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1,2-Alkyl Migration as a Key Element in the Invention of Cascade Reactions Catalyzed by π-Acids

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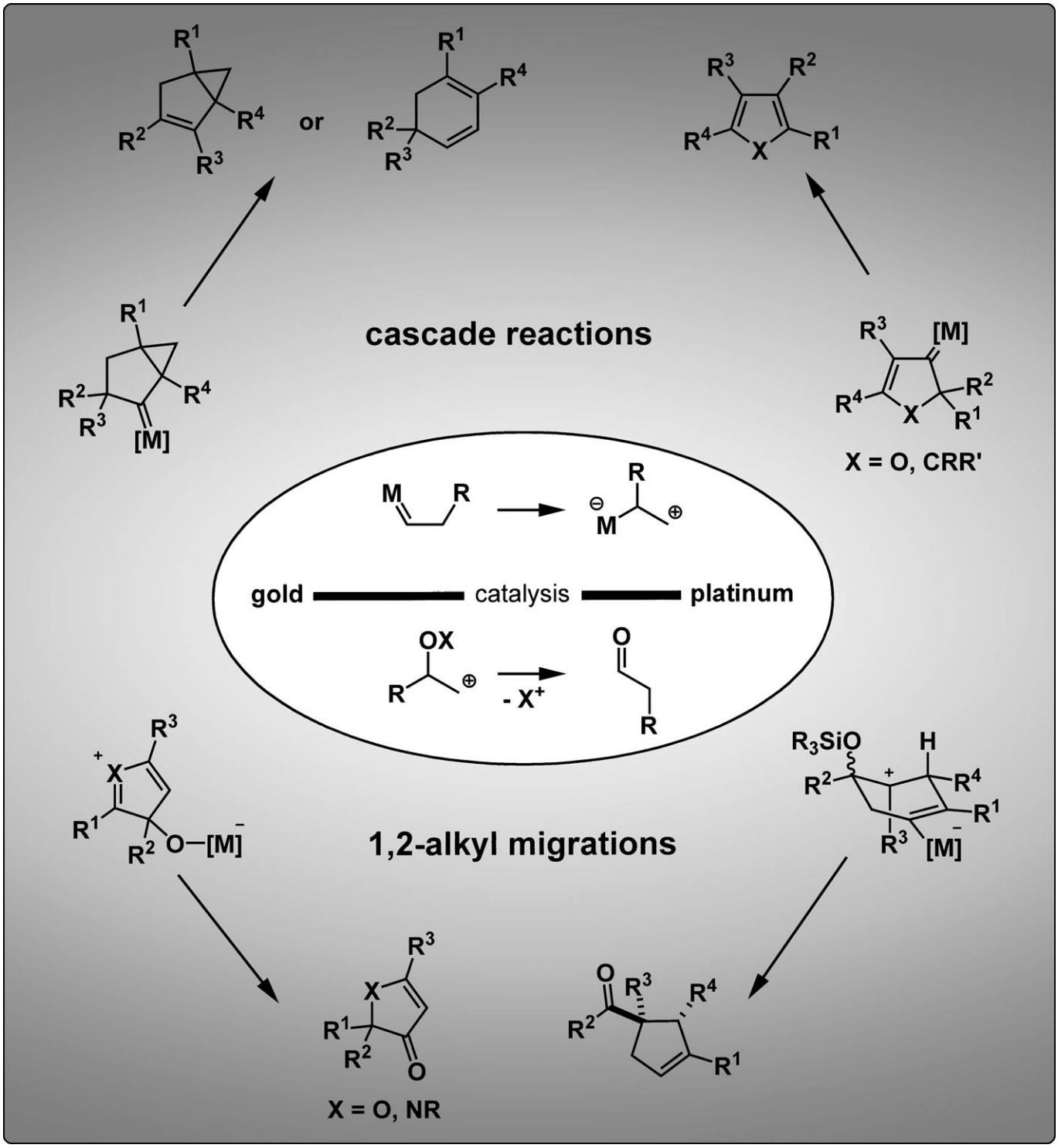

Abstract: This brief overview highlights recent progress in the field of cascade reactions that are initiated by the activation of a π-system using platinum and gold catalysts and that are coupled with a 1,2-alkyl migration step. While the reactions discussed aim to rapidly evolve molecular complexity, they are experimentally straightforward and easy to perform. Primarily guided by the type of 1,2-alkyl migration, methods are categorized as shifts to metal carbenoid centers and pinacol-type rearrangements.

Keywords: cascade reactions · catalysis · gold · platinum · rearrangement

Introduction

It has been only within the last decade that π-acids have been utilized to catalyze reactions of value.[1] Owing to their exceptional ability to activate all type of π-systems including alkenes,[2] allenes,[3] and alkynes[4] toward intermolecular and intramolecular nucleophilic attack, especially platinum and gold catalysts have been demonstrated to be powerful tools of synthetic organic chemistry. Generally, these processes are conveniently performed under experimentally simple reaction conditions; significant redox chemistry is not involved. Moreover, since platinum and gold catalysts show outstanding functional group tolerance, one might expect a considerable increase of applications in target-oriented synthesis[5] over the next couple of years.

One powerful method to rapidly construct molecular complexity from relatively simple starting materials is by combining two or more distinct reactions into a single transformation.[6] In this context, the diverse reactivity of platinum and gold complexes has attracted much interest in the development of cascade reactions that are initiated by a π-activation step. This account will illustrate a feature of reaction design, that is, the incorporation of a 1,2-alkyl migration step into the cascade reaction, which we have found to be particularly beneficial in the synthesis of architecturally complex molecules. Most but not all cascade reactions that are the subject of this account can be generally divided into two categories as depicted in Figure 1: first, 1,2-alkyl migration to an adjacent metal carbenoid center, the second, pinacol-type rearrangement to terminate the cascade reaction. The discussion will illustrate how 1,2-alkyl migrations have been employed as pivotal steps in cascade reactions catalyzed by π-acids. Since the vast majority of reactions of value are designed rather than being discovered by accident, the focus of this article lies on a better understanding of the elemental reaction design.

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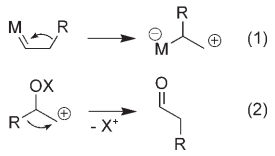


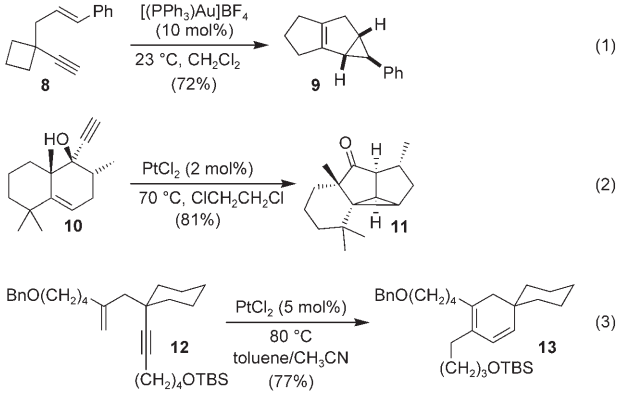
Figure 1. 1,2-Alkyl migration steps in cascade reactions catalyzed by π-acids.

1,2-Alkyl Migration of Metal Carbenes

For both free carbenes and metal carbenes, 1,2-migration represents a fundamental reaction pathway. Generally, the inherent migratory aptitude follows the order H > aryl > alkyl.[7] While this migratory preference and its distortions have been extensively studied for free carbenes and for the catalytic reaction of α-diazo carbonyls with rhodium or copper carbenes as reactive intermediates,[8] the migration of gold and platinum carbenes is far less understood.[9] Due to the fact that 1,2-hydrogen migration is usually predominant, 1,2-alkyl migration was only found in π-acid catalyzed processes when 1,2-hydrogen migration cannot compete. More specifically, a successful incorporation of a 1,2-alkyl migration step into a cascade reaction proceeding through a metal carbene intermediate requires the absence of a migrating hydrogen in this key intermediate.

A class of cascade reactions that include a 1,2-alkyl migration as an additional step is based on the cycloisomerization of 1,5-enynes **1** (Figure 2). Transition-metal induced activation of the alkyne followed by cyclization produces cyclopropyl metal carbene **2** as the key intermediate. Depending on the substitution pattern, two alternative reaction outcomes can be obtained: formation of bicyclo[3.1.0]hexane derivatives (path a) or formation of cyclohexadiene derivatives (path b). The competing reaction pathway that involves the 1,2-shift of R^4 cannot take place due to structural restraints.

The catalytic isomerization of 1,5-enynes **1** to bicyclo[3.1.0]hexenes **4** was thoroughly investigated by Toste and co-workers,[5h,10,11] albeit with a clear focus lying on a 1,2-hydrogen shift onto the metal carbene ($R^3 = H$). Transformations of 1,5-enynes **1** involving 1,2-alkyl migration of R^3 are strictly limited to compounds that bear a quaternary center (R^3 = alkyl, $R^2 \neq H$). As shown for the gold(I)-catalyzed reaction of 1,5-enyne **8** [Scheme 1, Eq. (1)], the formation of bicyclo[3.1.0]hexene **9** is driven by the release of ring strain. A related strategy utilizes the presence of a hydroxy group at the propargylic position ($R^2 = OH$) to trigger a 1,2-migration via path a. An interesting example of this strategy, which combines a cycloisomerization of 5-en-1-yn-3-ol **10** and a heteroatom-assisted 1,2-alkyl migration was developed



Scheme 1. Cycloisomerizations of 1,5-enynes.

by Fehr and co-workers for the synthesis of complex polycycle **11** [Scheme 1, Eq. (2)].[12] Both $Cu(BF_4)(CH_3CN)_4$ and $PtCl_2$ proved practical to catalyze this transformation.

Recent investigations by Kozmin and co-workers examined the alternative cycloisomerization pathway of substrates **1** that is proposed to proceed through a series of 1,2-alkyl shifts (path b, Figure 2).[13,14] These studies demonstrated that densely functionalized cyclohexadienes **7** are obtained from 1,5-enynes **1** in good yields using $PtCl_2$ at 80 °C [e.g., **12**→**13**; Scheme 1, Eq. (3)]. Importantly, a range of gold-based catalysts were inefficient for this transformation.

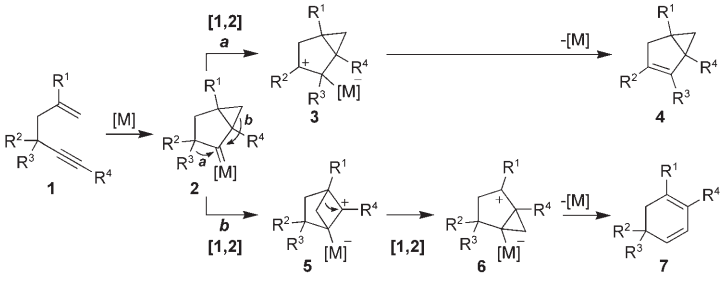


Figure 2. Diverse 1,2-alkyl shifts in the cycloisomerization of 1,5-enynes.

Whilst the isomerizations of 1,5-enynes proceed through cyclopropyl metal carbenes as common intermediates, allenes **14** are typically converted into cyclic metal carbenes **15** through a 5-*endo*-*dig* cyclization initiated by π-acid activation of the allene moiety (Figure 3). The subsequent 1,2-alkyl migration to the metal carbenoid center results in a versatile synthesis of highly substituted carbocycles (X = CRR′) and heterocycles (X = O) of type **17**. To avoid competing 1,2-hydrogen migration, the use of 1,1-disubstituted allenes is mandatory.

In this context, Gevorgyan and co-workers have investigated the utility of allenyl ketones for the synthesis of tri- and tetrasubstituted furans.[15] The furan formation depicted in Scheme 2 [Eq. (1)] is one example in which gold-catalyzed heterocycle formation is accompanied by phenyl migration. In general, 1,2-phenyl migration occurs predominantly over alkyl migration in allenyl ketones **14** (X = O) when $R^1 \neq R^2$. In contrast to the selective 1,2-migration of phenyl over methyl, 1,2-migration of an ethyl group was found to compete with the phenyl group, which resulted in the formation of a 2.3:1 mixture with the phenyl migration product as the major product. Based on this rare study on the migratory aptitude in gold carbenes, it was suggested that this furan synthesis proceeds more likely via cationic intermediates, although carbene intermediate **15** was not ruled out. For the synthetic chemist, the detailed mechanistic picture appears less important, since the reaction outcome can be understood in carbenoid, as shown in Figure 3, as well as in cationic terms.[1a] Nevertheless, in view of the fact that various effects on the 1,2-migration have not been studied systematically in such reactions, the migratory aptitude in gold and platinum carbenes remains to be fully elucidated.

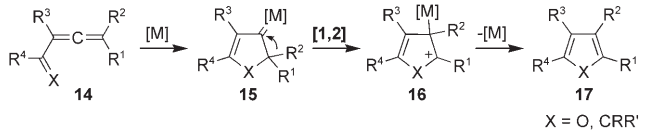
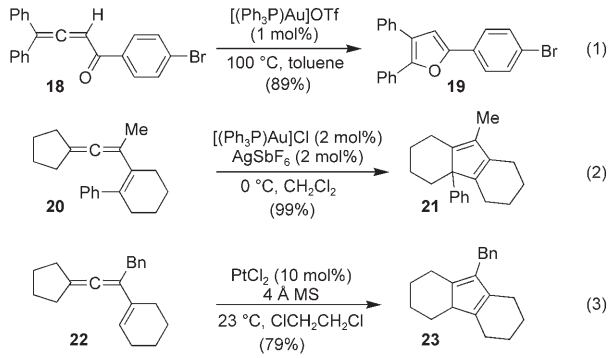


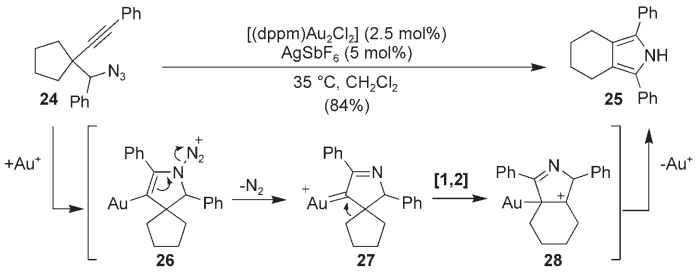
Figure 3. Catalyzed cyclization of allenyl compounds followed by 1,2-migration.



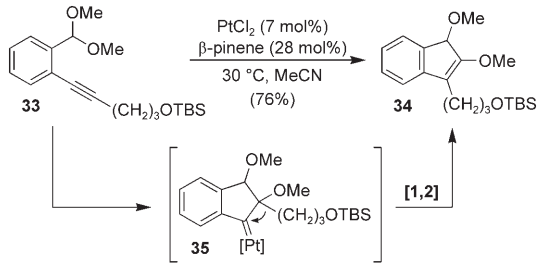
Scheme 2. Cycloisomerization of allenic compounds.

1,2,4-Trienes have been employed in numerous ways as suitable starting materials for the construction of functionalized cyclopentadienes.[16] As outlined in Figure 3 for X = CRR′, it is proposed that after allene complexation with the transition-metal catalyst cyclization forms a carbenoid intermediate of type **15** that undergoes 1,2-alkyl migration. For example, Toste and co-worker have described the reaction catalyzed by cationic triphenylphosphinegold(I) to give fully substituted cyclopentadiene **21** [Scheme 2, Eq. (2)].[16a] Iwasawa and co-workers have also reported cyclizations of related 1,2,4-trienes,[16b] in this case catalyzed by $PtCl_2$. Ring-enlargement reaction delivered the corresponding cyclopentadiene **23**, double-bond isomerization was not observed.

A fascinating cyclization–ring expansion strategy developed by Toste and co-workers provides access to pyrroles (Scheme 3).[17] It is proposed that the reaction proceeds via initial cyclization of the azide onto the alkyne moiety to produce cyclic intermediate **26**, which after loss of nitrogen



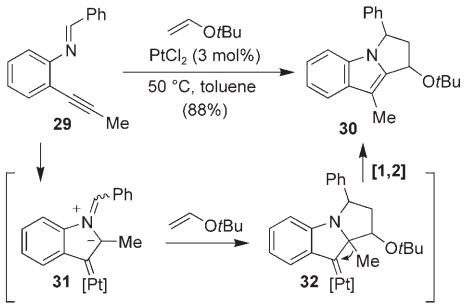
Scheme 3. Acetylenic Schmidt reaction.



Scheme 5. 1,2-Alkyl migration in combination with a carboalkoxylation process.

gives gold carbenoid **27**. A subsequent 1,2-alkyl shift to the gold carbenoid center followed by release of the catalyst and tautomerization generates tetrasubstituted 1*H*-pyrrole **25**.

An additional example of this 1,2-alkyl migration in cyclic metal carbenes is shown in Scheme 4 as part of a general method to convert readily available *N*-(2-alkynylphenyl)-



Scheme 4. 1,2-Alkyl migration in combination with a [3+2]-cycloaddition.

imines bearing an internal alkyne moiety into tricyclic indol derivatives (**29**→**30**).[18] The reaction sequence developed by Iwasawa and co-workers begins with the coordination of the nitrogen to the activated alkyne in substrates such as **29** followed by creation of platinum-containing azomethine ylide **31**. The 1,3-dipole is prone to undergo a [3+2]-cycloaddition resulting in the formation of cyclic carbene **32**. A subsequent 1,2-migration of the adjacent substituent to the carbenoid center finally gives indole **30**. The cascade reaction is catalyzed by $PtCl_2$ and $AuBr_3$, whereas both catalysts showed equal activity. A variation of this reaction employs 2-alkynylbenzoates, which on activation with the $PtCl_2$ catalyst generate a platinum-containing carbonyl ylide that can be trapped with a vinyl ether to produce a cyclic platinum–carbene intermediate.[19] Subsequent 1,2-alkyl migration results in the formation of substituted naphthalenes.

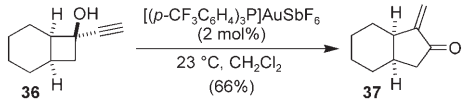
Another unique transformation that might involve a cyclic carbene intermediate is depicted in Scheme 5.[20,21] The use of $PtCl_2$ in the presence of olefins as the catalytic system led to the formation of functionalized indenes such as **34** from 2-alkynylbenzaldehyde acetals. The cyclization products have the alkyl group migrated from the starting acetylene carbon. Although further studies to understand the exact mechanism are desirable, a reaction intermediate to account for this 1,2-shift is carbenoid **35**.

Pinacol-Terminated Cascade Reactions

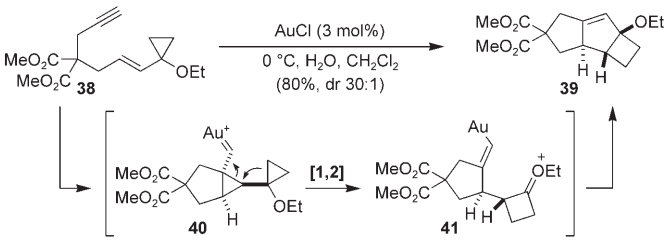
While the previous cascade reactions have dealt with intermediary metal carbenes that undergo 1,2-alkyl migration to the metal carbenoid center, the positive charge induced on an acetylenic ligand through transition-metal complexation opens the door to alternative reactivity as it is known from cationic cyclizations. Based on this consideration, a variety of π-acid-catalyzed processes have been developed, in which cationic intermediates are trapped by external or internal nucleophiles.[22] An alternative way to terminate a cationic cascade is by using a pinacol rearrangement, a strategy that has been shown to be of exceptional value.[23] Although various initiating groups[24] have been investigated in considerable detail to trigger a cyclization-pinacol event, only recently the use of a π-activation step to initiate a pinacol-terminated cascade reaction has been realized as a powerful entry to complex structures.

The guiding notion for the reactions discussed in this section is to trap a putative carbocation with a ring-expanding or ring-contracting pinacol-rearrangement following the generation of a positive charge from an initial π-activation. The use of π-acids to introduce a charged atom into an array of atoms undergoing bond reorganization is particularly attractive, since in most cases the transition-metal catalyst can be considered as a mild proton equivalent.

As an early example of this type of 1,2-migration, Toste and co-workers have described the gold(I)-catalyzed ring expansion of alkynylcyclopropanols and alkynylcyclobutanols (e.g., **36**→**37**; Scheme 6).[25] The positive charge induced on the alkyne moiety by coordination of the cationic gold(I) complex is responsible for the rearrangement. Echavarren and co-workers combined this ring-expansion with a cycloisomerization of 1,6-enynes to produce tricyclic carbon skeletons of high complexity (e.g., **38**→**39**; Scheme 7).[26]



Scheme 6. Gold-catalyzed ring expansion of cyclopropanols and cyclobutanols.



Scheme 7. Gold-catalyzed ring expansion in combination with the cycloisomerization of 1,6-enynes.

Next, a class of cascade reactions is discussed that combines an initial 6-*endo* carbocyclization with a pinacol rearrangement. In this context, we recently described a general method for synthesizing cyclopent-3-enecarbaldehydes **46** from readily available 3-silyloxy-1,5-enynes **42** (Figure 4).[27]

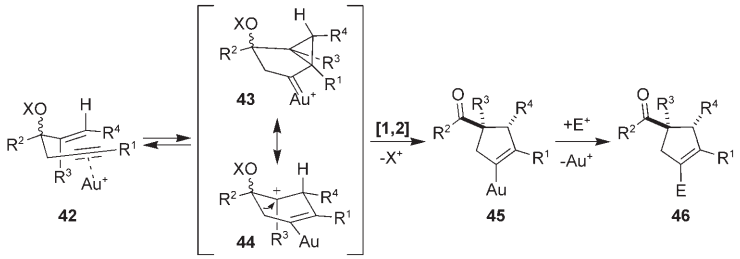


Figure 4. Possible mechanism for the cascade reaction consisting of cyclization and pinacol rearrangement.

Based on the typical reactivity of 1,5-enynes,[28] it was proposed that the initial coordination of the soft cation to the alkynyl moiety would give reactive intermediate **43** (or **44**). The reaction was designed to achieve the formation of cyclopentene **45** by providing the opportunity for cationic intermediate **44** to undergo an irreversible pinacol rearrangement. A representative example of this new, highly stereoselective synthesis of cyclopentenes is shown in Scheme 8 [**47**→**48**, Eq. (1)]. The rearrangement can be triggered by treating the alkyne with catalytic amounts of silver-free $[(Ph_3P)Au]SbF_6$. Since traces of $AgSbF_6$ were found to give complete decomposition of both starting material and product, $[(Ph_3P)Au]Cl$ was activated prior to use by reaction with 0.5 equiv of $AgSbF_6$ in CH_2Cl_2 at room temperature. Another characteristic of this cyclopentene synthesis is the requirement of an external proton source for protodemetallation of vinyl gold(I) intermediate **45** (E = H). While the use of water as the proton source led to diminished yields for the rearrangement product, sterically demanding alcohols such as isopropyl alcohol and *tert*-butyl alcohol proved to be effective. The proton source is essential, since 3-hydroxy-1,5-enynes possessing an internal proton source would undergo competitive heterocyclization through the free hydroxy group. Thus, 3-silyloxy-1,5-enynes were employed (X = SiR_3); both labile silyl ethers (X = Et_3Si, Me_3Si) and more robust silyl ethers (X = tBuMe$_2$Si, iPr$_3$Si) gave the rearrangement product.

The useful incorporation of iodine results when *N*-iodosuccinimide (NIS) is added to the reaction mixture instead of isopropyl alcohol as a proton source [Scheme 8, Eq. (2)]. Preliminary mechanistic investigations indicate that the selective introduction of the iodo substituent may be rationalized by a iododemetallation of vinyl gold(I) intermediate **45** (E = I).

The core functionality assembled by this cyclization-pinacol cascade is 4-acylcyclopentene (**51**, Figure 5). A definitive feature of this novel route to substituted cyclopentenes is that challenging elements of structure are readily accessed, as exemplified through the construction of all-carbon quaternary stereocenters and complex bicyclic compounds. The possible utility for the creation of molecular complexity still lacks further verification by its use as a key transformation in total synthesis.

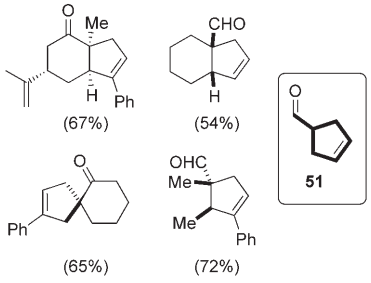
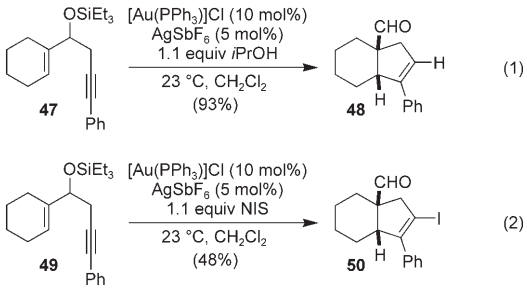
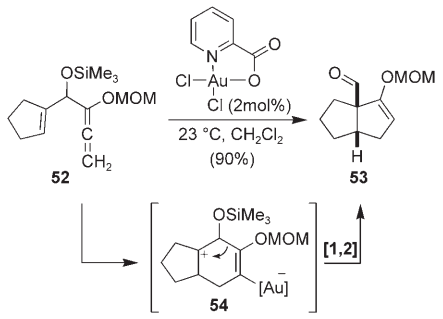


Figure 5. Representative cyclopent-3-enecarbaldehydes.



Scheme 8. Reaction conditions for the cylization–pinacol cascade.

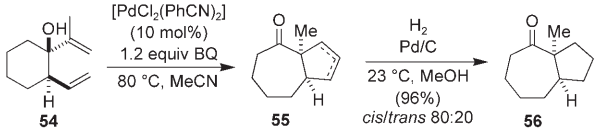
Zhang and co-worker have investigated the utility of 3-silyloxy-1,4,5-trienes in a gold-catalyzed route to 3-acylcyclopentenes (e.g., **52**→**53**; Scheme 9).[29] As in the closely related reaction discussed above, the initial carbocyclization is induced by the activation of the π-system which, in this case, is an allene moiety. The key step in the reaction pathway might involve a pinacol-type 1,2-migration of cationic intermediate **54** to provide the rearrangement product.[30] Notably, reaction of 3-silyloxy-1,4,5-trienes produces 3-acylcyclopentenes such as **53**, while the use of 3-silyloxy-1,5-enynes



Scheme 9. Cyclization–pinacol reaction of 3-silyloxy-1,4,5-trienes.

results in the formation of 4-acylcyclopentenes **51** as double-bond isomers.

Furthermore, Gagné and co-workers have demonstrated that activation of an alkene moiety using $[PdCl_2(PhCN)_2]$ induces a cyclization–pinacol reaction that complements the gold-catalyzed reactions initiated by activation of alkyne or allene moieties. For example, diene **54** was converted into ketone **55** (as a mixture of double bond isomers), which after hydrogenation gave the corresponding cycloheptanone **56** (Scheme 10).[31] A major drawback of this sequence is the



Scheme 10. Cyclization–pinacol reaction of 3-hydroxy-1,5-dienes.

fact that depending on the structure of the starting material various cyclization and rearrangement pathways are possible producing different types of products. Additionally, the use of a palladium(II) catalyst gives β-hydrogen elimination, thus requiring palladium reoxidation with 1,4-benzoquinone (BQ) to achieve catalyst turnover.

Another example that combines a carbocyclization with a pinacol rearrangement was recently described by Liu and co-workers as exemplified for the conversion of 4,6-dien-1-yn-3-ol **57** into aldehyde **58** (Scheme 11).[32] In this case, the $AuCl_3$-catalyzed cyclization proceeds via a 6-*exo* pathway to give a cationic intermediate, which subsequently undergoes a pinacol-type 1,2-shift. Importantly, chiral alcohols are transformed into the reorganized products with good chirality transfer.

While the previous transformations discussed in this section are a combination of carbocyclization and pinacol rearrangement, we recently described a general method for synthesizing substituted 3(2*H*)-furanones by combining an initial heterocyclization with a pinacol-type rearrangement (X = O, Figure 6).[33] The design of this reaction followed directly from our development of the 4-acylcyclopentene

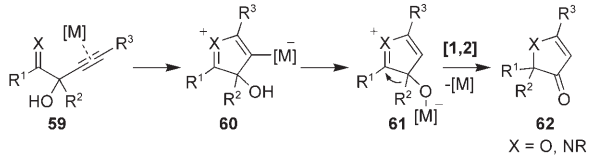
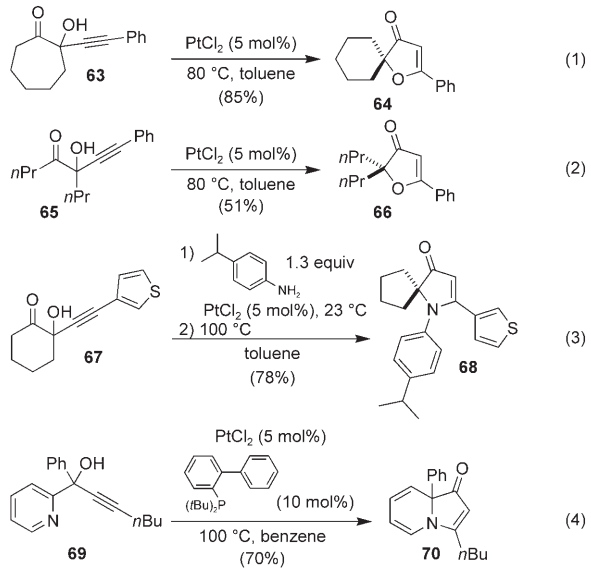


Figure 6. Proposed pathway for the synthesis of 3(2*H*)-furanone and 3-pyrrolones.

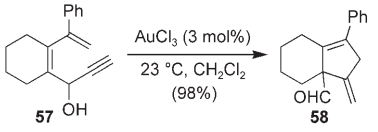
forming reaction. It is hypothesized that coordination of the alkyne moiety of propargylic alcohol **59** to a suitable transition-metal catalyst induces the intramolecular attack of the carbonyl group. The intermediate oxonium ion **61** (X = O) then triggers a 1,2-alkyl migration analogous to a formal α-ketol rearrangement, and subsequent protonation affords 3(2*H*)-furanone **62** and regenerates the catalyst. Representative examples of this synthesis of 3(2*H*)-furanones are illustrated in Scheme 12 [Eqs. (1)+(2)]. The rearrangement is



Scheme 12. Representative examples following a heterocyclization–1,2-migration pathway.

catalyzed by $PtCl_2$ in toluene at 80 °C. Alternatively, treatment with $AuCl_3$ gives product formation, albeit with a significantly reduced scope. Utilizing this strategy, spirocyclic furanones are easily accessible through ring-contracting cyclization. Acyclic systems also reacted by alkyl migration, although the yields were modest. Furthermore, preliminary experiments indicated that the rearrangement is stereospecific, thus enhancing the synthetic value of this reaction dramatically.

Many extensions of this new heterocycle synthesis are readily envisaged. For example, if the cationic intermediate

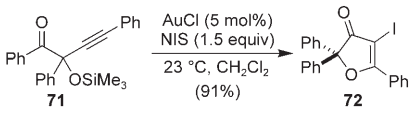


Scheme 11. Cyclization–pinacol reaction of 4,6-dien-1-yn-3-ols.

61 is an iminium ion, 3-pyrrolones will result (X=NR). In a convenient one-pot protocol, we realized the synthesis of pyrrolone products by simply adding a primary amine to the reaction mixture for an in situ condensation step [e.g., **67**→**68**; Scheme 12, Eq. (3)].[34] The conversion of 2-alkynyl-2-hydroxy carbonyl compounds into either 3(2*H*)-furanones or 3-pyrrolones highlights the ability of the underlying strategy to rapidly evolve both complexity and diversity.

In an independent study, Sarpong and co-workers found that preformed hydrazones are also suitable substrates for this rearrangement process (X=NNHTs).[35] Even more interesting, substrates containing a pyridine unit produced the corresponding indolizinones in good yields [e.g., **69**→**70**; Scheme 12, Eq. (4)]. Other examples required the addition of substoichiometric quantities of Cs_2CO_3 as a base. This 1,2-alkyl migration was found to proceed with chirality transfer.

Extension of the methodology developed for preparing 3(2*H*)-furanones was accomplished by using *N*-iodosuccinimide in a $AuCl_3$-catalyzed route to 4-iodo-3-furanones (Scheme 13).[36,37]

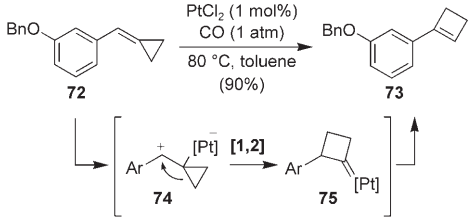


Scheme 13. Synthesis of 4-iodo-3-furanones.

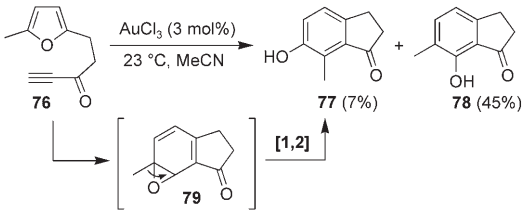
Miscellaneous 1,2-Alkyl Migrations

Although appearing as a straightforward ring-expansion, the $PtCl_2$-catalyzed rearrangement of methylenecyclopropanes developed by Fürstner and co-worker fits properly within the scope of this article. Initial coordination of $PtCl_2$ to the alkene induces a positive charge.[38] The resulting intermediate **74** is prone to rearrange to the corresponding cyclobutyl carbene **75**, which then gives cyclobutene product **76** via 1,2-hydrogen shift (Scheme 14). Notably, the reaction was significantly accelerated under an atmosphere of carbon monoxide that is suggested to enhance the cationic character of the platinum catalyst.[39]

Another fascinating 1,2-alkyl migration was observed by Hashmi and co-workers during their approach to the natural product jungianol.[40] In the presence of $AuCl_3$, furan **76** (Scheme 15) reacted to generate the expected phenol **78** in good yield. Nevertheless, the observed formation of the isomeric phenol **77** as a minor product might be attributed to an uncommon 1,2-methyl migration in the proposed arene oxide intermediate **79**.[41]



Scheme 14. Ring-expansion of methylenecyclopropanes.



Scheme 15. 1,2-Migration in the gold-catalyzed phenol synthesis.

Conclusion

The developments summarized herein confirm that the invention of cascade reactions, the initiation of which typically requires only activation of a π-system by platinum or gold π-acids, is of value for organic synthesis. The reactions highlighted herein are defined through the marked increase in molecular complexity that is achieved by introducing a 1,2-alkyl migration step into the cascade. Particularly powerful is the class of reactions that couple a cyclization with a pinacol-type rearrangement. These transformations broaden the range of potential approaches for the stereoselective creation of quaternary centers.

It is certain that many more strategies that combine a π-activation step with a 1,2-alkyl migration will be described in the future. Two future trends are easy to predict: a number of methods will be applied to the target-oriented synthesis of complex structures, and a new focus will be put on the development of asymmetric variants.

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