ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 8967–8969

www.rsc.org/chemcomm

COMMUNICATION

An unexpected palladium-catalyzed reaction of 2-alkynylhalobenzene with 2-alkynylaniline: a novel and efficient route to 11*H*-indeno[1,2-*c*]quinolin-11-ols†

Xiaolin Pan,[a] Yong Luo[a] and Jie Wu*[ab]

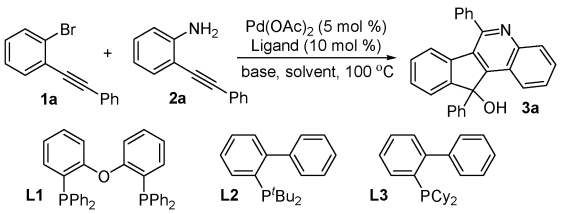
Received 10th May 2011, Accepted 23rd June 2011
DOI: 10.1039/c1cc12747k

An unexpected palladium-catalyzed cascade reaction of 2-alkynylhalobenzene with 2-alkynylaniline is reported, which provides a novel and efficient pathway for the synthesis of 11*H*-indeno[1,2-*c*]quinolin-11-ols.

Cascade reactions[1] have been demonstrated as an efficient tool for the introduction of molecular diversity and complexity[2] in an astonishing pathway. Such sequential processes frequently occur with enhanced chemo-, regio-, and diastereoselectivity for the overall transformation. Additionally, they offer a wide range of possibilities for the efficient generation of complex molecules in a single procedural step, and the need for several workup and purification operations is omitted. Recently, our laboratory has been involved in the development of methodologies of cascade reactions for the construction of nitrogen-containing heterocycles.[3] We discovered that 5*H*-cyclopenta[*c*]quinoline derivatives could be synthesized *via* a palladium-catalyzed cascade reaction of *o*-alkynylhalobenzene with amine.[3c] During the reaction process, a double insertion of a triple bond was believed to be the key step with high efficiency and selectivity. To expand the scope of such transformation, a reaction of 2-alkynylhalobenzene with 2-alkynylaniline was then studied.

The exploration was performed for the reaction of 1-bromo-2-(2-phenylethynyl)benzene **1a** with 2-(2-phenylethynyl)benzenamine **1b** catalyzed by palladium acetate (5 mol %). Initially, only a trace amount of the product was detected when the reaction occurred in the presence of tricyclohexylphosphine (10 mol%) and K_3PO_4 in 1,4-dioxane at 100 °C (Table 1, entry 1). No reaction took place when the base was changed to Cs_2CO_3, $^iPr_2NEt$, or DABCO (Table 1, entries 2–4). Gratifyingly, a product was observed in the presence of NaOH as the base when the reaction system was exposed to the air atmosphere after consumption of the starting materials (Table 1, entry 5). However, this product with a 70% isolated yield was not the expected 5*H*-cyclopenta[*c*]quinoline compound. After X-ray crystallography analysis, the structure of this compound was unambiguously identified as 11*H*-indeno[1,2-*c*]-quinolin-11-ol **3a** (Fig. 1, see the ESI†). This compound is interesting, since both quinoline and indenol skeletons are incorporated in one molecule. It is well recognized that the compounds with the quinoline substructure have been used as antimalarial, antiinflammatory agents, antiasthamatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[4] The indenol moiety is an important structural unit as well in various biologically active and pharmaceutical compounds.[5] Therefore, 11*H*-indeno[1,2-*c*]quinolin-11-ol can be also regarded as a privileged scaffold, and remarkable biological activities will be expected once the 11*H*-indeno[1,2-*c*]-quinolin-11-ols are evaluated in different biological assays.

Table 1 Initial studies for the palladium-catalyzed reaction of 2-alkynylbromobenzene **1a** with 2-alkynylaniline **2a**[a]



Entry	Ligand	Base	Solvent	Yield (%)[a]
1	PCy_3	K_3PO_4	1,4-Dioxane	Trace
2	PCy_3	Cs_2CO_3	1,4-Dioxane	nr
3	PCy_3	$^iPr_2NEt$	1,4-Dioxane	nr
4	PCy_3	DABCO	1,4-Dioxane	nr
5	PCy_3	NaOH	1,4-Dioxane	70
6	PCy_3	KOH	1,4-Dioxane	83
7	PCy_3	NaOMe	1,4-Dioxane	55
8	PCy_3	*t*-BuOLi	1,4-Dioxane	33
9	PCy_3	*t*-BuONa	1,4-Dioxane	95
10	PCy_3	*t*-BuOK	1,4-Dioxane	70
11	**L1**	*t*-BuONa	1,4-Dioxane	43
12	**L2**	*t*-BuONa	1,4-Dioxane	38
13	DPPF	*t*-BuONa	1,4-Dioxane	66
14	X-Phos	*t*-BuONa	1,4-Dioxane	47
15	PCy_3	*t*-BuONa	DMF	nr
16	PCy_3	*t*-BuONa	DMSO	nr
17	PCy_3	*t*-BuONa	Toluene	47

[a] Isolated yield based on 2-alkynylaniline **2a**.

[a] *Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China. E-mail: jie_wu@fudan.edu.cn; Fax: +86 21 6564 1740; Tel: +86 21 6510 2412*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

† Electronic supplementary information (ESI) available. CCDC 825072. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12747k

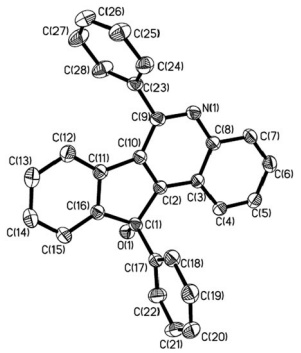
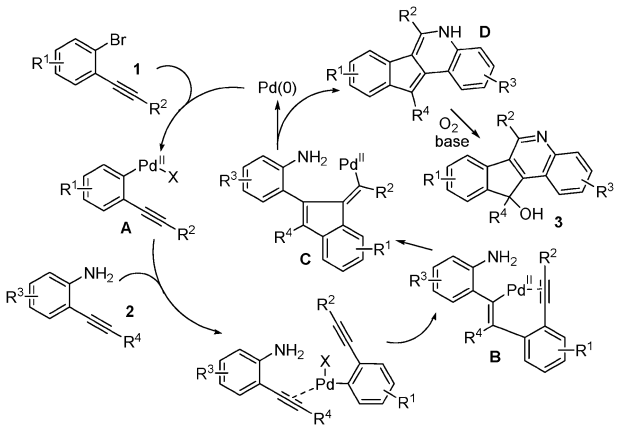


Fig. 1 ORTEP illustration of compound **3a** (30% probability ellipsoids).

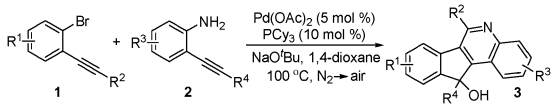


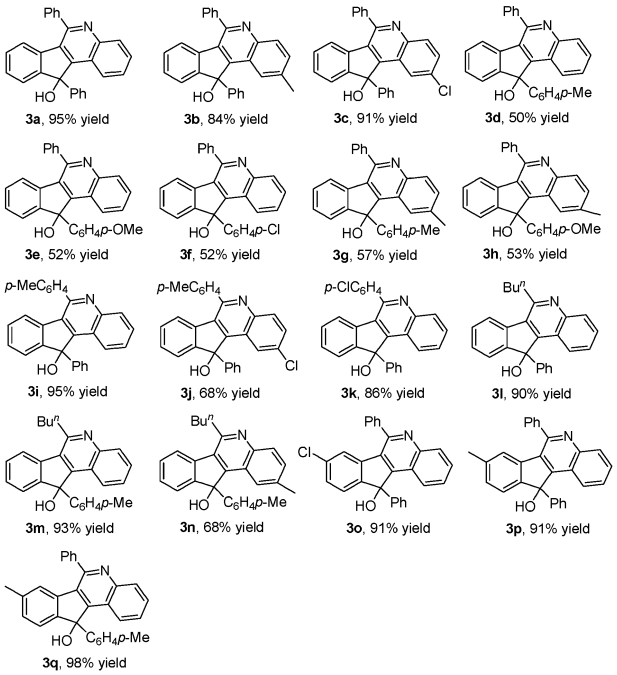
Scheme 1 A possible mechanism for palladium-catalyzed reaction of 2-alkynylbromobenzene **1** with 2-alkynylaniline **2**.

Interestingly, a much lower yield was isolated when the reaction was performed in a nitrogen atmosphere. With this promising result in hand, we reasoned that the oxygen might be involved in the conversion. Thus, the reaction was repeated, which took place under a nitrogen atmosphere first and was exposed to air for half an hour. As expected, the yield was comparable. Based on this result, the possible reaction pathway is illustrated in Scheme 1. We proposed that a palladium(II) species **A** would be formed after an oxidative addition of 2-alkynylbromobenzene **1** to Pd(0). This intermediate would coordinate with the triple bond of 2-alkynylaniline **2**. After insertion, the intermediate **B** would be produced, which then underwent another triple bond insertion to generate intermediate **C**. Intramolecular C–N bond formation occurred to furnish compound **D**, which subsequently converted to the final product **3** *via* oxidation in the presence of oxygen and base.[6]

Further screening of bases indicated that the reaction worked most efficiently in the presence of *t*-BuONa, which produced 11*H*-indeno[1,2-*c*]quinolin-11-ol **3a** in 95% yield (Table 1, entry 9). Several phosphine ligands were examined in the meantime (Table 1, entries 11–14). However, no better results were obtained. The reaction was tested in other solvents as well. No reaction took place when the reaction was performed in DMF or DMSO (Table 1, entries 15 and 16). Compound **3a** could be isolated in 47% yield when the reaction occurred in toluene (Table 1, entry 17). The reaction was retarded with diminished reactivity at lower temperature (data not shown in Table 1).

Table 2 Synthesis of 11*H*-indeno[1,2-*c*]quinolin-11-ols *via* a palladium-catalyzed reaction of 2-alkynylbromobenzene with 2-alkynylaniline[a]

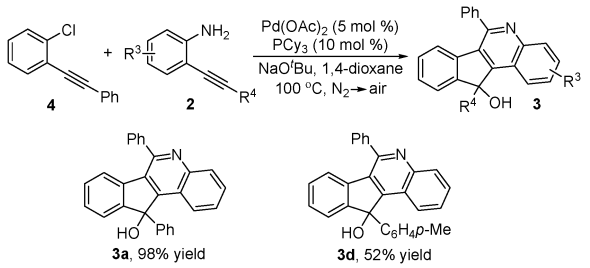




[a] Isolated yield based on 2-alkynylaniline **2**.

With the optimized conditions highlighted in Table 1 (5 mol% of palladium acetate, 10 mol% of tricyclohexylphosphine, *t*-BuONa, 1,4-dioxane, 100 °C), the scope of the palladium-catalyzed cascade reaction of 2-alkynylbromobenzene **1** with 2-alkynylaniline **2** was investigated. Table 2 shows the summary of results for the evaluation of various substituted 2-alkynylbromobenzenes **1** with 2-alkynylanilines **2**. In most cases, these reactions proceeded well leading to the corresponding 11*H*-indeno[1,2-*c*]quinolin-11-ol **3** in good to excellent yields. For example, substrates bearing either electron-rich or electron-poor substituents in the R^1 or R^3 position were converted to the desired products with good reactivity. Noticeably, the reaction was also workable for the substrates with an alkyl group attached to the triple bond. However, only moderate yields were obtained when the phenyl group was replaced by other aryl groups in the R^4 position (products **3d–3h**). The reactions of 2-alkynylchlorobenzene **4** with 2-alkynylanilines **2** were examined under the standard conditions in the meantime (Scheme 2). It was noteworthy that the reactivity was not diminished, which generated the desired product in a comparable yield.

In summary, we have described an unexpected palladium-catalyzed cascade reaction of 2-alkynylhalobenzene with 2-alkynylaniline, which provides a novel and efficient route for the



Scheme 2 Palladium-catalyzed reaction of 2-alkynylchlorobenzene **4** with 2-alkynylaniline **2**.

synthesis of 11*H*-indeno[1,2-*c*]quinolin-11-ols. Not only 2-alkynylbromobenzenes but also 2-alkynylchlorobenzenes are suitable partners in this transformation. This cascade reaction provides a good example for the introduction of molecular diversity and complexity with high efficiency and selectivity. Exploration of other transformations of 2-alkynylhalobenzenes is in progress in our laboratory.

Financial support from National Natural Science Foundation of China (No. 21032007) is gratefully acknowledged.

Notes and references

1 For selected reviews, see: (*a*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2006; (*b*) A. Meijere, P. V. Zezschwitz and S. Bräse, *Acc. Chem. Res*., 2005, **38**, 413; (*c*) P. Lu and Y.-G. Wang, *Synlett*, 2010, 165; (*d*) E. J. Yoo and S. Chang, *Curr. Org. Chem*., 2009, **13**, 1766; (*e*) *Multicomponent Reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, 2005; (*f*) K. C. Nicolaou, E. W. Yue and T. Oshima, in *The New Chemistry*, ed. N. Hall, Cambridge University Press, Cambridge, 2001, p. 168; (*g*) L. F. Tietze and F. Hautner, in *Stimulating Concepts in Chemistry*, ed. F. Vögtle, J. F. Stoddart and M.Shibasaki, Wiley-VCH, Weinheim, 2000, p. 38; (*h*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed*., 2000, **39**, 3168; (*i*) L. F. Tietze, *Chem. Rev*., 1996, **96**, 115; (*j*) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl*., 1993, **32**, 131.

2 (*a*) D. P. Walsh and Y.-T. Chang, *Chem. Rev*., 2006, **106**, 2476; (*b*) P. Arya, D. T. H. Chou and M.-G. Baek, *Angew. Chem., Int. Ed*., 2001, **40**, 339; (*c*) S. L. Schreiber, *Science*, 2000, **287**, 1964.

3 For recent selected examples, see: (*a*) S. Li and J. Wu, *Org. Lett*., 2011, **13**, 712; (*b*) Z. Chen, D. Zheng and J. Wu, *Org. Lett*., 2011, **13**, 848; (*c*) Y. Luo, X. Pan and J. Wu, *Org. Lett*., 2011, **13**, 1150; (*d*) H. Ren, Y. Luo, S. Ye and J. Wu, *Org. Lett*., 2011, **13**, 2552; (*e*) Y. Luo, L. Hong and J. Wu, *Chem. Commun*., 2011, **47**, 5298; (*f*) Z. Chen, C. Ye, L. Gao and J. Wu, *Chem. Commun*., 2011, **47**, 5623; (*g*) Z. Chen and J. Wu, *Org. Lett*., 2010, **12**, 4856; (*h*) G. Qiu, Q. Ding, H. Ren, Y. Peng and J. Wu, *Org. Lett*., 2010, **12**, 3975; (*i*) Z. Chen, X. Yu and J. Wu, *Chem. Commun*., 2010, **46**, 6356; (*j*) S. Ye, X. Yang and J. Wu, *Chem. Commun*., 2010, **46**, 5238; (*k*) S. Ye, X. Yang and J. Wu, *Chem. Commun*., 2010, **46**, 2950.

4 For selected examples, see: (*a*) R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. Zamboni, *J. Org. Chem*., 1996, **61**, 3398; (*b*) Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu and C. C. Tzeng, *J. Med. Chem*., 2001, **44**, 2374; (*c*) G. Roma, M. D. Braccio, G. Grossi and M. Chia, *Eur. J. Med. Chem*., 2000, **35**, 1021; (*d*) D. Doube, M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J. P. Falgueyeret, R. W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagari and R. N. Yong, *Bioorg. Med. Chem. Lett*., 1998, **8**, 1255; (*e*) M. P. Maguire, K. R. Sheets, K. Mcvety, A. P. Spada and A. Zilberstein, *J. Med. Chem*., 1994, **37**, 2129; (*f*) O. Bilker, V. Lindo, M. Panico, A. E. Etiene, T. Paxton, A. Dell, M. Rogers, R. E. Sinden and H. R. Morris, *Nature*, 1998, **392**, 289.

5 (*a*) K. Samula and B. Cichy, *Acta Pol. Pharm*., 1985, **42**, 256; (*b*) Y. Ishiguro, K. Okamoto, F. Ojima and Y. Sonoda, *Chem. Lett*., 1993, 1139.

6 Y. Wu, J. Zhang, Z. Fei and Z. Bo, *J. Am. Chem. Soc*., 2008, **130**, 7192.