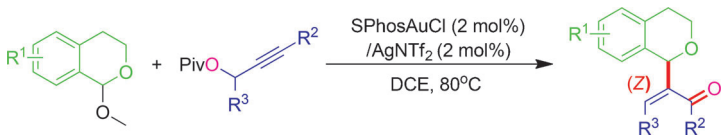
Communications

Gold Catalysis

Y. Yu, W. Yang, F. Rominger, A. S. K. Hashmi* _____ ■■■■–■■■■



In Situ Generation of Nucleophilic Allenes by the Gold-Catalyzed Rearrangement of Propargylic Esters for the Highly Diastereoselective Formation of Intermolecular $C(sp^3)$–$C(sp^2)$ Bonds

New perspectives, in particular for the synthesis of isochromane derivatives (see scheme), are provided by the title reaction. Excellent diastereoselectivites are achieved in this reaction which proceeds through a gold-catalyzed 1,3-acyloxy migration. In some cases exclusively the *Z* isomer is detected.

Gold Catalysis

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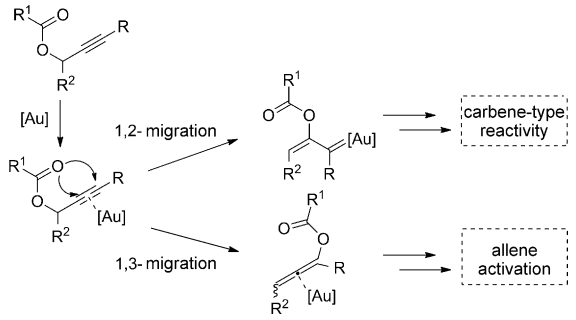
In Situ Generation of Nucleophilic Allenes by the Gold-Catalyzed Rearrangement of Propargylic Esters for the Highly Diastereoselective Formation of Intermolecular C(sp^3)–C(sp^2) Bonds**

*Yang Yu, Weibo Yang, Frank Rominger, and A. Stephen K. Hashmi**

In the last few years, in the field of homogeneous gold catalysis[1] rearrangement reactions involving propargylic esters have received considerable attention owing to the synthetic utility of these easily accessible compounds in a wide variety of intriguing, fascinating transformations.[2] It is established that in gold catalysis these propargylic esters can undergo 1,2- or 1,3-acyloxy migration leading to a gold vinyl carbenoid species or a gold allenic intermediate (Scheme 1),[3]



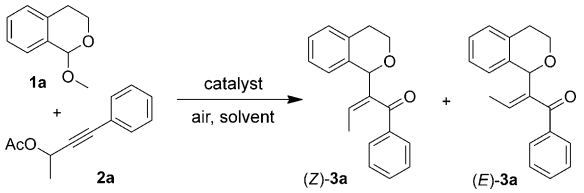
Scheme 1. Gold vinyl carbenoid and gold allenic intermediates.

which can be further trapped by other functional groups to allow the synthesis of diverse organic products. The gold vinyl carbenoid species can undergo prototypical reactions, for example the cyclopropanation of alkenes and dienes, as well as insertion into C–H bonds.[4] For the gold allenic intermediate, most studies cover intramolecular electrophilic addition reactions.[5]

In contrast, the few examples of the catalytic generation of nucleophilic gold allenic intermediate have been limited to the study of intramolecular reactions.[6] Only one intermolecular reaction involving C–X bond formation (X = iodine, bromide as electrophiles) has been reported by Zhang et al.[7] However, to the best of our knowledge, there are no examples in which nucleophilic allenes are generated in situ by gold-catalyzed acyloxy migration in propargylic esters for intermolecular C(sp^3)–C(sp^2) bond formation. This reactivity mode would considerably extend the potential of gold-catalyzed 1,3-acyloxy migration.

We were interested in developing this new type of gold-catalyzed intermolecular reaction. Here the gold catalyst should serve two purposes simultaneously: treatment of a propargylic ester of an internal alkyne with the gold catalyst would generate a nucleophilic allene in situ through the gold-catalyzed 1,3-acyloxy migration; at the same time the gold catalyst would serve as an Lewis acid, promoting the formation of electrophilic oxocarbenium ions[8] from isochromane acetals. Electrophilic attack of these oxocarbenium intermediates at the allene would lead to the desired C–C

Table 1: Optimization studies on the gold-catalyzed reaction of **1a** with **2a**.[a]



Entry	Catalyst	Solvent	t	Yield [%][b] (Z)-3a	(E)-3a
1	SPhosAuCl/$AgNTf_2$	DCE	10 min	68	trace
2[c]	SPhosAuCl/$AgNTf_2$	DCE	23 min	58	–
3	$Ph_3PAuNTf_2$	DCE	10 min	61	–
4	IPrAuCl/$AgNTf_2$	DCE	10 min	52	–
5[d]	[Au^{3+}]	DCE	24 h	trace	–
6	*p*-TsOH	DCE	8 h	–	trace
7	SPhosAuCl/$AgSbF_6$	DCE	10 min	63	–
8	SPhosAuCl/AgOTs	DCE	24 h	n.r.	–
9	$AgNTf_2$	DCE	24 h	16	–
10	SPhosAuCl/$AgNTf_2$	Toluene	8 h	32	–
11	SPhosAuCl/$AgNTf_2$	CH_3CN	8 h	22	–
12	SPhosAuCl/$AgNTf_2$	1,4-Dioxane	8 h	trace	–
13[e]	SPhosAuCl/$AgNTf_2$	DCE	2.5 h	62	trace
14[f]	SPhosAuCl/$AgNTf_2$	DCE	7 h	60	trace
15[g]	**SPhosAuCl/$AgNTf_2$**	**DCE**	**10 min**	**85**	**trace**

[a] Reaction conditions: substrate (100 μmol), [Au] (2 mol%), [Ag] (2 mol%), solvent (2 mL), in air, 80°C. The reaction was monitored by TLC. [b] Yield of isolated product. [c] [Au] 1 mol%, [Ag] 1 mol%. [d] Dichloro(2-picolinato)gold(III). [e] Reaction at 40°C. [f] Reaction at room temperature. [g] Pivaloyl ester. n.r. = no reaction.

[*] M. Sc. Y. Yu, M. Sc. W. Yang, F. Rominger, Prof. Dr. A. S. K. Hashmi
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: hashmi@hashmi.de
Homepage: http://www.hashmi.de
Prof. Dr. A. S. K. Hashmi
Chemistry Department, Faculty of Science
King Abdulaziz University
Jeddah 21589, Saudi Arabia

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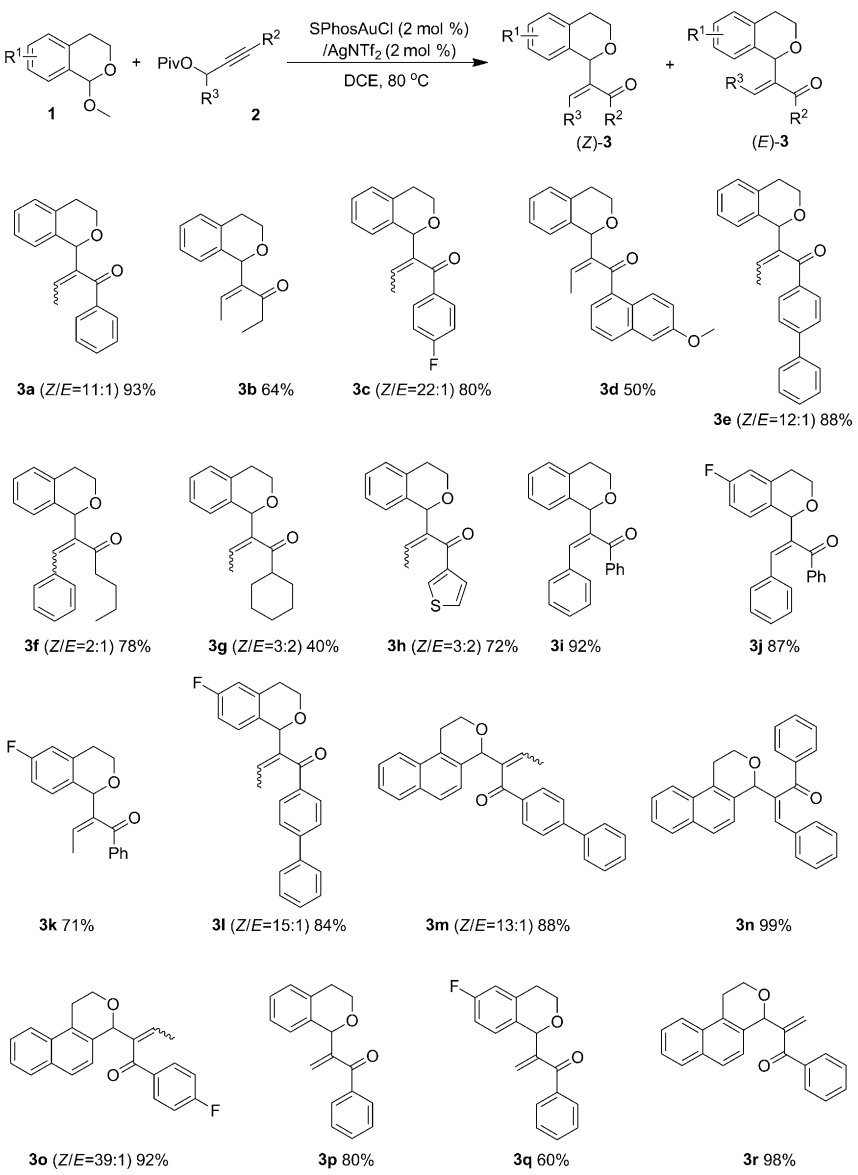
bond formation. We expected that this new type of transformation could be used for the efficient synthesis of various useful isochromane derivatives,[9] important building blocks for the total synthesis of natural products.

Based on these considerations, we chose **1a** and **2a** as model substrates for an initial optimization of the reaction conditions. The results obtained with various catalysts and solvents are summarized in Table 1. Among the catalysts tested, SPhosAuCl/$AgNTf_2$ was found to be the most effective one for this transformation (Table 1, entries 1–4). The desired product (*Z*)-**3a** (68%) was obtained in the presence of 2 mol% of this catalyst at 80°C after 10 min in air. Gratifying, 58% yield was still achieved when 1 mol% of catalyst was used (Table 1, entry 2). When the reaction was conducted with dichloro(2-picolinato)gold(III)[10] and *p*-TsOH, only a trace conversion was visible by TLC (Table 1, entries 5 and 6). Subsequently, in order to investigate the effects of the counterions, various silver salts were examined (Table 1, entries 7 and 8). Surprisingly, when SPhosAuCl/AgOTs was employed, no reaction was observed, even when we prolonged the reaction time to 24 h (Table 1, entry 8). The control experiment with $AgNTf_2$ gave (*Z*)-**3a** in only 16% yield (Table 1, entry 9). Changing to solvents such as toluene, CH_3CN, or 1,4-dioxane failed to improve the yield (Table 1, entries 10–12). Decreasing the temperature to 40°C or room temperature resulted in moderate yields of 62% and 60% (Table 1, entries 13 and 14). To our delight, when the acetate **2a** was replaced by the corresponding propargylic pivalate, the yield of (*Z*)-**3a** reached 85% together with (*E*)-**3a** as minor side product (Table 1, entry 15).



Scheme 2. Scope and limitation of the Au^I-catalyzed synthesis of **3**.[a]

We applied the optimized reaction conditions (Table 1, entry 15) to explore the generality of this intermolecular reaction. A variety of propargylic pivalates were investigated in combination with isochromane acetal **1a**. As presented in Scheme 2, all of these substrates delivered good to excellent yields. For substrates with aromatic substituents R^2, except for the thienyl group (**2h**), very good to excellent stereoselectivities favoring the *Z* isomer were observed. Under the standard conditions, substrates **2b**, **2d**, and **2i** deliver the *Z* isomer as a single stereoisomer. The structure of **3d** was proven unambiguously by an X-ray single-crystal structure analysis[11] and NOE spectra of (*Z*)-**3a** (Figure 1). In the case of substrates **2f** and **2h**, although the *Z*/*E* selectivities were diminished, good yields could still be obtained. Next, two different isochromane acetal substrates in combination with diverse propargylic pivalates were examined. Both the fluoro- and the naphthyl-substituted isochromane acetals were converted to the corresponding products in excellent yields with good to excellent selectivities. In particular, the reaction of substrate **2n** provides the product solely as the *Z* isomer in quantitative yield.

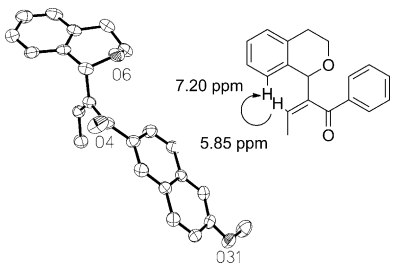
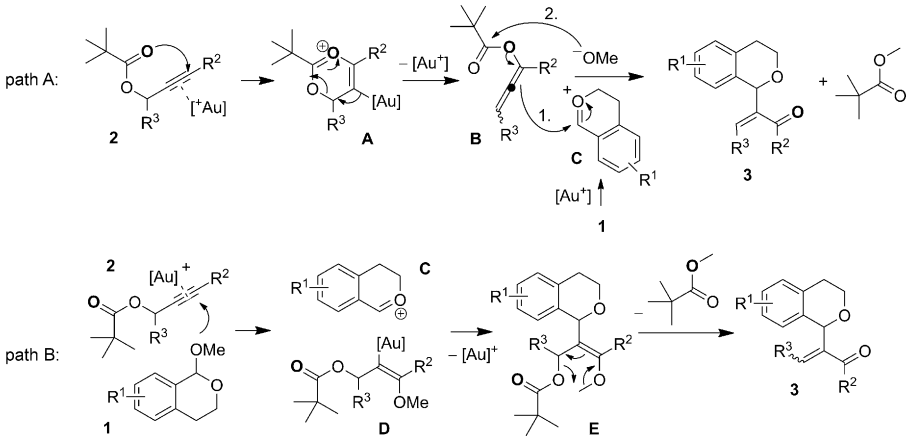


Figure 1. Left: Solid-state molecular structure of (*Z*)-**3d** (thermal ellipsoids at 50% probability); right: NOE observed in (*Z*)-**3a**.

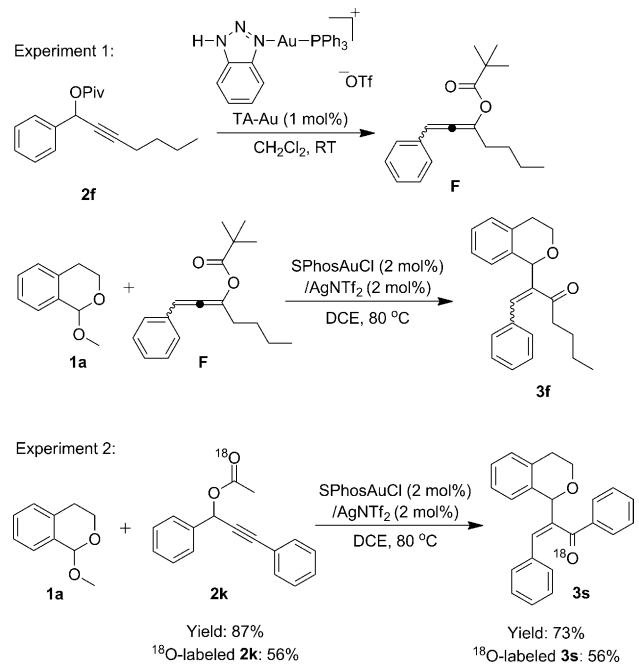


Scheme 3. Two possible mechanisms for the formation of **3** from **1** and **2**.

Two possible mechanistic pathways have to be considered (Scheme 3). In path A, the activation of the propargyl pivalate **2** by the gold catalyst would induce a 1,3-pivalate migration to generate the nucleophilic allene **B. B** then reacts with the oxocarbenium ion **C**, the latter generated from the isochromane acetal **1** by gold acting as a Lewis acid. The observed diastereoselectivity could then easily be explained by the preferred electrophilic attack at the π face of the enol ether substructure of the allene which is *anti* to the substituent R^3 (repulsion between R^3 and the incoming **C**). In path B, first MeO^- would be transferred from **1** to the alkyne, which is π-coordinated to gold. The reaction of **C** with the vinyl gold species **D** delivers intermediate **E**. Finally, elimination of methyl pivaloate delivers the product **3**.

Two supplementary experiments strongly support path A and clearly exclude path B (Scheme 4). Initially, we attempted to isolate the nucleophilic allene intermediate **B** with the novel and efficient catalyst triazole-Au (TA-Au), which was synthesized by Shi et al.[12] To our delight, the nucleophilic allene intermediate **F** was obtained in 85% yield. This allene intermediate was treated with **1a** under the standard gold-catalyzed reaction conditions; the transformation proceeded smoothly and the desired product **3f** was indeed formed in 78% yield. To exclude path B, we conducted an ^{18}O-labeling experiment with **2k**. The ^{18}O label was still present in the product **3s** (as detected by MS), and the fragmentation clearly shows its location in the carbonyl group ($PhC^{18}O^+$ with *m/z* 107.0385 is detected as the only location of ^{18}O).

In summary, we have developed a new stereocontrolled gold-catalyzed intermolecular $C(sp^3)$–$C(sp^2)$ bond-forming reaction involving the in situ generation of a nucleophilic allene and an electrophilic oxocarbenium ion. This new reactivity mode represents a considerable extension of the synthetic potential of gold-catalyzed 1,3-acyloxy migration as it not only allows a highly valuable C–C bond formation but also opens new perspectives for synthetic applications especially for the synthesis of isochromane derivatives. Good to excellent diastereoselectivities are achieved, in some cases only the *Z* isomer could be detected.



Scheme 4. Mechanistic control experiments provide evidence for path A.

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[11] CCDC 926852 ((*Z*)-**3d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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