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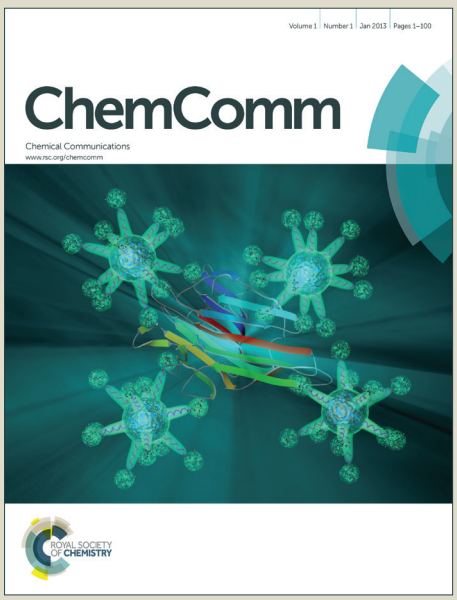

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Au(I)-Catalyzed Triple Bond Alkoxylation/Dienolether Aromaticity-Driven Cascade Cyclization to Naphthalenes†

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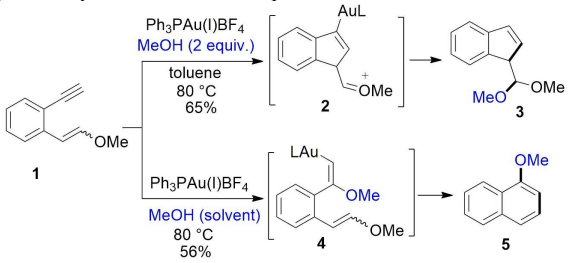
A novel strategy for the synthesis of multisubstituted naphthalenes was developed *via* a Au(I)-catalyzed alkyne alkoxylation/dienolether aromaticity-driven cascade cyclization using 1,5-enyne substrates. The functional group toleration was examined by synthesizing a series of substrates and the mechanism was also studied based on intermediates isolated through deuterium labeling experiments.

Gold-catalyzed cycloisomerization is one of the most important strategies for forming functionalized cyclic structures.[1] Specifically, cycloisomerization of 1,5-enyne substrates have been extensively studied and led to the discovery of a variety of scaffolds. Modifying the 1,5-enyne substrate and nature of Au(I) catalyst have been demonstrated to provide a variety of cyclic carbon scaffolds.[2-6] Mechanistic investigations of these cycloisomerizations are varied with regards to reactive intermediates most notably cyclopropane and gold carbene intermediates *via* either 5-*exo* or 6-*endo* manifolds,[1] which is often determined by the substitutions and electronic nature of the substrates. However, little has been known on the factors that affect reaction pathway of 1,5-enyne cycloisomerizations so far.

During the course of our studies we observed an interesting cyclization paths of a special 1,5-enyne substrate **1** with an electron-riched enolether. When the substrate was treated with Au(I) cationic species in toluene with 2 equivalents methanol as the nucleophile, activation of the alkyne by Au(I) species promotes an intramolecular alkene attack *via* a 5-*endo*-dig path[7] followed by a nucleophilic addition of methanol to the intermediate oxonium species **2** to form indene motif **3**.[8] However, if the reaction was conducted in toluene with more than 10 equivalents methanol or in methanol directly, a competitive pathway can occur, in which an intermolecular Markovnikov alkoxylation of the alkyne[9] predominated to provide a dienolether intermediate **4**, which underwent a regioselective 6-*endo*-trig cyclization to yield a naphthalene scaffold **5** exclusively after deauration[5,10] (Scheme 1). These initial findings suggested that the ratios of nucleophile methanol changed the reaction path from a normal intramolecular cyclization into an aromaticity-driven cascade process. *Herein, we describe the Au(I)-catalyzed cascade cyclization of aryl 1,5-enyne substrates to naphthalene derivatives.*



Scheme 1 Competitive cyclization paths of 1,5-enyne **1**

Table 1 shows a systematic optimization of cyclization conditions. Nonpolar solvents such as toluene and dichloroethane did not facilitate the cascade sequence and only the intramolecular 5-*endo*-dig cyclization product **3** was detected, even in the presence of 2-5 equivalents of methanol[11] (entries 1 and 2). High temperatures were required to promote the cascade cyclization in polar solvents and no cyclization product was detected at room temperature even after long times (entries 3 and 4). The influences of counterions in the catalyst were examined by combining the Ph_3PAuCl with several silver salts and AgOTf provided better yield (entries 5 and 6). Gold ligands were also screened by mixing [(IPr)AuCl] with silver salts resulting in the discovery that the combination of [(IPr)AuCl] precatalyst [IPr=1,3-bis(diisopropyl-phenyl)imidazol-2-ylidene] (5 mol %) and silver hexafluoroantimonate (5 mol %) was the optimal condition, providing the product in 77% isolated yield (entries 7 and 10). Decreasing the catalyst loading to 3 mol % reduced the yield by 10% (entry 8) while catalyst loadings of 0.5 mol % and 1 mol %, did not catalyze the cyclization, resulting in only ketone **6** derived from the corresponding aromatic ketone as the predominant product (entry 9). The precatalysts alone did not promote the cyclization at all (entries 11 and 12); $HAuCl_4$ can catalyze the cascade cyclization with a yield of 70%, which is less than the optimal conditions (entry 13). $AgSbF_6$

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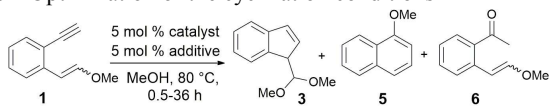
Table 1 Optimization of the cyclization conditions

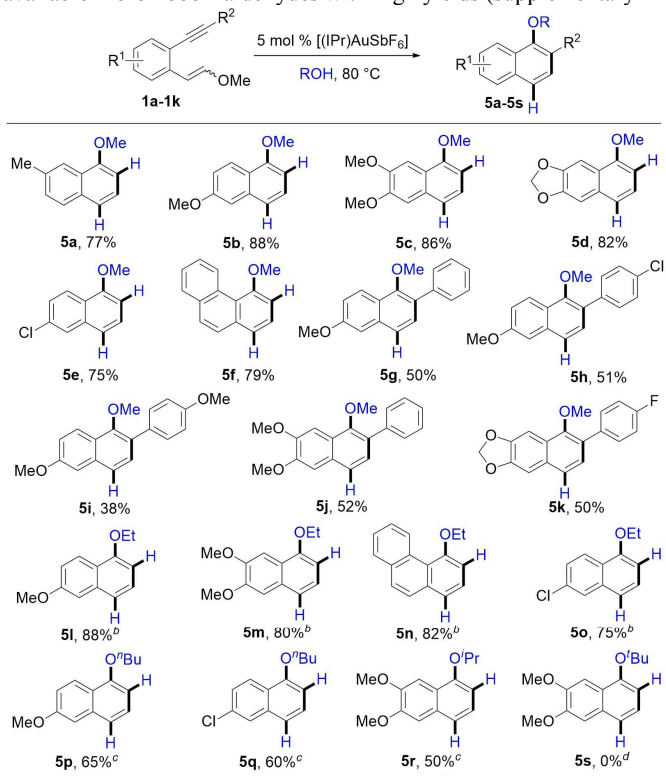


Entry	Catalyst	Additive	t [h]	Product	Yield (%)[a]
1	$Ph_3PAuNTf_2$	—	36	3	42[b]
2	$Ph_3PAuNTf_2$	—	36	3	33[c]
3	$Ph_3PAuNTf_2$	—	36	5	48
4	$Ph_3PAuNTf_2$	—	0.5	6	80[d]
5	Ph_3PAuCl	$AgSbF_6$	36	5	39
6	Ph_3PAuCl	AgOTf	36	5	63
7	[(IPr)AuCl]	$AgSbF_6$	36	5	77
8	[(IPr)AuCl]	$AgSbF_6$	36	5	68[e]
9	[(IPr)AuCl]	$AgSbF_6$	36	6	76[f]
10	[(IPr)AuCl]	AgOTf	36	5	54
11	Ph_3PAuCl	—	36	6	65
12	[(IPr)AuCl]	—	36	6	90
13	$HAuCl_4$	—	36	5	70
14	$AgSbF_6$	—	36	5	44
15	TsOH	—	36	5	42

[a] Average isolated yield of at least two runs; [b] Performed in toluene with 2 equivalents MeOH; [c] Performed in DCE with 2 equivalents MeOH; [d] Performed at room temperature; [e] Performed with 2 mol % [(IPr)AuSbF$_6$]; [f] Performed with 0.5 mol % or 1 mol % [(IPr)AuSbF$_6$].

itself and weak protic acid *p*-toluenesulfonic acid were ineffective at promoting the reaction and resulted in a complex reaction profile (entries 14 and 15).

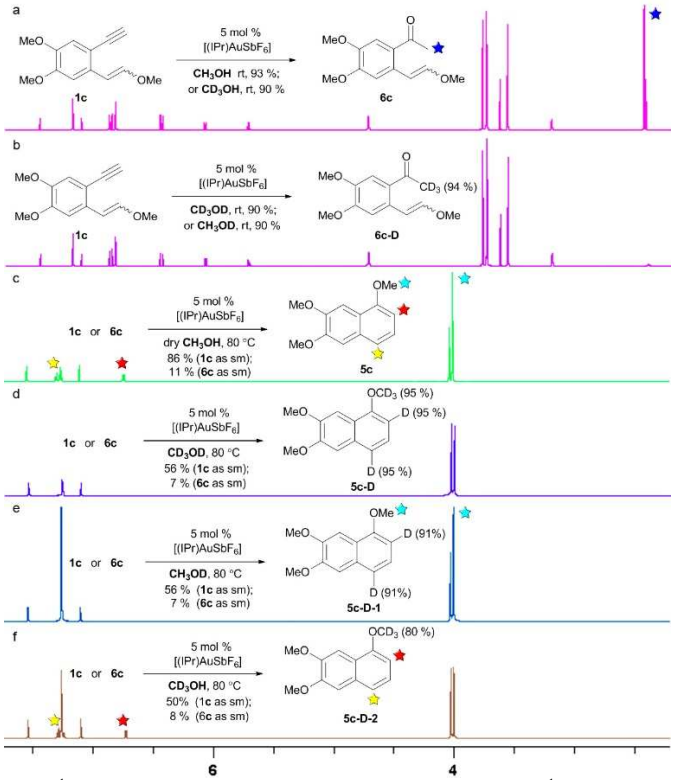
Firstly, we prepared various aryl 1,5-enyne substrates **1a-1k** *via* Sonogashira coupling and Wittig reaction from commercially available 2-bromobenzaldehydes with high yields (supplementary information). Most of the synthesized substrates gave satisfactory yields and went to completion in 30-120 h (Scheme 2). The formation of naphthalenes bearing electron-donating groups on the aryl ring proceeded in high yields (**5a-5d**, **5f**). Substrates containing an electron-withdrawing group on the phenyl ring were partially tolerated, only the chloride substituted substrate providing a clean naphthalene product while fluoride and nitro substituted substrates were unreactive under the standard conditions (**5e**). Phenyl-substituted alkynes required long reaction times and gave relatively lower yield of product compared to unsubstituted alkynes (**5g-5k**). The reaction solvent was not limited to methanol, with other nucleophilic alcohols such as ethanol, ^{n}butanol and ^{i}propanol providing good to satisfactory results (**5l-5q**), Among these solvents ^{i}propanol was not as efficient presumably due to the steric character of the secondary alcohol (**5r**). The metal precipitation at the relative high temperature will decrease the efficiency of these transformations (**5p-5s**). In addition to primary and secondary alcohol solvents: ^{t}butanol, active benzyl and allyl alcohols were tested and failed to provide the corresponding products (**5s**).



[a] Average isolated yield of at least two runs; [b] Performed at 120 °C; [c] Performed at 150 °C; [d] Performed at 150 °C and 6**c** was produced.

Scheme 2 Scope of Au(I)-catalyzed cyclization to naphthalenes[a]

To probe the mechanism we focused our studies on the isolation of reaction intermediates. There are several possible intermediates that may be formed during the course of the reaction including enolether, dimethyl ketal and ketone, which have been reported previously. [12] We tried to isolate these intermediates by treating substrate **1c** with 5 mol % [(IPr)AuSbF$_6$] in MeOH (or CD_3OH) at room temperature for 0.5 h, which resulted in the isolation of the ketone **6c**. We also performed the control experiment by using CD_3OD or CH_3OD as solvents and the deuterated product **6c-D** was obtained.[13] In order to examine whether the ketone is the real intermediate, **6c** was subjected to different deuterated methanols in the catalysis of gold(I)-species. However, only a small amount of naphthalene product could be isolated and most of the starting

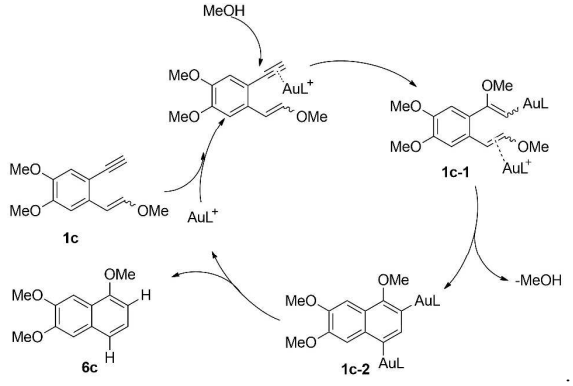


a. The ^{1}H NMR of the reaction of **1c** in CH_3OH (or CD_3OH); b. The ^{1}H NMR of the reaction of **1c** in CD_3OD (or CH_3OD); c. The ^{1}H NMR of the reaction of **1c** (or **6c**) in CH_3OH; d. The ^{1}H NMR of the reaction of **1c** (or **6c**) in CD_3OD; e. The ^{1}H NMR of the reaction of **1c** (or **6c**) in CH_3OD; f. The ^{1}H NMR of the reaction of **1c** (or **6c**) in CD_3OH.

Scheme 3 Deuterium labeling experiments

material was transformed to unidentifiable compounds, which suggests that the ketone is only the stable product at room temperature (Scheme 3, a-f), but not an active precursor at high temperature and the naphthalene product should be formed preferentially from other intermediates. Similar to the mechanism of diyne cyclization and the electron-riched feature of the enolether, [14] a dual activation process is reasonable. Activation of the alkyne promoted an alkoxylation by the alcohol, the very active enolether species will cyclize with the other electron-riched enolether activated by cationic gold species at high temperature. If the hypothesis is correct, we may detect the corresponding deuterium in the products by conducting deuterated labeling experiments. Three deuterated methanols were then tested in the reaction and the deuterium occurred in the products as expected, which supports our hypothesis very well. It should be mentioned that the water contained in the deuterated methaols reduced the yields of these three reactions compared with that under the standard conditions (Scheme 3, c-f).

On the basis of our experimental findings and by analogy with mechanisms proposed for related reactions,[14] a plausible mechanism is outlined in Scheme 4. First, the reaction is initiated by electrophilic activation of the alkyne to promote an intermolecular alkoxylation of the alkyne substrate **1c** by methanol to form the dienolether metal species **1c-1**. Then the electron-riched enolether was coordinated with the cationic gold catalyst to induce the second cyclization with tautomerism of oxonium and elimination of methanol spontaneously[15] to provide the naphthalene **6c** after deauration of the intermediate **1c-2**.



Scheme 4 Proposed mechanism of the cascade reaction

In summary, we have developed a novel approach to the construction of naphthalene derivatives using [(NHC)AuI]-based catalytic system and cascade cyclization strategy, which provides a unique example of the nucleophile ratios on changing pathways of Au(I)-catalyzed cyclization. It allows the preparation of a variety of substituted naphthalene derivatives from simple aromatic 1,5-enyne substrates. In addition to the development of novel methodology the mechanism of this cascade reaction has also been studied based on intermediates isolated through deuterium labeling experiments.

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Notes and references

1 (*a*) L. M. Zhang, J. W. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271; (*b*) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem. Int. Ed.*, 2006, **45**, 7896; (*c*) D. J. Gorin, B. D. Sherry and F. D. Toste,*Chem.Rev.*, 2008, **108**, 3351; (*d*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (*e*) A. Fürstner, *Chem. Soc. Rev.*, 2009, **38**, 3208; (*f*) M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448; (*g*) A. S. K. Hashmi and F. D. Toste, Modern Gold Catalyzed Synthesis, Wiley-VCH: Weinheim, 2012.

2 (*a*) A. S. K. Hashmi, T. M. Frost and J. W. Bats, *J. Am. Chem. Soc.* 2000, **122**, 11553; (*b*) V. Mamane, T. Gress, H. Krause and A. Fürstner, *J. Am. Chem. Soc.*, 2004, **126**, 8654; (*c*) M. R. Luzung, J. P. Markham and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 10858; (*d*) A. S. K. Hashmi, *Pure Appl. Chem.* 2010, **82**, 1517.

3 (*a*) L. M. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 11806; (*b*) J. Sun, M. P. Conley, L. M. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2006, **128**, 9705; (*c*) S. Z. Wang and L. M. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 14274.

4 F. Gagosz, *Org. Lett.*, 2005, **7**, 4129.

5 (*a*) T. Shibata, Y. Ueno and K. Kanda, *Synlett.*, 2006, 411; (*b*) D. Vasu, H. H. Hung, S. Bhunia, S. A. Gawade, A. Das and R. S. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 6911.

6 L. M. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2005, **127**, 6962.

7 (*a*) A. Martínez, P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez and R. Sanz, *Angew. Chem. Int. Ed.*, 2010, **49**, 4633; (*b*) P. García-García, M. A. Rashid, A. M. Sanjuán, M. A. Fernández-Rodríguez and R. Sanz, *Org. Lett.*, 2012, **14**, 4778.

8 (*a*) Y. Obora, M. Ki-mura, M. Tokunaga and Y. Tsuji, *Chem. Commun.* 2005, **21**, 901; (*b*) D. L. Usanov and H. Yamamoto, *Org. Lett.*, 2012, **14**, 414.

9 (*a*) R. Casado, M. Contel, M. Laguna, P. Romero and S. Sanz, *J. Am. Chem. Soc.*, 2003, **125**, 11925; (*b*) N. Marion, R. S. Ramón, S. P. Nolan, *J. Am. Chem. Soc.*, 2009, **131**, 448.

10 For recent examples of Au(I)-catalyzed naphthalene synthesis, see ref. 8 and (*a*) A. S. Dudnik, T. Schwier and V. Gevorgyan, *Org. Lett.*, 2008, **10**, 1465; (*b*) C. R. Solorio-Alvarado and A. M. Echavarren, *J. Am. Chem. Soc.* 2010, **132**, 11881; (*c*) W. Kong, C. Fu and S. Ma, *Eur. J. Org. Chem.*, 2010, 6545; (*d*) A. R. Jagdale, J. H. Park and S. W. Youn, *J. Org. Chem.*, 2011, **76**, 7204; (*e*) S. Wang, L. Zhang, X. Ding, Y. Zhou, J. Wang, H. Jiang and H. Liu, *J. Org. Chem.*, 2011, **76**, 4514; (*f*) X. Song, X. Xia, Q. Song, F. Yang, Y. Li, X. Liu and Y. Liang, *Org. Lett.*, 2012, **14**, 3344; (*g*) A. S. K. Hashmi, I. Braun, M. Rudolph and F. Rominger *Organometallics* 2012, **31**, 644.

11 A. K. Buzas, F. M. Istrate and F. Gagosz, *Angew. Chem. Int. Ed.*, 2007, **46**, 1141.

12 (*a*) J. H. Teles, S. Brode and M. Chabanas, *Angew. Chem. Int. Ed.*1998, **37**, 1415; (*b*) A. Leyva and A. Corma, *J. Org. Chem.*, 2009, **74**, 2067; (*c*) A. Corma, V. R. Ruiz, A. Leyva-Prez, M. J. Sabater, *Adv. Synth. Catal.* 2010, **352**, 1701; (*d*) T. De Haro and C. Nevado, *Adv. Synth. Catal.* 2010, **352**, 2767; (*e*) P. Nun, R. S. Ramón, S. Gaillard, S. P. Nolan, *J. Organomet. Chem.* 2011, **696**, 7.

13 A. S. K. Hashmi, S. Schäfer, M. Wölfle, C. D. Gil, P. Fischer, A. Laguna, M. C. Blanco and M. C. Gimeno *Angew. Chem. Int. Ed.* 2007, **46**, 6184.

14 K. Graf, P. D. Hindenberg,Y. Tokimizu, S. Naoe, M. Rudolph, F. Rominger, H. Ohno and A. S. K. Hashmi, *ChemCatChem.* 2014, **6**, 199.

15 Examples of the elimination of methanol and silanols for the formation of an aromatic systems, see (*a*) M. G. Christiane and B. Louis *Org. Lett.* 2006, **8**, 5905; (*b*) A. S. K. Hashmi and M. Wölfle *Tetrahedron*

2009, **65**, 9021; (*c*) A. S. K. Hashmi, W. Yang and F. Rominger *Angew. Chem. Int. Ed.* 2011, **50**, 5762.

