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COMMUNICATION

Remarkably reactive dihydroindoloindoles *via* palladium-catalysed dearomatisation†

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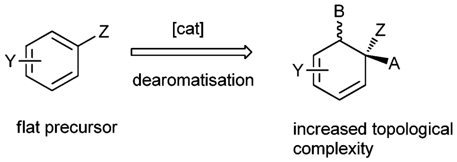
Palladium-catalysed dearomatisation reactions allow access to a previously unknown class of indoloindole heterocycle: 5,10b-dihydroindolo[2,3-b]indoles. The highly reactive nature of these compounds is demonstrated by their facile reactions with water and with hydride, alkyl, aryl and allyl-based organometallic nucleophiles.

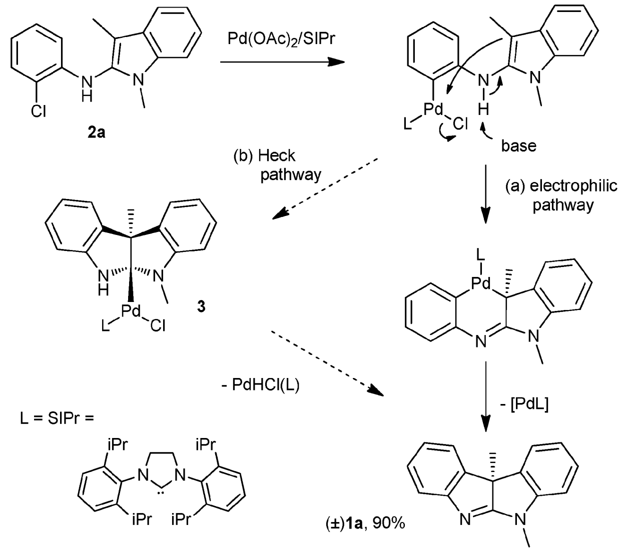
Catalytic dearomatisation reactions (Scheme 1) offer the expediency of transition-metal catalysed biaryl cross-coupling processes while increasing the extent of topological complexity *via* the introduction of chiral, quaternary sp^3 carbons (Scheme 1).

There are currently very few examples of transition metal-catalysed dearomatisation processes being exploited in synthesis and those examples are limited to the formation of stable products.[1,2] By contrast our interest lies in the synthesis of novel classes of molecules formed by catalytic dearomatisation that are ordinarily far too reactive to isolate. These highly labile species may reveal and facilitate unusual reactivities that can in turn be exploited in novel synthetic pathways. We recently demonstrated that this approach can be used successfully in the isolation of very reactive 4a-alkyl-4a*H*-carbazoles,[3] which had previously only been postulated as reactive intermediates formed during photolysis or flash vacuum pyrolysis experiments or isolated as electronically-stabilised benzannulated congeners.[1*b*,4]

We wished to show that palladium-catalysed dearomatisation could be exploited to generate previously unknown examples of reactive heterocycles and report here its application to the synthesis of a novel and highly reactive class of indoloindole, 5,10b-dihydroindolo[2,3-b]indoles, **1**.[5]



Scheme 1 Catalytic dearomatisation.



Scheme 2 Conditions: **2a** (0.5 mmol), Pd(OAc)$_2$ (5 mol%), SiPr (14 mol%), NaO^{t}Bu (1.5 mmol), toluene (5 ml), 100 °C, 16 h.

Scheme 2 illustrates the conversion of the precursor **2a**—synthesised by the Buchwald–Hartwig amination of 2-chloroaniline with the appropriate 2-bromoindole—to the desired product 5,10b-dimethyl-5,10b-dihydroindolo[2,3-b]-indole, (±)**1a**, in 90% spectroscopic yield (as determined by ^{1}H NMR spectroscopy) using sodium *tert*-butoxide as base. The catalyst used was formed *in situ* from palladium acetate and the *N*-heterocyclic carbene ligand SIPr, as its pentafluorobenzene adduct.[6] The intermediate formed by oxidative addition of **2a** to the palladium can undergo dearomatisation by at least two distinct routes: (a) an electrophilic or (b) a Heck pathway.

The Heck pathway seems less likely on the grounds of the high ring-strain of the *trans*-fused intermediate **3** which would be formed by the required *syn*-carbopalladation of the indole double bond. Furthermore the reaction was found to be strongly base dependent, as would be anticipated if the dearomatisation was indeed triggered by deprotonation of the NH function.[1*b*,3] Of the range of bases explored,[7] only NaO^{t}Bu and Cs$_2$CO$_3$ gave the desired product, the latter in somewhat diminished yield (60%), militating against a Heck-like process where all the bases tested are known to be effective.

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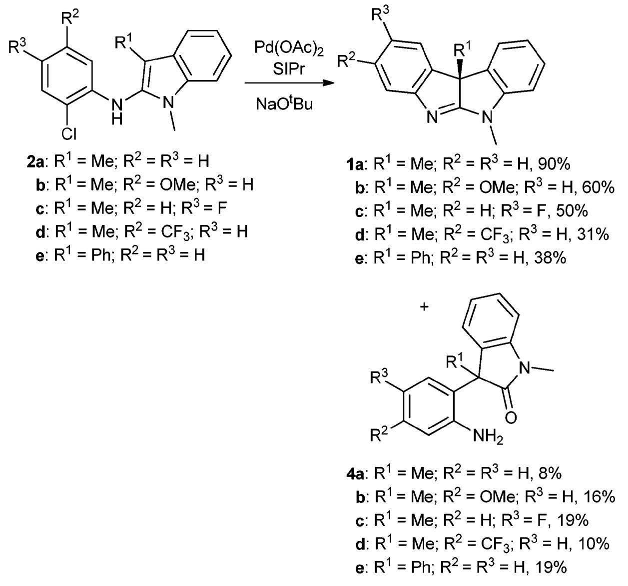
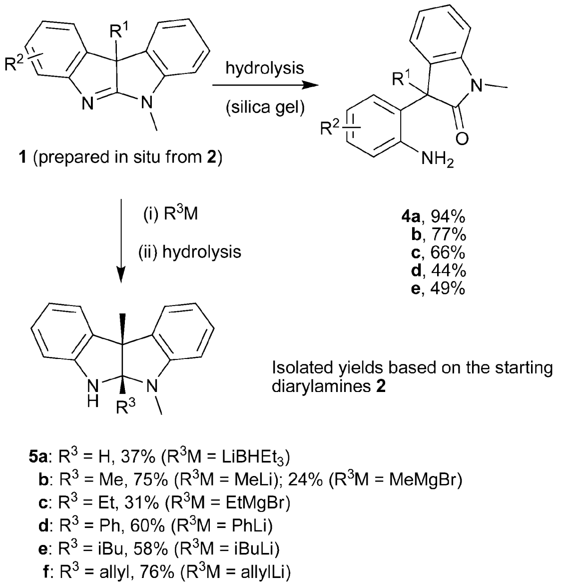


Scheme 3 Conditions: **2** (0.5 mmol), Pd(OAc)$_2$ (5 mol%), SiPr (14 mol%), NaO^{t}Bu (1.5 mmol), toluene (5 ml), 100 °C, 16 h. Spectroscopic yields, determined by ^{1}H NMR (1,3,5-MeOC$_6$H$_4$, internal standard).



Scheme 4 Reactivity of 5,10b-dihydroindolo[2,3-b]indoles.

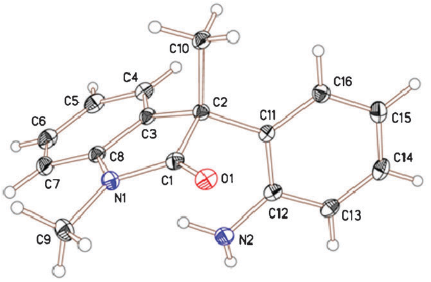


Fig. 1 X-Ray crystal structure of **4a**, thermal ellipsoids set at 30% probability level.

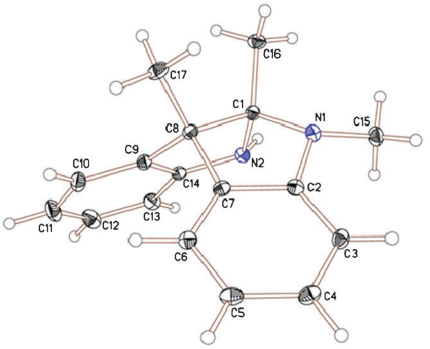


Fig. 2 X-Ray crystal structure of **5b**, thermal ellipsoids set at 30% probability level.

We next examined the extension of the catalytic dearomatisation methodology to other representative products **1** (Scheme 3). As can be seen both alkyl and aryl substitution was tolerated at the site of quaternisation, as were both electron-donating and withdrawing groups on the aryl chloride fragment.

All the products **1** proved to be highly moisture sensitive, undergoing facile hydrolysis with adventitious water, and in all cases they were produced as oils containing varying proportions of **4**. NMR and high-resolution mass spectroscopic data fully supported the structures of the indoloindoles **1**,[8,9] however the best confirmation of the identity of the labile species **1** came from their subsequent reactions which centered around their propensity to undergo nucleophilic attack at the iminic carbon.

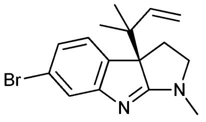
Thus the indoloindoles **1** could be cleanly converted to 3,3′-disubstituted oxindoles **4**, compounds with a range of interesting biological properties,[10] by simply subjecting them to column chromatography on silica (Scheme 4). In addition **1a** underwent reactions both with superhydride and a range of organometallic-based alkyl, aryl and allyl nucleophiles to generate the tetrahydroindolo[2,3-b]indoles **5**. To the best of our knowledge these are the first examples of tetrahydroindolo[2,3-b]indoles with alkyl and dialkyl substitution across the ring junction, indeed there has only been one other reported synthesis of tetrahydroindolo[2,3-b]indoles.[11] In all cases the reactions proceeded with strict *cis* diastereoselectivity across the C–C ring junction.

The X-ray crystal structures of representative hydrolysis and alkylation products, **4a** and **5b**, were determined, demonstrating unequivocally the site of C–C bond formation during the catalytic dearomatisation process (Fig. 1 and 2).

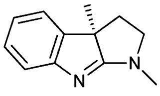
The facile reactivity of **1** with water is in stark contrast with the reactivity of known tetrahydropyrrolo[2,3-b]indole analogues, as exemplified by flustramine C,[12] which is moisture stable. This difference in reactivity is presumably large due to the far greater ring strain associated with the introduction of benzannulation, which would be relieved on removal of the imine bond. Indeed DFT calculations show that the model of **4a** (**4a***) lies 31.8 kcal mol^{-1} lower in energy than the reactants, while for the equivalent hydrolysis of tetrahydropyrroloindole **6*** this energy difference is reduced to 25.6 kcal mol^{-1}.[8,13]

It may be anticipated that the greater ring strain would lead to a longer and perhaps weaker C=N bond and thus more facile hydrolysis, however calculations showed the C4–N5 bond lengths to be very similar in the models **1a*** and **6*** (1.291 and 1.297 Å respectively).[8] In fact it appeared that changes in geometry around N3 on hydrolysis play a far more important role.[14]

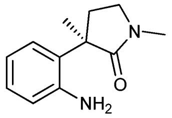
In summary, we have demonstrated that palladium-catalysed dearomatisation can be exploited in the synthesis of a previously unknown and highly reactive class of indoloindole which in turn serves as a starting point for the synthesis of heterocycles with non-planar, densely functionalised cores. We are currently exploring the extension of this novel catalytic dearomatisation to the synthesis of a range of heterocyles.



flustramine C



6*



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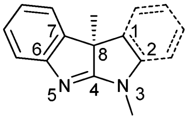

numbering for models **1a*** and **6***

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5 For related fused pyrroles see: L. Benati, G. Bencivenni, R. Leardini, M. Minozzi, D. Nanni, R. Scialpi, P. Spagnolo, G. Zanardi and C. Rizzoli, *Org. Lett.*, 2004, **6**, 417.

6 G. W. Nyce, S. Csihony, R. M. Waymouth and J. L. Hedrick, *Chem.–Eur. J.*, 2004, **10**, 4073.

7 NaOAc, K_3PO_4 and Cy_2NMe gave no dearomatised product only starting materials and some unidentified decomposition products.

8 See ESI†.

9 The ^{13}C NMR spectra showed peaks in the range 189.6–192.3 ppm corresponding to the iminic carbons, while the fused quaternary benzylic carbons were seen in the range 59.7–60.6 ppm.

10 (*a*) B. M. Trost, N. Cramer and H. Bernsmann, *J. Am. Chem. Soc.*, 2007, **129**, 3086; (*b*) H. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2003, **42**, 36; (*c*) X. Z. Wearing and J. M. Cook, *Org. Lett.*, 2002, **4**, 4237; (*d*) N. H. Greig, X. F. Pei, T. T. Soncrant, D. K. Ingram and A. Brossi, *Med. Res. Rev.*, 1995, **15**, 3.

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12 T. Lindel, L. Bräuchle, G. Golz and P. Böhrer, *Org. Lett.*, 2007, **9**, 283.

13 Transition state searches lay outside the scope of this work, as we have not yet established the detailed mechanism.

14 While the C2–N3–C4 angle increased by almost 5° on formation of **4a*** from **1a***, the equivalent structural change was somewhat smaller (3.4°) on going from **6*** to **7***. Furthermore, the N3 of **4a*** is essentially trigonal planar, this nitrogen atom is more pyramidal in the starting material **1a*** (Σ(angles) = 352.8°). In **6*** and **7*** these sums were much closer (355.6 and 356.2°, respectively), suggesting that the geometry around this nitrogen is less constrained and that relief of strain on breaking the C=N bond in **6*** would play much less of a role than in the equivalent hydrolysis of **1a***.