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Synthesis Design

Chemoselectivity and the Curious Reactivity Preferences of Functional Groups

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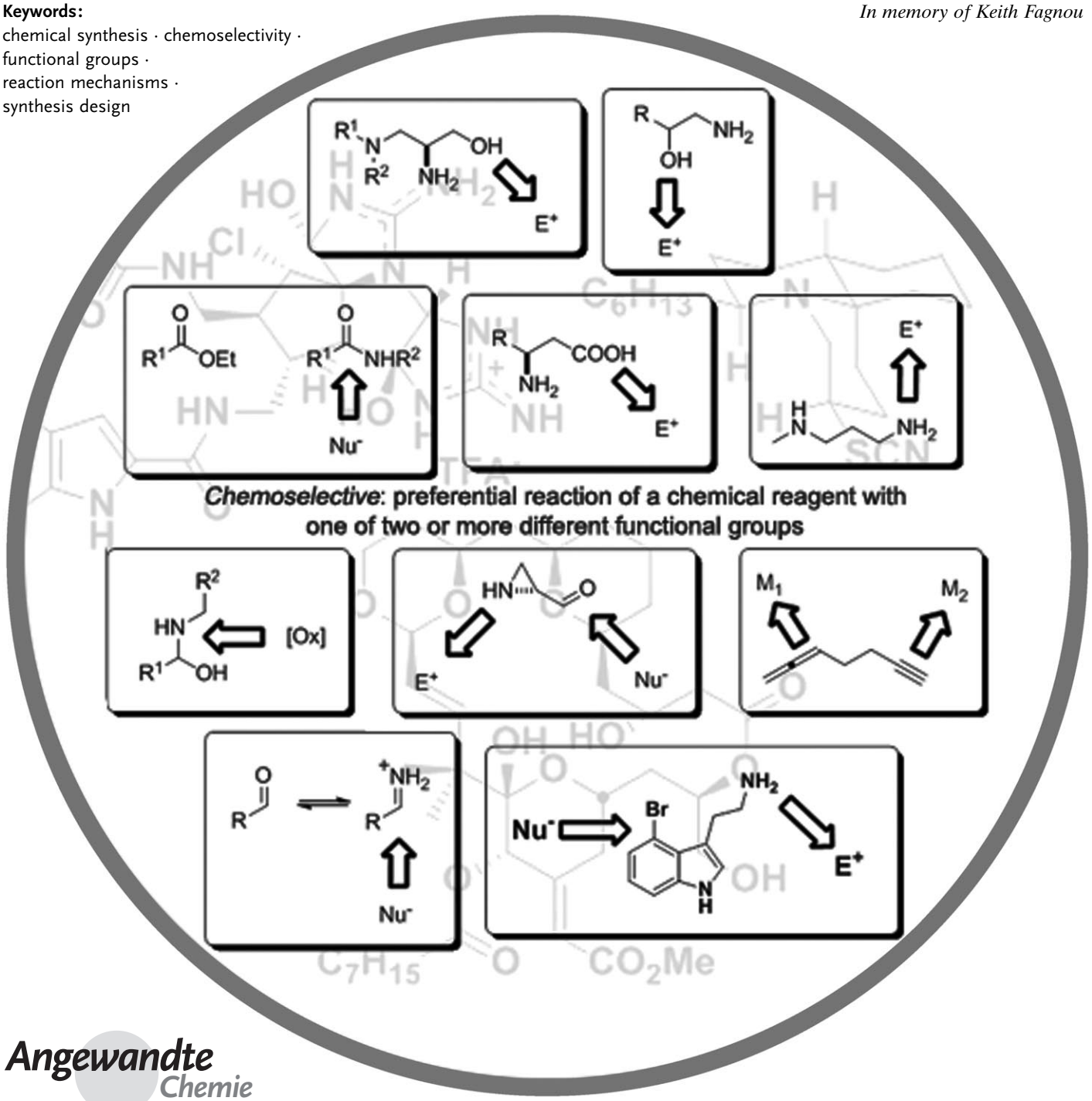
chemical synthesis · chemoselectivity · functional groups · reaction mechanisms · synthesis design

In memory of Keith Fagnou



Achieving high levels of chemoselectivity has been the Achilles' heel of chemical synthesis. The excitement generated by the successful realization of chemoselective strategies underscores the painstaking efforts to define a set of conditions conducive to selection among the available reaction pathways. We discuss in this Review various aspects of chemoselectivity that have been addressed in a range of synthetic methods over the past decade. We have focused on the proposed mechanistic basis of the reactions under consideration in an attempt to categorize them and highlight the key concepts that have been emerging on the basis of these studies. Our overview of recent advances in chemoselective processes suggests that significant progress has been made, but a lot of challenges lie ahead.

From the Contents

1. Introduction

In chemical synthesis, the term "selectivity" refers to the discrimination displayed by a reagent A when it reacts with two different reactants B and C. Selectivity can also refer to the discrimination between two different reaction pathways when A is made to react with a single reactant B.[1,2] There are also more specific terms that define a particular subtype of selectivity.

For example, "stereoselectivity" refers to controlling the stereochemical outcome of a reaction and can be further divided into enantio- and diastereselectivity. The term "regioselectivity" refers to the directional preference of the breaking or making of a chemical bond, whereas the term "chemoselectivity" describes the preferential reaction of a given reagent with one of two or more functional groups that are present in a reactant or a group of reactants.

A case can be made that biological and synthetic systems operate somewhat differently when it comes to imposing selectivity onto chemical transformations. The biosynthetic enzymes, which are tailored towards a specific substrate, work with high levels of stereo-, regio-, and chemoselectivity. The so-called Michaelis–Menten kinetics describes the enzyme/substrate pre-equilibrium before the transition state is reached.[3] An intricate superposition of hydrogen bonds and electrostatic interactions are involved in the kinetic discrimination among the available reaction pathways, and the high specificity of biological catalysts is driven by these interactions. On the other hand, synthetic approaches are more reductionist. The electronic and/or steric requirements of selected functional groups present in a given reactant are employed by chemists to explain and predict the selectivity of organic reactions. Redox potential, pK_a values, hard/soft acid/base considerations, and A values are the common metrics used by organic chemists to compare and predict the reactivity of different functional groups. Substrate specificity is hardly a desirable property for a synthetic reagent. On the contrary, generality and acceptance of a broad substrate scope are the most sought-after attributes.

Traditionally, the synthetic community has focused and dedicated more attention to the aspects of stereo- and regioselectivity rather than to those of chemoselectivity. Without a doubt, both stereo- and regiocontrol are central to synthesis. At the same time, achieving high levels of chemoselectivity is one of the most daunting challenges facing contemporary synthesis. Highly chemoselective reactions proceed with minimal reliance on protecting groups,[4] and contribute to both atom[5] and step economy.[6] In this Review, we discuss various aspects of chemoselectivity that have been addressed in a range of synthetic methods over the past decade. We have focused on the proposed reaction mechanisms in an attempt to categorize the reactions and highlight the key concepts that are emerging on the basis of these studies.

There are numerous examples where chemoselectivity has been driven by the innate reactivity of functional groups (for example,[8] the reduction of aldehydes in the presence of ketones). The sheer volume of material of this nature has resulted in these cases being beyond the scope of this Review. Instead, we examined reports in which unexpected selectivity was observed on the basis of an exogenous control element that exploits certain structural attributes of a substrate to achieve selectivity. The well known Luche reduction illustrates this point.[7] Unlocking selective ketone reduction in the presence of an aldehyde is possible in the presence of cerium trichloride. The in situ protection of the more reactive aldehyde as a cerium(III)-stabilized geminal diol is a simple means to access an unexpected reactivity manifold (Scheme 1).

Sections 2 and 3 contain selected examples that illustrate chemoselective transformations of molecules with saturated and unsaturated carbon–hetereoatom bonds, respectively.

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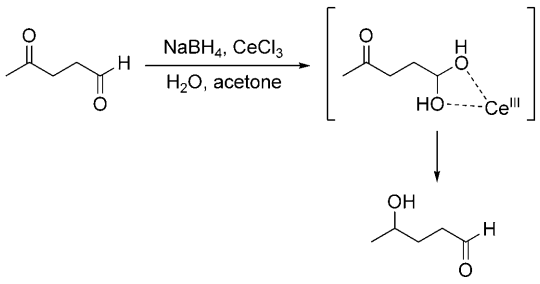

Scheme 1.

Section 4 deals with chemoselectivity attained in various metal-promoted carbon–carbon bond-forming reactions, while Section 5 focuses on the emerging field of C–H bond activation. Throughout these four sections we discuss the chemical tools that have been employed to address the challenges of chemoselectivity. These range from simple reagents such as Brønsted acids to elaborate transition-metal complexes. It was not always easy to make clear-cut decisions concerning where different cases belonged; there are instances which may fit in more than one category. The decisive step of a mechanism is in each case highlighted in a box within the scheme.

2. Chemoselective Transformations that Involve Saturated Carbon–Heteroatom Bonds

The vast majority of organic transformations belong to the so-called "polar" category.[8] Such reactions proceed by movement of pairs of electrons and involve nucleophiles and electrophiles as reaction partners. The delineation of factors that control the relative reactivity of polar functional groups is complicated. In addition to the inherent electronic properties of functional groups, their reactivity depends on the accessible conformational space and other factors. This underscores the difficulties in understanding the balance between steric and electronic factors that govern the outcome of organic transformations. Among the commonly utilized metrics of assessing polar reactivity, pK_a values are used most commonly. Chemists refer to the pK_a value of the conjugate acid of a given compound to assess its nucleophilicity. While a conceptual relationship exists between nucleophilicity and basicity, in many cases they do not correlate with each other. Nucleophilicity is a kinetic phenomenon defined as the effect of a Lewis base on the rate of a nucleophilic substitution reaction.[9] In contrast, basicity is a thermodynamic concept that describes the position of the equilibrium between a Lewis base and a proton. The assumption that strong bases are also strong nucleophiles is contingent on a minimal contribution from steric effects, solvation, and polarizability of the diffuse electrons of the heavier atoms, which is rarely the case.[10] Nonetheless, nucleophilicity and basicity remain intricately connected with each other. Accordingly, proton transfer can control the outcome of polar transformations.

Metal reagents and catalysts belong to another important group of control elements. The utility of metal-containing compounds, particularly transition-metal complexes, stems from the versatility of primary transformations such as ligand exchange, migratory insertion, oxidative addition, reductive elimination, and β elimination. These processes are intricately associated with species containing metal–hydrogen, metal–carbon, and metal–heteroatom bonds. The reactivity preferences of the corresponding organometallic intermediates are governed by the strengths of the metal–X bonds (X: hydrogen, carbon, or heteroatom). A distinction is typically made between dative and nondative metal–X bonds. The latter have significant ionic character and display nucleophilic reactivity. A correlation exists between the relative bond strength of the M–X bonds and those of the corresponding H–X bonds.[11] The corresponding organometallic intermediates can be powerful controllers of chemoselectivity in transforming saturated carbon–heteroatom bonds.

2.1. Selectivity between Amine and Hydroxy Groups

2.1.1. Proton-Mediated Chemoselectivity

As a result of their relevance in a wide range of areas, molecules that contain both amino and hydroxy functional groups have been a perfect testing ground for research on chemoselectivity. Proton transfer can lead to the formation of distinctly different bonding arrangements such as ionic, covalent, dipole–dipole, or hydrogen-bonding interactions. That reversible proton transfer can control reaction rates of polar transformations is familiar to everyone. Scheme 2 illustrates two "textbook" examples. In the first case a nucleophilic primary amine is rendered unreactive once the lone pair of electrons on the nitrogen atom has been protonated (Scheme 2 A). The lone pair of electrons on the nitrogen atom can also participate in an intramolecular

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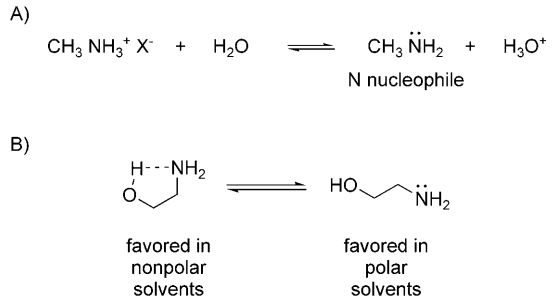
Professor Andrei K. Yudin obtained his BSc at Moscow State University and his PhD at the University of Southern California under the direction of Prof. G. K. Surya Prakash and Prof. George A. Olah. After a postdoctoral position with Prof. K. Barry Sharpless at the Scripps Research Institute, he moved to the University of Toronto, where in 2007 he became Full Professor. His research interests are in the development and application of novel synthetic methods that enable the discovery of functional molecules.



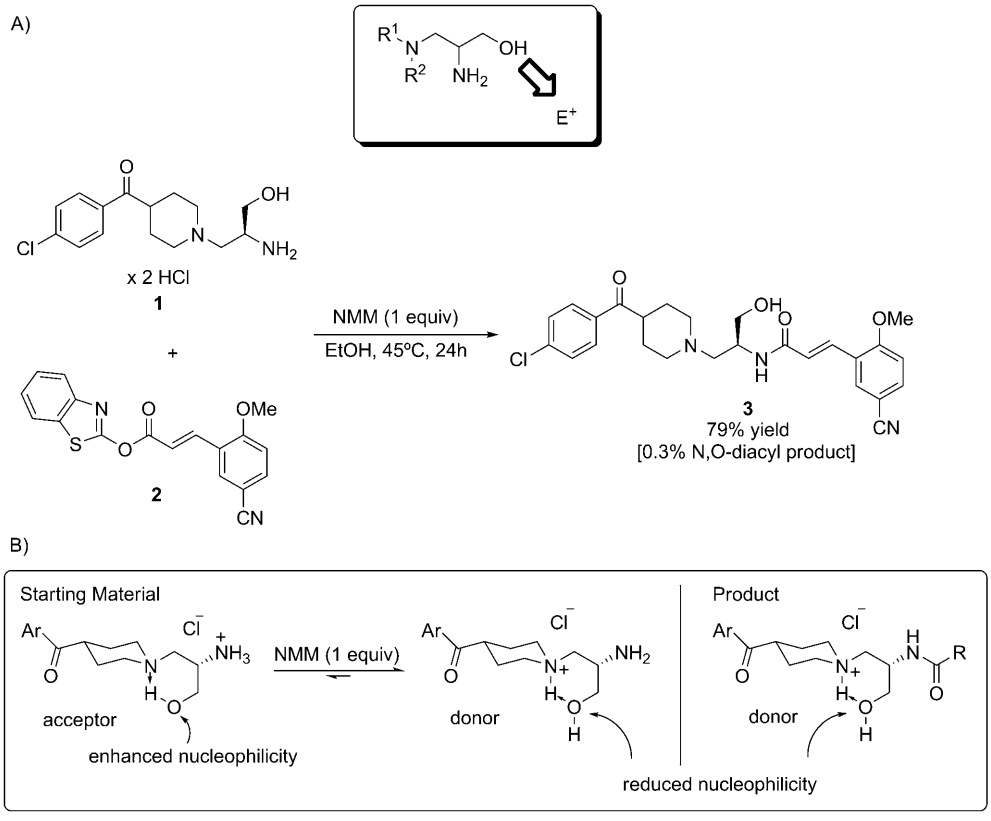
Scheme 2.

hydrogen bond, which modulates its nucleophilicity (Scheme 2B). In the examples that follow, a proton has been instrumental in modulating chemoselectivity.

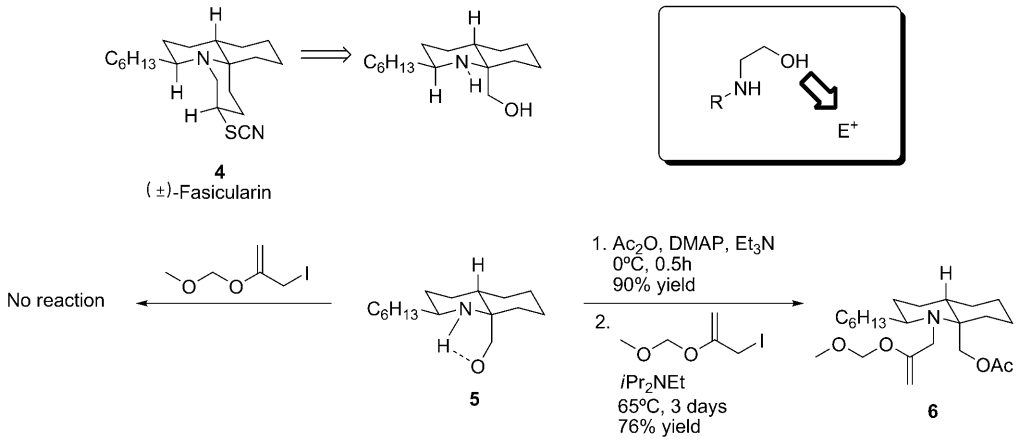
We start with an instructive case involving proton-driven chemoselectivity described by Storz et al.[12] They were in need of a process to selectively acylate the primary amino group of the α,β-diaminoalcohol dihydrochloride salt **1** with a substituted cinnamic acid side chain to generate **3** (Scheme 3A). Although a number of high-yielding procedures are available for the selective acylation of simple α- or β-aminoalcohols,[13] literature reports on the selective acylation of α,β-diaminoalcohols are scarce.[14] Initial attempts to couple **1** with the substituted cinnamic acid 3′-cyano-6′-methoxycinnamic acid in the presence of several activating agents such as acid chlorides, carbodiimides, or uronium and phosphonium reagents, delivered low yields. The reaction outcomes were complicated by the presence of significant amounts of N,O-diacylated by-product. Mercaptobenzothiazolyl-2-thioesters of carboxylic acids are highly selective N-acylating agents;[15] however, the use of the thioester of the substituted cinnamic acid **2** did not lead to higher yields. In fact, under most conditions, only the N,O-diacyl by-product was obtained.

An IR spectroscopic investigation revealed that the factor responsible for the low selectivities with regard to N- or O-acylation was an intramolecular N···H hydrogen bond in the starting material (Scheme 3B). This resulted in significant enhancement of the nucleophilicity of the hydroxy group producing high levels of O-acylation. The solution to this problem involved treating the dihydrochloride salt with only one equivalent of base, which resulted in selective deprotonation of the less basic primary nitrogen atom while the tertiary nitrogen atom remained protonated. This caused a reversal in the polarization of the hydrogen bond and effectively reduced the nucleophilicity of the hydroxy group. The use of ethanol as the solvent was found to be essential to high selectivity because of its ability to disrupt hydrogen bonds. Thus, coupling of **1** and **2** in the presence of one equivalent of *N*-methylmorpholine afforded **3** in 79% yield on a multigram scale with less than 0.3% of the N,O-diacyl by-product.

Another recent example underscores the importance of considering intramolecular bonding in the planning of syntheses. Maeng and Funk were faced with the challenge of overcoming an intramolecular hydrogen bond in a late-stage intermediate during their synthesis of the cytotoxin fasicularin (**4**).[16] This challenge arose when all attempts to alkylate the the secondary amine of advanced intermediate **5** proved unsuccessful and resulted in the recovery of starting material (Scheme 4). Interestingly, when **5** was treated with Ac_2O in the presence of a base and nucleophilic catalyst, only O-acylation was observed, despite the presence of a more nucleophilic amine. The factor responsible for this unusual selectivity was an intramolecular hydrogen bond between the alcohol and amine that attenuated the nucleophilicity of the basic nitrogen center. The reduced nucleophilicity of the N center was accompanied by a concomitant increase in the nucleophilicity of the oxygen atom,



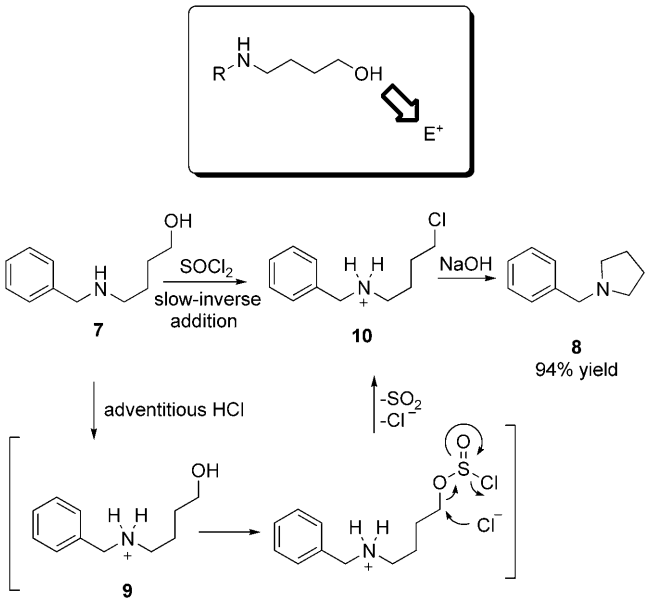
Scheme 3.



Scheme 4.

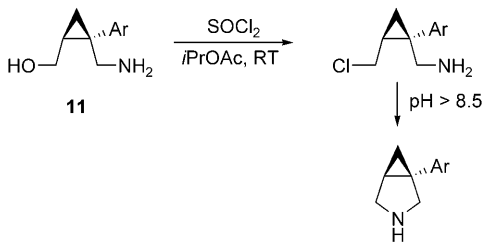
thereby resulting in selective O-acylation. Although requiring an extra step, acylation of the hydroxy group disrupted the hydrogen bond and allowed alkylation of the nitrogen center to proceed smoothly to afford the desired tertiary amine **6** in 76% yield. Reduction of the acyl group returned the alcohol that was then carried forward to the desired target.

As previously stated, protonation of nucleophilic reaction centers can be used to modulate chemoselectivity, but must be conducted in a controlled manner to avoid formation of by-products. Xu et al. at Merck utilized this approach in the development of a direct cyclodehydration strategy for the synthesis of cyclic amines from the corresponding amino alcohols.[17] The *indirect* synthesis of cyclic amines from linear amino alcohols is a tedious process that generally involves N protection/O activation/cyclization/deprotection sequences, which reduce the overall efficiency.[18] On the other hand, *direct* cyclodehydration strategies are more straightforward, but come at the expense of costly reagents and scale-up issues.[19] One simple and elegant solution to this problem entails the chlorination of the alcohol with $SOCl_2$ followed by ring closure. While conceptually simple, the successful implementation of this strategy has been problematic because of the competition between N- and O-sulfinylation followed by side reactions, which ultimately lead to low yields of the desired cyclic amines. Suppressing the nucleophility of the amine can mitigate the formation of by-products, but incomplete chlorination is often a problem because of the poor solubility of ammonium salts.[20] Xu et al. discovered that the "slow inverse-addition" of the amino alcohol substrate to $SOCl_2$, during which a solution of the amino alcohol is added to the $SOCl_2$ below the solvent level, suppresses by-product formation and can be applied to a variety of amino alcohols. For example, treatment of **7** with $SOCl_2$ under the "inverse-addition" mode delivered an excellent yield of cyclic amine **8** (Scheme 5). Mechanistically, the nucleophilic amine portion of the starting material is rapidly quenched upon protonation with adventitious HCl liberated from $SOCl_2$, thereby generating intermediate **9**. Chlorination to give **10** followed by quenching with aqueous base cleanly affords the desired cyclic amine. This in situ protection of the amine by the proton holds the key to the high efficiency of the reaction. The



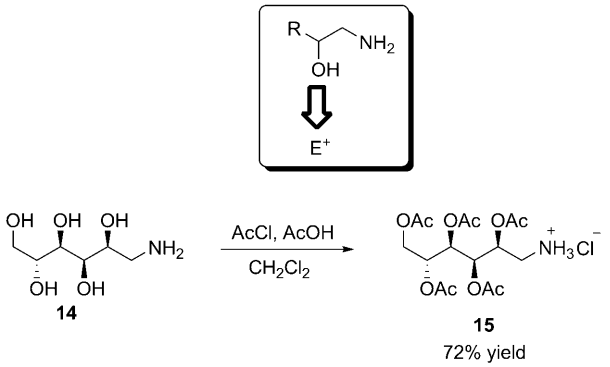
Scheme 5.

strategy proved effective in the asymmetric syntheses of the serotonin and norepinephrine reuptake inhibitors bicifadine **12** and DOV21947 **13** from amino alcohol **11**[21] (Scheme 6) by Merck. Previously reported syntheses of these drug candidates were racemic and low-yielding.



Scheme 6.

The synthesis of O-acetylated aminosugars generally requires that any other nucleophilic species be protected to prevent nonselective acylation. Thus, syntheses of polyacetylated sugars such as D-glucamine **15** are tedious and rely on protection/deprotection sequences that require several steps.[22] In a marked improvement to synthetic efficiency, Enick, Hamilton, and co-workers showed that protection and deprotection can be circumvented by performing the reaction under acidic conditions.[23] In the presence of AcOH, the nucleophilicity of the amine is attenuated, thereby allowing the acylation of all five hydroxy groups of D-glucamine (**14**) to occur in one step, thus affording **15** in 72% yield (Scheme 7).



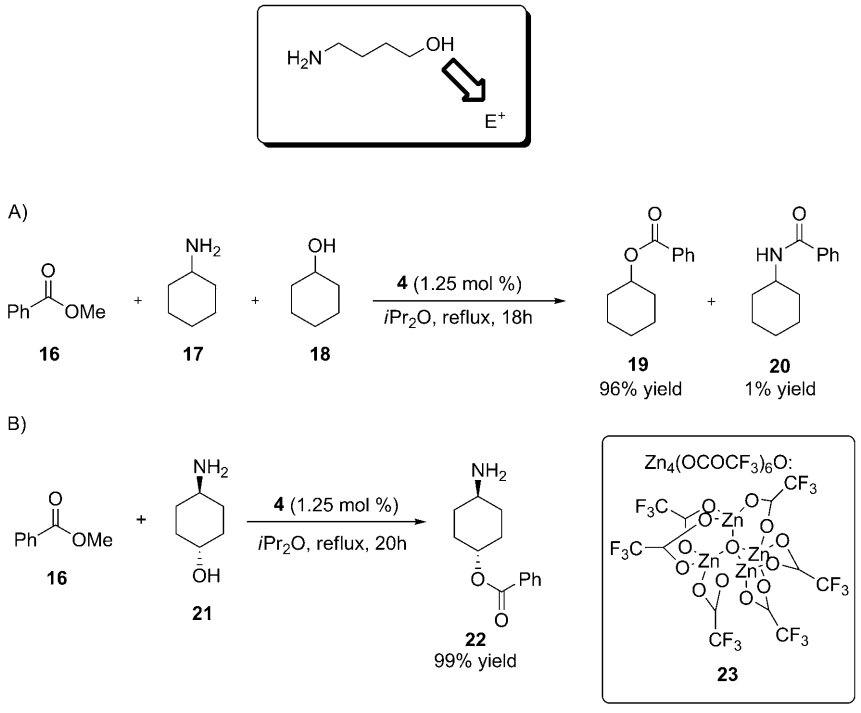
Scheme 7.

2.1.2. *Metal-Mediated Chemoselectivity*

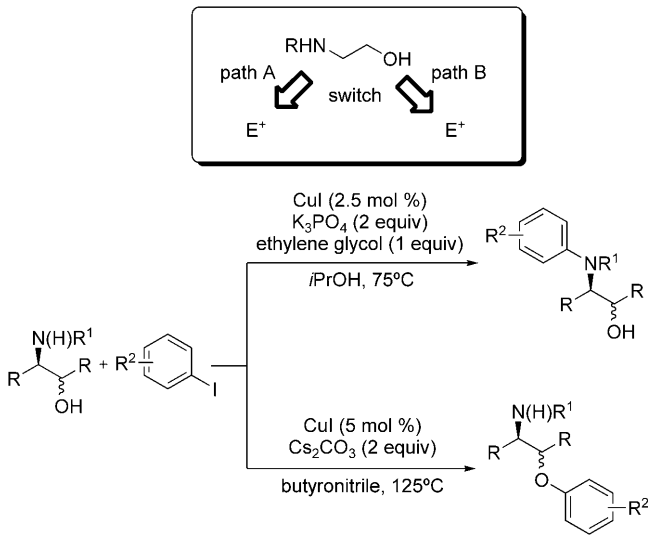
An understanding of the innate order of reactivity of functional groups is essential and is used routinely to effect chemoselective transformations with metals. The amino group is more nucleophilic than the hydroxy group,[24] a property that is exploited in the celebrated Schotten–Baumann process, in which an amine is selectively acylated in the presence of a hydroxy group.[25] The Schotten–Baumann reaction is unaffected by a vast excess of hydroxy groups and can be carried out in water.

Reversing the inherent reactivity of functional groups is challenging. Enzymes offer a solution to this problem; for example, lipases are proficient in the selective O-acylation of hydroxy groups in the presence of primary alkyl amines.[26] Until recently, synthetic catalysts have not been selective in differentiating between N- and O-acylation. In 2008, Ohshima, Mashima et al. offered a solution to this problem in the form of a direct catalytic conversion of alcohols into esters in the presence of amines by using tetranuclear zinc complexes.[27] For example, when cyclohexylamine (**17**) and cyclohexanol (**18**) were treated with methylbenzoate (**16**) in the presence of 1.25 mol% $Zn_4(OCOCF_3)_6O$ (**23**), cyclohexylbenzoate **19** was obtained almost exclusively (96% yield), with only a trace of *N*-cyclohexylbenzamide (**20**) and methanol as the only by-product (Scheme 8A). In another striking example, 4-aminocyclohexanol (**21**) was acylated at the hydroxy group to provide the ester **22** in 99% yield (Scheme 8B). The selectivity was slightly lower in the presence of linear alkyl amines or secondary alkyl amines, and afforded the corresponding esters in 92% and 86% yield, respectively. Monomeric zinc complexes showed only moderate selectivity, thus suggesting that a cooperative mechanism between the zinc centers is the key to success. Although the exact mechanism has not been delineated, it is clear that multiple metal centers are involved in the catalysis. The reaction is believed to proceed through simultaneous coordination of the alcohol and the ester to two different zinc ions of the cluster. The selectivity for the alcohol over the amine arises from the enhanced oxophilicity of the zinc ions conferred by a tetrahedral cluster reminiscent of the active site of a lipase.

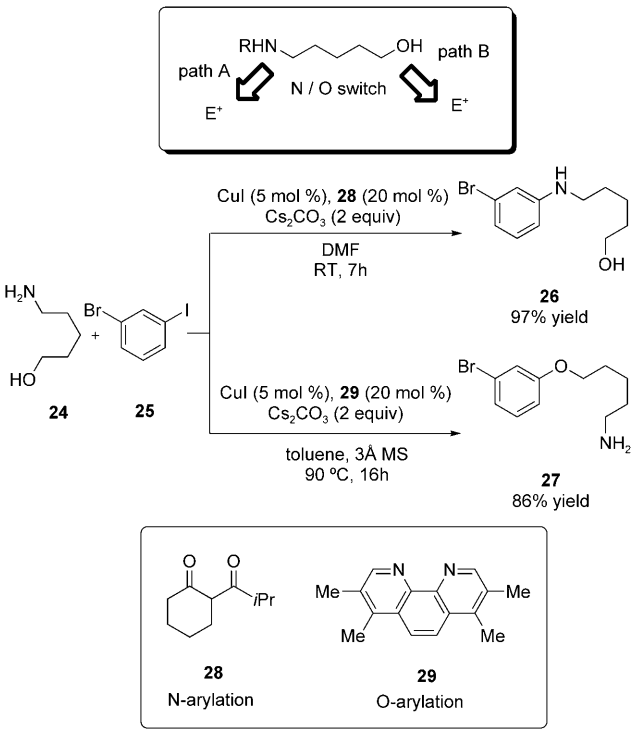
An illustrative case dealing with chemoselectivity using coppers catalysis was reported by Buchwald and co-workers. In this case, the challenge of the O-/N-arylation of β-amino alcohols was examined. An early report from Hida and co-workers detailed the increased reactivity of β-amino alcohols compared to simple amines in the Ullman condensation.[28] Postulating that the chelating ability of β-amino alcohols was responsible for this enhanced reactivity, Job and Buchwald examined a variety of conditions in an attempt to achieve selective N-arylation. Preliminary investigations revealed that competing O-arylation was a significant problem, thus eluding to the possibility of chemoselective O-arylation as well (Scheme 9).[29] Earlier work by the Buchwald research group identified ethylene glycol as an effective ligand for the copper-catalyzed arylation of aliphatic amines.[30] In this case, the addition of ethylene glycol was also crucial to suppressing



Scheme 8.



Scheme 9.

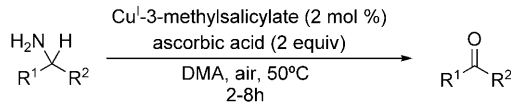


Scheme 10.

O-arylation. Thus, a mixture of CuI (2.5 mmol), ethylene glycol, and K_3PO_4 in *i*PrOH was determined to be the best conditions to afford N-arylated products in yields ranging from 66 to 76%. Importantly, simple amines were not arylated, thereby underscoring the significance of the chelating ability of β-amino alcohols for reactivity. CuI (5 mol%) and Cs_2CO_3 in butyronitrile were identified as the optimal system for O-arylation, and afforded the products in 47–74% yield despite the presence of unprotected primary and secondary amines. Under these conditions, simple alcohols did not react. Enantiopure amino alcohols were successfully arylated without detectable racemization. Unfortunately, distonic amino alcohols showed very low selectivity, possibly because of their reduced ability to form copper chelates. From a technical standpoint, it is worth mentioning that an excess of either substrate was not required.

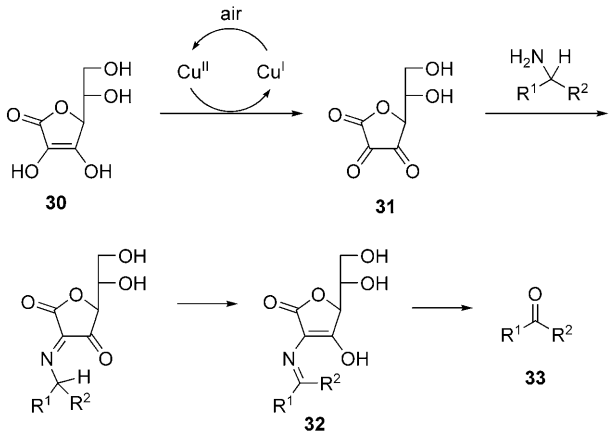
The challenge associated with distonic amino alcohols was addressed in 2007 by the same research group.[31] A ligand-assisted coupling was investigated to see whether a non-substrate ligand might be required to achieve chemoselectivity with amino alcohols lacking the ability to form tight chelates with copper ions. This strategy proved successful: high levels of O and N selectivity were attained by simply changing the ligand on the copper center (Scheme 10). For example, in the presence of CuI (5 mol%) and the diketone ligand **28**, 5-amino-1-pentanol (**24**) was successfully N-arylated with 3-iodobromobenzene (**25**) to generate **26** in 97% yield. On the other hand, **24** was O-arylated in the presence of CuI (5 mol%) and ligand **29**, thereby generating **27** in 88% yield. In general, it was found that a spacer of three or more methylene units between the amine and alcohol groups resulted in the highest levels of chemoselectivity, probably as a result of competing chelation by the amino alcohol.[32] Although the origin of selectivity has yet to be fully investigated, the chemoselectivity is likely governed by the coordination and deprotonation events occurring at the copper center. The anionic nature of ligand **28** attenuates the electrophilicity of the copper(I) center, which favors coordination of the amine to the copper(I) center, thereby leading to N-arylated products. On the other hand, the copper(I) species **29** is more electrophilic and may favor the binding of the alcohol, leading to deprotonation of the hydroxy group and ultimately O-arylated products.

Srogl and Voltrova reported a copper-catalyzed oxidation protocol for the chemoselective oxidation of primary amines to aldehydes in the presence of alcohols. This mild protocol is catalyzed by copper(I)/ascorbic acid (**30**) with O_2 as the terminal oxidant (Scheme 11).[33] The process hinges upon a



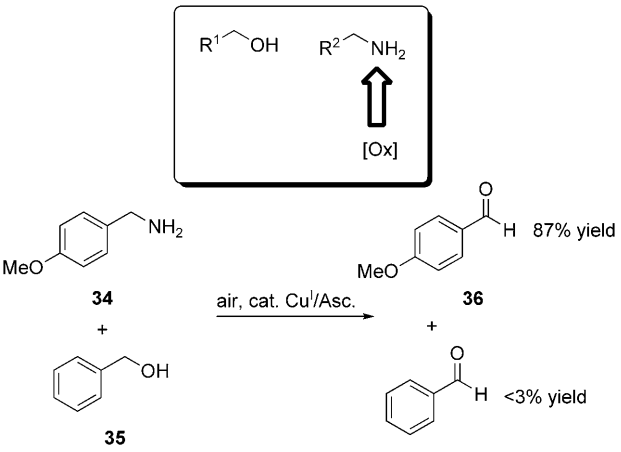
Scheme 11.

combination of an easily oxidizable metal and a reactive organic mediator (such as ascorbic acid, **30**) which, in its oxidized state, is capable of interacting with amines. The process begins with the oxidation of Cu^I to Cu^{II} by molecular oxygen. A subsequent transformation of ascorbic acid to dehydroascorbic acid (**31**) by the Cu^{II} complex ensues. The Schiff base **32** formed from the condensation of the amine with dehydroascorbic acid is finally hydrolyzed upon workup, thereby yielding the corresponding carbonyl compound **33** (Scheme 12). Copper(I)-3-methylsalicylate was found to be the optimal catalyst, while amidic solvents such as DMF and DMA resulted in the highest yields. Interestingly, a competition experiment between structurally similar *p*-methoxybenzylamine (**34**) and benzyl alcohol (**35**) revealed that the amine



Scheme 12.

was preferentially oxidized and resulted in the formation of *p*-methoxybenzaldehyde (**36**) in 87% yield. Less than 3% benzaldehyde was formed, thus showcasing the chemoselective nature of this process (Scheme 13). In addition, secondary amines were not oxidized, while primary amines underwent oxidation. This oxidation protocol can, therefore, be exploited in the synthesis of complex molecules to selectively transform primary amines without the requirement for protection of other potentially oxidizable functional groups.



Scheme 13.

2.2. Selectivity with Polyols

2.2.1. Chemoselectivity Using Peptide-Based Catalysts

Nature's enzymes can be tailored to specific transformations by a range of techniques, including directed evolution.[34] The availability of enzyme-inspired, but smaller, peptide catalysts capable of achieving similarly high levels of selectivity has been of interest. Biomimetic catalysts of this sort have emerged in recent years, and their chemoselectivity in site-directed differentiation of polyols can be quite high.

In a recent report, Lewis and Miller described the use of such a catalyst for the site-selective modification of the polyol erythromycin A (**37**; Figure 1).[35] Three hydroxy groups on

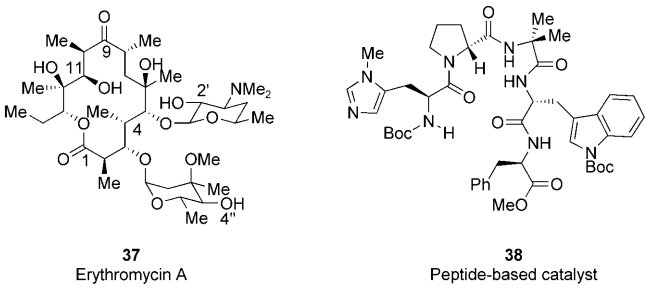


Figure 1.

erythromycin A were examined (C2′, C4″, C11). The C2′-hydroxy group is the first to be acylated in the presence of Ac_2O, a process believed to be facilitated in part by the vicinal tertiary amine. Next, C4″-acylation occurs, followed by C11-acylation after prolonged reaction times in the presence of excess Ac_2O and *N*-methylimidazole (NMI) or pyridine (Scheme 14). The use of NMI (10 mol%) or pyridine as a solvent resulted in a C4″/C11 ratio of about 4:1. The low overall conversion for this reaction and poor selectivity make the isolation of any C11-acylated product rather challenging. Interestingly, a screen of 137 peptide-based catalysts revealed that peptide **38** (Figure 1) exhibited preference towards C11- over C4-acylation, resulting in a C4″/C11 ratio of 1:5 and allowing the isolation of the C11-acylated product in 37% yield. The rate of acylation with catalyst **38** is faster than that with NMI or pyridine, and the process also appears to be general for other group-transfer reactions. For example, the site-selective lipidation of erythromycin exhibits striking selectivity, with a C4″/C11 ratio of 1:9, while the transfer of a β-alanyl moiety from a mixed anhydride occurs with a C4″/C11 ratio of 1:>10. Importantly, workup in MeOH cleaves the labile C2′-acetyl group, thus allowing isolation of the C11-acylated product.

Sugars are another family of polyols in which the similarities between multiple hydroxy groups often make it difficult to selectively functionalize a particular position. The primary hydroxy group of β-D-glucopyranoside can be selectively acylated by using the classical DMAP/acetyl chloride acylation system. Differentiating between the secondary hydroxy groups is a much more challenging task. Kawabata et al. have reported the chemoselective monoacylation of octyl-β-D-glucopyranoside **39** with near perfect selectivity for the secondary hydroxy group at the C4-position by using a C_2-symmetric catalyst **43** (Figure 2).[36] In the presence of catalyst **43**, **39** is selectively acylated with

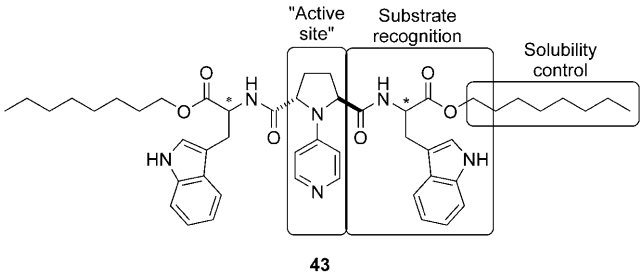
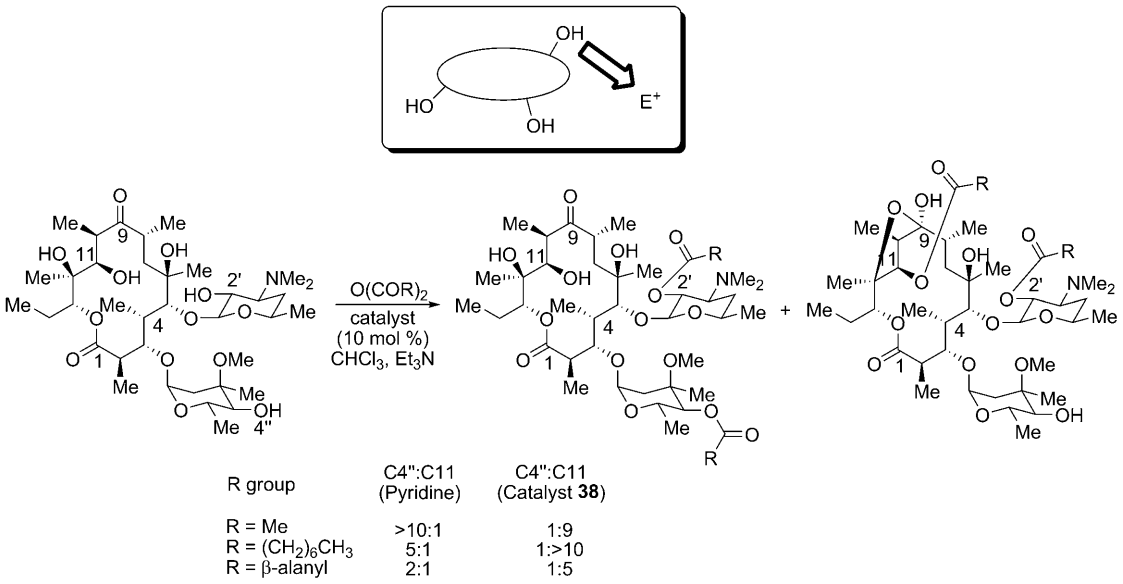
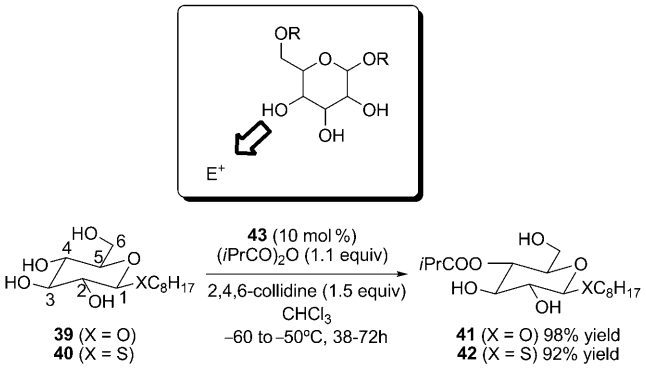


Figure 2.



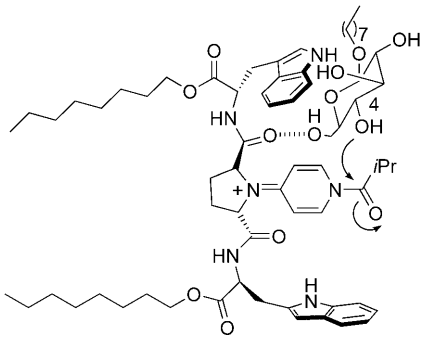
Scheme 14.

isobutyric anhydride to afford **41** in 98% yield (Scheme 15). Notably, **40** can also be acylated at the C4-position in 92% yield, which represents an important advance since acylated thioglycosides (**42**) are often used as glycosyl donors in synthesis. In contrast, contamination from polyacylation products was unavoidable when DMAP was used as the catalyst.



Scheme 15.

The authors propose a transition-state model in which the selectivity results from several critical hydrogen-bond contacts that affix the glycoside in a pocket created by the catalyst (Scheme 16). The highly reactive primary hydroxy group at the C6-position preferentially forms a hydrogen bond with the strongest hydrogen-bond acceptor of the acylpyridium ion, namely the amide. The C3-hydroxy group is proposed to engage in another hydrogen bond with the indole N-H atom, thereby positioning the C4-hydroxy group in proximity to the reactive acylating moiety. To test this model, the acylation of octyl-β-D-galactopyranoside was attempted. In this case, the axial configuration of the C4-hydroxy group does not allow it to achieve the necessary orientation in the available con-



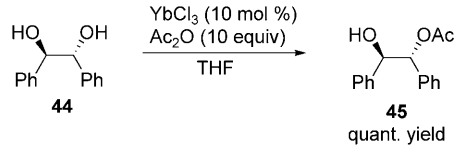
Scheme 16.

formational space of the catalyst pocket. Consequently, acylation occurs primarily at the C6-hydroxy group.

In comparison, the conventional protection/deprotection strategy affords the C4-monoacylated glucopyranoside in 46% overall yield after five steps.

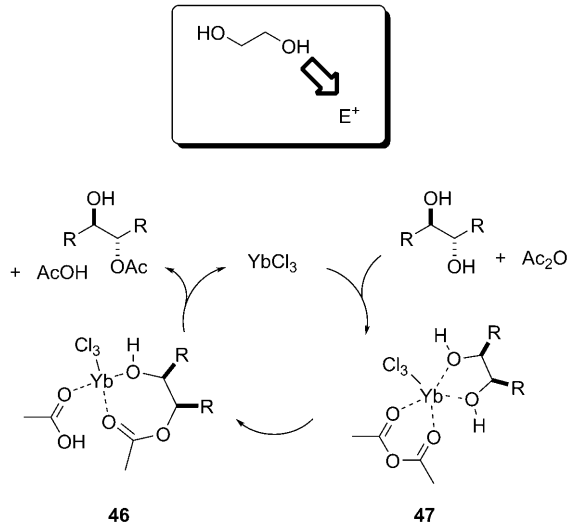
2.2.2. Chemoselectivity Using Metal-Based Catalysts

A highly efficient lanthanide(III)-catalyzed monoacylation of 1,2-, 1,3-, and 1,4-diols was reported by Clarke et al.[37] Catalyst loadings of $Yb(OTf)_3$ as low as 0.1 mol% were reported. Even in the presence of 10 equivalents of acetic anhydride, selectivity for the monoacylation reaction remained high. *meso*-Diols and cyclic *cis*-1,2-diols were acylated at reduced rates compared to the C_2-symmetric diols or cyclic *trans*-1,2-diols. For example, *meso*-diol **44** was monoacylated in quantitative yield in the presence of 10 mol% $YbCl_3$ to afford **45** (Scheme 17). On the basis of these experimental observations, a reaction mechanism was proposed which begins with a simultaneous coordination of both the diol and acetic anhydride to the lanthanide(III) salt to give complex **47** An intramolecular acyl transfer monoacylates the diol generating the seven-membered chelate



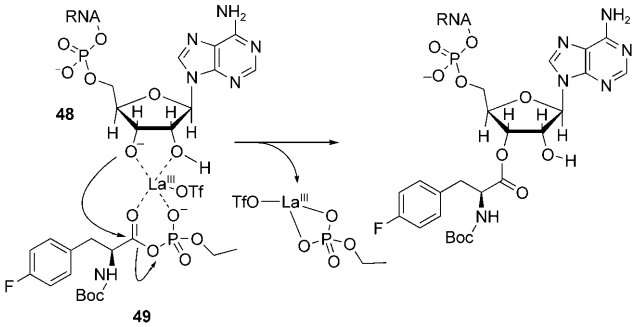
Scheme 17.

complex **46**, which is less stable than its five-membered predecessor. Afterwards, **47** is rapidly converted into the five-membered chelate form which drives the reaction forward (Scheme 18). In situ NMR experiments were used to substantiate this proposal. Significantly, monodentate complexes formed between ytterbium(III) centers and monoesters were found to be considerably less stable.



Scheme 18.

Lanthanide catalysis has recently been extended to the efficient biomimetic aminoacylation of ribonucleotides **48** with aminoacyl phosphate esters **49**.[38] Here too, the key to success is bidentate coordination of the diol moiety to the lanthanum ion (Scheme 19). Even though protected amino acids were used in this sequence, Tzvetzova and Kluger have found that protection of the the amino acid nitrogen atom is not necessary. The RNA-bound NH_2 functionalities are also



Scheme 19.

tolerated. The lanthanum ion appears to interact exclusively with the terminal 2′- and 3′-hydroxy groups. This coordination directs nucleophilic attack of the alkoxide to the carbonyl carbon atom of the acyl phosphate. The 1:2 ratio of 2′- to 3′-product is comparable with the equilibrium ratios previously reported for similar systems. Despite this fact, this study suggests that a direct and selective reaction at the 2′- and 3′-hydroxy groups can be achieved. If successful, this method could greatly facilitate the preparation of a wide range of aminoacylated tRNAs.

2.3. Chemoselective Transformations of Oligoamines

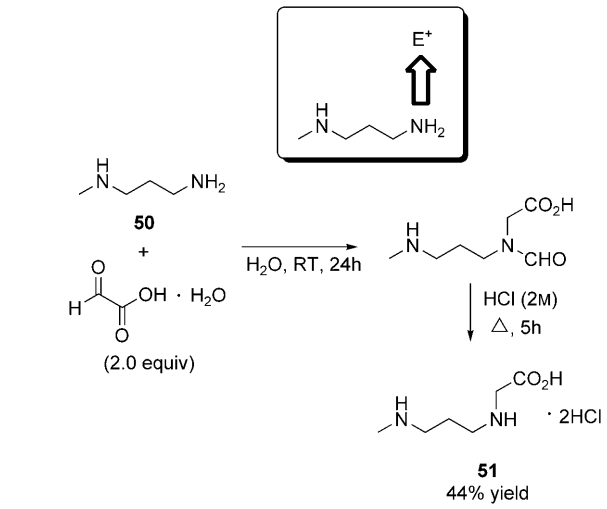
Molecules that contain several nucleophilic amine functional groups with different degrees of substitution offer an excellent testing ground for studies on chemoselectivity.

Overalkylation, the most commonly encountered problem in amine transformations, has a classical and tested solution—the Gabriel synthesis.[8] Renewed interest in this field has developed in recent years, and a number of imaginative approaches to solving this important problem have appeared.

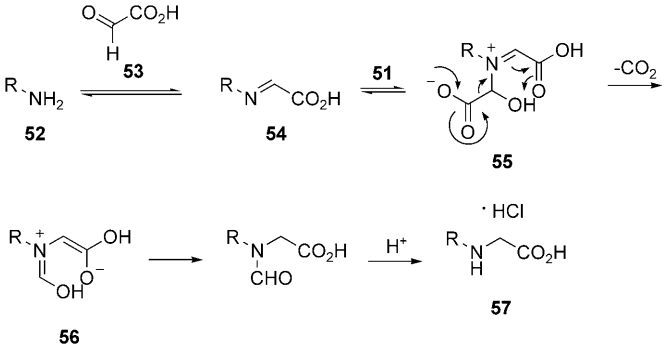
N-alkyl glycine derivatives belong to an important class of synthetically valuable precursors to biologically significant molecules. Tomkinson and co-workers showed that primary amines can be selectively monocarboxymethylated with two equivalents of glyoxylic monohydrate in the presence of unprotected secondary amines because the mechanism for monocarboxymethylation is not feasible with a secondary amine.[39] For example, diamine **50** was monocarboxymethylated to give **51** in 44% yield (Scheme 20). The role of glyoxylic acid as a hydride source, analogous to formic acid in reductive aminations, has been ruled out.[40] Instead, the postulated mechanism begins with the formation of imine **54** from a primary amine (**52**) and glyoxylic acid (**53**). Addition of a second equivalent of glyoxylic acid gives intermediate **55**, which undergoes decarboxylation to give **56**. Treatment with HCl finally yields the monocarboxymethylated products **57** as an HCl salt (Scheme 21). Apart from its attractive properties as a benign solvent, water is an important part of this process in that it allows one to avoid isolation of the formylated intermediate. Interestingly, chemoselective monocarboxymethylation of diamines was also possible by using this simple protocol.

The need for protection is inevitable in the palladium-catalyzed arylation of oligoamines. In 2005, Beletskaya et al. reported that selective monoarylation of the primary amine **58** can be achieved with 1,4-dibromobenzene **59** to give **60** in high yield despite the presence of an unprotected secondary amine (Scheme 22).[41] In 2007, Rouden and co-workers observed the opposite trend with cyclic diamine **61**,[42] namely selective arylation of the secondary amine occurred. A ligand screen revealed that two factors control the selectivity for primary versus secondary amine arylation: the ring size and the rate of reductive elimination, the latter of which can be modulated by the choice of ligand.

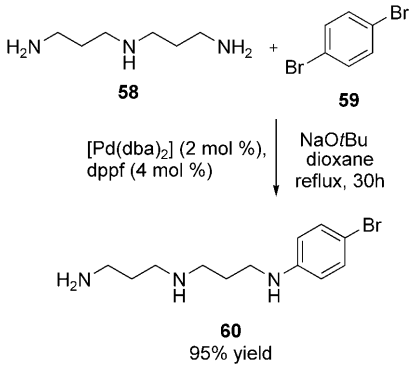
Arylation of the secondary amine in diamine **61** occurred selectively when either the binap ligand **L1** or the Josiphos



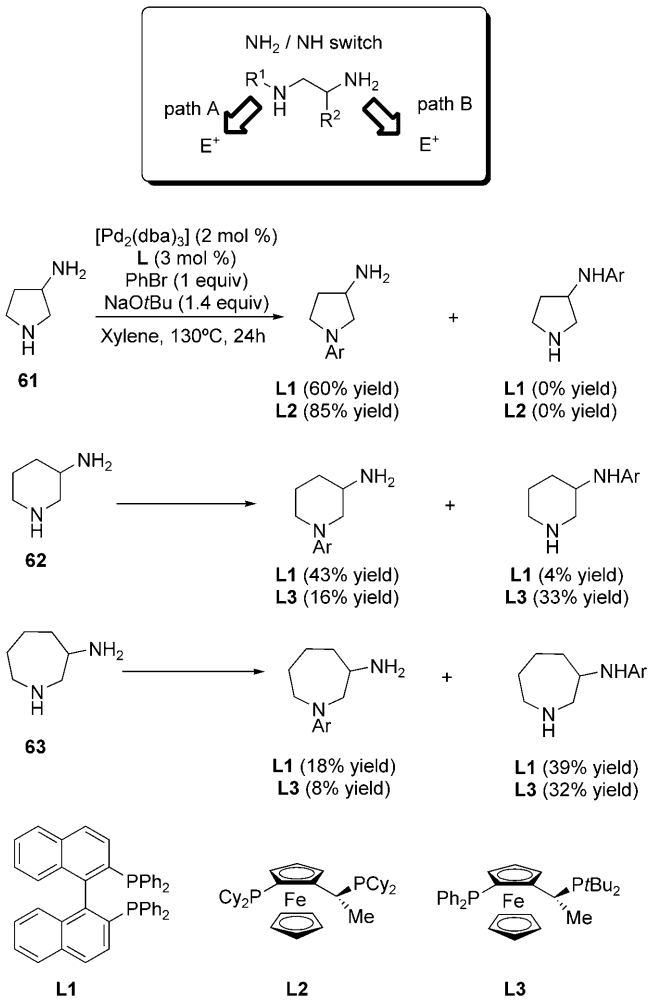
Scheme 20.



Scheme 21.



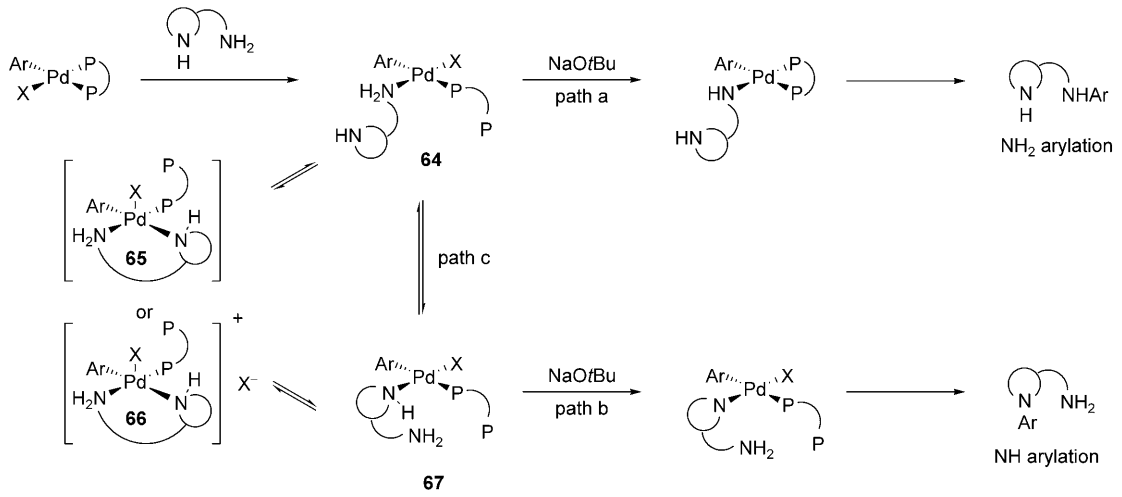
Scheme 22.



Scheme 23.

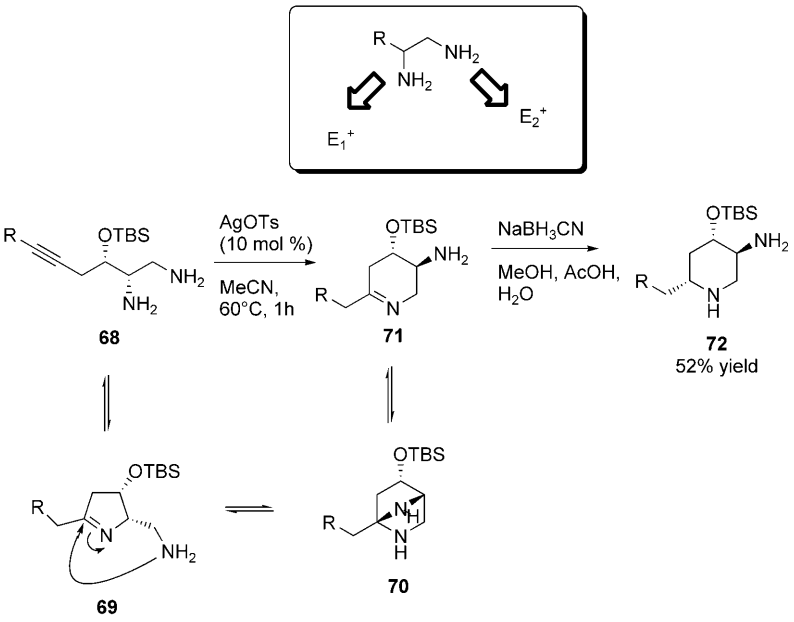
ligand **L2** were used. Increasing the ring size by one methylene spacer (diamine **62**) allowed arylation at either the primary or secondary amine, depending on the ligand. **L1** was selective for arylation of the secondary amine, while the modified Josiphos ligand **L3** was selective for the arylation of the primary amine. An additional increase in size (diamine **63**) resulted in selectivity for the primary amine, regardless of the ligand used (Scheme 23).

The chemoselectivity of the reaction was controlled by the steric and electronic environment of the ligands as well as the ring size of the diamine, which ultimately decided the fate of an equilibrium between the primary and secondary amine-bound palladium–amine complexes **64** (coordination to the primary amine) and **67** (coordination to the secondary amine; Scheme 24). Arylation of the secondary amine occurred preferentially for the less-flexible five-membered diamine **61**, while arylation of the primary amine was preferred for the most flexible diamine **63**. With **62**, the choice of ligand could modulate the selectivity. NMR measurements revealed that initial binding of the primary amine of **61** to the palladium center occurs, thereby generating **64**. This takes place despite the greater nucleophilicity of the secondary amine, and is likely due to steric factors. Although it was not possible to monitor the reaction at higher temperatures, it is plausible that increasing the temperature can override the increased steric demand for coordination of the palladium center to the secondary amine, thus allowing conversion into complex **67** through the azanorbornyl-type structures **65** or **66**.[43] The rigidity of the azanorbonyl-type structures demands rigidity in the substrate as well, thus it is feasible that interconversion occurs most readily with the smallest diamine **61**. Rapid



Scheme 24.

conversion into **67** and ultimately to path b in Scheme 24 leads to preferential arylation of the secondary amine. Adoption of the rigid azanorbonyl conformation should be more challenging as the flexibility of the diamine increases. In contrast, the flexibility of **63** is believed to be too great to promote the efficient conversion of **64** into **67.** Thus, path a in Scheme 24 dominates, which leads mainly to arylation of the primary amine. Diamine **62** is a particularly interesting case since arylation of either the primary or secondary amines could be achieved depending on the choice of ligand. The rate of reductive elimination is relatively fast with the sterically encumbered ligand **L3**, thus precluding efficient conversion of **64** into **67** and leading to the reaction following path a. The rate of reductive elimination with **L1** is slower,[44] thereby allowing enough time for conversion into the more stable species **67** and ultimately to the reaction following path b. Thus, the reason for the difference in the findings made by the research groups of Beletskaya and Rouden may lie in the ability of rigid cyclic diamines to efficiently interconvert between **64** and **67**. The flexibility of linear diamines makes this process unlikely. Clearly, complete chemoselectivity for the arylation of either the primary or secondary amine has not been achieved for all diamines, and competitive diarylation is also a problem that underscores the challenges in tuning each factor. Nevertheless, this detailed study provides a window into the competition of relative rates that ultimately leads to a given product distribution, which could lead to the development of new ligands to better control chemoselectivity.



Scheme 25.

Another instructive example of the differentiation between two amines comes from the synthesis of (+)-pseudodistomin D by Trost and Fandrick (Scheme 25).[45] This method incorporates chiral diamine **68** as the key intermediate. Silver(I)-catalyzed hydroamination on this diamine leads to the six-membered ring product **71**. The reaction is believed to proceed through a 5-*exo*-dig cyclization to furnish the five-membered ring imine **69**, which is in rapid equilibrium with the imine **70**. Since the rates for the reduction of an sp^2 to an sp^3 carbon center differ significantly between five- and six-membered rings, the selectivity of the subsequent reduction to **72** can be explained on the basis of the Curtin–Hammett principle. As a result, no protecting groups are needed to cleanly form the piperidine product from the diamine starting material.

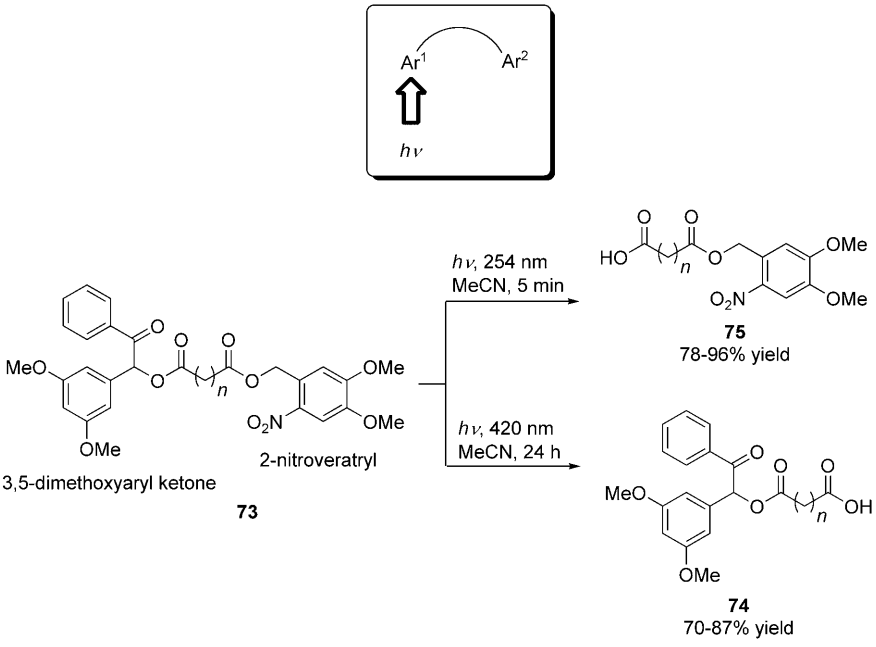
2.4. Electron Transfer: Electrosynthesis and Photochemistry

Chemical synthesis often relies on the use of orthogonal protecting groups, especially when a chemoselective protocol is unavailable. Orthogonal protecting groups are commonly chosen such that they can later be selectively removed at a desired point in the synthesis. Recently, an interesting

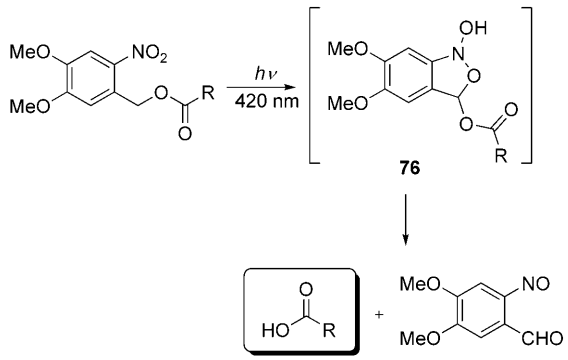
deprotection method termed "chromatic orthogonality" has received increased attention. In this approach, differentiation between protecting groups is made on the basis of their lability to a particular wavelength of incident light. Photolabile protecting groups have been known since the 1960s[46] and react through a variety of different mechanisms, depending on the chromophore.[47] For example, in 1970, Patchornik, Amit, and Woodward introduced the 2-nitroveratryl group as an amine protecting group which is labile at 420 nm.[48] Derivatives of the 3,5-dimethoxybenzyl alcohol protecting group can be removed with higher energy light (< 300 nm) and were shown to be inert above 350 nm, which suggests that it can be used in combination with the 2-nitroveratryl system for orthogonal protection.[49] Blanc and Bochet have shown that by carefully choosing two different carboxylic acid protecting groups, either could be selectively removed from the differentially protected diacid **73** with a particular wavelength of incident light.[50] The 2-nitroveratryl group was selectively cleaved by irradiation with 420 nm light to give the free acid **74**. Irradiation with higher energy light (254 nm) resulted in the selective deprotection of the 3,5-dimethoxyaryl ketone protecting group, thereby affording the acid **75** (Scheme 26).

The difference in the maximum absorbance values of these protecting groups allows for the success of this chromatically orthogonal approach. The possibility of energy transfer between the protecting groups was ruled out on the basis of UV spectroscopic measurements.[51] This is crucial since energy transfer can lead to nonselective cleavage. The reaction is believed to proceed through hydrogen abstraction at the benzylic position to generate intermediate **76**. Subsequent decarboxylation gives rise to a free acid (Scheme 27).[52]

Heterogeneous interactions between a metal and an organic molecule can be used in synthesis. For example, the

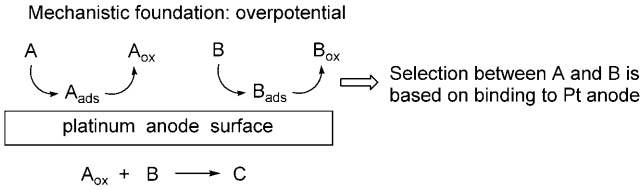


Scheme 26.



Scheme 27.

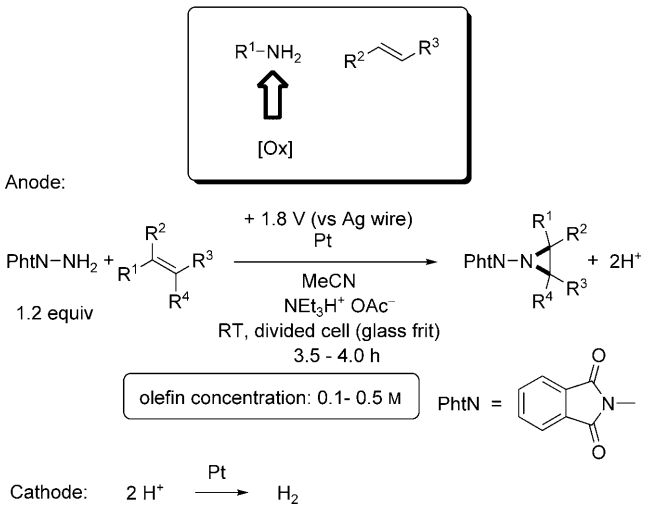
generation and trapping of highly reactive nitrene transfer reagents can be accomplished under mild conditions on platinum electrodes. The key factor that accounts for the high levels of chemoselectivity in this process is the heterogeneous phenomenon of overpotential (Scheme 28). By definition, overpotential is the "additional potential (beyond the thermodynamic requirement) needed to drive a reaction at a certain rate".[53] Under certain conditions, related to the electrode material and medium, various substrates possess different overpotentials depending on the nature of electrode. The phenomenon of overpotential can be used as a guiding principle to selectively oxidize a given species in the presence



Scheme 28.

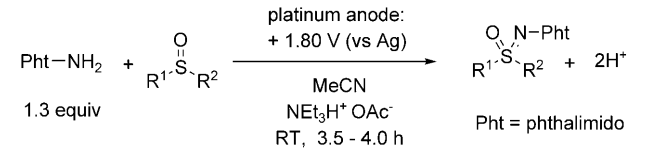
of a thermodynamically similar acceptor molecule, thus avoiding detrimental background reactions.

For example, a simple combination of platinum electrodes, triethylamine, and acetic acid has led to a highly efficient, nitrene transfer from *N*-aminophthalimide to olefins and sulfoxides at room temperature without the need for a soluble metal reagent. By using this approach, a wide range of structurally dissimilar olefins have been transformed into the corresponding aziridines by Yudin and co-workers (Scheme 29).[54] The electrochemical aziridination process gives good to excellent yields for both electron-rich and electron-poor olefins. The range of olefins compares favorably with the metal-catalyzed aziridination processes, which usually have limited substrate scope. The reaction utilizes only a small excess of *N*-aminophthalimide relative to the acceptor molecule and can be performed in a divided cell using silver wire as a pseudoreference electrode.



Scheme 29.

The nature of the electrode material was found to be critical in this chemistry. The nitrene-transfer reactions did not take place when platinum was replaced by carbon. Mechanistic studies revealed that anodic current corresponding to cyclohexene oxidation was comparable to that of *N*-aminophthalimide. Such a small difference in electroactivity apparently does not secure high selectivity in *N*-aminophthalimide oxidation, thus supporting the notion that selectivity can be obtained by maximizing the difference in overpotentials between the substrates. Under similar oxidizing conditions, sulfoxides were cleanly converted into the corresponding sulfoximines (Scheme 30). The reaction was not accompanied by the formation of the undesired sulfone by-products.



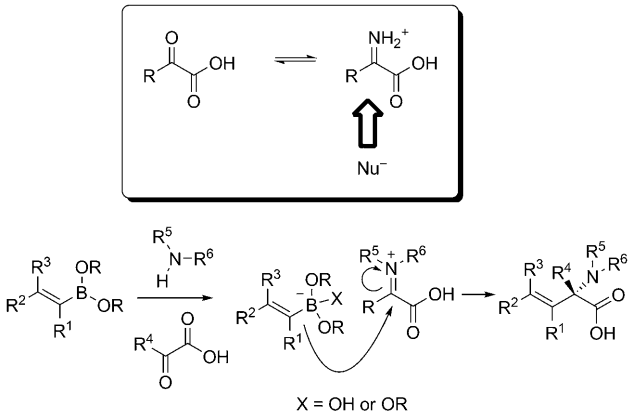
Scheme 30.

3. Chemoselectivity and Functional Groups with Unsaturated Carbon Atoms

Functional C=X groups (X = heteroatoms) are the pillars of chemical synthesis because of the staggering number of reactions available to them. In this section we have collected different approaches that have been used to tackle the issues of chemoselectivity while transforming carbonyl groups and their derivatives. The aldehyde/imine and ketone/imine equilibria continue to be exploited in a number of settings. A range of useful reactions, from reductive amination to the Ugi four-component condensation, proceed by the in situ creation of reactive iminium species.

3.1. Controlling the Fate of Iminium Electrophiles

An efficient three-component coupling involving the one-step condensation of alkenyl, aryl, or heteroaryl boronic acids with amines and carbonyl compounds was developed by Petasis and Zavialov (Scheme 31).[55] This room-temperature

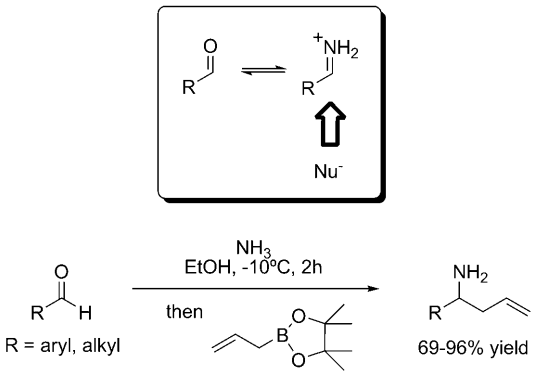


Scheme 31.

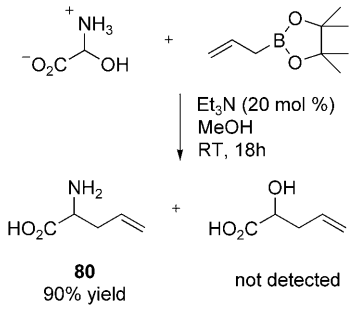
reaction operates in a variety of solvents that range in polarity from toluene to ethanol and delivers a wide range of chiral amines with high levels of enantio- and diasterocontrol. Although the exact mechanistic details of this process are still under intense exploration, it is clear that the reaction is a finely tuned process that involves formation of an iminium ion followed by its chemoselective capture by the boron "ate" complex. The fact that the reagents are employed in stoichiometric amounts underscores the bond-forming efficiency and the exquisite chemoselectivity of the "ate" complex towards the in situ formed iminium ion. The reaction is ideally positioned towards generating libraries of structurally diverse small molecules, and has been widely used in medicinal chemistry applications.

α-Aminoalkylations of carbonyl compounds are a class of synthetically useful three-component reactions involving the formation of both C–C and C–N bonds to the carbonyl carbon atom. The nature of the nucleophile can vary considerably, but the use of the simplest amine, ammonia, generally results in poor yields. In 2004, Kobayashi and coworkers demonstrated the use of ammonia in the α-aminoallylation of aldehydes (Scheme 32).[56] When ammonia is present in excess, the formation of an imine occurred, which was followed by reaction with allylboronates to afford primary homoallylamines with nearly complete chemoselectivity. In general, only small amounts of primary alcohols were observed.

An extension of this methodology in which hydroxyglycine was used as a carbonyl equivalent allows for the synthesis of unnatural unprotected α-amino acids.[57] The key here is the modular nature of amino acids at various pH values. At pH 6 hydroxyglycine **78** exists as a zwitterion, while at pH < 6 it decomposes to glyoxylic acid **77** and ammonia. If the solution



Scheme 32.



Scheme 33.

is maintaind above pH 6, then hydroxyglycine exists predominantly as the iminoacetate **79** (Figure 3), which should facilitate the chemoselective allylation of the imine and allow access to unprotected amino acids. Indeed, this turned out to be the case, although the addition of a catalytic amount of triethylamine (20 mol%) to promote the formation of **79** was critical for obtaining high yields of the corresponging allyl amino acid (**80**; Scheme 33). A variety of allylated and crotylated products could be obtained in moderate to high yields (66–93%) and with high diasteroselectivities.

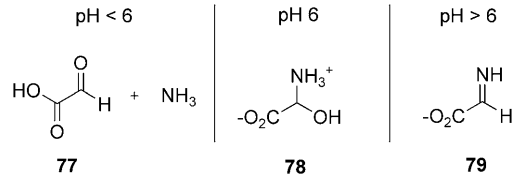
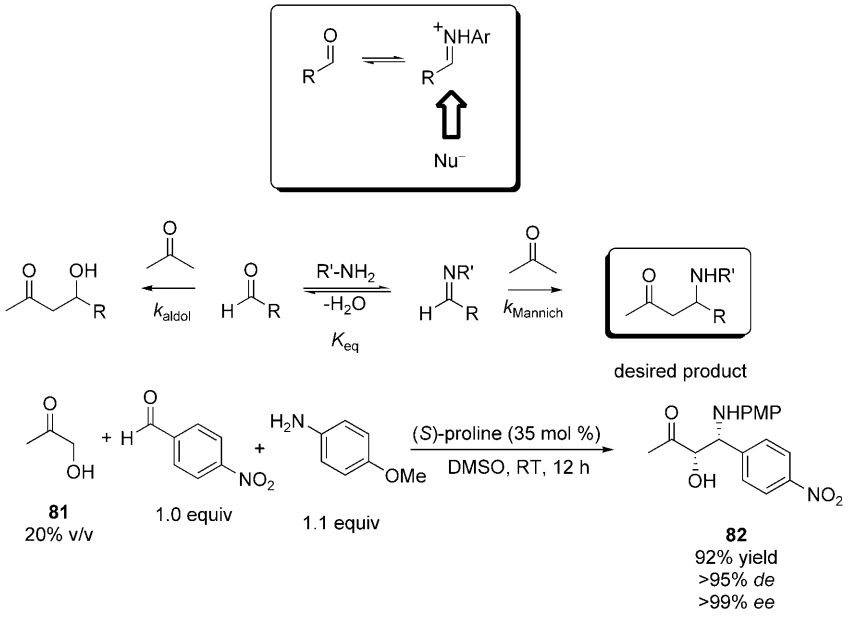


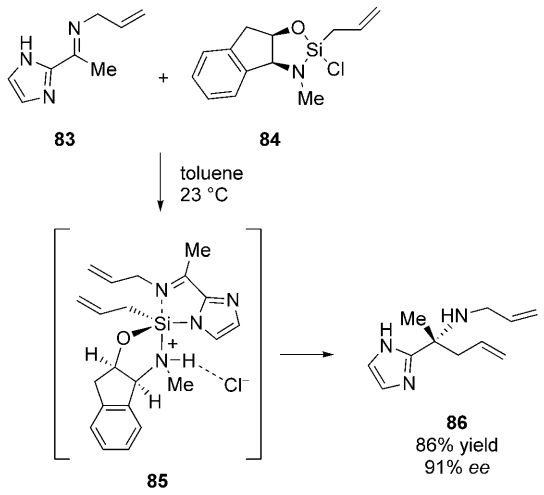
Figure 3.

Since the development of the Mannich reaction almost a century ago, it has become one of the most versatile methods for the synthesis of nitrogen-containing compounds.[58] Early reports by several research groups described the catalytic asymmetric Mannich reaction for the synthesis of enantiomerically enriched β-carbonyl compounds.[59] These metal-catalyzed reactions constitute indirect approaches that require the preformation of the imine and enol equivalents. On the other hand, direct approaches do not require the preformation of either component, but instead rely on the equilibrium between an aldehyde and amine for the in situ formation of an imine.[60] However, asymmetric induction using metal catalysts has met with limited success.[61] Organocatalysis proved more successful, as detailed by the research groups of List[62] and Barbas,[63] who showed that the proline-catalyzed reaction between an aldehyde, amine, and ketone delivers the Mannich product chemoselectively. The successful implementation of this strategy requires careful fine-tuning of multiple equilibria and reaction pathways to avoid an aldol process that typically competes if imines and enol equivalents are not preformed (Scheme 34). Specifically, nucleophilic addition of the proline-derived enamine to an imine should be appreciably faster than to the corresponding aldehyde, and the formation of the imine should be fast enough to avoid aldolization. High yields and high *ee* values could be achieved for this three-component process, although the ketone component must be used in excess. An important application makes use of hydroxyketone **81** to facilitate the synthesis of challenging *syn*-1,2-amino alcohols such as **82**. The reaction gives the highest yield with electron-deficient aldehydes and electron-rich amines.

A diverse array of imidazole-bearing chiral amines can be accessed by using a method developed by Perl and Leighton. We highlight this case here because of the role of the N-Si interaction, in which silicon plays the role of a proton surrogate.[64] This method allows the allylation of ketimines and aldimines by using allylchlorosilane reagents. For example, ketimine **83** can be allylated at room temperature in toluene (Scheme 35). Upon work-up, imidazole-bearing



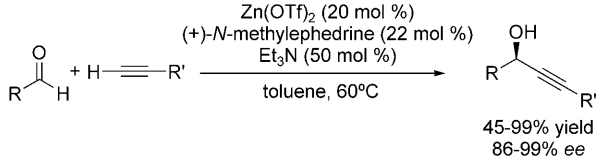
Scheme 34.



Scheme 35.

amine **86** was obtained in excellent yield and good enantioselectivity. This reaction is triggered by the interaction between chiral chlorosilane **84** and the imine nitrogen atom, which leads to the extrusion of HCl and the generation of a pentavalent anionic silicon interemediate **85**. The generated HCl protonates the amino group of the chiral auxiliary, thereby increasing the activity of the Lewis acid.

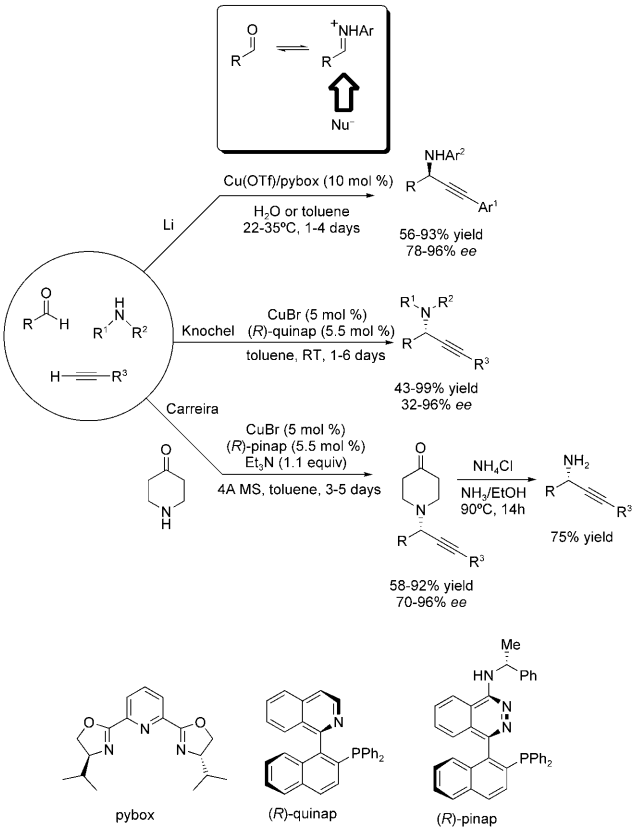
The nucleophilic addition of acetylides to aldehydes, ketones, and imines has attracted a great deal of attention as a powerful method for the construction of enantioenriched propargylic alcohols and amines.[65] Nucleophilic metal acetylides can be easily prepared by using a variety of methods,[66] but must generally be prepared in a separate pot prior to the reaction with an electrophile or generated in situ.[67] The reason for this is the sensitivity of the unsaturated carbon–heteroatom bonds to the harsh reagents required to generate the metal acetylides. To overcome this limitation, the Carreira research group reported that $Zn(OTf)_2$ can catalyze the addition of terminal acetylenes to aldehydes in a one-pot process that precludes the need for preformation of the zinc acetylide.[68] Remarkably, this highly selective deprotonation process is also tolerant of air and moisture, a feature not displayed by other systems. A variety of propargylic alcohols derived from aliphatic aldehydes could be synthesized in high yields and up to 99% *ee* by using 20 mol% $Zn(OTf)_2$ (Scheme 36).[69] In the same year, Wei and Li demonstrated that this reaction could be carried out in water by using a $RuCl_3/In(OAc)_3$ catalyst system.[70] Extending these conditions for the reduction of imines proved unsuccessful.



Scheme 36.

In 2002, Li reported the three-component coupling of an aldehyde, amine, and acetylene that chemoselectively delivered the corresponding propargyl amine, albeit in racemic form, without any trace of the propargyl alcohol.[71–73] Interestingly, this was achieved by changing the catalytic system to $RuCl_3/Cu^I$.[73] The origin of the chemoselectivity is believed to be the inability of the indium(III) center to coordinate and activate the imine in water. The softer copper(I) ions were more effective in this regard.[74]

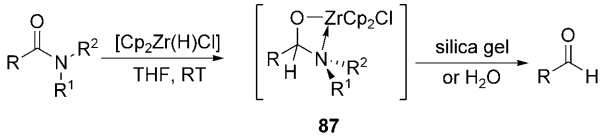
An enantioselective route to propargylamines in which a $RuCl_3/Cu^I$PyBox catalyst system was employed delivered enantioenriched propargylamines in high yields and enantiomeric excesses, although it was limited in scope to aromatic aldehydes, acetylenes, and anilines.[75] More recently, copper(I) complexes with pinap and quinap systems have been developed by the research groups of Carreira[76] and Knochel[77] for the three-component coupling of aldehydes, amines, and acetylenes with broader scope. The reaction tolerated enolizable aldehydes and aliphatic amines/acetylenes (Scheme 37). Interestingly, challenging primary propargylamines can be easily accessed by using the method developed by Carreira and co-workers. Once again, complete chemoselectivity was observed for the addition of acetylene to the aldehyde-derived iminium species, with no addition to the aldehyde observed. These reactions deliver propargylamines as the sole products in high yields and *ee* values and do not require a $RuCl_3$ co-catalyst.



Scheme 37.

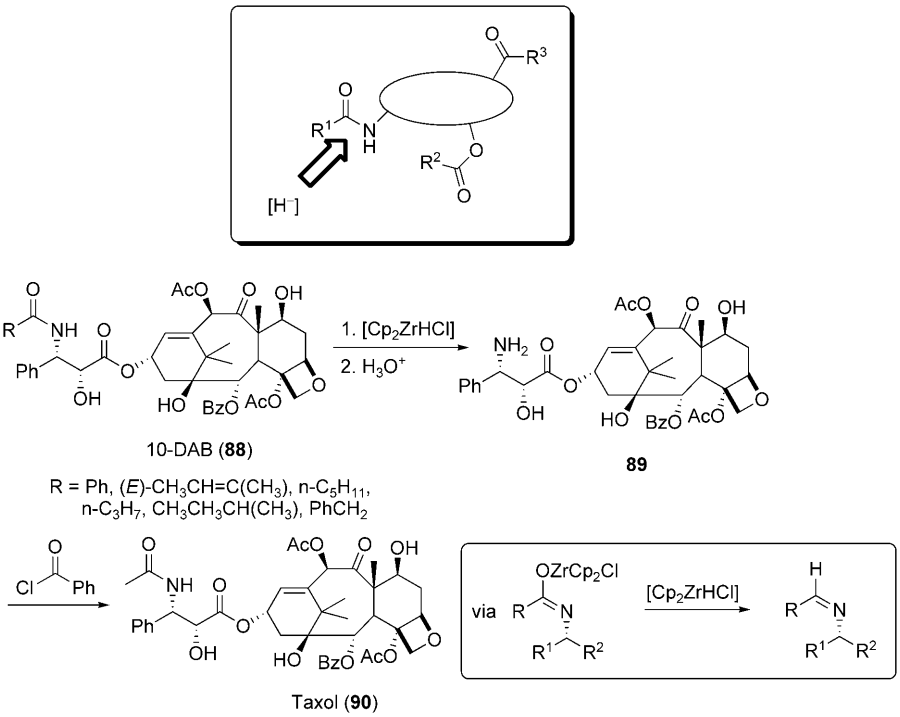
The reduction of amides to aldehydes is often complicated by contamination with the corresponding alcohol and amine overreduction products. In 2000, Georg and co-workers reported that the well-known Schwartz reagent, typically used in the hydrozirconation of alkenes and alkynes, reduces a variety of amides to the corresponding aldehydes in high yields and with excellent chemoselectivities under mild reaction conditions.[78] Although aromatic ketones and terminal alkynes are not compatible with the reaction, nitriles, nitro groups, carabamates, alkenes, and internal alkynes are all compatible with the procedure. Most notably, esters are tolerated and, for the first time, a chemoselective reduction of amides in the presence of esters was realized. Tertiary amides are reduced first, whereas primary and secondary amides undergo reduction in lower yields. Georg and co-workers noted that aldehydes formed prior to work-up are converted into alcohols immediately.[79] However, the absence of any alcohol products suggested the existence of a stable intermediate that collapses upon work-up; a process similar to that observed in the Weinreb reduction of amides to ketones.

Deuteration studies in conjunction with NMR and IR spectroscopy clarified that the intermediate was a stable 18-electron zirconacycle **87**, which is characterized by the interaction between the lone pair of electrons on the nitrogen atom and the empty orbital on the metal center, which gives zirconium its Lewis acidic properties (Scheme 38).[80] Competition experiments revealed the origin of the amide/ester selectivity. Substrates with increased donation ability of the nitrogen lone pair of electrons into the antibonding orbital of the carbonyl group were reduced faster than those with limited donation ability. This finding contrasts with the reduction performed with $LiAlH_4$, where high donation ability led to increased yields of the alcohol and amine relative to the aldehyde. Thus, an increase in the electron density of the carbonyl group resulted in higher yields for the reduction; the same effect also accounts for the increased yields of the aldehydes observed with tertiary amides relative to those with primary and secondary amides.



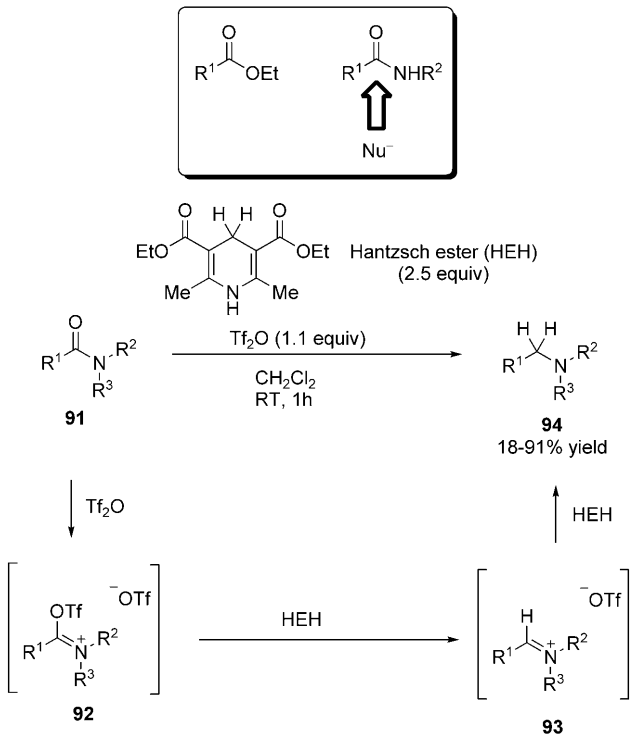
Scheme 38.

Schwartz's reagent has also been used in the reduction of secondary amides to imines.[81] This process occurs via the intermediacy of a zirconium–amide species, and has been used in the semisynthesis of one of the most successful anticancer drugs, paclitaxel (taxol) **90**.[82] The complex 10-DAB **88**, which is extracted from the leaves of the European yew tree, differs from taxol in the substitution on the amide group. This taxane is actually obtained as a mixture of six different primary taxanes. In a highly chemoselective reduction, all six taxane derivatives were treated with Schwartz's reagent to generate the corresponding imines, which were then hydrolyzed to yield the common intermediate **89**. Treatment of **89** with benzoyl chloride furnished taxol (Scheme 39).



Scheme 39.

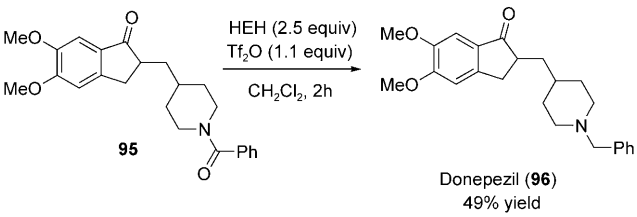
Reduction of amides to amines is well-established in the literature, but generally suffers from the requirement for highly reactive hydride sources such as aluminum and boron reagents. These reagents are intolerant of several sensitive functional groups and often necessitate tedious purification methods. To address this issue, Barbe and Charette recently described a mild and chemoselective method for the reduction of tertiary amides to tertiary amines with very high functional group tolerance.[83] Treating amide **91** with Tf_2O generates a highly electrophilic iminium intermediate **92**, which can then be selectively reduced by a mild reducing reagent, such as a Hantzsch ester, to generate **93**. The desired amine **94** is obtained upon further reduction (Scheme 40). Treatment of similar benzamide substrates with $LiAlH_4$ has been shown to generate considerable amounts of the corresponding secondary amines, especially when the nitrogen substituents are sterically imposing.[84] However, the conver-



Scheme 40.

sion of the amide oxygen atom into a triflate eliminated this possibility. The reaction conditions are amenable to amides with various steric and electronic characteristics. Most noteworthy is the high degree of chemoselectivity observed in the presence of other easily reducible functional groups. The increased electrophilicity of the in situ generated iminium ion allows it to be reduced in the presence of ketones, esters, α,β-unsaturated esters, nitriles, epoxides, alkynes, and ethers in high yields (65–91%). The power of this method has been demonstrated in the synthesis of the acetylcholine esterase inhibitor donepezil (**96**; aricept) used as a treatment for Alzheimer's disease. The reduction of the amide precursor **95** afforded donepezil in 49% yield (Scheme 41). Notably, no chromatography was required, since the pyridine by-products are removed during workup.

In the realm of acid/base chemistry, so-called amphoteric molecules have been known for a long time. The term "amphoteric" has been used to identify molecules that can act as both a Brønsted acid and base. Thus, amino acids are amphoteric compounds; they are characterized by an isoelectric point at which the molecule exists in its zwitterionic state. Depending on the pH value, the position of the proton can change, which affects the chemical behavior of the amino

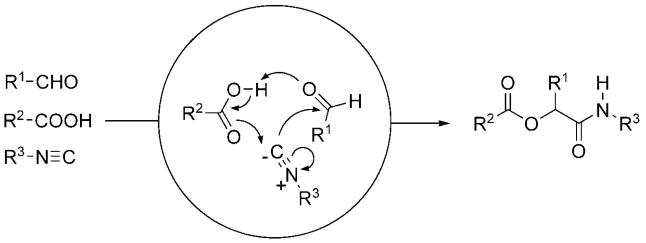


Scheme 41.

acid. The diffusion-limited proton transfer can temporarily stabilize molecules that contain nucleophilic and electrophilic centers. A general, yet difficult to implement, path to improving chemoselectivity is to impose kinetic constraints on the functional groups that are otherwise reactive towards each other. In this regard, molecules that are amphoteric on the grounds of kinetics can provide a useful approach to executing highly chemoselective processes.

The search for bifunctional molecules containing mutually exclusive nucleophilic and electrophilic functionalities has continued for more than a century. Fischer prepared glycinal in 1908 by reducing glycine ester, thereby demonstrating that protection of the amine functional group by a proton at an acidic pH value can stabilize the transient amino aldehyde. Myers et al. have used a similar method of amine protonation to establish the epimerization-free formation of an adduct between amino aldehydes and nucleophilic solvent molecules.[85] When the pH value of the medium was increased above 5, the amino aldehydes decomposed through self-condensation reactions.

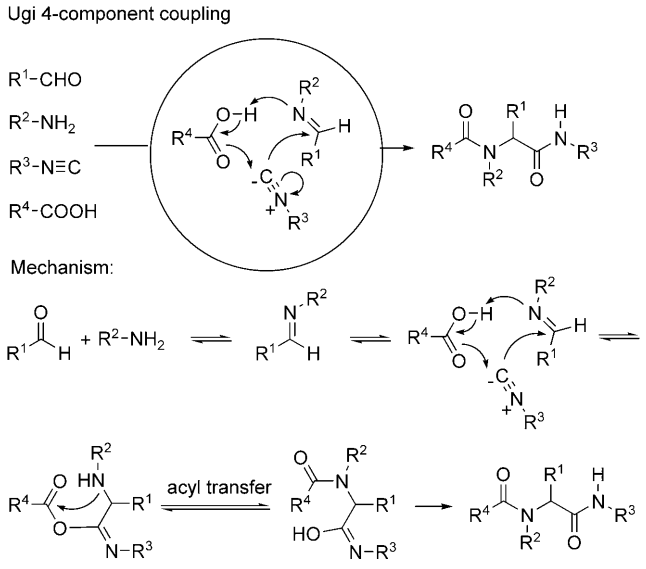
There are other examples of synthetically useful molecules that one can consider amphoteric purely on the basis of kinetic considerations. One of the most instructive cases is that of isocyanide, first prepared in 1859.[86] Two of the most widely used multicomponent reactions owe their efficiency to the amphoteric nature of the isocyanide group. The Passerini reaction involves a three-component condensation between an isocyanide, an aldehyde, and a carboxylic acid to generate α-acyloxycarboxamides (Scheme 42). By introducing an



Scheme 42.

amine into the reaction, Dömling and Ugi developed a four-component process, which is used to generate dipeptides and other valuable molecules.[87] The critical mechanistic point of this process is that the isocyanide carbon atom establishes a chemoselective connection between the nucleophile (carboxylic acid) and electrophile (aldehyde; Scheme 43). In the case of the Ugi four-component cyclization, the Passerini pathway is shut down. This attests to the in situ selection of the iminium ion, which is the most reactive electrophile formed under these conditions. The unique amphoteric nature of the isocyanide carbon center has facilitated the discovery of multicomponent processes using simple building blocks.[88]

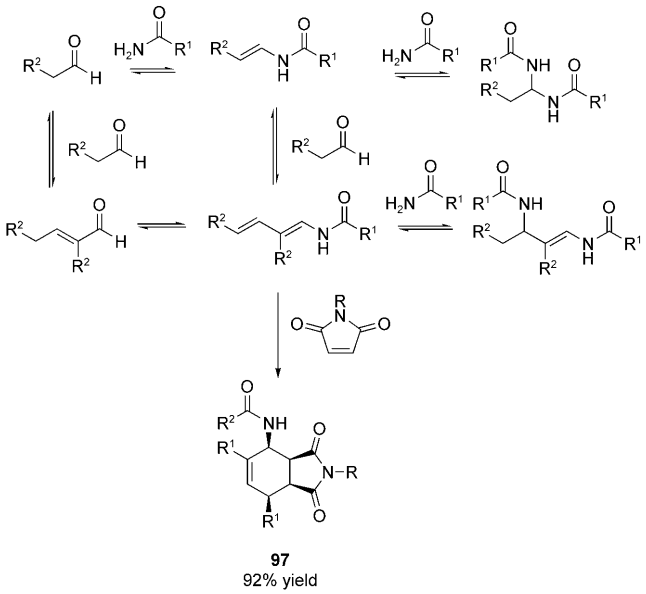
Another exciting example that is driven by participation of an iminum ion comes from Beller and co-workers, who have described an imaginative way of chemoselectively perturbing a mixture of equilibrating species derived from an enolizable aldehyde. The reaction commences with mixing



Scheme 43.

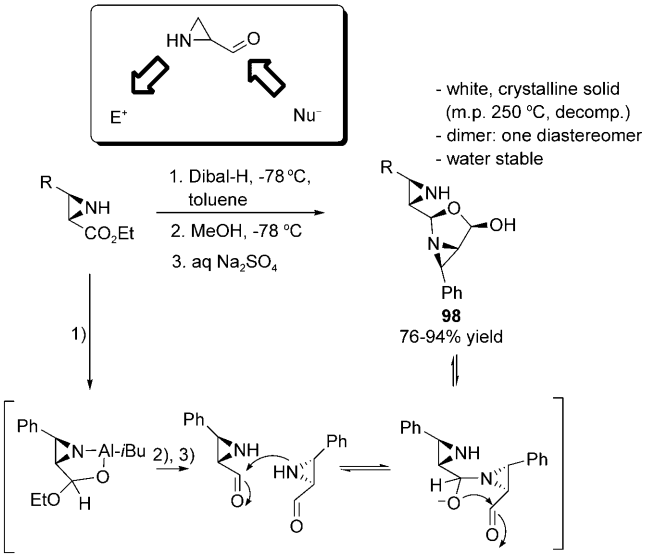
the molecules of an enolizable aldehyde, amide, and *N*-methylmaleimide. Subsequent to that, a complex equilibrating system is established by virtue of a range of pathways available to the reactants. Scheme 44 illustrates a few of the possibilities. Aldol condensation, enamine formation, tautomerization, conjugate addition, and aminal formation are all possible in this system. Yet, only one of the competing outcomes is uniquely eligible to further react with *N*-methylmaleimide in a Diels–Alder reaction. This reaction selectively affords compounds such as **97** in high yields. Remarkable levels of selectivity have been achieved in this system.

The lasting message of this study is that highly unstable intermediates need not be present in large amounts to secure high levels of conversion of the starting materials into valuable products. Even fleeting amounts may suffice if an appropriate reaction is engineered to orthogonally channel the system towards the desired outcome. The caveat is that the pathway being used during such channeling should not suffer from interference from the rest of the system. Many catalytic applications of the species generated under Beller's conditions have subsequently been reported.



Scheme 44.

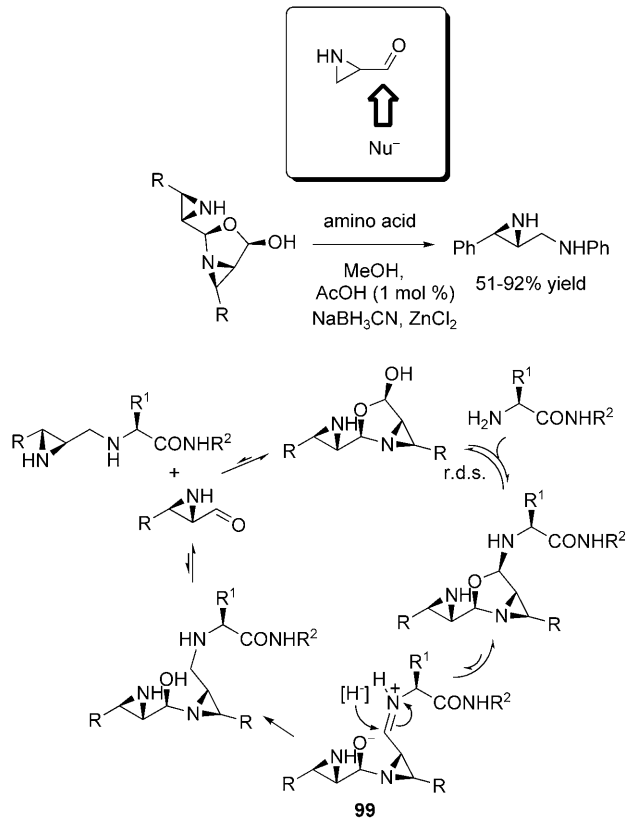
The recent studies by Hili and Yudin in the field of kinetically amphoteric molecules provided an opportunity to address some of the long-standing problems in the rapid formation of nitrogen-containing molecules. The undesired intermolecular formation of an iminium ion from an amphoteric aziridine aldehyde is thermodynamically disfavored because of an increase in the ring strain involved in such a process. The aziridine aldehydes can be prepared from simple starting materials, such as α-amino acids, and exist as stable dimers (**98**), with the monomer/dimer equilibrium lying towards the dimer in a variety of solvents.[89] The α stereocenter of aziridine carbonyl compounds is configurationally stable (Scheme 45).



Scheme 45.

These reagents have already been applied to a range of processes.[90] For example, unprotected amino aldehydes have helped address critical issues in reductive conjugation methods directed towards peptidomimetic protease inhibitors. Traditionally, the most widely employed strategy towards the so-called reduced amide bond isosteres has been based on N-protected amino aldehydes. The amino aldehydes, as well as their immediate precursors, are sensitive to epimerization. Typically, a peptide or a nitrogen-protected amino acid is converted into the corresponding aldehyde by first forming an ester or a Weinreb amide, which is subsequently reduced by a hydride transfer reagent. These steps are followed by reductive amination with an appropriate amine component.

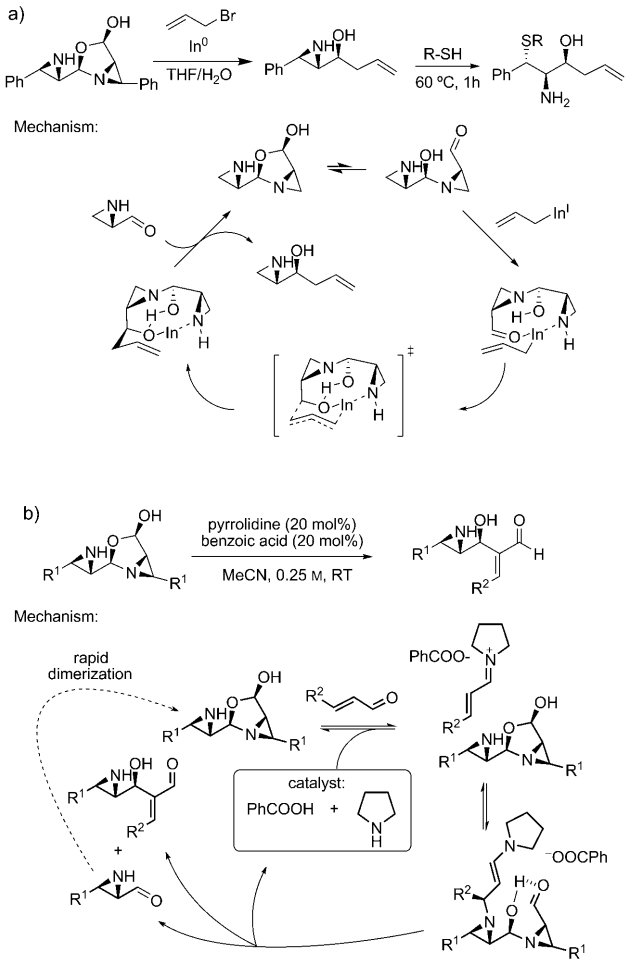
The $ZnCl_2/NaBH_3CN$ combination delivered optimal selectivity when amphoteric amino aldehydes were evaluated in their reductive conjugation with amino acids and peptides, (Scheme 46).[91a] The reaction was not accompanied by over-



Scheme 46.

alkylation or epimerization on either side of the peptidomimetic connection. A mechanistic investigation revealed that the formation of the monomeric imine from the amino aldehyde does not occur during the reaction. Instead, the "half-opened" form **99** is rapidly reduced by the hydride transfer agent. The short lifetime of **99** ensures that the rate of tautomerization and, therefore, epimerization, is negligible. A variety of unprotected amino aldehydes can be cleanly conjugated with α-amino acid derivatives.

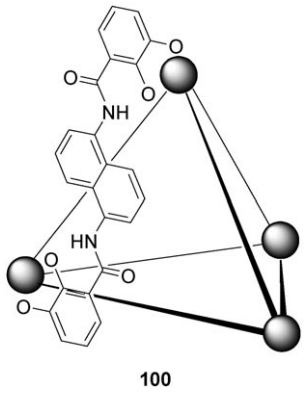
In addition, aziridine aldehydes can be derivatized to a variety of cyclic and acyclic amino alcohols through an indium-promoted allylation (Scheme 47). This direct approach to unprotected *syn*-amino alcohols is again possible by way of the equilibrium between the monomer and dimer. The so-called "half-open species" appears to be optimal in regard to selectivity during formation of the amino alcohol. The utility of the resulting products has been demonstrated in several one-flask operations that lead to stereochemically complex scaffolds. Recently, amphoteric amino aldehydes were applied to re-route a well known reaction, the aza-Michael addition (Scheme 47b).[91b] The resulting aza-Michael/aldol domino reaction with α,β-unsaturated aldehydes afforded stable 1,5-aminohydroxyaldehydes in high yields as well as high chemo- and diasteroeoselectivies. The reaction outcome hinges upon the orthogonality between the NH of the aziridine and the two aldehyde functionalities during the reaction. By employing reaction conditions that disfavor dimer dissociation, the aza-Michael process has been directed towards a novel 8-(enolendo)-*exo*-trig cyclization.



Scheme 47.

The results described herein further demonstrate the potential of amphoteric molecules in chemoselective reaction discovery.

The existence of a fast equilibrium between a substrate and an enzyme prior to the rate-limiting step is the main difference between synthetic and biological catalysts. The saturation kinetics in enzymatic systems, which is described by Michaelis–Menten kinetics, is rarely observed with synthetic reagents and catalysts since substrates are not bound to the catalyst prior to the rate-limiting step. Over the past several years, exciting developments that describe selectivity on the basis of pre-equilibria in purely synthetic settings have nonetheless appeared. The catalysts operating in these systems resemble enzyme systems in their mode of operation. Bergman and co-workers described a supramolecular host **100** (Figure 4) that relies mainly on electrostatic and hydrophobic interactions to bind protonated orthoformate guests on the basis of thermodynamic stabilization.[92] The stabilization of these orthoformates has been exploited to promote acid-catalyzed hydrolysis in a strongly basic solution. The metal–ligand supramolecular assembly, which consists of an M_4L_6 cluster that forms a tetrahedral structure with a 12^- overall charge, can accommodate monocationic guests in a 300 Å to 500 Å cavity, thus offering protection from the



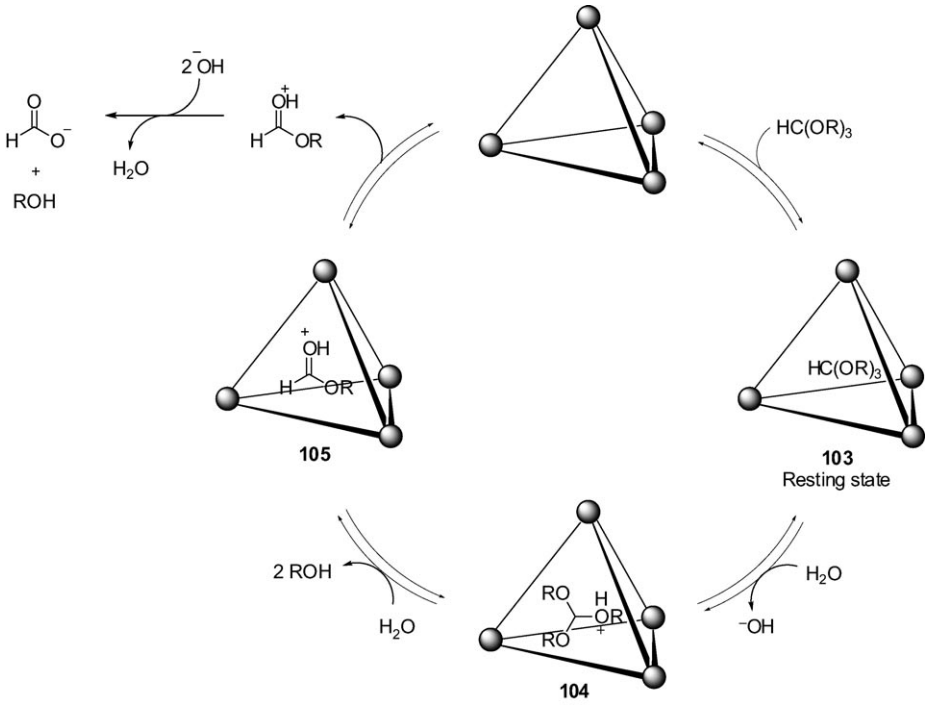
100

Figure 4.

solution. The hydrophobicity of the pocket is conferred by the naphthalene walls of the anionic ligands that form the tetrahedral enclosure. A substantial shift in the pK_a value was induced when guests were placed into the highly charged cavity, thereby confirming that the catalyst stabilizes protonated species.

For example, protonated *N*,*N*,*N*′,*N*′-tetraethyl-1,2-diaminoethane has a pK_a value of 10.8 in solution, whereas its effective basicity is shifted to 14.3 upon encapsulation and stabilization by the catalyst. This host-induced shift in basicity is the cornerstone for the orthoformate hydrolysis in basic solution. Orthoformates are quite stable in basic solution, but are readily hydrolyzed in acidic media.[93] However, in the presence of 1 mol% **100** in basic solution (pH 11), triethyl orthoformate (**101**) was hydrolyzed to the corresponding formate ester **102** ($t_{1/2}$ = 12 min) at ambient temperature (Scheme 48).

Kinetic experiments reveal that the mechanism involves the initial encapsulation of the neutral orthoformate to form a host–guest complex **103**. The subsequent protonation of the substrate likely occurs through deprotonation of water to generate complex **104**. Thereafter, the orthoformate is hydrolyzed twice to the protonated formate ester complex **105**,

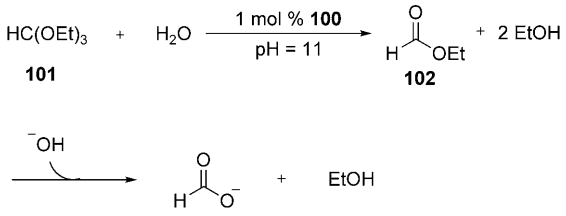


Scheme 49.

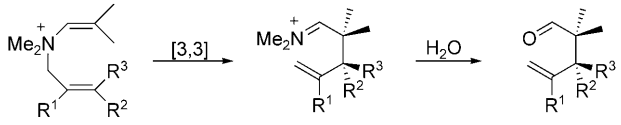
which is expelled from the cavity and then hydrolyzed in the basic solution, thereby giving rise to the formate anion (Scheme 49). The initial host–guest pre-equilibrium and first-order rate-limiting step are reminiscent of enzymatic pathways that obey Michaelis–Menten kinetics. The Michaelis–Menten parameters obtained from substrate saturation kinetics suggest a substantial rate acceleration of 560-fold for triethyl orthoformate ($k_{cat} = 8.06 \times 10^{-3}\ s^{-1}$, $k_{uncat} = 4.34 \times 10^{-6}\ s^{-1}$).

Interestingly, the specificity constant[94] for different orthoformate guests suggests that the catalyst has the ability to discriminate between various orthoformates on the basis of size. Moreover, the authors show that NEt_4^+ is a competitive inhibitor of the catalyst and can completely inhibit the hydrolysis of orthoformates. If the concentration of orthoformate is significantly increased, it can out-compete the inhibitor for the binding site, which suggests that the inhibitor binds to the same site as the substrate.

These metal clusters have also been reported to substantially accelerate the rate of cationic 3-aza-Cope rearrangements of enammonium cations (Scheme 50).[95] Several enammonium substrates were tested, and all the reactions displayed first order kinetics with 4- to 854-fold rate accelerations. The rate of the [3,3] sigmatropic shift is significantly

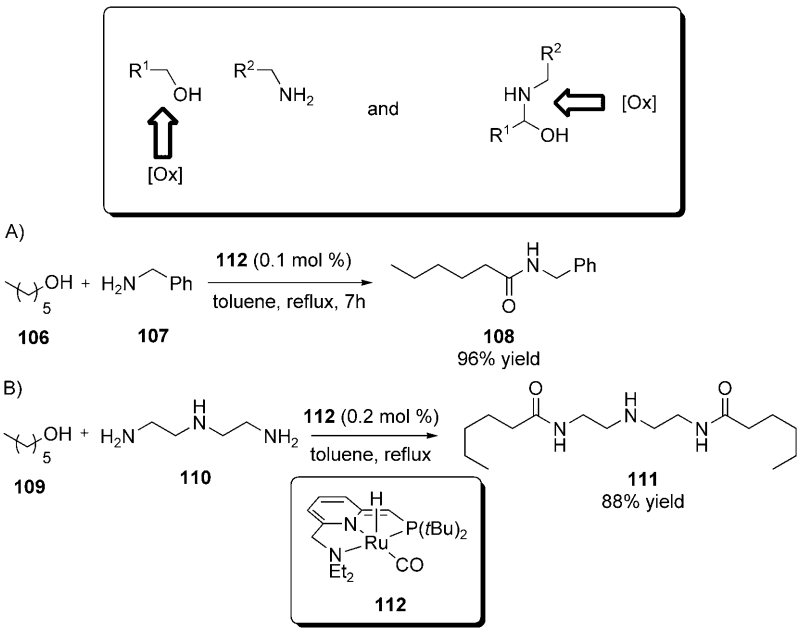


Scheme 48.



Scheme 50.

accelerated by the catalyst that promotes folding of the substrate into the reactive conformation. It was found in control experiments that there was no solvent dependence when the reactions were run in the absence of the assembly, thus eliminating the possibility that the rate enhancements were due to the more hydrophobic environment of the cavity. The negative charge within the host molecule was also ruled out as a cause for acceleration when a control experiment with 2 M KCl was run in the absence of the assembly.

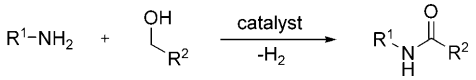


Scheme 52.

3.2. Metal-Based Redox Processes

Amide synthesis is of fundamental importance in synthetic chemistry, and a number of synthetic methods are available.[96] However, the synthesis of amides without the generation of substantial amounts of waste that proceeds under neutral conditions remains a challenging goal. While activated acids, acid/base-induced rearrangements, and transition-metal-catalyzed procedures are available, the conceptually simple and environmentally benign direct catalytic dehydrogenative acylation between an alcohol and an amine has, until recently, remained elusive.

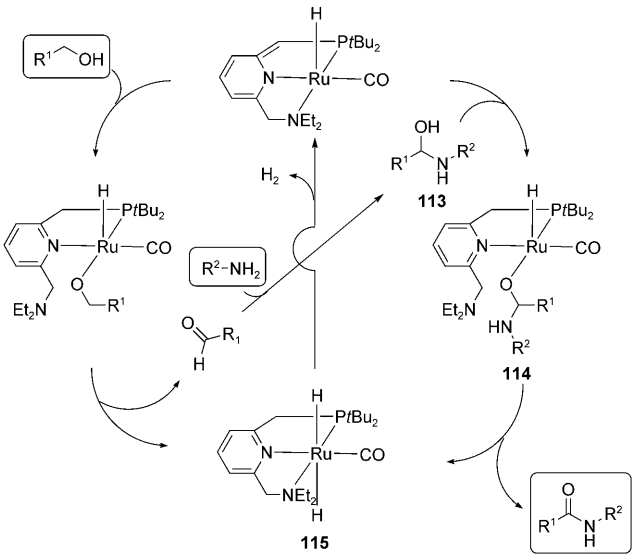
The release of H_2 is the thermodynamic driving force in a process recently discovered by Milstein and co-workers (Scheme 51).[97] Prior to this work, the authors found that



Scheme 51.

the dearomatized PNN pincer complex **112** efficiently catalyzes the homocoupling of primary alcohols to form esters under neutral conditions.[98] Remarkably, when a 1:1 mixture of 1-hexanol (**106**) and benzylamine (**107**) was refluxed with the ruthenium catalyst in toluene, *N*-benzylhexanamide (**108**) was isolated in 96% yield after 7 h (Scheme 52 A). The reaction was found to be sensitive to steric bulk at the α position of either the amine or alcohol to the extent that secondary amines did not react. This presented an opportunity for the highly selective formation of amides. The potential for chemoselectivity was demonstrated in the reaction of **109** with diethylenetriamine (**110**), which provided the bisamide **111** in 88% yield with no acylation of the secondary amine (Scheme 52 B).

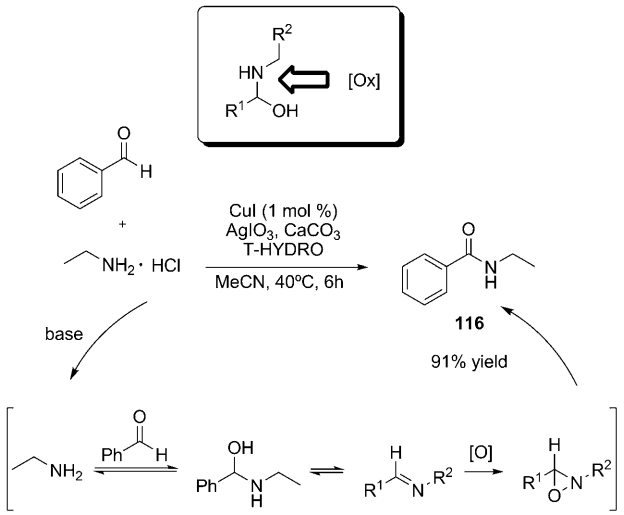
The mechanism is believed to involve the initial catalytic dehydrogenation of the alcohol to an aldehyde. This is followed by the formation of hemiaminal **113**, which forms a complex (**114**) with another equivalent of the catalyst prior to a β-hydride elimination step which generates the amide bond



Scheme 53.

and gives the dihydrogen complex **115** (Scheme 53). The catalyst is regenerated through the action of the dihydrogen complex on hemiaminal **113**, which gives H_2 as a by-product.

Yoo and Li approached the problem of amide synthesis from aldehydes and amines by using copper catalysis.[99] Similar to the ruthenium-promoted reaction disclosed by Milstein and co-workers, the copper-catalyzed process traverses a hemiaminal intermediate (Scheme 54). The competing amine oxidation has been circumvented by protonation of the nitrogen atom as an HCl salt. The optimal copper source was CuI, while T-HYDRO was found to be the best oxidant. This chemoselective transformation is high yielding (39–91%) and proceeds under mild conditions. For example, the

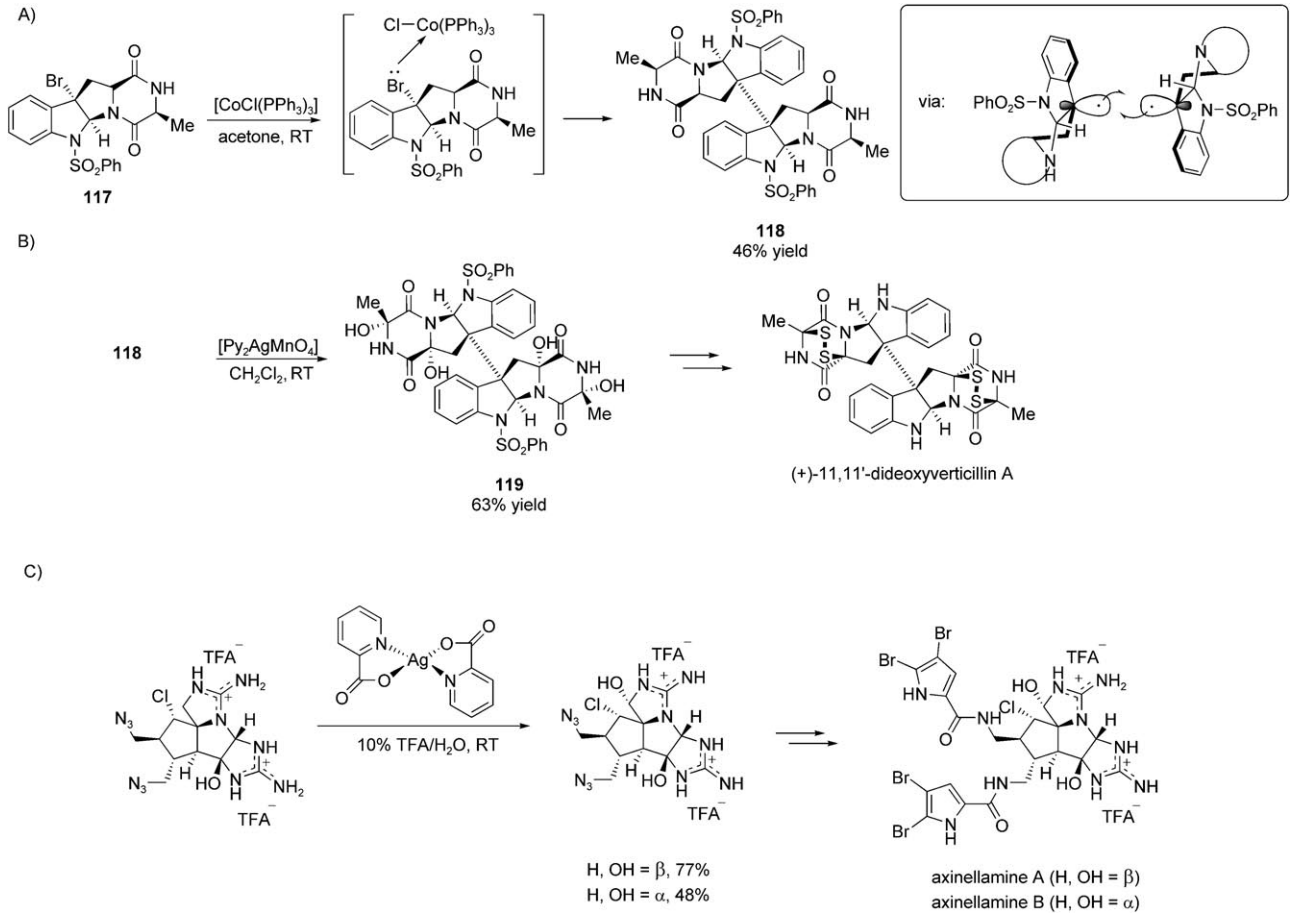


Scheme 54.

reaction between benzaldehyde and ethylamine hydrochloride affords product **116** cleanly in 91% yield.

Movassaghi and Schmidt have recently highlighted the utility of radical dimerizations and late-stage oxidations as highly chemoselective transformations in the enantioselective syntheses of members of the dimeric hexahydropyrroloindole and diketopiperazine alkaloid families.[100] One challenging member of this family recently synthesized is (+)-11,11′-dideoxyverticillin A, a cytotoxic diketopeperazine. A cobalt-catalyzed dimerization afforded the dimeric core **118** of (+)-11,11′-dideoxyverticillin A with two vicinal quaternary centers in 46% yield from the corresponding bromide precursor **117** (Scheme 55 A). Tris(triphenylphosphine)cobalt(I) chloride was found to be the most effective stoichiometric reducing agent. The mechanism of dimerization likely involves the initial abstraction of bromide from two molecules of **117** followed by the formation of a C–C bond between the incipient radicals. Subsequent to dimerization, oxidation at the four C_α-methine positions was required. Common strategies for the oxidation of the enol tautomers failed to deliver adequate results, but instead resulted in partial oxidation and diastereomeric products in addition to decomposition.

The use of mild oxidants to perform radical C–H abstraction proved to be a more successful strategy. The basis for this approach was that the C_α–H bonds are weak since the incipient radicals are stabilized. Bis(pyridine)silver(I) permanganate chemoselectively delivered the tetrahydroxylated product **119** in 63% yield (Scheme 55 B). Remarkably, a single diastereomer was obtained, the structure of which was suggestive of a short-lived radical species undergoing a rebound process (confirmed by radical clock studies).[101] Further elaboration of **119**



Scheme 55.

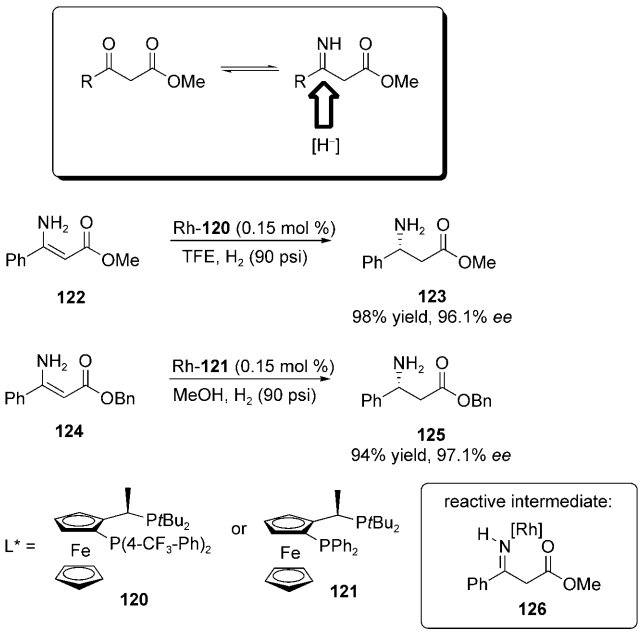
resulted in the first successful total synthesis of (+)-11,11′-dideoxyverticillin A.

In the pursuit of the complex natural products massadine, palau′amine, and the axinellamines A and B,[102] the Baran research group detailed the use of silver picolinate to achieve highly chemoselective late-stage C–H oxidation of densely functionalized intermediates bearing unprotected guanidine groups.[103] The corresponding hemiaminals could be obtained in high yields provided the reaction was conducted in the presence of trifluoroacetic acid, which resulted in a marked rate acceleration (Scheme 55 C). Remarkably, the reaction tolerated several unprotected amines and the presence of another hemiaminal. Moreover, no overoxidation to imidazolidinones was observed.

The catalytic hydrogenation of multiple carbon–heteroatom bonds is the workhorse of industrial catalysis. This area, too, has generated instructive examples that demonstrate chemoselectivity. Several recent imaginative approaches circumvented the requirement for protecting groups. One such example comes from the synthesis of amino acids, the preparation of which is often achieved by catalytic asymmetric hydrogenation. There is considerable interest in the practical, high-yielding, selective, and scalable preparation of β-amino acids. Their incorporation into peptides can have dramatic consequences on the properties, such as increased potency and stability relative to the naturally occurring counterparts.[104]

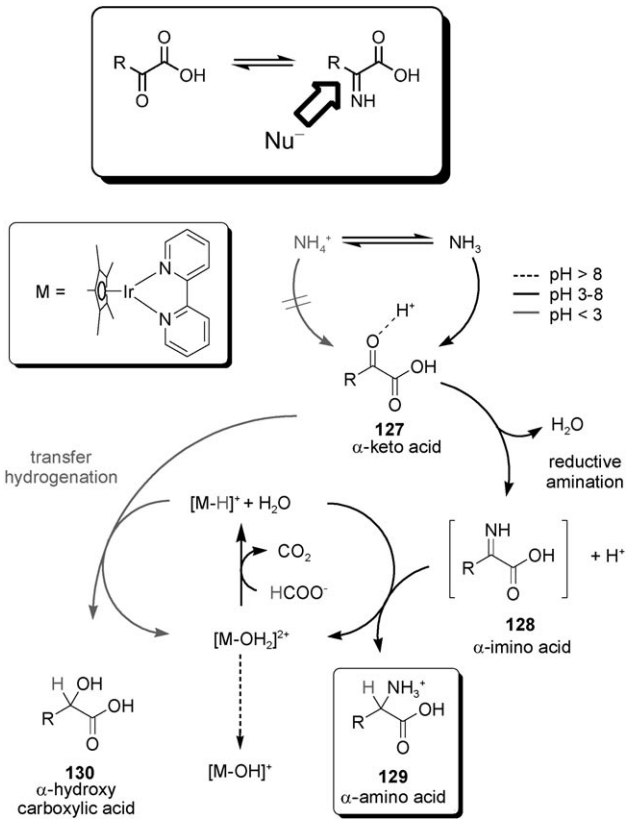
The application of asymmetric hydrogenation to the preparation of enantiopure β-amino acids would appear to be a logical solution. However, the preparation of β-amino acids continues to rely principally on the resolution of racemates[105] or on the use of chiral auxilaries.[106] The application of catalytic asymmetric hydrogenation has been hindered by the assumption that protection of the nitrogen atom is required to achieve high levels of selectivity by virtue of the formation of a six-membered ring chelate between the substrate and the metal. Hsiao et al. at Merck showed that in the presence of Josiphos ligands **120** and **121**, highly selective catalysts generated from [{RhCl(cod)}$_2$] reduced unprotected β-enamine esters **122** and amides **124** to the corresponding β-amino acid derivatives **123** and **125**, respectively (Scheme 56).[107] The solvent of choice was TFE for the hydrogenation of enamine esters, and MeOH for the enamine amides, thus highlighting the importance of solvent acidity in obtaining high yields and selectivities for different substrates. Despite the lack of an *N*-acyl directing group, the hydrogenation proceeds with high selectivity, which raises questions about the mechanism. Deuterium-labeling experiments revealed the incorporation of deuterium only at the β position, which suggests that the imine tautomer **126** is likely the key intermediate in the catalytic cycle. This mild and enantioselective approach provides a chemoselective strategy for the large-scale preparation of valuable β-amino acids.

Ogo et al. achieved impressive levels of chemoselectivity in the iridium-catalyzed reductive amination of α-keto acids in water to generate α-amino acids.[108] This environmentally benign approach mimics the biosynthetic pathway, which employs ammonia as the terminal nitrogen source. The first step in the reaction is the acid-catalyzed nucleophilic attack of



Scheme 56.

ammonia at the carbonyl carbon atom of the α-keto acid **127**. This step generates the intermediate α-imino acid **128**, which is reduced by the iridium–hydride complex to afford the corresponding α-amino acid **129** (Scheme 57).



Scheme 57.

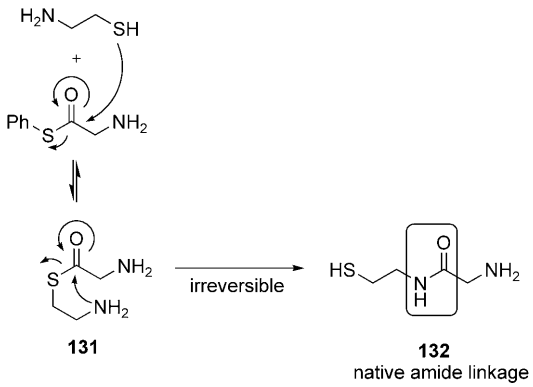
The practical challenges in this reaction arise from several competing pathways that need to be controlled to reach the desired levels of chemoselectivity. The pH value of the reaction is critical to success. The reaction medium must be acidic enough to activate the carbonyl group towards nucleophilic addition of ammonia and subsequent reduction with iridium hydride to the α-amino acid. However, if the conditions are too acidic, protonation of ammonia attenuates its nucleophilicity effectively, thereby giving rise to the competing ketone transfer hydrogenation pathway which leads to the undesired α-hydroxy acid **130**. At pH 5, this highly chemoselective reduction of α-keto acids to α-amino acids proceeds with negligible formation of the α-hydroxy acids.

3.3. Chemoselective Ligations

There has been enormous interest in recent years in the development and application of chemoselective ligation protocols. A common goal of these studies is to find conditions for the coupling of biomolecule fragments under mild reaction conditions. There has been an excellent recent review on chemoselective ligations,[109] and so in this Review we have focused our discussion on the mechanistic foundation of different ligation protocols.

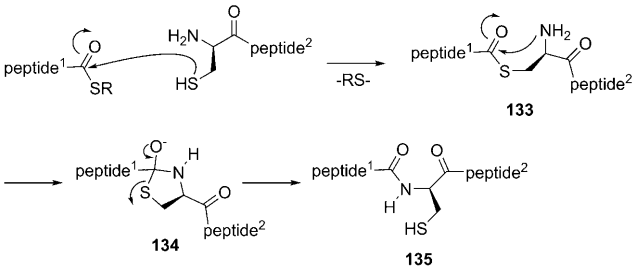
3.3.1. Cysteine-Mediated Ligations

A large proportion of contemporary ligation strategies rely on a capture/rearrangement (CR) mechanism to link two peptide fragments together. Many variants of the CR method rely on the unique properties of N-terminal cysteine residues that mediate the formation of native chemical bonds. The CR process was first noted by Wieland et al. when they were unable to isolate the desired glycine thioester of cysteamine **131** and concluded that an intramolecular rearrangement occurred in the form of an S→N transfer, thus resulting in the formation of amide **132** (Scheme 58).[110] This spontaneous transfer reaction would ultimately form the basis of the CR method which was exploited in the synthesis of a Val-Cys dipeptide containing a native chemical linkage.



Scheme 58.

The true power of native chemical ligation was demonstrated by Kent and co-workers in their development of a protocol based on the CR mechanism for linking peptide fragments under mild conditions.[111] Rather than relying on fully protected peptides for assembling large sequences, this method is based on a chemoselective transformation that allows the use of unprotected peptide coupling partners. The process involves a reaction between two fragments, one of which contains a C-terminal thioester functionality while the other incorporates unprotected cysteine at the N terminus. Initially, an exchange between the cysteine sulfhydryl group and the thioester takes place to generate intermediate **133** (Scheme 59). In the next step a thiazolidine intermediate **134** is formed through nitrogen attack at the thioester intermediate. The strength of the amide bond in **135** defines the endpoint of the process. This ligation mechanism is compatible with all side-chain functional groups found in proteins. Notably, other cysteine thiol side chains do not interfere with the desired intramolecular S→N shift because of the proximity of the terminal amino group to the thioester intermediate.

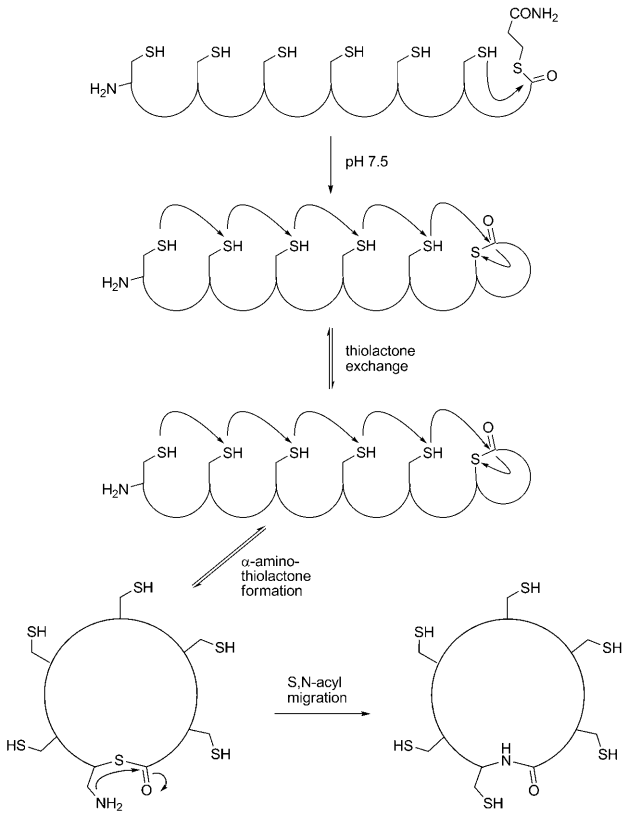


Scheme 59.

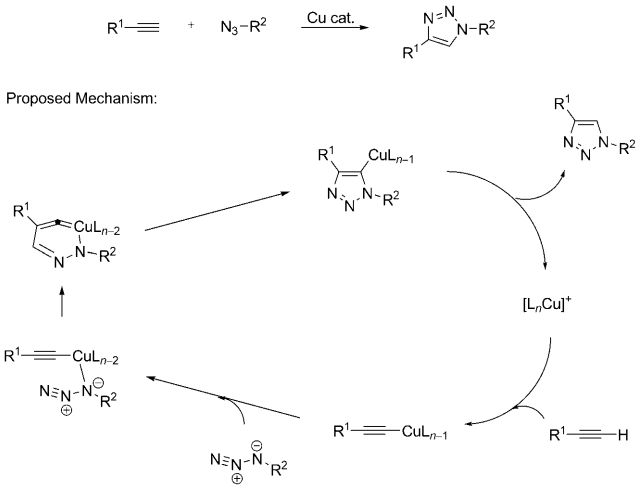
The S-to-N migration is the centerpiece of the "thia zip reaction" developed by Liu and Tam which has been employed for the synthesis of large end-to-end cyclic peptides.[112] This interesting sequence involves a series of rearrangements that proceed by intramolecular transthioesterification between an internal free thiol and a thioester. The thiolactone, formed during ring-chain equilibrium, favors ring formation in aqueous solution. This chemoselective ligation sequence distinguishes an α-amine from the ε-amines as well as other nucleophilic side chains without recourse to protecting groups. Thus, enthalpic activation by a coupling reagent and high effective molarity, typically required for cyclic peptide formation, are not needed (Scheme 60).

3.3.2. Click Chemistry

Dipolar cycloadditions are a class of reactions that provide direct access to a variety of heterocycles.[113] The fusion of two units is by nature a highly effective process, and the diverse array of dipoles and dipolarophiles make the structural diversity of the products virtually limitless. In recent years, a great deal of effort has been devoted to the development of a subset of this vast family of reactions: the azide–alkyne cycloaddition (AAC). Click chemistry was



Scheme 60.



Scheme 61.

defined by Sharpless and co-workers as a set of 'near-perfect' bond-forming reactions that are easy to perform and enable the rapid construction of molecules.[114] The products are recovered in high yields with little or no by-products and are tolerant of many conditions (including water), and are unaffected by the nature of the groups being connected to each other.

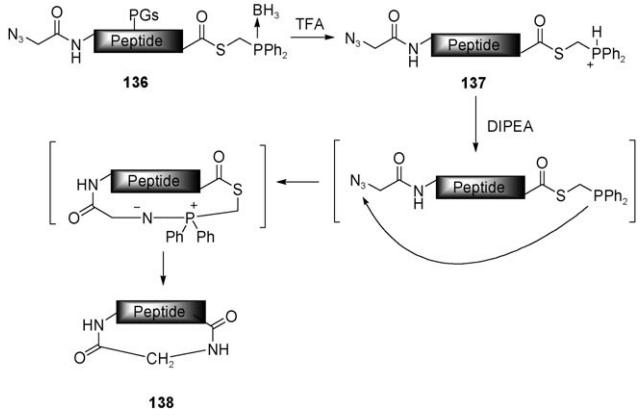
Click chemistry encompasses a variety of reactions, but is often used to describe the reaction between an azide and an alkyne. Azide and alkyne groups are stable in the presence of many nucleophiles, electrophiles, and solvents common to standard reaction conditions. This inertness of the azide is unique among 1,3-dipolar reagents, and its limited reactivity profile, which includes the alkyne, make these two functional groups ideal candidates for click reactions. The reaction between an azide and alkyne is not new; the thermal 1,3-dipolar AAC was reported by Michael over a century ago in the synthesis of the first 1,2,3-triazole from phenylazide and diethyl acetylene dicarboxylate.[115] It was not until much later that work by Huisgen, spanning three decades, led to a deeper understanding of this important class of reactions.[116] The reaction is strongly exothermic ($\Delta H° = -45$–55 kcal mol^{-1}) but has a high kinetic barrier (ca. 26 kcal mol^{-1} for methyl-azide and propyne) that necessitates long reaction times for unactivated substrates. The research groups of Meldal[117] and Sharpless[118] independently reported that copper induces a rate acceleration of about 10^7-fold relative to the uncatalyzed version, which allows the reaction to proceed under much milder conditions (Scheme 61).[119] The compatibility of the copper-assisted azide–alkyne cycloaddition (CuAAC) with a broad range of functional groups has virtually eliminated the need for protection of sensitive functionality attached to either species, and has found innumerous applications across medicinal chemistry, materials chemistry, and chemical biology.[120a]

One of the most valuable applications of click chemistry has been in the area of bioorthogonal reporters, which can be selectively tagged to study cells.[120b] Ideal reporters are small, relatively inert functional groups that are incorporated into the target biomolecule by using the cell's own biochemical machinery. Azides can be used for this purpose since they remain invisible to the cell's machinery.

3.3.3. Traceless Staudinger Ligation

Two common strategies exist for the construction of cyclic peptides. One strategy involves the cyclization of a peptide with protected side chains by using activating agents, while the other relies on the native chemical ligation technique, which involves an unprotected peptide containing a cysteine residue. The former is not restricted to any particular amino acid but suffers from multiple activation sequences and unfriendly reagents, while the latter is limited by the requirement of a Cys residue.

In a recent development, Kleineweischede and Hackenberger have applied the traceless Staudinger reaction pioneered by Bertozzi and co-workers[121] and Raines and co-workers[122] to the preparation of non-cysteine-containing head-to-tail unprotected cyclic peptides. The synthesis of the required bifunctional azidopeptide phosphinothioester is completed by solid-phase peptide synthesis to give a fully protected peptide **136** with a borane-protected phosphine (Scheme 62). Treatment with 97.5 % TFA and 2.5 % TIS leads to the full deprotection of the peptide and completes the cleavage of the borane to leave unprotected peptide **137** with a protonated phosphine. The addition of DIPEA initiates the traceless Staudinger reaction and affords fully unprotected cyclic peptide **138**.[123] This chemoselective ligation strategy

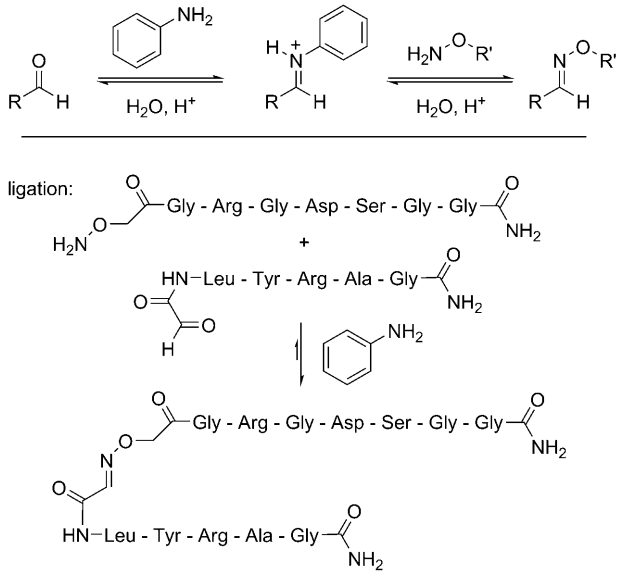


Scheme 62.

was used to cyclize the linear peptide sequence GAGHV-PEYFVG, which resembles the terminal circular loop of Microcin J25, in 36% yield.

3.3.4. *Oxime Ligations*

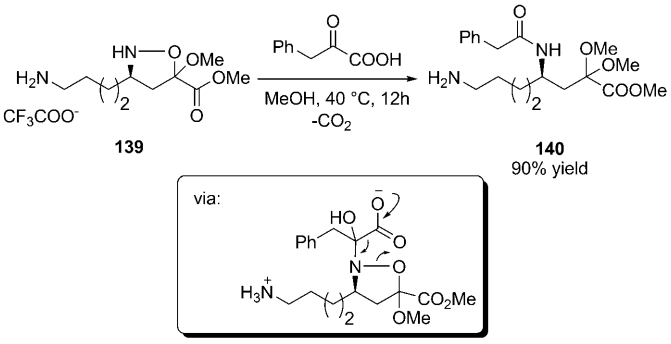
Another commonly used ligation technique, popular in synthetic and biological chemistry, relies on the reversible formation of an imine. A particularly useful variant of the reaction involves oxime-forming ligation, in which two peptide fragments are connected by way of a reversible oxime linkage (Scheme 63). Unfortunately, the reaction is exceedingly slow. In an exciting recent development, up to 400-fold rate enhancements were reported by Dawson and co-workers.[124] An aniline catalyst in an aqueous environment at pH 4–7 is currently the most efficient catalyst system for the formation of oximes. The fast kinetics of this system makes it particularly valuable for cellular and biomolecular applications.



Scheme 63.

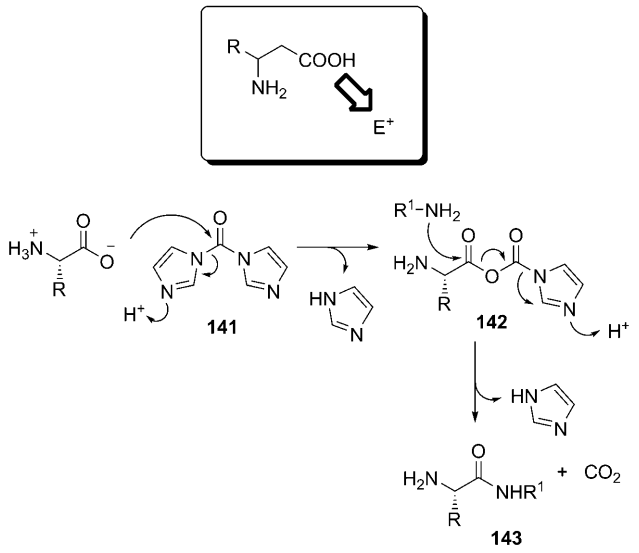
3.3.5. *Decarboxylative Amide Ligation*

The iterative, aqueous synthesis of α- and β-oligopeptides without coupling reagents, as developed by Bode et al., is notable for its chemoselectivity. The synthesis of α-oligopeptides hinges upon decarboxylative condensation of α-ketoacids and *N*-alkyl hydroxyamines.[125] This powerful transformation does not involve added reagents and produces no by-products. For the β-oligopeptide synthesis, isoxazolidine acetals, which are available in enantiomerically pure form by using Vasella's method, can be coupled with α-ketoacids.[126] In contrast to the formation of α-oligopeptides, which proceeds best in polar media, less-polar solvents such as dichloromethane and toluene were most effective in the synthesis of β-oligopeptides. The reaction is accompanied with visible loss of carbon dioxide. Notably, unprotected peptides containing Lys, Asp, Trp, Tyr, and Arg residues can be efficiently coupled. Scheme 64 exemplifies this method with an unprotected cyclic hydroxylamine **139**, which cleanly reacts with phenyl pyruvic acid to give amino acid derivative **140**, which contains an unprotected primary amine.



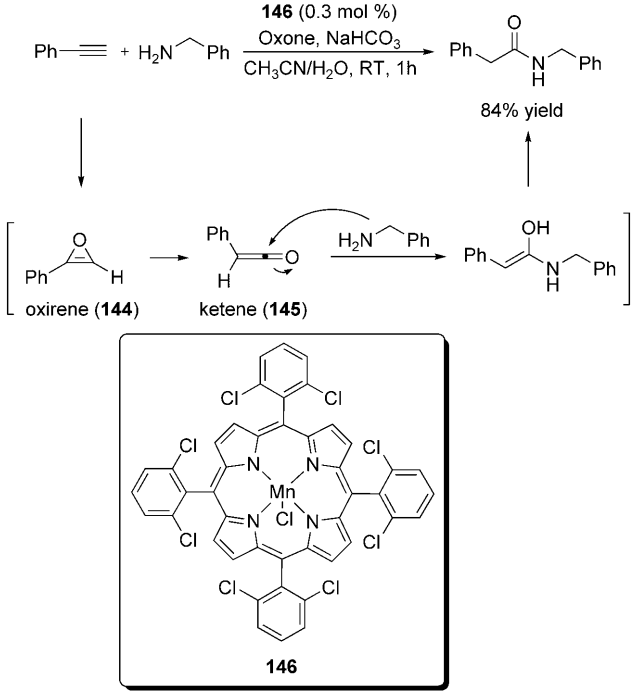
Scheme 64.

The carboxamide group is ubiquitous in natural products, pharmaceuticals, and commodity chemicals. It appears in more than 25% of marketed drugs.[127] 1,1′-Carbonyldiimidazole (CDI; **141**) is a common reagent for peptide coupling that operates by virtue of a carboxamide intermediate. The chemical synthesis of carboxamides from amino acids proceeds through initial activation of the amino acid carboxyl group. Protection of the amino group is generally needed to ensure high selectivity of coupling. In 2006, Sharma and Jain developed a protecting-group-free version of this reaction in water by taking advantage of the zwitterionic nature of amino acids.[128] In this approach the α-NH_2 group of the amino acid is kept in its protonated form, which significantly reduces its nucleophilicity. Meanwhile, the nucleophilic carboxylate end of the molecule reacts with CDI to give the mixed anhydride intermediate **142**, a necessary precursor to the ultimate carboxamide **143**. Subsequent attack by the amine nucleophile yields a variety of amino acid amides in yields of up to 73% (Scheme 65). Basic, neutral, and hydrophobic amino acids participate in this coupling reaction, with no need for side-chain protection.



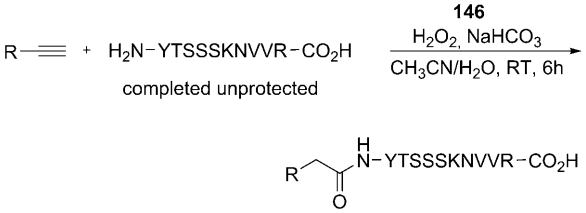
Scheme 65.

Wong, Che, and co-workers recently disclosed a method for the selective modification of the N-terminal amino groups of peptides by the oxidative synthesis of amides from acetylenes.[129] Despite the importance of such a modification for the study of bioconjugate materials, few methods are available for the functionalization of unprotected peptide sequences because of the nucleophilicity of amino acid side chains such as the lysine amino group. The authors found that by using the manganese–porphyrin catalyst [Mn(2,6-Cl_2tpp)Cl] (**146**; tpp = triphenylporphyrin) both aliphatic and aromatic acetylenes were converted into the corresponding amides through a ketene intermediate (Scheme 66).



Scheme 66.

Oxidation of the acetylene using oxone or H_2O_2 as the terminal oxidants is believed to occur to generate the oxirene intermediate **144**, which rearranges into ketene **145**. The amide is obtained upon nucleophilic attack of the amine at the ketene carbonyl group. Deuteration studies support the mechanism, which is also believed to account for the inhibition of cytochrome p450 by activated acetylenes. Fully unprotected peptide sequences with lengths of 9–13 residues were successfully amidated in good yields (Scheme 67). Notably, lysine residues did not interfere with the reaction. Currently, the main limitation is the oxidation of cysteine residues, which results in formation of a disulfide bond, and oxidation of methionine residues to the corresponding sulfoxides. Reduction of the disulfide bonds with dithiothreitol and reduction of the sulfoxides with *N*-methylmercaptoacetamide addresses this problem.



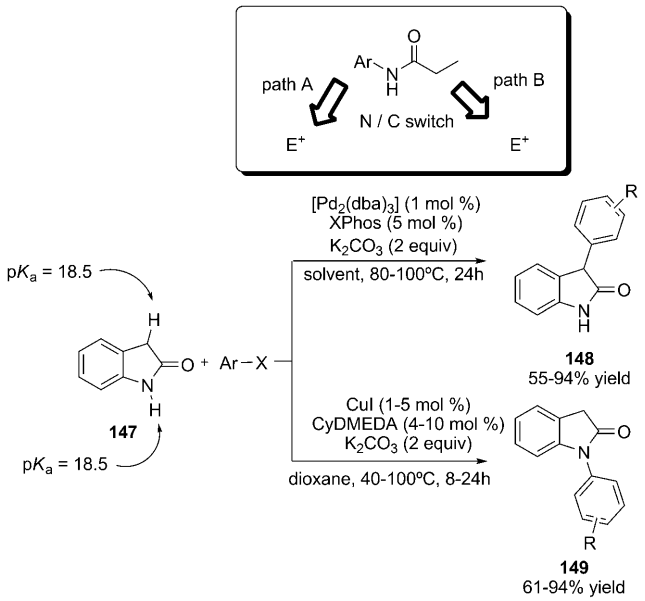
Scheme 67.

4. Formation of Carbon–Carbon Bonds: Choosing the Path and the Metal

A common feature among the majority of examples covered in the last section was the influence exerted by a carbonyl group or its derivative (such as an imine) on the reaction path. Many examples that were dealt with in the preceding chapter were centered around the formation of carbon–carbon bonds. The present section continues the discussion of carbon–carbon bond-forming processes, but the examples will now be based on operational principles that do not directly implicate carbonyl reactivity.

4.1. Selecting between Carbon–Carbon and Carbon–Heteroatom Coupling

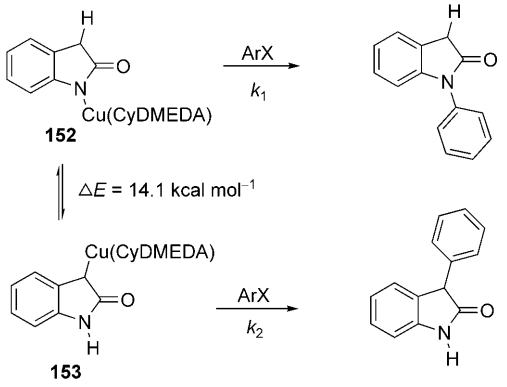
An example of the versatility of palladium in controlling the site of cross-coupling comes from the arylation of oxindole. The acidity of the N1 and C3 protons of oxindole are identical ($pK_a = 18.5$), which makes it a unique substrate that can potentially participate in cross-coupling reactions at either the N or C atom. Buchwald and co-workers reported conditions for the chemoselective arylation of oxindole **147** at either N or C3 (Scheme 68).[130] The use of 1 mol% [Pd_2-$(dba)_3$], 5 mol% XPhos, and K_2CO_3 as the base efficiently produced C3-arylated products **148** in yields of up to 94% from the unprotected N-H oxindoles. A catalyst system comprising CuI (1–5%), CyDMEDA (4–10%), and K_2CO_3 chemoselectively delivered similarly high yields of N-arylated products **149**.



Scheme 68.

Computational studies suggest that oxindole preferentially coordinates to the Pd and Cu centers as an N-bound amidate rather than as a C-bound enolate. In the case of the palladium system, N-bound amidate **150** was found to be 4.8 kcal mol^{-1} lower in energy than the C-bound enolate **151**. The observed chemoselectivity for preferential reductive elimination at the C3-position is therefore kinetically controlled according to the Curtin–Hammet principle. While **150** and **151** may be in rapid equilibrium, the activation barrier to reach **148** via **TS-151** is 2.4 kcal mol^{-1} lower than via **TS-150** leading to **149**. Therefore, **148** is formed from the rapid reductive elimination from the higher energy palladium enolate rather than the lower energy palladium amindate (Figure 5).

For the copper-based systems, where selectivity favors the N-arylated products, the N1 amidate **152** is 14 kcal mol^{-1} lower in energy than the C3-enolate **153** (Scheme 69). There



Scheme 69.

are two possible explanations for the observed selectivity. The first is that **153** does not exist in solution, since no pathway exists for the interconversion between **152** and **153**. Alternatively, an equilibrium may exist that allows the formation of small amounts of **153**, but activation of the aryl halide proceeds faster from the Cu–N intermediate than from the Cu–C intermediate ($k_1 \gg k_2$; the nature of the aryl halide activation step is not well understood).[131]

The transformation of ambident bis-nucleophilic species can also be controlled by using main-group elements. If a molecule contains more than one acidic functional group, the ambident nature of the conjugate base can be especially difficult to control since either one of the reactive centers can participate in a reaction with an added electrophile. Therefore, synthetic protocols that achieve reactivity exclusively at one of the two nodes are valuable. While pursuing the synthesis of the alkaloid aspidospermidine, Rubiralta and co-

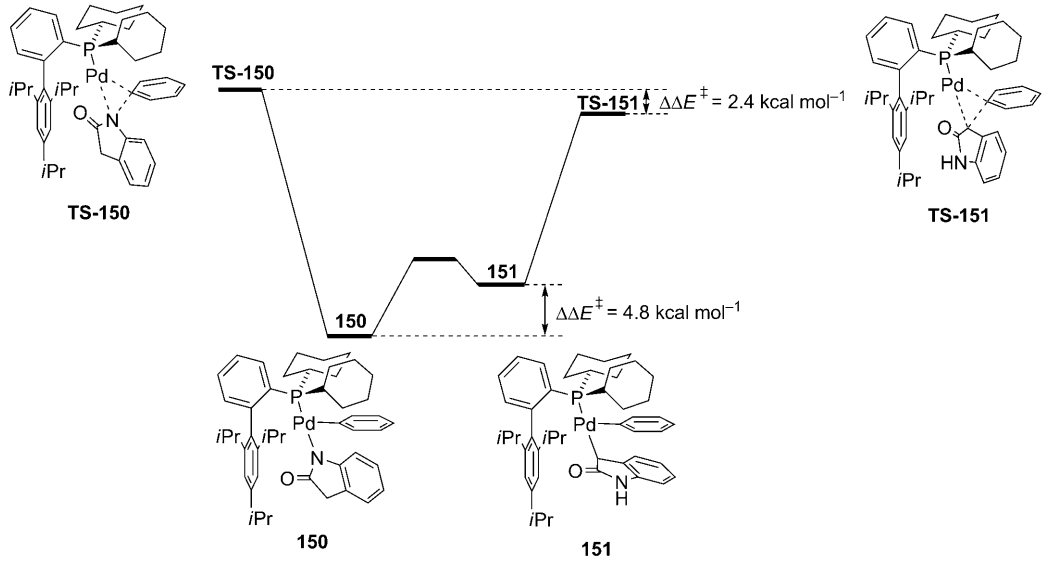
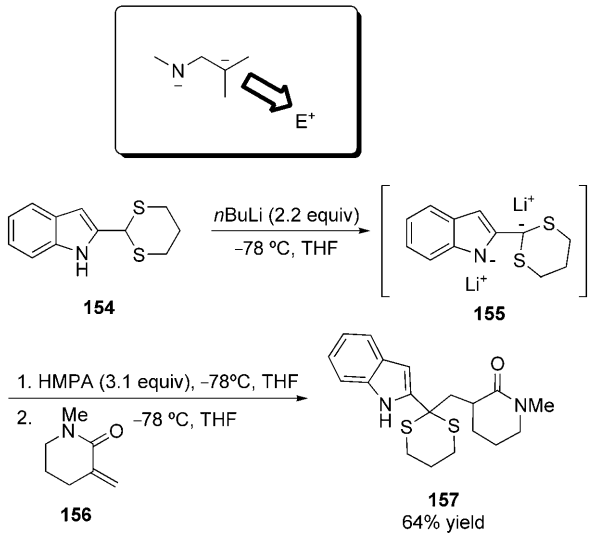


Figure 5.

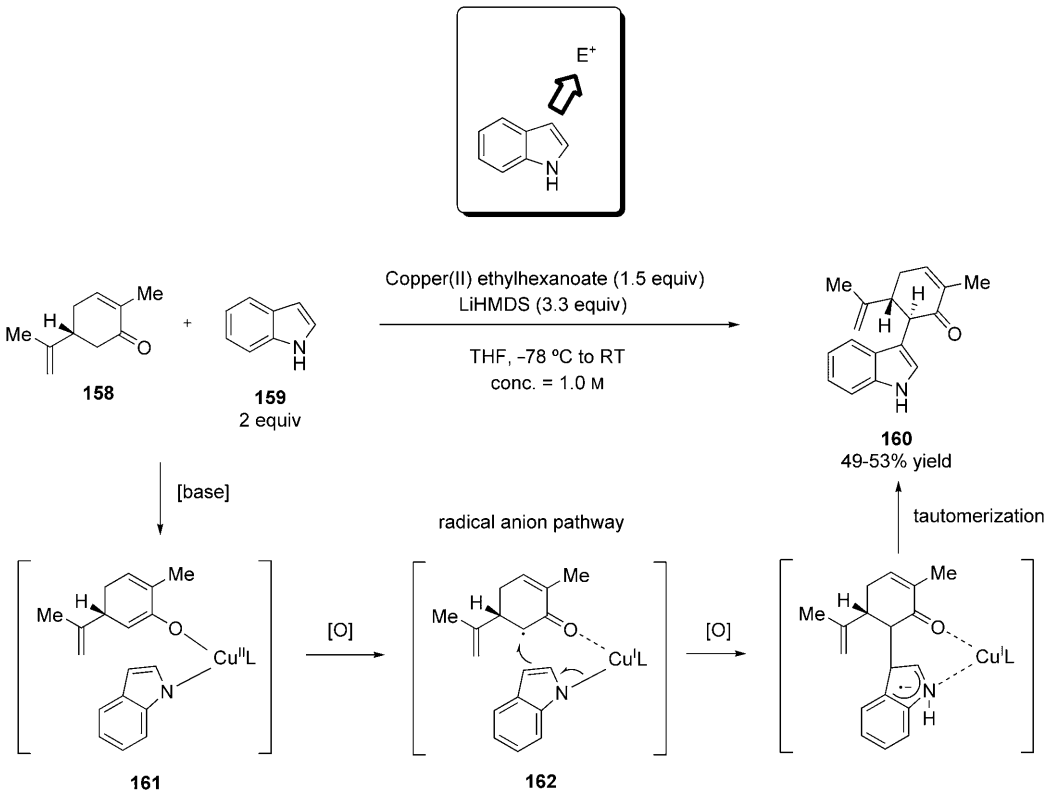
workers were faced with this issue when trying to construct the pyridocarbazole core by coupling the bis-nucleophile **154** with the Michael-acceptor **156** (Scheme 70).[132] Treatment of the dithioindole with *n*BuLi generated dianion **155**, which is capable of nucleophilic attack at the two sites. When the dianion was treated with **156**, the addition reaction proceeded slowly and afforded the products of bis-addition. The incorporation of hexamethylphosphoramide (HMPA) greatly improved the chemoselectivity and afforded the monoaddition product **157** in 64% yield without any competition from the aza-Michael reaction.



Scheme 70.

Over 70 years ago, Ivanoff and Spassoff[133] reported the first oxidative enolate coupling which they surmised proceeded via a radical intermediate, a proposal that remained for decades before being further investigated.[134] Today, the most widely accepted mechanistic hypothesis for the oxidative coupling is that oxidation of the enolate generates α-radical species which ultimately undergo dimerization.[135] Although oxidative enolate homodimerization is well-precedented, intermolecular dimerizations are considerably more challenging, often requiring prefunctionalization of one species or the use of a large excess of one coupling partner to achieve reasonable yields.[136] An efficient oxidative copper(II)-mediated protocol that promotes the coupling between the unprotected indole and carvone was developed by Baran and Richter.[137]

The core structure of a family of natural products including hapalindole, fischerindole, and ambiguine consists of an indole unit coupled to a carvone unit.[138] The core could, in theory, be accessed directly through an oxidative enolate heterocoupling, although the practical challenges associated with the simultaneous oxidation of different enolates and the avoidance of a statistical distribution of homo- and heterocoupled products would be challenging. Exposure of the carvone enolate and indole anion generated upon deprotonation of **158** and **159** with lithium hexamethyldisilazide (LiHMDS) to the copper(II) 2-ethylhexanoate oxidant successfully generated the desired product **160** in 53% yield (Scheme 71).

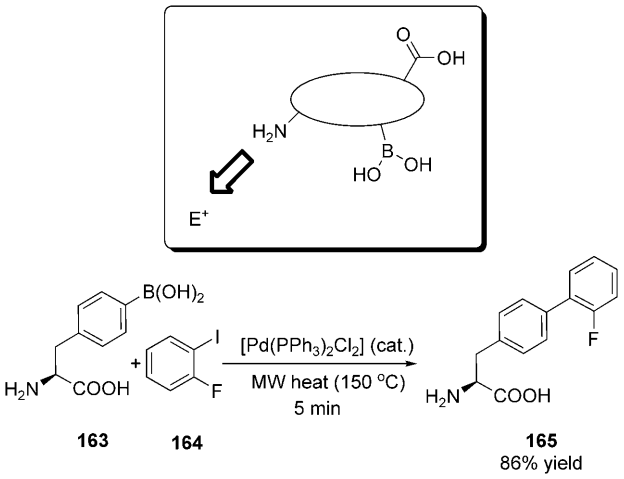


Scheme 71.

This method provided the key intermediate for the gram-scale production of the targeted natural products featuring this core.[139] A mechanistic investigation revealed that the first step in the mechanism likely involves deprotonation of the indole and enolization of the carbonyl group by LiHMDS to generate the copper(II)-chelate species **161**.[140] A single-electron transfer (SET) then generates a chelated α-keto radical that is attacked by the indole anion in proximity, thereby generating a radical anion. The radical intermediate **162** can be further oxidized by the adjacent copper(I) center to afford the product after tautomerization.

Of note, the hypothesis of a chelated species rather than discrete radical species may account for the lack of observed homodimerization, although other mechanisms cannot be ruled out at this point.[141] The coupling is highly chemoselective and displays broad functional-group tolerance including chloroketones, unprotected hydroxy groups, and epoxides.

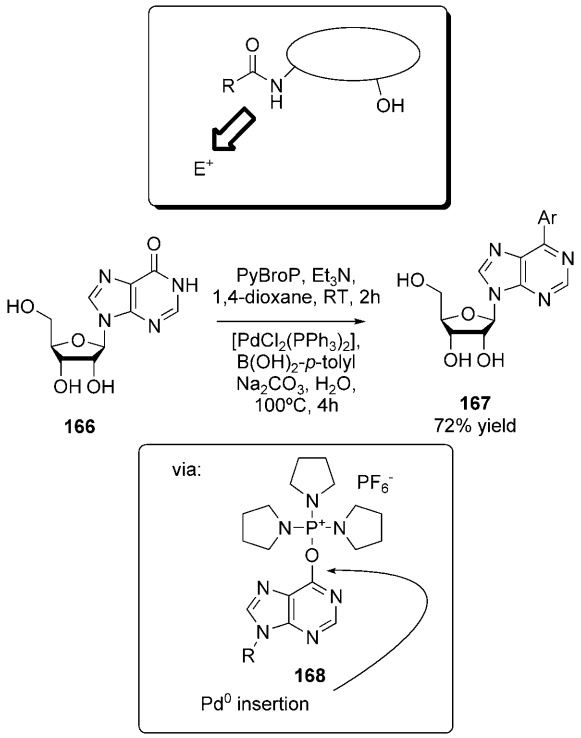
In 2002, Gong and He demonstrated that Suzuki cross-coupling reactions can be performed using unprotected amino acid derivatives containing aromatic boronic acid side chains.[142] By using this approach a wide range of pharmaceutically relevant biphenyl-containing unnatural amino acids can be accessed in short reaction times. For example, 4-boronophenylalanine (**163**) and 1-fluoro-2-iodobenzene (**164**) can be coupled in high yields to afford the biphenyl derivative **165** after only five minutes (Scheme 72). Microwave irradiation was found to be optimal with regard to yield and selectivity; traditional thermal modes of activation delivered substantially lower yields. Interestingly, this direct coupling under basic conditions was not accompanied by racemization, even at 150 °C.



Scheme 72.

Synthetic protocols for the synthesis of biaryls that do not rely on substrate preactivation have become highly valuable in contemporary organic synthesis.[143] In direct arylation, only one cross-coupling partner requires preactivation while the other does not, thereby minimizing the amount of waste products and superfluous functional-group interconversions.

Although direct arylation of Ar–H or even Ar–OR substrates has received a great deal of attention in recent years,[144] the arylation of Ar–OH has not.[145] In 2008, Kang and co-workers reported that the bromophosphonium salt PyBroP can be employed as an in situ activating agent to allow the direct arylation of tautomerizable heterocycles by Suzuki–Miyaura coupling.[146] The broad functional-group tolerance and high-yielding procedure allowed for the preparation of a range of biaryls including 6-aryl purine ribonucleosides, which display cytostatic and anti-HCV (HCV = hepatitis C virus) properties.[147] A chemoselective coupling was achieved at the more acidic phenolic OH group of inosine **166** to afford the 6-aryl purine ribonucleoside **167** in 72% yield in a single-step procedure from the fully unprotected substrate (Scheme 73). This represents a marked improvement over previously reported syntheses, which generally required four steps including protection and activation.[148]

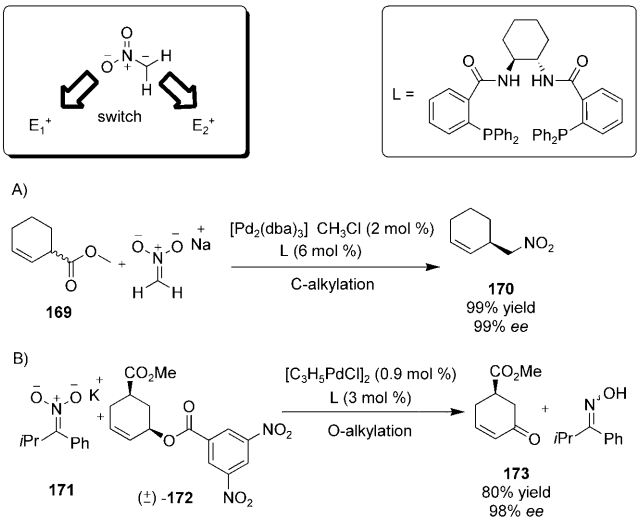


Scheme 73.

The key step in the modified Suzuki–Miyuara catalytic cycle proposed by Kang and co-workers is the oxidative addition of palladium(0) into the activated C–O bond of the aryl phosphonium species **168** generated upon base-promoted tautomerization of the heterocycle. The transmetalation of the resulting heterocycle-palladium(II)-phosphonium intermediate with an aryl boronic acid followed by reductive elimination of the biaryl product regenerates the palladium(0) catalyst.

Trost and Surivet have demonstrated the capacity of nitroalkanes to act as ambidentate nucleophiles that participate in both C- and O-alkylations. They reported the

palladium-catalyzed asymmetric allylic alkylation of nitroalkanes with allylic esters,[149] where the nitroalkane behaved as a C nucleophile. This methodology can be adapted, for example, to the desymmetrization of *meso*-diesters **169** to afford access to an important class of synthetic building blocks **170** in high yield and enantiomeric excess (Scheme 74 A).

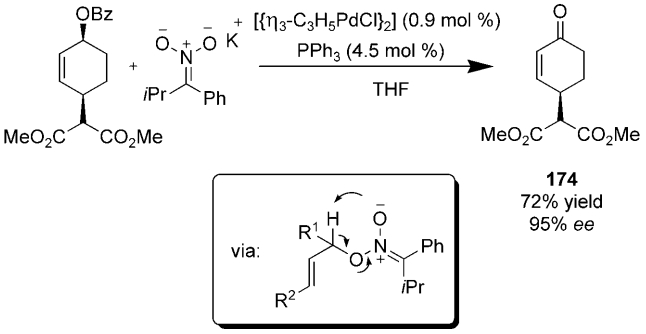


Scheme 74.

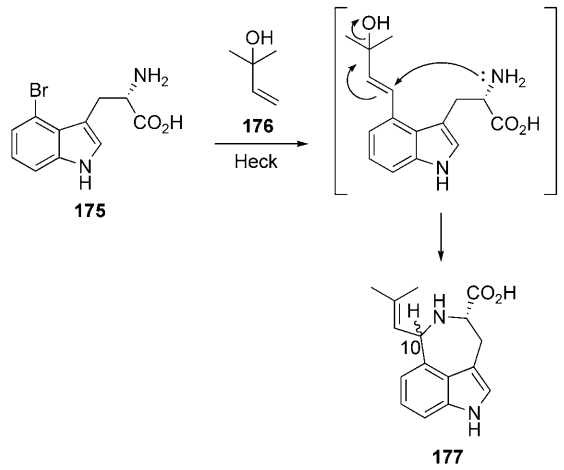
More recently, Trost et al. reported that by tuning the steric and electronic properties of the nitronate, O-alkylation can be favored over C-alkylation. Such a process that can be exploited to achieve the selective oxidative of allyl benzoates to enones.[150,151] The oxidation of allylic esters and carbonates can be achieved through the chemoselective O-alkylation of nitronates by utilizing a similar catalytic system. The oxidation mechanism involves initial nucleophilic attack of the nitronate potassium salt **171** onto the π-allylpalladium intermediate generated from **172**, followed by an intramolecular deprotonation to give rise to the corresponding enantiomerically enriched enone **173** (Scheme 74 B).

The 3,5-dinitrobenzoate moiety proved to be the best allylic leaving group, and afforded high yields of the enones after short reaction times. Functional groups such as tertiary amines, unprotected alcohols, and thioethers are incompatible with common oxidants, but were nonetheless carried through the transformation with no detectable oxidation. This protocol is also effective for the dynamic kinetic asymmetric transformation (DYKAT) of *meso*-esters, which allows access to the enantioenriched products in high enantioselectivity. In a demonstration of the synthetic utility of this oxidation, a key intermediate (**174**) in the synthesis of paenilactone A by Bäckvall and co-workers was constructed in two steps without compromising the enantiopurity (Scheme 75).[152]

In 2004, Yokoyama et al. described a protecting-group-free total synthesis of the ergot alkaloid clavicipitic acid (**177**).[153] A chemoselective palladium-catalyzed Heck reaction/cyclization between 4-bromotryptophan (**175**) and 2-methyl-3-buten-2-ol (**176**) is the cornerstone of this synthesis (Scheme 76). The striking feature of the Heck reaction is that



Scheme 75.

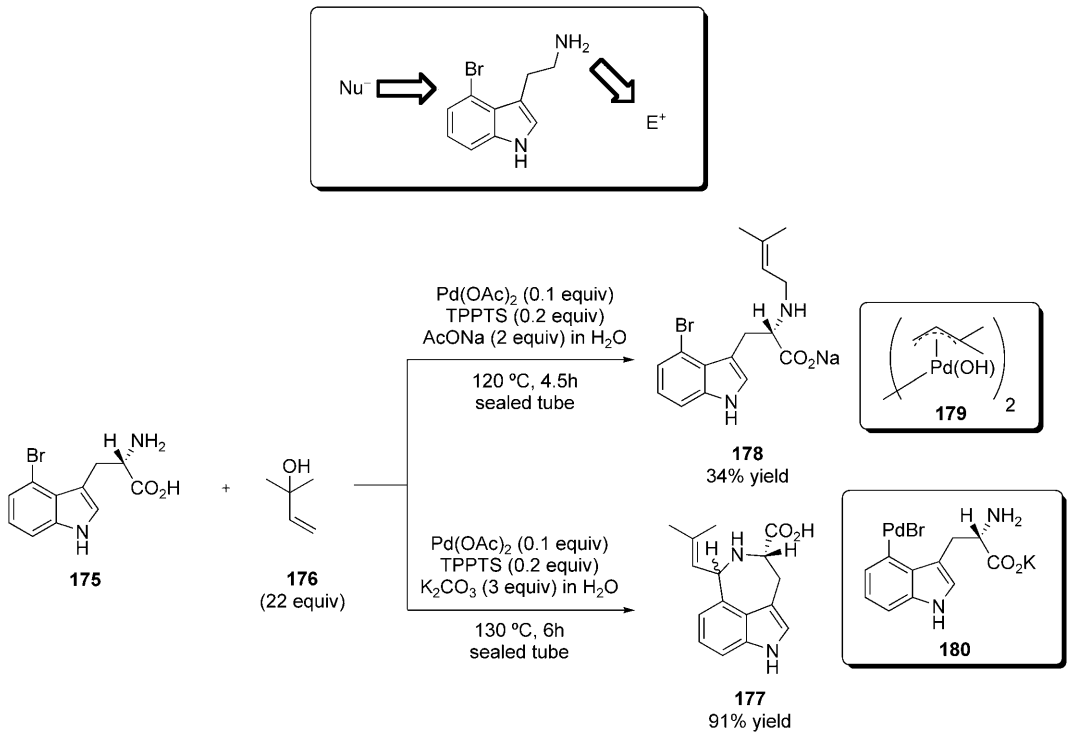


Scheme 76.

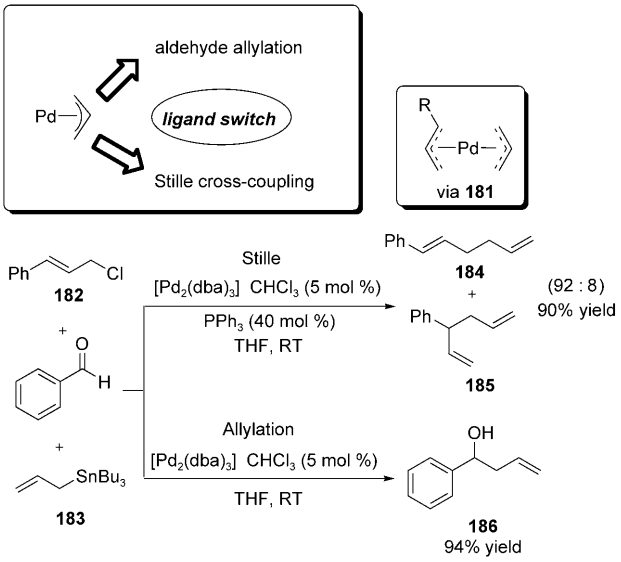
the reactive site on the molecule is determined by the pH value of the medium. Under weakly basic conditions, palladium(0) preferentially reacts with **176** to form the π-allyl complex **179**, which leads to the N-allylation product **178**. However, under strongly basic conditions, the σ complex (**180**) derived from oxidative addition to **175** leads to the desired cyclization product (Scheme 77). No racemization was detected under the strongly basic conditions required to perform the ring closure.

4.2. Selecting between Carbon–Carbon Coupling Reactions

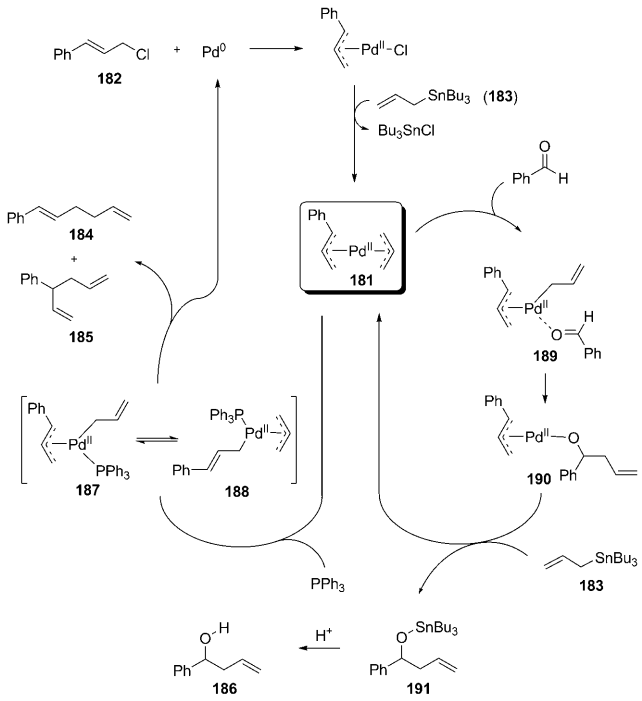
Yamamoto and co-workers have shown that the reactivity of bis(η^3-allyl)palladium complex **181** can be altered by triphenylphosphine (PPh_3).[154] The palladium-catalyzed Stille coupling between allylic halides and allyltributyl is known to proceed through **181** to yield the diene products **184** and **185** (Scheme 78). Yamamoto and co-workers have shown that the Stille coupling does not occur in the absence of PPh_3. Instead, the unsubstituted allyl group of **181** is transferred to both imines and aldehydes to furnish the corresponding allylated products. However, in the presence of four equivalents of PPh_3 (relative to Pd), the Stille coupling proceeds smoothly, despite the presence of imines and aldehydes. For example, in the reaction of cinnamyl chloride (**182**), benzaldehyde, and



Scheme 77.



Scheme 78.



Scheme 79.

allyl tributyltin (**183**), PPh_3 triggers a Stille reaction which affords the diene products **184** and **185** as a 92:8 mixture and 90% overall yield with quantitative recovery of benzaldehyde. On the other hand, in the absence of PPh_3, the homoallyl alcohol **186** is recovered in 94% yield.

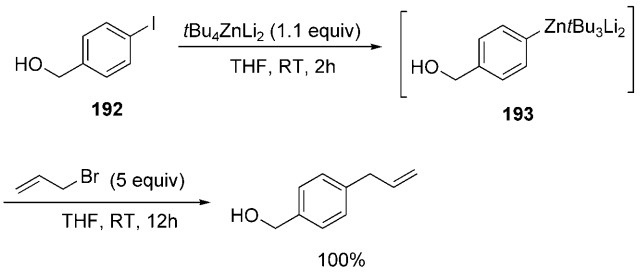
The postulated mechanism begins with the formation of **181** after oxidative addition of cinnamyl chloride and subsequent transmetalation from allyltributyltin to palladium (Scheme 79). If the phosphine ligand is present in sufficient amounts, it coordinates to the Pd^{II} center to afford a mixture of complexes **187** and **188**, which, upon reductive elimination, yield the classical Stille coupling products **184** and **185**, while also regenerating the active Pd^0 species. In the absence of PPh_3, benzaldehyde coordinates to the Pd^{II} center, thereby generating complex **189**, which can then undergo allylation to afford the homoallyloxypalladium complex **190**. Subsequent transmetalation with another equivalent of allyltributyltin

regenerates the active Pd species and homoallyloxytin **191**, which yields the allylated alcohol **186** upon workup. In this system, PPh_3 plays a crucial role in modulating the chemoselectivity.

Since the pioneering work of Gilman,[155] the use of organolithium and Grignard reagents in metal–halogen exchange reactions for the formation of carbon–carbon bonds has found widespread use. The high reactivity of many RX (X = Li, Mg) reagents is responsible for the low functional-group tolerance observed in many metal–halogen exchange reactions. Therefore, the development of reagents that do not require strict exclusion of acidic protons to avoid reagent quenching is desirable.

The low ionic character of C–Zn and C–Cu bonds[156] reduces their susceptibility to protonation, thus making these metals ideal candidates for chemoselective M–X exchange reactions. Early work by Knochel and co-workers demonstrated that alkyl zinc reagents prepared by the reaction of zinc dust with an appropriate organohalide were not destroyed in the presence of acidic protons (pK_a 18–35).[157,158]

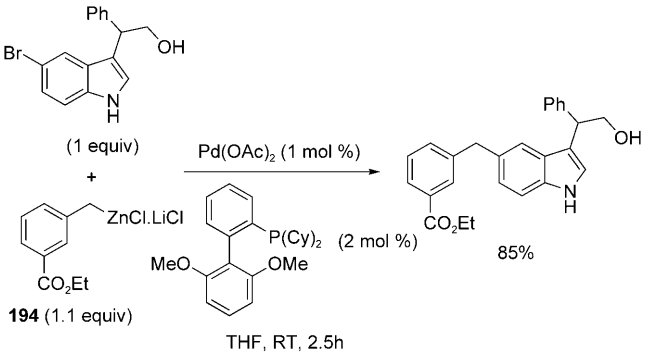
In 2006, Uchiyama et al. reported that the halogen–metal exchange of a haloarenes bearing acidic hydrogen atoms could be accomplished with tBu_4ZnLi_2 without quenching the reagent or the resulting aryl zincate.[159] For example, treatment of *p*-iodobenzylalcohol (**192**) with tBu_4ZnLi_2 generated **193**, which could be trapped with a variety of electrophiles in moderate to high yields (Scheme 80). Other acidic protons



Scheme 80.

such as amide N–H, phenolic O–H, and glycerol C2 protons were also tolerated. In addition, the aryl zincates were compatible with palladium- and copper-catalyzed C–C bond-forming reactions. Importantly, iodoarenes were required for high chemoselectivity since the elevated temperatures required for the zincation of bromoarenes resulted in proton quenching. It is also worth noting that in situ protection of the alcohol does not take place.[160]

In 2008, Knochel and co-workers reported an extensive study of the Negishi cross-coupling reactions of functionalized of aryl, alkyl, and benzylzincates with bromoarenes bearing acidic OH and NH_2 groups.[161] Here, the chemoselectivity was strongly influenced by the kinetic basicity of the various zincated species. For example, the relatively low kinetic basicity of $PhCH_2ZnCl{\cdot}LiCl_2$ (**194**), prepared by zinc insertion in the presence of LiCl, allowed for chemoselective coupling with bromoarenes bearing unprotected NHR and OH groups (Scheme 81). On the other hand, more-basic aryl zinc species



Scheme 81.

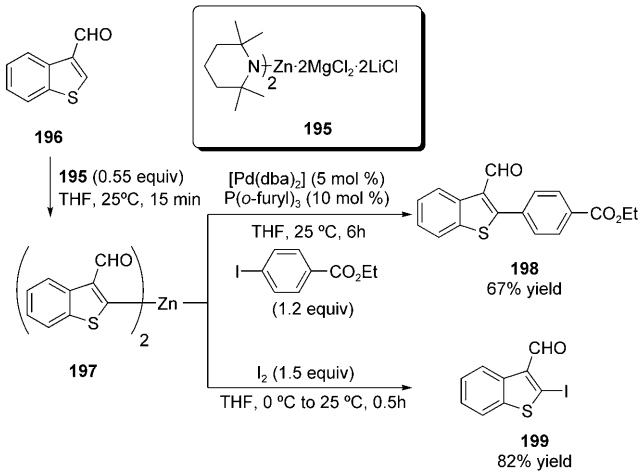
were rapidly quenched by phenolic protons and could only be cross-coupled with sterically hindered alcohols. Esters, ketones, cyano groups, primary and secondary amines, and aldehydes were all tolerated in the cross-coupling reaction carried out using a $Pd(OAc)_2$/*S*-phos catalytic system at 25 °C.

The direct metalation of arenes is an active area of research that parallels efforts in direct arylation to achieve highly selective functionalization of aromatic rings without the need for prefunctionalization of the substrate. Although traditional bases such as alkyl lithium compounds (RLi) or lithium amides (R_2NLi) are effective,[162] the limited functional-group tolerance of both these reagents and the resulting aryl lithium species remains a limitation.[163] Magnesium bases of the type (TMP)MgX developed by Eaton et al.[164] have enjoyed renewed interest since the corresponding aryl magnesiates have been shown to tolerate a range of electrophiles including esters, nitriles, and ketones.[165] However, their moderate solubility[166] and low kinetic basicity reduced their applications.[167] Interestingly, Knochel and co-workers found that the addition of LiCl generated mixed Mg/Li bases with enhanced functional-group tolerance, stability, and kinetic basicity. (TMP)MgCl·LiCl, prepared by the reaction of *i*PrMgCl·LiCl with TMPH, smoothly magnesiated aryl and heteroaryl species bearing esters, nitriles, ketones, and halides.[165a,b] Treatment of the magnesiated species with a variety of electrophiles afforded the cross-coupled products in high yields. The high solubility and kinetic basicity is attributed to LiCl, which is believed to be responsible for breaking up magnesium amide aggregates.

Crystal structures of TMPMgCl·LiCl recently obtained by Mulvey and co-workers have shed light on the synergistic effect of Li and Mg which confers strong metalating capability to the mixed bases.[168] Although effective, (TMP)MgCl·LiCl and other "ate" bases[169] are not compatible with certain heteroarenes[170] and the more sensitive nitro and aldehydes groups.

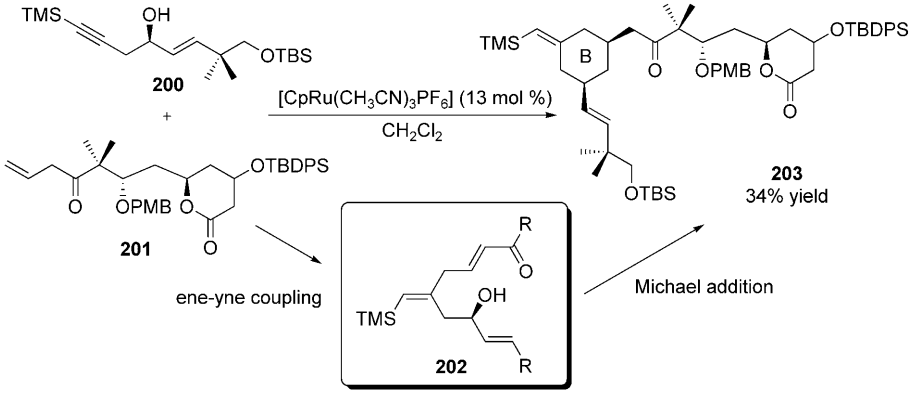
This limitation was addressed in 2007 with the introduction of the neutral base $(TMP)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (**195**), which is capable of zincating (hetero)arenes smoothly even in the presence of aldehyde and nitro groups.[171] The corresponding zincated nucleophiles were coupled with a variety of electrophiles in high yields with the generation of densely functionalized arenes. For example, treatment of 3-formylbenzothiophene (**196**) with **195** generated the zincated

nucleophile **197** in 15 minutes at 25 °C. Compound **197** was compatible with a variety of electrophiles such as I_2 as well as with the Negishi cross-coupling reaction to give the functionalized heterocyclic aldehydes **199** and **198** respectively, in good yields (Scheme 82). As previously reported, the combination of the Lewis acids $MgCl_2$ and LiCl, which form part of this complex base, was found to be essential for achieving high kinetic basicity and solubility in THF. The neutral species **195** is more tolerant towards sensitive functional groups than other bases that rely on their "ate" nature for high activity.



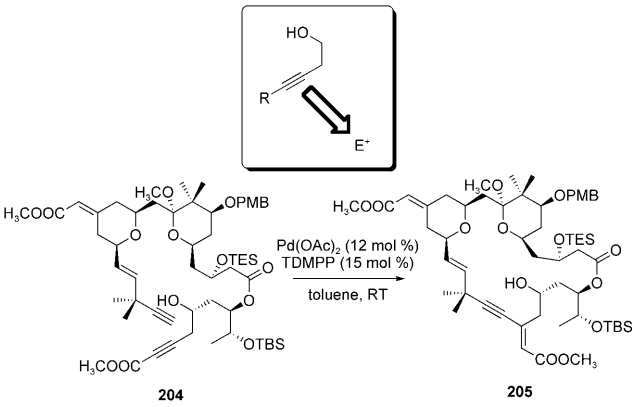
Scheme 82.

The synthesis of bryostatin by Trost and Dong exemplifies the utility of chemoselective transformations with alkynes.[172] A sequence of ruthenium- and palladium-catalyzed chemoselective transformations led to the shortest reported synthesis of bryostatin to date. The first of these reactions involves the contruction of the B ring of the molecule by using a ruthenium-catalyzed tandem alkene–alkyne coupling between **200** and **201** followed by an intramolecular Michael addition to intermediate **202** that gives rise to the desired *cis*-tetrahydropyran ring **203** in 34% yield (80% based on recovered starting material; Scheme 83).[173] The reaction proceeds despite the presence of several sensitive functional groups such as PMB/silyl ethers, a β,γ-unsatured ketone, a six-membered lactone, and an unprotected allylic alcohol.



Scheme 83.

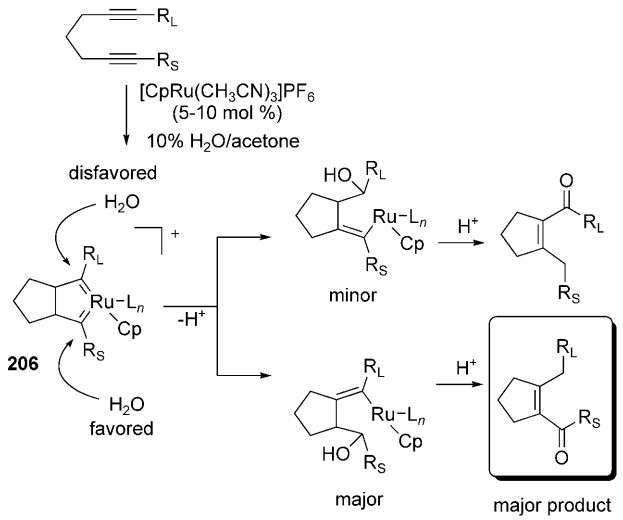
Nearing the final stages of the synthesis, Trost and Dong demonstrated that a palladium-catalyzed alkyne–alkyne coupling can be an efficient and atom-economical method for the construction of macrocycles. Macrocyclization of **204** to **205** occurs in 56% yield in the presence of $Pd(OAc)_2$ (12 mol%) and tris(2,6-dimethoxyphenyl)phosphine (15 mol%; Scheme 84). Mechanistically, this process begins with the chemoselective insertion of Pd into the terminal C–H bond of the alkyne followed by carbometalation of the disubstituted alkyne to form a vinylpalladium hydride species. Reductive elimination then creates the desired macrocycle and establishes the geometry of the new olefin. This reaction proceeds in relatively high yield despite the dense functionalization of **204**.



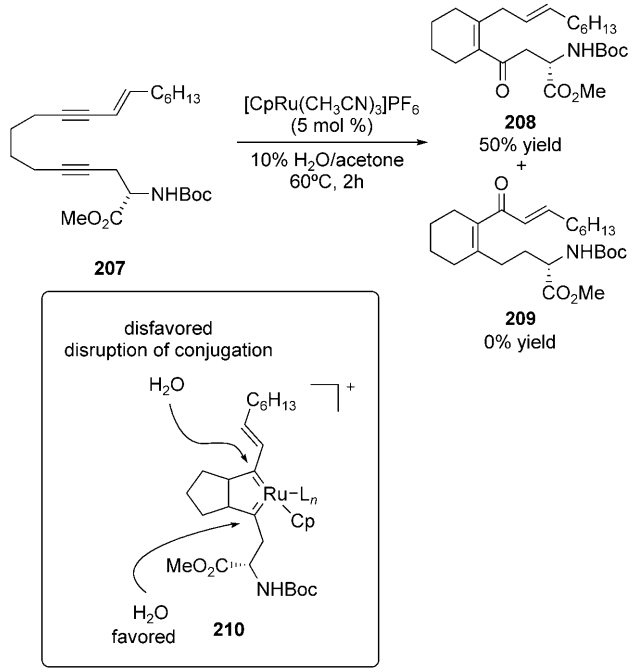
Scheme 84.

Trost and Rudd recently developed the ruthenium-catalyzed hydrative cyclization of diynes to cyclic enones.[174] They discovered that exposure of 1,6- and 1,7-diynes to a catalytic quantity of $[CpRu(CH_3CN)_3]PF_6$ in acetone/H_2O generated the corresponding five- and six-membered cyclic enones. Mechanistically, this process is proposed to involve the formation of a ruthenacyclodiene (**206**) followed by attack of water and an elimination step to regenerate the catalyst and expel the product (Scheme 85). With unsymmetrical diynes, the chemoselectivity was highly dependent on the steric environment of the ruthenacycle, with water attacking preferentially at the least hindered position.

Assuming that the attack by water was dominated by steric considerations, this method could be applied in the synthesis of a key intermediate of the tricyclic alkaloid cylindricine C. However, exposure of the precursor to cyclization **207** to $[CpRu(CH_3CN)_3]PF_6$ led to the isolation of the undesired enone **208** without any of the expected product **209**, despite the fact that the vinyl group is generally considered to be smaller than a β-branched alkyl chain (Scheme 86).[175] It was proposed that this



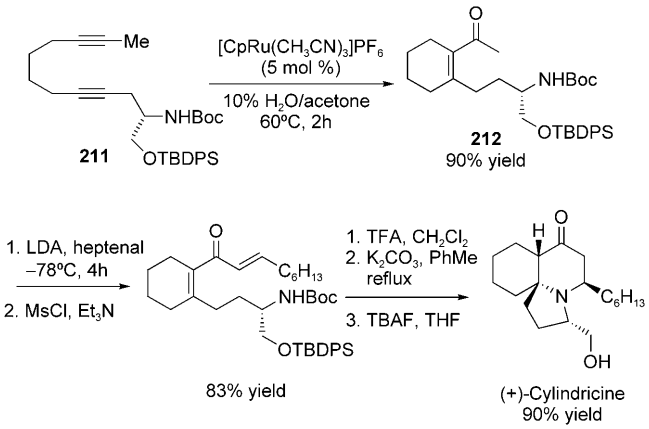
Scheme 85.



Scheme 86.

unusual reversal in chemoselectivity was the result of disrupted conjugation upon water attacking in proximity to the 'smaller' olefin of intermediate **210.**

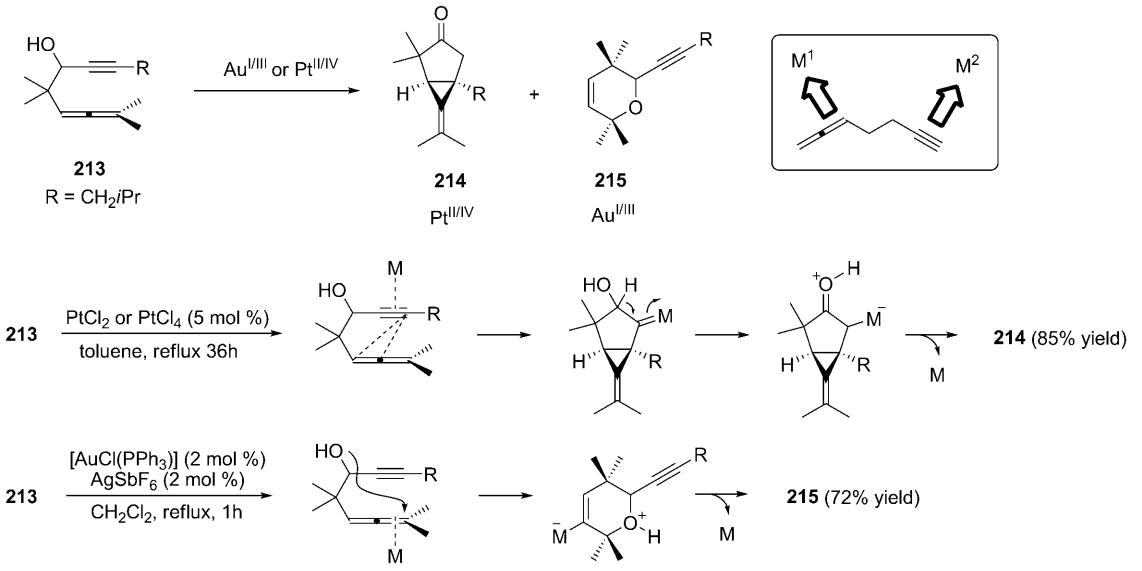
Replacing the vinyl with a methyl group in **211** allowed for the desired isomer (**212**) to be obtained in high yield (Scheme 87). Clearly, steric effects alone were not sufficient for predicting the chemoselectivity of the cyclization, thus highlighting the necessity for considering electronic effects as well. An aldol/dehydration sequence followed by double conjugate addition pioneered by Molander and Ronn,[176] and cleavage of the TBDPS group completed the synthesis of (+)-cyclindricine C.



Scheme 87.

The exceptional functional-group tolerance of gold catalysts and their interesting reactivity in the presence of unsaturated C–C bonds has elicited a strong interest in synthetic chemistry.[177] Platinum catalysts often behave in the same fashion as gold catalysts and generate similar products. Thus, cases of divergent reactivity between gold and platinum catalysts are intriguing.[178] One example highlighting this concept was reported by Fensterbank, Malacria, and coworkers.[179] While examining the reactivity of hydroxylated 1,5-alleneynes, they found that Pt and Au catalysts operate completely differently when given a choice to activate one of two π systems. Pt^{II}/Pt^{IV} salts displayed considerable affinity for the alkyne component while Au^{I} catalysts were more allenophylic. Consequently, two distinctly different skeletal arrangements could be induced with complete chemoselectivity from the same substrate. Treatment of **213** with a catalytic amount of $PtCl_2$ or $PtCl_4$ led to the exclusive formation of bicycle **214** in good yields, while treatment of the same substrate with $[AuCl(PPh_3)]/AgSbF_6$ generated **215** as the sole product. The mechanistic rationale is outlined in Scheme 88. Treating **213** with $PtCl_2$ resulted in alkyne activation, which facilitated intramolecular attack by the internal allene double bond. Subsequent 1,2-hydride migration and catalyst regeneration gave rise to the bicyclo-[3.1.0]hexane **214** in good yield. Alternatively, treatment of **213** with $[Au(PPh_3)]^+$ resulted in unexpected allene activation towards nucleophilic attack by the hydroxy group to give **215** in a reaction sequence analogous to that observed with β-hydroxyallenes.[180]

Interestingly, **215** was formed in the presence of $[Au(PPh_3)]^+$ irrespective of whether the solvent was toluene or CH_2Cl_2, although the latter resulted in higher yields. In contrast, **214** was the only isolable product when AuCl or $AuCl_3$ were employed as catalysts in toluene, while in CH_2Cl_2, **215** was the only product. Thus, in this case, chemoselectivity is not only dependent on the choice of catalyst but is also strongly dependent on the choice of solvent. It appears that the active catalyst generated from $[Au(PPh_3)]^+$ remains the same in both toluene and CH_2Cl_2, thereby giving the same product. In the absence of a stabilizing ligand (PPh_3) the active species generated from AuCl and $AuCl_3$ may be different depending on the solvent.

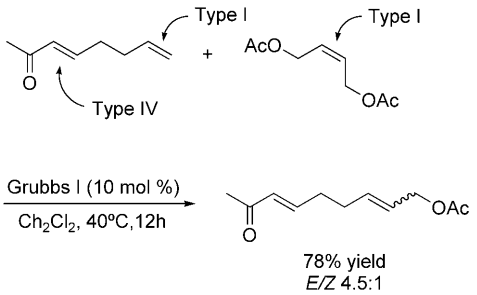


Scheme 88.

Olefin metathesis has become one of the most powerful transformations available to synthetic chemists. The use of olefin metathesis in the synthesis of complex molecules has been facilitated by the development of highly functional-group tolerant ruthenium-based catalysts by Grubbs and co-workers. In many of these cases, ring-closing metathesis (RCM) is used to "stitch" together a particular ring with very high selectivity. The selectivities achieved in RCM, which generally result from the proximity of the reacting olefins, cannot always be extended to cross-metathesis (CM) reactions. Statistical mixtures of homo- and heterodimerized products are often limiting to a maximum yield of 50% if the olefins are used in a 1:1 ratio.

To address this limitation, Grubbs and co-workers developed a set of empirical guidelines based on an olefin categorization system for predicting the outcome of cross-metathesis reactions.[181] Olefins were subdivided into four classes according to the rate at which they homodimerize or undergo self-metathesis. Type I olefins undergo rapid homodimerization, while type II are slow to homodimerize. Type III olefins do not homodimerize, whereas type IV olefins are spectators to metathesis and do not deactivate the catalyst. The rates of homodimerization correlate with reactivity in CM and depend on the electron density and steric bulk, especially at the allylic position and at the olefin substituents.

For the second generation Grubbs catalyst, terminal olefins and unhindered allylic alcohols typically fall under the type I category while acrylates and enones are classified as type II. 1,2-Disubstituted and nonbulky trisubstituted olefins are classified as type III, while very electron deficient olefins such as vinylnitroolefins are type IV. This classification allows the prediction and development of chemoselective CM reactions. For example, the reaction between two type I olefins occurs smoothly in the presence of a type IV olefin with the Grubbs first generation catalyst (Scheme 89).

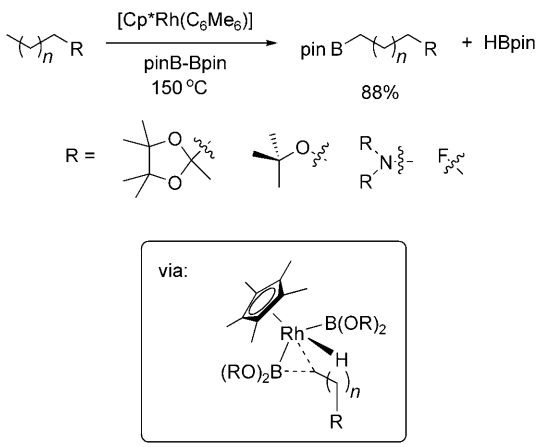


Scheme 89.

5. Metal-Catalyzed C–H Activation

An area of intense current interest is the selective transition-metal-catalyzed functionalization of unactivated C–H bonds. In this regard, the rhodium catalysts developed by Hartwig and co-workers have garnered a great deal of interest. Driven by steric effects, this rhodium-catalyzed reaction accomplishes highly selective borylation of unactivated alkanes at the terminal CH_3 group (Scheme 90).[182] The reaction accomplishes the delivery of a boryl fragment from the diboron (pinB-Bpin) reagent to the metal center. The functionalized product is formed by reductive elimination of the C–B bond from the resulting organometallic intermediate. Mechanistic studies suggest that a metal–boron species participates in the C–H activation step, which is followed by reductive elimination to form the C–B bond. Interestingly, DFT calculations lend support to the importance of an unoccupied p orbital on the boron atom in the course of the C–H activation process.

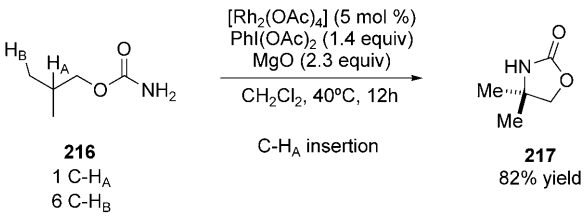
Recently, the development of catalysts that mediate the chemoselective insertions of nitrogen into particular C–H bonds has emerged as a powerful method for the construction of C–N bonds.[183] Early work in this field began with a seminal report by Kwart and Khan which detailed the metal-



Scheme 90.

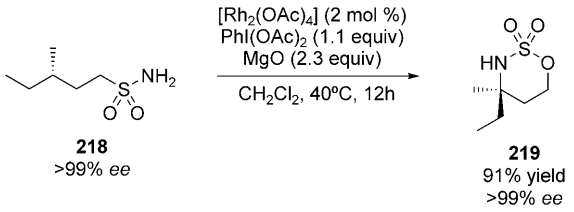
catalyzed C–H insertion of a nitrene generated by copper-catalyzed decomposition of benzenesulfonylazide in cyclohexane.[184] Subsequent work by Breslow and Gellman introduced iminoiodinanes as metal nitrene precursors in intramolecular C–H amination reactions, and identified dimeric rhodium complexes as efficient catalysts for C–H insertion processes.[185] Müller et al. studied intermolecular C–H amination with stable tosyl- and nosyl-functionalized iminoiodinanes, but a large excesse of alkane was required to achieve acceptable yields.[186] The problems generally associated with the isolation and purification of nonstabilized iminoiodananes[187] was circumvented by Che and co-workers with the development of an in situ protocol that generated nitrenes from $TsNH_2$ and $PhI(OAc)_2$ in the presence of a manganese-porphyrin catalyst.[188]

The practicality of C–H aminations employing metal nitrenes was dramatically increased by a report from Espino and Du Bois, who detailed a highly chemo- and stereoselective process whereby oxazolidinones **217** could be prepared from carbamates **216** through an intramolecular C–H amination (Scheme 91).[189] The reactive species is believed to be a



Scheme 91.

rhodium-nitrene intermediate arising from an iminoiodinane formed in a reaction between the carbamate and a hypervalent iodine reagent. The reaction is chemoselective for insertion into the most electron-rich C–H bond, thus tertiary C–H bonds are preferred over secondary C–H bonds despite an often large statistical preference for the latter. The same chemoselectivity is extended to sulfamate derivatives **218**,[190] except that the formation of the six-membered product **219** is preferred in this case (Scheme 92).[191] The retention of configuration at the reacting carbon atom is suggestive of a singlet nitrene insertion pathway, analogous to that observed

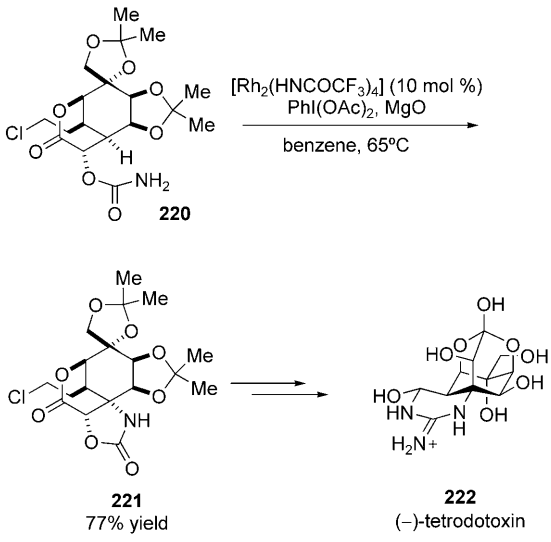


Scheme 92.

in the insertion of rhodium carbenes derived from diazo compounds into C–H bonds.[192] A DFT study by Che, Philips, Zhao, and co-workers has found that a concerted asynchronous pathway involving a singlet rhodium-nitrene species had a lower activation energy than the alternative step-wise diradical pathway.[193]

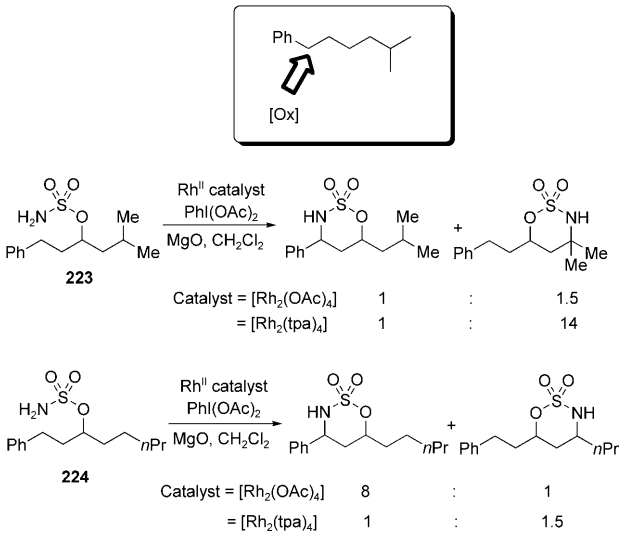
Du Bois and co-workers applied their C–H amination protocol to the synthesis of the natural product tetrodotoxin (**222**), a potent neurotoxin commonly associated with the Japanese *Fugu* (pufferfish).[194,195] A key step in this synthesis involved the late-stage installation of the challenging tetrasubstituted carbinolamine, which was carried out with a modified rhodium catalyst in good yields, despite the structural complexity of the substrate **220** and several reactive ethereal C–H bonds.[196] Elaboration of the resulting late-stage intermediate **221** afforded (−)-tetrodotoxin (Scheme 93).

Delineating the relative rates at which C–H bonds undergo oxidation provided useful insights into the origins of the chemoselectivity. By using different rhodium tetracarboxylate catalysts, a series of sulfamate derivatives differentially substituted with distinct C–H bonds at the γ and γ′ positions revealed the order of reactivity for amination:



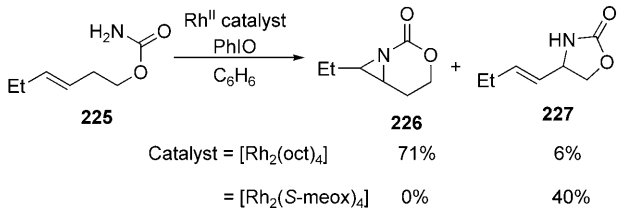
Scheme 93.

tertiary C–H > ethereal C–H ≈ benzylic C–H > secondary C–H ≫ primary C–H. In most cases, different catalysts produced the same sense of chemoselectivity and generally follow the prescribed reactivity pattern. However, in one instructive case, the selectivity was completely reversed by changing the ligand. For sulfamate **223**, prototypical tertiary C–H insertion is favored over benzylic C–H insertion irrespective of the catalyst. In contrast, for **224**, chemoselectivitiy was catalyst-dependent and secondary C–H oxidation was found to override benzylic C–H oxidation (Scheme 94). This observation indicates that electronic factors dominate the reactivity of the majority of substrates, however, steric impositions can supersede intrinsic electronic biases in certain substrate–catalyst combinations. It is worth noting that the ability of the catalyst to influence chemoselectivity provides more evidence for a tightly bound rhodium-nitrene species as the active oxidant.



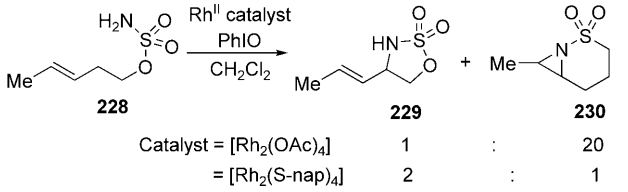
Scheme 94.

Given the propensity of nitrene species to perform aziridination reactions in the presence of olefins, an interesting opportunity for chemoselectivity exists in homoallylic substrates where both allylic C–H oxidation and aziridination are possible. When Hayes et al. generated a reactive nitrene species from homoallylic carbamate **225**, both the allylic oxidation product **226** and aziridination product **227** could be isolated,[197] although the choice of ligand was again found to have a strong influence on the product distribution (Scheme 95). Carboxylate ligands afforded mainly aziridination products, while carboxamidate ligands tended towards allylic oxidation products.



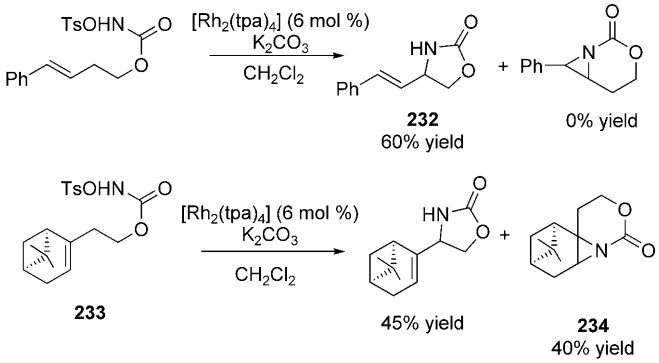
Scheme 95.

Du Bois and co-workers noted a similar trend in their investigation of homoallylic sulfamate **228**. They found that rhodium-carboxylate catalysts strongly favored aziridination to produce a six-membered ring product **230** over the five-membered allylic oxidation product **229** (Scheme 96).



Scheme 96.

In their work on hypervalent iodine-free rhodium-nitrene insertions, Lébèl et al. demonstrated that the choice of substrate can have a pronounced effect on the chemoselectivity, irrespective of the ligand choice.[198] For example, the catalytic decomposition of tosylcarbamate in the presence of $[Rh_2(tpa)_4]$ (tpa = triphenyl acetate) led to exclusive formation of C–H oxidation product **231**. However, substitution with a more electron rich olefin (**232**) led to the formation of a considerable amount of aziridine **233** using the same catalyst (Scheme 97).



Scheme 97.

Taken together, these results suggest that in the case of competing C–H sites, an electronic bias towards the most electron rich C–H bond appears to dominate the chemoselectivity. However, steric factors cannot be overlooked and can override the electronic bias in some cases. When it comes to allylic oxidation versus aziridination, it appears that rhodium-carboxylate catalysts tend to favor aziridination while rhodium-amidate catalysts favor allylic oxidation (Figure 6).

Du Bois and co-workers have also reported an easily preparable, stable, crystalline oxaziridine capable of selective oxidation of unactivated tertiary C–H bonds, and shown for the first time that catalytic turnover can be achieved

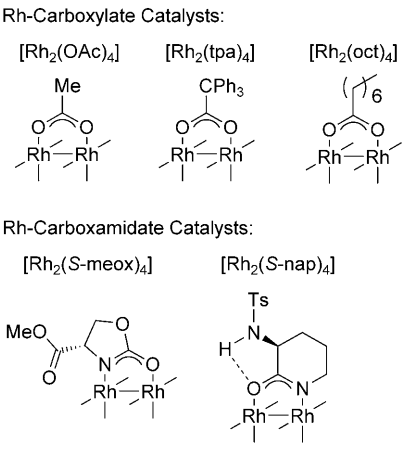
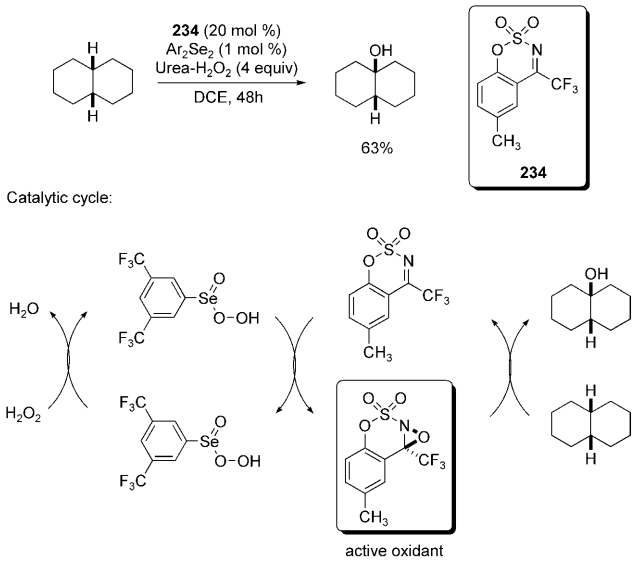


Figure 6.

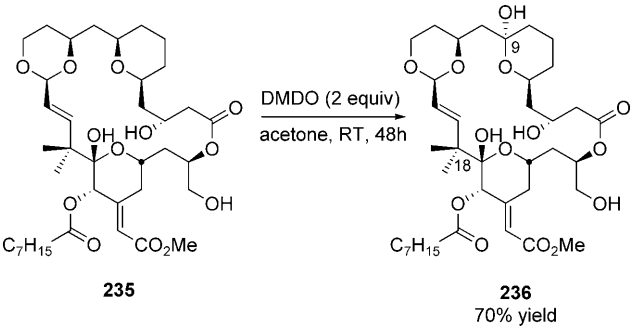
(Scheme 98).[199,200] The catalyst could be generated in situ by the action of perseleninic acid, itself generated from urea-H_2O_2 and a catalytic quantity of bis(3,5-bis(trifluoromethyl)-



Scheme 98.

phenyl) diselenide (Ar_2Se_2). After oxidation of the alkane by the catalyst, the resulting imine undergoes reoxidation, thereby enabling catalytic turnover. Substrate oxidation occurred at the most electron-rich C–H bond with retention of the configuration to afford optically pure tertiary alcohols.[201] The catalyst also displayed high activity for the epoxidation of alkenes, although no competition reactions between alkenes and tertiary C–H bonds were reported. While the concept of oxaziridine-mediated selective oxidation is known,[202] the novel 1,2,3-benzoxathiazine-2,2-dioxide scaffold on which **234** is built offers unprecedented opportunities for catalyst modification and tuning through varying the substitutents on the aromatic ring. Catalyst tuning may provide further opportunites in selective oxidation of functional groups.

When performing selective oxidations on sensitive and densely functionalized molecules, oxidants such as dimethyl dioxirane are typically not considered because of their promiscuity in oxidizing a variety of functional groups including alkenes,[203] alcohols,[204] hydrocarbons,[205] and ethers.[206] Despite this fact, Wender et al. achieved remarkable selectivity in the late-stage oxidation of bryostatin analogues with DMDO.[207] Treatment of **235** with two equivalents of freshly prepared DMDO resulted in stereospecific C–H oxidation at the C9-position to give **236**, despite the presence of a myriad of other sensitive functional groups including two alkenes, multiple ethereal bonds, a free primary hydroxy, and tertiary C–H bonds, all of which are susceptible to oxidation (Scheme 99). Given the highly electrophilic



Scheme 99.

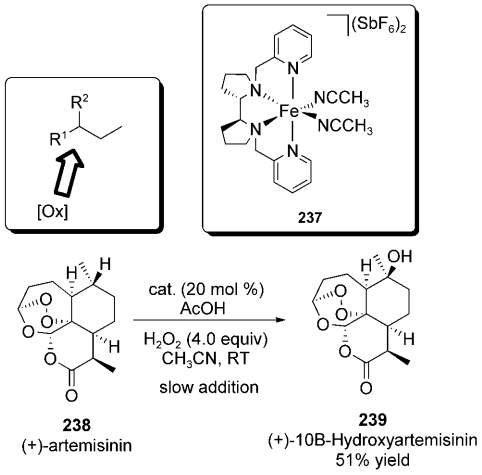
nature of this oxidant,[208] it is not surprising that the acrylic ester alkene was not epoxidized. In addition, the geminal dimethyl group at C17 may provide steric protection against oxidation of the adjacent alkene. Oxidation at the primary alcohol is likely avoided on kinetic grounds, but the lack of nonselective oxidation at the remaining vulnerable sites comes without an adequate explanation, although one possibility is that conformational rigidity of the molecule protects certain "buried" regions.

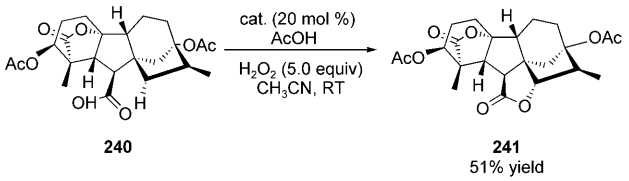
Iron-containing molecules play an essential role in selective hydrocarbon oxidations performed in nature.[209] For example, the heme-containing cytochrome P450 selectively oxidizes the long aliphatic side chain of cholesterol during the biosynthesis of the hormone progesterone.[210] However, application of these fragile biocatalysts in a laboratory setting is not practical. Thus, a great deal of work has centered around the development of biomimetic heme[211] and non-heme iron catalysts.[212] Ligands able to act as heme surrogates, such as pyridines and other cyclic amines, have attracted a great deal of attention. Early work on iron-catalyzed C–H oxidations with these ligand types was carried out by the research groups of Tabushi[213] and Barton,[214,215] and more recently by Que and co-workers.[216]

White and Chen have recently reported a highly selective iron(II) catalyst **237** capable of oxidizing tertiary C–H bonds in complex molecules.[217] An interplay between steric, electronic, and directing effects ultimately determines the site of oxidation. A case in point involves the antimalarial compound (+)-artemisinin **238**, which bears five tertiary C–H bonds and an endoperoxy functionality known to be sensitive

to iron(II)-mediated cleavage.[218] (+)-Artemisinin is selectively oxidized at the most electron-rich and least sterically crowded C10–H bond by **237**. (+)-10β-Hydroxyartemisinin (**239**) was obtained as the major product in 51% yield.

The oxidation of secondary C–H bonds was also achieved in the diastereoselective lactonization of the tetrahydrogibberellic acid analogue **240**, where the presence of a carboxylate directing group was found to override oxidation at tertiary centers. The oxidized product **241** was recovered in 51% yield (Scheme 100). In the preliminary study, the

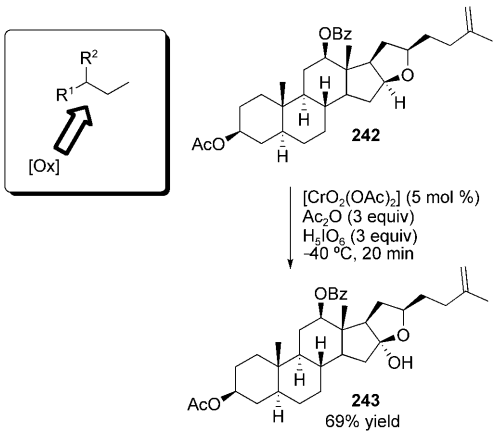




Scheme 100.

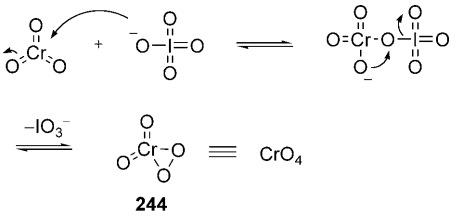
iterative addition of catalyst and oxidant (three times) was required to achieve good conversion. Moreover, recovered substrate was purified by flash chromatography and resubmitted to the reaction conditions to achieve an overall reasonable yield. Recently, a "slow-addition" protocol was reported, in which two separate solutions of catalyst and oxidant were added to the reaction mixture concomitantly over a period of 45 minutes, thereby eliminating the need for substrate recycling and iterative addition.[219] However, this practicality comes at the expense of an increased catalyst loading (from 15% over 3 iterative additions to 20% for slow addition protocol) because of rapid decomposition of the catalyst.

A report by Lee and Fuchs details the late-stage oxidation of **242** to hemiacetal **243** catalyzed by the Cr^{VI} species $[CrO_2(OAc)_2]$ with periodic acid as the terminal oxidant at −40 °C (Scheme 101).[220] Interestingly, the C–H oxidation proceeds in 69% yield, despite the presence of an olefin. Calculations performed by Rösch and co-workers indicated that the previously unknown monoperoxo Cr^{VI} species were less prone to epoxidation than similar Mo^{VI} or W^{VI} complexes.[221] While catalytic in chromium, the broad applicabil-

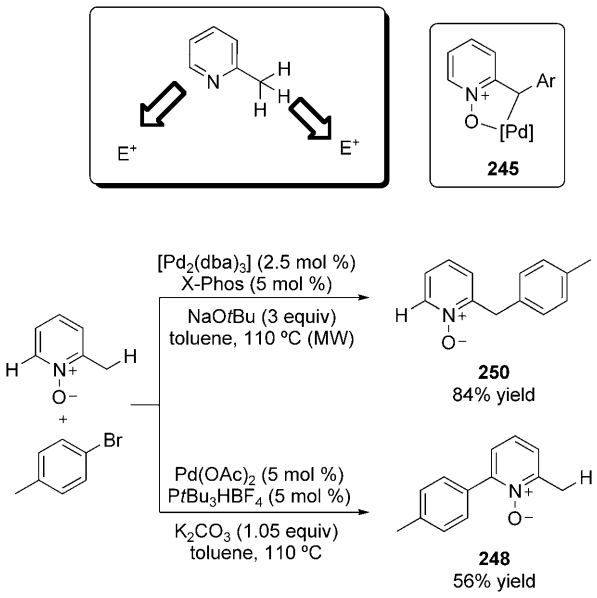


Scheme 101.

ity of this methodology is hampered by the strongly acidic conditions required for catalysis. Thus, Lee and Fuchs development a milder, albeit stoichiometric in chromium, adaptation with enhanced functional-group tolerance. In this case, the neutral CrO_4 species **244** generated in the reaction between CrO_3 and Bu_4NIO_4 is believed to serve as the active C–H oxidant (Scheme 102). The neutral monoperoxo chromium species, which bares resemblance to dioxiranes, is tolerant of the acetate, benzoate, TBDPS, and tosylate functional groups. Most notably, the olefin and iodide



Scheme 102.

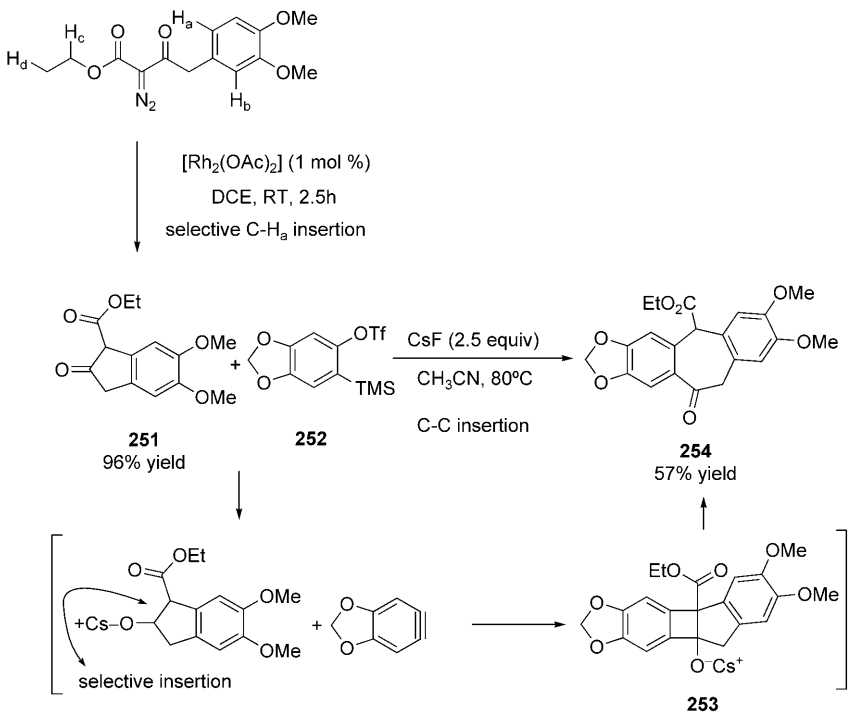


Scheme 103.

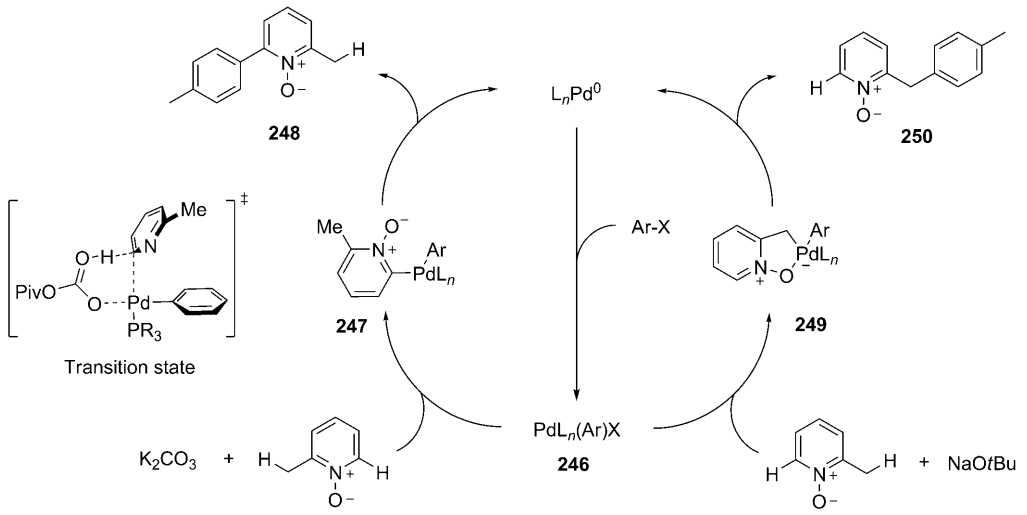
groups, which were oxidized by DMDO and *m*CPBA, were not affected in this highly chemoselective transformation. Oxidations in the presence of the olefin and iodide proceeded in high yields (84% and 73%, respectively) to give the desired products through what is believed to be a concerted "three-centered two-electron" oxenoid insertion.

The work by Fagnou and co-workers identified pyridine *N*-oxides as valuable surrogates to replace organometallic 2-pyridyl compounds[222] for the synthesis of 2-aryl pyridines.[223] Oxidation of the pyridine nitrogen dramatically increased the reactivity at the 2-position, thereby facilitating direct arylation as well as circumventing the need for prefunctionalization of one reaction partner. Interestingly, it was noted that direct arylation with pyridine *N*-oxides bearing a methyl proup at the 2-position resulted in poor yields for sp^2-arylation—a phenomenon attributed to catalyst poisoning through the formation of pallacycles of type **245**. Higher yields could be obtained by increasing the palladium/ligand ratio. More importantly, the formation of **245** alluded to a possible pathway for sp^3-arylation. Indeed, a reexamination of the reaction parameters identified a set of conditions that enabled selective sp^3-arylation (Scheme 103). The choice of base proved to be the determining factor controlling the site of arylation. A weaker base (K_2CO_3) delivered optimal yields for sp^3-arylation, while a stronger base (Na*t*OBu) was necessary for sp^2-arylation. On this basis, a catalytic cycle leading to both products was proposed (Scheme 104). After initial oxidative insertion of Pd^0 into the aryl halide bond to generate intermediate **246**, a base-dependent palladation step ensues. In the presence of the weaker base K_2CO_3, the most acidic site in the molecule, the sp^3-hybridized C–H bond, can be deprotonated through the proposed concerted metalation/deprotonation pathway[224] to give intermediate **247**, which undergoes reductive elimination to generate the sp^3 arylated product **248**. In the presence of Na*t*OBu, the less acidic sp^2-hybridized C–H can be deprotonated leading to palladacycle **249** and ultimately the product of sp^2 arylation **250**.

In 2006, the Stoltz research group reported their efforts towards the enantioselective total synthesis of (+)-amurensinine. The key features of this synthesis were the highly chemoselective insertion reactions that facilitated the construction of the carbon skeleton. The first involves a $Rh_2(OAc)_4$-catalyzed diazotization[225] followed by selective C–H



Scheme 105.



Scheme 104.

bond insertion into an aromatic C–H_α bond in an environment rich with potential insertion sites including secondary and tertiary positions as well as another *ortho*-C–H site (Scheme 105). The second key C–C bond-forming step occurs between the product of insertion **251** and the aryne precursor **252** to generate advanced intermediate **253** through the pentacyclic intermediate **254**.[226]

6. Summary and Outlook

Chemoselectivity has always been the Achilles' heel of chemical synthesis. This deficiency continues to haunt the non-enzymatic approaches to organic molecules. The excitement generated by the successful realization of chemoselective strategies underscores the painstaking efforts to define a set of conditions conducive to partitioning between the accessible reaction pathways. Our overview of recent advances in chemoselective processes suggests that significant progress has been made, but a lot of challenges lie ahead.

In particular, extracting synthetic value out of "innate" reactivity of organic molecules is likely to receive growing attention. A number of studies can already be considered as emerging benchmarks in their respective domains.

In these examples, reaction conditions call for reagents that range in complexity from a simple Brønsted acid to a finely tuned metal catalyst. Interestingly, we have seen cases where either can have an uncanny ability to affect relative rates of nontrivial transformations. The knowledge of well-known organic reactions can prove instrumental in forging connections between complex peptide building blocks under mild reaction conditions. Recent results suggest that there is also room for developing artificial catalysts that emulate enzymatic systems. However, more often than not, chemists demonstrate that even without control over the binding that results in transition-state stabilization, reductionist approaches to imposing selectivity can be exceptionally effective and can deliver reactions with truly broad scope.

Abbreviations

Ac	acyl
Asc.	ascorbic acid
Boc	*tert*-butoxycarbonyl
Bpin	pinacol borate
Bz	benzoyl
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
CyDMEDA	*trans-N,N′*-dimethylcyclohexan-1,2-diamine
dba	dibenzylideneacetone
DCE	dichloroethane
Dibal-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
HEH	Hantzsch ester
HMPA	hexamethyl phosphoramide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
NMM	*N*-methylmorpholine
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PyBroP	bromotris(pyrrolidino)phosphonium hexafluorophosphate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butylsilyl
TDMPP	tris(2,6-dimethoxyphenyl)phosphane
Tf	trifluoromethansulfonyl, SO_2CF_3
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIS	triisopropylsilane
tpa	triphenylacetate
TPPTS	tris(*m*-sulfonatophenyl)phosphane-trisodium salt
Ts	tosyl, toluenesulfonyl
TS	transition state

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[1] B. M. Trost, *Science* **1983**, *219*, 245 – 250.
[2] see the IUPAC Goldbook.
[3] D. L. Nelson, M. M. Cox, *Principles of Biochemistry*, 4th ed., Freeman, New York, **2005**.
[4] a) R. W. Hoffmann, *Synthesis* **2006**, 3531 – 3541; b) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193 – 205.
[5] B. M. Trost, *Science* **1991**, *254*, 1471 – 1477.
[6] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40 – 49.
[7] J.-L. Luche, A. L. Gemal, *J. Am. Chem. Soc.* **1979**, *101*, 5848 – 5849.
[8] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed. Wiley, New York, **2001**.
[9] C. G. Swain, C. B. Scott, *J. Am. Chem. Soc.* **1953**, *75*, 141 – 147.
[10] In an effort to address limitations of the p*K*a-nucleophilicity correlation, Mayr et al. defined a set of parameters for electrophiles and nucleophiles that quantitatively describe the rates of many reactions between electrophiles and π nucleophiles. The scale constructed from data accumulated using a set of π nucleophiles and aryl carbenium ions can be used to deduce reaction outcomes. See: H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66 – 77.
[11] J. R. Fulton, A. W. Holland, D. J. Fox, R. G. Bergman, *Acc. Chem. Res.* **2002**, *35*, 44 – 56.

[12] T. Storz, P. Dittmar, D. Grimler, M. Testa, H. Potgeter, D. Chappel, O. Hartmann, D. Niederer, M. Truby, *Org. Process Res. Dev.* **2006**, *10*, 1184 – 1191.

[13] a) M. Eckstein, M. Cegla, L, Gajewczyk, *Pol. J. Chem.* **1984**, *58*, 607 – 610; b) M. Bouzoubaa, G. Leclerc, J. D. Ehrhardt, G. Andermann, *Bull. Soc. Chim. Fr.* **1985**, 1230 – 1236; c) V. Gotor, *Org. Process Res. Dev.* **2002**, *6*, 420 – 426; d) B. C. Ranu, P. Dutta, A. Sarkar, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2223 – 2225; e) A. Morcuende, M. Ors, S. Valverde, B. Herradon, *J. Org. Chem.* **1996**, *61*, 5264 – 5270; f) T. Kunieda, T. Higuchi, Y. Abe, M. Hirobe, *Tetrahedron Lett.* **1980**, *21*, 3065 – 3066; g) S. Hanessian, G. Patil, *Tetrahedron Lett.* **1978**, *19*, 1035 – 1038.

[14] a) N. Vicker, L. Burgess, I. S. Chuckowree, R. Dodd, A. J. Folkes, D. J. Hardick, T. C. Hancox, W. Miller, J. Milton, S. Sohal, S. Wang, S. Wren, P. A. Charlton, W. Dangerfield, C. Liddle, P. Mistry, A. J. Stewart, W. A. Denny, *J. Med. Chem.* **2002**, *45*, 721 – 739; b) A. Naylor, D. B. Judd, J. E. Lloyd, D. I. C. Scopes, A. G. Hayes, P. J. Birch, *J. Med. Chem.* **1993**, *36*, 2075 – 2083; c) N. S. Chandrakumar, P. K. Yonan, A. Stapelfeld, M. Savage, E. Rorbacher, P. C. Contreras, D. Hammond, *J. Med. Chem.* **1992**, *35*, 223 – 233.

[15] J. H. Lee, J. D. Kim, *Bull. Korean Chem. Soc.* **1997**, *18*, 442 – 444.

[16] J. H. Maeng, R. L. Funk, *Org. Lett.* **2002**, *4*, 331 – 333.

[17] F. Xu, B. Simmons, R. A. Reamer, E. Corley, J. Murry, D. Tschaen, *J. Org. Chem.* **2008**, *73*, 312 – 315.

[18] a) A. B. Smith III, D.-S. Kim, *J. Org. Chem.* **2006**, *71*, 2547 – 2557; b) B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785 – 14803; c) S. G. Pyne, A. S. Davis, N. J. Gates, J. P. Hartley, K. B. Lindsay, T. Machan, M. Tang, *Synlett* **2004**, 2670 – 2680; d) T. Kan, H. Kobayshi, T. Fukuyama, *Synlett* **2002**, 697 – 699; e) H. Ina, C. Kibayashi, *J. Org. Chem.* **1993**, *58*, 52 – 61; f) K. Burgess, D. A. Chaplin, I. Henderson, Y. T. Pan, A. D. Elbein, *J. Org. Chem.* **1992**, *57*, 1103 – 1109; g) H. E. Schink, H. Pettersson, J. E. Bäckvall, *J. Org. Chem.* **1991**, *56*, 2769 – 2774.

[19] a) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *J. Org. Chem.* **2006**, *71*, 4147 – 4154; b) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, *128*, 9646 – 9647; c) R. Pulz, A. Al-Harrasi, H.-U. Reissig, *Org. Lett.* **2002**, *4*, 2353 – 2355; d) T. Nota, S.-I. Murahashi, *Synlett* **1991**, 693; e) S.-I. Murahashi, K. Kondo, T. Hakata, *Tetrahedron Lett.* **1982**, *23*, 229 – 232; f) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *Chem. Commun.* **1981**, 611 – 612; g) H. Tanaka, Y. Murakami, T. Aizawa, S. Torii, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3742 – 3744; h) C. Papageorgiou, X. Borer, *Helv. Chim. Acta* **1988**, *71*, 1079 – 1083; i) B. R. Castro, *Org. React.* **1983**, *29*, 1 – 162; j) R. Appel, *Angew. Chem.* **1975**, *87*, 863 – 874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801 – 811.

[20] a) T. G. Back, K. Nakajima, *J. Org. Chem.* **2000**, *65*, 4543 – 4552; b) M. Dobler, R. Beerli, W. K. Weissmahr, H.-J. Borschberg, *Tetrahedron: Asymmetry* **1992**, *3*, 1411 – 1420; c) J. Kóbor, F. Fülöp, G. Bernáth, P. Sohár, *Tetrahedron* **1987**, *43*, 1887 – 1887; d) J. E. Bäckvall, Z. D. Renko, S. E. Byström, *Tetrahedron Lett.* **1987**, *28*, 4199 – 4202; e) J. R. Piper, T. P. Johnston, *J. Org. Chem.* **1963**, *28*, 981 – 985; f) T. R. Norton, R. A. Seibert, A. A. Benson, F. W. Bergstrom, *J. Am. Chem. Soc.* **1946**, *68*, 1572 – 1576.

[21] F. Xu, J. A. Murry, B. Simmons, E. Corley, K. Fitch, S. Karady, D. Tschaen, *Org. Lett.* **2006**, *8*, 3885 – 3888.

[22] a) T. Hoeg-Jensen, S. Havelund, J. Markussen, PCT Int. Appl., WO2003048195, **2003**; b) M. Ávalos, R. Babiano, P. Cintas, M. B. Hursthouse, J. L. Jiménez, M. E. Light, J. C. Palacios, E. M. S. Pérez, *Eur. J. Org. Chem.* **2006**, 657 – 657.

[23] I.-H. Paik, D. Tapriyal, R. M. Enick, A. D. Hamilton, *Angew. Chem.* **2007**, *119*, 3348 – 3351; *Angew. Chem. Int. Ed.* **2007**, *46*, 3284 – 3287.

[24] M. Nahmany, A. Melman, *Org. Biomol. Chem.* **2004**, *2*, 1563 – 1572.

[25] a) C. Schotten, *Chem. Ber.* **1884**, *17*, 2544 – 2547; b) E. Baumann, *Chem. Ber.* **1886**, *19*, 3218 – 3222; c) N. O. V. Sonntag, *Chem. Rev.* **1953**, *52*, 237 – 416.

[26] L. Gardossi, D. Bianchi, A. M. Klibanov, *J. Am. Chem. Soc.* **1991**, *113*, 6328 – 6329.

[27] T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama, K. Mashima, *J. Am. Chem. Soc.* **2008**, *130*, 2944 – 2945.

[28] S. Arai, Y. Takamichi, S. Ototake, M. Hida, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547 – 548.

[29] G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703 – 3706.

[30] a) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727 – 7729; b) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581 – 584; c) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973 – 976; d) M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803 – 3805.

[31] A. Shafir, P. A. Lichtor, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3490 – 3491.

[32] F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th ed., Wiley, New York, **1988**.

[33] J. Srogl, S. Voltrova, *Org. Lett.* **2009**, *11*, 843 – 845.

[34] M. T. Reetz, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5716 – 5722.

[35] C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744 – 5747; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616 – 5619.

[36] T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890 – 12895.

[37] a) P. A. Clarke, R. A. Holton, N. E. Kayaleh, *Tetrahedron Lett.* **2000**, *41*, 2687 – 2690; b) P. A. Clarke, N. E. Kayaleh, M. A. Smith, J. R. Baker, S. J. Bird, C. Chan, *J. Org. Chem.* **2002**, *67*, 5226 – 5231; c) P. A. Clarke, *Tetrahedron Lett.* **2002**, *43*, 4761 – 4763; d) P. A. Clarke, P. L. Arnold, M. A. Smith, L. S. Natrajan, C. Wilson, C. Chan, *Chem. Commun.* **2003**, *9*, 2588 – 2589.

[38] S. Tzvetkova, R. Kluger, *J. Am. Chem. Soc.* **2007**, *129*, 15848 – 15854.

[39] T. J. K. Gibbs, M. Boomhoff, N. C. O. Tomkinson, *Synlett* **2007**, 1573 – 1576.

[40] a) S. Ram, R. E. Ehrenkaufer, *Synthesis* **1988**, 91 – 95; b) R. Leuckart, *Chem. Ber.* **1885**, *18*, 2341 – 2344; c) O. Wallach, *Chem. Ber.* **1891**, *24*, 3992 – 3993.

[41] I. P. Beletskaya, A. G. Bessmertnykh, A. D. Averin, F. Denat, R. Guilard, *Eur. J. Org. Chem.* **2005**, 261 – 280.

[42] N. Cabello-Sanchez, L. Jean, J. Maddaluno, M.-C. Lasne, J. Rouden, *J. Org. Chem.* **2007**, *72*, 2030 – 2039.

[43] a) A. Corruble, D. Davoust, S. Desjardins, C. Fressigné, C. Giessner-Prettre, A. Harrisson-Marchand, H. Houte, M.-C. Lasne, J. Maddaluno, H. Oulyadi, J.-Y. Valnot, *J. Am. Chem. Soc.* **2002**, *124*, 15267 – 15279; b) D. Kuppert, J. Sander, C. Roth, M. Wörle, T. Weyhermüller, G. J. Reiss, U. Schilde, I. Müller, K. Hegetschweiler, *Rurr. J. Inorg. Chem.* **2001**, 2525 – 2542; c) V. Moreno, G. Cervantes, G. B. Onoa, F. Sampedro, X. Santaló, X. Solans, M. Font-Bardía, *Polyhedron* **1997**, *16*, 4297 – 4303.

[44] G. Mann, Q. Shelby, A. H. Roy, J. F. Hartwig, *Organometallics* **2003**, *22*, 2775 – 2789.

[45] B. M. Trost, D. R. Fandrick, *Org. Lett.* **2005**, *7*, 823 – 826.

[46] a) J. C. Anderson, C. B. Reese, *Tetrahedron Lett.* **1962**, *3*, 1 – 4; b) J. A. Barltrop, P. Schofield, *Tetrahedron Lett.* **1962**, *3*, 697 – 699; c) D. H. R. Barton, Y. L Chow, A. Cox, G. W. Kirby, *Tetrahedron Lett.* **1962**, *3*, 1055 – 1057.

[47] a) C. G. Bochet, *J. Chem. Soc. Perkin Trans. 1*, **2002**, 125 – 152; b) V. N. Rajasekharan Pillai, *Org. Photochem.* **1987**, *9*, 225 – 323; c) V. N. R. Pillai, *Synthesis* **1980**, 1 – 26.

[48] A. Patchornik, B. Amit, R. B. Woodward, *J. Am. Chem. Soc.* **1970**, *92*, 6333 – 6335.

[49] a) J. W. Chamberlin, *J. Org. Chem.* **1966**, *31*, 1658 – 1660; b) J. A. Pincock, *Acc. Chem. Res.* **1997**, *30*, 43 – 49; c) C. G.

Bochet, *Tetrahedron Lett.* **2000**, *41*, 6341 – 6346; d) R. S. Givens, B. Matuszewski, *J. Am. Chem. Soc.* **1984**, *106*, 6860 – 6861; e) J. C. Sheehan, R. M. Wilson, *J. Am. Chem. Soc.* **1964**, *86*, 5277 – 5281; f) J. C. Sheehan, R. M. Wilson, A. W. Oxford, *J. Am. Chem. Soc.* **1971**, *93*, 7222 – 7228; g) M. C. Pirrung, S. W. Shuey, *J. Org. Chem.* **1994**, *59*, 3890 – 3897; h) Y. J. Shi, J. E. T. Corrie, P. Wan, *J. Org. Chem.* **1997**, *62*, 8278 – 8279; i) J. F. Cameron, C. G. Willson, J. M. J. Fréchet, *J. Chem. Soc. Chem. Commun.* **1995**, 923 – 924; j) M. C. Pirrung, J. C. Bradley, *J. Org. Chem.* **1995**, *60*, 1116 – 1117.

[50] a) C. G. Bochet, *Angew. Chem.* **2001**, *113*, 2140 – 2142; *Angew. Chem. Int. Ed.* **2001**, *40*, 2071 – 2073; b) C. G. Bochet, *Tetrahedron Lett.* **2000**, *41*, 6341 – 6346; c) A. Blanc, C. G. Bochet, *J. Org. Chem.* **2002**, *67*, 5567 – 5577.

[51] a) N. J. Turro, *Modern Molecular Photochemistry*, University Science Books, Sausalito, **1991**; b) T. Förster, *Ann. Phys.* **1948**, *2*, 55 – 75; c) D. L. Dexter, *J. Chem. Phys.* **1953**, *21*, 836 – 850.

[52] A. Blanc, C. G. Bochet, *J. Am. Chem. Soc.* **2004**, *126*, 7174 – 7175.

[53] A. J. Bard, L. R. Faulkner, *Electrochemical Methods: Fundamentals and Applications*, 2nd ed., Wiley, New York, **2000**.

[54] a) T. Siu, C. Picard, A. K. Yudin, *J. Org. Chem.* **2005**, *70*, 932 – 937; b) T. Siu, A. K. Yudin, *Org. Lett.* **2002**, *4*, 1839 – 1842; c) T. Siu, A. K. Yudin, *J. Am. Chem. Soc.* **2002**, *124*, 530 – 531.

[55] N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445 – 446.

[56] M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7182 – 7183.

[57] M. Sugiura, C. Mori, K. Hirano, S. Kobayashi, *Can. J. Chem.* **2005**, *83*, 937 – 942.

[58] C. Mannich, W. Krosche, *Arch. Pharm.* **1912**, *250*, 647 – 667.

[59] a) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060 – 2061; b) T. Kambara, M. A. Hussein, H. Fujieda, A. Iida, K. Tomioka, *Tetrahedron Lett.* **1998**, *39*, 9055 – 9058; c) K. Tomioka, H. Fujieda, S. Hayashi, M. A. Hussein, T. Kambara, Y. Nomura, K. Motomu, K. Koga, *Chem. Commun.* **1999**, 715 – 716; d) T. Kambara, K. Tomioka, *Chem. Pharm. Bull.* **1999**, *47*, 720 – 721; e) M. A. Hussein, A. Iida, K. Tomioka, *Tetrahedron* **1999**, *55*, 11219 – 11228; f) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153 – 7154; g) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431 – 432; h) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8180 – 8186; i) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474 – 2475; j) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450 – 5458; k) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548 – 4549; l) D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Lectka, *J. Org. Chem.* **1998**, *63*, 6090 – 6091; m) D. Ferraris, T. Dudding, B. Young, W. J. Drury III, T. Lectka, *J. Org. Chem.* **1999**, *64*, 2168 – 2169.

[60] K. Manabe, S. Kobayashi, *Org. Lett.* **1999**, *1*, 1965 – 1967.

[61] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron* **1999**, *55*, 8857 – 8867.

[62] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336 – 9337; b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827 – 833.

[63] W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199 – 201.

[64] N. R. Perl, J. L. Leighton, *Org. Lett.* **2007**, *9*, 3699 – 3701.

[65] For a review, see "Addition of Terminal Acetylides to C=O and C=N Electrophiles": P. Aschwanden, E. M. Carreira in *Acetylene Chemistry: Chemistry, Biology and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley, Weinheim, **2005**.

[66] a) B. J. Wakefield, *Organolithium Methods*, Academic Press, London, **1998**; b) B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis* Academic Press, London, **1995**; c) Y. Yamamoto, S. Nishii, K. Maruyama, *J. Chem. Soc. Chem. Commun.* **1986**, 102 – 103; d) E. J. Corey, K. A. Cimprich, *J. Am. Chem. Soc.* **1994**, *116*, 3151 – 3152; e) J. H. Ahn, M. J. Joung, N. M. Yoon, *J. Org. Chem.* **1995**, *60*, 6173 – 6175; f) D. A. Evans, D. P. Halstead, B. D. Allison, *Tetrahedron Lett.* **1999**, *40*, 4461 – 4462; g) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31 – 48; h) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207 – 2293; i) G. M. Romos Tombo, E. Didier, B. Loubinoux, *Synlett* **1990**, 547 – 548.

[67] a) Y. Yamamoto, S. Nishii, K. Maruyama, *J. Chem. Soc. Chem. Commun.* **1986**, 102 – 103; b) E. J. Corey, K. A. Cimprich, *J. Am. Chem. Soc.* **1994**, *116*, 3151 – 3152; c) J. H. Ahn, M. J. Joung, N. M. Yoon, *J. Org. Chem.* **1995**, *60*, 6173 – 6175; d) D. A. Evans, D. P. Halstead, B. D. Allison, *Tetrahedron Lett.* **1999**, *40*, 4461 – 4462; e) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31 – 48; f) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207 – 2293; g) G. M. Romos Tombo, E. Didier, B. Loubinoux, *Synlett* **1990**, 547 – 548; h) S. Niwa, K. Soai, *J. Chem. Soc. Perkin Trans. 1* **1990**, 937 – 943; i) G. Chelucci, S. Conti, M. Falorni, G. Giacomelli, *Tetrahedron* **1991**, *47*, 8251 – 8258; j) M. Ishizaki, O. Hoshino, *Tetrahedron: Asymmetry* **1994**, *5*, 1901 – 1904; k) Z. Li, V. Upadhyay, A. E. DeCamp, L. DiMichelle, P. J. Reider, *Synthesis* **1999**, 1453 – 1458; l) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757 – 824.

[68] a) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687 – 9688; b) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806 – 1807; c) D. Boyall, F. López, H. Sasaki, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233 – 4236; d) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373 – 381; e) H. Sasaki, D. Boyall, E. M. Carreira, *Helv. Chim. Acta* **2001**, *84*, 964 – 971; f) J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611 – 3612.

[69] The use of aromatic aldehydes resulted in dimished yields because of the competing Cannizzaro reaction.

[70] C. Wei, C.-J. Li, *Green Chem.* **2002**, *4*, 39 – 41.

[71] For the iridium-catalyzed alkyne-imine addition to preformed imines, see a) C. Fischer, E. M. Carreira, *Org. Lett.* **2001**, *3*, 4319 – 4321.

[72] For the addition of acetylenes to nitrones, see a) M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999 – 5004; b) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245 – 11246; c) R. Fässler, D. E. Frantz, J. Oetiker, E. M. Carreira, *Angew. Chem.* **2002**, *114*, 3180 – 3182; *Angew. Chem. Int. Ed.* **2002**, *41*, 3054 – 3056.

[73] C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268 – 269; for a gold(I)-catalyzed procedure, see C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584 – 9585; for a silver(I)-catalyzed procedure, see C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473 – 4475.

[74] C. Wei, J. T. Mague, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749 – 5754.

[75] C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638 – 5639.

[76] P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437 – 2440.

[77] N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941 – 5944; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763 – 5766.

[78] J. M. White, A. R. Tumoori, G. I. Georg, *J. Am. Chem. Soc.* **2000**, *122*, 11995 – 11996.

[79] J. T. Spletstoser, J. M. White, A. R. Tunoori, G. I. Georg, *J. Am. Chem. Soc.* **2007**, *129*, 3408 – 3419.

[80] *Titanium and Zirconium in Organic Synthesis*; (Ed.: I. Marek), Wiley, Weinheim, **2002**.

[81] a) D. J. A. Schedler, A. G. Godfrey, B. Ganem, *Tetrahedron Lett.* **1993**, *34*, 5035 – 5038; b) D. J. A. Schedler, J. Li, B. Ganem, *J. Org. Chem.* **1996**, *61*, 4115 – 4119; c) Q. Xia, B. Ganem,

Tetrahedron Lett. **2002**, *43*, 1597 – 1598; d) Q. Xia, B. Ganem, *Org. Lett.* **2001**, *3*, 485 – 487.
[82] B. Ganem, R. R. Franke, *J. Org. Chem.* **2007**, *72*, 3981 – 3987.
[83] G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 18 – 19.
[84] B. C. Challis, J. A. Challis, *The Chemistry of Amides* (Ed.: J. Zabicky), Wiley, New York, **1970**.
[85] A. G. Myers, D. W. Kung, B. Zhong, *J. Am. Chem. Soc.* **2000**, *122*, 3236 – 3237.
[86] W. Lieke, *Ann. Chem. Pharm.* **1859**, *112*, 316 – 321.
[87] a) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300 – 3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 – 3210; b) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley, New York, **2005**.
[88] L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366 – 374.
[89] R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772 – 14773.
[90] S. Baktharaman, R. Hili, A. K. Yudin, *Aldrichimica Acta* **2008**, *41*, 109 – 119.
[91] a) X. Li, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14152 – 14153; b) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2009**, *131*, 16404 – 16406.
[92] M. D. Pluth, R. G. Bergman, K. H. Raymond, *Science* **2007**, *316*, 85 – 88.
[93] E. H. Cordes, H. G. Bull, *Chem. Rev.* **1974**, *74*, 581 – 603.
[94] The specificity constant (k_{cat}/K_M) is a measure of the ability of two substrates to compete for the binding site of a catalyst.
[95] D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2004**, *116*, 6916 – 6919; *Angew. Chem. Int. Ed.* **2004**, *43*, 6748 – 6751.
[96] For general methods, see a) M. B. Smith, *Compendium of Organic Synthetic Methods*, *Vol. 9*, Wiley, New York, **2001**; for metal-catalyzed synthesis from nitriles, see b) C. J. Cobley, M. van den Heuvel, A. Abbadi, J. G. de Vries, *Tetrahedron Lett.* **2000**, *41*, 2467 – 2470; c) S.-I. Murahashi, T. Naota, E. Saito, *J. Am. Chem. Soc.* **1986**, *108*, 7846 – 7847; d) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *J. Org. Chem.* **1992**, *57*, 2521 – 2523; for the catalytic acylation of amines by aldehydes, see e) Y. Tamaru, Y. Yamada, Z. Yoshida, *Synthesis* **1983**, 474 – 476; f) A. Tillack, I. Rudloff, M. Beller, *Eur. J. Org. Chem.* **2001**, 523 – 528; from terminal alkynes, see g) W.-K. Chan, C.-M. Ho, M.-K. Wong, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 14796 – 14797; h) S. H. Cho, E. J. Yoo, I. Bae, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 16046 – 16047; i) M. P. Cassidy, J. Raushel, V. V. Fokin, *Angew. Chem.* **2006**, *118*, 3226 – 3229; *Angew. Chem. Int. Ed.* **2006**, *45*, 3154 – 3157.
[97] C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790 – 792.
[98] a) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840 – 10841; b) J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Dalton Trans.* **2007**, *107–113*; c) J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Organometallics* **2004**, *23*, 4026 – 4033.
[99] W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064 – 13065.
[100] a) M. Movassaghi, M. A. Schmidt, *Angew. Chem.* **2007**, *119*, 3799 – 3802; *Angew. Chem. Int. Ed.* **2007**, *46*, 3725 – 3728; b) M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Angew. Chem.* **2008**, *120*, 1507 – 1509; *Angew. Chem. Int. Ed.* **2008**, *47*, 1485 – 1487.
[101] a) E. Kaxiras, Y. Bar-Yam, J. D. Joannopoulos, K. C. Pandley, *Phys. Rev. B* **1987**, *35*, 9625 – 9635; b) G.-X. Qian, R. M. Martin, D. J. Chadi, *Phys. Rev. B* **1988**, *38*, 7649 – 7663.
[102] For recent reviews on these alkaloids, see a) H. Hoffmann, T. Lindel, *Synthesis* **2003**, 1753 – 1783; b) D. E. N. Jacquot, T. Lindel, *Curr. Org. Chem.* **2005**, *9*, 1551 – 1565.
[103] a) D. P. O'Malley, J. Yamaguchi, I. S. Young, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3637 – 3639; *Angew. Chem. Int. Ed.* **2008**, *47*, 3581 – 3583; b) S. Su, I. B. Seiple, I. S. Young, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 16490 – 16491.
[104] a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173 – 180; b) K. Gademann, T. Hintermann, J. V. Schreiber, *Curr. Med. Chem.* **1999**, *6*, 905 – 925.
[105] J. H. Cohen, M. E. Bos, S. Cesco-Cancian, B. D. Harris, J. T. Hortenstine, M. Justus, C. A. Maryanoff, J. Mills, S. Muller, A. Roessler, L. Scott, K. L. Sorgi, F. J. Villani, Jr., R. R. H. Webster, C. Weh, *Org. Process Res. Dev.* **2003**, *7*, 866 – 872.
[106] N. Ikemoto, D. M. Tellers, S. D. Dreher, J. Liu, A. Huang, N. R. Rivera, E. Njolito, Y. Hsiao, J. C. McWilliams, J. M. Williams, J. D. Armstrong III, Y. Sun, D. J. Mathre, E. J. J. Grabowski, R. D. Tillyer, *J. Am. Chem. Soc.* **2004**, *126*, 3048 – 3049.
[107] Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong III, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918 – 9919.
[108] S. Ogo, K. Uehara, T. Abura, S. Fukuzumi, *J. Am. Chem. Soc.* **2004**, *126*, 3020 – 3021.
[109] C. P. R. Hackenberger, D. Schwarzer, *Angew. Chem.* **2008**, *120*, 10182 – 10228; *Angew. Chem. Int. Ed.* **2008**, *47*, 10030 – 10074.
[110] T. Wieland, E. Bokelmann, L. Bauer, H. U. Lang, H. Lau, *Justus Liebigs Ann. Chem.* **1953**, *583*, 129 – 149.
[111] P. E. Dawson, T. W. Muir, I. Clark-Lewis, S. B. H. Kent, *Science* **1994**, *266*, 776 – 779.
[112] C. F. Liu, J. P. Tam, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 6584 – 6588.
[113] *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**.
[114] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056 – 2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004 – 2021.
[115] A. Michael, *J. Prakt. Chem.*. **1893**, *48*, 94 – 95.
[116] R. Huisgen in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**.
[117] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057 – 3062.
[118] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708 – 2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599.
[119] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210 – 216.
[120] a) P. Wu, V. V. Fokin, *Aldrichimica Acta* **2007**, *40*, 7 – 17; b) J. A. Prescher, C. R. Bertozzi, *Nat. Chem. Biol.* **2005**, *1*, 13 – 25.
[121] E. Saxon, J. I. Armstrong, C. R. Bertozzi, *Org. Lett.* **2000**, *2*, 2141 – 2143.
[122] a) B. L. Nilsson, L. L. Kiesling, R. T. Raines, *Org. Lett.* **2000**, *2*, 1939 – 1941; b) B. L. Nilsson, L. L. Kiesling, R. T. Raines, *Org. Lett.* **2001**, *3*, 9 – 12; c) M. B. Soellner, A. Tam, R. T. Raines, *J. Org. Chem.* **2006**, *71*, 9824 – 9830.
[123] R. Kleineweischede, C. P. R. Hackenberger, *Angew. Chem.* **2008**, *120*, 6073 – 6077; *Angew. Chem. Int. Ed.* **2008**, *47*, 5984 – 5988.
[124] A. Dirksen, T. M. Hackeng, P. E. Dawson, *Angew. Chem.* **2006**, *118*, 7743 – 7746; *Angew. Chem. Int. Ed.* **2006**, *45*, 7581 – 7584.
[125] J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem.* **2006**, *118*, 1270 – 1274; *Angew. Chem. Int. Ed.* **2006**, *45*, 1248 – 1252.
[126] N. Carrillo, E. A. Davalos, J. A. Russak, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 1452 – 1453.
[127] A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *J. Comb. Chem.* **1999**, *1*, 55 – 68.
[128] R. K. Sharma, R. Jain, *Synlett* **2007**, 603 – 606.
[129] W.-K. Chan, C.-M. Ho, M.-K. Wong, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 14796 – 14797.
[130] R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 9613 – 9620.

[131] a) S. L. Zhang, L. Liu, Y. Fu, Q. X. Guo, *Organometallics* **2007**, *26*, 4546 – 4554; b) S. Arai, M. Hida, T. Yamagishi, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277 – 282.

[132] P. Forns, A. Diez, M. Rubiralta, *J. Org. Chem.* **1996**, *61*, 7882 – 7888.

[133] D. Ivanoff, A. Spassoff, *Bull. Soc. Chim. Fr. Mem.* **1935**, *2*, 76 – 78.

[134] For reviews on enolate couplings, see a) N. L. Weinberg, H. R. Weinberg, *Chem. Rev.* **1968**, *68*, 449 – 523; b) T. Kauffmann, *Angew. Chem.* **1974**, *86*, 321 – 335; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 291 – 356; c) A. G. Csákÿ, J. Plumet, *Chem. Soc. Rev.* **2001**, *30*, 313 – 320; d) P. S. Baran, N. B. Ambhaikar, C. A. Guerrero, B. D. Hafensteiner, D. W. Lin, J. M. Richter, *Arkivoc* **2006**, *7*, 310 – 325.

[135] a) M. W. Rathke, A. Lindert, *J. Am. Chem. Soc.* **1971**, *93*, 4605 – 4606; b) R. M. Dessau, E. I. Heiba, *J. Org. Chem.* **1974**, *39*, 3457 – 3459; c) Y. Ito, T. Konoike, T. Harada, T. Saegusa, *J. Am. Chem. Soc.* **1977**, *99*, 1487 – 1493; d) R. H. Frazier, R. L. Harlow, *J. Org. Chem.* **1980**, *45*, 5408 – 5411; e) J. L. Belletire, D. F. Fry, *J. Org. Chem.* **1988**, *53*, 4724 – 4729; f) M. J. Aurell, S. Gil, A. Tortajada, R. Mestres, *Tetrahedron Lett.* **1988**, *29*, 6181 – 6182; g) N. Kise, K. Tokioka, Y. Aoyama, Y. Matsumura, *J. Org. Chem.* **1995**, *60*, 1100 – 1101; h) T. Langer, M. Illich, G. Helmchen, *Tetrahedron Lett.* **1995**, *36*, 4409 – 4412; i) Y. Matsumura, M. Nishimura, H. Hiu, M. Watanabe, N. Kise, *J. Org. Chem.* **1996**, *61*, 2809 – 2812; j) T. Langer, M. Illich, G. Helmchen, *Synlett* **1996**, 1137 – 1139; k) D. Enders, P. Müller, D. Klein, *Synlett* **1998**, 43 – 44; l) P. Q. Nguyen, H. J. Shäfer, *Org. Lett.* **2001**, *3*, 2993 – 2995; m) A. G. Csákÿ, J. Plumet, *Chem. Soc. Rev.* **2001**, *30*, 313 – 320; n) P. Renaud, M. A. Fox, *J. Org. Chem.* **1988**, *53*, 3745 – 3752.

[136] J. M. Richter, B. W. Whitefield, T. J. Maimone, D. W. Lin, M. P. Castroviejo, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 12857 – 12869, and references therein.

[137] P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450 – 7451.

[138] a) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 17938 – 17954; b) R. A. Shenvi, D. P. O'Malley, P. S. Baran, *Acc. Chem. Res.* **2009**, *42*, 530 – 541.

[139] a) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2005**, *127*, 15394 – 15396; b) P. S. Baran, J. T. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404 – 408; c) P. S. Baran, J. M. Richter, D. W. Lin, *Angew. Chem.* **2005**, *117*, 615 – 618; *Angew. Chem. Int. Ed.* **2005**, *44*, 609 – 612; d) P. S. Baran, C. A. Guerrero, N. B. Ambhaikar, B. D. Hafensteiner, *Angew. Chem.* **2005**, *117*, 612 – 615; Angew. Chem. Int. Ed. 2005, 44, 606 – 609; e) P. S. Baran, M. P. DeMartino, *Angew. Chem.* **2006**, *118*, 7241 – 7244; *Angew. Chem. Int. Ed.* **2006**, *45*, 7083 – 7086; f) M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546 – 11560.

[140] A chelated transition-state has also been proposed on the basis of observed diastereoselectivities: S. K. Chung, L. B. Dunn, Jr., *J. Org. Chem.* **1983**, *48*, 1125 – 1127.

[141] Limited evidence exists that questions the prevailing view that ketone dimerization occurs via two discreet radical species: a) N. A. Porter, Q. S. Jill, J. J. Harp, I. J. Rosenstein, A. T. McPhail, *Tetrahedron Lett.* **1993**, *34*, 4457 – 4460; b) T. Cohen, K. McNamara, M. A. Kuzemko, K. Ramig, J. J. Landi, Jr., Y. Dong, *Tetrahedron* **1993**, *49*, 7931 – 7942.

[142] Y. Gong, W. He, *Org. Lett.* **2002**, *4*, 3803 – 3805.

[143] For a review, see a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238.

[144] For direct arylations of ArOMe and direct alkylations of BnOMe by C–O bond activation, see a) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2004**, *126*, 2706 – 2707; b) S. Ueno, E. Mizushima, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2006**, *128*, 16516 – 16517; c) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, *Chem. Commun.* **2008**, 1437 – 1439; d) B.-T. Guan, S.-K. Xiang, B.-Q. Wang, Z.-P. Sun, Y. Wang, K.-Q. Zhao, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 3268 – 3269.

[145] a) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748 – 11749; b) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439 – 2463.

[146] F.-A. Kang, Z. Sui, W. V. Murray, *J. Am. Chem. Soc.* **2008**, *130*, 11300 – 11302.

[147] a) M. Hocek, A. Holy, I. Votruba, H. Dvorakova, *J. Med. Chem.* **2000**, *43*, 1817 – 1825; b) M. Hocek, P. Naus, R. Pohl, I. Votruba, P. A. Furman, P. M. Tharnish, M. J. Otto, *J. Med. Chem.* **2005**, *48*, 5869 – 5873.

[148] a) M. K. Lakshman, J. H. Hilmer, J. Q. Martin, J. C. Keeler, Y. Q. V. Dinh, F. N. Ngassa, L. M. Russon, *J. Am. Chem. Soc.* **2001**, *123*, 7779 – 7787; b) M. K. Lakshman, P. F. Thomson, M. A. Nuqui, J. H. Hilmer, N. Sevova, B. Boggess, *Org. Lett.* **2002**, *4*, 1479 – 1482; c) L.-L. Gundersen, J. Nissen-Meyer, B. Spilsberg, *J. Med. Chem.* **2002**, *45*, 1383 – 1386; d) P. Francom, M. J. Robins, *J. Org. Chem.* **2003**, *68*, 666 – 669; e) P. Gunda, L. M. Russon, M. K. Lakshman, *Angew. Chem.* **2004**, *116*, 6532 – 6537; *Angew. Chem. Int. Ed.* **2004**, *43*, 6372 – 6377; f) J. Liu, Z. Janeba, M. J. Robins, *Org. Lett.* **2004**, *6*, 2917 – 2919; g) J. Liu, M. J. Robins, *Org. Lett.* **2004**, *6*, 3421 – 3423; h) J. Liu, M. J. Robins, *Org. Lett.* **2005**, *7*, 1149 – 1151; i) M. K. Lakshman, P. Gunda, P. Pradhan, *J. Org. Chem.* **2005**, *70*, 10329 – 10335; j) P. Capek, R. Pohl, M. Hocek, *J. Org. Chem.* **2005**, *70*, 8001 – 8008; k) M. Hocek, P. Silhar, I. Shih, E. Mabery, R. Mackman, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5290 – 5293; l) P. Turek, P. Novak, R. Pohl, M. Hocek, M. Kotora, *J. Org. Chem.* **2006**, *71*, 8978 – 8981.

[149] B. M. Trost, J.-P. Surivet, *Angew. Chem.* **2000**, *112*, 3252 – 3254; *Angew. Chem. Int. Ed.* **2000**, *39*, 3122 – 3124.

[150] B. M. Trost, J. Richardson, K. Yong, *J. Am. Chem. Soc.* **2006**, *128*, 2540 – 2541.

[151] Hass and Bender reported that 2-nitropropane also undergoes O-alkylation ultimately leading to oxidation of benzylic halides to the corresponding aldehydes, see: H. B. Hass, M. L. Bender, *J. Am. Chem. Soc.* **1949**, *71*, 1767 – 1769.

[152] C. Jonasson, M. Roenn, J. E. Bäckvall, *Org. Chem.* **2000**, *65*, 2122 – 2126.

[153] Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama, Y. Hiroki, Y. Murakami, *Eur. J. Org. Chem.* **2004**, 1244 – 1253.

[154] H. Nakamura, M. Bao, Y. Yamamoto, *Angew. Chem.* **2001**, *113*, 3308 – 3310; *Angew. Chem. Int. Ed.* **2001**, *40*, 3208 – 3210.

[155] *Organic Chemistry* (Ed.: H. Gilman), Wiley, New York, **1943**.

[156] E. Negishi in *Organometallics in Organic Synthesis*, Wiley, New York, **1980**.

[157] H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974 – 5978.

[158] For examples of organozinc reactions in the presence of acidic hydrogens see: a) R. F. W. Jackson, N. Wishart, A. Wood, K. James, M. J. Wythes, *J. Org. Chem.* **1992**, *57*, 3397 – 3404; b) R. F. W. Jackson, R. J. Moore, C. S. Dexter, *J. Org. Chem.* **1998**, *63*, 7875 – 7884; c) R. F. W. Jackson, I. Rilatt, J. P. Murray, *Org. Biomol. Chem.* **2004**, *2*, 110 – 113; d) K. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229 – 8243; e) C. E. Tucker, P. Knochel, *J. Org. Chem.* **1993**, *58*, 4781 – 4782.

[159] M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8404 – 8405.

[160] F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288 – 2289.

[161] a) G. Manolikakes, C. M. Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422 – 8436; b) G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr,

P. Knochel, *Org. Lett.* **2008**, *10*, 2765 – 2768; c) Z. Dong, G. Manolikakes, J. Li, P. Knochel, *Synthesis* **2009**, 681 – 686.

[162] a) M. Schlosser, *Angew. Chem.* **2005**, *117*, 380 – 398; *Angew. Chem. Int. Ed.* **2005**, *44*, 376 – 393; b) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489 – 4505; c) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059 – 4090; d) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975 – 3984; e) D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7*, 2305 – 2308; f) J.-C. Plaquevent, T. Perrard, D. Cahard, *Chem. Eur. J.* **2002**, *8*, 3300 – 3307; g) C.-C. Chang, M. S. Ameerunisha, *Coord. Chem. Rev.* **1999**, *189*, 199 – 278; h) F. Leroux, M. Schlosser, E. Zohar, I. Marek, *Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**; i) K. W. Henderson, W. J. Kerr, *Chem. Eur. J.* **2001**, *7*, 3430; j) K. W. Henderson, W. J. Kerr, J. H. Moir, *Tetrahedron* **2002**, *58*, 4573 – 4587; k) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256 – 2276; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206 – 2225; l) G. Quéguiner, F. Marsais, V. Snieckus, J. Epsztajn, *Adv. Heterocycl. Chem.* **1991**, *52*, 187 – 304; m) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827 – 856; n) M. Kauch, D. Hoppe, *Synthesis* **2006**, 1575 – 1577; o) M. Kauch, D. Hoppe, *Synthesis* **2006**, 1578 – 1589; p) N. Plé, A. Turck, K. Couture, G. Quéguiner, *J. Org. Chem.* **1995**, *60*, 3781 – 3786; q) C. Metallinos, V. Snieckus, *Org. Lett.* **2002**, *4*, 1935 – 1938; r) W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 2434 – 2437; *Angew. Chem. Int. Ed.* **2006**, *45*, 2374 – 2377; s) D. M. Hodgson, S. M. Miles, *Angew. Chem.* **2006**, *118*, 949 – 952; *Angew. Chem. Int. Ed.* **2006**, *45*, 935 – 938.

[163] M. Yus, F. Foubelo, *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

[164] a) P. E. Eaton, R. M. Martin, *J. Org. Chem.* **1988**, *53*, 2728 – 2732; b) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016 – 8018; c) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370 – 11375; d) M.-X. Zhang, P. E. Eaton, *Angew. Chem.* **2002**, *114*, 2273 – 2275; *Angew. Chem. Int. Ed.* **2002**, *41*, 2169 – 2171.

[165] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024 – 3027; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958 – 2961; b) W. Lin, P. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673 – 5676; c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497 – 2500; d) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237 – 3239; e) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem.* **2007**, *119*, 7825 – 7828; *Angew. Chem. Int. Ed.* **2007**, *46*, 7681 – 7684; f) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem.* **2008**, *120*, 1526 – 1530; *Angew. Chem. Int. Ed.* **2008**, *47*, 1503 – 1507.

[166] The low solubility of magnesium bases was addressed by Eaton through the development of bases of the type R_2NMgR' and $(R_2N)_2Mg$, however large excess of both the magnesium amides (up to 12 equiv) and electrophile (up to 10 equiv) were necessary for achieving good conversion.

[167] a) O. Bayh, H. Awad, F. Mongin, C. Hoarau, L. Bischoff, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *J. Org. Chem.* **2005**, *70*, 5190 – 5196; b) O. Bayh, H. Awad, F. Mongin, C. Hoarau, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *Tetrahedron* **2005**, *61*, 4779 – 4784; c) E. Hevia, G. W. Honeyman, A. R. Kennedy, R. E. Mulvey, D. C. Sherrington, *Angew. Chem.* **2005**, *117*, 70 – 74; *Angew. Chem. Int. Ed.* **2005**, *44*, 68 – 72; d) M. Widhalm, K. Mereiter, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1233 – 1244.

[168] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem.* **2008**, *120*, 8199 – 8201; *Angew. Chem. Int. Ed.* **2008**, *47*, 8079 – 8081.

[169] a) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi, K. Morokuma, *J. Am. Chem. Soc.* **2006**, *128*, 8748 – 8750; b) W. Clegg, S. H. Dale, A. M. Drummond, E. Hevia, G. W. Honeyman, R. E. Mulvey, *J. Am. Chem. Soc.* **2006**, *128*, 7434 – 7435; c) E. Hevia, G. W. Honeyman, R. E. Mulvey, *J. Am. Chem. Soc.* **2005**, *127*, 13106 – 13107; d) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 3859 – 3862; *Angew. Chem. Int. Ed.* **2006**, *45*, 3775 – 3778; e) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatly, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921 – 1930.

[170] a) R. G. Micetich, *Can. J. Chem.* **1970**, *48*, 2006 – 2015; b) A. I. Meyers, G. N. Knaus, *J. Am. Chem. Soc.* **1974**, *95*, 3408 – 3410; c) G. N. Knaus, A. I. Meyers, *J. Org. Chem.* **1974**, *39*, 1189 – 1192; d) R. A. Miller, M. R. Smith, B. Marcune, *J. Org. Chem.* **2005**, *70*, 9074 – 9076; e) C. Hilf, F. Bosold, K. Harms, M. Marsch, G. Boche, *Chem. Ber. Rec.* **1997**, *130*, 1213 – 1221.

[171] S. H. Wunderlich, P. Knochel, *Angew. Chem.* **2007**, *119*, 7829 – 7832; *Angew. Chem. Int. Ed.* **2007**, *46*, 7685 – 7688.

[172] B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485 – 488.

[173] B. M. Trost, H. Yang, G. Wuitschik, *Org. Lett.* **2005**, *7*, 4761 – 4764.

[174] B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2003**, *125*, 11516 – 11517.

[175] a) N. L. Allinger, L. A. Freiberg, *J. Org. Chem.* **1996**, *61*, 894 – 897; b) E. L. Eliel, M. Manoharan, *J. Org. Chem.* **1981**, *46*, 1959 – 1962.

[176] G. A. Molander, M. Ronn, *J. Org. Chem.* **1999**, *64*, 5183 – 5187.

[177] For recent reviews on gold catalysis, see: a) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064 – 8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896 – 7936; b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271 – 2296; c) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555 – 4563; d) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206 – 209; *Angew. Chem. Int. Ed.* **2006**, *45*, 200 – 203; e) N. Marion, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 2806 – 2809; *Angew. Chem. Int. Ed.* **2007**, *46*, 2750 – 2752; f) A. Fürstner, P. W. Davis, *Angew. Chem.* **2007**, *119*, 3478 – 3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; g) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395 – 403; h) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211.

[178] a) A. Das, H.-K. Chang, C.-H. Yang, R.-S. Liu, *Org. Lett.* **2008**, *10*, 4061 – 4064; b) A. S. K. Hashmi, R. Kurpejovic, W. Frey, J. W. Bats, *Tetrahedron* **2007**, *63*, 5879 – 5885; c) G. Zhang, V. J. Catalano, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 11358 – 11359.

[179] R. Zriba, V. Gandon, C. Aubert, L. Fensterbank, M. Malacria, *Chem. Eur. J.* **2008**, *14*, 1482 – 1491.

[180] For a representative example, see: a) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485 – 4488; For the related α-aminoallene series, see: b) N. Morita, N. Krause, *Eur. J. Org. Chem.* **2006**, 4634 – 4641; c) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121 – 4123.

[181] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370.

[182] J. F. Hartwig, *Nature* **2008**, *455*, 314 – 322.

[183] a) C. G. Espino, J. Du Bois in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**. For recent reviews see: b) P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571 – 1586; c) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905 – 2920; d) H. M. L. Davies, M. S. Long, *Angew. Chem.* **2005**, *117*, 3584 – 3586; *Angew. Chem. Int. Ed.* **2005**, *44*, 3518 – 3520.

[184] H. Kwart, A. A. Khan, *J. Am. Chem. Soc.* **1967**, *89*, 1951 – 1953.

[185] a) R. Breslow, S. H. Gellman, *J. Chem. Soc. Chem. Commun.* **1982**, 1400 – 1401; b) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728 – 6729.

[186] a) P. Müller, C. Baud, Y. Jacquier, M. Moran, I. Nageli, *J. Phys. Org. Chem.* **1996**, *9*, 341 – 347; b) I. Nägeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Müller, *Helv. Chim.*

Acta **1997**, *80*, 1087 – 1105; c) P. Müller, C. Baud, I. Naegeli, *J. Phys. Org. Chem.* **1998**, *11*, 597 – 601.
[187] P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571 – 1586.
[188] X.-Q. Yu. , J.-S. Huang, X.-G. Zhou, C. M. Che, *Org. Lett.* **2000**, *2*, 2233 – 2236.
[189] C. Espino, J. Du Bois, *Angew. Chem.* **2001**, *113*, 618 – 620; *Angew. Chem. Int. Ed.* **2001**, *40*, 598 – 600.
[190] C. G. Espino, P. M. When, J. Chow, J. Du Bois, *J. Am. Chem. Soc.* **2001**, *123*, 6935 – 6936.
[191] 6-membered ring formation is presumably due to the elongated S–O and S–N bonds (1.58 Å) and the obtuse N-S-O angle (103°) of the sulfamate.
[192] a) E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc.* **2002**, *124*, 7181 – 7192; b) D. T. Nowlan III, T. M. Gregg, H. M. L. Davies, D. A. Singleton, *J. Am. Chem. Soc.* **2003**, *125*, 15902 – 15911; c) F. M. Wong, J. Wang, A. C. Hengge, W. Wu, *Org. Lett.* **2007**, *9*, 1663 – 1665.
[193] X. Lin, C. Zhao, C.-M. Che, Z. Ke, D. L. Phillips, *Chem. Asian J.* **2007**, *2*, 1101 – 1108.
[194] *Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel* (Eds.: C. Y. Kao, S. R. Levinson), New York Academy of Sciences, New York, **1986**.
[195] For completed total syntheses of tetrodotoxin, see: a) Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9217 – 9219; b) Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9219 – 9221; c) N. Ohyabu, T. Nishikawa, M. Isobe, *J. Am. Chem. Soc.* **2003**, *125*, 8798 – 8805.
[196] K. W. Fiori, J. J. Fleming, J. Du Bois, *Angew. Chem.* **2004**, *116*, 4449 – 4452; *Angew. Chem. Int. Ed.* **2004**, *43*, 4349 – 4352.
[197] C. J. Hayes, P. W. Beavis, L. A. Humphries, *Chem. Commun.* **2006**, 4501 – 4502.
[198] H. Lébèl, K. Huard, S. Lectard, *J. Am. Chem. Soc.* **2005**, *127*, 14198 – 14199.
[199] B. H. Brodsky, J. Du Bois, *J. Am. Chem. Soc.* **2005**, *127*, 15391 – 15393.
[200] For reports on the catalytic reactions of cationic oxaziridinium oxidants, see: a) J. Vachon, C. Pérollier, D. Monchaud, C. Marsol, K. Ditrich, K. Lacour, *J. Org. Chem.* **2005**, *70*, 5903 – 5911; b) P. C. B. Page, B. R. Buckley, H. Heaney, A. J. Blacker, *Org. Lett.* **2005**, *7*, 375 – 377; c) P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith, A. M. Z. Slawin, *J. Org. Chem.* **2001**, *66*, 6926 – 6931; d) A. Armstrong, G. Ahmed, I. Garnett, K. Goacolou, J. S. Wailes, *Tetrahedron* **1999**, *55*, 2341 – 2352.
[201] Stereoretention of oxidation is indicative of a concerted asynchronous transition state. This notion is supported by DFT calculations and intrinsic reaction coordinate analysis.
[202] For examples of selective oxaziridine-mediate oxidations see: a) V. A. Petrov, G. Resnati, *Chem. Rev.* **1996**, *96*, 1809 – 1823; b) A. Arnone, S. Foletto, P. Metrangolo, M. Pregnolato, G. Resnati, *Org. Lett.* **1999**, *1*, 281 – 284; c) D. D. DesMarteau, A. Donadelli, V. Montanari, V. A. Petrov, G. Resnati, *J. Am. Chem. Soc.* **1993**, *115*, 4897 – 4898.
[203] A. L. Baumstark, P. C. Vasquez, *J. Org. Chem.* **1988**, *53*, 3437 – 3439.
[204] a) C. P. Buxton, B. A. Marples, R. C. Toon, V. L. Waddington, *Tetrahedron Lett.* **1999**, *40*, 4729 – 4732; b) P. Bovicelli, P. Lupattelli, A. Sanetti, *Tetrahedron Lett.* **1994**, *35*, 8477 – 8480.
[205] a) P. Bovicelli, P. Lupattelli, V. Fiorini, *Tetrahedron Lett.* **1993**, *34*, 6103 – 6104; b) T. Horiguchi, Q. Cheng, T. Oritani, *Tetrahedron Lett.* **2000**, *41*, 3907 – 3910.
[206] a) R. Curci, L. D. Accolti, M. Fiorentino, C. Fusco, W. Adam, M. E. González-Nuñez, R. Mello, *Tetrahedron Lett.* **1992**, *33*, 4225 – 4228; b) F. R. Van Heerden, J. T. Dixon, C. W. Holzapfel, *Tetrahedron Lett.* **1992**, *33*, 7399 – 7402.
[207] P. A. Wender, M. K. Hilinski, A. V. W. Mayweg, *Org. Lett.* **2005**, *7*, 79 – 82.
[208] R. Curci, A. Dinoi, M. Rubino, *Pure Appl. Chem.* **1995**, *67*, 811 – 822.
[209] For reviews, see: a) B. J. Wallar, J. D. Lipscomb, *Chem. Rev.* **1996**, *96*, 2625 – 2657; b) L. Que, Jr., R. Y. N. Ho, *Chem. Rev.* **1996**, *96*, 2607 – 2624; c) L. Que, Jr. in *Bioinorganic Catalysis*, 2nd ed. (Eds.: J. Reedijk, E. Bouwman), Marcel Dekker, New York, **1999**.
[210] *Cytochrome P-450 Structure, Mechanism and Biochemistry*, 2nd ed. (Ed.: P. R. Ortiz de Montellano), Plenum, New York, **1995**.
[211] B. Meunier, *Chem. Rev.* **1992**, *92*, 1411 – 1456.
[212] M. Costas, K. Chen, L. Que, Jr., *Coord. Chem. Rev.* **2000**, *200–202*, 517 – 544.
[213] I. Tabushi, T. Nakajima, K. Seto, *Tetrahedron Lett.* **1980**, *21*, 2565 – 2568.
[214] D. H. R. Barton, M. J. Gastiger, W. B. Motherwell, *J. Chem. Soc. Chem. Commun.* **1983**, 41 – 43.
[215] For a review on Fe Gif oxidation systems, see: P. Stavropoulos, R. Celenligil-Cetin, A. E. Tapper, *Acc. Chem. Res.* **2001**, *34*, 745 – 753.
[216] a) H. Hirao, L. Que, Jr., W. Nam, S. Shaik, *Chem. Eur. J.* **2008**, *14*, 1740 – 1756; b) L. Que, Jr., W. B. Tolman, *Nature* **2008**, *455*, 333 – 340; c) A. Company, L. Gomez, M. Guell, X. Ribas, J. M. Luis, L. Que, Jr., M. Costas, *J. Am. Chem. Soc.* **2007**, *129*, 15766 – 16767; d) For a review for work prior to 2007, see: L. Que. , Jr., *Acc. Chem. Res.* **2007**, *40*, 493 – 500.
[217] M. C. White, M. S. Chen, *Science* **2007**, *318*, 783 – 787.
[218] J. Zhan, H. Guo, J. Dai, Y. Zhang, D. Guo, *Tetrahedron Lett.* **2002**, *43*, 4519 – 4521.
[219] N. A. Vermeulen, M. S. Chen, M. C. White, *Tetrahedron* **2009**, *65*, 3078 – 3084.
[220] S. Lee, P. L. Fuchs, *J. Am. Chem. Soc.* **2002**, *124*, 13978 – 13979.
[221] C. Di Valentin, P. Gisdakis, I. V. Yudanov, N. Rösch, *J. Org. Chem.* **2000**, *65*, 2996 – 3004.
[222] 2-pyridyl organometallics are limited by their instability and challenging preparation, see: a) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020 – 4028; b) M. D. Sindkhedkar, H. R. Mulla, M. A. Wurth, A. Cammers-Goodwin, *Tetrahedron* **2001**, *57*, 2991 – 2996; c) G. A. Molander, B. J. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302 – 4314; d) P. B. Hodgson, F. H. Salingue, *Tetrahedron Lett.* **2004**, *45*, 685 – 687.
[223] For applications of 2-aryl pyridines, see: a) I. W. Davies, J. F. Marcoux, P. J. Reider, *Org. Lett.* **2001**, *3*, 209 – 211; b) J. R. Roppe, B. Wang, D. Huang, L. Tehrani, T. Kamenecka, E. J. Schweiger, J. J. Anderson, J. Brodkin, X. Jiang, M. Cramer, J. Chung, G. Reyes-Manalo, B. Munoz, N. D. P. Cosford, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3993 – 3996; c) A. G. Fang, J. V. Mello, N. S. Finney, *Org. Lett.* **2003**, *5*, 967 – 970.
[224] S. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848 – 10849.
[225] a) D. F. Taber, E. H. Petty, *J. Org. Chem.* **1982**, *47*, 4808 – 4809; b) E. Wenkert, L. L. Davis, B. L. Mylari, M. F. Solomon, R. R. daSilva, S. Shulman, R. J. Warnet, P. Ceccherelli, M. Curini, R. Pellicciari, *J. Org. Chem.* **1982**, *47*, 3242 – 3247; c) D. F. Taber, R. E. Ruckle, Jr., *J. Am. Chem. Soc.* **1986**, *108*, 7686 – 7693.
[226] U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340 – 5341.

