Tetrahedron Letters 55 (2014) 27–30

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium(II)-catalyzed oxidative annulation of alkenylindoles with alkynes initiated by C–H activation

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ARTICLE INFO

Article history:
Received 1 July 2013
Revised 26 September 2013
Accepted 16 October 2013
Available online 22 October 2013

Keywords:
Alkenylindoles
Diarylethynes
C–H activation
Oxidative annulations
Pd(II)

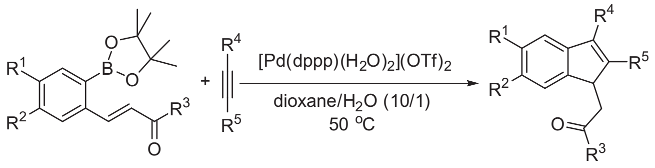
ABSTRACT

A palladium(II)-catalyzed annulation of alkenylindoles with diarylethynes initiated by C–H bond activation was developed. This method provided a convenient way for the synthesis of dihydrocyclopenta[*b*]indoles by enyne cyclization initiated by C–H bond activation.

Transition-metal-catalyzed organic reactions initiated by C–H bond activation represent a powerful way to construct C–C bonds, and a variety of processes has been developed.[1] In particular, annulation reactions initiated by C–H bond activation have exhibited enormous advantages in efficiency and atom economy for the construction of complex molecules. In C–H bond activation reactions, palladium-catalyzed activation of indoles is a convenient way for the synthesis of multiply substituted indoles[2] because this heterocyclic system is one of the most common motifs in biologically active molecules[3] and electron-rich to be activated on C-3 or C-2 position easily.[4] While enormous C–H bond activation reactions of indoles have been realized, the tandem reactions are scarcely studied.[5] Jiao and Miura independently reported the Pd-catalyzed direct dehydrogenative annulation of indoles with alkynes to form carbazoles or indole substituted tetrahydro-quinolines.[5d] In addition, Jiao also realized the cyclization reactions of indole-carboxamides or—imines with alkynes to afford carbolinones or carbolines.[5b,c] To the best of our knowledge, tandem annulation of alkynes with alkenes initiated by C–H activation of indoles has not been reported. Herein, we wish to report a palladium(II)-catalyzed tandem reaction between alkenylindoles and alkynes to generate dihydrocyclopenta[*b*]indoles.

Our group has focused on palladium(II)-catalyzed reactions for many years and some tandem reactions initiated by nucleopalladation of alkynes[6] or insertion of alkynes to arylpalladium species (which produced from transmetallation of arylboron reagents with palladium complexes)[7] have been successfully accomplished. Among all of these annulations, palladium(II) complexes will be regenerated and no redox system was needed. Based on these previous works, we then begin to explore some similar reactions initiated by C–H bond activation. Recently, we have reported a palladium(II)-catalyzed highly enantioselective tandem reaction of *ortho*-boronate substituted cinnamic ketones and alkynes.[7d] This is a tandem reaction initiated by transmetallation of arylboron reagents with palladium complex and quenched by conjugate addition to enones, in which the divalent palladium species was regenerated in the quenching step to complete the catalytic cycle (Scheme 1). Based on the above work, we are wondering if the enyne cyclizations initiated by C–H bond activation under the catalysis of palladium(II) complexes could be realized. Allowing for easy activation of C–H bond in 2 or 3-position of indoles, we then test the idea by using alkenylindoles and alkynes as the substrates.

First, indole (**1a**) was synthesized and reacted with diphenylethyne (**2a**). Unfortunately, the results of our trials indicate that the reaction did not occur when some palladium(II) complexes



Scheme 1. Palladium(II)-catalyzed tandem addition of *ortho*-boronate substituted cinnamic ketones and alkynes.

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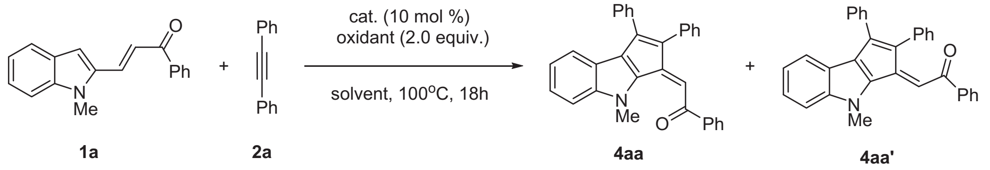
http://dx.doi.org/10.1016/j.tetlet.2013.10.079

Table 1
Optimization of the reaction conditions for Pd-catalyzed annulation[a]



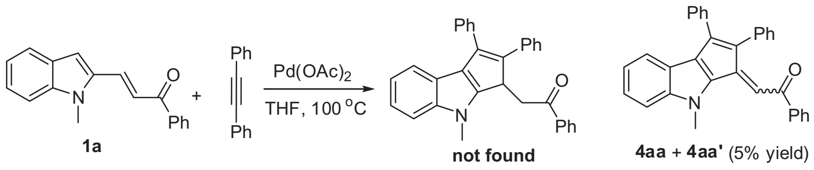
Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)	
				4aa	**4aa**′
1	$Pd(OAc)_2$/bpy	–	THF	–	–
2	$Pd(TFA)_2$	–	THF	–	–
3	$[Pd(dppp)(H_2O)_2](OTf)_2$	–	THF	–	–
4	$[Pd(dppp)(H_2O)_2](BF_4)_2$	–	THF	–	–
5	$Pd(OAc)_2$	–	THF	–	5
6	$Pd(OAc)_2$	BQ	THF	–	–
7	$Pd(OAc)_2$	O_2[c]	THF	18	<5
8	$Pd(OAc)_2$	Ag_2CO_3	THF	21	<5
9	$Pd(OAc)_2$	$Cu(OAc)_2$	THF	57	11
10	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	45	13
11	$Pd(OAc)_2$	$Cu(OAc)_2$	^{t}AmylOH	58	15
12	$Pd(OAc)_2$	$Cu(OAc)_2$	^{t}BuOH	66	7
13	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	48	<5
14	$Pd(OAc)_2$	$Cu(OAc)_2$	DMAc	56	25
16	$Pd(OAc)_2$	$Cu(OAc)_2$	Mixed[f]	61	27
17[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	Mixed[f]	60	25
18[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	Mixed[f]	53	10

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), catalyst (10 mol %), oxidant (2.0 equiv), solvent (1.0 mL) were heated in a sealed tube for 12 h at 100 °C.
[b] Isolated yield.
[c] An oxygen bubble was used.
[d] The reaction temperature was 120 °C.
[e] The reaction temperature was 80 °C.
[f] The solvent was ^{t}BuOH/DMAc/DMSO (6/3/1(v/v/v)).

were used as the catalysts (Table 1, entries 1–4). However, a mixture of products in a 5% yield can be isolated when substrates **1a** and **2a** were stirred at 100 °C in the solvent of THF under the catalysis of 10 mol % of $Pd(OAc)_2$ (Table 1, entry 5). From the spectra, we found that they might be a mixture of 3,4-dihydrocyclopenta[*b*]indoles **4aa** and **4aa**′ which contain an exocyclic double bond, instead of the expected conjugate addition product (Scheme 2). From the literature, it was known that although there are many methods to synthesize multiply substituted indoles, the reactions to obtain cyclopenta[*b*]indoles are scarce.[8] Therefore, the discovery of the products even in small amounts made our decision to study the reaction in detail. After considering the possible pathway for the formation of the products, it occurred to us that β-H elimination of the C–Pd bond might be the quenching step of the reaction, which will generate the Pd(0) species making the catalytic cycle impossible to occur. Thus, the addition of oxidants would be necessary for the completion of the reaction.

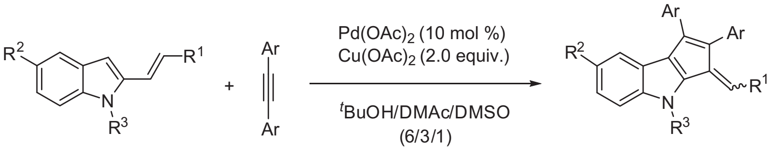
Initially, the screening of oxidants was investigated. It was found that benzoquinone was not effective for the reaction and lower yields were given utilizing oxygen or Ag_2CO_3 as the oxidants (Table 1, entries 6–8). The use of $Cu(OAc)_2$ can improve the reaction to obtain a mixture of two isomers **4aa** and **4aa**′ in 57% and 11% yields, respectively (Table 1, entry 9).[9] Further examination of solvent effects revealed that DMSO or DMF gave the two products in a little lower total yield, while DMAc or alcoholic solvents such as ^{t}AmOH or ^{t}BuOH can lead to a better yield (Table 1, entries 10–13). It is worth noting that the addition of DMSO suppressed the generation of some byproducts as observed from TLC. The best result was obtained in 88% total yields in mixed solvents of ^{t}BuOH/DMAc/DMSO (6/3/1) (Table 1, entry 16). Then the temperature was evaluated and it was found that a lower temperature will slightly decrease the yield (Table 1, entries 17 and 18). Finally, the optimal reaction conditions were selected as: alkenylindoles (0.1 mmol), alkynes (0.15 mmol), $Pd(OAc)_2$ (10 mol %), and $Cu(OAc)_2$ (0.2 mmol, 2.0 equiv) were stirred in ^{t}BuOH/DMAc/DMSO (6/3/1, 1.0 mL) at 100 °C for 12 h.

Under the optimal conditions, the scope of this process was investigated by using different 2-alkenylated indoles and 1, 2-diarylethyne. Some of the configurations of products were identified by X-ray crystallography or NOESY spectra. Notably, excellent total yields of the two isomers were achieved with indoles substituted with an enone (Table 2, entries 1–5). Compared to aryl enone substituted indoles, the alkyl enone substituted indoles exhibited higher reactivity and selectivity. Moreover, other 2-alkenylated indoles with an electron-withdrawing group such as ester and nitrile can also lead to good yields of corresponding products



Scheme 2. Preliminary study of the reaction of **1a** with diphenylethyne (**2a**).

Table 2
Annulation of 2-alkenylindoles with alkynes[a]



1 **2** **4(major)+4'(minor)**

Entry	1				2	Yield (%)[b]		
	R^1	R^2	R^3		Ar	**4** (major)	**4′** (minor)	Total
1[c]	COPh	H	Me	**1a**	Ph (**2a**)	61(**4aa**)	27(**4aa′**)	88
2[d]	COMe	H	Me	**1b**	Ph (**2a**)	84(**4ba**)	15(**4ba′**)	99
3	COC$_6$H$_4$-4-OMe	H	Me	**1c**	Ph (**2a**)	63(**4ca**)	19(**4ca′**)	82
4	COC$_6$H$_4$-4-Me	H	Me	**1d**	Ph (**2a**)	61(**4da**)	15(**4da′**)	76
5[d]	CO^{t}Bu	H	Me	**1e**	Ph (**2a**)	90(**4ea**)	6(**4ea′**)	96
6[d]	CN	H	Me	**1f**	Ph (**2a**)	76(**4fa**)	–[e]	76
7[c,d]	COOEt	H	Me	**1g**	Ph (**2a**)	80(**4ga**)	10(**4ga′**)	90
8	COMe	Cl	Me	**1h**	Ph (**2a**)	45(**4ha**)	36(**4ha′**)	81
9	COMe	Me	Me	**1i**	Ph (**2a**)	44(**4ia**)	–[f]	44
10	COPh	H	Bn	**1j**	Ph (**2a**)	51(**4ja**)	34(**4ja′**)	75
11	COMe	H	Me	**1b**	4-MeC$_6$H$_4$ (**2b**)	47(**4bb**)	15(**4bb′**)	62
12[d]	COMe	H	Me	**1b**	4-FC$_6$H$_4$ (**2c**)	58(**4bc**)	20(**4bc′**)	78
13	COMe	H	Me	**1b**	4-ClC$_6$H$_4$ (**2d**)	36(**4bd**)	15(**4bd′**)	51

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.15 mmol), Pd(OAc)$_2$ (10 mol %), Cu(OAc)$_2$ (2.0 equiv), ^{t}BuOH (0.6 mL), DMAc (0.3 mL), and DMSO (0.1 mL) were heated in a sealed tube for 12 h at 100 °C.

[b] Isolated yield. The configuration of the products in the entries without the annotation was not determined.

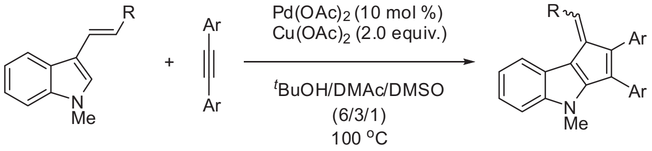
[c] X-ray crystallography shows that the configuration of the major product is *Z* and the minor one is *E*.

[d] The NOESY spectra show that the configuration of the major product is *Z* and the minor one is *E*.

[e] Another isomer was not observed.

[f] Another isomer cannot be separated from the substrate **1i**.

Table 3
Annulation of 3-alkenylindoles with alkynes[a]



3 **2** **5**

Entry	3	2	Yield[b] (%)
	R	Ar	
1[c]	COPh (**3a**)	Ph (**2a**)	50 (**5aa**)
2	COMe (**3b**)	Ph (**2a**)	45 (**5ba**)
3	CO^{t}Bu (**3c**)	Ph (**2a**)	42 (**5ca**)
4	COOEt (**3d**)	Ph (**2a**)	59 (**5da**)
5	COMe (**3b**)	4-MeC$_6$H$_4$ (**2b**)	63 (**5bb**)
6	COMe (**3b**)	4-FC$_6$H$_4$ (**2c**)	61 (**5bc**)
7	COMe (**3b**)	4-ClC$_6$H$_4$ (**2d**)	44 (**5bd**)

[a] Reaction conditions: **3** (0.10 mmol), **2** (0.15 mmol), Pd(OAc)$_2$ (10 mol %), Cu(OAc)$_2$ (2.0 equiv), ^{t}BuOH (0.6 mL), DMAc (0.3 mL), and DMSO (0.1 mL) were heated in a sealed tube for 12 h at 100 °C.

[b] Isolated yield. The configuration of the products was not determined except **5aa**.

(Table 2, entries 6 and 7). When the indole ring was substituted with the chlorine atom, the reaction proceeded smoothly to give a good total yield but with poor selectivity (Table 2, entry 8). Furthermore, only moderate yield was obtained with indole substituted by the methyl group (Table 2, entry 9). *N*-Bn-indole (**1j**) has a similar reactivity and a little lower selectivity compared with *N*-Me-indole (**1b**) (Table 2, entry 10). Finally, the reactions of indole **1b** with a set of 1,2-diarylethynes were investigated. It was found that the alkynes substituted with the methyl, fluorine, or chlorine group on the aryl ring can get acceptable results (Table 2, entries 11–13).

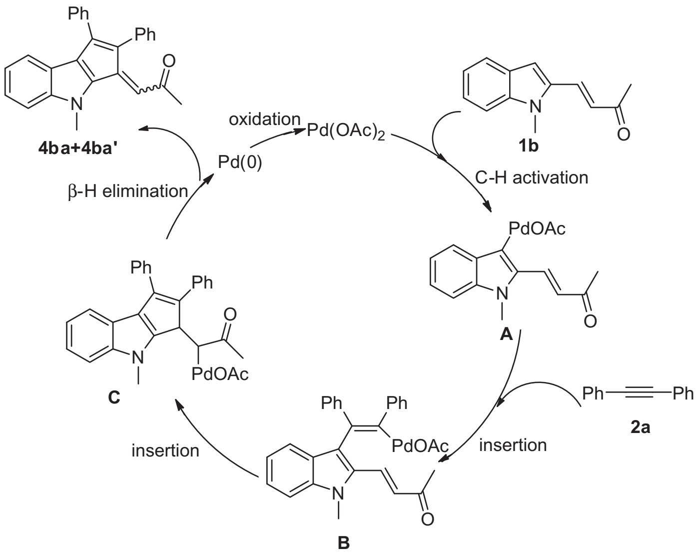
Next, our attention turned to the development of the corresponding annulation reaction of 3-alkenylated indoles with alkynes (Table 3). To our delight, the reaction could be carried out smoothly between 3-alkenylated indoles and 1, 2-diarylethyne to afford 1,4-dihydrocyclopenta[*b*]indoles in moderate yield under the same conditions as Table 2. Although the reactivity was inferior to 2-substituted counterpart, the selectivity was very good and only one isomer could be isolated. From the result of Table 3, it is shown that the substituents of both substrates have little effect on the annulation reactions.

A plausible mechanism for the reaction is shown in Scheme 3 using substrate **1b** as an example. First, C–H bond activation of indoles catalyzed by Pd(OAc)$_2$ generates intermediate A. Then, the alkyne inserts into the C–Pd bond of A to form the intermediate B. Intramolecular insertion of alkenes to C–Pd bond of B can obtain intermediate C, which undergoes β-H elimination to produce the products and Pd(0) species. The Pd(0) species then can be oxidized to Pd(II) by Cu(OAc)$_2$ to complete the catalytic cycle.

In conclusion, a novel palladium(II)-catalyzed annulation of 2 or 3-alkenylated indoles and substituted 1,2-diarylethynes initiated by C–H bond activation to afford 1,4 or 3,4-dihydrocyclopenta[*b*]indoles was developed. This type of transition-metal-catalyzed intermolecular enyne cyclization initiated by C–H bond activation has been reported scarcely in the literature and it may provide a possibility to accomplish some other tandem reactions to produce complex molecules in an efficient way.

Acknowledgements

We thank the National Basic Research Program of China (2009CB825304), National Natural Science Foundation of China



Scheme 3. The plausible mechanism for the annulation of alkenylindoles and alkynes.

(21232006, 21272249), and Chinese Academy of Sciences for financial support.

Supplementary data

Supplementary data (Copies of ^{1}H NMR and ^{13}C NMR spectra of substrates and products. Experimental procedures and data for substrates and products.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.079.

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9. The structure of **4aa**, **4aa**′, **4ga**, **4ga**′, and **5aa** were confirmed by X-ray crystallography. Deposit numbers of these compounds from Crystallographic Data Centre are: **4aa** (CCDC 952149), **4aa**′ (CCDC 952150), **4ga** (CCDC 952151), **4ga**′ (CCDC 952152), and **5aa** (CCDC 952153). Copies of the data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.