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Unprecedented synthesis of functionalized indoles of potential pharmacological interest has been developed *via* a Pd-mediated cascade reaction involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring in a single pot.

Rigid conformation *via* restriction of three dimensional relationships of multiple functional groups present on a polycyclic–heterocyclic system often renders specific and promising pharmacological properties, highly desirable for medicinal chemistry/drug discovery efforts. Cascade reactions[1] involving formation of several bonds and stereogenic centers in a single synthetic operation on the other hand are considered as powerful tools for the construction of such polycyclic–heterocyclic structures. Thus the development of cascade reactions especially those catalyzed by transition metals is of remarkable interest.

Indoles are prevalent in Nature and considered as valuable building blocks in organic synthesis[2] as well as privileged pharmacophores in drug discovery. For example, a fused indole *i.e.* 1,2,3,4-tetrahydrocyclopenta[*b*]indole is an integral part of natural product bruceollines[3a] and a known drug laropiprant.[3b] This prompted us to explore cyclopenta[*b*]indole **D** as a new class of potential inhibitors of phosphodiesterase 4 (PDE4). PDE4 inhibitors are proved to be promising anti-inflammatory agents for the potential treatment of chronic obstructive pulmonary disease (COPD) and asthma.[4] Our target molecules **D** derived from a known PDE4 inhibitor **A** *via* **B**[5a] and incorporating some of the structural features of another known inhibitor **C**[5b] (Fig. 1) were designed based on the *in silico* docking studies of a representative compound **E** in the active site of PDE4B (see **4b** in the ESI†).[5c]

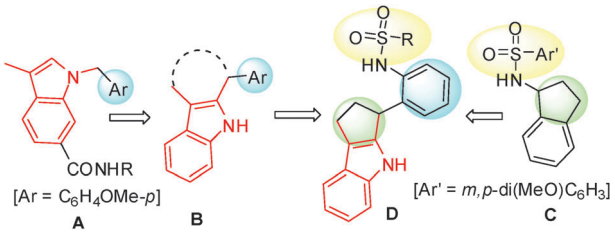
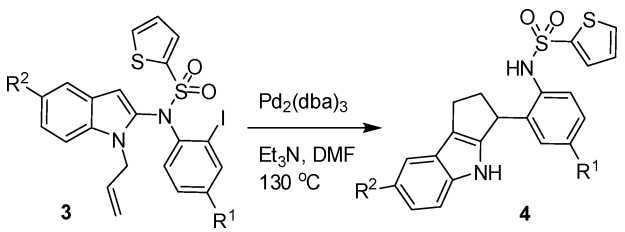


Fig. 1 Design of **D** as novel inhibitors of PDE4.

While elegant methods leading to cyclopenta[*b*]indoles *via* Lewis acid catalyzed formal [3+2] addition of indolylmethyl cations to alkenes[6a,b] or Pd-mediated approaches *e.g.* aerobic oxidative annulations of indoles[6c] or domino N–H/C–H bond activation[6d,e] are known none of them appeared to be handy for the quick access to **D**. As part of our ongoing studies on newer synthesis of functionalized heteroaromatics[7] including fused indoles[8] we further investigated the reactivity of *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(2-iodoaryl)thiophene-2-sulfonamides towards Pd catalysts. To our surprise the reaction followed an unusual path affording novel cyclopenta[*b*]indoles *i.e.* *N*-(2-(7-substituted-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-aryl)thiophene-2-sulfonamides as unexpected products (Scheme 1). We were delighted with this timely observation as this appeared to have potential to become a methodology for the direct access to a library of small molecules based on **D**. Herein we report conceptually new synthesis of functionalized cyclopenta[*b*]indoles *via* a Pd-mediated cascade reaction involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring as a result of



Scheme 1 Pd-mediated synthesis of novel cyclopenta[*b*]indoles.

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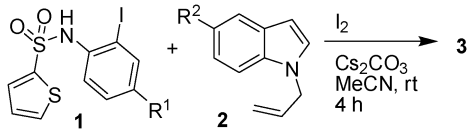
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of *in vitro* and docking study. CCDC 918746. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc42309c

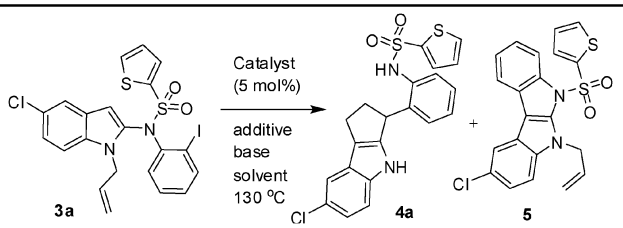


Scheme 2 Iodine-mediated synthesis of sulfonamide **3**.

cleavage of two C–N bonds and formation of several C–C bonds in a single pot.

The key starting material **3** required was prepared *via* C-2 amination of indoles (**2**) using *N*-sulfonyl arylamines (**1**) (Scheme 2).[9] The Pd-mediated cascade reaction of **3a** was then performed under a variety of conditions (Table 1) to establish the optimized reaction conditions. Initially, **3a** was treated with Pd_2dba_3 and Et_3N in EtOH at 80 °C for 15 h, when **4a** was obtained as a major product (48%) along with indolo[2,3-*b*]indole **5** (12%) and some unreacted **3a** (entry 1, in Table 1). Though the yield of **4a** was increased when the reaction was performed in PEG or DMF–H_2O (entries 2 and 3, Table 1) a significant improvement was observed when DMF alone was used (entry 4, Table 1). The use of other bases *e.g.* DBU or K_2CO_3 was not effective (entries 5 and 6, Table 1). **4a** was also not obtained when $Pd(OAc)_2$ was used as a catalyst (entry 7, Table 1), whereas the use of $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ or Pd/C-PPh_3 afforded **4a** in poor yield (entries 8–10, Table 1). The combination of $Pd(OAc)_2$ with PPh_3 or X-Phos (entries 11–13, Table 1) or the use of $Cu(OAc)_2$ as a co-catalyst (entries 14 and 15, Table 1) mainly

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst/additive	Base/solvent	Time (h)	Yield[b] (%) 4a	5
1[c,d]	$Pd_2(dba)_3$	Et_3N/EtOH	15	48	12
2	$Pd_2(dba)_3$	Et_3N/PEG	7	67	25
3	$Pd_2(dba)_3$	Et_3N/DMF : H_2O (8 : 2)	7	63	28
4	$Pd_2(dba)_3$	Et_3N/DMF	7	80	16
5	$Pd_2(dba)_3$	DBU/DMF	7	58	36
6	$Pd_2(dba)_3$	K_2CO_3/DMF	7	—	75
7	$Pd(OAc)_2$	Et_3N/DMF	4	—	84
8[e]	$Pd(PPh_3)_2Cl_2$	Et_3N/DMF	7	30	—
9[e]	$Pd(PPh_3)_4$	Et_3N/DMF	7	32	—
10[e]	Pd/C/PPh_3	Et_3N/DMF	12	30	—
11	$Pd(OAc)_2$/PPh_3	Et_3N/DMF	5	—	84
12	$Pd(OAc)_2$/X-Phos	Et_3N/DMF	4	22	70
13[f]	$Pd(OAc)_2$/X-Phos	Et_3N/DMF	4	—	83
14	$Pd(PPh_3)_2Cl_2$/ $Cu(OAc)_2$	Et_3N/DMF	4	—	81
15	$Pd_2(dba)_3$/$Cu(OAc)_2$	Et_3N/DMF	4	—	83
16	$Pd_2(dba)_3$/LiCl	Et_3N/DMF	7	47	48
17[g]	$Cu(OAc)_2$	Et_3N/DMF	8	—	—

[a] All the reactions were performed using **3a** (0.4 mmol), catalyst (5.0 mol%) and base (1.2 mmol) in a solvent (2.0 mL) at 130 °C. [b] Isolated yield. [c] The reaction was performed at 80 °C. [d] The starting material was not consumed completely. [e] Formation of an additional unidentified product was observed. [f] The reaction was performed at room temperature. [g] 1.0 mmol of catalyst was used.

Table 2 Synthesis of cyclopenta[*b*]indoles (**4**) (Scheme 1)[a]

Entry	Compound (3); R^1, R^2, X	Product (4); R^1, R^2	Yield[b] (%)
1	H, Cl, I (**3a**)	H, Cl (**4a**)	80
2	H, H, I (**3b**)	H, H (**4b**)	81
3	F, H, I (**3c**)	F, H (**4c**)	71
4	CH_3, H, I (**3d**)	CH_3, H (**4d**)	76
5	Cl, H, I (**3e**)	Cl, H (**4e**)	78
6	CH_3, Cl, I (**3f**)	CH_3, Cl (**4f**)	68
7	Br, Br, I (**3g**)	Br, Br (**4g**)	83
8	H, Br, I (**3h**)	H, Br (**4h**)	72
9	H, OMe, I (**3i**)	H, OMe (**4i**)	70
10	CH_3, OMe, I (**3j**)	CH_3, OMe (**4j**)	81
11	CH_3, Br, I (**3k**)	CH_3, Br (**4k**)	80
12	Br, OMe, I (**3l**)	Br, OMe (**4l**)	68
13	F, OMe, I (**3m**)	F, OMe (**4m**)	62
14	Br, H, I (**3n**)	Br, H (**4n**)	78
15	Br, Cl, I (**3o**)	Br, Cl (**4o**)	70
16	Cl, Cl, I (**3p**)	Cl, Cl (**4p**)	71
17	Cl, NO_2, I (**3q**)	Cl, NO_2 (**4q**)	66
18	Cl, Br, I (**3r**)	Cl, Br (**4r**)	68
19	F, Cl, I (**3s**)	F, Cl (**4s**)	68
20	Cl, CN, I (**3t**)	Cl, CN (**4t**)	59
21	F, NO_2, I (**3u**)	F, NO_2 (**4u**)	62
22	CH_3, NO_2, I (**3v**)	CH_3, NO_2 (**4v**)	73
23	Cl, OMe, I (**3w**)	Cl, OMe (**4w**)	69
24	CH_3, OMe, Br (**3x**)	No reaction	-

[a] Reactions were performed using **3** (0.4 mmol), $Pd_2(dba)_3$ (5 mol%) and Et_3N (1.2 mmol) in DMF (2 mL) at 130 °C for 7 h under N_2. [b] Isolated yield.

provided **5** as a major or the only product. The use of LiCl additive afforded a 1 : 1 mixture of **4a** and **5** (entry 16, Table 1) whereas $Cu(OAc)_2$ in place of the Pd-catalyst was found to be ineffective (entry 17, Table 1). Overall, $Pd_2(dba)_3$ and Et_3N in DMF (entry 4, Table 1) were found to be optimum for the preparation of **4a**.

We then performed the Pd-mediated cascade reaction using various indole derivatives **3** (Table 2). Substituents like F, Cl, Br, and OMe or electron withdrawing NO_2 and CN groups were well tolerated and afforded **4** in good to acceptable yields. Notably, unlike **3** its bromo analogue *i.e.* *N*-(1-allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(2-bromo-4-methylphenyl)thiophene-2-sulfonamide **3x** failed to participate in the present reaction (entry 24, Table 2). All the compounds synthesized were well characterized by spectral (NMR, IR and MS) data and the molecular structure of a representative compound **4b** was confirmed unambiguously by single crystal X-ray diffraction study (Fig. 2).[10]

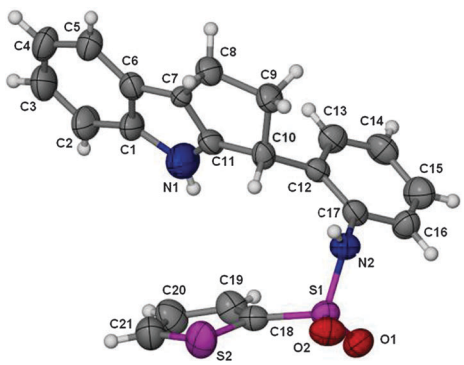
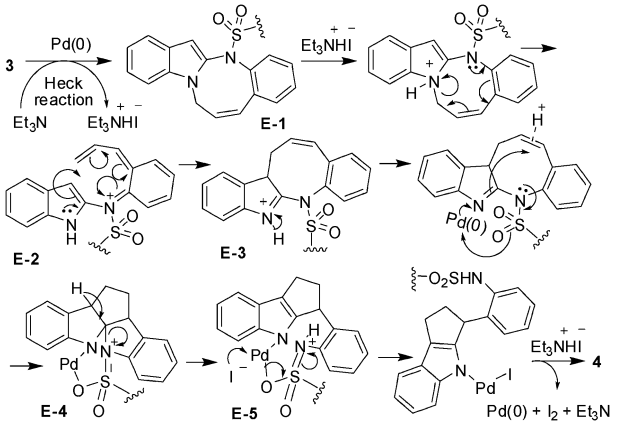


Fig. 2 ORTEP representation of **4b**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 3 The proposed reaction mechanism.

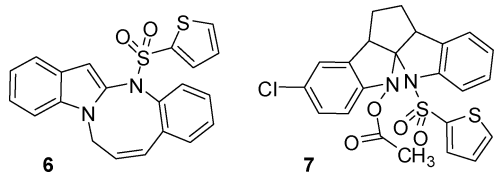


Fig. 3 The Heck product **6** isolated from the reaction of **3b** and the side product **7** isolated from **3a**.

Mechanistically, the reaction seemed to proceed *via* generation of **E-1** *in situ* as a result of an intramolecular Heck reaction which then undergoes a C–N bond cleavage near the indole nitrogen to give **E-2** (Scheme 3). A subsequent intramolecular attack of the indole ring *via* its C-3 position on –C═C– provides **E-3**. Activation of –C═N– of **E-3** in the presence of Pd(0) aided by the proximate sulfonamide moiety facilitated a further intramolecular attack on the olefinic bond leading to **E-4**. The six-membered Pd-containing ring of **E-4** then undergoes C–N bond cleavage to give **E-5** which after following a few more steps including the reductive elimination of Pd(0) to complete the catalytic cycle afforded product **4**. It is evident that the sulfonamide moiety played a key role in the present cascade reaction, the electron releasing property of which towards Pd was greatly facilitated by the electron rich thienyl moiety. This perhaps provides some explanations to the observation that replacing the thienyl moiety of **3** by a *p*-tolyl ring did not provide **4** as a major product.[8a] Nevertheless, it is evident from Table 1 that the formation of **4** was also dependent on the nature of catalyst/solvent used.

The initial Heck type coupling was supported by the fact that the corresponding Heck product **6** (*cf.* **E-1**, Fig. 3) was isolated from the reaction of **3b** (see ESI† for spectral data).[11] While all our attempts to isolate any other intermediates **E-2-5** were not successful we, however, were able to isolate a side product **7** (analogous to **E-4**) (Fig. 3) along with **4a** from the conversion of **3a** under the condition of entry 4 of Table 1 in the presence of catalytic acetic acid. Compound **7** seemed to have formed *via* a nucleophilic attack on the iminium nitrogen of the intermediate obtained from **E-3** by the acetate ion (instead of Pd, *cf.* Scheme 3). This suggests that the present cascade reaction arguably proceeds *via* **E-4**.

Some of the compounds synthesized were tested against PDE4B *in vitro*[12] when **4b**, **4e**, **4g**, **4i**, **4j**, **4k**, **4h**, **4n** and **4q** showed 43, 41, 40, 74, 49, 40, 42, 45 and 58% inhibition, respectively, at 30 μM and **4i** (IC_{50} > 5 μM *vs.* rolipram's IC_{50} ~ 1 μM) being the best among them.

In conclusion, novel cyclopenta[*b*]indoles have been synthesized as potential inhibitors of PDE4 *via* a Pd-mediated new cascade reaction involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring in a single pot.

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