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Gold-Catalyzed Stereocontrolled Synthesis of 2,3-Bis(acetoxy)-1,3-dienes

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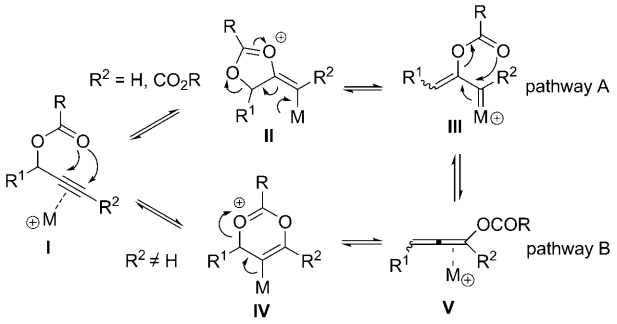
Gold complexes are powerful carbophilic Lewis acids[1] that efficiently activate propargyl carboxylates (**I**) towards 1,2-acyloxy migration and/or [3,3]-sigmatropic acyloxy rearrangement.[2] Two different but mechanistically related intermediates characterize these competitive processes: 1,2 migration proceeds via metal carbene **III**, whereas [3,3]-sigmatropic rearrangement forms allenyl acetate (**V**) in a single process or stepwise by a second acetate migration from **III** (Scheme 1).[3,4]

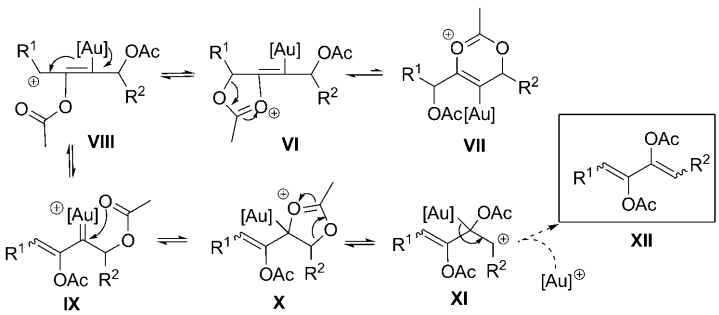


Scheme 1. 1,2- vs. 1,3-Acetate migration pathways.

It is widely accepted that terminal or electronically demanding alkynes react via pathway A,[5] whereas internal alkynes prefer pathway B,[6] and only few exceptions to this general pattern have been reported.[7] Recently, Zhang and co-workers have devised a Au-catalyzed 1,2-acyloxy migration on internal alkynes in which a bulky migrating group and catalyst were essential for successful reaction control.[8] In our view, general and selective 1,2- versus 1,3-acyloxy migration control is of key interest from both a mechanistic and a synthetic perspective.

Herein, we report that 1,4-bis(propargyl acetates) undergo a highly selective tandem 1,2-/1,2-bis(acetoxy) migration to give 2,3-bis(acetoxy)-1,3-dienes.[9] Furthermore, depending on the catalyst of choice, (1*Z*,3*Z*) or (1*Z*,3*E* and 1*E*,3Z)-1,3-dienes can be obtained in a stereocontrolled manner.

We envisioned that if a tandem reaction could occur after the formation of Au–carbene **III**, the reaction equilibrium would shift to 1,2-acyloxy migration. To design this domino process, we placed a second acyloxy moiety in the substrate so that the 1,3-acyloxy migration would be totally blocked, with the aim of producing a prevailing 1,2-(**VI**) over 1,3-(**VII**) complexation followed by a second acetate migration on carbene **IX** (Scheme 2). Due to the highly carbocationic



Scheme 2. Proposed tandem 1,2-/1,2-bis(acetoxy) migration.

character of the proposed intermediates (**VIII**, **XI**), we thought that substrates with stabilizing groups at the propargylic positions should enhance the proposed reactivity mode. To validate this hypothesis, we synthesized several symmetrically substituted 1,4-propargyl diacetates **1a–e** (Table 1).[10]

After an extensive screening of catalysts and reaction conditions using compound **1a**,[10] we were pleased to find that [(IPr)Au(NTf$_2$)] (IPr= bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) and pregenerated cationic AuI complexes, such as

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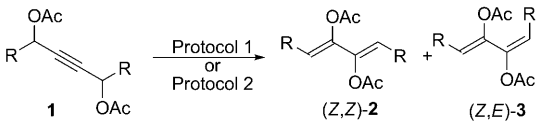
Table 1. Reaction scope in symmetrically substituted substrates.[a]



Entry	Substrate	Protocol	Ratio **2**:**3**[b]	Product (Yield [%])[c]
1	**1a** (R = Ph)	1	10:1	**2a** (86)
2	**1a**	2	1:9[d]	**3a** (80)
3	**1b** (R = 3-OMeC$_6$H$_4$)	1	8:1	**2b** (87)
4	**1b**	2	1:8[d]	**3b** (83)
5	**1c** (R = 3,5-dimethoxyphenyl)	1	13:1	**2c** (92)
6	**1c**	2	1:10	**3c** (92)
7	**1d** (R = cinnamyl)	1	8:1	**2d** (84)[e]
8	**1d**	2	1:7	**3d** (80)[f]
9	**1e** (R = 4-CF$_3$C$_6$H$_4$)	1	–	**1e**
10	**1e**	2	–	**1e**

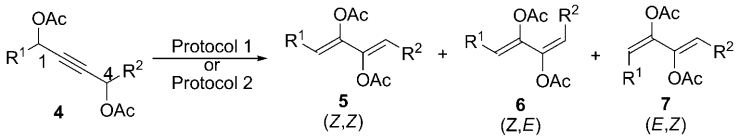
[a] Protocol 1: [(IPr)Au(NTf$_2$)] (5%), RT, CH_2Cl_2; Protocol 2: [(PPh$_3$)Au(NTf$_2$)] (2%), RT, CH_2Cl_2; see also reference [10]. [b] Ratio calculated by ^{1}H NMR. [c] Isolated yield after column chromatography. [d] The (*E*,*E*) isomer could be also detected. The effective ratios for entries 2 and 4 are (1:18:1) and (1:16:1).[10] [e] Complete isomerization at the cinnamyl moiety occurs to give (*Z*,*Z*,*Z*,*Z*). [f] The reaction was performed in acetonitrile. **3d** was isolated, and isomerized to **2d** upon standing in solution.

[(PPh$_3$)Au(NTf$_2$)], exclusively provide the 2,3-bis(acetoxy)-1,3-dienes in excellent yields (Table 1, entries 1, 2). Remarkably, no product of the potentially competitive 1,3-acetate migration could be detected. To our delight, a more careful analysis of the reaction mixtures revealed that of the three potential stereoisomers that the reaction could afford, a high stereoselectivity was observed, depending on the catalyst: [(IPr)Au(NTf$_2$)] selectively delivered the (1*Z*,3*Z*) isomers[11] (Table 1, entries 1, 3, 5, 7) whereas the more cationic [(PPh$_3$)Au(NTf$_2$)] afforded (1*Z*,3*E*) isomer as the major product of the reaction (Table 1, entries 2, 4, 6, 8). The importance of stabilizing the reaction intermediates (**VIII** and **XI**) was emphasized by the failure of substrate **1e** to undergo any type of rearrangement.

To examine the scope of this novel Au-catalyzed tandem 1,2-/1,2-bis(acetoxy) migration, we decided to apply both reaction protocols to a set of unsymmetrically substituted substrates. The results have been summarized in Table 2.

We found that the 1,2-bis(acetoxy) migration was favored in all studied cases and no allene product was observed in the reaction mixtures. Substrates such as **4a–d**, in which both R^1 and R^2 were able to stabilize positive electron density, showed a clear (*Z*,*Z*) selectivity under [(IPr)Au (NTf$_2$)] catalysis (Table 2, entries 1, 3, 5, 6) whereas [(PPh$_3$)Au(NTf$_2$)] favored the (1*E*,3*Z*) and (1*Z*,3*E*) selectivity (Table 2, entries 2, 4, 7), analogously to the previous results (Table 1). It is important to note that more sterically demanding substrate **4d** dramatically improved the selectivity towards **6d** compared with the previous examples, thus revealing the key role of sterics in the stereocontrol of these transformations. In addition, substrate **4e**, which features a pull–push system, delivered the corresponding dienes **5e** and **6e** as a 1:1 mixture, which clearly reflects the importance of electronic factors in the reaction stereocontrol. To further study the effect of steric factors, we decided to prepare substrates featuring similar electron-donating properties at C^1 and substituents of different sizes at C^4 (**4f–h**). Independent of the catalyst, we observed that (1*Z*,3*E*) isomers **6f–h** were always the major product of these reactions. Gratifyingly, increasing the sterical bulkiness from methyl to isopropyl (**4g** to **4f**) further enhanced the selectivity (Table 2, entries 11–13). However, further increase in the bulkiness (**4h**) was detrimental to the selectivity (Table 2, entries 14–15). In all cases and similarly to **4d**, not having a second stabilizing group clearly increased selectivity for products of type **6** over **7**.

Table 2. Reaction scope in nonsymmetrically substituted substrates.

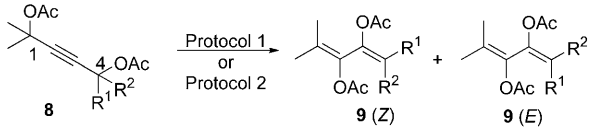


Entry	Substrate	Protocol[a]	Ratio **5**:**6**:**7**[b]	Product (Yield [%])[c]
1	**4a** (R^1 = Ph, R^2 = 3,5-dimethoxyphenyl)	1	>23:1:1	**5a** (73)
2	**4a**	2	1:14:10	**6a** (53), **7a** (40)
3	**4b** (R^1 = Ph, R^2 = 3-OMeC$_6$H$_4$)	1	8:1:0	**5b** (85)
4	**4b**	2	1:4.5:4	**6b**+**7b** (80)[d]
5	**4c** (R^1 = cinnamyl, R^2 = 3,5-dimethoxyphenyl)	1	13:1	**5c** (92)[e]
6	**4d** (R^1 = 4-OMeC$_6$H$_4$, R^2 = Me, Ph)	1	13:1:0	**5d** (83)
7	**4d**	2	1:10:0	**6d** (87)
8	**4e** (R^1 = 4-OMeC$_6$H$_4$, R^2 = 4-CF$_3$C$_6$H$_4$)	1	1:1:0	**5e**+**6e** (91)[d]
9	**4e**	2	1:1:0	**5e**+**6e** (78)[d]
10	**4f** (R^1 = 4-OMeC$_6$H$_4$, R^2 = Me)	1	1:9:0	**6f** (86)
11	**4f**	2	1:8:0	**6f** (80)
12	**4g** (R^1 = 4-OMeC$_6$H$_4$, R^2 = *i*Pr)	1	1:15:0	**6g** (81)
13	**4g**	2	1:10: 0	**6g** (69)
14	**4h** (R^1 = 4-OMeC$_6$H$_4$, R^2 = *t*Bu)	1	1:1.5:0	**5h**+**6h** (99)[d]
15	**4h**	2	1:1.5:0	**5h**+**6h** (44)[d]

[a] See Table 1 for details of the protocols used. [b] Ratio calculated by ^{1}H NMR. [c] Isolated yield of the major isomer after column chromatography. [d] Isolated yield of the mixture after column chromatography. [e] The cinnamyl moiety in **5c** isomerizes to the *Z* isomer (**5c′**) upon standing in solution.

To evaluate the single effect of the substituent attached to the acyloxy migrating group in the stereochemistry of the resulting vinyl acetate, we synthesized several bis(acetates) derived from commercially available 2-methyl-3-butyn-2-

Table 3. Reaction scope in bis(acetates) derived from acetone.



Entry	Substrate	Protocol[a]	Ratio $Z:E$[b,c]	Product (Yield [%])[d]
1	**8a** ($R^1=R^2=$-$(CH_2)_5$-)	1	–	**9a** (80)
2	**8b** ($R^1=R^2=$-$(CH_2)_4$-)	1	–	**9b** (75)
3	**8c** ($R^1=R^2=$Ph)	2	–	**9c** (78)
4	**8d** ($R^1=i$Pr, $R^2=$H)	1	–	**9d′** (78)[e]
5	**8e** ($R^1=t$Bu, $R^2=$Me)	1	–	**9e′** (50)[e]
6	**8f** ($R^1=$Ph, $R^2=$Me)	1	>20:1	(*Z*)-**9f** (80)
7	**8f**	2	>1:20	(*E*)-**9f** (82)
8	**8g** ($R^1=$Ph, $R^2=$H)	1	10:1	(*Z*)-**9g** (90)
9	**8g**	2	9:1	(*Z*)-**9g** (64)
10	**8h** ($R^1=$4-OMeC_6H_4, $R^2=$H)	1	18:1	(*Z*)-**9h** (93)
11	**8h**	2	17:1	(*Z*)-**9h** (34)
12	**8i** ($R^1=$4-$CF_3C_6H_4$, $R^2=$H)	1	1:4	**9i** (83)[f]
13	**8i**	2	1:7	**9i** (81)[f]

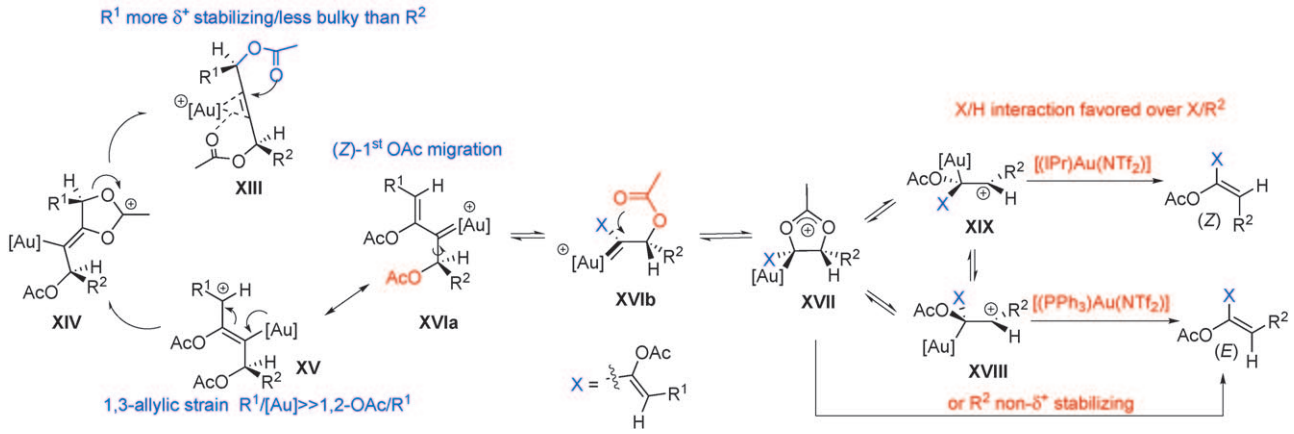
[a] See Table 1 for details of the protocols used. [b] Ratio calculated by ^{1}H NMR. [c] R^1 was considered to be higher priority than R^2. [d] Isolated yield of the major isomer (where applicable) after column chromatography. [e] See reference [13]. [f] Isolated yield of the mixture after column chromatography.

ol[10] (Table 3). Substrates derived from symmetric ketones, such as cyclopentanone (**8a**), cyclohexanone (**8b**), and benzophenone (**8c**), were smoothly converted to the corresponding products **9a–c** in high yields under [(IPr)Au(NTf_2)] catalysis (Table 3, entries 1–3).[12] Isopropyl **8d** and *tert*-butyl/methyl derivative **8e** also reacted, although in situ hydrolysis of the corresponding products to the 1,2-diketones (**9d′–e′**) could be partially observed under both reaction conditions (entries 4–5).[13] Surprisingly, more sterically hindered substrate **8f** resulted in a complete inversion of the *Z*/*E* selectivity upon treatment with a different catalyst (Table 3, entries 6–7). Next, we turned our attention to secondary acetates at the C^4 position (substrates **8g–i**). Phenyl- (**8g**) and *para*-methoxyphenyl-substituted (**8h**) substrates provided **9g** and **9h**, respectively, in excellent yields and high *Z* selectivity with both [(IPr)Au(NTf_2)] and [(PPh_3)Au(NTf_2)] catalysts (Table 3, entries 8–11). This observation is in sharp contrast to the results summarized in Table 1. In contrast, *para*-trifluoromethylphenyl-substituted substrate **8i** gave the *E* olefin product with both catalysts (Table 3, entries 12–13).

We explain the previous results in light of a distinct stereocontrol operating for the first versus the second acetate migration. Furthermore, the choice of the acetoxy migrating first seemed to be of key importance and is determined both by the electronic character and sterical bulkiness of substituents at the propargylic position. Our mechanistic proposal is shown in Scheme 3.[14] Upon gold activation of the triple bond, the acetoxy group next to groups able to stabilize the developing positive electron density will migrate first. In our view, **XV** is the key intermediate that determines the *Z* stereochemistry of the alkene linked to the gold carbenoid because it avoids the 1,3-allylic strain between Au and R^1.[15]

When the second acetate is also attached to a stabilizing group, the stereochemical outcome of the second acetoxy migration depends on the nature of the catalyst. Clearly, we demonstrated that [(IPr)Au(NTf_2)] afforded the *Z* olefin whereas [(PPh_3)Au(NTf_2)] favored *E* alkene formation. When R^2=alkyl, 4-CF_3Ph, the *E* double bond was selectively obtained after the second OAc migration, independent of the catalyst. To explain this observation, we propose that the carbonyl group of the second acetoxy group approaches the π* orbital of the gold carbenoid in **XVIa**. Two diastereofacial attacks are possible, although the steric hindrance between gold species and R^2 makes **XVII** the more favorable reaction intermediate (via **XVIb**).[16]

Consistent with the hypothesis that bulky ligands complicate intramolecular bond reorganization, gold(I) species such as [(PPh_3)Au(NTf_2)] might exit the reaction directly from **XVII** or via **XVIII** and thus result in *E* double bond formation.[17] In contrast, bulky NHC ligands, as in [(IPr)Au(NTf_2)], will favor isomerization to the more stable **XIX** rather than **XVIII** because of the steric interaction between R^2/X in the closely planar configuration of the latter.



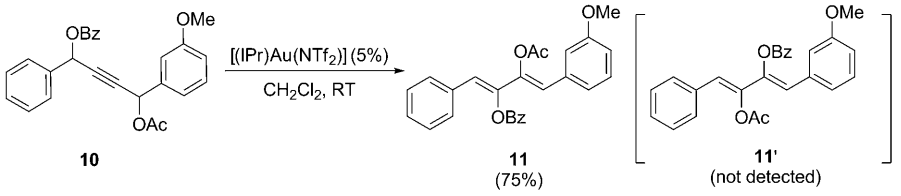
Scheme 3. Mechanistic proposal for 1,2-bis(acetoxy) migration.

Because OAc is much smaller than X, the equilibrium is shifted towards **XIX**, resulting in *Z*-isomer formation.[18]

When R^2 is aromatic, the equilibrium between **XVII**/**XVIII**/**XIX** becomes very important, accounting for the different selectivity with different catalysts. In contrast, when R^2 is an alkyl or electron-withdrawing group, the forming carbocation is not well stabilized and as a consequence the reaction proceeds directly from **XVII** to give the *E* isomer. In other words, the reaction is more concerted. The results summarized in Table 1 and Table 2 fit nicely with this mechanistic proposal. The steric interaction between R^2 and [Au] was comparable to the one between R^2 and X only when R^2 = *tert*-butyl (Table 2, entries 14–15). Therefore, the selectivity is dramatically decreased and the *E* isomer is still observed under both reaction conditions.

As mentioned above, steric factors could also influence the first acetoxy migration. For compounds **8g** and **h** in Table 3, the acetate next to a phenyl or *para*-methoxyphenyl group will migrate first to deliver the *Z* olefin no matter which catalyst is employed. In contrast, for substrate **8f** (Table 3, entries 6–7) the first migration occurs from the dimethyl part because the stereochemistry of the olefin in **9f** changed when the catalyst changed. Clearly Me/Me substituents are smaller than Me/Ph substituents, so bulkiness controls the reaction pathway in this case.

An alternative reaction pathway involving a double 1,3-bis(carboxylate) migration can be ruled out, since compound **10** was cleanly transformed in the presence of [(IPr)Au(NTf_2)] into compound **11** (Scheme 4).[10]



Scheme 4. 1,2- vs. 1,3-Bis(carboxylate) migration.

In conclusion, we have developed a new Au-catalyzed tandem 1,2-/1,2-bis(acetoxy) rearrangement of 1,4-bis(propargyl acetates) that provides access to synthetically useful 2,3-bis(acetoxy)-1,3-dienes in high yields. Upon careful selection of the electronic and steric features of the substrate, (1*Z*,3*Z*) or (1*Z*,3*E* and 1*E*,3*Z*)-1,3-dienes can be selectively obtained. The stereocontrol of the second acyloxy migration is determined by the nature of the ligand attached to the metal center. Such a direct influence of the ligand on the divergent reaction outcome is rare in gold catalysis. Further experimental and computational studies to confirm the nature of the intermediates participating in this rearrangement are currently ongoing and will be reported in due course.

Experimental Section

Typical procedure: [(IPr)Au(NTf_2)] (protocol 1, 0.02–0.05 equiv) or [(PPh_3)Au(NTf_2)] (protocol 2, 0.02 equiv; 0.05 M solution prepared from 1 equiv [(PPh_3)Au(Cl)] and $AgNTf_2$ in freshly distilled CH_2Cl_2) was added to a solution of bis(acetate) (1 equiv) in anhydrous CH_2Cl_2. The reaction was stirred for 2 h at RT, then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

Acknowledgements

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Keywords: dienes · gold · homogeneous catalysis · ligand effects · propargyl esters

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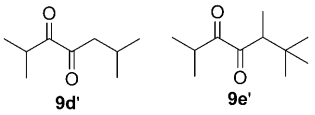
[10] See the Supporting Information for the preparation of starting materials, the complete set of optimization and control reactions on substrate **1a**, and full characterization of products.

[11] The structure of **2a** was unambiguously assigned by X-ray analysis, see reference [10].

[12] The reaction of **8a–b** with $[(PPh_3)Au(NTf_2)]$ or $[(PPh_3)Au(SbF_6)]$ also afforded compounds **9a–b**, albeit in lower yields.

[13] Yield upon in situ hydrolysis of the reaction mixture with K_2CO_3 (2 equiv) in MeOH.



9d' **9e'**

[14] The mechanism is outlined for one of the four possible isomers of the starting material.

[15] For *Z* selectivity upon OAc migration, see references [5c–f, 7e, 8]. When a subsequent cyclization process occurs, the *E* isomers prevail: see references [5a,b, 7a] and for computational studies on this process, see also: a) E. Soriano, J. M. Contelles, *J. Org. Chem.* **2005**, *70*, 9345–9353; b) O. N. Faza, C. S. López, R. Álvarez, A. R. de Lera, *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437. These results, together with the study presented herein, strongly suggest that the intermediates determining the stereochemistry of the olefin upon 1,2-acetoxy migration should be connected along the reaction pathway. To the best of our knowledge, no systematic study of this phenomenon has been reported.

[16] The opposite diastereofacial approach and further mechanistic considerations are shown in an extended version of Scheme 3 included in the Supporting Information.

[17] a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; b) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776–1782.

[18] The determining step for the *E* versus *Z* alkene formation seems to be under kinetic control. See the Supporting Information for additional studies.

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