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Gosteli–Claisen Rearrangement of Propargyl Vinyl Ethers: Cascading Molecular Rearrangements

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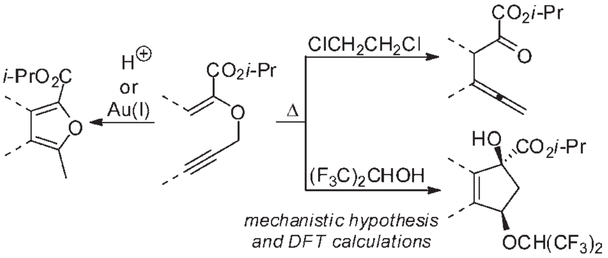
ABSTRACT



The ambivalent reactivity of 2-alkoxycarbonyl-substituted propargyl vinyl ethers has been explored. Depending on the conditions, the catalyzed and uncatalyzed Gosteli–Claisen rearrangement triggers downstream transformations that cascade from initially formed γ-allenyl α-keto esters to highly substituted furanes and cyclopentenes. In support of a mechanistic hypothesis, the results of a DFT study using the B1B95 and B3LYP functionals are revealed.

The Claisen rearrangement of allyl and propargyl vinyl ethers has a long and successful scientific history.[1] However, access to effectively stereodifferentiating chiral catalysts for the aliphatic Claisen rearrangement was still elusive at the end of the past century.[2] During the past 10 years, intense research efforts have then led to the identification of chiral σ-Lewis acids and Brønsted acids as catalysts for the Gosteli–Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers providing δ,ε-unsaturated α-keto esters as valuable building blocks.[3–6] In light of this development, we became interested in the Gosteli–Claisen rearrangement of propargyl vinyl ethers ("pve", Figure 1, R = CO_2R).[7] As elegantly demonstrated by Grissom,[8] Toste,[9] and Kirsch,[10] the formal Claisen rearrangement of pve with R = H or R = alkyl can be catalyzed by π-Lewis acids such as Ag(I) or Au(I);[11] this type of rearrangement presumably proceeds by a cyclization-induced mechanism and provides opportunity for 1,3-self-immolative chirality transfer.[12,13] Toste and Kirsch also ingeniously designed conditions under which the

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initially formed allenes are converted in situ into furans,[10] 2*H*-pyrans, or dihydropyrans.[14,15] However, the applicability of the established Au(I) or Ag(I) catalysis to 2-alkoxycarbonyl-substituted pve (R = CO_2R) remained unexplored.

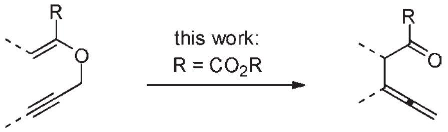
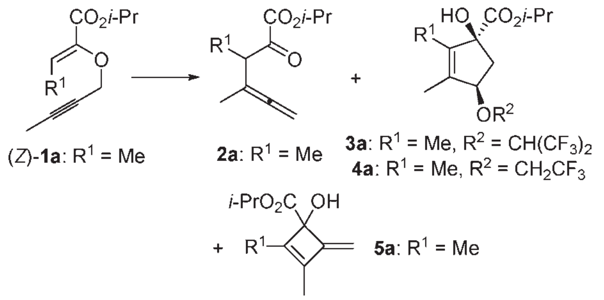


Figure 1. Gosteli–Claisen rearrangement (R = CO_2R) of propargyl vinyl ethers.

Our study commenced with an investigation of the uncatalyzed Gosteli–Claisen rearrangement. In the event of (*Z*)-**1a** (Table 1), heating in 1,2-dichloroethane (DCE) to 80 °C for 23 h provided incomplete conversion to the expected α-keto ester **2a** (Table 1, Entry 1).

Table 1. Uncatalyzed Gosteli–Claisen Rearrangement of (*Z*)-**1a** to **2a** and Formation of Unexpected Products **3a**–**5a**



entry	solvent[a]	temp (°C)	time (h)	yield[b] (%)	ratio[c] (**1a**:**2a**:**3**/**4a**:**5a**)
1	DCE	80	23	99	29:71:–:–
2	TFE	80	23	99	–:100:–:–
3	HFIP	60	23	99	22:78:–:–
4	HFIP	60	72	99	4:28:28:40
5	TFE	80	132	93	–:85:3:12

[a] DCE: 14 ppm H_2O, HFIP: 1 ppm H_2O, TFE: 14 ppm H_2O. [b] Yield of the unpurified product mixture. [c] Determined by ^1H NMR from the unpurified product mixture.

In order to accelerate the rearrangement, we exploited the solvent-rate effect of 1,1,1-trifluoroethanol (TFE).[16] As intended, full conversion to **2a** was observed after 23 h at 80 °C (Table 1, entry 2). The allene **2a** proved to be very sensitive, and purification by chromatography led to extensive decomposition. In search of milder conditions, we tested 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) for its rate-accelerating effect, and because warming to 60 °C for 23 h led to an incomplete conversion (Table 1, entry 3), we extended the reaction time to 72 h (Table 1, entry 4). The isolated product mixture then consisted of a residual amount of **1a**, the allene **2a**, and, notably, the cycloalkenes **3a** and **5a**. In analogy, warming **1a** in TFE for an extended period of time also led to the formation of the corresponding cyclization product **4a** and **5a**, albeit to a much lesser extent (Table 1, entry 5).

In order to explore the scope of the rearrangement chemistry delineated above, pve **1b**–**g** were synthesized and subjected to the conditions of the uncatalyzed Gosteli–Claisen rearrangement (Table 2).[17] Heating of **1a**–**f** in DCE for an optimized period of time led to the formation of the unstable allenes **2a**–**f**; extensive decomposition was observed for **1g**. Determination of the conversion after 38 h in refluxing DCE indicated a slighty higher reactivity of the aryl-substituted pve **1c**–**e** compared to **1a**,**b**,**f**.

Table 2. Uncatalyzed Gosteli–Claisen Rearrangement in 1,2-Dichloroethane (DCE)[a]

entry	substrate	R^1	time (h)	product	yield[b] (%)
1	**1a**	Me	65	**2a**	85[c]
2	**1b**	Bn	60	**2b**	99
3	**1c**	Ph	27	**2c**	99
4	**1d**	*p*-MeO–C_6H_4	48	**2d**	99
5	**1e**	*p*-NO_2–C_6H_4	27	**2e**	99
6	**1f**	$H_2C{=}CH$	47	**2f**	99
7	**1g**	MeC≡C	38	**2g**	99[d]

[a] Conditions: substrate, DCE, 80 °C. [b] Isolated yield of unpurified allene. [c] Loss of mass due to volatility of **2a**. [d] Incomplete conversion: **1g**:**2g** = 41:59. Prolonged reaction times resulted in extensive decomposition.

Next, we subjected **1b**–**g** to the conditions that had promoted cycloalkene formation from **1a** (Table 3). NMR analysis of the crude product mixture indicated the formation of **3** and **5**, except for **1b**. The extent and ratio of the formation of **3** and **5** is markedly substrate-dependent. In particular, we note the propensity of **1e** (R^1 = *p*-NO_2–C_6H_4) and **1g** (R^1 = MeC≡C) for the formation of **3e** and **3g** in moderate yield (60%). Remarkably, using HFIP which contained small amounts (370 ppm) of water prevented cycloalkene formation and led only to the allenes **2a**–**g**. Control experiments in which **2a**–**g** were warmed in dry HFIP (1 ppm H_2O) also provided mixtures of **3a**–**g** and **5a**–**g** suggesting that the allenes are intermediates in a multistep mechanism (vide infra). The structures of **3a**–**g** were deduced from NMR studies and corroborated by an X-ray crystal structure analysis of **3g** which also provided the basis for the assignment of the relative configuration of **3a**–**g**.[18] The structural assignment of the very sensitive

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cyclobutenes **5**, which could not be completely separated from **3**, is based on NMR investigations.

Table 3. Dependence of Product Ratio in Hexafluoroisopropanol (HFIP) on Substrate Structure[a]

entry	substrate	R^1	ratio[b] (**1**:**2**:**3**:**5**)	yield of **3**[c] (%)
1	**1b**	Bn	–:100:–:–	–
2	**1c**	Ph	–:–:40:60	28
3	**1d**	*p*-MeO–C_6H_4	–:–:55:45	21
4	**1e**	*p*-NO_2–C_6H_4	–:–:85:15	52
5	**1f**	$H_2C{=}CH$	–:–:33:67	14
6	**1g**	MeC≡C	7:–:93:–	60

[a] Conditions: substrate, dry HFIP (1 ppm H_2O as determined by Karl–Fischer titration), 60 °C, 72 h. [b] Determined from the ^1H NMR of the crude product mixture. [c] Isolated yield after chromatography.

A mechanistic hypothesis for the formation of **3a**,**g** from **1a**,**g** along with relative energies from a DFT study using the meta hybrid functional B1B95[19] and the hybrid functional B3LYP[20] is depicted in Figure 2.[21] Without considering the explicit role of the solvent HFIP, we propose that the mechanistic cascade is initiated by the concerted Gosteli–Claisen rearrangement of **1a**,**g** via the transition-state structures **6a**,**g** to deliver the experimentally detectable allenes **2a**,**g**. The computational study supports our proposal by predicting a reasonable gas-phase barrier and a significant driving force.[22,23] We then suggest the formation of the dienones **8a**,**g** from **2a**,**g** by consecutive 1,3- and 1,5-sigmatropic hydrogen shifts.[24] The results of our calculation indicate that this process would traverse via energetically accessible enols **7a**,**g** to more stable dienones **8a**,**g**;[25] structurally, the calculations predict a nonplanar, helical conformation of **8a**,**g** as a consequence of steric interference between the substituents at the tetrasubstituted double bond. Due to a favorable balance in π- to σ-bond conversion, a very large driving force is predicted for the formation of **3a**,**g** from **8a**,**g**.

The formation of the methylidenecyclobutenes **5** from the vinyl allenes **7** by electrocyclization appears plausible,[26] and a stepwise mechanism via the cyclopentenyl cation **11** could account for the cyclization of **8** to **3** (Figure 3).[27] Imitating the strong hydrogen bond donor ability of HFIP[28] by assuming an initial protonation of the carbonyl group of **8a**,**g** to afford **9a**,**g**, our calculations predict a low barrier and a significant driving force for the formation of **11a**,**g** by nucleophilic attack of the terminal double bond on the carbonyl group. Subsequent nucleophilic attack by HFIP would lead to **3a**,**g**.

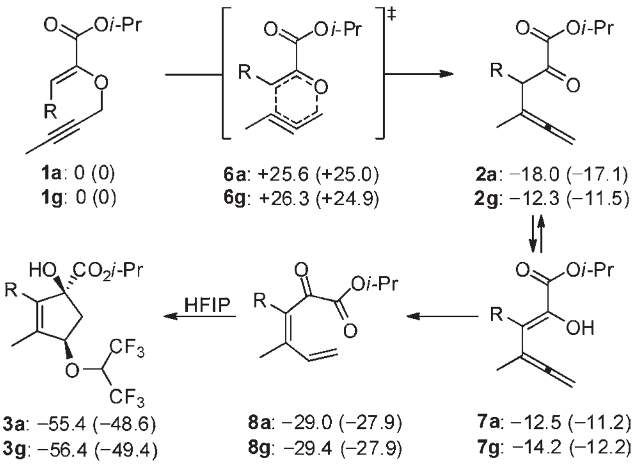

Figure 2. B1B95/6-31+G(d,p)-calculated (relative) electronic plus zero-point energies (ΔE) at 298.15 K in kcal/mol. B3LYP/6-31+G(d,p)-values are given in parentheses. **1a**: R^1 = Me, **1g**: R^1 = MeC≡C. HFIP = hexafluoroisopropanol.

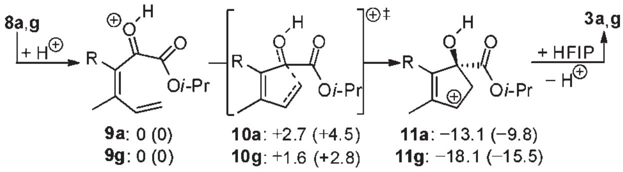

Figure 3. B1B95/6-31+G(d,p)-calculated ΔE at 298.15 K in kcal/mol. B3LYP/6-31+G(d,p)-values are given in parentheses.

It seemed obvious at that point that the presence of a Brønsted acid could further promote the cyclization. Therefore, we treated **1a**–**g** with $HOSO_2CF_3$ (HOTf, 0.5 equiv) in HFIP containing 370 ppm of H_2O. In the event, however, formation of tetrasubstituted furans was triggered (Table 4). In detail, conversion of the methyl-substituted pve **1a** proceeded sluggishly and delivered the furan **12a** in a mediocre yield (Table 4, entry 1); interestingly, a much slower reaction and the formation of the allene **2a** were observed in dry HFIP (Table 4, entry 2). Replacement of HFIP by DCE or CH_2Cl_2 led to enol ether hydrolysis and formation of isopropyl 2-oxo-butyrate; no

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(21) For computational details, see Supporting Information. The calculations were carried out with Gaussian03; see: Frisch, M. J. et al. *Gaussian 03*, revision E.01; Gaussian, Inc.: Wallingford, CT, 2004. Full reference given in the Supporting Information.

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(23) For a computational study on the Gosteli–Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers, see: Rehbein, J.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 4336–4342.

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(25) The attempted catalytic asymmetric Gosteli–Claisen rearrangement of **1a** using $[Cu\{(S,S)\text{-}t\text{-}Bu\text{-}box\}(H_2O)_2](SbF_6)_2$ (20 mol%) in CH_2Cl_2 at ambient temperature provided (±)-**2a**. We assume a rapid racemization of **2a** via the enol **7a** in the presence of the Lewis acid.

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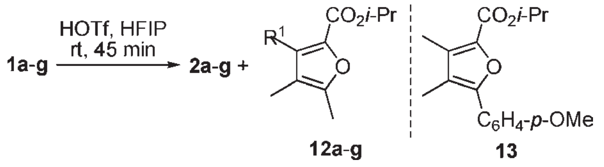
reaction was observed in wet *i*-PrOH. The conversion of the Bn-substituted pve **1b** was low yielding, and a significant amount of the allene **2b** was detected (Table 4, entry 3).[29] The phenyl-substituted derivative **1c** underwent furan formation in good yield (Table 4, entry 4); notably, the presence of a *p*-MeO-Ph group resulted in the formation of large amounts of the "abnormal" furan **13** (Table 4, entry 5). Replacement of the *p*-MeO by a *p*-NO_2 group retarded furan formation (Table 4, entry 6). The vinyl- and the 1-propinyl-substituted pve **1f** and **1g** showed no propensity at all for the formation of furans under Brønsted acid catalysis (Table 4, entries 7,8).[30]

Table 4. Brønsted Acid Promoted Furan Formation in Wet HFIP (370 ppm H_2O)



entry	substrate	R^1	yield[a] (%)	ratio[b] **1**:**2**:**12**(:**13**)
1	**1a**	Me	44	–:–:100
2[c]	**1a**	Me	70	69:16:15
3	**1b**	Bn	34	–:43:57
4	**1c**	Ph	84	–:1:99
5	**1d**	*p*-MeO–C_6H_4	99	–:–:27(:73)
6	**1e**	*p*-NO_2–C_6H_4	86	49:22:29
7	**1f**	H_2C=CH	47	100:–:–
8	**1g**	MeC≡C	–	[d]

[a] Isolated yield after chromatography. [b] Determined from the ^1H NMR of the isolated product mixture. [c] Run in dry HFIP (1 ppm H_2O). [d] Small amounts of an unindentified byproduct were detected.

In light of these results, we surmised that the lack of efficiency of the Brønsted acid catalyzed cascade reaction, which culminates in furan formation, was caused by the ineffective catalysis of the initiating Gosteli–Claisen rearrangement. Consequently, and guided by the groundbreaking contributions of Toste and Kirsch (vide supra), we turned our attention to Au(I) catalysis (Table 5). Much to our delight, a precatalyst system consisting of Ph_3PAuCl (0.05 equiv) and $Ag(SbF_6)$ (0.05 equiv) in CH_2Cl_2 at ambient temperature, as reported by Kirsch,[10] catalyzed the formation of the furans **12a**–**f** in moderate to excellent yield (48–96%),[31] even with the capricious **1d** (48%) or previously unreactive **1f** (57%). No furan formation was detected in control experiments using only Ph_3PAuCl or $AgSbF_6$. Alternatively, AuCl (0.1 equiv) in CH_2Cl_2 or the combination of Ph_3PAuCl (0.1 equiv) and $Ag(BF_4)$ (0.1 equiv) in CH_2Cl_2 also catalyzed furan formation but, in our hands, appeared to be less active. Notably, for **1b** and **1c**, $Cu(OTf)_2$ (0.1 equiv) in wet HFIP at ambient temperature catalyzed the formation of the furans **12b** (75%) and **12c** (84%) in good yield. As before, the 1-propinyl-substituted pve **1g** opposed the participation in the cascade process under various conditions and currently represents the limiting case for the established methodology.

Table 5. Au(I)-Catalyzed Gosteli–Claisen Rearrangement/Cycloisomerization of **1a**–**f** to the Furans **12a**–**f**[a]

entry	substrate	R^1	product	*t* (min)	yield (%)[b]
1	**1a**	Me	**12a**	20	78
2	**1b**	Bn	**12b**	20	89
3	**1c**	Ph	**12c**	20	90
4	**1d**	*p*-MeO–C_6H_4	**12d**	150	48[c]
5	**1e**	*p*-NO_2–C_6H_4	**12e**	20	96
6	**1f**	H_2C=CH	**12f**	20	57
7	**1g**	MeC≡C	**12g**	24 h	[d]

[a] Conditions: substrate, dry CH_2Cl_2, Ph_3PAuCl (0.05 equiv), $Ag(SbF_6)$ (0.05 equiv), rt. [b] Isolated yield after chromatographic purification. [c] Along with 8% of **13**. [d] 77% **1g** reisolated.

In conclusion, during the development of a catalyzed cascade reaction that transforms 2-alkoxycarbonyl-substituted propargyl vinyl ethers into tetrasubstituted furans, we observed an unprecedented carbacyclization involving fluorinated alcohols as nucleophiles; we are currently exploring the synthetic opportunities arising from the discovery of this cascade reaction.

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Supporting Information Available. Text, tables, and figures giving computational details, experimental procedures, spectral and analytical data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) The formation of allenes at ambient temperature under the reaction conditions indicates that the Gosteli–Claisen rearrangement proceeds under specific-acid catalysis by the hydronium ion.

(30) **1a**–**g** were also treated with PTSA•H_2O (0.1 equiv) in HFIP (370 ppm H_2O) at ambient temperature for 23 h. In the event, furan formation was much slower for **1a**–**e**; neither **1f** nor **1g** was converted into the corresponding furan. Interestingly, however, subjecting the allenes **2a** and **2c** to the identical conditions led to the high-yielding formation of **12a** (99%) and **12c** (83%).

(31) We did not attempt a rigorous optimization of the catalyst loading.