Published in final edited form as:

Chem Soc Rev. 2013 June 21; 42(12): 4991–5001. doi:10.1039/c3cs35514d.

Metal-Catalyzed Double Migratory Cascade Reactions of Propargylic Esters and Phosphates

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Abstract

Propargylic esters and phosphates are easily accessible substrates, which exhibit rich and tunable reactivities in the presence of transition metal catalysts. π -acidic metals, mostly gold and platinum salts, activate these substrates for an initial 1,2- or 1,3-acyloxy and phosphatyloxy migration processes to form reactive intermediates. These intermediates are able to undergo further cascade reactions leading to a variety of diverse structures. This *tutorial review* systematically introduces the double migratory reactions of propargylic esters and phosphates as a novel synthetic method, in which further cascade reaction of the reactive intermediate is accompanied by a second migration of a different group, thus offering a rapid route to a wide range of functionalized products. The serendipitous observations, as well as designed approaches involving the double migratory cascade reactions, will be discussed with emphasis placed on the mechanistic aspects and the synthetic utilities of the obtained products.

1. Introduction

Cascade transformations offer enhancement of molecular complexity and diversity from simpler molecules, which are often accompanied by high degrees of chemo-, regio-, diastereo-, and enantioselectivity.^{1–3} Compared to the stepwise reactions, these step-economical processes represent environmentally and economically more favored approaches. One of the remarkable examples of such transformations is a transition metal-catalyzed molecular rearrangement of readily available propargylic esters and phosphates.^{4–6} Earlier cases include copper-,⁷ silver-,⁷ zinc-,⁸ and palladium-⁹ catalyzed reactions. However, extensive studies were triggered by discovery of ruthenium-,¹⁰ platinum-,¹¹ and gold-¹² catalyzed processes. It is generally accepted that metal catalysts, especially π -acidic gold salts, can activate the triple bond of **I** for further transformations (Scheme 1). Thus, it can undergo a 6-*endo-dig* cyclization to produce intermediate **II**, which further rearranges into allene **III** (**path a**, Scheme 1). Overall, this formal [3,3]-rearrangement represents a 1,3-OXO (X=CR, P(OR)₂) migration process. Alternatively, an activated substrate **I** can undergo a 5-*exo-dig* cyclization to form intermediate **IV**, which

upon ring opening forms the metal-stabilized carbene **V** (**path b**, Scheme 1). This process, which involves a 1,2-OXO migration, is often referred as a Rautenstrauch rearrangement.⁹

Generally, the regiochemistry of **I** for 1,3-OXO migration to form **III** (Scheme 1, **path a**) or 1,2-OXO migration to generate **V** (Scheme 1, **path b**) can be predicted. As a rule of thumb, if substrates **I** possess electronically unbiased internal alkynes ($R^3 = H$), the 1,3-OXO migration takes place.¹³ Alternatively, for tertiary or benzyl alcohol derived substrate **I**, possessing terminal alkynes ($R^3 = H$)¹⁴ and electronically biased internal alkynes ($R^3 = \text{EWG}$),^{15,16} the 1,2-OXO migration is preferred. However, other factors, such as the choice of metal catalyst,¹⁷ substitution pattern at propargyl moiety,¹⁸ and temperature,¹⁹ in some cases have been reported to govern the regiochemical outcome of these reactions.

Interestingly, reactive compounds **III** and **V**, which possess additional functional groups, can undergo further cascade transformations, including intra-²⁰ or intermolecular²¹ trapping, cycloaddition,²² cross-coupling,²³ and oxidation reactions.²⁴ Alternatively, if these intermediates possess appropriately situated migrating groups, such as hydrogen, halogen, or alkyl-, acyl-, and acyloxy groups, then a second migration can occur, thus offering an easy route to diverse functionalized products (Scheme 2). The double migratory cascade approach allows for a rapid building of molecular complexity including synthetically useful cyclic, acyclic and polycyclic structures.

This *tutorial review* focuses on gold-, copper-, and platinum-catalyzed cascade reactions of propargylic esters and phosphates, in which two migration processes of different groups take place. First, the double migratory transformations that are initiated with a 1,3-OXO migration are discussed (Scheme 2, right). The cascade reactions involving an initial 1,2-OXO migration (Scheme 2, left) are covered in the second part. Throughout the text, major concepts, synthetic applications and mechanisms of the given transformations are highlighted.

2. Double migratory transformations with an initial 1,3-OXO migration

2.1 Cascade 1,3-OXO/hydride migration

2.1.1 Double 1,3-OXO/1,2-H migration—In 2006, Zhang and co-workers reported the Au(I)-catalyzed cascade reaction of propargylic esters **1** into the cyclopentenone **6** (Scheme 3).²⁵ This reaction proceeds well with various cyclic and acyclic substrates providing cyclopentanone products in good to excellent yields. The proposed mechanism involves an initial 1,3-acyloxy migration to form allenylacetate **2** (*vide supra*), which in the presence of the gold catalyst transforms into the vinyl gold species **3**. The Nazarov cyclization of the latter produces cyclic gold-stabilized carbene **4**, which upon a subsequent 1,2-hydride shift affords dienyl acetate **5**. Hydrolysis of **5** by wet dichloromethane furnishes the cyclopentenone **6**.

Festerbank and Malacria disclosed an analogous Au(I)-catalyzed reaction of analogous enynyl acetates **7** bearing a tethered olefin at the propargylic position (Scheme 4).²⁶ It is believed that after the 1,3-OAc migration/Nazarov cyclization sequence, the compound **8** (an analogue of **4**) is formed. Depending on the length of the tether, different reactivity of

the gold-carbene **8** was observed. When $n=3$ (**7a**), the discussed above 1,2-hydride shift²⁵ takes place to produce the cyclopentadienyl acetate **9**. However, in the reaction of substrate with a shorter tether (**7b**, $n=2$), an exclusive formation of tricyclic compound **10** via an electrophilic cyclopropanation reaction was observed. DFT calculations supported the cyclopropanation reaction for compound **8b** into **10**, which is both kinetically and thermodynamically favored over the 1,2-hydride shift that leads to **9**.

Gagosz and co-workers have demonstrated an efficient Au(I)-catalyzed synthesis of bicyclic framework **15** from 5-yn-1-yl acetate **11** (Scheme 5).²⁷ The products with a variety of different substituents at R^1 , R^2 , R^3 and R^4 positions were formed in high yields under mild reaction conditions. Treatment of propargylic acetate **11** with the gold catalyst initiates the 1,3-acyloxy migration to form the allene **12**, which further undergoes a nucleophilic attack of the alkene moiety at the metal-activated allene via a 6-*endo-trig* cyclization to generate carbocation **13**. A subsequent intramolecular attack of the vinyl gold moiety of the latter at the cationic center produces a cyclopropyl-containing gold-stabilized carbene **14**, which upon the 1,2-hydride shift furnishes the final bicyclic product **15**. Interestingly, the intermediacy of cation **17** was further confirmed in the reaction of enantioriched substrate **16** by trapping it with methanol to give the methoxylated product **18a** as a 1:1.5 ratio of diastereomers (Scheme 6). Moreover, in the presence of a base and methanol, the produced cation **17** underwent a deprotonation/hydrolysis sequence to produce cyclohexenone **18b**. In both cases, complete preservation of chirality was observed.

In 2007, Zhang's group developed the Pt(II)-catalyzed synthesis of tetracyclic 2,3-indoline-fused cyclopentenones **24** from the propargylic 3-indoleacetates **19** (Scheme 7).²⁸ This reaction exhibited a wide substrate scope, as various groups at propargylic position, nitrogen atom, and terminus alkyne of **19** were well-tolerated under the reaction conditions. According to the mechanistic hypothesis, the 1,3-migration of indoleacetate group produces allene **20**, which then in the presence of platinum catalyst gives the oxocarbenium species **21**. Following the C3 attack of the indole moiety at the electrophilic center of the latter, the vinyl platinum **22** is formed. A subsequent 5-*exo-trig* cyclization of **22** produces the platinum carbene-containing tetracyclic compound **23**, which undergoes a 1,2-hydride shift to furnish the final tetracyclic product **24**. Notably, a synthetic utility of this transformation was demonstrated by a short synthesis of compound **27**, a tetracyclic core of vindolinine (Scheme 8). Thus, propargylic ester **25** under these reaction conditions produced compound **26**, which upon sequential functional group interconversion was efficiently transformed into the indoline-containing alkaloid **27** in a reasonable overall yield.

Gevorgyan's group demonstrated the copper-catalyzed synthesis of various heterocycles **32** from propargylic phosphates **28** (Scheme 9).²⁹ A variety of substituted furanes and indolizines could be efficiently accessed via this cascade transformation. The proposed mechanism involves the Cu-catalyzed 1,3-phosphatyloxy migration to produce allene **29**, which upon a nucleophilic attack of the heteroatom at the metal-activated allene via a 5-*endo-trig* process generates **30**. The latter then converts into the heterocyclic copper carbene **31**, which further undergoes a subsequent 1,2-hydride shift to furnish heterocycle **32**. Employment of analogous acyloxy-containing substrate in this reaction was less efficient.

To better understand the mechanism of the reaction, the [^{17}O]-enriched alkynyl pyridine **33** was treated under the reaction conditions (Scheme 10). Subsequently, the corresponding indolizine **35** with the labeled bridging phosphate oxygen was isolated as a major isotopomer with traces of **38** observed. Thus, this observation strongly supports that migratory cycloisomerization of substrate **33** involves the formation of allene **34** (the result of a 1,3-phosphatyl-oxy migration) rather than isotopomeric allene **37** (the product of two sequential 1,2-phosphatyl-oxy migrations).³⁰

The synthetic utility of the obtained phosphatyl-oxy-containing heterocycles **39** in this cascade reaction was demonstrated by an efficient Kumada cross-coupling reaction to produce a variety of substituted furans and indolizines **40** (Scheme 11).

It is worth mentioning that the second migration process in the above-discussed methods (*i.e.* formation of **42** from metal carbene **41**) has been proposed to occur via a 1,2-hydride shift, which is well-established for related processes (Equation 1, Scheme 12).³¹ However, in the discussed above double migratory cascade reactions this route has not been proven yet. Alternatively, the pathway including a deprotonation of **41** to form **43** followed by a protodemetalation step may account for the formation of **42** (Equation 2, Scheme 12).²⁵

2.1.2 Double 1,3-EXO/1,5-H migration—It was shown by Liu's group that propargylic acetate **44** could be converted into the tricyclic structure **48** in the presence of either gold(I) or platinum(II) catalysts (Scheme 13).³² The mechanism of this reaction involves the metal-triggered 1,3-OAc migration to produce allene **45**, which upon a 5-*endo-trig* cyclization generates the bicyclic metal carbene **46**. A followed 1,5-hydride shift from acetal moiety of the latter to the electrophilic metal carbene center produces **47**, which then undergoes a nucleophilic attack of the allyl metal moiety at the electrophilic oxocarbenium center to furnish the final tricyclic product **48**.

2.2 Cascade 1,3-EXO/alkyl migration

2.2.1 Double 1,3-EXO/1,2-alkyl migration—Gevorgyan and co-workers reported the gold-catalyzed cascade reaction of the propargylic esters and phosphates **49a** and **49b** (Scheme 14).^{33,34} The substrate **49a**, which possesses a strained cyclobutyl ring at the α -position of the propargylic ester,³⁵ underwent the gold-catalyzed 1,3-OAc migration/ring expansion sequence to produce 1,3-diene **50**. Interestingly, incorporation in the structure of propargylic esters or phosphates **49b** other migrating groups, such as phenyl and methyl, led to unsymmetrically substituted naphthalenes **51**. It was proposed that substrate **49b** initially undergoes the gold-catalyzed 6-*endo-dig* cyclization to produce the cyclic intermediate **52** (Scheme 15). According to the **path a**, a 1,2- R^2 migration in the latter takes place to form the benzylic carbocation **53**, which upon a proton loss/protodeauration sequence gives the diene **54**. A subsequent cyclization of **54** via either 6 π -electrocyclization or Friedel-Crafts reactions furnishes the naphthalene product **51**. Alternatively, ring opening of **52** gives the allene **55**, which upon hydroarylation affords 1,4-dihydronaphthalene **56** (**path b**). The following 1,2- R^2 migration in the latter produces the naphthalene product **51**.

2.2.2 Double 1,3-OXO/1,3-alkyl migration—In 2008, Wang, Nevado, and Goeke reported the gold-catalyzed cascade reaction of propargylic ester **57** into cyclopentenylketone **61** (Scheme 16).³⁶ Based on the proposed mechanism, the cyclopropyl-containing substrate **57** undergoes a 1,3-OAc migration to produce the carbenium ion **58**, which upon ring opening of cyclopropane moiety generates the allylic cation **59**. Nucleophilic attack of the vinyl gold moiety in the latter at the cationic center leads to exocyclic vinyl acetate **60**, which upon hydrolysis/double bond isomerization sequence affords the corresponding cyclopentenylketone **61**.³⁷

In an independent study, Toste's group provided more mechanistic details on the reversibility of the 1,3-pivaloxy migration process in an analogous reaction of stereochemically defined propargylic pivalate **62** (Scheme 17).³⁸ In the presence of the gold(I)-catalyst, the substrate **62** undergoes a 6-*endo-dig* cyclization to produce cyclic intermediate **63**. Following the ring opening of the latter, the metal-activated allene **64** is formed, which upon *cis-trans* isomerization produces the thermodynamically more stable *trans*-cyclopropane **65**, although the detailed mechanism of this step remains unclear.³⁸ The following concerted ring expansion of **64** or **65** affords the pentannulated product **66**.

In 2011, Toste and co-workers disclosed the gold-catalyzed enantioselective synthesis of chromenyl derivatives **71** from the propargylic pivalates **67** (Scheme 18).³⁹ Among all chiral ligands tested the acyclic 3,3'-functionalized BINAM ligand **A** showed the best enantioselectivity. The mechanism of the reaction involves an initial 1,3-pivaloxy migration to yield the metal-activated axially chiral allene **68**, which in the presence of the gold catalyst transforms into the achiral carbocation **69**. The latter, which is stabilized by the oxygen atom of the migrated group, possesses a chiral ligand at the gold moiety. Therefore, the dynamic kinetic asymmetric 6-*endo-trig* cyclization leads to the enantioenriched oxonium compound **70**. Further carbodemetalation of the vinyl gold moiety in latter via the 1,3-alkyl migration affords the C3-substituted chromenyl pivalate **71**. Interestingly, it was shown that in the presence of LiAlH₄, the vinyl pivalate moiety of **71** could be further converted to the corresponding ketone to give access to enantioenriched chromanones.

2.3. Cascade 1,3-OXO/acyl migration

2.3.1. Double 1,3-OXO/1,3-acyl migration—Zhang's group reported the gold(III)-catalyzed cascade reaction of propargylic esters **72** into α -ylidene- β -diketones **76** and **77** (Scheme 19).⁴⁰ Substrate **72**, possessing different substituents at the terminal alkyne and the propargylic positions, reacted in a highly efficient manner. Notably, not only propargylic pivalates, but also acrylates, benzoates, and carbonate were employed in this double migratory process. According to the mechanistic hypothesis, the propargylic ester **72** undergoes a 1,3-OCOR migration to form the allenylcarboxylate **73**, which in the presence of the gold catalyst transforms into a vinyl gold species **74**. Intramolecular nucleophilic attack of the vinyl gold moiety at the acylium ion in the later produces a four-membered oxacycle **75**, which upon rearrangement affords the (*E*)- α -ylidene- β -diketone **76**. The *Z* diastereomer **77** is believed to form via isomerization of the *E* analogue in the presence of Au(III) catalyst.

2.3.2 Double 1,3-OXO/1,5-acyl migration—It was shown by Malacria, Gandon, and Fensterbank that δ -diketones **79** can be formed via the gold-catalyzed double migratory cascade reaction of hepta-1,6-diyn-3-yl esters **78** (Scheme 20).⁴¹ A number of cyclic and acyclic 1,6-diynes **78** possessing different substituents at R¹, R² and R³ positions reacted well under these mild reaction conditions.

The proposed mechanism of this reaction was validated by DFT computations, where the simplified AuPH₃ was used as the catalyst (Scheme 21). After an initial 1,3-OCOR migration in **78**, the allene **80** is produced, which further undergoes a low-barrier 5-*exo-dig* cyclization to generate vinyl gold species **81**. Rotation of the acyloxy group in the latter needs 5.4 kcal/mol to form the correct rotamer **82**, which provides suitable orbital overlap for the further reaction. The following exothermic 1,5-acyl migration takes place via a nucleophilic attack of the vinyl gold of **82** at the acyl moiety to furnish the *E* product **83**. The triene **84** obtained via this chemistry, in the presence of silica, underwent an interesting transformation into a complex tricyclic compound **86**, presumably via initial double bond isomerization to **85**, followed by its intramolecular [4+2] cycloaddition (Scheme 22).

2.4 Cascade 1,3-OXO/1,3-halogen migration

Recently, Gevorgyan and co-workers reported a stereodivergent synthesis of highly functionalized (*Z*)-1,3-dienes **88** and (*E*)-1,3-dienes **89** from α -halo propargylic phosphates **87** via a double migratory cascade reaction (Scheme 23).⁴² It was found that in the presence of catalytic amount of [CuOTf]₂•PhH, the *Z*-diene **88** was formed; while employment of (*p*-CF₃-C₆H₄)₃PAuCl catalyst resulted in the formation of the corresponding *E*-dienes **89**. A variety of cyclic-, acyclic- and heterocyclic-containing substrates **87** were efficiently converted into 1,3-dienes. Chlorine, bromine, and iodine atoms underwent the 1,3-migration in an efficient manner. The proposed mechanism of this cascade reaction involves the coordination of the metal to the π system of the alkyne **90**, which triggers a 6-*endo-dig* cyclization to produce cyclic intermediate **91** (Scheme 24). In the case of the gold catalyst, ring opening of the latter takes place to generate α -halo allenyl phosphate **92**, which upon halogen abstraction by gold produces the allyl cation **93**. A subsequent delivery of the halide from the gold halide species to **93** takes place *anti* to the phosphate group to furnish the (*E*)-diene **89**. Alternatively, in the presence of the copper catalyst, allene **94** is generated, in which an additional coordination of the phosphate group to the copper catalyst takes place. Halogen abstraction by the copper in latter produces the π -allyl complex **95**, which upon a subsequent phosphate-directed delivery of the halide furnishes the (*Z*)-diene **88**. The synthetic utility of the obtained (*Z*)-1,3-diene **96** was highlighted in an efficient Diels-Alder reaction with bromomaleic anhydride to afford the corresponding benzene derivative **97** (Scheme 25). The Miyaura-Suzuki cross-coupling reaction of the vinyl bromide moiety followed by the Kumada cross-coupling reaction on terminus phosphate group afforded the hydrocarbon **98**. A sequential Miyaura-Suzuki cross-coupling reactions of the vinyl bromide and the phosphate moieties gave access to a multisubstituted diene **99**.

3. Double migratory transformations with an initial 1,2-OXO migration

3.1 Cascade 1,2-OXO/1,2-hydride migration

In 2008, Zhang's group reported the gold-catalyzed stereoselective reaction of propargylic ester **100** toward (1Z, 3E)-diene **103** (Scheme 26).⁴³ Control over regioselectivity in this reaction was achieved by taking advantage of the reversible nature of these transformations. Thus, the electronically unbiased propargyl ester **100** initially undergoes a 1,3-OPiv migration, which is usually preferred for internal alkynes, to produce allene **101** (*vide supra*). If the latter does not undergo further reactions,⁴⁰ then the equilibrium shifts back to propargylic pivalate **100**. The latter then undergoes a less facile for internal alkynes 1,2-pivaloxy migration to generate the gold carbene **102**, which upon irreversible 1,2-hydride shift, produces the 1,3-diene **103**.

Notably, the obtained dienes in this chemistry were shown to be good partners in the Diels-Alder reaction (Scheme 27). Under the reaction conditions, the propargylic pivalates **104** and **107** initially underwent the double migratory cascade reaction to produce expected 1,3-dienes **105** and **108**, which upon the following inter- and intramolecular Diels-Alder reactions furnished the cycloadducts **106** and **109**, respectively, in good yields and selectivity.

Lee and a co-worker disclosed the Pt-catalyzed synthesis of 1,3-dienes **112** from propargylic acetate **110** (Scheme 28).⁴⁴ The 1,3-dienes **112** were formed in good yields, albeit with low level of stereoselectivity. Control of regioselectivity was achieved by incorporation of an electron-withdrawing oxygen substituent at the alkyne moiety of the substrate **110**. Thus, the 1,2-acyloxy migration occurred over the competitive 1,3-migration to produce platinum carbene **111**. The latter, underwent a 1,2-hydride shift⁴⁵ to furnish the 1,3-diene **112**. It is worth mentioning that even in the presence of a tethered alkene, the bicyclic compound **113**, the product of potential intramolecular cyclopropanation reaction, was not detected.²⁶

3.2 Cascade 1,2-OXO/1,4-allyl migration

In 2008, Davies reported the gold-catalyzed cascade reaction of propargylic esters **114** in the presence of allyl sulfide and AuCl catalyst to produce 1,5-diene **118** (Scheme 29).^{46, 47} Various dienes **118**, possessing different groups at R, R¹, and R², were obtained under mild reaction conditions. According to the proposed mechanism, the substrate **114**, possessing a terminal alkyne moiety, undergoes a 1,2-OCOR² migration to produce gold carbene **115**, which is further attacked by the thioether intermolecularly to afford the thio ylide **116**. A subsequent nucleophilic substitution of the enol acetate moiety of the latter at the allylsulfonium moiety results in a formal 1,4-allyl migration to produce compound **117**, which upon elimination of the gold catalyst, furnishes the (*E*)-1,5-diene **118**. It is worth mentioning that using propargylic thioether as a nucleophile in the reaction of **119** led to the expected products **121**, together with the homopropargyl ketone **123** (Scheme 30). It is believed that after a 1,2-OPiv-migration/nucleophilic attack sequence, ylide **120** (analogue of **116**) is formed, which upon 1,4-propargyl migration/hydrolysis affords the expected product **121**. In contrast, a 1,2-propargyl migration in **120** gives **122**, which is then hydrolyzed into **123**.

It was shown by Toste's group that benzopyran **128** can be synthesized via a gold-catalyzed enantioselective cascade 1,2-OPiv/1,4-allyl migration of **124** (Scheme 31).⁴⁸ Thus, propargyl pivalates **124**, possessing a number of different groups at the aromatic ring, the propargylic, and the allylic positions, underwent an efficient and highly enantioselective transformations in the presence of the (R)-MeO-DTBM-BIPHEP- (AuCl)₂/AgSbF₆ catalyst system. According to the mechanistic hypothesis, substrate **124** possessing a terminal alkyne moiety undergoes a gold-promoted 1,2-pivaloxy migration to produce carbene **125**, which upon nucleophilic attack of the ether oxygen atom at the electrophilic center generates the oxonium intermediate **126**. Ionization of the allylic group of the latter produces compound **127**. The following nucleophilic attack of the allyl gold moiety at the allylic cation furnishes benzopyran **128**. Interestingly, when substrate **129**, bearing an electron rich para-methoxybenzyl ether moiety, was subjected to the reaction conditions, the benzopyrane **131** was formed (Scheme 32). This observation provides strong support for the formation of intermediate **130** (an analogue of **127**), thus suggesting the cationic nature of the second migrating group in this cascade transformation.⁴⁸

3.3 Cascade 1,2-OXO/1,2-acyloxy migration

Nevado and co-workers disclosed a stereodivergent formation of 1,3-dienes **133** and **134** via the gold-catalyzed double 1,2-acyloxy migration cascade from the 1,3-bis-propargyl acetate **132** (Scheme 33).^{49,50} Thus, use of IPrAu(NTf)₂ catalyst produces the (Z, Z)-1,3-dienes **133**, while employment of Ph₃PAuNTf₂ catalyst gives the (Z, E)-1,3-diene **134**. The proposed mechanism of this reaction involves the gold-promoted 1,2-acyloxy migration to produce compound **135**, in which the Z-selectivity of the first migration is dictated by avoiding the 1,3-allylic strain between [Au] and R¹ groups (Scheme 34)⁴⁹. The produced gold carbene **136**, upon rotation around the C–C bond and subsequent nucleophilic attack of the adjacent oxygen at the carbene center, gives cyclic intermediate **137**. Ring opening of the latter produces cation **138**, which in the case of Ph₃PAuNTf₂ catalyst used directly produces the (Z-E)-1,3-diene **134**. On the other hand, **138**, possessing bulky IPr ligand of [(IPr)Au(NTf)₂] isomerizes to more stable cation **139**, which upon elimination of gold produces the (Z-Z)-1,3-diene **133**.

In the following report, the same group clarified more mechanistic details, such as substitution effects at the propargylic position of **132** on the stereochemical outcome of this cascade reaction.⁵⁰ Additionally, the synthetic utility of obtained products via this chemistry was demonstrated (Scheme 35).⁵⁰ Thus, after the double migratory cascade reaction of the 1,4-bis-propargylic acetates **140**, the obtained dienes **141** could be hydrolyzed to produce the unsymmetrical 1,2-diketones **142**. A one-pot cascade double migration/hydrolysis followed by condensation with aromatic 1,2-diamines produced quinoxalines **143** in good yields. The obtained dienes were also shown to be good partners in Diels-Alder reaction with *N*-phenylmaleimide to produce the cycloadducts **144** with moderate *endo* selectivity.

4. Conclusions

It was demonstrated that the metal-catalyzed 1,3- and 1,2-OXO migrations of propargylic esters and phosphates, which produce activated allenes and metal carbenes, can efficiently

be followed by the second migration of different groups. It was shown that the 1,2-H migration in the second process lead to mono-,^{25,26} bi-,²⁷ tri-,³² tetra,²⁸ and hetrocyclic²⁹ scaffolds, as well as to acyclic 1,3-dienes.^{43,44} Moreover, employment of alkyl as the second migrating group in these cascade reactions, gaving access to a variety of products including naphthalenes,^{33,34} dienes,^{33,36,38,46,47} and substituted chromens.^{39,48} In addition, double migratory processess involving halogen, acyl, and acyloxy migrating groups, affords β -⁴⁰ and δ -diketones,⁴¹ as well as substituted 1,3-dienes.^{42,49,50} These cascade reactions are triggered by simple and available catalysts, are highly efficient, and usually take place under mild conditions. A wide range of functional groups such as halogen, allyl, phenoxide, cyclopropane, vinyl silane, olefine, alkyne, acetal, ester, protected alcohol, and protected amine, are tolerated in these transformations. Importantly, the products of the double migratory reactions could be further functionalized, thus offering a set of novel powerful tools for organic synthesis. We anticipate that this *tutorial review* which highlights this new emerging field, would help researchers to better undrestand the chemistry of migratory cascades, which, in turn, may lead to design of novel useful transformations toward synthetically challenging structures.

Acknowledgments

We greatly acknowledge the National Institute of Health (GM-64444) for financial support.

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Scheme 1.

Competitive 1,2- or 1,3-migration of propargylic esters and phosphates

Scheme 2.

Double migratory cascade reactions of propargylic esters and phosphates.

Scheme 3.
Gold-catalyzed 1,3-OAC/1,2-H migration cascade towards cyclopentenone.²⁵

Scheme 4.
Competitive 1,2-H shift versus cyclopropanation.²⁶

Scheme 5.

Gold-catalyzed 1,3-OAc/1,2-H migration cascade for the synthesis of bicyclo[3.1.0]hexenes.²⁷

Scheme 6.
Further reactions of propargylic acetates.²⁷

Scheme 7.

Platinum-catalyzed 1,3-OCOR/1,2-H migration cascade towards tetracyclic 2,3-indoline-fused cyclopentenones.²⁸

Scheme 8. Toward the synthesis of the tetracyclic core of vindoline.²⁸

Scheme 9. Copper-catalyzed $1,3\text{-OP(O)(OEt)}_2/1,2\text{-H}$ migration cascade towards heterocycles.²⁹

Scheme 10.
Cycloisomerization of a labeled phosphatyloxy alkynyl pyridine.²⁹

Scheme 11.

Kumada cross-coupling of obtained phosphatidyloxy-containing heterocycles.²⁹

Scheme 12.

Alternative pathways for 1,2 hydrogen shifts to metal carbenes.

Scheme 13.

Metal-catalyzed 1,3-OAc/1,5-H migration cascade for the synthesis of polycyclic compounds.³²

Scheme 14.

Gold-catalyzed 1,3-OXO/1,2-alkyl migration cascade towards dienes and naphthalenes.^{33,34}

Scheme 15.

Proposed mechanism for the gold-catalyzed 1,3-OXO/1,2-alkyl migration cascade.^{33,34}

Scheme 16.
Gold-catalyzed 1,3-OAc migration/ring expansion cascade.³⁶

Scheme 17.

Further insight into the mechanism of gold-catalyzed 1,3-OAc migration/ring expansion cascade.³⁸

Scheme 18. Gold-catalyzed enantioselective 1,3-OPiv/1,3-alkyl migration cascade.³⁹

Scheme 19. Gold-catalyzed 1,3-OCOR/1,3-acyl migration cascade.⁴⁰

Scheme 20.
Gold-catalyzed 1,3-OAc/1,5-acyl migration cascade.⁴¹

Scheme 21.

Mechanism of gold-catalyzed 1,3-OAc/1,5-acyl migration cascade supported by DFT calculations.⁴¹

Scheme 22.

Intramolecular [4+2] cycloaddition of obtained dienes.⁴¹

Scheme 23.

Stereocontrolled gold- and copper-catalyzed 1,3- OP(O)(OEt)₂/1,3-halogen migration towards dienes.⁴²

Scheme 24.
Mechanism of the stereodivergent reaction.⁴²

Scheme 25. Selective transformations of an obtained product.⁴²

Scheme 26.

Gold-catalyzed 1,2-OPiv/1,2-H migration cascade for synthesis of 1,3-dienes.⁴³

Scheme 27.

One-pot Au-catalyzed diene formation/Diels-Alder reaction sequence of propargylic pivalates.⁴³

Scheme 28.

Pt-catalyzed 1,2-OAc/1,2-H migration cascade for synthesis of 1,3-dienes.⁴⁴

Scheme 29. Gold-catalyzed 1,2-OAc/1,4-allyl migration cascade.^{46–47}

Scheme 30. Employment of propargylic thioester in gold-catalyzed double migration.^{46, 47}

Scheme 31.
Enantioselective gold-catalyzed 1,2-OPiv/1,4-allyl migration cascade.⁴⁸

Scheme 32.
Mechanistic studies of the second migration process.⁴⁸

Scheme 33. Stereocontrolled double 1,2-acyloxy migration cascades.^{49,50}

Scheme 34.
Mechanism of double 1,2-acyloxy migration.⁴⁹

Scheme 35.

Synthetic utilities of obtained 2,3-bis-acetoxy-1,3-dienes.⁵⁰