VIP Gold Catalysis

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Gold-Catalyzed Cycloaromatization of 2,4-Dien-6-yne Carboxylic Acids: Synthesis of 2,3-Disubstituted Phenols and Unsymmetrical Bi- and Terphenyls**

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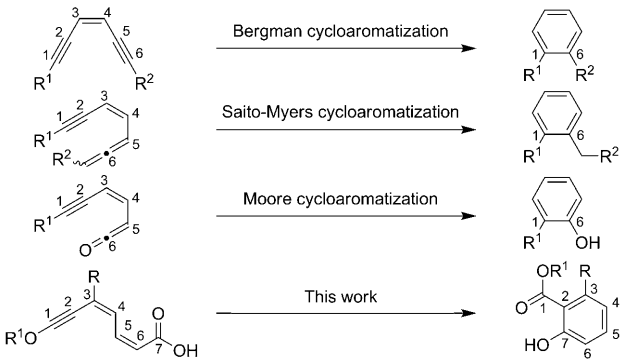
Cycloaromatization reactions of conjugated polyenyne systems, such as the Bergman (enediynes), Saito–Myers (enyne–allene), or Moore (enyne–ketene) cyclizations, have become reliable methods for the formation of aromatic compounds (Scheme 1).[1] The specific and limited substitution pattern of

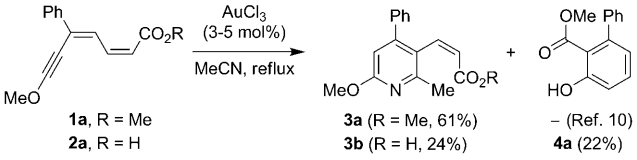


Scheme 1. Cycloaromatization reactions of conjugated polyenynes.

the starting materials as well as the harsh reaction conditions traditionally required for these transformations can be partially overcome by stoichiometric, metal-based triggering reactions.[2] Ruthenium- and tungsten-catalyzed 6π cycloaromatizations via metal vinylidene species have also been reported.[3] Furthermore, Rh, Fe, and Pt catalysts are able to promote the cyclization of conjugated enynes containing internal alkyne units.[4] However, all of these processes are limited to a specific substitution or require high temperatures, high catalyst loadings, or long reaction times.

The notorious ability of gold derivatives to activate triple bonds for attack by different nucleophiles[5] has resulted in the development of an impressive array of organic transformations[6]—predominantly intramolecular cyclizations.[7] One such example is the synthesis of substituted naphthalenes under mild conditions by a 6-*endo*-dig gold(I)-catalyzed cycloaromatization of aromatic 1,5-enynes bearing a substituent on their alkyne terminus.[8]

We have recently described an efficient and simple procedure for the synthesis of captodative dienynes **1** and **2**,[9] which could be appropriate substrates for metal-catalyzed transformations. In this sense, non-activated nitriles regioselectively attack the metal-complexed triple bond of **1** which leads, after cyclization, to tetrasubstituted pyridines **3** in an intermolecular hetero-dehydro-Diels–Alder reaction.[10] However, when the analogous dienyne carboxylic acid **2a** was treated under very similar reaction conditions, a mixture of the corresponding pyridine **3b** and 2,3-disubstituted phenol **4a**[11] was obtained (Scheme 2). Remarkably, the cycloaroma-



Scheme 2. Gold-catalyzed reaction of push-pull dienynes **1a** and **2a**.

tization of **2a** to form **4a** is very different from the above-mentioned cyclizations involving 6π electrons. In the present case, a new C–C bond is formed between carbon atoms 2 and 7 of the π-conjugated system, instead of the more common creation of a bond between carbon atoms 1 and 6 (Scheme 1). Herein we report our study of this novel transformation as well as a related cyclization-decarboxylation sequence that occurs with noncaptodative dienyne carboxylic acids.

The initial experiments were carried out with dienyne **2a** to allow optimization of several parameters. In contrast to the situation in acetonitrile, reaction takes place at room temperature in other solvents to exclusively form phenol derivative **4a**. Thus, CH_2Cl_2 led to better results than toluene, THF, diethyl ether, hexane, or methanol.[12] Cationic gold(I) complexes, generated in situ with silver salts, were also able to catalyze the reaction (Table 1, entries 3–11). The counterion of the silver salt was found to be important: $AgSbF_6$ provided

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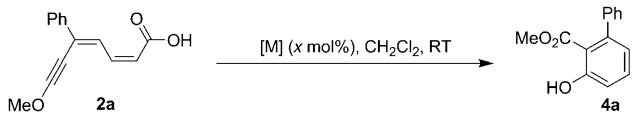
Table 1: Catalyst screening for the cyclization of **2a**.

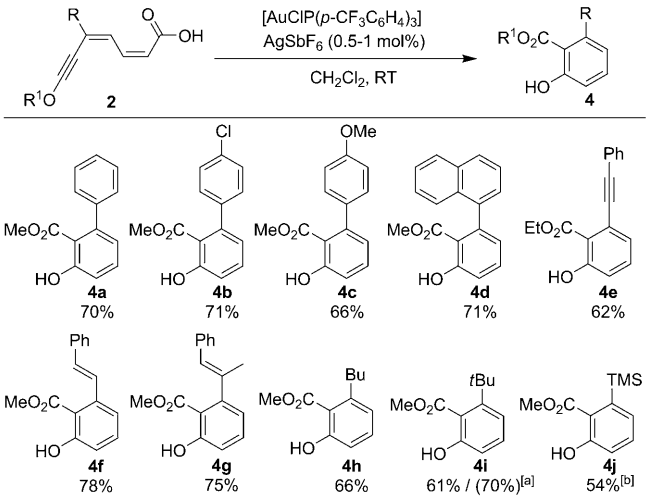


Entry	[M]	cat. mol%	**4a**[a]
1	$AuCl_3$	3	41
2	$AgSbF_6$	5	27[b]
3	$AuCl/AgSbF_6$	3	(37)
4	$[AuClPPh_3]/AgSbF_6$	3	61 (45)
5	$[AuClPEt_3]/AgSbF_6$	3	(33)
6	$[AuClP(p\text{-}MeOC_6H_4)_3]/AgSbF_6$	3	(33)
7	$[AuClP(o\text{-}MeC_6H_4)_3]/AgSbF_6$	3	62
8	$[AuClP(p\text{-}CF_3C_6H_4)_3]/AgSbF_6$	3	72[c]
9	$[AuClP(C_6F_5)_3]/AgSbF_6$	3	54
10	$[AuCl\{P(1\text{-naphthyl})(t\text{Bu})_2\}]/AgSbF_6$	3	47
11	$[AuClP(OPh)_3]/AgSbF_6$	3	44
12	$[AuClP(p\text{-}CF_3C_6H_4)_3]/AgSbF_6$	3	64[c,d]
13	$[AuClP(p\text{-}CF_3C_6H_4)_3]/AgSbF_6$	1	69[c]
14	$[AuClP(p\text{-}CF_3C_6H_4)_3]/AgSbF_6$	0.5	70[c]

[a] Yield of isolated product; in parenthesis, yield obtained without premixing the gold precatalyst with the silver salt. [b] Reaction carried out under argon (reaction time: >5 h). [c] Reaction time: entry 8, <5 min; entry 12, 20 min; entry 13, 30 min; entry 14, 2 h. [d] Reaction performed at 0 °C.

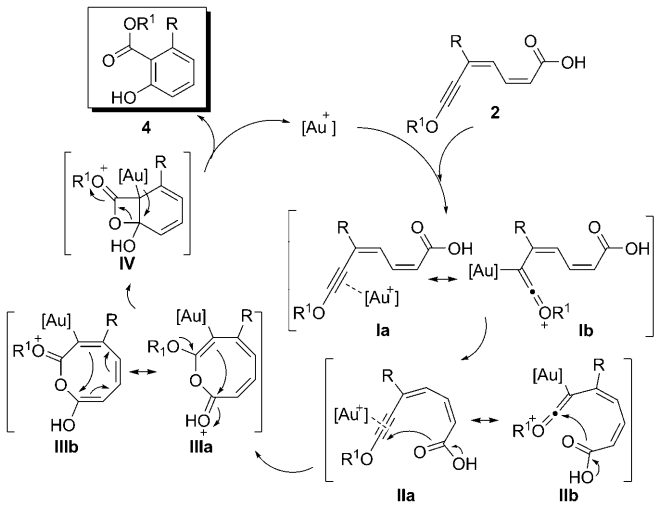
higher yields of **4a** than did AgOTf or $AgBF_4$.[13] $AgSbF_6$ by itself also promotes the reaction, although it leads to a lower yield after a longer reaction time and requires strictly anhydrous conditions (entry 2), otherwise hydration of the triple bond was observed. Two crucial factors for achieving good reaction yields are: a) premixing the gold catalyst (3 mol%) with the silver salt (entry 4) and b) the premixing time: an optimum time of 30 minutes leads to the best yields.[13] With these conditions established, the reactivity of cationic gold(I) catalysts was modulated by incorporating a phosphite and several phosphine ligands[14] with a broad range of electron-donating abilities and steric effects. Thus, aliphatic phosphines (entry 5), aromatic phosphines with electron-donating (entries 6 and 7) and electron-withdrawing substituents (entries 8 and 9), sterically hindered phosphines (entry 10), as well as an aromatic phosphite (entry 11) were tested. Among them, the $[AuClP(p\text{-}CF_3C_6H_4)_3]/AgSbF_6$ system afforded the best result (entry 8). The high activity of the catalytic system for this transformation is noteworthy since it allows the use of low catalyst loadings and mild reaction conditions. Thus, reducing the catalyst loading to 0.5 mol% afforded phenol **4a** in nearly the same yield (entries 13 and 14); such a catalyst loading is one order of magnitude lower than the amount employed in most gold-catalyzed processes.[6,7,15] The mild conditions and the short reaction times are especially noteworthy compared to other related cyclizations:[16] reactions occur in less than 5 minutes at room temperature (entry 8) or in 20 min at 0 °C (entry 12) for a 3 mol% catalyst loading.

After establishing the optimum conditions (entries 13 and 14) for the desired transformation, the scope and limitations of this novel approach to synthesize 2,3-disubstituted phenols was analyzed by testing a wide variety of dienyne acids **2** (Scheme 3). The reaction is effective when R is an aromatic ring (**4a–d**), with either electron-withdrawing (**4b**) or electron-donating (**4c**) substituents. It also leads to good yields for alkynyl- (**4e**), alkenyl- (**4f,g**), linear or branched alkyl- (**4h,i**), and silyl-substituted (**4j**) dienyne carboxylic acids. In all cases, complete regioselectivity was observed in the cycloaromatization.[17]



Scheme 3. Scope of the cyclization of dienynes **2**. [a] 3 mol% catalyst loading. [b] Partial decomposition of the starting dienyne acid **2j** was observed during reaction set-up.

A mechanism that would explain the formation of phenols **4** is depicted in Scheme 4. Initial coordination of the gold catalyst to the triple bond to form intermediate **Ia**, which is stabilized by the electron-donating ability of the alkoxy group through resonance structure **Ib**, is followed by a *s-trans-s-cis* isomerization to give intermediates **IIa** or **IIb**. An intramolecular regioselective nucleophilic attack of the carboxylic group to the more electrophilic of the two sp-hybridized carbon atoms should take place to give the eight-membered

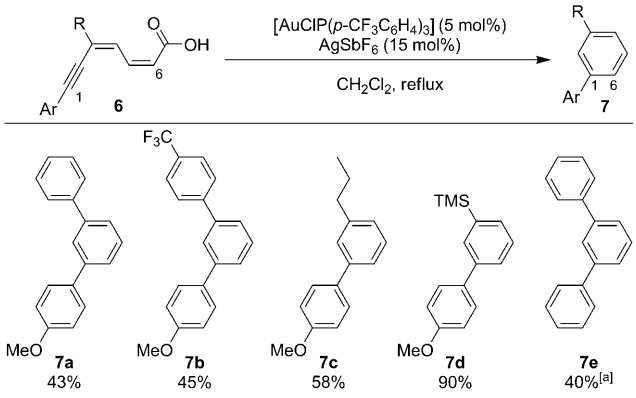


Scheme 4. Proposed mechanism for the 2,7-cycloaromatization of **2**.

cyclic intermediates **III**.[18] The alkoxy group is important in promoting such a cyclization: in the case of dienyne acid **2e** (R = −C≡C−Ph, R^1 = Et), which exhibits two triple bonds of different electronic nature, the nucleophilic attack of the carboxylic group takes place chemoselectively at the ethoxy-substituted triple bond. Both the activation and subsequent nucleophilic attack of triple bonds are well documented for gold-mediated transformations.[6,7,18] The alkoxy group would also promote the evolution of intermediate **IIIa** by an intramolecular attack on the activated carbonyl group, thereby forming bicyclic species **IV**.[19] A final aromatization would trigger the ring opening of the four-membered cycle in intermediate **IV** to give the final product **4**, and would regenerate the catalyst, which may be incorporated into a new cycle. The catalytic cycle in Scheme 4 represents the first transition-metal-catalyzed cycloaromatization reaction of dienyne carboxylic acids.

We considered that the electronic requirements of the substrate were crucial for the reaction, as found for the [4+2] intermolecular reaction of captodative enynes with nitriles.[10] To test our assumptions, we prepared dienyne carboxylic acids **6a–d**, which contain a *p*-methoxyphenyl group instead of an alkoxy group linked to the triple bond.[20] When **6a** (Ar = 4-$MeOC_6H_4$, R = Ph) was treated under the typical reaction conditions described in Scheme 3, *m*-terphenyl **7a** was isolated in low yield, with no traces of the phenol derivative detected. Interestingly, **7a** results from a sequence involving cyclization—by creation of a bond between C1 and C6—and decarboxylation. Consequently, a strong electron-donating group linked to the triple bond appears to be a requisite to promote 2,7-cycloaromatization.

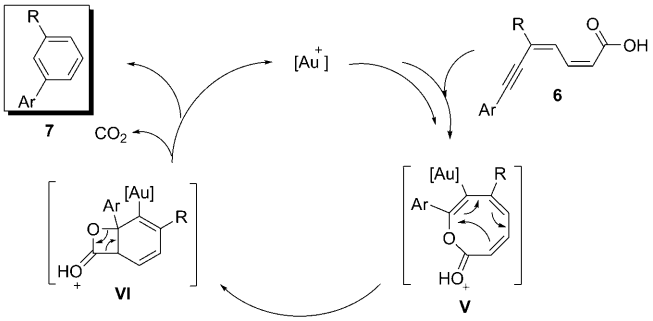
This 1,6-cyclization/decarboxylation sequence also proved to be general, although higher catalyst loadings ([AuClP(*p*-$CF_3C_6H_4)_3$] (5 mol%)/$AgSbF_6$ (15 mol%)) and a higher temperature (reflux in CH_2Cl_2) were required. Accordingly, different *p*-methoxyphenyl-substituted dienyne carboxylic acids **6a–c** could be converted into unsymmetrical *m*-terphenyl derivatives[21] **7a**,**b** or biphenyl **7c** in moderate yields (Scheme 5). Notably, silyl-substituted dienyne carboxylic acid **6d** (Ar = 4-$MeOC_6H_4$, R = TMS) provided high yields of silylated biphenyl **7d**, which is amenable to further elaboration. The reaction time for this transformation must be controlled (< 2 h) to avoid desilylation.



Scheme 5. Cyclization of dienynes **6**. [a] 56% conversion; reaction conducted in toluene at reflux and with a higher catalyst loading ([AuClP(*p*-$CF_3C_6H_4)_3$] (10 mol)/$AgSbF_6$ (30 mol%). TMS = trimethylsilyl.

This cyclization/decarboxylation sequence takes place even with a non-activated substrate. Phenyl-substituted dienyne carboxylic acid **6e** (Ar = Ph, R = Ph) reacts to form *m*-terphenyl **7e**, although higher temperatures (refluxing toluene) and catalyst loadings ([AuClP(*p*-$CF_3C_6H_4)_3$] (10 mol%)/$AgSbF_6$ (30 mol%)) were needed, and the conversion did not proceed beyond 56%, probably because of thermal decomposition of the catalyst.

The formation of biphenyl and terphenyl derivatives **7** would probably follow a similar pathway to that proposed for phenols **4** at the earlier stages of the mechanism (metal coordination, *s-trans-s-cis* isomerizacion, and nucleophilic attack of a carboxylic acid). However, the absence of a strong electron-donating group results in intermediate **V** (an analogue of **III**), which undergoes an electrocyclic ring closure between positions 1 and 6 to give **VI**. Aromatization should then occur to form **7** by CO_2 extrusion and the regeneration of the gold catalyst (Scheme 6).



Scheme 6. Proposed mechanism for the 1,6-cycloaromatization of **6**.

In summary, we have reported a novel gold-catalyzed 2,7-cycloaromatization reaction of captodative dienyne carboxylic acids which occurs at room temperature with short reaction times, low catalyst loading, and with total regioselective control. The reaction is dependent on the electronic properties of the dienyne acid: if a strong electron-donating group is not directly linked to the triple bond, a regioselective 1,6-cyclization-decarboxylation sequence takes place upon warming, thereby leading to biphenyl or *m*-terphenyl derivatives in moderate to high yields.

Experimental Section

General procedure for the synthesis of phenols **4**: $AgSbF_6$ (0.5–1.0 mol%, 0.4–0.8 mg) was added to a solution of [AuClP(*p*-$CF_3C_6H_4)_3$] (0.5–1.0 mol%, 0.9–1.8 mg) in dry CH_2Cl_2 (2 mL) and the reaction mixture was stirred for 30 min. A solution of the corresponding dienynoic acid **2** (0.5 mmol) in dry CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred at RT until complete disappearance of the dienynoic acid was observed by TLC (1–2 h). The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel. The corresponding phenols **4** were isolated in the yields reported in Scheme 3.

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[13] See the Supporting Information.

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[19] Alternatively, a 6π electrocyclization through mesomeric intermediate **IIIb** may take place to give **IV**.

[20] The strong electron-donating effect displayed by the methoxy group compared to the *p*-methoxyphenyl and the phenyl groups is clearly indicated by the ^{13}C shifts of the β-alkyne carbon atom in the NMR spectra of compounds **2** ($\delta = 33.9$–39.5 ppm) versus **6a–d** ($\delta = 84.3$–87.3 ppm) and **6e** ($\delta = 85.8$ ppm).

[21] For general methodologies for the synthesis of unsymmetrical terphenyls, see J. M. Antelo Míguez, L. A. Adrio, A. Sousa-Pedrares, J. M. Vila, K. K. (M.) Hii, *J. Org. Chem.* **2007**, *72*, 7771 – 7774, and references therein.

