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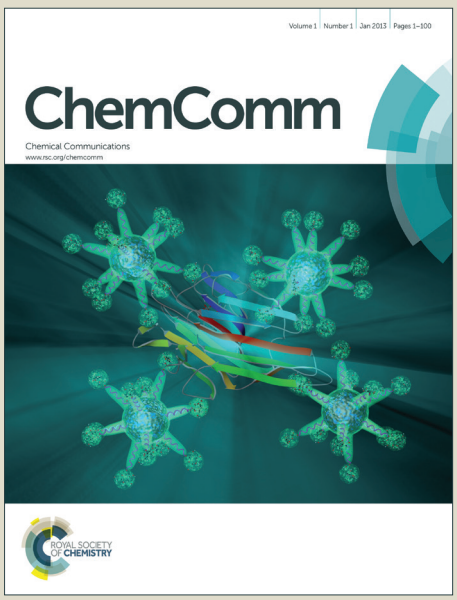

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COMMUNICATION

Solvent Free Selective Dehydrogenation of Indolic and Carbazolic Molecules with an Iridium Pincer Catalyst

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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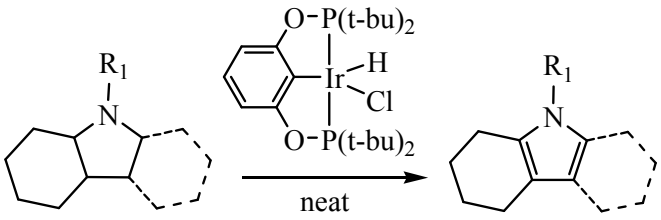
A previously known iridium POCOP pincer catalyst was found to selectively dehydrogenate the heterocyclic portion of several indolic and carbazolic molecules. These molecules were found to have an "activity window" (172-178 ºC) upon which only the heterocyclic ring underwent dehydrogenation. All reactions were run solvent free, yields for selected substrates were excellent, and the products were isolated by either distillation or alumina plug filtration.

Pyrroles and pyrrolidines are important starting materials and components of many biologically active natural products.[1-4] Specifically the indole skeleton is a ubiquitous motif in naturally occurring alkaloids, and other bio active molecules like tryptamine, serotonin, and physostigmine. Interest is growing in related tetrahydroindole molecules as they have proven to be active in the treatment of neurodegenerative diseases with activity similar to dopamine.[5]

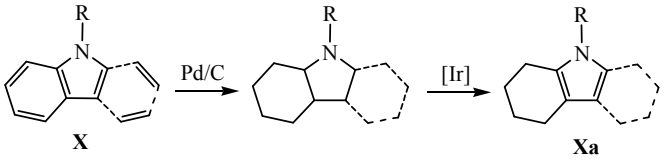
Scheme 1



During the course of our studies on hydrogen storage materials we focused on homogeneous catalytic dehydrogenations of pyrrolidine based molecules.[6] While investigating methyl indole as a potential liquid organic carrier (LOC) of hydrogen we serendipitously discovered this unique selective dehydrogenation, Scheme 1. The iridium (POCOP)t-butyl pincer was found to preferentially dehydrogenate only the heterocyclic ring of indolic and carbazolic molecules yielding tetrahydroindoles and octahydrocarbazoles respectively. These tetrahydroindoles and octahydrocarbazoles can then be isolated by vacuum distillation or alumina plug filtration. To our knowledge only three reports exist in which the tetrahydroindoles are synthesized by direct hydrogenation or dehydrogenation methods.[3, 7, 8] These reports all describe the

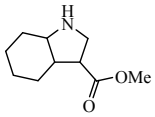
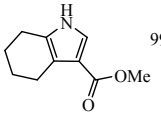
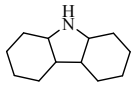
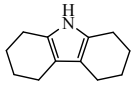
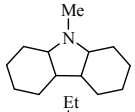
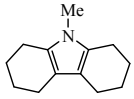
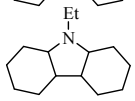
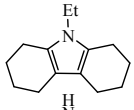
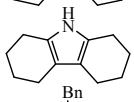
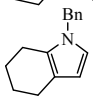
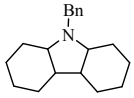
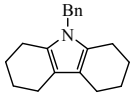
common feature of statistical variation of dehydrogenated-hydrogenated products.[7-9] This is of significant interest as 4,5,6,7-tetrahydroindole derivatives are classically made by multi-step cyclization methods.[2, 3, 5, 10] Herein we describe a two step approach via complete hydrogenation yielding the perhydro molecule followed by the selective dehydrogenation of the heterocyclic ring, Scheme 2.

Scheme 2



Each molecule was found to have a selective "activity window" within which dehydrogenation of only the heterocyclic ring occurs. For slower reactions the catalyst loading was increased (from 1 mol % up to 4 mol %) to expedite the reaction times. All the indolic molecules began to undergo dehydrogenation of the heterocyclic ring at 170 ºC and did not start to dehydrogenate the cyclohexane ring until 200 ºC. Thus indolic substrates were run at 195 ºC to ensure a reasonable rate of dehydrogenation while leaving the cyclohexane ring untouched. All the carbazolic molecules had a much narrower activity window (172 ºC to 178 ºC) above which both of the cyclohexane rings began to undergo dehydrogenation. We have previously shown for pincer catalyst that the rate is predictably slower at lower temperatures, thus most carbazole substrates required longer reaction times combined with higher catalyst loadings.[6]

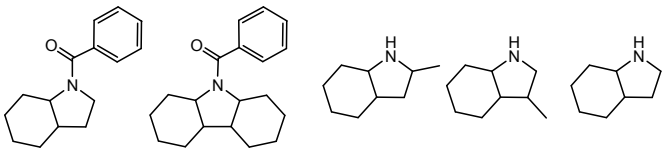
Table 1

Entry	Starting Material	Time	Temp	Catatylst loading	Product	Yield[A]
1		48 h	195 ºC	1%		99 (93)%
2		72 h	195 ºC	1%		99(89)%
3		72 h	172 ºC	4%		99 (92)%
4		48 h	172 ºC	2.5%		99 (91)%
5		48 h	178 ºC	2.5%		89 (86)%
						11 (09)%
6		48 h	195 ºC	2.5%		89 (86)%
7		48 h	178 ºC	2.5%		91 (87)%

Standard reaction conditions were solvent free, a reaction time of 24 hours, 1 mol % catalyst, and a reaction temperature of 195 ºC for indolic and 176 ºC for carbazolic substrates. All reactions were monitored by GCMS, substrates **1-5** were dehydrogenated in quantitative yield, Table 1. Although ethylperhydrocarbazole, (EPHC **5**) exhibited complete dehydrogenation of the heterocyclic ring, for still unclear reasons cleavage of the ethyl group occurred, giving an isolated yield of 86% ethyloctahydrocarbazole (EOHC) and 9% octahydrocarbazole (OHC). Benzylated substrates BPHI **(6)** and BPHC **(7)** reached a maximum conversion near 90% regardless of any increase in reaction time or catalyst loadings. Our substrate scope (**1-12**) was limited to those shown in Table 1 and Scheme 3, as we explored only commercially available indoles and carbazoles that could withstand the per-hydrogenation conditions (Pd on carbon at 100ºC and 100 atm of hydrogen gas). As our original focus was on liquid heterocycles as hydrogen storage materials all our reactions were run solvent free.

Benzoyl perhydroindole ByPHI (**8**) and benzoyl perhydrocarbazole ByPHC (**9**), both showed minimal dehydrogenation of only 6% and 8% respectively, Scheme 3. Commercially available indolic substrates perhydro-2-methylindole (**10**), perhydoskatole (**11**), and perhydroindole (**12**) also displayed poor dehydrogenation yields of 1.5%, 2.5% and 3%, respectively, Scheme 3. The yields were only marginally improved upon increasing the reaction time and catalyst loading, thus substrates **8-12** were abandoned.

Scheme 3



8 **9** **10** **11** **12**

Conclusions

Our two step synthesis of various tetrahydroindoles and octahydrocarbazoles represents a significant improvement over previously described methods. Specifically our procedure provides a single product with excellent yields, facile purification (distillation or alumina filtration vs. chromatography), lower catalyst loading (1% vs 5% mol), and simpler reagents (Ir catalyst vs. Li metal and liquid ammonia).[3, 7]

Notes and references

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†**General Procedures.** All solvents used were reagent grade and anhydrous solvents were distilled from calcium hydride. All other chemicals were purchased from Aldrich and used as received. Where anaerobic techniques were required, glove-box and standard Schlenk techniques were used. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at ambient temperature with chemical shifts specified in ppm relative to the specified solvent. NMR solvents were distilled over calcium hydride and degassed prior to use. Elemental analyses were performed by Desert Analytics, Phoenix, AZ. The iridium pincer catalyst 2 $IrHCl\{C_6H_3\text{-}2,6\text{-}(OPBu^t_2)_2$ was made according to literature procedures.[11] The identity and purity of all products in general were determined using a gas chromatograph GC HP 5890 Series II with a mass selective detector HP 5971 (GC-MS) and ^{1}H and ^{13}C NMR.

Catalytic activity check. The activity of the iridium catalysts was checked prior to use and followed the format outlined by Gottker-Schnetmann et al., in which the active catalyst is generated in situ from the parent hydrido chloride compound.[11] Turn over numbers (TON) in the range from 800 to 1,200 were considered to be acceptable.

General preparation of perhydro indolic compounds. The desired LOC (5 mL) was loaded into a high pressure Parr bench top reactor with palladium on carbon (1 g). The vessel was purged for 20 minutes with hydrogen gas, then heated to 120 °C and pressurized to 100+ bar with hydrogen gas. The reaction was left to stir for two days. The reactor was then allowed to cool to room temperature, depressurized, and the palladium filtered by washing with hexanes. The hexanes were removed in vacuo, after which the LOC was stored over molecular sieves in an argon glovebox. The perhydro LOCs purity was confirmed by GCMS and ^{1}H NMR prior to use.

General preparation of benzyl and benzoyl substrates. The desired perhydro LOC substrate was benzoylated and then reduced with $LiAlH_4$ following literature procedures.[12]

General dehydrogenation conditions (substrates 1 through 12). The desired indolic compound and premixed pincer complex with sodium tert-butoxide (1.0 mol %) were washed with pentane into a 10 ml Schlenk flask with an integrated water cooled condenser. The integrated flask was connected to an oil bubbler, purged with argon, and the pentane was boiled off (60 °C) over the course of 20 minutes. Upon removal of the pentane the flask was completely immersed in an oil bath at the prescribed temperature (indolic compounds at 195 ºC and carbazolic compounds at 172-178ºC). Reactions were monitored by GCMS. After a specified period of time (48 to 72 hours depending on the compound) the products were either distilled directly from the reaction mixture or filtered through an alumina plug and then confirmed by ^{1}H & ^{13}C NMR. All products are previously known however those for which NMR shifts could not be found in the literature have been reported here.

Methyl perhydroindole, MePHI (1) to Methyl tetrahydroindole, MeTHI, $C_9H_{13}N$ (1a). MePHI followed the standard dehydrogenation techniques described above for indolic compounds (48 hours, 1 mol %, 195 ºC). The reaction is quantitative by GCMS and 93% was isolated by distillation. ^{1}H NMR (300 MHz, $CDCl_3$): 6.51 (s, 1H), 5.94 (s, 1H), 3.50 (s, 3H), 2.58-2.50 (m, 4H), 1.92-1.81 (m, 2H), 1.79-1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): 128.1, 119.5, 117.2, 105.9, 32.8, 23.5, 23.3, 23.2, 21.6.

Perhydroindole-3-carboxylate methyl ester, PHI-3-CO_2Me (2) to Tetrahydroindole-3-carboxylate methyl ester, THI-3-CO_2Me, $C_{10}H_{13}NO_2$ (2a).[7] The window of activity for PHI-3-CO_2Me was similar to all other indolic molecules described above, and only deviated by requiring an extra 24 hours (72 hours total) for completion. The reaction is quantitative by GCMS and 89% isolated by distillation.

Perhydrocarbazole, PHC (3) to Octahydrocarbazole, OHC, $C_{12}H_{17}N$ (3a).[13] PHC deviated from the standard dehydrogenation techniques by requiring an extra 24 hours (72 hours total) for completion and quadrupling the catalyst loading (4%). The reaction was found to be quantitative by GCMS and was isolated by alumina filtration (92%).

Methyl perhydrocarbazole, MePHC (4) to Methyl octahydrocarbazole, MeOHC, $C_{13}H_{19}N$ (4a). MePHC deviated from the standard dehydrogenation techniques by requiring an increase the catalyst loading (2.5%). The reaction was found to be quantitative by GCMS and was isolated by alumina filtration (91%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.31 (s, 3H), 2.52 (m, 4H), 2.41 (m, 4H), 1.84 (m, 4H) 1.74 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): 126.16, 114.35, 29.70, 23.58, 23.50, 21.69, 21.23.

Ethyl perhydrocarbazole, EPHC (5) to Ethyl octahydrocarbazole, EOHC, $C_{14}H_{21}N$ (5a). EPHC's selective dehydrogenation window is much narrower, activity starts at 172 ºC, but the outer rings begin to undergo dehydrogenation at 180 ºC. The optimum temperature was found to be 178 ºC and two days for complete conversion (EPHC completely consumed, GCMS). At some point prior to isolation the ethyl group is cleaved, giving 86% ehtyloctahydrocarbazole (EOHC) and 9% octahydrocarbazole (OHC). The same product distribution is observed whether isolated via distillation or by alumina plug filtration. ^{1}H NMR (300 MHz, $CDCl_3$): 3.72 (q, J = 7 Hz, 2H), 2.55 (m, 4H), 2.41 (m, 4H), 1.85-1.74 (m, 8H), 1.24 (t, J = 7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 125.21, 114.27, 37.24, 23.49, 23.47, 21.59, 21.16, 16.41.

Benzyl perhydroindole, BPHI (6) to Benzyl tetrahydroindole, BTHI, $C_{15}H_{17}N$ (6a).[14] BPHI deviated from the standard indolic dehydrogenation techniques as regardless of ramping up mol % of catalyst or extending the reaction time (48 hours) the conversion never exceeded 89% (GCMS) and was isolated by alumina filtration (86%).

Benzyl perhydrocarbazole, BPHC (7) to Benzyl octahydrocarbazole BOHC, $C_{19}H_{23}N$ (7a).[15] **(7a).** BPHC deviated from the standard carbazolic dehydrogenation techniques as regardless of ramping up mol % of catalyst or extending the reaction time (48 hours) the conversion never exceeded 91% (GCMS) and was isolated by alumina filtration (87%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.31-7.20 (m, 3H), 6.99 (m, 2H), 4.90 (s, 2H), 2.44 (m, 8H), 1.82-1.71 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$): 139.05, 128.57, 126.85, 126.22, 126.18, 114.73, 46.19, 23.62, 23.55, 21.83, 21.36.

Acknowledgment. This work was supported by the Department of Energy.

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