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Palladium(II) in electrophilic activation of aldehydes and enones: efficient C-3 functionalization of indoles

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ABSTRACT

The regioselective C-3 alkylation of indoles with aldehydes and enones as electrophiles is catalyzed by a d^8 late transition metal complex PdCl₂(MeCN)₂ at room temperature in the presence of air/moisture and in the absence of any additional acid/base, additive, or ligand. The active catalyst in this alkylation is an organometallic intermediate **C1** which is formed from the reaction of indole with the palladium(II) pre-catalyst. The crystallographic characterization and reactivity of **C1** and its analogs with indoles and surrogates is in progress.

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Alkylated indoles are important structural motifs frequently found in natural products, pharmaceuticals, and other functional synthetics.¹ Bisindolylmethane (hereafter BIM) derivatives show promising biological activities such as anti-pyretic, anti-fungal, anti-inflammatory, anti-convulsant, cardiovascular, selective $\beta\mbox{-glucuronidase}$ and COX-2 inhibitory activities. 2,3 In addition, the oxidized forms of BIMs are utilized as dyes as well as colorimetric chemosensors.² Hence, the development of highly selective and efficient strategies for the synthesis of these moieties has captured wide attention. A number of protic and Lewis acids are reported for the synthesis of BIMs from indole and carbonyl compounds.^{2,4} Other catalysts ranging from dinuclear zirconium(IV) complex, and phenalenyl (PLY) cation to one dimensional CdS nanorods have found place in recent literature.⁵ It may be noted that the pursuit to develop new catalysts for BIMs arises from issues such as (a) minimizing the catalyst loading, (b) enhancing the turnover frequency, and (c) easing the work-up protocol. We believe that a strategy which addresses the above issues for the synthesis of BIMs will be highly attractive.

In parallel to our major research program on multimetallic catalysis,⁶ recently we noted that Pd(II) efficiently catalyzes the

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http://dx.doi.org/10.1016/j.tetlet.2015.08.080 0040-4039/© 2015 Published by Elsevier Ltd. allylation and benzylation of indoles with respective alcohols.⁷ Aided by this insight and excited by the opportunity that BIMs provide, we present here an efficient and regioselective C-3 functionalization of indoles with aldehydes and enones using PdCl₂(MeCN)₂ as the catalyst. It is well known that the said Pd(II) catalyst is either readily available or can be prepared in the laboratory very easily. More importantly the title reaction neither requires the assistance of external acid/base, additive, and ligand, nor is it sensitive toward moisture and air. The work-up procedure is also easy.

In model studies, we examined the reaction of indole **1a** with benzaldehyde **2a** at room temperature for 10 h leading to the formation of bis(indolyl)methane **3a** as the desired product; the solvents and catalysts (5 mol % loading) being varied (Table 1). In case of palladium(II) catalysts, simple salts as well as complexes were included. While the conversion was very low with palladium(II) acetate (entry 2), with palladium(II)chloride the conversion (70%) and isolated yield of **3a** (65%) were moderate (entry 3). Among the complexes screened, only PdCl₂(MeCN)₂ showed promising catalytic activity in 1,2-dichloroethane (DCE) as the solvent, with >95% conversion; the isolated yield of **3a** being 80% (entry 6). When the reaction was conducted in toluene, the conversion (70%) and isolated yield of **3a** (62%) were moderate (entry 7). In contrast, very poor conversion was observed in coordinating solvents like acetonitrile and methanol (entries 8 and 9). *It may*

S. S. Mohapatra et al./Tetrahedron Letters xxx (2015) xxx-xxx

Table 1

Catalyst screening^a



70 10 Cu(NO3)2.3H2O DCF ~ 80 11 SnCl₂·2H₂O DCE ~55 50 70 12 Sc(OTf)₃ DCE ~ 80 13 InBr₃ DCE ~75 62

 a Unless otherwise mentioned, reaction condition: aldehyde (0.25 mmol), indole (0.5 mmol), catalyst (5 mol %) in 2 mL of DCE at 30 °C for 10 h.

^b From ¹H NMR.

1

2

3

4

5

6

7

^c Isolated yield of chromatographically pure product.

^d Reaction time **4d**.

^e bpy = 2,2'-bipyridine.

Table 2 PdCl₂(MeCN)₂ catalyzed synthesis of bis(indolyl)methanes: substrate scope^a

be noted that, while initial studies were conducted using Schlenk technique, soon it was found that the reactions could be conducted in simple glass vials and in the presence of air and moisture. Under similar conditions, we also checked a few known catalysts, which resulted in isolated yields ranging from 50–70% (entries 10–13).

The scope and limitation of the BIM-forming reaction were evaluated under the optimized conditions (Table 1, entry 6) using various substituted aldehydes 2 and ring substituted (but N-unsubstituted) or N-substituted (alkyl, benzyl, allyl, and propargyl)indoles 1 (Table 2). Gratifyingly, in most cases the corresponding BIM derivatives 3 were obtained in moderate to good yields (Table 2, entries 1–19). Notably, in all cases where we have used *N*-unsubstituted indoles, the reactions were completely C-3 selective and no N-alkyl products were formed (entries 1-9). Aromatic aldehydes, with electron-withdrawing groups at o- and p-positions, provided products in good vields and at shorter reaction time (entries 14-16, 18 and 19). On the other hand, reaction of aldehydes with electron donating groups took a longer time for full conversion and the isolated yields of desired products were moderate (entries 7, 10, and 12). This could probably be due to the decrease in electrophilicity at the aldehydic carbon atom.⁸ Gratifyingly, under the present reaction conditions, heterocyclic aldehydes like **2b** or **2f** survived well without the formation of any side products and the corresponding bis(indolyl)methanes **3b** or **3f** were isolated in good yield. However aliphatic aldehydes 2c and 2d (entries 3 and 4) showed lower reactivity compared to their aromatic counterparts; while aromatic ketones (entries 20 and 21) were totally

-N R ¹ 1	2 R ¹	3 R ¹	
Indole	Carbonyl compound	Time (h)	Yield of 3 (%)
1a H	CHO 2a	10	3a , 80
Ia H	OHC O 2b	10	3b, 82
N 1a H	CHO 2c	16	3c , 61
N 1a H	H ₃ C ^{(CH₂)₇CHO 2d}	15	3d , 50
MeO 1b H	CHO 2e	7	3e , 96
MeO N 1b H	OHC S 2f	10	3f , 80
Br N 1c H	CH ₃ CHO 2g	24	3 g, 48

PdCl₂(MeCN)₂ (5 mol%)

S. S. Mohapatra et al./Tetrahedron Letters xxx (2015) xxx-xxx

Table 2 (continued)

#	Indole	Carbonyl compound	Time (h)	Yield of 3 (%)
8	Br N 1c H		24	3h , 85
9	Br N 1c H		10	3i , 60
10	1d Me	CH3 CHO 2g	24	3j , 81
11	1d Me	CI CHO 2i	24	3k , 75
12	1e ^{Ph}	CHO CHO	10	31 , 80
13	1e ^{Ph}	CHO 2e	10	3m , 86
14	1e ^{Ph}	CHO CI 2k	4	3n , 88
15	1f	CHO 2h	8	30 , 90
16			6	3 p, 74
17		CHO 2g CHO	3	3q , 97
18		CI 2k	2	3r , 75
19	1g		4	3s , 95
20	1a H	2m	10	NR ^b
21	N, 1a H	Ph 2n	10	NR ^b

^a All reactions for the preparation of BIM's were carried out with aldehyde (0.25 mmol), indole (0.5 mmol), and PdCl₂(MeCN)₂ (5 mol %) in 2 mL of DCE at room temperature 30 °C. ^b NR: no reaction.

S. S. Mohapatra et al./Tetrahedron Letters xxx (2015) xxx-xxx



Figure 1. ORTEP diagram of 3q with 30% probability thermal ellipsoid (CCDC No. 1405691).



Scheme 1. Aldehyde selective C-3 alkylation.

Table 3				
PdCl ₂ (MeCN) ₂ catalyzed	C-3 functionalization	of indoles	with	enones



#	Indole	Enone	Time (h)	Yield of 5 (%)
1	1h Et	4a 0	6	5a , 72
2	1a H	4a 0	6	5b , 70
3	Br N 1c H	4b 0	6	5c , 80
4	1a H	4b 0	2	5d , 89
5	1a H	Ph 4c O	6	5e , 70
6	1a H	Ph 4d O	12	NR ^b

^a All Michael addition reactions were carried out with enone (0.6 mmol), indole (0.5 mmol), and PdCl₂(MeCN)₂ (5 mol %) in 2 mL of DCE at room temperature 30 °C. ^b NR: no reaction.



Scheme 2. Formation of complex C1.

 Table 4

 Complex C1 catalyzed synthesis of bis(indolyl)methanes: substrate scope^a





 $^{\rm a}$ All reactions for the preparation of BIM's were carried out with aldehyde (0.25 mmol), indole (0.5 mmol), and complex C1 in 2 mL of DCE at room temperature 30 °C.

unreactive. It may be noted that, the crystal structure of **3q** showed that the two *N*-allyl groups are furthest away from each other in the molecule (Fig. 1).

The sharp difference in the reactivity between an aldehyde and a ketone in the title reaction, prompted us to investigate the chemoselectivity of the reaction. Reaction of a 1:1:2 mixture of benzaldehyde, acetophenone (or benzophenone), and indole for 10 h afforded exclusively the corresponding benzaldehyde derived bis(indolyl)methane **3a** (Scheme 1). These results show the high chemoselectivity toward the aldehyde in the present method.

With the success as above we next explored the scope of the present palladium catalyzed C-3 alkylation of indole with electrophiles other than aldehydes. In our hand electrophiles such as enones were also effective at room temperature (Table 3). Michael addition of indoles with enones **4a–4c** furnished corresponding products **5a–5e** in moderate to good yield (entries 1–5). On the other hand chalcone **4d** was inactive (entry 6).

During the course of experimentation, we noticed that the color of the solution turns to ochre-red after the addition of $PdCl_2(MeCN)_2$ to a solution of only indole or to a mixture containing indole and the electrophile (aldehyde or enone) in DCE or DCM. Previously we have shown that, due to the labile nature of acetonitrile ligand, the reaction of $PdCl_2(MeCN)_2$ and indole leads to the formation of an ochre-red colored complex **C1** (Scheme 2).⁷ The complex **C1** was characterized in detail and the probable structure was enumerated.⁹

4

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To test whether complex **C1** is indeed the active catalyst in the present alkylation reaction, we briefly tested its efficiency in the reaction of indoles with aromatic aldehydes (Table 4).¹⁰ We are delighted to find that, the yields of BIMs obtained with complex **C1** as catalyst are comparable to those of $PdCl_2(MeCN)_2$ (entries 1, 3 and 4). Interestingly, the reaction of **1a** with **2a** is promoted by complex **C1** even at 3% loading (entry 2 vs entry 1).

From the above results, it is therefore evident that $PdCl_2(MeCN)_2$ is a pre-catalyst in the present alkylation reaction. Once in solution, an active catalyst (akin to complex **C1**) is formed from the corresponding indole and $PdCl_2(MeCN)_2$. These results also explain the inactivity or less reactivity of other Pd(II) complexes with strong donor ligands (like PPh₃, bipy or acetate) (Table 1, entries 2, 4, and 5).

In conclusion we would like to apprise the reader about the highlights and immense scope of the present work. The present work demonstrates the ability of a Pd(II) catalyst, belonging to a d^8 late transition element, for the electrophilic activation of carbonvl. leading to C-C bond formation in a Friedel-Crafts like alkylation reaction. It is well known that Pd(II) is highly capable for π -activation (typically for alkenes or alkynes). It will be interesting therefore to explore in future the simultaneous activation of a soft- π bond and a carbonyl moiety by a catalyst belonging to a d⁸-element.¹¹ From the mechanistic point of view, our demonstration that complex **C1** is an active catalyst is very exciting. Note that, in our view, complex C1 is an organometallic species. Efforts are going on in our laboratory to grow crystals of this active catalyst and their analogs with other indoles and surrogates. Once we succeed in enumerating the structure through crystallographic evidence, a new series of reactions pertaining to classical organometallic/organic reactivity will emerge beyond that of the chemistry of indoles. From a purely synthetic organic point of view, we believe that the present demonstration only opens up a new chapter in the chemistry of indoles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08. 080.

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- 9. For a discussion on the formation, detailed characterization and probable
- structure of complex **C1**, please see Ref. 7.
- 10. We thank one of the reviewers for the suggestion to explore the catalytic activity of complex **C1**.
- 11. The activation of enone may possibly be governed by such interaction. Efforts are underway to isolate active species from the reaction of complex **C1** with enone to look into the above hypothesis.