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Strained Dehydrogenative Ring Closure of Phenylcarbazoles

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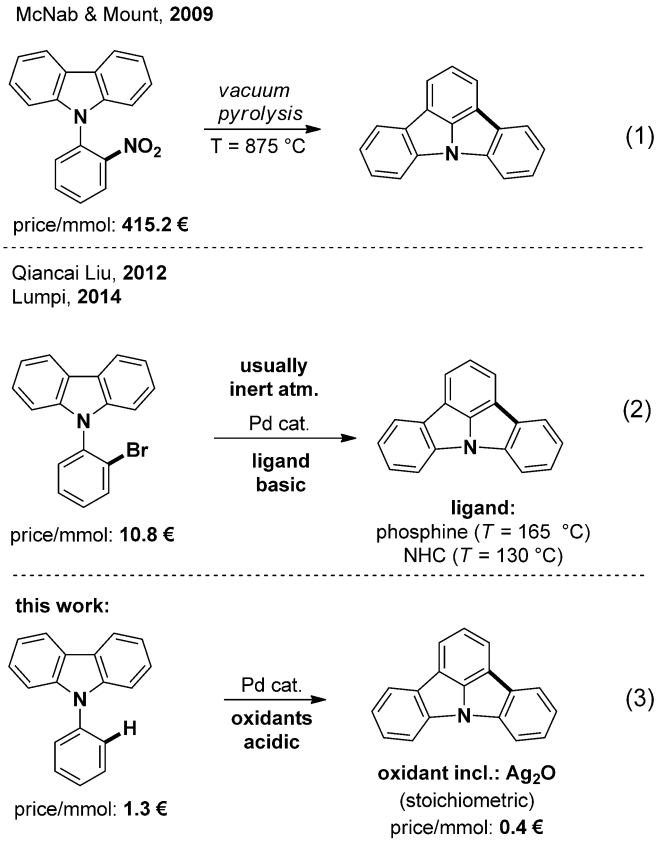
Abstract: What does it take to force a rigid and strained dehydrogenative ring closure, for example, in phenylcarbazoles? Since the works of Buchwald and Fagnou, palladium-catalysed ring-closing dehydrogenative reactions are legion, but will not operate when the strain at the reductive elimination stage becomes too large. We propose here a "muscled up" super-oxidative palldium-catalysed C–H activation method for the ring closure of strained phenylcarbazoles.

Keywords: C–H activation; cooperative oxidation; dehydrogenative cyclisation; palladium; strained reductive elimination

Interest in the structural motif of carbazole has been strong and steady over the past decades/years. It is not only part of biologically active compounds and pharmaceuticals,[1] but has also shown its applicability in polymeric materials with electrical, electrochemical, and optical properties.[2] Synthetically, a variety of approaches leading to carbazole and its derivatives, has been reported.[3] One of the more useful and modern methods to prepare carbazoles is perhaps the Pd-catalysed oxidative cyclisation of diarylamines (Fagnou, 2008),[4] or alternatively that of *ortho*-biphenylamine derivatives (Buchwald, 2005),[5] with only "H_2" as the formal by-product, usually scavenged with simple, easily handled, external oxidants. These so-called dehydrogenative methods represent an important step-minimised alternative to classical approaches for C–C bond formation. Thereafter, numerous ring-closing dehydrogenative methods based on these principles have been reported yielding versatile, often unprecedented, heteroaromatic compounds.[6]

It occurred to us that based on these pioneering methods and while utilising the proper oxidising strength, it might be possible to construct very strained heteroaromatic structures by a simple and convenient dehydrogenative ring closure. As a study case, we considered the strained oxidative cyclisation of phenylcarbazole **1a**, which we ambitioned to turn into indolo[3.2.1-*jk*]carbazole **2a** in a double C–H activation step.[7] To the best of our knowledge, synthetising expensive Indolo[3.2.1-*jk*]carbazoles in a dehydrogenative mode has never been achieved, in spite of the promising photophysical properties of the latter products, and the recent increasing interest of the chemical community for this very strained heterocyclic motif (Scheme 1).[8,9]

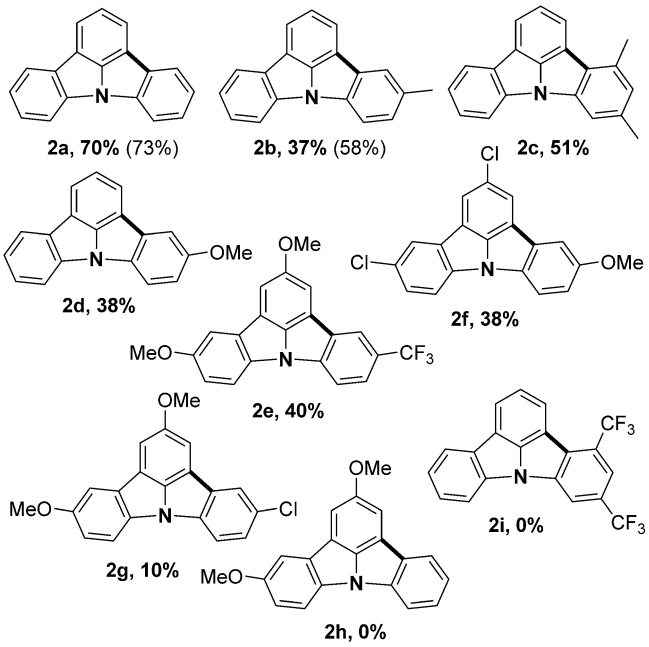


Scheme 1. Phenylcarbazole ring-closing strategies.

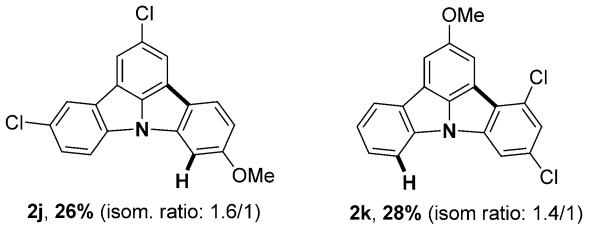
Table 1. Optimization for the intramolecular dehydrogenative coupling of *N*-phenylcarbazole.[a]

Entry	Catalyst	Oxidants	Solvent	Yield [%][b]
1[c]	$Pd(OAc)_2$	air	PivOH	<1
2	$Pd(OAc)_2$	Ag_2O, O_2	AcOH	29
3	$Pd(OAc)_2$	Ag_2O, CuO, O_2	AcOH	40
4	$Pd(OAc)_2$	CuO,[d] O_2	AcOH	–
5[e]	$Pd(OAc)_2$	Ag_2O, CuO, O_2	PivOH	62 (62)
6	$Pd(OAc)_2$	Ag_2O, CuO, O_2	PivOH	71
7[f]	$Pd(OPiv)_2$	Ag_2O, CuO, O_2	PivOH	**73 (70)**

[a] *Reaction conditions:* substrate (**1**, 1 mmol), Pd catalyst (10 mol%), Ag_2O oxidant (1.2 equiv.), CuO oxidant (1.2 equiv.), in acid (3 mL) for 24 h at 140 °C.
[b] NMR yields (isolated yields in parentheses).
[c] *Conditions:* substrate (**1**, 2 mmol), Pd catalyst (5 mol%), K_2CO_3 (10 mol%), in pivalic acid (2 mL) for 21 h under air at 110 °C.
[d] 2.0 equiv of CuO.
[e] Solvent mixture of PivOH/C_2Cl_4 (1:1), 3 mL each.
[f] Carried out at 130 °C.



Scheme 2. Isolated yields (NMR yields in parentheses), arylcarbazole **1** (1 mmol), $Pd(OPiv)_2$ (0.1 mmol), Ag_2O (1.2 mmol), CuO (1.2 mmol), PivOH (3 mL), O_2 (1 atm), 130 °C, 24 h.

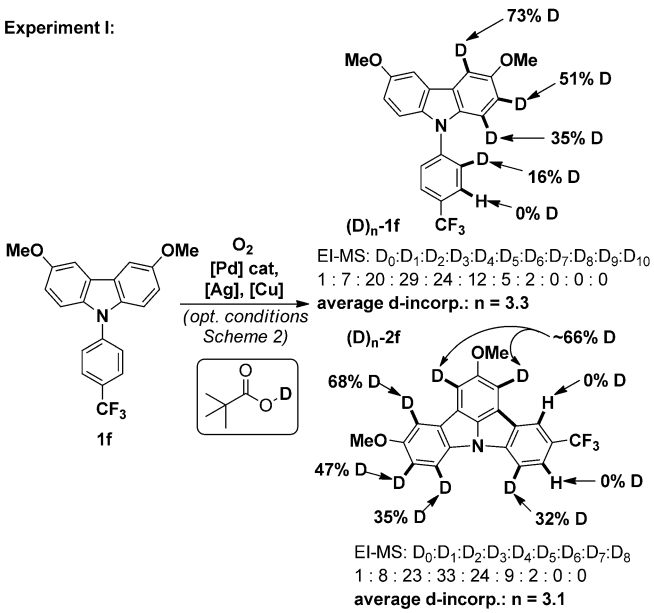


Scheme 3. Regioisomeric competition experiments (NMR yields). In the case of **2j**, the major isomer (depicted) could be separated. The two isomers of **2k** could not be separated from one another.

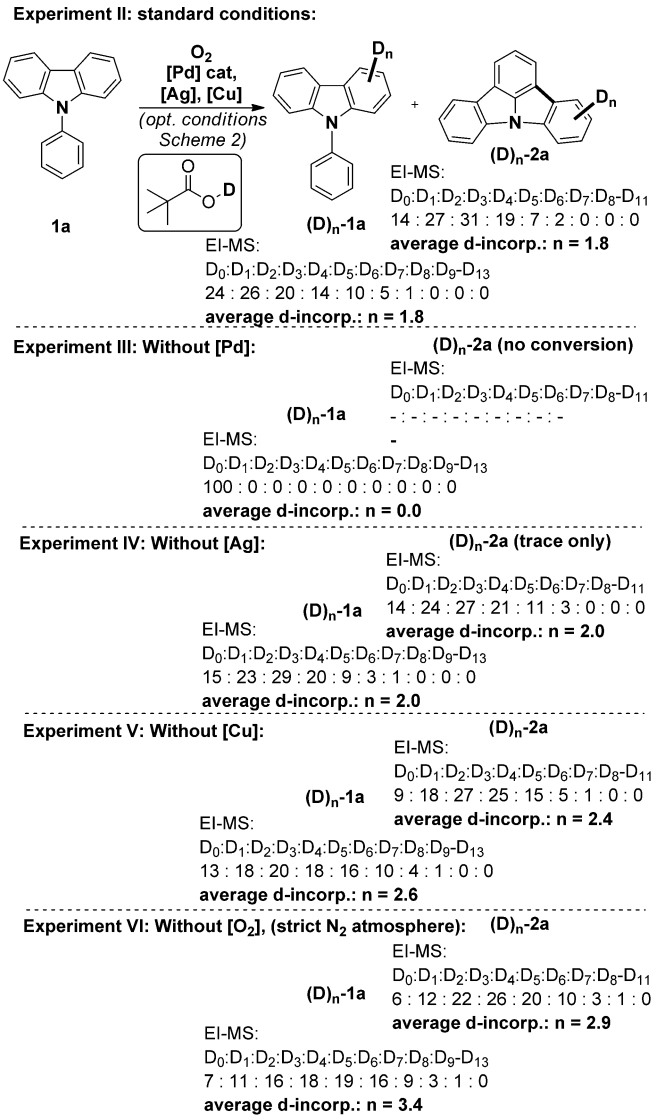
We commenced our investigation starting from Fagnou's Pd-catalysed dehydrogenative ring-closing carbazole synthesis. Not too surprisingly (Fagnou's method was designed for far less strained systems),[4] engaging phenylcarbazole **1a** did not yield any conversion under those conditions (Table 1, entry 1). Significant improvement was made while increasing stepwise the oxidising strength. The most significant elements of this optimisation are summarised in Table 1, entries 2–7. Interestingly, the triple combination of Ag_2O, CuO, and O_2 is significantly superior to any of these oxidants operating alone, suggesting a cooperative effect between those components. It should be noted that no other silver salt we tried performs better than Ag_2O, and that pivalic acid and pivalate are significantly superior to any other solvent-ligand combination we tried. The ideal reaction temperature was found to be 130 °C, above which decomposition becomes significant. We thus settled for the optimised conditions of entry 7.[10]

With those in hand, we then examined functional group tolerance (Scheme 2). Diverse electron-donating (methyl, methoxy) and electron-withdrawing (chloro, CF_3) functional groups were tolerated (**2b–f**), although typically with more moderate conversions and yields than for optimised product **2a**. The reaction is thus clearly dependent on the electronic disposition of the substrates. Generally, very eletron-rich substrates (**1g**, **1h**), tend to over-react and lead to substantial decomposition, while very electron-poor substrates (**1i**) tend to be recovered unreacted. Moreover, unsymmetrical substrates, whether at the phenyl moiety (**1j**), or at the carbazole moiety (**1k**), lead only to moderate C–H regioisomeric selectivities, up to 1.6/1 (Scheme 3). The current method thus serves as proof of a challenging concept, but more efficient future methodologies will be needed to unlock electronically diverging and other classes of substrates. However, considering the high price of synthesising some of those precious molecules (**2a–f**) through previously described multistep procedures, our dehydrogenative method can be regarded as competitive, and in some cases, depending on overall cost differences, probably superior. Moreover, our method operates in aerobic and acidic conditions, which strongly contrasts with the previously described basic and generally inert conditions of Liu and Lumpi.[8c,d] Thus our method complements well the organic chemistry toolbox.

As mechanistic investigation, we performed an H/D scrambling experiment, replacing the PivOH solvent with labelled PivOD, in otherwise standard reaction



Scheme 4. Positional H/D scrambling experiment.



Scheme 5. Component influence on H/D scrambling.

conditions. Substrate **1f** was preliminary chosen for NMR spectral clarity.[10] We were surprised by the overwhelming deuteration at almost all available C–H positions (Experiment **I**, Scheme 4).

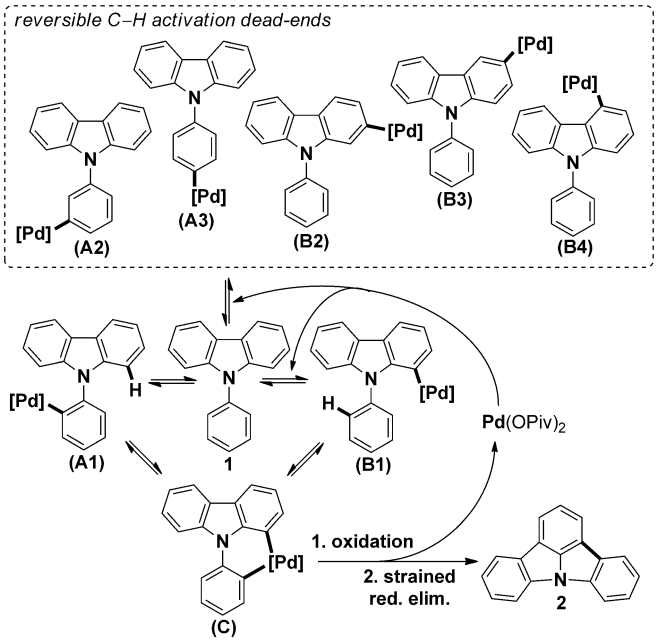
This means that both the C–H activation step at the carbazole moiety and at the phenyl moiety are reversible under catalytic conditions. Thus, neither is rate-limiting, in spite of the total absence of directing groups on either side. Moreover, this system seems extremely potent for C–H activation, whether at electron-rich (methoxycarbazole side), or electron-poor C–H positions (trifluorotolyl side). A second set of H/D scrambling experiments was also carried out on substrate **1a**, first under standard conditions (Experiment **II**, Scheme 5), then alternatively omitting each component of the reaction (Experiments **III** to **VI**, Scheme 5). Significantly, only the omission of the Pd salt quenches H/D scrambling activity (Experiment **III**). Neither omission of Ag, Cu, nor O_2 is able to suppress H/D scrambling (Experiments **IV**, **V**, **VI**, respectively). These results unambiguously indicate that Pd is involved in the reversible C–H activation steps, presumably in a classical concerted metallation deprotonation (CMD) mechanism involving pivalate ligands.[11] The other components however, the Ag and Cu salts, and O_2, are more likely involved in the later steps of the catalytic cycle. Interestingly, the apparent correlation between oxidation strength (Ag-Cu-O_2 triple oxidising system), and reaction efficiency (Table 1), suggests that the final strained reductive elimination step must be preceded by or simultaneous to a high oxidation event at Pd (intermediate **C**, Scheme 6). The latter high oxidation step, either alone or combined with the reductive elimination, is probably rate-limiting, which is also consistent with the very strained and rigid nature of the product.

In conclusion, we have developed an unprecedented method for the direct dehydrogenative synthesis of precious indolo[3.2.1-*jk*]carbazoles. This Pd-catalysed method, which relies on the cooperative oxidative action of Ag_2O,[11] CuO and O_2, is expected to find further applications for the direct dehydrogenative ring closure of other desirable but rigid, strained, or otherwise deactivated aromatic structures.

Experimental Section

General Methods

All reactions were carried out in dried reaction vessels with sealed Teflon screw caps under oxygen or nitrogen, unless



Scheme 6. Proposed mechanism.

otherwise specified. NMR spectra were obtained on Bruker AMX 400 or on Bruker Avance 600 systems using $CDCl_3$ or $(CD_3)_2SO$ as solvents, with proton and carbon resonances at 400/600 MHz and 101/151 MHz, respectively. Coupling constants (J) are quoted in Hz. Flash chromatography was performed on silica gel (40–63 mesh) by standard techniques. For the preparative HPLC the following conditions were used: HPLC, Dionex UltiMate 3000; column, Thermo Fisher, BetaBasic-18, 250×21.2 mm, 5 μm particle size; flow, 12 mL min^{-1}; eluent, organic: acetonitrile. GC-MS were recorded on a Bruker 436-GC/SCION SQ Premium EI, 230 V. The major signals are quoted in m/z with the relative intensity in parentheses. The method used starts with the injection temperature T_0. After holding this temperature for 3 min, the column is heated to temperature T_1 (ramp) and this temperature is held for an additional time t. Method: 50 40: T_0=50 °C, T^1=320 °C, ramp=40 °C min^{-1}; t=5 min. Some substrates were purchased either from Sigma Aldrich, Acros or TCI, and engaged directly. Other substrates were prepared according to standard procedures.

General Procedure for Ullmann Coupling Between Carbazole and Iodoarene

Unless otherwise specified, the carbazole (5.00 mmol), the phenyl iodide (5.00 mmol), CuI (952 mg, 5.00 mmol), and K_3PO_4 (1061 mg, 5.00 mmol) were united under air in a 170-mL reactor equipped with a Teflon screw cap. The reactor was flushed with nitrogen, DMF (10 mL) was added before the reactor was sealed and the reaction mixture was stirred at 150 °C for 24 h. The reactor was then cooled to room temperature and the crude material directly engaged (unless otherwise specified) on SiO_2 gel column chromatography for purification, which gave the desired product after concentration under vacuum.

General Procedure for Dehydrogenative Ring-Closing Products

Unless otherwise specified, the substrate (1.00 mmol), palladium(II) pivalate (31 mg, 0.10 mmol), Ag_2O (278 mg, 1.20 mmol), CuO (96 mg, 1.20 mmol), and pivalic acid (2715 mg) were united under air in a 170-mL reactor equipped with a Teflon screw cap. The reactor was flushed with oxygen and sealed, after which the reaction mixture was stirred at 130 °C for 24 h. The reactor was then cooled to room temperature and the crude material directly engaged (unless otherwise specified) on SiO_2 gel column chromatography for purification, which gave the desired product after concentration under vacuum.

For detailed procedures and characterization data/spectra of all products, please see the Supporting Information.

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[9] Prices from the Sigma–Aldrich catalogue, accessed in November 2014.

[10] See the Supporting Information.

[11] Given the large excess of pivalic acid and the relatively high temperature, it is safe to assume that under the reaction conditions, at least part of the Ag_2O and CuO salts are converted to AgOPiv and $Cu(OPiv)_2$, by simple water displacement. In any case, we showed that neither Ag nor Cu are essential to the C–H activation events (respectively, experiments IV and V, Scheme 5). This seems to indicate that neither Ag_2O nor AgOPiv significantly act as external base, but solely as oxidant. This is also in line with the observation of a thin layer of Ag(0) mirror inside the glass reactor.

