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Synthesis of Carbazoles based on Gold-Copper Tandem Catalysis

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An efficient synthetic method for carbazoles has been developed employing diazo anilinoalkynes as substrates. Sequential activation of the orthogonal functional groups embedded in diazo anilinoalkyne substrates by tandem gold-copper catalysis leads to the formation of highly substituted carbazoles. Substrate scope reveals a broad tolerability toward the substitution on aryl groups.

Owing to their various useful properties including their intriguing electrical and optical properties, there has been a great deal of interest in carbazoles.[1] Furthermore, a large number of carbazole-containing compounds are under intense investigation for their pharmacological activities including antitumor, antibiotic, antioxidative, antiviral, and antimalarial.[2] For example, staurosporine is an ATP-competitive kinase inhibitor with anti-fungal and anti-hypertensive activity. Clausenawalline A possesses cytotoxic activity against human cancer cell lines. Claulansine A exhibits anti-inflammatory and antitumor properties against various human cancer cell lines (Figure 1).[3]

Therefore, the increasing demand for carbazoles necessitates the development of efficient synthetic methods. Broadly, approaches for carbazole synthesis have been reported by employing substituted indoles and diarylamines/ biarylamines as substrates: i) Diels-Alder reaction,[4] electrocyclization,[5] and benzannulation[6] of substituted indoles, ii) dehydrogenative cyclization[7] of diarylamines, iii) nitrene insertion[8] and N-arylation[9] of biarylamines (Scheme 1).

Tandem catalysis offers many advantages including atom economy, environmental impact, issues with isolation of unstable intermediates. Nevertheless, tandem catalysis presents significant challenges including compatibility of catalysts and solvents involved in individual catalytic cycles.[10] While the reported synthetic methods for carbazoles typically require pre-assembled bicyclic substrates, we aimed to develop a method that enables bis-annulation from monocyclic substrates in a single operation. To this end, our approach has been carefully designed such that tandem gold-copper dual catalysis sequentially activates orthogonal functional groups by respective catalysts to allow direct formation of products with higher complexity obviating the isolation of intermediates. Thus, two consecutive annulations employing diazo anilinoalkynes as substrates leads to the formation of a carbazole scaffold.

The ability of gold complexes for activation of C-C multiple bonds has received a great deal of interest in the past decade.[11] Addition of various heteroatom nucleophiles onto alkynes activated by gold complexes has proven to be a powerful method for heterocycle synthesis.[12] Given their importance, many different approaches for the synthesis of indoles have been developed including gold-catalyzed 5-endo cyclization of anilinoalkynes.[13] Meanwhile, the reactivity of carbenes for heterocycle synthesis has been extensively exploited by us[14] and others.[15] While there are a few reports

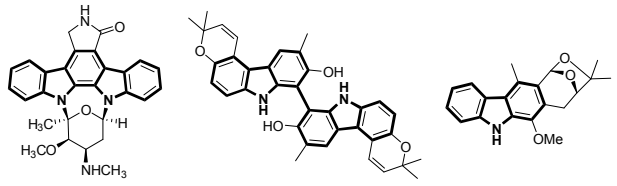
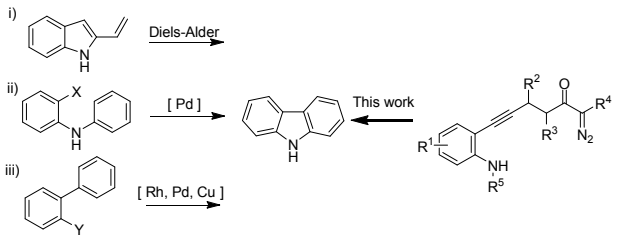


Figure 1. Carbazole alkaloids



Scheme 1. Synthetic Approaches to the Synthesis of Carbazoles

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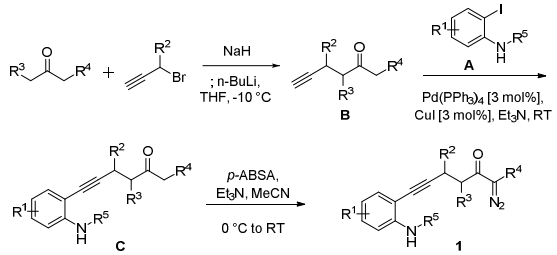
for gold-catalyzed synthesis of carbazoles from indoles,[16] to the best of our knowledge, no literature examples have been reported with sequential activation of multi-functional groups with orthogonal reactivity by tandem gold-copper catalysis (Scheme 1). With our continued interest in heterocycle synthesis, we describe herein a new synthesis of carbazoles that allows direct conversion of readily accessible simple acyclic substrates into carbazoles with obviating the necessity for isolation of intermediates, in contrast to the previous methods, which involve stepwise synthesis.

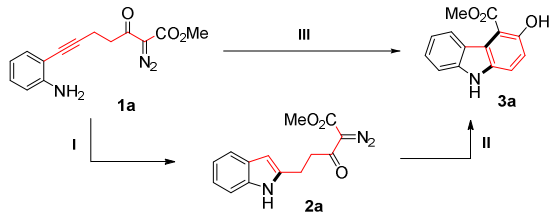
We hypothesized that gold-catalyzed cycloisomerization of diazo anilinoalkynes would provide indoles with a pendant diazo group, which serves as a latent functionality. In the second cycle, copper-catalyzed activation of the diazo group should form a copper carbene complex, and subsequent electrophilic substitution with indole would provide carbazole after oxidation of dihydrocarbazole. In this approach, the following few points are worthy of attention: 1) catalyst-dependent selective activation of anilinoalkynes and diazo groups. 2) chemoselective electrophilic substitution of carbenes towards indoles over N-H insertion. We have established a highly efficient synthetic route for the requisite substrates (Scheme 2). Sonogashira coupling of iodoanilines **A** with keto alkynes **B** prepared by alkylation of ketones with propargyl bromide provided anilinoalkynes **C**, which was transformed into diazo anilinoalkynes **1** by diazo transfer.

As an initial attempt, we began by screening various catalysts and reaction conditions on diazo anilinoalkyne **1a** as a substrate (Table 1, **I**). A survey of various dirhodium catalysts on diazo anilinoalkyne **1a** gave mostly disappointing results with complex mixtures, among which only $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ afforded minute quantities of carbazole **3a** in 19% and 10%, respectively (entries 1 and 4), via spontaneous oxidation of dihydrocarbazole.[17,18] The use of $Cu(hfacac)_2$ gave a similar result (20%, entry 6). With the array of reported reactions on gold carbene complexes, we also examined gold catalysts bearing various ligands. An initial attempt with $Au(PPh_3)OTf$ under reflux conditions furnished carbazole **3a** in 20%, whereas **2a** was obtained in 91% when the reaction was performed at RT (entries 7 and 8), despite the potential deactivation of the cationic gold complexes by the free amine in **1a**. While mixtures of **2a** and **3a** were obtained with $Au[P(t\text{-}Bu)_3]OTf$ and Au(SIPr)OTf, the use of $Au(JohnPhos)SbF_6$ and Au(JohnPhos)OTf provided **3a** in 46% and 62%, respectively (entries 10 - 13). On the other hand, the efficiency decreased when $PtCl_2$ was employed as a catalyst (entry 14). At this



Scheme 2. Preparation of Substrates

Table 1. Optimization of Carbazole Formation[a]



	Entry	Catalyst[b] (mol%)	Oxidant	T (°C)	Yield [%] 2a	Yield [%] 3a
I	1	$Rh_2(OAc)_4$ (2)	--	90	0	19
	2	$Rh_2(hfb)_4$ (2)	--	90	0	0
	3	$Rh_2(oct)_2$ (2)	--	90	0	0
	4	$Rh_2(esp)_2$ (2)	--	90	0	10
	5	$Rh_2(tpa)_4$ (2)	--	90	0	0
	6	$Cu(hfacac)_2$ (4)	--	90	0	20
	7	$Au(PPh_3)OTf$ (5)	MnO_2	90	0	20
	8	**$Au(PPh_3)OTf$ (2)**	**--**	**RT**	**91**	**0**
	9	$Au(PPh_3)NTf_2$ (2)	--	RT	85	0
	10[c]	$Au[P(t\text{-}Bu)_3]OTf$ (2)	MnO_2	RT; 90; RT	26	17
	11[c]	Au(SIPr)OTf (2)	MnO_2	RT; 90; RT	7	6
	12[c]	$Au(JohnPhos)SbF_6$ (2)	MnO_2	RT; 90; RT	0	46
	13[c]	Au(JohnPhos)OTf (2)	MnO_2	RT; 90; RT	0	62
	14	$PtCl_2$ (5)	MnO_2	50; 90; RT	0	31
II	15[d]	$Rh_2(OAc)_4$ (2)	--	RT	0	35
	16	CuOTf (4)	MnO_2	90	0	45
	17	$Cu(OTf)_2$ (4)	MnO_2	90	0	55
	18	$Cu(hfacac)_2$ (4)	MnO_2	90	0	76
	19	**$Cu(hfacac)_2$ (4)**	**MnO_2**	**90; RT**	0	**90**
III	20	$Au(PPh_3)OTf$ (2) $Cu(hfacac)_2$ (4)	MnO_2	RT; 90; RT	0	72
	21[c]	**$Au(PPh_3)OTf$ (2) $Cu(hfacac)_2$ (4)**	**MnO_2**	**RT; 90; RT**	0	**82**
	22	AgOTf (2) $Cu(hfacac)_2$ (4)	--	60	0	0

[a] Reaction conditions : DCE (0.02 M), MnO_2 addition at RT, All reactions were performed under N_2; [b] hfb = heptafluorobutyrate, oct = octanoate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, tpa = triphenyl acetate, hfacac = hexafluoroacetylacetonate, NTf_2 = bis(trifluoromethanesulfonyl)imide, OTf = trifluoromethanesulfonate, JohnPhos = 2-(di-t-butylphosphino)-1,1'-biphenyl, SIPr = 1,3-bis[2,6-bis(1-methylethyl)phenyl]-4,5-dihydroimidazol-2-ylidene; [c] AgCl removed by filtration; [d] N-H insertion product was obtained in 15% yield. See supporting information.

juncture, we turned our attention to taking advantage of indole **2a** as an intermediate and examined the feasibility of cyclization into carbazole **3a** by the generation of metal carbene complexes (Table 1, **II**). Whereas a mixture of carbazole **3a** (35%) and N-H insertion product (15%) was obtained with the use of $Rh_2(OAc)_4$ (entry 15, see the supporting information), copper salts proved to display better conversion with $Cu(hfacac)_2$ delivering **3a** in 76% yield. Furthermore, we found it beneficial for yields to perform the oxidation with MnO_2 at RT (entry 19). With these results in hand, we set out to investigate tandem catalysis by combining the two catalytic cycles, indole formation and subsequent cyclization of carbene (Table 1, **III**). Gratifyingly, the combination of $Au(PPh_3)OTf$ and $Cu(hfacac)_2$ gave **3a** in 72% yield (entry 20). Further improvement in yield was achieved

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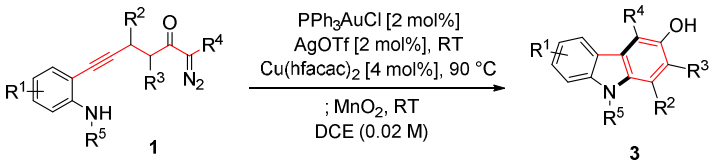
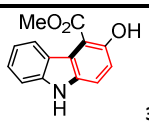
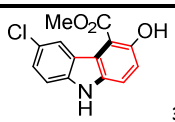
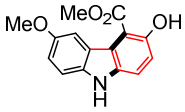
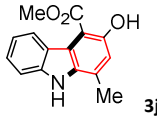
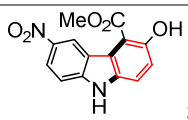
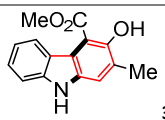
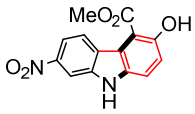
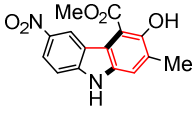
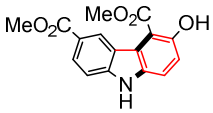
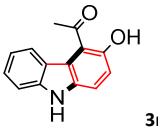
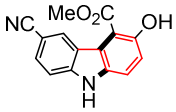
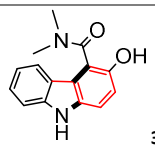
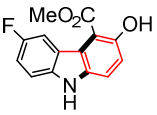
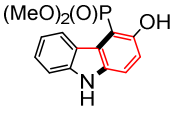
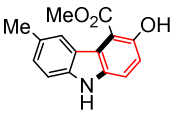
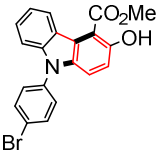
Table 2. Substrate Scope



1 3

Entry	R^1, R^2, R^3, R^4, R^5	Product	Yield (%)	Entry	R^1, R^2, R^3, R^4, R^5	Product	Yield (%)
1	H, H, H, CO_2Me, H	 **3a**	82	9	4-Cl, H, H, CO_2Me, H	 **3i**	72
2	4-MeO, H, H, CO_2Me, H	 **3b**	83	10	H, Me, H, CO_2Me, H	 **3j**	65
3	4-NO_2, H, H, CO_2Me, H	 **3c**	61	11	H, H, Me, CO_2Me, H	 **3k**	70
4	5-NO_2, H, H, CO_2Me, H	 **3d**	66	12	4-NO_2, H, Me, CO_2Me, H	 **3l**	49
5	4-CO_2Me, H, H, CO_2Me, H	 **3e**	68	13	H, H, H, COMe, H	 **3m**	78
6	4-CN, H, H, CO_2Me, H	 **3f**	72	14	H, H, H, $C(O)NMe_2$, H	 **3n**	79
7	4-F, H, H, CO_2Me, H	 **3g**	80	15	H, H, H, $P(O)(OMe)_2$, H	 **3o**	72
8	4-Me, H, H, CO_2Me, H	 **3h**	83	16	H, H, H, CO_2Me, 4-BrPh	 **3p**	50

when AgCl salt was removed from the cationic gold catalyst by filtration (entry 21). A control experiment in the absence of the gold catalyst failed to produce **3a** (entry 22).

With the optimized reaction conditions in hand, we set out to establish the substrate scope of the tandem catalytic carbazole synthesis (Table 2). With the anticipation that electronic effect may be among dominant factors that influence the efficiency of the cyclization, we examined several aryl groups bearing substituents with electron-donating and withdrawing capability. From the study, pronounced electronic effect was observed that substrates with electron-rich aryl groups provided the corresponding carbazoles in higher yields compared to those with electron-deficient aryl groups. 4-methoxyaniline gave carbazole **3b** in 83%, while a substantially lower yield of **3c** (61%) was obtained from an electron-deficient substrate, 4-nitroaniline. Likewise, other electron-deficient aryl substrates bearing ester and nitrile groups displayed the similar trend (**3e** and **3f**). Although fluorine is considered as an electron-withdrawing group, its electronic influence was negligible in this reaction, providing a comparable yield with methyl substitution (**3g** and **3h**, respectively, 80% vs. 83%). Next, we turned our attention to examine the influence of substitution on the tether. When compared to that with unsubstituted substrate **3a**, tether

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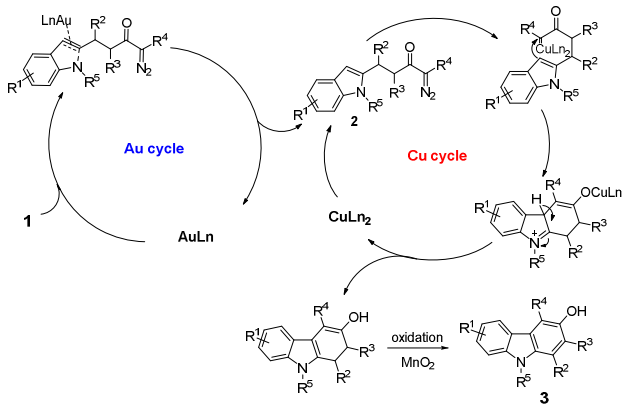
Scheme 3. Proposed Mechanism



substitution showed an adverse effect on the cyclization (**3j** and **3k**, respectively, 65% and 70%). When two negative factors, electron-withdrawing group and tether substitution were combined, the efficiency of the tandem reaction further decreased (**3l**, 49%). In addition, we investigated the impact of the functional groups adjacent to the diazo group. Ketone and amide groups were well tolerated to afford the corresponding carbazoles with high yields (**3m** and **3n**, 78% and 79%). Phosphonate gave **3o** with slightly diminished but synthetically useful yield (72%). Lastly, biaryl aniline **1p** smoothly reacted to give N-aryl substituted carbazole **3p** (50%).

Mechanistically, the formation of carbazoles from diazo anilinoalkyne is proposed to begin with gold-mediated hydroamination of anilinoalkyne **1** to form indole **2** (Scheme 3). Subsequent activation of the diazo group of **2** results in the formation of copper carbene, which undergoes electrophilic cyclization with the indole moiety to afford carbazole **3** after oxidation.

In sum, we have successfully developed efficient synthesis of carbazoles employing diazo anilinoalkynes as substrates based on gold copper tandem catalysis. Each of the two catalysts promotes sequential activation of the orthogonal functionalities, alkynyl and diazo groups, resulting in the formation of carbazoles via indoles as the intermediates. This method has proven to offer a valuable synthetic tool for carbazoles featuring a broad substrate scope.

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Notes and references

1 (a) Y. Tao, Q. Wang, C. Yang, Q. Wang, Z. Zhang, T. Zou, J. Qin and D. Ma, *Angew. Chem. Int. Ed.*, 2008, **47**, 8104; (b) J. V. Grazulevicius, P. Strohriegl, J. Pielichowski and K. Pielichowski, *Prog. Polym. Sci.*, 2003, **28**, 1297.

2 (a) T. A. Choi, R. Czerwonka, W. Fröhner, M. P. Krahl, K. R. Reddy, S. G. Franzblau and H.-J. Knölker, *ChemMedChem*, 2006, **1**, 812; (b) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193.

3 (a) P. Rongved, G. Kirsch, Z. Bouaziz, J. Jose and M. Le Borgne, *Eur. J. Med. Chem.*, 2013, **69**, 465; (b) W. Maneerat, T. Ritthiwigrom, S. Cheenpracha, U. Prawat and S. Laphookhieo, *Tetrahedron Lett.*, 2011, **52**, 3303; (c) S. B. Markad and N. P. Argade, *J. Org. Chem.*, 2016.

4 (a) N. H. Krishna, A. P. Saraswati, M. Sathish, N. Shankaraiah and A. Kamal, *Chem. Commun.*, 2016; (b) M. F. Martínez-Esperón, D. Rodríguez, L. Castedo and C. Saá, *Org. Lett.*, 2005, **7**, 2213.

5 (a) V. Dhayalan, J. A. Clement, R. Jagan and A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, 2009, **2009**, 531; (b) J. K. Laha and N. Dayal, *Org. Lett.*, 2015, **17**, 4742.

6 (a) T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura and E. Shirakawa, *J. Am. Chem. Soc.*, 2008, **130**, 15823; (b) X. Zheng, L. Lv, S. Lu, W. Wang and Z. Li, *Org. Lett.*, 2014, **16**, 5156.

7 (a) M. E. Budén, V. A. Vaillard, S. E. Martin and R. A. Rossi, *J. Org. Chem.*, 2009, **74**, 4490; (b) C. Schuster, M. Rönnefahrt, K. K. Julich-Gruner, A. Jäger, A. W. Schmidt and H.-J. Knölker, *Synthesis*, 2016, **48**, 150.

8 (a) B. J. Stokes, B. Jovanović, H. Dong, K. J. Richert, R. D. Riell and T. G. Driver, *J. Org. Chem.*, 2009, **74**, 3225; (b) B. J. Stokes, K. J. Richert and T. G. Driver, *J. Org. Chem.*, 2009, **74**, 6442.

9 (a) S. H. Cho, J. Yoon and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 5996; (b) S. W. Youn, J. H. Bihn and B. S. Kim, *Org. Lett.*, 2011, **13**, 3738.

10 (a) J. H. Kim, S. Y. Choi, J. Bouffard and S.-g. Lee, *J. Org. Chem.*, 2014, **79**, 9253; (b) J. Um, H. Yun and S. Shin, *Org. Lett.*, 2016, **18**, 484.

11 (a) J. Mo, D. Kang, D. Eom, S. H. Kim and P. H. Lee, *Org. Lett.*, 2013, **15**, 26; (b) A. M. Asiri and A. S. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 4471; (c) M. Bandini, *Chem. Soc. Rev.*, 2011, **40**, 1358.

12 (a) H.-S. Yeom, Y. Lee, J.-E. Lee and S. Shin, *Org. Biomol. Chem.*, 2009, **7**, 4744; (b) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028.

13 (a) E. Chong and S. A. Blum, *J. Am. Chem. Soc.*, 2015, **137**, 10144; (b) I. Nakamura, U. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Angew. Chem. Int. Ed.*, 2007, **46**, 2284.

14 (a) Y. Jiang, V. Z. Y. Khong, E. Lourdusamy and C.-M. Park, *Chem. Commun.*, 2012, **48**, 3133; (b) N. S. Y. Loy, S. Choi, S. Kim and C.-M. Park, *Chem. Commun.*, 2016; (c) N. S. Y. Loy, S. Kim and C.-M. Park, *Org. Lett.*, 2015, **17**, 395; (d) Y. Jiang and C.-M. Park, *Chem. Sci.*, 2014, **5**, 2347; (e) N. S. Y. Loy, A. Singh, X. Xu and C.-M. Park, *Angew. Chem. Int. Ed.*, 2013, **52**, 2212; (f) Y. Jiang, W. C. Chan and C.-M. Park, *J. Am. Chem. Soc.*, 2012, **134**, 4104; (g) X. Qi, L. Dai and C.-M. Park, *Chem. Commun.*, 2012, **48**, 11244; (h) X. Qi, X. Xu and C.-M. Park, *Chem. Commun.*, 2012, **48**, 3996; (i) X. Qi, Y. Jiang and C.-M. Park, *Chem. Commun.*, 2011, **47**, 7848; (j) E. Lourdusamy, L. Yao and C.-M. Park, *Angew. Chem.*, 2010, **49**, 7963.

15 (a) J. He, Y. Shi, W. Cheng, Z. Man, D. Yang and C. Y. Li, *Angew. Chem. Int. Ed.*, 2016, **55**, 4557; (b) V. V. Pagar and R. S. Liu, *Angew. Chem. Int. Ed.*, 2015, **54**, 4923.

16 (a) Y. Qiu, W. Kong, C. Fu and S. Ma, *Org. Lett.*, 2012, **14**, 6198; (b) B. Alcaide, P. Almendros, J. M. Alonso, E. Busto, I. Fernández, M. P. Ruiz and G. Xiaokaiti, *ACS Catal.*, 2015, **5**, 3417.

17 (a) B. Alcaide, P. Almendros, J. M. Alonso, S. Cembellin, I. Fernandez, T. M. del Campo and M. R. Torres, *Chem. Commun.*, 2013, **49**, 7779; (b) B. Guo, X. Huang, C. Fu and S. Ma, *Chemistry – A European Journal*, 2016, **22**, 18343.

18 The structure of the dihydrocarbazole corresponding to 3a has been confirmed by NMR (see the supplementary information).