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Unusual Au(III)-catalyzed dimerization of benzoxazol-2-yloxy enynes: Formation of substituted 1,5-cyclooctadienes

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ABSTRACT

Symmetric 1,5-cyclooctadienes were formed via Au-catalyzed dimerization of benzoxazol-2-yloxy enynes, involving double nucleophilic attacks of alkenylgolds toward allylic cations.

1. Introduction

Homogeneous Au catalysis has recently attracted much attention in synthetic community not only because of the shattering of old perceptions of the chemical inertness of gold but also the plethora of versatile transformations that Au complexes can catalyze [1–10]. Much of the novel reactivities of Au complexes start from efficient activation of π systems, especially alkynes, followed by attack of various inter-/intramolecular nucleophiles. The common intermediate formed in the case of alkyne substrates is alkenylgold. Although Au is the most electronegative metal in Pauling's scale (2.54) [11], the Au–C(sp^2) bond has been shown to be nucleophilic and can participate in C–C bond formation processes [12–18]. While the nature of the C–C bond formation is to be established [19], the reactivity does provide a new dimension for Au-catalyzed reactions of alkynes and warrants more studies. We have recently developed several versatile synthetic methods taking advantage of the nucleophilicity of alkenylgolds [14–16]. In continuation of our interest in this area, herein we report an unusual Au-catalyzed dimerization of benzoxazol-2-yloxy enynes, where two new C–C single bonds are formed involving the reaction of nucleophilic Au–C(sp^2) bonds.

2. Results and discussion

Our initial design to explore the nucleophilicity of Au–C(sp^2) bonds was shown in Scheme 1. We surmise that the imidoyloxy group in homopropargylic imidate **1** can migrate upon Au activation of the C–C triple bond, forming zwitterionic alkenylgold **B**. This migration should be substantially facilitated by the transformation of an imidate moiety into a thermodynamically much more stable amide group [20]; moreover, the C–C double bond at the propargylic position stabilizes the carbon cation via resonance. We have previously advanced a novel concept of 'Au-containing all-carbon 1,*n*-dipoles' and applied it in studying the generation of 1,4-dipoles [21] and 1,3-dipoles [22] in [4 + 2] and [3 + 2] cycloaddition reactions, respectively. Intermediate **B** can be viewed as another example of Au-containing all-carbon 1,4-dipoles, and it is envisioned that dipole **B** could couple with various polarized double bonds involving a key nucleophilic cyclization of the Au–C(sp^2) bond (i.e., from **C** to **2**), yielding [4 + 2] adduct **2** (see Scheme 2).

We began with enynyl carbinol **3**, prepared in two steps from 2-iodocyclohex-2-enone –[23] Due to the difficulty in synthesis and handling of imidates [24], we decided to convert alcohol **3** into benzoxazol-2-yloxy enyne **4** [25], where an imidoyloxy moiety is embedded. Thus, alcohol **3**, upon deprotonation, was reacted with 2-chlorobenzoxazole rather efficiently to give the desired enyne product **4** after desilylation by TBAF.

To our surprise, treatment of enyne **4** with various Au catalysts in the presence of a range of dipolarophiles including aldehydes, imines, ethyl vinyl ether, methyl vinyl ketone did not give expected [4 + 2] adducts. Interestingly, we observed in all these trials two new spots. With no dipolarophile present, those two spots were also observed. Subsequently, they were isolated in 32.5% and 7.5% yields, respectively, after enyne **4** was treated with 5 mol% of dichloro(pyridine-2-carboxylato)gold(III) (**5**) [26] in 1,2-dichloroethane at room temperature for 10 h. Spectroscopic studies of these compounds revealed that (a) their ^{1}H NMR spectra were

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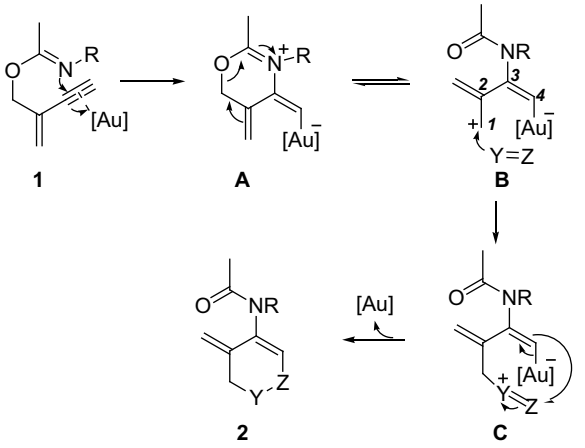
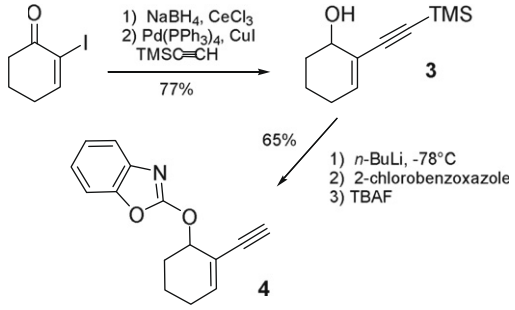
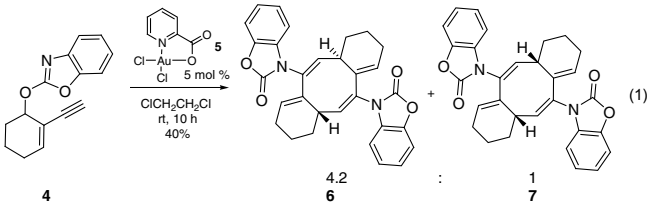


Scheme 1. Exploring the nucleophilicity of Au–C(sp^2) bonds.



Scheme 2. Preparation of benzoxzaol-2-yloxy enyne **4**.

rather simple, (b) their ^{13}C NMR had the same number of signals as **4**, and (c) their molecular weights revealed by ESI^+ doubled that of **4**. As a result, we reasoned that these products must be symmetric dimers of **4**, and assigned 1,5-cyclooctadiene structures to both of them with one of center symmetry (i.e., the *meso*-isomer **6**, Eq. (1)) and the other of C_2 symmetry (i.e., *rac*-isomer **7**, Eq. (1)). Fortunately, the major product was crystalline, and its single crystal X-ray crystallography (Fig. 1) indeed verified that it possesses a 1,5-cyclooctadiene core. Moreover, it was the *meso*-isomer **6**



(1)

This unprecedented dimerization of **4** is rather surprising, especially considering the formation of the 8-membered ring. Notwithstanding, the formation of **6** and **7** can be explained by invoking the formation of a Au-containing all-carbon 1,4-dipole of type **B**. Hence, as shown in Scheme 3, Au(III)-catalyzed migration of the benzoxazol-2-yloxy group leads to the formation of Au-containing 1,4-dipole **D**. The facile dimerization of **D** must be assisted by some type of bimolecular association as reactions of **D** with dipolarophiles were not observed. Although much study is warranted to understand the nature of this association, we surmise that there may be significant Au–Au interaction [27] between two molecules of dipole **D**, thus facilitating their union. Both new C–C bonds should then be formed via nucleophilic attack of the Au–C(sp^2) bonds toward the allylic cations [17], forming diastereoisomers **6** and **7**.

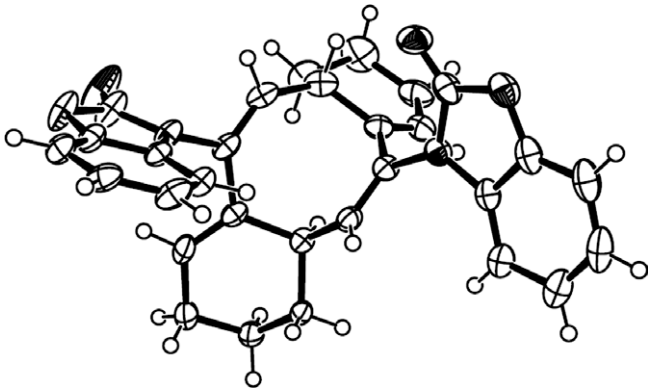
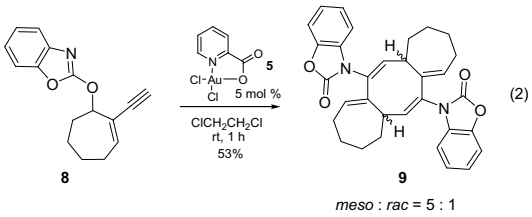


Fig. 1. ORTEP representation of cyclooctadiene **6**.

Various reaction conditions as well as Au catalysts were examined to improve the overall yield and improve the diastereoselectivity. Some of the results were shown in Table 1. While the yield of this reaction could not be improved substantially by changing reaction temperatures (entries 1–3) and solvents (entries 4–6) as well as catalysts (entries 7–10), noteworthy are that Au(I) complex $Ph_3PAuNTf_2$ resulted in the opposite diastereoselectivity and that $PtCl_2$ did not catalyze this reaction.

Our attempts to expand the scope of this chemistry were hampered by the unstable nature of benzoxzaol-2-yloxy enynes. Most substrates studied were prone to allylic rearrangement during either their preparations or their reactions with Au catalysts, leading to the formation of undesired carbamates. One exception is enyne **8** prepared from 2-iodocyclohept-2-enone. Reaction of **8** in the presence of Au(III) complex **5** afforded an inseparable mixture of cyclooctadiene diastereomers **9** (*meso*-isomer:*rac*-isomer = 5:1) in 53% yield (Eq. (2)). The structures of **9** were deduced by comparing the NMR spectra with those of **6** and **7**



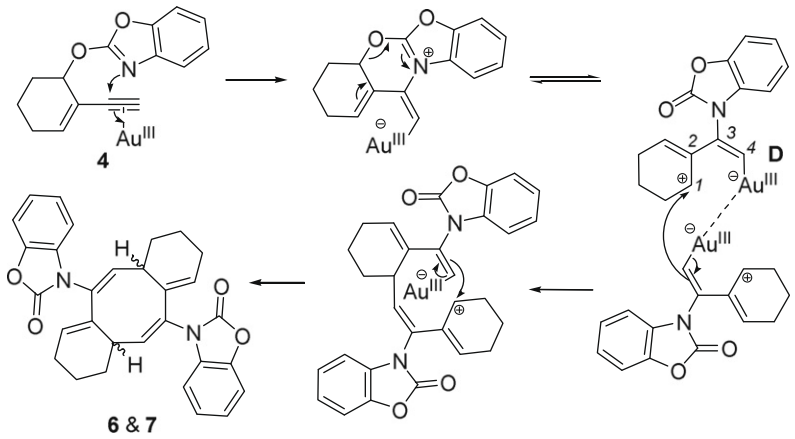
(2)

In summary, an unusual Au-catalyzed dimerization of benzoxazol-2-yloxy enynes was discovered. 1,5-Cyclooctadienes were formed in fair yields as mixtures of *meso*- and *rac*-isomers. Although the scope was limited, this unprecedented reaction revealed an unknown aspect of Au chemistry. While the formation of the two C–C single bonds can be readily explained by invoking the nucleophilicity of alkenylgold species, substantial attractive interaction between two molecules of the Au-bound dipolar intermediates seems necessary considering their low concentrations in the reactions. This interaction may be general to Au-catalyzed reactions, and understanding of its nature will be of significance for advancing Au catalysis.

3. Experimental

3.1. Au-catalyzed dimerization of *4*

To a solution of benzoxazol-2-yloxy enyne **4** (58 mg, 0.24 mmol, 1 equiv.) in 4 mL of anhydrous 1,2-dichloroethane was added dichloro(pyridine-2-carboxylato)gold(III) (4.7 mg, 0.012 mmol, 0.05 equiv.). The resulting mixture was stirred at 60 °C for 1 h. The solvent was evaporated, and the residue was eluded through



Scheme 3. Proposed mechanism for 1,5-cyclooctadiene formation.

Table 1
Au-catalyzed dimerization of **4** under various reaction conditions

Entry	Catalyst (5 mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	**6**:**7**[b]
1	**5**	$ClCH_2CH_2Cl$	40	3	42	4.5:1
2	**5**	$ClCH_2CH_2Cl$	60	1	56	4.2:1
3	**5**	$ClCH_2CH_2Cl$	80	1	33	3.9:1
4	**5**	THF	60	1	55	4.5:1
5	**5**	Toluene	60	1	52	6.4:1
6	**5**	MeCN	60	1	17	2.5:1
7	$AuCl_3$	$ClCH_2CH_2Cl$	60	1	46	3.8:1
8	$Ph_3PAuNTf_2$	$ClCH_2CH_2Cl$	60	1	52	1:2.1
9	$PyAuCl_3$	$ClCH_2CH_2Cl$	60	1	52	3.9:1
10	$PtCl_2$	Toluene	60	1	–	–

[a] Estimated by using diethyl phthalate as reference.
[b] Determined by ^1H NMR.

silica gel column using flash chromatography. *meso*-Dimer **6** was isolated in 41% yield and the *rac*-dimer **7** was obtained in 9% yield. *Meso*-Dimer **6**: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.21–7.05 (m, 8H), 5.93 (d, 2H, J = 8.0 Hz), 5.83 (m, 2H), 3.58 (m, 2H), 2.20–2.14 (m, 4H), 2.07–2.00 (m, 2H), 1.75–1.58 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.2, 142.7, 133.3, 133.1, 132.2, 131.5, 130.4, 123.9, 122.5, 109.9, 109.6, 38.6, 29.0, 25.3, 20.4. IR (neat): 3352, 2936, 2254, 1771, 1601, 1482, 1379, 1045, 985; MS (ES^+). Calculated for $[C_{30}H_{26}N_2O_4Na]^+$ 501.1; Found: 501.0. Racemic dimer 7: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22–7.20 (m, 2H), 7.12–7.04 (m, 4H), 6.84–6.81 (m, 1H), 5.79–5.77 (m, 2H), 5.75 (d, 2H, J = 8.8 Hz,), 4.20–4.13 (m, 2 H), 2.20–2.14 (m, 2H), 2.07–2.01 (m, 4H), 1.82–1.62 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.6, 142.5, 133.6, 132.4, 131.9, 131.7, 131.1, 123.9, 122.5, 109.8, 109.7, 36.5, 29.9, 25.4, 19.4. IR (neat): 2964, 2869, 2358, 1733, 1683, 1593, 1506, 1464, 1362, 1267, 910; MS (ES^+). Calculated for $[C_{30}H_{26}N_2O_4Na]^+$ 501.1; Found: 501.0.

Acknowledgments

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Appendix A. Supplementary material

CCDC 644034 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. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.09.011.

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