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Pd-Catalyzed Intramolecular Cyclization via Direct C−H Addition to Nitriles: Skeletal Diverse Synthesis of Fused Polycyclic Indoles

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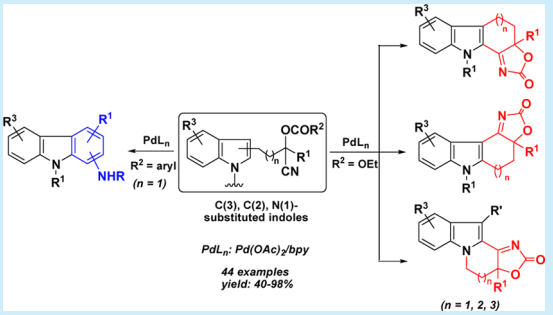
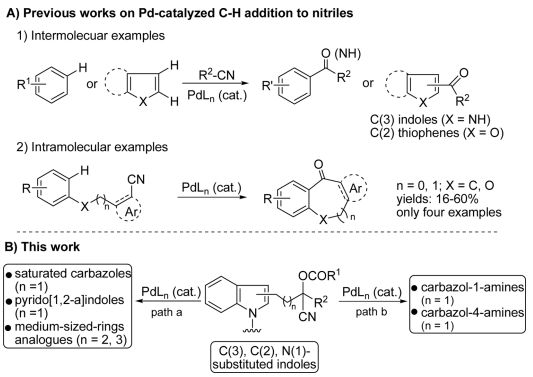
Supporting Information

ABSTRACT: The first example of Pd-catalyzed intramolecular C−H addition of indoles bearing cyanohydrin components at the C(3), C(2), and N(1) positions to nitriles is described. A wide range of functionalized partially saturated carbazoles, tetrahydropyrido[1,2-*a*]-indole, and carbazoles can be prepared in good to excellent yields under the optimal conditions. In addition, fused polycyclic indoles with seven- or eight-membered rings can also be formed smoothly.



The development of efficient synthetic approaches to construct complex molecular architectures via direct C−H bond functionalization has been gaining intense interest within the chemical community.[1] Transition-metal-catalyzed annulations via direct coupling of a C(sp^2)−H bond with C−C multiple bonds constitute a robust and appealing motive due to their high efficiencies in the construction of cyclic compounds which hold a vital position in modern organic chemistry.[2] By contrast, catalytic transformations of this type involving C−H bond addition to polar unsaturated carbon−heteroatom bonds such as nitriles have been received less consideration, presumably due to the inherently inert nature of nitriles.[3] Since Larock's pioneering contributions to the Pd-catalyzed direct C(sp^2)−H addition to nitriles,[4a,b] several elegant works involving Pd (Scheme 1A-1) and Wang's Mn/Lewis acid dual activation have been demonstrated in this appealing research topic.[4c−g,5] However, very limited examples in which benzocyclic ketones were synthesized by a Pd catalyst in low to moderate yields indicated that intramolecular variations of this transformation are much more challenging (Scheme 1A-2),[4a,b,f,g] which cumbered their synthetic application on the preparation of functionalized cyclic compounds.

Scheme 1. Pd-Catalyzed C(sp^2)−H Addition to Nitriles



Fused polycyclic indoles including six-membered ring systems such as carbazoles, pyrido[1,2-*a*]indoles, and their partially saturated counterparts represent a prominent class of heterocyclic compounds with varied and often potent biological activity.[6] In addition, corresponding medium-sized-ring analogues are also the constituents of a variety of natural products and pharmaceutical agents.[6c,d,7] Therefore, it is of great significance for the construction of these molecular architectures.[8] Considerable progress in transition-metal-catalyzed synthesis of these molecular skeletons via intramolecular indolyl C−H bond functionalization involving C−C multiple bonds has been achieved.[9] However, catalytic conversion of the indole nucleus into fused polycyclic indoles through indolyl C−H bond addition to nitrile remains underdeveloped. On the other hand, considering the structural diversity and complexity of pharmacologically active indole derivatives, the development of a novel strategy for efficient catalytic construction of structurally diverse fused polycyclic indoles through C−H bond functionalization is in great demand.

As functionalized nitriles, cyanohydrins which are readily prepared from ketones and aldehydes have demonstrated considerable synthetic potential as useful building blocks.[10] Cyanohydrins were also employed as reaction partners in several transition-metal-catalyzed reactions in which the cyano group remained intact generally.[11] Herein, we report a diverse synthesis of indole-fused polycyclic derivatives by a Pd-catalyzed intramolecular cyclization of indoles bearing cyanohydrin units with unique features that include (1) the first direct C−H bond addition of indoles bearing cyanohydrin

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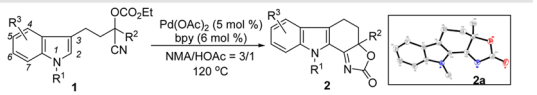
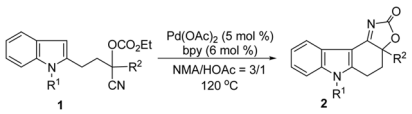
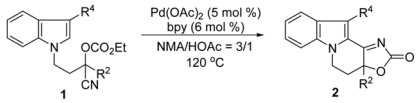
units at the C(3), C(2) or N(1) positions to nitriles and subsequent cyclization of resultant imines furnishing functionalized partially saturated carbazoles and tetrahydropyrido[1,2-*a*]indole derivatives with high efficiency; (2) facile manipulations of cyanohydrin units enabling ready modulation of this transformation to deliver carbazoles via a novel cyclization-aromatization sequence; and (3) indole-annulated medium-sized-ring skeletons that can also be readily prepared (Scheme 1B).

Initially, we envisioned that the incorporation of cyanohydrin units into substrates would possess two merits as follows: (1) it would enable readily accessing starting materials bearing cyano-group; (2) resultant imines from direct C−H addition of indoles to nitriles would undergo a subsequent cyclization with an adjacent acyl group of cyanohydrin units to furnish fused polycyclic indoles. To this end, the feasibility of Pd-catalyzed intramolecular cyclization of *N*-methylindole **1a** bearing an *O*-ethoxycarbonyl substituted cyanohydrin unit at the 3-position was examined. Considering that neither an inter- or intramolcular case of indole(C2) C−H addition to nitrile has hitherto been reported, various reaction parameters such as Pd-catalysts, ligands, solvents, and temperatures were evaluated (see Supporting Information for details). To our delight, a 75% yield of dihydro-3a*H*-oxazolo[4,5-*a*]carbazol-2(10*H*)-one **2a** which was confirmed by X-ray analysis can be obtained at 120 °C in the presence of $Pd(OAc)_2$ (10 mol %) and 2,20-bipyridine (bpy) (12 mol %) by using NMA as a solvent. Furthermore, the use of NMA with the addition of HOAc as a cosolvent led to a dramatic acceleration of this reaction and enabled this process to afford the desired product **2a** in almost quantitative yield by using 5 mol % of $Pd(OAc)_2$ and 6 mol % ligand (Table 1, entry 1).[12] Notably, no cyclic ketone product generated from the hydrolysis of the resultant imine intermediate was observed during the course of investigation.

With the optimal reaction conditions in hand, we first examined the scope of this cyclization with the indole tethered cyanohydrin moieties at the C-3 position by variation of the substitution patterns on the indole core and R^2 groups on cyanohydrin units (Table 1). N(1)-Substitution (R^1) affected the investigated process greatly. N-Benzyl substituted indole gave an excellent yield of **2b**, while the *N*-phenyl analogue produced **3c** in moderate yield presumably due to the electronic effect of the phenyl group. Free (NH) indole could also be employed in the cyclization reaction, albeit with a lower yield (**2e**). No cyclization occurred when N-acylated indole was employed (Table 1, entry 4). Various *N*-methylindoles with both electron-rich (Me, OMe, **2f**, **2g**, and **2k**) and electron-poor (Br, Cl, **2h**, **2i**, and **2j**) groups (R^3) worked well and gave rise to the corresponding C(2) cyclization products in good to excellent yields, regardless of the substitution patterns. However, the yields were slightly reduced when the R^3 groups were halogen substituents (**2h**, **2i**, and **2j**), compared to other substituents. The substituents on cyanohydrin units (R^2) were very compatible, and indoles with alky and aryl substituted cyanohydrins units gave the desired products in high to excellent yields (**2a**, **2l**−**2o**), except for substrate **1p** with the cyanohydrin unit containing an α-H which did not give the desired product, possibly because of the gem-disubstituent effect.[13] Notably, the halogen groups on both the indole ring and cyanohydrin unit were all compatible (**2h**−**2i**, **2n**−**2o**). Additionally, to test the practicality of this method, the cyclization of **1a** was conducted on a gram scale, and product **2a** was obtained in comparable yield (1.06 g of product, 95% yield, 4 h). Next, the cyclizations of indoles bearing cyanohydrin units at the C-2 position through indolyl(C3) C−H bond addition to nitriles were estimated (entries 17−20). Gratifyingly, Pd-catalyed cyclization of these C(2) substituted *N*-methylindoles proceeded smoothly to give 4,5-dihydro-3a*H*-oxazolo[5,4-*c*]carbazol-2(6*H*)-ones (**2q**−**2s**) in high yields under the standard reaction conditions. Notably, unlike **1e**, C(2)-substituted N-unprotected indole **1t** gave the desired product **2t** in moderate yield. Encouraged by these results, indoles with N(1)-substituted cyanohydrin moieties were employed to extend the potential synthetic application of this transformation for the construction of tetrahydropyrido-[1,2-*a*]indole derivatives (entries 21−24). The cyclization of N(1)-substituted analogue **1u** gave the desired tetrahydro-pyrido[1,2-*a*]indole **2u** in 60% yield in the presence of 10 mol % of $Pd(OAc)_2$ and 12 mol % of bpy in diluted concentration. Considering the reactive C-3 site of product **2u**, C-3 methyl substituted indole **1v** was examined. To our delight, an excellent yield of the desired product **2v** was obtained without

Table 1. Pd-Catalyzed Intramolecular Cyclization of Indoles with Cyanohydrin Units at C-3, C2, N-1 Positions[a]

entry	1	2	*t* (h)	yield (%)[b]
				
1	**1a** (R^1 = Me, R^2 = Me, R^3 = H)	**2a**	2	98
2	**1b** (R^1 = Bn, R^2 = Me, R^3 = H)	**2b**	3	98
3	**1c** (R^1 = Ph, R^2 = Me, R^3 = H)	**2c**	20	60
4	**1d** (R^1 = Ac, R^2 = Me, R^3 = H)	**2d**	24	nd
5	**1e** (R^1 = H, R^2 = Me, R^3 = H)	**2e**	19	48
6	**1f** (R^1 = Me, R^2 = Me, R^3 = 4-Me)	**2f**	3	89
7	**1g** (R^1 = Me, R^2 = Me, R^3 = 5-MeO)	**2g**	2	98
8	**1h** (R^1 = Me, R^2 = Me, R^3 = 5-Br)	**2h**	5	67
9	**1i** (R^1 = Me, R^2 = Me, R^3 = 5-Cl)	**2i**	3	76
10	**1j** (R^1 = Me, R^2 = Me, R^3 = 6-Cl)	**2j**	3	80
11	**1k** (R^1 = Me, R^2 = Me, R^3 = 7-Me)	**2k**	3	95
12	**1l** (R^1 = Me, R^2 = Et, R^3 = H)	**2l**	3	96
13	**1m** (R^1 = Me, R^2 = Ph, R^3 = H)	**2m**	3	98
14	**1n** (R^1 = Me, R^2 = 4-ClC_6H_4, R^3 = H)	**2n**	3	90
15	**1o** (R^1 = Me, R^2 = 3,4-$Cl_2C_6H_3$, R^3 = H)	**2o**	3	96
16	**1p** (R^1 = Me, R^2 = H, R^3 = H)	**2p**	11	nd
				
17	**1q** (R^1 = Me, R^2 = Me)	**2q**	11	83
18	**1r** (R^1 = Me, R^2 = Ph)	**2r**	11	86
19	**1s** (R^1 = Me, R^2 = 4-ClC_6H_4)	**2s**	11	89
20	**1t** (R^1 = H, R^2 = Me)	**2t**	7	67
				
21[c]	**1u** (R^2 = Me, R^4 = H)	**2u**	2	60
22	**1v** (R^2 = Me, R^4 = Me)	**2v**	2	96
23	**1w** (R^2 = Me, R^4 = CH_2CO_2Me)	**2w**	3	67
24	**1x** (R^2 = Ph, R^4 = Me)	**2x**	2	97

[a]Reactions were performed with **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), and bpy (6 mol %) in solvent (NMA/HOAc = 3/1, *c* = 0.4 M). [b]Isolated yields. [c]The results were obtained with $Pd(OAc)_2$ (10 mol %), bpy (12 mol %), and solvent (NMA/HOAc = 3/1, *c* = 0.1 M) in 140 °C. NMA: *N*-Methylacetamide.

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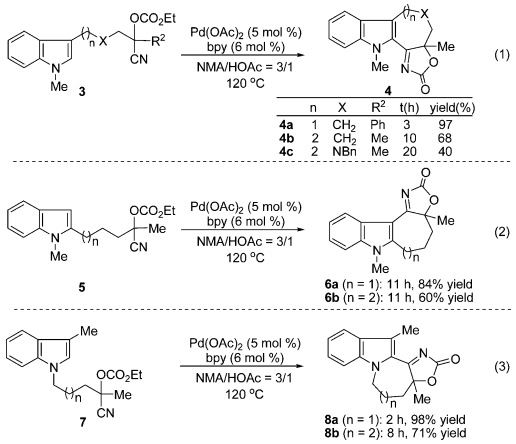
modifying the standard reaction conditions. Notably, the pendent ester group at the C-3 position of the indole core was well tolerated and gave the desired product **2w** in 67% yield. A substrate bearing an aryl-substituted cyanohydrin unit can also undergo the cyclization to give the desired product **2x** in excellent yield.

On the basis of these, the application of this Pd-catalyzed approach to the construction of the indole-annulated medium-sized-ring skeletons was investigated, and the results are summarized in Scheme 2. It was found that indole-annulated

Scheme 2. Pd-Catalyzed Cyclization for Preparation of Indole-Annulated Medium-Sized Rings



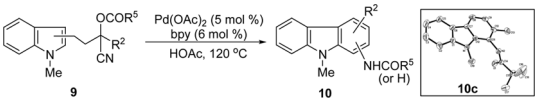
	n	X	R^2	t(h)	yield(%)
4a	1	CH_2	Ph	3	97
4b	2	CH_2	Me	10	68
4c	2	NBn	Me	20	40

seven-membered rings from C-3, C-2, N-1 substituted substrates could be constructed readily in good to excellent yields regardless of the locations of tethered cyanohydrins units (**4a**, **6a**, **8a**, n = 1). By adding one more methylene in the linker (n = 2), the reactions could provide indole-annulated eight-membered rings in reasonable yields under the standard conditions (**4b**, **6b**, **8b**).[14] Additionally, an eight-membered-ring product (**4c**) bearing the N linker could be prepared in 40% yield from the corresponding tryptamine-based substrate under the standard conditions.

Further studies on the skeletal diverse synthesis of fused indoles by using the current method revealed that unsaturated six-membered rings, namely carbazole derivatives, can be constructed by the employment of indole substrates **9** with *O*-aryl or alkyl acyl substituted cyanohydrin units under slightly modified reaction conditions (Table 2). Treatment of substrate **9a** bearing an *O*-benzoyl substituted cyanohydrin unit at the 3-position with 5 mol % of $Pd(OAc)_2$ and 6 mol % of bpy in HOAc furnished *N*-acylated carbazol-1-amine **10a** in good yield. Pivaloyl substituted analogue **9c** gave a similar result, while substrate **9b** with an acetylated cyanohydrin unit did not provide the desired product. Various aroyl substituted indoles were employed, and the reactions furnished the corresponding N-aroyl substituted carbazoles in good yields (**10d**–**10f**). R^2 substituents such as an ethyl and phenyl group were also well tolerated (**9g**–**9h**). In parallel, C-2 substituted analogues were also examined, and the reactions provided N-unprotected carbazol-4-amines (**10i**–**10j**) in good yields instead.[15]

In addition, multisubstituted carbazole and partially saturated derivatives can also readily accessed by employing indoles with the substituents on the linkers between the indole core and cyanohydrin unit (Scheme 3). Unseparated diastereomers **1l** bearing an *O*-ethoxycarbonyl substituted cyanohydrin unit

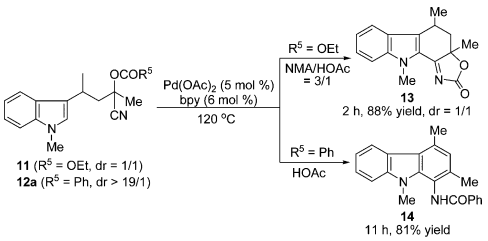
Table 2. Pd-Catalyzed Cyclization for Preparation of Carbazolamines[a]



entry	9	10	t (h)	yield(%) [b]
1	**9a** (R^2 = Me, R^5 = Ph)	**10a**	11	76
2	**9b** (R^2 = Me, R^5 = Me)	**10b**	11	nd
3	**9c** (R^2 = Me, R^5 = *t*Bu)	**10c**	11	75
4	**9d** (R^2 = Me, R^5 = 4-MeC_6H_4)	**10d**	11	87
5	**9e** (R^2 = Me, R^5 = 4-BrC_6H_4)	**10e**	11	90
6	**9f** (R^2 = Me, R^5 = 4-$NO_2C_6H_4$)	**10f**	20	85
7	**9g** (R^2 = Et, R^5 = Ph)	**10g**	11	85
8	**9h** (R^2 = Ph, R^5 = 4-$NO_2C_6H_4$)	**10h**	30	78
9	**9i** (R^2 = Me, R^5 = Ph)	**10i**	11	75
10	**9j** (R^2 = Et, R^5 = Ph)	**10j**	11	81

[a]Reactions were performed with **9** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), and bpy (6 mol %) in HOAc (c = 0.4 M). [b]Isolated yields.

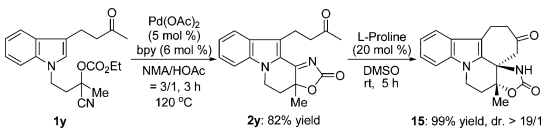
Scheme 3. Synthesis of Multisubstituted Fused Indoles



delivered the desired multisubstituted product **13** (dr = 1/1) in good yield, while diastereomer **12a** bearing an *O*-benzoyl substituted cyanohydrin unit gave multisubstituted carbazole **14** in 81% yield.[16]

To further demonstrate the utility of this Pd-catalyzed cyclization, the fused tricyclic indole **15** was readily prepared from substrate **1y** with a cyanohydrin unit at the C-2 position (Scheme 4). Subjecting **1y** to this Pd-catalyzed cyclization

Scheme 4. Synthesis of Fused Tricyclic Indole 15



reaction afforded product **2y** in 82% yield, which underwent a proline-catalyzed Mannich reaction to furnish **15** in almost quantitive yield with excellent diastereoselectivity.

In analogy to other processes involving Pd-catalyzed C–H bond functionalization,[4,13,17] a proposed mechanism is illustrated for this Pd-catalyzed cyclization (see Supporting Information for details).

In summary, we have developed an unprecedented strategy for skeletal diverse synthesis of fused indoles by a Pd-catalyzed intramolecular C–H addition of indoles bearing cyanohydrin units at the C(3), C(2), and N(1) positions to nitriles. Under

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the optimal conditions, a diversity of functionalized partially saturated carbazoles, tetrahydropyrido[1,2-*a*]indoles, and carbazoles can be prepared in good to excellent yields. In addition, fused indoles with seven- or eight-membered rings can also be formed smoothly. The catalytic system tolerates a broad substrate scope. Further expansion of this strategy of catalytic construction of six-membered and medium-sized ring structures is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02460.

Experimental procedures and analytical data for all new compounds (PDF)
^{1}H and ^{13}C NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The product with a nine-membered ring cannot be prepared by using this protocol currently.

(15) A pivaloyl substituted (C2) analogue (R^2 = Me, R^5 = tBu) gave the same product as substrate **9i**. The amide groups of N-acylated carbazol-4-amines, which were situated in less sterically hindered circumstances than that of N-acylated carbazol-1-amines, tended to be hydrolyzed into N-unprotected carbazol-4-amines (**10i**–**10j**).

(16) The fact that the cyclization of another diastereomer **12b** proceeded sluggishly under the same reaction conditions (11 h, 25% yield, 35% conversion) indicated that these cyclizations strongly depended on the stereo conformation and size of the substituent (R^5).

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