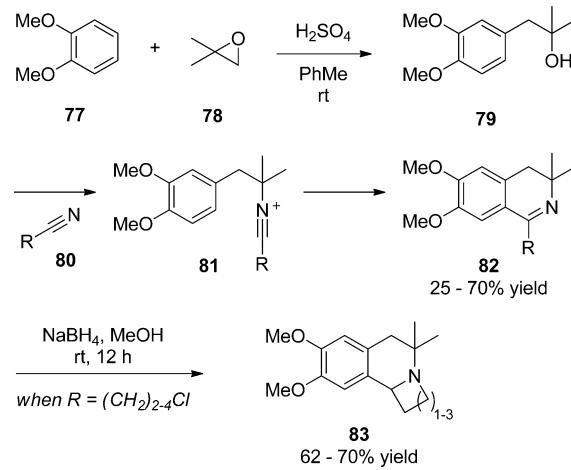
**Scheme 17.** Ring Expansion of Epoxides by Carbonylation and Sulfur Incorporation



of CO (9.7 atm) were required to induce the transformation. Reactivity was highly dependent on substitution of **75**, with terminal alkyl epoxides providing the best yields, in excess of 87%. Cis-disubstituted substrates underwent stereospecific conversion to *trans*-**76** (35–61% yield), while *trans*-**75** led to *cis*-**76**, in generally lower yields (0–16%). The presence of aromatic rings in substrates proved to be a challenge, and it was found that molecular selenium, present in catalytic quantities, significantly improved the yields of these products. For example, styrene oxide derived **76** ( $R^1 = Ph$ ;  $R^2$ ,  $R^3 = H$ ) was formed in 39% yield in the absence of Se and in 79% yield with the catalyst present. Molecular selenium readily forms carbonyl selenide with carbon monoxide under basic conditions, and the exchange reaction with elemental sulfur is rapid.<sup>32</sup> It is possible that selenium catalyzed the formation of carbonyl sulfide or that an acyl selenide underwent substitution with sulfur.

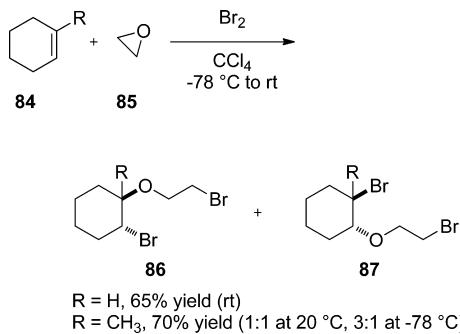
Electron-rich arenes (**77**) can be used under appropriate conditions for epoxide ring opening, leading to MCRs that produce valuable heterocycles. A multicomponent Ritter-type reaction has been applied to make substituted dihydroisoquinolines (**82**). The 3CR of **77**, isobutylene oxide (**78**), and a nitrile (**80**) was performed in a mixture of toluene and concentrated H<sub>2</sub>SO<sub>4</sub> to promote formation of intermediate **81** through an S<sub>N</sub>1 mechanism (Scheme 18).<sup>33</sup> After reduction with sodium borohydride, tetrahydroisoquinolines could be accessed. When  $\omega$ -chloro alkyl nitriles were used, the reduced amine underwent cyclization to give racemic fused products **83**. This work highlights the use of isobutylene epoxide as a cation surrogate.

**Scheme 18. Three-Component Ritter Reaction Using Isobutylene Oxide (78) To Access Dihydroisoquinolines (82) and a Variation To Produce Fused Tetrahydroisoquinolines 83**



Epoxide ring expansion can occur by participation of epoxide oxygen atoms in the opening of bromonium ions. While most examples of this synthetic strategy have relied on intramolecular epoxide ring expansion to cyclic ethers,<sup>34–37</sup> multicomponent reactions have also been reported. An early report of this MCR was the reaction of cyclohexenes (84), ethylene oxide (85), and bromine to produce 2-bromoethyl *trans*-2-bromocyclohexyl ethers (86 and 87,  $R = H$ , Scheme 19).<sup>38</sup> This example documents the reactivity of oxirane with bromonium ions in solution. Thiirane and methyloxirane did not produce the analogous products.

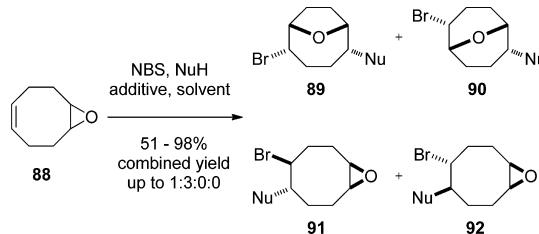
**Scheme 19. Three-Component Reaction of Cyclohexene, Ethylene Oxide and Bromine**



A second strategy for MCRs that employ epoxides for attack on bromonium ions is the introduction of an additional nucleophile to conduct the terminal ring opening, rather than bromide formed in situ. Since such ring-opening steps often occur by the stereospecific  $S_N2$  mechanism, stereochemical information is efficiently communicated to products. Braddock and co-workers developed this methodology using cyclooctadiene monooxide (88).<sup>39</sup> Treatment of 88 with *N*-bromosuccinimide (NBS) in the presence of acetic acid and tetramethylguanidine (TMG) led to a mixture of [4.2.1]-bicycloether (89), [3.3.1]bicycloether (90), as well as two additional epoxybromoacetates (91, 92) that result from direct attack of acetate on the bromonium ion. The observed products confirm ring-opening stereospecificity over the course of the

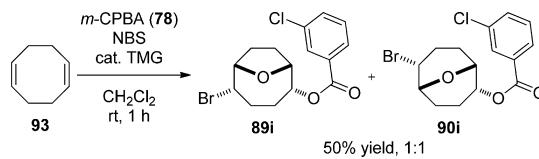
reaction. Other capable nucleophiles included carboxylates as well as chloride ion (derived from TMSCl or LiCl), alcohols, and water (Scheme 20). Reactions run in alcohol or aqueous

**Scheme 20. Three-Component Reaction of Epoxide 88 with NBS and Nucleophile<sup>a</sup>**



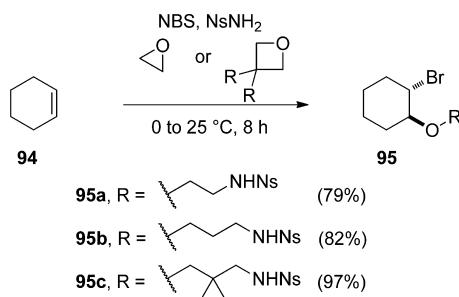
solvents were entirely selective for the bicycloether products (89, 90) over the epoxides (91, 92). This is particularly interesting given that 89 and 90 can only be formed if the bromonium ion occurs on the opposite face of the ring from the epoxide, whereas 91 and 92 can be formed regardless of which face the bromonium forms on. Remarkably, bromotetrafluorobenzoate epoxide 92d transformed on standing into products 89d, 90d, 91d (and 92d) in similar proportions to those observed from the reaction of 88 with NBS and 2,3,4,5-tetrafluorobenzoic acid (Scheme 20). This suggests not only that the bromonium ion intermediate is accessible from product 92d but also, on the basis of the formation of 91d, that electrophilic bromine can be released into the bulk medium and return to form a bromonium ion on the opposite face of the alkene. The authors further reported on a second three-component reaction that combines 1,5-cyclooctadiene (93), NBS, *m*-CPBA, and TMG to generate 89i and 90i, forming four stereocenters as a 1:1 mixture of two diastereomers (Scheme 21).

**Scheme 21. Diastereoselective Three-Component Reaction of 1,5-Cyclooctadiene, *m*-CPBA and NBS To Form 89i and 90i as the Sole Products**

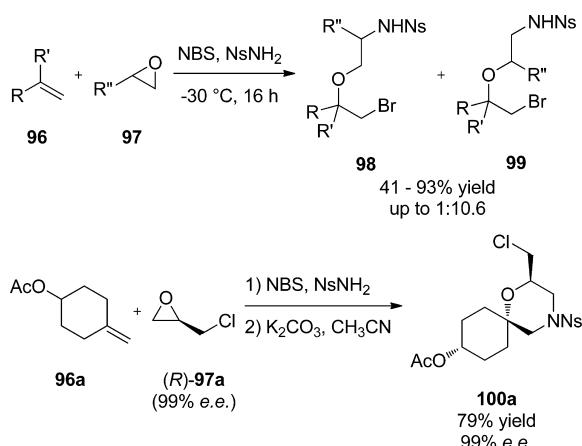


Nitrogen-based nucleophiles, such as nosylamide, have also been reported in a similar system to effect aminoalkylation of olefins (Scheme 22).<sup>40</sup> Epoxides and oxetanes underwent ring-opening when mixed with cyclic or terminal olefins, NBS, and  $NsNH_2$ . Epichlorohydrin provided the best yields and regioselectivity for the anti-Markovnikov products (99) (Scheme 23).<sup>41</sup> These products could be transformed into morpholine derivatives (100) by treatment with potassium carbonate. Furthermore, *meso*-olefin 96a was desymmetrized using enantiomerically enriched epichlorohydrin [(R)-97a] in a one-pot procedure to generate morpholine 100a. It is unclear whether this is a result of the acetyl group of 96a directing the bromonium ion to a single face of the olefin or if bromonium ion formation is reversible<sup>39</sup> and (R)-97a traps only a single

**Scheme 22. Aminoalkylation Using Cyclic Ether Mediated Opening of Bromonium Ions with Nosylamide**



**Scheme 23. Aminoalkylation of Olefins Leading to Morpholine Derivatives Using a 3CR of Olefins, Epoxides and NBS, Followed by Treatment with Potassium Carbonate<sup>a</sup>**



<sup>a</sup>Epichlorohydrin (97a) was the best epoxide in terms of yield (often >80%) and regioselectivity (99:98 often >6:1). Desymmetrization of *meso*-olefin 96a was accomplished with enantiomerically enriched 97a.

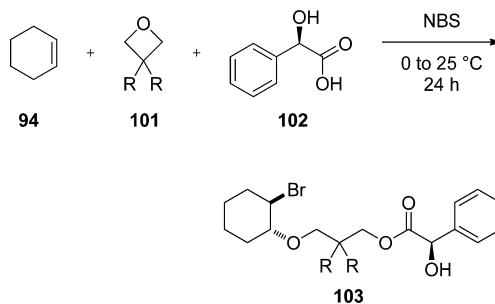
diastereomer of the intermediate. Regardless, this desymmetrization is a nice example of the synthetic utility of MCRs that involve stereospecific elementary steps.

### 2.5. Oxetane Openings

Compared to epoxides, oxetanes, four-membered ring cyclic ethers, are much less frequently employed as synthetic intermediates. This is likely due to the relative dearth of methods for their preparation, as well as their diminished reactivity in polar ring opening reactions. While four-membered rings possess similar strain energy to their three-membered congeners, the rate of ring opening is notably diminished for the larger ring sizes.<sup>42</sup>

External oxygen-based nucleophiles have been evaluated as terminal nucleophiles for oxetane ring-opening in two additional studies of bromoetherification (see section 2.4 and Scheme 22) of cyclohexene.<sup>43,44</sup> Among carboxylic acids, electron-rich and electron-neutral benzoic acids were inferior to electron-deficient pentafluorobenzoic acid, as well as glycolic acid, salicylic acid, and their derivatives (Scheme 24).<sup>43</sup> Presumably, the carboxylate is a favored reactive site for these *ortho*- or  $\alpha$ -hydroxy carboxylic acids because the hydroxyl groups are unlikely to be deprotonated. Still, masking the hydroxyl groups as methyl ethers led to diminished chemical yields (e.g., 87% for (R)-2-hydroxy-2-phenylacetic acid 102 compared to 60% for its methyl ether).

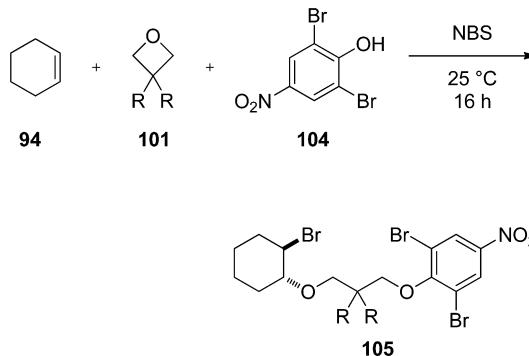
**Scheme 24. Four-Component Reaction of Cyclohexene with NBS, Oxetanes, and 2-Hydroxy-2-phenylacetic Acid (102)<sup>a</sup>**



<sup>a</sup>R = H (33% yield), CH<sub>3</sub> (57% yield).

Phenol and electron-deficient phenol derivatives provided similar reactivity, with 2,6-dibromo-4-nitrophenol (104) providing the highest chemical yield (96%) within this class of nucleophiles (Scheme 25).<sup>44</sup> While more electron-rich

**Scheme 25. Four-Component Reaction of Cyclohexene with NBS, Oxetanes, and 2,6-Dibromo-4-nitrophenol (104)<sup>a</sup>**

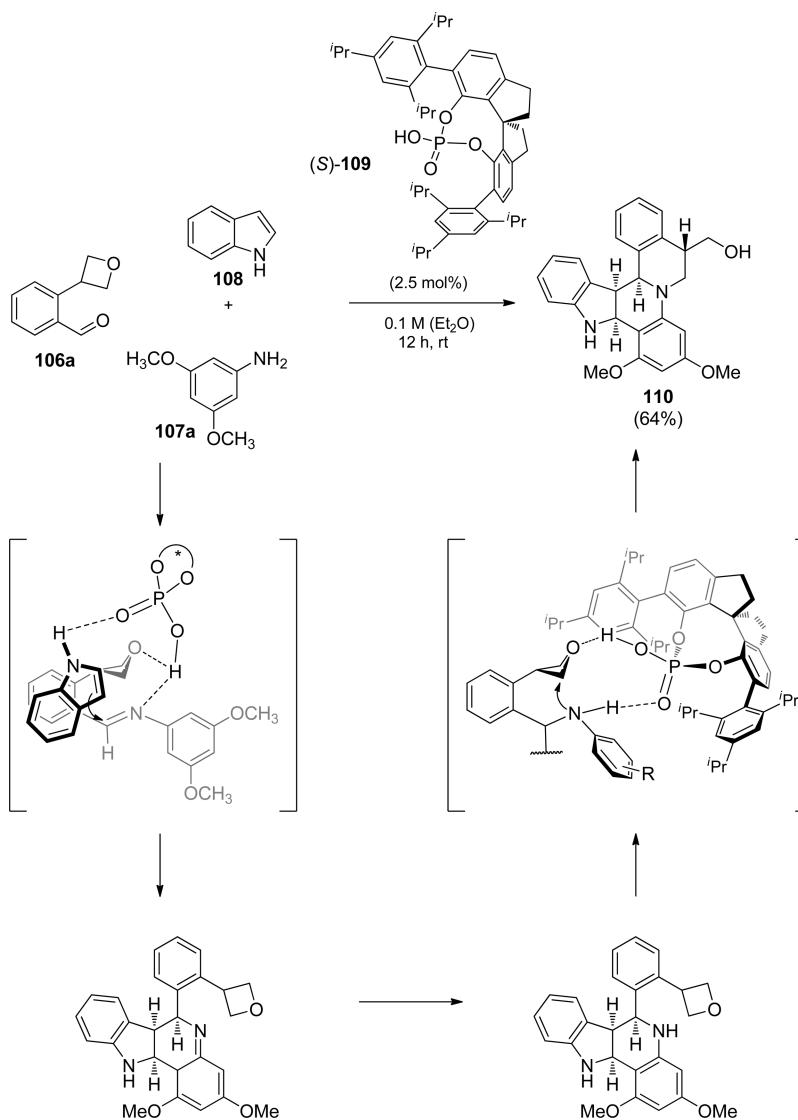


<sup>a</sup>R = H (78% yield), CH<sub>3</sub> (87% yield).

phenols were unreactive (e.g., 2,6-dibromo-4-methylphenol), extremely electron-deficient phenols led to low yields of products (e.g., pentafluorophenol, 18%). With cyclohexene and 104, the scope of cyclic ethers included oxetane and 3,3-dimethyloxetane, affording products 105 in good yields. In probing the mechanism, the authors hypothesized that the acid component of such reactions (i.e., NsNH<sub>2</sub>,  $\alpha$ -hydroxy acids, or phenols) is essential for activation of NBS to facilitate bromonium ion formation. Evidence was presented to suggest that 2,4,6-tribromo-4-nitro-2,5-cyclohexadienone is formed by treatment of 104 with NBS. While this compound could be the active brominating agent in this example, pentafluorophenol did not show similar reactivity to NBS. It is not yet known whether this compound is a viable intermediate to olefin bromination or subsequent reactions.

Sun and co-workers have explored the concept of amphoteric reactivity using oxetane aldehydes. Their design was driven by an interest in preparing challenging medium-sized rings through annulation with dipolarophiles. The authors demonstrated an efficient [6 + 2] cyclization with siloxy alkynes.<sup>45</sup> As a result, the first intermolecular synthesis of eight-membered lactones was demonstrated. Drawing on their initial discovery, Sun and co-workers later expanded the utility of oxetane aldehydes to multicomponent reactions.<sup>46</sup> A chiral phosphoric acid catalyst [(S)-109] was used in order to facilitate imine

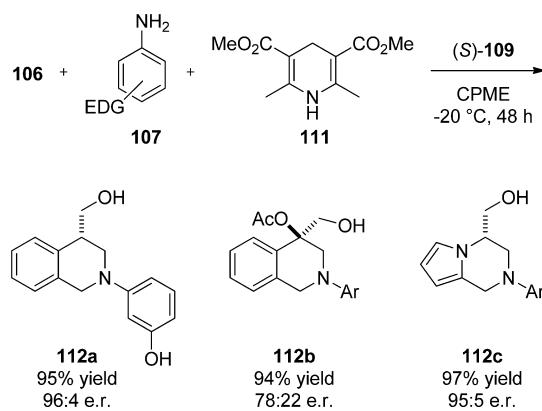
**Scheme 26. Multicomponent Reaction of Anilines, Indoles, and Oxetane Aldehydes Catalyzed by Chiral Phosphoric Acid (*S*)-109**



formation from an oxetane aldehyde (**106**) and to trigger a subsequent aza-Diels–Alder cycloaddition (Scheme 26). On its way to the aza-Diels–Alder product (**110**), the process involved intramolecular oxetane desymmetrization by the nitrogen nucleophile. The reaction displayed high levels of diastereo- and enantioselectivity and generated four new bonds and four new stereogenic centers in one pot from three achiral compounds. In the presence of (*S*)-**109**, a range of complex polycyclic alkaloid-type molecules with anticancer activity were rapidly assembled. Thus, the oxetane ring was shown to be a superb directing group that played a crucial role in achieving both high yields and high enantioselectivities in an amphoteric molecule-driven multicomponent reaction.

The same Brønsted acid catalyst was employed in oxetane desymmetrization to prepare C4-chiral tetrahydroisoquinolines.<sup>47</sup> In this case, substrates **106** were reacted with electron-rich anilines (**107**) and a Hantzsch ester (**111**) in the presence of **109** to give high yields of **112** with improved enantioselectivity, except for when forming quaternary centers (Scheme 27). Mechanistically, it is not clear whether reductive amination precedes oxetane ring opening, and it is likely that a

**Scheme 27. Preparation of 1,2,3,4-Tetrahydroquinolines (**112**), Using a 3CR of Oxetane Aldehydes (**106**), Anilines (**107**), and a Hantzsch Ester (**111**) Reducing Agent<sup>a</sup>**



<sup>a</sup>Ar = 3,4,5-trimethoxyphenyl; CPME, cyclopentyl methyl ether.

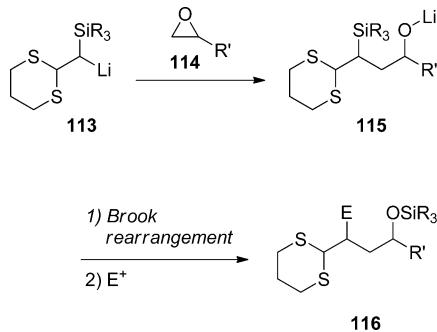
number of pathways are operative and are substrate-dependent. As the authors note, asymmetric methods leading to chiral

heterocycles could be appealing for natural product synthesis and drug discovery.

## 2.6. Anion-Relay Chemistry

Anion relay chemistry (ARC) employs the 1,4-Brook rearrangement to control the reactivity of multicomponent couplings with small heterocyclic substrates. Most often, ARC relies on nucleophilic epoxide ring opening to initiate an intramolecular silyl migration (Brook rearrangement<sup>48</sup>) that “relays” the anion to a carbon atom for further bond formation, eventually with a terminal electrophile. Lithium 1,3-dithianes **113** (Scheme 28)

**Scheme 28. General Mechanistic Representation of Anion-Relay Chemistry (ARC)**

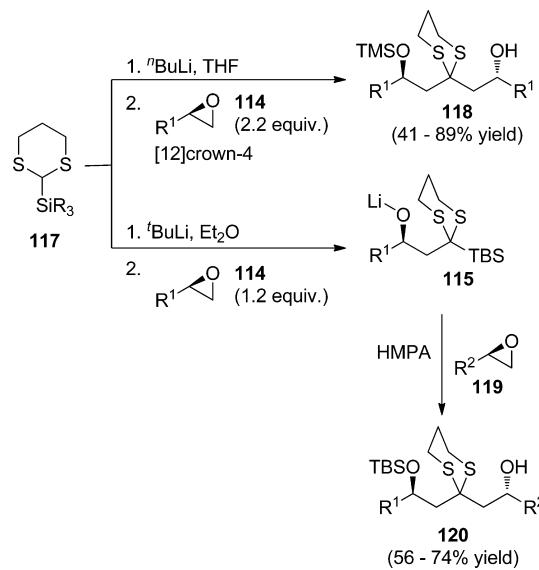


are attractive linchpin nucleophiles for this purpose and for umpolung-based synthesis in general, as they provide a stabilized carbanion necessary to initiate the ARC cascade and supply a masked carbonyl group for downstream transformations.<sup>49</sup> Intermediate **115** is afforded by the initial reaction of **113** with an epoxide **114** and undergoes a 1,4-Brook rearrangement to reestablish the carbanion, which is then quenched by a terminal electrophile.

Tietze and co-workers first demonstrated the use of the 2-(trialkylsilyl)-1,3-dithiane **117** linchpins in ARC for the formation of monosilylated 1,5-diols (Scheme 29).<sup>50</sup> The original protocol used <sup>7</sup>BuLi in THF for lithiation, conditions which were not suitable for asymmetric synthesis. Smith and co-workers resorted to <sup>7</sup>BuLi in THF/HMPA (hexamethylphosphoramide) to generate nucleophiles from dithianes with more hindered silyl groups, which proved to be more resilient over the course of the 3CR and useful in natural product synthesis.<sup>51</sup> Shinokubo et al. demonstrated that the 1,3- and 1,4-Brook rearrangements could be suppressed under similar conditions by excluding HMPA.<sup>52</sup> Accordingly, Smith and Boldi found that the reaction could be halted after the first alkylation event (intermediate **115**) in the absence of HMPA, or it could be combined with a second epoxide and HMPA to induce a solvent-controlled Brook rearrangement, yielding unsymmetrical alkylated products **120**.<sup>53</sup> Through precise understanding of its mechanistic underpinnings (i.e., the requirement of HMPA to facilitate the Brook rearrangement), an intriguing MCR was harnessed to develop a more useful one-pot methodology. The authors further showcased this method with an MCR using epichlorohydrin **121** to yield building blocks for 1,3-polyol natural products **122** (Scheme 30).

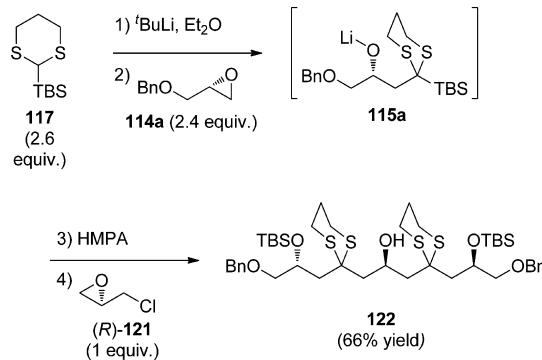
In an effort to expand upon the diversity of products accessible through ARC, Smith and co-workers investigated the use of vinyl epihalohydrins<sup>54</sup> in these reactions.<sup>55</sup> Vinyl epoxides can undergo either S<sub>N</sub>2 or S<sub>N</sub>2' ring opening with nucleophiles. Sterically hindered nucleophiles lead to increased

**Scheme 29. Preparation of Monosilylated 1,5-Diols by a 3CR<sup>a</sup>**



<sup>a</sup>The solvent-controlled Brook rearrangement enables the synthesis of unsymmetrical alkylated products via the lithiated dithiane linchpins.

**Scheme 30. Synthesis of Roflomycoin Backbone Fragment Using Multicomponent Anion-Relay Chemistry with Epichlorohydrin**

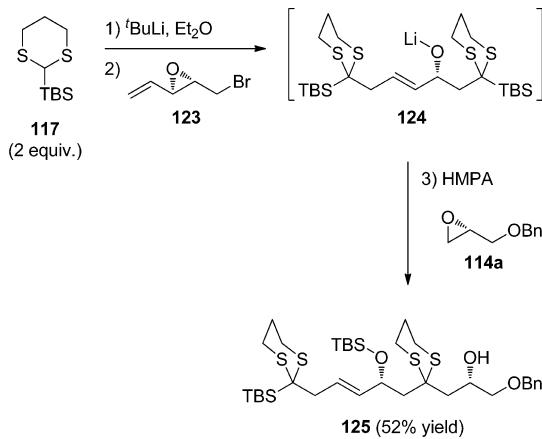


selectivity for the S<sub>N</sub>2' process. Importantly, the products of S<sub>N</sub>2' ring opening of vinyl epoxides with **117** did not undergo Brook rearrangement and, when vinyl epibromohydrin **123** was used, could then undergo S<sub>N</sub>2 addition with a second equivalent of **117**, constituting a 3CR (Scheme 31). The intermediates **124** were then elaborated by addition of HMPA (which facilitates Brook rearrangement) and a terminal epoxide **114a** to give **125**.

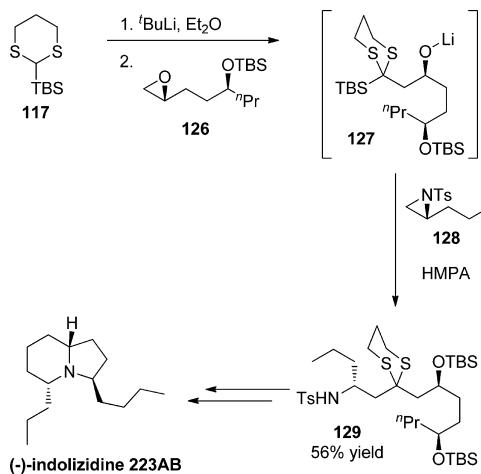
Aziridines have also been employed in ARC but only as the terminal electrophile. In their efforts toward the total synthesis of (−)-indolizidine 223AB, Smith and Kim used ARC with an epoxide **126** as the first strained ring electrophile, followed by a protected aziridine **128** (Scheme 32).<sup>56</sup> In this example, addition of the two electrophiles was separated by 5 h with intervening temperature changes, likely not meeting the standards of true multicomponent reactions. Still, ARC was used to directly provide the scaffold **129** for formation of the indolizidine ring in a one-pot transformation, which certainly demonstrates the utility of this method.

Aziridines have also been deployed as terminal electrophiles in the diversity-oriented synthesis of 2,4,6-trisubstituted

**Scheme 31.** Application of Vinyl Epibromohydrin 123 in a 3CR Anion-Relay Chemistry Reaction Takes Advantage of Selectivity for the 1,4-Brook Rearrangement

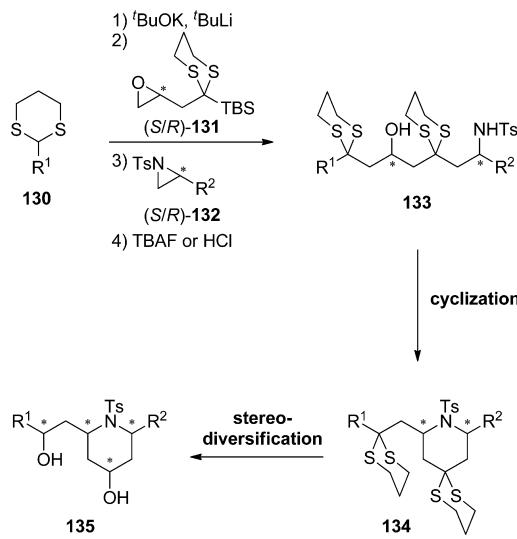


**Scheme 32.** Approach to Indolizidine 223AB Using Anion-Relay Chemistry with Sequential Epoxide and Aziridine Ring Opening



piperidines by ARC.<sup>57</sup> In this example, the incoming nucleophile 130 does not contain a silyl group and, instead, its primary role is to propagate the reactive anion to a distal site.<sup>58</sup> The backbone was formed by a three-component coupling of dithiane 130, epoxide 131, and aziridine 132 (Scheme 33). In contrast to the approach to indolizidine (see above), both electrophiles were added under the same reaction conditions and with a shorter interval (30 min). Still, it is not clear whether the first epoxide ring opening is compatible with the presence of all components of this reaction. Piperidines 135 were formed by intramolecular S<sub>N</sub>2 displacement of a hydroxyl group. Product diversification was accomplished by selective deprotection of dithianes to ketones and then reduction to alcohols 135. While stereoselective reduction of ketones was not achievable in all cases, this was in part desirable for the diversity-oriented synthesis approach to the library, as purification of mixtures of diastereomers was attainable. Using this strategy and starting with a mixture of enantiomers of both 131 and 132, all 16 possible stereoisomers of 135 were prepared and isolated.

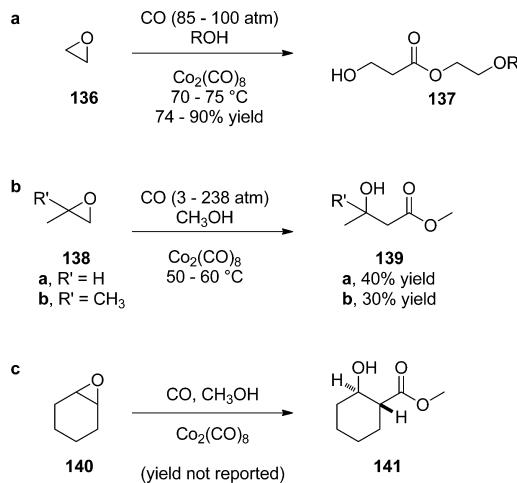
**Scheme 33.** Diversity-Oriented Synthesis for All 16 Possible Diastereomers of the 2,4,6-Trisubstituted Piperidines 135



## 2.7. Metal-Catalyzed Carbonylations

Multicomponent reactions based on the cobalt-catalyzed carbonylation of epoxides can be traced as far back as the late 1950s. Building on previous research into hydroformylation of olefins,<sup>59</sup> ethylene oxide (136) can be converted into ethylene glycol hydracrylates (137) using carbon monoxide and water or alcohols in the presence of cobalt carbonyl complexes (Scheme 34a).<sup>60</sup> When unsymmetrical epoxides (138) were

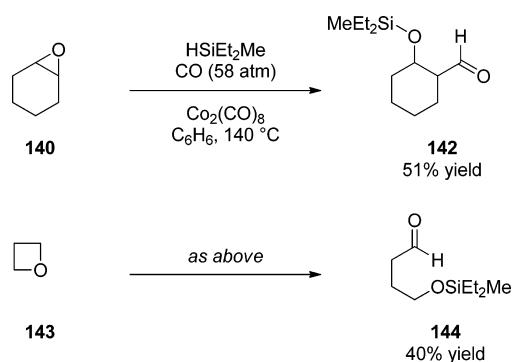
**Scheme 34.** Carbonylation of Small Epoxides Using Dicobalt Octacarbonyl



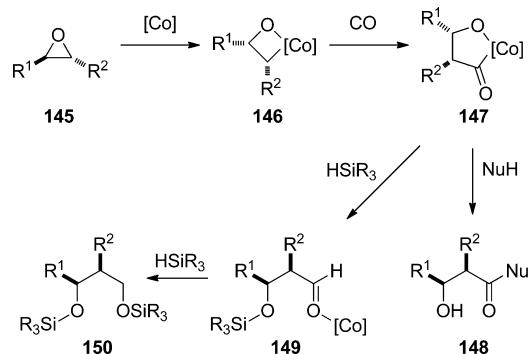
subjected to carbonylation conditions in methanol, methyl β-hydroxybutyrates (139) were the major reaction products (Scheme 34b).<sup>61,62</sup> Notably, the branched ester was not observed under these conditions. When cyclohexene oxide 140 was subjected to hydroformylation conditions, the product was solely the trans-isomer (141, Scheme 34c).<sup>62</sup> This strongly suggests an ionic mechanism wherein a cobalt complex opens the epoxide by nucleophilic attack with inversion of stereochemistry (Scheme 36).

The strategy of adapting olefin hydroformylation reactions<sup>63</sup> to cyclic ethers was fruitful in the synthesis of silyl-protected hydroxyaldehydes.<sup>64</sup> Upon subjecting cyclic ethers to hydro-

**Scheme 35. Reaction of Some Cyclic Ethers with Carbon Monoxide and an Alkylsilane**



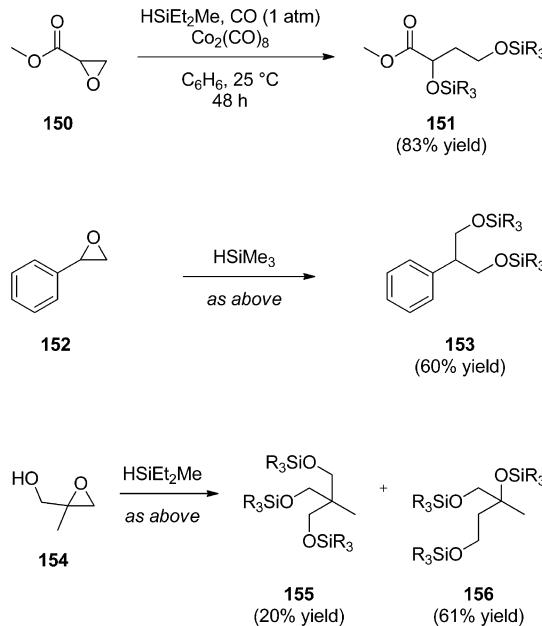
**Scheme 36. Proposed Monometallic Mechanism for Carbonylation of Epoxides with Addition of Nucleophile (NuH) or followed by Hydrosilylation**



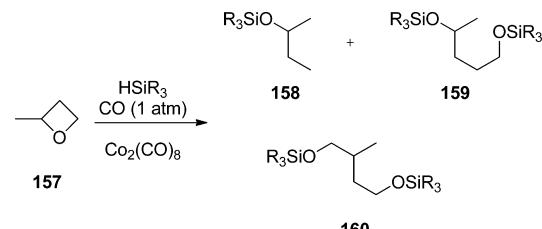
formylation conditions in benzene and with added silane present, products of epoxide, oxetane, and tetrahydrofuran ring-opening hydroformylation were isolated in useful yields (Scheme 35). Under modified conditions of lower temperature and increased quantities of silane, analogous 1,3-diol disilyl ethers were isolated from the reactions using epoxides (Scheme 37).<sup>65,66</sup> Again, high linear regioselectivity and trans-stereo-specificity were observed. Exceptional cases included styrene oxide (152), which produced the branched isomer (153) due to stabilization of the benzyl cation. Unsymmetrical 1,2-disubstituted epoxides reacted with low regioselectivity, except in cases with strong electronic bias. Geminal disubstituted epoxides such as 154 could undergo silyloxymethylation to form all-carbon quaternary centers (155), though only as minor components of the product mixtures. To form this product, carbonylation occurs at the more sterically congested site, in contrast to the other reactions we have discussed.

While epoxides and tetrahydrofurans<sup>67</sup> were good substrates for reductive carbonylation, oxetanes proved to be the most reactive cyclic ethers surveyed.<sup>66</sup> A major side reaction was premature reduction (prior to CO insertion) to generate simple silyl ethers such as 158.<sup>68</sup> Product distribution was highly solvent-dependent: reactions conducted in dichloromethane favored product 158, while reactions conducted in *n*-hexane underwent carbonylation to generate primarily 1,4-diol disilyl ethers (159, Table 1). In a related methodology, lactones, including  $\beta$ -butyrolactone (161), could be converted to silyl enol ethers under cobalt-catalyzed carbonylation conditions in the presence of diethylmethylsilane and pyridine (Scheme 38).<sup>69</sup>

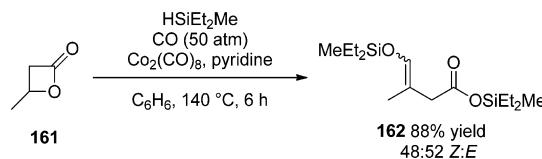
**Scheme 37. Reductive Silyloxymethylation of Epoxides**



**Table 1. Selectivity of Substituted Oxetane under Reductive Silyloxymethylation Conditions**



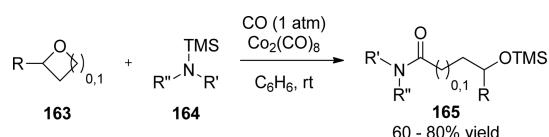
**Scheme 38. Synthesis of Silyl Enol Ether 161 from  $\beta$ -Butyrolactone (162)**



$\beta$ - And  $\gamma$ -silyloxyamides (165) have been prepared using cobalt catalysis for carbonylation in the presence of silanamines (164).<sup>70</sup> At room temperature and ambient pressure the reactions proceeded with excellent regioselectivity and good yields (Scheme 39).<sup>71</sup> Significantly, no carbonylation products were formed when the nonsilylated amines were used in place of 164. This suggests that the silyl groups are required to facilitate epoxide ring-opening in the absence of an additional Lewis acid. Primary or secondary silanamines participated in the reaction, though the more hindered TBS-protected benzylamine and *N*-silylanilines were unreactive.

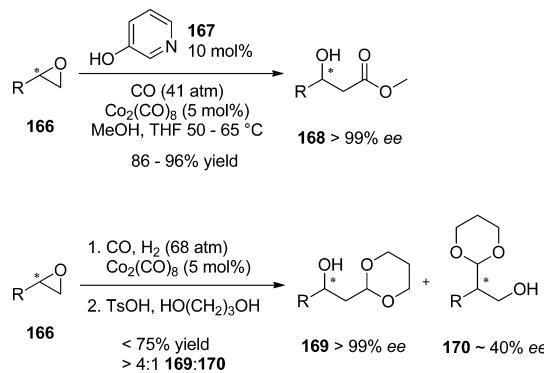
Several improvements to cobalt-catalyzed carbonylation MCRs have been reported. Pyridines had been employed

**Scheme 39.** Ring-Opening Carbonylation of Cyclic Ethers Using Silanamines 164



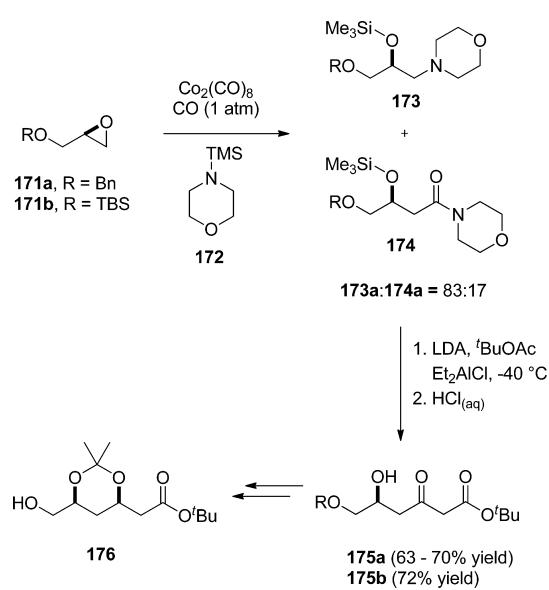
previously to generate the active cobalt catalyst,<sup>66,69</sup> and the addition of 3-hydroxypyridine (167) was found to increase the rate and selectivity of carbonylation reactions.<sup>72</sup> Following efficient hydrolytic kinetic resolution of epoxides (166),<sup>73,74</sup> enantiomerically pure  $\beta$ -hydroxy esters (168) and  $\beta$ -hydroxy acetals (169) were prepared using related methodologies (Scheme 40).<sup>75</sup>

**Scheme 40.** Preparation of Enantiopure  $\beta$ -Hydroxy Acetals (169) and  $\beta$ -Hydroxy Esters (170) Using Cobalt-Catalyzed Carbonylation of Epoxides



Enantiomerically enriched epoxides (171) were also applied with *N*-(trimethylsilyl)morpholine (172) to prepare  $\beta$ -silyloxy morpholine amides (174) with no observed racemization (Scheme 41).<sup>76</sup> With terminal epoxides, the carbonylations

**Scheme 41.** Preparation of  $\beta$ -Silyloxy Morpholine Amides (174), En Route to Valuable Chiral Building Blocks 175 and 176



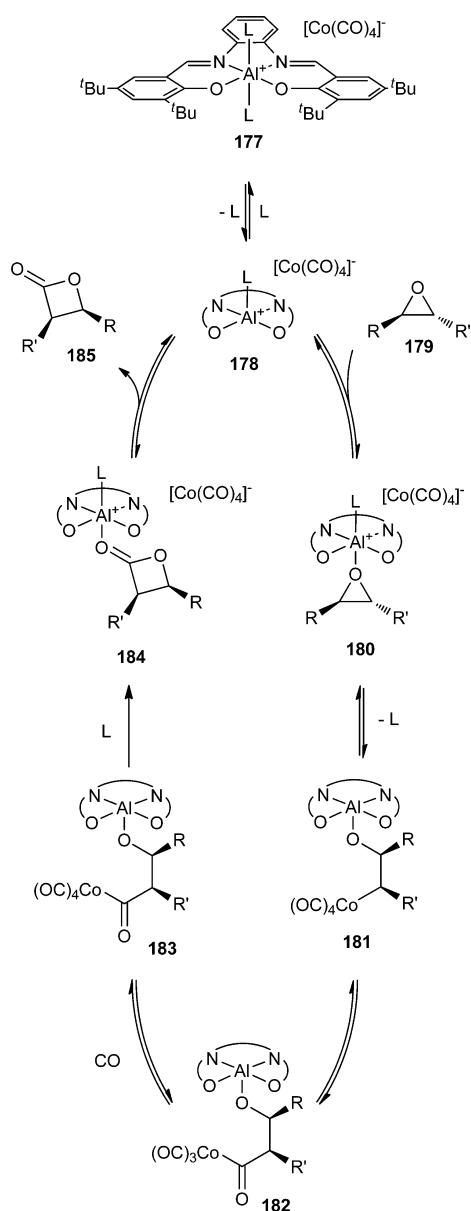
were completely regioselective in the absence of a pyridine additive. Trace amounts of morpholine or water, however, led to significant (8–20%) amounts of tertiary amine products (173) derived from epoxide ring opening, which could not be suppressed. The utility of this methodology was demonstrated by the synthesis of  $\beta$ -keto ester 175, a chiral building block for HMG-CoA reductase inhibitors (Scheme 41).

Denmark and Ahmad later reported that carbonylative ring opening of propylene oxide to prepare methyl  $\beta$ -hydroxybutyrate was efficient at room temperature under 1 atm of CO and in the absence of a pyridine cocatalyst such as 167.<sup>77</sup> These conditions were general for several terminal aliphatic epoxides, including ones containing ether functionality, but gave low conversion for substrates containing carbonyl groups or acetals as well as cyclohexene oxide (140).

Carbonylation of epoxides for the preparation of  $\beta$ -lactones has been the subject of substantial research over the past 20 years.<sup>72</sup> Coates and co-workers developed bimetallic catalysts incorporating cobalt carbonyl compounds and Lewis acids coordinated by porphyrin or salen-based scaffolds (e.g., 177, Scheme 42), including catalysts capable of scalable epoxide carbonylation at ambient temperature and pressure.<sup>78–81</sup> During the course of their research, Coates and co-workers closely investigated the mechanism of these transformations and found the resting state of one such catalyst to be a ( $\beta$ -metalloxy)acylcobalt species 183, with Lewis base coordination necessary for ring closure and  $\beta$ -lactone release.<sup>82</sup> This observation allowed intermediate 183 to be intercepted using electrophiles, such as isocyanates. In the event, by employing less-coordinating solvents such as 1,2-difluorobenzene (in which formation of  $\beta$ -lactone product 185 is slow), 1,3-oxazine-2,4-dione 188 could be detected as a minor (<17%) component of the product mixture.<sup>82</sup> The authors later optimized the reaction conditions to achieve high selectivity for 188 using hexanes as a reaction medium and a relatively high pressure of CO at room temperature (Scheme 43).<sup>83</sup> Electron-deficient isocyanates were superior substrates for this reaction, often failing to produce detectable levels of  $\beta$ -lactone, while ethyl isocyanate, for example, produced 185 and 188 in low amounts. It is possible that these latter substrates are not only less reactive toward the multicomponent process but can also effectively catalyze  $\beta$ -lactone formation (see Scheme 42). Sterically hindered epoxides produced low conversions to 188, but in general the nature of the epoxide did not compromise selectivity for the multicomponent process, which proceeded well in the presence of esters, ethers, olefins, and epichlorohydrin. This methodology also struggled with certain disubstituted epoxides, notably *trans*-2,3-epoxybutane—which produces *cis*-188 (R, R' = CH<sub>3</sub>, R'' = 4-nitrophenyl)—and *cis*-cyclooctene oxide. Products 188 are formed stereospecifically, with retention of configuration at C-6 and inversion at C-5.

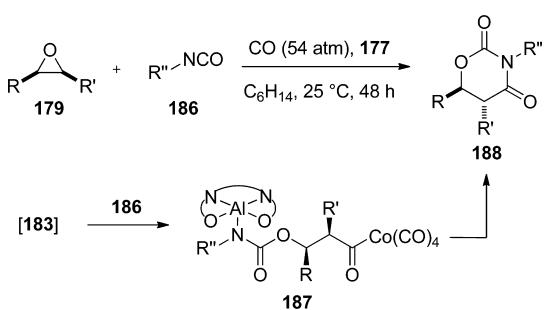
Haloxydrin esters can be prepared from acyl halides and epoxides; however, the regioselectivity is poor (53:47 branched:linear). A rhodium-catalyzed three-component coupling of alkyl bromides or iodides (189), carbon monoxide, and epoxides (190) was found to selectively (>92:8) generate branched haloxydrin ester 191 in the presence of a pyridine additive (Scheme 44).<sup>84</sup> Modest to good yields were obtained with a variety of terminal epoxides and activated organic halides at high pressure (59 atm). Similar to the cobalt-catalyzed carbonylations, cyclohexene oxide formed *trans*-193 (Figure 2). In contrast to the rhodium catalyst, cobalt- and manganese-

**Scheme 42.** Proposed Mechanistic Cycle for 177-Catalyzed Synthesis of  $\beta$ -Lactones 185<sup>a</sup>



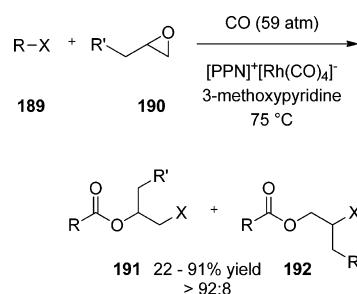
<sup>a</sup>L = Lewis base (i.e., solvent, epoxide, lactone).

**Scheme 43.** Synthesis of 1,3-Oxazine-2,4-diones 188 from 3CR Catalyzed by 177<sup>a</sup>



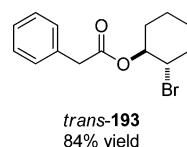
<sup>a</sup>Isocyanate 186 undergoes insertion into intermediate 183 (see Scheme 42) followed by cyclization with the acyl cobalt functional group.

**Scheme 44.** Three-Component Synthesis of Branched Halohydrin Esters (191)<sup>a</sup>



<sup>a</sup>R = benzyl, methyl, allyl,  $-\text{CH}_2\text{CO}_2\text{CH}_3$ ; X = Br, I; R' = H, Br, OBN; [PPN]<sup>+</sup> = bis(triphenylphosphoranylidene)iminium.

based analogues were of limited reactivity and without selectivity.



**Figure 2.** Product of rhodium-catalyzed 3CR of cyclohexene oxide, benzyl bromide, and carbon monoxide.

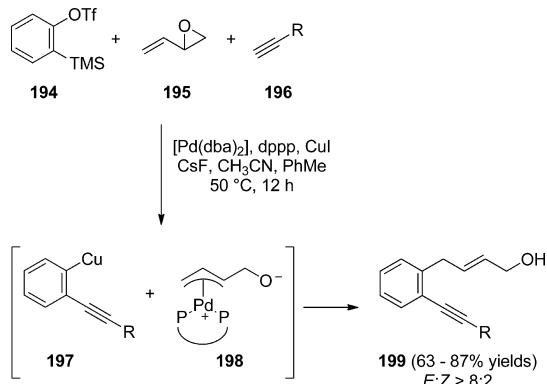
Metal-catalyzed carbonylative ring opening of epoxides and oxetanes represents an underappreciated strategy for the preparation of cyclic and acyclic chiral esters. Perhaps due to the requirements of high pressures and limited functional group tolerance, these methods have seldom been applied for synthesis of complex molecules. Still, the strengths and utility of these methods have been well-demonstrated in bringing together simple reactants in MCRs to generate valuable chiral building blocks.

## 2.8. Reactions Involving Benzyne Intermediates

Similar to isocyanides, arynes are amphoteric molecules that form the basis of several multicomponent reactions.<sup>85-88</sup> In the presence of compatible nucleophiles, arynes lead to anions that can react with electrophiles such as carbonyl compounds and sulfonylimines. Benzyne have been a fruitful platform for development of MCRs thanks to their ability to engage both electrophiles and nucleophiles in a single transformation. In 2009, Cheng and co-workers reported a three-component reaction with benzyne precursor (194), vinyl epoxides (195), and terminal alkynes (196).<sup>89</sup> The reaction was initiated by the addition of CsF to 194 to form benzyne, which, in the presence of Pd(0), reacted with the terminal alkyne and an epoxide to form two different C–C bonds (Scheme 45). The addition of a Cu(I) cocatalyst was necessary to obtain high linear-to-branched regioselectivity [ $\sim$ 3:2 with Pd(0) alone]. The authors ascribe this to the alkynylcupration of benzyne to afford the arylcuprate intermediate (197), which attacks the unhindered carbon of the Pd  $\pi$ -allyl complex (198). In this case, cooperative catalysis brought about regioselectivity with allylic epoxides and expands on this class of 3CRs to include small rings.<sup>90</sup>

Pineschi and co-workers expanded the 3CR with benzyne to include aziridine substrates (200).<sup>91</sup> In contrast to vinyl epoxides, a copper catalyst alone was sufficient for regioselective incorporation of C-vinylaziridines into the MCR

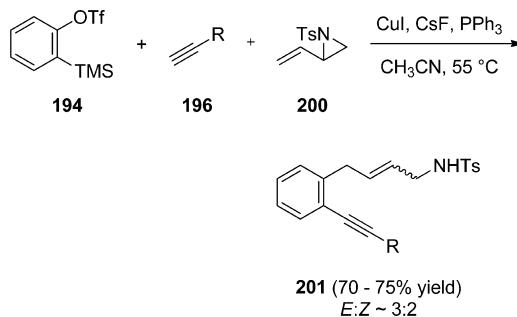
**Scheme 45. Pd(0)- and Cu(I)-Catalyzed 3CR of Vinyl Epoxide, Benzyne, and Terminal Alkyne To Produce *o*-Alkynylallylarenes (199)<sup>a</sup>**



<sup>a</sup>dppp, 1,3-bis(diphenylphosphino)propane.

(Scheme 46). The S<sub>N</sub>2' attack is favorable such that the main byproduct, hydroalkynylation (seen with epoxides in the

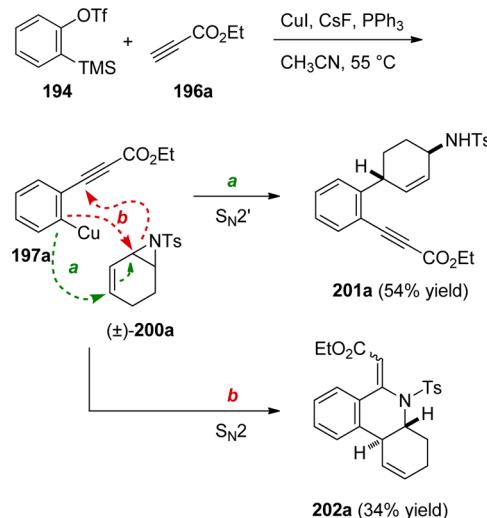
**Scheme 46. Cu(I)-Catalyzed 3CR of C-Vinylaziridine, Benzyne, and Terminal Alkyne To Produce Allyl Amines 201**



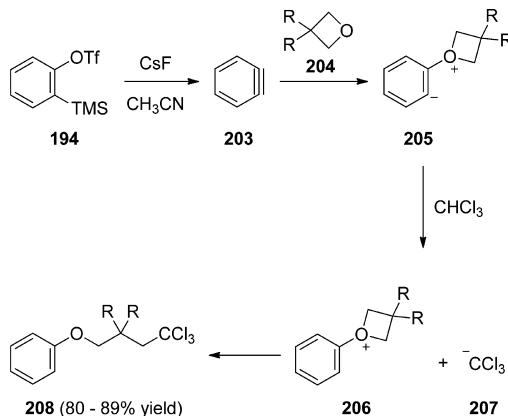
absence of palladium catalysis), was only observed in low amounts (<10%). The arylation of cyclohexadiene imine (200a), however, led also to products of direct aziridine ring-opening, followed by annulation with a conjugated alkyne (Scheme 47).

Besides the conjugate additions discussed above, benzenes can also be coupled directly to strained rings. Okuma and co-workers described the three-component reaction of aryne precursors (194), cyclic ethers, and chloroform.<sup>92</sup> The MCR proceeds by attack of the cyclic ether onto 203, followed by hydrogen abstraction from chloroform by betaine intermediate 205 and finally ring-opening nucleophilic attack by the carbanion 207 on the cyclic ether (Scheme 48). In a competition experiment with equimolar amounts of oxetane (204a, R = CH<sub>3</sub>) and THF, products derived from 204a were observed in a >4:1 ratio compared to those derived from THF, demonstrating the greater reactivity of the four-membered ring. Epoxides were found to be much less reactive than oxetanes in this context, to the point where homocoupling of benzenes was observed (211, Scheme 49a). The optimized reaction conditions for epoxides succeeded by limiting the rate of aryne formation from 194 (CsF has low solubility in the reaction solvent, acetonitrile), thereby slowing the undesired homocoupling. From epoxides, the authors were able to obtain

**Scheme 47. MCR with Domino C–N Bond Formation To Yield a Three-Ring Nitrogen-Containing System**

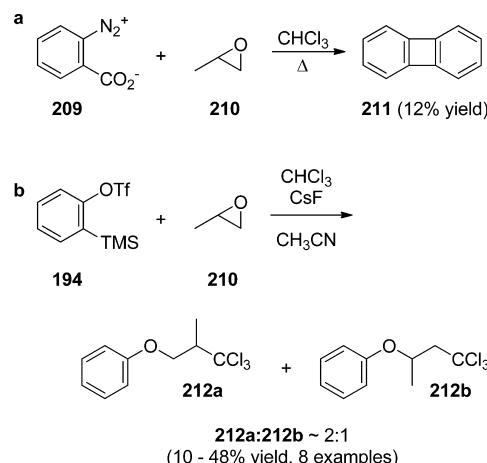


**Scheme 48. Synthesis of Trichloroalkyl Phenyl Ethers by MCR of Benzyne, Oxetanes, and Chloroform<sup>a</sup>**



<sup>a</sup>R = H, CH<sub>3</sub>.

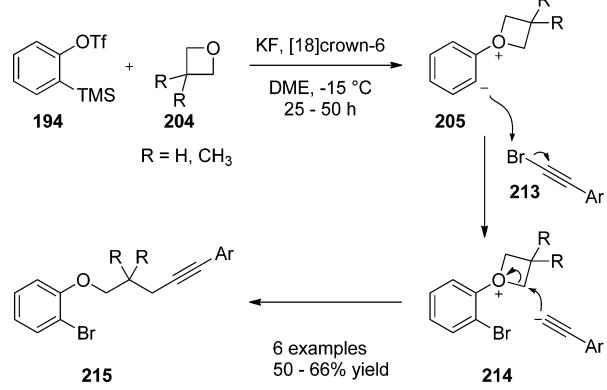
**Scheme 49. Epoxides Are Less Reactive Toward Benzyne than Oxetanes, and Successful Reaction Conditions Require a Low Concentration of Benzyne To Prevent Cycloladduct Products (211)**



phenyl ethers (**212a/b**) in 10–48% yields as mixtures of isomers (Scheme 49b).

Yoshida and co-workers explored the reaction of arynes with oxetanes (**204**) and alkynyl bromides **213** to give 2-bromoaryl ethers **215** in yields ranging from 50 to 66%.<sup>93</sup> Mechanistically, the authors proposed that the cyclic ethers (THF was also an eligible substrate) react with the aryne to form a 1,3-zwitterion (**205**), which inserts into the C(sp)–Br bond in a stepwise fashion with cleavage of the cyclic ether (Scheme 50). The

**Scheme 50. Proposed Mechanism for Three-Component Coupling of Aryne (generated from precursor **194**), Oxetane (**204**), and Alkynyl Bromide (**213**)**



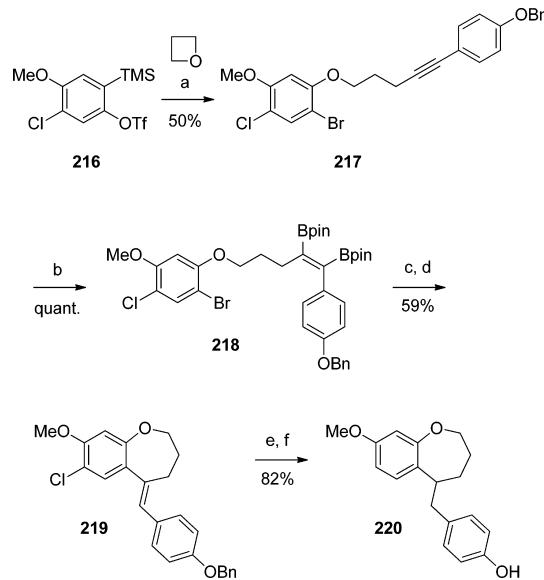
utility of this reaction was demonstrated in the synthesis of a benzo[*b*]oxepine-based nonsteroidal estrogen (**220**, Scheme 51). A regioselective 3CR using aryne precursor **216** was followed by diborylation of **217** and intramolecular Suzuki–Miyaura coupling to form the benzo[*b*]oxepine core, which could be elaborated to the target in three further steps. The reactivity dependence of cyclic ethers on ring size is nicely demonstrated in this example (tetrahydropyran was unreactive, while epoxides led to complex mixtures), as well as the enabling properties of bireactive functional groups, such as arynes and small cyclic ethers.

A 3CR of benzynes with small-ring nitrogen heterocycles (**221**) and acetonitrile has been reported to give  $\gamma$ - or  $\delta$ -aminonitriles (**224**, Scheme 52).<sup>94</sup> *N*-Alkyl-C-vinyl- or -arylaaziridines were proposed to attack the benzynes, leading to aziridinium intermediates. The resulting aryl anion would then abstract a proton from acetonitrile, and nucleophilic ring opening to generate the products would proceed. Carbon–carbon bond formation always occurred at an allylic or benzylic site, and enantiomerically pure *N*-(phenylethyl)aziridine substrates afforded the corresponding products with >95:5 dr. A single example of an azetidine ring opening represents this additional class of products (**224c**, Figure 3).

## 2.9. Azide–Alkyne Cycloadditions

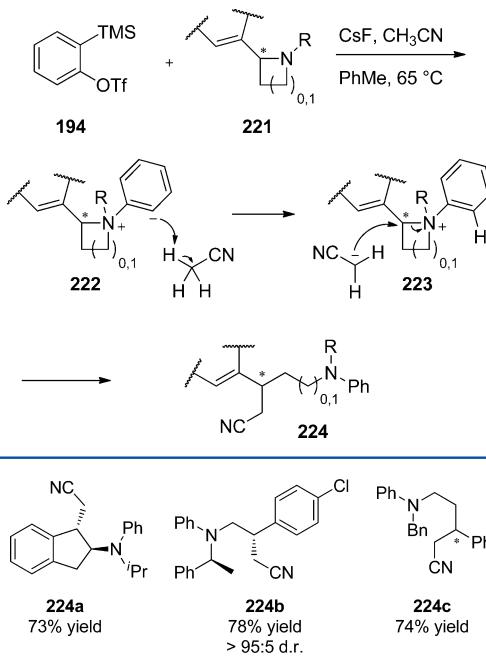
Copper-catalyzed cycloadditions of alkynes (**225**) and sulfonyl azides (**226**) (CuAAC) form triazoles (**227**) that can undergo elimination of nitrogen with heating to release *N*-sulfonyl ketenimines (**228**) (Scheme 53). Cui and co-workers showed that **228**, which they had previously used for the synthesis of iminocoumarins,<sup>95</sup> could be intercepted with aziridine ketones (**230**), ultimately leading to ring expansion products (**233**).<sup>96</sup> In the proposed mechanism, the aziridine attacks **228**, which is derived from sulfonyl azide and alkyne, and the resulting zwitterion undergoes intramolecular condensation to form five-

**Scheme 51. Application of Aryne–Oxetane–Alkynyl Bromide Coupling to Synthesis of a Target Compound (**220**)<sup>a</sup>**



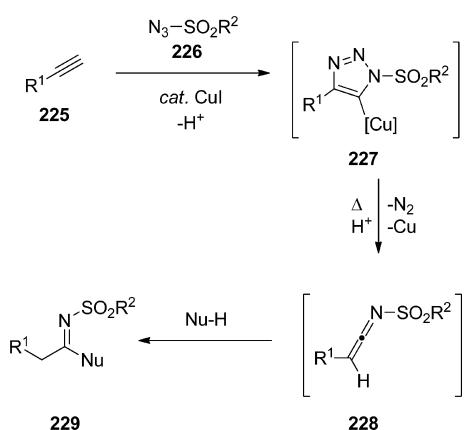
<sup>a</sup>Reagents and conditions: (a) **216** (2 equiv), oxetane (1 equiv), 1-(benzyloxy)-4-(bromoethynyl)benzene (2 equiv), KF (4 equiv), [18]crown-6 (4 equiv), DME, -15 °C, 27 h. (b) B<sub>2</sub>(pin)<sub>2</sub> (1.1 equiv), [Pt(PPh<sub>3</sub>)<sub>4</sub>], DMF, 80 °C, 22 h. (c) Cs<sub>2</sub>CO<sub>3</sub> (1.2 equiv), [Pd(PBu<sub>3</sub>)<sub>2</sub>], H<sub>2</sub>O (33 equiv), DME, 80 °C, 24 h. (d) Cs<sub>2</sub>CO<sub>3</sub> (1.2 equiv), H<sub>2</sub>O (33 equiv), DME, 80 °C, 24 h. (e) H<sub>2</sub> (4 atm), 10% Pd/C, MeOH, rt, 48 h. (f) Na (14 equiv), <sup>3</sup>BuOH (5 equiv), THF, 70 °C, 65 h.

**Scheme 52. Synthesis of  $\gamma$ - and  $\delta$ -Aminonitriles (**224**) by a 3CR of Aziridines or Azetidines (**221**), Benzyne Precursor **194**, and Acetonitrile**

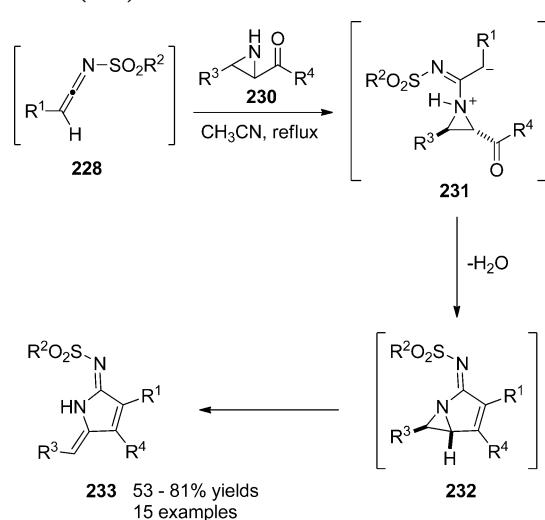


**Figure 3. Products of a 3CR of aziridines or azetidines (**221**) with benzyne precursor **194** and acetonitrile are  $\gamma$ - and  $\delta$ -aminonitriles (**224**).**

**Scheme 53. Formation and Reactivity of N-Sulfonyl Ketenimines Using CuAAC**



membered ring 232 (Scheme 54). Subsequent  $\alpha$ -elimination leads to the final product 5-arylidene-2-imino-3-pyrrolines (233)

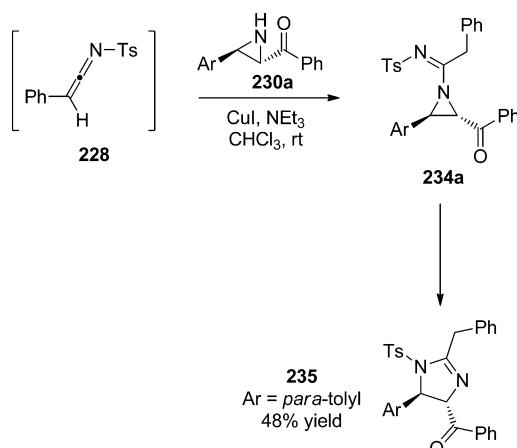


(233). Elimination of byproducts (N<sub>2</sub> and H<sub>2</sub>O), as well as the release of strain and formation of conjugated unsaturated ring systems all contribute to this energetically favorable process.

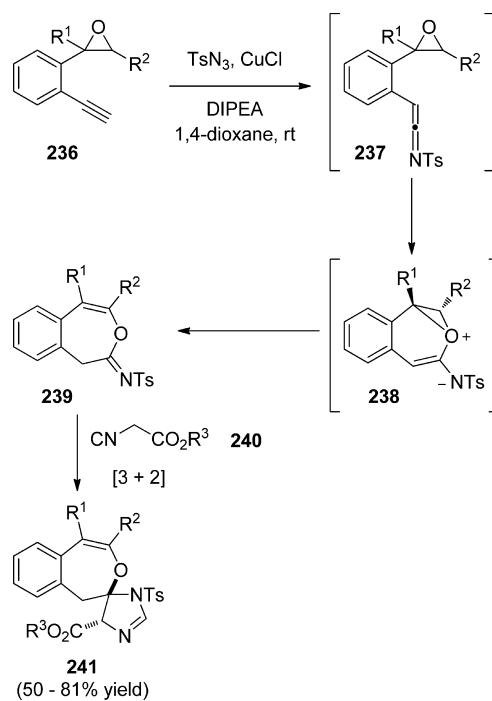
Using a similar approach, Han and co-workers explored the room temperature coupling of 228 and 230.<sup>97</sup> Interestingly, under their conditions intramolecular condensation to form the fused bicyclic 232 did not take place, but rather, aziridine amidines 234 were isolated. An MCR was developed to prepare 2-imidazolines (235) through in situ isomerization of 234 (Scheme 55). In both of the Cui and Han works, the scope was limited to aryl-substituted aziridines and alkynes.

Epoxides have also been shown to be reactive nucleophiles with ketenimines, provided the two are properly positioned toward an intramolecular reaction. Li and Wu found that *o*-ethynyl styrene oxides (236), when subjected to CuAAC conditions, formed the cyclic imide 239 (Scheme 56).<sup>98</sup> Though strictly this represents a three-center–two-component reaction, the reactivity displayed is characteristic of MCRs. The authors proposed oxonium intermediate 238, which could

**Scheme 55. A Copper-Catalyzed MCR of Alkynes, Tosylazide, and Aziridine Ketone 230a To Form *trans*-Imidazoline 235**



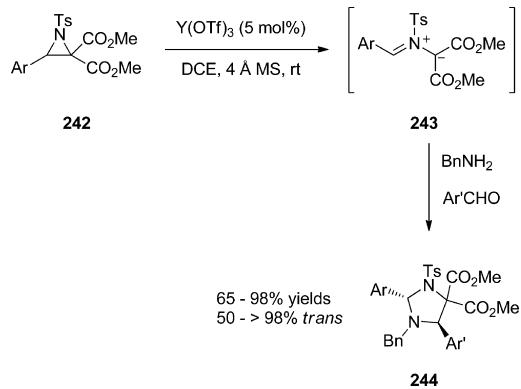
**Scheme 56. Azide–Alkyne Coupling with an Intramolecular Epoxide and Subsequent [3 + 2] Cycloaddition To Yield Complex Ring Systems**



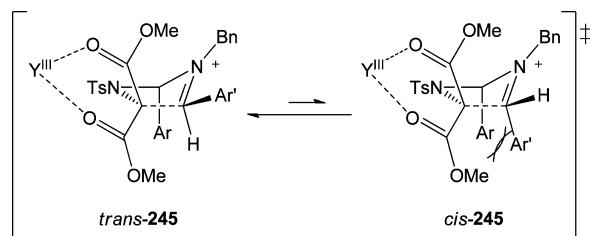
rearrange into 239. In the presence of isocyanoacetates, the stage was set for a [3 + 2] cycloaddition to furnish spirocyclic aminal 241. This methodology expands the use of ketenimine intermediates to oxygen-containing strained rings.

## 2.10. Other Cycloadditions

Wu and Zhang reported on the three-component reaction of amines, aldehydes, and aziridine-2,2-diesters (242, Scheme 57).<sup>99</sup> Aldimines derived from the condensation of amines and aldehydes engaged in a [3 + 2] cycloaddition with azomethine ylides (243) formed when donor–acceptor aziridines (242) were exposed to Lewis acids such as Y(OTf)<sub>3</sub>. The diastereoselectivity of the reaction was found to be highly dependent on the nature of the aldehyde. Electron-deficient examples (e.g., 4-cyanobenzaldehyde, 4-bromo-2-fluorobenzal-

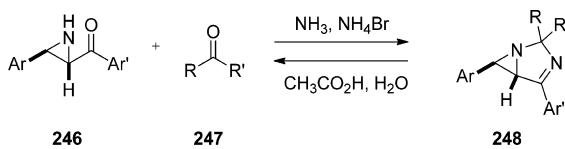
**Scheme 57. Synthesis of *trans*-2,5-Diarylimidazolines (244)**

dehyde) produced  $>50:1$  *trans:cis*-244, while more electron-rich examples (e.g., 2-furaldehyde, *p*-anisaldehyde) showed little to no selectivity. In a proposed mechanism, transition state *trans*-245, leading to *trans*-imidazolidines, is favored due to alleviation of *syn*-pentane interactions found in *cis*-245 (Figure 4). This example highlights the utility of donor–acceptor aziridines and their derivative azomethine ylides for engaging  $\pi$ -systems in cycloadditions.

**Figure 4. Transition-state models to explain the diastereoselectivity of 245.**

## 2.11. Condensations

The first use of aziridine ketones in multicomponent reactions is likely represented by a report describing the preparation of 1,3-diazabicyclo[3.1.0]hex-3-enes (248).<sup>100</sup> *trans*-2-Aryl-3-ary laziridines were treated with ammonia and aldehydes or ketones to generate such fused bicyclic products (Scheme 58). This transformation reflects some of the features of

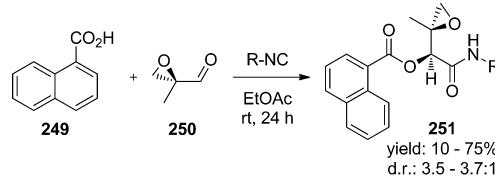
**Scheme 58. Reversible Condensation of Aziridine Ketones (246) with Ketones (247) To Produce Fused Aminal (248)**

aziridine aldehyde multicomponent reactions currently being explored. First, the reaction is reversible. When the components are mixed with ammonium bromide in an alcoholic solvent, the condensation product is formed. In dilute aqueous acetic acid, however, the starting materials are recovered unchanged. Second, no epimerization of the aziridine is observed during either the forward or reverse reactions. Finally, the apparent stability of the products to aziridine-N-imine formation is crucial to this arrangement. Each of these properties is critical

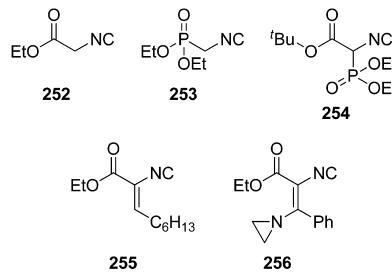
to the success of aziridine aldehyde-mediated multicomponent reactions discussed elsewhere in this review.

## 2.12. Stereoinduction by Small Rings

Azinomycin B (also known as carzinophilin) is an antitumor antibiotic isolated from the broth of *Streptomyces sahachiroi*. The accepted mechanism of action is the formation of major groove intrastrand cross-links between guanine and purine residues that lie two bases apart.<sup>101</sup> The key structural features of the compound are the epoxide and aziridine moieties—for each alkylation event—as well as the naphthyl group for DNA intercalation. After achieving the linear syntheses of azinomycin B and several analogues, Moran and Armstrong designed a convergent approach to the left-hand portion of the molecule that relied on a Passerini 3CR to bring together the key structural features about the acylhydroxyamide core. The authors exposed 2-methylglycidal (250) to 1-naphthoic acid (249) and a range of isocyanides, including isocyanoacetates (252),  $\alpha$ -isocyano- $\alpha$ -phosphonoacetates (254), and vinyl isocyanides (255), and achieved diastereoselectivities in the range of 3.5–3.7:1 in favor of the desired isomer (251) (Scheme 59).<sup>102</sup> Later, the scope was expanded to include

**Scheme 59. Synthesis of Azinomycin Analogues Using a P3CR Approach with Aldehyde 250 To Induce Moderate Diastereoselectivity**

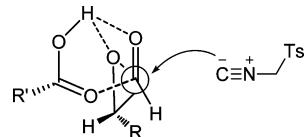
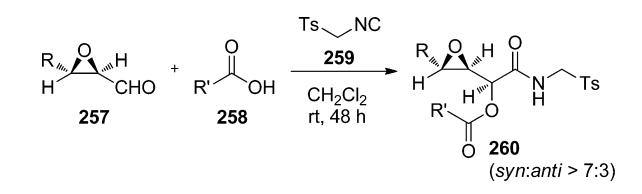
Examples of isocyanides:



isocyanides with pendant *N*-vinylaziridines (256), to access analogues with both heterocycles intact via a solution phase approach.<sup>103</sup> This method was applied in array synthesis to conduct structure–activity relationship studies on the azinomycin scaffold. Arrays could also be synthesized on resin using a photocleavable linker to immobilize the carboxylic acid functionality.<sup>104</sup> The use of sterically congested epoxyaldehydes represents a useful approach to the long-standing challenge of stereoinduction in isocyanide-mediated MCRs.

Another example of using epoxides for stereoinduction in the Passerini reaction explored the effect of the substituents *cis* and *trans* to the aldehyde functionality. A mildly diastereoselective P3CR was reported with chiral 2,3-epoxyaldehydes (257), *p*-toluenesulfonylmethyl isocyanide (TosMIC, 259), and a variety of carboxylic acids (258) (Scheme 60, Figure 5).<sup>105</sup> The dr of P3CR products (260) remained modest with  $>7:3$  ratio for each of the reported reactions. The relative stereochemistry of the epoxides was found to determine the major diastereomer;

**Scheme 60.** Asymmetric Induction Using 2,3-Epoxyaldehydes (257) with TosMIC (259) and Carboxylic Acids (258)

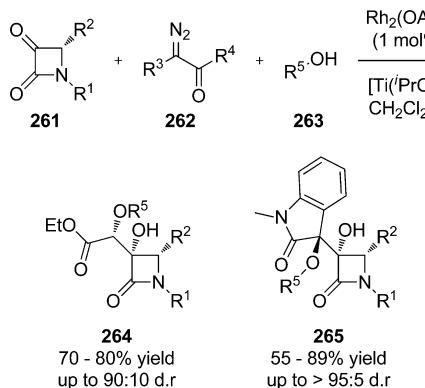


**Figure 5.** Model illustrating how precomplexation of 2,3-epoxyaldehydes (257) with carboxylic acids (258) biases facial selectivity for TosMIC (259) addition. Chiral carboxylic acids can enhance diastereoselectivity in “matched” cases.

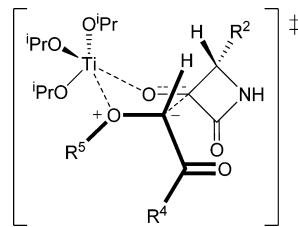
*trans*-epoxides provided *syn*-P3CR products, while *cis*-epoxides led to the anti-isomers. The dr could be elevated as high as 93:7 when chiral amino acid components were used as substrates in “matched” cases. In contrast to other examples discussed above (see section 2.1), the epoxides in the reactants did not undergo ring-opening in this P3CR. Epoxides remain in the products, having contributed to asymmetric induction<sup>106</sup> of an adjacently formed stereocenter.

Alcaide and co-workers have investigated diastereoselective MCRs of azetidine-2,3-diones (261) with diazo compounds (262) and alcohols (263) (Scheme 61). A rhodium catalyst was

**Scheme 61.** A 3CR with Azetidine-2,3-diones (261), Diazo Compounds (262), and Alcohols (263) Is Catalyzed by Rhodium Acetate and Generates Products 264 or 265 with Moderate to Good Diastereoselectivity



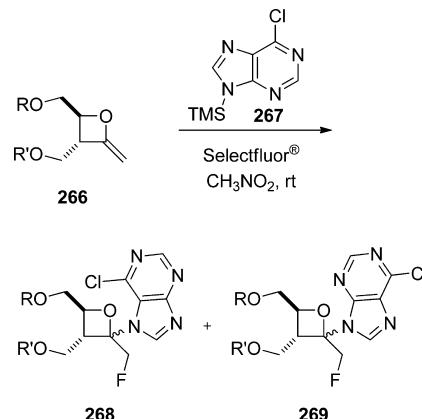
used to generate a rhodium carbene, which was susceptible to nucleophilic attack from the alcohol. The resulting oxonium ylide then engaged 261 to set two adjacent stereocenters in a single addition.<sup>107</sup> Diastereoselectivity was controlled by both the C4 substituent of the 261 and substitution of 262 and was typically moderate (65–90% *syn*) but could be improved by the addition of titanium(IV) isopropoxide, which was proposed to generate a more ordered transition state (Figure 6). In addition to ethyl diazoacetate, a selection of diazoisatins was employed in this reaction to prepare  $\beta$ -lactam–oxindole conjugates with adjacent quaternary stereocenters (265).<sup>108</sup>



**Figure 6.** Transition state model to explain the diastereoselectivity of 3CR of 261, 262, and 263, with titanium isopropoxide additive.

A three-component reaction of 2-methyleneoxetanes with Selectfluor and a purine derivative was investigated as a possible route to fluorinated oxetanocin A derivatives.<sup>109</sup> The initial reactivity investigations using silyl-protected 266 provided a mixture of two regioisomers 268 and 269, each of which was isolated with modest diastereoselectivity (Table 2). Attempts to

**Table 2.** Attempts To Direct Fluoroamination of Methylenoxetanes 266 Using Anchimeric Assistance



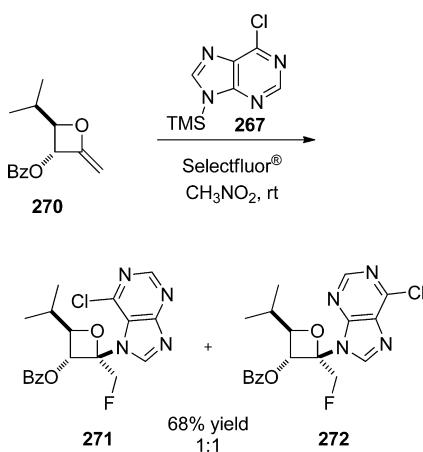
entry	substrate	R	R'	yield (%)	product ratio <sup>a</sup>
1	266a	TBS	TBS	76	3:3:2:1
2	266b	Bz	Bz	<20	n/a
3	266c	TBS	Bz	53	4:3:3:2
4	266d	Bz	TBS	45	4:2:1:1

<sup>a</sup>Determined by a combination of both crude <sup>1</sup>H NMR and product masses.

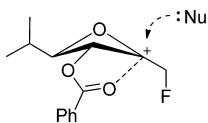
induce greater stereoselectivity focused on manipulation of the diol protecting groups in the hopes of accessing a neighboring-group participation effect. These designs were ultimately unsuccessful in achieving the desired levels of selectivity, since they would require formation of fused six- or seven-membered rings, rather than the more commonly observed five-membered rings. Indeed, under identical reaction conditions, substrate 270 formed both regioisomers with high diastereoselectivity (271 and 272, Scheme 62), as expected if anchimeric assistance through a five-membered ring were involved (Figure 7). Both regioisomers were formed due to the low rate of reaction allowing for the purine nucleophile (267) to isomerize. This also suggests that the site of bond formation was highly hindered, potentially precluding effective attack of the nucleophile on the proposed anchimerically stabilized cation.

Aziridine aldehyde dimers (56) have been explored as substrates for the Petasis borono-Mannich reaction to prepare chiral diamines.<sup>110</sup> In contrast to  $\alpha$ -hydroxyaldehydes, which

**Scheme 62.** Fluoroamination of **270** Is Highly Diastereoselective Due to Anchimeric Assistance<sup>a</sup>



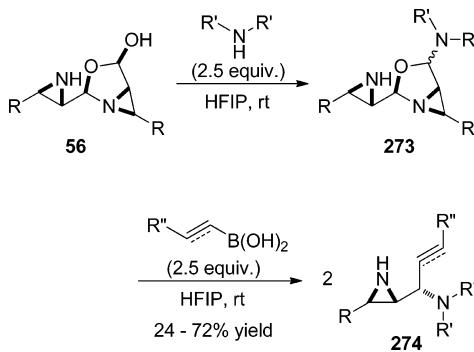
<sup>a</sup>In contrast to analogous reactions from **266**, the hypothesized neighboring group participation is achieved through a six-membered ring.



**Figure 7.** Model illustrating anchimeric assistance in diastereoselective fluoroamination of **270**.

generated *anti*-diamines,  $\alpha$ -aziridine aldehydes produced exclusively *syn*-diamines (**274**) from styrylboronic acids and secondary amines (Scheme 63). Heteroaryl and alkynyl boronic

**Scheme 63.** Petasis Borono-Mannich Reaction Using Aziridine Aldehyde Dimers Produced Solely *syn*-Diamines (**274**) Using Styryl Boronic Acids<sup>a</sup>



<sup>a</sup>Alkynyl boronic acids led to 63–91% yields of *syn*-**274**. Amines used included morpholine, pyrrolidine, dibenzylamine, and diallylamine.

acids were also employed in the reaction, though the latter proceeded with reduced diastereoselectivity. Yields were generally modest, and the reaction showed a marked solvent dependence, with the aziridine aldehyde dimer–amine adduct (**273**) comprising the major side product. Aziridine aldehyde dimers have been shown to exhibit solvent-sensitive reactivity previously.<sup>111</sup> In this MCR, 1,1,1,3,3-hexafluoroisopropanol (HFIP) was found to be the optimum solvent. The observed diastereoselectivity was rationalized using theoretical models of a proposed  $N,\text{O}$ -boronate intermediate, which revealed a

greater steric obstacle to formation of the anti-product over the syn-isomer. It was then suggested that the aziridines play key roles in establishing a rigid surface on which the multicomponent reaction occurs, while also coordinating the boronic acid and activating it to alkenyl group migration. The authors also demonstrated the utility of these products by subjecting them to aziridine ring opening with thiobenzoic acid and *p*-nitrobenzoic acid to prepare a selection of 1,2- and 1,3-diamines with control of relative chirality.

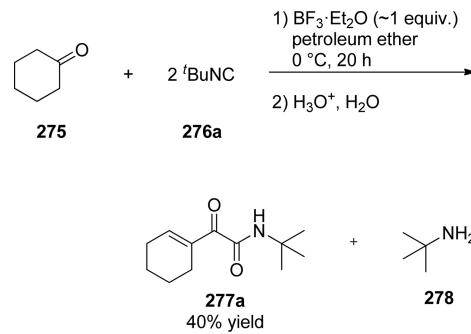
### 3. MULTICOMPONENT REACTIONS PRODUCING HETEROCYCLES

#### 3.1. Reactions of Isocyanides with Oxo Compounds

Isocyanides are indelibly linked with multicomponent reactions such as the Passerini and Ugi reactions in the minds (and noses) of synthetic chemists. While the utility of such reactions justifies this association, less well appreciated are multicomponent reactions in which 2 or even 3 equiv of isocyanide are consumed to generate a single product. Indeed, this reactivity represents the challenges sometimes encountered when working with amphoteric molecules. Under mild conditions, isocyanides can undergo oligo- and polymerization reactions. Within the subset of transformations where multiple equivalents of isocyanide react with oxo compounds, this reactivity has been successfully harnessed to produce some remarkable heterocycles. That oxetanes (strain energy 26 kcal·mol<sup>-1</sup>)<sup>112</sup> have been frequently accessed in this manner is a demonstration of the inherent energy stored within the isocyanide functional group, which can be kinetically controlled to produce such strained rings. Oxetane rings are justifiable synthetic targets in their own right and serve as important structural components of taxol,<sup>113</sup> merrilactone A,<sup>114</sup> thromboxane A<sub>2</sub>,<sup>115</sup> and oxetanocin.<sup>116</sup>

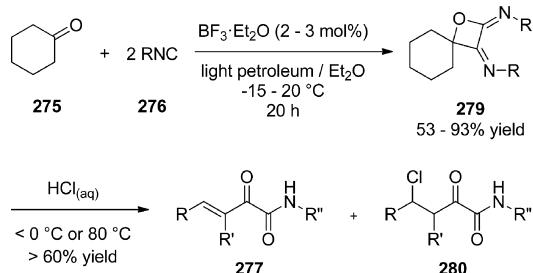
In 1966, Zeeh reported the reaction of cyclic ketones such as **275** with *tert*-butyl isocyanide (**276**) in the presence of stoichiometric  $\text{BF}_3\cdot\text{Et}_2\text{O}$  to form unsaturated oxoacetamides (**277a**) after aqueous acidic workup (Scheme 64).<sup>117</sup> While the

**Scheme 64.** Synthesis of Oxetanes by a 3CR with 2 equiv of Isocyanide **276** and Their Transformations under Acidic Conditions

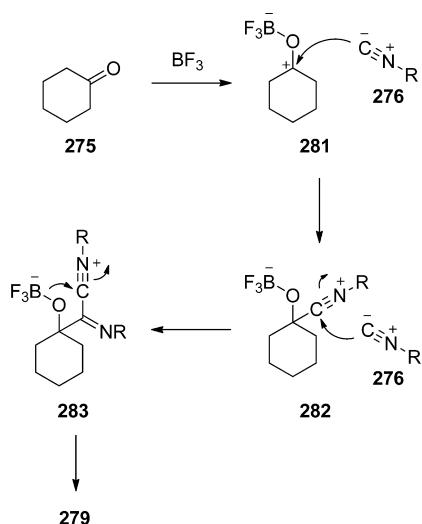


mechanism for this 3CR was unclear at the time, Kabbe later reported a catalytic variant and after neutral or basic workup isolated oxetane-2,3-diimine products (**279**, Scheme 65).<sup>118</sup> Mechanistically, oxetanes are proposed to form by addition of an isocyanide to a Lewis acid-activated ketone (**281**, Scheme 66). A second equivalent of **276** attacks the generated isonitrilium **282**, followed by ring formation from a second isonitrilium intermediate (**283**). These products could then be

**Scheme 65.** Catalytic 3CR for the Synthesis of Oxetane-2,3-diimines (279) and Their Subsequent Conversion to Oxoacetamides (277)



**Scheme 66.** Proposed Mechanism for Formation of Oxetane 279

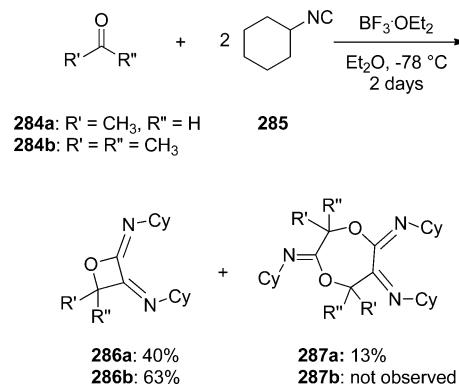


converted to 277 as well as halide 280 by treatment with HCl (Scheme 65),<sup>119</sup> which strongly suggests the intermediacy of oxetane 279 and its reactivity to  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  under the stoichiometric Lewis acid conditions.<sup>120</sup> The nature of the acid hydrolysis product was dependent both upon the substitution of the oxo compound, as well as the conditions under which hydrolysis was conducted.

Concurrently, Saegusa and co-workers explored the oligo- and polymerization of acetaldehyde and acetone with cyclohexyl isocyanide catalyzed by  $\text{BF}_3 \cdot \text{OEt}_2$  at low temperature.<sup>121</sup> Both oxetanes 286 and seven-membered rings 287 could be isolated, along with higher molecular weight fractions (Scheme 67). On the basis of these results and the detection of 2-methoxyamide 288 and methyl ester 289 when methanol was added to quench reaction mixtures, Saegusa proposed the intermediacy of iminooxirane 290 and suggested its involvement in the Passerini 3CR as well (Figure 8).<sup>122</sup> Zeeh later demonstrated that selectivity for 286 and 287 could be controlled through the stoichiometry of isocyanide present in the reaction.<sup>120</sup>

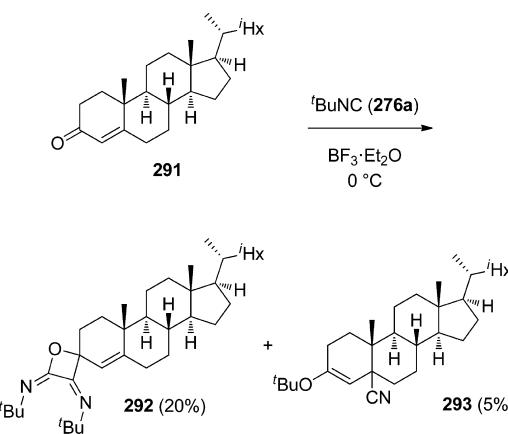
This class of oxetane-producing MCRs encounters chemoselectivity issues when the oxo compound is an  $\alpha,\beta$ -unsaturated ketone, as in 4-cholestren-3-one (291). When this substrate was reacted with 2 equiv of 276, oxetane 292 was isolated in low yield, along with enol ether 293, which is presumably formed from a five-membered ring intermediate and contains the residue of only a single equivalent of 276 (Scheme 68).<sup>123</sup>

**Scheme 67.** Implications of Substrate Control in Oxetane Synthesis



**Figure 8.** Byproducts 288 and 289 were detected by Saegusa from the reactions of acetone or acetaldehyde with cyclohexylisocyanide, leading to the proposal of intermediate 290.

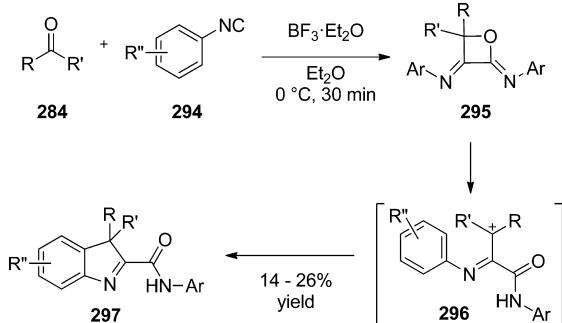
**Scheme 68.** Synthetic Challenges with  $\alpha,\beta$ -Unsaturated Carbonyl Compounds in Oxetane Synthesis<sup>a</sup>



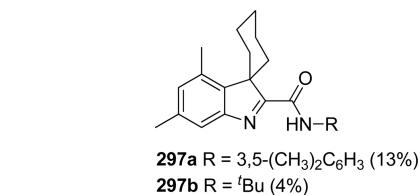
<sup>a</sup>iHx, isohexyl.

Zeeh further explored the reactivity of oxetanes derived from aryl isocyanides (294), from which 3*H*-indole-2-carboxamides (297) were produced (Scheme 69).<sup>124</sup> The reaction was promoted by electron-rich aryl isocyanides, such as *p*-methoxyphenyl isocyanide, and sterically unencumbered ketones, though in all cases the indoles were accompanied by open-chain products (277, Scheme 64). Mechanistically, the oxetane intermediate 295 is thought to undergo Lewis acid-assisted ring opening to give carbocation 296. Ring fusion then occurs by intramolecular electrophilic aromatic substitution. Naturally, 297 could not be accessed using aryl isocyanides with two ortho-substituents, such as 2,6-dimethylphenyl isocyanide. Zeeh managed to prepare indole 297b, derived from two distinct isocyanides, though the major product of this reaction (297a) contained residues of 2 equiv of the more accessible aryl isocyanide (Figure 9). While the chemical yields for this transformation suggest it is not an appealing method for preparative purposes, the reactivity is thought-provoking and is

**Scheme 69. Preparation of 3,3-Disubstituted-3*H*-indoles (297) from Ketones (284) and Aryl Isocyanides (294)<sup>a</sup>**



<sup>a</sup>A major byproduct is oxoacetamide 277.



**Figure 9.** Products of the three-component reaction between cyclohexanone, *tert*-butyl isocyanide, and 3,5-dimethylphenyl isocyanide.

a demonstration of the utility of strained rings as chemical intermediates.

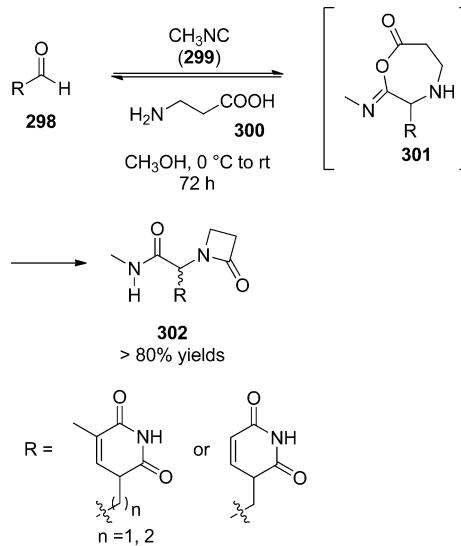
### 3.2. Ugi Reactions

The Ugi MCR is one of the most established routes to synthesize  $\beta$ -lactams that are otherwise challenging to form owing to Baeyer strain.<sup>125</sup> In a typical reaction, an amine, a carboxylic acid, an aldehyde or a ketone, and an isocyanide react together to form a mixed anhydride through a set of reversible transformations. Irreversible transacylation or solvolysis of the mixed anhydride renders the product, which is a peptide derivative. With  $\beta$ -amino acid substrates, the final intramolecular  $O,N$ -acyl migration forms a  $\beta$ -lactam. Typically, it is challenging to achieve good stereoselectivity in these transformations.

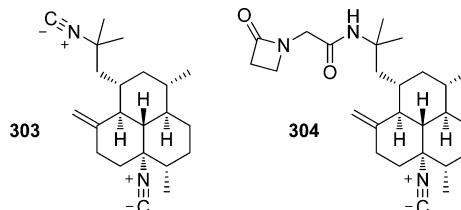
Ugi and co-workers reported syntheses of nucleoside analogs of  $\beta$ -lactams in high yields starting from nucleobase-aldehyde conjugates (298) with methyl isocyanide 299 and  $\beta$ -alanine 300 (Scheme 70).<sup>126</sup> This four-center–three-component reaction is an operationally simple and modular method for preparation of  $\beta$ -lactams (302) with appended pharmacophores. Substituted  $\beta$ -phenyl- $\beta$ -alanine had previously been found to yield  $\beta$ -lactams smoothly with oxo components and isocyanides.<sup>127</sup> This approach was also found suitable for a combinatorial approach, demonstrated by the parallel synthesis of a 126-member library of monocyclic  $\beta$ -lactams.<sup>128</sup>

In another example, a single-step semisynthesis of monamphilectine A (304, Figure 10) was enabled by a U-3CR.<sup>129</sup> This diterpenoid-lactam alkaloid was isolated from marine sponge *Hymeniacidon* sp. and structural connectivity was established by spectroscopic methods and comparison with related natural products. To confirm the stereochemistry of 304, a semisynthesis was designed from 8,15-diisocyano-11(20)-amphilectene (303),<sup>130</sup> which is likely a biogenetic precursor of 304, is of known absolute configuration, and was also isolated from the same sponge.<sup>131</sup> In the event,  $\beta$ -alanine

**Scheme 70. Synthesis of  $\beta$ -Lactam-Nucleosides<sup>a</sup>**



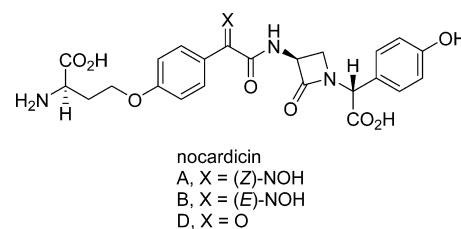
<sup>a</sup>Diastereomeric ratios not reported.



**Figure 10.** Monamphilectine A (304) and precursor 303.

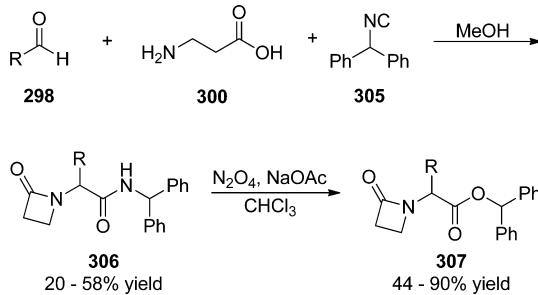
300, formaldehyde, and 303 underwent condensation over 24 h in methanol to give 304 in 61% yield. The product was characterized in complete agreement with the natural sample to confirm absolute stereochemistry.

Nocardicins A–G share a 2-oxo-1-azetidinylacetic acid core, which appears to be accessible by an Ugi MCR (Figure 11).<sup>132</sup>

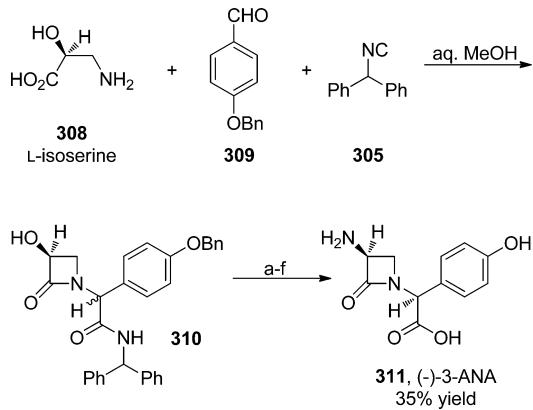


**Figure 11.** A selection of the nocardicin family of natural products.

However, chemoselective transformation of amides into esters or free acids is challenging owing to the presence of a  $\beta$ -lactam ring. Hofheinz and co-workers reported that diphenylmethyl-substituted *N*-nitrosoamides can render easy cleavage into esters. In a one-pot protocol, *N*-(diphenylmethyl) amides 306 were synthesized—from  $\beta$ -alanine 300, a variety of aldehydes 298, and diphenylmethyl isocyanide 305—and then converted into the corresponding esters 307 by nitrosation (Scheme 71). Unfortunately,  $\alpha,\beta$ -unsaturated aliphatic aldehydes and partially protected diaminopropanoic acid were found to be poor substrates in Ugi four-center–three component reaction (U4C–3CR), which would have provided a direct route to the nocardicins.

**Scheme 71. Synthesis of  $\beta$ -Lactam Core of the Nocardicins**

This strategic approach was later employed using isoserine **308**, diphenylmethyl isocyanide **305**, and *p*-(benzyloxy)-benzaldehyde **309** for the synthesis of 3-aminonocardicinic acid **311** (Scheme 72).<sup>133</sup> After using the MCR to form the  $\beta$ -

**Scheme 72. An MCR Approach Used for the Total Synthesis of Nocardicins<sup>a</sup>**

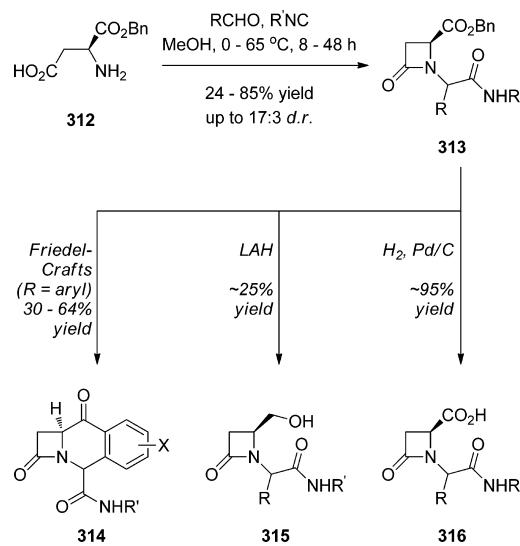
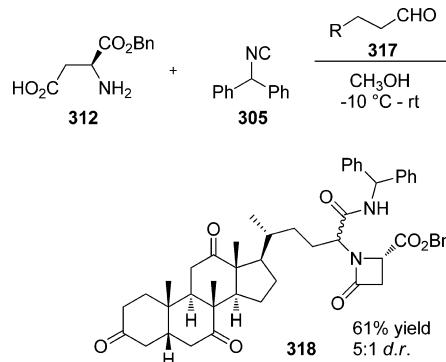
<sup>a</sup>Reagents and conditions: (a) DEAD, PPh<sub>3</sub>, CH<sub>3</sub>Br, THF (57% yield); (b) NaN<sub>3</sub>, DMSO; (c) N<sub>2</sub>O<sub>4</sub>, CHCl<sub>3</sub> (62% yield, two steps); (d) DBU, CH<sub>2</sub>Cl<sub>2</sub>; (e) H<sub>2</sub>, Pd/C, NaHCO<sub>3</sub>, EtOAc, H<sub>2</sub>O; (f) 1 N aq HCl (>99% yield).

lactam **310**, the diastereomers were separated to provide enantiopure product. Following installation of an azide at C(3) by double inversion, treatment with N<sub>2</sub>O<sub>4</sub> furnished **311**, the core of the nocardicins. A protected side chain of nocardicin D was synthesized from D-asparagine and coupled with **311** to provide nocardicins A, B, and D using literature protocols.

Aspartic acid derivatives have been sourced to prepare chiral  $\beta$ -lactams using the Ugi reaction. An early example demonstrated the preparation of novel tricyclic  $\beta$ -lactams (**314**) using the  $\alpha$ -carboxylate of aspartic acid, which was protected during the MCR, as a handle for intramolecular Friedel–Crafts annulation (Scheme 73).<sup>134</sup> Also beginning from L-Asp-OBn (**312**),  $\beta$ -lactam formation could be followed by selective reduction using LiAlH<sub>4</sub>, or deprotection by hydrogenolysis.<sup>135</sup> The dr for various derivatives of **313** ranged from 1:1 to 17:3.

A derivative of  $\beta$ -lactam steroid pachystermin A, isolated from the buxaceous plant *Pachysandra terminalis*, was synthesized by U4C–3CR with L-aspartic acid  $\alpha$ -benzyl ester **312**. In this case, the steroid moiety was introduced using the aldehyde reaction component **317**, and the product **318** was isolated in 5:1 dr (Scheme 74).<sup>136</sup>

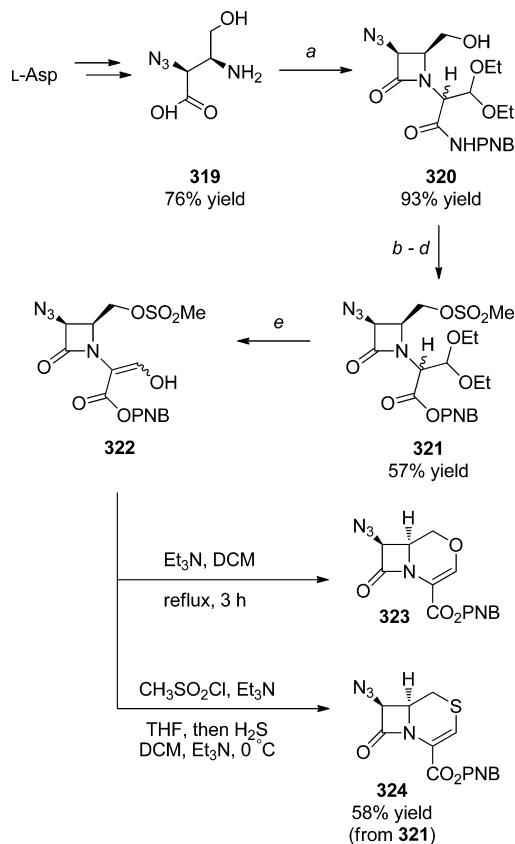
2-Isocephems and 2-isooxacephems constitute another class of  $\beta$ -lactam antibiotics. Their syntheses were facilitated by

**Scheme 73. Application of Aspartic Acid Derivatives in Preparation of  $\beta$ -Lactams, and Subsequent Transformations****Scheme 74. Synthesis of Pachystermin A Derivative 318**

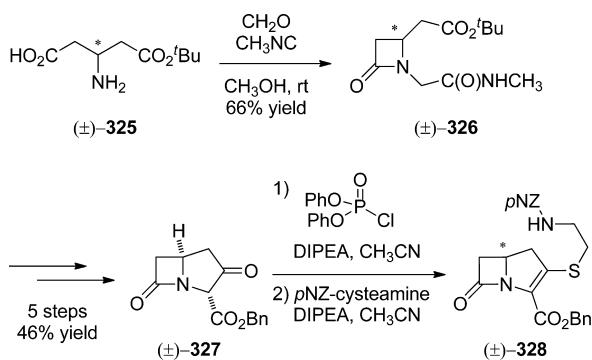
U4C–3CR of  $\beta$ -amino acid **319** synthesized from L-aspartic acid (Scheme 75).<sup>137</sup> The MCR of **319**, *p*-nitrobenzyl isocyanide, and 2,2-diethoxyacetaldehyde resulted in azetidinone **320** in good yield but with no measurable diastereoselectivity. These monocyclic azetidinones serve as intermediates for the synthesis of 2-isocephalosporin and 2-isooxacephalosporin.<sup>138</sup>

One approach to the carbapen-2-em ring system, core of thienamycin derivatives, made use of an Ugi reaction using a partially protected derivative of 3-aminoglutamic acid (**325**).<sup>139</sup> The  $\beta$ -lactam product (**326**) can be manipulated to effect a Dieckmann-type reaction providing the fused product **327** (Scheme 76). This is followed by condensation with a protected cysteamine to give a simplified thienamycin derivative **328**.

Alicyclic  $\beta$ -amino acids **329** were successfully utilized in U4C–3CR to form  $\beta$ -lactams **330**. It is interesting to note that *trans*- $\beta$ -amino acids failed to cyclize as the ring strain inhibits the formation of *trans*- $\beta$ -lactam. On the contrary, *cis*- $\beta$ -amino acids smoothly afford the desired products in methanol at room temperature within 24 h (Scheme 77a).<sup>140</sup> The diastereomeric ratio for these transformations was substrate-dependent and varied widely (14–82%). This methodology was found to be suitable to generate a mixture-based combinatorial library of  $\beta$ -lactams.

Scheme 75. Synthesis of 2-Isocephem and 2-Iooxacephem<sup>a</sup>

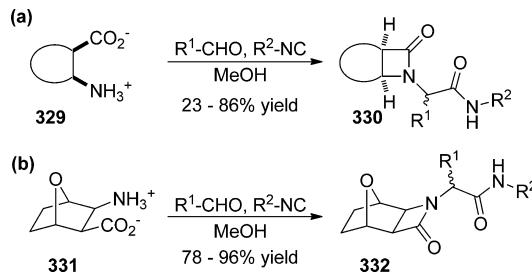
<sup>a</sup>Reagents and conditions: (a) (EtO)<sub>2</sub>CHCHO *p*-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NC, MeOH, rt, 10 h. (b) MeSO<sub>2</sub>Cl, Et<sub>3</sub>N THF, rt, 10 h. (c) N<sub>2</sub>O<sub>4</sub>, CHCl<sub>3</sub>, AcONa, 0 °C, 1 h. (d) CCl<sub>4</sub>, reflux, 3 h. (e) CF<sub>3</sub>COOH. The yield for 323 was not reported. For similar syntheses of 323 and 324, see ref 138.

Scheme 76. Synthesis of Racemic Thienamycin Core Using an Ugi Reaction and a Dieckmann Condensation<sup>a</sup>

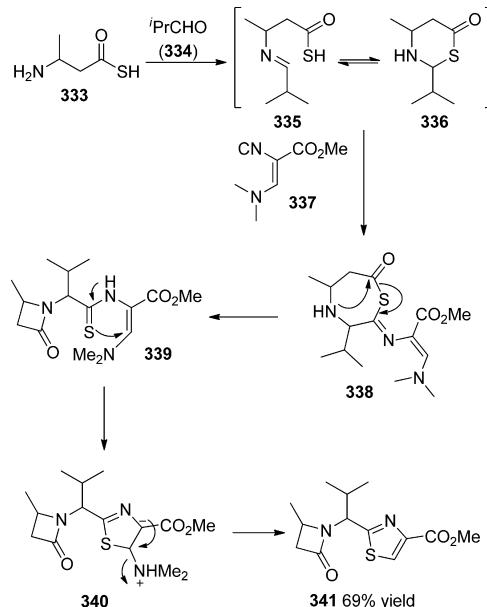
<sup>a</sup>The yield of 328 was not reported. *p*NZ, *p*-nitrobenzyloxycarbonyl.

Basso et al. also demonstrated the utilization of bicyclic  $\beta$ -amino acids 331 that underwent intramolecular Ugi MCRs with various aldehydes and isocyanides in methanol, leading to the corresponding  $\beta$ -lactams 332 (Scheme 77b).<sup>141</sup> Unfortunately, the rigid oxabicyclo[2.2.1]heptane chiral backbone did not translate to high diastereoselectivities observed in these transformations (0–42%).

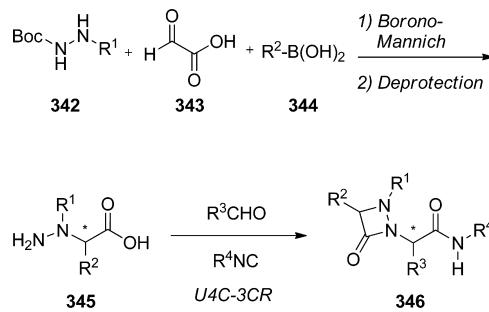
In a condensation of  $\beta$ -aminothiocarboxylic acid (333), aldehyde 334, and 3-dimethylamino-2-isocyanoacrylate (337),

Scheme 77. Synthesis of Alicyclic  $\beta$ -Lactams 330 and 332

a thiazole and  $\beta$ -lactam ring are formed simultaneously under mild conditions.<sup>142</sup> To generate the product (341), one C–C, two C–S, and two C–N bonds are formed in a MCR starting from acyclic precursors (Scheme 78).

Scheme 78.  $\beta$ -Aminothiocarboxylic Acid 333 in an Ugi Reaction

Petasis (or borono-Mannich) reactions were used to render  $\alpha$ -hydrazinocarboxylic acids 345 from protected hydrazines (342), glyoxylic acid (343), and boronic acids (344). Compounds 345 can be thought of as aza- $\beta$ -amino acids, and they were found to behave analogously to  $\beta$ -amino acids in the context of Ugi MCRs, producing aza- $\beta$ -lactams (346, Scheme

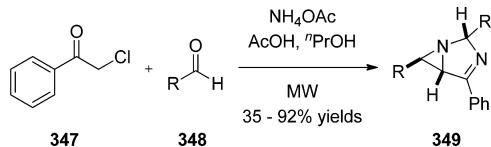
Scheme 79. Synthesis of Aza- $\beta$ -lactams 346, by Sequential Petasis MCR and Ugi MCR

79).<sup>143</sup> Aza- $\beta$ -lactams have been investigated for their biological activity in addition to their utility as synthetic intermediates.<sup>144</sup>

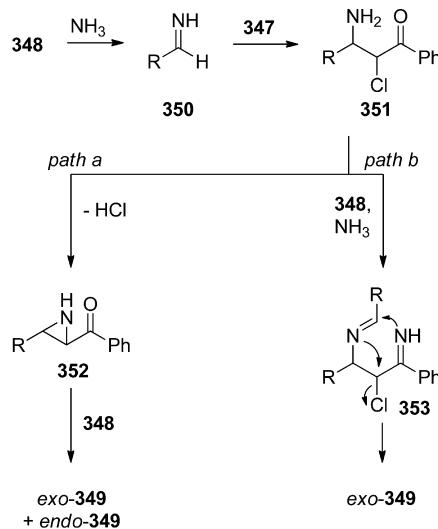
### 3.3. Condensations

Photolysis of small ring heterocycles has been explored in the hopes of uncovering mechanistic insight into excited state rearrangements, development of photochromic materials, as well as for synthetic approaches to aromatic heterocycles. Among these systems, the synthesis of fused 1,3-diazabicyclo[3.1.0]hex-3-ene has remained a challenge due to the perceived requirement of preparing NH-aziridine ketones as starting materials and the reversibility of imidazoline formation under the reaction conditions.<sup>100,145–147</sup> An MCR approach to this scaffold was developed using microwave heating of ammonium acetate, phenacyl chloride (347), and a benzaldehyde derivative (348) in the presence of acid and molecular sieves to generate 349 as a racemic single exo-diastereomer, as confirmed by 2D-NMR and X-ray crystallography (Scheme 80).<sup>148</sup> Aliphatic aldehydes containing  $\alpha$ -hydrogens did not give

**Scheme 80. Diastereoselective Synthesis of Exo-Fused 349 under Microwave Conditions**



**Scheme 81. Proposed Mechanism for Diastereoselective Preparation of exo-349<sup>a</sup>**



<sup>a</sup>Path a was obviated on the basis of the known reactivity of intermediate 352.

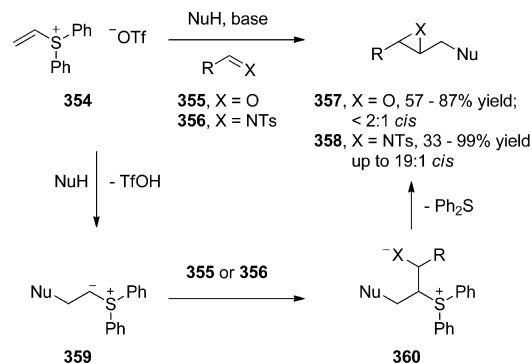
the desired products, though pivalaldehyde did produce 349 in reduced yield. Aziridine ketone 352 is unlikely to be an intermediate in this reaction due to the observed high diastereoselectivity, which is in contrast with preparations of similar products from such reactants (Scheme 81, path a). Rather, bis-imine 353 is proposed to undergo 6-endo-trig cyclization followed by 3-exo-tet to form the aziridine (path b).

### 3.4. Addition-Elimination Reactions

Vinyl sulfonium salts have been applied in multicomponent reactions to give both epoxides (357) and aziridines (358).<sup>149</sup>

Diphenylvinylsulfonium triflate (354) was reacted with a variety of nucleophiles and aldehydes (355) to produce substituted epoxides with moderate diastereoselectivity (Scheme 82). It was necessary to use 5 equiv of aldehyde

**Scheme 82. Three-Component Epoxidation and Aziridination Reactions Using Vinyl Sulfonium Salt 354<sup>a</sup>**



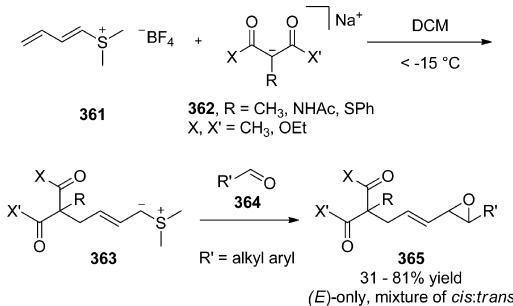
<sup>a</sup>Nucleophiles include tosylmethylamide, benzyl alcohol, thiophenol, pyrrolidine, and diethyl 2-methylmalonate.

and slow addition of 354 to the basic reaction mixture (<sup>t</sup>BuOK, CH<sub>2</sub>Cl<sub>2</sub>) to prevent the ylide intermediate 359 from reacting with 354 in preference to the aldehyde. By replacing the aldehyde with a preformed imine (356), aziridines 358 were generated with greater diastereoselectivity, particularly for more electron-rich imines, which lead to highly cis-selective products. The authors proposed that  $\pi$ -stacking of the electron-rich imine with the diphenyl sulfonium leaving group favors a transition state arrangement leading to *cis*-aziridine products.

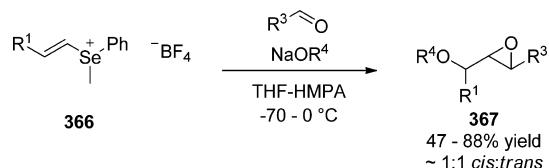
Sulfur ylides have been extensively employed for synthesis of small heterocycles, perhaps most famously by Aggarwal.<sup>150,151</sup> Using butadienedimethylsulfonium tetrafluoroborate (361), a 3CR with sodium enolates (362) and aldehydes (364) was achieved.<sup>152</sup> Substituted sodium malonates were crucial as soft nucleophiles to enforce 1,4-addition to the butadienesulfonium ion and to prevent cyclopropanation.<sup>153</sup> Vinyl sulfur ylide 363 reacts with the aldehyde with high regioselectivity, followed by elimination of dimethyl sulfide to release the vinyl epoxide products (365, Scheme 83).

Addition-elimination reactions using vinyl selenonium salts were investigated in an effort to produce epoxides in a 3CR.<sup>154</sup> (Scheme 84). While carbon-based nucleophiles failed to undergo conjugate addition with the selenonium salt (366) in favor of direct methylation, oxygen-based nucleophiles fared better. Sodium allyl oxide, added to a solution of 366 in the

**Scheme 83. Three-Component Synthesis of Vinyl Epoxides Using Butadienedimethylsulfonium Tetrafluoroborate (361)**



**Scheme 84. Reactions of Vinylselenonium Salts with Carbon and Oxygen Nucleophiles To Form Small Rings**

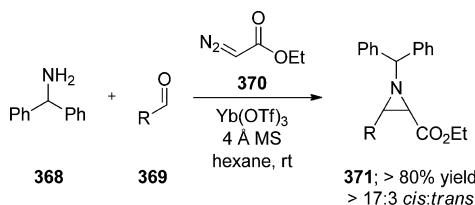


presence of 3 equiv of benzaldehyde, produced the desired epoxide (367) in 70% yield, as a mixture of diastereomers (Scheme 84). Other alkoxides could be employed in the epoxide preparation, with the notable exceptions of phenoxide and methoxide. The major challenge for this reaction was regioselectivity regarding the vinyl selenonium electrophile. While the electron-withdrawing selenonium activates the vinyl group for conjugate addition and serves as a good leaving group later in the reaction, demethylation was competitive in both elementary steps. Hypothetically, this issue could be attenuated with less reactive or cyclic substituents on the selenium center.

### 3.5. Reactions of Diazo Compounds

The Darzens reaction is a preparation of epoxides from ketones by reaction with an  $\alpha$ -halo or  $\alpha$ -azo ester.<sup>155</sup> The aza-Darzens reaction produces aziridines from imines under similar conditions.<sup>156</sup> A major limitation of the aza-Darzens reaction has been the incompatibility of imine-forming conditions with aziridination, making isolable imines the required starting material. Nagayama and Kobayashi attempted to overcome this limitation with the use of Lewis acid salts. For couplings of *N*-diphenylmethyl arylimines with ethyl diazoacetate (EDA, 370),  $\text{Yb}(\text{OTf})_3$  was identified as a useful catalyst for improving yields of *cis*-aziridines.<sup>157</sup> They then demonstrated the 3CR of aryl and alkyl aldehydes with diphenylmethylamine (368) and EDA in the presence of  $\text{Yb}(\text{OTf})_3$  and 4 Å molecular sieves (Scheme 85). As the authors noted, this represented the first such

**Scheme 85. Ytterbium-Catalyzed Aza-Darzens Reaction<sup>a</sup>**



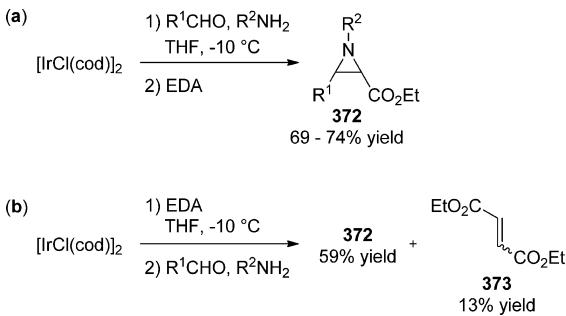
<sup>a</sup> R = Ph, C(O)Ph, alkyl.

aziridine synthesis from aliphatic imines having  $\alpha$ -hydrogen substituents, which have a propensity toward enamine formation. Yields for the 3CR were generally better than 80%, and the diastereoselectivity in most cases was greater than 17:3 (cis:trans).

Another approach to the three-component aza-Darzens reaction was to forego dehydrating agents by using an iridium-based catalyst to activate imines toward addition of EDA.<sup>158,159</sup> Solvent and catalyst ligands had a strong effect on product diastereoselectivity, which was generally modest unless bulky amines, such as *tert*-butyl amine (cis:trans 24:1 with butyraldehyde), were employed. Alkyl aldehydes and amines were preferred substrates, while benzaldehyde and aniline were unreactive. It can be argued, however, that this reaction should not qualify as a true MCR, as aldehyde and amine were mixed

in the presence of the catalyst prior to addition of EDA. In fact, the order of reactant addition influenced the chemoselectivity of the reaction. When *n*-butylamine and *n*-butyraldehyde or the preformed imine derived from this pair were added to the catalyst solution prior to EDA, the product aziridine was formed in 69–73% yield (Scheme 86). When the order of

**Scheme 86. Influence of the Order of Addition on Reaction Outcome of Ir-Catalyzed Aza-Darzens Reactions**

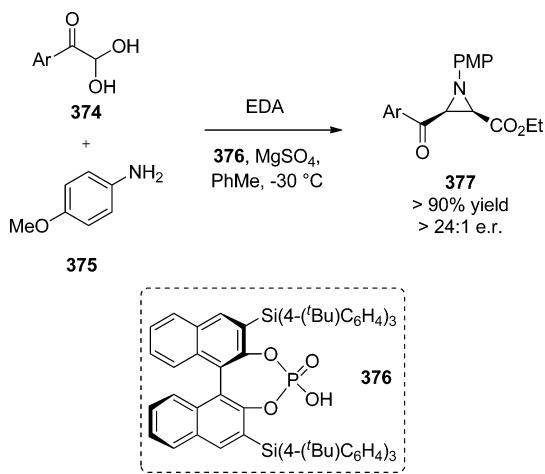


addition was reversed (i.e., EDA was added to the catalyst solution followed by imine) the aziridine was isolated in 59% yield with a 13% yield (based on 2 equiv of EDA) of homocoupling products of an Ir–carbene complex. The authors therefore suggested the importance of an Ir–imine complex to the aziridination and explain the lack of reactivity of *N*-benzylideneaniline as due to poor substrate–catalyst complexation. Unfortunately, a three-component reaction involving simultaneous addition of all components was not reported.

Other Lewis acids have been examined in the three-component aza-Darzens reaction. Yadav and co-workers reported on the application of  $\text{LiClO}_4$ <sup>160</sup> and  $\text{Bi}(\text{OTf})_3$ –[Bmim] $\text{PF}_6$ <sup>161</sup> catalysts to prepare *cis*-aziridine-2-carboxylates 372. The use of an ionic liquid in conjunction with the bismuth(III) catalyst was suggested to improve yields and diastereoselectivities by suppression of enamine formation. Yields and stereoselectivities were uniformly high using either catalyst system.

Chiral phosphoric acids have also been investigated as catalysts for the aza-Darzens reaction to form aziridines. Initial studies of the two-component reaction using preformed aldimine revealed that phosphoric acid 376 could effect high levels of enantioselectivity on a model substrate.<sup>162</sup> The reaction using arylglyoxal monohydrates (374), *p*-anisidine (375), and EDA in the presence of 376 and  $\text{MgSO}_4$  produced solely *cis*-aziridines in high (>24:1) levels of enantioselectivity and excellent (>90%) chemical yields (Scheme 87). Crystalllography of one product revealed the absolute stereochemistry to be (2*R*,3*S*). The *p*-anisyl group on the amine was required to promote aziridination, though it could be removed from the products using ceric ammonium nitrate with minimal erosion of enantiopurity. For similar reasons to those outlined above, it can be argued that this methodology does not constitute a true MCR. The aniline and arylglyoxal hydrate were premixed at room temperature with the catalyst, evidently to promote full conversion to aldimine, prior to addition of EDA at -30 °C. Unfortunately, no experiments involving simultaneous addition of all reaction components were reported on. A similar procedure has been described for the synthesis of  $\text{CF}_3$ -substituted aziridines using freshly prepared diazotrifluoro-

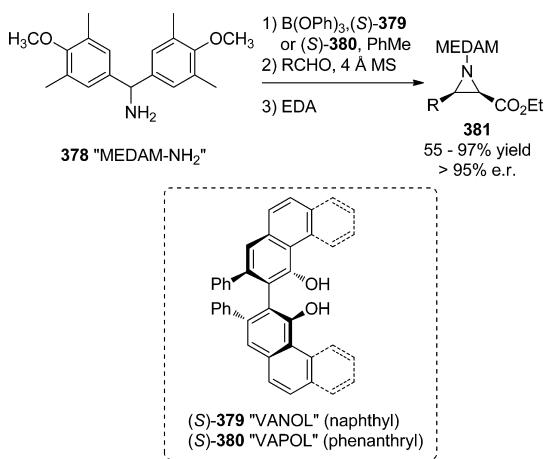
**Scheme 87. Enantioselective Synthesis of *cis*-Aziridines Using Chiral Phosphoric Acid Catalyst 376**



ethane, with very high diastereo- and enantioselectivities reported.<sup>163</sup>

Wulff and co-workers have also developed chiral Brønsted acids for the asymmetric synthesis of aziridines from imines and diazo compounds. To form the active catalyst, sterically hindered axially chiral diols 379 or 380 were mixed with triphenyl borate in the presence of an amine or preformed imine to generate a boroxinate salt. A bulky protected amine, bis(dimethylanisyl)methylamine (MEDAM-NH<sub>2</sub>, 378), was used to induce high stereoselectivity. By using a multicomponent strategy involving preparation of the boroxinate catalyst with 380 followed by addition of aldehyde and EDA (370), aryl and branched and unbranched alkyl *cis*-MEDAM-aziridines (381) could be formed in good yields and high enantioselectivities (Scheme 88).<sup>164</sup> The order of addition of

**Scheme 88. Multicomponent Asymmetric Aziridination Using *In Situ* Generated Vaulted Biaryl Boroxinate Catalysts**

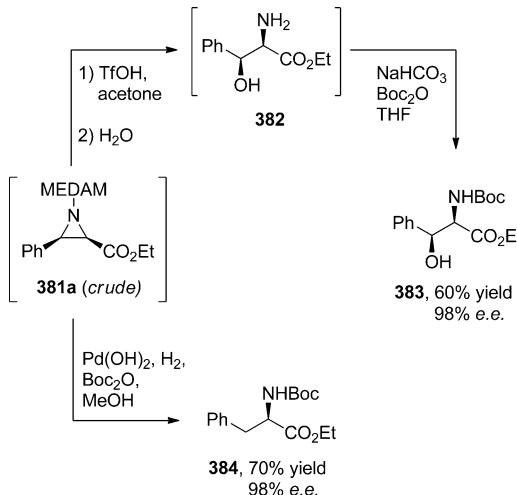


aldehyde or EDA did not affect the reaction outcomes, demonstrating that imine formation could occur in the presence of EDA under these conditions.<sup>165</sup> No product was formed if stoichiometric amounts of aldehyde were employed, or if excesses of other amines (e.g., 20 mol % Et<sub>3</sub>N) were present. This is due to strong interactions of more basic or higher affinity amines for the catalyst outcompeting imine binding. This suggests that the first stage of the reaction

is conversion of most of the amine to imine, at which point imine can competitively bind the catalyst and undergo aziridination in the presence of EDA. The chemoselectivity for aziridination in the presence of the boroxinate catalyst is remarkable given the large number of products isolated from a control reaction using only EDA, benzaldehyde, and B(OPh)<sub>3</sub>. To demonstrate this, all five reactants or reagents were added to a flask along with molecular sieves, followed by solvent for dissolution, and desired product 381 was still isolated in good yield.<sup>165</sup>

The products 381 could be deprotected with aqueous ring opening or by hydrogenation to give amino esters with excellent enantiopurity (Scheme 89).<sup>164</sup> In a more recent

**Scheme 89. MEDAM-Deprotected Amino Alcohol (383) and Amino Ester (384) Were Accessible from 381a<sup>a</sup>**

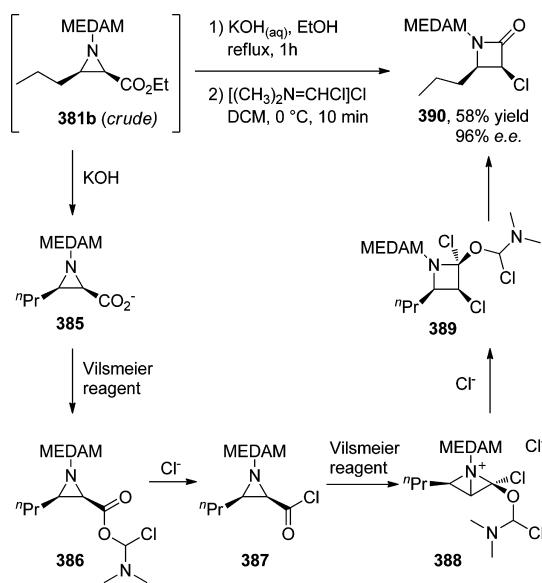


<sup>a</sup>Yields are based on 378 in the boroxinate-catalyzed aziridination reaction (Scheme 88).

report, *n*-propyl-substituted aziridine 381b was shown to undergo saponification followed by ring expansion when treated with the Vilsmeier reagent, giving access to *cis*- $\beta$ -lactam 390 (Scheme 90).<sup>166</sup> All four stereoisomers of sphinganine have been prepared by a general synthetic route that begins with enantioselective aza-Darzens MCRs, followed by stereospecific aziridine ring opening reactions.<sup>167</sup>

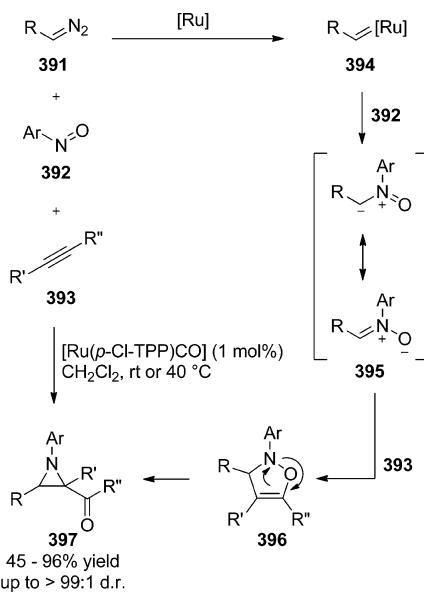
Diazo compounds have been used in MCRs beyond the aza-Darzens reaction. Rajasekar Reddy et al. have explored the reactivity of a variety of diazo compounds (391) with nitrosoarenes (392) and unsaturated carbon–carbon bonds. In the presence of a ruthenium–porphyrin complex, they were able to coerce stereoselective isoxazolidine formation from alkenes at room temperature.<sup>168</sup> When alkynes (393) were used under similar conditions, aziridine formation was observed.<sup>169</sup> The authors postulated that 391 is converted into ruthenium carbenes (394), which add to 392 to form nitrones (395) (Scheme 91). These intermediates are activated to participate in 1,3-dipolar cycloadditions with terminal or electron-deficient alkynes, giving isoxazolines (396), which thermally rearrange to C-acylaziridine products (397). Indeed, 396 could be isolated from control reactions conducted at reduced temperature. In addition to EDA, diazoaryl ketones and phosphonates were used to give aziridine ketones and aziridine phosphonates, respectively. Diastereoselectivity was often very high and was very sensitive to substitution of 391.

**Scheme 90.** One-Pot Preparation of *cis*- $\beta$ -Lactam 390, following Three-Component aza-Darzens Aziridination<sup>a</sup>



<sup>a</sup>Yield is based on 378 (Scheme 88).

**Scheme 91.** Ruthenium-Catalyzed Preparation of Aziridines by a 3CR Using Diazo Compounds (391), Nitrosoarenes (392), and Alkynes (393)<sup>a</sup>

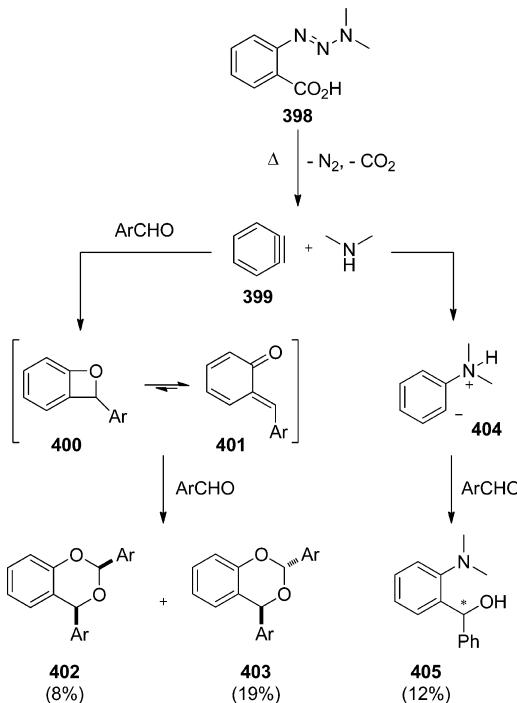


<sup>a</sup>R = CO<sub>2</sub>Et, COAr, PO(OMe)<sub>2</sub>.

### 3.6. Reactions Involving Benzyne Intermediates

The propensity for benzyne to undergo [2 + 2] cycloadditions with carbonyl groups was proposed by Heaney and Jablonski in 1968.<sup>170</sup> Previously, Yaroslavsky had shown that DMF reacts with benzyne to produce salicylaldehyde after hydrolysis.<sup>171</sup> Later, Nakayama et al. extended this methodology to a 3CR by heating benzyne precursor 398 in benzaldehyde at 160 °C.<sup>172</sup> In addition to 2-dimethylaminobenzhydrol (405), isomeric benzodioxins (402 and 403) were isolated (Scheme 92). Mechanistically, the [2 + 2] benzoxete 400 goes through a ring opening to quinone-methide 401, followed by 1,4-addition with a second equivalent of the aldehyde.

**Scheme 92.** Reactivity of Benzyne Precursor 398 When Heated in the Presence of Aryl Aldehydes<sup>a</sup>

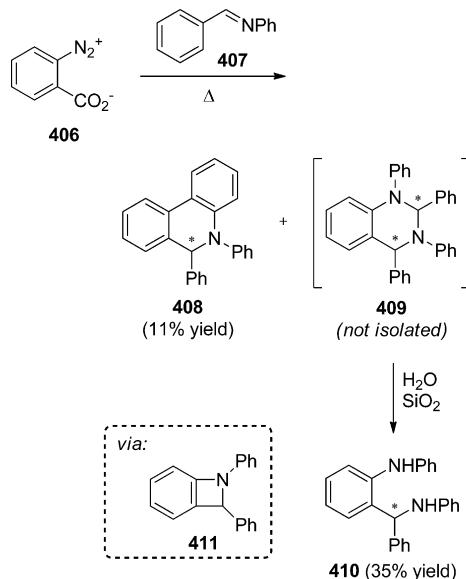


<sup>a</sup>Ar = Ph, 4-(CH<sub>3</sub>O)C<sub>6</sub>H<sub>4</sub>, 4-(Cl)C<sub>6</sub>H<sub>4</sub>.

This mode of reactivity was later extended to carbon–nitrogen double bonds in the reaction of benzyne with *N*-benzylideneaniline (407). The expected tetrahydroquinazoline product (409) was hydrolyzed during silica gel purification to diamine 410, which was isolated in 35% yield. Product 408 was also isolated in 11% yield and represents the product of 2 equiv of benzyne with 1 equiv of *N*-benzylideneaniline (Scheme 93).<sup>173</sup>

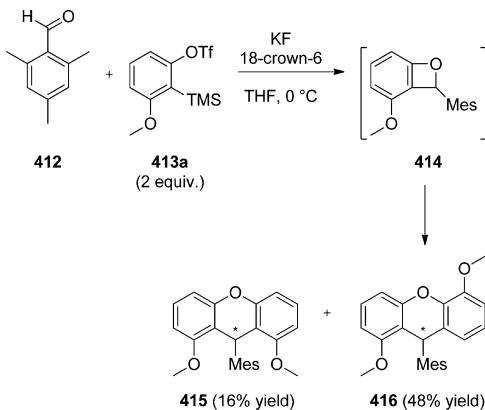
The 2:1 coupling of arynes with aryl aldehydes to produce symmetrical xanthenes has also been reported.<sup>174</sup> Electron-rich

**Scheme 93.** Benzyne Cycloaddition Products with *N*-Benzylideneaniline 407



naphthaldehydes and benzaldehydes were eligible substrates, while electron-neutral and electron-deficient substrates gave poor results. In these reactions the *o*-quinone methide derived from 414 (see 401, Scheme 92) reacted with a second equivalent of benzyne in a formal [4 + 2] cycloaddition to furnish the xanthene product. The substituted 3-methoxybenzene produced two regioisomers (415 and 416, Scheme 94).

**Scheme 94. Synthesis of Xanthenes by 2:1 Aryne:Aldehyde Addition<sup>a</sup>**

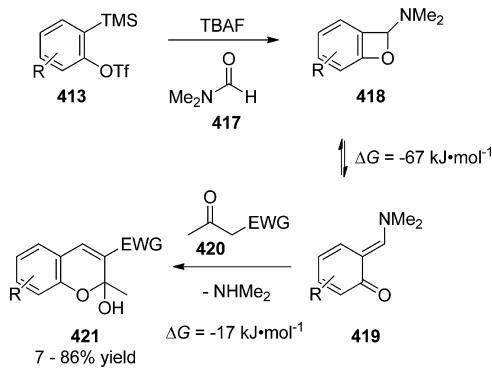


<sup>a</sup>Two of a possible four regioisomers are formed due to high selectivity in formation of fused oxetane 414. Mes, mesityl (2,4,6-trimethylphenyl).

The initial [2 + 2] reaction proceeded selectively, with the carbon–oxygen bond formed meta to the methyl ether (i.e., no other isomer of 414 is formed). The second benzene reacted unselectively. To date, the 3CR using two different aryne equivalents has not been described.

The reactivity of arynes toward both activated  $\sigma$ -bonds and  $\pi$ -bonds presents challenges toward developing selective MCRs using such insertions. One successful approach used DMF (417) as both reactant and solvent in the presence of an active methylene compound (0.15 M) to establish selective conditions.<sup>175</sup> The aryne undergoes insertion into the C=O bond of DMF to form a fused oxetane 418, in equilibrium with *o*-quinone methide 419 (Scheme 95). Such intermediates have been previously prepared<sup>171</sup> and then trapped using organometallic reagents in a sequential one-pot procedure.<sup>176</sup> In the

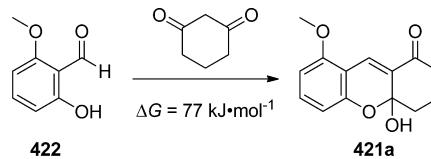
**Scheme 95. Synthesis of Chromenes 421 from Benzene Precursors (413), DMF, and Activated Ketones (420)<sup>a</sup>**



<sup>a</sup>For Gibbs free energy calculations, ketone is 1,3-cyclohexanedione at 325.15 K.

MCR approach, intermediate 419 added to activated ketones or esters to form substituted chromenes 421.<sup>175</sup> The 2-methoxy-substituted precursor 413 produced a single regioisomer, while the 3-methoxy-substituted analogue showed low regioselectivity. Compounds 418 and 419 were likely the reactive intermediates in favor of the hydrolyzed salicylaldehyde 422. When 422 analogues were separately prepared and tested under the reaction conditions, the rates of transformation to chromenes 421 were significantly diminished (Scheme 96).

**Scheme 96. Salicylaldehyde 422 is Unlikely To Be an Intermediate in the Multicomponent Reaction on the Basis of Control Experiments That Showed Sluggish Conversion to Chromene 421a<sup>a</sup>**

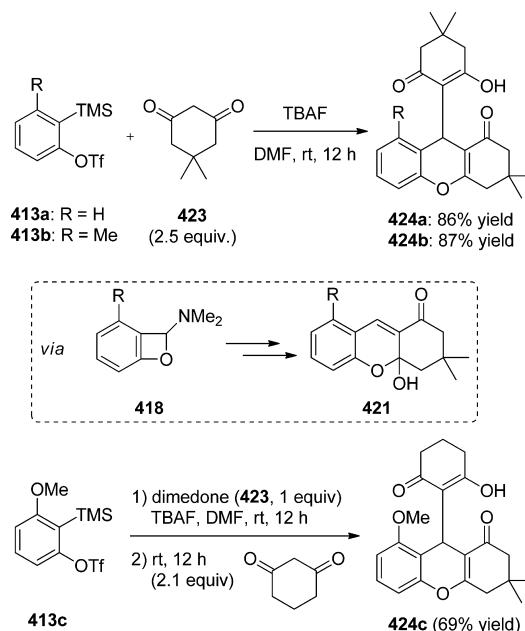


<sup>a</sup>Change in Gibbs free energy calculation was conducted at 325.15 K.

Calculation of the Gibbs free energy changes also shows the transformation of 422 to 421 to be endothermic, in contrast to the transformation of 419 to product (418 to 419 is also an exothermic process).

Several activated ketones and esters could be used in this reaction with variable yields. The authors demonstrated the utility of this approach in the synthesis of a neuropeptide Y receptor Y<sub>5</sub> agonist derived from 2 equiv of dimedone (423) (Scheme 97). Similarly, they demonstrated that the multicomponent chromene synthesis could be followed by addition

**Scheme 97. Synthesis of Substituted Xanthenes Based on a 3CR To Assemble Chromenes<sup>a</sup>**



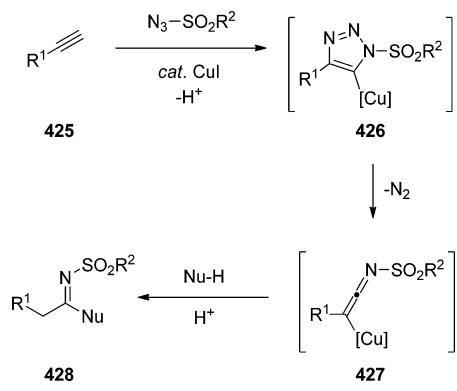
<sup>a</sup>The top reaction is a 4CR (ayne, DMF, 2 equiv of dimedone 423). The lower reaction is a 3CR (ayne, DMF, 1 equiv of dimedone), followed by addition of 1,3-cyclohexanedione in a one-pot process. Both syntheses proceed through intermediates 418 and 421 (Scheme 95).

of a second  $\beta$ -diketone in a one-pot approach to xanthene derivative **424c**. Though currently limited to DMF and requiring large excesses of the amide substrate, this approach exemplifies how strain energy can be released over the course of a multistep transformation toward buildup of useful molecules.

### 3.7. Azide–Alkyne Couplings

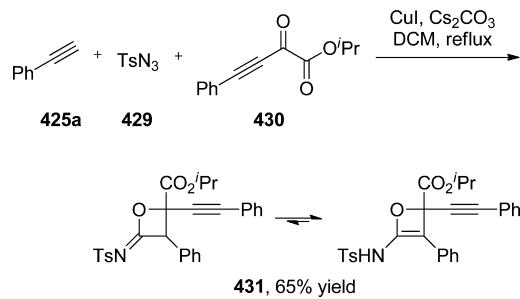
Ketenimines are highly reactive intermediates that have found application in the syntheses of diverse heterocycles due to their propensity to undergo [2 + 2] cycloadditions. The products of copper-catalyzed azide–alkyne coupling (CuAAC) reactions using sulfonyl azide substrates have been shown to degrade to *N*-sulfonyl ketenimines, which can be trapped using a variety of nucleophiles (Scheme 98; see also section 2.9).<sup>177</sup> In the

**Scheme 98. Copper-Catalyzed Azide–Alkyne Coupling (CuAAC) Leading to *N*-Sulfonyl Ketenimine and Trapping by a Nucleophile**



context of MCRs, terminal alkynes,  $TsN_3$ , and alkynyl keto alkyl esters (**430**) were reacted in the presence of copper iodide to form 2-iminooxetanes (**431**, Scheme 99).<sup>178</sup> These hetero-

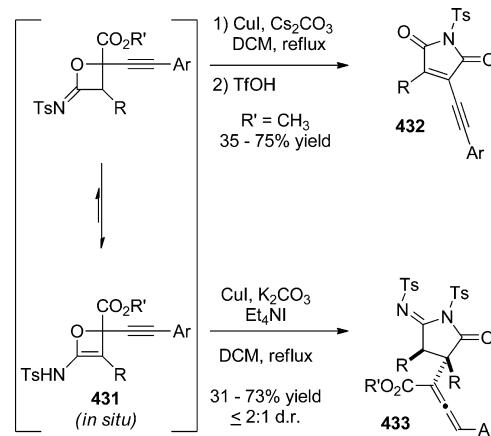
**Scheme 99. Synthesis and Isolation of 2-Iminooxetane 431**



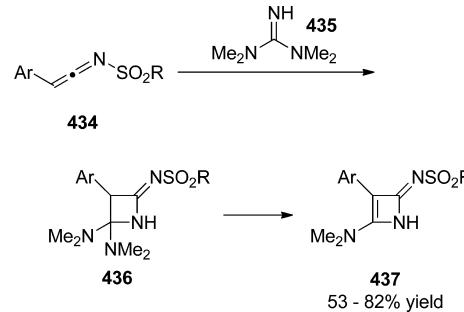
cycles were either isolable or further reacted via ring-expansion processes. Iminooxetanes themselves were isolable as a mixture of tautomers using  $Cs_2CO_3$  as base and low-temperature silica-gel column chromatography. Intramolecular amidation to form substituted maleimides (**432**) could be promoted using methyl esters or  $Cs_2CO_3$  as base, with addition of TfOH prior to workup (Scheme 100). Finally, 5-iminopyrrolidinones, products of a formal [3 + 2] cycloaddition of **431** with an additional equivalent of ketenimine, were formed in the presence of  $K_2CO_3$  and  $Et_4NI$ . Product diastereoselectivities were low (1:1–2:1), in favor of the syn-isomer.

When tetramethylguanidine **435** was used to trap ketenimine intermediates such as **434**, 1,4-dihydroazete derivatives (**437**) were produced (Scheme 101).<sup>179</sup> Nucleophilic addition of **435**

**Scheme 100. Other Products Available through 2-Iminooxetanes (431) Include Maleimides (432) and 5-Iminopyrrolidinones (433)**



**Scheme 101. Synthesis of 437 from Arylacetylenes, Sulfonyl Azides, and Tetramethylguanidine**

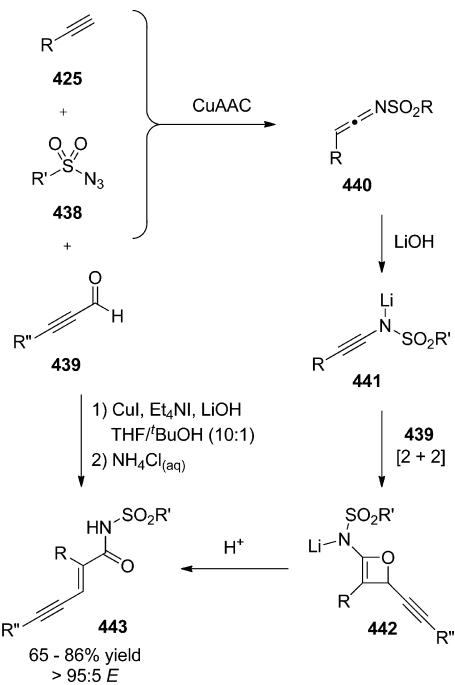


is followed by intramolecular cyclization and elimination of dimethyl amine to produce **437**. The reaction worked best with phenylacetylene, and aryl or aliphatic sulfonyl azides were tolerated.

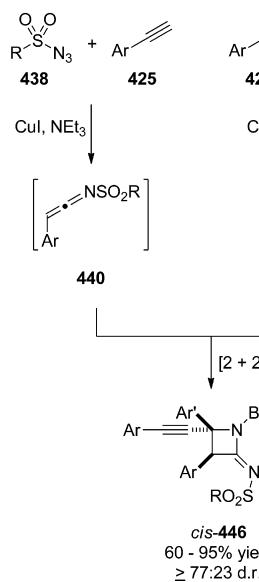
Another application of the ketenimines produced by CuAAC is in the synthesis of conjugated enynes. Ketenimines were shown to further react with propioldehydes (**439**) to produce conjugated enynes of the type **443** (Scheme 102).<sup>180</sup> Inorganic bases were found to be necessary for the reaction, with stoichiometric LiOH and 10 mol %  $Et_4NI$  being optimal. A variety of ynals (**439**), azides, and alkynes could be deployed with good yields and very high *E*-selectivity observed in the products. It was shown that triazoles of the type derived from CuAAC could be used as starting materials by activation with  $^7BuLi$ , which supports the hypothesis of lithium ynamide intermediates (**441**). A formal [2 + 2] cycloaddition with the carbonyl group of **439** produces substituted oxetenes (**442**), which generate the final product through ring opening.

Ketenimines derived from CuAAC have recently been exploited for [2 + 2] cycloadditions to produce azetidin-2-imines (**446**).<sup>181</sup> This was achieved using four substrates in a parallel copper catalysis route. Two equivalents of a terminal alkyne **425** were mixed with 1 equiv each of a sulfonyl azide (**438**) and an imidoyl chloride (**444**), with 10 mol % CuI and triethylamine in dichloromethane at room temperature (Scheme 103). The copper salt catalyzed both azide–alkyne coupling to produce a sulfonyl ketenimine (**440**) as well as  $sp-sp^2$  coupling between **425** and **444** to generate an ynimine (**445**), which underwent the [2 + 2] cycloaddition to form **446**.

**Scheme 102.** Three-Component Reaction and Proposed Mechanism for Synthesis of Conjugated Ynals through Oxetene Intermediate 442



**Scheme 103.** Parallel Catalysis Approach To Generate Intermediates 440 and 445, Leading to Azetidin-2-imine 446



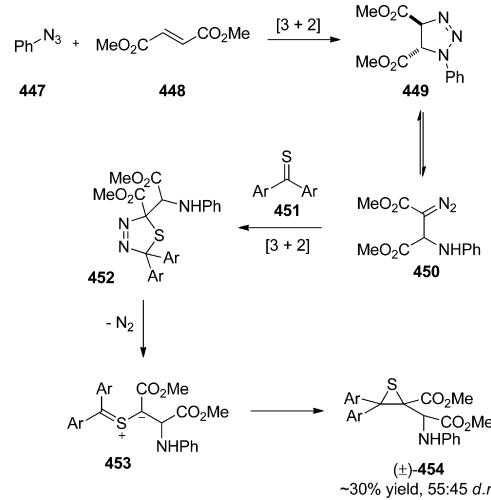
Similar diastereoselectivity was observed using a preformed ynimine, supporting its intermediary. Also reported was a reaction using two different alkynes by first coupling the imidoyl chloride to phenylacetylene, followed by addition of tosyl azide and 1-hexyne. The direct access to complex heterocyclic scaffolds using commercially available reagents and highly selective reactions makes this methodology attractive from a synthetic perspective.

### 3.8. Other Cycloadditions

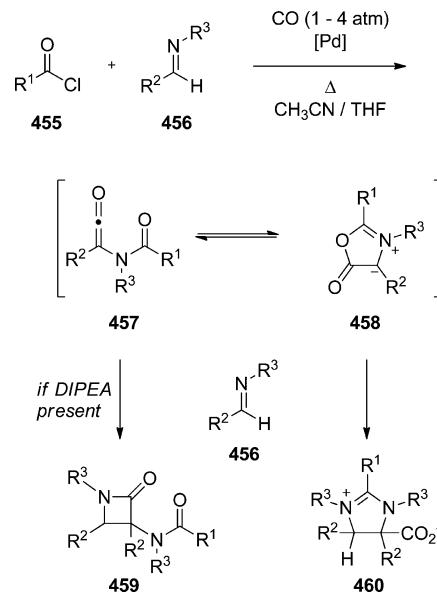
The three-component reaction of thioketones with phenyl azide and dimethyl fumarate produced diastereomeric mixtures

of thiiranes.<sup>182</sup> The proposed mechanism involves an initial [3 + 2] cycloaddition between the azide and fumarate to give triazoline 449 and its diazo isomer 450 (Scheme 104). A

**Scheme 104.** Synthesis of Racemic, Unstable Thiiranes 454 through Three-Component Reaction of Phenyl Azide, Dimethyl Fumarate, and Diaryl Thioketones



**Scheme 105.** Multicomponent Syntheses of Münchnones (458),  $\beta$ -Lactams (459), and Imidazolines (460)<sup>a</sup>



<sup>a</sup>Consumption of HCl generated during formation of 457 and 458 was essential to accessing 459, which was isolated exclusively as the trans-isomer.

second [3 + 2] cycloaddition with the thioketone 451 leads to dihydrothiadiazole 452, which loses N<sub>2</sub> to give a thiocarbonyl ylide electrocyclicization precursor (453). The thiirane products 454 were found to be thermally unstable but could be desulfurized in the presence of hexamethyl phosphorus triamide. In previous studies, the authors explored the reactivity of alkyl thioketones and did not isolate thiirane products but, rather, 1,3-oxathiolane derivatives.<sup>183</sup> This is explained by the differential reactivity of the thiocarbonyl ylide.

Arndtsen and co-workers demonstrated the palladium-catalyzed multicomponent synthesis of müchnones (**458**) using acyl chlorides (**455**), imines (**456**), and carbon monoxide (Scheme 105).<sup>184</sup> These zwitterionic heterocycles could be isolated or converted *in situ* to other products, including imidazolines (**460**), by a 1,3-dipolar cycloaddition with a second equivalent of imine.<sup>185</sup> The authors postulated that a formal [2 + 2] cycloaddition of **456** with ketene intermediate **457** (in equilibrium with müchnone **458**) would provide access to  $\beta$ -lactams (**459**). Consumption of HCl generated during the MCR with sterically hindered nitrogen base DIPEA proved to be the key to realizing this hypothesis.<sup>186</sup> Under optimized conditions, a variety of  $\beta$ -lactams were prepared in moderate to good yields, with electron deficient imines serving as more challenging substrates.  $\beta$ -Lactams derived from two nonidentical imines could also be prepared. In this case, 1 equiv of **456** was added to the reaction mixture using a slightly different palladium catalyst, followed by a second imine after 24–30 h. While this represents a less convergent approach to the products, it is perhaps more synthetically useful.

#### 4. CONCLUSIONS

The driving force of a multicomponent reaction arises from the energy embedded in one or more of the starting materials. Driven by strain release, multicomponent reactions employing small ring heterocycles offer opportunities for atom-economical synthesis of organic molecules. It is noteworthy that alternate factors can also provide the driving force, leading to opportunities to retain the core structures of small heterocycles in products. Many instances covered in this review describe strained rings that are being preserved in the products, which provide further opportunities for site-selective structural modification. In some cases, small ring heterocycles can even be *built* during multicomponent synthesis. On balance, the analysis of trends we discussed in this paper indicates that novel examples of cascade and multicomponent reactions are most likely to be identified by either considering transition-metal catalysis or by designing new densely functionalized building blocks.

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##### Notes

The authors declare no competing financial interests.

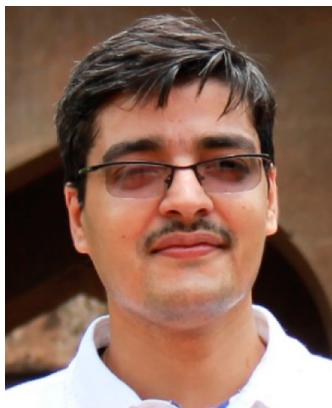
##### Biographies



Benjamin Rotstein studied chemistry (B.Sc.H 2007) at Dalhousie University and University of King's College (Halifax, Canada). He moved to University of Toronto (Toronto, Canada) to continue his education under the supervision of Prof. Andrei Yudin, earning a Ph.D. in 2012. During this time, his research focused on multicomponent reactions, amphoteric reactivity, and peptide chemistry, and included medicinal chemistry research at GlaxoSmithKline (Durham, NC). He is currently an NSERC (Canada) Postdoctoral Fellow with Dr. Neil Vasdev at Harvard Medical School and Massachusetts General Hospital (Boston, MA), where he is studying carbon-11 and fluorine-18 radiochemistry and neuroimaging using positron emission tomography (PET).



Serge Zaretsky was born in Moscow, Russia, and grew up in Toronto, Canada. He received his B.Sc. degree in Biochemistry from McGill University (Montreal, Canada) in 2009. There, he performed research in the Tsantrizos group, Moitessier group, and the Stone Pain Lab. He then joined the University of Toronto (Toronto, Canada) in order to pursue a Ph.D. degree in Organic Chemistry under the supervision of Prof. Andrei Yudin. His graduate research has focused on the development of multicomponent reactions and peptide macrocyclization techniques. A major element of his studies has been the application of cyclic peptides in the fields of chemical biology and medicinal chemistry.



Vishal Rai received his Ph.D. in 2008 working in the area of asymmetric synthesis from the Department of Chemistry at Indian Institute of Technology Bombay (Mumbai, India), under the supervision of Prof. I. N. N. Namboothiri. In 2008, he joined the group of Prof. Andrei Yudin in the Department of Chemistry, University of Toronto (Toronto, Canada) and worked on chemoselective methodologies and peptide macrocycles. Vishal joined Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal (Bhopal, India) as Assistant Professor and

Ramanujan Fellow in May 2011. His research group is interested in development of chemical tools for site-selective protein labeling.



Andrei K. Yudin started his independent career at the University of Toronto in 1998. His research interests are in the area of organic synthesis. He became an Associate Professor in 2002, followed by promotion to the rank of a Full Professor in 2007. Since 2011, he has served as the Associate Editor for *Organic and Biomolecular Chemistry* (a publication of the Royal Society of Chemistry, U.K.). In 2012, he started Encycle Therapeutics, a Toronto-based company aimed at target-driven drug discovery propelled by the macrocyclization technologies developed by Yudin and his colleagues. He has been recognized with a number of awards, and in 2013, he was elected as a Fellow of the Royal Society of Canada (Academy of Science).

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## ABBREVIATIONS USED

[18]crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
3CR	three-component reaction
Ac	acetyl
Ar	aryl
ARC	anion relay chemistry
ASG	anion stabilizing group
Asp	aspartic acid
ATPH	aluminum tris(2,6-diphenylphenoxyde)
Bmim	1-butyl-3-methylimidazolium
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bz	benzoyl
CuAAC	copper-catalyzed azide–alkyne cycloaddition
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIC	N,N'-dicyclohexylcarbodiimide
DIPEA	N,N-diisopropylethylamine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DPBS	Dulbecco's phosphate-buffered saline
dppp	1,3-bis(diphenylphosphino)propane
Et	ethyl

EWG	electron-withdrawing group
HATU	N-[1H-1,2,3-triazolo[4,5- <i>b</i> ]pyridin-1-yloxy)-(dimethylamino)methylene]-N-methylmethanaminium hexafluorophosphate
HMPA	hexamethylphosphoramide
IC <sub>50</sub>	half-maximal inhibitory concentration
<i>i</i> Hx	isohexyl
<i>i</i> Pr	isopropyl
LDA	lithium diisopropyl amide
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
MCR	multicomponent reaction
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
Ms	mesyl
MW	microwave heating
NBS	N-bromosuccinimide
<i>n</i> -Bu	<i>n</i> -butyl
NHS	N-hydroxysuccinimide
<i>n</i> -Pr	<i>n</i> -propyl
Ns	<i>p</i> -nitrobenzenesulfonyl
Nu	nucleophile
OTf	trifluoromethanesulfonate
P3CR	Passerini three-component reaction
Ph	phenyl
Pht	phthalyl
pin	pinacol
PMP	<i>p</i> -methoxyphenyl
PNB	<i>p</i> -nitrobenzyl
<i>p</i> NZ	<i>p</i> -nitrobenzyloxycarbonyl
PPN	bis(triphenylphosphoranylidene)iminium
pyr	pyridine
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	tert-butyldimethylsilyl
<i>t</i> Bu	tert-butyl
TCEP·HCl	tris(2-carboxyethyl)phosphine hydrochloride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TMG	tetramethylguanidine
TMS	trimethylsilyl
TosMIC	<i>p</i> -toluenesulfonylmethyl isocyanide
Ts	<i>p</i> -toluenesulfonyl
U4CR	Ugi four-component reaction

## REFERENCES

- (1) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
- (2) Maeda, S.; Komagawa, S.; Uchiyama, M.; Morokuma, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 644.
- (3) Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2003**, 2988.
- (4) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582.
- (5) Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2005**, 1787.
- (6) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
- (7) Chéron, N.; Ramozzi, R.; Kaïm, L. E.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1361.
- (8) For an example of the U4CR using aqueous solvent, see the following: Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444.
- (9) Quast, H.; Aldenkortt, S. *Chem.–Eur. J.* **1996**, *2*, 462.
- (10) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971.
- (11) White, C. J.; Yudin, A. K. *Nat. Chem.* **2011**, *3*, 509.
- (12) Failli, A.; Immer, H.; Götz, M. *Can. J. Chem.* **1979**, *57*, 3257.
- (13) Hili, R.; Rai, V.; Yudin, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 2889.
- (14) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772.

- (15) Londregan, A. T.; Farley, K. A.; Limberakis, C.; Mullins, P. B.; Piotrowski, D. W. *Org. Lett.* **2012**, *14*, 2890.
- (16) Scully, C. C. G.; Rai, V.; Poda, G.; Zaretsky, S.; Burns, D. C.; Houlston, R. S.; Lou, T.; Yudin, A. K. *Chem.—Eur. J.* **2012**, *18*, 15612.
- (17) Robinson, J. A. *Acc. Chem. Res.* **2008**, *41*, 1278.
- (18) (a) Sahoo, H.; Roccatano, D.; Hennig, A.; Nau, W. M. *J. Am. Chem. Soc.* **2007**, *129*, 9762. (b) Arora, P. S.; Ansari, A. Z.; Timothy, P.; Ptashne, M.; Dervan, P. B. *J. Am. Chem. Soc.* **2002**, *124*, 13067.
- (c) Schuler, B.; Lipman, E. A.; Steinbach, P. J.; Kumke, M.; Eaton, W. A. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 2754.
- (19) Rotstein, B. H.; Winternheimer, D. J.; Yin, L. M.; Deber, C. M.; Yudin, A. K. *Chem. Commun.* **2012**, *48*, 3775.
- (20) (a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science* **1994**, *266*, 776. (b) Kent, S. B. H. *Chem. Soc. Rev.* **2009**, *38*, 338.
- (21) (a) Martin, N. I. *J. Biol. Chem.* **2003**, *278*, 13124. (b) Tran, A. X.; Lester, M. E.; Stead, C. M.; Raetz, C. R. H.; Maskell, D. J.; McGrath, S. C.; Cotter, R. J.; Trent, M. S. *J. Biol. Chem.* **2005**, *280*, 28186. (c) Ellerby, H. M.; Bredesen, D. E.; Fujimura, S.; John, V. J. *Med. Chem.* **2008**, *51*, 5887.
- (22) Rotstein, B. H.; Mourtada, R.; Kelley, S. O.; Yudin, A. K. *Chem.—Eur. J.* **2011**, *17*, 12257.
- (23) (a) Horton, K. L.; Stewart, K. M.; Fonseca, S. B.; Guo, Q.; Kelley, S. O. *Chem. Biol.* **2008**, *15*, 375. (b) Yousif, L.; Stewart, K. M.; Horton, K. L.; Kelley, S. O. *ChemBioChem.* **2009**, *10*, 2081.
- (24) Rotstein, B. H.; Rai, V.; Hili, R.; Yudin, A. K. *Nat. Protoc.* **2010**, *5*, 1813.
- (25) Roxin, A.; Chen, J.; Scully, C. C. G.; Rotstein, B. H.; Yudin, A. K.; Zheng, G. *Bioconjugate Chem.* **2012**, *23*, 1387.
- (26) Rotstein, B. H.; Yudin, A. K. *Synthesis* **2012**, *44*, 2851.
- (27) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.
- (28) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.
- (29) Saito, S.; Yamazaki, S.; Shiozawa, M.; Yamamoto, H. *Synlett* **1999**, 581.
- (30) Kim, J. H.; Jung, S. H. *Tetrahedron Lett.* **2007**, *48*, 4243.
- (31) (a) Nishiyama, Y.; Katahira, C.; Sonoda, N. *Tetrahedron Lett.* **2004**, *45*, 8539. (b) Nishiyama, Y.; Katahira, C.; Sonoda, N. *Tetrahedron* **2006**, *62*, 5803.
- (32) Sonoda, N.; Mizuno, T.; Murakami, S.; Kondo, K.; Ogawa, A.; Ryu, I.; Kambe, N. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 452.
- (33) Glushkov, V. A.; Stryapunina, O. G.; Dolzhenko, A. V.; Syropyatov, B. Y.; Shklyaev, Y. V. *Pharm. Chem. J.* **2009**, *43*, 245.
- (34) Davies, S. G.; Polywka, M. E. C.; Thomas, S. E. *Tetrahedron Lett.* **1985**, *26*, 1461.
- (35) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487.
- (36) Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084.
- (37) Bonney, K. J.; Braddock, D. C. *J. Org. Chem.* **2012**, *77*, 9574.
- (38) Davies, S. G.; Polywka, M. E.; Thomas, S. E. *J. Chem. Soc. Perkin Trans 1* **1986**, 1277.
- (39) Bonney, K. J.; Braddock, D. C.; White, A. J. P.; Yaqoob, M. J. *Org. Chem.* **2011**, *76*, 97.
- (40) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 10245.
- (41) Zhou, J.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2012**, *14*, 5250.
- (42) Wolk, J. L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* **2001**, *66*, 915.
- (43) Chen, J.; Chng, S.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 6456.
- (44) Ke, Z.; Yeung, Y.-Y. *Org. Lett.* **2013**, *15*, 1906.
- (45) Zhao, W.; Wang, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6209.
- (46) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2027.
- (47) Chen, Z.; Wang, Z.; Sun, J. *Chem.—Eur. J.* **2013**, *19*, 8426.
- (48) (a) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.
- (49) Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.
- (50) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511.
- (51) (a) Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994**, *35*, 4271. (b) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407. (c) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011.
- (52) (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503.
- (53) Smith, A. B.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925.
- (54) Singh, G. S.; Mollet, K.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2012**, *113*, 1441.
- (55) Smith, A. B.; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435.
- (56) Smith, A. B.; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493.
- (57) Smith, A. B.; Han, H.; Kim, W. *Org. Lett.* **2011**, *13*, 3328.
- (58) (a) Smith, A. B., III; Duffey, M. O. *Synlett* **2004**, *8*, 1363. (b) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2007**, *9*, 3311.
- (59) Natta, G.; Pino, P.; Ercoli, R. *J. Am. Chem. Soc.* **1952**, *74*, 4496.
- (60) Seon, M.; Leleu, J. U.S. Patent 2782226, 1957.
- (61) Eisenmann, J.; Yamartino, R.; Howard, J. *J. Org. Chem.* **1961**, *26*, 2102.
- (62) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 1460.
- (63) Seki, Y.; Hidaka, A.; Murai, S.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 174.
- (64) Seki, Y.; Murai, S.; Yamamoto, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 789.
- (65) Murai, T.; Kato, S.; Murai, S.; Toki, T.; Suzuki, S.; Sonoda, N. *J. Am. Chem. Soc.* **1984**, *106*, 6093.
- (66) Murai, T.; Yasui, E.; Kato, S.; Hatayama, Y.; Suzuki, S.; Yamasaki, Y.; Sonoda, N.; Kurosawa, H.; Kawasaki, Y.; Murai, S. *J. Am. Chem. Soc.* **1989**, *111*, 7938.
- (67) Murai, T.; Hatayama, Y.; Murai, S.; Sonoda, N. *Organometallics* **1983**, *2*, 1883.
- (68) Murai, T.; Furuta, K.; Kato, S.; Murai, S.; Sonoda, N. *J. Organomet. Chem.* **1986**, *302*, 249.
- (69) Chatani, N.; Fujii, S.; Yamasaki, Y.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1986**, *108*, 7361.
- (70) Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *J. Chem. Soc. Chem. Commun.* **1989**, 1253.
- (71) Watanabe, Y.; Nishiyama, K.; Zhang, K.; Okuda, F.; Kondo, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 879.
- (72) Drent, E.; Kragtwijk, E. Carbonylation of epoxides. US5310948 A, 1994.
- (73) Tokunaga, M. *Science* **1997**, *277*, 936.
- (74) Schaus, S. E.; Brandes, B. D.; Larow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
- (75) Hinterding, K.; Jacobsen, E. N. *J. Org. Chem.* **1999**, *64*, 2164.
- (76) Goodman, S. N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4703.
- (77) Denmark, S. E.; Ahmad, M. *J. Org. Chem.* **2007**, *72*, 9630.
- (78) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174.
- (79) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781.
- (80) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11426.
- (81) Kramer, J. W.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett.* **2006**, *8*, 3709.
- (82) Church, T. L.; Getzler, Y. D. Y. L.; Coates, G. W. *J. Am. Chem. Soc.* **2006**, *128*, 10125.
- (83) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156.
- (84) Nakano, K.; Kodama, S.; Permana, Y.; Nozaki, K. *Chem. Commun.* **2009**, 6970.
- (85) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987.

- (86) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550.  
 (87) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215.  
 (88) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502.  
 (89) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 391.  
 (90) (a) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280. (b) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729. (c) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12686. (d) Bhuvaneswari, S.; Jeganmohan, M.; Yang, M.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2158.  
 (91) Berti, F.; Crotti, P.; Cassano, G.; Pineschi, M. *Synlett* **2012**, *23*, 2463.  
 (92) (a) Okuma, K.; Hino, H.; Sou, A.; Nagahora, N.; Shioji, K. *Chem. Lett.* **2009**, *38*, 1030. (b) Okuma, K.; Fukuzaki, Y.; Nojima, A.; Sou, A.; Hino, H.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1238.  
 (93) Yoshida, H.; Asatsu, Y.; Mimura, Y.; Ito, Y.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9676.  
 (94) Stephens, D.; Zhang, Y.; Cormier, M.; Chavez, G.; Arman, H.; Larionov, O. V. *Chem. Commun.* **2013**, *49*, 6558.  
 (95) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517.  
 (96) Cui, S.; Wang, J.; Wang, Y. *Org. Lett.* **2007**, *9*, 5023.  
 (97) Han, Y.; Xie, Y.-X.; Zhao, L.-B.; Fan, M.-J.; Liang, Y.-M. *Synthesis* **2008**, 87.  
 (98) Li, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 8973.  
 (99) Wu, X.; Zhang, J. *Synthesis* **2012**, *44*, 2147.  
 (100) Heine, H. W.; Weese, R. H.; Cooper, R. A.; Durbetaki, A. J. *J. Org. Chem.* **1967**, *32*, 2708.  
 (101) Armstrong, R. W.; Salvati, M. E.; Nguyen, M. *J. Am. Chem. Soc.* **1992**, *114*, 3144.  
 (102) Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 3807.  
 (103) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.  
 (104) Armstrong, R. W. WO1995002566 A1, 1995.  
 (105) Radha Krishna, P.; Lopinti, K. *Synlett* **2007**, 83.  
 (106) Another report describing the use of 2,3-epoxyaldehydes in the P3CR found little evidence for “matched–mismatched” interactions between the aldehydes and protected proline derivatives and “no significant stereochemical induction”. However, these studies were conducted under decidedly different reaction conditions. Deobald, A. M.; Corrêa, A. G.; Rivera, D. G.; Paixão, M. W. *Org. Biomol. Chem.* **2012**, *10*, 7681.  
 (107) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P.; Torres, M. R. *J. Org. Chem.* **2009**, *74*, 8421.  
 (108) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P.; Torres, M. R. *Eur. J. Org. Chem.* **2012**, 2359.  
 (109) Liang, Y.; Hnatiuk, N.; Rowley, J. M.; Whiting, B. T.; Coates, G. W.; Rablen, P. R.; Morton, M.; Howell, A. R. *J. Org. Chem.* **2011**, *76*, 9962.  
 (110) Liew, S. K.; He, Z.; St. Denis, J. D.; Yudin, A. K. *J. Org. Chem.* **2013**, *78*, 11637.  
 (111) Assem, N.; Hili, R.; He, Z.; Kasahara, T.; Inman, B. L.; Decker, S.; Yudin, A. K. *J. Org. Chem.* **2012**, *77*, 5613.  
 (112) Libmann, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.  
 (113) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J. E.; Couladouros, A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.  
 (114) Huang, J.-M.; Yokokawa, R.; Yang, C.-S.; Fukuyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6111.  
 (115) Bhalgwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372.  
 (116) Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217.  
 (117) Müller, E.; Zeeh, B. *Justus Liebigs Ann. Chem.* **1966**, *696*, 72.  
 (118) (a) Kabbe, H.-J. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 389. (b) Kabbe, H.-J. *Chem. Ber.* **1969**, *102*, 1404.  
 (119) Kabbe, H.-J. *Chem. Ber.* **1969**, *102*, 1410.  
 (120) Zeeh, B. *Synthesis* **1969**, 65.  
 (121) Saegusa, T.; Takaishi, N.; Fujii, H. *Polym. Lett.* **1967**, *5*, 779.  
 (122) Saegusa, T.; Takaishi, N.; Fujii, H. *Tetrahedron* **1968**, *24*, 3795.  
 (123) Zeeh, B. *Tetrahedron Lett.* **1969**, *2*, 113.  
 (124) Zeeh, B. *Chem. Ber.* **1969**, *102*, 1876.  
 (125) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810.  
 (126) Dömling, A.; Starnecker, M.; Ugi, I. *Angew. Chem., Int. Ed.* **1995**, *34*, 2238.  
 (127) (a) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267. (b) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 2802.  
 (128) Pitlik, J.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3129.  
 (129) Aviles, E.; Rodriguez, A. D. *Org. Lett.* **2010**, *12*, 5290.  
 (130) Wratten, S. J.; Faulkner, D. J.; Hirotsu, K.; Clardy, J. *Tetrahedron Lett.* **1978**, *19*, 4345.  
 (131) Ciavatta, M. L.; Gavagnin, M.; Manzo, E.; Puliti, R.; Mattia, C. A.; Mazzarella, L.; Cimino, G.; Simpson, J. S.; Garson, M. J. *Tetrahedron* **2005**, *61*, 8049.  
 (132) Isenring, H. P.; Hofheinz, W. *Synthesis* **1981**, 385.  
 (133) Isenring, H. P.; Hofheinz, W. *Tetrahedron* **1983**, *39*, 2591.  
 (134) Sato, A.; Hirata, T.; Nakamizo, N. *Agric. Biol. Chem.* **1983**, *47*, 799.  
 (135) Kehagia, K.; Ugi, I. *Tetrahedron* **1995**, *51*, 9523.  
 (136) Dömling, A.; Kehagia, K.; Ugi, I. *Tetrahedron* **1995**, *51*, 9519.  
 (137) Nitta, H.; Hatanaka, M.; Ishimaru, T. *J. Chem. Soc., Chem. Commun.* **1987**, 51.  
 (138) (a) Doyle, T. W.; Belleau, B.; Luh, B.-Y.; Conway, T. T.; Menard, M.; Douglas, J. L.; Chu, D. T.-W.; Lim, G.; Morris, L. R.; Rivest, P.; Casey, M. *Can. J. Chem.* **1977**, *55*, 484. (b) Doyle, T. W.; Douglas, J. L.; Belleau, B.; Meunier, J.; Luh, B.-Y. *Can. J. Chem.* **1977**, *55*, 2873.  
 (139) Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883.  
 (140) Gedey, S.; Van der Eycken, J.; Fulop, F. *Org. Lett.* **2002**, *4*, 1967.  
 (141) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587.  
 (142) Kolb, J.; Beck, B.; Dömling, A. *Tetrahedron Lett.* **2002**, *43*, 6897.  
 (143) Naskar, D.; Roy, A.; Seibel, W. L.; West, L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 6297.  
 (144) Bachovchin, D. A.; Mohr, J. T.; Speers, A. E.; Wang, C.; Berlin, J. M.; Spicer, T. P.; Fernandez-Vega, V.; Chase, P.; Hodder, P. S.; Schürer, S. C.; Komura, D. K.; Rosen, H.; Fu, G. C.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6811.  
 (145) Padwa, A.; Clough, S.; Glazer, E. *J. Am. Chem. Soc.* **1970**, *92*, 1778.  
 (146) Padwa, A.; Glazer, E. *J. Am. Chem. Soc.* **1972**, *94*, 7788.  
 (147) Mahmoodi, N. O.; Kiyani, H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1417.  
 (148) Risitano, F.; Grassi, G.; Foti, F.; Moraci, S. *Synlett* **2005**, 1633.  
 (149) Kokotos, C.; McGarrigle, E.; Aggarwal, V. *Synlett* **2008**, 2191.  
 (150) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644.  
 (151) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.  
 (152) Rowbottom, M. W.; Mathews, N.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3927.  
 (153) Braun, H.; Huber, G. *Tetrahedron Lett.* **1976**, *17*, 2121.  
 (154) Watanabe, Y.; Ueno, Y.; Toru, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2042.  
 (155) Ballester, M. *Chem. Rev.* **1955**, *55*, 283.  
 (156) Cainelli, G.; Panunzio, M.; Giacomini, D. *Tetrahedron Lett.* **1991**, *32*, 121.  
 (157) Nagayama, S.; Kobayashi, S. *Chem. Lett.* **1998**, 685.  
 (158) Kubo, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 625.  
 (159) Ishii, Y.; Sakaguchi, S. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 909.

- (160) Yadav, J. S.; Reddy, B. V. S.; Shesha Rao, M.; Reddy, P. N. *Tetrahedron Lett.* **2003**, *44*, 5275.
- (161) Yadav, J. S.; Reddy, B. V.; Reddy, P. N.; Rao, M. S. *Synthesis* **2003**, 1387.
- (162) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445.
- (163) Chai, Z.; Bouillon, J.-P.; Cahard, D. *Chem. Commun.* **2012**, *48*, 9471.
- (164) Gupta, A. K.; Mukherjee, M.; Wulff, W. D. *Org. Lett.* **2011**, *13*, 5866.
- (165) Gupta, A. K.; Mukherjee, M.; Hu, G.; Wulff, W. D. *J. Org. Chem.* **2012**, *77*, 7932.
- (166) Huang, L.; Zhao, W.; Staples, R. J.; Wulff, W. D. *Chem. Sci.* **2013**, *4*, 622.
- (167) Mukherjee, M.; Zhou, Y.; Gupta, A. K.; Guan, Y.; Wulff, W. D. *Eur. J. Org. Chem.* **2014**, 1386.
- (168) Rajasekar Reddy, A.; Guo, Z.; Siu, F.-M.; Lok, C.-N.; Liu, F.; Yeung, K.-C.; Zhou, C.-Y.; Che, C.-M. *Org. Biomol. Chem.* **2012**, *10*, 9165.
- (169) Reddy, A. R.; Zhou, C.-Y.; Che, C.-M. *Org. Lett.* **2014**, *16*, 1048.
- (170) Heaney, H.; Jablonski, J. M. *Chem. Commun. London* **1968**, 1139.
- (171) Yaroslavsky, S. *Tetrahedron Lett.* **1965**, *6*, 1503.
- (172) Nakayama, J.; Yoshida, M.; Simamura, O. *Chem. Lett.* **1973**, *2*, 451.
- (173) Nakayama, J.; Midorikawa, H.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1063.
- (174) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049.
- (175) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638.
- (176) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956.
- (177) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. J. *Org. Chem.* **2008**, *73*, 5520.
- (178) Yao, W.; Pan, L.; Zhang, Y.; Wang, G.; Wang, X.; Ma, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 9210.
- (179) Yavari, I.; Nematpour, M. *Synlett* **2012**, *23*, 2215.
- (180) Cheng, D.; Ling, F.; Li, Z.; Yao, W.; Ma, C. *Org. Lett.* **2012**, *14*, 3146.
- (181) Xing, Y.; Zhao, H.; Shang, Q.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2013**, *15*, 2668.
- (182) Młostoiń, G.; Romański, J.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1997**, *80*, 1992.
- (183) Młostoiń, G.; Romański, J.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1996**, *79*, 1305.
- (184) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474.
- (185) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228.
- (186) Dhawan, R.; Dghaym, R. D.; St. Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927.