ORGANIC LETTERS
2010
Vol. 12, No. 7
1540−1543

Pd(II)-Catalyzed Synthesis of Carbolines by Iminoannulation of Internal Alkynes via Direct C−H Bond Cleavage Using Dioxygen as Oxidant

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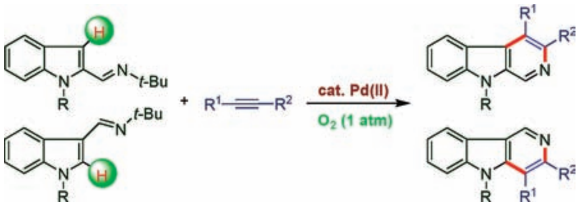
Received February 2, 2010

ABSTRACT



A palladium-catalyzed iminoannulation of internal alkynes via direct C−H bond cleavage was developed. Dioxygen was employed as a clean oxidant in this kind of catalysis. Carbolines were synthesized from *tert*-butylimines of N-substituted indole-2-carboxaldehydes or indole-3-carboxaldehydes.

Pyrido[3,4-*b*]indoles[1] and pyrido[4,3-*b*]indoles,[2] commonly known as β- and γ-carbolines, are of great importance in the areas of pharmaceuticals and are also versatile building blocks for natural products, bioactive compounds, and drugs.[3] Compounds containing the β-carboline units have been found to exhibit a wide range of biological activities, such as possessing potent and varied CNS and antitumor properties, acting as inhibitors of IκB kinase and PDE5, etc.[4] γ-Carbolines have also been investigated as antitumor agents.[3g,5] Their importance has stimulated considerable attention from

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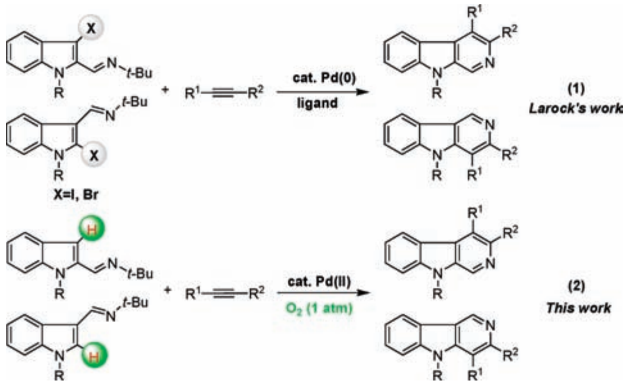
10.1021/ol100272s

organic chemists and encouraged the development of new synthetic strategies to construct carbolines.[6] Recently, Larock and co-workers developed a palladium-catalyzed annulation between internal alkynes and *tert*-butylimines of N-substituted 3-iodoindole-2-carboxaldehydes or 2-haloindole-3-carboxaldehydes (eq 1, Scheme 1).[6a,d] However, aryl halides were required and halide byproducts were produced via these methods. With the development of chemical science, C−H functionalization has received substantial attention, because of its sustainable and environmentally benign features.[7] Herein, we describe a Pd(II)-catalyzed iminoannulation of internal alkynes and *tert*-butylimines of N-substituted indole-carboxaldehydes via direct C−H bond activation using dioxygen as a clean oxidant (eq 2, Scheme 1).

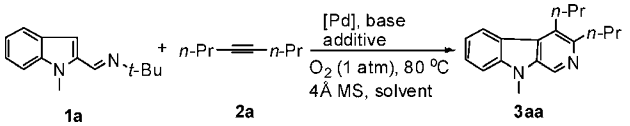
Scheme 1. Pd-Catalyzed Approaches to Carbolines



We recently developed direct-dehydrogenative anulation (DDA) reactions of simple anilines[8] or biaryls[9] with internal alkynes to generate indoles and carbazole derivatives, respectively, using O_2 as the oxidant.[10] On the basis of these results, we envisioned a direct-dehydrogenative anulation (DDA) of internal alkynes and *tert*-butylimines of N-substituted indole-carboxaldehydes to generate carboline derivatives (eq 2).

The initial iminoannulation of internal alkynes was examined by the reaction of the *tert*-butylimine of 1-methylindole-2-carboxaldehyde (**1a**) with 4-octyne (**2a**) in DMF in the presence of $Pd(OAc)_2$ (10 mol %), K_2CO_3, and 4 Å MS (150 mg) under O_2 (1 atm). The expected product β-carboline **3aa** was successfully obtained in 48% yield (entry 1, Table 1). The yield was slightly improved to 55% when TBAB (1 equiv) was added (entry 2, Table 1). As other bases such as Na_2CO_3, $HCOONa{\cdot}2H_2O$, pyridine, and $NaHCO_3$ (entries 3−6, Table 1) were tested in the reaction,

Table 1. Optimization of Pd-Catalyzed Annulation Conditions[a]



entry	[Pd]	base	additive	solvent	yield (%)[b]
1	Pd $(OAc)_2$	K_2CO_3		DMF	48
2	Pd $(OAc)_2$	K_2CO_3	TBAB	DMF	55
3	Pd $(OAc)_2$	Na_2CO_3	TBAB	DMF	58
4	Pd $(OAc)_2$	$HCOONa{\cdot}2H_2O$	TBAB	DMF	30
5	Pd $(OAc)_2$	pyridine	TBAB	DMF	35
6	**$Pd(OAc)_2$**	**$NaHCO_3$**	**TBAB**	**DMF**	**71**
7	Pd $(OAc)_2$	$NaHCO_3$	TBAC	DMF	45
8	Pd $(OAc)_2$	$NaHCO_3$	TBAF	DMF	28
9	Pd $(OAc)_2$	$NaHCO_3$	TBAB	DMA	31
10	Pd $(OAc)_2$	$NaHCO_3$	TBAB	DMSO	62
11	Pd $(OAc)_2$	$NaHCO_3$	TBAB	CH_3CN	49
12	Pd $(OAc)_2$	$NaHCO_3$	TBAB	toluene	22
13	Pd $(OAc)_2$	$NaHCO_3$	TBAB	THF	18
14	$PdCl_2$	$NaHCO_3$	TBAB	DMF	55
15	Pd $(PhCN)_2Cl_2$	$NaHCO_3$	TBAB	DMF	59
16[c]	Pd $(OAc)_2$	$NaHCO_3$	TBAB	DMF	54
17[d]	Pd $(OAc)_2$	$NaHCO_3$	TBAB	DMF	38

[a] **1a** (0.20 mmol), **2a** (0.40 mmol), [Pd] (10 mol %), base (0.40 mmol), additive (0.20 mmol), 4 Å MS (150 mg), and solvent (2 mL) were heated in a sealed tube under O_2 (1 atm), 80 °C, 24 h. [b] Isolated yields. [c] 5 mol % $Pd(OAc)_2$ was employed. [d] The reaction was carried out under air.

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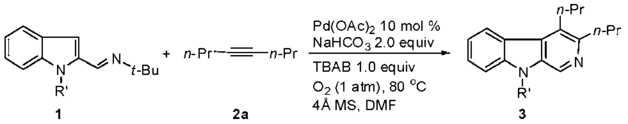
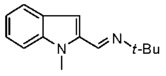
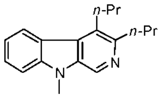
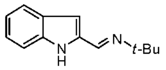
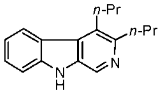
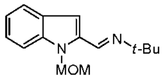
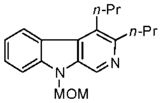
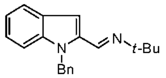
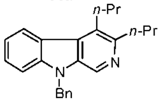
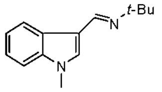
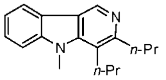
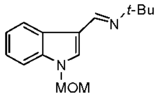
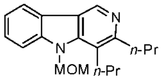
it was revealed that $NaHCO_3$ is the most effective base for this transformation (71% yield, entry 6, Table 1). Under these conditions, different phase-transfer catalysts (entries 7 and 8, Table 1), solvents (entry 9−13, Table 1), and Pd catalysts (entries 14 and 15, Table 1) were investigated but gave lower efficiencies. β-Carboline **3aa** was produced in 38% yield when this reaction was carried out under air (entry 17, Table 1).

Under the optimal conditions, we then investigated the scope of this transformation by different N-substituted *tert*-butylimines of indole-carboxaldehydes (Table 2). Using N-substituted *tert*-butylimines of indole-2-carboxaldehydes led to good yields of the corresponding β-carbolines (entries 1, 3, and 4, Table 2). Moreover, when the N-substituted *tert*-butylimines of indole-3-carboxaldehydes were allowed to react with 4-octyne, the C−H bond at C-2 could also be cleaved, generating the corresponding γ-carbolines with moderate yields (entries 5 and 6, Table 2). However, the *tert*-butylimine of indole-2-carboxaldehyde **1b** did not work under these conditions (entry 2, Table 2).

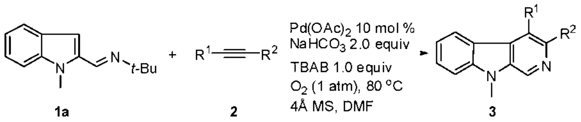
Table 2. $Pd(OAc)_2$-Catalyzed DDA Reaction of **1** with **2a**[a]

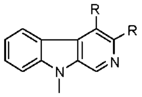
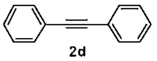
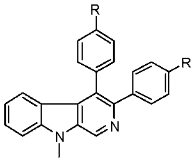
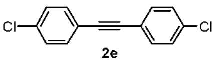
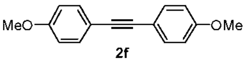
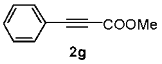
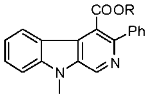
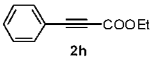
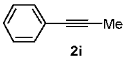
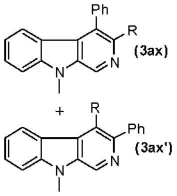
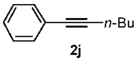
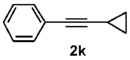
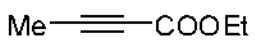
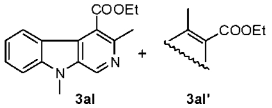


entry	imine	product	yield (%)[b]
1	 **1a**	 **3aa**	71
2	 **1b**	 **3ba**	0
3	 **1c**	 **3ca**	51
4	 **1d**	 **3da**	64
5	 **1e**	 **3ea**	37
6	 **1f**	 **3fa**	40

[a] Conditions: **1** (0.40 mmol), **2a** (0.80 mmol), $Pd(OAc)_2$ (10 mol %), TBAB (0.40 mmol), $NaHCO_3$ (0.80 mmol), and 4 Å MS (300 mg) in 4 mL of DMF under O_2 (1 atm), 80 °C, 36 h. [b] Isolated yield.

Table 3. $Pd(OAc)_2$-Catalyzed DDA Reaction of **1a** with Internal Alkynes **2**[a]



entry	alkyne	product		yield (%)[b]
1	 **2b**	 R = *n*-Bu, CH_2OAc	**3ab**	69
2	 **2c**		**3ac**	42
3	 **2d**	 R = H, Cl, OMe	**3ad**	45
4	 **2e**		**3ae**	45
5	 **2f**		**3af**	41
6	 **2g**	 R = Me, Et	**3ag**	52
7	 **2h**		**3ah**	57
8	 **2i**	 R = Me, *n*-Bu, cyclopropyl	**3ai+3ai'**	52 (1:2.5)[c]
9	 **2j**		**3aj+3aj'**	64 (1:3.8)[c]
10	 **2k**		**3ak+3ak'**	56 (1.3:1)[c]
11	 **2l**	 **3al** + **3al'**		37 (1:2)[c]

[a] Conditions: **1a** (0.40 mmol), **2** (0.80 mmol), $Pd(OAc)_2$ (10 mol %), TBAB (0.40 mmol), $NaHCO_3$ (0.80 mmol), and 4 Å MS (300 mg) in 4 mL of DMF under O_2 (1 atm), 80 °C, 36 h. [b] Isolated yield. [c] The ratio was determined by ^{1}HNMR.

The scope of the direct-dehydrogenative annulation (DDA) reaction was further expanded to a variety of internal alkynes (Table 3). The results in Table 3 demonstrate that this transformation has a high degree of functional group tolerance in the internal alkyne partners. Alkyl groups, aryl

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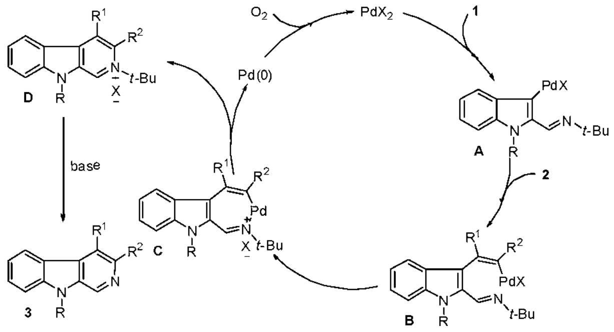
(10) For some reviews, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329–2364. For some Pd-catalyzed examples, see: (c) Stahl, S. S. *Science* **2005**, *309*, 1824–1826. (d) Nielsen, R. J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2006**, *128*, 9651–9660. (e) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355. (f) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (g) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733–4736. (h) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191. (i) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753–5762. For some our recent works, see: (j) Chen, A; Lin, R.; Liu, Q; Jiao, N. *Chem. Commun.* **2009**, 6842–6844. (k) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28–29.

groups, and esters are well tolerated, generating the corresponding carbolines in moderate yields. But-2-yne-1,4-diyl diacetate (**2c**) smoothly underwent cyclization with **1a**, leading to **3ac** in 42% yield (entry 2, Table 3). It is particularly noteworthy that with unsymmetrical alkynes with an ester group and an aryl group, such as 3-phenylpropiolates, a single carboline isomer was obtained with high regioselectivity (entries 6 and 7, Table 3). However, other unsymmetrical alkynes, such as 1-phenylpropyne, 1-phenylhexyne, phenylcyclopropylacteylene, and but-2-ynyl acetate, produced two regioisomers.

A plausible mechanism for the DDA reaction of **1** with alkyne **2** is illustrated in Scheme 2. The initiated electrophilic aromatic palladation[11] affords a Pd^{II} intermediate **A**. The resulting intermediate **A** subsequently inserts into **2** to produce a vinylic palladium(II) intermediate **B**, followed by reaction with the neighboring imine substituent to form a seven-membered palladacyclic immonium salt **C**. Subsequent reductive elimination generates a *tert*-butylcarbolinium salt **D** as well as a Pd^0 complex, which can be reoxidized to a Pd^{II} species for a new catalytic cycle by O$_2$ (1 atm). As previously suggested by Heck[12] and Larock,[6a,d] the *tert*-butyl group of the *tert*-butylcarbolinium salt **D** apparently fragments to produce carbolines **3** (Scheme 2).

Scheme 2. Plausible Mechanism for the DDA Reaction



In summary, we have demonstrated a novel Pd(II)-catalyzed direct-dehydrogenative annulation (DDA) of internal alkynes and *tert*-butylimines of N-substituted indolecarboxaldehydes via direct C−H bond activation leading to carboline derivatives. Use of dioxygen (1 atm) as the oxidant and the absence of ligands make this approach very easy to handle. Further efforts to expand the scope of this transformation and the synthetic applications are ongoing in our laboratory.

Acknowledgment. Financial support from Peking University, National Science Foundation of China (Nos. 20702002, 20872003), and National Basic Research Program of China (973 Program) (Grant No. 2009CB825300) are greatly appreciated. We thank Wei Jia and Riyuan Lin in this group for reproducing the results of **3da**, **3ad**, and **3ag**.

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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