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Efficient generation of indeno[1,2-*c*]chromenes *via* the Pd-catalyzed reaction of 2-alkynylhalobenzenes with 2-alkynylphenols†

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A palladium-catalyzed reaction of 2-alkynylhalobenzenes with 2-alkynylphenols in the presence of PCy_3 is discovered, which provides an efficient and facile route to indeno[1,2-*c*]chromenes. This reaction works efficiently, leading to the corresponding products in good to excellent yields.

Gnetuhainin S, isolated from *Gnetum macrostachyum* lianas, shows antioxidant activity when subjected to an examination of its radical scavenging against DPPH (Fig. 1).[1] However, there is lack of efficient ways to access this [6-5-6-6] tetracyclic skeleton.[2] With an expectation to generate a small library of indeno[1,2-*c*]chromene (a precursor of Gnetuhainin S, Fig. 1) for the subsequent biological screening, development of useful and efficient synthetic methodologies for the scaffold construction is extremely important. Recently, intense interest has been directed toward the strategy of diversity-oriented synthesis[3] for the efficient construction of structurally complex compounds. Among the approaches, cascade reaction which uses easily available starting materials is attractive due to its well-known advantages.[4,5] The features of cascade reaction prompt us to design novel routes for the efficient assembly of indeno[1,2-*c*]chromene derivatives. Recently, we described a novel method for the synthesis of 5*H*-cyclopenta[*c*]quinoline derivatives *via* a palladium-catalyzed reaction of 2-alkynylhalobenzene with amine.[6] Inspired by the structural similarity of 5*H*-cyclopenta[*c*]quinoline and indeno[1,2-*c*]chromene, we conceived that the indeno[1,2-*c*]chromene scaffold could be formed *via* a palladium-catalyzed reaction of 2-alkynylhalobenzene with 2-alkynylphenol. Herein, we wish to disclose our recent efforts for this transformation.

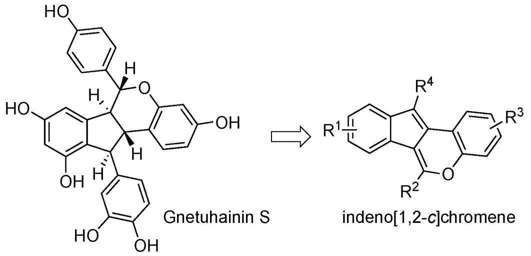
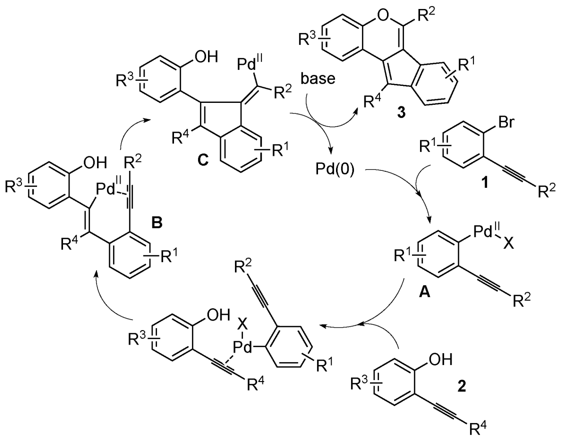


Fig. 1 Structures of Gnetuhainin S and indeno[1,2-*c*]chromene.

2-Alkynylphenols are the most widely used substances for the synthesis of benzo[*b*]furans.[7] Among the reaction process, nucleophilic addition of the phenolic oxide to the metal-activated triple bond is the key step (R–Pd^{II}X is involved in most cases). Additionally, to the best of our knowledge, there are no reports for the *syn*-insertion of R–PdX to the triple bond against the hydroxy group. We hypothesized that the oxidative addition would take place to afford an intermediate **A** when 2-alkynylbromobenzene was employed in the reaction (Scheme 1). The Pd(II) would selectively activate the triple bond of 2-alkynylphenol. If the *syn*-insertion of R–Pd^{II}X to triple bond occurred first, followed by a second insertion to the triple bond of 2-alkynylbromobenzene and intramolecular C–O bond formation, indeno[1,2-*c*]chromene which contains the [6-5-6-6] tetracyclic skeleton would be formed. This synthetic hypothesis seems feasible. However, several factors have to be considered in this strategy: (1) a benzo[*b*]furan can be easily generated by direct cyclization of 2-alkynylphenol;[7b,c]



Scheme 1 Possible mechanism for indeno[1,2-*c*]chromenes generation *via* a Pd-catalyzed reaction of 2-alkynylhalobenzene with 2-alkynylphenol.

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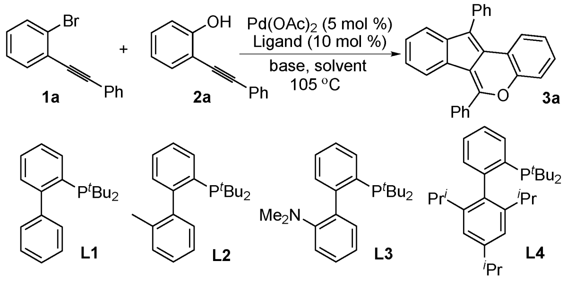
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**, and X-ray crystal data of compound **3a**. CCDC 815061. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11169h

(2) aryl halide reacts with 2-alkynylphenol in the presence of a palladium catalyst leading to 2,3-diarylbenzo[*b*]furan;[7c] (3) the direct C–O bond formation of aryl halide and phenol which is established[8] cannot be excluded in our protocol. However, as mentioned above for the 5*H*-cyclopenta[*c*]quinoline generation through a palladium-catalyzed reaction of *o*-alkynylhalobenzene with amine,[6] the double triple bond insertion and subsequent C–N bond formation would occur under suitable conditions in the reaction process. Encouraged by this result, we conceived that the proposed synthetic route showed in Scheme 1 was possible. Thus, we started to investigate the practicability for the synthesis of indeno[1,2-*c*]chromenes *via* a palladium-catalyzed cascade reaction of 2-alkynylhalobenzene with 2-alkynylphenol.

The preliminary screening was performed for the reaction of 1-bromo-2-(phenylethynyl)benzene **1a** with 2-(2-phenylethynyl)-phenol **2a** catalyzed by palladium acetate (5 mol%) at 105 °C (Table 1). Only a trace amount of product was detected when the reaction occurred in the presence of ligand **L1** (10 mol%) and K_3PO_4 in toluene (Table 1, entry 1). Similar results were observed when the ligand was changed to **L2–L4** and ^{t}Bu$_3$P (Table 1, entries 2–5). The reaction was complex when DPPF was utilized as a replacement of the ligand (Table 1, entry 6). Employing BINAP as a ligand in the reaction could not improve the final outcome (Table 1, entry 7). Gratifyingly, the desired product **3a** was obtained in 59% yield when the reaction proceeded with tricyclohexylphosphine (PCy_3) as the ligand (Table 1, entry 8). The structure of compound **3a** was illustrated by X-ray diffraction analysis in the meantime (see the ESI†). With these results in hand, we next screened different bases. Sodium methanolate ($NaOCH_3$) was demonstrated as the best choice (95% yield, Table 1, entry 14). Further screening of solvents discovered that the reaction worked efficiently in 1,4-dioxane, which furnished the corresponding product in 96% yield (Table 1, entry 16). The reactivity was diminished when the reaction occurred at a lower temperature (data not shown in Table 1).

Table 1 Initial studies for the palladium-catalyzed reaction of 1-bromo-2-(phenylethynyl)benzene **1a** with 2-(2-phenylethynyl)phenol **2a**



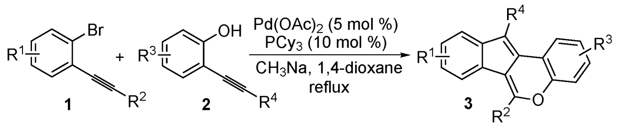
Entry	Ligand	Base	Solvent	Yield[a] (%)
1	**L1**	K_3PO_4	Toluene	Trace
2	**L2**	K_3PO_4	Toluene	Trace
3	**L3**	K_3PO_4	Toluene	Trace
4	**L4**	K_3PO_4	Toluene	Trace
5	^{t}Bu$_3$P·HBF$_4$	K_3PO_4	Toluene	Trace
6	DPPF	K_3PO_4	Toluene	Complex
7	BINAP	K_3PO_4	Toluene	Trace
8	PCy_3	K_3PO_4	Toluene	59
9	PCy_3	NaO^{t}Bu	Toluene	87
10	PCy_3	K_2CO_3	Toluene	79
11	PCy_3	KO^{t}Bu	Toluene	67
12	PCy_3	LiO^{t}Bu	Toluene	81
13	PCy_3	KOH	Toluene	55
14	PCy_3	$NaOCH_3$	Toluene	95
15	PCy_3	Cs_2CO_3	Toluene	72
16	PCy_3	$NaOCH_3$	1,4-Dioxane	96
17	PCy_3	$NaOCH_3$	DMF	Trace
18	PCy_3	$NaOCH_3$	DMSO	nr

[a] Isolated yield based on 1-bromo-2-(phenylethynyl)benzene **1a**.

Under the optimized conditions [Pd(OAc)$_2$ (5 mol%), PCy_3 (10 mol%), $NaOCH_3$, 1,4-dioxane, 105 °C], the palladium-catalyzed cascade reactions of 2-alkynylbromobenzenes with 2-alkynylphenols were then carried out to define the protocol generality (Table 2). In all cases, the reactions produced the desired indeno[1,2-*c*]chromenes in 63–96% yield. Substituents on the aromatic ring of the substrates or attached on the triple bond did not obviously affect formation of the expected products. For instance, 1-bromo-2-(phenylethynyl)benzene **1a** reacted with 2-alkynylphenols **2a–2d** leading to the corresponding indeno[1,2-*c*]chromenes in good yields (Table 2, entries 1–4). When 2-alkynylbromobenzene **1b** was utilized in the reaction, excellent results were obtained as well (Table 2, entries 5 and 6). Additionally, 4-methyl or 4-chloro substituted 2-alkynylbromobenzene and 2-alkynylphenol were examined. These reactions worked efficiently as well to afford the corresponding indeno[1,2-*c*]chromenes in good yields.

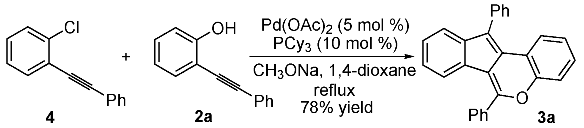
Moreover, the reaction of 1-chloro-2-(2-phenylethynyl)-benzene **4** with 2-(2-phenylethynyl)phenol **2a** was explored under the standard conditions in the meantime (Scheme 2). From the result (78% yield), it showed that aryl chloride was a

Table 2 Synthesis of indeno[1,2-*c*]chromenes *via* a Pd-catalyzed reaction of 2-alkynylbromobenzene with 2-alkynylphenol[a]



Entry	R^1, R^2	R^3, R^4	Yield[b] (%)
1	H, C_6H_5 (**1a**)	H, C_6H_5 (**2a**)	96 (**3a**)
2	H, C_6H_5 (**1a**)	H, 4-MeC_6H_4 (**2b**)	82 (**3b**)
3	H, C_6H_5 (**1a**)	H, 4-MeOC_6H_4 (**2c**)	76 (**3c**)
4	H, C_6H_5 (**1a**)	H, 4-ClC_6H_4 (**2d**)	79 (**3d**)
5	H, *n*-Bu (**1b**)	H, C_6H_5 (**2a**)	95 (**3e**)
6	H, *n*-Bu (**1b**)	H, 4-MeC_6H_4 (**2b**)	95 (**3f**)
7	H, 4-MeC_6H_4 (**1c**)	H, C_6H_5 (**2a**)	81 (**3g**)
8	H, 4-MeC_6H_4 (**1c**)	H, 4-ClC_6H_4 (**2d**)	90 (**3h**)
9	H, 4-MeC_6H_4 (**1c**)	4-Me, C_6H_5 (**2e**)	94 (**3i**)
10	H, 4-MeOC_6H_4 (**1d**)	H, C_6H_5 (**2a**)	90 (**3j**)
11	H, 4-MeOC_6H_4 (**1d**)	H, 4-MeOC_6H_4 (**2c**)	96 (**3k**)
12	H, 4-MeOC_6H_4 (**1d**)	4-Me, 4-ClC_6H_4 (**2f**)	79 (**3l**)
13	H, 4-ClC_6H_4 (**1e**)	H, C_6H_5 (**2a**)	95 (**3m**)
14	H, 4-ClC_6H_4 (**1e**)	H, 4-MeC_6H_4 (**2b**)	86 (**3n**)
15	H, 4-ClC_6H_4 (**1e**)	4-Me, C_6H_5 (**2e**)	86 (**3o**)
16	H, 4-ClC_6H_4 (**1e**)	4-Me, 4-ClC_6H_4 (**2f**)	93 (**3p**)
17	H, 4-ClC_6H_4 (**1e**)	4-Cl, C_6H_5 (**2g**)	70 (**3q**)
18	4-Me, C_6H_5 (**1f**)	H, C_6H_5 (**2a**)	74 (**3r**)
19	4-Cl, C_6H_5 (**1g**)	H, C_6H_5 (**2a**)	63 (**3s**)

[a] Reaction conditions: 2-alkynylbromobenzene **1** (0.40 mmol), 2-alkynylphenol **2** (0.60 mmol), Pd(OAc)$_2$ (5 mol%), PCy_3 (10 mol%), CH_3ONa (0.8 mmol), 1,4-dioxane (3.0 mL), reflux. [b] Isolated yield based on 2-alkynylbromobenzene.



Scheme 2 Palladium-catalyzed reaction of 1-chloro-2-(phenylethynyl)-benzene **4** with 2-alkynylphenol **2a**.

suitable partner in this transformation, which expands the substrate scope of this reaction.

In summary, we have described an efficient assembly of indeno[1,2-*c*]chromene derivatives *via* a palladium-catalyzed cascade reaction of 2-alkynylhalobenzene with 2-alkynylphenol. The reaction works efficiently with excellent selectivity, and the reaction scope is demonstrated. The related library construction is currently ongoing.

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Notes and references

1 (*a*) S. Saisin, S. Tip-pyang and P. Phuwapraisirisan, *Nat. Prod. Res.*, 2009, **23**, 1472; (*b*) S. Zhou, Y. H. Wang and M. Lin, *Chin. Chem. Lett.*, 2002, **13**, 549.

2 (*a*) R. Singh, M. K. Parai and G. Panda, *Org. Biomol. Chem.*, 2009, **7**, 1858; (*b*) M. Chakraborty, D. B. McConville, T. Saito, H. Meng, P. L. Rinaldi, C. A. Tessier and W. J. Youngs, *Tetrahedron Lett.*, 1998, **39**, 8237.

3 (*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.

4 L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2006.

5 For recent examples, see: (*a*) P. Lu and Y.-G. Wang, *Synlett*, 2010, 165; (*b*) E. J. Yoo and S. Chang, *Curr. Org. Chem.*, 2009, **13**, 1766; (*c*) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming and W.-J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 6946; (*d*) X.-F. Wang, J.-R. Chen, Y.-J. Cao, H.-G. Cheng and W.-J. Xiao, *Org. Lett.*, 2010, **12**, 1140; (*e*) W. Song, W. Lu, J. Wang, P. Lu and Y. Wang, *J. Org. Chem.*, 2010, **75**, 3481; (*f*) W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782.

6 Y. Luo, X. Pan and J. Wu, *Org. Lett.*, 2011, **13**, 1150.

7 For selected examples, see: (*a*) A. Arcadi, S. Cacchi, G. Fabrizi and L. Moro, *Eur. J. Org. Chem.*, 1999, 1137; (*b*) Y. Hu, Y. Zhang, Z. Yang and R. Fathi, *J. Org. Chem.*, 2002, **67**, 2365; (*c*) Y. Hu, K. J. Nawoschik, Y. Liao, J. Ma, R. Fathi and Z. Yang, *J. Org. Chem.*, 2004, **69**, 2235; (*d*) Y. Nan, H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 297; (*e*) H.-A. Du, X.-G. Zhang, R.-Y. Tang and J.-H. Li, *J. Org. Chem.*, 2009, **74**, 7844; (*f*) Y. Liao, J. Smith, R. Fathi and Z. Yang, *Org. Lett.*, 2005, **7**, 2707; (*g*) Y. Liang, S. Tang, X.-D. Zhang, L.-Q. Mao, Y.-X. Xie and J.-H. Li, *Org. Lett.*, 2006, **8**, 3017; (*h*) C. Martínez, R. Álvarez and J. M. Aurrecoechea, *Org. Lett.*, 2009, **11**, 1083; (*i*) M. Nakamura, L. Ilies and S. Otsubo, *Angew. Chem., Int. Ed.*, 2006, **45**, 944.

8 Selected examples for Pd-catalyzed intermolecular C–O bond formation: (*a*) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 4369; (*b*) Q. Shelby, N. Kataoka, G. Mann and J. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 10718; (*c*) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monseesb and M. Beller, *Tetrahedron Lett.*, 2005, **46**, 3237.