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Copper-, Silver-, and Gold-Catalyzed Migratory Cycloisomerizations Leading to Heterocyclic Five-Membered Rings

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Keywords

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1. Introduction

Aromatic heterocycles are highly important structural units that are found in a vast number of biologically active natural compounds, pharmaceuticals, and materials.[1] Aromatic heterocycles are important intermediates in organic synthesis, often providing access to other highly desirable structures.[2] A myriad of methodologies and protocols have been developed for their synthesis,[1] and, although generally high efficiencies and selectivities can be achieved, a large number of these methodologies are limited to the preparation of heterocycles with particular substitution patterns. Thus, there is a compelling need to develop novel and more general methods for the synthesis of heterocycles.

In recent years, the use of transition-metal-catalyzed transformations truly revolutionized the area of heterocyclic chemistry.[3–15] Many research groups have focused on the development of general methods that utilize readily accessible starting materials under mild reaction conditions for the synthesis of densely functionalized heterocyclic cores to achieve better functional group compatibilities and greater levels of molecular complexity. A particularly attractive approach toward this goal involves the incorporation of molecular rearrangement steps into the transition-metal-catalyzed cycloisomerization cascade reactions. In most cases, this approach provides a significant advantage over alternative routes in the convergent preparation of heterocycles with new substitution patterns. This review covers the most important recent advances in the Cu-,[11,16–19] Ag-,[12] and Au-catalyzed[20–27] syntheses of five-membered aromatic heterocycles proceeding with 1,*n* migrations of various groups during the assembly of the heterocyclic ring. The main organization of this review is based on the type of migrating group, and the discussion of a particular migrating group is structured by the type of its 1,*n* shift. The concepts underlying a given transformation and the synthetic applicability of the corresponding method are emphasized. A brief discussion

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of the mechanism is given where needed to shed some light on possible reaction intermediates in the catalytic transformation.

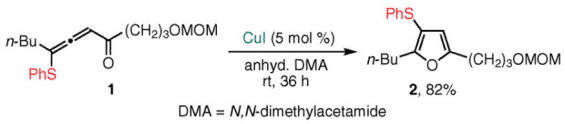
2. Synthesis of Heterocycles via Migratory Cycloisomerizations

2.1. Formal Hydrogen Migration

Among a variety of transition-metal-catalyzed syntheses of aromatic heterocycles containing five-membered rings, the cycloisomerization of *single-component* acyclic precursors represents the most versatile, atom-economical, and direct approach.[15,21,28] Moreover, a major fraction of the corresponding *multicomponent* syntheses[10,29,30] also relies on the fundamental reactivities of these key acyclic precursors. Extensive research on the synthesis of aromatic heterocycles through transition-metal-catalyzed cycloisomerizations has been stimulated by the pioneering work of Heilbron (1947; Hg, 2-en-4-yne-1-ols),[31] Castro (1966; Cu, *ortho*-alkynyl anilines),[32] Miller (1969; Hg, alkynyl epoxides),[33] Huang (1986 and 1987; Pd, alkynyl ketones[34] and propargyl ketones[35]), and Marshall (1990; Ag, Rh, allenyl ketones).[36] The cycloisomerizations of allenyl- or alkynyl-containing substrates, catalyzed by Ag, Cu, or Au complexes,[11–13,28] have been extensively utilized in the construction of heterocyclic cores (Figure 1). Mechanistically, these reactions proceed via formal 1,2- or 1,3-hydrogen migrations (prototropic isomerizations, G = H), which limit these methodologies to the preparation of heterocyclic frameworks with at least one unsubstituted position. In recent years, researchers have sought to develop novel strategies that might help overcome this limitation. One of the possible solutions involves the introduction of a migrating group other than hydrogen into the transition-metal-catalyzed cascade cycloisomerizations of allenes and alkynes. Subsequent sections of this review describe advances in this exciting and growing area.

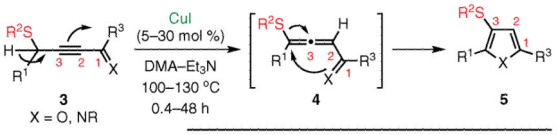
2.2. Sulfur and Selenium Migrations

In 2003, our group discovered that the Cu(I)-catalyzed cycloisomerization of 4-thio-substituted allenone **1** proceeded very efficiently with a 1,2 migration of the phenylsulfanyl group,[37,38] providing 3-thio-substituted furan[39]**2** in high yield.[40] This discovery led us to formulate a general concept of transition-metal-catalyzed cascade cycloisomerizations of alkynyl and allenyl systems involving the formal 1,2 migration of different functional groups as the key step in a rapid assembly of densely functionalized heterocyclic cores (vide infra).



eq 1

(Ref. 40)

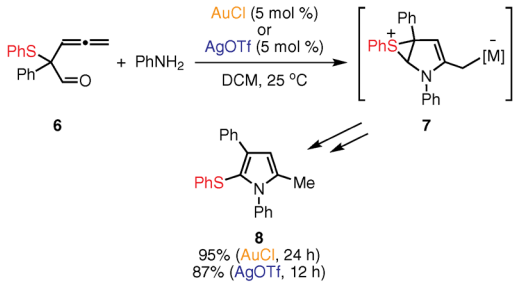


X[a]	R1	R2	R3	Yield
O	*n*-Bu	Ph	Ph	91%
O	*n*-Bu	Ph	Me	76%
O	*n*-Bu	Ph	*t*-Bu	89%
O	*n*-Bu	Ph	Me_2C=CH	95%
O	*n*-Bu	Ph	H	71%
O	Me	Ph	$MeO_2C(CH_2)_2$	71%
O	$THPO(CH_2)_3$	Ph	Me	93%
O	*n*-Bu	*n*-dodecyl	Me	72%
N*t*-Bu	*n*-Bu	Ph	H	78%
NTr	*n*-Bu	Ph	H	85%
NEB	*n*-Bu	Ph	H	74%
N*t*-Bu	*n*-Bu	*n*-dodecyl	H	86%
NEB	$THPO(CH_2)_3$	Ph	H	78%
NEB	*n*-Bu	*n*-dodecyl	H	67%
b,c	*n*-Bu	Ph	*c*	53%

[a] Tr = Ph_3C; EB = $CH(Me)CH_2CO_2Et$; THP = tetrahydropyran-2-yl. [b] Reaction carried out with CuBr (50 mol %) at 150 °C for 12 h. [c] 3-*n*-Butyl-5-methyl-2-phenylthioindolizine was isolated.

eq 2

(Ref. 40,46)



eq 3

(Ref. 48)

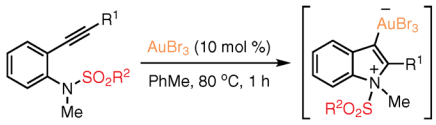
This report had been preceded by our disclosure in 2001 and 2002 that alkynyl imines and ketones (see Figure 1; G = H, X = NR or O) could be transformed highly efficiently into pyrroles[41,42] and furans[43] via the Cu(I)-catalyzed cycloisomerization. In this way, the alkynyl imines and ketones serve as surrogates of reactive allenyl intermediates generated in situ by the base-assisted propargyl–allenyl isomerization. In light of these findings from 2001–2003, our group next attempted a migratory cycloisomerization of substituted propargyl sulfides **3**, undoubtedly superior precursors when compared with their allenyl sulfide analogues from a synthetic point of view. We found that 3-sulfanyl-substituted furans, pyrroles,[44] and even indolizines[45]**5** are efficiently accessed via the Cu(I)-catalyzed migratory cycloisomerization of the corresponding propargyl sulfides (eq 2).[40,46] The

alkylsulfanyl group migrates with efficiency comparable to that of its phenylsulfanyl analogue, and a variety of functional groups are perfectly tolerated under these reaction conditions. It is believed that, mechanistically, this transformation proceeds through the Cu(I)-catalyzed cycloisomerization of reactive allenyl sulfide **4**, wherein a 1,2 migration of an alkylthio or arylthio group[47] occurs via a thiirenium intermediate (vide infra). This transformation represents the first example of 1,2 migration of the sulfanyl group from an olefinic sp^2 carbon to an sp center.[37]

Recently, Wang and co-workers reported another example of a 1,2-sulfur migration that was utilized in the assembly of polysubstituted pyrroles **8** via an acid-catalyzed cascade reaction sequence of skipped allenyl aldehydes **6** and anilines. They also demonstrated that this reaction could be catalyzed by Au(I) or Ag salts, wherein the 1,2 migration of the sulfanyl group occurs intramolecularly via the proposed thiiranium intermediate **7** (eq 3).[48]

In 2007, Yamamoto's group showed that cycloisomerization of *ortho*-alkynylsulfonanilides in the presence of a Au(III) catalyst produces 3-sulfonylindoles via a 1,3 migration of a sulfonyl group (eq 4).[49,50] This reaction is compatible with a variety of alkyl, aryl, and terminal alkynes and provides the indole products in generally high yields. The proposed mechanism involves Au-catalyzed 5-*endo*-*dig* cyclization of *ortho*-alkynylsulfonamides to the zwitterionic indolyl–gold intermediate **9**, in which the 1,3 migration of the sulfonyl group occurs intramolecularly.

Our group recently extended the 1,2-sulfur migration approach (see eq 2) to the related 1,2-selenium migration in the Cu(I)-catalyzed cycloisomerization cascade of propargyl selenides into polysubstituted 3-selenylfurans and pyrroles (eq 5).[46] Remarkably,



R^1	R^2	Yield
H	Me	71%
Cy	Me	62%
n-Pr	Me	95%
Ph	Me	92%
4-$MeOC_6H_4$	Me	81%
4-$F_3CC_6H_4$	Me	51%
n-Pr	4-$MeOC_6H_4$	85%
n-Pr	4-AcC_6H_4	80%
n-Pr	Me[a]	60%

[a] N(*i*-Pr) instead of NMe.

eq 4

(Ref. 50) the 1,2 migration of the seleno group is more facile than that of the thio groups; this fact permits such cycloisomerizations to be carried out under significantly milder reaction conditions. The proposed mechanism for selenium migration is analogous to that suggested for the Cu(I)-catalyzed cycloisomerization of propargyl sulfides and involves formation of the reactive allenyl intermediate **10** via the initial prototropic rearrangement.

2.3. Halogen Migration

In 2005, our group reported a very efficient and regiodivergent Au-catalyzed haloallenyl ketone cycloisomerization that proceeds with a 1,2 migration of iodine, bromine, or chlorine atoms,[51] and leads to 3-halofurans with 1–4 substituents (eq 6).[52] Remarkably, in the presence of the Au(III) catalyst, 1,2 migrations of bromine and iodine are more facile than 1,2-alkyl and even 1,2-hydrogen shifts in these allenyl ketones. In contrast, employment of a Au(I) catalyst, Et_3PAuCl, for the cycloisomerization of ambident C-4 monohalo-substituted allenones (see eq 6, R^1 = H) furnishes 2-halofuran products via exclusive 1,2-hydrogen migration. It was demonstrated that various functionalities, including alkene and free hydroxyl groups, are tolerated under the reaction conditions. Iodo- and bromo-substituted substrates were shown to be more efficient in this cycloisomerization than their chloro-substituted analogues. The 3-halofurans thus obtained can easily be further functionalized at the C-3 position via cross-coupling protocols.[53]

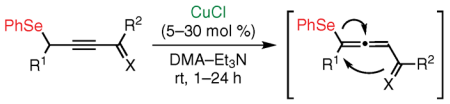
Thorough mechanistic studies, including high-level Density Functional Theory (DFT) calculations, have indicated that activation of the distal double bond of the allene with either a Au(I) or Au(III) catalyst leads to the formation of the gold–carbene intermediate **11**, wherein a kinetically favored 1,2-halogen migration gives 3-halofuran **12** (Scheme 1).[54] However, the use of $Au(PR_3)L$ (L = Cl, OTf; R = Et, Ph) catalysts in the case of ambident haloallenones triggers the stepwise counterion- or ligand-assisted[55] hydrogen shift, leading to 2-halofurans **13**. This observation indicates that, in these Au-catalyzed processes, whether hydrogen or bromine migrates is determined by the nature of the ligand on Au.[52,54] In addition, switching the reaction solvent from toluene to THF, which is capable of assisting the stepwise 1,2-hydrogen migration, provides the regiodivergent formation of 2-halofurans **13**.[52]

2.4. Carbon Migration

The first example of a 1,2-alkyl shift[56,57] in the Au-catalyzed synthesis of heterocycles was reported by Toste and co-workers in 2005.[58] In the presence of a cationic Au(I) catalyst, homopropargylic azides possessing cyclobutyl or cyclopentyl substituents undergo an acetylenic Schmidt reaction leading to C-3–C-4-fused pyrroles in good yields (eq 7).[58] This protocol allows for the rapid assembly of N-unprotected pyrroles possessing 1–4 substituents. According to the mechanistic hypothesis, the Au(I) catalyst activates the alkyne moiety toward nucleophilic attack by the azide to produce gold–carbene **14** with loss of dinitrogen. A subsequent 1,2 migration of a CH_2 group in the cyclobutyl or cyclopentyl ring to the gold–carbene center furnishes the pyrrole product after tautomerization.

Aiming to incorporate various 1,2-migratory groups into the cycloisomerization cascade, we developed an efficient synthesis of furans with 1–4 substituents. The synthesis proceeds by a 1,2 migration of alkyl or aryl groups in allenyl ketones in the presence of π-philic Au(I), Ag, Cu(I), or Cu(II) catalysts (eq 8).[59] Based on studies of the migratory aptitude of various groups, we proposed this cycloisomerization to occur via metal–oxonium ion intermediate **15**. The latter can be viewed as a resonance form of a metal–carbene intermediate analogous to **11**, but with the carbon atom attached to the metal possessing more cationic than carbene-like character.[46,59]

In 2006, Iwasawa and co-workers established an efficient Au(III)-catalyzed protocol for the construction of N-1–C-2-fused polycyclic indole skeletons via a cycloisomerization–



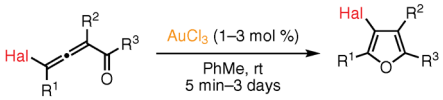
X	R^1	R^2	Yield
N(*t*-Bu)	*n*-Bu	H	74%
N(EB)	*n*-Bu	H	57%
NTr[a]	*n*-Bu	H	54%
O	*n*-Bu	H	74%
O	*n*-Bu	Me	71%
O	*n*-Bu	Ph	84%
O	Bn	*t*-Bu	71%
O	Bn	H	53%

[a] At 110 °C.

DMA = *N*,*N*-dimethylacetamide
Tr = trityl (Ph_3C)
EB = ethyl butyryl or $CH(Me)CH_2CO_2Et$

eq 5

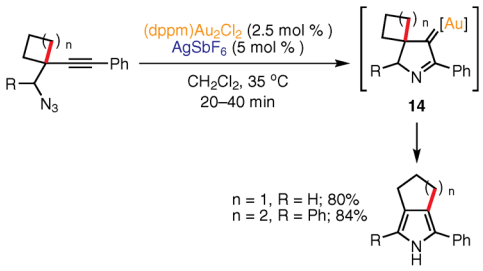
(Ref. 46)



Hal	R^1	R^2	R^3	Yield
Br	H	H	*n*-Oct	86%
I	H	H	*n*-Oct	97%
Br	*n*-Bu	Ph	Ph	75%
I	*n*-Bu	Ph	Ph	73%
Br	*n*-Hep	Me	H	73%
I	H	H	Ph	71%
Br	$TBSO(CH_2)_2$	Ph	Ph	73%
Br	$HOCH_2$	Ph	Ph	61%
Cl	$TBSO(CH_2)_2$	Ph	Ph	48%
Br	$H_2C{=}CHCH_2CH(Ph)$	Ph	Ph	88%

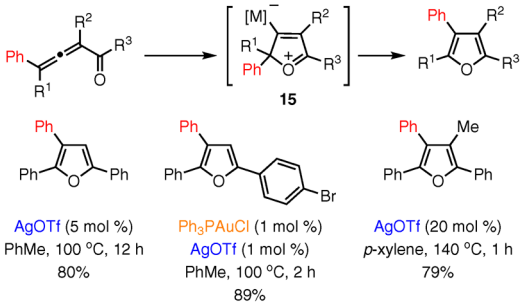
eq 6

(Ref. 52)



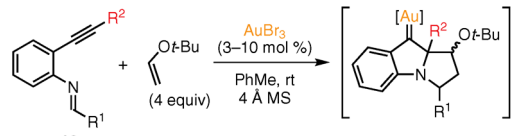
eq 7

(Ref. 58)



eq 8

(Ref. 46,59)

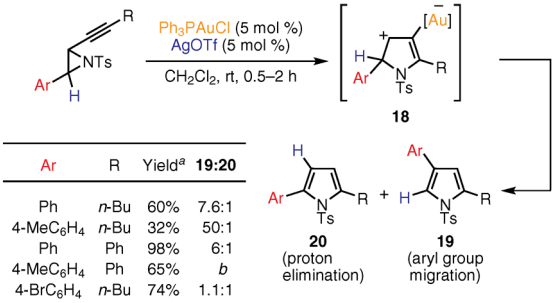


R^1	R^2	Hours	Yield
Ph	*n*-Pr	2.5	80%
Ph	Me	22	81%
Ph	Cy	2	89%
Ph	Ph	0.5	62%
i-PrO[a]	*n*-Pr	1	60%

[a] 10 equiv of $H_2C{=}CHOt\text{-}Bu$ was used.

eq 9

(Ref. 60)



Ar	R	Yield[a]	19:20
Ph	*n*-Bu	60%	7.6:1
4-MeC_6H_4	*n*-Bu	32%	50:1
Ph	Ph	98%	6:1
4-MeC_6H_4	Ph	65%	*b*
4-BrC_6H_4	*n*-Bu	74%	1.1:1

[a] Isolated yield of **19** + **20**.
[b] Only **19** was observed.

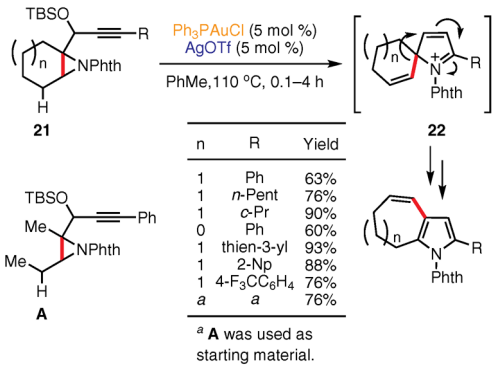
eq 10

(Ref. 62) cycloaddition reaction sequence of alkene enol ethers with *ortho*-alkynylphenylanilides **16**.[60] Iwasawa's group showed that the latter substrates (i.e., *ortho*-alkynylphenylanilides), upon activation with the Au(III) catalyst, generate reactive azomethine ylides.[61] Interception of such ylides with *tert*-butyl vinyl ether via a [3 + 2] cycloaddition leads to the formation of the key gold–carbene intermediates. 1,2-Alkyl migration to the Au-stabilized carbene center in the latter intermediates affords fused indole products in moderate-to-high yields (eq 9).[60]

Very recently, another example of the synthesis of heterocycles via a 1,2-aryl group migration to a cationic center was reported by Davies and Martin.[62] In this study, alkynyl aziridines were shown to undergo the Au(I)-catalyzed cycloisomerization, providing mixtures of regioisomeric pyrroles **19** and **20** (eq 10). According to the proposed mechanism, ring-opening of the aziridine and subsequent nucleophilic attack of the nitrogen atom at the distal position of the alkyne, activated by the Au(I) catalyst, affords the metal-substituted intermediate **18**. Interestingly, 1,2 migration of the phenyl group is preferred in this intermediate over the generally facile proton elimination, leading to pyrrole **19** as the major product. Introduction of electron-rich aryl groups provides **19** exclusively, whereas the isomerization of substrates with electron-deficient aryl substituents (e.g., 4-bromo) exhibits poor selectivity. The authors also demonstrated that the use of a more basic tosylate-containing, instead of triflate-containing, Au(I) catalyst[55] favors the proton elimination pathway, furnishing pyrroles **20** as the sole regioisomers in excellent yields.

The utility of aziridines in the synthesis of pyrroles was further demonstrated by Tu and co-workers, who reported that cycloisomerization of skipped alkynyl aziridines **21** in the presence of a Au(I) catalyst affords polysubstituted 3-vinylpyrroles via a formal 1,2-alkenyl shift (eq 11).[63] Various alkyl-, aryl-, and heteroaryl-substituted alkynes were easily transformed into pyrrole products in good yields. A mechanistic hypothesis for this transformation cascade features the 1,2-alkenyl migration in the spirocyclic iminium intermediate **22**, while formation of the alkenyl unit in the latter arises from the prior proton elimination step. The authors showed that this reaction could equally efficiently proceed with a ring expansion of the five- and six-membered rings fused to the aziridine moiety, as well as with a 1,2-propenyl shift in the case of acyclic substrates.

Besides migratory cycloisomerizations proceeding by 1,2 shifts, several groups have recently reported examples of Au- and Ag-catalyzed counterparts taking place by 1,3 migrations of alkyl,



n	R	Yield
1	Ph	63%
1	*n*-Pent	76%
1	*c*-Pr	90%
0	Ph	60%
1	thien-3-yl	93%
1	2-Np	88%
1	4-$F_3CC_6H_4$	76%
a	*a*	76%

[a] **A** was used as starting material.

eq 11

(Ref. 63) alkenyl, and carbonyl groups. Similarly to the Pt(II)-catalyzed migratory cycloisomerizations leading to benzofuran[64–68] and indole[64,68,69] cores, Yamamoto's group disclosed the Au(I)-catalyzed cycloisomerization of *ortho*-alkynylthiophenol alkyl ethers into 2,3-disubstituted benzothiophenes in excellent yields. This transformation is believed to occur by an intramolecular 1,3 migration of the alkyl group attached to sulfur in intermediate **23** (eq 12).[70] Remarkably, a variety of 1,3-migrating groups, including Si-containing and cyclic tetrahydropyranyl ones, were easily incorporated into this transformation cascade. Other sulfur substituents capable of stabilizing the incipient positive charge, such as allyl and *para*-methoxybenzyl,[71,72] were also efficiently employed, leading to 3-allyl- or 3-benzylbenzothiophenes, respectively. According to the proposed mechanism, this reaction cascade begins with the Au-catalyzed 5-*endo*-*dig* cyclization of the *ortho*-alkynylthiophenol alkyl ether to give the gold-substituted benzothiophenium intermediate **23**, which subsequently undergoes intramolecular 1,3-alkyl migration to give the rearranged final product.

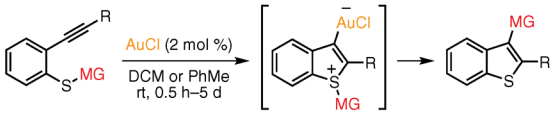
Following this report, the same group later disclosed that the Au(I)-catalyzed carbothiolation reaction of optically active *ortho*-alkynylphenyl 1-phenylethyl sulfides proceeded with predominant retention of the configuration in the 1-phenylethyl migrating group (see eq 12, last two entries).[73] This observation indicates that, at least in the case of 1-arylethyl groups, 1,3-alkyl migration proceeds through formation of a contact ion pair during the migration process.

Oh and co-workers have very recently demonstrated that a variety of 3-vinylindoles, possessing different alkyl and aryl substituents at C-2, can be accessed efficiently through a 1,3-alkenyl shift in a Ag-catalyzed cascade reaction (eq 13).[74] The authors have proposed that the initial condensation of *N*-(alkynylphenyl)formimidate **24** with malonate derivative **25**, and subsequent cyclization in the presence of the silver catalyst, provide *N*-alkenyl intermediate **26**. The 1,3 shift of the alkenyl group in this intermediate from N to C-3 gives indole derivative **27**. However, the exact mechanism and nature of this interesting 1,3 migration remain unknown.

In 2007, Istrate and Gagosz reported that *N*,*N*-disubstituted (*Z*)-(2-en-4-ynyl)amines, with a second allyl group attached to the nitrogen atom, undergo a Au(I)-catalyzed cycloisomerization with a 1,3-allyl shift to afford tri- and tetrasubstituted pyrroles (eq 14, conditions A).[75] This transformation allows for the synthesis of homoallyl-substituted pyrroles bearing various functional groups in good-to-excellent yields. The proposed mechanism involves, in the first step, activation of the alkyne moiety toward 5-*exo*-*dig* cyclization to give the cyclic vinyl–gold intermediate **28**. A subsequent 1,3-allyl shift[64,76] occurs via a Au(I)-catalyzed aza-Claisen-type rearrangement, furnishing the corresponding pyrrole. More recently, Heugebaert and Stevens applied the same concept to the synthesis of isoindoles from *N*-allyl-benzylamine derivatives (see eq 14, conditions B).[77]

Zhang and co-workers recently synthesized a variety of tri- and tetrasubstituted N–C-2-fused pyrroles by the Au(I)-catalyzed cycloisomerization of (*Z*)-(2-en-4-ynyl)lactams **29** (eq 15).[78] This interesting synthesis proceeds by a formal ring expansion of the β-lactam moiety via a 1,3-carbonyl migration.[79] Similarly to Gagosz's rationale, the Au(I)-catalyzed 5-*exo*-*dig* cyclization is followed by lactam ring opening, which leads to the formation of nucleophilic vinyl–Au species **30**. A subsequent 1,2 addition of the latter functional group to the activated carbonyl function produces the fused pyrrole product.

Finally, several migratory cycloisomerizations involving a Claisen-type rearrangement of the carbon skeleton of the substrate prior to the heterocyclization step have been reported. Kirsch and co-workers first reported that vinyl propargyl ethers **31** could be converted into densely substituted furans via a Au(I)-catalyzed cycloisomerization reaction (Scheme 2, **Part (a)**)[80,81] Thus, a variety of tetrasubstituted alkyl, aryl, and heteroarylfurans possessing a carbonyl group at C-3 were obtained under very mild reaction conditions. It is believed that this cascade process begins



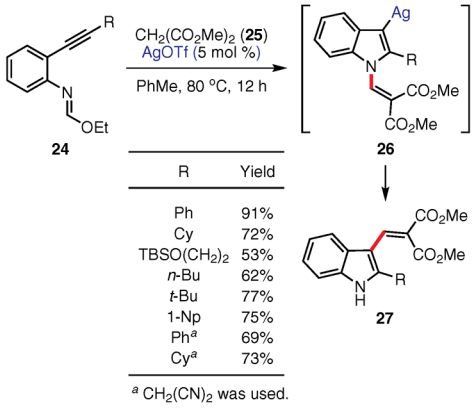
23

R	MG[a]	Yield
n-Pr	$MeOCH_2$	93%
4-$F_3CC_6H_4$	$MeOCH_2$	100%
4-$MeOC_6H_4$	$MeOCH_2$	96%
EtO_2C	$MeOCH_2$	85%
Ph	$TBSOCH_2$	99%
Ph	2-THP	93%
Ph	allyl	93%
Ph	PMB	98%
4-$MeOC_6H_4$	(*R*)-MeCH(Ph) (97% ee)	98% (88% ee)
4-$F_3CC_6H_4$	(*R*)-MeCH(Ph) (95% ee)	87% (72% ee)

[a] MG = migrating group.

eq 12

(Ref. 70,73)

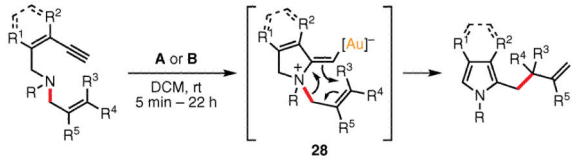


R	Yield
Ph	91%
Cy	72%
TBSO(CH2)2	53%
n-Bu	62%
t-Bu	77%
1-Np	75%
Ph[a]	69%
Cy[a]	73%

[a] $CH_2(CN)_2$ was used.

eq 13

(Ref. 74)



R^1	R^2	R^3	R^4	R^5	Yield[a]
H	Ph	H	H	H	72%
H	Me	H	H	Me	89%
Cl	Me	H	Ph	H	98%
H	Me	Me	Me	H	90%
H	Me	Me	HC≡C	H	84%

[a] **A** = $(4\text{-}F_3CC_6H_4)_3PAuNTf_2$ (2 mol %); R = Ts.

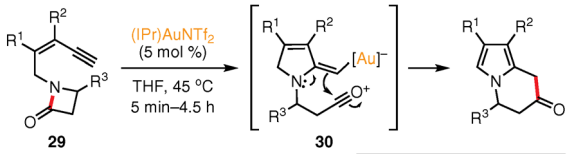
R	R^3	R^4	R^5	Yield[a]
allyl	H	H	H	98%
Bn	Me	Me	H	72%
n-Pr	Ph	H	H	98%
n-Pr	Ph	H	Cl	76%

[a] **B**: $AuCl_3$ (1 mol %); R^1,R^2 = HC=CH-CH=CH.

eq 14

(Ref. 75,77) with a Au(I)-catalyzed Claisen-type rearrangement[82] and leads to the formation of the reactive skipped allenyl ketone intermediate **32**, which undergoes a Au(I)-catalyzed 5-*exo*-*dig* cyclization to produce the furan ring.

The same group later disclosed that vinyl propargyl ethers **31** could also be employed in a very efficient synthesis of densely substituted pyrroles via the Ag–Au(I)-catalyzed condensation- cycloisomerization reaction sequence (see Scheme 2, Part (b))[83] Thus, skipped allenyl ketones **32**, formed by the Ag-catalyzed



R^1	R^2	R^3	Yield
H	H	*n*-Pr	78%
H	$BnO(CH_2)_2$	Me	74%
Ph	H	Me	90%
H	*n*-Pr	Bn	66%
a	*a*	Me	70%

[a] $R^1,R^2 = -(CH_2)_5-$

eq 15

(Ref. 78) Claisen rearrangement, were intercepted by the amination reaction with various anilines and the resulting imines underwent the Au(I)-catalyzed 5-*exo*-*dig* cyclization to furnish the corresponding pyrroles. The authors demonstrated that a variety of pyrroles possessing different labile groups could be rapidly obtained in moderate-to-high yields under mild reaction conditions. In addition, the reaction was quite general with respect to the aromatic amine component, whereas aliphatic amines (R^5 = Me, *i*-Pr, Bn) did not undergo this transformation at all.

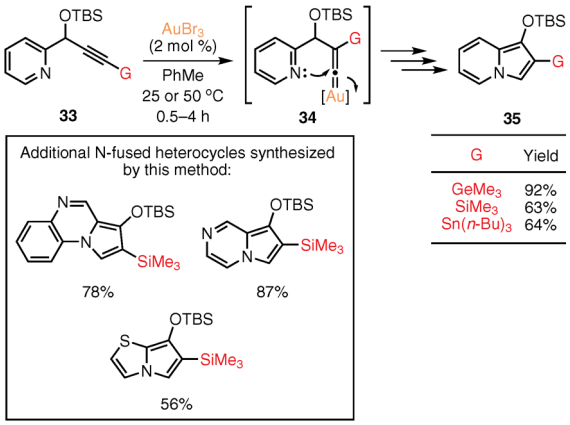
More recently, Saito et al. applied the above methodology to the direct synthesis of pyrroles from vinyl propargyl amines **31** (X = Y = NTs) in the presence of an (NHC)Au(I) catalyst[84] (see Scheme 2, Part (c)).[85] Furthermore, this new catalytic system was shown to be highly efficient for the cycloisomerization of ether analogues as well (X = Y = O, see Scheme 2, Part (c), conditions (ii)).

2.5. Silicon, Germanium, and Tin Migrations

Aiming at the efficient synthesis of not-so-easily accessible C-2-substituted indolizines, our group developed a highly efficient, Au(III)-catalyzed cascade cycloisomerization of skipped propargylpyridines 33 into indolizines 35 (eq 16).[86,87] This cascade is proposed to occur with a facile 1,2 migration of a silyl, stannyl, and even germyl group via an alkyne–vinylidene isomerization[88] of propargyl substrate 33 to give the reactive organogold species 34. A subsequent cyclization of the intermediate, 34, followed by a series of 1,2-hydride shifts, furnishes the corresponding indolizine. We have further demonstrated the synthetic utility of this methodology by carrying out the facile synthesis of various N-fused heterocycles, including pyrrolo[1,2-*a*]quinoxaline, pyrrolo[1,2-*a*]pyrazine, and pyrrolo[2,1-*b*]thiazole.

Yamamoto's group has developed the Au(I)-catalyzed, high-yield synthesis of 3-silyl-substituted benzothiophenes through a 1,3-silyl group migration during the cycloisomerization cascade of *ortho*-alkynylthiophenol silyl ethers (eq 17).[89] However, lower yields were obtained for substrates bearing very bulky or strong electron-withdrawing substituents, or containing less nucleophilic silyl migrating groups. In contrast to the intramolecular nature of the 1,3-alkyl-group migration in the analogous system (see eq 12),

the observed crossover of two different silyl groups during the cycloisomerization of two different substrates indicated that the 1,3 migration of the silyl group proceeds intermolecularly. The observed crossover was rationalized by the suggested longer



eq 16

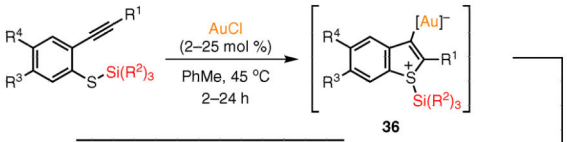
(Ref. 86) lifetime of the gold–silylsulfonium ion intermediate 36 due to the lower migratory ability of a silyl group relative to that of an alkyl group.

2.6. Acyloxy, Phosphatyloxy, and Sulfonyloxy Migrations

In 2004, our group envisioned that highly reactive allenyl substrates could be accessed via a formal 1,3 migration in propargyl acetates,[90–92] phosphates, or sulfonates.[93] This early concept later evolved into a series of highly efficient, practical, and general methodologies for the assembly of polysubstituted furans and indolizines. Accordingly, we demonstrated that an array of densely functionalized 3-acyloxyfurans could be synthesized via a Cu(I)-catalyzed cycloisomerization cascade of conjugated alkynyl ketone acetates proceeding through a formal 1,2-acyloxy-group migration (eq 18).[93] The nature of the base required for the selective formation of the 3-acyloxy regioisomer supported possible involvement of allene intermediate 37, which is generated upon initial prototropic rearrangement of the substrate. Based on further mechanistic studies involving ^{17}O-labeled substrates, we proposed that this formal 1,2-acyloxy-group migration[94,95] likely occurs through the involvement of a dioxolenylium intermediate.[96]

Our group also investigated the Cu(I)-catalyzed cycloisomerization of conjugated keto or pyridino propargyl phosphates in the absence of a base (eq 19).[96] This transformation allowed for a highly efficient synthesis of 3-phosphatyloxy furans and indolizines[97] via a formal 1,3-phosphatyloxy group migration.[96] Thorough mechanistic studies of this transformation with the aid of ^{17}O-labeled substrates revealed that the cycloisomerization proceeds via an initial formal [3,3]-sigmatropic rearrangement of propargyl phosphates into the reactive allenyl phosphates 38. It should be noted that the phosphatyloxy-containing furans and indolizines represent versatile synthons, as the phosphatyloxy group can efficiently be substituted with various alkyl and aryl groups by the Kumada cross-coupling reaction.[96]

Next, we developed an alternative route to tetrasubstituted and even to fused furans via a transition-metal-catalyzed migratory cycloisomerization of skipped propargylic substrates. Thus, alkynyl acetates 39 underwent, in the presence of a silver catalyst at room temperature, a formal 1,2-acyloxy-group migration furnishing fully substituted 3-acyloxyfurans in high yields (eq 20).[93,96] The



R¹	R²	R³	R⁴	Yield
n-Pr	*i*-Pr	H	H	98%
2,4-$(MeO)_2C_6H_3$	*i*-Pr	H	H	99%
4-$MeOC_6H_4$	*i*-Pr	H	H	99%
4-$F_3CC_6H_4$	*i*-Pr	H	H	60%
4-$MeOC_6H_4$	*i*-Pr	*a*	*a*	72%
n-Pr	Ph	H	H	40%
4-$MeOC_6H_4$	*i*-Pr	F	H	88%
n-Hex	*b*	H	H	100%
4-$MeOC_6H_4$	*i*-Pr	F	H	51%

[a] $R^3,R^4 = OCH_2O$. [b] $Si(R^2)_3 = Si(s\text{-}Bu)(i\text{-}Pr)_2$.

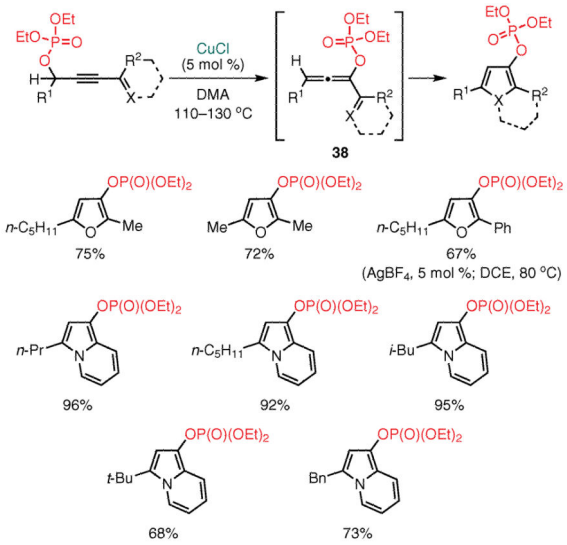
eq 17

(Ref. 89)

R¹	R²	R³	Yield
Ph	Me	Ph	82%
Me	Me	Ph	81%
Et	Me	Ph	69%
i-Pr	Me	Ph	90%
t-Bu	Me	Ph	86%
Ph	*n*-Pent	Ph	80%
Ph	(*S*)-TBSOC(Me)H	Ph	83%
Piv	*n*-Pent	*t*-Bu	80%

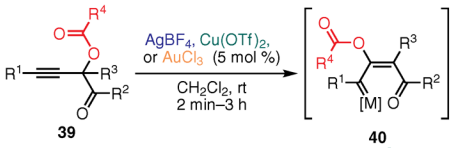
eq 18

(Ref. 93,96)



eq 19

(Ref. 96)



R1	R2	R3	R4	Yield
n-Bu	Ph	Ph	Me	60%
n-Bu	Ph	Ph	*t*-Bu	81%
Ph	Ph	Ph	Me	91%
TMS[a]	Ph	Ph	Me	78%
t-Bu	Ph	Ph	Me	>99%
t-Bu	Ph	Ph	*t*-Bu	73%
t-Bu	Ph	Me	Me	84%
t-Bu	Me	Ph	Me	73%
t-Bu	Me	Me	Me	90%
t-Bu	*b*	*b*	Me	86%

[a] In PhMe. [b] $R^2,R^3 = (CH_2)_4$

eq 20

(Ref. 93,96) mechanism for the cycloisomerization of skipped alkynyl ketones 39 is suggested to follow a Rautenstrauch-type 1,2 migration,[98] resulting in intermediate 40, and subsequent cycloisomerization to the furan ring.[96] Several other transition-metal complexes, including Cu(II) and Au(III), also catalyzed this transformation. Furthermore, phosphatyloxy and tosyloxy groups underwent an analogous 1,2 migration from propargyl (41) and allenyl (42) substrates, providing 3-phosphatyloxy- and 3-tosyloxyfurans, respectively (Scheme 3). In the case of skipped phosphatyloxy alkynyl ketones, 41, cycloisomerization proceeds via two consecutive 1,2 migrations leading to the formation of

allene intermediate 42 and a formal 1,3 shift. Subsequent 1,2 migration gives rise to the final product, 3-phosphatyloxy- or 3-tosyloxyfuran.

3. Conclusions and Outlook

This review highlighted a growing interest in the development of novel cascade transformations that incorporate various molecular rearrangements and functional-group migrations. Recent reports featuring this approach established new, general, highly efficient, and atom-economical transformations that lead to complex and densely functionalized aromatic heterocycles with diverse substitution patterns. These heterocycles are not easily available via alternative routes. A variety of functional groups—including S-, Se-, Hal-, C-, Si-, Ge-, Sn-, and O-containing functionalities—undergo various types of 1,*n* migrations during these heterocycle syntheses. In recent years, in addition to the continuing interest in the traditional Ag and Cu catalysts, the focus of many research groups has shifted to the remarkably efficient and mild gold catalysis. Although further development of novel, more general, and efficient migratory methodologies is certainly highly warranted, the progress achieved so far in this area bodes well for broad application in organic synthesis.

Acknowledgments

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Biographies

Alexander S. Dudnik was born in Krasnodar, Russia. He received his B.S. degree in 2005 from the M. V. Lomonosov Moscow State University. Between 2003 and 2005, he worked as a visiting researcher at the Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. He is currently a fifth-year graduate student in Professor Gevorgyan's group at the University of Illinois at Chicago. A major part of his research in Prof. Gevorgyan's group is devoted to the development of new Lewis acid and gold-, copper-, and silver-catalyzed methodologies involving C–C or C–heteroatom bond-forming reactions and molecular rearrangements leading to carbo- and heterocycles. Alexander has recently received a University of Illinois Graduate College Dean's Scholar Award. After completion of his Ph.D. requirements, he will join the laboratory of Professor Gregory C. Fu at the Massachusetts Institute of Technology as a postdoctoral associate.

Natalia Chernyak was born in Riga, Latvia. She received her B.S. degree in 2002 and M.S. degree in 2005 from Riga Technical University. Between 2000 and 2005, she worked as a researcher at the Latvian Institute of Organic Synthesis. In 2005, she joined the laboratory of Professor Gevorgyan at the University of Illinois at Chicago, where she is currently a fifth-year graduate student. Her dissertation research has focused on the development of novel Pd-catalyzed direct/directed CH-functionalization processes, C–C-bond-forming reactions proceeding via CH activation, and the Cu-catalyzed multicomponent synthesis of heterocycles. Recently, her research achievements were recognized with a Moriarty Graduate Fellowship. Upon graduation, she will join the laboratory of Professor Stephen L. Buchwald at the Massachusetts Institute of Technology, as a postdoctoral associate.

Vladimir Gevorgyan was born in Krasnodar, Russia. He received his B.S. degree in 1978 from Kuban State University and his Ph.D. degree in 1984 from the Latvian Institute of Organic Synthesis, where he was promoted to Group Leader in 1986. He spent two years (1992–1994) in Tohoku University in Sendai, Japan, the first as a Japan Society for the Promotion of Science (JSPS) Postdoctoral Fellow and the second as a Ciba-Geigy International Postdoctoral Fellow. The following year (1995), he was a Visiting Professor at Consiglio Nazionale delle Ricerche (CNR) in Bologna, Italy. He returned to Tohoku University in 1996 as an Assistant Professor and was promoted to Associate Professor in 1997. In 1999, he moved to the University of Illinois at Chicago as an Associate Professor, and was promoted to the rank of Professor in 2003. Prof. Gevorgyan's current research interests cover four main areas: (i) highly selective Pd-catalyzed benzannulations, (ii) novel transition-metal-catalyzed reactions for the synthesis of heterocyclic and naturally occurring compounds, (iii) selective Lewis acid catalyzed bond formation and cleavage reactions, and (iv) the chemistry of strained-ring systems. In 2008, his contributions to the field of organic chemistry were recognized with the University of Illinois at Chicago Researcher of the Year Award.

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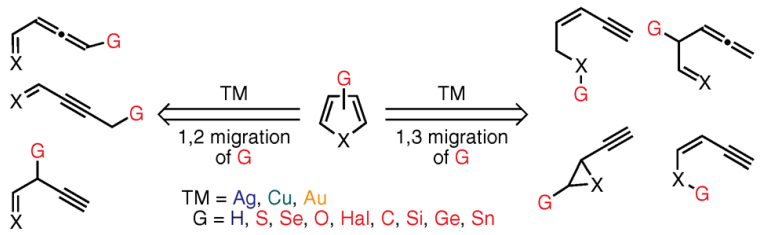
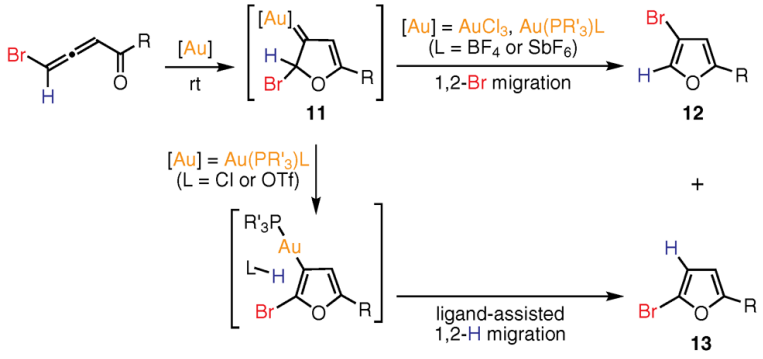


Figure 1.

Retrosynthetic Analysis of Traditional Transition-Metal-Catalyzed Cycloisomerizations Leading to Aromatic Heterocycles.(Ref. 11–13, 28)

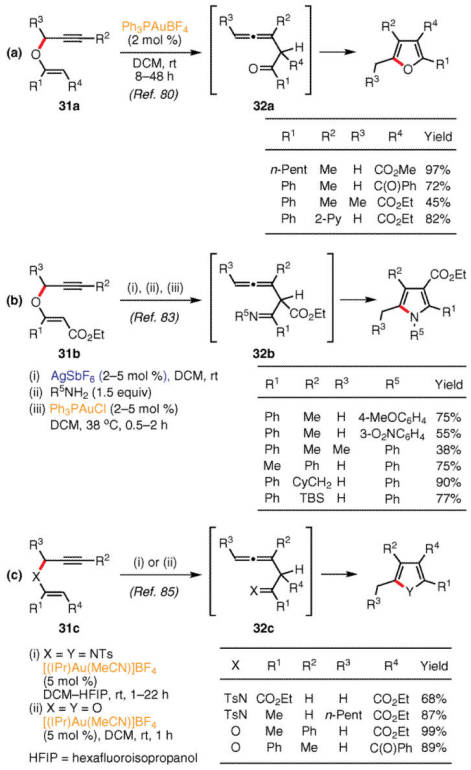


R	[Au][a]	Solvent	12:13
n-Oct	$AuCl_3$	THF	5:95
n-Oct	Et_3PAuCl	PhMe	<1:99
Me	$AuCl_3$	PhMe	96:4
Me	Ph_3PAuBF_4	PhMe	>98:2
Me	$Ph_3PAuOTf$	PhMe	0:100
Me	$Ph_3PAuSbF_6$	PhMe	100:0

[a] 1–5 mol %.

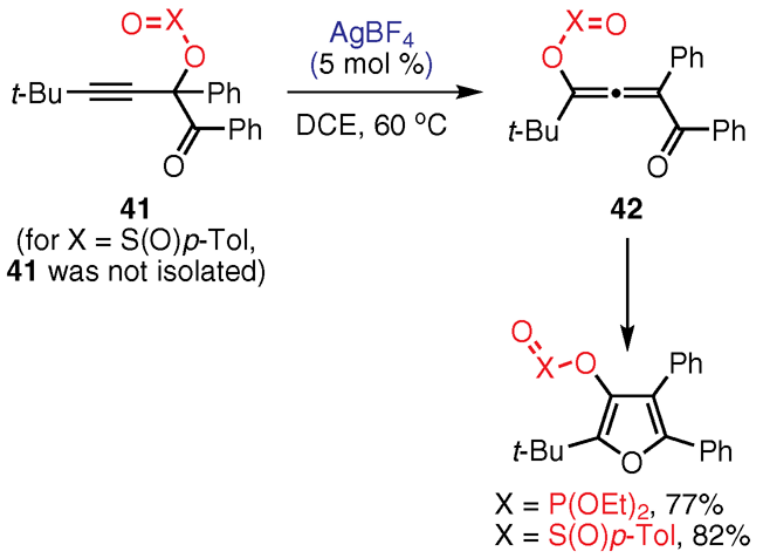
Scheme 1.

Ligand-Controlled Hydrogen vs Bromine 1,2 Migration.(Ref. 52,54)



Scheme 2.

Migratory Cycloisomerizations Involving a Claisen-Type Rearrangement Prior to Heterocyclization.



Scheme 3.

Tetrasubstituted Furans by the Migratory Cycloisomerization of Skipped Propargylic Substrates. (Ref. 93,96)