DOI: 10.1002/adsc.201300512

Palladium-Catalyzed Oxidative Annulation *via* C–H/N–H Functionalization: Access to Substituted Pyrroles

Shiyong Peng,[a] Lei Wang,[a] Jiayao Huang,[a] Shaofa Sun,[b] Haibing Guo,[b] and Jian Wang[a,*]

[a] Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543
E-mail: chmwangj@nus.edu.sg
[b] Hubei Collaborative Innovation Center for Non-power Nuclear Technology, College of Chemistry and Biological Sciences, Hubei University of Science and Technology, Hubei Province 437100, People's Republic of China

Received: June 11, 2013; Revised: June 26, 2013; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300512.

Abstract: Pyrroles, ubiquitous bioactive heterocycles in nature, are readily prepared *via* a palladium-catalyzed oxidative annulation of cyclic *trans*-enamines to various internal alkynes in the absence of a directing group.

Keywords: C–H functionalization; N–H functionalization; oxidative annulations; palladium; pyrroles

The synthesis of N-heterocycles is an important field of research because of their prevalence in natural products and drugs.[1] Of the N-heterocycles, pyrroles are well-known five-membered nitrogen-containing heterocycles that form the structural scaffold of many pharmaceuticals,[2] therefore, they are often used as structural elements in medicinal chemistry. For example, Atorvastatin (**A**) (Figure 1), marketed by Pfizer under the trade name Lipitor, is a member of the drug class known as statins, used for lowering blood cholesterol.[3] Lamellarin D (**B**) has been found to be cytotoxic to a wide range of cancer cell lines, and is also a potent inhibitor of human topisomerase I60.[4] Zomepirac (**C**) is an orally effective non-steroidal anti-inflammatory drugs (NSAID) that has antiopyretic actions.[5] Compound (**D**) was identified as an anti-cancer drug candidate.[6]

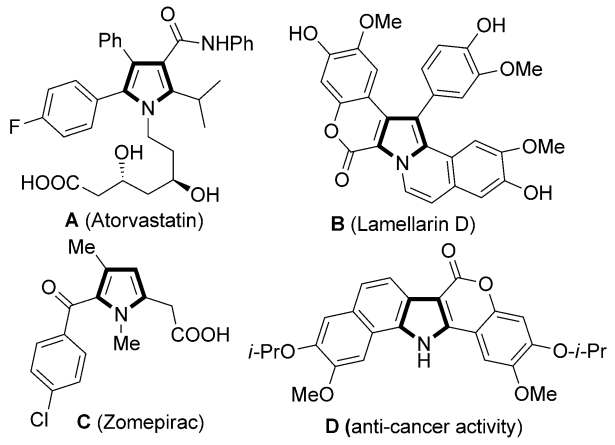
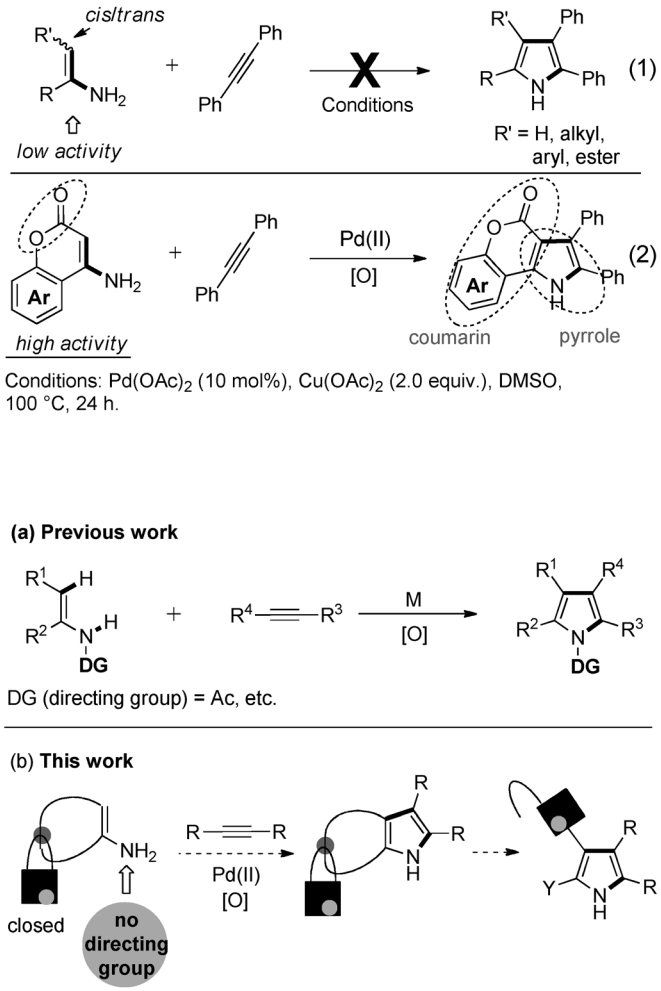


Figure 1. Examples of pyrrole pharmaceuticals.

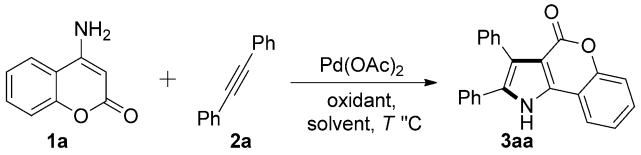
A number of methods have been reported for the synthesis of pyrroles. The traditional methods are Knorr,[7] Paal–Knorr,[8] and Hantzsch reactions.[9] Although these methods are very helpful in assembling pyrrole molecules, they exhibit some significant drawbacks (e.g., low availability of starting materials, low compatibility of functional groups, multiple synthetic steps, and harsh reaction conditions), which have largely limited their applications. However, the high value of the pyrrole scaffold in medicinal chemistry has still driven organic chemists to continue developing novel synthetic methods to prepare differentially substituted pyrroles. Aside from traditional methods, one of the most attractive modern approaches for the direct synthesis of substituted pyrroles is the transition metal-catalyzed annulation reaction.[10,11] Specifically, the groups of Glorius,[12] Fagnou,[13]and Ackermann[14] have independently reported Rh(III)- or Ru(II)-catalyzed oxidative couplings using a directing group (DG) for aryl C–H bond functionalization followed by insertion of an internal alkyne leading to various substituted pyrroles (Scheme 1a).[15,16] In this article, we wish to disclose a new synthetic approach through a direct Pd(II)-catalyzed oxidative coupling of *trans*-enamines with internal alkynes in the absence of DG [Eq. (2)].

In connection to our group's continued interest in developing efficient and direct palladium-catalyzed C–H functionalization strategies,[17] we decided to



Scheme 1. Strategies involving C–H functionalization for the preparation of pyrroles. a) Directing group-assisted approach; b) No directing group-assisted approach.

Table 1. Optimization of reaction conditions.[a]

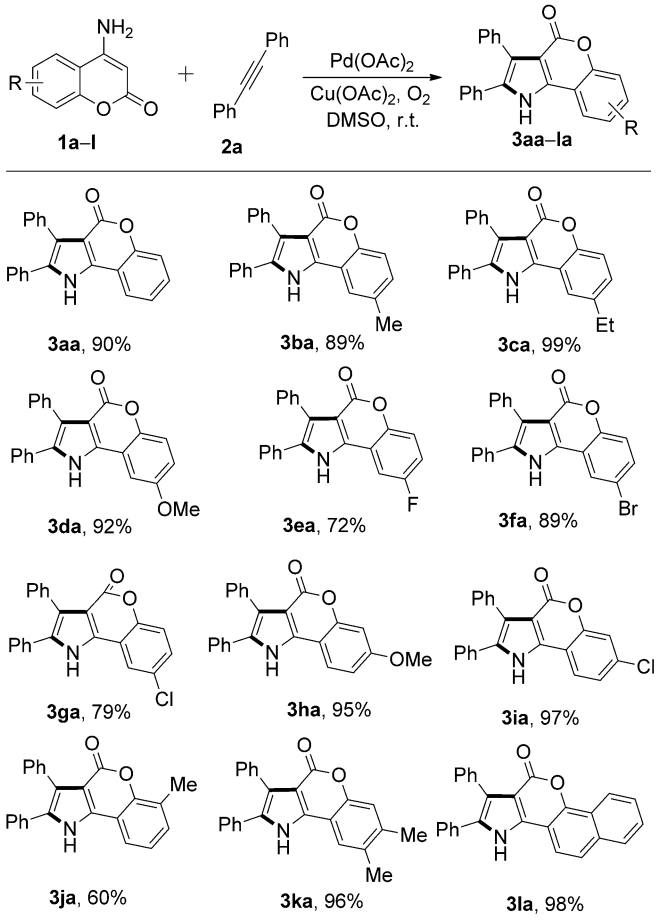


Entry	Oxidant	Solvent	Temp. [°C]	Time [h]	**3aa** [%][b]
1	–[c]	DMA[g]	100	12	–[d]
2	AgOAc	DMA	100	12	24
3	$CuCl_2$	DMA	100	12	–[d]
4	$PhI(OAc)_2$	DMA	100	12	–[d]
5	Oxones	DMA	100	12	–[d]
6	BQ[e]	DMA	100	12	–[d]
7	DDQ[f]	DMA	100	12	–[d]
8	$Cu(OAc)_2$	DMA	100	12	23
9	$Cu(OAc)_2$	DMSO	100	12	71
10	$Cu(OAc)_2$	NMP[h]	100	12	32
11	$Cu(OAc)_2$	MeCN	100	12	17
12	O_2	DMA	100	12	28
13	O_2	DMSO	100	12	97
14	O_2	DMSO	r.t.[j]	72	45
15	$Cu(OAc)_2$	DMSO	r.t.[j]	72	91
16	**$Cu(OAc)_2/O_2$[i]**	**DMSO**	**r.t.**[j]	**72**	**90**

[a] *Reaction conditions:* **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), oxidant (2.0 equiv.), DMSO (1 mL), 100 °C.
[b] Isolated yield.
[c] No oxidant.
[d] No desired product was detected.
[e] 1,4-Benzoquinone.
[f] 2,3-Dichloro-5,6-dicyanobenzoquinone.
[g] Dimethylacetamide.
[h] Methylpyrrolidone.
[i] $Cu(OAc)_2$ (20 mol%) and O_2 balloon.
[j] Room temperature.

employ $Pd(OAc)_2$ as the catalyst to explore the direct annulation reaction of enamines[18] with alkynes. As shown in Eq. (1), no reaction happened even when a less bulky enamine was used (R′ = H; NB: no directing group on N atom) (see the details in Supporting Information). Surprisingly, both *cis*/*trans* β-enamino esters exhibited poor reactivites even if they usefully considered as more active nucleophiles [Eq. (1): R = H, R′ = CO_2Et; < 5%]. We considered whether the substrate reactivity is largely affected by both the geometry and the steric hindrance of nucleophiles. To test our hypothesis, a *trans*- and a less sterically hindered 4-aminocoumarin **1a** was synthesized and applied to the annulation reaction. Initially, a number of oxidants was screened. As shown in Table 1, oxidants were identified to be a critical factor in the process. The reaction only occurred in the presence of a stoichiometric amount of oxidant AgOAc or $Cu(OAc)_2$ at 100 °C (entries 7 and 8, 24% and 23% yield, 2.0 equiv., respectively). To further improve the efficacy of this reaction, various solvents (e.g., DMA, NMP, MeCN and DMSO) were examined (Table 1, entries 9–11), whereupon it was discovered that only DMSO afforded a good chemical yield in 12 h (entry 11, 71%). Having the optimized oxidant, $Cu(OAc)_2$, and solvent, DMSO, in hand we then investigated the effect of temperature. Pleasingly, a high chemical yield was afforded at room temperature even though a longer reaction time was required (entry 15, 91%, 72 h). However, a stoichiometric amount of $Cu(OAc)_2$ as oxidant was still used. Taking into account the factors of the environment and costs we tested a mixed oxidant of $Cu(OAc)_2$ (20 mmol%) and O_2 (balloon) in the light of oxygen's green and sustainable features.[19,20] Gratifyingly, a high chemical yield was afforded by using a catalytic amount of $Cu(OAc)_2$ (20 mol%) and an O_2 ballon at room temperature (entry 13, 90%, 72 h). We speculate that oxygen plays a very important role in here. Firstly, oxygen can itself work as an oxidant to directly recy-

Table 2. Scope of 4-aminocoumarins.[a]



[a] *Reaction conditions:* **1a–l** (0.2 mmol, 1.0 equiv.), **2a** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (20 mol%), DMSO (1.0 mL), room temperature and O_2 balloon.

cle the palladium catalyst by oxidizing Pd(0) to Pd(II). Secondly, oxygen can regenerate the oxidant $Cu(OAc)_2$ by oxidizing the Cu(I) species to Cu(II).[20]

Under the optimal reaction conditions, various 4-amino-2*H*-chromen-2-ones were surveyed (Table 2). Reactions of 4-amino-2*H*-chromen-2-ones **1a–l** having electron-withdrawing or electron-donating groups proceeded efficiently with moderate to excellent yields (60–99%).[21] To further indicate the generality and potential of our approach, we then investigated different alkynes **2**. Table 2 and Table 3 show a broad substrate tolerance among internal alkynes. In general, electron-rich symmetrical alkynes gave high reaction yields (Table 3, **3ab–ac**, **3af–ah**, room temperature) while electron-deficient systems were less facile (Table 3, **3ad** and **3ae**, 80 °C). Heteroaryl and aliphatic alkynes were also tolerated (**3aj** and **3ak**). When asymmetrical internal alkynes were employed, two regioisomers were usually observed (Table 4, **3al–aq**, r.r. ~1:1 to 2:1).[22] In the event that the internal alkynes were highly electron deficient (**2r** and **2s**), only one regioisomer formed by following Markovnikov's rule in the alkyne addition step (Table 4, **3ar** and **3as**). However, when dimethyl acetylenedicarboxylate (**2t**) was used as the alkyne, the reaction failed (**3at**, < 5%).

To our delight, *N*-protected 4-aminocoumarin (**1m**) underwent the Pd-catalyzed oxidative annulations with good reactivity [Eq. (3), 60%]. Importantly, this compatibility also extended to β-enaminones (**1n–o**), as evidenced by the synthesis of **3na** and **3oa** with good yields under standard conditions [Eq. (4), 85% and 80%, respectively]. As heterocyclic molecules show dramatically different bioactive and electronic properties, we also tried to expand our reaction to

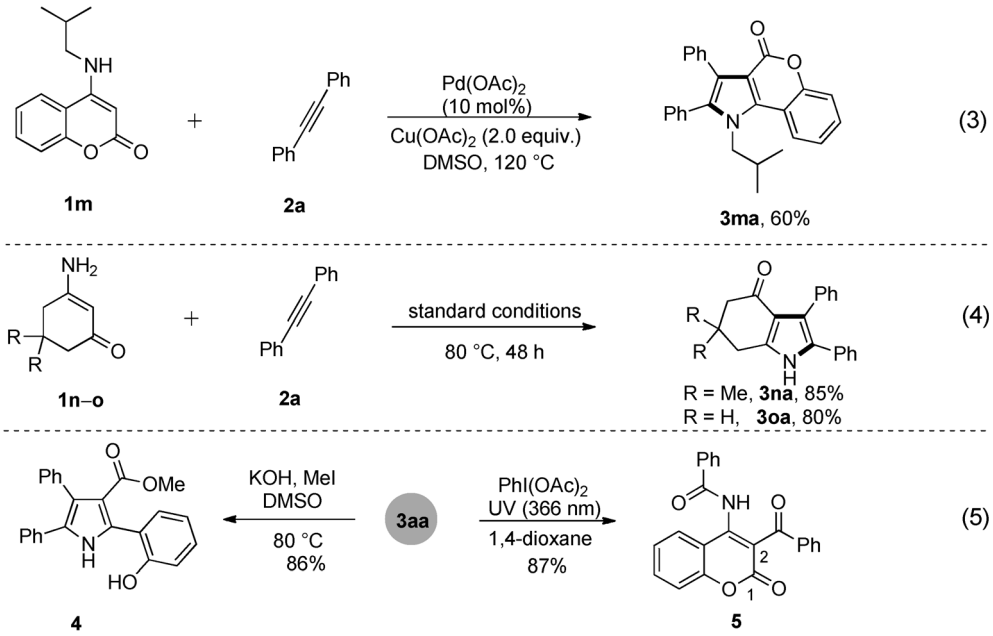
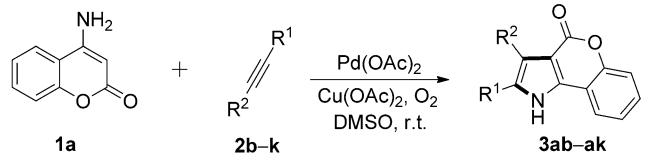
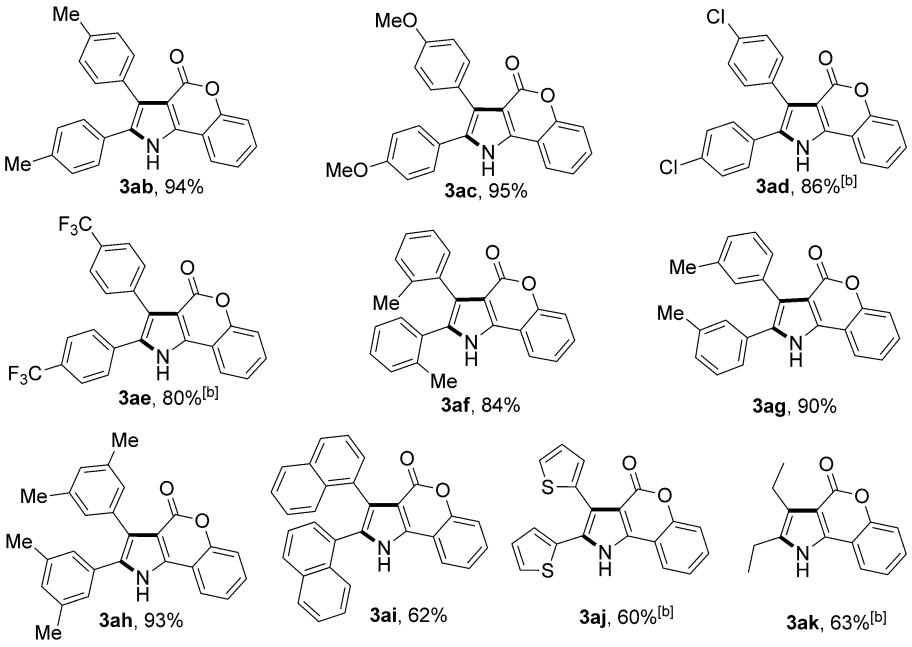


Table 3. Scope of symmetric alkynes.[a]



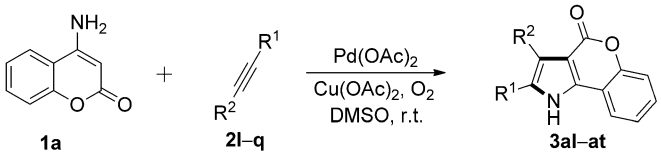
1a **2b–k** **3ab–ak**



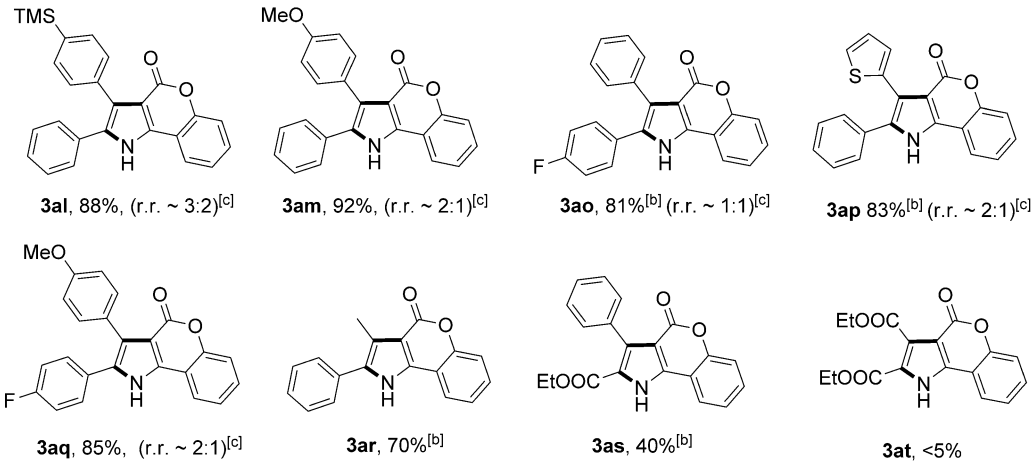
3ab, 94% **3ac**, 95% **3ad**, 86%[b] **3ae**, 80%[b] **3af**, 84% **3ag**, 90% **3ah**, 93% **3ai**, 62% **3aj**, 60%[b] **3ak**, 63%[b]

[a] *Reaction conditions:* **1a** (0.2 mmol, 1.0 equiv.), **2b–k** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (20 mol%), DMSO (1.0 mL), room temperature and O_2 balloon.
[b] Reaction temperature: 80 °C.

Table 4. Scope of asymmetric alkynes.[a]



1a **2l–q** **3al–at**



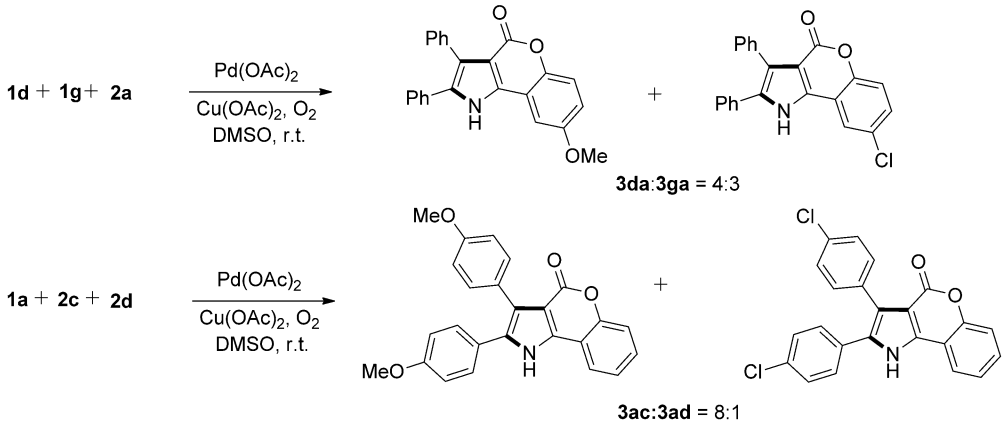
3al, 88%, (r.r. ~ 3:2)[c] **3am**, 92%, (r.r. ~ 2:1)[c] **3ao**, 81%[b] (r.r. ~ 1:1)[c] **3ap** 83%[b] (r.r. ~ 2:1)[c] **3aq**, 85%, (r.r. ~ 2:1)[c] **3ar**, 70%[b] **3as**, 40%[b] **3at**, <5%

[a] *Reaction conditions:* **1a** (0.2 mmol, 1.0 equiv.), **2l–q** (0.6 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (20 mol%), DMSO (1.0 mL), room temperature and O_2 balloon.
[b] Reaction temperature: 80 °C.
[c] Ratio of regioisomers (r.r.).

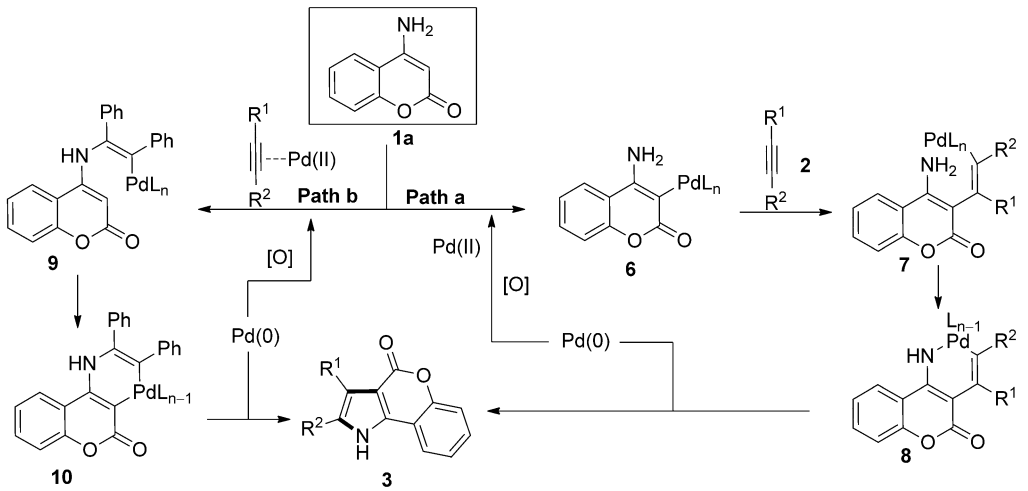
construct some other useful frameworks. Upon treatment of product **3aa** with KOH and MeI in DMSO at 80 °C for 1 h, the highly functionalized pyrrole **4** was obtained in 86% yield [Eq. (5)]. Additionally, the photolysis of **3aa** was also accomplished in the presence of iodobenzene diacetate under UV light, smoothly affording the C-2 functionalized coumarin **5**.[23] Interestingly, most products **3** showed fluorescence in toluene within a range of 350–450 nm (for details see the Supporting Information).

To further understand the electronic effects of substituents, two comparative experiments were conducted (Scheme 2). Electron-rich 4-aminocoumarin **1d** and electron-deficient **1g** exhibit similar reactivity (Scheme 2, **3da**:**3ga** = 4:3). However, electron-rich alkyne **2c** was more favoured in the oxidative annulation process than electron-deficient alkyne **2d** (Scheme 2, **3ac**:**3ad** = 8:1).

On the basis of known transition metal-catalyzed C–H functionalization/oxidative annulation reactions, we propose two possible mechanisms (Scheme 3). For path a, the formation of pyrrole **3** presumably commences with the palladation of 4-aminocoumarin **1a** to yield the palladium intermediate **6** (Scheme 3). This is followed by *syn*-addition of the intermediate **6** to an internal alkyne **2a** to generate the vinylpalladium intermediate **7**. Finally, intramolecular palladation of **7** will lead to the formation of the palladacyclohexene intermediate **8**, which subsequently undergoes reductive elimination to yield the coumarin-fused pyrrole **3**. Alternatively, alkyne **2** is initially activated by palladium(II) which acts as a Lewis acid,[24] and subsequent aminopalladation[25] of alkyne **2** could occur to form the intermediate **9** (Scheme 3, path b), which generates the intermediate **10** by an acid-promoted electrophilic aromatic palladation and subsequent proton abstraction.[26] The intermediate **10** then undergoes reductive elimination to give the expected product. The resulting palladium(0) is additionally oxidized to palladium(II) to complete this catalytic cycle.



Scheme 2. Competition experiments.



Scheme 3. Plausible mechanism.

In summary, we have developed an efficient synthesis of highly substituted pyrroles. The method utilizes simple and readily available enamines and alkynes, and employs direct Pd(II)-catalyzed oxidative annulation. A mechanistic investigation of pyrrole-forming reaction established a viable catalytic cycle. The mild nature of the reaction (room temperature was used in most of the pyrrole syntheses) should facilitate its practical application in settings that feature multiple labile functional groups. The significance of the pyrrole scaffold as structural element should also render this method attractive for both synthetic and medicinal chemistry.

Experimental Section

Typical Procedure

4-Aminocoumarin **1a** (0.2 mmol), diphenylacetylene **2a** (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol) and $Cu(OAc)_2$ (0.04 mmol) were added into DMSO (2 mL). The mixture was stirred at r.t. under O_2 atmosphere for 72 h. The crude product was purified by column chromatography on silica gel eluted by EtOAc/hexane = 1:4 to afford the desired product **3aa** as a white solid; yield: 90%. ^{1}H NMR (500 MHz, DMSO-d_6, 298 K): δ = 12.80 (s, 1H), 8.37–8.17 (m, 1H), 7.56–7.20 (m, 13H); ^{13}C NMR (125 MHz, DMSO-d_6, 298 K): δ = 157.74, 151.61, 135.78, 133.88, 133.55, 131.49, 131.07, 129.24, 128.82, 128.18, 128.09, 127.14, 124.39, 122.11, 121.09, 117.00, 113.86, 107.29, 40.73, 40.46, 40.18, 39.90, 39.62, 39.35, 39.07; HR-MS (ESI): m/z = 338.1177, calcd. for $[C_{23}H_{15}NO_2+H]^+$: 338.1176.

Acknowledgements

Financial support from Singapore Ministry of Education (Academic Research Grant: R143000443112, R143000532112), China Hubei Collaborative Innovation 2011 Project and National Nature Science Foundation of China (21202136) is greatly appreciated.

References

[1] a) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 4th edn., Blackwell, Oxford, UK, **2000**; b) J. Bergman, T. Janosik, *Modern Heterocyclic Chemistry*, Wiley-VCH, Weinheim, **2011**; c) R. J. Sundburg, *Comprehensive Heterocyclic Chemistry II*, Pergamon Press, Oxford, **1996**; d) H. Fan, J. Peng, M. T. Hamann, J.-G. Hu, *Chem. Rev.* **2008**, *108*, 264.

[2] a) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337; b) I. Bauer, H.-J. Knoelker, *Top. Curr. Chem.* **2012**, *309*, 203; c) P. J. Brothers, *Inorg. Chem.* **2011**, *50*, 12374; d) M. S. T. Goncalves, *Chem. Rev.* **2009**, *109*, 190; e) G. A. Pinna, M. M. Curzu, M. Sechi, G. Chelucci, E. Maciocco, *Farmaco* **1999**, *54*, 542; f) G. Murineddu, G. Loriga, E. Gavini, A. T. Peanna, A. C. Mule, G. A. Pinna, *Arch. Pharm.* **2001**, *334*, 393.

[3] a) E. S. Istvan, J. Deisenhofer, *Science* **2001**, *292*, 1160; b) B. D. Roth, *Prog. Med. Chem.* **2002**, *42*, 1; c) B. D. Roth, C. J. Blankley, A. W. Chucholowski, E. Ferguson, M. L. Hoefle, D. F. Ortwine, R. S. Newton, C. S. Sekerke, D. R. Sliskovic, C. D. Stratton, M. W. Wilson, *J. Med. Chem.* **1991**, *34*, 357.

[4] a) R. J. Andersen, D. J. Faulkner, C. H. He, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1985**, *107*, 5492; b) A. R. Quesada, M. D. G. Gravalos, J. L. F. Puentes, *Br. J. Cancer* **1996**, *74*, 677.

[5] a) J. E. Stambaugh, C. Sarajian, *J. Clin. Pharm.* **1981**, *21*, 501; b) J. R. Lewis, *JAMA J. Am. Med. Assoc.* **1981**, *246*, 377.

[6] M. Iwao, F. Ishibashi, T. Fukuda, H. Hasegawa, *PCT Int. Appl.* WO2012/099129, **2012**.

[7] L. Knorr, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635.

[8] C. Pall, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367.

[9] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.

[10] For selected examples of pyrrole synthesis through transitional metal-catalyzed cyclization, see: a) D. J. Gorin, N. R. Davis, D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260; b) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Quian, R. A. Windenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066; c) M. D. Mihovilovic, P. Stanetty, *Angew. Chem.* **2007**, *119*, 3684; *Angew. Chem. Int. Ed.* **2007**, *46*, 3612; d) V. Cadierno, J. Gimerno, N. Nebra, *Chem. Eur. J.* **2007**, *13*, 9973; e) L. Peng, X. Zhang, J. Ma, Z. Zhong, J. Wang, *Org. Lett.* **2007**, *9*, 1445; f) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin, Y. Jia, *Org. Lett.* **2010**, *12*, 4066; g) E. Benedetti, G. Lemière, L. L. Chapellet, A. Penoni, G. Palmisano, M. Malacria, J. P. Goddard, L. Fensterbank, *Org. Lett.* **2010**, *12*, 4396; h) R.-L. Yan, J. Luo, C.-X. Wang, C.-W. Ma, G. S. Huang, Y.-M. Liang, *J. Org. Chem.* **2010**, *75*, 5395; i) A. Takahashi, S. Kawai, I. Hachiya, M. Shimizu, *Eur. J. Org. Chem.* **2010**, 191; j) Y.-J. Bian, X.-Y. Liu, K.-G. Ji, X.-Z. Shu, L.-N. Gou, Y. M. Liang, *Tetrahedron* **2009**, *65*, 1424; k) M. Zhang, H. Neumann, M. Beller, *Angew. Chem.* **2013**, *125*, 625; *Angew. Chem. Int. Ed.* **2013**, *52*, 597; l) D. Srimani, Y. Ben-David, D. Milstein, *Angew. Chem.* **2013**, *125*, 4104; *Angew. Chem. Int. Ed.* **2013**, *52*, 4012; m) Z. Shi, M. Suri, F. Glorius, *Angew. Chem.* **2013**, *125*, 4992; *Angew. Chem. Int. Ed.* **2013**, *52*, 4892; n) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140; o) B. Pan, C. Wang, D. Wang, F. Wu, B. Wan, *Chem. Commun.* **2013**, *49*, 5073; p) R. J. Billedeau, K. R. Klein, D. Kaplan, Y. Lou, *Org. Lett.* **2013**, *15*, 1421; q) K. Iida, T. Miura, J. Ando, S. Saito, *Org. Lett.* **2013**, *15*, 1436; r) X. Feng, Q. Wang, W. Lin, G.-L. Dou, Z.-B. Huang, D.-Q. Shi, *Org. Lett.* **2013**, *15*, 2542; s) J. Liu, Z. Fang, Q. Zhang, Q. Liu, X. Bi, *Angew. Chem.* **2013**, *125*, 7091; *Angew. Chem. Int. Ed.* **2013**, *52*, 6953; t) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem.* **2013**, *125*, 7096; *Angew. Chem. Int. Ed.* **2013**, *52*, 6958; u) Y. Hu, C. Wang, D. Wang, F. Wu, B. Wan, *Org. Lett.* **2013**, *15*, 3146; v) M.-N. Zhao, H. Liang, Z.-H. Ren, Z.-H. Guan, *Adv. Synth. Catal.* **2013**, *355*, 221; w) X. Xin, D. Wang, X. Li, B. Wan, *Angew. Chem.* **2012**, *124*, 1725; *Angew. Chem. Int. Ed.* **2012**, *51*, 1693.

[11] For recent reviews and selected examples on C–H functionalization with applications to heterocyclic synthesis, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173. Other selected reviews and examples on C–H functionalization, see: e) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936; f) K. Chen, P. S. Baran, *Nature* **2009**, *459*, 824; g) E. M. Simmons, J. F. Hartwig, *Nature* **2012**, *483*, 70; h) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; i) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783; j) H. Li, B.-J. Li, Z.-J. Shi, *Cat. Sci. Technol.* **2011**, *1*, 191; k) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; l) O. Daugulis, H.-Q. Do, D. Shabashow, *Acc. Chem. Res.* **2009**, *42*, 1074; m) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; n) K. Godula, D. Sames, *Science* **2006**, *312*, 67; o) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; p) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910; q) M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. Eur. J.* **2011**, *17*, 8248; r) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; s) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874; t) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447; u) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; v) K. Fagnou, *Top. Curr. Chem.* **2010**, *292*, 35; w) E. M. Beck, M. J. Gaunt, *Top. Curr. Chem.* **2010**, *292*, 85; x) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 66; y) T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science* **2012**, *338*, 500; z) L. Ackermann, *Acc. Chem. Res.* **2013**, *46*, DOI:10.1021/ar3002798.

[12] S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585.

[13] a) D. R. Stuart, P. Alsabeh, m. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; b) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem.* **2011**, *123*, 1374; *Angew. Chem. Int. Ed.* **2011**, *50*, 1338.

[14] L.-H. Huang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176.

[15] For reviews of various directing groups, see: a) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; b) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; c) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788. The term "non-chelate-assisted" C–H functionalization has been previously used to describe C–H functionalization reactions of simple arenes: d) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731.

[16] A review presenting the concept of removable directing groups, see: a) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450. For some recent examples based on removable directing groups, see: b) C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang, *Angew. Chem.* **2012**, *124*, 7354; *Angew. Chem. Int. Ed.* **2012**, *51*, 7242; c) J. Cornella, M. Righi, I. Larrosa, *Angew. Chem.* **2011**, *123*, 9601; *Angew. Chem. Int. Ed.* **2011**, *50*, 9429; d) M. Yu, Z. Liang, Y. Wang, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 4987; e) N. Chernyak, A. S. Dudnik, C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 8270.

[17] For examples of our group recent developed palladium catalyzed C–H functionalization in the absence of directing groups, see: a) L. Wang, J. Y. Huang, S. Y. Peng, H. Liu, X.-F. Jiang, J. Wang, *Angew. Chem.* **2013**, *125*, 1812; *Angew. Chem. Int. Ed.* **2013**, *52*, 1768; b) L. Wang, S. Y. Peng, J. Wang, *Chem. Commun.* **2011**, *47*, 5422.

[18] For selected examples and reviews of indole synthesis *via* enamine, see: a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröger, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; b) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; c) w. Yu, Y. Du, K. Zhao, *Org. Lett.* **2009**, *11*, 2417; d) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078; e) M. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 2243; f) J. Barluenga, F. Rodriguez, F. J. Fananas, *Chem. Asian J.* **2009**, *4*, 1036.

[19] For selected reviews, see: a) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329; b) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400.

[20] For selected palladium-catalyzed examples by using dioxygen as oxidant, see: a) S. S. Stahl, *Science* **2005**, *309*, 1824; b) R. J. Nielsen, W. A. Goddard III, *J. Am. Chem. Soc.* **2006**, *128*, 9651; c) B. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1131; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115; d) G. Liu, G. Yin, L. Wu, *Angew. Chem.* **2008**, *120*, 4811; *Angew. Chem. Int. Ed.* **2008**, *47*, 4733; e) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190; f) M. M. Konnick, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 5753; g) M. M. M. Konnick, I. A. Guzaei, S. S. Stahl, *J. Am. Chem. Soc.* **2004**, *126*, 10212; h) S. S. Stahl, J. L. Thorman, R. Nelson, M. A. Kozee, S. S. Stahl, *J. Am. Chem. Soc.* **2001**, *123*, 7188; i) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851–863; j) A. Wang, H.-F. Jiang, H. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3846; k) A. Wang, H.-F. Jiang, *J. Am. Chem. Soc.* **2008**, *130*, 5030.

[21] CCDC 910095 (the structure of compound **3da** was determined by X-ray crystal analysis) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[22] To explain the regioselectivity of asymmetrical internal alkynes, the regioisomers of compound **3ao** (CCDC 910096) were determined by X-ray crystal analysis and NMR (see the Supporting Information). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[23] CCDC 917809 (the structure of compound **5** was determined by X-ray crystal analysis) contains the supple-

mentary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[24] a) N. Asao, T. Nogami, K. Takahashi, Y. Yammamoto, *J. Am. Chem. Soc.* **2002**, *124*, 764; b) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903.

[25] For examples of aminopalladiation of alkynes, see: a) A. Lei, X. Lu, *Org. Lett.* **2000**, *2*, 2699; b) A. Minatti, K. Muniz, *Chem. Soc. Rev.* **2007**, *36*, 1142.

[26] C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633.