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Synthesis of β- and γ-Carbolinones via Pd-Catalyzed Direct Dehydrogenative Annulation (DDA) of Indole-carboxamides with Alkynes Using Air as the Oxidant

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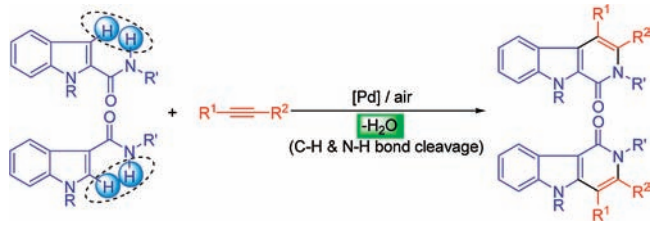
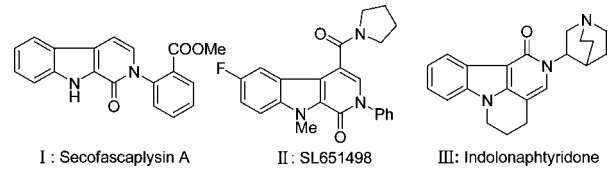
ABSTRACT



A palladium-catalyzed direct dehydrogenative annulation (DDA) of indolecarboxamides with internal alkynes via C−H and N−H bond cleavage using air as the oxidant was developed. With this method, both β- and γ-carbolinones can be easily prepared under the mild conditions.

β-Carbolinone skeletons are found in natural products (Figure 1), which have received considerable attention in view of their remarkable biological and pharmacological activities.[1] For example, the first naturally occurring β-carbolinone secofascaplysin A, **I**, was isolated from the *F. reticulata* in 1991.[2] SL651498, **II**, was identified as a drug development candidate from a research program designed to discover subtype-selective GABAA receptor agonists for the treatment of generalized anxiety disorder and muscle spasms.[3] However, in contrast, the isomeric γ-carbolinones are less widespread. One γ-carbolinone ring system is presented in indolonaphthyridone **III**, which acts as a conformationally restricted 5-HT3 receptor antagonist.[4]



I : Secofascaplysin A II : SL651498 III: Indolonaphtyridone

Figure 1. Structures of some biologically active β- and γ-carbolinones.

The synthesis of β- and γ-carbolinones has attracted considerable interest in recent years,[5] among which the

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(1) (a) Larsen, L. K.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1994**, *57*, 419. (b) Mouaddib, A.; Joseph, B.; Hasnaoui, A.; Merour, J.-Y. *Synthesis* **2000**, 549.

(2) Jimenez, C.; Quinoa, E.; Adamczeski, M.; Hunter, L. M.; Crews, P. *J. Org. Chem.* **1991**, *56*, 3403.

(3) Griebel, G.; Perrault, G.; Simiand, J.; Cohen, C.; Granger, P.; Depoortere, H.; Françon, D.; Avenet, P.; Schoemaker, H.; Evanno, Y.; Sevrin, M.; George, P.; Scatton, B. *CNS Drug Rev.* **2003**, *9*, 3.

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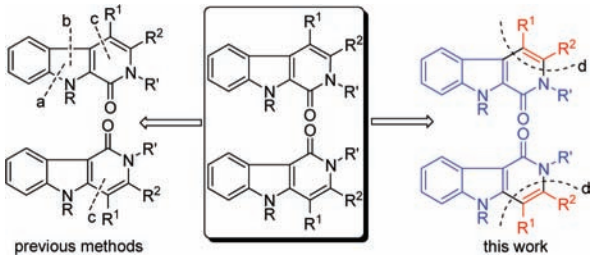
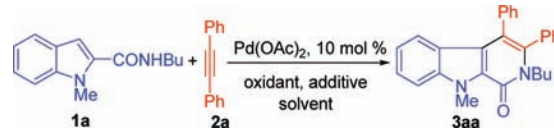
Scheme 1. Retrosynthetic Analysis of β- and γ-Carbolinones



intramolecular cyclization through path a, b, or c is the most common strategy (Scheme 1). For example, Beccalli et al. described an intramolecular Heck reaction of 2- and 3-iodoindole derivatives for the synthesis of β- or γ-carbolinones.[6] Padwa and co-workers developed an approach to β-carbolinones in high yields through a $AuCl_3$-catalyzed cycloisomerization of *N*-propargylindole-2-carboxamides.[7] However, several steps are generally required to prepare the relative complicated substrates for these intramolecular annulations. Alternatively, we envisioned that the β- and γ-carbolinones presumably can be constructed through an intermolecular annulation between indolecarboxamides and alkynes via C−C and C−N bond formations (path d, Scheme 1).

Compared with the traditional methods, C−H activation presents an advantage of convenience and atom economy, which has been applied successfully in synthesis of some aromatic and heteroaromatic compounds such as naphthalenes, indoles, isoquinolines, carbazoles, benzothiazoles, and pyridines.[8] Recently, we developed the direct dehydrogenative annulation (DDA) of simple anilines or biaryls with internal alkynes to generate indoles, carbazole, and carboline derivatives using O_2 as the oxidant.[9] Our interest in the minimization of substrate preactivation in metal-catalyzed processes led us to investigate the possibility of the direct dehydrogenative annulation (DDA) of indolecarboxamides with internal alkynes leading to β- and γ-carbolinone derivatives.

Table 1. Optimization of Reaction Conditions for the Preparation of **3aa**[a]



entry	oxidant	additives (equiv)	solvent	temp (°C)	yield (%)[b]
1	O_2 (1 atm)	—	DMF	100	18
2	O_2 (1 atm)	K_2CO_3 (3.0)	DMF	100	58
3	O_2 (1 atm)	K_2CO_3 (3.0)	DMA	100	69
4	air	K_2CO_3 (1.0)	DMA	100	70
5	air	CsOPiv (1.0)	DMA	100	76
6	air	TBAB (1.0)	DMA	100	86
7[c]	air	TBAB (1.0)	DMA	100	72
8	air	TBAB (1.0)	DMA	50	92

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.25 mmol), $Pd(OAc)_2$ (0.02 mmol), and solvent (2.0 mL) were heated in an open tube for 15 h. DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide, Piv = pivalyl, TBAB = tetra-*n*-butylammonium-bromide. [b] Isolated yield. [c] 5 mol % of $Pd(OAc)_2$ was used.

We initiated this project by investigating the reaction of *N*-butyl-1-methyl-1*H*-indole-2-carboxamide (**1a**) and diphenylethyne (**2a**) catalyzed by $Pd(OAc)_2$. When O_2 was used as the oxidant in this reaction, the expected β-carbolinone product **3aa** was successfully produced in 18% yield at 100 °C in DMF (entry 1, Table 1). To our delight, 58% of **3aa** was achieved in the presence of 3.0 equiv of K_2CO_3 (entry 2, Table 1). It is noteworthy that air could serve as the oxidant as good as O_2 in this reaction (cf. entries 3 and 4). The reaction in DMA gave better results than that in DMF (cf. entries 2 and 3, Table 1). Moreover, the amount of the additive can be reduced to 1 equiv. The additives screen revealed that the yield of **3aa** could be further increased to 86% by using TBAB as the additive (entry 6, Table 1). The yield decreased slightly with the lower catalyst loading (5 mol %) (cf. entries 6 and 7, Table 1). After screening on different parameters, the highest yield (92%) of **3aa** was achieved, when the reaction was carried out at 50 °C (entry 8, Table 1).

Under these optimized reaction conditions, although free (NH)-indoles **1b** could not be transformed into the desired products **3ba** (entry 2, Table 2), substrate with protecting groups such as Bn was well tolerated to give **3ca** (entry 3,

(4) Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C.-H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.

(5) (a) Cincinelli, R.; Dallavalle, S.; Merlini, L. *Synlett* **2008**, 1309. (b) Lu, S.; Zhang, W.; Pan, J.; Zhang, J. *Synthesis* **2008**, 1517. (c) Miki, Y.; Kuromatsu, M.; Miyatake, H.; Hamamoto, H. *Tetrahedron Lett.* **2007**, *48*, 9093. (d) Hudlicky, T.; Rinner, U.; Finn, K. F.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490. (e) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444. (f) Wang, S.; Dong, Y.; Wang, X.; Hu, X.; Liu, J.; Hu, Y. *Org. Biomol. Chem.* **2005**, *3*, 911. (g) Mmutlane, E. M.; Harris, J. M.; Padwa, A. *J. Org. Chem.* **2005**, *70*, 8055. (h) Tahri, A.; De Borggraeve, W.; Buysens, K. J.; Van Meervelt, L.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **1999**, *55*, 14675. (i) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444.

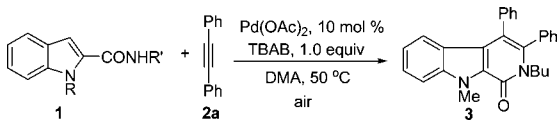
(6) Baccalli, E. M.; Broggini, G.; Marchesini, A.; Rossi, E. *Tetrahedron* **2002**, *58*, 6673.

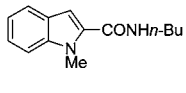
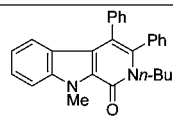
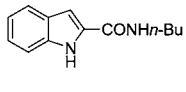
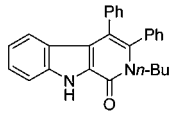
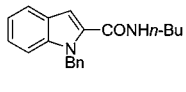
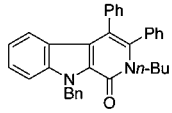
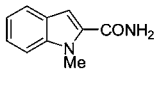
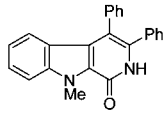
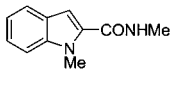
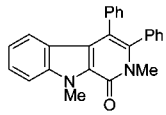
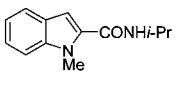
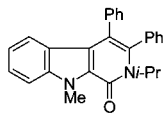
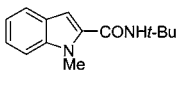
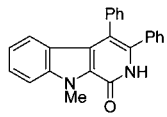
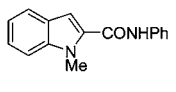
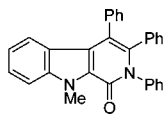
(7) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631.

(8) For a recent review, see: (a) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874. For some recent examples, see: (b) Umeda, U.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (c) Wu, Y.-T.; Huang, K.-H.; Shin, C.-C.; Wu, T.-C. *Chem.—Eur. J.* **2008**, *14*, 6697. (d) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572. (e) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (f) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (g) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (h) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed* **2008**, *47*, 7230. (i) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636. (j) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462. (k) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046.

(9) (a) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (b) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895. (c) Ding, S.; Shi, Z.; Cui, Y.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540. (d) Shi, Z.; Zhang, B.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4036.

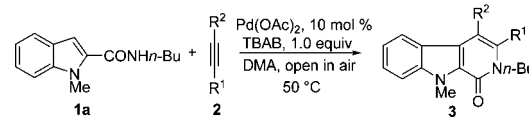
Table 2. $Pd(OAc)_2$-Catalyzed DDA Reaction of Indole-2-carboxamides **1** and Diphenylethyne **2a**[a]

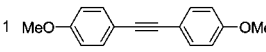
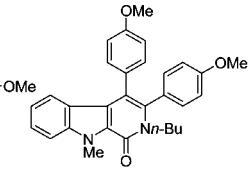
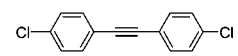
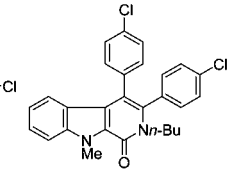
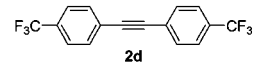
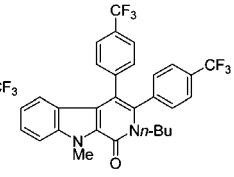
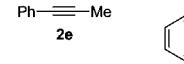
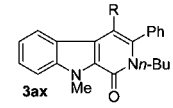
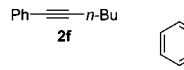
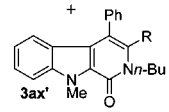
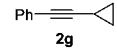
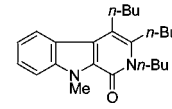


entry	1		product		yield (%)[b]
1		**1a**		**3aa**	92
2		**1b**		**3ba**	N.R
3		**1c**		**3ca**	75
4		**1d**		**3da**	63
5		**1e**		**3ea**	77
6		**1f**		**3fa**	87
7		**1g**		**3da**	40[c]
8		**1h**		**3ha**	81

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.25 mmol), $Pd(OAc)_2$ (0.02 mmol), DMA (2.0 mL), in an open tube, at 50 °C, 15 h. [b] Isolated yield. [c] This reaction was carried out at 100 °C.

Table 3. $Pd(OAc)_2$-Catalyzed DDA Reaction of *N*-Butyl-1-methyl-1*H*-indole-2-carboxamide **1a** and Internal Alkynes **2**[a]



entry	2		product		yield (%)[b]
1		**2b**		**3ab**	70
2		**2c**		**3ac**	72
3		**2d**		**3ad**	42
4		**2e**		**3ae+3ae'**	89 (82:18)[c]
			3ax		
5		**2f**		**3af+3af'**	79 (90:10)[c]
			3ax'		
6		**2g**	R = Me, *n*-Bu, cyclopropyl	**3ag+3ag'**	82 (92:8)[c]
7		**2h**		**3ah**	78

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (0.02 mmol), DMA (2.0 mL), in an open tube, at 50 °C, 15 h. [b] Isolated yield. [c] The structures and the ratio of the regioisomers were determined by $^1H-^1H$ NOESY and ^1H NMR analysis, respectively.

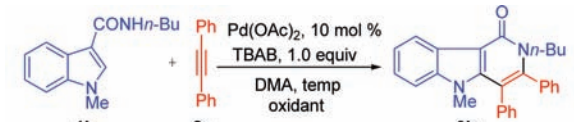
Table 2). Notably, 1-methyl-1*H*-indole-2-carboxamide **1d** was successfully converted to the desired product **3da**, which can easily be transformed into other β-carboline derivatives.[10] Moreover, the substrate **1g** containing the *N*-*tert*-butyl substituent produced **3da** in 40% yield with the release of the *tert*-butyl group (entry 7, Table 2). *N*-Phenyl-substituted substrate **1h** can also be converted into the interesting product **3ha** in 81% yield (entry 8, Table 2).

The scope of alkynes was then investigated using *N*-butyl-1-methyl-1*H*-indole-2-carboxamide (**1a**) as a partner. These results indicate that diarylacetylenes with electron-withdrawing or electron-donating groups proceeded well (42−72%, entries 1−3, Table 3). When unsymmetrical alkynes, such as 1-phenylpropyne, 1-phenyl-1-hexyne, or phenylcyclopropylacteylene, were employed, two regioisomers were obtained in 79−89% yield with good regioselectivity (entries 4−6, Table 3). Moreover, alkyl-substituted alkynes such as dec-5-yne (**2h**) were converted to **3ah** in good yield (entry 7, Table 3).

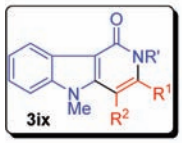
We next attempted the synthesis of γ-carbolinones under the above optimized conditions. However, *N*-butyl-1-methyl-1*H*-indole-3-carboxamide (**1i**) reacted with diphenylethyne (**2**a) producing the desired product **3ia** only in 25% yield (Scheme 2). The yield increased to 55% when the reaction

(10) For some examples, see: (a) Kuwada, T.; Fukui, M.; Hata, T.; Choshi, T.; Nobuhiro, J.; Ono, Y.; Hibino, S. *Chem. Pharm. Bull.* **2003**, *51*, 20. (b) Naoko, K.; Tominari, C.; Takeshi, K.; Eiichi, S.; Satoshi, H. *Heterocycles* **2000**, *53*, 1877. (c) Franz, B.; Dirk, H. *Tetrahedron* **1994**, *50*, 12329. (d) Georges, D.; Jack, D.; Guy, Q. *J. Heterocycl. Chem* **1983**, *20*, 967.

Scheme 2. $Pd(OAc)_2$-Catalyzed DDA Reaction of Indole-3-carboxamides **1** and Internal Alkynes **2**[a,b,c]



temp (°C)	oxidant	yield of **3ia** (%)
50	air	25
100	air	55
100	O_2 (1atm)	78

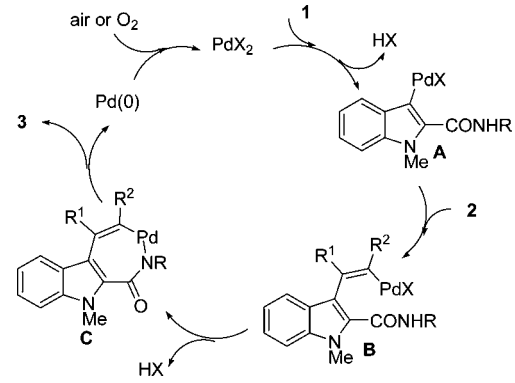


R' = *n*-Bu, R^1 = R^2 = Ph	**3ia**	78%
R' = *n*-Bu, R^1 = Me, R^2 = Ph	**3ie+3ie'**	60% (57:43)[c]
R' = *n*-Bu, R^1 = *n*-Bu, R^2 = Ph	**3if+3if'**	74% (67:33)[c]
R' = R^1 = R^2 = *n*-Bu	**3ii**	42%
R' = Ph, R^1 = R^2 = Ph	**3ja**	85%

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (0.02 mmol), DMA (2.0 mL), O_2 (1 atm), at 100 °C, 20 h. [b] Isolated yield. [c] The structures and the ratio of the regioisomers were determined by $^1H-^1H$ NOESY and ^1H NMR analysis, respectively. The above-described structure is the main isomer.

was performed at 100 °C. Moreover, the reaction efficiently produced **3ia** in 78% yield using O_2 (1 atm) instead of air as the oxidant in DMA at 100 °C (Scheme 2). Under these conditions, both aryl- and alkyl-substituted alkynes are tolerant of this transformation, leading to the corresponding γ-carbolinones (42−85% yields, Scheme 2). Compared with the reactions of **1a** with unsymmetrical alkynes (entries 4−6, Table 3), the regioselectivities in the synthesis of corresponding γ-carbolinones from **1i** with **2e** or **2f** are lower

Scheme 3. Plausible Mechanism for the DDA Reaction of **1** with **2**



(Scheme 2). Furthermore, 1-methyl-*N*-phenyl-1*H*-indole-3-carboxamide (**1j**) reacted with **2a**, providing **3ha** in good yield (85%).

A plausible mechanism for the reaction of **1** with alkynes **2** is illustrated in Scheme 3. The initiated electrophilic aromatic palladation[11] affords Pd^{II} intermediates **A**,[12] which appear to be the key process for the DDA reaction. The resulting intermediates **A** subsequently insert into alkynes **2** to produce vinylic palladium(II) intermediates **B**, which undergo proton abstraction[13] to afford seven-membered palladacycles **C**.[14] Subsequent reductive elimination generates the β- or γ-carbolinones as well as a Pd^0 complex that can be reoxidized to the Pd^{II} species by air or O_2 (Scheme 3).

In conclusion, we have demonstrated a novel palladium-catalyzed direct dehydrogenative annulation (DDA) of indolecarboxamides with internal alkynes using air or O_2 (1 atm) as the oxidant. The reaction provides a new strategy for the synthesis of synthetically and medicinally important β- and γ-carbolinone derivatives with H_2O as the byproduct via C−H and N−H bond cleavage. Studies are ongoing in our laboratory to discover the synthetic applications.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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