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Contiguous Quaternary Centers from a Au(I)-Catalyzed Nazarov Cyclization

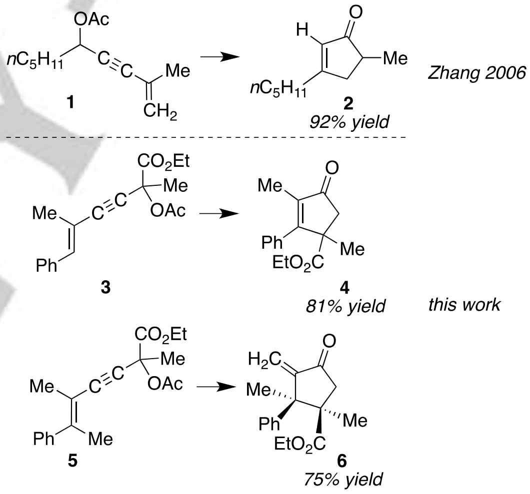
Jonathan Congmon, and Marcus A. Tius*[a]

Abstract: The cationic Au(I)-catalyzed cyclization of highly substituted enynes has been shown to provide cyclopentenones with up to two contiguous, all-carbon atom quaternary centers in a diastereospecific process. In the more challenging examples in which two contiguous quaternary centers are formed during cyclization, the essential role of a carboethoxy group to control the reaction outcome has been demonstrated. The less challenging examples that lead to a single quaternary center in the ring require no activation by aryl or by electron withdrawing groups.

The Nazarov cyclization continues to provide efficient access to cyclopentenones more than 70 years after its discovery.[1] In some cases the relative and the absolute stereochemistry of the product can be controlled,[2] rendering the method especially valuable in total synthesis.[3] Nazarov cyclizations leading to cyclopentenones bearing one or more all-carbon atom quaternary centers represent the most difficult case. We have recently developed asymmetric Pd(0)- and chiral Bronsted acid (CBA)-catalyzed diastereo- and enantioselective Nazarov cyclizations. The CBA-catalyzed cyclization leads to products with adjacent all-carbon atom quaternary centers.[4] Predictably, the reaction is slower for highly congested systems, enabling competing processes to take place. Our preliminary results indicated that a heavy catalyst load is required in the Pd(0)-catalyzed reaction in order to prepare cyclopentenones bearing adjacent all-carbon atom quaternary centers, suggesting the need for more reactive catalysts.

Our search for a more effective way to assemble adjacent all-carbon atom quaternary centers led us to the 2006 report by Zhang and Wang describing the cationic Au(I)-catalyzed cyclization of enynyl acetate **1** to cyclopentenone **2** (Scheme 1).[5] Since 2006 a number of related Au(I)- and Au(III)-catalyzed Nazarov reactions have been described,[6] including one that demonstrates good levels of asymmetry transfer.[6c] Asymmetry transfer has also been demonstrated for the related Au(I)-catalyzed Rautenstrauch rearrangement.[7,8] In the majority of cases cyclization is initiated either by [1,3]- or by [1,2]-oxa migration, typically of acetate, that is triggered through alkyne activation by the catalyst. There appears to be a delicate balance between the factors that favor [1,3]- over [1,2]-oxa migration.[9,10]

We questioned whether enynyl acetates such as **3** and **5**[11] would be capable of undergoing Au(I)-catalyzed cyclization, or whether other rearrangements might compete. In Zhang's reaction [1,2]-hydride migration takes place immediately following cyclization. An analogous [1,2]-alkyl or aryl migration that might have taken place during the rearrangement of **3** or **5** could have led to complex product mixtures.[12] Even if five-membered ring formation represented the dominant reaction pathway for enynes **3** and **5**, it seemed likely that the reaction of **5** would lead to mixtures of diastereomers. Very surprisingly, the cyclization of **5** and of all related enynes that we examined led to *single* diastereomers of the cyclopentenone product.



Scheme 1. Cationic Au(I)-Catalyzed Nazarov Cyclizations.

The conditions for the cyclization were optimized using enyne **3** (Table 1). The cationic Au(I) catalyst in each case was prepared *in situ* from equimolar quantities of the appropriate ligated AuCl and silver(I) triflimide that were delivered as standard solutions in dichloromethane.[13] A significantly faster reaction was observed in the case of the triphenylphosphino complex (entry 1), but under identical conditions the yield of **4** was better with the aryl phosphite ligand (entry 3), so it was chosen.[14] Since there was no significant difference between 1,2-dichloroethane and dichloromethane (entries 3, 4) dichloromethane was selected.[15] The Au(I) catalyst was in all cases highly reactive and as little as 0.5 mol% led to acceptable results (entry 7).[16] Entries 8–10 refer to control experiments that showed that both Au(I) and Ag(I) were necessary in order for reaction to take place. Since $AgNTf_2$ might have been the source of a small amount of the strong Bronsted acid Tf_2NH, the control experiment of entry 10 was carried out. Within 10 min of exposure to 1 equivalent of Tf_2NH all of **3** had been consumed,

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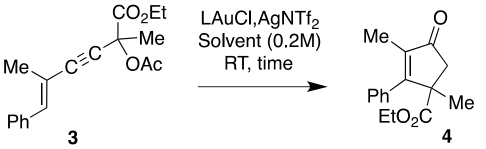
and no **4** was detected by TLC in the complex reaction mixture, making it unlikely that **4** is formed through Bronsted acid catalysis. The reaction conditions of entries 4 and 6 were used for slow- and fast-reacting enynes, respectively.

Table 1. Optimization of the Reaction Conditions.

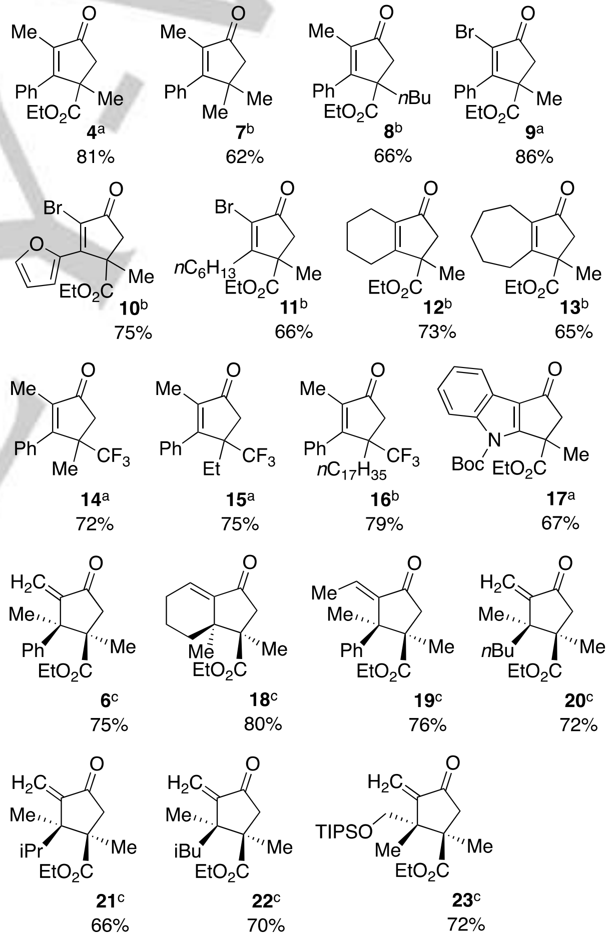


Entry	LAuCl (mol %)[a]	Solvent	Time	Yield (%)
1	Ph$_3$PAuCl (5)	DCE	30 min	70
2	IPrAuCl (5)	DCE	1 h	71
3	(ArO)$_3$PAuCl (5)	DCE	1 h	76
4	(ArO)$_3$PAuCl (5)	DCM	1 h	81[b]
5	(ArO)$_3$PAuCl (2.5)	DCM	4 h	68
6	(ArO)$_3$PAuCl (1)	DCM	16 h	67
7	(ArO)$_3$PAuCl (0.5)	DCM	3 d	65[c]
8	no AgNTf$_2$; (ArO)$_3$PAuCl (5)	DCE	3 h	no rxn
9	no Au(I); AgNTf$_2$ (5)	DCE	3 h	no rxn
10	no Au(I), Ag(I); Tf$_2$NH (100)	DCE	3 h	[d]

[a] Equimolar amounts of Au(I) and Ag(I) were used unless stated otherwise. All reactions with 5 mol% catalyst were performed on a 0.2 mmol scale. Reactions with 2.5, 1 and 0.5 mol% catalyst were performed on a 1 mmol scale. [b] Performed on a 0.3 mmol scale. [c] 5 mol% of Ag(I) was used. [d] No **3** or **4** was detected by TLC after 10 min. The same decomposition products were detected when 5 mol% Tf$_2$NH was used. DCE, 1,2-dichloroethane; DCM, dichloromethane; IPr, 1,3-*Bis*(2,6-diisopropylphenyl)imidazol-2-ylidene; Ar, 2-*tert*-butylphenyl.

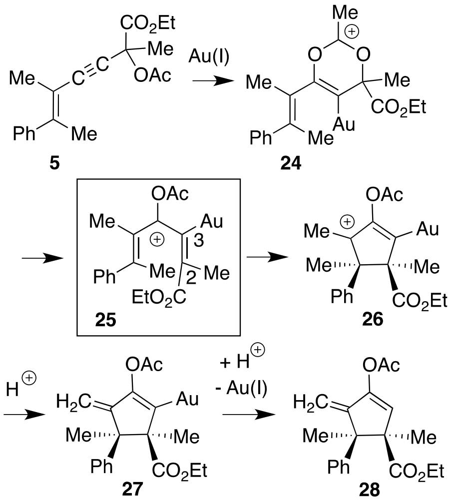
Table 2 summarizes our findings. The carboethoxy group was not required and a moderately activated substrate led to **7**, albeit in a slower reaction and in slightly lower yield. Compounds bearing □n α vinyl bromine atom (**9–11**) were formed readily.[17] The activating aryl group was not required, and the all-aliphatic cases (**11–13**, **18** and **20–23**) all proceed in good yield. Cyclization to β-trifluoromethyl cyclopentenones **14-16** took place in good yield.[18,19] Cyclopentenones **6** and **18–23** deserve special mention. Because the loss of a proton from one of the carbon atoms in the ring is not possible, in these examples the reaction is terminated through proton loss from an exocyclic carbon atom. Significantly, all compounds in this series were isolated as single diastereomers of adjacent, all-carbon atom quaternary centers.[20] The stereochemical assignment in **6**, **18**, **19** and **28** (Scheme 2) was made on the basis of the positive nOe between the two *cis* methyl groups. This has implications for the mechanism, which we postulate to follow the pathway outlined in Scheme 2.[21] Complexation of the cationic Au(I) catalyst to the alkyne function of **5** leads to **24** through participation of the acetoxy group. Rearrangement to pentadienyl cation **25**[22] is followed by cyclization to **26**. Proton loss from the exocyclic carbon atom results in protiodeauration of **27** with formation of dienol acetate **28** and regeneration of the catalyst. Whereas enol acetate cleavage was required as a separate step in the case of **6** and **18–23**, in all other cases hydrolytic cleavage of the acetate through adventitious water took place during the reaction, and the odor of acetic acid was detected during workup. Adding 0.5 g/mmol of powdered 4Å molecular sieves to the reaction mixture made it possible to isolate the enol acetate in all cases. If a significant amount of water is present during the reaction, cyclization is not observed, presumably because protiodeauration takes place prematurely. For example, in wet dichloromethane dienone **29** was formed as the sole product in 70% yield as a single geometrical isomer from the corresponding enyne. The *Z* stereochemistry was assigned on the basis of the positive nOe between the C2-H and C3-Me.[23]

Table 2. Examples of the Cyclization.



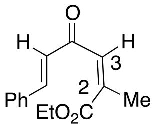
(a) (ArO)$_3$PAuCl/AgNTf$_2$ (1 mol%), DCM, 12 h. (b) (ArO)$_3$PAuCl/AgNTf$_2$ (5 mol%), DCM, 1 h. (c) 1. (ArO)$_3$PAuCl/AgNTf$_2$ (1 mol%) 2. K$_2$CO$_3$, EtOH, rt, 3 h, yield over 2 steps. Ar, 2-*tert*-butylphenyl; DCM, dichloromethane; TIPS, triisopropylsilyl.

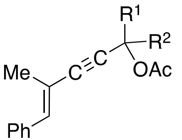
Enynes **30–32** represent examples that failed to undergo cyclization and that were recovered intact from the reaction mixture in each case. In the case of **30** the two trifluoromethyl groups presumably inhibit the formation of the cation and no reaction was observed after 2 d under the optimized reaction conditions. The nucleophilic carbonyl oxygen atom of the morpholino amide in **31** probably intercepts the alkyne-gold complex more effectively than the acetate, thus inhibiting the [1,3]-oxa migration. No reaction was observed after 1 d. Aromatic π bonds also appear to be unreactive as evidenced by the inertness of **32** that was recovered unchanged after 2 d.

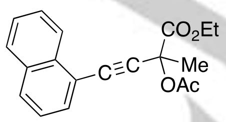


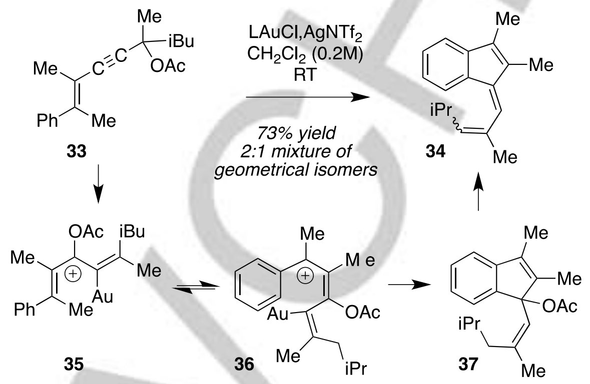
Scheme 2. Postulated Mechanism.

The rearrangement that leads to the examples of Table 2 is a delicately balanced process, as indicated by the results that are summarized in Scheme 3. Although the preparation of **7** (Table 2) shows that the presence of an electron withdrawing group is not a strict requirement for the success of the cyclization to cyclopentenones bearing a single quaternary center, we wished to determine whether a carboethoxy group was required for the preparation of the far more challenging products that incorporate adjacent quaternary carbon atoms. Accordingly, enyne **33** was exposed to the optimized reaction conditions. No cyclopentenone was produced but instead hydrocarbon **34** was formed in 73% yield as a *ca.* 2:1 mixture of geometrical isomers. We assume that pentadienyl cation **35** was formed as an intermediate according to the postulated mechanism, and differing from **25** only in having an isobutyl group in place of carboethoxy. In the absence of the favorable polarization by an electron withdrawing carboethoxy group, cation **35** undergoes a competitive *aromatic* Nazarov cyclization through conformer **36**. Proton loss followed by protiodeauration gives tertiary, benzylic, *bis*-allylic acetate **37** that loses acetic acid to form **34**. A comparison of the reactions of **33** and of **5** highlights the essential role of the carboethoxy group that accelerates the desired cyclization to cyclopentenone **6**.


29


30 $R^1,R^2 = CF_3$
31 $R^1 = CH_3$,
$R^2 = CON[(CH_2CH_2)_2O]$


32



Scheme 3. Anomalous cyclization of **33**.

Conclusions. Of the compounds shown in Table 2, only cyclopentenone **7** represents a known structure.[24] The novelty of this cyclization is showcased by the synthesis of□ cyclopentenones substituted by a trifluoromethyl group or that incorporate a α-bromovinyl. Significantly, the method also provides access to compounds bearing contiguous, all-carbon atom quaternary centers as single diastereomers. The high diastereoselectivity of the process is the result of rapid isomerization, relative to cyclization, of the intermediate pentadienyl carbocation that is bonded to the gold atom, e.g. **25**. This is likely due to the same effect that we had observed during our study of a Pd(0)-catalyzed Nazarov-type cyclization in which electron pair-electron pair repulsions between ester carbonyl and hydroxyl oxygen atoms strongly favor a single geometrical isomer of an alkene.[25,26] In Scheme 2 the repulsive interaction between the covalently bonded Au atom and the carboethoxy group results in the formation of a single geometrical isomer of **25**, ultimately leading to a single diasteroisomer of **28**. The preparation of **29** as a single C2-C3 geometrical isomer suggests that this effect may be exploited for the synthesis of trisubstituted alkenes.[27] The stereochemical outcome in **6** and in **18**–**23** provides experimental evidence that this family of Au(I)-catalyzed cyclizations are conrotatory processes. Control of the stereochemistry of adjacent, all-carbon atom quaternary centers is still a very challenging problem for which this work provides an efficient solution. The ability to prepare the enyne starting materials easily and in good yield through several different routes, as well as the indication that it will be possible to develop an effective catalytic asymmetric version of the reaction suggest that it will be valuable in synthesis.[28]

Experimental Section

Experimental Details. Alkyne **5** (94 mg, 0.30 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2 mL) and 1 mL of the standard solution of the active gold catalyst was added. The reaction mixture was allowed to stir at room temperature overnight. The volatiles were removed *in vacuo* and the product was purified by silica gel column chromatography (3% EtOAc/hexanes to 5% EtOAc/hexanes) to provide cyclopentene **28** (74 mg, 78%) as a pale yellow oil. To enol acetate **28** (60 mg, 0.19 mmol, 1 equiv.) in EtOH was added K_2CO_3 (40 mg, 0.29 mmol, 1.5 equiv.) in one portion at room temperature. After stirring for 3 h at room temperature, the reaction mixture was washed with water and extracted with EtOAc (x3). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, and concenrated *in vacuo*. The product was purified by silica gel column chromatography (10% EtOAc/hexanes) to provide cyclopentenone **6** (50 mg, 96%; 75% overall) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) □□0.99 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 3H), 1.74 (s, 3H), 2.27 (d, *J* = 18.1 Hz, 1H), 3.07 (d, *J* = 18.1 Hz, 1H), 3.78 (dq, *J* = 7.2, 0.8 Hz, 2H), 5.35 (s, 1H), 6.39 (s, 1H), 7.12 – 7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 13.6, 20.3, 23.3, 46.8, 52.5, 53.5, 60.8, 119.9, 127.0, 127.2, 128.0, 143.6, 152.7, 174.2, 204.1; IR (neat, cm^{-1}) 3025, 2979, 1723, 1641, 1450, 1387, 1289, 1213, 1028; HRMS (ESI^+) *m/z* calculated for $C_{17}H_{21}O_3$ $[M+H]^+$: 273.1491; found: 273.1619.

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Keywords: Nazarov • cationic Au(I) • quaternary carbon • cyclization • diastereoselectivity

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[16] Enyne **5** did not react after 24 h at room temperature in the presence of 5 mol% of the catalyst derived from an equimolar mixture of IPrAu(III)(biphenyl)Cl and $AgNTf_2$. See: C-Y. Wu, T. Horibe, C. B. Jacobsen, F. D. Toste, *Nature*, **2015**, *517*, 449 – 454.

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[18] Examples of Nazarov cyclizations leading to trifluoromethyl cyclopentenones: (a) J. Ichikawa, M. Fujiwara, T. Okauchi, T. Minami, *Synlett* **1998**, 927 – 929; (b) M. A. Tius, H. Hu, J. K. Kawakami, J. Busch-Petersen, *J. Org. Chem.* **1998**, *63*, 5971 – 5976.

[19] Occhiato and coworkers have prepared a compound related to indole **17** through a Au(I)-catalyzed cyclization. See reference 6a.

[20] a) M. Bueschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156 – 4186; b) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181 – 191.

[21] A significant difference between the mechanism of Scheme 2 the following in that no [1,2]-hydride migration step takes place: F-Q. Shi, X. Li, Y. Xia, L. Zhang, Z-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 15503 – 15512.

[22] Loss of cationic Au(I) from **24** in a reversible process may lead to an allene which reacts with the catalyst to give **25**.

[23] See the S.I.

[24] J. Matsuo, M. Kawano, R. Okuno, H. Ishibashi, *Org. Lett.* **2010**, *12*, 3960 – 3962.

[25] The difference in A values between methyl and carboethoxy groups is 0.5 – 0.6 kcal/mol. “Stereochemistry of Organic Compounds”, E. L. Eliel and S. H. Wilen, John Wiley & Sons, Inc., New York, 1994; pp. 695 – 697.

[26] For a related example of electron pair-electron pair repulsions controlling the geometry of a tetrasubstituted alkene see: a) A. K. Basak, N. Shimada, W. F. Bow, D. A. Vicic, M. A. Tius, *J. Am. Chem. Soc.* **2010**, *132*, 8266 – 8267; b) A.H. Asari, Y. Lam, M. A. Tius, K. N. Houk, *J. Am. Chem. Soc.* **2015**, *137*, 13191 – 13199.

[27] Compare with the results of Malacria, Fensterbank and coworkers in which isomerization of an allyl group *Z* to the gold precedes cyclization. See Scheme 10 in reference 7c.

[28] A limited screen of chiral, non-racemic ligands for Au(I) was performed. In the presence of 5 mol% each of the 2 to 1 complex of AuCl with (*R*)-(+)-2,2′-bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl and $AgNTf_2$ in dichloromethane cyclopentenone **9** was formed in 67/33 e.r. See the S.I. and M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002 – 18003.

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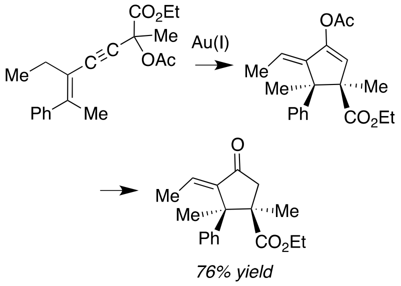
COMMUNICATION

The cationic Au(I) catalyzed cyclization of substituted enynes leads to cyclopentenones through a cascade of reactions. The highly diastereoselective synthesis of cyclopentenones bearing adjacent, all-carbon atom quaternary centers is reported.



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