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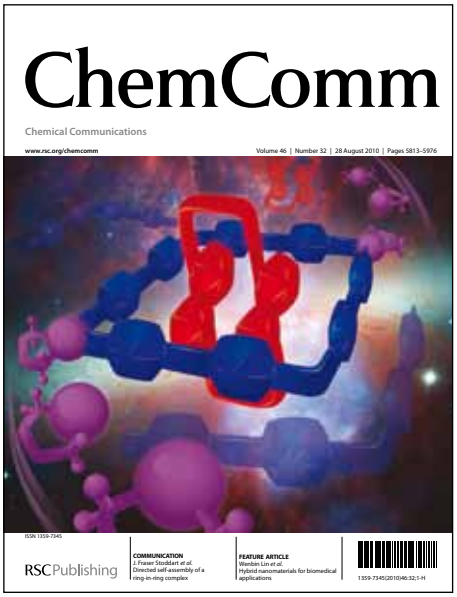

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ARTICLE TYPE

Synthesis of Fused N-Heterocycles via Tandem C-H Activation

Ge Meng,[a] Hong-Ying Niu,[b] Gui-Rong Qu,[a] John S. Fossey,[a,c] Jian-Ping Li,*[a] and Hai-Ming Guo,*[a]

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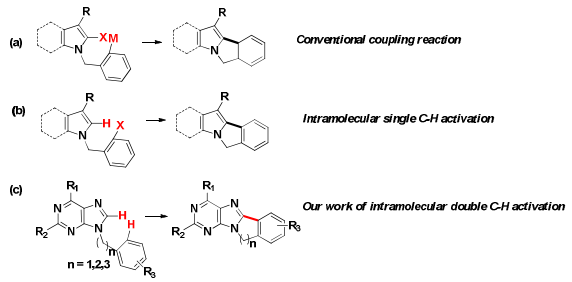
A novel and convenient method for the synthesis of fused N-heterocycles has been developed through highly efficient intramolecular cyclization of purines or benzimidazoles catalyzed by $Pd(OAc)_2$ in normal acidic condition without any base or ligand. A range of medium and large rings, including five- to nine-membered rings, are prepared by this process.

Fused *N*-heterocyclic building blocks are ubiquitous in natural products and play a significant role in the pharmaceutical industry and material science.[1] Coupling strategies have previously been used for the construction of *N*-fused heterocycles (Scheme 1, (a)).[2] Tiecco employed a cobalt-catalysed reductive cyclisation of diphenylethene to successfully deliver a phenanthrene structure,[3] which was followed by a large number of fused ring structures were constructed *via* coupling reactions, e.g. radical-mediated reductive coupling,[4] Negishi coupling,[5] domino coupling[6] and Suzuki coupling.[7] Since the 1990s, the transition metal-catalysed single C-H bond activation has emerged as an appealing complementary approach for the synthesis of *N*-fused heterocycles (Scheme 1, (b)).[8] A convenient aspect to this strategy was that C-C bonds could be formed by intramolecular direct aryl-aryl bond formation between an actived C-H bond and its coupling partners (C-X, X = Cl, Br, I, OTf etc).[9] As a result, numerous substrates with electron-withdrawing and electron-donating groups were used in order to obtain the corresponding cyclisation products.[10] However, besides these fruitiful accomplishments, both of the approaches did have drawbacks. Scope was limited to indoles, pyrroles and benzenes, in this context, some efforts have been directed to the development of transition metal-catalysed intramolecular double C-H activation with the purpose of higher efficiency and generality.[11] Greaney and co-workers reported an elegant indole-fused rings synthesis *via* intramolecular double C-H activation under basic conditions,[12] but there is still room for improved efficiency and extended generality and scope.

Cyclic nucleosides exist in biological metabolites[13] and synthetic intermediates[14] which have been extensively investigated for their significant antiviral activities. Herein, we report our recent findings[15] on the synthesis of multi-fused rings *via* intramolecular double C-H activation in purines and benzimidazole structures (Scheme 1, (c)). The biggest challenge remains enhancemnt of the selectivity and the activity, since multiple nitrogen atoms of purine or benzimidazole may result in complicated reactions and low activity. Herein we report on palladium catalysed double C-H cyclisation under acidic conditions.

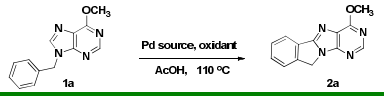
6-Methoxy-9-benzyl purine (**1a**) was initially selected as substrate (**Table** 1). To our delight, we found that an intramolecular cyclisation took place in the presence of a catalytic amount of $PdCl_2$ (2 mol%) and 1 equiv of CuCl as an oxidant albeit in a poor yield (15%, entry 1). Other palladium sources were also screened, such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$, which revealed $Pd(OAc)_2$ to be the best choice (entries 1-6). Silver acetate was the best oxidant of those tried with 2 equiv proving optimal reaction effect (entries 4 versus 9-13). Raising the loading of palladium acetate proved less than effective (entry 4 versus 7-8) in this reaction, acetic acid was used as solvent since one of its functions is believed to be that it serves to attenuate poisoning of the catalyst by the nitrogen atoms of the N-heterocycles.[16]



Scheme 1. Strategies for the Synthesis of *N*-Fused Heterocycles

With the optimised condition in hand, a variety of 2,6-substituted-9-benzyl purines were used as substrates to examine the scope of the reaction, the results are shown in Table 2. All substrates were smoothly transformed into the corresponding products *via* intramolecular double C-H activation, and most of the yields were satisfactory. Purines with methoxyl, methyl, piperidyl or ethoxy groups were all applicable to five-membered ring formation (entries 1-4). But the yield was a little lower when the C2-position was occupied by groups like methoxy, ethoxy, benzylamino or dibenzylamino (70-82%, entries 5-10). Notably, substituents on benzyl group did not affect the reaction too much, both **2k** and **2l** were obtained in excellent yields (entries 11-12). Most importantly, the cyclisation could also proceed successfully to deliver medium sized rings **2m** and **2n** when the N9-carbon chain was extended.

Table 1. Intramolecular cyclisation of 9-benzyl purine via Pd-catalysed double C-H activation[a]

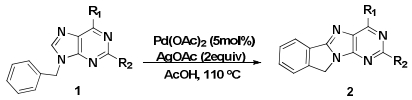


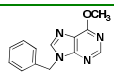
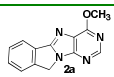
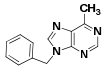
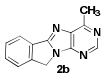
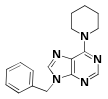
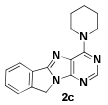
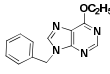
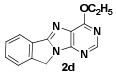
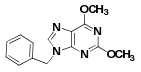
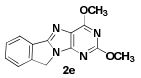
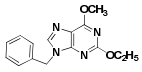
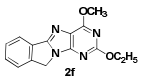
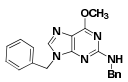
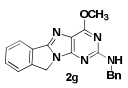
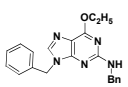
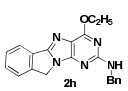
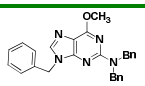
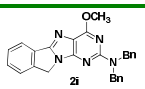
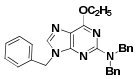
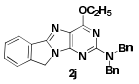
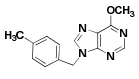
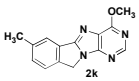
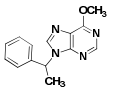
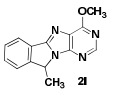
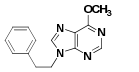
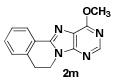
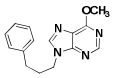
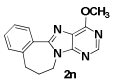
entry	catalyst(mol %)	oxidant(equiv)	yield/%[b]
1	$PdCl_2$ (2)	CuCl (1)	15
2	$PdCl_2$ (5)	CuCl (2)	27
3	$Pd(OAc)_2$ (2)	CuCl (2)	40
4	$Pd(OAc)_2$ (5)	AgOAc (2)	87
5	No Palladium	AgOAc (2)	N.R.[c]
6[c]	$Pd(PPh_3)_4$ (5)	AgOAc (2)	N.R.[c]
7	$Pd(OAc)_2$ (10)	AgOAc (2)	86
8	$Pd(OAc)_2$ (20)	AgOAc (2)	43
9	$Pd(OAc)_2$ (5)	AgOAc (5)	86
10	$Pd(OAc)_2$ (5)	BQ (2)	35
11	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (2)	44
12	$Pd(OAc)_2$ (5)	$FeCl_3$ (2)	26
13	$Pd(OAc)_2$ (5)	Oxone (2)	trace

[a] Conditions: **1a** (0.3 mmol), AcOH (1.8 mL), in a sealed tube at 110 °C for 36 h. [b] Isolated yields. [c] N.R. = No Reaction.

To extend the substrate scope, the protocol was extended to the formation of other fused heterocycles such as benzimidazole. As shown in Table 3, the reactions proceeded effectively and the anticipated five-, six- and seven-membered fused rings were obtained in moderate to good yields (58-81%).

Table 2. Intramolecular cyclisation of various 2,6-substituted-9-benzyl purines[a]

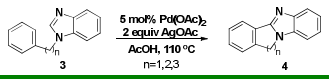


entry	substrate	product	yield/%[b]
1			87
2			91
3[c]			80
4			88
5[c]			78
6[d]			78
7			70
8			80
9			82
10[d]			80
11[c]			80
12			87
13			85
14[d]			83

[a] Unless otherwise mentioned, all of the reactions were carried out with **1a** (0.3 mmol), catalyst (5 mol %), AgOAc (2 equiv), AcOH (1.8 mL) in a Schlenk tube at 110 °C for 36 h. [b] Isolated yield. [c] 110 °C for 24 h. [d] 120 °C for 48 h.

A possible mechanism for the reaction is outlined in Scheme 2. It was speculated that palladation of purine at C8 formed the complex **I**. Then the intermediate **II** was formed from **I** through a metalation-deprotonation process. After which the target compound **III** and Pd(0) were produced by reductive elimination, Pd(0) is then reoxidized to Pd(II) by AgOAc and took part into the catalyst circle.

Table 3. Intramolecular cyclisation of 1-substituted benzimidazoles[a]



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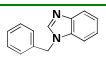
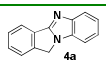
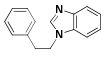
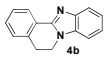
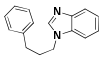
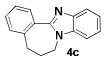
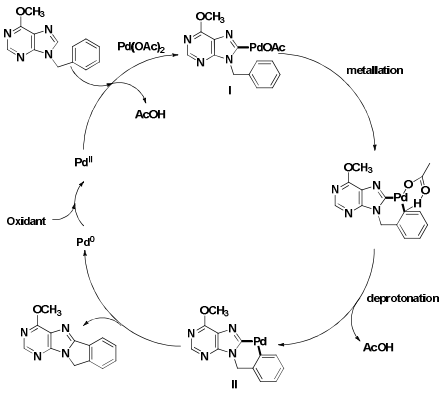
1[c]			58
2			81
3			75

[a] Unless otherwise mentioned, all of the reactions were carried out with **1a** (0.3 mmol), catalyst (5 mol %), AgOAc (2 equiv), AcOH (1.8 mL) in a Schlenk tube at 110 °C for 36 h. [b] Isolated yield. [c] 120 °C for 48 h.

Encouraged by the above results, a novel strategy for the construction of larger rings was envisaged. Iodobenzene was chosen as a pre-arylation reagent, which might afford a phenyl group to the C8 position of purine before the intramolecular cyclization (Table 4). It was pleasing to find that both the purine and benzimidazole substrates were smoothly transformed into the anticipated products. This method presents a promising new approach to large-ring compounds since it is synthetically difficult to efficiently construct seven-, eight-, or nine-membered rings in compound **6** otherwise.

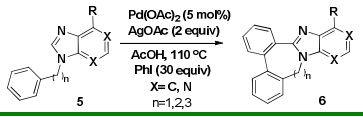
In summary, we have developed a novel and convenient method for highly efficient intramolecular cyclisation of purines and benzimidazoles catalysed by $Pd(OAc)_2$ to synthesise *N*-fused

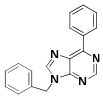
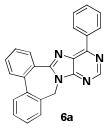
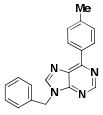
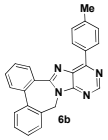
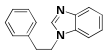
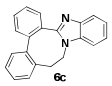
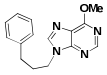
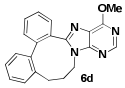
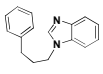
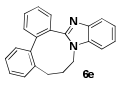
heterocycles. This intramolecular direct double C-H activation is conducted under normal acidic conditions without any base or ligand. A range of medium and large rings were formed from purine or benzimidazole containing substrates, which extended the substrate scope of the available methods and shows the generality of the process. Additionally the seven-, eight- and nine-membered rings could have potential biological activity which will be investigated separately. Further mechanistic investigation and synthetic application will be attempted in our laboratory.



Scheme 2. Proposed mechanism of double C-H activation.

Table 4. Intramolecular cyclisation of purines and benzimidazoles with iodobenzene[a]



entry	substrate	product	yield/%[b]
1[c]			45
2			63
3			69
4			49
5			79

[a] Unless otherwise mentioned, all of the reactions were carried out with **1a** (0.3 mmol), catalyst (5 mol %), AgOAc (2 equiv), AcOH (1.8 mL) in a Schlenk tube at 110 °C for 36 h. [b] Isolated yield.

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Notes and references

[a] *College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang 453007, Henan, China. Fax: 86 373 3329276; Tel: 86 373 3329255; E-mail: jplig@163.com; guohm518@hotmail.com.*

[b] *School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China.*

[c] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK. E-mail: j.s.fossey@bham.ac.uk.*

† Electronic Supplementary Information (ESI) available: [Experimental procedures, compound characterizations, and the copies of ^{1}H NMR and ^{13}C NMR spectra.]. See DOI: 10.1039/b000000x/

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Graphical Abstract

Synthesis of Fused N-Heterocycles via Tandem C-H Activation

Ge Meng, Hong-Ying Niu, Gui-Rong Qu, John S. Fossey, Jian-Ping Li,* and Hai-Ming Guo,*

College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang 453007, China. guohm518@hotmail.com

A novel and convenient method for the synthesis of fused N-heterocycles has been developed through highly efficient intramolecular cyclization of purines or benzimidazoles catalyzed by Pd(OAc)2 in normal acidic condition without any base or ligand. A range of medium and large rings, including five- to nine-membered rings, are prepared by this process, which extend the substrates' scope of the available methods and show the generality of the process.