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Gold-catalyzed intermolecular oxidation of *o*-alkynylbiaryls: an easy and practical access to functionalized fluorenes†

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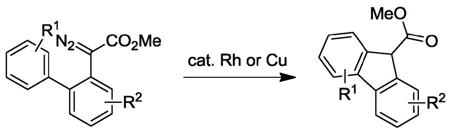
A novel gold-catalyzed intermolecular oxidation of *o*-alkynylbiaryls has been developed. A variety of functionalized fluorenes are readily accessed by utilizing this non-diazo approach, thus providing a viable alternative to synthetically useful fluorenes.

Among the polycyclic aromatic hydrocarbons (PAH), fluorenes are core structures employed in a variety of practical applications in materials chemistry as dyes and optical brightening agents.[1] In addition, fluorenyl functions have also played important roles in the field of organic synthesis, mainly as unique protecting groups in peptide synthesis.[2] Somewhat surprisingly, however, only a few preparative methods have been reported.[3] Therefore, the development of novel strategies, especially those based on assembling structures directly from readily available and easily diversified building blocks, is highly desirable.

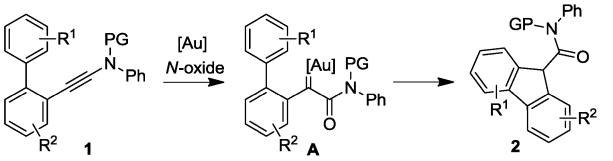
In recent years, significant progress has been made in the gold-catalyzed intermolecular alkyne oxidation to make alkynes as equivalents of α-diazo ketones.[4–6] For example, this non-diazo approach offers a viable alternative for the transition metal-catalyzed intramolecular aromatic carbenoid insertion of diazo compounds.[7,8] In this regard, L. Zhang and co-workers reported an elegant protocol for the synthesis of variously substituted chroman-3-ones involving a gold-catalyzed intermolecular oxidation of propargyl aryl ethers.[7a] Later, J. Zhang and co-workers realized a gold-catalyzed oxidation/C–H functionalization reaction of electron-deficient *N*-arylpropiolamides for the construction of 3-acyloxindoles.[7b] The group of Gagosz disclosed a gold-catalyzed oxidative cyclization of propynyl arenes, allowing rapid and practical access to a variety of functionalized indan-2-ones.[7c] Recently, Li and co-workers reported that the preparation of oxindoles could be achieved *via* a gold-catalyzed intermolecular oxidation of *N*-arylynamides.[7d] Despite these significant achievements, these oxidative cyclizations, presumably involving the intramolecular trapping of the α-oxo gold carbenoids by the aryl ring, are limited to terminal alkynes or electron-deficient internal alkynes, as electron-rich internal alkynes often suffer the competing overoxidation of the carbene center by the very oxidant.[9,7d] Recently, Chang and co-workers described a general route for the synthesis of fluorenes that involves a rhodium- or copper-catalyzed intramolecular aromatic carbenoid insertion of biaryldiazoacetates (Scheme 1a).[10] Inspired by these studies and our recent findings on the gold-catalyzed synthesis of polycyclic aromatic hydrocarbons,[11] we envisioned that these synthetically useful fluorene skeletons might be accessed directly from *o*-alkynylbiaryls through a gold-catalyzed intermolecular alkyne oxidation (Scheme 1b). In this communication, we describe herein the realization of such a gold-catalyzed oxidative protocol, providing a flexible and alternative way for the preparation of versatile fluorene derivatives.

Ynamide **1a** was chosen as a model substrate for our initial study and some of the results are outlined in Table 1.[12] The screening of different gold catalysts was first performed (Table 1, entries 1–8). In most cases, diketone compound **3a** was detected as a major product (Table 1, entries 1–6). To our delight, the use of the bulky gold catalysts could dramatically suppress the undesired

(a) Rh- or Cu-catalyzed aromatic carbenoid insertion of biaryldiazoacetates (Chang)



(b) Au-catalyzed intermolecular oxidation of *o*-alkynylbiaryls (this work)



Scheme 1 Formation of functionalized fluorenes through gold-catalyzed intermolecular alkyne oxidation.

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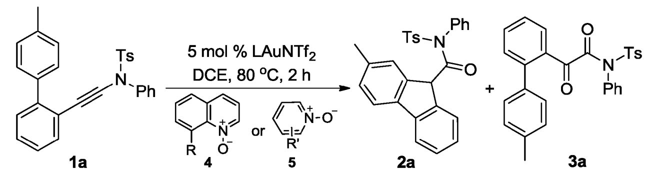
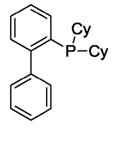
† Electronic supplementary information (ESI) available. CCDC 1015243. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc05115g

Table 1 Optimization of reaction conditions[a]

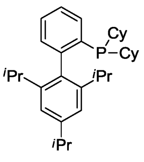


Entry	L	Oxidant (R)	Yield[b] (%)	
			2a	**3a**
1	Et_3P	**4a** (Et)	<5	>95
2	Ipr	**4a** (Et)	21	65
3	PPh_3	**4a** (Et)	<5	>95
4	$P(4\text{-}CF_3C_6H_4)_3$	**4a** (Et)	<5	>95
5	Cy-JohnPhos	**4a** (Et)	<5	>95
6	Xphos	**4a** (Et)	18	75
7	BrettPhos	**4a** (Et)	78	<2
8	$Me_4{}^tBuXPhos$	**4a** (Et)	62	<2
9	BrettPhos	**4b** (Me)	50	25
10	BrettPhos	**4c** (^{i}Pr)	60	<2
11	BrettPhos	**5a** (R′ = 2-Br)	<5[c]	12
12	BrettPhos	**5b** (R′ = 2,6-Br_2)	<5[d]	10
13	BrettPhos	**5c** (R′ = 3,5-Cl_2)	30	14
14[e]	BrettPhos	**4a** (Et)	47	<2
15[f]	BrettPhos	**4a** (Et)	62	<2
16[g]	BrettPhos	—	0	0

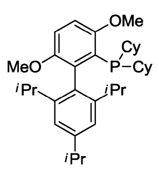
[a] Reaction conditions: [**1a**] = 0.05 M, oxidant (2.0 equiv.); DCE: 1,2-dichloroethane. [b] Estimated by ^1H NMR using diethyl phthalate as the internal reference. [c] 70% of **1a** remained unreacted. [d] 75% of **1a** remained unreacted. [e] Reaction was run in H_2O. [f] Reaction was run in H_2O–DCE = 1 : 1. [g] The corresponding phenanthrene **3a**′ was obtained in 85% yield (see ESI for details).



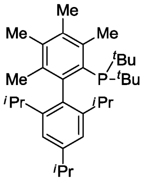
Cy-JohnPhos



XPhos

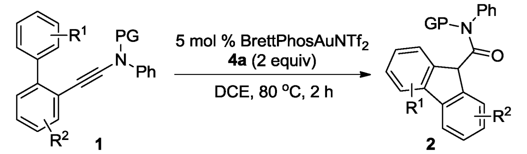


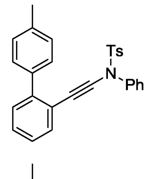
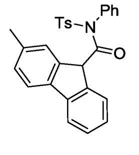
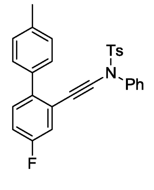
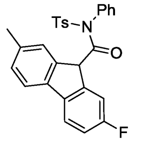
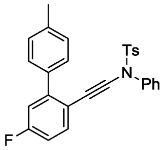
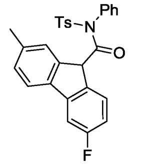
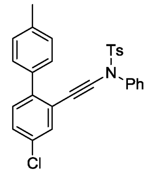
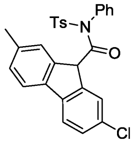
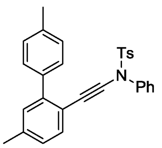
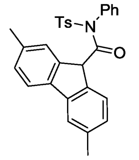
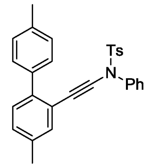
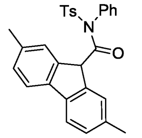
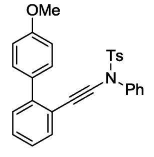
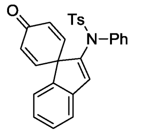
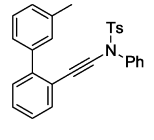
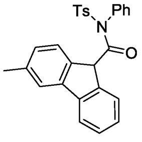
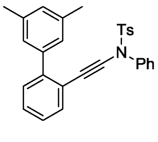
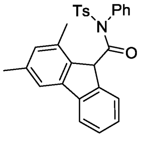
BrettPhos



$Me_4{}^tBuXPhos$

Table 2 Reaction scope study[a]

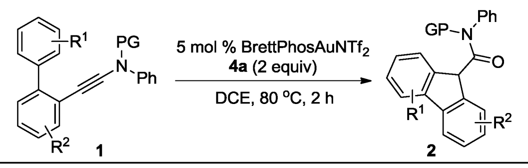


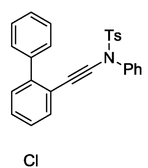
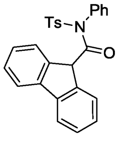
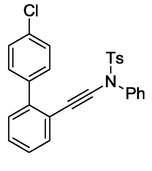
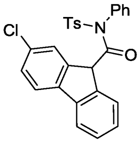
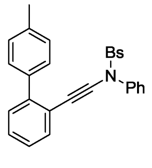
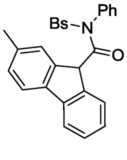
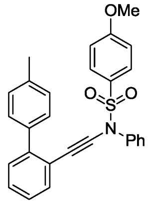
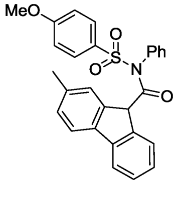
Entry	Substrate	1	Product	2	Yield (%)
1		**1a**		**2a**	77
2		**1b**		**2b**	75
3		**1c**		**2c**	56
4		**1d**		**2d**	67
5		**1e**		**2e**	58
6		**1f**		**2f**	64
7		**1g**		**2g**′	86
8[b]		**1h**		**2h**	72
9		**1i**		**2i**	88

overoxidation (Table 1, entries 7 and 8) and the desired fluorene **2a** was obtained in 78% yield when using $BrettPhosAuNTf_2$ as the gold catalyst (Table 1, entry 7). Here, the bulky ligand likely prevents the overoxidation of the carbene center by the very oxidant *via* intermolecular reactions as the carbene center is sterically shielded.[7a] Attempts to improve the yield of this reaction by the screening of other quinoline *N*-oxides and pyridine *N*-oxides were unsuccessful (Table 1, entries 9–13). As water could assist some gold-catalyzed oxidative reactions,[6a] water was used as the solvent or mixture solvent to further improve this reaction but resulted in a decrease of the yield (Table 1, entries 14 and 15). Of note, without a gold catalyst, the reaction failed to give even a trace of fluorene **2a**, and $PtCl_2$ and $AgNTf_2$ could not catalyze this reaction. Finally, it should be specially mentioned that the corresponding phenanthrene **3a**′ was obtained in 85% yield without the addition of *N*-oxide (Table 1, entry 16), indicating that the gold-catalyzed 6-*endo-dig* cycloisomerization can be suppressed by the oxidant.[13]

With the optimized reaction conditions in hand (Table 1, entry 7), we subsequently investigated the substrate scope of this oxidative cyclization. Different functional groups such as

Table 2 (*continued*)



Entry	Substrate	1	Product	2	Yield (%)
10		**1j**		**2j**	54
11		**1k**		**2k**	<10[c]
12		**1l**		**2l**	<10[c]
13		**1m**		**2m**	71

[a] Reactions run in vials; [**1**] = 0.05 M; isolated yields are reported. [b] **2h**/**2h′**= 3/1, determined by ^{1}H NMR integration of the crude mixture. [c] Estimated by ^{1}H NMR using diethyl phthalate as the internal reference.

fluoro, chloro and methyl on the 4′-methyl-1,1′-biaryl ring were tolerated in this mild transformation, providing the corresponding fluorene derivatives **2b–2f** in moderate to good yields (Table 2, entries 2–6). Notably, the reaction of methoxy-substituted ynamide **1g** only afforded spiro compound **2g′**[14] through a gold-catalyzed 5-*endo-dig* cyclization and no fluorene formation could be observed (Table 2, entry 7). When the substrate bearing methyl substituent at the *meta*-position (**1h**) was employed, a 3/1 regioselectivity and 72% combined yield of **2h** and **2h′** could be achieved (Table 2, entry 8). In the case of more electron-rich 3′,5′-dimethyl-1,1′-biphenyl **1i**, the reaction could give the desired product **2i** in 88% yield (Table 2, entry 9). In addition, ynamide **1j** was also a suitable substrate for this oxidative cyclization to furnish the corresponding **2j** in a serviceable yield (Table 2, entry 10) while no reactivity was observed with the electron-deficient ynamide **1k** (Table 2, entry 11). In spite of this limitation, the electron-deficient fluorene can be obtained from another aryl ring of the biphenyl due to the symmetric structure of the fluorene compound (Table 2, entries 2–4). Subsequent investigation of *N*-protecting groups demonstrated that Bs (*p*-bromobenzenesulfonyl) protected substrate **1l** did not undergo this oxidative cyclization (Table 2, entry 12), but for MBS (*p*-methoxybenzenesulfonyl) protected substrate **1m**, the reaction could lead to a respectable 71% yield (Table 2, entry 13).

In summary, we have developed a gold-catalyzed intermolecular oxidation of *o*-alkynylbiaryls, allowing the convenient synthesis of functionalized fluorenes in generally moderate to good yields. In comparing our method with literature protocols, this non-diazo approach offers a convenient and viable alternative for the preparation of synthetically useful fluorenes. Other notable features of this method include widespread availability of the substrates, a simple procedure, and mild reaction conditions and, in particular, no need to exclude moisture or air ("open flask"). Further studies on the mechanism and synthetic application of the current reaction are ongoing in our group.

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Notes and references

1 For selected recent examples, see: (*a*) J. L. Zafra, J. Casado, I. I. Per-epichka, M. R. Bryce, F. J. Ramirez and J. T. L. Navarrete, *J. Chem. Phys.*, 2011, **134**, 044520; (*b*) M. Zhu, T. Ye, C.-G. Li, X. Cao, C. Zhong, D. Ma, J. Qin and C. Yang, *J. Phys. Chem. C*, 2011, **115**, 17965; (*c*) K.-Y. Pu, R. Zhan and B. Liu, *Chem. Commun.*, 2010, 1470; (*d*) S. M. Aly, C.-L. Ho, W.-Y. Wong, D. Fortin and P. D. Harvey, *Macromolecules*, 2009, **42**, 6902; (*e*) H.-C. Yeh, C.-H. Chien, P.-I. Shih, M.-C. Yuan and C.-F. Shu, *Macromolecules*, 2008, **41**, 3801; (*f*) Y. Mo, X. Jiang and D. Cao, *Org. Lett.*, 2007, **9**, 4371.

2 For selected examples, see: (*a*) O. Bassas, J. Huuskonen, K. Rissanen and A. M. P. Koskinen, *Eur. J. Org. Chem.*, 2009, 1340; (*b*) M. R. Paleo, N. Aurrecoechea, K.-Y. Jung and H. Rapoport, *J. Org. Chem.*, 2003, **68**, 130; (*c*) Y. Ding, J. Wang, K. A. Abboud, Y. Xu, W. R. Dolbier Jr. and N. G. J. Richards, *J. Org. Chem.*, 2001, **66**, 6381; (*d*) K. D. Stigers, M. R. Koutroulis, D. M. Chung and J. S. Nowick, *J. Org. Chem.*, 2000, **65**, 3858; (*e*) L. A. Carpino, *J. Org. Chem.*, 1980, **45**, 4250; (*f*) L. A. Carpino and G. Y. Han, *J. Am. Chem. Soc.*, 1970, **92**, 5748.

3 For recent examples, see: (*a*) M. Itoh, K. Hirano, T. Satoh, Y. Shibata, K. Tanaka and M. Miura, *J. Org. Chem.*, 2013, **78**, 1365; (*b*) K. Morimoto, M. Itoh, K. Hirano, T. Satoh, Y. Shibata, K. Tanaka and M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 5359; (*c*) X.-C. Wang, R.-L. Yan, M.-J. Zhong and Y.-M. Liang, *J. Org. Chem.*, 2012, **77**, 2064; (*d*) T.-P. Liu, C.-H. Xing and Q.-S. Hu, *Angew. Chem., Int. Ed.*, 2010, **49**, 2909; (*e*) F.-L. Sun, M. Zeng, Q. Gu and S.-L. You, *Chem. – Eur. J.*, 2009, **15**, 8709; (*f*) D. J. Gorin, I. D. G. Watson and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 3736; (*g*) K. Fuchibe and T. Akiyama, *J. Am. Chem. Soc.*, 2006, **128**, 1434.

4 For reviews, see: (*a*) H.-S. Yeom and S. Shin, *Acc. Chem. Res.*, 2014, **47**, 966; (*b*) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877; (*c*) J. Xiao and X. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 7226.

5 For recent examples, see: (*a*) S. N. Karad and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 5444; (*b*) T. Wang, S. Shi, M. M. Hansmann, E. Rettenmeier, M. Rudolph and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2014, **53**, 3715; (*c*) M. D. Santos and P. W. Davies, *Chem. Commun.*, 2014, 6001; (*d*) J. Li, K. Ji, R. Zheng, J. Nelson and L. Zhang, *Chem. Commun.*, 2014, 4130; (*e*) G. Wu, R. Zheng, J. Nelson and L. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 1229; (*f*) K. Ji and L. Zhang, *Org. Chem. Front.*, 2014, **1**, 34; (*g*) P. Nösel, L. N. dos Santos Comprido, T. Lauterbach, M. Rudolph, F. Rominger and A. S. K. Hashmi, *J. Am. Chem. Soc.*, 2013, **135**, 15662; (*h*) L. Wang, X. Xie and Y. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13302; (*i*) S. K. Pawar, C.-D. Wang, S. Bhunia, A. M. Jadhav and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 7559; (*j*) K. Ji, Y. Zhao and L. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 6508; (*k*) S. Ghorpade, M.-D. Su and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 4229; (*l*) J. Fu, H. Shang, Z. Wang, L. Chang, W. Shao, Z. Yang and Y. Tang, *Angew. Chem., Int. Ed.*, 2013, **52**, 4198; (*m*) D. B. Huple, S. Ghorpade and R.-S. Liu, *Chem. – Eur. J.*, 2013, **19**, 12965; (*n*) S. Shi, T. Wang, W. Yang, M. Rudolph and A. S. K. Hashmi, *Chem. – Eur. J.*, 2013, **19**, 6576;

(*o*) R. K. Kawade and R.-S. Liu, *Org. Lett.*, 2013, **15**, 4094; (*p*) H.-H. Hung, Y.-C. Liao and R.-S. Liu, *J. Org. Chem.*, 2013, **78**, 7970.

6 (*a*) L. Li, C. Shu, B. Zhou, Y.-F. Yu, X.-Y. Xiao and L.-W. Ye, *Chem. Sci.*, 2014, **5**, DOI: 10.1039/C4SC00983E; (*b*) C. Shu, L. Li, X.-Y. Xiao, Y.-F. Yu, Y.-F. Ping, J.-M. Zhou and L.-W. Ye, *Chem. Commun.*, 2014, 8689; (*c*) C. Shu, L. Li, Y.-F. Yu, S. Jiang and L.-W. Ye, *Chem. Commun.*, 2014, 2522.

7 (*a*) Y. Wang, K. Ji, S. Lan and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 1915; (*b*) D. Qian and J. Zhang, *Chem. Commun.*, 2012, 7082; (*c*) G. Henrion, T. E. J. Chava, X. Le Goff and F. Gagosz, *Angew. Chem., Int. Ed.*, 2013, **52**, 6277; (*d*) L.-Q. Yang, K.-B. Wang and C.-Y. Li, *Eur. J. Org. Chem.*, 2013, 2775.

8 For a metal-free oxidative cyclization of alkynyl aryl ethers to benzofuranones, see: K. Graf, C. L. Rühl, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2013, **52**, 12727.

9 (*a*) K.-B. Wang, R.-Q. Ran, S.-D. Xiu and C.-Y. Li, *Org. Lett.*, 2013, **15**, 2374; (*b*) R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.*, 2012, 7200; (*c*) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15372; (*d*) D. Vasu, H.-H. Hung, S. hunia, S. A. Gawade, A. Das and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 6911; (*e*) C.-F. Xu, M. Xu, Y.-X. Jia and C.-Y. Li, *Org. Lett.*, 2011, **13**, 1556; (*f*) C.-W. Li, K. Pati, G.-Y. Lin, S. M. A. Sohel, H.-H. Hung and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2010, **49**, 9891.

10 J. Kim, Y. Ohk, S. H. Park, Y. Jung and S. Chang, *Chem. – Asian J.*, 2011, **6**, 2040.

11 (*a*) C. Shu, L. Li, C.-B. Chen, H.-C. Shen and L.-W. Ye, *Chem. – Asian J.*, 2014, **9**, 1525; (*b*) C. Shu, C.-B. Chen, W.-X. Chen and L.-W. Ye, *Org. Lett.*, 2013, **15**, 5542.

12 For recent reviews on ynamide reactivity, see: (*a*) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski and R. P. Hsung, *Acc. Chem. Res.*, 2014, **47**, 560; (*b*) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064; (*c*) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840.

13 For the synthesis of phenanthrenes *via* transition metal-catalyzed 6-*endo* cyclization of *o*-alkynylbiaryls, see: (*a*) K. Komeyama, R. Igawa and K. Takaki, *Chem. Commun.*, 2010, 1748; (*b*) A. Fürstner and J. W. J. Kennedy, *Chem. – Eur. J.*, 2006, **12**, 7398; (*c*) V. Mamane, P. Hannen and A. Fürstner, *Chem. – Eur. J.*, 2004, **10**, 4556; (*d*) A. Fürstner and V. Mamane, *J. Org. Chem.*, 2002, **67**, 6264.

14 CCDC 1015243 (**2g′**).