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C–H Functionalization

C–H Bond Functionalization through Intramolecular Hydride Transfer**

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Dedicated to Professor Robert S. Atkinson

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Known for over a century, reactions that involve intramolecular hydride-transfer events have experienced a recent resurgence. Undoubtedly responsible for the increased interest in this research area is the realization that hydride shifts represent an attractive avenue for C–H bond functionalization. The redox-neutral nature of these complexity-enhancing transformations makes them ideal for sustainable reaction development. This Review summarizes recent progress in this field while highlighting key historical contributions.

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1. Introduction

The functionalization of relatively unreactive C–H bonds remains an area of intense interest within organic chemistry, particularly from the viewpoint of sustainability and efficiency in organic synthesis. Goldberg and Goldman have termed the C–H bond "the un-functional group," highlighting its privileged status both as a tool for synthesis and as a target for methodology.[1]

Many noteworthy examples of C–H functionalization can be classified as oxidative, including the classic work of Shilov and Fujiwara.[2,3] More recent work has brought forth advances in photoredox catalysis,[4] processes where molecular oxygen serves as the terminal oxidant,[5] and site-selective transition-metal-catalyzed C–H oxygenation.[6] C–H functionalizations based on carbene insertion[7] have been elegantly applied, most prominently in total synthesis.[8] Typically, an organic carbene precursor and a transition-metal catalyst are combined to insert the carbene unit into a C–H bond. Substrates in these reactions can range from highly complex natural product precursors to methane. Named reactions involving a radical hydrogen atom abstraction en route to C–H functionalization have a venerable history in organic chemistry with the Hofmann–Löffler–Freytag[9] and Barton[10] reactions being the most well-known examples. More recently, this concept has been extended to a more general class of substrates and reactions.[11]

Interest in redox/atom economy[12] and the continued move towards green chemistry[13] have helped inspire the development of redox-neutral C–H functionalization processes. Redox-neutral C–H functionalizations based on transition-metal insertions into C–H bonds[14] represent a well-documented body of work. Beginning with fundamental contributions by Lewis and Murai,[15] insertion of C–C multiple bonds into C–H bonds proximal to a directing group has become a well-explored motif. Recently, the borrowing hydrogen/interrupted hydrogenation concept has been significantly extended in terms of molecular complexity.[16] Finally, depending on the system, C–H functionalization processes involving the dehydrogenation of alkyl groups can be considered redox-neutral.[17]

Fundamentally different from a mechanistic point of view is the class of typically redox-neutral C–H functionalization reactions that involve an intramolecular hydride shift as a key step, and which is the topic of this Review. We aim to cover the progress in this field since the last review[18] of aspects of this subject in 2006. Additionally, we have sought to include important historical examples of this reaction that have not been widely discussed in previous reviews or more recent publications.

A general scheme illustrating C–H functionalization through intramolecular hydride transfer is shown in Figure 1. The substrate requires a hydride acceptor moiety

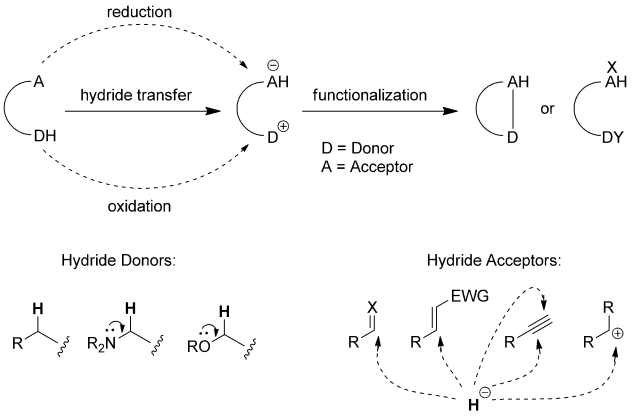

Figure 1. C–H functionalization by means of an intramolecular hydride shift.

proximal to a C–H bond. The reaction is initiated by a hydride shift (or related H-atom-transfer step), which formally oxidizes the carbon donor and reduces the hydride acceptor. The resulting zwitterionic intermediate then undergoes functionalization at the site of C–H bond transfer, usually by ring closure with the reduced hydride-acceptor moiety. For illustrative purposes and to highlight similarities, we have included examples that do not necessarily strictly follow this process. Due to their common attributes with hydride-shift

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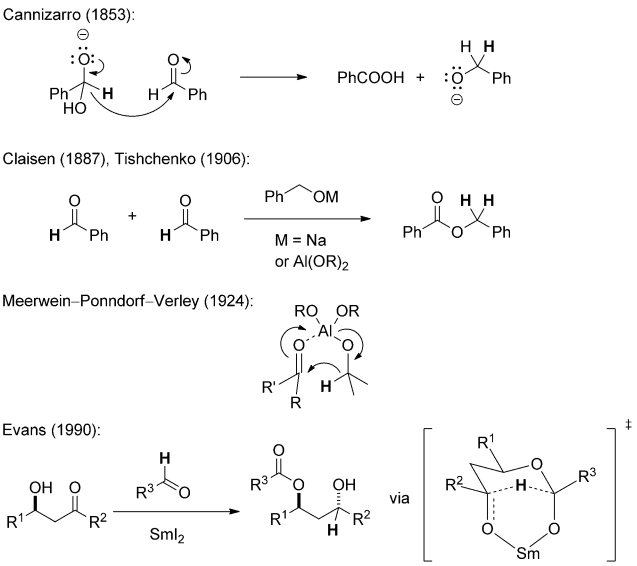
reactions and because they are often virtually indistinguishable, we have also included examples that may alternatively be classified as 1,5-sigmatropic rearrangements.

Reactions following the general pathway shown in Figure 1 involving aromatic amine hydride donors have historically been classified under the term "*tert*-amino effect".[19] This name refers to the tendency of substituted *N*,*N*-dialkylanilines to undergo unusually facile ring-closing reactions involving various groups at the *ortho* position. Indeed, 2-substituted dialkyl anilines have historically been the most popular scaffold for this reaction. Previous reviews have focused largely on this class of substrates, beginning with Pinnow's seminal example from 1895.[20] However, the tertiary amine group is neither necessary nor sufficient to guarantee a successful reaction outcome for a particular substrate. The defining characteristic for these reactions is the functionalization of a C–H bond concurrent with a hydride shift. In most examples, the new C–X bond will be formed at the hydride-donor atom, after the hydride shift takes place. Focusing more on the unique hydride-shift mechanism that draws together a diverse group of substrates, the names proposed by Sames ("HT-cyclization") and Akiyama ("Internal Redox Cascade") seem more appropriate, at least for intramolecular examples.

2. Background: Organic Molecules as Hydride Donors

The rich history of organic molecules serving as hydride donors began in 1853 with Cannizzaro's report on the base-mediated disproportionation of benzaldehyde into benzyl alcohol and benzoic acid (Scheme 1).[21] The eponymous reaction proceeds by intermolecular hydride transfer from a deprotonated hemiacetal intermediate onto an aldehyde,[22] although some evidence exists for the reaction to proceed, at least partially, by single-electron transfer.[23] Under slightly different conditions (catalytic sodium alkoxide base), Claisen reported the dimerization of aldehydes into esters in 1887.[24] This reaction is now known by the name of the chemist who discovered in 1906 that aluminum alkoxides were superior catalysts, tolerating both enolizable and non-enolizable aldehydes.[25] The Tishchenko reaction may be considered the seminal example of a reaction proceeding by a hydride



Scheme 1. Organic molecules as hydride donors.

shift, followed by a bond-formation event at the oxidized carbon atom. Significant applications of this reaction range from the industrial synthesis of ethyl acetate[26] to the elegant diastereoselective reduction of β-hydroxy ketones in the Evans–Tishchenko[27] reaction.

It is interesting to note that the first mechanistic proposal for these related reactions invoked a 1,3-hydride shift to explain the internal redox step, but subsequent experiments by Ogata and Kawasaki led to the modern understanding of the mechanism in which Al^{3+} coordinates an aldehyde and deprotonated hemiacetal into a preorganized configuration, followed by a 1,5-hydride shift.[28] Nearly 50 years after the Woodward–Hoffmann rules and frontier molecular orbital (FMO) theory,[29] 1,3-hydride shifts are still occasionally invoked to explain other redox-neutral reaction mechanisms despite the severe geometrical constraints imposed by orbital overlap requirements.

By changing the redox state of the reactants in the Tishchenko reaction, we arrive at the Meerwein–Pondorf–Verley (MPV) reduction (1924), and the reverse Oppenauer oxidation, which operate by means of an identical Al^{3+}-preorganized 1,5-hydride shift.[30]

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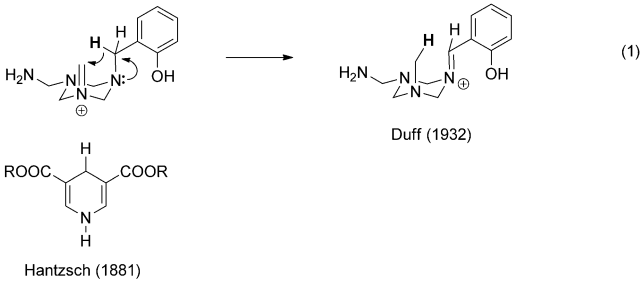
Daniel Seidel studied chemistry at the Friedrich-Schiller-Universität Jena and at the University of Texas at Austin (Diplom 1998). He performed his graduate studies in the lab of Prof. Jonathan L. Sessler, obtaining his PhD in 2002. From 2002 to 2005, he was an Ernst Schering Postdoctoral Fellow in the group of Prof. David A. Evans at Harvard University. He started his independent career at Rutgers University in 2005 and was promoted to Associate Professor in 2011. Research in his group is focused on new concepts for asymmetric catalysis and synthetic methodology.

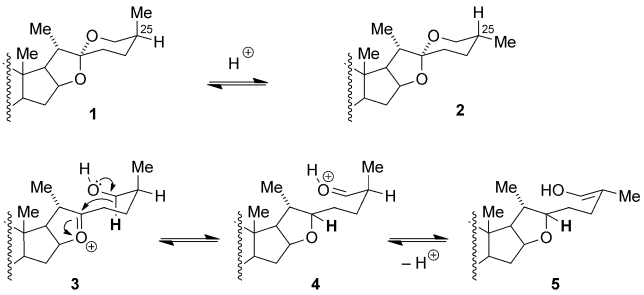
Several years after the discovery of the MPV reduction, Duff reported the synthesis of aromatic aldehydes through the hydrolysis of arene–hexamethylenetetramine adducts.[31] Subsequent mechanistic studies established that the hydrolysis involves the 1,5-hydride shift shown in Equation (1).[32]



(1)

The Duff reaction may thus be considered an early example of a hydride shift adjacent to a benzylic amine. While the oxidation of dihydropyridines to form pyridines was reported by Hantzsch in 1881,[33] the potential of the Hantzsch esters to serve as organic hydride (and proton) donors has been more recently realized by several prominent groups.[34]

An early example of a reversible intramolecular redox event was reported by R. B. Woodward et al. (Scheme 2).[35] The



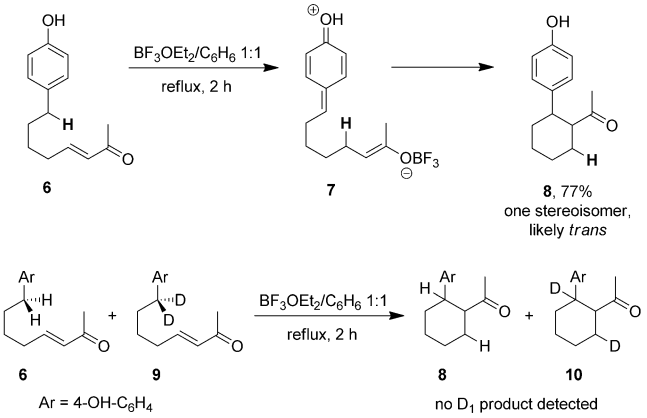
Scheme 2. Acid-catalyzed interconversion of sapogenins through reversible 1,5-hydride transfer.

curious observation that sapogenins **1** undergo an acid-catalyzed epimerization at C25 was rationalized on the basis of a reversible 1,5-hydride shift. Protonation of the acetal moiety of **1** leads to oxocarbenium ion **3** which is in equilibrium with oxocarbenium ion **4**. Epimerization of C25 occurs through the keto–enol equilibrium between **4** and **5**. Evidence for the proposed mechanism was later obtained by Seo and co-workers who demonstrated through deuterium-labeling studies that a reversible 1,5-hydride shift indeed occurs.[36]

3. C–H Functionalization by Intramolecular Hydride Transfer

3.1. Early Examples outside of the tert-Amino Effect

Given the well-documented intermediacy of hydride-transfer steps in several organic reactions, when did chemists start reporting subsequent bond formation following a hydride transfer from a relatively unreactive C–H bond? The seminal contributions of Pinnow[20] (discovery) and Suschitzky, Meth-Cohn, and Reinhoudt (development)[19] to reactions using aromatic amine hydride donors have been previously reviewed. To the best of our knowledge, the first non-amine example was reported in a 1969 communication from R. S. Atkinson.[37a] As shown in Scheme 3, heating the (*p*-hydroxyphenyl)-substituted enone **6** in excess $BF_3{\cdot}OEt_2$ produced the cyclized product **8** in high yield as a single diastereomer.

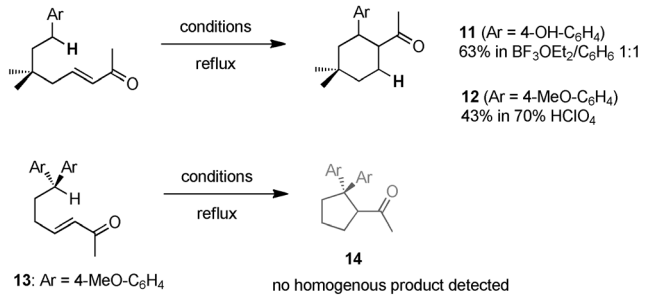


Scheme 3. Acid-catalyzed benzylic C–H functionalization.

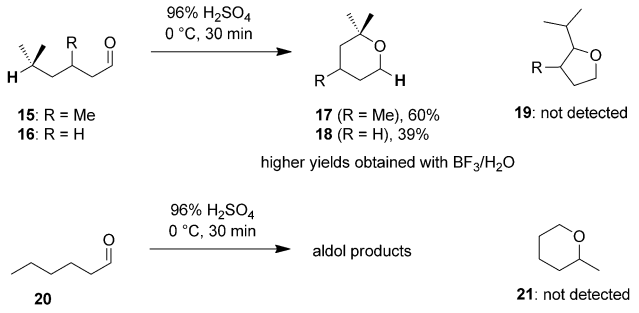
Atkinson proposed that **6** generates zwitterionic intermediate **7** through a 1,5-hydride shift, citing Woodward's study[35] as a precedent. Intermediate **7** was then transformed into **8** by attack of the boron enolate at the benzylic carbocation position. The ability of $BF_3{\cdot}OEt_2$ to activate the ketone in **6** lowers the energetic barrier for hydride transfer. In a crucial mechanistic experiment, Atkinson observed no monodeuterated products in the crossover experiment between **6** and **9**. Only **8** and **10** were observed by mass spectrometry of the reaction mixture. This result established that the redox step occurred intramolecularly.

In a subsequent full study,[37b] Atkinson and Green identified 70% aq. $HClO_4$ as another effective promoter for this transformation (Scheme 4). Notably, cyclizations that would be expected to involve a 1,4-hydride shift, such as the transformation of **13** into **14**, failed.

Another notable early example using unactivated substrates, aliphatic aldehydes, was reported in 1978 by Schulz



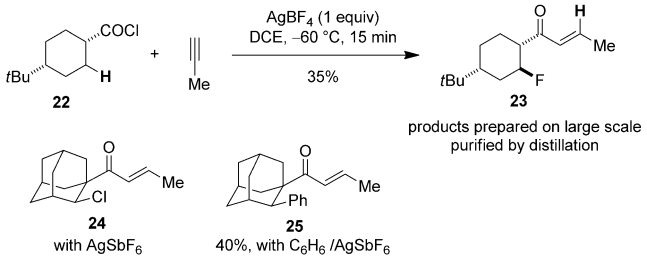
Scheme 4. Further exploration of Atkinson's reaction.



Scheme 5. Acid-catalyzed alkyl C–H functionalization.

and Onopchenko at Gulf (Scheme 5).[38] The cyclization of methyl-substituted aldehydes **15** and **16** could be carried out at low temperatures in 96% H_2SO_4 to yield the substituted tetrahydropyrans **17** and **18** on a 10–100 g scale. The absence of products such as **19** is invoked to argue against a desaturation-based mechanism. The authors propose that a 1,5-hydride shift from the tertiary C–H bond of **15** to the protonated carbonyl moiety occurs, followed by attack of the pendant hydroxy group at the new carbocation. Both methyl groups at the H-donor carbon are necessary for the transformation, as shown by the failure of **20** to yield **21** under similar conditions.

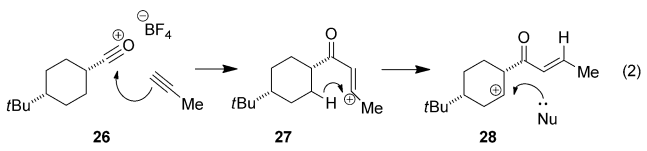
In 1979, Smit, Caple, and co-workers reported the fascinating aliphatic C–H fluorination, chlorination, and arylation cascade processes shown in Scheme 6.[39b] Treatment



Scheme 6. Stereoselective alkyl C–H halogenation and arylation.

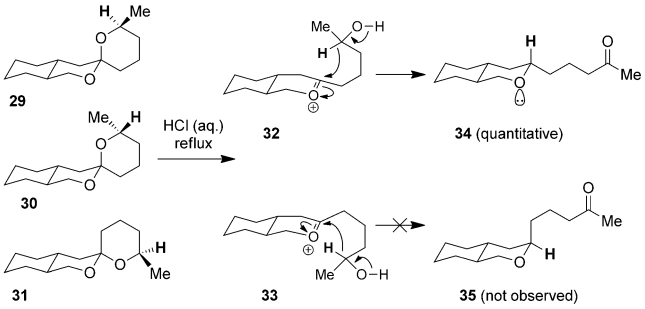
of aliphatic acid chlorides with $AgBF_4$ in the presence of a terminal alkyne afforded alkyl vinyl ketones with concurrent C–H functionalization at the β-position of the acid chloride. Depending on the conditions, this C–H bond could be fluorinated, chlorinated, or arylated with complete diastereoselectivity.

The three different types of products were proposed to form via the common intermediate **28** [Eq. (2)]. Treatment of **22** with $AgBF_4$ generates the highly reactive oxonium salt **26**. Intermediate **26** is attacked by propyne to yield the vinylic



carbocation **27**, which in turn generates **28** by means of a 1,5-hydride shift. A 1,5-hydride shift was previously proposed in a similar system in a 1974 report[39a] by several of the coauthors. In the $AgBF_4$ system, **28** is attacked by a B–F bond (similar to the Sandmeyer reaction) to yield the aliphatic fluoride **23**. Use of $AgSbF_6$ yields alkyl chlorides such as **24**. Presumably, the solvent acts as the source of chloride. Arylation to form **25** occurs by a Friedel–Crafts reaction. In light of both great demand for efficient C–H functionalization and fluorination methodology at present, this work certainly merits further attempts at extension.

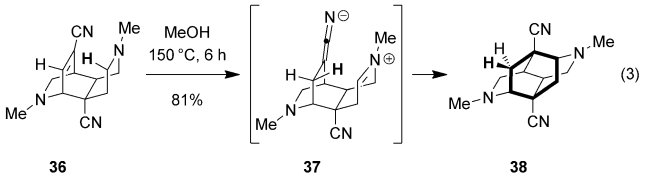
Closely related to the studies concerning the isomerization of the sapogenins, in 1981 Deslongchamps and co-workers reported what they termed the "oxido-reduction" of tricylic spiroketals (Scheme 7).[40] Apparently driven by the



Scheme 7. Acid-catalyzed redox ring-opening of acetals under stereoelectronic control.

thermodynamic stability of the open-chain product, exposure of spiroketal **29** to aqueous hydrochloric acid under reflux resulted in the quantitative formation of **34**. Interestingly, two isomers of **29**, namely **30** and **31**, also converted to product **34** upon exposure to identical reaction conditions. The authors proposed that all reactions proceed through common intermediate **32**, consistent with β-attack (axial attack) on the oxocarbenium ion. This is in agreement with the stereoelectronic requirement of placing the newly formed oxygen lone pair in a position that is antiperiplanar to the forming C–H bond. The alternative α-attack (cf. **33**) and consequent formation of **35** was not observed which is in perfect agreement with stereoelectronic considerations that would require a strained intermediate.

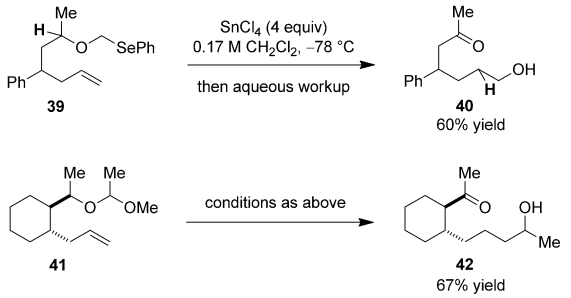
The final example highlighted in this section was discovered by a Merck team led by E. Grabowski [Eq. (3)] and published in 1976.[41] In the process of preparing novel rigid structures for biological evaluation, these researchers noted the unusual skeletal rearrangement of **36** (obtained from the reductive Diels–Alder dimerization of 1-methyl-4-cyanopyr-



idinium iodide and subsequent hydrogenation over PtO_2) to **38**. A detailed investigation, including D-labeling studies led to the conclusion that this reaction occurs by a 1,5-hydride shift/ring-closure sequence involving zwitterionic intermediate **37**. Polar protic solvents are required for this reaction to proceed with methanol providing optimal yields in a reaction conducted at 150 °C. Interestingly, the rearrangement can also be performed in refluxing water, albeit less efficiently. Little conversion was observed in DMSO at 150 °C and no reaction at all occurred in xylenes at 140 °C. The C_2-symmetrical product **38** could be resolved into its enantiomers with dibenzoyl-D-tartaric acid. Grabowski's reaction predates the extensive studies on the *tert*-amino effect by Reinhoudt and is also the seminal example of this type of C–H functionalization using an aliphatic amine. To the best of our knowledge, this work has not previously been discussed in a review in the context of C–H functionalization, nor is this fundamental example well-cited in the literature.

3.2. Ethers and Acetals as Hydride Donors

In 1993, Kataoka and co-workers reported an unusual functionalization of olefins bearing pendant O or Se acetal moieties (Scheme 8).[42] O,Se-acetal **39** was treated with

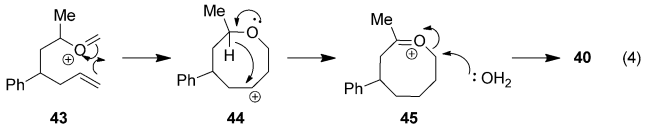


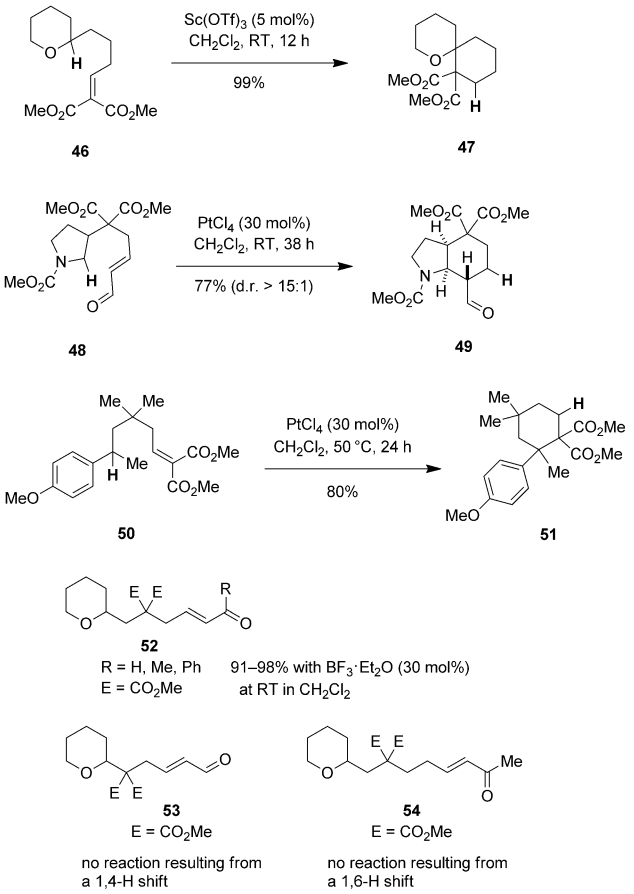
Scheme 8. Hydrofunctionalization of olefins bearing acetals.

excess $SnCl_4$ at low temperature, yielding hydroxyketone **40** after aqueous workup. Similarly, acetal **41** was converted to **42** in fair yield.

The authors proposed that in both classes of substrates, the acetal undergoes Sn^{4+}-mediated elimination to form an oxocarbenium ion such as **43**. A Prins cyclization on **43** leads to carbocationic intermediate **44**, which is now primed for a transannular 1,5-hydride shift. The resulting intermediate **45** undergoes hydrolysis during workup to afford the hydroxyketone **40** as shown in Equation (4).

In 2005 Sames et al. reported the results of a key study aimed at generalizing hydride-shift sequences for the selective functionalization of C–H bonds (Scheme 9).[43] The main

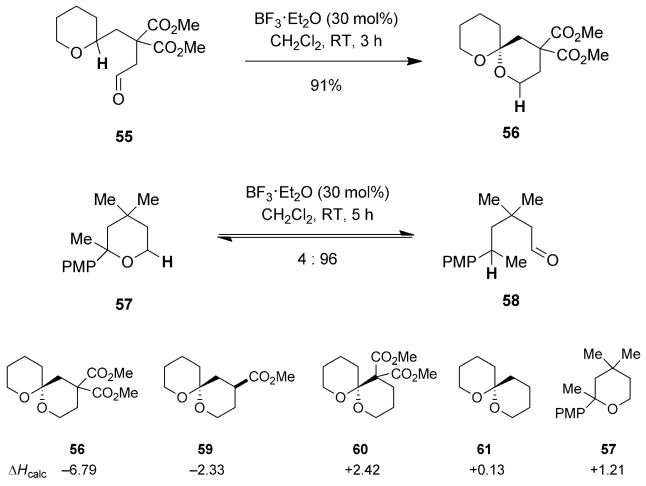




Scheme 9. Lewis acid catalyzed 1,5-hydride transfer.

emphasis was placed on developing catalytic approaches at low temperatures. By applying scandium(III) triflate as a catalyst (5 mol%), they converted tetrahydropyran **46** with a pendant alkylidenemalonate moiety readily to spirocyclic product **47**. Remarkably, the reaction proceeded at room temperature and provided **47** in essentially quantitative yield. Other types of C–H bonds could also be functionalized, including C–H bonds α to a carbamate nitrogen (**48**→**49**) and benzylic C–H bonds (**50**→**51**). The latter two transformations required the use of $PtCl_4$ (30 mol%) as the catalyst. A series of experiments clearly demonstrated the importance of an appropriate distance between the hydride-donor and -acceptor sites. Whereas compounds **52** readily underwent 1,5-hydride transfer/cyclization to the expected spirocyclic compounds in the presence of $BF_3{\cdot}OEt_2$, **53** and **54** failed to undergo the corresponding reactions that would have to involve a 1,4- or a 1,6-hydride shift.

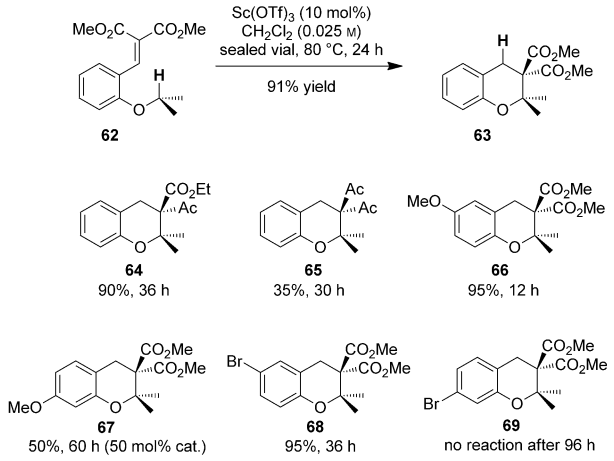
In a subsequent publication, Sames and co-workers explored the formation of spirocyclic acetals (Scheme 10).[44] A catalytic amount of $BF_3{\cdot}OEt_2$ (30 mol%) facilitated the formation of a number of spiroacetals at room temperature (e.g., **55**→**56**). As noted by the authors, many of these redox isomerizations are close to thermoneutral, with the acyclic form being more stable in some cases. In agreement with DFT calculations that predict **56** to be more stable than **55** by 6.79 kcal mol^{-1}, **56** was obtained in excellent yield. A similar



Scheme 10. Formation of spirocyclic acetals.

observation was made for **59**. Also in accord with calculated energies, compound **60** could not be obtained and the preparation of **61** succeeded in poor yields only. Good correlation between computed energies and experimental results was also observed for the equilibrium of tetrahydropyrane **57** and aldehyde **58**. Independently prepared **57** converted almost completely to the open-chain form when exposed to typical isomerization conditions, similar to Deslongchamps' reaction (Scheme 7).[40]

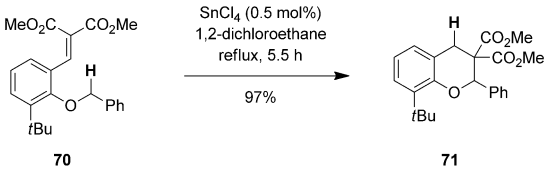
In a further extension, Sames and co-workers developed a catalytic system capable of cyclizing (*o*-alkoxy)benzylidene derivatives such as **62** (Scheme 11).[45] $Sc(OTf)_3$ was a uniquely



Scheme 11. Lewis acid catalyzed 1,5-hydride transfer of phenyl ethers.

effective catalyst for this transformation: a number of other lanthanide triflates provided no conversion of **62**. Several reactivity trends can be inferred by substrates **64**–**69**. Esters are more effective activating groups for the hydride acceptor than ketones. Ring substitution is much better tolerated at the *para*-position relative to the alkoxide substituent, and electron-donating groups increase the rate of the reaction.

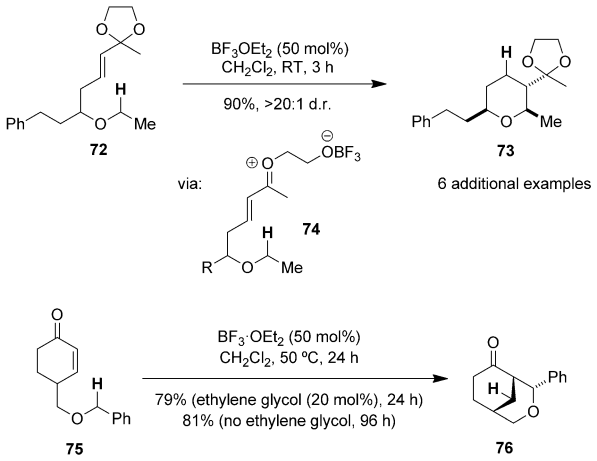
In a related study, the group of Akiyama reported the functionalization of benzylic ethers through intramolecular redox isomerization [Eq. (5)].[46] Tin tetrachloride proved to



(5)

be the optimal catalyst for this transformation (e.g., **70**→**71**). The presence of an *ortho*-substituent had a dramatic effect on reaction rates and for the substrate with a *tert*-butyl group the reaction could be performed with a low catalyst loading of just 0.5 mol%. Replacement of the *tert*-butyl group for sterically less demanding substituents led to lower reaction rates and the requirement for higher catalyst loadings. Removal of the *ortho*-substituent altogether resulted in a significantly retarded reaction rate. These finding were rationalized on the basis that an *ortho*-substituent enforces the proper conformation required for hydride transfer.

Sames and McQuaid investigated a class of substrates with ethers tethered to α,β-unsaturated ketones.[47] Unlike the corresponding ether-aldehydes, these systems only underwent hydride-transfer/cyclization after long reaction times in the presence of $BF_3{\cdot}OEt_2$. Transformation of the ketones into acetals such as **72** drastically accelerated the reaction rate (**72**→**73**) and improved the yield (Scheme 12). The authors

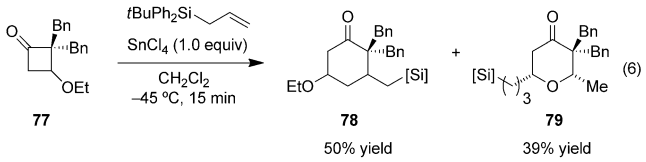


Scheme 12. Activation of ketone hydride acceptors using diethylene glycol.

attributed this effect to the formation of strongly activating oxocarbenium ions **74** in the presence of $BF_3{\cdot}OEt_2$ through the opening of the acetal. In addition to substituted tetrahydropyrans similar to **73**, the bridged bicyclic system **76** could be generated from ketone **75**, using a catalytic amount of ethylene glycol. The same transformation took four times longer to reach similar conversion without ethylene glycol.

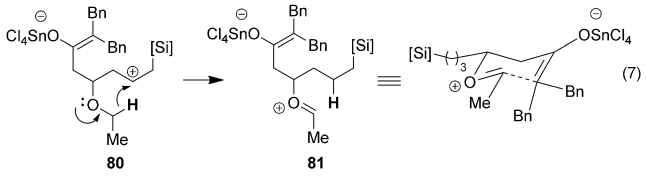
Concurrent with the above intentional implementations of hydride transfer from ethers, several reports have documented the serendipitous discovery of similar processes. During an investigation of a Lewis acid catalyzed [4+2]

cycloaddition of allylsilanes to cyclobutanones, Matsuo and co-workers observed the formation of unexpected products resulting from a 1,5-hydride shift process shown in Equation (6).[48] Treatment of **77** with $SnCl_4$ and the bulky TBDPS



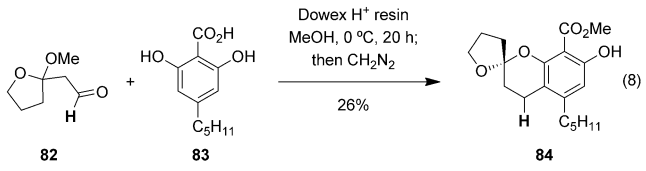
allylsilane led to the formation of both the expected cyclohexanone **78** and the diastereomerically pure 4-chromanone **79**. Product **79** apparently resulted from final bond formation occurring at the α-position of the ethyl ether, rather than the β-position of the silane.

The authors proposed that the initially formed zwitterion **80** could undergo the 1,5-hydride shift shown in Equation (7).



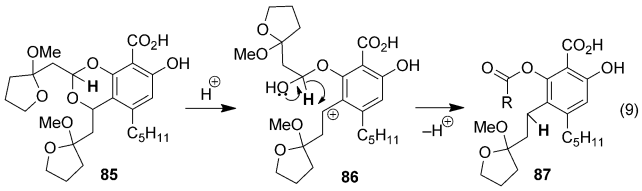
The resulting oxocarbenium **81** then cyclizes via the chairlike transition state shown to form the observed 4-chromanone product **79**. Interestingly, other allylsilanes (TIPS, TMS, or Me_2BnSi) afforded only the cyclohexanone products under the same conditions, leading the authors to propose that the carbocation-stabilizing properties of the phenyl substituents in TBDPS may be critical for achieving the 1,5-hydride shift.

During their synthesis of the core of berkelic acid, Zhou and Snider observed an unexpected redox activity during the later stages of their route.[49] Their investigation of this reaction on a model system is shown in Equation (8). Condensation of **82** with **83** in the presence of an acidic resin led to the formation of spirocyclic acetal **84** (isolated as the methyl ester following treatment with diazomethane).



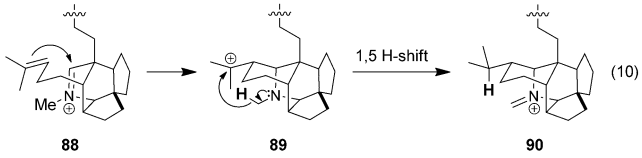
The authors proposed a mechanism related to the Cannizarro and Tishchenko reactions. Acid-catalyzed addition of **83** to the aldehyde **82** provided a 1,3-diol which underwent acetalization with another equivalent of **82** to form **85**. Protonation of this intermediate, followed by ring opening, triggered a 1,5-hydride shift from the acetal to the benzylic carbocation of **86**. Subsequent hydrolysis of ester **87** and transacetalization led to the observed product [Eq. (9)].

Other examples featuring ether hydride donors are covered in the sections on alkyne acceptors (Section 3.5) and enantioselective variants (Section 3.6).



3.3. Amines as Hydride Donors

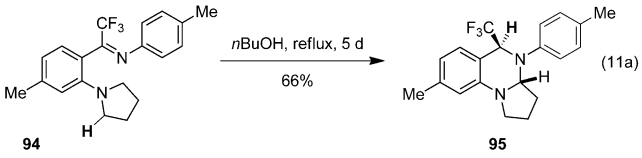
In the course of their synthetic studies on the daphniphylline alkaloids, Heathcock et al. discovered the interesting transformation outlined in Equation (10).[50] Iminium ion **88**



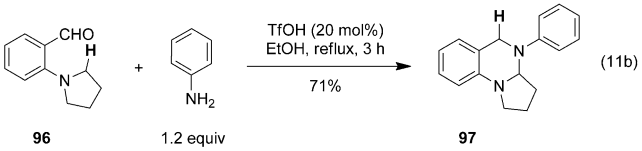
underwent intramolecular attack by a pendant olefin to give intermediate carbocation **89**. This cation was reduced to an alkyl group via intramolecular 1,5-hydride transfer of an amine α-C–H bond. The resulting iminium ion **90** was subsequently hydrolyzed to provide the corresponding secondary amine.

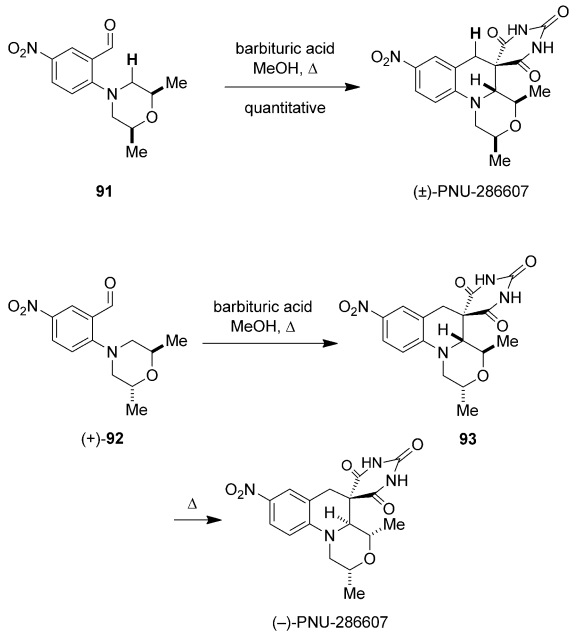
Inspired by the studies of Reinhoudt et al., a team of medicinal chemists at Pfizer led by Ruble and Hurd reported the synthesis of the antibacterial agent PNU-286607 by a redox-neutral reaction cascade (Scheme 13).[51] A synthesis of racemic PNU-286607 was first developed starting from achiral **91** and barbituric acid. The corresponding asymmetric synthesis is interesting in that it utilizes the optically pure starting material (+)-**92**. Upon reaction with barbituric acid, (+)-**92** is initially converted to **93**, which represents an undesired product diastereomer. Further heating of **93** results in isomerization to the desired product isomer (presumably via a ring-opened enamine intermediate) which was obtained in enantiopure form.

Based on an earlier study by Reinhoudt and co-workers who reported the thermal rearrangement of imine **94** to aminal **95** [Eq. (11a)],[52a] our group recently developed



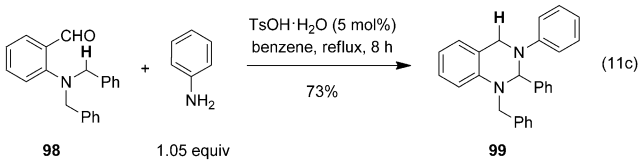
a one-pot Brønsted acid catalyzed approach to this transformation [Eq. (11b)] that significantly accelerates aminal



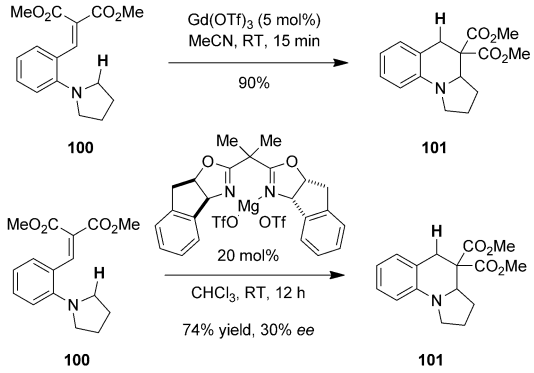


Scheme 13. Synthesis of (±)-PNU-286607.

formation.[52b] Exposure of **96** to a slight excess of aniline in the presence of catalytic amounts of triflic acid (TfOH) in refluxing ethanol led to the formation of aminal **97** in 71% yield. This reaction was applicable to a range of tertiary aminobenzaldehydes and primary amines, including aliphatic amines. Aliphatic amines performed best in the presence of trifluoroacetic acid (1.2 equiv) as a promoter. In an independent study, Akiyama and co-workers developed a very similar approach to aminals such as **99** [Eq. (11c)].[52c] These researchers identified *p*-toluenesulfonic acid as an efficient catalyst.



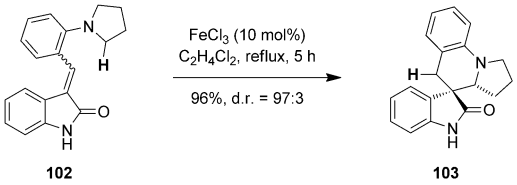
Traditionally, reactions related to the *tert*-amino effect have been conducted under thermal conditions. The lack of methods that rely on external reagents or catalysts to lower the reaction barriers for these rearrangements prompted our group to explore the use of catalysts to accelerate the rearrangement of pyrrolidine-alkylidenemalonate **100** to tricyclic tetrahydroquinoline **101** (Scheme 14).[53] It was found that many simple Lewis acids were capable of catalyzing this transformation at room temperature. Out of a survey of catalysts, gadolinium(III) triflate was found to provide the best results, outperforming scandium(III) triflate. Under optimized conditions, the transformation of **100** to **101** with 5 mol% of gadolinium(III) triflate proceeded in only 15 min at room temperature in acetonitrile. Initial attempts to render this reaction enantioselective were met with limited success. The best result was obtained with magnesium(II) triflate used



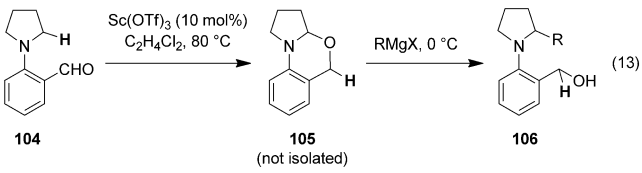
Scheme 14. Lewis acid catalyzed reaction based on the *tert*-amino effect and an asymmetric variant.

in combination with a C_2-symmetric bisoxazoline ligand. In this instance **101** was recovered with only 30% *ee*. Exposure of enantioenriched **101** to gadolinium(III) triflate led to product racemization, illustrating the reversibility of the Mannich-type ring-closure step.

Yuan and co-workers reported the formation of spirooxindoles such as **103** through the iron(III) chloride catalyzed rearrangement of **102** [Eq. (12)].[54] Products were obtained in high yields and with excellent diastereoselectivities. The scope of this transformation extends to piperidine, morpholine, and tetrahydroisquinoline analogues of **102**.

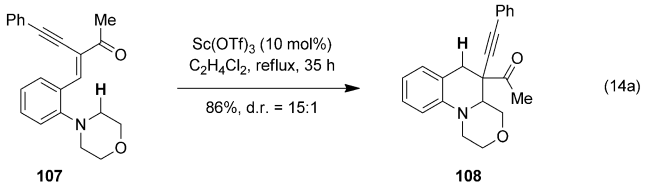


Maulide and co-workers developed an efficient α-functionalization of *N*-aryl amines **104** to give **106** via intermediate N,O-acetals **105** [Eq. (13)].[55] Intermediate **105** is obtained



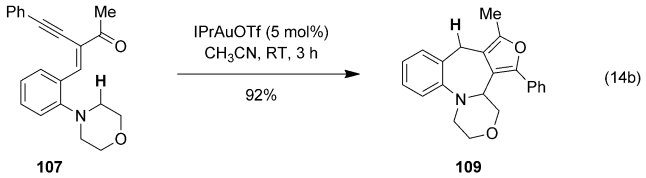
from **104** by a 1,5-hydride shift/ring closure sequence. This transformation had been reported previously but was known to suffer from low conversions. The group of Maulide dramatically improved this process by employing scandium triflate as an efficient catalyst. Crossover experiments confirmed that the hydride-transfer event is a strictly intramolecular process. N,O-acetals **105** were not isolated but rather treated in situ with various nucleophiles including a broad range of Grignard reagents and lithium alkynyl trifluoroborates to access α-functionalized amines **106** in a convenient one-pot process. This strategy was applied in a concise synthesis of (±)-indolizidine 167B.

Zhang and co-workers reported two divergent redox-isomerization pathways for compounds such as **107**.[56] Exposure of **107** to catalytic amounts of scandium(III) triflate in refluxing 1,2-dichloroethane led to the typical 1,5-hydride shift/ring-closure rearrangement and formation of **108** [Eq. (14a)]. Interestingly, when the catalyst was changed to



(14a)

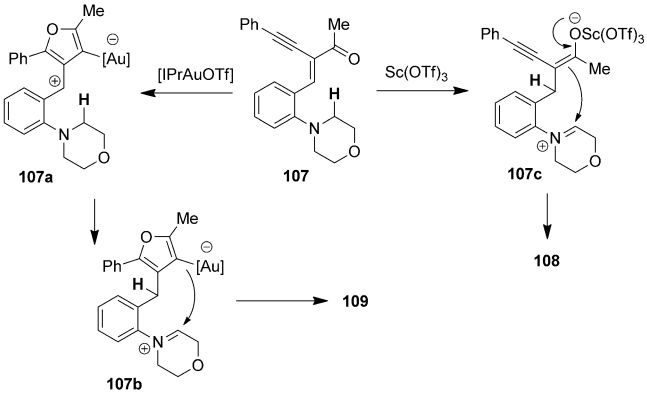
a cationic gold complex, **107** was efficiently converted to **109** through an intriguing cascade process with concomitant formation of a furan-fused benzazepine species [Eq. (14b)].



(14b)

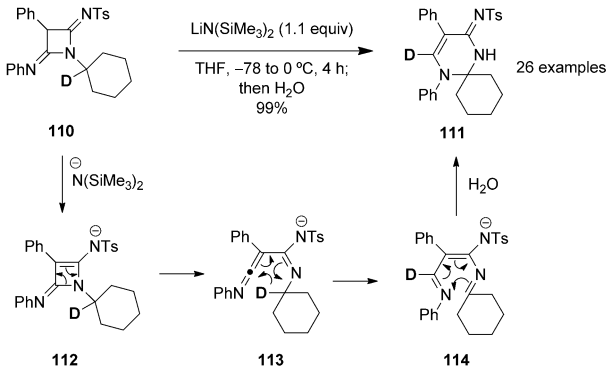
This unusual transformation occurred readily at room temperature in acetonitrile. The formation of furan-fused benzazepines in this cascade can be compared to the generation of indole and pyrrole-fused benzazepines by a different cascade process (see Scheme 17). An enantioselective variant of this process was later developed by employing a catalytic amount of a chiral gold–bisphosphine complex (see Section 3.6).[90]

The authors proposed that the reaction pathways diverge at **107** depending on whether a carbophilic or oxophilic Lewis acid was used. In the mechanism shown in Scheme 15, activation of the alkyne unit in **107** by Au^{I} leads to the formation of the zwitterionic furan intermediate **107a**. Instead of the traditional protodeauration pathway, a 1,5-hydride transfer occurs to form **107b**, which is now primed for intramolecular ring closure to generate furan-fused benzazepine **109**. Conversely, coordination of oxophilic Sc^{III} to the keto group of **107** activates the alkylidine system towards a 1,5-hydride shift. The expected zwitterionic intermediate **107c** goes on to form the observed tetrahydroquinoline **108** after ring closure.



Scheme 15. Divergent pathways in Zhang's C–H functionalization.

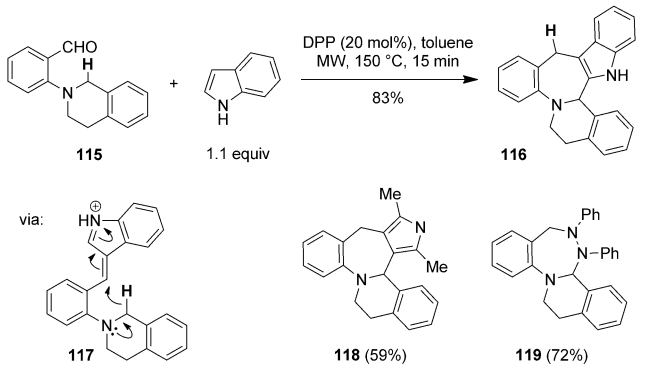
Zhang, Xi, and co-workers discovered a fascinating ring-expansion sequence starting from 2,4-diiminoazetidines **110**.[57] Treatment of **110** with stoichiometric $LiN(SiMe_3)_2$, followed by workup afforded **111** in excellent yield (Scheme 16). A large number of diiminoazetidines bearing



Scheme 16. Azetidine ring expansion through 1,5-hydride transfer.

a cycloalkyl substituent at the aziridine nitrogen undergo this transformation in excellent yield. The authors' proposed mechanism begins with electrocyclic ring-opening of the deprotonated starting material **112** to generate **113**. Intermediate **113** undergoes a sigmatropic 1,5-hydride shift, followed by electrocyclic ring closure of imine **114** to generate the product. This elegant mechanism is consistent with deuteration and intermediate trapping experiments.

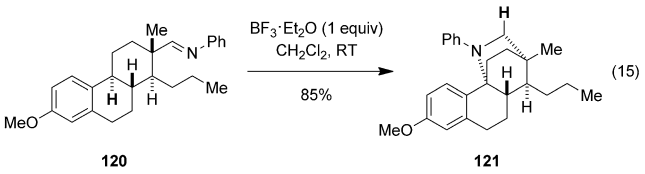
With few exceptions [see e.g. Eq. (14b)], redox isomerizations initiated by a 1,5-hydride shift ultimately lead to the formation of a new six-membered ring. In an effort to develop extended reaction cascades that enable access to compounds with larger rings, our group explored the reaction of tertiary aminobenzaldehydes with doubly nucleophilic compounds such as indoles (Scheme 17).[58] Exposure of **115** and indole to catalytic amounts of diphenyl phosphate (DPP, 20 mol%) under microwave irradiation led to the formation of indole-fused benzazepine **116** in 83% yield. This reaction is thought to proceed by 1,5-hydride transfer via an intermediate vinylogous iminium (azafulvenium) ion **117**, followed by ring closure. The well-known addition of indole to azafulvenium ions such as **117** has been shown to occur under the reaction conditions. However, this did not represent a dead end since the formation of the corresponding bisindolyl methanes was shown to be reversible. The scope of this transformation includes other double nucleophiles such as pyrroles (product **118**) and hydrazines (product **119**).



Scheme 17. Extended rearrangements with dinucleophiles.

3.4. Hydride Donors without α-Heteroatoms

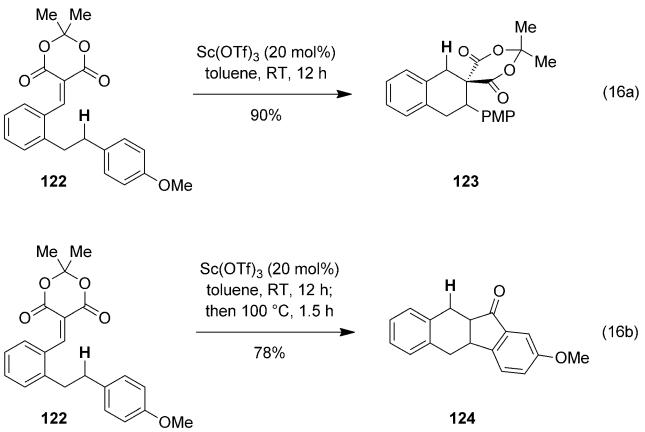
An intriguing internal redox transformation was discovered by Tietze and co-workers in the course of their work on novel steroid derivatives [Eq. (15)].[59a,b] Exposure of imine



(15)

120 to $BF_3{\cdot}OEt_2$ in dichloromethane solution led to the unexpected formation of polycyclic amine **121** in high yield. The simultaneous reduction of the imine and replacement of a benzylic C–H bond for a C–N bond was rationalized with a 1,5-hydride shift/ring-closure sequence with a stabilized benzyl cation intermediate. Consistent with this proposal, replacement of the methoxy group for acetoxy resulted in a substrate with lower reactivity. Frank et al. later extended the scope of this transformation to the corresponding oximes and hydrazones.[59c]

Benzylic C–H bond functionalization by hydride transfer has also been reported by the Fillion group [Eqs. (16a) and (16b)]. Scandium(III) triflate proved to be an excellent catalyst for the transformation of **122** to **123** through 1,5-

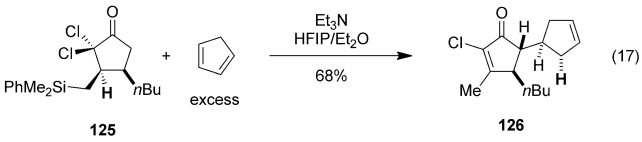


(16a)

(16b)

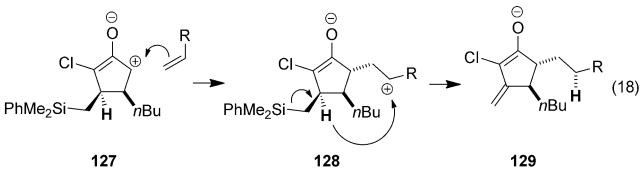
hydride shift/ring closure.[60] This reaction proceeded readily at room temperature. When conducted at 100 °C, the reaction cascade was extended further to include a Friedel–Crafts acylation (**122**→**124**). The outcome of the overall reaction was shown to be dependent on subtle electronic features. While an electron-rich benzylic C–H bond was found to be important for hydride transfer to occur, substitution with more than one methoxy group led to a competing Friedel–Crafts alkylation process (direct attack of aryl ring on alkylidene moiety to form a seven-membered ring, not shown).

Harmata, Schreiner, and co-workers reported the unexpected formation of **126** from **125** and cyclopentadiene, under conditions intended to facilitate a [4+3] cycloaddition [Eq. (17)].[61] This reaction proved to be general for several substituted olefins, and typically proceeded in moderate to high yield under mild conditions.



(17)

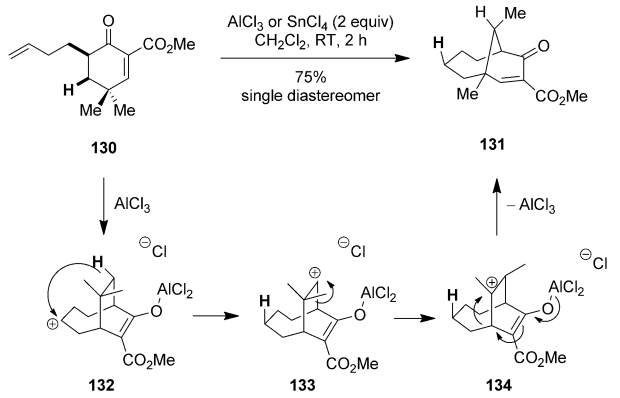
The authors proposed a mechanism consistent with DFT calculations and a deuterium-labeling study [Eq. (18)]. Eno-



(18)

lization of **125**, followed by loss of chloride anion generates zwitterion **127**. Intermediate **127** is attacked by the olefin to generate **128**, which is now primed for a 1,5-hydride shift triggered by desilylation. Isomerization of the resulting anion **129** affords the observed product. This transformation differs from most examples reviewed here in that a new σ bond is not formed at the hydride-donor carbon that links it to an acceptor moiety. However, this distinction should merely serve as encouragement to envision new pathways forward for the construction of molecular complexity subsequent to the hydride-shift step.

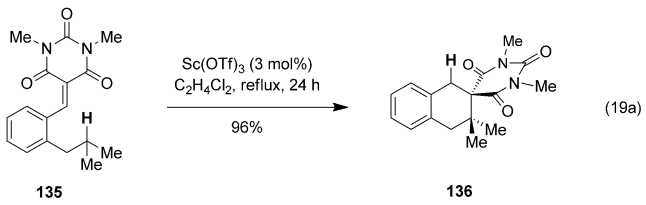
In order to effect a polyene cyclization, Shia and co-workers subjected diene **130** to Lewis acidic conditions at room temperature (Scheme 18).[62] Instead of the expected product, the unusual bicylic structure **131** was formed as a single diastereomer in good yield. The identity of **131** was confirmed by X-ray crystallography. Treatment of **130** with $AlCl_3$ was proposed to mediate the addition of the terminal olefin to the Lewis acid activated enone system, generating **132**. Cation **132** then undergoes a 1,5-hydride shift from the bridging methylene group to the carbocationic position in the ring. The proximity of these positions is enforced by the rigid bicyclic geometry, similar to Grabowski's system [cf. Eq. (3)]. Transfer of the carbocation to the bridging methylene carbon



Scheme 18. An unusual alkyl-to-alkyl hydride-shift cascade.

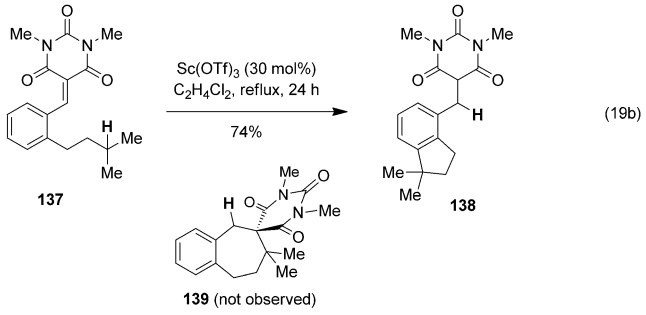
initiates a series of alkyl shifts, eventually resulting in the observed product.

A challenging functionalization of aliphatic C–H bonds by a hydride-transfer-initiated reaction cascade was realized by Akiyama and co-workers.[63a] Key to success was the use of a highly electrophilic barbiturate-based acceptor moiety [Eq. (19a)]. Specifically, exposure of compound **135** to



(19a)

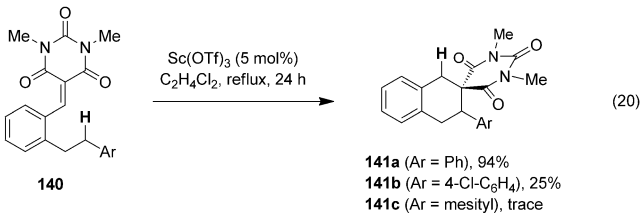
3 mol% of scandium(III) triflate in 1,2-dichloroethane at reflux resulted in efficient rearrangement to product **136**, presumably via an intermediate zwitterion with a tertiary carbocation moiety. Substrates analogous to **135** but with secondary aliphatic C–H bonds proved unreactive. Interestingly, a slight change in the structure of the substrate led to an entirely different reaction outcome [Eq. (19b)]. Substrate



(19b)

137, bearing an additional CH_2 linker between the hydride donor and acceptor sites exclusively provided product **138**, the result of a 1,6-hydride transfer followed by a Friedel–Crafts alkylation. An alternate scenario, namely a 1,5-hydride transfer followed by a 1,2-hydride transfer and Friedel–Crafts alkylation was ruled out on the basis of deuterium-labeling experiments that established transfer of a hydride originating from the tertiary C–H bond.

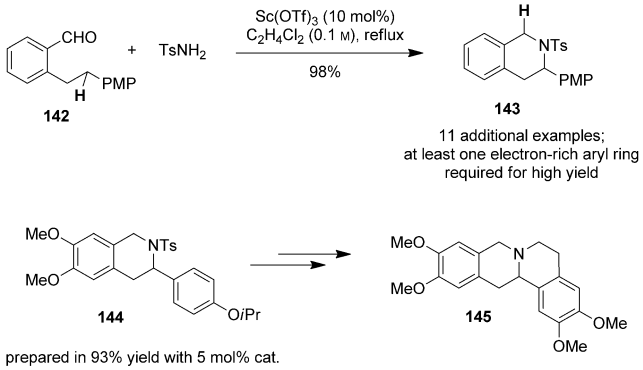
In a continuation of their work, Akiyama and co-workers extended the scope of the 1,5-hydride shift/ring-closure reaction of alkylidene barbituates to benzylic C–H bonds [Eq. (20)].[63b] The nature of the aryl substituent in **140** had a profound effect. Whereas a phenyl substituent allowed for



(20)

a good reaction rate with 5 mol% of scandium(III) triflate (94% yield of product **141a** in 24 h), a *p*-methoxyphenyl group led to a dramatic rate acceleration (96% yield of product after 8 h with only 1 mol% of catalyst). Accordingly, a *p*-chlorophenyl group retarded the reaction rate substantially. Interestingly, a mesityl group proved to be even less reactive. This was rationalized with the inability of the π-system to properly align with the σ* C–H orbital of the transferring hydride.

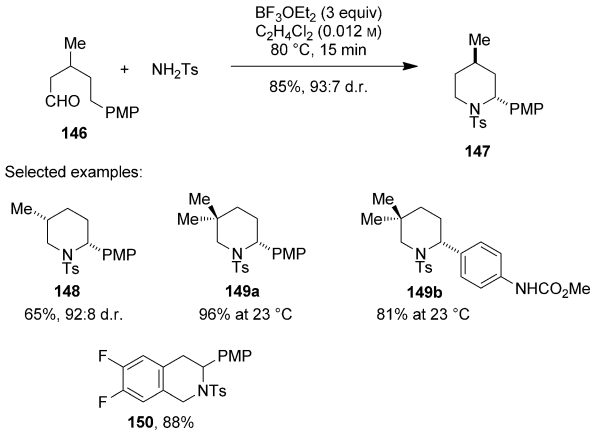
Independent efforts from the Sames[64a] and Akiyama[64b] groups culminated in the hydride-transfer cyclization of systems containing benzylic C–H donors and *N*-tosylimine acceptors to form *N*-tosylamines (Schemes 19 and 20). The



Scheme 19. Lewis acid catalyzed synthesis of tetrahydroisoquinolines through benzylic C–H functionalization.

products of these reactions can be readily transformed into synthetically useful free secondary amines. Akiyama and co-workers found that scandium(III) triflate was an effective catalyst for the condensation and cyclization of **142** and tosylamine in refluxing dichloroethane, affording protected tetrahydroisoquinoline **143**. This reaction proceeded in excellent yield, as did most examples with relatively electron-rich aryl rings. Highlighting the use of the tetrahydroisoquinoline products, **144** was synthesized efficiently and transformed into a known precursor of (±)-tetrahydropalmatine (**145**).

The optimal conditions in Sames's study were found to be similar, although $BF_3{\cdot}OEt_2$ was used as the Lewis acid. The high conversion and diastereoselectivity observed for the transformation of **146** into piperidine **147** is typical for a range

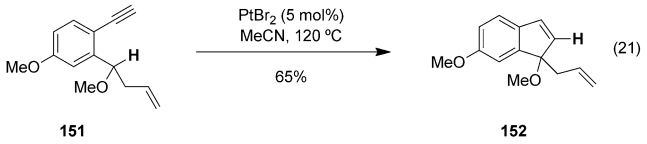


Scheme 20. Lewis acid catalyzed synthesis of piperidines through benzylic C–H functionalization.

of alkyl-linked substrates bearing at least one substituent to favor ring closure. Several substrates even cyclized at room temperature under the powerful activation of $BF_3{\cdot}OEt_2$.

3.5. Alkynes as Hydride Acceptors

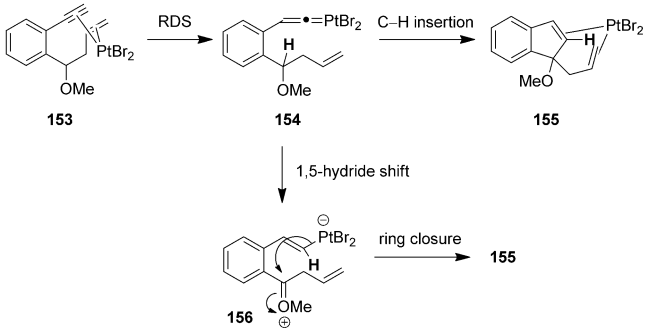
In 2006, Yamamoto and co-workers reported the transformation shown in Equation (21).[65] Using $PtBr_2$ as a catalyst



in MeCN, the authors reported the formation of indene derivatives from *o*-alkylphenylacetylenes, such as **152** from **151**. Other substrates were often accompanied by minor amounts of a vinylnaphthalene side product. Deuteration studies show the transfer of the hydrogen shown in bold face in **151** with complete specificity for a related substrate.

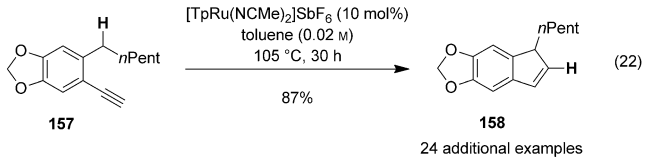
Curiously, although the graphical abstract of this paper depicts a mechanism based on a 1,5-hydride shift on Pt–vinylidine **154**, the text of the abstract and computational study describe a different sequence of events (Scheme 21). After (rate-determining) formation of **154**, a transition state was located leading directly to the product–$PtBr_2$ complex **155** by C–H insertion. The mechanism of the 1,5-hydride shift (shown in the article's abstract and in the lower half of Scheme 21) was apparently not investigated under the same computational system. Nonetheless, direct C–H insertion remains an important potential mechanism for such reactions involving the activation of terminal alkynes by transition metals that has, perhaps understandably, not been evaluated by subsequent work.

Liu and co-workers reported a related catalytic indene synthesis from (*o*-alkyl)alkynylarenes, using a cationic Ru^{II} complex as the catalyst [Eq. (22)].[66] Arene **157** could be cyclized to form the corresponding indene **158** in high yield.

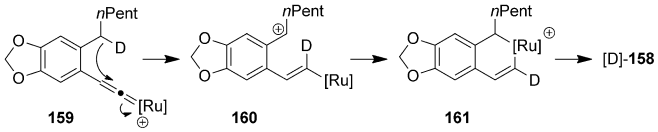


Scheme 21. Calculated mechanisms based on a Pt vinylidine insertion and alternatively a hydride shift.

Deuteration studies revealed that the benzylic hydrogen was transferred intramolecularly to the C2 position of the indene product.



The reaction proceeds by formation of a ruthenium vinylidine complex as shown in Scheme 22. The authors

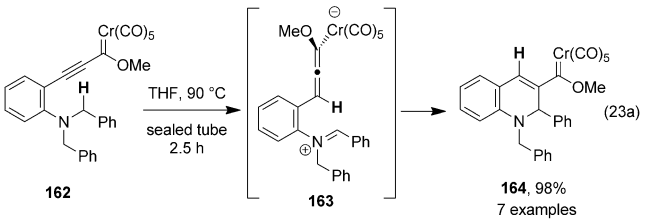


Scheme 22. Proposed hydrogen-transfer mechanism.

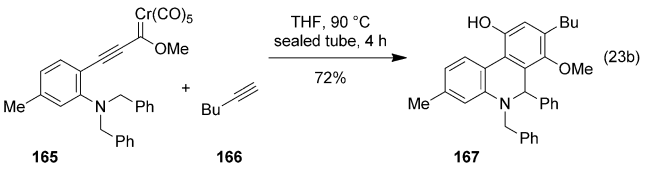
propose a sigmatropic rearrangement to account for the hydrogen transfer to form **160**, although a 1,5-hydride shift on alkylidine **159** is also possible. Reductive elimination from **161** generates the indene product and frees the catalyst. As is the case with most of these reactions that invoke a metal vinylidine, the possibility for direct C–H insertion of the carbene is not discussed but must be considered a mechanistic alternative.

In 2008, Barluenga and co-workers significantly extended this class of reactions by pairing alkyne acceptors with amine hydride donors for the first time [Eq. (23a)].[67a] Electrophilic alkynyl Fischer carbenes such as **162** underwent a 1,5-hydride shift upon heating to generate 1,2-dihydroquinolinyl carbenes **164** via zwitterionic intermediate **163**. This study is also unique in its use of Fischer carbenes as electrophilic activating groups for the acceptor moiety.

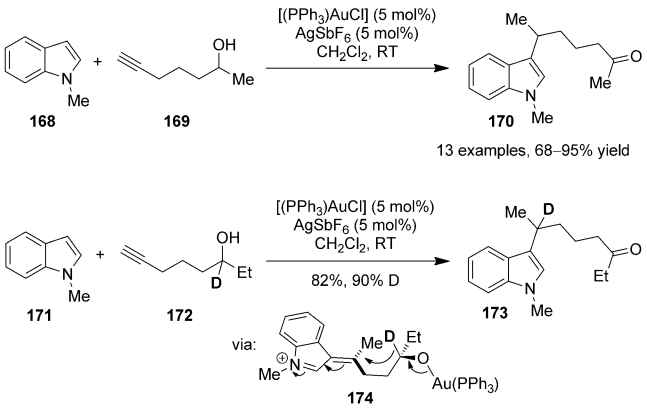
The cyclization cascade could be extended into a Dötz benzannulation in the presence of an alkyne [Eq. (23b)]. For example, the densely substituted ring-fused dihydroquinoline **167** could be obtained in high yield from **165** and 1-hexyne. DFT calculations supported the authors' proposed mechanism. Later, the same group extended this type of cascade to



include a diverse collection of termination reactions with the Fischer carbene moiety.[67b]



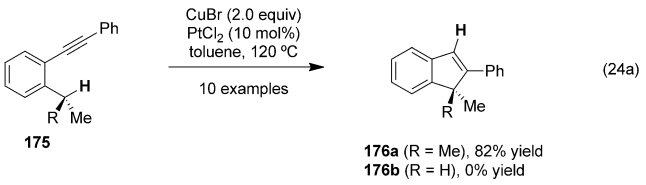
In a 2009 study, Barluenga and co-workers observed that the Au^{+}-catalyzed addition of indole **168** to alkyne **169** was accompanied by an internal redox isomerization to form saturated ketone **170** (Scheme 23).[68] This process was



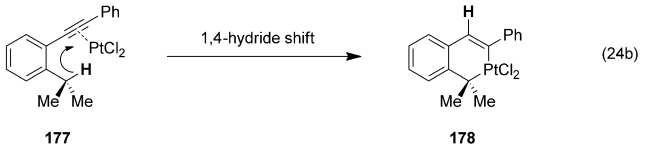
Scheme 23. Gold-catalyzed alkylation and redox isomerization of alkynols.

generalized to include substituted indole, pyrrole, and various alkynol substrates forming the desired products in excellent yields. A deuteration experiment supported the proposed mechanism: azafulvenium ion **174** undergoes a 1,4-hydride shift leading directly to the observed product **173**. It would be intriguing to determine whether this reaction is stereospecific given the proposed mechanism.

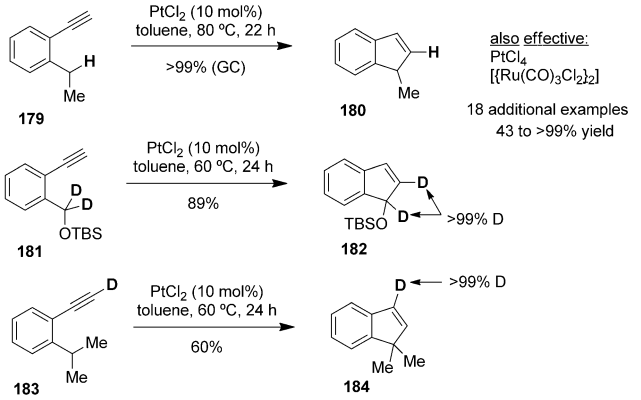
In 2009, He and co-workers were able to extend the scope of Yamamoto's system to include simple alkyl groups as hydride donors [Eq. (24a)].[69a] They found that a catalyst system combining $PtCl_2$ and excess CuBr was optimal for the formation of indene derivatives such as **175**. The reaction worked well with substrates bearing tertiary benzylic C–H bonds, but failed with secondary ones. The role of CuBr was unclear, although it was observed to suppress the dimerization of the alkyne substrates. Based on deuteration studies, a mechanism involving the formation of **178** by a 1,4-hydride



shift onto the Pt-activated alkyne in **177** was proposed [Eq. (24b)]. The possibility of the C–H insertion pathway proposed in the earlier Yamamoto work was not discussed for examples with terminal alkynes.



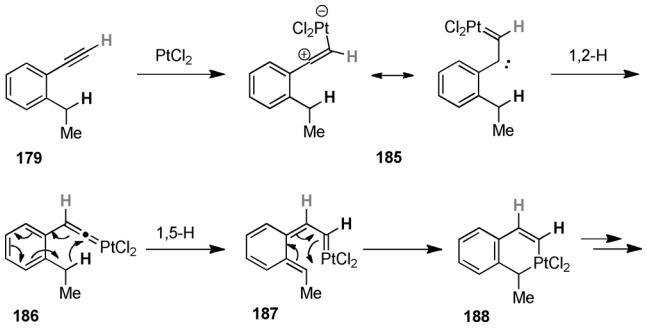
Also in 2009, Chatani and co-workers tackled a similar class of substrates in a closely related study (Scheme 24).[69b]



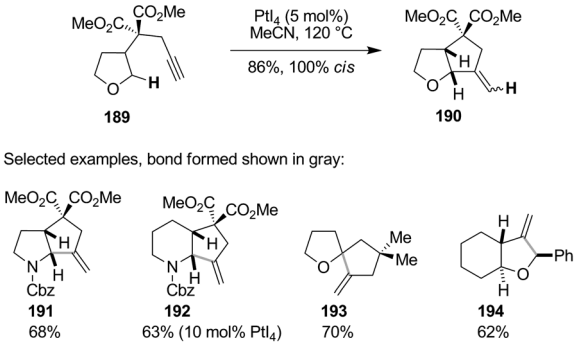
Scheme 24. Platinum-catalyzed cyclization of unactivated (2-alkylphenyl)acetylenes.

Chatani's substrates are mainly terminal alkynes, which appear to be much more reactive than He's internal alkynes. For example, $PtCl_2$ (an inferior catalyst in He's and Sames' studies) is able to effect the quantitative cyclization of **179**, which bears a less reactive secondary alkyl C–H bond as a donor moiety.

Extensive deuteration studies conclusively established the source of both olefinic protons in the products **182** and **184**. The fate of the alkyne proton in particular strongly suggests the formation of a platinum vinylidine complex through a 1,2-hydrogen shift, as had been proposed in the earlier Yamamoto study with terminal olefins. This process is illustrated in Scheme 25. Despite Yamamoto's computational evidence for a C–H insertion role for a platinum vinylidine intermediate similar to **186**, Chatani proposes a 1,5-hydrogen migration to generate dearomatized carbene **187**. A sigmatropic rearrangement was proposed to generate **188**, which can generate the observed product by reductive elimination. The mechanism proposed here is similar to the mechanism for Sames' system discussed in Scheme 27.



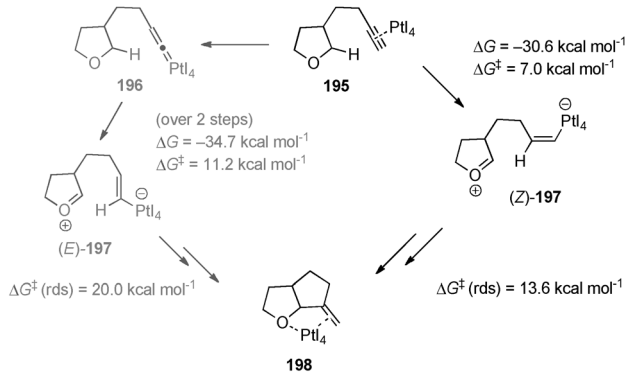
Scheme 25. Chatani's proposed mechanism involving sigmatropic rearrangements.



Scheme 26. Platinum-catalyzed cyclization of alkyne-tethered ethers and carbamates.

Concurrently, Sames and Vadola extensively investigated the use of tethered terminal alkynes as hydride acceptors with various heteroatomic donors (Scheme 26).[70a] Optimal conditions were identified using PtI_4 as the catalyst for most substrates, although a few more reactive systems benefitted from use of the less active K_2PtCl_4. Compound **189** is transformed into **190** with 100% diastereoselectivity. Other O and N hydride-donor systems were also successfully cyclized to yield **191**–**194** as single diastereomers. This work is particularly noteworthy because readily deprotectable carbamates can be used instead of the more common tertiary amine hydride donors, leading to products **191** and **192**. Deuteration studies were consistent with either a 1,5- or a 1,6-hydride shift, but could not distinguish between the two pathways.

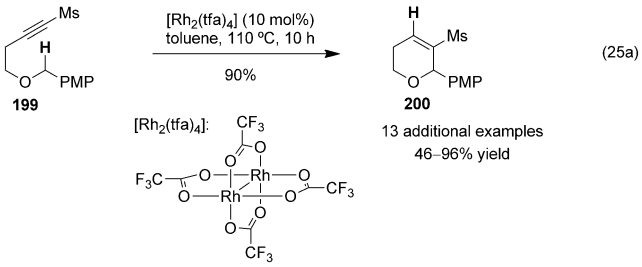
Recently, Zhao and co-workers computationally investigated the mechanism of this reaction, using DFT calculations and the simplified substrate–catalyst complex **195** as their zero point (Scheme 27).[70b] Both the 1,5- (right) and 1,6-hydride-shift (left) pathways were calculated using the B3LYP functional and IEF-PCM solvent model. The 1,5-hydride-shift step is preferred kinetically by roughly 6 kcal mol^{-1}, although the resulting intermediate (*Z*)-**197** is slightly higher in free energy than (*E*)-**197** (resulting from a 1,6-hydride shift). It turns out, however, that the rate-determining step in both pathways is the subsequent ring closure. (*E*)-**197** has a significantly higher activation energy ($\Delta G^{\neq}$) for this step than does (*Z*)-**197**, consistent with the reaction proceeding by means of a 1,5-hydride shift. This study elegantly illustrates



Scheme 27. Computed mechanisms (B3LYP, IEF-PCM solvent model): 1,5-hydride shift leads to more kinetically facile ring closure.

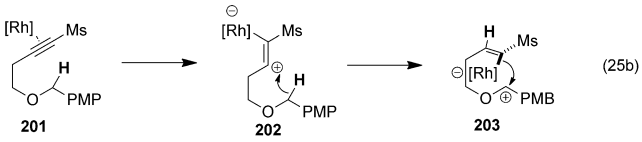
the importance of considering the geometrical and structural requirements of the hydride-shift process when planning subsequent ring-closure reactions.

Also in 2009, Urabe and co-workers extended the scope of the alkyne-acceptor system [Eq. (25a)].[71] Heating **199** in the presence of catalytic $[Rh_2(tfa)_4]$ led to the formation of **200** in excellent yield. Deuterium labeling indicated the transfer of the hydrogen atom shown in bold face.



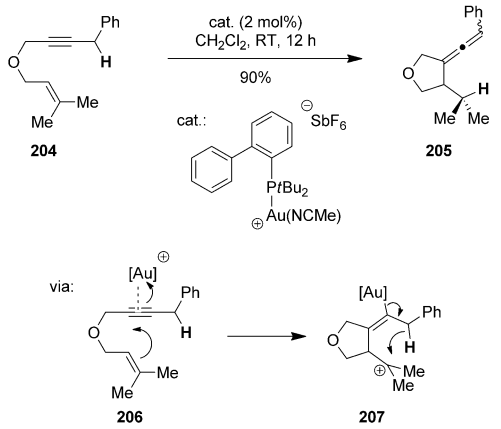
(25a)

While a strongly activated alkyne (with a methanesulfonyl (Ms) group) is a necessary component, the authors' system tolerates simple alkyl linkers between the ether and the alkyne. Previous alkyne systems required either an aromatic linker or an alkyl chain containing a disubstituted carbon. The reaction was proposed to occur by the formation of zwitterion **202** from the initial rhodium alkyne complex **201** [Eq. (25b)]. A 1,5-hydride shift generates **203**, which cyclizes to form the observed dihydropyran product.



(25b)

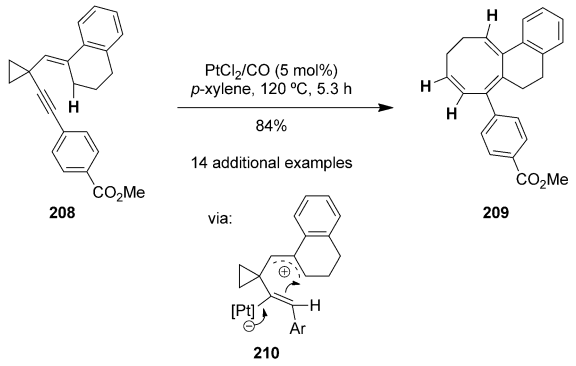
Taking alkyne–gold systems in a new direction, a team led by Malacria, Gandon, and Fensterbank reported the cyclization of ether-linked enynes **204** in 2010 (Scheme 28).[72] A cationic phosphine–gold complex served as the catalyst and allene-substituted tetrahydrofuran **205** was obtained in excellent yield. Deuteration experiments uncovered the hydrogen transfer shown in bold face, and ruled out intermolecular



Scheme 28. Formation of exocyclic allenes by a cascade reaction.

scrambling. The proposed mechanism involves an initial enyne cyclization to generate the cationic gold–vinyl complex **207** from **206**. A 1,5-hydride shift initiated at the Au–C bond then generates the observed allene product. This cascade is unusual because the cyclization precedes the hydride shift. The hydride shift itself can be considered an umpolung version of the more common proto-deauration mechanism by which Au^+-catalyzed cyclizations are typically terminated.

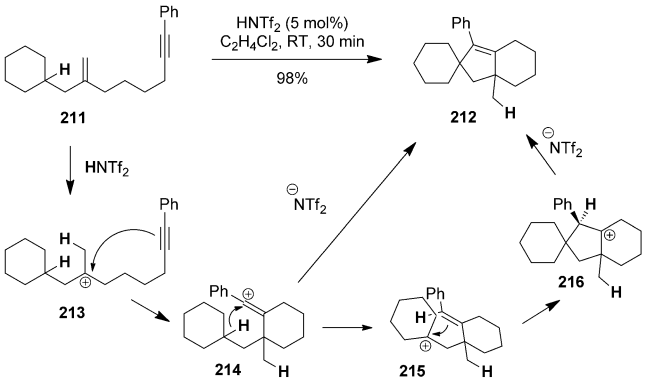
Liu and co-workers were able to extend the level of complexity generated by using an alkyne as the hydride acceptor in their 2010 synthesis of ring-fused cyclooctatrienes (Scheme 29).[73] Heating 1,4-enyne **208** in the presence of



Scheme 29. Hydride transfer to an alkyne followed by ring expansion.

catalytic $PtCl_2$/CO led to the formation of **209** in high yield. The combination of $PtCl_2$ and CO was essential, as other known catalytic systems based on Pt, Pt/Cu, and Au resulted in low conversion or mixtures of products. A range of substrates with different electron-donating and -withdrawing substituents were also cyclized in similarly high yields. A substrate labeled with deuterium at the allylic position generated products with deuterium distributed evenly at the three vinylic positions of the cyclooctatriene ring. The proposed mechanism begins with the formation of the Pt–alkyne complex of **208**. After a 1,5-hydride shift to form zwitterionic complex **210**, the Pt–vinyl fragment attacks the allyl cation to generate a neutral carbene complex. Further ring expansion over several additional steps affords the observed product. The role of CO in the catalytic system is not specified, but it possibly serves to stabilize the platinum complex in the nonpolar solvent at high temperatures used.

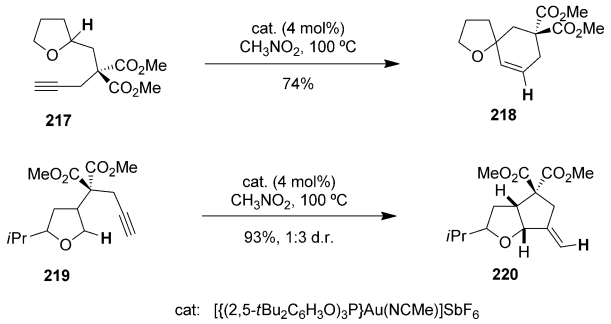
In 2010, Jin, Yamamoto, and co-workers found that unactivated enynes could be cyclized in moderate to excellent yield using catalytic HOTf or $HNTf_2$ (Scheme 30).[74] The



Scheme 30. Brønsted acid catalyzed alkyl C–H functionalization.

reaction is initiated by the protonation of alkene **211** with $HNTf_2$ to form **213**, followed by cation—π cyclization to form **214**. At this point, the authors favor a concerted mechanism in which NTf_2^- coordinates to the vinyl cation and initiates a cyclization by deprotonating the methine C–H bond. This step would lead directly to the observed product **212**. An alternative mechanism was also proposed where **214** would undergo a 1,5-hydride shift to form carbocation **215**. An additional cation—π cyclization, followed by deprotonation of **217** would generate the product. The deprotonation event in this mechanism would be decidedly more feasible in terms of pK_a, although the novel concerted mechanism also proposed by the authors could indeed provide additional stabilization. A computational comparison of the mechanisms would be a worthy endeavor.

A team lead by Gagosz extensively investigated gold-catalyzed cyclizations of ether-alkyne systems bearing both terminal and internal alkynes in 2010 (Scheme 31).[75] They

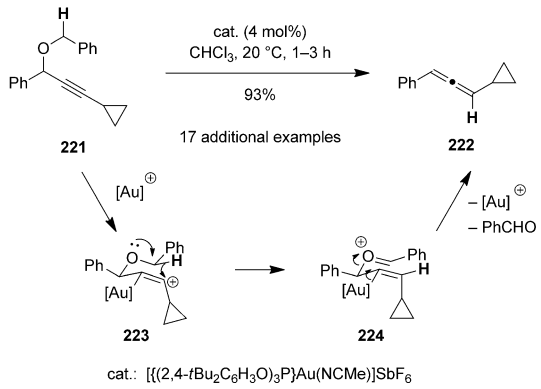


Scheme 31. Gold(I)-catalyzed cyclization of alkyne-tethered ethers.

initially targeted substrate **217** and found that the previously reported Pt catalysts for ether-alkyne systems were ineffective, as were simple Au salts. The combination of bulky phosphine and phosphinite-ligated gold catalysts and nitromethane solvent proved crucial for the efficient transformation of **217** into the spirocyclic ether **218**. Based on deuteration studies, the authors suggest a 1,5-hydride shift onto the Au-activated alkyne in their proposed mechanism.

In substrates with a terminal alkyne, the acetylenic proton does not undergo a 1,2-shift, which excludes the formation of a gold–vinylidine intermediate. A wide range of substrates with various substitution patterns and geometries were successfully cyclized in this system, such as **219**. An electron-withdrawing substituent is required on internal alkynes.

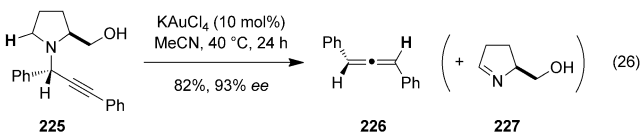
Further work reported by the same group in 2010 extended this methodology to include a synthesis of allenes from benzylic propargyl ethers triggered by a 1,5-hydride shift.[76] In a typical example (Scheme 32), **221** is transformed



Scheme 32. Catalytic synthesis of allenes using a tethered hydride donor.

into allene **222** under very mild conditions in excellent yield using the group's cationic gold–phosphinite catalyst. The reaction generates ester, ether, and aryl-substituted allenes in generally excellent yield. In designing this reaction, the authors envisioned a 1,5-hydride shift from the benzylic position of initial adduct **223** resulting in the formation of oxonium cation **224**, which bears the now familiar gold vinyl fragment. Loss of benzaldehyde from **224** leads to formation of the product and regenerates the cationic gold catalyst. Deuteration experiments supported this proposal. Transfer of chirality was not addressed in this initial communication.

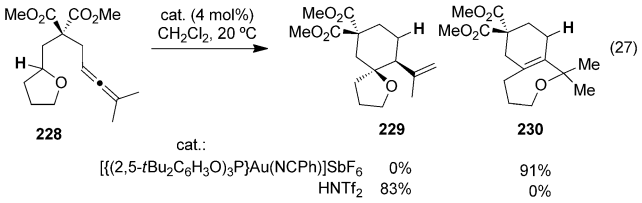
Prior to Gagosz's synthesis of allenes from benzylic propargyl ethers, the related formation of allenes from propargylic amines was studied by a number of groups.[77] Based on the seminal findings of Nakamura and co-workers, who disclosed the first examples of this reaction,[77a] Che et al. developed an asymmetric gold-catalyzed synthesis of allenes from the corresponding propargylic amines [e.g. **225**→**226**, Eq. (26)].[77b] The proposed mechanism involves activation of the alkyne by the gold catalyst, followed by a 1,5-hydride shift. Subsequent elimination of imine **227** results in formation of highly enantioenriched allenes, illustrating an efficient



(26)

transfer of chirality. While the initial study was limited to the enantioselective formation of diaryl allenes, these restrictions were overcome in subsequent work. Silver and zinc catalysts were also shown to catalyze this transformation.[77]

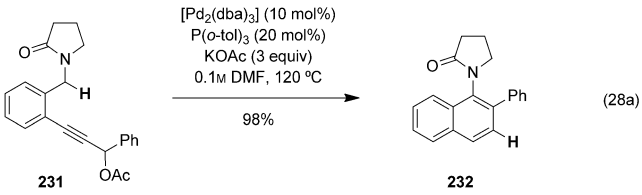
In 2011, Gagosz and Bolte successfully utilized allenes as hydride acceptors in the cyclization of **228** and related ether donors [Eq. (27)].[78] Catalytic amounts of $HNTf_2$ were used



(27)

and spirocyclic ether **229** was obtained in excellent yield at 20 °C, whereas the cationic gold complex used in earlier studies induced an additional rearrangement to form bicyclic ether **230**. Deuteration studies support a 1,5-hydride shift mechanism similar to that of the related alkyne systems.

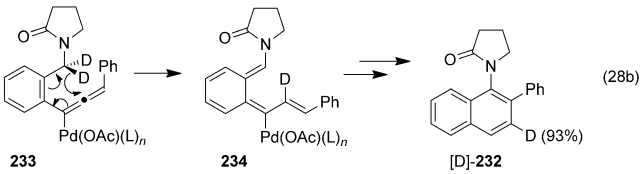
Liang and co-workers further extended the scope of alkyne-acceptor systems in their 2011 palladium-catalyzed synthesis of amidonaphthalenes [Eq. (28a)].[79] In this trans-



(28a)

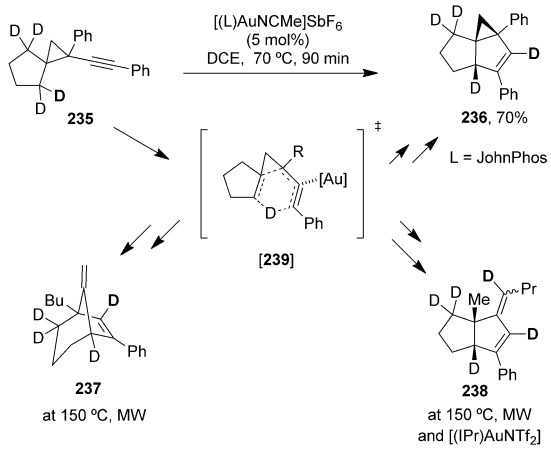
formation, **231** rearranges with concurrent loss of acetate to form substituted naphthalene **232** in excellent yield. Yields are highly dependent on the electronic properties of the propargylic substituent. Surprisingly, amides and sulfamides react much more readily than amines in this process, despite being poorer hydride donors.

The authors favor a sigmatropic 1,5-hydrogen shift on intermediate **233**, which would transfer a benzylic deuteride to the position determined in the labeling experiment shown in Equation (28b).



(28b)

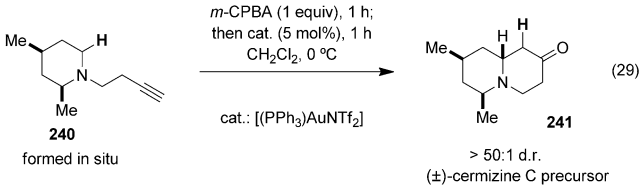
Many of the strategies for activation discussed above seek to modify the electronics of the alkyne to increase its hydride-



Scheme 33. Diverse C–H functionalization cascades of a sterically constrained alkyne.

acceptor ability. Barluenga, Ballesteros, and co-workers employed structural constraints in their 2012 study to favor the hydride-shift step in electronically unactivated systems (Scheme 33).[80] When the cyclopropane-linked alkyne **235** is heated in the presence of a cationic (Johnphos)Au catalyst, **236** is formed in good yield after a net functionalization of an alkane C–H bond. Under slightly different conditions, two other structural classes of products can be formed (**237** and **238**). The cyclopropane linker serves two purposes: to bring the methylene C–H bond closer to the alkyne and to stabilize the transition state for the 1,5-hydride transfer ([**239**]) In [**239**] the hydride transfer occurs with concurrent opening of the tetrasubstituted cyclopropane, alleviating ring strain. [**239**] was proposed to be a common transition state on the mechanistic pathway to all three classes of products. A detailed mechanistic discussion on the divergent reaction pathways was provided.

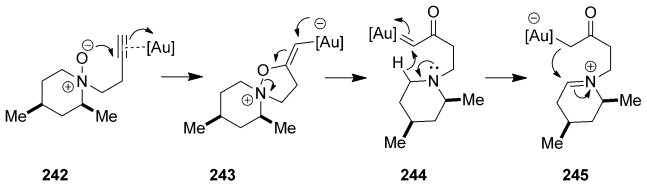
Building on their previous discovery of the generation of α-oxo gold carbenes through oxidation by tethered N-oxides, Zhang and co-workers designed the hydride-shift-triggered construction of piperidinones shown in Equation (29).[81a] The



(29)

usefulness of this transformation is demonstrated by an elegant total synthesis of (±)-cermizine C. The readily available alkynyl piperidine **240** was oxidized to the corresponding N-oxide **242** by *m*-CPBA which subsequently rearranged in the presence of a cationic gold(I) complex to generate precursor **241**. Deoxygenation of **241** provided (±)-cermizine C.

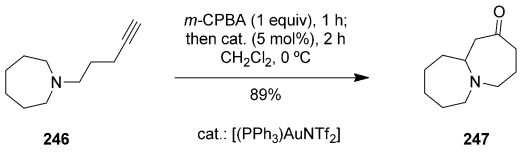
Initially, the authors proposed the mechanism depicted in Scheme 34. Transfer of the oxygen atom to the alkyne was proposed to occur by a Au^I-mediated route through inter-



Scheme 34. Proposed 1,5-hydride shift onto a gold carbene acceptor.

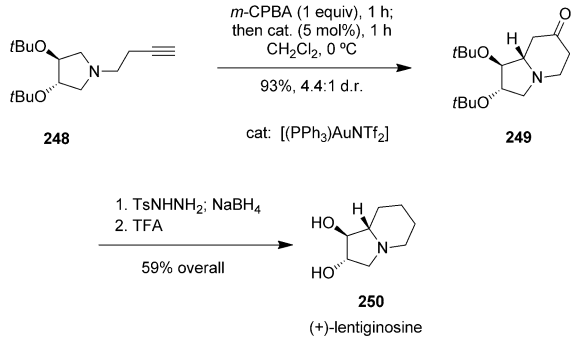
mediate **243** to form the α-oxo gold carbene **244**. This key intermediate undergoes a 1,6-hydride shift from the amine to the electrophilic gold carbene, forming zwitterion **245**. Intermediate **245** then cyclizes stereospecifically to form **241** in good yield (63% including the formation of **240** by N-alkylation).

Zhang also reported that homologous alkynyl amines are also viable substrates for the same transformation, allowing for the generation of larger-ring analogues such as **247** [Eq. (30)].[81b] Generally, the azepinones are obtained in



(30)

higher yield than the corresponding piperidinones, which would presumably reflect the widely observed trend in hydride-donor ability of the parent amines. However, the mechanism proposed above would require a less-common 1,7-hydride shift to account for the formation of seven-membered rings. Later, this methodology was applied to the stereoselective total synthesis of the natural product (+)-lentiginosine (**250**), a bioactive azasugar.[81c] As shown in Scheme 35,

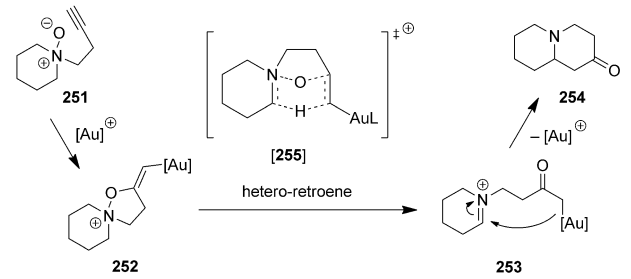


Scheme 35. Total synthesis of (+)-lentiginosine.

readily available butynylpyrrolidine **248** is subjected to a protocol similar to that in the cermizine synthesis. *tert*-Butyl protecting groups were found to give the highest level of diastereoselectivity for the formation of **249**, although the minor diastereomer could be carried through to afford the corresponding epimer of the natural product.

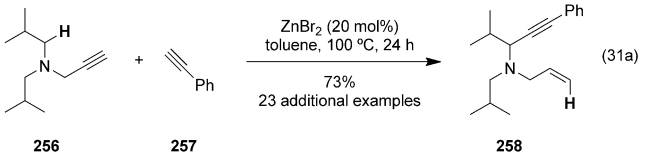
In 2012, Gong and co-workers showed that a similar amine-alkyne system can be cyclized in a related process

using 2,6-dichloropyridine *N*-oxide and MsOH.[81d] As the key Au–carbene intermediates cannot form here, it appears that this type of cyclization may occur by an alternative mechanism. Concurrently, Zhang and Houk presented a revised mechanism for the Au-catalyzed system based on both DFT calculations and deuterium-labeling studies on an original substrate in Zhang's 2009 study (Scheme 36).[81e] Accordingly, the internal redox step occurs by the unusual hetero-retroene transition state [**255**].

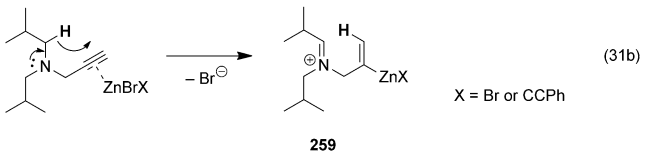


Scheme 36. Concerted C–H functionalization/N–O cleavage mechanism.

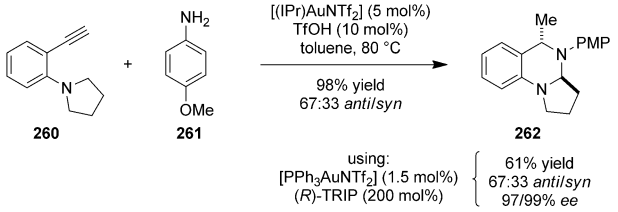
In 2012, Sugiishi and Nakamura reported an interesting zinc-catalyzed cross-dehydrogenative coupling of alkynes with amines in which a tethered alkyne served as the internal oxidant in a 1,5-hydride shift [Eq. (31a)].[82] When a bulky dialkyl propargyl amine such as **256** and phenylacetylene were heated in the presence of catalytic $ZnBr_2$, the α-alkynylated *N*-allylamine **258** was obtained in good yield.



The hydride-shift step was proposed to occur by Zn^{2+} activation of the tethered alkyne π system, generating allyliminium **259** from **256** [Eq. (31b)]. Similar to the formation of allenes from propargylic amines discussed above [Eq. 26)],[77] this work is notable for demonstrating that relatively mild, non-noble-metal Lewis acids are capable of activating terminal alkynes for hydride-transfer cascades.



Until very recently, the imine derivatives required for hydride-shift cyclizations to form aminals were generated by means of a condensation of an amine with an appropriate aminoaldehyde. In 2013, Gong and co-workers discovered an alternative approach: the generation of imine hydride acceptors by the gold-catalyzed Markovnikov hydroamination of alkynes (Scheme 37).[83] This allowed the authors to cyclize

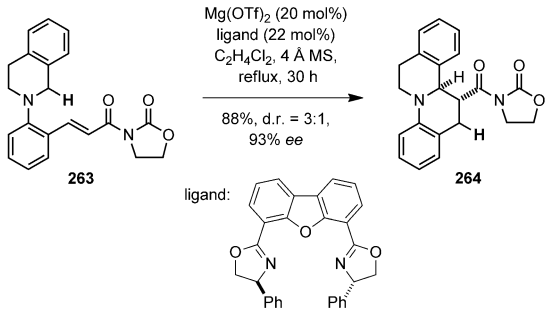


Scheme 37. Tandem hydroamination/*tert*-amino effect cyclization.

the imine derived from **260** and *p*-methoxyaniline to form **262**. The gold carbene complex [(IPr)$AuNTf_2$] and TfOH were found to be optimal cocatalysts for the reaction cascade. In exciting preliminary studies, the authors also found that this reaction could be carried out in a highly enantioselective manner, although two equivalents of an expensive chiral phosphoric acid are required. Interestingly, the diastereoselectivity for a particular substrate appears to be independent of the catalyst or *ee*. This suggests that the enantioselectivity may result from the ring-closure step, rather than the hydride-shift step as was the case in Reinhoudt[19b] and Akyiama's[86] (Scheme 39) seminal mechanistic studies of related systems. An enantioselectivity-determining hydride-transfer step would set both stereocenters at once (by means of both point and helical chirality), and presumably lead to at least slightly different d.r. values for different catalysts.

3.6. Catalytic Enantioselective C–H Functionalizations

In 2009, our group reported the first successful catalytic enantioselective C–H functionalization through intramolecular hydride shift and ring closure (Scheme 38).[84] Earlier

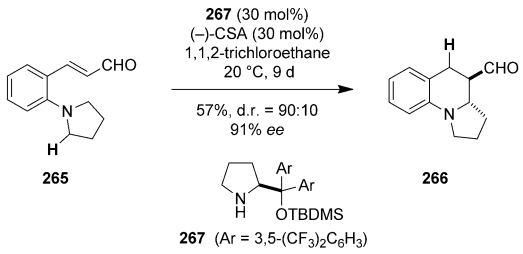


Scheme 38. Initial example of a catalytic enantioselective variant.

attempts (Scheme 14) were hindered by the reversibility of the ring-closure step in the presence of strong Lewis acid catalysts. We reasoned that the propensity for the undesired reverse reaction could potentially be reduced through the use of only one activating group on the hydride-acceptor moiety. An oxazolidinone-bearing substrate (e.g., **263**) proved suitable for this purpose. When this material was heated with a chiral magnesium(II) DBFox complex in refluxing 1,2-dichloroethane, product **264** was obtained in good yield and

excellent enantioselectivity albeit moderate diastereoselectivity.

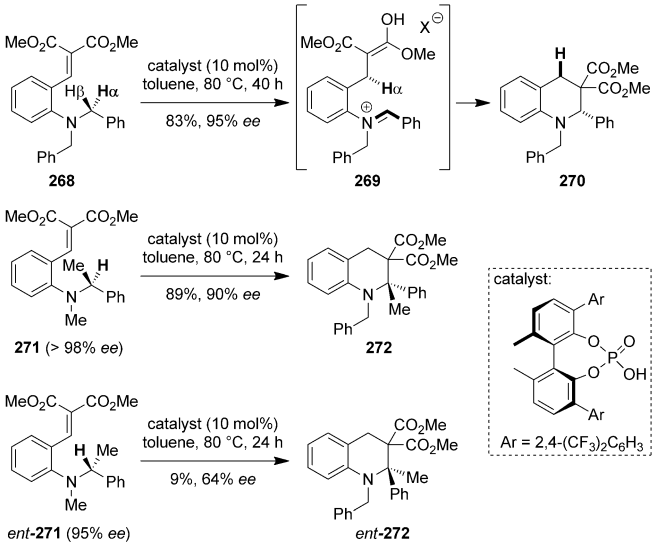
Kim and co-workers reported the first organocatalytic enantioselective 1,5-hydride shift/cyclization cascade by employing an iminium-catalyzed pathway [Eq. (32)].[85] Ter-



(32)

tiary aminobenzaldehydes were converted to ring-fused tetrahydroquinolines in excellent enantioselectivities and good diastereoselectivities (e.g., **265**→**266**). Although the reaction times are relatively long, it is impressive that these rearrangements occur at room temperature despite the presence of only one activating group on the hydride-acceptor moiety. The nature of the acid additive had a profound effect on the enantioselectivity of the process, with (−)-camphorsulfonic acid (CSA) providing the best results.

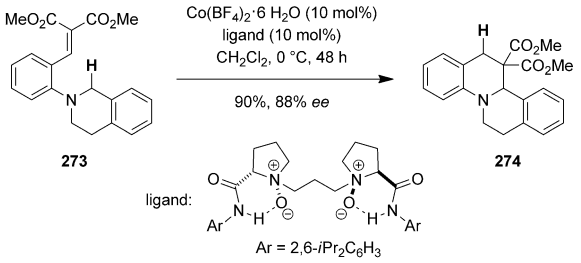
Another asymmetric variant of an intramolecular redox process was reported by Akiyama et al. (Scheme 39).[86] By



Scheme 39. Phosphoric acid catalyzed asymmetric variant.

employing a chiral phosphoric acid based strategy, substrates such as **268** were transformed to the corresponding tetrahydroquinolines **270** with excellent yields and enantioselectivities. However, substrates possessing cyclic amine moieties such as isoquinoline or pyrrolidine gave low enantioselectivities. Important insights into the enantioselectivity-determining steps of this transformation were obtained through a series of detailed studies. Interestingly, the enantioselectivity of the reaction is not determined during the ring-closure step but rather by selective activation of one of the two enantiotopic protons (H_α vs. H_β) of the starting material. This is in accord with studies by Reinhoudt et al.,[19b] who established that chiral nonracemic substrates undergo stereospecific rearrangements (memory of chirality). Cationic intermediate **269** adopts a helically chiral conformation that preserves the stereochemical integrity of this intermediate. Further support for this notion was obtained from an evaluation in which highly enantioenriched **271** served as the starting material. Under reaction conditions that were successful for achiral substrates, tetrahydroquinoline **272** was obtained in good yield and with 90% *ee*. In the mismatched scenario, *ent*-**271** was treated with catalyst under identical conditions, leading to formation of *ent*-**272** in only 9% yield and with 64% *ee*.

Feng and co-workers published a study that details the catalytic enantioselective rearrangement of alkylidene malonates such as **273** [Eq. (33)].[87a] When a chiral cobalt(II) catalyst was employed, these substrates could be transformed into the corresponding products (e.g., **274**) in excellent yields and high enantioselectivities. Notably, the reactions proceeded readily at temperatures as low as 0 °C.



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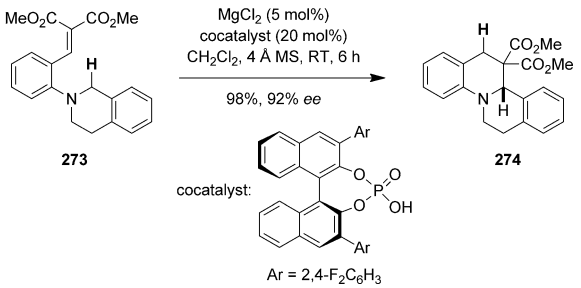
Luo et al. subsequently improved this process by applying a combination of magnesium(II) chloride and a chiral phosphoric acid cocatalyst [Eq. (34)].[87b] A 1:4 ratio of the two

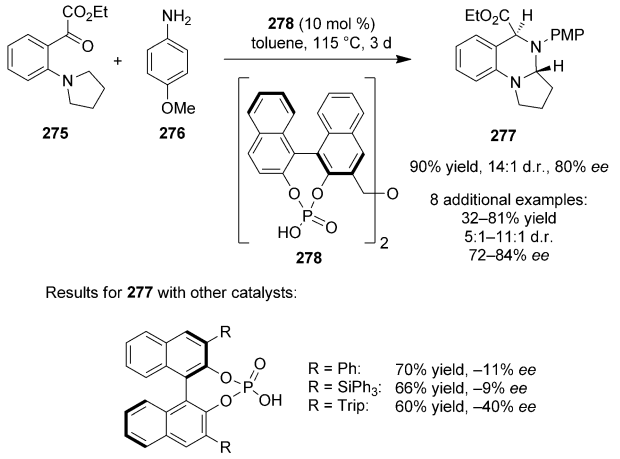


(34)

catalyst components was found to give optimal results with regard to enantioselectivity. Interestingly, the corresponding chiral magnesium bisphosphate, while catalytically active, gave rise to racemic product. In accord with the findings by Akiyama et al., deuterium-labeling studies revealed that the 1,5-hydride shift occurs suprafacially and that the enantioselectivity-determining step is hydride transfer rather than ring closure. Further support for this mechanistic feature was obtained from a detailed computational investigation of this

reaction. The active catalyst was determined to be a 1:1 complex of magnesium(II) chloride and the chiral phosphoric acid.

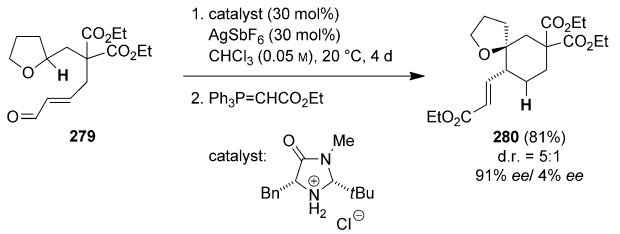
During efforts to develop an enantioselective variant of the redox-neutral aminal formation reaction reported by Akiyama and Seidel,[52] Gong and co-workers introduced (2-aminophenyl)ketoesters as a new donor–acceptor platform (Scheme 40).[88] The reaction of **275** with *p*-anisidine (**276**) to



Scheme 40. Enantioselective cyclization of α-imino esters.

form aminal **277** is proposed to occur by the same mechanism as the analogous condensation with 2-aminobenzaldehydes. Use of bisphosphoric acid **278** as the catalyst afforded **277** in high yield, d.r., and *ee* after 3 days at elevated temperature. Use of monophosphoric acids in place of **278** caused a significant drop in yield and *ee*. The highest *ee* value achieved was 84%, although this implies that catalyst **278** is in fact quite selective given the high reaction temperature.

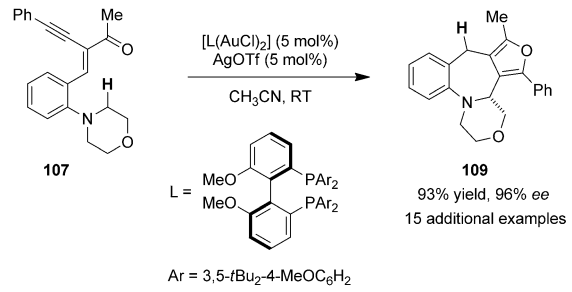
Inspired by the work of the Sames and Kim groups, Tu and co-workers developed a catalytic enantioselective approach to the synthesis of spirocyclic ethers (Scheme 41).[89] Using an



Scheme 41. Enantioselective formation of spirocyclic ethers.

iminium catalysis approach, the racemic compound **279** was successfully converted to **280** (two steps) in good yield and diastereoselectivity and excellent enantioselectivity for the major diastereomer. The addition of silver hexafluoroantimonate was crucial, as no reaction was observed in the absence of this additive. The exchange of chloride for hexafluoroantimonate serves to increase the electrophilicity of the iminium ion, increasing its propensity to act as a hydride acceptor. Interestingly, although racemic starting materials were employed, excellent yields of highly enantioenriched products were obtained in many cases. This seems to suggest that the enantioselectivity of the reaction is determined during the ring-closure step or possibly by a dynamic kinetic resolution process.

In further development of their reaction described in Equation (14b), Zhang and co-workers reported an enantioselective variant using cationic diphosphine digold(I) complexes as catalysts (Scheme 42).[90] Treatment of alkyne-

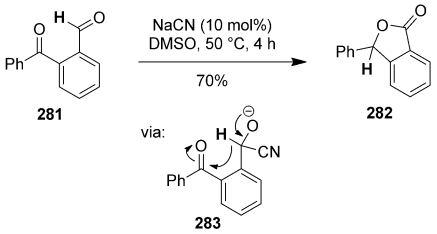


Scheme 42. Enantioselective gold(I)-catalyzed process.

ketone acceptor substrate **107** with the $(AuCl)_2$ precatalyst and a cocatalytic amount of AgOTf or $AgBF_4$ results in the formation of furan-fused benzazepine **109** in high yield and excellent enantioselectivity. The reactions take place at room temperature and are generally complete in less than 24 h when AgOTf is used.

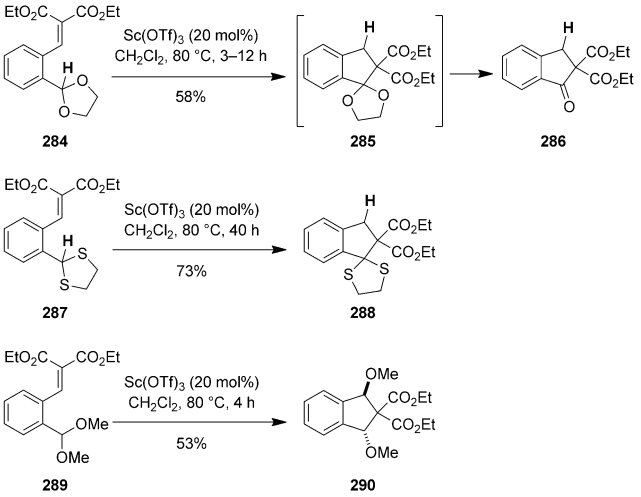
3.7. Less Common Hydride Shifts and Substrates

A rare example of a cascade reaction initiated by a 1,4-hydride transfer was reported by Schmalz et al. (Scheme 43).[91] The transformation of ketoaldehydes such



Scheme 43. Lactone formation by 1,4-hydride transfer.

as **281** to lactones **282** proceeds under catalysis of sodium cyanide by a Cannizarro–Tishchenko-type mechanism involving intermediate **283**. The process occurs under mild conditions, is applicable to a range of aromatic ketoaldehydes, and was applied in a synthesis of the natural product pestalalactone. Interestingly, the reaction can also be performed under photochemical conditions in the absence of

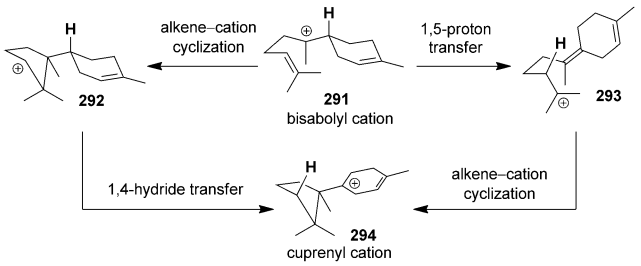


Scheme 44. (Thio)acetals as donors in 1,4-hydride-shift reactions.

a catalyst. In this case a different mechanism is thought to be operative.

Alajarin, Vidal, and co-workers reported an interesting 1,4-hydride shift/ring-closure reaction in which (thio)acetals act as hydride donors (Scheme 44).[92] Scandium triflate was identified as an efficient catalyst for these transformations. In the case of acetal starting material **284**, the initial rearrangement product **285** was not isolated as acetal hydrolysis was observed under the reaction conditions to directly give product **286**. In contrast, the thioacetal product **288** was found to be stable under the reaction conditions. Interestingly, in the case of acyclic acetal **289**, a methoxy transfer rather than a hydride transfer was observed resulting in product **290**. The analogous reaction was also observed for acyclic thioacetals.

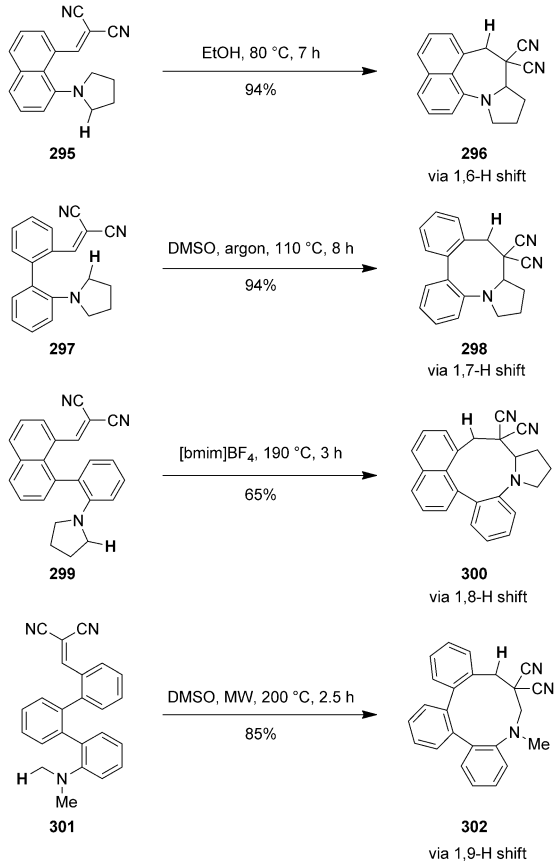
An excellent study by Tantillo et al. nicely demonstrates that in specific cases, alternate reaction pathways lower in energy may be available for reactions that involve apparent hydride-transfer steps (Scheme 45).[93] In the course of the



Scheme 45. 1,5-Proton transfer as a lower energy alternative to a 1,4-hydride shift.

transformation of farnesyl diphosphate to trichodiene, it is generally accepted that bisabolyl cation (**291**) rearranges to cuprenyl cation (**294**). A pathway via **292** with subsequent 1,4-hydride transfer to give **294** had previously been invoked. However, no energy minimum could be located for **292** as its formation would be accompanied by an asynchronous but concerted 1,2-methyl shift to generate another tertiary carbocation (not shown). The lowest energy pathway connecting **291** and **294** was in fact shown to proceed by means of a 1,5-proton transfer via **293**, followed by an alkene–cation cyclization.

In a series of publications, Mátyus and co-workers reported remarkable extensions of the *tert*-amino effect that allow for the synthesis of medium-size rings which would be difficult to prepare by other methods (Scheme 46).[94] The

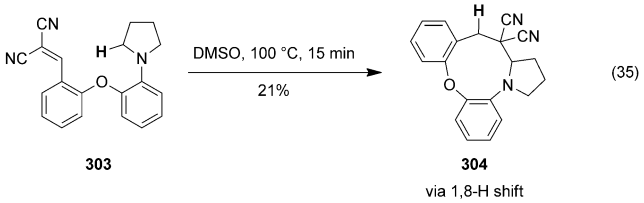


Scheme 46. Synthesis of medium-size rings through hydride transfer.

length of the linker between the hydride donor and acceptor sites was varied systematically by addition of sp^2-hybridized carbons. While the starting materials displayed a range of reactivities, good to excellent yields of medium-size rings were obtained in many instances. Although alternate reaction pathways cannot be ruled out in all cases, the formation of seven- to ten-membered rings is consistent with 1,6-, 1,7-, 1,8-, and 1,9-hydride-transfer processes. In the case of the dimethylamine analogue of **295**, the authors demonstrated through deuterium-labeling experiments that hydride transfer occurs intramolecularly in what appears to be the rate-limiting step of this reaction.

Another rare example of an apparent 1,8-hydride transfer with ultimate formation of a nine-membered ring was reported by Mátyus and co-workers [Eq. (35)]. Brief heating of diaryl ether **303** in DMSO resulted in the formation of **304**

which was characterized by X-ray crystallography. The relatively low yield was attributed to product instability.[95]



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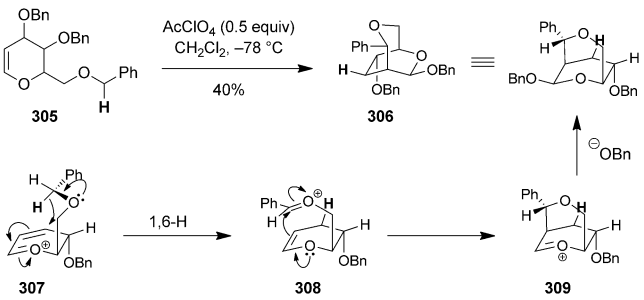
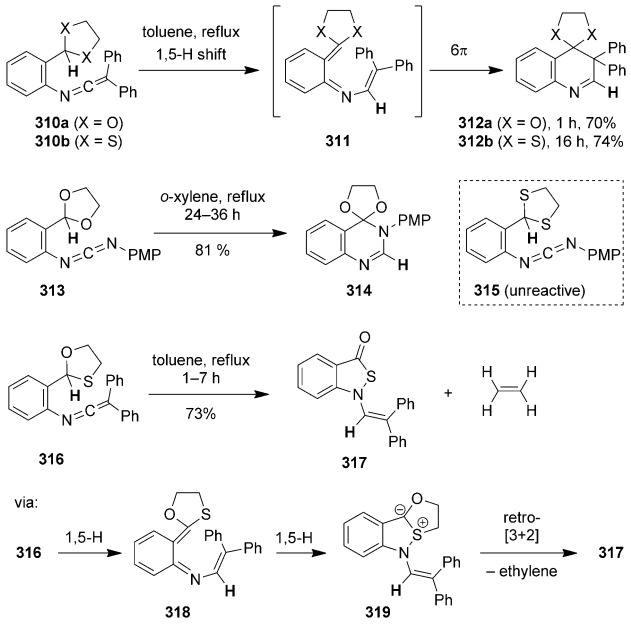


Scheme 47. Formation of a bicyclic compound through 1,6-hydride transfer.

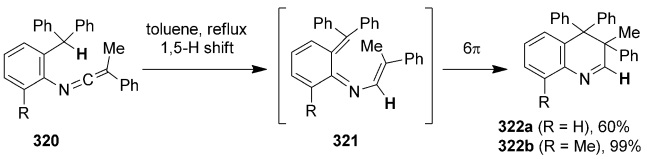


Scheme 48. Redox transformations of 1,3-dioxolanes, dithiolanes, and oxothiolanes.

A remarkable rearrangement of a glycal was reported by Lehmann, Steel, and co-workers (Scheme 47).[96] When glycal **305** was exposed to acetyl perchlorate at low temperatures, the bicyclic compound **306** was observed as the major product in place of the expected glycal dimer. This finding was rationalized by the authors as follows: The action of acetyl perchlorate on **305** initially leads to the formation of oxocarbenium ion **307** by elimination of benzyloxide anion. Subsequent 1,6-hydride transfer results in oxocarbenium ion **308** which ring-closes to bicyclic oxocarbenium ion **309**. Finally, capture of **309** by benzyloxide anion results in product **306**.

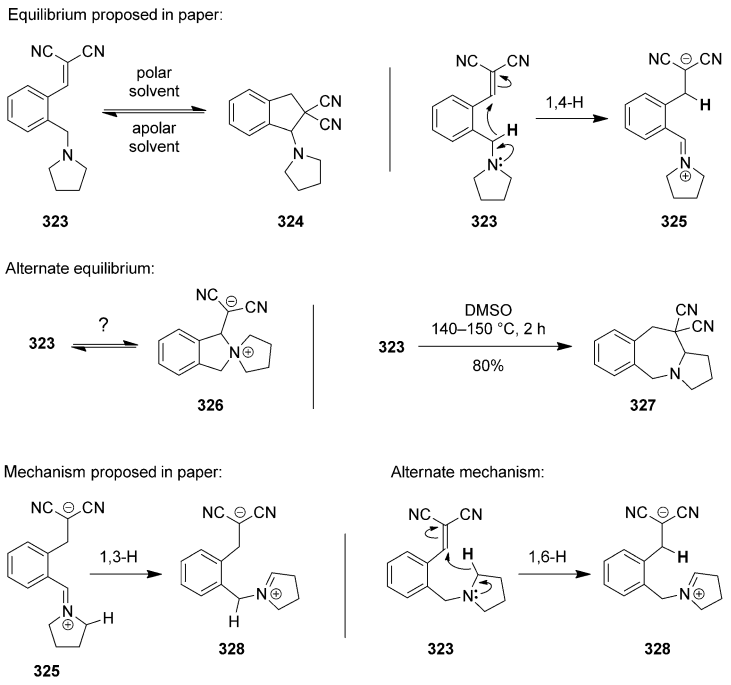
Alajarin and co-workers published a series of contributions that highlight the hydride-donating ability of 1,3-dioxolanes, dithiolanes, and oxothiolanes (Scheme 48).[97] For instance, exposure of compounds **310** to reflux in toluene led to 1,5-H-shift/6π-electrocyclization cascades to give products **312**. Interestingly, the dioxolane **310a** was shown to react substantially faster than the corresponding dithiolane **310b**. In addition to ketenimines as acceptors, carbodiimides were also shown to react (e.g. **313**→**314**). However, more forcing reaction conditions were required and the corresponding 1,3-dithiolane **315** proved unreactive under the conditions tested. Remarkably, the seemingly minor modification of using 1,3-oxothiolane **316** as the starting material resulted in an entirely different reaction outcome (formation of **317**). While compound **316** underwent the initial 1,5-H shift to form intermediate **318**, the reaction pathway then diverted. A 1,5-electrocyclization involving a lone pair on sulfur followed to provide unusual intermediate **319** which subsequently underwent a retro-[3+2] cycloaddition with loss of ethylene to give product **317** in good yield. Additional modifications to the processes outlined in Scheme 48 were also reported and all proposed reaction pathways are well supported by a series of detailed computational studies. In all cases, the initial 1,5-H shift was shown to be the rate-limiting step.

As an interesting variation, Alajarin, Vidal, and co-workers also investigated the use of triarylmethane units as hydride donors (Scheme 49).[98] In analogy to the rearrangements of 1,3-dioxolanes and dithiolanes as outlined in Scheme 48, compounds **320** rearranged smoothly to the corresponding products **322** via intermediate **321**. Interestingly, the presence of an *ortho*-methyl group in **320** led to a dramatic increase in reaction efficiency, as this presumably leads to a greater population of the substrate conformation required for a 1,5-H shift. This is in accord with observations by Akiyama [Eq. (5)]. Replacement of the methyl group on the ketenimine for an aryl substituent had a profound effect and led to a number of other rearrangements, including those that involve a 1,5-aryl shift.



Scheme 49. Triarylmethane moieties as hydride donors.

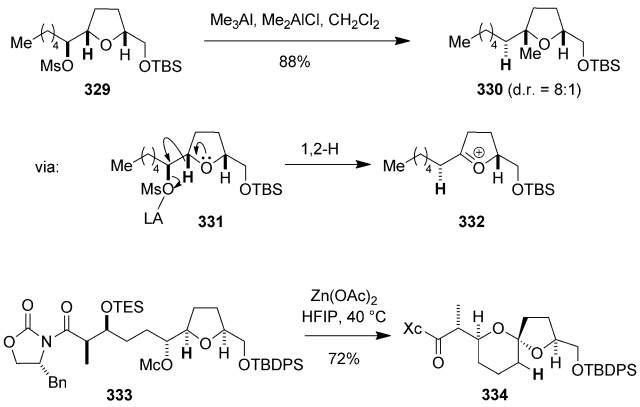
Tverdokhlebov and co-workers reported an interesting redox process that they classified as an example of a homologous *tert*-amino effect (Scheme 50).[99] Astonishingly, the starting material for this process (**323**) was reported to instantly and reversibly convert to indane **324** upon simple dissolution in a polar solvent (e.g., DMSO or acetone). This



Scheme 50. Homologous *tert*-amino effect.

isomerization is proposed to take place by means of a 1,4-hydride shift (**323**→**325**) followed by ring closure. In contrast, in $CDCl_3$ the starting material exists exclusively as **323**. Another potential equilibrium that would be consistent with solvent polarity (reversible transformation of **323** to **326**) was not discussed although zwitterionic species related to **326** were invoked by Mátyus et al.[94] Compound **323** was shown to efficiently convert to benzazepine product **327** upon heating in DMSO. The authors proposed that this transformation occurs through an unusual 1,3-hydride shift (**325**→**328**) followed by ring closure. Another perhaps more plausible mechanism which, surprisingly, was not discussed by the authors would involve a 1,6-hydride shift (**323**→**328**). An isotopic labeling study (e.g., bis-deuteration of the benzylic CH_2 group in **323**) should provide clarity as to which mechanism is in fact operative.

While 1,2-hydride-transfer reactions are occasionally observed as unexpected and undesired side reactions,[100] Donohoe and co-workers designed an elegant strategy in which a 1,2-hydride shift is followed by a C–C bond formation at the hydride-donor site (Scheme 51).[101a] Accordingly, exposure of tetrahydrofuran **329** to dimethylaluminum chloride and trimethylaluminum in dichloromethane led to the stereoselective formation of product **330** in excellent yield. This reaction occurs through Lewis acid activation of the substrate via **331** which triggers a 1,2-hydride shift with elimination of mesylate to give oxocarbenium ion **332**, a species that is subsequently trapped with an external nucleophile. Stereospecific reduction of related oxocarbenium ions with intramolecular hydride delivery from a pendant silane to furnish 2,5-*trans*-substituted tetrahydrofurans was also reported. In a further application of their general concept, Donohoe et al. reported the successful synthesis of the spirocyclic acetal **334** from linear precursor **333** as a key step in their synthesis of the ABC spiroketal ring system of pectenotoxin-4.[101b]



Scheme 51. 1,2-hydride transfer with subsequent C–C and C–O bond formation. Mc = α-chloromesylate.

4. Conclusions and Comments

In this Review, we hope to have appropriately highlighted the extensive progress made in the field of C–H functionalizations related to a hydride shift over the past decade. In this time, the functional group diversity of the substrates has vastly increased, in particular in systems that use alkynes as hydride acceptors. Enantioselective C–H functionalizations based on either enantiospecific hydride transfer or subsequent bond formation have now been developed. 1,5-Hydride shifts can now lead to the formation of seven-membered rings, and higher hydride shifts can lead to the formation of even larger ring systems. The use of deuterium-labeled substrates and computational investigations has uncovered mechanistic insights, both predicted and unexpected. Finally, we hope that some of the earlier work highlighted in Section 3.1 will inspire the further expansion of the types of molecular architecture that can be prepared under this collective mechanism.

As is evident by some of the proposed mechanisms reviewed here, there is still potential ambiguity with regard to whether some reactions involve a hydride shift, a proton abstraction, or a sigmatropic rearrangement.[102] Some of these distinctions seem hard to resolve experimentally, and one would hope to see more computational investigations in the future. There does also seem to be some need for additional mechanistic studies in reactions using alkynes as acceptors and noble-metal catalysts. We note that at least three different mechanisms are proposed for a very similar set of substrates in this area. The possibility that some of the reactions using alkynes as hydride acceptors actually proceed through direct C–H insertion was discussed in Section 3.5. Interestingly, it appears that the converse may also be true:

some C–H insertion reactions that employ more obvious metal carbene precursors have been found by Davies and Autschbach to occur by mechanisms that involve concerted 1,2- or 1,5-hydride transfer/C–C bond formation.[103] The potential interplay between these types of C–H functionalization is an attractive avenue for future work. Future studies should compare these possible mechanisms side-by-side for the same set of substrates. We would also like to point out that many of the catalytic conditions used appear to be at least suspect "hidden Brønsted acid"[104b] catalysts. Control experiments similar to those used by Hartwig[104a] and Hintermann[104a] to differentiate between organometallic/Lewis acid and Brønsted acid mechanisms may be prudent.

On a final note, we believe that the types of reactions highlighted in this Review should not only serve as a novel route to complex structures, but additionally as a proving ground for newer, more powerful catalysts developed by the community. While significant advances in catalyst/substrate design enabled most of the recent progress in this field, there is still much ground to cover from the standpoint of efficiency. In enantioselective examples, reaction times of one week are not uncommon, as are elevated temperatures (80–115 °C). In hydride shifts from some ether and non-heteroatomic donors, excess amounts of very strong acids are still required for catalysis. Hopefully, recent advances in the development of more powerful and selective (chiral) catalysts can be applied to this mechanistically unique family of transformations.

Addendum

After the submission of this Review, several other relevant examples have appeared. Akiyama and co-workers reported the first examples of double C–H functionalization by means of two sequential hydride shifts.[105a] The initial step, either a 1,4- or 1,6-hydride shift, is determined by the substitution pattern of the hydride acceptor. The same research group also reported the formation of 1-aminoindanes by a 1,4-hydride shift/ring closure sequence.[105b] Yuan and co-workers reported the use of alkylidene azlactones as hydride acceptors in a cyclization to yield spirooxindole products.[106] Alajarin, Sanchez-Andrada, Vidal, and co-workers reported an interesting thermal reaction where a 1,5-hydride shift is followed by either a 6π or 8π electrocyclization step, depending on the steric properties of the substrate. The proposed mechanism is supported by DFT calculations.[107] Vidal and co-workers reported an extension of their earlier studies in which diazoacetates serve as in situ sources of ketene hydride acceptors in the Wolff rearrangement.[108] Bandini and co-workers developed a gold-catalyzed synthesis of substituted polyacenes in which a 1,5-hydride shift step from a benzhydryl carbon was indicated by deuterium labeling.[109] Kang and Kim have reported an interesting extension of their earlier work[85] using oxidative enamine catalysis to cyclize aminoaldehydes in high enantioselectivities.[110a] Kim has also reported work related to his group's 2010 study in which α,β-unsaturated ketones serve as hydride acceptors under similar catalytic conditions to provide racemic products.[110b]

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