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Metal-Catalyzed 1,2-Shift of Diverse Migrating Groups in Allenyl Systems as a New Paradigm toward Densely Functionalized Heterocycles

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Abstract: A general, mild, and efficient 1,2-migration/cycloisomerization methodology toward multisubstituted 3-thio-, seleno-, halo-, aryl-, and alkyl-furans and pyrroles, as well as fused heterocycles, valuable building blocks for synthetic chemistry, has been developed. Moreover, regiodivergent conditions have been identified for C-4 bromo- and thio-substituted allenones and alkynones for the assembly of regioisomeric 2-hetero substituted furans selectively. It was demonstrated that, depending on reaction conditions, ambident substrates can be selectively transformed into furan products, as well as undergo selective 6-*exo*-dig or Nazarov cyclizations. Our mechanistic investigations have revealed that the transformation proceeds via allenylcarbonyl or allenylimine intermediates followed by 1,2-group migration to the allenyl *sp* carbon during cycloisomerization. It was found that 1,2-migration of chalcogens and halogens predominantly proceeds via formation of irenium intermediates. Analogous intermediate can also be proposed for 1,2-aryl shift. Furthermore, it was shown that the cycloisomerization cascade can be catalyzed by Brønsted acids, albeit less efficiently, and commonly observed reactivity of Lewis acid catalysts cannot be attributed to the eventual formation of proton. Undoubtedly, thermally induced or Lewis acid-catalyzed transformations proceed via intramolecular Michael addition or activation of the enone moiety pathways, whereas certain carbophilic metals trigger carbenoid/oxonium type pathway. However, a facile cycloisomerization in the presence of cationic complexes, as well as observed migratory aptitude in the cycloisomerization of unsymmetrically disubstituted aryl- and alkylallenes, strongly supports electrophilic nature for this transformation. Full mechanistic details, as well as the scope of this transformation, are discussed.

Introduction

Furans and pyrroles are ubiquitous heterocycles, broadly found in naturally occurring and biologically active compounds,[1,2] as well as in material science.[3] Among these, heterosubstituted furans and pyrroles represent an important subclass, both as synthons[4] and themselves as functionalized heterocycles. Approaches toward functionalized five-membered heterocycles can be divided into two groups: functionalization of a preexisting heterocyclic core, and assembly of the ring from acyclic precursors.[5] Among the two, the latter route has greater potential for rapidly obtaining diversity in functionalized heterocycles. Within this group,[6] the variations of Paal-Knorr synthesis[5] has proven to be the most powerful method for the synthesis of furans and pyrroles. However, this approach is unsuitable for acid-sensitive substrates, as well as C-2 unsubstituted heterocycles, owing to the instability of the precursors.

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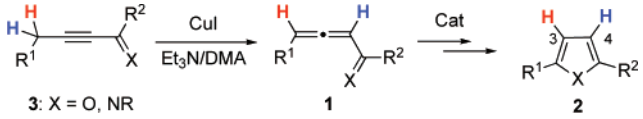
As an alternative, focus has shifted lately to catalytic approaches toward furans[7] and pyrroles[8] from acyclic substrates, which often employ milder conditions and provide easy access to multisubstituted heterocyclic cores. Atom-economical cycloisomerization methods are particularly attractive. Among them, transition metal-catalyzed cycloisomerizations of allenyl ketones **1** introduced by Marshall[7m−q] (Cat = Ag) and then elaborated by Hashmi[7i] (Cat = Au) have become one of the most powerful methods for assembly of furan ring **2**. Along this line, we have recently developed a mild and efficient Cu-catalyzed cycloisomerization of alkynyl imines[9] and ketones **3**[10] into the respective heterocycles **2** (Scheme 1). The reaction conditions, which were developed, are compatible with both acid- and base-sensitive substrates.[9,10] Moreover, this method proved to be especially efficient for the synthesis of C-2 unsubstituted pyrroles **2**, which are not readily available through traditional condensation methods (Scheme 1).[5] Mechanistic investigations revealed that the reaction proceeds through an allenylimine or -ketone intermediate **1**, and that the propargylic protons ultimately reside at the C-3 and C-4 positions of the ring (Scheme 1).[9,11]

Scheme 1. General Cu-Catalyzed Cycloisomerization of Alkynyl Ketones and Imines toward Furans and Pyrroles



Despite a number of advantages of these protocols, their scope is limited to the preparation of C-3 and C-4 unsubstituted heterocycles only. We reasoned that this problem could be alleviated if one of the hydrogens at C-4 in **4** is replaced with a suitable migrating group Y. Thus, aiming at expanding the scope of the migrating group, we have recently developed a set of cascade methods for the synthesis of C-3 substituted pyrroles and furans **7** proceeding via 1,2-shift of thio-,[12] halogen-,[13] and aryl/alkyl-[14] groups in allene **5** (Scheme 2).

Herein, we describe a more detailed study of these transformations, the synthesis of seleno-heterocycles including unprecedented 1,2-selenium migration, as well as a more thorough mechanistic investigation of these unique cascade cycloisomerizations.

Results and Discussion

1,2-Sulfur Migration in the Synthesis of Heterocycles. 1,2-Migration of chalcogenides[15] is an important chemical transformation, which is extensively used in carbohydrate chemistry for substitution at the anomeric center,[16,17] as well as in the synthesis of stereodefined, nonaromatic heterocycles[18,19] and allylsulfides.[18] Furthermore, 1,2-thio-shift is known to occur in

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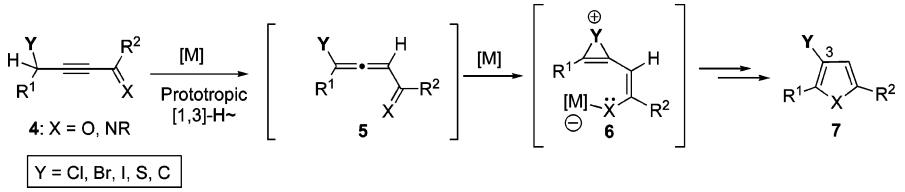
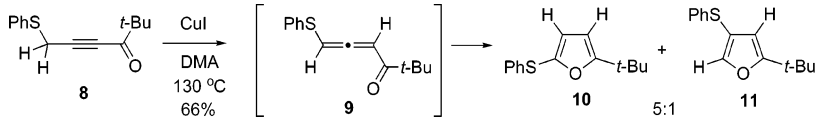
Scheme 2. Introduction of Different Migrating Groups toward Trisubstituted Heterocycles



Scheme 3. 1,2-H Vs 1,2-S Migration during Cycloisomerization

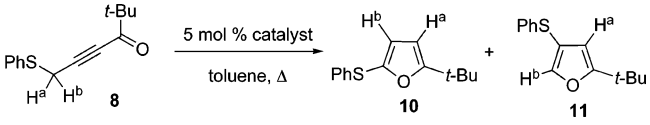


aromatic rings[20] and to carbenoid centers.[21] Known 1,2-migrations of chalcogens can be classified as two types: 1,2-migration from sp^3 center to adjacent sp^3 center via a thiiranium or seleniranium intermediate[16] and 1,2-migration from either sp^3 or sp^2 center to another sp^2-carbon.[7an,20,22] However, prior to our work,[12] there were no reports on 1,2-migration of the thio-group from an olefinic sp^2 carbon to an sp center.

During investigation of the scope of the recently found Cu-catalyzed transformation of alkynyl ketones and imines **3** into 2,5-disubstituted furans[10] and pyrroles **2**,[9] it was discovered that heating of thioalkynyl ketone **8** in DMA in the presence of CuI (10 mol %) not only produced the targeted 2,5-disubstituted furan **10** but also a small amount of the 2,4-disubstituted furan **11** (Scheme 3).

Brief optimization of this reaction revealed that $AuCl_3$, $PtCl_2$, and $PdCl_2(MeCN)_2$ led largely to decomposition. However, employment of $(Et_3P)AuCl$ afforded a 20:1 mixture of regioisomeric furans favoring "normal" product **10**, likely resulting from an even more preferential 1,2-hydrogen vs 1,2-thio shift in **9** (Table 1).

Table 1. Optimization of Cycloisomerization of Thioalkynones



entry	catalyst	GC ratio **10**:**11**	NMR yield (%)[a]
1	CuI	5:1	66[b]
2	$AuCl_3$	1:1.4	5
3	$PtCl_2$	1:2.5	traces
4	$Pd(MeCN)_2Cl_2$	1:3.5	2
5	$(Et_3P)AuCl$	20:1	63

[a] NMR yields calculated using dibromomethane as an internal standard. [b] DMA used as solvent.

Intrigued by the unexpected observation of the 3-thiofuran **11**, we endeavored to investigate the formation of this product more thoroughly. Initially, we hypothesized that the two products arise from a common allenyl ketone intermediate **9**.[9,23] The "normal" product **10** forms from the copper-assisted ring closure, followed by the base-assisted intramolecular proton transfer.[9,10] The regioisomeric furan **11** was thought to result from the intramolecular Michael addition of sulfur at the allenic carbon, forming an intermediate aromatic thiirenium zwitterion **6** (Scheme 2),[24,25] which underwent further cycloisomerization to give **11**. It occurred to us that if the above concept is correct, then replacement of one of the propargylic hydrogens in **8** with any other nonmigrating group should enforce selective 1,2-migration of the thio group to produce the 3-thio substituted furan. To examine this proposal, thioalkynone **12a** was subjected to the cycloisomerization conditions described above. Remarkably, cycloisomerization of **12a** proceeded smoothly to give 3-thio substituted furan **14a** as a single regioisomer in excellent yield (Scheme 4).

Naturally, next we investigated the scope of a selective migrative cycloisomerization of substituted propargylsulfides

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Scheme 4. Selective 1,2-Sufur Migration during Cycloisomerization of **12a**

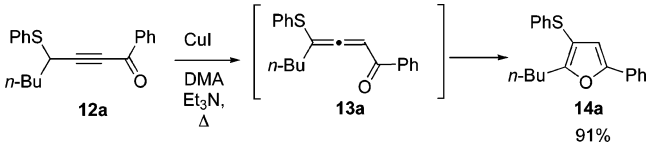
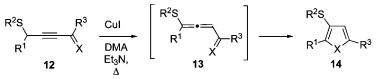
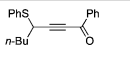
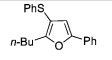
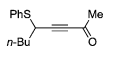
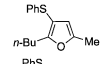
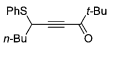
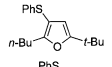
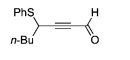
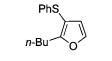
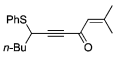
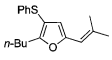
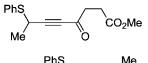
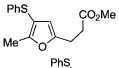
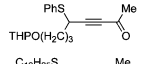
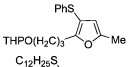
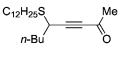
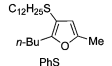
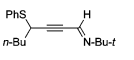
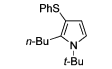
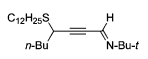
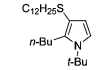
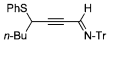
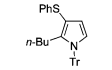
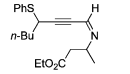
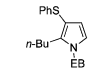
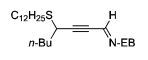
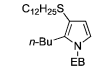
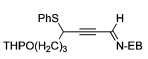
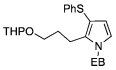
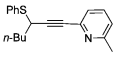
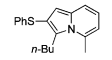


Table 2. Cycloisomerization of Thioalkynones and Thioalkynimines **12** into 3-Thiofurans **14**



Entry	Substrate	Product		Yield (%)[a]
1			**14a**	91
2			**14b**	76
3			**14c**	89
4			**14d**	71
5			**14e**	95
6			**14f**	71
7			**14g**	93
8			**14h**	72
9			**14i**	78
10			**14j**	86
11			**14k**	85
12			**14l**	74
13			**14m**	67
14			**14n**	78
15			**14o**	53[b]

[a] Isolated yields, reactions were performed on 1 mmol scale. [b] Reaction was performed on 3.89 mmol scale under the following conditions: 0.5 equiv CuBr, 1:7 Et_3N:DMA, 0.08M, 150 °C, 12 h.

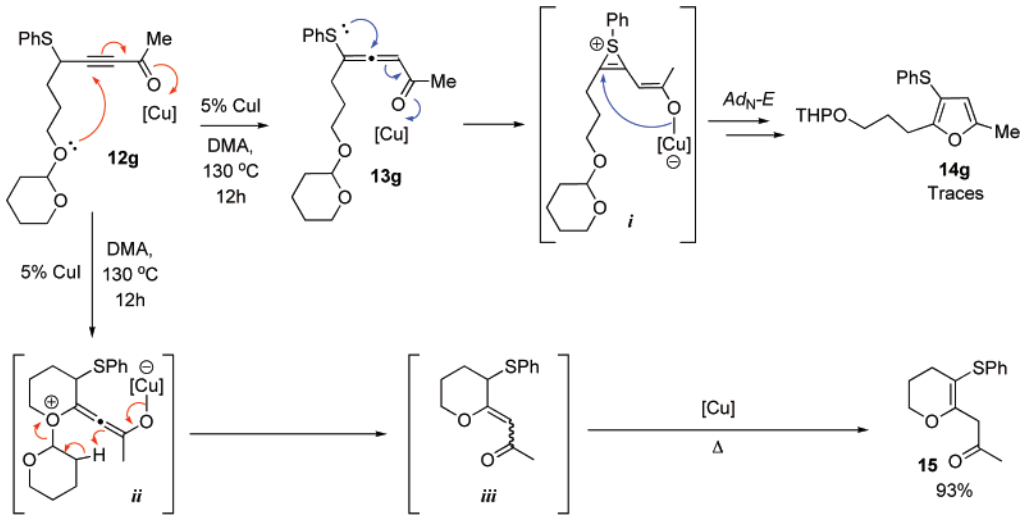
en route to 3-thiosubstituted heterocycles. Accordingly, a series of alkyl-substituted propargyl sulfides **12** were synthesized and subjected to the cycloisomerization reaction (Table 2). Cycloisomerization of thiopropargylketones **12a**,**b**,**c** proceeded uneventfully, affording the trisubstituted furans **14a**,**b**,**c** in good to excellent yields (entries 1−3). Gratifyingly, thiopropargylaldehyde **12d** underwent smooth and selective cycloisomerization, producing 2-butyl-3-(phenylthio)furan (**14d**) in 71% yield as a single reaction product (Table 2, entry 4). Cycloisomerization of (phenylthio)propargylketones possessing alkenyl- (**12e**), ester- (**12f**), and tetrahydro-2*H*-pyran-2-yloxy- (**12g**) functionalities in the side chain proceeded readily, affording the corresponding trisubstituted furans **14e**−**g** in good to very high yields (entries 5−7). The alkylsulfanyl group migrated with efficiency comparable to its phenylsulfanyl-analog to give the corresponding furan **14h** in 72% yield (entry 8). Moreover, it was found that thiopropargyl imines **12i**−**n** underwent a similar transformation in the presence of CuI to give the corresponding 3-thio-substituted pyrroles **14i**−**n** in good yields (entries 9−14). Again, the dodecylsulfanyl-group (entry 10) migrated comparably to the phenylsulfanyl-analog (entry 9) and the THP-protected alcohol functionality was tolerated (entry 14). It is worth mentioning that all synthesized pyrroles have deprotectable groups at the nitrogen atom, such as *tert*-butyl- (**14i**,**j** entries 9,10),[26] trityl- (**14k**, entry 11),[27] and 3-(ethylbutyryl)- (EB)[9,28] (**14l**−**n**, entries 12−14), and thus can be easily further functionalized at the nitrogen site. In addition, fused pyrroloheterocycle **14o** was smoothly synthesized in a preparative scale from **12o**.

Generally, transformation of thiopropargyl-ketones or imines **12** into furans and pyrroles **14** required presence of 0.2−5 equiv of triethylamine as a base.[11] However, when phenylthiopropargylketone **12g** possessing tetrahydro-2*H*-pyran-2-yloxy moiety was subjected to the cycloisomerization conditions in the absence of the base, dihydro-2*H*-pyran-6-yl derivative **15** was formed in 93% yield along with the trace amounts of the expected furan **14g** (Scheme 5). Normally, in the presence of base, **12g** undergoes a facile prototropic rearrangement to allenylsulfide **13g**, which via a putative thiirenium intermediate ***i***, transforms into furan **14g**. We hypothesized that in the absence of base this route is unlikely. Instead, **12g** undergoes a competitive 6-*exo*-dig cyclization to form 2-yledene-tetrahydro-2*H*-pyranium intermediate ***ii*** which, upon fragmentation with the loss of 3,4-dihydro-2*H*-pyran, gives enone ***iii***. Subsequent Cu-assisted isomerization of the latter produces the thermodynamically more stable enone **15**. This was confirmed by DFT calculations (B3LYP; 6-31G*: +3.6 kcal/mol and +6.6 kcal/mol ground state energy differences for (E)-***iii*** and (Z)-***iii*** over **15**, accordingly).

1,2-Selenium Migration in the Synthesis of Heterocycles. Motivated by the successful 1,2-thio migration during the cycloisomerization reaction of alkynyl ketones and imines, we next attempted to incorporate 1,2-selenium migration into the cycloisomerization cascade. Selenoheterocycles are important units which have found broad applications in biological studies as cytotoxic antitumor agents,[29] as NMR active tracers, and in protein−enzyme interaction studies.[30] Synthesis of nonaromatic selenoheterocycles, including selenolactones, is well known. The majority of syntheses involve electrophilic activation of an unsaturated bond followed by intramolecular ring closure.[31] In contrast, only a few scattered methods have been reported for the synthesis of 3-seleno-furans and pyrroles, including a Paal−Knorr approach,[32] unselective electrophilic selenation,[33] and

(26) For deprotection of *N*-Bu-*t*-group in pyrroles, see: (a) Leroy, J.; Wakselman, C. *Tetrahedron Lett.* **1994**, *35*, 8605. (b) La Porta, P.; Capuzzi, L.; Bettarini, F. *Synthesis* **1994**, *3*, 287.
(27) For deprotection of *N*-Tr-group in pyrroles, see: Chadwick, D. J.; Hodgson, S.T. *J. Chem. Soc. Perkin Trans 1* **1983**, 93.
(28) For deprotection of analogous group in pyrroles, see: Roder, E.; Wiedenfeld, H.; Bourauel, T. *Liebigs Ann. Chem.* **1985**, 1708.
(29) Abele, E.; Popelis, J.; Shestakova, I.; Domracheva, I.; Arsenyan, P.; Lukevics, E. *Chem. Heterocycl. Comp.* **2004**, *40*, 742.
(30) (a) Budisa, N.; Pal, P. P.; Alefelder, S.; Birle, P.; Krywcun, T.; Rubini, M.; Wenger, W.; Bae, J. H.; Steiner, T. *Biol. Chem.* **2004**, *385*, 191. (b) Bae, J. H.; Alefelder, S.; Kaiser, J. T.; Friedrich, R.; Moroder, L.; Huber, R.; Budisa, N. *J. Mol. Biol.* **2001**, *309*, 925. (c) Boles, J. O.; Henderson, J.; Hatch, D.; Silks, L. A. *Biochem. Biophys. Res. Commun.* **2002**, *298*, 257. (d) Welch, M.; Phillips, R. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 637.

Scheme 5. Competitive 6-*exo*-dig Cyclization of **12g** in the Absence of the Base

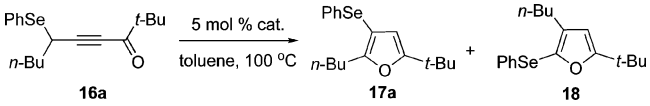


halogen−selenium exchange.[34] These methods suffer from significant drawbacks, including limited scope of products, imperfect regioselectivity, and low yields. We reasoned that our 1,2-migration/cycloisomerization methodology might be a perfect and convenient solution for the synthesis of 3-seleno-furans and pyrroles.

To this end, cycloisomerization of propargylselenoalkynone **16a** toward furan **17a** was examined in the presence of different transition metal catalysts (Table 3). Surprisingly, cycloisomerization of **16a** in the presence of gold, platinum, and palladium catalysts (entries 1−3) provided formation of furan **17a** along with notable amounts of regioisomeric furan **18**, *product of the competitive 1,2-alkyl migration/cyclization cascade*. It was found that heating of **16a** in toluene without catalyst afforded the target furan **17a** almost exclusively, albeit in 38% yield (entry 4). The selectivity and yield were improved by employing CuCl as the catalyst, affording **17a** as the sole regioisomer in 57% yield (entry 5). Employment of CuCl catalyst in DMA:Et_3N solvent mixture *at room temperature* produced furan **17a** in 96% yield (entry 6).

Next, the scope of this transformation was examined employing the optimized reaction conditions. It was found that, in addition to the *t*-butyl ketone **16a**, alkynal **16b** and methyl- and phenyl ketones **16c** and **16d** underwent cycloisomerization cleanly to afford the corresponding furans **17b**−**d** in good yields (Table 4, entries 1−3). A benzylic group was also tolerated, affording trisubstituted furan **17e** in 71% yield and even disubstituted furan **17f** in 53% yield (entries 4, 5).[35] Next, we tested the feasibility of applying this methodology for the synthesis of selenopyrroles. Indeed, it was found that propargylseleno alkynylimines **16g**,**h** smoothly underwent cycloisomerization at room temperature to afford the corresponding N-protected[9,26−28] pyrroles **17g**,**h** in 74 and 57% yields, respectively (Table 4, entries 6, 7). However, cycloisomerization of sterically hindered *N*-trityl alkynyl imine **16i** required heating at 110 °C to give pyrrole **17i** in 54% yield (Table 4, entry 8).

Table 3. Cycloisomerization of Selenoalkynone **16a** into Furans **17a** and **18**



16a **17a** **18**

entry	catalyst	**17a** (%)[a]	**18** (%)[a]
1	$AuCl_3$	24	34
2	$PtCl_2$	70	30
3	$Pd(MeCN)_2Cl_2$	13	33
4	none	38	–
5	CuCl	57[b]	–
6	CuCl	96[c]	–

[a] NMR yields calculated using dibromomethane as an internal standard for reactions performed on 0.1 mmol scale. [b] Reaction was performed on 0.5 mmol scale under the following conditions: 5 mol % CuCl, 10:1 DMA:Et_3N, rt.

1,2-Halogen Migration in the Synthesis of Halofurans. Transformations involving selective 1,2-halogen migration have not been reported until recently,[36] when Iwasawa and then Fürstner disclosed 1,2-iodine,[37] and 1,2-iodine and -bromine

(31) (a) Nicolau, K. C. *Tetrahedron* **1981**, *37*, 4097. (b) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884. (c) Clive, D. L. J.; Chittattu, G. *J. Chem. Soc. Chem. Commun.* **1977**, 484. (d) Aprile, C.; Gruttadauria, M.; Amato, M. E.; D'Anna, F.; Lo Meo, P.; Riela, S.; Noto, R. *Tetrahedron* **2003**, *59*, 2241. (e) Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* **2003**, 655. (f) Tiecco, M.; Testaferri, L.; Bagnoli, L. *Tetrahedron* **1996**, *52*, 6811. (g) Van de Weghe, P.; Bourg, S.; Eustache, J. *Tetrahedron* **2003**, *59*, 7365. (h) Denmark, S. E.; Edwards, M. G. *J. Org. Chem.* **2006**, *71*, 7293. (i) Back, T. G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* **2002**, *67*, 499. (j) Wang, X.; Houk, K. N.; Spichty, M.; Wirth, T. *J. Am. Chem. Soc.* **1999**, *121*, 8567. (k) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. Larock, R. C. *J. Org. CHem.* **2002**, *67*, 1905. (l) Pannecoucke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 995. (m) Berthe, B.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393. (n) Jones, A. D.; Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267. (o) Jones, A. D.; Redfern, A. L.; Knight, D. W.; Morgan, I. R.; Williams, A. C. *Tetrahedron* **2006**, *62*, 9247.

(32) (a) D'Onofrio, F.; Margarita, R.; Parlanti, L.; Pernazza, D.; Piancatelli, G. *Tetrahedron* **1997**, *53*, 15843.

(33) (a) Hartke, K.; Wendebourg, H. H. *Liebigs Ann. Chem.* **1989**, *5*, 415. (b) Hartke, K.; Wendebourg, H. H. *Heterocycles* **1988**, *27*, 639.

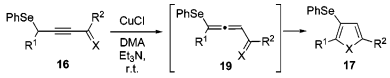
(34) (a) Agenas, L. B.; Lindgren, B. *Arkiv foer Kemi* **1968**, *29*, 479. (b) Agenas, L. B.; Lindgren, B. *Arkiv foer Kemi* **1967**, *28*, 145. (c) Chierici, L. *Farm. Ed. Sci.* **1953**, *8*, 156. (d) Vvedensky, V. Yu.; Brandsma, L.; Shtefan, E. D.; Trofimov, B. A. *Tetrahedron* **1997**, *53*, 13079. (e) Vvedensky, V. Yu.; Brandsma, L.; Shtefan, E. D.; Trofimov, B. A. *Tetrahedron* **1997**, *53*, 16783. See also ref 28.

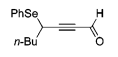
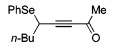
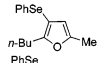
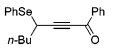
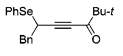
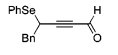
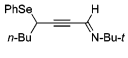
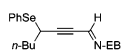
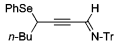
(35) It should be mentioned, however, that attempts to cycloisomerize primary propargyl selenides led to formation of detectable amounts of diphenyl diselenide only, probably due to the lower stability of the less substituted allene intermediate **19**.

(36) For scattered reports on non-selective halogen migration in unsaturated systems, see for example: (a) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *54*, 140. (b) Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993**, *34*, 4481. (c) Samuel, S. P.; Nin, T.-q.; Erickson, K. L. *J. Am. Chem. Soc.* **1989**, *111*, 1429.

(37) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518.

Table 4. Synthesis of 3-Seleno-Furans and Pyrroles **17**



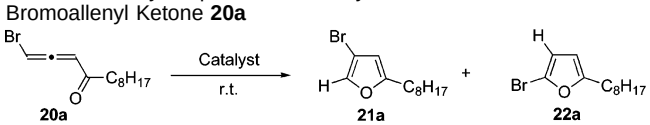
Entry	Substrate	Product		Yield (%)[a,b]
1			**17b**	74
2			**17c**	71[c]
3			**17d**	84
4			**17e**	71
5			**17f**	53
6			**17g**	74[d]
7			**17h**	57[d]
8			**17i**	54[e]

[a] Isolated yields for reactions performed on 0.5 mmol scale. [b] 15 mol % CuCl, 20% Et_3N, 0.5 M in DMA, rt. [c] 5 mol % CuCl, 10:1 DMA:Et_3N, rt. [d] 30 mol % CuCl, 5 equiv Et_3N, 0.5 M in DMA, rt. [e] 30 mol % CuCl, 5 equiv Et_3N, 0.5 M in DMA, 110 °C.

migration,[38] respectively, in alkynyl halides to produce fused haloarenes. Furthermore, Liu showed 1,2-iodine shift in a Ru alkylidene complex.[39] Some of these transformations involved metal carbenoid intermediates and were used in the synthesis of carbocycles.[38,39] To the best of our knowledge, the synthesis of halogenated heterocycles proceeding through a halirenium intermediate has not been previously reported.

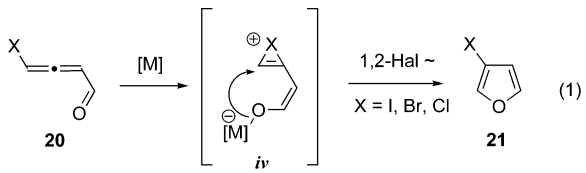
Halofurans, important building blocks, are traditionally obtained by electrophilic halogenation of furans,[40] via halogen-induced cyclizations,[41] or cyclocondensations of halogenated precursors.[42] Most of these approaches require employment of strongly electrophilic reagents, thus limiting their application to substrates lacking acid-sensitive functionalities. With the successful development of 1,2-thio- and seleno migration/cycloisomerization approach for the synthesis of trisubstituted furans and pyrroles, we sought to further expand the scope of this methodology. Thus, we turned our attention to the synthesis of 3-halofurans.

Table 5. Catalyst Optimization for Cycloisomerization of Bromoallenyl Ketone **20a**



entry	cat. (mol %)	solvent	time	GC yield, % (**21a**:**22a**)
1	CuCl (10)	toluene	1 day	29 (**21a** only)
2	CuI (10)	toluene	1 day	21 (**21a** only)
3	$AgBF_4$ (5)	DCM	1 day	traces
4	$PtCl_2$ (5)	toluene	3 h	50 (96:4)
5	$AuCl_3$ (1)	toluene	5 min	86 (95:5)
6	$AuCl_3$ (1)	THF	5 min	78 (5:95)
7	$Au(PPh_3)Cl$ (1)	toluene	9 h	N/D (16:84)
8	$Au(PEt_3)Cl$ (1)	toluene	9 h	N/D (<1:99)
9	$AlCl_3$ (50)	toluene	16 h	27 (**21a** only)
10	SiO_2	toluene	16 h	21 (**21a** only)

We hypothesized that replacement of chalcogens (X = RS and RSe) with halogen (X = Cl, Br, I) in the proposed intermediate ***iv***[12] might provide convenient access to 3-halofurans (eq 1). To test this idea, the Cu-catalyzed cycloisomerization of bromoallenyl ketone **20a**[43] was examined, which, indeed, led to the

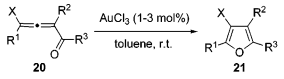


(1)

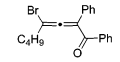
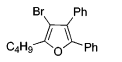
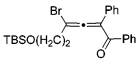
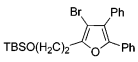
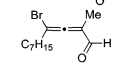
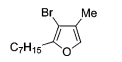
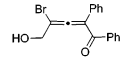
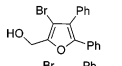
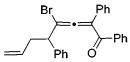
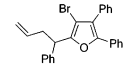
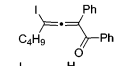
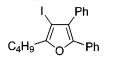
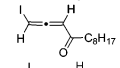
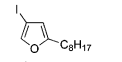
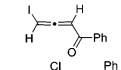
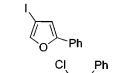
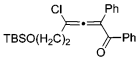
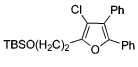
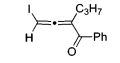
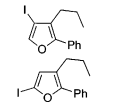
formation of 3-bromofuran **21a**, albeit in poor yield (Table 5, entries 1−2). In contrast, $AgBF_4$, which proved efficient in cycloisomerization of different allenyl ketones,[44] did not catalyze this reaction at all (entry 3). Employment of $PtCl_2$, however, produced 3-bromofuran **21a** in 50% yield along with small amounts of 2-bromofuran **22a** (entry 4). To our delight, employment of $AuCl_3$ afforded 3-bromofuran **21a** in 86% yield with high selectivity (Table 5, entry 5).[43,45] Surprisingly, switching solvent to THF caused a dramatic change in selectivity, affording 2-bromofuran **22a** as a major product (entry 6). The latter was also exclusively obtained in the presence of $Au(PEt_3)Cl$ (entry 8). It was found that selective cycloisomerization of **20a** can be also achieved in the presence of $AlCl_3$ and even silica gel, affording 3-bromofuran **21a**, though in low yield (entries 9−10).

(38) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.−Eur. J.* **2004**, *10*, 4556.
(39) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762.
(40) For examples on electrophilic halogenations of furans, see: (a) Keegstra, M. A.; Klomp, A. J. A.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3371. (b) Verkruijsse, H. D.; Keegstra, M. A.; Brandsma, L. *Synth. Commun.* **1989**, *19*, 1047. (c) Song, Z. Z; Wong, H. N. C. *Liebigs Ann. Chem.* **1994**, *1*, 29. (d) Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583. (e) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *11*, 3539. (f) Gilman, H.; Mallory, H. E.; Wright, G. F. *J. Am. Chem. Soc.* **1932**, *54*, 733. (g) Dickman, D. A; Ku, Y.-Y.; Morton, H. E.; Chemburkar, S. R.; Patel, H. H.; Thomas, A.; Plata, D. J.; Sawick, D. P. *Tetrahedron: Asymm.* **1997**, *8*, 1791. (h) Aiello, E.; Dattolo, G.; Cirrincione, G.; Almerico, A. M.; D'Asdia, I. *J. Heterocycl. Chem.* **1982**, *19*, 977. (i) Belen'kii, L. I.; Gromova, G. P.; Gol'dfarb, Ya. L. *Chem. Heterocycl. Comp.* **1978**, 246. (j) Oleinik, A. F.; Solov'ena, N. P.; Turchin, K. F.; Sheinker, Yu. N.; Novitskii, K. Yu.; Smirnova, E. N.; Dozorova, E. N. *Chem. Heterocycl. Comp.* **1980**, 334. (k) Belen'kii, L. I.; Gromova, G. T.; Gol'dfarb, Ya. L. *Chem. Heterocycl. Comp.* **1975**, 1249. (l) Nolan, S. M.; Cohen, T. *J. Org. Chem.* **1981**, *46*, 2473. (m) Nazarova, Z. N.; Babaev, Yu. A.; Umanskaya, L. G. *Chem. Heterocycl. Comp.* **1969**, *5*, 17. (n) Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1988**, *29*, 1247. (o) Bures, E.; Nieman, J. A.; Yu, S.; Spinazze, P. G.; Bontront, J.-L. J.; Hunt, I. R.; Rauk, A.; Keay, B. A. *J. Org. Chem.* **1997**, *62*, 8750. (p) Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362. (q) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T *J. Am. Chem. Soc.* **1999**, *121*, 3539.
(41) For halogen induced cyclizations, see: (a) Bew, S. P.; Knight, D. W. *Chem. Commun.***1996**, 1007. (b) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945. (c) Rao, M. S.; Esho, N.; Sergeant, C.; Dembinski, R. *J. Org. Chem.* **2003**, *68*, 6788. (d) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (e) Schultz-Fademrecht, C.; Zimmerman, M.; Frohlich, R.; Hoppe, D. *Synlett* **2003**, 1969. (f) Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447. (g) Reich, H. J.; Olson, R. E. *J. Org. Chem.* **1987**, *52*, 2315. (h) Gorzynski, M.; Rewicki, D. *Liebigs Ann. Chem.* **1986**, 625.
(42) For examples of cyclocondensation of halogen-containing precursors, see: (a) Tanabe, Y.; Wakimura, K.; Nishii, Y.; Muroya, Y. *Synthesis* **1996**, 388. (b) Mee, S. P. H.; Lee, V.; Baldwin, J. E.; Cowley, A. *Tetrahedron* **2004**, *60*, 3695. (c) Kraus, G. A.; Wang, X. *Synth. Commun.* **1998**, *28*, 1093. (d) Reich, H. D.; Olson, R. E. *J. Org. Chem.* **1987**, *52*, 2315.
(43) Bromoallene **20a** contained trace to notable amounts of bromopropargyl ketone, from which it was obtained. Under reaction conditions bromopropargyl ketone underwent rapid isomerization to **20a**. The same applies to iodoallenes **20i** and **20k** (see Table 6). Facile propargyl−allenyl isomerization of propargyl ketones in the presence of gold catalyst was previously observed; see ref 7i.
(44) (a) See ref 7n. (b) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280.

Table 6. 1,2-Halogen Migration/Cycloisomerization toward Halofurans **21**



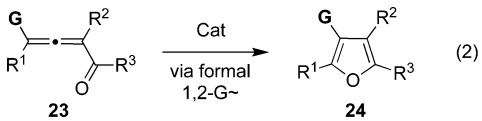
20 21

Entry	Substrate	Time	Product		Yield (%)[a]
1		1 day		**21b**	75
2		1 day		**21c**	73
3		1 hr		**21d**	73
4		1 day		**21e**	61
5		0.5 hr		**21f**	88
6		3 days		**21g**	73
7		5 min		**21h**	97
8[b]		1 hr		**21i**	71
9		3 days		**21j**	48
10[b]		1 hr		**21k** **21l**	67[c]

[a] Isolated yields, reactions were performed on 0.29−1 mmol scale with 1 M concentration of **20**. [b] Mixture of allene and corresponding propargyl isomer was employed (see Supporting Information). [c] Mixture (2:1) of **21k** and **21l** by ^{1}H NMR.

Next, we investigated the scope of this cascade transformation. Thus, differently substituted haloallenyl ketones were subjected to Au(III)-catalyzed cycloisomerization (Table 6). It was found that a variety of alkyl and aryl-substituted bromoallenyl ketones and aldehydes **20** underwent smooth cycloisomerization, affording 3-bromofurans **21** in good to excellent yields (entries 1−5). Remarkably, this method allowed for efficient synthesis of halofurans possessing hydroxymethyl (**21e**) and alkene (**21f**) functionalities, which are incompatible with known methods employing electrophilic reagents. It was found that fully substituted iodoallenyl ketone **20g** reacted more slowly than its bromo-analogs, producing corresponding furans **21g** in good yield (entry 6). Gratifyingly, ambident disubstituted allenyl iodides **20h**,**i** underwent exclusive 1,2-iodine migration to afford 2-alkyl and -aryl substituted iodofurans **21h**,**i** in 97 and 71% yields, respectively (entries 7,8). Chloroallene **20j** also underwent this transformation to produce 3-chlorofuran **21j**. However, the observed much more sluggish reaction of **20j** was attributed to the decreased ability of chlorine to form halirenium species ***iv*** (eq 1). Cycloisomerization of ambident trisubstituted allenyl iodide **20k** possessing more bulky *n*-propyl group at C-2 than that in iodoallenes **20h**,**i** produced of 2:1 mixture of 3- and 2-iodofurans **21k** and **21l**, respectively.

1,2-Alkyl/Aryl Migration in the Synthesis of Furans. As discussed above, cycloisomerization of C-4 monosubstituted allenyl ketones **23** in the presence of transition metal catalysts can be used as an efficient approach for the assembly of the furan ring via formal 1,2-hydrogen shift (eq 2).[7i,m−q]



(2)

23 **24**

Marshall (**G** = H, Cat = *Ag*)
Hashmi (**G** = H, Cat = *Pd, Au*)

Inspired by the observation of competitive 1,2-alkyl migration during cycloisomerization of selenoalkynone **16a** into 3-alkylfuran **18** (Table 3, entries 1−3), we envisioned that development of a cascade transformation involving a 1,2-migration of an alkyl/aryl group[8k,46,47,48,49] in allenylketones is also feasible. If successful, this approach may allow for the rapid assembly of fully carbon-substituted furans. To this end, the possible cycloisomerization of allene **25** into furan **26** in the presence of different catalysts was tested (Table 7). It was found that employment of Au(I) and Au(III) halides gave low yields of furan **26**. Gratifyingly, switching to cationic Au(I) complexes lead to formation of expected furan in nearly quantitative yield (entries 3−4). Analogously to gold halides, Pt(II), Pt(IV), and Pd(II) salts were inefficient in this reaction (entries 5−7). Use of Cu(I) halides resulted in no reaction, whereas employment of cationic Ag(I), Cu(I), and Cu(II) salts produced **26** in moderate to high yields. Encouraged by these results, we have also examined main group metals in this reaction. Surprisingly, Al-, Si-, Sn-, and In triflates provided moderate to excellent yields of desired furan **26**. Although $Au(PPh_3)OTf$, AgOTf, $In(OTf)_3$, $Sn(OTf)_2$, and TIPSOTf were nearly equally efficient in the cascade cycloisomerization of **25** to **26**, $In(OTf)_3$ appeared to be a more general catalyst with respect to the substrate scope.[11]

(45) For recent reviews on Au-catalyzed reactions, see: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (b) Hashmi, A. S. K. *Gold Bull*. **2004**, *37*, 51. (c) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180. (d) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. For selected examples of Au-catalyzed synthesis of heterocycles, see: (f) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (g) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (h) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. For Au-catalyzed carbocyclizations, see for example: (i) Fürstner, A.; Hannen, P. *Chem. Comm.* **2004**, 2546. (j) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (k) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (l) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (m) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. See also ref. 38. (n) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (o) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

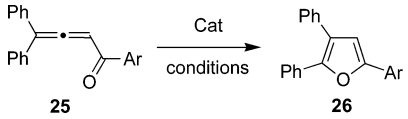
(46) For examples of 1,2-shift in carbenoids, see: (a) Xiao, F.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5789, and references therein. (b) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. (c) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (d) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310.

(47) For general reviews, see: (a) Ducrot, P. H. In *One or more CH and/or CC bond(s) formed by rearrangement*; Katritzky, A. R., Taylor, R. J. K., Eds.; Comprehensive Organic Functional Group Transformations II; Elsevier: Oxford, UK, 2005; Vol. 1, p 375. (b) Constantieux, T.; Rodriguez, J. In *Synthesis by fragmentation and rearrangement*; Cossy, J., Ed.; Science of Synthesis; Thieme: New York, 2005; Vol. 26, p 413. (c) Pattenden, G., Ed.; In *Carbon-Carbon σ-Bond Formation: Rearrangement Reactions*; Trost, B. M., Fleming, I., Eds.; Comprehensive organic synthesis: selectivity, strategy, and efficiency in modern organic chemistry; Pergamon Press: New York, 1991; Vol. 3, p 705.

(48) For a synthesis of carbocycles involving 1,2-alkyl shift to carbenoid center in allenes, see: (a) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2006**, *46*, 909. (b) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912.

(49) (a) For a synthesis of dehydrofuranones via 1,2-alkyl shift, analogous to a formal ketol rearrangement, see: Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878, and references therein. (b) See, also: Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435.

Table 7. Optimization of Reaction Conditions for Cycloisomerization of **25**



25 **26**

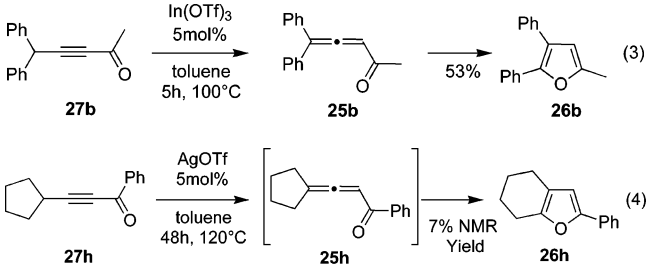
entry	cat	mol %	solvent	*T*, °C	yield (%)[a]
1	$AuBr_3$	5	toluene[b]	100	23
2	AuI	5	toluene[b]	100	traces
3	$Au(PPh_3)OTf$	1	toluene[b]	100	100 (89)
4	$Au(PPh_3)OTf$	5	DCM[c]	rt	99
5	$PtCl_2$	5	toluene[d]	100	21
6	$PtCl_4$	5	toluene[d]	100	21
7	$Pd(PhCN)_2Cl_2$	5	toluene[d]	100	35
8	CuX (X=Cl, Br, I)	5	toluene[d]	100	0
9	$[CuOTf]_2$•PhH	5	toluene[d]	100	42
10	$Cu(OTf)_2$	5	toluene[e]	100	95
11	$AgPF_6$	5	toluene[e]	100	47
12	AgOTf	5	toluene[e]	100	(80)
13	AgOTf	20	DCM[c]	rt	70 (62)
14	$Al(OTf)_3$	5	toluene[e]	100	64
15	$Zn(OTf)_2$	5	toluene[e]	100	39
16	TMSOTf	20	DCM[d]	rt	82 (62)
17	$In(OTf)_3$	5	toluene[e]	100	91 (81)
18	$Sn(OTf)_2$	5	toluene[e]	100	97 (81)
19	TIPSOTf	5	toluene[e]	100	100 (81)
20	$TMSNTf_2$	5	toluene[e]	100	72

[a] NMR yield, isolated yield in parentheses (entries 1−4: Ar = *p*-Br−C_6H_4; entries 5−20: Ar = Ph). [b] Solution (0.05 M) of **25**. [c] Solution (0.02 M) of **25**. [d] Solution (1 M) of **25**. [e] Solution (0.1 M) of **25**.

In light of the recent observations that eventual Brønsted acids are the true catalysts in some transition metal-catalyzed transformations,[50] we investigated what role, if any, Brønsted acids may play in the herein described cycloisomerization reaction. To this end, the cycloisomerization of **25** by several catalysts in the presence of proton scavenger, TTBP, was examined (Table 8).[51] It was found that cycloisomerization of allenyl ketone **25** at 100 °C in toluene in the presence of TfOH or $Sn(OTf)_2$ provided furan **26** in almost quantitative NMR yield with comparable rates (entries 1 and 10). The same result was observed for reactions performed in 1,2-dichloroethane for AgOTf, TMSOTf, and TfOH catalysts (entries 4, 6, and 8). Addition of the TTBP negligibly affected cycloisomerization reaction for both catalysts in toluene solvent series (entries 2 and 3), owing to the most probable dissociation of Lewis acid−Lewis base complex at the elevated temperature. In contrast, addition of TTBP for the 1,2-dichloroethane experiments completely suppressed the cycloisomerization reaction at room temperature for TfOH and TMSOTf, and even at 80 °C for AgOTf (entries 5, 8, and 11). However, elevation of the reaction temperature allowed for the formation of furan **26** albeit in lower yields and increased reaction times (entries 6, 9 and 12). Accordingly, TMSOTf-TTBP pair provided 61% of furan product, whereas only 36% yield was achieved for the TfOH-TTBP pair after more prolonged reaction time. Thus, taking into consideration the more efficient cycloisomerization in the presence of TTBP for TMSOTf vs TfOH, observed reactivity for the Lewis acid catalysts cannot be attributed to the formation of eventual Brønsted acid catalyst. It should be emphasized, however, that TfOH, indeed, is able to catalyze cycloisomerization of **25** into **26** even with slightly better efficiency for some 4,4-diaryl substituted allenyl ketones (entry 14 vs 15). However, cycloisomerization of 4-methyl-1,4-diphenyl allenylketone in the presence of TfOH catalyst appeared to be notably less efficient (entry 16) compared to that in the presence of $In(OTf)_3$ (entry 17).

Having in hand a set of optimized conditions, cycloisomerization of differently substituted allenyl ketones **25a**−**n** was examined (Table 9). Cycloisomerization of 4,4-diphenyl substituted allenyl ketones **25a**−**d** proceeded smoothly to provide good to high yields of furans **26a**−**d**. Selective 1,2-migration of phenyl over methyl group occurred in allenyl ketone **25e** to give **26e** in 72% yield (entry 5). In contrast to the methyl-, 1,2-migration of the ethyl group competed with the phenyl group in **25f**, which resulted in formation of a 2.3:1 mixture of regioisomeric furans **26f** and **26g**, respectively (entry 6).[52] Cyclopentylideneallenyl ketone **25h** underwent smooth cyclization with ring expansion to give fused furan **26h** in 75% yield (entry 7). Not surprisingly, cycloisomerization of allenyl ketone **25i**, possessing more thermodynamically stable 6-membered ring or **25j**, having two methyl groups, provided corresponding furans **26i** and **26j** in low yields only (entries 8 and 9). It was also demonstrated that a variety of functional groups such as methoxy- (entry 10), bromo- (entry 11), nitro- (entry 12), and cyano- (entry 13) were perfectly tolerated under these reaction conditions.

It was also shown that trisubstituted furan **26b** can be directly obtained from alkynyl ketone **27b** (eq 3), albeit the yield for this one-pot transformation was somewhat lower compared to that for cycloisomerization of allene **25b** (Table 9, entry 2). The intermediacy of **25b** has been confirmed by GC/MS monitoring of the reaction course. However, this approach is moderately efficient only for the propargylic systems which can undergo facile alkynyl-allenyl isomerization, such as in the **27b**, as attempts on direct cycloisomerization of cyclopentyl-substituted alkynone **27h** failed (eq 4).



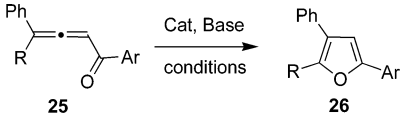
It should be noted that the cycloisomerization course of C-1 phenyl substituted allenyl ketones in the presence of Lewis acid catalysts is greatly affected by the bulkiness of C-2 substituent. Thus, cycloisomerization of C-2 methyl substituted allenylketone **25d** in the presence of main group triflates produced furan **26d** along with notable amounts of methylene-indan-1-one **28d**.[11] Employment of TMSOTf allowed for the formation of **28d** in 95% yield as a sole product (Scheme 6). We hypothesized that

(50) There has been a recent discussion on the role of Brønsted acids in homogenous transition metal-catalyzed reactions. For the most relevant references, see: (a) Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211. (b) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (d) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493.

(51) For, use of TTBP as a TfOH scavenger, see for example: Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473.

(52) See mechanistic discussion below and refs 70 and 71.

Table 8. Comparison of Lewis and Brønsted Acid Catalysts for Cycloisomerization of Allenyl Ketones

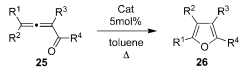


25 **26**

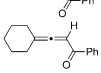
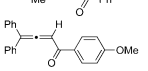
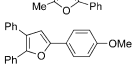
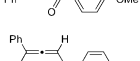
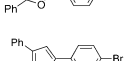
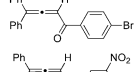
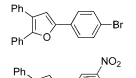
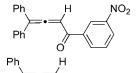
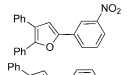
entry	R	Ar	cat (mol %)	additive (mol %)	solvent	*T*, °C	time, h	NMR yield (%)[a,b]
1	Ph	*p*-C_6H_4-CN	TfOH (10)	–	toluene	100	1.5	96
2	Ph	*p*-C_6H_4-CN	TfOH (10)	TTBP (40)	toluene	100	2.0	>99
3	Ph	*p*-C_6H_4-CN	$Sn(OTf)_2$ (5)	TTBP (20)	toluene	100	2.0	91
4	Ph	*p*-C_6H_4-CN	TfOH (20)	–	DCE	rt	1.0	96
5	Ph	*p*-C_6H_4-CN	TfOH (20)	TTBP[c] (40)	DCE	rt	24	0
6	Ph	*p*-C_6H_4-CN	TfOH (20)	TTBP (40)	DCE	95	48	36
7	Ph	*p*-C_6H_4-CN	TMSOTf (20)	–	DCE	rt	1.0	>99
8	Ph	*p*-C_6H_4-CN	TMSOTf (20)	TTBP (40)	DCE	rt	4.0	0
9	Ph	*p*-C_6H_4-CN	TMSOTf (20)	TTBP (40)	DCE	95	24	61
10	Ph	*p*-C_6H_4-CN	AgOTf (20)	–	DCE	80	2.0	>99
11	Ph	*p*-C_6H_4-CN	AgOTf (20)	TTBP (40)	DCE	80	2.0	0
12	Ph	*p*-C_6H_4-CN	AgOTf (20)	TTBP (40)	DCE	95	48	19
13	Ph	*p*-C_6H_4-CN	$Sn(OTf)_2$ (5)	–	toluene	100	1.5	>99
14	Ph	*p*-C_6H_4-OMe	TfOH (10)	–	toluene	100	1.0	88
15	Ph	*p*-C_6H_4-OMe	$In(OTf)_3$ (5)	–	toluene	100	2.0	79
16	Me	Ph	TfOH (10)	–	toluene	100	1.0	52
17	Ph	Ph	$In(OTf)_3$ (5)	–	toluene	100	12	77

[a] Reactions were performed on 0.1 mmol scale. [b] Dibromomethane was used as the standard. [c] TTBP = 2,4,6-tris-*tert*-butylpyrimidine.

Table 9. Metal-Catalyzed Synthesis of Furans **26**



25 **26**

Entry	Substrate	Cat (mol%)	T, °C	Product		Yield (%)[a,b]
1		$Sn(OTf)_2$ (5)	100		**26a**	81
2		$In(OTf)_3$ (10)	115		**26b**	64
3		$In(OTf)_3$ (5)	100		**26c**	90
4		AgOTf (20)	140		**26d**	79[c]
5		$In(OTf)_3$ (5) $Au(PPh_3)OTf$ (2)	100		**26e**	72 52[d]
6		$In(OTf)_3$ (5) $Au(PPh_3)OTf$ (1)	"	 	**26f** **26g**	88[e] 76[d,f]
7		$In(OTf)_3$ (5)	"		**26h**	75
8		"	"		**26i**	18[d]
9		"	"		**26j**	10[d]
10		"	"		**26k**	62
11		$In(OTf)_3$ (5) $Au(PPh_3)OTf$ (1)	"		**26l**	93 89
12		$Sn(OTf)_2$ (5)	"		**26m**	85
13		"	"		**26n**	94

[a] Isolated yield. [b] Reactions were performed on 0.25−0.8 mmol scale. [c] *p*-Xylene was used as a solvent. [d] NMR yield. [e] Mixture (2.3:1) of **26f:26g** by ^{1}H NMR. [f] Mixture (2.2:1) of **26f:26g** by ^{1}H NMR.

activation of the carbonyl function in **25d** by a Lewis acid produces rotamers ***v*** and ***vi***. The latter, in the case of **25d**, is favored over ***v***, which suffers the repulsion between methyl and phenyl groups. A facile aromatic Nazarov cyclization of ***vi*** produces indanone **28d**[53] in nearly quantitative yield (Scheme 6).

Mechanistic Discussion. Naturally, we were interested in the investigation of the mechanisms of herein described 1,2-migration/cycloisomerization cascade transformations of alkynyl- or allenylketones and -imines into corresponding furans and pyrroles. Our thorough studies revealed many similarities observed during cascade cycloisomerizations of C-4 diversely substituted alkynyl and allenyl systems involving 1,2-migration of various groups as the key step in the assembly of heterocyclic cores.

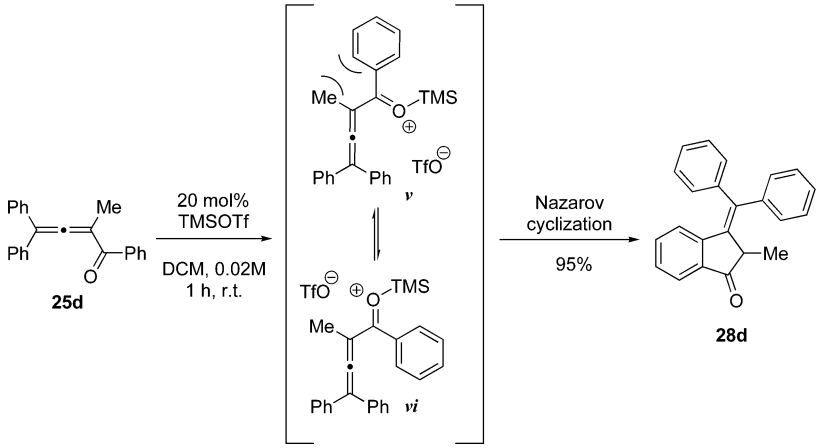
Initially, we hypothesized that migrative cycloisomerization of thioalkynones **12** involves a Cu-assisted prototropic rearrangement, thus proceeding via involvement of a reactive allenyl intermediate **9**/**13**.[9,10,12,54] Analogous allenyl intermediate **19** was proposed for 1,2-selenium migrative cycloisomerization of selenoalkynones **16**, whereas 1,2-halogen or 1,2-alkyl/aryl migrations were achieved utilizing the corresponding allenyl compounds **20** and **25** as starting materials. Indeed, failure to perform efficient cycloisomerization directly from propargylic ketones (eq 3 vs eq 4), where essential propargyl-allenyl isomerization is largely suppressed, confirmed the allenyl system to be a viable and necessary intermediate in the 1,2-alkyl/aryl migrative cycloisomerization.

Moreover, to gain the support for the involvement of allenyl intermediate **13**, thioallenones **13a**,**p** were prepared by independent methods and subjected to the cycloisomerization conditions described above (see Table 2). Remarkably, it was found that thioallenyl arylketone **13a**, even in the absence of CuI catalyst, underwent *quantitative thermal transformation to*

(53) (a) For the most recent reviews on Nazarov cyclization and related transformations, see: (a) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577, and references therein. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479, and references therein. (c) Tius, M. A.; *Acc. Chem. Res.* **2003**, *36*, 284. (d) Tius, M. A.; *Eur. J. Org. Chem.* **2005**, 2193. (e) See also: Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491.

(54) For the cuprate-assisted transformation of propargylic thioacetals into allenyl copper species, see: ref 8c and d.

Scheme 6. Nazarov Cyclization of Tetrasubstituted Phenyl-allenylketone **25d**



14a. In contrast, attempts to perform analogous thermal cycloisomerization of thioallenylalkylketone **13p** resulted in a total decomposition of the starting material, whereas 82% of **14p** was isolated when reaction was performed at room temperature in the presence of 5 mol % of CuI (Figure 1).

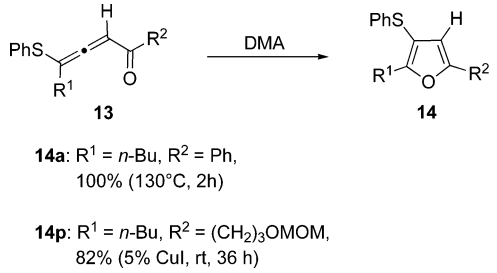
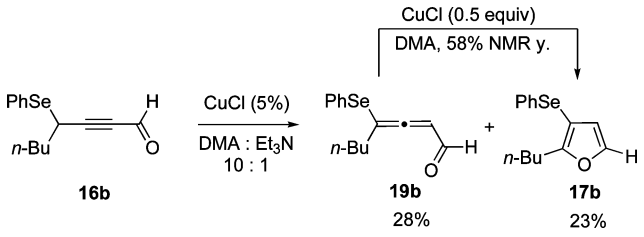


Figure 1. Direct Cycloisomerization of Thioallenones **13** into Furans **14**.

Furthermore, we hypothesized that, considering the enhanced acidity of the propargylic proton of selenoalkynones **16**,[55] cycloisomerization of the latter should involve very facile propargyl-allenyl isomerization, leading to allenone intermediate **19**. Indeed, when a subcatalytic loading of copper chloride was used (Scheme 7 vs Table 4, entry 1), allenal **19b**

Scheme 7. Direct Observation of Selenoallenic Intermediate **19b**

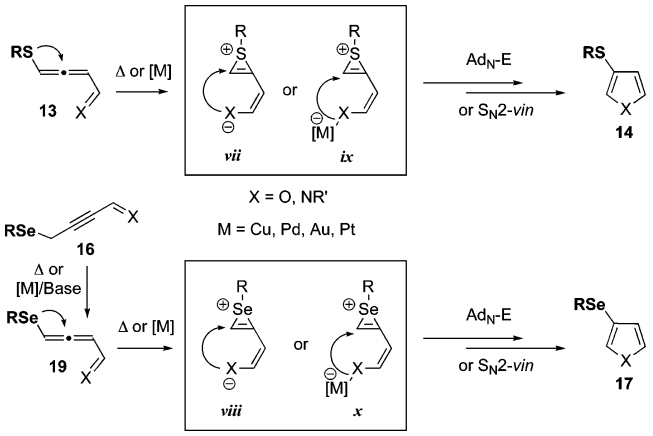


accumulated in the reaction mixture (Scheme 7). Subsequent treatment of the isolated allenal **19b** with copper chloride in DMA at room temperature afforded furan **17b** in good yield (Scheme 7).[56]

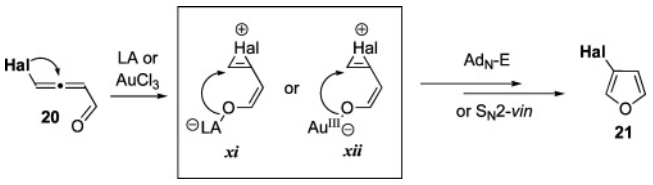
(55) (a) Reich, H. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 3112. (b) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1977**, *99*, 263. (c) Reich, H. J.; Gold, P. M.; Chow, F. *Tetrahedron Lett.* **1979**, 4433.

(56) The more facile propargyl-allenyl isomerization for selenoalkynones is well supported by notable cycloisomerization of **16a** under thermal conditions in the absence of base and Cu-catalyst (Table 3, entry 4).

Scheme 8. Proposed Irenium Intermediates in the 1,2-Chalcogen Migration/Cycloisomerization Cascade



Scheme 9. Proposed Halirenium Intermediates in the 1,2-Halogen Migration/Cycloisomerization Cascade

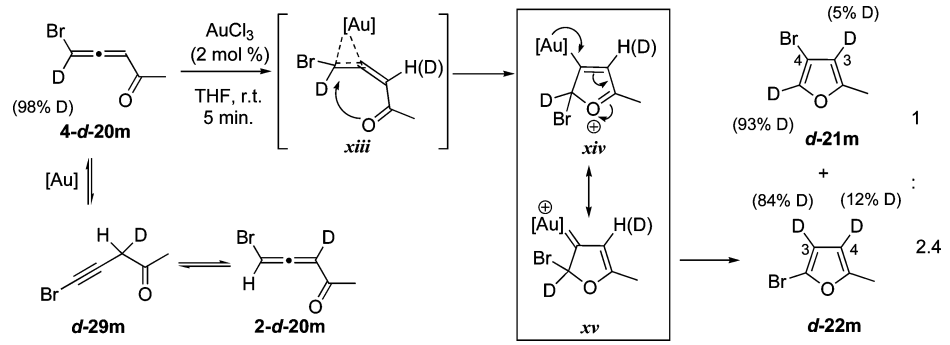


Thus, based on the experimental data disclosed above, it is believed that all of the herein reported 1,2-migration/cycloisomerization cascade transformations most likely proceed via allenyl intermediates.

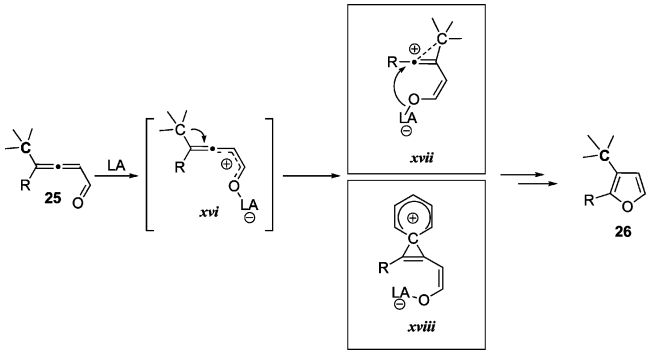
As discussed above, both thioallenone **13a** (Figure 1) and seleno alkynone **16a** (Table 3, entry 4) in the absence of the copper catalyst underwent thermal 1,2-migration/cycloisomerization transformation to give corresponding 3-chalcogenofurans. Such reactivity can only be rationalized by involvement of intramolecular Michael addition of chalcogen at the enone moiety of the allenone to give intermediate thiirenium[24,25] or selenirenium[57] zwitterions ***vii*** and ***viii*** respectively (Scheme 8). Subsequent nucleophilic attack by oxygen or nitrogen at the irenium moiety, followed by either Ad_N-E or S_N2-*vin*[25] processes, furnishes the formation of furan **14**. Employment of transition metal catalysts, such as Cu, Au, Pd, and Pt, in similar

(57) (a) Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett.* **1975**, 3991. (b) Poleschner, H.; Seppelt, K. *J. Chem. Soc. Perkin Trans. 1* **2002**, *23*, 2668.

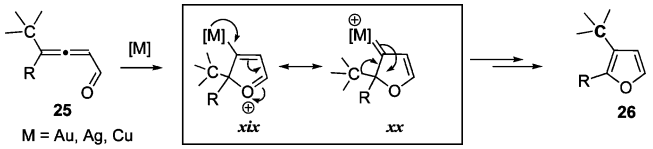
Scheme 10. Deuterium Labeling Study of Bromoallenone **4-*d*-20m**



Scheme 11. Proposed Cationic Intermediates in the 1,2-Alkyl/Aryl Migration/Cycloisomerization Cascade Triggered by Lewis Acid Catalysts



Scheme 12. Proposed Intermediates in the Transition Metal-catalyzed 1,2-Alkyl/Aryl Migration/ Cycloisomerization Cascade



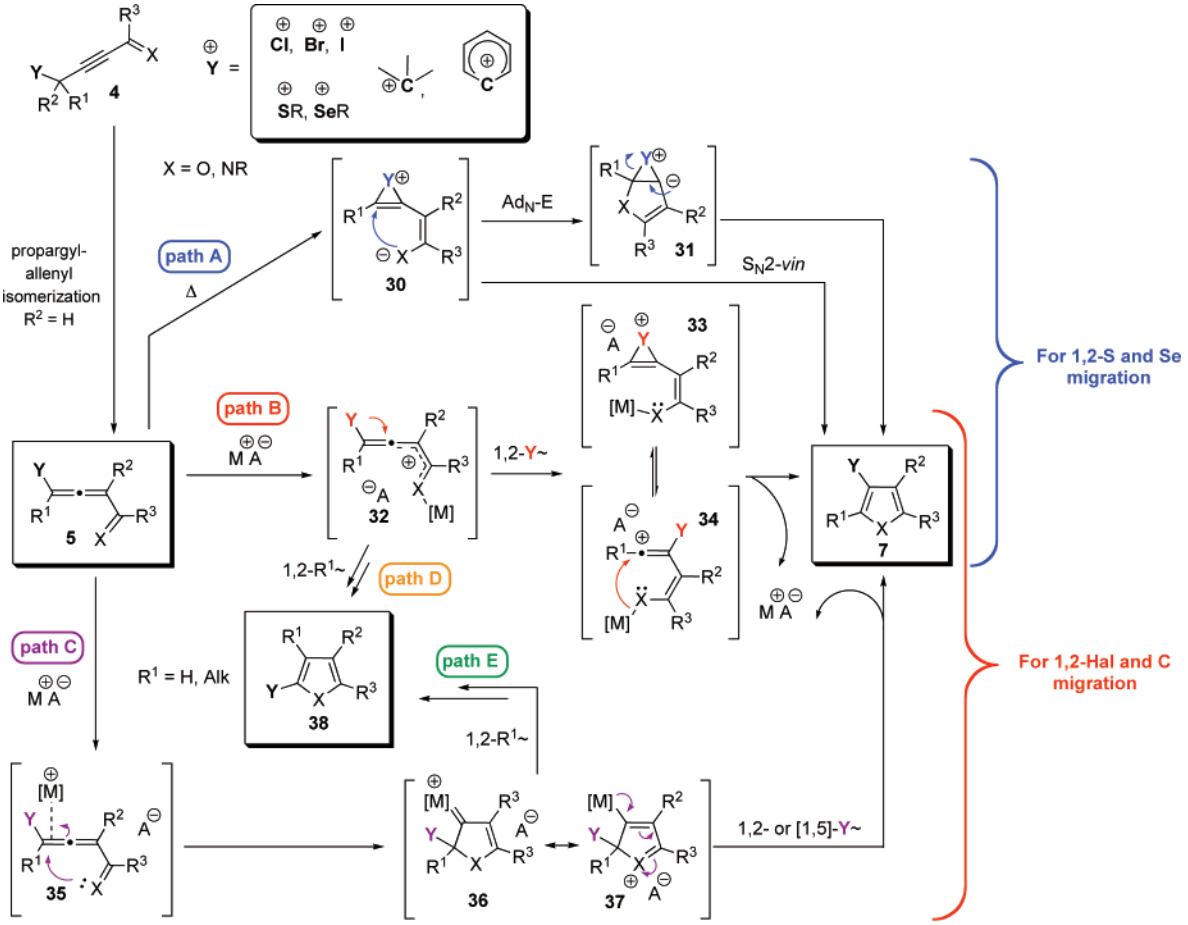
cycloisomerizations facilitated the propargyl-allenyl isomerization, and potentially also stabilized the formed enolate or enaminate in irenium species ***ix*** and ***x***, which undergent analogous to ***vii*** and ***viii*** cyclization into 3-chalcogeno-furans **17** (Scheme 8).[58]

An analogous scenario involving 1,2-migration of nucleophilic entities to the electrophilic *sp* center of allenone is responsible for the migrative cycloisomerization catalyzed by Lewis or Brønsted acids. In these cases, activation of enone moiety by these catalysts dramatically increases electrophilicity at C-3 of allenyl intermediate and, thus, provokes a more facile 1,2-migration of an adjacent group. Indeed, observed selective cycloisomerization of bromoallenylketone **20a** into 3-bromofuran **21a** in the presence of $AlCl_3$ or silica gel (Table 5, entries 9−10) could only be explained by involvement of a similar to ***vii-x*** halirenium intermediate ***xi***.[59] This, taken together with the reasonably high oxophilicity of $AuCl_3$ in noncoordinating media,[60] suggests that 1,2-halogen migration/cycloisomerization cascade proceeds via analogous to 1,2-chalcogen migration pathway involving intermediate ***xii*** to give 3-halofuran **21** (Scheme 9). The reversal of regioselectivity observed in the $AuCl_3$-catalyzed reaction in THF (Table 5, entry 6), can be attributed to a decreased oxophilicity of Au(III) complex in ethereal solvent. The same reactivity was observed for more π-philic Au(I) species (Table 5, entries 7 and 8). To verify whether selective formation of 2-bromofuran **22** proceeds through any type of carbenoid intermediates, we subjected deuterated allenyl ketone **4-*d*-20m** to the cycloisomerization conditions (Scheme 10). This reaction produced a mixture of 2- and 3- bromo-furans ***d*-22m** and ***d*-21m** in a ratio of 2.4:1 respectively without a detectable loss of deuterium.[61,62] It appears that rapid $AuCl_3$-catalyzed propargyl-allenyl isomerization is responsible for partial incorporation of deuterium in position 3 of ***d*-21m** (4 for ***d*-22m**). Nonetheless, observation of the clean 1,2-hydride shift[63] was rationalized by involvement of resonance intermediates ***xiv*** and ***xv*** (Scheme 10). Accordingly, more π-philic Au species ($AuCl_3$ in ethereal solvents, as well as $R_3PAu(I)Cl$ catalysts) coordinate to the distal double bond of allene (***xiii***), activating it toward intramolecular nucleophilic attack of oxygen followed by tautomerization to form gold carbenoid species ***xv***. The latter furnishes 2-bromofuran ***d*-22m** after subsequent 1,2-hydride shift.[63]

As it was proposed for 1,2-halogen migration in haloallenones **20** in the presence of oxophilic catalysts (Scheme 9), 1,2-migration of alkyl/aryl group in allenylketones **25**, which required employment of highly cationic metal triflates or strong Brønsted acids, could be, in turn, rationalized only via involvement of the similar intermediates ***xvi*−*xviii*** (Scheme 11). Thus,[1,2]-alkyl or -aryl migration in the intermediate Lewis acid-activated enone moiety of allenone **25**, ***xvi***,[64] produces either vinyl cation ***xvii***[65] or phenonium intermediate ***xviii***. Direct cyclization of ***xvii*** or, alternatively, sequence of either Ad_N-E or S_N2-*vin* processes from ***xviii*** furnishes furan **26** (Scheme 11).

(58) It should be noted that involvement of any possible ionization pathways during cycloisomerization of thioalkynones **12** was ruled out by the absence of scrambling for alkyl- and arylthio- groups in crossover experiment.
(59) For halirenium species, see for example: (a) Noguchi, M.; Okada, H.; Watanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581. (b) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1995**, *117*, 2297.
(60) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.
(61) This is in striking contrast to cycloisomerization of alkynyl imines and ketones, where significant loss of deuterium was observed; see refs 9 and 12.
(62) Decrease in regioselectivity of deuterium vs bromine migration is explained by the isotope effect analogous to that observed by Hashmi in the Pd-catalyzed cycloisomerization of allenyl ketones; see ref 7s.
(63) For 1,2-hydride shift in Au- and Pt-carbenoid intermediates, see for example: (a) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. See also refs 8k, 45h, and 48a,b.
(64) For activation of enone moiety by Lewis acids see, for example: (a) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. (b) Schwier, T.; Gevorgyan, V. *Org. Lett.* **2005**, *7*, 5191.
(65) For examples of 1,2-shift in vinyl cations, see: (a) Capozzi, G.; Lucchini, V.; Marcuzzi, F.; Melloni, G. *Tetrahedron Lett.* **1976**, *17*, 717. (b) Jaeckel, K. P.; Hanack, M. *Tetrahedron Lett.* **1974**, *15*, 1637.

Scheme 13. Generalized Mechanism for the Metal-Catalyzed Synthesis of Furans via Allene Intermediate Involving 1,2-Migration of Different Migrating Groups



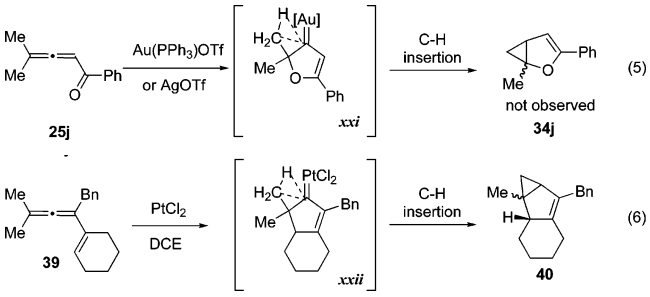
Taking into account the successful transformation of **25** into **26** employing cationic Au(I), Ag(I), and Cu(I) catalysts, we hypothesized that in the case of π-acids, migrative cascade cycloisomerization of allenone **25** follows the pathway analogous to that proposed for 1,2-halogen migration[66] (Scheme 10) and involves similar to ***xiv*** and ***xv*** resonance metal-oxonium ***xix*** and carbenoid ***xx*** intermediates. Thus, sequence of [1,5]-alkyl/aryl shift[67] and metal elimination or direct 1,2-alkyl/aryl shift[63] in ***xix*** or ***xx***, respectively, produces furan **26** (Scheme 12).

Considering all the experimental data disclosed above, a generalized mechanism for the synthesis of furans involving 1,2-migration of different migrating groups is outlined in Scheme 13. It is proposed that a thermally induced and Cu-catalyzed 1,2-migration of chalcogenides (Y = SR and SeR) proceeds via paths **A** and **B**, respectively.[68] Alternatively, Lewis or Brønsted acid-catalyzed cycloisomerization of allenones (X = O) involving 1,2-shifts of halogen (Y = Hal), alkyl, and aryl (Y = C) groups is postulated to follow path **B**, whereas carbophilic catalysts trigger reaction which proceeds through path **C**. Nevertheless, employment of transition metal catalysts in the 1,2-chalcogen migration/cycloisomerization cascade, such as Au(I), Au(III), Pd(II), and Pt(II),[69] may involve a competitive π-system activation pathway **C** proceeding via 1,2-[21] or 1,5-chalcogen migration in the carbenoid/oxonium intermediates **36**/**37**.

The observed competitive 1,2-hydrogen migration for thioalkynone **4** (R^1, R^2 = H, **8**, Table 1, entries 2−5), and competing 1,2-migration of butyl group in selenoalkynone **4** (R^1 = Bu, R^2 = H, **16a**,Table 3, entries 1−3), in case of π-philic catalysts, can be attributed to the 1,2-hydride or -alkyl shifts to the electrophilic center in **36**/**37** (Path **E**). Alternatively, 1,2-shifts[65] of these groups can also occur through the activated enone intermediate **32** via equally feasible path **D**. In contrast to that discussed above, selective/competitive 1,2-hydrogen vs -halogen migration in haloallenones **5** (R^1 = H, **20**, Table 5), catalyzed by carbophilic gold catalysts, can only be rationalized via the path **E**. The observed migratory aptitude trends during 1,2-alkyl/aryl migration/cycloisomerization cascade strongly support

(66) See also ref 7q.
(67) (a) Miller, B. *J. Am. Chem. Soc.* **1970**, *92*, 432. (b) Dolbier, W. R.; Anapolle, K. E.; McCullagh, L.; Matsui, K.; Riemann, J. M.; Rolison, D. *J. Org. Chem.* **1979**, *44*, 2845. (c) Oda, M.; Breslow, R. *Tetrahedron Lett.* **1973**, *14*, 2537.
(68) A control experiment, where thioalkynone **8** was subjected to the prolonged cycloisomerization conditions and monitored by GC for changes in distribution of products **10** and **11**, ruled out any routes involving intraannular 1,2-sulfur migration[20] from 2-thio- to 3-thiofuran after assembly of the furan core.
(69) For Pd-carbenoid species in the synthesis of furans, see ref 7s. For Pd-catalyzed rearrangement see: (a) Rautenstrauch, V.; Burger, U.; Wirthner, P. *Chimia* **1985**, *39*, 225. (b) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950. (c) Kataoka, H.; Watanabe, K.; Goto, K. *Tetrahedron Lett.* **1990**, *31*, 4181. (d) Mahrwald, R.; Schick, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 593. (e) Kato, K.; Yamamoto, Y.; Akita, Y. H. *Tetrahedron Lett.* **2002**, *43*, 6587. For Pt-catalyzed rearrangment see: (f) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouries, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. For Au-catalyzed rearrangement, see: (g) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. See also refs 8k and 45.

predominant involvement of cationic intermediate represented by the resonance structure **37** over metal-carbenoid resonance structure **36** for Au and Ag triflate catalysts. Thus, the migratory aptitude of phenyl- vs methyl group (>100:1) is in a good agreement with that reported in literature for the cationic rearrangements.[70,71] In addition, no cyclopropanation product **34j** was observed in the cycloisomerization of dimethylallenyl ketone **25j** in the presence of Au(I) and Ag(I) catalysts, although this transformation proceeding via carbenoid intermediate ***xxii*** was reported[48a] to give fused cyclopropane **40** as a major product in the cycloisomerization of a carbocyclic analog of **25j**, **39** (eq 5 and 6). Thus, although carbenoid intermediate, such as ***xxi*** or **37**, and/or its attributed reactivity cannot be completely ruled out at this point for 1,2-alkyl/aryl migrative cyclization, it is considered to be substantially less likely.



(70) Saunders, W. H.; Paine, R. H. *J. Am. Chem. Soc.* **1961**, *83*, 882.
(71) The observed migratory aptitude trends (Ph vs. Et, and Ph vs. Me) do not correspond to those reported in literature for 1,2-alkyl migration to carbenoid center. See, for example: (a) Philip, H.; Keating, J. *Tetrahedron Lett.* **1961**, *2*, 523. (b) Graf von der Schulenburg, W.; Hopf, H.; Walsh, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1128.

Conclusion

In conclusion, a mild, efficient, and functional group-tolerant migration/cycloisomerization approach toward multisubstituted heterocycles has been developed. This cascade reaction has proven to be a powerful methodology toward diversely substituted heterocycles. The cycloisomerization approach is general: a variety of propargyl sulfides and selenides, as well as haloallenes or aryl- and alkylallenones, have been successfully employed to produce hetero-substituted furans, pyrroles, and even an indolizine in good to excellent yields. Moreover, regiodivergent conditions have been identified for cycloisomerization of bromo- and thioallenones to obtain regioisomeric 2-hetero substituted furans selectively. Mechanistic studies strongly support the involvement of an irenium type intermediate in all cases where migration occurs. Additionally, mechanistic studies indicate that propargyl chalcogenides undergo necessary isomerization into the corresponding allene during the cascade cycloisomerization. Even though the involvement of π-system activation pathway for certain transition metal-catalyzed cycloisomerizations of chalcogenoalkynones or -allenones could not be completely ruled out, it is considered as less likely. Facile cycloisomerization in the presence of cationic complexes, as well as observed migratory aptitude in the cycloisomerization of unsymmetrically substituted aryl- and alkylallenes, strongly supports electrophilic mechanism for this transformation.

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Supporting Information Available: Experimental procedures and analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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