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Azaanthraquinone Assembly from *N*-Propargylamino Quinone via a Au(I)-Catalyzed 6-*endo-dig* Cycloisomerization

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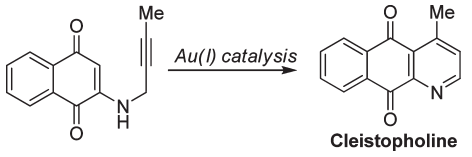

A methodology to assemble the azaanthraquinone skeleton from *N*-propargylamino quinone by a Au(I)-catalyzed 6-*endo-dig* cycloisomerization was developed. The catalytic process was applied to the synthesis of alkaloid cleistopholine and its analogues. A mechanism involving benign nucleophilicity of the aminoquinone was proposed.

Naturally occurring tricyclic quinone alkaloids possess extensive biological properties ranging from antimicrobial capacity to cytotoxicity.[1,2] Among them, cleistopholine along with its hydroxy/methoxy-substituted counterparts were isolated from *Porcelia macrocarpa* and feature a 4-methyl-substituted azaanthraquinone ring.[1c] Ring structures related to azaanthraquinone can also be found in polycyclic alkaloids such as sampangine and meridine (Figure 1).[3]

The classical strategy to construct an azaanthraquinone framework involves a hetero-Diels−Alder reaction between α,β-unsaturated *N*,*N*-dimethylhydrazone and quinone (Figure 2, route I).[4] Although this method has been applied extensively, there are still drawbacks:[5] (i) the dimethylamine liberated from the initial Diels−Alder adduct would react with the quinone dienophiles, thus substantially decreasing the reaction efficiency, and (ii) low regioselectivities were encountered with unsymmetric dienophiles, and product purification was difficult.

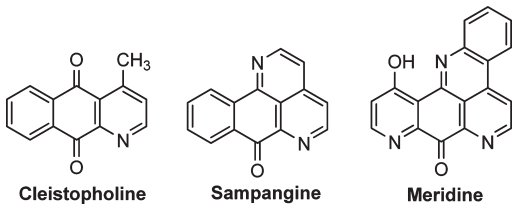

FIGURE 1. Azaanthraquinone and related alkaloids.

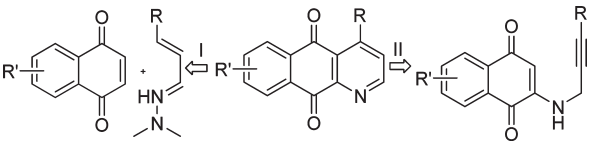

FIGURE 2. Strategies to assemble azaanthraquinone.

Our interest in alkaloid synthesis prompted us to consider whether the azaanthraquinone skeleton could be assembled through a cycloisomerization of *N*-propargylamino quinone (Figure 2, route II). Notably such enyne substrates can be easily prepared. Meanwhile, the nucleophilicity of electron-rich double bonds such as enamine, enaminone, and enamide in transtion-metal-catalyzed cycloisomerization has been disclosed recently by different groups.[6] For instance, Arcadi and Cacchi independently reported enamines/enaminones tethered by alkyne units proceeded cycloisomerization efficiently to afford pyridine derivatives when catalyzed by $NaAuCl_4$ or CuBr salts.[6a,i] Dake found that cyclic enamides appended by alkyne units underwent $PtCl_2$-catalyzed cycloisomerization to afford azahydrindans and spiro-fused heterocycles regioselectively.[6c−f] Inspired by the findings, we envisioned a gold-catalyzed annulation of the azaanthraquinone ring.[7] As shown in Scheme 1, a gold complex selectively activates the C−C triple bond, promoting nucleophilic attack by the double bond of aminoquinone via a 6-*endo-dig* cyclization, and then the cyclized intermediate would undergo tautomerization and aromatization, affording the azaanthraquinone skeleton.

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(3) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825.

(4) Serckx-Poncin, B.; Hebain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261.

(5) For a review, see: Pautet, F.; Nebois, P.; Bouaziz, Z.; Fillion, H. *Heterocycles* **2001**, *54*, 1095.

(6) (a) Abbiati, G.; Acradi, A.; Bianchi, G.; Giuseppe, S. D.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959. (b) Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025. (c) Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929. (d) Kozak, J. A.; Dake, G. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221. (e) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367. (f) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023. (g) Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791. (h) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287. (i) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629.

(7) For selected reviews on homogeneous gold catalysis, see: (a) Arcadi, A. *Chem. Rew.* **2008**, *108*, 3266. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (d) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (e) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Furstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (g) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

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SCHEME 1. Proposed Synthesis of Azaanthraquinone via a 6-*endo-dig* Cycloisomerization

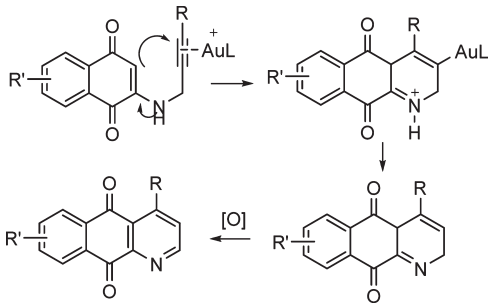
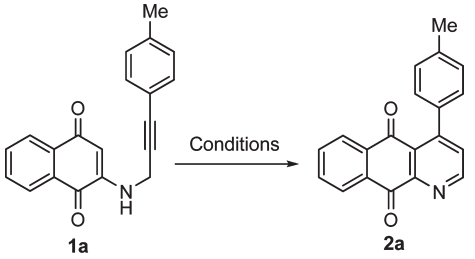


TABLE 1. Optimization of Reaction Conditions



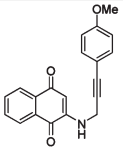
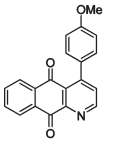
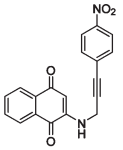
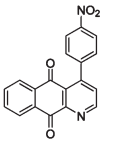
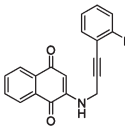
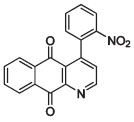
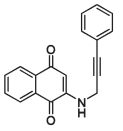
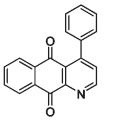
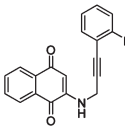
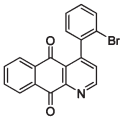
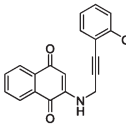
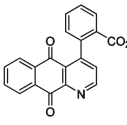
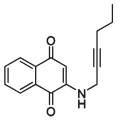
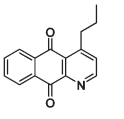
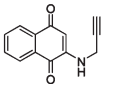
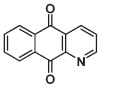
entry	condition[a]	yield (%)
1	10 mol % $Ph_3PAuOTf$, $(ClCH_2)_2$, 80 °C, 6 h	64
2	10 mol % $Ph_3PAuOTf$, $PhCH_3$, 100 °C, 6 h	82
3	10 mol % $Ph_3PAuOTf$, Dioxane, 100 °C, 12 h	55
4	10 mol % $Ph_3PAuOTf$, THF, 60 °C, 12 h	19
5	10 mol % $Ph_3PAuOTf$, HOAc, 100 °C, 1 h	85
6	5 mol % $Ph_3PAuOTf$, HOAc, 100 °C, 6 h	25
7	10 mol % $PtCl_2$, HOAc, 100 °C, 2 h	49
8	10 mol % $NaAuCl_4 \cdot 2H_2O$, HOAc, 100 °C, 4 h	34
9	10 mol % CuBr, HOAc, 100 °C, 4 h	14
10	10 mol % AgOTf, HOAc, 80 °C, 12 h	0[b]
11	HOAc, 80 °C, 12 h	0[b]
12	10 mol % Ph_3PAuCl, HOAc, 100 °C, 4 h	19
13[c]	10 mol % $Ph_3PAuOAc$, toluene, 100 °C, 6 h	< 5

[a]The reaction was open in air. [b]No azaanthraquinone detected. [c]The catalyst was generated *in situ* from 10 mol % Ph_3PAuCl and AgOAc.

We initiated the study by using enyne **1a** as substrate. As shown in Table 1, when 10 mol % of $Ph_3PAuOTf$, generated *in situ* from Ph_3PAuCl and AgOTf, was employed, the anticipated 1-azaanthraquinone **2a** was indeed formed. However, except for the unreacted starting material, no dihydroazaanthraquinone intermediate was isolated. The structure of **2a** was confirmed by X-ray crystallography.[8] Different solvents including dichloroethane, toluene, dioxane, THF, and HOAc were screened (entries 1−5), and both acetic acid and toluene led to good yields, although the reaction in the former solvent completed in just 1 h. The amount of $Ph_3PAuOTf$ was necessary as prelonged reaction and a much lower yield was observed in the presence of 5 mol % of the catalyst (entry 6). In addition, other metal salts such as $PtCl_2$, $NaAuCl_4 \cdot 2H_2O$, and CuBr also catalyzed this transformation albeit with much lower efficiency (entries 7−9). Control experiments indicated that the gold complex was necessary for the observed reaction (entries 10−13).

(8) CCDC 748374 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.

TABLE 2. Azaanthraquinone Assembly via a Au^I-Catalyzed 6-*endo-dig* Cycloisomerization[a]

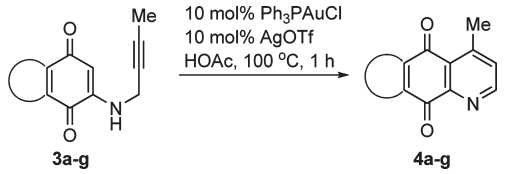
entry	aminoquinone		azaanthraquinone		yield (%)
1		**1b**		**2b**	95[b]
2		**1c**		**2c**	52
3		**1d**		**2d**	57
4		**1e**		**2e**	75
5		**1f**		**2f**	82
6		**1g**		**2g**	80
7		**1h**		**2h**	84
8		**1i**		**2i**	64

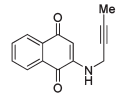
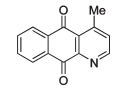
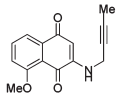
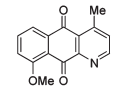
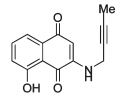
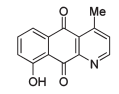
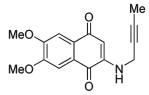
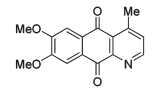
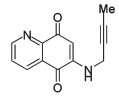
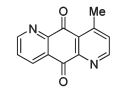
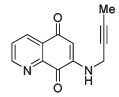
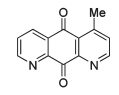
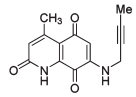
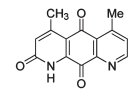
[a]All reactions performed at 0.05 M. [b]Reaction time 0.5 h.

The scope of the transformation was next investigated according to the optimized reaction conditions (Table 1, entry 5). Enynes with various substituted aryl groups at the alkyne terminus were examined. As shown in Table 2, a *p*-MeO group faciliated the reaction, and azaanthraquinone **2b** was formed in 95% yield after 0.5 h (entry 1). In contrast, electron-withdrawing substitutents such as *p*-NO_2 and *o*-NO_2 hindered the reaction, and the 4-nitrophenyl and 2-nitrophenyl azaanthraquinones **2c**−**d** were obtained in only 52% and 57% yield, respectively (entries 2 and 3). For a Ph group, the reaction yield was moderate (entry 4). Different from the electronic effect, the steric effect was minimal as substitutents such as *o*-Br and *o*-CO_2Me were tolerated without compromising the yields (entries 5 and 6). In addition, enynes containing alkyl substituent and terminal alkynes also underwent the cycloisomerization smoothly to afford azaanthraquinone **2 h**−**i** in 84% and 64% yield (entries 7 and 8).

Since a characteristic 4-methyl group is found on the azaanthraquinone moiety of natural alkaloids such as cleistopholine, our attention was then turned to the 6-*endo-dig* cycloisomerization of enynes derived from 2-butynylamine

TABLE 3. 4-Methyl-azaanthraquinone Assembly via a Au^I-Catalyzed 6-*endo-dig* Cycloisomerization[a]



entry	aminoquinone		azaanthraquinone		yield (%)
1		**3a**		**4a**	60
2		**3b**		**4b**	66
3		**3c**		**4c**	77
4		**3d**		**4d**	65
5		**3e**		**4e**	65
6		**3f**		**4f**	67
7		**3g**		**4g**	84

[a][**3**] = 0.05 M.

and different quinones (Table 3). Hence, starting from enyne **3a**, cleistopholine was directly prepared in one step in 60% yield (entry 1), demonstrating the synthetic power of this new approach. Similarly, 8-methoxycleistopholine, 8-hydroxycleistopholine, and 6,7-dimethoxycleistopholine were synthesized smoothly in fairly good yields from enynes **3b**−**d** (entries 2−4). Furthermore, enynes **3e**−**g** containing pyridine and pyridone units were readily tolerated to deliver 1,5-diazaanthraquinone and 1,8-diazaanthraquinone, suggesting the generality of this cycloisomerization (entries 5−7).

In conclusion, an anternative approach to attain azaanthraquinones from *N*-propargylamino quinones was developed by employing a Au(I)-catalyzed 6-*endo-dig* cycloisomerization. Synthesis of alkaloid cleistopholine and its hydroxy/methoxy-substituted counterparts was easily achieved using this gold catalysis.

Experimental Section

General Procedure for the Au(I)-Catalyzed 6-*endo-dig* Cycloisomerization. Chloro(triphenylphosphine)gold(I) (14.9 mg, 0.03 mmol) was added to a stirred solution of AgOTf (7.8 mg, 0.03 mmol) in acetic acid (6.0 mL) at room temperature. After 5 min, *N*-propargylamino quinone (0.3 mmol) was put in one portion. Then the reaction was heated at 100 °C for 1 h. After cooling, the solvent was distilled under vacuum pressure. The residue was dissolved in CH_2Cl_2 (20 mL), and then the organic layer was washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL) successively. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography to get pure product.

4-(4-Methylphenyl)-benzo[*g*]quinoline-5,10-dione (2a). Yellow needle, mp 243−245 °C (EtOH); IR (KBr) ν_{max} 1684, 1592, 1571, 1300, 1287, 955, 823, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (d, J = 5.1 Hz, 1H), 8.41−8.38 (m, 1H), 8.16−8.13 (m, 1H), 7.85−7.77 (m, 2H), 7.52(d, J = 4.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.25−7.22 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 181.6, 153.3, 152.7, 150.0, 138.3, 136.0, 134.6, 134.2, 133.8, 132.5, 130.6, 128.9, 128.2, 127.6, 127.33, 127.26, 21.3; MS (EI) m/z 299 (M^+, 17), 298 (M − 1, 54), 284 (100). Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.35; H, 4.37; N, 4.67.

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Supporting Information Available: Experimental details for the synthesis and ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.