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Synthesis of multi-substituted pyrroles using enamides and alkynes catalyzed by Pd(OAc)₂ with molecular oxygen as an oxidant[†]

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A cyclization reaction between enamides and alkynes catalyzed by palladium(n) acetate is described. In this method, the molecular oxygen serves as an efficient oxidant for the Pd(n)/Pd(0) catalytic cycle. The simple reaction conditions permit this methodology to be used as a general tool for the preparation of multi-substituted pyrroles.

The pyrrole ring is a core structure that features in a wide variety of natural products, organic materials and pharmaceuticals.¹ It is also an important industrial synthetic building block.² Consequently, the synthesis of the multi-substituted pyrroles has attracted much attention among organic chemists.3 Among the methods developed, metal-mediated or -catalyzed reaction using enamides as the starting materials is one of the best methods to access the pyrrole products.⁴ In 2006, Crawley and co-workers adapted the "Larock Indole Synthesis" approach and developed an efficient palladium-catalyzed pyrrole synthesis by the reaction of 2-amino-3-iodoacrylates with alkynes.5 Following this finding, Stuart and Fagnou reported a rhodium(m)-catalyzed cyclization reaction of enamides and alkynes to afford the pyrroles.⁶ Simultaneously, Glorius found that the multisubstituted pyrroles could be achieved from the coupling of enamines with alkynes using [Cp*RhCl₂]₂ as catalyst via allylic sp³ C-H activation of enamines.7 Recently, Wang's and Ackermann's research groups, respectively, developed a ruthenium-catalyzed pyrrole synthesis reaction using enamides and alkynes as the starting materials.8 Inspired by these pioneering studies, and following our continuing interest in direct functionalization of B C-H bonds of palladiumcatalyzed enamides,9 we would like to report a new method to synthesize the multi-substituted pyrroles via coupling of enamides with alkynes catalyzed by a palladium catalyst by using molecular oxygen as an oxidant.¹⁰ In this method, the need to use the

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preformed halogenated substrates and an excess amount of metal salt as an oxidant is avoided.

The feasibility of the coupling reaction was initially examined using enamide **1a** and diphenylacetylene (Table 1). A careful examination of the solvents in the presence of 10 mol% Pd(OAc)₂ and 2 equivalents of NaOAc as additives revealed that DMSO is a better choice for this reaction (Table 1, entries 1–5). Different palladium catalysts were tested and only Pd(OAc)₂ could afford the deacylation product **3a**. Other Pd(II) catalysts afforded the product in poor yield and/or chemoselectivity (Table 1, entries 7–10). When different bases were added as additives to promote the reaction, NaHCO₃ was found to efficiently afford a mixture of products (**3a**: **3a**' > 95:5 Table 1, entry 11). Other bases such as K₂CO₃, CS₂CO₃ or Et₃N gave the

Table 1 Optimization of the reaction conditions⁴

Ph	NHAc + Ph——PhPh	PC, 24 h P	$h \stackrel{N}{\underset{H}{\overset{N}{\overset{N}{\overset{N}{\overset{P}}}}}}_{3a} Pl$	h + Ph	Ph N Ac, 3a'
Entry	Catalyst (mol%)	Base	Solvent	3a/3a'	$\operatorname{Yield}^{b}(\%)$
1	$Pd(OAc)_2$ (10)	NaOAc	Toluene	_	_
2	$Pd(OAc)_2$ (10)	NaOAc	Dioxane	—	—
3	$Pd(OAc)_2$ (10)	NaOAc	t-Am-OH	_	_
4	$Pd(OAc)_2$ (10)	NaOAc	DMF	_	_
5	$Pd(OAc)_2$ (10)	NaOAc	DMSO	>99:1	53
6	$Pd(OAc)_2$ (10)	NaOAc	DMSO	>99:1	17^c
7	$Pd(PhCN)_2Cl_2$ (10)	NaOAc	DMSO	58:42	36
8	$Pd(OTFA)_2$ (10)	NaOAc	DMSO	98:2	32
9	$Pd(acac)_2$ (10)	NaOAc	DMSO	60:40	30
10	$[Pd(CH_3CN)_4](BF_4)_2$ (10)	NaOAc	DMSO	10:90	51
11	$Pd(OAc)_2$ (10)	NaHCO ₃	DMSO	>95:5	67
12	$Pd(OAc)_2$ (10)	K ₂ CO ₃	DMSO	>95:5	31
13	$Pd(OAc)_2$ (10)	Cs_2CO_3	DMSO	>95:5	< 5
14	$Pd(OAc)_{2}$ (10)	Et ₃ N	DMSO	>95:5	21
15	$Pd(OAc)_{2}$ (10)	KŐAc	DMSO	>99:1	67
16	$Pd(OAc)_{2}$ (5)	KOAc	DMSO	>99:1	56
17	$Pd(OAc)_2$ (10)	CsOAc	DMSO	>99:1	72

^{*a*} Unless noted otherwise, the reaction was carried out on enamide **1a** (0.4 mmol), diphenylacetylene **2a** (0.44 mmol), and base (2 equiv.) with palladium catalyst (10 mol%) under oxygen (1 atm) in solvent (4.0 mL). TFA = trifluoroacetyl. ^{*b*} Isolated yield. ^{*c*} Under 1 atm N₂ atmosphere.

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product in poor yield (Table 1, entries 12–14). But it was observed that KOAc and CsOAc both could generate only **3a** in good yield (Table 1, entries 15 and 17). When the catalyst loading was reduced, a slightly lower yield of **3a** was found (Table 1, entry 16). Due to the moisture sensitive nature of CsOAc in air, we decided to use KOAc as the additive.

With the optimized reaction conditions in hand, we next examined the scope of the enamide in this reaction (Table 2). It was noticed that the substituent on the phenyl ring of compound 1 affected the product's yield significantly. The substrates with an electron-donating group favored this cyclization reaction (Table 2, entries **3b**, **3c** and **3d**). The naphthalene substituted substrate could also afford the product in good yield (Table 2, entry **3e**). When the halogens were introduced at the *para*position of the phenyl ring, the desired cyclization products were still preferred (Table 2, entries **3f**, **3g** and **3h**). The tolerance of halogen substituents will permit the product to be used for further functionalization in the next step. However, a low yield of the product was obtained when *N*-(1-(furan-2-yl)vinyl)acetamide was applied in this reaction (Table 2, **3i**).

Next, we turned our attention to test the scope of the acetylene derivatives. We applied the N-(1-phenylvinyl)acetamide (1a) to react with different acetylene derivatives under the standard reaction conditions. As outlined in Table 3, all the symmetrical



^{*a*} Reaction conditions: enamide 1 (0.4 mmol), diphenylacetylene **2a** (0.44 mmol), KOAc (2.0 equiv.) and Pd(OAc)₂ (10 mol%) in DMSO (4.0 mL) under oxygen (1 atm) was heated for 24 h at 80 °C. ^{*b*} Isolated yields of the products. ^{*c*} The reaction time is 36 h.

 Table 3
 Cyclization of enamide 1a with different disubstituted alkynes^a



^{*a*} Reaction conditions: unless otherwise noted, enamide **1a** (0.40 mmol), alkyne (0.44 mmol), KOAc (2.0 equiv.) and $Pd(OAc)_2$ (10 mol%) in DMSO (4.0 mL) under oxygen (1 atm) was heated for 24 h at 80 °C. ^{*b*} Isolated yields of the products.

diarylsubstituted ethyne could afford the corresponding cyclization products in good yields (Table 3, entries 1–5). Only 34% yield of the product **4f** was obtained when the 1,2-bis(2-fluorophenyl)ethyne was used as the coupling partner. The aliphaticsubstituted ethyne does not favor this cyclization reaction (Table 3, entry 8). Furthermore, the non-symmetrical disubstituted ethynes could be successfully employed in this palladiumcatalyzed cyclization reaction. The products **4** and **4**' could be obtained in reasonable to good yields but with poor regioselectivities (Table 3, entries 9–11).



 $\label{eq:scheme1} \begin{array}{l} \mbox{Possible mechanism for the cyclization reaction catalyzed by palladium(1) acetate.} \end{array}$

Based on the observed results, a possible catalytic cycle was proposed as shown in Scheme 1. Firstly, a vinylpalladium species **B** was formed *via* the addition of palladium(π) acetate to the enamide (**A**) or *via* direct vinyl C–H bond activation.^{9b} Next the alkyne replaces DMSO and coordinates with the palladium center followed by migratory insertion to give intermediate **D**. The *cis*-configuration of two phenyl groups favors the new C–N bond formation. After palladium reductive elimination, the final product was formed under basic hydrolysis.¹¹ The Pd(0) generated was oxidized back to Pd(π) and involved in the next catalytic cycle.

In conclusion, we have developed a palladium-catalyzed cyclization reaction of enamides and internal alkynes to prepare multi-substituted pyrroles in reasonable yields. The scope of tolerated substrates in this work is rather broad. Moreover, the reaction conditions of this method are quite mild in which only molecular oxygen was used as the oxidant to recycle the palladium catalyst.

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Notes and references

 (a) X. Sui, R. Zhu, G. Li, X. Ma and Z. Gu, J. Am. Chem. Soc., 2013, 135, 9318; (b) L. McMurray, F. O'Hara and M. J. Gaunt, Chem. Soc. Rev., 2011, 40, 1885; (c) Z. Gu and A. Zakarian, Org. Lett., 2010, 12, 4224; (d) I. S. Young, P. D. Thornton and A. Thompson, Nat. Prod. Rep., 2010, 27, 1801; (e) E. M. Beck, R. Hatley and M. J. Gaunt, Angew. Chem., Int. Ed., 2008, 47, 3004; (f) C. T. Walsh, S. Garneau-Tsodikova and A. R. Howard-Jones, Nat. Prod. Rep., 2006, 23, 517; (g) P. M. Jordan, in *Biosynthesis of Tetrapyrroles*, ed. P. M. Jordan, Elsevier, Amsterdam, 1991, vol. 19, pp. 1–66; (h) The Chemistry of Pyrroles, ed. A. R. Jones and G. P. Bean, Academic Press, London, 1977.

- 2 A. L. Harreus, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, 2000.
- 3 (a) G. Mass, Science of Synthesis, Thieme, New York, 2001; (b) V. Ferriera, Org. Prep. Proced. Int., 2001, 33, 411; (c) Handbook of Heterocyclic Chemistry, Pergamon, San Diego, 2nd edn, 2000. Part of recently reported examples of transition-metal catalyzed or mediated synthesis of pyrroles; (d) Z. Chen, B. Lu, Z. Ding, K. Gao and N. Yoshikai, Org. Lett., 2013, 15, 1966; (e) W. Yang, L. Huang, H. Liu, W. Wang and H. Li, Chem. Commun., 2013, 49, 4667; (f) L. Ran, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, Green Chem., 2014, 16, 112; (g) M. Gao, C. He, H. Chen, R. Bai, B. Cheng and A. Lei, Angew. Chem., Int. Ed., 2013, 52, 6958; (h) X. Tang, L. Huang, Qi, W. Wu and H. Jiang, Chem. Commun., 2013, 49, 9597; (i) M. Zhang, H. Neumann and M. Beller, Angew. Chem., Int. Ed., 2013, 52, 597; (j) J. Schranck, A. Tlili and M. Beller, Angew. Chem., Int. Ed., 2013, 52, 7642 and references therein; (k) A. Abdukader, Q. Xue, A. Lin, M. Zhang, Y. Cheng and C. Zhu, Tetrahedron Lett., 2013, 54, 5898; (1) X. Wang, X.-P. Xu, S.-Y. Wang, W. Zhou and S.-J. Ji, Org. Lett., 2013, 15, 4246; (m) D. G. Dunford, D. W. Knight and R. C. Wheeler, ARKIVOC, 2012, 253; (n) M. Zhao, F. Wang and X. Li, Org. Lett., 2012, 14, 1412; (o) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin and Y. Jia, Org. Lett., 2010, 12, 4066; (p) J.-X. Chen, M.-C. Liu, X.-L. Yang, J.-C. Ding and H.-Y. Wu, J. Braz. Chem. Soc., 2008, 19, 877; (q) R. Martín, C. H. Larsen, A. Cuenca and S. L. Buchwald, Org. Lett., 2007, 9, 3379.
- 4 Part of recently reported studies of using enamides as starting materials in organic synthesis, see: (a) M. Chen, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, Angew. Chem., Int. Ed., 2013, 52, 14196; (b) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, Chem. Commun., 2012, 48, 8105; (c) Z.-H. Guan, K. Huang, S. Yu and X. Zhang, Org. Lett., 2009, 11, 481; (d) D. R. Carbery, Org. Biomol. Chem., 2008, 6, 3455 and references therein; (e) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu and H. Chen, J. Org. Chem., 2004, 69, 2355 and references therein; (f) W. Tang and X. Zhang, Chem. Rev., 2003, 103, 3029 and references therein; (g) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, Adv. Synth. Catal., 2003, 345, 103; (h) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang and Q.-L. Zhou, Angew. Chem., Int. Ed., 2002, 41, 2348; (i) I. D. Gridnev, M. Yasutake, N. Higashi and T. Imamoto, J. Am. Chem. Soc., 2001, 123, 5268; (j) M. J. Burk, J. R. Lee and Y. M. Wang, J. Am. Chem. Soc., 1996, 118, 5142.
- 5 M. L. Crawley, I. Goljer, D. J. Jenkins, J. F. Mehlmann, L. Nogle, R. Dooley and P. E. Mahaney, *Org. Lett.*, 2006, **8**, 5837.
- 6 D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, J. Am. Chem. Soc., 2010, **132**, 18326.
- 7 S. Rakshit, F. W. Patureau and F. Glorious, J. Am. Chem. Soc., 2010, 132, 9585.
- 8 (a) B. Li, N. Wang, Y. Liang, S. Xu and B. Wang, Org. Lett., 2013, 15, 136; (b) L. Wang and L. Ackermann, Org. Lett., 2013, 15, 176.
- 9 (a) H. Zhou, Y. H. Xu, W. J. Chang and T. P. Loh, Angew. Chem., Int. Ed., 2009, 48, 5355; (b) Y. H. Xu, Y. K. Chok and T. P. Loh, Chem. Sci., 2011, 2, 1822; (c) C. Feng and T. P. Loh, Chem. Sci., 2012, 3, 3458; (d) S. Pankajakshan, Y. H. Xu, J. K. Cheng, M. T. Low and T. P. Loh, Angew. Chem., Int. Ed., 2012, 51, 5701.
- 10 For another example of palladium-catalyzed coupling reaction between enamides and alkynes for the synthesis of pyrroles appearing after submission of this work, see: M. N. Zhao, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Org. Lett.*, 2014, **16**, 608.
- 11 (a) P. Linda, A. Stener, A. Cipiciani and G. Savelli, *J. Heterocycl. Chem.*, 1983, **20**, 247; (b) A. Cipiciani, P. Linda and G. Savelli, *J. Phys. Chem.*, 1983, **87**, 5262.