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Gold(I)-Catalyzed Regiodivergent Rearrangements: 1,2- and 1,2′-Alkyl Migration in Skipped Alkynyl Ketones

Wenbo Li, Yuying Li, Guanghua Zhou, Xiangshu Wu, and Junliang Zhang*[a]

Abstract: A series of 2-alkynyl carbonyl compounds that contain a cyclopentene ring or a heterocycle can be transformed into various fused dihydrobenzofurans and tetrahydrofuro[2,3-*c*]pyridines by means of a 1,2-alkyl migration process. Both of these reactions proceed with excellent regioselectivity and stereospecificity when using a cationic gold(I) catalyst. Treatment of 4-styrylcyclopent-1-enecarboxylates under different conditions affords a range of highly functionalized dihydrobenzofurans and dihydroisobenzofurans. A divergence in product selectivity, which depends on the anion of the silver salts used, was observed. Interestingly, ring-fused tetrahydroquinolines undergo only 1,2′-alkyl migration reaction by means of a C–C cleavage/cyclization sequence to provide tetrahydroazepine derivatives. Mechanistic studies suggest that the gold complexes catalyze 1,2-alkyl migration reactions through a concerted reaction pathway and 1,2′-alkyl migration reactions through a stepwise reaction pathway.

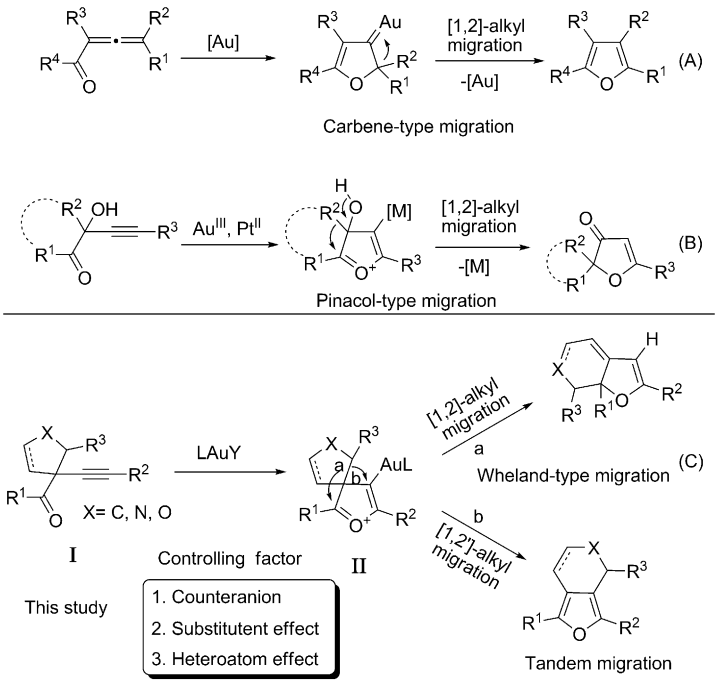
Keywords: alkyl migration · gold · ketones · regioselectivity · tandem reactions

Introduction

It is well known and widely observed that a reaction pathway can be redirected to a different product by changing reaction conditions, which are referred to as "divergent", and this term is broadly applied to many fields such as methodology,[1] synthesis,[2] reactivity, and selectivity,[3] as well as others.[4] However, synthesis of different products from the same starting material(s) in synthetically meaningful yields by subtle choice of different catalysts is rare.[5]

Synthesis of various heterocycles has been a subject of research for over a century, and a variety of well-established methods are available in the literature. In the past decade, cationic gold(I) complexes have evolved as mild Lewis acid catalysts for transformations that require the activation of π bonds.[6] Incorporation of a 1,2-alkyl migration step into the gold-catalyzed cascade reaction is particularly beneficial in the synthesis of densely substituted heterocycles.

Most types of 1,2-alkyl migration[7] in gold catalysis can be divided into two categories: 1) shifts to metal carbenoid centers, and 2) pincol-type rearrangement. Gevorgyan and co-workers showed the utility of allenyl ketones for the synthesis of multisubstituted furans by a 1,2-group migration to the allenyl sp carbon during cycloisomerization.[8] Among them, 1,2-migration of alkyl, aryl, and halogens predominantly proceed through the formation of carbene intermediates (Scheme 1A).[9,10] Moreover, this method proved to be especially efficient for the regiodivergent synthesis of silylfurans and halofurans, which are controlled by counterion, ligand, or solvent effects.[8a,b,11] An alternate strategy that uses a pinacol rearrangement has been realized as a power-



Scheme 1. A), B) 1,2-Alkyl migration in previous works and C) the present work.

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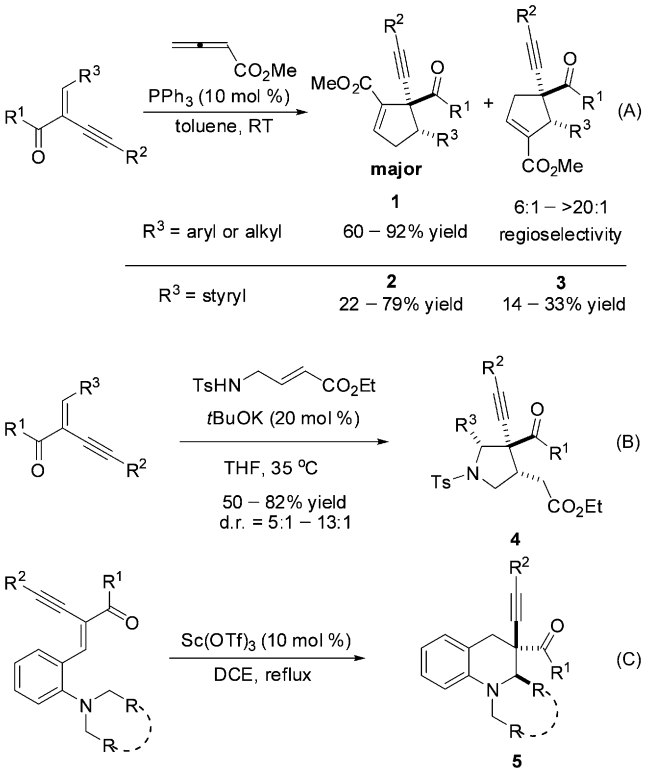
ful entry into the synthesis of complex structures.[12] For example, Toste et al. and Liu et al. have respectively described the gold-catalyzed rearrangement reactions of 2-alkynyl-1-ols,[13] whereas Kirsch and co-workers have employed a similar pathway that uses 3-silyoxy-1,5-enynes.[14] The positive charge induced on the alkyne moiety by coordination of the cationic gold(I) complex is responsible for the rearrangement. Another example that combined heterocyclization and a pinacol-type rearrangement has also been reported by Kirsch et al. using 2-alkynyl-2-hydroxy carbonyl compounds (Scheme 1B).[15]

Building upon these precedents, we recently developed a highly regio- and stereoselective intramolecular 1,2-alkyl migration and heterocyclization process of 2-alkynyl carbonyl compounds with a cyclopentane ring.[16] Furthermore, we were interested to explore whether furyl-derived Whelandtype intermediate **II** could trigger two different 1,2-alkyl migration processes through path a and path b, which was less documented (Scheme 1C). Herein we provide a full account of our study that resulted in the development of gold-catalyzed regiodivergent migration reactions of 2-alkynyl carbonyl compounds[17] with an unsaturated ring and a heterocycle. The structure of the substrates and the nature of the ion pairs formed by silver salts and its cationic counterpart are likely to be essential to these transformations. A more detailed mechanistic investigation of origins of the regiodivergent rearrangements might give a better understanding of the gold-catalyzed alkyl migration chemistry. This chemistry can be extended to the synthesis of polycyclic furan-based compounds.

Results and Discussion

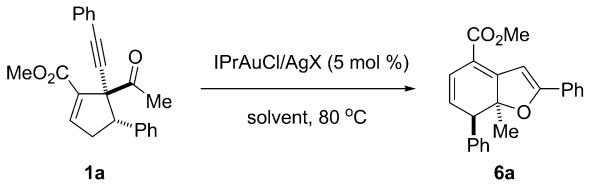
The cyclopentene derivatives were prepared according to the corresponding known methods with modification (Scheme 2A).[18] A series of highly functionalized cyclopentenes **1** that contain two contiguous stereocenters can be synthesized with high diastereoselectivity and good regioselectivity. Notably, the reaction has been applied to dienones to produce 4-styrylcyclopentenes **2** in acceptable isolated yield and a trace amount of 5-styrylcyclopentenes **3**. Functionalized pyrrolidines **4** can be accessed from the reactions of 2-(1-alkynyl)-2-alken-1-ones with the γ-amine α,β-unsaturated ester in moderate to good yields (Scheme 2B).[19] Recently, we developed the $Sc(OTf)_3$-catalyzed (Tf = trifluoromethanesulfonate) intramolecular redox domino reaction to afford ring-fused tetrahydroquinolines **5** (Scheme 2C).[20a]

We examined the reaction of cyclopentene derivative **1a** under gold(I)-catalyzed conditions (as shown in Table 1).[21] In the present study, different silver salts such as $AgPF_6$, AgOTf, $AgSbF_6$, AgOMs (Ms = mesyl), and $C_3F_7CO_2Ag$ were investigated at 80 °C using dry dichloroethane (DCE) as the solvent (Table 1, entries 1–5). The use of $AgSbF_6$ with gold(I) catalyst[22] for the transformation of **1a** afforded **6a** in 98% yield by a selective migration of the sp^3-carbon atom rather than the sp^2-carbon atom (Table 1, entry 3).[23]



Scheme 2. Synthesis of starting materials.

Table 1. Optimization of the reaction conditions.[a]



1a 6a

Entry	AgX	Solvent	*t* [h]	Yield[b] [%]
1	$AgPF_6$	DCE	5	97
2	AgOTf	DCE	96	82
3	$AgSbF_6$	DCE	9	98
4	AgOMs	DCE	5	97
5	$C_3F_7CO_2Ag$	DCE	5	97
6	$AgSbF_6$	toluene	3	98
7	$AgSbF_6$	DMF	3	96
8	$AgSbF_6$	CH_3CN	9	93
9[c]	$AgSbF_6$	THF	16	94

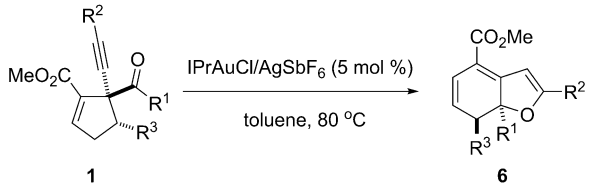
[a] Reactions carried out on 0.25 mmol scale, 2.5 mL solvent. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [b] Isolated yield. [c] Reaction run at 70 °C.

Subsequently, we screened different solvents with the use of $IPrAuCl/AgSbF_6$ (5 mol %) as a catalyst system (Table 1, entries 6–9). Toluene appeared to be the most effective solvent for this transformation (Table 1, entry 6).

Having determined the reaction conditions for the highly selective transformation of **1a**, we conducted experiments to explore the scope of the gold(I)-catalyzed stereoselective 1,2-alkyl migration of substituted cyclopentenes (Table 2).

The cyclopentenes **1b** and **1c** with a *p*-methoxyphenyl and a *p*-chlorophenyl group successfully produced the dihydrobenzofurans **6b** and **6c** in 93 and 99% yield, respectively

Table 2. Results of gold(I)-catalyzed 1,2-alkyl migration of substituted cyclopentenes **1**.[a]



1 **6**

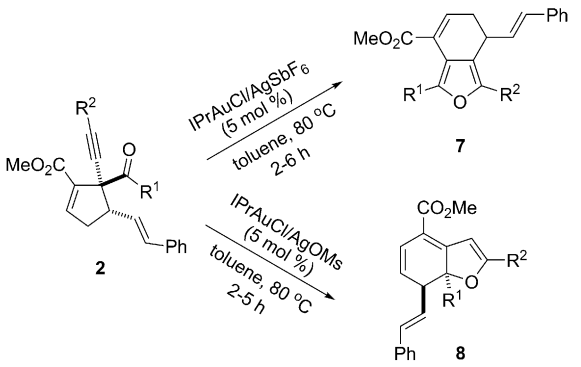
Entry	$R^1/R^2/R^3$	*t* [h]	Product **6**	Yield[b] [%]
1	Me/Ph/Ph	3	**6a**	98
2	Me/Ph/4-$MeOC_6H_4$	5	**6b**	93
3	Me/Ph/4-ClC_6H_4	2	**6c**	99
4[c]	Me/Ph/nC_4H_9	10	**6d**	82
5[c]	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$	120	**6e**	88
6[c]	Me/4-$NO_2C_6H_4$/Ph	11	**6f**	81
7	Me/4-$MeOC_6H_4$/Ph	4	**6g**	88
8	Me/1-cyclopropyl/Ph	10	**6h**	64
9	Me/nC_4H_9/Ph	5	**6i**	76
10[c]	Me/1-naphthyl/Ph	120	**6j**	81
11[c]	Me/1-naphthyl/4-$MeOC_6H_4$	72	**6k**	67
12[d]	Ph/Ph/Ph	18	**6l**	76

[a] Reactions were carried out using cyclopentenes **1** (0.25 mmol), IPrAuCl (5 mol%), and $AgSbF_6$ (5 mol%) in toluene at 80°C. [b] Isolated yield. [c] Reaction run in DCE. [d] Reaction run in DMF.

(Table 2, entries 2 and 3). To our surprise, even the reaction of the cyclopentene ring with an aliphatic group ($R^3 = nC_4H_9$) also proceeded to afford the corresponding dihydrobenzofuran **6d** in 82% yield (Table 2, entry 4). When the substrates that contained electron-donating and -withdrawing groups on the alkynyl moiety were subjected to the reaction, the corresponding dihydrobenzofurans were obtained in good yields (Table 2, entries 5–7, 10, and 11). The reactions of the substrates **1h** and **1i**, which have a cyclopropyl and a butyl, respectively, also afforded the desired dihydrobenzofurans **6h** and **6i** in moderate yields (Table 2, entries 8 and 9). The substrate **1l**, which has a phenyl group on the α position of ketone, was converted to the dihydrobenzofurans **6l** in 76% yield (Table 2, entry 12). The structure of **6f**, including the stereochemistry, was confirmed by X-ray crystallographic analysis (see the Supporting Information). It is worth noting that all these products were obtained as a single diastereomer during the process.

We sought to gain further insight into the reaction scope of the gold-catalyzed 1,2-alkyl migration with R^3 = styryl. To our delight, treatment of (*E*)-methyl 5-benzoyl-5-(phenylethynyl)-4-styrylcyclopent-1-enecarboxylate (**2a**) with precatalyst IPrAuCl and $AgSbF_6$ provided 6,7-dihydroisobenzofuran (**7a**) in 90% yield, whereas the reaction with AgOMs under otherwise identical conditions provided 7,7a-dihydrobenzofuran (**8a**) in 90% yield (Table 3, entries 1 and 2). Gratifyingly, products that differed in structure could be selectively prepared simply by changing the silver salt cocatalyst in conjunction with IPrAuCl, which demonstrated a dramatic counterion effect on the regioselectivity of the reactions.

Table 3. Regiodivergent 1,2′- and 1,2-alkyl migration of 4-styrylcyclopentenes **2**.[a]



Entry	Substrate R^1/R^2 **2**	*t* [h]	Product **7/8**	Yield[b] [%]
1	Ph/Ph, **2a**	4	**7a**	90
2	**2a**	4	**8a**	90
3	Ph/4-$NO_2C_6H_4$, **2b**	3	**7b**	83
4	**2b**	3	**8b**	77
5	Ph/4-$MeOC_6H_4$, **2c**	3	**7c**	48[c]
6	**2c**	3	**8c**	84
7	Ph/4-MeC_6H_4, **2d**	3	**7d**	88
8	**2d**	3.5	**8d**	90
9	4-BrC_6H_4/Ph, **2e**	66	**7e**	88
10	**2e**	5	**8e**	95
11	4-$MeOC_6H_4$/Ph, **2f**	4	**7f**	77
12	**2f**	4.5	**8f**	98
13	Me/Ph, **2g**	4	**8g**	74(70)[d]
14	Ph/nC_4H_9, **2h**	5	**8h**	56(88)[d]

[a] Conditions A to give **7**: IPrAuCl (5 mol%) and $AgSbF_6$ (5 mol%) in toluene at 80°C. Conditions B to give **8**: IPrAuCl (5 mol%) and AgOMs (5 mol%) in toluene at 80°C. [b] Isolated yield. [c] The 1,2-alkyl migration product **8c** was isolated in 40% yield. [d] Result in parentheses was obtained from IPrAuCl (5 mol%)/$AgSbF_6$ (5 mol%) catalyst.

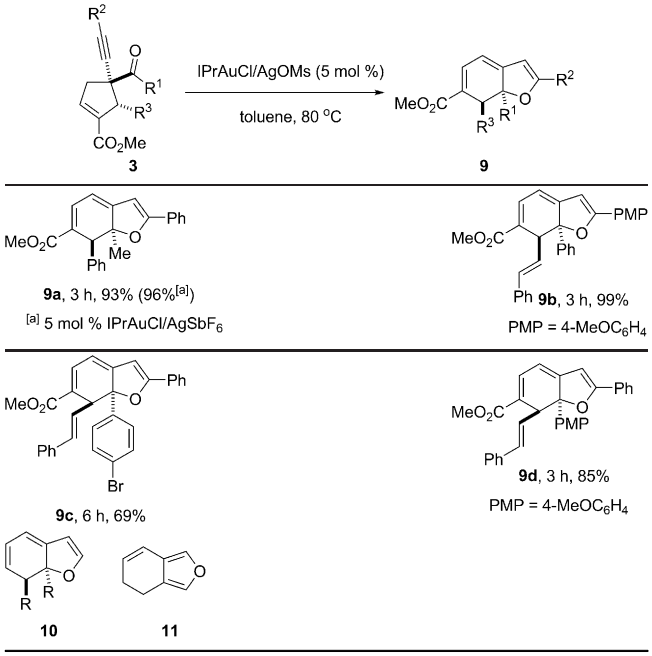
With these results in hand, we next examined the generality of this IPrAuCl/$AgSbF_6$ system. 2-Alkynyl carbonyl compounds with a variety of substituted patterns were tolerated, however, transformations of 4-styrylcyclopentene derivatives **2** that involved 1,2′-alkyl migration were limited to compounds that cannot bear an alkyl group (R^1 = aryl, R^2 = aryl). Both electron-donating and -withdrawing functionalities at the alkynyl moiety and carbonyl moiety were fully compatible with the method (**7b–f**). In addition, treatment of **2c** with a *p*-methoxyphenyl group on the alkyne moiety not only led to the desired product **7c** in 48% yield but also gave a 1,2-alkyl migration product **8c** in 40% yield (Table 3, entry 5), probably on account of the strong electronic effects.

The scope of the 1,2-alkyl migration reaction of 4-styrylcyclopentenes **2** in the presence of IPrAuCl/AgOMs is summarized in Table 3. The reaction shows excellent scope in terms of the alkynyl and carbonyl substituents. Moreover, both electron-rich and electron-poor 4-styrylcyclopentenes gave the 1,2-alkyl migration products **8b–f** in good to excellent yields. Interestingly, under both reaction conditions, substrates **2** with alkyl groups for R^1 or R^2 afforded 7,7a-di-

hydrobenzofuran **8** in moderate to good yield. Similarly, excellent regio- and diastereoselectivity were observed in the reaction of **8g** and **8h** in 74 and 56% yield, respectively (Table 3, entries 13 and 14).

To further demonstrate the generality of this method, we hypothesized that an analogous 1,2-alkyl migration of substituted 5-aryl/styrylcyclopentenes **3** as the minor byproducts in [3+2] cycloadditions of allenes and enones might allow for the construction of dihydrobenzofurans (Table 4). We

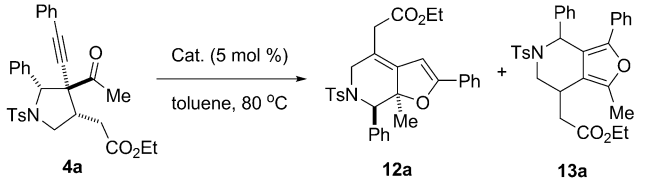
Table 4. Results of gold(I)-catalyzed 1,2-alkyl migration of highly functionalized cyclopentenes **3**.



were pleased to find that aryl and styryl substituents at the R^3 position underwent effective 1,2-alkyl migration. As mentioned above, when the reaction of **3a** with a methyl group on the α position of ketone was carried out, the corresponding product **9a** was obtained in excellent yield under both conditions by chemoselective cleavage of the C–C (aryl-substituted) bond. The substrate **3b** was also converted to 7,7a-dihydrobenzofuran **9b** in 99% yield catalyzed by IPrAuCl/AgOMs, whereas the use of $AgSbF_6$ led to complicated complexes. Additionally, substrates that possessed aromatic substituents on the carbonyl moiety (**3b–d**) were generally well tolerated, with the electron-deficient 5-styrylcyclopentene (**3c**) requiring longer reaction times. The core functionality assembled by this 1,2-alkyl migration is dihydrobenzofuran (**10**), and the one by 1,2′-alkyl migration is dihydroisobenzofuran (**11**).[24] Interestingly, compounds **6**, **8**, and **9** with the structure of dihydrobenzofurans are all bright red except for **6h**, **6i**, and **8h**. A definitive feature of this novel route to substituted dihydrobenzofurans is that challenging structural elements are readily accessed, as exemplified through the construction of an all-carbon quaternary center and complex bicyclic compounds with highly diastereoselectivity.

Furthermore, the presence of a nitrogen-containing heterocycle rather than a cyclopentane in 2-alkynyl carbonyl compounds could be expected to have a significant impact on both reactivity and regioselectivity in these rearrangement reactions. Application of this strategy to substituted pyrrolidines opened up a novel way for the catalytic construction of bicyclic skeletons that bear two heteroatoms. Employing highly substituted pyrrolidine **4a** resulted in a mixture of tetrahydrofuro[2,3-*c*]pyridine **12a** (52%) and tetrahydrofuro[3,4-*c*]pyridine **13a** (30%) with IPrAuCl/$AgSbF_6$ (Table 5, entry 1). Similar results were obtained with IPrAuCl/$AgBF_4$ and IPrAuCl/$AgNTf_2$ (Table 5, entries 3 and 4). These results suggested that compound **12a** was formed through 1,2-alkyl migration with competing 1,2′-alkyl migration. The higher selectivity for the formation of compound **12a** in the presence of AgOMs or AgOTf was obtained, and the formation of compound **13a** was almost completely suppressed (Table 5, entries 2 and 5). Interestingly, its treatment with PPh_3AuCl/AgOTf in toluene did not lead to an efficient reaction (Table 5, entry 6). Remarkably, the PPh_3AuCl/AgOMs-catalyzed reaction provided **12a** in 80% yield (Table 5, entry 7). Further studies revealed that the optimized reaction conditions (IPrAuCl/AgOTf (5 mol%), toluene, 80°C) was a slightly more suitable system.[25]

Table 5. Reaction conditions for gold(I)-catalyzed 1,2-alkyl migration of highly functionalized pyrrolidines **4a**.[a]

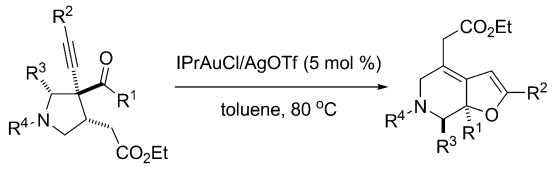


Entry	Catalyst	*t* [h]	Yield of **12a**[b] [%]	Yield of **13a**[b] [%]
1	IPrAuCl/$AgSbF_6$	5.5	52	30
2	IPrAuCl/AgOMs	4	71	–
3	IPrAuCl/$AgBF_4$	7	60	15
4	IPrAuCl/$AgNTf_2$	3.5	63	24
5	IPrAuCl/AgOTf	3.5	76	–
6[c]	PPh_3AuCl/AgOTf	8	–	–
7	PPh_3AuCl/AgOMs	8	80	–

[a] Reactions carried out on 0.25 mmol scale, 2.5 mL solvent. [b] Isolated yield. [c] Complicated complex.

Next, 1,2-alkyl migration of differently substituted pyrrolidines **4b–j** was examined by utilizing the optimized reaction conditions (Table 6). Notably, when using inseparable diastereomers **4b** and **4c**, the corresponding products **12b** and **12c** were obtained in good yields as a single diastereomer (Table 6, entries 1 and 2). Substrates (**4b–f**) that possessed aromatic or aliphatic substituents on the alkynyl moiety were generally well tolerated, with the more electron-deficient pyrrolidine **4f** affording the corresponding bicyclic compound **12f** in lower yield (Table 6, entries 1–5). Elec-

Table 6. Results of gold(I)-catalyzed 1,2-alkyl migration of highly functionalized pyrrolidines **4**.[a]



4a-j, R^4 = Ts
4k, R^4 = Ns

12

Entry	Substrate **4**	$R^1/R^2/R^3$	*t* [h]	Product **12**	Yield[b] [%]
1[c]	**4b**	Me/4-$MeOC_6H_4$/Ph	5.5	**12b**	77
2[c]	**4c**	Me/4-MeC_6H_4/Ph	7.5	**12c**	76
3	**4d**	Me/1-naphthyl/Ph	4.5	**12d**	84
4	**4e**	Me/1-cyclopropyl/Ph	2	**12e**	74
5	**4f**	Me/4-$NO_2C_6H_4$/Ph	2.5	**12f**	53
6	**4g**	Me/Ph/4-$MeOC_6H_4$	7	**12g**	60
7	**4h**	Me/Ph/4-ClC_6H_4	4	**12h**	60
8	**4i**	Ph/Ph/Ph	7.5	**12i**	62[d,e]
9	**4j**	4-ClC_6H_4/Ph/Ph	6	**12j**	51[e,f]
10[g]	**4k**	Me/Ph/Ph	3	**12k**	90

[a] Reactions were carried out using substituted pyrrolidines **4** (0.3 mmol), IPrAuCl (5 mol%), and AgOTf (5 mol%) in toluene at 80°C. [b] Isolated yield. [c] Inseparable diastereomers **4b**, isolated d.r. 10.0:1; inseparable diastereomers **4c**, isolated d.r. 12.5:1. [d] The structure of **12i** was established by X-ray crystallography. [e] Reaction was carried out in the presence of PPh_3AuCl (5 mol%) and AgOMs (5 mol%). [f] The 1,2′-alkyl migration product **13j** was isolated in 15% yield and the decomposed product **14j** from **12j** was isolated in 21% yield. [g] Inseparable diastereomers **4k**, isolated d.r. 8.3:1.

tron-donating and -withdrawing groups on the phenyl ring of R^3 were compatible, and the reactions gave compounds **12g** and **12h** in moderate yields (Table 6, entries 6 and 7). Exceptionally, when **4i** and **4j** were used as the substrates, the IPrAuCl/AgOTf catalysis led to the formation of compounds **13** as the major products through 1,2′-alkyl migration. When the reaction of **4i** was carried out with 5 mol% PPh_3AuCl/AgOMs, 1,2-alkyl migration occurred to give bicyclic compound **12i** in 62% yield (Table 6, entry 8). The structure of **12i** was confirmed by X-ray crystallographic analysis. As expected, tetrahydrofuro[2,3-*c*]pyridine **12j** was formed, albeit in moderate yield; however, it was accompanied by a small amount of the unexpected regioisomer **13j** and the decomposed product **14j** from **13j** (Table 6, entry 9). Encouraged by these results, we attempted incorporation of an Ns group into the 1,2-migration reaction. It was found that the 8.3:1 mixture of two stereoisomers of **4k** underwent 1,2-alkyl migration at 80°C in the presence of 5 mol% IPrAuCl/AgOTf to afford **12k** in 90% yield (Table 6, entry 10). To make the N-substituent effect much clearer, we attempted to synthesize the *N*-alkyl pyrrolidine-derived 2-alkynyl carbonyl compounds. It was a pity that a projected cascade aza-Michael–Michael reaction of 2-(1-alkynyl)-2-alken-1-ones with the γ-amine α,β-unsaturated ester could not be realized under various conditions.[26] Thus, the anion of the silver salt and the structure of the substrates **4** are two factors that are interconnected and their combined effect has a dramatic influence on the regioselectivity of the rearrangement reactions. In addition, these different substitutions on the R^2 typically result in significant changes in the photophysical properties of the fluorophore. The electron-donating **12c** to electron-withdrawing **12f** revealed a significant redshift in the emission spectrum of the formed compound (Figure 1). The measured redshift was from $\lambda_{max}=441$ nm (assigned to **12c**) to $\lambda_{max}=593$ nm (assigned to **12f**).

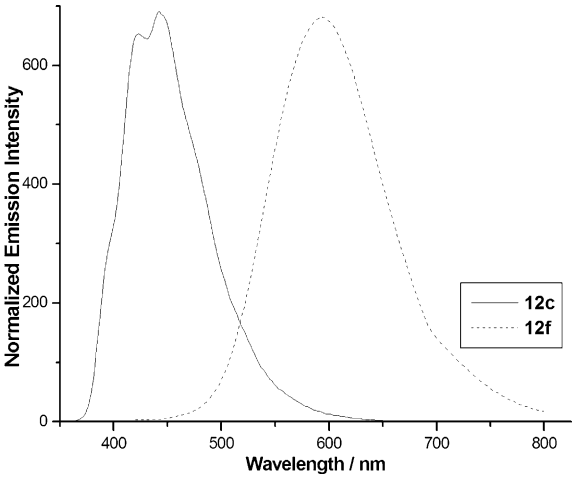
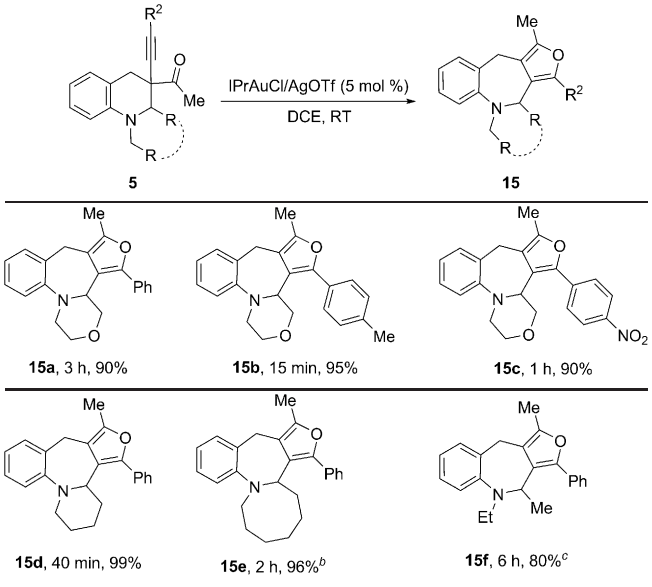


Figure 1. Fluorescence spectra of **12c** and **12f**.

Gratifyingly, the ring-fused tetrahydroquinolines[20] produced the 1,2′-alkyl migration product **15** as the sole isomer by employment of IPrAuCl/AgOTf as catalyst (Table 7). This rearrangement was successfully performed with different amino groups such as morphlione (**5a–c**), piperidine (**5d**), an eight-membered cyclic amino group (**5e**), and an acyclic amino group (**5f**), and the desired ring-fused tetrahydroazepines were obtained in good to excellent yields. Notably, the aryl unit (R^2) with electron-withdrawing and -donating groups displayed high reactivity. These results support that the reaction would prefer to proceed by means of a tandem 1,2′-alkyl migration with the more stable iminium ion.

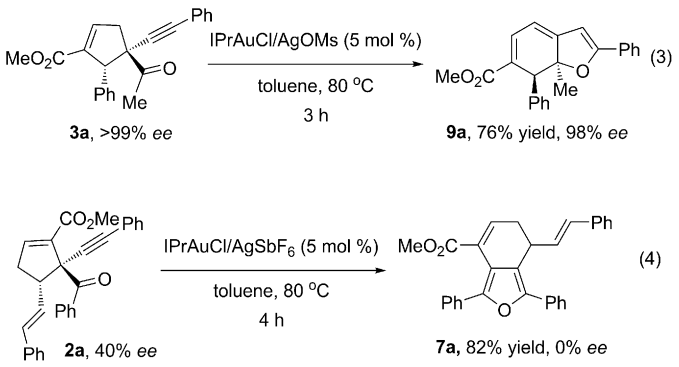
We sought to gain further insight into the reaction mechanisms of both 1,2- and 1,2′-alkyl migration reactions. To trap some cationic intermediates, an excess amount of methanol was added to the reaction mixture.[27] Interestingly, the rearrangement of **2a** catalyzed by IPrAuCl/$AgSbF_6$ favors formation of dihydroisobenzofuran **7a**; however, the reaction with MeOH (10 equiv) gave rise to a 1:1.2 mixture of **7a** and **8a** [Eq. (1)]. Moreover, the reaction of **2a** with MeOH (100 equiv), catalyzed by IPrAuCl/$AgSbF_6$, provided **8a** as the major product (**7a**/**8a**=1:8.5). In contrast, the reaction of **2a** with MeOH (10 equiv), catalyzed by IPrAuCl/AgOMs, gave rise to a single product **8a** [Eq. (2)]. The results show the variation of selectivity with respect to an interaction between anion and cationic gold. The more nucleophilic anion leads to a 1,2-shift product in a concerted fash-

Table 7. Results of gold(I)-catalyzed 1,2′-alkyl migration of substituted tetrahydroquinolines **5**.[a]

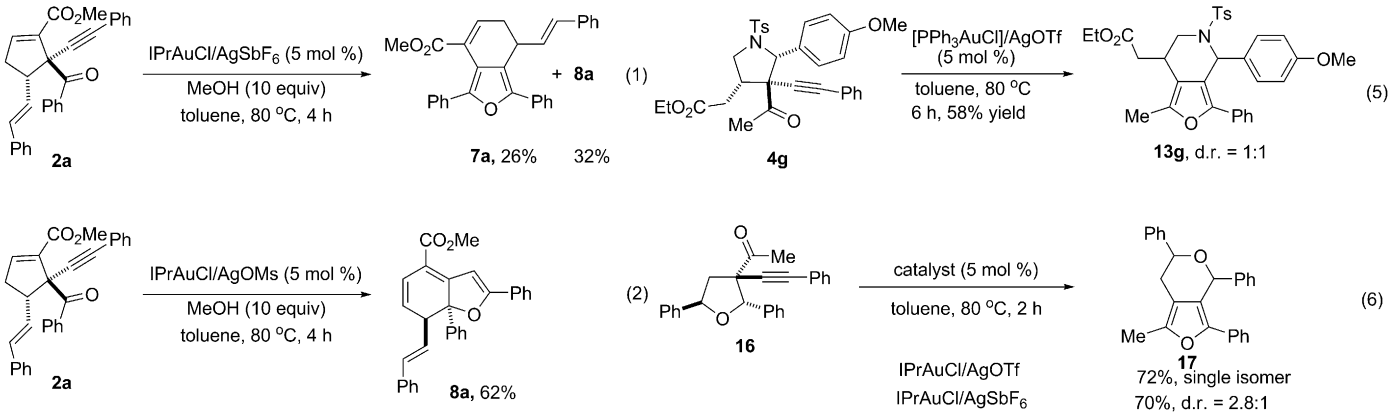


[a] Reactions were carried out using substituted tetrahydroquinoline **5** (0.3 mmol), IPrAuCl (5 mol%), and AgOTf (5 mol%) in toluene at 25°C. [b] Inseparable diastereomers **5e**, isolated d.r. 2.0:1. [c] Inseparable diastereomers **5f**, isolated d.r. 1.0:1.

ion, and the non-nucleophilic anion favors a 1,2′-shift ring-expanded product.

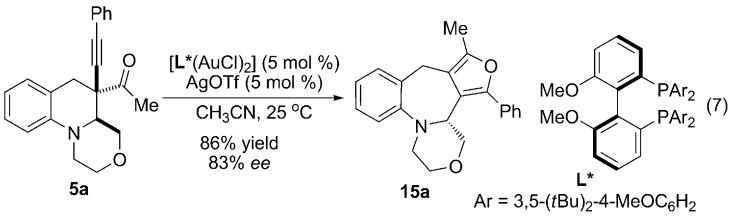


1,2′-alkyl migration product **13g** with 1:1 diasteromeric ratio (d.r.) in moderate yield [Eq. (5)], thus suggesting that this reaction might involve a carbocation mechanistic pathway and the ligand is essential for the rearrangement regioselectivity. In the case of 2,5-*trans*-disubstituted tetrahydrofuran **16**, the 1,2′-alkyl migration product **17** was obtained in 72% yield as the sole regioisomer under catalysis by IPrAuCl/AgOTf. Similarly, the rearrangement of **16** using IPrAuCl/$AgSbF_6$ afforded the 1,2′-alkyl migration product **17** with 2.8:1 d.r. in 70% yield [Eq. (6)]. It seems that the more stable intermediate oxonium ion is contributing to the regioselectivity of the reaction. Additionally, the tetrahydroquinoline **5a** catalyzed by a chiral gold complex gave rearrangement product **15a** with 83% *ee* [Eq. (7)].

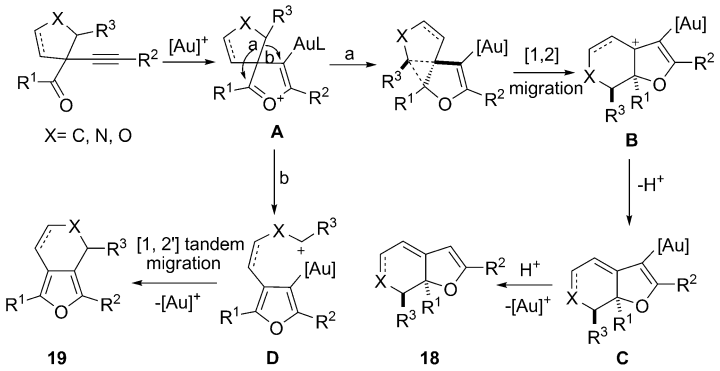


Next, to probe the stereoselectivity of the 1,2- and 1,2′-alkyl migration steps, optically active **3a** (>99% *ee*) and **2a** (40% *ee*) were prepared. This 1,2-alkyl migration step provided product **9a** without loss of enantiopurity of the material [Eq. (3)]. This result indicated that the 1,2-alkyl migration is a stereospecific concerted reaction. Treatment of enantioenriched **2a** with 5 mol% IPrAuCl/$AgSbF_6$ in toluene at 80°C for 4 h furnished 6,7-dihydroisobenzofuran **7a** in 82% yield as a racemic product, which was regarded as evidence of a stepwise one [Eq. (4)].

Meanwhile, the substrate **4g**, by treatment with PPh_3AuCl/AgOTf in toluene, gave the nonstereospecific



A possible mechanism for these transformations is shown in Scheme 3. After coordination to the triple bond, the gold catalyst induces an intramolecular attack of the carbonyl group to the alkyne to give the spiro intermediate **A**,[28]



Scheme 3. Proposed mechanism.

which might in turn undergo a 1,2-alkyl migration through pathway a, or a 1,2′-alkyl migration through pathway b. Through path a, intermediate **A** forms the allylic cation-containing vinyl–gold intermediate **B** by the selective 1,2-alkyl migration from the 3- to the 2-position by means of a three-membered cyclic transition state. Upon subsequent deprotonation and protodeauration, intermediate **B** would give the [2,3-*c*]furan **18**. Through path b, oxonium-containing vinyl–gold intermediate **A** would undergo 1,2′-alkyl migration from the 3- to the 4-position by means of a C–C bond cleavage and subsequently ring closing[29] to produce [3,4-*c*]furan **19**. The rearrangement that possesses a more stable cation intermediate **D** favors undergoing a 1,2′-alkyl migration reaction.

The generally observed divergence in product selectivity can be thoroughly explained by the nature of the counteranion and the stability of intermediates. In general, if the effect favors the formation a more stable carbocation **D**, the 1,2′-migration pathway will be the predominant one. 1) For 4-styrylcyclopentene derivatives **2**, counteranion factors govern the regioselectivity of the reaction. The 4-styrylcyclopentene derivatives can participate in either a 1,2- or 1,2′-alkyl migration pathway. When a more nucleophilic anion (OMs^-) is used, 1,2′-alkyl migration pathway is disfavored due to the fact that free carbocation **D** might react with the nucleophilic anion and hinder the subsequent cyclization. 2) The heteroatom effect was crucial for the regioselectivity of the rearrangement. Indeed, tetrahydrofuran-based 2-alkynyl carbonyl compound **16** favors the formation of the carbocation **D** stabilized by the oxygen (also called oxonium intermediate), thus leading to a 1,2′-alkyl migration product. 3) A substituent with a different electronic nature at the N position did alter the reactivity: substrates **4** with the electron-withdrawing Ts group reacted smoothly to afford 1,2-alkyl migration products, and those compounds **5** with an electron-donating alkyl group afforded 1,2′-alkyl migration products under the reaction conditions, which probably originates from stabilization of the iminum ion intermediate.

Conclusion

Although there have been numerous reports of reactions that incorporate a 1,2-alkyl migration step, only a few processes had been described that employ the same substrates to provide different products along different rearrangement pathways. In this report, we have shown that a range of cyclopentene-based 2-alkynyl carbonyl compounds can be transformed into various dihydrobenzofurans by following a 1,2-alkyl migration sequence catalyzed by a gold(I) complex. Furthermore, treatment of 4-styrylcyclopent-1-ene-carboxylates **2** with gold(I) catalyst that possesses non-nucleophilic SbF_6^- counterion affords a range of highly functionalized dihydroisobenzofurans **7**; and with the OMs^- counterion, highly substituted dihydrobenzofurans **8** can be obtained. Thus, a clear-cut divergence in rearrangement directions was observed, which indicates that the regioselectivity of Au-catalyzed 1,2- versus 1,2′-alkyl migration is counterion-dependent. In addition, it was found that the 2-alkynyl carbonyl heterocyclic compounds that contain pyrrolidine rings underwent a 1,2-alkyl migration step, and in the case of tetrahydroquinoline, the substrate-assisted 1,2′-alkyl migration is the major process. The present study might provide a better understanding of the reaction of 1,2-alkyl migration by a concerted mechanism and the reaction of 1,2′-alkyl migration by means of a key C–C bond cleavage and C–Au bond-substitution pathway. Nevertheless, in light of the fact that various effects on the rearrangement reactions have not been studied systematically, the migratory aptitude remains to be fully elucidated. This method allows for efficient synthesis of multisubstituted and fused furans, and we anticipate that an array of other processes might benefit from this approach.

Experimental Section

General procedure for the preparation of compounds 7: IPrAuCl (0.0125 mmol), $AgSbF_6$ (0.0125 mmol), and dry toluene (2.5 mL) were added to a dry Schlenk tube, and the mixture was stirred at room temperature for 0.5 h in the dark. Compound **2** (0.25 mmol) was added, and the resulting mixture was stirred at 80 °C for 2–6 h. After the reaction was complete, which was determined by TLC analysis, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes/acetate = 5:1) to give **7** as a yellow solid.

General procedure for the preparation of compounds 8: IPrAuCl (0.0125 mmol), AgOMs (0.0125 mmol), and dry toluene (2.5 mL) were added to a dry Schlenk tube, and the mixture was stirred at room temperature for 0.5 h in the dark. Compound **2** (0.25 mmol) was added, and the resulting mixture was stirred at 80 °C for 2–5 h. After the reaction was complete, which was determined by TLC analysis, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes/acetate = 5:1) to give **8** as a red solid or oil.

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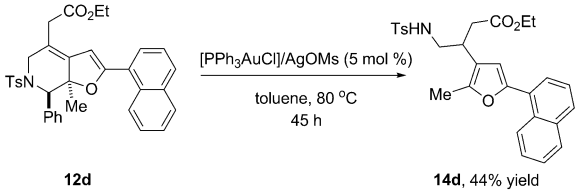
[25] During our study, in most cases, reactions of **4** catalyzed by $PPh_3AuCl/AgOMs$ produced **12** with lower yield and over a longer reaction time. With $PPh_3AuCl/AgOMs$, the slow decomposition of the substrate **12** was observed.



12d **14d**, 44% yield

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